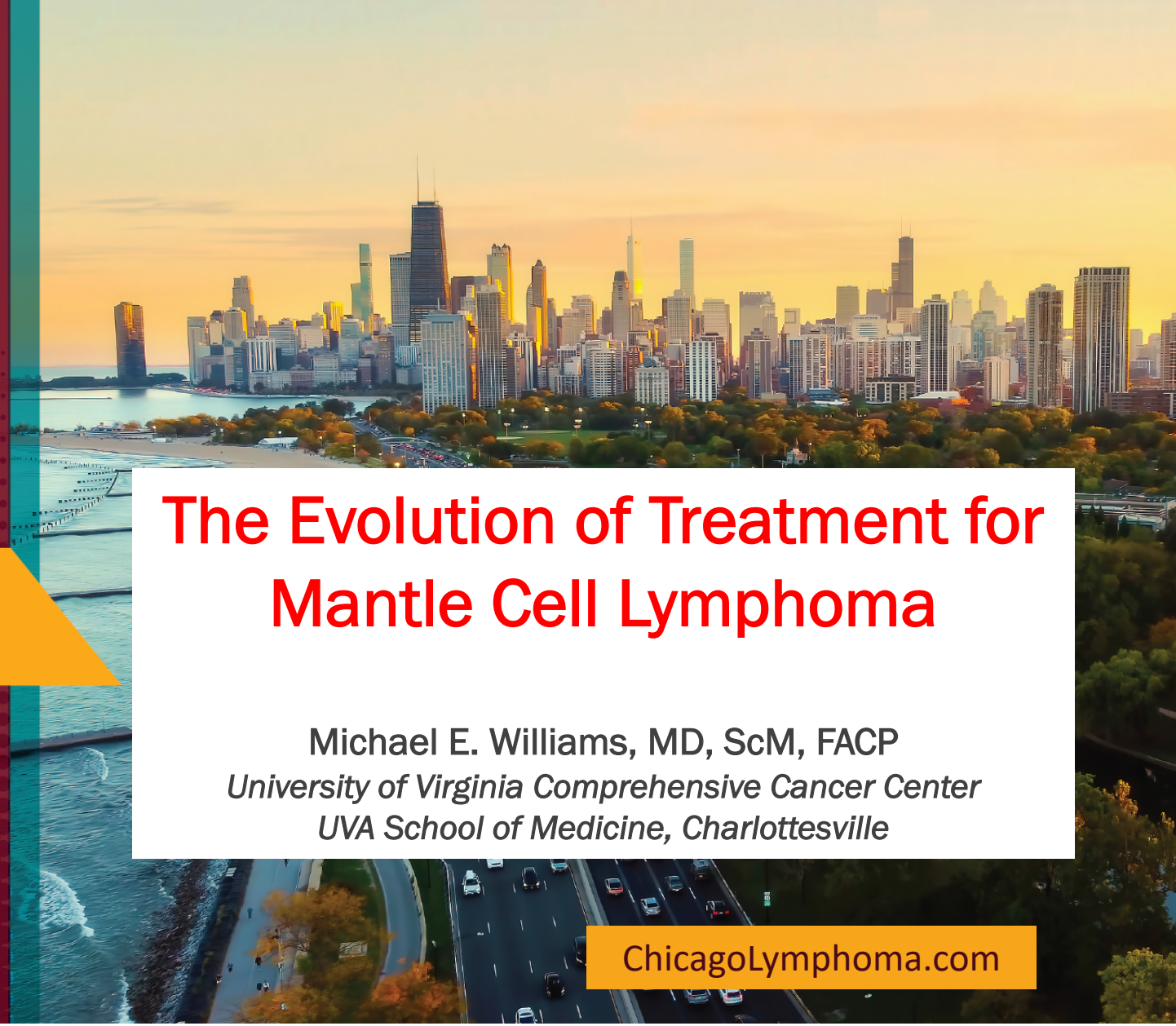
23rd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 10-11, 2026

JW MARRIOTT CHICAGO

#IUCLS2026



The Evolution of Treatment for Mantle Cell Lymphoma

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ChicagoLymphoma.com

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The Evolution of Treatment for Mantle Cell Lymphoma

Keynote Presentation

23rd International Ultmann Chicago Lymphoma Symposium
April 10-11, 2026

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Hematology/Oncology Division
University of Virginia Comprehensive Cancer Center
Charlottesville

UVA Cancer Center
An NCI Comprehensive Cancer Center

UVA Health

Disclosures: Michael E. Williams, MD, ScM

- Clinical trial grant support (PI) to the University of Virginia School of Medicine:
  - Janssen, Pharmacyclics
- Consultant:
  - Abbvie, Astra-Zeneca, BeOne
- Other:
  - American Board of Internal Medicine, Hematology Longitudinal Knowledge Assessment Committee

Centrocytic Lymphoma:

Recognition of a new entity

K.Lennert, **Kiel Classification**, *Lancet 1974*

MORPHOLOGICAL AND IMMUNOLOGICAL DEFINITION OF A MALIGNANT LYMPHOMA DERIVED FROM GERMINAL-CENTRE CELLS WITH CLEAVED NUCLEI (CENTROCYTES)

G. TOLKSDORF, H. STEIN AND K. LENNERT

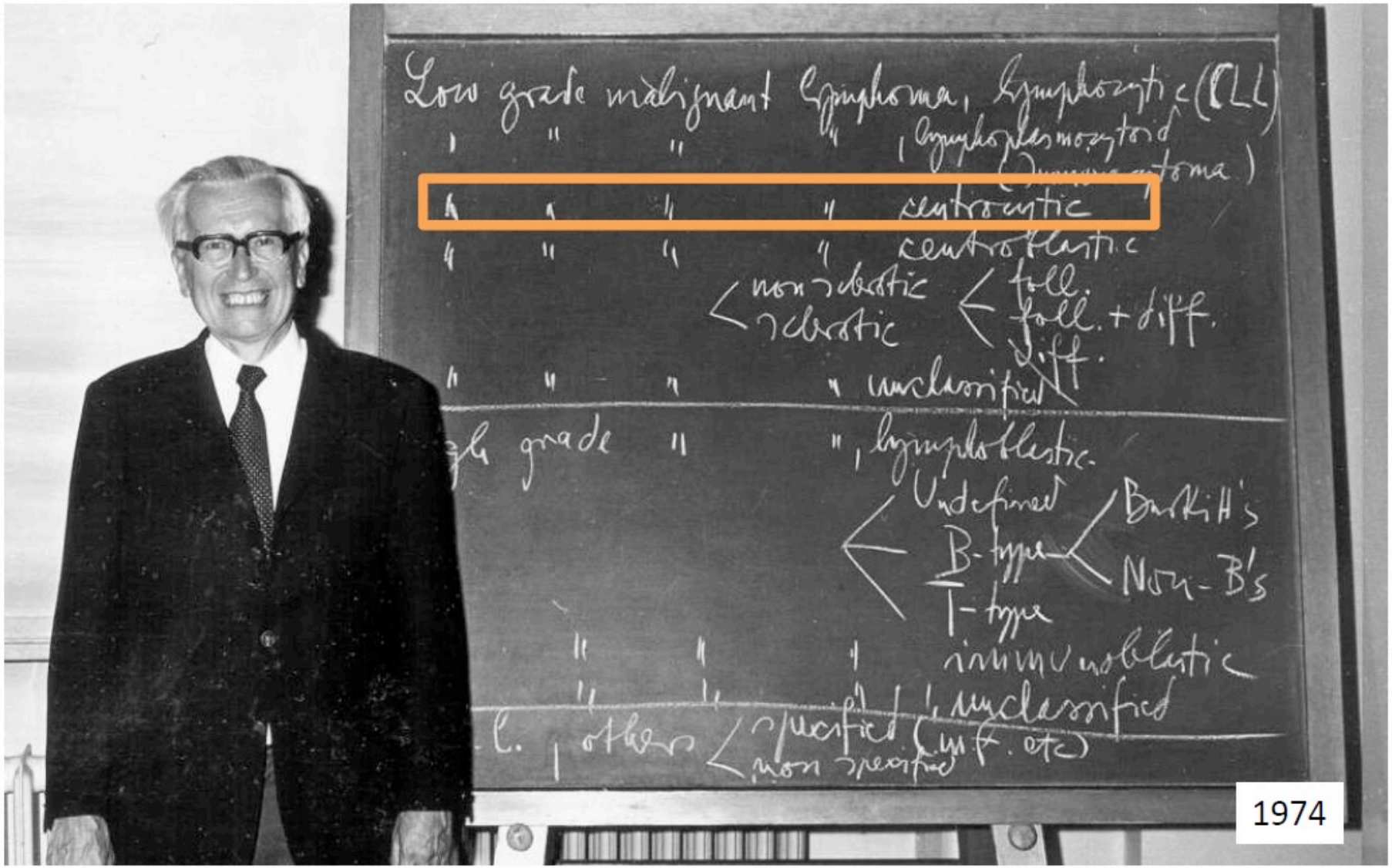
From the Institute of Pathology, University of Kiel, West Germany

Brit J Cancer 1980

….the cells of this type of lymphoma (a) differ morphologically and/or immunologically from the cells of all other known types of non-Hodgkin's lymphoma and (b) resemble centrocytes (cleaved follicular-centre cells) of reactive germinal centres.

Thus, this type of lymphoma appears to be an entity that is closely related to, or even derived from, centrocytes.

Professor Karl Lennert, University of Kiel, Germany

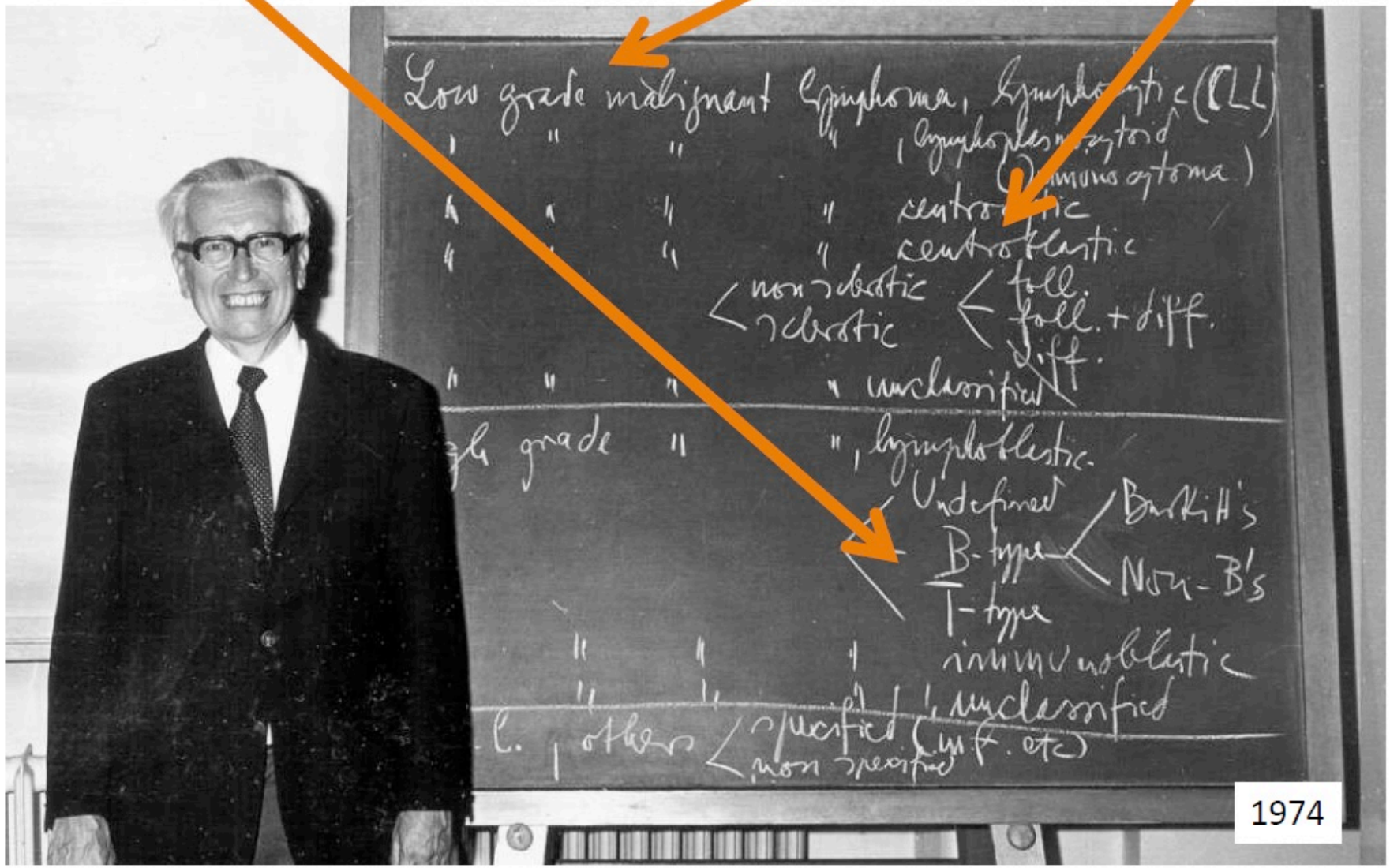


Slides courtesy of Wolfram Klapper, MD

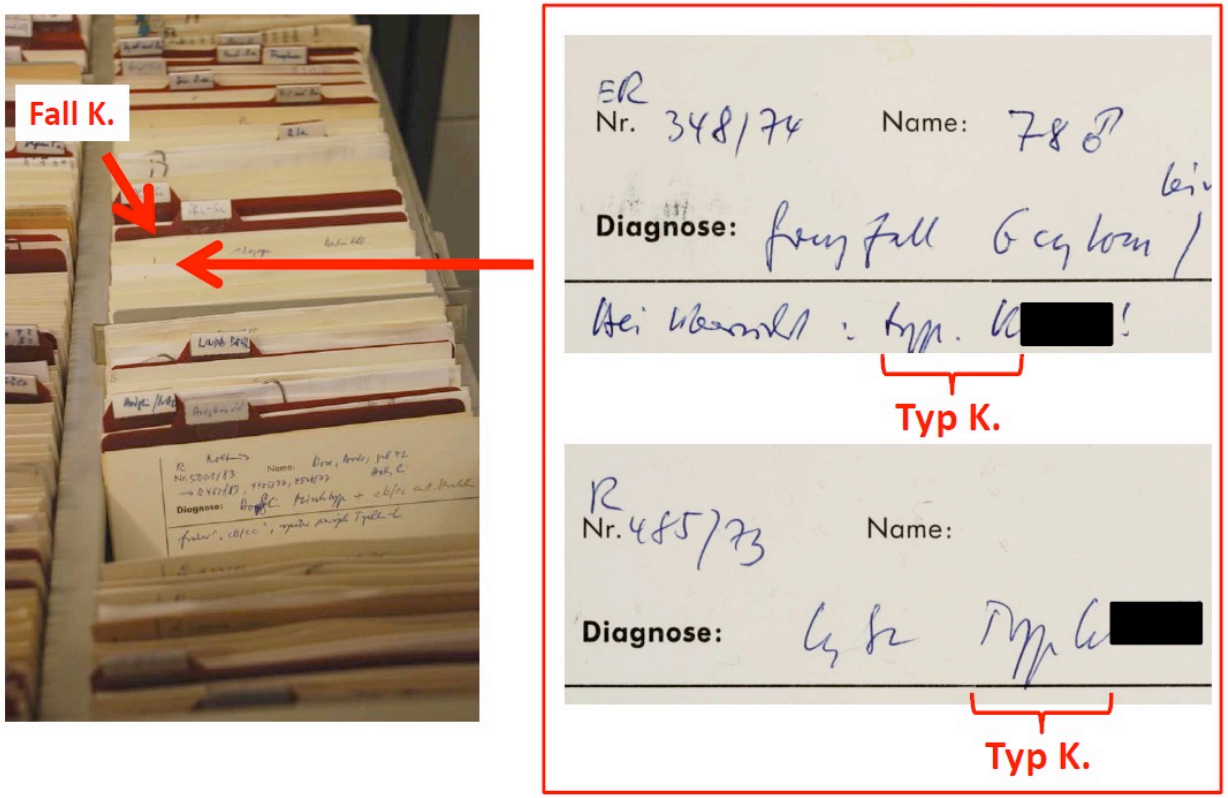
Biologisches Konzept:
B-Zell und T-Zell Lymphome

Biologisches Konzept:
aggressiv und indolent

Biologisches Konzept:
„cell of origin“



Patient „K.“
starting point of a new entity



Case index files, Professor Karl Lennert, University of Kiel, Germany
Courtesy of Prof. Wolfram Klapper

Patient K (with permission of his family)
Lennert Symposium, University of Kiel:
***50 Years of the Kiel Classification*, July 2024**
“Presented in June 1968 with abdominal pain and enlarged nodes, biopsy showed a ‘previously unknown type of lymphoma’.
Responded to a ‘novel chemotherapy’, but relapsed 3 years later and died in November 1972.”

Genotypic Characterization of Centrocytic Lymphoma: Frequent Rearrangement of the Chromosome 11 *bcl-1* Locus. Williams ME, Westermann CD, Swerdlow SH. *Blood* 1990; 76: 1387-91

> "Thus, centrocytic lymphomas appear to be distinct from other cleaved FCC lymphomas by immunophenotype and by the absence of bcl-2 rearrangement. Furthermore, the chromosome 11 bcl-1 locus is rearranged in 28% of cases as compared with less than *5%* in other B-cell lymphomas, *suggesting a potential role in pathogenesis…….. Centrocytic lymphoma may also prove to be a useful tumor model for the identification and characterization of the putative bcl-1 oncogene product."*

bcl-1 rearrangement in lymphocytic lymphoma of intermediate differentiation:

- Rimokh R, Berger F, et al. *Genes, Chromosomes & Cancer* 1990; 2:223-6: *"….rearrangement of the BCL1 locus.……could be considered as a genotypic marker of this lymphoma subtype."*

- Medeiros LJ, van Krieken JH, Jaffe ES, Raffeld M. *Blood* 1990; 76:2086-90: *"…….abnormalities of this locus may be important in the pathogenesis of IDL."*

Centrocytic and Intermediate Lymphocytic Lymphoma → **Mantle Cell Lymphoma**

Additional 11q13 translocation breakpoints showed that 12/23 (52%) centrocytic lymphomas had bcl-1 rearrangements. Williams ME, Meeker TC, Swerdlow SH. *Blood* 1991; 78:493-8

bcl-1, t(11;14), and Mantle Cell-Derived Lymphomas. Raffeld M, Jaffe ES. *Ibid*, pp. 259-63
"**IDL and CC are identical neoplasms** derived from follicular mantle cells and should be unified under a common terminology. They have common morphologic features, common immunologic features, and have now been shown to have common cytogenetic and molecular genetic features. ***We propose the term mantle cell lymphoma, nodular or diffuse variant……."***

The American Journal of Surgical Pathology *16(7): 637–640, 1992*

Mantle Cell Lymphoma

A Proposal for Unification of Morphologic, Immunologic, and Molecular Data

P.M. Banks, M.D., J. Chan, M.D., M.L. Cleary, M.D.,
G. Delsol, M.D., C. De Wolf-Peeters, M.D., K. Gatter, M.D.,
T.M. Grogan, M.D., N.L. Harris, M.D., P.G. Isaacson, M.D.,
E.S. Jaffe, M.D., D. Mason, M.D., S. Pileri, M.D.,
E. Ralfkiaer, M.D., H. Stein, M.D., and R.A. Warnke, M.D.

The first mammalian G1 cyclin

A novel cyclin encoded by a bcl1-linked candidate oncogene.
Motokura T, Bloom T, Kim H, Juppner H, Ruderman J, Kronenberg H, Arnold A. *Nature* 1991; 350: 512

The first mammalian G1 cyclin was cloned from a chromosome 11 paracentric inversion that juxtaposed the PTH promoter on 11p with a coding region at 11q13, designated *"PRAD1" [parathyroid adenoma 1].*

"These data suggest that PRAD1 encodes a novel cyclin whose overexpression may play an important part in the development of various tumours with abnormalities in 11q13"

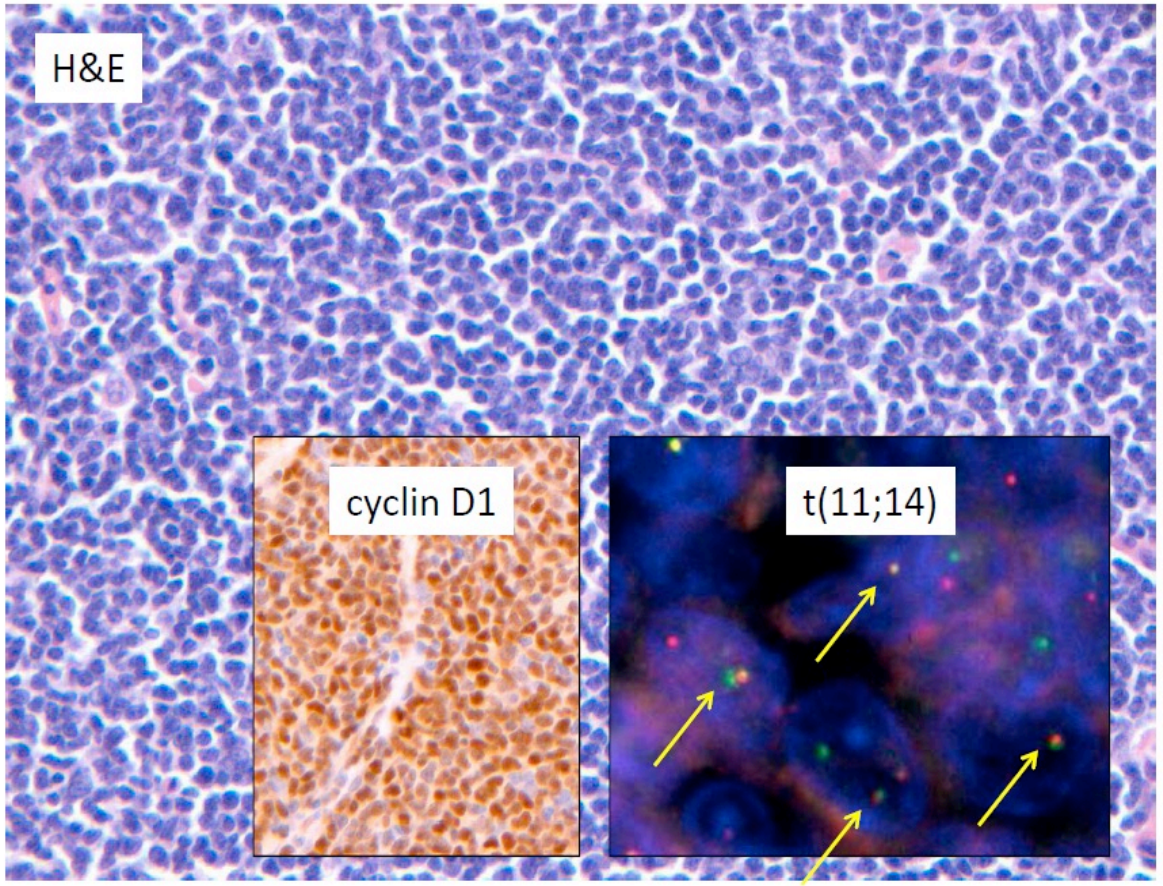
PRAD1 [*CCND1*] later confirmed as the bcl-1 gene in centrocytic/mantle cell lymphoma

- **Multiple *PRAD1* translocation breakpoints:** Williams ME, Swerdlow SH, Rosenberg CL, Arnold A. *Cancer Res* 1992; 52(Suppl.):5541; *Leukemia* 1993; 7:241-245

- **Cyclin D1 expression:** Swerdlow SH, Yang W-I, Zukerberg LR, Harris NL, Arnold A, Williams ME. Expression of cyclin D1 protein in centrocytic/mantle cell lymphomas with and without rearrangement of the BCL1/cyclin D1 gene. *Human Pathol 1995;* 26:999-1004

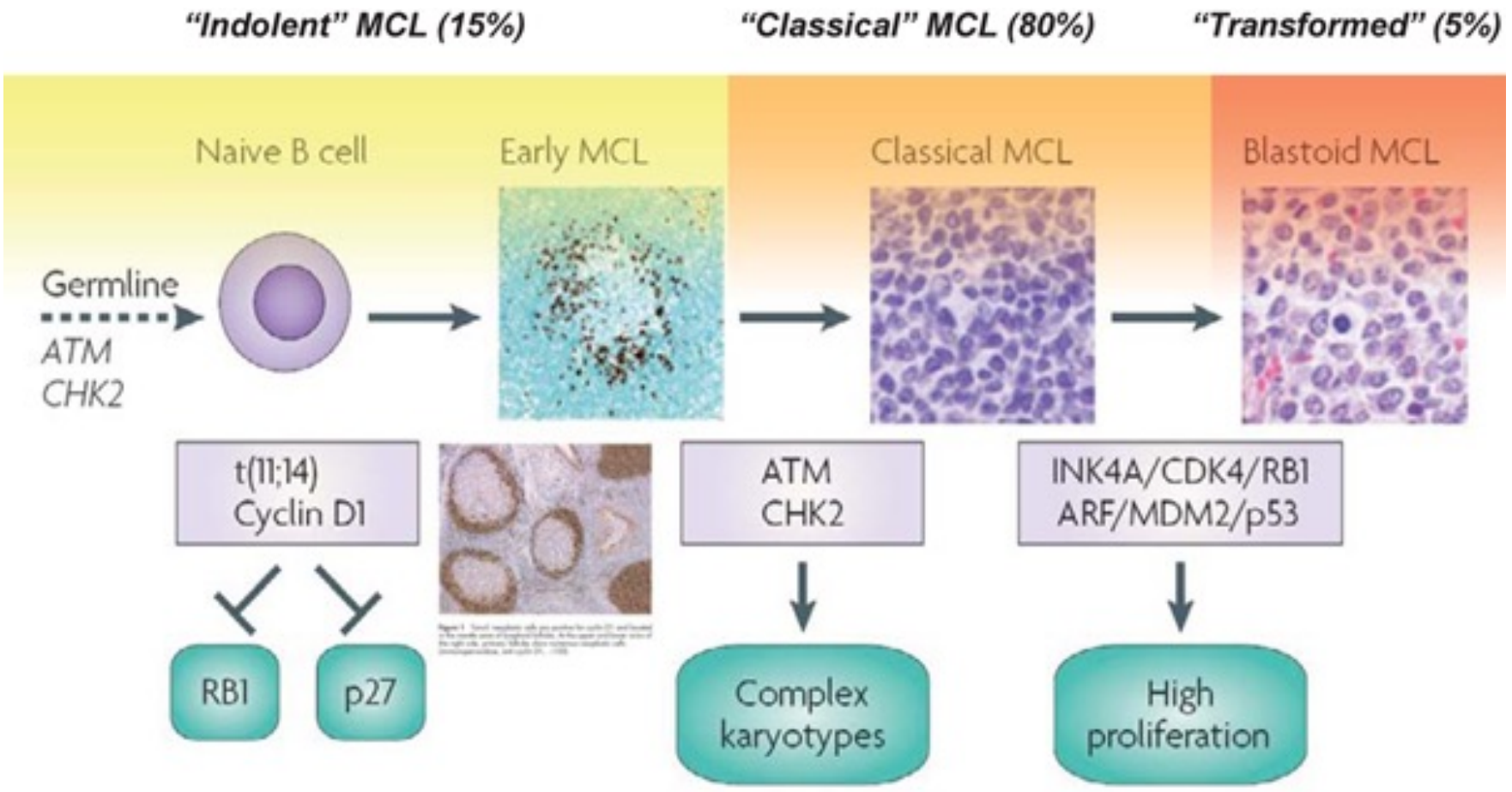
Prof. Karl Lennert's Index case of Centrocytic Lymphoma:

Patient K (1974)



Klapper, Leukemia 2013

Pathogenesis and Progression of Mantle Cell Lymphoma



M. Dreyling et al. Ann Oncol 2014

MCL: Typical Presentation

- 74% male
- Median age 63 years
- Over 90% present with advanced-stage disease
  - **Diffuse adenopathy, splenomegaly**
  - **Extranodal disease, esp. GI tract, leukemic phase**
  - **Constitutional symptoms common at diagnosis**
- Clinically and biologically heterogeneous

Mantle Cell Lymphoma: Prognostic Factors at Diagnosis

Biomarker	Favorable	Unfavorable
MIPI or MIPI-c Score	Low	High
Ki-67 Score	< 30%	>/= 30%
Chromosome 17p	Intact	Deleted
TP53	Wild type	Mutated
Clinical/Morphologic	Leukemic/Non-nodal subtype	Blastoid or Pleomorphic MCL
Post-induction Measurable Residual Disease (MRD)	Negative	Positive
MCL35 Proliferation Assay	Low-risk	High-risk
Anti-LRPAP1 seropositive *(Proposed)*	Present	

Williams ME. *Blood* 2021; 137:3158-60

Mantle Cell Lymphoma: Prognostic Factors at Diagnosis

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C		
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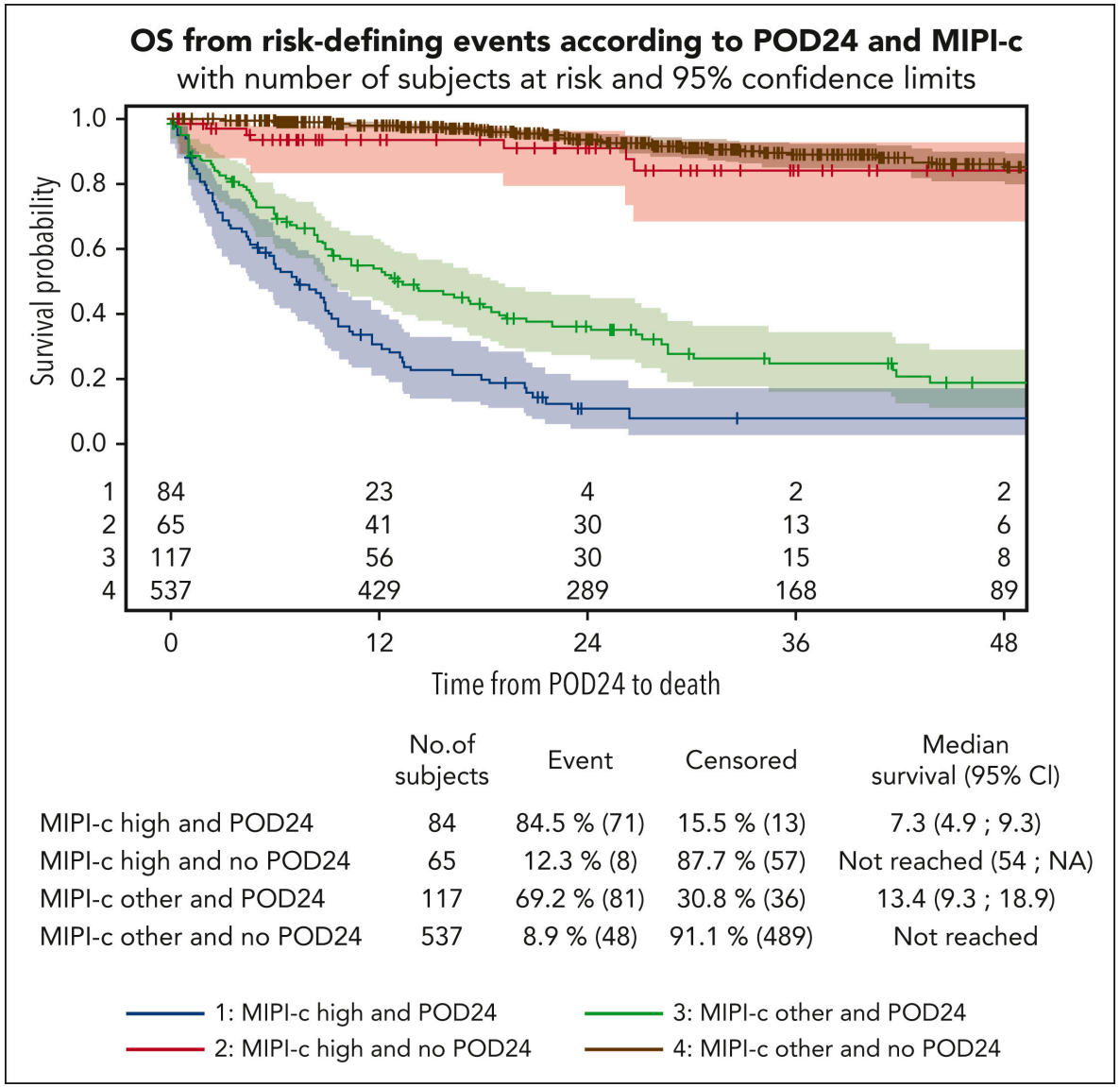
Anti-LRPAP1 seropositive *(Proposed)*	Present	

These factors are not currently utilized to guide initial therapy, aside from TP53-mutated MCL

Williams ME. *Blood* 2021; 137:3158-60

MCL Outcomes: Impact of POD24 and MIPI-c Score on Overall Survival in 800 Patients



Silkenstedt E, Dreyling M. *Blood,* 2025; 145:673-82

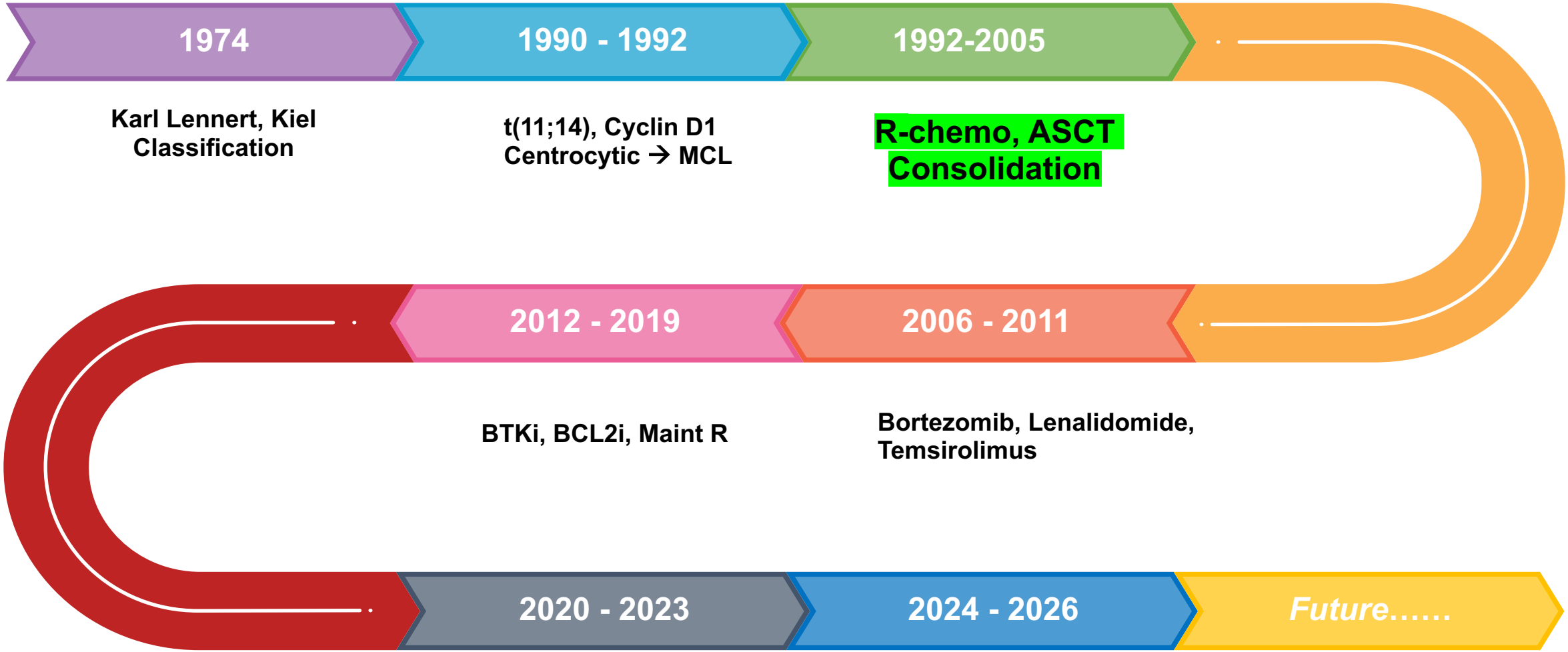
MCL 2026: Front-Line *Therapy is Evolving Rapidly …..*

- Watch/Wait patients (~15-20%)
  - Indolent subtype, low tumor burden, asymptomatic

- Risk-adapted therapy and MRD-driven endpoints

- Induction is no longer based on “transplant eligible/ineligible”
  - Bendamustine/Rituximab +Acalabrutinib → Maintenance R +/- Acala
  - BTKi + Rituximab
  - BTKi/Venetoclax +/- anti-CD20
  - Lenalidomide plus anti-CD20, +/- BTKi
  - Bispecific or CAR-T consolidation in high-risk patients?

Therapeutic Evolution in Mantle Cell Lymphoma



Selected MCL Immuno-chemotherapy Induction Regimens*

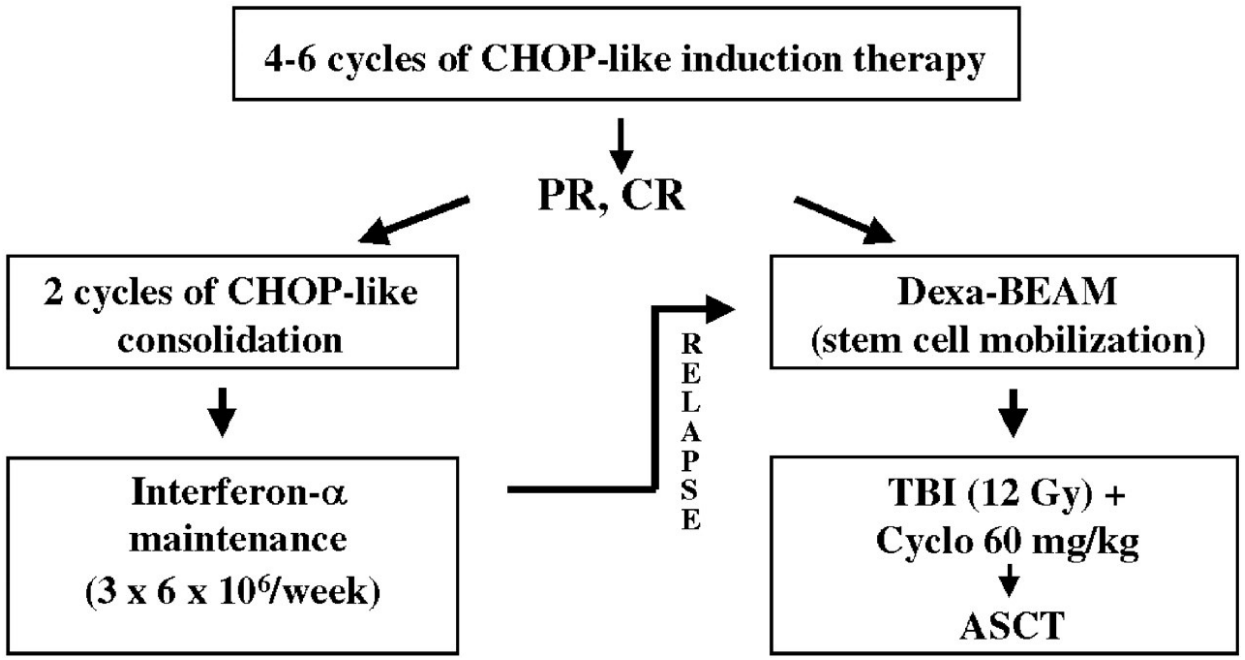
	n	Age	ORR	CR	mPFS
R-CHOP	**244**	**66**	**89%**	**42% (CT)**	**14.4 mo**
VR-CAP	**243**	**65**	**92%**	**53% (CT)**	**24.7 mo**
BR**	**188**	**70**	**~90%**	**~45% (CT)**	**35-48 mo**
RBAC$_{500}$	**57**	**71**	**91%**	**91% (PET)**	**Not reached**

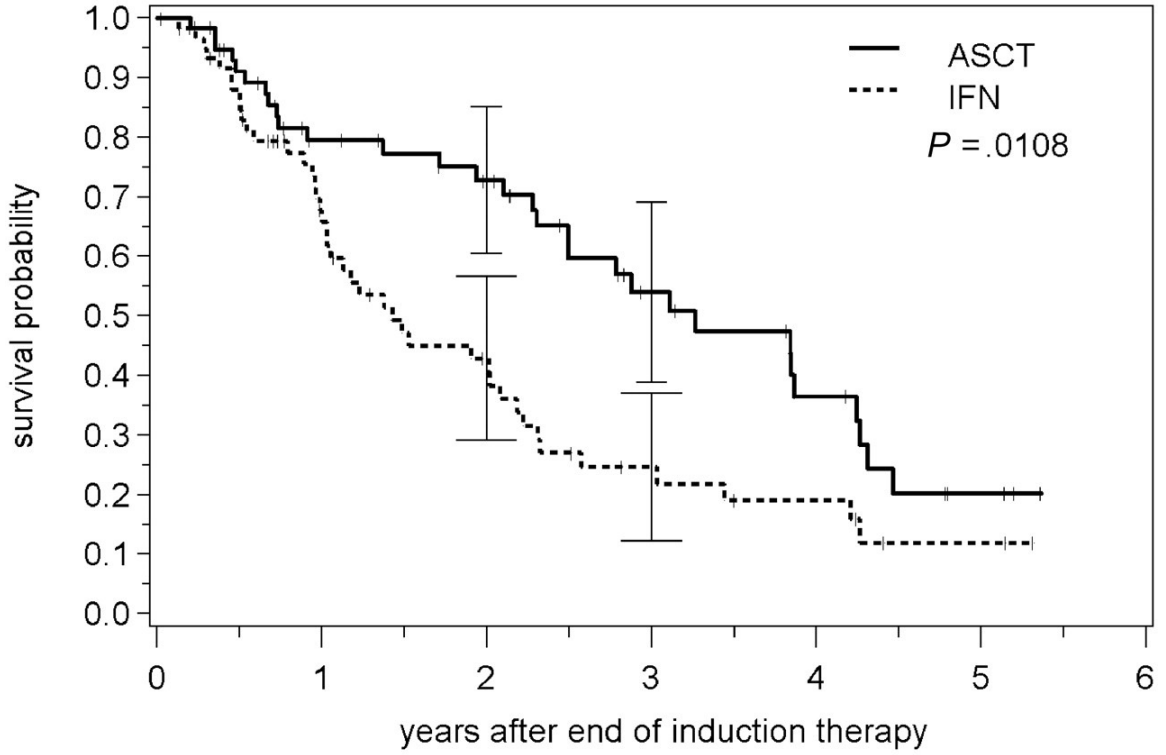
*no maintenance therapy
**pooled data from 3 trials

Why ASCT?**……..*High ORR but short PFS and OS with chemo-immunotherapy alone…..*

Early consolidation by myeloablative radiochemotherapy followed by **autologous stem cell transplantation in first remission** significantly prolongs PFS in MCL:

Results of a prospective randomized trial of the European MCL Network**



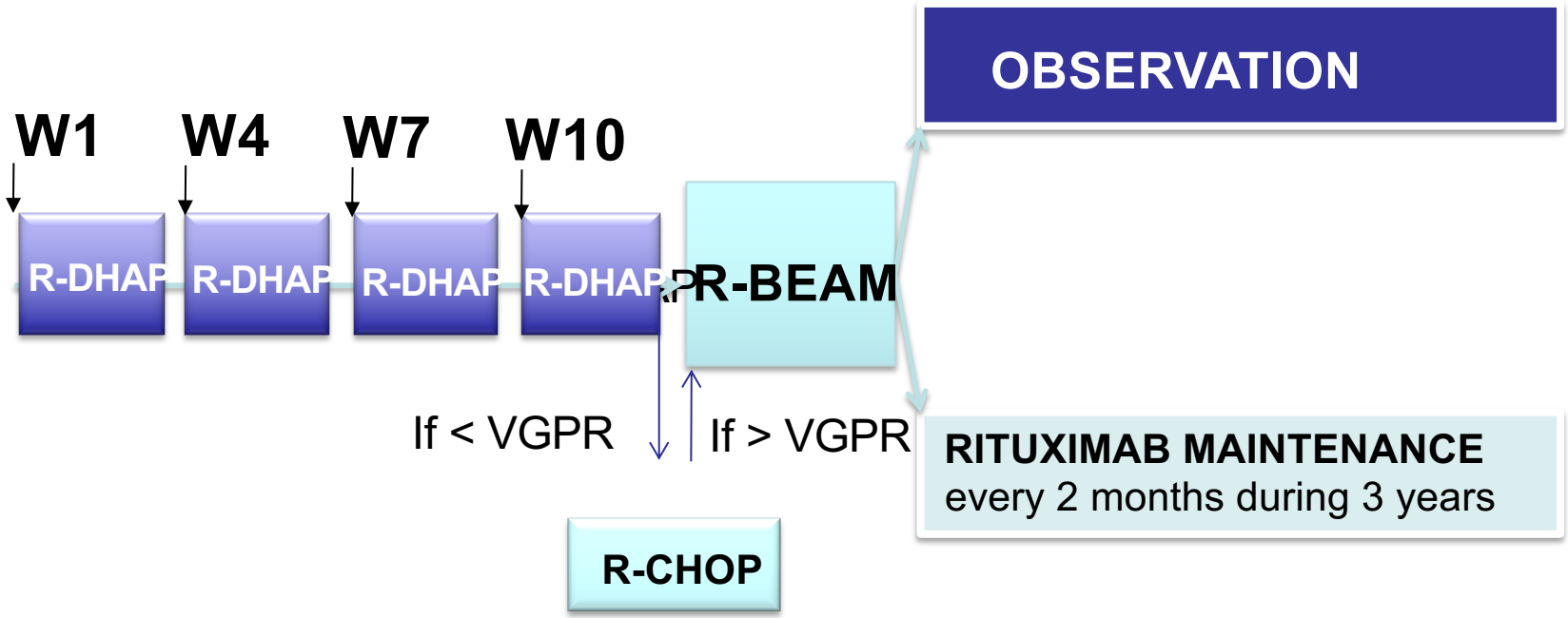


numbers of patients at risk

ASCT	62	38	31	17	10	3
IFN	60	33	19	9	6	2

Dreyling M, et al. ***Blood* 2005**; 105: 2677–84

LyMa trial: ASCT +/- Rituximab maintenance in MCL (LeGouill et al, *NEJM* 2017)

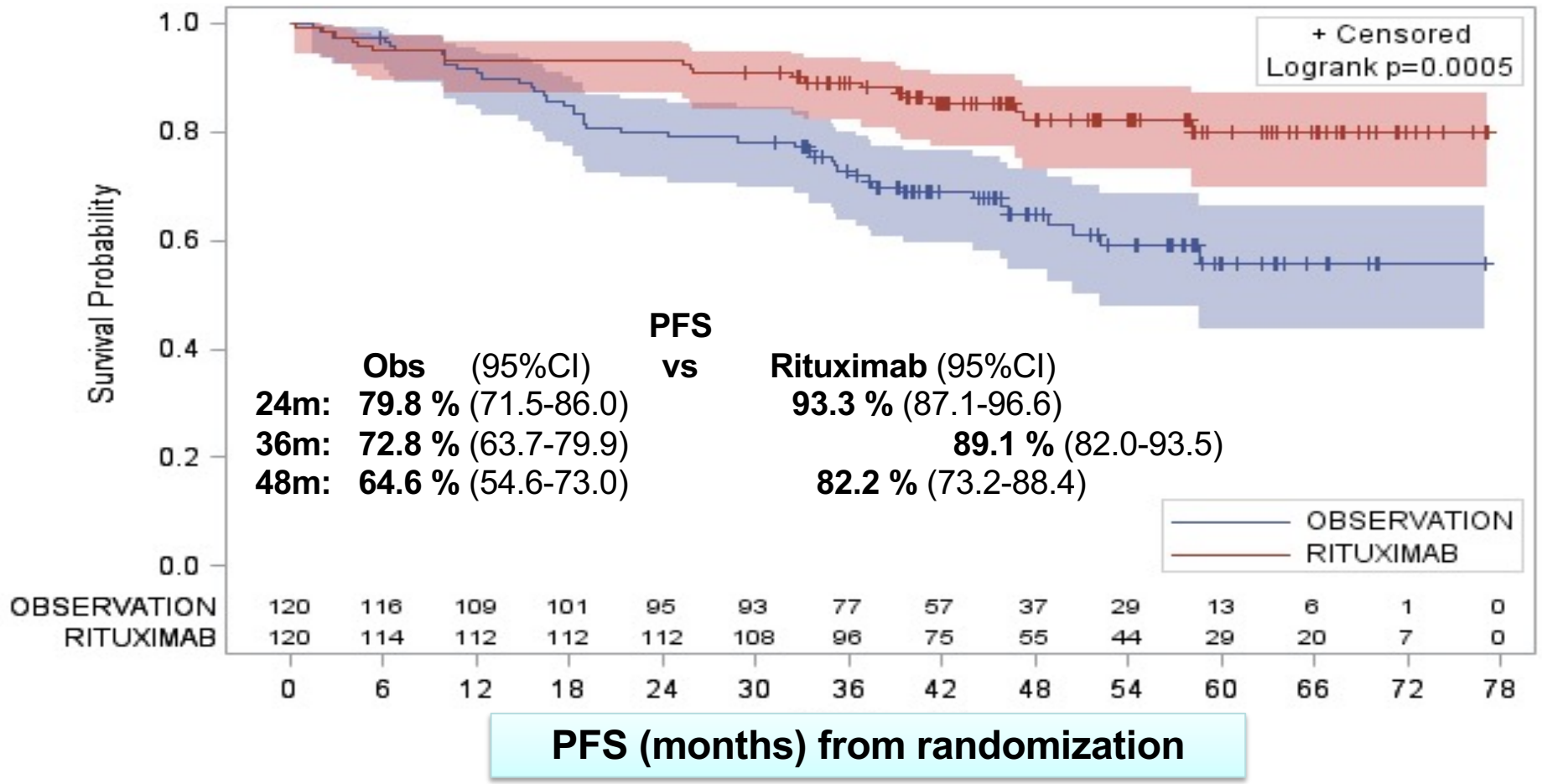


R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or **oxaliplatin** or carboplatin)

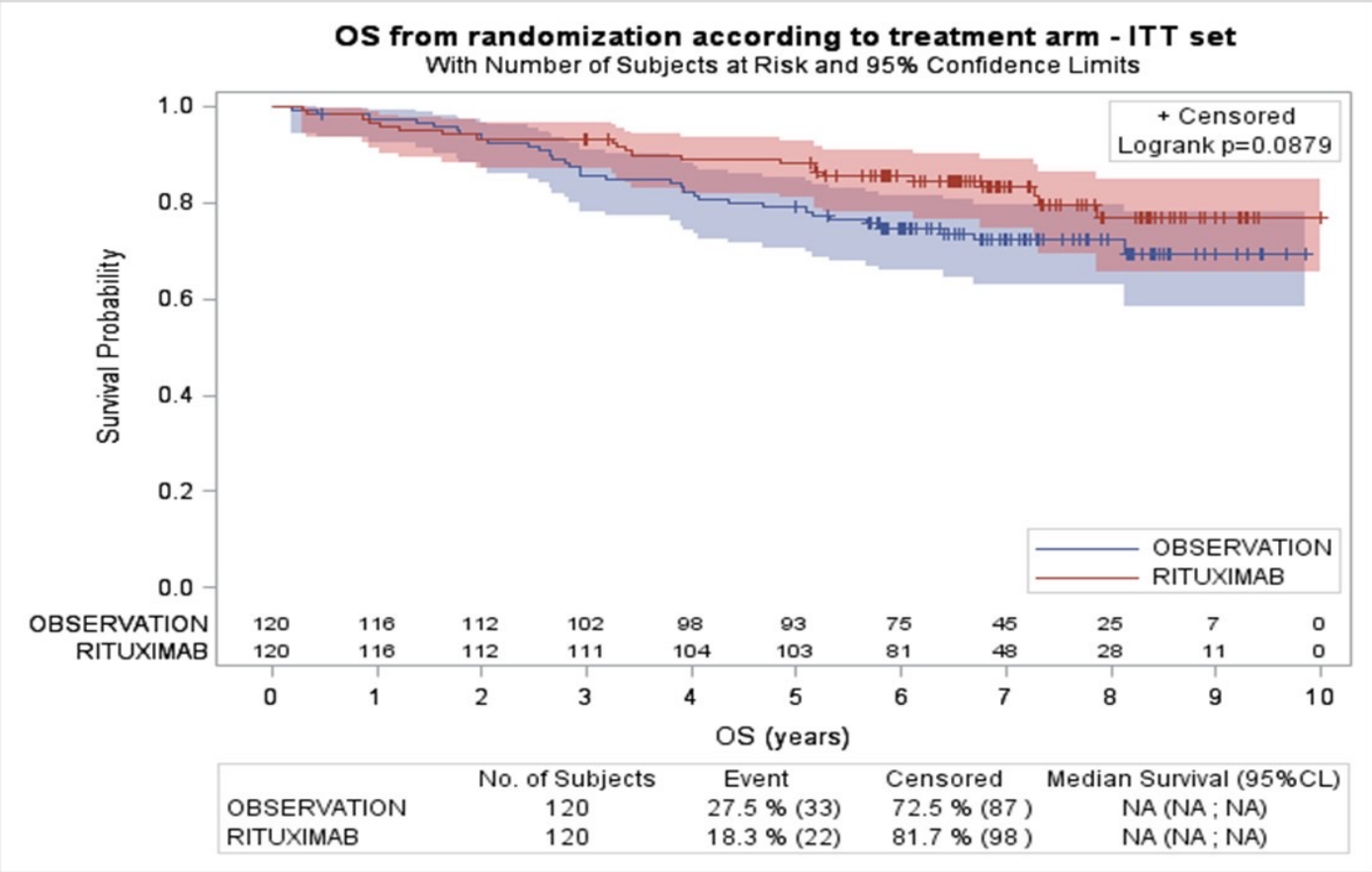
R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

LyMa: PFS from Randomization

mFU: 50.2m (46.4-54.2)



Overall Survival from randomization



Cause of death	Observation, N=33/120 (27.5%)	Rituximab, N=22/120 (18%)
Lymphoma	16 (48.5%)	11 (50%)
Secondary Malignancies	6 (18%)	7 (32%)
Treatment related: infectious	3 (9%)	1 (5%)
Vascular event	2 (6%)	0 (0%)
Treatment related during allotransplant	2 (6%)	2 (9%)
Other	2 (6%)**	1 (4%)*
Unknown	2 (6%)	0

*Suicide, **acute respiratory distress, car accident,

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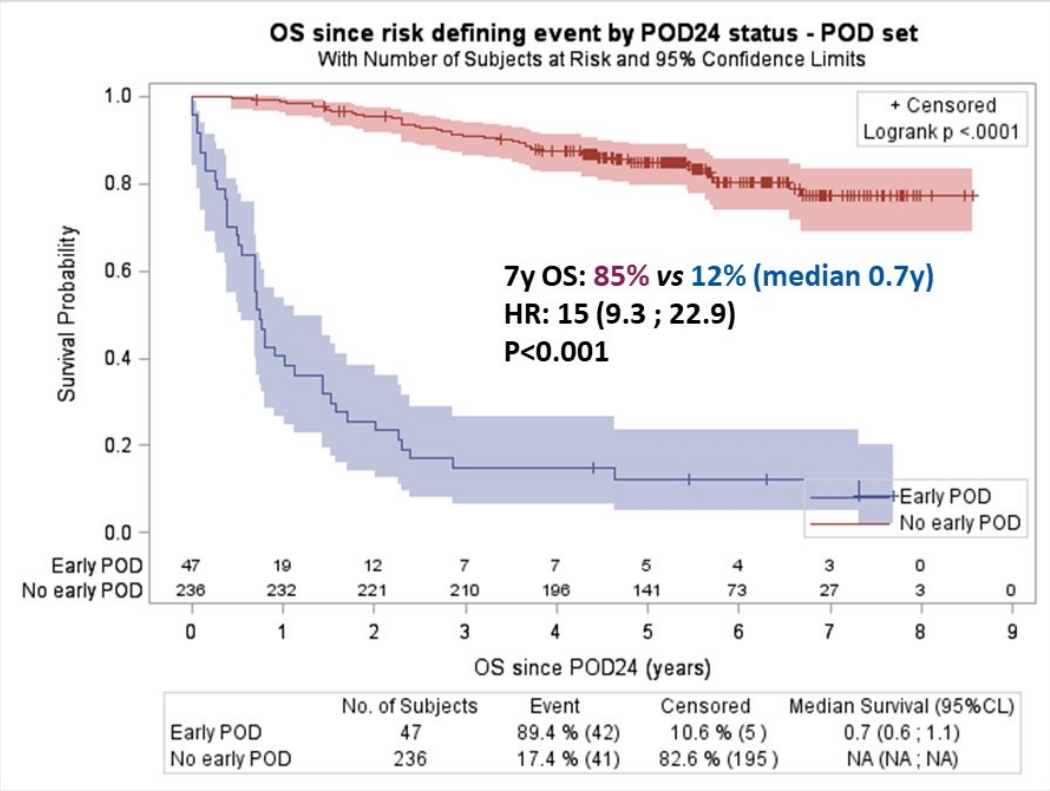
12 ASCO, abstract 7508, June 6th 2023

Sarkozy C, et al. *J Clin Oncol* 2024; 42:769-73

OS according to POD24 and randomization arm

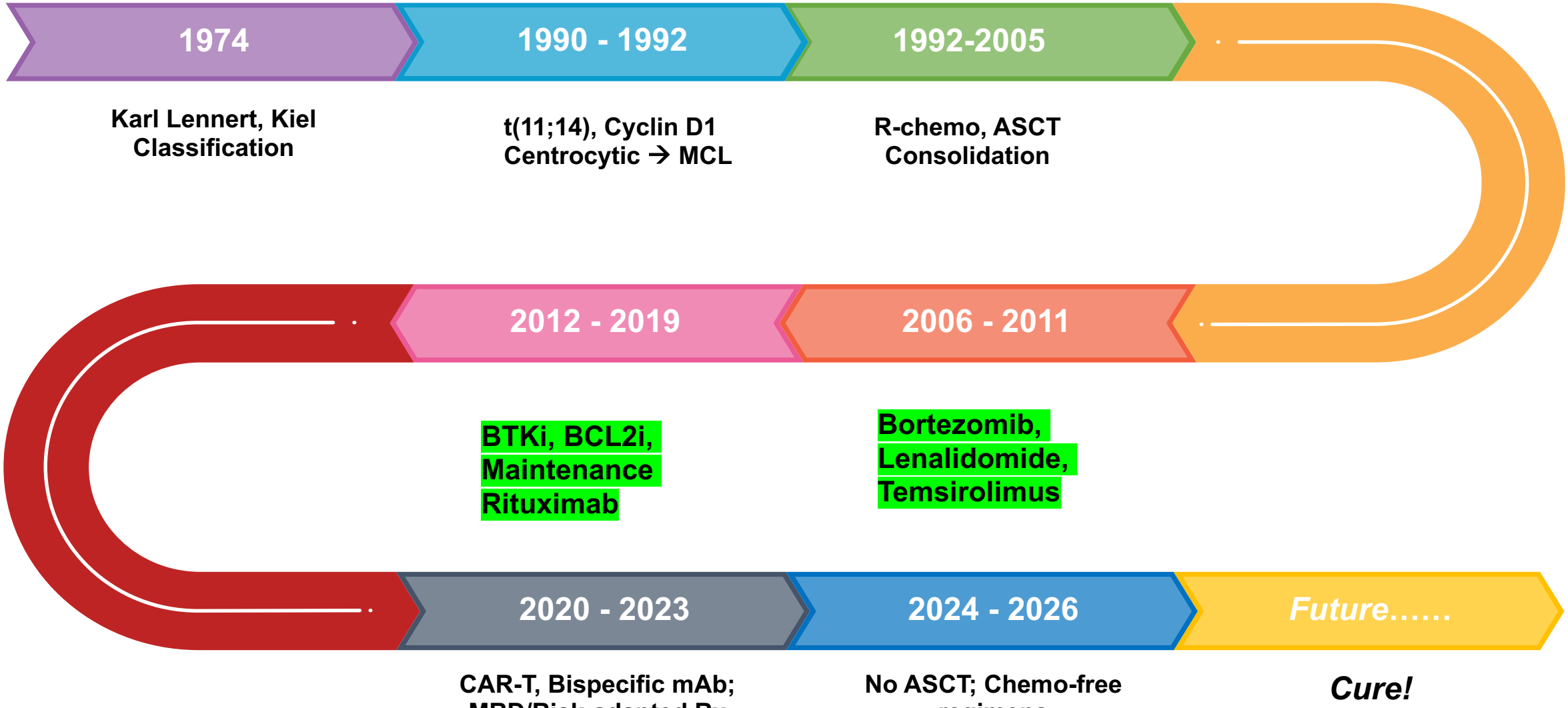
All Patients



ASCO, abstract 7508, June 6th 2023

Sarkozy C, et al. *J Clin Oncol* 2024; 42:769-73

Therapeutic Evolution in Mantle Cell Lymphoma



Targeted Agent Evolution in R/R MCL: *circa* 2020…..

Agent	N	Response Rate	mDOR (mo.)
Bortezomib	155	33%	9.2 m
Temsirolimus	54	22%	7.1 m
Lenalidomide	134	28%	16.6 m
Lenalidomide-rituximab	52	57%	18.9 m
Idelalisib	40	40%	4 m
Ibrutinib	111	68%	17.5 m
Acalabrutinib	124	81%	72% at 12 m
Zanabrutinib	86	84%	16.7 m
Venetoclax	28	75%	12 m
Pirtobrutinib	20	65%	Varied by prior cBTKi
Ibrutinib-Venetoclax	24	71% (all CR)	80% at 12 m

Covalent BTKi in R/R MCL

- Most commonly used 2nd-line therapy following 1st-line R-chemo
  - **Efficacy is similar across the agents, but toxicities differ**
  - **BTKi outperform most CIT in 2nd line, with fewer toxicities**
  - In U.S., ibrutinib withdrawn for the MCL indication in 2023
  - **Acalabrutinib or zanubrutinib now utilized, alone or in combination**

Acalabrutinib, single agent:

- n = 124
- ORR 82%; CR 48%
- With median f/u 38 mo:
  - DOR 29 mo; PFS 22 mo
  - Median OS 59 mo

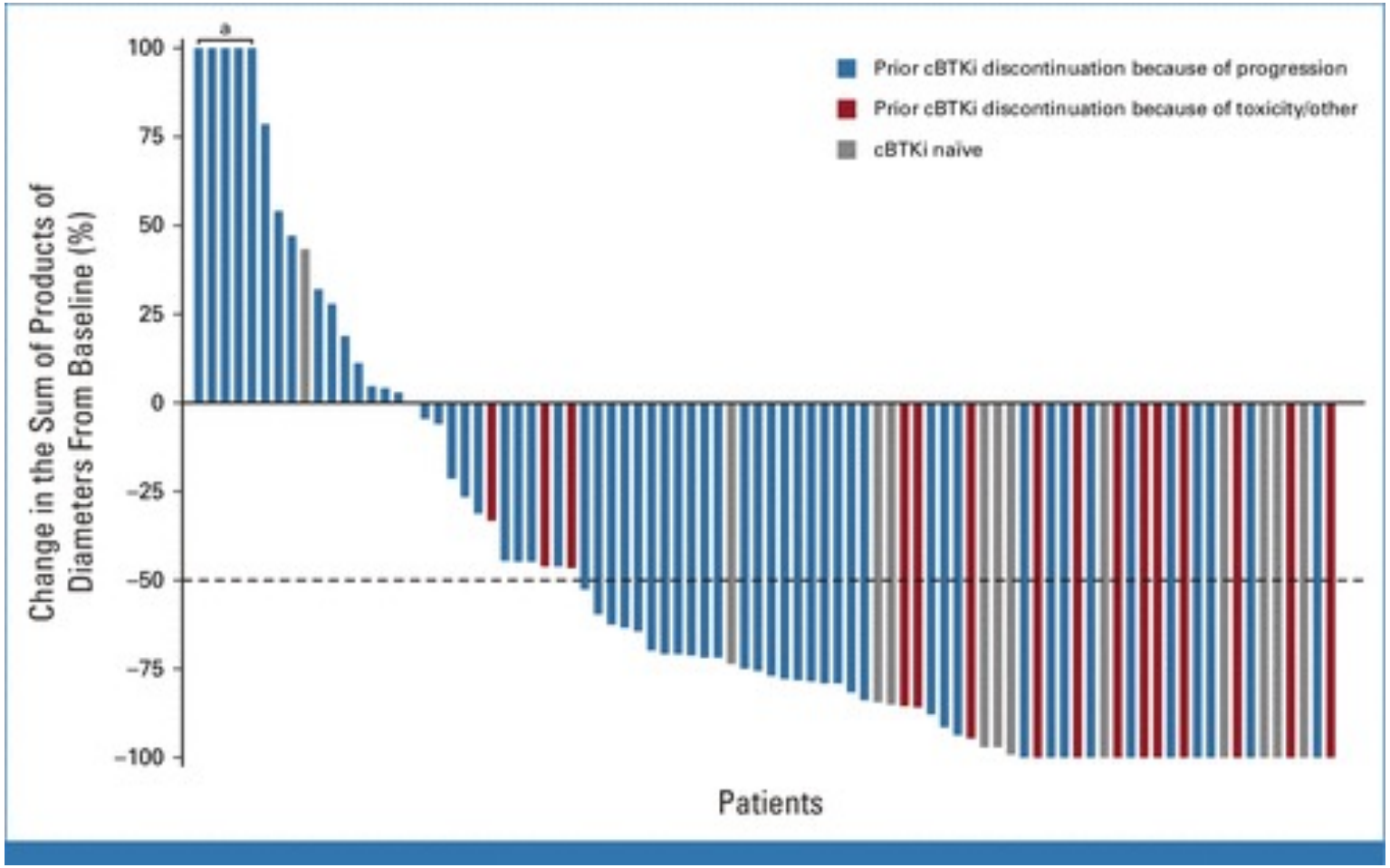
LeGouill et al, *Haematologica* 2023

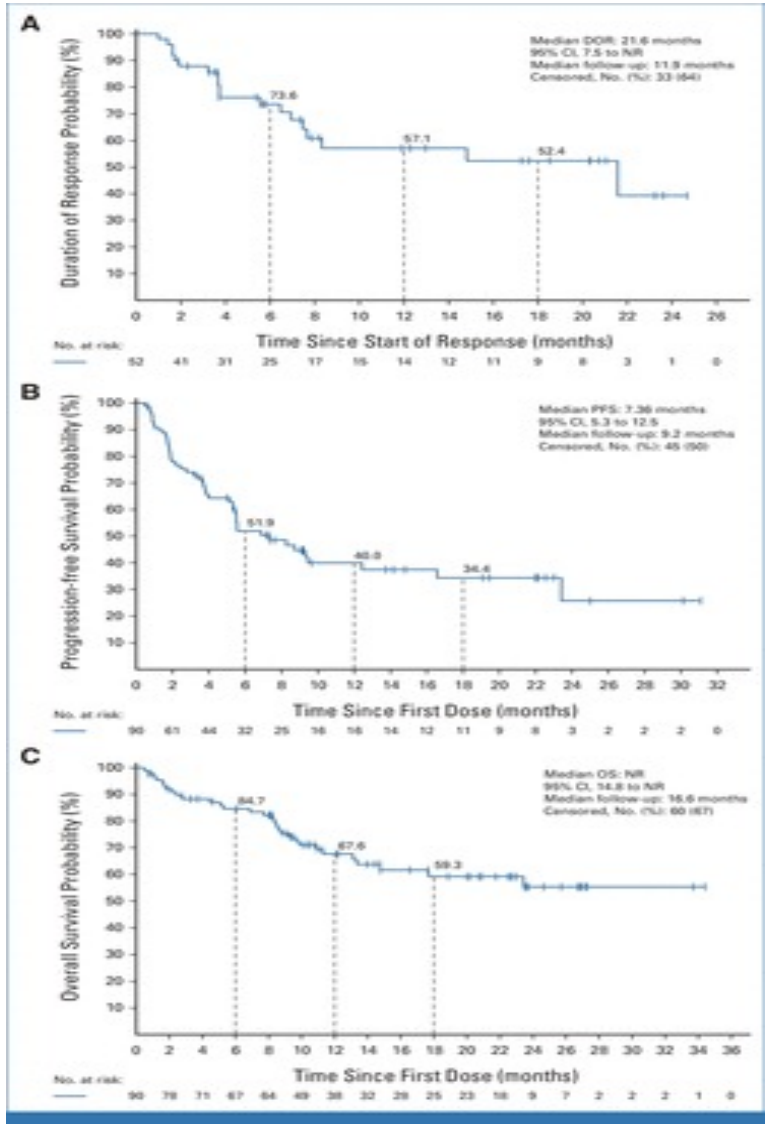
Zanubrutinib, single-agent:

- n = 86
- ORR 84%; CR 78%
- With median f/u 35 mo:
  - 3 y PFS 48%
  - 3 y OS 75%

Song et al, *Blood* 2022

Pirtobrutinib in R/R and covalent BTKi-pretreated MCL
Wang ML, et al. *J Clin Oncol* 2023; 41:3988





DOR

PFS

OS

FDA 2023: accelerated approval for MCL with at least 2 prior therapies

Bendamustine/Rituximab plus BTKi: Front-line MCL

	Regimen	PFS	OS	Toxicity	Reference
Real-world, in CR post BR induction	BR-Maint R vs BR	47 vs 30 mo	136 vs 76 mo	NR	ASCO 2024
Phase III Trials:					
ECHO	BR-Acala vs BR	66 vs 50 mo	No diff.*	Increased	EHA 2024
MANGROVE	BR vs Zanu+R	*Ongoing*			
SHINE	BR-Ibrut vs BR	81 vs 53 mo	No diff.	Increased	*NEJM* 2022
ENRICH	Ibrut-R vs BR or R-CHOP	65 vs 42 mo**	No diff.	Afib 6.6 vs 0.5% Better QOL w IR	ASH 2024
ECOG EA4181	3-arm trial, including BR-Acala				ASH 2024

*Crossover from BR to Acala allowed at progression
**PFS better for BR vs R-CHOP: 50 mo vs 27 mo

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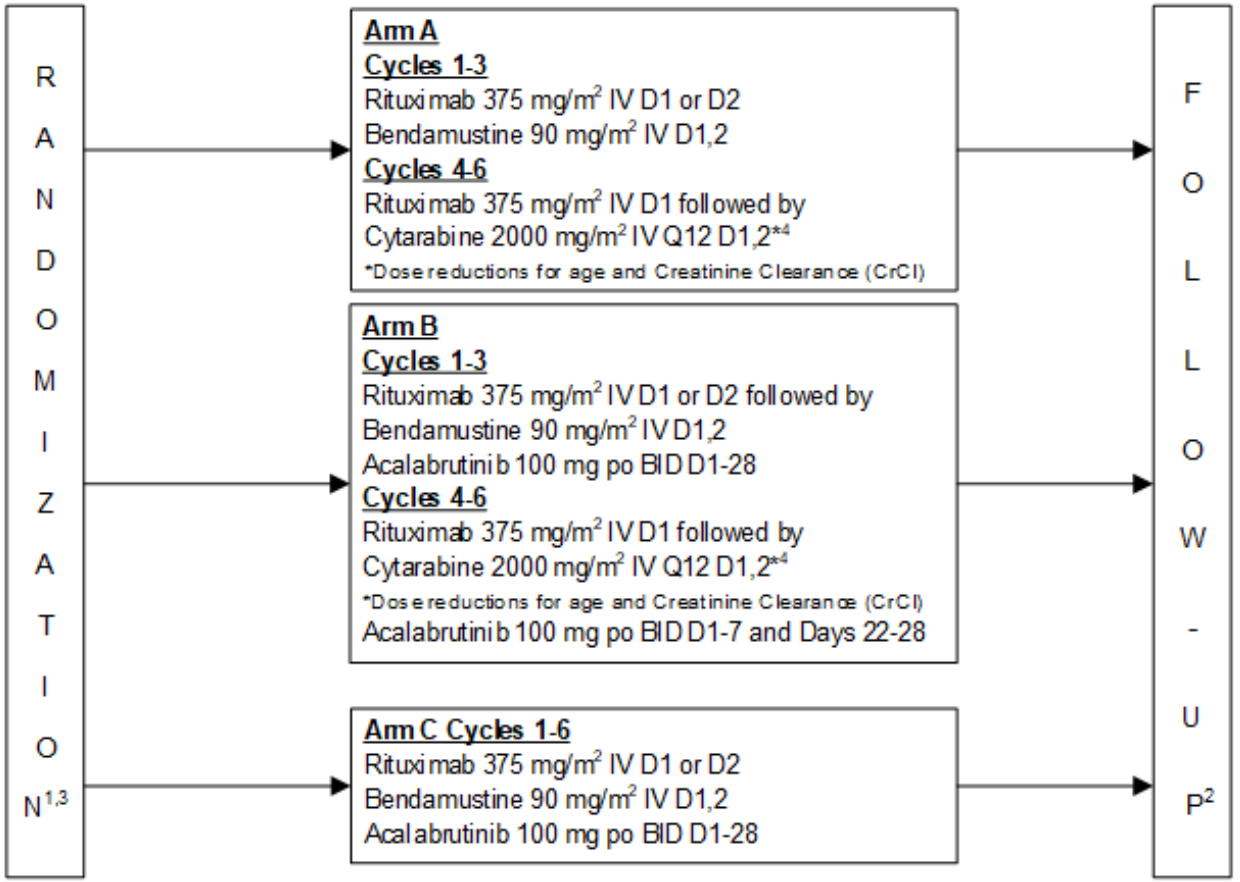
ECOG EA4181	3-arm trial, including BR-Acala				ASH 2024

To be determined: Treatment approaches, responses and outcomes after front-line BTKi

*Crossover from BR to Acala allowed at progression
**PFS better for BR vs R-CHOP: 50 mo vs 27 mo

ECOG EA4181: Front-line MCL (age </=70 y)

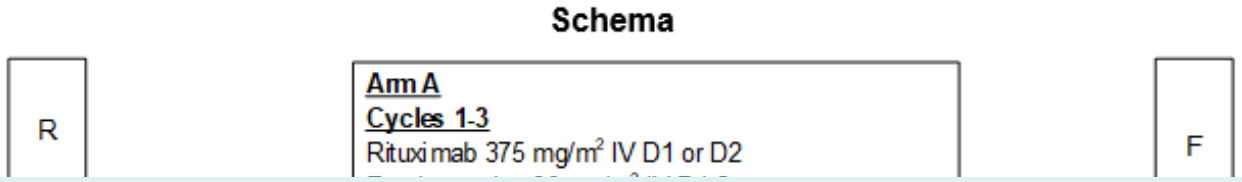
Schema



1 Cycle = 28 days
Accrual Goal: 369

1. Stratify using the MIPI risk score: high vs. intermediate vs. low. Diagnositc FFPE tumor tissue (or involved bone marrow) must be sent to Adaptive within 60 days of enrollment.
2. Patients will be followed per Section 5.5. MRD will be assessed 3-8 weeks after completion of study treatment and specimen submissions should follow guidelines in Section 7.2.
3. Randomization will occur 1:1:1 between Arms A, B, and C.
4. If treatment initiation is urgent and acalabrutinib is not available for cycle 1, treatment with bendamustine and rituximab may begin up to 4 days prior to acalabrutinib start.

ECOG EA4181: Front-line MCL (age </=70 y)



Nina Wagner-Johnston, Study PI for U.S. Intergroup:

- Trial opened in 2019
- ***Accrual completed 31 March 2023***
- Total accrual 352 (planned 360)

Among the study objectives:

- *Does the inclusion of a novel agent improve the MRD-negative CR rate?*
- *Does inclusion of a novel agent allow de-intensification of therapy?*

marrow) must be sent to Adaptive within 60 days of enrollment.

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ECOG EA4181: Results and Conclusions

Wagner-Johnston et al, ASH 2024, Abstract #236

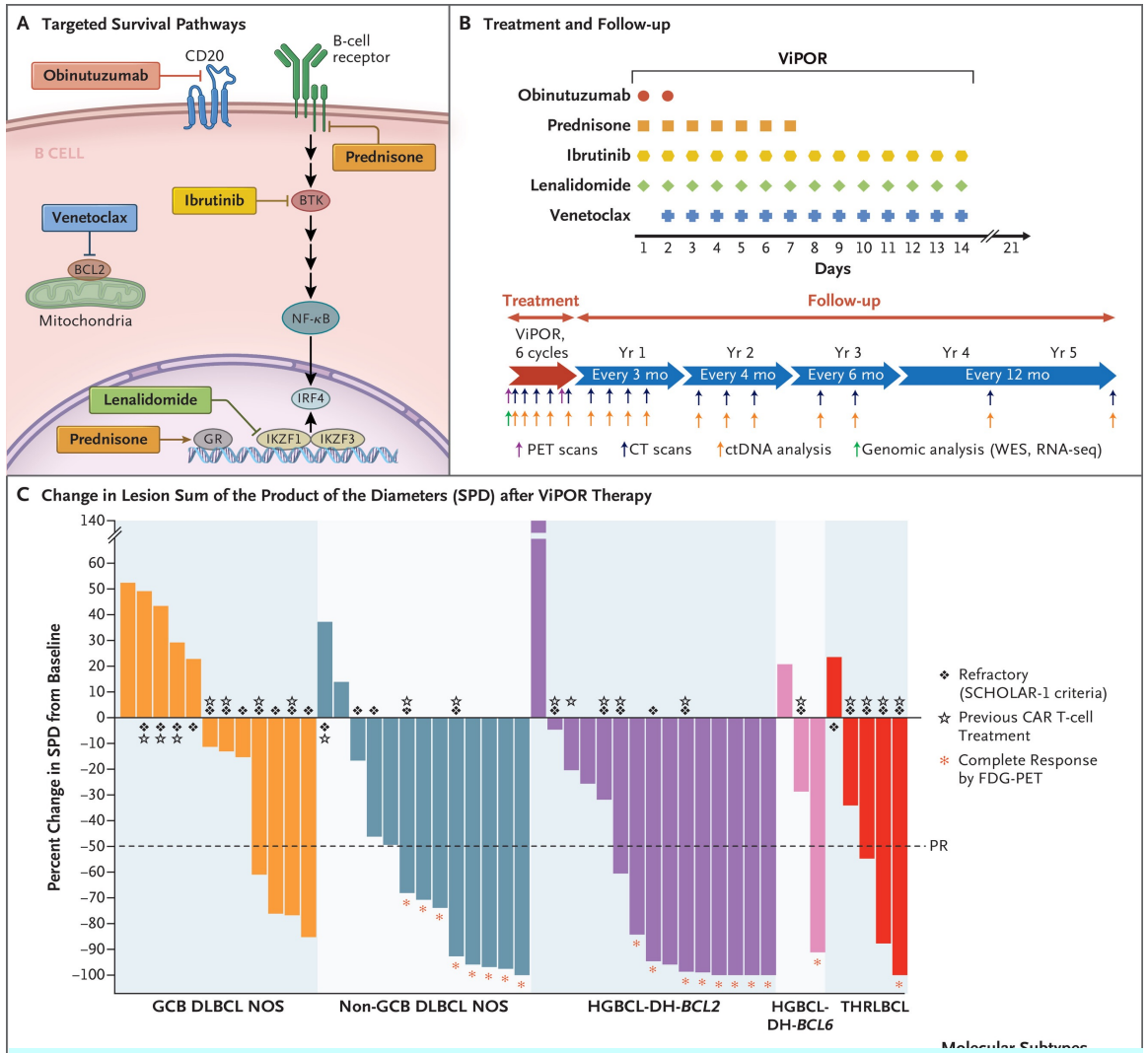
	Number with EOT MRD result	PET CMR *and* uMRD	12 m PFS/OS (med. f/u 28 m)	Treatment discontinued due to AE
Benda R/ Cytarabine R	85	82%	86%/94%	5%
BR/CR + Acala	98	82%	89%/98%	7%
BR + Acala	77	78%	87%/95%	8%

Conclusions:

- High PET-CT complete metabolic responses and uMRD rates were seen in all 3 arms
- BR/CR can be considered a standard induction regimen in patients < 70 y
- Addition of Acala to the standard regimen added toxicity without improved efficacy
- BR-A was not superior to BR/CR and study arm was closed by DSMC…….

- ***However, BR-A was the least toxic arm and had similar efficacy, and is thus an appealing option to avoid high-dose cytarabine***

Phase 1b/2 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide (ViPOR) in R/R and Treatment-Naïve MCL: Preliminary Analysis of Safety, Efficacy, and Minimal Residual Disease. Melani C, et al. *Blood* 2024 (ASH abstract #750)



Combination Targeted Therapy in Relapsed Diffuse Large B-Cell Lymphoma. Melani et al, *NEJM* 2024; 390:2143-55

36 MCL patients enrolled: R/R= 16; TN= 20

- Half had prior BTKi; none had Ven or Len
- No maintenance therapy; 1 R/R pt → allo SCT
- No DLT in Ph 1b → Ven 400 mg as RP2D

Biomarkers: Blastoid in 25%, Ki-67>30% in 37%, TP53 mutation or deletion in 32%

Toxicity: grade 3-4 cytopenias in 10-15%; no febrile neutropenia; hypokalemia 89%, rash 58%

Response after 6 cycles (n=35): CR = 100%

- @ median f/u 24 mo: 19/20 TN and 11/15 R/R responses are ongoing
- End-of-therapy uMRD in 27/28

Can incorporation of a BTKi with induction and maintenance therapy eliminate the need for ASCT in MCL?

Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE):

A three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network

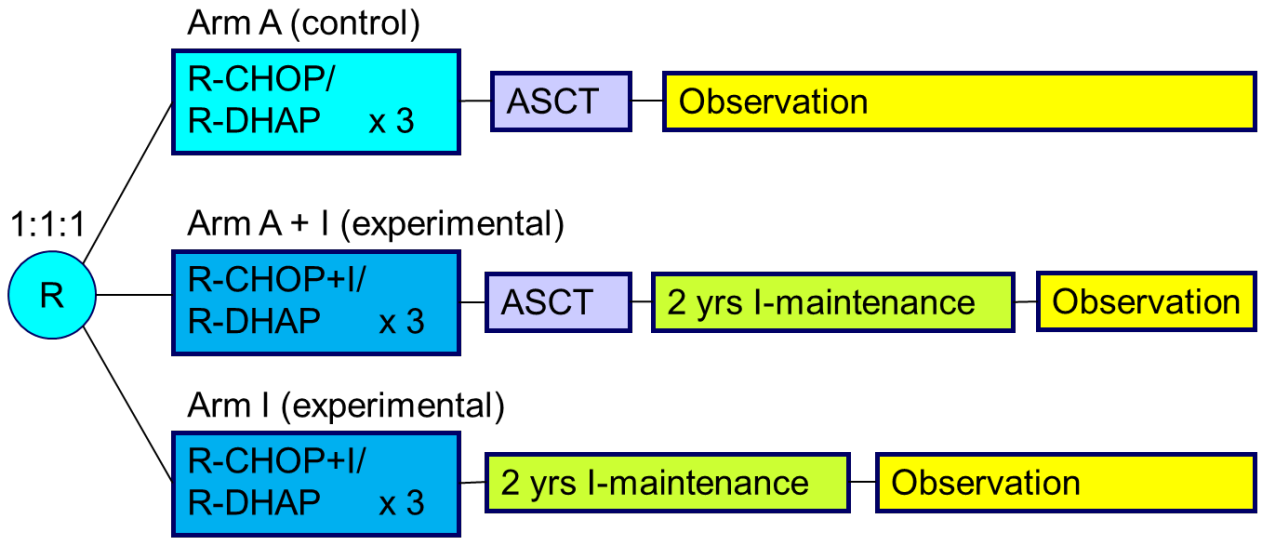
Dreyling M, et al, Lancet 2024

TRIANGLE: MCL Trial Design

- **870 patients**
- Previously untreated
- Stage II-IV
- > 66 yo; 77% M, 98% White
- Suitable for HA and ASCT
- ECOG 0-2

- **Primary outcome: FFS**

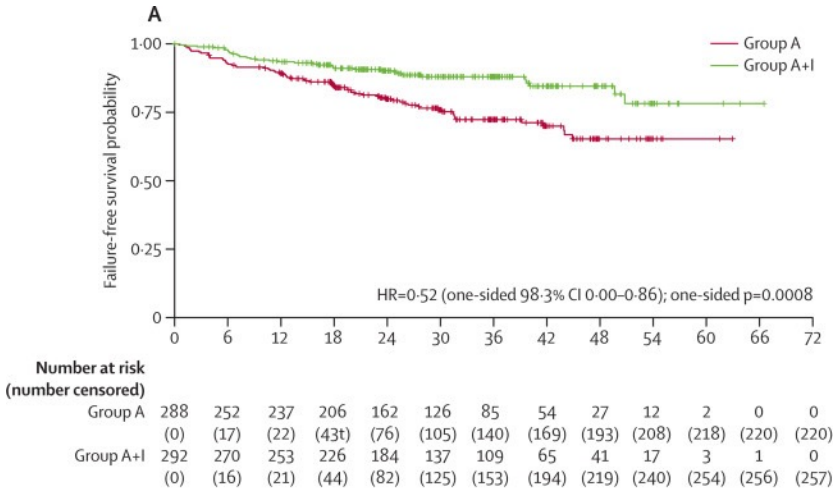
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

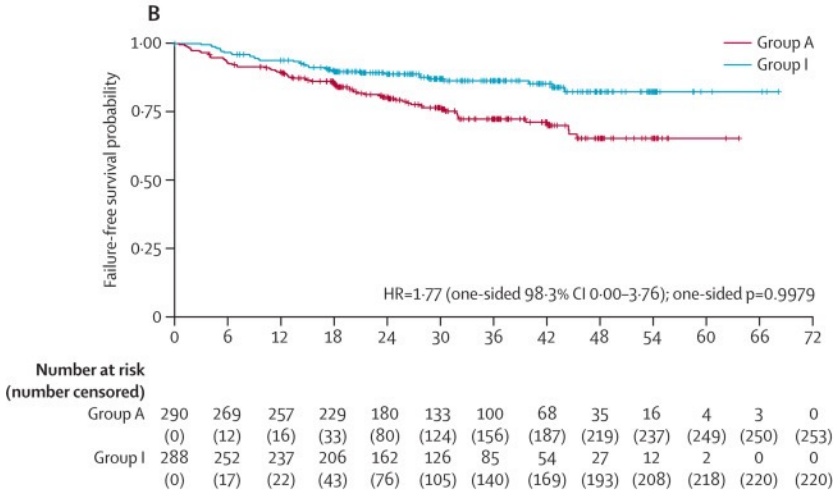


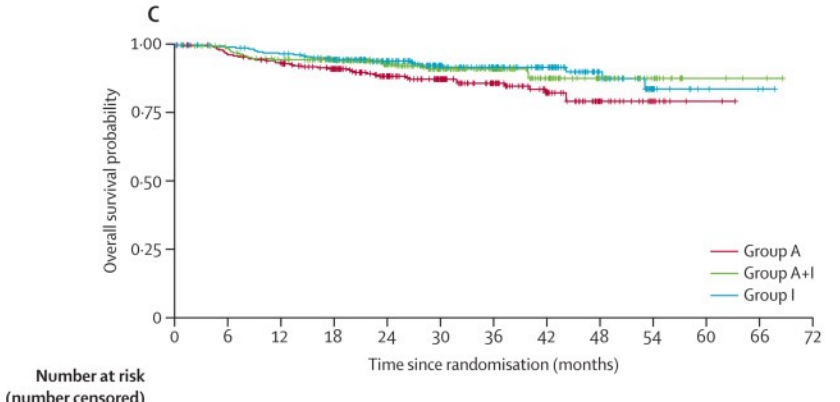
- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

TRIANGLE: Results

Dreyling et al, *Lancet* 2024







Failure-free survival
Median follow-up = 31 months

Significant benefit for ibrutinib plus chemo/ASCT (green) vs chemo/ASCT (**red**; p<.0008)

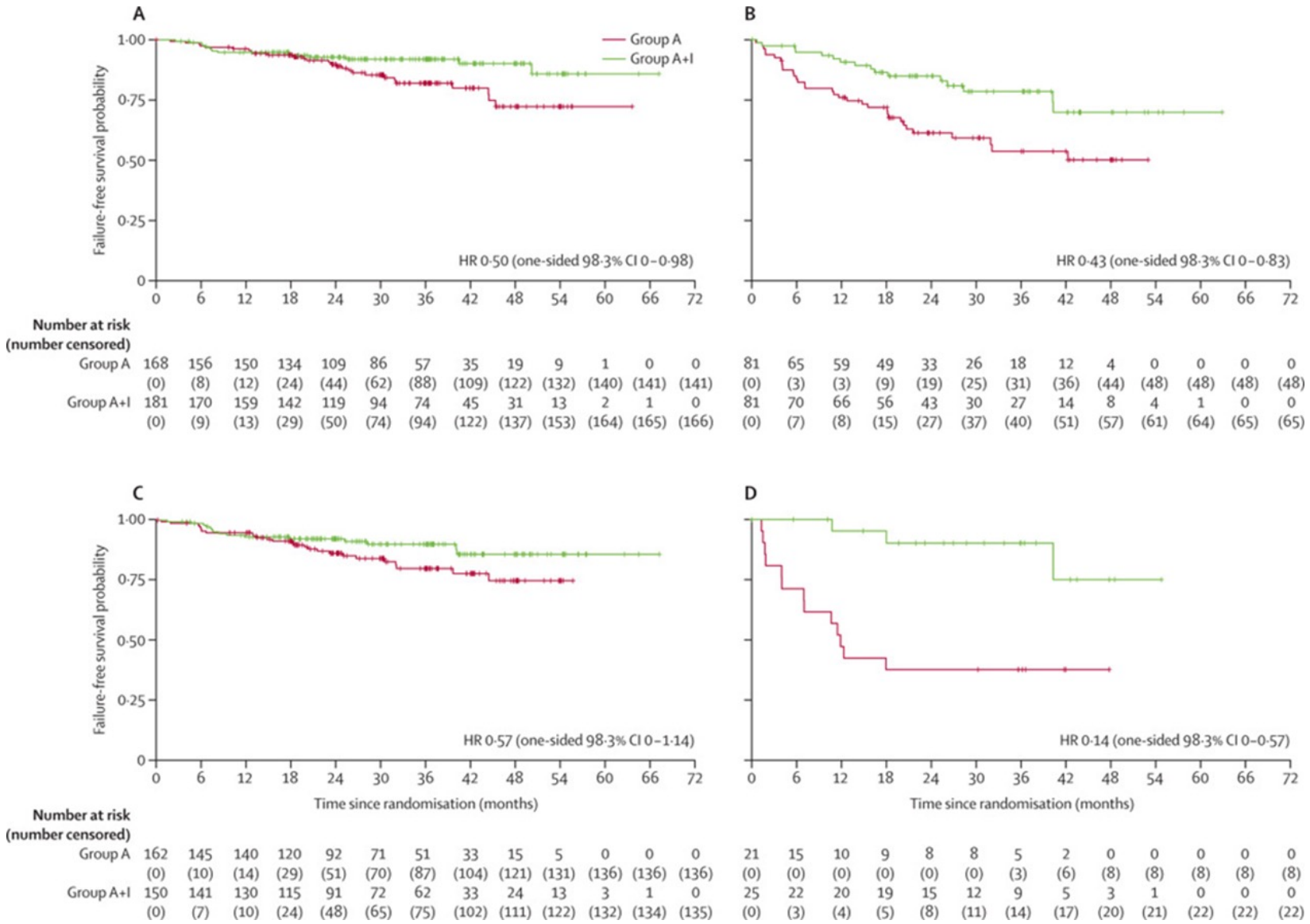
To date, Chemo/ibrutinib (no ASCT; blue) not statistically superior to chemo/ASCT, but 3 yr FFS favors Ibrutinib arm (86% vs 72%; NS)

Overall Survival also trending in favor of Ibrutinib-containing arms

- difficult to show OS benefit due to effective 2nd - and 3rd-line therapies

Outcomes in poor-risk groups:

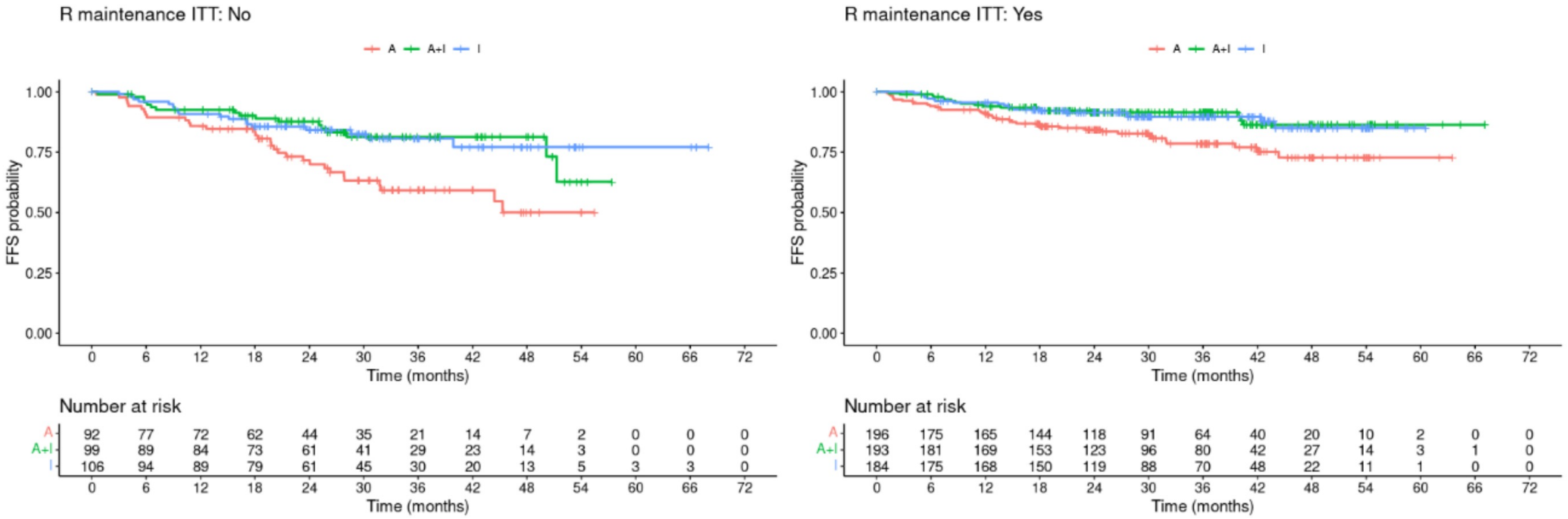
FFS in Low (<30%; A) vs High (B) Ki67 Proliferation Index, and Low (<50%; C) vs High (D) p53 expression (ASCT vs ASCT + Ibrutinib)



TRIANGLE: Rituximab maintenance

- Was allowed per national guidelines in all 3 trial arms (study conducted in 14 countries)
- R maintenance (with or without concurrent Ibrutinib) was administered in:

Arm A = 168 (58 %) ; **Arm A+I** = 165 (57 %) ; **Arm I** = 158 (54 %) of randomized patients



- FFS benefit conferred by Ibrutinib appeared more modest among those getting Rituximab
- More grade 3-5 infections with Ibrutinib plus RM (25-31%) vs Ibrutinib alone (11-15%)

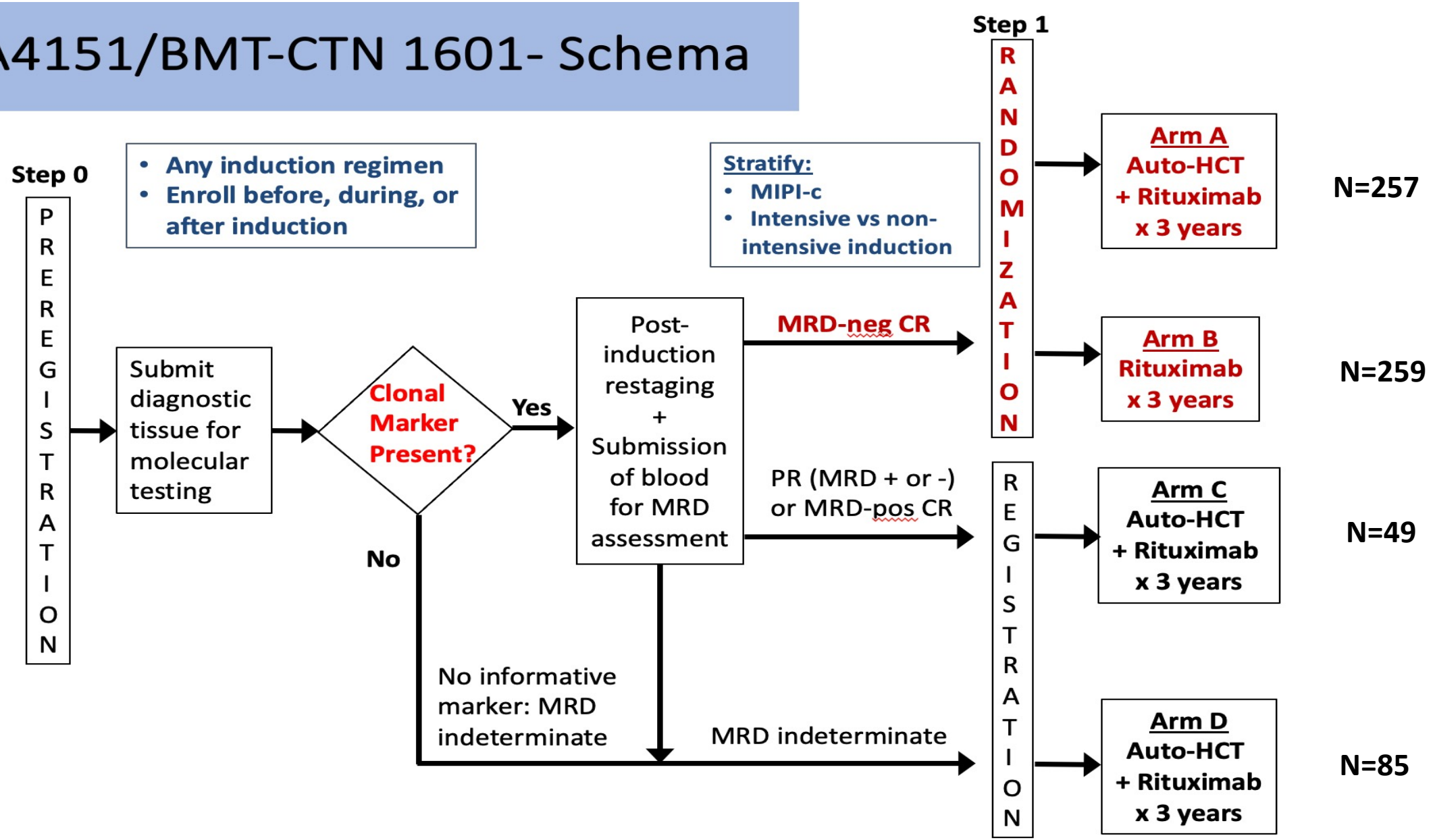
Dreyling et al, *Suppl. Fig. S3; Lancet* 2024 (slide modified from B. Shah); also see Ladetto et al, ASH 2024, abstract # 237

Lack of Benefit of Autologous Hematopoietic Cell Transplantation (auto-HCT) in Mantle Cell Lymphoma (MCL) Patients (pts) in First Complete Remission (CR) with Undetectable Minimal Residual Disease (uMRD): Initial Report from the ECOG-ACRIN EA4151 Phase 3 Randomized Trial

Timothy S. Fenske, Xin Victoria Wang, Brian G. Till, Kristie A. Blum, Matthew Lunning, Hillard M. Lazarus, Paul A.S. Fishkin, Lale Kostakoglu Shields, David W. Scott, Ann S. LaCasce, Patrick B. Johnston, Amanda F. Cashen, Leslie L. Popplewell, Robert M. Dean, Nausheen Ahmed, Nirav N. Shah, Nina D. Wagner-Johnston, Boyu Hu, Bhagirathbhai R. Dholaria, Richard F. Little, Jonathan W. Friedberg, John P. Leonard, and Brad S. Kahl, MD

ECOG-ACRIN
cancer research group

EA4151/BMT-CTN 1601- Schema

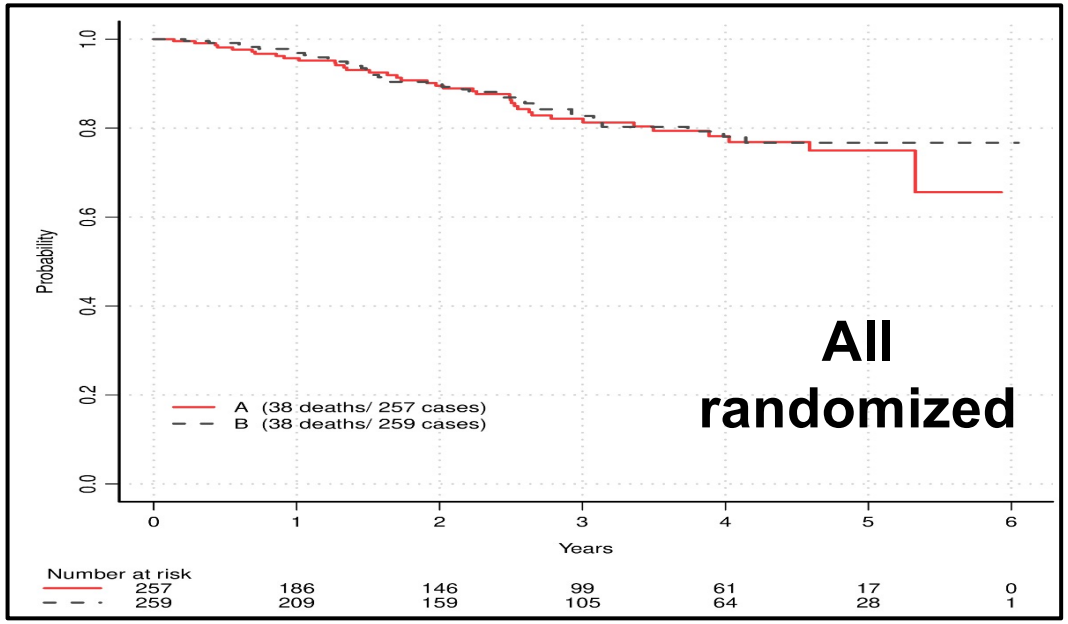


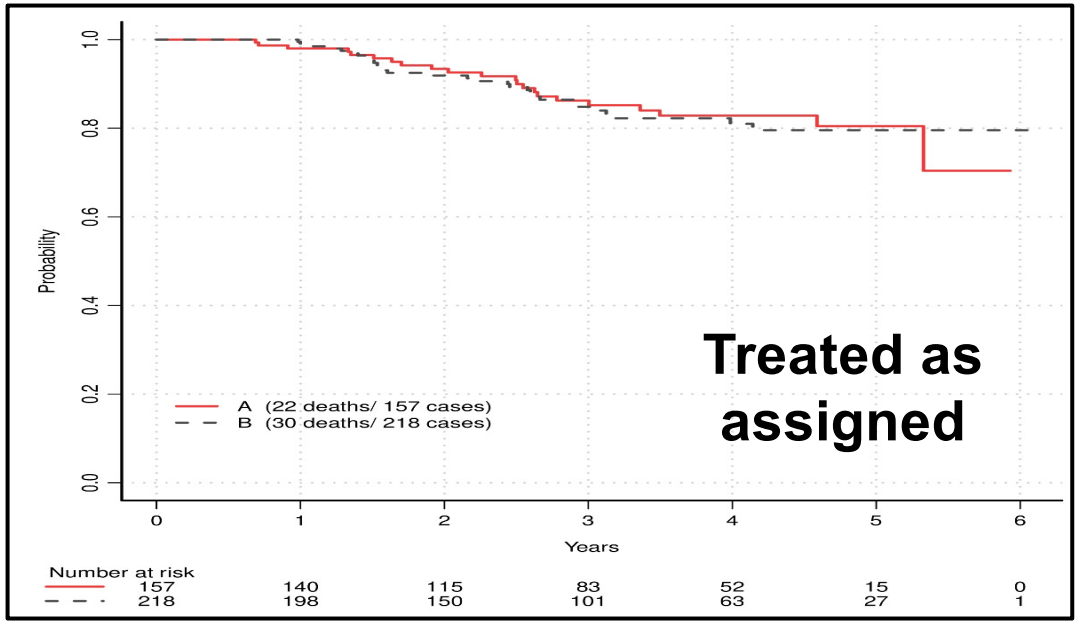
Statistical Analysis

- Primary analysis population included all randomized pts.
- As some pts **refused their assigned treatment (N=65 [25.3%] for arm A** and **N=2 [0.8%] for arm B),** a “treated as assigned” analysis was also performed.
- Analysis of OS and PFS were both performed
- Stratified logrank test was used to compare survival distributions. P-values are two-sided.

OS – Arms A & B

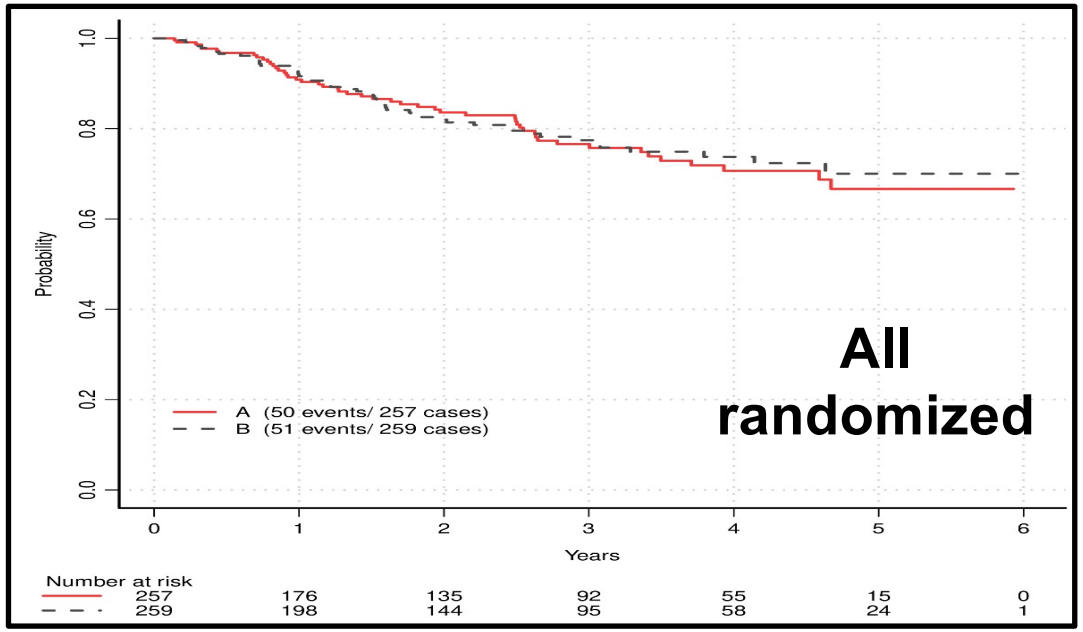
- With median follow up of 2.7 years, the futility boundary was an OS hazard ratio (HR) of 0.984 for Arm A vs B.
- The estimated OS HR for Arm A vs B in all randomized (n=516) and pts treated as assigned (n=375) were 1.11 (CI 0.71-1.74, p=0.66) and 1.00 (CI 0.58-1.74, p=0.99), respectively **and crossed the futility boundary**.
- The 3 year OS for Arms A and B were 82.1% and 82.7% in all randomized pts, and 86.2% and 84.8% in pts treated as assigned.

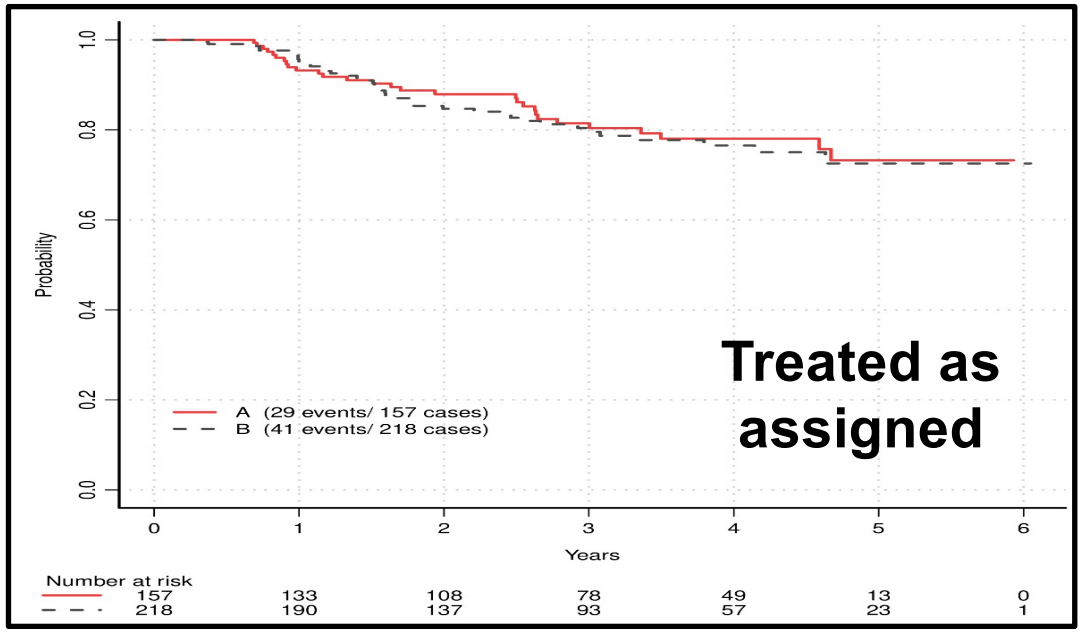




PFS – Arms A & B

- The estimated PFS HR for Arm A vs B in all randomized (n=516) and pts treated as assigned (n=375) were 1.05 (CI 0.71-1.56, p=0.79) and 0.95 (CI 0.59-1.54, p=0.84), respectively.
- The 3 year PFS for Arms A and B were 76.6% and 77.4% in all randomized pts, and 81.5% and 80.4% in pts treated as assigned.

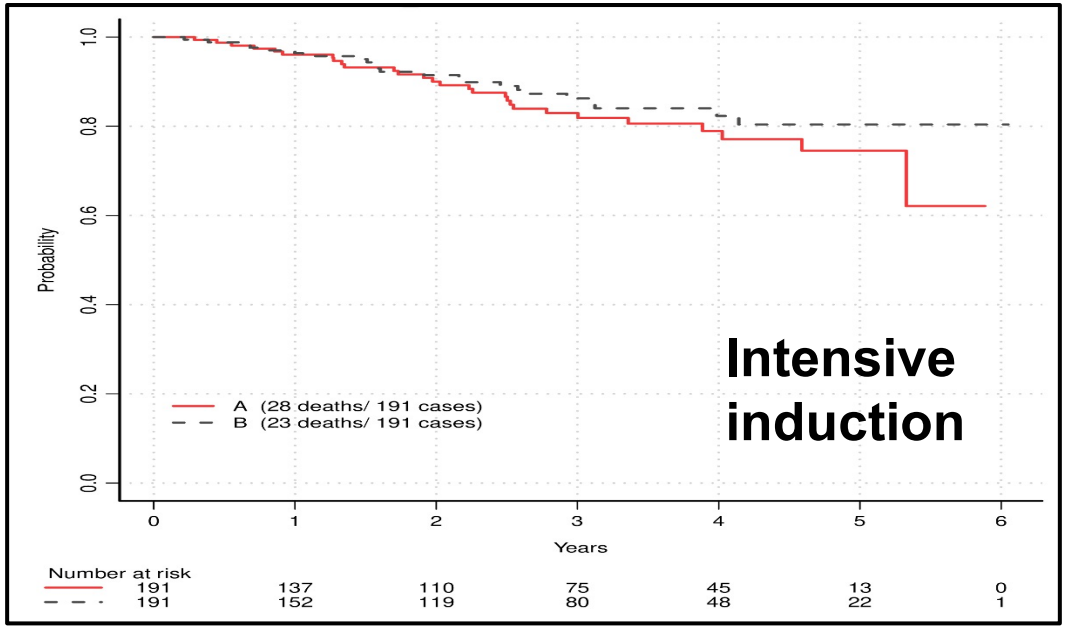


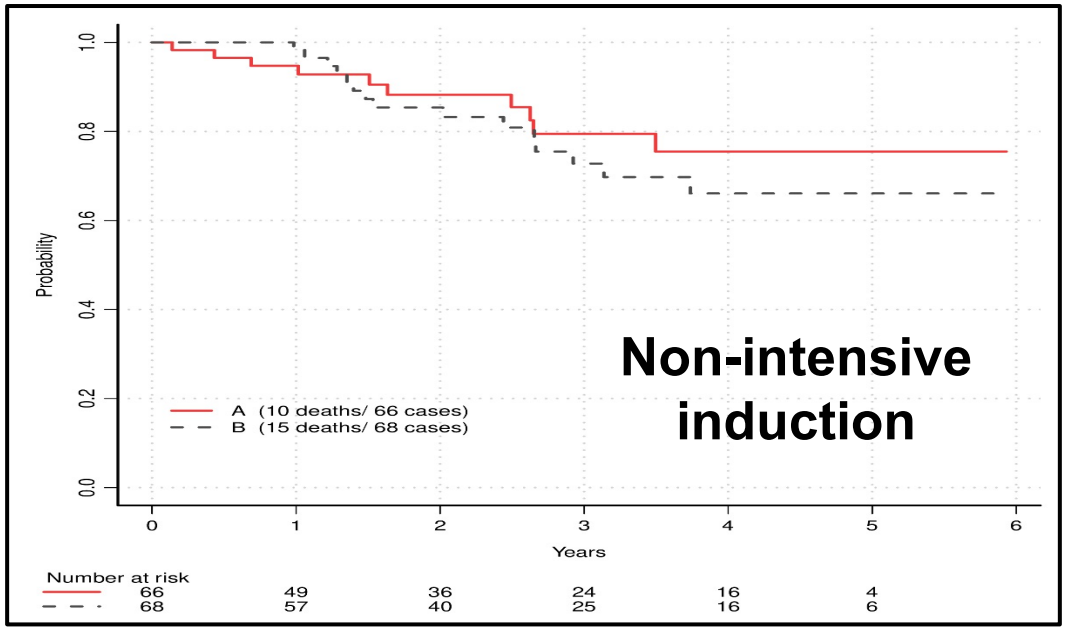


OS – Arms A & B

by intensive vs non-intensive induction

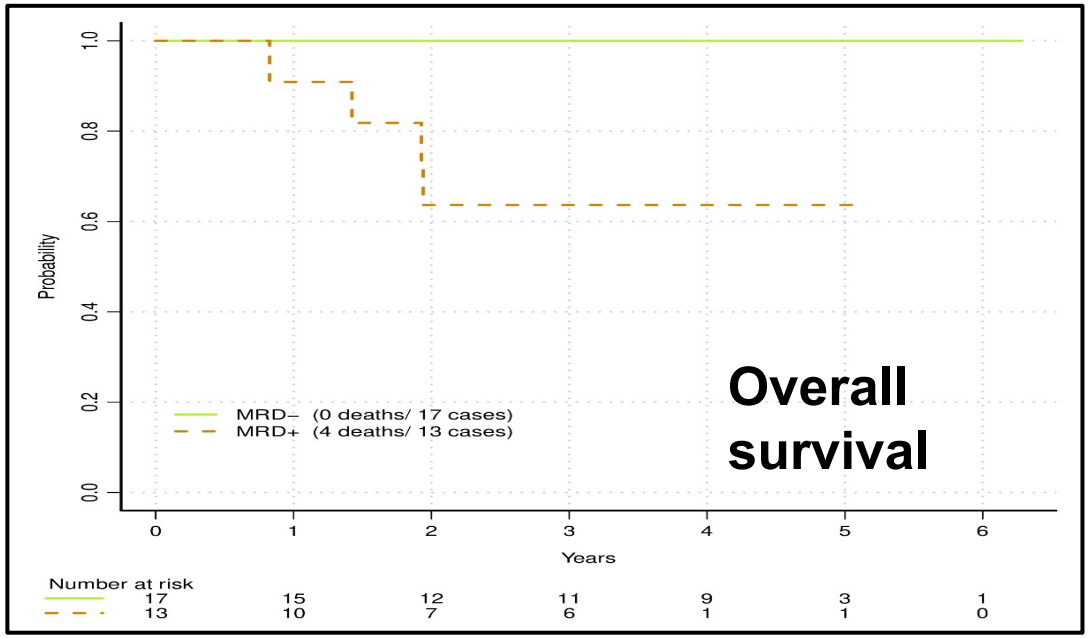
- For the intensive induction group, 3 yr OS was 83.0% vs 86.2% for Arm A vs B (p=0.30)
- In the non-intensive induction group, 3 yr OS was 79.5% vs 72.8% for Arm A vs B (p=0.48).

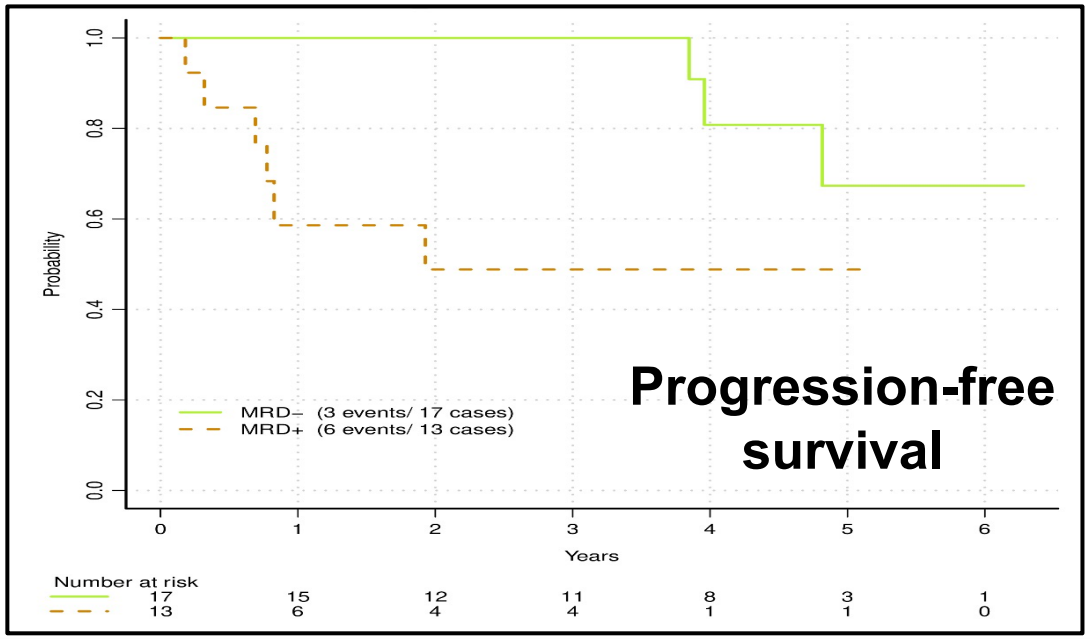




Arm C (MRD+ pts)
by post-transplant MRD status

- Exploratory analysis of **MRD+ pts (Arm C) showed that 3 yr OS in pts who converted to uMRD6 post auto-HCT (n=17) was 100%,** versus 63.6% in those who remained MRD+
- Similarly, 3 yr PFS in pts who converted to uMRD6 post auto-HCT was 100% versus 48.8% in those who remained MRD+

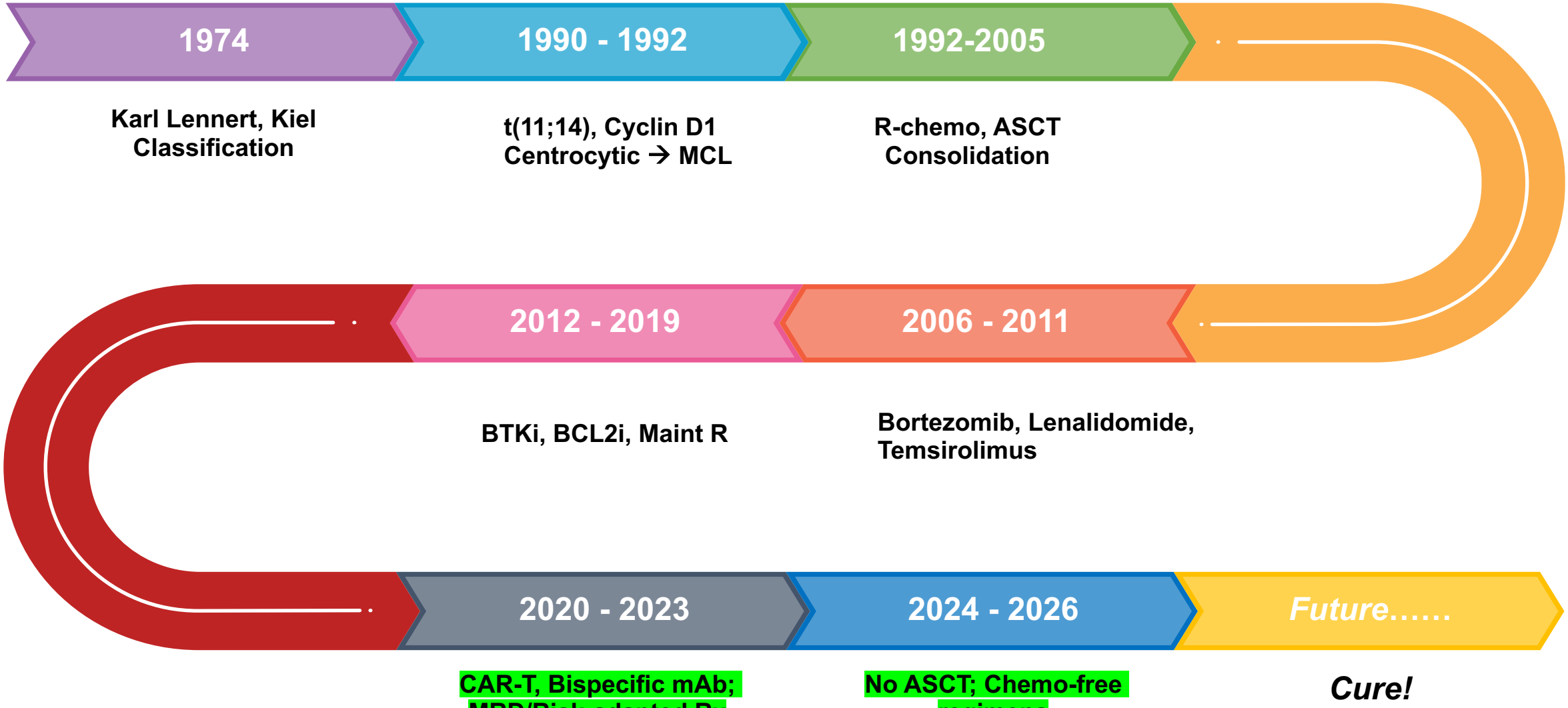




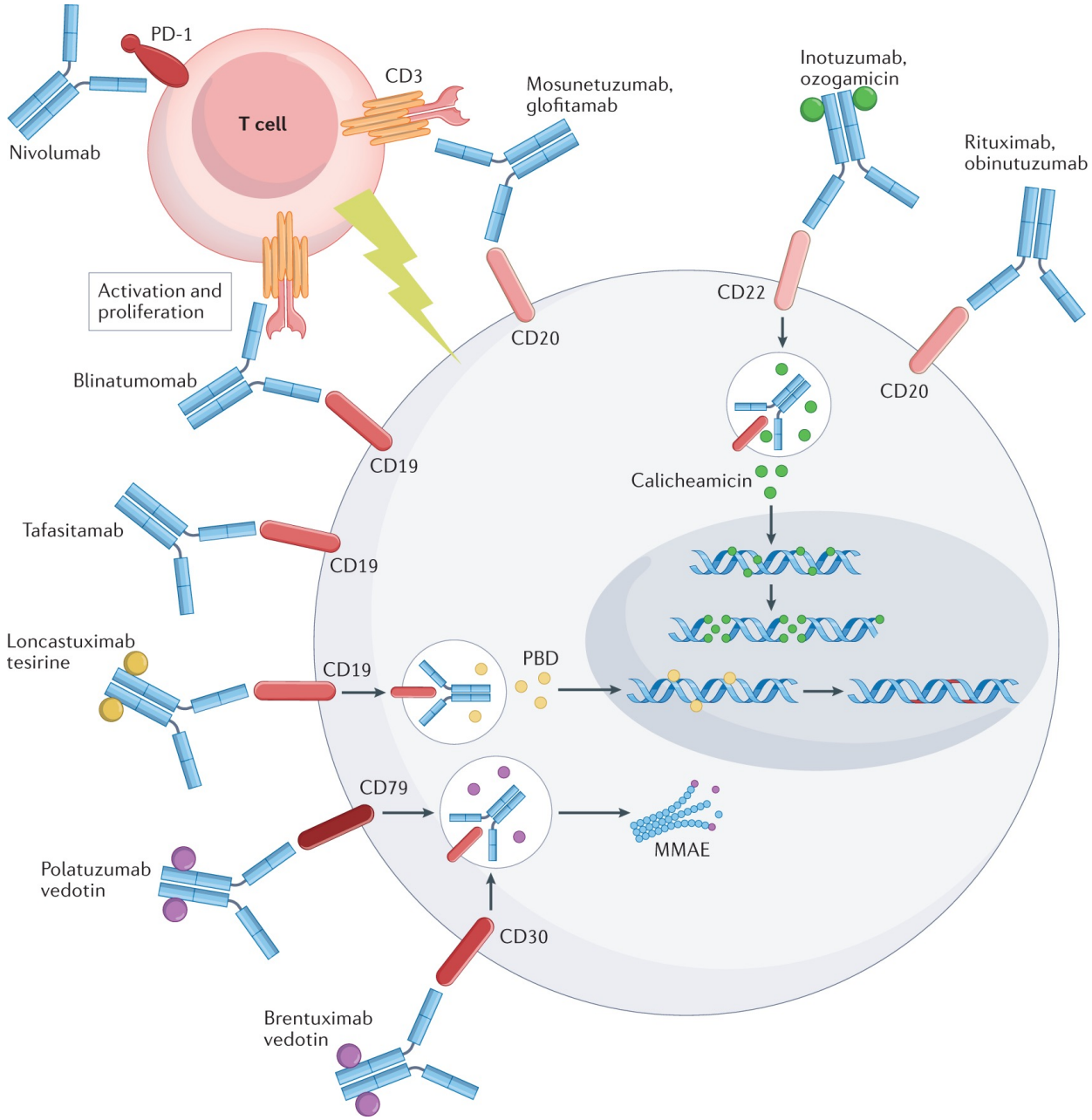
Conclusions

- In this initial analysis, in the era of highly effective induction and maintenance regimens, MCL pts in first CR with uMRD6 did not benefit from consolidative auto-HCT.
- Pts who remain MRD+ after induction may benefit from auto-HCT. MRD+ patients who converted to uMRD6 post auto-HCT appeared to have improved OS and PFS.
- Longer follow-up will be important to confirm these findings.

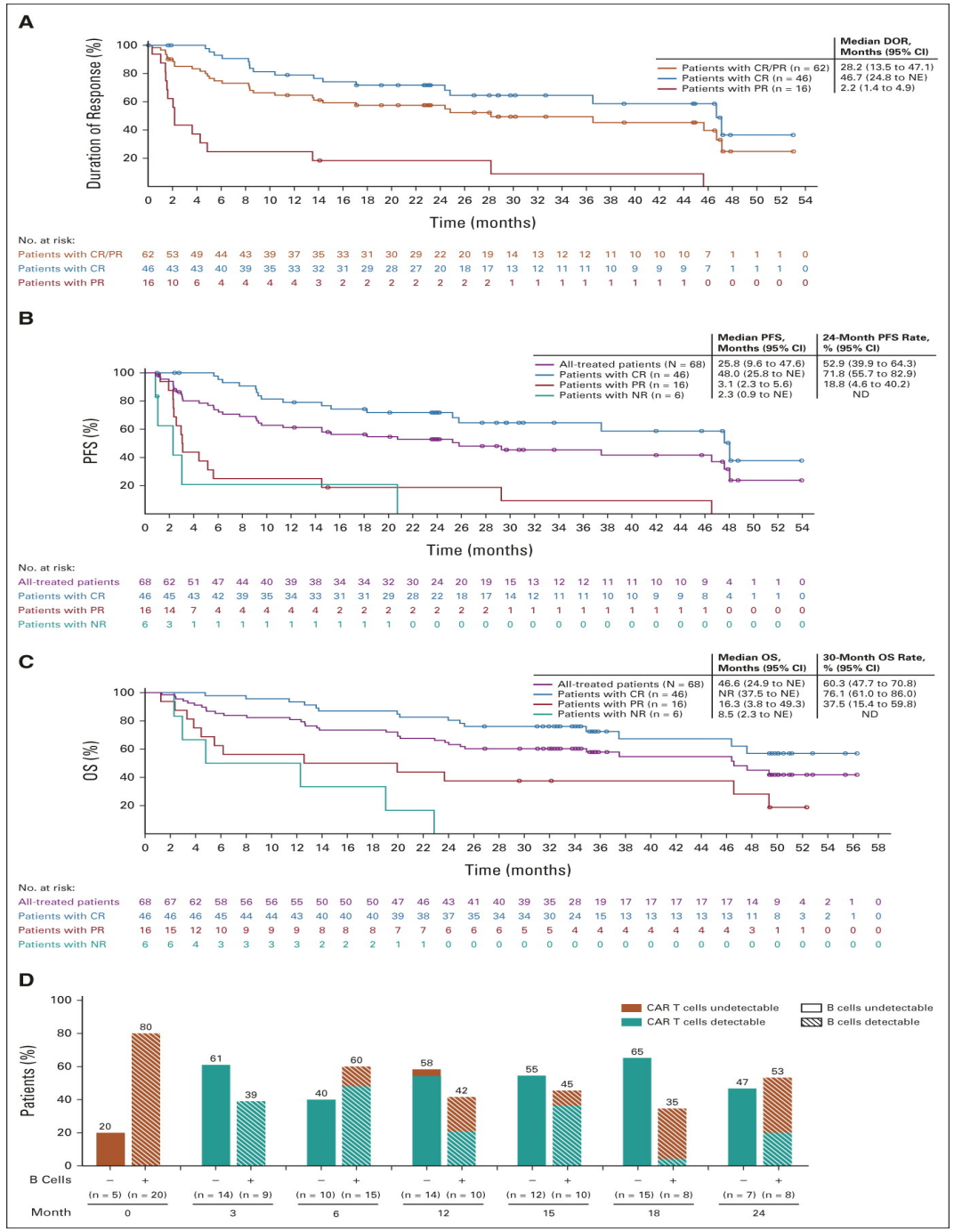
Therapeutic Evolution in Mantle Cell Lymphoma



Immunotherapy-based options for Lymphoma



Amini et al, Nature Reviews 2022



ZUMA-2: Results (n=68)

Cohort 1: R/R MCL *with* prior cBTKi

Median Follow-up: 36 mo

Conclusions:

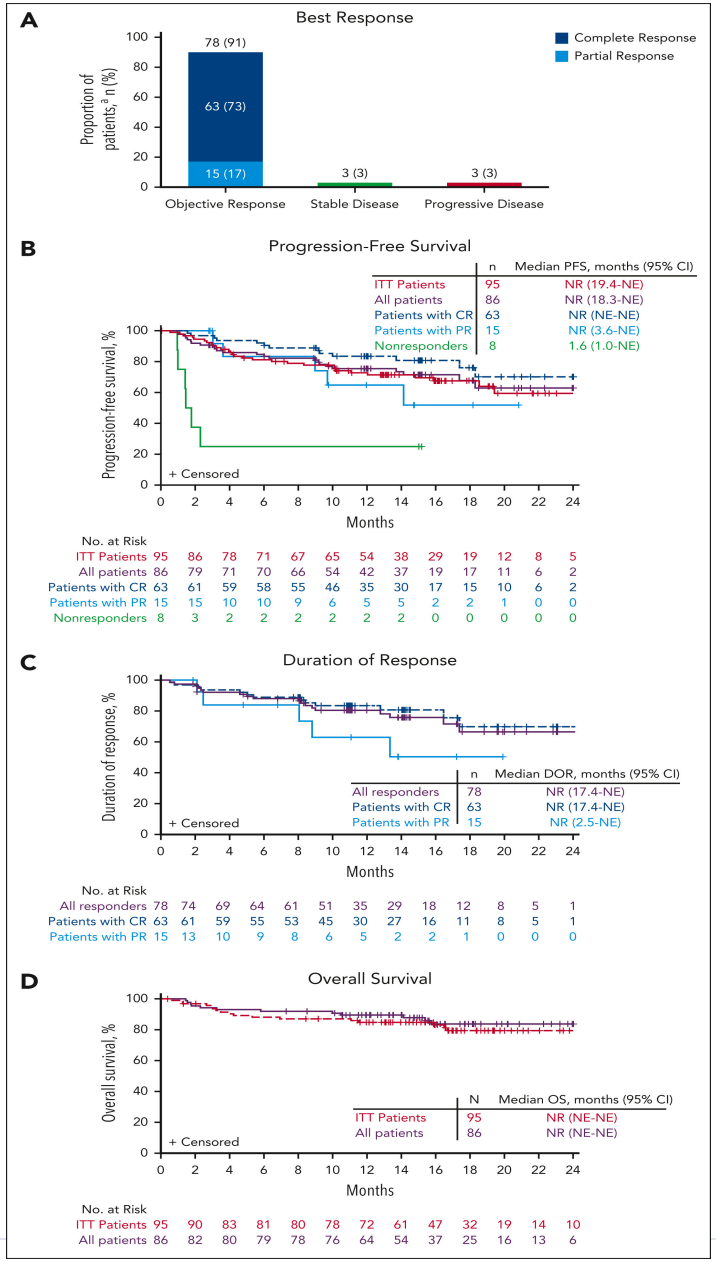
- Durable responses and sustained survival
- Manageable safety profile in R/R MCL

Relevance (per J. Friedberg):

"Durable outcomes suggest that the use of KTE-X19 in earlier lines of treatment may be beneficial for patients with R/R MCL, including those with high-risk characteristics"

Wang M, et al. *Journal of Clinical Oncology* 2023 41555-567.
DOI: 10.1200/JCO.21.02370

Brexucabtagene autoleucel for BTKi-naive relapsed/refractory mantle cell lymphoma: primary analysis of ZUMA-2 cohort 3



ZUMA-2: Results (n=95; 86 rec'd brexu-cel)

Cohort 3: R/R MCL *without* prior cBTKi

Median Follow-up: 15.5 mo

Primary endpoint met (n=86):

ORR by IRC 91% (CR 73%)

12 mo OS = 90%

Grade >/=3 AE in 88%; four grade 5 events

Conclusions:

- Further supports use of brexu-cel in R/R MCL
  - But do risks justify use prior to BTKi?
- Consider in high-risk patients prior to BTKi?
  - Need longer f/u of this cohort
- Consider randomized trial of CAR-T or Bispecific Ab as consolidation in high-risk patients

van Meerten T, et al. Blood 2026; 147:1302-14.

Shah N. Editorial; ibid, pp.1244-6

Lisocabtagene Maraleucel [Liso-cel] in Relapsed/Refractory Mantle Cell Lymphoma

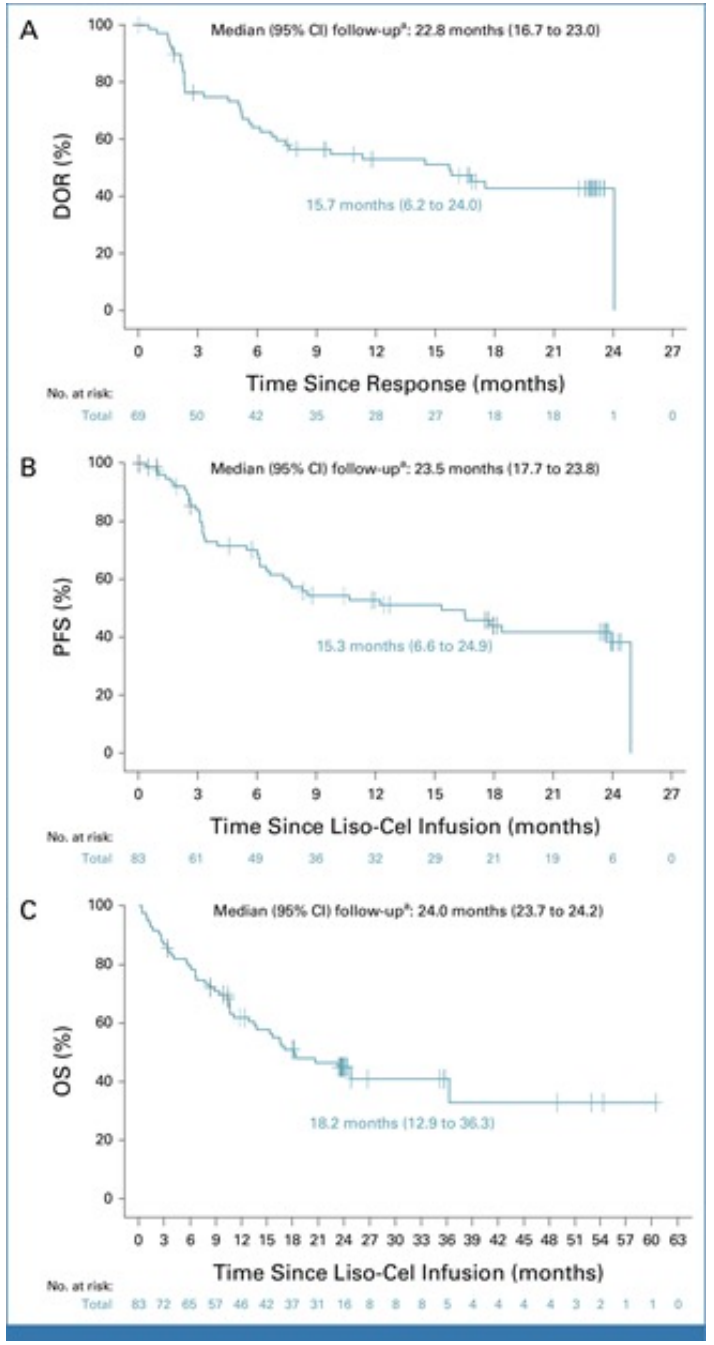
Wang M, et al; *J Clinical Oncology* 2024; 42:1146-57

- Evaluable patients = 83
- All relapsed after 2 or more prior regimens that included an anti-CD20 mAb, an alkylator and a BTKi

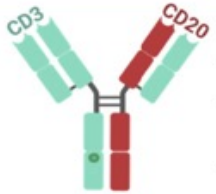
- ORR 83%
- CR 72%, including:
  - **11/19 with TP53 mutation**
  - **17/27 with Blastoid MCL**
  - **6/7 with CNS MCL**
- Very low rates of grade 3-4 CRS and neurotoxicity

Conclusions:

- High responses in poor-risk, heavily pretreated pts
- Favorable toxicity versus other CAR-T in MCL
- *Testing Liso-cel as an earlier line of therapy is warranted*



DOI: 10.1200/JCO.23.02214

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats	Ref.
blinatumomab	**CD19 x CD3**		• two murine scFv joined by a glycine-serine linker • monovalent CD19 and monovalent CD3 binding • cloned from anti-CD19 (clone HD37) and anti-CD3 (clone L2K-07) murine mAbs	1, 2, 3
mosunetuzumab	**CD20 x CD3**		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	4
glofitamab	**$(CD20)_2$ x CD3**		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	5
odronextamab	**CD20 x CD3**		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb	6
epcoritamab	**CD20 x CD3**		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield	7

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcγR, Fc gamma receptor

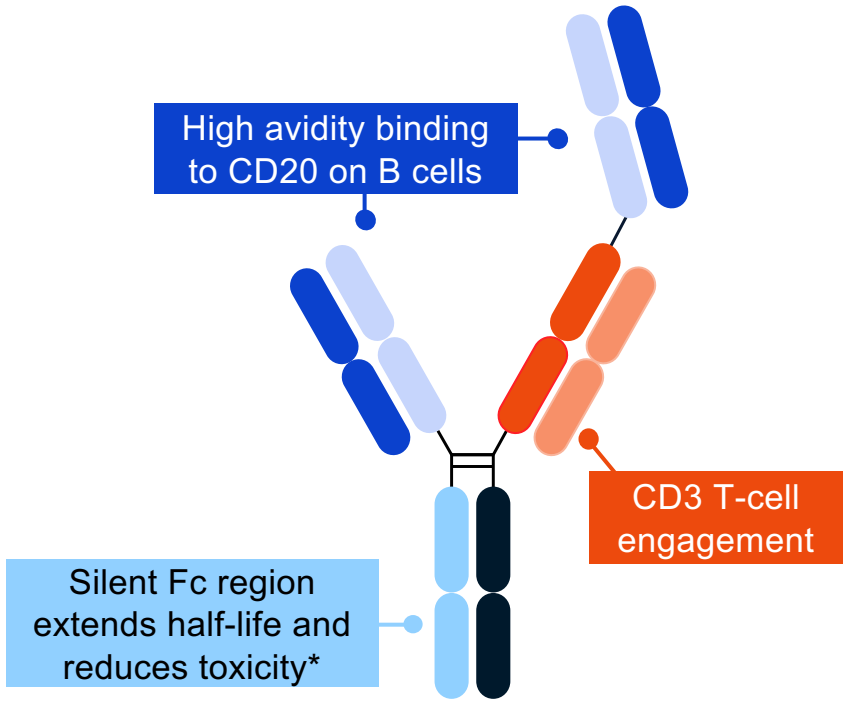
[1]Dufner V, *et al*. Blood Adv (2019) 3:2491; [2]Goebeler ME, *et al*. J Clin Oncol (2016) 34:1104; [3]Viardot *et al*. Blood (2016) 127(11):1410; [4]Schuster SJ, *et al*. ASH 2019, Plenary Abstract 6; [5]Hutchings M, *et al*. ASH 2020, Abstract 403; [6]Bannerji R, *et al*. ASH 2020, Abstract 400; [7]Hutchings M, *et al*. ASH 2020, Abstract 406

From: Schuster SJ. *Hematological Oncology* 2021

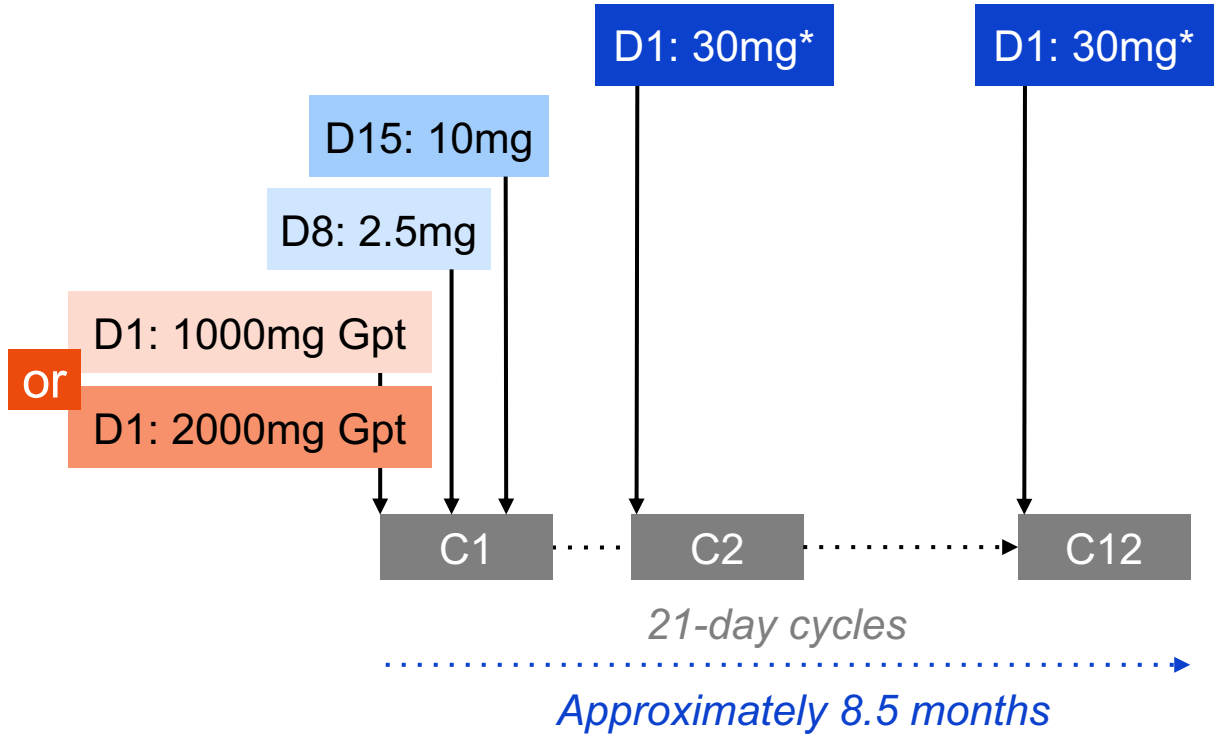
Glofitamab in R/R MCL (NP30179): Phase I/II

Slide courtesy of T. Phillips. *J Clin Oncol 2025*; 43:318-28

Glofitamab: *CD20xCD3 bispecific antibody with 2:1 format for increased potency versus 1:1 format*[1]



Dosing schedule



Clinical cut-off date: September 04, 2023.

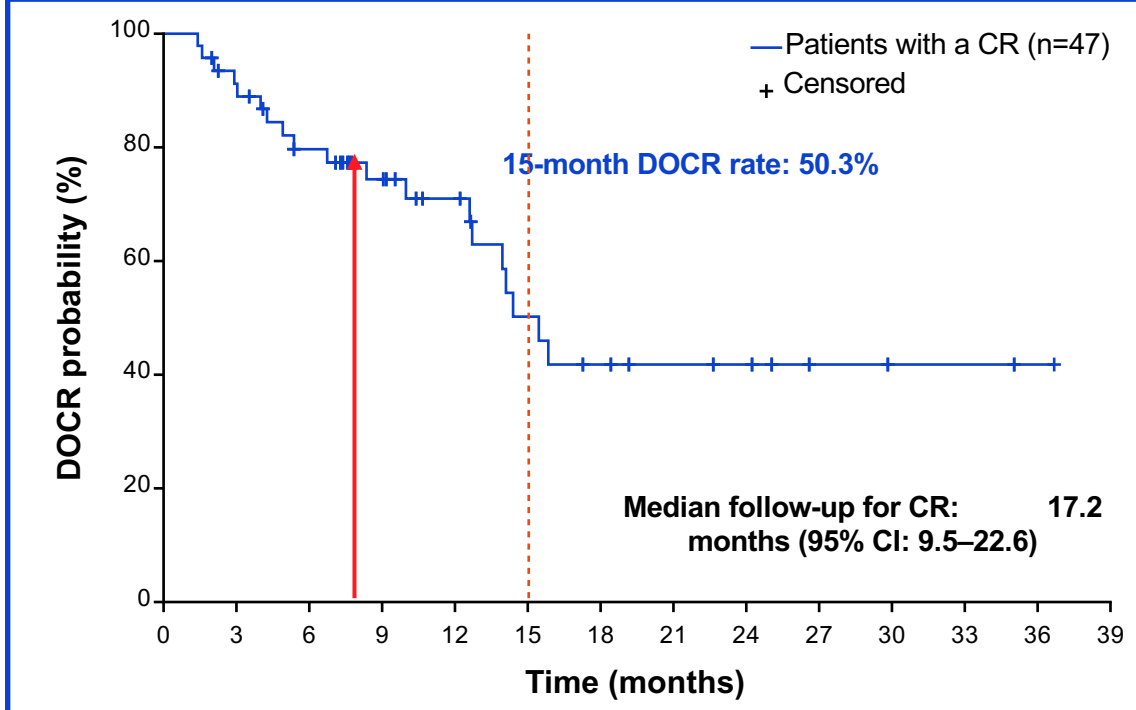
*In the 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose in the dose escalation phase.

C, cycle; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pretreatment; IV, intravenous. **NCT03075696.** Available at: https:www.clinicaltrials.gov

Glofitamab in R/R MCL: Duration of response

DOCR*	Prior BTKi n=22	All patients n=47
Median DOCR, months (95% CI)	12.6 (5.4–NE)	15.4 (12.7–NE)
15-month DOCR rate, % (95% CI)	33.5 (10.6–56.4)	50.3 (32.0–68.6)
Ongoing CR, n (%)	10 (45.5)	28 (59.6)
DOR*	**n=23**	**n=51**
Median DOR, months (95% CI)	12.6 (7.4–NE)	16.2 (12.6–NE)
15-month DOR rate, % (95% CI)	38.0 (15.5–60.6)	59.7 (44.1–75.3)
Ongoing response, n (%)	10 (43.5)	28 (54.9)

DOCR*



Clinical cut-off date: September 04, 2023. Investigator-assessed.
DOR, duration of response; DOCR, duration of complete response; NE, not estimable.

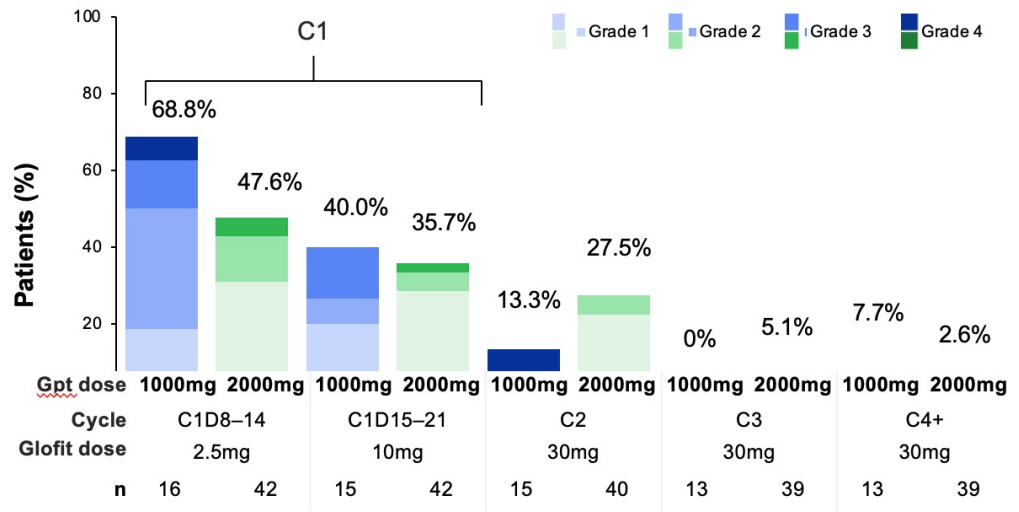
Slide courtesy of T. Phillips. *J Clin Oncol* 2025; 43:318-28

Glofitamab in R/R MCL: CRS by cycle and grade

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)
Any grade CRS*	14 (87.5)	28 (63.6)
Grade 1	4 (25.0)	18 (40.9)
Grade 2	6 (37.5)	7 (15.9)
Grade 3	2 (12.5)	3 (6.8)
Grade 4	2 (12.5)	0
Serious AE of CRS†	11 (68.8)	12 (27.3)

	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
2.5mg glofitamab			
Median time to CRS* onset, hours (range)	6.1 (3.4–13.0)	17.5 (4.0–46.3)	9.7 (3.4–46.3)
Median CRS duration, hours, (range)	53.3 (9.0–171.2)	21.0 (2.0–692.7)	49.0 (2.0–692.7)
10mg glofitamab			
Median time to CRS onset, hours (range)	17.5 (8.5–34.3)	20.6 (6.7–32.6)	20.6 (6.7–34.3)
Median CRS duration, hours (range)	44.9 (1.0–625.5)	19.5 (1.5–83.0)	24.6 (1.0–625.5)

CRS events by cycle, grade* and Gpt dose



CRS events were predominantly in Cycle 1, and the median duration of CRS was shorter in patients in the 2000mg versus 1000mg cohort

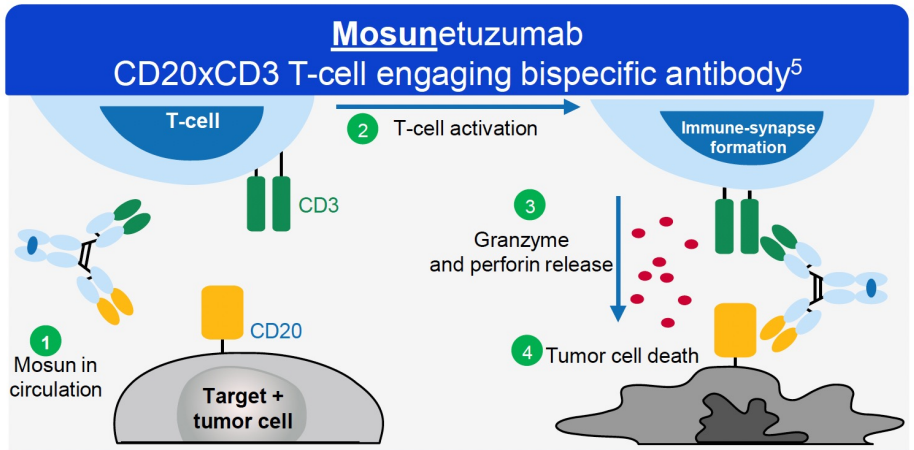
Clinical cut-off date: September 04, 2023.
*CRS by ASTCT consensus grading criteria.[1]
Glofit, glofitamab.

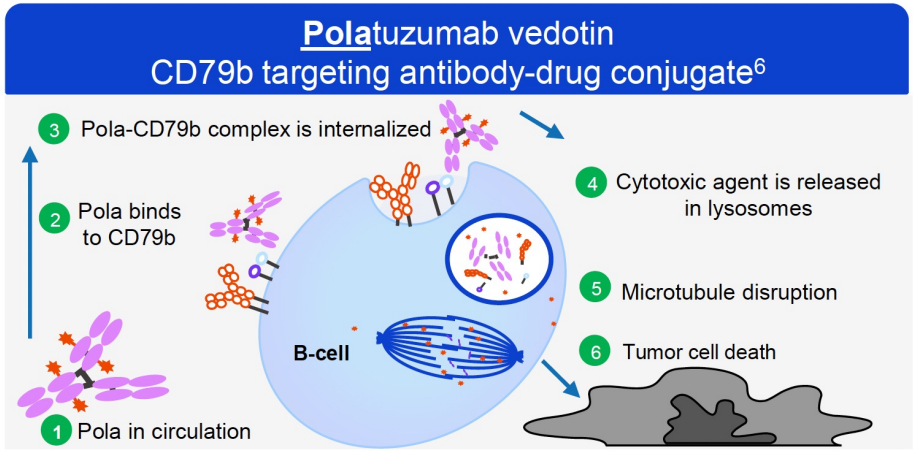
Slide courtesy of T. Phillips. *J Clin Oncol* 2025; 43:318-28

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38

Fixed-duration outpatient **Mosunetuzumab + Polatuzumab** in R/R MCL post-BTKi

Wang ML, et al. *Clin Lymph, Myeloma & Leukemia*, Sept. 2025





We report updated data from the Phase II expansion cohort (NCT03671018) in patients with R/R MCL who had received prior BTKi therapy

Mosun-Pola fixed duration administration (NCT03671018)

Mosun

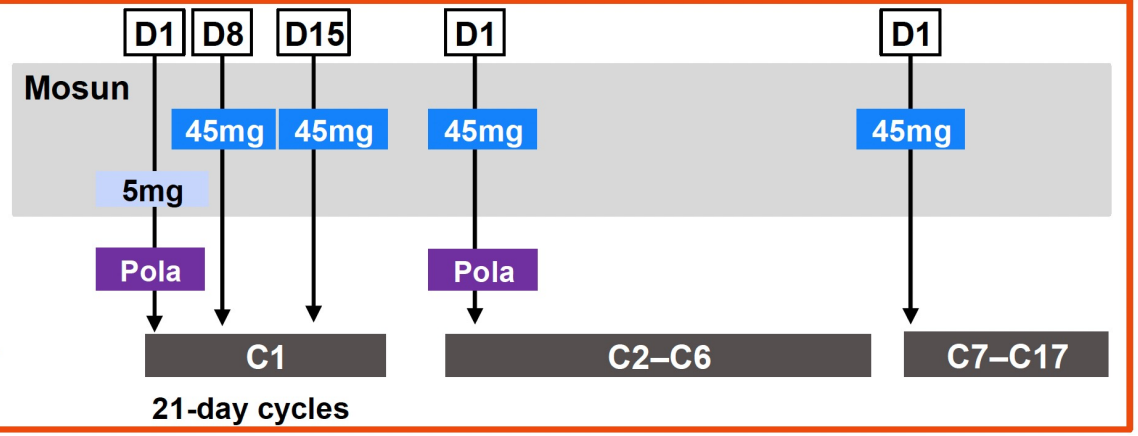
- SC administered in 21-day cycles with step-up dosing in C1; total of 17 cycles

Pola

- 1.8mg/kg IV on D1 of C1–6

No mandatory hospitalization

Corticosteroid premedication was given prior to each dose in C1*



Mosun/Pola, R/R MCL, Phase 2 cohort: **Results**

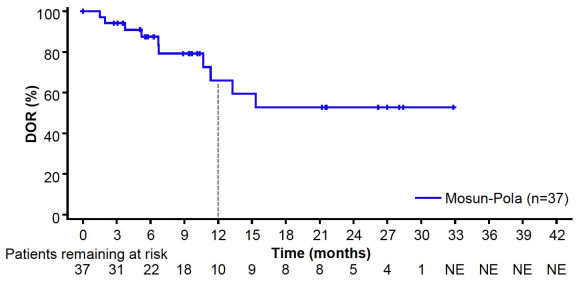
Wang ML, et al. *Clin Lymph, Myeloma & Leukemia*, Sept. 2025

- n = 42, median 3 (2-9) prior lines Rx
- Prior CAR-T = 26%
- Refractory to last Rx = 93%

DOR and DOCR

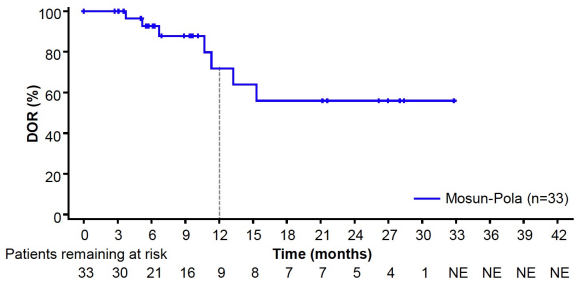
Median follow-up: 15.9 months (95% CI: 13.6–29.0)

Duration of response*



Patients with response	n=37
Median time to first response, months (range)	2.7 (1–7)
Median DOR, months (95% CI)	NR (11.4–NE)
12-month rate, % (95% CI)	66.0 (45.0–86.9)

Duration of complete response*



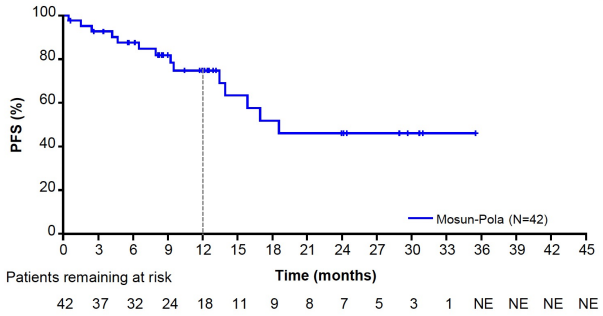
Patients with complete response	n=33
Median time to first CR, months (range)	2.8 (2–18)
Median DOCR, months (95% CI)	NR (11.4–NE)
12-month rate, % (95% CI)	71.9 (49.2–94.6)

Mosun-Pola demonstrated early and durable responses

CCOD: November 8, 2024. *IRC-assessed. CI, confidence interval; NE, not evaluable; NR, not reached.

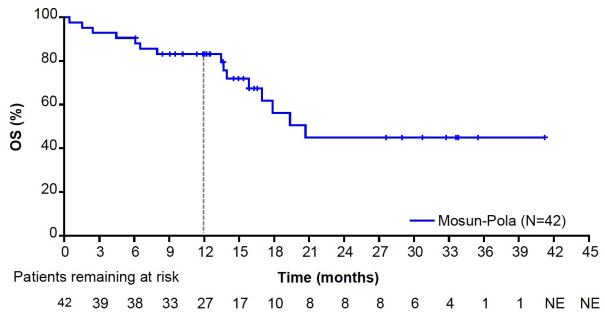
PFS and OS

Progression-free survival*



Patient population	n=42
Median PFS, months (95% CI)	18.6 (13.9–NE)
12-month rate, % (95% CI)	74.8 (60.2–89.4)

Overall survival



Patient population	n=42
Median OS, months (95% CI)	20.7 (17.0–NE)
12-month rate, % (95% CI)	83.1 (71.7–94.5)

Mosun-Pola demonstrated promising PFS and OS

- **Best ORR = 88%, CR = 79%**
- **Consistent efficacy across high-risk groups**
- CRS Gr 1-2 = 43%; one Gr 2 ICANS
- 5 deaths: pneumonia, Covid (3), West Nile

Current/Upcoming BsAb Combination Studies in MCL

Courtesy of T. Phillips, March 2026

>/= 2nd line and R/R:

- Glofitamab + Pirtobrutinib
  - Australia/US
  - Glofitamab With venetoclax +/- zanubrutinib in High-risk Mantle-cell Lymphoma (GLOASIS)
    - France/Belgium
- Glofitamab + lenalidomide (US)
- Glofitamab + Polatuzumab (US/Lycon)
- Glofitamab + Loncastuximab (US-COH

Front-line:

- Glofitamab and ibrutinib (US)
  - Glofitamab With venetoclax +/- zanubrutinib in High-risk Mantle-cell Lymphoma (GLOASIS)
    - France/Belgium

➢ Several recently approved Mosun/Pola + BTKi concepts (US)

Front-line chemo-free combinations for MCL

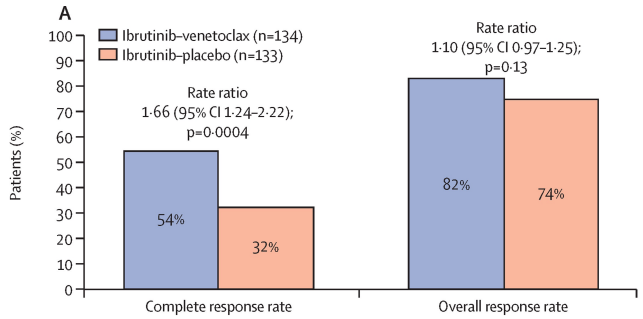
“New Strategies”

Ibrutinib Combined With Venetoclax in Relapsed Mantle Cell Lymphoma (SYMPATICO)

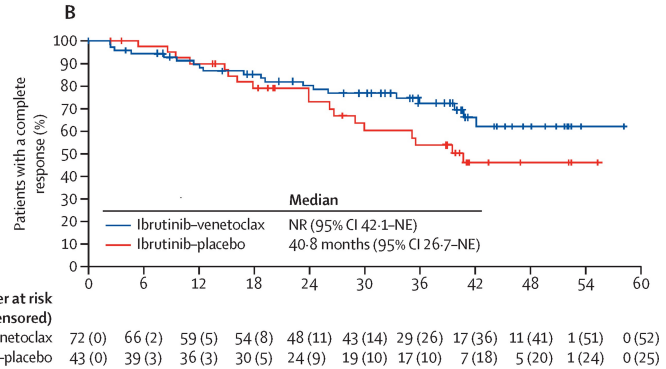
Wang ML et al, Lancet Oncol 2025;

Phase 3 double-blind study: **Ibrutinib/Venetoclax vs. Ibrutinib/Placebo** in R/R MCL, 1-5 prior lines of Rx

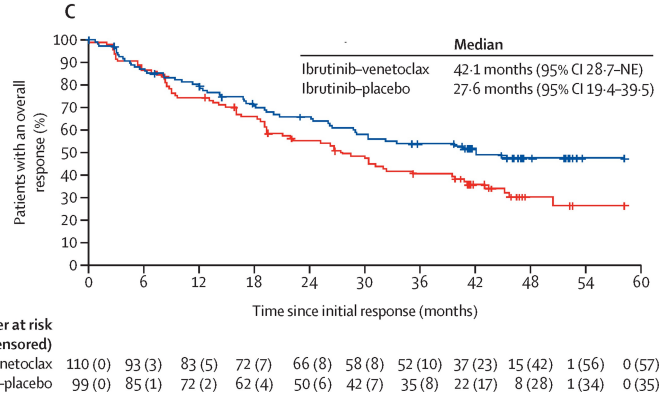
CR and ORR

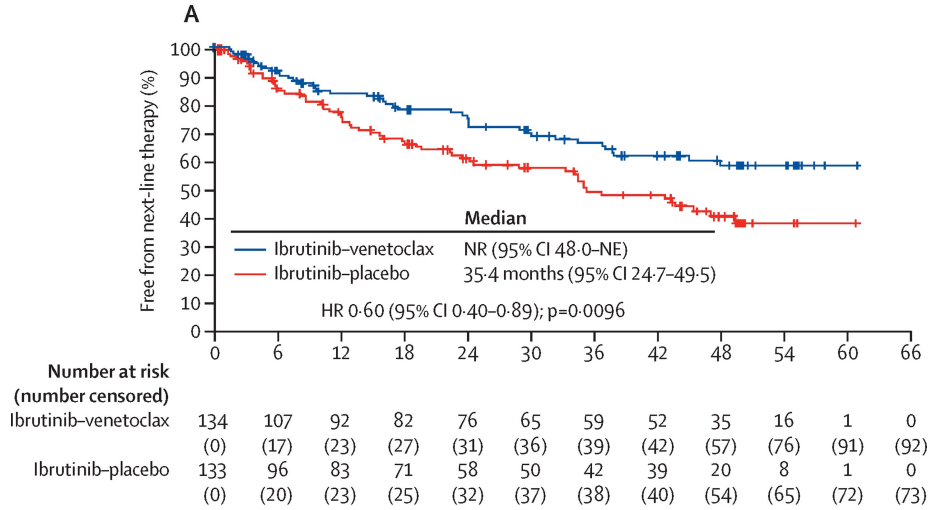


PFS: pts with CR

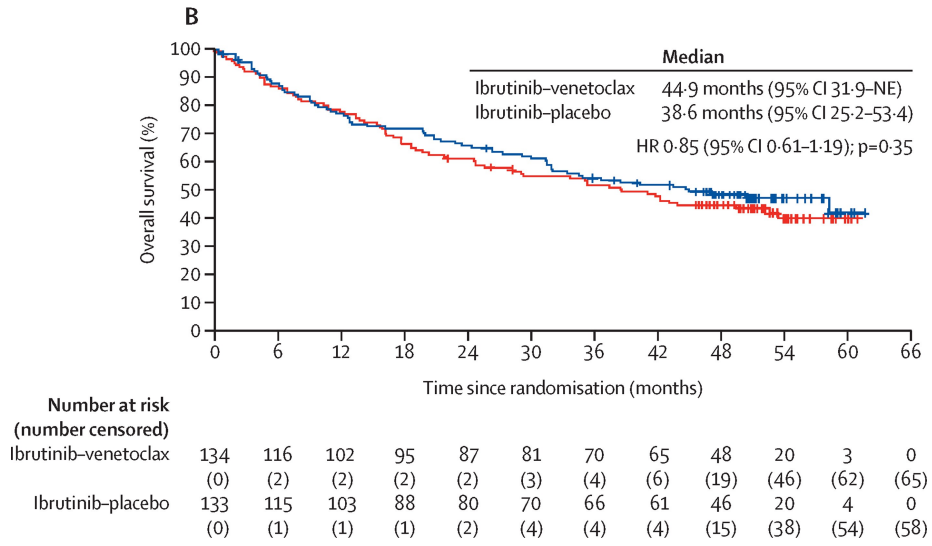


PFS: pts with response





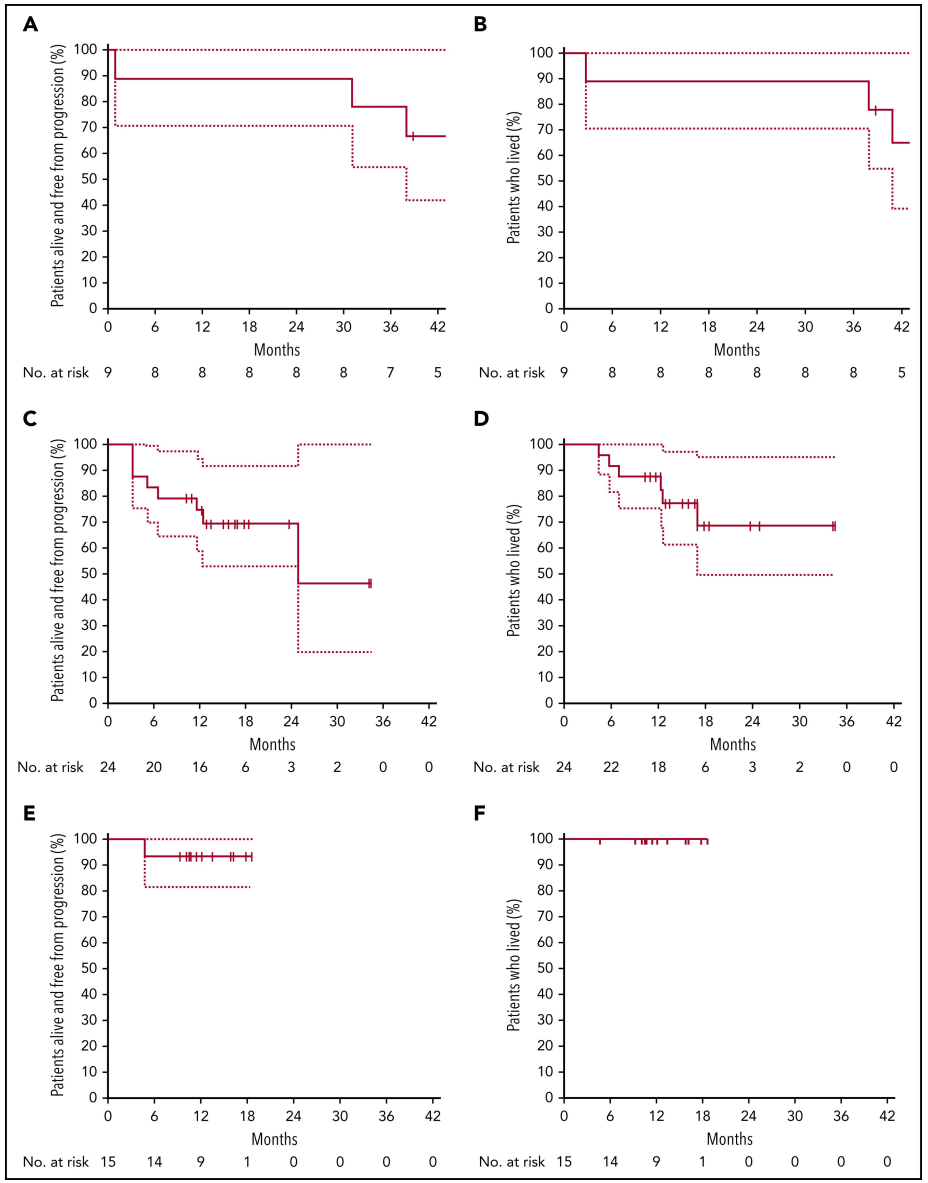
Free from next Rx



OS

Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with MCL:

a phase 1/2 trial (**OAsIs Trial**). LeGouill, et al. *Blood* 2021; 137:877-87



PFS and OS according to cohort:

PFS (A) and OS (B) in cohort A (ibrutinib plus obinutuzumab), **relapsed** patients; 7/9 achieved CR

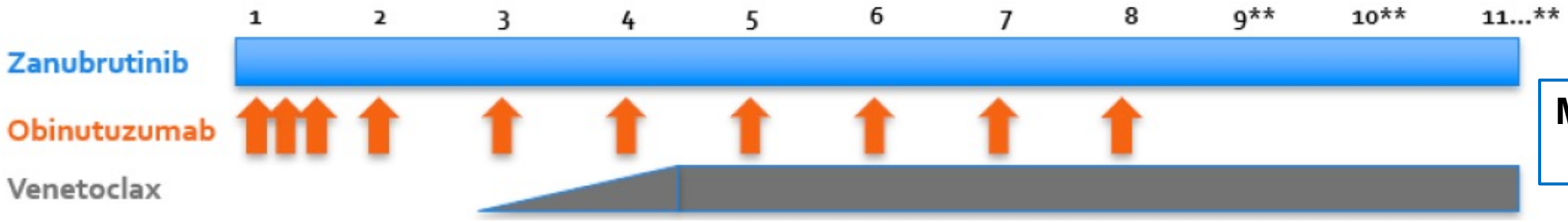
PFS (C) and OS (D) in cohort B (ibrutinib, obinutuzumab, and venetoclax), **relapsed** patients; 16/24 achieved CR

PFS (E) and OS (F) in cohort C (ibrutinib, obinutuzumab plus venetoclax), **untreated** patients; 14/15 achieved CR

Toxicities: grade 3-4 neutropenia and thrombocytopenia; Afib (1 pt), TLS (2 pts); no DLT

Study Design for BOVen

Kumar A, et al, Blood 2025; 145: 497–507



Minimum of 24 cycles

Dosing:

Zanubrutinib 160 mg oral twice daily

Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

CR and uMRD	→	Stop treatment
<CR and/or dMRD	→	Continue ZANU and VEN

Key Eligibility Criteria:

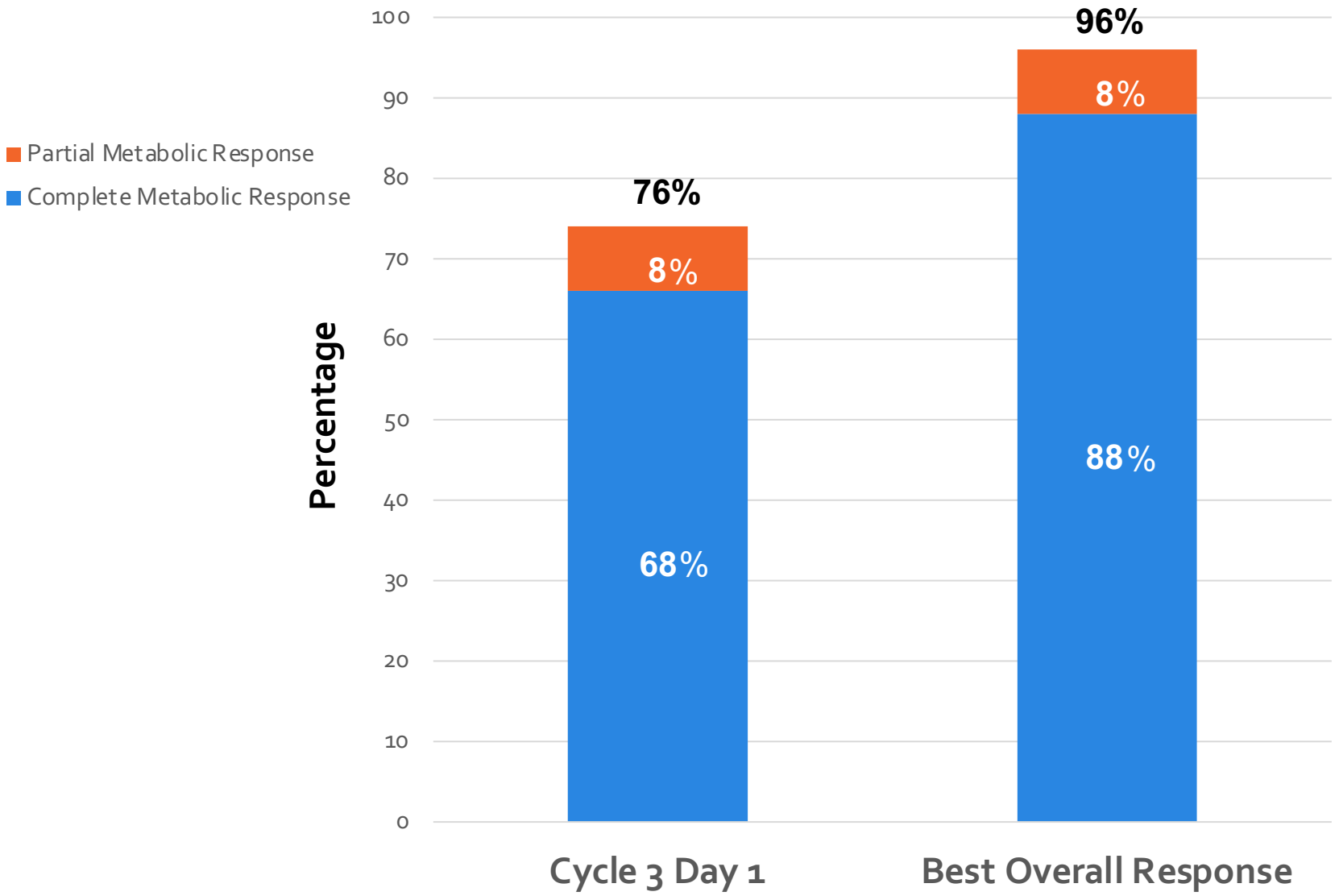
- Previously untreated MCL (except localized RT prior)
- *TP53* mutation (of any variant allele frequency)
- ECOG ≤2, adequate organ and hematologic function (ANC >1, PLT >75, HGB ≥9 (unless due to MCL))

Primary Endpoint:

- 2-year progression-free survival.
- A promising 2-yr PFS rate ≥55% and an unacceptable rate ≤30%
- If ≥11 patients were progression-free at 2 years, the treatment regimen would be declared effective

Response Rates By Timepoint

Kumar A, et al. Blood 2025; 145: 497–507

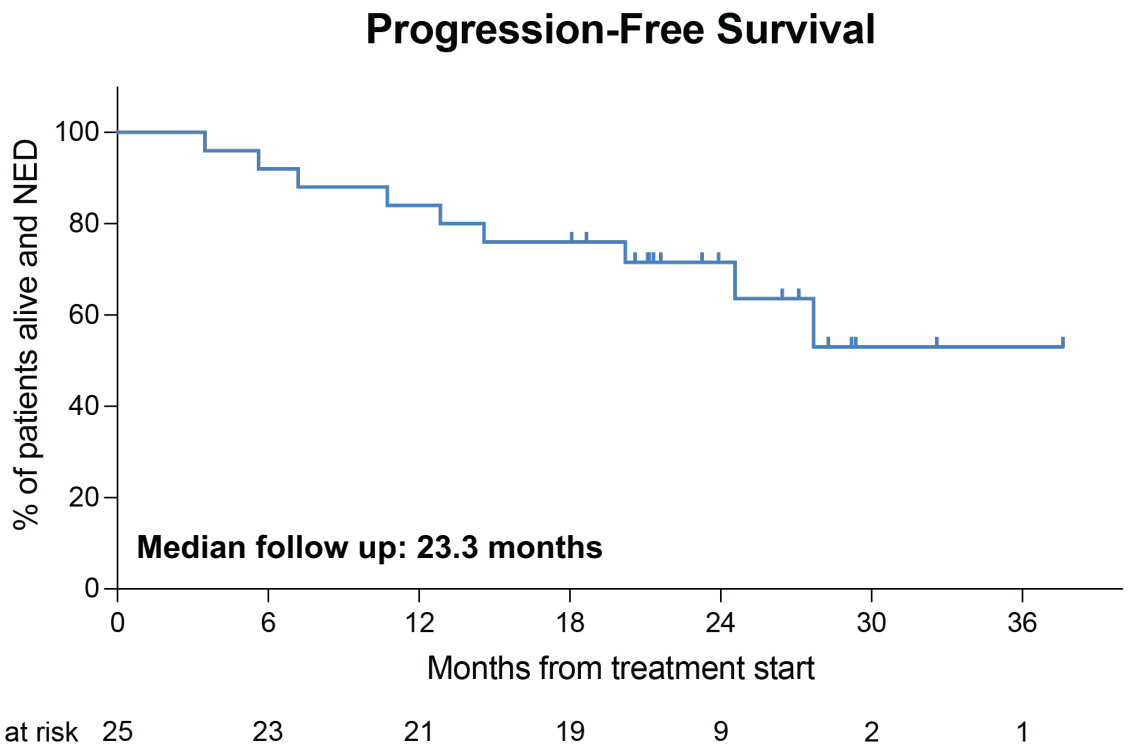


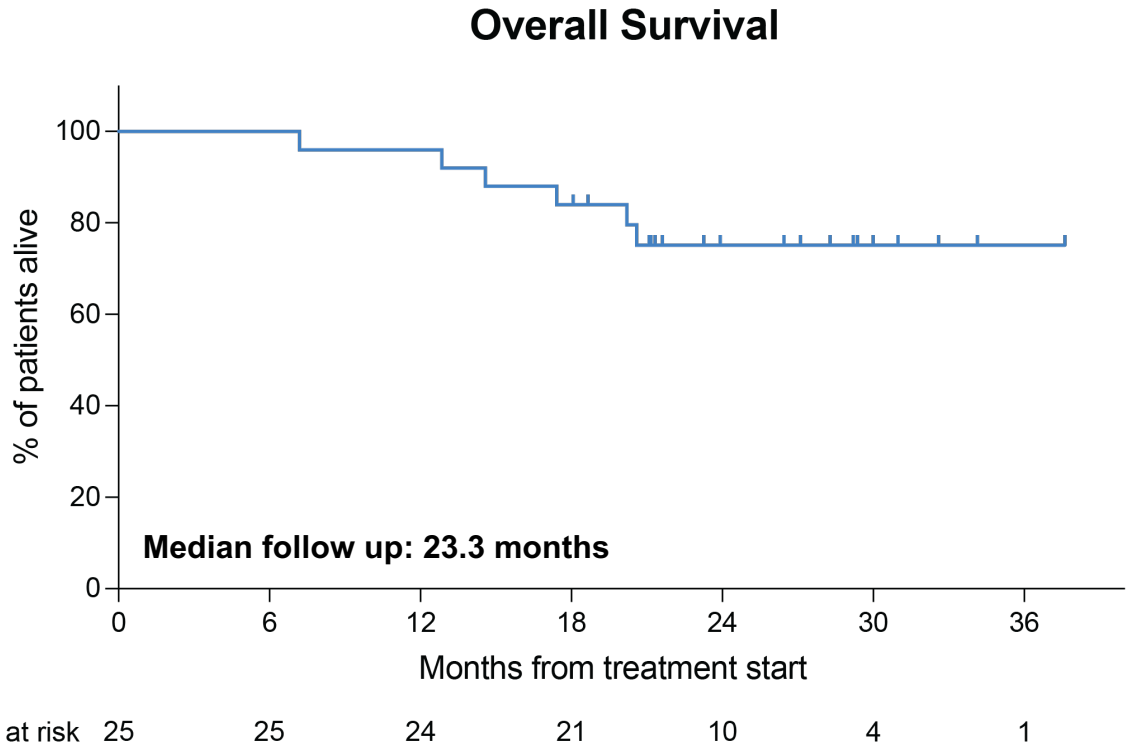
- **High Metabolic Response Rates after 2 cycles of Zanu+Obin**
- **High Overall Metabolic Response Rate with Zanu+Obin+Ven**

Memorial Sloan Kettering Cancer Center

BOVen: PFA and OS Outcomes

Kumar et al, Blood 2025; 145: 497–507





2-year PFS: 72% [95% CI: 56, 92]
Median PFS: not reached

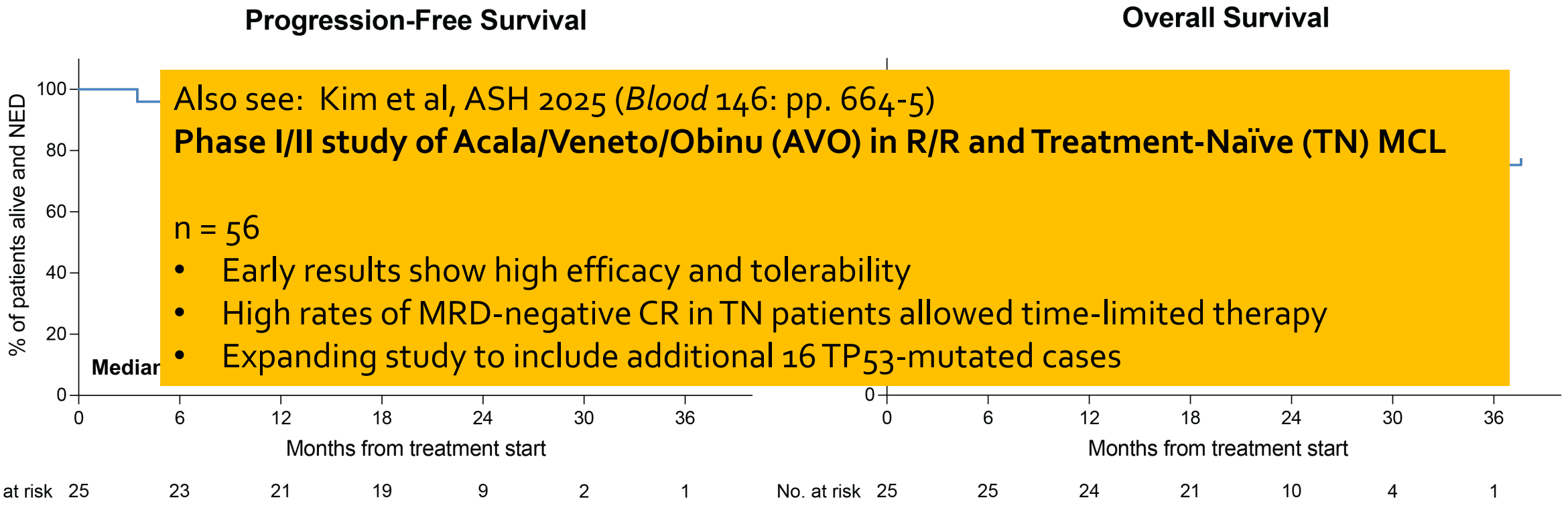
2-year OS: 75% [95% CI: 58, 93]
Median OS: not reached

Primary PFS Endpoint is Met:
11 patients progression-free at 2 years

Memorial Sloan Kettering Cancer Center

BOVen: PFA and OS Outcomes

Kumar et al, Blood 2025; 145: 497–507



Also see: Kim et al, ASH 2025 (*Blood* 146: pp. 664-5)

Phase I/II study of Acala/Veneto/Obinu (AVO) in R/R and Treatment-Naïve (TN) MCL

n = 56

- Early results show high efficacy and tolerability
- High rates of MRD-negative CR in TN patients allowed time-limited therapy
- Expanding study to include additional 16 TP53-mutated cases

2-year PFS: 72% [95% CI: 56, 92]
Median PFS: not reached

2-year OS: 75% [95% CI: 58, 93]
Median OS: not reached

Primary PFS Endpoint is Met:
11 patients progression-free at 2 years

Memorial Sloan Kettering Cancer Center

MRD-Driven Time-Limited Therapy of Acalabrutinib and Lenalidomide Plus Rituximab (**ALR**) or Obinutuzumab (**ALO**) in Patients with **Treatment-Naive MCL**: Phase 2 Trial Outcomes with MRD and cfDNA Analyses

- Len/Ritux is highly active as frontline therapy (Ruan et al, *Blood* 2018)

- Regimens:
  - **Acala 100 mg bid continuously**
  - **Len 15-20 mg d 1-21 x 12 (induction), then 15 mg during maintenance**
  - **ALR → Rituximab weekly x 4 in cycle 1, then q 2 mo including maintenance**
  - **ALO → Obinutuzumab weekly x3 cycle 1, monthly cycles 2-6, then q 2 mo**

- **Primary endpoint**: MRD negative @ 10^{-6} post-induction (PB, by ClonoSeq)

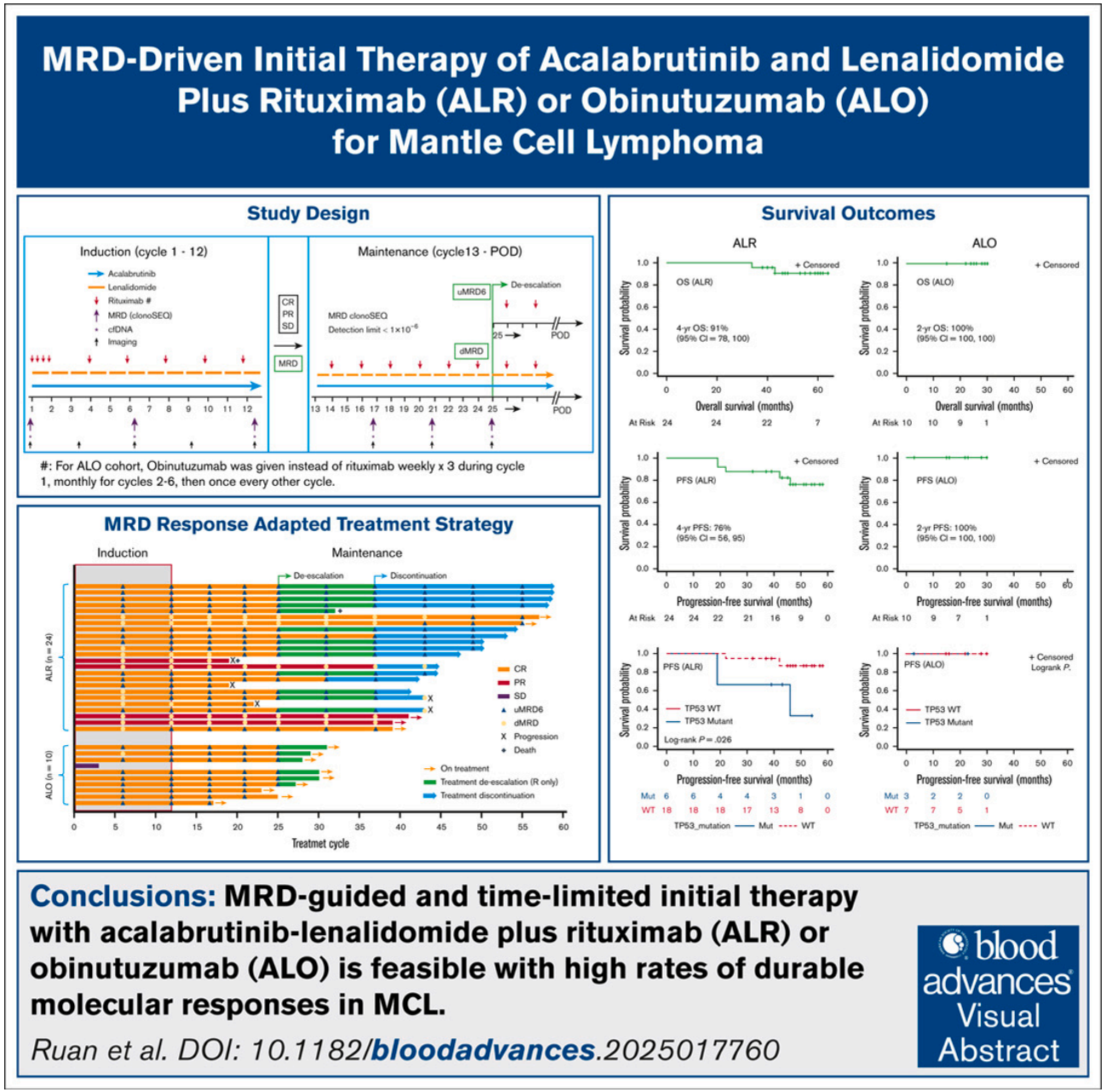
Ruan J, et al. ASH 2024, abstract #746

- **ALR:** end of induction ORR 100%, CR 83%
  - **MRD negative** = 67% after 12 cycles, 83% after 24 cycles
  - **3-year PFS 88%,** OS 95%
  - MIPI score, Ki67 >30% and TP53 mutation had no impact on Rx response
- **ALO:**
  - 1-year OS and PFS = 100%

Conclusions:

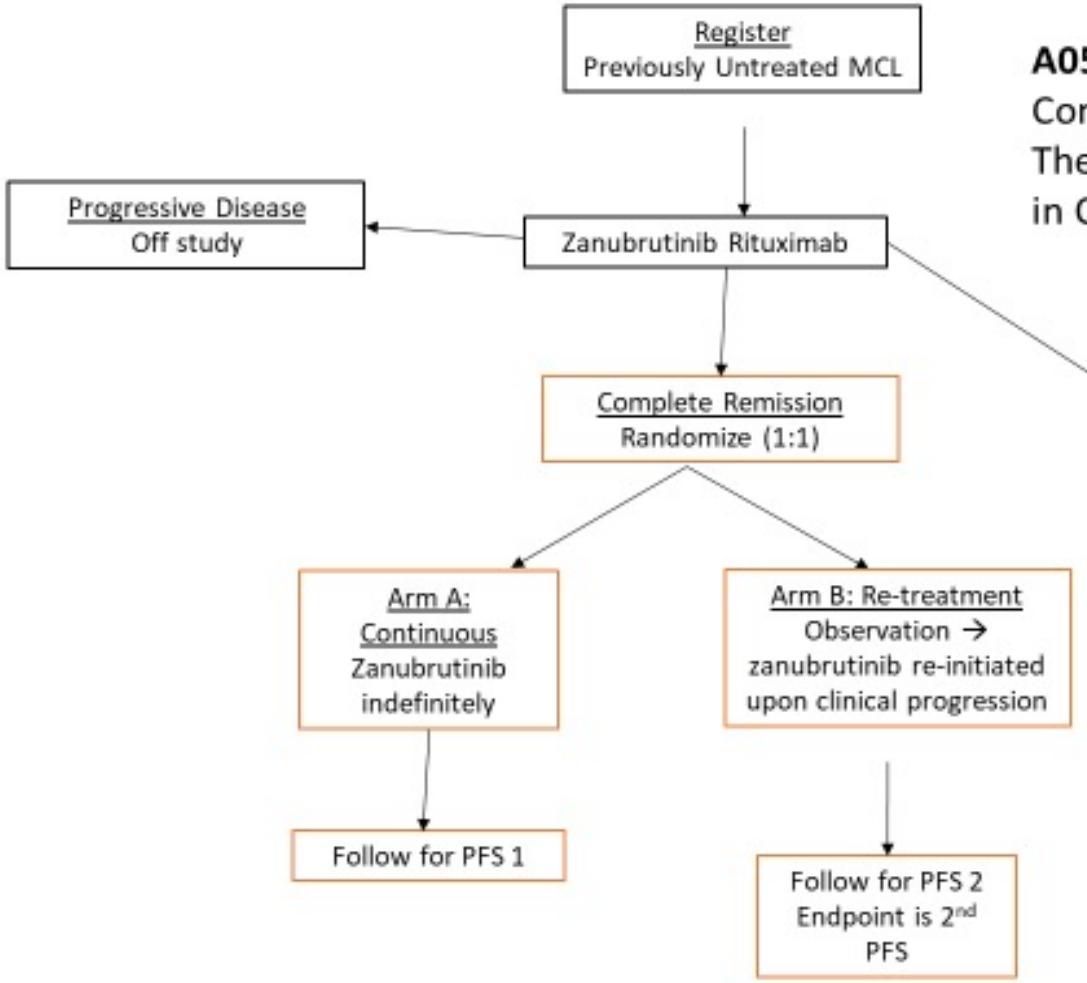
- High rates of CR and MRD-negative, including high-risk pts
- Well-tolerated
- Allows treatment de-escalation and time-limited therapy

Ruan Jia, et al. *Blood* 2024; ASH abstract



Continuous Versus Intermittent Zanubrutinib for Older Patients With Previously Untreated MCL

Opened to accrual September 2023, U.S. Intergroup Trial (NCT05976763)



A052101: A Randomized Phase 3 Trial of Continuous vs. Intermittent Maintenance Therapy with Zanubrutinib as Upfront Treatment in Older Patients with Mantle Cell Lymphoma

- Patients with PR/SD go off study
- Age >/= 60 y; not transplant eligible
- PD defined by clinical (Lugano) criteria, not by MRD
- **Primary endpoint:** compare time to PD or death (PFS1) in Arm A to time to second PD or death (PFS2) in Arm B
- Accrual as of September 2025: **147/421**

Intergroup Study Chair, Alliance: Anne Beaven (Univ. of North Carolina)
ECOG Study Champion: Jonathon Cohen (Emory Univ.)
SWOG Study Champion: Tycel Phillips (City of Hope)

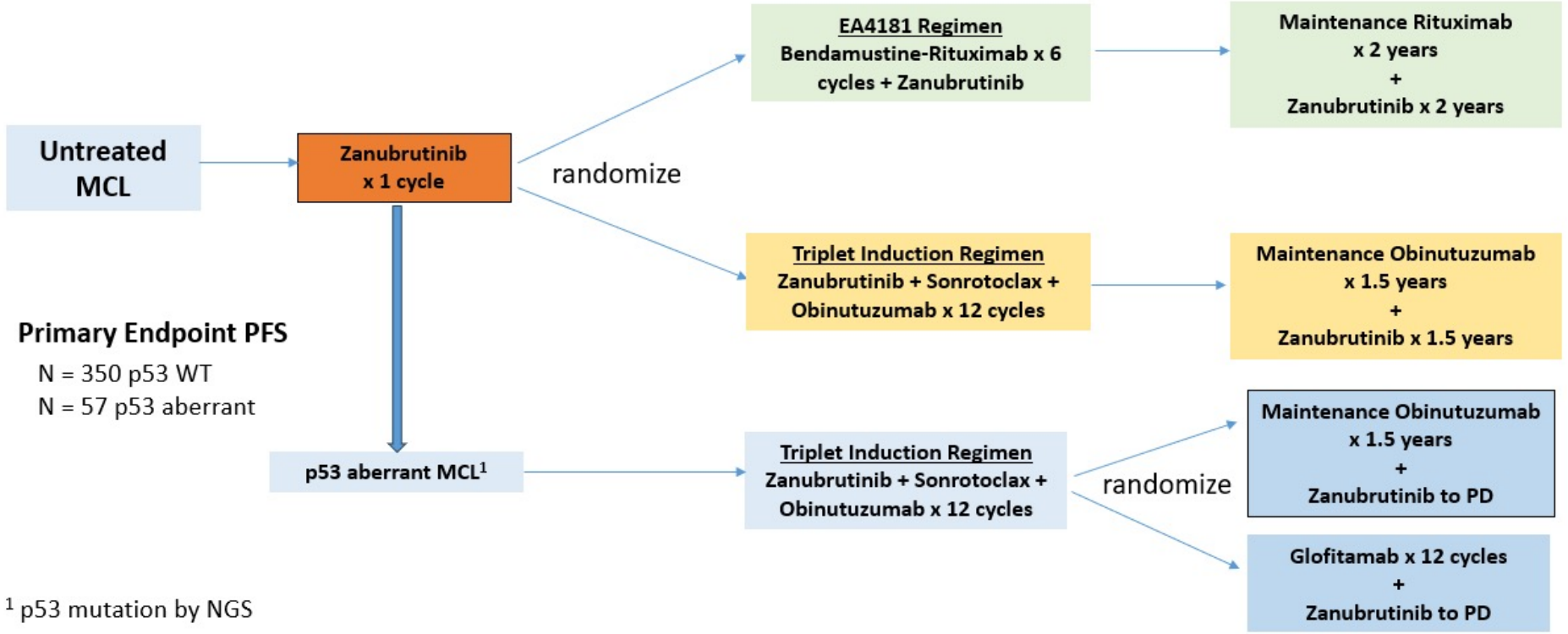
Proposal

Can we improve patient outcomes with a chemotherapy free induction/maintenance compared to current chemotherapy + BTKi approaches? Dr. Nirav Shah, Study PI

Primary Outcome=3-year PFS

Key Secondary Endpoints

- 6-month ORR/CR rates
- OS
- DOR
- Occurrence of Grade 3-4 AEs, infection, secondary malignancies



ECOG-ACRIN cancer research group

High-risk MCL:
Proposed Study Schema
Dr. Nirav Shah, PI

TO BE ELIGIBLE

Received two cycles of appropriate systemic induction therapy, which includes a CD20 antibody +/- cytotoxic therapy +/- oral targeted therapy (e.g., BTKi, IMIDs).

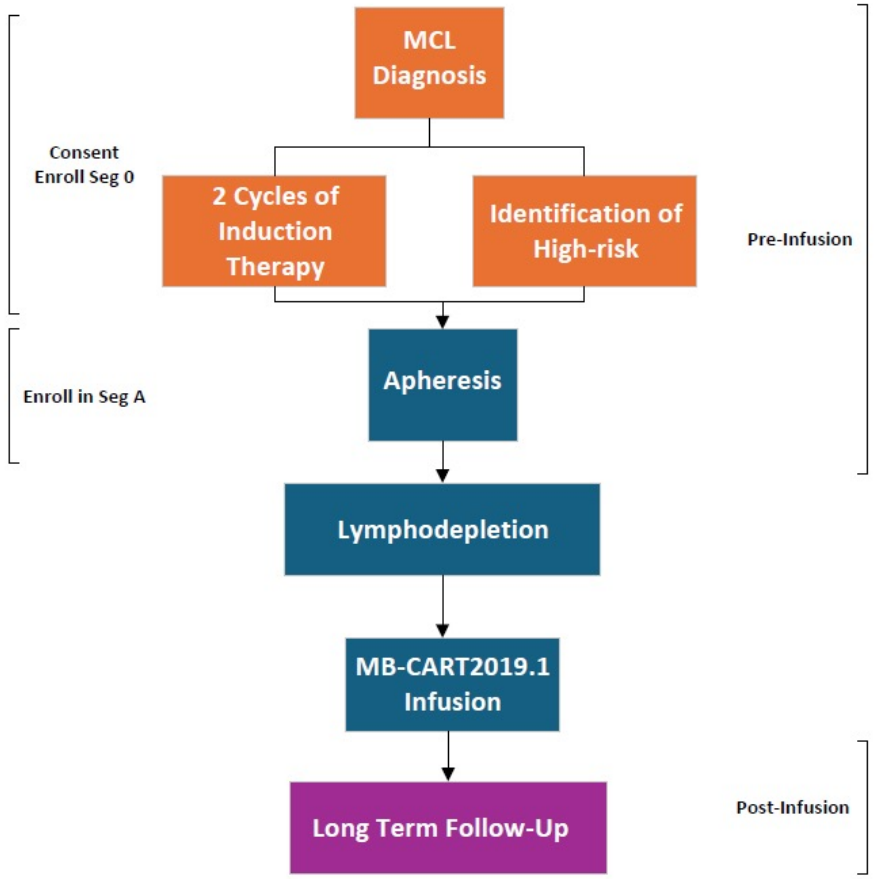
a. CD20 antibody alone is not adequate

b. Induction cycles do not have to be identical

c. For BTK inhibitors and/or lenalidomide a cycle is defined as 14-28 days and will be based on institutional treatment regimens.

d. Intrathecal chemotherapy will not count towards a cycle of treatment

e. Radiation therapy will not count towards a cycle of treatment

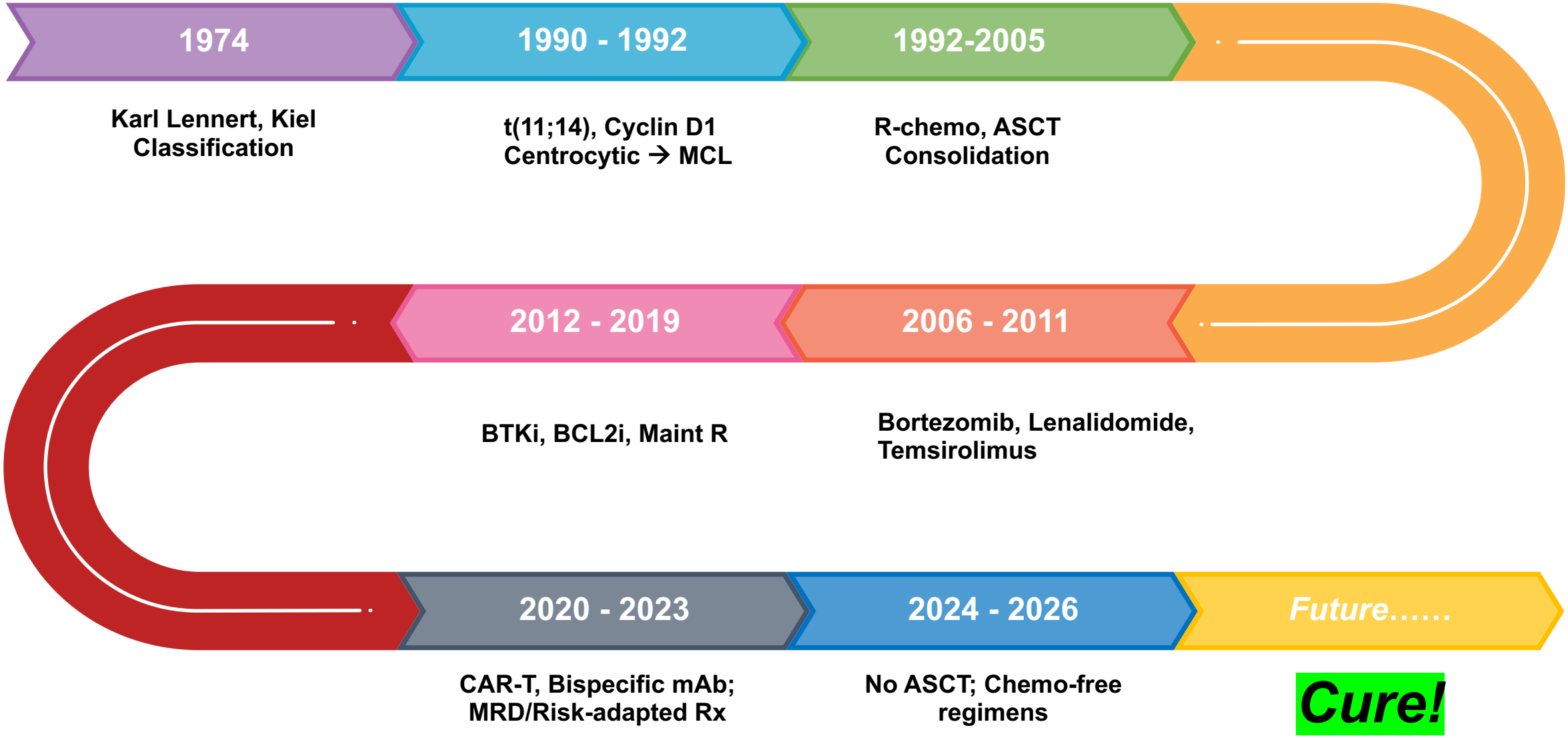


BMT CTN
Blood & Marrow Transplant Clinical Trials Network®

Phase 3 Trials: Preferred primary endpoints??

- Stratify for “high-risk” MCL
  - Blastoid/Pleomorphic, Ki67 >50%,TP53 abnormal, High MIPI score
- PFS
- OS
  - As outcomes improve, is this feasible?
- MRD
  - Which assays?
  - Risk-adapted therapy →Rx escalation vs de-escalation?

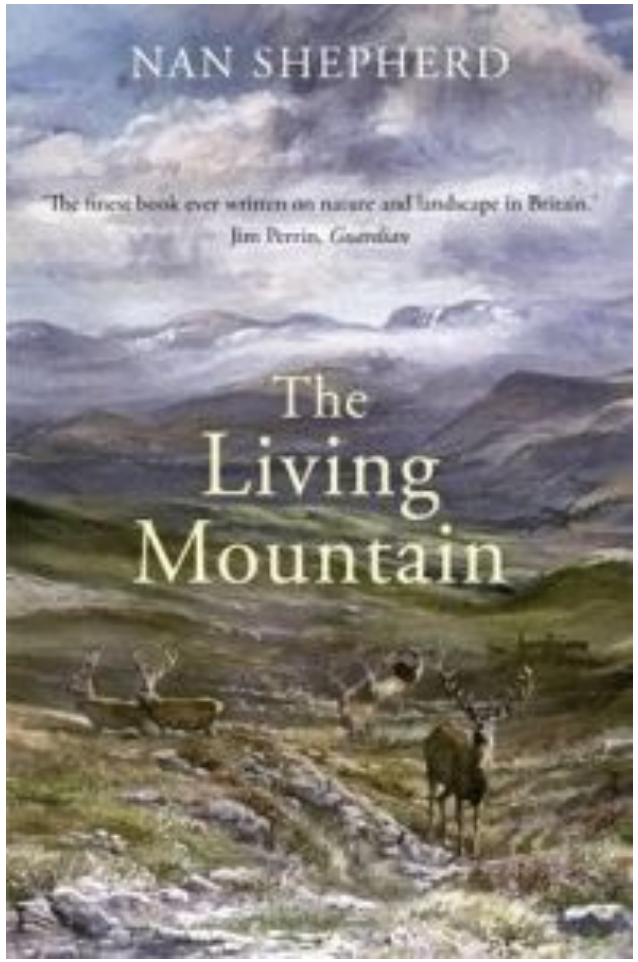
Therapeutic Evolution in Mantle Cell Lymphoma



The evolving therapeutic landscape for R/R MCL in 2026….

- New realities of front-line therapy
  - ***…. De-escalated induction therapy: No high-dose cytarabine, no ASCT***
  - ***…. BTKi incorporation into induction and maintenance regimens***
  - ***…. Chemo-free regimens: BOVen, AVO, ALR***
- Younger, medically fit at relapse
  - ***…. Re-induction → CAR-T consolidation? Maintenance?***
  - ***…. Allo transplant? (remains the only established curative therapy)***
- Older or less fit at relapse
  - ***…. CAR-T or Bispecific mAb in selected patients***
  - ***…. BTKi +/- anti-CD20 mAb, BCL2i; Lenalidomide/anti-CD20 mAb***
- Focus on high-risk MCL → Risk-adapted therapy
  - ***…. TP53-mutated, Blastoid variant, MRD status, POD24 vs later relapse***

“The thing to be known grows with the knowing”



The Cairngorm Mountains, Scotland

Thanks!!

University of Virginia Founded by Thomas Jefferson, 1819