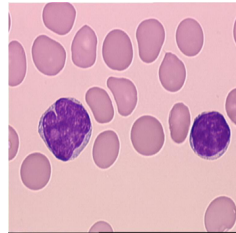
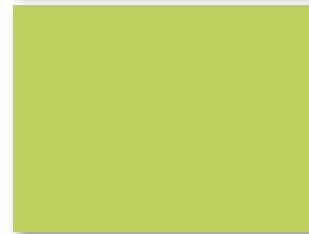
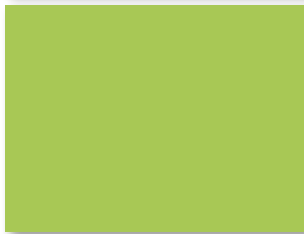
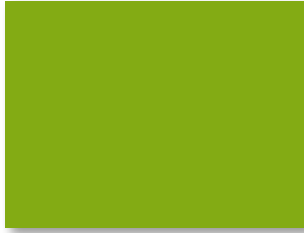
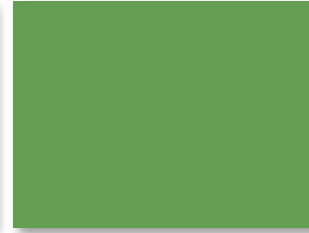


**Please note, these are the actual
video-recorded proceedings from the
live CME event and may include the use of
trade names and other raw, unedited content.**

Mantle cell lymphoma: *Role of targeted therapies*

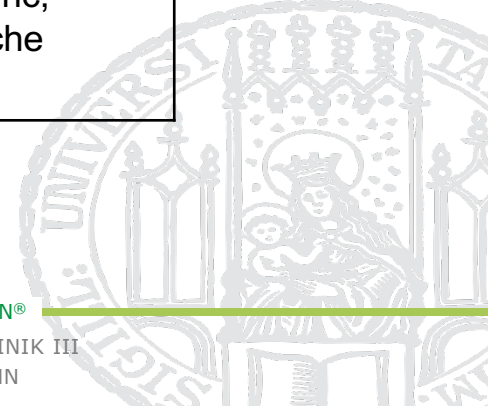


Prof. Dr. Martin Dreyling
Medizinischen Klinik III
LMU München



Disclosures

Advisory Committee	Bayer HealthCare Pharmaceuticals, Celgene Corporation, Gilead Sciences Inc, Janssen Biotech Inc, Pfizer Inc, Roche Laboratories Inc
Speakers Bureau	Bayer HealthCare Pharmaceuticals, Celgene Corporation, Gilead Sciences Inc, Janssen Biotech Inc, Roche Laboratories Inc
Other Remunerated Activities	Celgene Corporation, Janssen Biotech Inc, Mundipharma International Limited, Roche Laboratories Inc



Case presentation 9: Dr Brenner

66-year-old man evaluated for kidney stones and found to have abnormal bowel wall thickening

- Colonoscopy: MCL with extensive GI involvement
- Observed for 2 years
- Developed acute onset GI bleed
 - Colonoscopy: Significant disease in stomach requiring treatment
- Received BR x 6 cycles
 - Tolerated well but the patient did not achieve CR



Case presentation 10: Dr Nadeem

64-year-old man

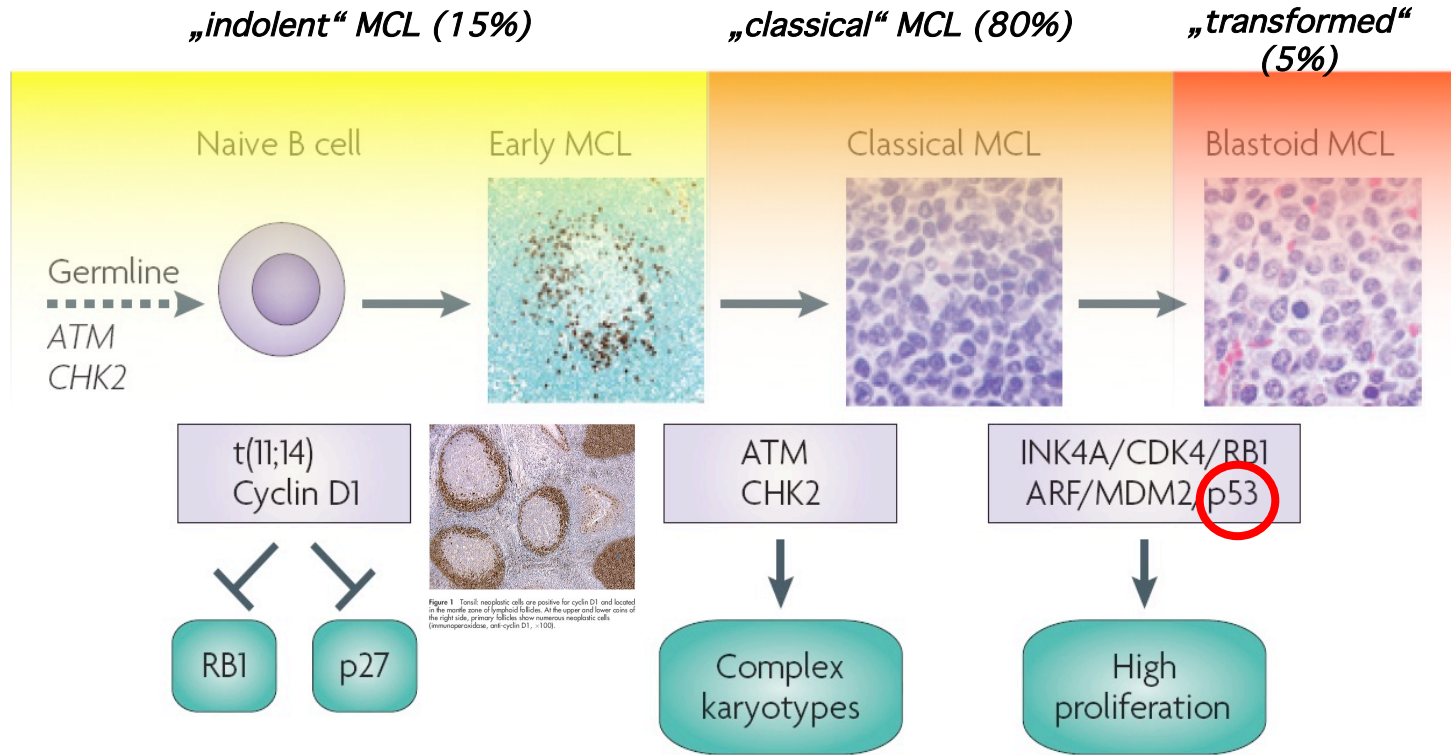
- 2012: Diagnosed with MCL
 - MIPI 5.8 (INT), Ki-67 20%
 - Received 6 cycles of Nordic regimen (R-maxi-CHOP/HiDAC) followed by ASCT
 - Complete remission
- February 2017: Dysphagia
 - Imaging: Compressive adenopathy
 - Biopsy: Recurrent MCL
 - Ibrutinib for 2 months: Complete remission
- June 2017: AlloSCT
- Currently on ibrutinib maintenance on clinical trial



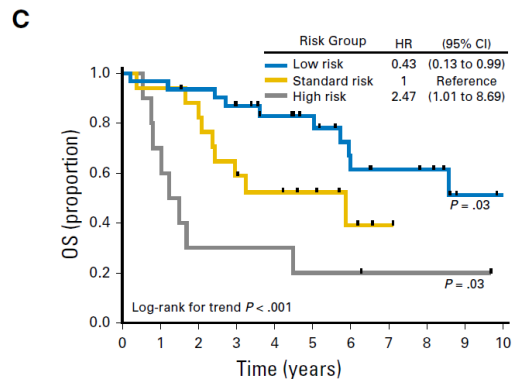
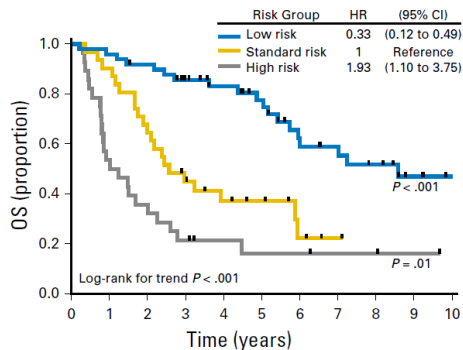
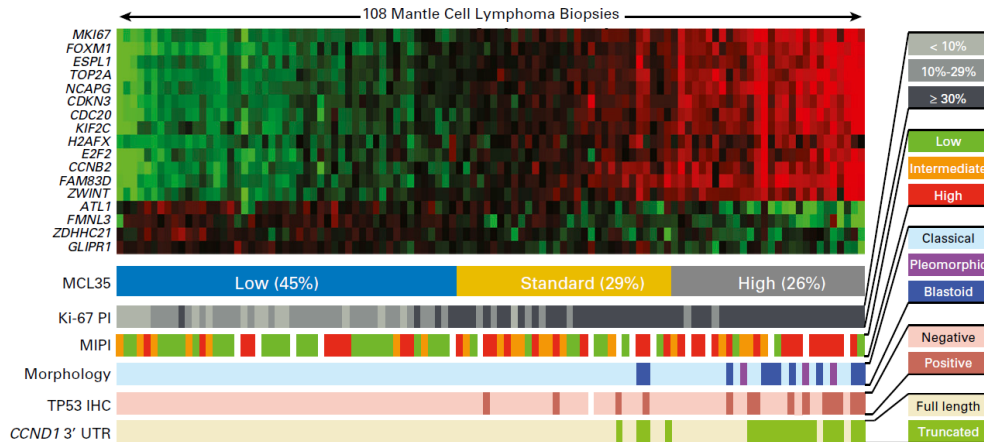
Compressive adenopathy



MCL: A spectrum of disease



Risk factor proliferation: MCL 35

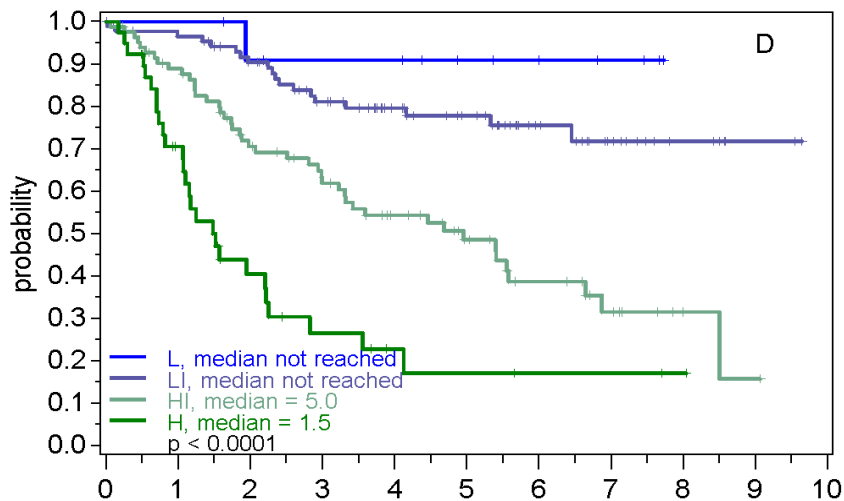


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Combined MIPI-c Overall survival

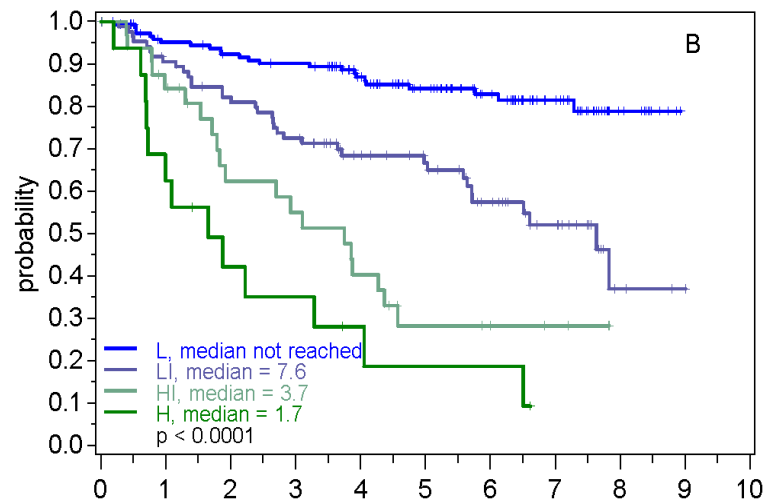
Patients >65 years



Numbers At Risk

	0	1	2	3	4	5	6	7	8	9	10
L	12	10	9	6	4	3	0	0	0	0	0
LI	88	82	72	58	45	37	21	13	6	2	0
HI	83	70	52	42	32	22	14	8	2	1	0
H	39	24	12	7	4	3	2	1	0	0	0

Patients <65 years



Numbers At Risk

	0	1	2	3	4	5	6	7	8	9	10
L	150	135	129	125	101	80	61	37	11	0	0
LI	87	76	67	60	45	39	27	17	3	0	0
HI	33	26	17	15	11	6	4	3	0	0	0
H	16	10	6	5	3	2	0	0	0	0	0

young patient (≤ 65)

elderly patient (>65)

compromised patient

First line treatment

**dose-intensified
immuno-chemotherapy**
(e.g. R-CHOP, high dose Ara-C)
⇒ Autologous SCT
⇒ Rituximab maintenance

**conventional
immuno-chemotherapy**
(e.g. R-CHOP, VR-CAP, BR)
↓
Rituximab maintenance

**Best supportive care?
R-Chlorambucil
BR (dose-reduced)
R-CVP**

1. relapse

immuno-chemotherapy
(e.g. R-BAC, BR)
or targeted approaches
↓
discuss:
- allogeneic SCT

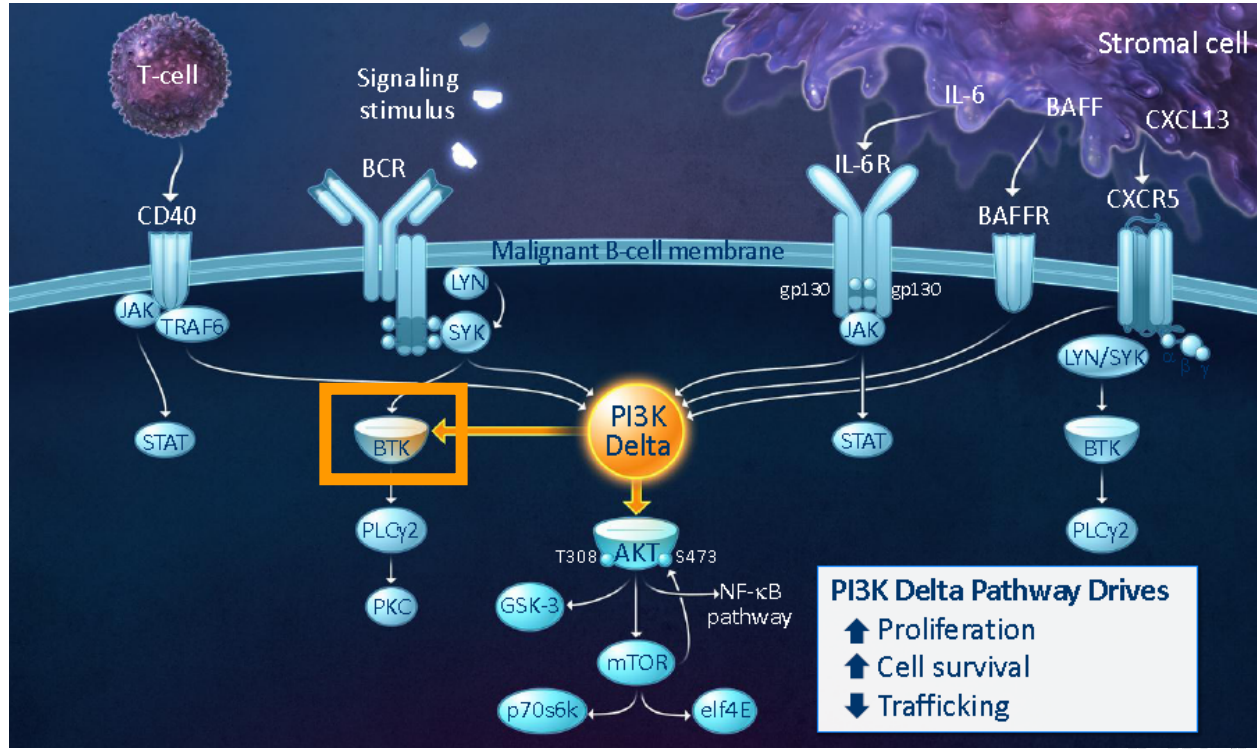
immuno-chemotherapy
(e.g. BR, R-BAC)
or targeted approaches
↓
discuss:
- Rituximab maintenance
- radioimmunotherapy

Immuno-chemotherapy
(e.g. BR)
or targeted
approaches

higher relapse

**Targeted approaches: Ibrutinib, Lenalidomide,
Temsirrolimus, Bortezomib (preferable in combination)**
Alternatively: repeat previous therapy (long remissions)

Mantle cell lymphoma B-cell receptor pathway



Ibrutinib in RR MCL: bleeding events



Courtesy of S Rule

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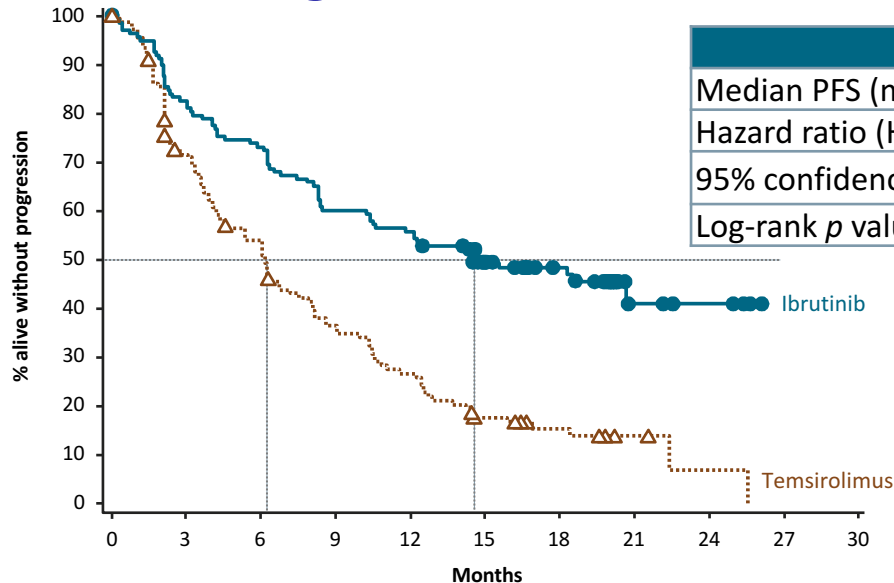
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Ibrutinib vs. Temsirolimus

Progression-free survival

ITT population
Median follow-up:
20 months



	Ibrutinib	Temsirolimus
Median PFS (months)	14.6	6.2
Hazard ratio (HR)	0.43	
95% confidence interval (CI)	0.32-0.58	
Log-rank <i>p</i> value	< 0.0001	

Patients at risk	0	3	6	9	12	15	18	21	24	27	30
Ibrutinib	139	114	101	83	77	45	34	8	5	0	0
Temsirolimus	141	93	69	45	33	19	11	3	1	0	0

At a 2-year landmark, the PFS rate was 41% for ibrutinib versus 7% for temsirolimus
Investigator-assessed HR for ibrutinib versus temsirolimus was 0.43 (95% CI, 0.32-0.58)

Acalabrutinib in MCL

Response rates

Table. Response by investigator assessment based on the Lugano Classification (Cheson, et al. 2014)

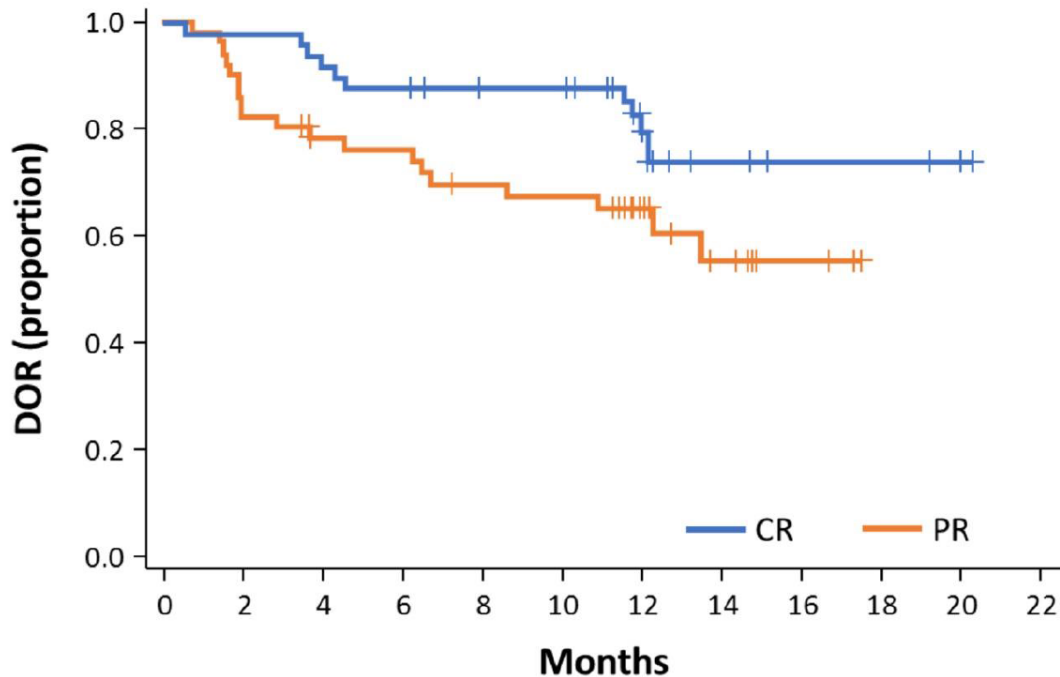
	All patients (N=124)	
	n (%)	95% CI, %
ORR (CR + PR)	100 (81)	73-87
Best response		
CR	49 (40)	31-49
PR	51 (41)	32-50
SD	11 (9)	5-15
PD	10 (8)	4-14
NE	3 (2)	1-7

Abbreviations: CR = complete response; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.



Acalabrutinib in MCL

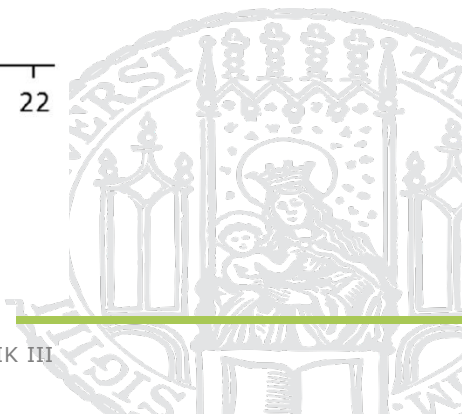
Duration of response



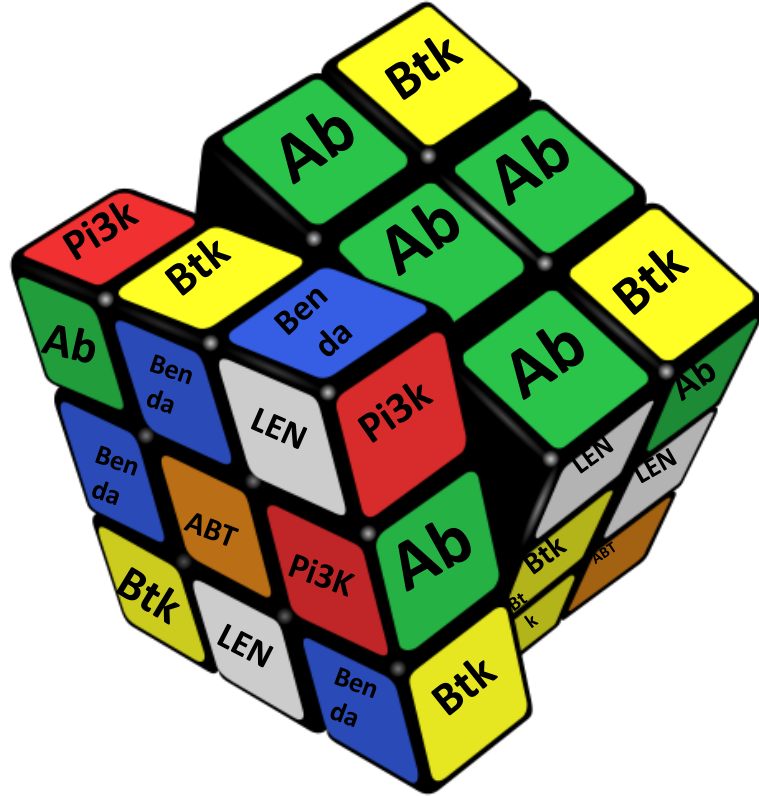
At Risk		0	2	4	6	8	10	12	14	16	18	20
TN	49	48	45	43	40	40	40	15	7	5	5	4
R/R	51	42	36	35	31	30	30	18	10	3	0	

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The era of combinations

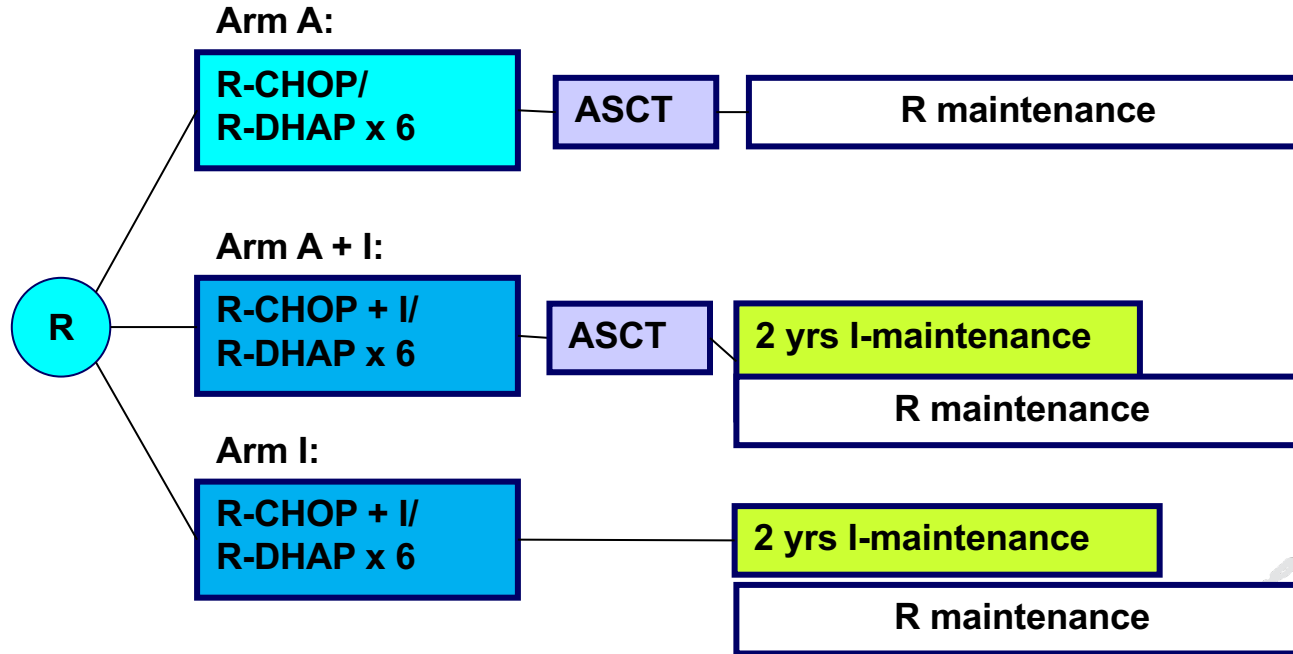


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Phase III TRIANGLE Trial *add on vs head to head comparison*



superiority/non-inferiority: time to treatment failure
HR: 0.60; 65% vs. 77% vs. 49% at 5 years

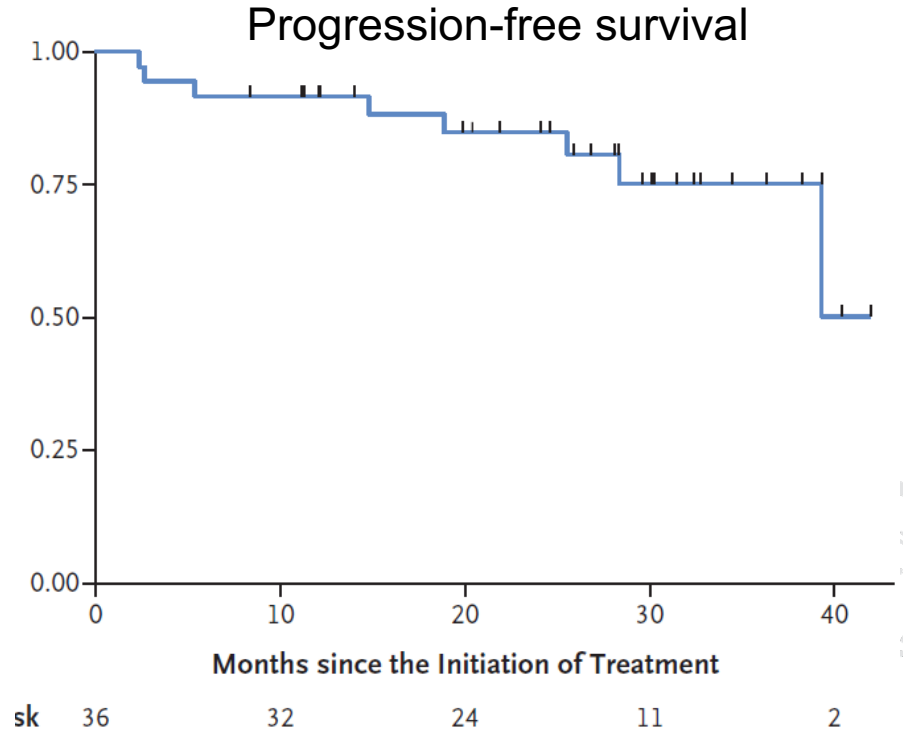
R = Rituximab; I = Ibrutinib



Mantle cell lymphoma (first line)

Rituximab-Lenalidomide

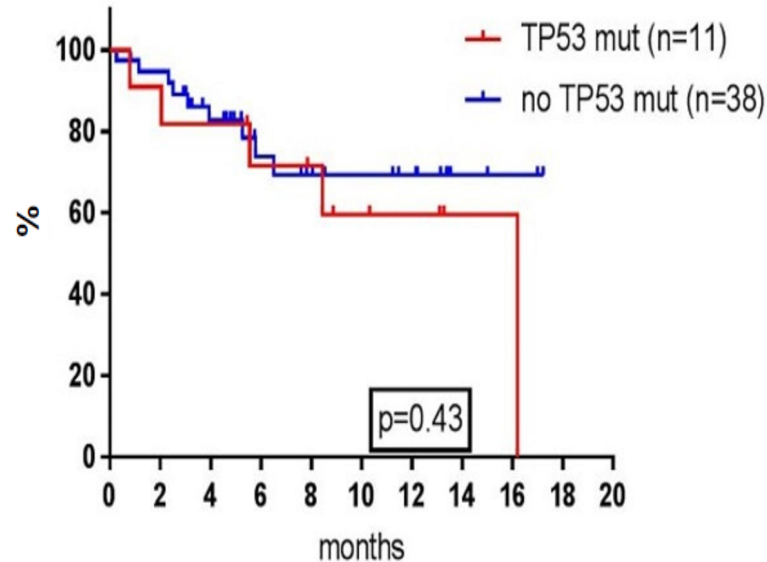
Response	Patients <i>no.</i>	Intention-to-Treat Population (N = 38)
Overall response	33	87
Complete response*	23	61
Partial response	10	26
Stable disease	1	3
Progressive disease†	2	5
Could not be evaluated‡	2	5



Relapsed mantle cell lymphoma

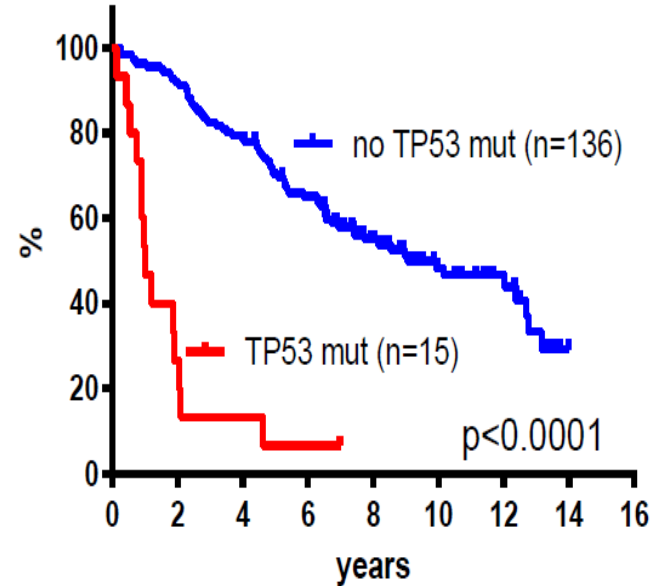
Ibrutinib-Lenalidomide-R

NORDIC MCL6 PHILEMON



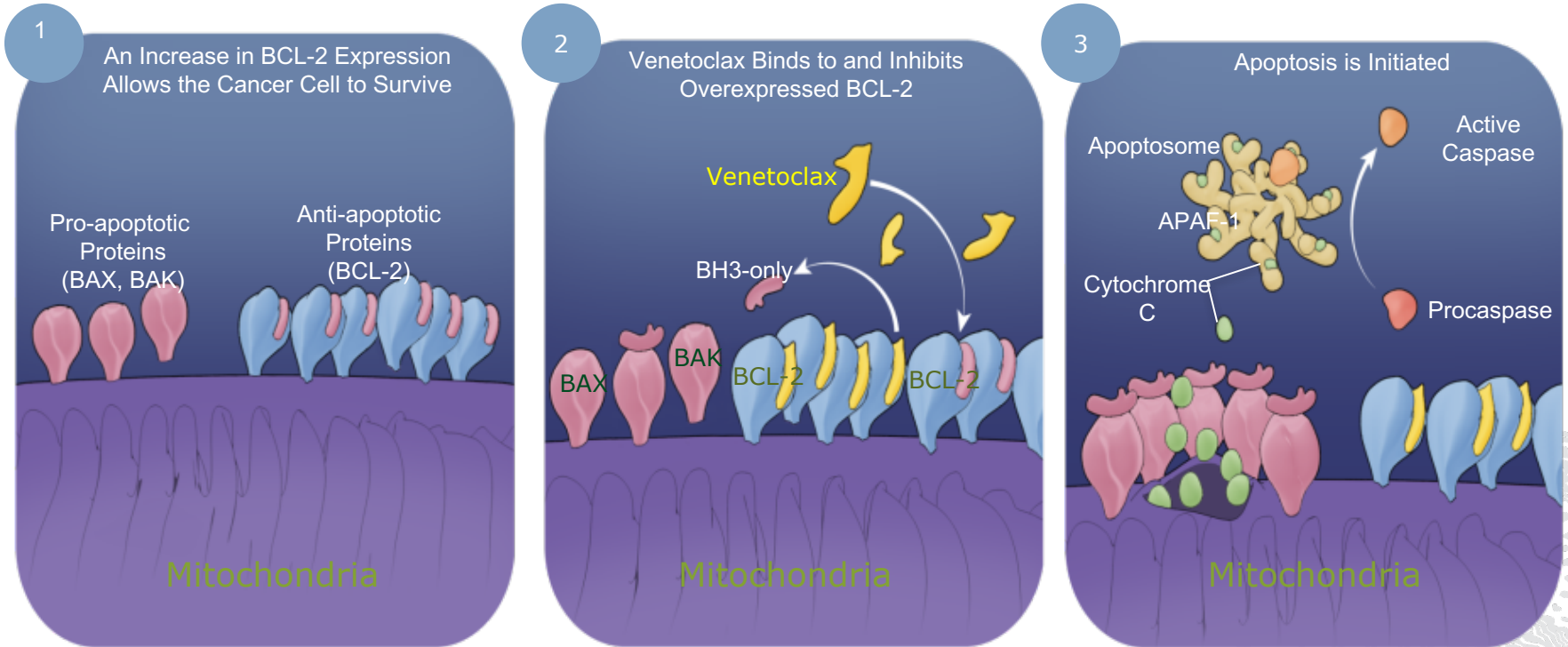
Eskelund, Blood 2017

NORDIC MCL2/3

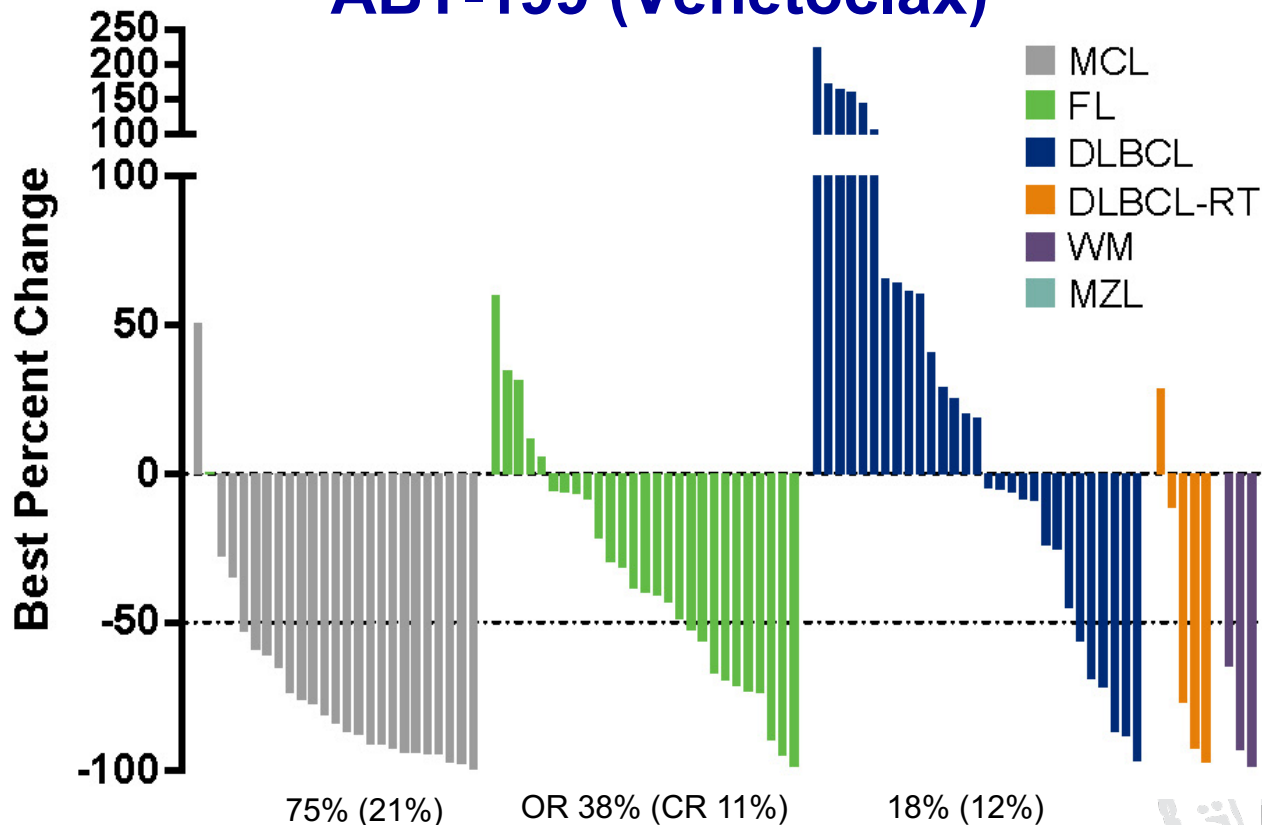


Eskelund, ASH 2016

Background: Mechanism of action of Venetoclax



Objective responses ABT-199 (Venetoclax)



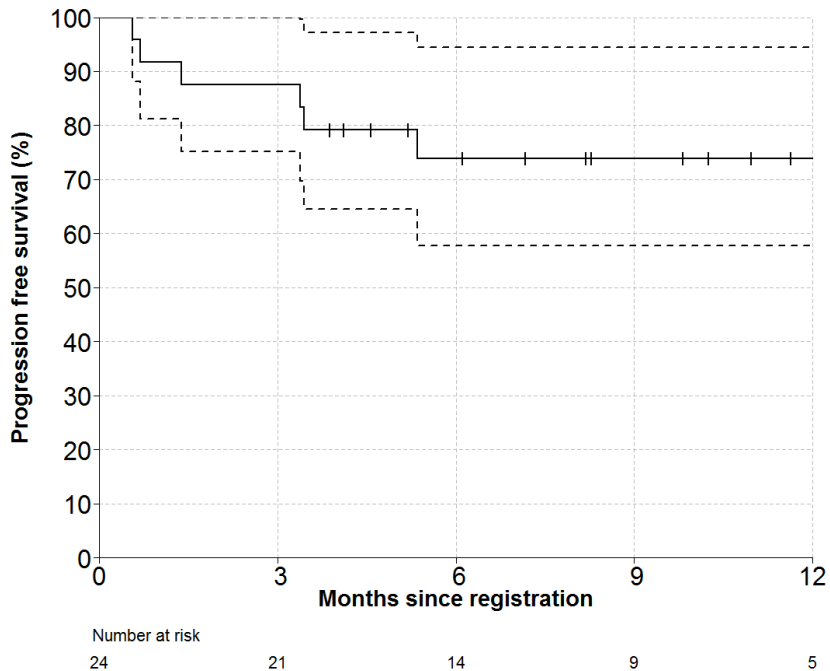
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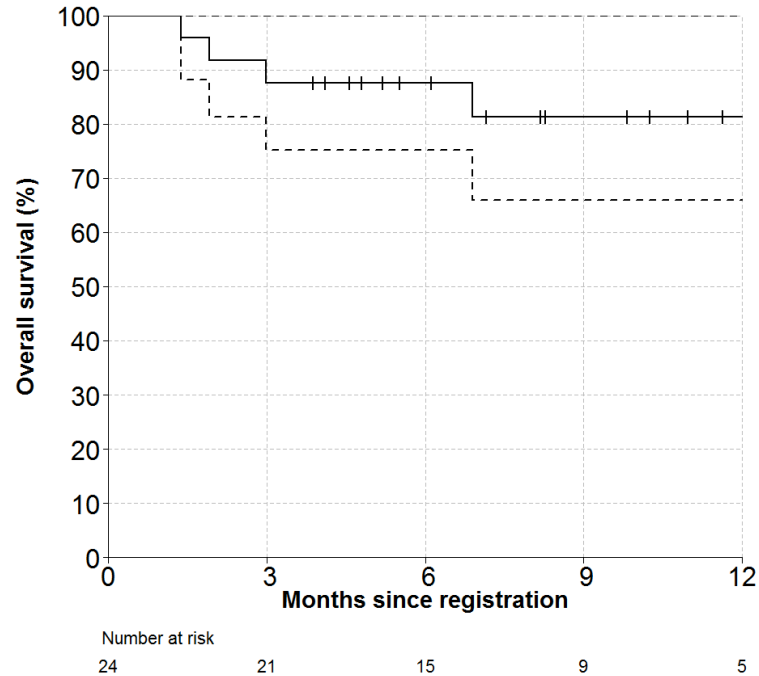
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AIM: Progression Free & Overall Survival

Progression Free Survival

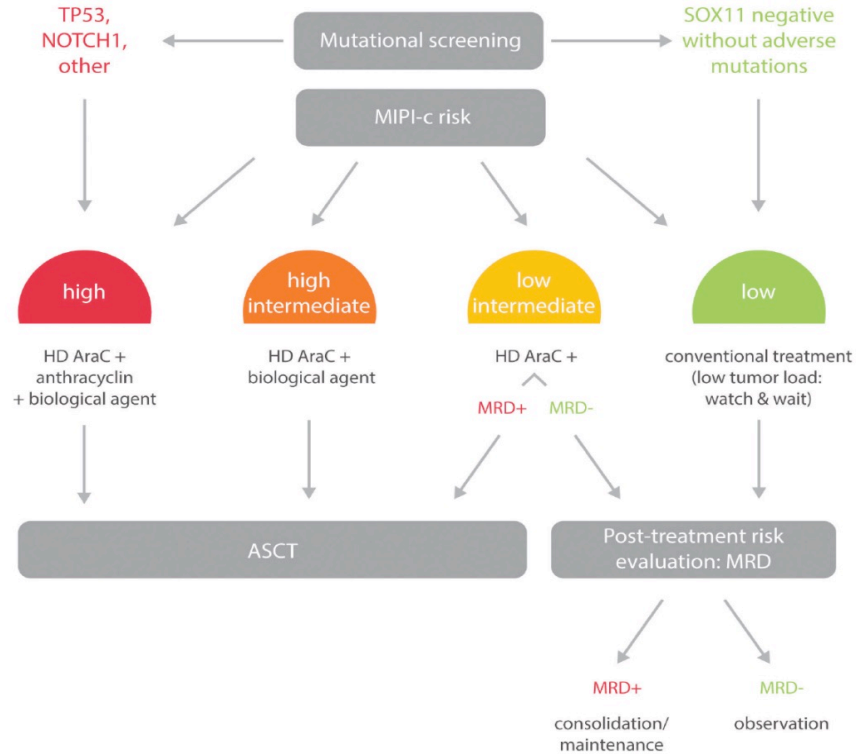


Overall Survival



Mantle cell lymphoma

Suggested therapeutic algorithm



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European MCL Network Study generation 2017

< 65 years

MCL younger:

R-CHOP/DHAP =>ASCT

R-CHOP/DHAP+I =>ASCT => I

R-CHOP/DHAP + I => I

> 60 years

MCL elderly R2:

R-CHOP vs R-CHOP/Ara-C

=> Rituximab M

+/-Lenalidomide

> 65 years

MCL elderly I:

BR +/- Ibrutinib

=> Rituximab M

+/- Ibrutinib

1. Relapse

R-HAD +/- Bortezomib

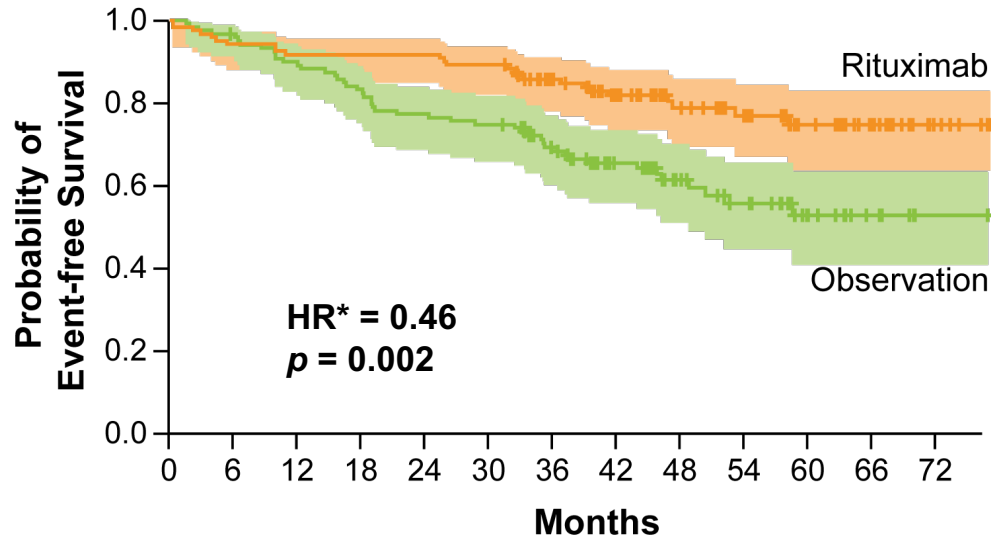
2. Relapse (or not qualifying for R-HAD)

Ibrutinib vs
Temsirolimus

BeRT
BR-Temsirolimus



LyMa: Rituximab Maintenance After Autologous Stem Cell Transplant



* Disease progression, relapse, death, rituximab allergy or severe infection

	R (n = 120)	Observation (n = 120)
Median EFS	Not reached	Not reached

- PFS (4-y): R, 83%; observation, 64% ($p < 0.001$)
- OS (4-y): R, 89%; observation, 80% ($p = 0.04$)

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