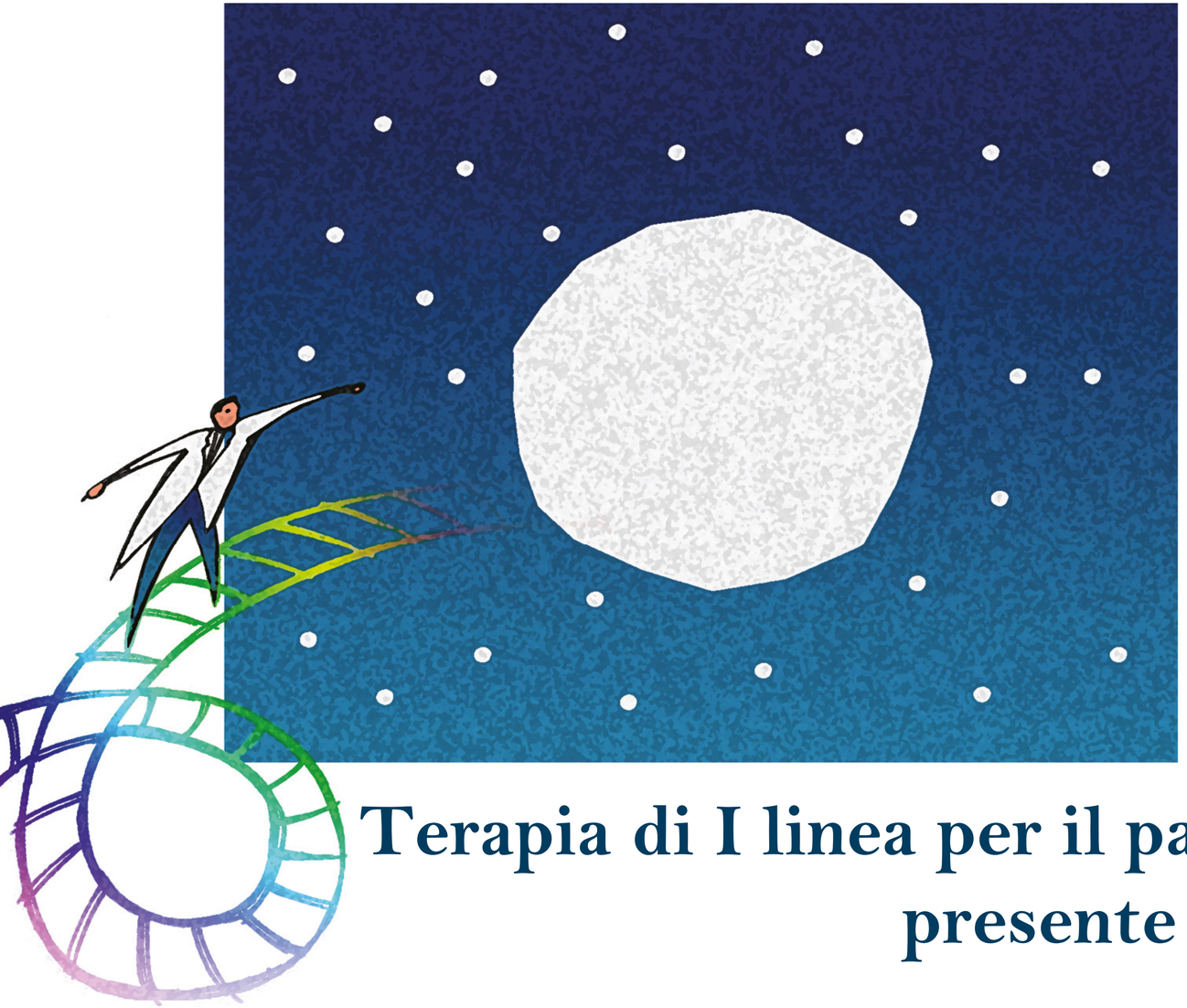


The young side of
LYMPHOMA

gli under 40 a confronto

Verona, Centro Congressi Camera di Commercio
26-27 settembre 2025

Terapia di I linea per il paziente anziano con MCL: presente e futuro

Alessia Moioli

Centro Ricerche Cliniche,
Verona

My Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
No disclosures							

CASO CLINICO

Maschio, 70 anni, FIT *according to FIL-geriatric assessment*

Ipertensione arteriosa in ramipril; DM in ipoglicemizzanti orali

Ott 2022

Sintomi/esame obiettivo febbricola, calo ponderale 4 Kg in un mese; PS ECOG 1, linfoadenopatia ascellare destra 3 cm, non altre linfoadenopatie superficiali; milza a 3 cm dall'arco a riposo

Hb 13 g/dL, PLTs 120.000/mmc, GB 4200/mmc, N 2180/mmc, Ly 1850/mmc;
LDH 230 U/L (v.n 150-200 U/L)

CASO CLINICO

Nov 2022

- ✓ Biopsia escissionale linfonodo ascellare:
  - 📌 *Linfoma mantellare, variante classica, SOX 11 +, Ki67 25%, TP53 unknown*

- ✓ *PET/TC*

  linfoadenopatie sotto e sovra diaframmatiche (SUV max ascella dx pari a 9); ipermetabolismo splenico diffuso (SUV max 4,5)

- ✓ *BOM positiva* (minima localizzazione, 10%)

Diagnosi

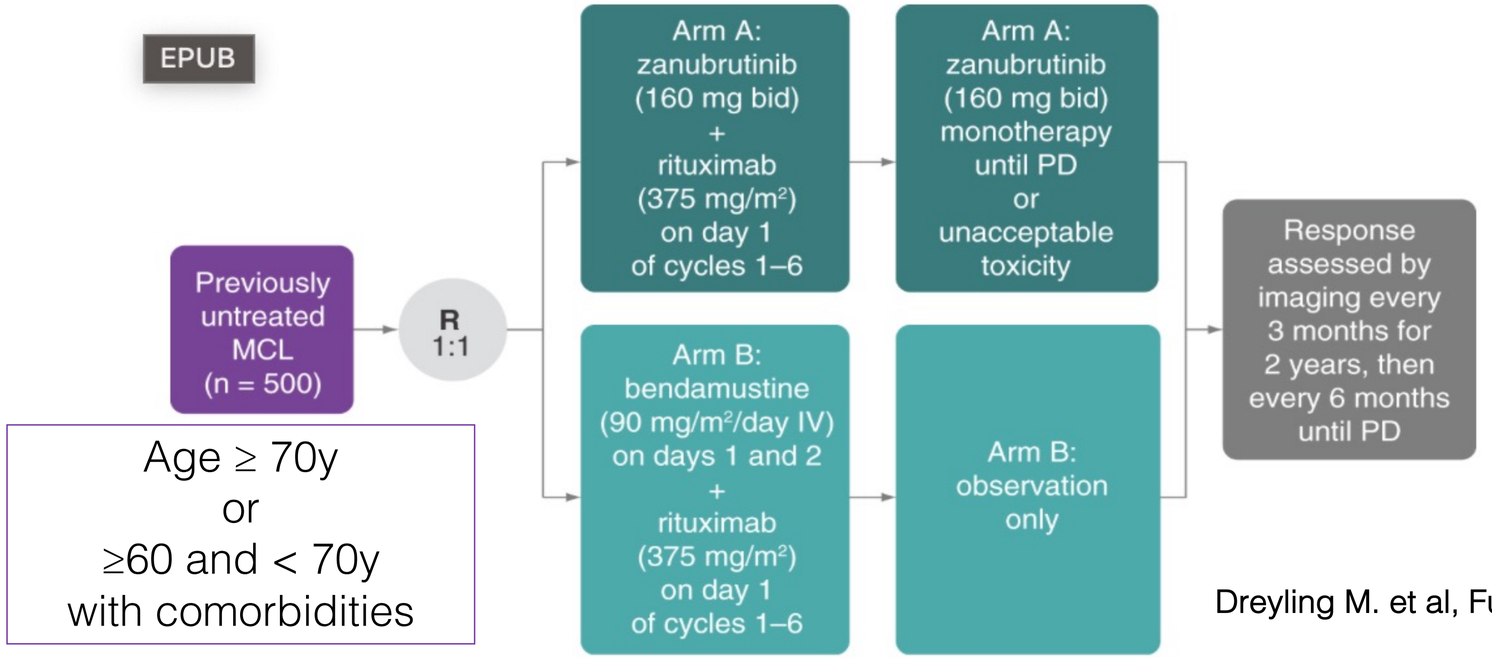
Linfoma mantellare, variante classica, s.c. IVB; MIPI high risk

CASO CLINICO

Dic 2022

MANGROVE trial

Studio di fase III, randomizzato, open label, multicentrico; zanubrutinib + rituximab (A) vs bendamustina + rituximab (B) in pazienti con MCL non trattato e non eleggibili al trapianto



Age ≥ 70y
or
≥60 and < 70y
with comorbidities

Dreyling M. et al, Future Oncology 2021, Jan; 17(3):255-262

CASO CLINICO

MANGROVE trial

BRACCIO B
(BENDAMUSTINA + RITUXIMAB per 6 cicli)

AE: neutropenia febbrile dopo C2;
episodio di bradicardia

BR
Cicli 1-4

PR
Linfonodo tronco celiaco 2 cm

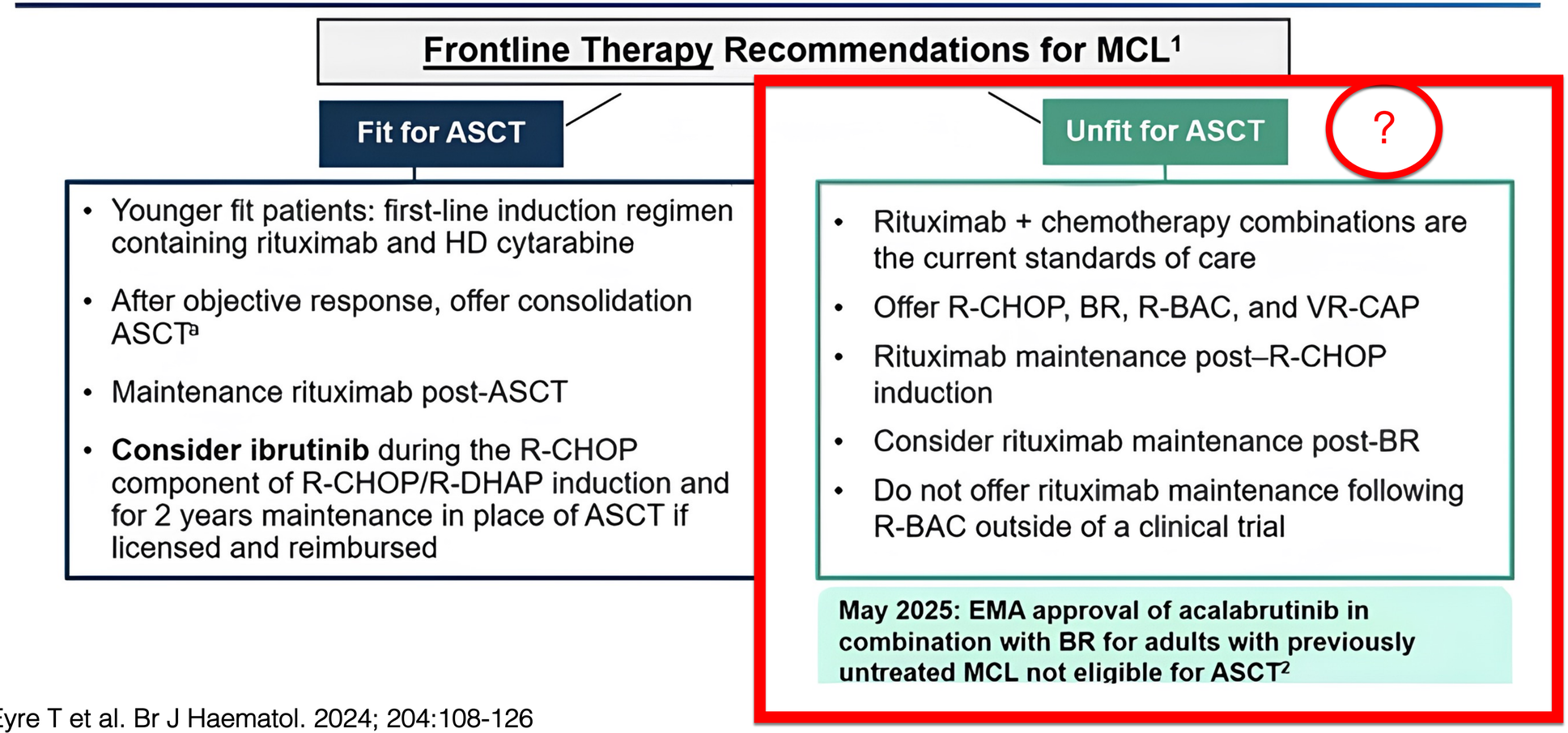
BR
Cicli 5-6

CR

Follow up

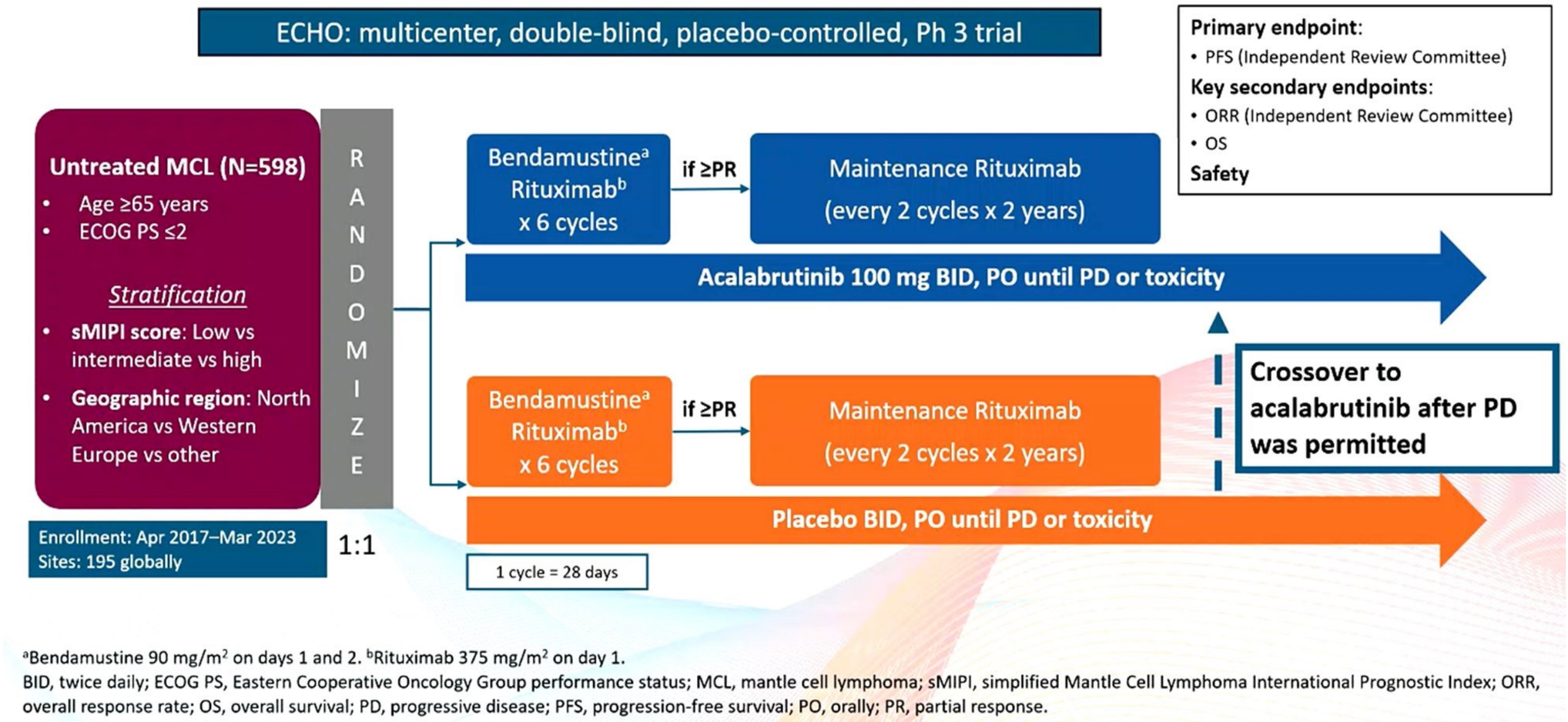
Ultimo FUP 06/25: CR

TERAPIA I LINEA MCL ANZIANO
IL PRESENTE



1. Eyre T et al. Br J Haematol. 2024; 204:108-126

Phase III ECHO Trial: Acalabrutinib + BR (ABR) in MCL

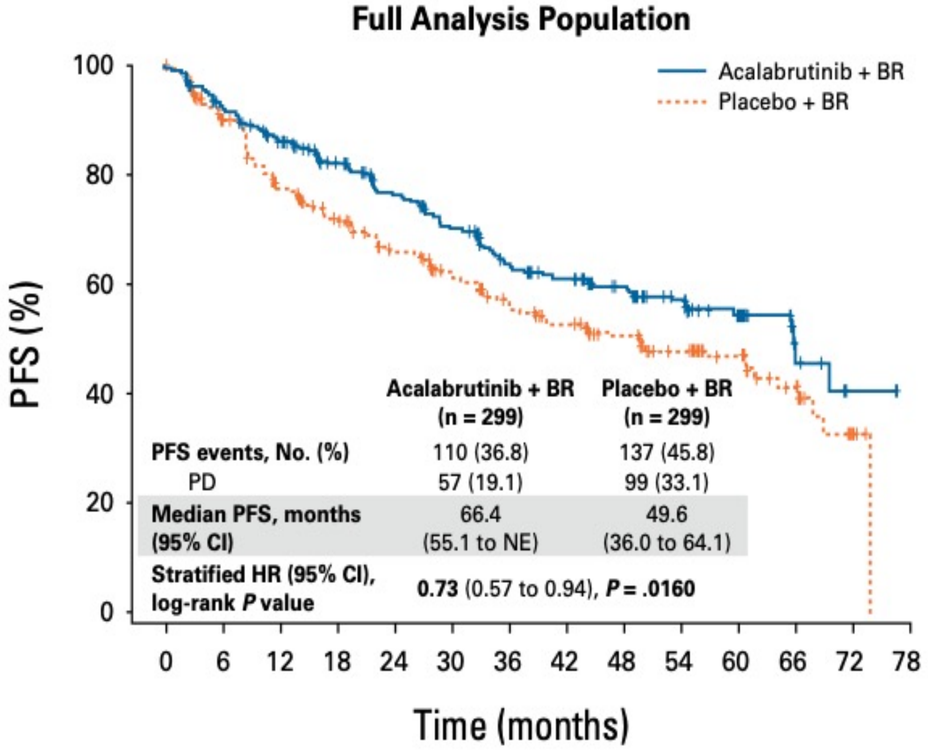


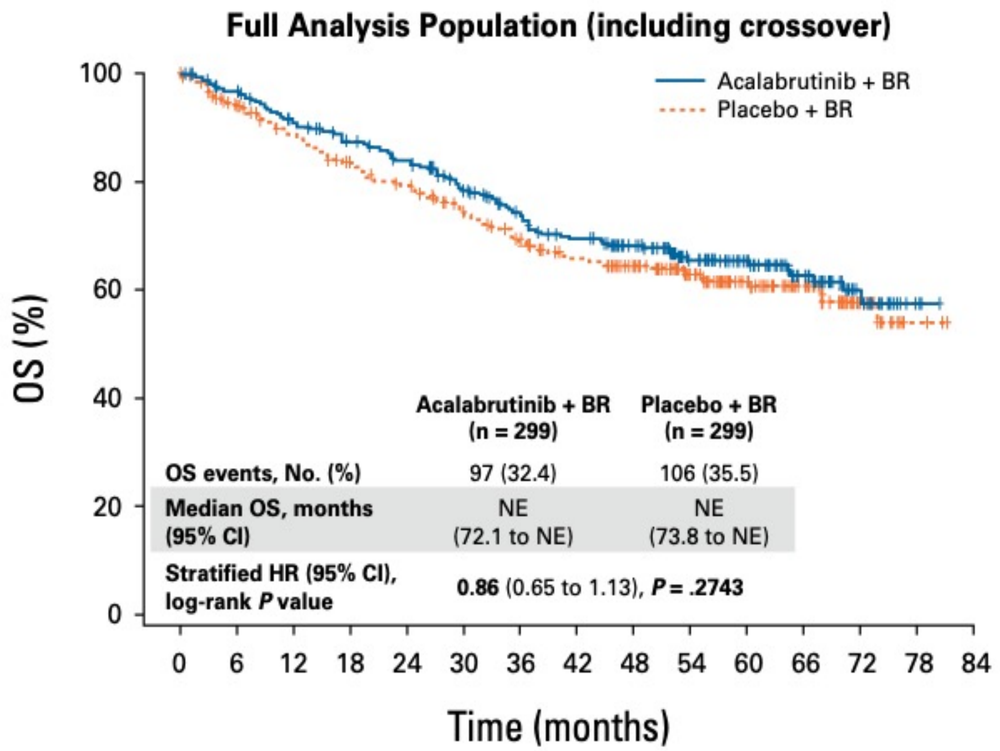
[a]Bendamustine 90 mg/m^2 on days 1 and 2. [b]Rituximab 375 mg/m^2 on day 1.
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; PR, partial response.

https://clinicaltrials.gov/study/NCT02972840

ABR: improved PFS vs BR; a positive OS trend

NOT ONLY …





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

Number at risk

Acalabrutinib + 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

36% risk reduction when censoring COVID19 deaths

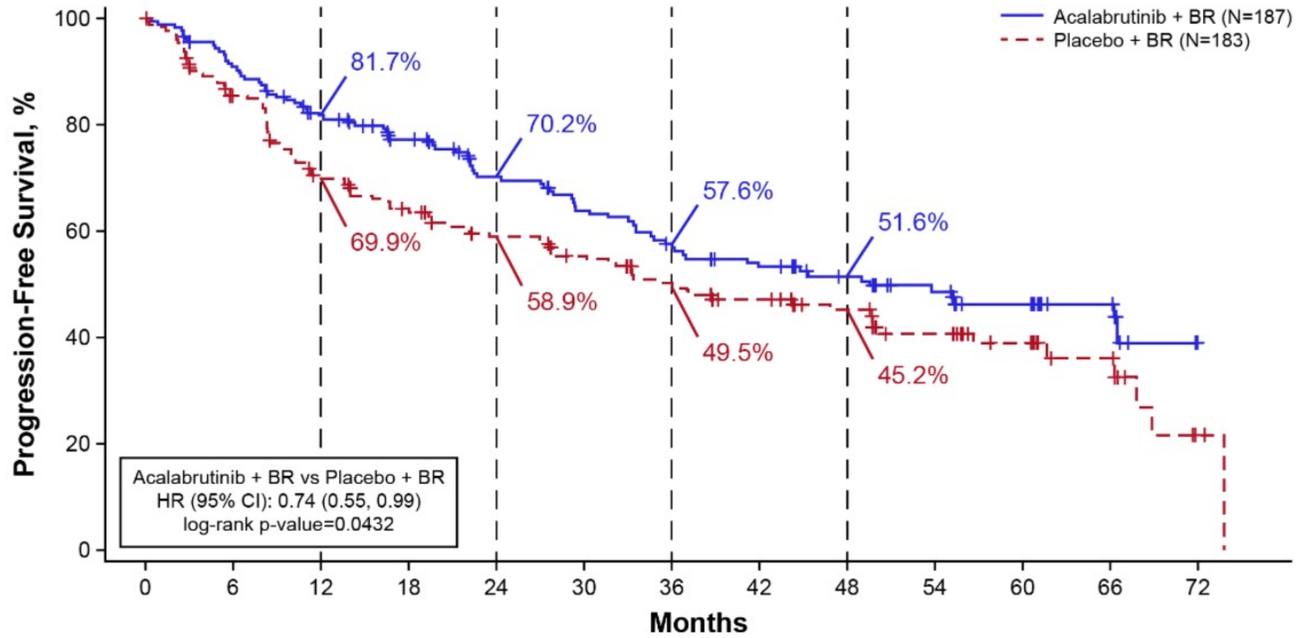
Wang M et al. JCO May 2025

Sustained MRD negativity

Dreyling M et al. ASH 2024; *Blood* (2024) 144 (Supplement 1): 1626.

Improved PFS in patients with HIGH RISK FEATURES

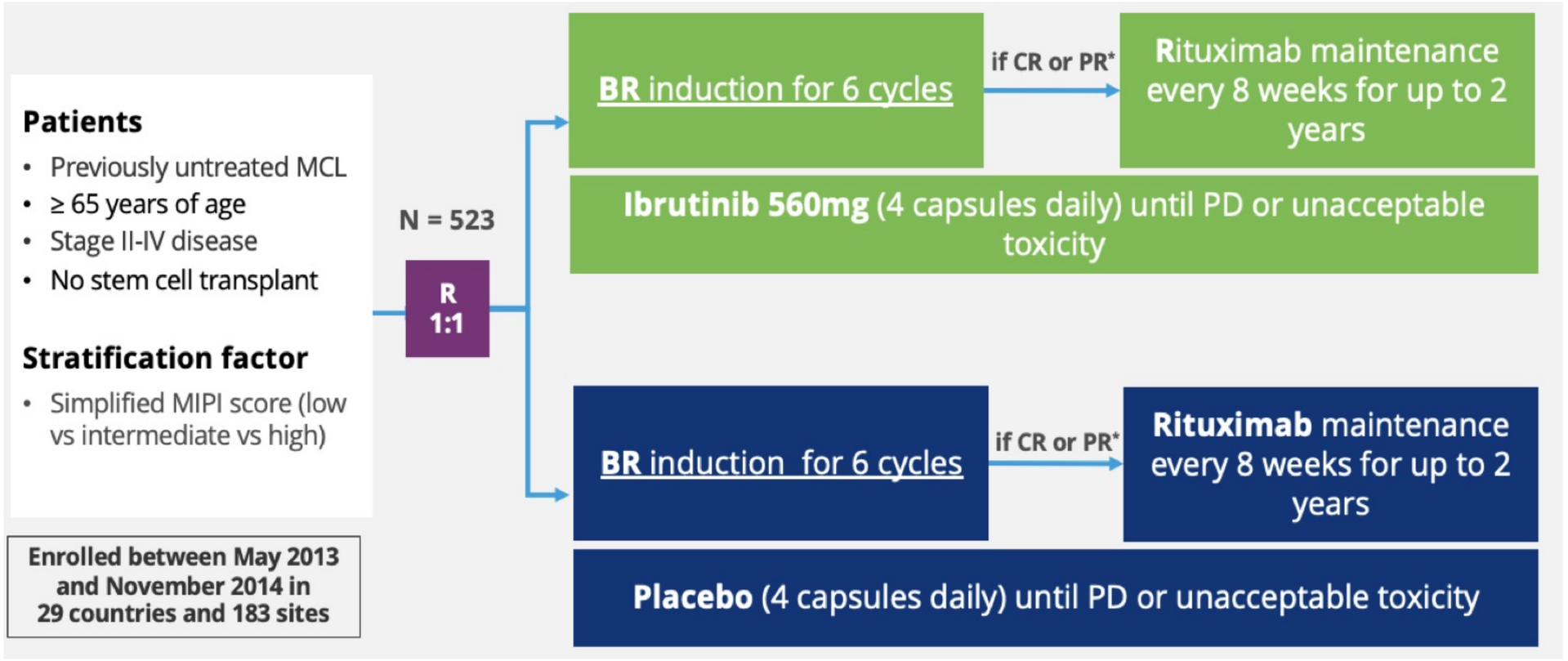
In *high risk MCL* (high MIPI score [6-11], ki67 index ≥ 30%, blastoid/pleomorphic histology, TP53 mutations; tot 370 pts) ABR provides more CR (68% vs 48%) and a more pronounced benefit in PFS compared with the total study population (49,5 vs 36 months)



BR, bendamustine-rituximab; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; MCL, mantle cell lymphoma; PFS, progression-free survival.
The high-risk MCL population represented in this figure includes patients with high-risk MCL Lymphoma International Prognostic Index (6–11), *TP53* mutation, Ki-67 index ≥30%, and/or blastoid/pleomorphic histology.

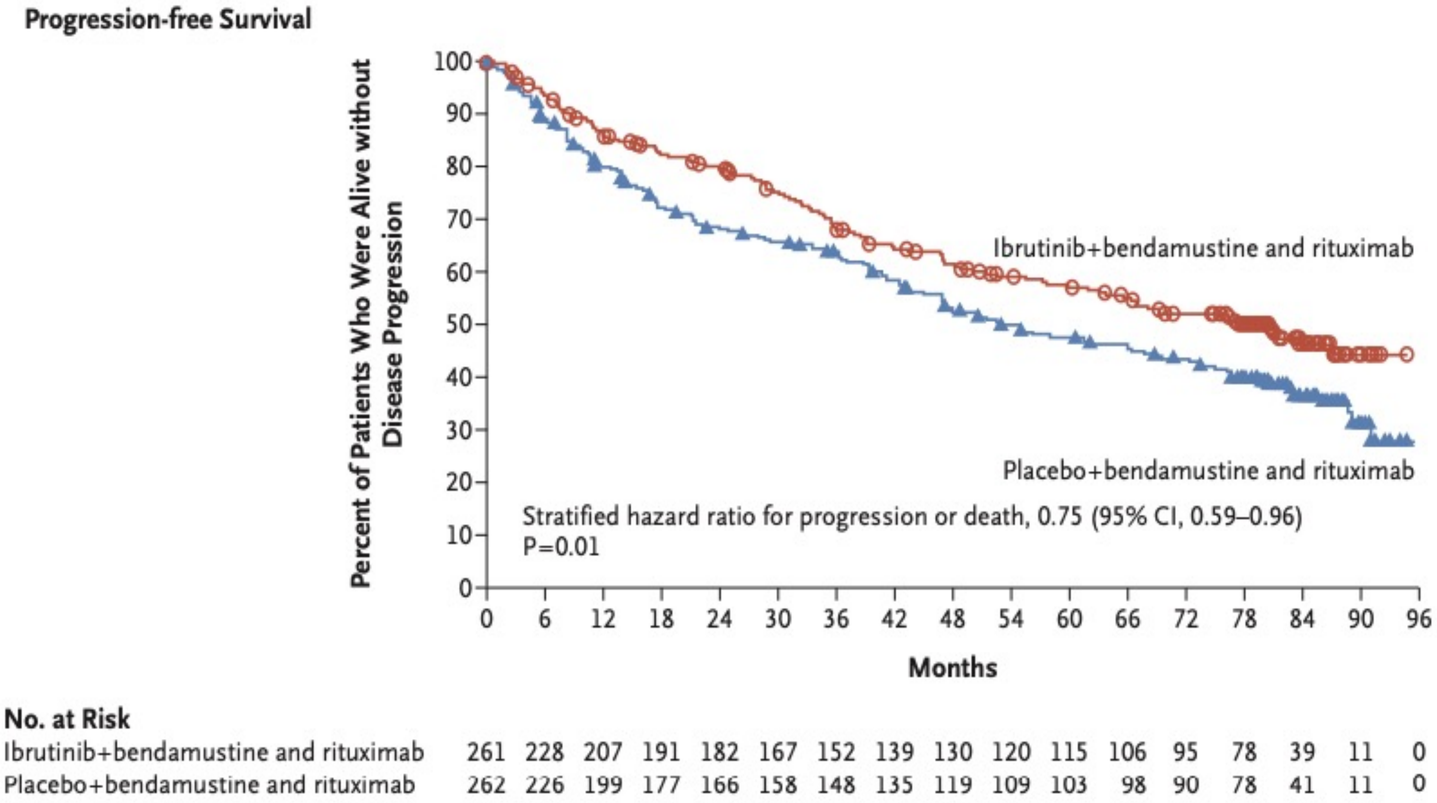
Dreyling M. et al. EHA 2025; abstract S233

Phase III SHINE Trial: Ibrutinib + BR in MCL



Wang ML et al. NEJM 2022; 386:2482-2494

Phase III SHINE Trial: Ibrutinib + BR in MCL

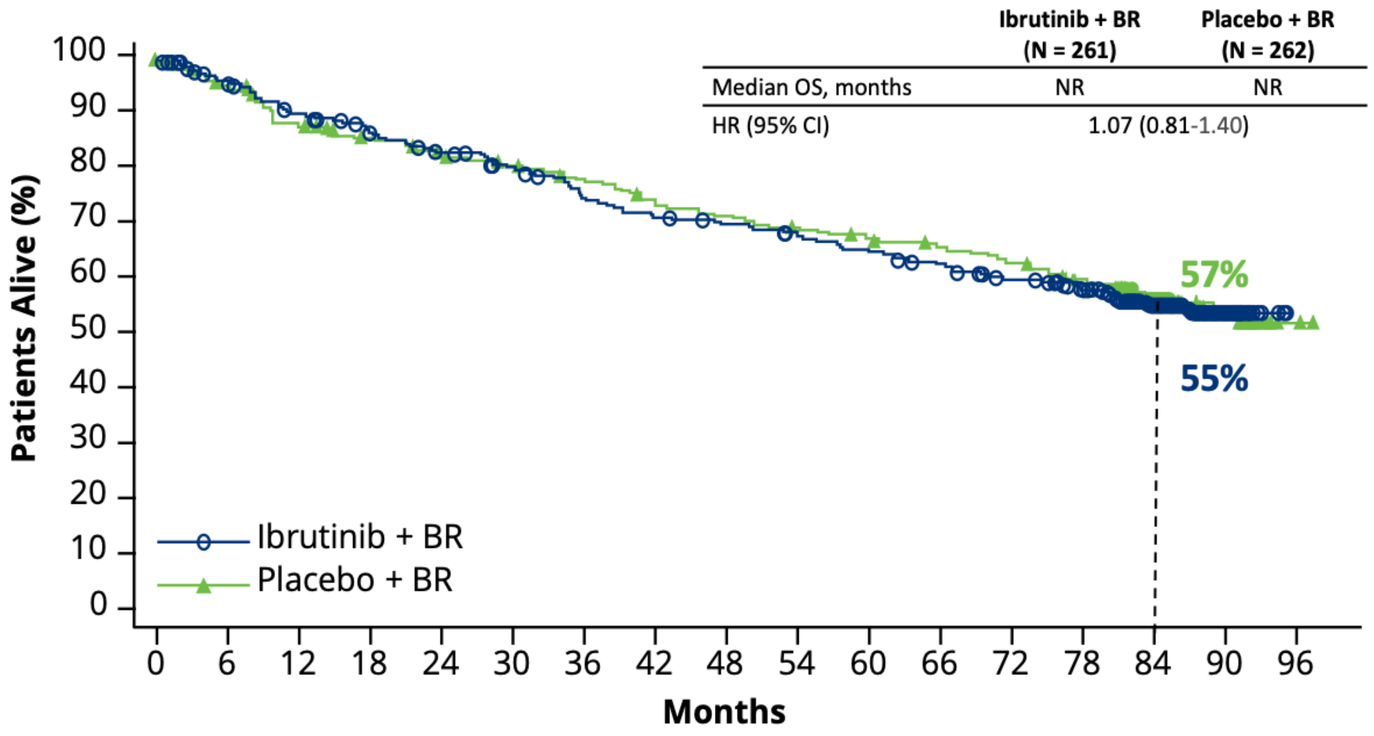


mPFS 80,6 vs 52,9 months
(+2,3 years)

IMPROVED PFS WITH I+BR
BUT…

Wang ML et al. NEJM 2022; 386:2482-2494

…NOT IMPROVED OS



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

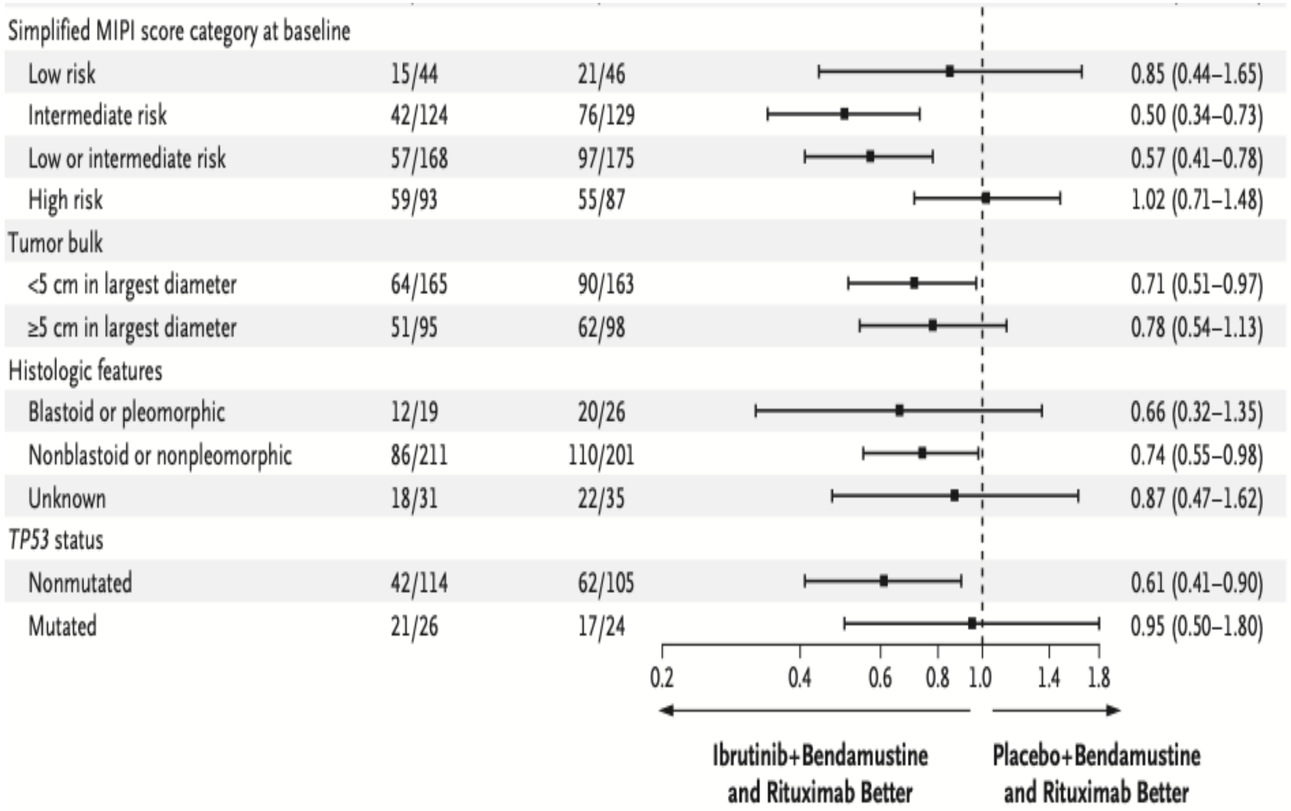
Cause of death	Ibrutinib+BR (N=261)	Placebo+BR (N=262)
Death due to PD	30 (11.5%)	54 (20.6%)
Death due to TEAEs*	28 (10.7%)	16 (6.1%)
Death during post-treatment follow-up period excluding PD	46 (17.6%)	37 (14.1%)
Total deaths	**104 (39.8%)**	**107 (40.8%)**

*The most common Grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 vs 5 patients. Grade 5 TEAE of cardiac disorders in 3 vs 5 patients, respectively.

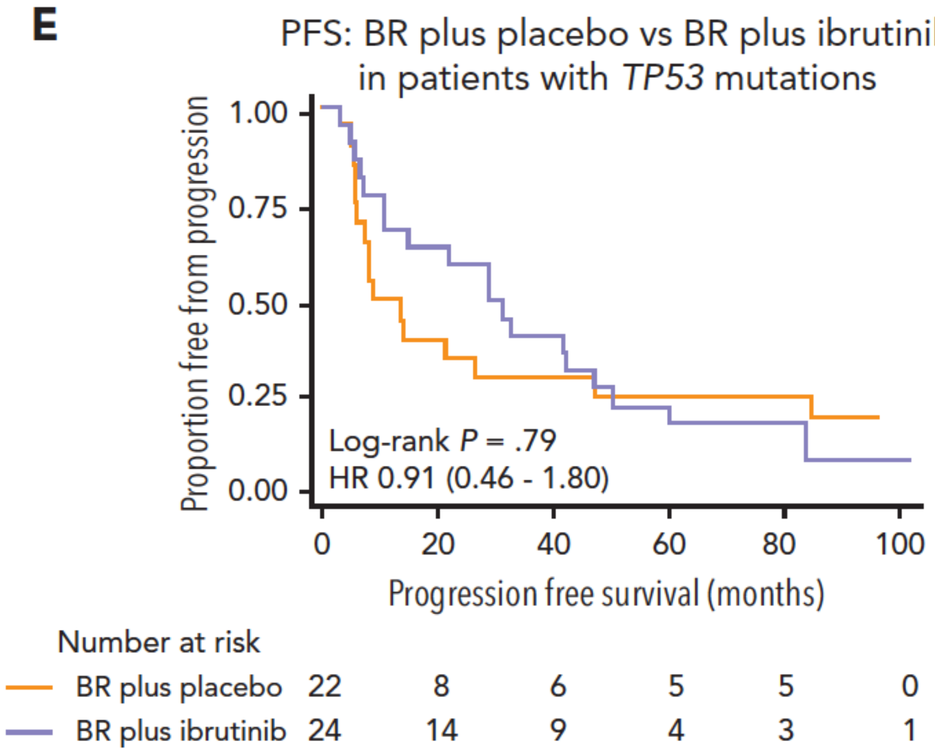
	Ibrutinib + BR (N = 259)		Placebo + BR (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any bleeding*	42.9%	--	21.5%	--
Major hemorrhage	5.8%	3.5%	4.2%	1.5%
Atrial fibrillation	13.9%	3.9%	6.5%	0.8%
Hypertension	13.5%	8.5%	11.2%	5.8%
Arthralgia	17.4%	1.2%	16.9%	0

Wang et al., EHA 2022; S209 (oral presentation; Wang et al., N Engl J Med. 2022 Jun 3. doi: 10.1056/NEJMoa2201817

…and NO DIFFERENCE IN HIGH RISK PATIENTS with TP53 mutations

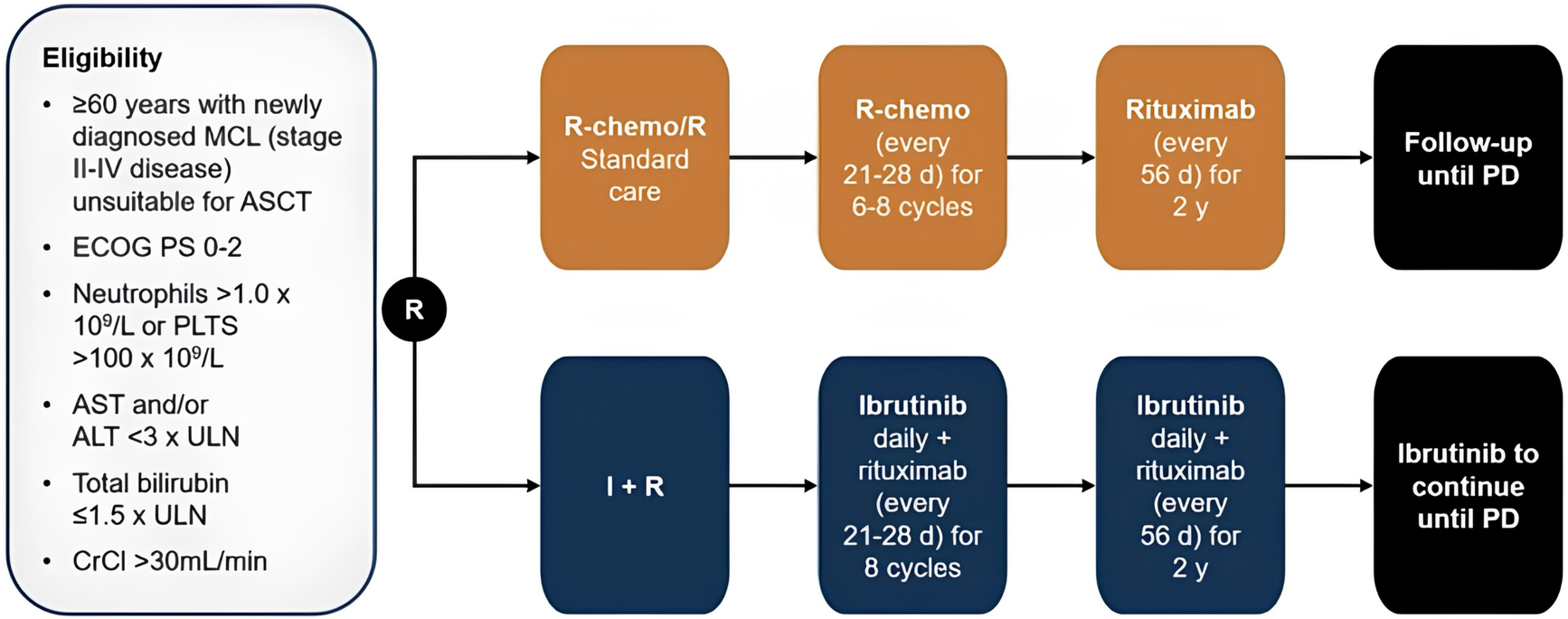


Wang ML et al. NEJM 2022; 386:2482-2494



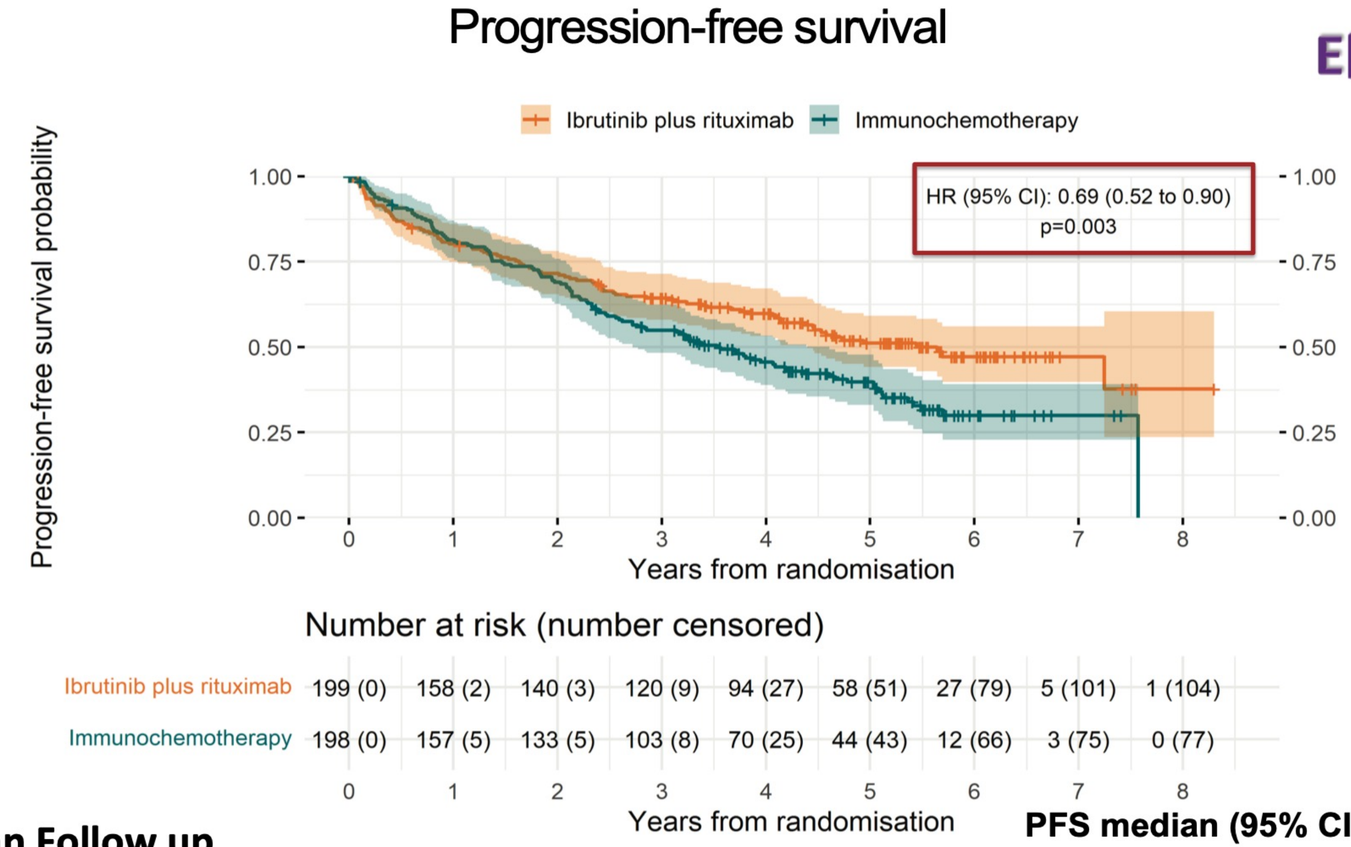
Freeman C.L. et al. Blood 2025

Phase II/III ENRICH Trial: Ibrutinib + R vs R-CHOP/B in elderly MCL



https://clinicaltrials.gov/ct2/show/NCT01880567

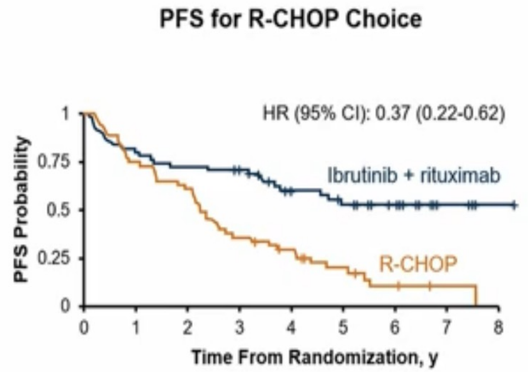
Phase III ENRICH Trial: Ibrutinib + R improves PFS



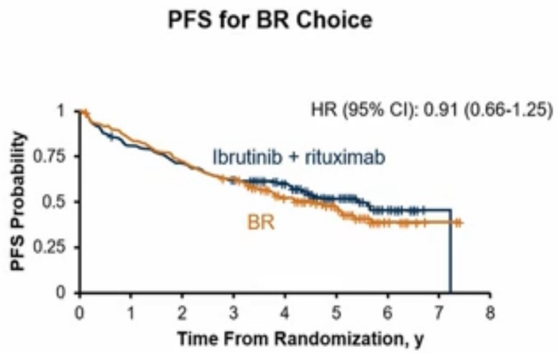
Median Follow up
47.9 months

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

BUT the CIT choice makes a difference



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



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

Lewis D et al. ASH 2024. Abstract 235

SUGGESTED ALGORITHM IN ELDERLY PATIENTS

MCL newly diagnosed and requiring treatment

Age > 65, no trasplant eligible

BTKi not available in first line

CT induction
(R-CHOP, BR, R-BAC, VR-CAP)

R maintenance

BTKi available

BR-acalabrutinib induction
ECHO

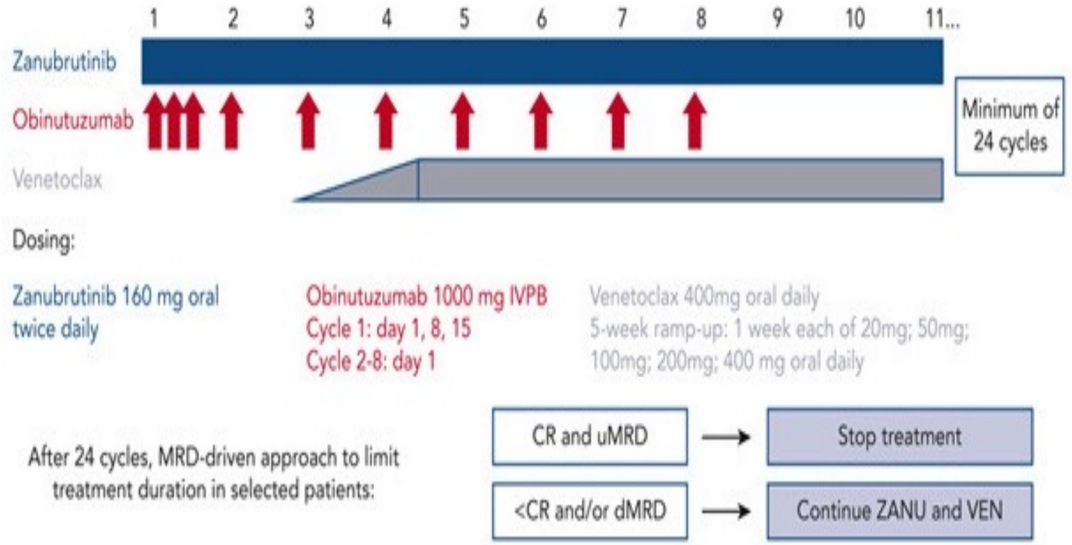
2y R-maintenance + acalabrutinib

to progression or toxicity

HIGH RISK STILL AN UNMET NEED

BOVEN

Zanubrutinib, obinutuzumab and venetoclax in newly diagnosed high risk MCL
(100% with TP53 aberrant disease)



Kumar A. et al. Blood 2024; 145:497-507.

V-RBAC

Rituximab, bendamustine, and cytarabine followed by venetoclax in older patients with high-risk mantle cell lymphoma (FIL_V-RBAC): a multicentre, single-arm, phase 2 study

*Carlo Visco, Valentina Tabanelli, Maria Vittoria Sacchi, Andrea Evangelista, Francesca Maria Quaglia, Stefano Fiori, Riccardo Bomben, Maria Chiara Tisi, Marcello Riva, Anna Merli, Francesco Rotondo, Costanza Fraenza, Maria Elena Carazzolo, Paolo Corradini, Lucia Farina, Claudia Castellino, Alessia Castellino, Vittorio Ruggero Zilioli, Cristina Muzi, Francesco Piazza, Alessandro Re, Stefan Hohaus, Francesca Gaia Rossi, Gerardo Musuraca, Alice Di Rocco, Benedetta Puccini, Roberta Sciarra, Filippo Ballerini, Federica Cavallo, Riccardo Bruna, Riccardo Moia, Alessia Moioli, Andrea Bernardelli, Daniela Drandi, Annalisa Arcari, Francesco Merli, Guido Gini, Roberto Freilone, Monica Tani, Vincenzo Pavone, Marco Ladetto, Stefano Aldo Pileri, Monica Balzarotti, on behalf of the Fondazione Italiana Linfomi**

Visco C. et al, Lancet Hematol 17 Sept 2025

FUTURE SUGGESTED ALGORITHM IN ELDERLY PATIENTS

MCL newly diagnosed and requiring treatment

FITNESS
RISK
(morphology, ki67, MIPI, p53..)

HIGH RISK

BR-acalabrutinib induction + R maintenance (ECHO)

TRIPLET CHEMO FREE COMBINATIONS

CLINICAL TRIAL

First line BTKi

UNFIT/LOW RISK

R-cBTKi
ENRICH, MANGROVE,ALTAMIRA

2y R-maintenance +cBTKi to progression or toxicity

Tornando al nostro caso clinico (70 anni FIT), se avessi accesso a tutte queste opzioni,
quale sceglieresti?

A. Rituximab + Bendamustina + R mantenimento/ RBAC500

B. R-CHOP/R-DHAP + I e I di mantenimento (TRIANGLE, braccio I)

C. Acalabrutinib + BR poi A+R di mantenimento (ECHO)

D. Ibrutinib + Rituximab (ENRICH)

E. Ho clinical trial aperto (es VIRAL)

… e se il paziente fosse TP53 mutato,
quale sceglieresti?

A. R-CHOP/R-DHAP + I e ASCT, I di mantenimento (TRIANGLE, braccio A+I)

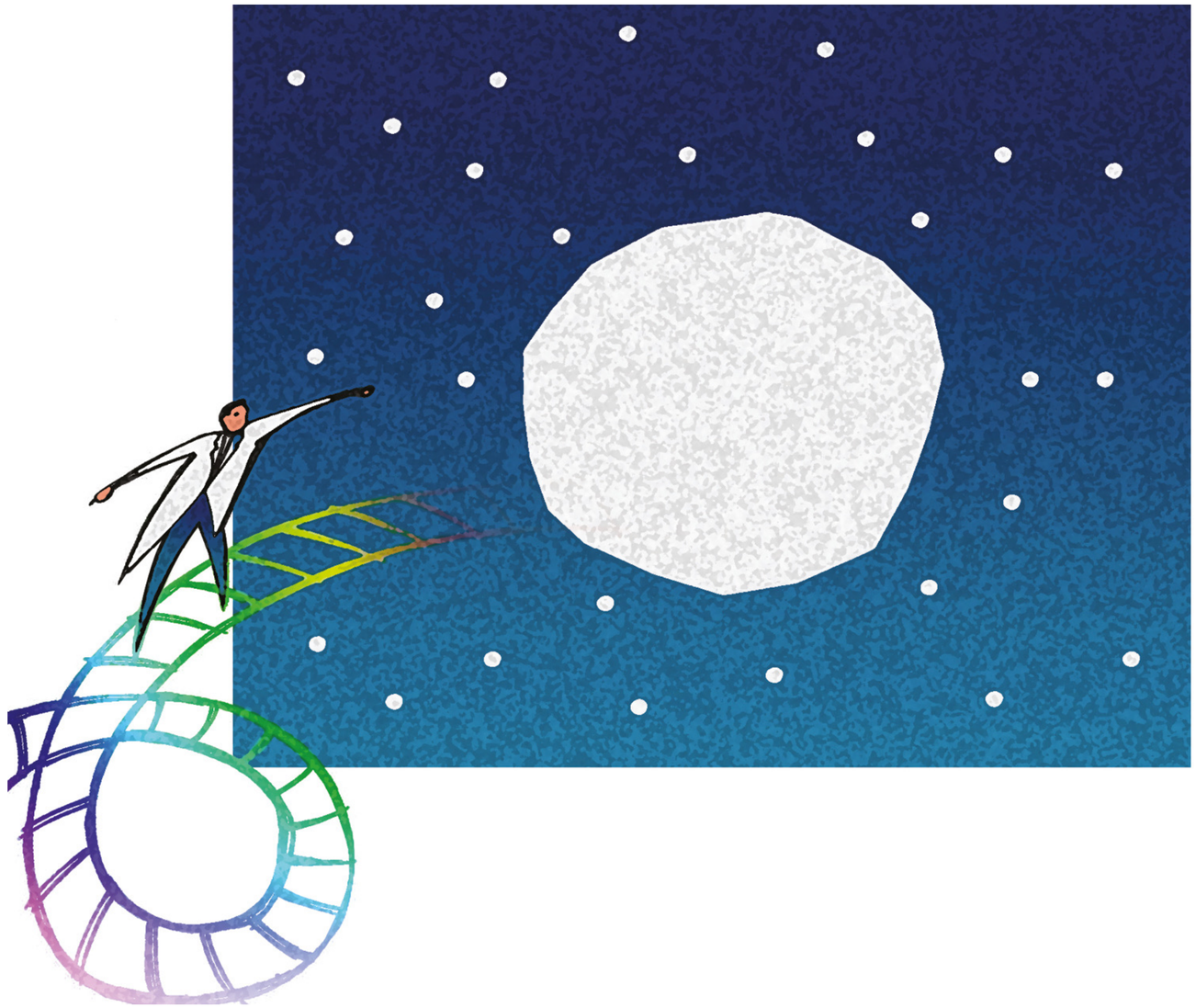
B. Rituximab + Bendamustina + R mantenimento/ RBAC500

C. Acalabrutinib + BR poi A+R di mantenimento (ECHO)

D. Triplet regimen/clinical trial (BoVen, Viral)

CONCLUSIONI

- ✓ **Il nuovo concetto di "anziano/unfit" :** l'età non è più l'unico criterio guida
- ✓ **BTK frontline** anche nell'anziano: combinazione BTK (acalabrutinib) + BR (ECHO), ha mostrato risultati promettenti nel paziente anziano (↑ PFS, *positive trend* in OS), rispetto ai dati meno favorevoli dello studio SHINE.
- ✓ Approcci chemo-free come nell' **ENRICH per** i pazienti **più fragili/unfit**.
- ✓ **I pazienti ad alto rischio** rappresentano ancora un **unmet clinical need**. In questo setting sono in studio nuove combinazioni (es. **VR-BAC**, **regimi chemo-free in triplette come in BOVEN)**



GRAZIE PER L'ATTENZIONE !!