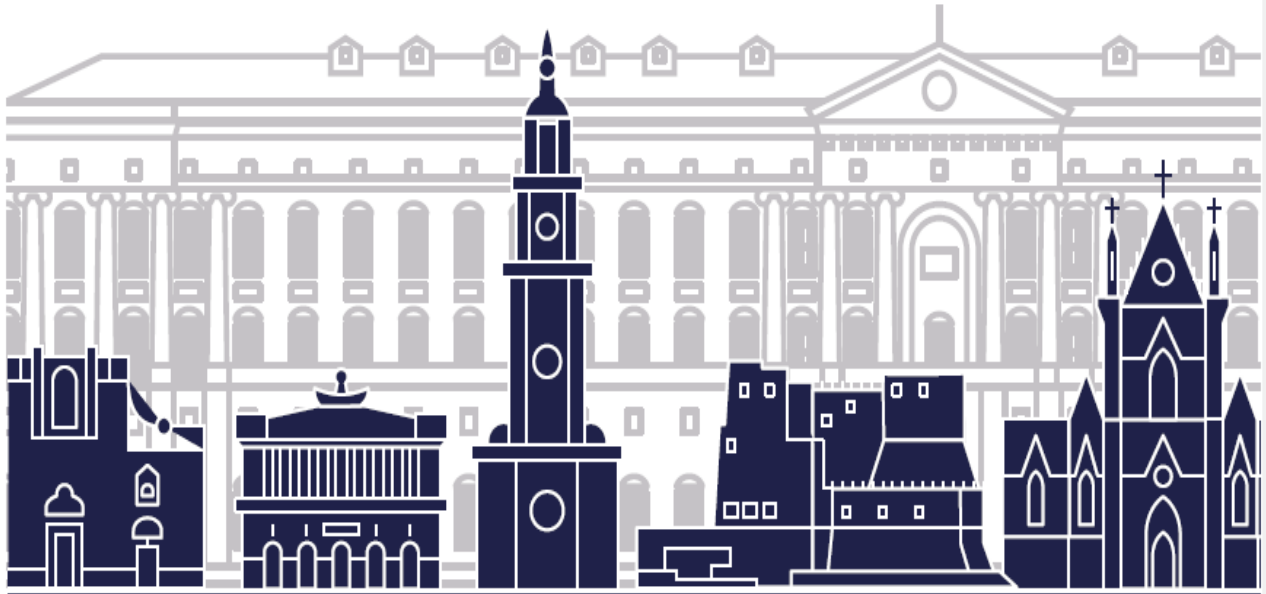
con il patrocinio di

AIL Caserta Valentina Picazio
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE • LINFOMI E MIELOMA

SIE
Società Italiana
di Ematologia

La rivoluzione terapeutica nel **linfoma** e nel **mieloma**

Napoli, Hotel Royal Contintental • 14–15 Maggio 2026



La terapia di I linea attuale e uno sguardo al futuro prossimo

Maurizio Martelli
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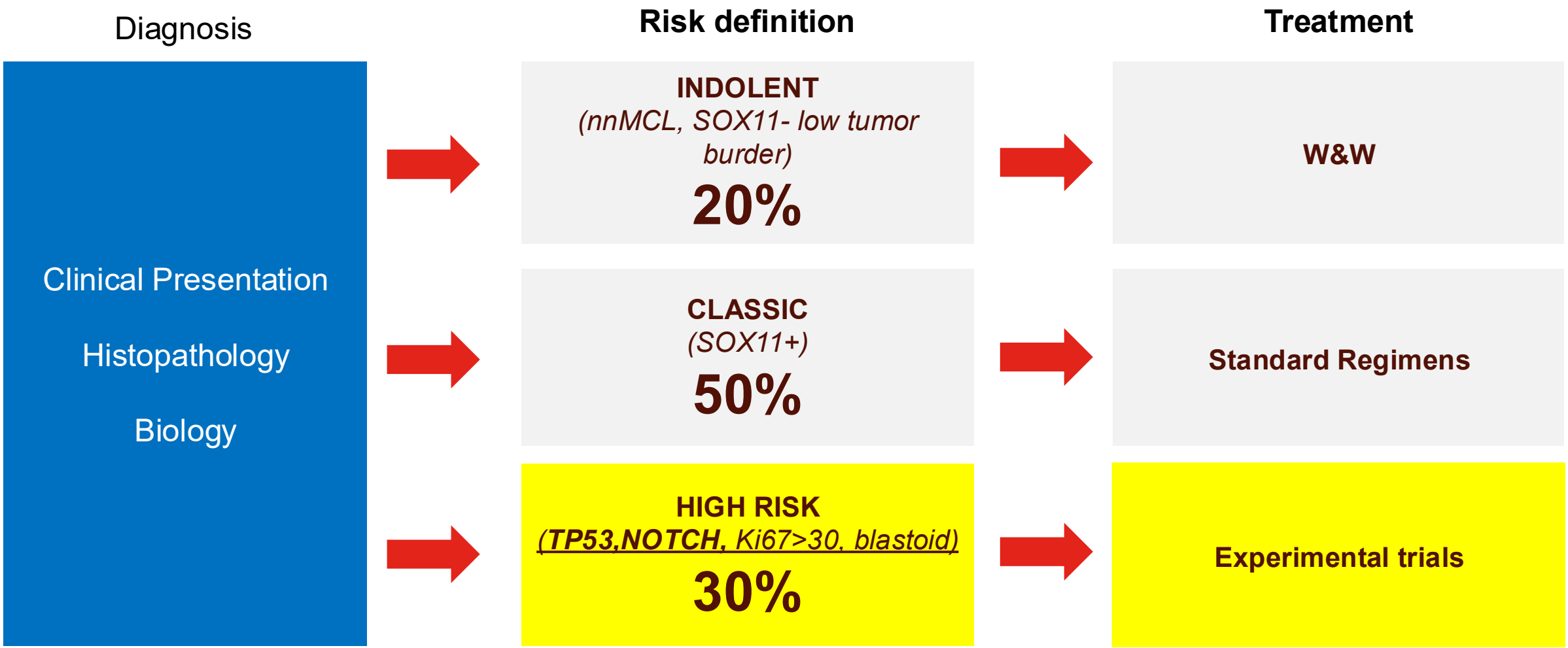
Università Sapienza/ Policlinico Umberto1 Roma

Disclosure: Maurizio Martelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X	X	
Gilead					X	X	
Novartis						X	
Takeda						X	
Eusapharma					X	X	
Incyte					X	X	
Janssen	X				X	X	
BMS						X	
Beigene					X	X	
Alexion	X						

New therapeutic approach in MCL



High risk features distribution

	Young (MCL-0208)	Nordic (MCL2-3)	Elderly (VR-BAC)
All patients	190	183	140
Ki67>30%	50 (28%)	68 (43%)	34 (24%)
TP53 mut	15 (8%)	20 (11%)	**28 (20%)**
TP53 del	**25 (13%)**	**29 (16%)**	**19 (14%)**
TP53 mut/del	31 (17%)	37 (20%)	34 (24%)
Blastoid	16 (8%)	31 (17%)	13 (9%)

Ferrero S et al, Haematologica 2020; Visco C et al, partial at ASH 2021; Eskelund et al, Blood 2017

Old Treatment in Mantle Cell Lymphoma

Preferred First-line Treatment Options

Aggressive Chemotherapy
R-DHAP (cisplatin, or oxaliplatin)
R-CHOP/R-DHAP (alternating)
NORDIC (maxi-CHOP/R + HD cytarabine)

→ **Consolidation and Maintenance**
HDT + ASCT → R maint for 3 yr

Less Aggressive Chemotherapy
BR
R-CHOP
RBAC

→ **Maintenance**
After R-CHOP: R maint until Progression.

Preferred Second-line Treatment Options

BTK inhibitor
- Ibrutinib

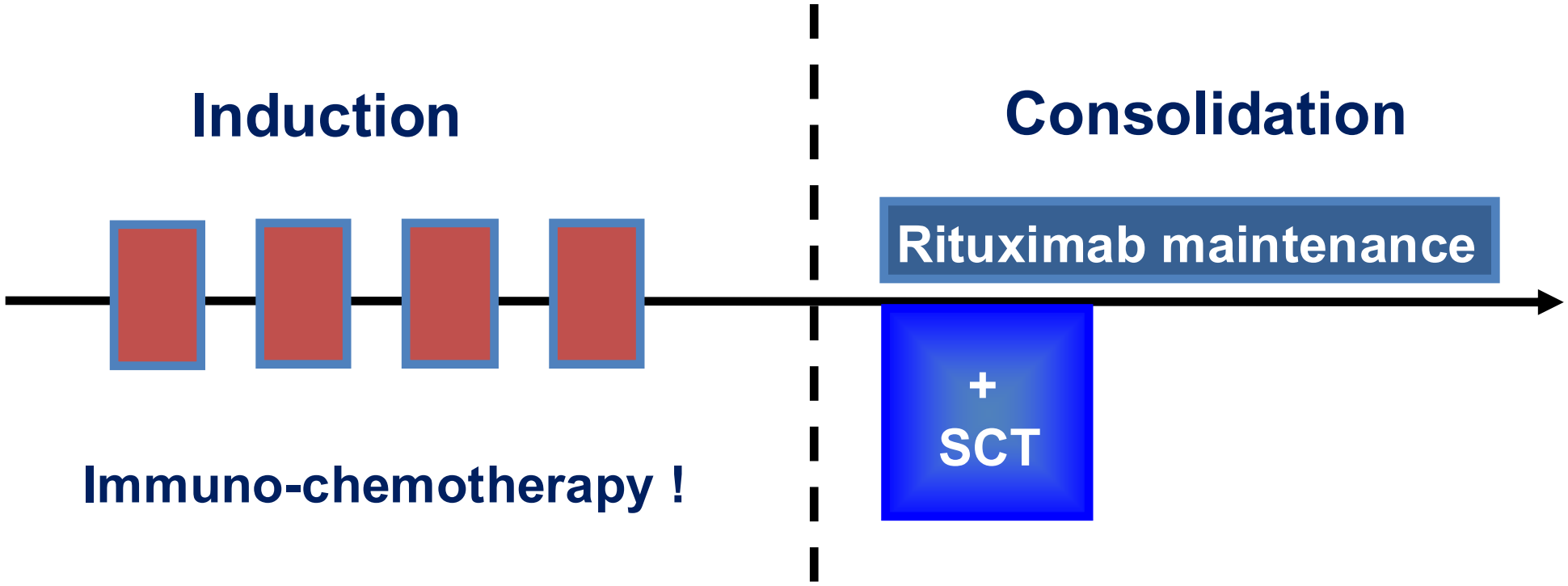
Third-line Treatment

Brexucabtagene autoleucel (after chemoimmunotherapy and BTK inhibitor)

Pirtobrutinib

Adattato da NCCN guidelines version 1.0 2024.

Front line therapy in Mantle Cell Lymphoma

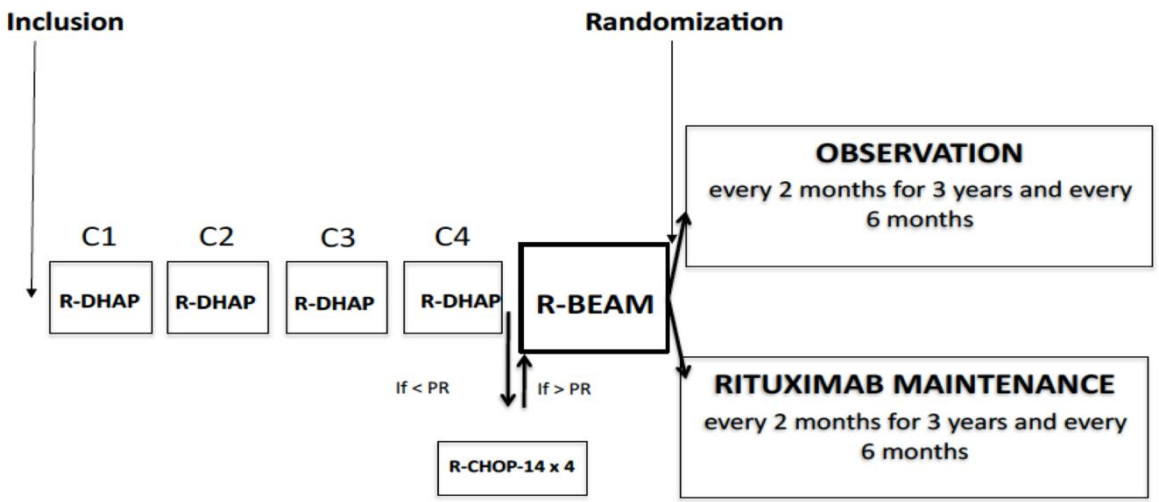


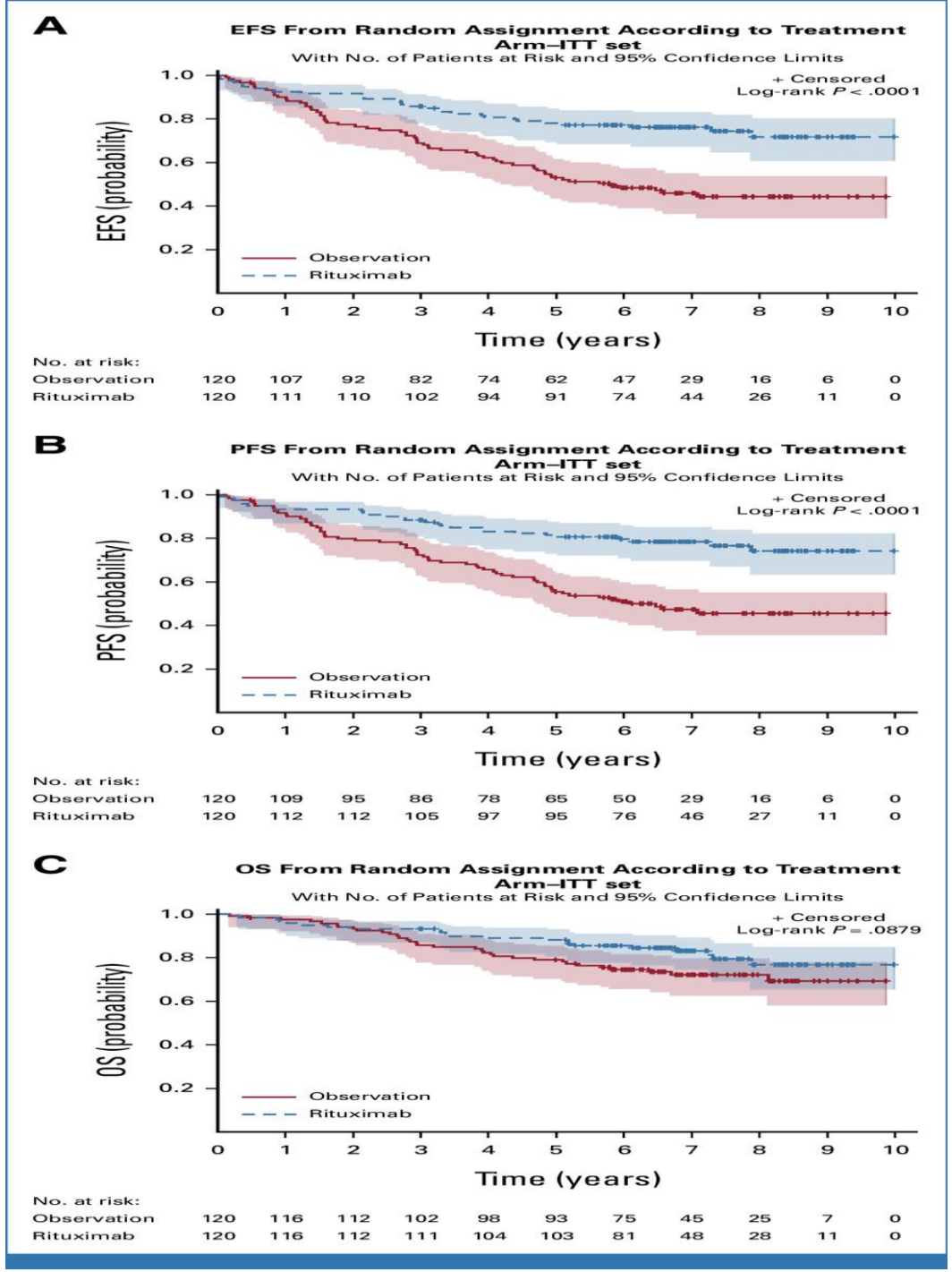
PARTIAL ACCESS | CLINICAL TRIAL UPDATES | December 18, 2023

Long-Term Follow-Up of Rituximab Maintenance in Young Patients With Mantle-Cell Lymphoma Included in the LYMA Trial: A LYSA Study

Authors: Clémentine Sarkozy, MD, PhD, Catherine Thieblemont, MD, PhD, Lucie Oberic, MD, Anne Moreau, MD, Krimo Bouabdallah, MD, Gandhi Damaj, MD, PhD, Thomas Gastinne, MD, ... SHOW ALL ... , and Steven Le Gouill, MD, PhD | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 7 • https://doi.org/10.1200/JCO.23.01586



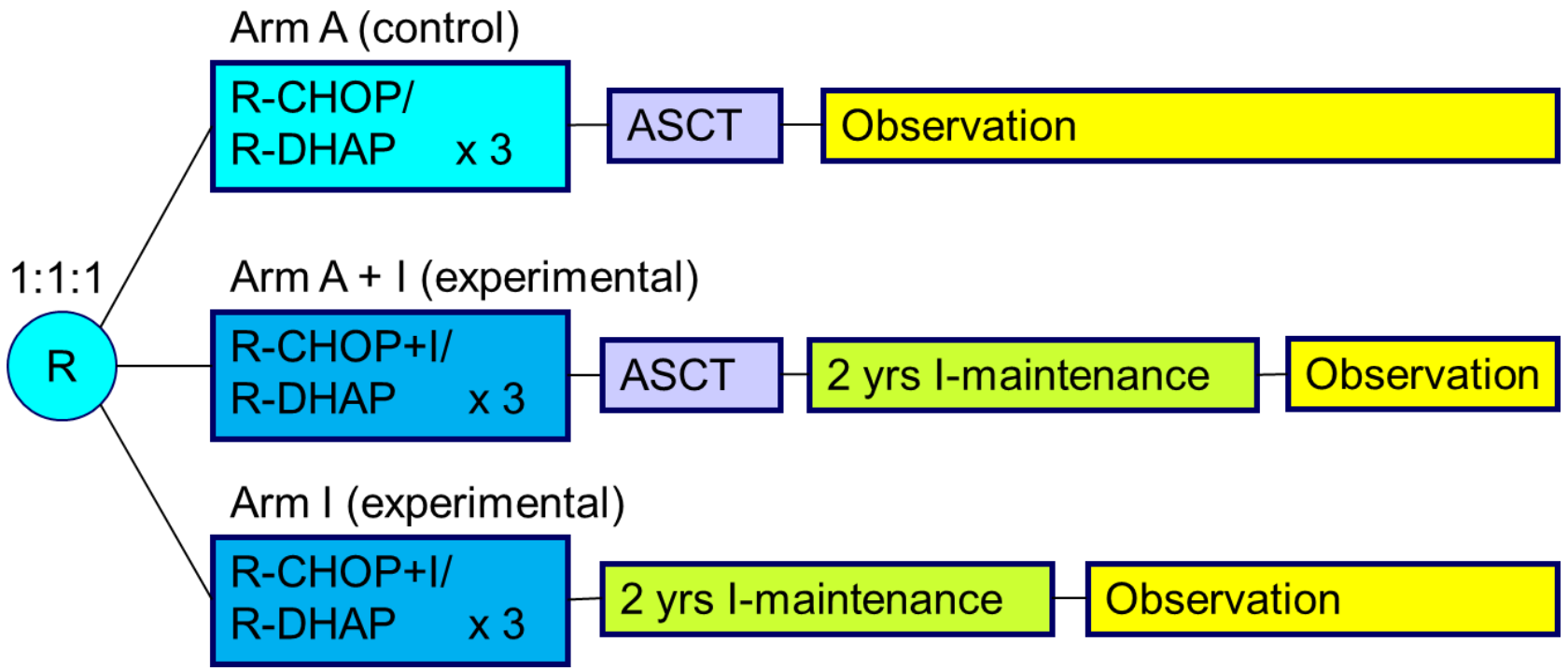


TRIANGLE: Trial Design

- 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



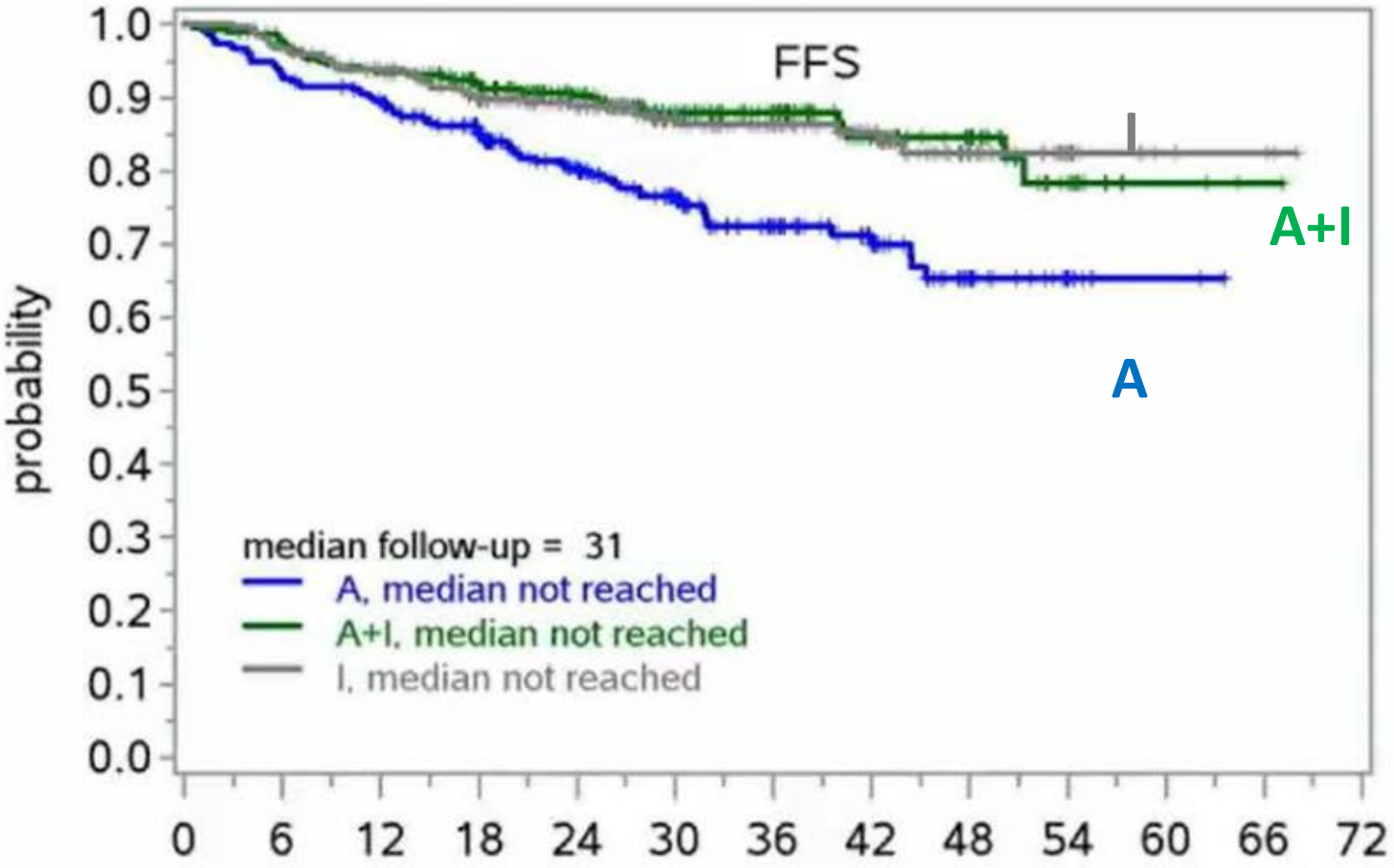
- **R maintenance was added following national guidelines in all 3 trial arms**
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

TRIANGLE: Response at End of Induction

	Overall	A	A+I/I	A+I	I
ED	2 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0%)
PD	17 (2%)	11 (4%)	6 (1%)	3 (1%)	3 (1%)
SD	7 (1%)	4 (1%)	3 (0.5%)	1 (0.4%)	2 (0.7%)
PR	458 (55%)	158 (58%)	300 (54%)	152 (54%)	148 (53%)
CR	347 (42%)	98 (36%)	249 (45%)	124 (44%)	125 (45%)
CR+PR	805 (97%)	256 (94%)	549 (98%)	276 (98%)	273 (98%)
Total	831	272	559	281	278
NE	29	11	18	8	10
ND	10	5	5	3	2

Dreyling M, et al. Lancet. 2024 May 25;403(10441):2293-2306.

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



Numbers At Risk

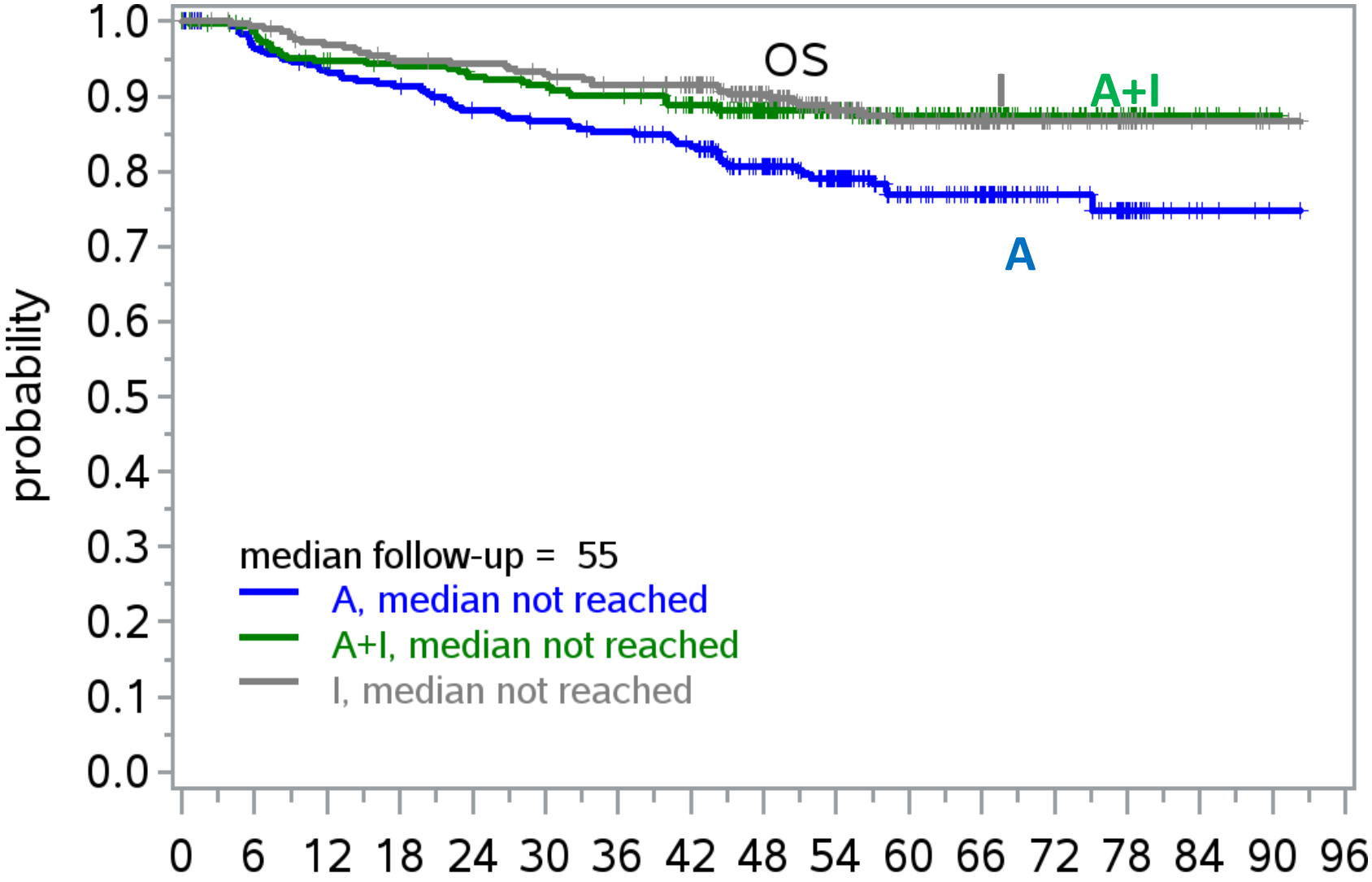
A	288	252	237	206	162	126	85	54	27	12	2	0
A+I	292	270	253	226	184	137	109	65	40	17	3	1
I	290	269	257	229	180	133	100	68	34	16	4	3

- 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 M, et al. Lancet. 2024 May 25;403:2293-2306.

TRIANGLE: Overall survival



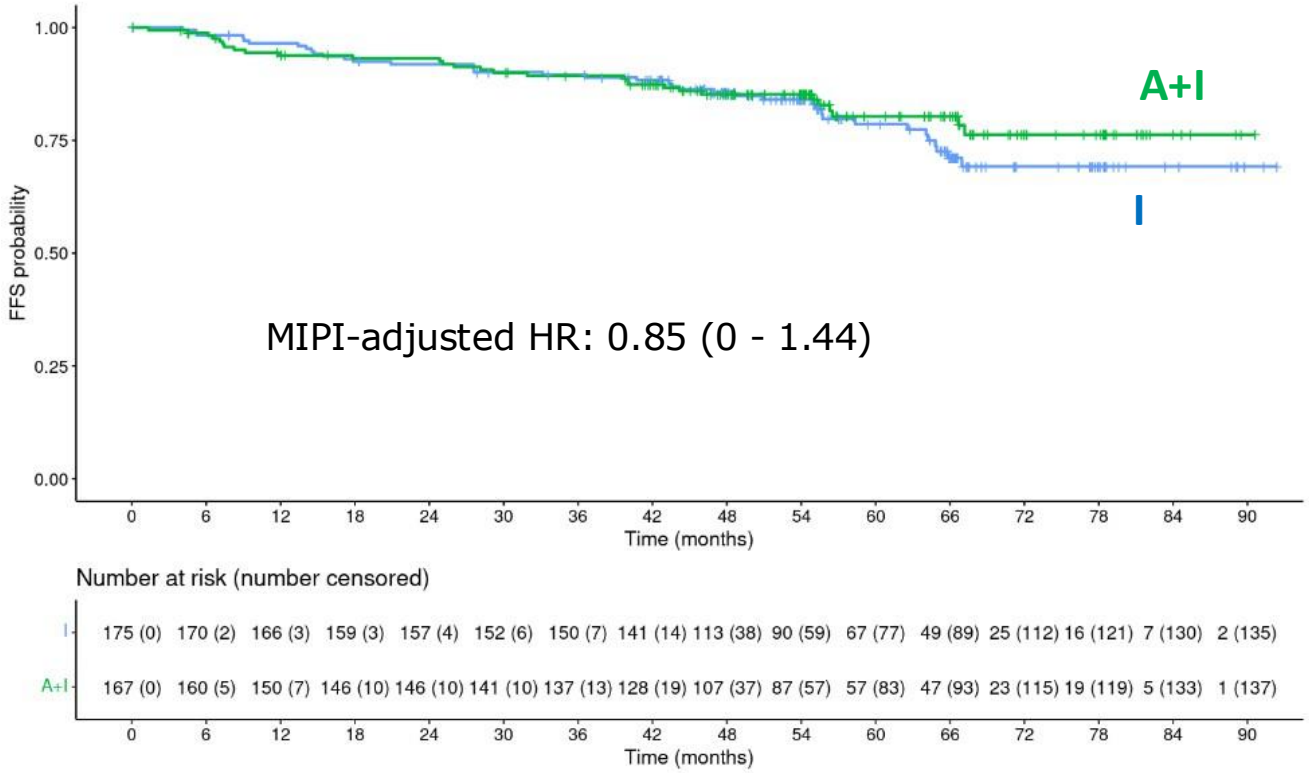
- 4-year OS:
  - A: 81%
    (MCL Younger exp.: 80%)
  - A+I: 88%
  - I: 90%

- two-sided test, (α = 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**

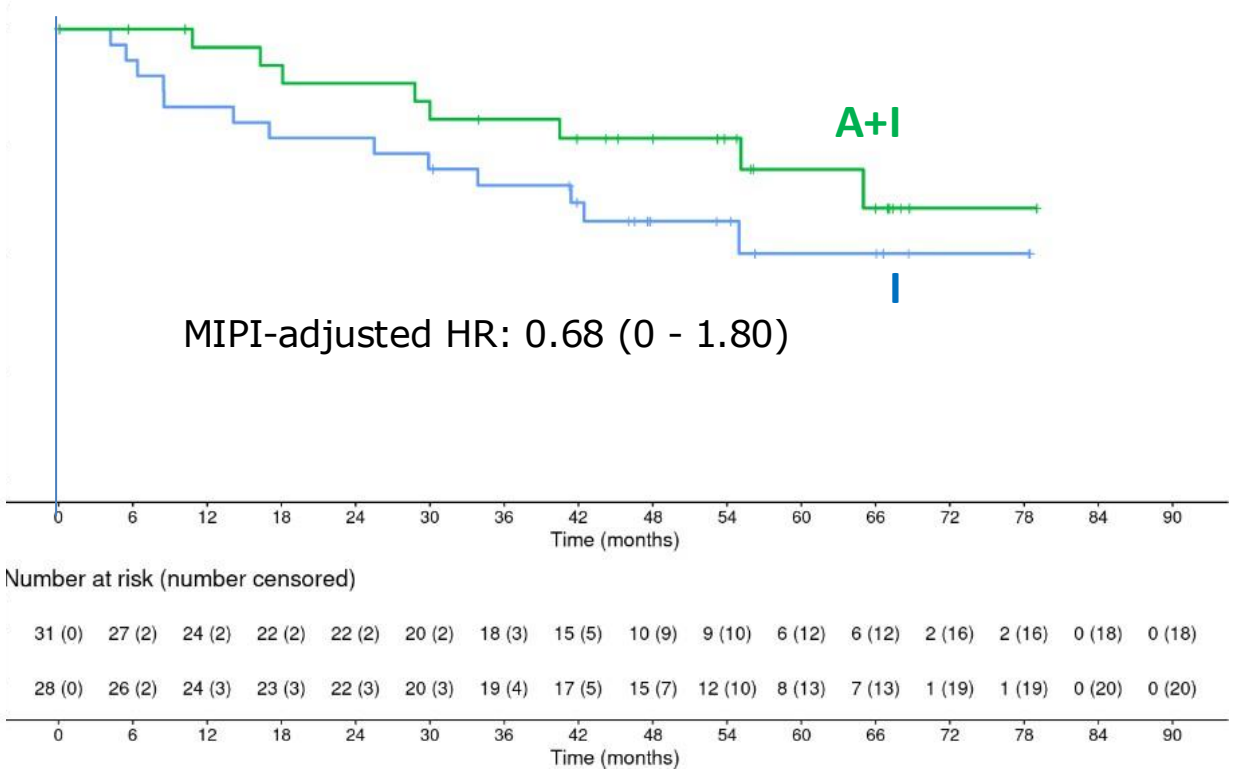
Dreyling M, et al. Lancet. 2024 May 25;403:2293-2306.

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

P53 low



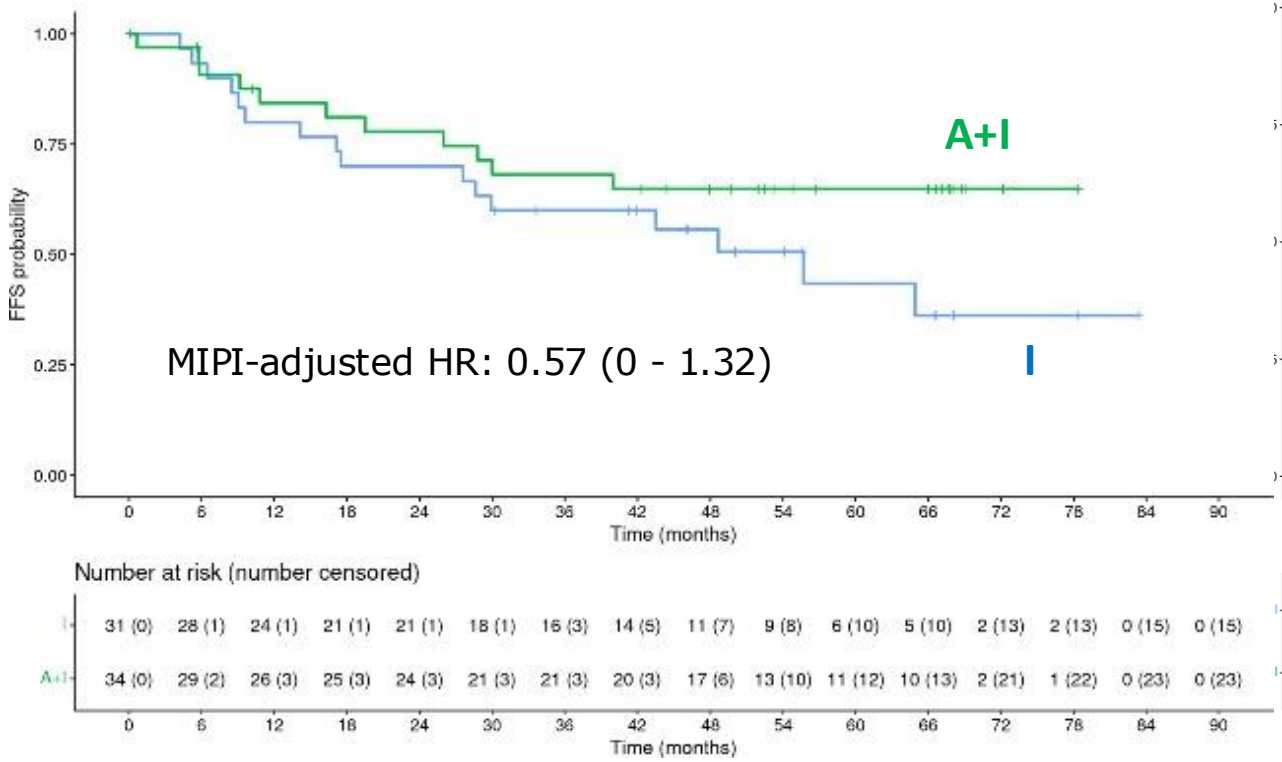
P53 high



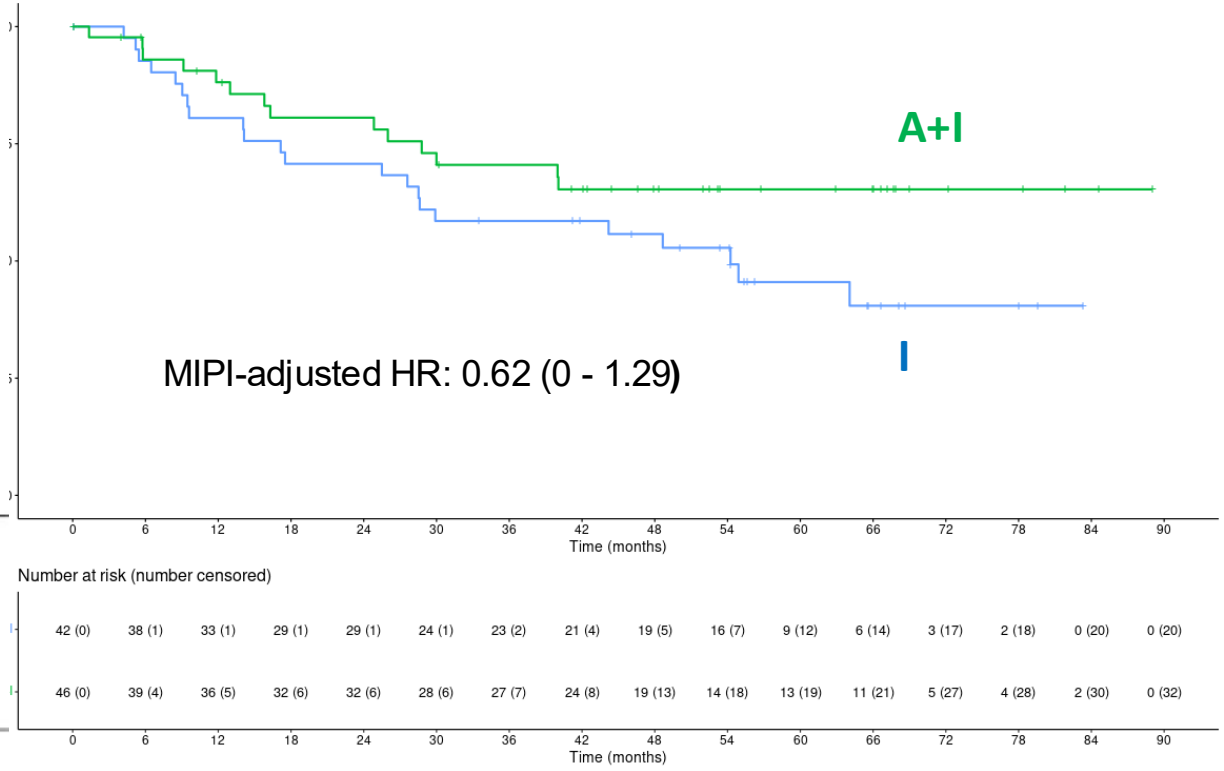
Dreyling M, et al. Lancet. 2024 May 25;403:2293-2306.

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

Citology Blastoid



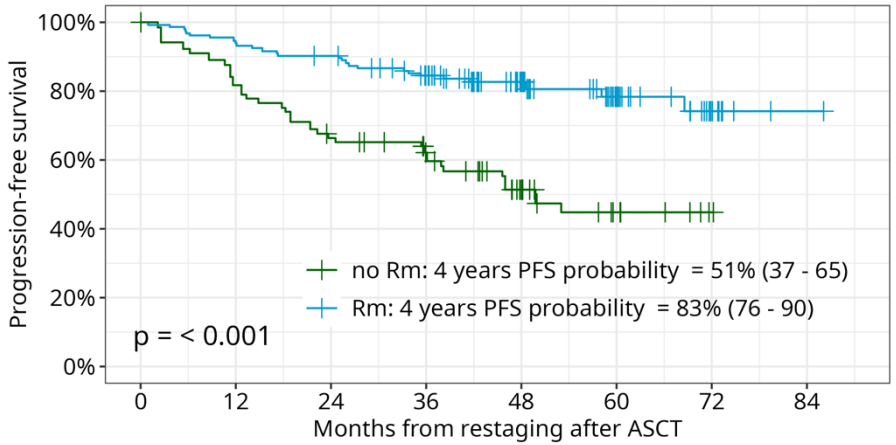
Ki67 > 50%



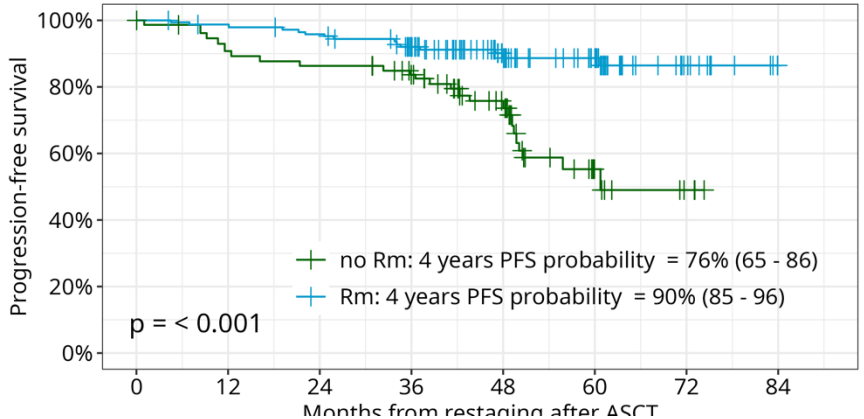
Dreyling M, et al. Lancet. 2024 May 25;403:2293-2306.

TRIANGLE: Rituximab manteinance vs no manteinance

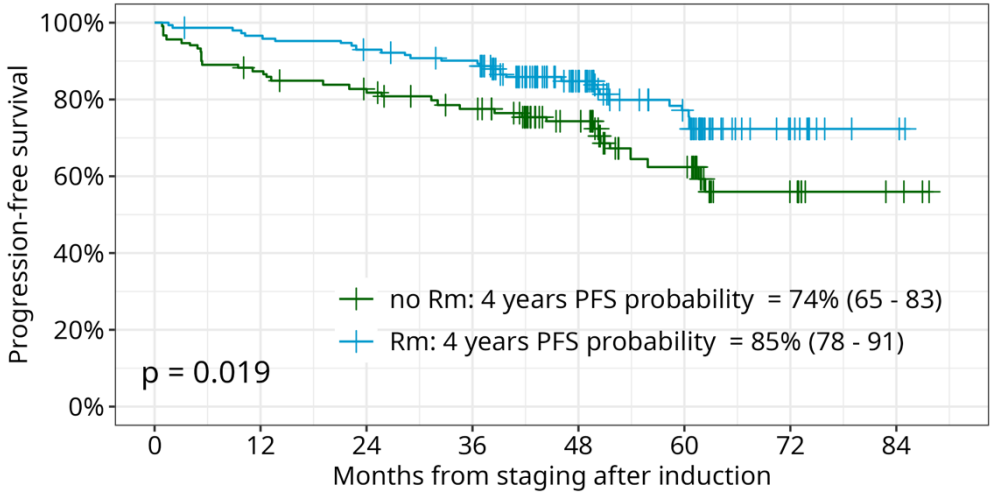
Arm A: PFS



Arm A+I: PFS



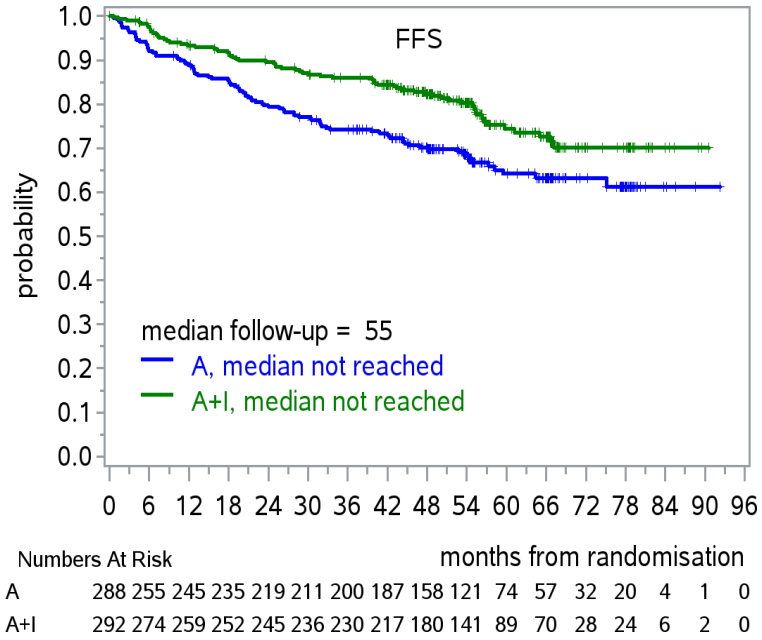
Arm I: PFS



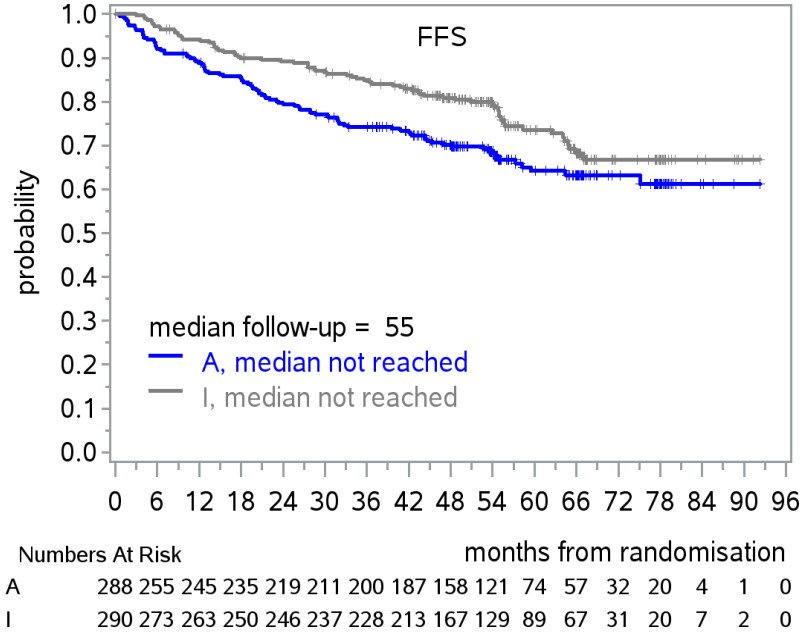
Ladetto M et al, ASH 2024

TRIANGLE: update Failure Free Survival

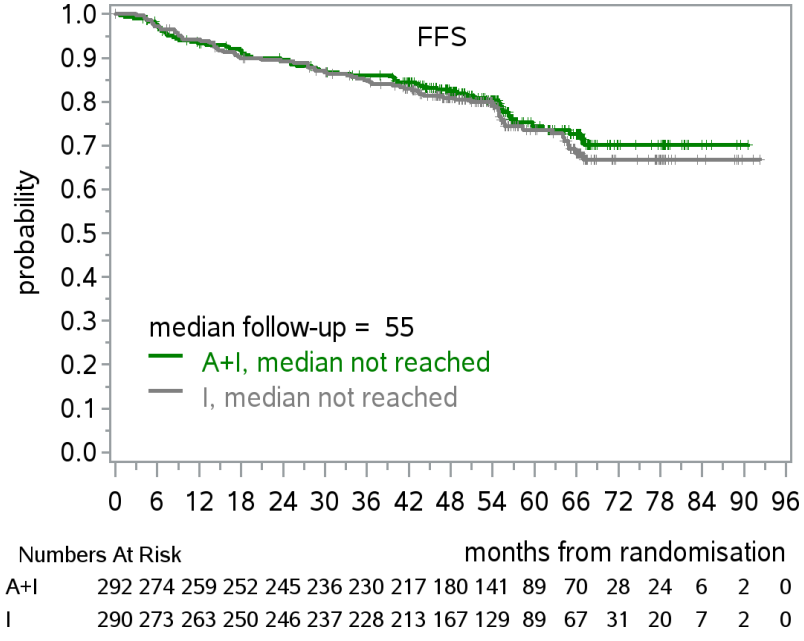
FFS Superiority of A+I vs. A



FFS Superiority of A vs. I

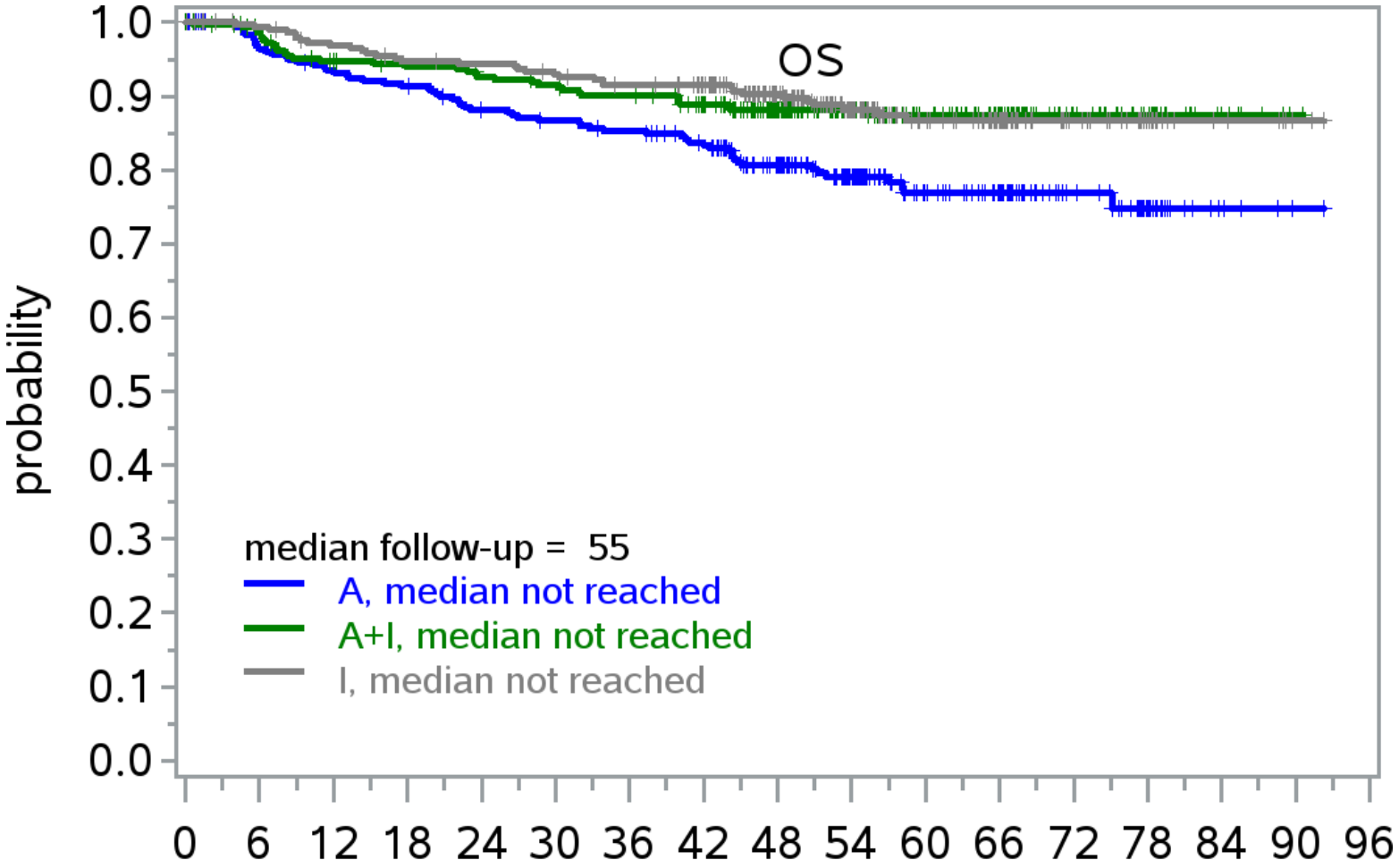


FFS Superiority of A+I vs. I



Dreyling et al, Lancet, in press

TRIANGLE: update Overall survival



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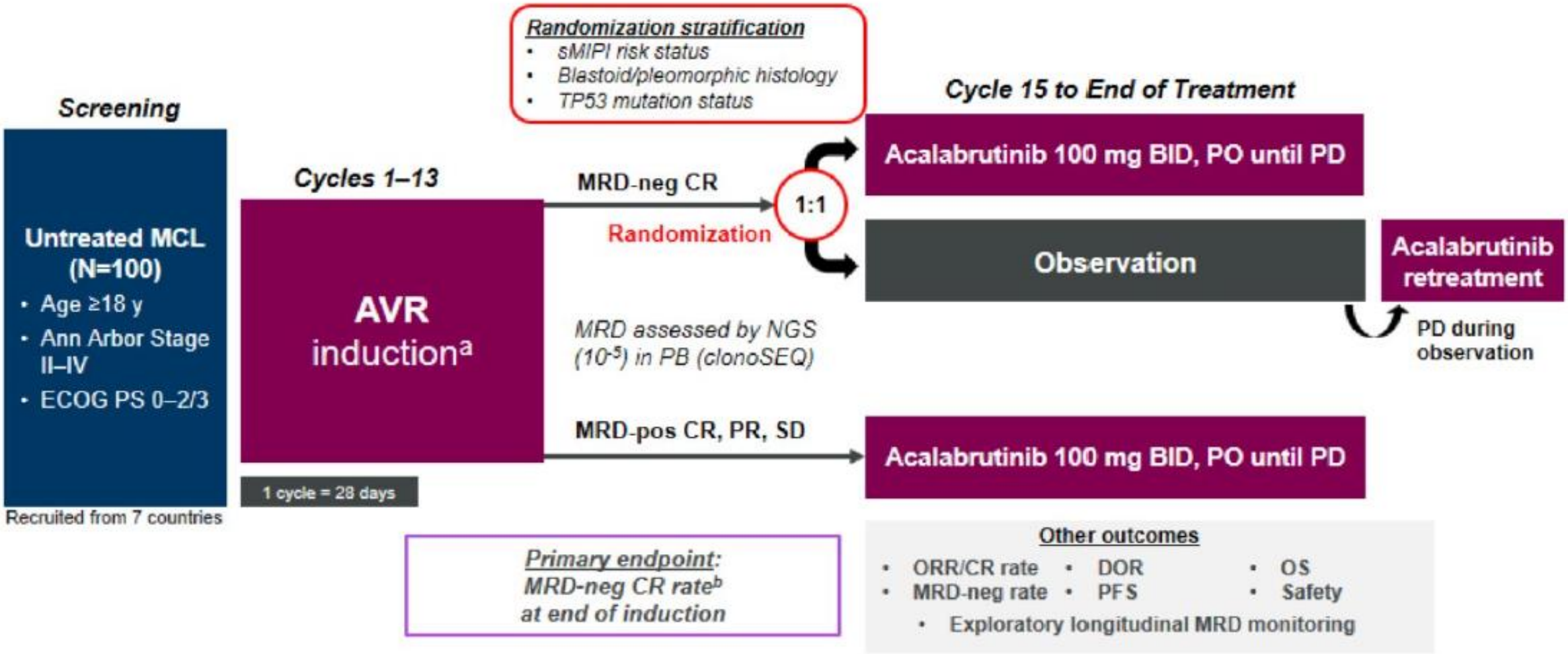
  - A+I vs. I: ongoing

Dreyling et al, Lancet, in press

TrAVeRse study design: open label phase 2 trial



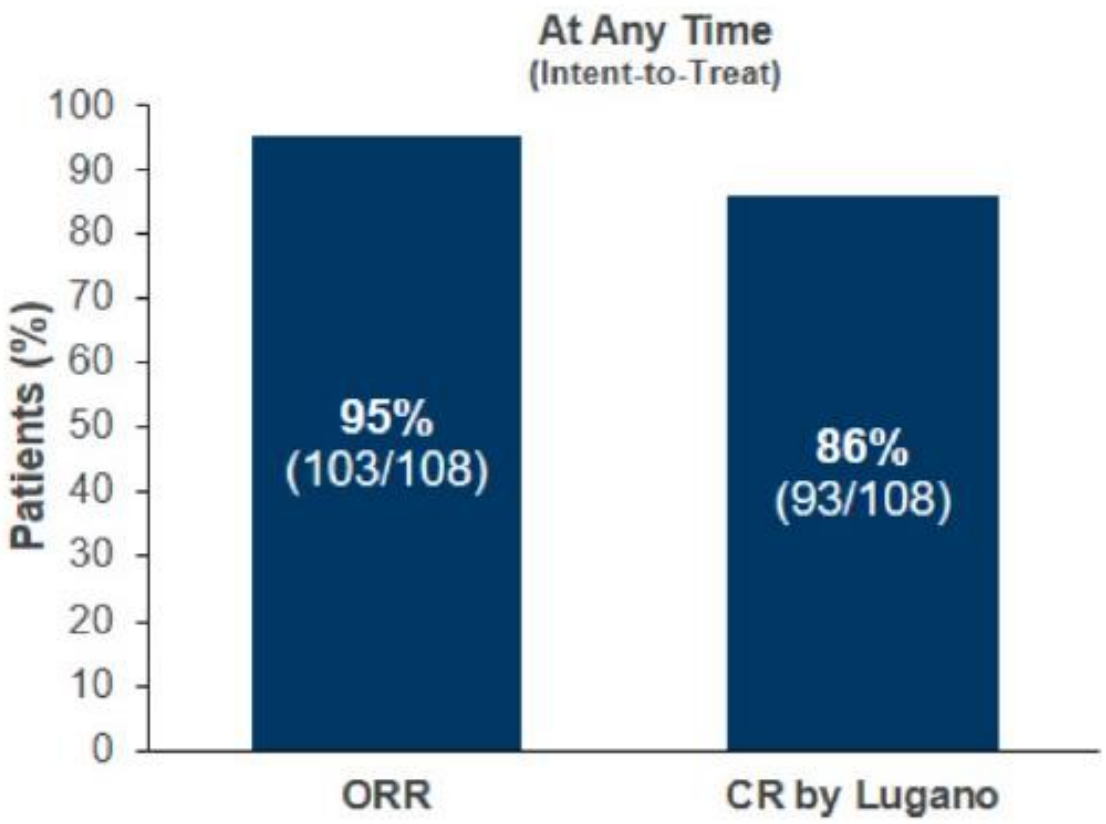
Hawkes E.A. et al ASH 2025

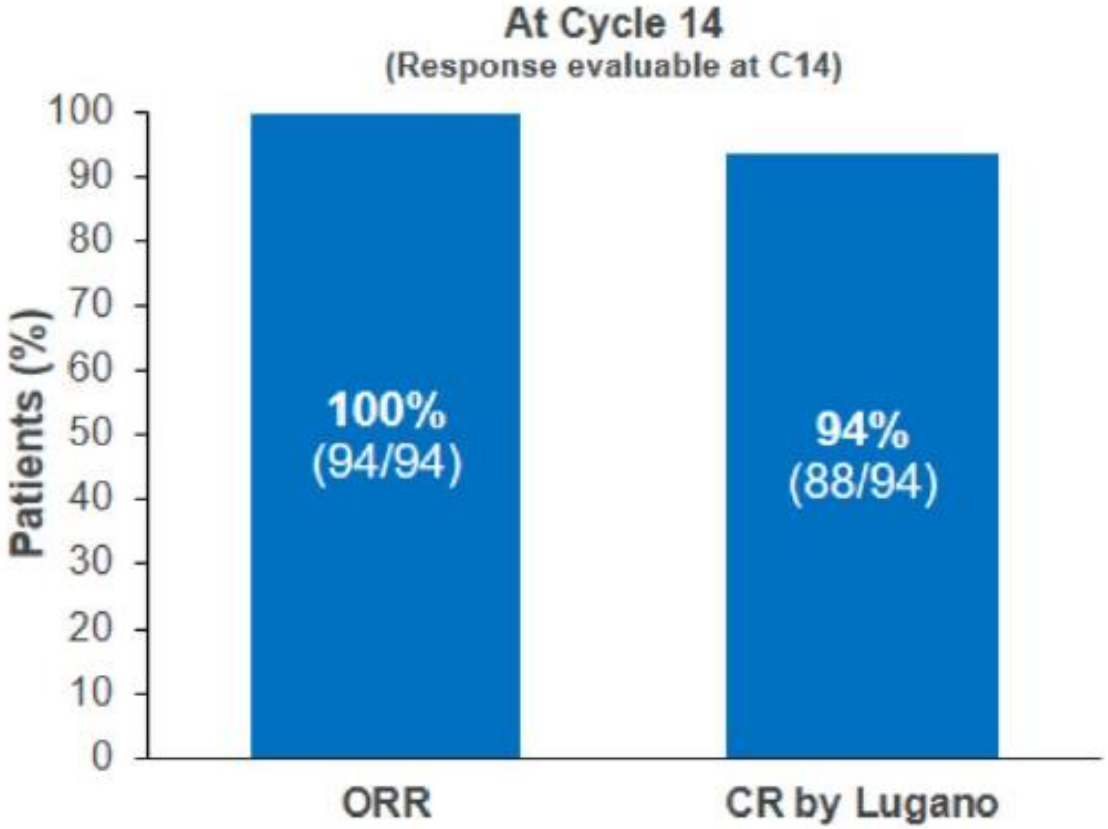
Baseline patients characteristics

Characteristic	AVR (N=108)
Age, median (range), years	69 (40–89)
Age <65 years, n (%)	42 (38.9)
Male, n (%)	80 (74.1)
White, n (%)	94 (87.0)
Ann Arbor stage IV, n (%)[a]	99 (91.7)
Extranodal involvement, n (%)	102 (94.4)
Bone marrow involvement, n (%)	90 (83.3)
Ki-67 ≥30%, n (%)	41 (38.0)
Blastoid/pleomorphic histology, n (%)[b]	9 (8.3)
p53 expression by IHC, n (%)	
Positive	34 (31.5)
Negative	68 (63.0)
Missing	6 (5.6)
TP53 mutation by NGS, n (%)	
Mutated	17 (15.7)
Unmutated	73 (67.6)
Unknown	18 (16.7)
Simplified MIPI, n (%)	
Low risk (0–3)	30 (27.8)
Intermediate risk (4–5)	45 (41.7)
High risk (≥6)	33 (30.6)

Hawkes E.A. et al ASH 2025

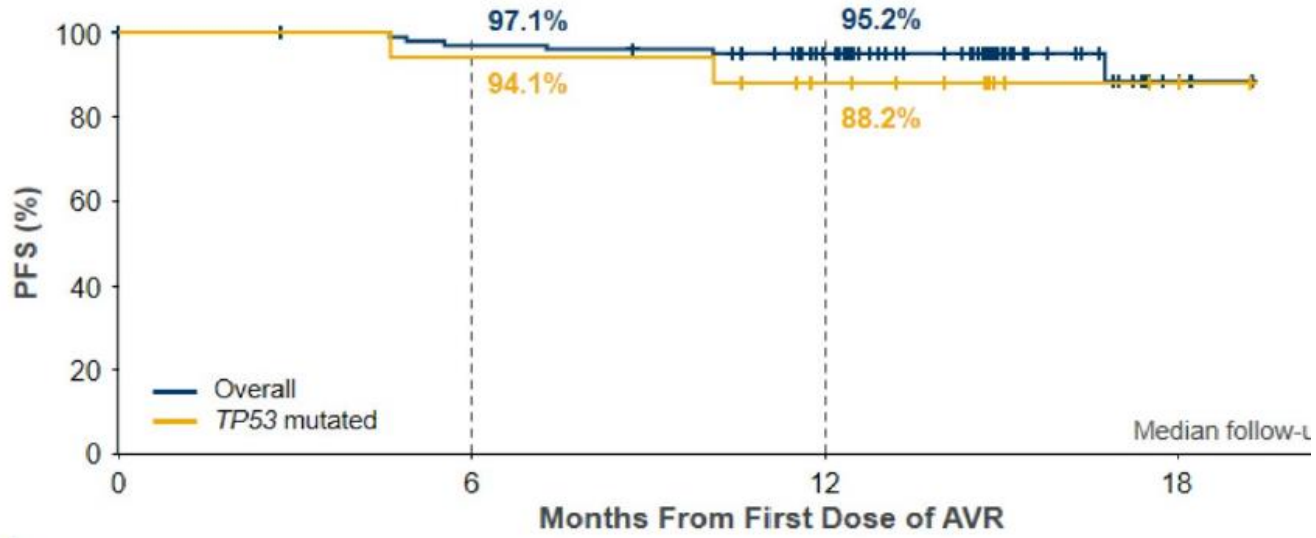
Overall response and complete response rate





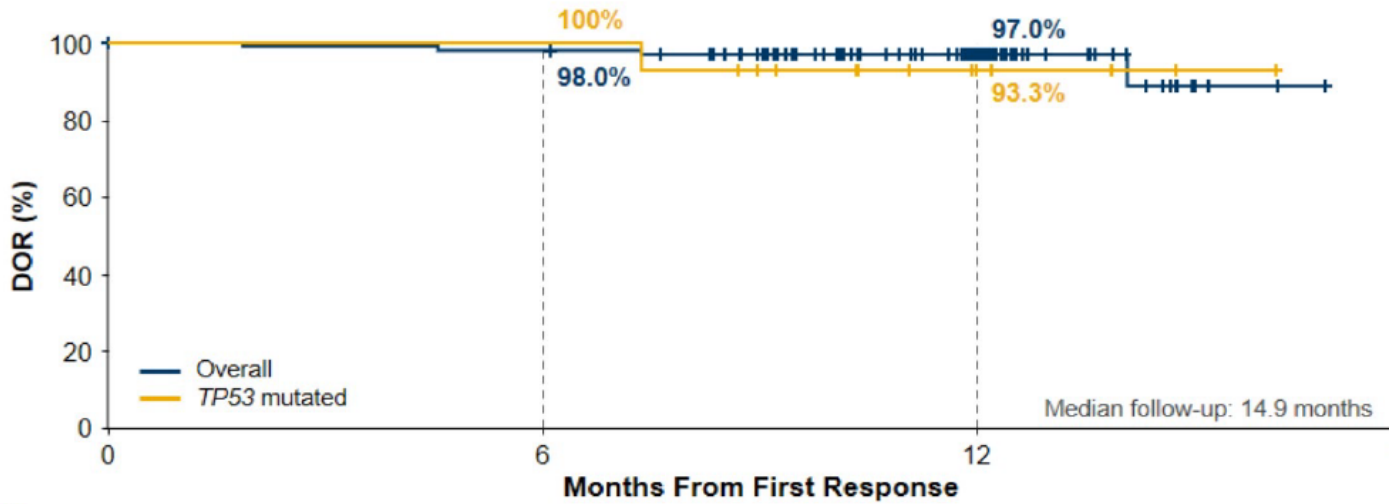
Hawkes E.A. et al ASH 2025

Progression free survival



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

Duration of response



No. at risk			
Overall	103	100	46
TP53 mutated	15	15	5

Hawkes E.A. et al ASH 2025

Old Treatment in Mantle Cell Lymphoma

Preferred First-line Treatment Options

Aggressive Chemotherapy
R-DHAP (cisplatin, or oxaliplatin)
R-CHOP/R-DHAP (alternating)
NORDIC (maxi-CHOP/R + HD cytarabine)

→ **Consolidation and Maintenance**
HDT + ASCT → R maint for 3 yr

Less Aggressive Chemotherapy
BR
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Preferred Second-line Treatment Options

BTK inhibitor
- Ibrutinib

Third-line Treatment

Brexucabtagene autoleucel (after chemoimmunotherapy and BTK inhibitor)

Pirtobrutinib

Adattato da NCCN guidelines version 1.0 2024.

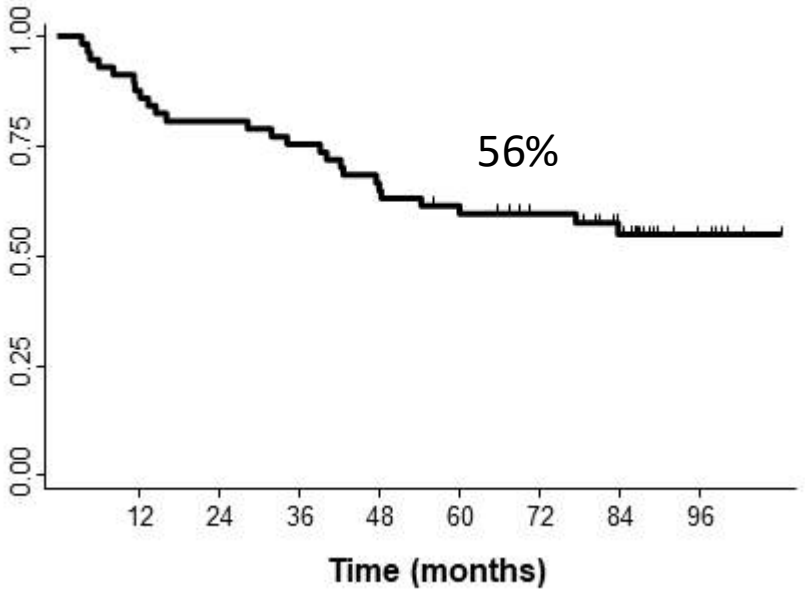
Rituximab Plus Bendamustine and Cytarabine (R-BAC) in Elderly Patients with Newly Diagnosed Mantle Cell Lymphoma: Long Term Follow-up and Mrd Results of a Phase 2 Study from the Fondazione Italiana Linfomi

FIL-RBAC500

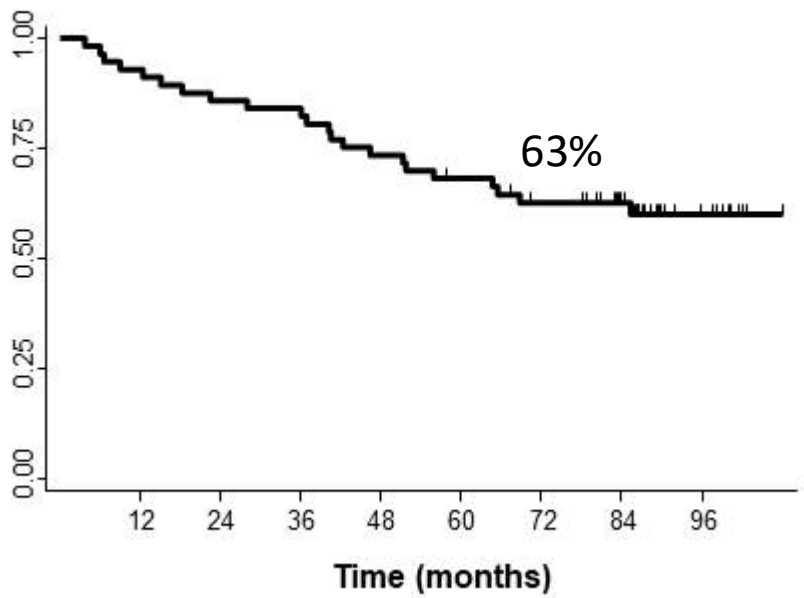
FONDAZIONE ITALIANA LINFOMI

- 7 years of median follow-up (86 months, range 57-107),
- median OS and PFS for all patients were not reached

7-yrs PFS



7-yrs OS



- Adverse predictive factors affecting PFS were blastoid morphology ($p<0.05$), elevated Ki67 $\geq$ 30% ($p<0.05$), and failure to achieve CR after 2 cycles ($p=0.03$).

Tisi MC et al. Blood 2021 (384)

Trials of relevance for an elderly population

- **SHINE trial: BR + ibrutinib until PD**
- **ECHO: BR + acalabrutinib until PD**
- **ENRICH: Ibrutinib-R vs. BR/R-CHOP**
- **VR-BAC: venetoclax consolidation after R-BAC**

PUBLISHED RESULTS

- MANGROVE: Zanubrutinib-R vs. BR
- BOVen study : Zanubrutinib, Obino ,Ven

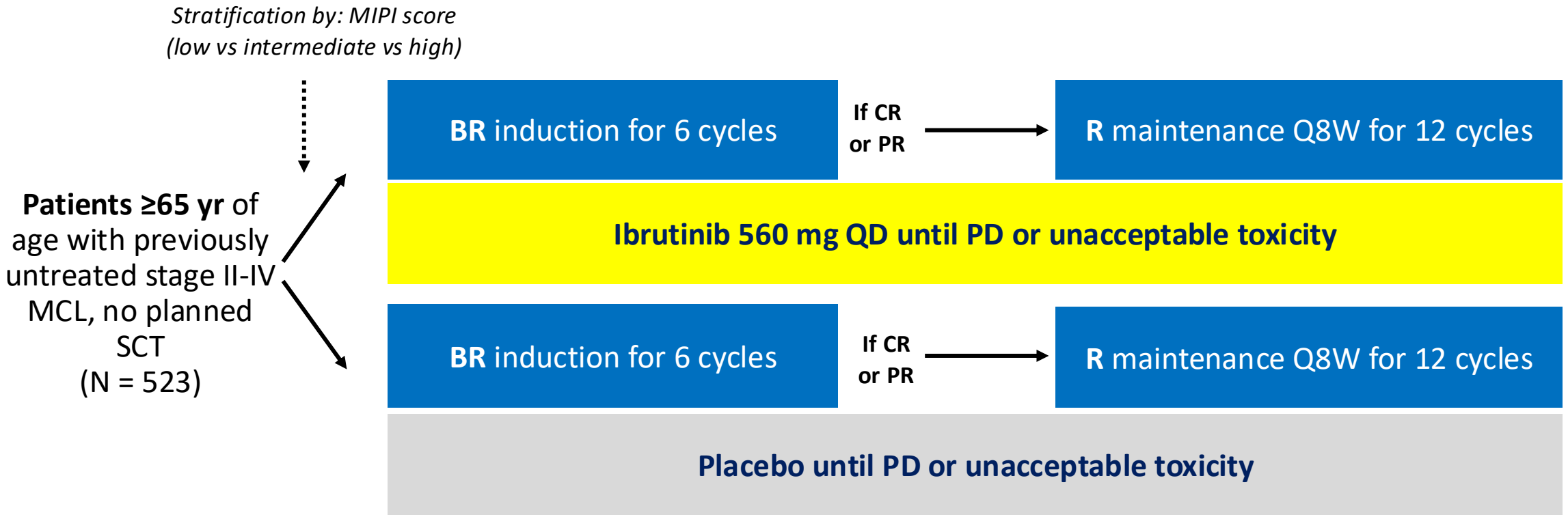
PENDING RESULTS

- **VIRAL: VR+ibrutinib vs V+R-benda+ibrutinib**

ONGOING TRIAL

SHINE: A Randomized, Double-Blind, Phase 3 Study

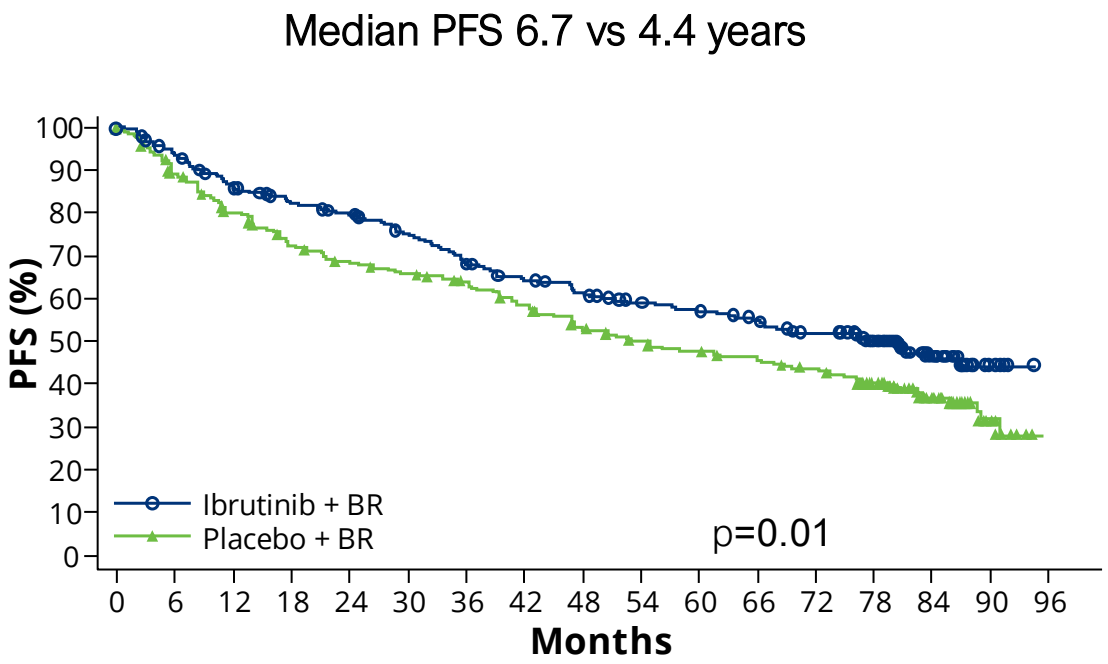
- Multicenter, randomized, double-blind, placebo-controlled phase III trial



- **Primary endpoint:** investigator-assessed PFS (in ITT)
- **Key secondary endpoints:** ORR, time to next treatment, OS, safety

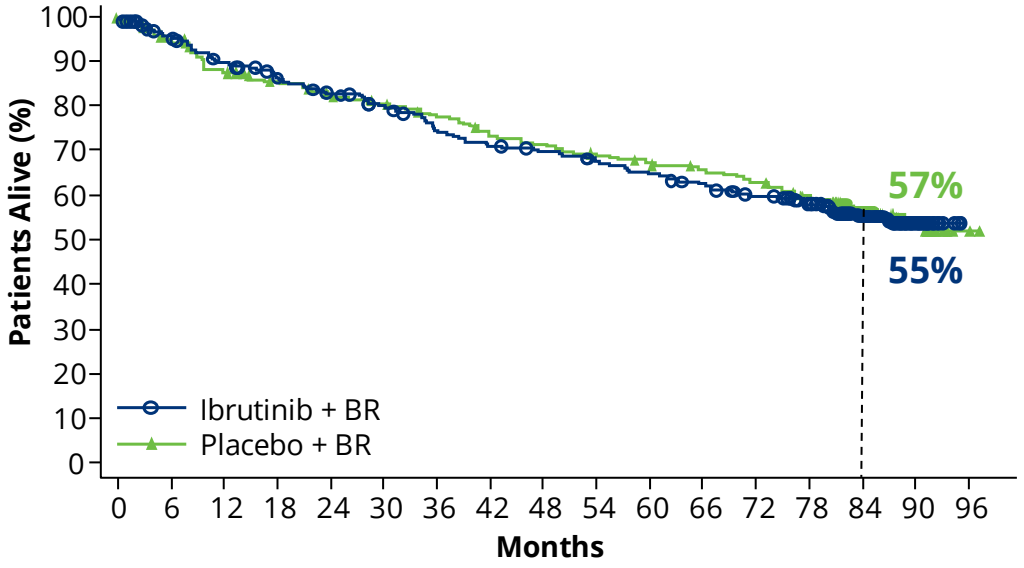
Wang M et al . NEJM. 2022;[Epub].

SHINE: A Randomized, Double-Blind, Phase 3 Study



Patients at Risk

Ibrutinib + BR	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo + BR	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

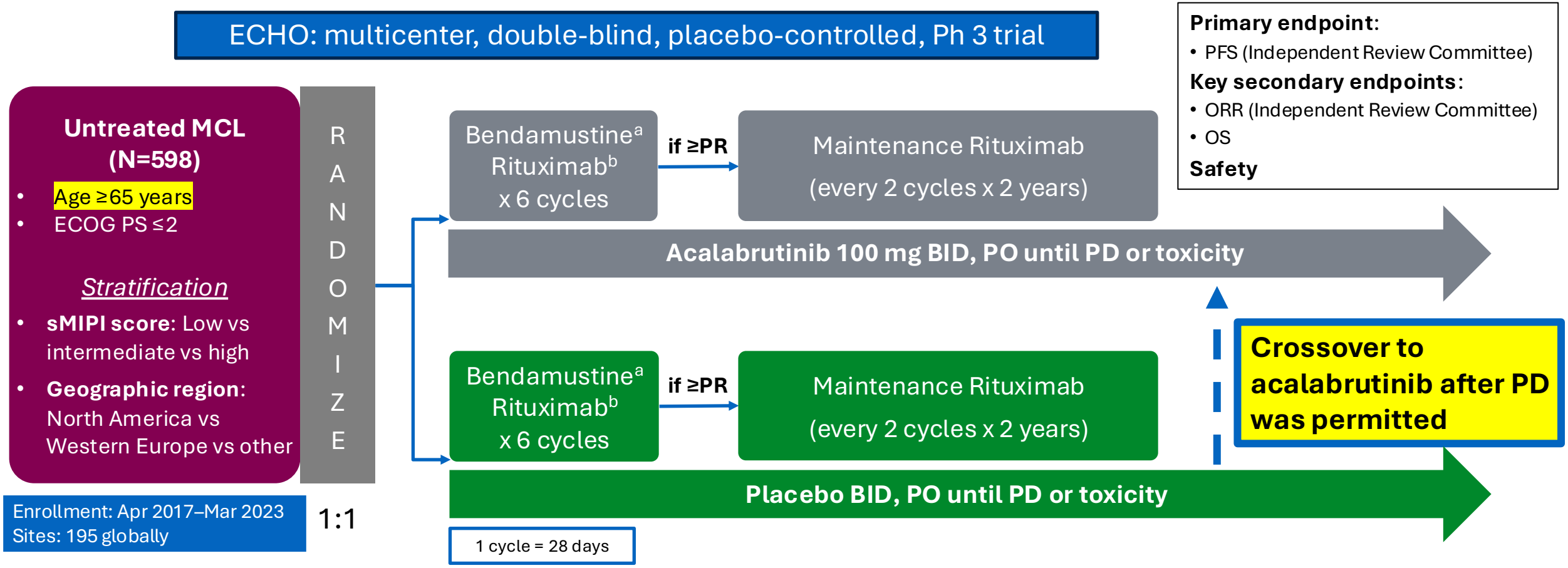


Patients at Risk

Ibrutinib + BR	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
Placebo + BR	262	244	223	212	203	197	188	177	171	165	159	154	147	137	90	31	2

Wang M et al . NEJM. 2022;[Epub].

ECHO: study Design



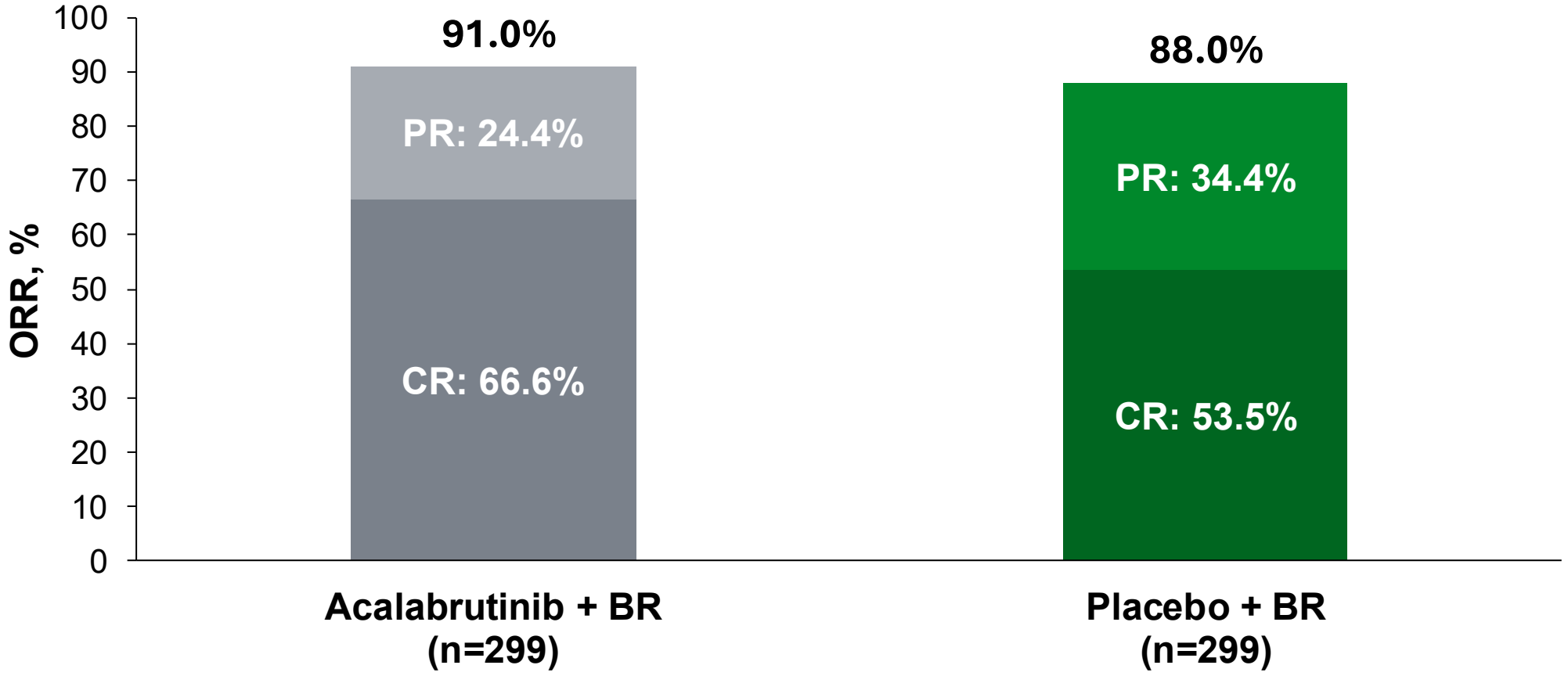
Wang M et al . J.Clin. Oncol. 2025

Demographics and Baseline Characteristics

	Acalabrutinib + BR (n=299)	Placebo + BR (n=299)
Age, median (range), y	71 (65–85)	71 (65–86)
≥75 y, n (%)	84 (28.1)	77 (25.8)
Male, n (%)	214 (71.6)	209 (69.9)
ECOG PS, n (%)		
1	129 (43.1)	132 (44.1)
2	12 (4.0)	23 (7.7)
Tumor bulk ≥5 cm, n (%)	112 (37.5)	113 (37.8)
Blastoid/pleomorphic histology, n (%)	41 (13.7)	38 (12.7)
Simplified MIPI score, n (%)		
Low risk	99 (33.1)	101 (33.8)
Intermediate risk	128 (42.8)	125 (41.8)
High risk	72 (24.1)	73 (24.4)
Extranodal disease, n (%)	264 (88.3)	277 (92.6)
TP53 status, n (%)[a]		
Mutated	22 (7.4)	29 (9.7)
Unmutated	97 (32.4)	83 (27.8)
Ki-67, n (%)		
<30%	133 (44.5)	126 (42.1)
≥30%	139 (46.5)	147 (49.2)

Best Overall Response and Complete Response Rates

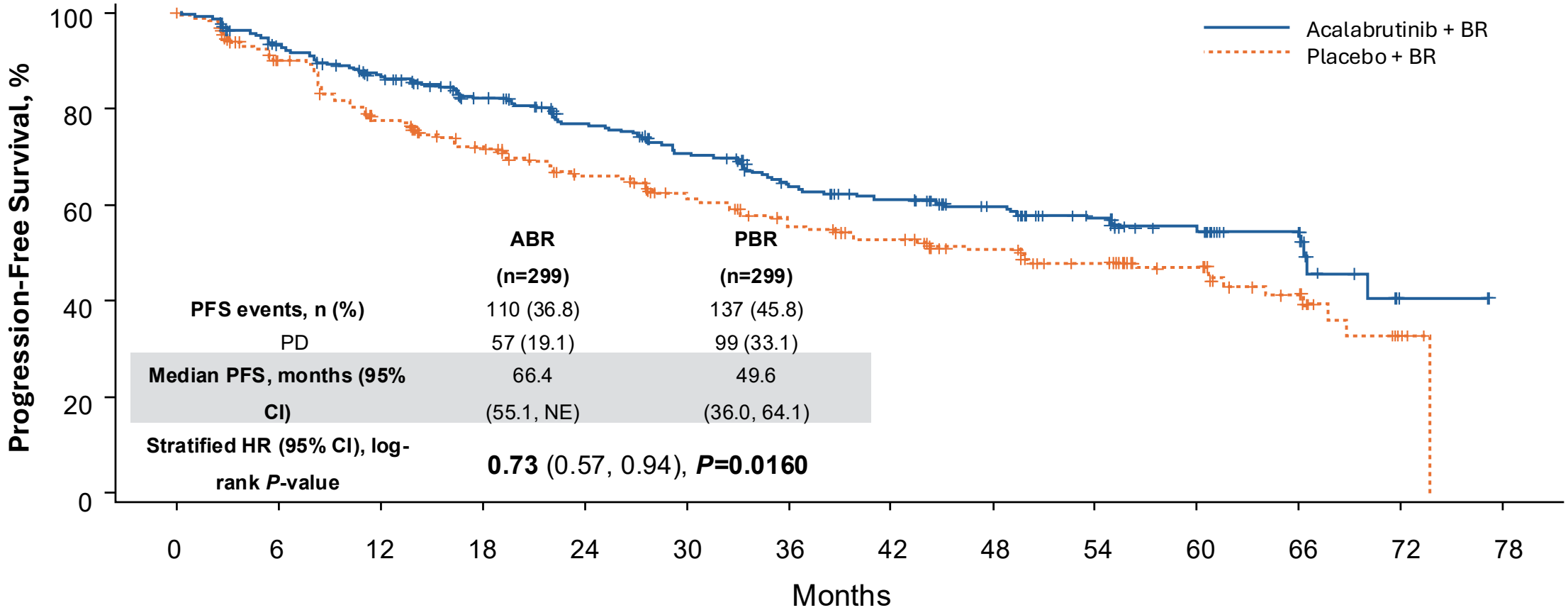
An additional 13% of patients achieved CR with acalabrutinib + BR



Wang M et al . J.Clin. Oncol. 2025

PFS (primary endpoint) Acala + BR

Median follow-up of 45 months.

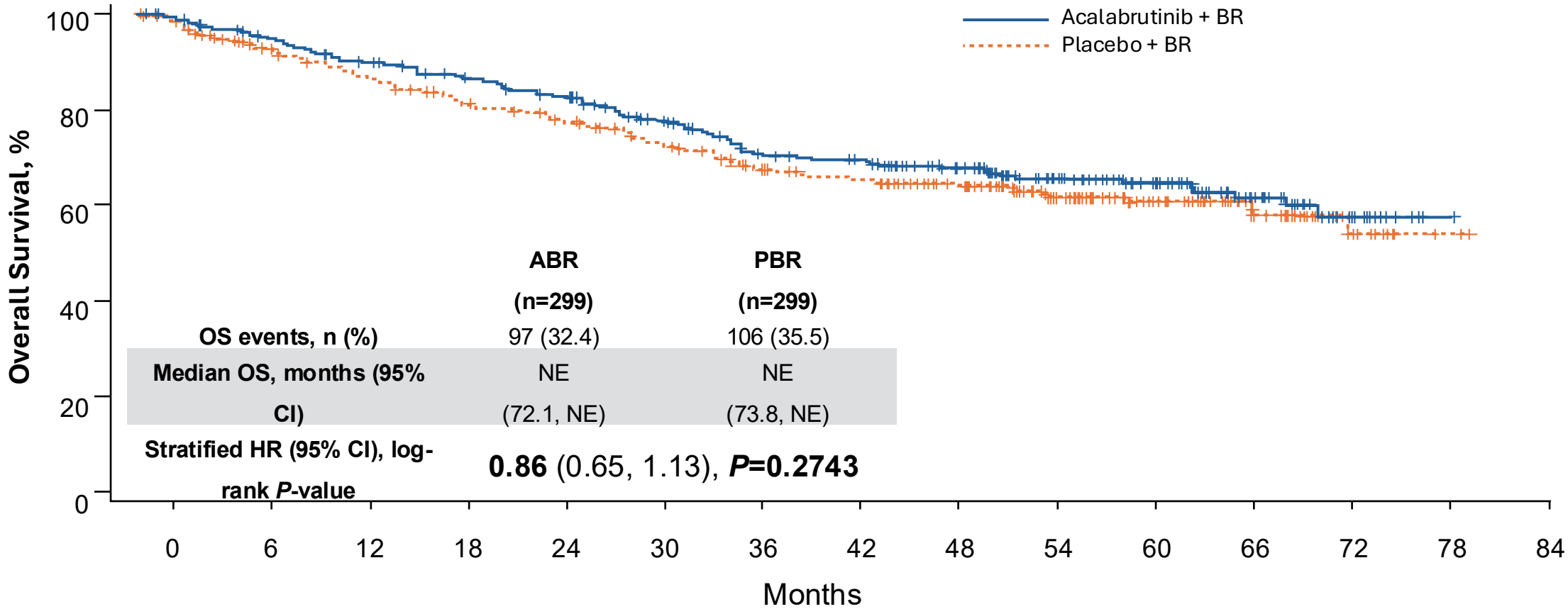


	ABR (n=299)	PBR (n=299)
PFS events, n (%)	110 (36.8)	137 (45.8)
PD	57 (19.1)	99 (33.1)
Median PFS, months (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
Stratified HR (95% CI), log-rank *P*-value	**0.73** (0.57, 0.94), ***P*=0.0160**	

Number at risk														
Acala + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

Overall Survival Including Crossover

Median follow-up of 45 months.



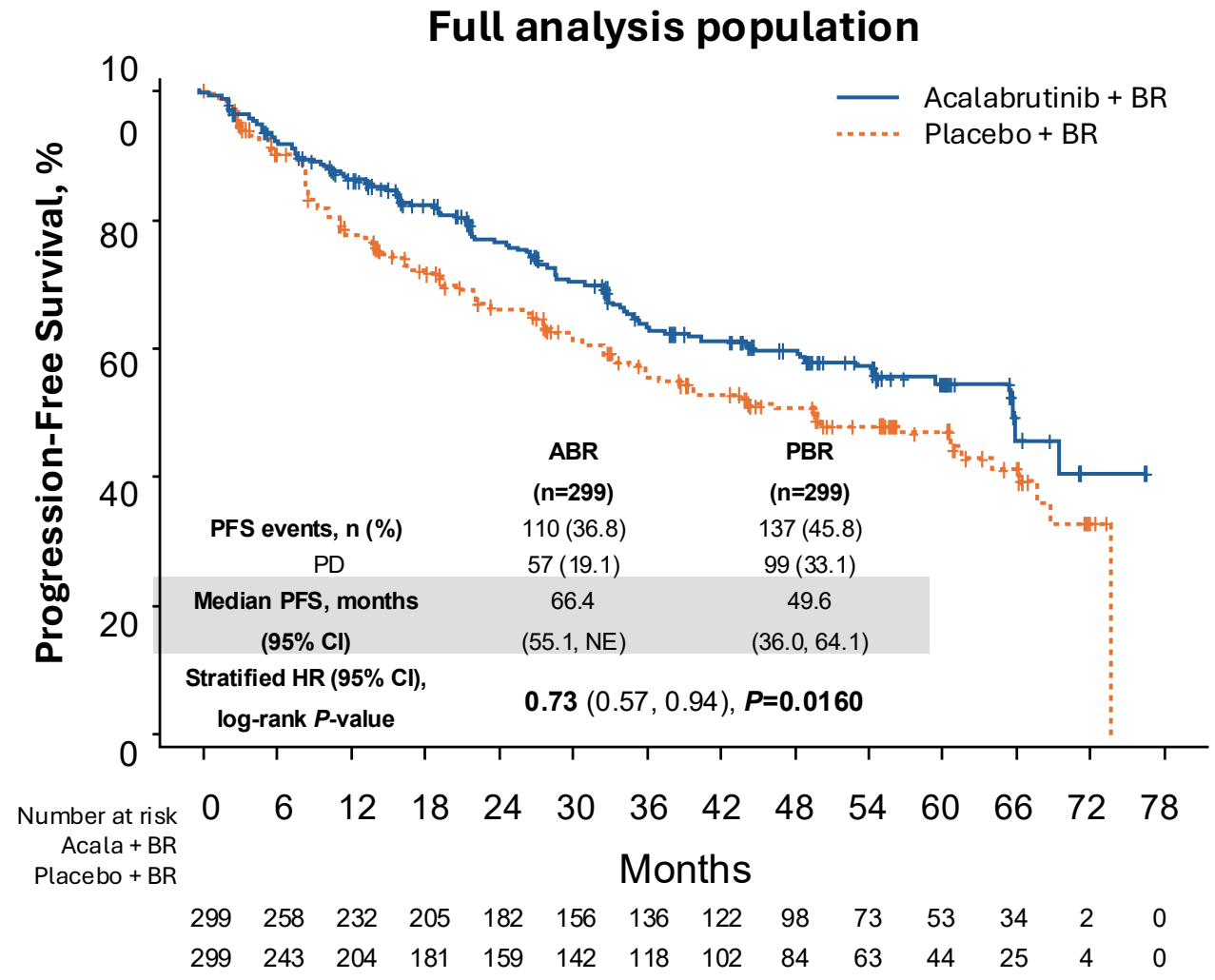
	ABR (n=299)	PBR (n=299)
OS events, n (%)	97 (32.4)	106 (35.5)
Median OS, months (95% CI)	NE (72.1, NE)	NE (73.8, NE)
Stratified HR (95% CI), log-rank *P*-value	**0.86** (0.65, 1.13), ***P*=0.2743**	

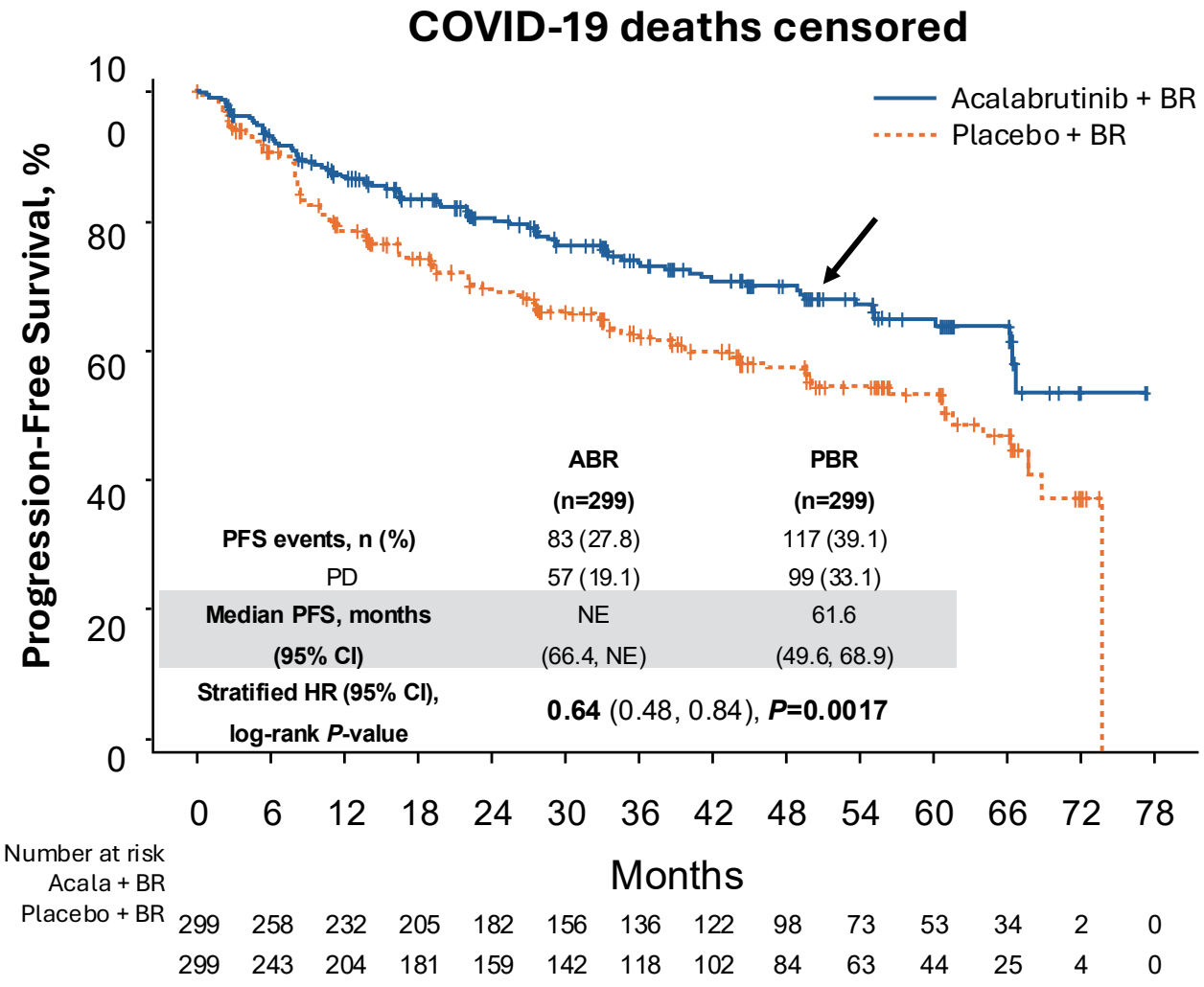
Number at risk															
Acala + BR	299	280	259	243	230	207	181	163	146	110	86	58	25	3	0
Placebo + BR	299	268	247	229	215	193	175	157	141	108	78	51	21	3	0

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)	

PFS With and Without COVID-19 Deaths

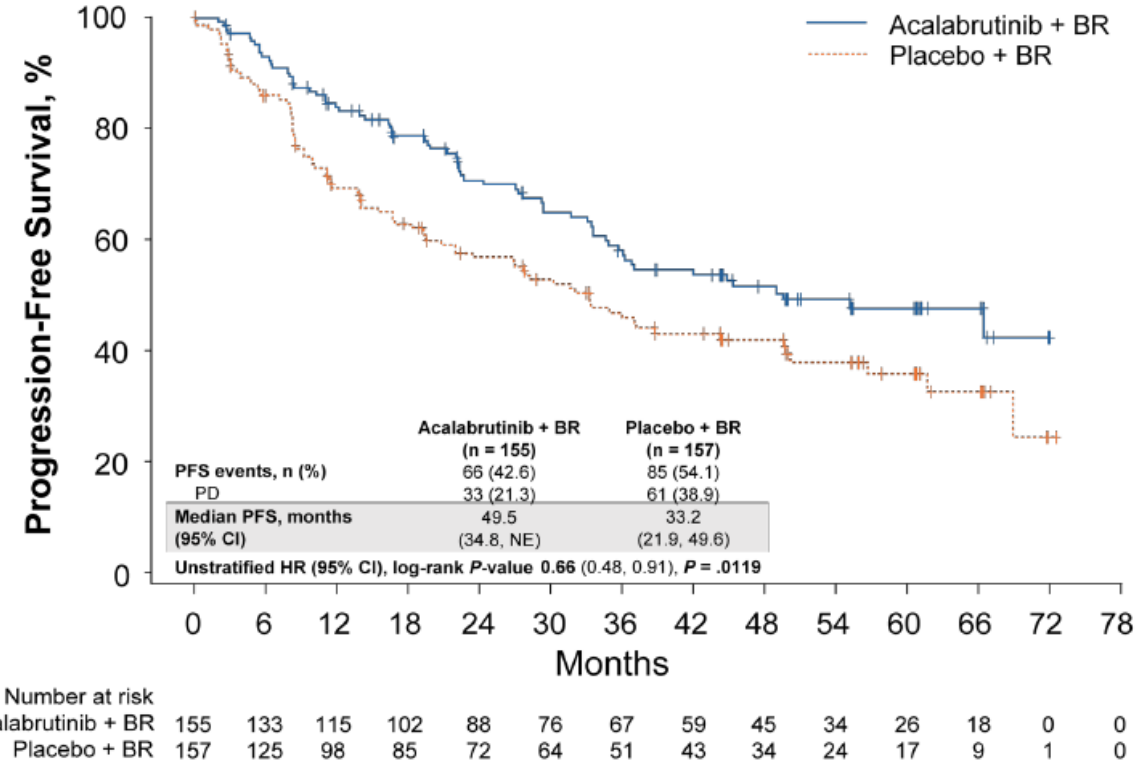




36% risk reduction when **censoring COVID-19 deaths**

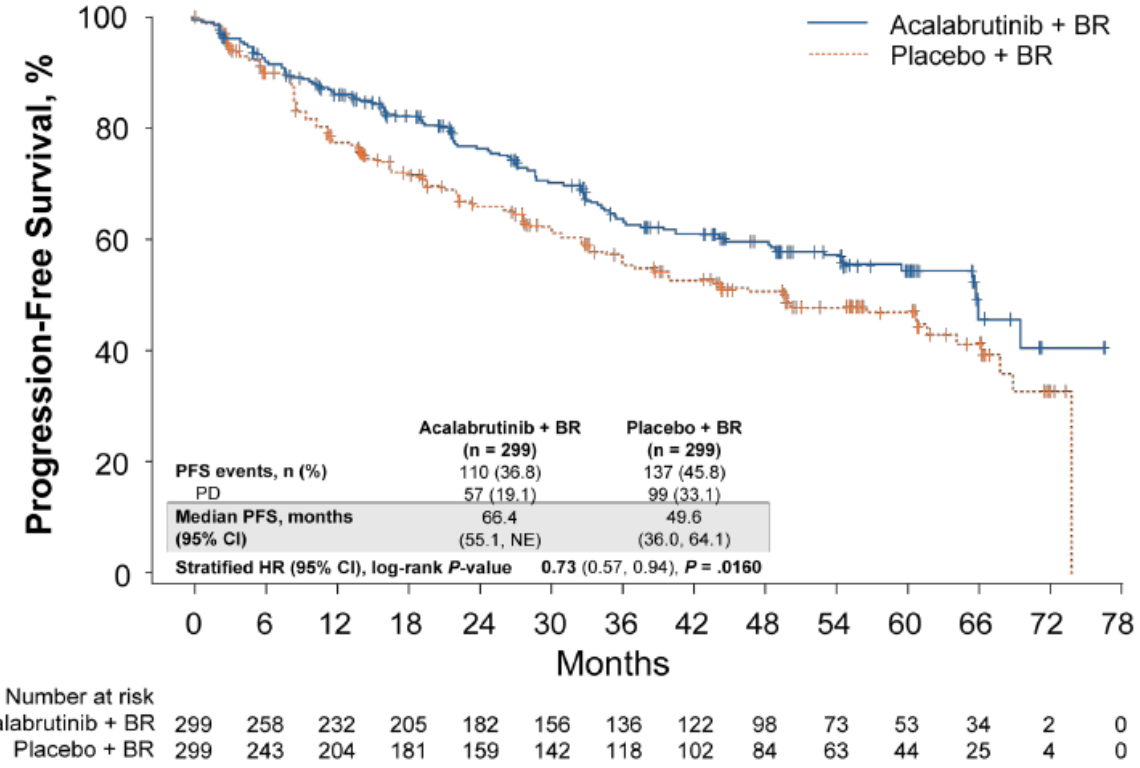
ECHO High risk Analysis: PFS

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



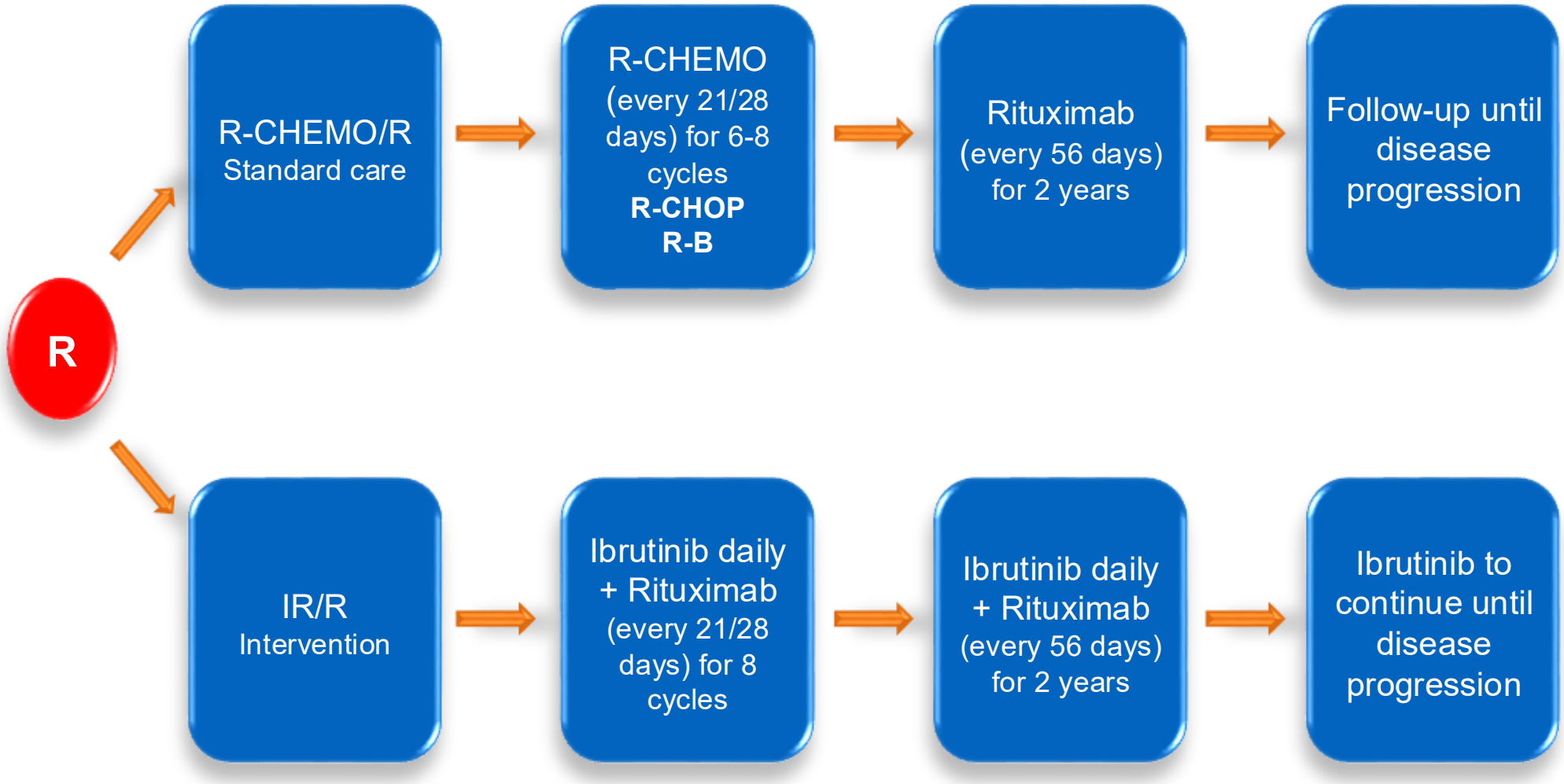
Number at risk														
Acalabrutinib + BR	155	133	115	102	88	76	67	59	45	34	26	18	0	0
Placebo + BR	157	125	98	85	72	64	51	43	34	24	17	9	1	0

PFS in Full Analysis Population[1]



Number at risk														
Acalabrutinib + BR	299	258	232	205	182	156	136	122	98	73	53	34	2	0
Placebo + BR	299	243	204	181	159	142	118	102	84	63	44	25	4	0

Elderly mantle cell lymphoma ENRICH – NCRI multicentre Randomised open label phase II/III trial



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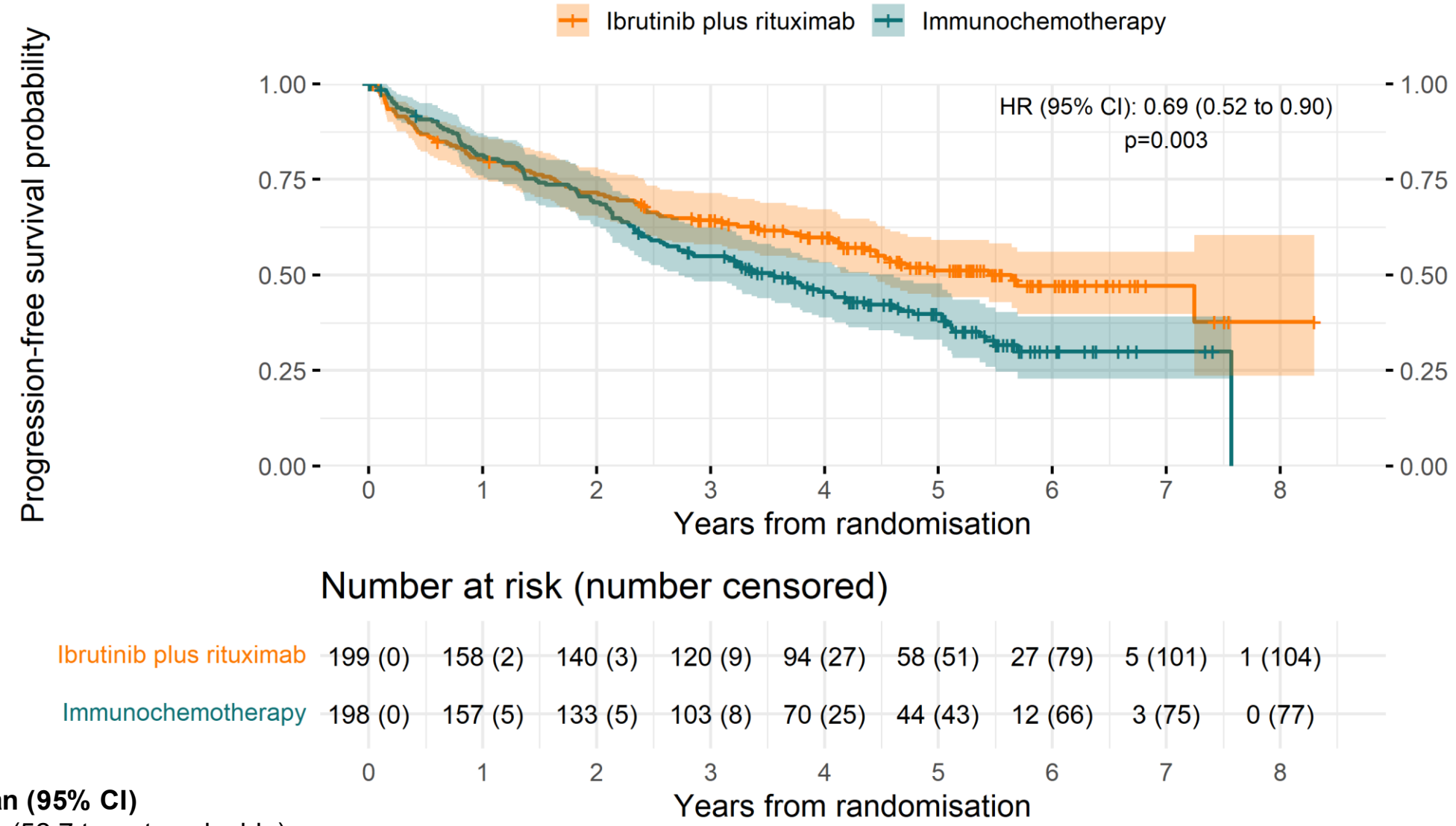
Progression-free survival



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

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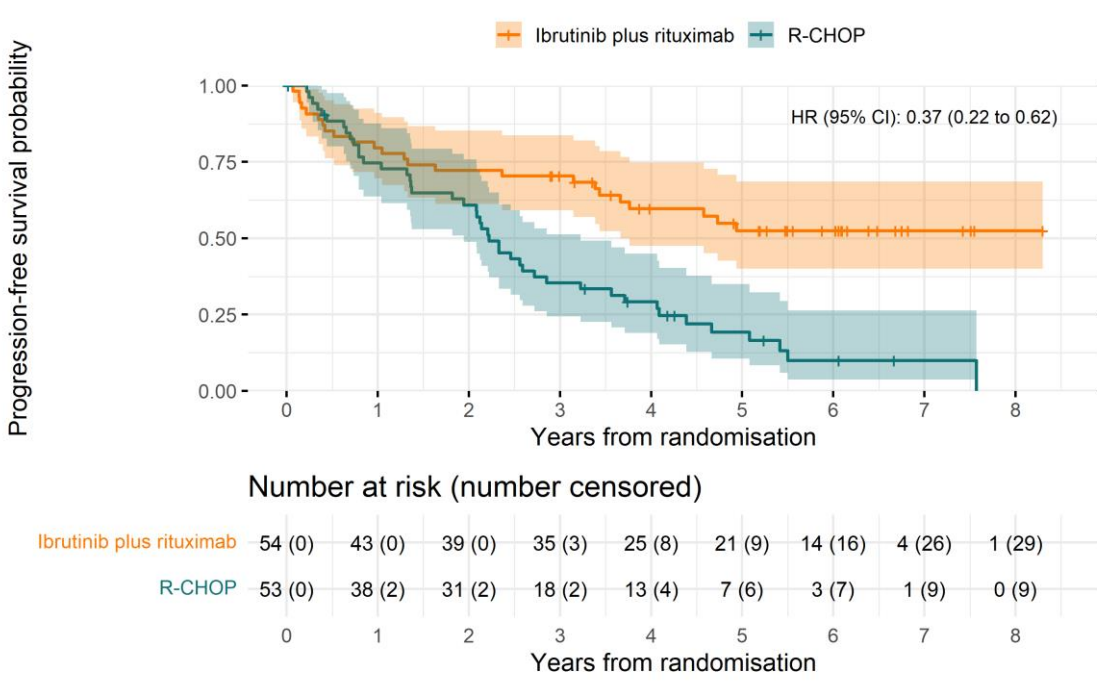
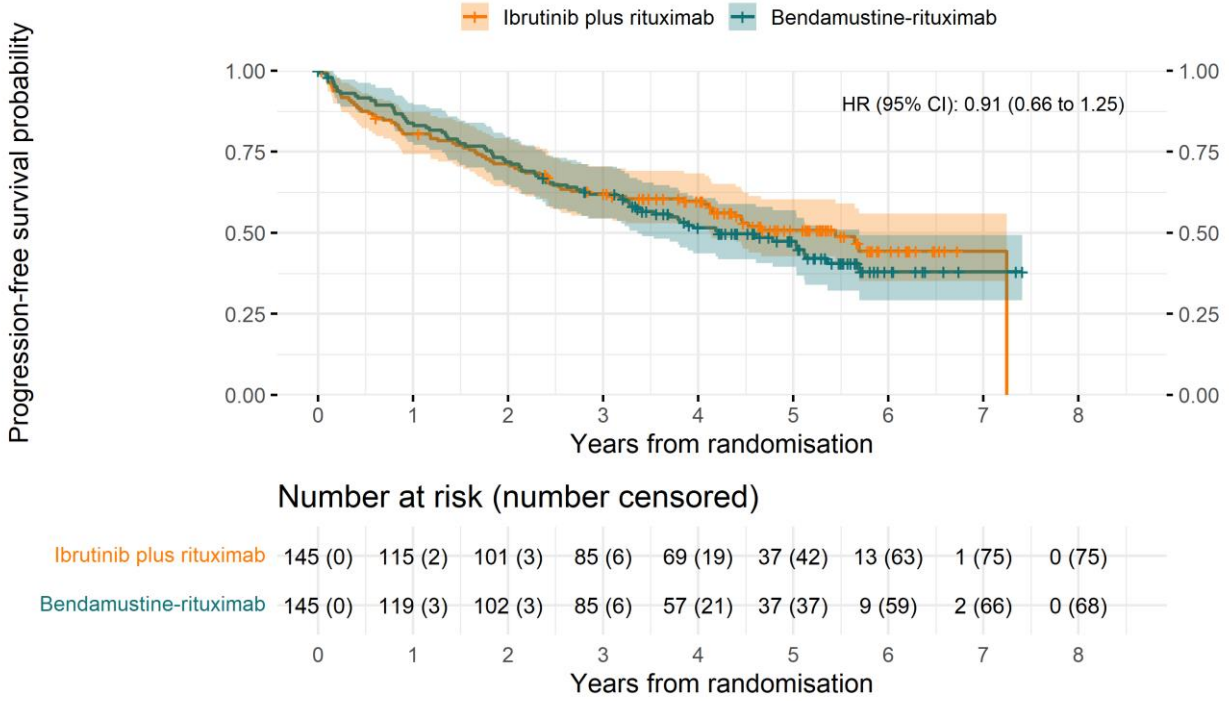
PFS for R-CHOP and BR choice





5-year PFS (95% CI)
IR: 52.4% (40.0% to 68.6%)
R-CHOP: 19.2% (10.6% to 35.1%)

5-year PFS (95% CI)
IR: 50.8% (42.8% to 60.4%)
BR: 47.4% (39.5% to 56.9%)

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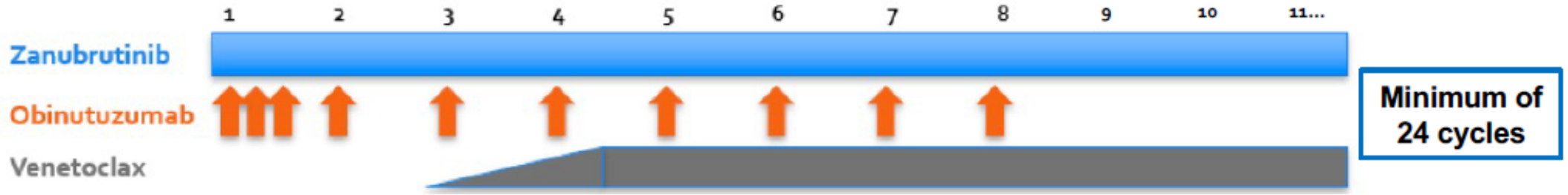
BOVen study design



Dosing:

Zanubrutinib 160 mg oral twice daily

Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

CR and uMRD6 →	Stop treatment
<CR and/or dMRD6 →	Continue ZANU and VEN

Key Eligibility Criteria:

- Previously untreated MCL
- ≥ 65 years of age or with comorbidities precluding autologous stem cell transplantation
- ECOG ≤2, adequate organ and hematologic function (ANC >1, PLT >75, HGB ≥9 (unless due to MCL))

Primary Endpoint:

- 3-year progression-free survival
- A promising 3-yr PFS rate ≥70% and an unacceptable rate ≤50% (historical comparison to Bendamustine-Rituximab)

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Baseline clinical characteristics (50 pts)

Characteristic	N(%)
Enrollment Site	
Memorial Sloan Kettering	20 (40%)
Massachusetts General Hospital	27 (54%)
Northwestern University	3 (6%)
Age in years	
Median (range)	72 (47-89)
≥75 years of age	17 (34%)
Sex	
Male	32 (64%)
MCL Histology	
Classical	35 (73%)
Blastoid/Pleomorphic	7 (15%)
Non-nodal leukemic	6 (13%)
Unknown	2
MIPI Classification	
Low	4 (8%)
Intermediate	11 (22%)
High	35 (70%)

Characteristic	N(%)
Ki-67 Proliferation Rate	
<30%	24 (49%)
≥30% and <50%	11 (22%)
≥50%	14 (29%)
Unknown	1
***TP53* mutation by NGS**	
Yes	13 (28%)
No	33 (72%)
Unknown	4
17p deletion by FISH / SNP Array	
Yes	10 (20%)
No	40 (80%)
Unknown	
TP53 Mutation and 17p deletion	
Yes	7 (14%)
No	39 (78%)
Unknown	4

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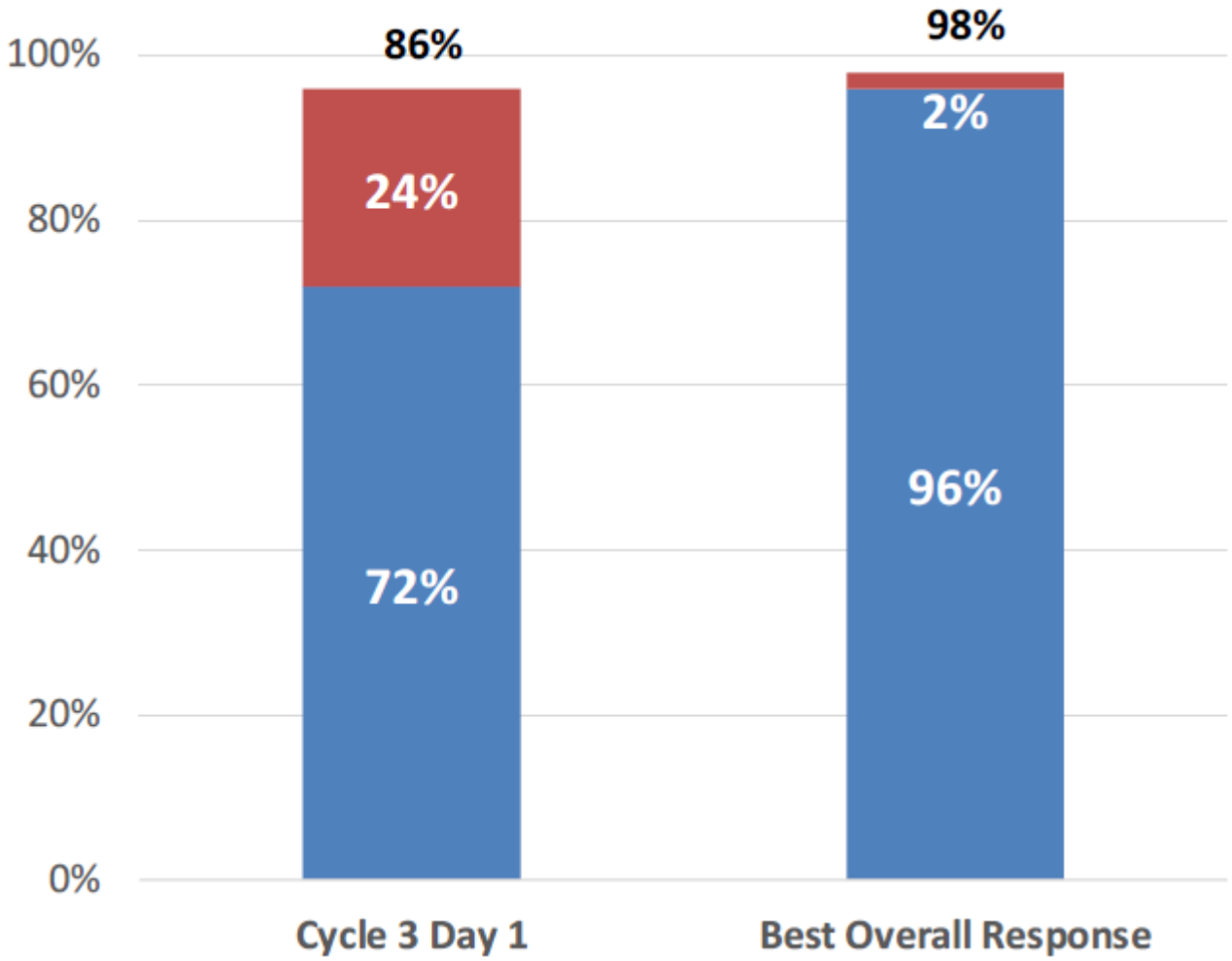
Metabolic response



High Overall Metabolic Response Rate

- Partial metabolic response
- Complete metabolic response

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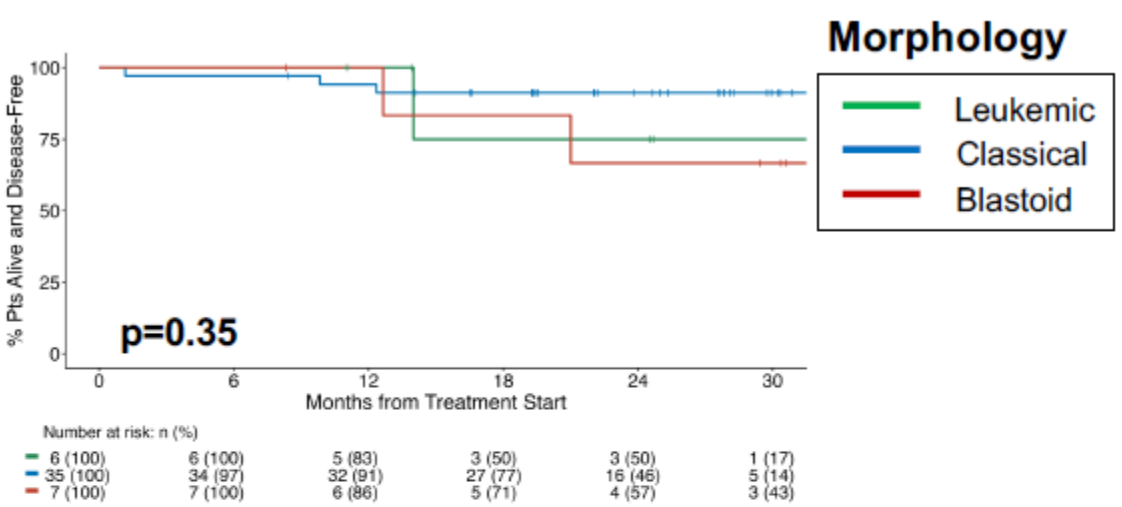
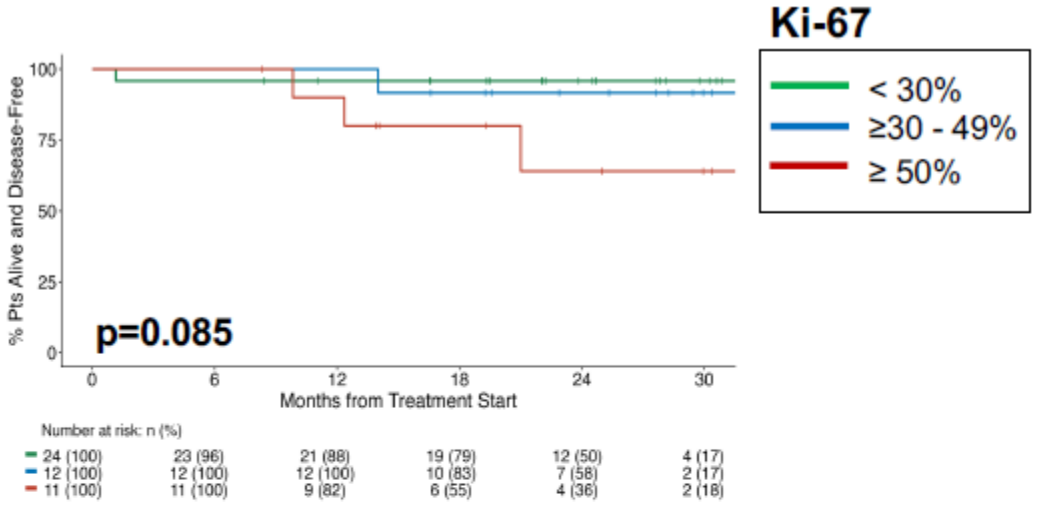
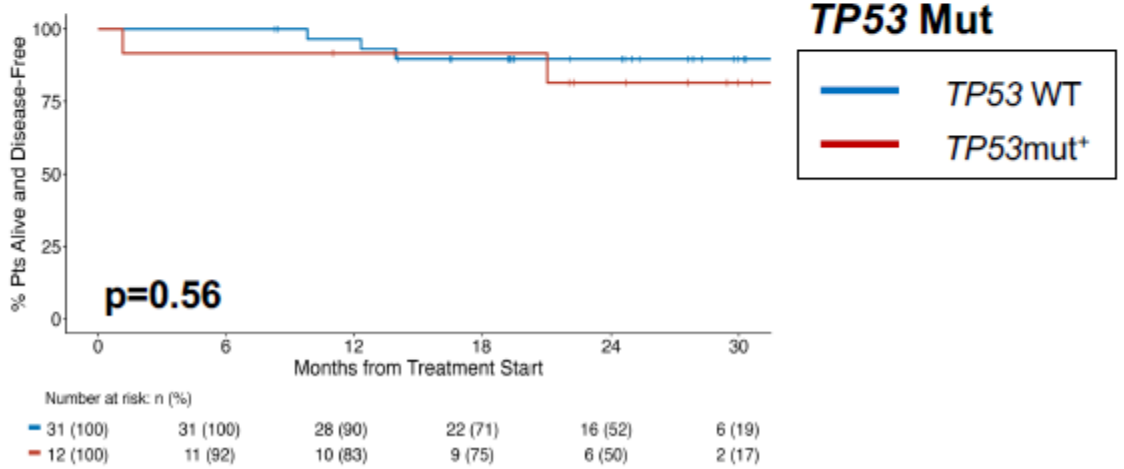
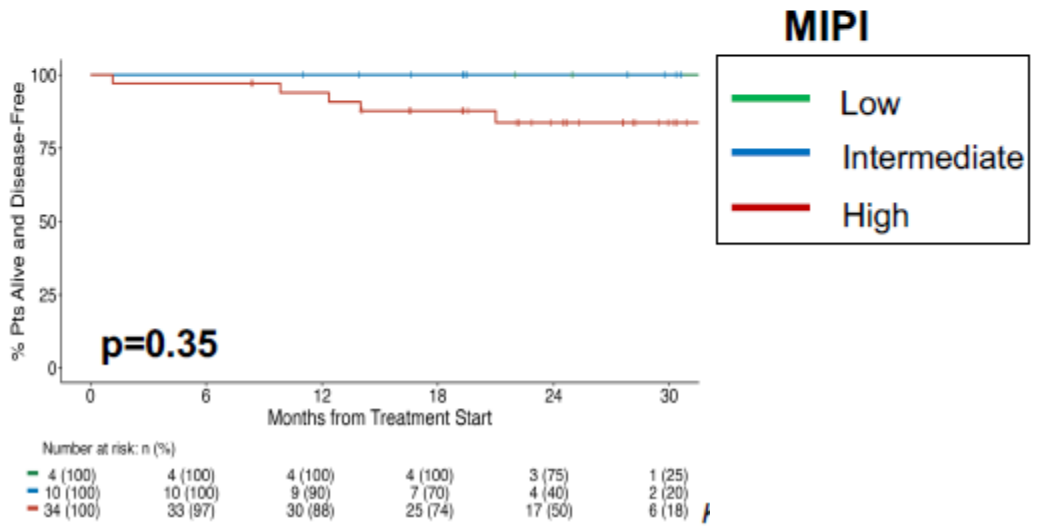
PFS by baseline factors









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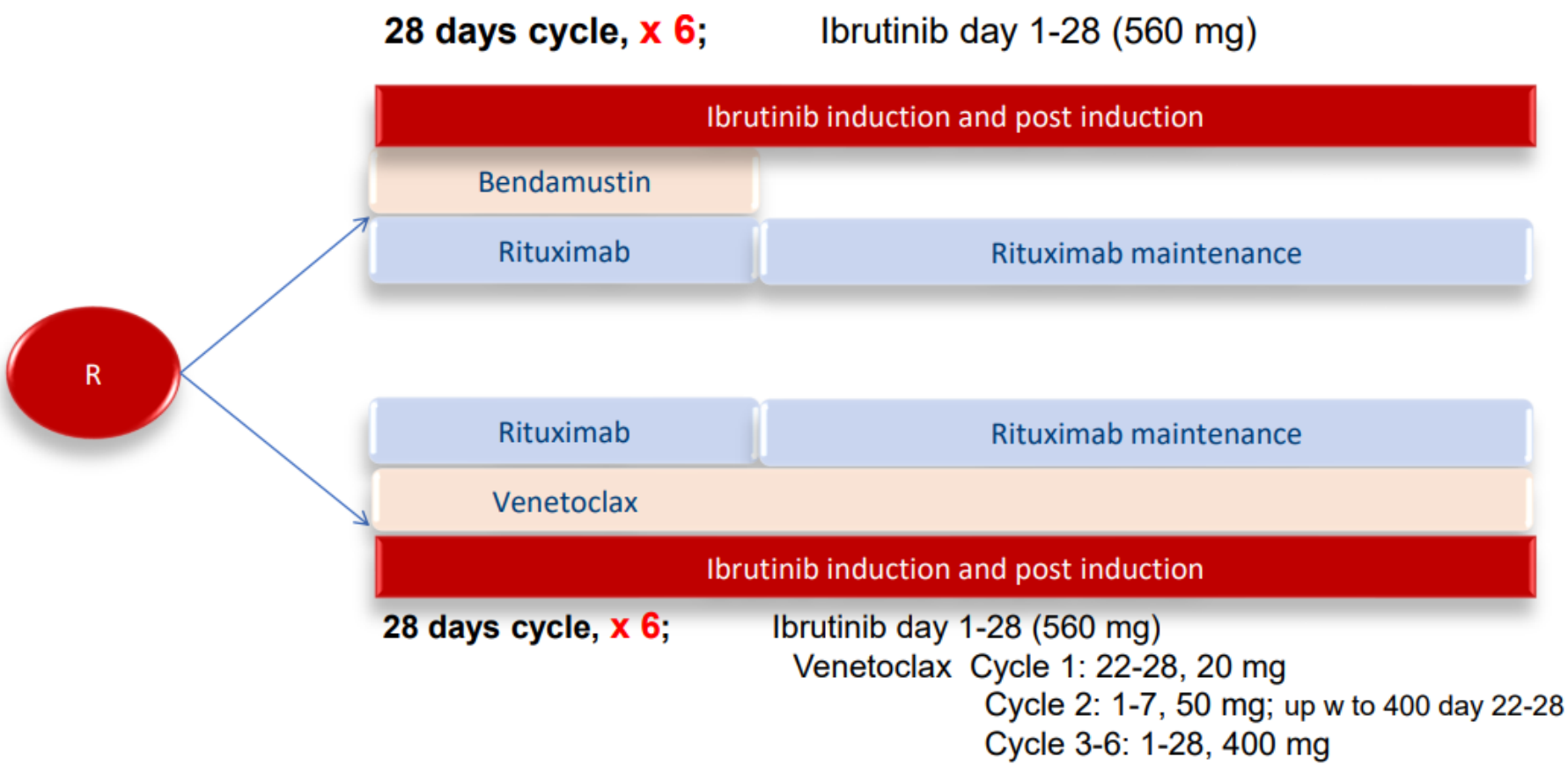
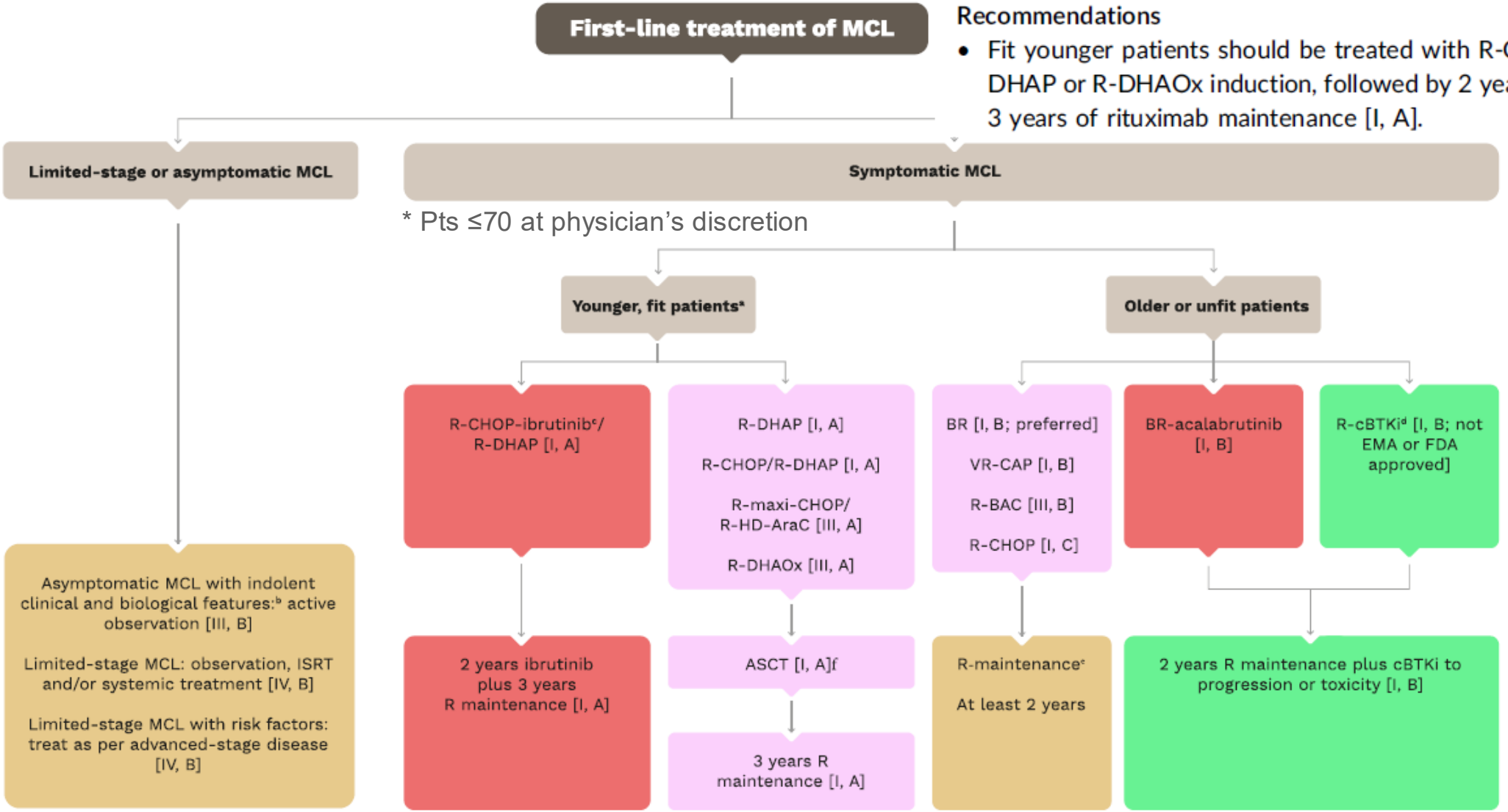
VIRAL: study design



Conclusions

- The Triangle regimen (R-CHOP/R-DHAP plus Ibrutinib followed by R+Ibrutinib for 2 y) has enchaced the treatment of algorithm of mantle cell lymphoma
- The Triangle regimen will become the standard treatment for MCL pts ≤65 years and for selected fit patients from 65 y to ≤70 years (depending on the reimbursement label), who are eligible for R-CHOP/R-DHAP induction therapy
- High-Risk MCL is still un unmet medical need however, the results of Triangle (+/- ASCT) in this population are promising, but not all patients achieving durable complete remission
- Future new chemo-free treatment strategy may improve the outcome of High Risk MCL patients

EHA-EU MCL GUIDELINES



Recommendations

- Fit younger patients should be treated with R-CHOP-Ibrutinib/R-DHAP or R-DHAOx induction, followed by 2 years of ibrutinib and 3 years of rituximab maintenance [I, A].

Jerkeman M et al, Hemasphere 2025

Treatment algorithm

Upfront

Standard first line

TRIANGLE-like + Ibrutinib (no ASCT)

BR+R + Acalabrutinib [R-BAC500]

Gruppo per la terapia dei linfomi non Hodgkin
Ematologia Sapienza Roma

Roche

SAPIENZA
UNIVERSITÀ DI ROMA

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERO-UNIVERSITARIA
POLICLINICO UMBERTO I

FONDAZIONE
ITALIANA
LINFOMI

Grazie!

… a voi tutti per l'attenzione

Hematological ONCOLOGY

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