CORSO EDUCAZIONALE COMMISSIONE ANZIANI

XIII EDIZIONE

Giardini Naxos - Marriott Delta Hotels
17-18 aprile 2026

FONDAZIONE ITALIANA LINFOMI

La terapia del linfoma mantellare nel paziente anziano nell'era dei BTKi in prima linea

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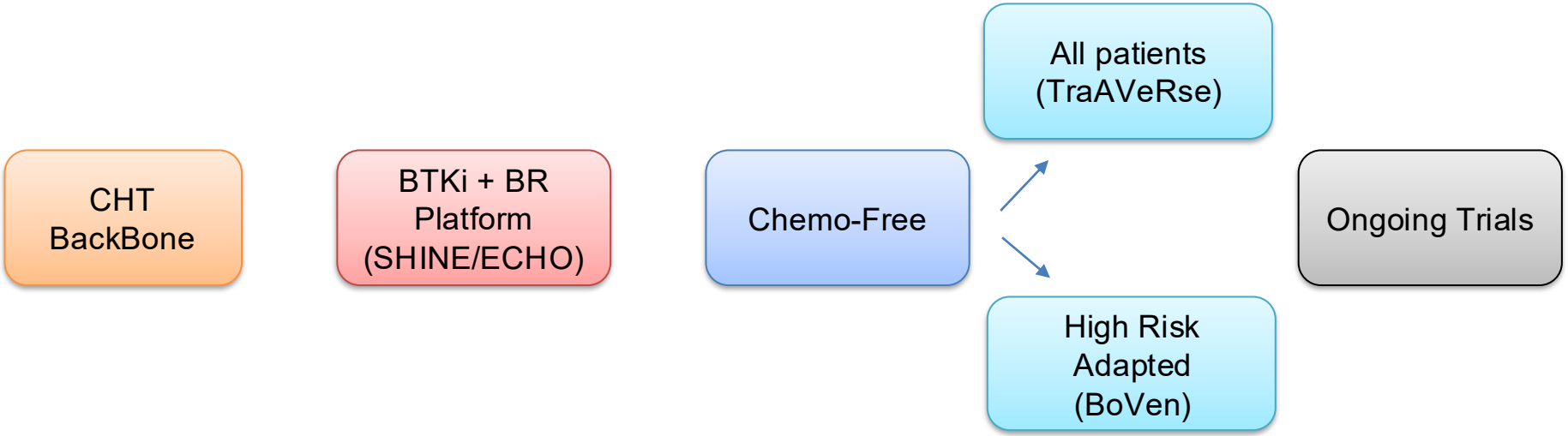
UOC Ematologia Vicenza

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead Science					X	X	
Novartis					X	X	
BMS					X	X	
Janssen					X		
Sobi					X	X	
AstraZeneca					X	X	
Lilly					X		
BeOne						X	
Roche					X	X	
Abbvie					X		

Outline


CHT BackBone
BTKi + BR Platform (SHINE/ECHO)
Chemo-Free
All patients (TraAVeRse)
High Risk Adapted (BoVen)
Ongoing Trials

Outline

CHT
BackBone

BACKBONE: Induction strategies in the elderly population

StiL NHL and BRIGHT study

R-CHOP platform

R-Benda platform

Bendamustine improves survival[1,2]

Add on with:

- Rituximab Maintenance[3]
- Lenalidomide[4]
- Bortezomib/Lenalidomide[5]
- **BTKi**
- Cytarabine[6]

1.Rummel MJ et al, Lancet 2013; 2.Flinn et al, Blood 2014; 3.Rummel MJ et al, JCO 2016; 4.Ruan J et al, Blood 2016; 5.Smith M et al, Blood 2024; 6.Visco C, et al, Lancet Haematology 2017

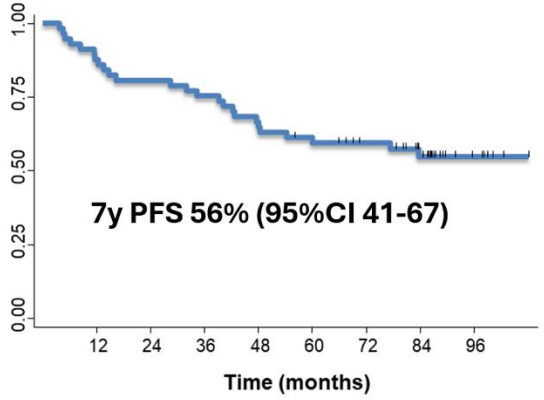
Results - LONG TERM FOLLOW-UP – 7Y

FIL_RBAC500

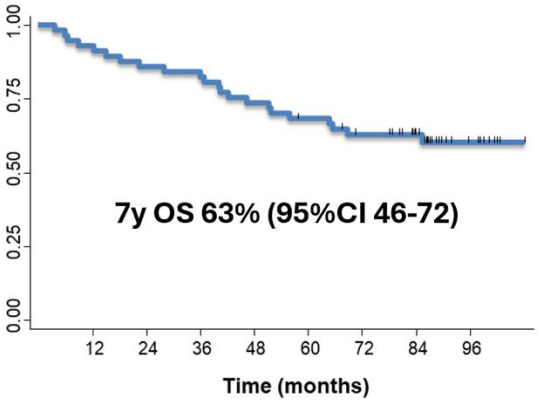
FONDAZIONE ITALIANA LINFOMI

Treatment	Day 1	2	3	4
Rituximab 375 mg/m²	↓			
Bendamustine 70 mg/m²		↓	↓	
Ara-C 500 mg/m²		↓	↓	↓

Median follow-up 86 months (57-107)

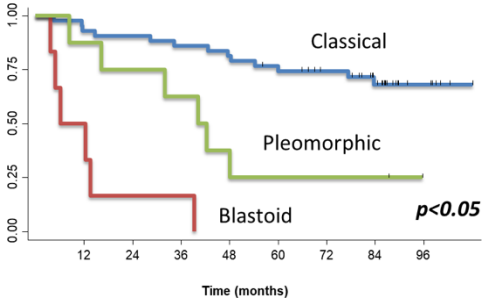


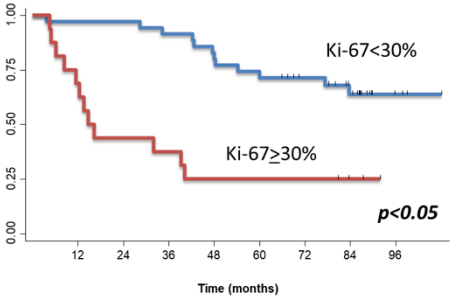
7y PFS 56% (95%CI 41-67)



7y OS 63% (95%CI 46-72)

Univariate analysis for PFS





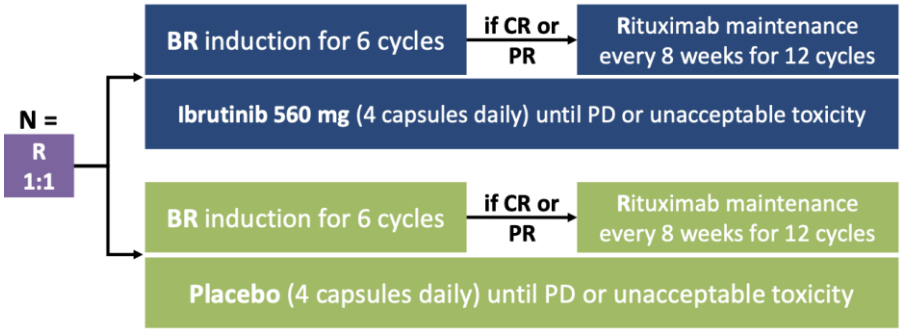
Visco C et al, Lancet Haematololgy, 2017; Tisi MC et al, Blood Advances, 2023

Outline

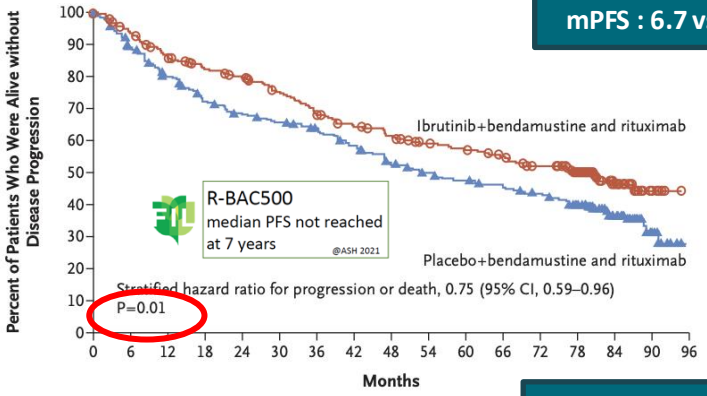
CHT BackBone

BTKi + BR Platform (SHINE/ECHO)

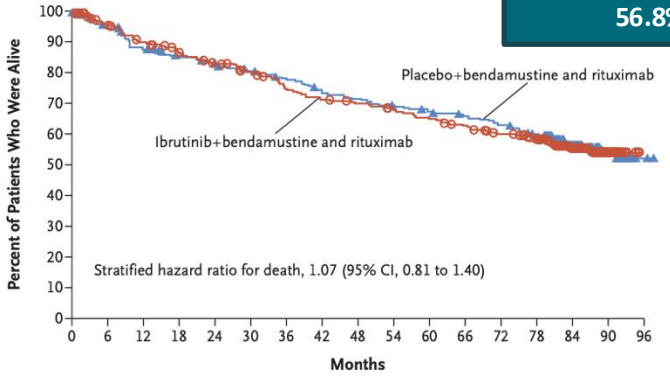
SHINE: Ibrutinib + BR in untreated, elderly MCL patients



mPFS : 6.7 vs 4.4y



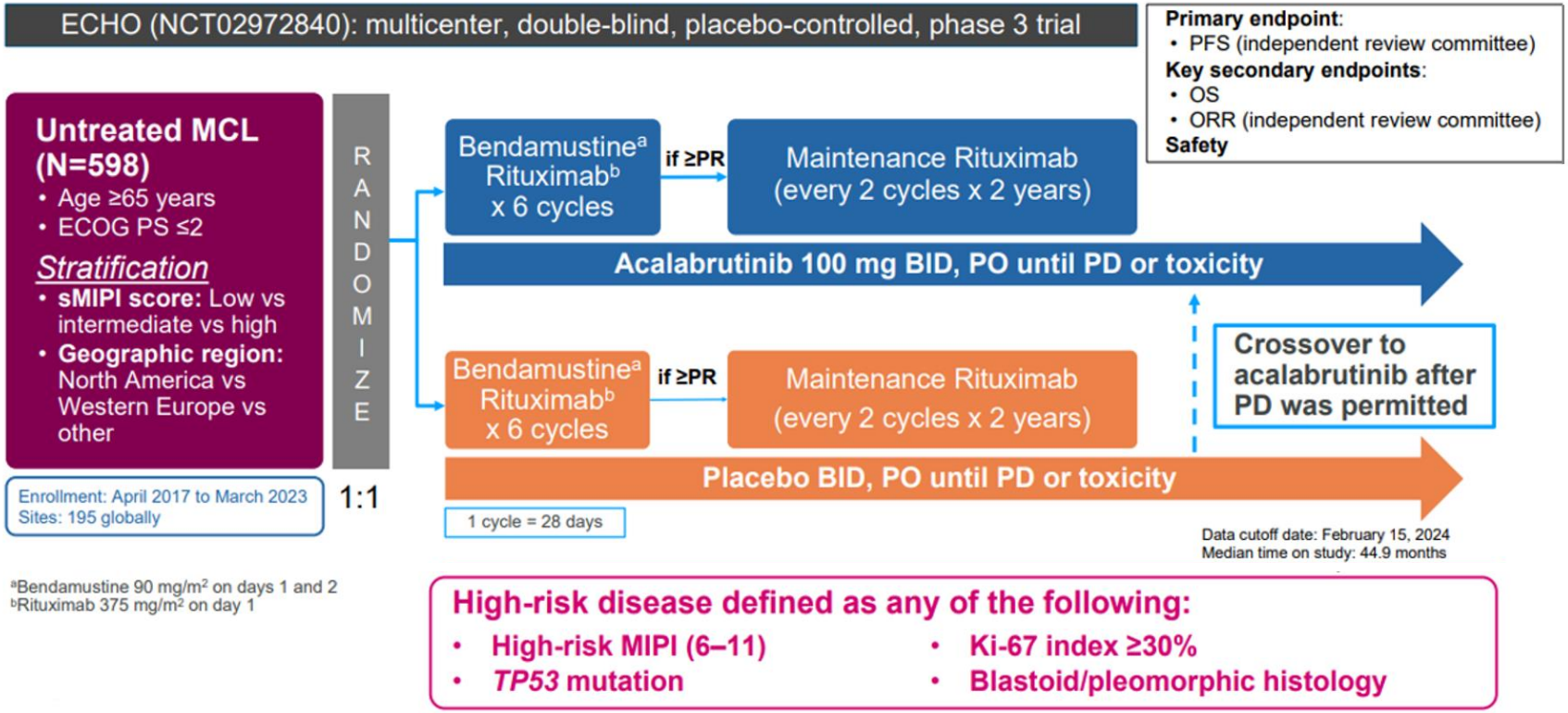
mOS 7y: 55% vs 56.8%



523 pts, median f-up 84.7 mo
Median age 71 (65-87) – 10% tp53 mut, 7% blastoid, 35% MIPI HR (I group)
Pts in CR: 65.5% I vs 57.6% P (p=0.01)
<u>No clear advantage in high risk subgroups</u>
Incidence of G3-4 AE: 81.5% I vs 77.3% P
"One hypothesis for further exploration could be the time-limited use of ibrutinib to retain efficacy but avoid ongoing toxic effects"

Wang et al, NEJM, 2022

ECHO Study Design



Wang M et al, JCO, 2025

Demographic and baseline characteristics

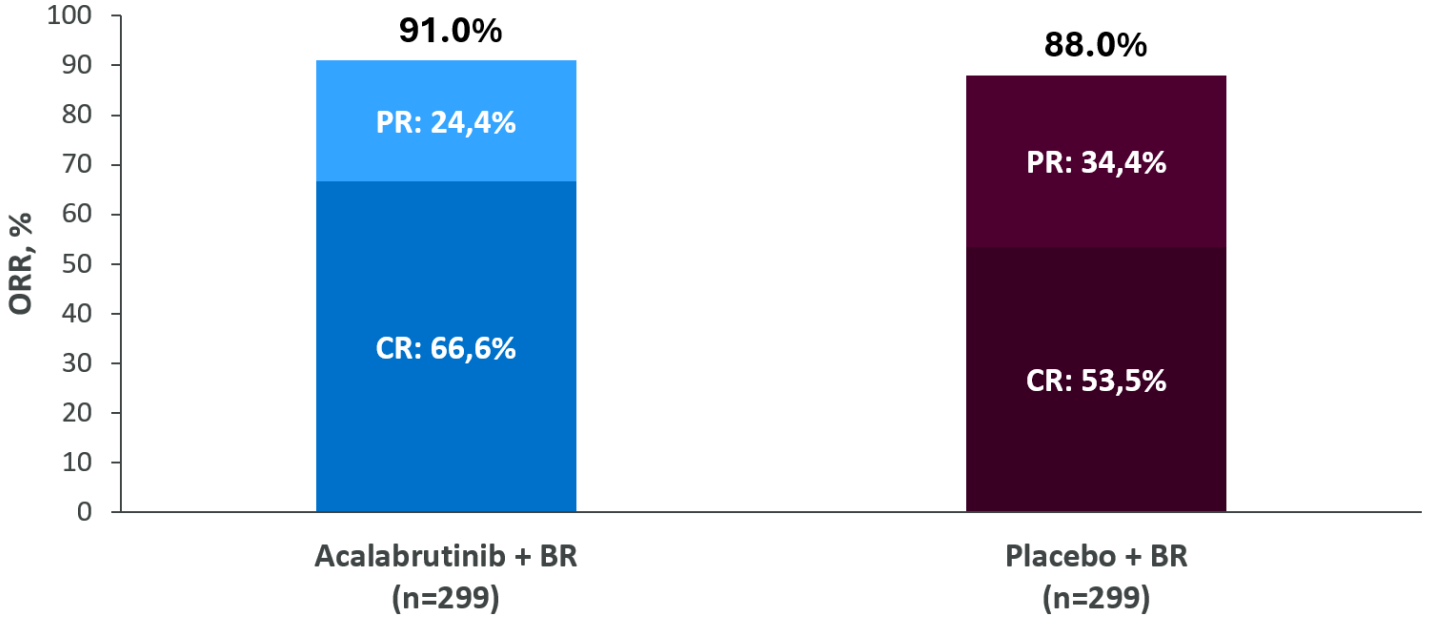
	Acalabrutinib + BR (n=299)	Placebo + BR (n=299)
Age, median (range), y	71 (65–85)	71 (65–86)
≥75 y, n (%)	84 (28.1)	77 (25.8)
Male, n (%)	214 (71.6)	209 (69.9)
ECOG PS, n (%)		
1	129 (43.1)	132 (44.1)
2	12 (4.0)	23 (7.7)
Tumor bulk ≥5 cm, n (%)	112 (37.5)	113 (37.8)
Blastoid/pleomorp		38 (12.7)
Simplified MIPI sc		
Low risk		01 (33.8)
Intermediate ris		25 (41.8)
High risk		73 (24.4)
Extranodal disease		77 (92.6)
TP53 status, n (%)[a]		
Mutated		29 (9.7)
Unmutated		83 (27.8)
Ki-67, n (%)		
<30%		26 (42.1)
≥30%		47 (49.2)

Characteristic, % [n]	Acalabrutinib + BR (n = 299)	Placebo + BR (n = 299)
High-risk MIPI (6–11)	24.1 [72]	24.4 [73]
Ki-67 ≥30%	46.5 [139]	49.2 [147]
Ki-67 ≥50%	20.7 [62]	24.7 [74]
Blastoid/pleomorphic histology	13.7 [41]	12.7 [38]
TP53 mutation	7.4 [22]	9.7 [29]
TP53 status missing	60.2 [180]	62.5 [187]
Total high-risk	**62.5 [187]**	**61.2 [183]**

Wang M et al, JCO, 2025

Best Overall Response and Complete Response Rates

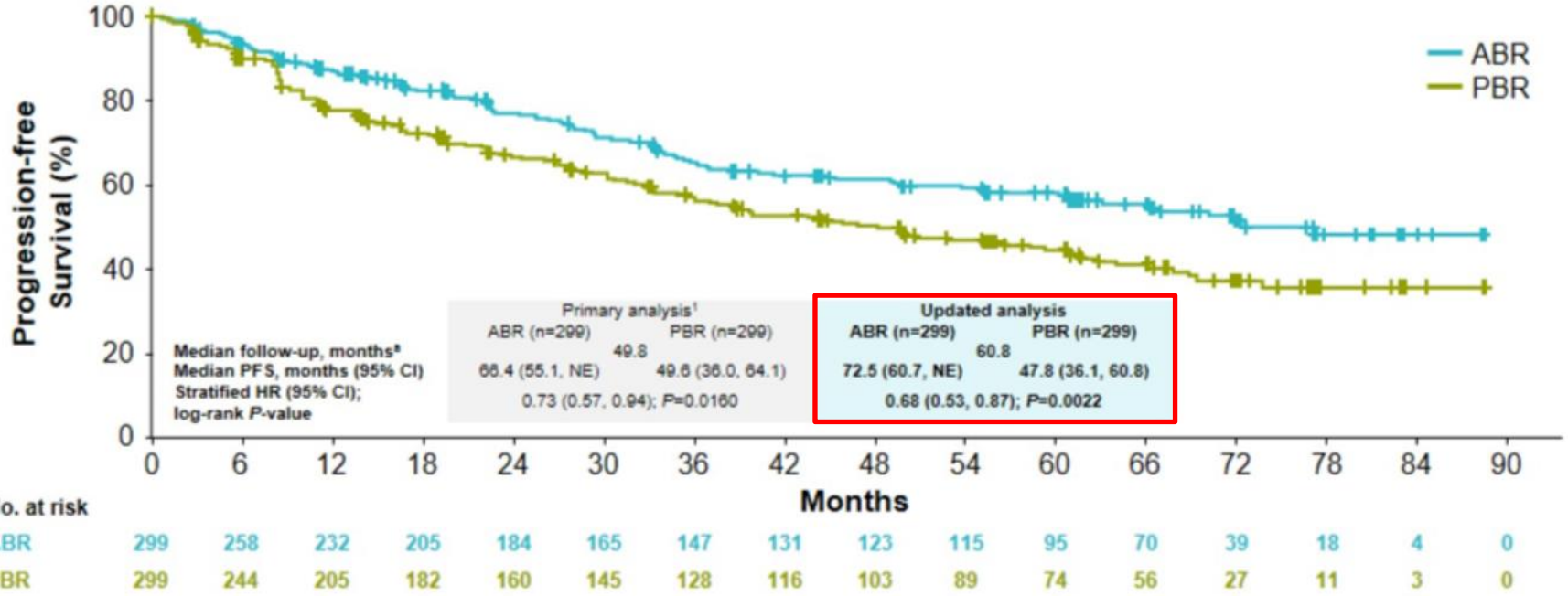
- An additional 13% of patients achieved CR with acalabrutinib + BR



Wang M et al, JCO, 2025

PFS further improved with ABR vs PBR

Median f-up 60.8 mo

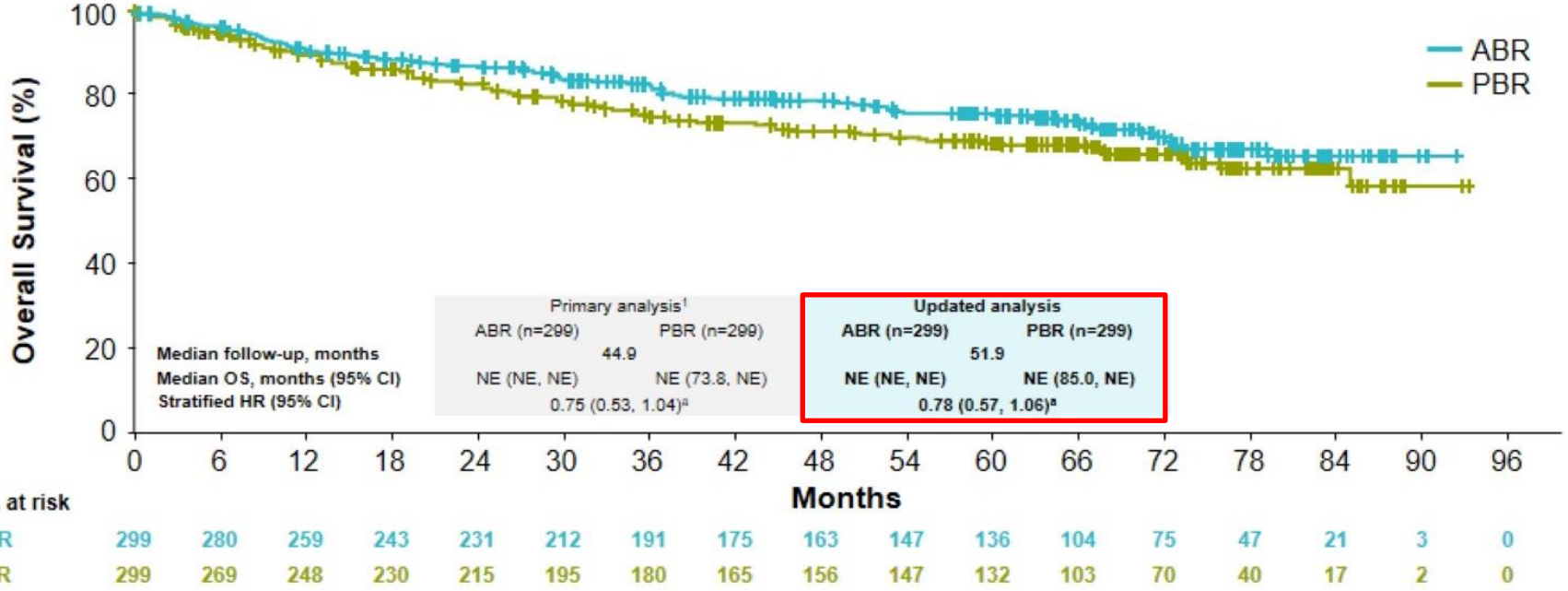


- PFS risk reduction with ABR vs PBR increased from 27% (primary analysis) to 32% (updated analysis)
- Median PFS was longer with ABR vs PBR (6 years vs 4 years)

Wang M et al, ASH 2025

OS Analysis - Censoring for COVID-19 deaths

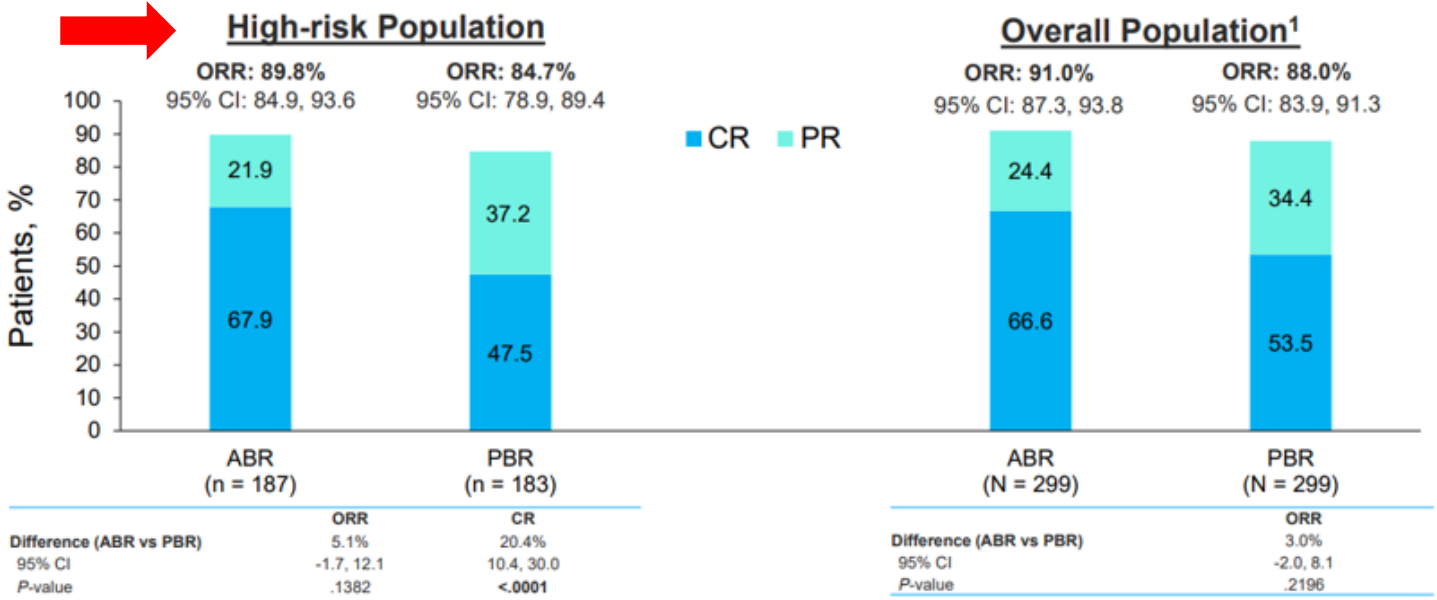
Median f-up 60.8 mo



Similar Trend as the Primary Analysis

Wang M et al, ASH 2025

ECHO – Response in patients with High-risk MCL



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

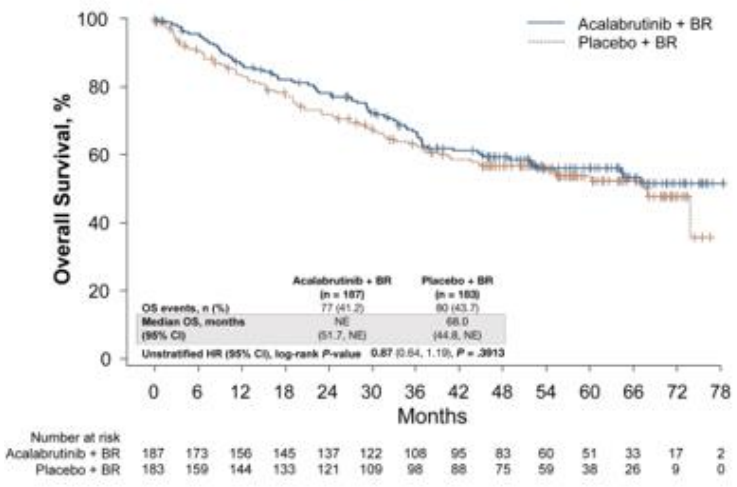
	ORR
Difference (ABR vs PBR)	3.0%
95% CI	-2.0, 8.1
P-value	.2196

Best response of CR significantly higher with ABR in patients with high-risk MCL

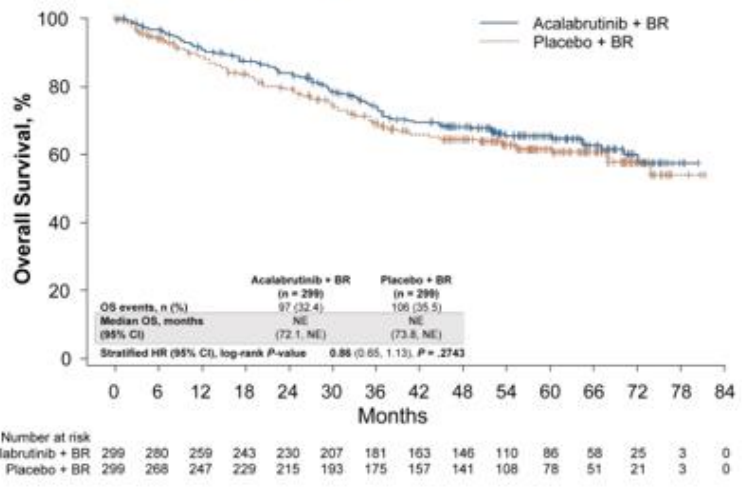
Wang M et al, JCO, 2025

ECHO – Survival in patients with High-risk MCL

OS in High-risk Population (including crossover)



OS in Full Analysis Population (including crossover)[1]



- OS maturity rate was 42%

The hazard ratio for OS comparing ABR with PBR was 0.87 (95% CI: 0.64, 1.19)

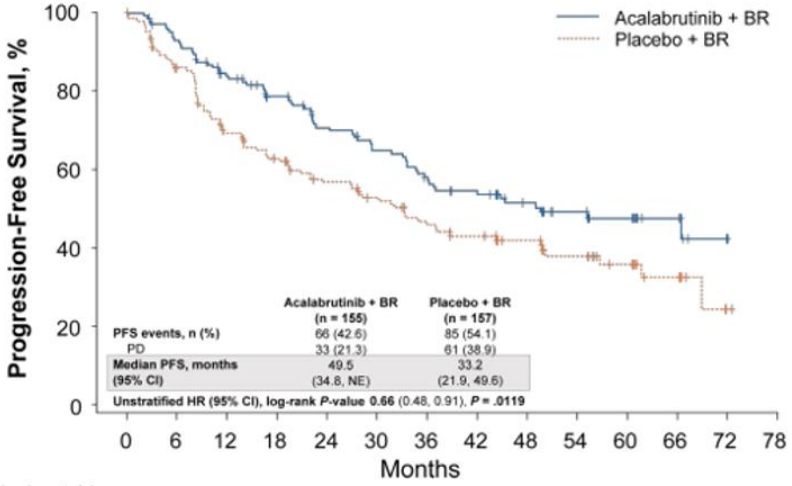
CROSS-OVER

Censorizzando le morti per COVID - OS raggiunge un trend si superiorità (p=0.07)

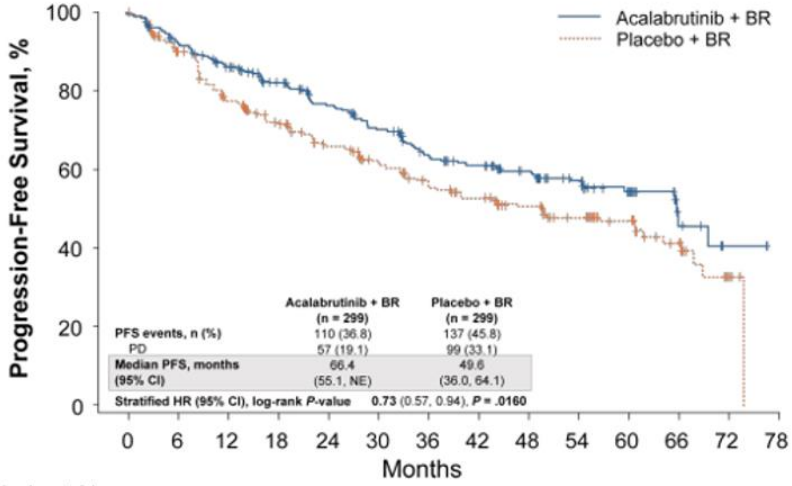
Wang M et al, JCO, 2025

ECHO – Longer PFS in patients with High-risk MCL

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



PFS in Full Analysis Population[1]

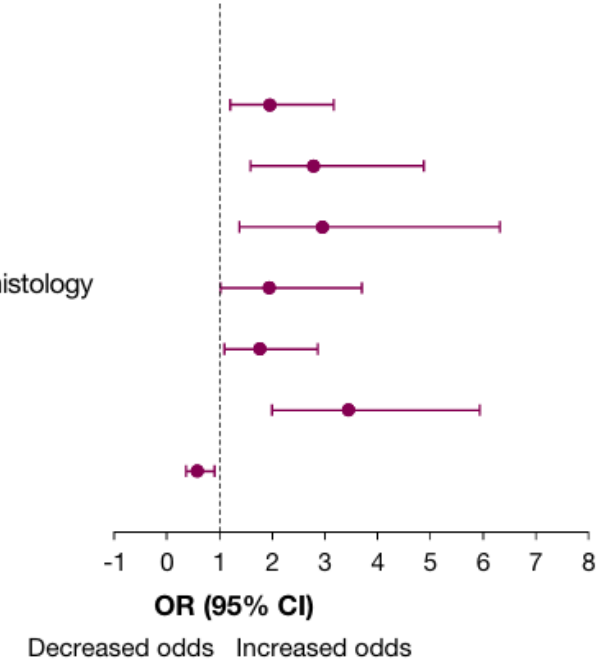


- This grouping removes MIPI, which was considered less important than biological factors in the phase 2 ALTAMIRA trial[2]
- When only patients with Ki-67 index ≥30% and/or blastoid/pleomorphic histology were evaluated, PFS was longer with ABR vs PBR (HR 0.64; 95% CI 0.46, 0.90; *P* = .0092)

Dreyling M et al, EHA 2025

Factors impacting on POD24 Status

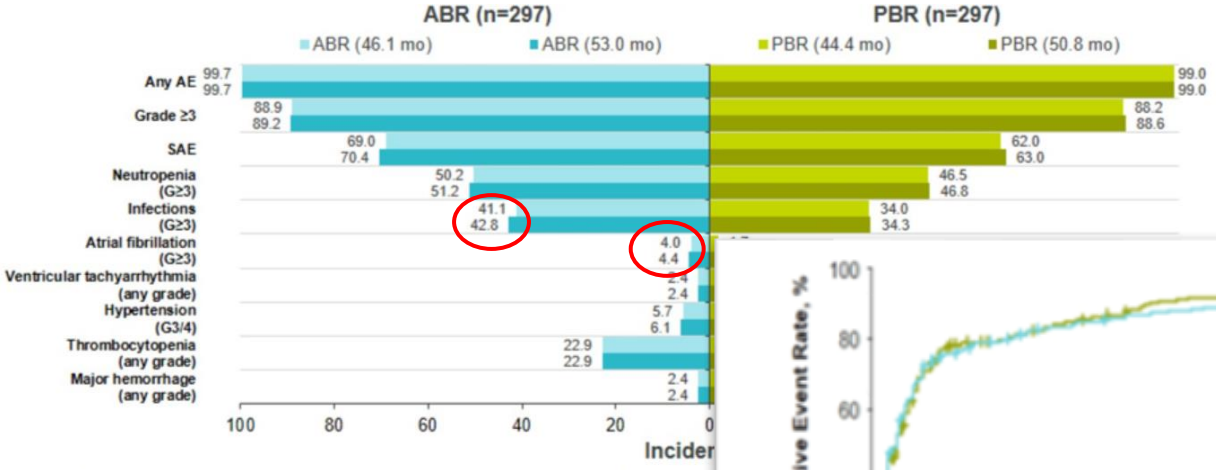
Comparison	OR	95% CI	*P*-value
Age ≥75 vs <75 y	1.950	1.200, 3.168	0.0070
Male vs female	2.782	1.587, 4.875	0.0004
Ann Arbor stage IV vs stage I–III	2.951	1.378, 6.320	0.0054
Blastoid/pleomorphic vs classic or other histology	1.943	1.020, 3.701	0.0434
Ki-67 ≥30% vs <30%	1.768	1.091, 2.864	0.0207
LDH ≥ULN	3.444	1.997, 5.939	<0.0001
Acalabrutinib vs Placebo	**0.577**	**0.366, 0.909**	**0.0177**



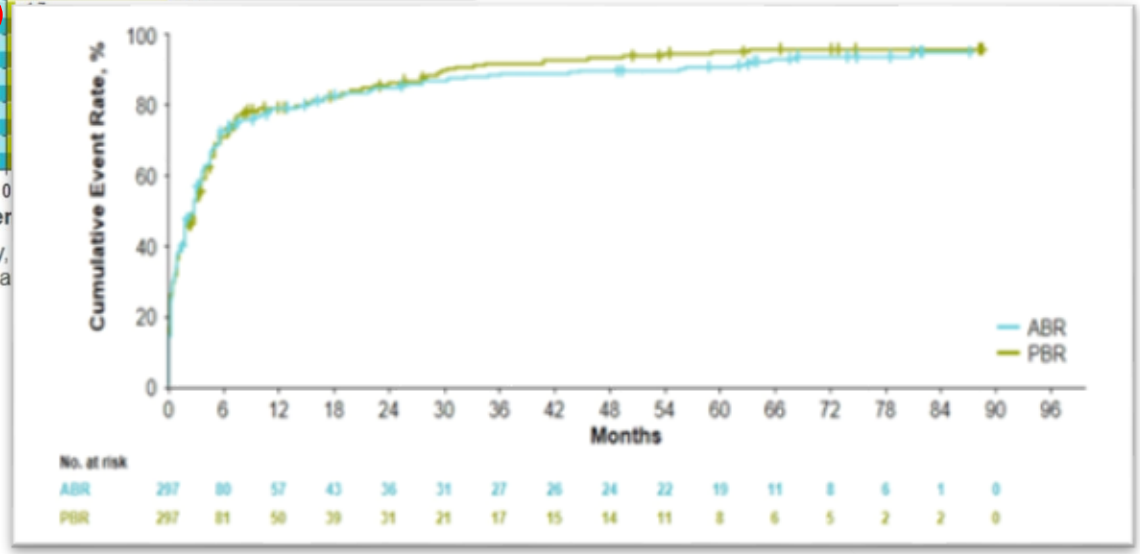
Il trattamento con ABR *vs* PBR **riduce significativamente il rischio di POD24**, dopo aggiustamento per i fattori correlati col rischio di progressione precoce

Cheah C et al, ASH 2025

Cumulative Event Rate of Grade ≥3 Events



- ABR arm[a]: 1 new case of grade ≥3 atrial fibrillation reported (primary,
- PBR arm[a]: 1 new case of ventricular tachyarrhythmia reported (prima



Comparable between arms

Wang M et al, JCO, 2025

Outline

CHT BackBone

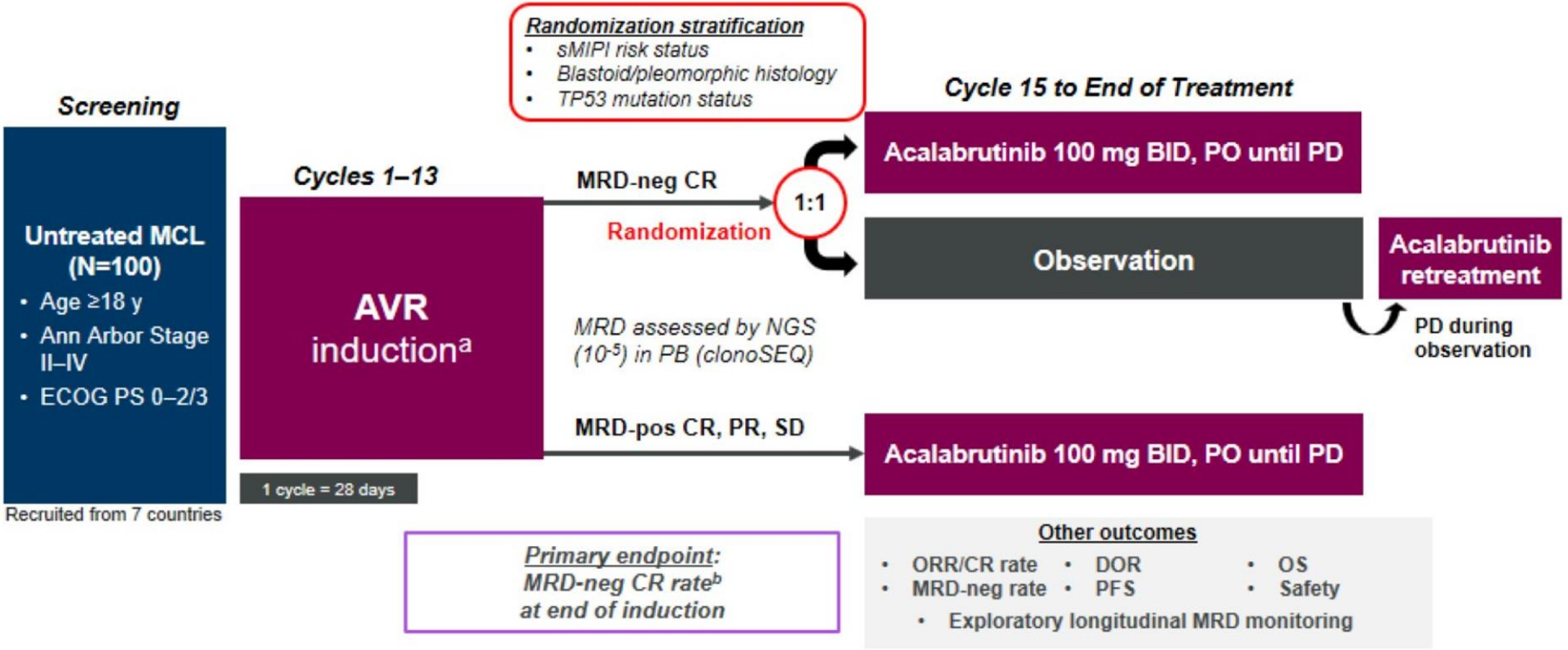
BTKi + BR Platform (SHINE/ECHO)

Chemo-Free

All patients (TraAVeRse)

High Risk Adapted (BoVen)

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

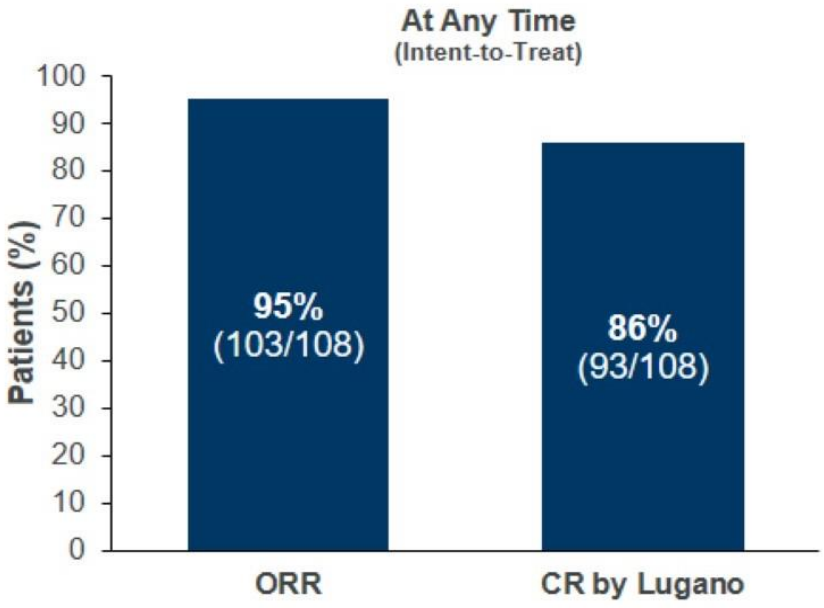


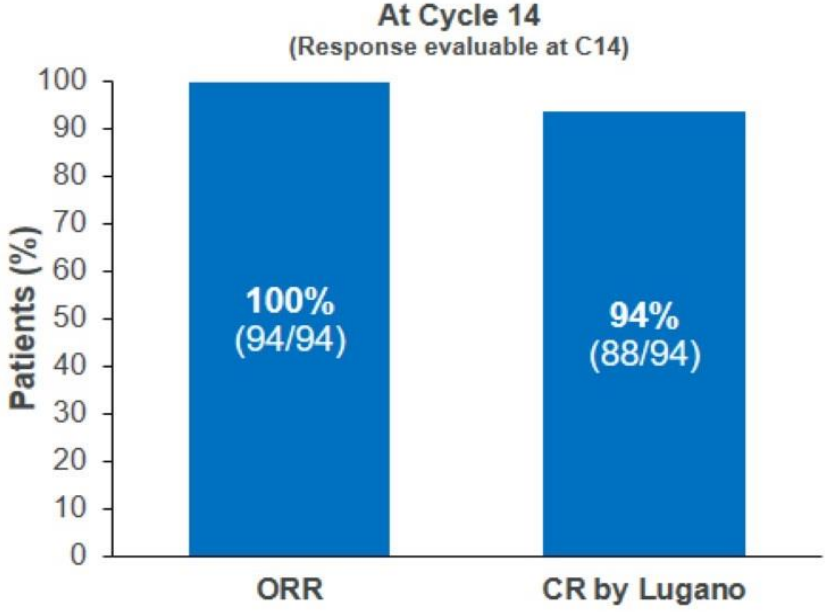
AVR: Acalabrutinib, Venetoclax, Rituximab

Median Age 69 (40-89); < 65y: 38.9%

Hawkes EA, ASH 2025

TrAVeRse: Response and Survival





Median f-up 14.8 mo

12mo PFS: 95.2% (tp53 mut 88.2%)
12mo DOR: 97% (tp53 mut 93,3%)

Hawkes EA, ASH 2025

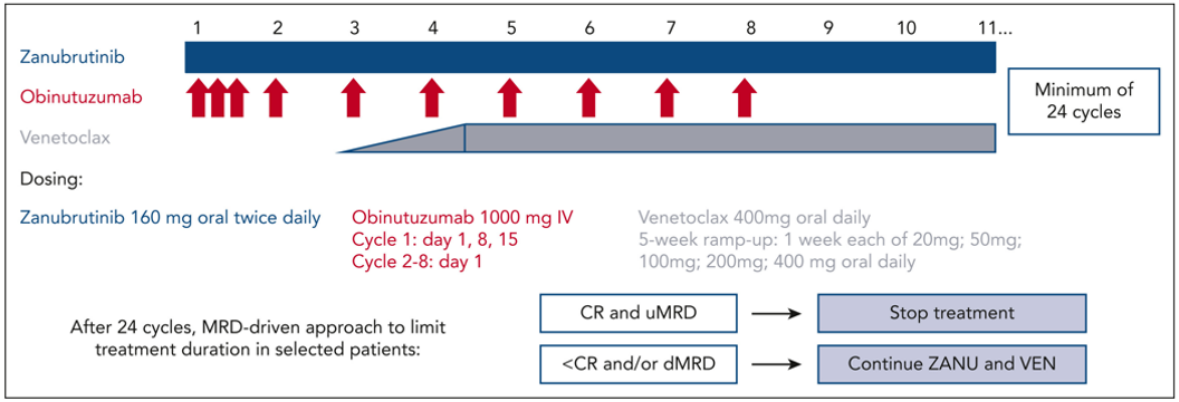
BOVen Study Design: Multicenter, Open-label, Phase 2 Trial

CLINICAL TRIALS AND OBSERVATIONS | JANUARY 30, 2025

Zanubrutinib, obinutuzumab, and venetoclax for first-line treatment of mantle cell lymphoma with a *TP53* mutation

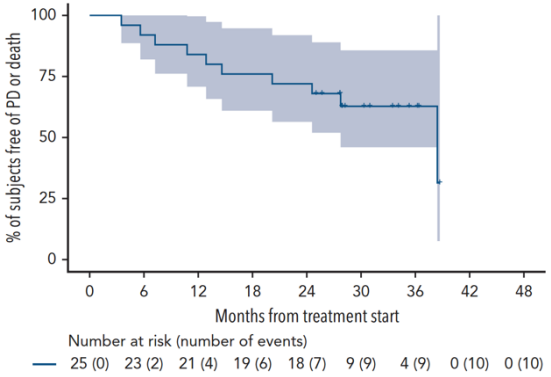
Clinical Trials & Observations

Anita Kumar, Jacob Soumerai, Jeremy S. Abramson, Jeffrey A. Barnes, Philip Caron, Shalini Chhabra, Maria Chabowska, Ahmet Dogan, Lorenzo Falchi, Clare Grieve, J. Erika Haydu, Patrick Connor Johnson, Ashlee Joseph, Hailey E. Kelly, Alyssa Labarre, Jennifer Kimberly Lue, Rosalba Martignetti, Joanna Mi, Alison Moskowitz, Colette Owens, Sean Plummer, Madeline Puccio, Gilles Salles, Venkatraman Seshan, Elizabeth Simkins, Natalie Slupe, Honglei Zhang, Andrew D. Zelenetz



25 tp53 mut pts
Median age 68 y (29-82)
Best ORR 94% (24/25) – CR 88%

Median follow-up of 28.2 months



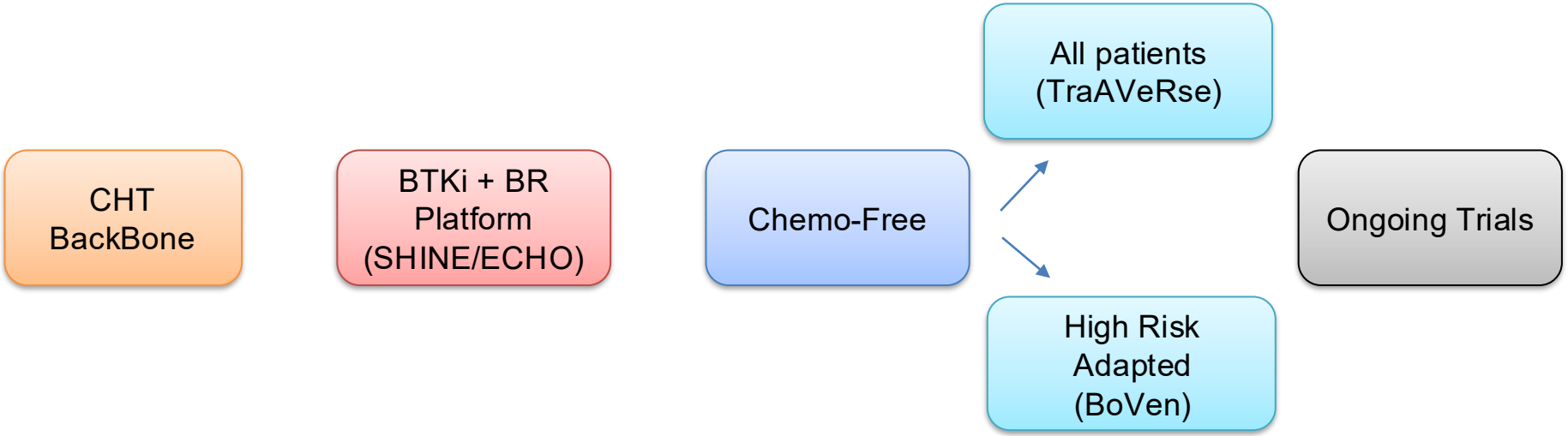
2y PFS 72%
2y OS 76%

Tailored treatment

Common Aes low grade (included diarrhea – 64%, neutropenia – 32%, ingusion-related reactions - 24%

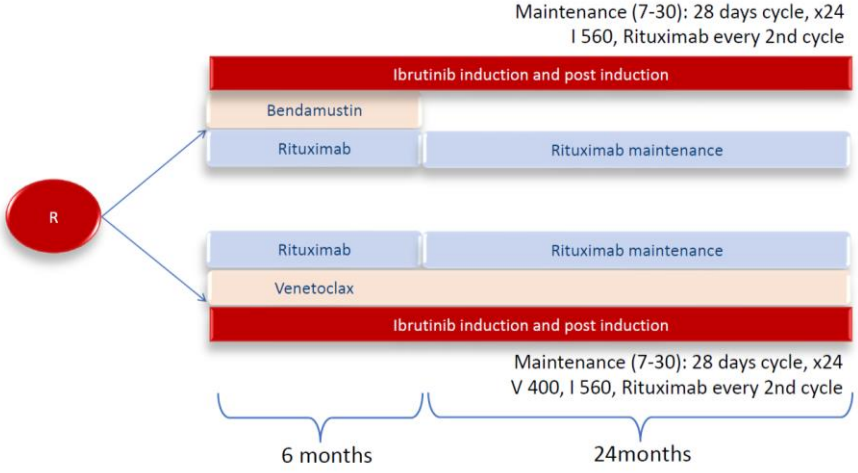
Kumar A et al, Blood 2025

Outline


CHT BackBone
BTKi + BR Platform (SHINE/ECHO)
Chemo-Free
All patients (TraAVeRse)
High Risk Adapted (BoVen)
Ongoing Trials

Ongoing Trials

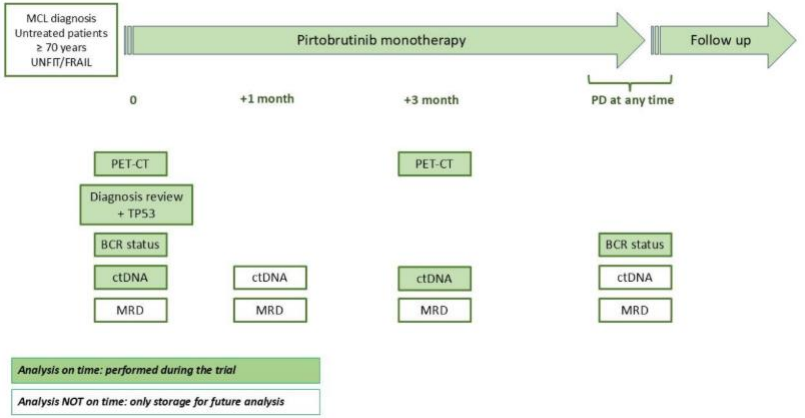
VIRAL – Phase II randomized



Recruiting: 123/150 pts

FONDAZIONE ITALIANA LINFOMI

PUMA Study



STARTING

Conclusions – Take home messages

- BR+Acalabrutinib soon available and standard option for patients not eligible to ASCT (≥65?), with interesting results in **high risk MCL**
- Chemo-free triplets (ZVO and AVR) are highly active, with early and sustained benefit, overall metabolic response rate consistently >90%, no additive toxicity observed, **discontinuation** possible?
- Comparable benefit was seen in *TP53* mutated patients, though numbers still small, and longer follow-up is needed
- Open questions for BTK RR


Thank You
For Your
Attention