9th POSTGRADUATE
Lymphoma
Conference

The Copernican revolution on the basis of theTRIANGLE study

Martin Dreyling
LMU Hospital

Florence,
March 20-21, 2025

Hotel Brunelleschi

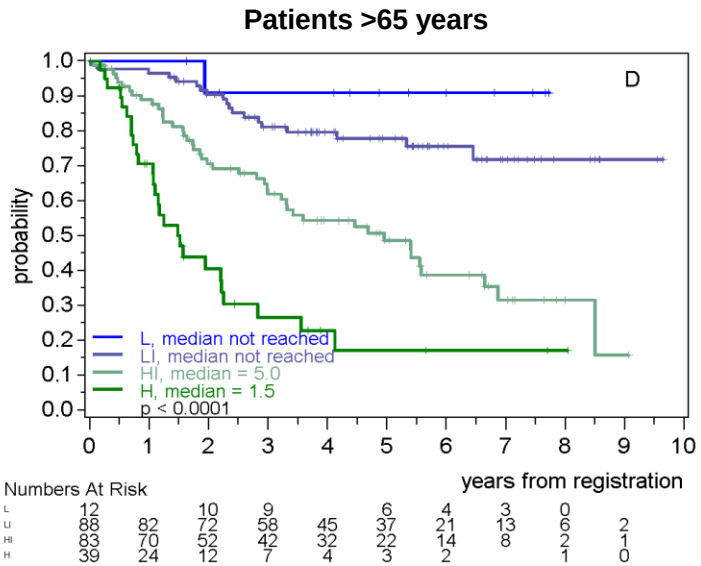
President:
P.L. Zinzani

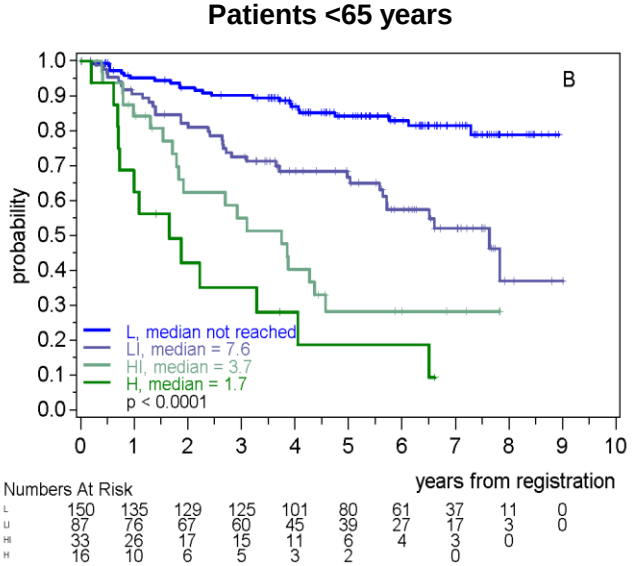
Mantle cell lymphoma
Overview

- **Clinical/biological risk profile**
- **First line: chemotherapy standards**
- **targeted approaches**

Combined MIPI-c
Overall survival

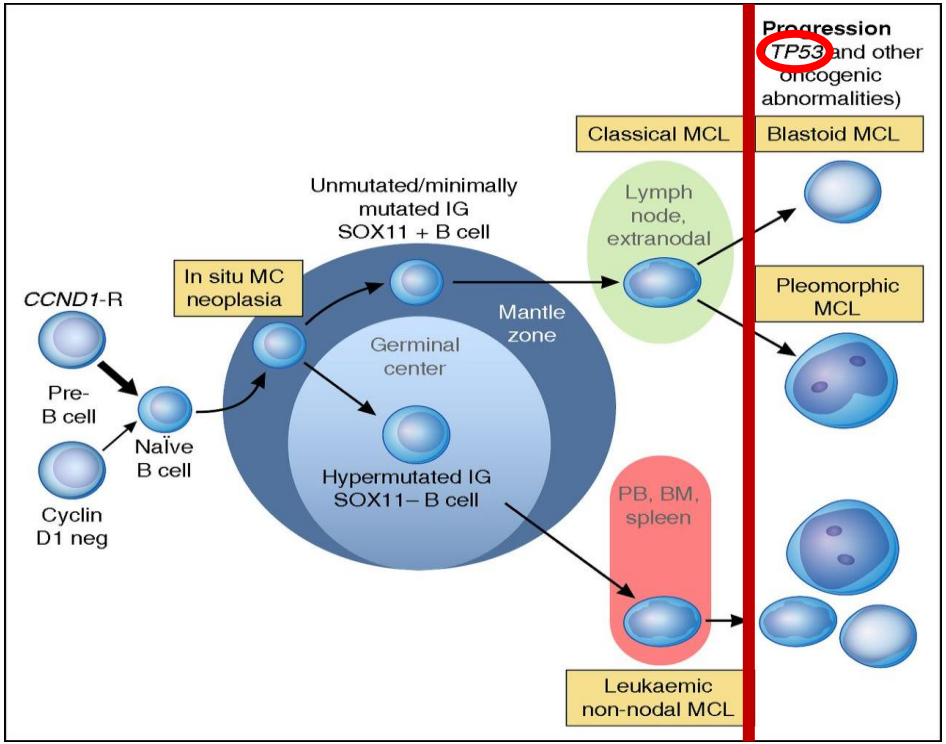
LMU KLINIKUM





Hoster, JCO 2016

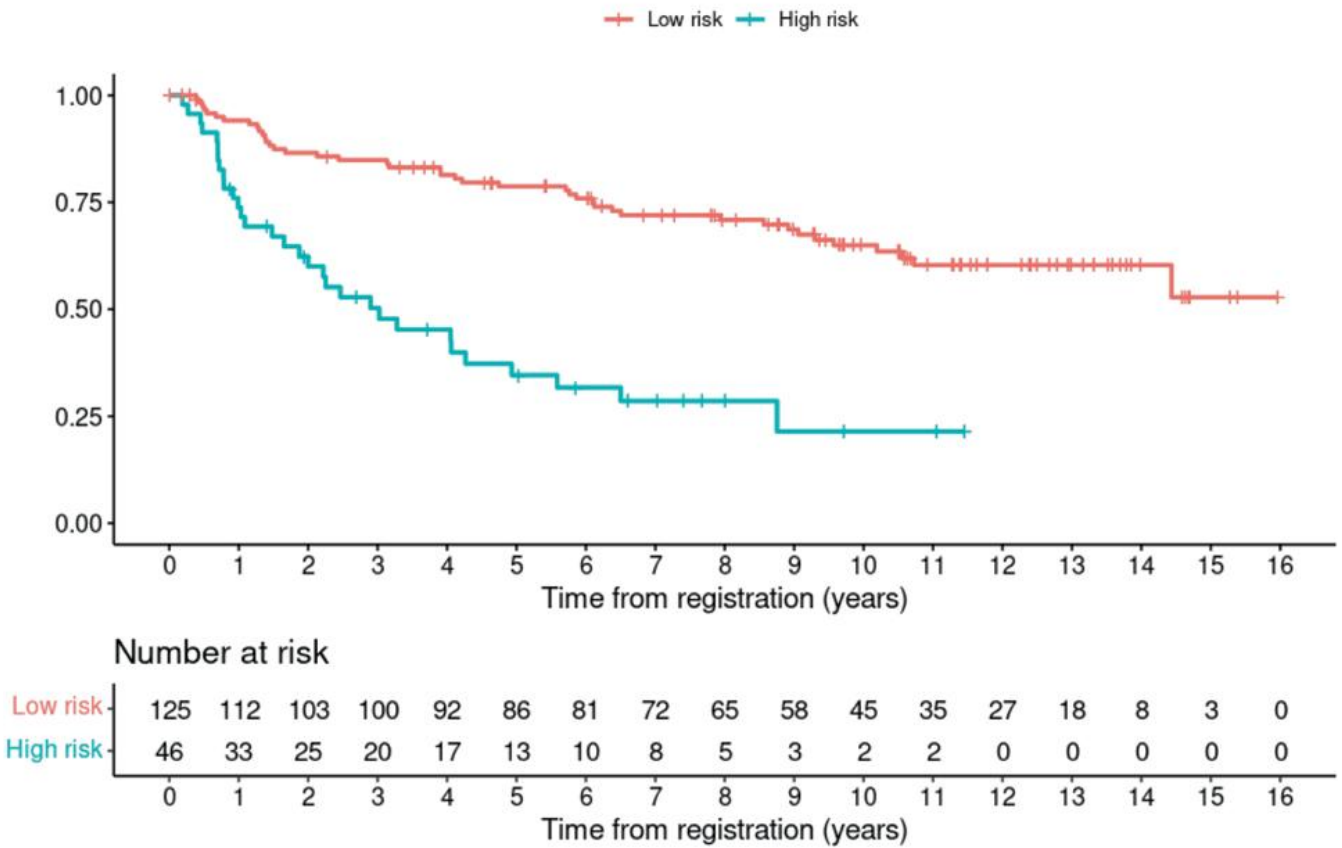
Mantle cell lymphoma
Spectrum of disease



Dreyling, Ann Oncol 2017

High risk Mantle cell lymphoma (young patients)

Overall survival (n=465)



Scheubeck, Leukemia 2023

Mantle cell lymphoma
Overview

- Clinical/biological risk profile
- chemotherapy standards in first line
- targeted approaches

Mantle cell lymphoma
Therapeutic algorithm

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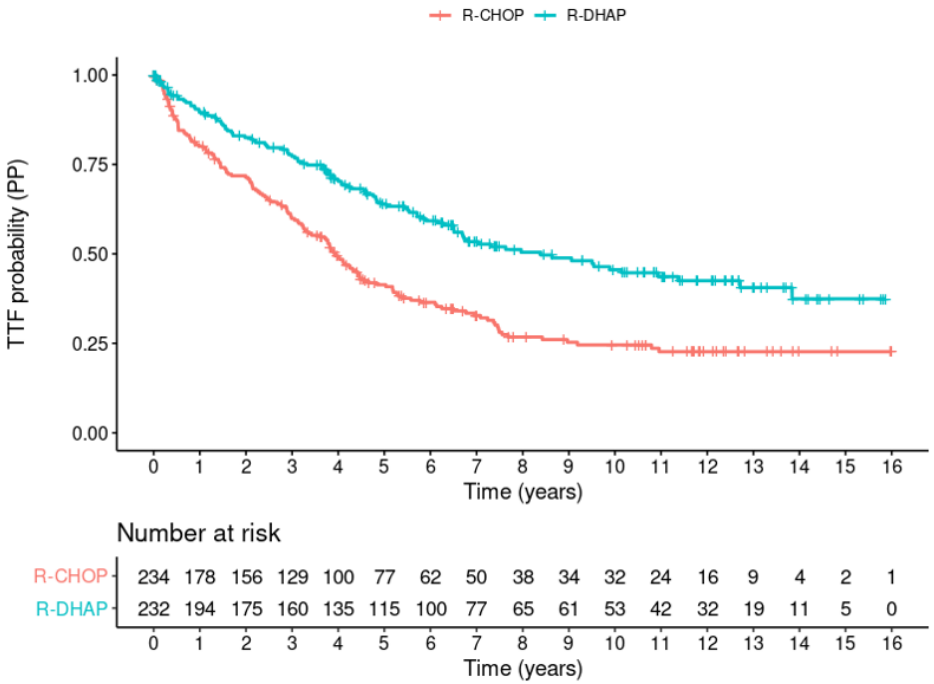
young patient (≤65)	elderly patient (>65)	compromised patient
First line treatment		
dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (VR-CAP, R-CHOP,BR, R-BAC) ⇓ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP
1. relapse		
immuno-chemotherapy (R-BAC, BR) or targeted approaches ⇓ discuss: - allogeneic SCT	immuno-chemotherapy (BR, R-BAC) or targeted approaches ⇓ discuss: - Rituximab maintenance - radioimmunotherapy	Immuno-chemotherapy (BR) or targeted approaches
higher relapse		
Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination) Alternatively: repeat previous therapy (long remissions)		

Dreyling, ESMO CR MCL 2017 (updated)

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):

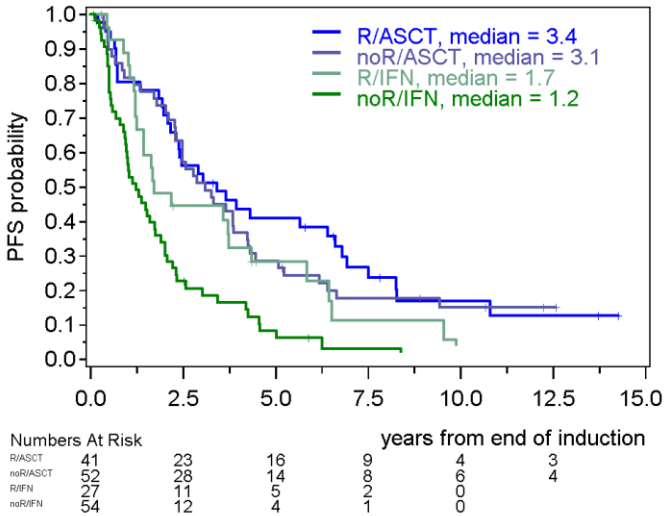
  R-CHOP 25% (19% - 32%)

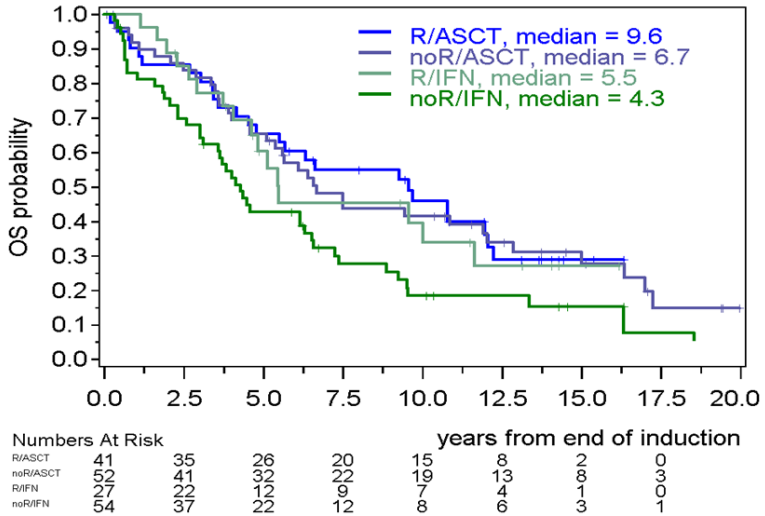
  R-DHAP 46% (39% - 54%)
- Overrunning analysis (adjusted for interim analyses):

  Hazard ratio 0.59 (p=0.038)

Hermine, ASH 2021, #380, JCO 2022

Mantle cell lymphoma
Autologous SCT (first line)



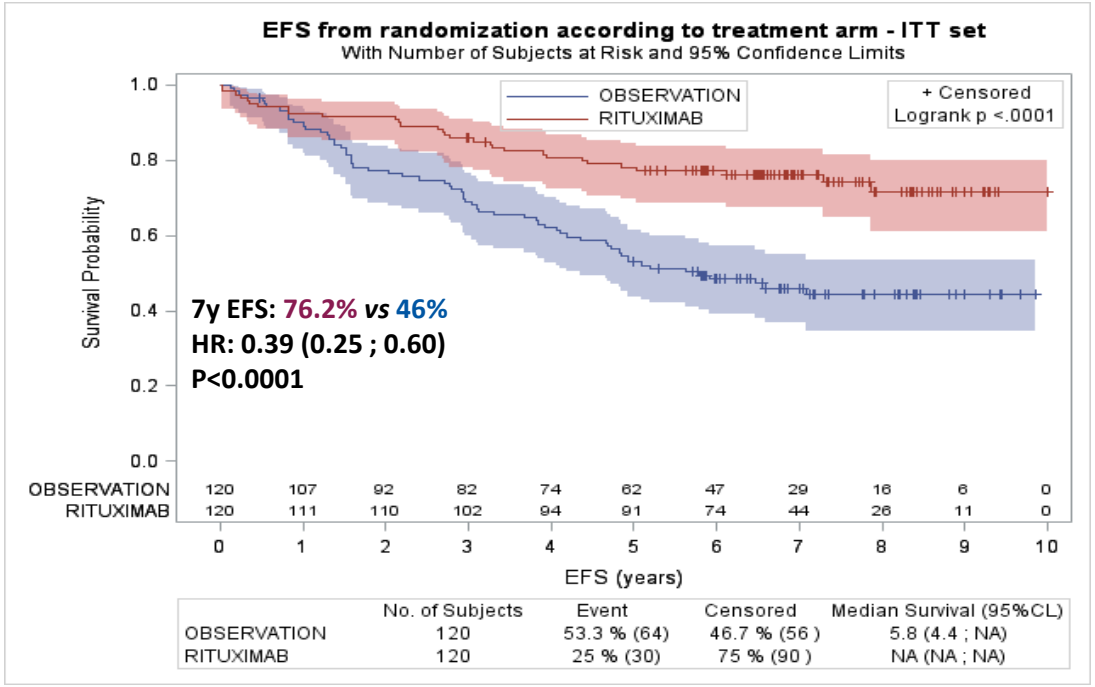


Zöllner, Lancet Hematol 2021 (in press)

EFS from randomization

Median FU for living patients:

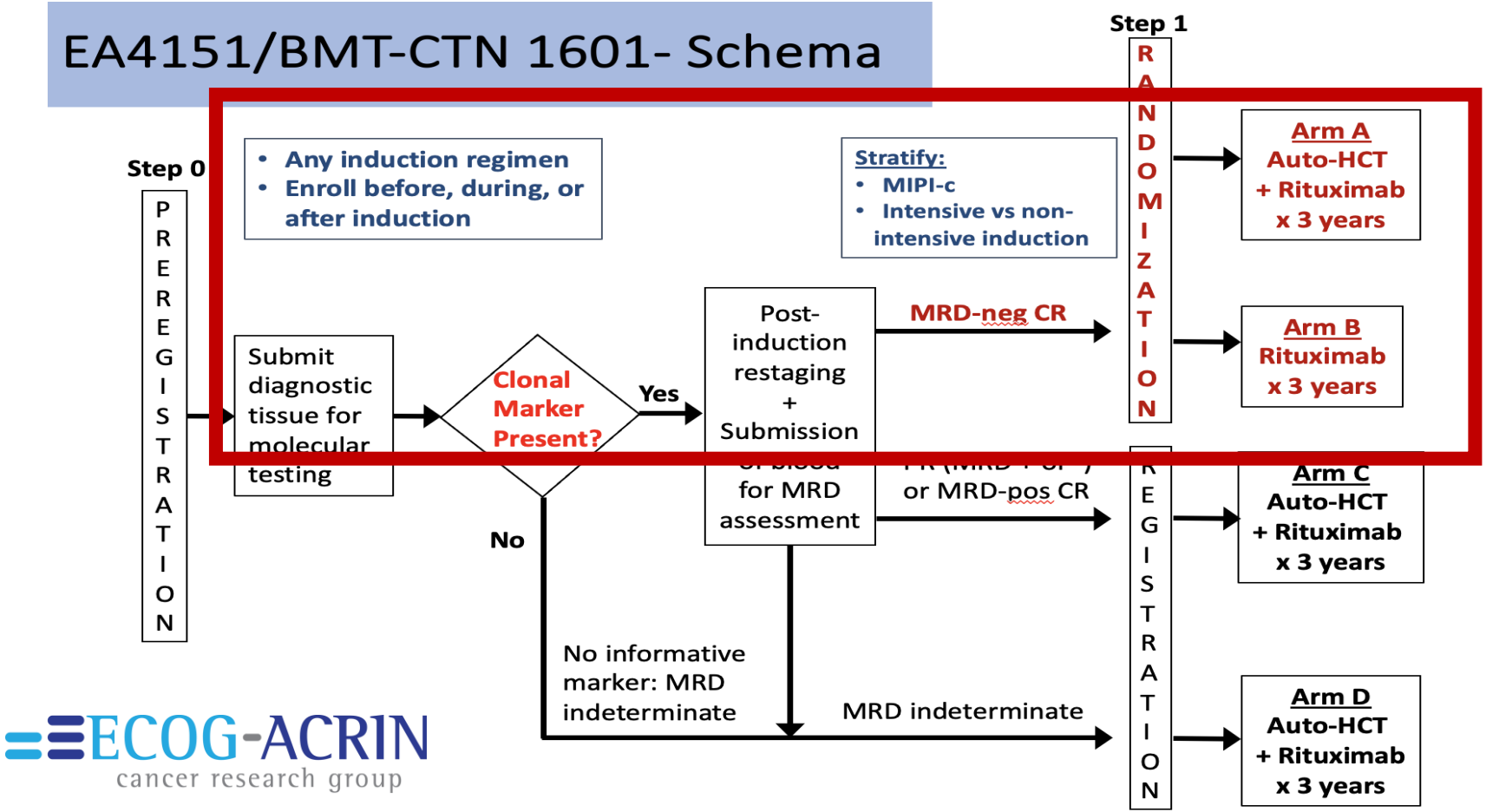
- **from inclusion: 7.5 y (95% CI 7.4-7.7)**
- **from randomization: 7 y (95% CI 6.8-7.2)**



Nature of first Event	Observation, N=64/120 (53%)	Rituximab N=30/120 (25%)
Relapse	51 (80%)	19 (63%)
Death w/o relapse	9 (14%)	6 (20%)
Serious infections	4 (6%)	4 (13%)
Life threatening allergy to R	0	1 (4%)

Sarkozy, ICML: # 100

EA4151/BMT-CTN 1601- Schema



ECOG-ACRIN
cancer research group

Dreyling, ASH 2024: LBA #6

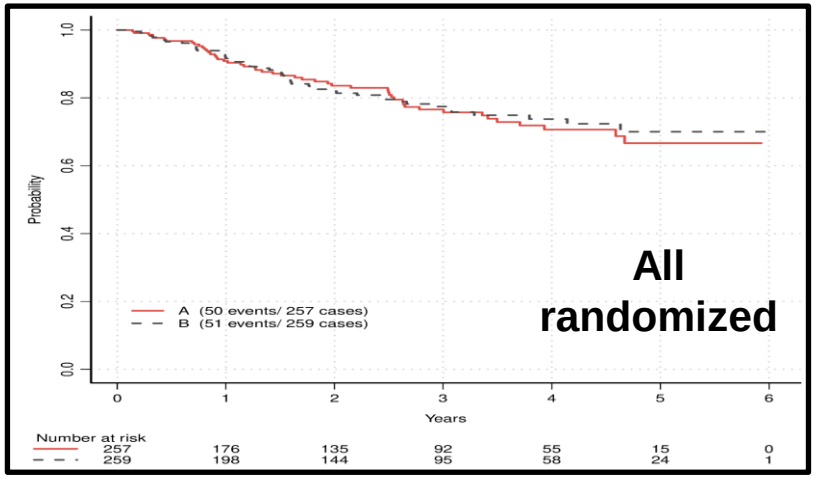
Patient Characteristics

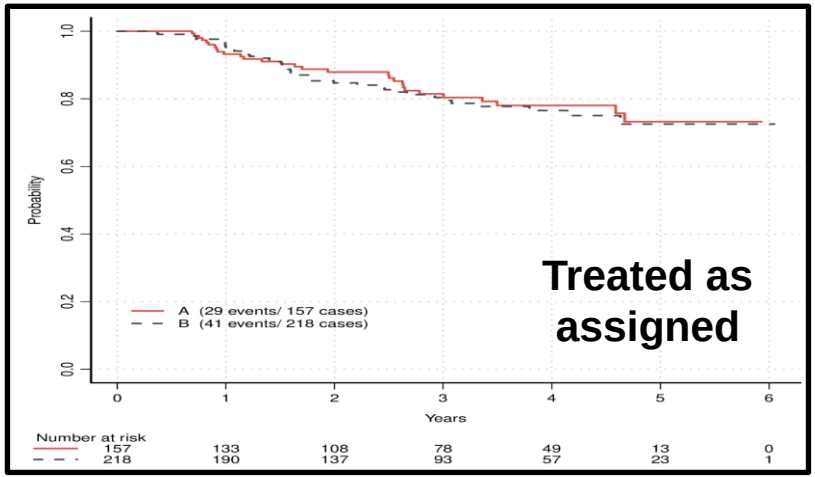
Variable		Arm A (AutoHCT) N=257	Arm B (no AutoHCT) N=259	Arm C (MRD+) N=49	Arm D (MRD indet) N=85	Total N=650
Age	Median Range	**59** **(28-71)**	**61** **(27-70)**	60 (33-70)	60 (41-70)	60 (27-71)
Sex	Male Female	**81%** **19%**	**77%** **23%**	76% 24%	82% 18%	79% 21%
Race	White Black	**92%** **5%**	**92%** **5%**	87% 11%	96% 1%	92% 5%
Elev LDH		**66%**	**66%**	36%	32%	34%
MIPI-c	High/Hi-int Low/Low-int	**33%** **67%**	**37%** **63%**	42% 58%	42% 58%	37% 63%
Intensive induction	Yes No	**74%** **26%**	**74%** **26%**	69% 31%	68% 32%	73% 27%
BTK-i	Induction Maintenance	**7.4%** **0**	**7.7%** **0.4%**	6.1% 2.0%	5.9% 0	7.2% 0.3%

Dreyling, ASH 2024: LBA #6

PFS – Arms A & B

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





Dreyling, ASH 2024: LBA #6

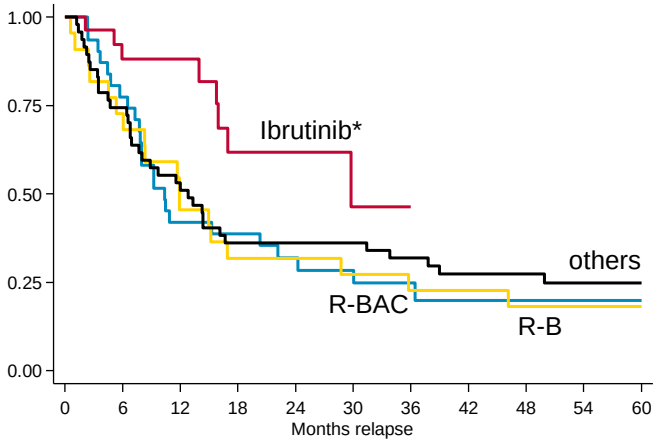
Mantle cell lymphoma
Overview

- Clinical/biological risk profile
- chemotherapy standards in first line ?
- targeted approaches

copyright G. Hess

Ibrutinib in relapsed MCL (POD 24)
Overall survival

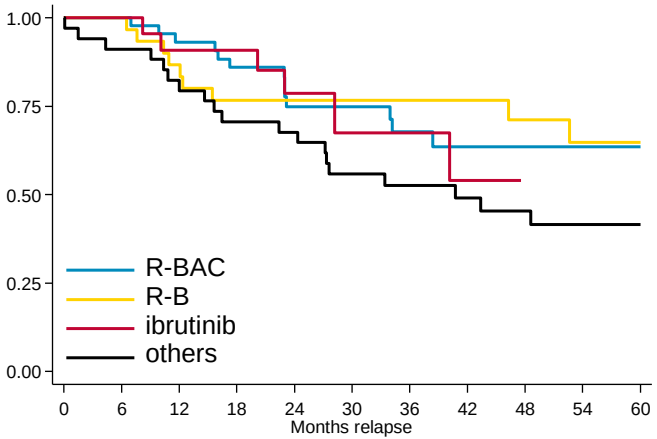
Early POD



At risk:											
BAC	31	24	13	12	9	8	5	4	3	3	3
BR	22	16	10	7	7	6	5	5	4	3	2
ibru	27	21	16	8	5	3	0	0	0	0	0
other	47	35	24	17	17	17	15	11	11	10	6

*Ibru vs R-B and R-BAC (P=0.02); vs others (P=0.03)

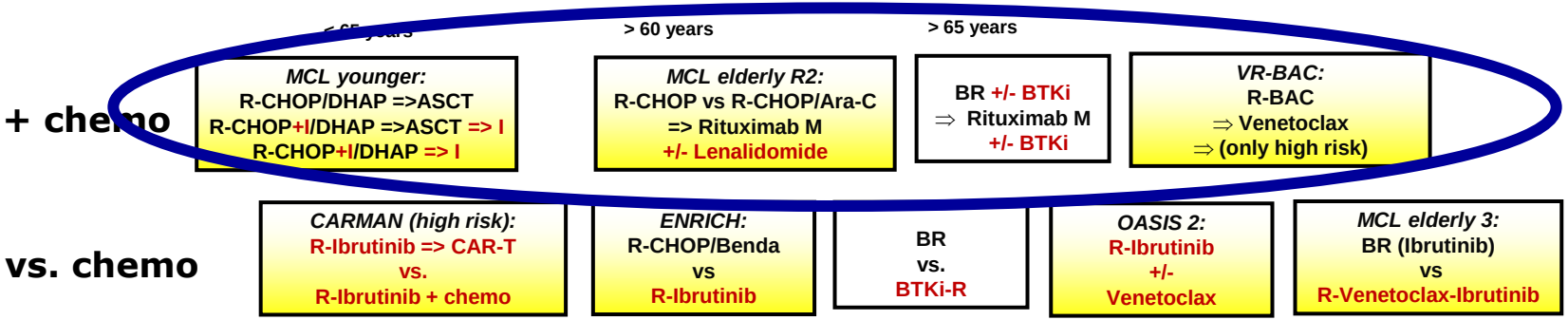
Late-POD



At risk:											
BAC	45	45	40	35	26	23	16	14	12	8	7
BR	32	30	26	23	22	20	16	15	13	10	9
ibru	23	22	20	18	10	6	6	4	0	0	0
other	34	31	27	24	23	19	16	13	12	8	7

Visco, Leukemia 2021

European MCL Network
Study generation 2025



Relapse

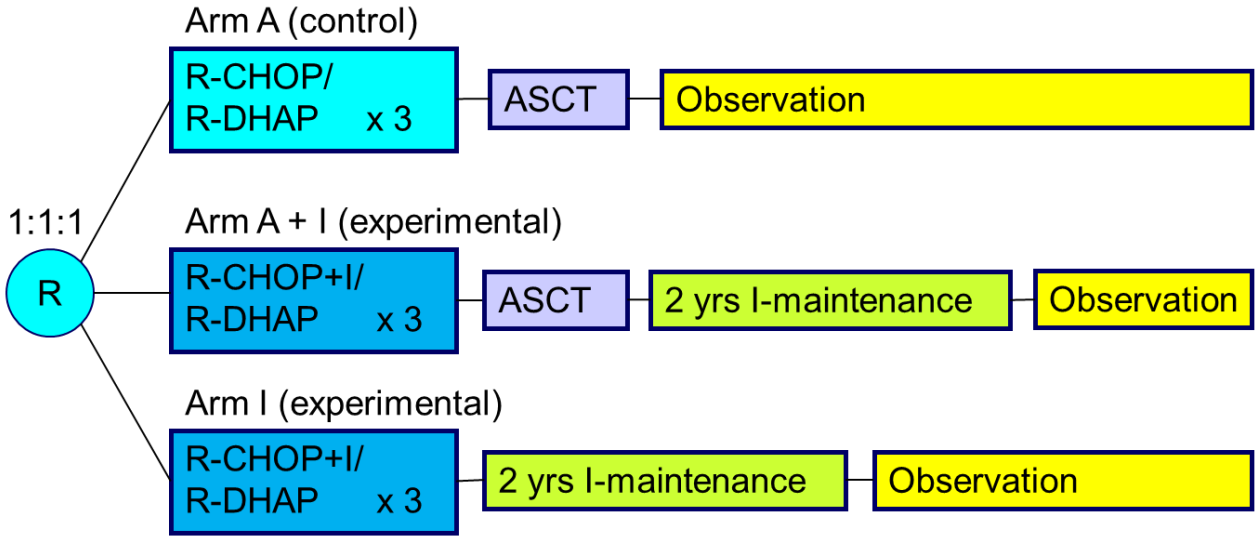
Ibrutinib/ Bortezomib	Ibrutinib +/- ABT-199	Pirtobrutinib + Glofitamab

TRIANGLE: Trial Design

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

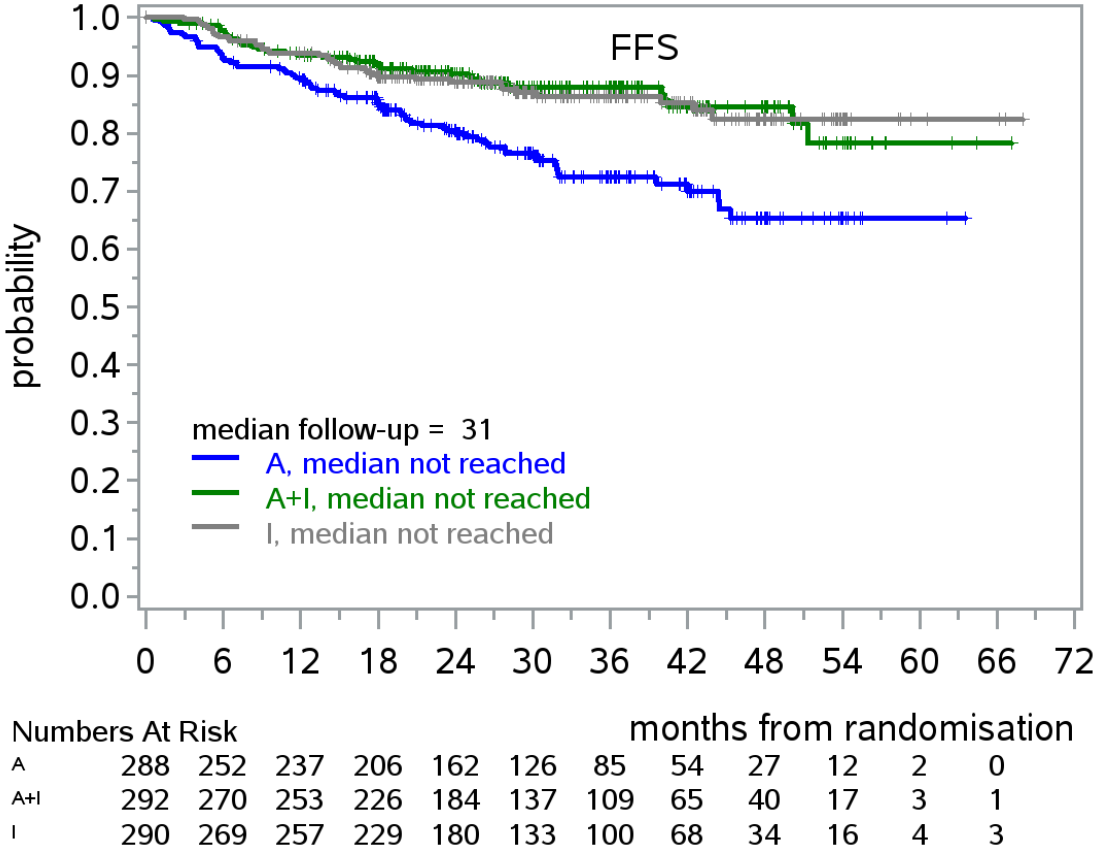
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety



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

Dreyling, ASH 2022:#1, Lancet 2024

TRIANGLE: FFS Superiority of A+I vs. I ?



- Test A+I vs. I ongoing, no decision yet

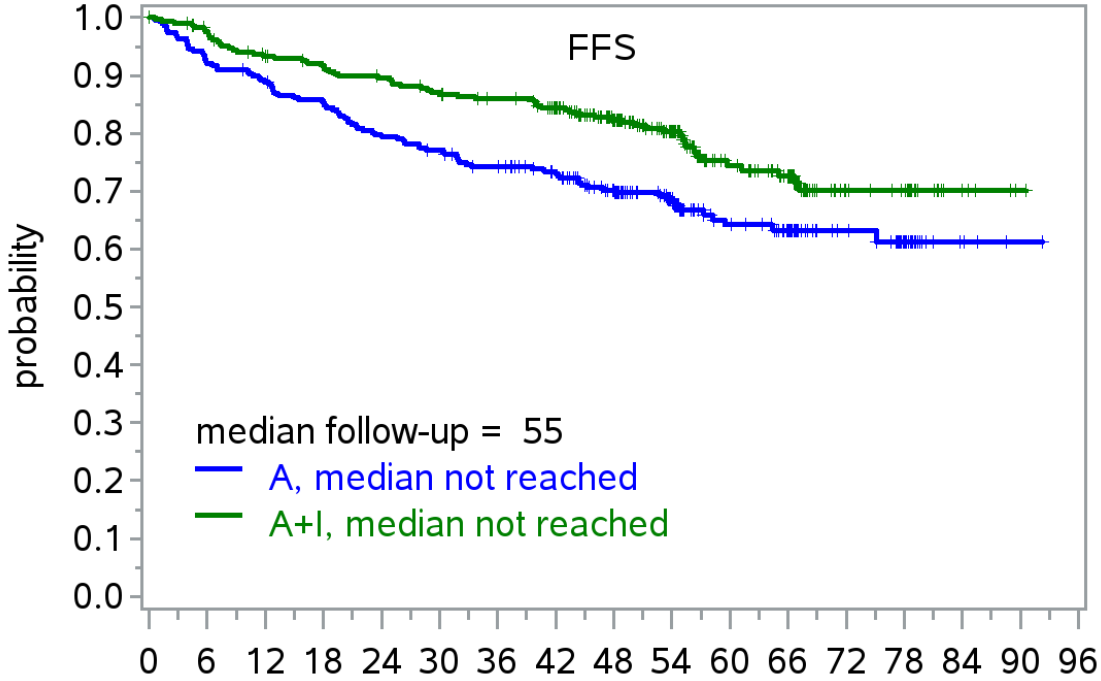
Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

Dreyling, ASH 2022: #1 A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Mantle cell lymphoma ASH 2022
Open questions

- longer follow-up (from 31 to 55 months)
- significance of OS ?
- R maintenance in the era of ibrutinib containing regimens ?
- ASCT in the era of ibrutinib containing regimens ?

TRIANGLE: FFS Superiority of A+I vs. A

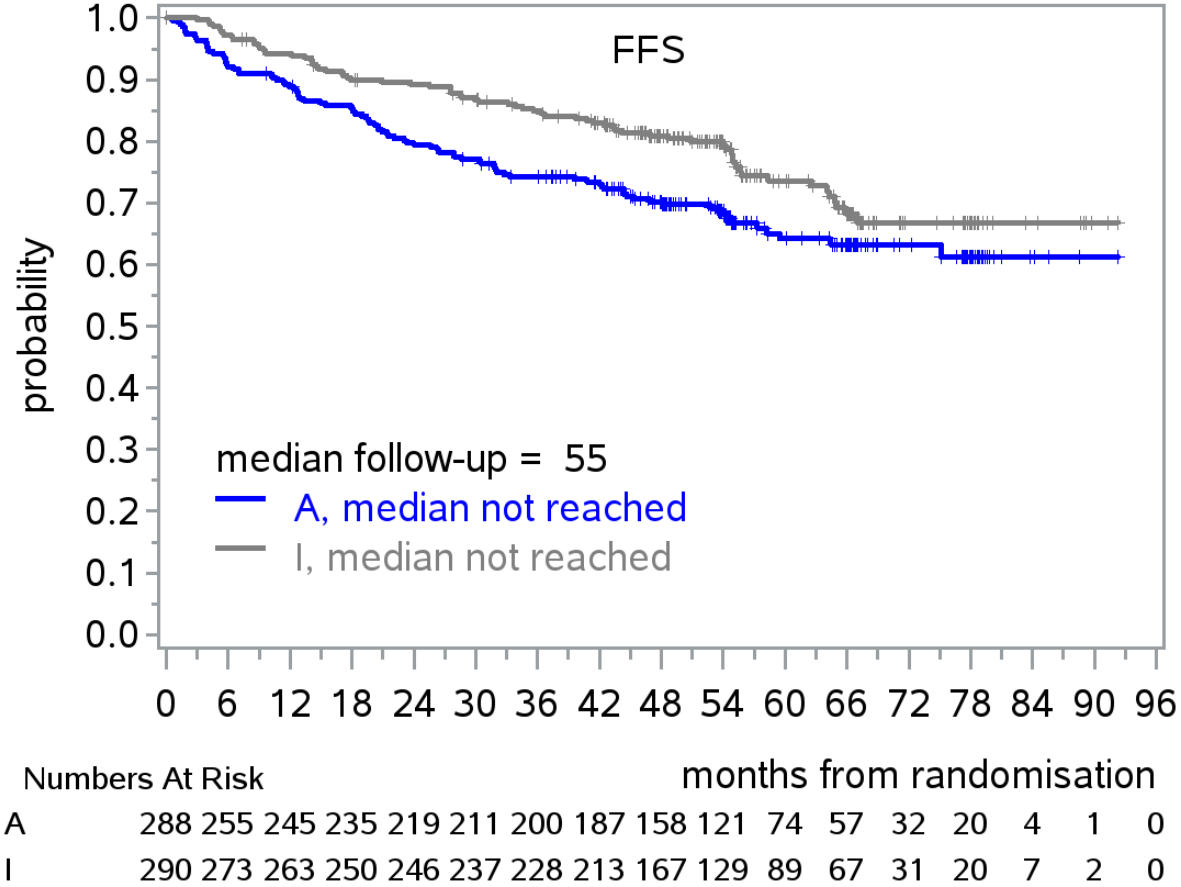


Numbers At Risk

A	288	255	245	235	219	211	200	187	158	121	74	57	32	20	4	1	0
A+I	292	274	259	252	245	236	230	217	180	141	89	70	28	24	6	2	0

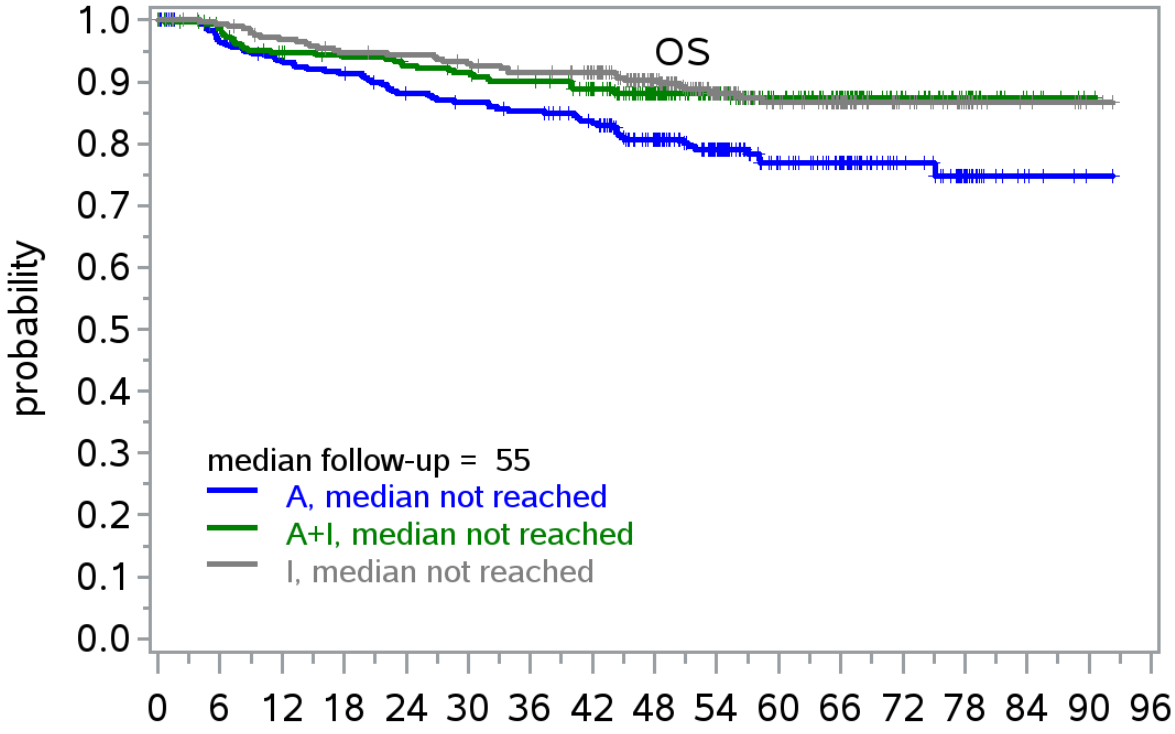
- Superiority of A+I vs. A
  - 4-year FFS A+I: 82%
  - 4-year FFS A: 70%
- p-value (overrunning, one-sided): p=0.0026
- HR (A+I vs. A): HR=0.64

TRIANGLE: No FFS Superiority of A vs. I



- Superiority of A vs. I rejected
  - 4-year FFS A: 70% (MCL Younger: 70%)
  - 4-year FFS I: 81%
- p-value (overrunning, one-sided): p=0.9890
- HR (A vs. I): HR=1.29
- Superiority of I (two-sided, retrospective) p=0.0208

TRIANGLE: Overall survival



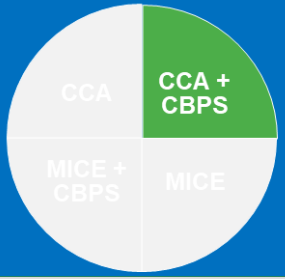
Numbers At Risk

A	288	270	260	255	243	238	233	222	186	145	92	73	41	23	5	1
A+I	292	281	267	262	257	253	248	235	201	160	107	83	39	26	8	2
I	290	282	273	266	264	259	253	243	194	147	101	78	41	21	7	2

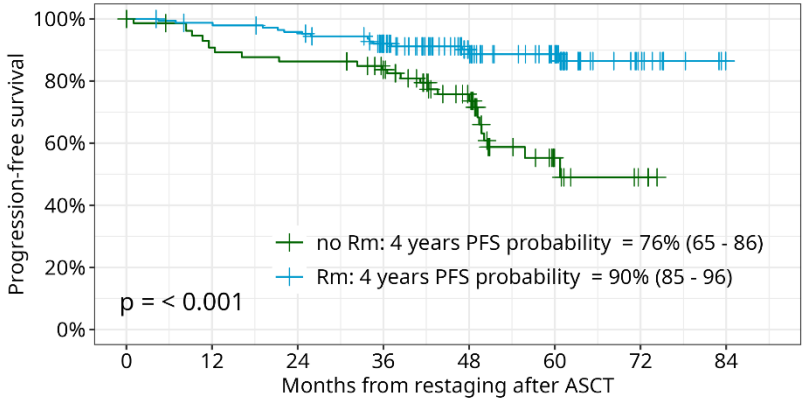
- 4-year OS:
  - A: 81%
    (MCL Younger exp.: 80%)
  - A+I: 88%
  - I: 90%

- two-sided test, (a = 5%):
  - A vs. I: p=0.0019, HR: 0.565
  - A vs. A+I: p=0.0036, HR I: 0.587
  - A+I vs. I: ongoing

Primary endpoint: Progression-free survival Weighted Kaplan-Meier curves*

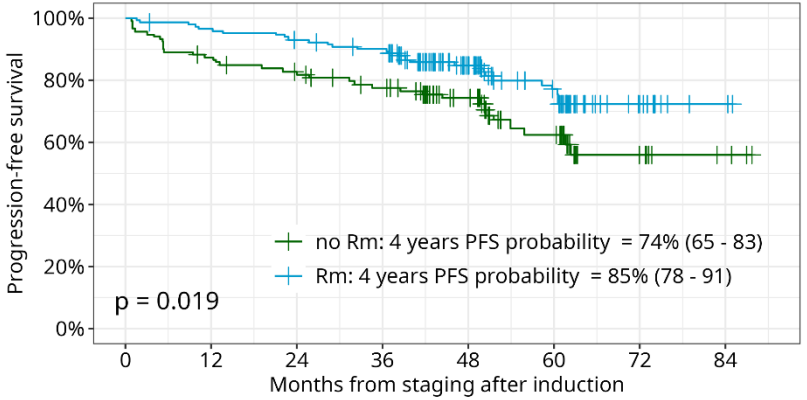


Arm A+I: PFS



noRm group								
At risk	85.3	75.1	71.6	63.8	41	12.9	6	0
Event	0	8.1	11.5	13.5	19.5	28.7	29.7	29.7
Rm group								
At risk	151.8	146.9	142.1	125.8	85.7	63	24.5	0
Event	0	3.1	6.9	12.8	14.6	15.5	16.6	16.6

Arm I: PFS

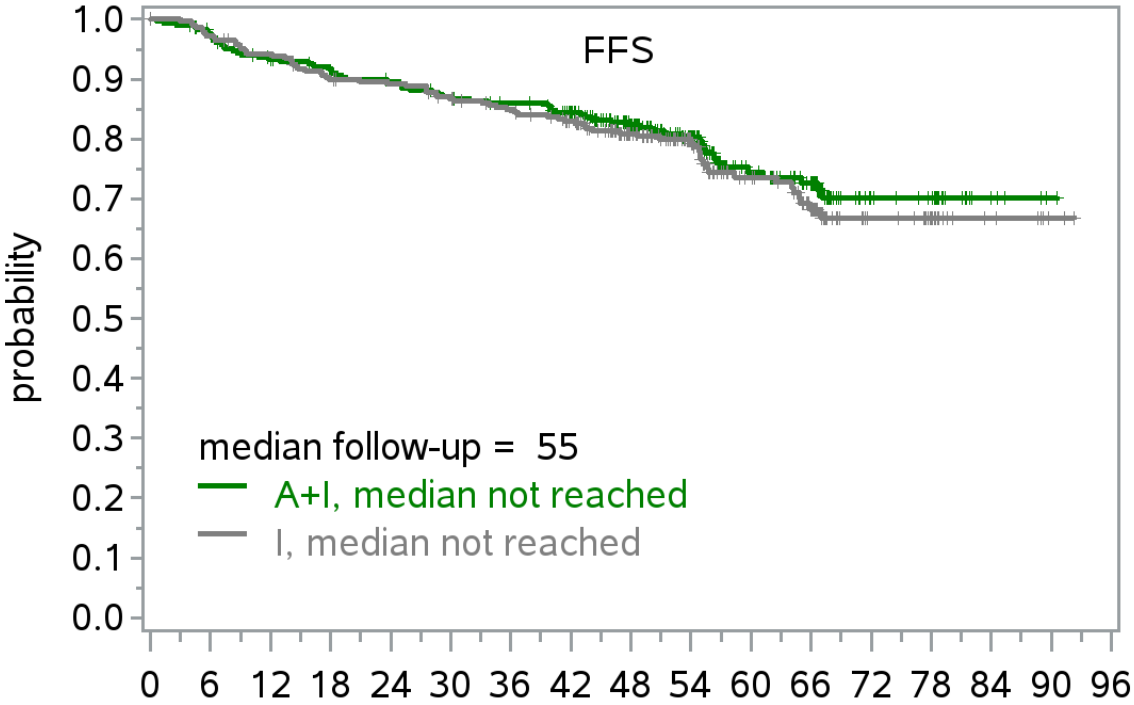


noRm group								
At risk	116.7	100.7	92.5	82.6	59.8	38.2	19.3	6
Event	0	14.1	20.2	26.2	29.2	35.8	37.7	37.7
Rm group								
At risk	157.2	148.3	141.5	135.3	87.3	57.9	23	3.9
Event	0	7	12.8	16.9	22.8	28.7	30.6	30.6

*Propensity Score including MIPI single variables, response after induction (arm I)/ after ASCT (arm A, A+I), Ki67, cytology

Ladetto, ASH 2024, #237

TRIANGLE: FFS Superiority of A+I vs. I ?



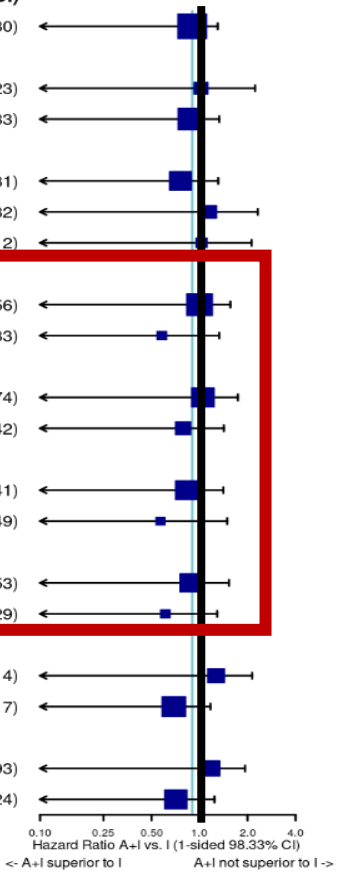
Numbers At Risk

A+I	292	274	259	252	245	236	230	217	180	141	89	70	28	24	6	2	0
I	290	273	263	250	246	237	228	213	167	129	89	67	31	20	7	2	0

- Superiority of A+I vs. I rejected
  - 4-year FFS A+I: 82%
  - 4-year FFS I: 81%
- p-value (overrunning, one-sided): p=0.21
- HR (A+I vs. I): HR=0.83

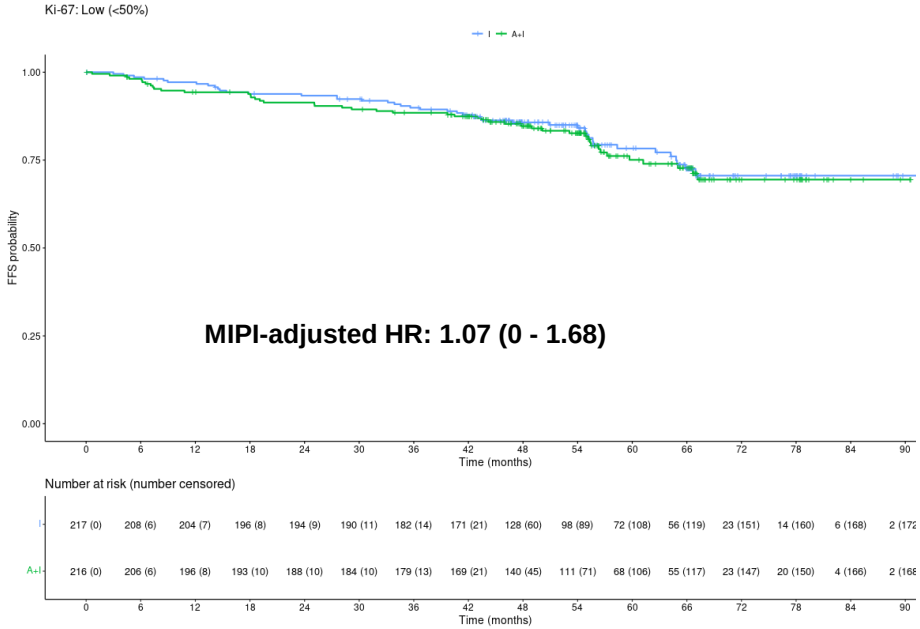
TRIANGLE: No FFS Superiority of A+I vs. I

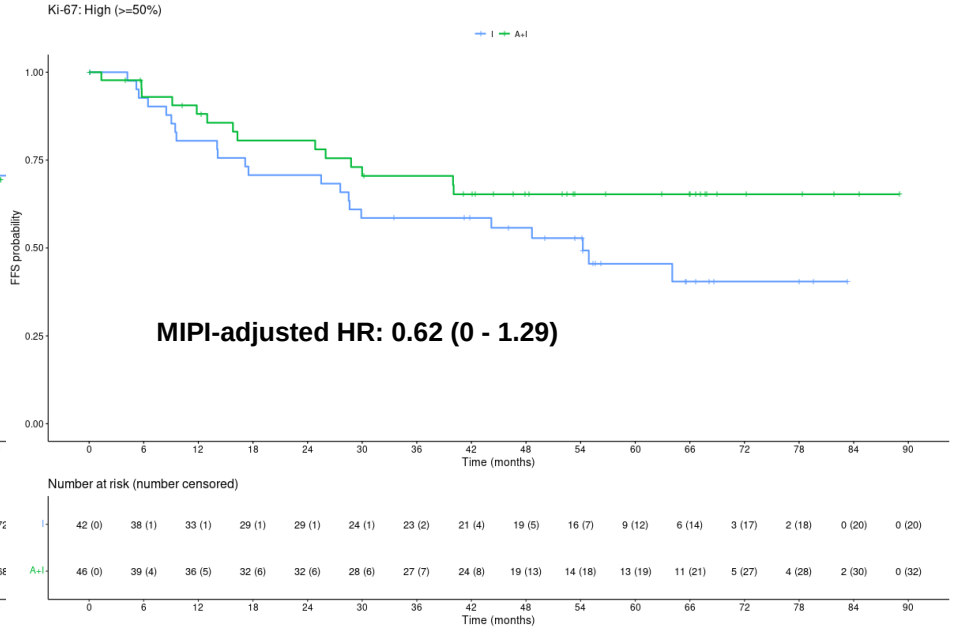
Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	582	134	0.90 (0 - 1.30)
Sex (p=0.71)			
Female	138	30	1.02 (0 - 2.23)
Male	444	104	0.88 (0 - 1.33)
MIPI			
Low	336	62	0.76 (0 - 1.31)
Intermediate (p=0.33)	157	37	1.15 (0 - 2.32)
High (p=0.56)	89	35	1.03 (0 - 2.12)
Cytology (p=0.15)			
Non-blastoid	461	92	1.00 (0 - 1.56)
Blastoid	65	27	0.58 (0 - 1.33)
Ki-67 (p=0.41)			
Low	357	71	1.05 (0 - 1.74)
High	164	54	0.79 (0 - 1.42)
P53 expression (p=0.43)			
Low	342	67	0.83 (0 - 1.41)
High	59	21	0.57 (0 - 1.49)
High risk biology (p=0.33)			
Low	323	60	0.88 (0 - 1.53)
High	64	34	0.61 (0 - 1.29)
R maintenance ITT (p=0.081)			
No	196	66	1.27 (0 - 2.14)
Yes	386	68	0.69 (0 - 1.17)
R maintenance mAT (p=0.14)			
No	228	76	1.18 (0 - 1.93)
Yes	354	58	0.71 (0 - 1.24)



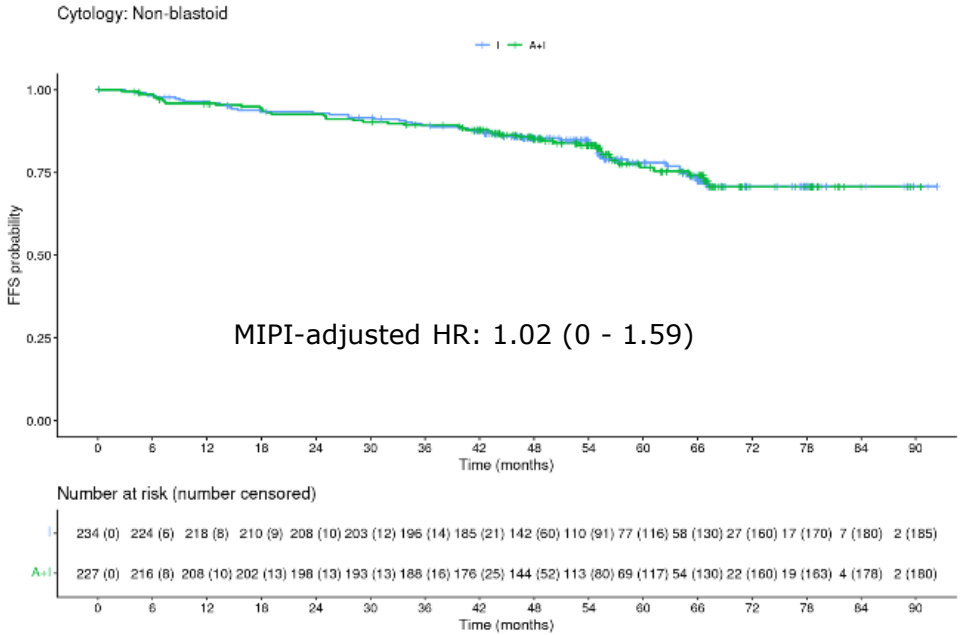
- trend towards superiority of A+I over I in patients in high risk patients:
  - Ki-67 >30%
  - blastoid cytology or
  - high p53 expression

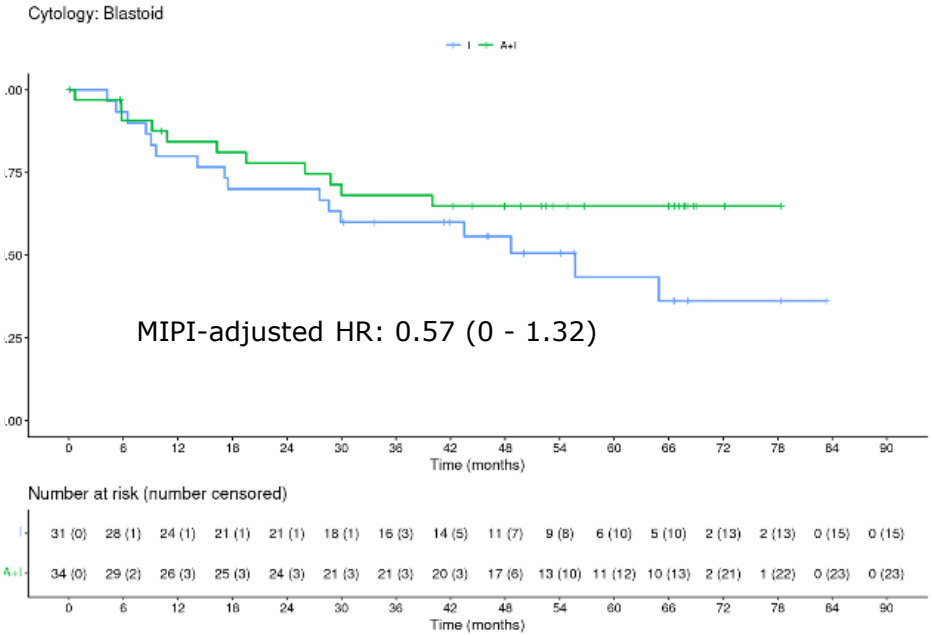
TRIANGLE: A+I vs. I (FFS) and Ki-67 (50% cut-off)



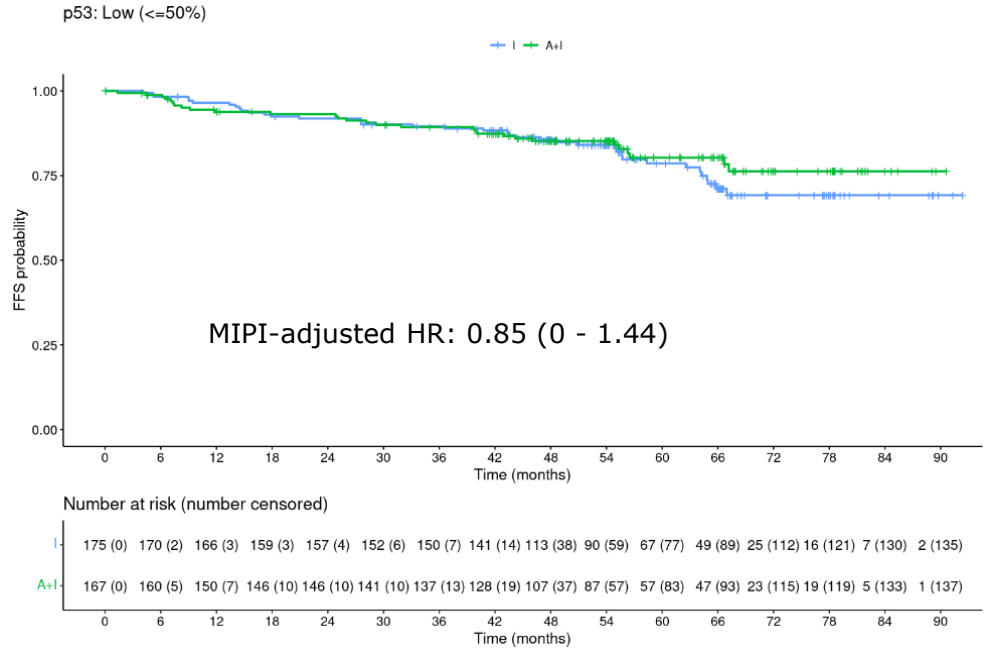


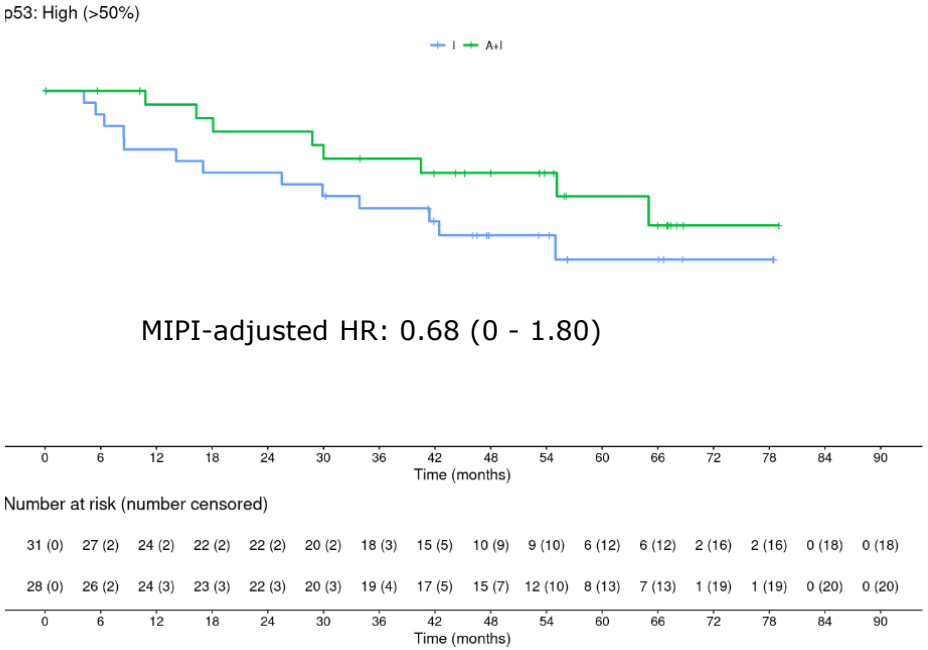
TRIANGLE: A+I vs. I (FFS) and blastoid variant



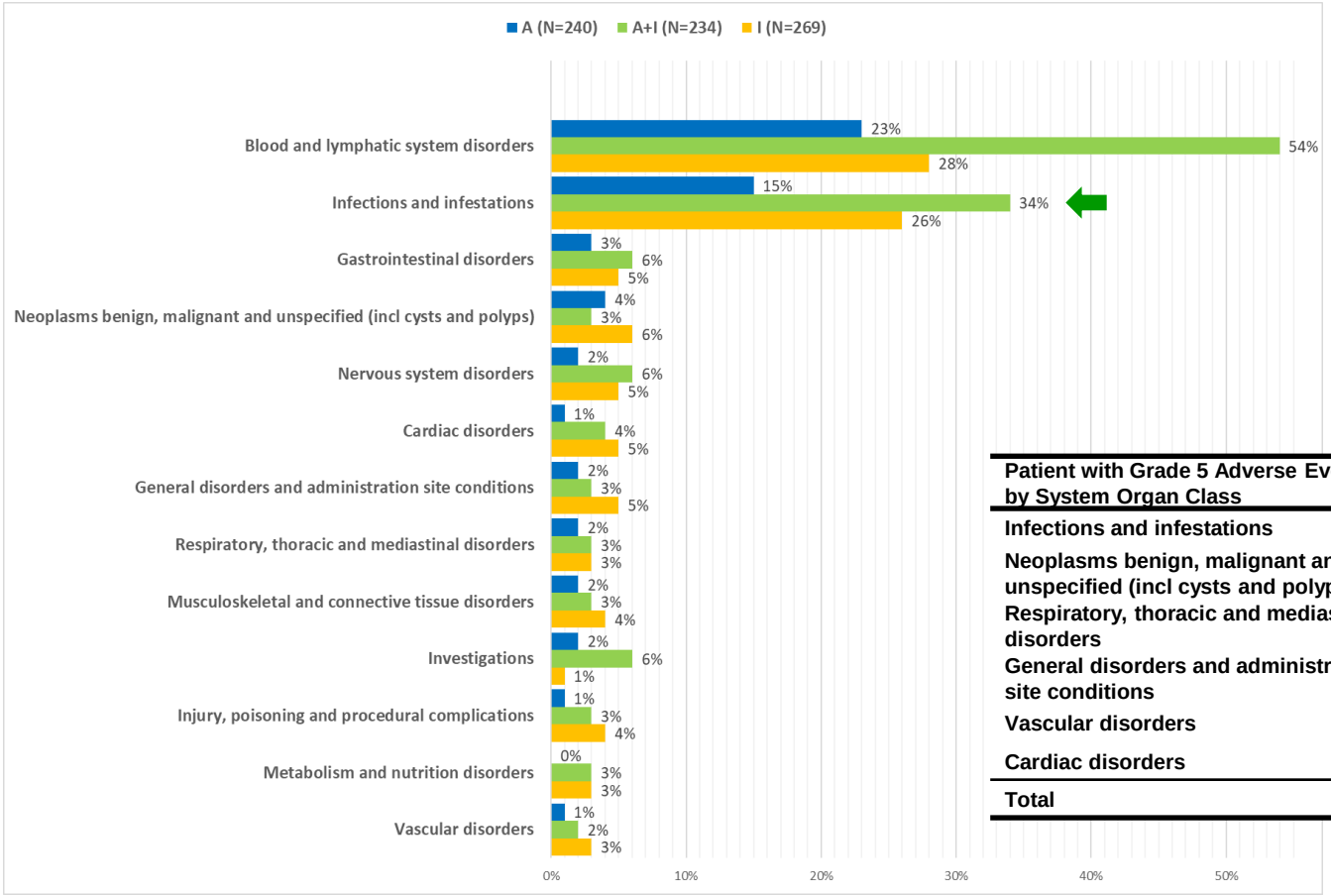


TRIANGLE: A+I vs. I (FFS) and p53 high expression





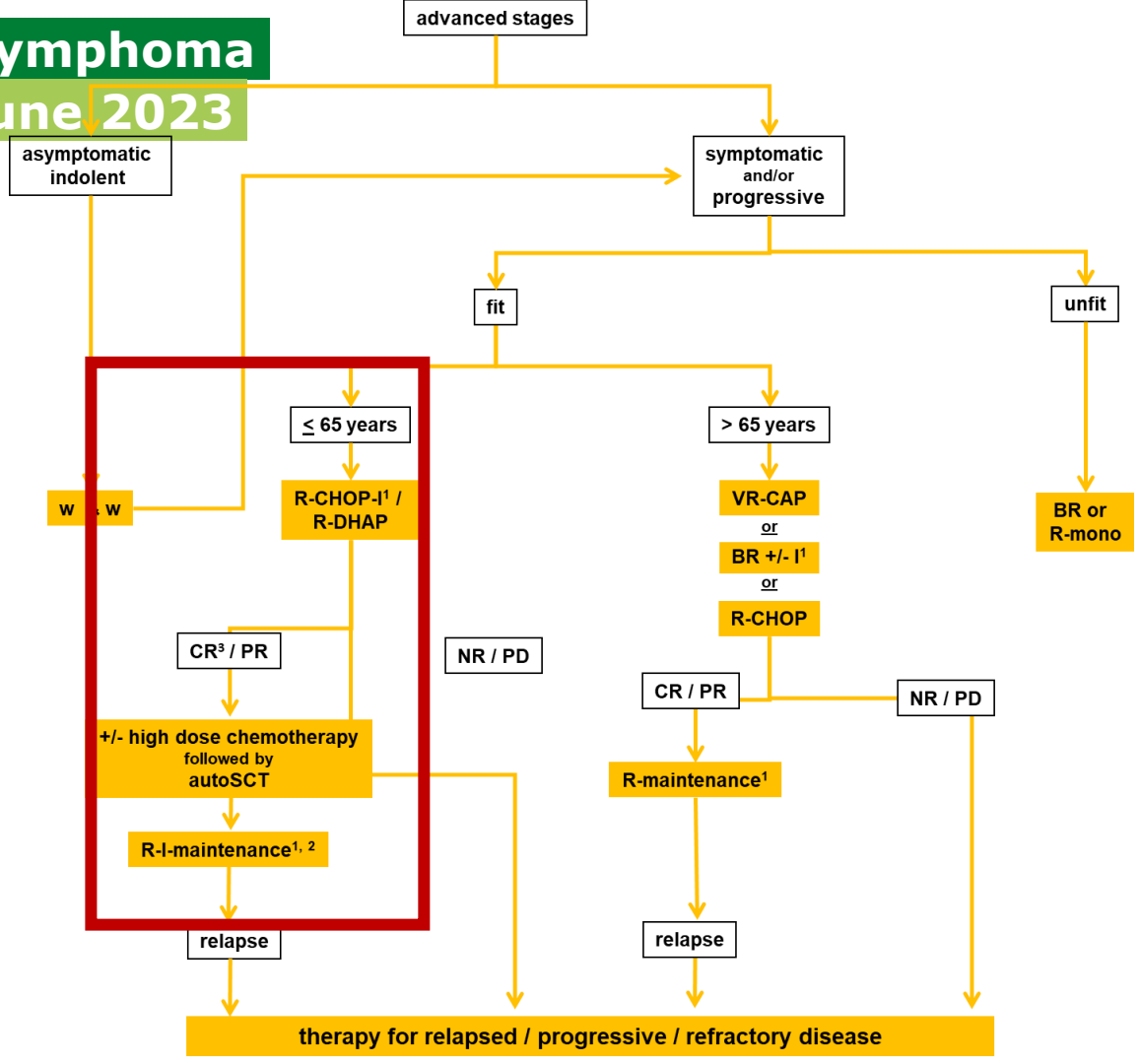
TRIANGLE: Grade ≥3 AEs (maintenance/follow-up)



Patient with Grade 5 Adverse Events by System Organ Class	A (N=240)		A+I (N=234)		I (N=269)	
Infections and infestations	5	2%	4	2%	5	2%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	2%	3	1%	2	1%
Respiratory, thoracic and mediastinal disorders	0	0%	0	0%	2	1%
General disorders and administration site conditions	0	0%	0	0%	1	0%
Vascular disorders	1	0%	0	0%	0	0%
Cardiac disorders	0	0%	0	0%	1	0%
Total	11	5%	7	3%	11	4%

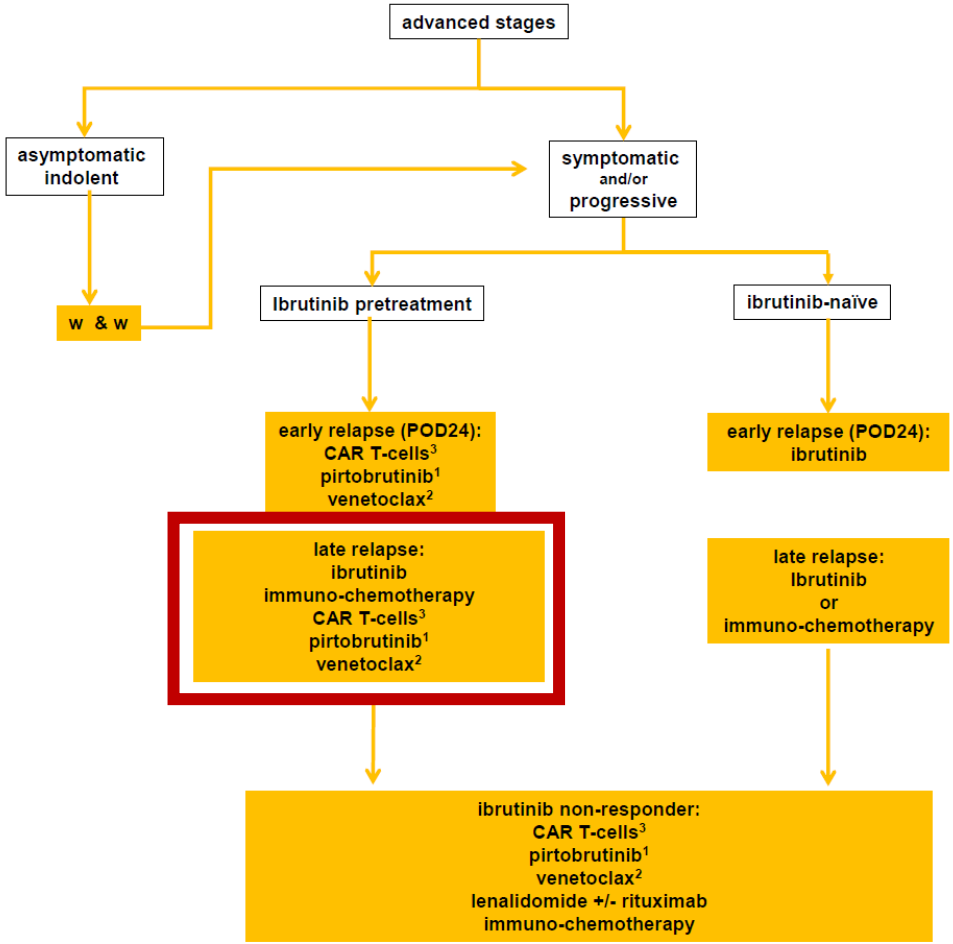
Mantle cell Lymphoma

Onkopedia June 2023



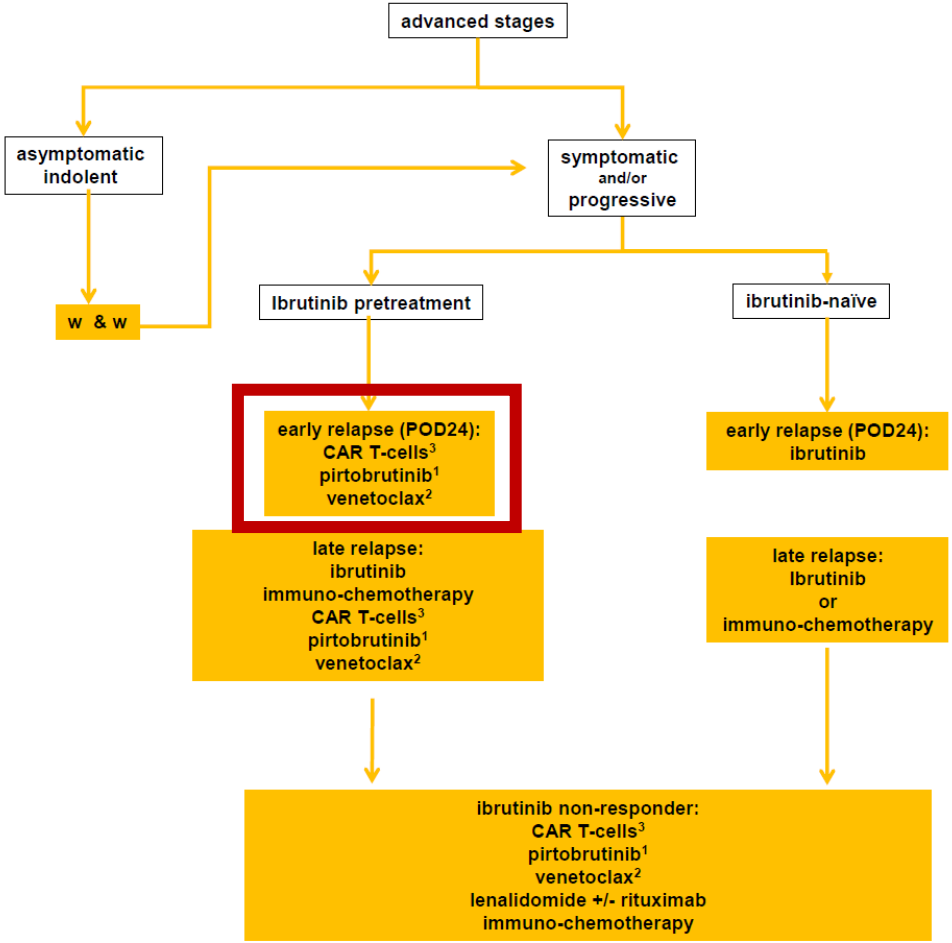
Relapsed Mantle cell Lymphoma

Onkopedia 2023

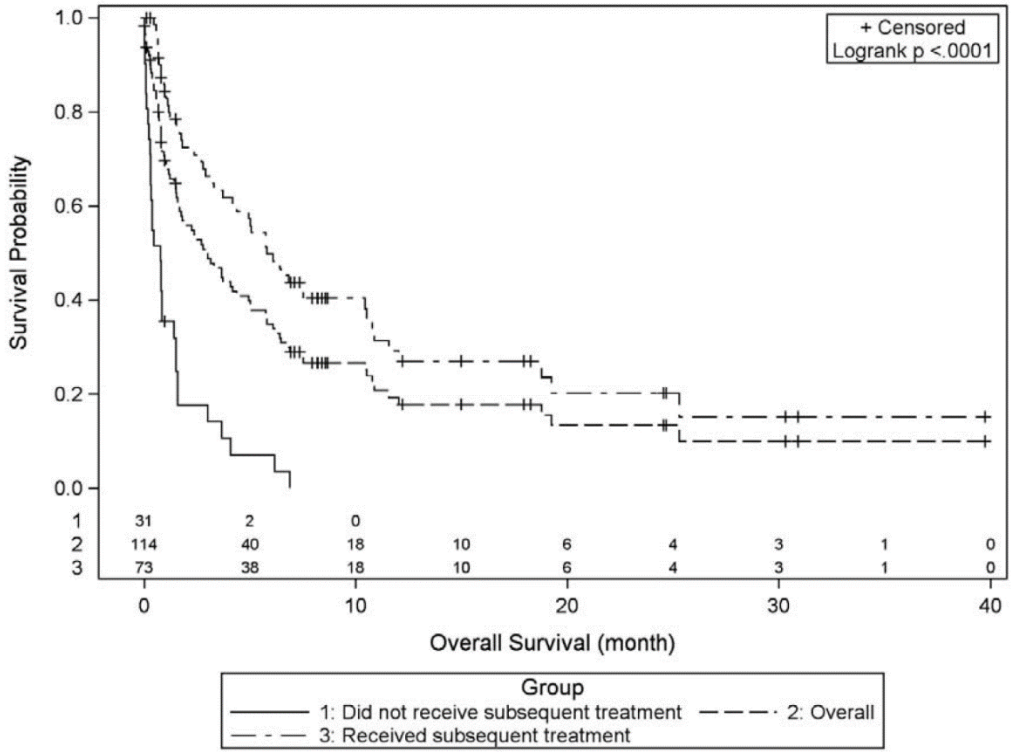


Relapsed Mantle cell Lymphoma

Onkopedia 2023



Relapsed mantle cell lymphoma
Failure under ibrutinib

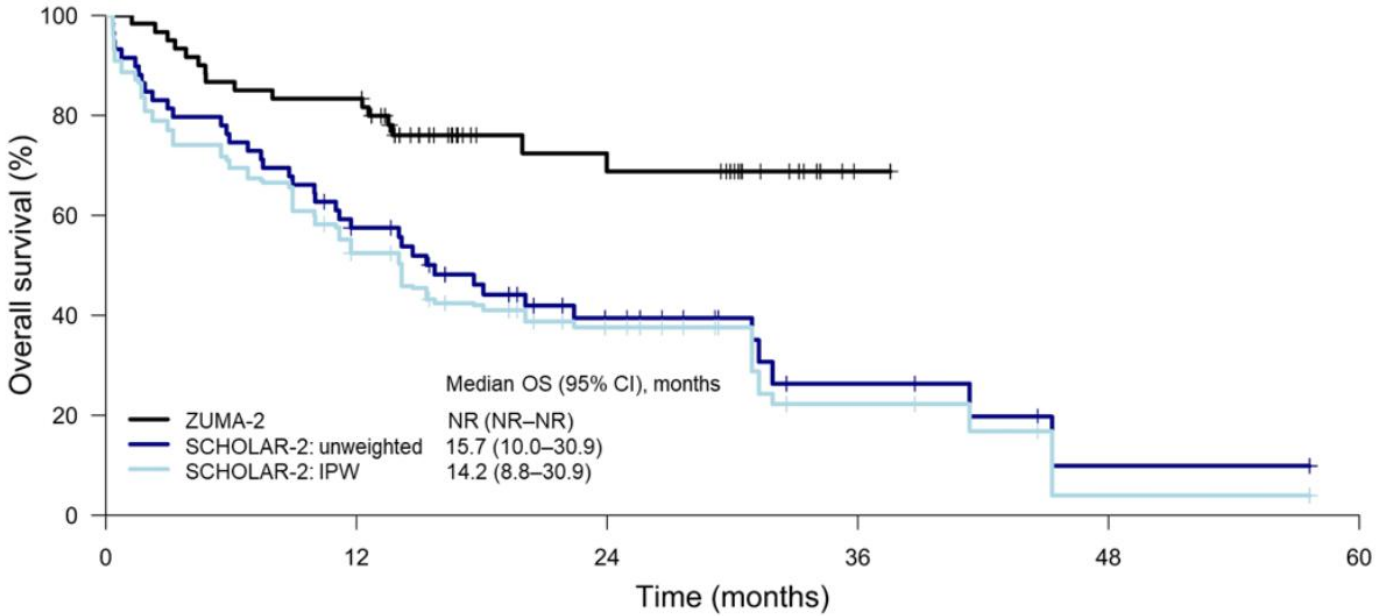


Martin, Blood 2016

KTE-X19 versus Standard of Care for Relapsed/Refractory Mantle Cell Lymphoma Previously Treated with Bruton Tyrosine Kinase Inhibitors: Real-World Evidence from Europe

EHA-1751

Georg Hess* [1], Martin Dreyling[2], Lucie Oberic[3], Eva Gine[4], Pier Luigi Zinzani[5], Kim Linton[6], Adam Vilmar[7], Mats Jerkeman[8], Jenny MH Chen[9], Anke Ohler[1], Stephan Stilgenbauer[10], Catherine Thieblemont[11], Jonathan Lambert[12], Vittorio Ruggero Zilioli[13], Juan Manuel Sancho[14], Ana Jimenez Ubieto[15], Luca Fischer[2], Sam Keeping[9], Julie E Park[9], Gregory A. Maglinte[16], Liliosa Nyamutswa[16], Rubina Siddiqi[16], John Reitan[17], Sally Wade[18], Gilles Salles[19]

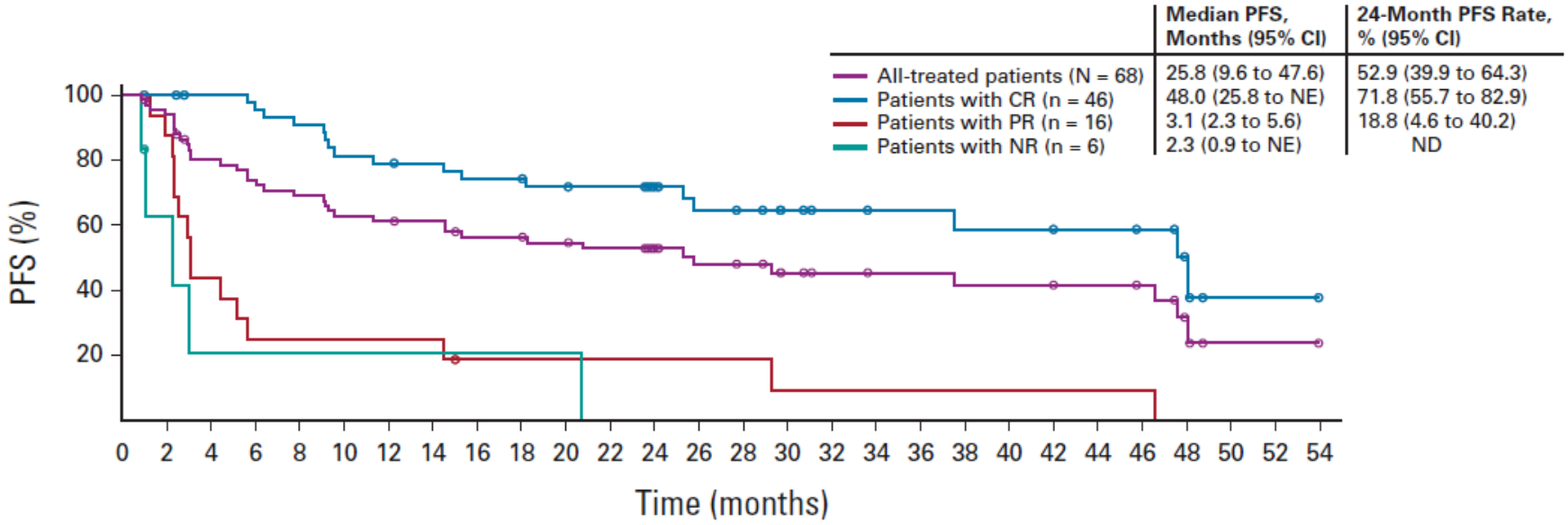


Number at risk
(number censored)

ZUMA-2	60 (0)	50 (0)	19 (25)	1 (43)	0 (44)	0 (44)
SCHOLAR-2 (unweighted)	59 (0)	32 (2)	15 (10)	5 (17)	1 (19)	0 (20)
SCHOLAR-2 (IPW)	59 (0)	30 (1)	15 (8)	4 (16)	0 (18)	0 (19)

Hess, Dreyling, Leuk Lymphoma 2024

Relapsed Mantle cell Lymphoma (after BTKi)
CAR T-cells: Survival rates



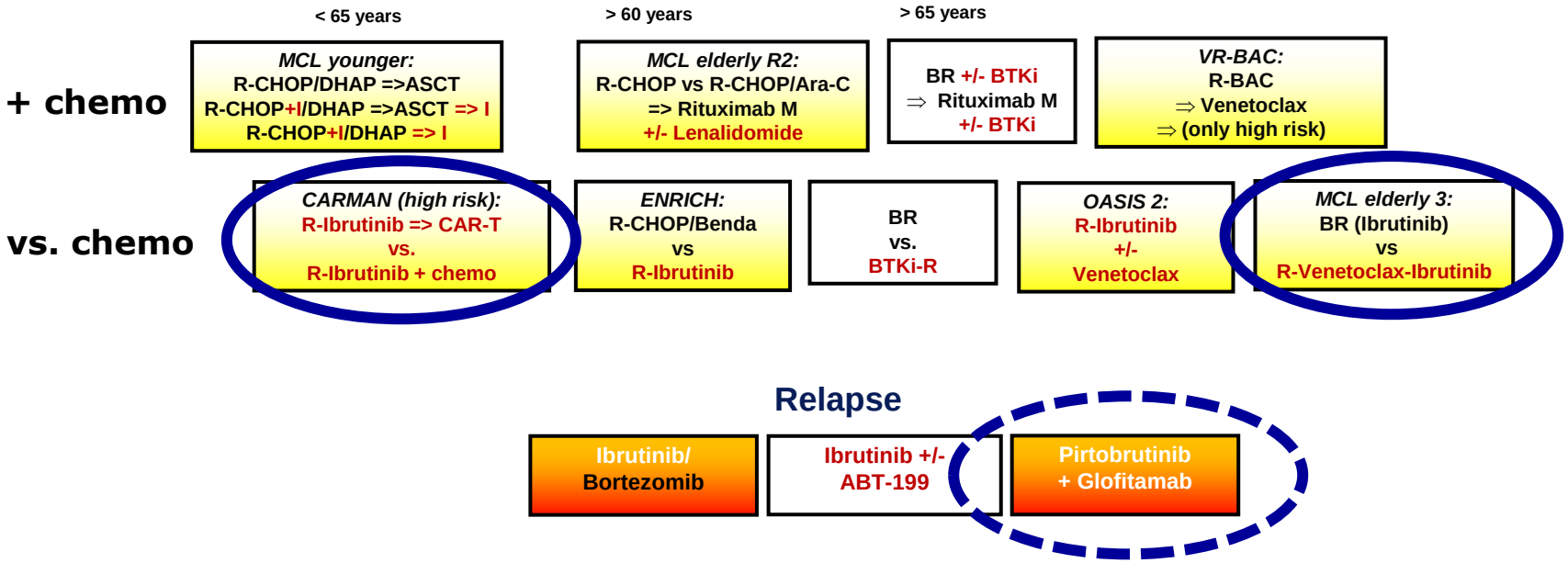
No. at risk:

All-treated patients	68	62	51	47	44	40	39	38	34	34	32	30	24	20	19	15	13	12	12	11	11	10	10	9	4	1	1	0
Patients with CR	46	45	43	42	39	35	34	33	31	31	29	28	22	18	17	14	12	11	11	10	10	9	9	8	4	1	1	0
Patients with PR	16	14	7	4	4	4	4	4	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	0	0	0	0
Patients with NR	6	3	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Wang, JCO 2022

European MCL Network
Study generation 2025

LMU KLINIKUM



Mantle cell lymphoma
Take home message

LMU KLINIKUM

First line:

- **Younger patients:**

  TRIANGLE (+ Ibrutinib) improves PFS and OS

  + ASCT in high risk patients (?)

- ***In studies: non-chemo BTK-combinations***

  (high risk: + CAR-T cells?)

TRIANGLE: 25th annual meeting in Lisbon 2024