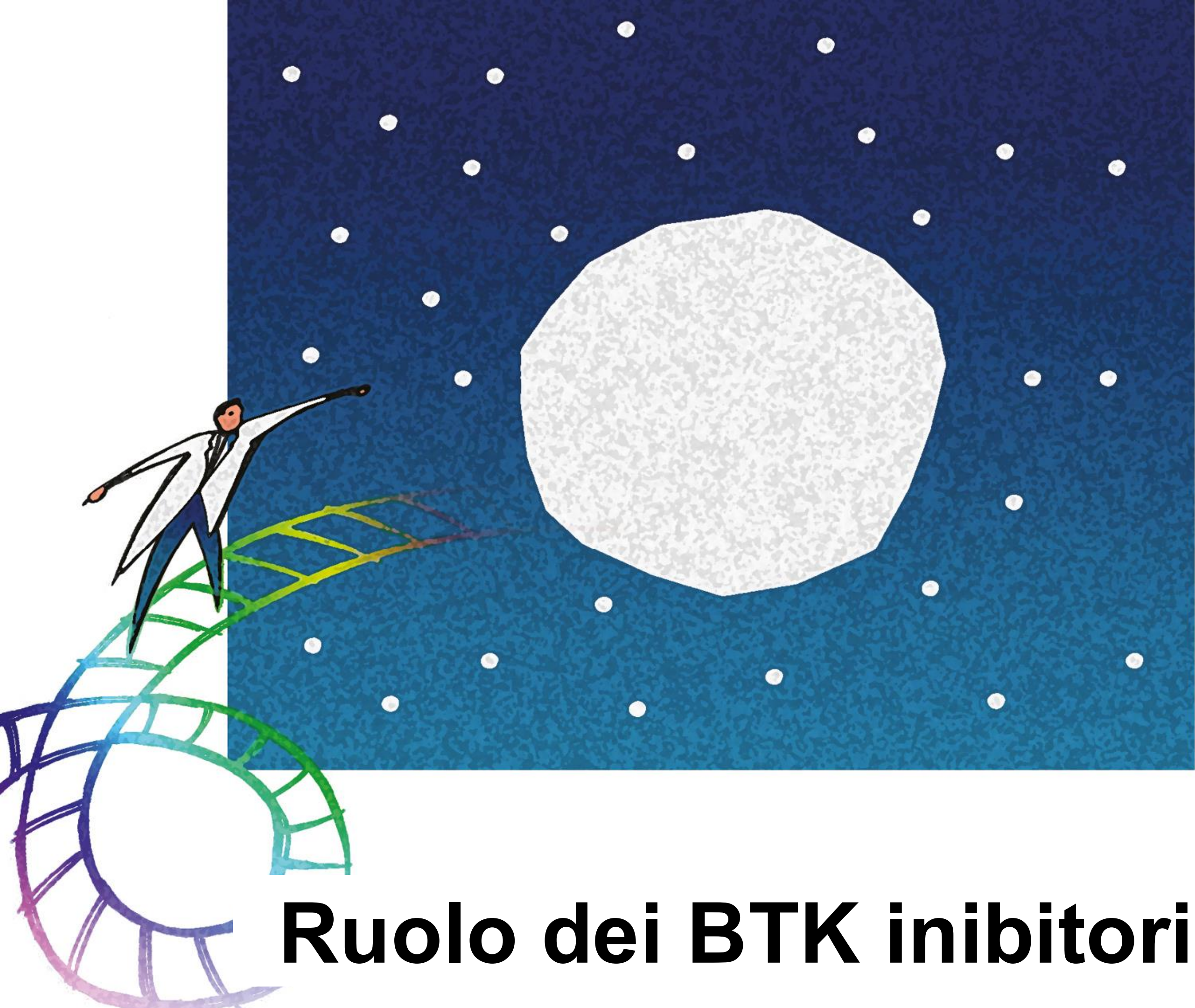




The young side of **LYMPHOMA**

gli under 40 a confronto

Reggio Emilia, Hotel Mercure Astoria
2-3 ottobre 2026

Ruolo dei BTK inibitori nel linfoma mantellare

Mariella Lo Schirico
Istituto Oncologico Veneto IRCCS



Disclosures of Mariella Lo Schirico

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

DOMANDA

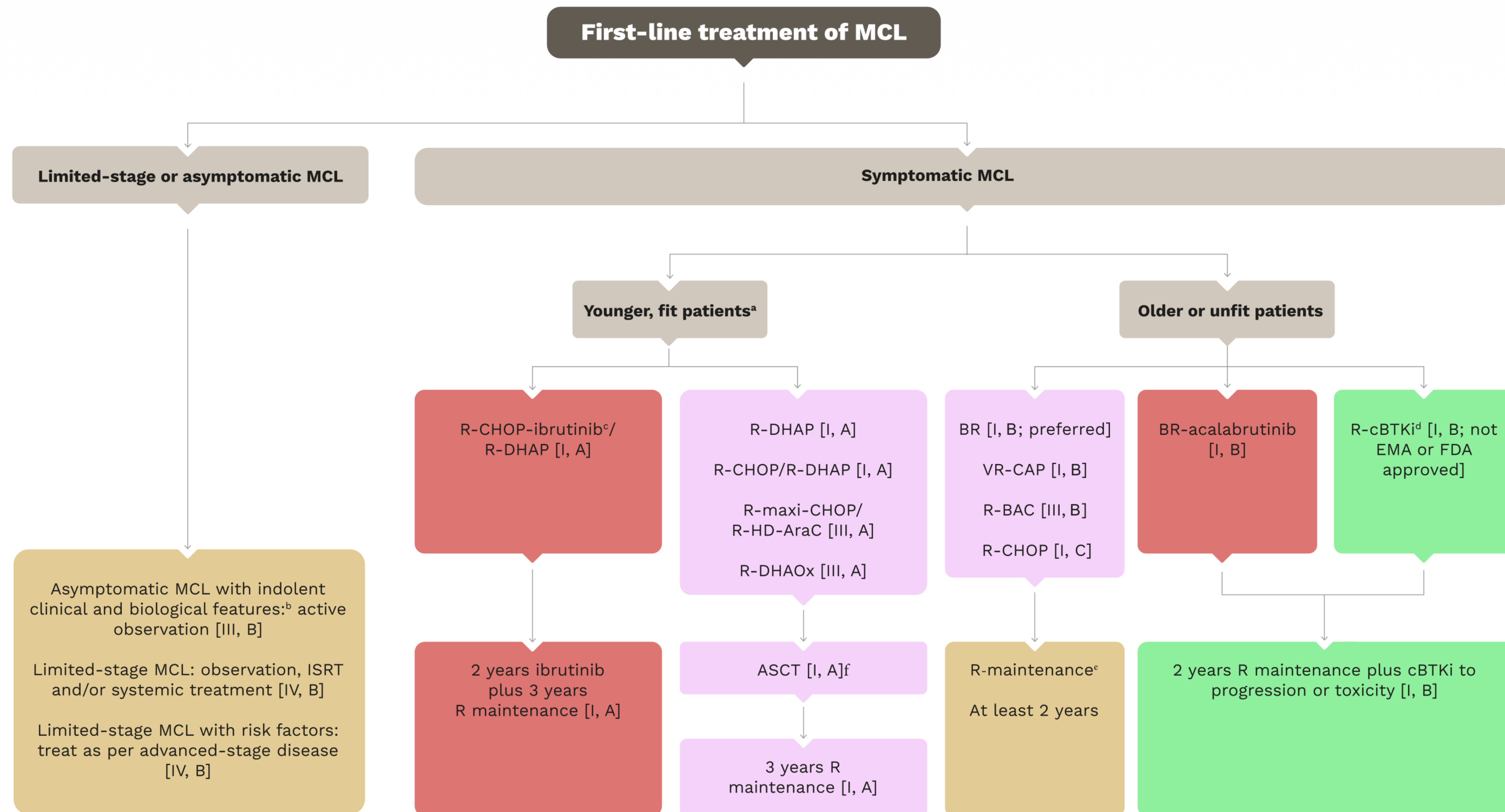
Paziente di 66 anni, M

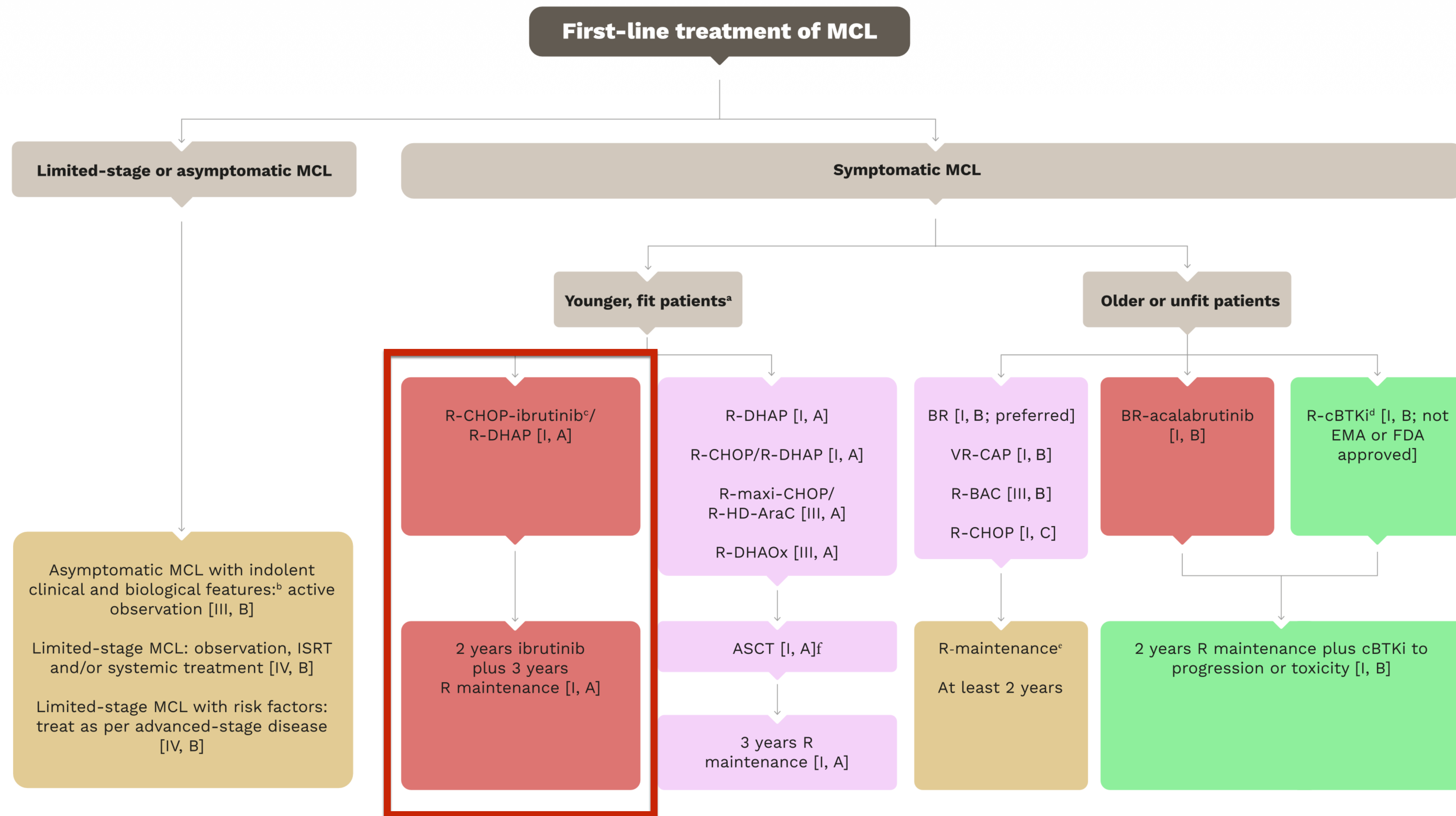
APR: ipertensione arteriosa, diabete mellito

MCL classico, stadio IV (BM), MIPI 6 (int.), Ki67 40%, P53 neg (IHC)

Quale terapia?

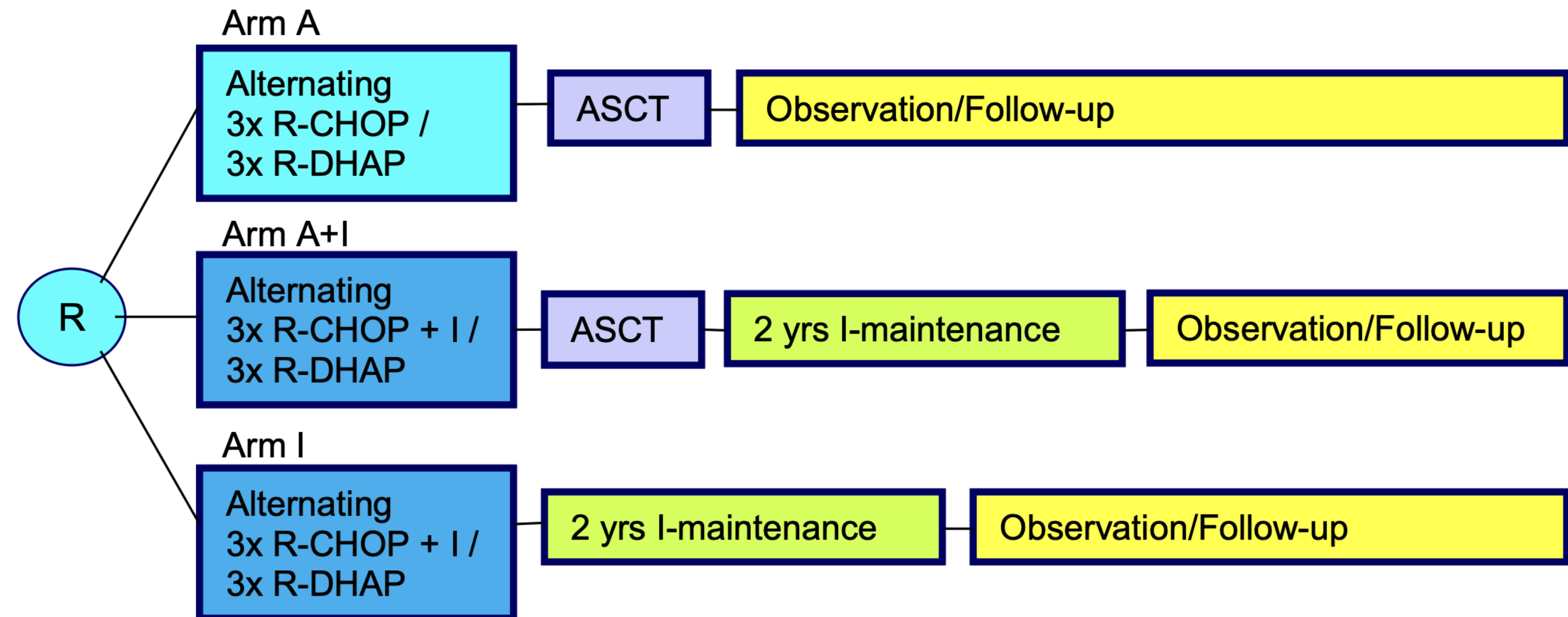
- A. R-CHOP+Ibrutinib/R-DHAOx + ASCT + R-I mant.
- B. R-CHOP+Ibrutinib/R-DHAOx + R-I mant.
- C. R-BAC + R mant.
- D. R-Benda + Acalabrutinib





TRIANGLE

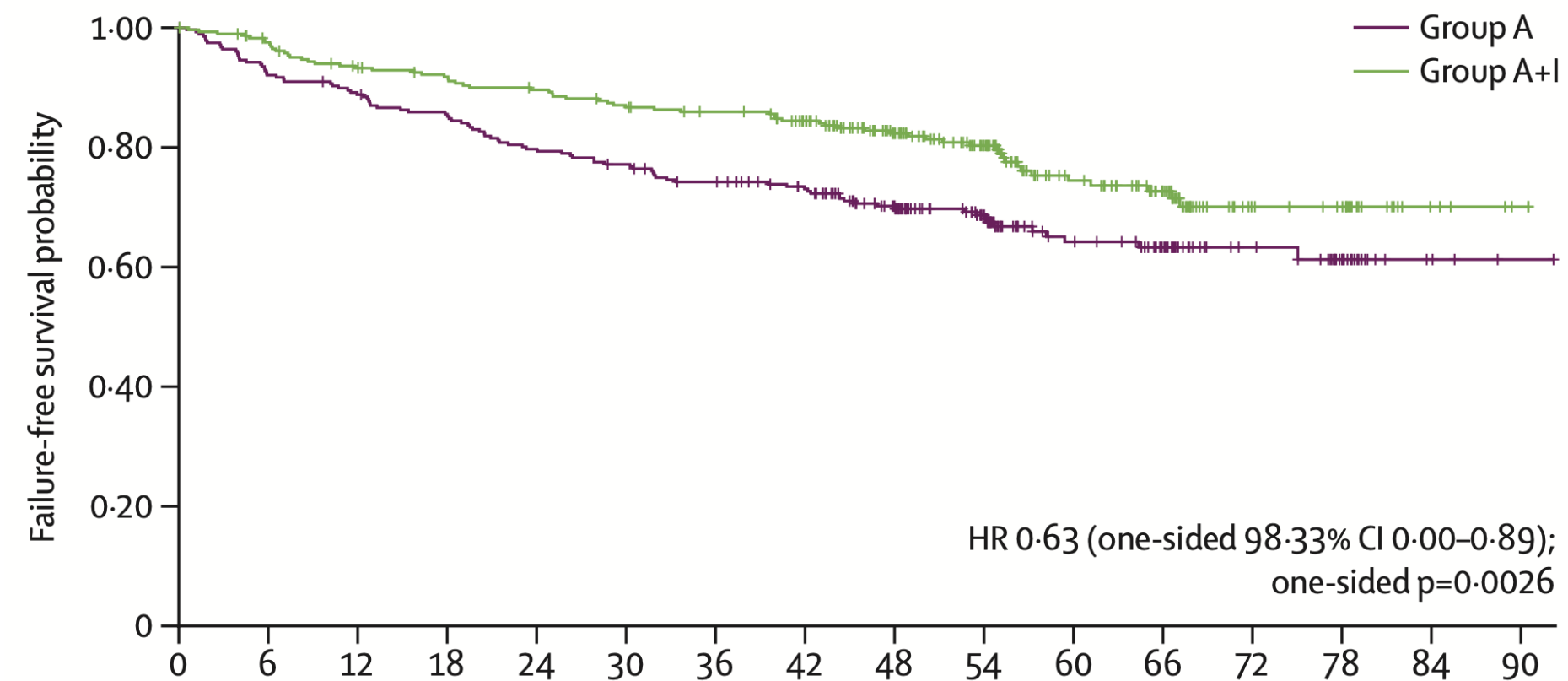
- 870 pts
- Younger than 66y
- Stage II-IV
- Suitable for ASCT



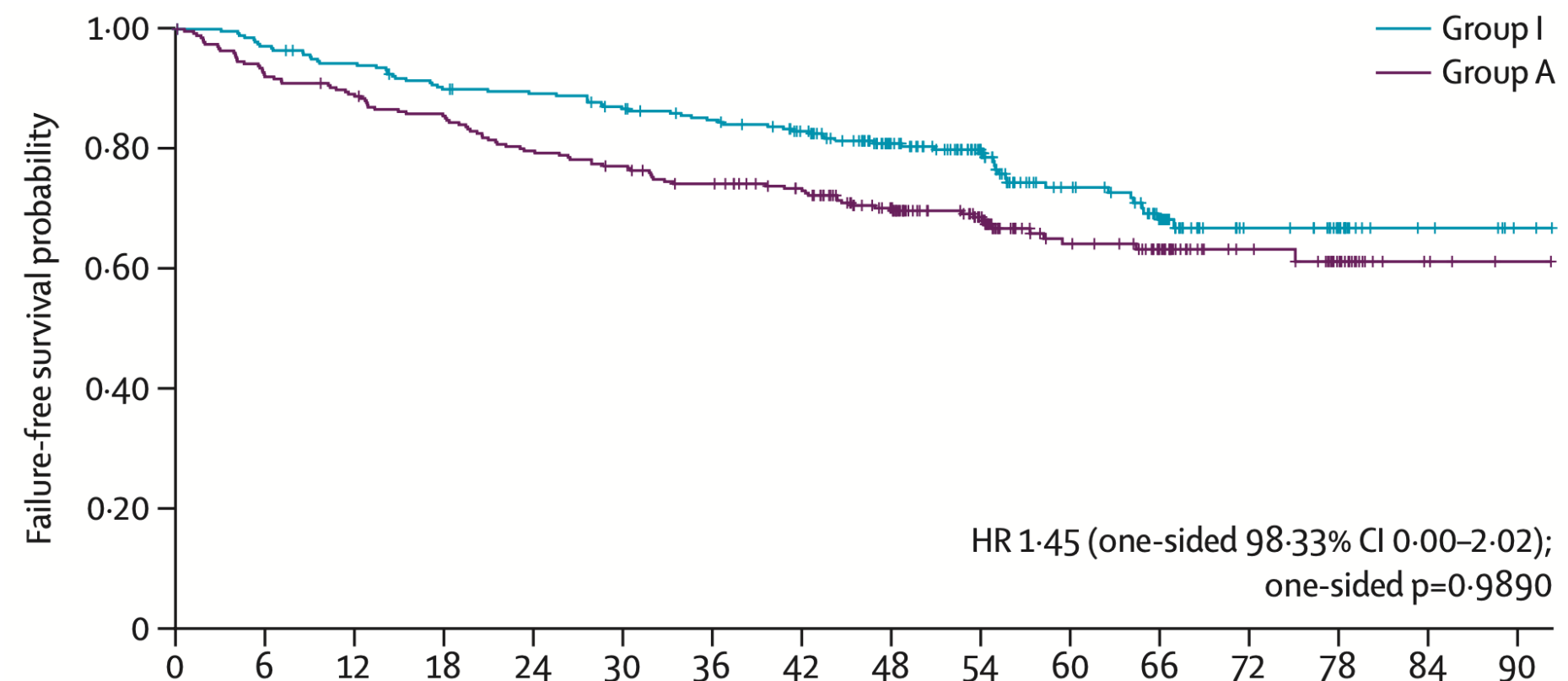
The young side of LYMPHOMA

gli under 40 a confronto

FFS

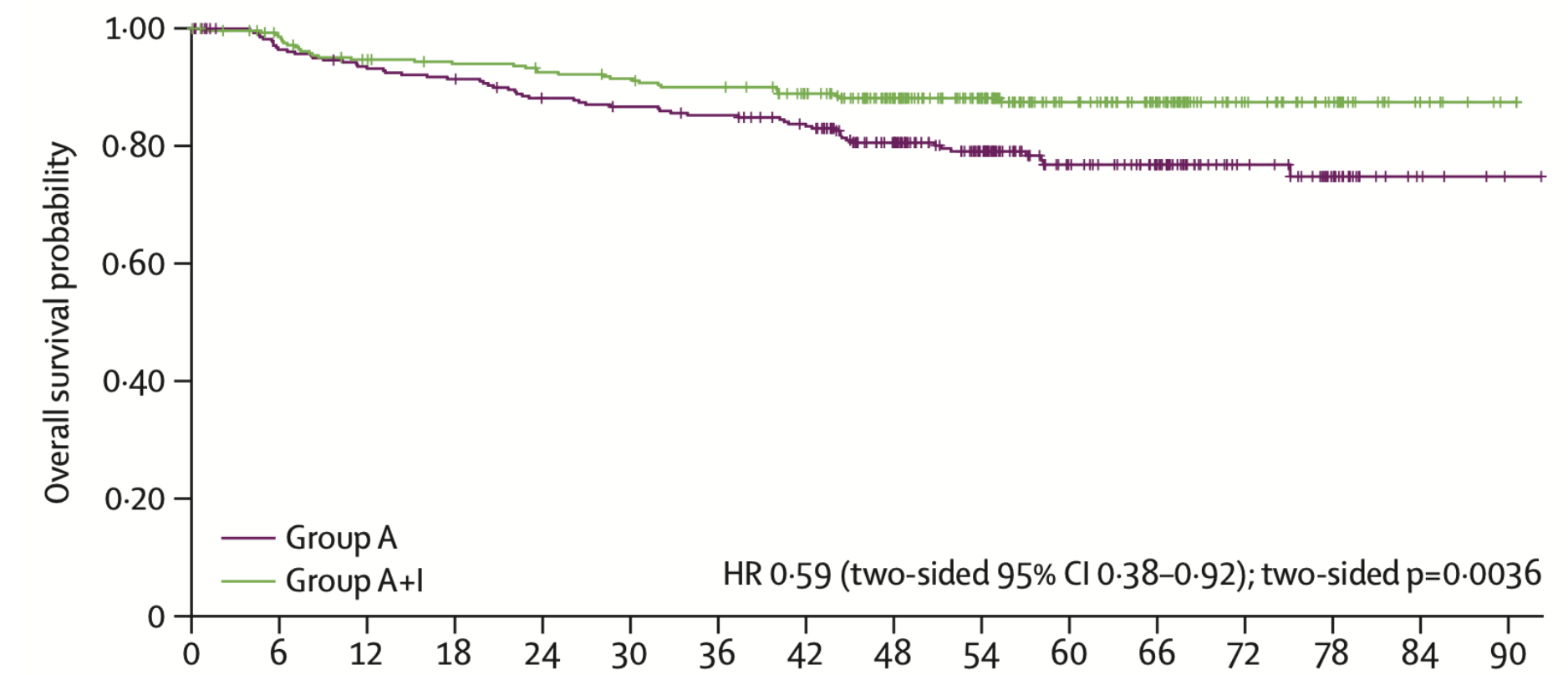


82%
70%

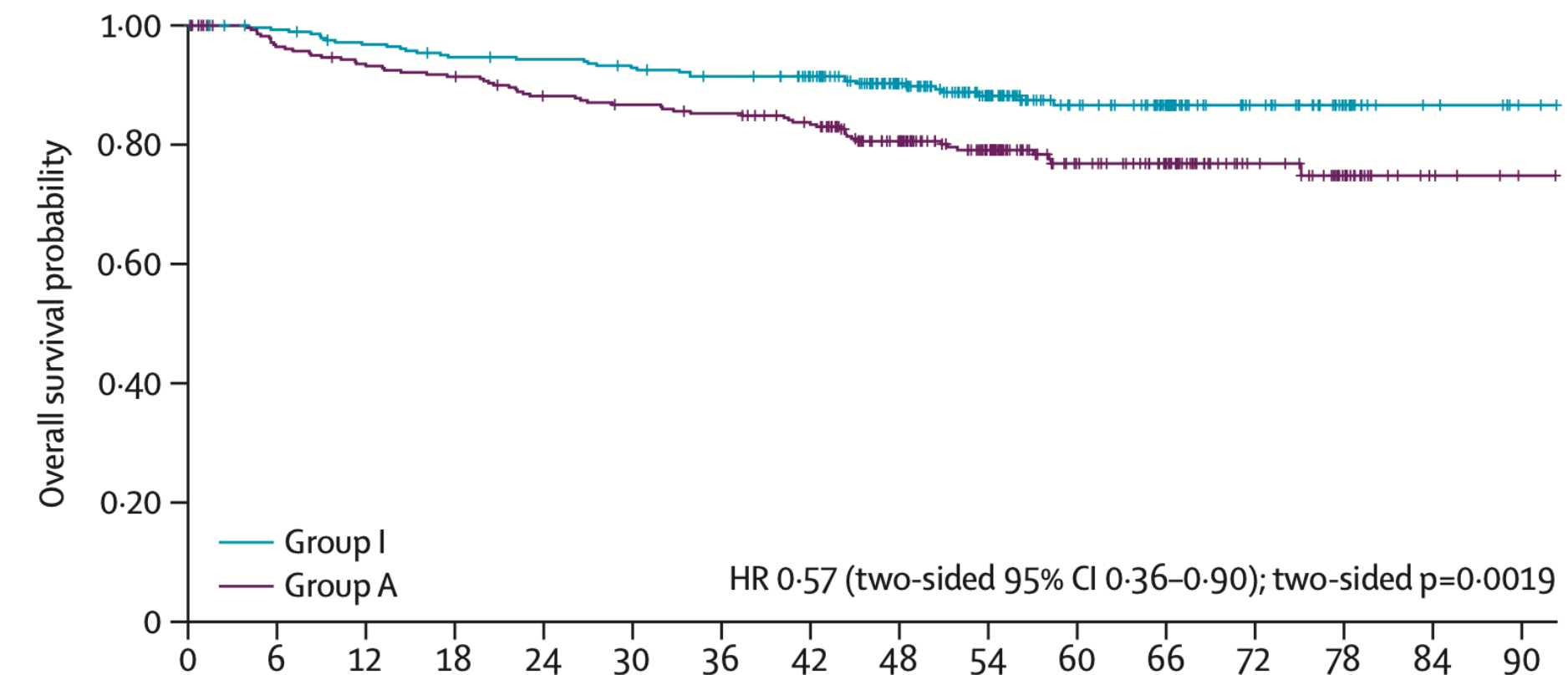


81%
70%

OS



88%
81%



90%
81%

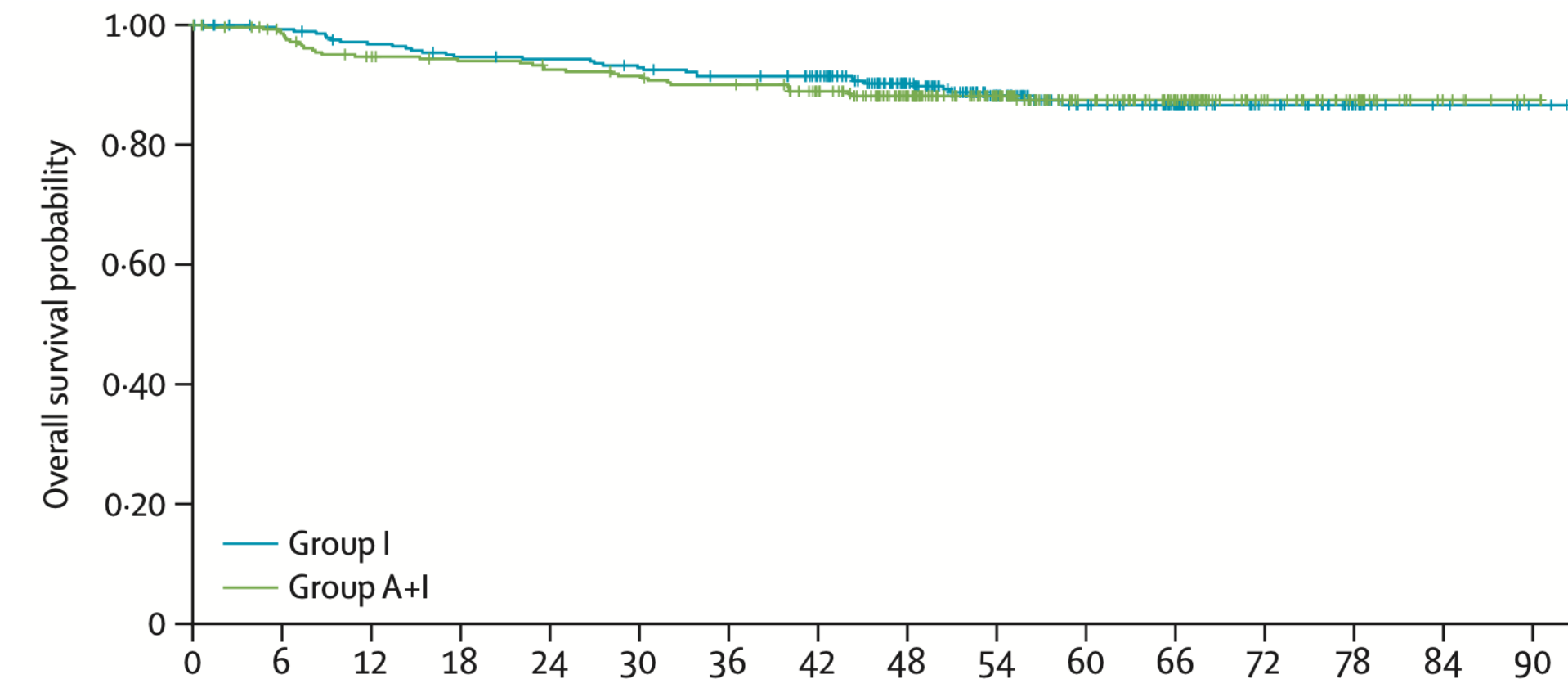
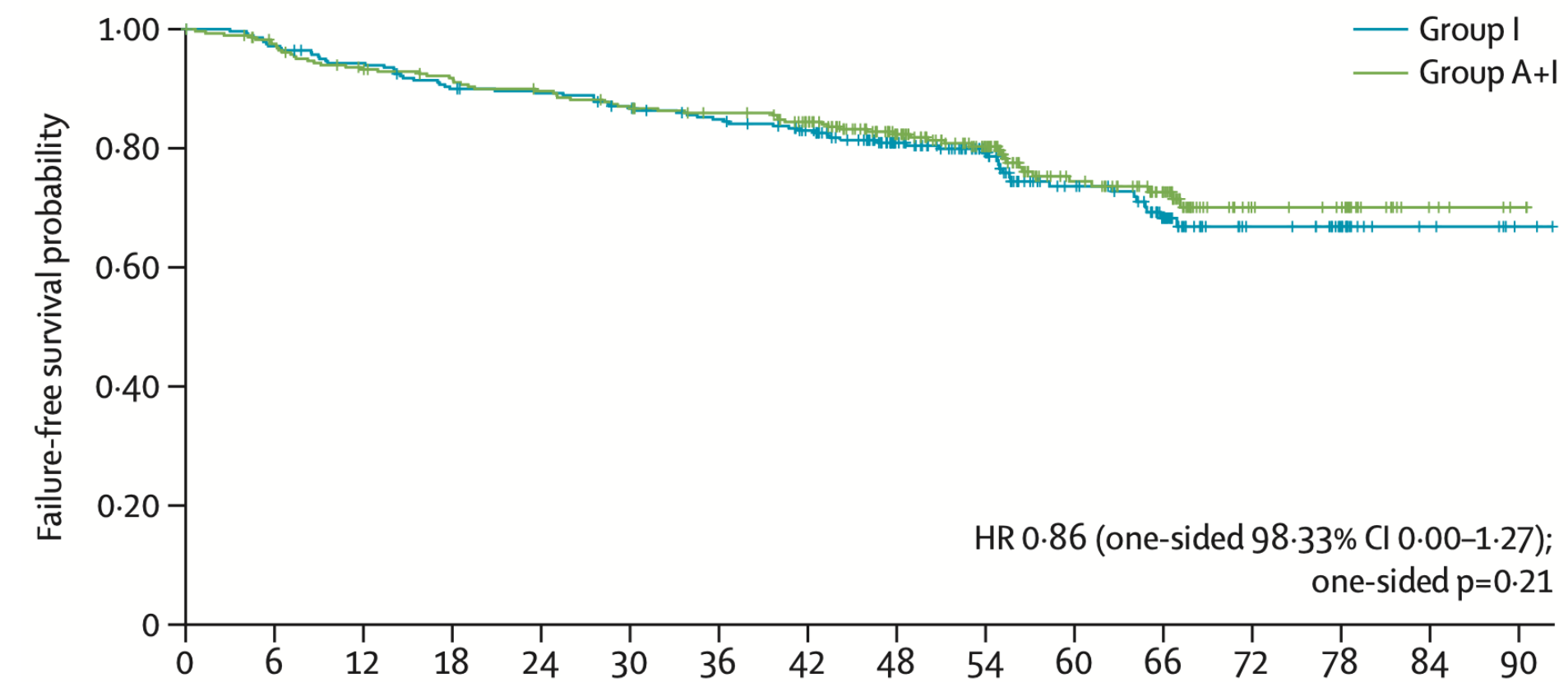
Dreyling et al., Lancet 2026

Reggio Emilia, 2-3 ottobre 2026

The young side of LYMPHOMA

gli under 40 a confronto

A+I vs I



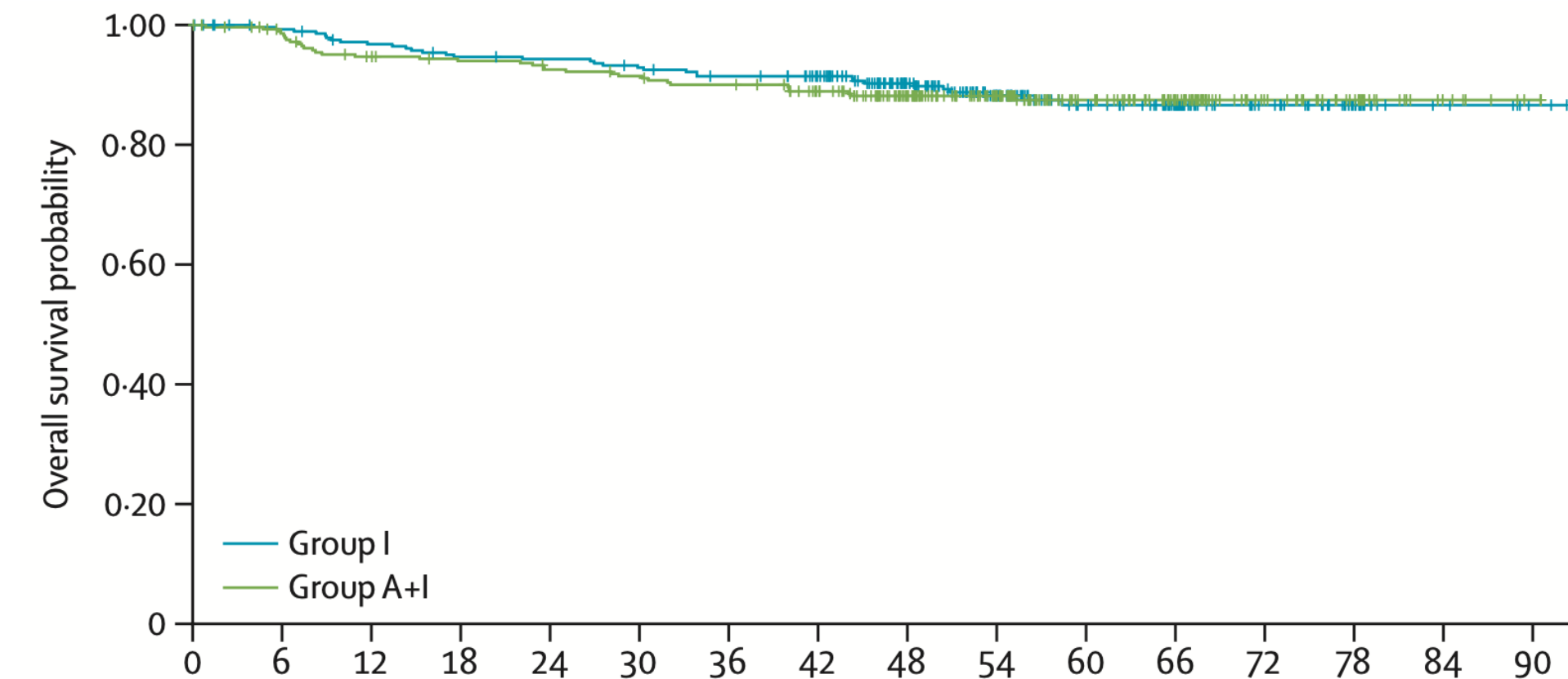
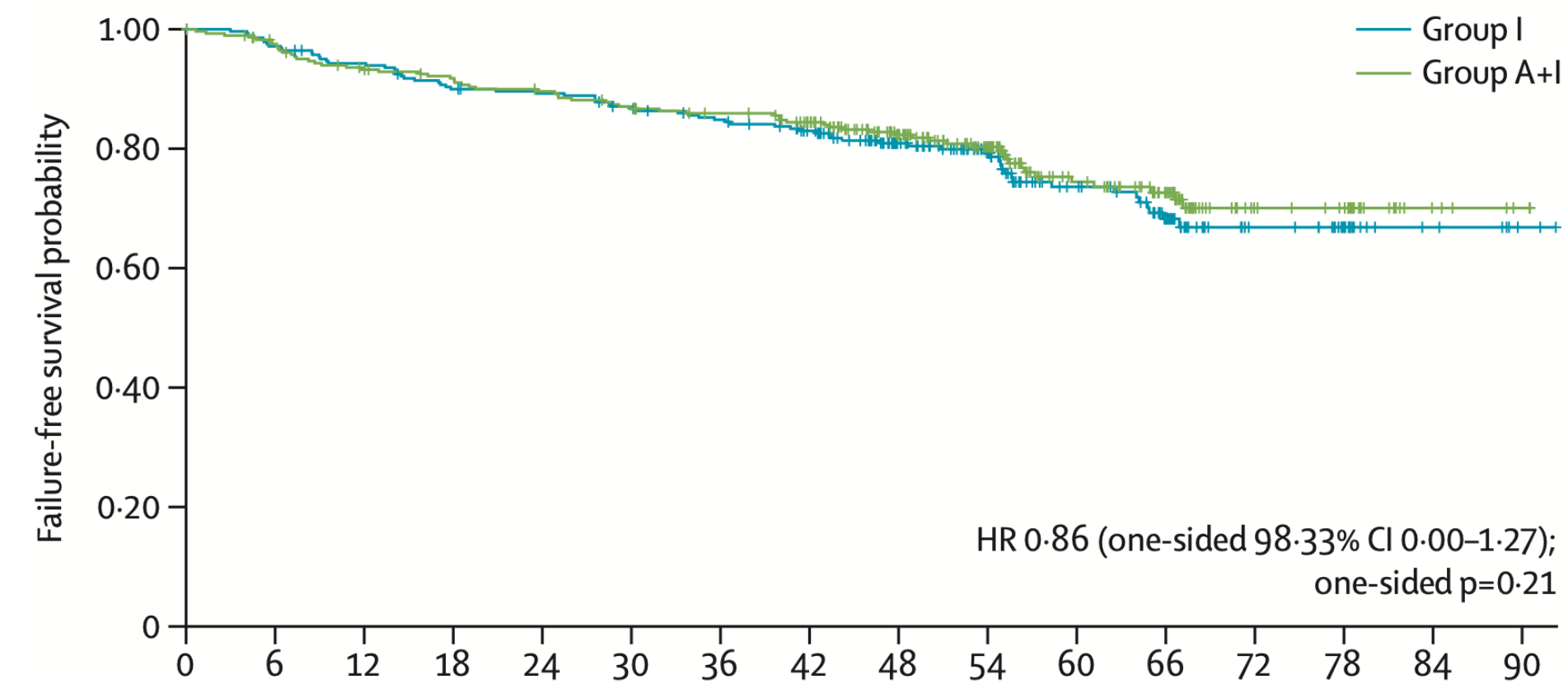
Dreyling et al., Lancet 2026

Reggio Emilia, 2-3 ottobre 2026

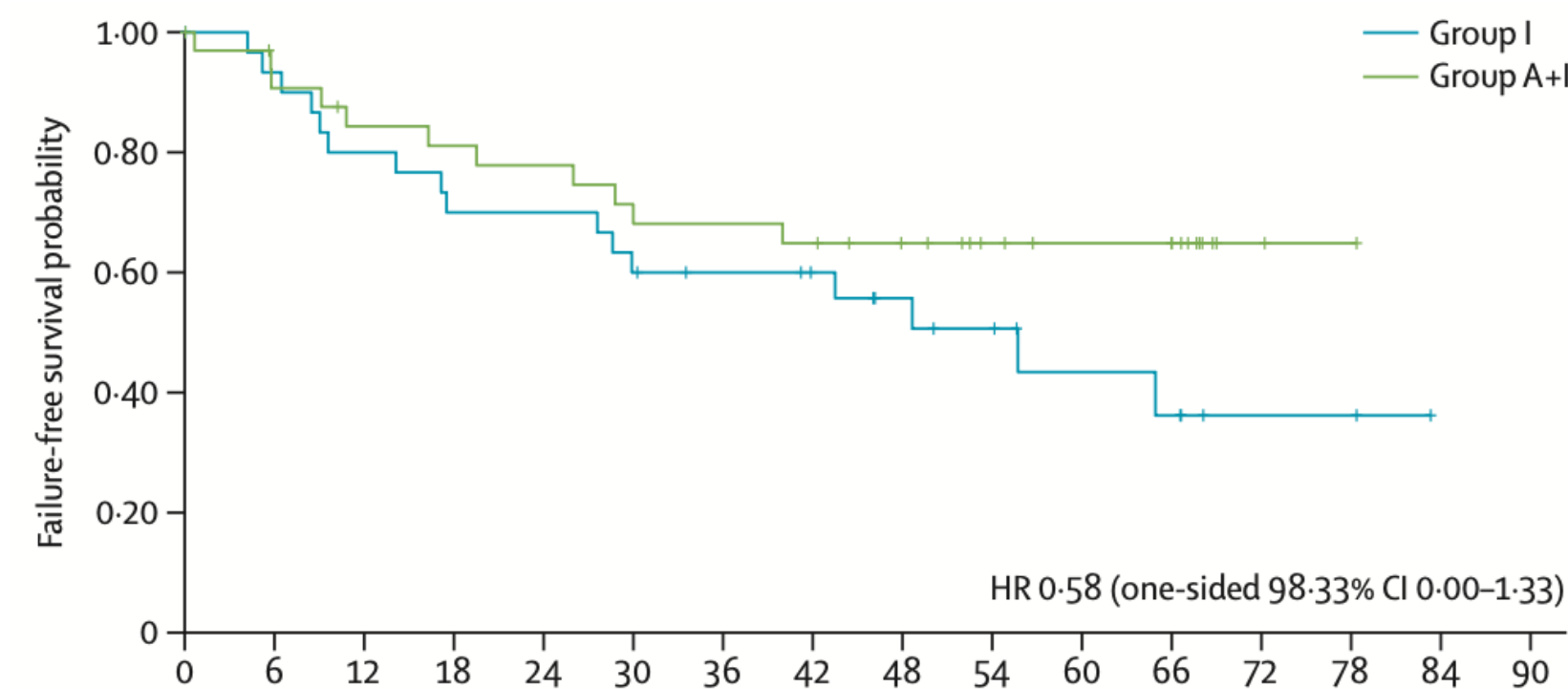
The young side of LYMPHOMA

gli under 40 a confronto

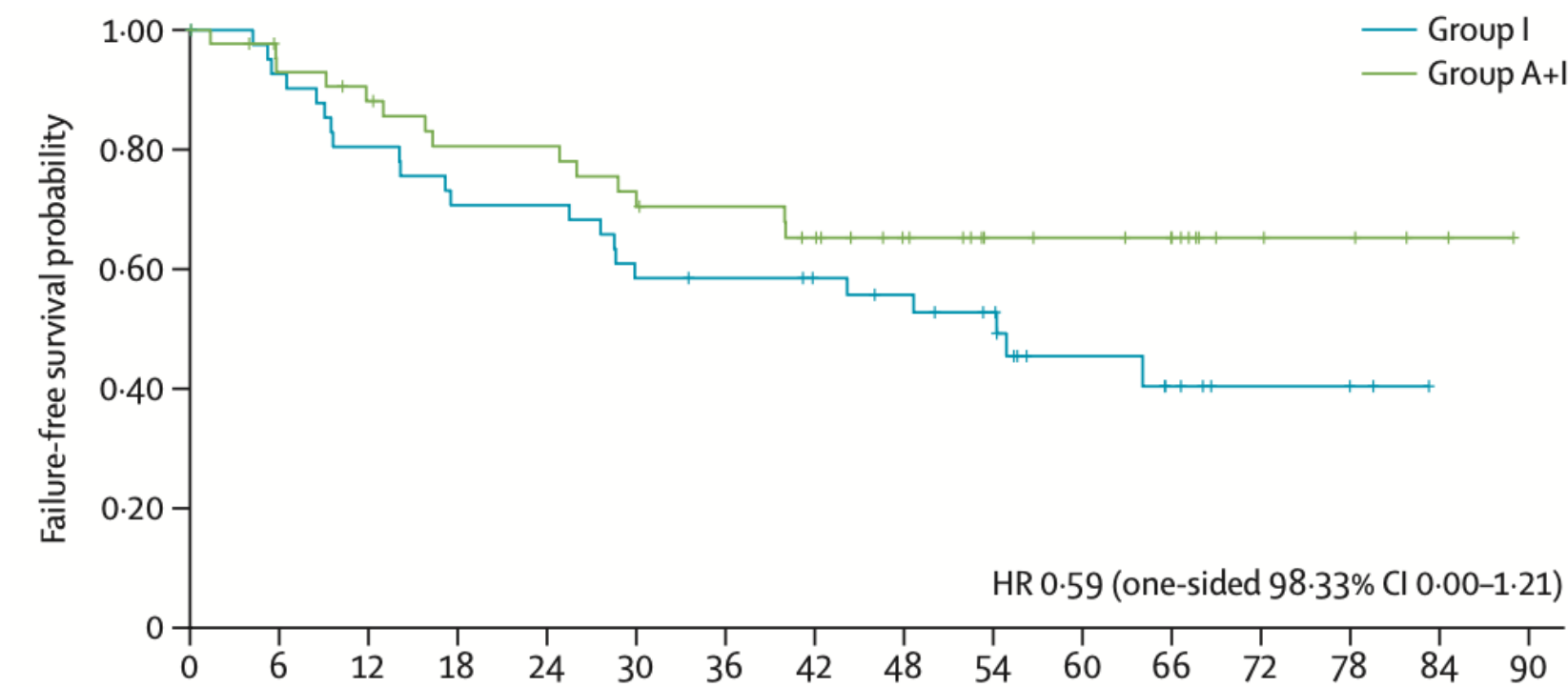
A+I vs I



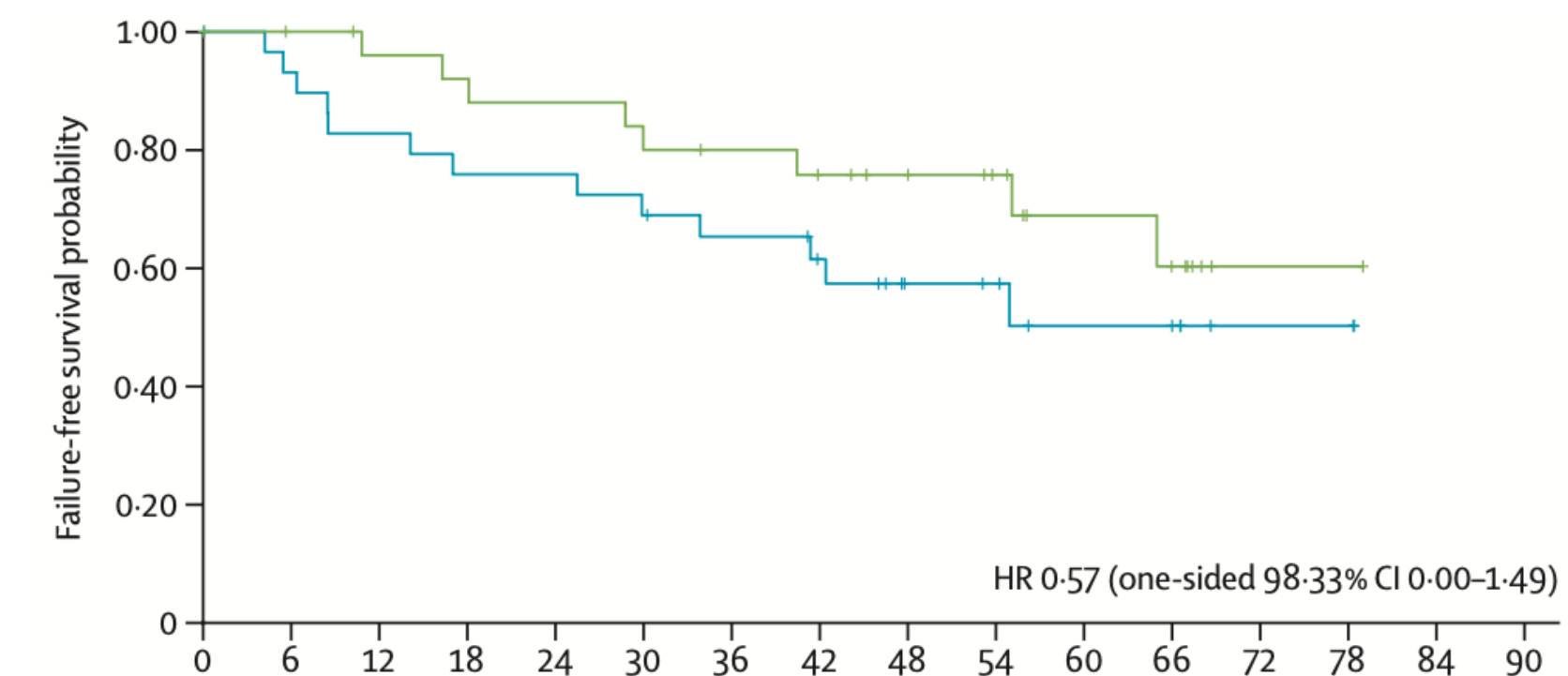
Blastoid (12%)



Ki67>50% (15%)



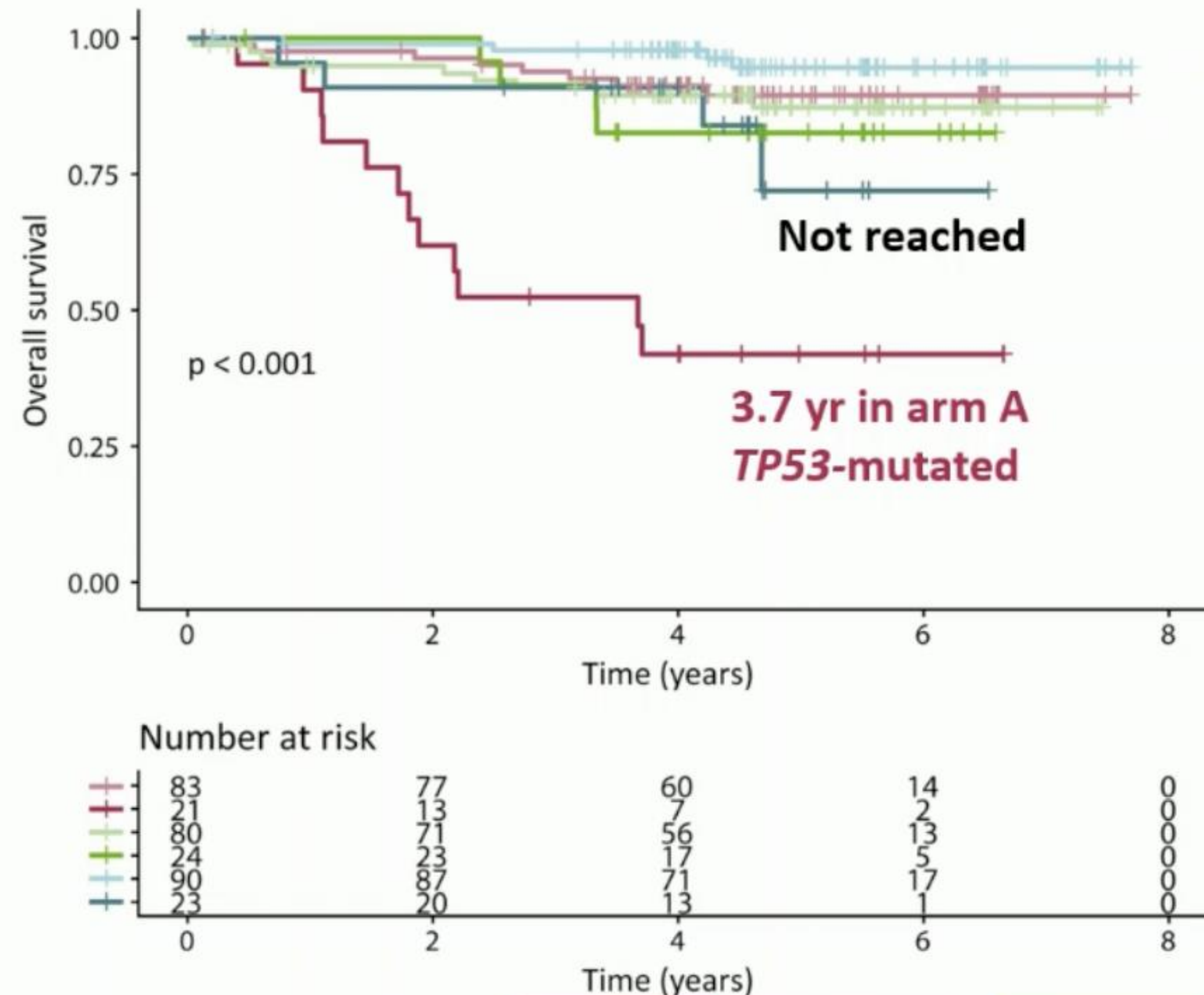
High P53 by IHC (15%)



Dreyling et al., Lancet 2026

Reggio Emilia, 2-3 ottobre 2026

Clinical impact of *TP53* mutation across treatment arms



A differential effect of *TP53*-mutations across treatment arms was observed (P for interaction = 0.048)

Ibrutinib appeared to partially abrogate the adverse prognostic impact of *TP53* mutations

No conclusions can be derived regarding which of the two experimental arms is superior in *TP53*-mutated cases

N = 321

Arm A
altered

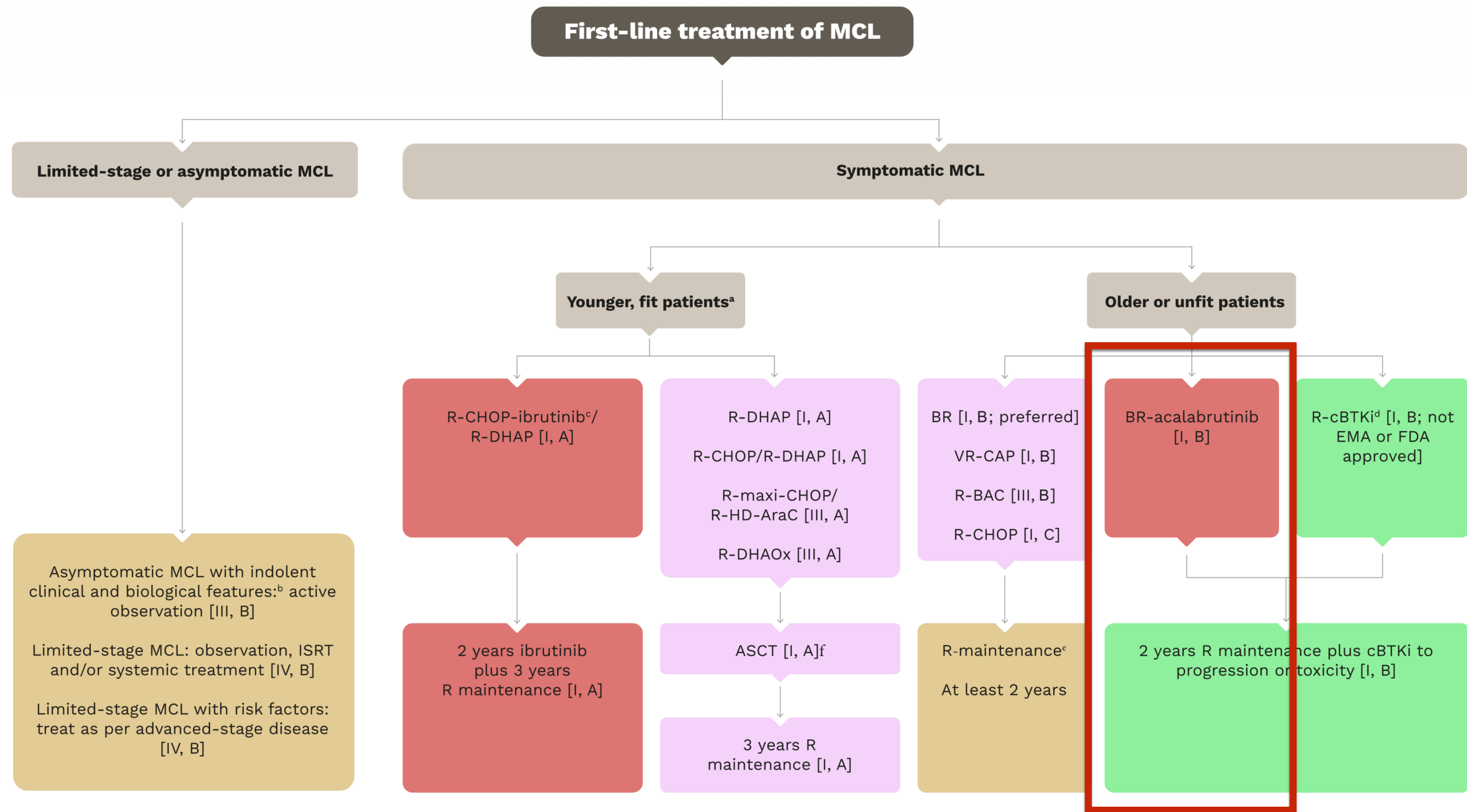
Arm A
wt

Arm A+I
altered

Arm A+I
wt

Arm I
altered

Arm I
wt

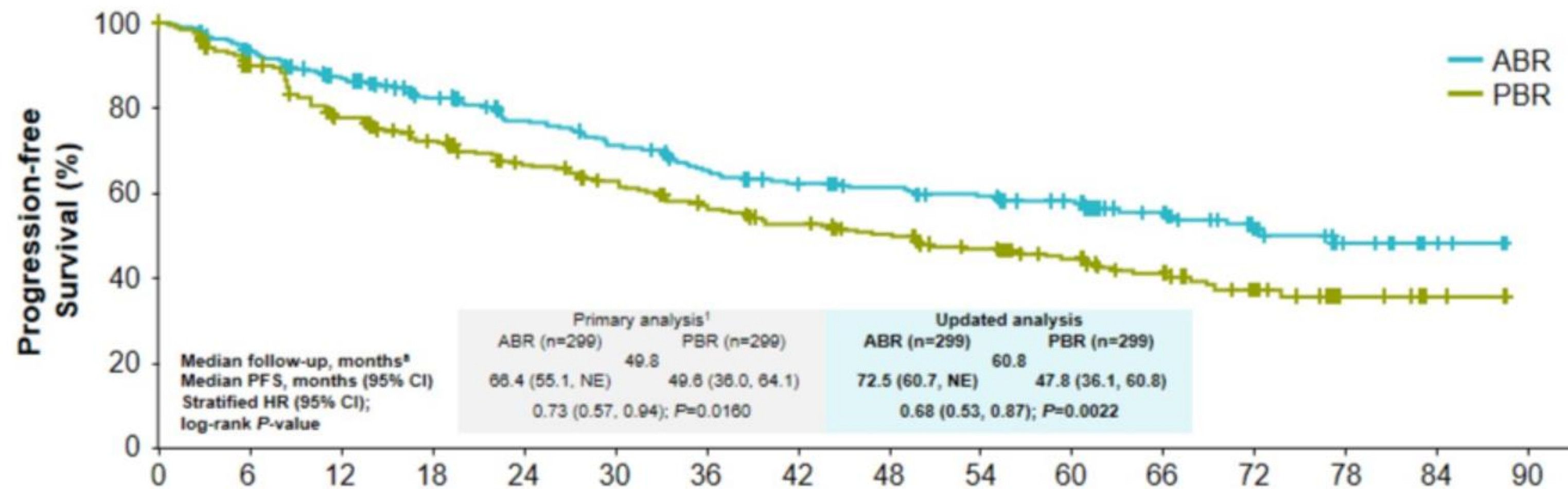


ECHO

Phase 3

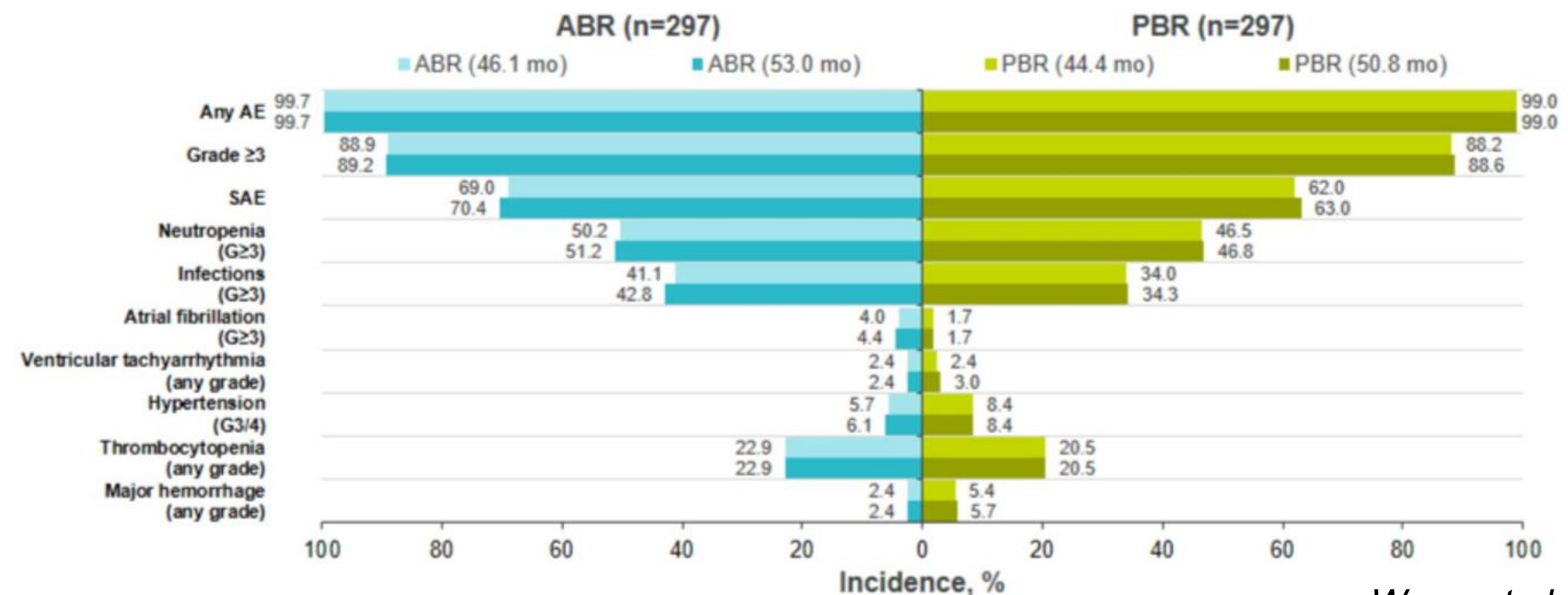
Randomized, placebo-controlled
65 years or older

598 patients



Median FU: 60,8 mo

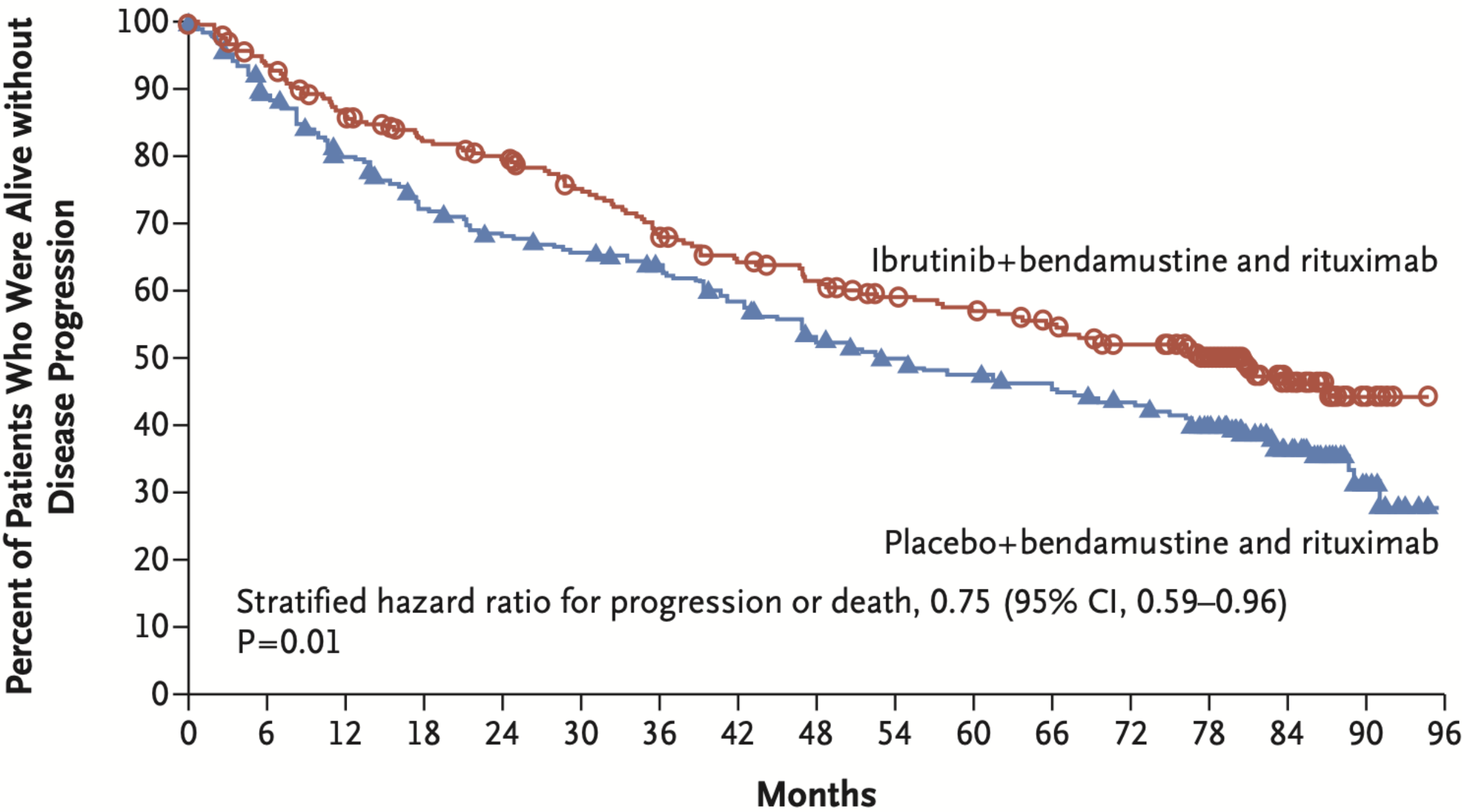
Median PFS: **72,5** vs **47,8** mo



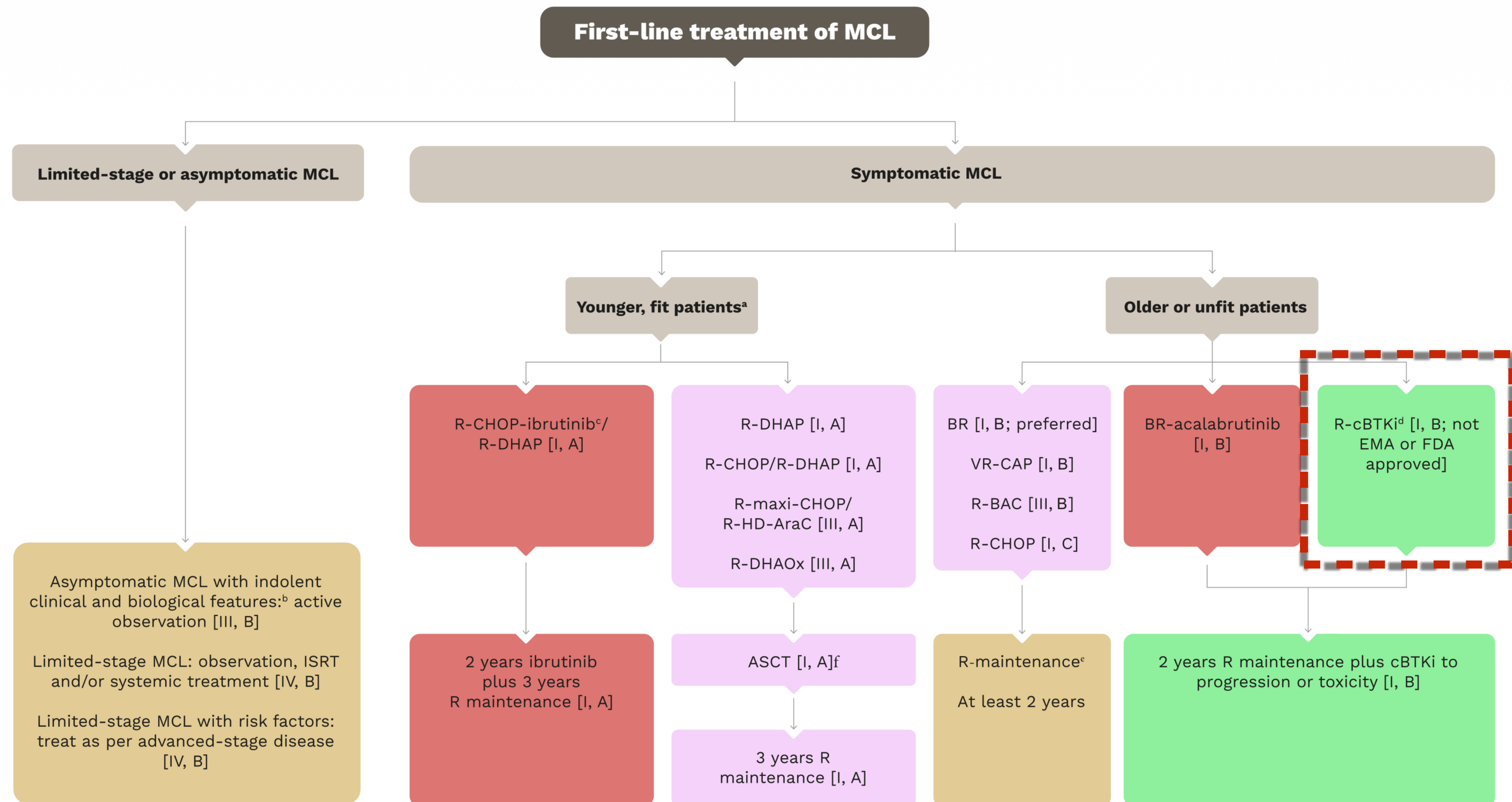
Wang et al., ASH 2025

SHINE

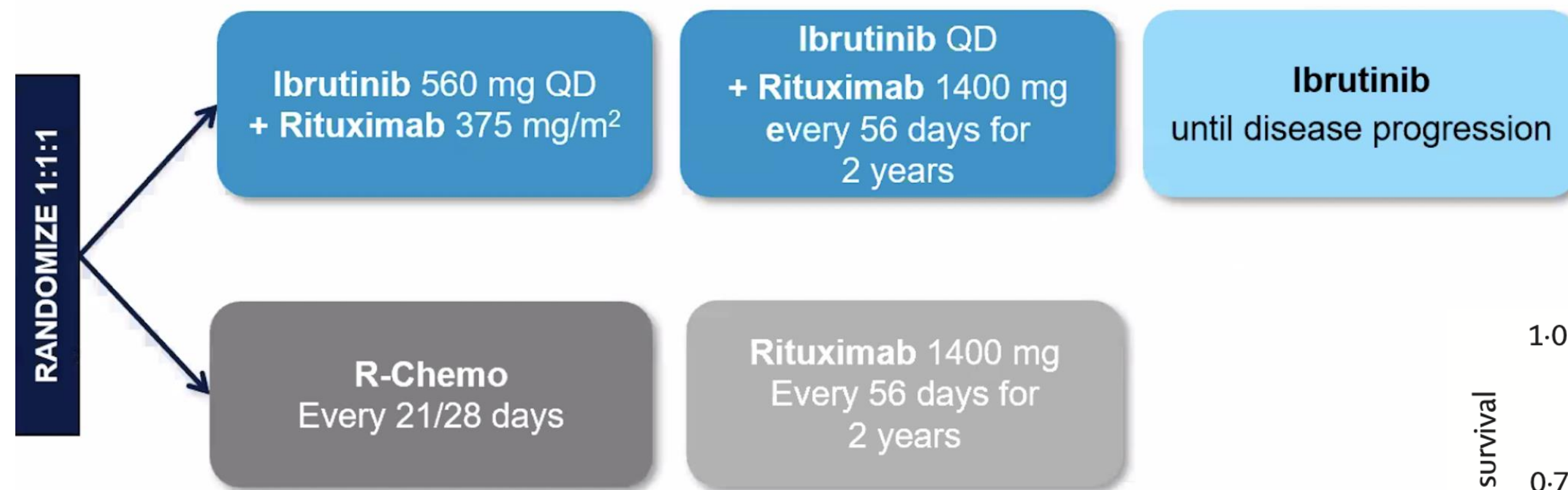
BR + Ibrutinib



System Organ Class and Preferred Term	Ibrutinib Group (N = 259)		Placebo Group (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Pneumonia	87 (33.6)	52 (20.1)	61 (23.5)	37 (14.2)
Neutropenia	133 (51.4)	122 (47.1)	136 (52.3)	125 (48.1)
Anemia	87 (33.6)	40 (15.4)	64 (24.6)	23 (8.8)
Thrombocytopenia	93 (35.9)	33 (12.7)	69 (26.5)	34 (13.1)
Cardiac disorder: atrial fibrillation	36 (13.9)	10 (3.9)	17 (6.5)	2 (0.8)

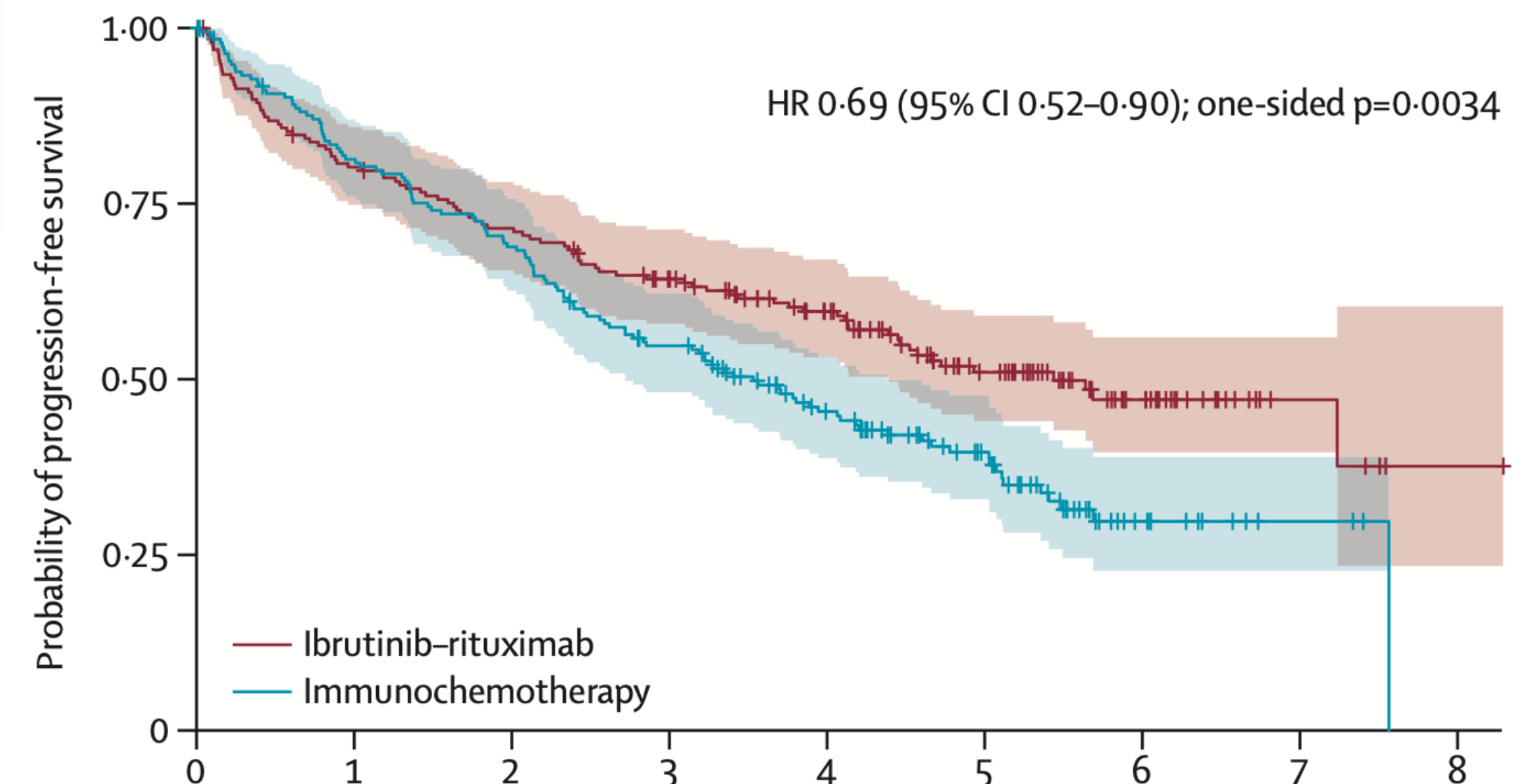


ENRICH R + Ibrutinib



Phase 2/3
60 years or older
397 patients

- PFS for R-Benda and R+I were comparable
- Worse outcome in the R-CHOP control group
- Blastoid disease had longer PFS with ChT
- *TP53* mutated had longer PFS with R+I



Lewis et al., Lancet 2025

ALTAMIRA **R + Acalabrutinib**

- Phase 2
- 81 patients, 60 years or older
- Not eligible for ASCT

Treatment schedule:

Acalabrutinib 100 mg BID + **Rituximab** 375 mg/mq q4w x 6, then q8w for a total of 3 yrs

Risk- and response-adapted treatment:

- High risk (*TP53* mutated or blastoid): treated until PD
- Low risk: discontinue Acalabrutinib when MRD negative (minimum treatment 1 yr)

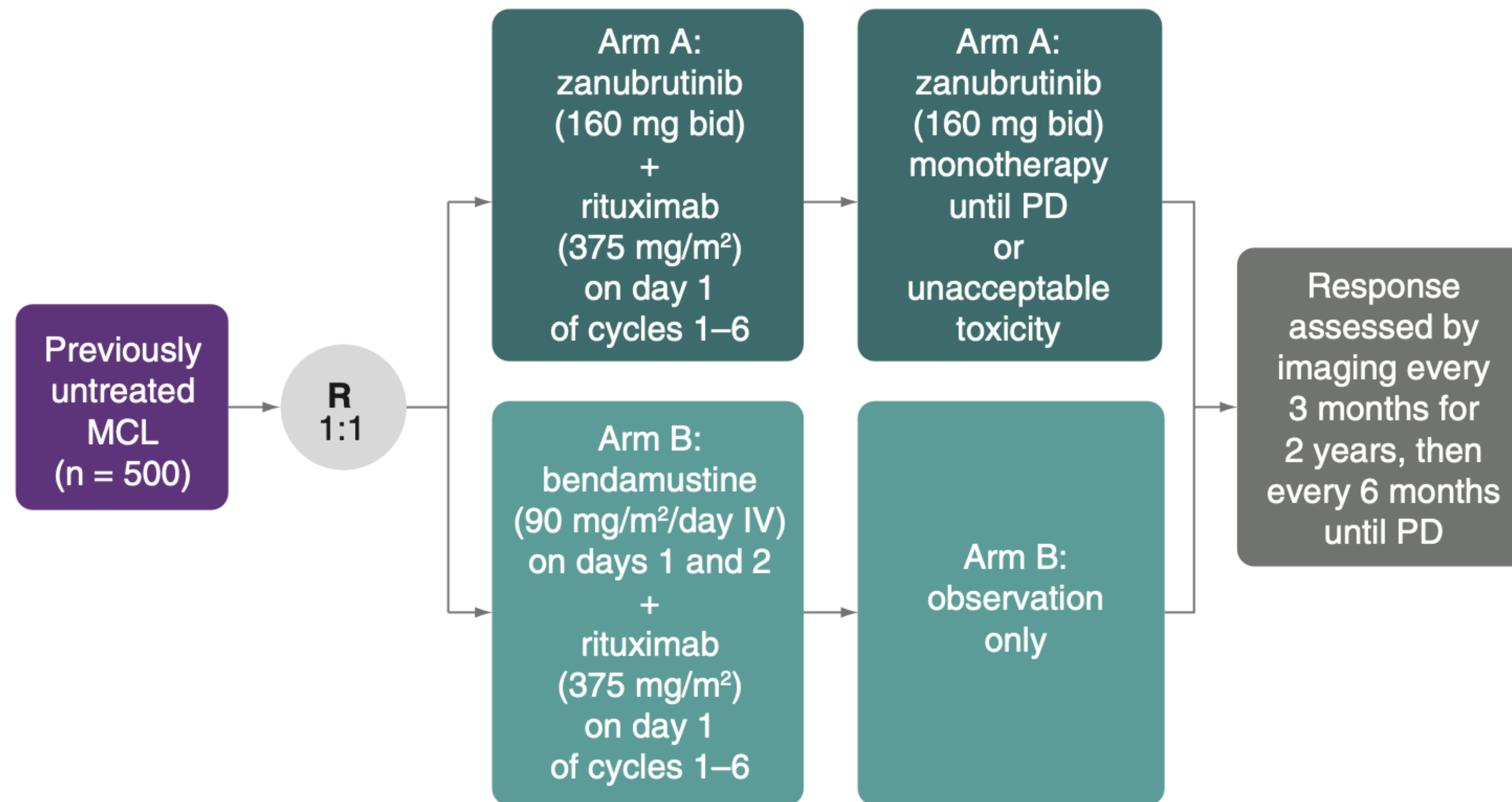
Median follow-up: 15,5 mo

- **1-yr PFS: 86,5%** (95% CI 78,8-94,8)
- **1-yr OS: 92,9%** (95% CI 87,1-99,2)

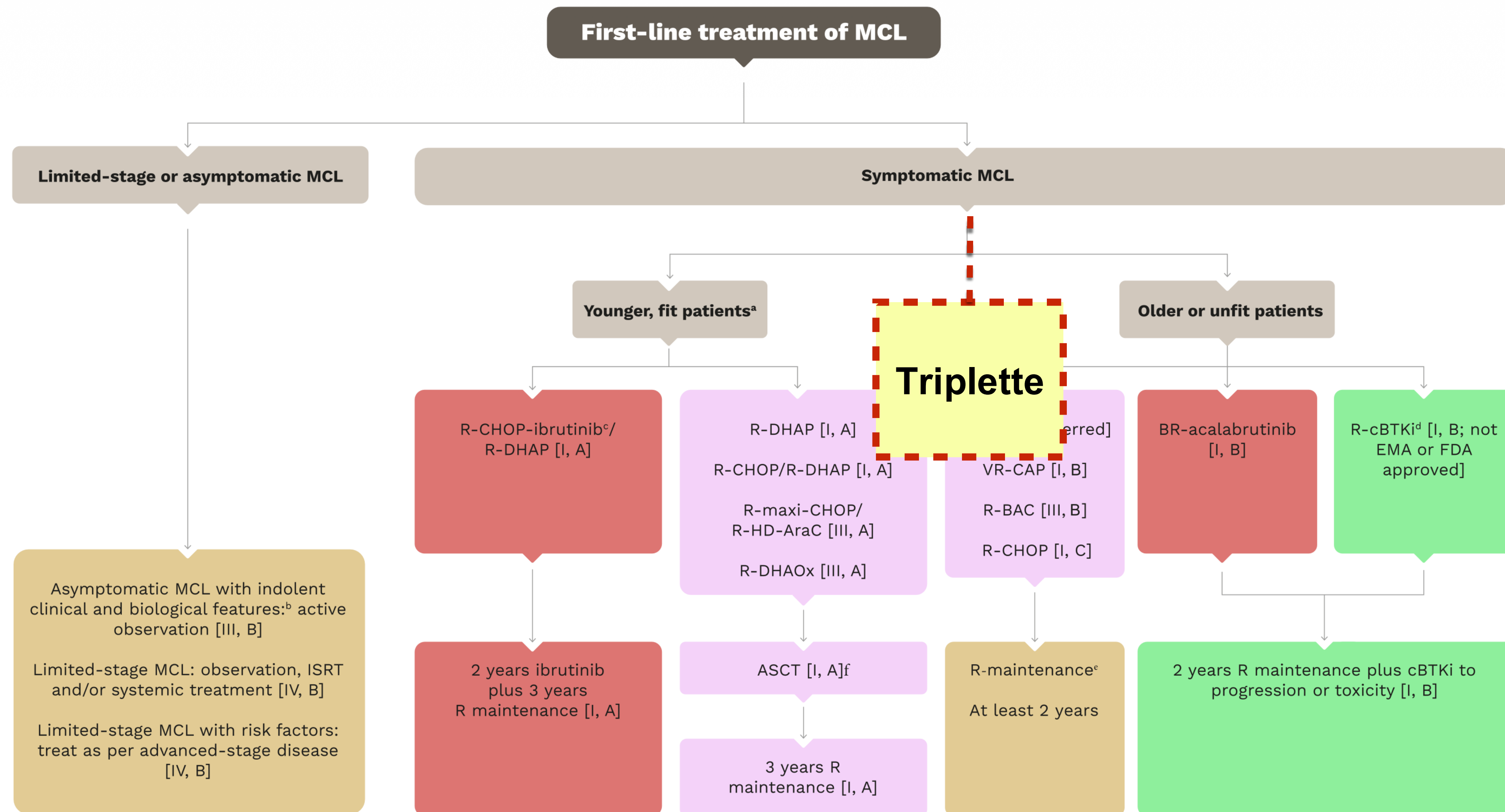
Grade 3-4 AE: neutropenia (11 pts), infection (10), CV toxicity (7)

Jerkeman et al., ASH 2024

MANGROVE R + Zanubrutinib

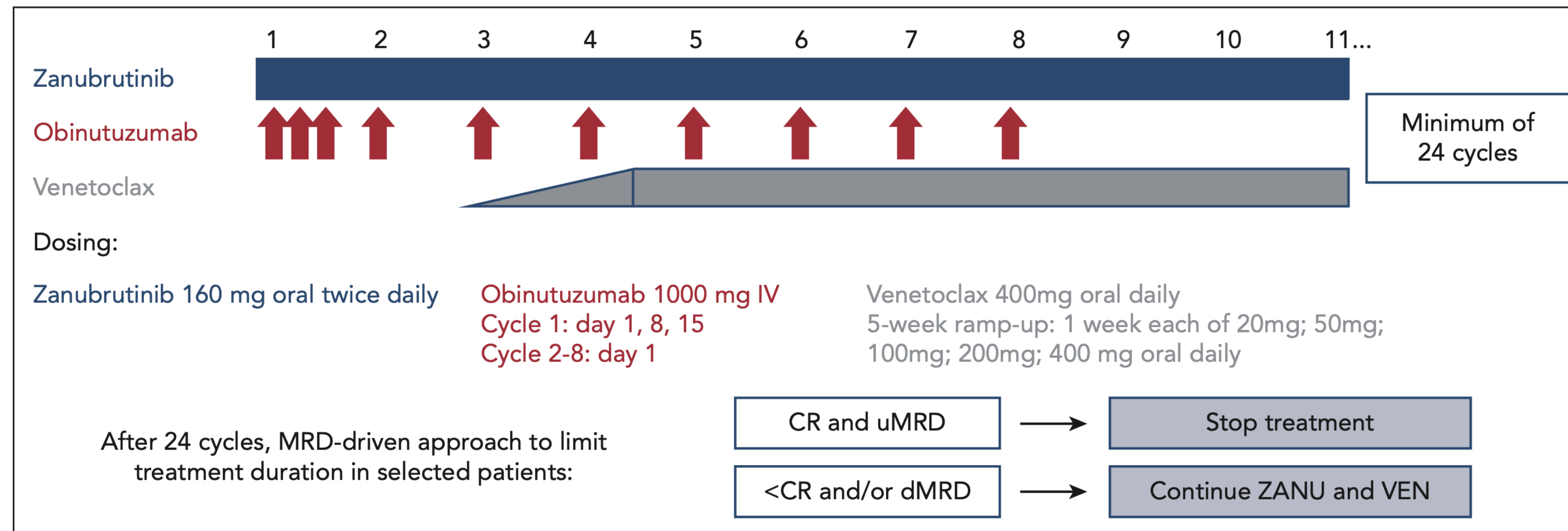


Phase 3
>70y or >65y with comorbidities



BOVen

Zanubrutinib + Obinutuzumab + Venetoclax



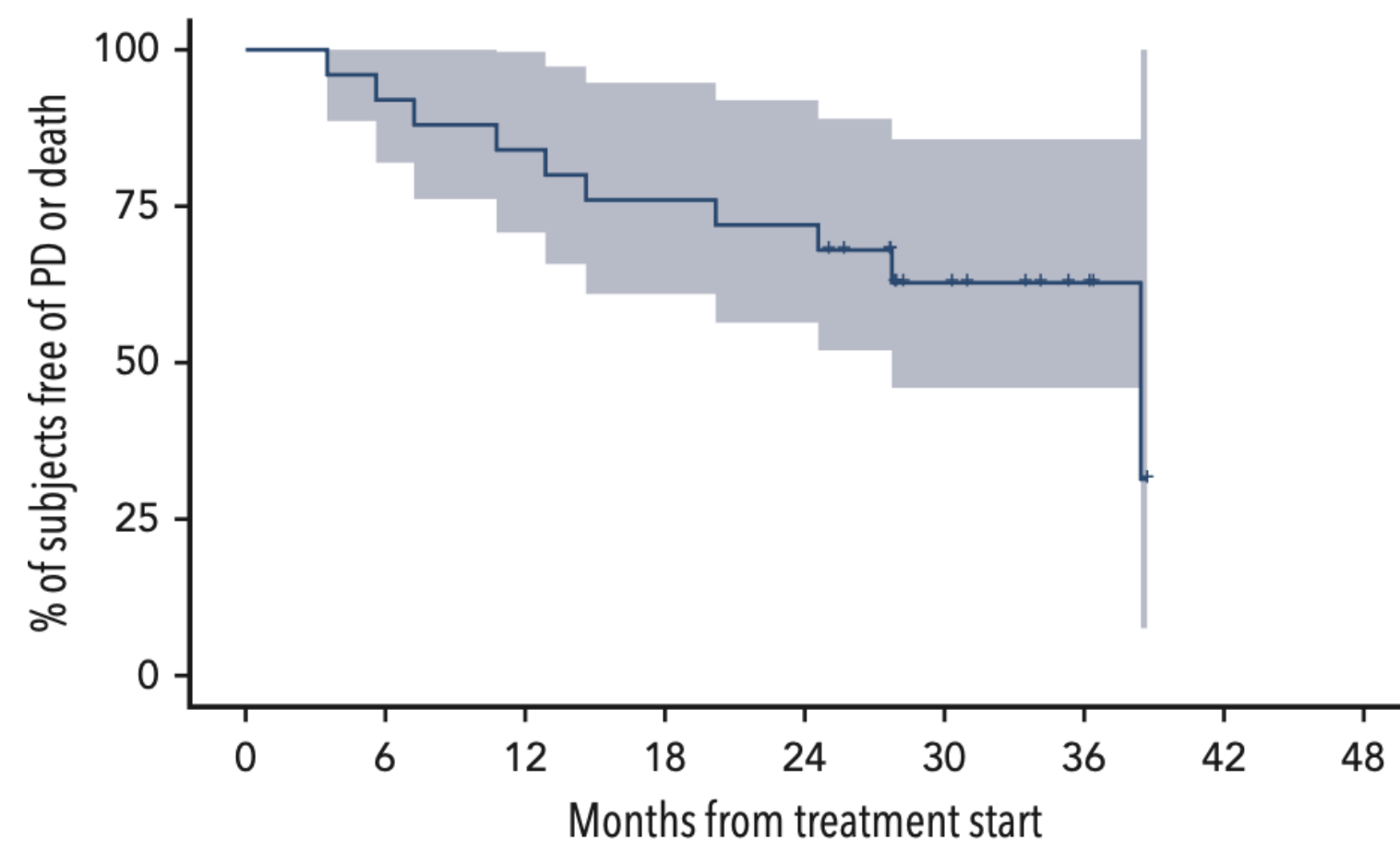
- 50 pts
- Median age 72y
- 70% MIPI high
- 28% *TP53* mutated
- Median FU 25 mo

ORR 98%, CR 94%
 2y-PFS: **86%** (95% CI 77,97)
 2y-OS: **92%** (95% CI 84,100)

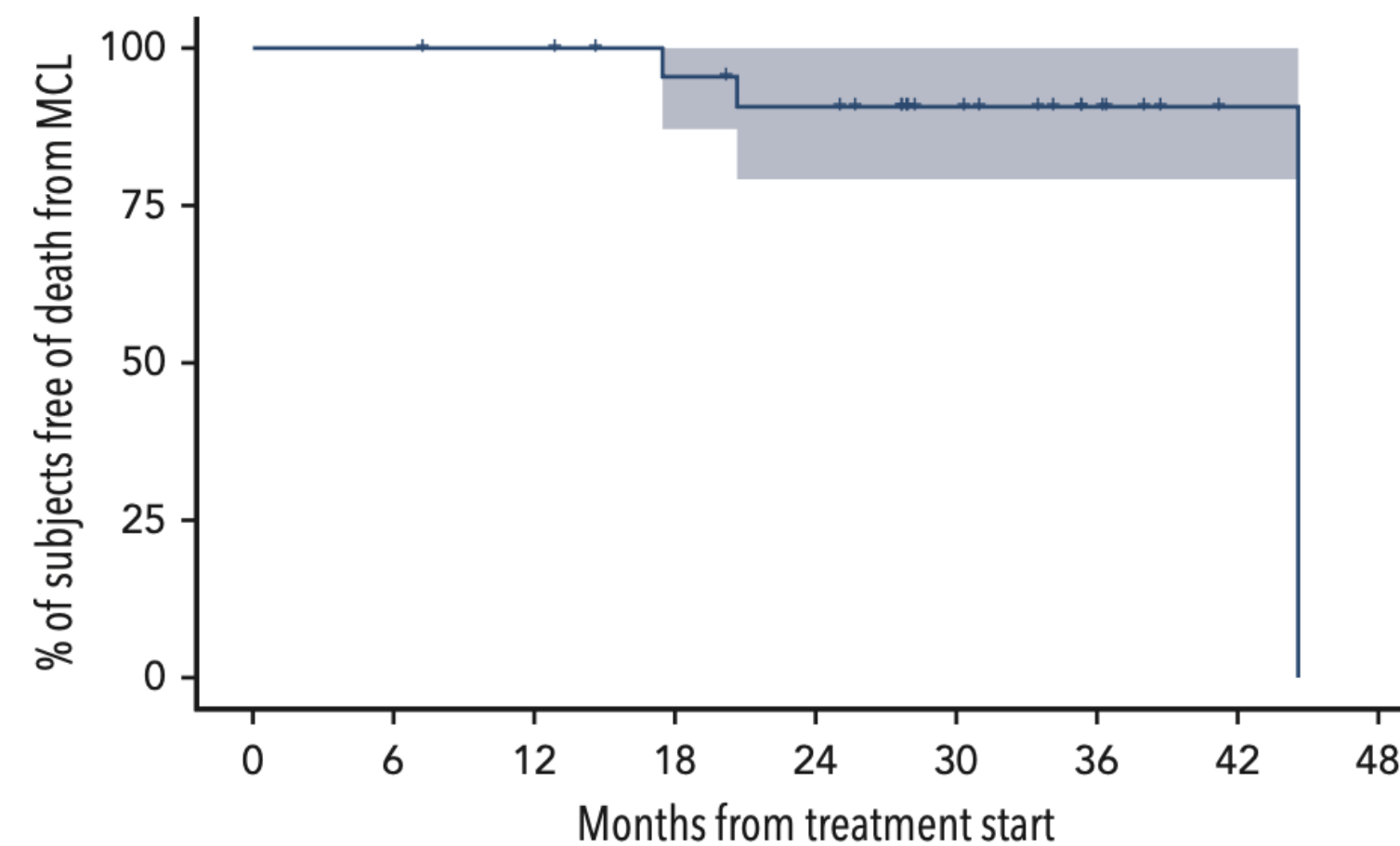
MRD negativity: 28% at C3, 87% at C13, 93% at EOT

Grade 3-4 AE: neutropenia (20%), thrombocytopenia (8%), infections (22%)

BOVen Zanubrutinib + Obinutuzumab + Venetoclax TP53 mutated



PFS



DFS

- 25 pts
- Median age 68y
- VAF 4,9 - 96,2%
- Median FU 28,2 mo

ORR **96%**, CR **88%**
2y-PFS: **72%** (95% CI 56,92)
2y-DFS: **91%** (95% CI 79,100)

OASIS II

Ibrutinib + Obinutuzumab + Venetoclax

18 years or older

Phase 2, randomized

Fixed duration: 2y

- Arm A: Ibrutinib + anti-CD20mAb
- Arm B: Ibrutinib + anti-CD20mAb + **Venetoclax**

102 patients, 51 in each arm

	ARM A	ARM B
MRD-neg	53,8%	81,2%
CR (C6)	54%	69%

TrAVeRse **Acalabrutinib + Rituximab + Venetoclax**

18 years or older

AVR induction: A (C1–C13), V (C2–C13), and R (375 mg/m² on D1 of C1–12).

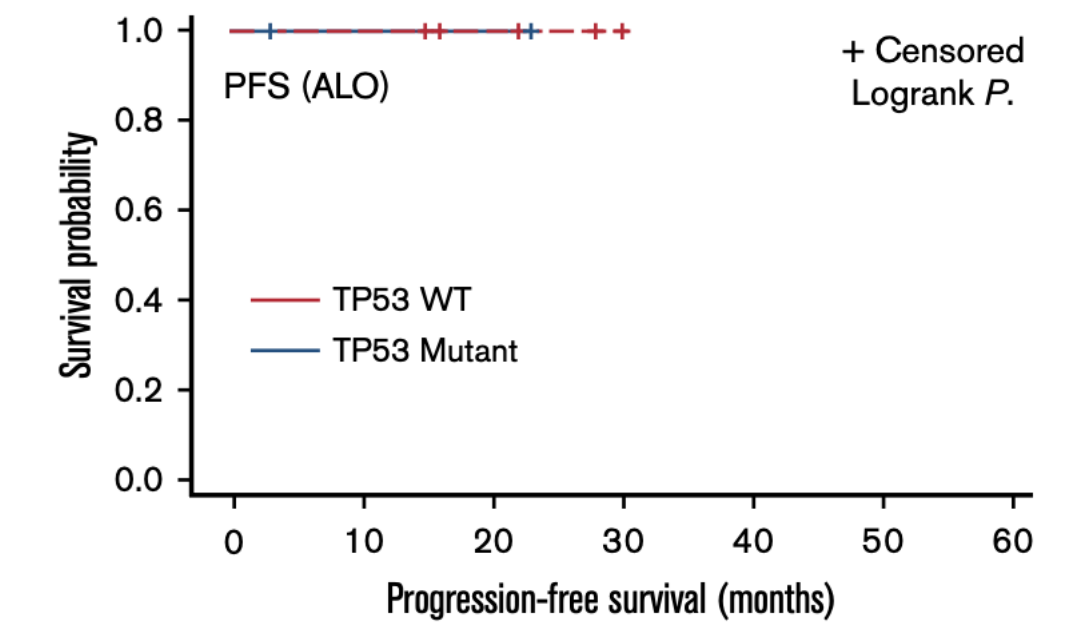
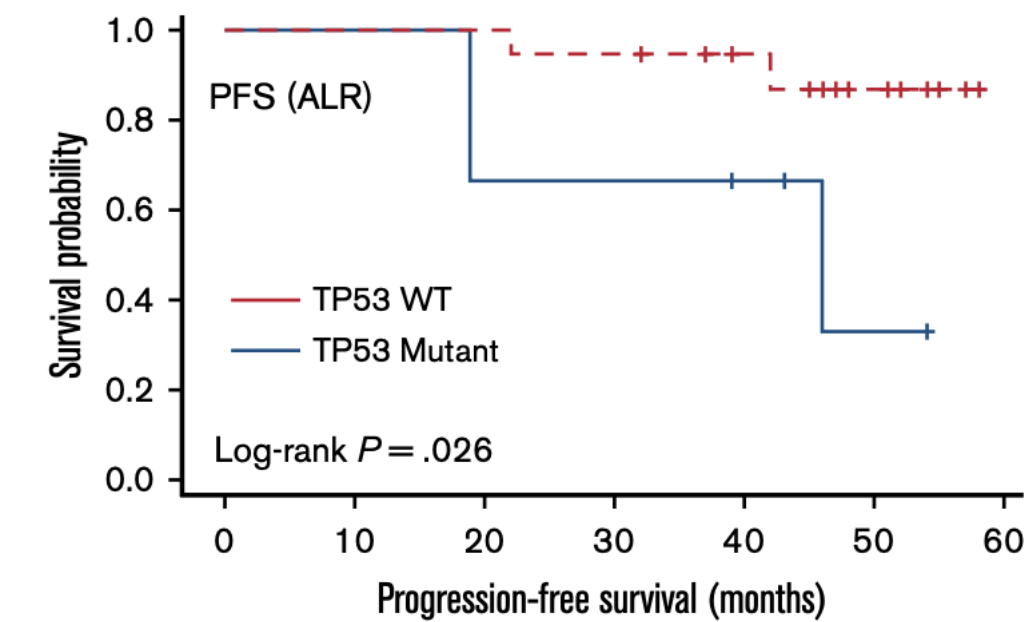
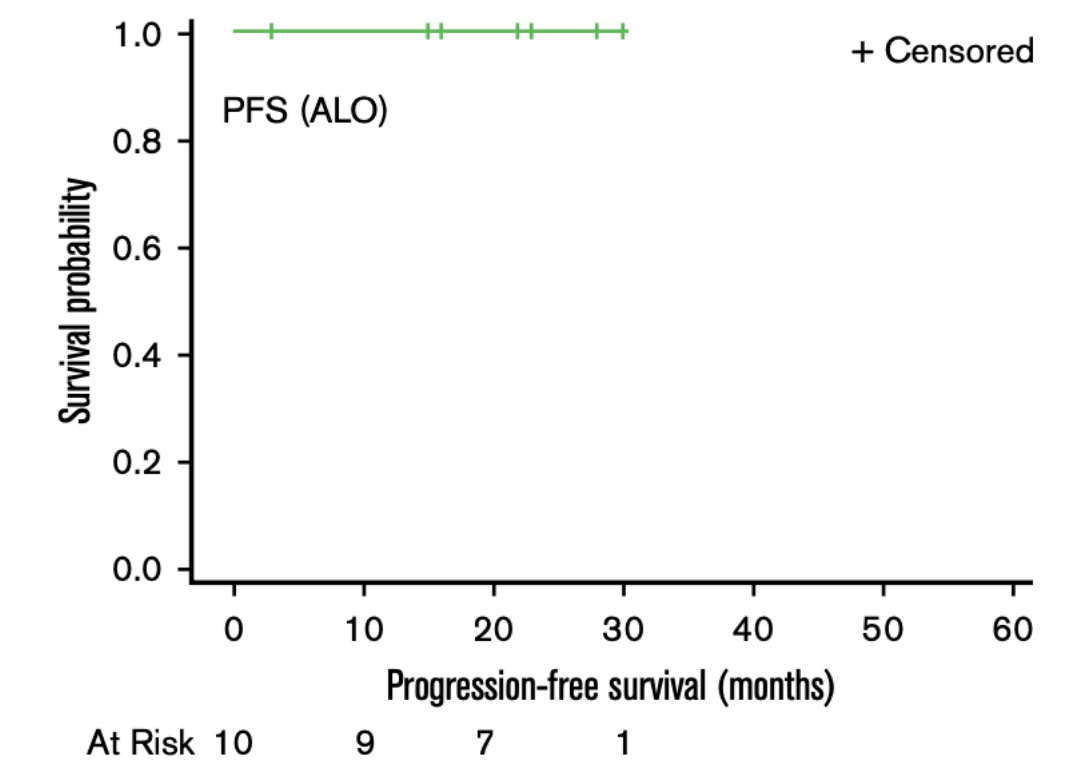
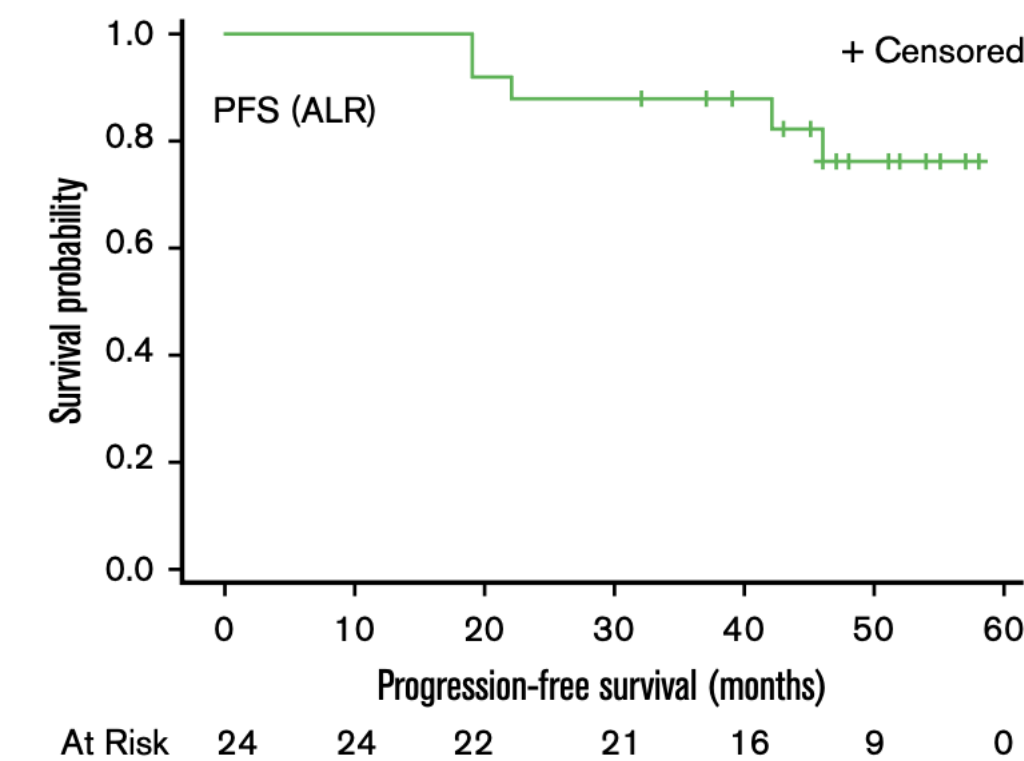
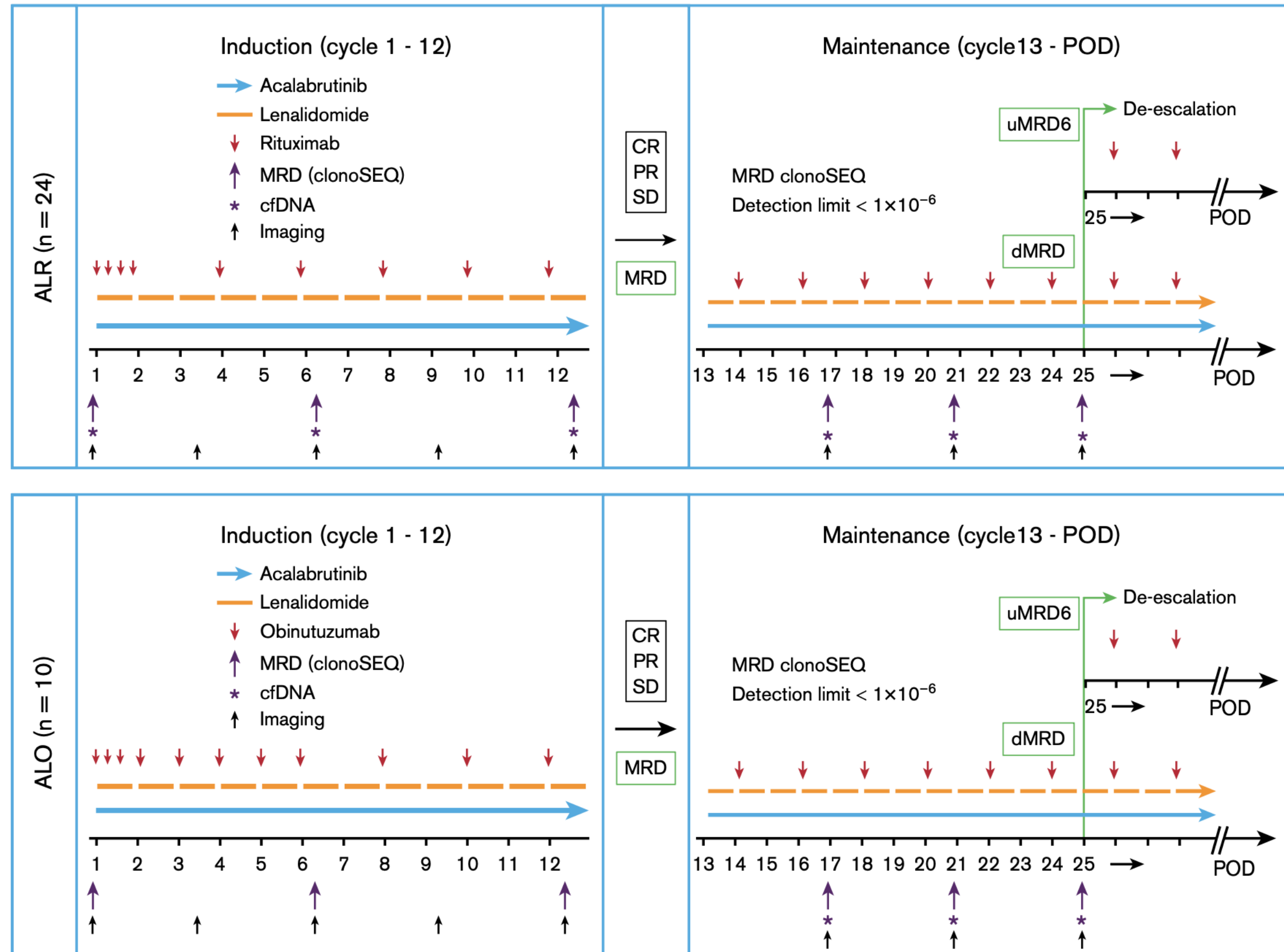
- MRD-pos CR, PR, SD: continued A until PD
- MRD-neg CR: randomized 1:1 —> continued A until PD
—> observation until PD with the option to restart A at relapse

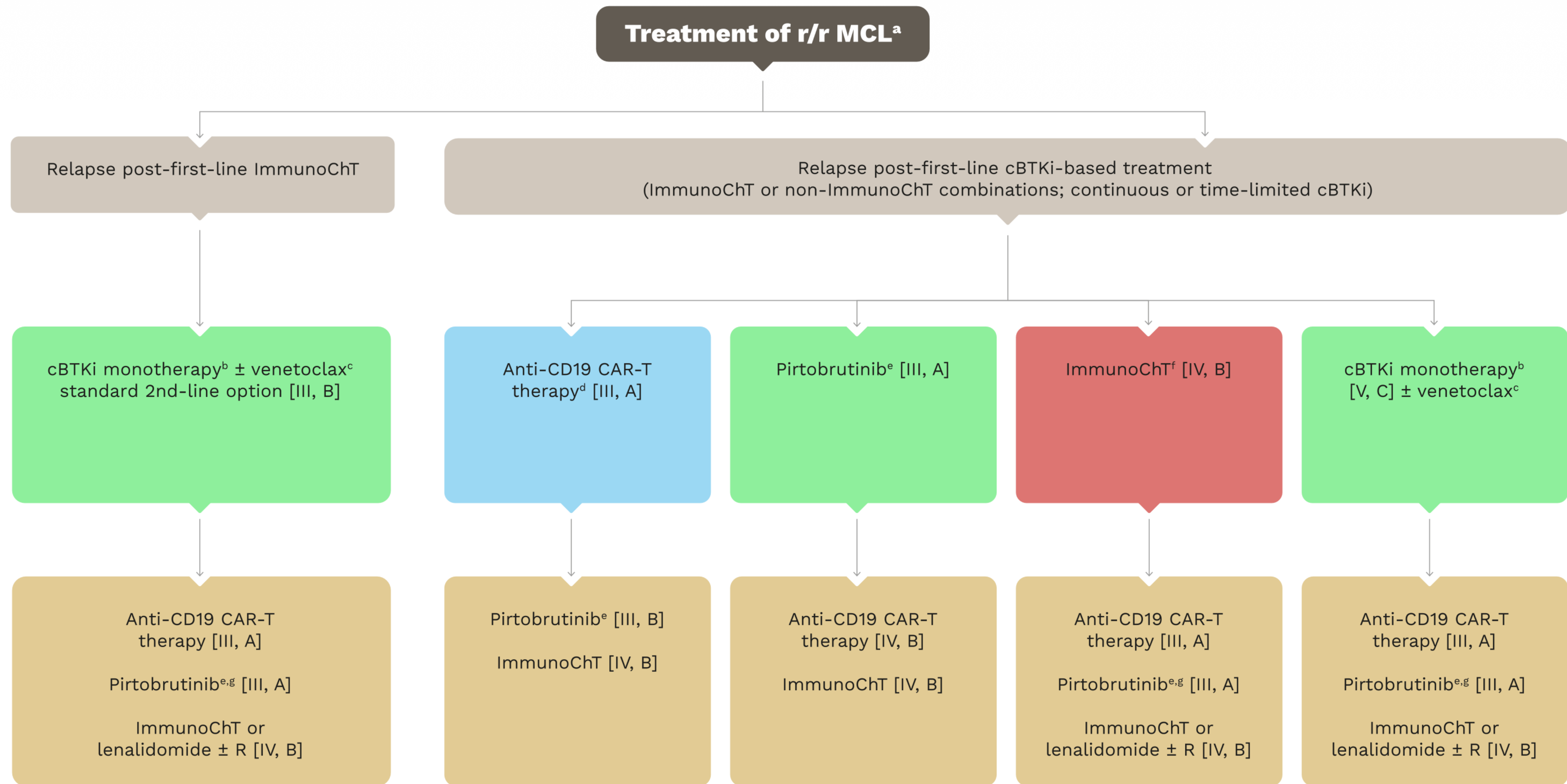
- 108 pts
- Median age 69y
- **TP53** mut 19,1%
- Median FU 10,5 mo

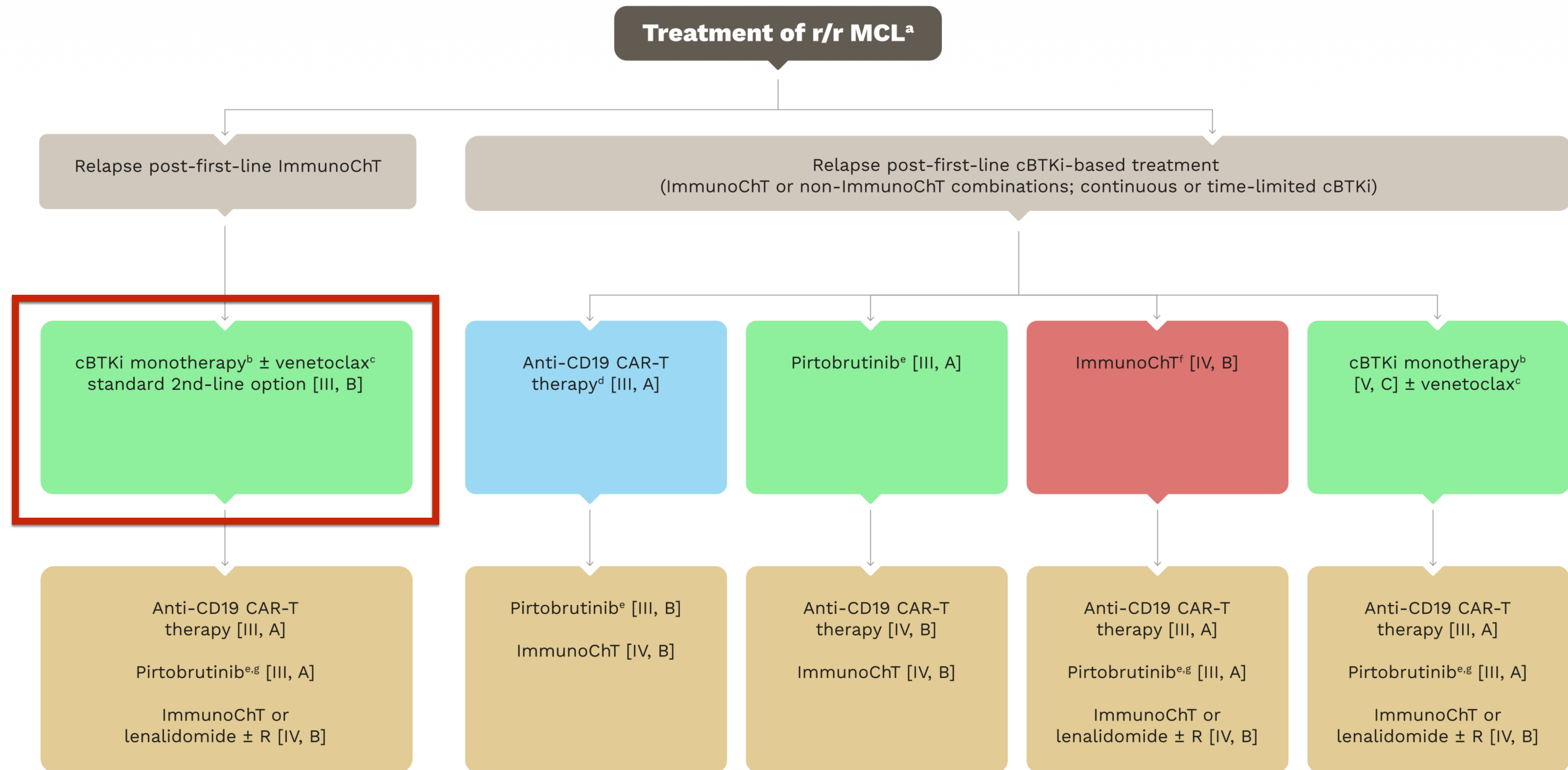
- **ORR 95,4%, CR 63%**
- Overall, **95,4% of pts achieved MRD-neg**
- Among the 17 pts with **TP53m**, 15 (88.2%) achieved objective response, 11 (64.7%) achieved CR, and 16 (94.1%) achieved MRD-neg

ALR/ALO

Acalabrutinib + Lenalidomide + Rituximab/Obinutuzumab

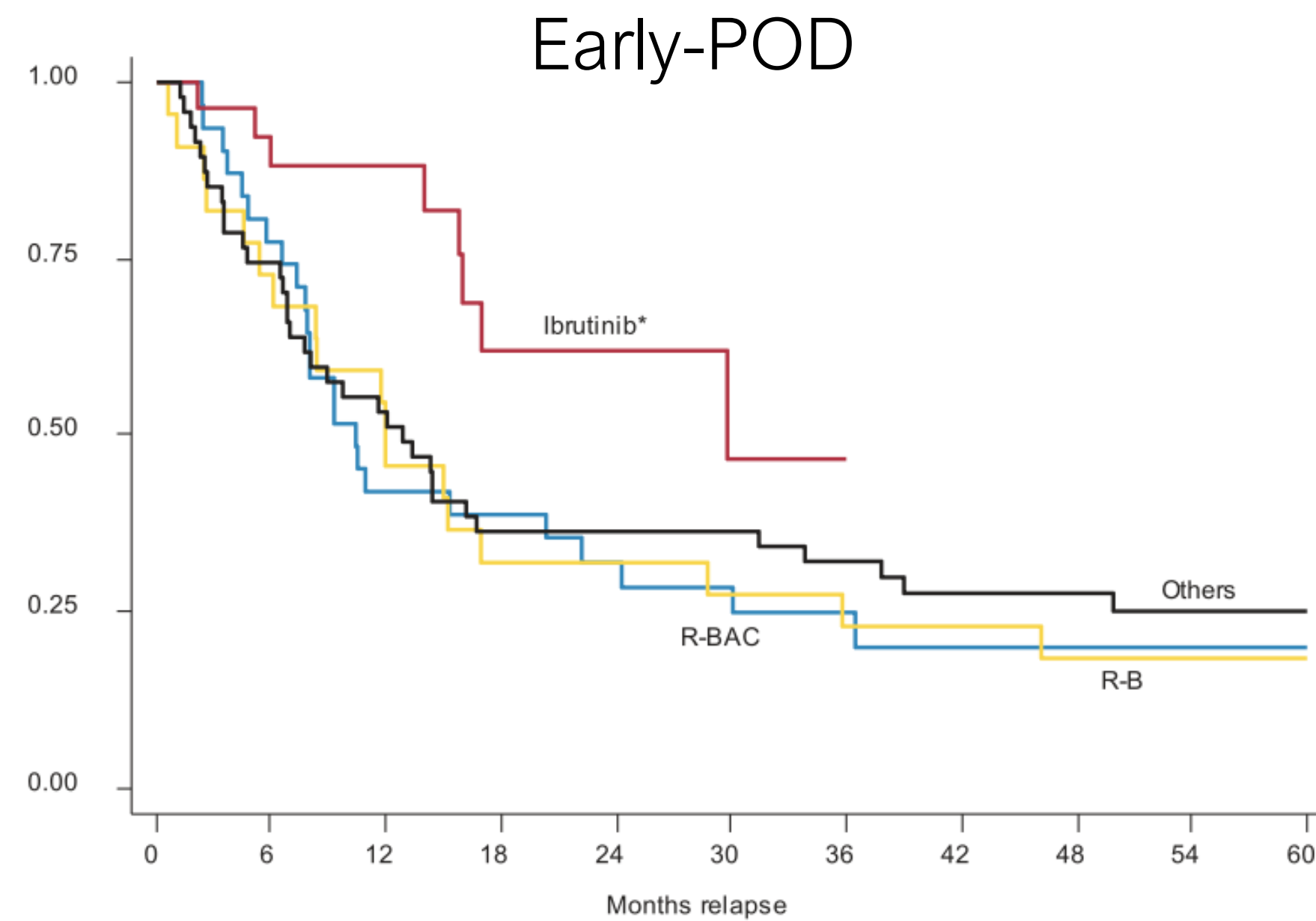




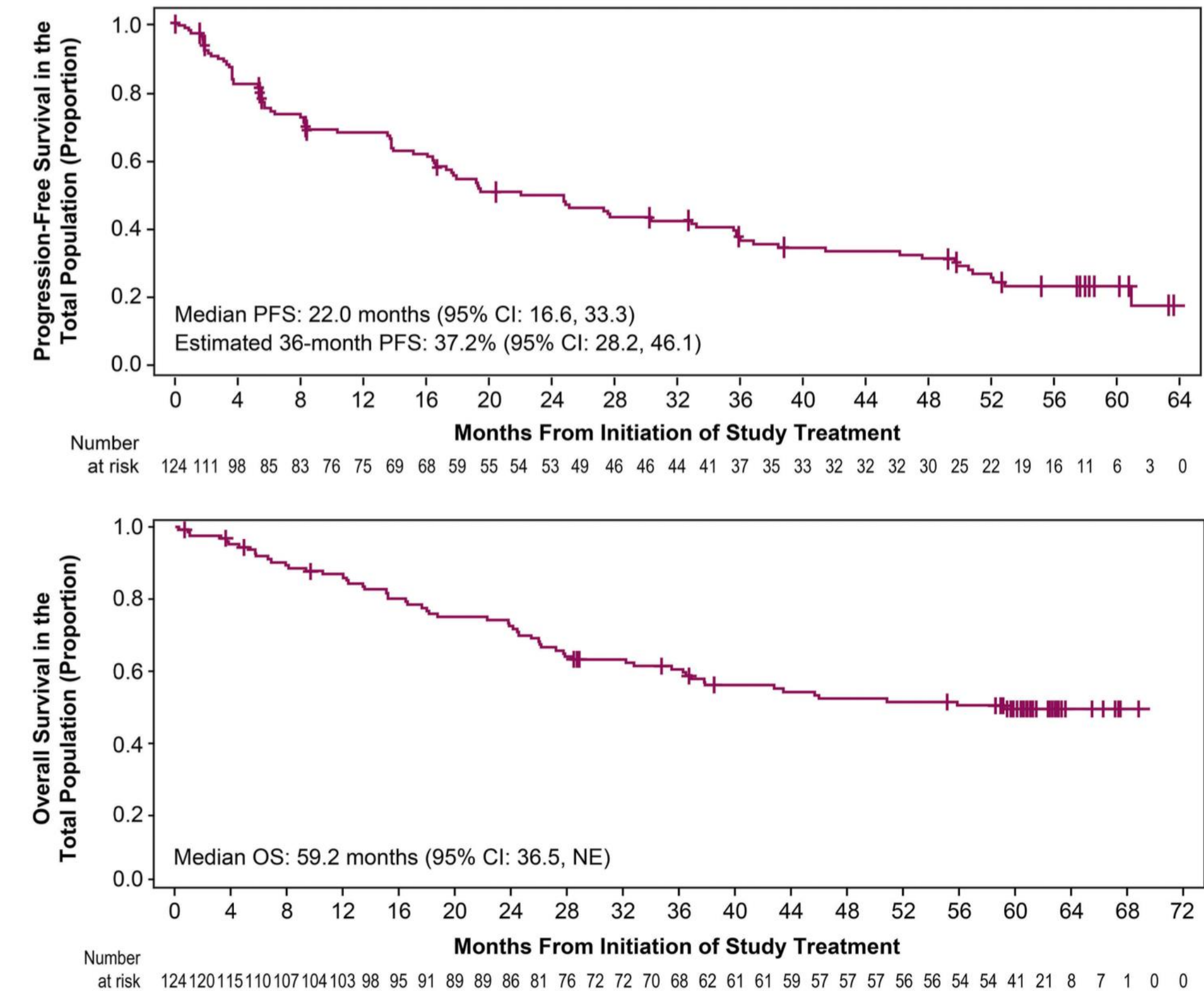


IBRUTINIB

ACALABRUTINIB



Visco et al., Leukemia 2021



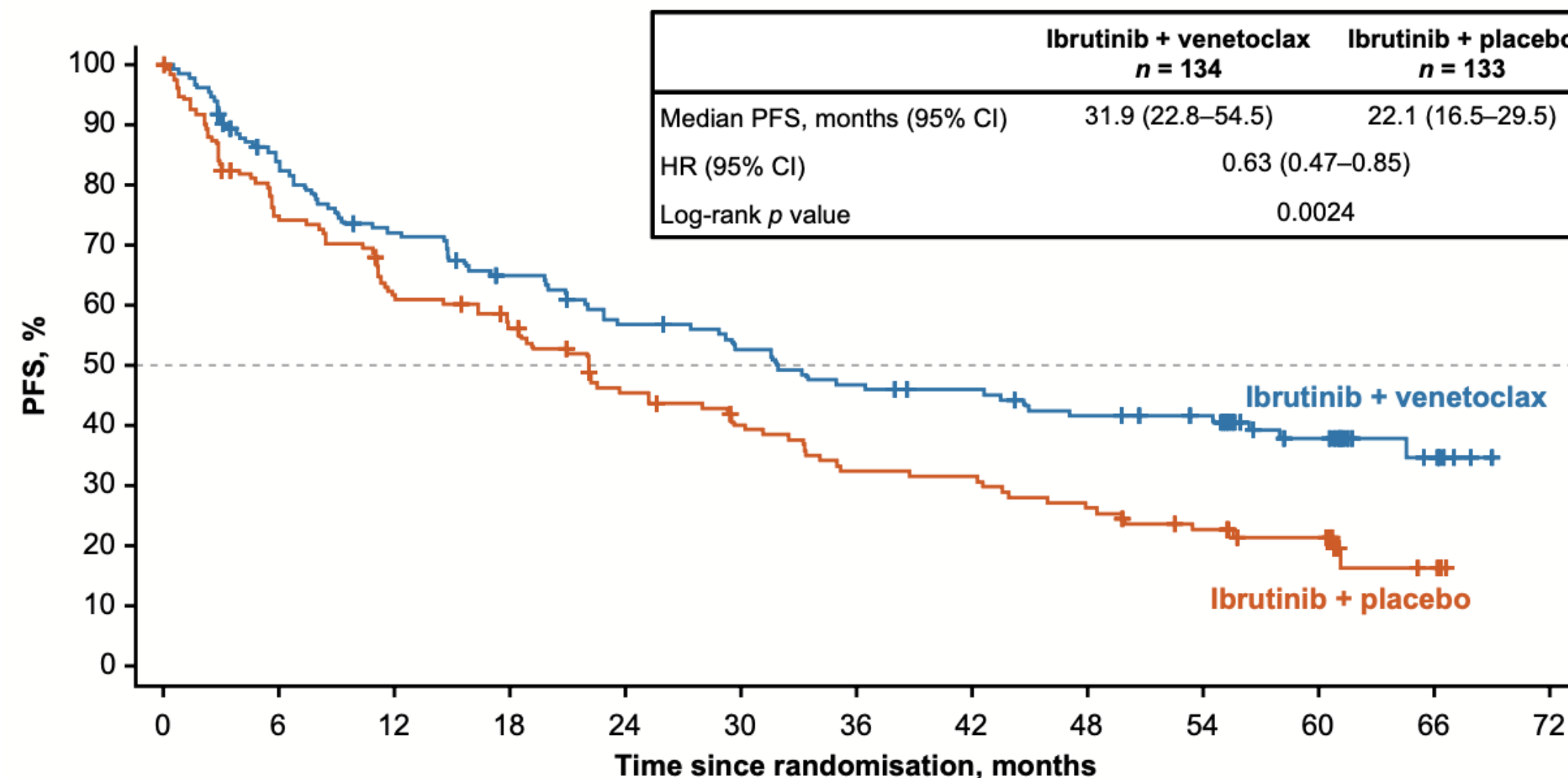
Le Gouill et al., Haematologica 2024

SYMPATICO

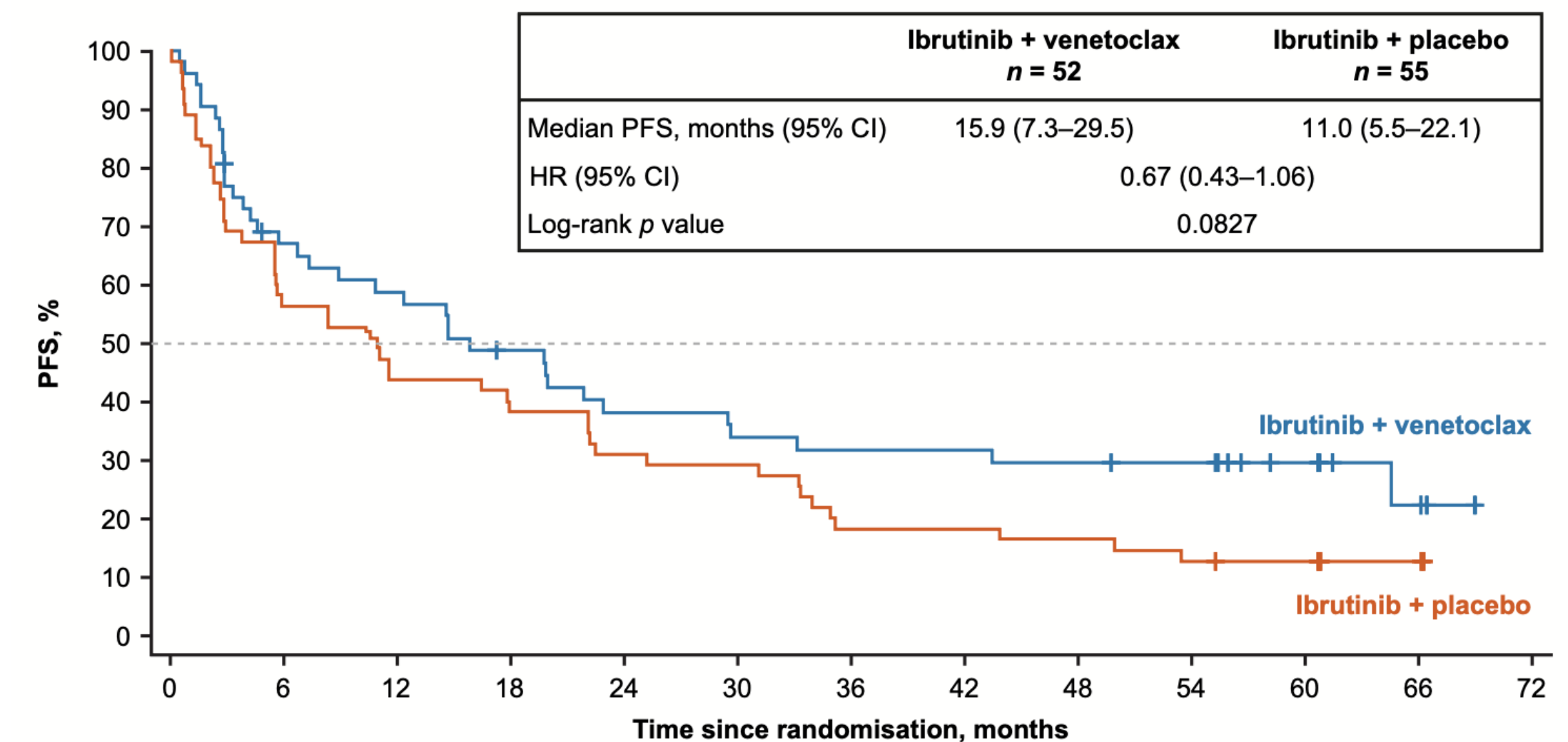
Ibrutinib + Venetoclax

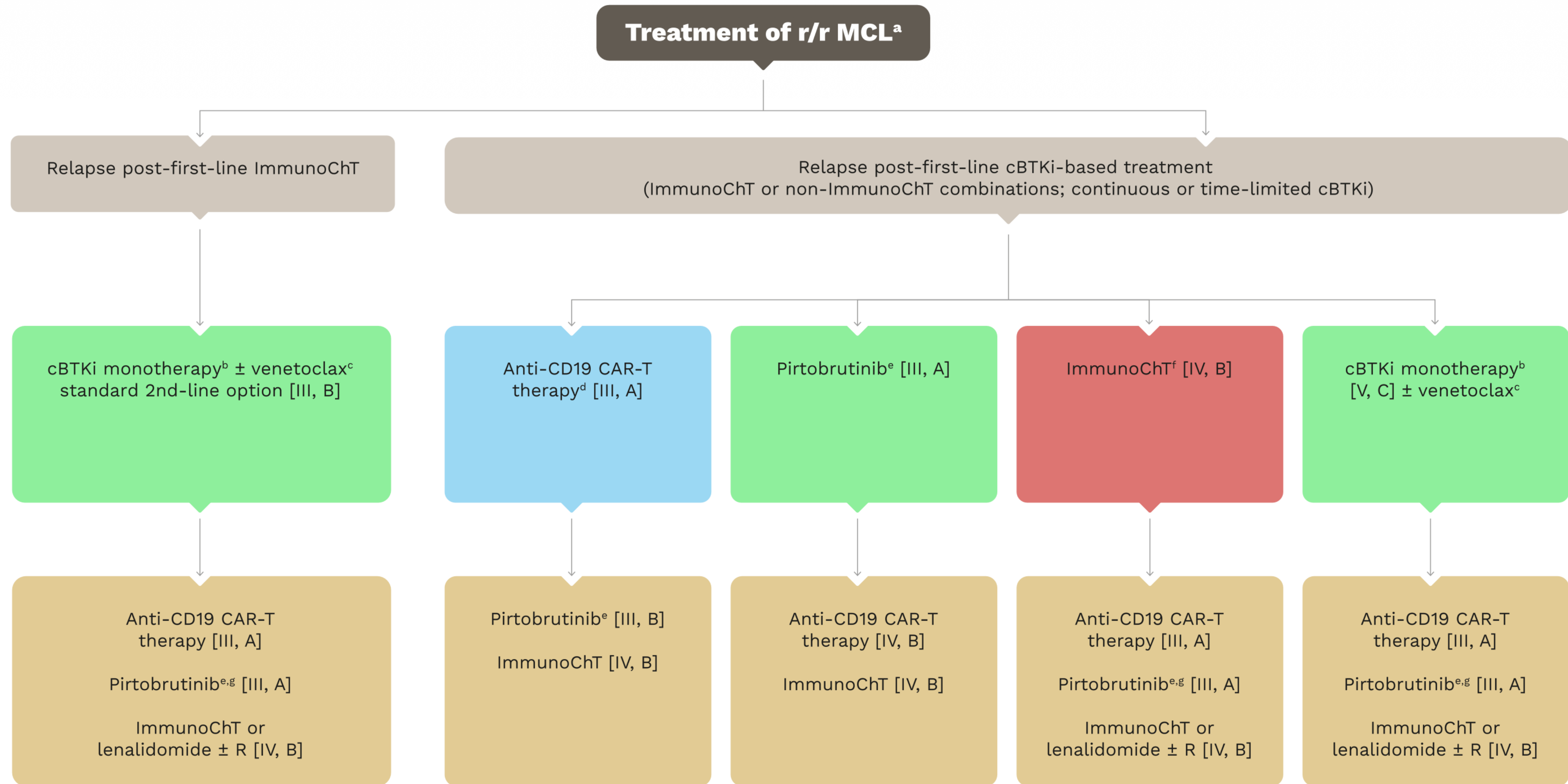
- Randomized, double-blind, placebo-controlled, phase 3 study
- Ibrutinib + venetoclax vs Ibrutinib + placebo for 24 months
- then continuous single agent ibrutinib until progression

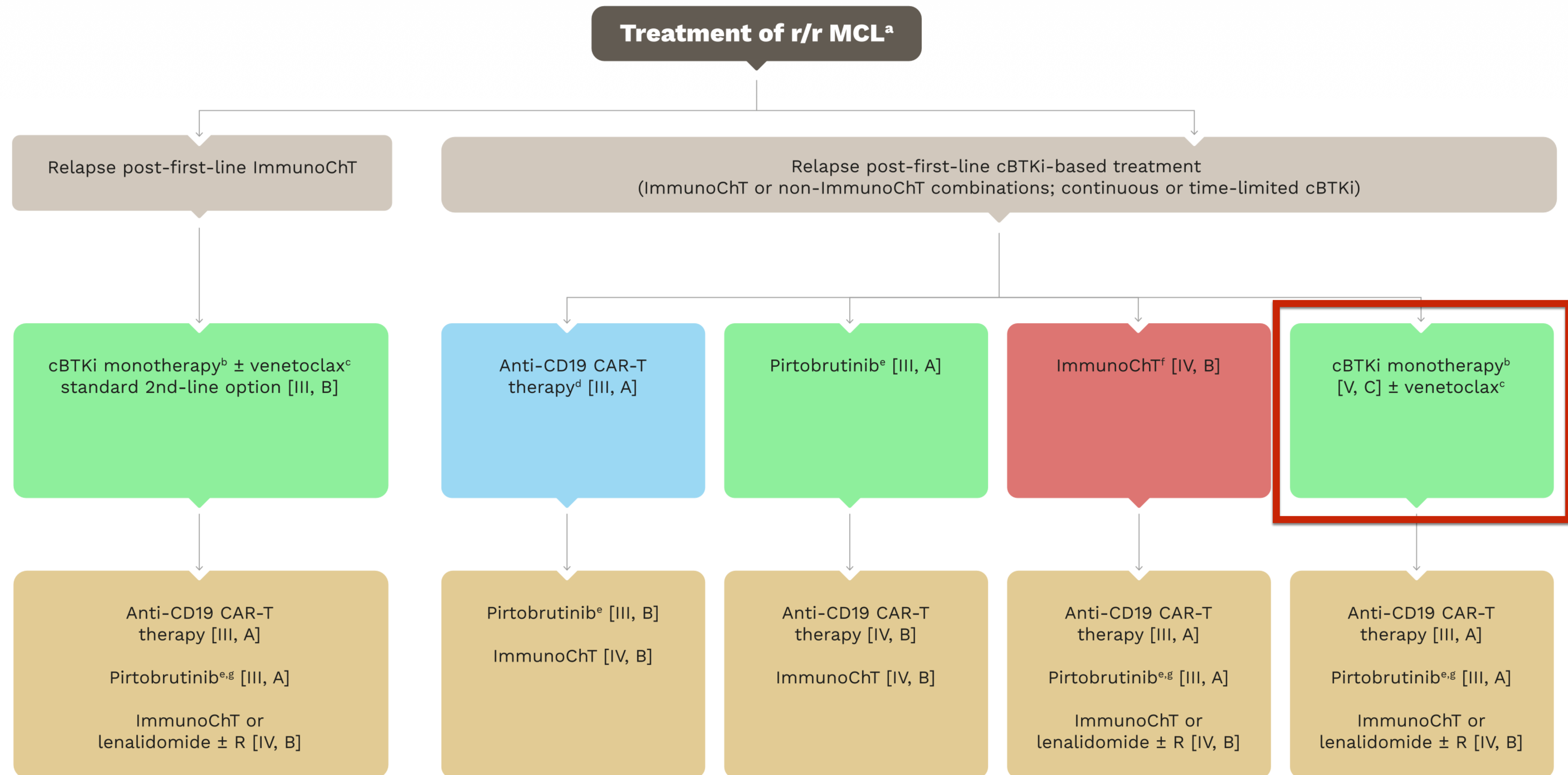
PFS - all

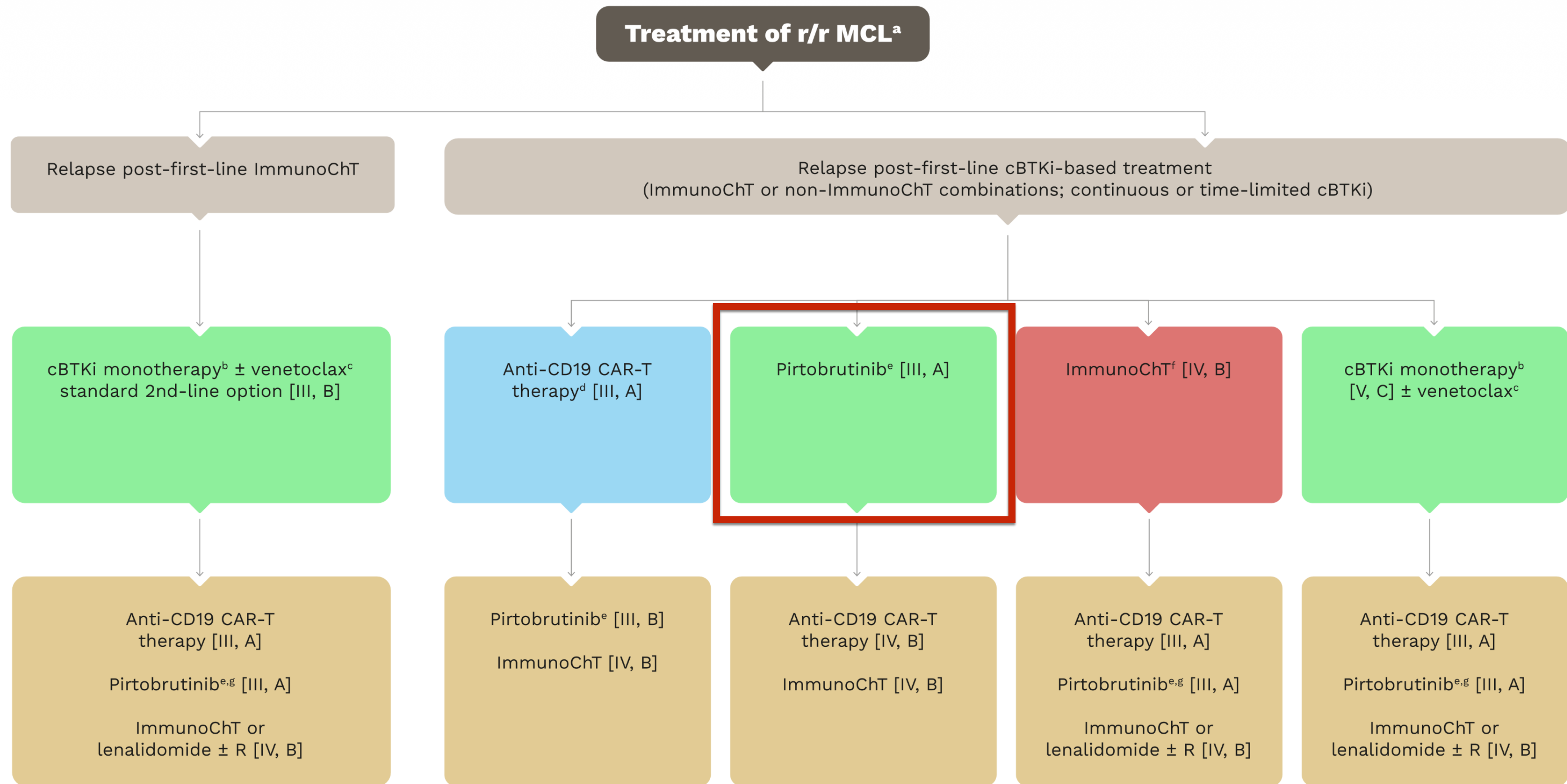


PFS - POD24



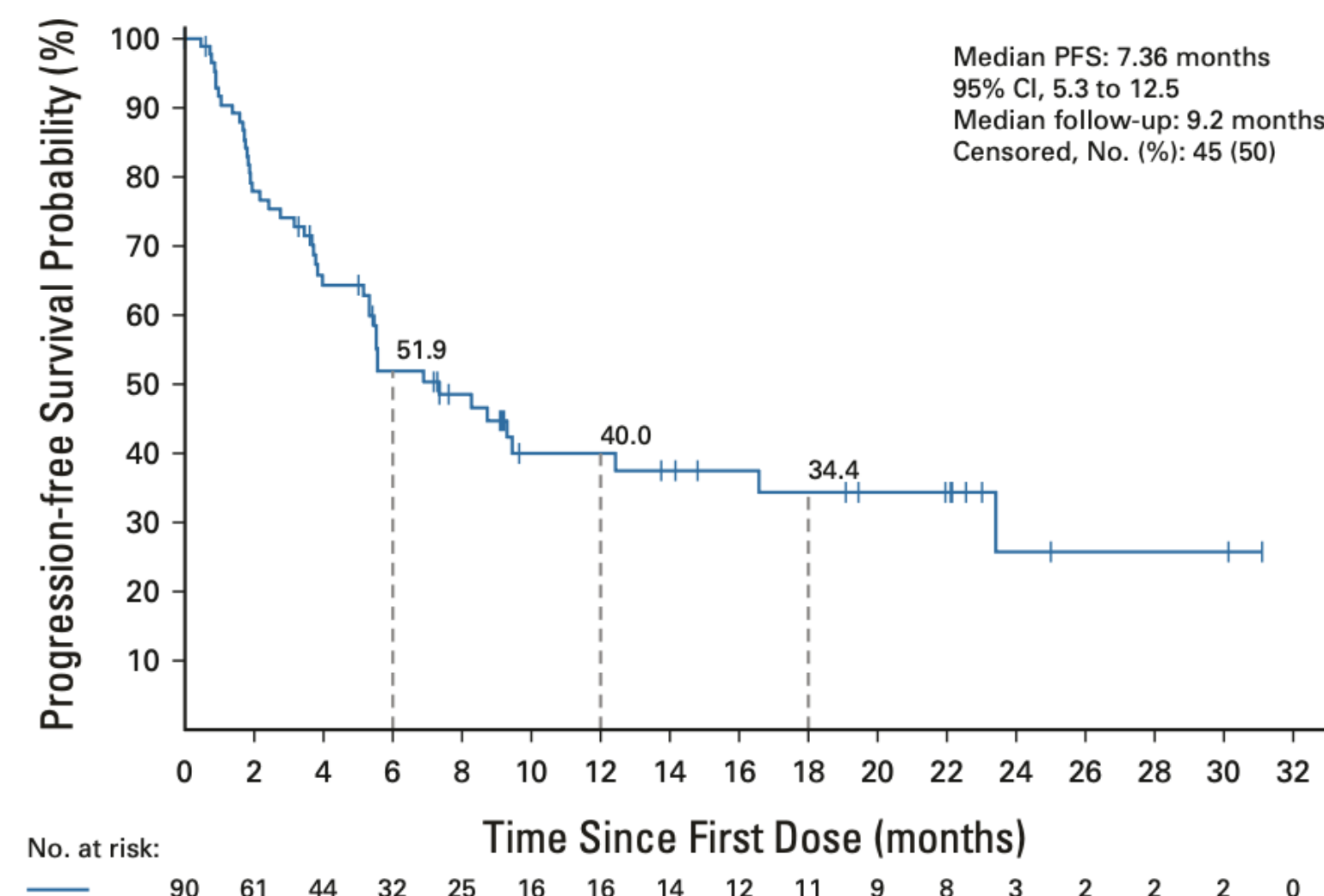
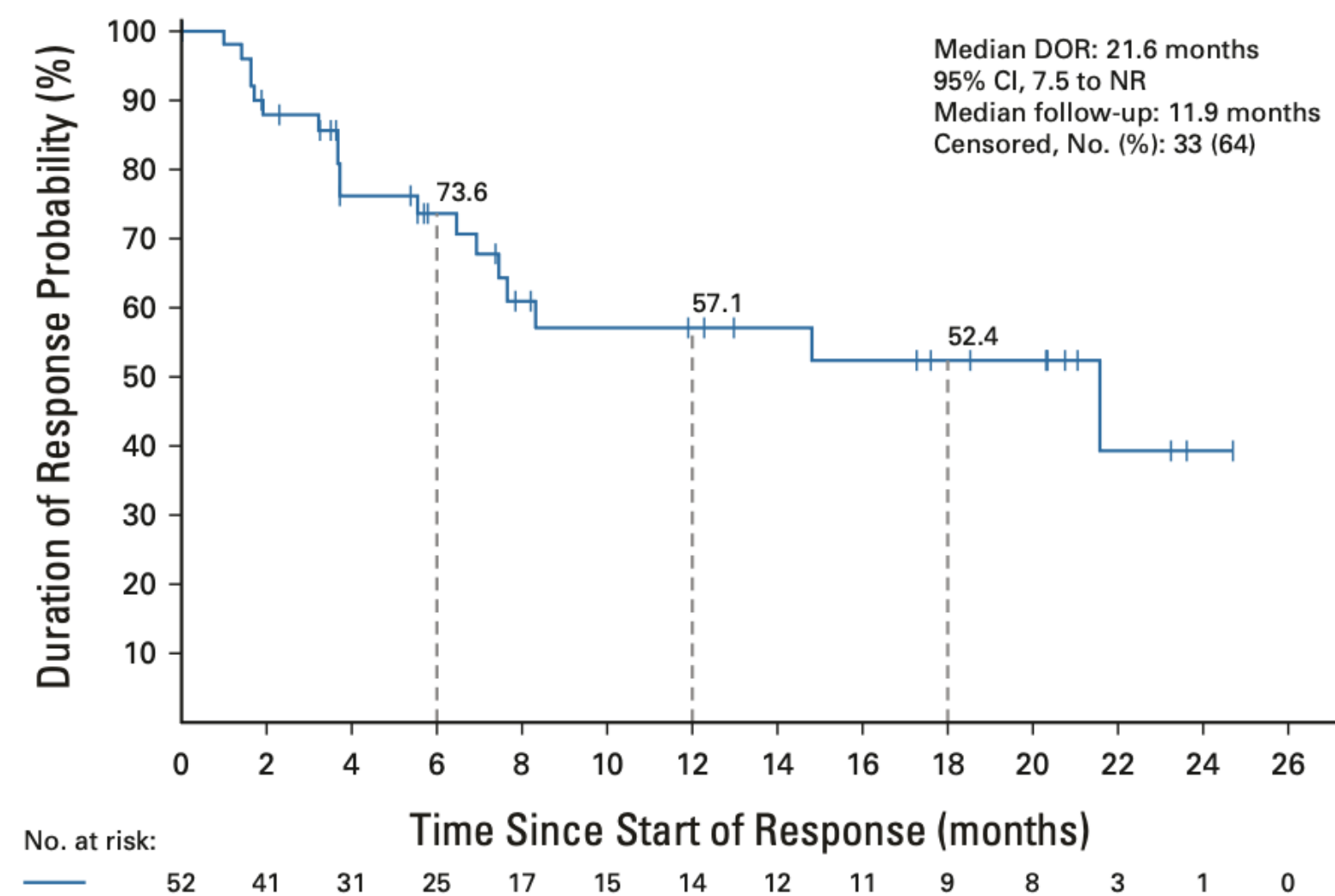






PIRTOBRUTINIB

- Non covalent, reversible BTKi
- Highly selective
- Inhibits both wild-type and C481-mutant BTK
- Favorable oral pharmacology
- Continuous BTK inhibition



BRUIN study, ASH2025

- Follow-up: 5y
- 166 pts
- Median prior lines: 3
- **ORR: 49,3%, CR 15,8%**
- Median **DOR: 21,6 mo**
- Median **PFS: 5,6 mo**

BTK COMBINATIONS IN R/R

- **AVO** (*Kim et al., ASH 2025*)
Acalabrutinib + Venetoclax + Obinutuzumab
20 pts in the R/R cohort
ORR: 86%, CR: 75%
- **VIPOR** (*Melani et al., ASH 2024*)
Venetoclax + Ibrutinib + Prednisone + Obinutuzumab + Lenalidomide
16 pts in the R/R cohort
2y-PFS 75%

CONCLUSIONI

BTKi costituiscono un caposaldo della terapia del MCL

I linea

- **Triangle** nel paziente giovane e fit
- **ECHO** nel paziente anziano/unfit
- **R + BTKi**: opzione sicura ed efficace per pazienti a basso rischio biologico o unfit per chemioterapia full-dose
- **TP53** mutati: no standard of care
- Possibilità: **triplette** BTKi + anti-CD20 + BCL2i

R/R

- BTKi naive: cBTKi (+ ven?)
- BTK exposed: **Pirtobrutinib** —> CAR-T

Altre opzioni:

- combinazioni chemio-free
- Anticorpi bispecifici
- BTK degraders
- Sonrotoclax
- anti-ROR1 drug conjugates
- AlloSCT

The young side of LYMPHOMA

gli under 40 a confronto

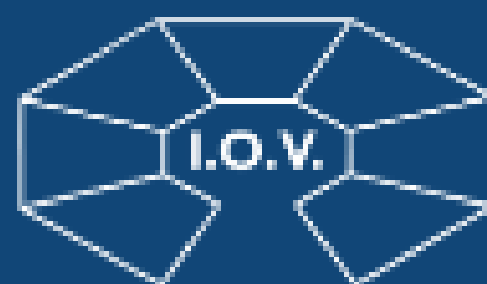


The young side of LYMPHOMA

gli under 40 a confronto



20 ANNI
2005 - 2025



ISTITUTO
ONCOLOGICO VENETO
IRCCS

Grazie!

Reggio Emilia, 2-3 ottobre 2026