FOCUS SUL LINFOMA MANTELLARE

Come il BTKi di seconda generazione cambia l'approccio di prima linea

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Disclosures of Enrico Derenzini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda	X					X	
Roche					X	X	
Incyte	X				X	X	
ADC-Therapeutics	X						
Beigene						X	X
AbbVie					X	X	
Astra Zeneca			X			X	
Lilly						X	
Sobi					X	X	
Gilead						X	
Regeneron			X				
J&J						X	
BMS						X	

Drivers of therapeutic decision-making in MCL

PATIENT'S AGE/FITNESS

Age vs Transplant eligibility vs Cytarabine-based induction eligibility

1° vs 2° gen cBTKi

BIOLOGIC-RISK MCL

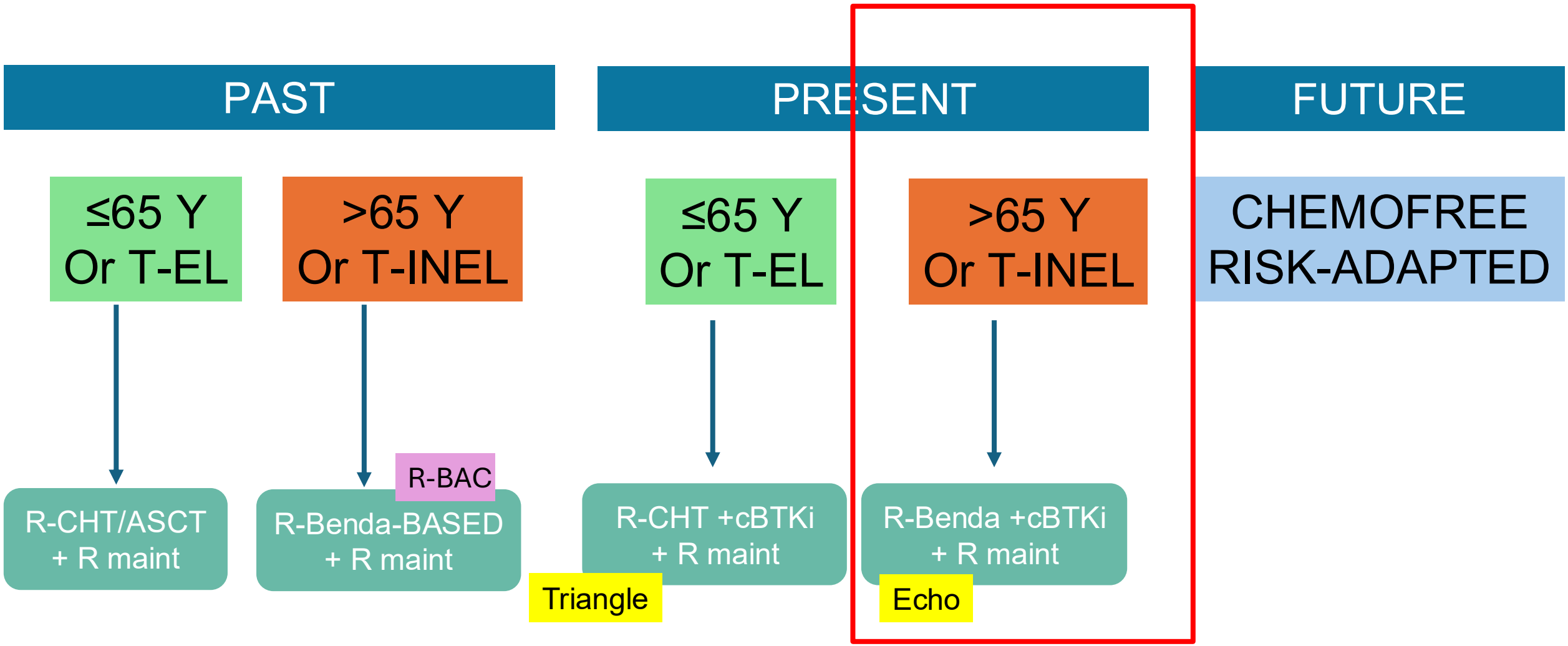
Tailored therapeutic strategies according to biologic risk in MCL?

OPTIMAL SEQUENCING

Is there an optimal sequencing strategy?

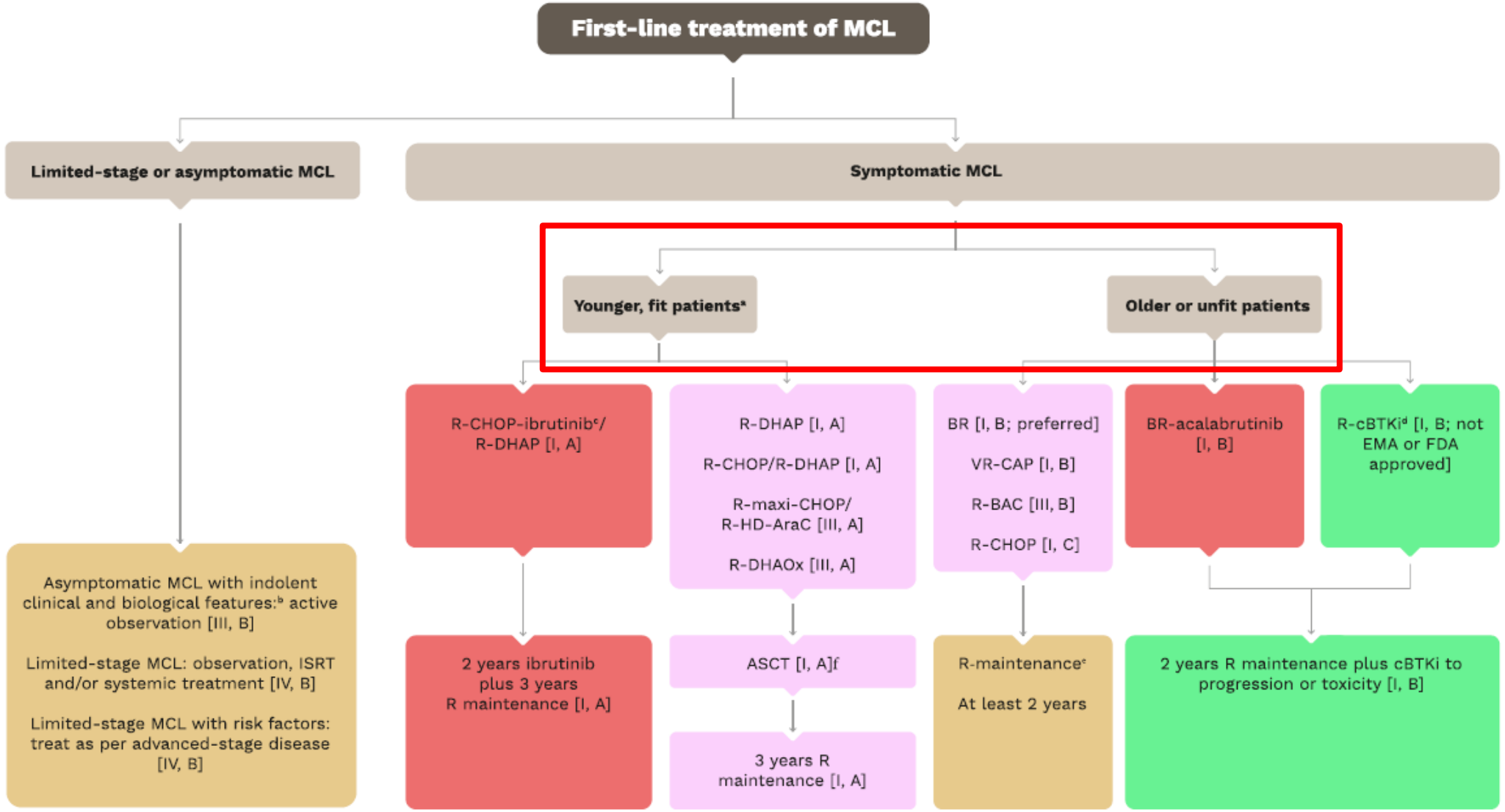
MCL: past, current & future treatment scenario

FIRST LINE



Patient's Age/Fitness And Eligibility To Treatment

EHA-EU MCL GUIDELINES

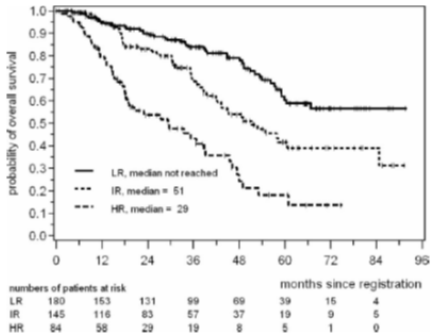


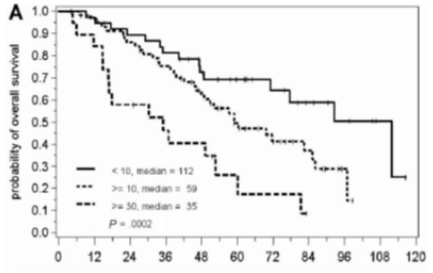
Jerkeman M et al, Hemasphere 2025

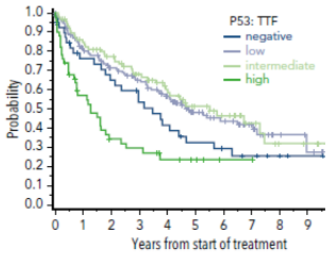
High-Risk MCL

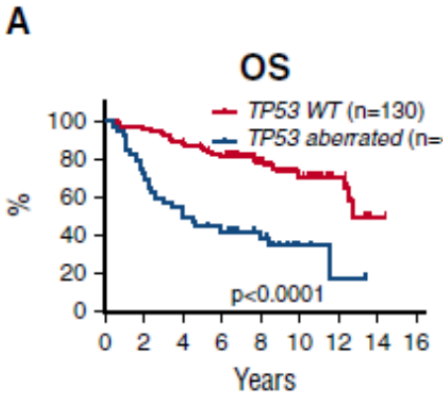
MIPI — Ki-67 — P53 expr. — TP53 status — Histology

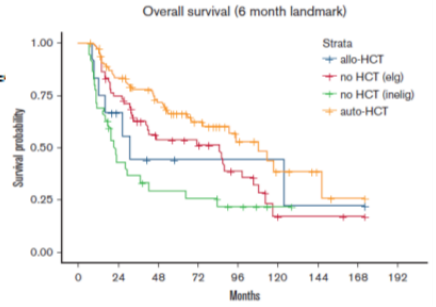
455 pts included
in 3 clinical trials











Tiemann et al BJH 2005 — Determann E et al, Blood 2008 — Aukema et al, Blood 2018 — Eskelund et al, Blood 2017 — Gerson et al, Blood Adv 2023

MIPI score [0.03535 **age** (years)]
age (years)]
0.6978 (if **ECOG** 1)
[1.367 log10(**LDH**/ULN)]
[0.9393 log10(**WBC** count)]

Ki67>30%/50%

p53>50%

TP53 mut/del

Blastoid morphology

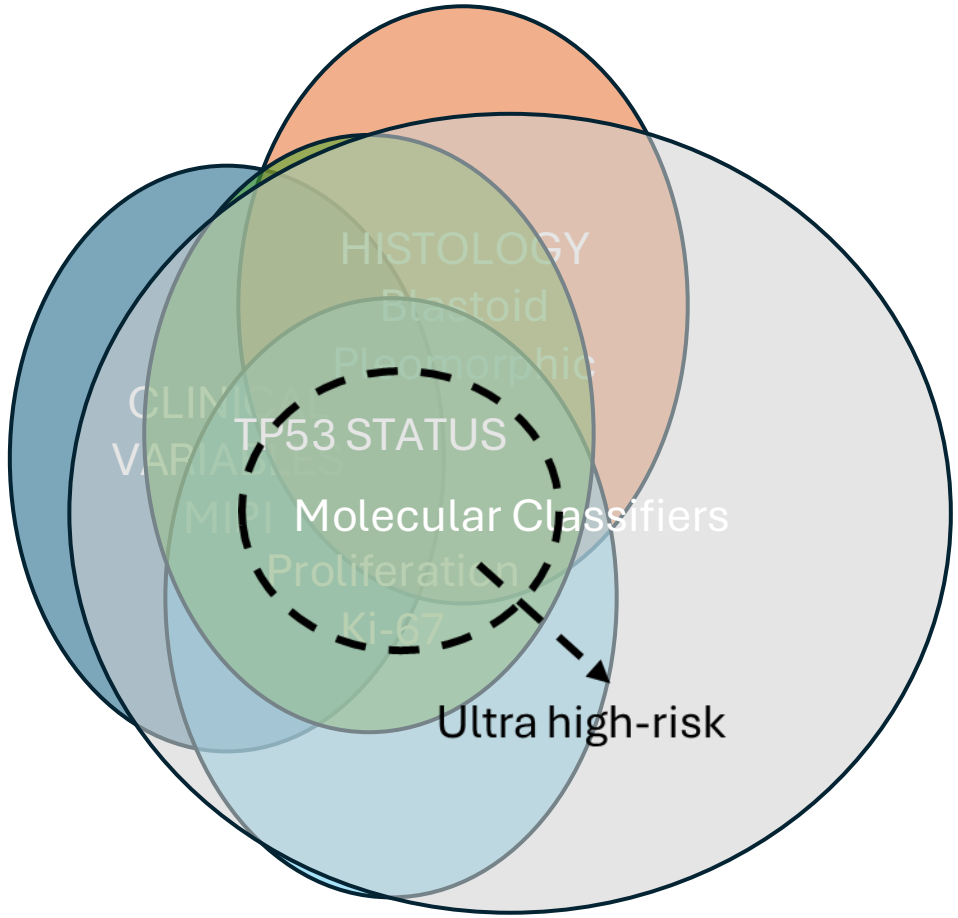
+ Ki 67 (MIPIb)

Poor Outcome

HIGH RISK AND ULTRA-HIGH RISK MANTLE CELL LYMPHOMA

Features	Newly diagnosed MCL
Accepted ultra-high-risk features	De novo blastoid or pleomorphic histology with high-risk mutations[40] Ki-67% ≥50%† in involved tissue biopsy with blastoid or pleomorphic histology[12,41] ‡*TP53* mutation (R273) with other high-risk gene mutations (*KMT2D, NSD2, CCND1, NOTCH1, CDKN2A, NOTCH2,* or *SMARCA4* mutations) and extensive disease burden[42] CNS involvement with systemic disease[43]
Accepted high-risk features	Blastoid or pleomorphic histology[40] Ki-67 ≥50%† in involved tissues with classic histology[12,41] *TP53* mutation[14] and/or del(17p) by FISH, *TP53* overexpression by IHC, and/or non-*TP53* mutations (*NOTCH1/NOTCH2, KMT2D, NSD2,* and *SMARCA4* mutations)[44] CK[45] *MYC* rearrangement and/or amplification[46-50] *TP53* expression in >50% of cells or a high combined MIPI score Simplified MIPI score ≥6.2[51] Bulky disease‖

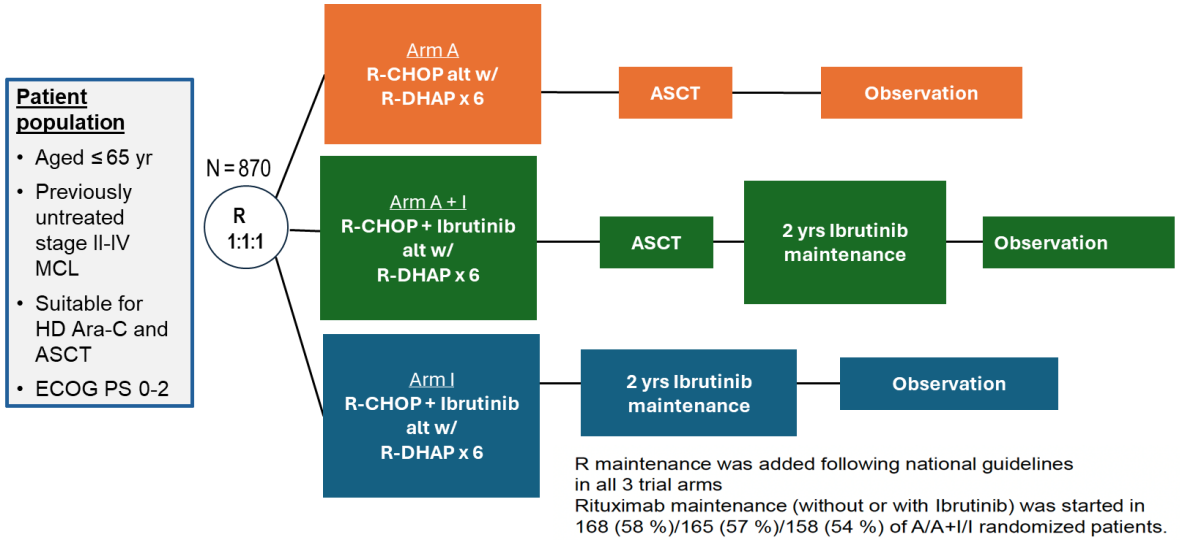
Concept of ultra-high risk MCL:
Clusters of
High-risk factors



Jain and Wang, Blood 2025

cBTKi based 1L regimens

TRIANGLE



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.

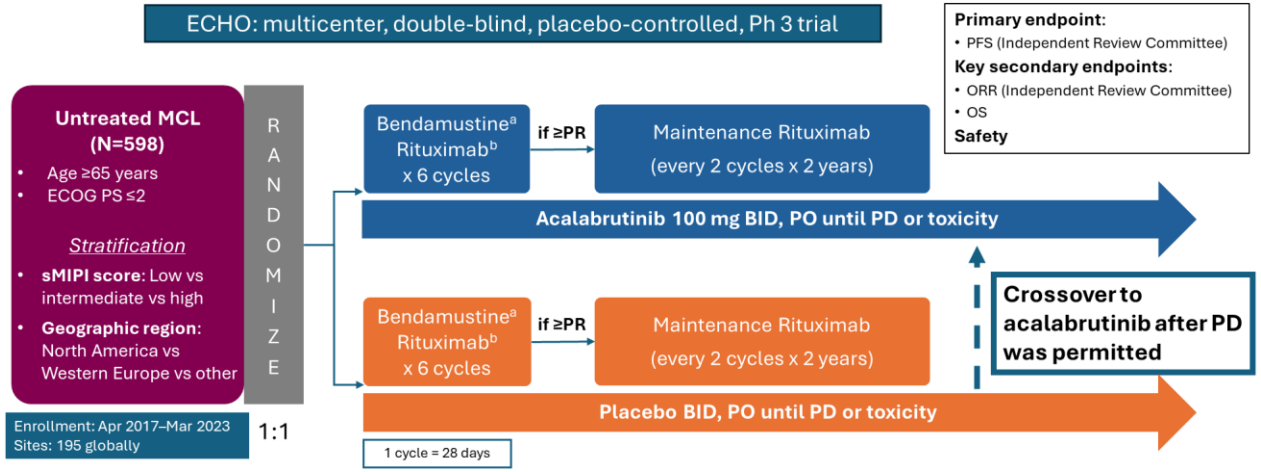
Primary Endpoint
• FFS
Key Secondary Endpoints
• Response rates • PFS • RD • OS • Safety

MIPI int-high 41-43%

Ki67 ≥30% 31-33%

Blastoid 11-13%

ECHO



Primary Endpoint
• PFS by independent review committee (IRC)
Key Secondary Endpoints
• PFS by investigator (INV) • ORR by INV and IRC • DoR by IRC • OS

sMIPI int-high 66-67%

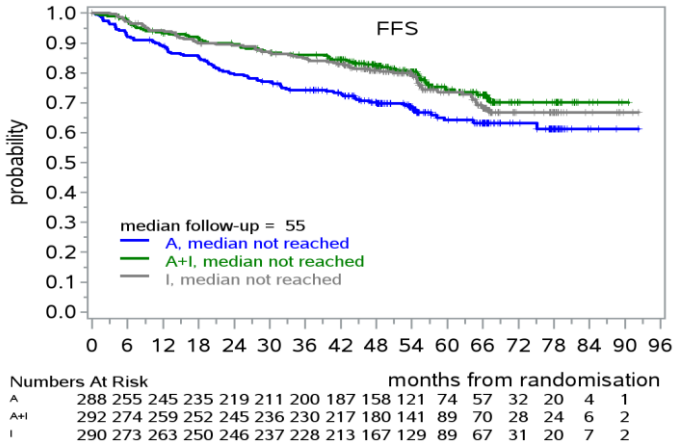
Ki67 ≥30% 46-49%

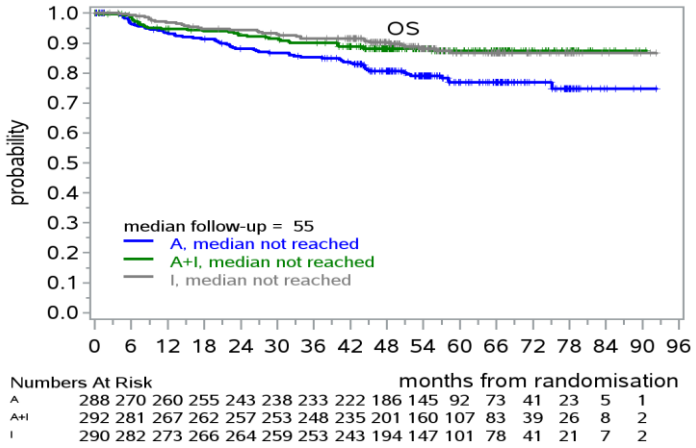
Blastoid/pleomorphic 13-14%

Dreyling M, et Al. Lancet. 2024 May 25;403(10441):2293-2306. doi: 10.1016/S0140-6736(24)00184-3. Epub 2024 May 2. PMID: 38705160.
Michael Wang et al.. J Clin Oncol 43, 2276-2284(2025).DOI:10.1200/JCO-25-00690

cBTKi based 1L regimens

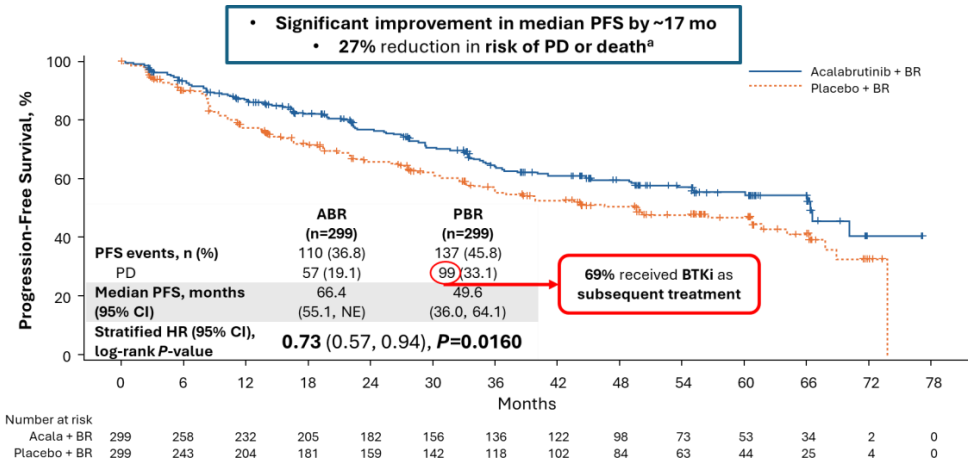
TRIANGLE

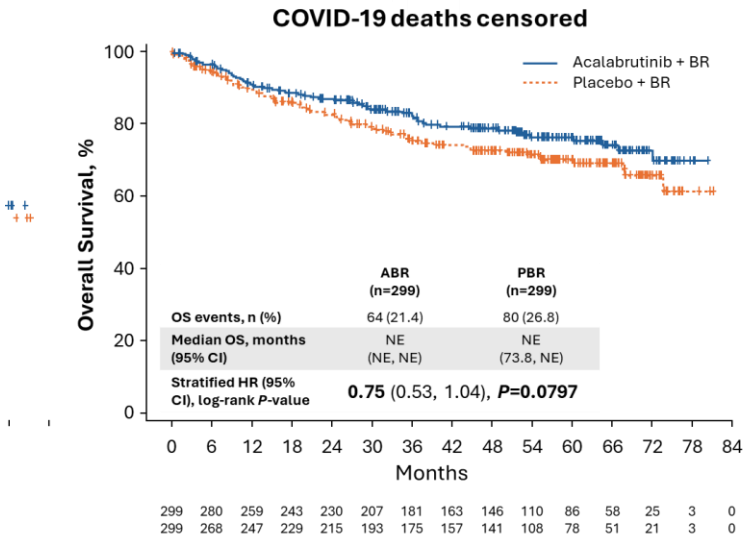




Dreyling et al ASH 2022; Dreyling at al *Lancet* 2024

ECHO

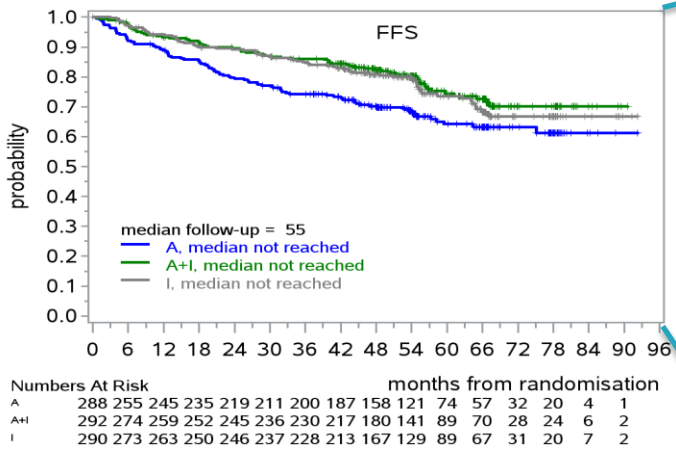




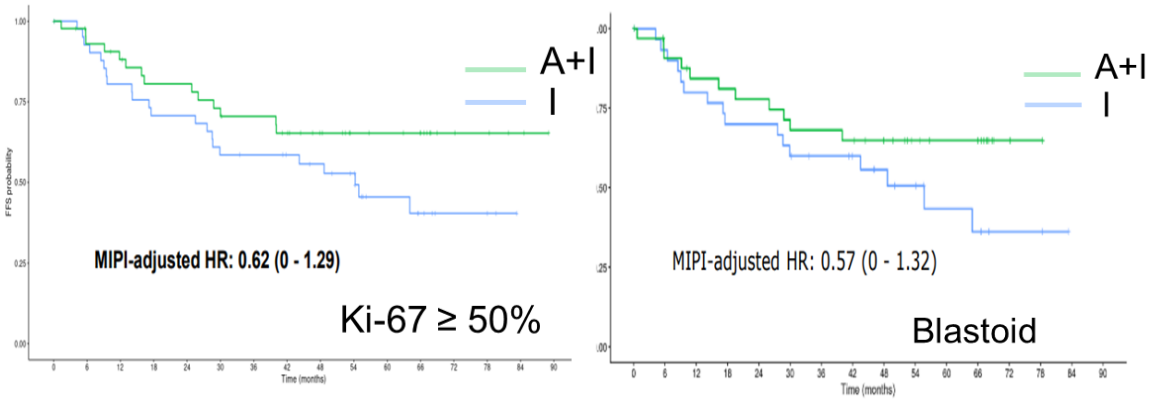
Michael Wang et al.. J Clin Oncol 43, 2276-2284(2025).DOI:10.1200/JCO-25-00690

cBTKi based 1L regimens in young, fit, high-risk MCL

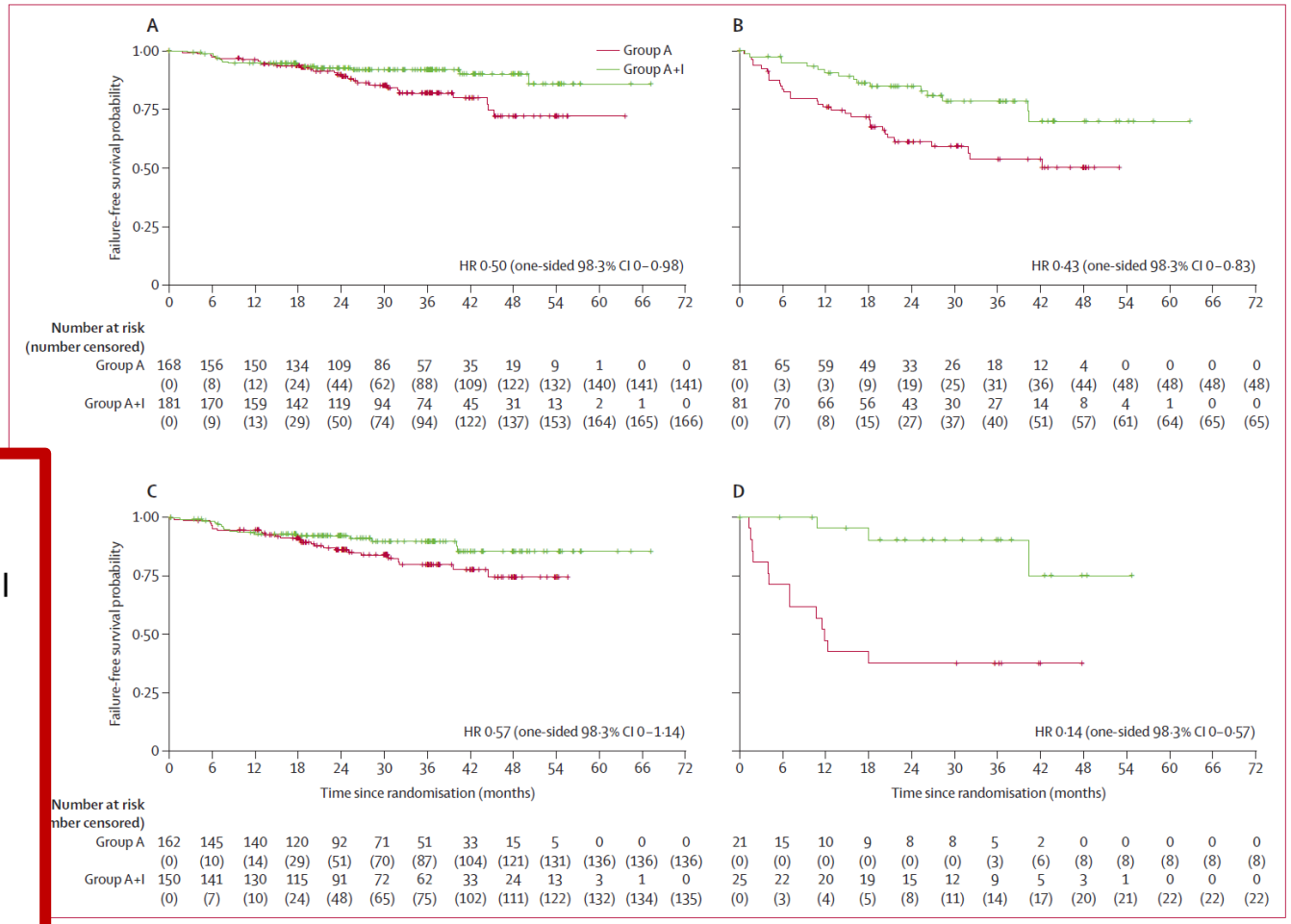
TRIANGLE



- 4-year FFS A: 70%
- 4-year FFS A+I: 82%
- 4-year FFS I: 81%



TRIANGLE: Greater benefit of A+ I over A in high-risk patient as defined by high p53 expressors and high-risk biology (p53 > 50% or Ki67 ≥30%)

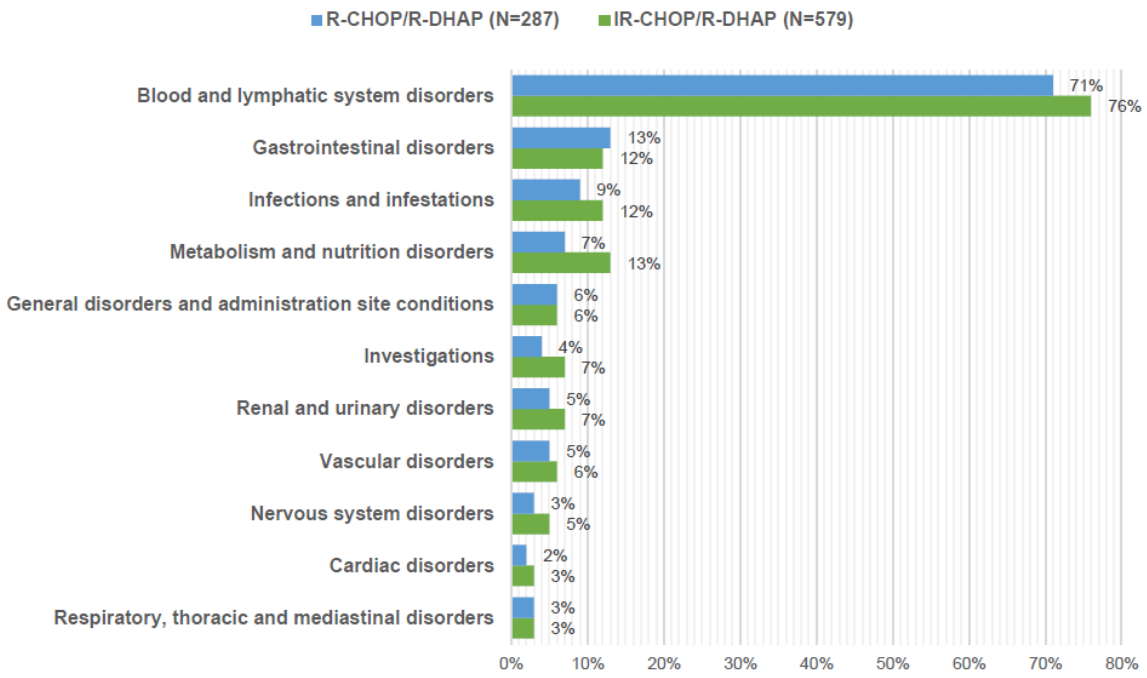


4: Failure-free survival for group A+I *vs* group A in selected subgroups of patients with low (<30%) Ki-67 (A), high (≥30%) Ki-67 (B), low (≤50%) p53 (C), and high (>50%) p53 (D)
HR=hazard ratio.

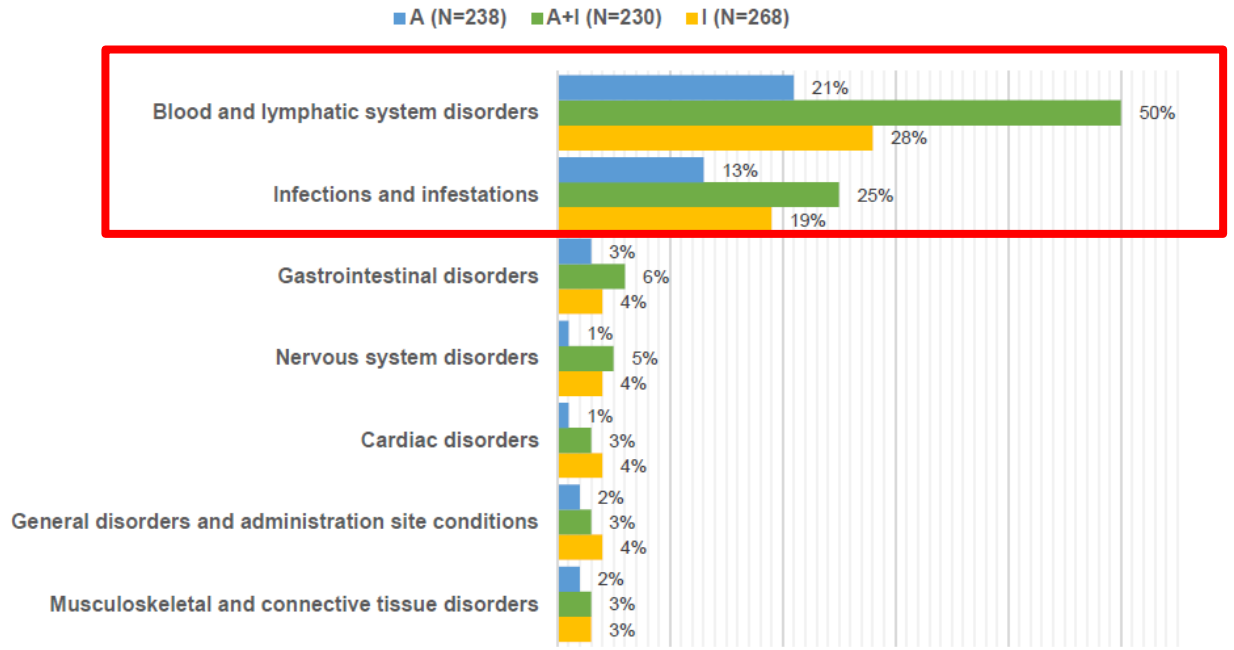
Dreyling et al ASH 2022; Dreyling at al *Lancet* 2024

cBTKi based 1L regimens in young, fit MCL

TRIANGLE



Induction



Maintenance phase

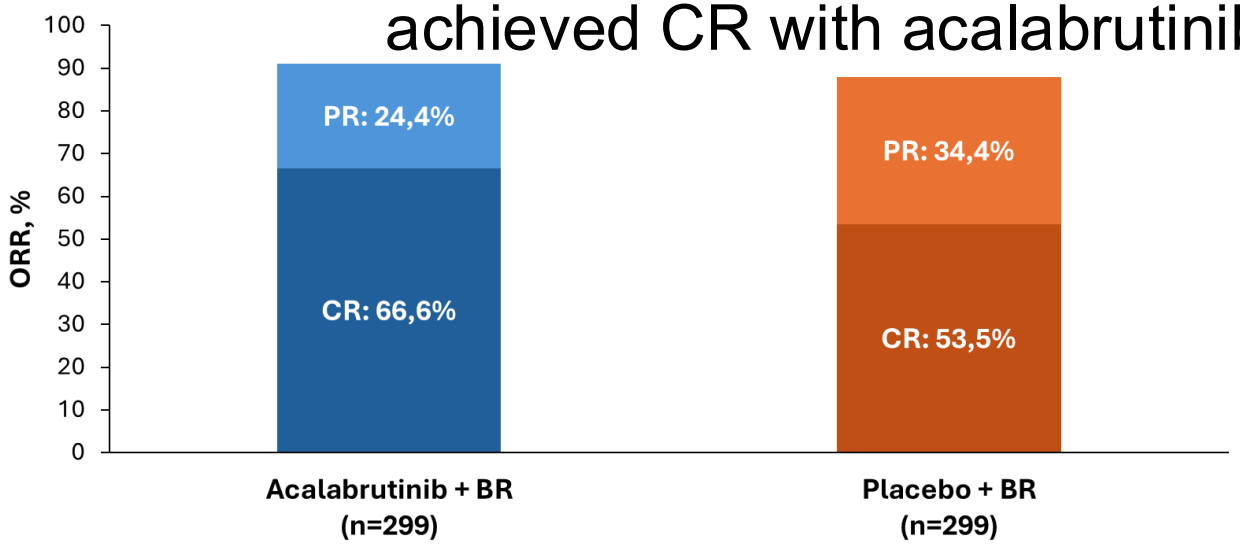
Dreyling et al ASH 2022; Dreyling at al *Lancet* 2024

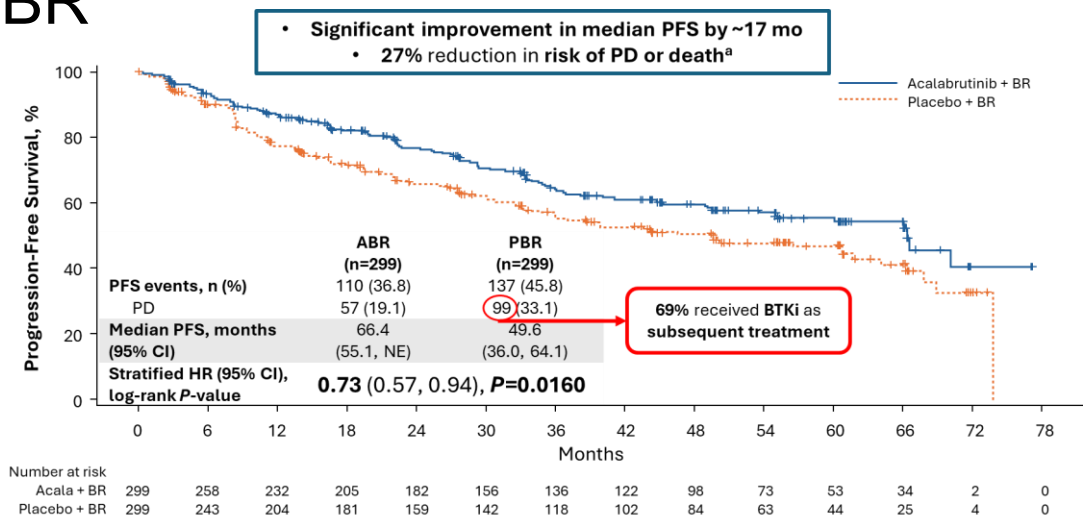
cBTKi based 1L regimens in elderly, unfit MCL

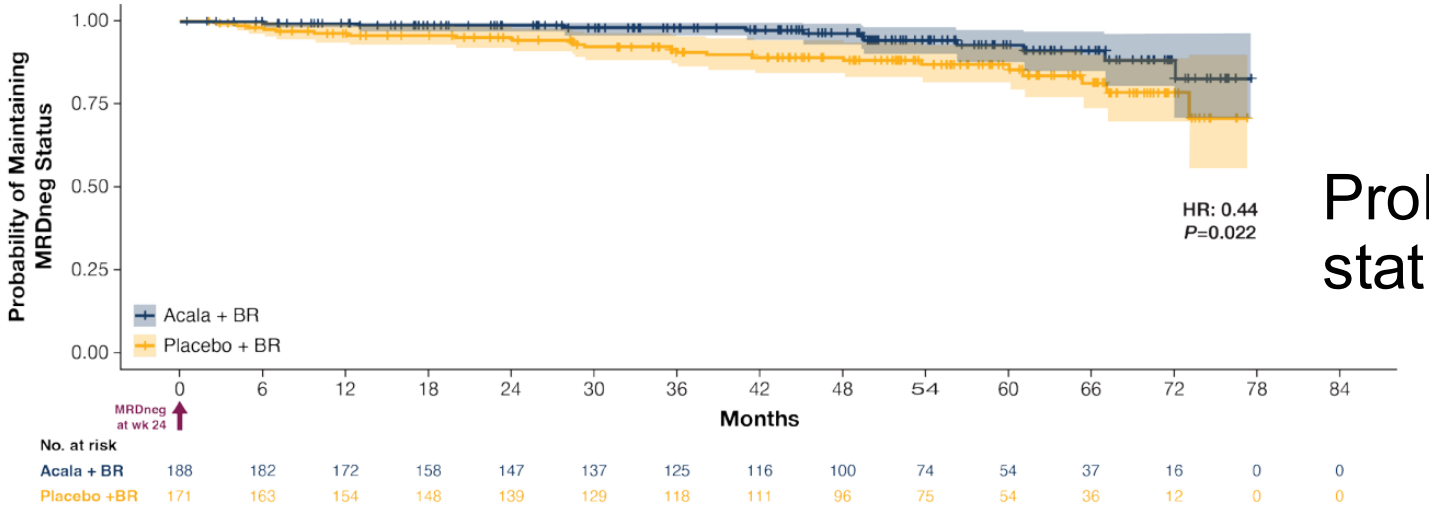
ECHO Study

EFFICACY

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







Probability of mantaining MRD-negative status after induction by treatment arm

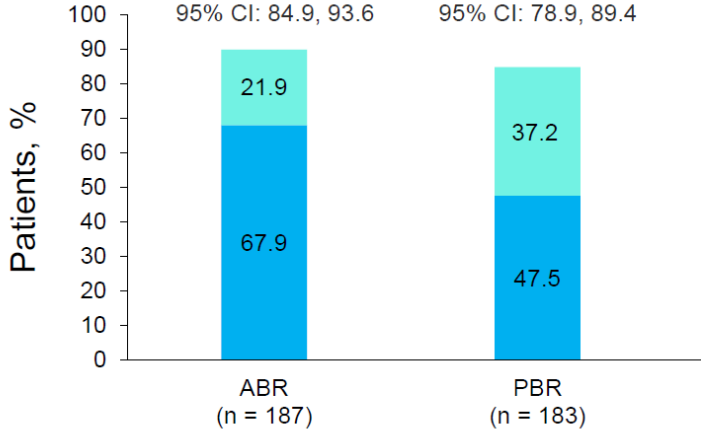
- The probability of maintaining MRD negativity after induction was 2.3-fold greater for the acala arm than the placebo arm

Wang et al *JCO* 2025

ECHO Study: High-risk Subset

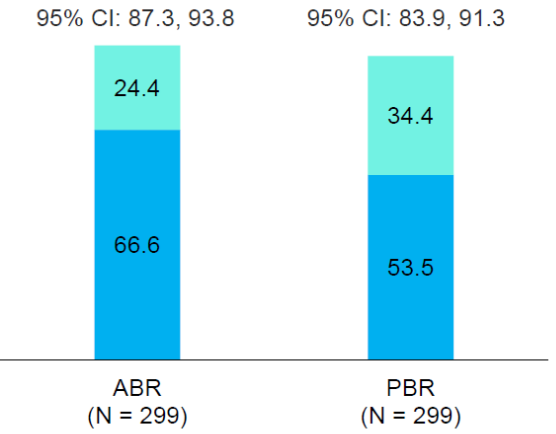
HIGH-RISK

High-risk Population



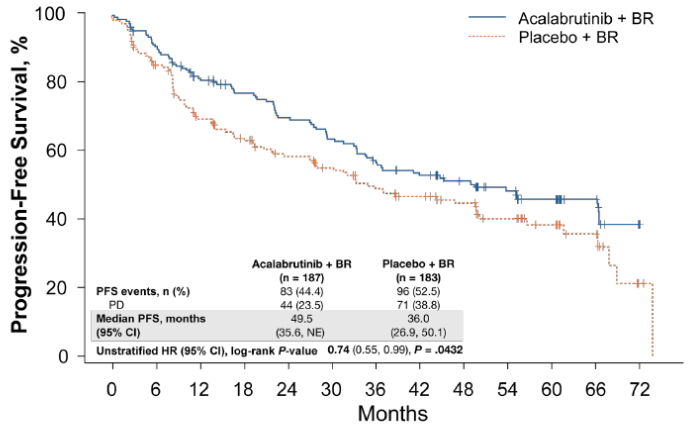
	ORR	CR
Difference (ABR vs PBR)	5.1%	20.4%
95% CI	-1.7, 12.1	10.4, 30.0
P-value	.1382	**<.0001**

Overall Population[1]



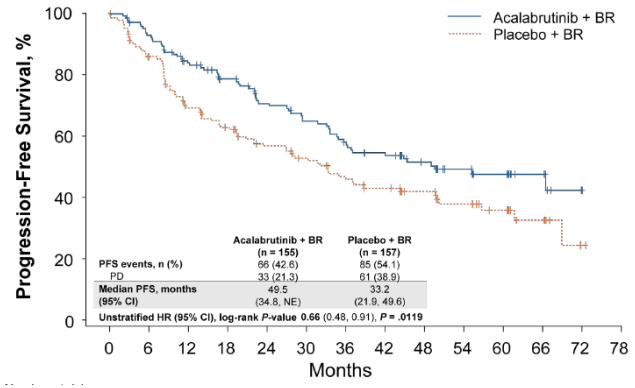
	ORR
Difference (ABR vs PBR)	3.0%
95% CI	-2.0, 8.1
P-value	.2196

PFS in High-risk Population

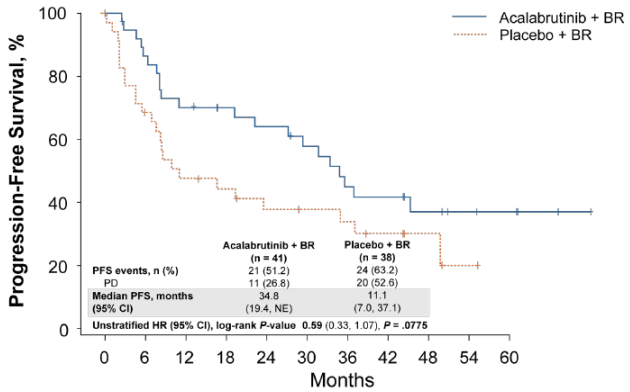


- After PD, 38 (53.5%) of 71 patients with high-risk disease who progressed on placebo crossed over to acalabrutinib

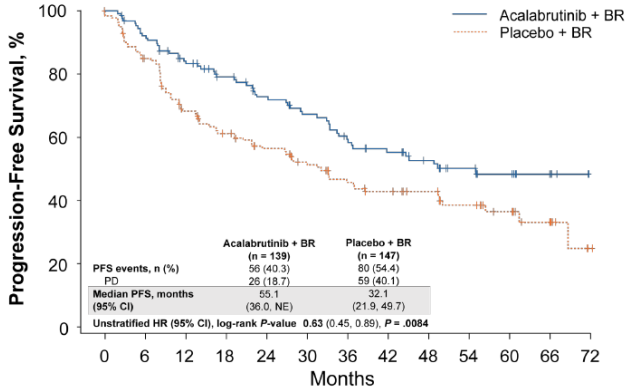
PFS in Patients With Ki-67 ≥30%, Blastoid/ Pleomorphic Histology, and/or *TP53* Mutation



PFS in Patients With Blastoid/Pleomorphic Histology



PFS in Patients With Ki-67 Index ≥30%



Dreyling et al. EHA 2025:Abstract LB3439; Wang et al *JCO* 2025

ECHO Study: Safety

AEs of INTEREST

Adverse Events of Interest

Event, n (%)	Acalabrutinib + BR (n=297)		Placebo + BR (n=297)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Atrial fibrillation				
Hypertension				
Major bleeding[a]				
Infections[b]				
Second primary malignancies (excluding non-melanoma skin)[b]				
Median treatment exposure (range), months				

n (%)	COVID-19–related AEs	
	Acalabrutinib + BR (n=297)	Placebo + BR (n=297)
Any AE	121 (40.7)	88 (29.6)
Grade ≥3	60 (20.2)	50 (16.8)
Grade 5	28 (9.4)	20 (6.7)
SAEs	60 (20.2)	52 (17.5)
Grade ≥3	58 (19.5)	48 (16.2)
AE leading to acalabrutinib/ placebo discontinuation	31 (10.4)	19 (6.4)

[a]Grouping of preferred terms; defined as a hemorrhagic event that is serious, or grade ≥3 in severity, or that is a CNS hemorrhage (any severity grade). [b]Grouping of preferred terms.
BR, bendamustine + rituximab; CNS, central nervous system.

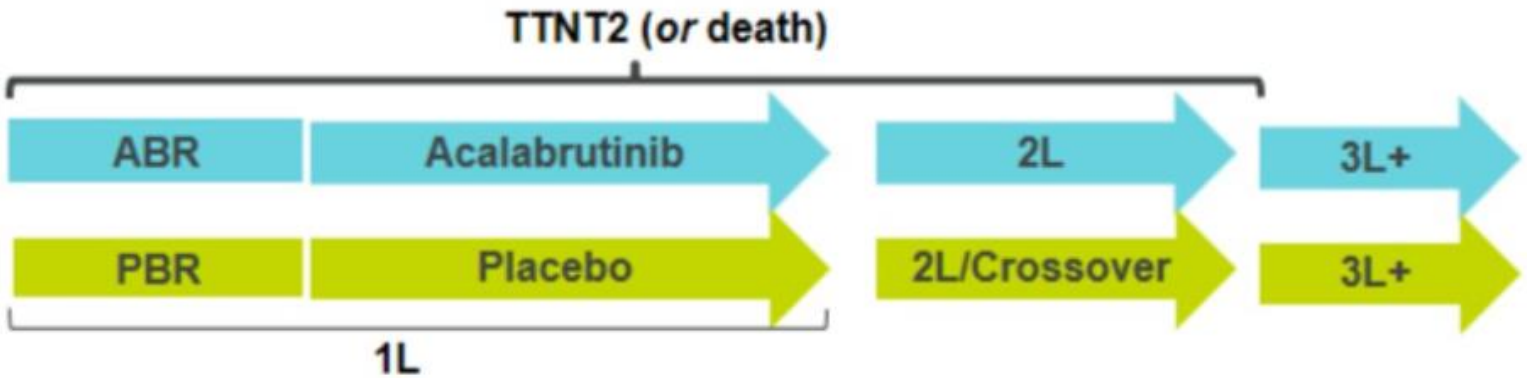
Wang M, JCO 2025

ECHO Study: Long Term FUP

LONG-TERM FUP & TTN2

Methods:

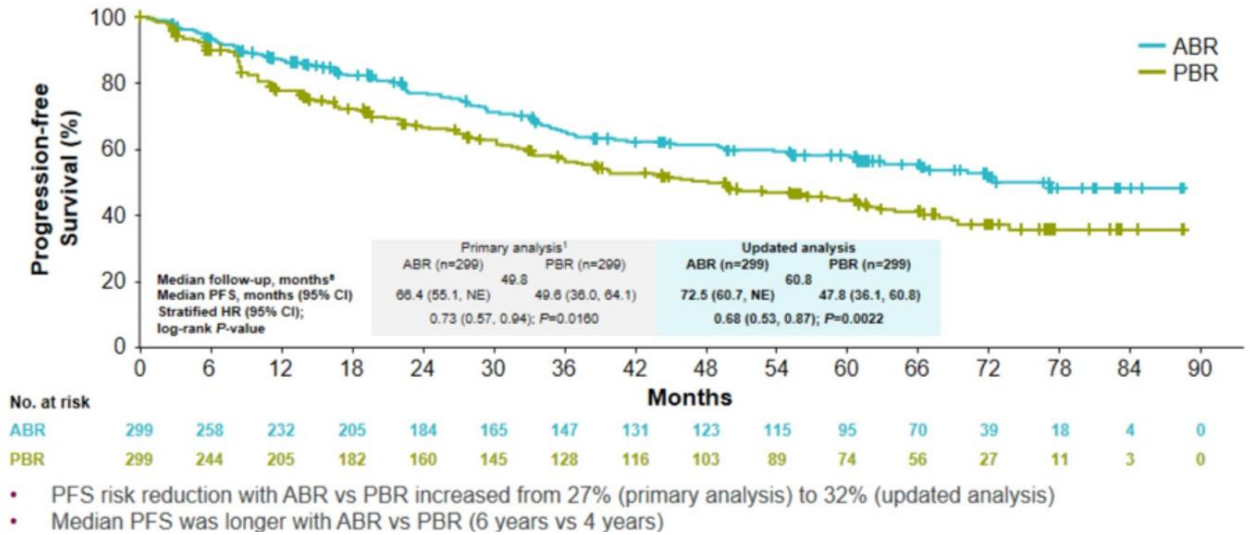
- Median follow-up was 60.8 months (range 0-88.5) per reverse K-M for PFS
- Median time on study was 51.9 months (range 0.03-93.04) for all other outcomes
- TTNT2 was assessed in a post hoc analysis
- TTNT2 was defined as the time from randomization to either the start of 3L antilymphoma treatment after discontinuation of randomized treatment or death



Wang M, ASH 2025

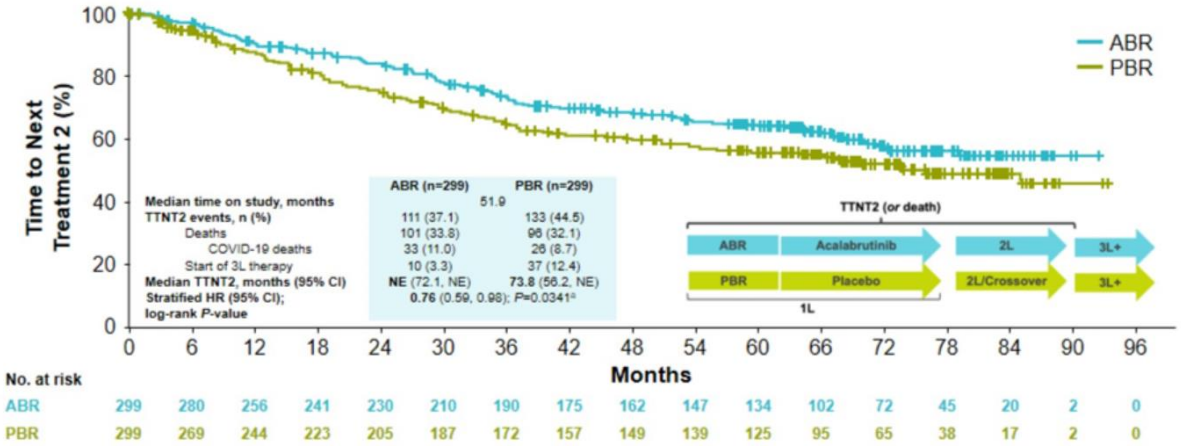
ECHO Study: Long Term FUP

LONG-TERM FUP & TTN2



- PFS risk reduction with ABR vs PBR increased from 27% (primary analysis) to 32% (updated analysis)
- Median PFS was longer with ABR vs PBR (6 years vs 4 years)

At 60.8 months of Follow-up PFS further improved with ABR vs PBR



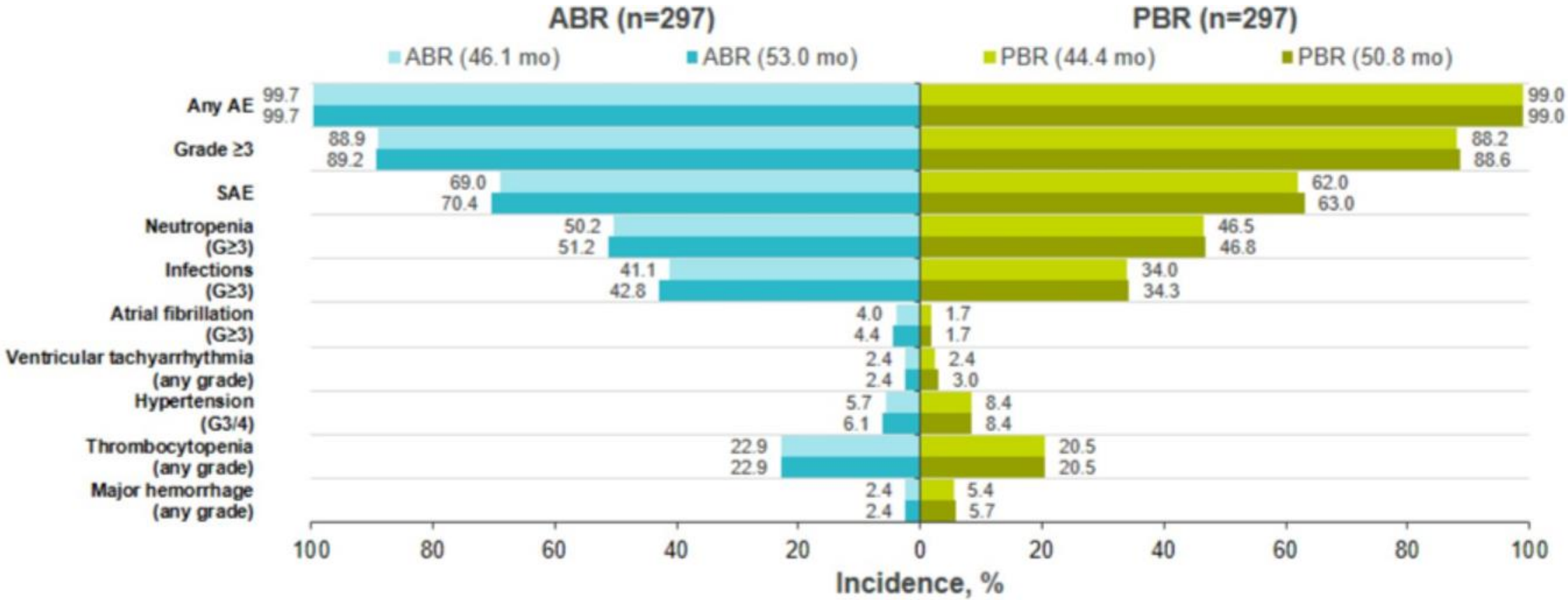
- At 48 months, the rate of patients who had not yet initiated 3L therapy or had not died was 67.6% for ABR vs 59.2% for PBR

ABR lowered the risk of needing 3L therapy (TTNT2) by 24% compared with PBR

Wang M, ASH 2025

ECHO Study: Long Term Safety

Safety & Long Term FUP



- ABR arm[a]: 1 new case of grade ≥3 atrial fibrillation reported (primary, 4.0%; updated, 4.4%)
- PBR arm[a]: 1 new case of ventricular tachyarrhythmia reported (primary, 2.4%; updated, 3.0%)

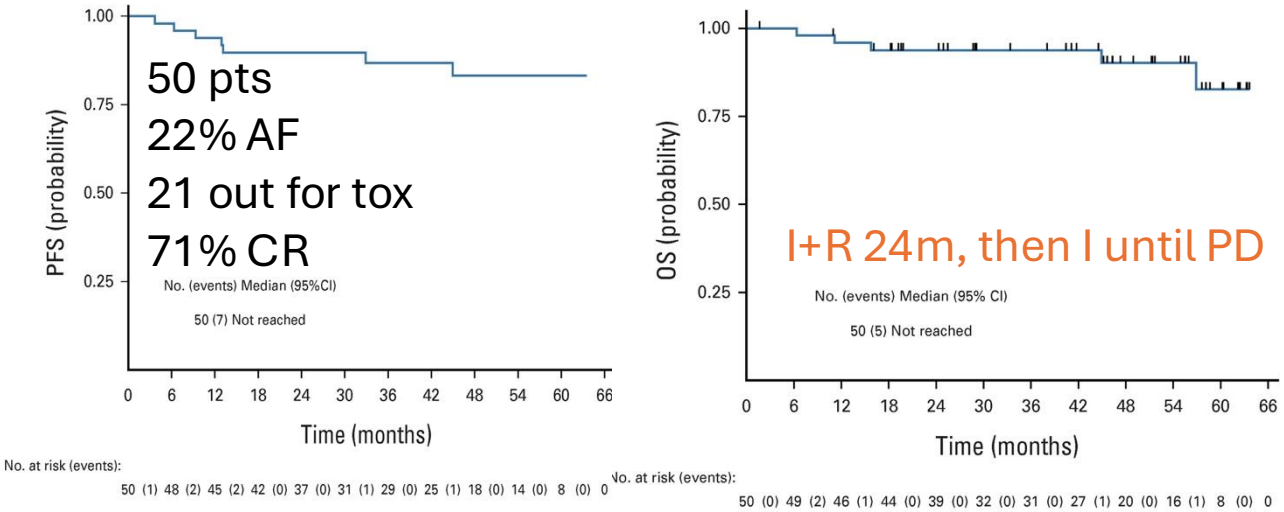
Wang M, ASH 2025

cBTKi + Anti CD20

Chemofree 1L: Phase 2

Towards a chemofree 1L therapy in MCL

R + Ibrutinib



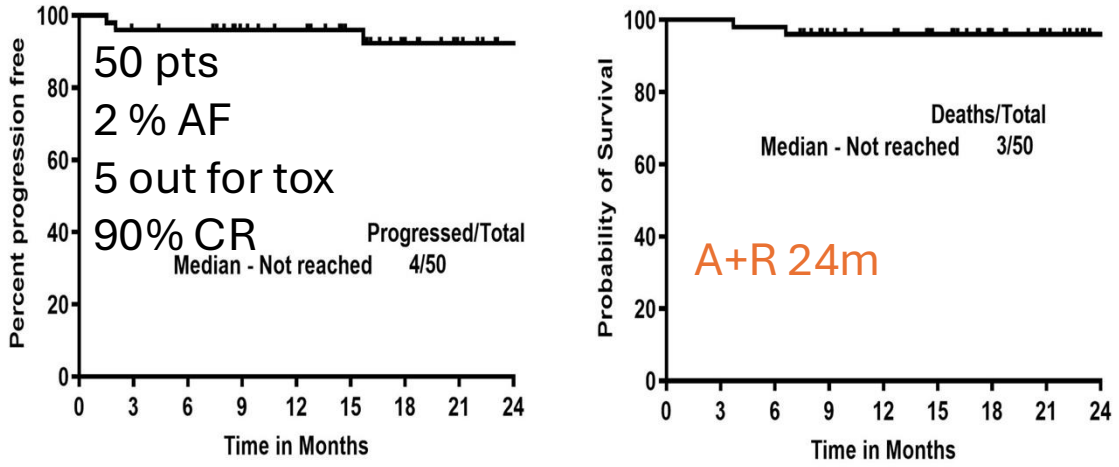
Median PFS NR
3-year 87%

Median OS NR
3-year 94%

Ki-67% > 50% and blastoid excluded.
Ki67 30-50% in 24% pts. s-MIPI high in 16%

Jain at al. JCO 2021

R+ Acalabrutinib



Median PFS NR
2-year 92%

Median OS NR
2-year 96%

Ki-67% > 50% in 31% pts, 3 blastoid,
s-MIPI high in 22% pts

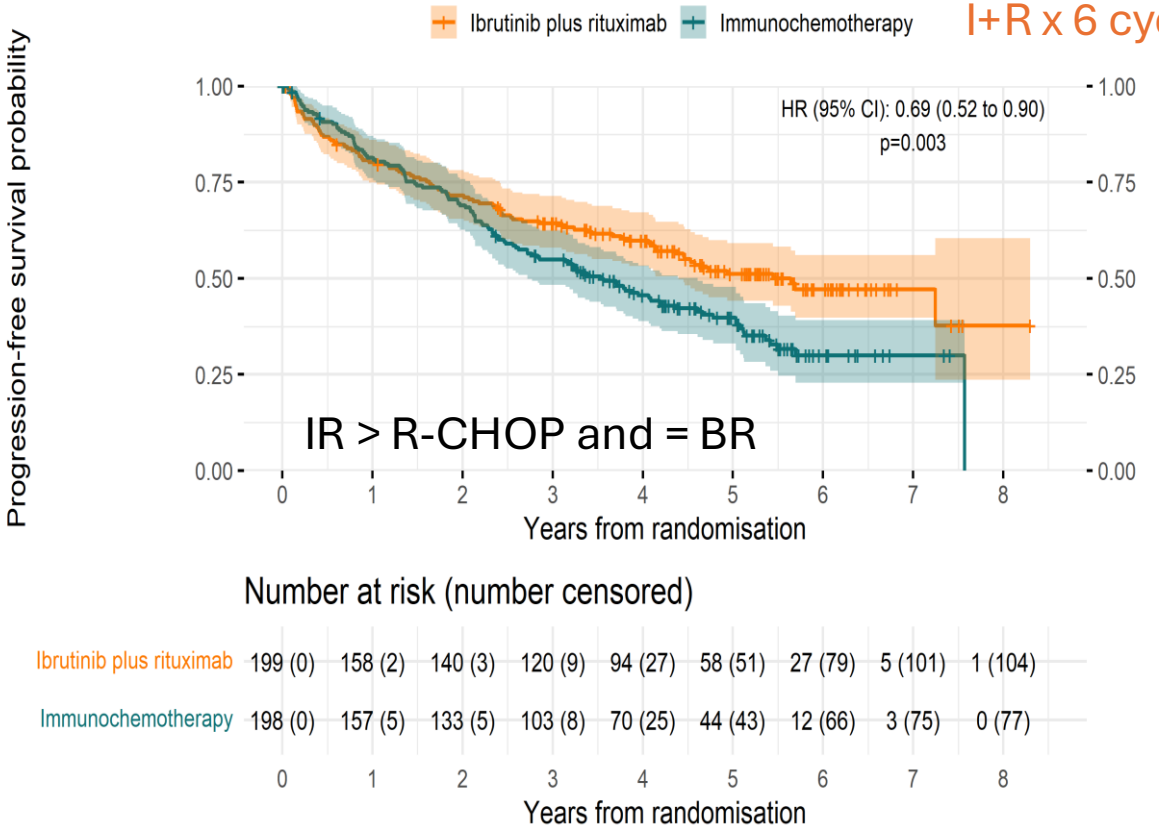
Jain at al. ASH 2023

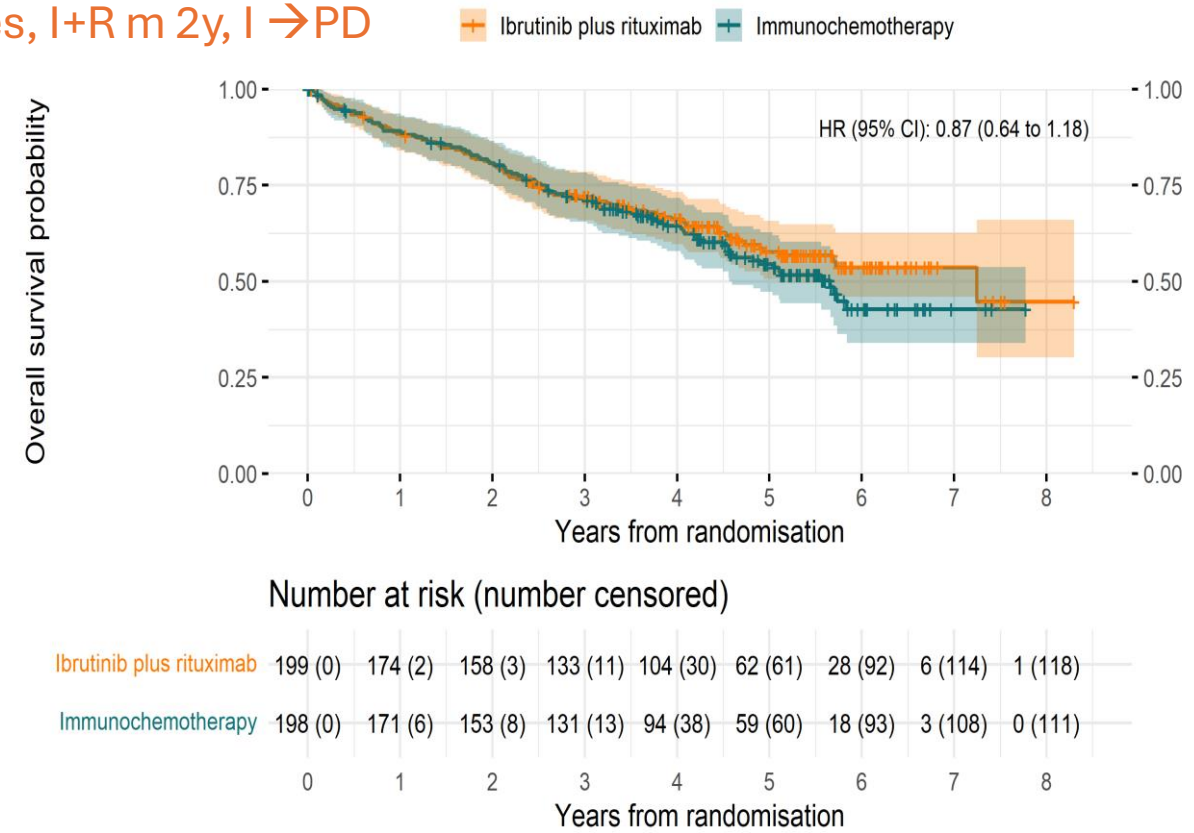
ENRICH Study

Chemofree 1L: Phase 3

Towards a chemofree 1L therapy in MCL

I+R x 6 cycles, I+R m 2y, I →PD





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

Lewis et al ASH 2024, Lancet 2025

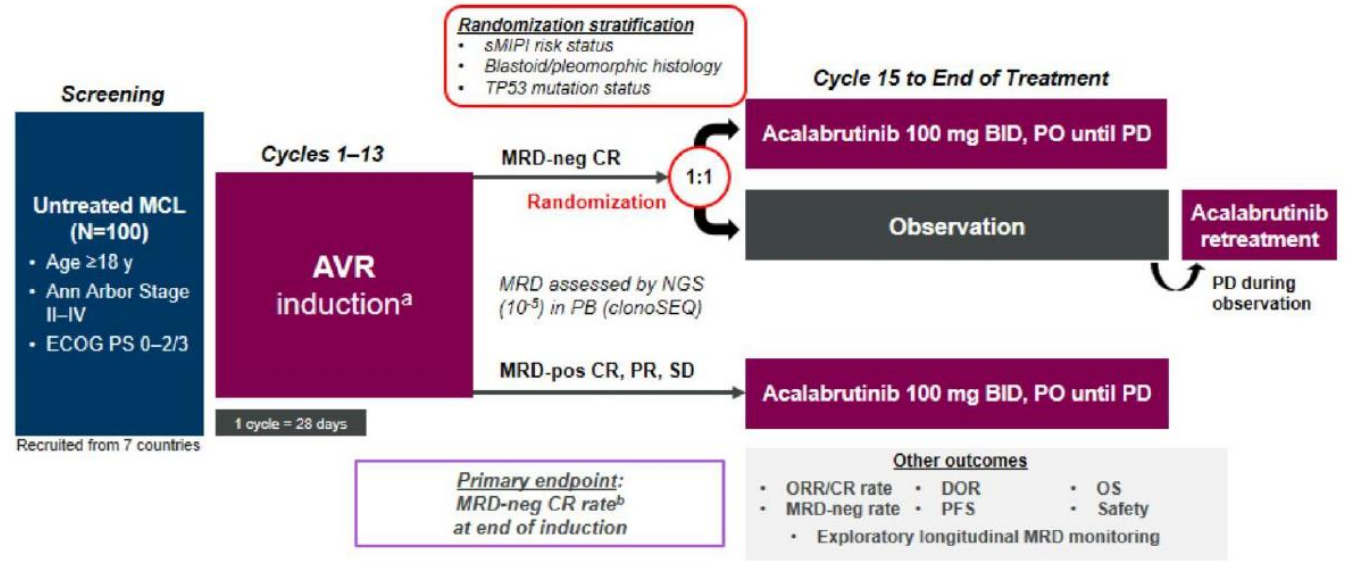
5-year OS (95% CI)
IR: 57.7% (50.6% to 65.7%)
R-Chemo: 54.5% (47.3% to 62.8%)

IR: CR 54%
R-chemo: CR 53%

TrAVeRse Study

Chemofree 1L Triplets

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



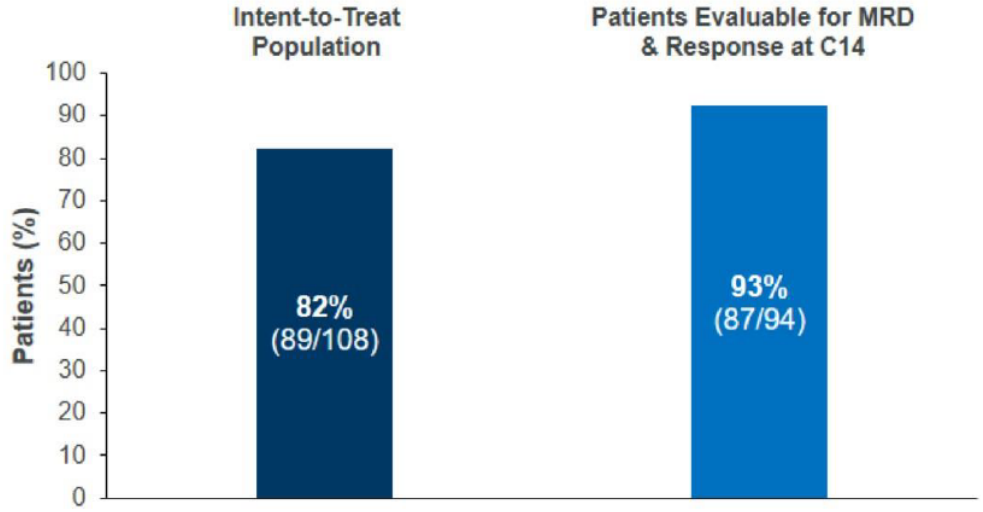
NCT05951959.

[a]AVR induction: acalabrutinib 100 mg BID (C1–C13; also given in C14 post-induction), venetoclax (C2–C13 [5-week ramp-up in C2: 20 mg up to 400 mg daily]), rituximab (375 mg/m² day 1 of C1–12).

[b]MRD-neg (in PB by NGS [10^{-5}; clonoSEQ]) while in CR (per Lugano criteria).

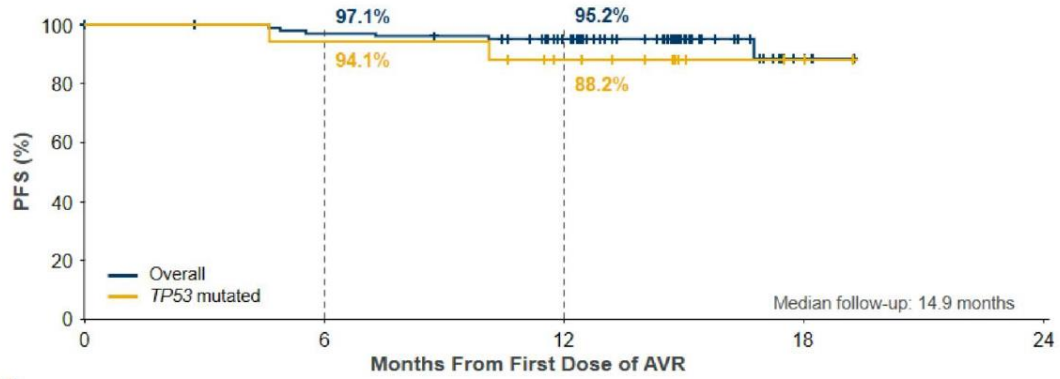
AVR, acalabrutinib + venetoclax + rituximab; BID, twice daily; C, cycle; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MRD, measurable residual disease; neg, negative; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; PO, orally; pos, positive; PR, partial response; SD, stable disease; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; TN, treatment-naive.

TrAVeRse



Progression-free Survival

PFS rates were high, regardless of TP53 mutation status

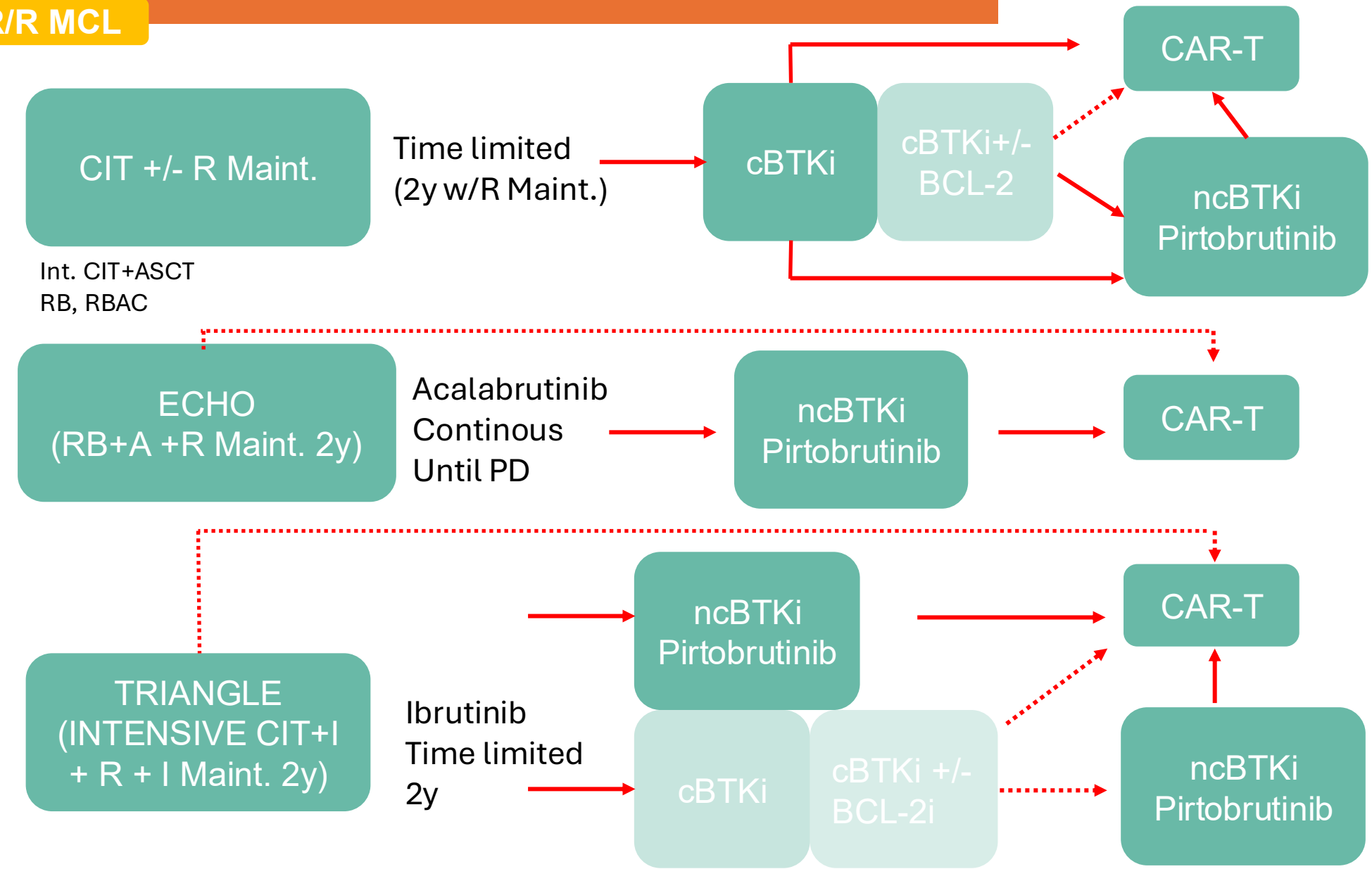


No. at risk					
Overall	108	102	90	3	0
TP53 mutated	17	16	12	2	0

Hawkes et al. ASH 2025

MCL: past, current & future treatment scenario

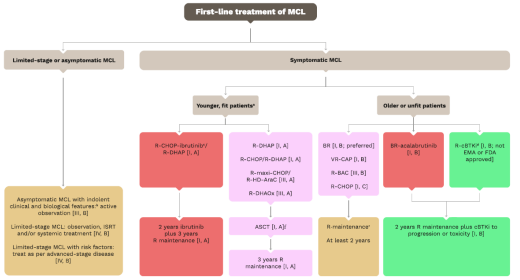
R/R MCL



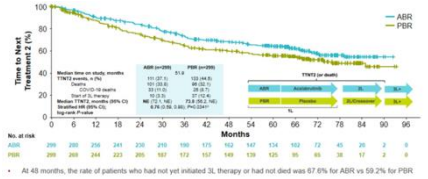
Eyre TA, et AL. Lymphomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025 Nov;36(11):1263-1284.
doi: 10.1016/j.annonc.2025.07.014. Epub 2025 Aug 5. PMID: 40774601.

Conclusions

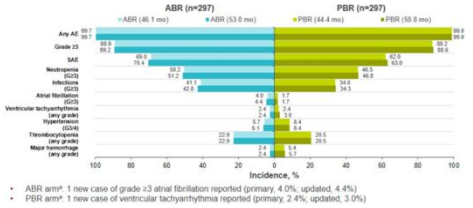
cBTKi containing regimens have reshaped the treatment of algorithm of mantle cell lymphoma, with a profound impact on the natural history of MCL



In elderly/unfit patients, the combination of cBTKi (Acalabrutinib) and BR (ECHO regimen) increases the quality of initial response, with significant impact on long-term outcomes (TTN2)



With longer follow-up, there are no safety signals with ECHO regimen (Acalabrutinib-BR)



In light of the data of chemofree trials of Anti CD20 mAbs+BTKi, consider de-escalating bendamustine in selected patients populations (Frail or *TP53* mutated) treated with the ECHO regimen. Triplets will replace immunochemotherapy in the future