



How will first-line treatment for mantle cell lymphoma change in the coming years?

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Disclosures

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
Genmab						X	
Pierre Fabre			X				
Research to Practice					X		
Kite Pharma			X				

Outline

- **Background/risk factors**
- **Initial therapy for fit patients**
- **Role of transplant**
- **Incorporating novel agents**
- **Therapy for elderly patients**

Background/risk factors

Mantle cell lymphoma: clinical features

6-7% of NHL in US

70% males

Median age 65

**>80% stage
III/IV**

**GI tract involvement
common**



Subtypes:

Nodal MCL:

>75% cases

**Involves nodes, spleen and/or
extranodal sites**

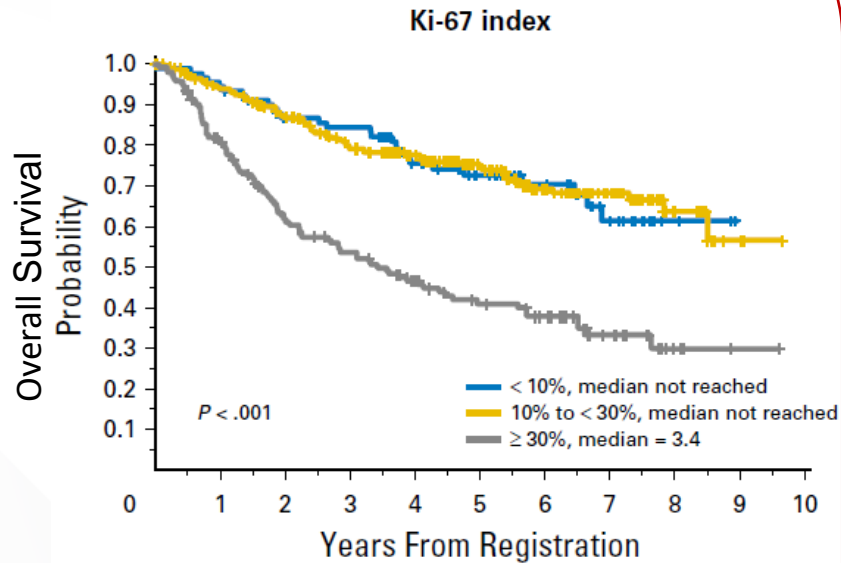
Leukemic non-nodal:

Circulating disease

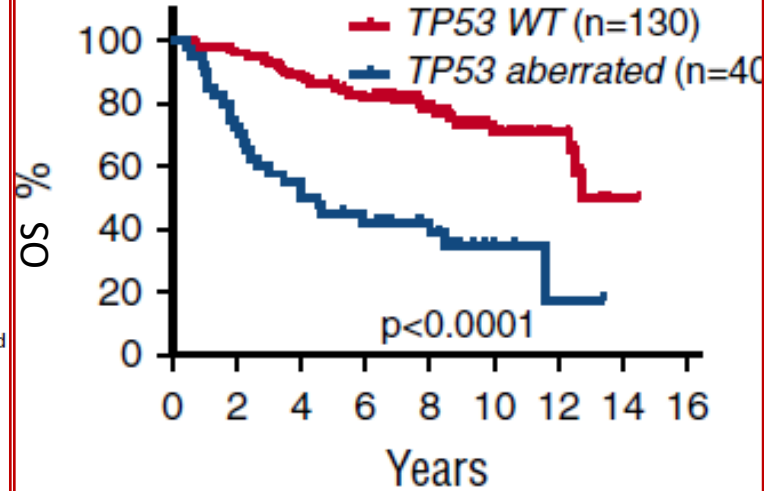
Splenomegaly

SOX-11 neg

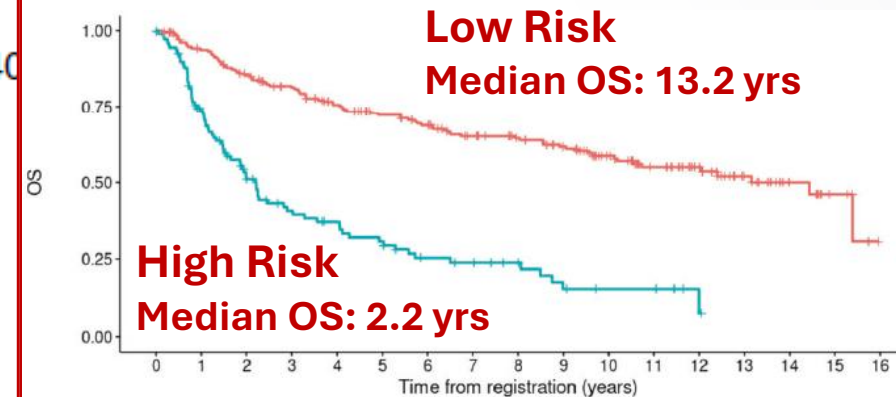
High-risk MCL includes high Ki67 & TP53-aberrant disease



MCL Younger & MCL Elderly Trials
Hoster et al. JCO 2016

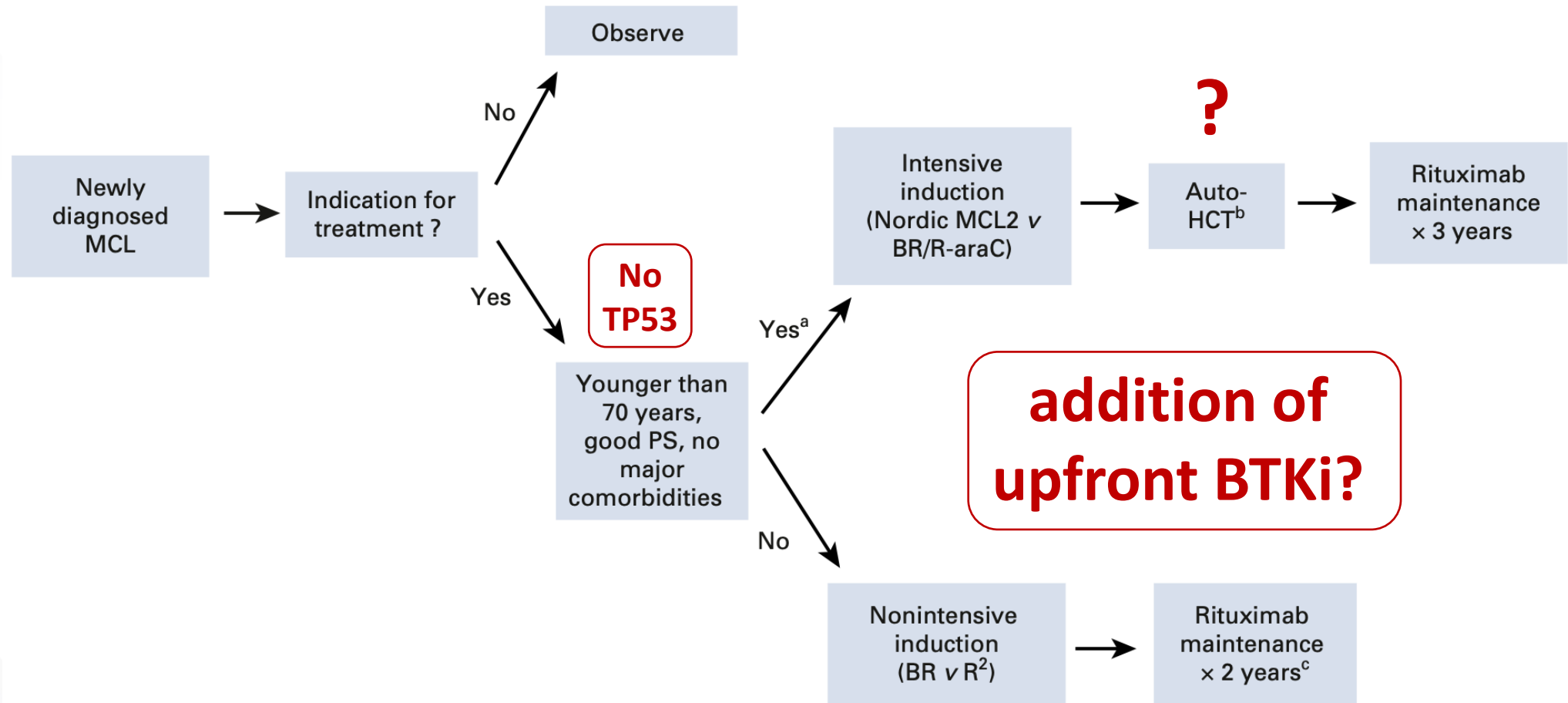


Nordic MCL2 and MCL3 Trials
Eskelund et al. Blood 2017



MCL Younger & MCL Elderly Trials
Scheubeck et al. Leukemia 2023

Treatment landscape for MCL in 2022





**Management of patients who
are candidates for intensive
therapy**

Why has ASCT consolidation been standard of care for 2 decades?

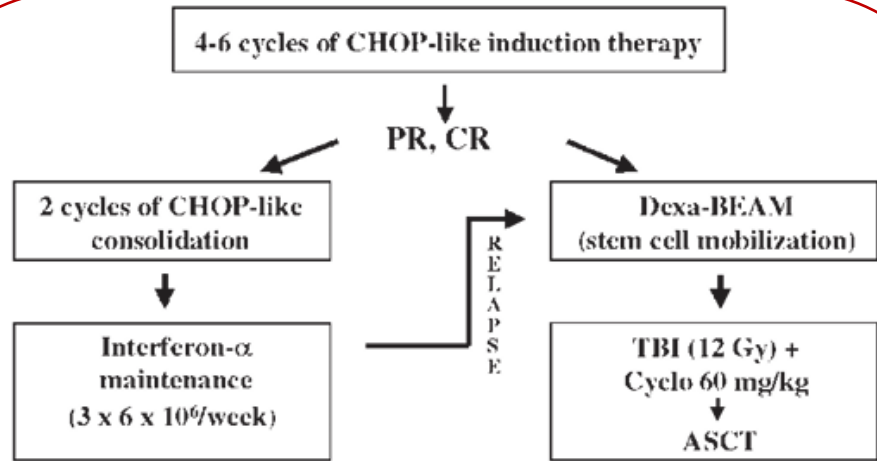
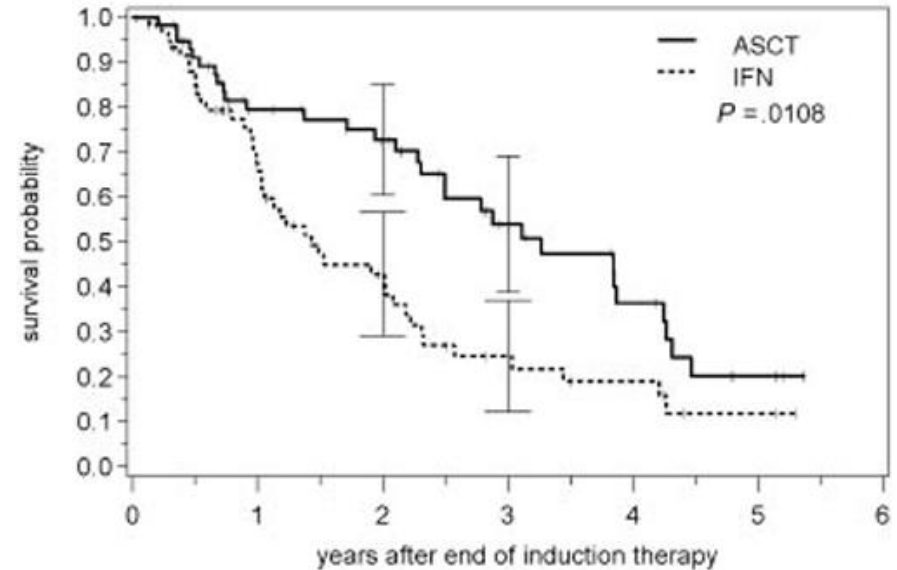


Table 1. Patient characteristics

	IFN	ASCT	Total
Patients evaluable, no.	60	62	122
Median age of evaluable patients in years (range)	55.2 (37-65)	55.6 (35-65)	55.6 (35-65)
IPI, n = 108 (%)			
Low-risk	22 (42)	24 (44)	46 (43)
Low-intermediate risk	23 (43)	21 (38)	44 (41)
High-intermediate risk	6 (11)	6 (11)	12 (11)
High-risk	2 (4)	4 (7)	6 (6)
Male (%)	42 (70)	48 (77)	90 (74)
Stage IV (%)	47 (78)	52 (84)	99 (81)
Elevated serum LDH, n = 111 (%)	14 (26)	14 (25)	28 (25)
ECOG score greater than 1 (%)	3 (5)	2 (3)	5 (4)
B-symptoms (%)	20 (33)	25 (40)	45 (37)
Induction therapy (%)			
CHOP	35 (58)	39 (63)	74 (61)
R-CHOP	14 (23)	18 (29)	32 (26)
Other CHOP-like regimens	11 (18)	5 (8)	16 (13)



numbers of patients at risk

	0	1	2	3	4	5	6
ASCT	62	38	31	17	10	3	
IFN	60	33	19	9	6	2	

No difference in OS

Dreyling et al. Blood 2005

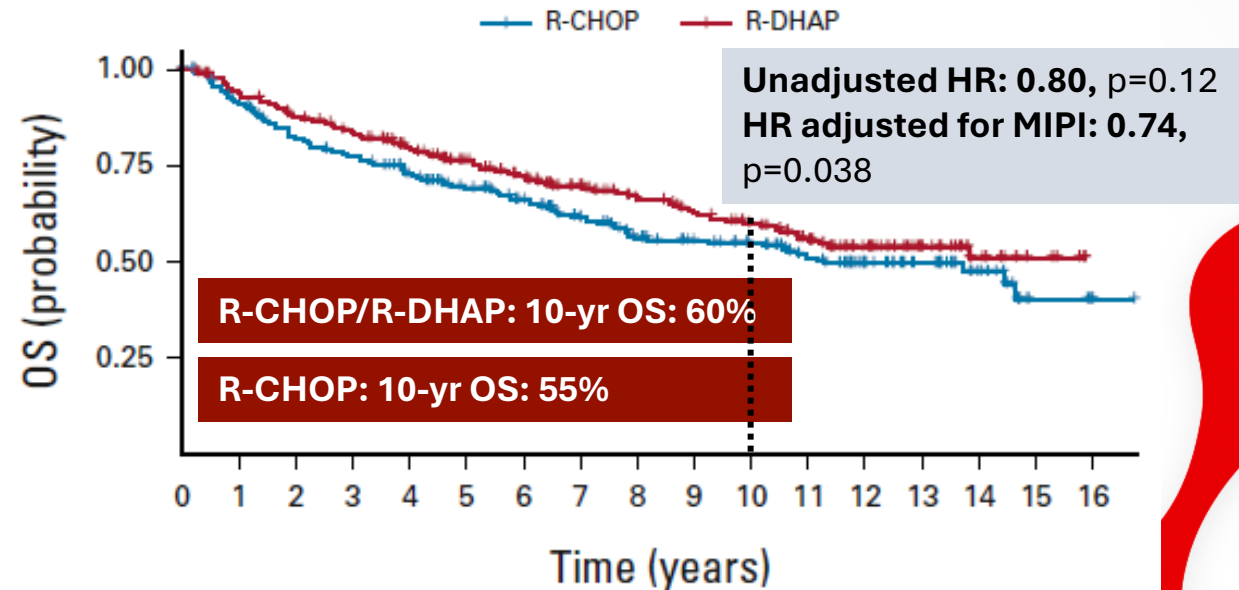
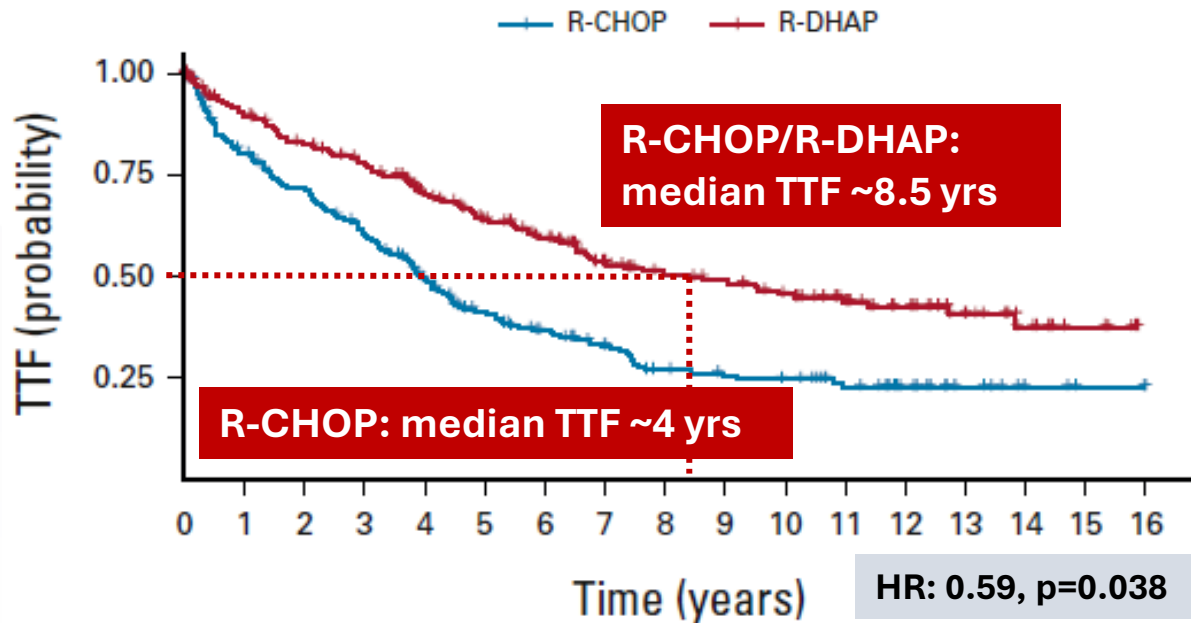
Intensified Induction with ASCT Consolidation

Group	Regimen	n	PFS	OS	ref
LyMA	RDHAP x 4	120 (obs)	7 yr 47%	7 yr 72%	Sarkozy JCO 2024
	CHOP if < CR +/- MR	120 (MR)	7 yr 79%	7 yr 83%*	
Nordic regimen	R+maxiCHOP + R-cytarabine	159	Med 9 yr	13 yr	Eskelund Br J Heme 2016
DFCI/ Wash U	BR + R-cytarabine	88	8 yr 68%	8 yr 76%	Ryan ASH 2024

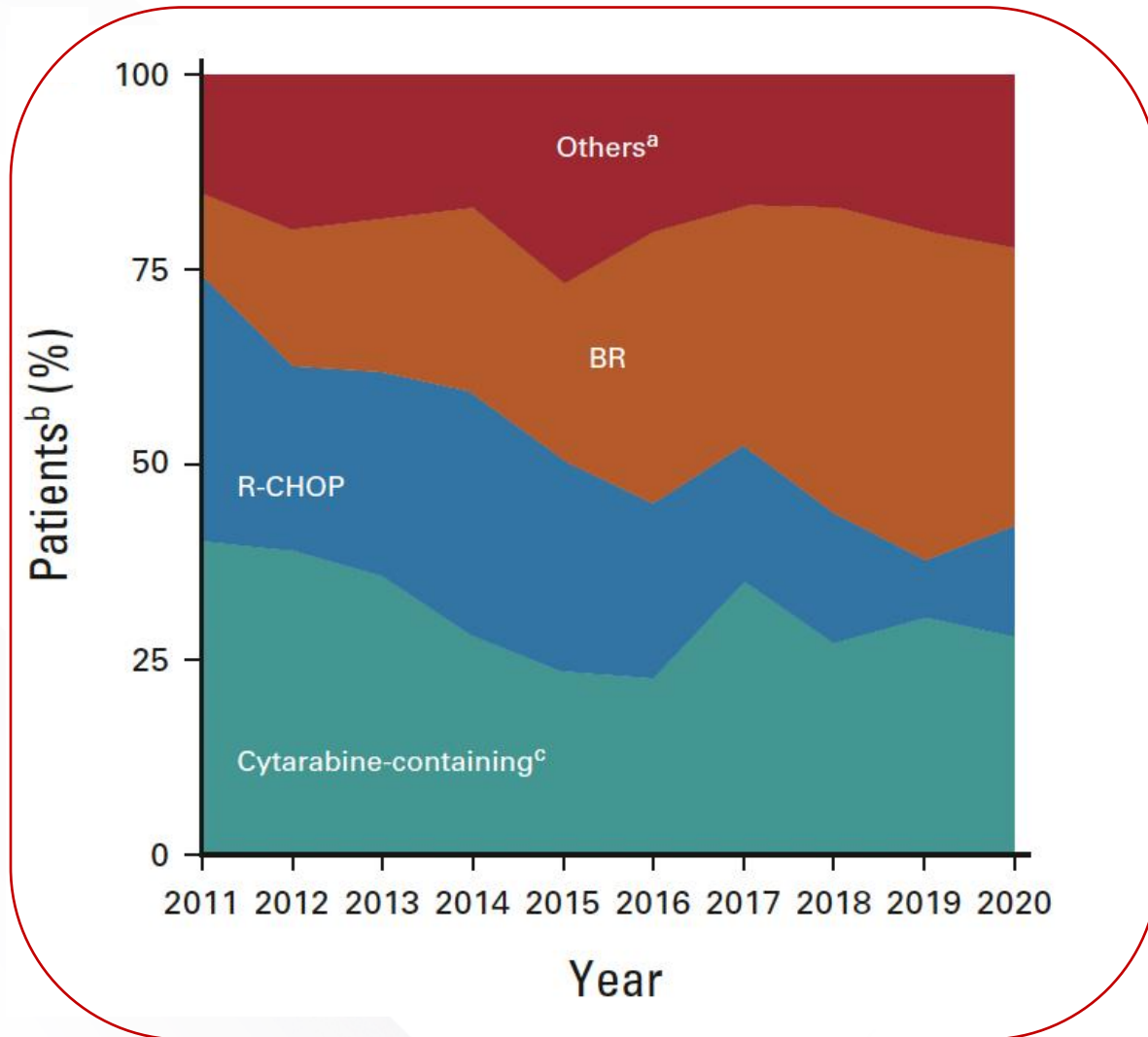
* OS benefit not statistically significant

MCL Younger: superior PFS with inclusion of cytarabine in induction therapy

European MCL Network Trial
Previously untreated MCL (n=466)
Age ≤ 65 yrs



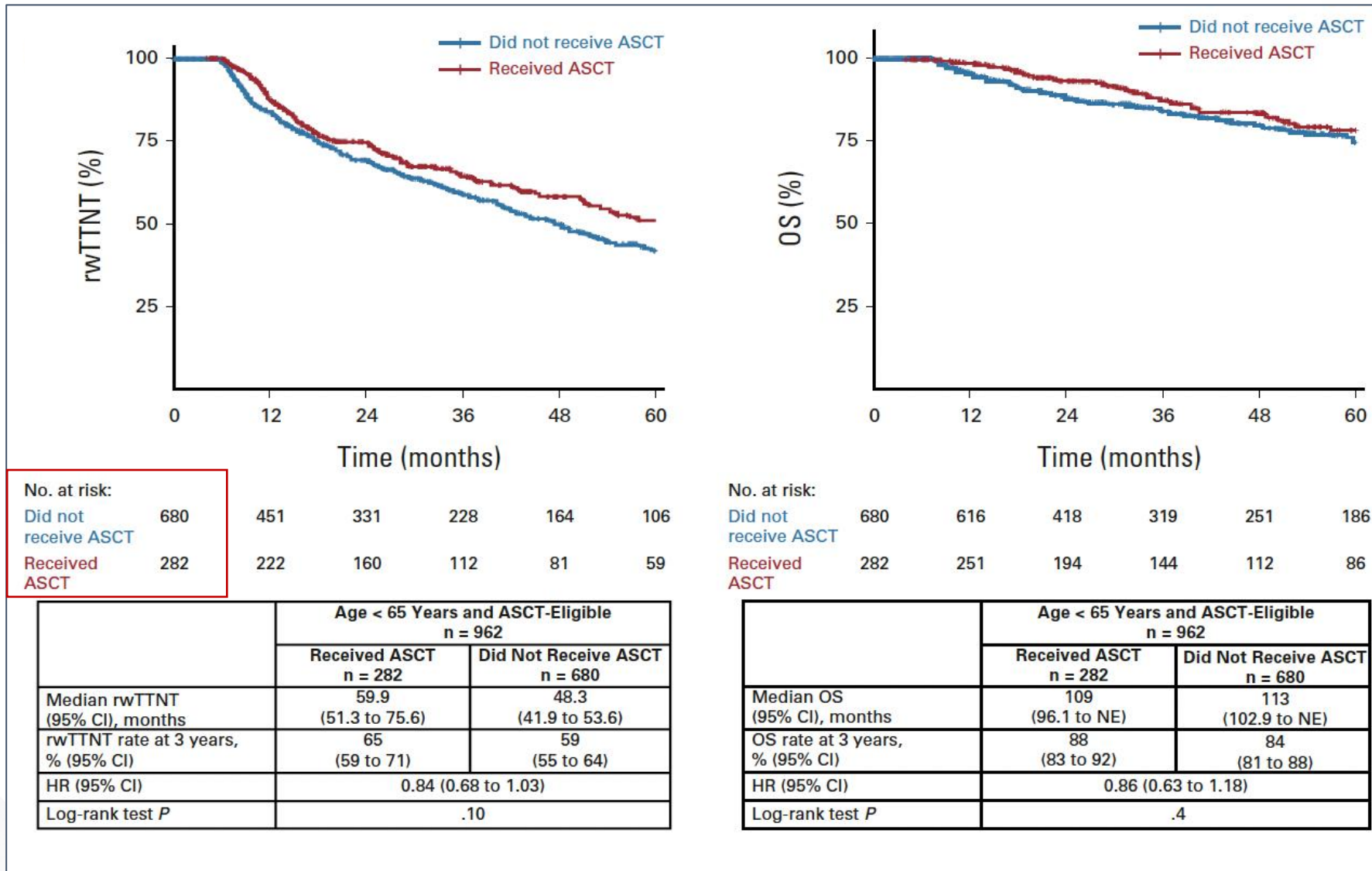
“Real world” first-line management MCL in the US: transplant-eligible patients



Age < 65

Martin et al. JCO 2023

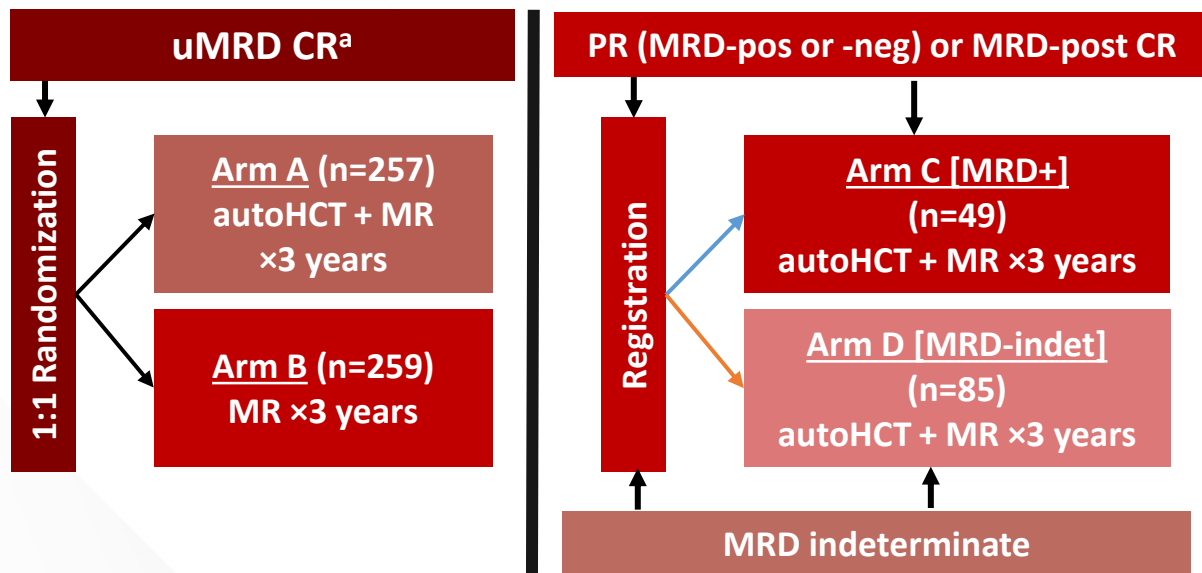
No significant difference in TTNT or OS with ASCT



EA4151: testing the benefit of ASCT in patients with uMRD after induction

Key Eligibility Criteria

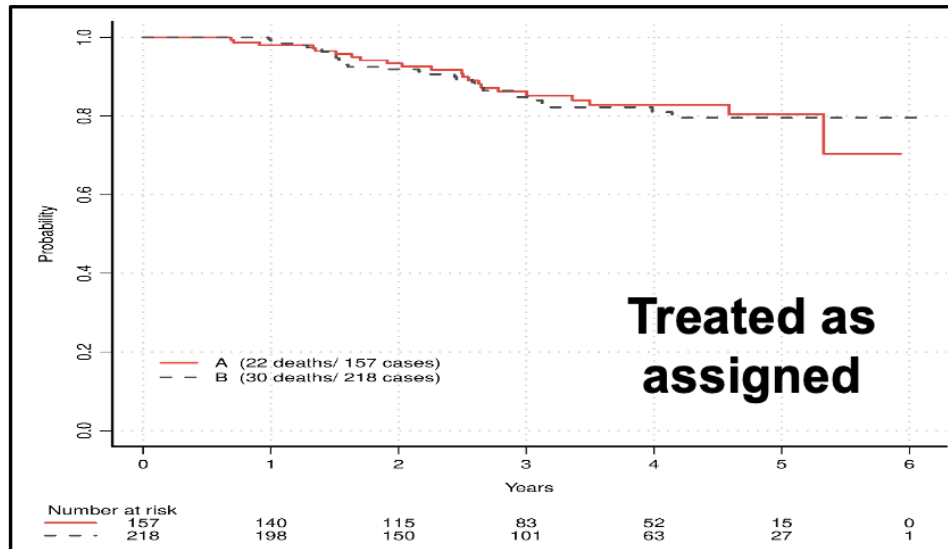
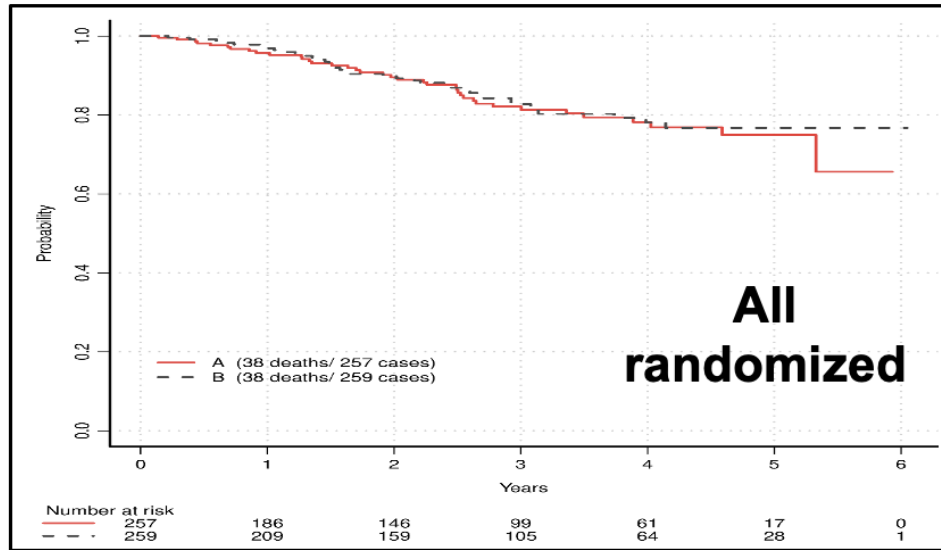
- Aged 18-70 years
- MCL in first remission
- R-containing induction was allowed, including BTKi



Primary endpoint: Comparative OS between autoHCT with R maintenance and maintenance R monotherapy alone
Key secondary endpoints: PFS, MRD+ conversion rate to uMRD following autoHCT (Arm C)

Patient Characteristics, %		Arm A (n=257)	Arm B (n=259)	Arm C (n=49)	Arm D (n=85)	Total (N=650)
Median age (range), years		59 (28-71)	61 (27-70)	60 (33-70)	60 (41-70)	60 (27-71)
Sex	Male	81	77	76	82	79
	Female	19	23	24	18	21
Race	White	92	92	87	96	92
	Black	5	5	11	1	5
Elevated LDH		66	66	36	32	34
MIPI-c	High/High-int	33	37	42	42	37
	Low/Low-int	67	63	58	58	63
Intensive induction	Yes	74	74	69	68	73
	No	26	26	31	32	27
BTKi	Induction	7.4	7.7	6.1	5.9	7.2
	Maintenance	0	0.4	2.0	0	0.3

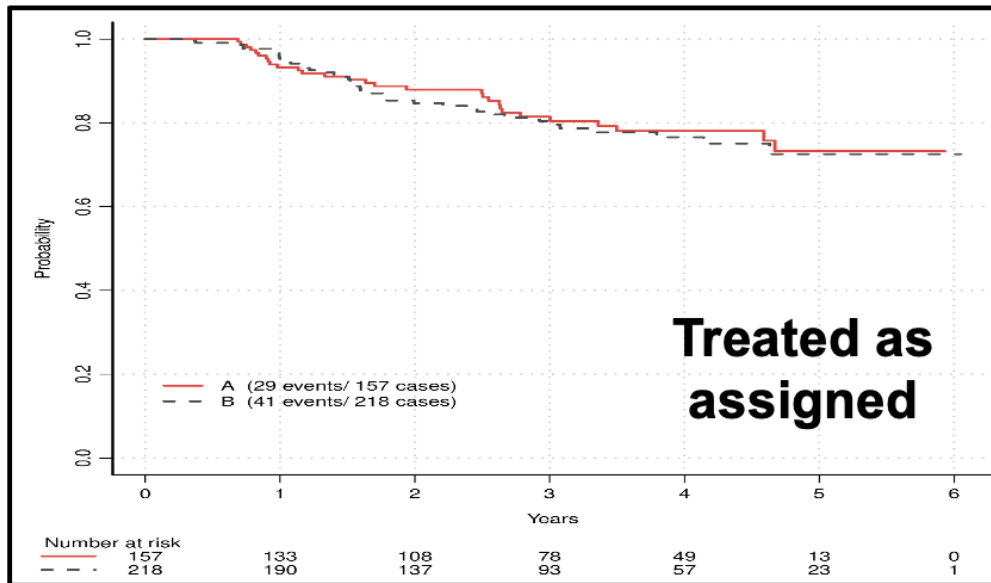
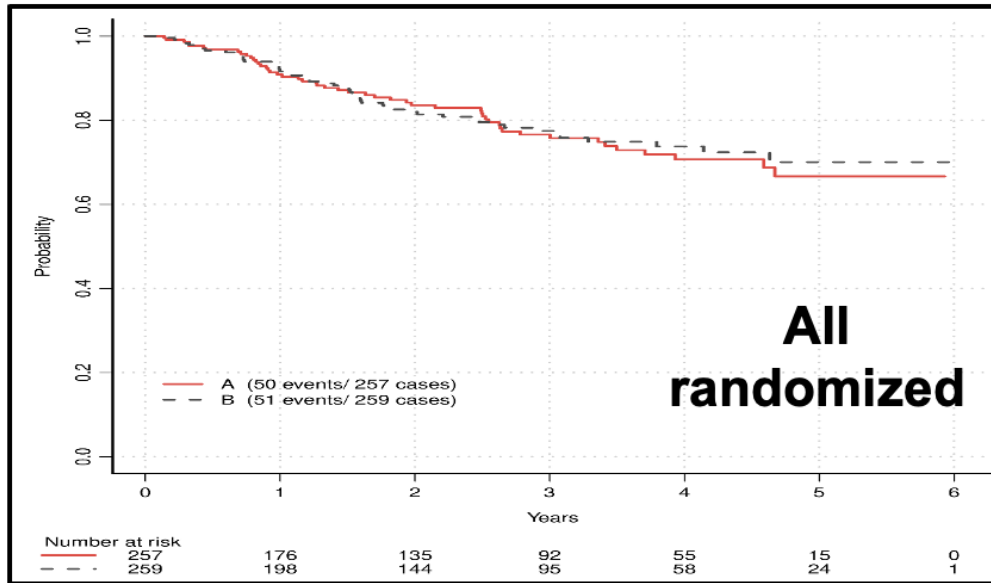
No difference in OS between ASCT + MR vs MR alone



		Arm A vs Arm B All Randomized (n=516)	Arm A vs Arm B Treated as Assigned (n=375)
Efficacy			
OS HR		0.984	-
Estimated OS HR (95% CI)		1.11 (0.71-1.74)	1.00 (0.58-1.74)
P-value		0.66	0.99
		Arm A	Arm B
3-year OS, %	All randomized	82%	83%
	Treated as assigned	86%	85%

Median follow-up: 2.7 years

No difference in PFS between with ASCT + MR vs MR alone

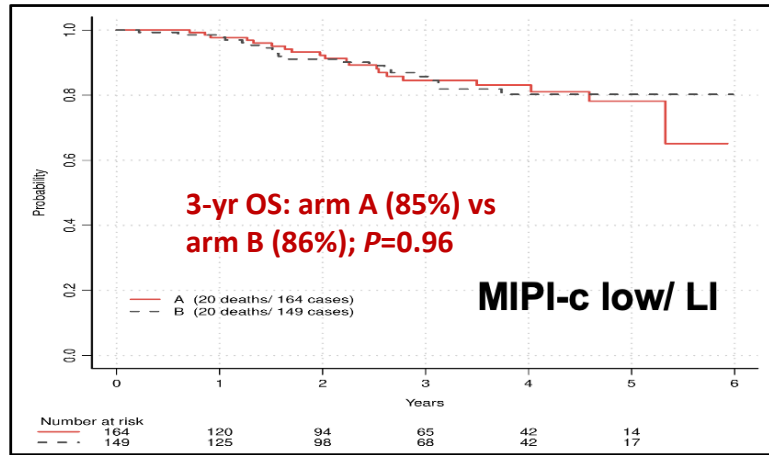


Efficacy		Arm A vs Arm B All Randomized (n=516)	Arm A vs Arm B Treated as Assigned (n=375)
Estimated PFS HR (95% CI)		1.05 (0.71-1.56)	0.95 (0.59-1.54)
P-value		0.79	0.84
		Arm A	Arm B
3-year PFS, %	All randomized	77%	77%
	Treated as assigned	82%	80%

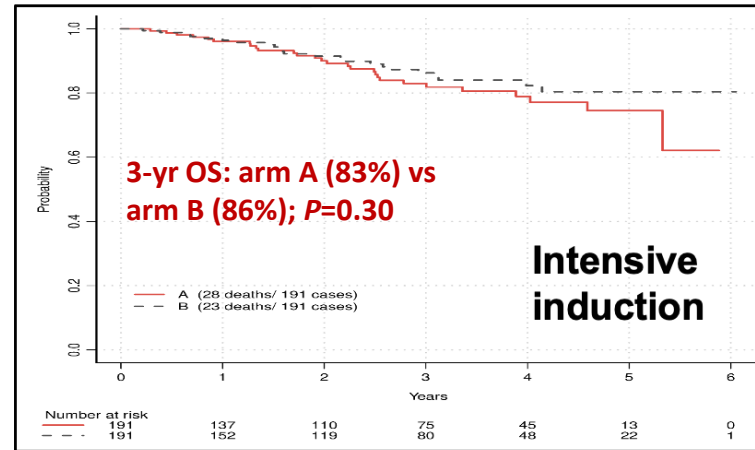
Fenske T. ASH 2024. Abstract LBA-6.

No difference in OS by MIPI/intensity of induction and outcomes in arms C+D

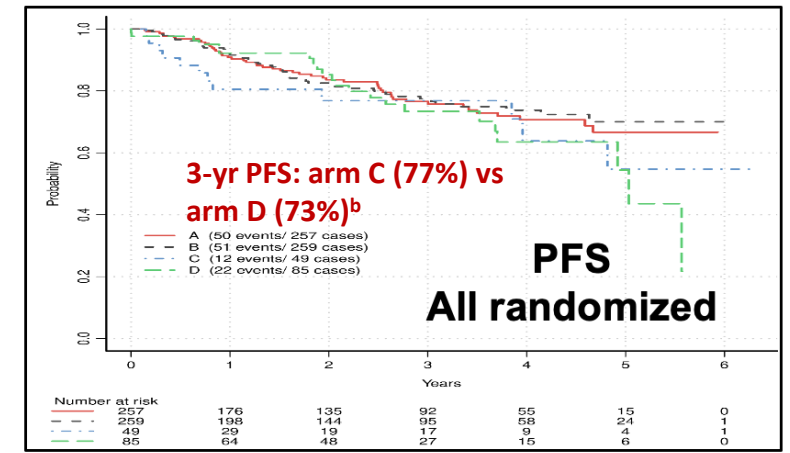
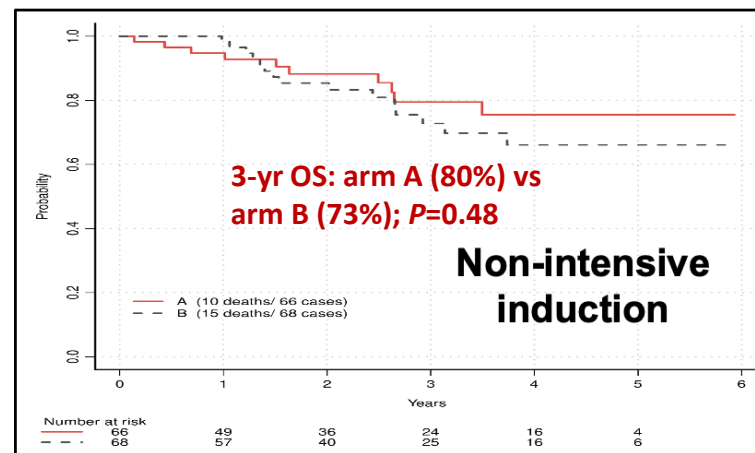
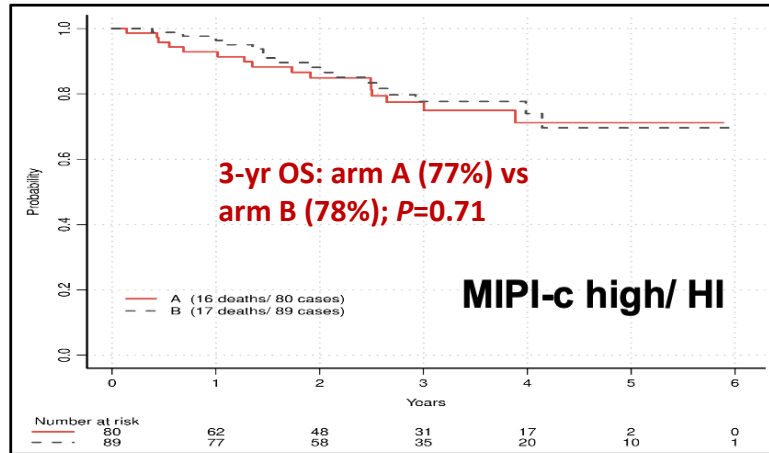
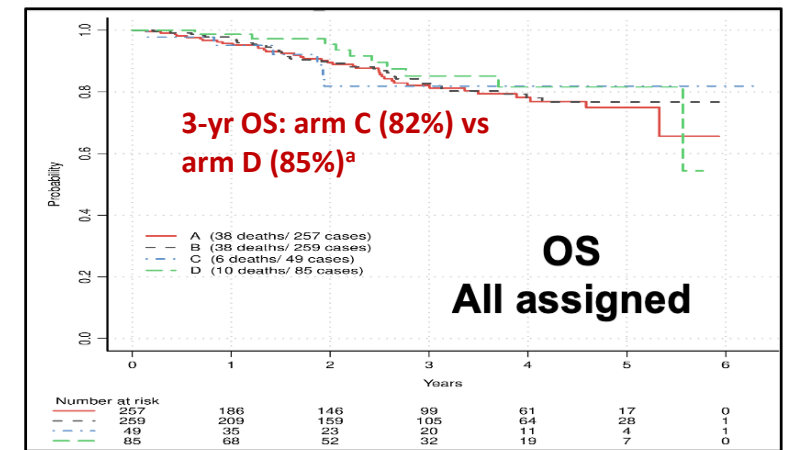
OS by MIPI-c of arms A & B



OS by intensive vs non-intensive induction

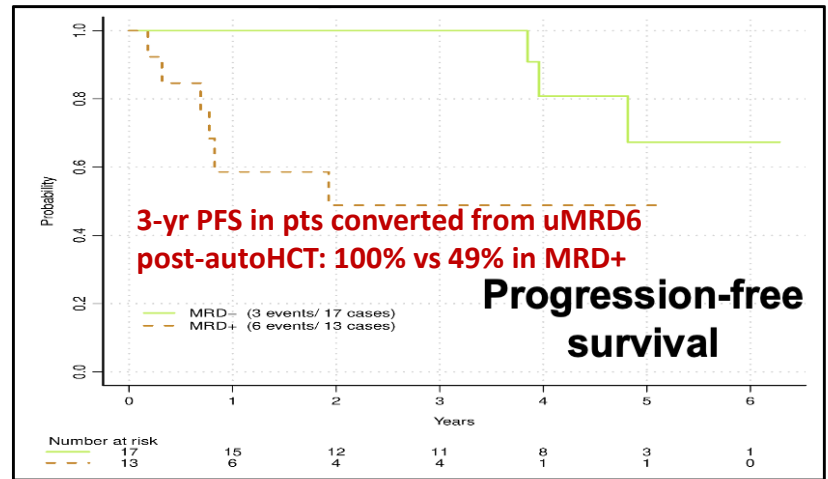
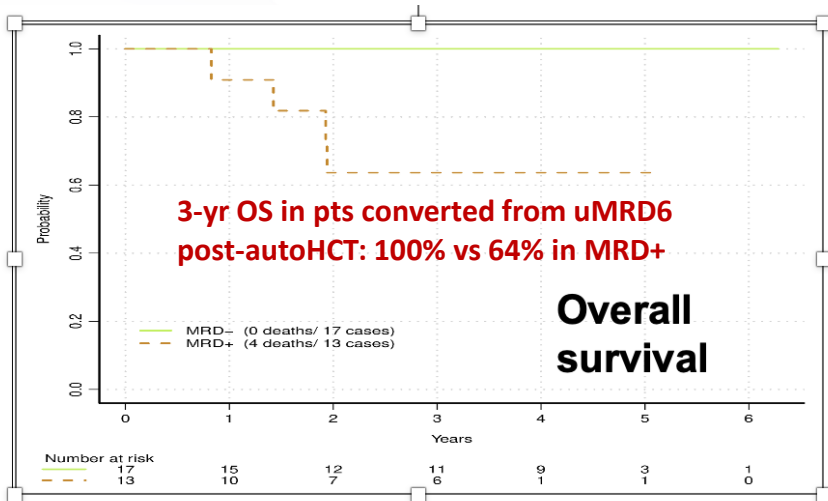


OS (top) and PFS (bottom) of arm C & D



PFS and OS improved in patients who converted to MRD undetectable after ASCT

OS (top) and PFS (bottom) of Arm C



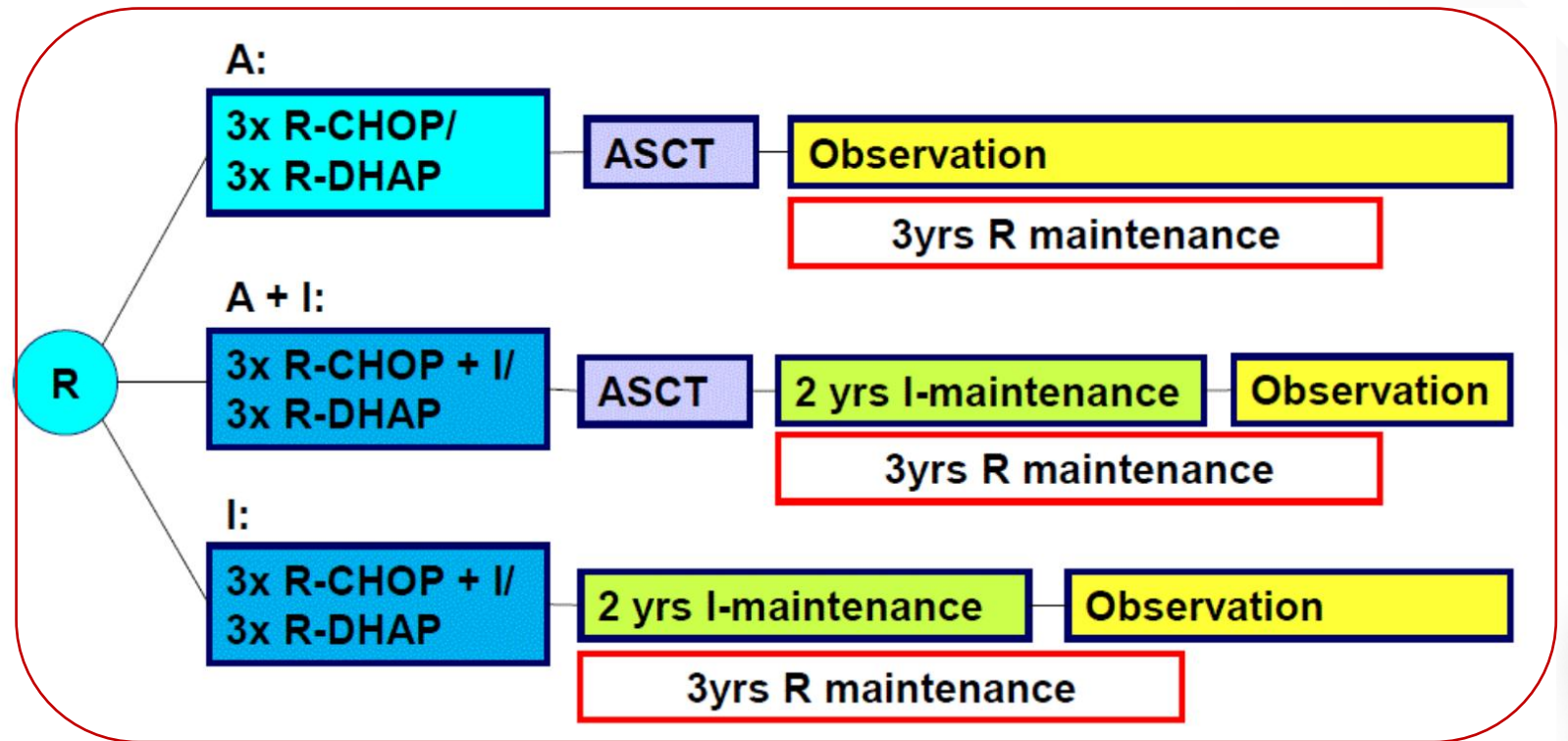
Cause of Death, n (%)	Arm A (n=257)	Arm B (n=259)	Arm C (n=49)	Arm D (n=85)
Lymphoma	12 (4.7)	9 (3.5)	1 (2.0)	2 (2.4)
COVID-19	13 (5.1)	17 (6.6)	1 (2.0)	3 (3.5)
Other	9 (3.5)	8 (3.1)	3 (6.1)	5 (5.8)
Unknown	4 (1.6)	4 (1.5)	1 (2.0)	-

Fenske T. ASH 2024. Abstract LBA-6.

TRIANGLE: does the addition of ibrutinib improve outcomes and preclude the need for ASCT?

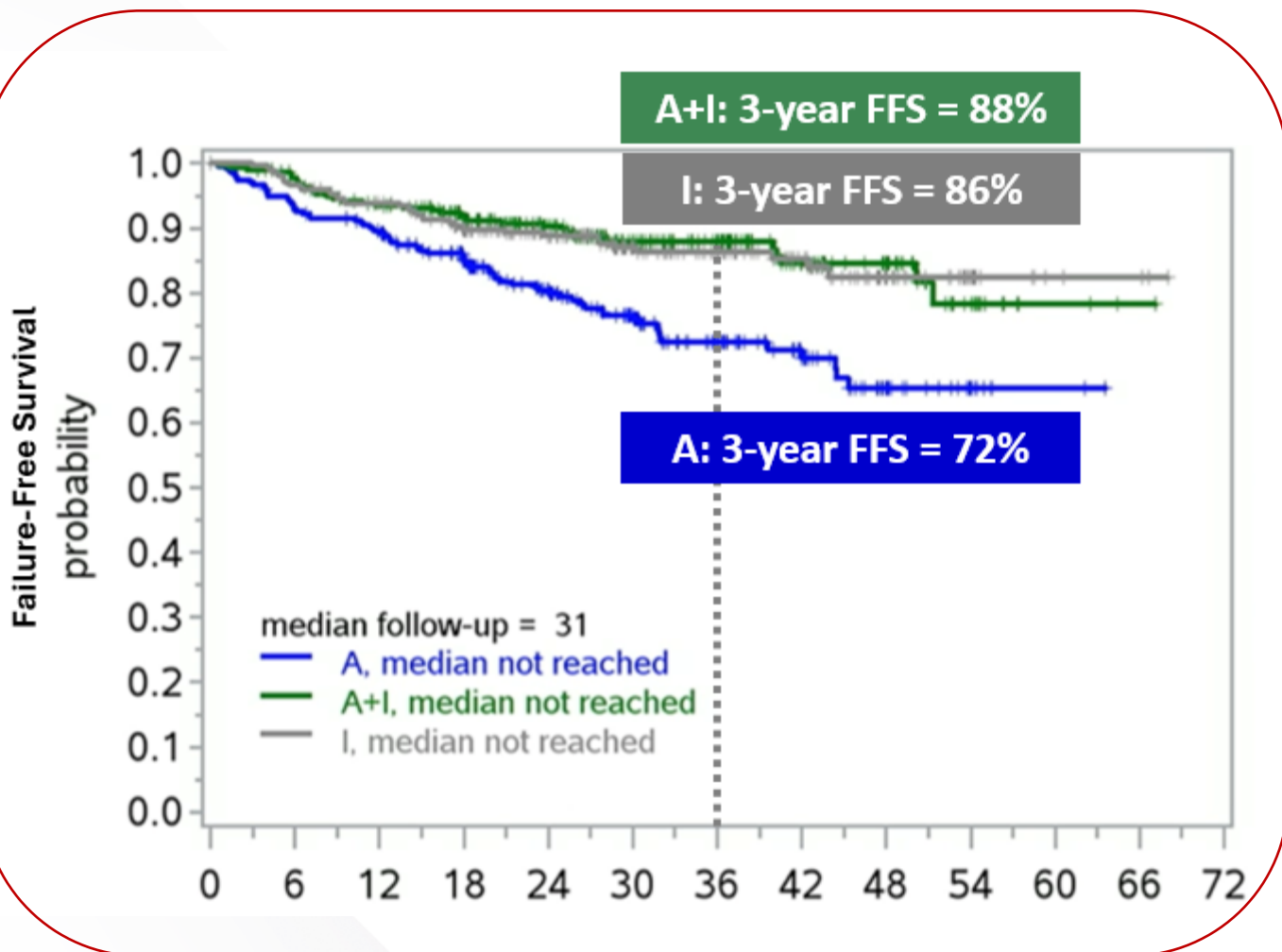
- Previously untreated with MCL
- Stage II-IV
- Younger than 66 years
- Suitable for high-dose cytarabine and ASCT

- **N=870**
- Age: median = 57 (27-68)
- Male: 76%
- ECOG >1 : 1%
- MIPI: Low: 58%, Intermediate: 27%, High: 15%



Rituximab maintenance added in all 3 arms following updated national guidelines (~56% of patients)

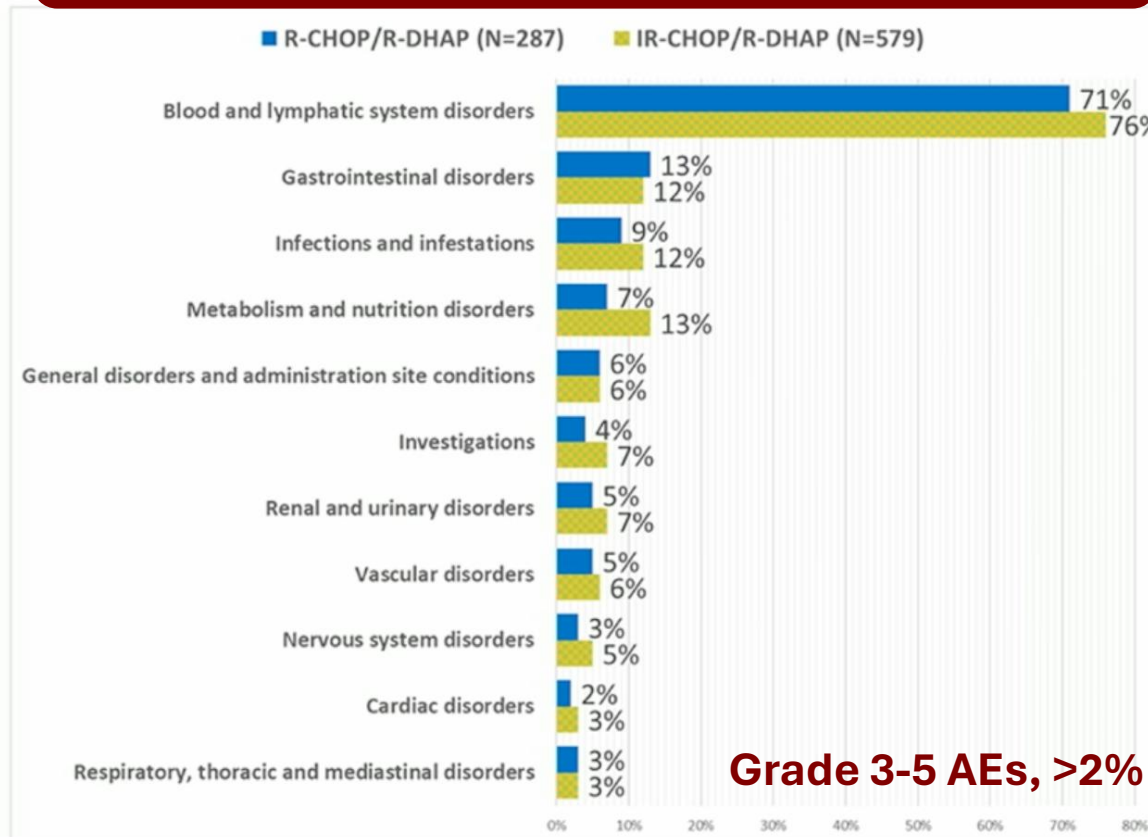
ASCT + ibrutinib with superior FFS compared to ASCT alone. ASCT is not superior to ibrutinib.



Is there a FFS benefit of ASCT in first remission with inclusion of ibrutinib?
Likely NO

Ibrutinib added to toxicity during maintenance

Addition of ibrutinib to R-CHOP/R-DHAP did not significantly increase toxicity during induction

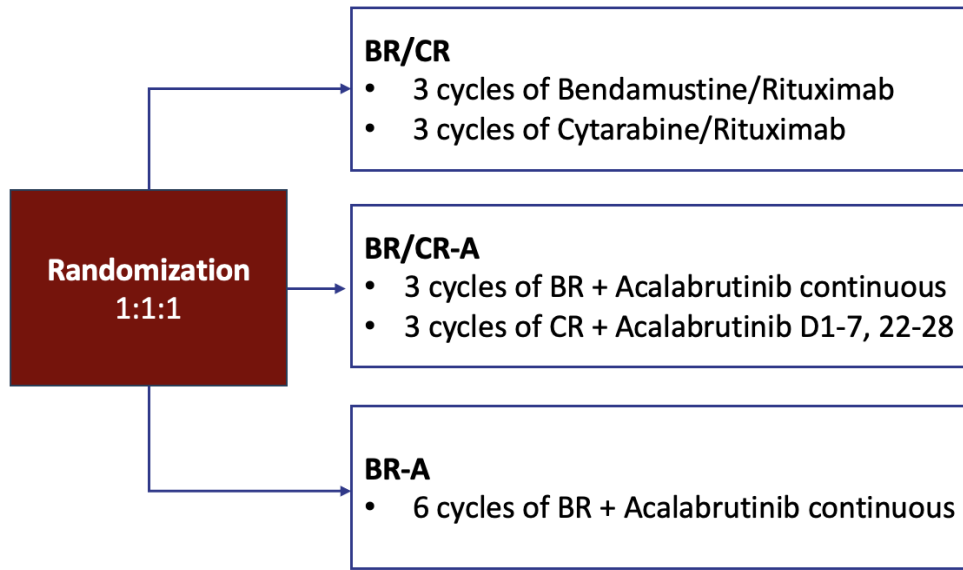


Addition of ibrutinib to maintenance following ASCT led to increased toxicity

<u>Grade 3-5 AEs</u>	Group A (n=238)	Group A+I (n=231)	Group I (n=269)
Blood & lymphatic system disorders	51 (21%)	114 (50%)	74 (28%)
Neutrophil count decreased	40 (17%)	101 (44%)	62 (23%)
Infections & infestations	32 (13%)	58 (25%)	52 (19%)
Lung infection	13 (5%)	22 (10%)	18 (7%)

Grade 3-5 Infections w/ rituximab maintenance
A+I (n=149): 31% **I (n=155): 25%**

Addition or Substitution of Acalabrutinib in Intensive Frontline Chemoimmunotherapy for Patients ≤ 70



Key Eligibility

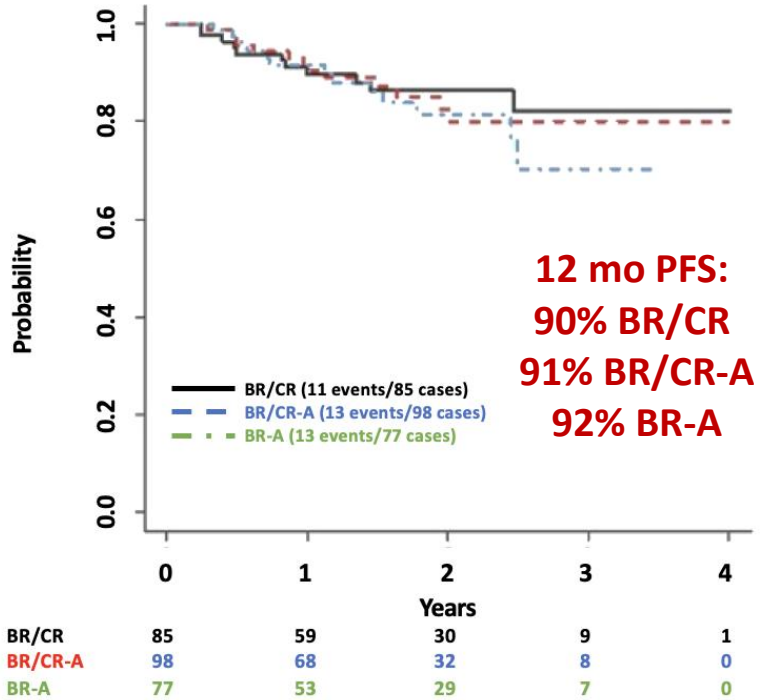
- Untreated mantle cell lymphoma
- Age 18 - 70
- ECOG PS 0-2
- Adequate organ and marrow function

Hypothesis:
Acalabrutinib to either experimental arm (BR/CR-A or BR-A) will improve the PET/CT CR/MRD negative rate by 15%

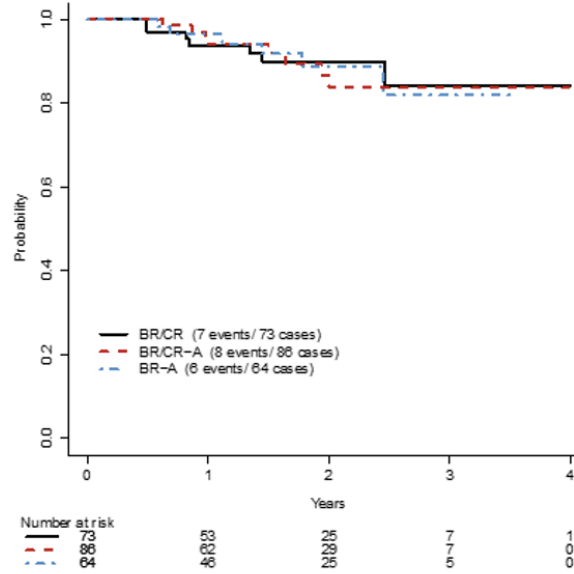
Patient Characteristics, All Randomized Patients, n (%)		BR/CR (n=128)	BR/CR-A (n=129)	BR-A (n=102)
Aged ≥65		37 (29)	36 (28)	35 (34)
Race	White	119 (93)	109 (84)	90 (88)
	Amer Indian/Native	–	4 (3)	–
	Asian	–	3 (2)	–
	Black	3 (2)	4 (3)	4 (4)
	Native Hawaiian	–	1 (1)	–
Ethnicity, Hispanic		6 (5)	5 (4)	6 (6)
MIPI	Low	22 (17)	24 (19)	19 (19)
	Intermediate	55 (43)	55 (43)	44 (43)
	High	51 (40)	50 (39)	39 (38)
Morphology, blastoid/pleomorphic		9 (7)/2 (2)	7 (5)/8 (6)	9 (9)/4 (4)

No significant difference in PFS/OS by arm

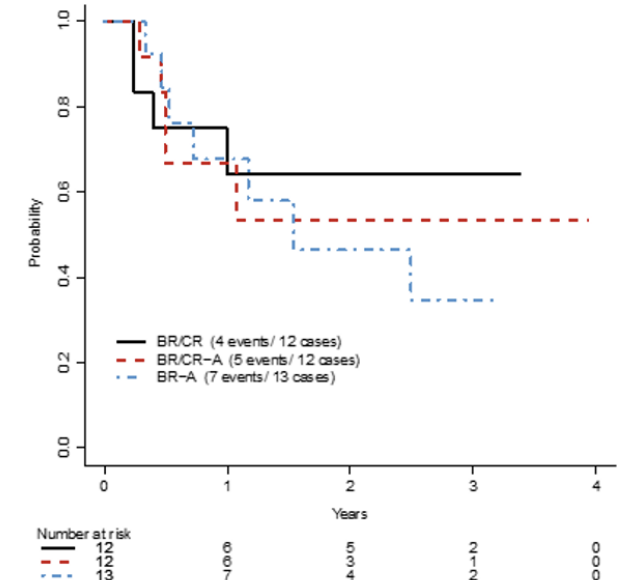
Approx 75% PETCR/uMRD across arms



PFS



uMRD



MRD +

Wagner-Johnston et al. ASH 2024

Conclusion/interpretation E4181

**Addition of
acalabrutinib to
BR/CR added toxicity
without improving
efficacy**

**BR-A was not
superior and closed
early by the DSMC**

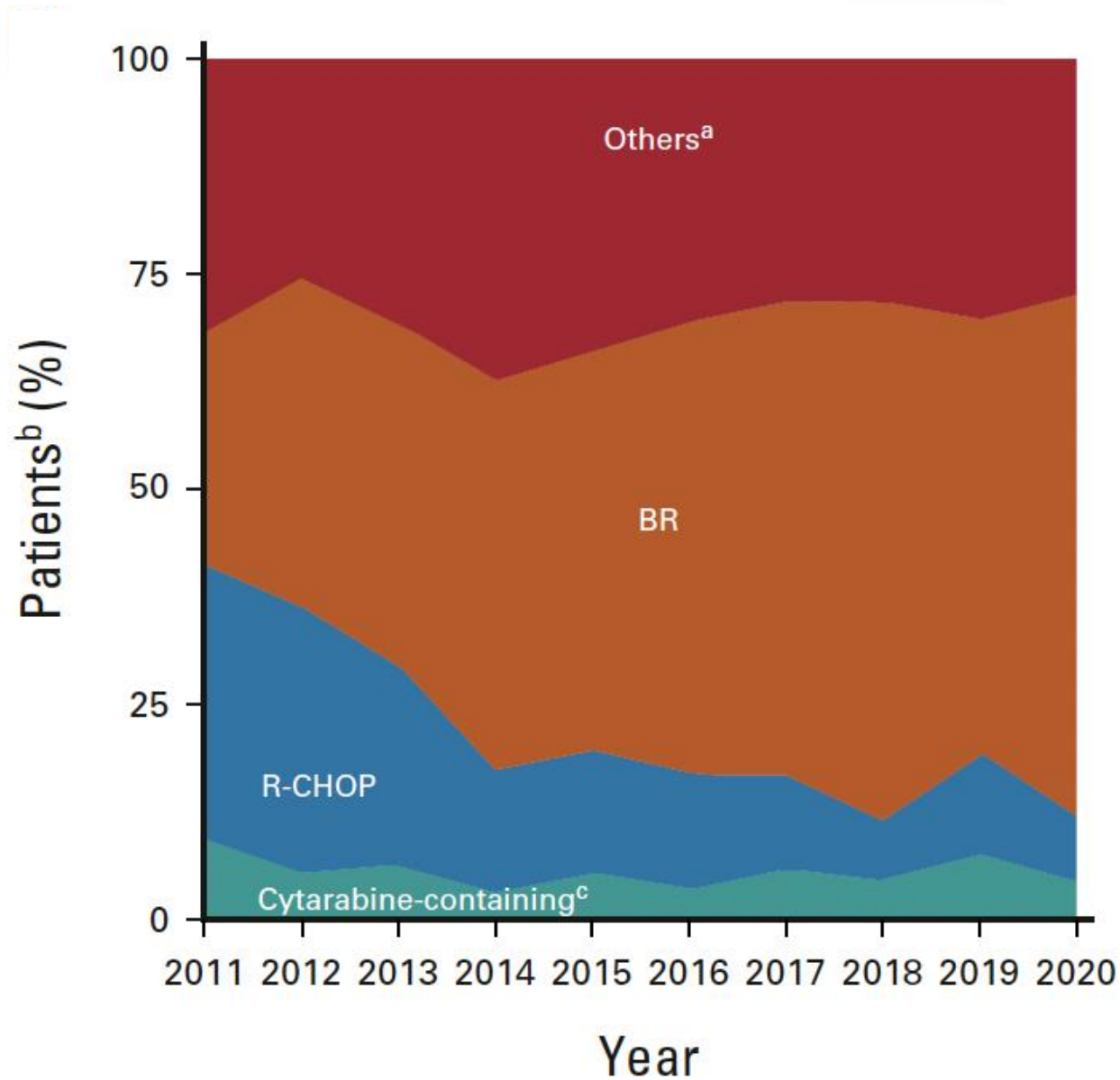
**Adopt BR-A as
induction for all
patients**

**Reserve A for use
in second line**

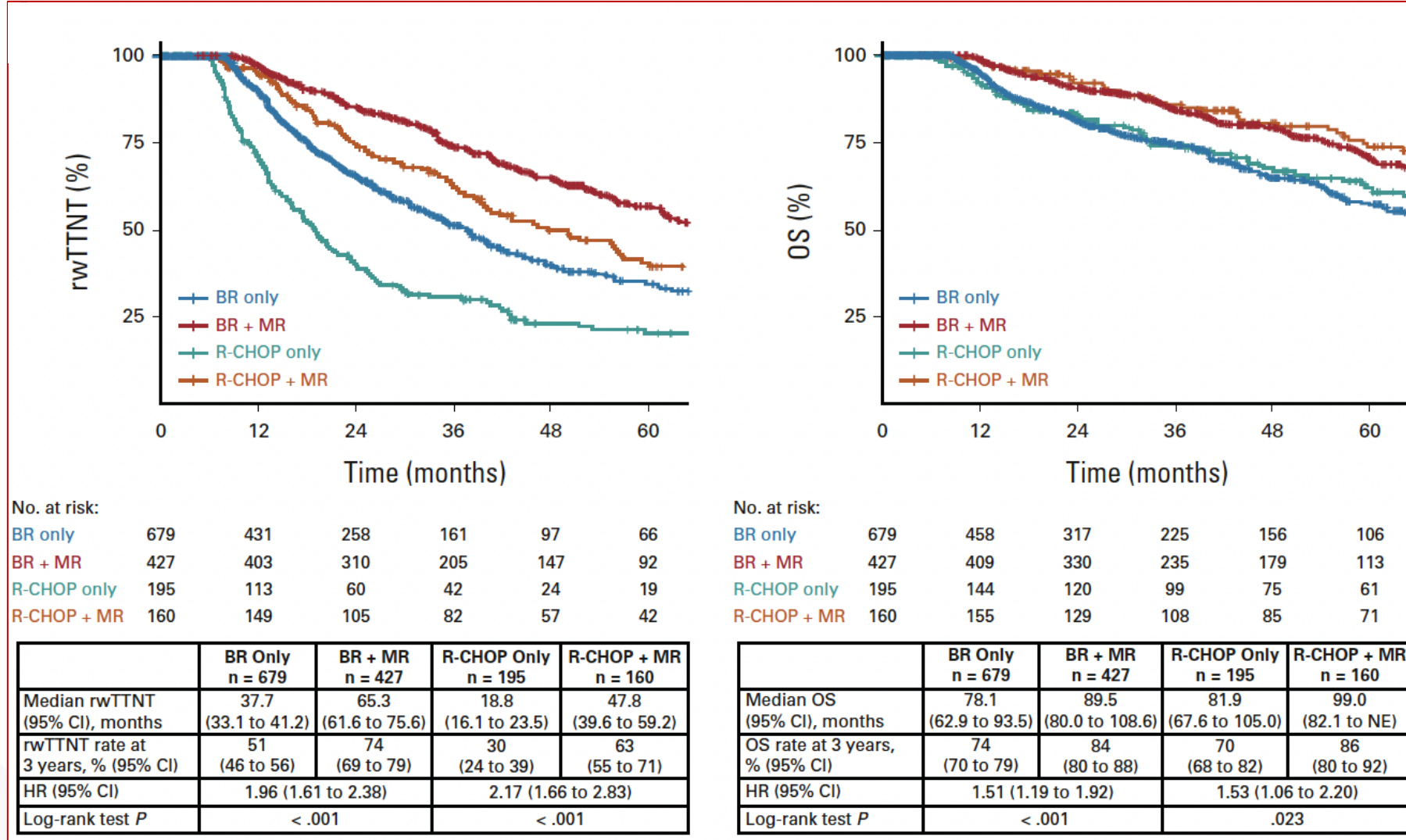
**Management of patients not
appropriate for intensive
chemotherapy**

“Real world” Front-line management older patients in the US

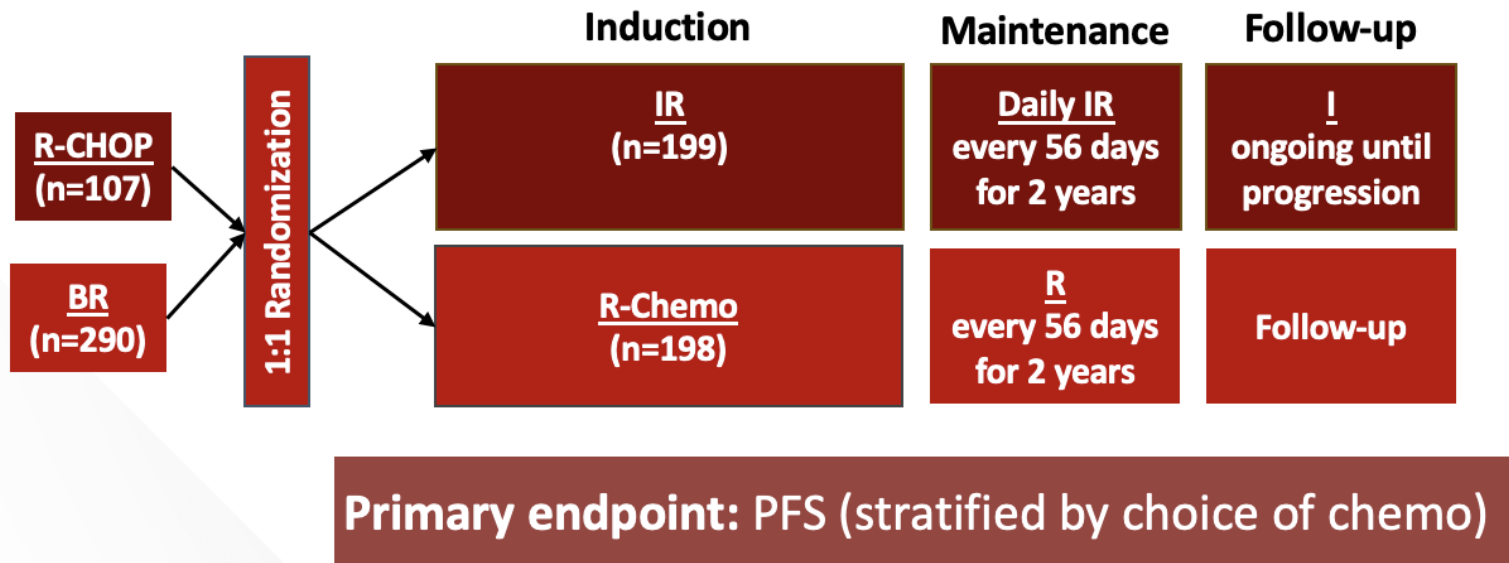
Age \geq 65



Rituximab maintenance associated with improved TTNT and OS



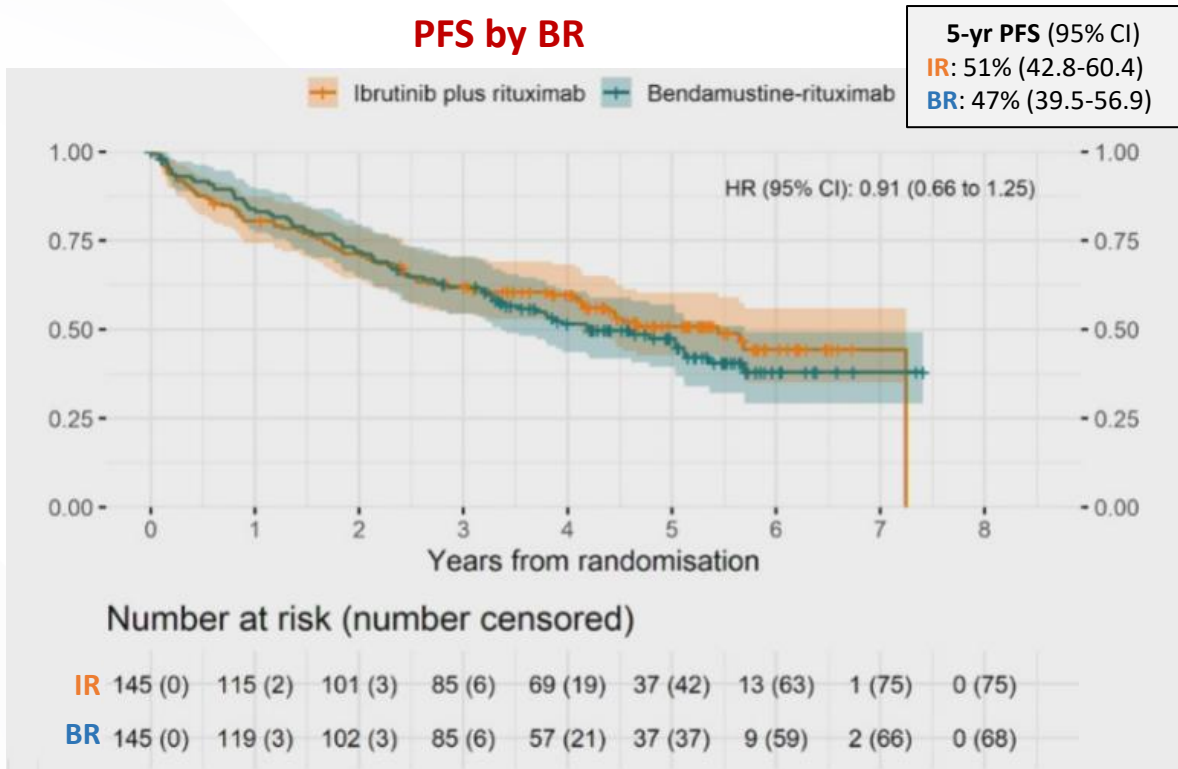
Phase 2/3 ENRICH: Ibrutinib-R vs R-chemo in patients ≥ 60



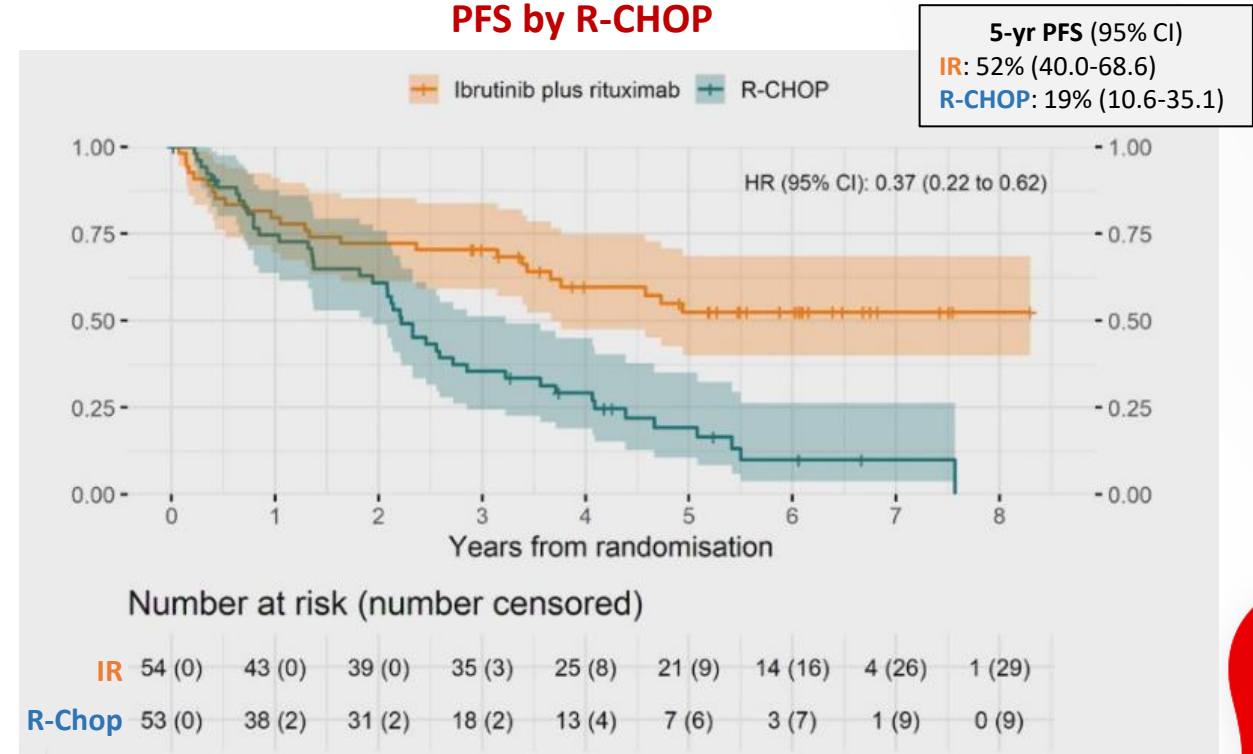
Patient Characteristics (ITT)		IR (n=199)	R-Chemo (n=198)
Median age (IQR), yr		74 (70-77)	74 (70-78)
Male		75.4%	73.7%
ECOG	0	62.3%	54.0%
	1	32.2%	40.4%
	2	5.5%	5.6%
Stage IV		87.9%	92.4%
Blastoid		5.6%	7.8%
Ki-67 $\geq 30\%$		38.7%	45.2%
MPI	Low	11.6%	11.8%
	Intermediate	32.3%	31.3%
	High	56.1%	56.9%
TP53mut		27.5%	24.0%

Difference in PFS driven by RCHOP treated patients

PFS by BR



PFS by R-CHOP



Overall PFS in the ITT

- Median F/U of 47.9 mo
- **IR: 65 mo** (52.7-NE)
- **R-Chemo: 42 mo** (32.7-55.3)
 - HR 0.69 (95% CI, 0.52-0.90); $P=0.003$

Lewis DJ et al. ASH 2024.

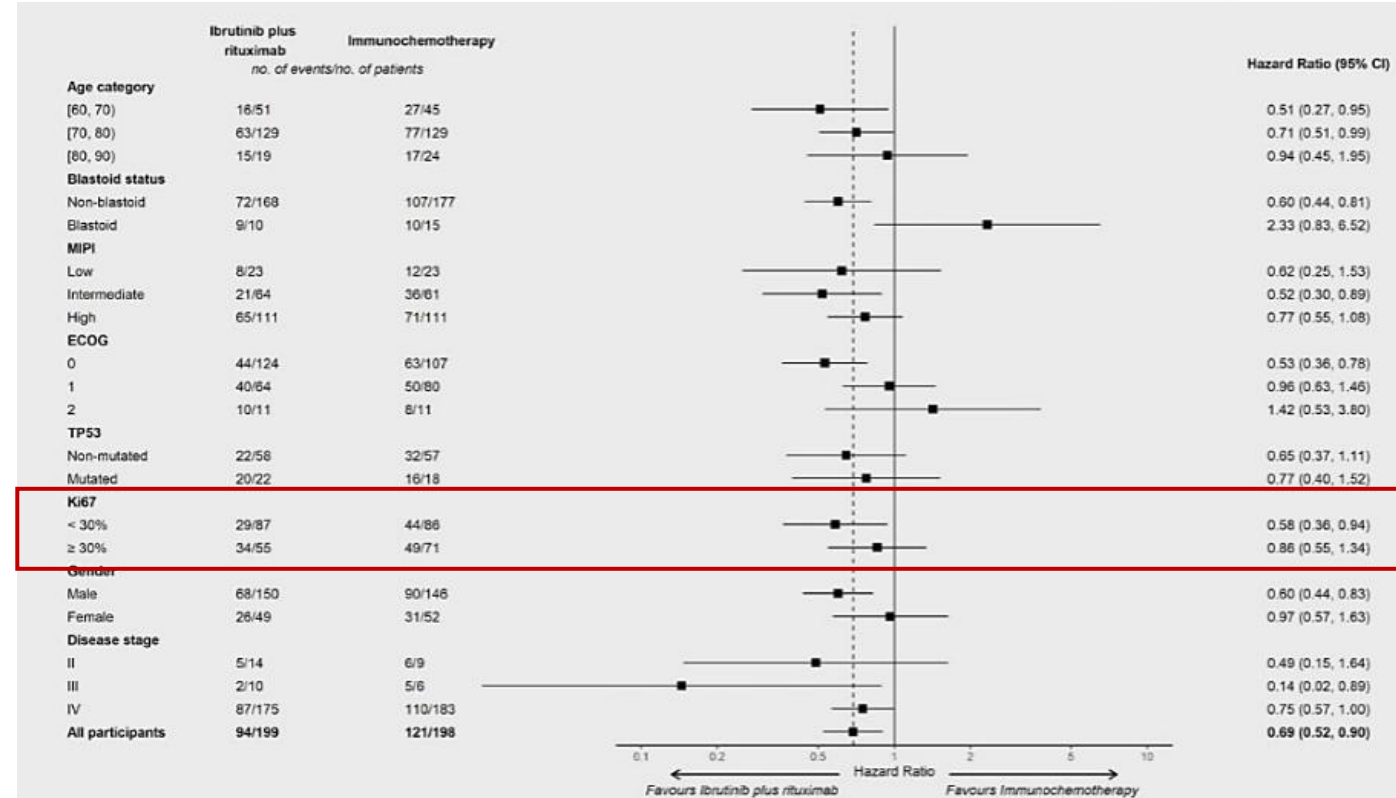
Median PFS poor with IR in blastoid disease though more favorable with aberrant TP53

Median PFS (95% CI)	IR	R-Chemo
Blastoid disease	7 m (1.9-NE)	21 m (9.8-NE)
HR	2.33 (0.83-6.52)	
TP53mut	19 m (4.2-46.2)	9 m (2.9-25.7)
HR	0.77 (0.40-1.52)	

Gr3/4 AEs During Induction and Maintenance in the Safety Population^a

Gr3/4 AE Overview	IR (n=198)	BR (n=143)	R-CHOP (n=52)
Total	63.1%	67.8%	69.2%
All cardiac AEs	22.2%	4.9%	13.5%
All bleeding AEs	5.1%	2.1%	5.8%
Atrial fibrillation	6.1%	0.7%	0%
Neutropenia	9.1%	18.9%	21.2%
Neutropenic sepsis	3.0%	1.4%	15.4%
Corona virus infection	5.1%	7.0%	0%

PFS in subgroups



Lewis DJ et al. ASH 2024.

BR + Ibrutinib (SHINE) with Improved PFS But Not OS

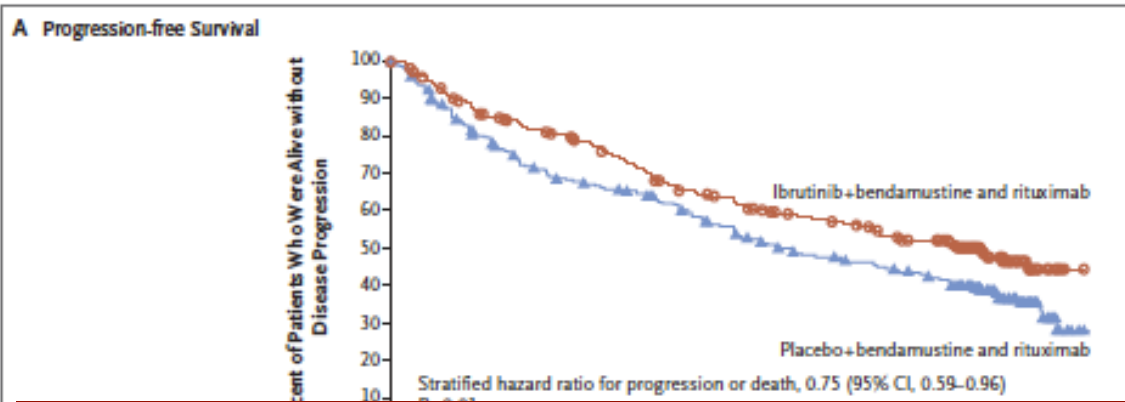
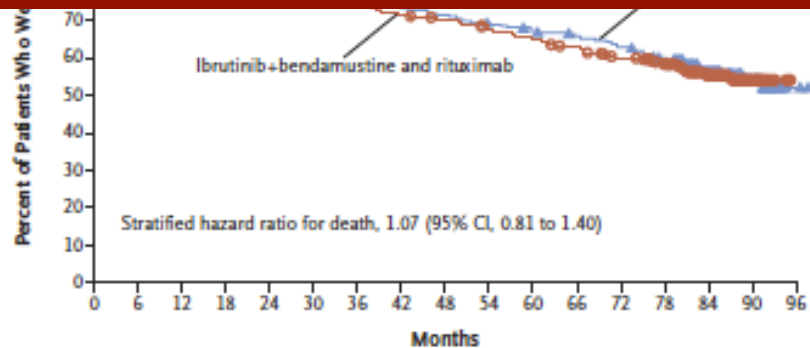


Table 3. Causes of Death Due to Adverse Events during Treatment.*

Cause	Ibrutinib Group (N=261)	Placebo Group (N=262)
Respiratory disorder — no.	1	2
General physical health deterioration — no.	1	0
Traumatic intracranial hemorrhage — no.	1	0
Tumor lysis syndrome — no.	1	1
Cancer — no.‡	1	2
Ischemic stroke — no.	1	0
Hemorrhagic stroke — no.	0	1

Ibrutinib voluntarily withdrawn in US for MCL



No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Ibrutinib+ bendamustine and rituximab	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
Placebo+ bendamustine and rituximab	262	244	223	212	203	197	188	177	171	165	159	154	147	137	90	31	2

ECHO Study of Bendamustine plus Rituximab +/- Acalabrutinib in older patients

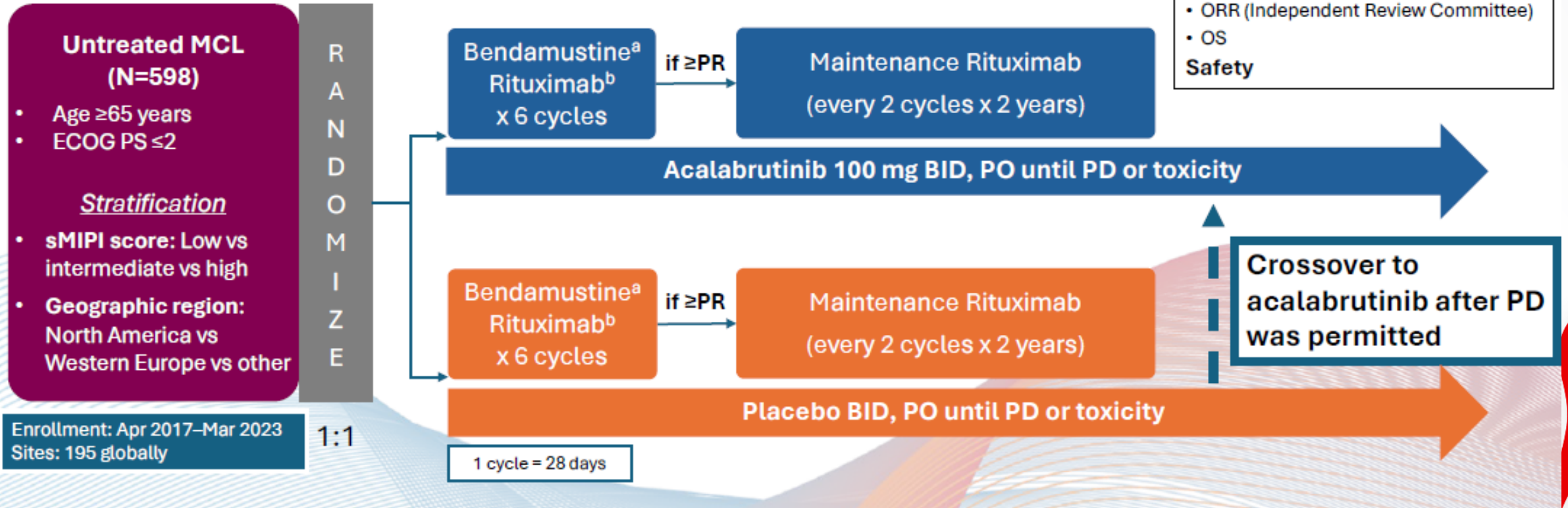
ECHO: multicenter, double-blind, placebo-controlled, Ph 3 trial

Primary endpoint:

- PFS (Independent Review Committee)

Key secondary endpoints:

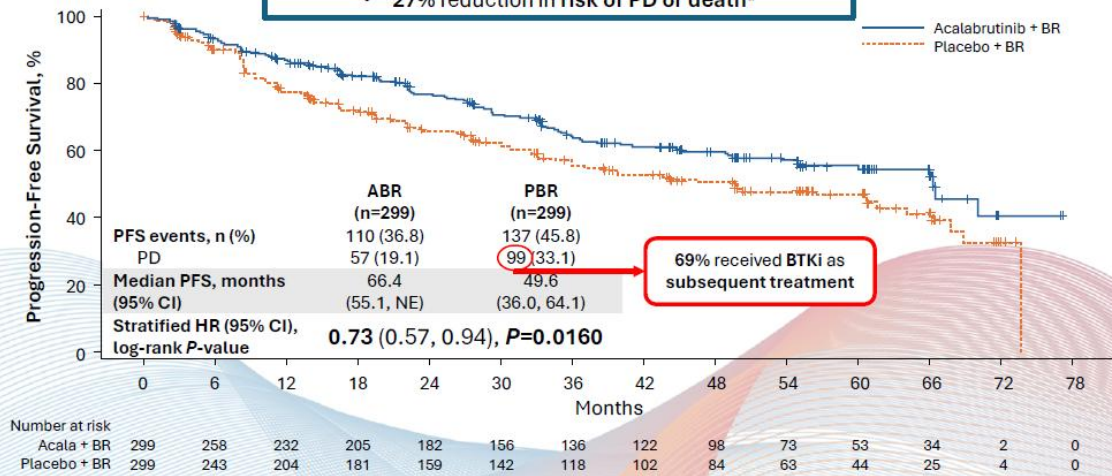
- ORR (Independent Review Committee)
- OS
- Safety



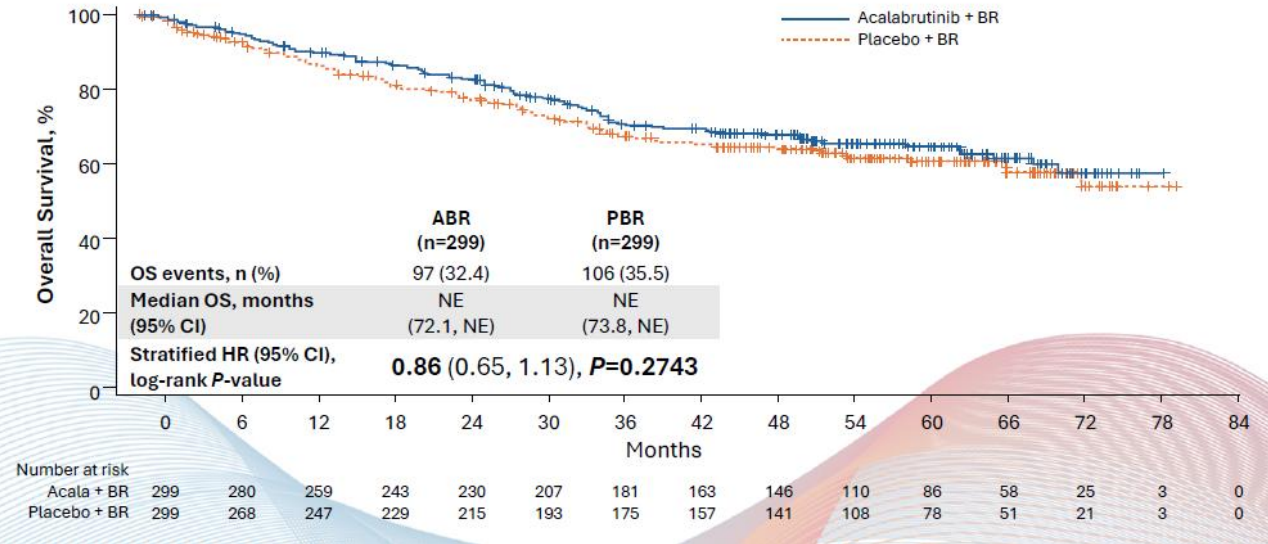
Acalabrutinib associated with improved PFS without OS benefit

PFS (primary endpoint) Was Significantly Improved With Acalabrutinib + BR

- Significant improvement in median PFS by ~17 mo
- 27% reduction in risk of PD or death^a

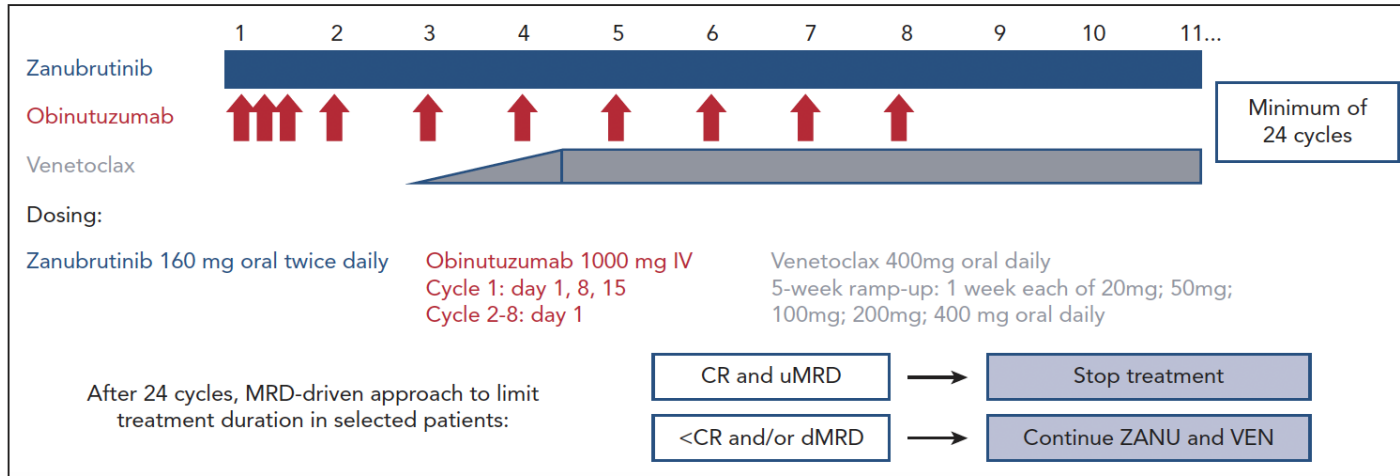


Overall Survival Including Crossover



Management of patients with TP53 aberrancy

TP53 mutated MCL: zanubrutinib + obinutuzumab + venetoclax

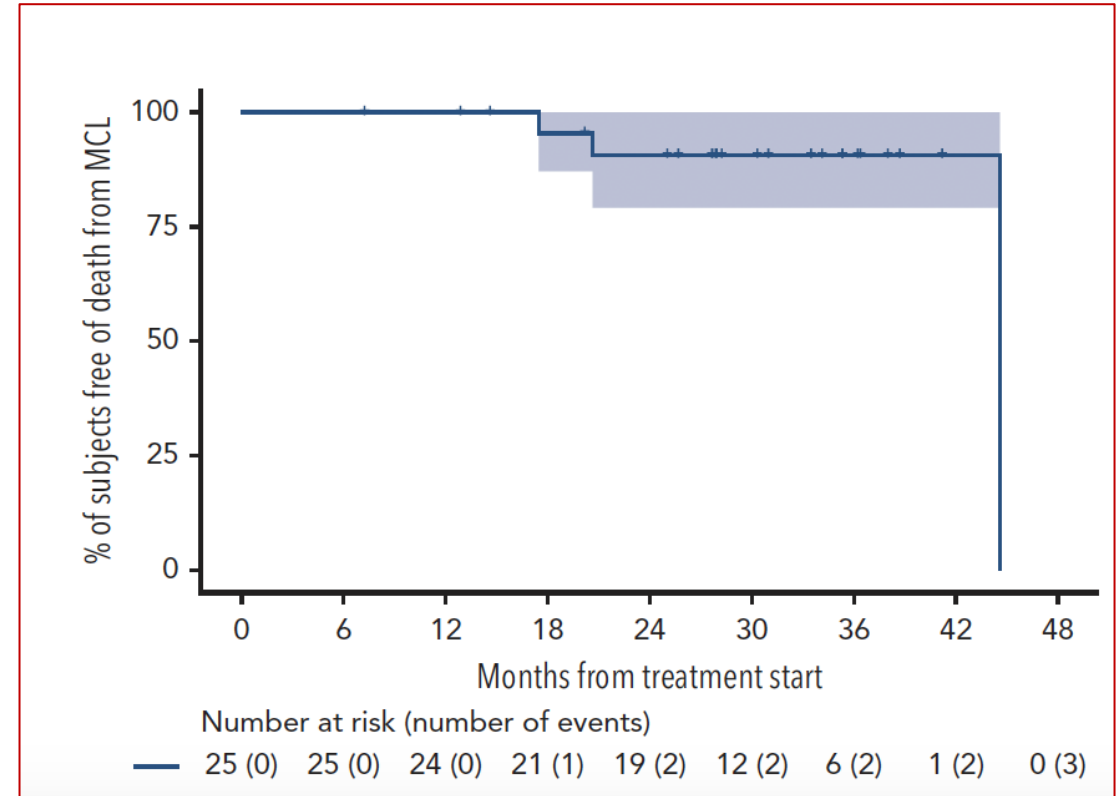
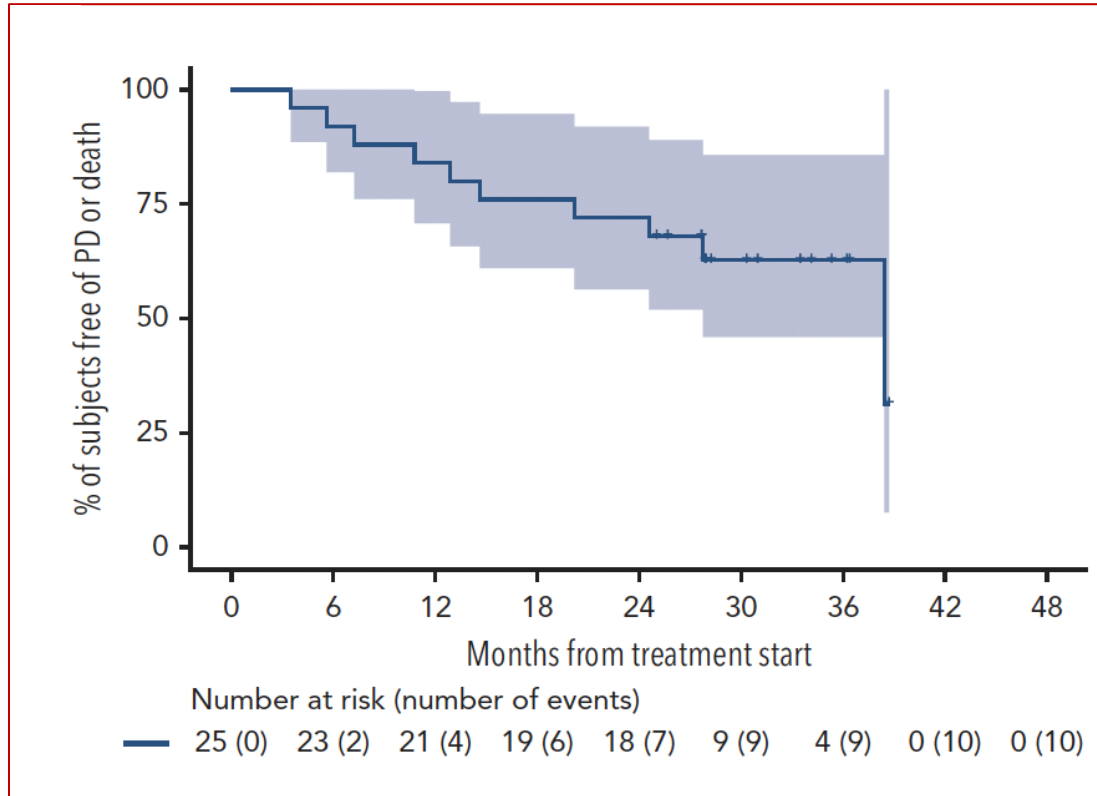


Kumar et al. Blood 2025

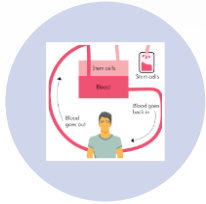
N=25 heterogeneous patient population

MCL histology	
Blastoid	5 (20%)
Classic	17 (68%)
Non-nodal leukemic*	3 (12%)
Disease stage, IV	
	25 (100%)
Ki-67 proliferation rate	
<30%	8 (32%)
30%-49%	6 (24%)
At least 50%	7 (28%)
Unknown	4 (16%)
SOX-11 expression by IHC	
Positive	12 (48%)
Negative	10 (40%)
Unknown	3 (12%)
TP53 expression by IHC§	
Positive	18 (72%)
Negative	3 (12%)
Unknown	4 (16%)
IGHV mutation	
Mutated	5 (20%)
Unmutated	13 (52%)
Unknown	7 (28%)
17p deletion by FISH	
Yes	12 (48%)
No	13 (52%)

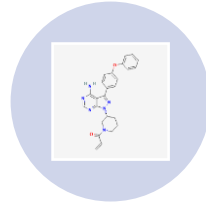
PFS encouraging, though follow-up too limited to determine if discontinuation in uMRD is a good strategy.



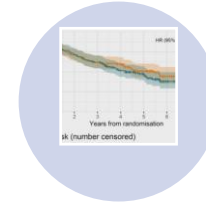
Summary



ASCT does not improve outcomes in uMRD patients



Addition of BTKi with intensive induction appears to improve PFS



BR + MR with similar efficacy in older patients compared to IR



Addition of BTKi to BR improves PFS with added toxicity



Novel agent combinations promising in TP53 mutated patients

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