10th POSTGRADUATE
Lymphoma
Conference

MCL: Frontline algorithm

Martin Dreyling

LMU Hospital Munich, Dept. of Medicine III

Venice,
March 12-13, 2026

Hotel Monaco & Grand Canal

President:
P.L. Zinzani

Mantle cell lymphoma
Disclosures

https://bureaucracyincts.eu

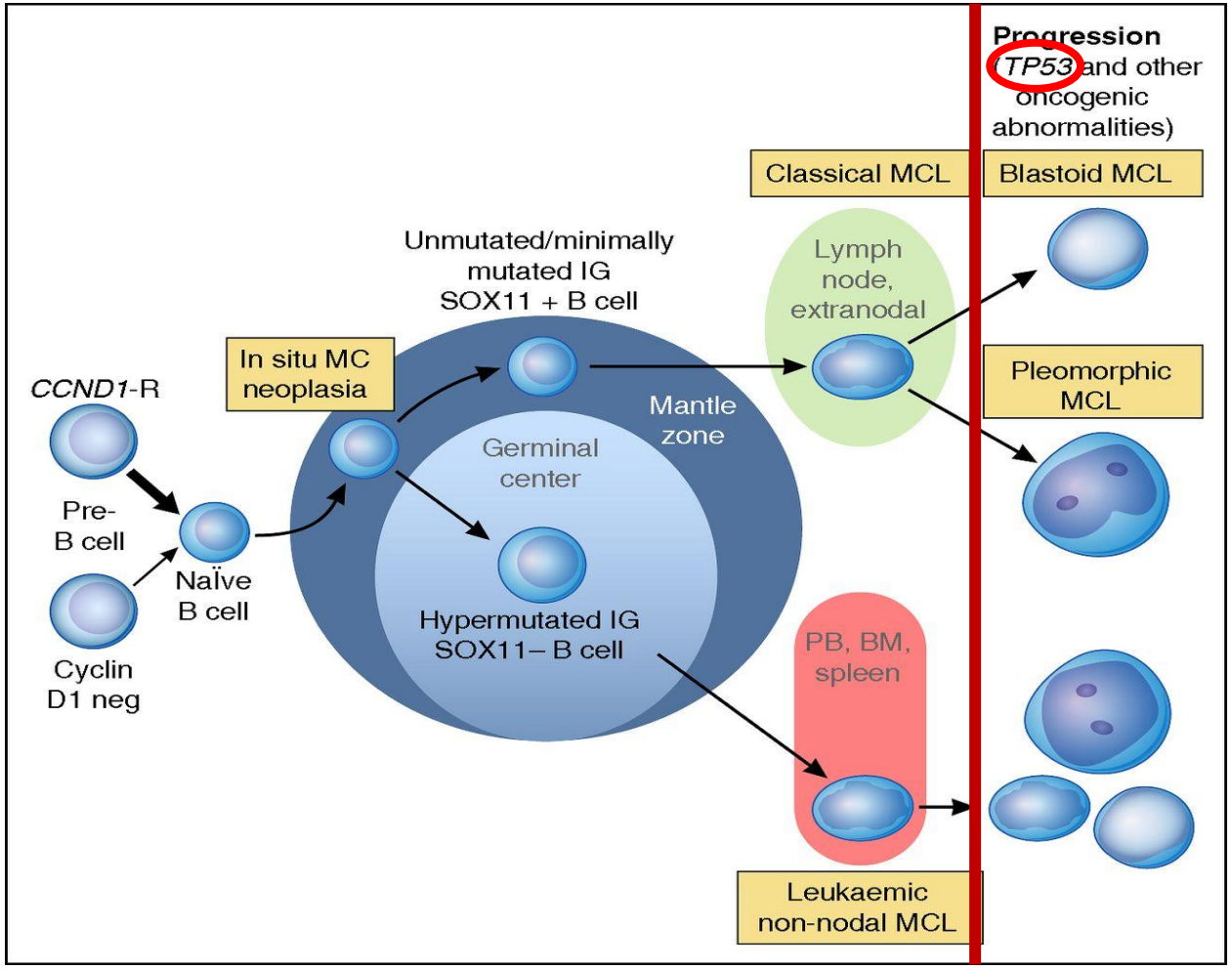
Research Support (institution)	**Abbvie, Gilead/Kite, Janssen, Lilly, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**-**
Speakers Honoraria	**Abbvie, Astra Zeneca, BeOne, BMS, Gilead/Kite, Janssen, Lilly, Roche, Sobi**
Scientific Advisory Board	**Abbvie, Astra Zeneca, AvenCell, BeOne, BMS, Genmab, Gilead/Kite, Incyte, Janssen, Lilly, Novartis, Roche, Sobi**

Mantle cell lymphoma
Overview

LMU KLINIKUM

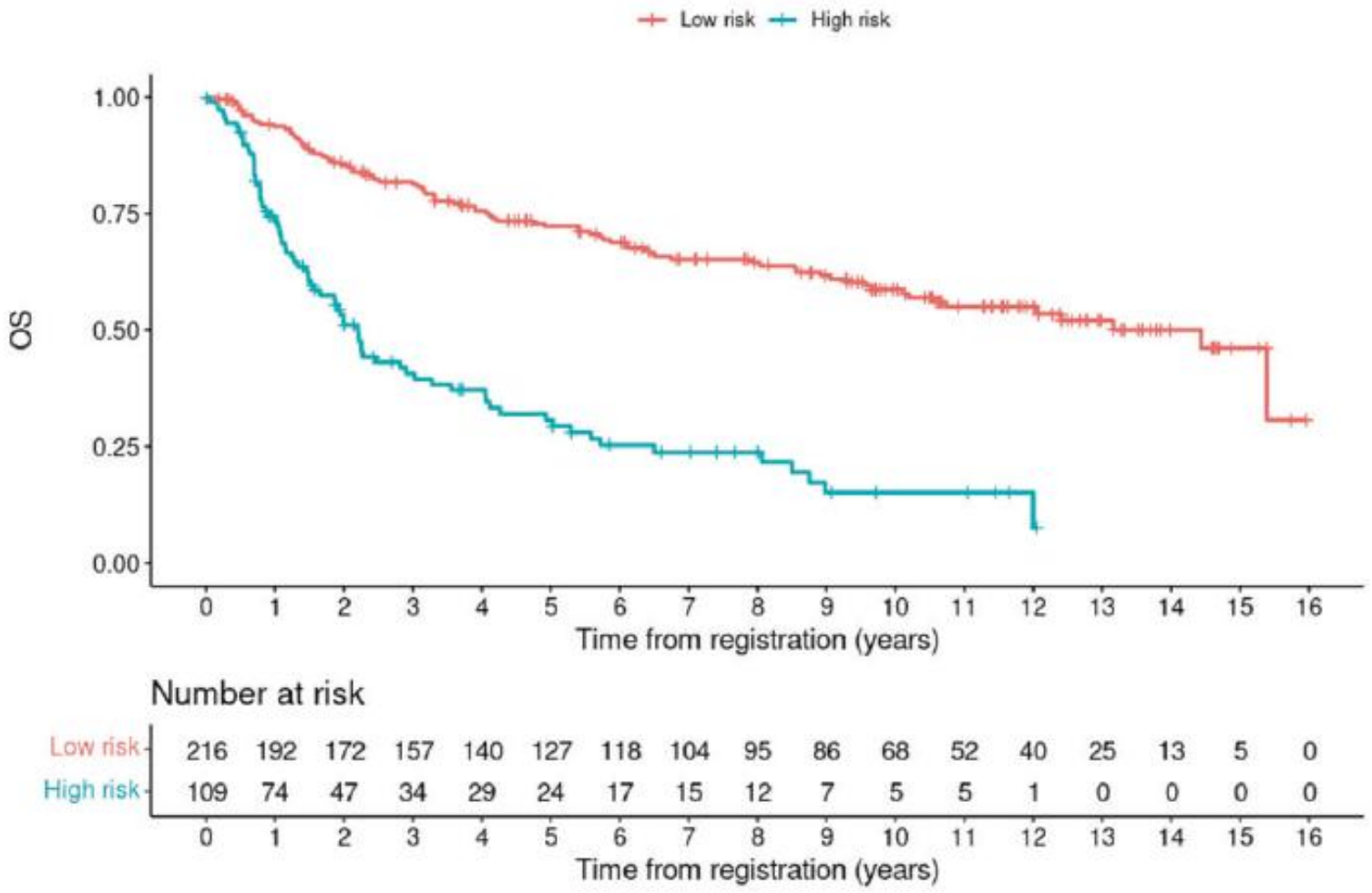
- **Clinical/biological risk profile**
- **chemotherapy standards**
- **targeted approaches**

Mantle cell lymphoma
Spectrum of disease



Dreyling, Ann Oncol 2017

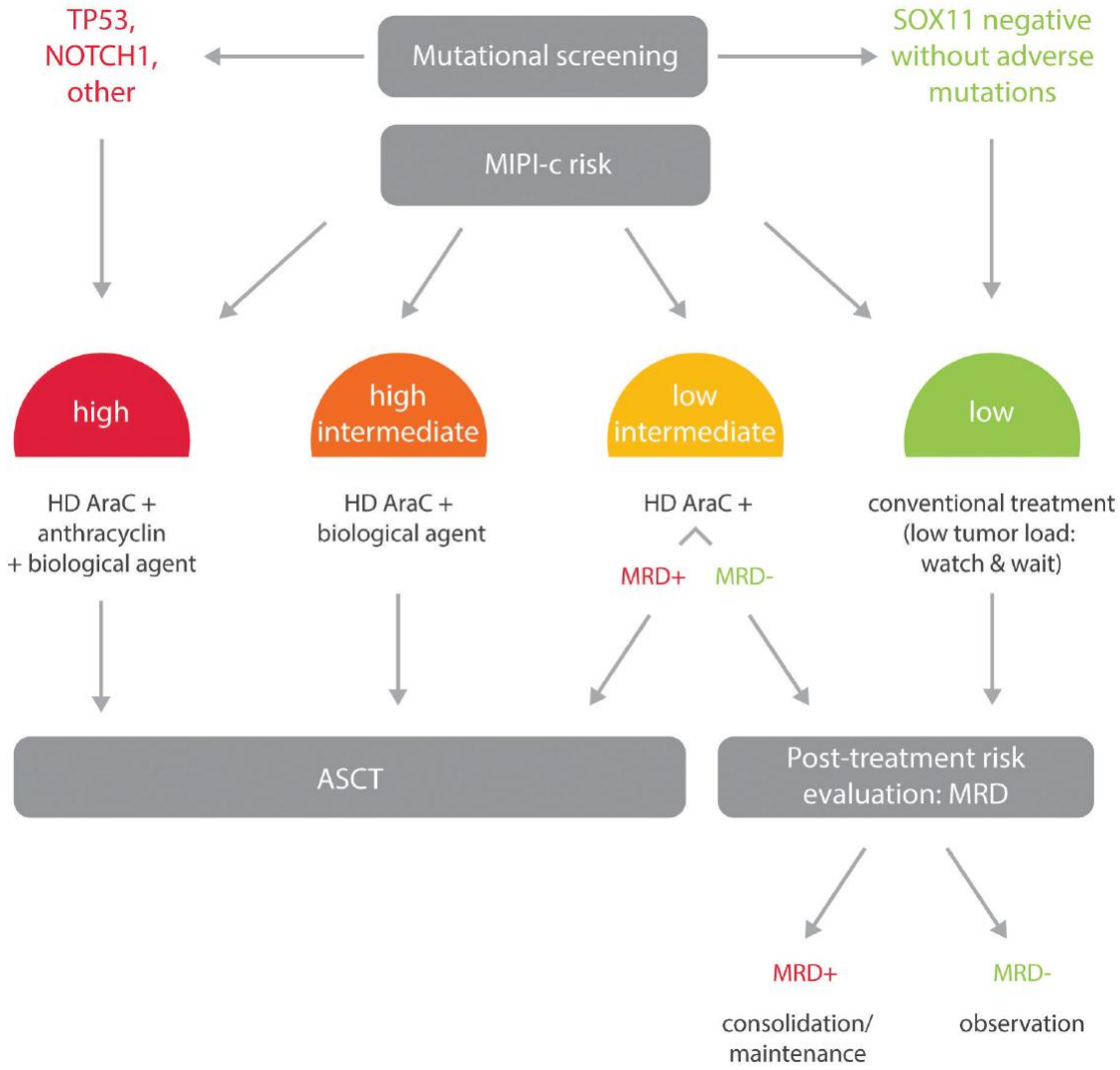
High risk Mantle cell lymphoma
Overall survival (n=465)



Scheubeck, Leukemia 2023

European MCL Network

Suggested therapeutic algorithm



Dreyling, Haematologica 2016

Mantle cell lymphoma
Overview

- **Clinical/biological risk profile**
- **chemotherapy standards**
- **targeted approaches**

Mantle cell lymphoma
Therapeutic algorithm

LMU KLINIKUM

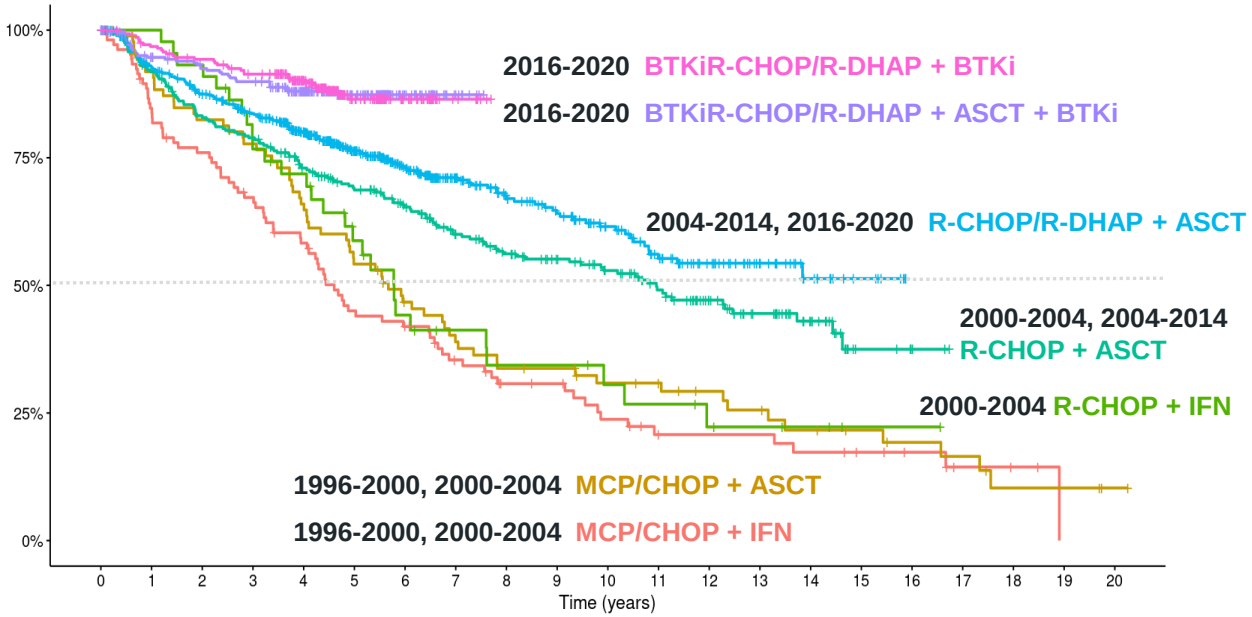
young patient (≤65)	elderly patient (>65)	compromised patient
First line treatment		
dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (VR-CAP, R-CHOP,BR, R-BAC) ⇓ Rituximab maintenance	Best supportive care? R-Chlorambucil 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)

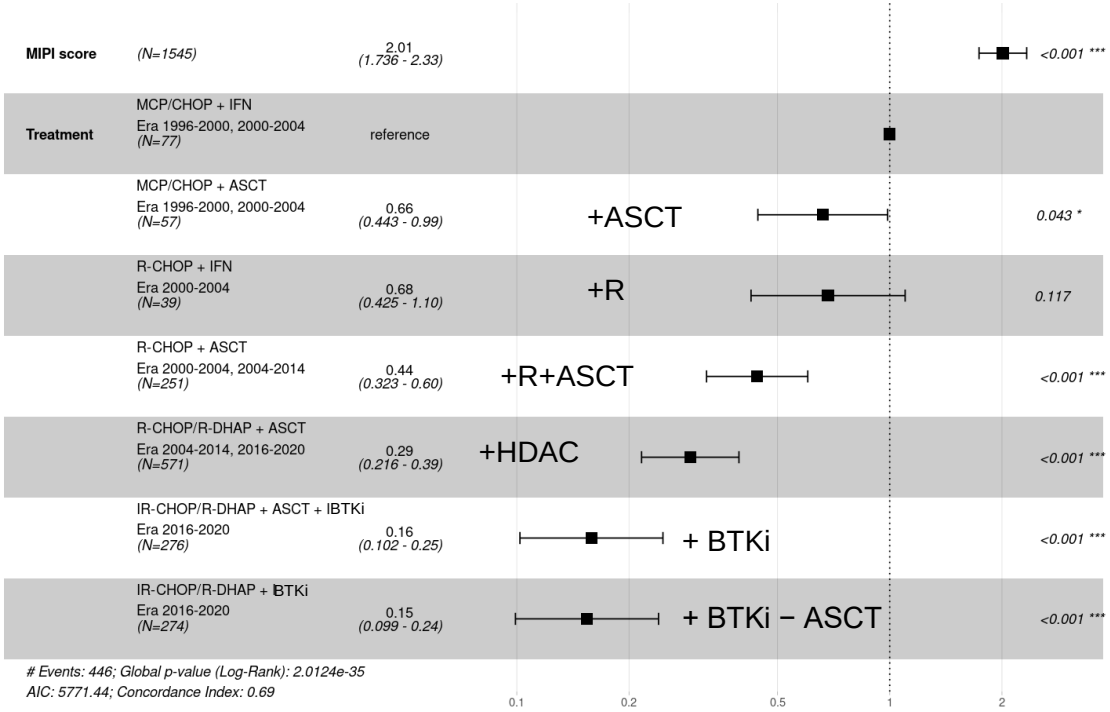
Not all regimens mentioned above are registered in Australia. Please refer to the relevant product information before prescribing

Results: Survival trends – younger: impact of treatment

By eras and treatment



Treatment effects



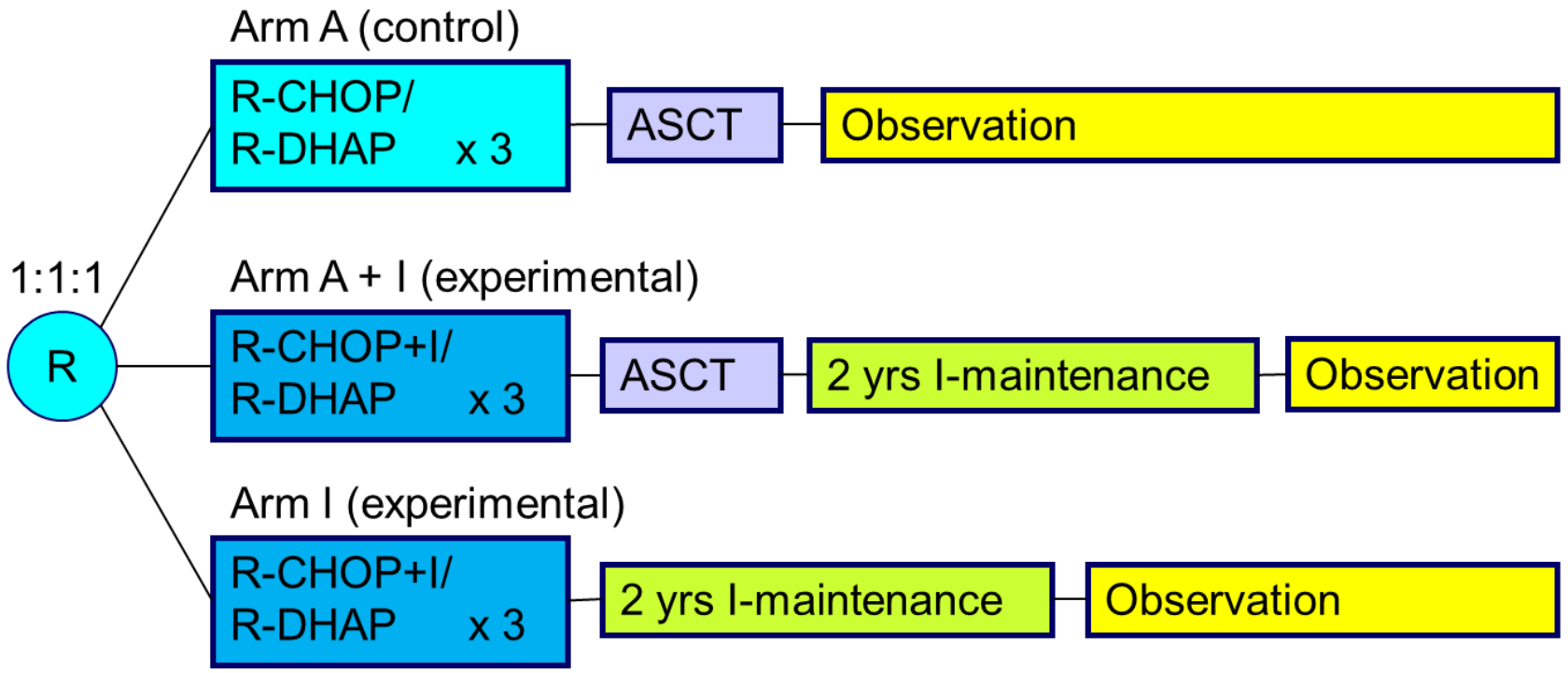
Jiang, Haematologica 2025

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

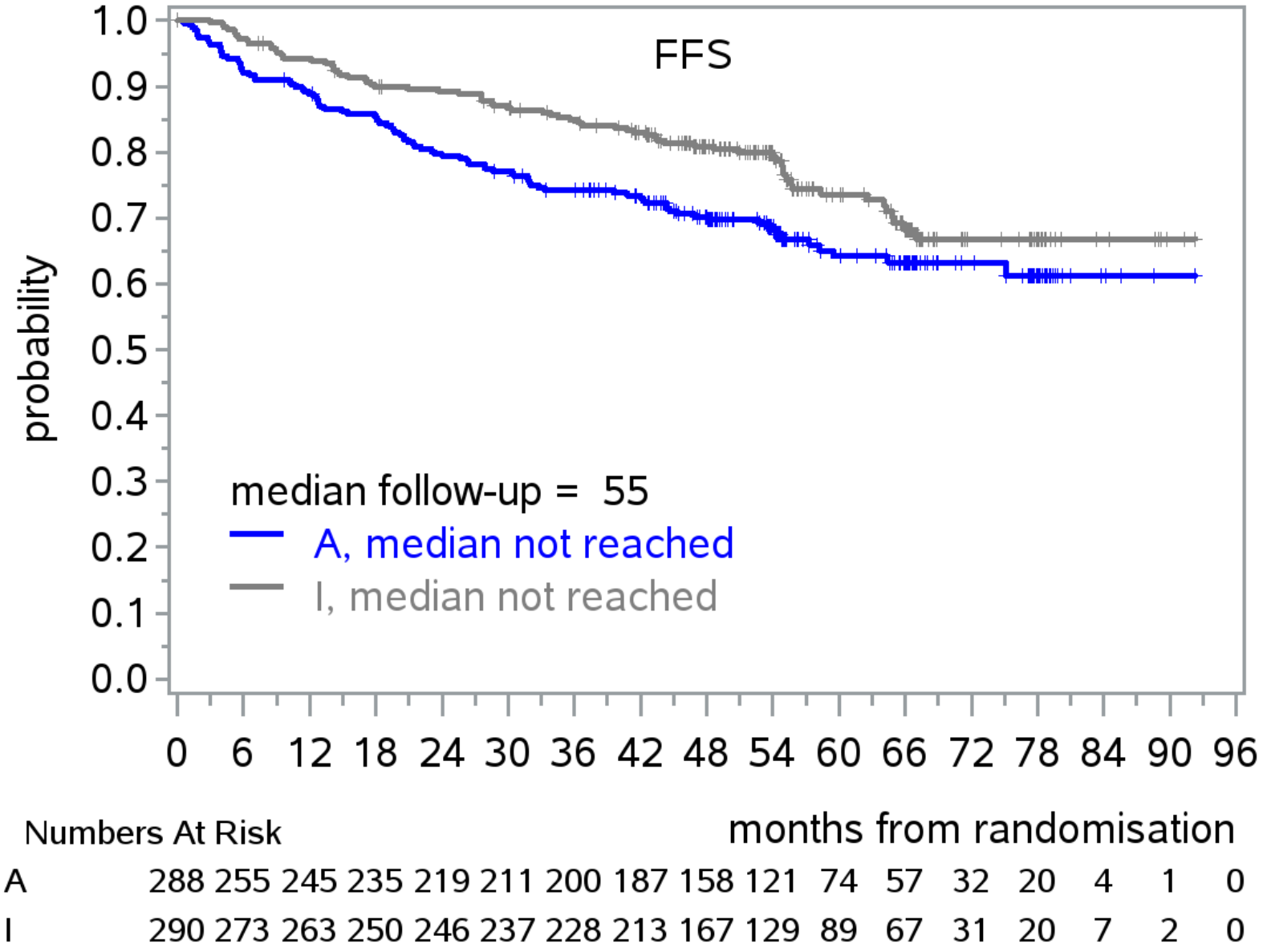
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety



- 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

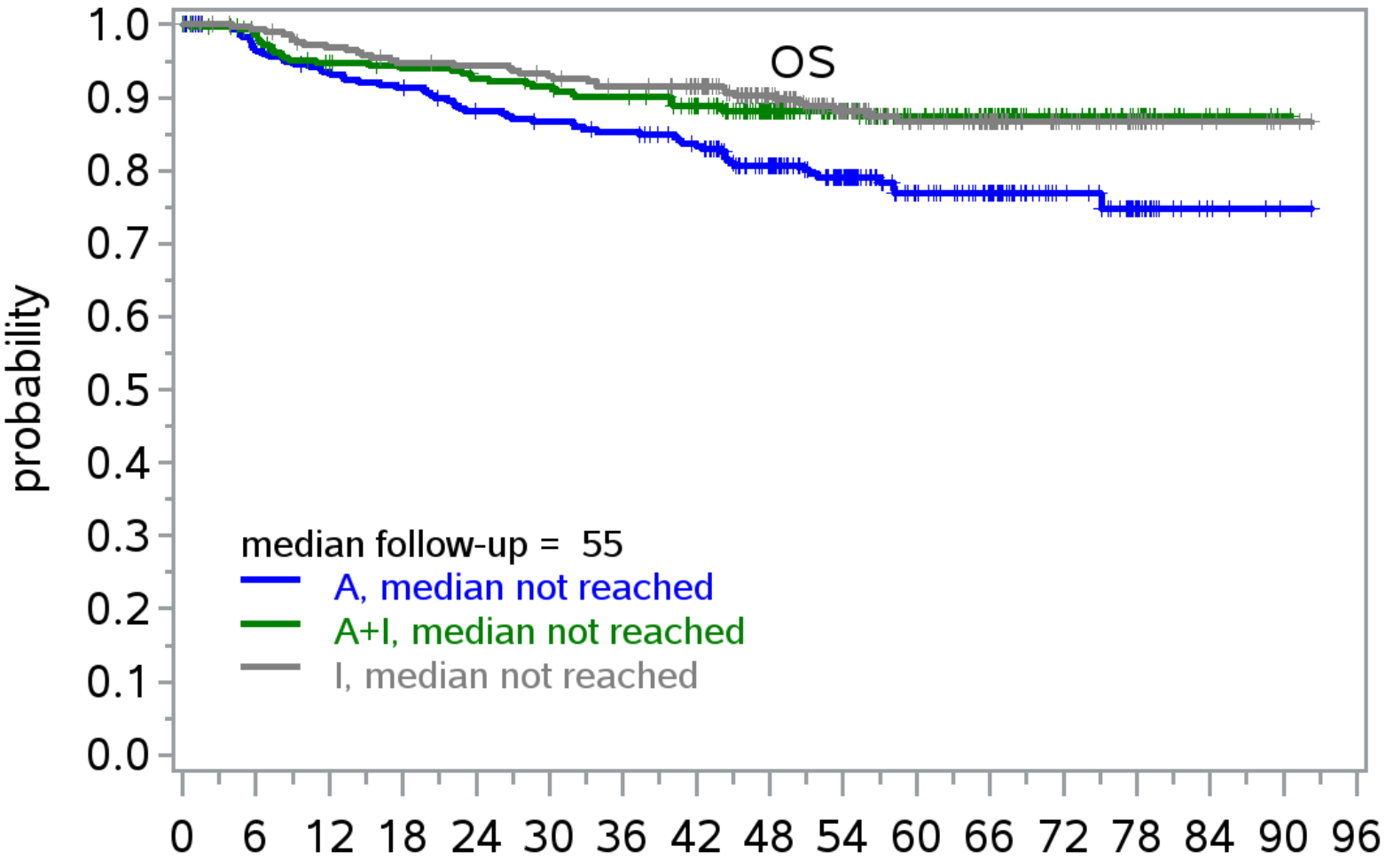
TRIANGLE: No FFS Superiority of A vs. I



- 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

Dreyling, ASH 2024, Lancet 2026

TRIANGLE: Overall survival



Numbers At Risk

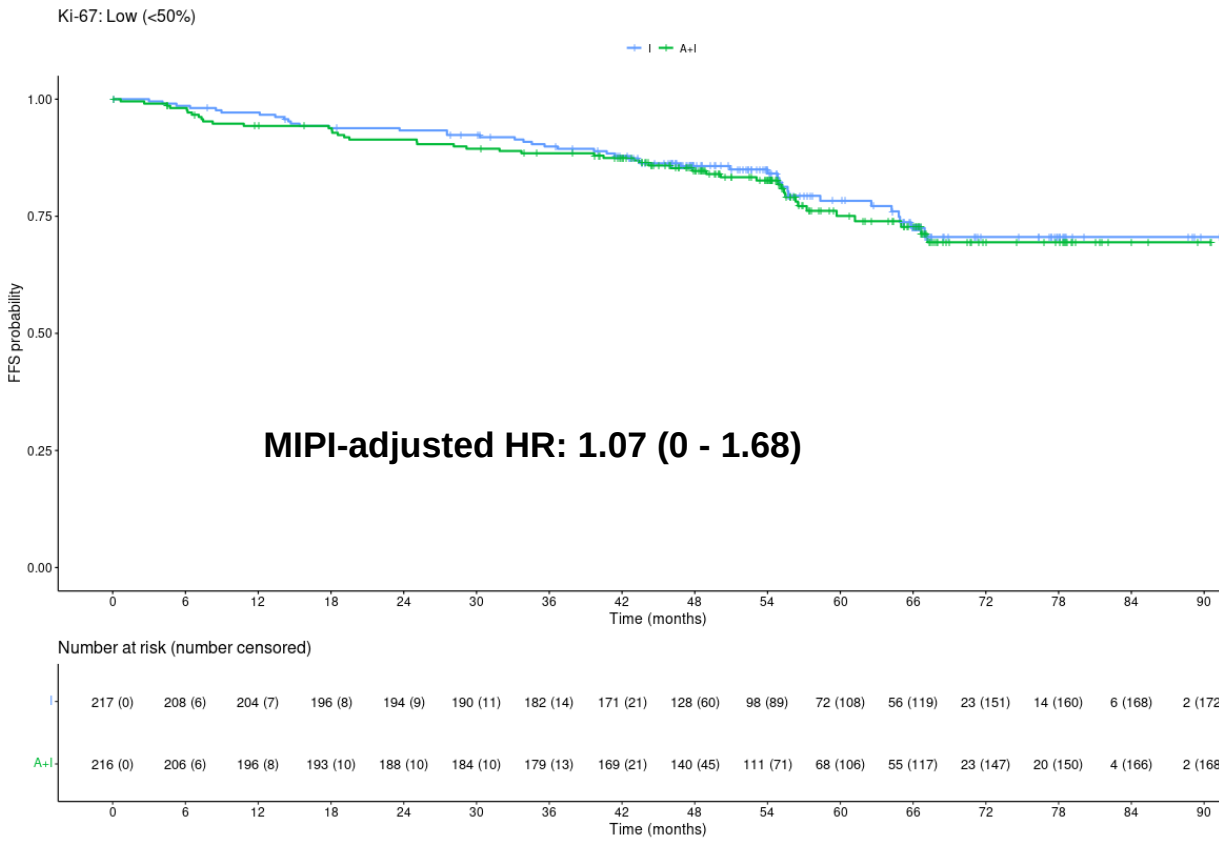
A	288	270	260	255	243	238	233	222	186	145	92	73	41	23	5	1
A+I	292	281	267	262	257	253	248	235	201	160	107	83	39	26	8	2
I	290	282	273	266	264	259	253	243	194	147	101	78	41	21	7	2

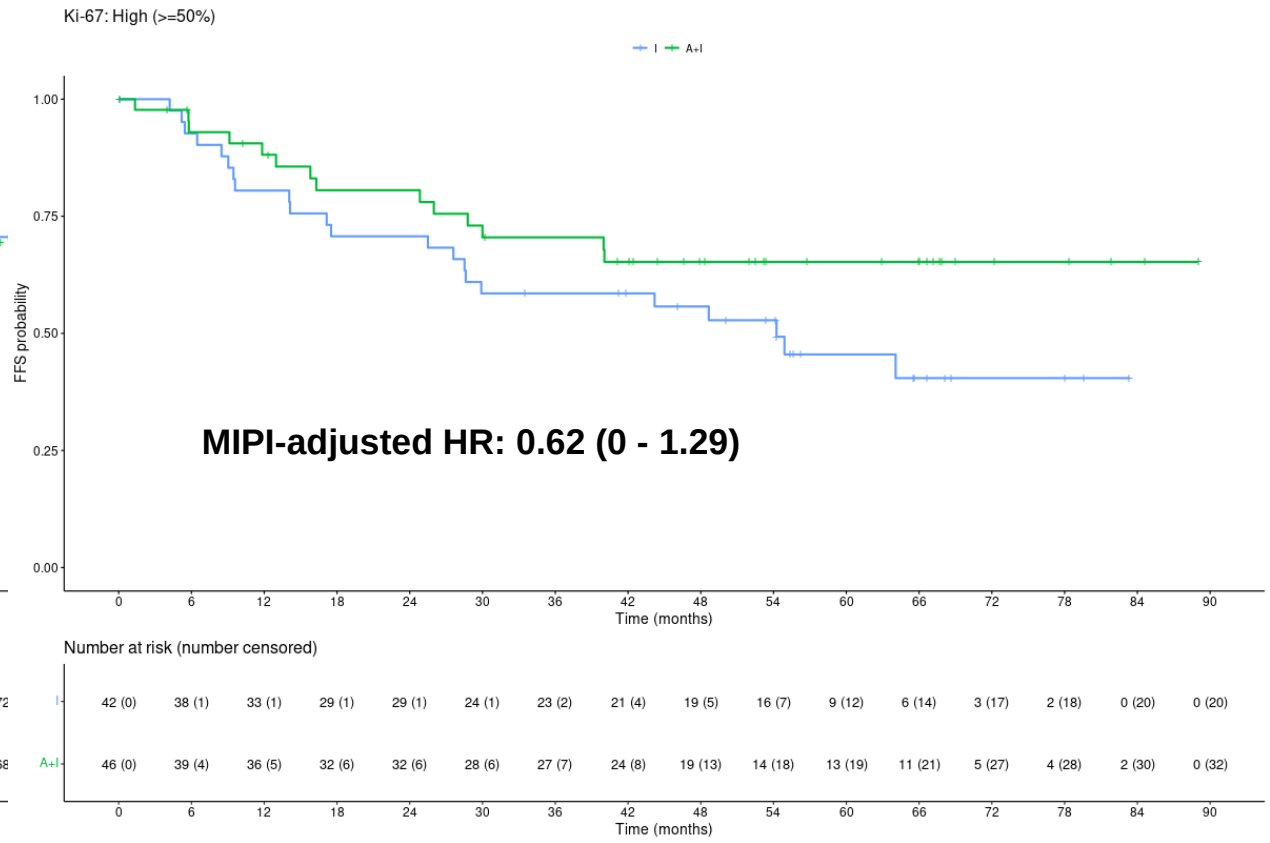
- 4-year OS:
  - A: 81%
    (MCL Younger exp.: 80%)
  - A+I: 88%
  - I: 90%

- 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

Dreyling, ASH 2024, Lancet 2026

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



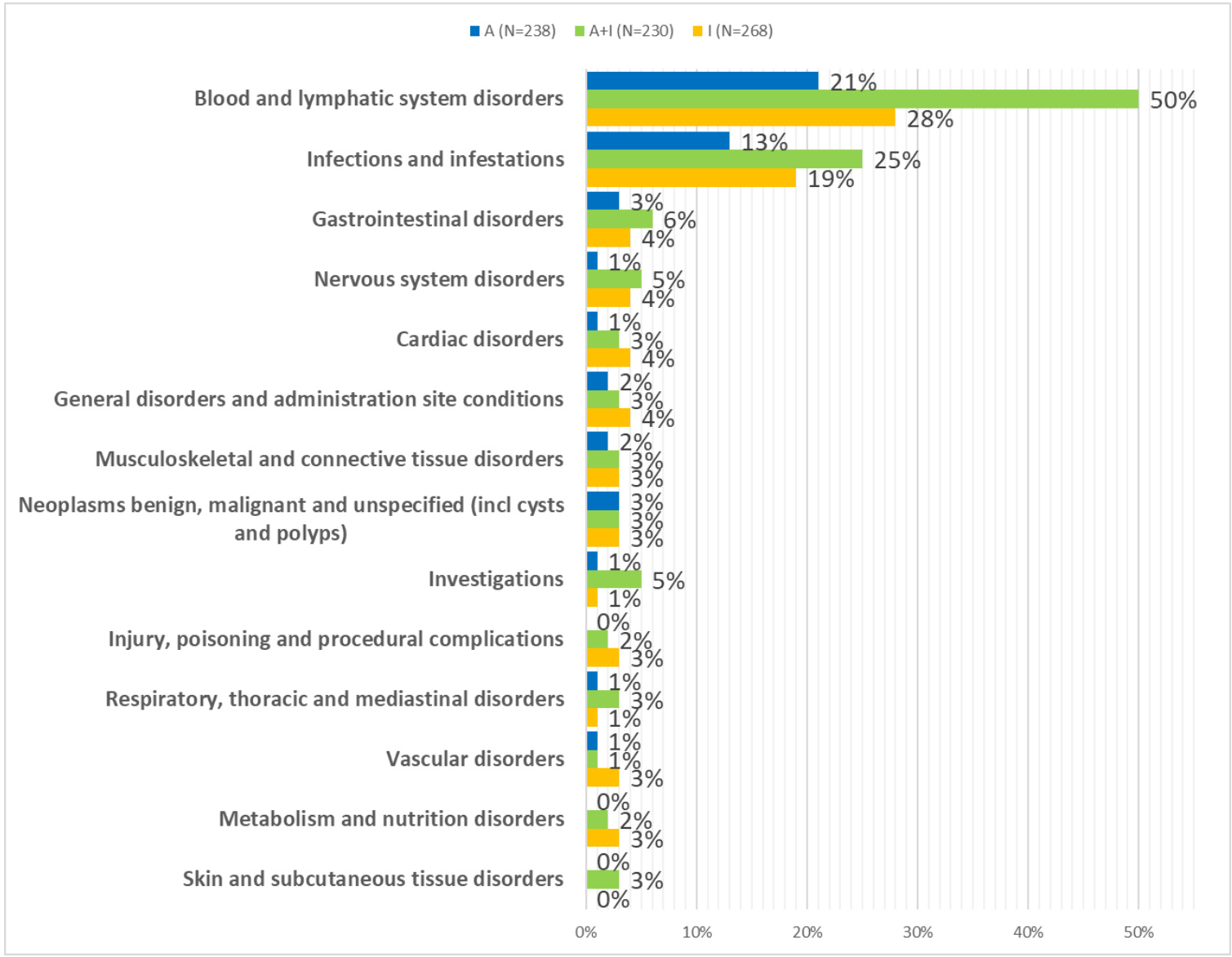


Dreyling, ASH 2024, Lancet 2026

Mantle cell Lymphoma

MCL younger +/- Ibrutinib

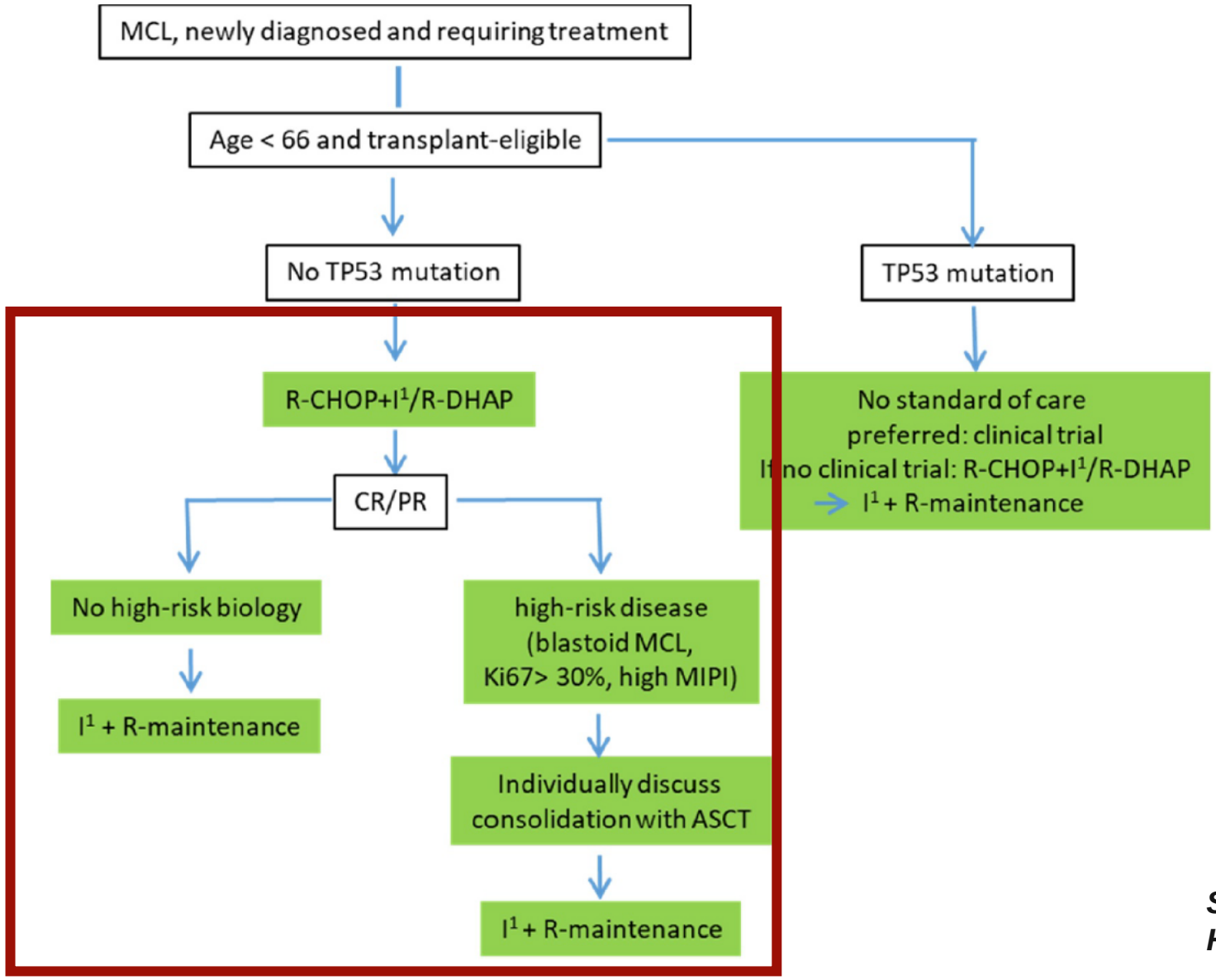
Dreyling, ASH 2022, #1



Dreyling, ASH 2024, Lancet 2026

How do I treat MCL (younger patients)

Suggested therapeutic algorithm



Silkenstedt & Dreyling, Hematological Oncology 2025

MCL Case report 1
Optimal therapy ?

- 64-year-old male, newly diagnosed with classic nodal MCL.
- Stage IV with MO+, mildly elevated LDH, Ki-67 25%, no altered TP53, intermediate MIPI
- Comorbidities: Well-controlled hypertension, old paroxysmal AF (no episodes within the last 2 years; CHADS-VASc 2, anticoagulated with apixaban), glomerular filtration rate 55 ml/min/1.73 m², ECOG 1. Cardiac function preserved (LVEF 55%)
- Wishes to maintain work activity

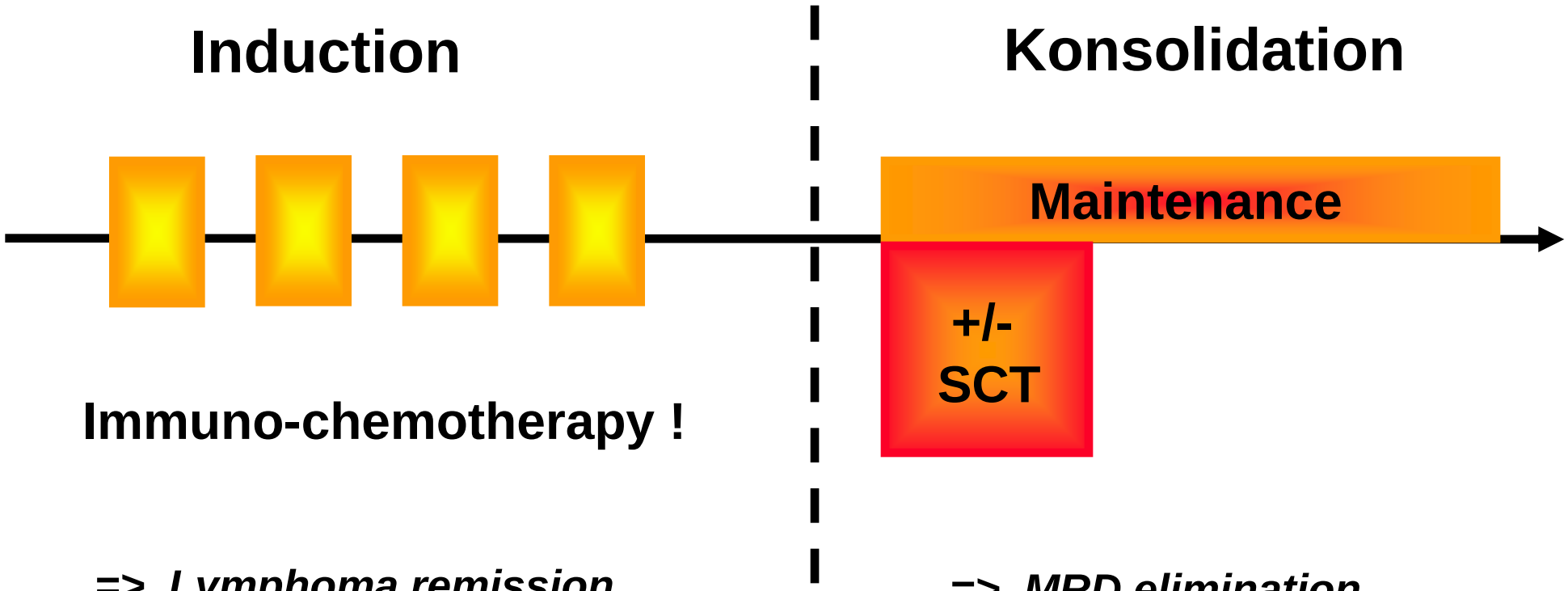
Therapeutic algorithm

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)		

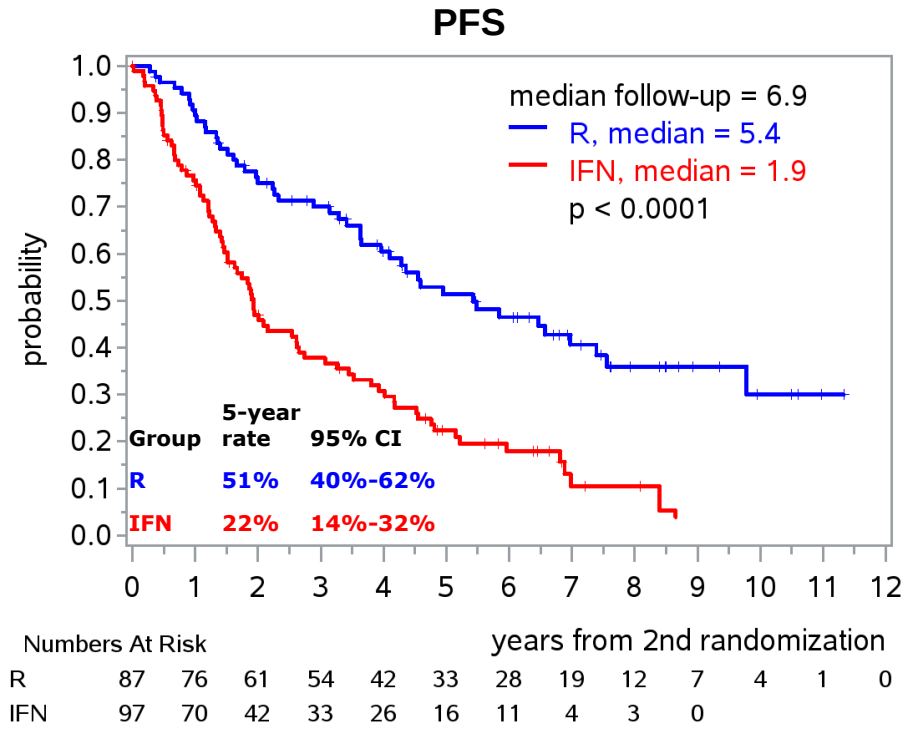
Dreyling, ESMO CR MCL 2017 (updated)

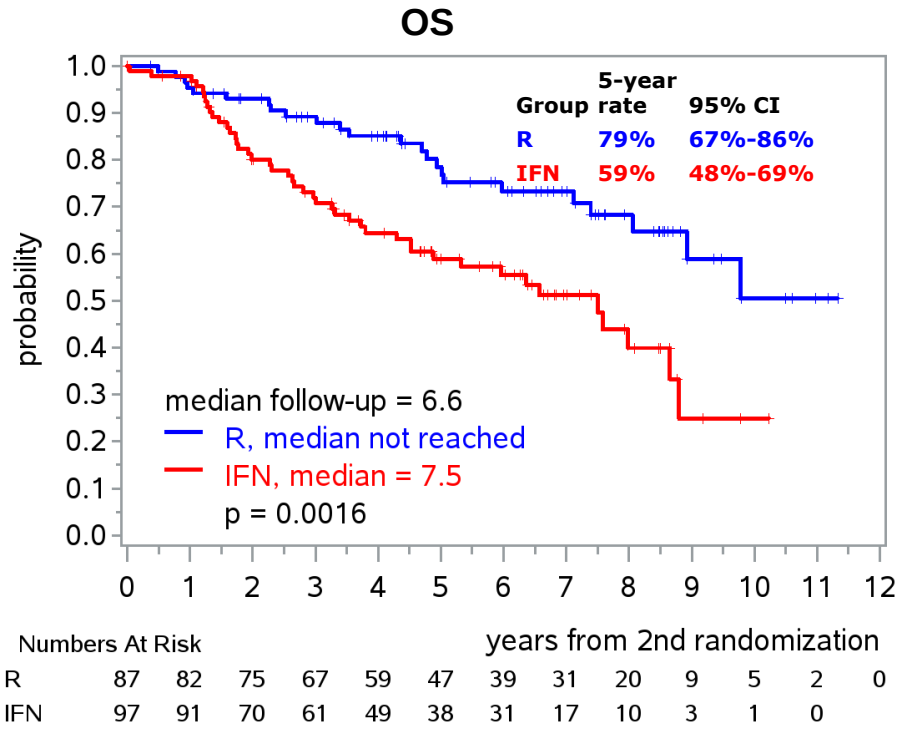
Not all regimens mentioned above are registered in Australia. Please refer to the relevant product information before prescribing'

Optimal Therapy of MCL



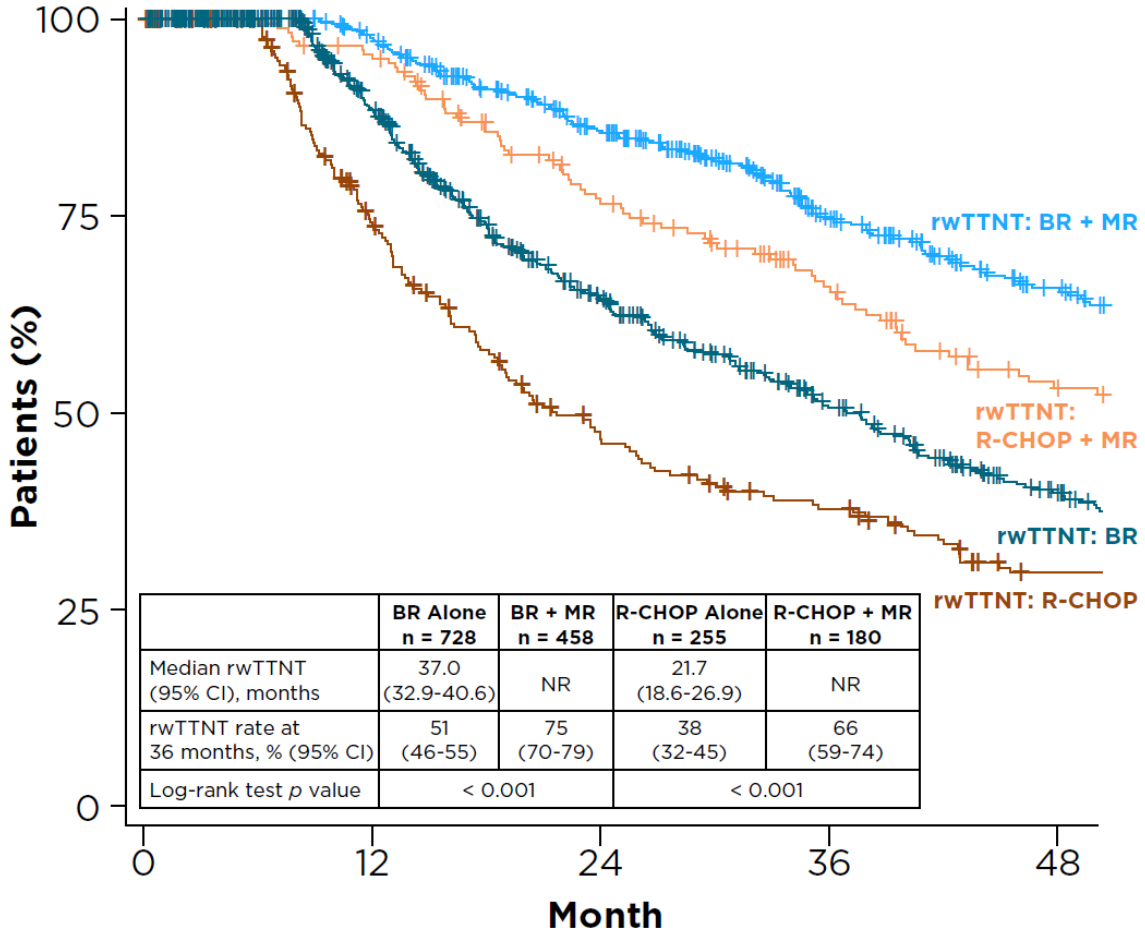
R-CHOP +/- R maintenance



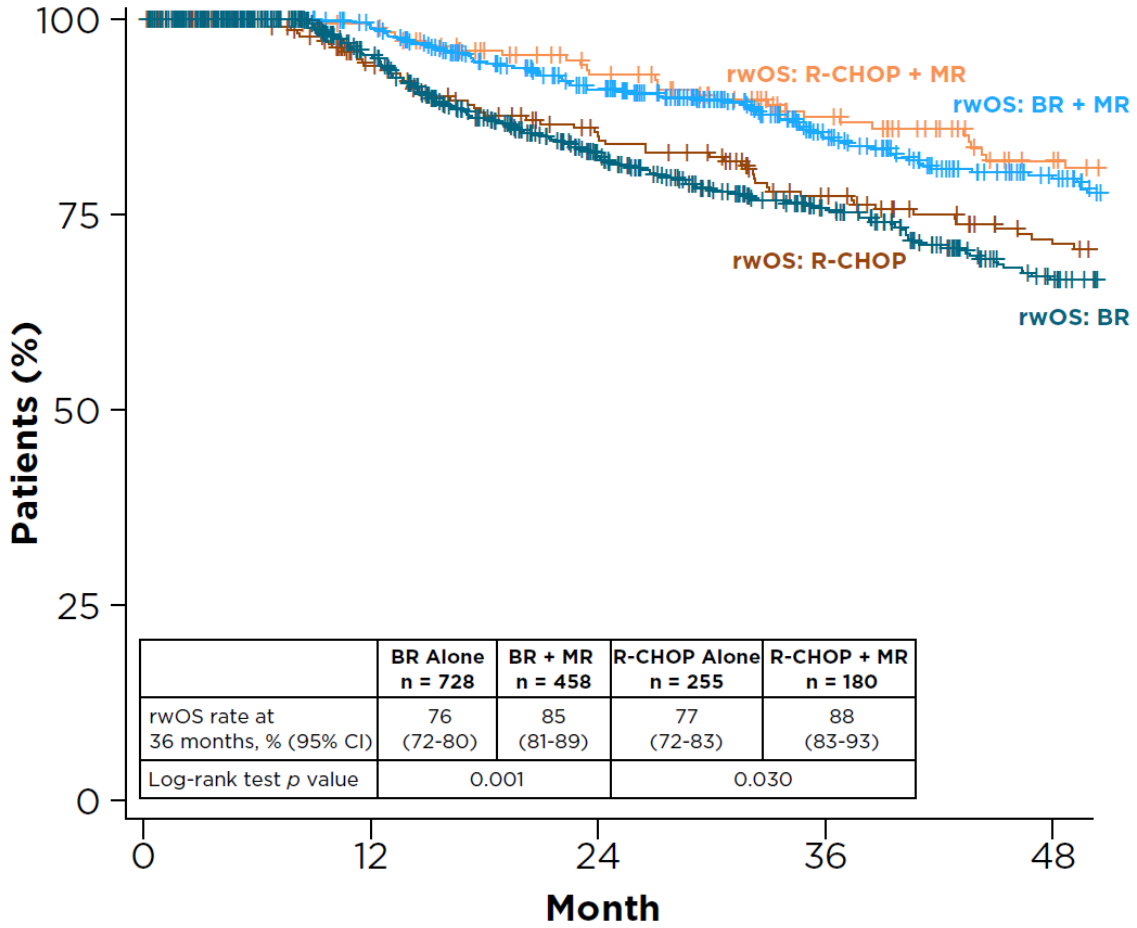


Kluin-Nelemans, 2020

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



	BR Alone n = 728	BR + MR n = 458	R-CHOP Alone n = 255	R-CHOP + MR n = 180
Median rwTTNT (95% CI), months	37.0 (32.9-40.6)	NR	21.7 (18.6-26.9)	NR
rwTTNT rate at 36 months, % (95% CI)	51 (46-55)	75 (70-79)	38 (32-45)	66 (59-74)
Log-rank test *p* value	< 0.001		< 0.001	

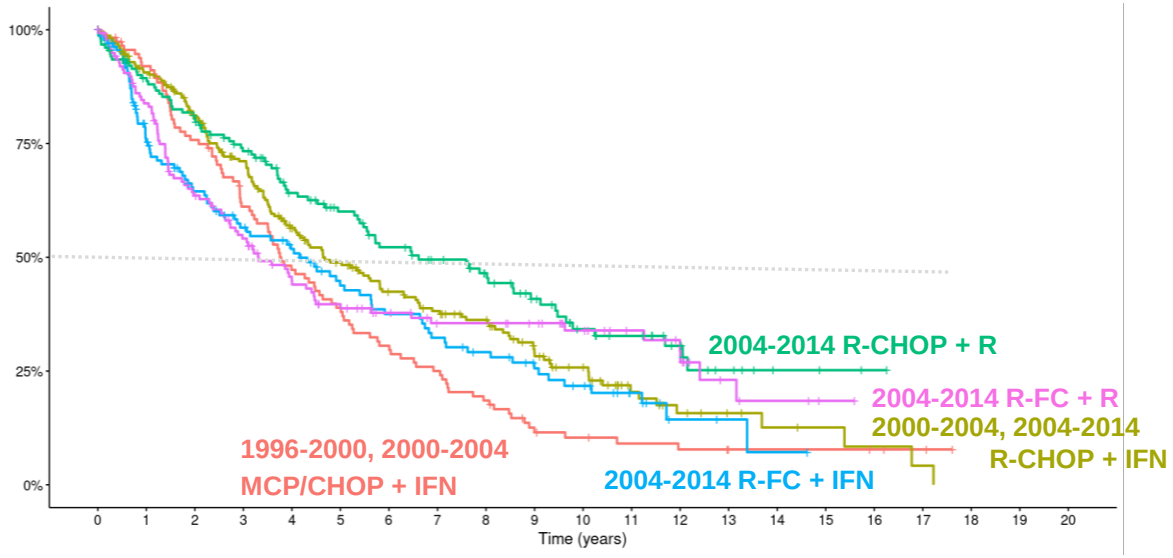


	BR Alone n = 728	BR + MR n = 458	R-CHOP Alone n = 255	R-CHOP + MR n = 180
rwOS rate at 36 months, % (95% CI)	76 (72-80)	85 (81-89)	77 (72-83)	88 (83-93)
Log-rank test *p* value	0.001		0.030	

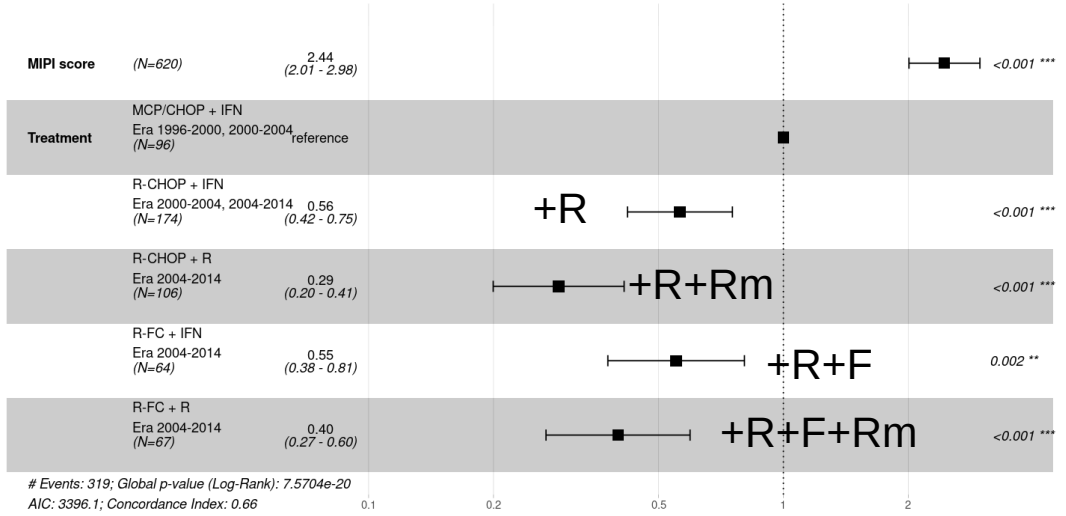
Salles, EHA 2021, JCO 2023

Results: Survival trends – older: impact of treatment

By eras and treatment



Treatment effects



Adding rituximab during induction and as maintenance improved OS

Jiang, Haematologica 2025

MCL Case report 2
Optimal therapy ?

- 74-year-old male, MCL with leukemic non-nodal presentation (SOX11-)
- Stage IV due to BM+. Normal LDH. Splenomegaly of 14.8 cm. MIPI intermediate-low, Ki-67 20% determined in BM, no altered TP53
- Comorbidities: Controlled hypertension and dyslipidemia; COPD GOLD1 (mild). Normal renal and cardiac function. ECOG 1
- Initial strategy: Active observation
- Evolution at 15 months:
  - Refers asthenia, but maintains good general condition, with ECOG 1 and well controlled comorbidities
  - Progressive splenomegaly, current 17.3 cm
  - Lymphocytosis with accelerated doubling: current 88 x109/L
  - Progressive anemia, 9.8 g/dL
  - LDH 1.5 x ULN. Liver and renal function preserved
  - Ki-67 20% in new BM biopsy. Without alterations of TP53
  - MIPI Intermediate-high

ECHO Study Design

TGA indication: CALQUENCE +BR is indicated for adult patients with previously untreated MCL who are ineligible for ASCT.

ECHO (NCT02972840): multicenter, double-blind, placebo-controlled, phase 3 trial

Primary endpoint:
- PFS (independent review committee)

Key secondary endpoints:
- OS
- ORR (independent review committee)

Safety

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: April 2017 to March 2023
Sites: 195 globally

RANDOMIZE

1:1

Bendamustine[a] Rituximab[b] x 6 cycles → if ≥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 ≥PR → Maintenance Rituximab (every 2 cycles x 2 years)

Placebo BID, PO until PD or toxicity

Crossover to acalabrutinib after PD was permitted

1 cycle = 28 days

Data cutoff date: February 15, 2024
Median time on study: 44.9 months

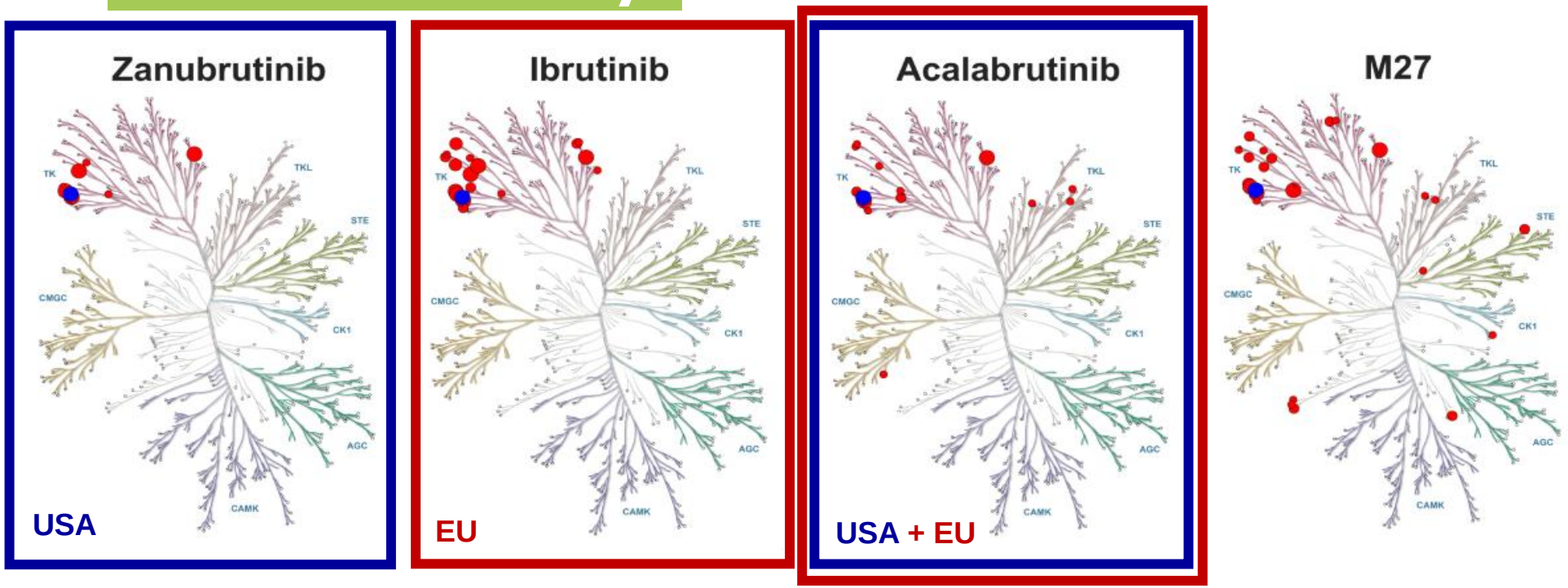
[a]Bendamustine 90 mg/m^2 on days 1 and 2
[b]Rituximab 375 mg/m^2 on day 1

High-risk disease defined as any of the following:
- **High-risk MIPI (6–11)**
- ***TP53* mutation**
- **Ki-67 index ≥30%**
- **Blastoid/pleomorphic histology**

Dreyling, EHA 2025

ECHO High Risk Analysis

BTKi in Lymphoma
Kinase Selectivity



- BTK
- Off target kinases

- 95-100% inhibition
- 90-95% inhibition
- 75-90% inhibition
- 50-75% inhibition

- Bruton tyrosine kinase inhibitors (BTKi) provide effective treatment to several B-cell malignancies; however, duration of treatment is limited by AEs leading to treatment discontinuation, which occur early[1-3]
- BTKi-associated AEs are believed to be due to off-target effects of BTK inhibitors[4]

Mato AR, Haematologica.. Yazdy MS, Blood. 2019 ; Tam CS, EHA 2019. Lipsky A. ASH Educational 2020. Kaptein. Cancer Res. 2019; ***Mato AR, Lancet 2021.*** *Shadman, ASH 2021*

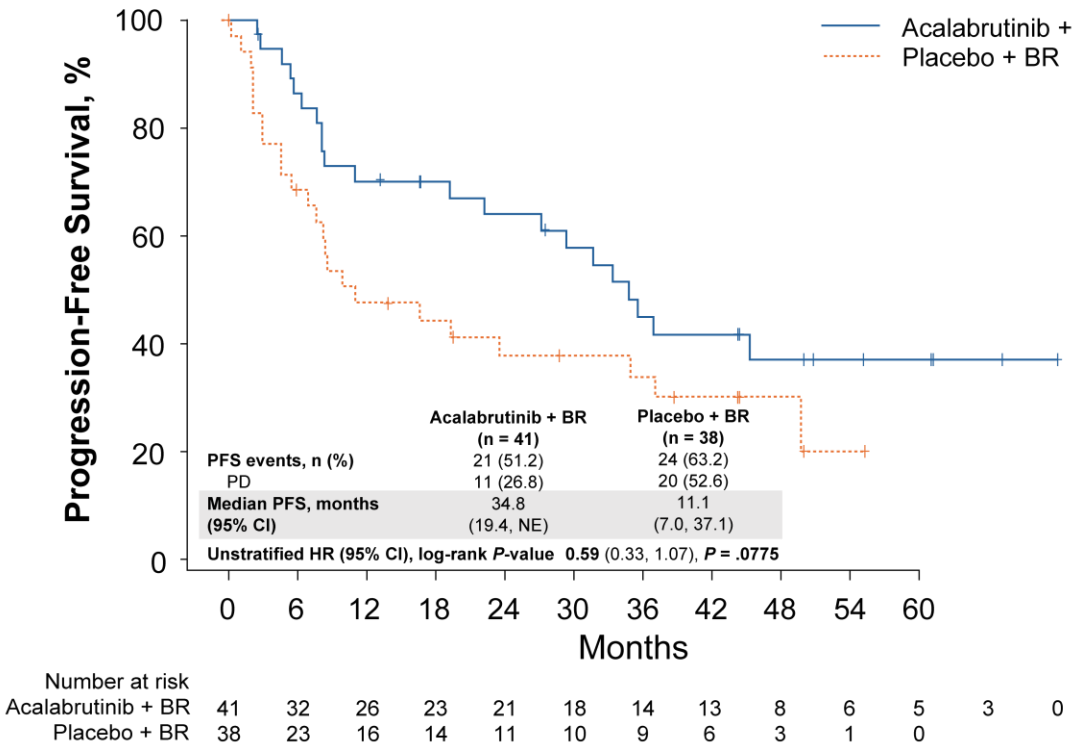
Adverse Events of Interest

	Acalabrutinib + BR (n=297)		Placebo + BR (n=297)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Event, n (%)				
Atrial fibrillation	18 (6.1)	11 (3.7)	13 (4.4)	5 (1.7)
Hypertension	36 (12.1)	16 (5.4)	47 (15.8)	25 (8.4)
Major bleeding[a]	7 (2.4)	6 (2.0)	16 (5.4)	10 (3.4)
Infections[b]	232 (78.1)	122 (41.1)	211 (71.0)	101 (34.0)
Second primary malignancies (excluding non-melanoma skin)[b]	29 (9.8)	16 (5.4)	32 (10.8)	20 (6.7)
Median treatment exposure (range), months	29 (0.1, 80.1)		25 (0.03, 76.4)	

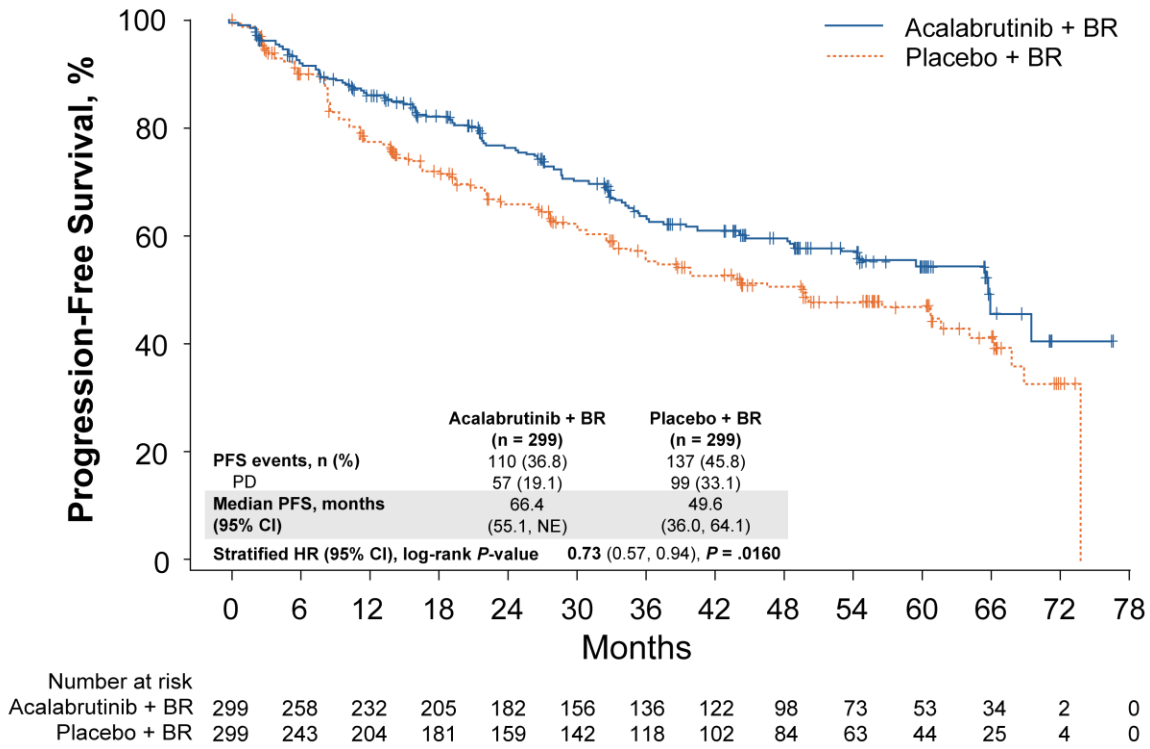
Dreyling, EHA 2025

PFS in Patients With Blastoid/Pleomorphic Histology

PFS in Patients With Blastoid/Pleomorphic Histology



PFS in Full Analysis Population[1]



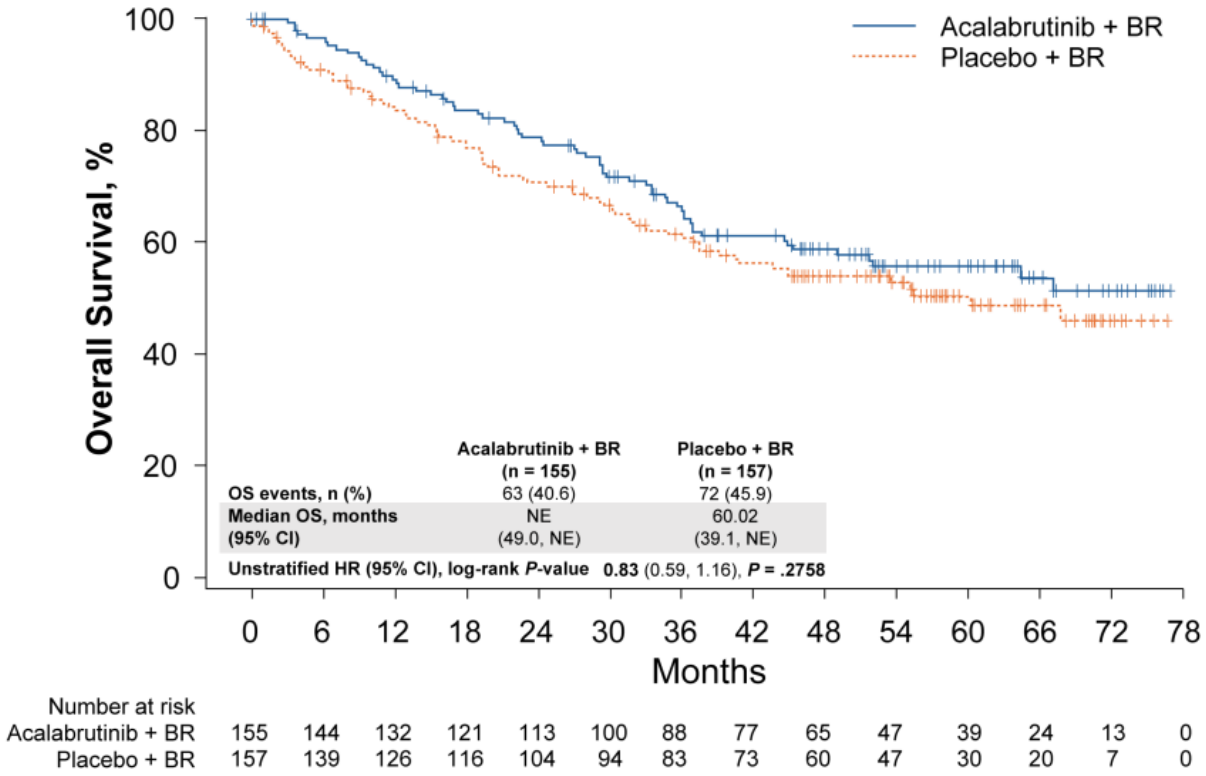
- Sample size in this subgroup was small; the difference in median PFS was ~24 months

Dreyling, EHA 2025

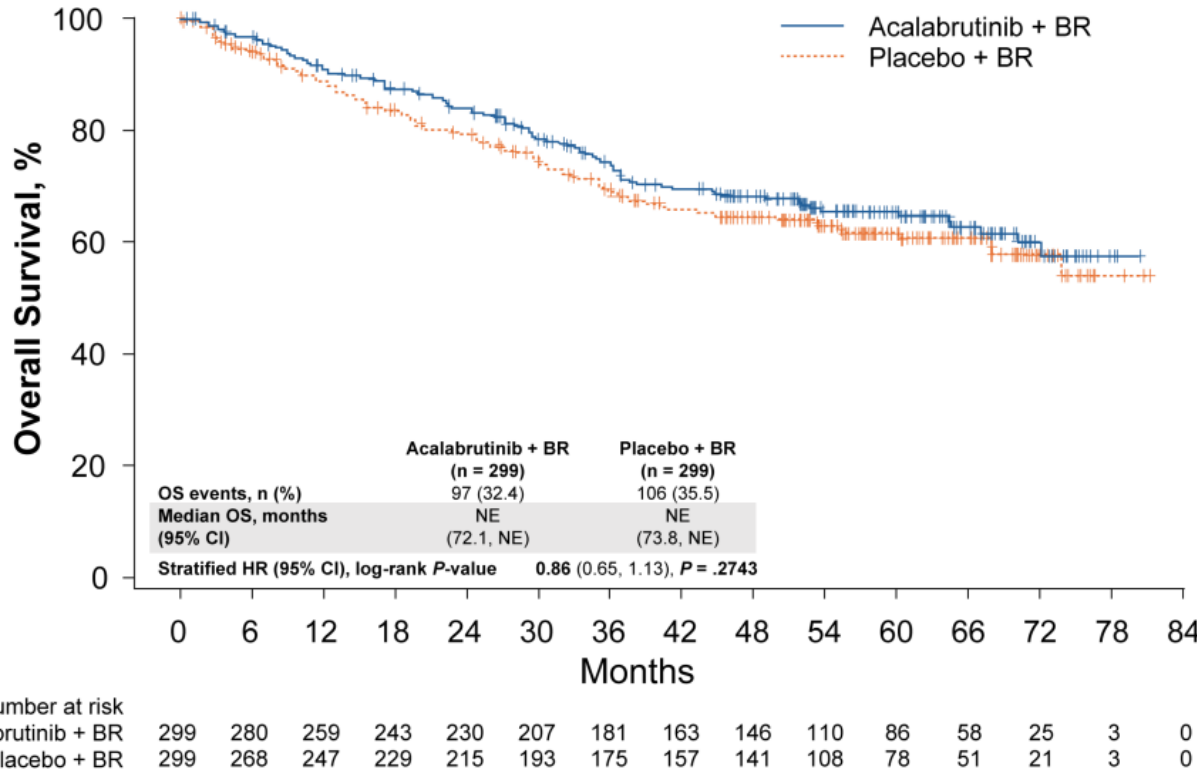
ECHO High Risk Analysis

OS in Patients With High risk Mantle cell lymphoma

OS in Patients With Ki-67 ≥30%, Blastoid/ Pleomorphic Histology, and/or *TP53* Mutation



OS in Full Analysis Population (including crossover)[1]

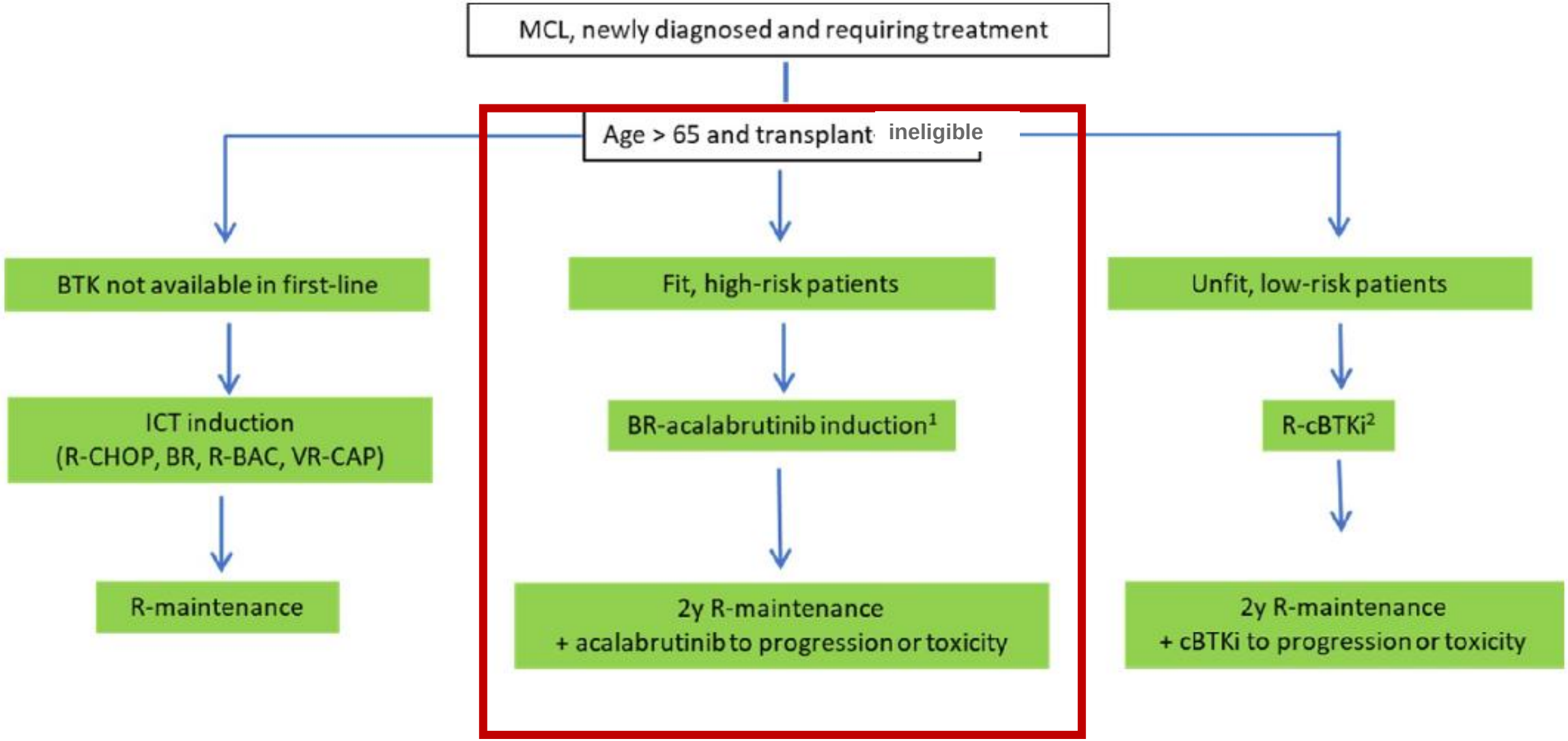


Dreyling, EHA 2025

ECHO High Risk Analysis

How do I treat MCL (elderly patients)

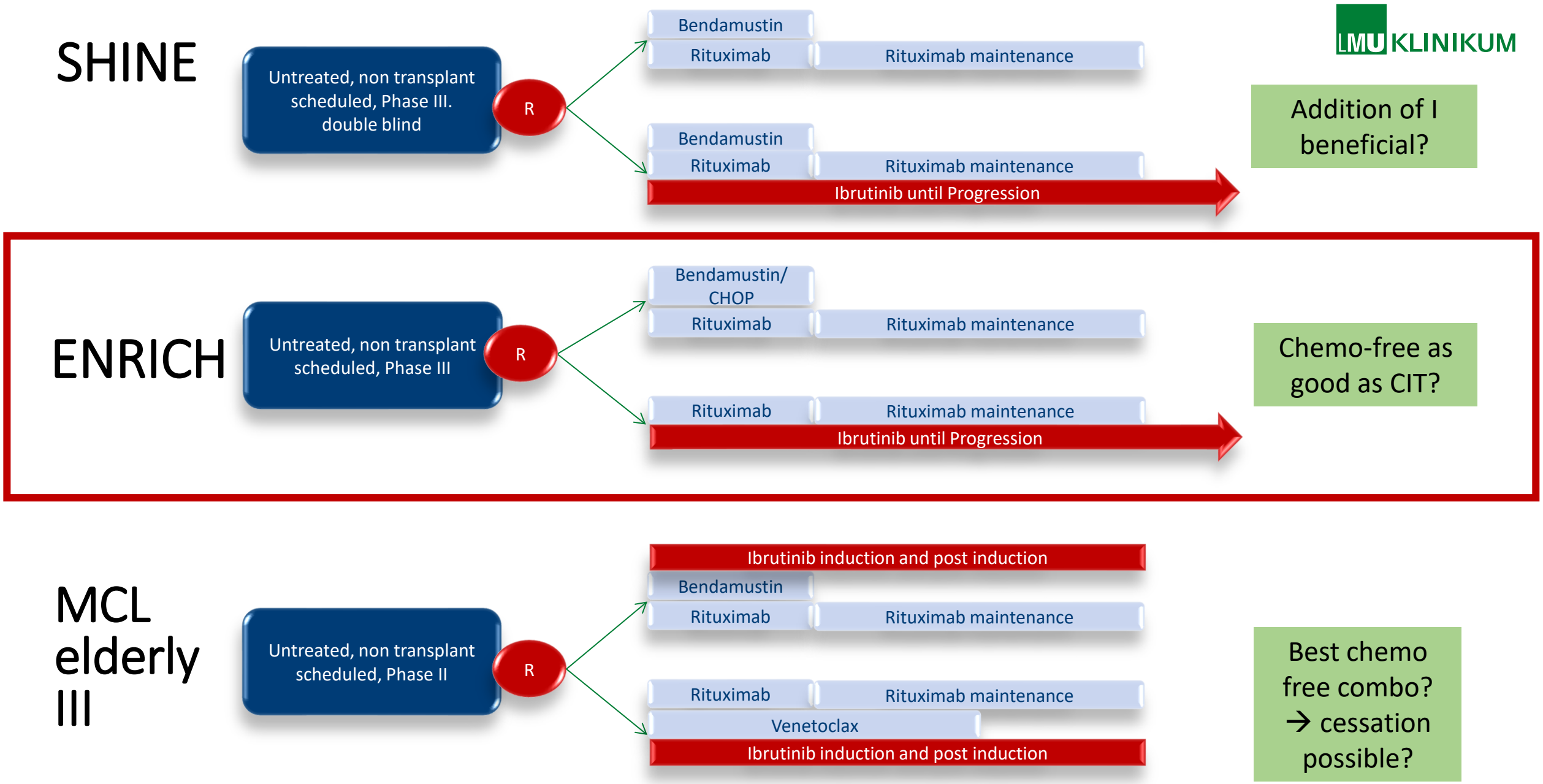
Suggested Therapeutic algorithm



Silkenstedt, Dreyling, Hematological Oncology 2025

MCL Case report 2
Optimal therapy ?

- 74-year-old male, MCL with leukemic non-nodal presentation (SOX11-)
- Stage IV due to BM+. Normal LDH. Splenomegaly of 14.8 cm. MIPI intermediate-low, Ki-67 20% determined in BM, no altered TP53
- Comorbidities: Controlled hypertension and dyslipidemia; COPD GOLD1 (mild). Normal renal and cardiac function. ECOG 1
- Initial strategy: Active observation
- Evolution at 15 months:
  - Refers asthenia, but maintains good general condition, with ECOG 1 and well controlled comorbidities
  - Progressive splenomegaly, current 17.3 cm
  - Lymphocytosis with accelerated doubling: current 88 x109/L
  - Progressive anemia, 9.8 g/dL
  - LDH 1.5 x ULN. Liver and renal function preserved
  - Ki-67 20% in new BM biopsy. Without alterations of TP53
  - MIPI Intermediate-high


SHINE
Untreated, non transplant scheduled, Phase III. double blind
R
Bendamustin
Rituximab
Rituximab maintenance
Bendamustin
Rituximab
Rituximab maintenance
Ibrutinib until Progression
Addition of I beneficial?
ENRICH
Untreated, non transplant scheduled, Phase III
R
Bendamustin/ CHOP
Rituximab
Rituximab maintenance
Rituximab
Rituximab maintenance
Ibrutinib until Progression
Chemo-free as good as CIT?
MCL elderly III
Untreated, non transplant scheduled, Phase II
R
Ibrutinib induction and post induction
Bendamustin
Rituximab
Rituximab maintenance
Rituximab
Rituximab maintenance
Venetoclax
Ibrutinib induction and post induction
Best chemo free combo? → cessation possible?

Grade 3-4 Adverse events

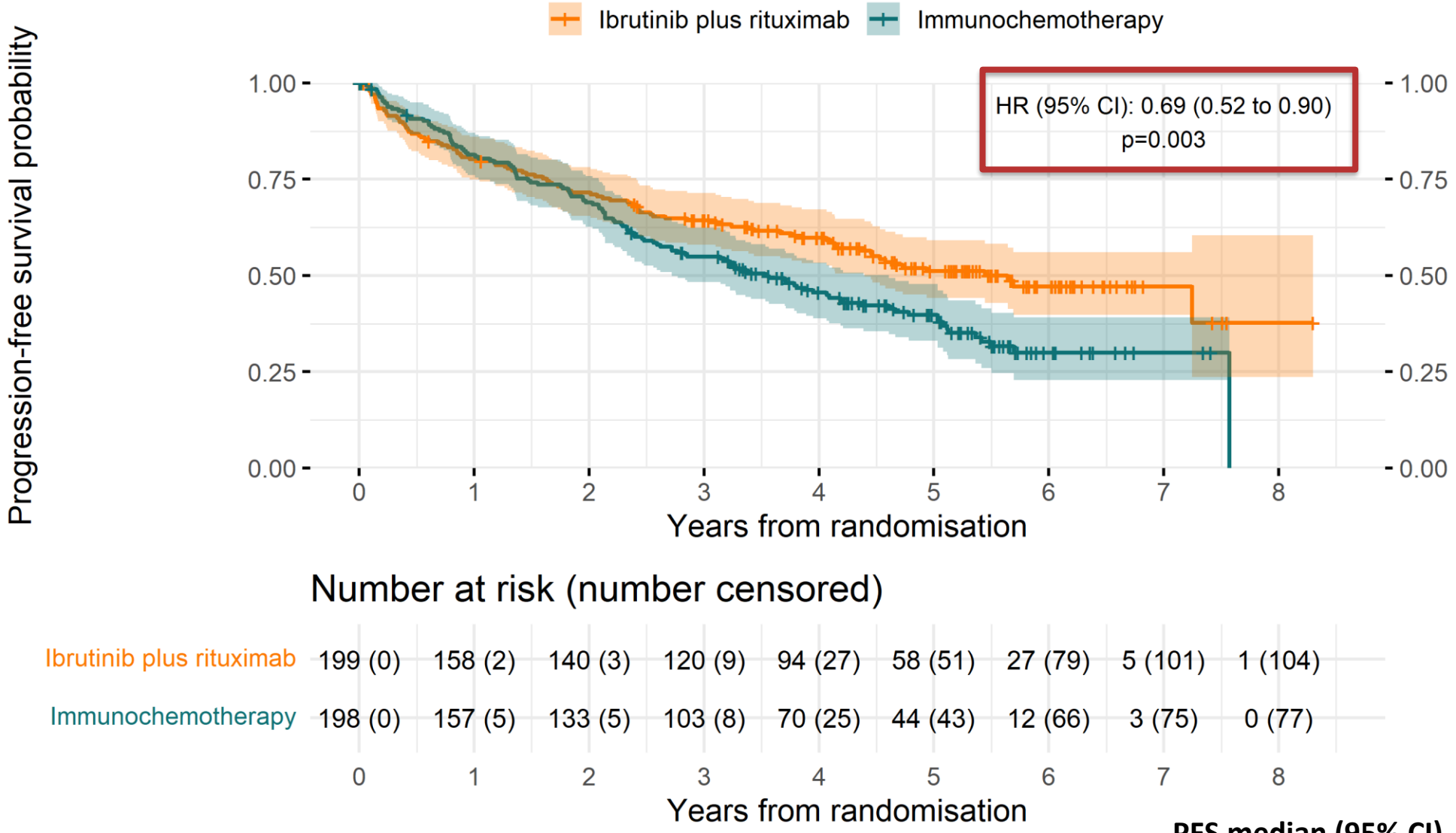
N participants (% of safety population)	**Ibrutinib plus rituximab, N=198**	**Bendamustine-rituximab, N=143**	**R-CHOP, N=52**
Total	125 (63.1%)	97 (67.8%)	36 (69.2%)
All Cardiac AEs	44 (22.2%)	7 (4.9%)	7 (13.5%)
All bleeding AEs	10 (5.1%)	3 (2.1%)	3 (5.8%)
Atrial Fibrillation	12 (6.1%)	1 (0.7%)	0
Neutropenia	18 (9.1%)	27 (18.9%)	11 (21.2%)
Neutropenic sepsis	6 (3.0%)	2 (1.4%)	8 (15.4%)
Corona virus infection	10 (5.1%)	10 (7.0%)	0

Grade 3 and 4 adverse events during induction treatment and maintenance

Safety population - patients who had at least one cycle of treatment

Lewis, Lancet 2025

Progression-free survival



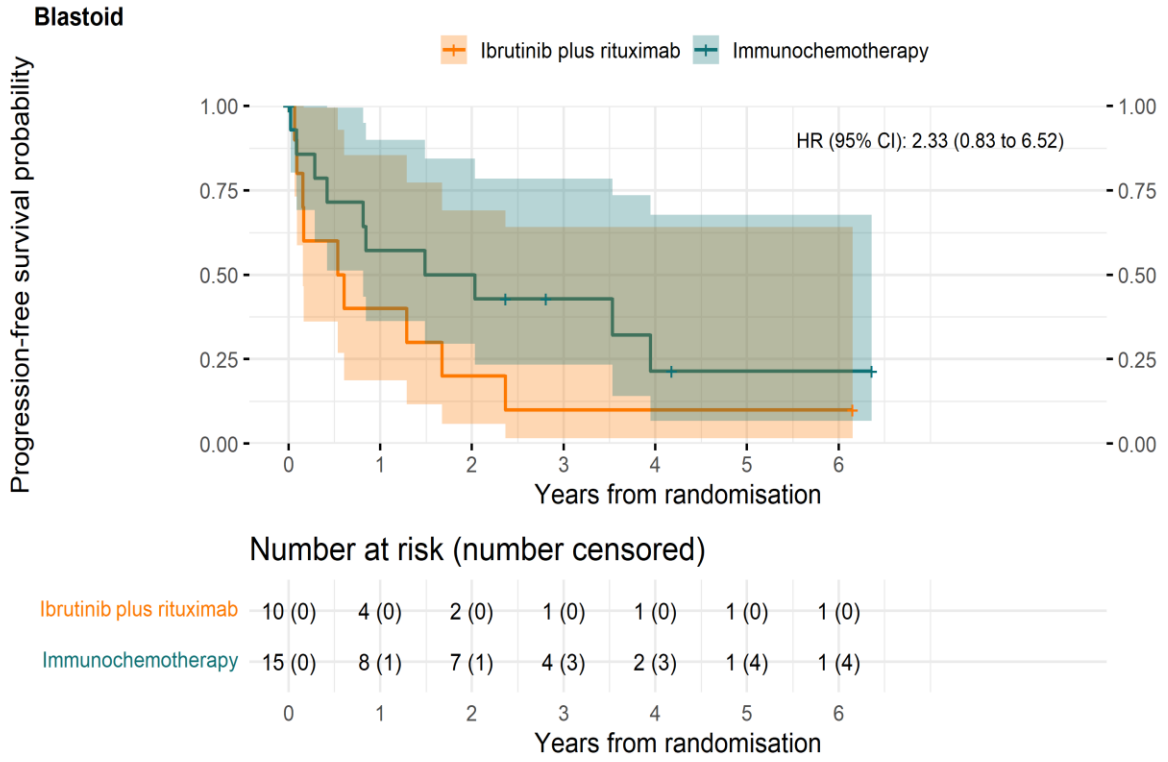
Lewis, Lancet 2025

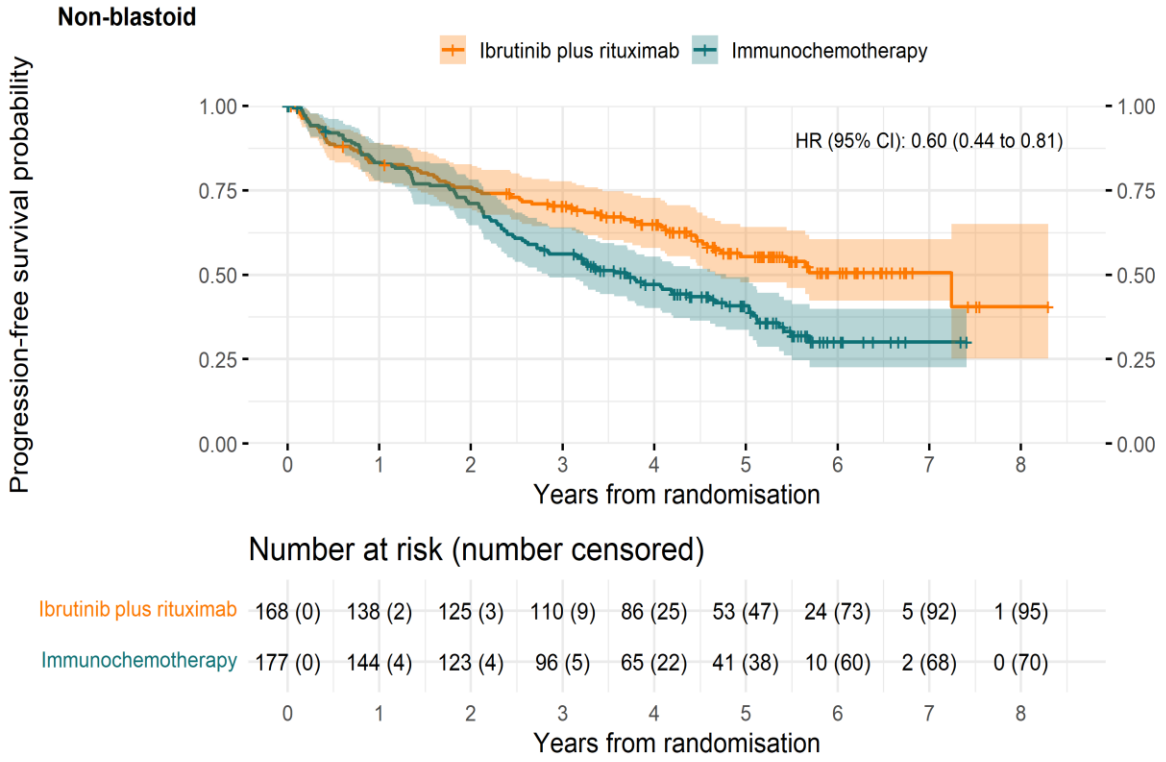
Median Follow up 47.9 months

PFS median (95% CI)
IR: 65.3 mo (52.7 to not evaluable)
R-chemo: 42.4 mo (32.7 to 55.3)

Blastoid disease

Suggestion of inferior PFS for blastoid disease for those randomised to IR

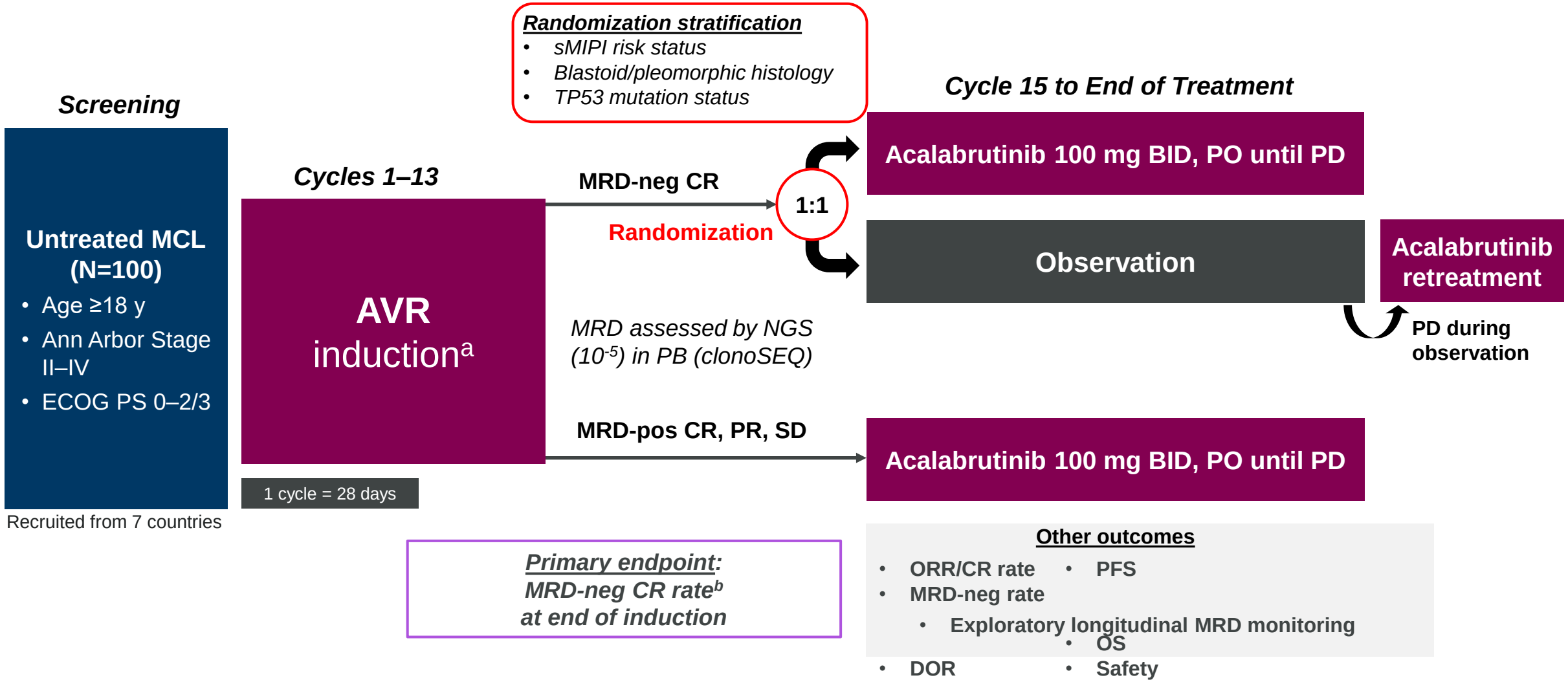




Blastoid subgroup (n=25) PFS 6.9 (95% CI 1.9 to NE) months for IR vs 21.1 (95% CI 9.8 to NE) months for immunochemotherapy); HR 2.33, 95% CI 0.83 to 6.52

Lewis, Lancet 2025

TrAVeRse Study Design: Multicenter, Open-label, Phase 2 Trial

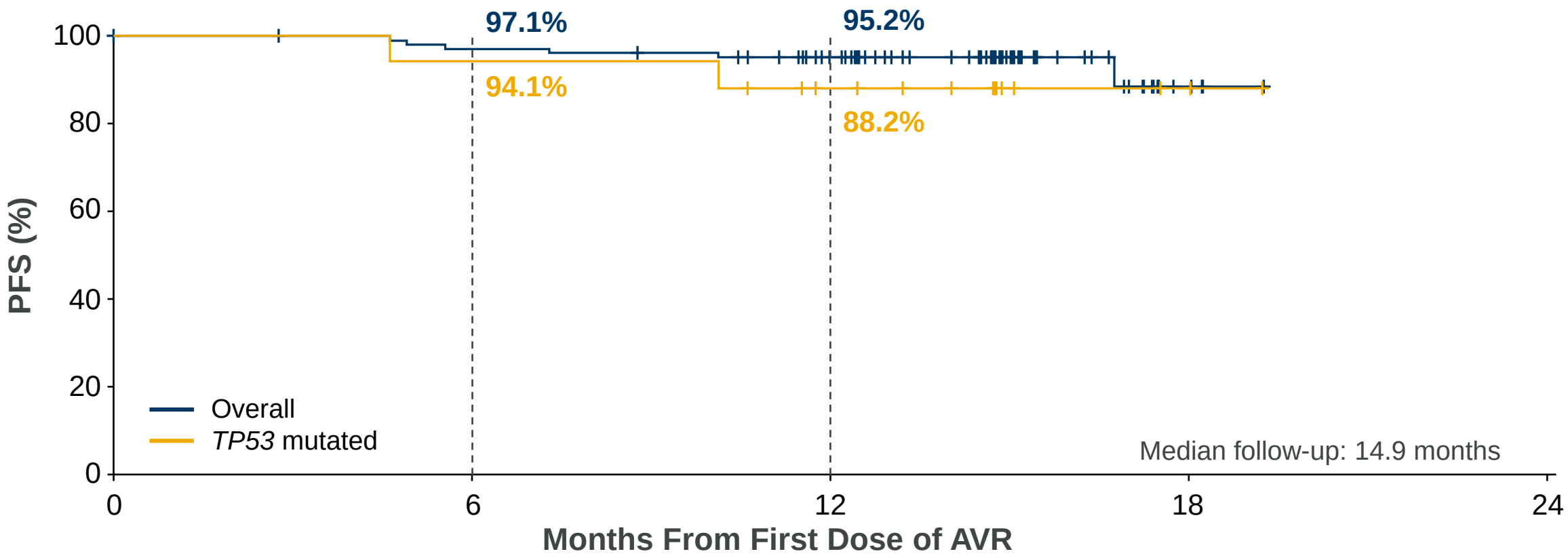


Hawkes, ASH 2025

TrAVeRse

Progression-free Survival

PFS rates were high, regardless of TP53 mutation status

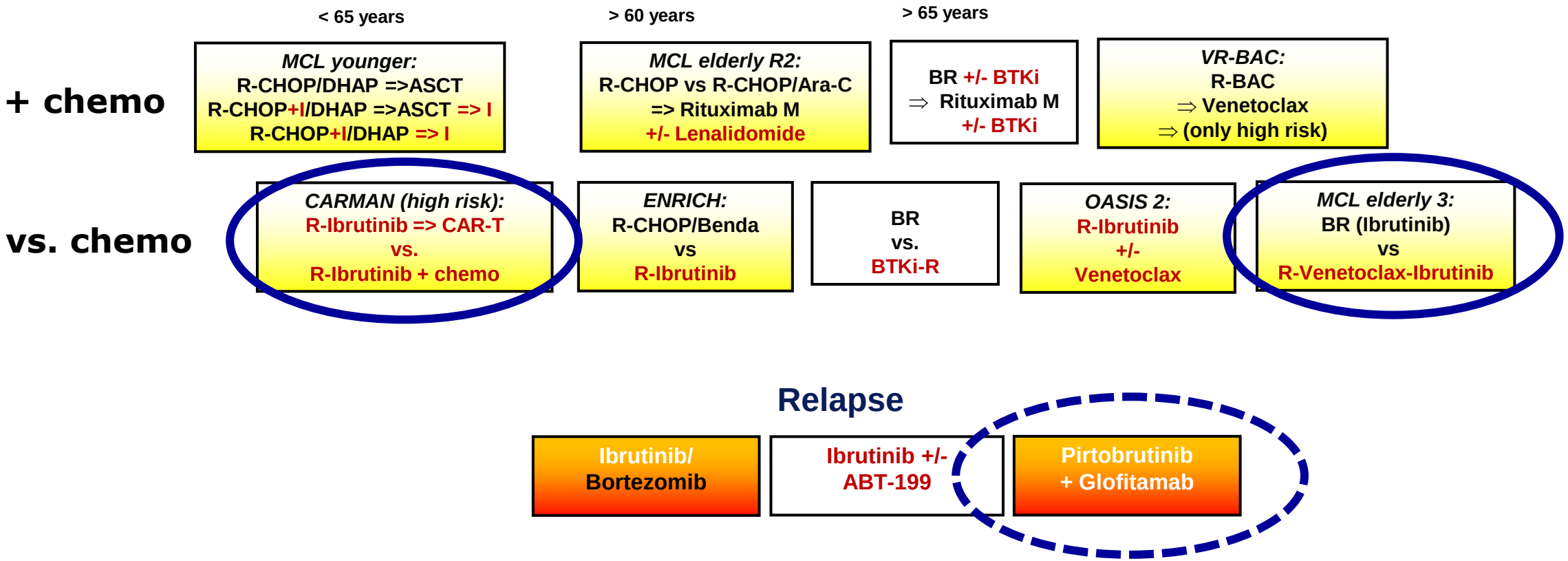


No. at risk					
Overall	108	102	90	3	0
TP53 mutated	17	16	12	2	0

Hawkes, ASH 2025

TrAVeRse

European MCL Network
Study generation 2026



Relapse

Mantle cell lymphoma
Take home message: first line

- **Biological risk factors : Ki-67, p53, blastoid**
- ***younger patients:***

  TRIANGLE new standard (OS: +10%)
- ***older patients:***

  BR-Acalabrutinib significantly improves PFS (high risk)
- **R-BTKi is superior to R-Chemo (?) (low risk)**
- ***In studies: combined targeted/immune therapy***