

The background features a dark blue gradient with several bright, curved light trails in blue, purple, and yellow. These trails originate from the bottom center and curve upwards and outwards, creating a sense of motion and depth. The text is centered over this abstract design.

Shifting Landscape of Treatment in Indolent B-Cell Lymphoma



Shifting Landscape of Treatment in Mantle cell lymphoma

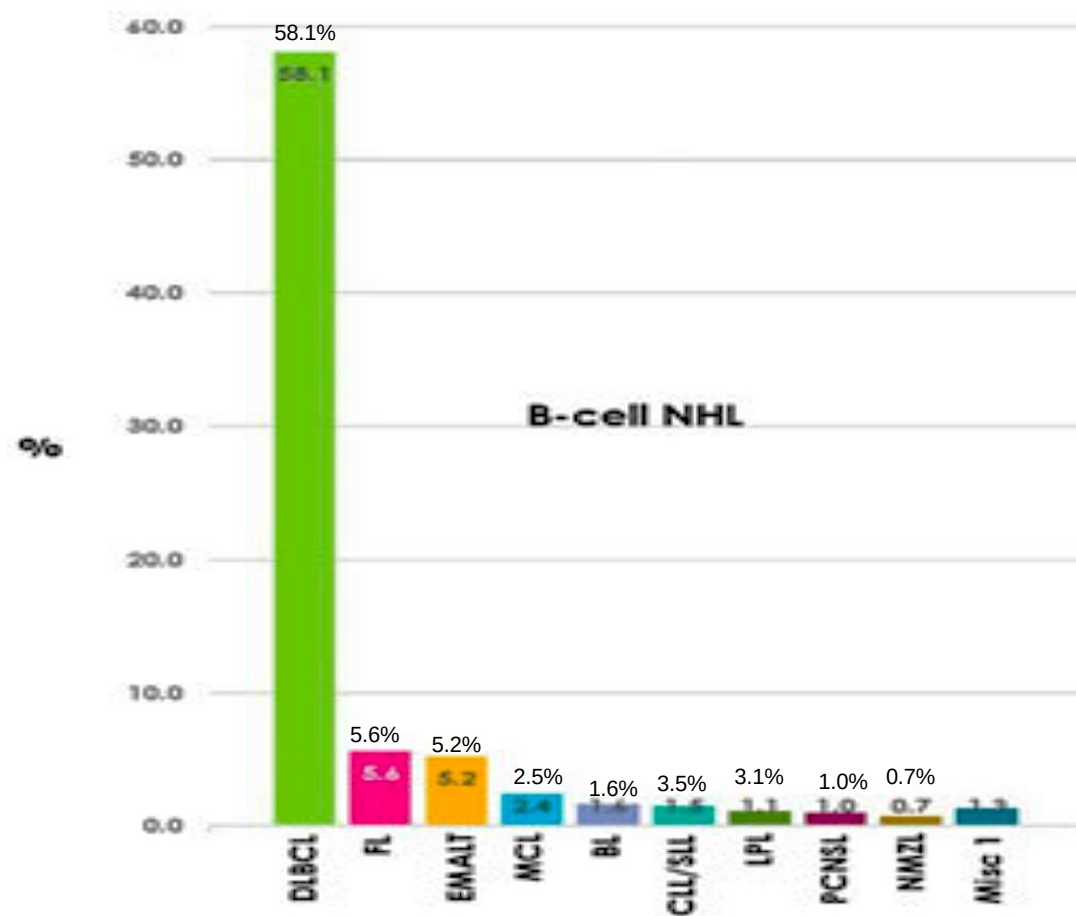
Lalita Norasetthada, MD
Chiang Mai University

OUTLINES

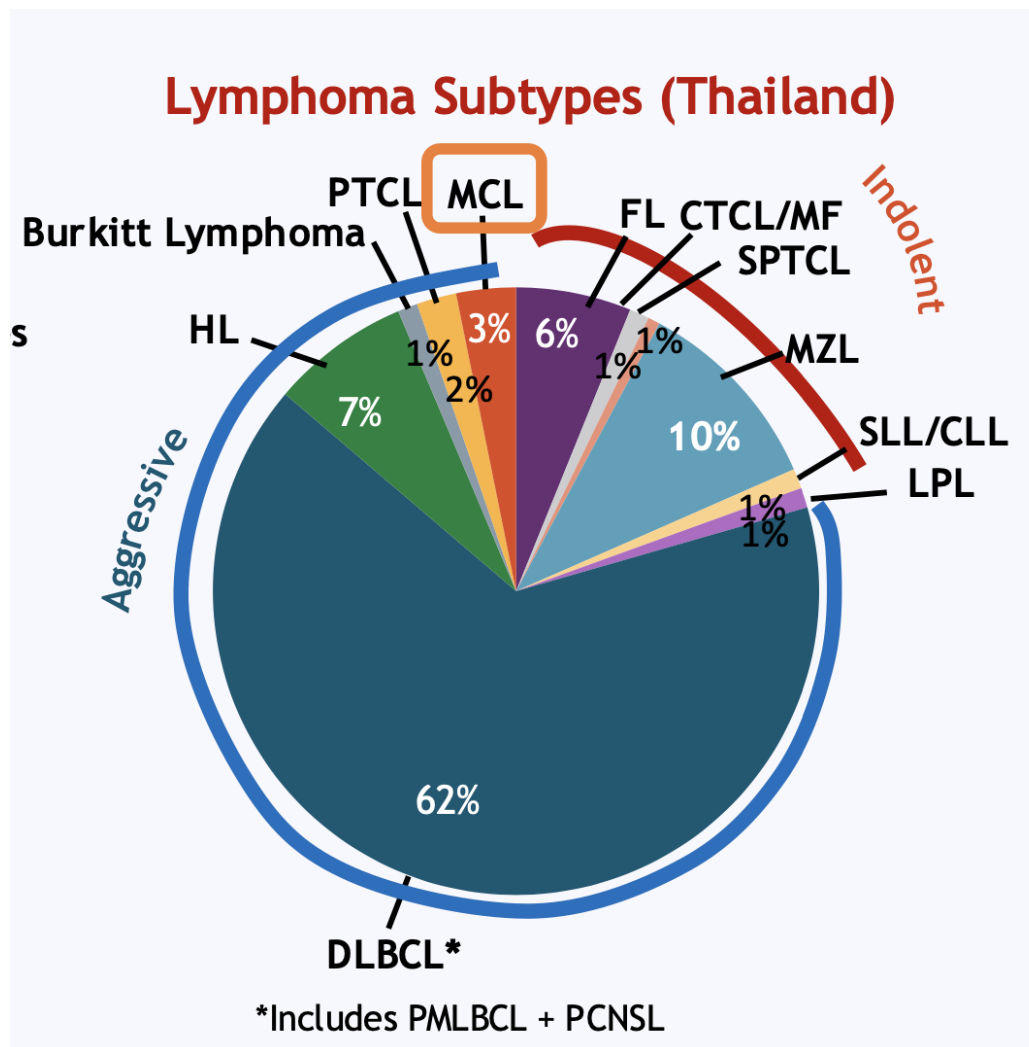
- INTRODUCTION
- ROLE OF CHEMOIMMUNOTHERAPY IN 1L TREATMENT
- EVIDENCE OF SHIFTING TREATMENT PARADIGM
- NOVEL THERAPY FOR RELAPSED/REFRACTORY MCL

Distribution of histological subtypes of B-cell lymphoma from TLSG Cohort

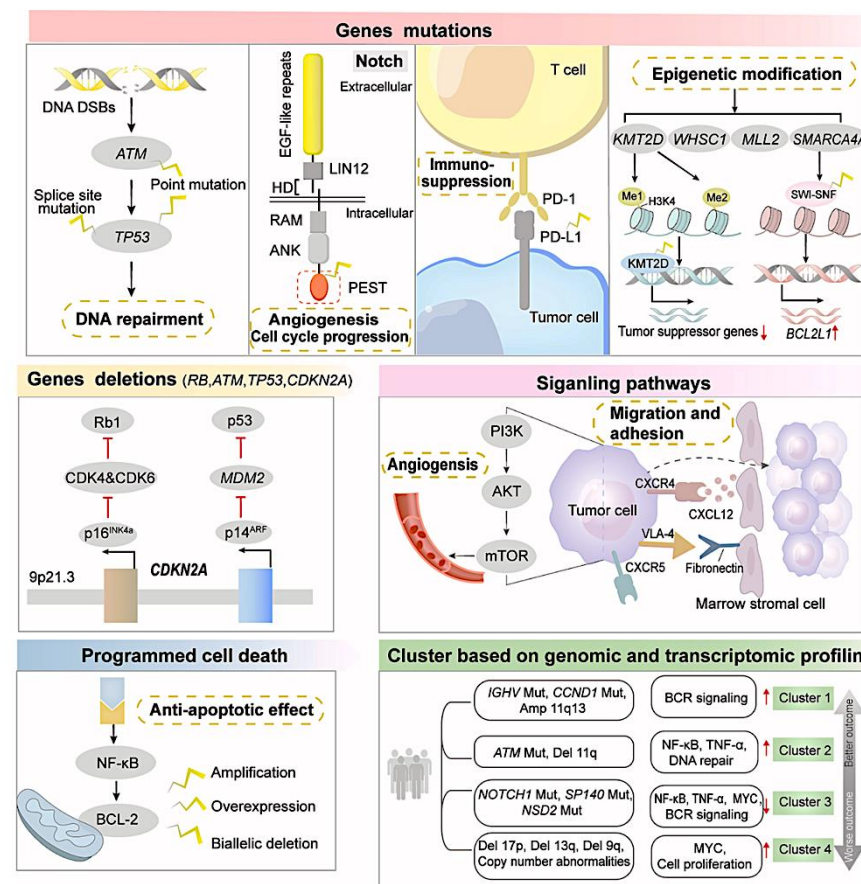
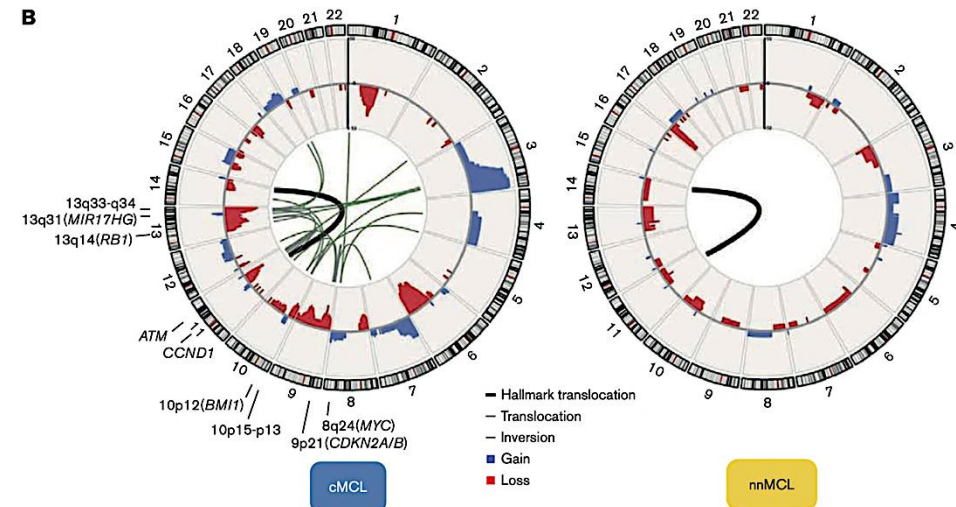
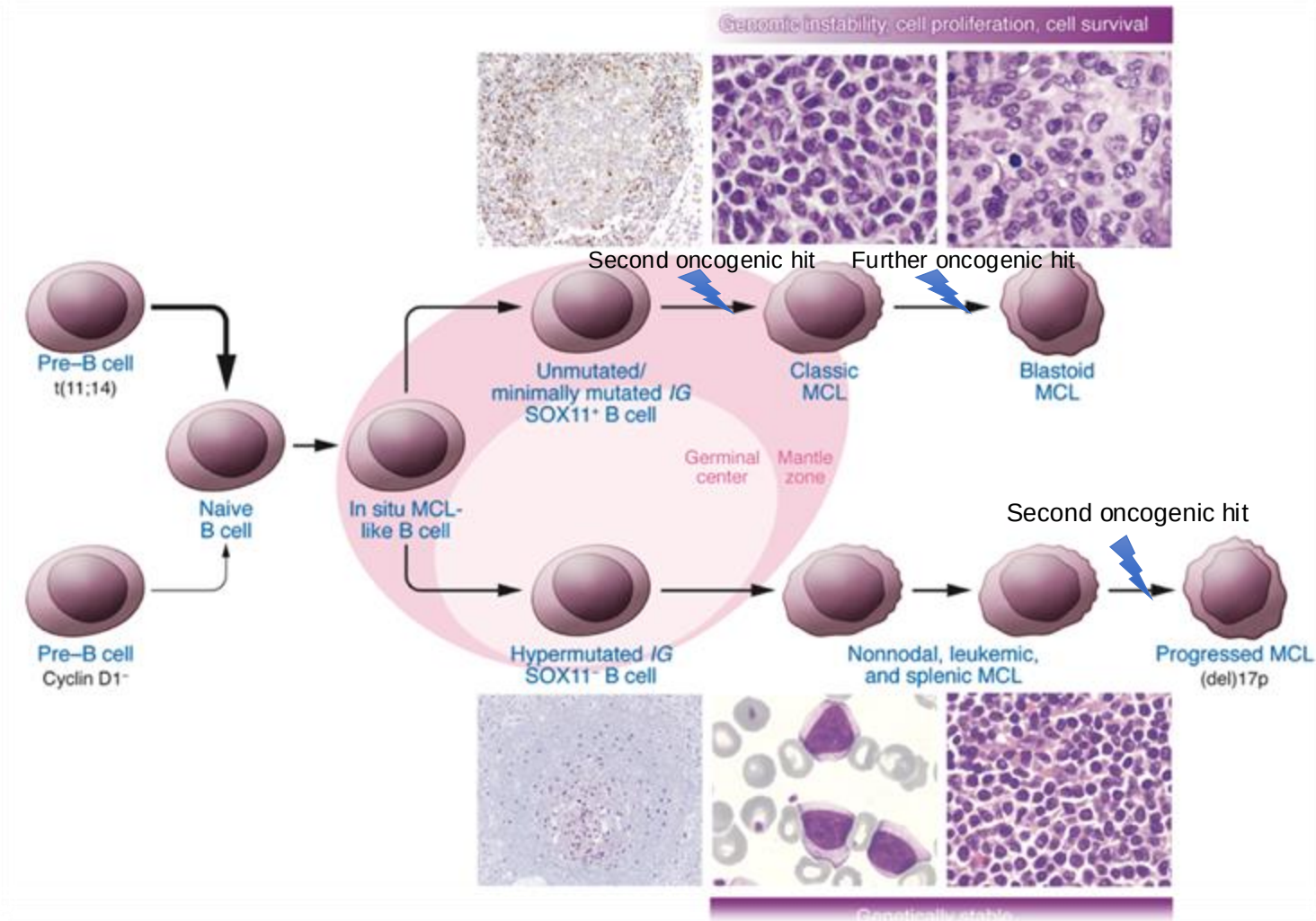
2007-2012, (N = 4056)



20013-2024, (N = 6051)



Molecular pathogenesis of MCL



MCL is biologically heterogeneous

Low Risk

- Low KI-67 ($\leq 10\%$)
- SOX-11 negative
- IGHV hypermutated
- Stable karyotype

**Indolent
MCL**

Intermediate Risk

- Low KI-67 (10-30%)
- SOX-11 positive
- IGHV unmutated

**Classic
MCL**

High Risk

- Blastic/blastoic/pleomorphic
- High Ki-67 ($>30\%$)
- Complex karyotype
- *TP53* deletion or mutations

**Blastic
MCL**

MIPI-c Calculator: Integrating Biologic and Clinical Risk Predictors

sMIPI



Age



WBC count



Serum concentration of LDH



ECOG PS

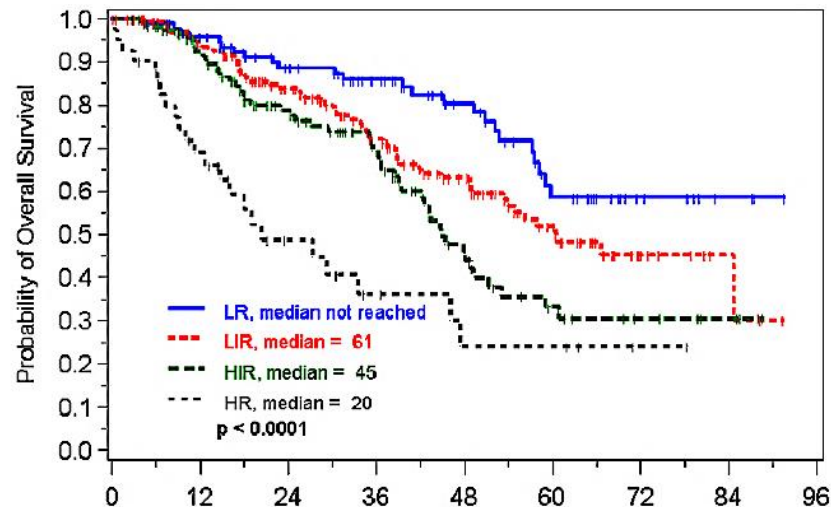
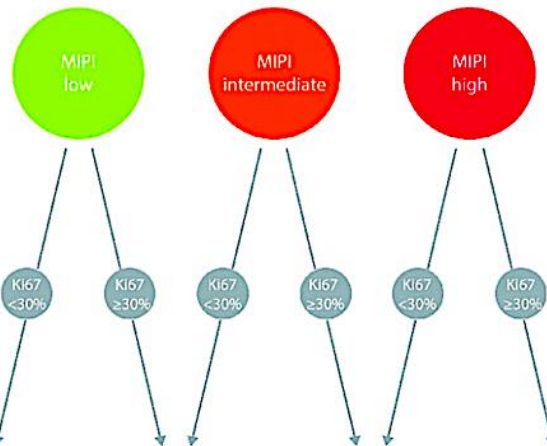
Points	Age, y	ECOG	LDHULN	WBC, 10 ⁹ /L
0	<50	0-1	<0.67	< 6.700
1	50-59	—	0.67-0.99	6.700-9.999
2	60-69	2-4	1.000-1.49	1.000-14.999
3	≥70	—	≥1.5000	≥15000

0 to 3 = low risk (LR); 4 to 5 points = intermediate risk (IR); 6 to 11 points = high risk (HR)

MIPIb



Ki67 score^a



	months since registration				months since registration			
LR	99	86	70	55	38	21	9	3
LIR	173	142	111	78	53	30	9	3
HIR	119	94	65	47	25	13	7	4
HR	41	24	12	7	4		1	0

MIPI-c risk group	MIPI risk group	Ki-67, %	Median OS, years
Low	Low	<30	9.4
Low-intermediate	Low	≥30	4.9
	Intermediate	<30	
High-intermediate	Intermediate	≥30	3.2
	High	<30	
High	High	≥30	1.8

<https://www.european-mcl.net/home/scores-mipi-mipi-c-19.html>

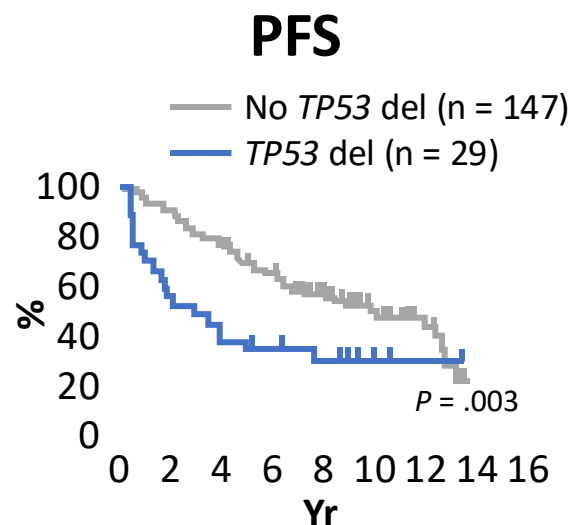
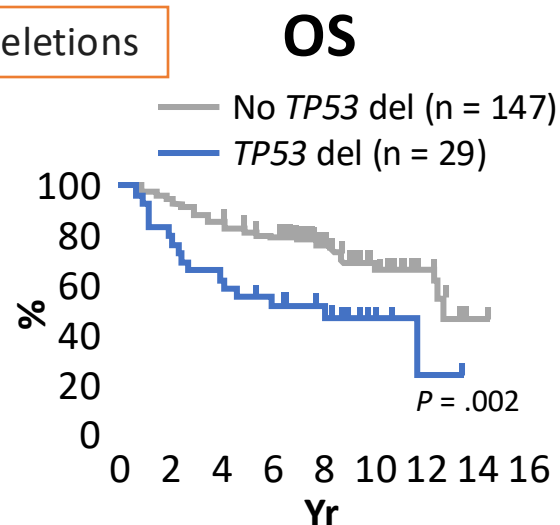
- Often not helpful for clinical decision-making
 - Young patients typically have low-risk disease
 - Older patients more likely to have high-risk disease
- Can help when on the fence regarding treatment options
- Very helpful for interpreting single-arm studies

TP53 Mutations Associated With Poor Outcomes With Chemoimmunotherapy/ASCT

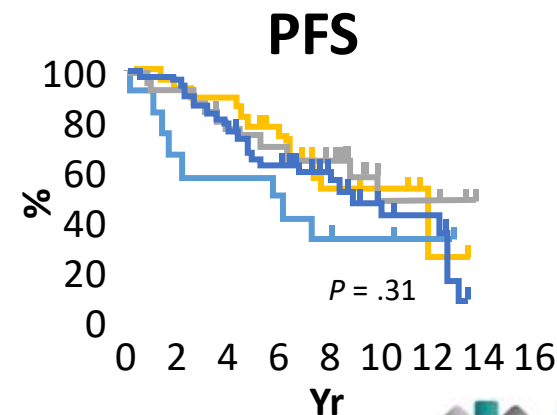
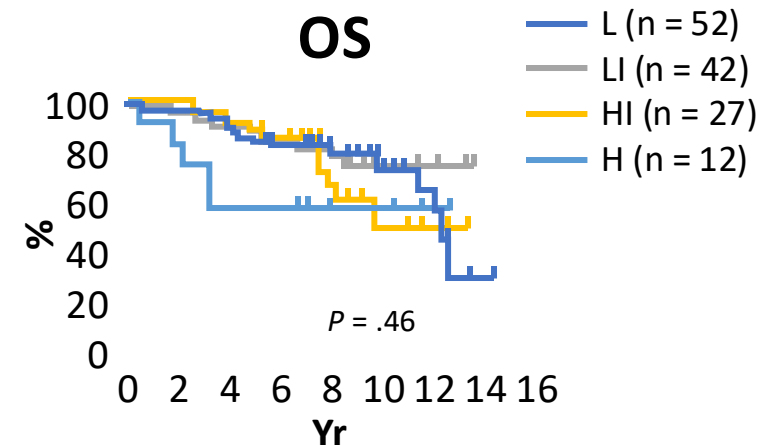
NORDIC MCL2/MCL3 Studies in young patients

Survival by TP53 Status

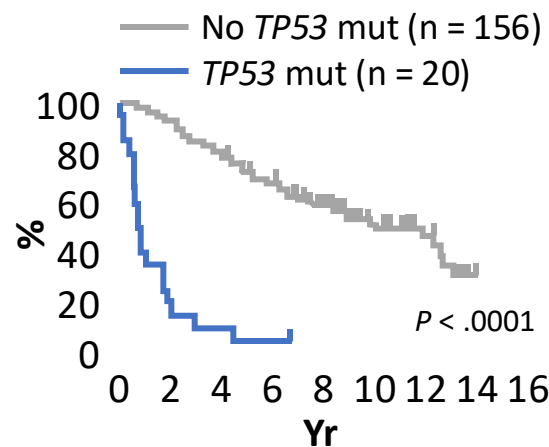
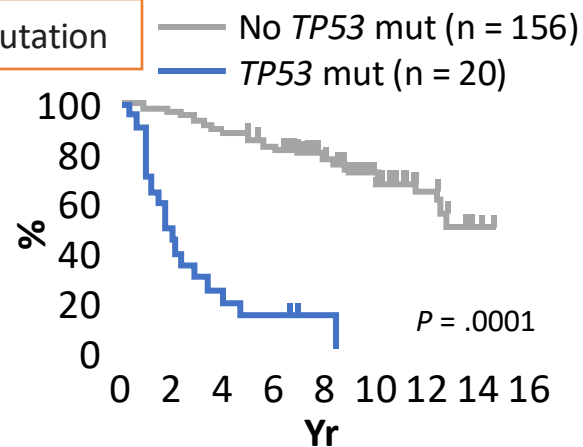
TP53 deletions



Survival by MIPI-c Index in TP53-Unmutated Cases



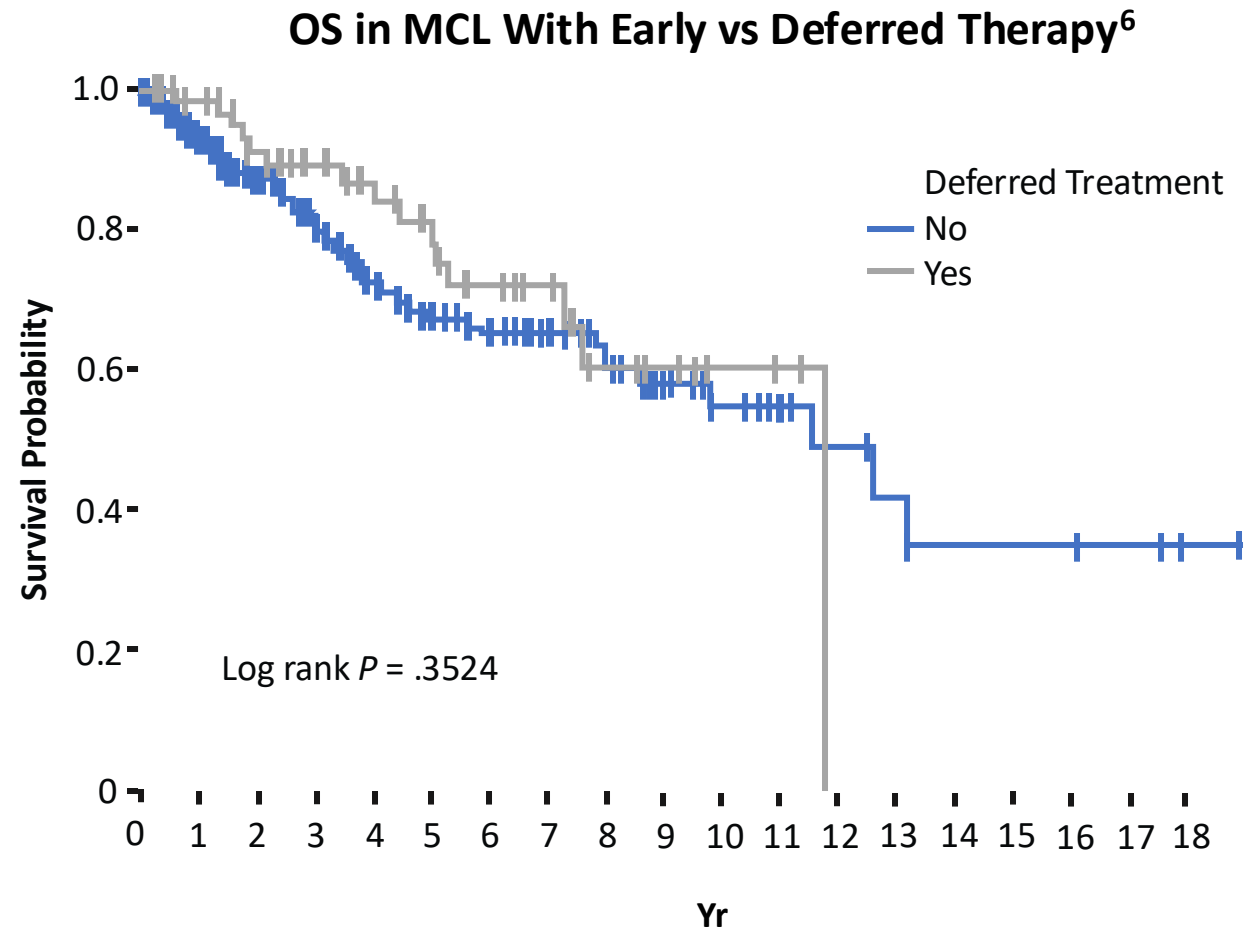
TP53 mutation



TP53-mutated cases had a dismal outcome, with a median OS of 1.8 years

MCL: Who Can Undergo Watch and Wait?

- Not blastoid morphology¹
- Normal LDH²
- Ki-67 <30%³
- Less frequent or no B symptoms³
- Mutated *IGHV*⁴
- Nonnodal⁵
- MIPI score is NOT defining characteristic



1. Martin. JCO. 2022;[Epub]. 2. Abrahamsson. Blood. 2014;124:1288. 3. Abrisqueta. Ann Oncol. 2017;28:2489.
4. Orchard. Blood. 2003;101:4975. 5. Ondrejka. Haematologica. 2011;96:1121. 6. Calzada. Leuk Lymphoma. 2018;59:2862.

Benefit of Chemoimmunotherapy in MCL

RCT: R-CHOP vs CHOP in Front line advanced stage MCL

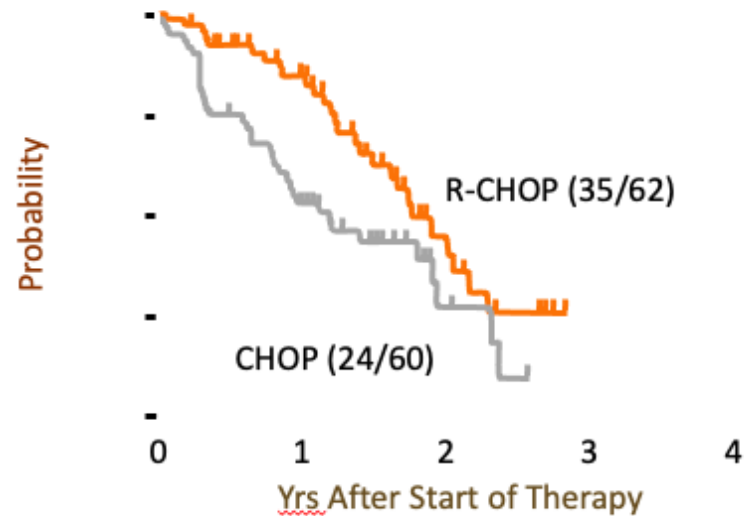
P	Patients, age 18 with advanced stage MCL
I	R-CHOP
C	CHOP
O	CR rate

CR rates

7% vs 34%, $P = .00024$

Median TTF

14 vs 21 mos, $P = .0131$



Pts at risk, n

R-CHOP	62	52	41	22	10	4
CHOP	60	43	26	15	4	1

After a long-term FU of 65 months

	R-CHOP	CHOP	
TTF (months)	28	14	$p = 0.0003$
Response duration (months)	29	18	$p = 0.0052$
5-y OS	59%	46%	$p = 0.27$

1. Lenz G, Dreyling M, Hoster E, et al. 2005;23:1984-1992.
2. Hoster E, Unterhalt M, Wormmann B, et al. Blood. 2008;112:16.

Addition of rituximab to chemotherapy alone as first-line therapy improves OS in elderly patients with MCL

Real-world data from Surveillance Epidemiology and End Results (SEER)–Medicare data

Table 2. Chemotherapy regimens

Chemotherapy regimen	First-line treatment					
	Rituximab + chemotherapy (n = 407)		Chemotherapy alone (n = 231)		Overall (n = 638)	
	n	%	n	%	n	%
CHOP	208	51.1	78	33.8	286	44.8
CNOP	18	4.4	16	6.9	34	5.3
CVP	51	12.5	44	19.0	95	14.9
Other*	130	31.9	93	40.3	223	35.0

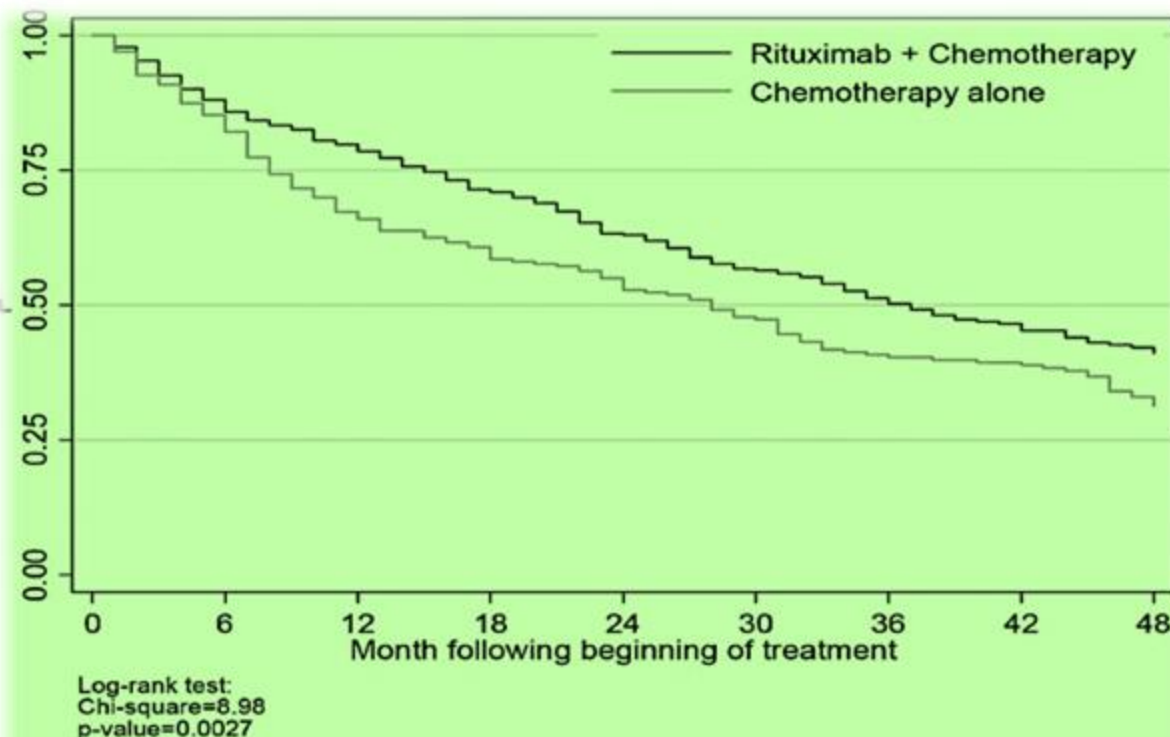


Figure 2. Overall survival.

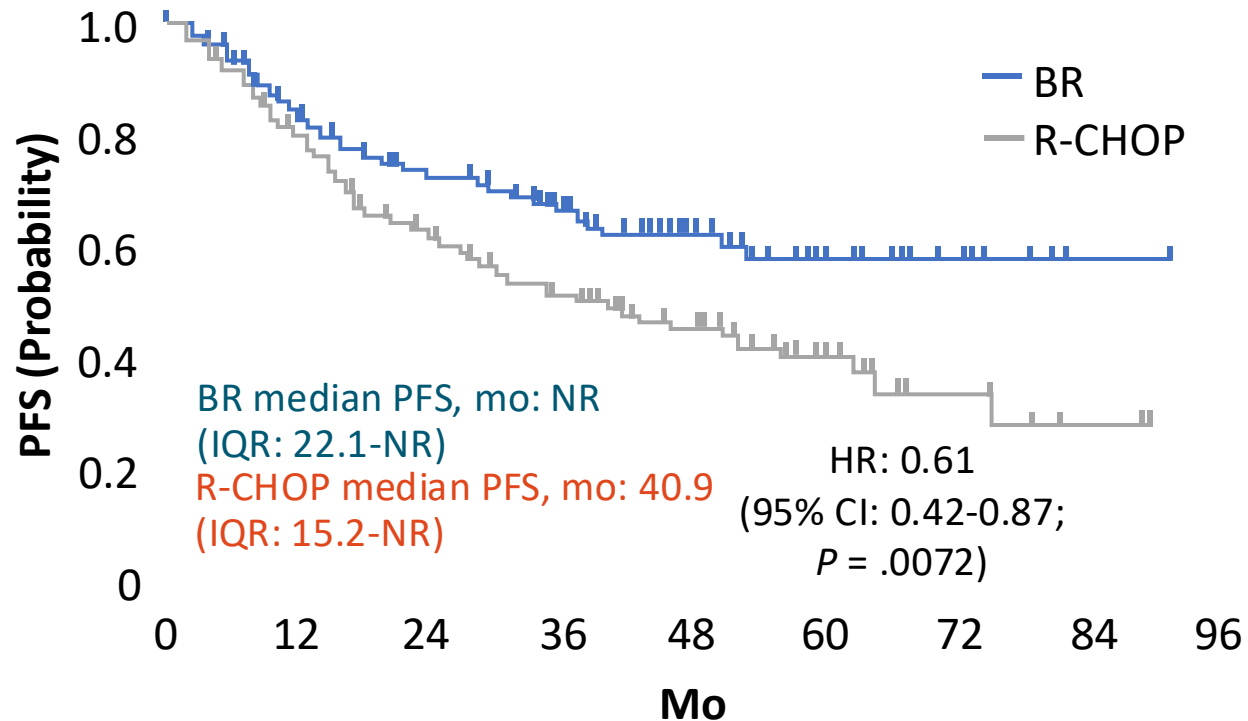
Table 3. Multivariate survival analysis: 2-year all-cause, cancer, and noncancer mortality

	All-cause mortality				Cancer mortality				Noncancer mortality			
	HR	95% CI	P		HR	95% CI	P		HR	95% CI	P	
First-line treatment												
Chemotherapy alone												
Rituximab + chemotherapy	0.58	0.41 0.82	< .01		0.56	0.37 0.84	< .01		0.83	0.25 2.80	.77	

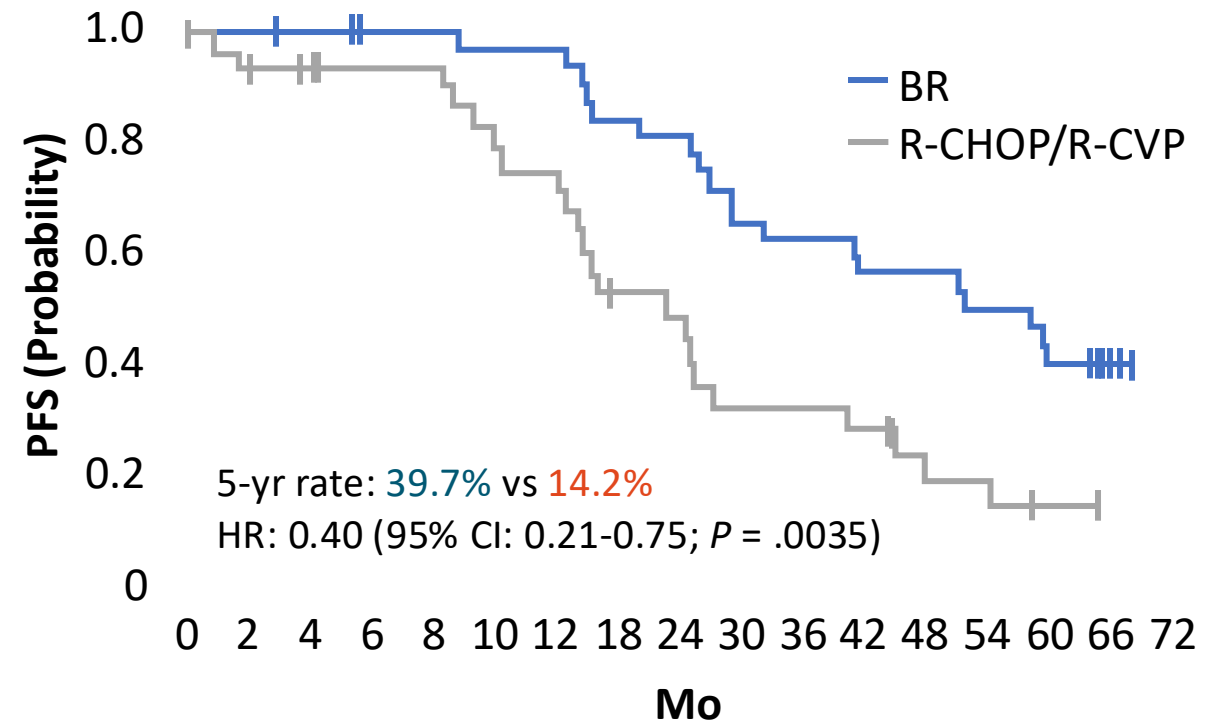
Chemoimmunotherapy induction regimens for older patients with MCL

STiL and BRIGHT Phase III Trials: PFS with BR Superior to R-CHOP in Untreated MCL Cohorts

STiL: Progression-Free Survival¹



BRIGHT: Progression-Free Survival^{2,3}

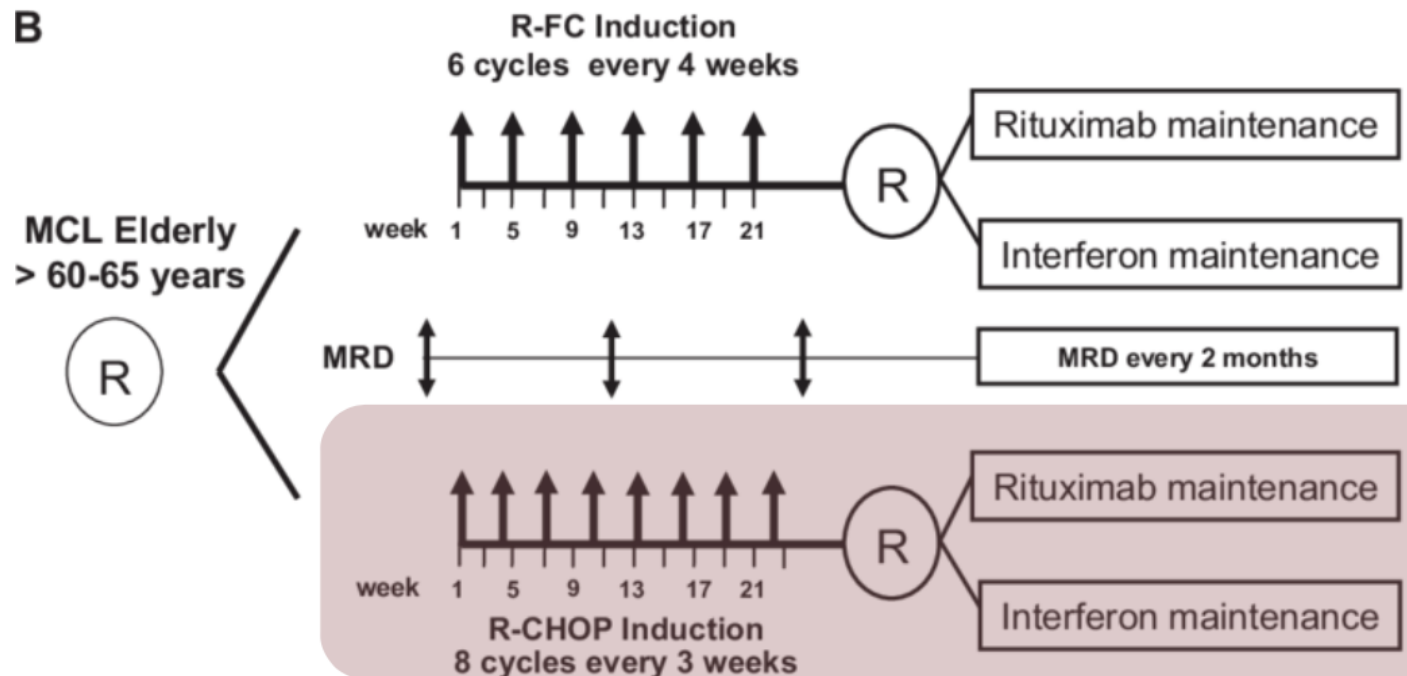


1. Rummel. Lancet. 2013;381:1203.

2. Flinn. ASCO 2017. Abstr 7500.

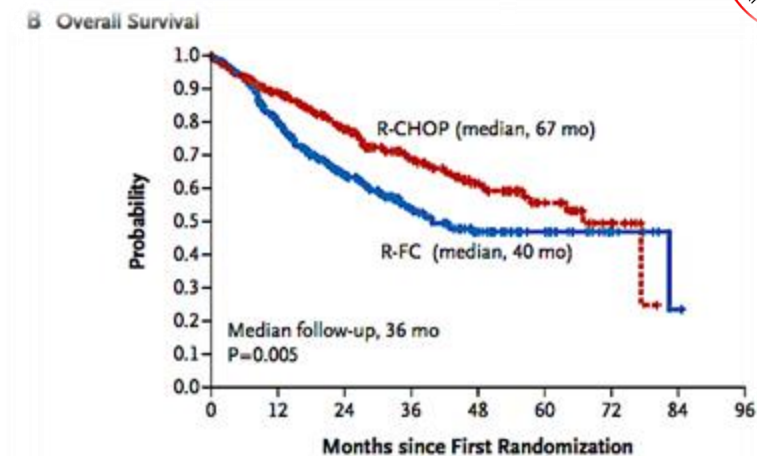
3. Flinn. JCO. 2019;37:984.

RCT: R-CHOP v R-FC for first-line treatment in elderly patients with MCL



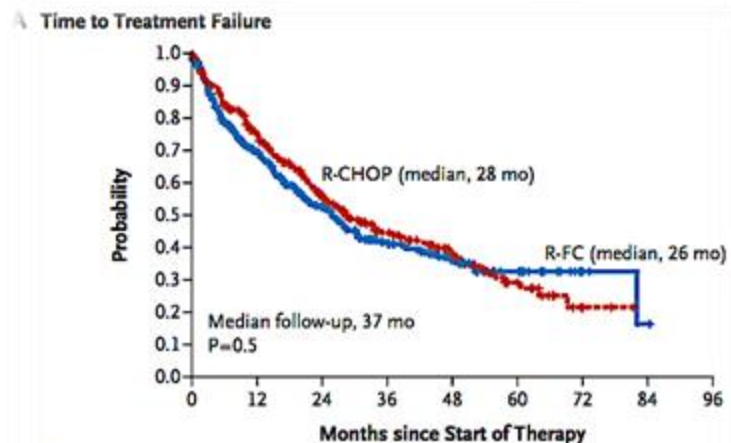
	R-FC (n =246)	R-CHOP (n =239)	p-value
CR (%)	40	34	0.1
PD (%)	14	5	

R-FC regimen was not more effective but was more toxic than R-CHOP



No. at Risk

R-FC	280	196	123	74	46	25	7	1	0
R-CHOP	280	214	150	95	55	26	8	0	



No. at Risk

R-FC	276	164	104	61	36	18	3	1	0
R-CHOP	274	179	107	64	36	16	2	0	

Key randomized trials for frontline chemoimmunotherapy in non-transplant candidate MCL

STiL BR vs R-CHOP

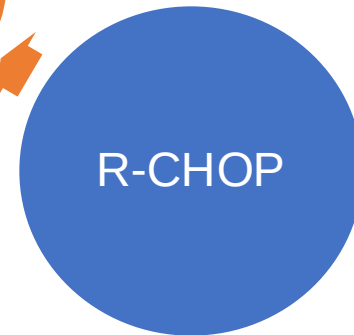
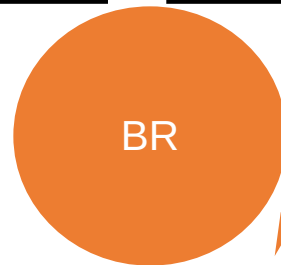
PFS 35.4 mo (**BR**) vs 22.1mo
PFS HR 0.49 P=0.005

Rummel, et al. Lancet 2013

BRIGHT BR vs RCHOP or R-CVP

5-y PFS: 66% (**BR**) vs 56%
PFS HR 0.4 P=0.035

Flinn, et al. JCO 2019



European MCL Elderly FCR vs R-CHOP

OS HR 1.5 , P=0.005
Inferior OS in R-FC

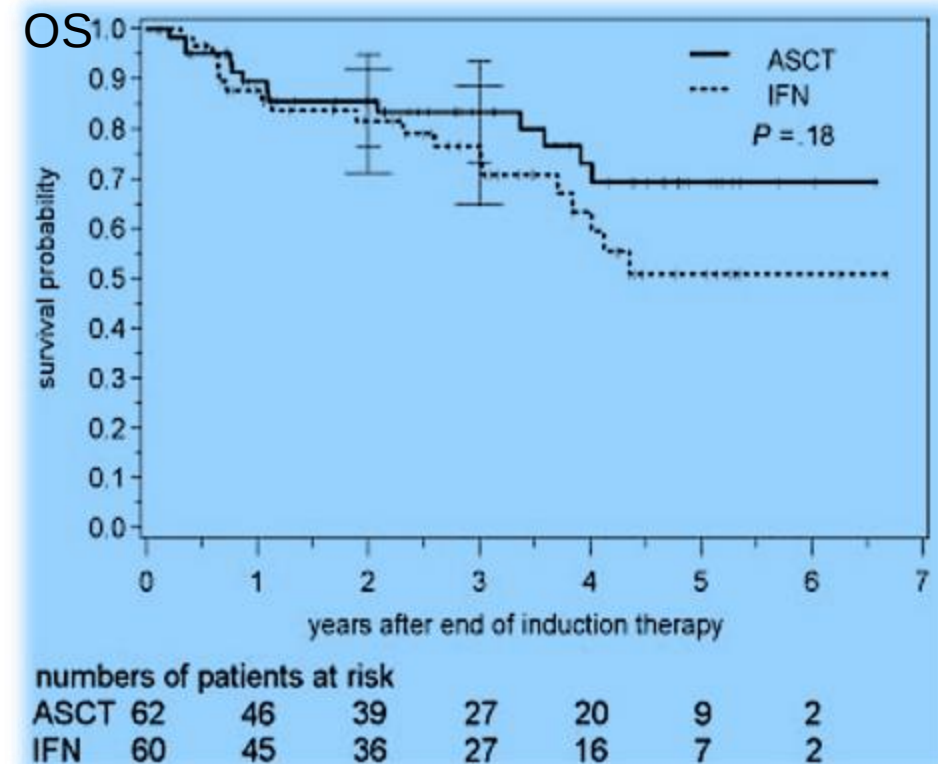
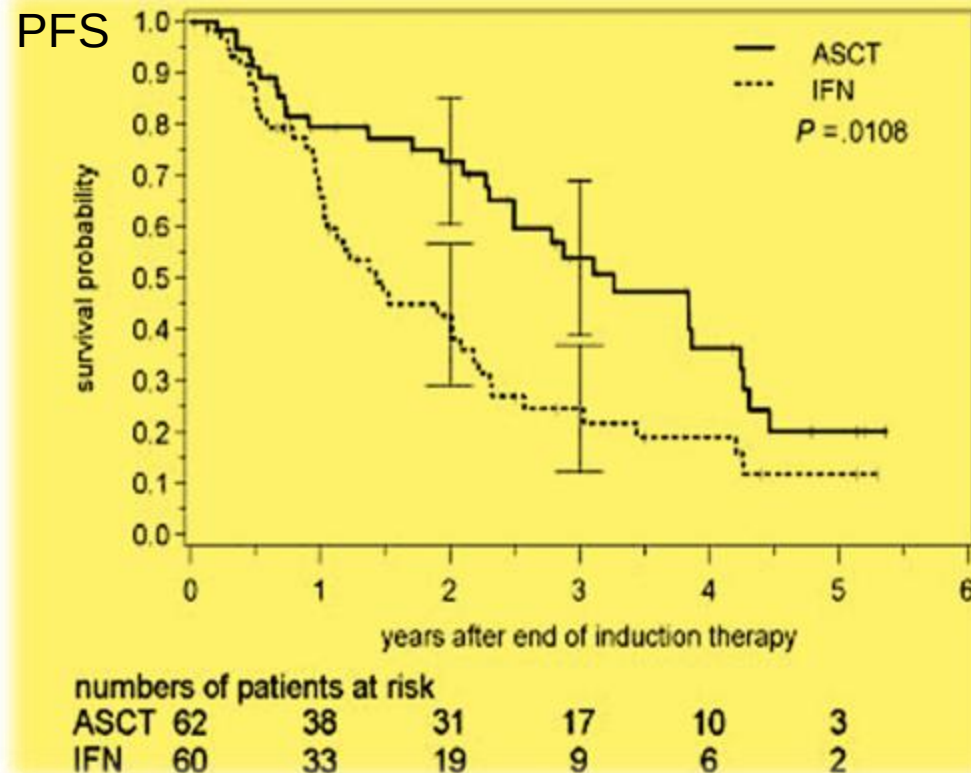
Kluin-Nelemans, et al. N Engl J Med 2012

Role of autologous stem cell transplantation for younger patients with MCL

Early consolidation by ASCT after R-CHOP like regimens in first remission significantly prolongs PFS in MCL

Results of a prospective RCT of the European MCL Network

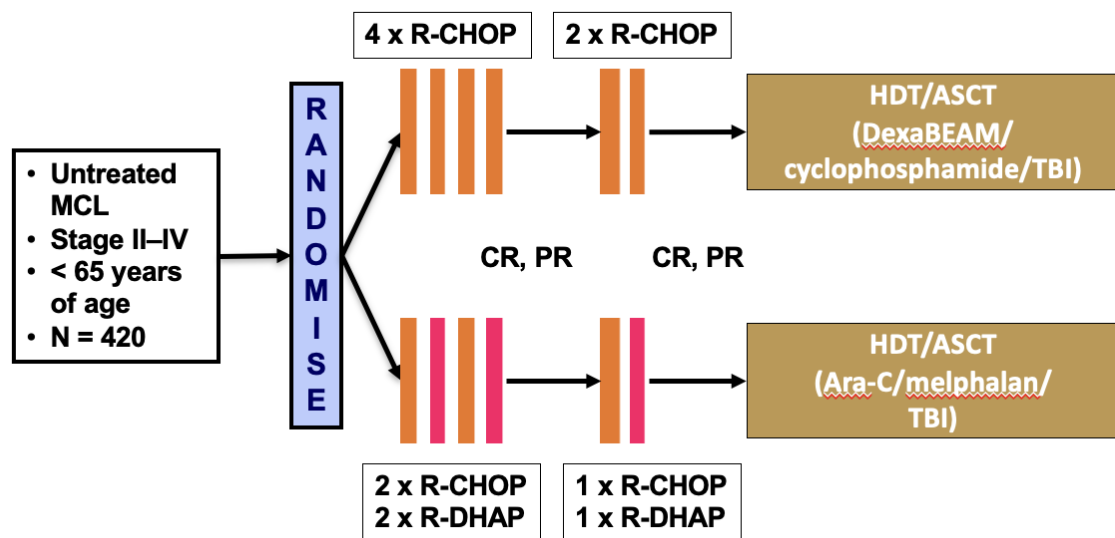
Upfront ASCT demonstrates benefits when used with a low-intensity R-CHOP-like induction regimen



Chemoimmunotherapy induction regimen for younger patients with MCL

R-CHOP/R-DHAP followed by a high-dose Ara-C ASCT is superior to followed by ASCT in MCL:

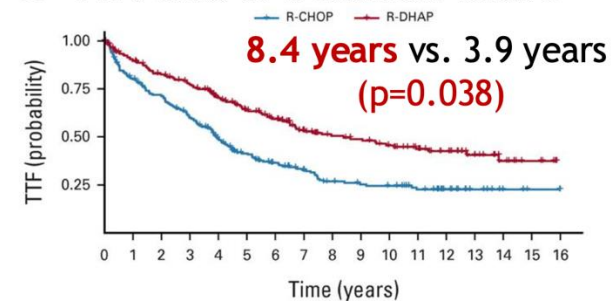
Update of results of the MCL younger trial of European Mantle Cell Lymphoma Network



	R-CHOP (n = 212)	R-CHOP/R-DHAP (n = 208)	p value
TTF	49	NR	0.0382
Response duration after ASCT	48	NR	0.0059
Overall survival	NR	NR	0.3700

FU 10.6 years

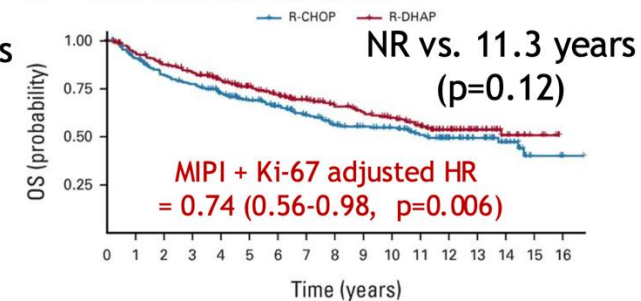
A TTF: time-to-treatment failure



No. at risk:

R-CHOP	234	178	156	129	100	77	62	50	38	34	32	24	16	9	4	2	1
R-DHAP	232	194	175	160	135	115	100	77	65	61	53	42	32	19	11	5	0

B OS: overall survival



No. at risk:

R-CHOP	249	219	194	182	163	145	130	111	94	85	78	64	46	35	19	5	2
R-DHAP	248	227	209	196	174	155	141	121	103	94	85	70	51	31	16	7	0

BR and R-cytarabine induction therapy for transplant-eligible MCL

DFCI phase II trial (n=23) (2012-2014)

DFCI off-trial (n=47) (2014-2018)



WUSTL phase II trial (n=18) (2016-2018)



Autologous stem cell transplantation

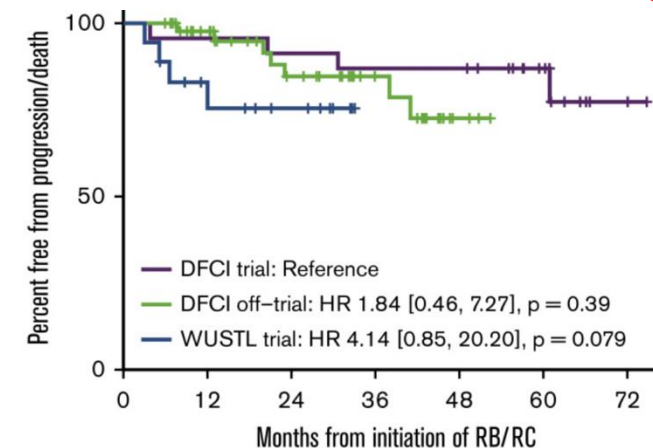
RB

- Rituximab – 375 mg/m², day 1
- Bendamustine – 90 mg/m², days 1-2

RC

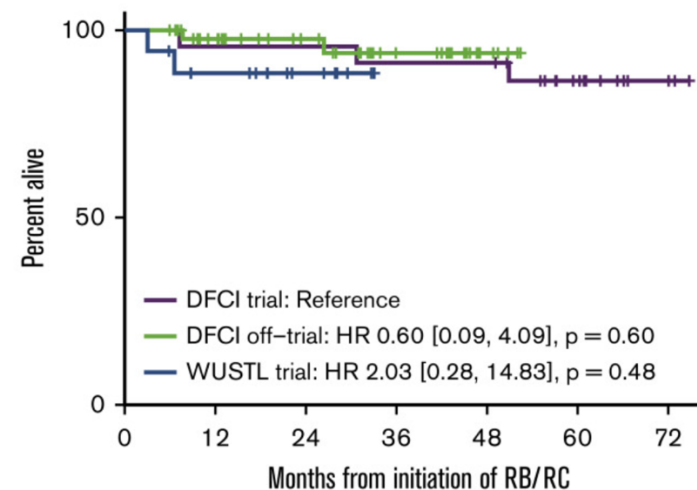
- Rituximab – 375 mg/m², day 1
- Cytarabine – 3 gm/m² BID days 1-2*

- End-of-induction CR rates: 90%
 - FN 15% during induction
 - Gr4 Neutropenia 68%
- MRD negativity rates after ASCT: 100%
- The 3-year PFS 83%
- The 3-year OS 92%



Number at risk

23	22	21	20	20	13	3
47	37	24	14	3		



Number at risk

23	22	22	21	21	13	4
47	38	27	16	5		
18	13	7				

Key frontline chemoimmunotherapy in transplant candidate MCL

Population-based COHORT BR vs R-CHOP/R-DHAP

PFS HR, 0.87; P= .56

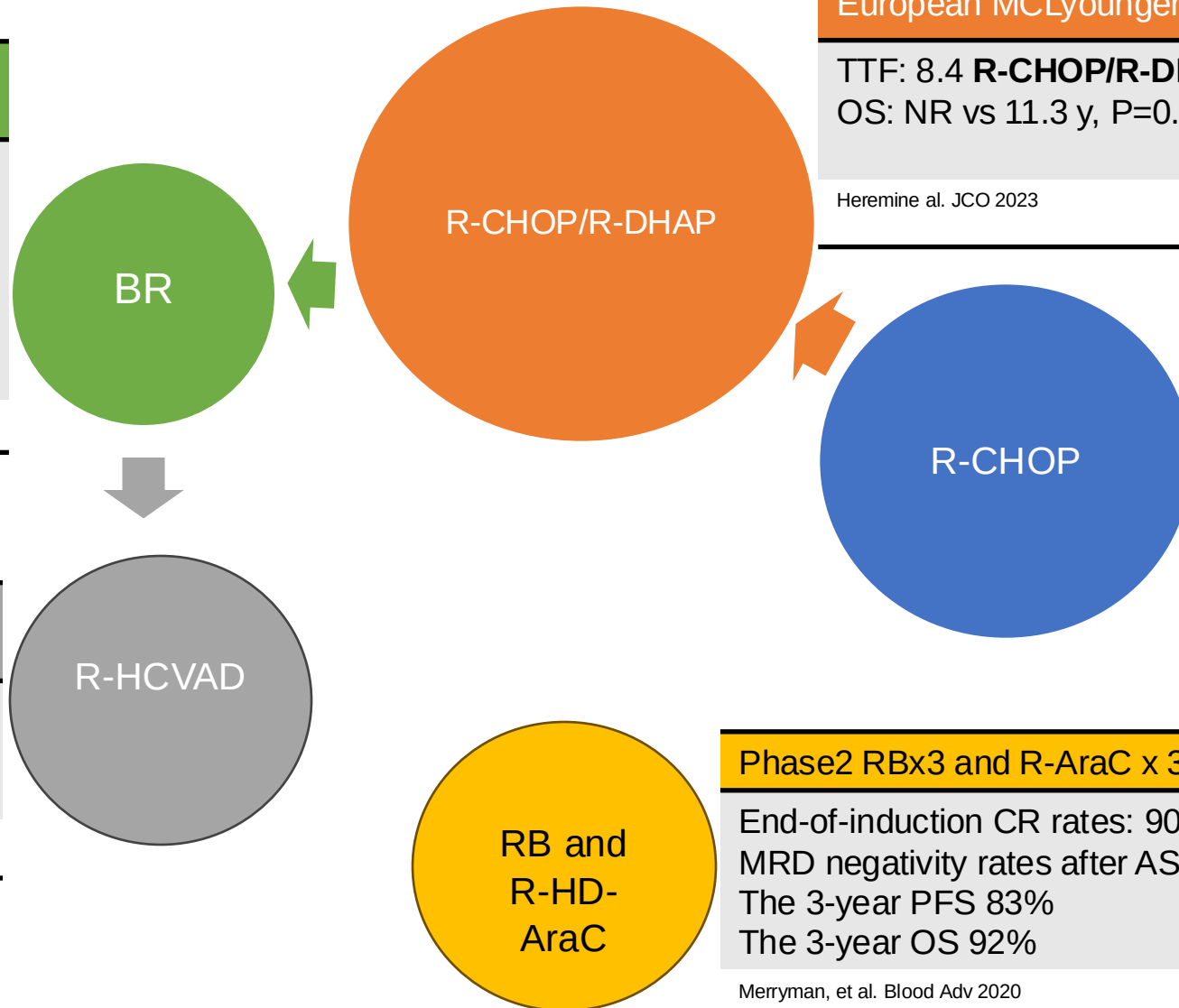
(ASCT 77% vs 78%
R-maintenance 78% in BR vs 2%
in R-CHOP/R-DHAP)

Villa et al. Blood Adv 2022

SWOG S1106 BR vs R- HyperCVAD

Early termination due to toxicity
5-year PFS: 66% **BR** vs 62%
5-year OS: 80% **BR** vs 74%

Kamdar et al. Blood Adv 2019



European MCLyounger R-CHOP/R-DHAP vs R-CHOP

TTF: 8.4 **R-CHOP/R-DHAP** vs 3.9 y , P=0.03
OS: NR vs 11.3 y, P=0.12

Heremine al. JCO 2023

Phase2 RBx3 and R-AraC x 3

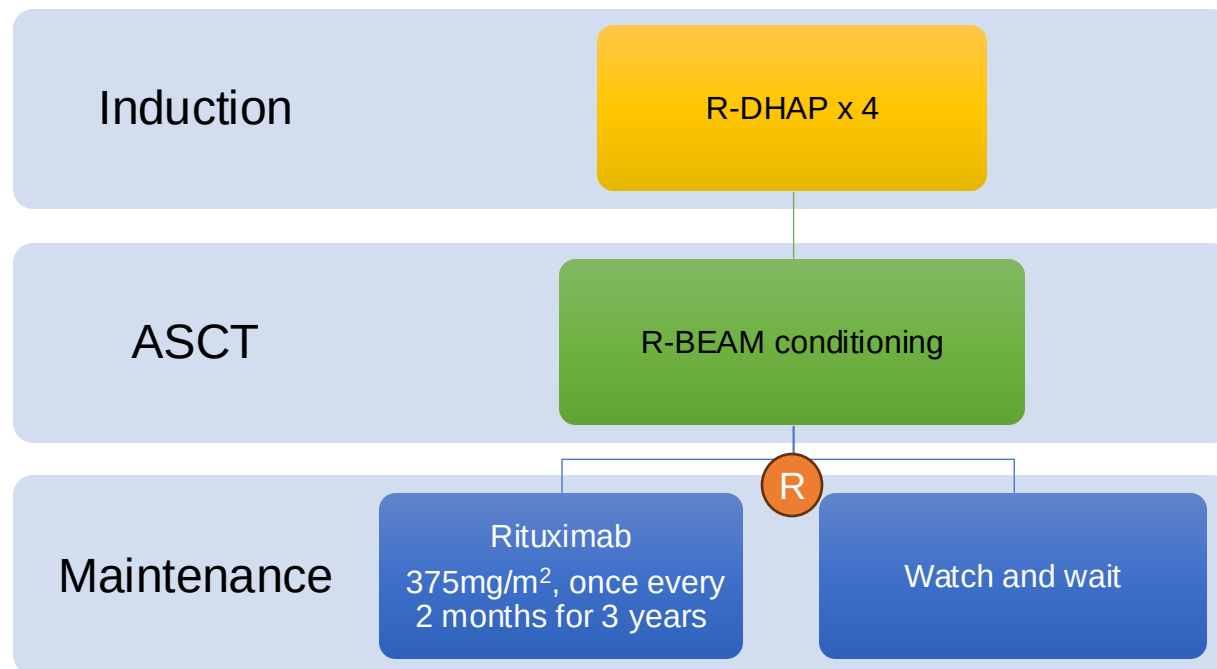
End-of-induction CR rates: 90%
MRD negativity rates after ASCT: 100%
The 3-year PFS 83%
The 3-year OS 92%

Merryman, et al. Blood Adv 2020

Role of maintenance treatment for patients with MCL

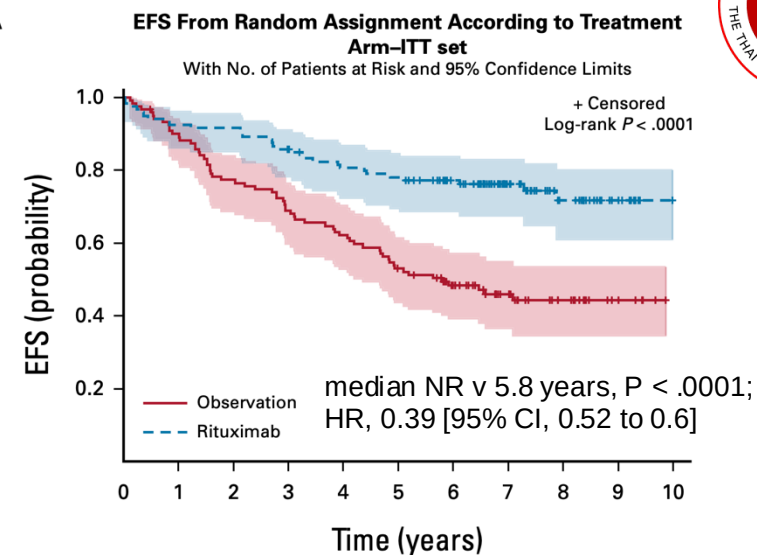
Long-term FU of R-maintenance after ASCT in younger patients with MCL: LYMA trial

Median FU 7.5 years



At Median FU 7.5 years

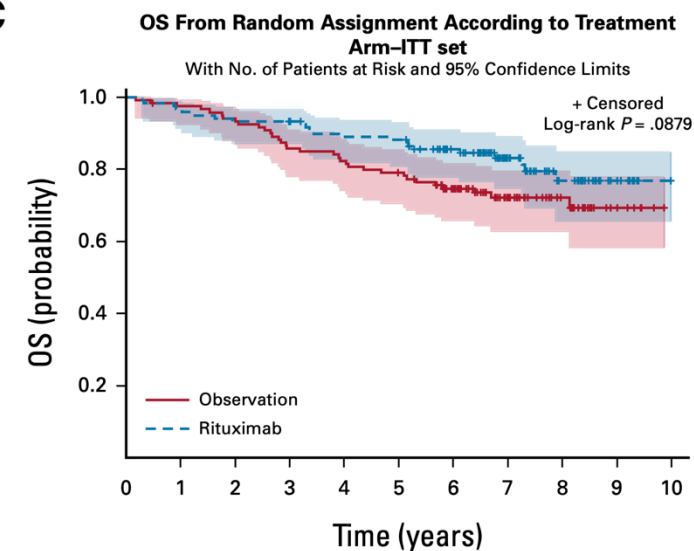
A



No. at risk:

Observation	120	107	92	82	74	62	47	29	16	6	0
Rituximab	120	111	110	102	94	91	74	44	26	11	0

C



No. at risk:

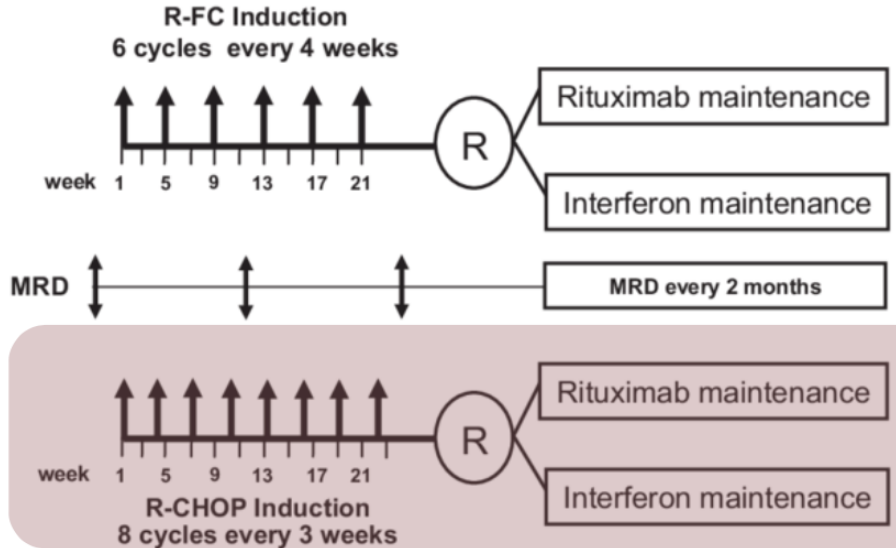
Observation	120	116	112	102	98	93	75	45	25	7	0
Rituximab	120	116	112	111	104	103	81	48	28	11	0

RCT: R-CHOP v R-FC for first-line RX in elderly patients with MCL

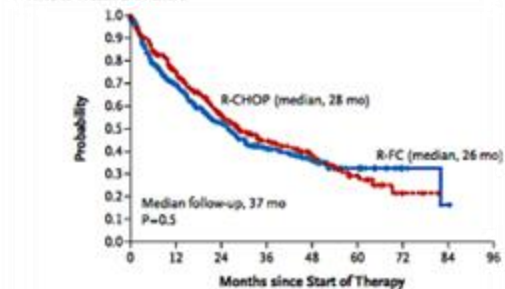
MCL Elderly study maintenance treatment

B

MCL Elderly
 > 60-65 years

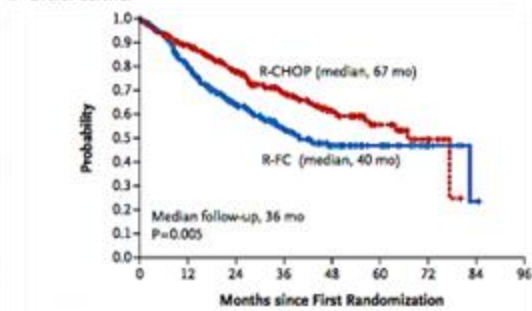


Time to Treatment Failure



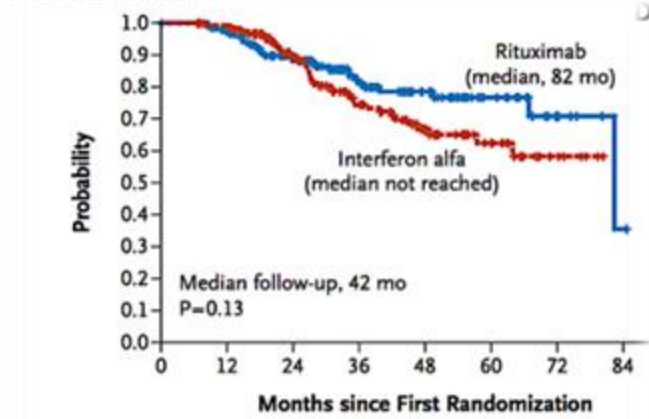
No. at Risk	0	12	24	36	48	60	72	84	96
R-FC	276	164	104	61	36	18	3	1	0
R-CHOP	274	179	107	64	36	16	2	0	0

Overall Survival



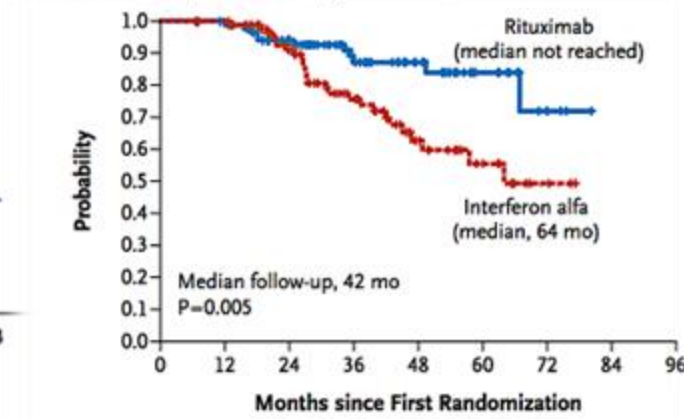
No. at Risk	0	12	24	36	48	60	72	84	96
R-FC	280	196	123	74	46	25	7	1	0
R-CHOP	280	214	150	95	55	26	8	0	0

C Overall Survival



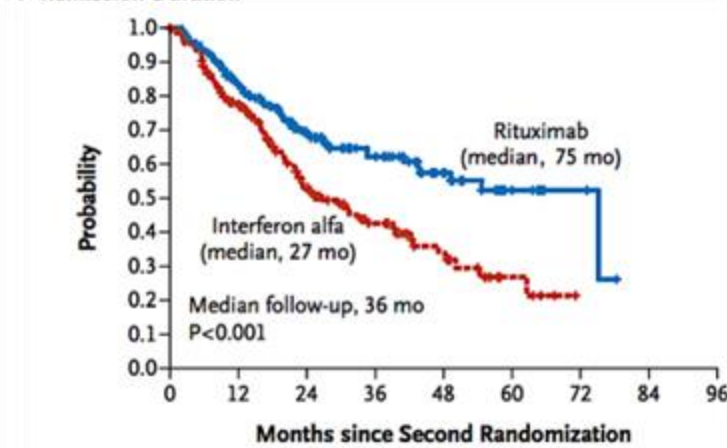
No. at Risk	0	12	24	36	48	60	72	84
Rituximab	155	148	113	71	47	22	6	1
Interferon alfa	161	153	109	71	40	21	6	0

D Overall Survival, Patients Assigned to R-CHOP



No. at Risk	0	12	24	36	48	60	72	84	96
Rituximab	87	86	71	46	30	13	3	0	0
Interferon alfa	97	92	65	43	22	11	3	0	0

A Remission Duration

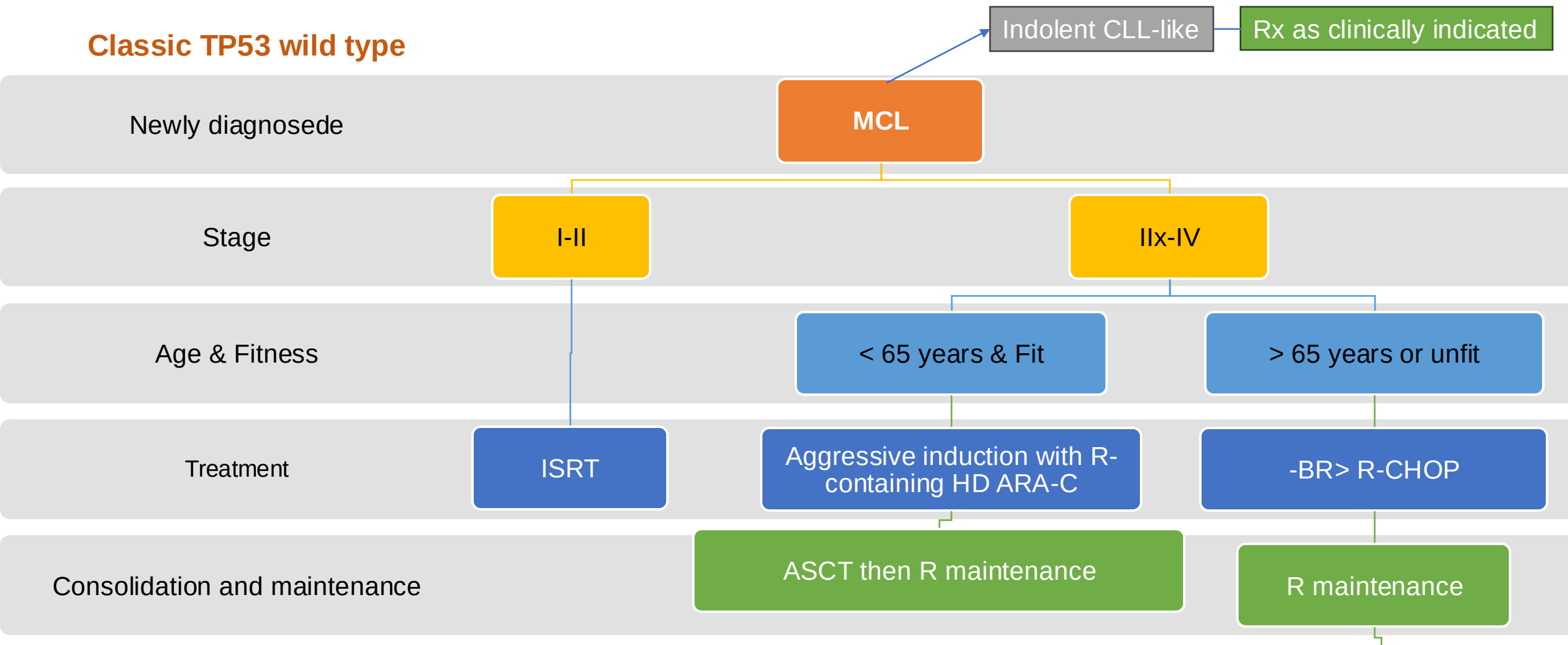


No. at Risk	0	12	24	36	48	60	72	84	96
Rituximab	155	116	76	50	27	9	3	0	0
Interferon alfa	161	109	59	33	17	5	0	0	0

OS benefit in R-CHOP induction

Treatment plan for MCL

Classic TP53 wild type



Shifting Landscape of treatment in 1L therapy for MCL



Role of ASCT

Should all transplant eligible patients proceed to ASCT?



Adding targeted agents to chemoimmunotherapy backbone



Chemo-free regimens



Improving the options for maintenance Rx

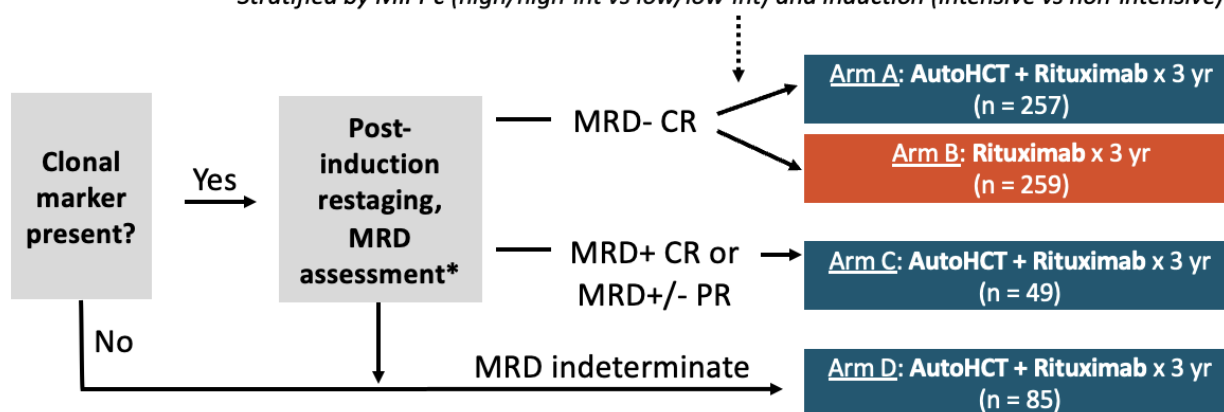
ASCT in MRD-Negative Patients MCL in First CR

ECOG-ACRIN EA4151: Phase III

- International, open-label, randomized phase III trial

Stratified by MIPI-c (high/high-int vs low/low-int) and induction (intensive vs non-intensive)

Patients aged ≥ 18 and ≤ 70 yr with MCL in first remission; considered candidates for autoHCT per treating physician; any rituximab-containing induction regimen allowed (including BTKi); if completed induction therapy, must be within 120 days prior to preregistration and <300 days between first day of therapy and preregistration (N = 650)



- Primary endpoint:** OS (Arm A vs Arm B)
- Key secondary endpoints:** PFS (Arm A vs Arm B), PFS (Arms C and D), MRD conversion rate post autoHCT, safety

*Included PET/CT, bone marrow biopsy, and MRD from peripheral blood measured using clonoSEQ, with a sensitivity of 1×10^{-6} .

		Arm A: MRD-, AutoHCT	Arm B: MRD-, No AutoHCT	HR (95% CI)
3-Yr OS, %	All randomized (n = 516)	82.1	82.7	1.11 (0.71-1.74) P = .66
	Treated as assigned (n = 375)	86.2	84.8	1.00 (0.58-1.74) P = .99
3-Yr PFS, %	All randomized (n = 516)	76.6	77.4	1.05 (0.71-1.56) P = .79
	Treated as assigned (n = 375)	81.5	80.4	0.95 (0.59-1.54) P = .84

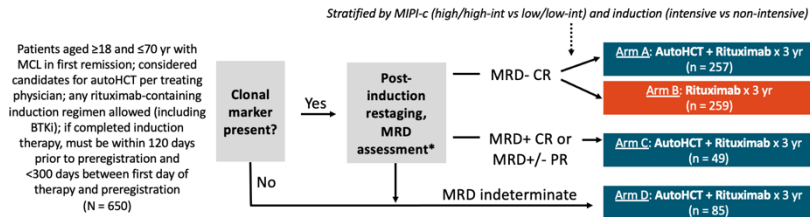
	Arm C: MRD+, AutoHCT (n = 49)	Arm D: MRD indet, AutoHCT (n = 85)
3-Yr OS, %	81.9 (CI: 69.6-96.4)	85.1 (CI: 76.0-95.4)
3-Yr PFS, %	76.9 (CI: 64.4-91.7)	73.4 (CI: 62.7-85.9)

ASCT in MRD-Negative Patients MCL in First CR

ECOG-ACRIN EA4151: Phase III

- At a median follow-up of 2.7 yr, the futility boundary was an OS HR of 0.984 (Arm A vs Arm B); estimated OS HR crossed this boundary

- International, open-label, randomized phase III trial



- Primary endpoint:** OS (Arm A vs Arm B)
- Key secondary endpoints:** PFS (Arm A vs Arm B), PFS (Arms C and D), MRD conversion rate post autoHCT, safety

*Included PET/CT, bone marrow biopsy, and MRD from peripheral blood measured using clonoSEQ, with a sensitivity of 1×10^{-4} .

- Patients with MCL who achieved CR and MRD negativity after induction did not benefit from autoHCT
- The additional follow-up is needed to confirm these initial findings

		Arm A: MRD-, AutoHCT	Arm B: MRD-, No AutoHCT	HR (95% CI)
3-Yr OS, %	All randomized (n = 516)	82.1	82.7	1.11 (0.71-1.74) P = .66
	Treated as assigned (n = 375)	86.2	84.8	1.00 (0.58-1.74) P = .99
3-Yr PFS, %	All randomized (n = 516)	76.6	77.4	1.05 (0.71-1.56) P = .79
	Treated as assigned (n = 375)	81.5	80.4	0.95 (0.59-1.54) P = .84

	Arm C: MRD+, AutoHCT (n = 49)	Arm D: MRD indet, AutoHCT (n = 85)
3-Yr OS, %	81.9 (CI: 69.6-96.4)	85.1 (CI: 76.0-95.4)
3-Yr PFS, %	76.9 (CI: 64.4-91.7)	73.4 (CI: 62.7-85.9)

Shifting paradigm of treatment in 1L therapy for MCL



Role of ASCT

Should all transplant eligible patients proceed to ASCT?



Adding targeted agents to chemoimmunotherapy backbone

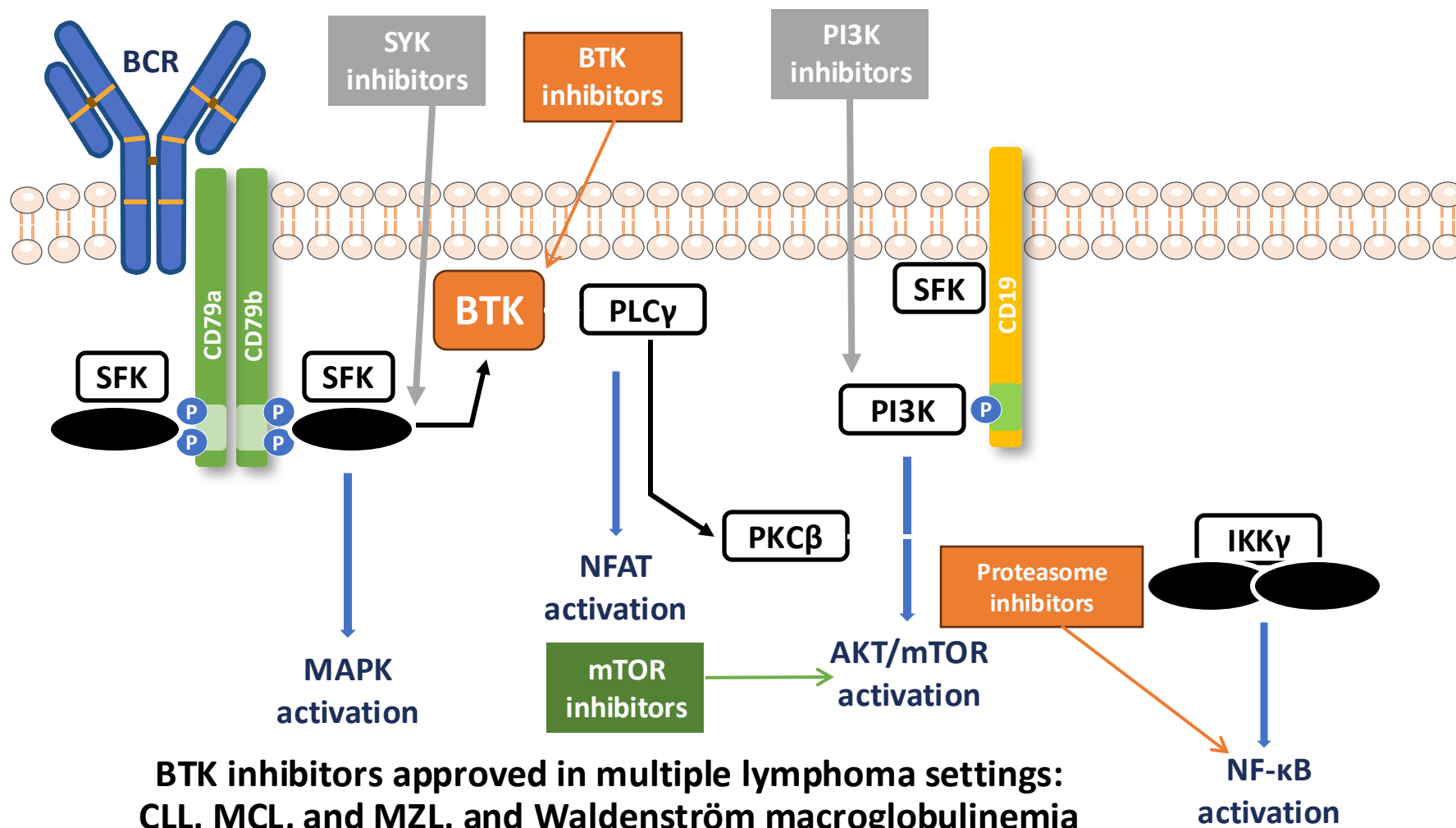


Chemo-free regimens



Improving the options for maintenance Rx

BTK in B-Cell Malignancies



Bortezomib-Based Therapy for Newly Diagnosed MCLw

Superior PFS with VR-CAP vs R-CHOP

Primary endpoint: PFS

Newly diagnosed MCL pts
Stage II-IV, ECOG PS 0-2
Ineligible or not
considered for BMT
(N = 487)

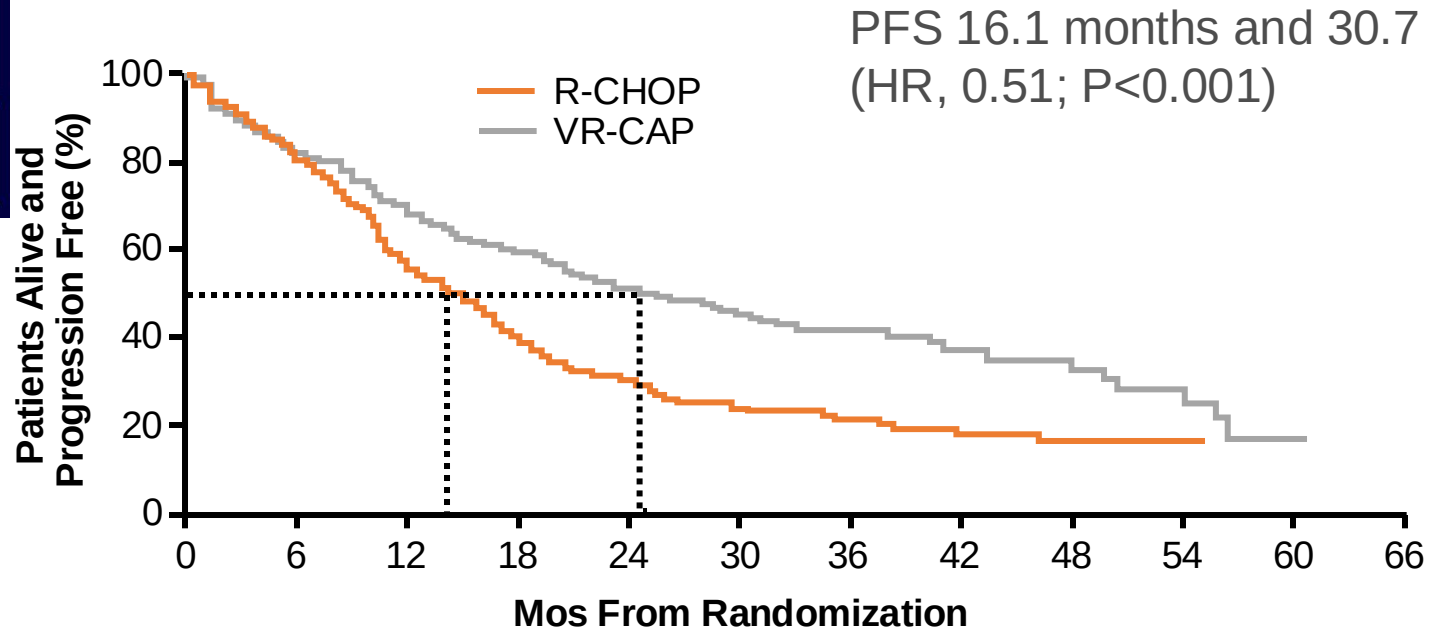
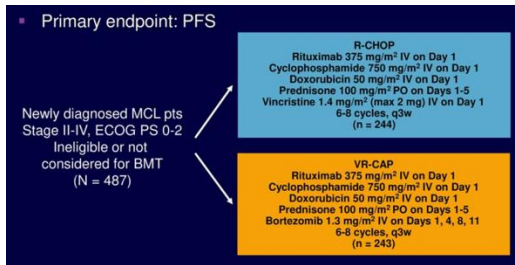
R-CHOP
Rituximab 375 mg/m² IV on Day 1
Cyclophosphamide 750 mg/m² IV on Day 1
Doxorubicin 50 mg/m² IV on Day 1
Prednisone 100 mg/m² PO on Days 1-5
Vincristine 1.4 mg/m² (max 2 mg) IV on Day 1
6-8 cycles, q3w
(n = 244)

VR-CAP
Rituximab 375 mg/m² IV on Day 1
Cyclophosphamide 750 mg/m² IV on Day 1
Doxorubicin 50 mg/m² IV on Day 1
Prednisone 100 mg/m² PO on Days 1-5
Bortezomib 1.3 mg/m² IV on Days 1, 4, 8, 11
6-8 cycles, q3w
(n = 243)

No maintenance Rx

Bortezomib-Based Therapy for Newly Diagnosed MCLw

Superior PFS with VR-CAP vs R-CHOP



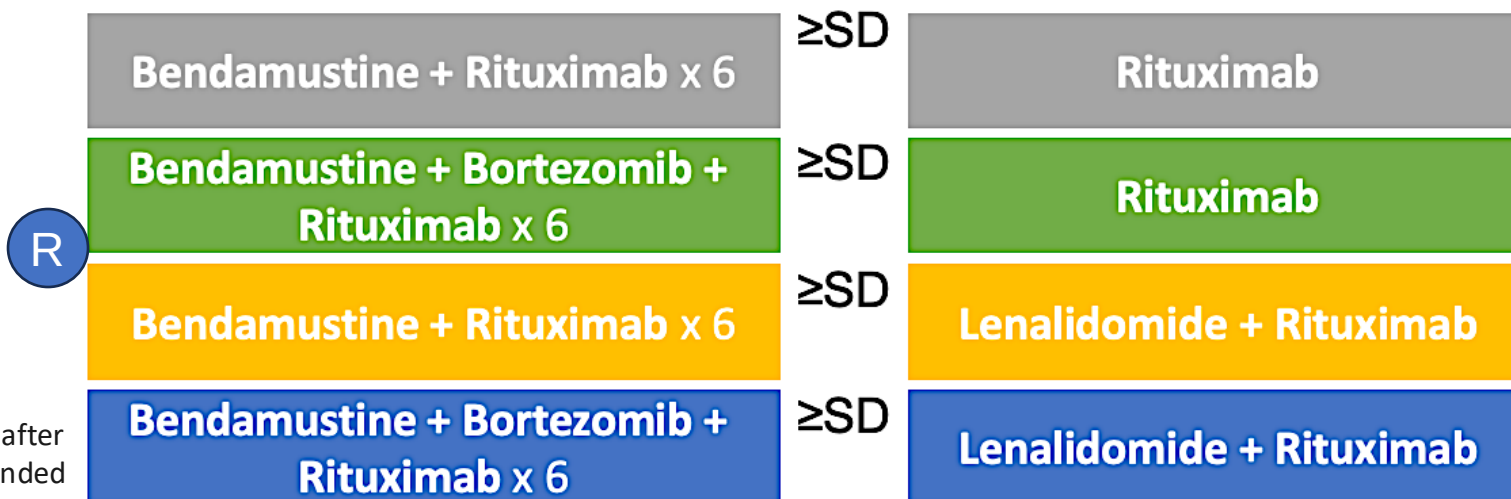
Additional Outcomes	R-CHOP	VR-CAP	OR	P Value
CR + CRu, %	42	53	1.69	.007
ORR (CR + CRu + PR), %	90	92	1.43	.275
Median duration of response, mos	15.1	36.5	NA	NA
4-yr OS rate, %	53.9	64.4	NA	NA

Randomized phase II study of induction with **bendamustine-rituximab ± bortezomib (BVR vs BR)** and maintenance with **rituximab vs R-lenalidomide** for MCL

- An open-label, randomized phase II trial

Patients with
treatment-naïve MCL
requiring therapy;
ECOG PS 0-2
(N = 373)

Initially restricted to patients aged >60 years, after
the early closure of S1106, eligibility was amended
to include all ages >18 years



- **Primary endpoint:** PFS (BR vs BVR and R vs LR)
- **Main secondary endpoints:** PET-documented CR, ORR

Induction: bendamustine 90 mg/m²/d IV Days 1, 2; rituximab 375 mg/m² IV Day 1; bortezomib 1.3 mg/m² IV or SC Days 1, 4, 8, 11 (later amended to 1.6 mg/m² Days 1, 8) in 28-day cycles

Consolidation: rituximab 375 mg/m² every 8 wk x 12 doses ± lenalidomide 15 mg/d 21/28 days x 24 cycle

Randomized phase II study of induction with bendamustine-rituximab $\pm$ bortezomib and maintenance with rituximab vs R-lenalidomide for MCL

- An open-label, randomized phase II trial

87% aged ≥ 60 years

Patients with treatment-naïve MCL requiring therapy; ECOG PS 0-2 (N = 373)

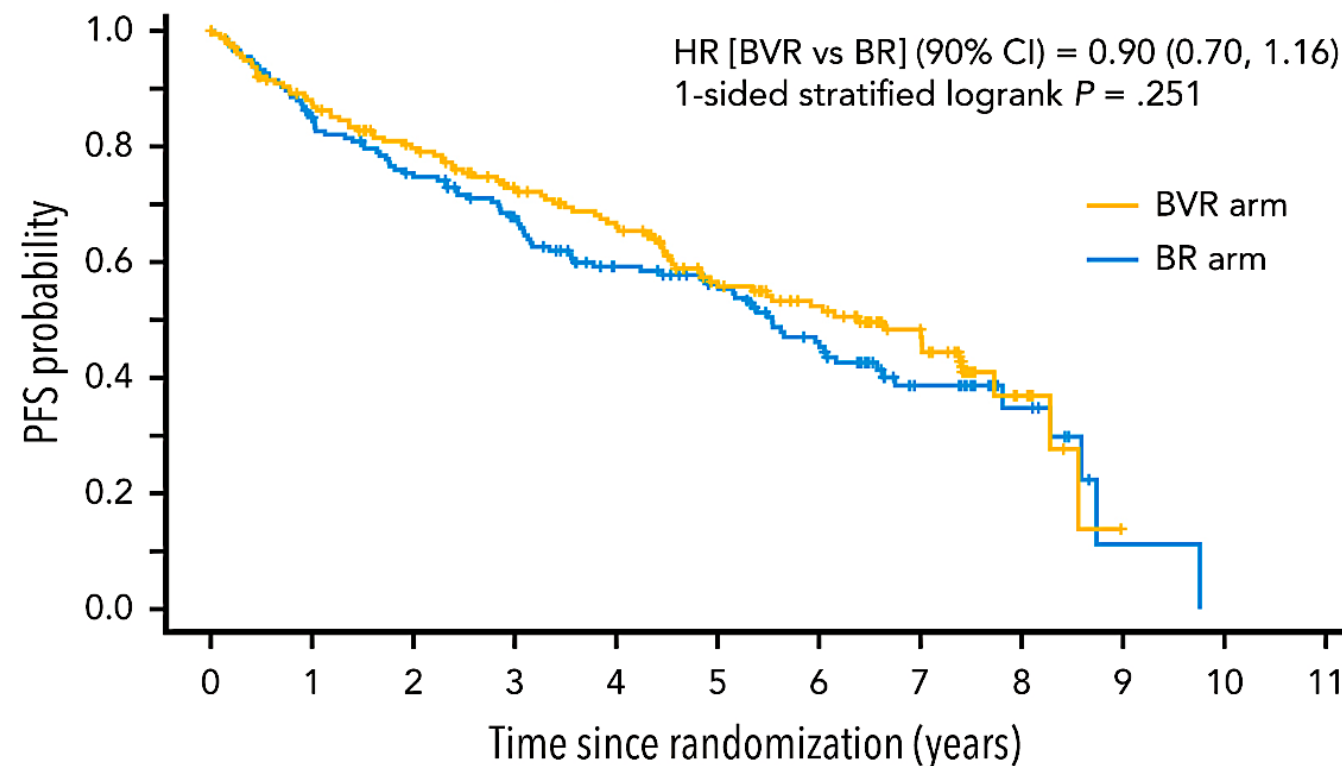
Bendamustine + Rituximab $\times 6$	$\geq$ SD	Rituximab
Bendamustine + Bortezomib + Rituximab $\times 6$	$\geq$ SD	Rituximab
Bendamustine + Rituximab $\times 6$	$\geq$ SD	Lenalidomide + Rituximab
Bendamustine + Bortezomib + Rituximab $\times 6$	$\geq$ SD	Lenalidomide + Rituximab

- Primary endpoint:** PFS (BR vs BVR and R vs LR)
- Main secondary endpoints:** PET-documented CR, ORR

A

PFS by treatment arm (step 1)

HR [BVR vs BR] (90% CI) = 0.90 (0.70, 1.16)
1-sided stratified logrank $P = .251$



	Nos. at risk										
BVR arm:	179	150	131	111	97	72	58	38	7	0	0
BR arm:	179	144	122	104	81	70	53	24	9	1	0

— BVR: 2-year PFS (95% CI) = 79.7% (72.9, 85.0)
5-year PFS (95% CI) = 56.6% (48.3, 64.0)

— BR: 2-year PFS (95% CI) = 74.8% (67.5, 80.6)
5-year PFS (95% CI) = 56.2% (48.1, 63.5)

— BVR: median (95% CI); n/events = 6.4 (4.8, 7.7); 179/86

— BR: median (95% CI); n/events = 5.5 (4.5, 6.6); 179/95

Key messages for frontline chemoimmunotherapy in non-transplant candidate MCL

STIL BR vs R-CHOP

PFS 35.4 mo (**BR**) vs 22.1mo
PFS HR 0.49 P=0.005

Rummel, et al. Lancet 2013

BRIGHT BR vs RCHOP or R-CVP

5-y PFS: 66% (**BR**) vs 56%
PFS HR 0.4 P=0.035

Flinn, et al. JCO 2019

E1411 BVR vs BR

Median PFS 6.2 y vs 6.0 y
HR 0.9

Smith, et al. Blood 2022

**Rituximab-Bendamustine is
a standard care for older
patients with MCL**

LYM-3002 VR-CAP vs R-CHOP

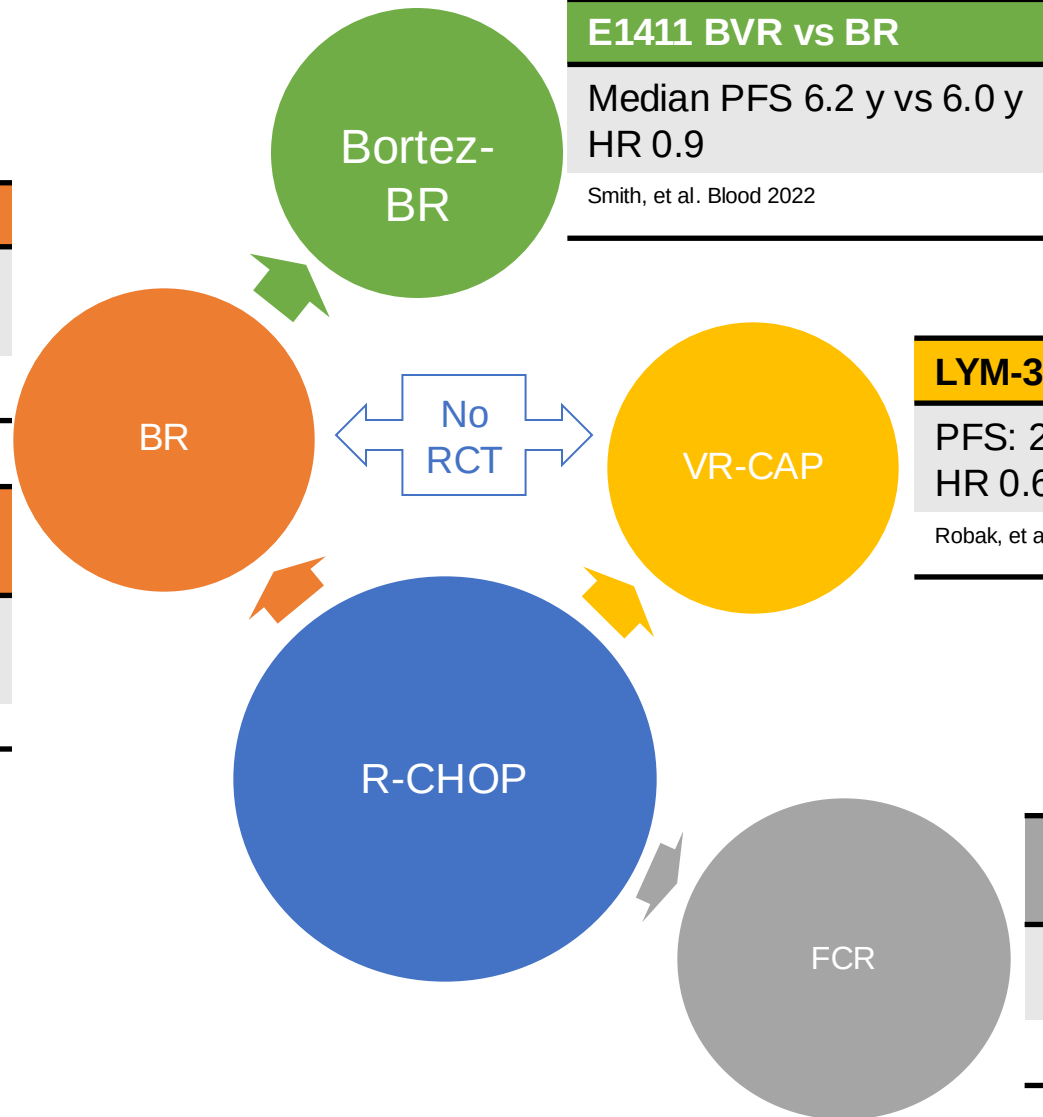
PFS: 24.7 mo (**VR-CAP**) vs 14.4 mo
HR 0.63, P<0.001

Robak, et al. N Eng J Med 2015

European MCL Elderly FCR vs R-CHOP

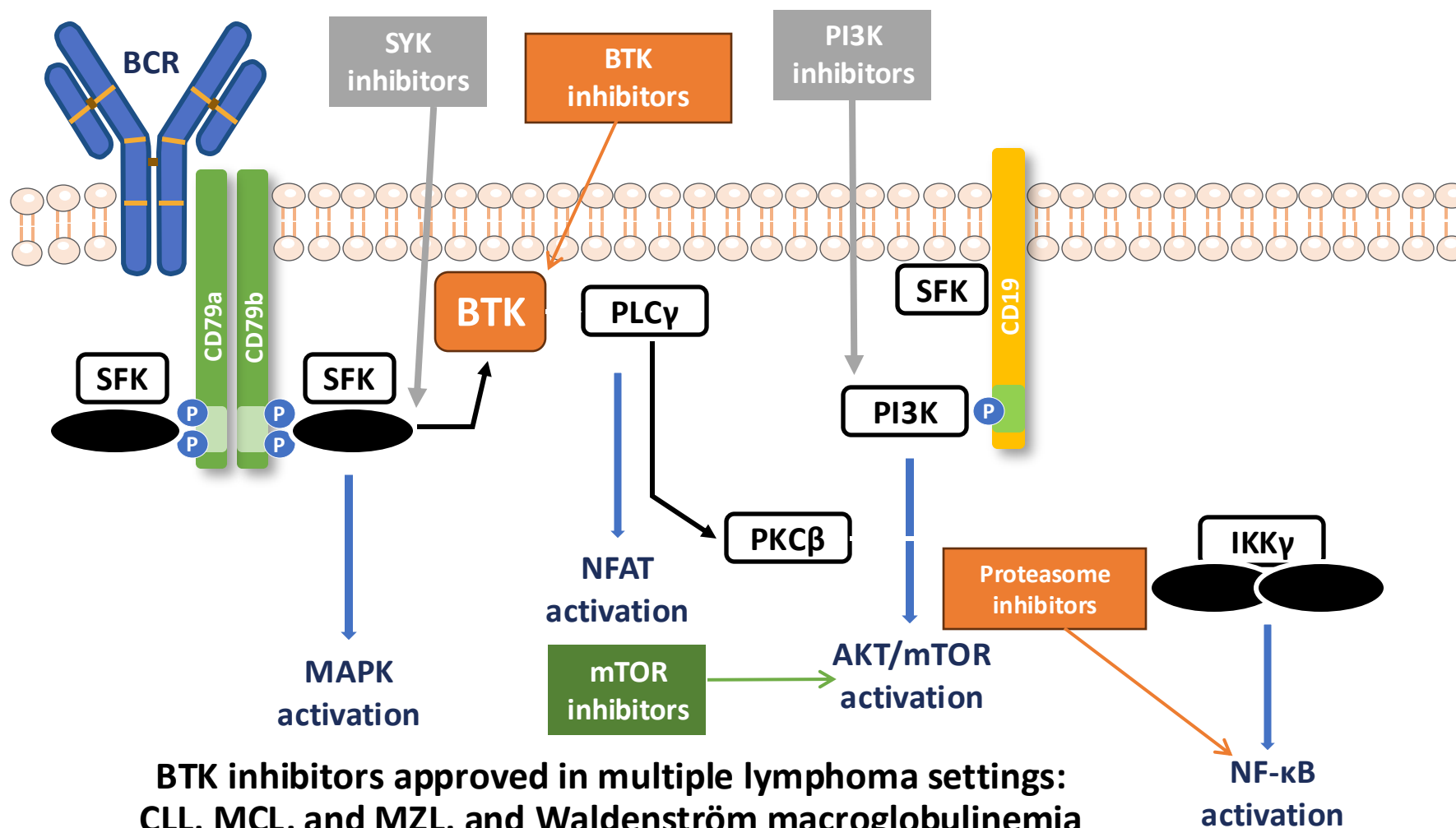
OS HR 1.5 , P=0.005
Inferior OS in R-FC

Kluin-Nelemans, et al. N Engl J Med 2012

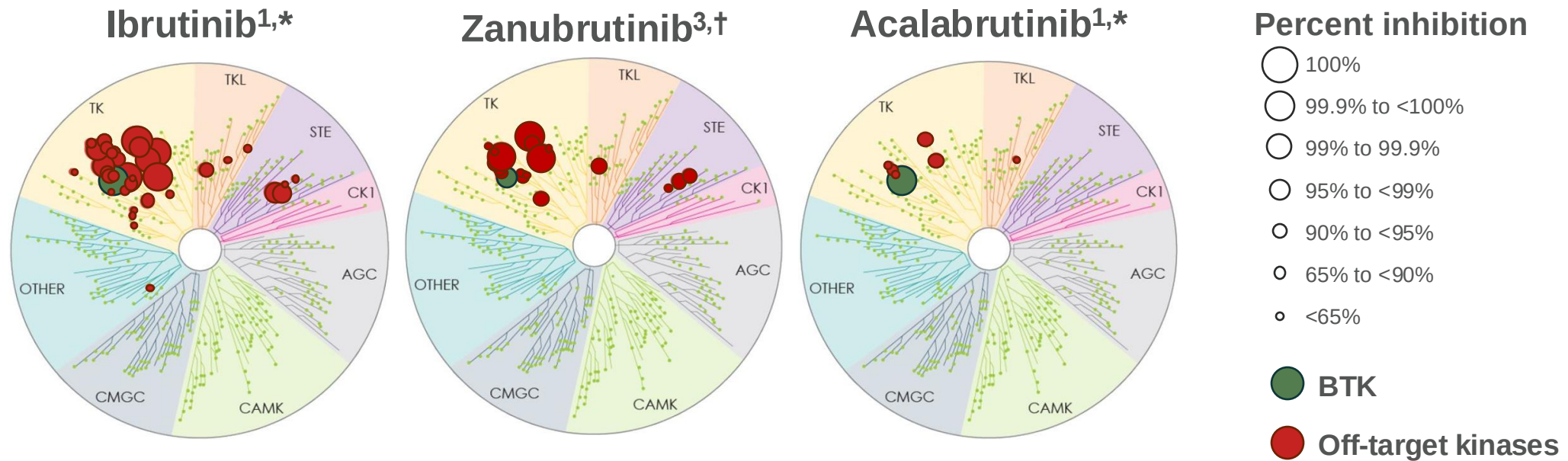


BTK in B-Cell Malignancies

- BCR pathway plays role in growth, proliferation, and survival of normal and malignant B-cells
- BTK is essential enzyme in BCR signaling pathway
- Inhibition of BTK leads to downstream mitigation of cell growth, proliferation, adhesion, migration, and survival of malignant B-cells



THAI FDA approved indication of BTKi in R/R MCL



The clinical relevance of these pharmacologic data has not been determined.^{1,2}
There are no head-to-head trials between acalabrutinib and zanubrutinib comparing safety and efficacy.

*Adapted from Barf T, et al. J Pharmacol Exp Ther. 2017;363(2):240-252. Profile of CALQUENCE and ibrutinib in a competitive binding assay of 456 human kinases (of which 395 were non-mutant protein kinases) and disease-relevant mutants when tested at a single concentration of 1 μ M. The degree of inhibition vs untreated control is represented by circle size.¹

†Adapted from Podoll T, et al. J Pharmacol Exp Ther. 2023;384:173-186. Profiles based on an active site competitive binding assay implicating kinase inhibition at a single dose (1 μ M). A total of 395 non-mutant kinases were screened in the testing of CALQUENCE and ibrutinib (conducted in 2014). Testing of zanubrutinib (conducted in 2017) included 8 additional non-mutant kinases (total of 403 screened); the 8 additional kinases were not inhibited by $\geq 65\%$ by zanubrutinib.³ The degree of inhibition versus untreated control is represented by circle size.¹

1. Barf T et al. J Pharmacol Exp Ther. 2017;363(2):240-252. 2. Bond DA, Woyach JA. Curr Hematol Malig Rep. 2019;14(3):197-205.

Summary of phase 2 single agents BTKi in R/R MCL

	Ibrutinib pool analysis (three phase 2 studies N=370)	Acalabrutinib (phase 2 LY-004 study) N=124	Zanubrutinib (Phase 2 in Chinese population N=86)
EFFICACY			
Median number of prior lines	2 (1-9)	2 (1-5)	2 (1-4)
TP53 mutation	14%	24%	28%
ORR	70%	82%	84%
CR	28%	48%	78%
Median PFS	12.5 months	22 months	33 months
PFS in 1 prior line of Rx	Median 25.4 months	-	-
SAFETY			
AF	6.8%	2.4%	1.8%
Major Bleeding	7.3%	4.0%	3.5%
Pneumonia	NR	12%	16%

Adverse Events of Available Covalent BTK Inhibitors

Ibrutinib

Cytopenias (Grade 3/4)

- Neutropenia: 13%-29%
- Thrombocytopenia: 5%-17%
- Anemia: 0%-13%

Infection (Grade 3-5)

- 14%-29%

Bruising and Hemorrhage

- Grade ≥ 3 hemorrhage: up to 6%

Lymphocytosis

- Lymphocytosis: 77%

Gastrointestinal

- Diarrhea 34%-63% (up to 5% gr ≥ 3)
- Nausea 21%-31% (2% gr ≥ 3)

Acalabrutinib

Cytopenias (Grade 3/4)

- Neutropenia: 10%-23%
- Thrombocytopenia: 5%-8%
- Anemia: 5%-11%

Infection (Grade 3-5)

- 11%-18%

Bruising and Hemorrhage

- Grade ≥ 3 hemorrhage: up to 3%

Lymphocytosis

- Lymphocytosis: 26%

Gastrointestinal

- Diarrhea 18%-35% (up to 1.3% gr ≥ 3)
- Nausea 22% (0% gr ≥ 3)

Zanubrutinib

Cytopenias (Grade 3/4)

- Neutropenia: 15%-27%
- Thrombocytopenia: 5%-10%
- Anemia: 8%

Infection (Grade 3-5)

- 23%

Bruising and Hemorrhage

- Grade ≥ 3 hemorrhage: 2%

Lymphocytosis

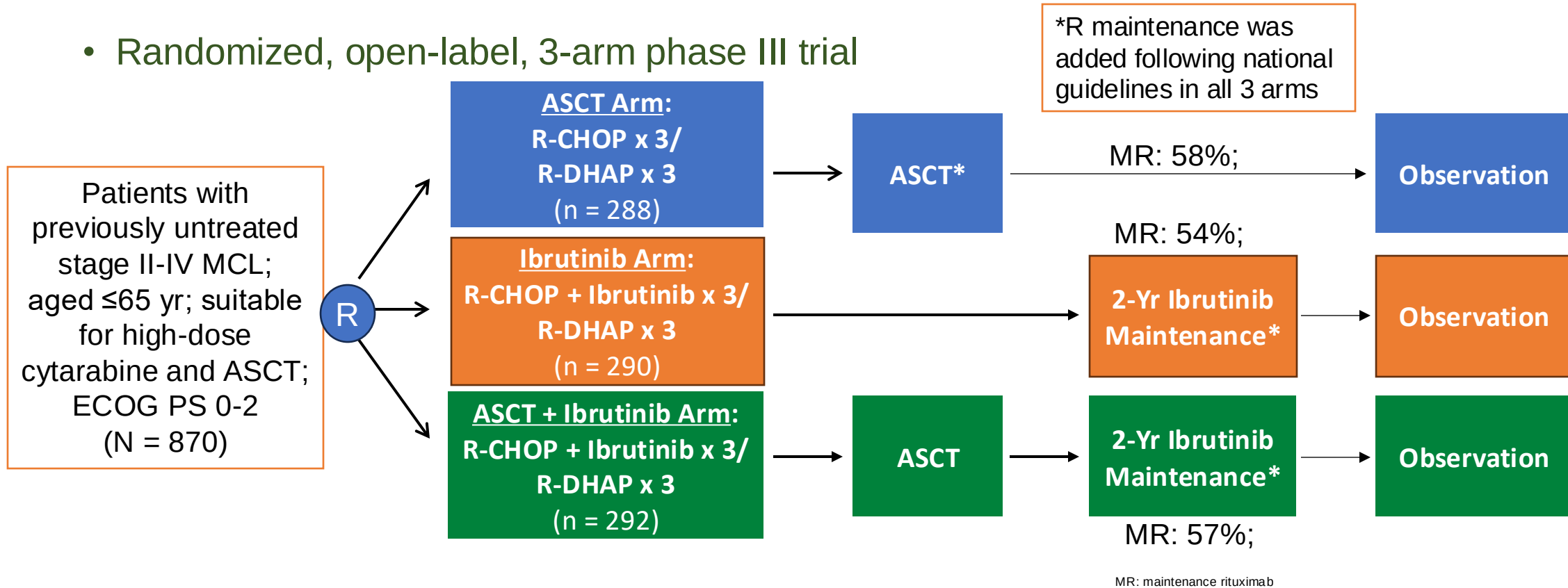
- Lymphocytosis: 41%

Gastrointestinal

- Diarrhea 23% (<1% gr 3)
- Nausea <10%

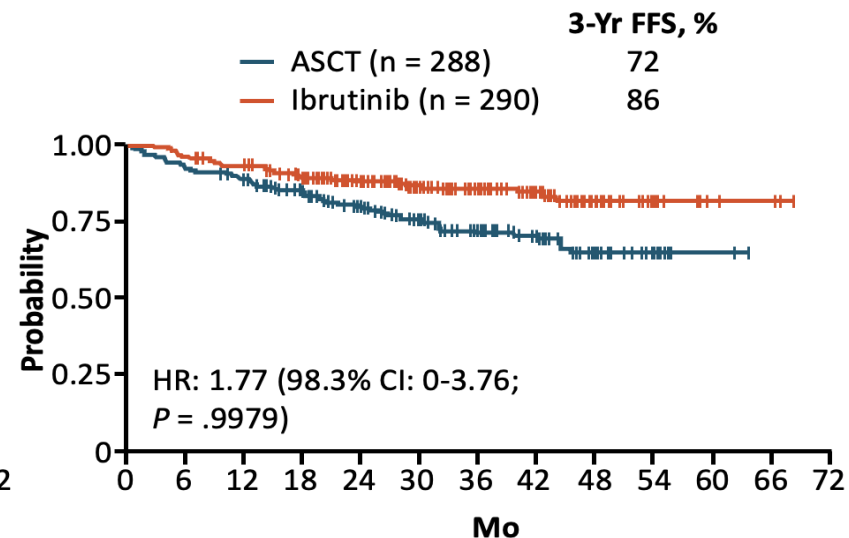
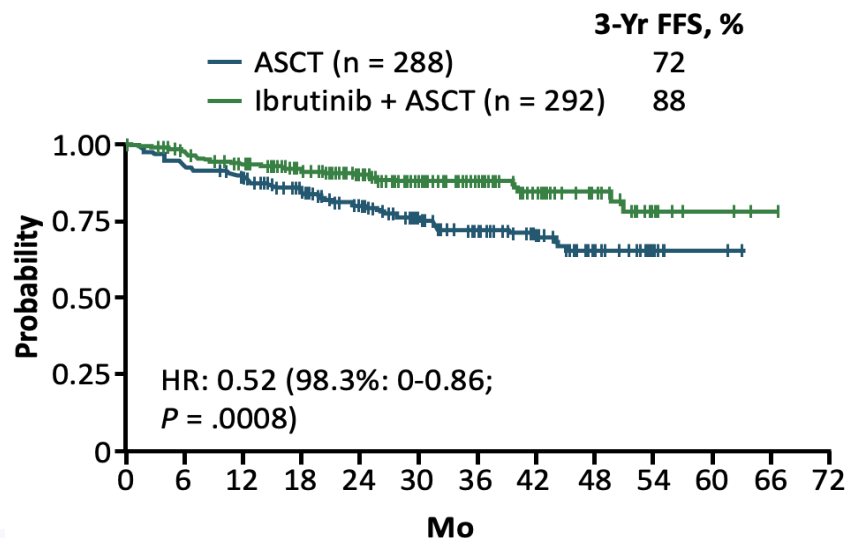
TRIANGLE: Addition of Ibrutinib to CIT with or without ASCT in Patients With MCL

- Randomized, open-label, 3-arm phase III trial

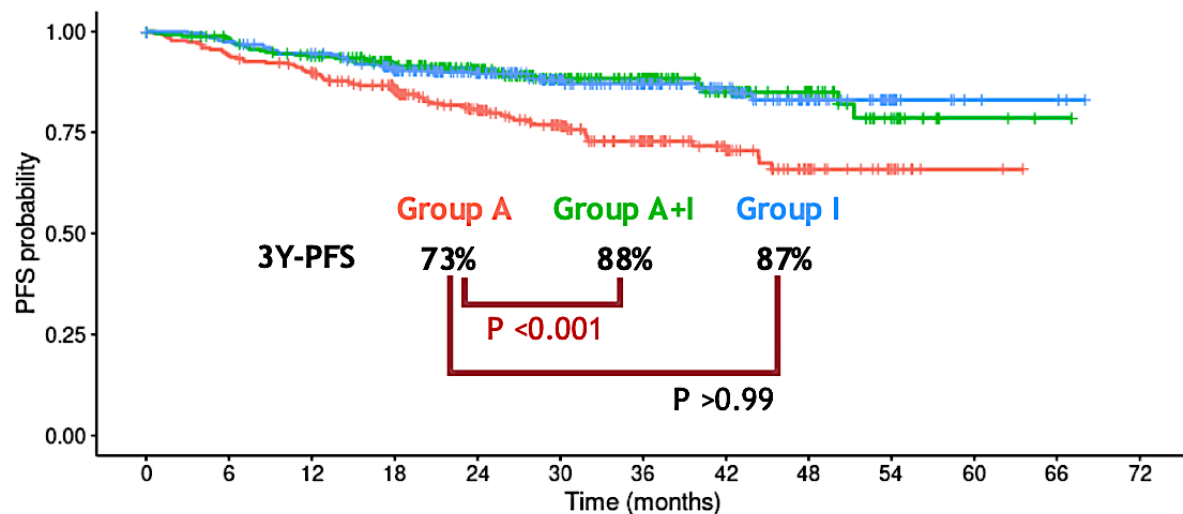


- Primary endpoint:** FFS
- Secondary endpoints:** response rates, PFS, OS, safety

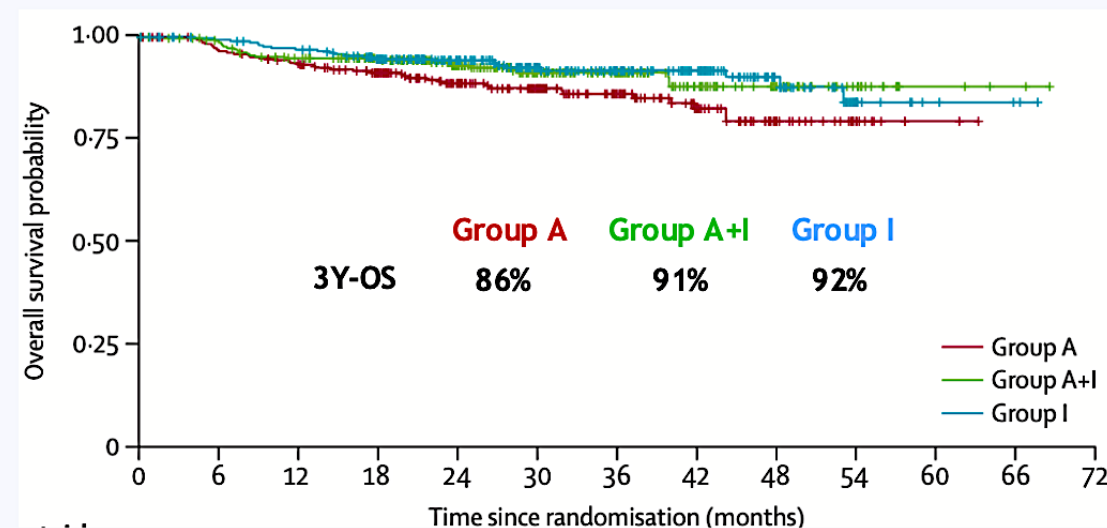
TRIANGLE: 3-yr FFS PFS and OS



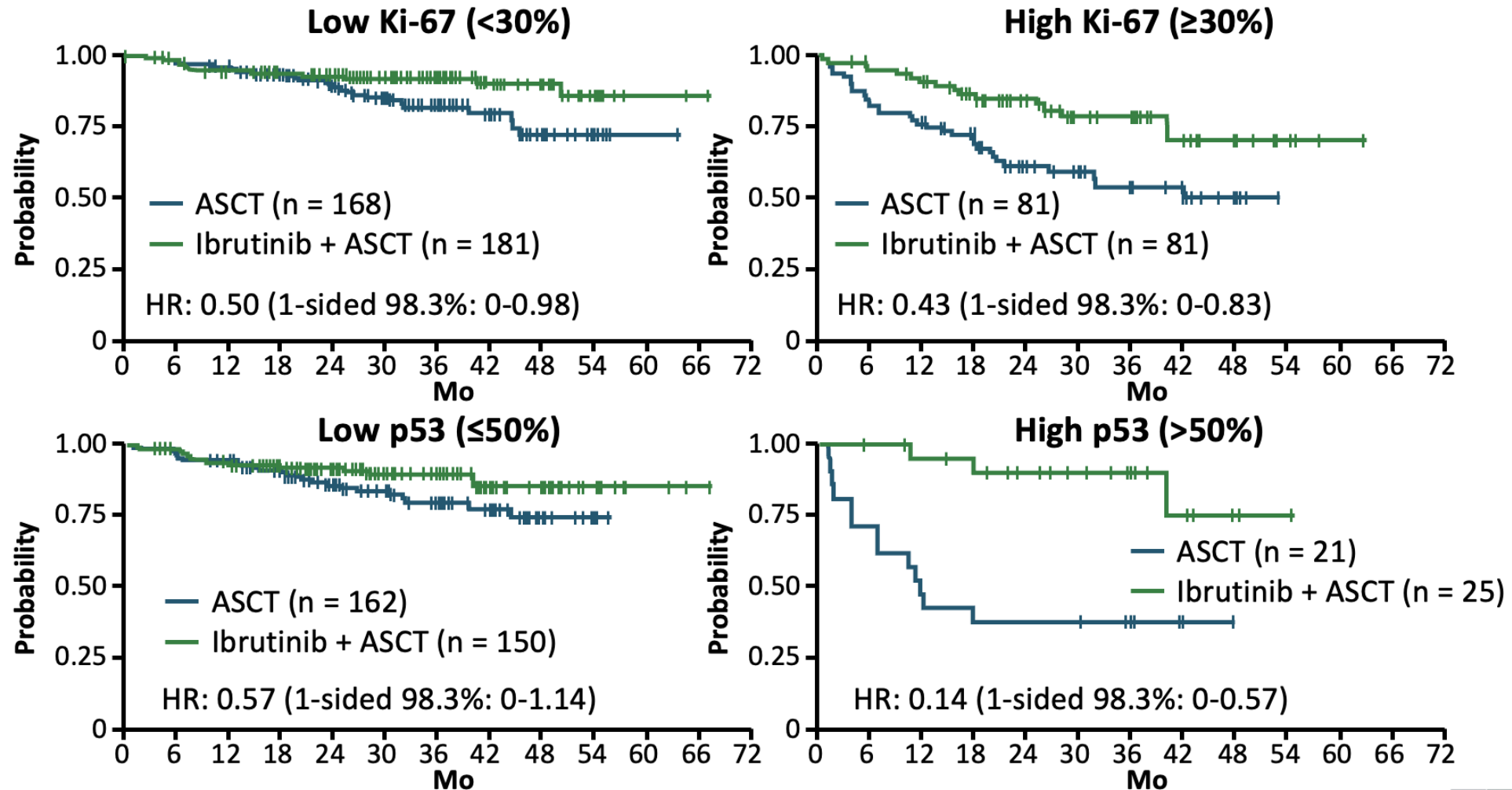
Progression-free survival



Overall survival



TRIANGLE: Failure-Free Survival by Ki-67 and *p53* Status

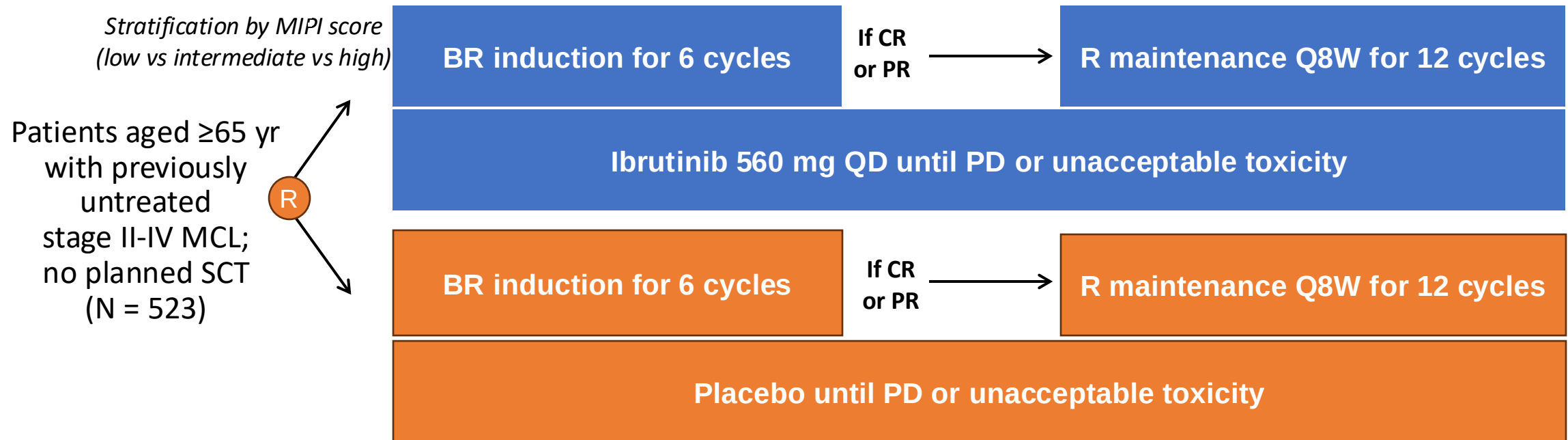


Key message from TRIANGLE study

- Additional of ibrutinib, omission of ASCT did not impair failure-free survival and was associated with reduced toxicity
 - However, benefit of ASCT has not been demonstrated with more effective induction regimens than R-CHOP
 - Pt who achieved undetectable MRD after induction therapy, ASCT can be omitted, in combination with R maintenance
- Ibrutinib was only added to 3 of the CIT induction cycles, it is likely that its benefit is principally attributable to the 2 years of maintenance

SHINE: First-line **Ibrutinib + BR** Followed by Rituximab Maintenance in Older Patients With MCL

- Multicenter, randomized, double-blind, placebo-controlled phase III trial



- Primary endpoint:** investigator-assessed PFS (in ITT)
- Key secondary endpoints:** ORR, time to next treatment, OS, safety

SHINE: Ibrutinib + BR vs BR in elderly untreated MCL

Ibrutinib with chemoimmunotherapy improved progression-free survival for newly diagnosed mantle cell lymphoma patients

THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center
"Making Cancer History"

SHINE Phase III randomized clinical trial

Examined Bruton's tyrosine kinase inhibitor in first-line setting

523 patients
age 65+ with mantle cell lymphoma

183 sites

28 countries

7 years

Methods

Arm 1

Ibrutinib

Arm 2

Placebo

+

bendamustine

rituximab

and
rituximab maintenance therapy

Results

Arm 1

80.6 months

Progression-free survival

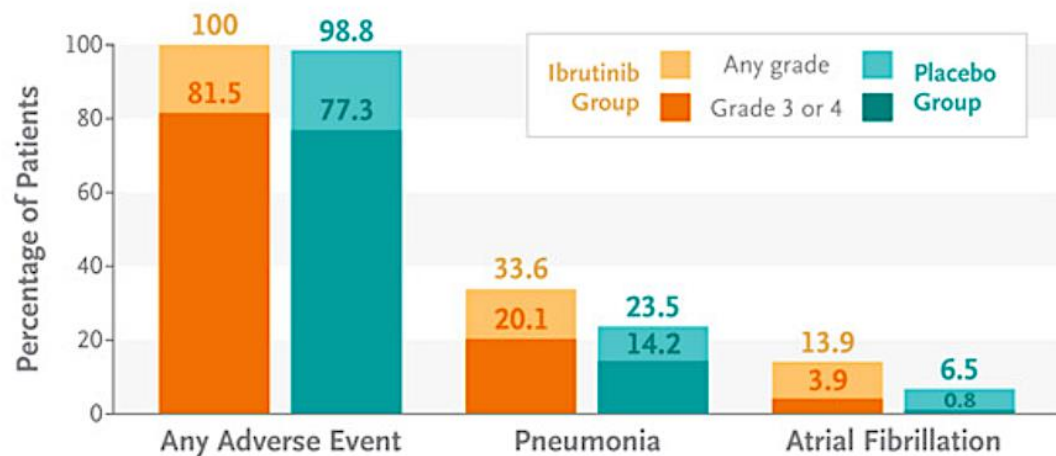
Arm 2

52.9 months

Progression-free survival

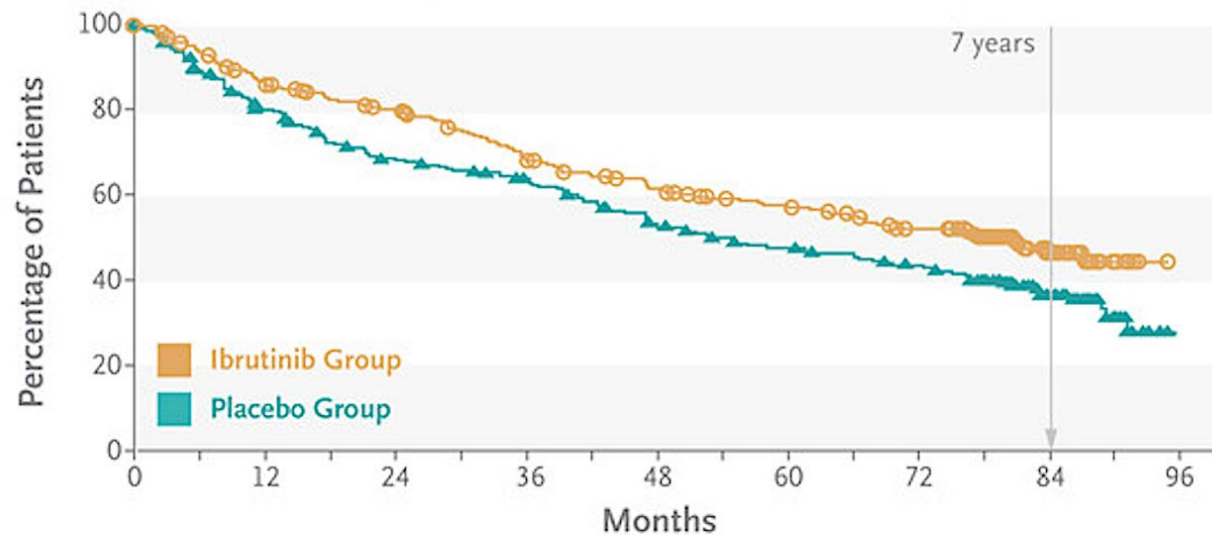
Wang, et al. 2022 American Society of Clinical Oncology Annual Meeting.

Adverse Events during Treatment



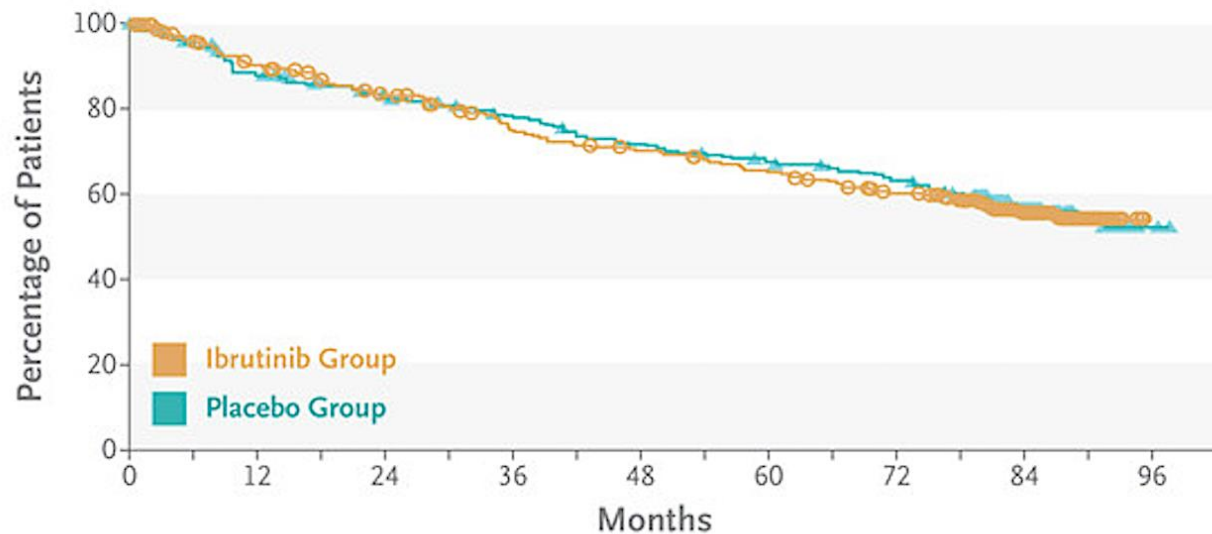
Progression-free Survival

HR for disease progression or death, 0.75 (95% CI, 0.59–0.96); P=0.01



Overall Survival

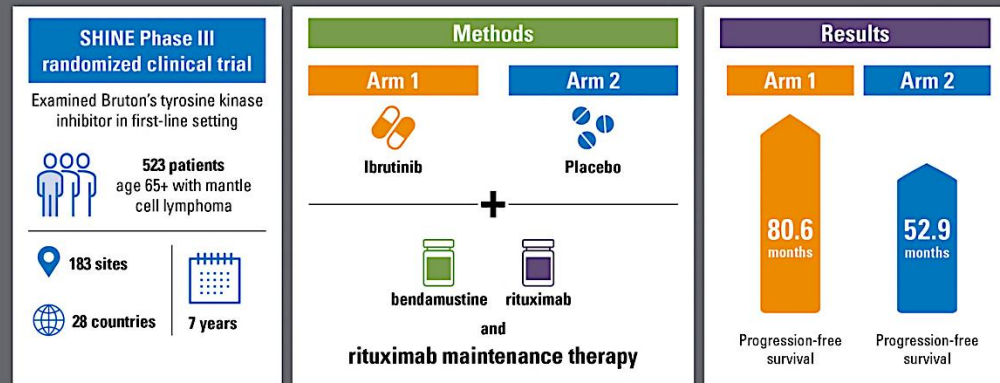
HR for death, 1.07 (95% CI, 0.81–1.40)



SHINE: Ibrutinib + BR vs BR in elderly untreated MCL

Ibrutinib with chemoimmunotherapy improved progression-free survival for newly diagnosed mantle cell lymphoma patients

THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center
Making Cancer History®



Wang, et al. 2022 American Society of Clinical Oncology Annual Meeting.

Adverse Events during Treatment

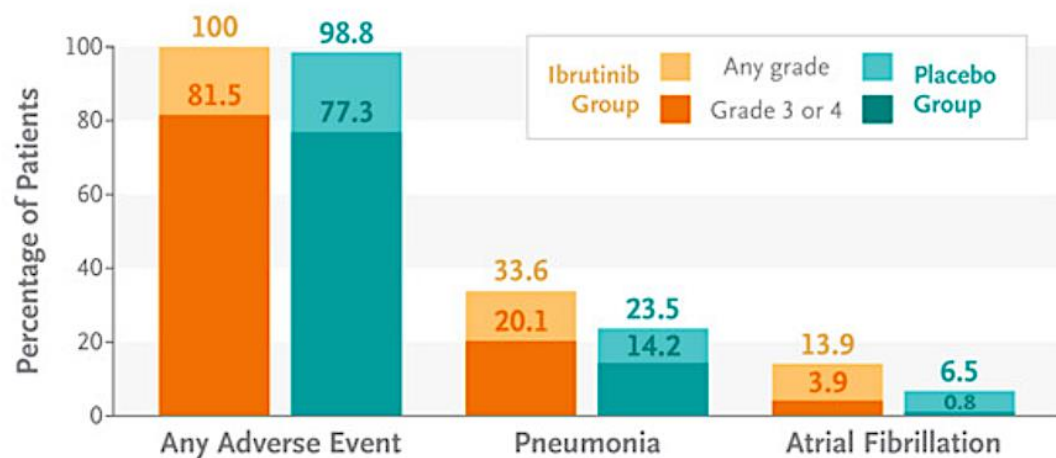


Table 3. Causes of Death Due to Adverse Events during Treatment.*

Cause	Ibrutinib Group (N = 261)	Placebo Group (N = 262)
Adverse event during treatment — no. (%)	28 (10.7)	16 (6.1)
Infection or infestation, excluding Covid-19 — no.†	9	5
Covid-19–related event — no.	3	0
Unknown cause — no.	3	0
Cardiac disorder — no.‡	3	5
Sudden death — no.	2	0
Multiple organ dysfunction syndrome — no.	2	0

Ibrutinib: Where It All Started

- **Accelerated Approval:**

- Ibrutinib received accelerated approval from the U.S. FDA based on promising early-stage clinical trial in MCL patients in 2013.
- **Accelerated approvals are contingent on subsequent confirmatory trials to verify the clinical benefit.**

- **Confirmatory Trials:**

- The drug's manufacturer, conducted Phase 3 trials to confirm the drug's efficacy
 - The **SHINE** trial did meet its primary end point of PFS, there were also increases in adverse reactions.
 - The **SELENE** trial, which was for MZL, did not meet its primary end point.



FEDERAL REGISTER
The Daily Journal of the United States Government



Notice

Pharmacyclics LLC.; Withdrawal of Approval of Indications for Mantle Cell Lymphoma and Marginal Zone Lymphoma for IMBRUVICA (ibrutinib) Capsules and Tablets

- **Withdrawal:** 18 Dec 2023
 - This was due to the requirements of the accelerated approval process.
- **Key points:**
 - **The withdrawal primarily affected the U.S. market.**
 - **Other approved indications for ibrutinib are not affected.**
 - Second generation BTK inhibitors are still available.

ECHO (ACE-LY-308): Acalabrutinib + BR vs BR in Older Patients With Untreated MCL

- International, randomized, double-blind phase III trial

6 v 28-day

ECHO: multicenter, double-blind, placebo-controlled, Ph 3 trial

Untreated MCL (N=598)

- Age ≥ 65 years
- ECOG PS ≤ 2

Stratification

- sMIPi score: Low vs intermediate vs high
- Geographic region: North America vs Western Europe vs other

Enrollment: Apr 2017–Mar 2023
Sites: 195 globally

R
A
N
D
O
M
I
Z
E

1:1

Bendamustine^a
Rituximab^b
x 6 cycles

if $\geq$ PR

Maintenance Rituximab
(every 2 cycles x 2 years)

Acalabrutinib 100 mg BID, PO until PD or toxicity

Bendamustine^a
Rituximab^b
x 6 cycles

if $\geq$ PR

Maintenance Rituximab
(every 2 cycles x 2 years)

Placebo BID, PO until PD or toxicity

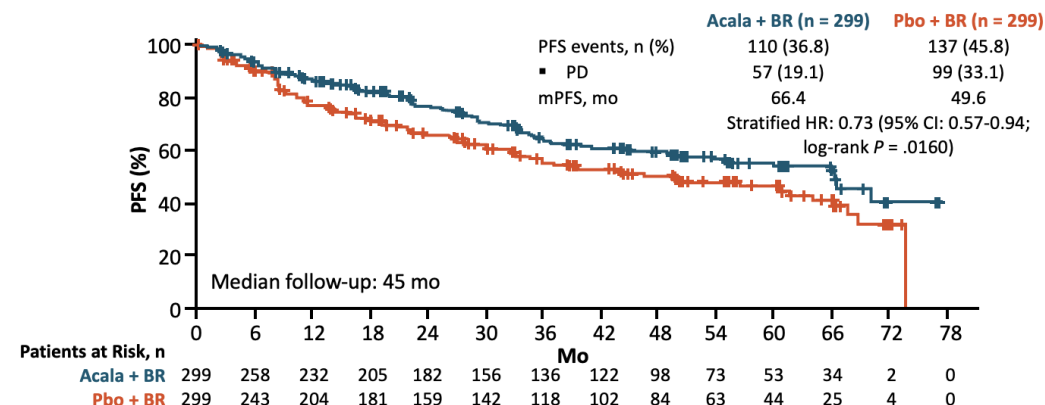
1 cycle = 28 days

Primary endpoint:

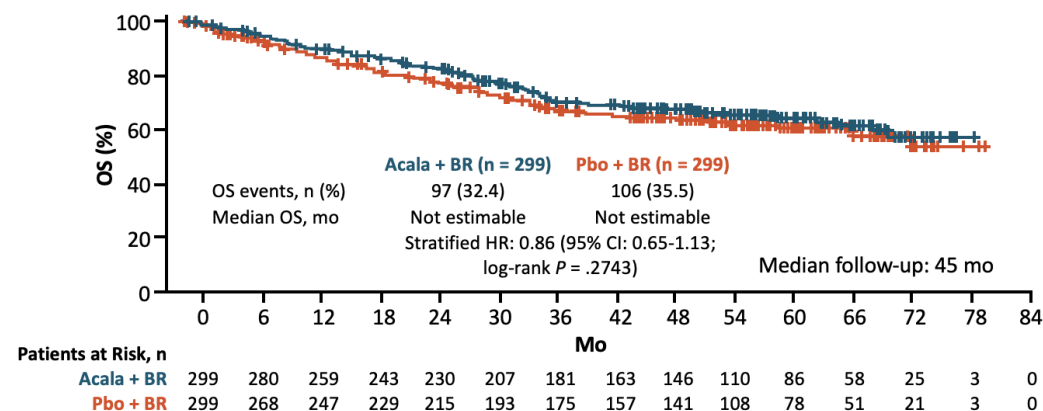
- PFS (Independent Review Committee)
- Key secondary endpoints:
 - ORR (Independent Review Committee)
 - OS
 - Safety

Crossover to
acalabrutinib after PD
was permitted

ECHO: PFS (Primary Endpoint)



- Acala + BR significantly prolonged mPFS by ~17 mo vs Pbo + BR
- Of the 99 patients with PD on Pbo + BR, 69% subsequently received a BTK inhibitor



ECHO: Acalabrutinib + BR vs BR

Prespecified Sensitivity Analyses of PFS and OS With and Without COVID-19 Deaths

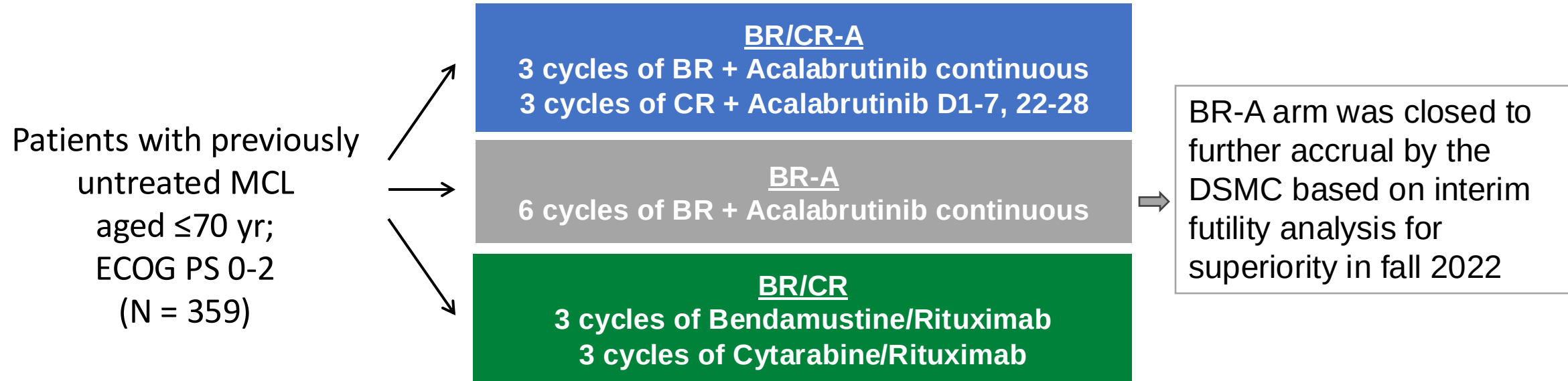
Prespecified Sensitivity Analysis of PFS	Acala + BR (n = 299)	Pbo + BR (n = 299)
Full analysis population (primary endpoint)		
▪ Median	66.4	49.6
▪ HR (95% CI)	0.73 (0.57-0.94; log-rank <i>P</i> = .0160)	
COVID-19 deaths censored		
▪ Median	Not estimable	61.6
▪ HR (95% CI)	0.64 (0.48-0.84; log-rank <i>P</i> = .0017)	

Prespecified Sensitivity Analysis of OS	Acala + BR (n = 299)	Pbo + BR (n = 299)
Full analysis population (including crossover)		
▪ Median	Not estimable	Not estimable
▪ HR (95% CI)	0.86 (0.65-1.13; log-rank <i>P</i> = .2743)	
COVID-19 deaths censored		
▪ Median	Not estimable	Not estimable
▪ HR (95% CI)	0.75 (0.53-1.04; log-rank <i>P</i> = .0797)	

- When censoring COVID-19 deaths, Acala + BR reduced the risk of progression or death by 36% vs Placebo + BR

ECOG-ACRIN EA4181: Addition of Acalabrutinib to Frontline CIT for Patients Aged ≤ 70 Yr with MCL

- Randomized, 3-arm phase II trial



Cytarabine 2 g/m² every 12 hr x 4, with dose reductions based on age and creatinine clearance.
Acalabrutinib 100 mg BID continuously on BR cycles, 100 mg BID on Days 1-7 and 22-28 with CR cycles.

- Primary endpoint:** composite PET/CT CMR and peripheral blood uMRD rate
- Secondary endpoints:** PFS, OS, ORR, and safety

BRIDGE: Zanubrutinib-Based Induction and Maintenance in Young, Fit Patients With Untreated MCL

- Prospective, single-center phase II study in China (preliminary data)

Regeneration of peripheral blood count
after last cycle of induction or ASCT
(ANC $\geq 1 \times 10^9/L$ + platelets $\geq 50 \times 10^9/L$)

Patients aged 18-65 yr
with previously
untreated, Ann Arbor
stage II-IV MCL;
ECOG PS 0-2;
no CNS involvement
or prior SCT
(estimated N = 47;
enrolled N = 7)

Induction

R-CHOP x 3 alternating with
R-DHAOx x 3
every 21 days
+
Zanubrutinib in cycles 1, 3, and 5
with R-CHOP

**$\geq$ PR to ASCT
conditioning***

*Dexamethasone,
rituximab,
cytarabine.

Optional ASCT
(investigators'
discretion)

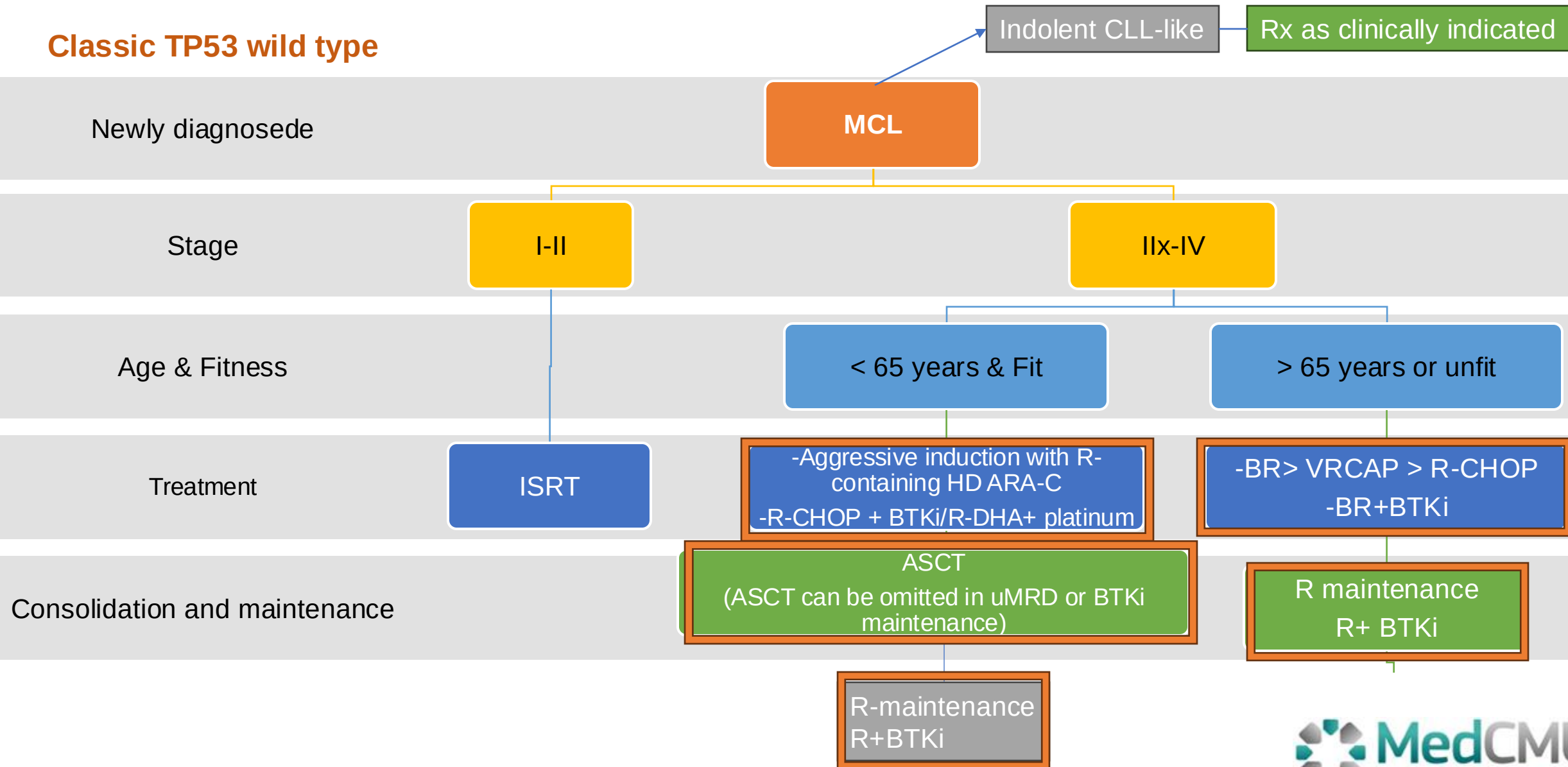
Maintenance

Zanubrutinib
160 mg PO BID
Continuously x 2 yr
or until PD

- Primary endpoint:** MRD negativity rate
- Secondary endpoints:** duration of MRD negativity, PFS, OS

Key Summary Shifting Paradigm in Treatment plan for MCL

Classic TP53 wild type



Shifting paradigm of treatment in 1L therapy for MCL



Role of ASCT

Should all transplant eligible patients proceed to ASCT?



Adding targeted agents to chemoimmunotherapy backbone



Chemo-free regimens



Improving the options for maintenance Rx

First-line Lenalidomide + Rituximab in untreated MCL

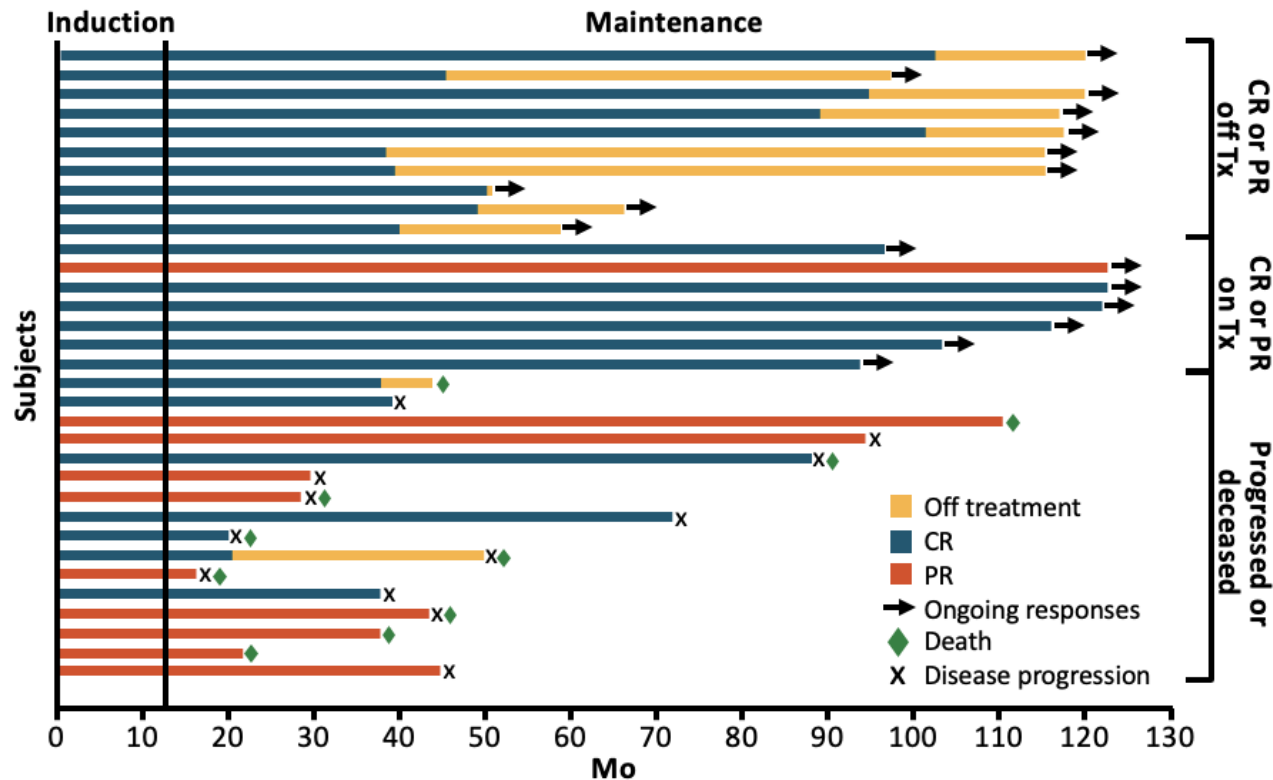
Patients with untreated MCL, tumor mass ≥ 1.5 cm, MIPI low to intermediate risk (or high risk if ineligible for or declined CT)

Induction

Rituximab 375 mg/m² Q1W C1-3, then Q2M C4+
Lenalidomide 20-25 mg Days 1-21 of 28-day cycle

Maintenance

Rituximab 375 mg/m² Q2M starting cycle 14
Lenalidomide 15 mg Days 1-21 of 28-day cycle



- 33 of 36 evaluable patients had PR or CR on study treatment
- Median PFS: 9 yr
 - 15 patients with PD (n = 3 during induction, n = 12 during maintenance)
- 7-yr PFS: 61%; 9-yr PFS: 51%
- 7-yr OS: 76%; 9-yr OS: 66%

ENRICH: Ibrutinib-Rituximab vs Chemo-Rituximab in Previously Untreated Older Patients With MCL

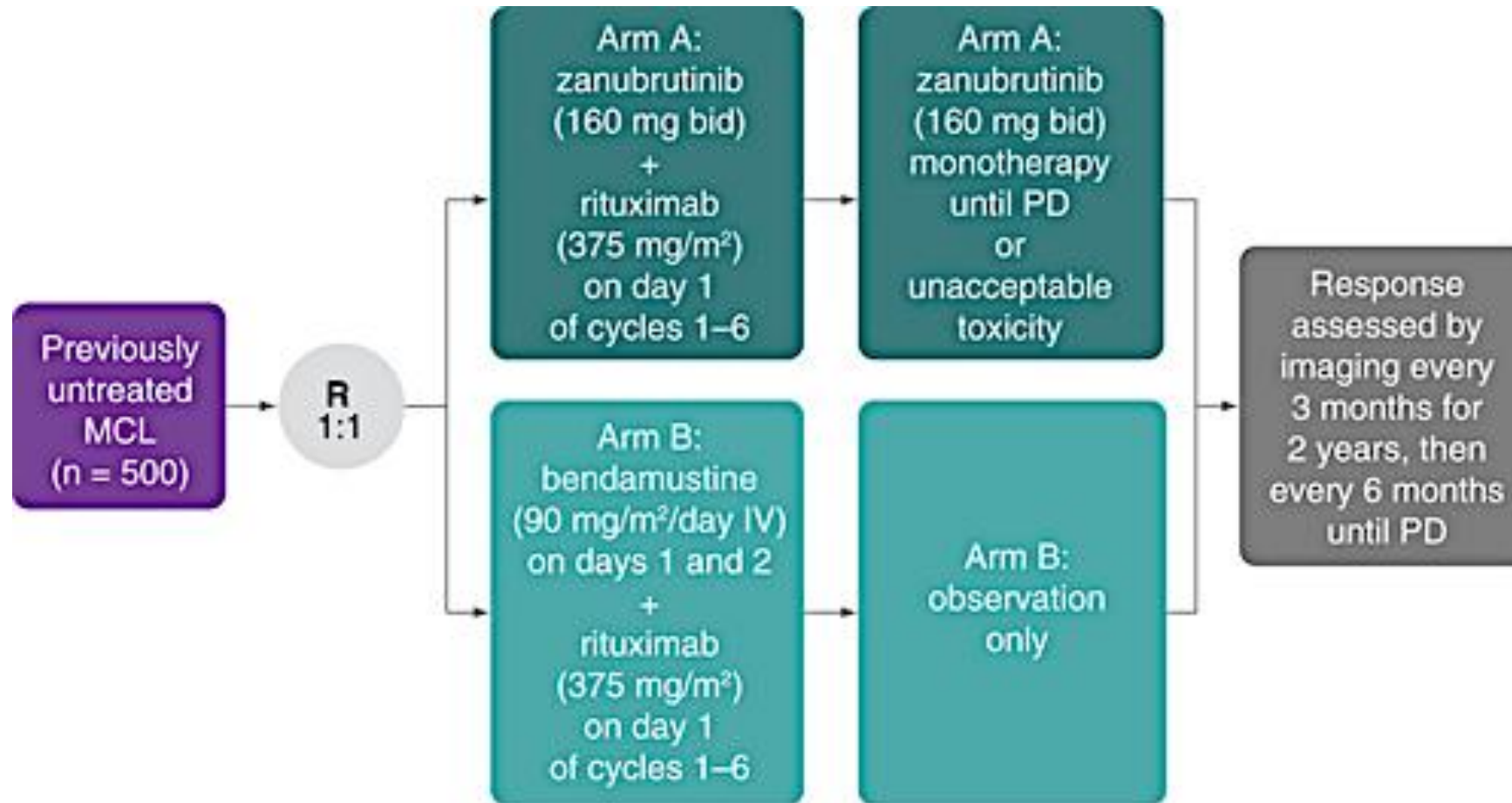
Outcome	Ibrutinib-R (n = 199)	Chemo-R (n = 198)
Median PFS, mo	65.3	42.4
HR (95% CI)	0.69 (0.52-0.90); P = .003	
5-yr OS, %	57.7	54.5
HR (95% CI)	0.87 (0.64-1.18)	

- Grade ≥ 3 nonhematologic AEs:
 - 61.1% I-R, 51.9% R-CHOP, and 51.7% BR
- Grade ≥ 3 hematologic AEs:
 - 16.7% I-R, 50.0% R-CHOP, and 33.6% BR
- Grade ≥ 3 AF:
 - 6.6% I-R and 0.5% R-chemo

Outcome	Ibrutinib-R	R-CHOP
Median PFS, mo	NR	26.6
HR (95% CI)	0.37 (0.22-0.62)	
5-yr OS, %	59.4	46.3
HR (95% CI)	0.64 (0.36-1.13)	

Outcome	Ibrutinib-R	BR
Median PFS, mo	65.3	50.5
HR (95% CI)	0.91 (0.66-1.25)	
5-yr OS, %	57.2	58.1
HR (95% CI)	1.00 (0.70-1.44)	

MANGROVE: Zanubrutinib-R vs BR in in Previously Untreated Older Patients with MCL



Primary end point is PFS

Phase II Trial of BOVen (Zanubrutinib + Obinutuzumab + Venetoclax) in Older Patients With Untreated MCL

Phase 2 Multicenter, single-arm, open-label, multicohort trial

Study Identifier:
BOVen,

Primary Endpoint: 2-year PFS*

KEY ELIGIBILITY CRITERIA

- Aged ≥18 years
- ECOG PS 0-2
- Previously untreated MCL (except localized prior RT)
- *TP53* mutation (of any variant allele frequency)
- Adequate organ and hematological function

SCREENING

TREATMENT



Zanubrutinib 160 mg PO BID
D1 C1 until PD or trial completion

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

Venetoclax 400 mg PO QD
5-week ramp-up initiated from D1 C3
1 week each of 20, 50, 100, 200, 400 mg

uMRD ASSESSMENT

CR and uMRD: Stop treatment

<CR and/or dMRD: Continue zanubrutinib and venetoclax

FOLLOW-UP

Safety and survival

MRD, n/N (%)

Patients

Cycle 3

- uMRD5*
- uMRD6†

21/42 (50)
11/42 (26)

Cycle 13

- uMRD5*
- uMRD6†

23/23 (100)
20/23 (87)

Study Sponsor: Memorial Sloan Kettering Cancer Center. Study Collaborators: BeiGene USA, Inc.; Roche-Genentech; Massachusetts General Hospital

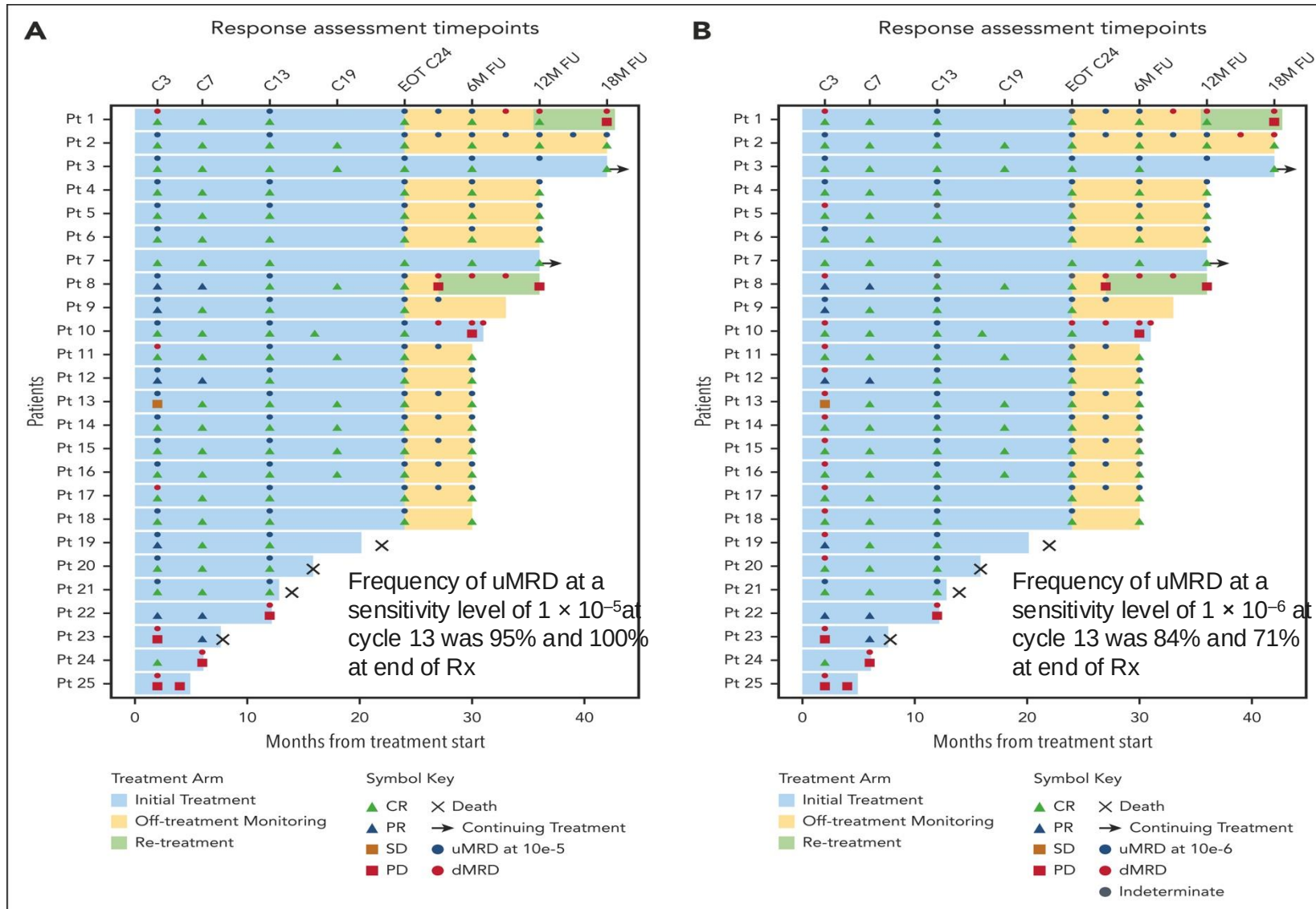
*A promising 2-year PFS rate would be ≥55% and unacceptable rate ≤30%. If ≥11 patients were progression-free at 2 years, the treatment regimen would be declared effective.

BID=twice daily, C=cycle, CR=complete response, D=day, dMRD=detectable minimal residual disease, ECOG PS=Eastern Cooperative Oncology Group performance status, MCL=mantle cell lymphoma, MRD=minimal residual disease, PFS=progression-free survival, PO=orally, QD=once daily, uMRD=undetectable minimal residual disease.

1. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03824483>. Accessed 1 July 2022; 2. Kumar A et al. Oral presentation at ASH 2023; abstract 738; 3.

BOVen - (Zanubrutinib + Obinutuzumab + Venetoclax)

TP53 mutant MCL



2-year PFS rate was 72%
(95% CI, 56-92)

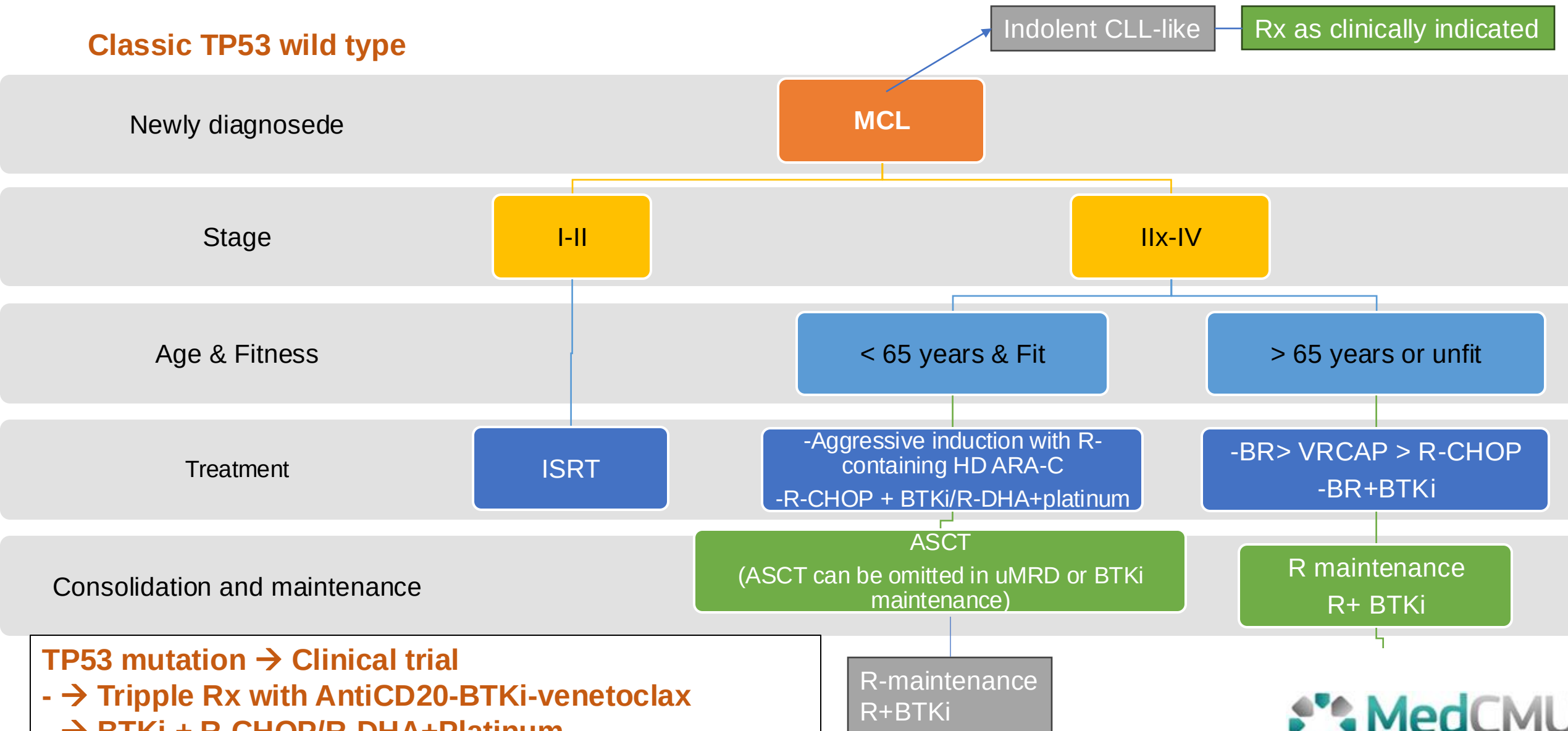
2-year OS rate was 76%
(95% CI, 61-95)

Key summary: Future direction of Chemo-free regimen

- If the result of phase 3 a BTKi-R doublet vs SOC CIT showed superiority
 - ENRICH: ibrutinib/R vs BR or R-CHOP
 - MANGROVE: zanubrutinib/R vs BR.
 - **Chemo-free regimen could potentially establish a new SOC in older patients with MCL**
- Triplet regimen—BTKi + antiCD20 + BCL2i showed promising results in phase 2 study
 - **OAsIs**: Ibrutinib, Obinutuzumab and Venetoclax
 - **TrAVeRse**: Acalabrutinib, Rituximab and Venetoclax
 - **BOVEN**: Zanubrutinib, Obinutuzumab and Venetoclax

Key Summary Shifting Paradigm in Treatment plan for MCL

Classic TP53 wild type



Shifting paradigm of treatment in 1L therapy for MCL



Role of ASCT

Should all transplant eligible patients proceed to ASCT?



Adding targeted agents to chemoimmunotherapy backbone



Chemo-free regimens

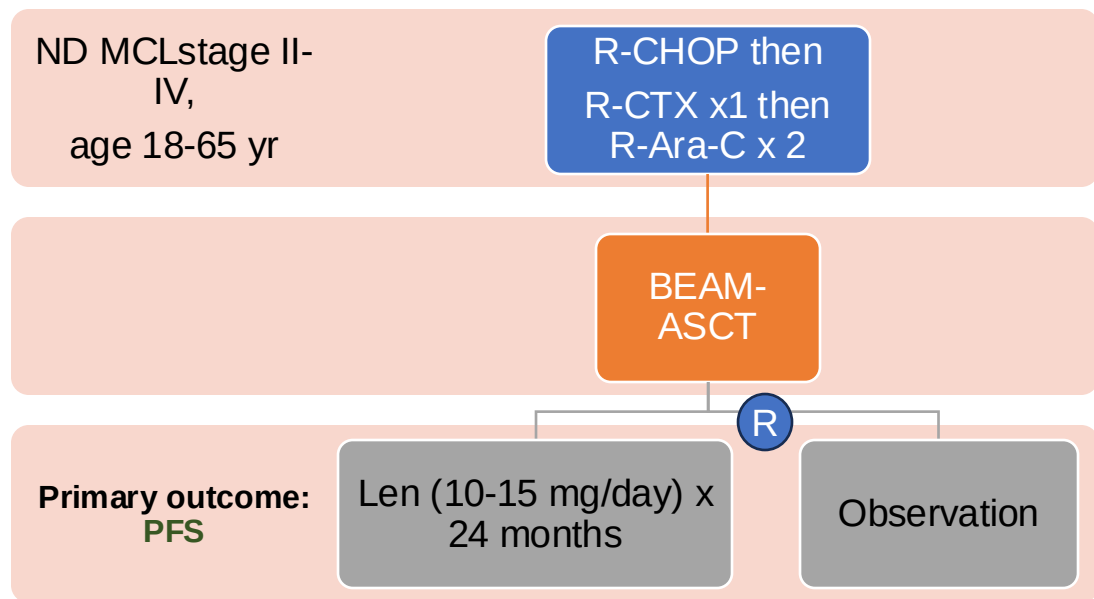


Improving the options for maintenance Rx

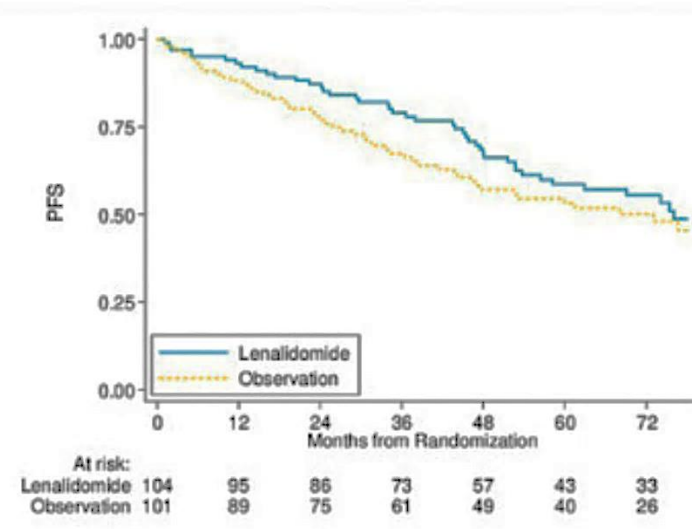
Lenalidomide maintenance after ASCT in MCL: A results of a Fondazione Italiana Linfomi (FIL) multicentre, randomised, phase 3 trial

At a median follow-up of 38 months

- **PFS:** Significant improvement with Lenalidomide
 - HR: 0.58; 95% CI 0.43–0.78; $p < 0.001$
 - 3-year PFS: **80% (Lenalidomide) vs. 64%**



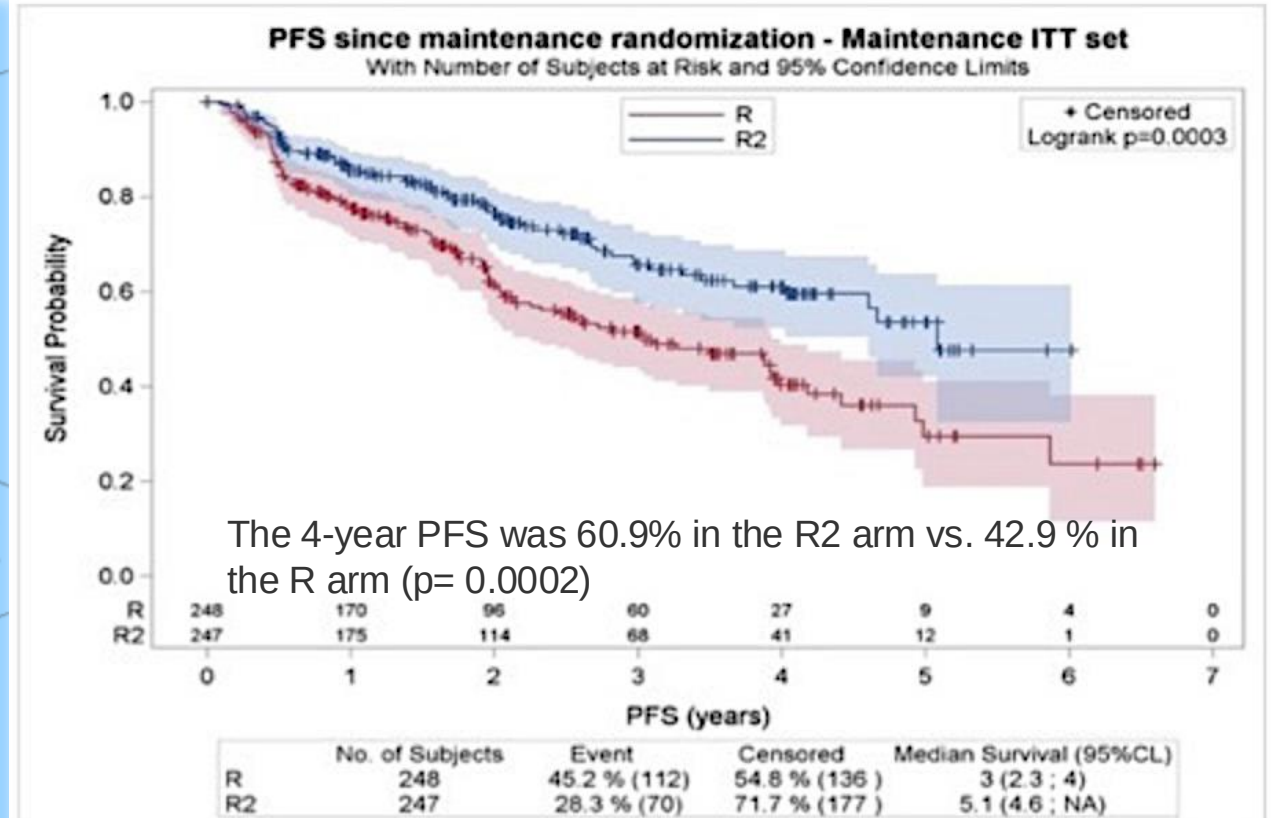
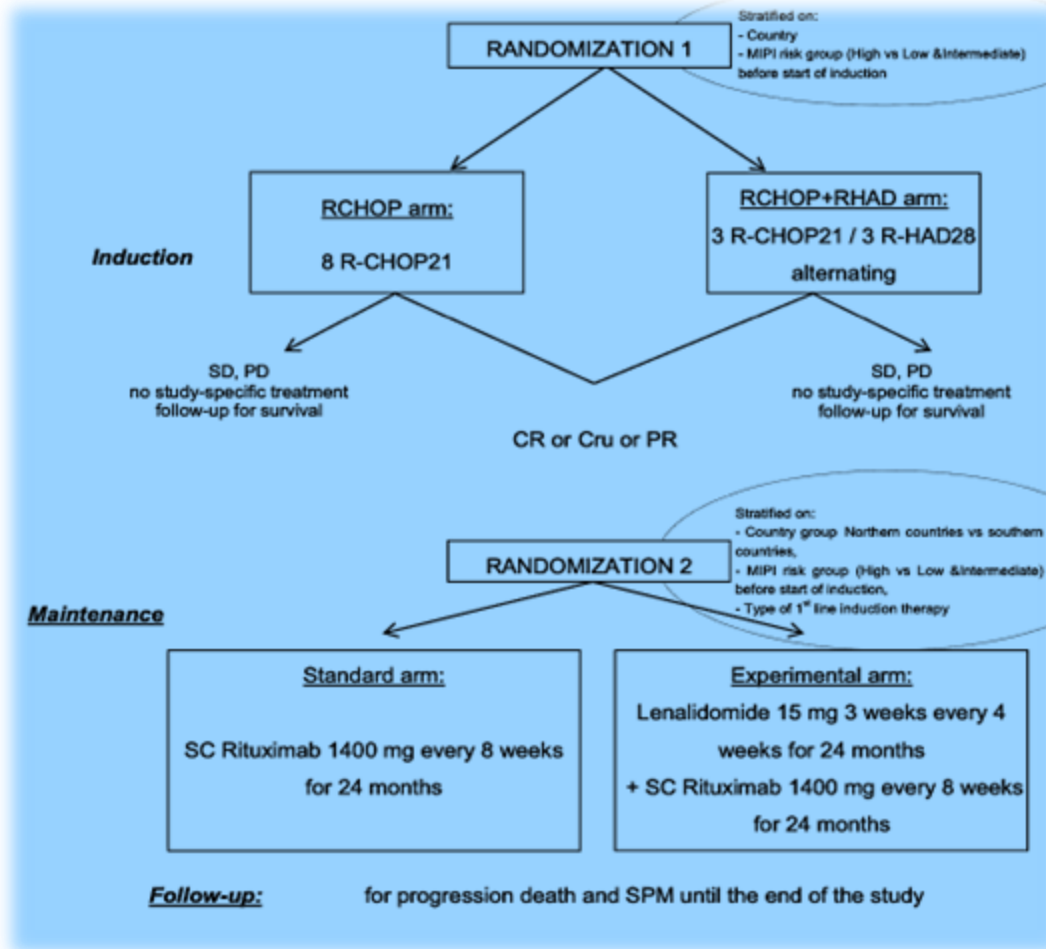
- Grade 3/4 neutropenia:
56% (Lenalidomide) vs. 22% (observation)).



The toxicity of lenalidomide and the absence of R in the control arm have limited the adoption of this approach

Double-Randomized MCL R2 Elderly Clinical Trial By the European Mantle Cell Lymphoma Network: R vs R2 maintenance

Median FU 4.2 years



AEs grade >3 : neutropenia (50.8% vs 19.2%)

Given the toxicity of lenalidomide, a role for R2 maintenance should be considered in relatively fit patients with high-risk features

Randomized phase II study of induction with bendamustine-rituximab ± bortezomib and maintenance with rituximab vs R-lenalidomide for MCL

- An open-label, randomized phase II trial

Patients with
treatment-naïve MCL
requiring therapy;
ECOG PS 0-2
(N = 373)

Bendamustine + Rituximab x 6	≥SD	Rituximab
Bendamustine + Bortezomib + Rituximab x 6	≥SD	Rituximab
Bendamustine + Rituximab x 6	≥SD	Lenalidomide + Rituximab
Bendamustine + Bortezomib + Rituximab x 6	≥SD	Lenalidomide + Rituximab

- Primary endpoint:** PFS (BR vs BVR and R vs LR)
- Main secondary endpoints:** PET-documented CR, ORR

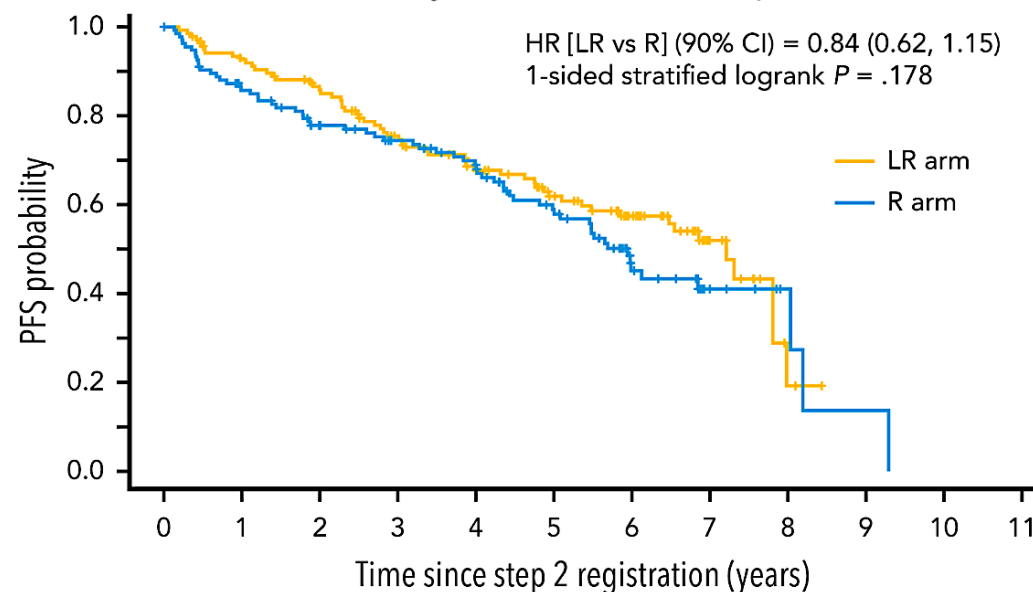
Induction: bendamustine 90 mg/m²/d IV Days 1, 2; rituximab 375 mg/m² IV Day 1; bortezomib 1.3 mg/m² IV or SC Days 1, 4, 8, 11 (later amended to 1.6 mg/m² Days 1, 8) in 28-day cycles

Consolidation: rituximab 375 mg/m² every 8 wk x 12 doses ± lenalidomide 15 mg/d 21/28 days x 24 cycle

B

PFS in R vs LR : 5.9 vs 7.2 years;

PFS by treatment arm (step 2)



Nos. at risk

LR arm:	140	123	110	91	75	59	43	14	2	0	0	0
R arm:	136	110	94	84	74	56	26	9	3	1	0	0

— LR: 2-year PFS (95% CI) = 85.8% (78.6, 90.7)

5-year PFS (95% CI) = 61.9% (52.5, 69.9)

— R: 2-year PFS (95% CI) = 77.8% (69.7, 84.0)

5-year PFS (95% CI) = 58.9% (49.3, 67.3)

— LR: median (95% CI); n/events = 7.2 (5.5, 7.8); 140/59

— R: median (95% CI); n/events = 5.9 (5.0, 8.2); 136/65

Randomized phase II study of induction with bendamustine-rituximab $\pm$ bortezomib and maintenance with rituximab vs R-lenalidomide for MCL

- An open-label, randomized phase II trial

Patients with treatment-naïve MCL requiring therapy; ECOG PS 0-2 (N = 373)

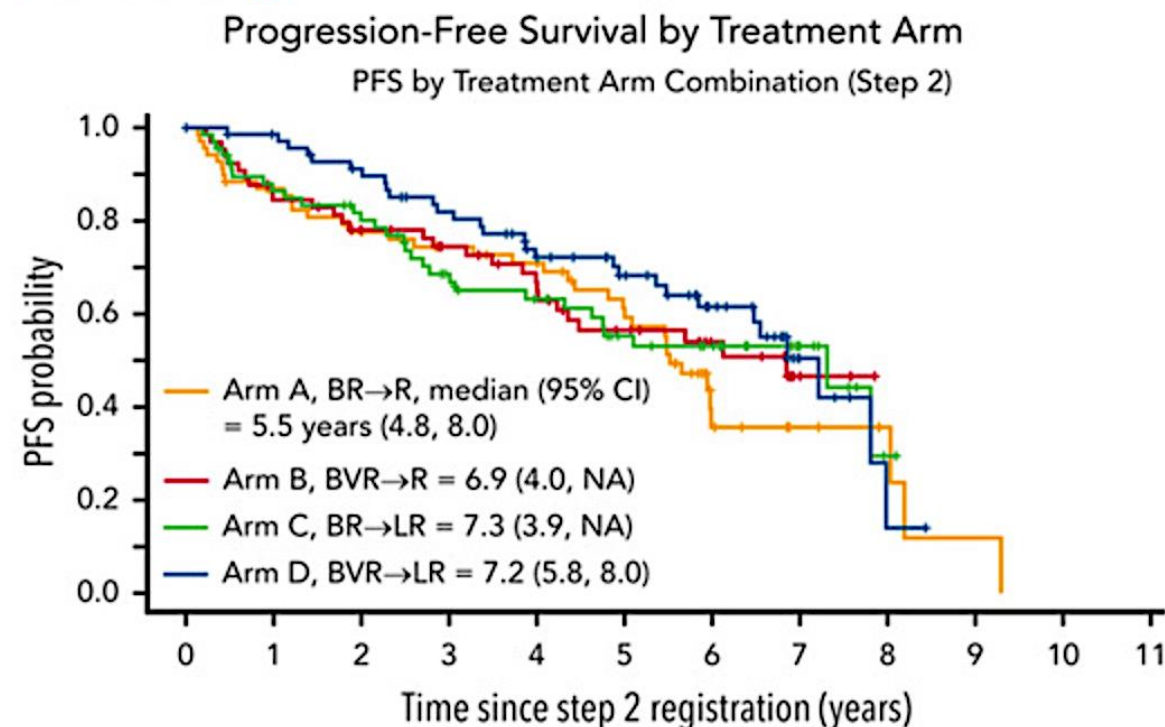
Bendamustine + Rituximab $\times$ 6	$\geq$ SD	Rituximab
Bendamustine + Bortezomib + Rituximab $\times$ 6	$\geq$ SD	Rituximab
Bendamustine + Rituximab $\times$ 6	$\geq$ SD	Lenalidomide + Rituximab
Bendamustine + Bortezomib + Rituximab $\times$ 6	$\geq$ SD	Lenalidomide + Rituximab

- Primary endpoint:** PFS (BR vs BVR and R vs LR)
- Main secondary endpoints:** PET-documented CR, ORR

Induction: bendamustine 90 mg/m²/d IV Days 1, 2; rituximab 375 mg/m² IV Day 1; bortezomib 1.3 mg/m² IV or SC Days 1, 4, 8, 11 (later amended to 1.6 mg/m² Days 1, 8) in 28-day cycles

Consolidation: rituximab 375 mg/m² every 8 wk $\times$ 12 doses $\pm$ lenalidomide 15 mg/d 21/28 days $\times$ 24 cycle

Main Finding



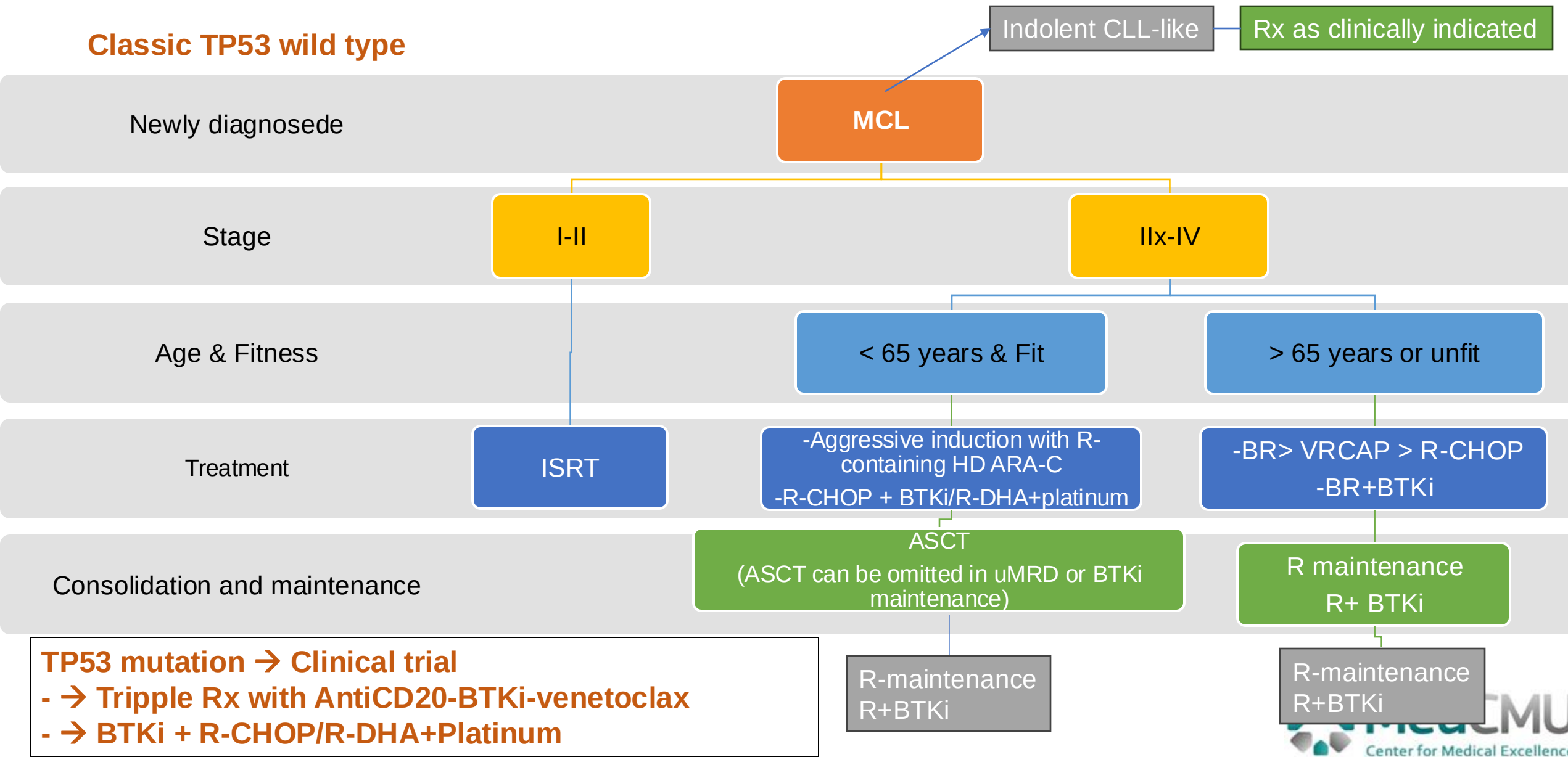
NOs. at Risk

Arm A	70	57	49	44	40	31	9	5	3	1	0	0
Arm B	66	53	45	40	34	25	17	4	0	0	0	0
Arm C	69	56	50	39	33	25	21	8	1	0	0	0
Arm D	71	67	60	52	42	34	22	6	1	0	0	0

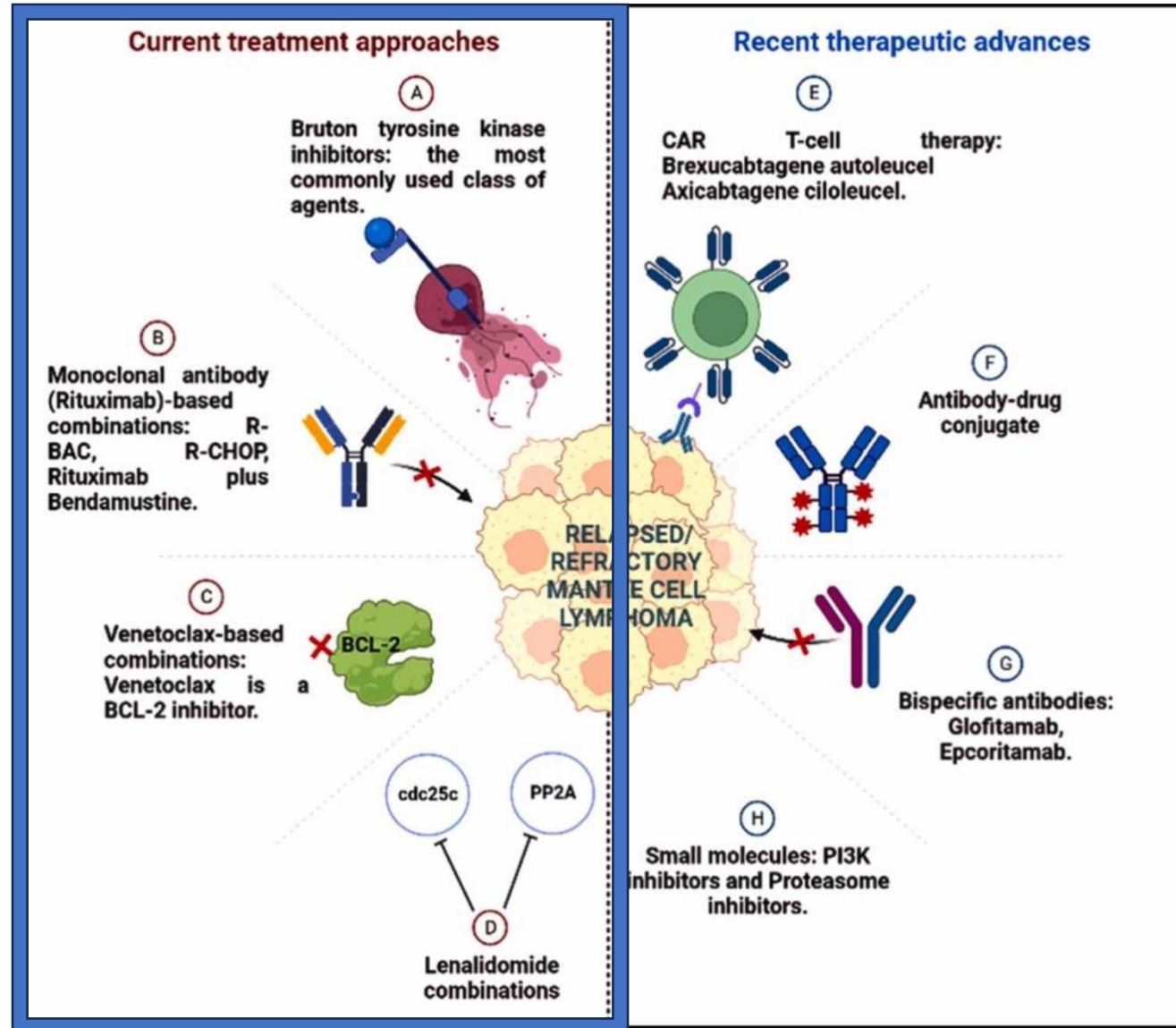
- Arm A, 2-year PFS (95% CI) = 77.7% (65.7, 85.9); 5-year PFS (95% CI) = 61.2% (47.6, 72.3)
- Arm B = 78.0% (65.7, 86.4); 56.5% (42.3, 68.4)
- Arm C = 80.1% (68.2, 88.0); 55.3% (41.7, 67.0)
- Arm D = 91.2% (81.4, 95.9); 68.3% (55.1, 78.3)

Key Summary Shifting Paradigm in Treatment plan for MCL

Classic TP53 wild type



Shifting paradigm of treatment in R/R MCL



Lenalidomide versus investigator's choice in R/R MCL (MCL-002; SPRINT): a phase 2, randomised, multicentre trial

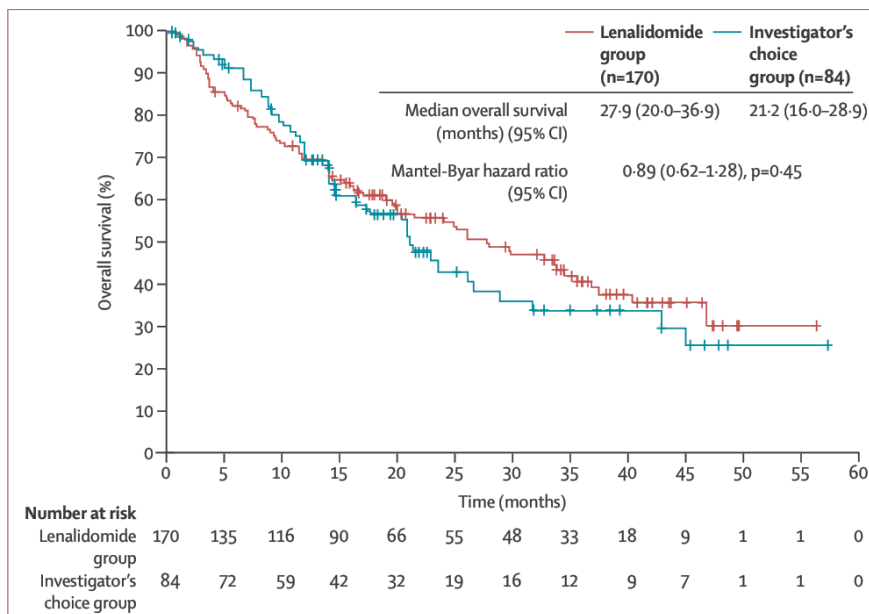
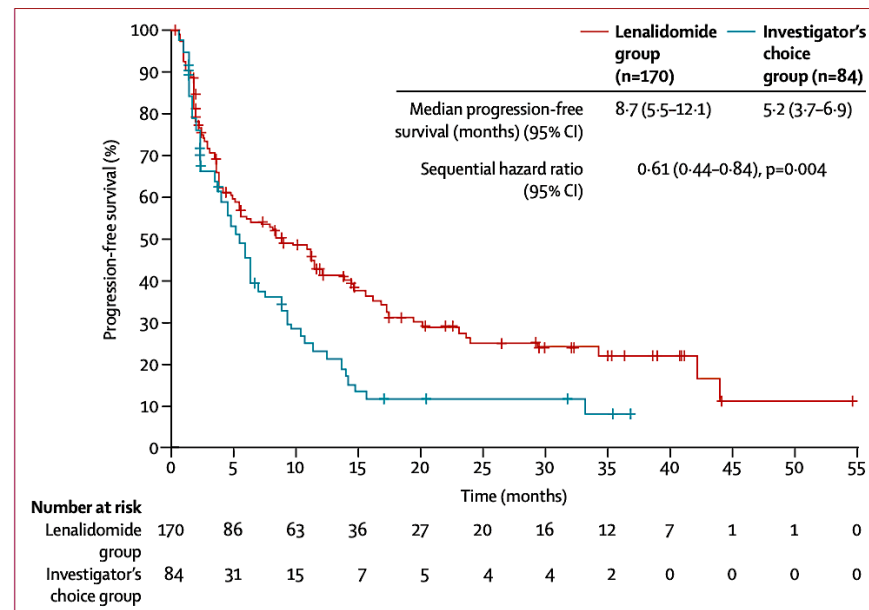
Patients RR MCL, > 18 years who relapsed one to three times, ECOG 0–2

R 2:1

Lenalidomide
25 mg orally on days 1–21 every 28 days until progressive disease or intolerability

Single-agent investigator's choice of either rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine

No difference in term of toxicities



Ibrutinib versus Temsirolimus in patients with R/R MCL: an international, randomised, open-label, phase 3 study

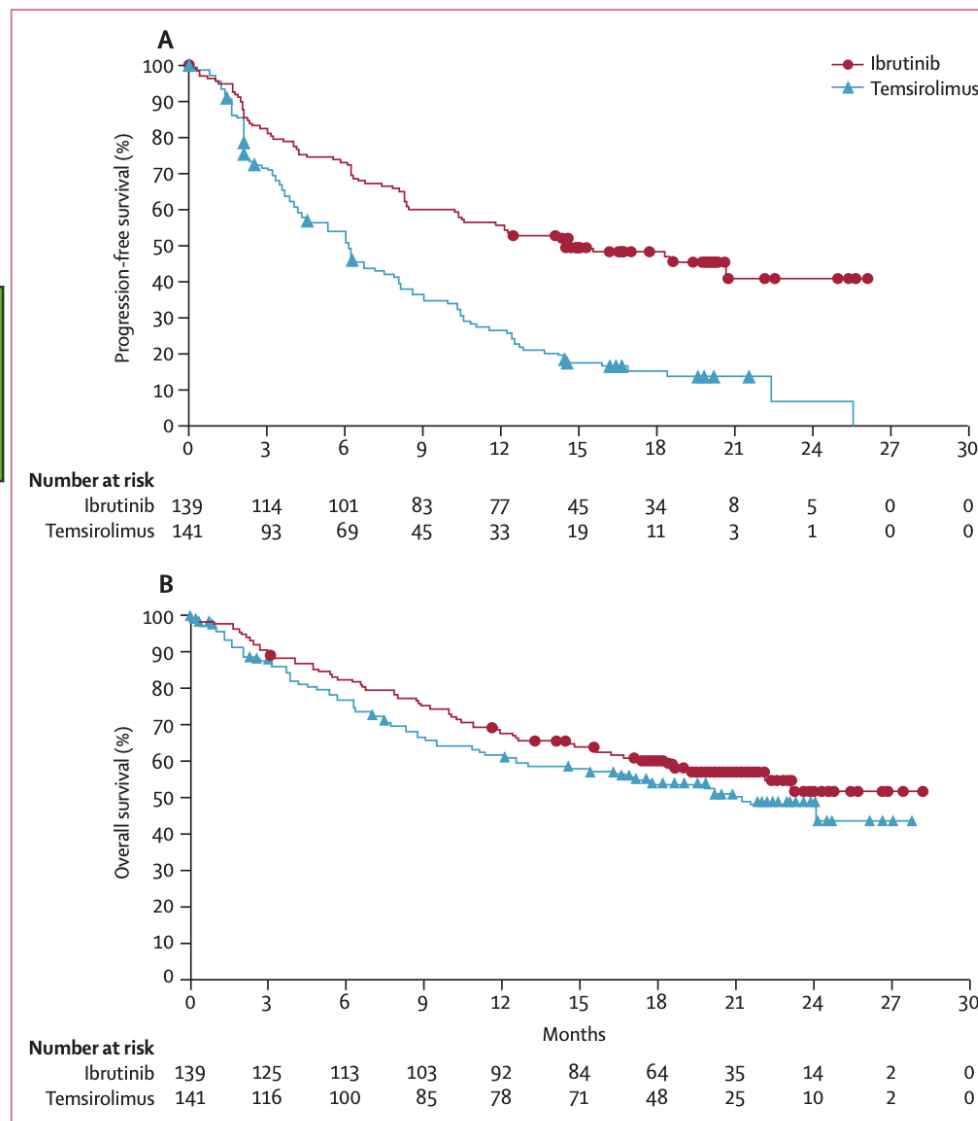
patients with R/R MCL after > 1L of rituximab containing regimens

R

ibrutinib 560 mg/day

temsirolimus IV
175 mg on days 1, 8, and 15 of cycle 1; 75 mg on days 1, 8, and 15 of subsequent 21-day cycles

	Ibrutinib (n=139)		Temsirrolimus (n=139)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
Haematological				
Thrombocytopenia	25 (18%)	13 (9%)	78 (56%)	59 (42%)
Anaemia	25 (18%)	11 (8%)	60 (43%)	28 (20%)
Neutropenia	22 (16%)	18 (13%)	36 (26%)	23 (17%)
Non-haematological				
Diarrhoea	40 (29%)	4 (3%)	43 (31%)	6 (4%)



Ibrutinib plus venetoclax in R/R MCL (SYMPATICO): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study



SYMPATICO Study Design

- SYMPATICO (NCT03112174) is multinational, randomized, double-blind, placebo-controlled, phase 3 study

SYMPATICO (N=267)

- Age ≥ 18 years
- R/R MCL
- 1–5 prior therapies for MCL
- ≥ 1 prior rituximab/anti-CD20-containing regimen
- ECOG PS 0–2

Randomized 1:1

Ibrutinib + venetoclax (n=134)
Ibrutinib 560 mg once daily +
venetoclax 5-week ramp-up to
400 mg once daily for 24 months

Ibrutinib + placebo (n=133)
Ibrutinib 560 mg once daily +
placebo once daily for 24 months

Single-agent
ibrutinib 560 mg
once daily until PD
or unacceptable
toxicity

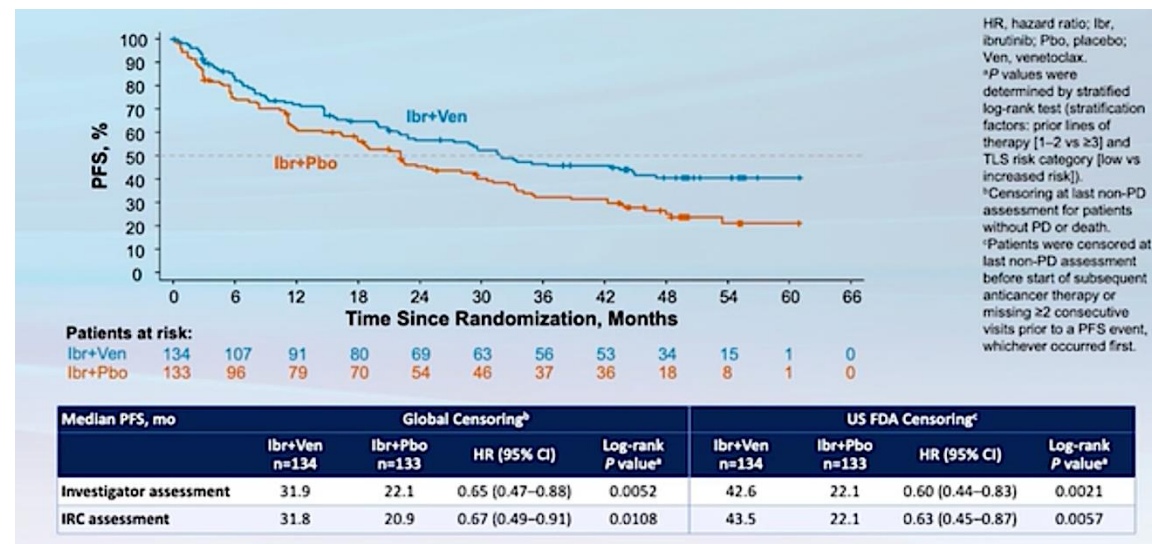
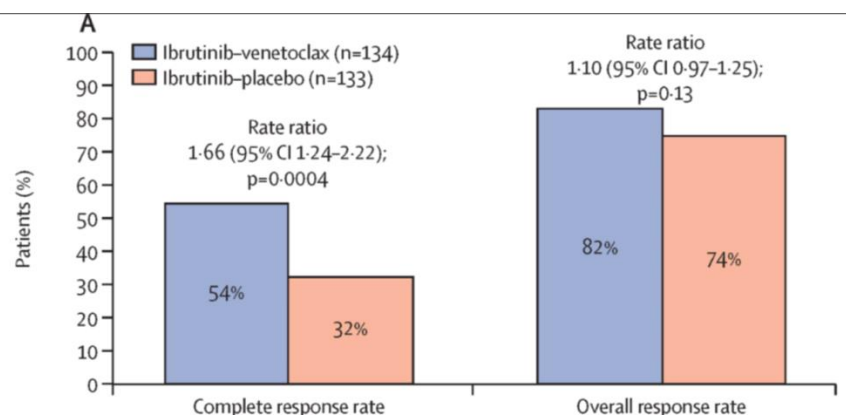
Stratification: ECOG PS, prior lines of therapy, TLS risk^a

Primary endpoint:

- PFS by investigator assessment using Lugano criteria

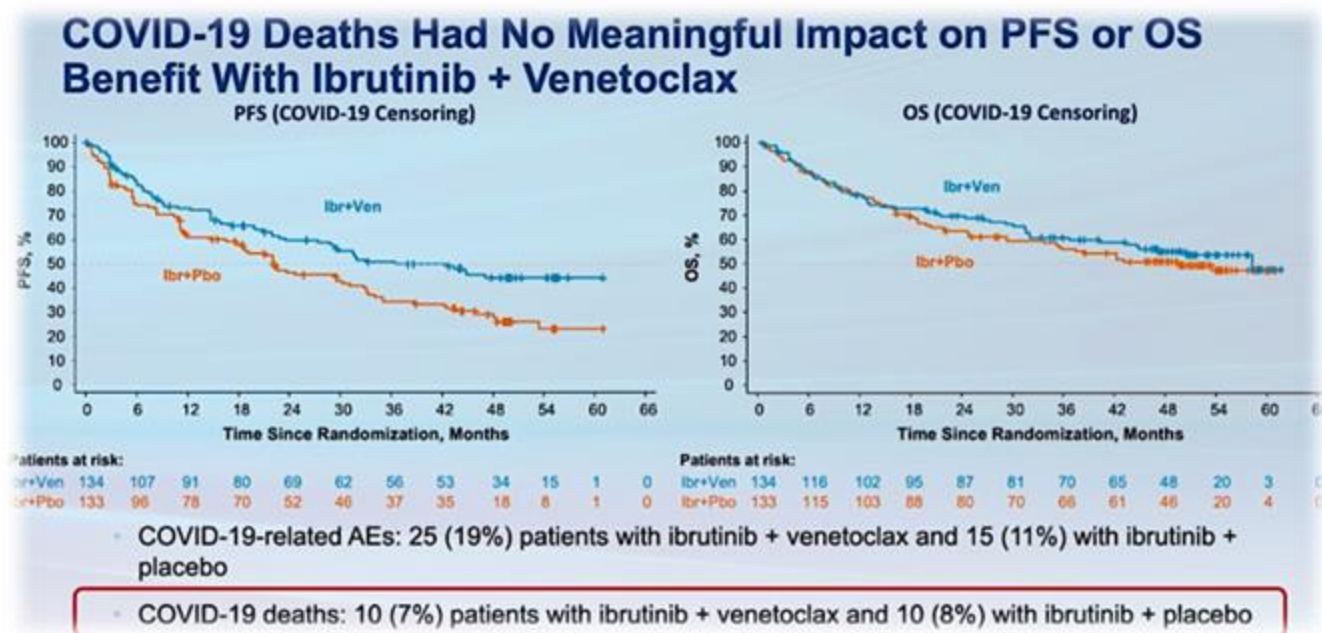
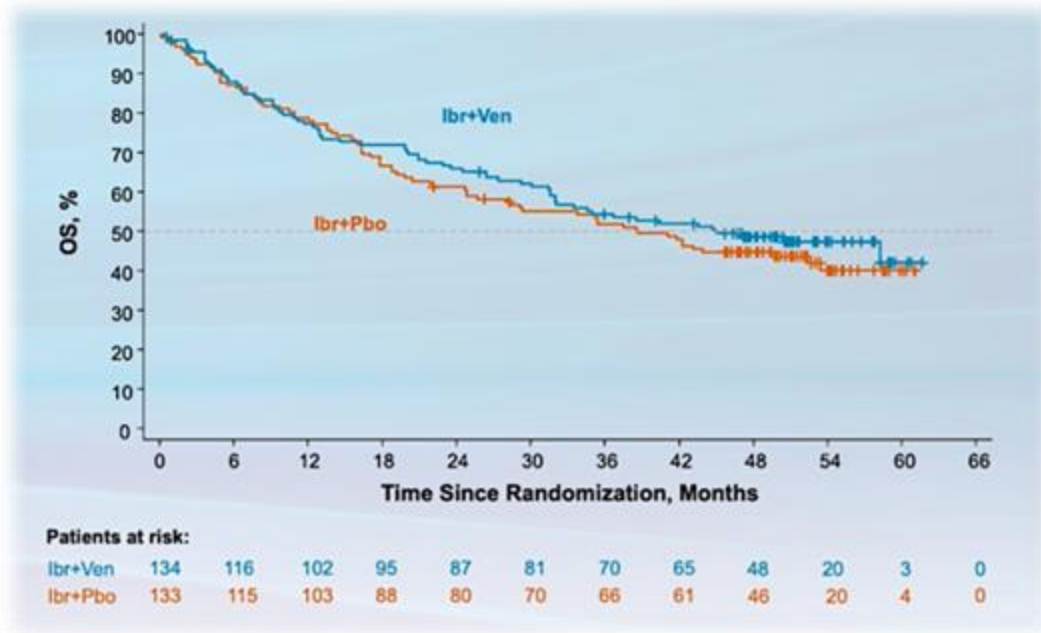
Secondary endpoints (tested hierarchically in the following order):

- CR rate by investigator assessment
- TTNT^b
- OS (interim analysis)
- ORR by investigator assessment



- With a median follow-up of 51.2 months,
- Ibrutinib-venetoclax group median PFS 31.9 months (95% CI 22.8–47.0) vs 22.1 months (16.5–29.5)
- hazard ratio 0.65 [95% CI 0.47–0.88]; p=0.0052

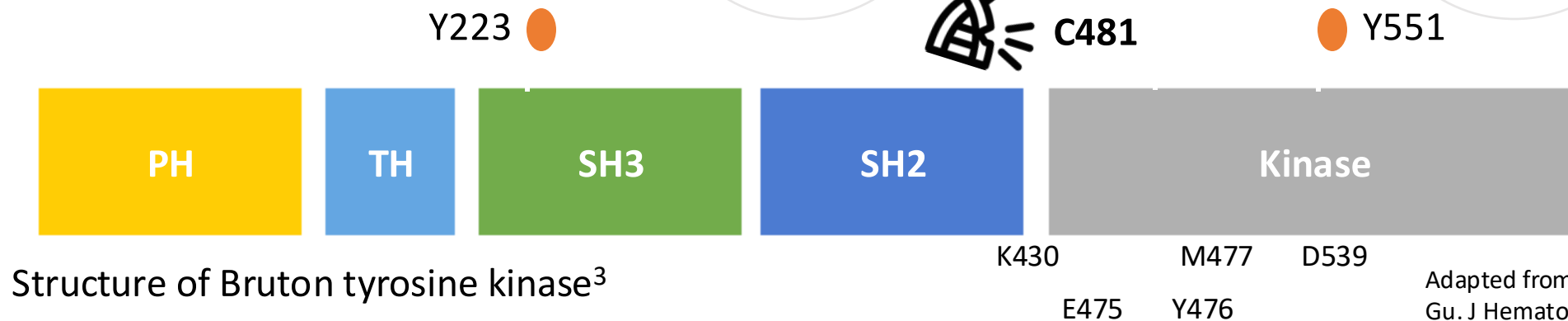
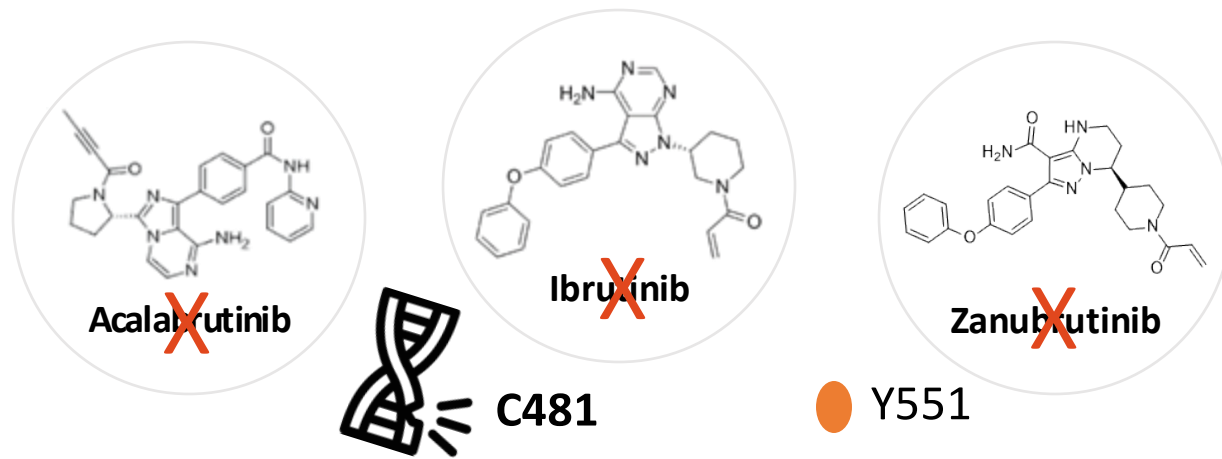
Ibrutinib plus venetoclax in R/R MCL (SYMPATICO): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study



Grade 3-4	Ibrutinib+Venetoclax	Ibrutinib
Neutropenia	31%	11%
Thrombocytopenia	13%	8%
Pneumonia	12%	11%
SAE	60%	60%
Treatment related death	2%	2%

Acquired Resistance to Covalent BTK Inhibitors

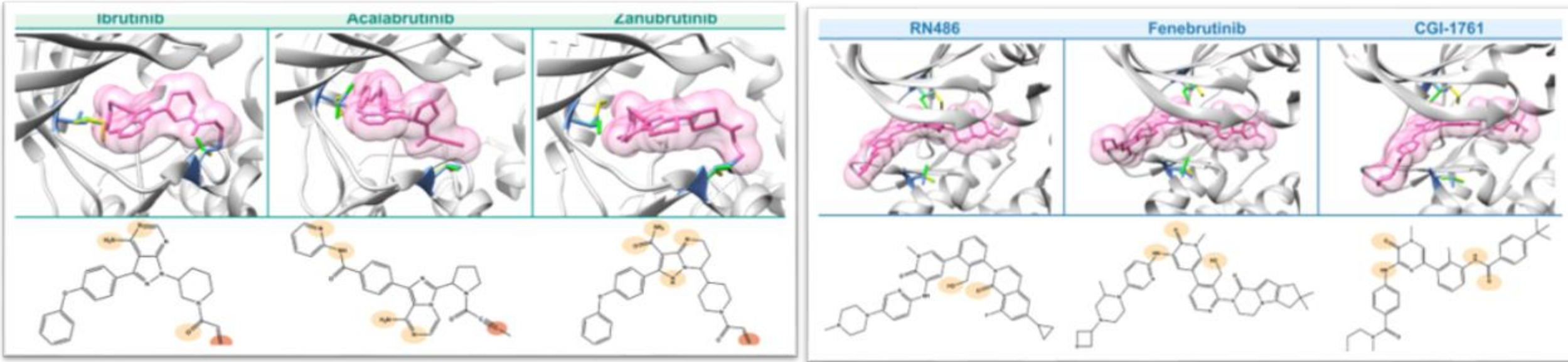
BTK C481 mutations, most of which are C481S mutations, have been found in patients with CLL and MCL after treatment with a covalent BTK inhibitor^{1,2}



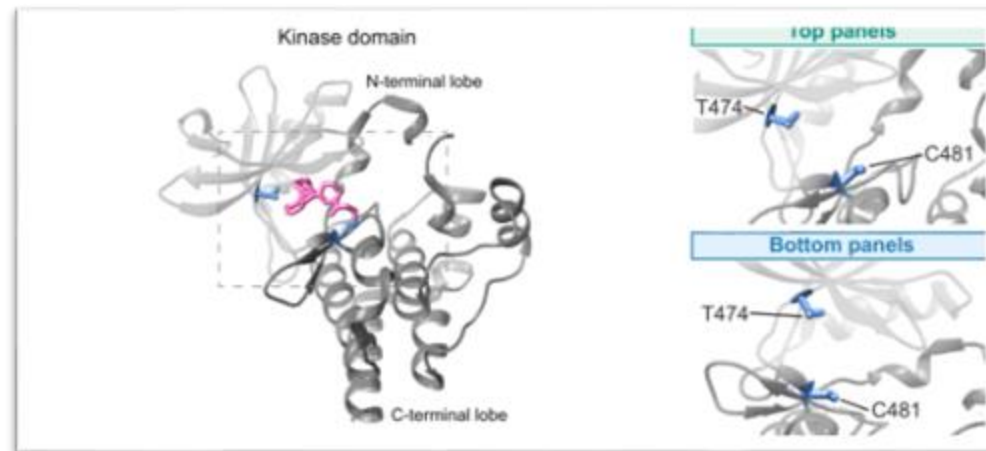
Adapted from:
Gu. J Hematol Oncol. 2021;14:40.

In summary, BTK resistance contributes to disease progression and diminishes the efficacy of *all covalent BTK inhibitors*

Covalent vs Noncovalent BTK Inhibitors



Covalent inhibitors bind to residue C481 and block ATP-binding site



However, mechanisms underlying BTK inhibitor resistance in MCL are not well understood and mostly do not rely on point mutations, as observed in CLL

Pirtobrutinib in R/R MCL Patients with Prior cBTKi: Safety and Efficacy Including High-Risk Subgroup Analyses from the Phase 1/2 BRUIN Study

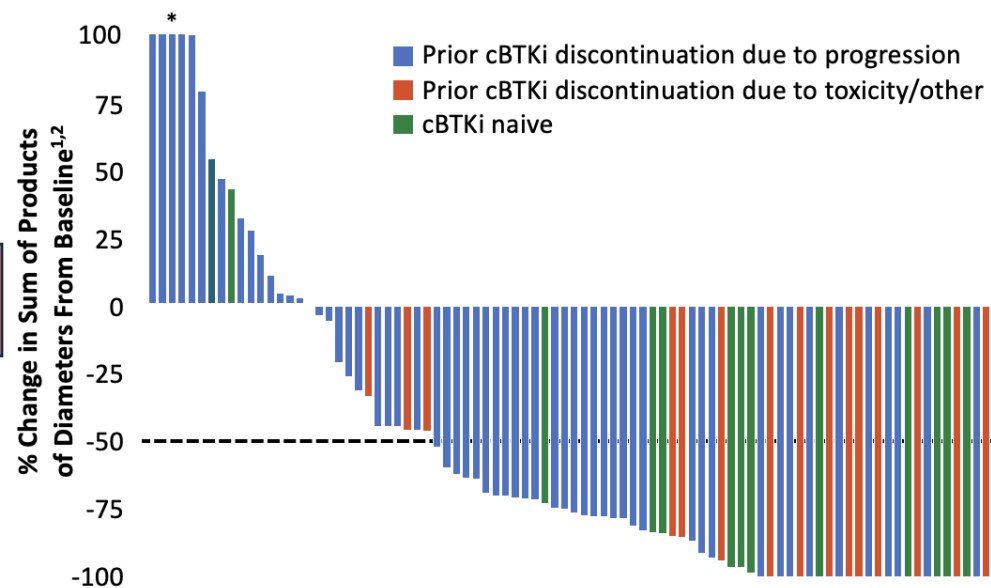
Overall Response Rate and Duration of Response by Subgroup

		cBTKi pre-treated MCL (n)	Number with Response (n)	ORR, % (95% CI)	DOR, median (95% CI)
Overall		152	75	49.3 (41.1-57.6)	21.6 (9.2-27.2)
MCL histology	Classic/Leukemic	120	61	50.8 (41.5-60.1)	17.7 (7.7-NE)
	Blastoid	15	6	40.0 (16.3-67.7)	NE (1.4-NE)
	Pleomorphic	17	8	47.1 (23.0-72.2)	21.6 (3.7-NE)
TP53 mutation^a	Yes	30	13	43.3 (25.5-62.6)	17.6 (1.7-NE)
	No	30	15	50.0 (31.3-68.7)	14.8 (1.9-NE)
Ki-67 Index^a	<30%	18	12	66.7 (41.0-86.7)	17.7 (1.9-NE)
	≥30%	45	20	44.4 (29.6-60.0)	21.6 (5.6-27.2)
sMIPI	Low	30	20	66.7 (47.2-82.7)	27.2 (6.5-NE)
	Intermediate	79	42	53.2 (41.6-64.5)	17.7 (7.4-NE)
	High	43	13	30.2 (17.2-46.1)	14.8 (5.2-21.6)
Discontinuation from any prior BTKi^{a, b}	Disease Progression	128	55	43.0 (34.3-52.0)	14.8 (7.3-27.2)
	Toxicity/Other	21	19	90.5 (69.6-98.8)	25.3 (9.2-NE)

Table 1. ORR and DOR in cBTKi pre-treated pts and high-risk subgroups

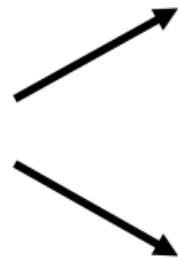
^aPatients with missing data were not included in the analysis.

^b"Disease Progression" is selected if "PD" for any prior BTK; otherwise "Toxicity" is selected if toxicity from any prior BTK; otherwise "Other".



BRUIN-MCL-321: Phase I-II Pirtobrutinib vs Investigator's Choice BTKi in RR MCL

Patients with MCL;
previously treated with
≥1 systemic tx; no prior
BTKi; ECOG PS 0-2
(planned N = 500)



Pirtobrutinib 200 mg PO QD

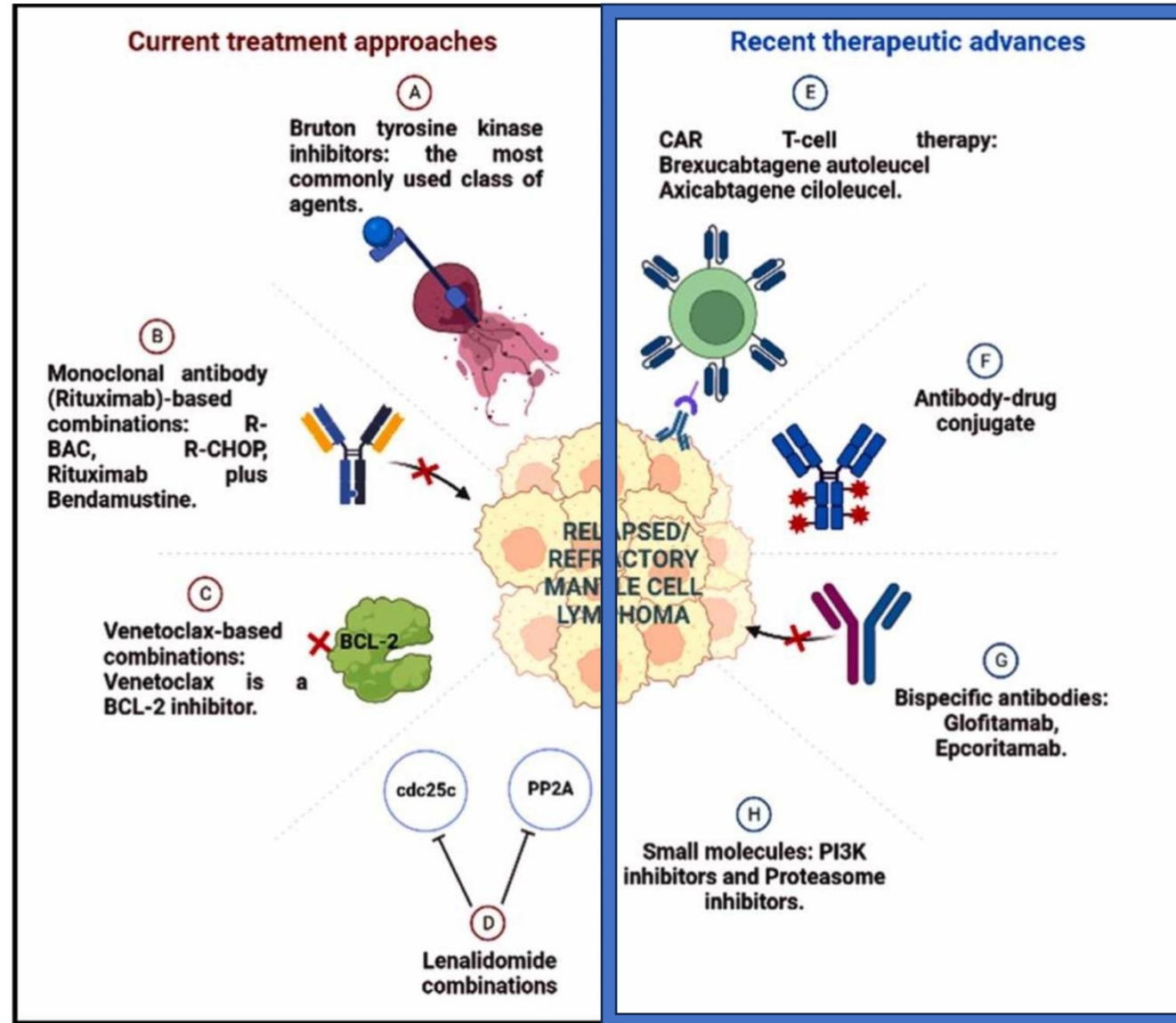
Investigator's Choice BTKi*
(ibrutinib, acalabrutinib, zanubrutinib)

*Ibrutinib: 560 mg PO QD.
Acalabrutinib: 100 mg PO BID.
Zanubrutinib 160 mg PO BID or 320 mg PO QD.

Primary endpoint: PFS

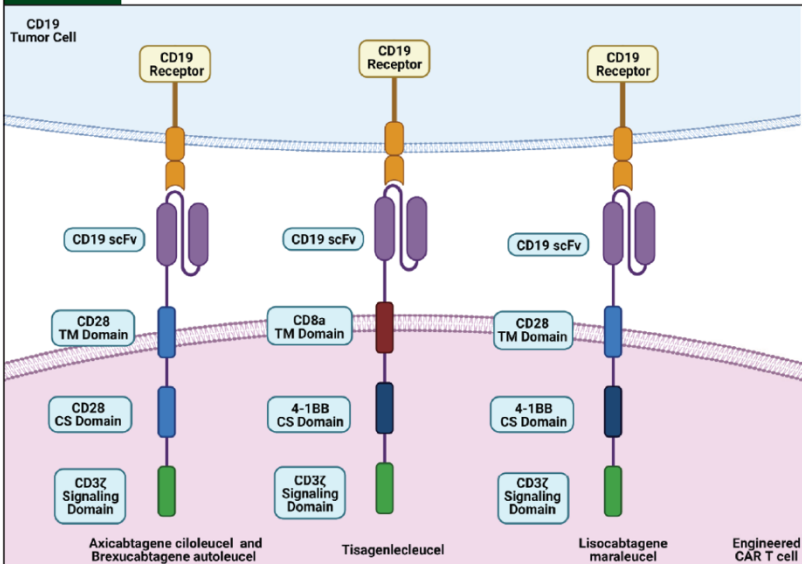
Secondary endpoints: EFS, ORR, DoR, OS, TTF, time to worsening of MCL-related symptoms, tolerability

Shifting paradigm of treatment in RR MCL



Brexucabtagene autoleucel (brexu-cel) in R/R MCL (ZUMA-2)

Figure 1 Comparison of FDA-Approved CAR T-Cell Therapies for the Treatment of NHL



CAR indicates chimeric antigen receptor; CS, co-stimulatory; NHL, non-Hodgkin lymphoma; scFv, single-chain variable fragment; TM, transmembrane.

Wells D. et al *J Hematol Oncol Pharm.* 2022;12(1):30-42

Enrollment/Leukapheresis



Optional Bridging Therapy

Dex 20-40 mg PO or IV daily for 1-4 days, or ibrutinib 560 mg PO daily, or acalabrutinib 100 mg PO twice daily



Conditioning Chemotherapy

Flu 30 mg/m² IV and Cy 500 mg/m² IV on Days -5, -4, -3



CAR T-Cell Dose

2×10⁶ KTE-X19 cells/kg on Day 0



First Tumor Assessment on Day 28

Primary endpoint: ORR

Table 1. Baseline Characteristics of All 68 Treated Patients.*

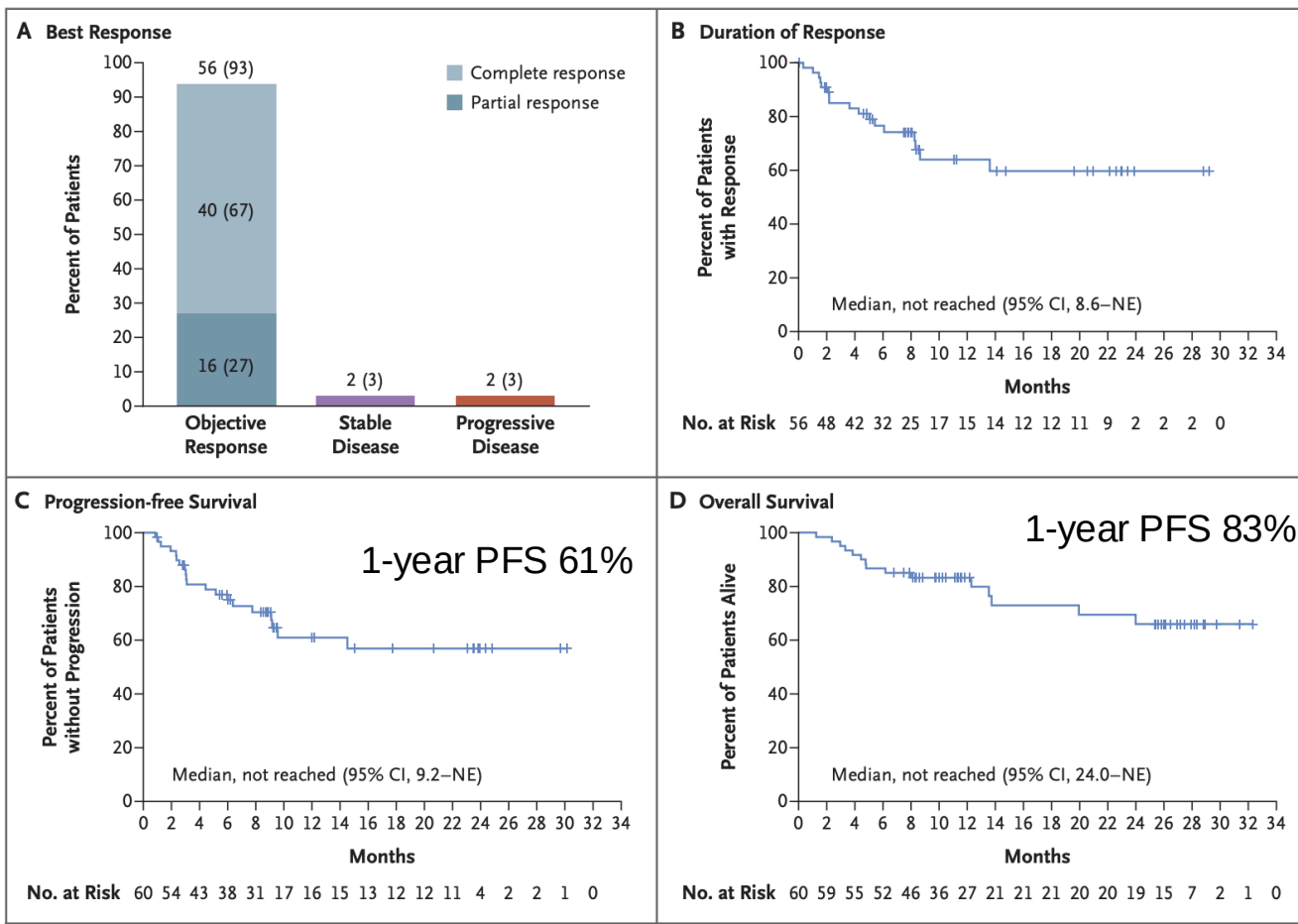
Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)

Brexucabtagene autoleucel in R/R MCL (ZUMA-2)

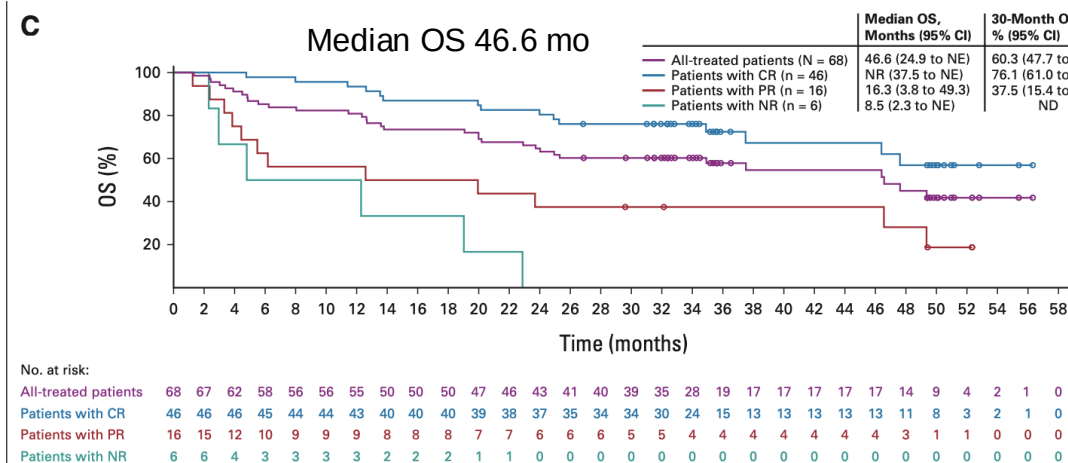
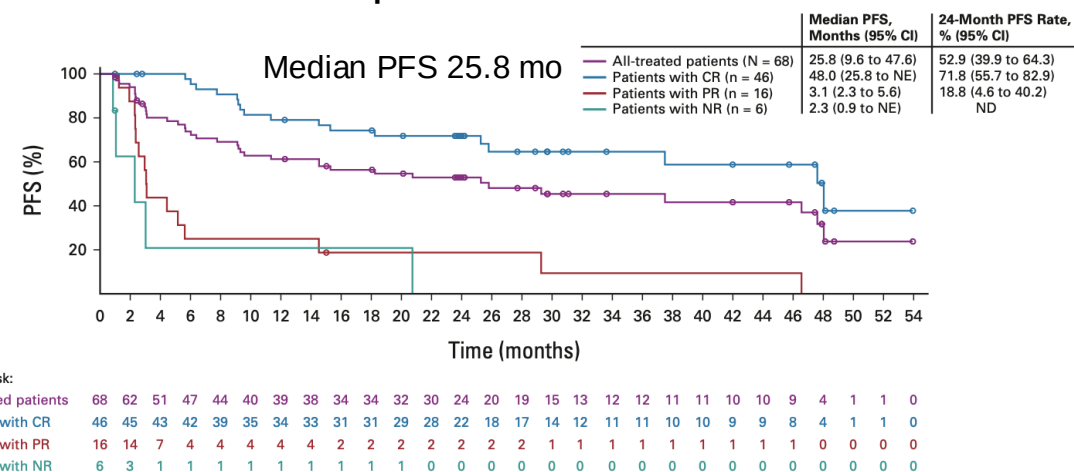
At a median follow-up of 12.3 months



At a median follow-up of 35.6 months



≥ Grade 3 CRS 15%; ICANS 31%



Glofitamab Step-up Dosing Induces High Response Rates in Patients with R/R MCL, Most of Whom Had Failed Prior BTKi Therapy

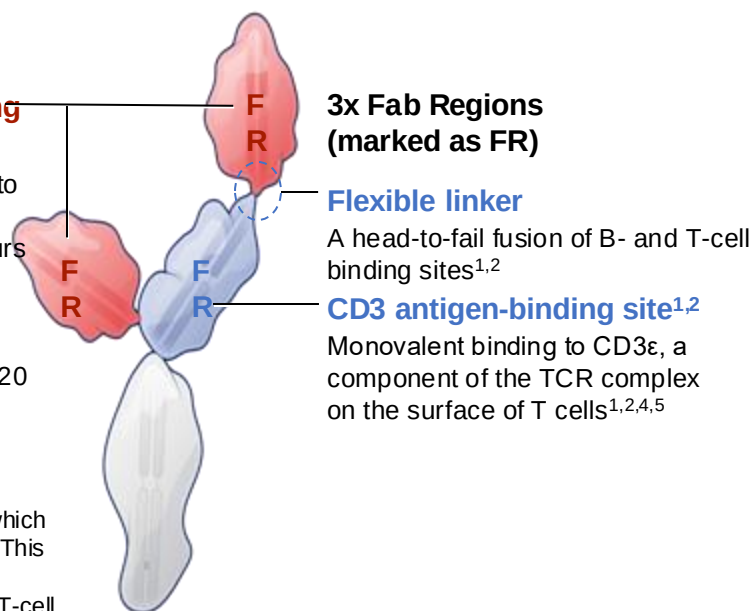
Glofitamab is a full-length, humanised IgG1 bispecific antibody with two 'Fab' regions that bind to CD20 and one that binds to CD3 in a 2:1 (CD20:CD3) format

Two CD20 antigen-binding sites^{1,2}

High-avidity, bivalent binding to CD20, which is expressed on the surface of B cells,¹⁻³ favours tumor targeting and retention, and facilitates combination therapy with standard-of-care anti-CD20 monoclonal antibodies²

Silent Fc region^{1,2}

Glofitamab has an Fc region which extends the half-life vs BiTEs. This silent region abrogates ADCC/ADCP/CDC to prevent T-cell lysis^{1,2}



Glofitamab IV administration

- Fixed-duration treatment: maximum 12 cycles

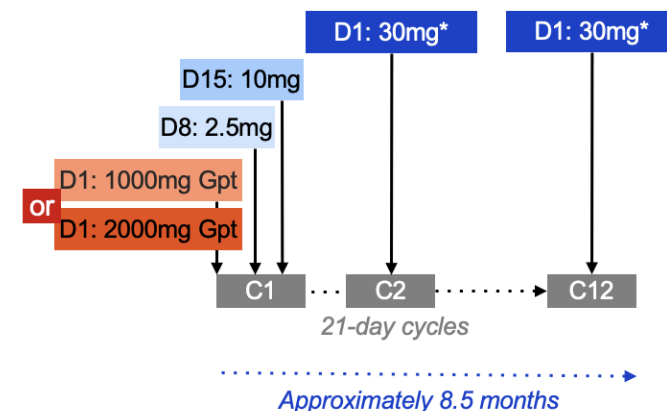
Population characteristics

- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS 0 or 1

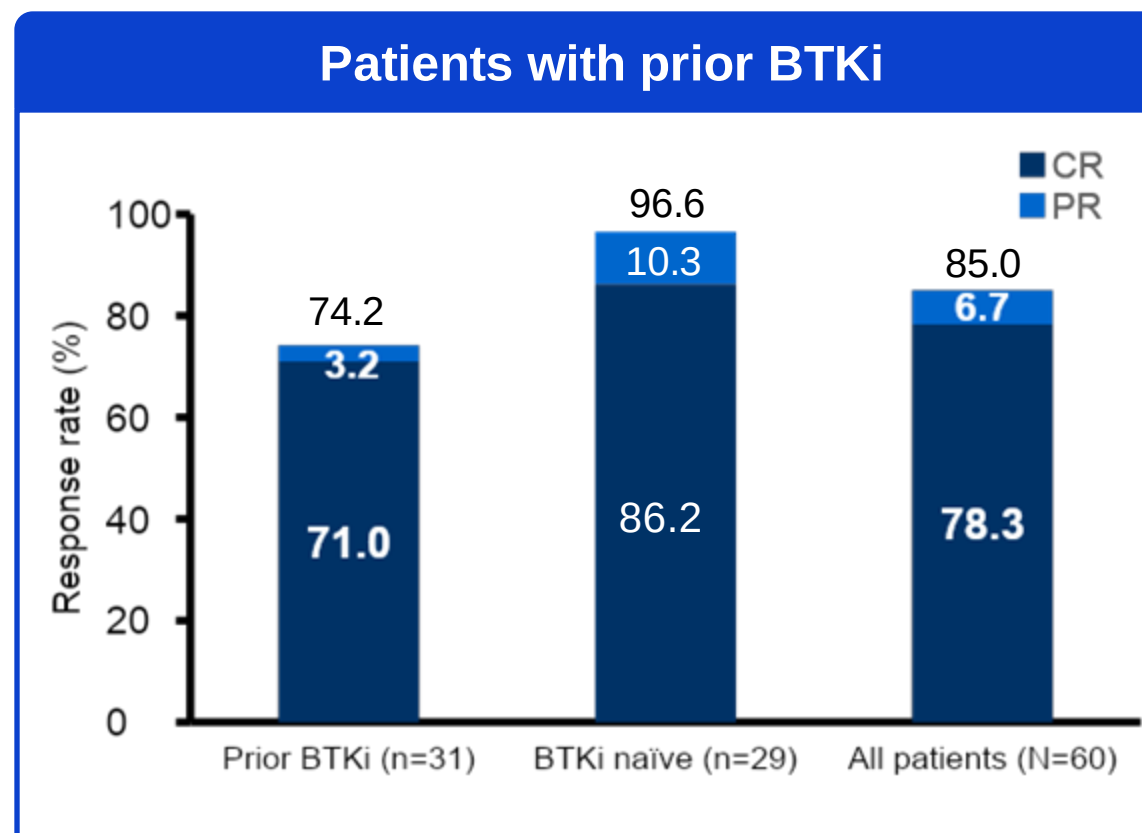
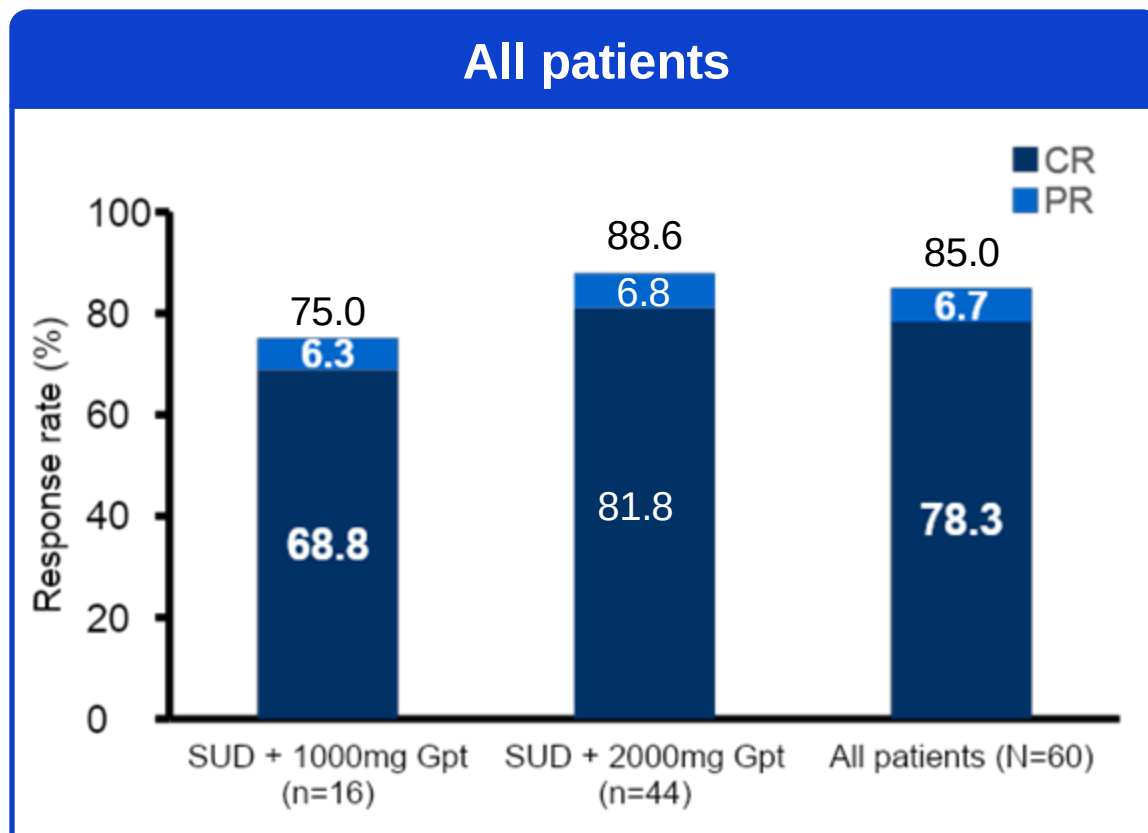
CRS mitigation

- Obinutuzumab pretreatment (1000mg or 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

Dosing schedule



Glofitamab step-up dosing: Response rates* by regimen and prior BTKi



- Median time to first response among responders (n=51): 42 days (95% CI: 42.0–45.0)
- High response rates in the overall population and in both BTKi-naïve patients and those with prior BTKi therapy

Clinical cut-off date: September 04, 2023. Response rates shown for the efficacy-evaluable population.

*Investigator-assessed.

BTKi, Burton's Tyrosine Kinase inhibitor; CI, confidence interval; CR, complete response; Gpt, obinutuzumab pretreatment.

PR, partial response; SUD, step-up dosing.

1. Cheson BC, et al. J Clin Oncol 2014;20:3059–68;

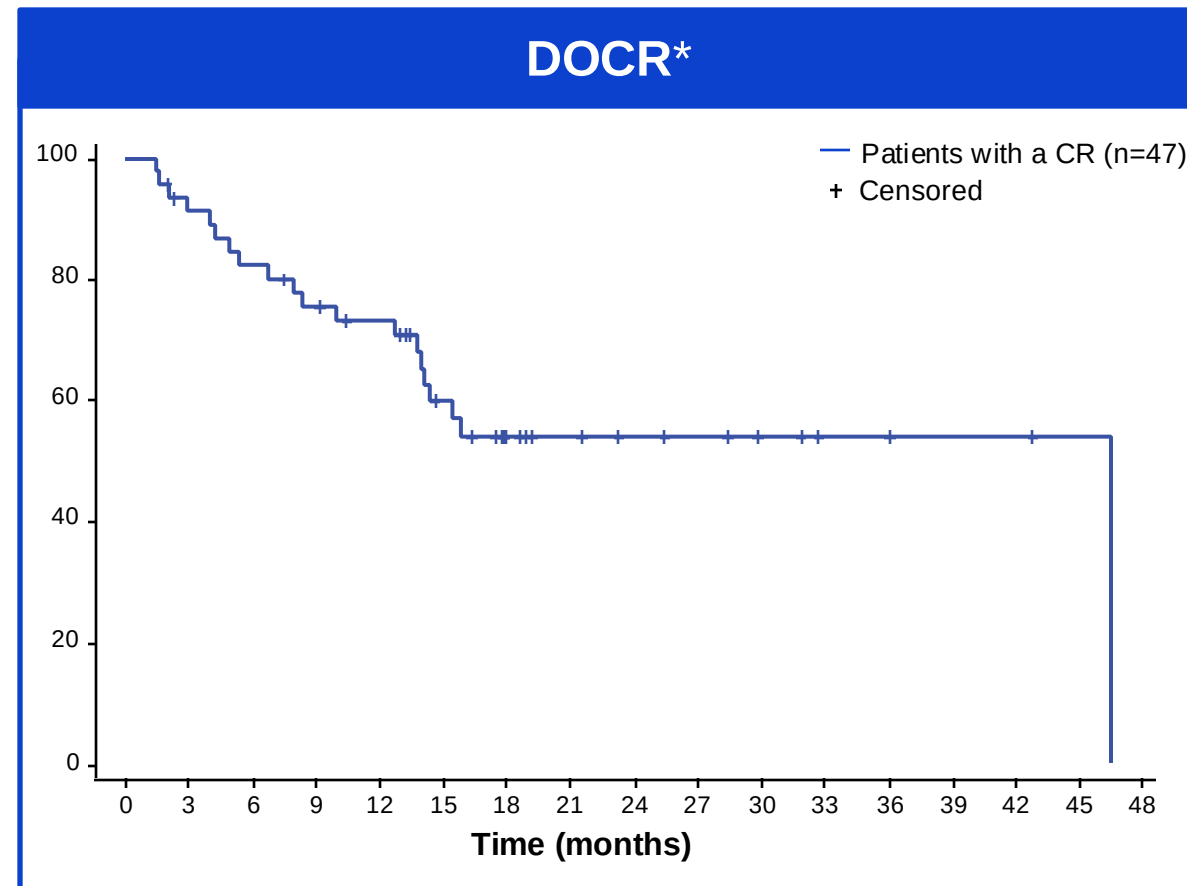
2. Philips T, et al. J Clin Oncol 2024; doi:10.1200/JCO.23.02470 (online ahead of print);

3. Philips T, et al. ASCO 2024; oral presentation (abstract #7008).

Glofitamab step-up dosing: efficacy after extend follow-up

Response rate*	All patients N=61
ORR, %	82
CR, %	77
Median time to first response, days (range)	42 (29–164)
DOCR*	n=47
Median DOCR, months (95% CI)	46.5 (14.4–NE)
12-month event-free rate, % (95% CI)	73.3 (60.3–86.2)

- Median PFS: 18.0 months (95% CI: 11.3–NE)
- Median OS: NE (95% CI: 21.6–NE)

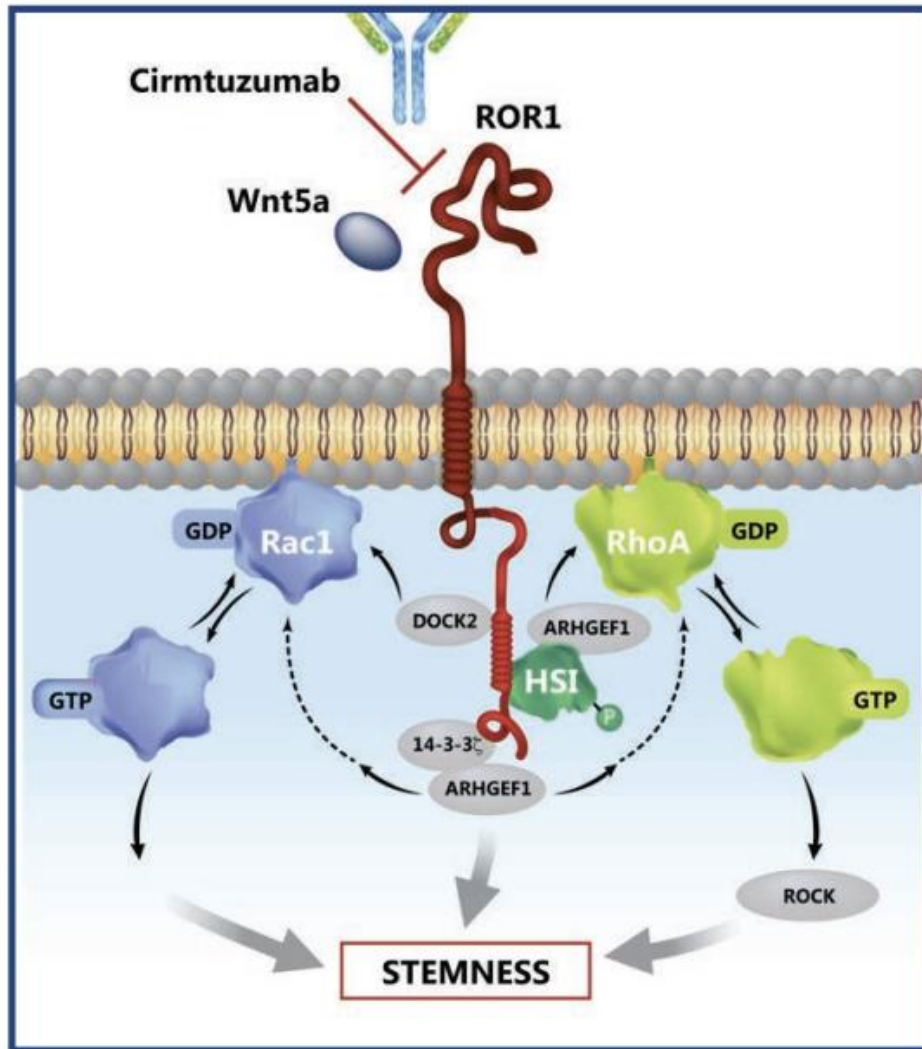


Currently, Phase 3 Glofitamab vs BR or R2 is ongoing

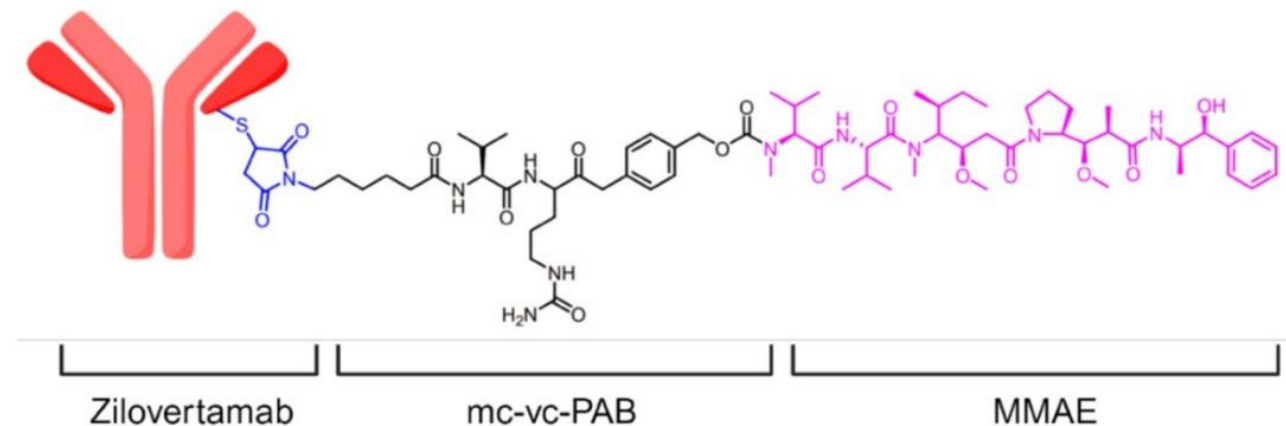
Clinical cut-off date: May 17, 2024. *Investigator-assessed.
CI, confidence interval; CR, complete response; DOCR, duration of complete response; NE, non estimable;
PFS, progression-free survival; OS, overall survival; ORR, overall response rate.

Philips T, et al. ASH 2024; poster presentation (abstract #1631).

Antibody drug conjugate : Zilovertamab vedotin



- ROR1 is an onco-embryonic tyrosine kinase-like receptor that is re-expressed at high levels on many solid and hematologic cancers including MCL, CLL, and MZL but not on normal adult tissues
- ROR1 binds Wnt5a, resulting in increased tumor growth, survival, metastasis, cancer cell stemness and epithelial mesenchymal transition.



PHASE 1/2 STUDY OF ZILOVERTAMAB VEDOTIN AND IBRUTINIB IN MCL, CLL and MZL

Phase 1/2 Study Design

Treatment naïve (TN) or Relapsed/Refractory (R/R) CLL/SLL;
R/R MCL and MZL; prior BTKi allowed for MCL and MZL

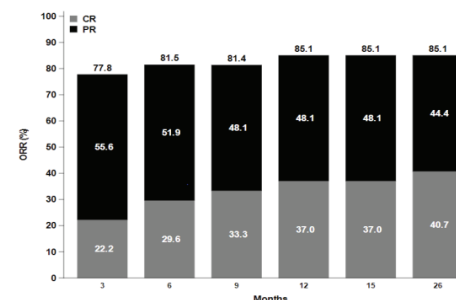
Phase 1	Phase 2	
Part 1 (MCL & CLL)	Part 2 (MCL, CLL & MZL)	Part 3 (CLL)
DOSE-FINDING COHORT 2, 4, 8 & 16mg/kg and 300 & 600mg doses of zilovetamab^a evaluated - Ibrutinib added after 1 month (420mg CLL, 560mg MCL, qd po) - No DLTs, MTD not reached - RDR^b: 600mg IV q2wks X 3 then q4wks in combination with ibrutinib at approved doses per indication	DOSE-EXPANSION COHORT - Confirmed RDR^b of zilovetamab^a (600mg) + ibrutinib at approved dose (420mg CLL, 560mg MCL and MZL) - Primary objective: To further characterize safety, pharmacology, and clinical response using RDR^b	RANDOMIZED EFFICACY - Zilovetamab^a + ibrutinib vs. ibrutinib - Randomization ratio = 2:1 - Primary objective: Complete Response Rate
Enrolled CLL n = 18 MCL n = 12	Enrolled CLL n = 16 MCL n = 21 <i>MZL soon open for enrollment</i>	Enrolled n = 31

a – Formerly cirmtuzumab; b – recommended dosing regimen

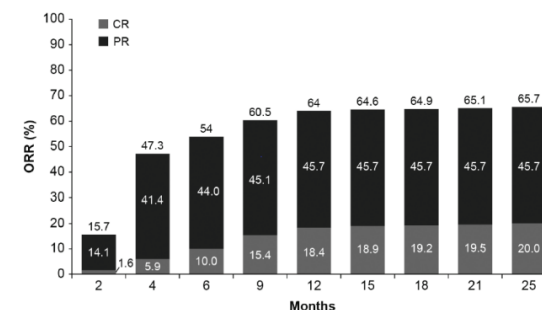
Combination treatment with zilovetamab + ibrutinib is generally well tolerated, with a safety profile similar to that of ibrutinib alone

Clinical Response	Zilovetamab + ibrutinib	Historical ibrutinib Rule, 2017 ^a
	N = 27	N = 370
ORR, n (%)	23 (85.2)	234 (63.2)
CR, n (%)	11 ^b (40.7)	74 (20.0)
PR, n (%)	12 (44.4)	160 (45.6)
SD, n (%)	2 (7.4)	50 (13.5)
PD, n (%)	2 (7.4)	86 (23.2)

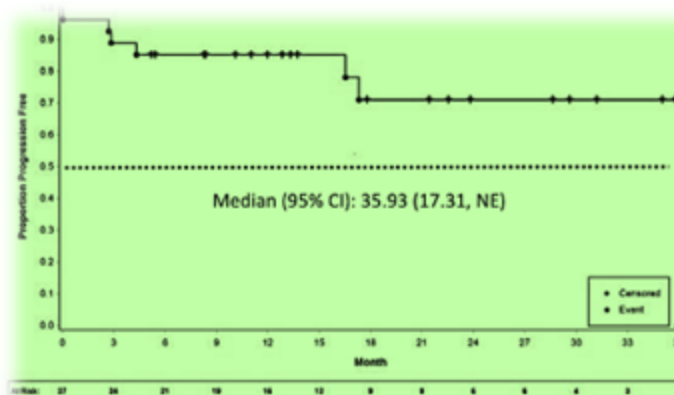
Clinical Response Rates Over Time



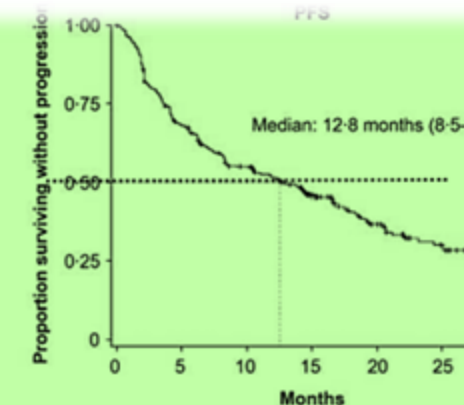
Zilovetamab + ibrutinib



Historical ibrutinib, Rule 2017^a

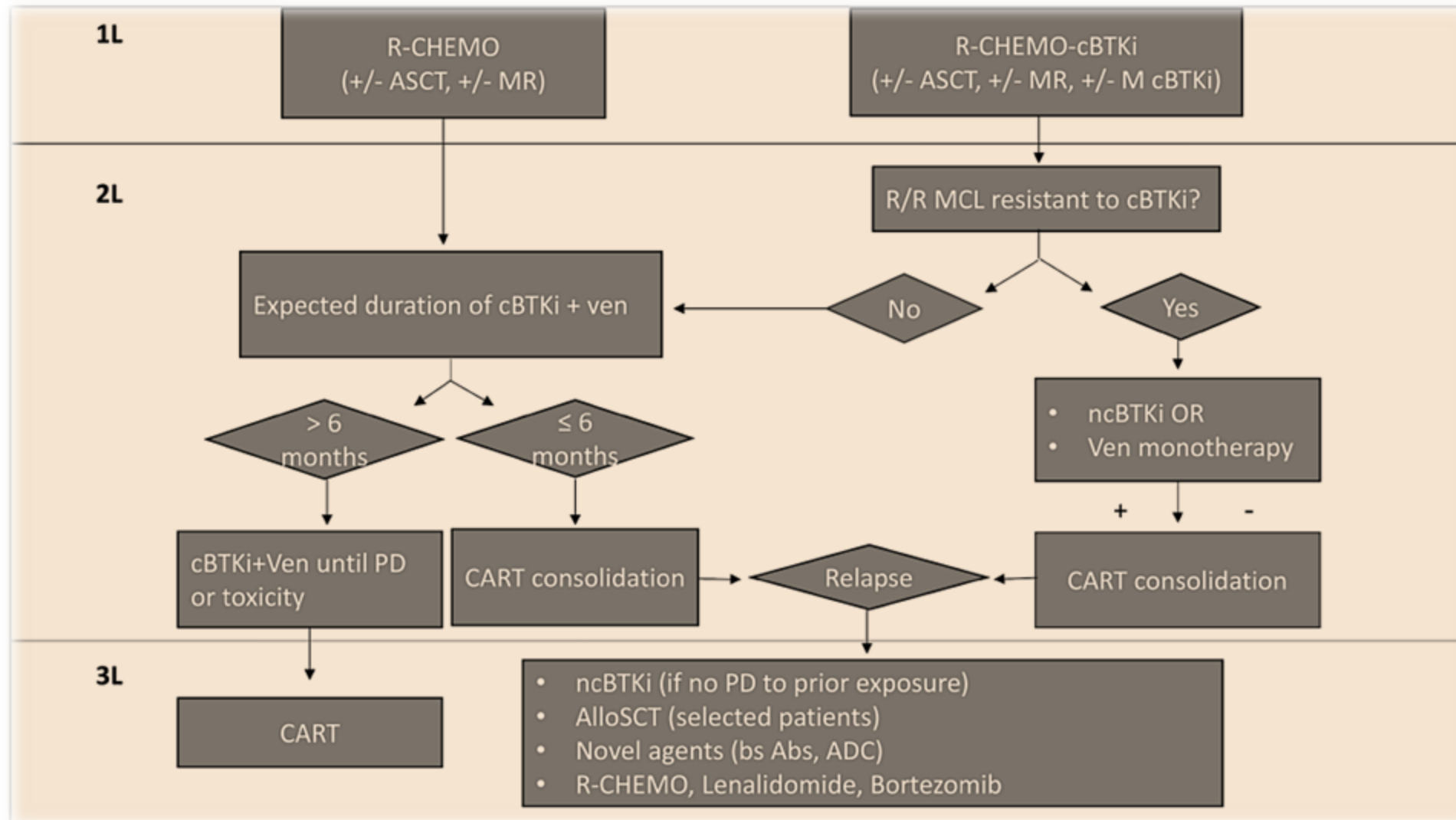


Zilovetamab + ibrutinib



Historical ibrutinib, Rule 2017^a

A proposed treatment algorithm for the management of patients with R/R MCL



Key summary

- BTKi demonstrate the benefit in both newly diagnosed and relapsed/refractory MCL
 - Combination with CIT, though showing benefit, but trading with higher toxicity
 - The way to integrate BTKi to the treatment still need to be further explore
 - Sequential BTKi maintenance after CIT induction may be pertain benefit with less toxicity
- Chemofree regimen by combining BTKi and BCL2 inhibitor is show promising result and may become the standard of care in the near future
- CAR T-cell, bispecific antibody as well as drug conjugate Abs demonstrated clinical benefit and can be considered as a later line therapy for MCL

Key summary

BTK inhibitors (BTKi) demonstrate clinical efficacy in both newly diagnosed and R/R MCL

- While **combination with chemoimmunotherapy (CIT)** has shown benefit, it often **trades efficacy for increased toxicity**, highlighting the need to refine treatment strategies.
- The **optimal integration of BTKi into therapeutic algorithms** remains an area requiring further exploration.
 - For instance, **sequential BTKi maintenance following CIT induction** may retain clinical benefit while reducing toxicity, offering a potential balance for long-term management.

Chemotherapy-free regimens, such as combinations of BTKi and BCL2 inhibitors have shown **promising efficacy** could emerge as a **future standard of care**, particularly for older or less fit patients.

Novel therapies like **CAR T-cell therapy**, **bispecific antibodies**, and **antibody-drug conjugates (ADCs)** have demonstrated robust clinical activity in advanced MCL.

- These modalities are increasingly positioned as **later-line options** for patients who progress after BTKi or other targeted therapies.