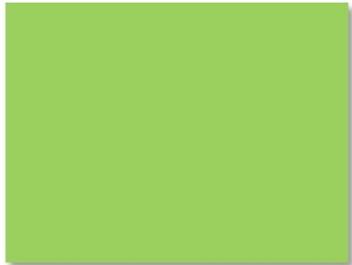
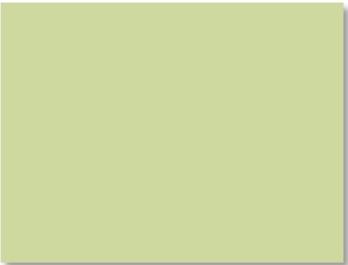
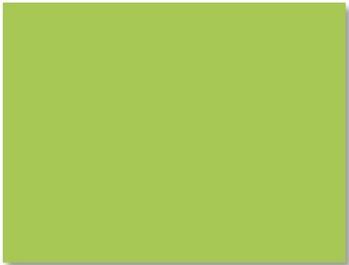
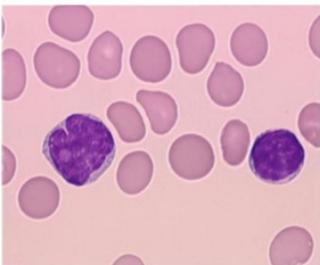
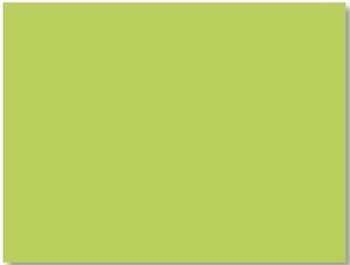


MANTLE CELL LYMPHOMA: FRONTLINE: OVERVIEW OF THE THERAPEUTIC ALGORITHM



Mantle Cell Lymphoma

Disclosures

<https://bureaucracyincts.eu>



Research Support (institution)	Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche
Employee	-
Major Stockholder	-
Speakers Bureau	-
Speakers Honoraria	Amgen, Astra Zeneca, Bayer, BMS/Celgene, Gilead/Kite, Incyte, Janssen, Novartis, Roche
Scientific Advisory Board	Astra Zeneca, Bayer, Beigene, BMS/Celgene, Genmab, Gilead/Kite, Incyte, Janssen, Lilly/Loxo, Morphosys, Novartis, Roche

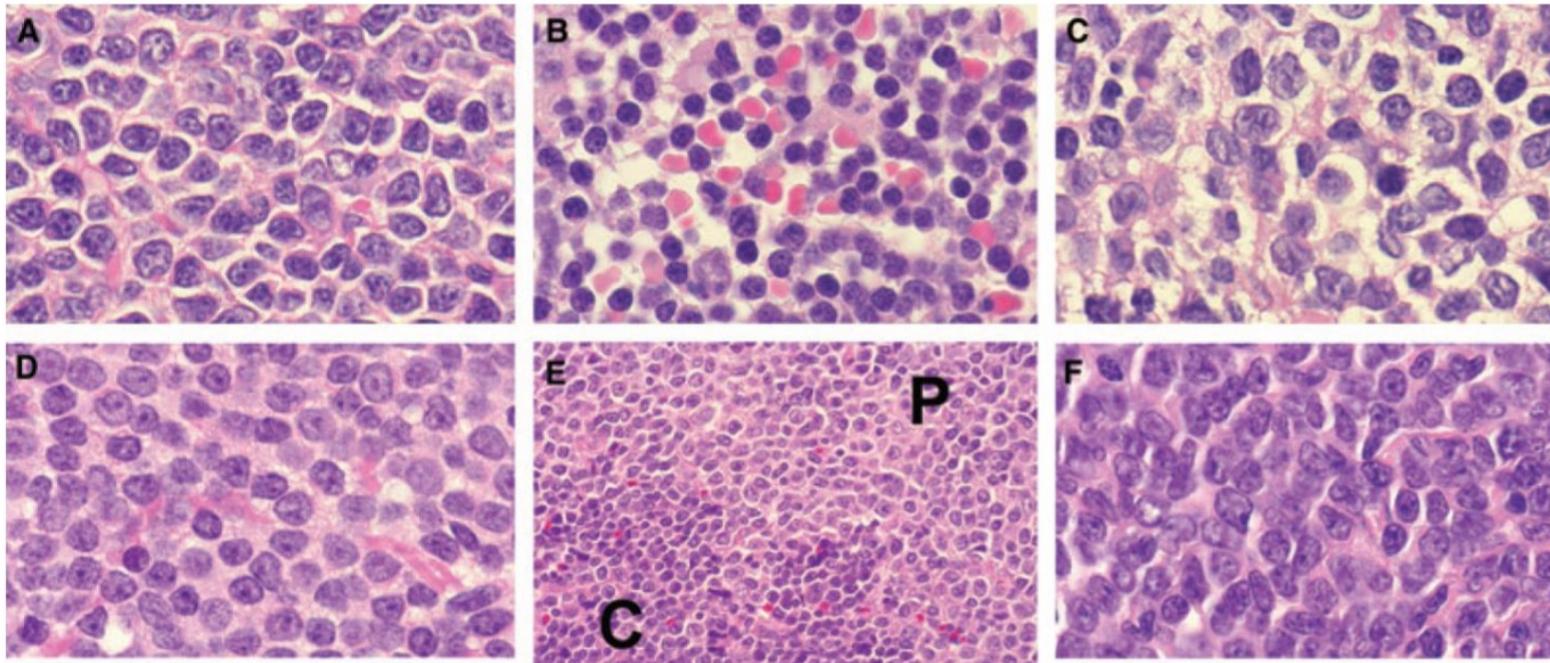
Mantle cell lymphoma

Overview

- **molecular risk factors**
- **chemotherapy standards
in first line**
- **BTK inhibitors (and „friends“)**

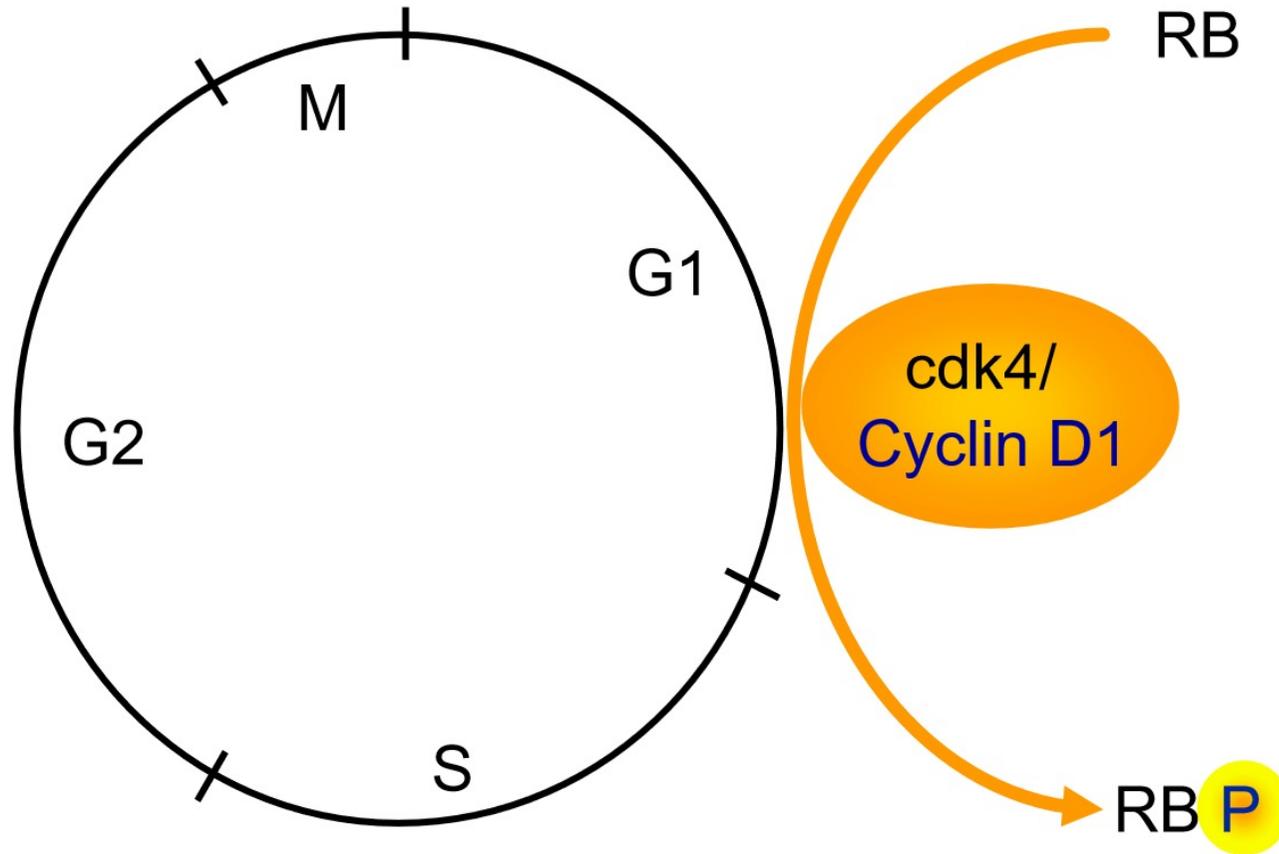


Mantle cell lymphoma Histology



A classical; B small cell; C pleomorphic; D: blastoid;
E: classical & pleomorphic; F: classical/pleomorphic

Retinoblastoma (RB) signal pathway in MCL

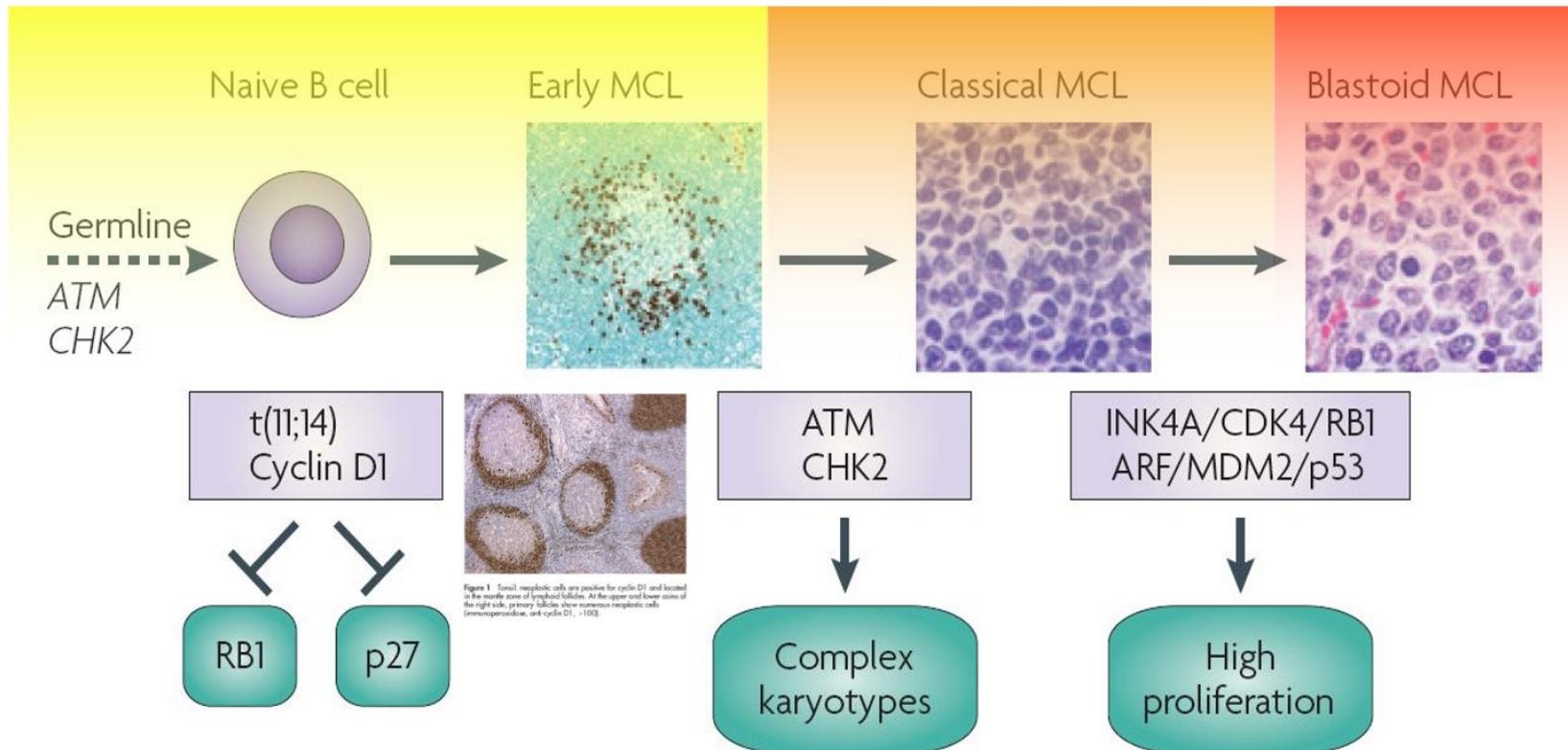


MCL: a spectrum of disease

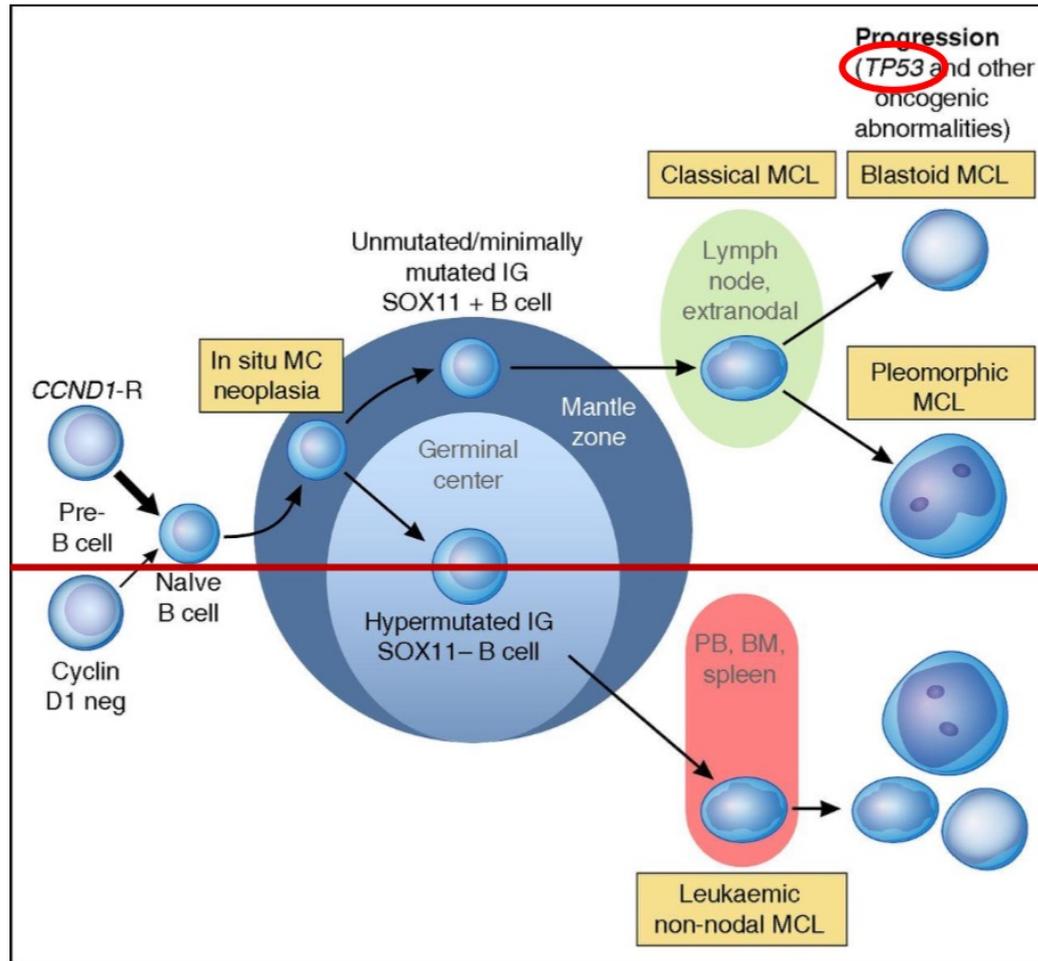
„indolent“ MCL (15%)

„classical“ MCL (80%)

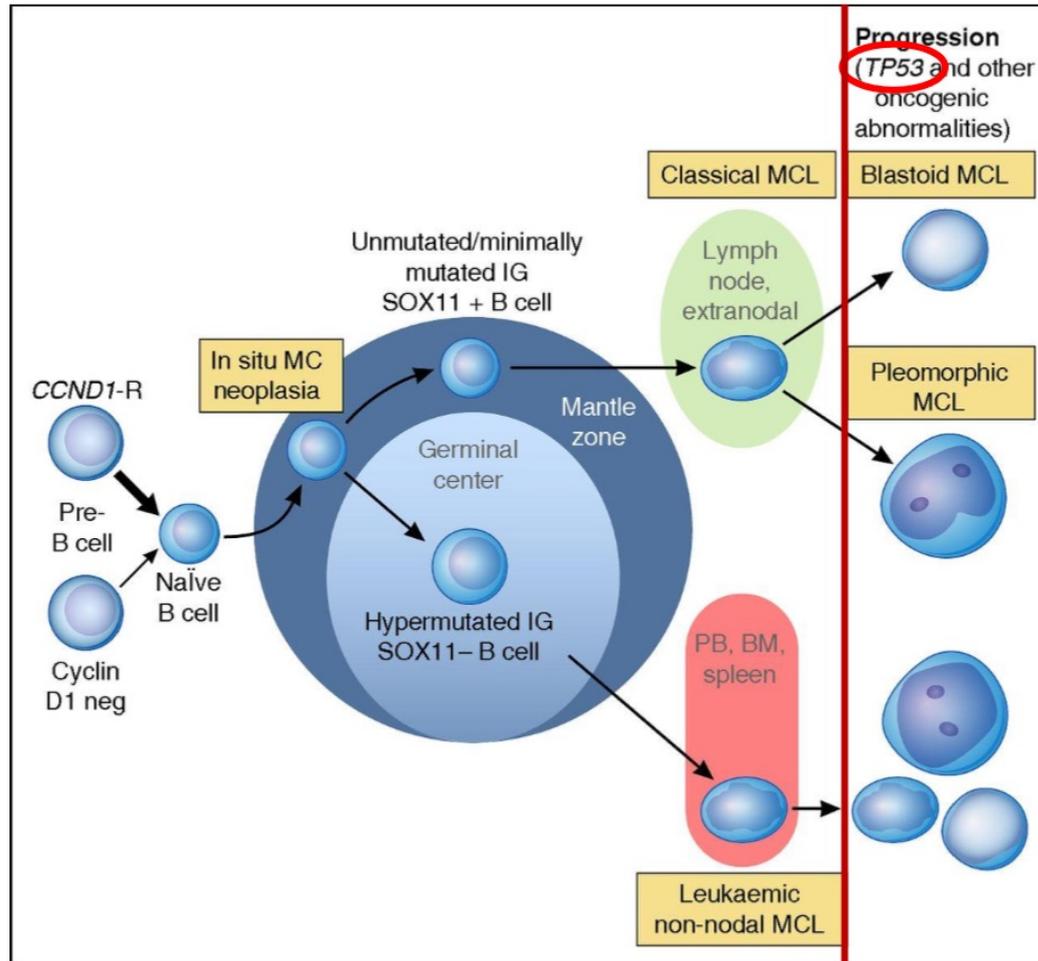
„transformed“ (5%)



MCL: two kind of diseases

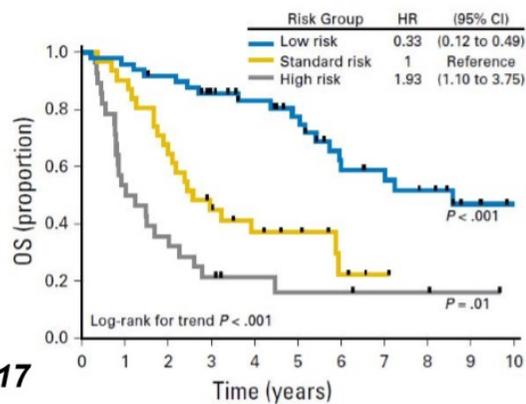
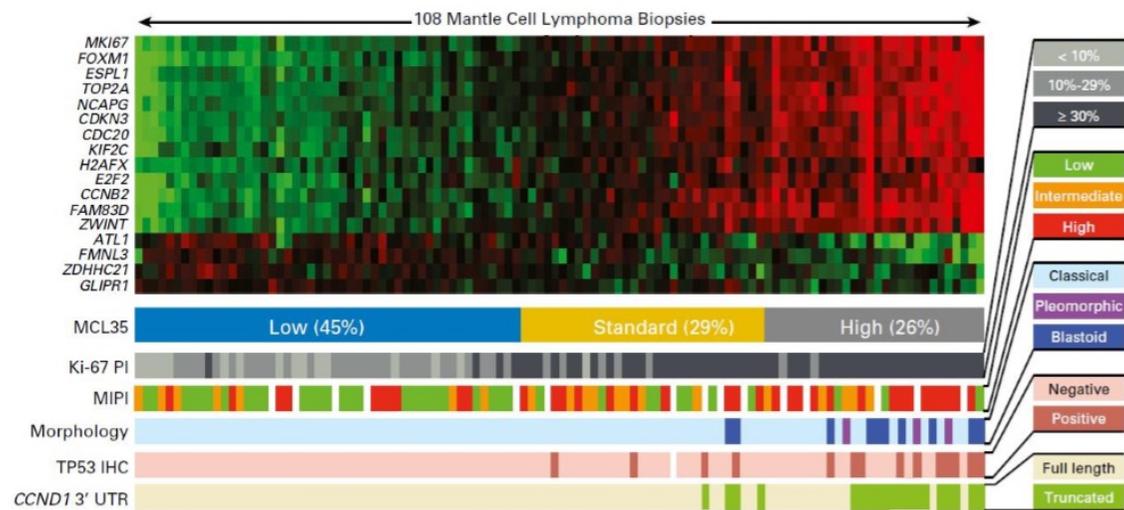


MCL: two kind of diseases

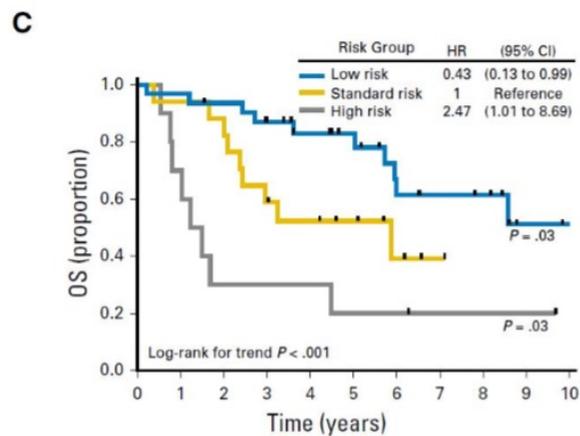


Molecular features of high risk MCL

Risk factor proliferation: MCL 35

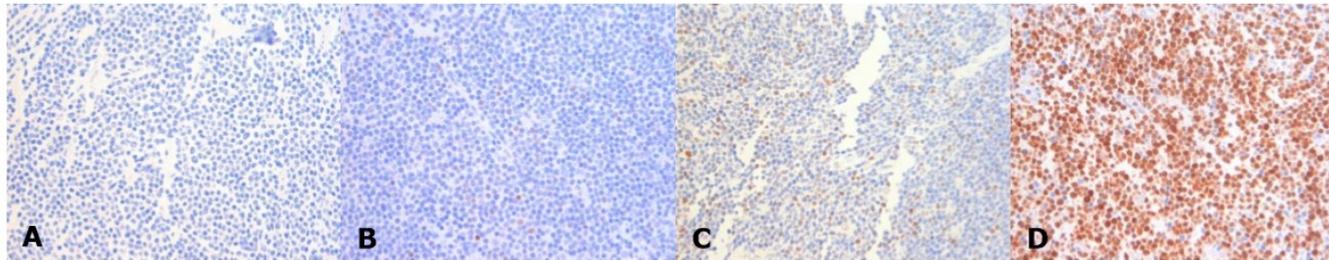


Scott, JCO 2017

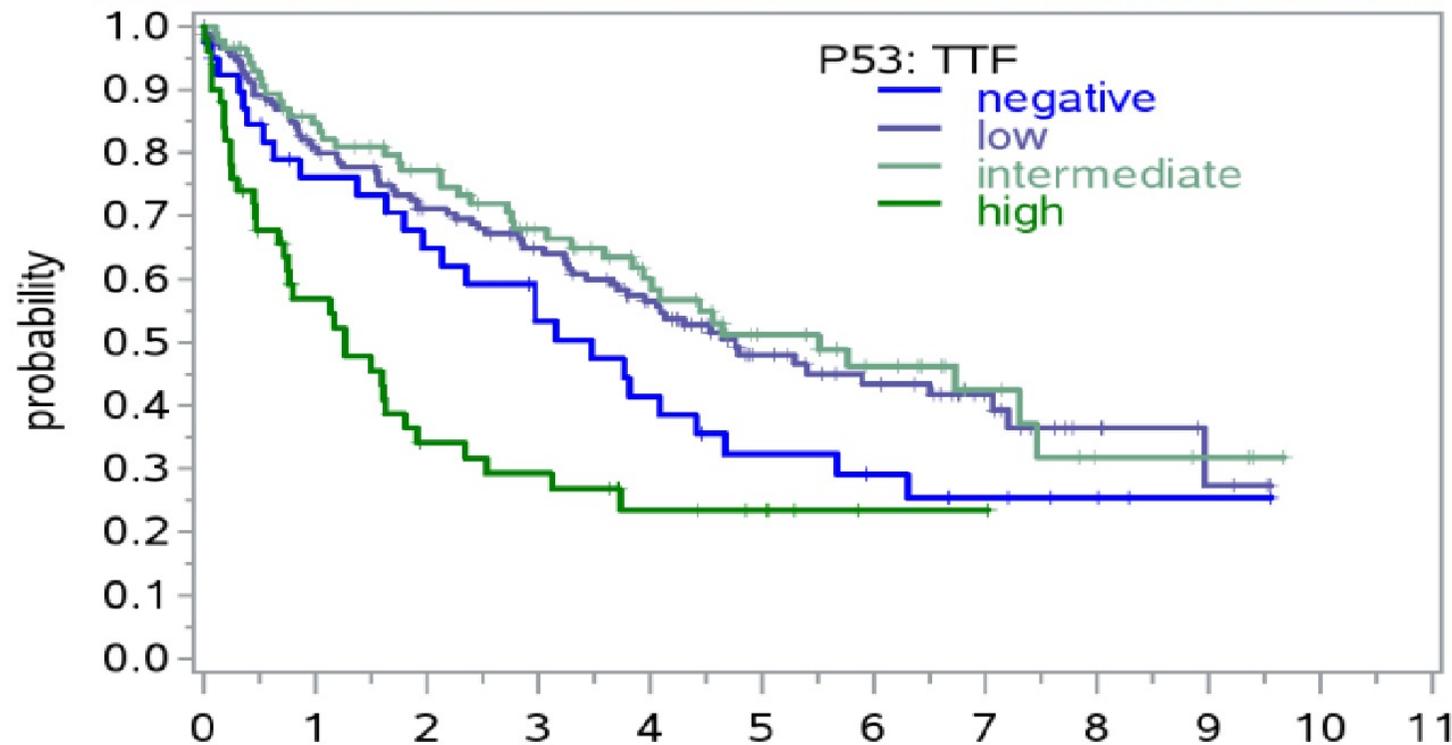


Biological features of high risk MCL

p53 immunohistochemistry



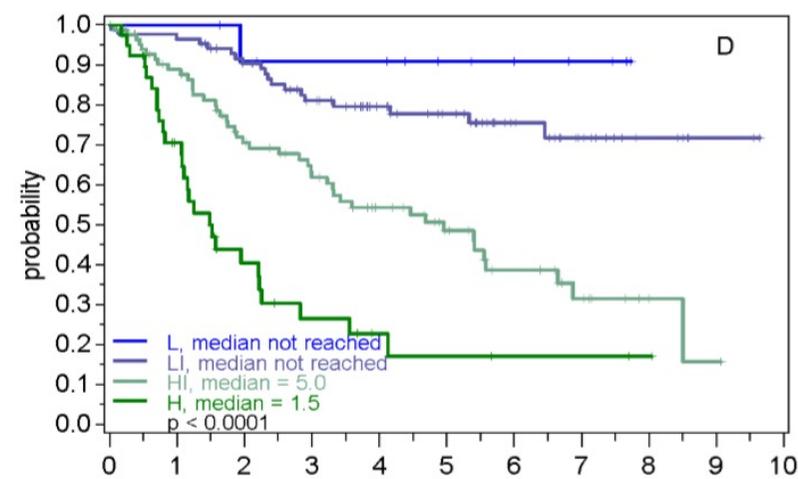
- (A) p53 0%
- (B) p53 1-10%
- (C) p53 11-50%
- (D) p53 >50%



Aukema, Blood 2018

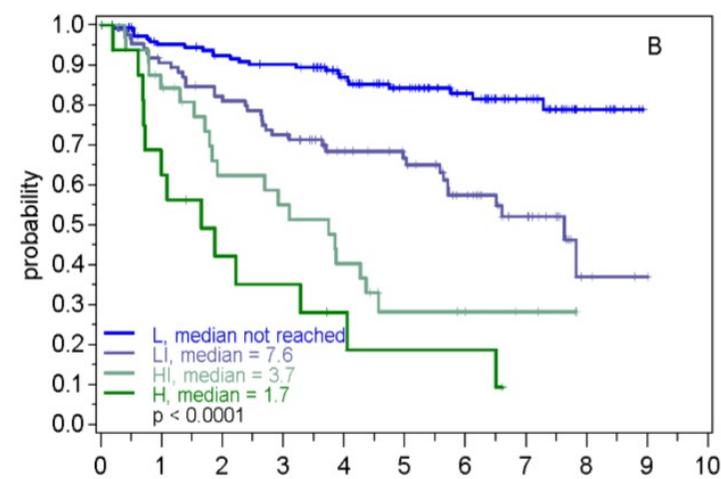
Combined MIPI-c Overall survival

Patients >65 years



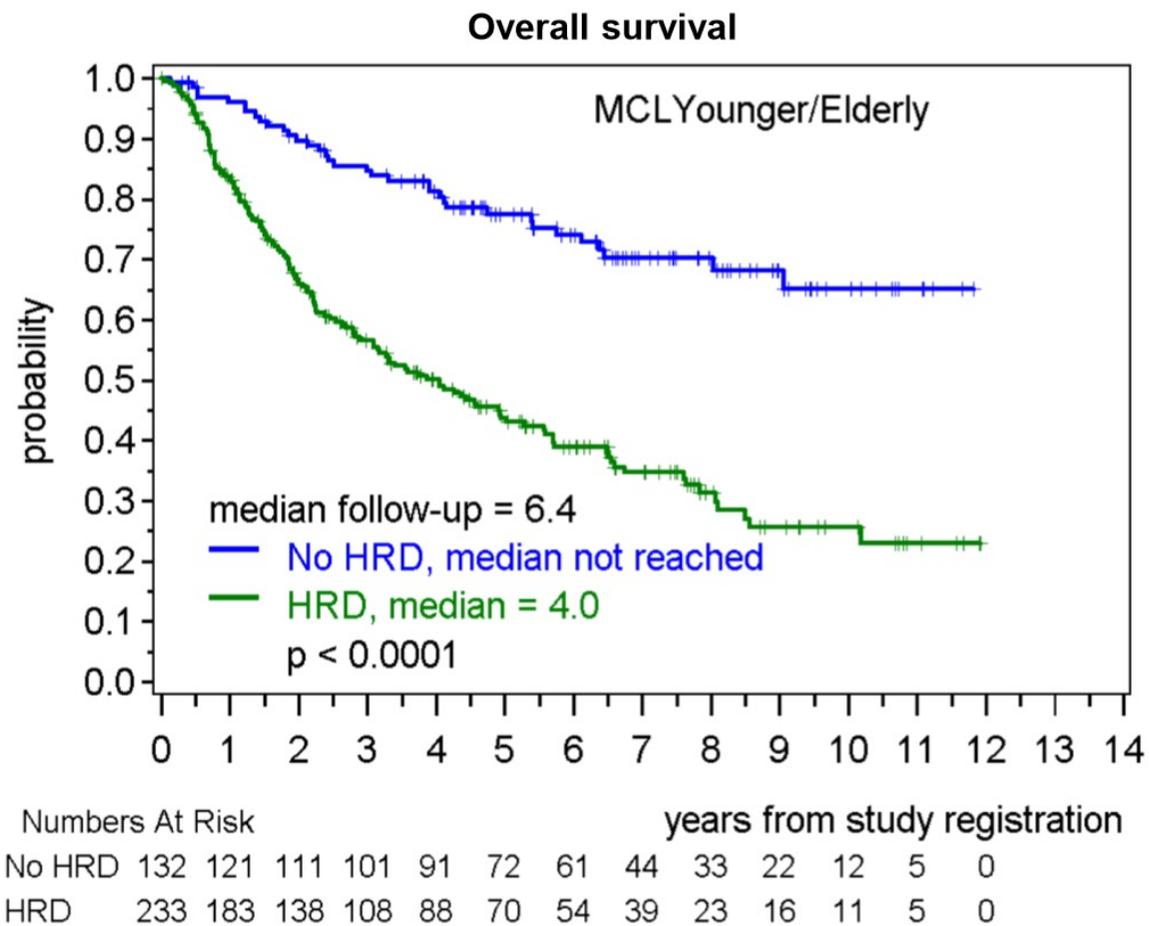
	Numbers At Risk										
	0	1	2	3	4	5	6	7	8	9	10
L	12	10	9	6	4	3	0	0	0	0	0
LI	88	82	72	58	45	37	21	13	6	2	0
HI	83	70	52	42	32	22	14	8	2	1	0
H	39	24	12	7	4	3	2	1	0	0	0

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

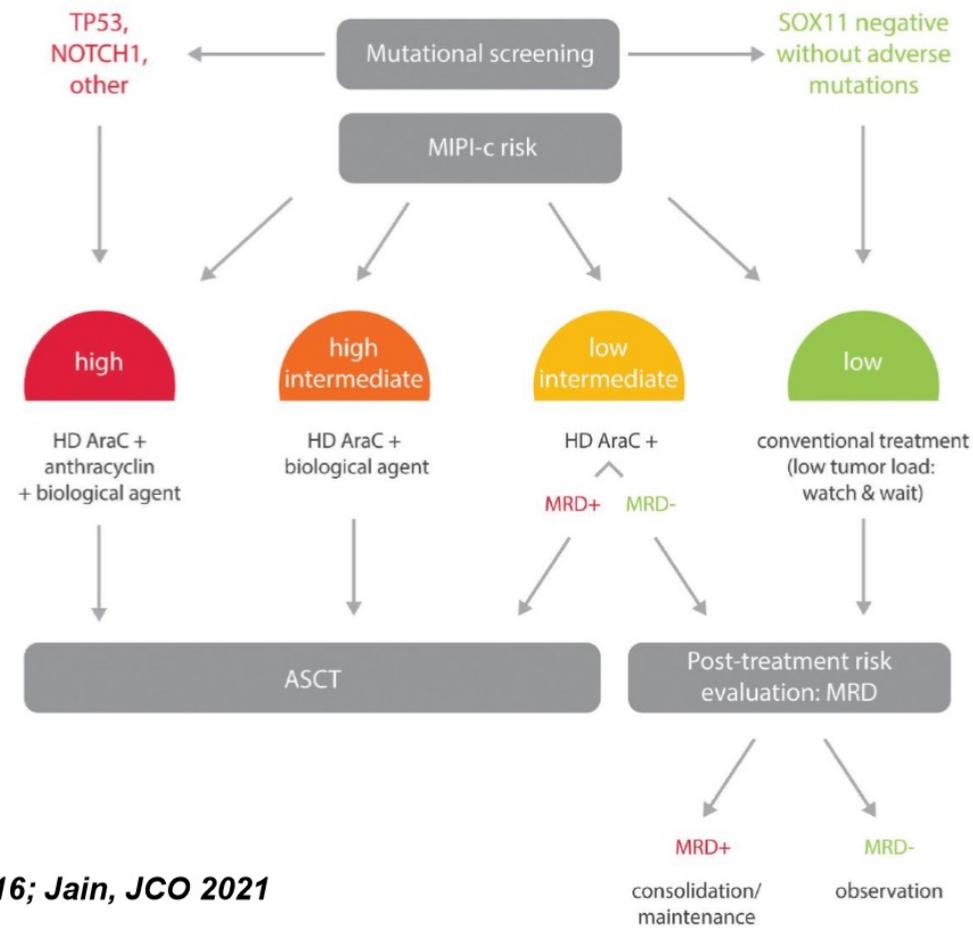
Characteristics of high risk MCL (blastoid, Ki-67 >30%, or p53mut)



Dreyling, EHA 2020

European MCL Network

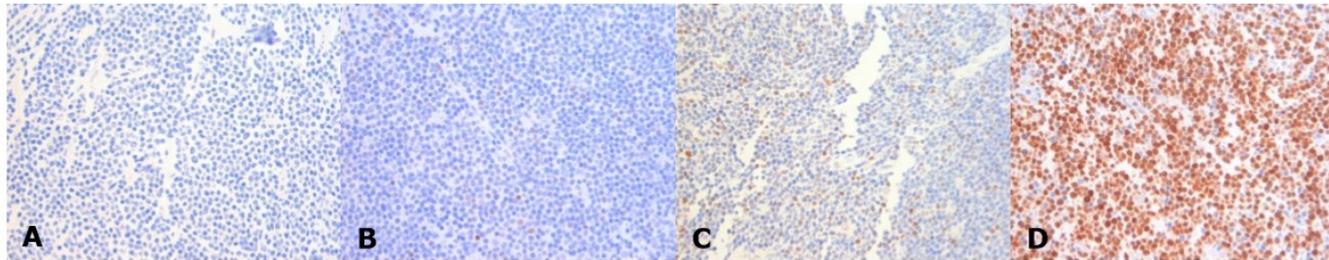
Suggested therapeutic algorithm



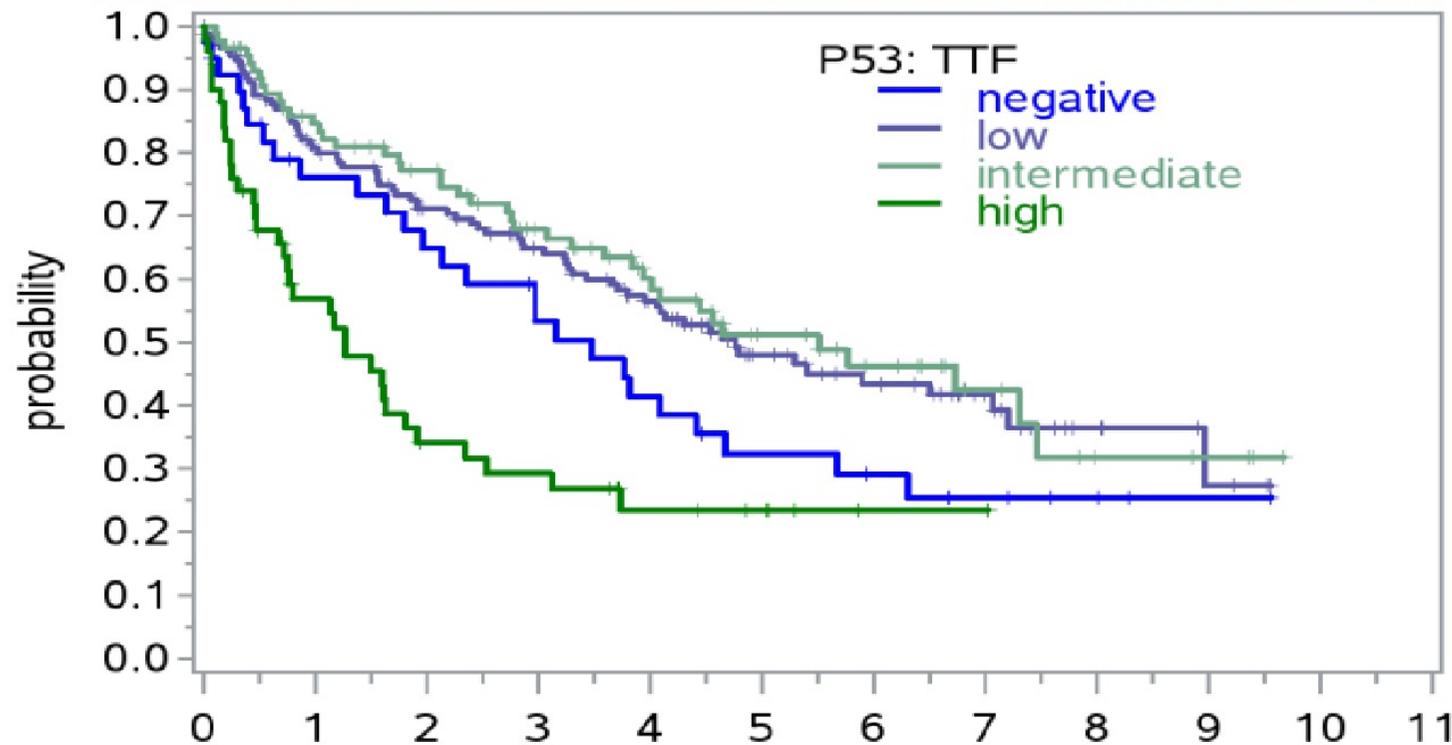
Dreyling, Haematologica 2016; Jain, JCO 2021

Biological features of high risk MCL

p53 immunohistochemistry



- (A) p53 0%
- (B) p53 1-10%
- (C) p53 11-50%
- (D) p53 >50%



Aukema, Blood 2018

Mantle cell lymphoma

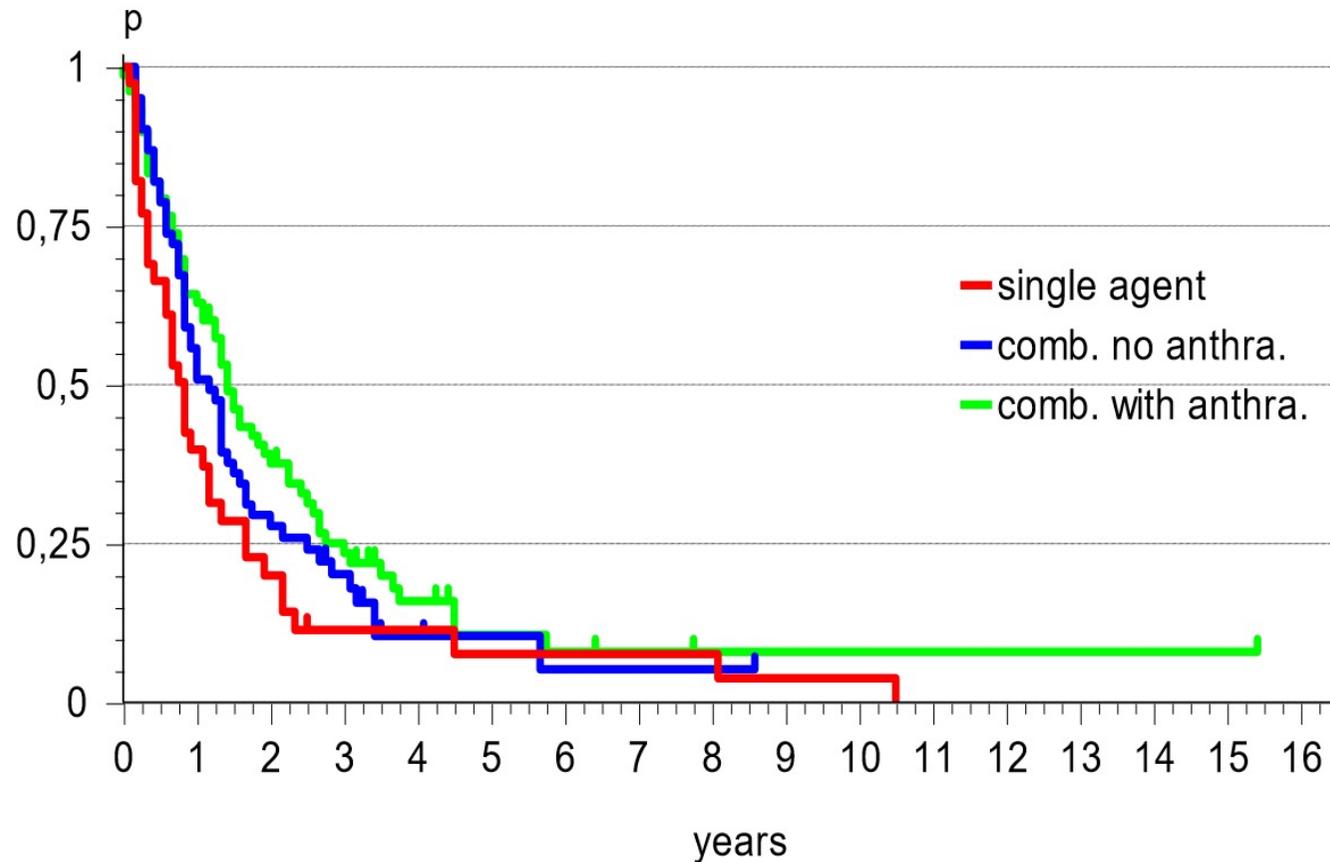
Overview

- **molecular risk factors**
- **chemotherapy standards
in first line**
- **BTK inhibitors (and „friends“)**

Multicenter Evaluation of MCL

Agency Criteria fulfilled

event free interval after chemotherapy in stages III + IV



Dreyling, ASCO 1999

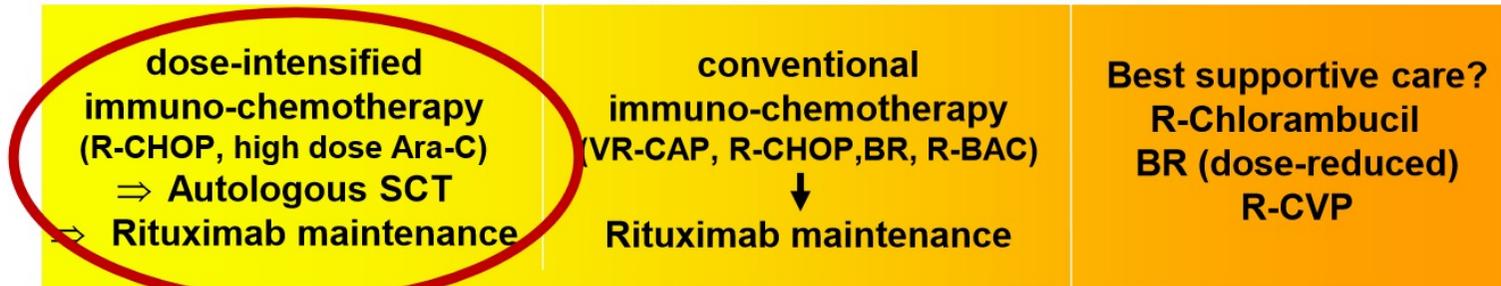
Mantle cell lymphoma

Therapeutic algorithm

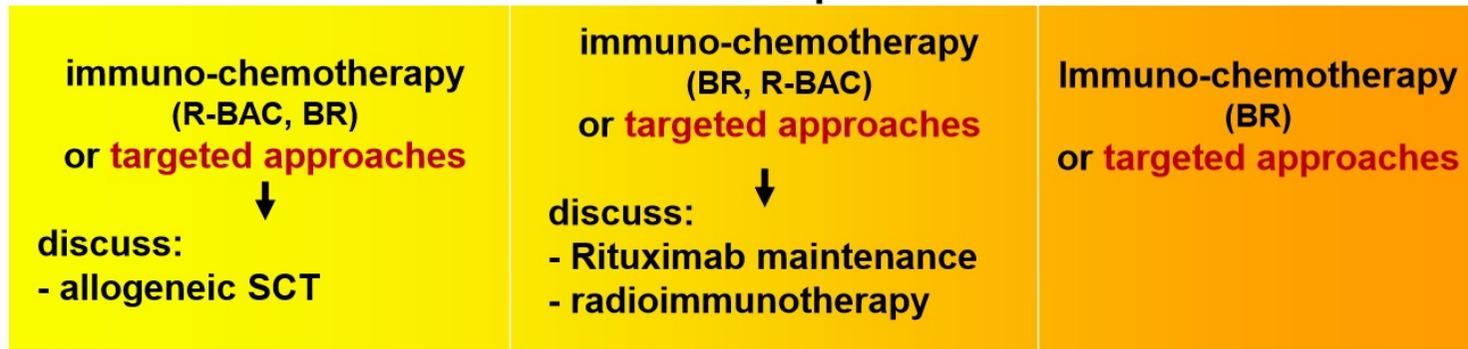
young patient (≤ 65)

elderly patient (>65)
First line treatment

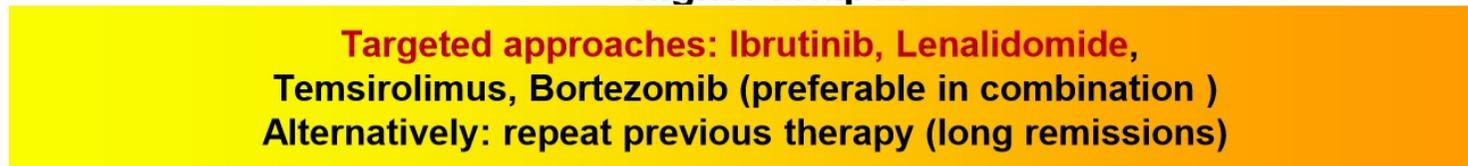
compromised patient



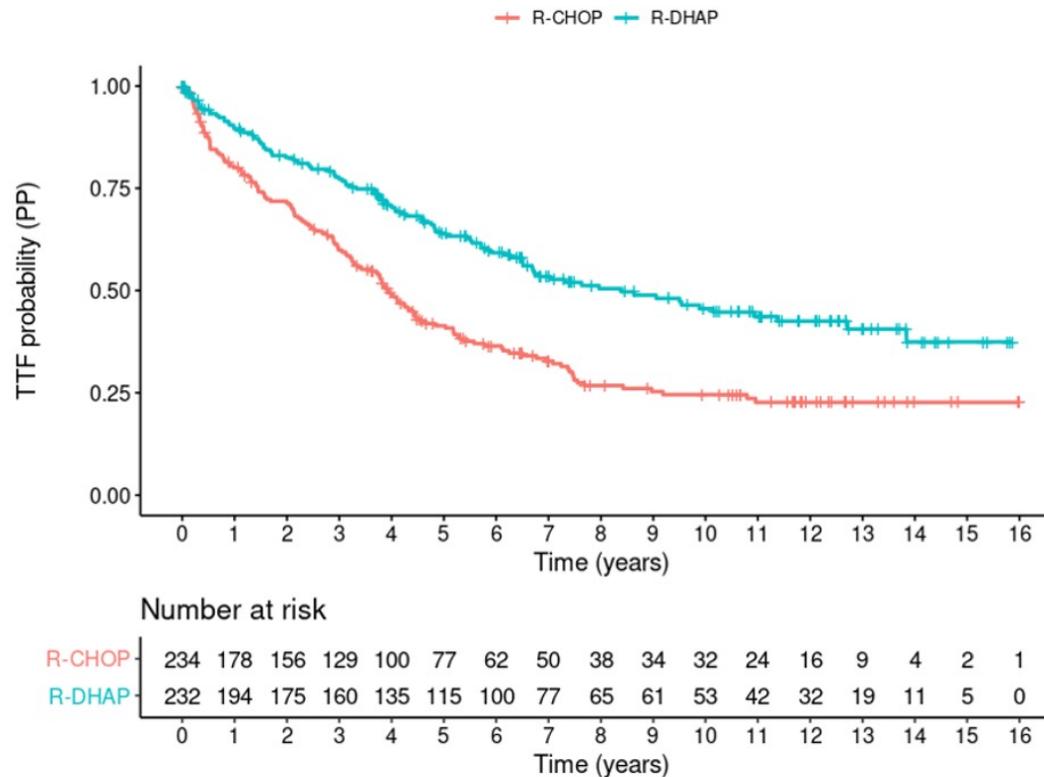
1. relapse



higher relapse



Updated Results 2021 – TTF (PP)



- Median follow-up 10.6 years

- Median TTF:

- R-CHOP 3.9 years

- R-DHAP 8.4 years

- 10-year TTF (95% CI):

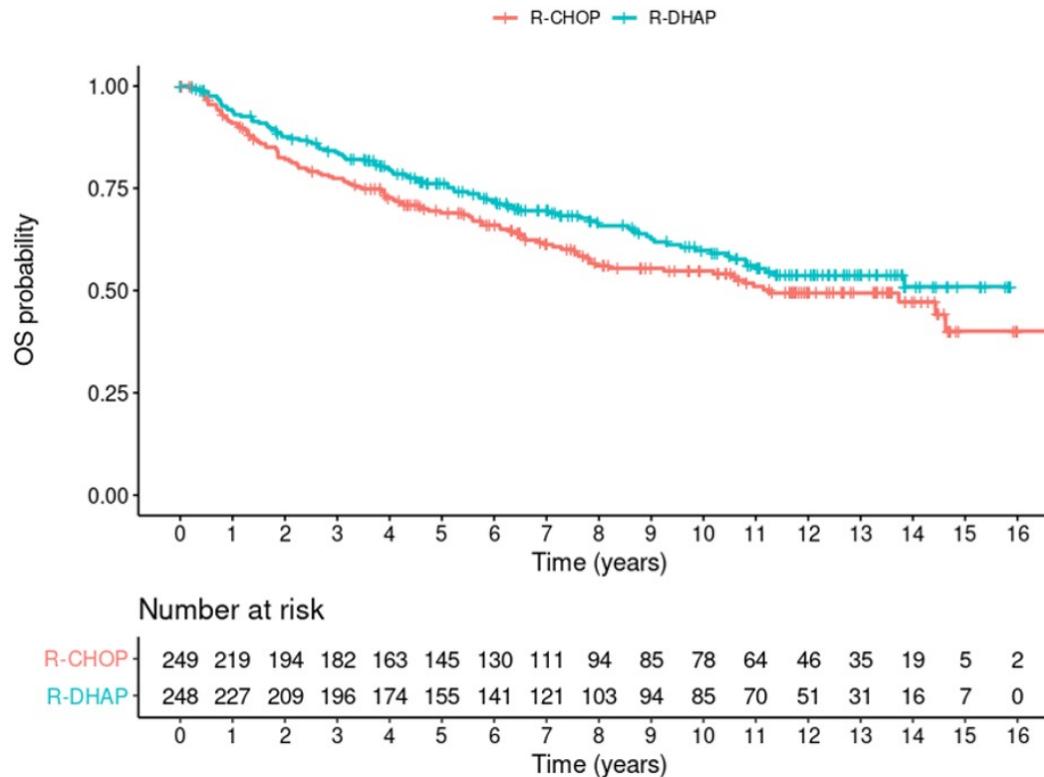
- R-CHOP 25% (19% - 32%)

- R-DHAP 46% (39% - 54%)

- Overrunning analysis (adjusted for interim analyses):

Hazard ratio 0.59 (p=0.038)

Updated Results 2021 – Overall Survival

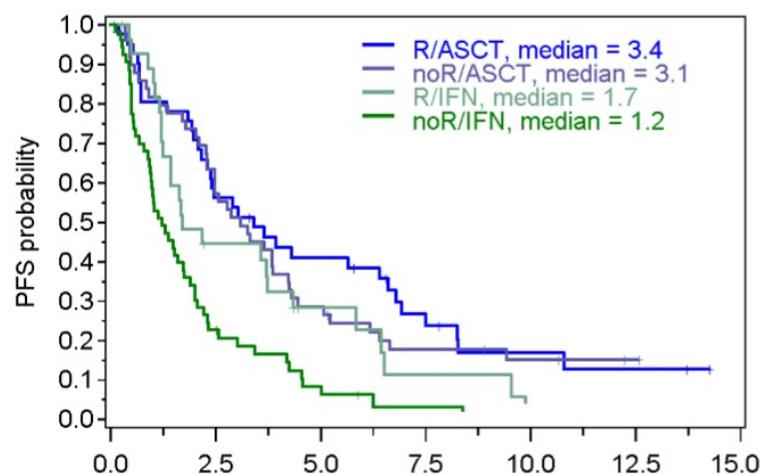


- Median follow-up 11.0 years
 - Median OS:
 - R-CHOP 11.3 years
 - R-DHAP not reached
 - $p=0.12$
 - 10-year OS (95% CI):
 - R-CHOP 55% (48% - 62%)
 - R-DHAP 60% (53% - 67%)
 - Hazard Ratio 0.80 (0.61-1.06), $p=0.12$
 - MIPI-adjusted Hazard ratio 0.74 (0.56-0.98), $p=0.038$
- MIPI and Ki-67-adjusted hazard ratio (N=297):**
0.60 (0.41-0.87), $p=0.0066$

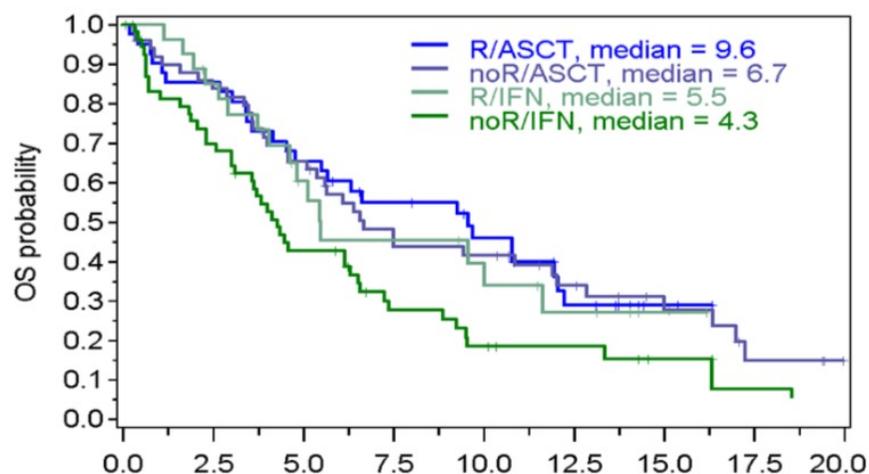
Hermine, ASH 2021, #380

Mantle cell lymphoma

Autologous SCT (first line)



	Numbers At Risk						years from end of induction							
	0.0	2.5	5.0	7.5	10.0	12.5	15.0	0.0	2.5	5.0	7.5	10.0	12.5	15.0
R/ASCT	41	23	16	9	4	3		41	23	16	9	4	3	
noR/ASCT	52	28	14	8	6	4		52	28	14	8	6	4	
R/IFN	27	11	5	2	0			27	11	5	2	0		
noR/IFN	54	12	4	1	0			54	12	4	1	0		



	Numbers At Risk								years from end of induction									
	0.0	2.5	5.0	7.5	10.0	12.5	15.0	17.5	20.0	0.0	2.5	5.0	7.5	10.0	12.5	15.0	17.5	20.0
R/ASCT	41	35	26	20	15	8	2	0		41	35	26	20	15	8	2	0	
noR/ASCT	52	41	32	22	19	13	8	3		52	41	32	22	19	13	8	3	
R/IFN	27	22	12	9	7	4	1	0		27	22	12	9	7	4	1	0	
noR/IFN	54	37	22	12	8	6	3	1		54	37	22	12	8	6	3	1	

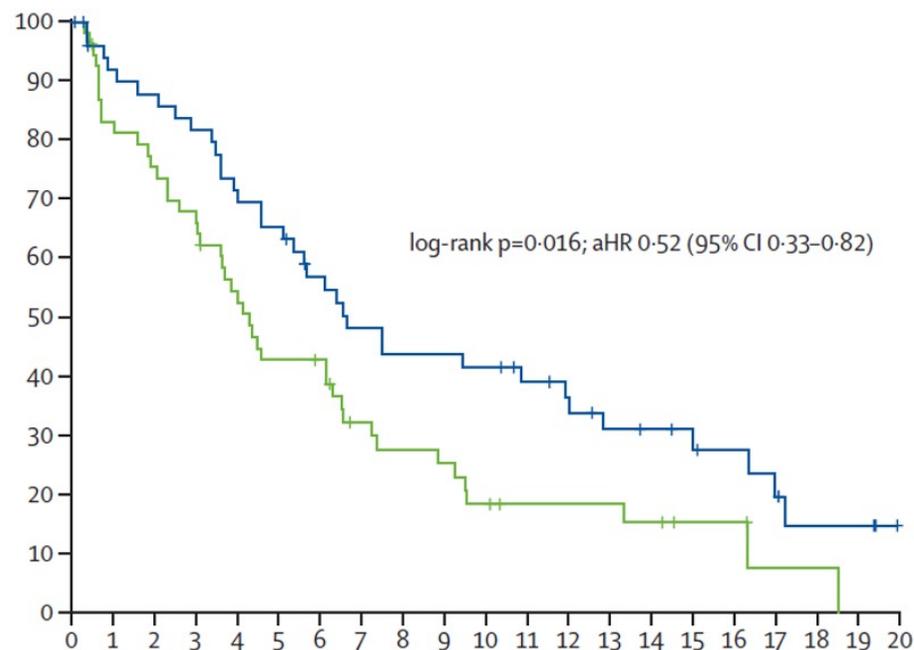
Zöllner, Lancet Hematol 2021

Mantle cell lymphoma

Autologous SCT (first line)



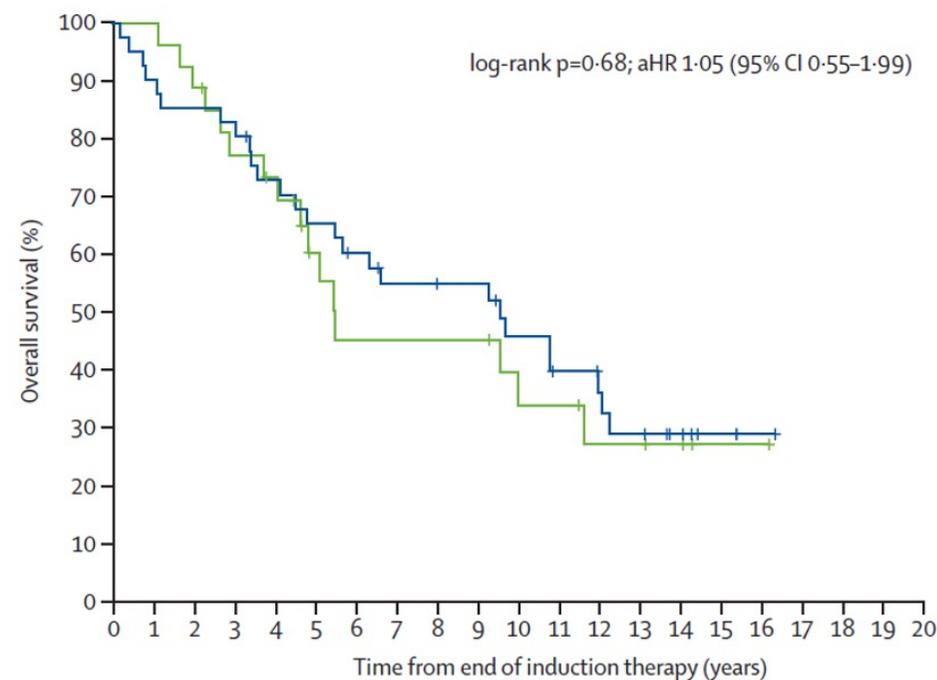
- rituximab



log-rank p=0.016; aHR 0.52 (95% CI 0.33-0.82)

54	44	40	36	28	22	21	14	12	11	8	6	6	6	5	3	3	1	1	0	0
(0)	(1)	(1)	(1)	(2)	(2)	(3)	(5)	(5)	(5)	(5)	(7)	(7)	(7)	(7)	(9)	(9)	(10)	(10)	(10)	(10)
52	45	43	40	35	32	26	22	20	20	19	16	14	11	10	8	7	5	3	3	0
(0)	(3)	(3)	(3)	(3)	(3)	(5)	(5)	(5)	(5)	(5)	(7)	(8)	(9)	(10)	(11)	(12)	(12)	(13)	(13)	(16)

+ rituximab

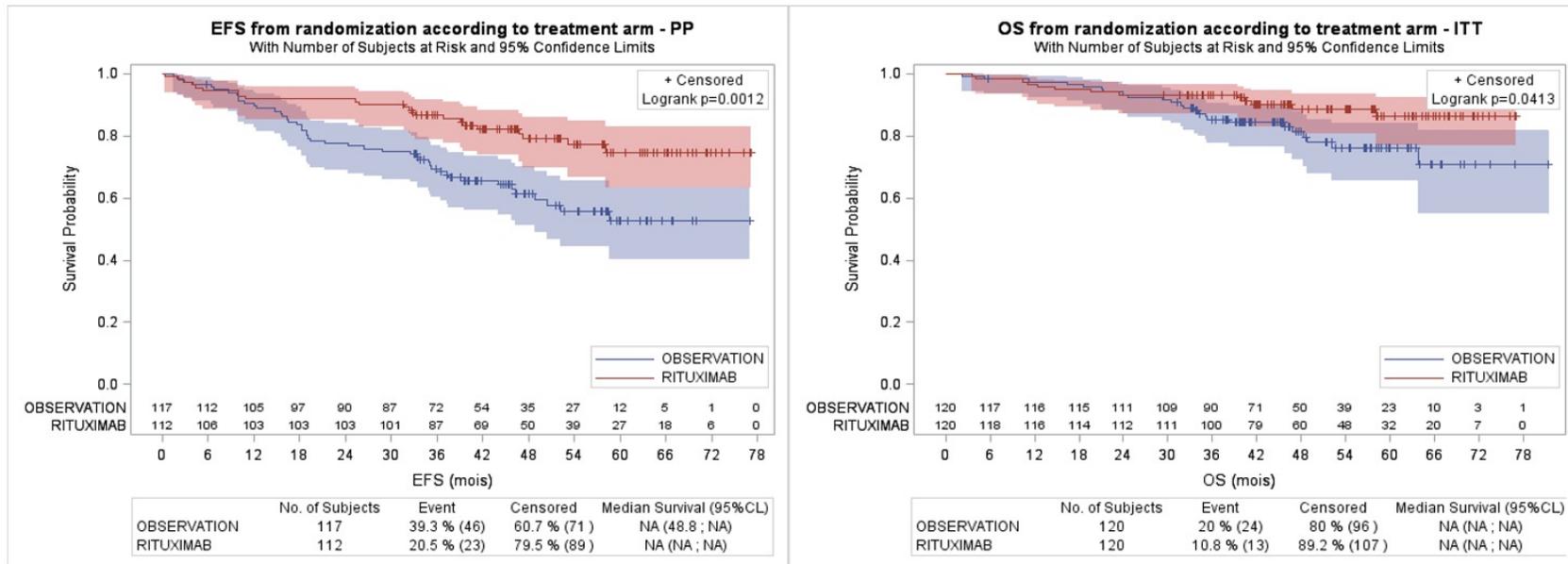


log-rank p=0.68; aHR 1.05 (95% CI 0.55-1.99)

27	27	24	20	18	12	9	9	9	9	7	6	4	4	3	1	1	0	0	0	0
(0)	(0)	(0)	(1)	(2)	(5)	(5)	(5)	(5)	(5)	(6)	(6)	(7)	(7)	(8)	(10)	(10)	(11)	(11)	(11)	(11)
41	37	35	34	29	26	23	20	20	19	15	12	10	8	5	2	1	0	0	0	0
(0)	(0)	(0)	(0)	(1)	(1)	(2)	(3)	(3)	(4)	(5)	(6)	(7)	(7)	(10)	(13)	(14)	(15)	(15)	(15)	(15)

Zöllner, Lancet Hematol 2021

Survival rates from Randomization

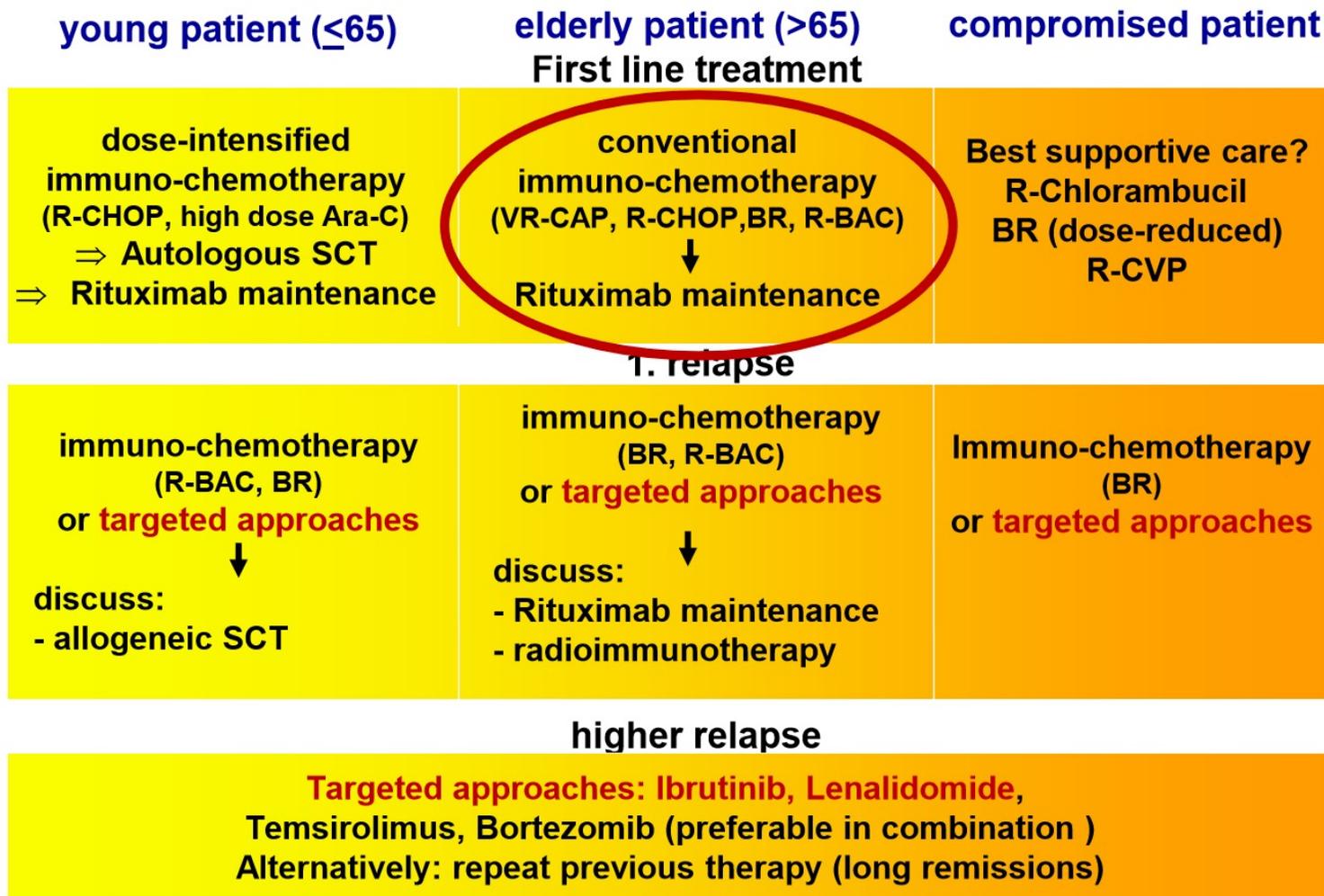


22 14.06.2022

Le Gouill, NEJM 2017

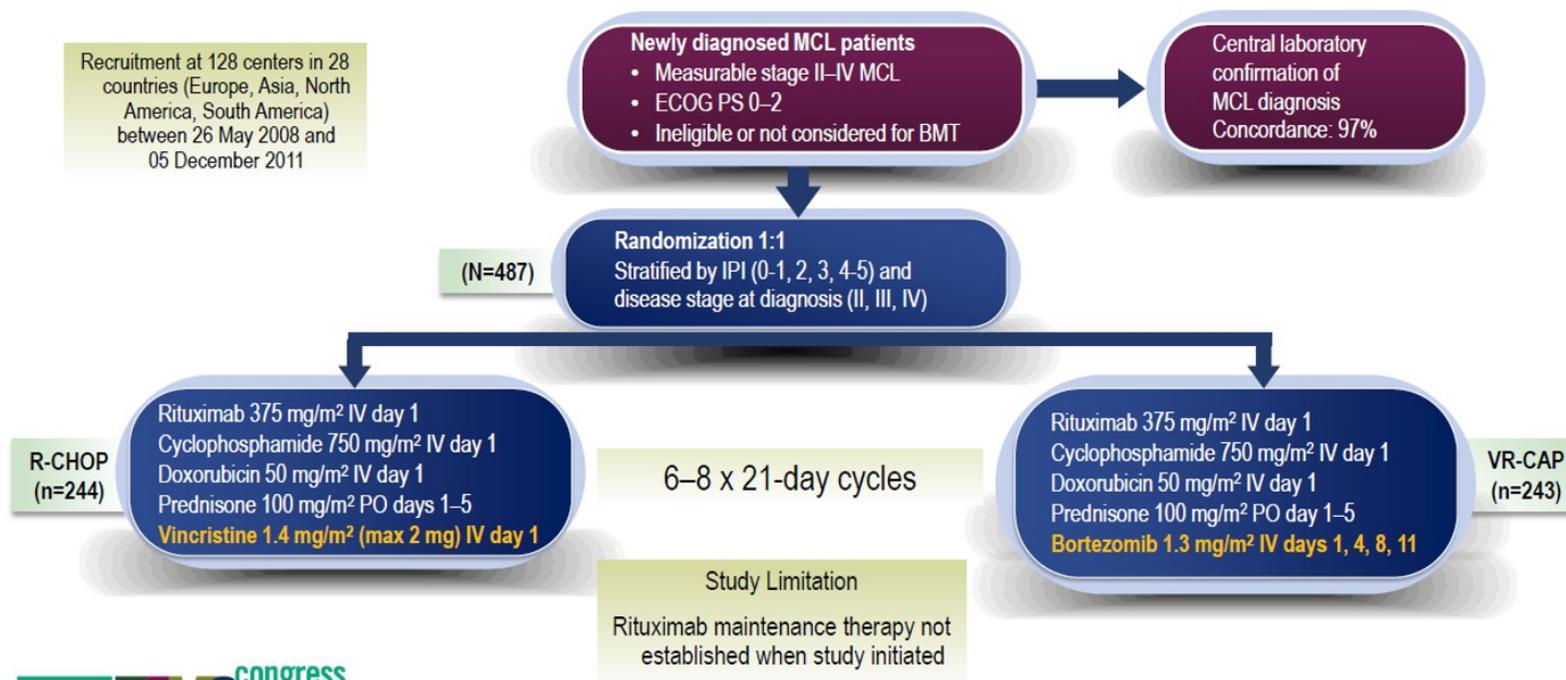
Mantle cell lymphoma

Therapeutic algorithm



Mantle cell lymphoma

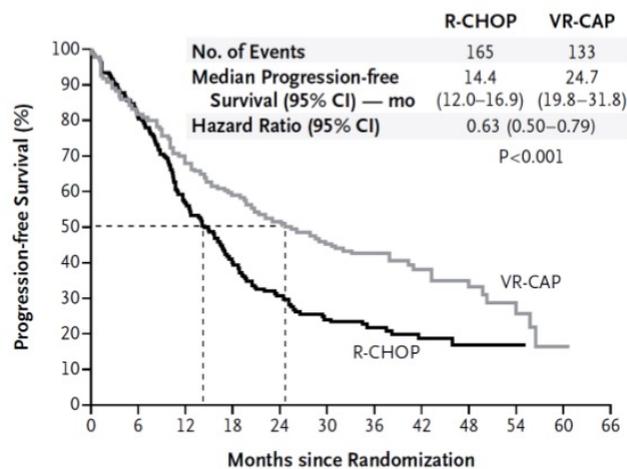
VR-CAP vs. R-CHOP



Mantle cell lymphoma

VR-CAP vs. R-CHOP

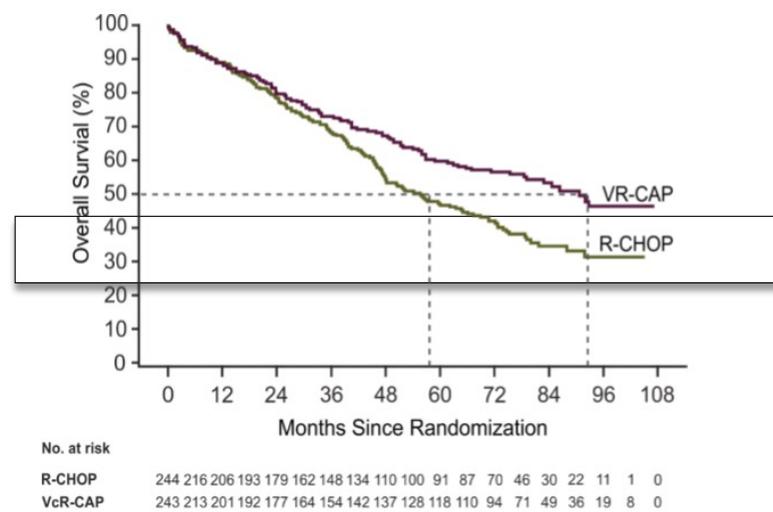
Progression-free Survival



No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66
R-CHOP	244	181	116	79	55	36	22	16	9	3	0	0
VR-CAP	243	187	146	122	94	66	42	28	17	8	1	0

Robak, NEJM 2015

Overall Survival

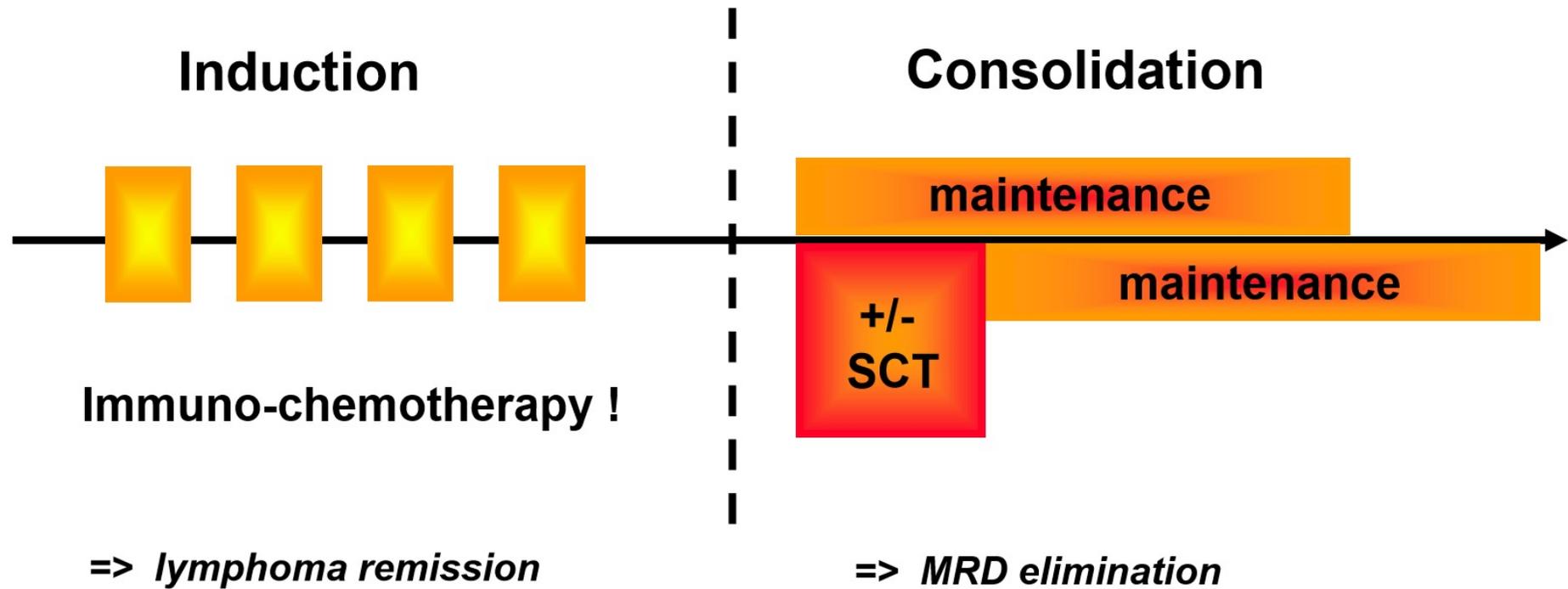


Median follow-up: approx. 80 months

Robak, Lancet Oncol 2019

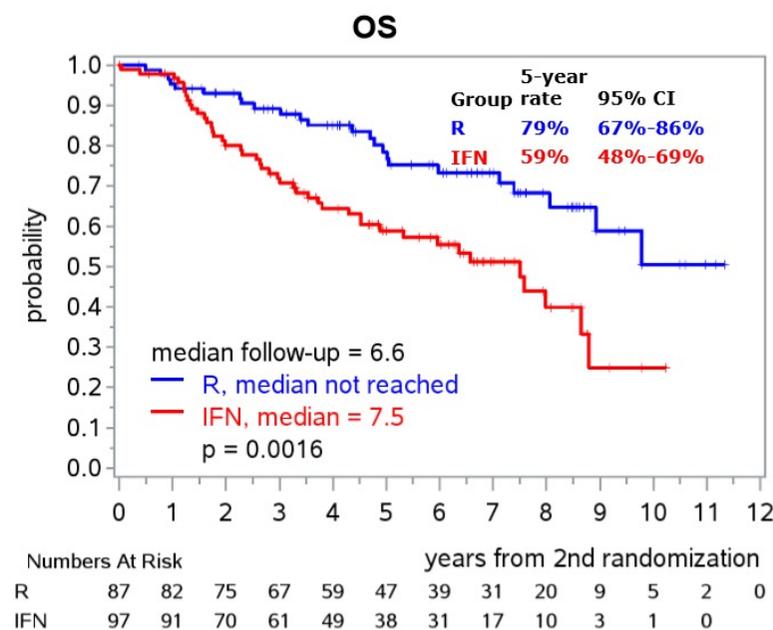
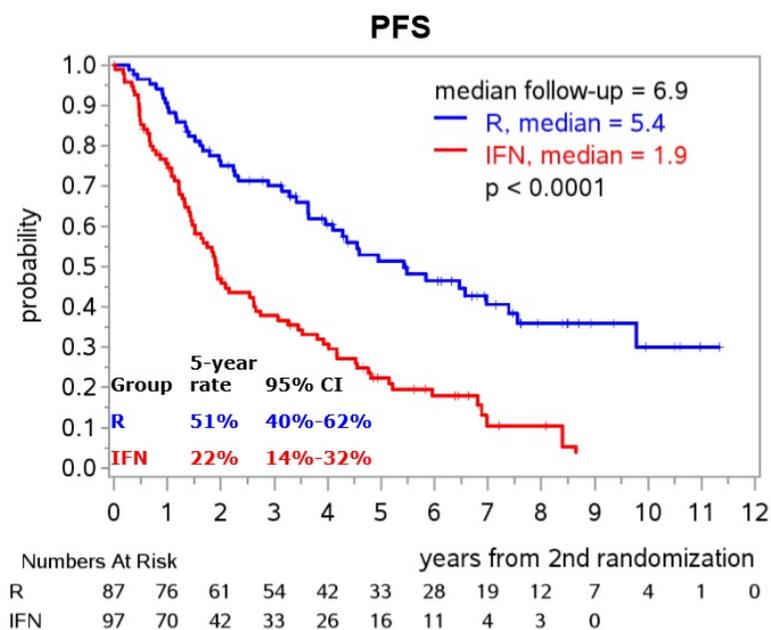
Mantle cell lymphoma

Optimal treatment?



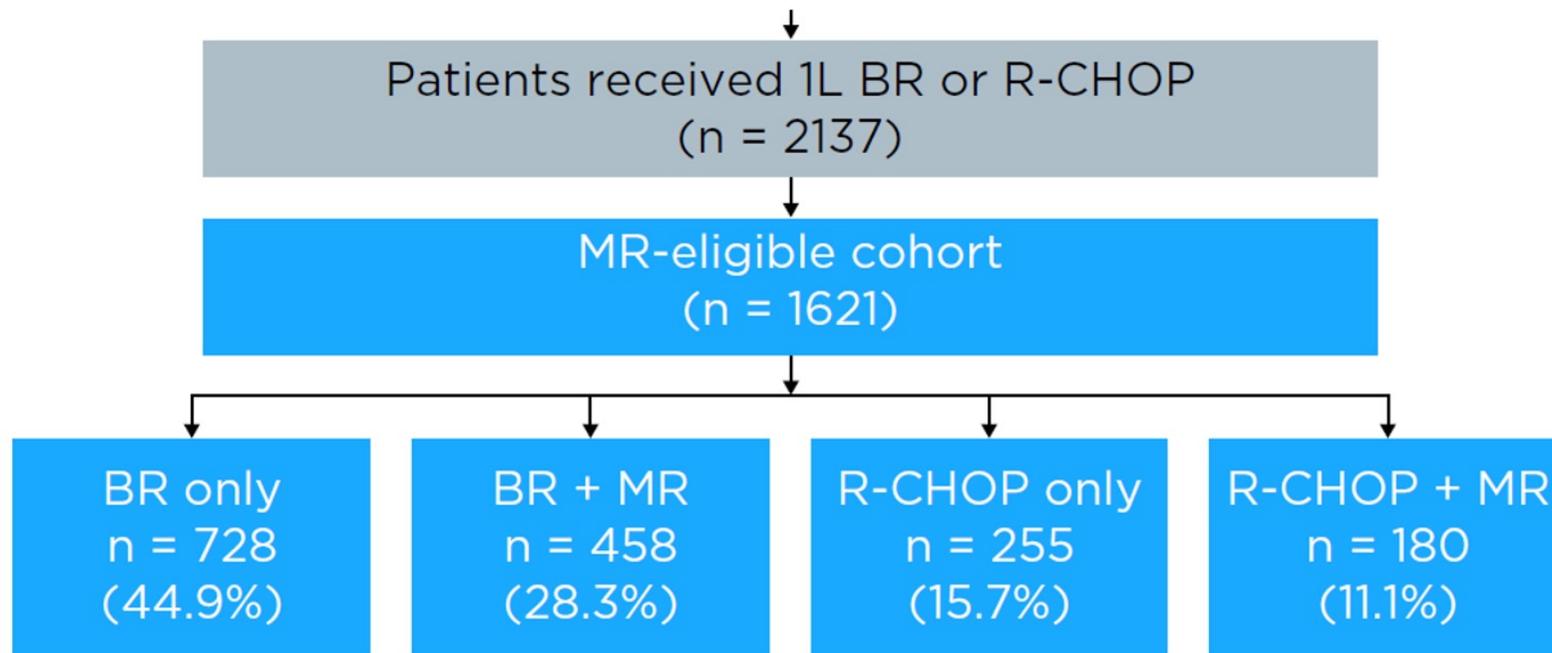
Mantle cell lymphoma

R-CHOP +/- R maintenance

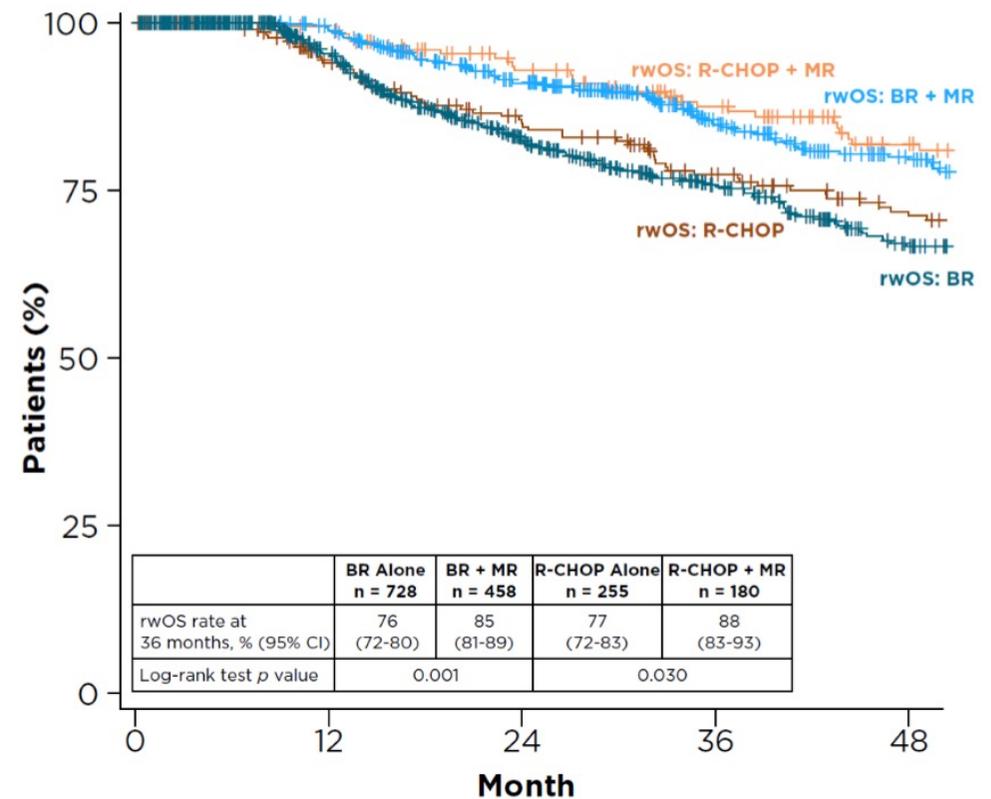
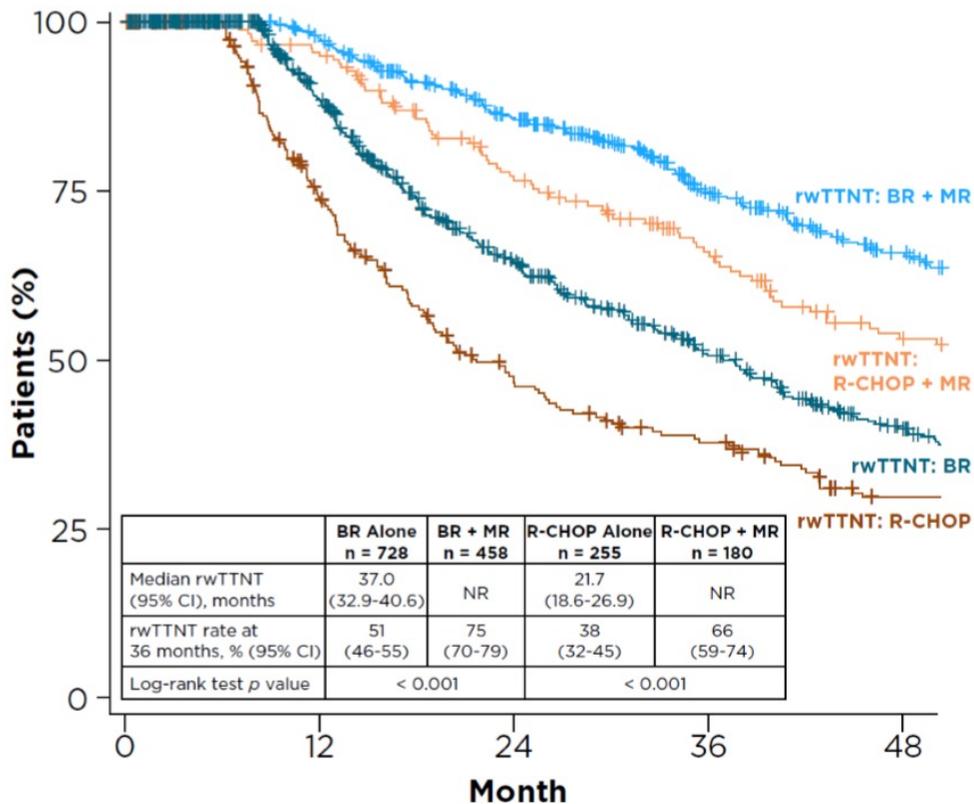


Kluin-Nelemans, 2020

ROLE OF MAINTENANCE RITUXIMAB AFTER FIRST-LINE BR OR R-CHOP IN MCL PATIENTS FROM A LARGE US REAL-WORLD COHORT



ROLE OF MAINTENANCE RITUXIMAB AFTER FIRST-LINE BR OR R-CHOP IN MCL PATIENTS FROM A LARGE US REAL-WORLD COHORT



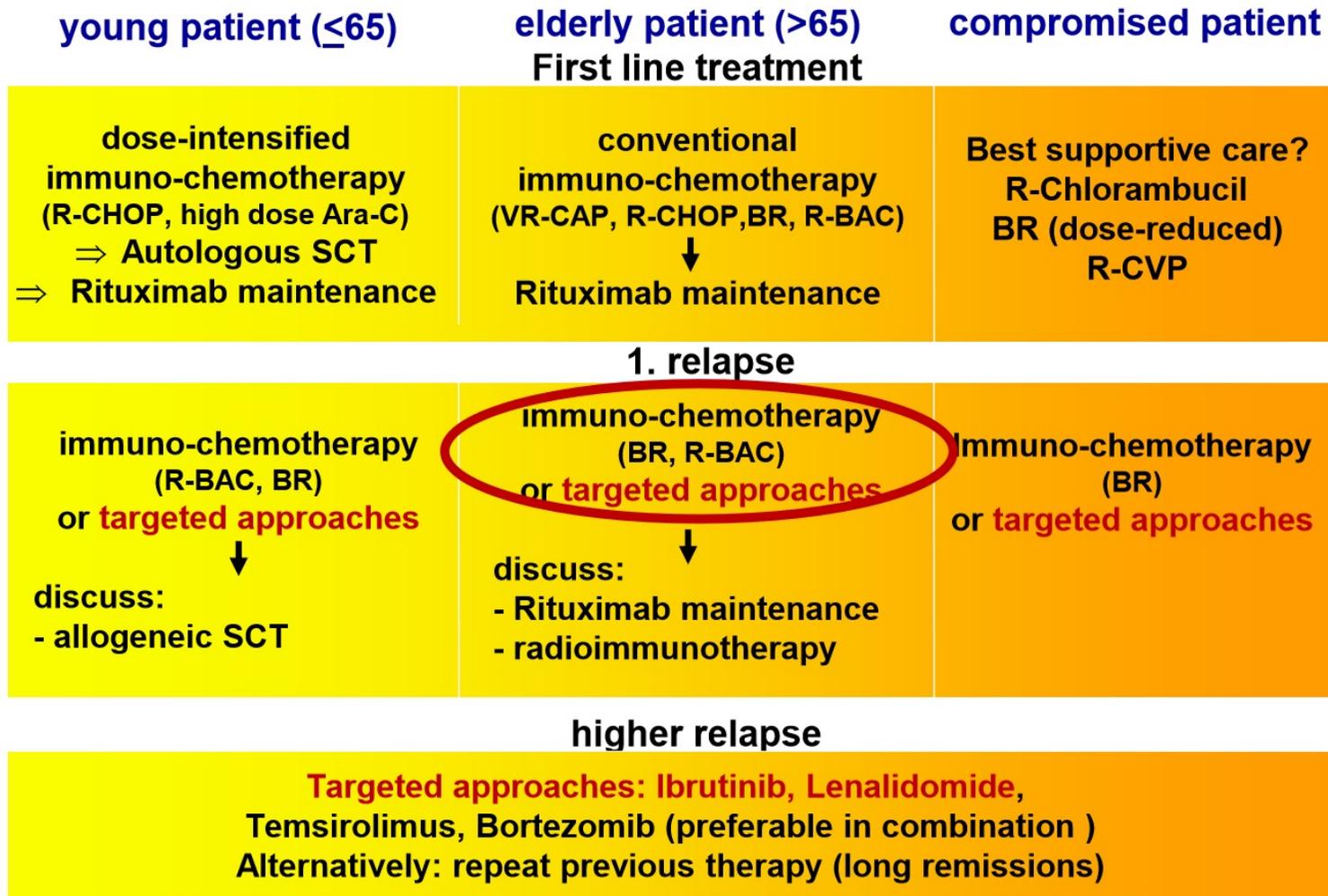
Salles, EHA 2021

ROLE OF MAINTENANCE RITUXIMAB AFTER FIRST-LINE BR OR R-CHOP IN MCL PATIENTS FROM A LARGE US REAL-WORLD COHORT

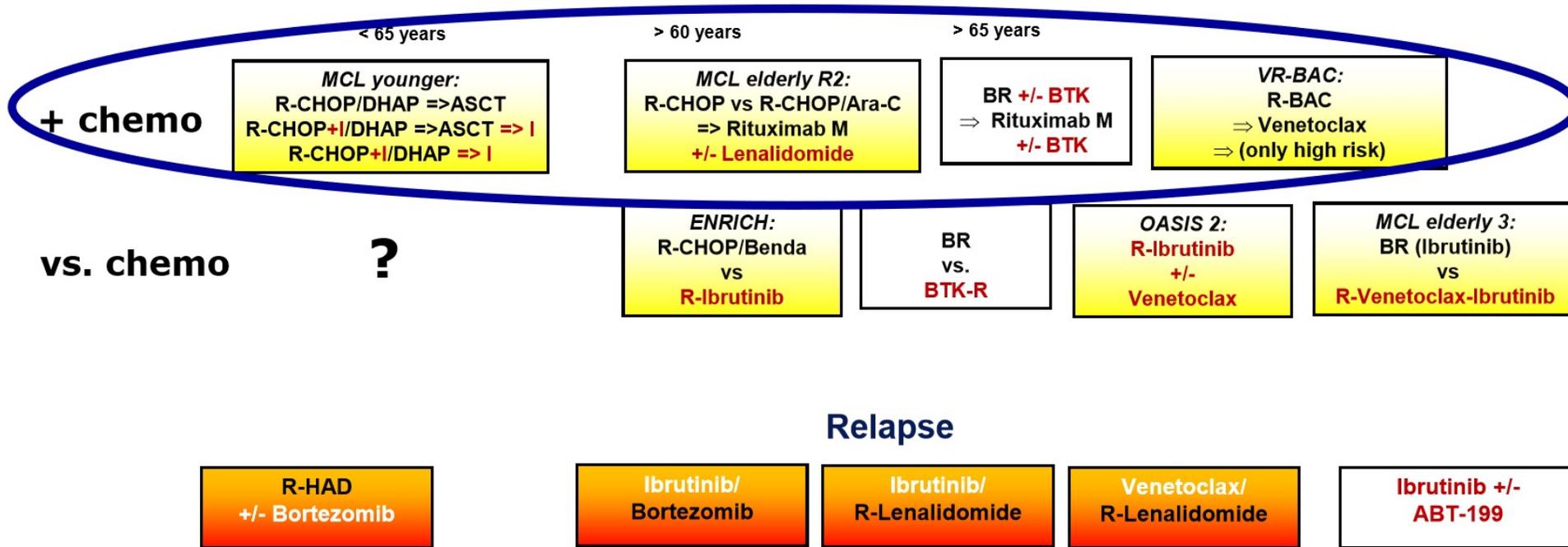
Variables	MR-Eligible Cohort (N = 1621)					
	rwTTNT			rwOS		
	HR	95% CI	p Value	HR	95% CI	p Value
MR: No vs Yes	2.13	1.82-2.48	< 0.001	1.69	1.38-2.06	< 0.001
Age: ≥ 65 years	1.53	1.28-1.82	< 0.001	2.70	2.07-3.54	< 0.001
LDH/ULN: ≥ 1.00 vs < 1.00	1.36	1.06-1.75	0.017	1.51	1.11-2.06	0.008
Blastoid/pleomorphic MCL: Yes vs No	1.54	1.19-2.01	0.001	1.56	1.12-2.17	0.008
Bulky disease: Yes vs No	1.32	1.08-1.61	0.007	1.35	1.04-1.75	0.022
WBC: ≥ 10 × 10 ⁹ /L vs < 10 × 10 ⁹ /L	1.11	0.90-1.36	0.300	1.24	0.96-1.61	0.110
ECOG PS: ≥ 2 vs 0-1	0.95	0.63-1.43	0.800	1.57	0.98-2.52	0.061

Mantle cell lymphoma

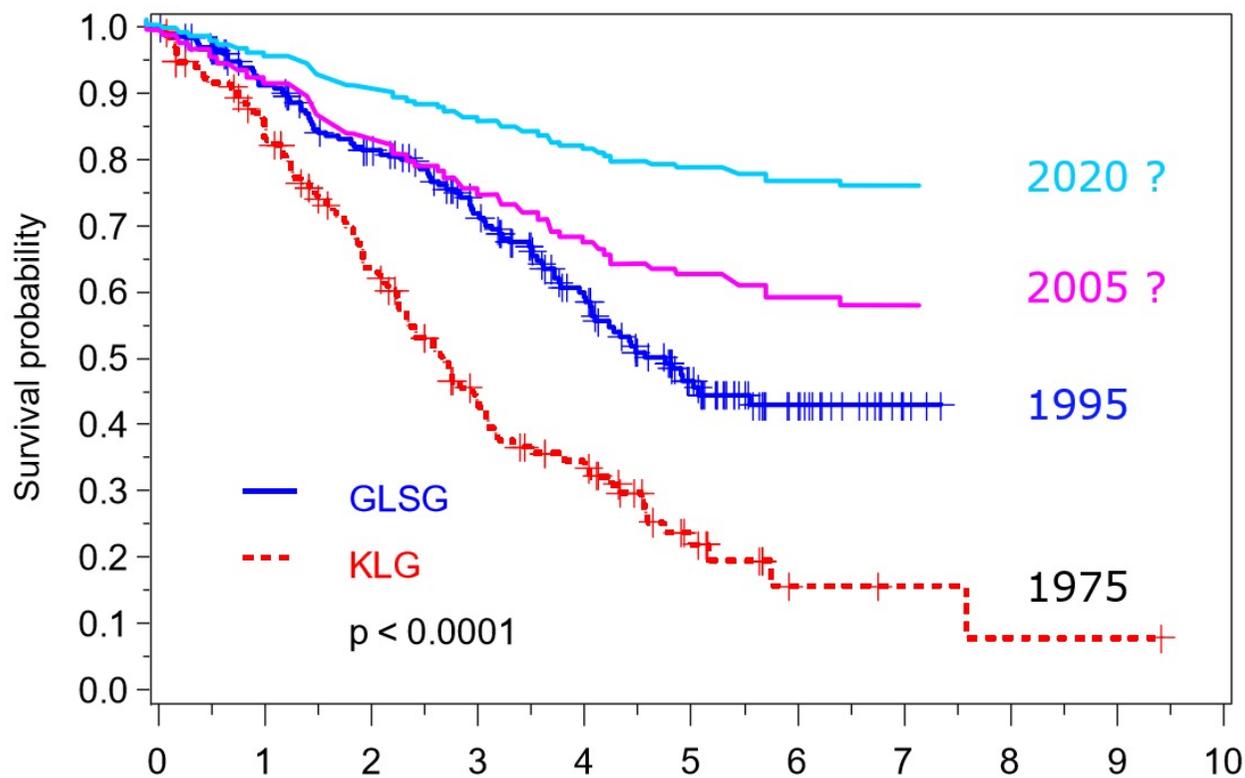
Therapeutic algorithm



European MCL Network Study generation 2022



Prognosis of MCL



Patients at risk

	0	1	2	3	4	5	6	7	8	9	10
GLSG	202	171	145	117	82	47	20	3	0		
KLG	134	105	74	43	30	12	3	2	1		

Herrmann, ASH 2006

Acknowledgement

