Addressing Current Questions and Controversies in the Management of Hodgkin and Non-Hodgkin Lymphoma — What Clinicians Want to Know

Part 2 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
3:15 PM – 5:15 PM CT

Faculty

Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD
David G Maloney, MD, PhD
Loretta J Nastoupil, MD
Sonali M Smith, MD

Moderator

Neil Love, MD

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Faculty

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Director, James P Wilmot Cancer Institute
University of Rochester
Rochester, New York

Brad S Kahl, MD
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Washington University School of Medicine
Director, Lymphoma Program
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Medical Director
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Leonard and Norma Klorfine Endowed Chair for Clinical Research
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Professor of Medicine, Division of Oncology
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Associate Professor
Section Chief, Indolent Lymphoma
Section Chief, New Drug Development
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Sonali M Smith, MD
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Chief, Section of Hematology/Oncology
Co-Leader, Cancer Service Line
Co-Director, Lymphoma Program
The University of Chicago
Chicago, Illinois

Moderator
Neil Love, MD
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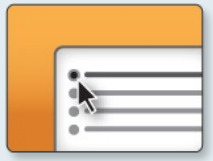
Clinicians in the Meeting Room

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 pre- and postmeeting surveys.

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.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

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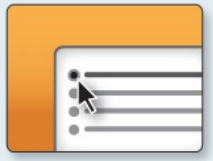
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the pre- and postmeeting surveys.

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

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

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About the Enduring Program

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

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Addressing Current Questions and Controversies in the Management of Multiple Myeloma — What Clinicians Want to Know

Part 3 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Jesús G Berdeja, MD
Rafael Fonseca, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD

Moderator

Neil Love, MD

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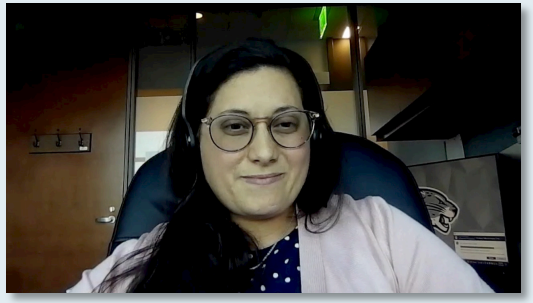
Florida Cancer Specialists
Lutz, Florida

Rahul Gosain, MD
Guthrie Corning Cancer Center
Corning, New York

Spencer Henick Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida



Amany R Keruakous, MD, MS
Georgia Cancer Center
Augusta University
Augusta, Georgia

Bhavana (Tina) Bhatnagar, DO
WVU Cancer Institute
Wheeling, West Virginia

Kapisthalam (KS) Kumar, MD
Florida Cancer Specialists
Trinity, Florida

Jennifer L Dallas, MD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Yanjun Ma, MD
Tennessee Oncology
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Neil Morganstein, MD
Atlantic Health System
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Vignesh Narayanan, MD
Colorado Permanente Medical Group
Lone Tree, Colorado

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Oncologist
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Drexel University College of Medicine
West Reading, Pennsylvania

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Commercial Support

This activity is supported by educational grants from ADC Therapeutics, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Genentech, a member of the Roche Group, Kite, A Gilead Company, MEI Pharma Inc, Novartis, and Seagen Inc.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Friedberg — Disclosures

No relevant conflicts of interest to disclose.

Dr Kahl — Disclosures

No relevant conflicts of interest to disclose.

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Dr Maloney — Disclosures

Advisory Committee	Chimeric Therapeutics, Genentech, a member of the Roche Group
Consulting Agreements	Bristol-Myers Squibb Company, Caribou Biosciences Inc, Celgene Corporation, Gilead Sciences Inc, Incyte Corporation, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Legend Biotech, Lilly, Mustang Bio, Novartis, Umoja Biopharma
Contracted Research	Celgene Corporation, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Legend Biotech

Dr Nastoupil — Disclosures

Advisory Committee	Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Janssen Biotech Inc, Kite, A Gilead Company, Novartis, Takeda Pharmaceuticals USA Inc
Contracted Research	Bristol-Myers Squibb Company, Caribou Biosciences Inc, Epizyme Inc, Genentech, a member of the Roche Group, Genmab, IGM Biosciences Inc, Janssen Biotech Inc, Kite, A Gilead Company, Novartis, Takeda Pharmaceuticals USA Inc
Data and Safety Monitoring Board/Committee	Denovo Biopharma, Genentech, a member of the Roche Group, MEI Pharma Inc, Takeda Pharmaceuticals USA Inc

Dr Smith — Disclosures

Consulting Agreements	Bristol-Myers Squibb Company, Gilead Sciences Inc, MorphoSys
Contracted Research	Acerta Pharma — A member of the AstraZeneca Group, Bristol-Myers Squibb Company, Celgene Corporation, Curis Inc, Epizyme Inc, Forty Seven Inc, Genentech, a member of the Roche Group, Karyopharm Therapeutics, Pharmacyclics LLC, an AbbVie Company, Portola Pharmaceuticals Inc, TG Therapeutics Inc
Nonrelevant Financial Relationship	Spouse is employed at Caris Life Sciences

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Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Friedberg

Module 2: Follicular Lymphoma (FL) — Dr Nastoupil

Module 3: Hodgkin Lymphoma (HL) — Dr Smith

Module 4: Chimeric Antigen Receptor (CAR) T-Cell Therapy for Non-Hodgkin Lymphoma — Dr Maloney

Module 5: Mantle Cell Lymphoma (MCL) — Dr Kahl

Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Friedberg

▸ *Real World Cases and Questions*

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▸ *Real World Cases and Questions*

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Module 1: Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Friedberg

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Case Presentation: 62-year-old woman with DLBCL with renal and subcutaneous involvement

Dr Erik Rupard (West Reading, Pennsylvania)

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Dr Tina Bhatnagar
(Wheeling, West Virginia)

Case Presentation: Otherwise healthy 86-year-old woman with an orbital mass diagnosed with Stage IE DLBCL

Dr Yanjun Ma
(Murfreesboro, Tennessee)

Case Presentation: 81-year-old man with Stage IIIB DLBCL, GCB type and LVEF 35%-40% due to prior MI and CAD

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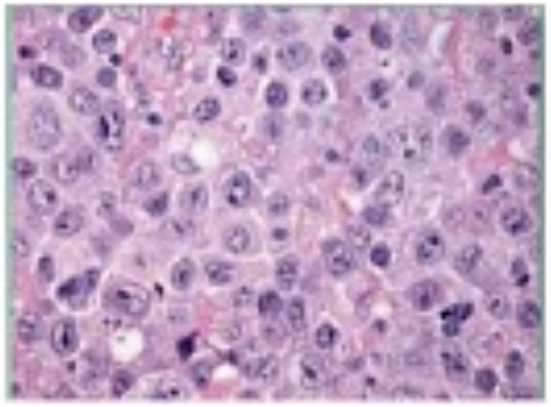
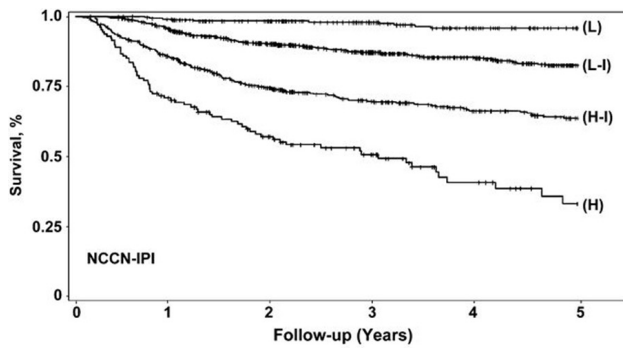
Therapy of Diffuse Large B-cell Lymphoma (DLBCL)

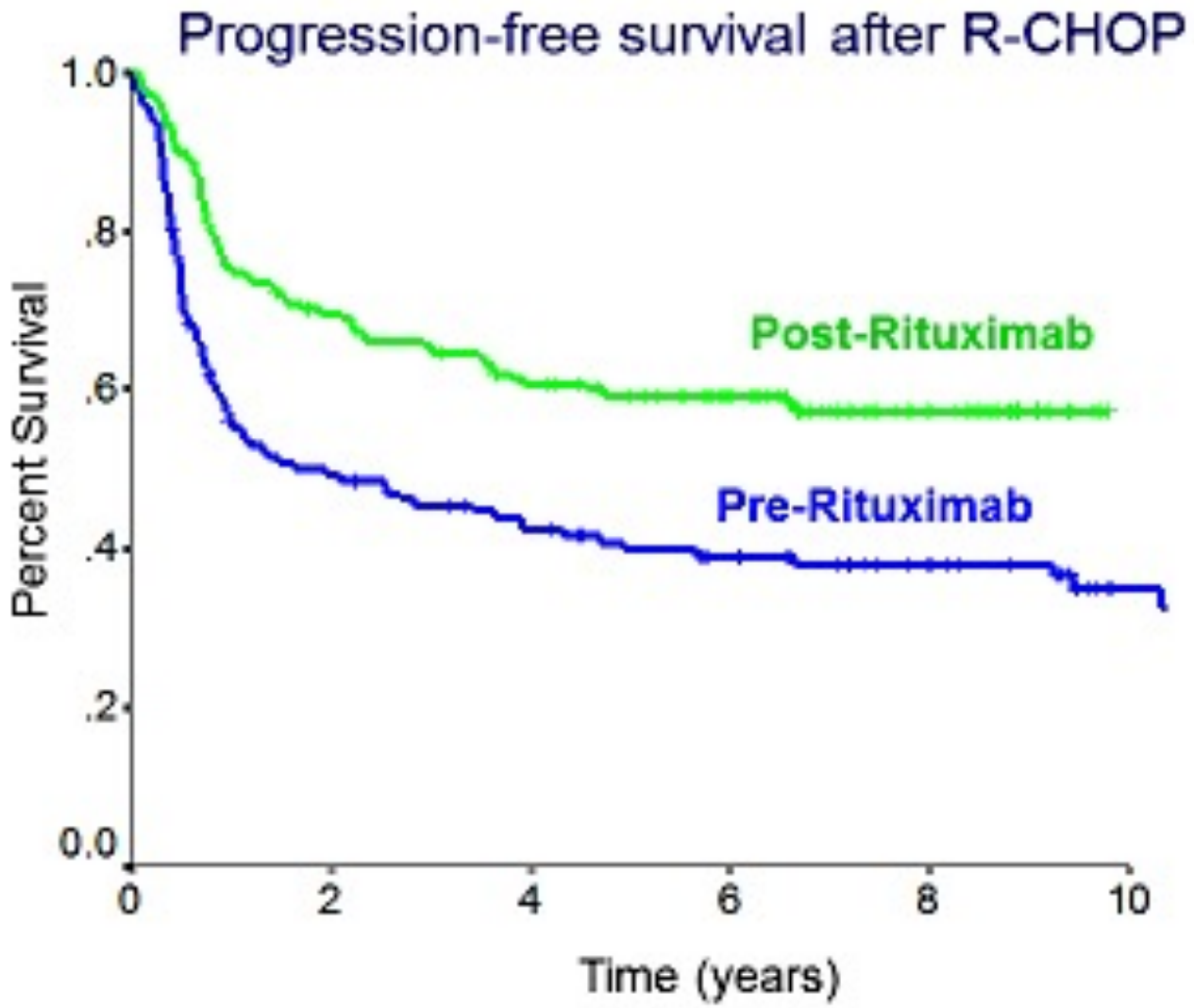
Jonathan W. Friedberg M.D.

RCHOP has been the “standard” therapy of DLBCL





Zhou et al, *Blood* 123: 837, 2014



Updated from Sehn, L et al, *J Clin Oncol* 23:5027, 2005

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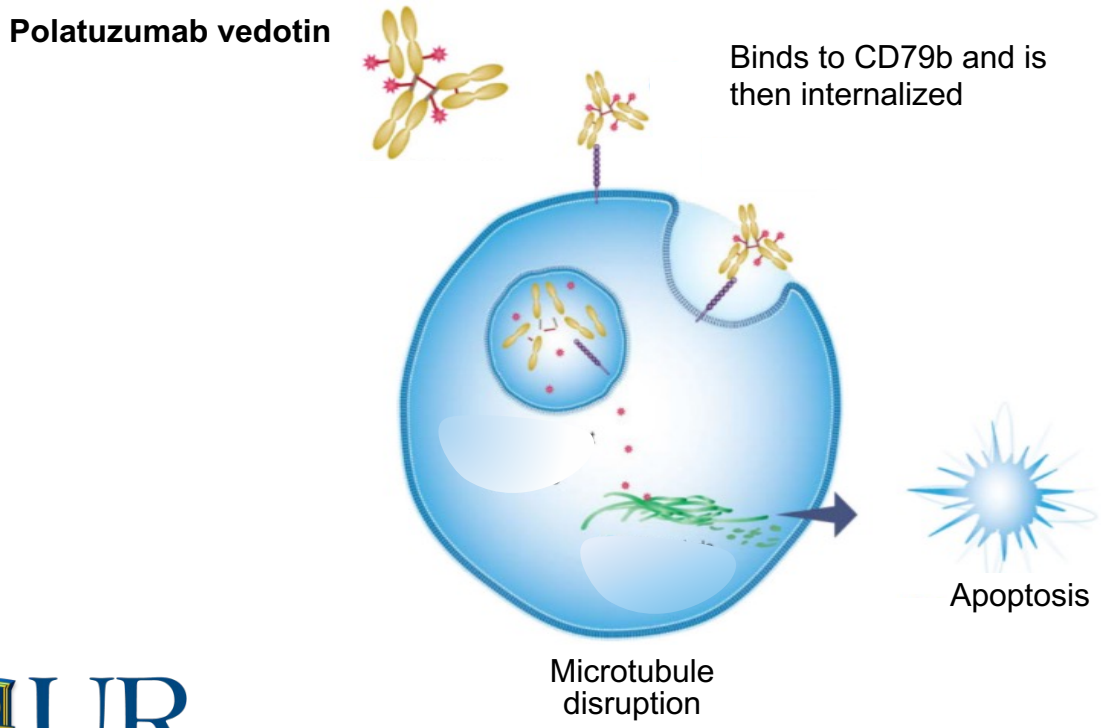
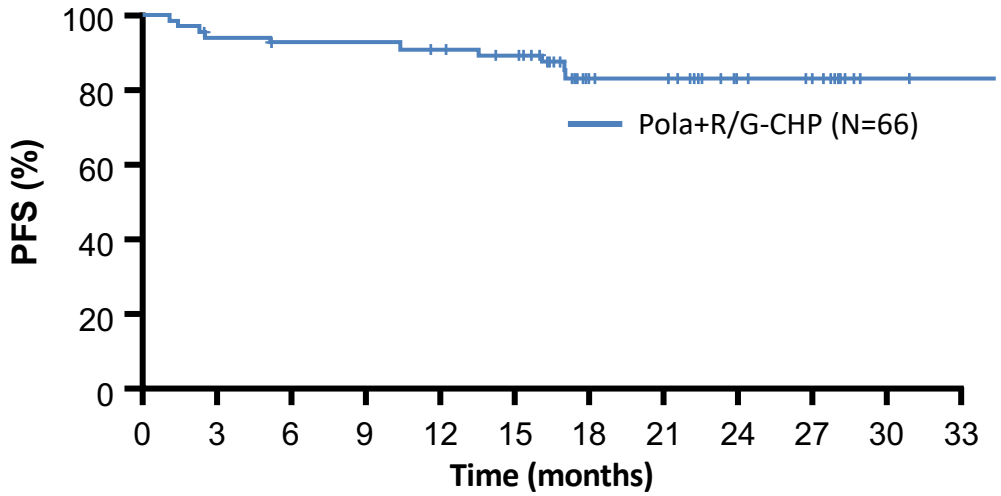
Polatuzumab vedotin is an ADC targeting CD79b

CD79b is ubiquitously expressed on DLBCL cells



PFS after Pola+R/G-CHP in first-line DLBCL



Tilly H, et al. *Lancet Oncol* 2019;20:998–1010.

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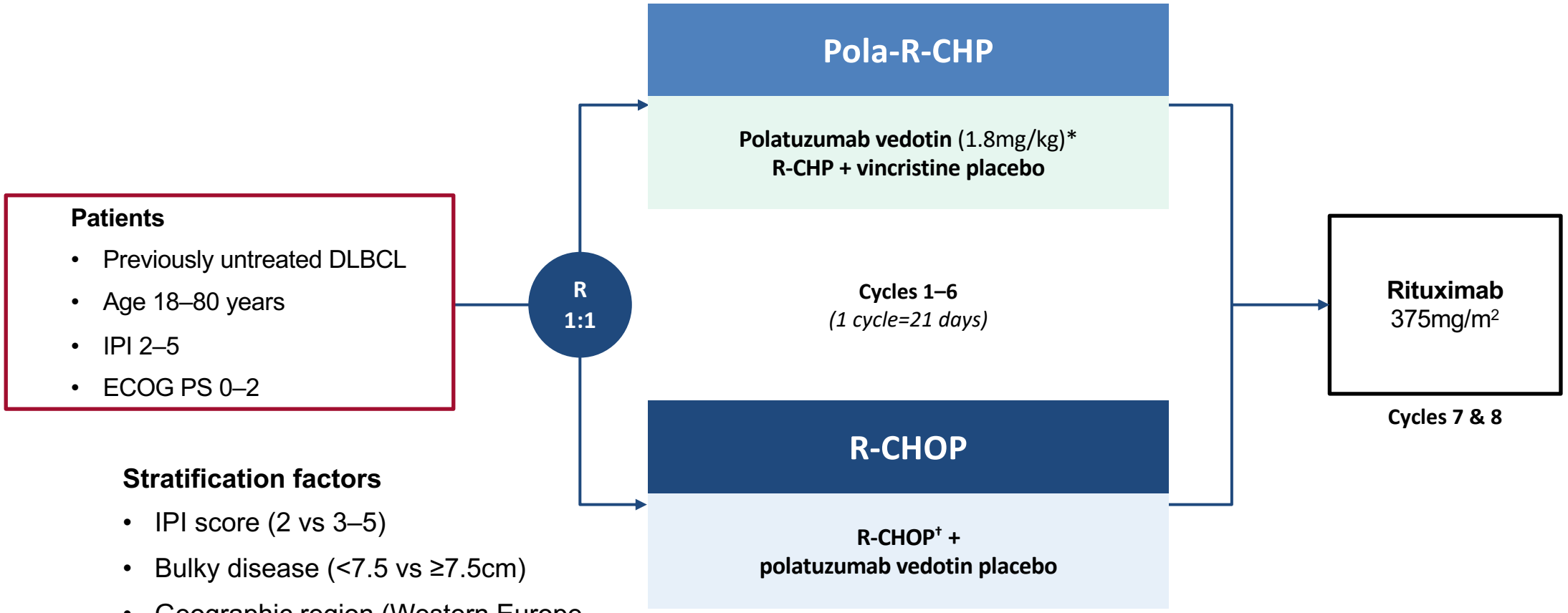
POLARIX: A randomized double-blinded study



Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

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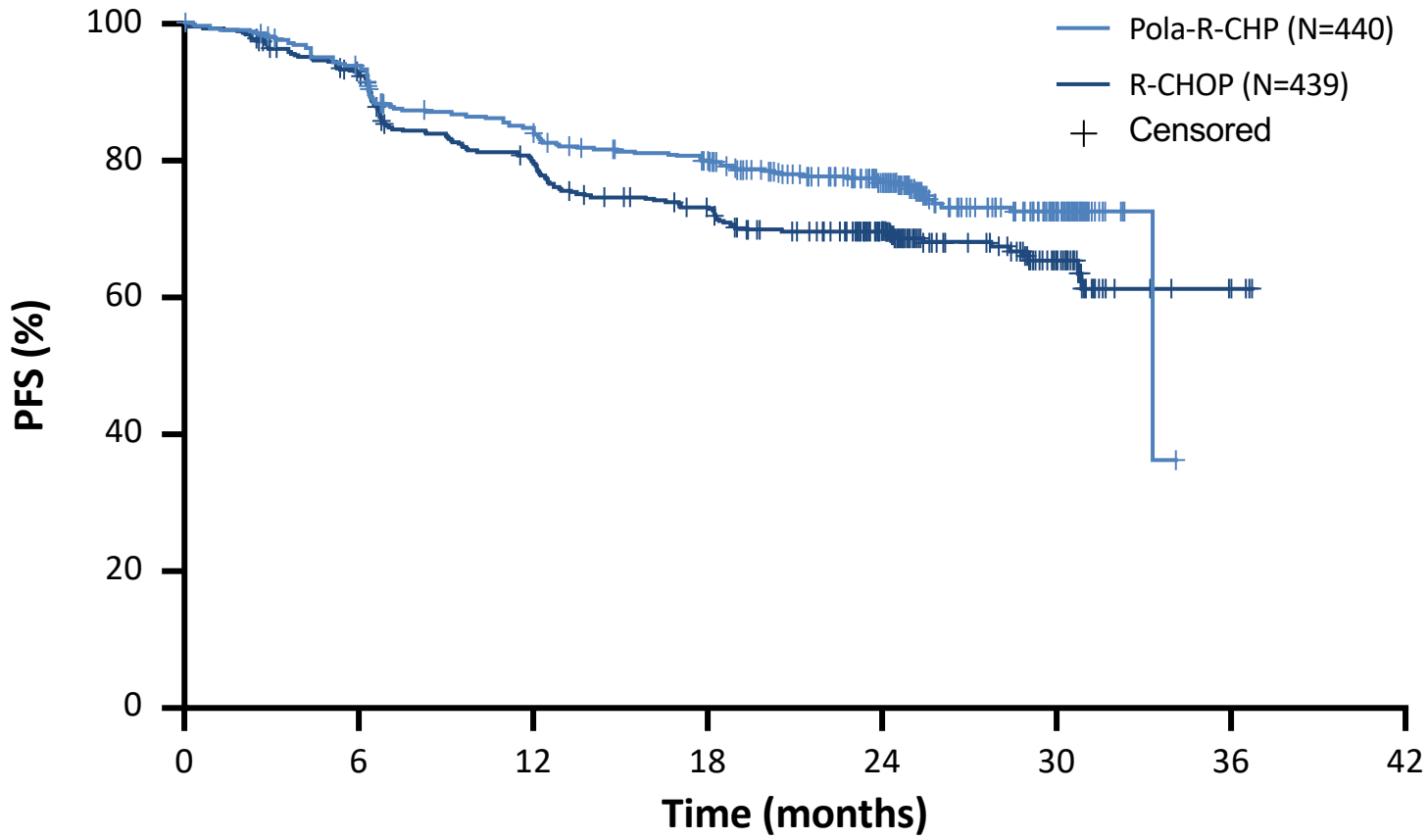
Tilly et al., *New Engl J Med* 386:351-63 2022

POLARIX Primary endpoint: Progression-free survival



HR 0.73 (P<0.02)

- **24-month PFS:**
  76.7% with Pola-R-CHP
  70.2% with R-CHOP
  (Δ**=6.5%**)

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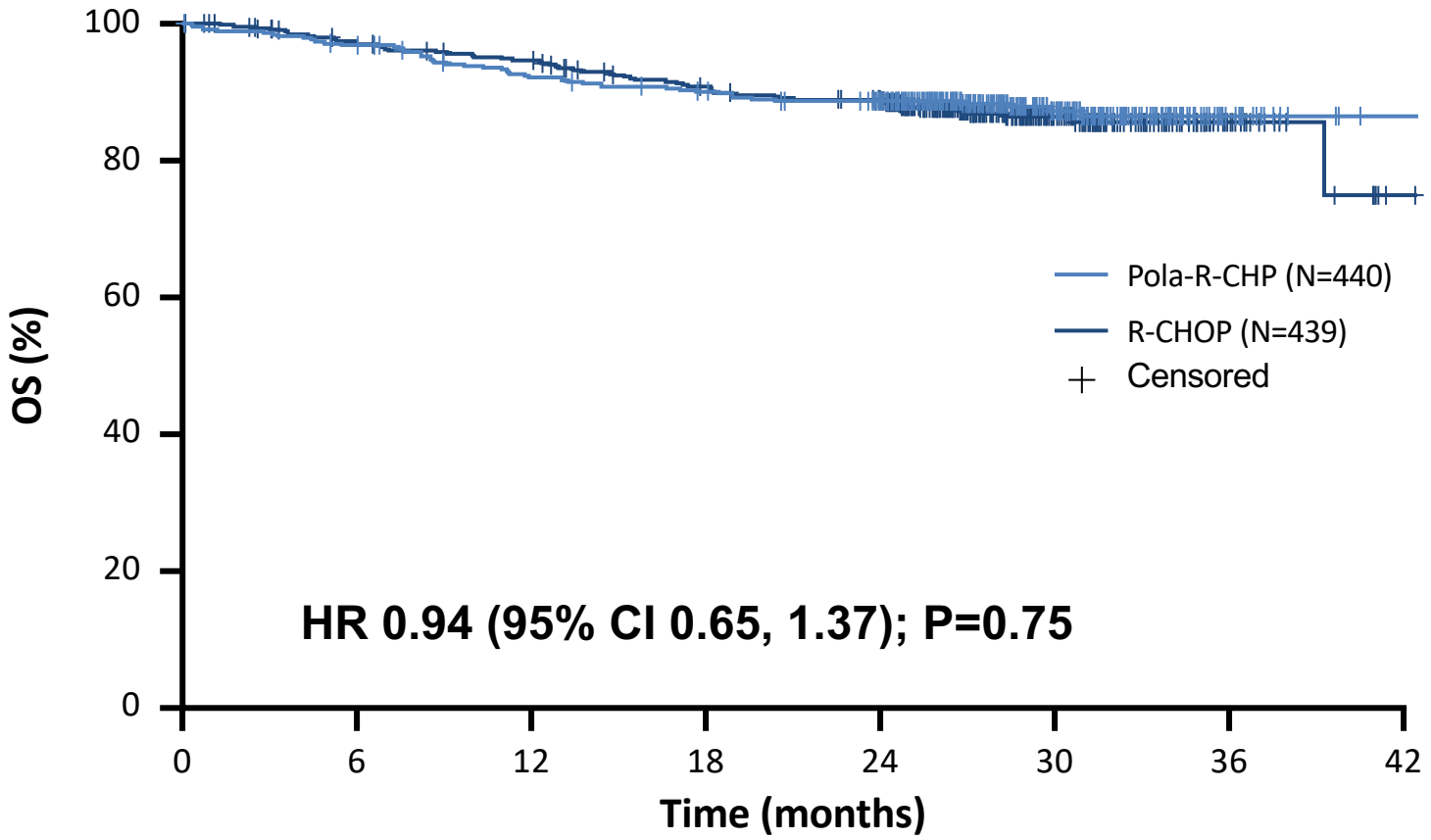
Tilly et al., *New Engl J Med* 386:351-63 2022

Overall survival: POLARIX trial



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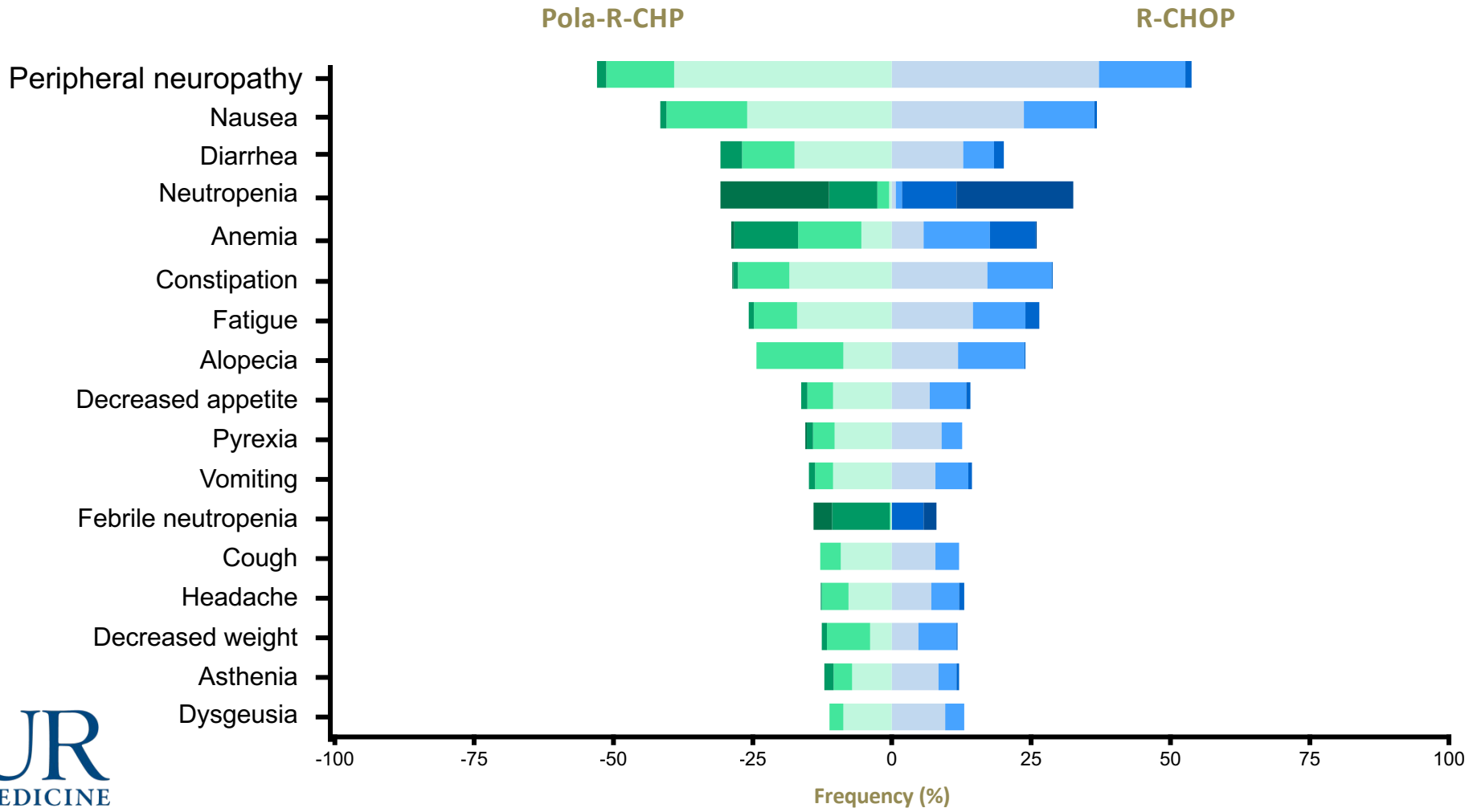
Tilly et al., *New Engl J Med* 386:351-63 2022

Common adverse events: POLARIX trial



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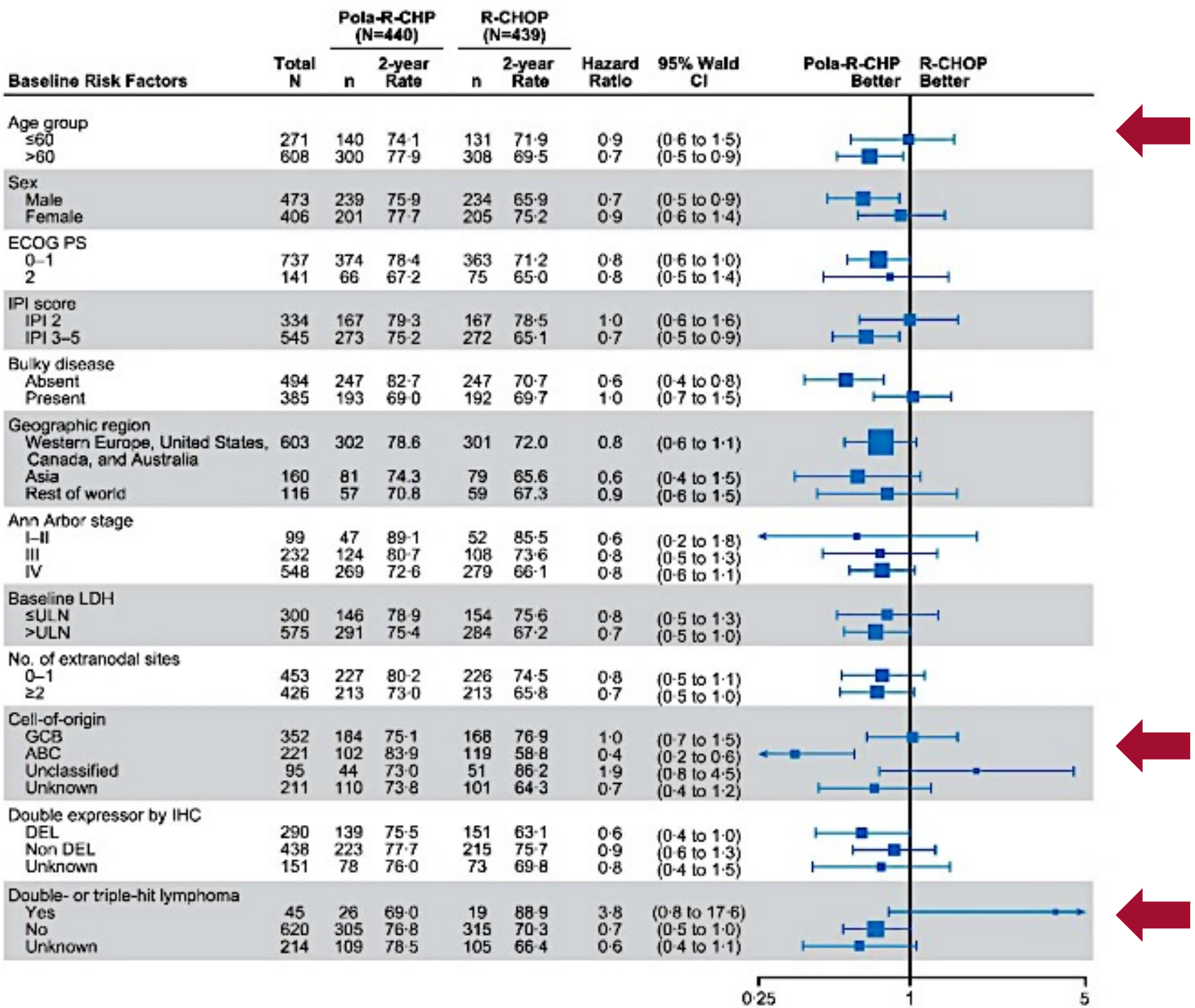
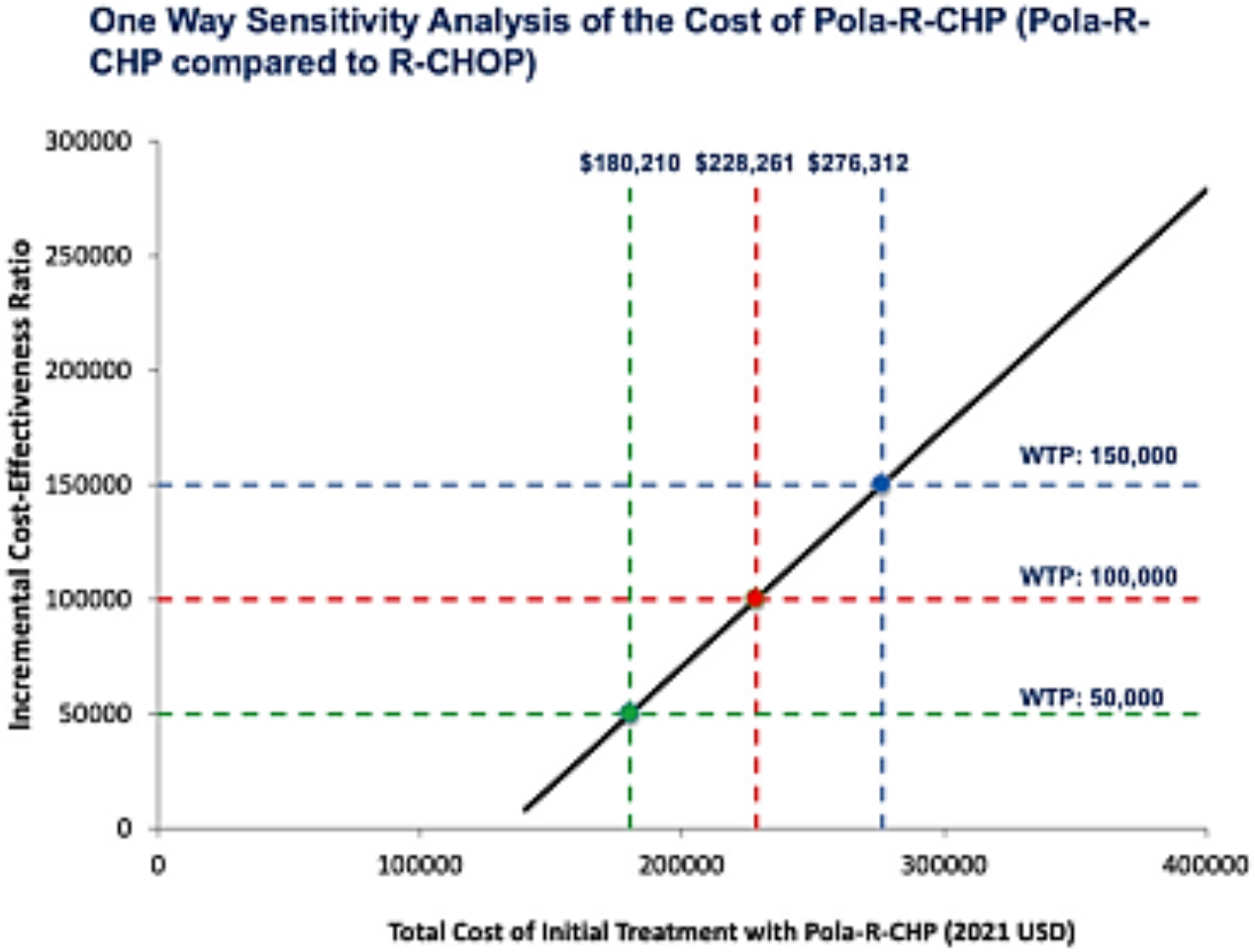
Tilly et al., *New Engl J Med* 386:351-63 2022



Tilly et al., *New Engl J Med* 386:351-63 2022

Cost effectiveness of R-Pola-CHP depends upon long-term outcomes

- Routine use of R-Pola-CHP will add significantly to health expenditures.
- Markov Model
  - Threshold 150K/QALY
  - If 5 year PFS > 66%, then cost-effective
- Identifications of subgroups that have maximal benefit would improve cost-effectiveness.



Kambhampati et al., *Blood* online June 14, 2022

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Should R-Pola-CHP replace RCHOP?

Strengths:

- Enhanced PFS with median follow-up of more than two years: likely cures.
- No toxicity differences; double-blind design
- Higher risk patients appeared to disproportionately benefit
- Borderline cost-effective when considering costs (financial and physical) of salvage therapy

Concerns:

- Relatively small (6%) PFS difference at two year benchmark
- Certain subsets (GCB, double hit) appear to not benefit
- Expensive
- Uncertain impact on outcome of salvage treatments
- No overall survival benefit (yet)

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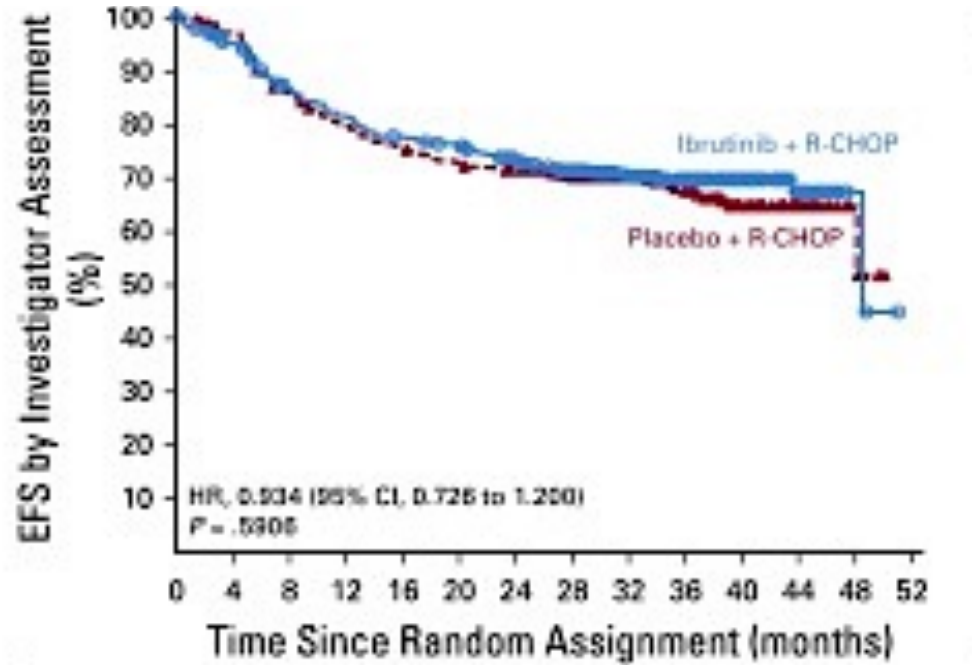
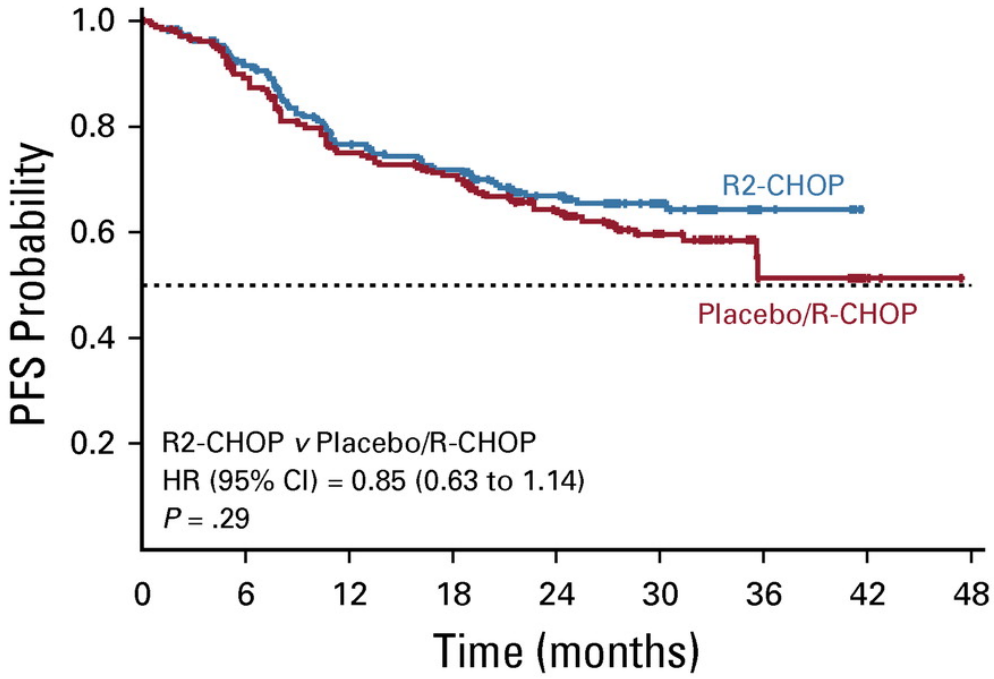
Rational agents targeting ABC DLBCL have single agent activity, but do not improve outcome when added to RCHOP

Ibrutinib



Lenalidomide



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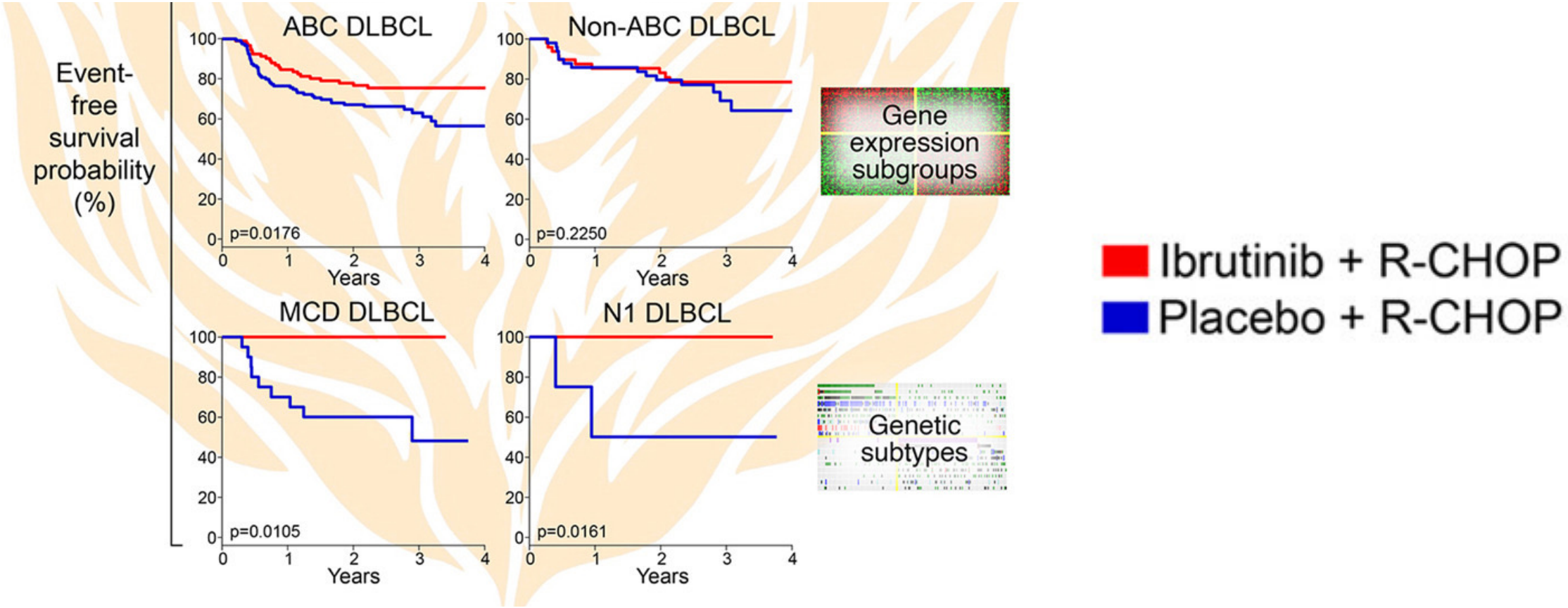
Younes et al., *J Clin Oncol* 37:1285-95 2019
Nowakowski et al., *J Clin Oncol* 39:1317-28 2021

Sequencing reveals further heterogeneity of DLBCL: Analysis of phase III PHOENIX trial

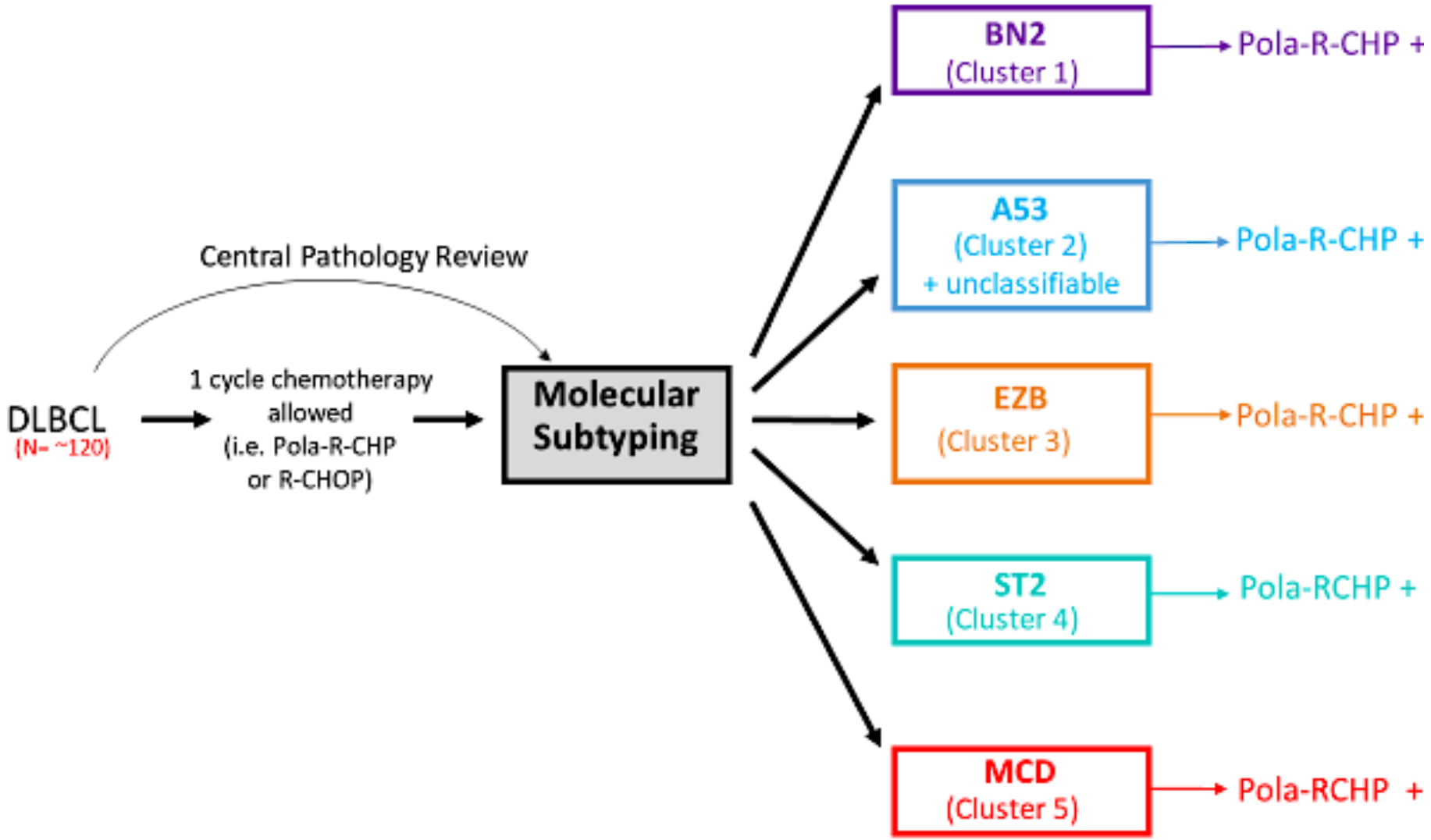


Wilson et al., *Cancer Cell* 12: 1643-53 2020

Ongoing trials

- Tafasitamab/Lenalidomide + RCHOP vs. RCHOP (high int and high risk)
- Acalabrutinib + RCHOP vs. RCHOP (nonGCB; < age 70)
- Epcoritamab + RCHOP vs. RCHOP (pending; IPI 2-5)
- Elderly studies:
  - Azacitidine + RminiCHOP vs. RminiCHOP (SWOG S1918; > age 75)
  - Mosunetuzumab +/- polatuzumab
  - Loncastuximab + rituximab

The future: ECOG trial concept



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Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL)

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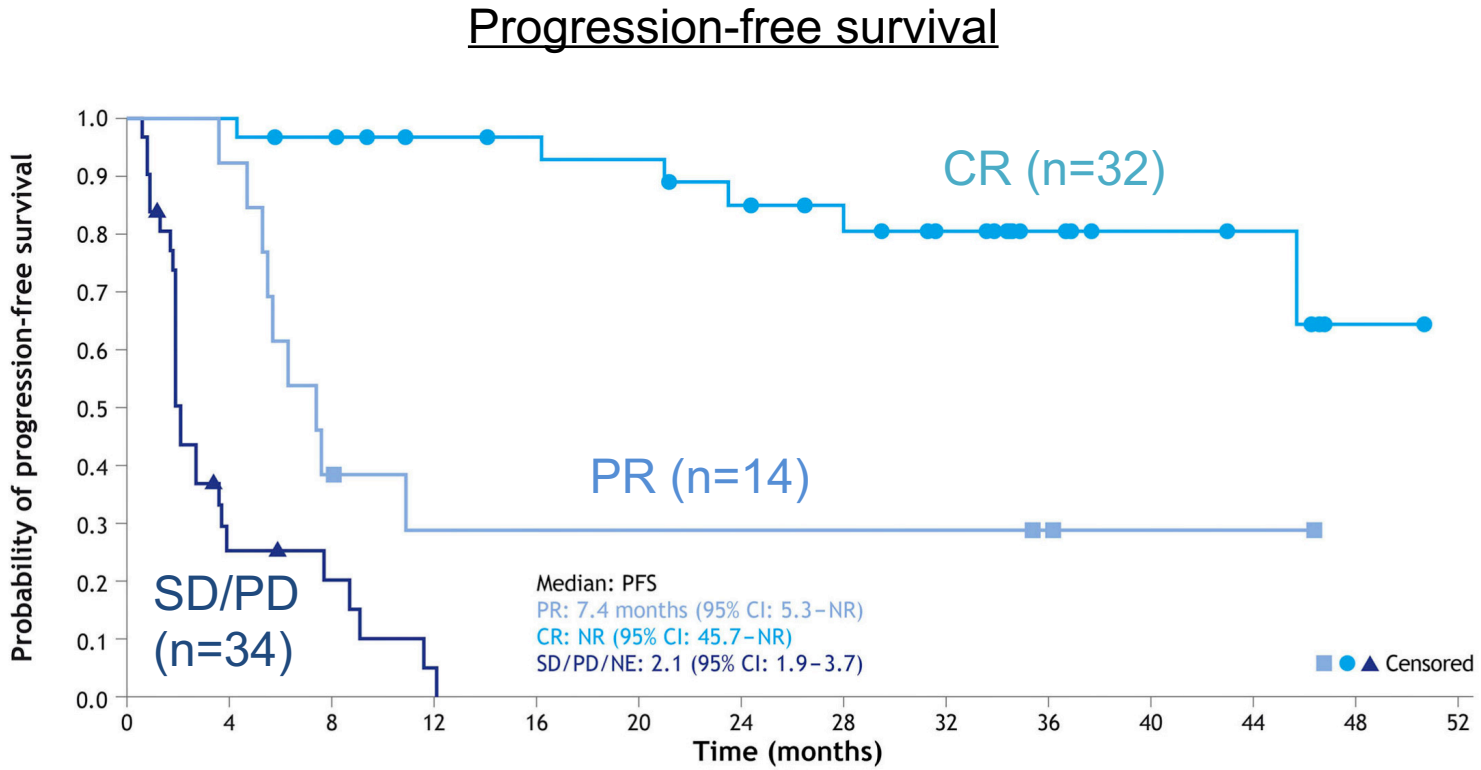
Tafasitamab (anti-CD19) + Lenalidomide pivotal trial

- 12 months combined therapy, then tafasitamab alone q 2 weeks
- ORR 57%; CR 40%
- Median OS 33 months
- Key adverse events
  - Neutropenia, infections
  - 42 deaths; 31 from PD

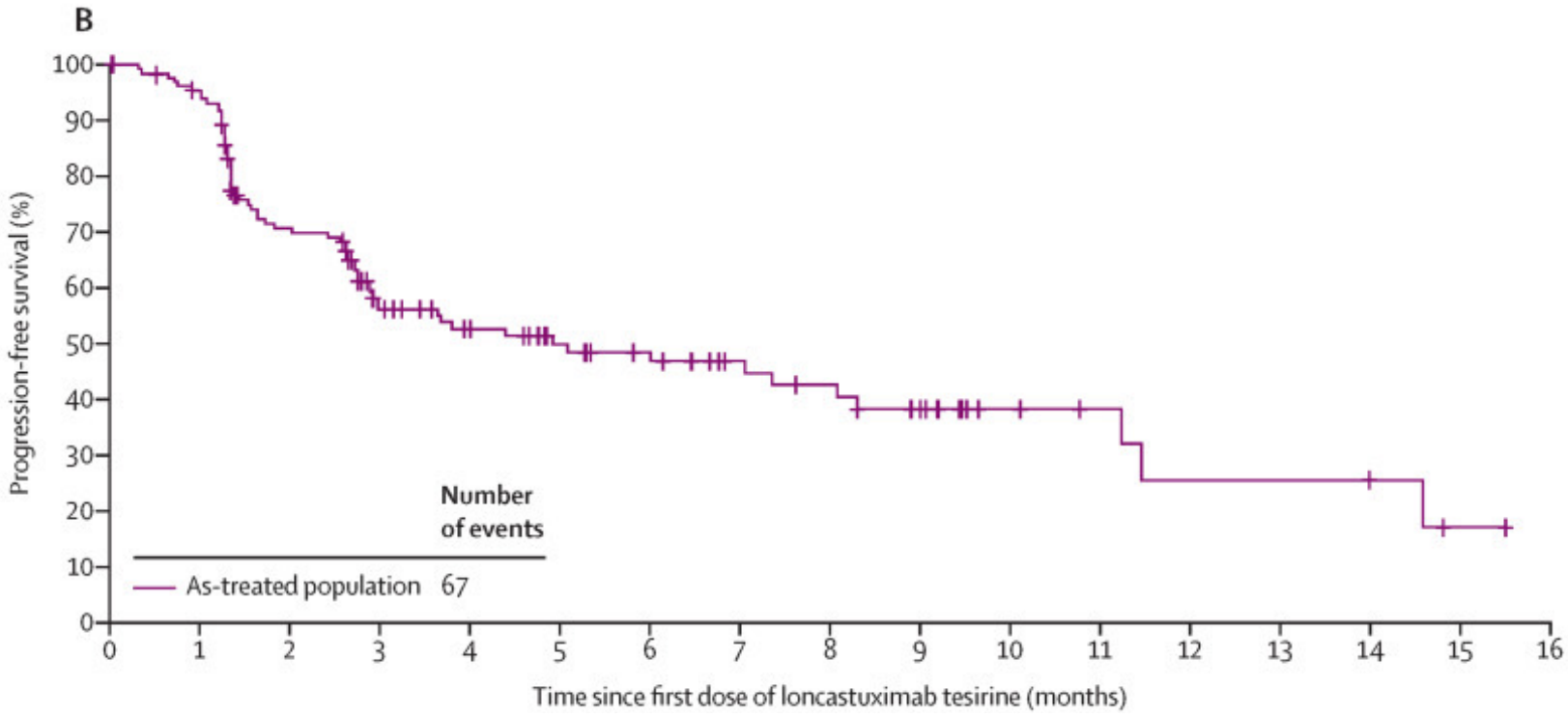


Duell et al., *Haematologica* 106, 2021

Loncastuximab (CD19 ADC) pivotal trial

- 12 months q 3 weeks
- ORR 46%; CR 19%
- Key adverse events
  - Neutropenia, infections
  - Increased GGT
  - Edema/effusions
  - Dose delays common

Progression-free survival (n=145)

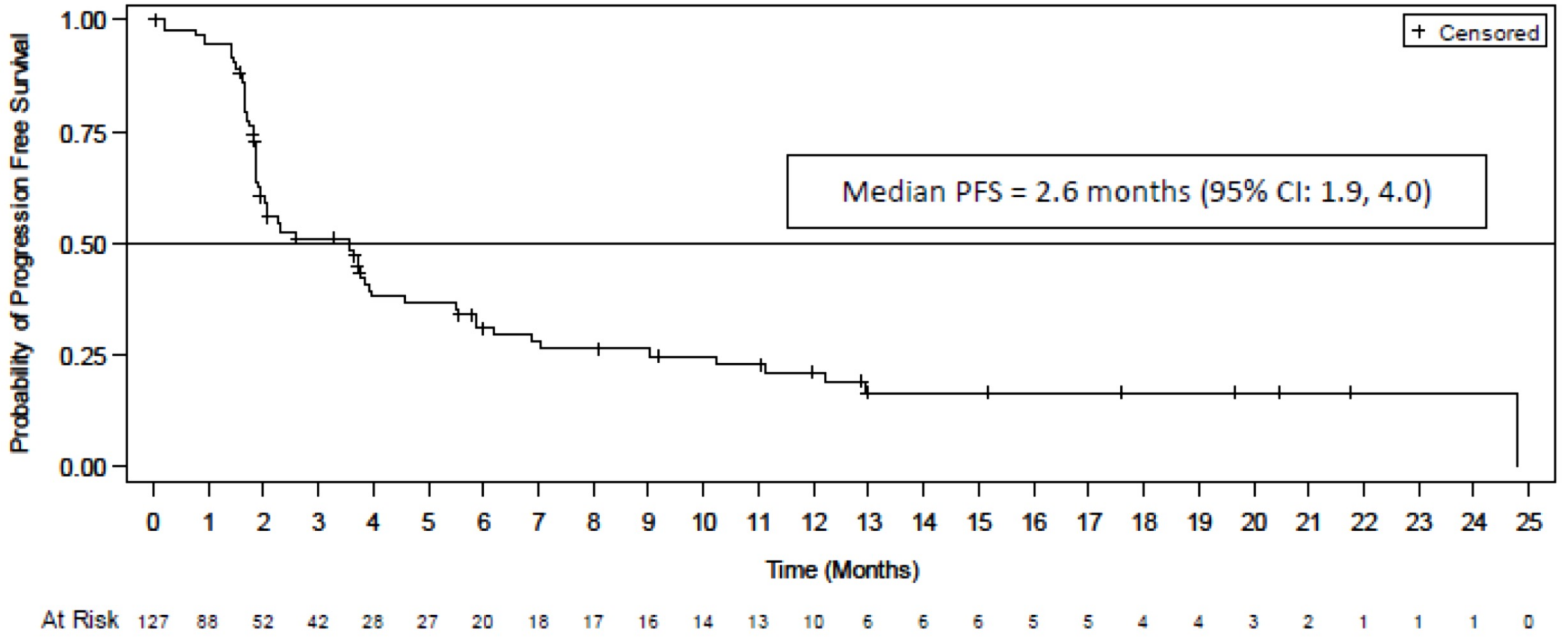


Caimi et al., *Lancet Oncol 22:*790-800, 2021

Selinexor (exportin-1) pivotal trial

- Oral therapy twice weekly
- ORR 28%; CR 12%
- Key adverse events
  - Neutropenia, thrombocytopenia
  - Fatigue
  - Nausea
  - Dose delays common

Progression-free survival (n=127)



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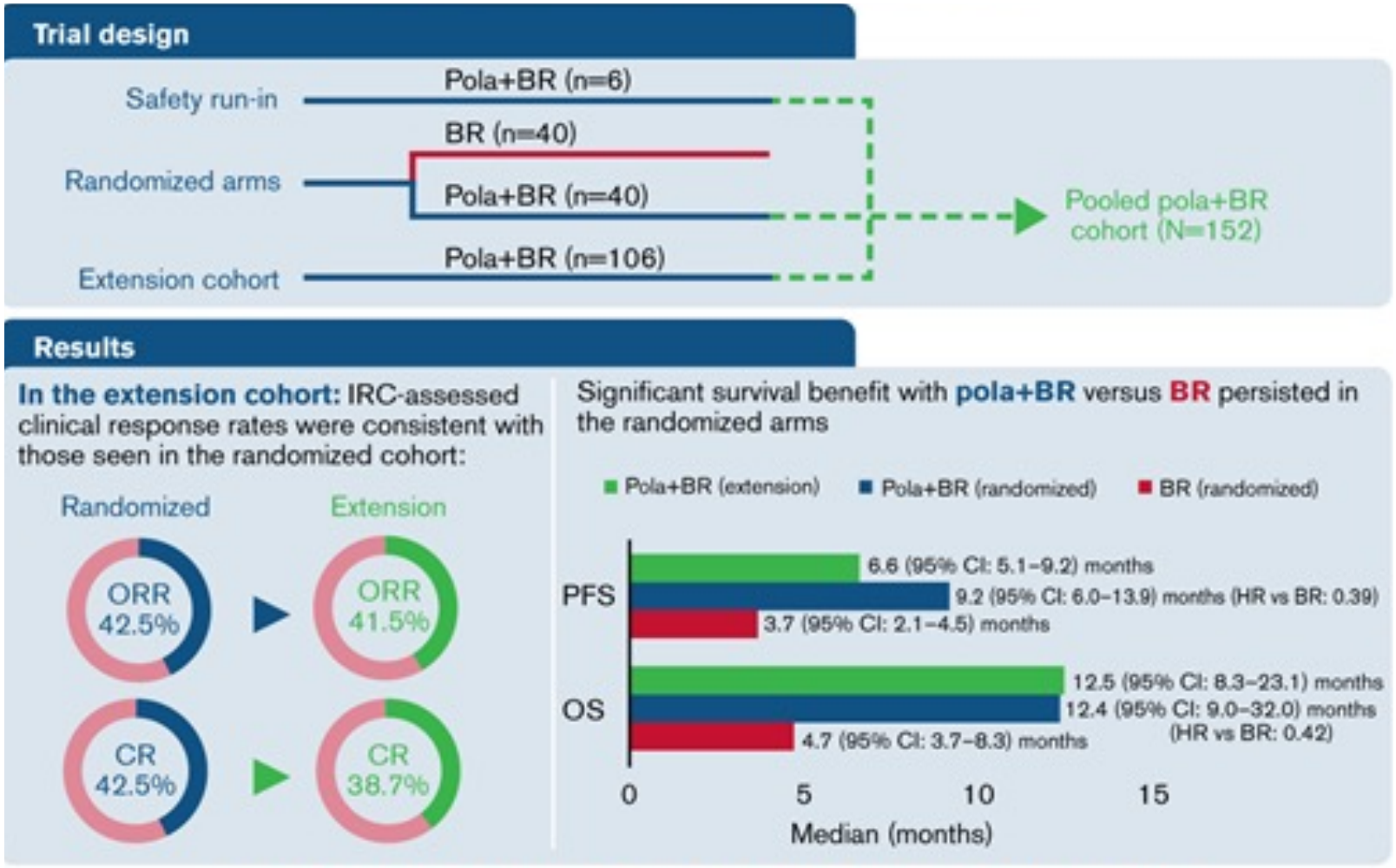
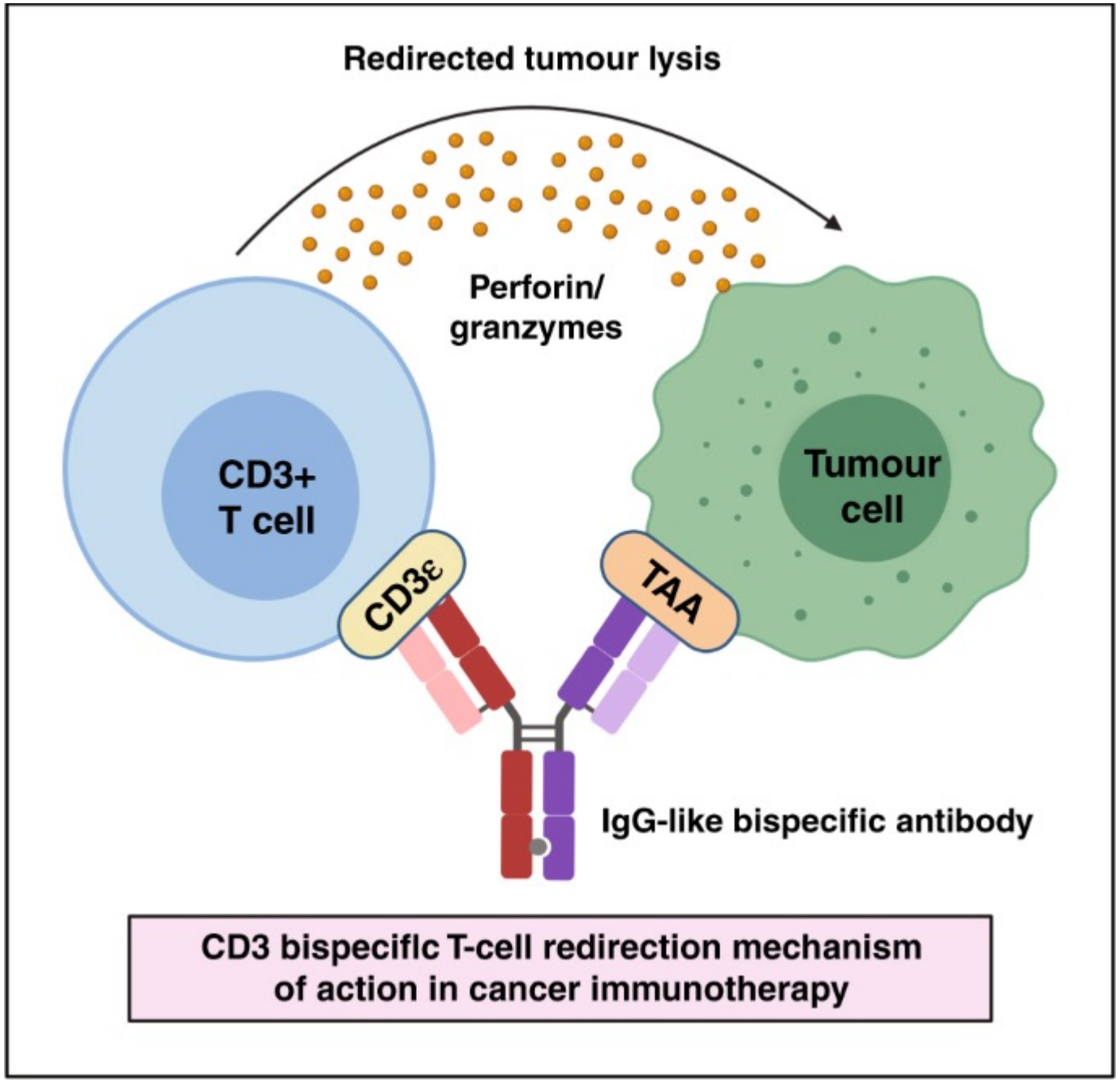
Kalakonda et al., *Lancet Haem 7:*511-22, 2020

Bendamustine/rituximab +/- polatuzumab (CD79b ADC)

- 6 cycles of therapy
- ORR and CRs
  - BR: 18%;
  - BR/pola: 42%
- Key adverse events
  - Neutropenia, anemia, thrombocytopenia
  - Increased GGT



Sehn et al., *Blood Adv 6:*533-43, 2022



CD3 bispecific T-cell redirection mechanism of action in cancer immunotherapy

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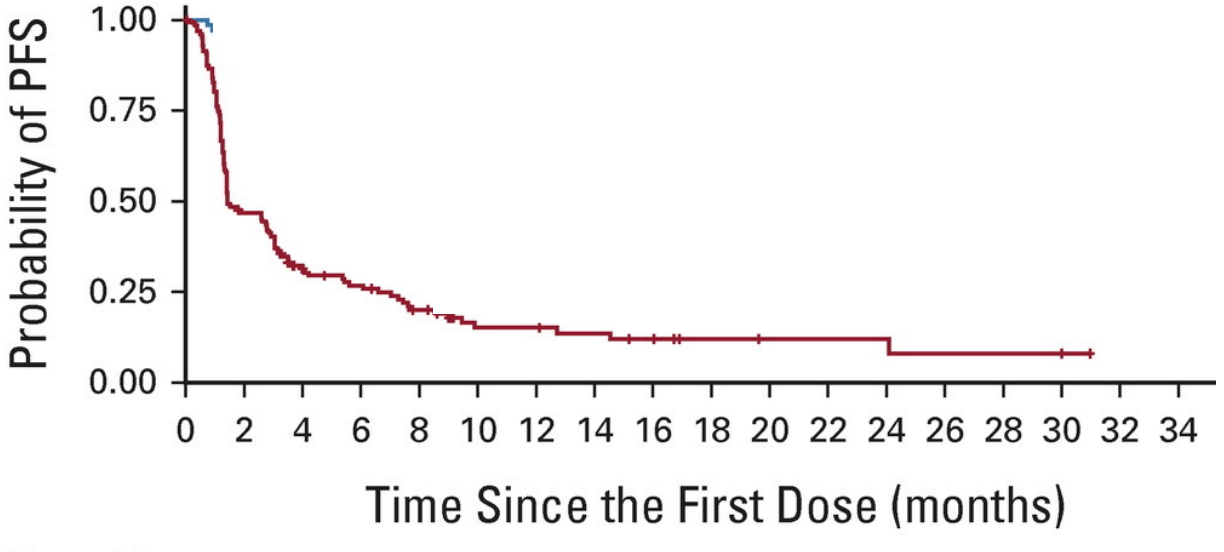
Mosunetuzumab experience

- 82 patients with DLBCL; additional patients with transformed and mantle cell lymphoma.
- ORR 35%; CR 19%
- Key adverse events
  - Neutropenia
  - CRS (low grade; cycle 1)
  - Diarrhea

Progression-free survival (n=129)

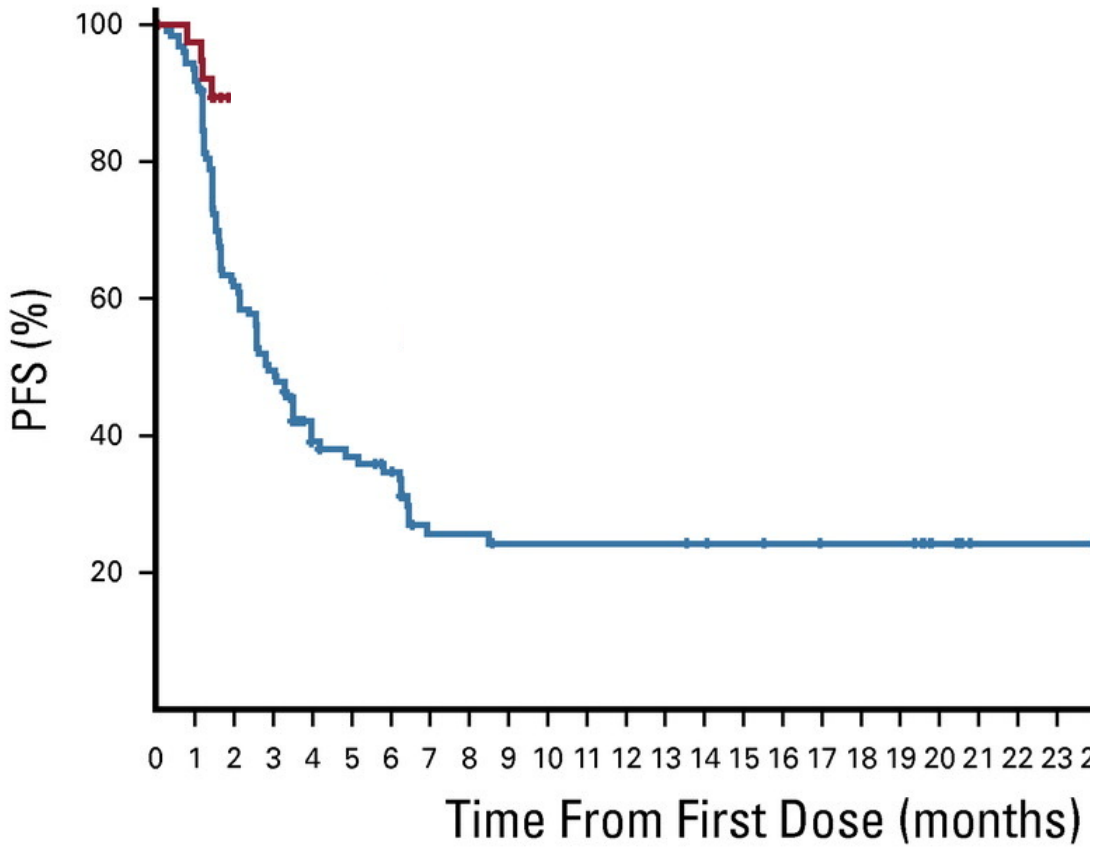


Budde et al., *J Clin Oncol* 40:481-91, 2022

Glofitamab experience

- 73 patients with DLBCL; additional patients with transformed and mantle cell lymphoma.
- ORR 48%; CR 39%
- Key adverse events
  - Neutropenia
  - CRS (low grade; cycle 1)
  - 2 cases of neurotoxicity

Progression-free survival (n=127)

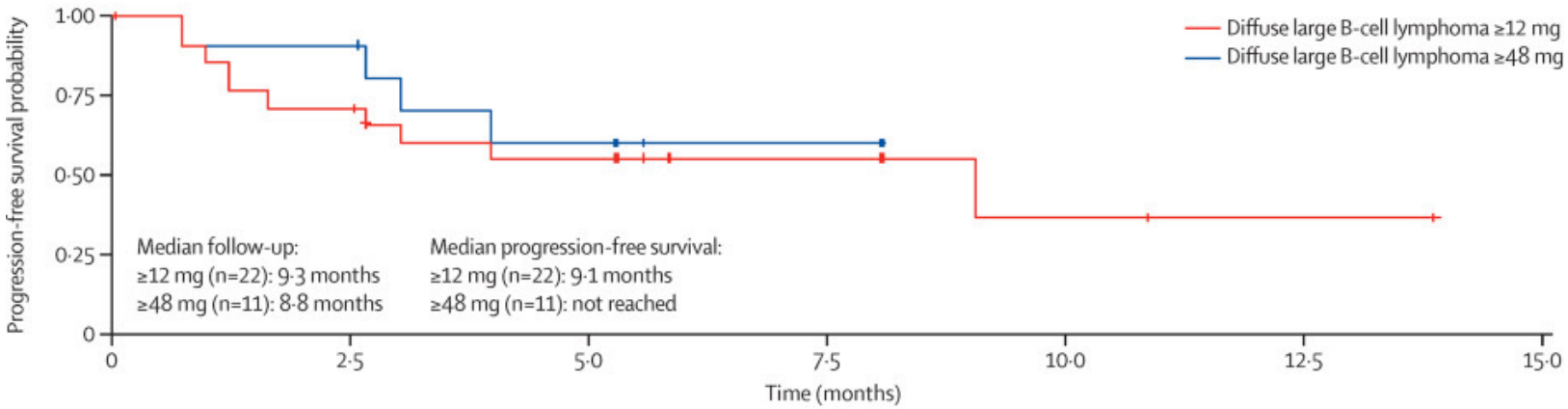


Hutchings et al., *J Clin Oncol* 39:1959-70, 2021

Epcoritamab experience

- Subcutaneous administration
- ORR 68%; CR 45%
- Key adverse events
  - Fever
  - CRS
  - Injection site reactions

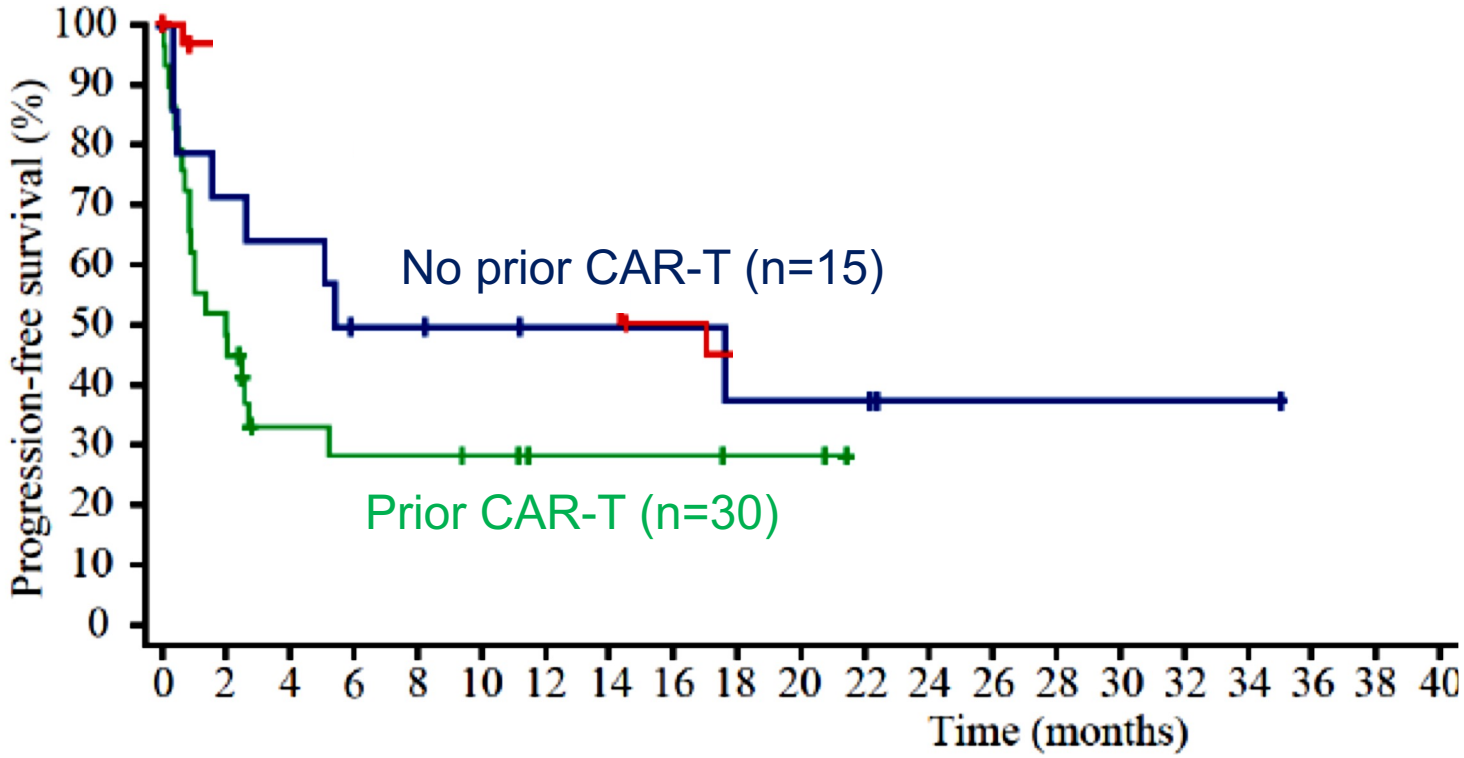
Progression-free survival (n=22)



Hutchings et al., *Lancet 398:*1157-69, a 2021

Odronextamab experience

- ORR: 53% no CAR-T; 33% post CAR-T
- Key adverse events
  - Anemia
  - Fever, CRS
  - Infections



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Bannerji et al., *Lancet Haem 9:*327-39, 2022

Some key ASH abstracts on bispecifics in DLBCL

- 737 Glofitamab + RCHOP
- 441 Glofitamab relapses rare after CR

- 443 Epcoritamab + RDAx/C as salvage therapy

- 444 Odronextamab in relapsed/refractory DLBCL

- 738 Mosunetuzumab monotherapy for elderly patients with DLBCL

Discussion Question

Outside of a clinical trial setting, what is your usual third line systemic therapy for an elderly patient with DLBCL after RCHOP followed by tafasitamab/lenalidomide who is not eligible for aggressive treatment?

- Loncastuximab tesirine
- Selinexor
- Polatuzumab vedotin/BR
- Other

RTP
RESEARCH
TO PRACTICE

Module 2: Follicular Lymphoma (FL) — Dr Nastoupil

RTP
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TO PRACTICE

Case Presentation: 69-year-old man with progressive Grade I/II follicular lymphoma after observation for many years

Dr Neil Morganstein (Summit, New Jersey)

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Case Presentation: 60-year-old woman with Grade II follicular lymphoma, s/p BR and maintenance rituximab

Dr Jennifer Dallas (Charlotte, North Carolina)

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Follicular Lymphoma

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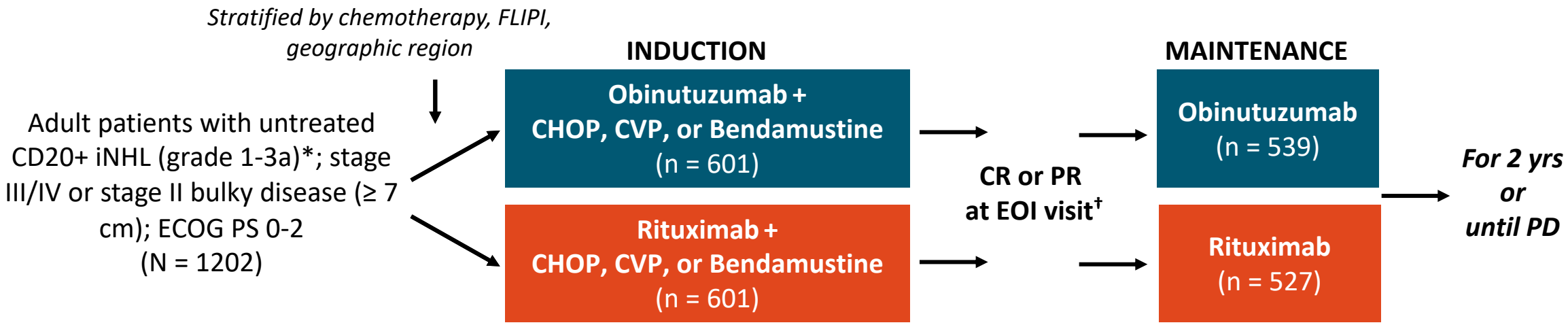
GALLIUM: Frontline Obinutuzumab-Based vs Rituximab-Based Chemoimmunotherapy

- International randomized, open-label phase III study
  - Obinutuzumab was designed to achieve enhanced therapeutic activity compared with rituximab

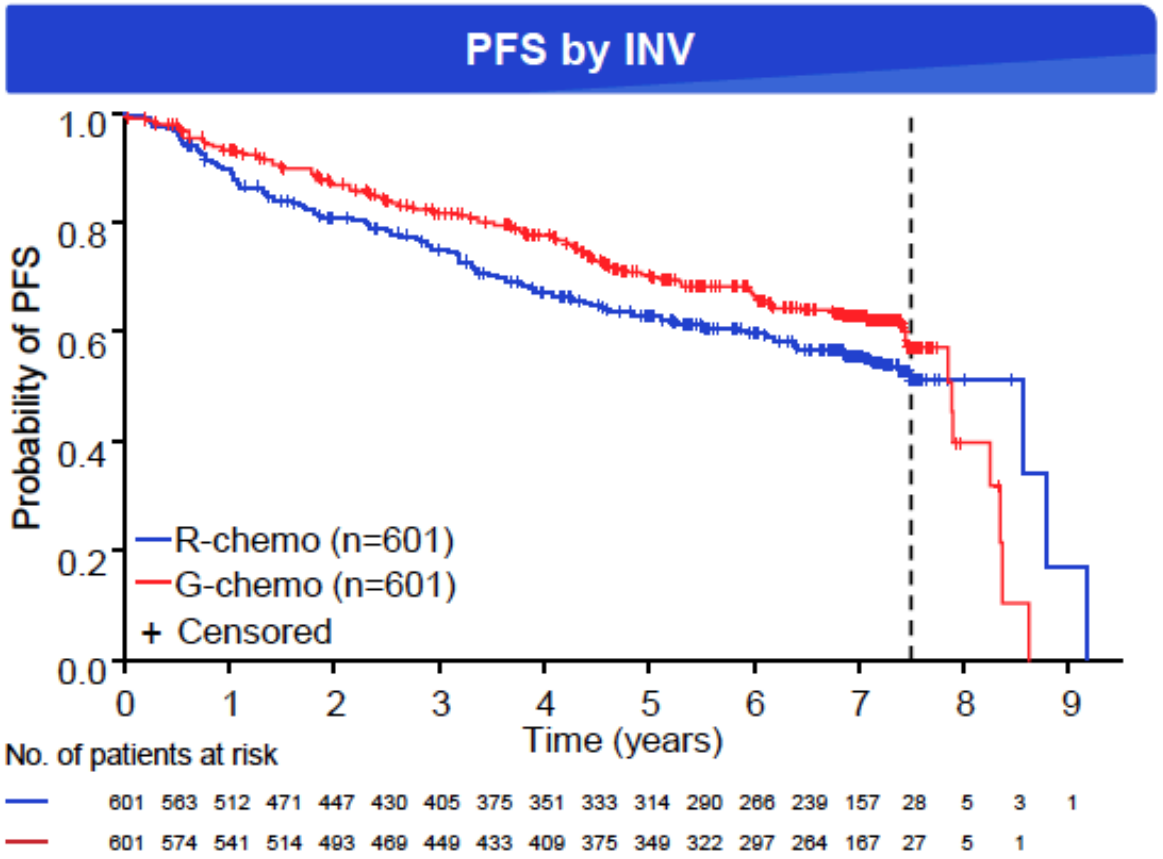


*All data presented for patients with FL, although study also enrolled patients with MZL (randomized separately).
†Patients with SD at EOI followed up to 2 yrs for PD.

- Primary endpoint: PFS by investigator in patients with FL
- Secondary endpoints: PFS by IRC, OS, DFS, DoR, TTNT, CR/ORR at EOI (± FDG-PET), safety

Marcus et al *NEJM* 2017

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



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

Median observation time: 7.9 (0.0–9.8) years

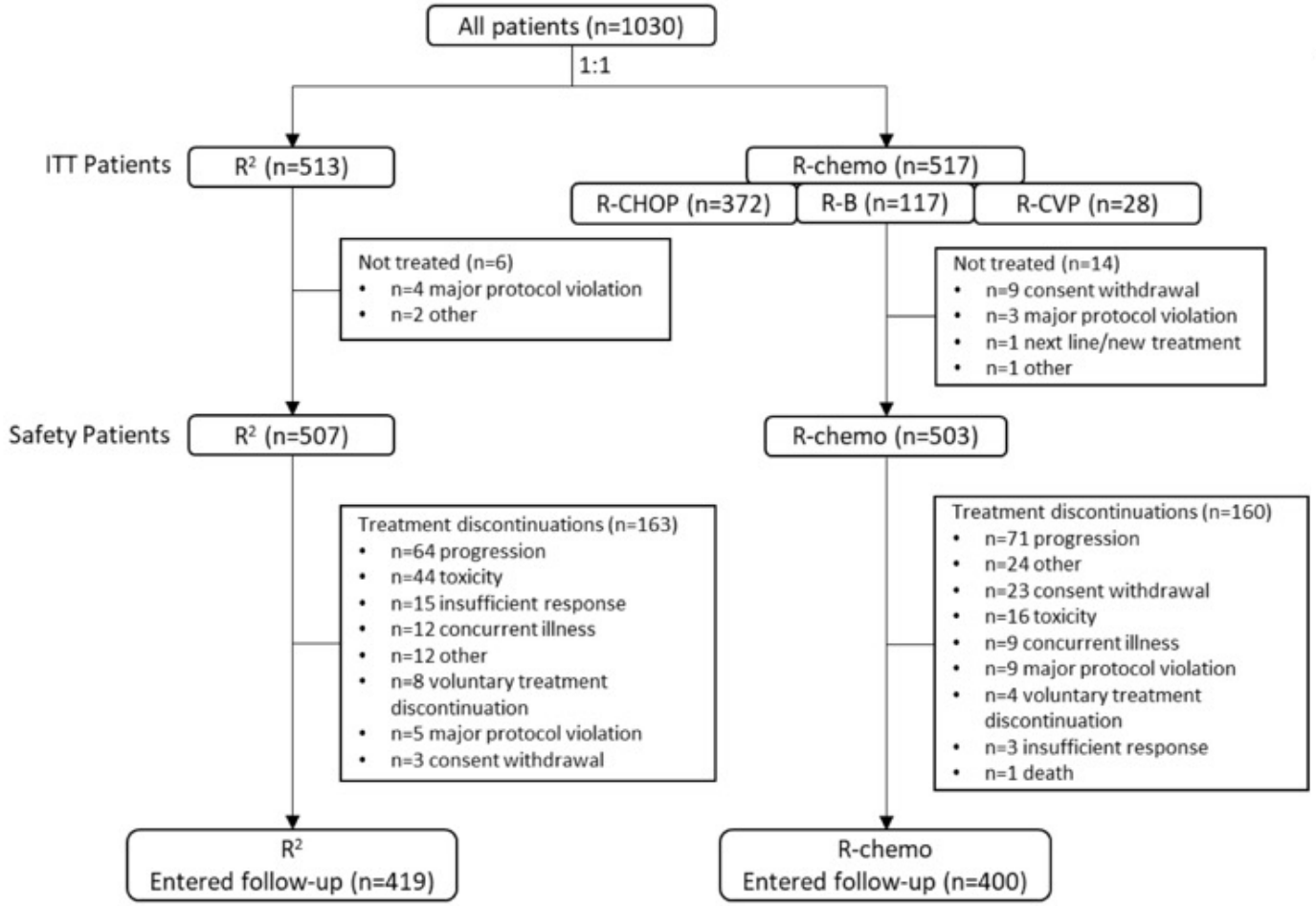
INV-assessed PFS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	206 (34.3)	244 (40.6)
7-year PFS, % (95% CI)	63.4 (59.0–67.4)	55.7 (51.3–59.9)
HR (95% CI)*	0.77 (0.64–0.93)	
P-value	0.006	

R = rituximab; G = obinutuzumab

Townsend W et al. EHA 2022;Abstract S206.

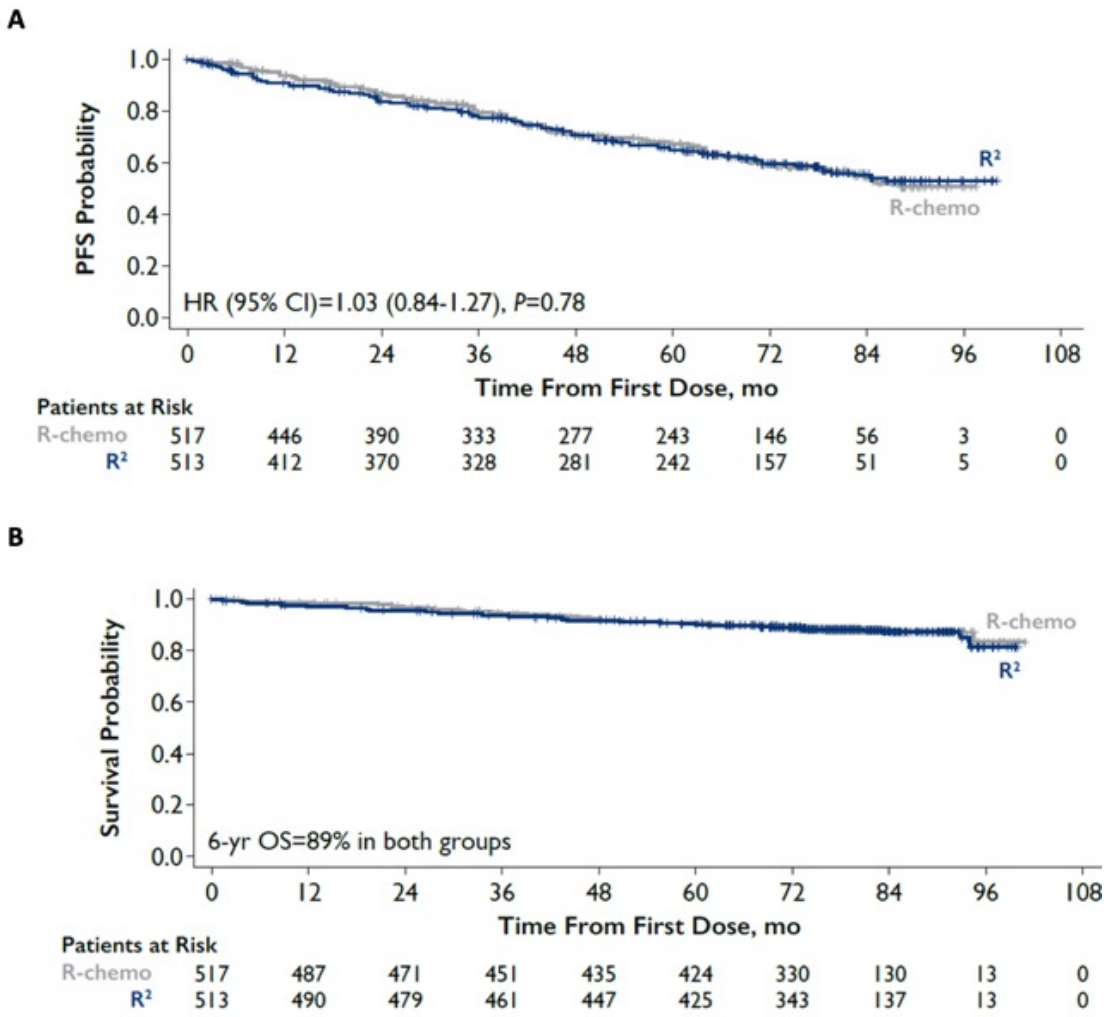
RELEVANCE: R2 vs. R-chemo in frontline FL, 6 year follow-up

Figure 1. Consort Diagram



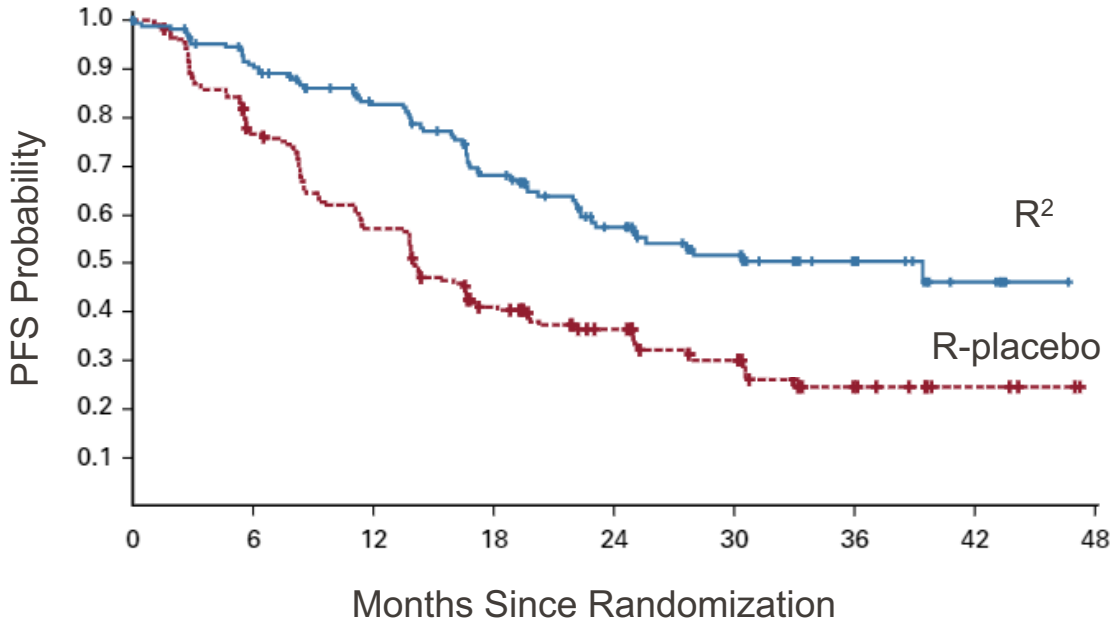
Morschhauser et al. *JCO* 2022

Figure 2. Progression-free Survival by IRC (A) and Overall Survival (B) in the Intention-to-Treat Population



AUGMENT: Rituximab + Lenalidomide vs. Rituximab+ placebo
Efficacy

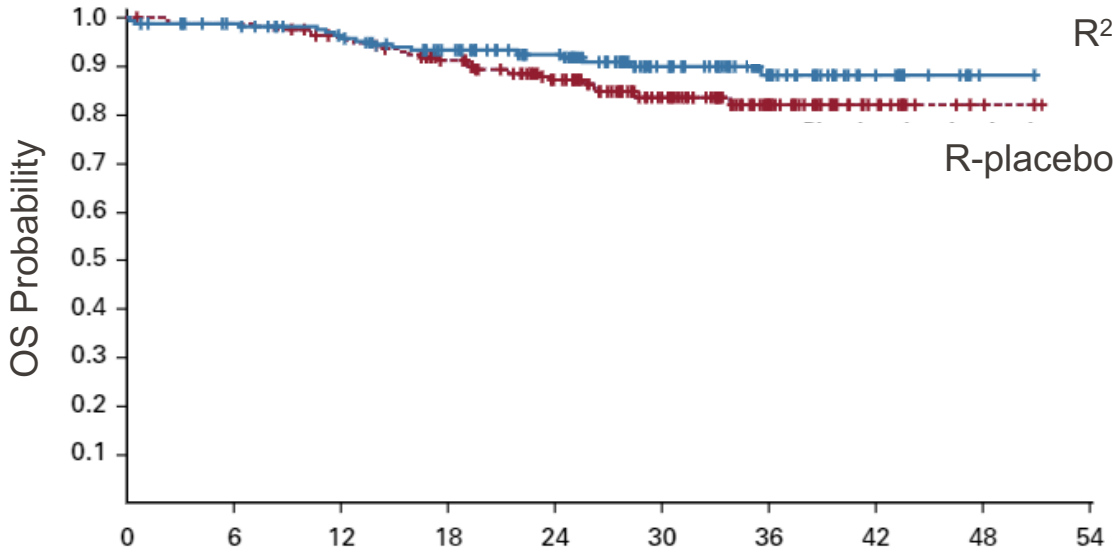
Progression-Free Survival



Median PFS by IRC
- R^2 = 39.4 months
- R-placebo = 14.1 months

HR = 0.46

Overall Survival

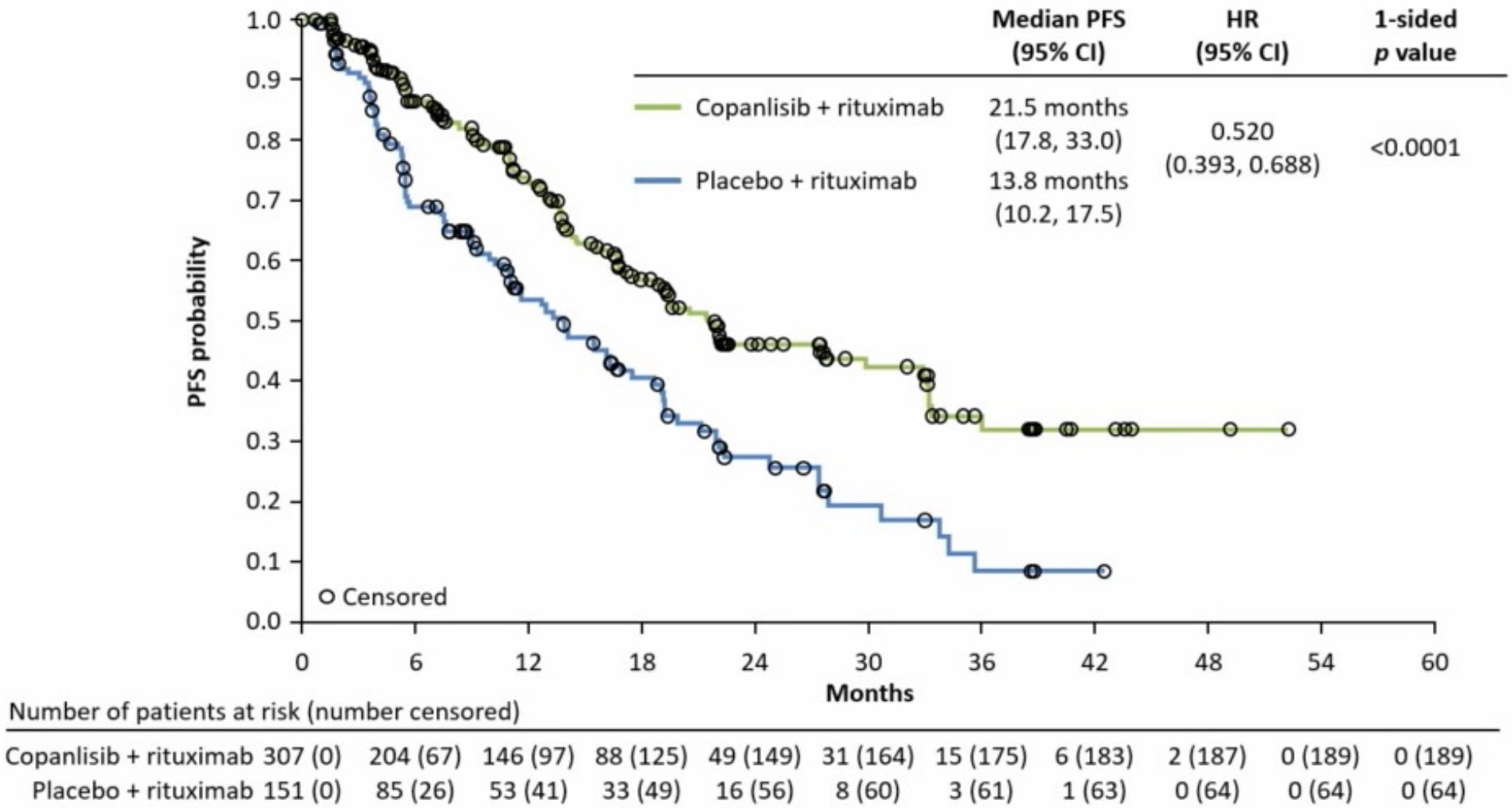


2-year OS
- R2 = 93%
- R-placebo = 87%

Median follow-up 28.3 months

- Leonard JP, et al. *J Clin Oncol*. 2019;37:1188-1199.

CHRONOS-3 in R/R iNHL: PFS



- Median follow-up of 19.2 months

Number of patients at risk (number censored)

Copanlisib + rituximab	307 (0)	204 (67)	146 (97)	88 (125)	49 (149)	31 (164)	15 (175)	6 (183)	2 (187)	0 (189)	0 (189)
Placebo + rituximab	151 (0)	85 (26)	53 (41)	33 (49)	16 (56)	8 (60)	3 (61)	1 (63)	0 (64)	0 (64)	0 (64)

- Zinzani PL. et al. EHA 2021, abstract S211.

PI3K Inhibitors: Emerging Agents

Zandelisib: Phase III COASTAL Study for FL and MZL

ELIGIBILITY CRITERIA

Major Inclusion Criteria

- Adult male or female subjects
- Histologically confirmed diagnosis of CD20-positive iNHL with histological subtype limited to:
  - FL Grades 1, 2, or 3a
  - MZL (splenic, nodal, or extra-nodal)
- R/R FL or MZL who received ≥ 1 prior line of therapy, which must have included an anti-CD20 antibody in combination with chemotherapy or lenalidomide
- At least one bi-dimensionally measurable lesion > 1.5 cm
- Adequate hematological, renal, and hepatic function
- Eastern Cooperative Oncology Group performance status score 0-1

Major Exclusion Criteria

- Histologically confirmed diagnosis of FL Grade 3b or transformed disease
- Subjects who received both R + bendamustine and R + CHOP (or other anthracycline-containing regimen) as previous lines of therapy, and those who received only single-agent anti-CD20 mAb therapy as a prior line of treatment
- Prior therapy with PI3K inhibitors
- Ongoing or history of drug-induced pneumonitis
- Known lymphomatous involvement of the central nervous system
- Seropositive for or active viral infection with HBV, HCV, or HTLV-1

N = 534 participants

CD20 positive iNHL:
- FL Gr 1, Gr 2, or Gr 3a
- MZL (splenic, nodal, or extra-nodal)

≥1 prior lines of therapy*

R 375 mg/m^2 4 x weekly in cycle 1, then Day 1 of Cycles 3-6

Zandelisib IDT of 60 mg/day on Days 1-7 of each 28-day cycle

Rituximab + B (28 D cycles) x 6 or
Rituximab + CHOP (21 D cycles) x 6

Primary endpoints
PFS
Secondary endpoints
ORR, CRR, OS, TTNT, PFS2, PRO, Safety

Jurczak, et al. *Blood*. 2021; 138 (Supplement 1): 2430.

BGB-3111-212 – ROSEWOOD STUDY

ROSEWOOD
Phase 2 Relapsed/Refractory FL

A Phase 2, Multicenter, Open-Label, Randomized Trial for Patients with Relapsed or Refractory Follicular Lymphoma

Eligibility

- Adult patients with histologically confirmed grade 1-3a FL
- Patients with R/R disease, previously treated with ≥ 2 prior systemic treatments including an anti-CD20 antibody and an appropriate alkylator-based combination therapy
- Measurable disease
- ECOG-PS 0-2
- Adequate organ functions
- No prior BTK inhibitor exposure

Stratification factors
- Number of prior lines
- Rituximab refractory status
- Geographic region

ARM A
Zanubrutinib plus obinutuzumab
N = 140
Until PD/unacceptable toxicity

ARM B
Obinutuzumab
N = 70
Option to crossover to arm A if PD/SD centrally confirmed at 12 months

Assuming ORR_A = 0.55 and ORR_B = 0.30, 210 patients will be enrolled in a 2:1 ratio to provide a power of approximately 91% in testing ORR_A versus ORR_B using a normal approximation to binomial distribution with a 2-sided significance level of 0.05 with continuity correction

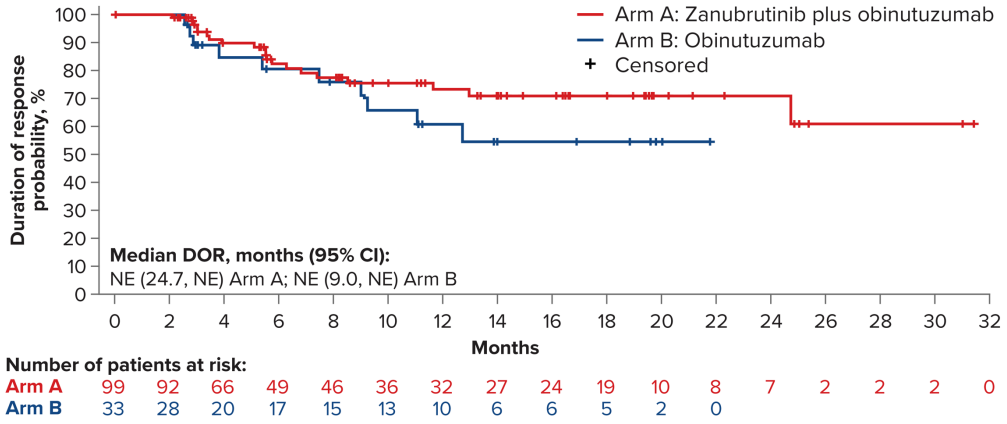
Primary Endpoint:
ORR assessed by ICR according to Lugano classification

Secondary Endpoints:
- ORR assessed by investigator
- DOR and PFS determined by ICR review and investigator assessment
- Overall survival
- CR and CMR rate assessed by ICR and investigator assessment
- TTR assessed by ICR and investigator assessment
- Patient-reported outcome measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires
- Safety/Tolerability
- Pharmacokinetics parameters (combination arm only)

Exploratory Endpoint:
- ORR after crossover to arm A

EFFICACY ENDPOINTS: ROSEWOOD STUDY
(ITT ANALYSIS SET)

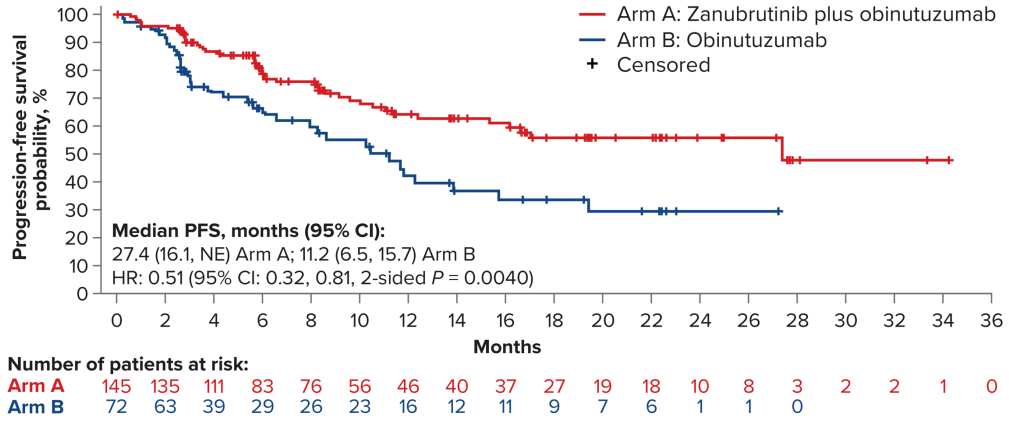
Duration of Response (IRC)



Number of patients at risk:

Arm A	99	92	66	49	46	36	32	27	24	19	10	8	7	2	2	2	0
Arm B	33	28	20	17	15	13	10	6	6	5	2	0					

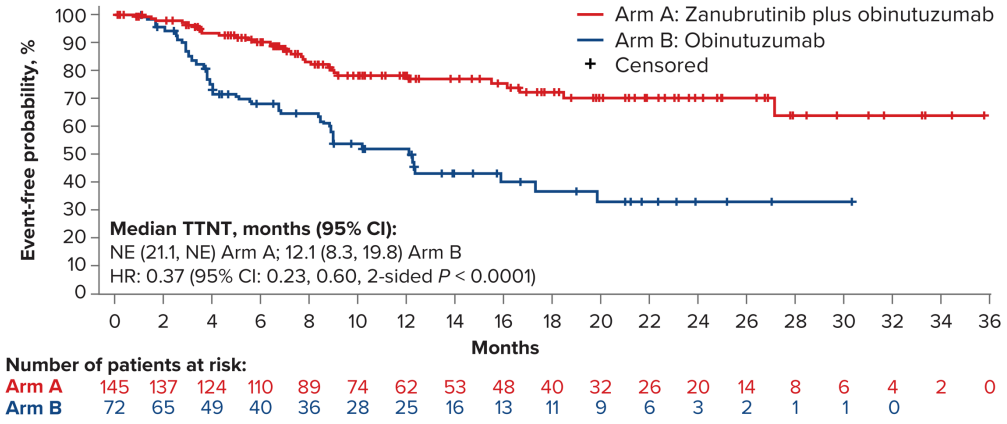
Progression-free survival (IRC)



Number of patients at risk:

Arm A	145	135	111	83	76	56	46	40	37	27	19	18	10	8	3	2	2	1	0
Arm B	72	63	39	29	26	23	16	12	11	9	7	6	1	1	0				

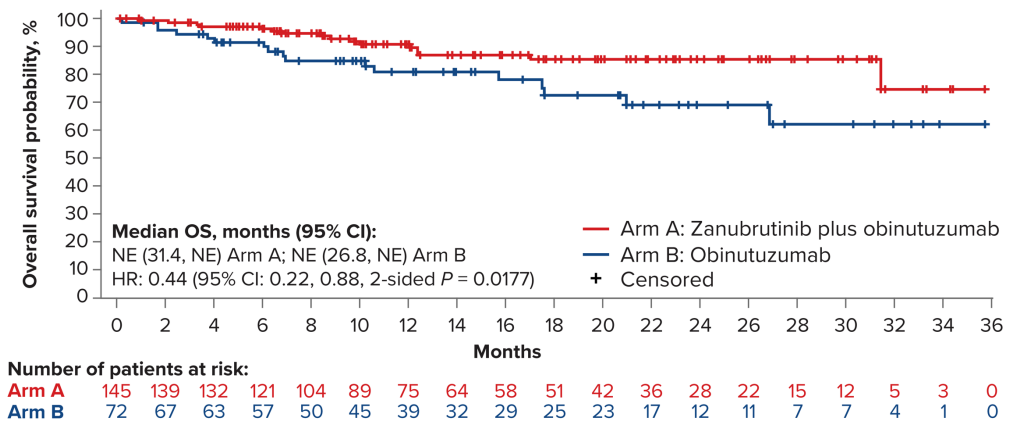
Time to Next Antilymphoma Treatment



Number of patients at risk:

Arm A	145	137	124	110	89	74	62	53	48	40	32	26	20	14	8	6	4	2	0
Arm B	72	65	49	40	36	28	25	16	13	11	9	6	3	2	1	1	0		

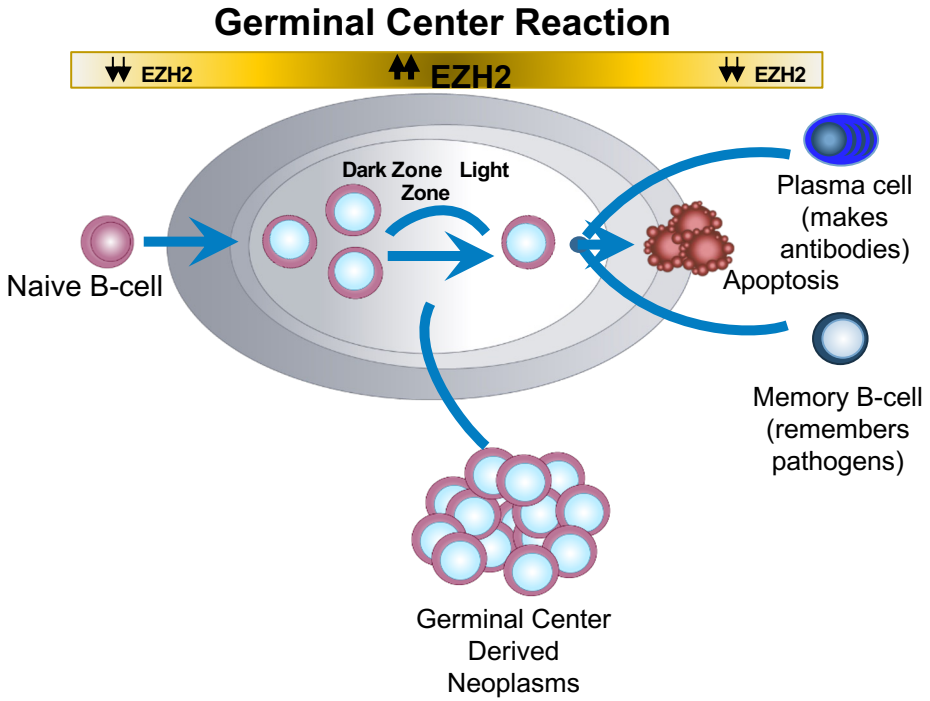
Overall survival

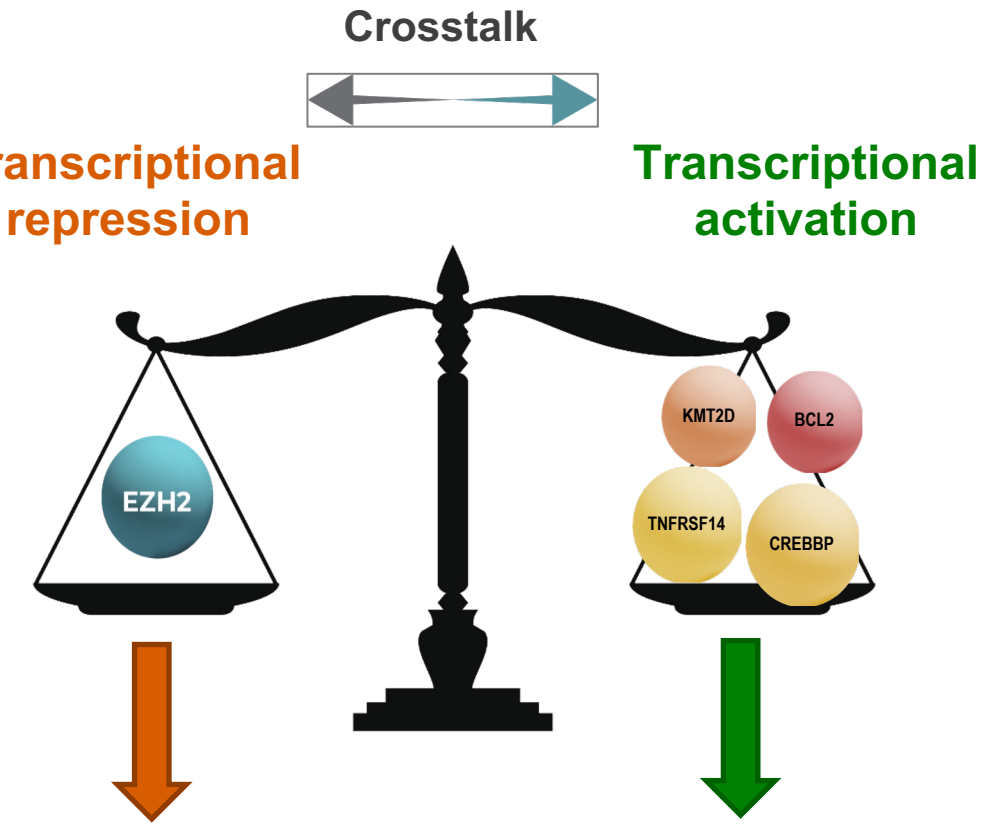


Number of patients at risk:

Arm A	145	139	132	121	104	89	75	64	58	51	42	36	28	22	15	12	5	3	0
Arm B	72	67	63	57	50	45	39	32	29	25	23	17	12	11	7	7	4	1	0

Tazemetostat: Follicular Lymphoma and *EZH2*





EZH2 an epigenetic regulator of gene expression and cell fate decisions[1]

EZH2 is required for normal B-cell biology and germinal center formation[2]

- Oncogenic mutations in *EZH2* suppress exit from germinal state and "lock" B cells in this state thereby transforming into a cancer[2]

1. Gan L, et al. *Biomark Res*. 2018;6(1):10; 2. Béguelin W, et al. *Cancer Cell*. 2013;23(5)677-692.

Tazemetostat for R/R FL

Phase 2, Open-Label, Multicenter Study

Response in the MT *EZH2* Cohort

Response in MT EZH2 (n=45)	IRC	INV
ORR, n (%) [95% CI[a]]	31 (69) [53, 82]	35 (78) [63, 89]
CR, n (%)	6 (13)	4 (9)
PR, n (%)	25 (56)	31 (69)
SD, n (%)	13 (29)	10 (22)
PD, n (%)	1 (2)	0

- 44 of 45[b] (98%) patients with evidence of tumor reduction, by IRC
- mPFS, 13.8 mos (95% CI, 10.7-22.0)

Response in the WT *EZH2* Cohort

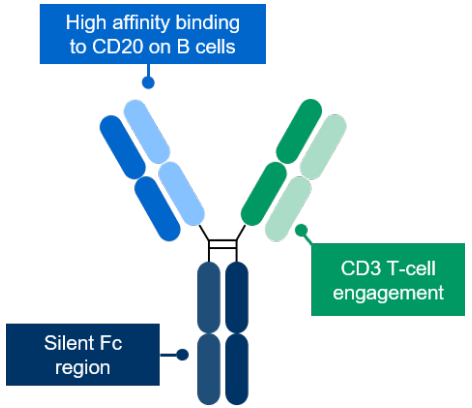
Response in WT EZH2 (n=54)	IRC	INV
ORR, n (%) [95% CI[a]]	19 (35) [23, 49]	18 (33) [21, 48]
CR, n (%)	2 (4)	3 (6)
PR, n (%)	17 (31)	15 (28)
SD, n (%)	18 (33)	16 (30)
PD, n (%)	12 (22)	16 (30)
NE/missing/unknown,[b] n (%)	5 (9)	4 (7)

- 37 of 49[c] (69%) patients with evidence of tumor reduction, by IRC
- mPFS, 11.1 mos (95%CI, 3.7-`14.6)

[a]By Brookmeyer and Crowley method. [b]4 subjects with missing post-baseline values and 1 subject with poor image. [c]Best overall response based on Cheson (2007) criteria for lymphomas.

Morschhauser F, et al. *Lancet Oncol.* 2020;21(11):1433-1442

Mosunetuzumab: CD20xCD3 Bispecific



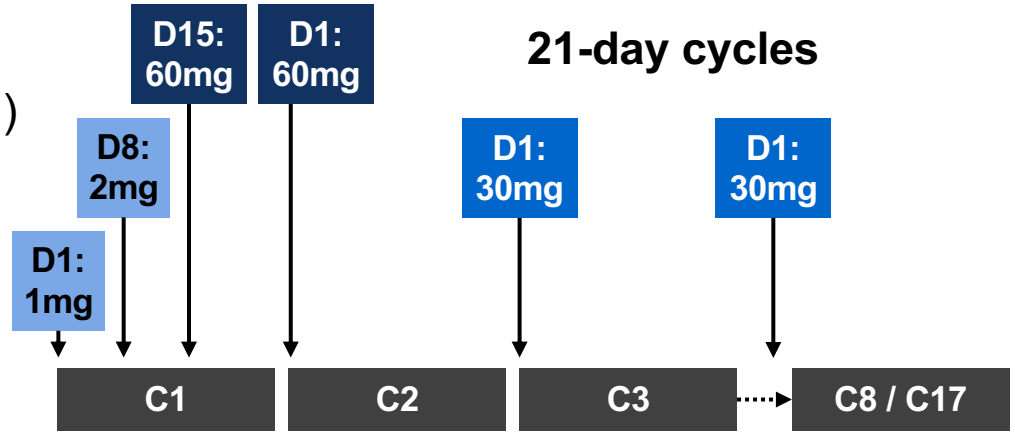
- Single-arm, pivotal Phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

- FL (Grade 1–3a)
- ECOG PS 0–1
- ≥2 prior regimens, including
  - ≥1 anti-CD20 Ab
  - ≥1 alkylating agent

Mosunetuzumab administration

- Q3W intravenous administration
- C1 step-up dosing (CRS mitigation)
- **Fixed-duration treatment**
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**



Endpoints

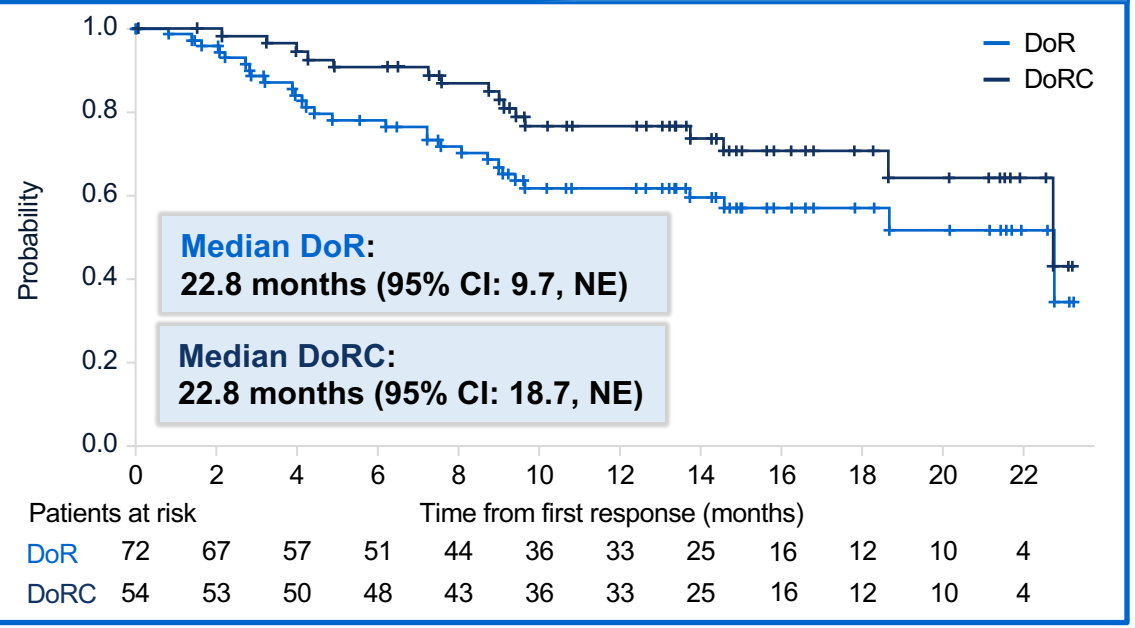
- Primary: CR (best response) rate by IRF* – assessed vs 14% historical control CR rate[1]
- Secondary: ORR, DoR, PFS, safety and tolerability

*assessed by CT and PET-CT using Cheson 2007 criteria[2]; Ab, antibody; CR, complete response; CT, computed tomography; D, Day; DoR, duration of response; IRF, independent review facility; ORR, objective response rate; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; Q3W, once every 3 weeks; SD, stable disease

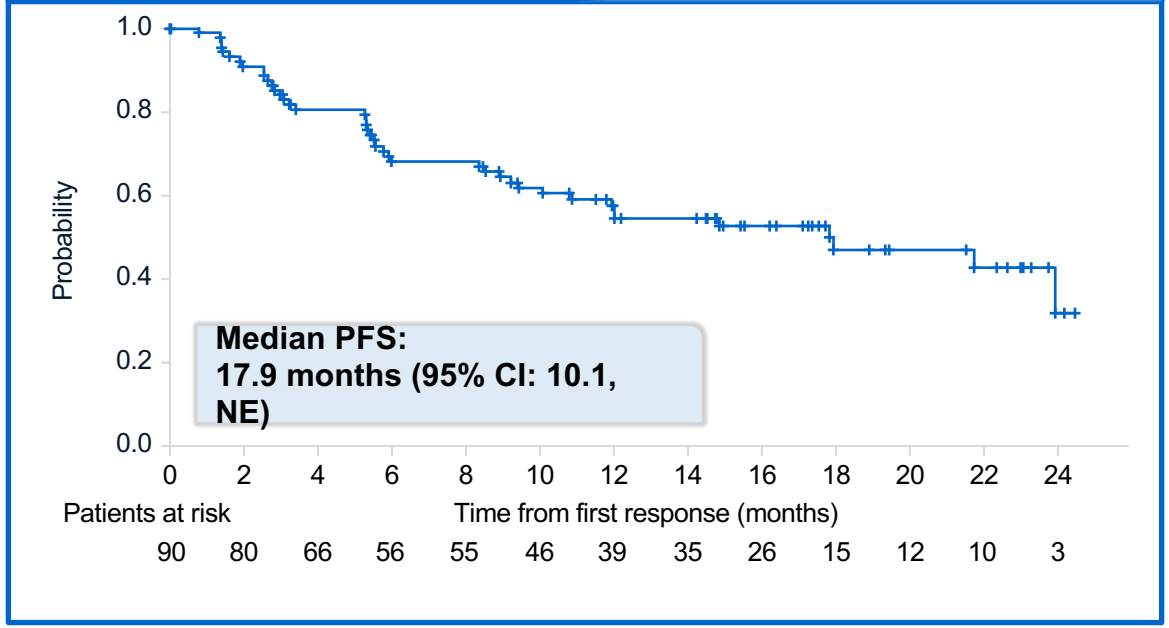
1. Dreyling et al. J Clin Oncol 2017;35:3898–905
2. Cheson et al. J Clin Oncol 2007;25:579–86

Duration of response and progression-free survival

Duration of response



Progression-free survival



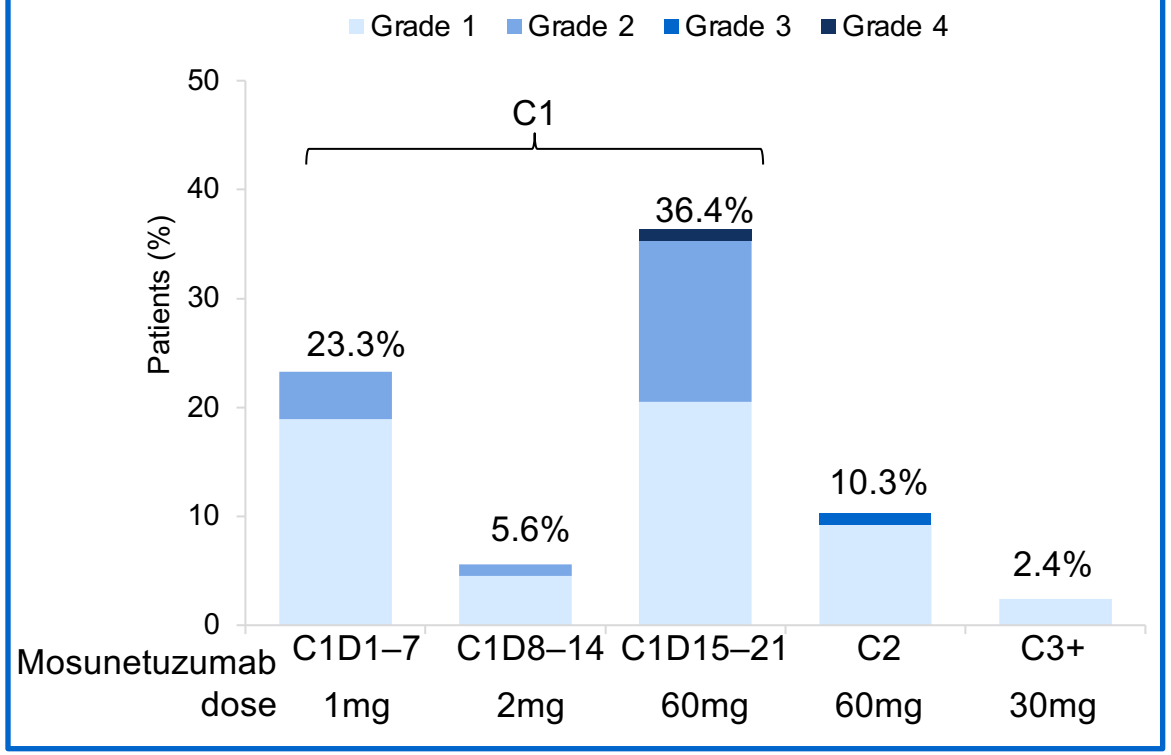
	DoR	DoRC
Median time to first response, mo (range)	1.4 (1.1, 8.9)	3.0 (1.1, 18.9)
12-month event-free rate, % (95% CI)	62% (50%, 74%)	76% (65%, 88%)
18-month event-free rate, % (95% CI)	57% (44%, 70%)	70% (57%, 84%)

DoRC, duration of response in complete responders; DoR, duration of response in responders; mo, month; NE, not estimable

Cytokine release syndrome

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

CRS by Cycle and Grade



- **CRS was predominately low Grade and in Cycle 1. All events resolved.**

*assessed using ASTCT criteria[1]; †patient with leukemic phase FL

1. Lee et al. Biol Blood Marrow Transplant 20192019;25:625–38

MOSUN+LENALIDOMIDE PHASE 1B

Key inclusion criteria

- CD20+ FL Grade 1–3a
- R/R to ≥1 prior chemo-immunotherapy regimen including an aCD20 antibody; prior lenalidomide allowed
- ECOG PS 0–2

Objectives

- Primary: safety and tolerability of M-Len
- Other: efficacy (response, durability of response) and pharmacokinetics

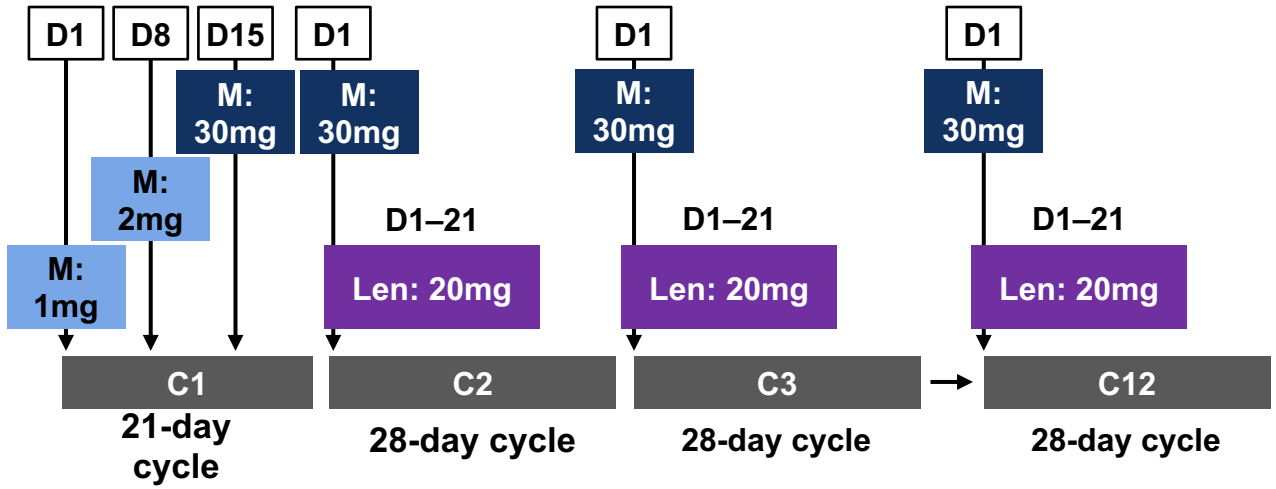
M-Len administration

Mosunetuzumab

- IV administration for 12 cycles (C1: Q3W; C2–12: Q4W)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Lenalidomide

- Oral administration for 11 cycles (C2–12)



C, Cycle; CRS, cytokine release syndrome; D, Day; IV, intravenous; Q3W, once every 3 weeks; Q4W, once every 4 weeks

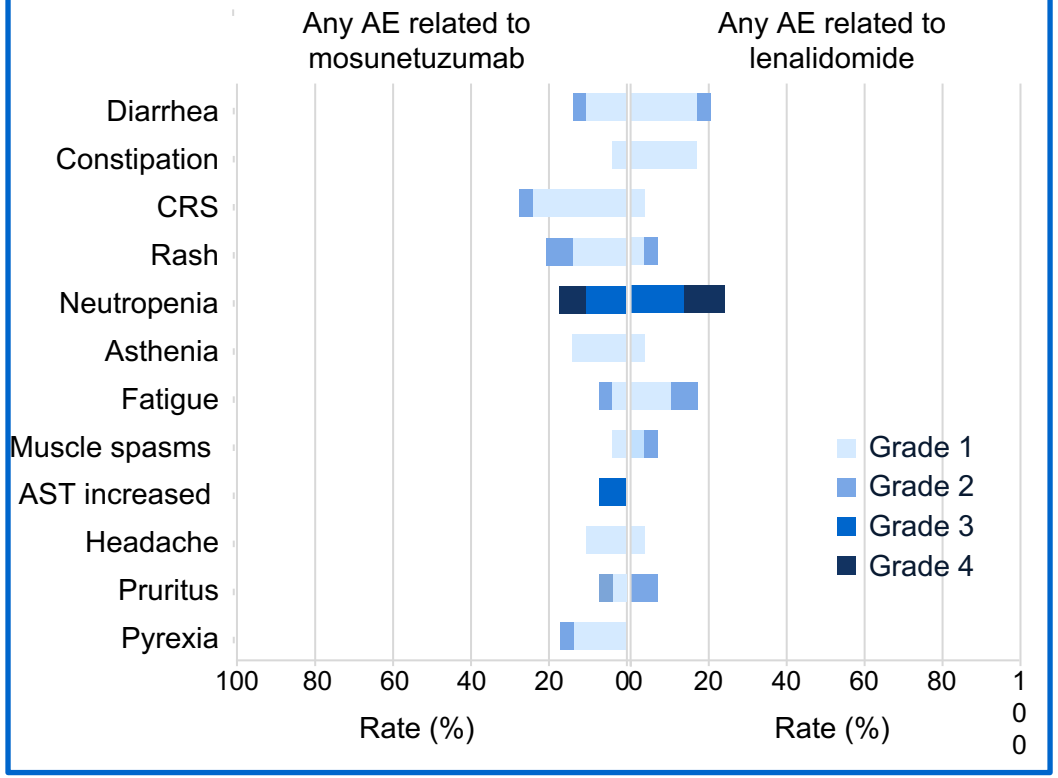
Morschhauser ash 2021 abstract

Adverse event summary

- Median duration of follow-up: 5.4 months (range: 3–12)

	N=29
AE Related to mosunetuzumab / lenalidomide	29 (100%) 27 (93.1%) / 23 (79.3%)
Grade 3–4 AE Related to mosunetuzumab / lenalidomide	13 (44.8%) 1 (3.4%) / 1 (3.4%)
Serious AE Related to mosunetuzumab / lenalidomide	9 (31.0%) 6 (20.7%) / 1 (3.4%)
Grade 5 (fatal) AE	0
AE leading to mosunetuzumab / lenalidomide discontinuation	0 / 1 (3.4%)
AE leading to mosunetuzumab dose delay	6 (20.7%)
AE leading to lenalidomide dose reduction	2 (6.9%)
AE leading to lenalidomide temporary dose interruption	6 (20.7%)
AE leading to lenalidomide dose reduction AND temporary dose interruption	4 (13.7%)

AEs with ≥15% incidence overall and corresponding rates of treatment-related events by Grade



- **M-Len had a favorable safety profile. No AEs led to mosunetuzumab discontinuation.**

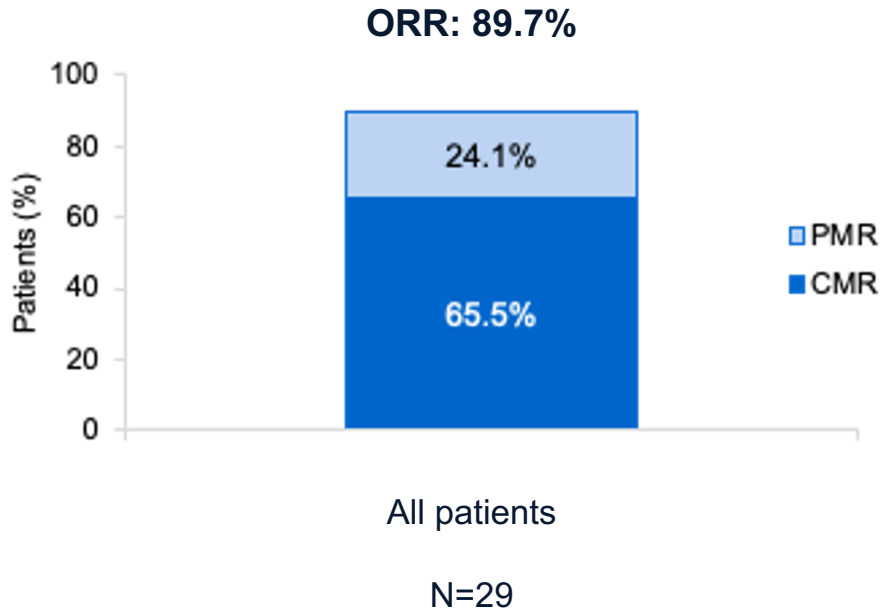
AE, adverse event; AST, aspartate aminotransferase

Morschhauser ASH 2021 abstract

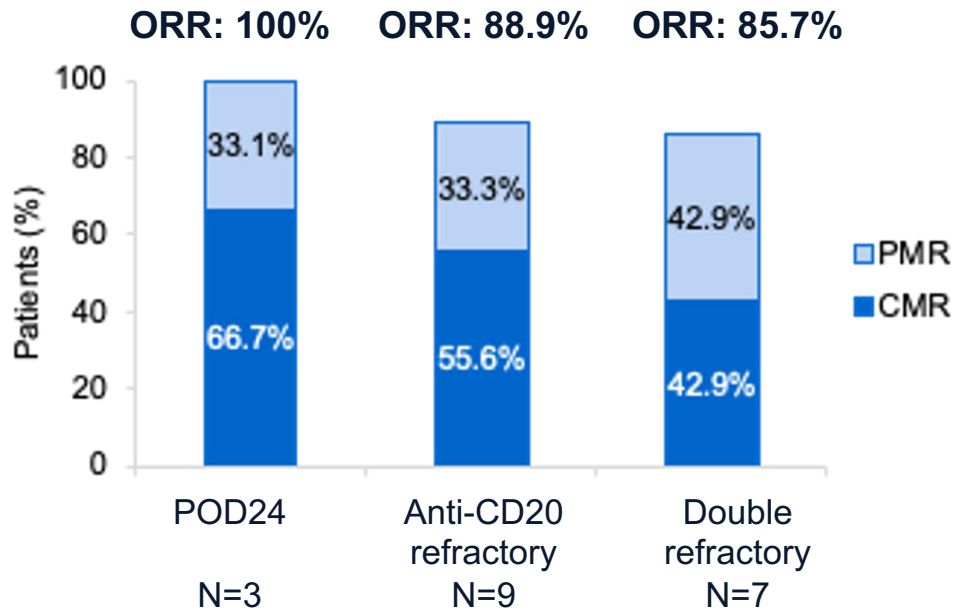
MOSUN+LEN PHASE 1B EFFICACY

- Median time to first / best response: 2.5 mo (range: 1.4–5.3) / 2.5 mo (range: 1.4–10.7)

Best response by PET-CT in all patients*



Best response by PET-CT in patient subgroups*



- **High ORR and CMR rate in overall population and in patients with high-risk disease**

*assessed by investigators using Lugano 2014 criteria[1]; CMR, complete metabolic response; mo, months; ORR, overall response rate; PET-CT, positron emission tomography-computed tomography; PMR, partial metabolic response

1. Cheson et al. J Clin Oncol 2014;32:3059–67

Bispecific Ab Epcoritamab + R2 in R/R FL

Phase I/II EPCORE NHL-2 Trial

N=74

- Adults with R/R CD20+ FL; grade 1-3A
- Stage II-IV
- Treatment needed based on symptoms or disease burden per GELF criteria
- Measurable disease by CT/MRI
- Adequate organ function
- ECOG PS 0-2

Dose Escalation (n = 6)

Cohort 2a
Epcoritamab 24 or 48 mg SC*
QW for C1-3, Q2W for C4-9, Q4W for C10+
+
R² for C1-12†

Dose Expansion (n = 68)

Cohort 2a
Epcoritamab 48 mg SC*
QW for C1-3, Q2W for C4-9, Q4W for C10+
+
R² for C1-12†

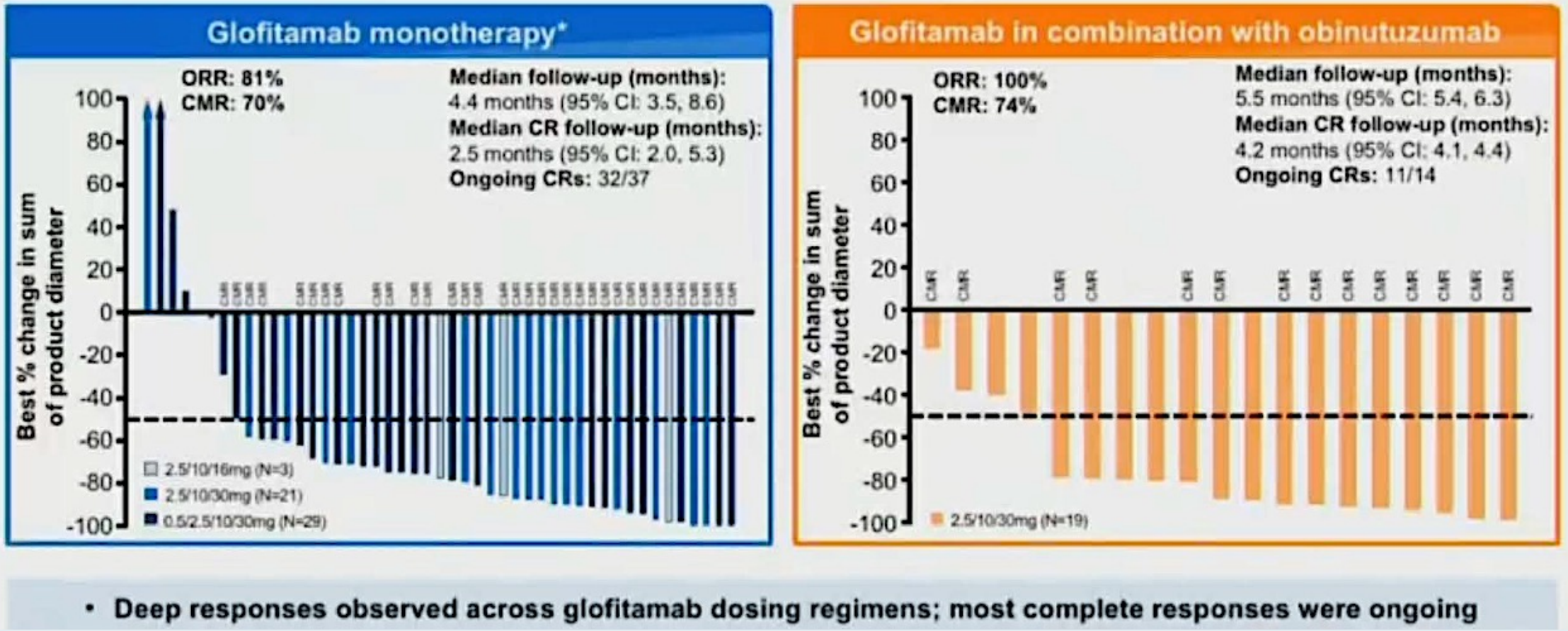
Cohort 2b
Epcoritamab 48 mg SC*
QW C1-2, Q4W for C3+
+
R² for C1-12†

Best Overall Response,* n (%)	Arm 2a		Arm 2b
	At Any Time (n = 28†)	At 6 Wk (n = 27)	At 6 Wk (n = 28)
ORR	28 (100)	25 (93)	26 (93)
• CMR	27 (96)	19 (70)	17 (61)
• PMR	1 (4)	6 (22)	9 (32)
SD	0	2 (7)	1 (4)
PD	0	0	1 (4)

- Half of patients experienced CRS, which was predominantly low grade and resolved in all cases
- 1 patient experienced ICANS (grade 2) that resolved

Falchi L, et al. *J Clin Oncol*. 2022;40(suppl 16):7524.

Phase I/II Study of Glofitamab as Monotherapy or in Combination with Obinutuzumab for R/R FL



- **Deep responses observed across glofitamab dosing regimens; most complete responses were ongoing**

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

Morschhauser F et al. ASH 2021;Abstract 128.

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Conclusions

- Outcomes for the majority of patients with FL are favorable.
- Balancing the goals of therapy with patient specific characteristics generally informs treatment selection given the number of therapies available.
- An unmet need is identifying optimal sequencing of therapy or predictive biomarkers.
- The goal of treatment is to achieve a normal life expectancy without negatively impacting quality of life.

Discussion Question

Outside of a clinical trial setting, what is your usual third line systemic therapy for a patient with follicular lymphoma who received BR followed by R^2?

- Copanlisb
- Tazemetostat
- Tazemetostat but only EZH2-mutated
- Other

Update on Zandelisib Development Outside of Japan

Press Release – December 5, 2022

"Today [it was] announced that after receiving the most recent guidance from a late November meeting with the US Food and Drug Administration (FDA), the companies are discontinuing global development of zandelisib outside of Japan for B-cell malignancies. [The company] is continuing the ongoing clinical trials including Phase 2 MIRAGE study evaluating Japanese patients with relapsed or refractory indolent B-cell non-Hodgkin lymphomas and will explore the potential for a submission to Japanese health authorities based on data from the MIRAGE and TIDAL clinical trials.

'Based on the most recent guidance received from the FDA at a late November meeting, we have jointly decided to discontinue development of zandelisib outside of Japan. We are very disappointed to share this decision in light of our belief in the potential of zandelisib to benefit patients and meet the ongoing need for new options to treat relapsed or refractory indolent non-Hodgkin lymphomas,' said Daniel P Gold, PhD, president and chief executive officer. 'However, in light of FDA's guidance, we no longer believe clinical development can be completed within a time period that would support further investment, or with sufficient certainty of the regulatory requirements to justify continued global development efforts.'"

https://www.meipharma.com/press-releases/mei-pharma-and-kyowa-kirin-announce-discontinuation-zandelisib-development-outside

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Module 3: Hodgkin Lymphoma (HL) — Dr Smith

Case Presentation: 80-year-old woman with newly diagnosed classical Hodgkin lymphoma

Dr KS Kumar (Trinity, Florida)

RTP RESEARCH TO PRACTICE

Dr Susmitha Apuri
(Lutz, Florida)

Case Presentation: 37-year-old woman with newly diagnosed classical Hodgkin lymphoma

Dr Amany Keruakous
(Augusta, Georgia)

Case Presentation: 60-year-old man with newly diagnosed Stage IV classical Hodgkin lymphoma who receives BV + AVD

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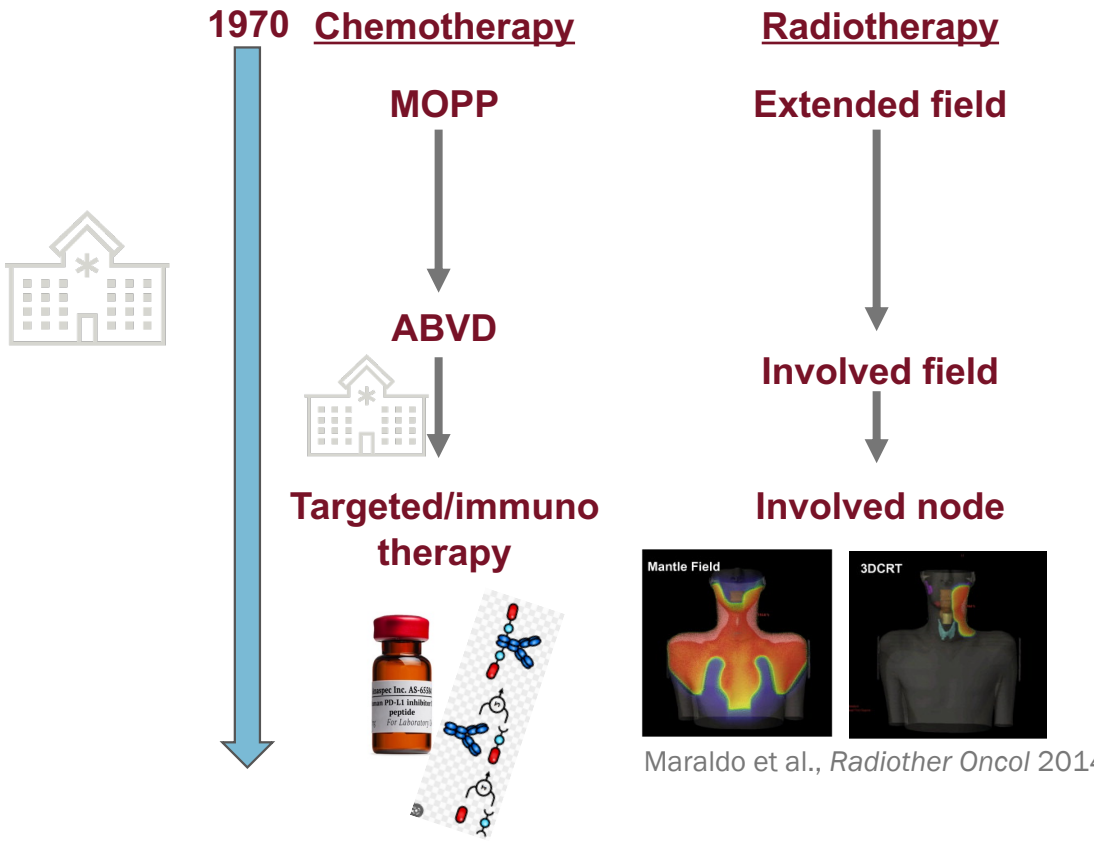
ASH 2022
HODGKIN LYMPHOMA

Sonali M. Smith, MD FASCO
Elwood V. Jensen Professor of Medicine
Chief, Section of Hematology/Oncology
Co-Leader, Cancer Service Line
The University of Chicago

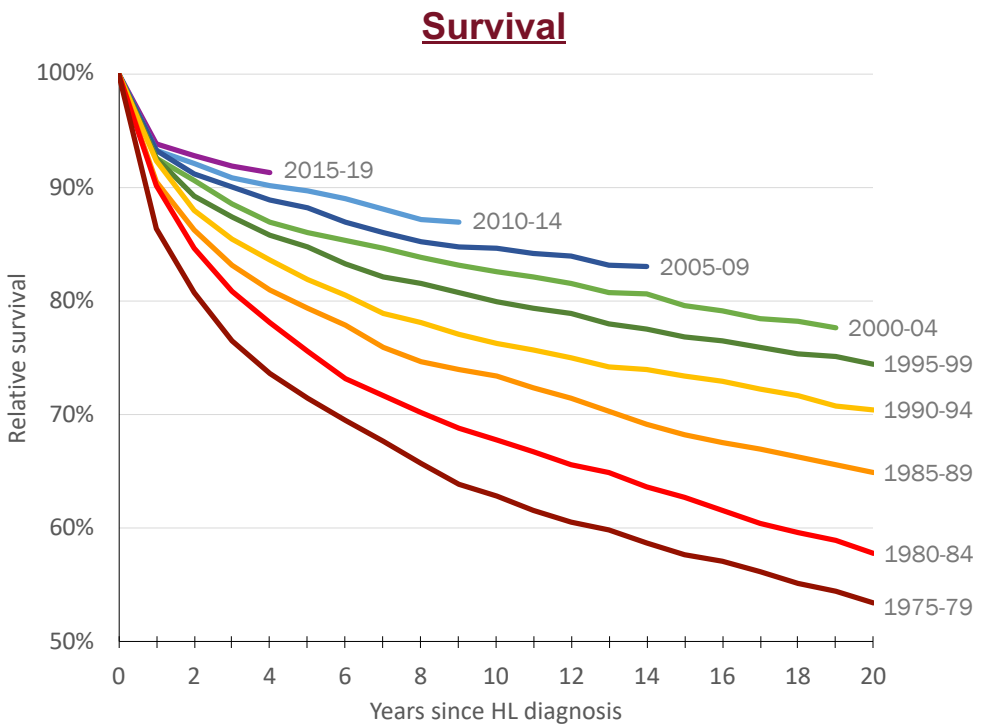
Hodgkin Lymphoma

- Long-term follow-up from the Phase III ECHELON-1 trial of first-line brentuximab vedotin (BV) with AVD for advanced classical HL
- Early findings with BV-based therapy for early-stage, unfavorable-risk HL
- Available data with BV for older patients with newly diagnosed advanced HL
- Mechanism of action of and available efficacy and safety findings with camidanlumab tesirine for patients with R/R HL
- Other promising investigational strategies for patients with HL (eg, novel immunotherapeutic strategies, CAR T-cell therapy)

Evolution of Hodgkin Lymphoma Treatment



Maraldo et al., *Radiother Oncol* 2014



SEER 8 registries, 1975-2019

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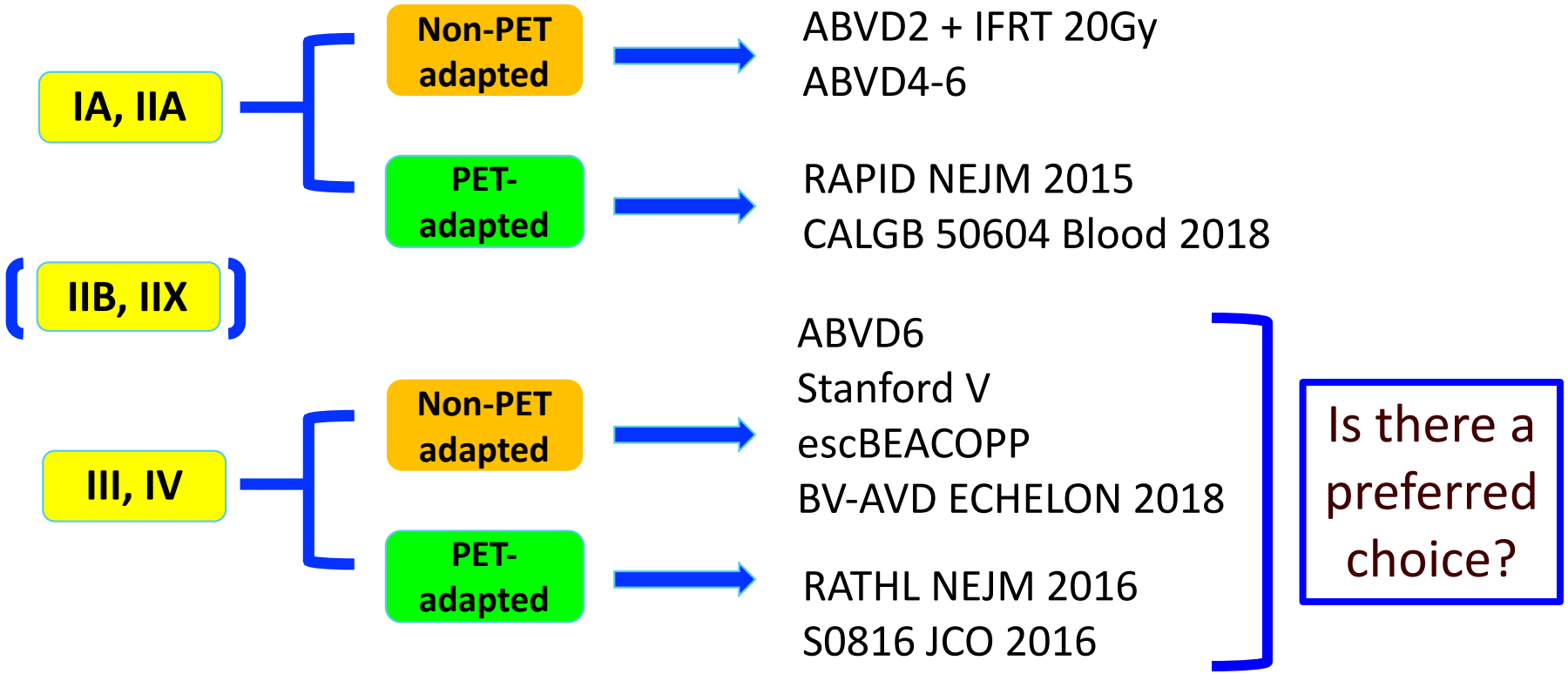
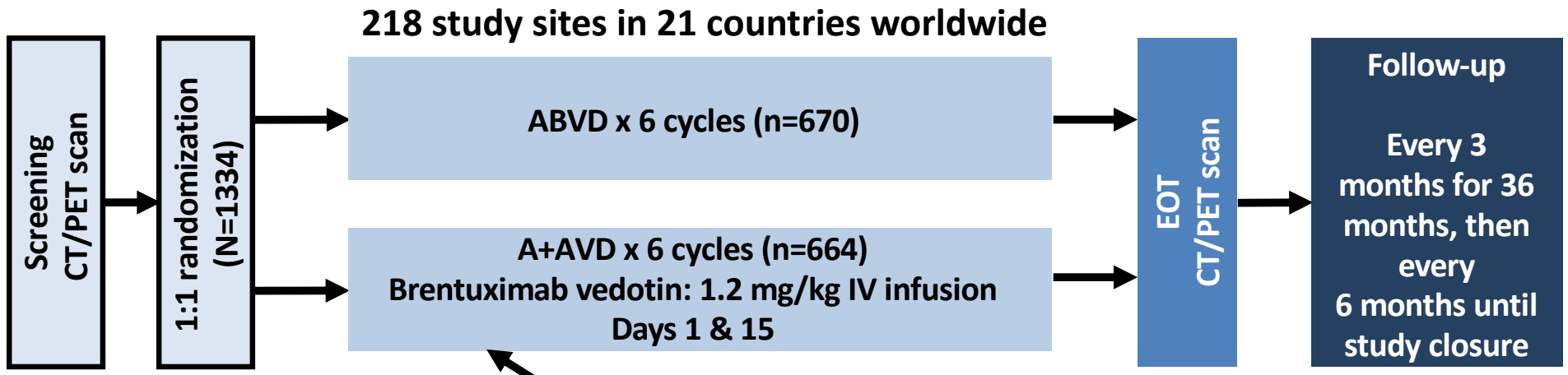
UChicago Medicine

Slide courtesy of Lindsay Morton, PhD, NCI, REG

Hodgkin lymphoma: frontline standard treatment approach can be PET-adapted or non PET-adapted



ECHELON-1: BV-AVD vs. ABVD (not PET-adapted)



- **Inclusion criteria**
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function

End-of-Cycle-2 PET scan

- Deauville 5; could receive alternate therapy per physician's choice (not a modified PFS event)

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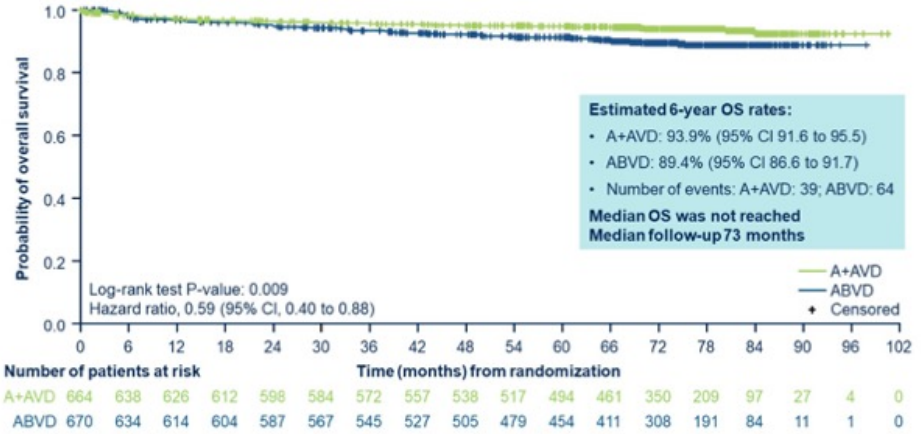
Ansell 2022 ASCO Annual Meeting. Abstract 7503

ECHELON-1 results (73m median f/u)

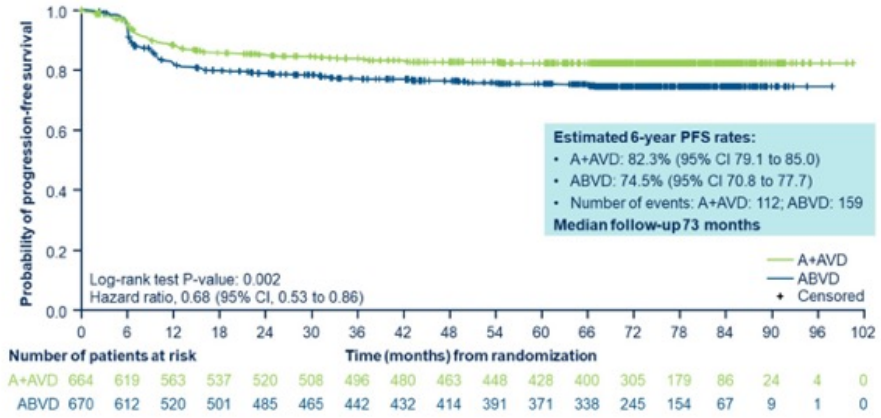
BV-AVD arm

- Fewer disease- or treatment-related progression and deaths
- Fewer second malignancies and fewer deaths due to second malignancies
- More reported pregnancies (113 vs. 78)
- 86% of pts had resolution of peripheral neuropathy symptoms

A+AVD significantly improved OS with a 41% reduction in risk of death compared with ABVD



A+AVD reduced the risk of progression or death by 32% when compared with ABVD



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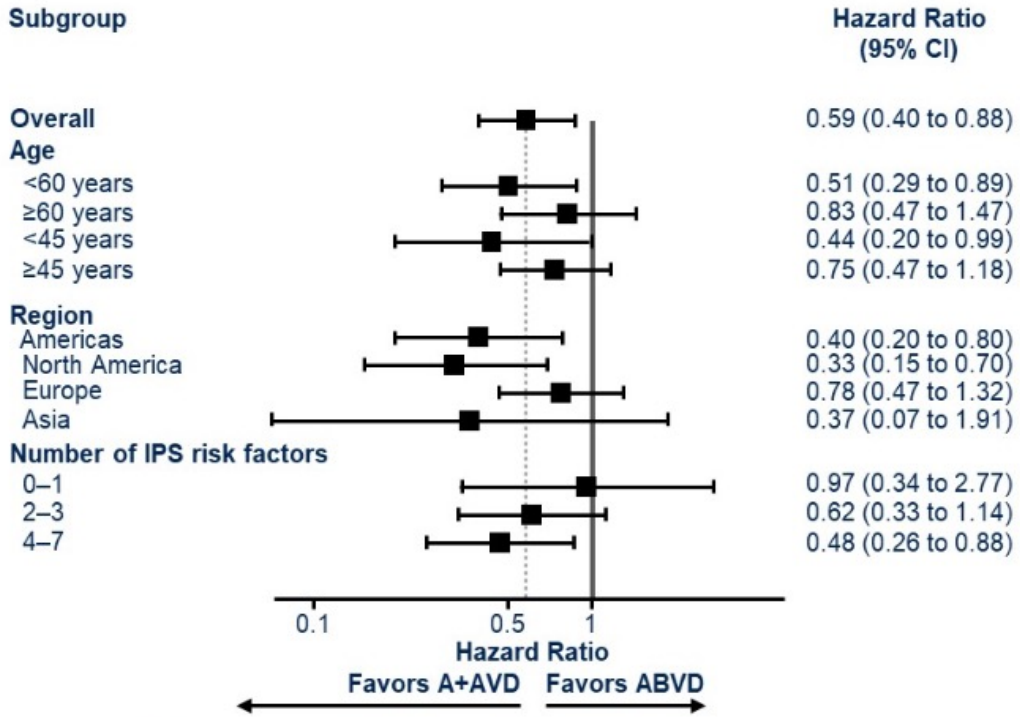
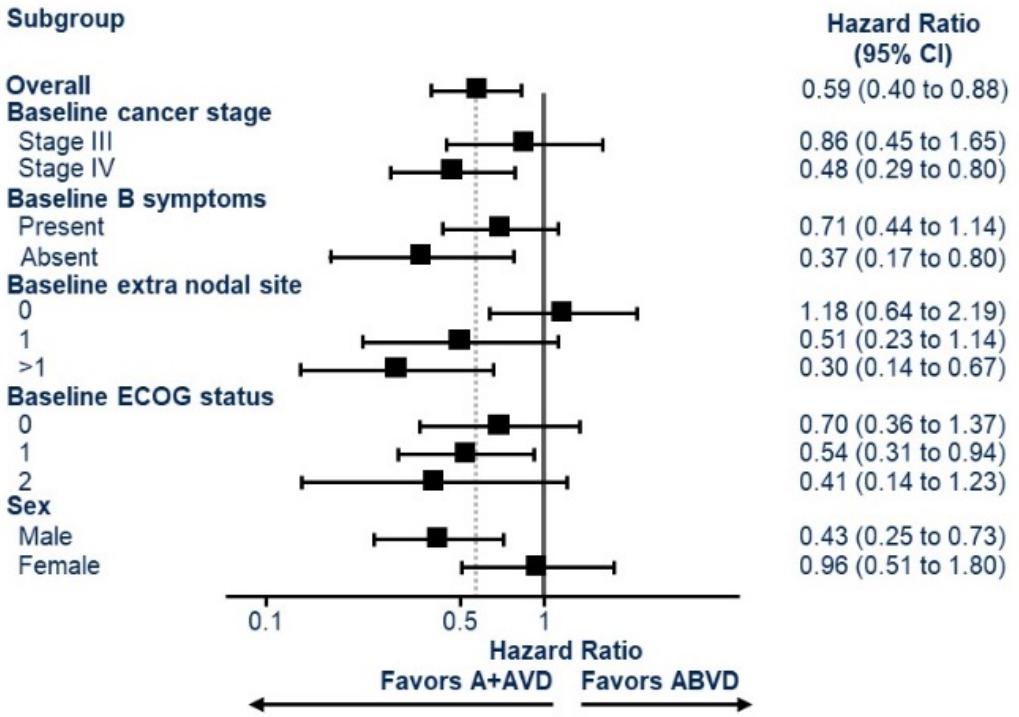
Ansell 2022 ASCO Annual Meeting. Abstract 7503

OS benefit across subgroups





- The OS benefit with A+AVD was preserved in a multivariable analysis when simultaneously adjusting for baseline demographic and disease factors (HR 0.53; 95% CI, 0.34 to 0.83)
  - Age, non-white race, ECOG performance status score, and PET2 status were identified as the covariates with greatest evidence of association with overall survival

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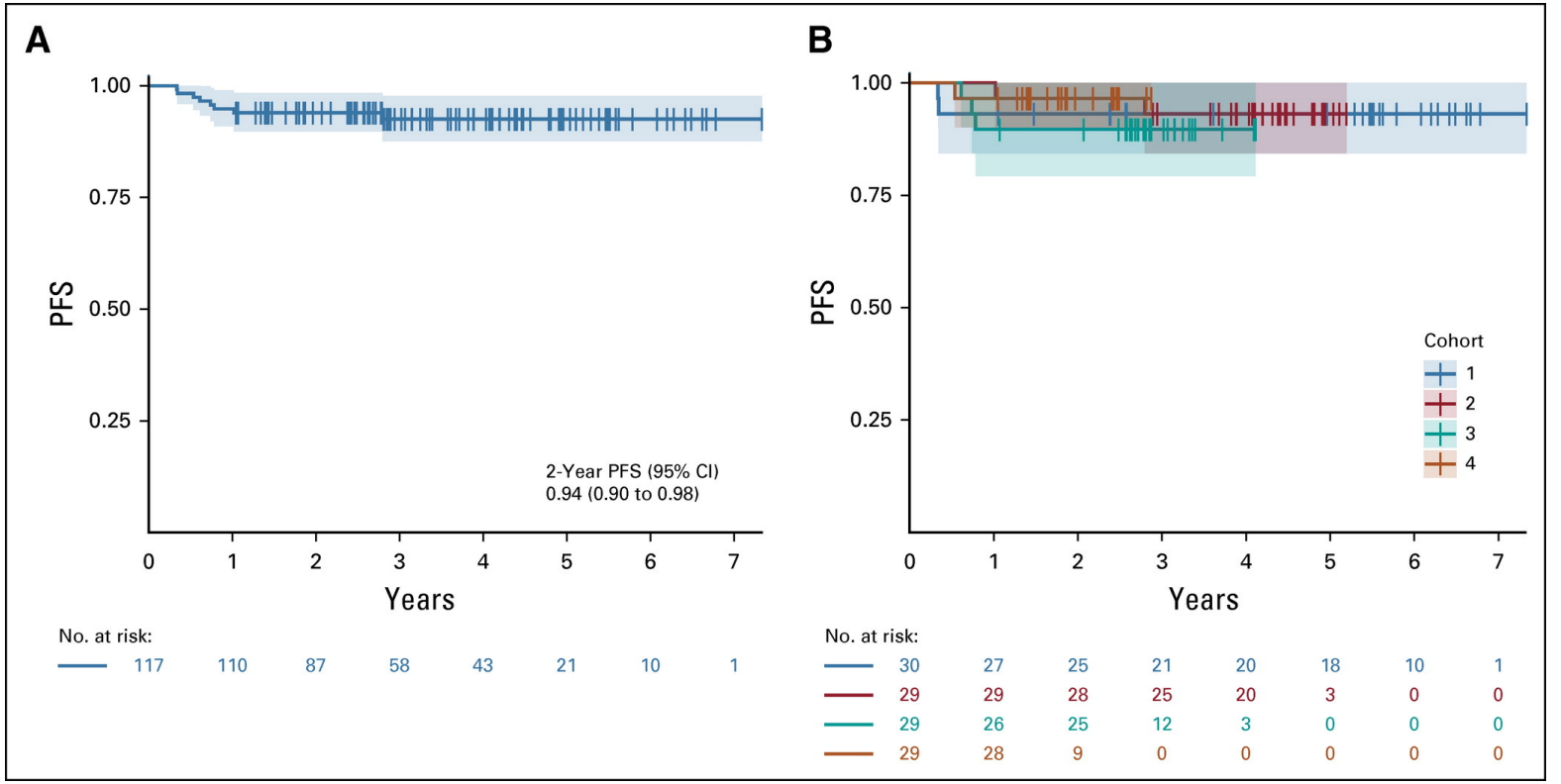
Ansell 2022 ASCO Annual Meeting. Abstract 7503

BV-based regimens in limited stage cHL

Early stage cHL with unfavorable features (including bulky disease)

BV-AVD x 4 → if PET neg → 3 RT cohorts
1 no RT cohort



N=117

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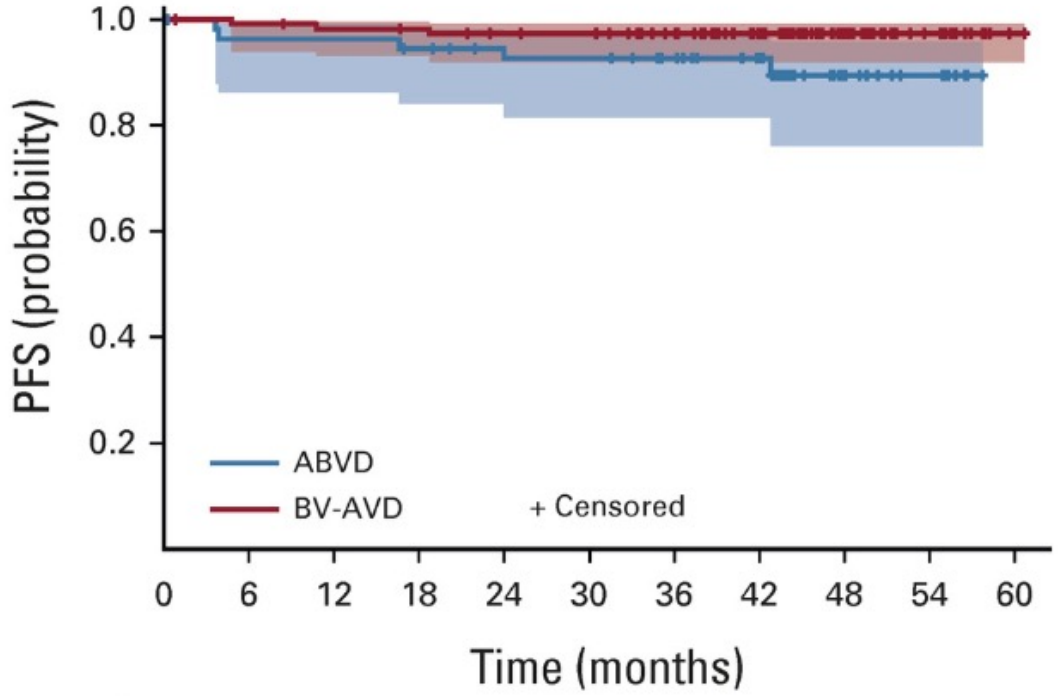
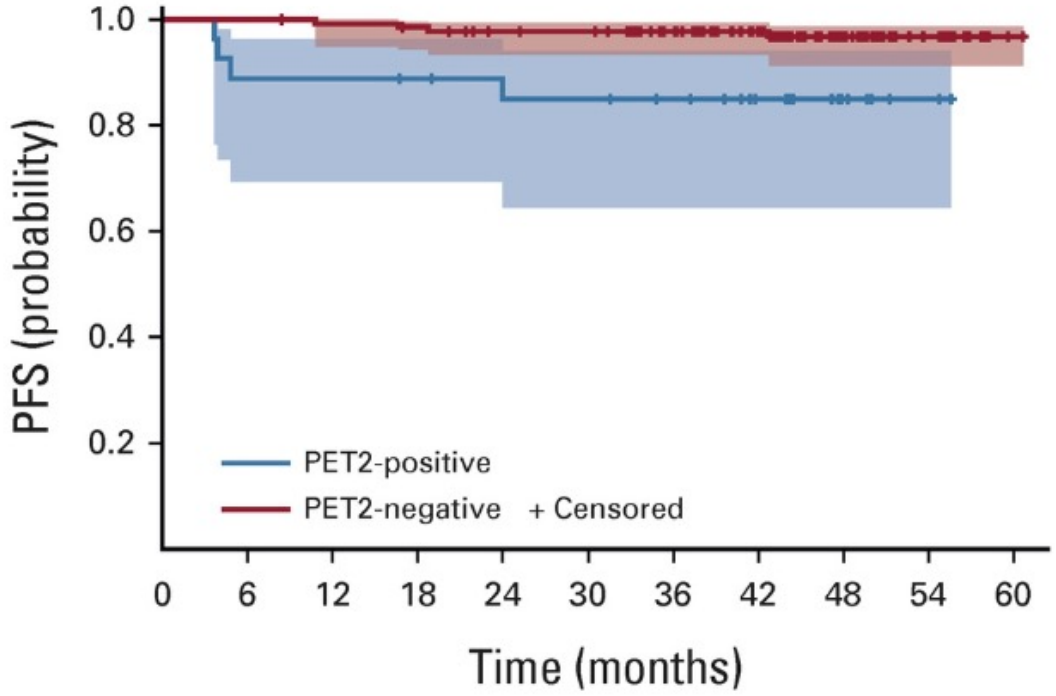
Kumar J Clin Oncol 2021 Jul 10;39(20):2257-2265

RP2 trial of BV-AVD v. ABVD (2:1) in limited stage unfavorable cHL (LYSA-FIL-EORTC Intergroup): BREACH trial



No. at risk:											
ABVD	57	53	53	51	47	47	42	33	15	7	0
BV-AVD	113	111	109	108	105	104	97	80	44	17	2

PFS by treatment arm



No. at risk:											
PET2-positive	27	24	24	23	21	21	19	14	7	2	0
PET2-negative	136	136	134	132	127	126	116	95	50	21	1

PFS by PET2 status

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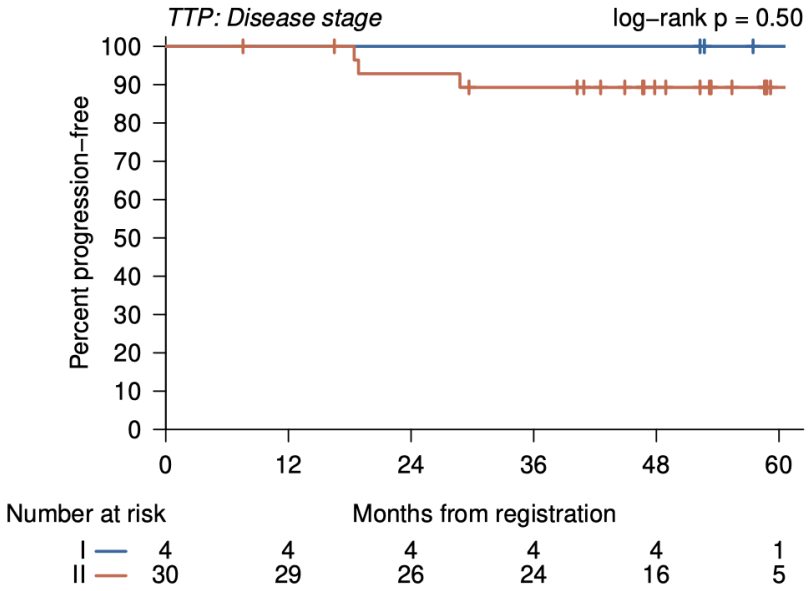
Fornecker J Clin Oncol 2022 Jul 22;JCO2101281

If BV is used, can vinblastine be omitted? Can nivo be added?

BV plus AD x 4-6 cycles (N=34)
PET-adapted phase 2 trial
non-bulky, limited st dz
Med f/u 53m



BV plus nivo plus AD (AN-AD) x 4
non-bulky, limited st dz
(abstract 4230)

BV-AVD x 3 → Nivo consol.
non-bulky, limited st dz
(abstract 728)

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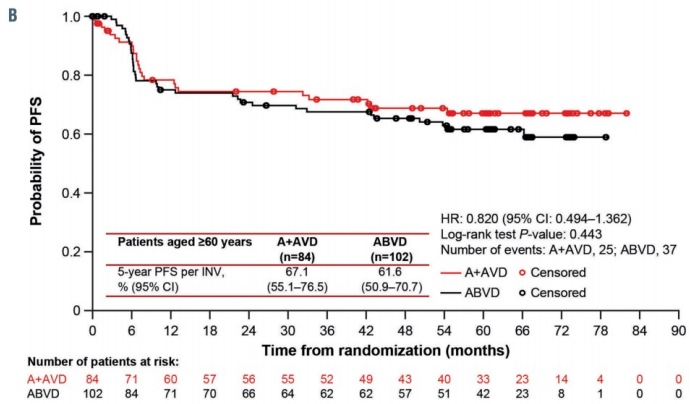
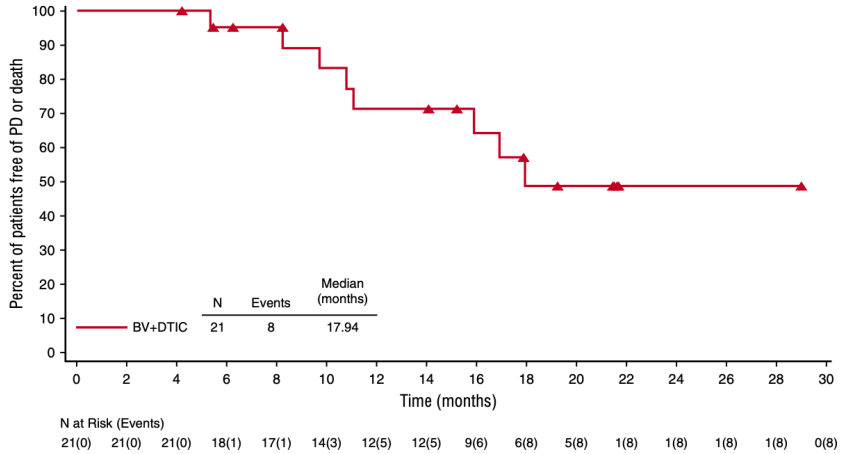
Abramson Blood Adv 2022 Sep 2;bloodadvances.2022008420
Park ASH 2022 Abstract 728 (Oral Monday)
Lee ASH 2022 Abstract #4230 (Poster Hall Monday)

Treatment of older patients with cHL

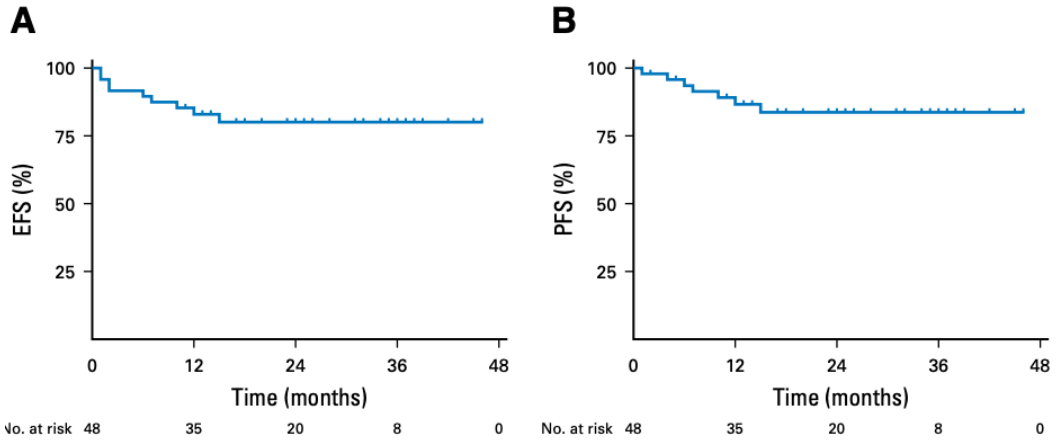




ECHELON-1: BV-AVD = ABVD

(more neuropathy and neutropenia but less pulmonary toxicity than ABVD)

BV plus DTIC



Other:

- RATHL approach (only 10% ≥ 60y)
- AVD
- CHOP

BV → AVD → BV

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Evens J Clin Oncol. 2018 Oct 20;36(30):3015-3022
Evens Haematologica 2022 May 1;107(5):1086-1094;
Friedberg Blood. 2017 Dec 28;130(26):2829-2837

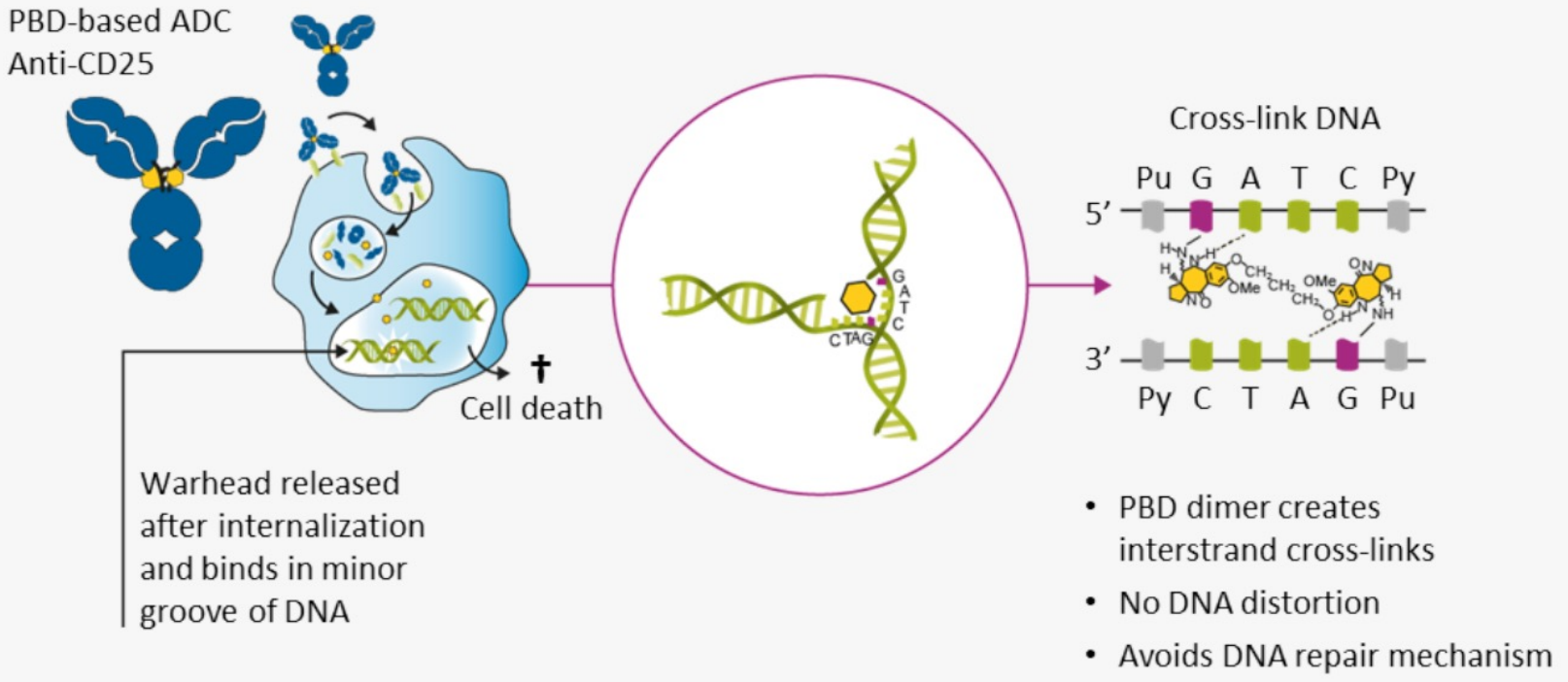
Camidanlumab tesirine: anti-CD25 plus PBD dimer ADC

Cami composition

- Human IgG1 anti-CD25 mAb stochastically conjugated to PBD dimer warhead

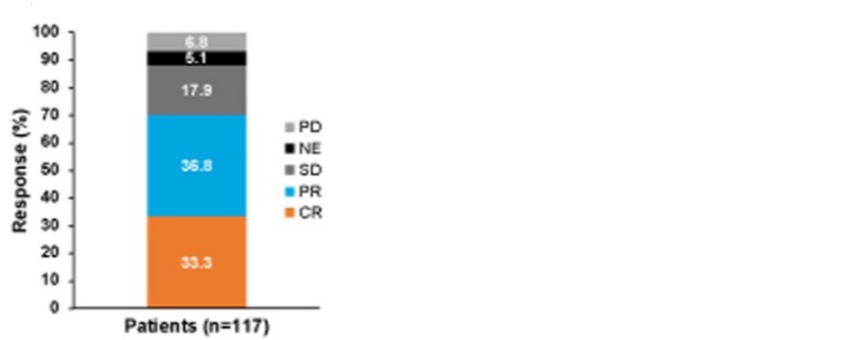
Mechanism of action[1–3]

- Death of CD25-expressing tumor cells
- Depletion of CD25-expressing T cells in HL tumor microenvironment
- Possible bystander killing of CD25-negative cells

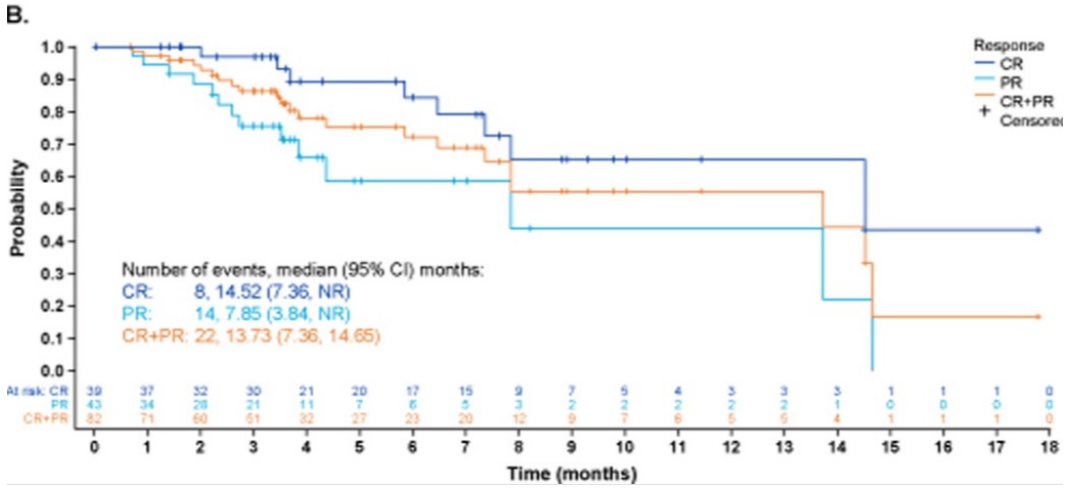


1. Hartley JA. *Expert Opin Investig Drugs* 2011;20:733–44; 2. Flynn MJ, et al. *Mol Cancer Ther* 2016;15:2709–21; 3. Zammarchi F, et al. *J ImmunoTher Cancer* 2020;8:e000860.
ADC, antibody-drug conjugate; **IgG**, immunoglobulin G; **mAb**, monoclonal antibody; **PBD**, pyrrolobenzodiazepine.

Ph 2 International monotherapy trial of cami (NCT04052997)



CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease



Key findings:

N=117 with med SIX prior regimens

ORR 70.1% (CR: 33.3%)
Response independent of age, sex, response to last PD-1 inhibitor

Median DOR of 13.7m
Median PFS of 9.1m

Guillan-Barre syndrome in 8 pts

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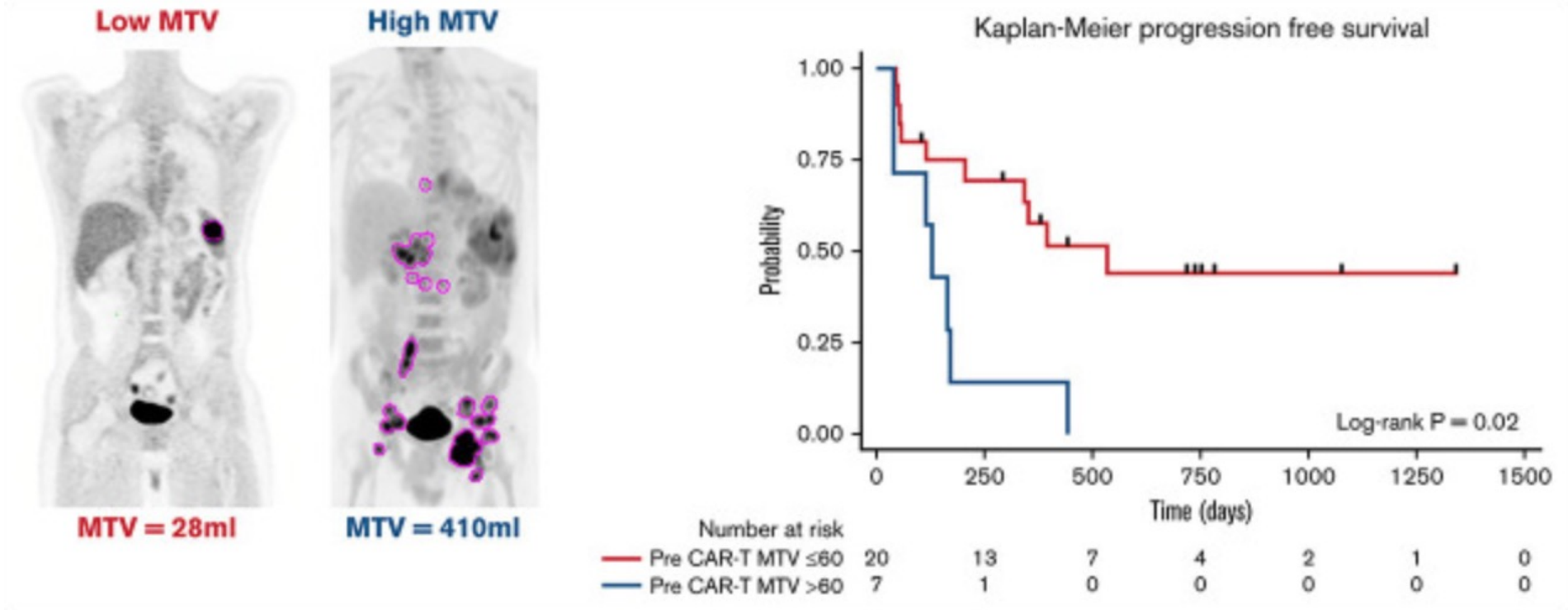
UChicago Medicine

Carlo-Stella HemaSphere6:102-103, June 2022
Herrera ASH 2022 abstract 1594 (Saturday poster)

Emerging therapies: anti-CD30 CAR-T



CAR-T outcomes in cHL by pre-CAR-T MTV (n=27)

Emerging CAR-T for cHL: “off the shelf”
ASH 2022 Abstract 167 CD30.CAR-Modified Epstein-Barr Virus-Specific T Cells (CD30.CAR EBVSTs) Provide a Safe and Effective Off-the-Shelf Therapy for Patients with CD30-Positive Lymphoma

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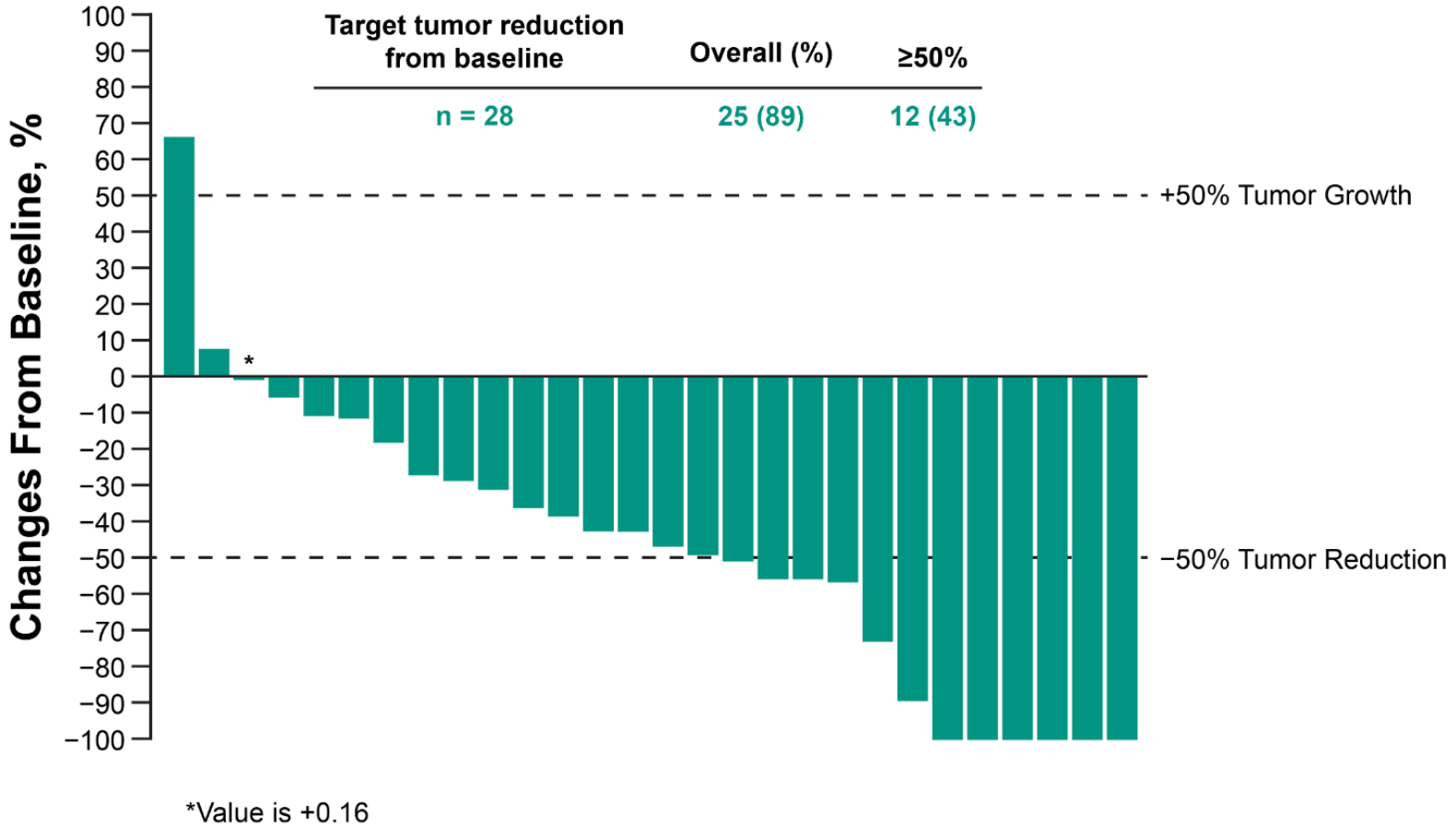
UChicago Medicine

Voorhees Blood Adv. 2022 Feb 22;6(4):1255-1263

Next steps for immunotherapy in cHL? Dual blockade of LAG-3 and PD-1



*Value is +0.16

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ASH 2022 abstract 316 Updated Results from an Open-Label Phase 1/2 Study of Favezelimab (anti–LAG-3) Plus Pembrolizumab in Relapsed or Refractory Classical Hodgkin Lymphoma after Anti–PD-1 Treatment (Timmerman)

Module 4: Chimeric Antigen Receptor (CAR) T-Cell Therapy for Non-Hodgkin Lymphoma — Dr Maloney

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Dr Vignesh Narayanan
(Lone Tree, Colorado)

Case Presentation: 57-year-old man who presents with a large cecal mass and mesenteric adenopathy and is diagnosed with “double hit” DLBCL

Dr Rahul Gosain
(Corning, New York)

Case Presentation: 70-year-old woman with DLBCL treated with R-CHOP, now with PD 6 months later

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Case Presentation: 73-year-old woman with rapid relapse after R-CHOP then R-ICE/ASCT who achieves a CR with CAR T-cell therapy but experiences significant pancytopenias

Dr John Yang (Fall River, Massachusetts)

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Chimeric Antigen Receptor (CAR) T-Cell Therapy for Non-Hodgkin Lymphoma

David Maloney, MD, PhD

Medical Director, Cellular Immunotherapy
Bezos Family Immunotherapy Clinic
Professor of Medicine, Division of Oncology
Fred Hutchinson Cancer Center and the University of Washington

FRED HUTCH
CURES START HERE™

Commercial CD-19 CAR-T cell therapy for NHL

- **Aggressive NHL**
  - Tisagenlecleucel
  - Axicabtagene ciloleucel (Axi-cel)
  - Lisocabtagene maraleucel (Liso-cel)

- **Follicular Lymphoma**
  - Axicabtagene ciloleucel
  - Tisagenlecleucel

Mantle Cell lymphoma

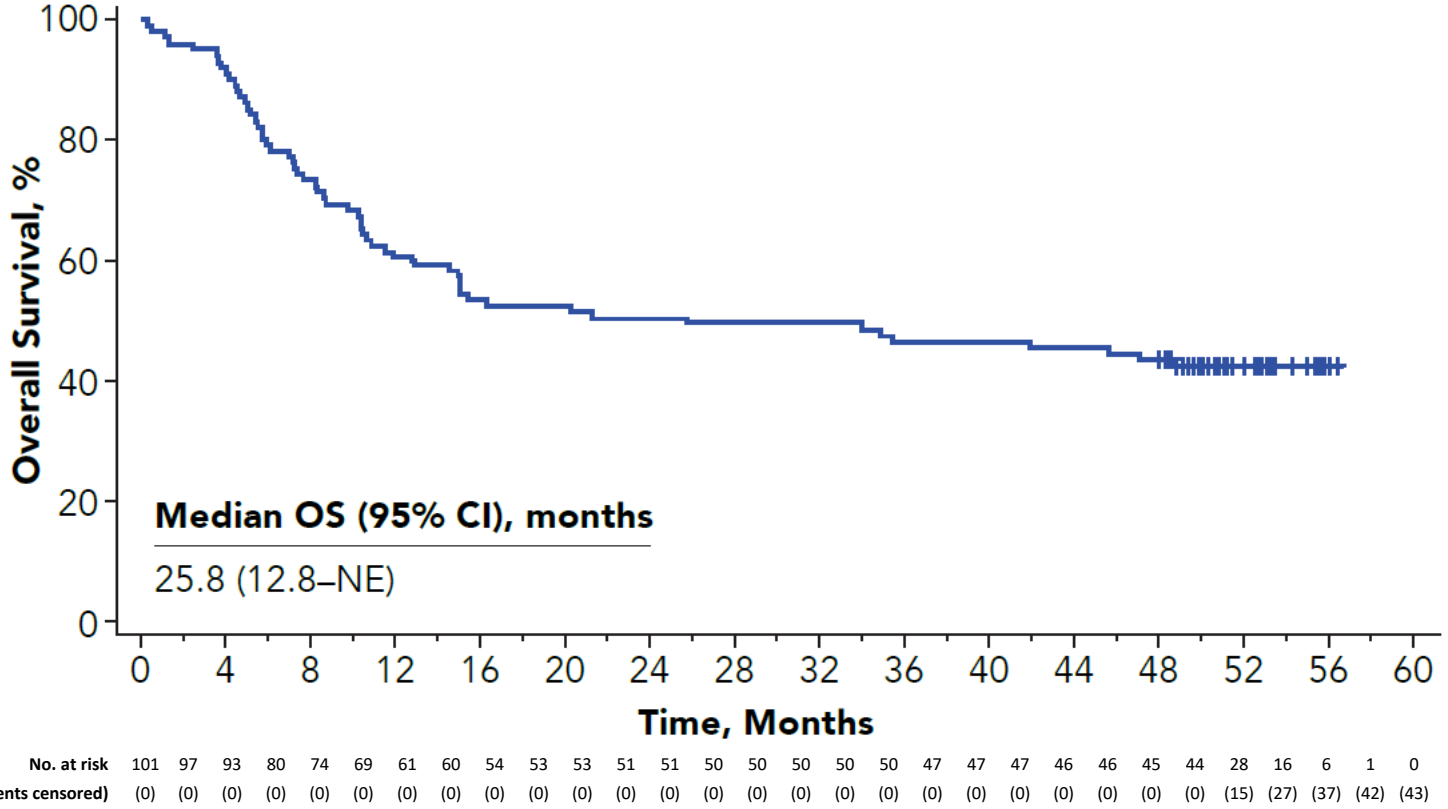
- Brexucabtagene autoleucel

Aggressive lymphoma: commercial CD19 CAR T cell products

Feature	Tisagenlecleucel	Axi-cel	Liso-cel
Construct	FMC-63 murine scFv 4-1BB co-stimulatory domain	FMC-63 murine scFv CD28 co-stimulatory domain	FMC-63 murine scFv 4-1BB co-stimulatory domain
Viral transfer	Lentiviral	Gamma retroviral	Lentiviral
Collection	Resting state apheresis Cryopreserved Bulk cells	Resting state apheresis Fresh only Bulk cells	Resting state apheresis Fresh only Selection CD4 and CD8
Manufacture	CD3/CD28 stimulation	CD3/CD28 stimulation	CD4, CD8 selection CD3/CD28 stimulation
Dose administered	0.6–6.0 × 10^8 CAR T cells CoA based on cell recovery	2 × 10^6/kg Max. 200 × 10^6 No CoA	100 × 10^6 (CD4/CD8) in separate vials (1:1) Dose based on recovery
Histology	DLBCL tFL	DLBCL PMBCL tFL	DLBCL, HGBCL PMBCL Indolent (FL, CLL, MZL)
CNS involvement	No	No	Yes, secondary

ZUMA-1: durable responses with axi-cel in patients with r/r DLBCL

Updated long-term data (median follow-up: 51.1 months)



Patients, n (%)	Axi-cel (N = 111)
Deaths	66 (59)
Primary cause of death	
PD	52 (47)
Other	8[a] (7)
AEs	5[b] (5)
Secondary malignancy	1 (1)

Data cut-off date: August 11, 2020.

[a] Three events had no causal relationship (MDS, cardiac arrest), 4 events occurred post subsequent therapy (sepsis, infection, and pulmonary nocardiosis), and 1 event was unknown.

[b] One event was related to conditioning chemotherapy, 2 events had no causal relationship, and 2 events were related to axi-cel.

AE, adverse event; CI, confidence interval; MDS, myelodysplastic syndrome; NE, not estimable; PD, disease progression; RR, relapsed/refractory.

Jacobson C, et al. Long-term survival and gradual recovery of B cells in patients with refractory large B-cell lymphoma treated with axicabtagene ciloleucel. Poster presented at TCT 2021;abstract 494.

CIBMTR Analysis of Commercial Axi-cel

Characteristics	RWE	ZUMA-1
n	1297 tx	111 101 tx (91%)
Median age (range)	62 (20-91)	58 (23-76)
ECOG PS >1	5%	0
High risk IPI (≥ 3)	NR	485
Median prior tx	3	3
Bridging therapy	22%	0
Prior ASCT	28%	21%
Histology DLBCL HGBCL PMBCL Other	 79% 16% 3% 1%	 76% NR 8% NA
Ineligible for pivotal trial	57%	0

Reasons for Zuma-1 Ineligible	N=76
Pulmonary disease	50%
Cardiac dysfunction	23%
Prior malignancy	23%
ECOG >1	8%
Rheumatologic disease/IBD	8%
Active infection	7%
Ineligible histology	6%
Prior checkpoint inhibitor	5%
Hepatic dysfunction	4%
Renal dysfunction	4%
CNS involvement	3%
Allo SCT	2%

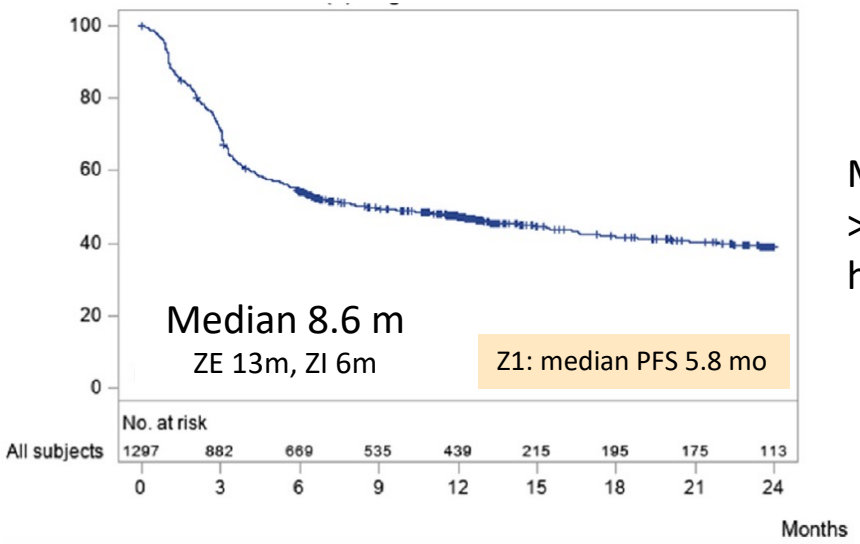
Median infusion time 28 days from apheresis

Jacobson, et al. JTCT 2022

CIBMTR Analysis of Commercial Axi-cel: Efficacy

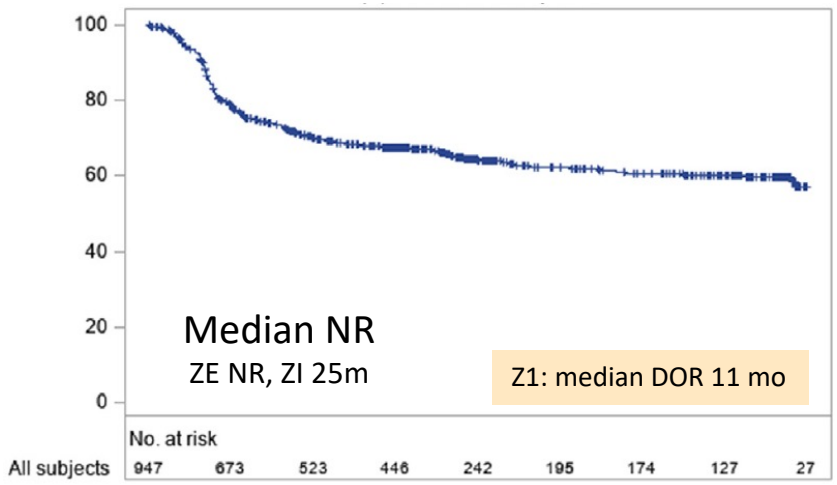
Response	Total N=1297	Z-1 eligible N=558	Z-1 inelig N=739	ZUMA-1
ORR	73%	76%	71%	83%
CR	56%	60%	52%	58%

Progression-free Survival

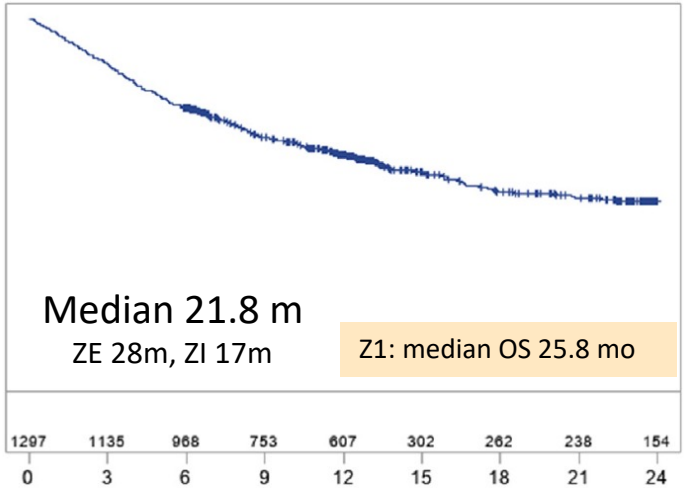


MVA: Inferior PFS with ECOG >1, chemoresistant, severe hepatic disease

Duration of Response (median f/u 23 m)



Overall Survival



MVA: Inferior OS with ECOG >1, chemoresistant

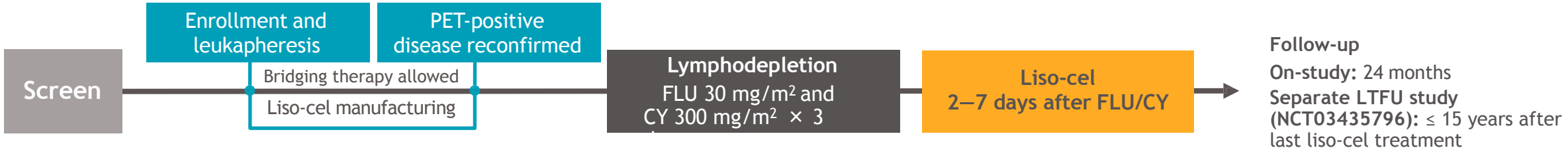
Jacobson, et al. JTCT 2022

CIBMTR Analysis of Commercial Axi-cel: CRS and ICANS

Toxicity	Total N=1297	Z-1 eligible N=558	Z-1 inelig N=739	ZUMA-1
Any grade CRS	83%	83%	83%	93%
≥Grade 3 CRS	8%	6%	10%	13%
Any grade neurotoxicity	55%	58%	72%	64%
≥ Grade 3 neurotoxicity	24%	26%	36%	28%
ICU transfer	28%	17%	34%	NR
Tocilizumab +/- steroid	58%	59%	57%	43%
Steroids alone	7%	8%	7%	27%

Jacobson, et al. JTCT 2022

TRANSCEND NHL 001, a seamless design, pivotal, phase 1 study[1,2]



Patient eligibility

- Age ≥ 18 years
- LBCL after ≥ 2 lines of therapy
  DLBCL NOS (de novo; transformed from FL, CLL, MZL, or other)
  HGBCL (double/triple hit), PMBCL, FL3B
- Prior HSCT allowed (autologous/allogeneic)
- ECOG PS of 0–2
- Patients with secondary CNS lymphoma were eligible
- CrCl > 30 mL/min/1.73 m², LVEF ≥ 40%
- No lower threshold for ALC, ANC, platelets, or hemoglobin

Endpoints

Primary: AEs, ORR by IRC

Secondary: CR rate by IRC, DOR, PFS, OS, PK

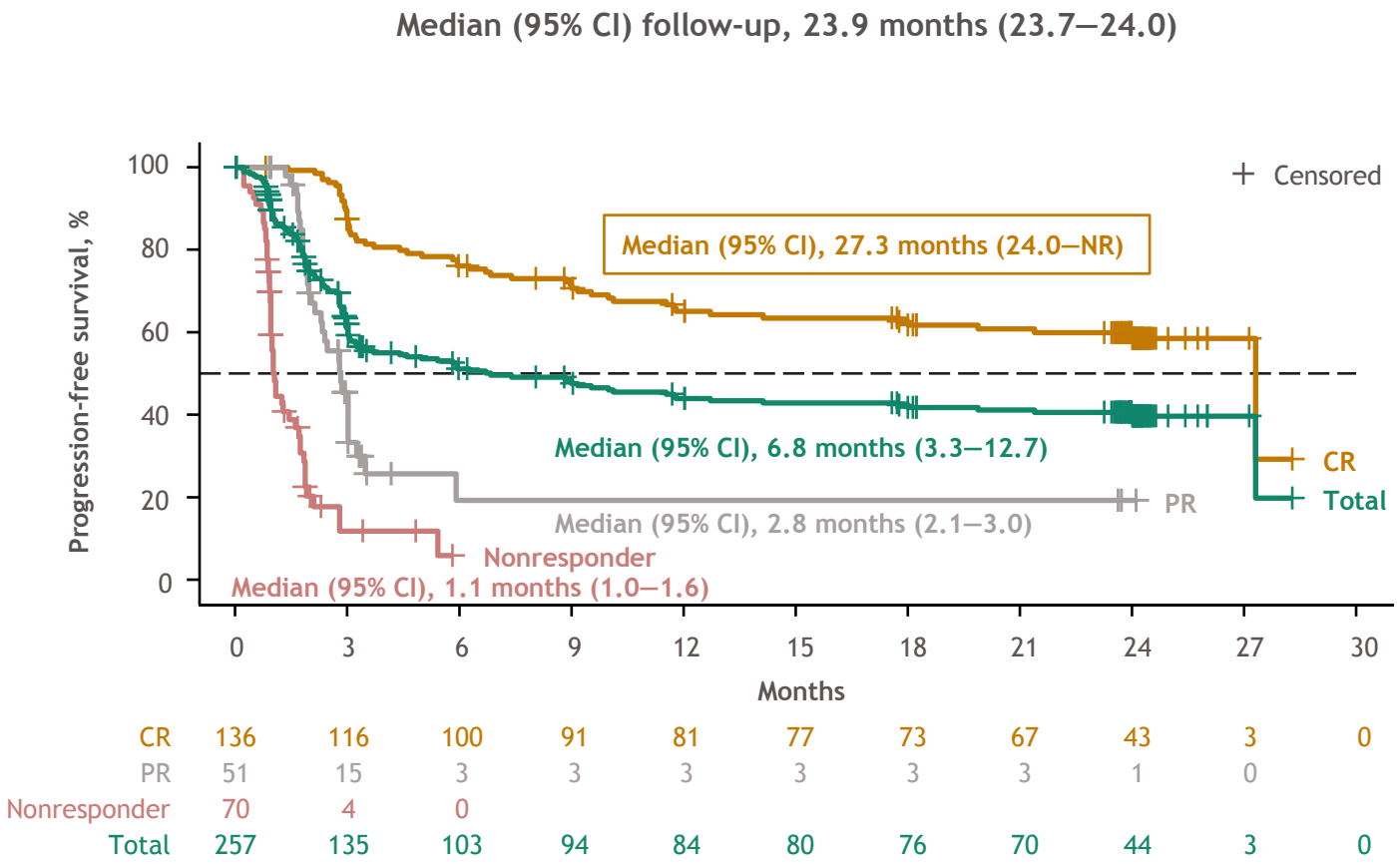
Analysis sets

- **Safety analysis set (N = 270):** patients who received ≥ 1 dose of liso-cel
- **Efficacy-evaluable set (N = 257):** patients with confirmed PET-positive disease who received ≥ 1 dose of liso-cel

- In TRANSCEND, patients were followed for 2 years after the last dose of liso-cel. As of the January 2021 data cut, study is ongoing; 268 patients had ≥ 24 months of follow-up, or died, or withdrew from the study
- Of 120 patients in the liso-cel—treated set who completed TRANSCEND, 81 consented to a separate long-term follow-up study of safety and OS for up to 15 years; however, no IRC response assessments were performed (NCT03435796)

1. Abramson JS, et al. *Lancet* 2020;396:839—852; 2. ClinicalTrials.gov identifier: NCT02631044.

Progression-free survival by IRC assessment per Lugano 2014 criteria[1,a]



- Median (95% CI) PFS was 6.8 months (3.3–12.7)
- Probability (95% CI) of PFS at 2 years was 40.6% (34.0%—47.2%)

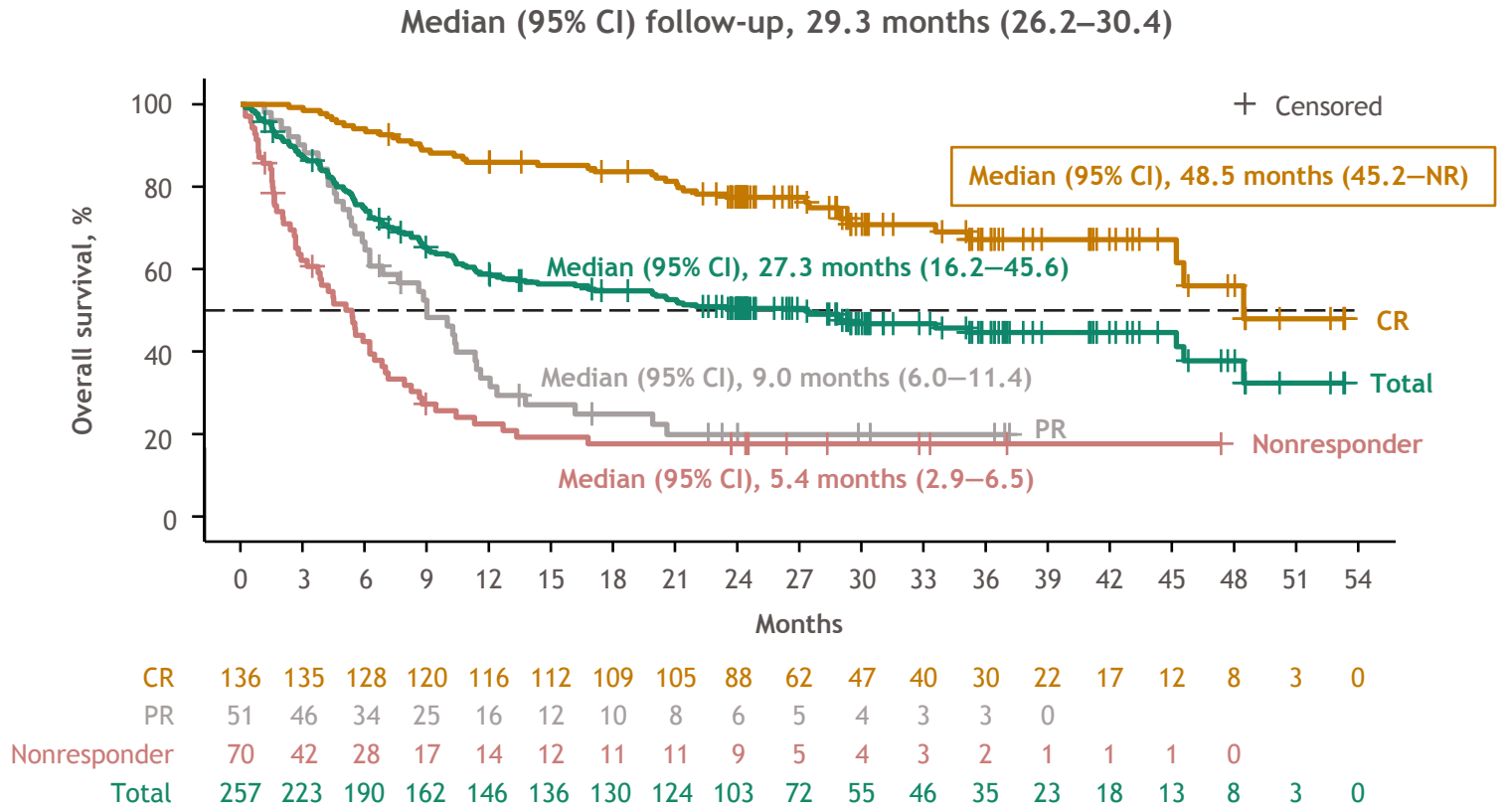
- At 27 months after liso-cel infusion, 1 patient (same as in the DOR curve at 26 months) died because of sepsis and had ongoing CR

[a]KM method was used to calculate median (95% CI) of PFS; reverse KM method was used to calculate median (95% CI) of follow -up. Only includes data from TRANSCEND.
PFS, progression-free survival.

1. Cheson BD, et al. *J Clin Oncol* 2014;32:3059—3068.

Abramson J, TCT, 2022

Overall survival[a]



- Median (95% CI) OS was 27.3 months (16.2–45.6)
- Probability (95% CI) of OS at 2 years was 50.5% (44.1%—56.5%)

- Three deaths occurred after 45 months
  - Two patients died because of unknown causes and had ongoing response
  - One patient died because of disease progression
- CAR T cell persistence was detected at 48 months in the LTFU study and in 37% (26 of 70 patients) of patients at 24 months in TRANSCEND

OS analysis incorporated survival data from the separate LTFU study (**NCT03435796**)

[a]KM method was used to calculate median (95% CI) of OS; reverse KM method was used to calculate median (95% CI) of follow -up. Includes survival data from patients who completed TRANSCEND and enrolled in the subsequent LTFU study.
LTFU, long-term follow-up.

Abramson J, TCT, 2022

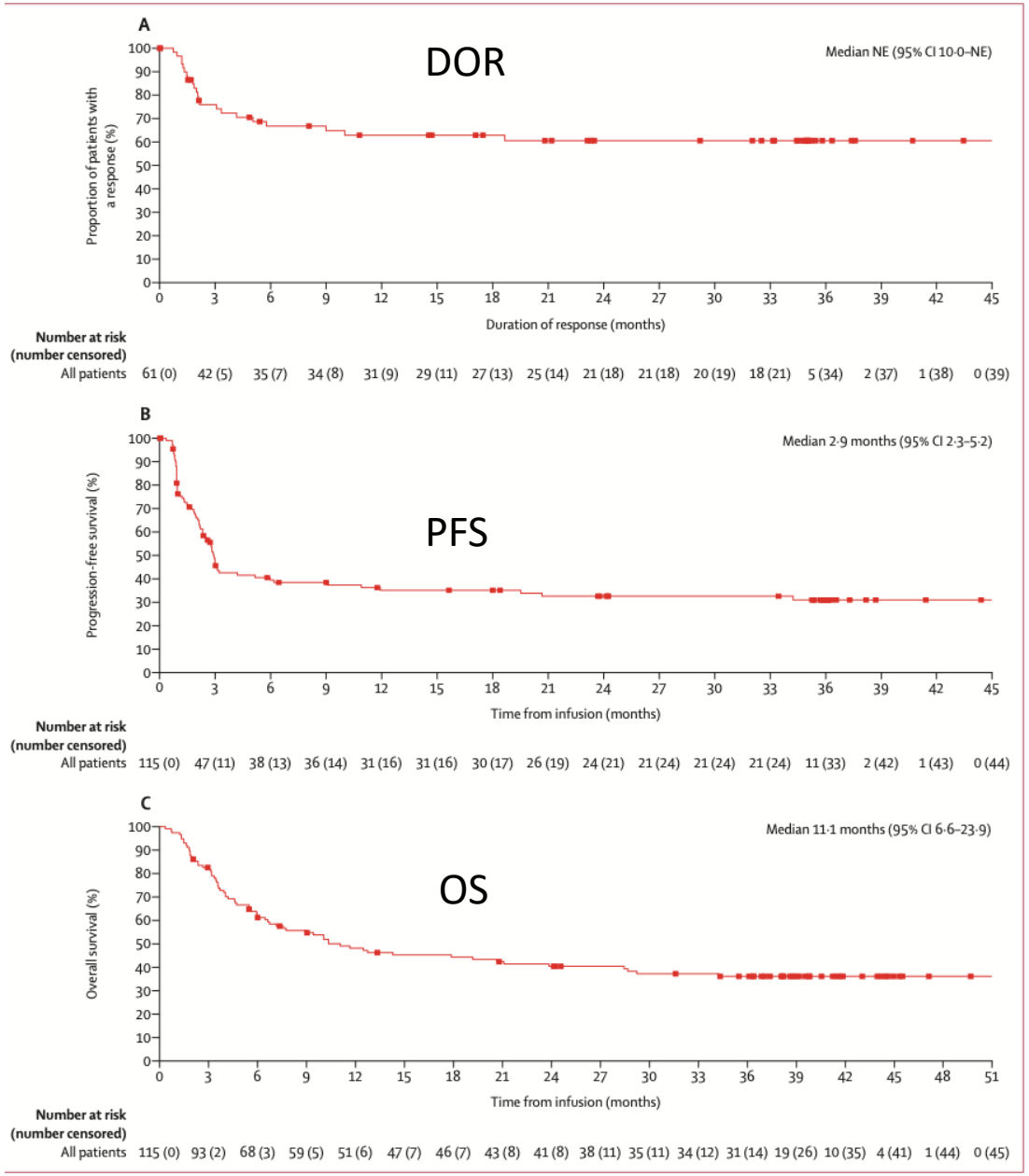
Tisagenlecleucel for Aggressive NHL: JULIET trial

Phase II trial, CD19 directed CAR-T

Enrolled = 167
Infused = 115

ORR = 53%
CR = 39%

CRS = 27%

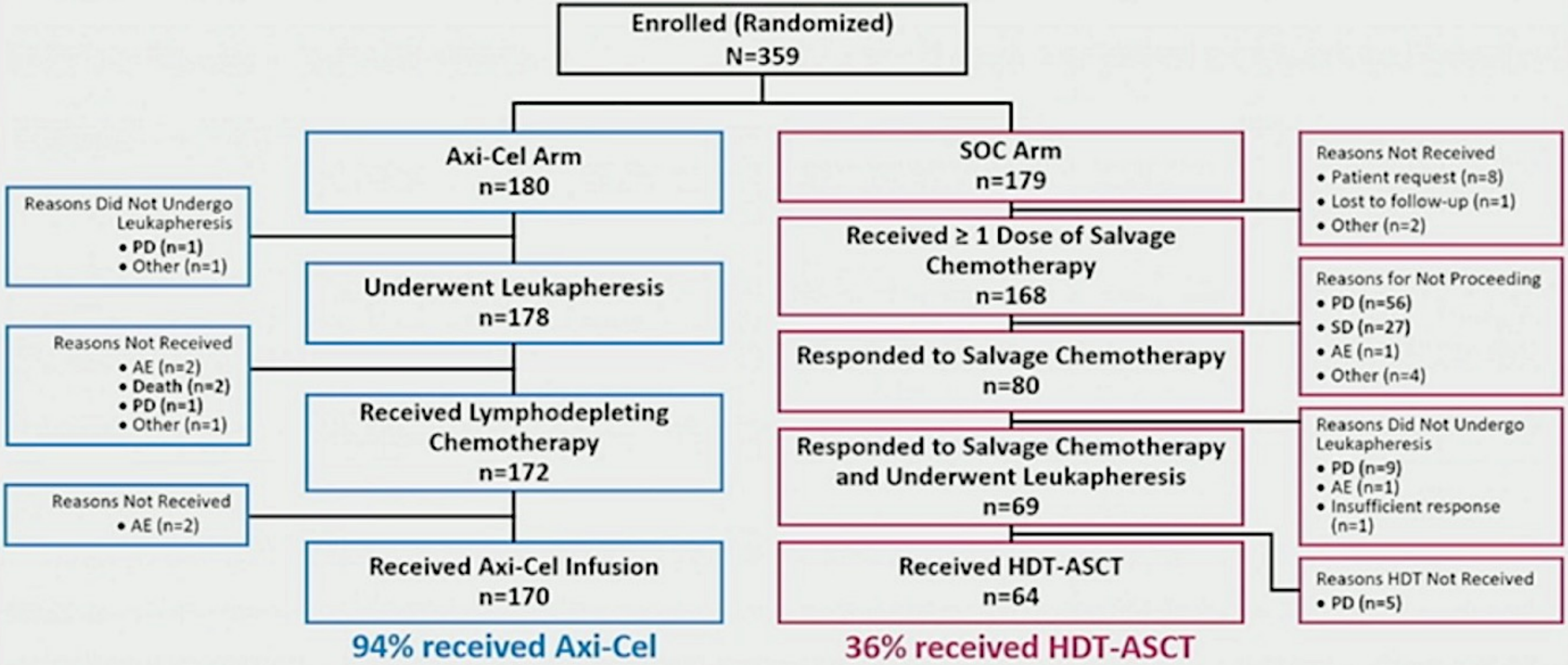


Schuster, SJ Lancet Oncology, 2021

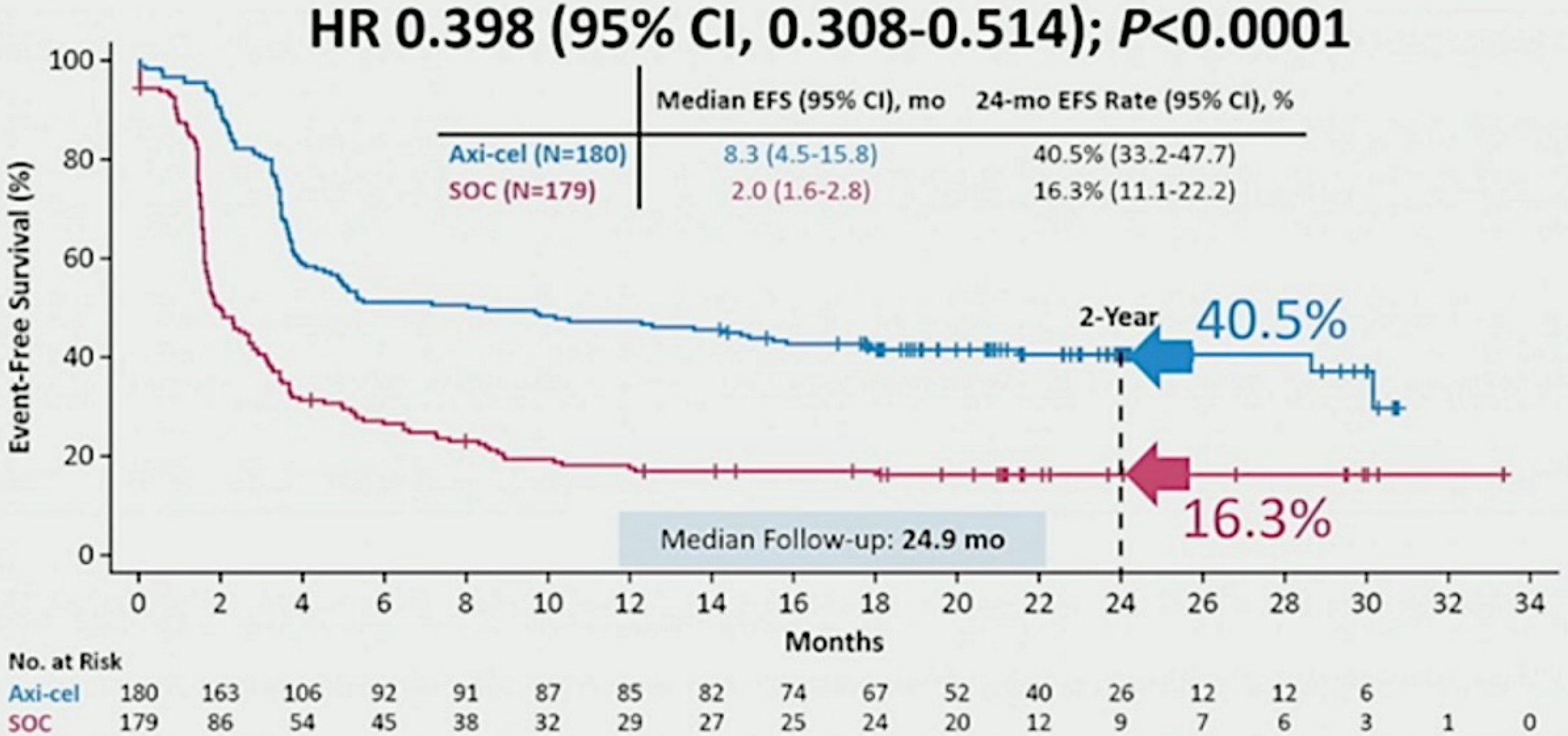
CD19 Directed CAR-T for Aggressive NHL in Second Line

- ZUMA-7
  - Axi-cel vs SOC for transplant eligible, early relapse
- TRANSFORM
  - Liso-cel vs SOC for transplant eligible, early relapse
- PILOT
  - Liso-cel for transplant ineligible patients

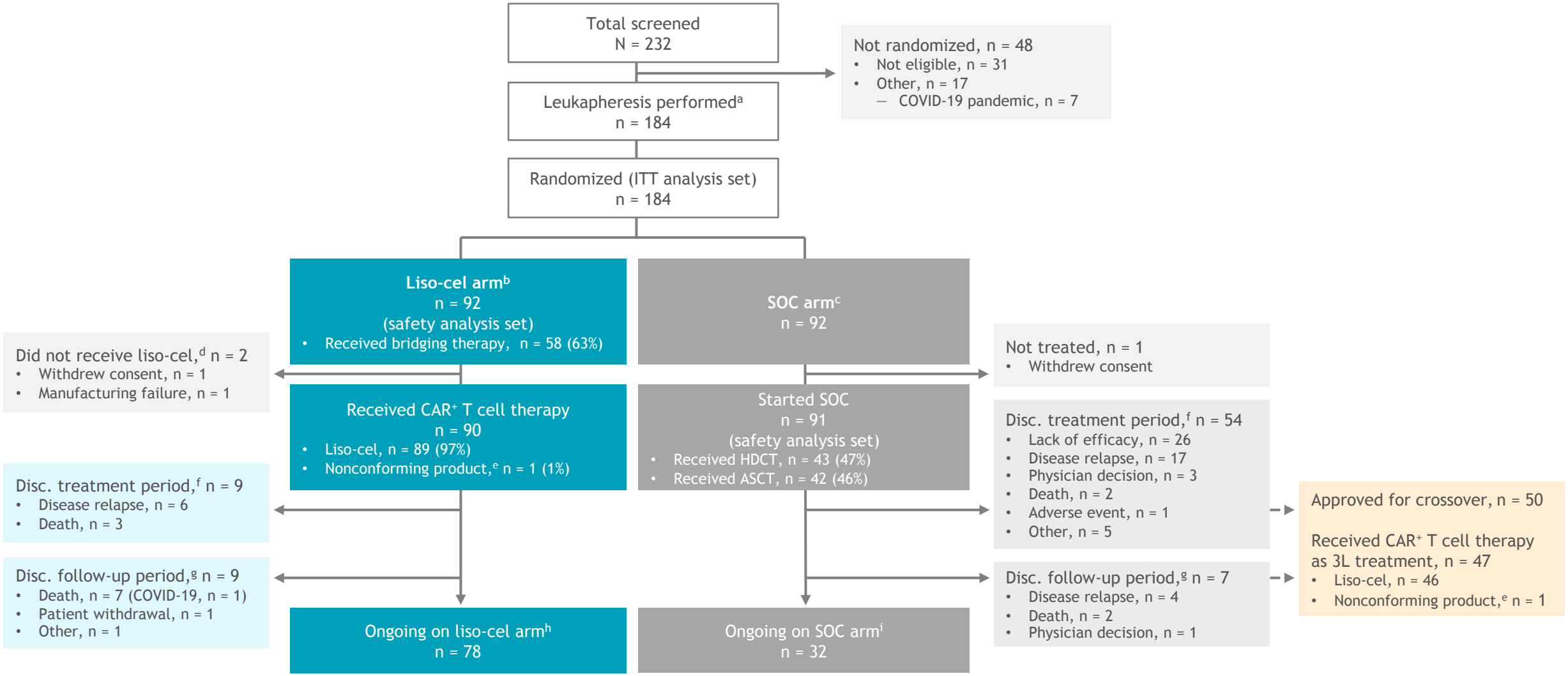
Patient Disposition: Nearly 3× as Many Axi-Cel Patients Received Definitive Therapy Versus SOC Patients



Primary EFS Endpoint: Axi-Cel Is Superior to SOC



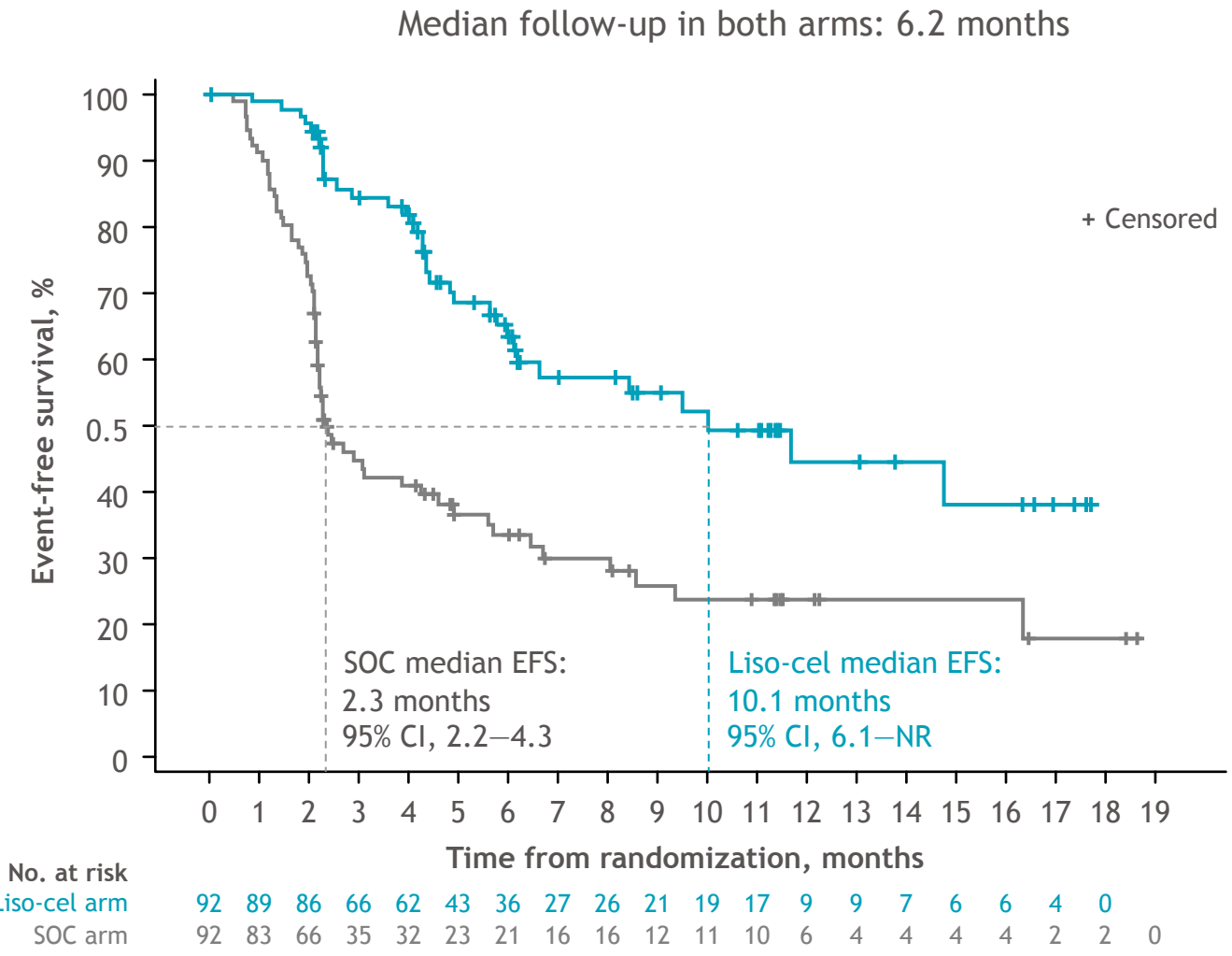
TRANSFORM: CONSORT diagram



[a]During screening, patients were assessed for eligibility, underwent unstimulated leukapheresis, and subsequent randomization; [b]Patients received LDC followed by liso-cel infusion; bridging therapy was allowed per protocol; [c]Patients received 3 cycles of SOC salvage CT (see Methods for details) followed by HDCT and ASCT; [d]Patients received bridging therapies and, therefore, were included in the safety analysis set; [e]Nonconforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet release criteria for liso-cel but was considered safe for infusion; [f]Patients could discontinue the treatment period, defined as the period from randomization to Week 18, but continue to be followed up for OS; [g]Patients could discontinue the follow-up period, defined as the period from Week 18 to Month 36, but continue to be followed up for OS; [h]Six patients who discontinued the treatment period remained in the study follow-up period; [i]One patient who discontinued the treatment period remained in the study follow-up period.
Disc., discontinued.

Kamdar M, et al. ASH 2021 [Abstract #91]

TRANSFORM: Event-free survival per IRC (ITT set; primary endpoint)



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	**0.349** (0.229—0.530)	
	***P* < 0.0001**	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0—74.7	23.0—43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4—59.6	13.4—34.1

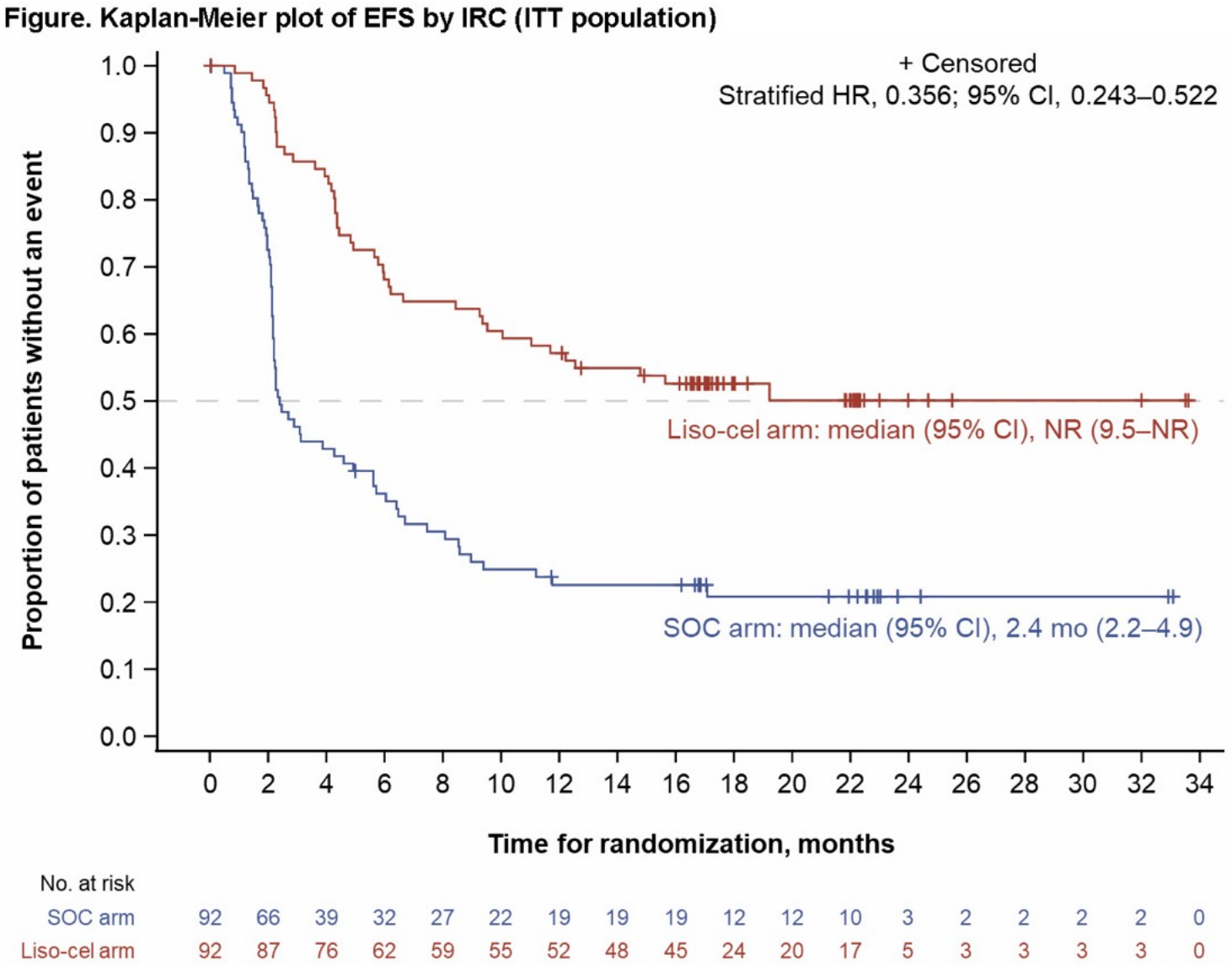
One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.
CI, confidence interval; HR, hazard ratio; NR, not reached; SE, standard error.

Kamdar M, et al. ASH 2021 [Abstract #91]

TRANSFORM: Event-free survival per IRC –ASH update

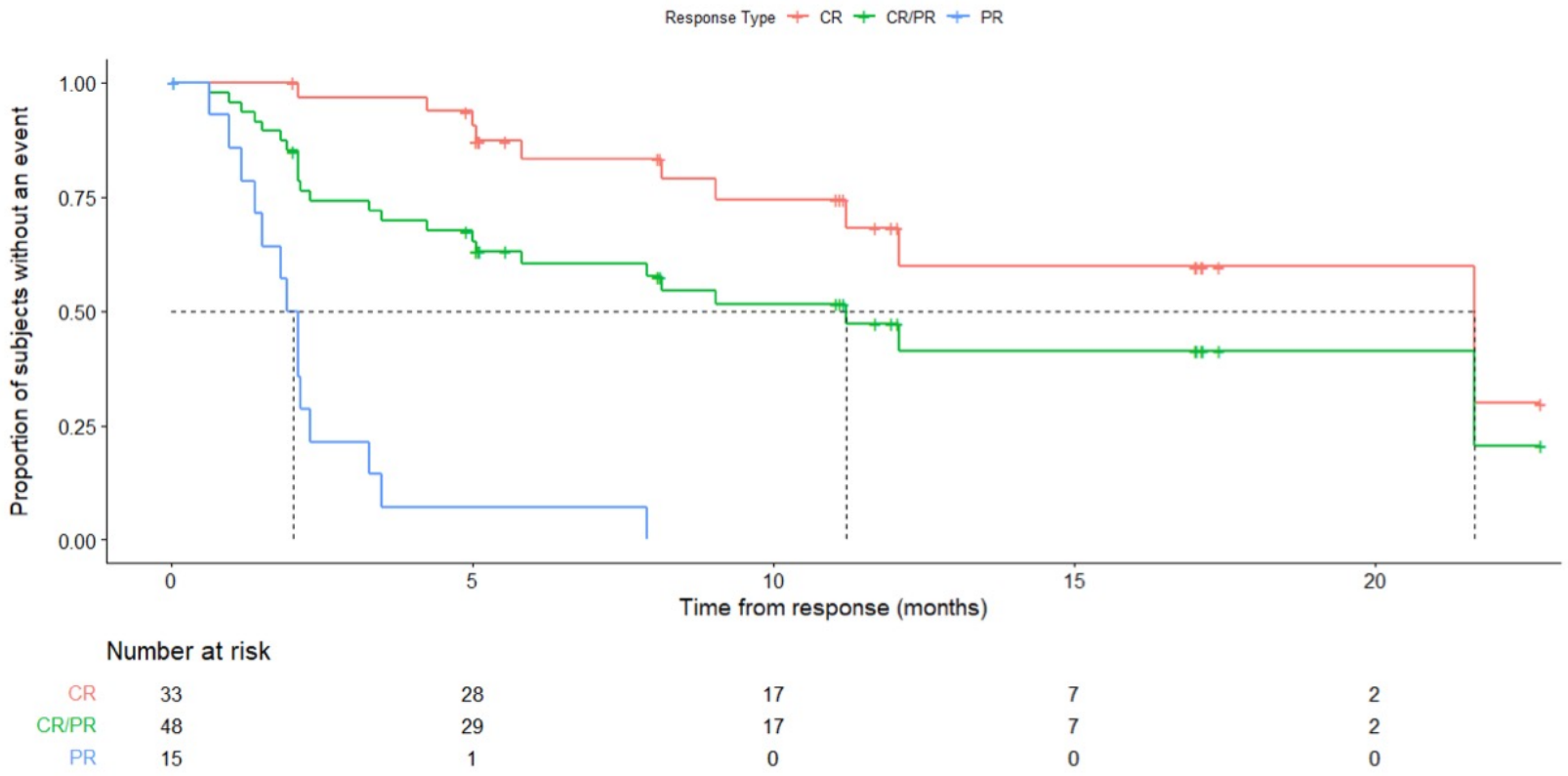
- Primary analysis at 17.5 mo
- N=184 randomized
  - 92 Liso-cel
  - 92 SOC
- Liso-cel CR= 74%
- SOC CR = 43%



Abramson, JS ASH 2022 #655

PILOT: Liso-cel for transplant ineligible aggressive NHL in Second line

- N= 61 treated, 74 apheresis
  - —Age = 74 years
  - —ECOG 2 = 26%
  - —Refractory = 54%
  - —Rel < 1 year = 21%
- ORR = 80%,
- CR = 54%
- CRS = 38%, 1 pt grade 3
- ICANS = 31%, 3 pt grade 3



(Source: FDA statistical reviewer's analysis)

ASCO 2022 #7062, FDA approval

Moving CAR T cell therapy to the first line?

ZUMA-12: a phase 2, multicenter, open-label, single-arm study of axi-cel as part of first-line treatment in patients with high-risk LBCL

Eligibility criteria

- Age ≥ 18 years
- High-risk LBCL
  - HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations, or
  - LBCL with IPI score ≥ 3 any time before enrollment
- 2 cycles of anti-CD20 plus anthracycline-containing regimen
- Positive interim PET (DS 4 or 5)
- ECOG PS score 0 or 1

Enrollment/leukapheresis → Optional nonchemotherapy bridging therapy[a] →

Conditioning chemotherapy + axi-cel infusion

- Conditioning
  - Flu 30 mg/m^2 i.v. and Cy 500 mg/m^2 i.v. on Days −5, −4, and −3
- Axi-cel
  - Single i.v. infusion of 2 × 10^6 CAR T cells/kg on Day 0

Primary endpoint

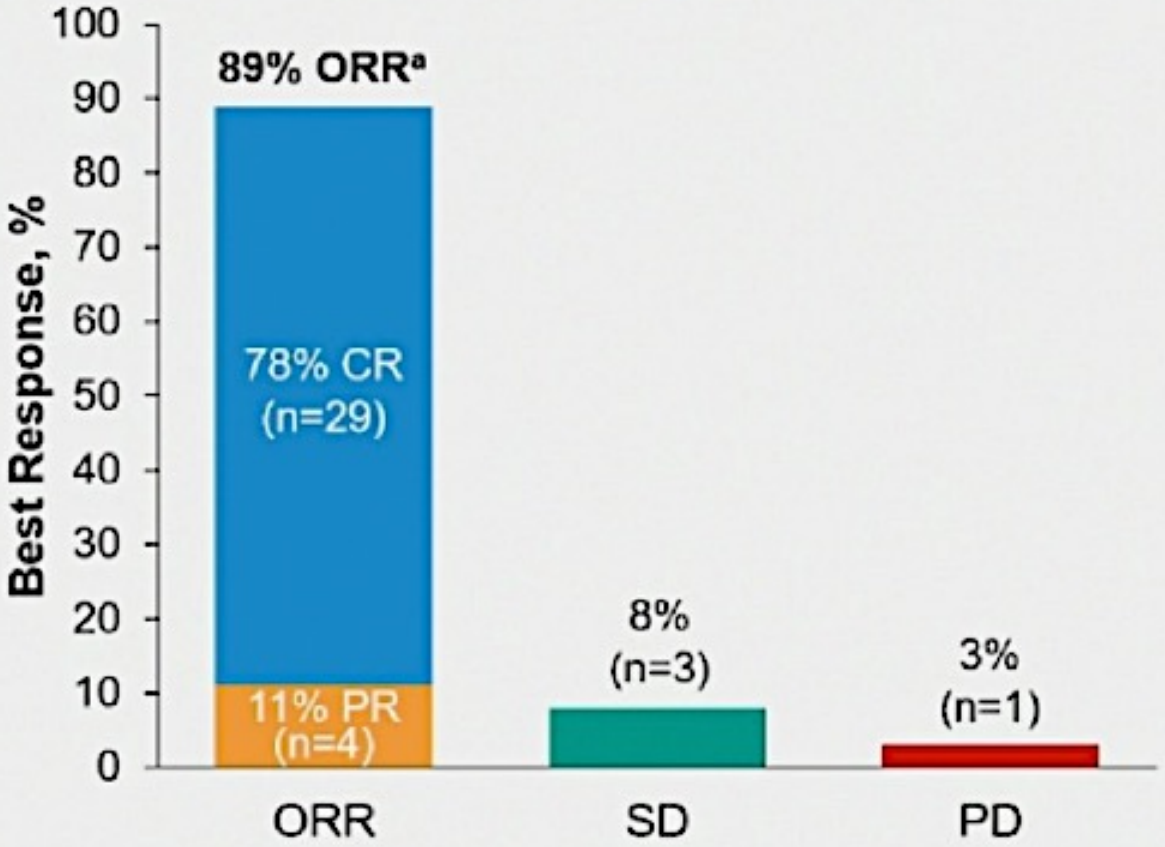
- CR[b]

Key secondary endpoints

- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum

[a] Administered after leukapheresis and completed prior to initiating condition chemotherapy; PET-CT was required after bridging.
[b] Per 2014 Lugano criteria.
DS, Deauville score; IPI, International Prognostic Index; i.v., intravenous.
Neelapu SS, et al. Interim analysis of ZUMA-12: A phase 2 study of axicabtagene ciloleucel (axi-cel) as first-line therapy in patients (Pts) with high-risk large B cell lymphoma (LBCL). Oral presentation at ASH 2020;abstract 405.

ORR Was 89% (95% CI, 75–97) and CR Rate Was 78% (95% CI, 62–90) Among Efficacy-Evaluable Patients

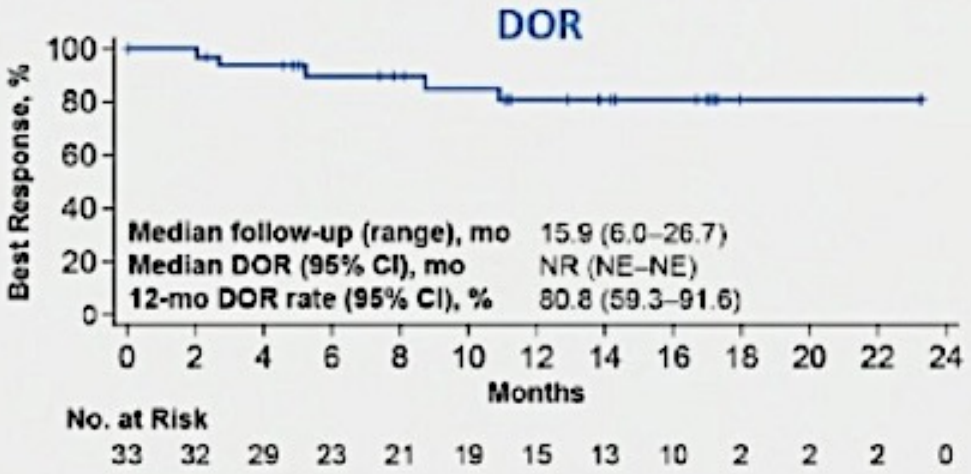


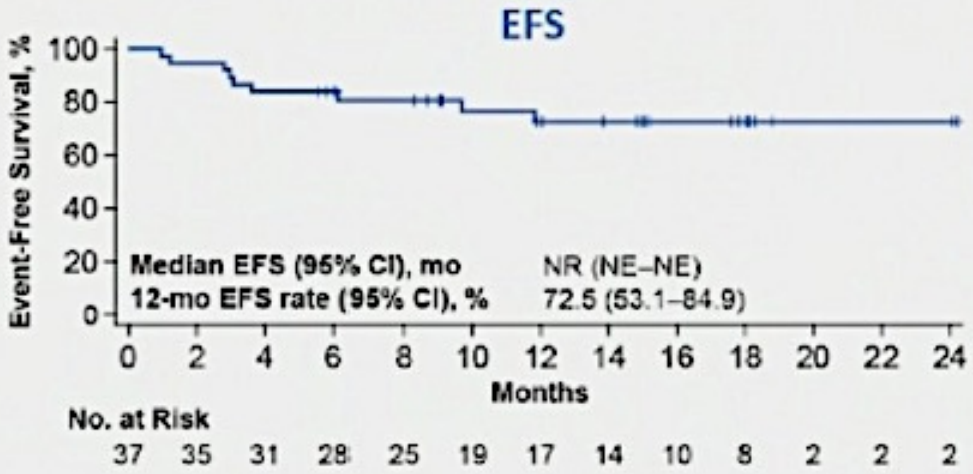
	Efficacy Evaluable N=37[b]
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
Initial CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%)[c]	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

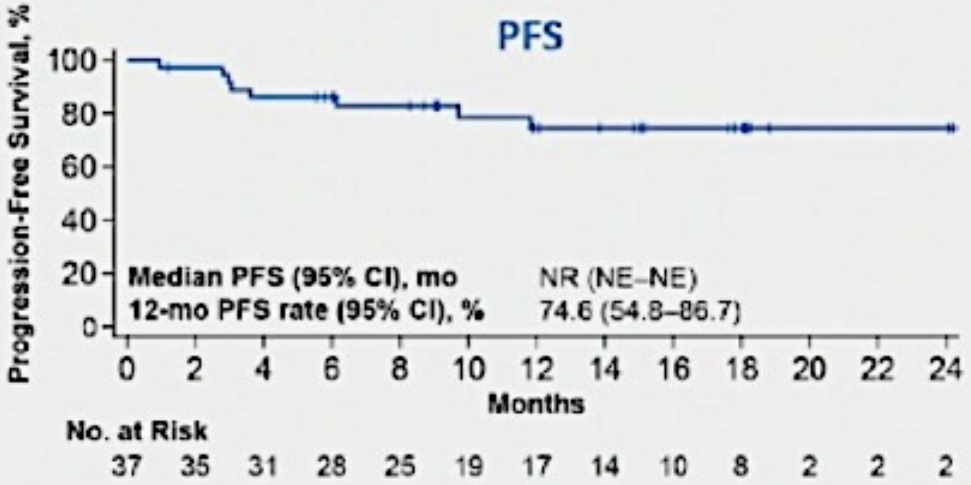
- Among all treated patients (N=40), ORR was 90% (95% CI, 76–97); CR rate was 80% (95% CI, 64–91)

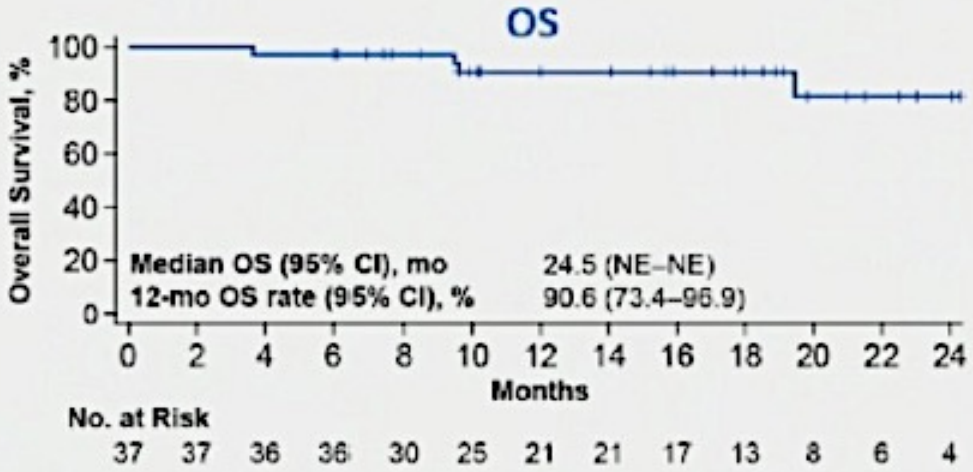
[a] Response assessments are based on best overall response. [b] Includes all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.
[c] All 7 patients converted to a CR by Month 6 postinfusion.
CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response, Event-Free Survival, Progression-Free Survival, and Overall Survival[a]







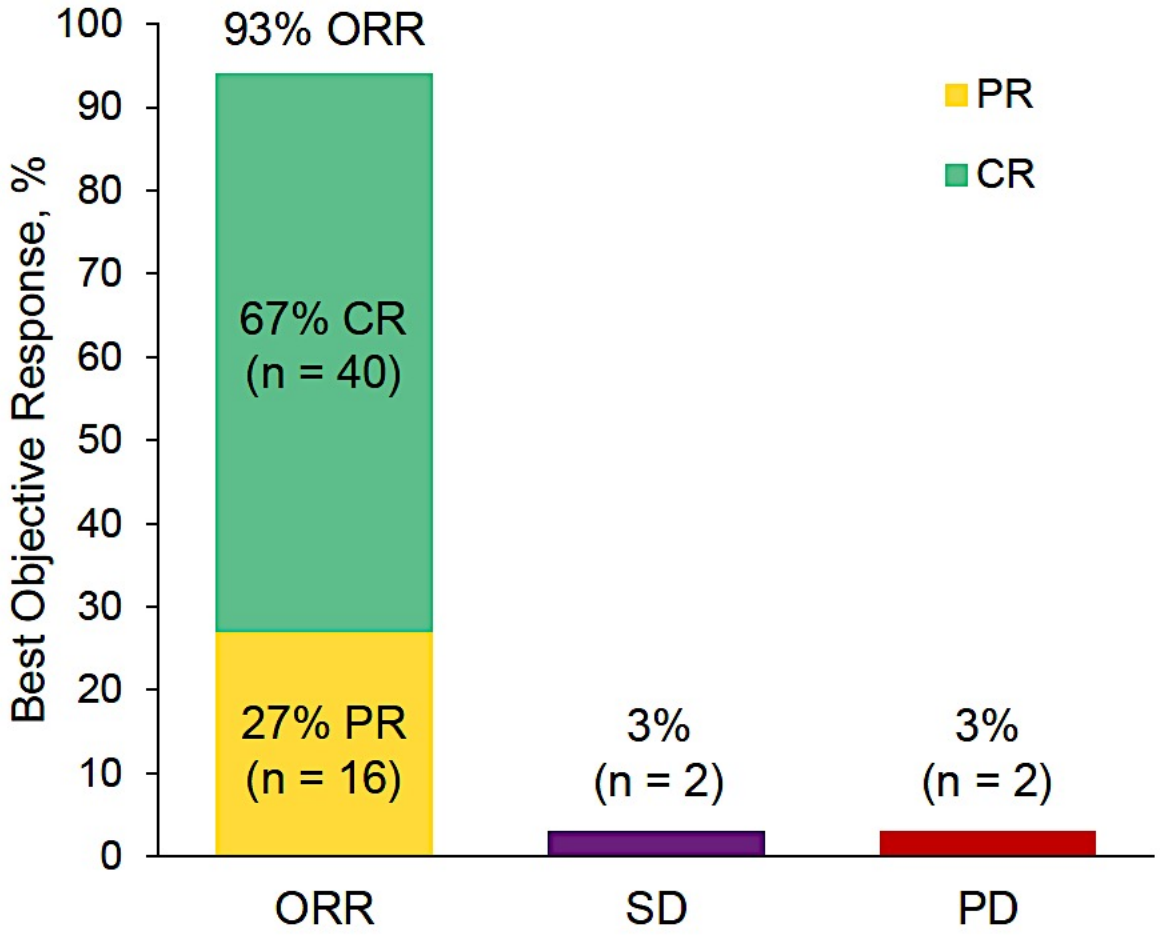


[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.
DOR, duration of response; EFS, event-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

CD19 CAR-T cells for Mantle cell and Indolent NHL

- Brexucabtagene autoleucel for Mantle cell Lymphoma
- Tisagenlecleucel for Follicular Lymphoma
- Axi-cel for Follicular Lymphoma and Marginal zone lymphoma

ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)

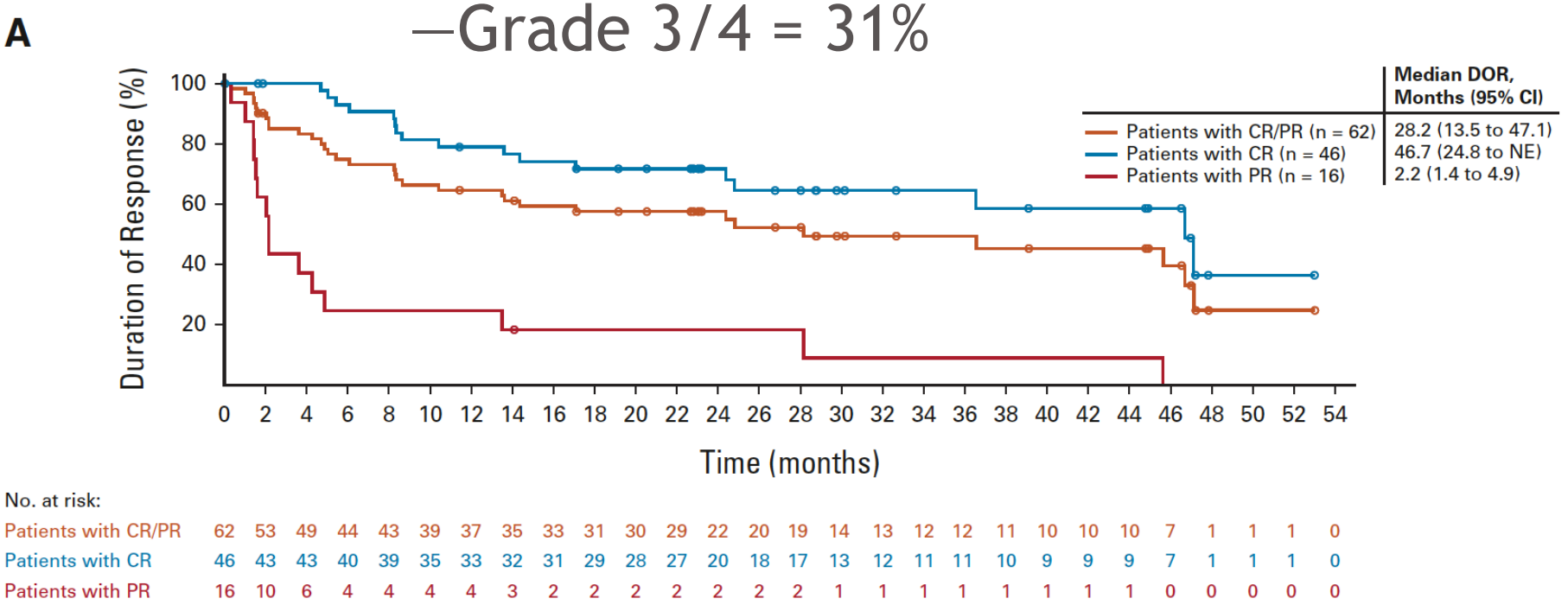


	Efficacy-Evaluable N = 60
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

Investigator-assessed ORR in N = 60 was 88% (CR rate 70%), with 95% and 90% concordance between IRRC- and investigator-assessed ORR and CR rate, respectively. IRRC-assessed ORR in ITT (N = 74) was 85% (CR Rate 59%).
CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

ZUMA-2: Brexu-cel CD-19 Directed CAR-T cell therapy for Mantle Cell NHL - 3 year update

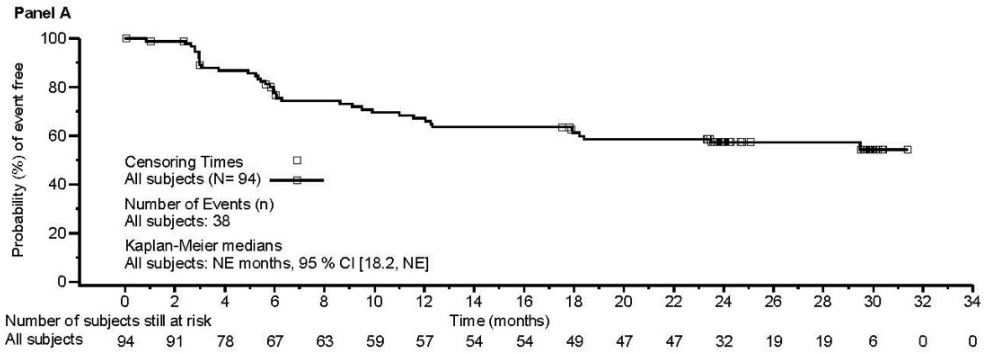
- N= 68 infused
- ORR = 91%
  - —CR = 68%
- DOR = 28.2 mo
- PFS = 25.8 mo
- OS = 46.6 mo
- BTKi exposed
  - —Similar outcome
- CRS = 91%
  - —Grade 3/4 = 15%
- ICANS = 63%
  - —Grade 3/4 = 31%

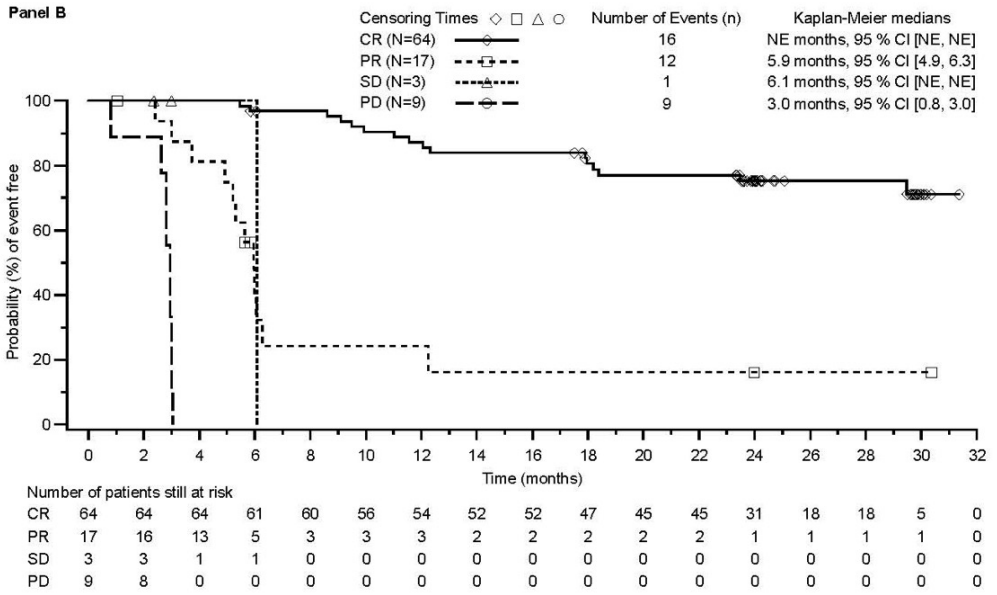


Wang M, JCO 2022

ELARA: Tisagenlecleucel for Follicular NHL- ASH 2022 update

- N= 94 (evaluable) with relapsed/ref FL
- ORR = 86.2%
- CR = 68%
- CRS = 48.5%
  - —Grade 3/4 = 0%
- NT = 37.1%
  - —Grade 3/4 = 3%
- Median f/u 28.9 mo
- 24% received subsequent Rx

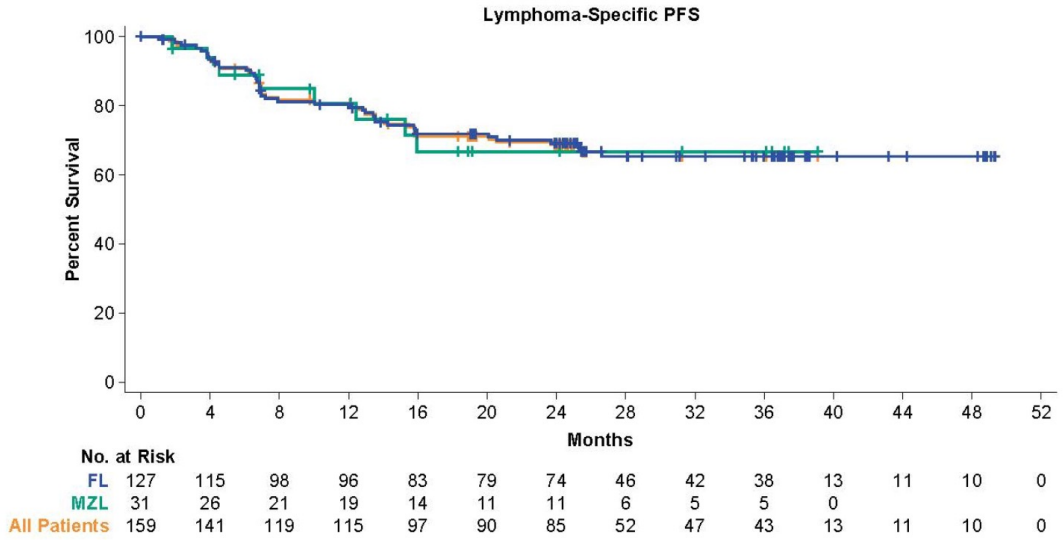


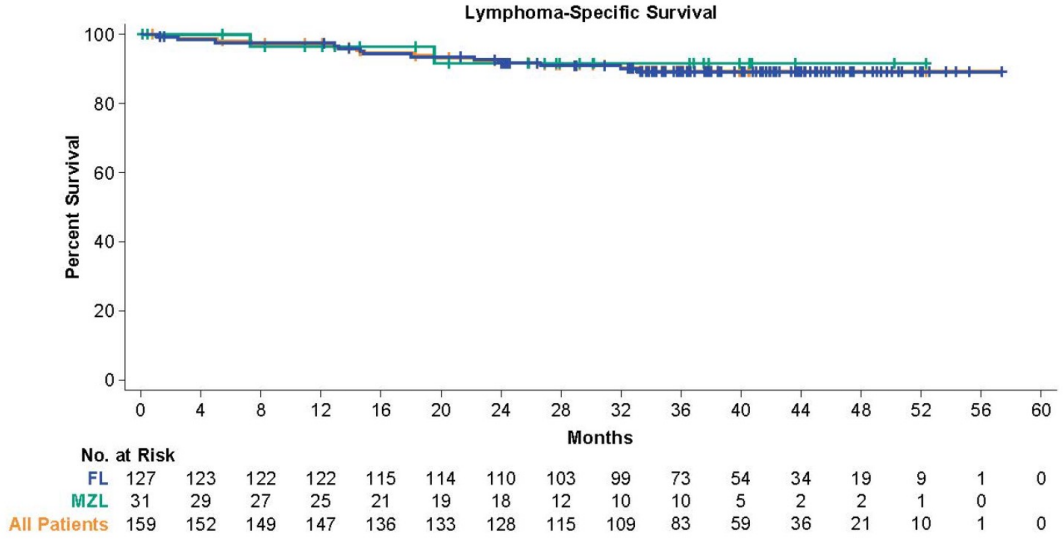


Dreyling M ASH 2022 #608, Fowler NH Nat Med 2022

ZUMA-5: Axi-cel CAR-T cell therapy for Follicular NHL and MZL- ASH 2022 3-year update

- N= 159 enrolled, 152 treated
- Follicular NHL = 124
- Marginal zone NHL 28
- Flu/Cy lymphodepletion and 2 x 10^6 CAR-T cells/kg
- ORR
  - FL = 94%, MZL = 83%
- CR
  - FL = 79%, MZL = 65%
- CRS ≥ grade 3 = 10 (7%)
- NT ≥ grade 3 = 28 (19%)



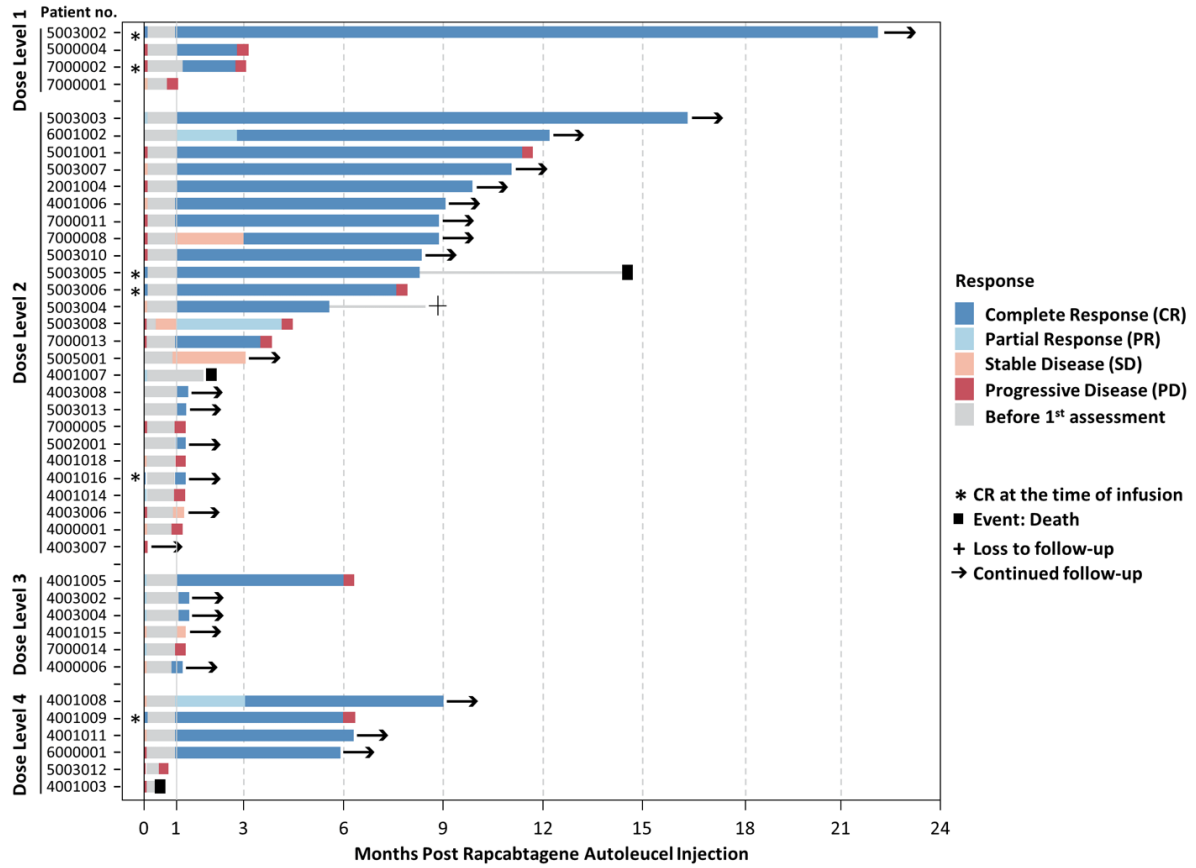


Neelapu SS ASH 2022 # 4660, Jacobson CA Lancet Onc 2022

YTB323 (Rapcabtagene Autoleucel) CD-19 Directed CAR-T cell therapy for Large B cell NHL

- Rapid 2 day manufacturing preserving T cell “stemness”
- Phase 1 study
- Dose level 2 (**12.5 x 10^6**) chosen as recommended Ph 3 dose
- N=28 treated at DL 2
  - —CR = 65%
  - —ICANS in 3 pts
  - —CRS in 10 pts, onset median d9

Figure 1. Response durability following rapcabtagene autoleucel injection.



Conclusions and Future Directions

- Approval of 4 CD19 CAR-T cell products for Aggressive NHL, FL and MCL
- Treatments appear to lead to long lasting remissions especially for patients with Complete Remissions
- Second line randomized trials for aggressive large B cell lymphoma superior to SOC/autologous HCT
- CAR-T now FDA approved in second line for transplant eligible (relapse < 1 year, axi-cel and liso-cel) and transplant ineligible patients (liso-cel).
- Product selection needs to consider **efficacy**, **safety**, as well as **production reliability** and **cost**
- Exciting new constructs and combinations being evaluated

Immunotherapy is changing the way cancer is treated!

BEZOS FAMILY IMMUNOTHERAPY CLINIC

Photograph courtesy of Ron hood, Fred Hutch

Fred Hutchinson Cancer Center

Module 5: Mantle Cell Lymphoma (MCL) — Dr Kahl

Case Presentation: 78-year-old man with high-risk relapsed MCL s/p BR and maintenance rituximab x 3 years

Dr Raman Sood (Dunkirk, New York)

RTP RESEARCH TO PRACTICE

Case Presentation: 85-year-old man with prior treatment for prostate cancer who presents with low-volume indolent MCL with a TP53 mutation

Dr Spencer Bachow (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

Mantle Cell Lymphoma - What did we learn in 2022?

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 2022

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

RELAPSED/REFRACTORY

- BTK inhibitors
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
- Lenalidomide-Rituximab (R2)
- Brexucabtagene Autoleucel (brexu-cel)

New in 2022 (Frontline Management)

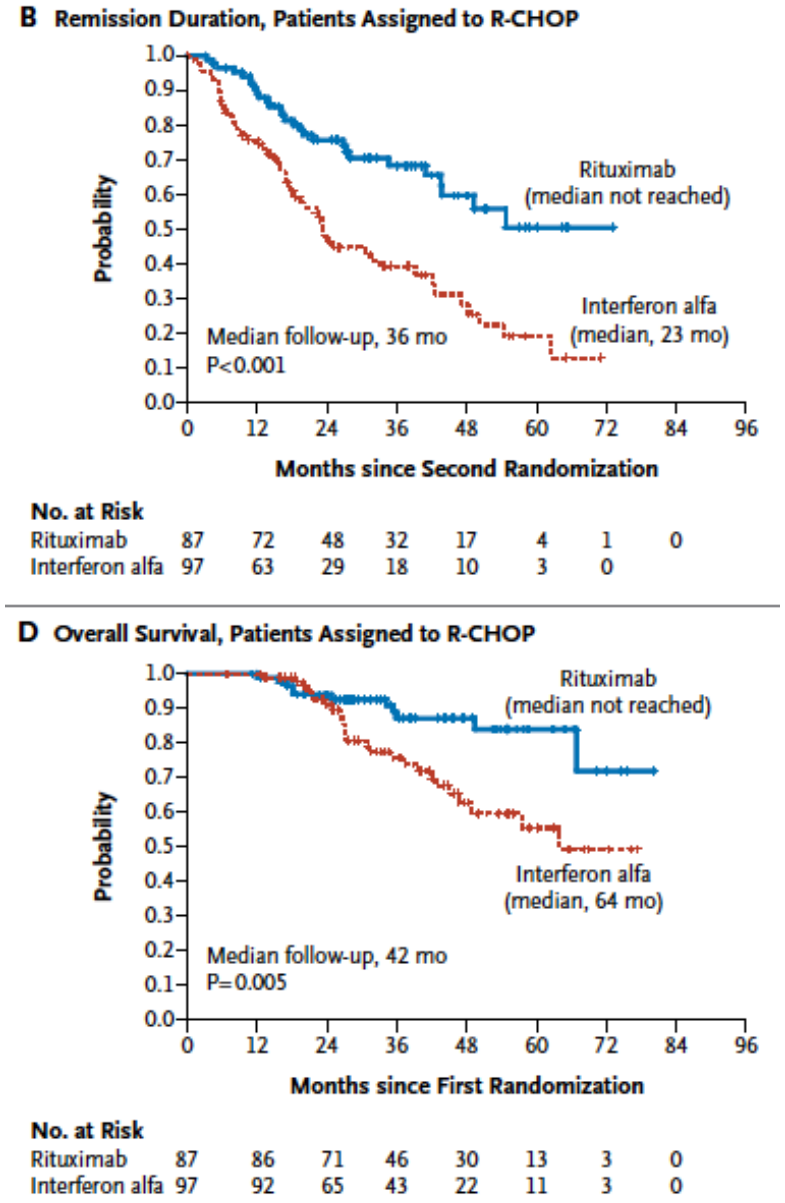
1. Solid evidence supporting MR after BR
   - Flatiron Database analysis (Martin et al, JCO 2022)

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)

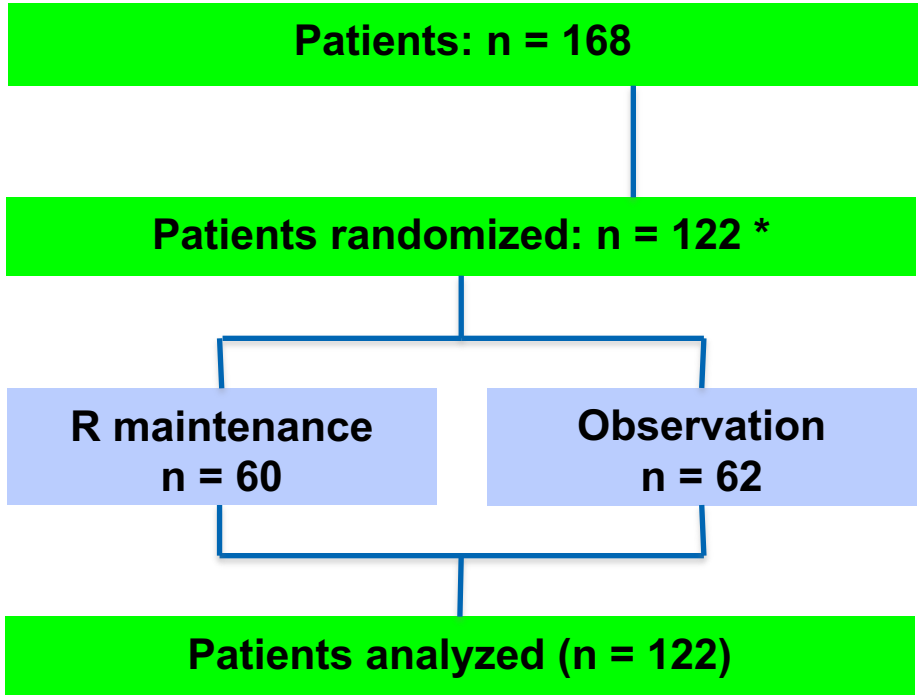
Maintenance Rituximab

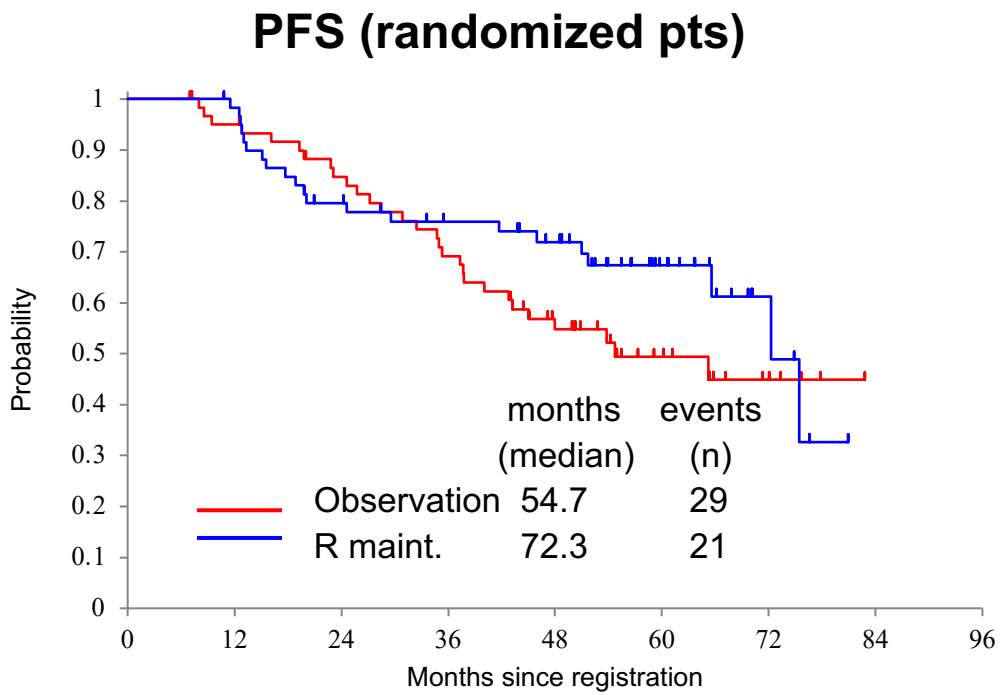
- European MCL Network Study
- N = 532. Median age 70.
- R-CHOP > FCR as induction strategy
- Responding patients randomized to interferon alfa vs. MR given indefinitely
- MR not beneficial after FCR
- What about after BR???



Kluin-Nelemans et al, NEJM, 2012

How about MR after bendamustine-rituximab?



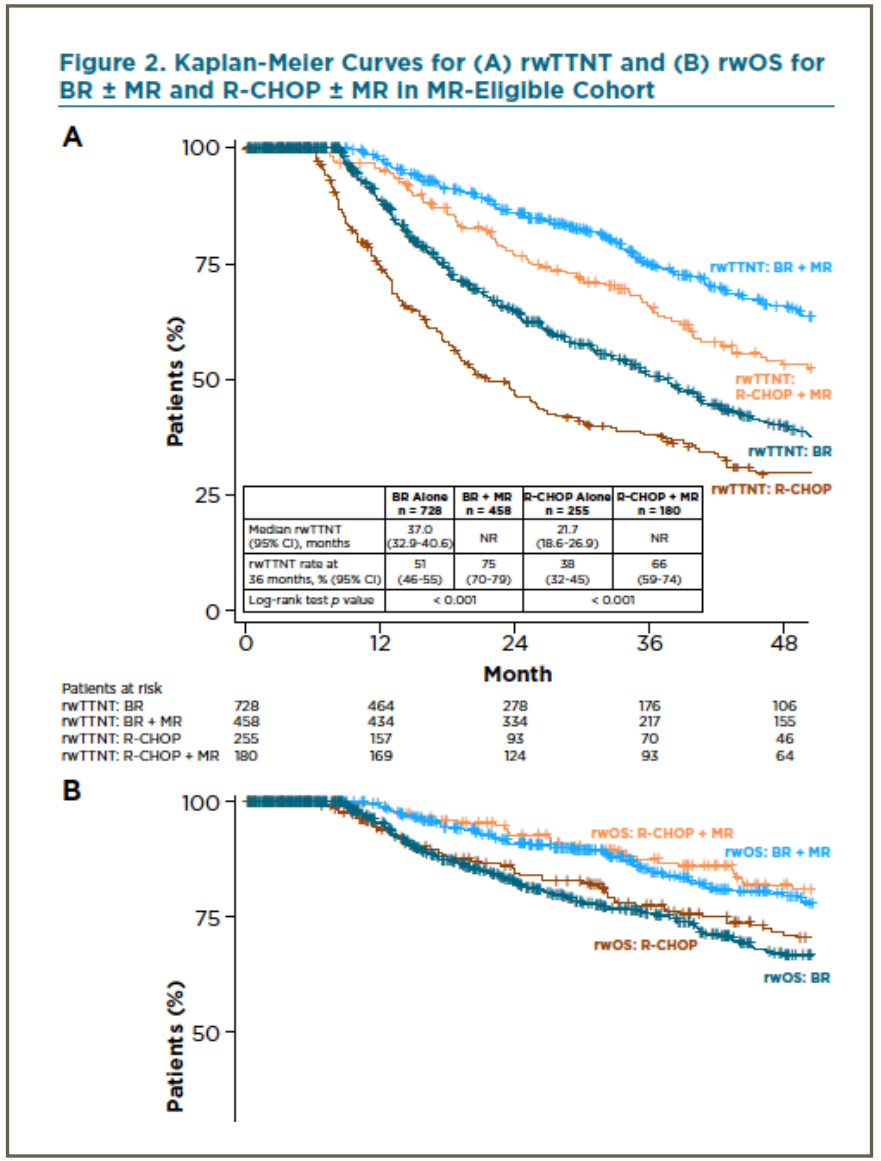


Rummel et al, ASCO 2016

Flatiron Database

- “Real world” analysis of 1621 patients
- Show large benefit for MR
  - TTNT
  - OS
  - After both R-CHOP and BR

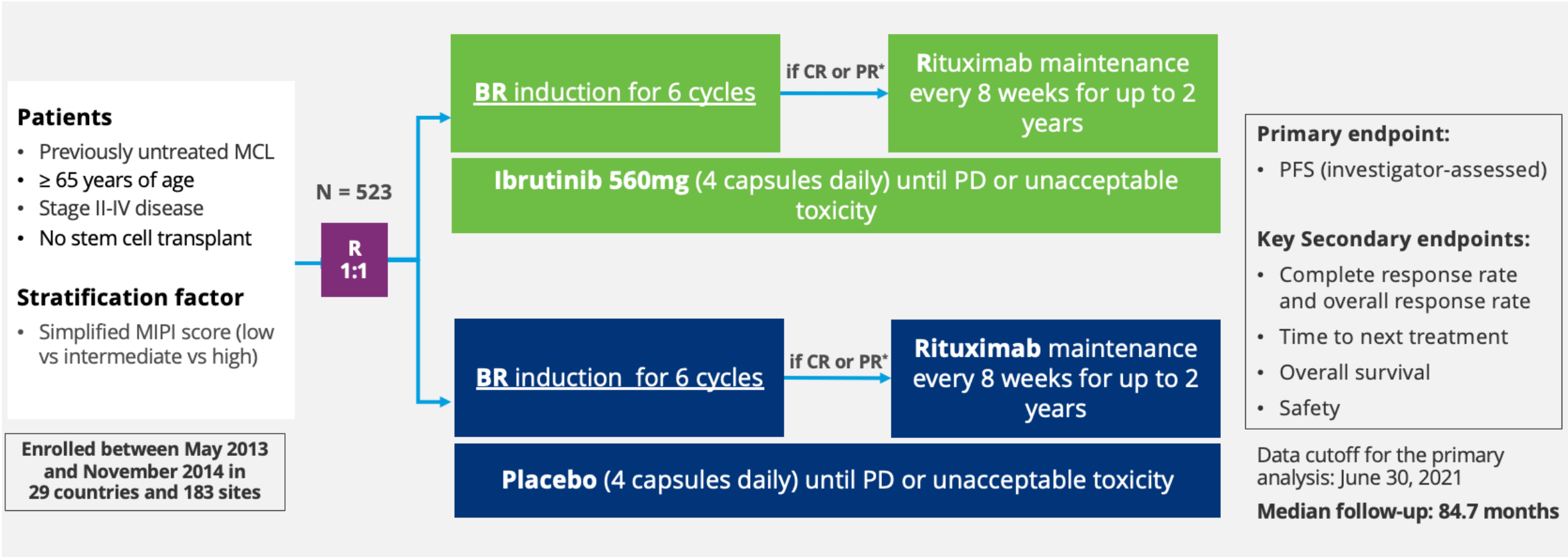
Martin et al, JCO 2022



Thoughts on Maintenance Rituximab

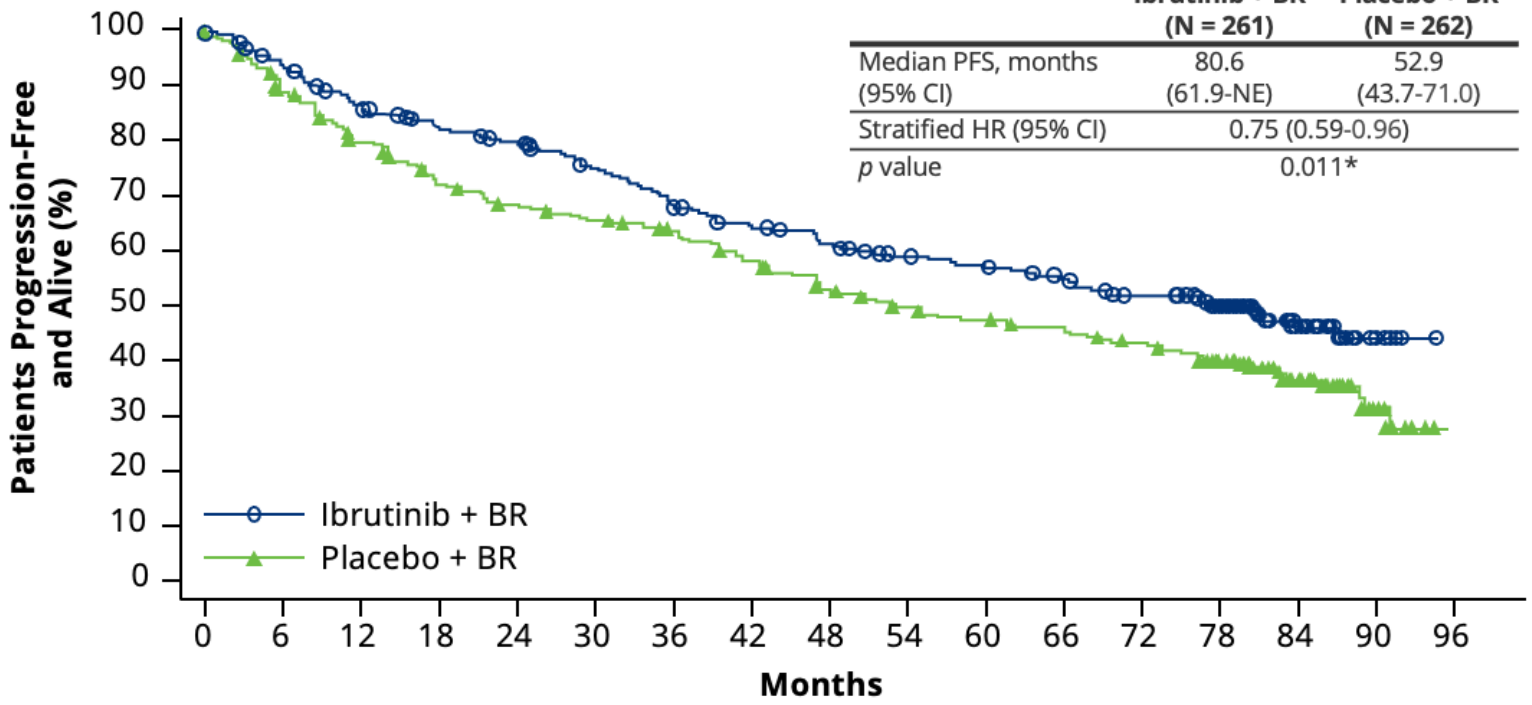
- Preponderance of data suggests major benefit in MCL
- Actually impacts OS, not just PFS (as in follicular lymphoma)
- Still unclear regarding “optimal duration”
  - 2 yrs vs. 3 yrs vs. 5 yrs vs. indefinite?
- COVID 19 Pandemic has created new challenges
  - Prolonged B cell depletion leads to worse infections and 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*	

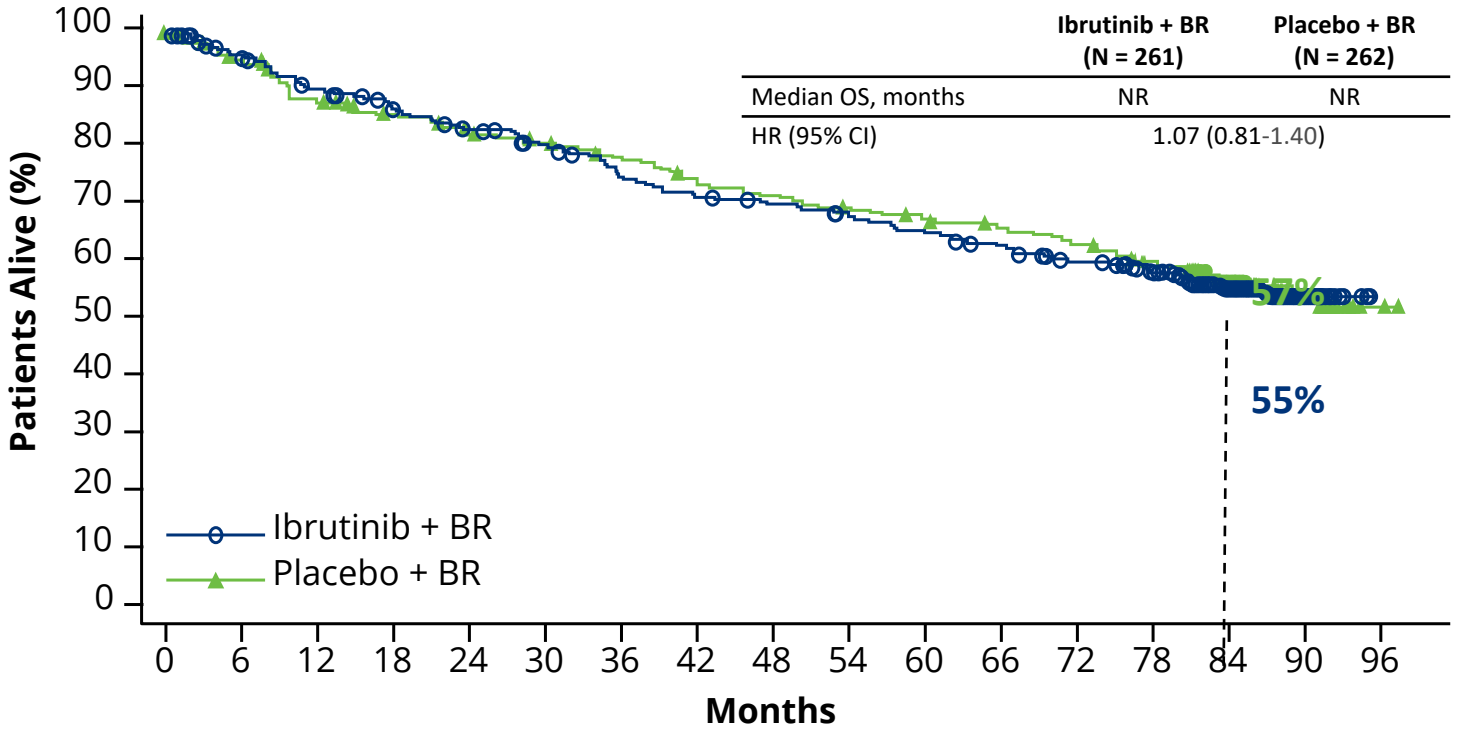
Patients at Risk

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 month (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: My thoughts

- Pro's for adding ibrutinib
  - No question adding ibrutinib 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

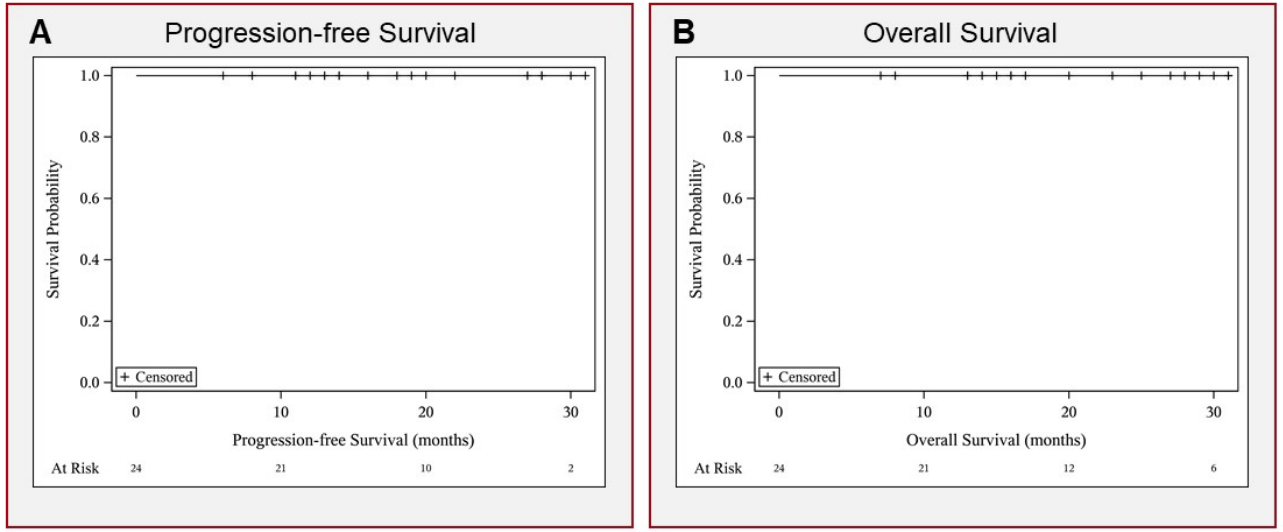
- I will discuss with patients but do not see myself recommending it

MCL Treatment: The Horizon for Older MCL

1. SHINE trial: BR ± ibrutinib until PD
2. ECHO: BR ± acalabrutinib until PD
3. E1411: BR ± bortezomib. R maintenance ± lenalidomide
4. MANGROVE: Zanubrutinib-R vs. BR
5. ENRICH: Ibrutinib-R vs. BR/R-CHOP

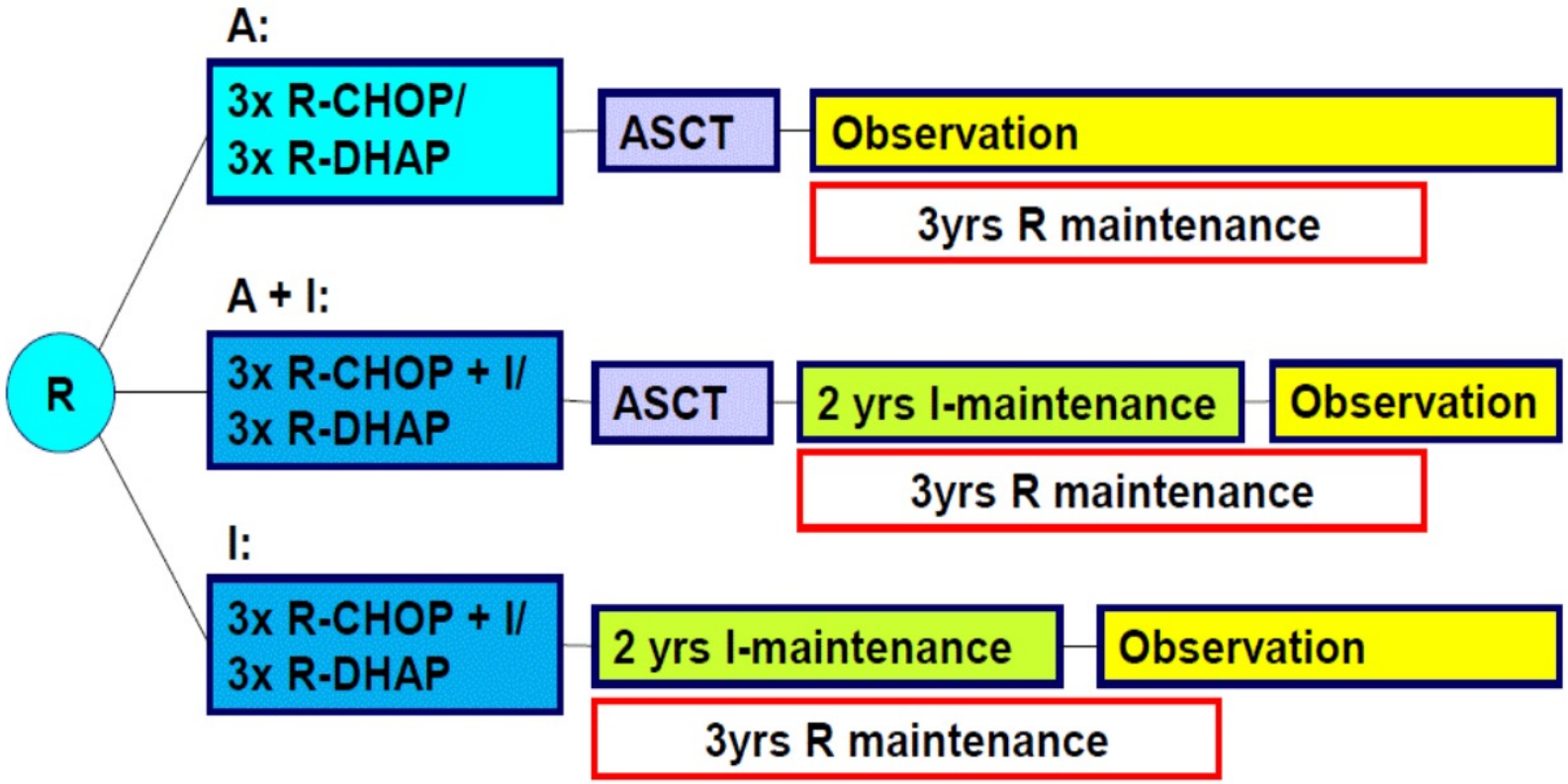
R2 plus Acalabrutinib for Untreated MCL. Ruan et al. #73

- N = 24. Median age 64.
- MIPI low/int/high = 37/42/21%
- P53 mutations in 7 patients
- <u>RESULTS</u>
  - ORR 100%. CR 90%.
  - MRD negative at 12 months in 71%
  - No unexpected toxicities
  - Rash 42%

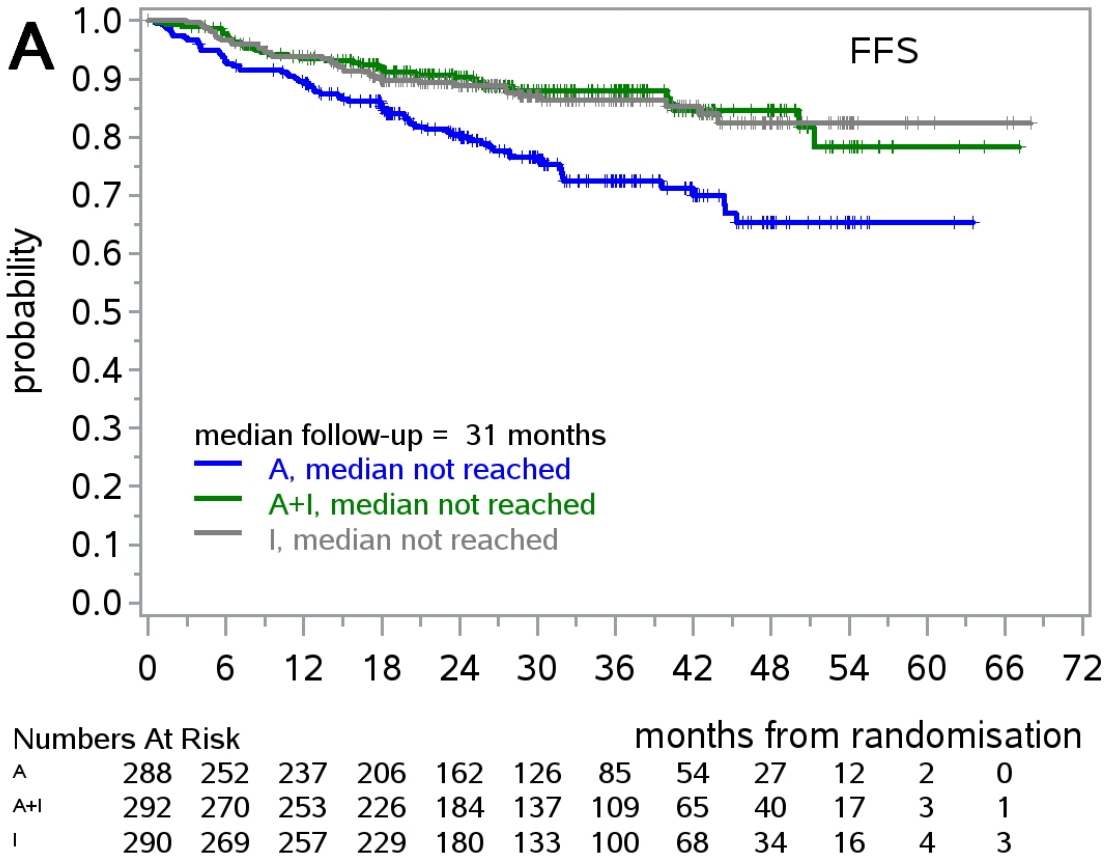


TRIANGLE Trial (European MCL Network)

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

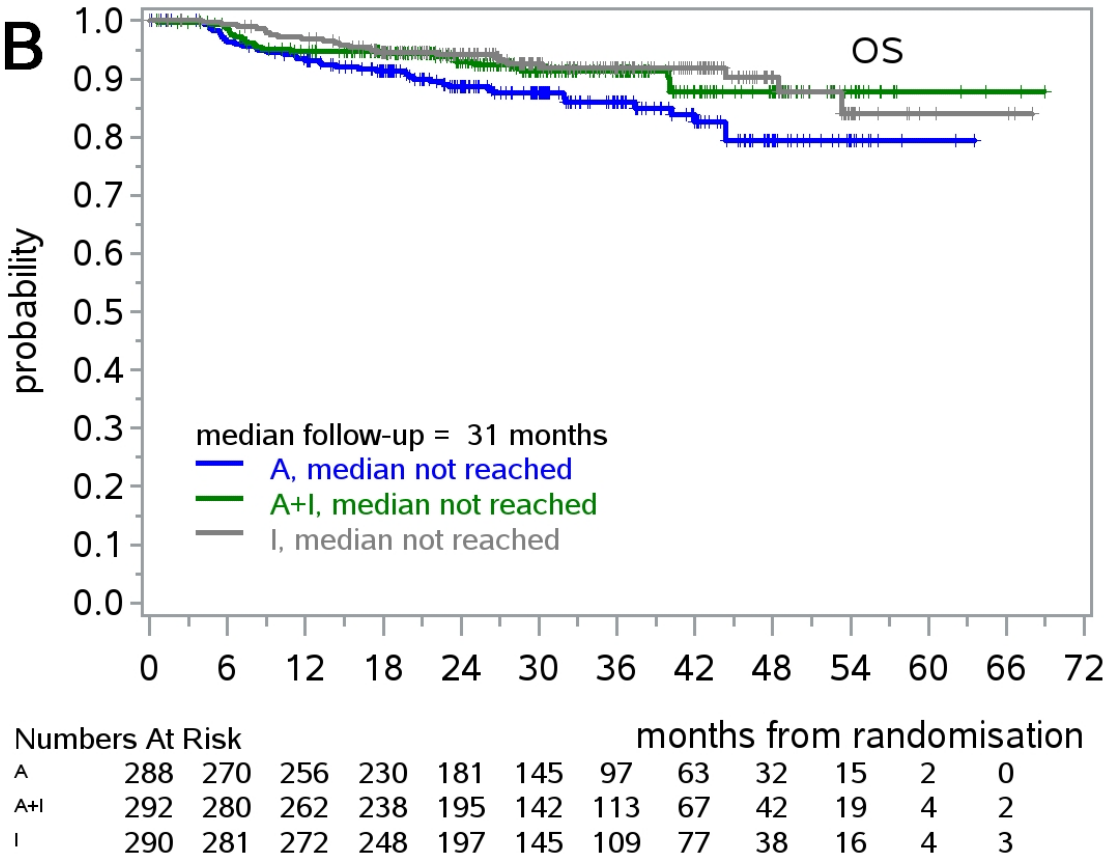


TRIANGLE Trial, Dreyling et al, Abstract #1



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

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

Three FDA-approved BTK inhibitors in R/R MCL

	Ibrutinib	Acalabrutinib	Zanubrutinib
Approval Date	November 13, 2013	October 31, 2017	November 14, 2019
Dose	560 mg QD	100 mg BID	160 mg BID or 320 QD
Trial Size	N = 111	N = 124	N = 86
ORR	68%	89%	84%
CR	21%	48%	78%
mDOR	~18 months	~28 months	~36 months

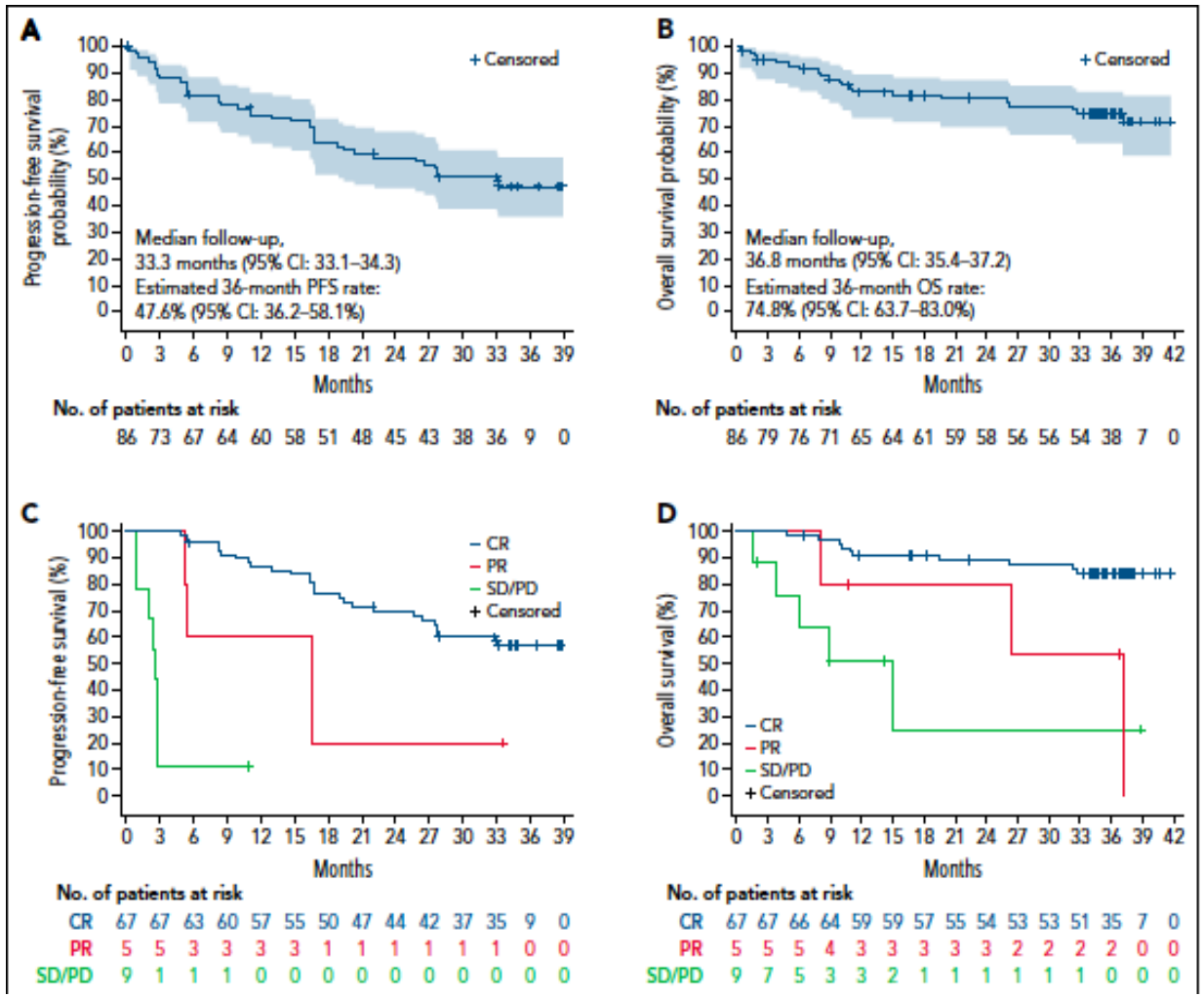
CLINICAL TRIALS AND OBSERVATIONS

Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study

Yuqin Song,[1] Keshu Zhou,[2] Dehui Zou,[3] Jianfeng Zhou,[4] Jianda Hu,[5] Haiyan Yang,[6] Huilai Zhang,[7] Jie Ji,[8] Wei Xu,[9] Jie Jin,[10] Fangfang Lv,[11] Ru Feng,[12] Sujun Gao,[13] Haiyi Guo,[14] Lei Zhou,[15] Jane Huang,[16] William Novotny,[16] Pil Kim,[16] Yiling Yu,[14] Binghao Wu,[14] and Jun Zhu[1]

Table 1. Summary of investigator-assessed efficacy

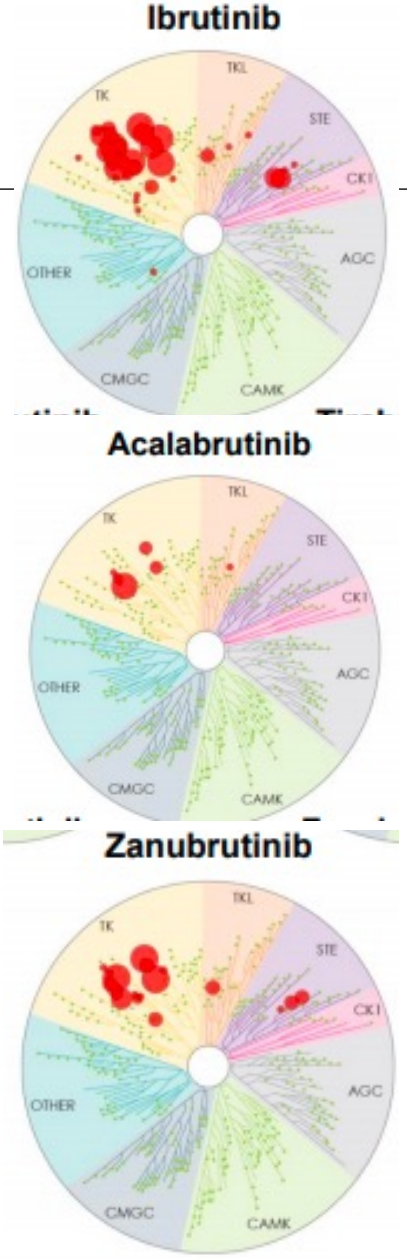
Efficacy variable	n = 86
ORR (CR + PR), % (95% CI)*	83.7 (74.2-90.8)
Best response, n (%)	
CR	67 (77.9)
PR	5 (5.8)
SD	1 (1.2)
PD	8 (9.3)
Discontinued before first assessment	5 (5.8)
Time to response (mo)	
Median (range)	2.7 (2.5-3.0)
Time to CR (mo)	
Median (range)	2.8 (2.5-16.7)
Response duration (mo)	
Median† (range)	NE (2.3-36.2+)
95% CI	(24.9-NE)
Event-free rates‡ at 30 mo (%)	57.3
95% CI	(44.9-67.9)



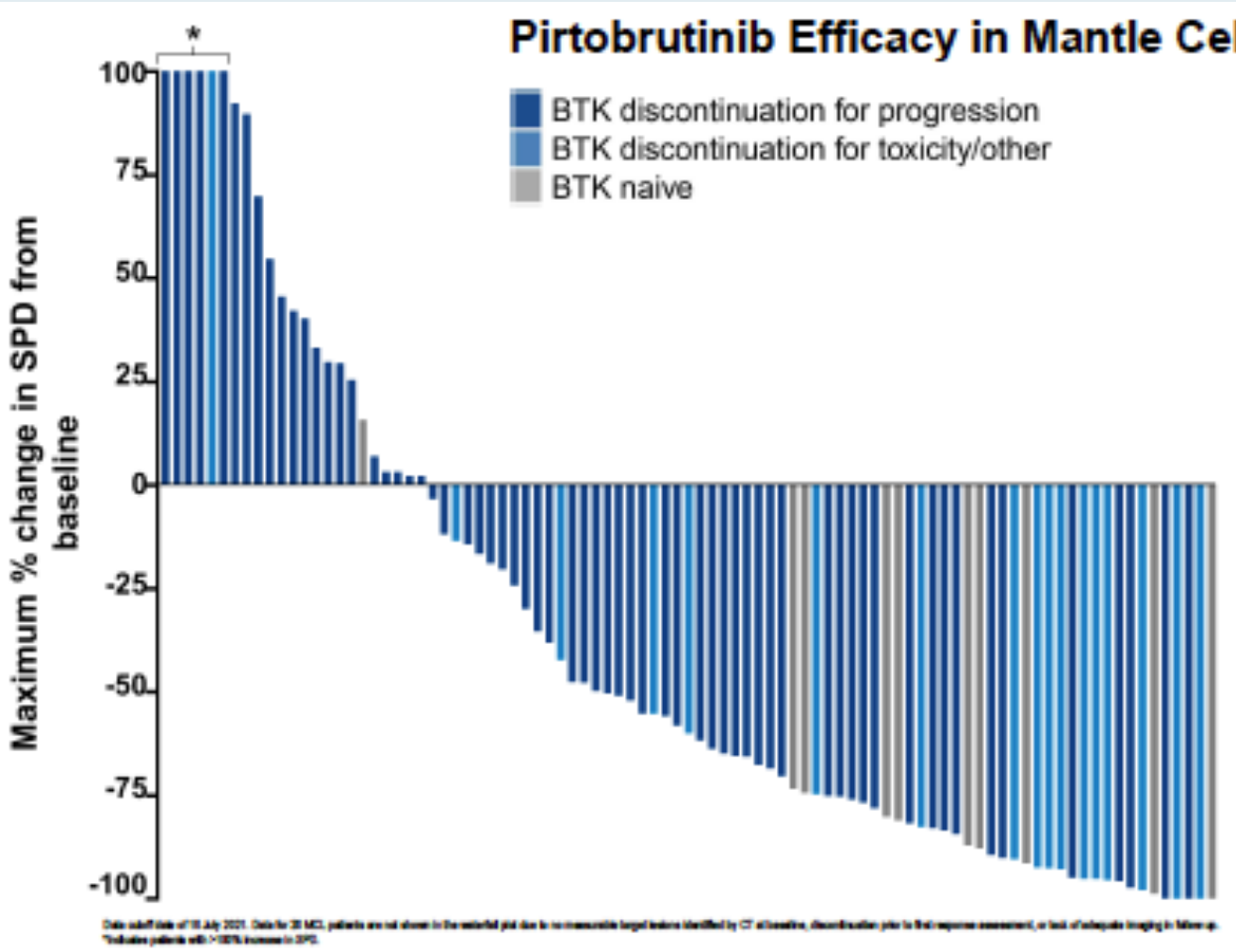
Blood, May 2022

BTKi Comparisons

- Acalabrutinib and Zanubrutinib better tolerated than Ibrutinib in CLL and WM
  - ELEVATE R/R trial
  - ALPINE Trial
  - ASPEN Trial
- Zanubrutinib more active than ibrutinib in CLL
  - ALPINE Trial
- Zanubrutinib vs. Acalabrutinib never done
  - Cross trial comparisons suggest similar efficacy and tolerability
- I prefer zanubrutinib/acalabrutinib over ibrutinib for MCL



BRUIN: Updated Results with Pirtobrutinib for MCL



BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

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

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

BRUIN: Updated Safety Results with Pirtobrutinib for MCL

All Doses and Patients (n=618)							
	Treatment-Emergent AEs, (≥15%), %					Treatment-Related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

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

R/R MCL: BTK plus…

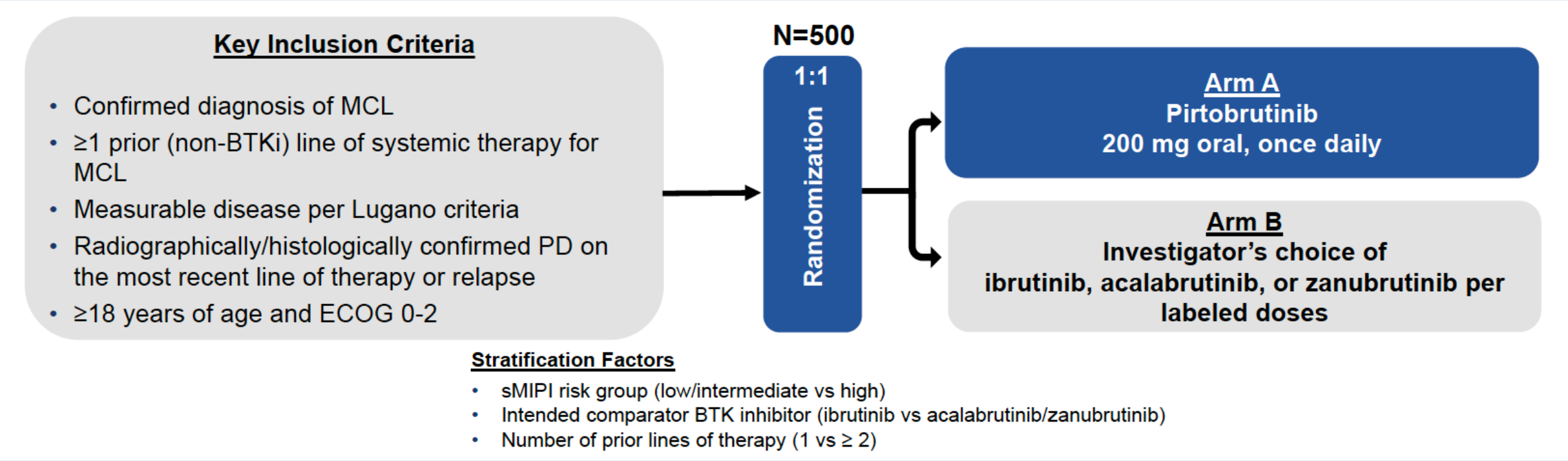
Completed

1. Ibrutinib plus Venetoclax - 71% CR (AIM Study)
2. Ibrutinib + Obinutuzumab + Venetoclax - 67% CR (OASIS study)

Ongoing Phase III Trials

1. Ibrutinib vs. Ibrutinib plus Venetoclax (SYMPATICO)
2. Pirtobrutinib vs. SOC BTK (LOXO 305)

BRUIN MCL-321 Phase III Study Design



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

Glofitamab for R/R MCL. Philips et al. Abstract #74.

Patient Characteristics

- N = 37
- Median Age 72
- Median prior therapy 3 (1-5)

Treatment Schedule

- Obinutuzumab D1
  - 1000 vs 2000 mg
- Glofit step up dosing D 8, 15
- Glofit 30mg q 3w x 12 cycles

Results

- ORR 84%
- CR 73%
- Median f/u 8 months
- Median DOR 12.6 months
- CRS 76%
  - Tocilizumab in 17 patients
- Neurotox 51% (gr 1-2)

R2 plus Venetoclax for R/R MCL. Abstract 76. Zandelisib plus Zanubrutinib for R/R MCL. Abstract 78.

Jerkeman et al, #76

- N = 59, Median age 73
- Median prior lines 2
- Ven 600 mg. Len 15 mg.
- ORR 63%. CR 49%.
- Durability ?
- Grade 3-4 neutropenia in 88%.
- Grade 3-4 thrombocytopenia 36%.
- Grade 3-4 infection 14%.
- Grade 3 rash in 8%.

Soumerai et al, #78

- N = 19. Median age 67.
- Median prior lines 2
- Zandelisib 60 mg. Zanu 80 mg BID.
- ORR 76%. CR 35%.
- Median PFS 10 months
- Diarrhea 32%
- Headache 18%
- Arthralgia 16%
- Rash 16%

Addressing Current Questions and Controversies in the Management of Hodgkin and Non-Hodgkin Lymphoma — What Clinicians Want to Know

Part 2 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
3:15 PM – 5:15 PM CT

Faculty

Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD
David G Maloney, MD, PhD
Loretta J Nastoupil, MD
Sonali M Smith, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Addressing Current Questions and Controversies in the Management of Multiple Myeloma — What Clinicians Want to Know

Part 3 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Jesús G Berdeja, MD
Rafael Fonseca, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD

Moderator

Neil Love, MD

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