

MINI REVIEW

Effect of Acalabrutinib in Combination with Bendamustine plus Rituximab on Survival Endpoints in Older Patients with Mantle Cell Lymphoma: Insights from the ECHO Trial

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Mantle cell lymphoma (MCL) is a rare and often aggressive type of non-Hodgkin lymphoma that predominantly affects older adults and presents significant treatment challenges due to its clinical complexity and poor prognosis. Current frontline chemoimmunotherapy approaches frequently fail to provide long-term disease control. However, incorporating acalabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, into standard chemoimmunotherapy regimens shows promise in reducing disease progression and improving outcomes in older and unfit MCL patients.

The ECHO study evaluates the efficacy of acalabrutinib in combination with bendamustine plus rituximab (BR) in older MCL patients, aiming to provide a more effective and better-tolerated treatment option. Primary results demonstrate a significant improvement in progression-free survival and increased response rates with the acalabrutinib plus BR regimen compared with BR alone. While overall survival data are still maturing, early data show a modest trend favoring the acalabrutinib combination, indicating potential long-term benefits for this patient population.

Promising findings from the ECHO trial suggest that integrating acalabrutinib with standard therapy could set a new standard for frontline treatment in older/unfit MCL patients. This approach offers hope for improved outcomes and reduced toxicity, thereby addressing the unmet needs of this vulnerable population. Further research and exploration of this treatment paradigm hold promise for advancing the care and prognosis of patients with MCL.

PEER REVIEWED ARTICLE

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Introduction

Mantle cell lymphoma (MCL), with an incidence of 0.5 per 100,000 people in Western countries, is a rare subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 3–6% of all NHL cases.^{1,2} It primarily affects older adults, with a median age at diagnosis between 60 and 70 years, and has a male predominance of approximately 2:1.^{3,4} The incidence of MCL is increasing, particularly within the aging population, which presents unique challenges in treatment and management.⁵

The World Health Organization (WHO)/International Consensus Classification (ICC) 2022 classification divides MCL into two distinct categories: the nodal form, comprising 80–90% of cases, and the non-nodal leukemic subtype, accounting for 10–20% of cases.⁶ The nodal form involves an unmutated immunoglobulin heavy-chain variable region (*IGHV*) gene and *SOX11* overexpression, and is often associated with an aggressive course. In contrast, the non-nodal leukemic form is characterized by mutated *IGHV*, negativity for *SOX11* and an indolent behavior. Additionally, blastoid morphology is typically associated with aggressive progression, whereas the presence of small cells suggests a more indolent course. Almost all MCLs are characterized by the t(11;14) translocation, leading to cyclin D1 overexpression.^{6–8}

MCL exhibits a heterogeneous clinical course, often relapsing and currently lacking curative options.^{6,7} The disease frequently presents at an advanced stage with widespread involvement of lymph nodes, spleen, bone marrow and gastrointestinal tract.^{8,9} Despite initial response to standard therapies, patients almost invariably relapse, leading to a former median overall survival (OS) of 3–5 years (nowadays probably slightly longer).^{8,9} The biological complexity of MCL, coupled with the frailty and comorbidities common in older patients, complicates treatment decisions and limits therapeutic options.¹⁰

In clinical practice, patients are generally categorized into three groups based on their fitness. For young and fit patients, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) and rituximab maintenance is commonly recommended as first-line treatment ([Figure 1](#)).¹¹ However, it remains to be determined whether ASCT still adds benefit to immunochemotherapy in combinations with a Bruton's tyrosine kinase inhibitor (BTKi), according to the results from the TRIANGLE trial ([Table](#)

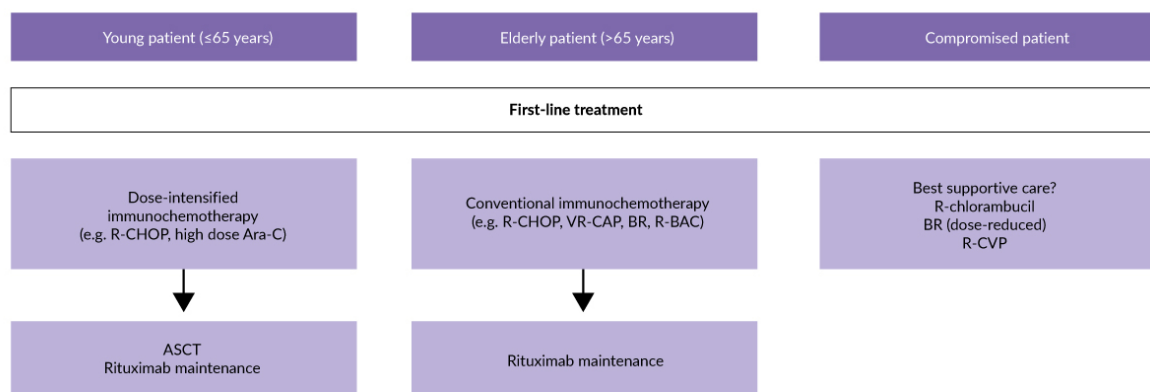


Figure 1. Current European Society for Medical Oncology (ESMO) therapeutic recommendations for treatment-naïve patients with mantle cell lymphoma (MCL).

ASCT, autologous stem cell transplantation; BAC, bendamustine and cytarabine; BR, bendamustine and rituximab; Ara-C, cytarabine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CVP, cyclophosphamide, vincristine and prednisone; R, rituximab; VR-CAP, rituximab, cyclophosphamide, doxorubicin and prednisone with bortezomib. Adapted from Dreyling et al. 2017.¹¹

1).¹² For fit, older patients (over 65 years) or younger patients not fit enough to undergo ASCT, the standard of care involves less intensive first-line chemoimmunotherapy, typically comprising a combination of rituximab (R) with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), BAC (bendamustine, cytarabine) or V-CAP (bortezomib, cyclophosphamide, doxorubicin and prednisone), followed by rituximab maintenance ([Figure 1](#)).^{11,13,14} Older frail patients usually benefit from a combination of rituximab and bendamustine (BR).

Although these regimens can induce remissions, they often do not achieve long-term disease control.¹⁵ Relapse is common, with the duration of response decreasing with subsequent lines of therapy.¹⁶ Additionally, the cumulative toxicity of repeated chemotherapy cycles poses significant challenges, especially in older/unfit patients who may already manage multiple comorbidities.¹⁷ There is an urgent need for novel therapeutic strategies that offer improved efficacy and manageable safety profiles for this vulnerable population.

The BTKi acalabrutinib, with its targeted mechanism of action and favorable safety profile, is an attractive candidate for combination with a standard chemoimmunotherapy regimen. Acalabrutinib is currently approved in the US as monotherapy for treating patients with relapsed or refractory (R/R) MCL. This approval was primarily based on Study LY-004, an open-label, phase II trial ([NCT02213926](#)), which addressed the unmet needs in the treatment of older MCL patients by exploring acalabrutinib as a monotherapy option in frontline treatment.¹⁸ Incorporating the BTKi ibrutinib into standard immunochemotherapy with BR also showed

Table 1. Efficacy and safety results from the ECHO, SHINE and TRIANGLE trials on treatment-naïve patients with mantle cell lymphoma.

	Efficacy	Safety
Acalabrutinib	Phase III ECHO trial (acalabrutinib plus BR vs placebo plus BR)²⁰	
	- Median PFS: 66.4 months vs 49.6 months (HR: 0.73 [95% CI: 0.57–0.94]; p=0.0160) - Median OS: NR vs NR (HR: 0.86 [95% CI: 0.65–1.13]; p=0.2743) - ORR: 91.0% vs 88.0%; CRR: 66.6% vs 53.5%	- TEAEs (any-grade): 99.7% vs 99.0% - Grade ≥3 AEs: 88.9% vs 88.2%; grade 5 TEAEs: 8.4% vs 9.0% - Grade ≥3 serious AEs: 64.3% vs 55.9% - TEAE-related discontinuation rate: 42.8% vs 31.0% - Grade ≥3 AEs of interest: atrial fibrillation (3.7% vs 1.7%), hypertension (5.4% vs 8.4%), major bleeding (2.0% vs 3.4%), infections (41.1% vs 34.0%)
Ibrutinib	Phase III SHINE trial (ibrutinib plus BR vs BR)¹⁹	
	- Median PFS: 80.6 months vs 52.9 months (HR: 0.75 [95% CI: 0.59–0.96]; p=0.01) - Median OS: NR vs NR; 7-year OS rates: 55.0% vs 56.8% (HR: 1.07 [95% CI: 0.81–1.40]) - ORR: 89.7% vs 88.5%; CRR: 65.5% vs 57.6% (p=0.06)	- Grade 3–4 AEs: 81.5% vs 77.3%, neutropenia (47.1% vs 48.1%), pneumonia (20.1% vs 14.2%), lymphopenia (16.2% vs 11.9%); grade 5 AEs: 10.7% vs 6.1% (cardiac disorders: n=3 vs n=5) - AEs of interest: atrial fibrillation (13.9% vs 6.5%), hypertension (13.5% vs 11.2%), diarrhea (46.3% vs 36.9%), major hemorrhage (5.8% vs 4.2%), arthralgia (17.4% vs 16.9%)
	Phase III TRIANGLE trial (ibrutinib plus IC and ASCT [arm A+I] vs ibrutinib plus IC [arm I] vs IC plus ASCT [arm A])¹²	
	3-year FFS rate: 88% in the A+I vs 72% in arm A (HR: 0.52 [98.3% CI: 0–0.86]; p=0.0008); 72% in arm A vs 86% in arm I (HR: 1.77 [98.3% CI: 0–3.76]; p=0.9979) 3-year OS rate: 91% in arm A+I vs 86% in arm A vs 92% in arm I 3-year PFS rates: 88% in arm A+I vs 73% in arm A (HR: 0.46 [98.3% CI: 0.00–0.72]; p=0.00012); 73% in arm A vs 87% in arm I (HR: 2.10 [98.3% CI: 0.00–3.28]; p>0.99) - ORR: * 98% in arms A+I and I combined vs 94% in arm A (p=0.0025); CRR: * 45% in arms A+I and I combined vs 36% in arm A (p=0.020)	- During induction: most common grade 3–5 AEs were blood and lymphatic system disorders (71% in arm A and 76% in arm A+I and I: decreased platelets (59% vs 61%); decreased neutrophil count (47% vs 50%), anemia (22% vs 24%) - During ASCT: most common grade 3–5 AEs were blood and lymphatic system disorders (59% in each arm A and A+I), general disorders and administration site conditions (20% vs 21%), GI disorders (21% vs 20%), infections and infestations (17% vs 20) - During maintenance/follow-up: grade 3–5 hematological AEs: 50% in arm A+I vs 28% in arm I vs 21% in arm A; infections: 25% vs 19% vs 13%; fatal infections: 1% in all three arms

*At the end of induction. AE, adverse event; ASCT, autologous stem cell transplant; BR, bendamustine plus rituximab; CRR, complete response rate; FFS, failure-free survival; GI, gastrointestinal; IC, immunochemotherapy; NR, not reached; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

promising results in the phase III SHINE trial, as reported by Wang et al. (2022) ([Table 1](#)).¹⁹ The efficacy results from SHINE were confirmed in the phase III ECHO study ([NCT02972840](#)), which assessed acalabrutinib with standard treatment to provide a more effective and better tolerated therapeutic option for older MCL patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.²⁰ This approach has the potential to set a new standard for frontline treatment in this challenging patient population, offering new hope for those battling this aggressive disease.

This mini-review summarizes the latest findings from the ECHO trial, presented by Michael Wang at the 2024 European Hematology Association (EHA) Congress in Madrid, Spain,²⁰ and discusses potential implications of these new findings on the treatment paradigm for MCL.

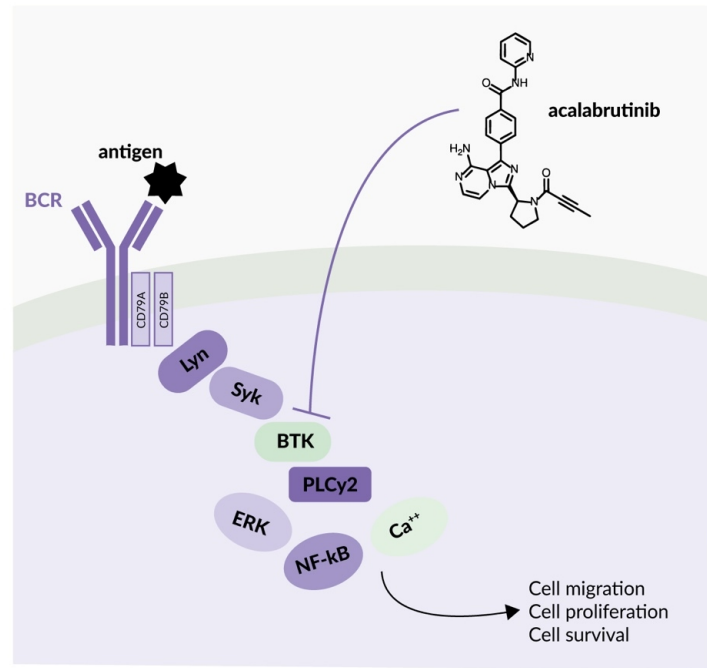


Figure 2. Schematic overview of the acalabrutinib structure and mechanism of action.

Adapted from Vitale et al. 2021.²²

Acalabrutinib, a highly selective second-generation BTKi

Acalabrutinib exerts its antitumor effects through targeted inhibition of the BTK pathway.^{21,22} BTK is a key enzyme in the B-cell receptor signaling cascade, vital for the proliferation, survival and migration of malignant B-cells ([Figure 2](#)).²² Acalabrutinib effectively blocks BTK activity, thereby disrupting downstream signaling pathways such as NF-κB, PI3K and MAPK.²³ This disruption induces apoptosis and inhibits cellular proliferation in MCL and chronic lymphocytic leukemia (CLL) cells. The high specificity of acalabrutinib for BTK minimizes off-target effects, reducing the incidence of adverse events commonly associated with first-generation BTK inhibitors such as ibrutinib.²¹⁻²³ This enhanced selectivity not only improves the safety profile but also allows for sustained inhibition of BTK, resulting in more effective disease control.²³ Clinical studies have demonstrated that incorporating acalabrutinib into MCL treatment regimens significantly improves overall response rate (ORR) and progression-free survival (PFS), offering a promising therapeutic option for patients with this often aggressive form of lymphoma.^{23,24}

About ECHO

ECHO was a randomized, multicenter, double-blind, placebo-controlled phase III study conducted across 195 sites in 26 countries from 2017 to 2023, including the period of the COVID-19 pandemic.²⁵ Its primary objective was to investigate the efficacy of BR combined with acalabrutinib versus BR alone in previously untreated MCL patients. A total of 598 patients were randomly

assigned in a 1:1 ratio to receive BR plus oral acalabrutinib or BR alone until disease progression or toxicity. If patients in both arms achieved at least a partial response to BR, they received maintenance rituximab for two years. The primary endpoint was PFS by an Independent Review Committee, with secondary endpoints including ORR, OS, duration of response and time to response.

Eligible patients were 65 years or older, had a confirmed diagnosis of MCL, an ECOG performance status of ≤ 2 and documented chromosome translocation t(11;14)(q13;q32) and/or relevant overexpression of cyclin D1. These requirements ensured that all patients were capable of independent self-care activities and had specific genetic markers indicative of MCL.²⁵ Patients with significant cardiovascular disease, malabsorption syndrome or uncontrolled infections were excluded from participating in ECHO, which might explain in part the lower incidence of severe adverse events (AEs) with acalabrutinib-containing compared with ibrutinib-containing regimens.^{19,20} [Table 1](#) provides a list of certain efficacy and safety results of SHINE, TRIANGLE and ECHO, taking into account the sometimes different inclusion criteria.

ECHO interim results

The interim analysis at a median follow-up of 45 months included 598 patients (median age, 71 years) treated with BR in combination with either acalabrutinib (n=299) or placebo (n=299).²⁰ PFS was significantly longer in the acalabrutinib group, with a median of 66.4 months compared with 49.6 months in the placebo group (HR: 0.73 [95% CI: 0.57–0.94]; p=0.0160) ([Figure 3](#)).²⁰ The ORR and the complete response (CR) rate were also higher in the acalabrutinib plus BR treatment group compared with the BR alone group, with ORR of 91.0% versus 88.0% and a CR rate of 66.6% versus 53.5%, respectively ([Figure 4](#)).²⁰

In the prespecified sensitivity analysis for PFS in the acalabrutinib group, 19.1% of patients experienced progressive disease (PD), compared with 33% in the placebo group.²⁰ In the OS analysis, the median OS was not significantly improved in the acalabrutinib arm (HR: 0.86 [95% CI: 0.65–1.13]; p=0.2743) ([Figure 5](#)).²⁰ Considering that 51 patients switched to acalabrutinib due to disease progression, this remains a noteworthy outcome and suggests a trend towards improved OS with combination therapy, despite the lack of statistical significance.²⁰

A prespecified sensitivity analysis that adjusted for censored COVID-19 deaths showed that the median PFS was not reached with acalabrutinib plus BR, while it was 61.6 months with placebo plus BR. The HR of 0.64 (95% CI: 0.48–0.84); p=0.0017) for PFS indicated a statistically significant improvement in PFS favoring the acalabrutinib plus BR group ([Figure 6](#)).²⁰ For OS, the median OS was not reached in either treatment groups. However,

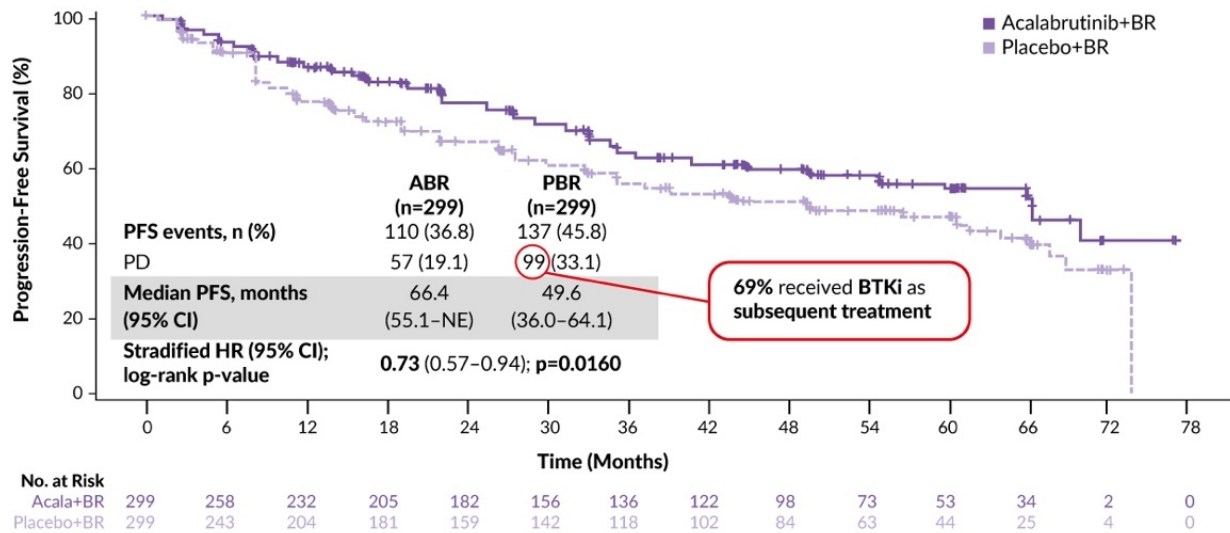


Figure 3. Progression-free survival (PFS) at a median follow-up of 45 months in ECHO.

ABR, acalabrutinib plus BR; BR, bendamustine plus rituximab; BTKi, Bruton's tyrosine kinase inhibitor; NE, not estimable; PBR, placebo plus BR; PD, progressive disease. Adapted from Wang et al. 2023.²⁰

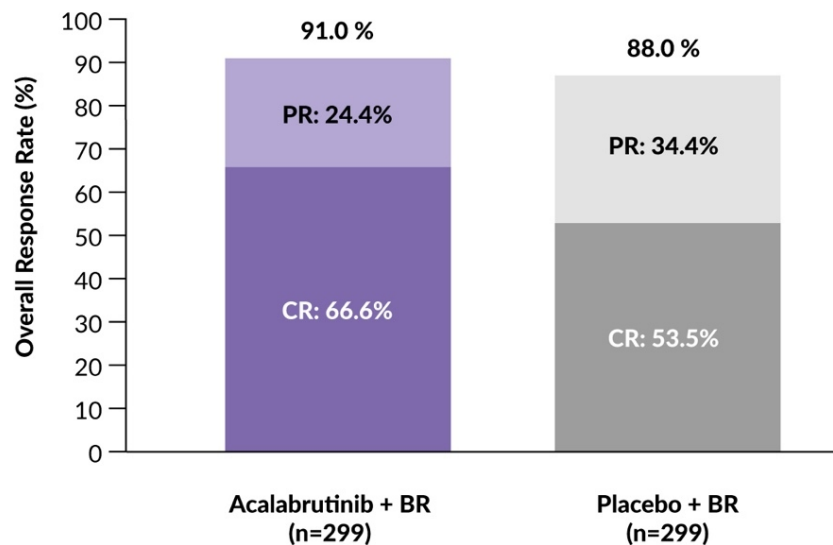


Figure 4. Best overall response rate (ORR) and complete response (CR) rate (ECHO interim analysis).

BR, bendamustine plus rituximab; PR, partial response. Adapted from Wang et al. 2023.²⁰

the acalabrutinib plus BR group showed a 25% reduction in the risk of death compared with the placebo plus BR group, with an HR of 0.75 (95% CI: 0.53–1.04), suggesting a trend toward improved OS outcomes (p=0.0797) (Figure 7).²⁰ These favorable survival outcomes observed in the sensitivity analysis, excluding COVID-19-related deaths, might be influenced by the

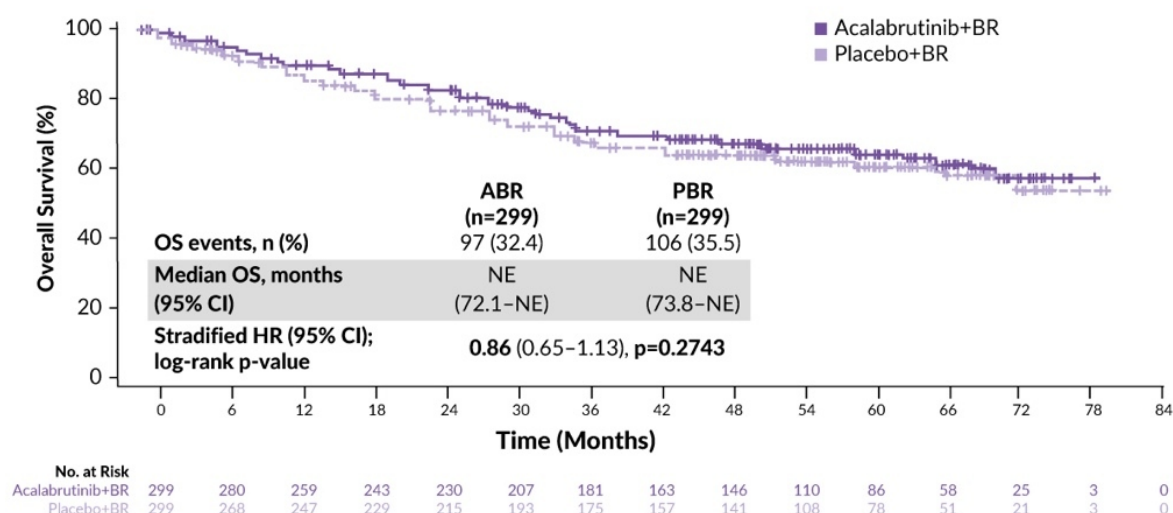


Figure 5. Sustained overall survival (OS) trend favors acalabrutinib plus bendamustine and rituximab (BR) despite most patients receiving a Bruton's tyrosine kinase inhibitor as a salvage therapy after progressive disease with BR (ECHO interim analysis).²⁰

The median follow-up of 45 months. ABR, acalabrutinib plus BR; NE, not estimable; PBR, placebo plus BR. Adapted from Wang et al. 2023.²⁰

fact that patients in the acalabrutinib plus BR arm might have been more vulnerable to COVID-19 infection compared with those in the BR alone arm, thus potentially favoring the combination arm.

Safety profile and adverse events with acalabrutinib plus standard chemoimmunotherapy

The median treatment exposure was longer in the acalabrutinib arm than in the placebo arm (29.0 months vs 25.0 months).²⁰ Treatment-emergent AEs (TEAEs) were present in most patients receiving acalabrutinib combined with BR (99.7%) and those receiving placebo combined with BR (99.0%) ([Table 1](#)).²⁰ Grade ≥ 3 AEs occurred at similar rates in both treatment groups, affecting 88.9% of patients in the acalabrutinib groups and 88.2% of those in the placebo group.²⁰ TEAEs leading to death were observed in 8.4% of patients in the acalabrutinib group and 9.0% in the placebo group.²⁰ Serious AEs of grade ≥ 3 were reported more frequently in acalabrutinib-treated patients compared with placebo-treated patients (64.3% vs 55.9%).²⁰ The discontinuation rate due to TEAEs was distinctly lower with placebo plus BR than with acalabrutinib plus BR (31.0 % vs 42.8%).

Notable grade ≥ 3 AEs of interest included atrial fibrillation (3.7% vs 1.7%), hypertension (5.4% vs 8.4%), major bleeding (2.0% vs 3.4%), infections (41.1% vs 34.0%) and second primary malignancies excluding non-melanoma skin cancer, with varying incidence rates between the treatment groups.²⁰ The

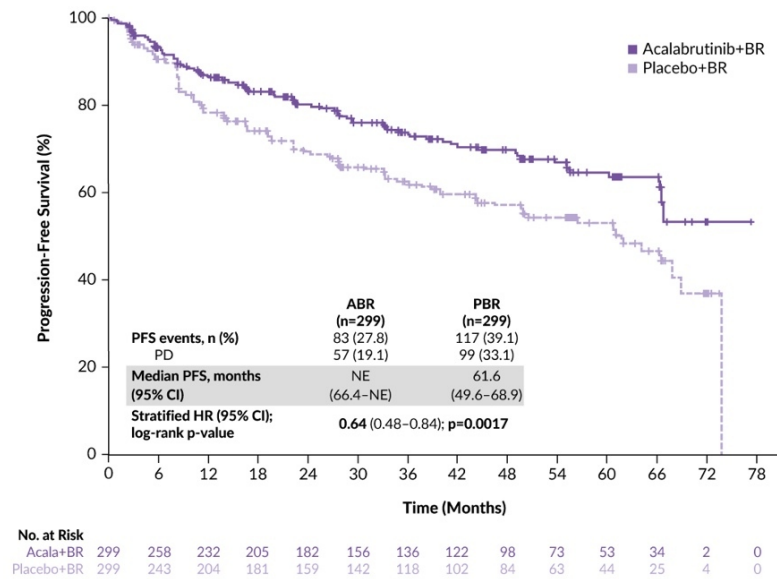


Figure 6. Progression-free survival (PFS) censored for COVID-19 deaths (ECHO prespecified sensitivity analysis).

ABR, acalabrutinib plus BR; BR, bendamustine plus rituximab; COVID-19, coronavirus disease 2019; NE, not estimable; PBR, placebo plus BR. Adapted from Wang et al. 2023.²⁰

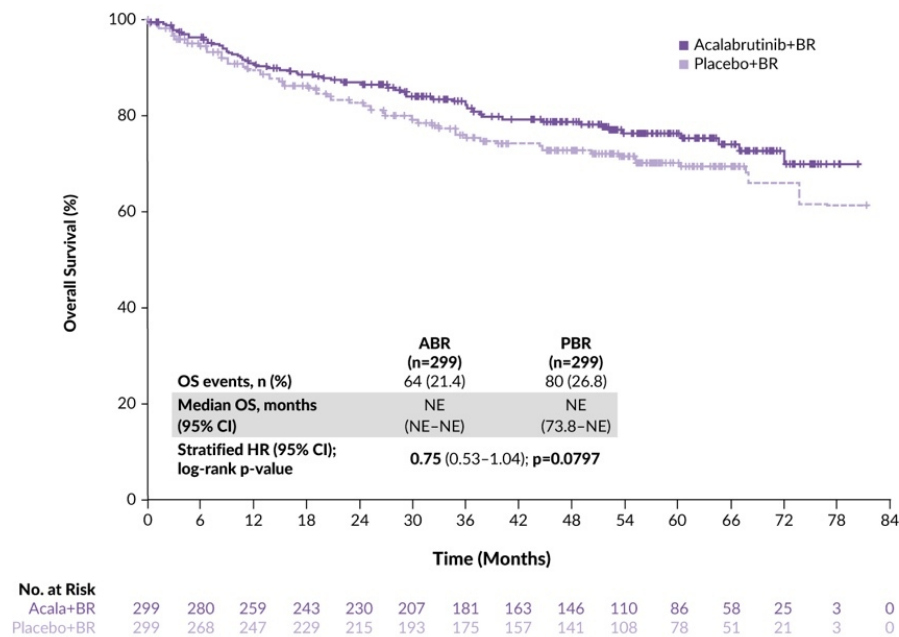


Figure 7. Overall survival (OS) censored for COVID-19 deaths (ECHO prespecified sensitivity analysis).

ABR, acalabrutinib plus BR; BR, bendamustine plus rituximab; COVID-19, coronavirus disease 2019; NE, not estimable; PBR, placebo plus BR. Adapted from Wang et al. 2023.²⁰

overall mortality rate was slightly lower in the acalabrutinib plus BR group compared with the placebo group (97 deaths [32.4%] vs 106 deaths [35.5%], respectively), with different causes attributed to the fatalities in each group, including disease progression and AEs within 30 days after the last dose.²⁰

Results further showed that COVID-19 influenced the mortality rate in both treatment arms, with more COVID-19-related AEs (grade 5) occurring among patients receiving acalabrutinib plus BR than those receiving placebo plus BR (9.4% vs 6.7%).²⁰

Overall, the safety findings from ECHO are consistent with the known safety profiles of the individual drugs.²⁰ Efficacy and safety outcomes of the ECHO trial are comparable to those observed in the SHINE study on ibrutinib plus BR ([Table 1](#)).¹⁹

Conclusion and future perspectives

Current frontline chemoimmunotherapies, such as BR, often do not achieve long-term remission, resulting in frequent relapses among patients with MCL. Over the past years, the use of BTK inhibitors have increased dramatically in patients with MCL, a population with a great unmet medical need. Earlier incorporation of a BTKI inhibitor has been shown to improve clinical outcomes,²⁶ suggesting a greater clinical activity in treatment-naïve patients. Recent trials therefore aimed to assess the efficacy and safety of BTK inhibitor-based regimens as frontline therapy, with promising results with acalabrutinib and ibrutinib therapies.^{12,19,20,27}

More specifically, the addition of acalabrutinib to BR was associated with a significant reduction on the risk of disease progression and a clinically meaningful, albeit not statistically significant, reduction in the risk of disease progression or death, providing an effective alternative for both intermediary and advanced groups of patients.²⁰ The safety profile observed with the acalabrutinib plus BR combination aligns with that of the individual drugs, indicating a manageable AE profile that supports its use in frontline therapy for MCL. The interim analysis from the ECHO trial shows a significant PFS benefit and promising signs of a positive OS trend, even within a cross-over study design, by adding a BTKi to frontline chemoimmunotherapy for older MCL patients. These results suggest potential improvements in long-term outcomes for this patient population.

Overall, the interim results from ECHO present a promising outlook for managing both fit and unfit older MCL patients, emphasizing the potential of acalabrutinib in improving outcomes and shaping future frontline therapeutic strategies in this patient population. Additionally, pirtobrutinib, a third-generation, non-covalent BTKi, is emerging into the treatment landscape and is being currently investigated in patients with BTK inhibitor-naïve MCL in the phase III BRUIN MCL-321 study.^{28,29} Several other trials

on the first-line use of acalabrutinib and ibrutinib are ongoing, including the EA4181 (acalabrutinib combinations in younger patients; [NCT04115631](#)), ACCRU-LY-1804 (modified VR-CAP plus acalabrutinib; [NCT04626791](#)), ACE-LY-308 (acalabrutinib plus BR; [NCT02972840](#)), ALTAMIRA (acalabrutinib and rituximab in elderly patients; [NCT05214183](#)), ENRICH (ibrutinib plus rituximab in older patients) and OASIS-2 (time-limited combination therapy with ibrutinib, venetoclax and rituximab; [NCT04802590](#)). Continued research and exploration of this treatment paradigm hold significant potential for advancing care and prognosis for patients with MCL.

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Conflict of interest

Adrian Schmidt received honoraria from Takeda, Janssen, Celgene, Sobi, Roche, Sanofi, Amgen, Beigene, Novartis, Incyte, Eli Lilly and Bayer.

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REFERENCES

1. Ladha A, Zhao J, Epner EM, Pu JJ. Mantle cell lymphoma and its management: where are we now? *Exp Hematol Oncol*. 2019;8:2. doi:[10.1186/s40164-019-0126-0](https://doi.org/10.1186/s40164-019-0126-0)
2. Alnassfan T, Cox-Pridmore MJ, Taktak A, Till KJ. Mantle cell lymphoma treatment options for elderly/unfit patients: A systematic review. *EJHaem*. 2021;3(1):276-290. doi:[10.1002/jha2.311](https://doi.org/10.1002/jha2.311)
3. Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol*. 2017;92(8):806-813. doi:[10.1002/ajh.24797](https://doi.org/10.1002/ajh.24797)
4. Pease DF, Morrison VA. Treatment of mantle cell lymphoma in older adults. *J Geriatr Oncol*. 2018;9(4):308-314. doi:[10.1016/j.jgo.2017.12.001](https://doi.org/10.1016/j.jgo.2017.12.001)
5. Epperla N, Hamadani M, Fenske TS, Costa LJ. Incidence and survival trends in mantle cell lymphoma. *Br J Haematol*. 2018;181(5):703-706. doi:[10.1111/bjh.14699](https://doi.org/10.1111/bjh.14699)
6. Ruan J. Molecular profiling and management of mantle cell lymphoma. *Hematology*. 2019;2019(1):30-40. doi:[10.1182/hematology.2019000011](https://doi.org/10.1182/hematology.2019000011)
7. Scheubeck G, Jiang L, Hermine O, et al. Clinical outcome of mantle cell lymphoma patients with high-risk disease (high-risk MIPI-c or high p53 expression). *Leukemia*. 2023;37(9):1887-1894. doi:[10.1038/s41375-023-01977-y](https://doi.org/10.1038/s41375-023-01977-y)
8. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. *Blood*. 2009;114(8):1469-1476. doi:[10.1182/blood-2009-02-179739](https://doi.org/10.1182/blood-2009-02-179739)
9. Vose JM. Mantle cell lymphoma: 2015 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol*. 2015;90(8):739-745. doi:[10.1002/ajh.24094](https://doi.org/10.1002/ajh.24094)
10. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008;112(7):2687-2693. doi:[10.1182/blood-2008-03-147025](https://doi.org/10.1182/blood-2008-03-147025)
11. Dreyling M, Campo E, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl_4):iv62-iv71. doi:[10.1093/annonc/mdx223](https://doi.org/10.1093/annonc/mdx223)
12. Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. *Lancet*. 2024;403(10441):2293-2306. doi:[10.1016/S0140-6736\(24\)00184-3](https://doi.org/10.1016/S0140-6736(24)00184-3)
13. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210. doi:[10.1016/s0140-6736\(12\)61763-2](https://doi.org/10.1016/s0140-6736(12)61763-2)
14. B-cell lymphomas - NCCN guidelines. National Comprehensive Cancer Network (NCCN). Accessed July 2024. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1480>
15. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369(6):507-516. doi:[10.1056/NEJMoa1306220](https://doi.org/10.1056/NEJMoa1306220)
16. Bock AM, Gile JJ, Larson MC, et al. Evolving treatment patterns and improved outcomes in relapsed/refractory mantle cell lymphoma: a prospective cohort study. *Blood Cancer J*. 2023;13(1):169. doi:[10.1038/s41408-023-00942-3](https://doi.org/10.1038/s41408-023-00942-3)

17. Visco C, Tisi MC, Evangelista A, et al. Time to progression of mantle cell lymphoma after high-dose cytarabine-based regimens defines patients risk for death. *Br J Haematol*. 2019;185(5):940-944. doi:[10.1111/bjh.15643](https://doi.org/10.1111/bjh.15643)
18. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet*. 2018;391(10121):659-667. doi:[10.1016/s0140-6736\(17\)33108-2](https://doi.org/10.1016/s0140-6736(17)33108-2)
19. Wang ML, Jurczak W, Jerkeman M, et al. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. *N Engl J Med*. 2022;386(26):2482-2494. doi:[10.1056/NEJMoa2201817](https://doi.org/10.1056/NEJMoa2201817)
20. Wang ML, Mayer J, Belada D, et al. Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma: results from the phase 3, double-blind, placebo-controlled ECHO trial. Presented at: 2024 European Hematology Association Congress; June 13-16, 2024. Madrid, Spain. Oral presentation LBA3439. <https://library.ehaweb.org/eha/2024/eha2024-congress/4136515/michael.wang.acalabrutinib.plus.bendamustine.and.rituximab.in.untreated.mantle.html>
21. Kriegsmann K, Kriegsmann M, Witzens-Harig M. Acalabrutinib, a second-generation bruton's tyrosine kinase inhibitor. *Recent Results Cancer Res*. 2018;212:285-294. doi:[10.1007/978-3-319-91439-8_14](https://doi.org/10.1007/978-3-319-91439-8_14)
22. Vitale C, Gibbons JL, Ferrajoli A. Targeted treatment of chronic lymphocytic leukemia: Clinical utility of acalabrutinib. *Onco Targets Ther*. 2021;14:5507-5519. doi:[10.2147/ott.S303060](https://doi.org/10.2147/ott.S303060)
23. Girard J, Reneau J, Devata S, et al. Evaluating acalabrutinib In the treatment of mantle cell lymphoma: Design, development, And place in therapy. *Onco Targets Ther*. 2019;12:8003-8014. doi:[10.2147/ott.S155778](https://doi.org/10.2147/ott.S155778)
24. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma: Long-term efficacy and safety results from a phase 2 study. *Blood*. 2020;136(suppl_1):38-39. doi:[10.1182/blood-2020-134824](https://doi.org/10.1182/blood-2020-134824)
25. Wang M, Belada D, Cheah C, et al. A phase 3 study of acalabrutinib plus bendamustine and rituximab in elderly (aged ≥ 65 years) treatment-naïve patients with mantle cell lymphoma. *Hematol Oncol*. 2019;37(S2):554-555. doi:[10.1002/hon.2632](https://doi.org/10.1002/hon.2632)
26. Rule S, Dreyling M, Goy A, et al. Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis. *Haematologica*. 2019;104(5):e211-e214. doi:[10.3324/haematol.2018.205229](https://doi.org/10.3324/haematol.2018.205229)
27. Wang M, Robak T, Maddocks KJ, et al. Acalabrutinib plus venetoclax and rituximab in treatment-naïve mantle cell lymphoma: 2-year safety and efficacy analysis. *Blood Adv*. 2024;8(17):4539-4548. doi:[10.1182/bloodadvances.2023012424](https://doi.org/10.1182/bloodadvances.2023012424)
28. Cohen JB, Shah NN, Jurczak W, et al. Pirtobrutinib in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) Patients with Prior cBTKi: Safety and Efficacy Including High-Risk Subgroup Analyses from the Phase 1/2 BRUIN Study. *Blood*. 2023;142(suppl_1):981. doi:[10.1182/blood-2023-181627](https://doi.org/10.1182/blood-2023-181627)
29. Wang M, Eyre TA, Shah NN, et al. BRUIN MCL-321: A phase 3, open-label, randomized study of pirtobrutinib versus investigator choice of BTK inhibitor in patients with previously treated, BTK inhibitor naïve mantle cell lymphoma. *J Clin Oncol*. 2023;41(suppl_16):TPS7587. doi:[10.1200/JCO.2023.41.16_suppl.TPS7587](https://doi.org/10.1200/JCO.2023.41.16_suppl.TPS7587)