MCL-725

Efficacy of Rituximab-Bendamustine With or Without Acalabrutinib in Patients With Untreated, High-risk Mantle Cell Lymphoma: An Analysis of the Phase 3 ECHO Trial

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Objective

- To examine efficacy outcomes in patients with high-risk MCL in the ECHO trial

Conclusions

- ABR significantly improved PFS in patients with high-risk MCL compared with PBR
- A significantly higher proportion of patients in the ABR arm had CR compared with the PBR arm among patients with high-risk MCL
- The hazard ratio for OS comparing ABR with PBR was 0.87 (95% CI: 0.64, 1.19)
- Patients with biological high-risk features had a numerically more pronounced benefit in PFS (blastoid/pleomorphic: HR 0.59; Ki-67 ≥30%: HR 0.63) compared with the total study population (HR 0.73)
  - Data on *TP53* alterations were incomplete and did not allow for meaningful analysis
- Efficacy outcomes in the subgroup of patients with high-risk MCL aligned with those in the overall ECHO study population

Plain language summary

Why did we perform this research?

- Mantle cell lymphoma, or MCL, is a rare type of blood cancer affecting white blood cells that is largely considered incurable. A phase 3 clinical trial (the ECHO study) assessing the drug acalabrutinib in combination with a chemoimmunotherapy regimen (bendamustine plus rituximab) in older patients who were previously untreated for their MCL showed that the triple-drug regimen (acalabrutinib with 2-drug chemoimmunotherapy) was more effective compared with the 2-drug regimen of chemoimmunotherapy without acalabrutinib. This research focuses on the effectiveness of these regimens in subgroups of patients who have disease features that typically result in poorer outcomes (or "high-risk" features), including high risk according to a prognostic scale (called MIPI), disease that is proliferating quickly (Ki-67 ≥30%), disease that looks a certain way under a microscope (blastoid/pleomorphic histology), and disease that has a specific mutation (in the *TP53* gene).

How did we perform this research?

- Data from the phase 3 ECHO study were used to assess treatment effectiveness in a select group of study patients with at least 1 of 4 specific high-risk disease features.

What were the findings of this research?

- Similar to the overall ECHO study population, the triple therapy of acalabrutinib with chemoimmunotherapy was more effective in this group of patients with high-risk disease features than chemoimmunotherapy without acalabrutinib.

What are the implications of this research?

- Clinicians will understand that even if older patients with MCL have these high-risk disease features, triple-combination therapy of acalabrutinib with chemoimmunotherapy will likely treat their disease more effectively than chemoimmunotherapy alone.

Where can I access more information?

- Information about the medicine(s) being used in this study and the people who could participate can be found here: https://clinicaltrials.gov/study/NCT02972840.

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Poster

Supplementary material

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials.

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Presented at the Society of Hematologic Oncology (SOHO) Annual Meeting; September 3–6, 2025; Houston, TX

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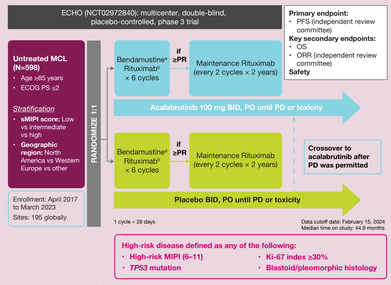
Introduction

- Triple-combination therapy with ABR significantly improved PFS over PBR (HR 0.73; 95% CI 0.57, 0.94; *P* = .0160) in older patients with previously untreated MCL in the randomized, double-blind, placebo-controlled, phase 3 ECHO trial (NCT02972840)[1]
- Patients with high-risk features, namely Ki-67 index ≥30%, high-risk MIPI, blastoid/pleomorphic histology, or *TP53* mutation, tend to respond poorly to conventional treatment[2]

Methods

- The study design is shown in **Figure 1**
- Efficacy outcomes (PFS and OS) were analyzed in the subgroup of patients with high-risk disease, defined as any of the following:
  - Ki-67 index ≥30%
  - High-risk MIPI (6–11)
  - Blastoid/pleomorphic histology
  - *TP53* mutation (assessed via FFPE analysis)
  - Any of 3 biological high-risk factors (Ki-67 index ≥30%, blastoid/pleomorphic histology, *TP53* mutation), removing MIPI, which was considered less important than biological factors in the phase 2 ALTAMIRA trial[3]
  - Any of 2 biological high-risk factors (Ki-67 index ≥30%, blastoid/pleomorphic histology)
    - *TP53* mutation status was not routinely collected for the study population with >60% missing data; therefore, the data may not be representative of the population with *TP53* mutation
- PFS was also analyzed by individual high-risk factors as exploratory outcomes (blastoid/pleomorphic histology, Ki-67 index ≥30%, Ki-67 index ≥50%)

Figure 1. ECHO Study Design



[1]Bendamustine 90 mg/m^2 on days 1 and 2.
[2]Rituximab 375 mg/m^2 on day 1.

Results

Patients

- As of February 15, 2024, 299 patients each were randomly assigned to the ABR and PBR arms
- Among them, 62.5% (n = 187) and 61.2% (n = 183) of patients had high-risk disease in the ABR and PBR arms, respectively; proportional breakdown of each high-risk feature is shown in **Table 1**
- Demographics and baseline characteristics were similar between patients with high-risk disease and the overall study population, with the exception of a greater proportion of patients with high LDH (**Table 2**)

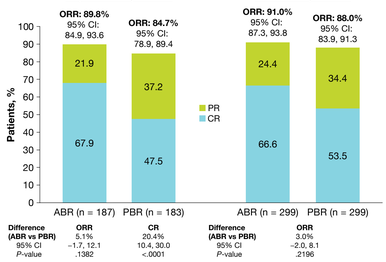
Efficacy

- In patients with high-risk disease, ORR was 89.8% with ABR vs 84.7% with PBR
- The proportion with best overall response of CR was significantly higher with ABR vs PBR (**Figure 2**)
- Median PFS among patients with high-risk disease was significantly longer with ABR vs PBR (HR 0.74; 95% CI 0.55, 0.99; *P* = .0432; **Figure 3A**)
  - After disease progression, 38 patients with high-risk disease who received placebo crossed over to acalabrutinib
  - Of the 99 patients who progressed on placebo, 75 (75.8%) received at least 1 subsequent anticancer therapy, and among these 75, 68 (90.7%) received BTKis, including 51 patients who crossed over to acalabrutinib within the trial[1]
- With an OS maturity rate of 42%, the HR for OS comparing ABR vs PBR was 0.87 (95% CI 0.64, 1.19; *P* = .3913; **Figure 3B**)
  - When deaths due to COVID-19 were censored (24 COVID-19 deaths in the ABR arm and 17 in the PBR arm), the HR for OS comparing ABR vs PBR was 0.76 (95% CI 0.53, 1.10; *P* = .1459; **Supplemental Figure 1**)
- When considering only patients with any of the 3 biological risk factors (Ki-67 index ≥30%, *TP53* mutation, and blastoid/pleomorphic histology), ABR also demonstrated significantly longer PFS vs PBR (**Figure 4A**) and a HR of 0.83 (95% CI 0.59, 1.16) in OS (**Figure 4B**)
  - Results were similar when patients with 2 biological risk factors (Ki-67 index ≥30% and/or blastoid/pleomorphic histology) were evaluated: PFS was significantly longer with ABR vs PBR (HR 0.64; 95% CI 0.46, 0.90; *P* = .0092), and HR for OS was 0.85 (95% CI 0.60, 1.20; *P* = .3574)
- There was a positive trend favoring ABR in patients with blastoid/pleomorphic histology
  - The sample size in this subgroup was small; the difference in median PFS was ~24 months (**Figure 5**)
- PFS was significantly improved with ABR in patients with Ki-67 index ≥30% (**Figure 6**)
  - There was a positive trend favoring ABR in patients with Ki-67 index ≥50% (**Supplemental Figure 2**), although the number of patients was low in this subgroup

Table 1. Summary of Patients With High-risk Disease

Characteristic, % [n]	Acalabrutinib + BR (n = 299)	Placebo + BR (n = 299)	Total (N = 598)
High-risk MIPI (6–11)	24.1 [72]	24.4 [73]	24.2 [145]
Ki-67 ≥30%	46.5 [139]	49.2 [147]	47.8 [286]
Ki-67 ≥50%	20.7 [62]	24.7 [74]	22.7 [136]
Blastoid/pleomorphic histology	13.7 [41]	12.7 [38]	13.2 [79]
TP53 mutation	7.4 [22]	9.7 [29]	8.5 [51]
TP53 status missing	60.2 [180]	62.5 [187]	61.4 [367]
Total high-risk	**62.5 [187]**	**61.2 [183]**	**61.9 [370]**

Figure 2. IRC-assessed ORR in Patients With High-risk MCL



	High-risk Population		Overall Population[1]	
Difference (ABR vs PBR)	5.1%	20.4%	3.0%	
95% CI	−1.7, 12.1	10.4, 30.0	−2.0, 8.1	
P-value	.1382	<.0001	.2196	

Figure 3. (A) IRC-assessed PFS and (B) OS in the High-risk Population and Overall Population

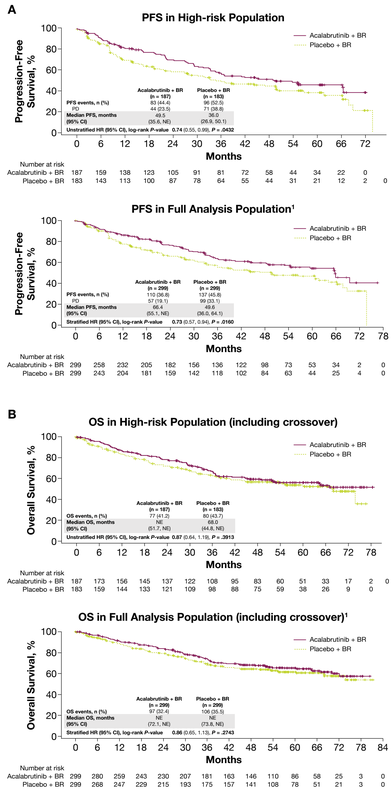


Figure 4. (A) IRC-assessed PFS and (B) OS in Patients With Biological Risk Factors

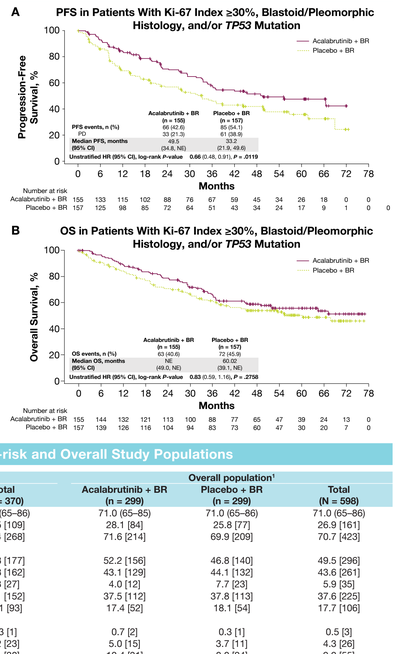


Table 2. Demographics and Baseline Characteristics of High-risk and Overall Study Populations

	High-risk population			Overall population[1]		
Characteristic[a]	Acalabrutinib + BR (n = 187)	Placebo + BR (n = 183)	Total (N = 370)	Acalabrutinib + BR (n = 299)	Placebo + BR (n = 299)	Total (N = 598)
Age, median (range), years	72.0 (65–85)	72.0 (65–86)	72.0 (65–86)	71.0 (65–85)	71.0 (65–86)	71.0 (65–86)
Age ≥75 years	31.0 [58]	27.9 [51]	29.5 [109]	28.1 [84]	25.8 [77]	26.9 [161]
Male	75.4 [141]	69.4 [127]	72.4 [268]	71.6 [214]	69.9 [209]	70.7 [423]
ECOG PS						
0	50.3 [94]	45.4 [83]	47.8 [177]	52.2 [156]	46.8 [140]	49.5 [296]
1	43.9 [82]	43.7 [80]	43.8 [162]	43.1 [129]	44.1 [132]	43.6 [261]
2	5.4 [9]	9.8 [18]	7.3 [27]	4.0 [12]	7.7 [23]	5.9 [35]
Tumor bulk ≥5 cm	38.5 [72]	43.7 [80]	41.1 [152]	37.5 [112]	37.8 [113]	37.6 [225]
LDH > ULN	24.1 [45]	26.2 [48]	25.1 [93]	17.4 [52]	18.1 [54]	17.7 [106]
Ann Arbor stage						
I	0	0.5 [1]	0.3 [1]	0.7 [2]	0.3 [1]	0.5 [3]
II	7.5 [14]	4.9 [9]	6.2 [23]	5.0 [15]	3.7 [11]	4.3 [26]
III	8.6 [16]	7.7 [14]	8.1 [30]	10.4 [31]	8.0 [24]	9.2 [55]
IV	84.0 [157]	86.9 [159]	85.4 [316]	83.9 [251]	88.0 [263]	86.0 [514]
High-risk MIPI (6–11)	38.5 [72]	39.9 [73]	39.2 [145]	24.1 [72]	24.4 [73]	24.2 [145]

[a]All characteristics are % [n] unless specified otherwise.

Figure 5. PFS in Patients With Blastoid/Pleomorphic Histology

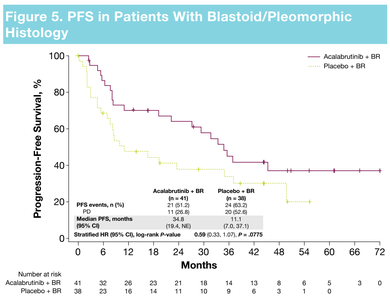
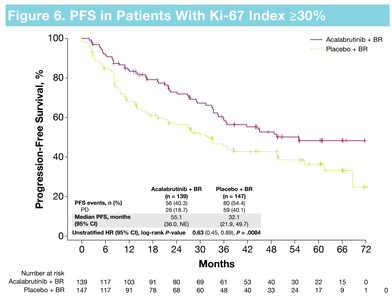


Figure 6. PFS in Patients With Ki-67 Index ≥30%



References

1. Wang M, et al. *J Clin Oncol*. 2025;43(20):2276-84. 2. Jain P, et al. *J Clin Oncol*. 2020;38(26):3052-16. 3. Jurkarran M, et al. ASH 2024. Abstract #747.

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Abbreviations

ABR, acalabrutinib + bendamustine + rituximab; BID, twice daily; BR, bendamustine + rituximab; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed paraffin-embedded; HR, hazard ratio; IRC, independent review committee; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MIPI, MCL International Prognostic Index; NE, not estimable; ORR, overall response rate; OS, overall survival; PBR, placebo + bendamustine + rituximab; PD, progressive disease; PFS, progression-free survival; PO, orally; PR, partial response; sMIPI, simplified MCL International Prognostic Index; ULN, upper limit normal.