Algoritmo di trattamento nel linfoma mantellare

Carlo Visco

CAR-T:
e la storia continua...
migliorando

Verona, 11 novembre 2024
Hotel Indigo Verona – Grand Hotel Des Arts

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	X				X	X	
Kite-Gilead						X	
Janssen	x		x		X	X	
Gentili					X	X	
Novartis						X	
Pfizer			x		X	X	
Roche						X	
Incyte					X	X	
Servier					X		
Astra Zeneca					X		
BMS						X	
Kyowa Kirin					X		

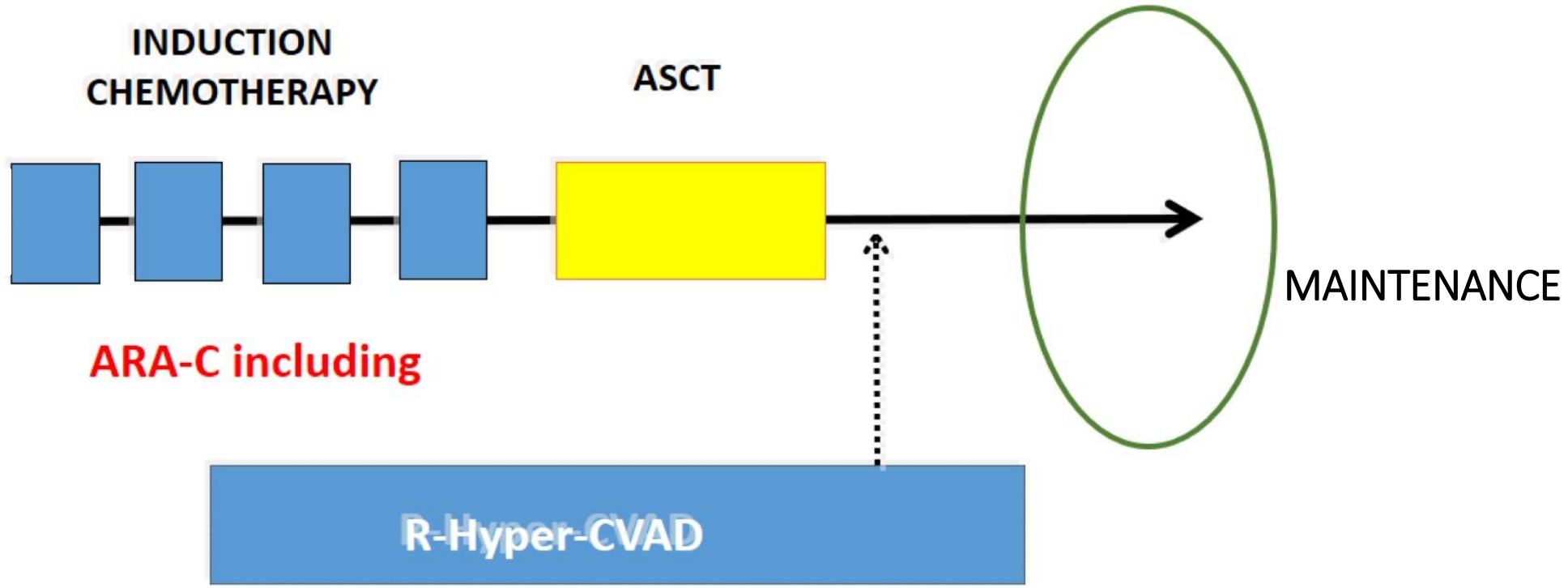
Updates

- How induction treatment is changing

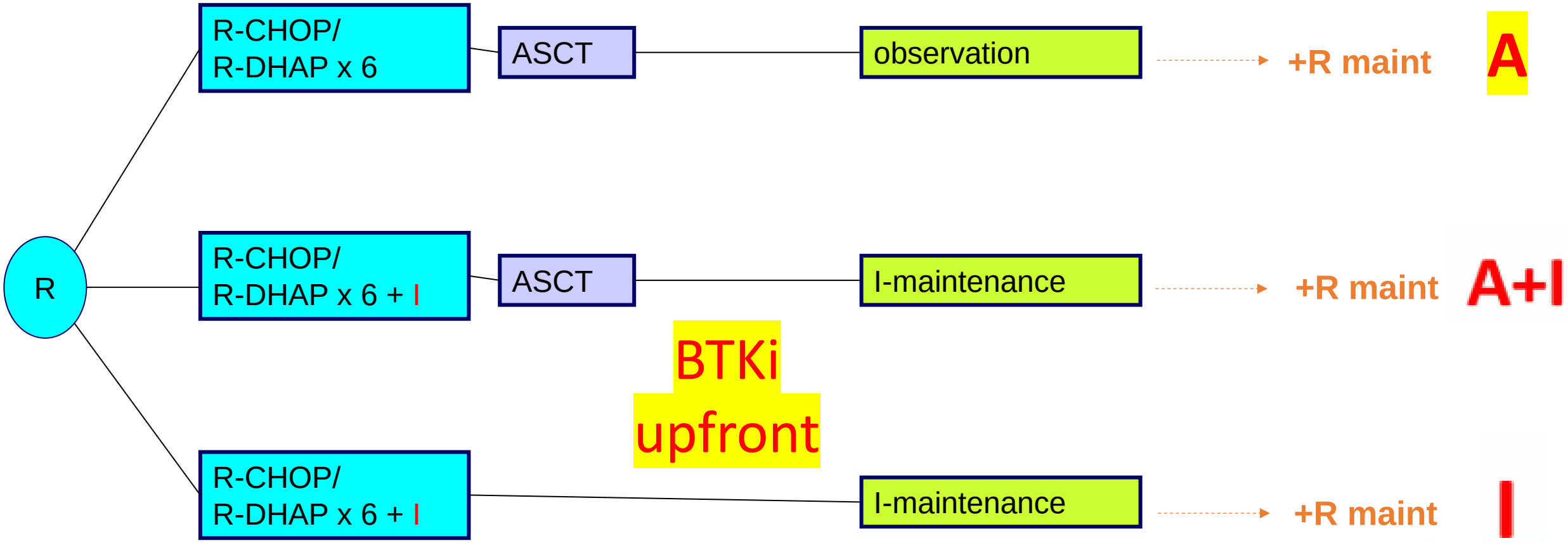
Challenges

- R/R patients
- High-risk subgroups

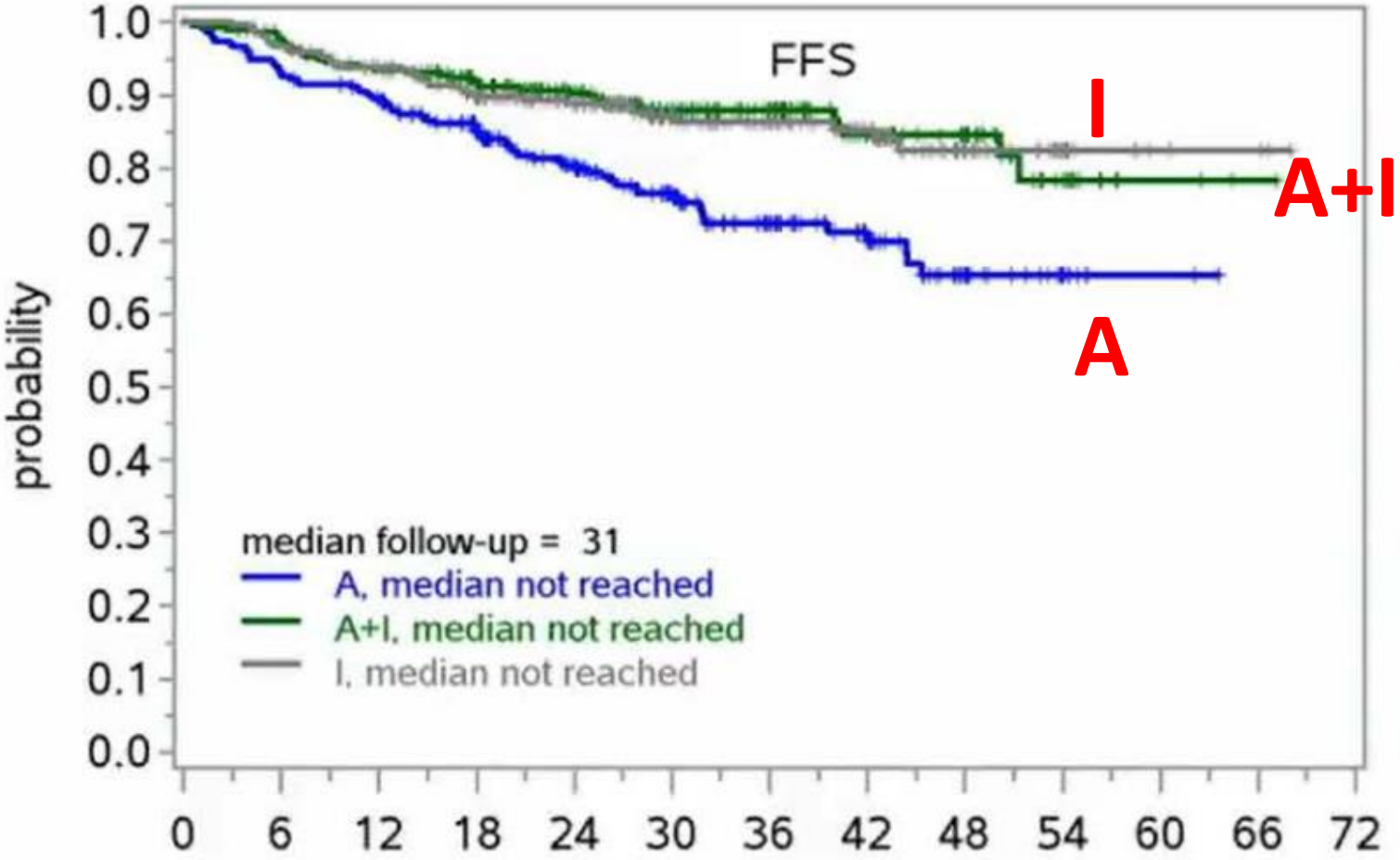
Standard upfront regimens for younger/fit patients



TRIANGLE Phase III Trial



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

Induction strategies in the elderly population

2 randomized studies
favour the use of R-Benda

R-CHOP platform

Add on with:

- Rituximab Maintenance
- Bortezomib
- Cytarabine/Lenalidomide°

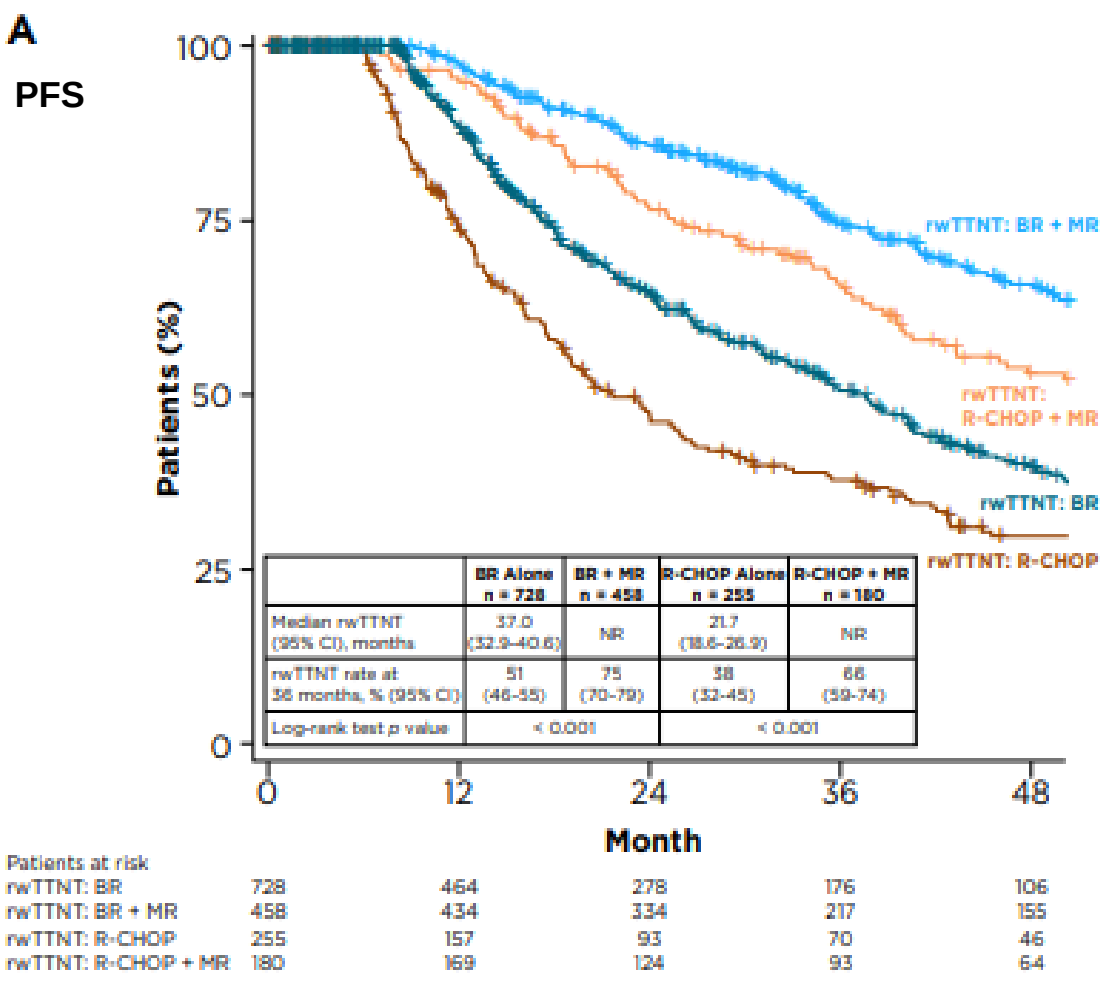
R-Benda platform

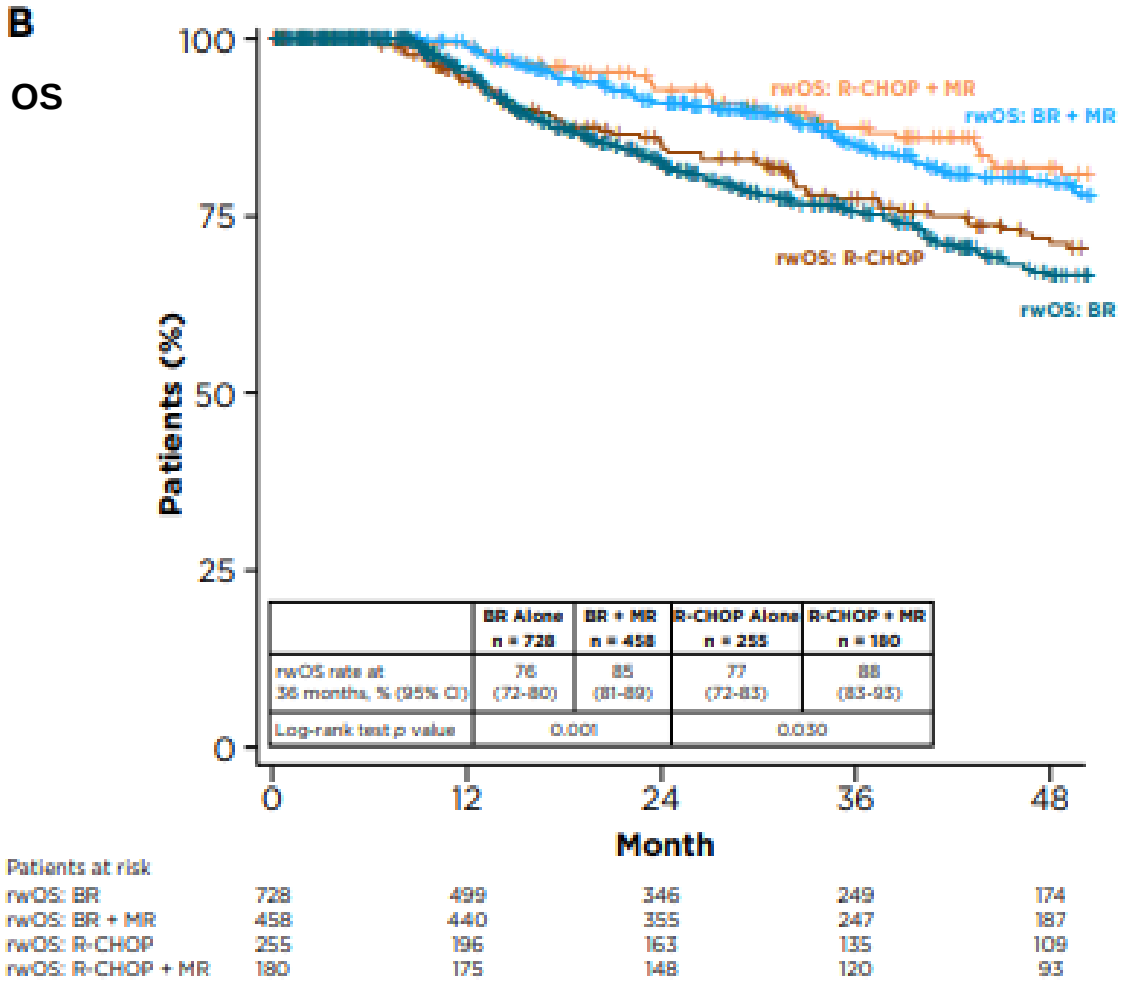
Add on with:

- Rituximab Maintenance
- Lenalidomide
- Bortezomib/Lenalidomide°
- Ibrutinib°
- Cytarabine
- Temsirolimus

Elderly patients

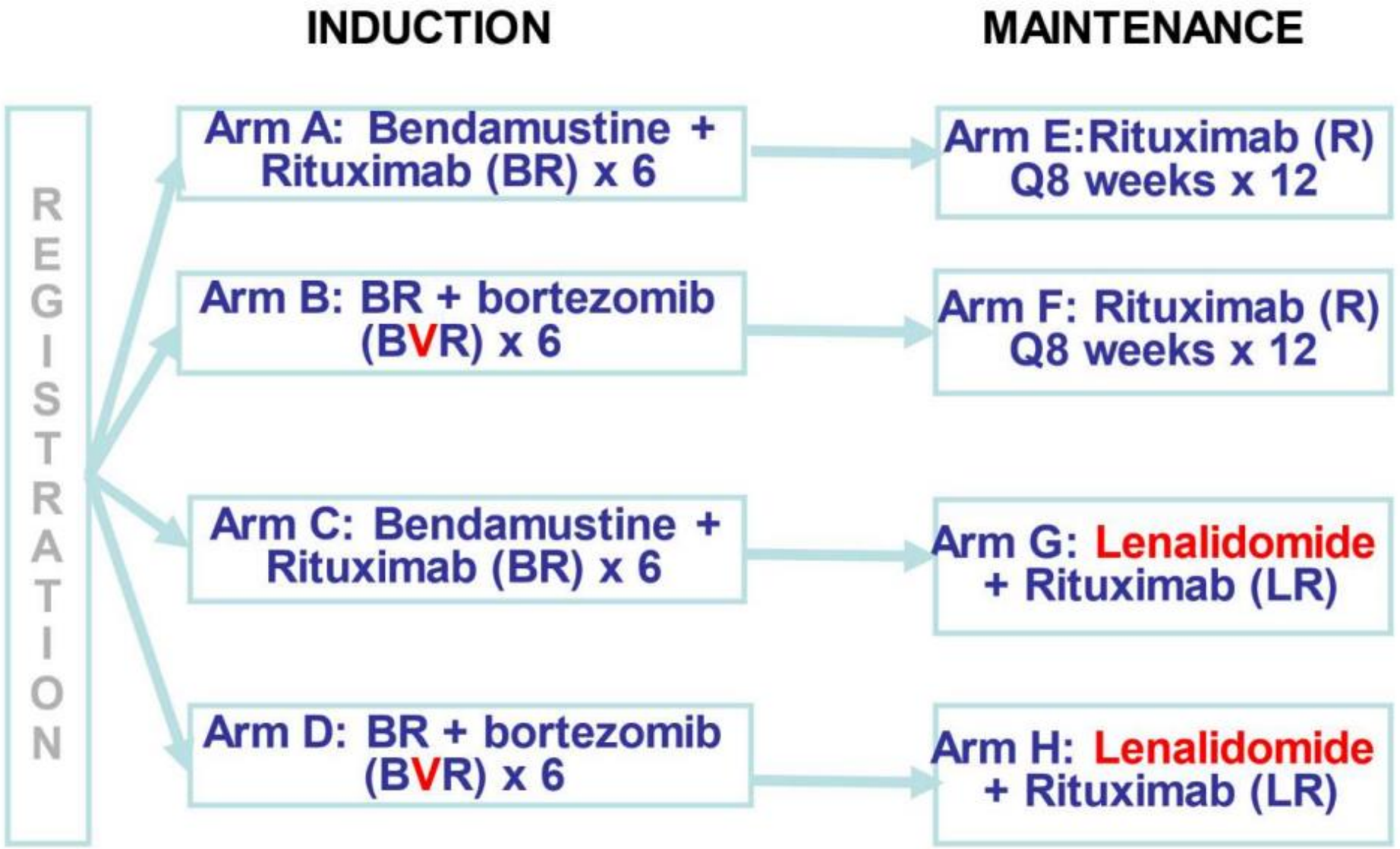
Role of maintenance after 1st line in the elderly population (real life)





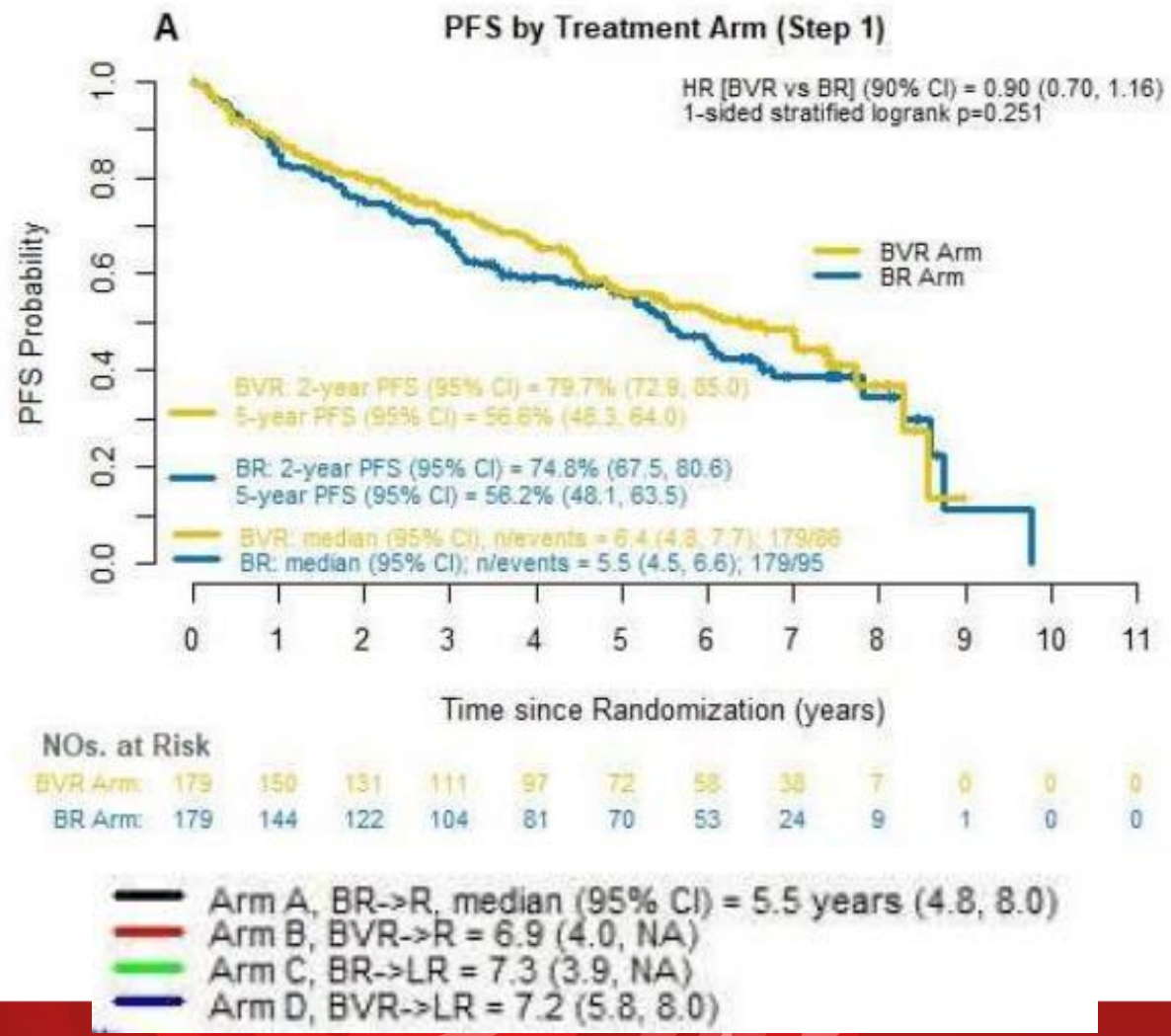
Wang et al, ASCO 2021

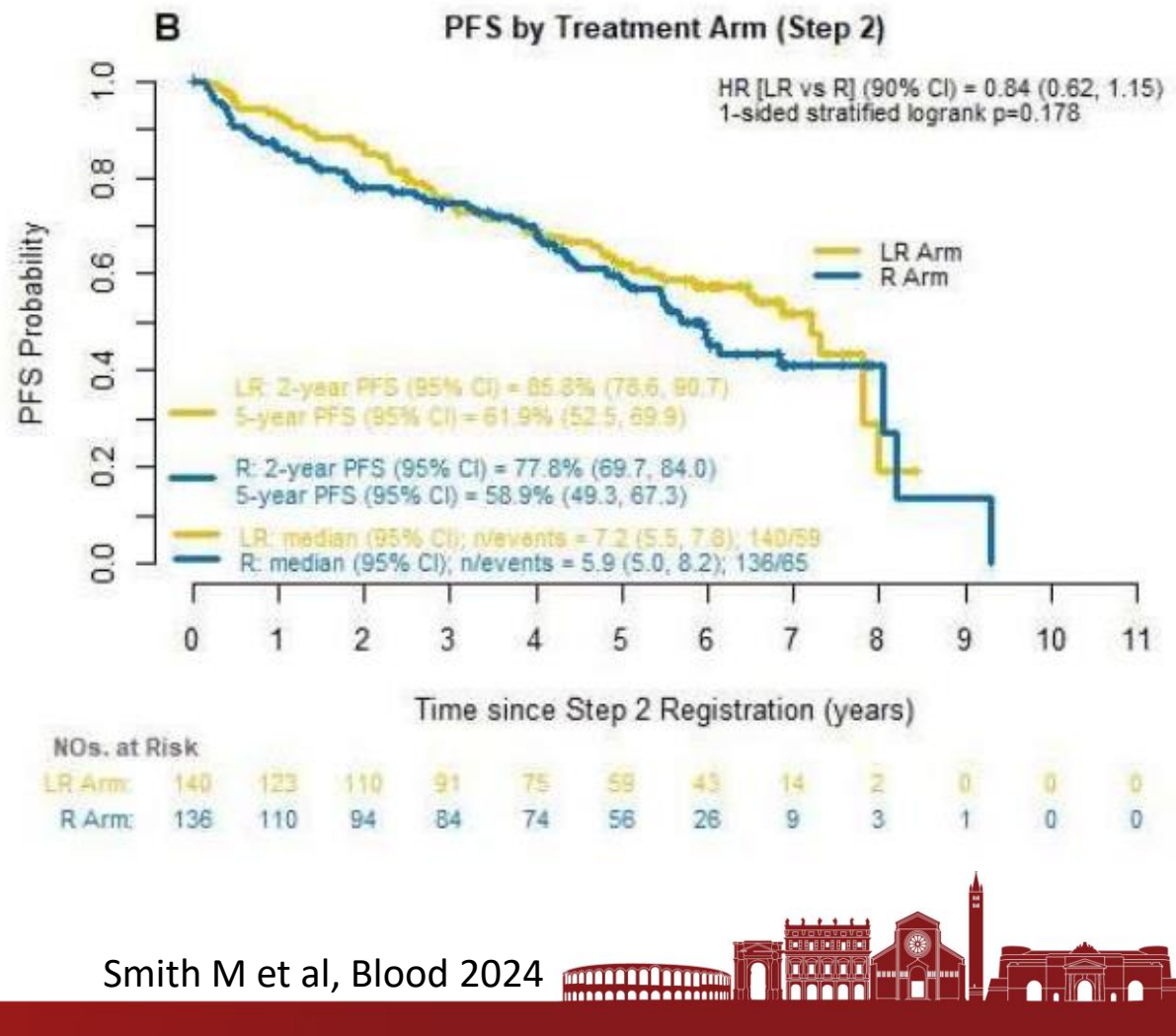
North American Cooperative Group, phase 2 E1411 trial [adding Lena/Bortezomib]



Median age 67 (42-90)

North American Cooperative Group, phase 2 E1411 trial [adding Lena/Bortezomib]





Arm A, BR->R, median (95% CI) = 5.5 years (4.8, 8.0)
Arm B, BVR->R = 6.9 (4.0, NA)
Arm C, BR->LR = 7.3 (3.9, NA)
Arm D, BVR->LR = 7.2 (5.8, 8.0)

Smith M et al, Blood 2024

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

Patients

- Previously untreated MCL
- ≥ 65 years of age
- Stage II-IV disease
- No planned stem cell transplant

Stratification factor

- Simplified MIPI score (low vs intermediate vs high)

Enrolled between May 2013 and November 2014 at 183 sites

N =

R 1:1

BR induction for 6 cycles → **if CR or PR** → **R**ituximab maintenance every 8 weeks for 12 cycles

Ibrutinib 560 mg (4 capsules daily) until PD or unacceptable toxicity

BR induction for 6 cycles → **if CR or PR** → **R**ituximab maintenance every 8 weeks for 12 cycles

Placebo (4 capsules daily) until PD or unacceptable toxicity

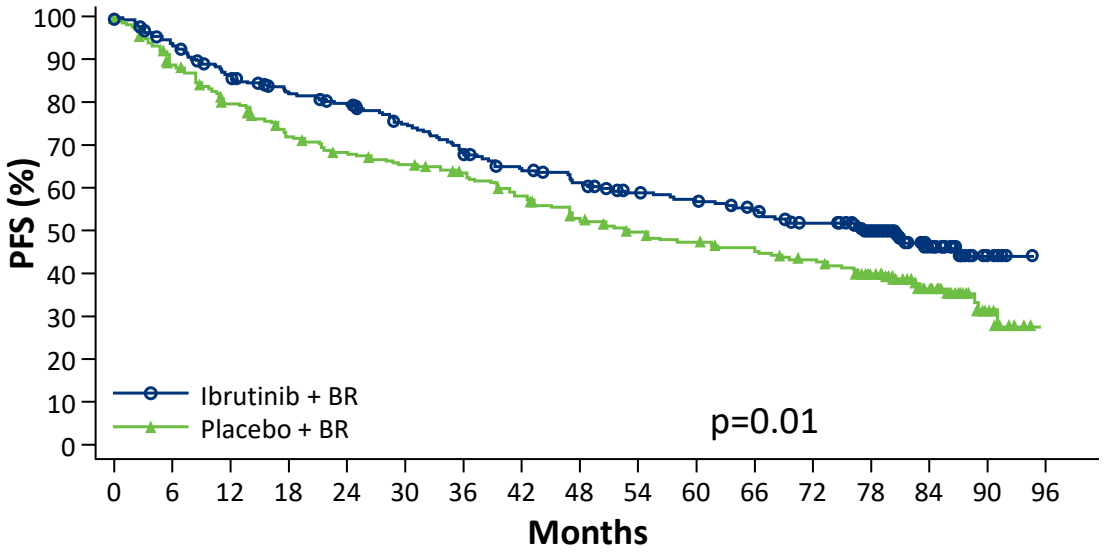
Primary end point: PFS (investigator-assessed) in the ITT population

Key secondary end points: response rate, time to next treatment, overall survival, safety

Induction: **B**endamustine 90 mg/m2 Days 1 and 2, **R**ituximab 375 mg/m2 Day 1, Q4W. A cycle is defined as 28 days.
CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.

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

Median PFS 6.7 vs 4.4 years

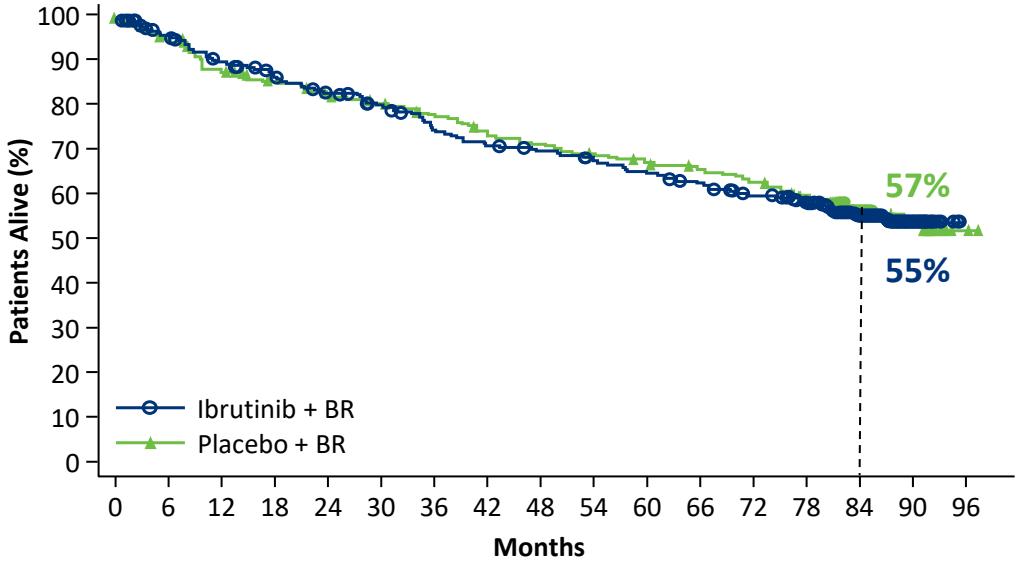


Patients at Risk

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

R-BAC500
median PFS not reached
at 7 years

Tisi et al, BA 2022



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 ML et al, NEJM 2022

ECHO, double blind Phase III trial

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: Apr 2017–Mar 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

Primary endpoint:
- PFS (Independent Review Committee)

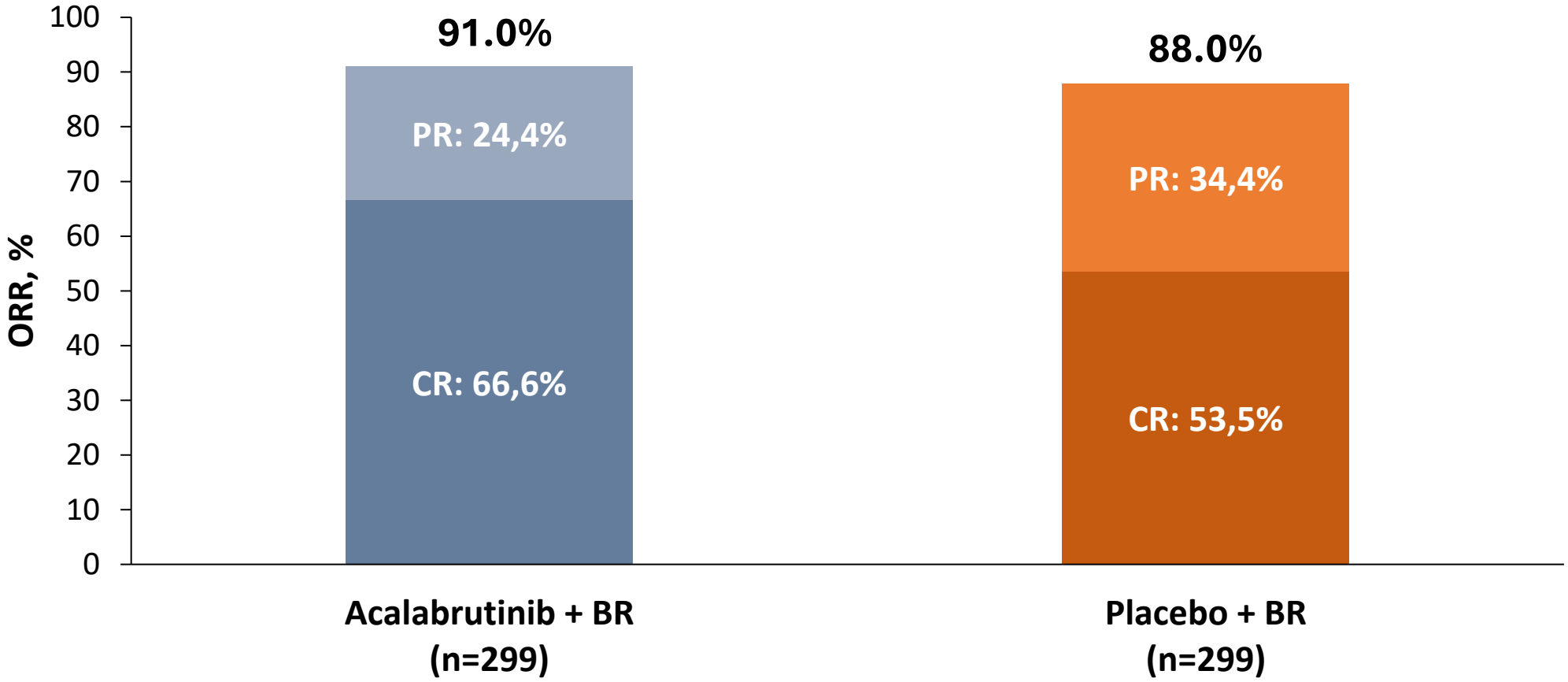
Key secondary endpoints:
- ORR (Independent Review Committee)
- OS

Safety

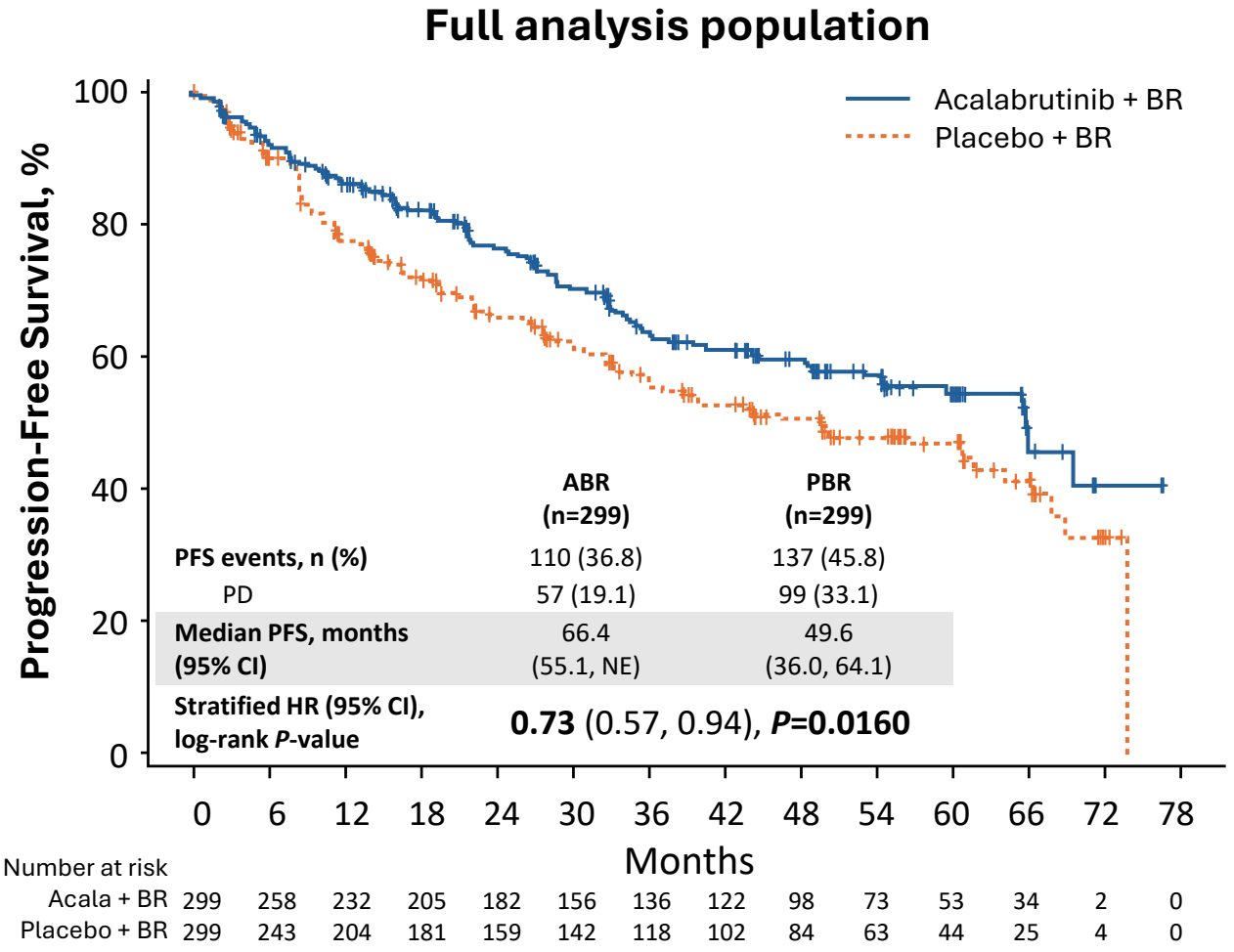
Demographics and Baseline Characteristics

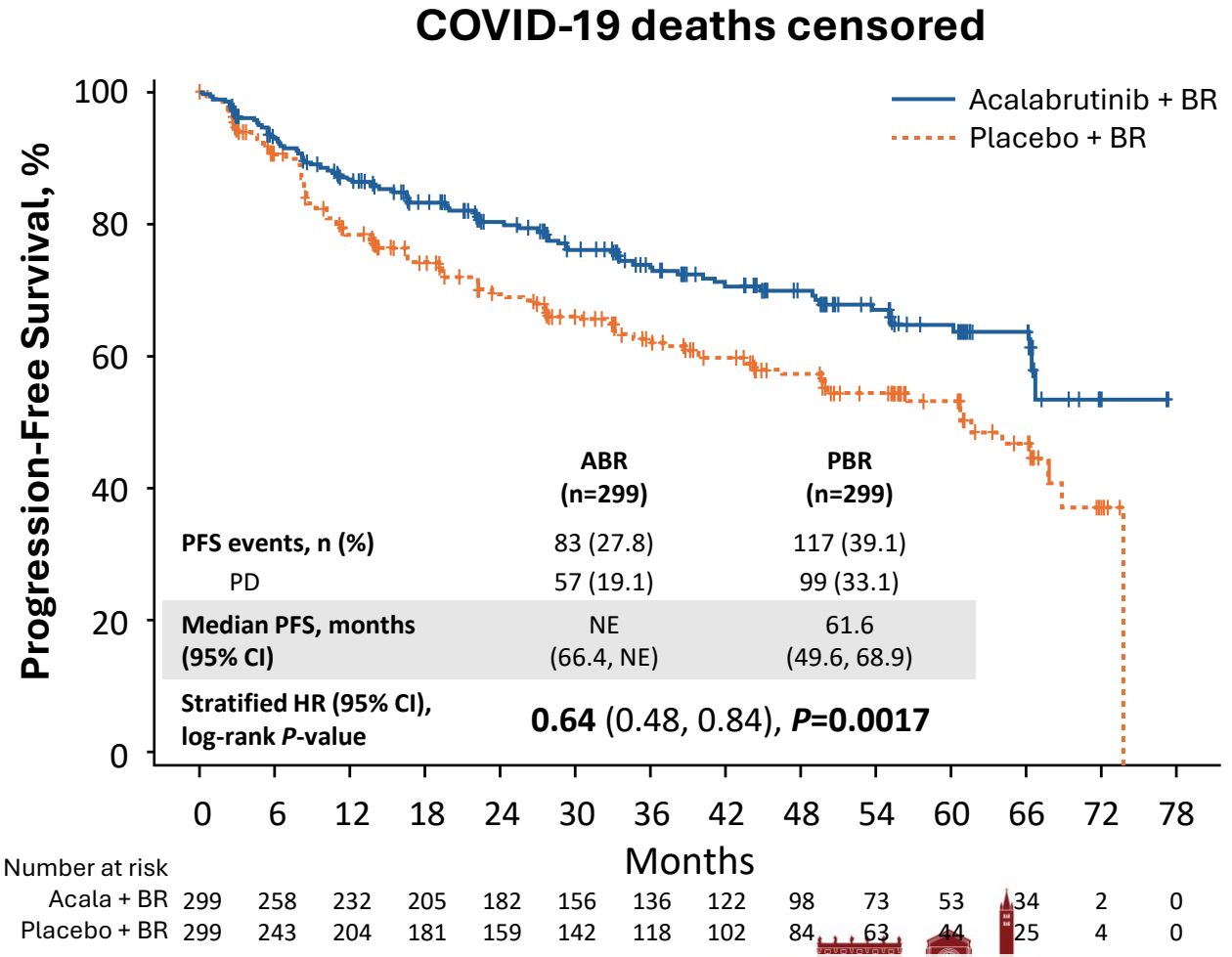
	Acalabrutinib + BR (n=299)	Placebo + BR (n=299)
Age, median (range), y	71 (65–85)	71 (65–86)
≥75 y, n (%)	84 (28.1)	77 (25.8)
Male, n (%)	214 (71.6)	209 (69.9)
ECOG PS, n (%)		
1	129 (43.1)	132 (44.1)
2	12 (4.0)	23 (7.7)
Tumor bulk ≥5 cm, n (%)	112 (37.5)	113 (37.8)
Blastoid/pleomorphic histology, n (%)	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



PFS With and Without COVID-19 Deaths: Prespecified Sensitivity Analysis

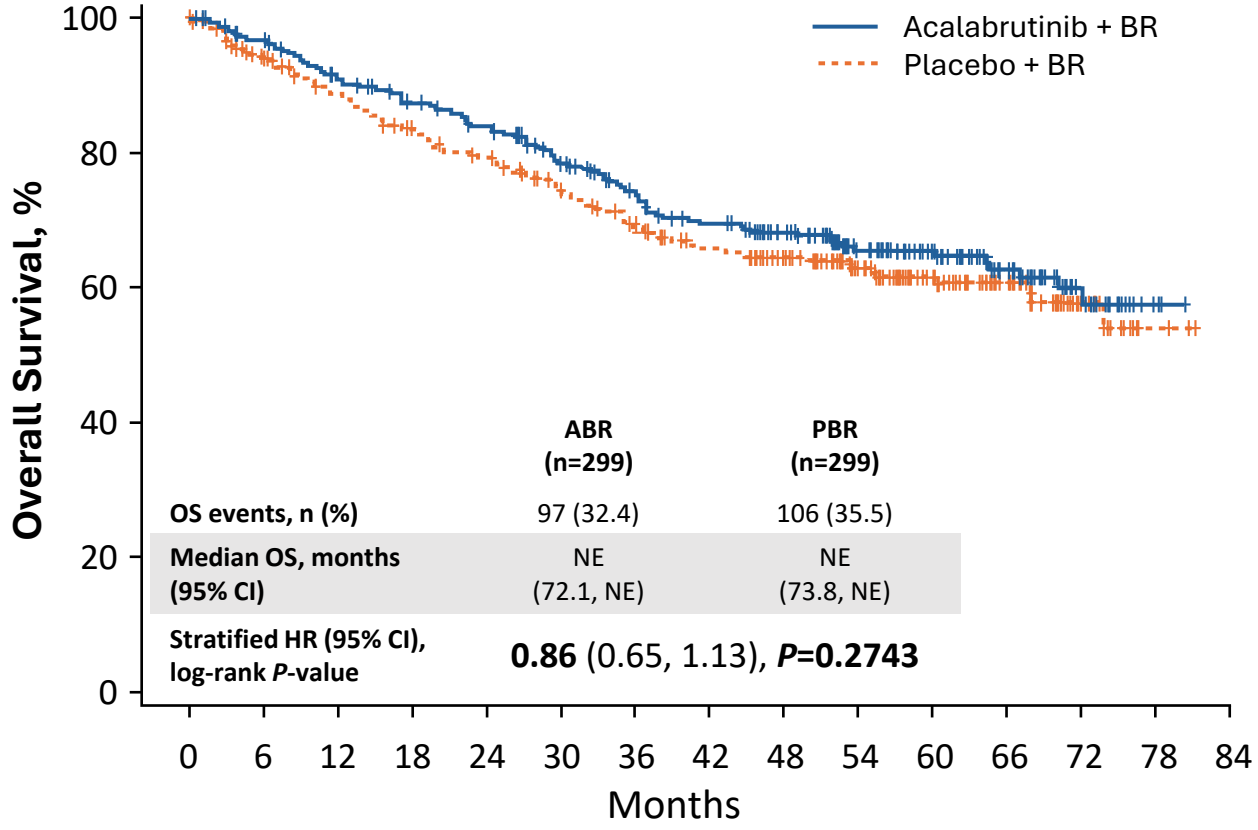




36% risk reduction when **censoring COVID-19 deaths**

OS With and Without COVID-19 Deaths: Prespecified Sensitivity Analysis

Full analysis population (including crossover)

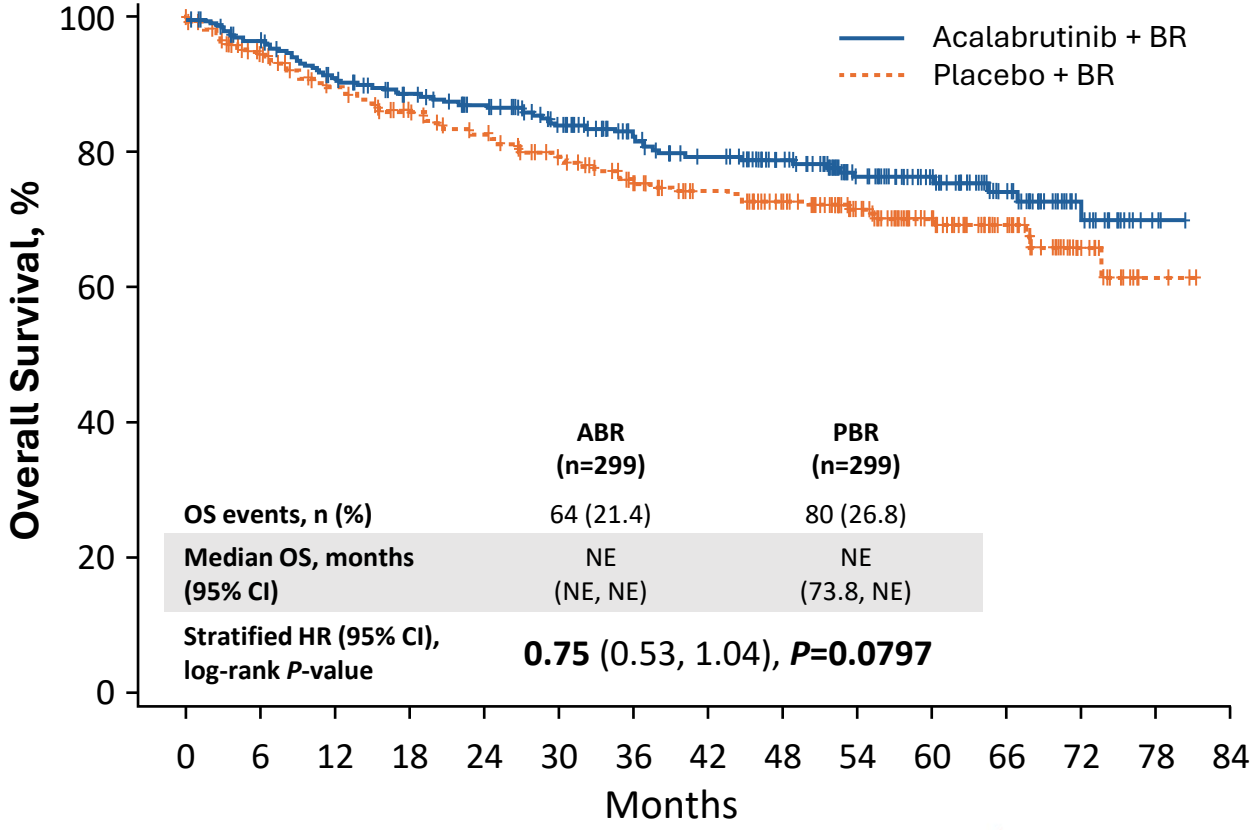


	ABR (n=299)	PBR (n=299)
OS events, n (%)	97 (32.4)	106 (35.5)
Median OS, months (95% CI)	NE (72.1, NE)	NE (73.8, NE)
Stratified HR (95% CI), log-rank *P*-value	**0.86** (0.65, 1.13), ***P*=0.2743**	

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

COVID-19 deaths censored

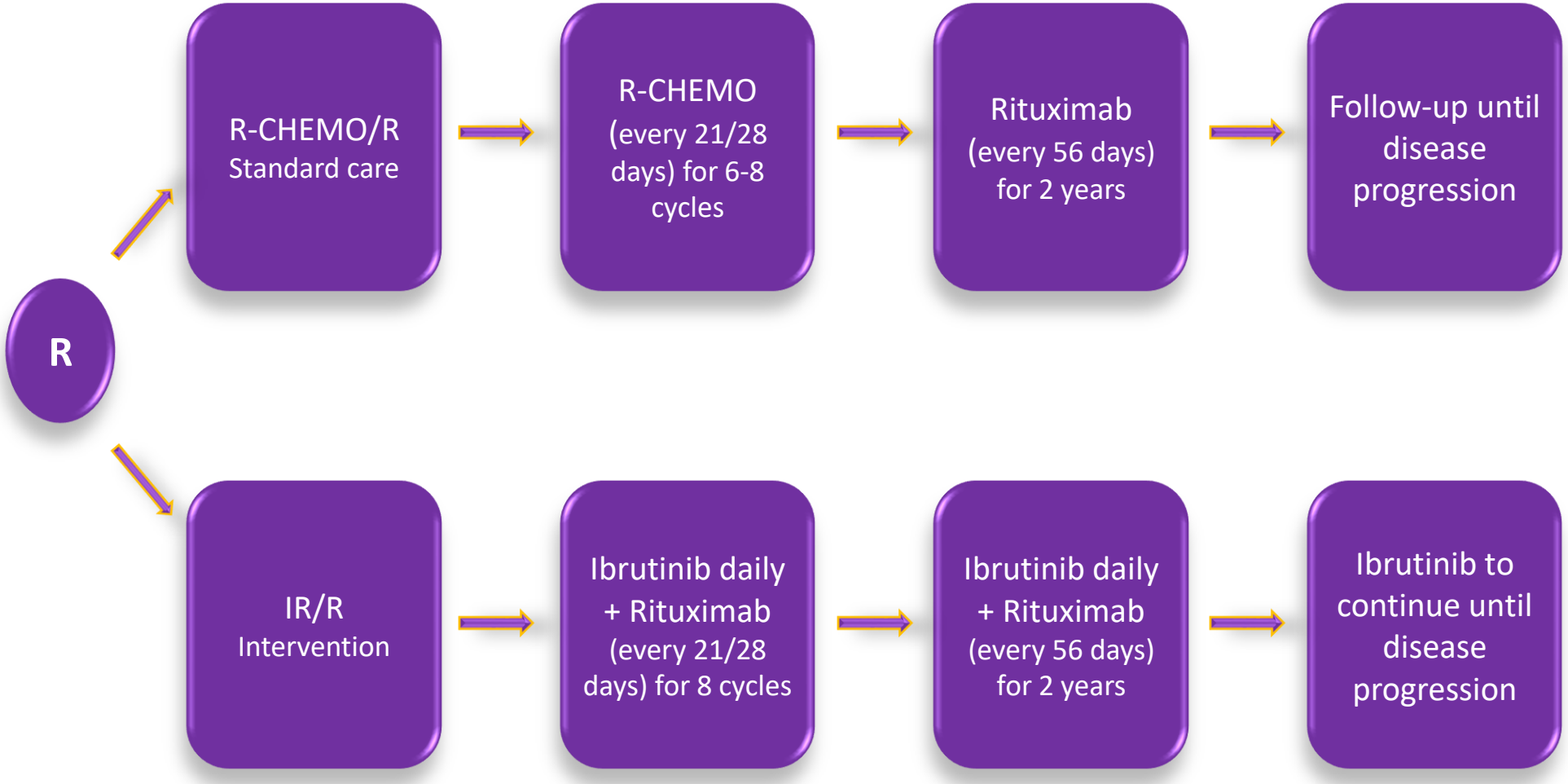


	ABR (n=299)	PBR (n=299)
OS events, n (%)	64 (21.4)	80 (26.8)
Median OS, months (95% CI)	NE (NE, NE)	NE (73.8, NE)
Stratified HR (95% CI), log-rank *P*-value	**0.75** (0.53, 1.04), ***P*=0.0797**	

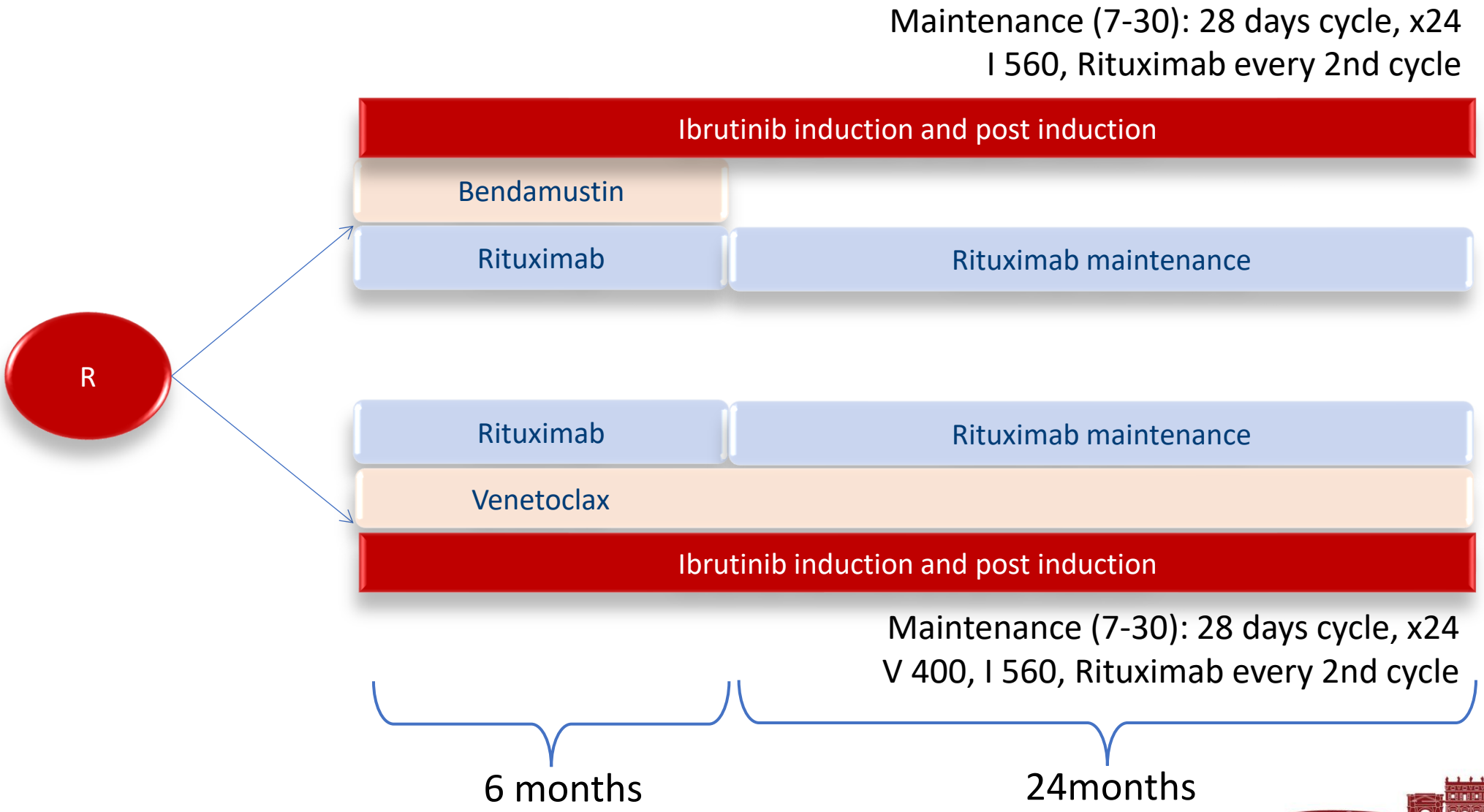
Number at risk

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

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



VIRAL – Phase II randomized



Updates
- How induction treatment is changing

Challenges

- R/R patients
- High-risk subgroups

Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline

Treatment	Reference	Study	N	Median age, years	Median prior lines (range)	High-risk-MIPI	Response	Median PFS (months; 95% CI)
Ibrutinib	Wang et al. 2013[96]	Phase II	111	68	3 (1–5)	49%	ORR 68%; CR 21%	13.9 (7.0-NE)
Ibrutinib	Dreyling et al. 2016[97]	Phase III	139	67	2 (1–9)	22%	ORR 72%; CR 19%	14.6 (10.4-NE)
Ibrutinib	Rule et al. 2017[98]	Pooled analysis	370	68	2 (1–9)	32%	ORR 70%; CR 27%	12.5 (9.8–16.6)
Acalabrutinib	Wang et al. 2018[101]	Phase II	124	68	2 (1–2)	17%	ORR 81%; CR 40%	22 (16.6–33.3)
Zanubrutinib	Song et al. 2020[102]	Phase II	86	60.5	2 (1–4)	38.4%	ORR 83.7%; CR 77.9%	33 (19.4-NE)
Zanubrutinib	Tam et al. 2021[110]	Phase I/II	32	70.5	1 (1–4)	31.3%	ORR 90.6%; CR 31.3%	21.1 (13.2-NE)

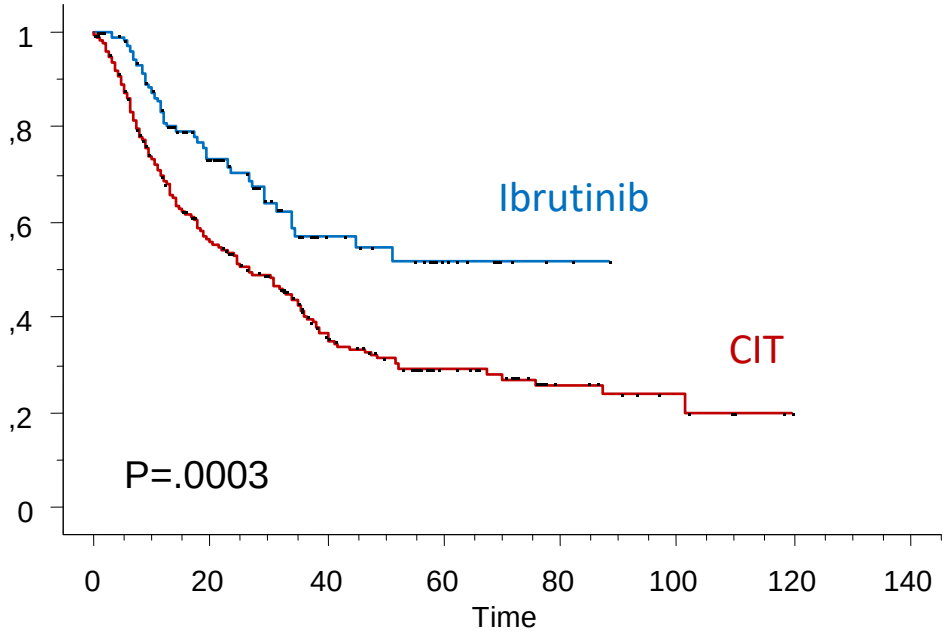
Eyre et al, BJH 2023

Survival curves of late-POD patients according to second line treatment

Ibrutinib *vs* **Chemoimmunotherapy (CIT)**

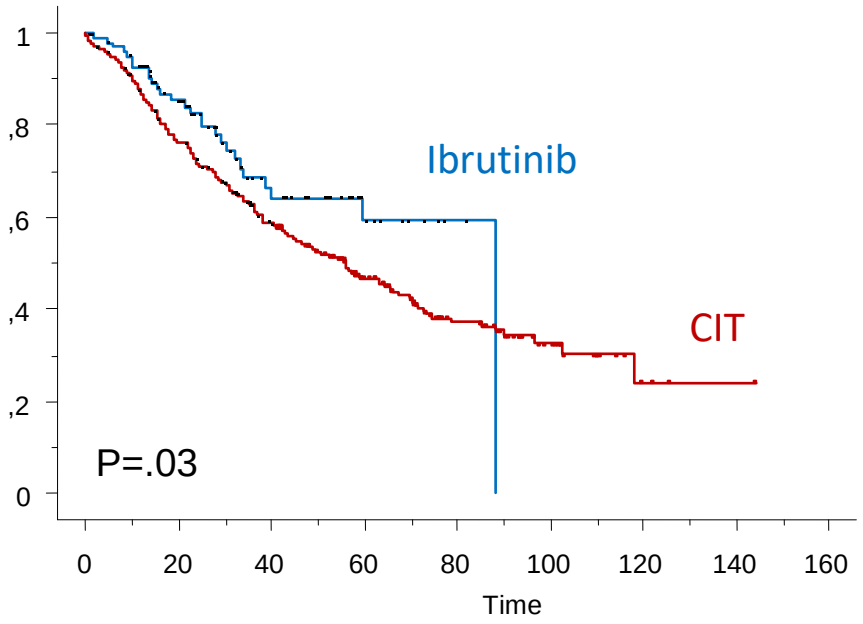
LATE-POD

PFS-2



Median 26 months for CIT;
NR for Ibrutinib

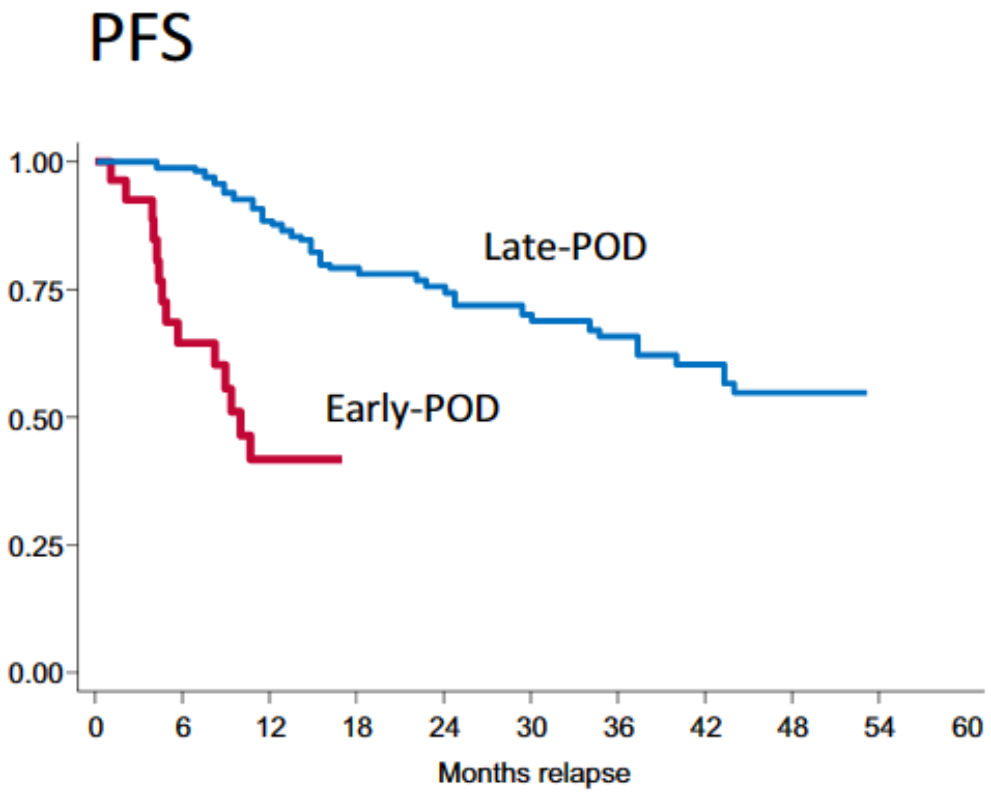
OS-2

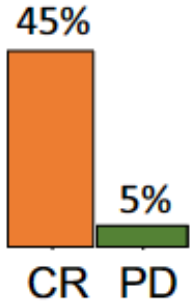


Median 56 months for CIT;
88 for Ibrutinib

Malinverni et al, Blood 2024

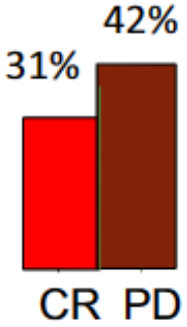
Ibrutinib at first relapse: late versus early POD





Late-POD

Standard approach during BTKi
Refer to CAR-T centre if suboptimal response or high-risk features (i.e. TP53 mutation)

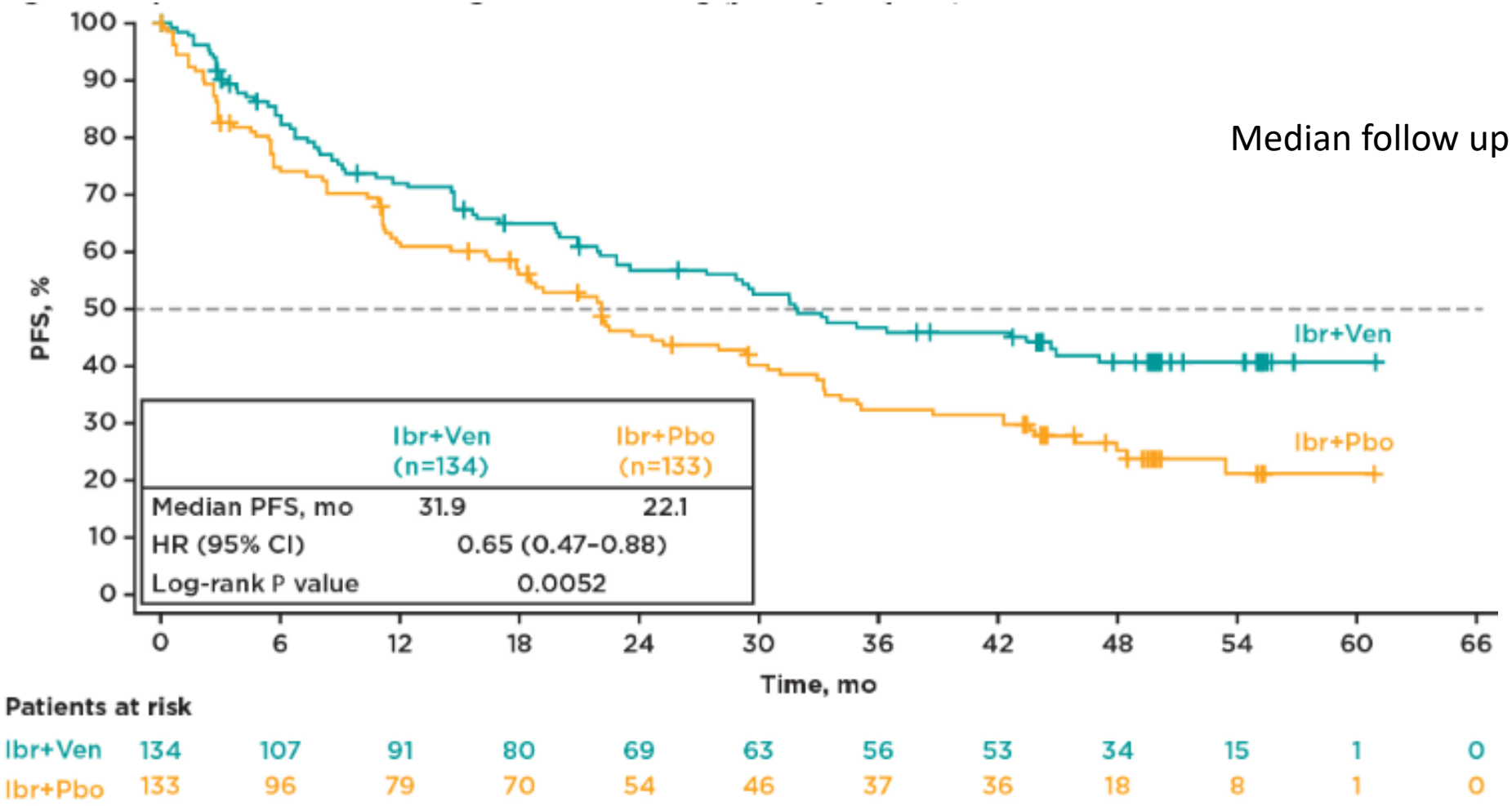


Early-POD

Refer to CAR-T centre at start of therapy
Close clinical monitoring
Restage 8-12 weeks

Visco, BJH 2023

Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study



Median follow up 51 months

Wang M et al, ASH 2023

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%)

VR-BAC
(elderly population)
38% HR

Ferrero S et al, Haematologica 2020;
Visco C et al, ASH 2023;
Eskelund et al, Blood 2017

TP53 mutation

NORDIC MCL-2 and MCL-3

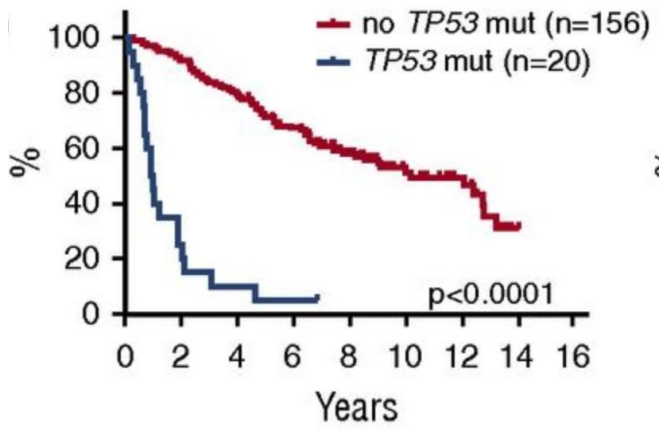
TP53-mutant mantle cell lymphoma (MCL) is associated with poor survival outcomes in patients treated with CIT

No standard frontline treatment exists

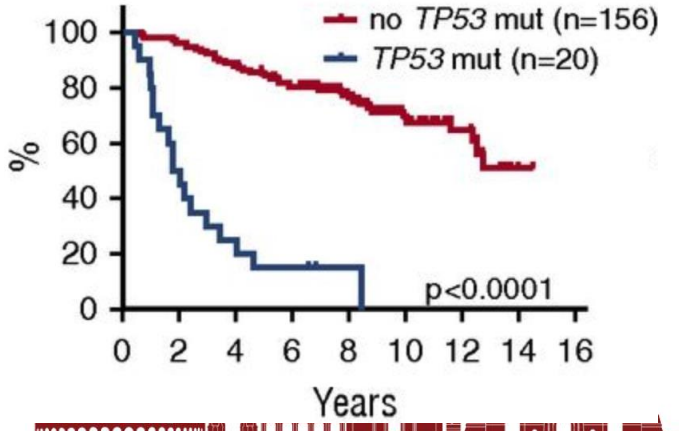
The triplet (ibrutinib, obinotuzumab, and venetoclax) was efficacious in R/R and untreated MCL, including *TP53*-mutant MCL (OAsIs)

Two studies upfront @ASH2023: The BOVen triplet (zanubrutinib, obinutuzumab, and venetoclax) and the V-RBAC trial (RBAC+Venetoclax)

Progression Free Survival



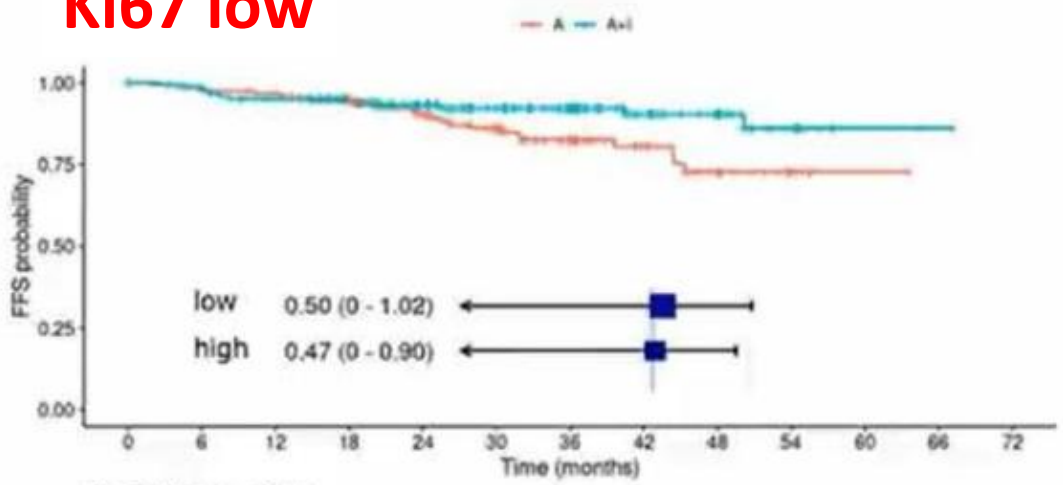
Overall Survival



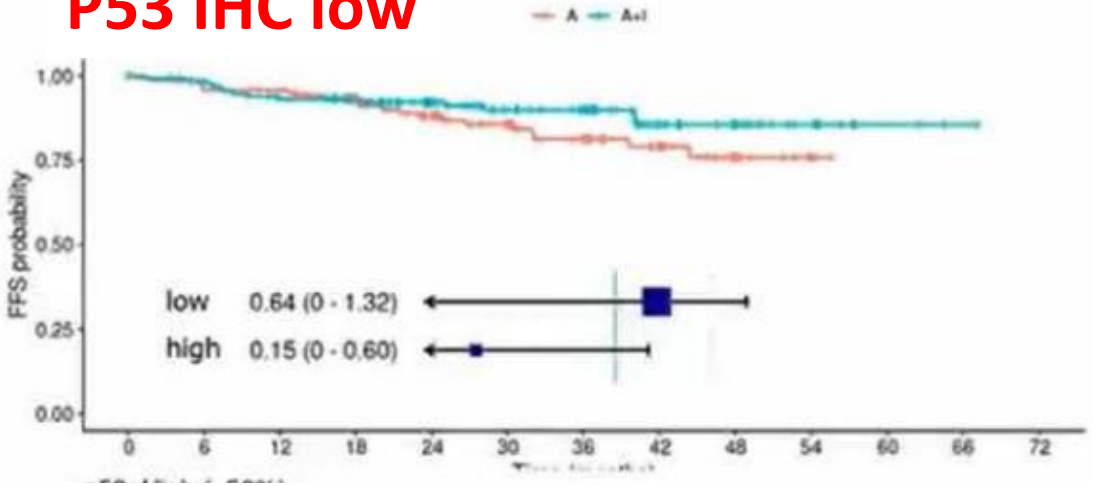
Eskelund Blood 2017; Tam NEJM 2018; Wang ASH 2023; Le Gouill Blood 2021

TRIANGLE: FFS Superiority of A+I vs. A

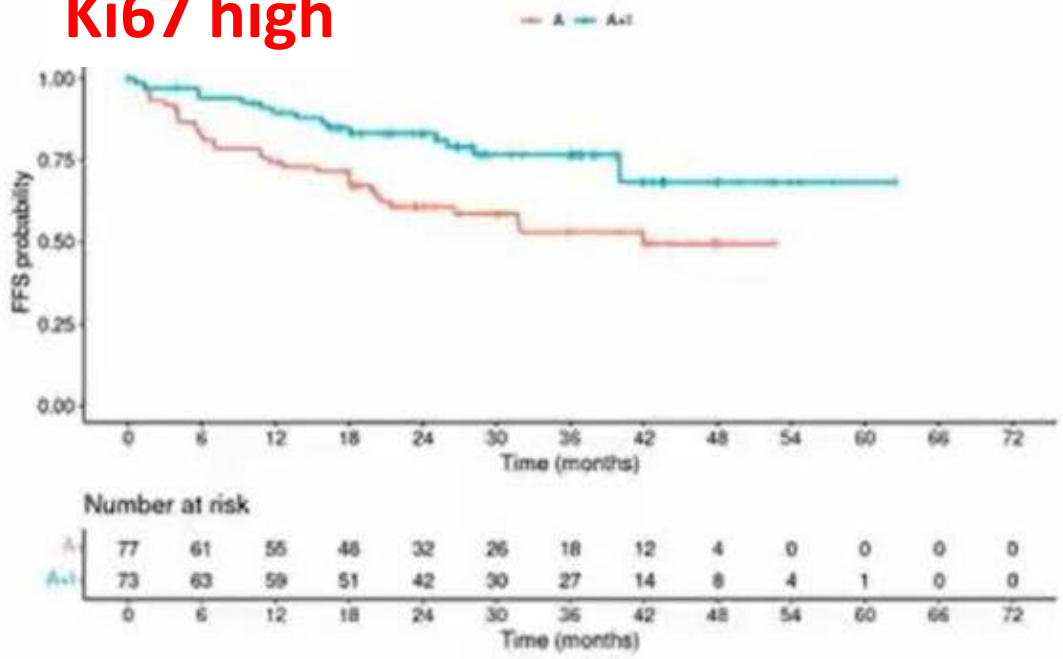
Ki67 low



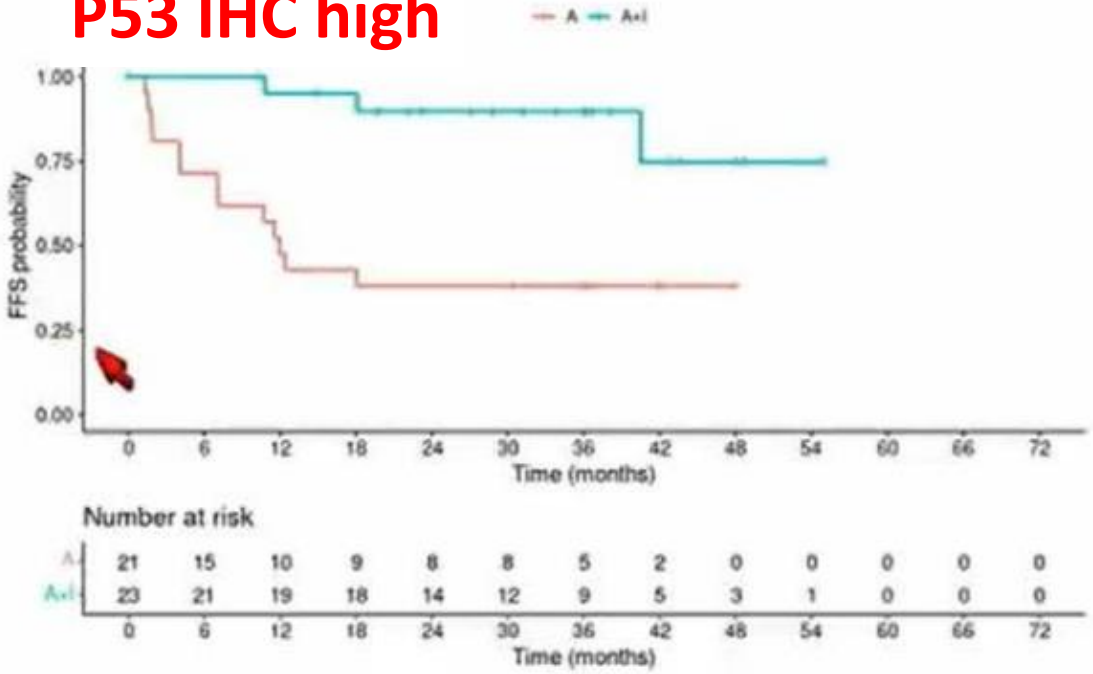
P53 IHC low



Ki67 high



P53 IHC high



Efficacy and safety of ibrutinib plus venetoclax in patients with mantle cell lymphoma (MCL) and *TP53* mutations in the SYMPATICO study (*ASCO/EHA 2024*)

Outcomes (95% CI)	1L	R/R	Total
Pts without *TP53* mutations	n=44	n=75	N=119
Median PFS, mo	NR (NE–NE)	46.9 (31.5–NE)	NR (36.4–NE)
Pts with *TP53* mutations	n=29	n=45	N=74
Median PFS, mo	22.0 (9.2–NE)	20.9 (13.0–33.1)	20.9 (14.7–30.6)
ORR, %	90 (73–98)	80 (65–90)	84 (73–91)
CR rate, %	55 (36–74)	58 (42–72)	57 (45–68)
Median duration of response, mo	20.5 (12.0–NE)	26.5 (16.8–NE)	26.0 (16.8–32.2)
Median duration of CR, mo	20.5 (5.4–NE)	NR (18.7–NE)	32.2 (18.7–NE)
Median OS, mo	NR (30.6–NE)	35.0 (14.1–NE)	47.1 (30.6–NE)

Treatment algorithm

Upfront

First relapse

Standard first line

TRIANGLE-like + BTKi (no ASCT)

BR+R + BTKi

Covalent BTKi + BCL2i

Treatment algorithm

Upfront

First relapse

Second relapse or further

Standard first line

TRIANGLE-like + BTKi (no ASCT)

BR+R + BTKi

Covalent BTKi + BCL2i

CarT candidate?

NO

-Pirtobrutinib
-R-BAC
-Explore
AlloSCT
-Bispecifics
-Lenalidomide
-Clinical Trial

YES

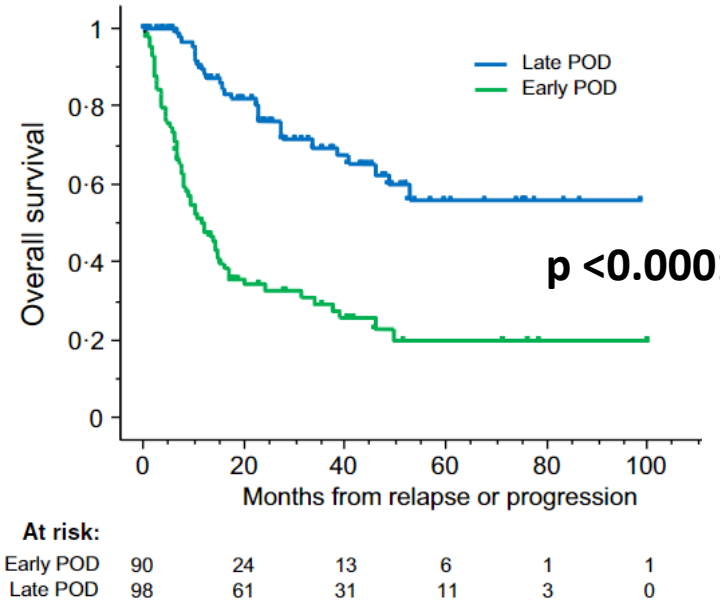
Brexu-Cell

Relapse

FONDAZIONE ITALIANA LINFOMI

Thanks for your attention

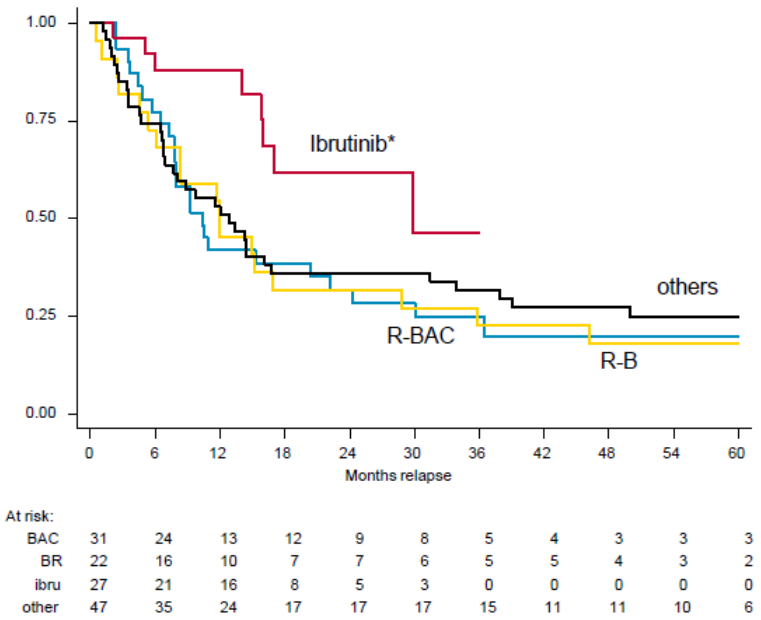
POD24[1]



p <0.0001

At risk:						
Early POD	90	24	13	6	1	1
Late POD	98	61	31	11	3	0

Early POD [2]

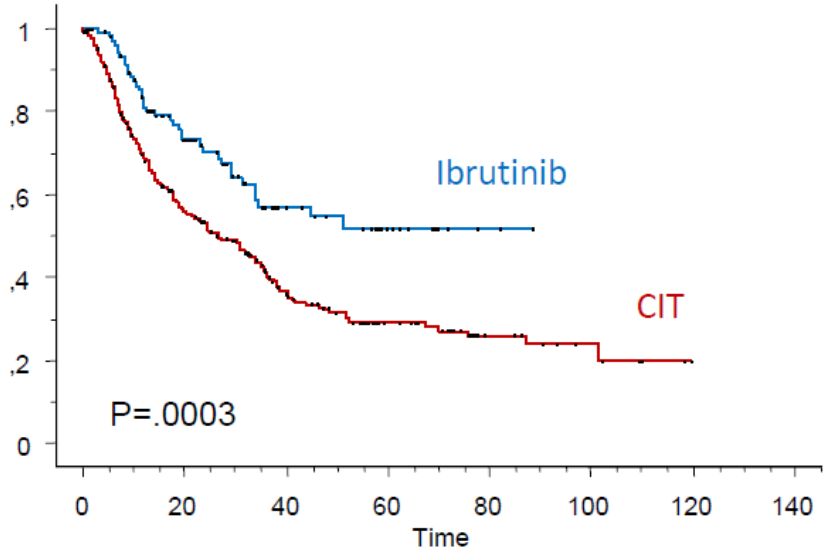


At risk:											
BAC	31	24	13	12	9	8	5	4	3	3	3
BR	22	16	10	7	7	6	5	5	4	3	2
ibru	27	21	16	8	5	3	0	0	0	0	0
other	47	35	24	17	17	17	15	11	11	10	6

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

Ibrutinib best choice in early-POD

PFS-2 [3]



Median 26 months for CIT;
NR for Ibrutinib

OS-2 p=.03

Ibrutinib best choice in late-POD

1.Visco C et al, BJH 2019; 2.Visco C et al, Leukemia 2020; 3.Malinverni C et al, Blood 2024