

Integrating Acalabrutinib Plus Bendamustine/Rituximab in the Frontline MCL Treatment Protocol

In a recent *Between the Lines* program, Brad S. Kahl, MD, and Tycel Phillips, MD, discussed the use of the Bruton tyrosine kinase (BTK) inhibitor acalabrutinib (Calquence) in combination with bendamustine (Treanda) and rituximab (Rituxan) for patients with untreated mantle cell lymphoma (MCL) based on findings from the phase 3 ECHO trial (NCT02972840). They highlighted how these data may impact the current frontline therapy paradigm and any potential barriers to integrating this acalabrutinib-based combination into clinical practice.

Kahl is a professor in the Division of Oncology in the John T. Milliken Department of Medicine at Washington University School of Medicine in St Louis. Phillips is an associate professor in the Division of Lymphoma and Department of Hematology & Hematopoietic Cell Transplantation at City of Hope in Duarte, California.

Current Treatment Options in Older Patients With MCL

Kahl and Phillips contextualized the findings from the ECHO trial by outlining the currently available therapeutic strategies for patients with newly diagnosed MCL, particularly among those who are above the age of 65 years.

Apart from enrolling patients on clinical trials, Phillips highlighted bendamustine/rituximab and rituximab/lenalidomide (Revlimid) as common treatment strategies at academic centers. In his experience with administering bendamustine/rituximab at his practice, Phillips noted some degree of venous irritation in patients, although he did not report any neuropathy, hair loss, or cardiotoxicity. Kahl noted some nausea and fatigue among his patients, stating that treatment usually goes

well for most who receive the combination.

Compared with other types of lymphoma, the use of maintenance rituximab appears to be more effective in MCL. Both Kahl and Phillips agreed on using a maintenance therapy duration of approximately 2 years with rituximab for patients who are older. Additionally, suitable preventive medications included *Pneumocystis jirovecii* pneumonia prophylaxis following the completion of bendamustine and acyclovir (Sitavig) to mitigate the risk of reactivating shingles.

Turning their attention to potential unmet needs among this patient population, Kahl and Phillips described how the efficacy of bendamustine/rituximab may be limited for patients with *TP53* aberrations and highly proliferative disease.

“I don’t know what necessarily works for those patients, but chemotherapy does not seem to necessarily give us a lot of bandwidth or wiggle room, especially with bendamustine/rituximab,” Phillips stated. “For some of these patients, the next step is trying to get to chimeric antigen receptor [CAR] T-cell therapy, and if they get a very short response to bendamustine/rituximab, that does impede our ability to go to CAR T in the second line.”



Brad S. Kahl, MD



Tycel Phillips, MD

ECHO Trial Data

In the phase 3 ECHO trial, 598 patients with untreated MCL received bendamustine/rituximab with or without acalabrutinib.¹ All patients were assigned to receive bendamustine plus rituximab for six 28-day cycles; those who had at least a partial response (PR) in the experimental arm and better than a PR in the placebo arm were eligible to undergo maintenance therapy with rituximab every 2 cycles for 2 years.

Additionally, patients were randomly assigned 1:1 to receive acalabrutinib at 100 mg twice daily orally (n=299) or matched placebo (n=299) until disease progression or toxicity, with those in the placebo arm being eligible to cross over to the acalabrutinib arm in the event of progressive disease.

The trial's primary end point was progression-free survival (PFS). Secondary end points included objective response rate and overall survival (OS).

Patients 65 years and older with an ECOG performance status of 0 to 2 were eligible for enrollment on the trial. Investigators stratified patients by simplified MCL International Prognostic Index scores (low vs intermediate vs high) and geographic region (North America vs Western Europe vs other).

According to data presented at the 2024 European Hematology Association Congress, acalabrutinib in combination with bendamustine/rituximab produced a median PFS of 66.4 months (95% CI, 55.1-not evaluable [NE]) compared with 49.6 months (95% CI, 36.0-64.1) among those who received bendamustine/rituximab alone (HR, 0.73; 95% CI, 0.57-0.94; $P = .0160$). Additionally, the acalabrutinib-based combination numerically reduced the risk of death (OS HR, 0.86; 95% CI, 0.65-1.13; $P = .2743$).

When censoring for patient deaths related to COVID-19, the median PFS was not reached (95% CI, 66.4-NE) in the acalabrutinib arm vs 61.6 months (95% CI, 49.6-68.9) in the placebo arm (HR, 0.64; 95% CI, 0.48-0.84; $P = .0017$). Regarding OS, a reduction in the risk of death was noted with acalabrutinib-based treatment when censoring for COVID-19-related deaths (HR, 0.75; 95% CI, 0.53-1.04; $P = .0797$).

"[The data] speak to some of the issues with B-cell-depleting or B-cell-suppressing agents when you have viruses," Phillips stated regarding the survival outcomes when censoring for deaths related to COVID-19 in the ECHO trial. "Most of the trial was conducted during the [COVID-19] pandemic, suggesting that patients on these types of treatments are more at risk [of infection]. The [acalabrutinib arm] vs the [placebo] arm was more adversely affected during the pandemic. Some of these patients in the standard of care arm have recovered some of their B cells and immunoglobulins up to finishing [rituximab] maintenance, where you'll probably still get some suppression with continuous acalabrutinib."

Kahl seconded Phillips' notion, stating that halting treatment with acalabrutinib at the same time that maintenance rituximab stops may have mitigated the risk of COVID-19-related infections in the ECHO trial. The panelists noted that most, if not all, lymphoma trials conducted during the COVID-19 pandemic were negatively impacted by infection-related deaths.

"I could easily see many clinicians adopting this as their new standard, but I can equally see a number of clinicians saying, 'Yeah, it's a positive study, but you took my best second-line therapy and moved it into the front line for a modest PFS benefit without an OS benefit. I'm not sure that's worth it,'" Kahl said regarding the efficacy findings for the acalabrutinib combination. "I'm predicting we're going to get a variety of opinions about the clinical impact of this data set."

In the acalabrutinib and placebo arms of the ECHO trial, respectively, 99.7% and 99.0% of patients experienced any-grade treatment-emergent adverse effects (TEAEs). In each treatment arm, investigators also reported grade 3 or higher TEAEs (88.9% vs 88.2%) and grade 5 TEAEs (12.1% vs 10.1%).



Serious AEs (SAEs) affected 69.0% of those in the acalabrutinib arm compared with 62.0% of patients in the placebo arm, with grade 3 or higher SAEs occurring in 64.3% vs 55.9% of patients, respectively. Additionally, 68.0% and 55.6% of patients in each arm had TEAEs associated with study therapy and 42.8% and 31.0% discontinued treatment due to TEAEs.

"With some of the grade 5 AEs, attribution is always important," Phillips said. "In these situations, especially now, most of these trials tend not to attribute COVID-19-related events to the study treatment. I find that hard to fathom, how you could separate the two."

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The median length of treatment was 29 months (range, 0.1-80.1) in the acalabrutinib arm and 25 months (range, 0.03-76.4) in the placebo arm. Common any-grade AEs of interest in each respective arm included infections (78.1% vs 71.0%), hypertension (12.1% vs 15.8%), second primary malignancies apart from nonmelanoma skin cancer (9.8% vs 10.8%), atrial fibrillation (6.1% vs 4.4%), and major bleeding (2.4% vs 5.4%). Infections were the most common grade 3 or higher AE, affecting 71.0% of those who received acalabrutinib and 34.0% of those who were treated with the placebo.

According to Kahl, there appears to be an added risk of toxicity with acalabrutinib compared with placebo, especially in terms of infections.

Key Takeaways and Considerations in Frontline MCL

Phillips highlighted that the PFS benefit with acalabrutinib in the ECHO trial may be higher compared with any other potential outcomes using bendamustine/rituximab alone. Although this PFS improvement may support the use of the acalabrutinib regimen as a new standard of care in a vacuum, Phillips noted some nuances to incorporating the combination into the MCL treatment protocol.

Continuous treatment with a BTK inhibitor in the first-line setting may not leave many therapeutic options for the second-line setting, especially in areas where patients may not have access to CAR T-cell therapy. Pirtobrutinib (Jaypirca) may be an option under these circumstances, but Phillips stated that the agent was not a long-term solution for those who progress on a covalent BTK inhibitor.

“I would have liked to have seen more curve separation [in

the survival data] to make me more enthusiastic about using up my covalent BTK inhibitor in the first line,” Kahl said when reviewing the efficacy findings from the ECHO trial.

The FDA granted priority review to a supplemental new drug application for acalabrutinib in patients with untreated MCL based on data from the ECHO trial in October 2024.² The regulatory agency set a Prescription Drug User Fee Act in the first quarter of 2025 for this indication.

If the acalabrutinib regimen receives FDA approval in this population, Phillips said that it would likely see use in a community setting. However, when community physicians refer their patients to an academic center for treatment, there may be less time to give patients their next line of treatment depending on the timing of the referral and the extent of their disease progression. Kahl stated that academic centers may be a little more selective when choosing to administer acalabrutinib-based therapy based on some of the nuances that he and Phillips highlighted in the ECHO trial.

Overall, Kahl stated that the addition of acalabrutinib to bendamustine/rituximab in the ECHO trial produced a modest PFS benefit without an OS benefit. Although he interpreted the results of the study positively, he was not certain about determining how the data may impact clinical practice while weighing the benefits of using up a covalent BTK inhibitor in the frontline setting. Additionally, he described the need to see more granular details for the toxicity data.

“I do think [the ECHO trial will] change practice for a number of investigators around the country and perhaps around the world, but it still leaves lots of room for improvement in the frontline management of older [patients with] MCL,” Kahl concluded.

Phillips expressed his curiosity in seeing how the ECHO trial results will pan out for high-risk subgroups, including patients with elevated proliferation or *p53*-mutated disease. If minimal residual disease statuses were collected among patients, he also wanted to observe how these statuses may correlate with PFS outcomes.

“Sometimes, the best-designed trials depend on how long they take to read out.... We’ve come a long way since ECHO started enrolling patients, and I think we’ll continue to improve how we treat our patients with clinical research and some of the questions we’re answering,” Phillips said. ■

REFERENCES

1. Wang M, Mayer J, Belada D, et al. Acabrutinib 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. Abstract LBA3439.
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