

BC Cancer Protocol Summary for Treatment of Mantle Cell Lymphoma with Acalabrutinib, Bendamustine and ritUXimab

Protocol Code

LYMCABENDR

Tumour Group

Lymphoma

Contact Physicians

LY Systemic Therapy

ELIGIBILITY:

Patients must:

- Have pathologically confirmed mantle cell lymphoma (MCL),
- Have not received previous systemic therapy for MCL,
- Be ineligible for autologous stem cell transplant (ASCT),
- Be 65 years of age or older, or deemed ineligible for ASCT by the treating healthcare provider

Patients should have:

- Good performance status

EXCLUSIONS:

Patient must not have:

- Signs of CNS involvement or leptomeningeal disease

CAUTION:

- Creatinine clearance (CrCl) less than 40 mL/min
- AST or ALT greater than 2.5 times upper limit of normal and total bilirubin greater than 1.5 times upper limit of normal

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, total bilirubin
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with Cycle 2): HBsAg, HBsAb, HBcoreAb
- Baseline, if clinically indicated: PTT, INR, ECG
- Cycles 2 to 16, prior to Day 1: CBC & Diff, total bilirubin, ALT
- Cycles 17 onward, prior to each doctor visit: CBC & Diff, total bilirubin, ALT
- If clinically indicated: creatinine, PTT, INR, ECG, HBV viral load (see protocol [SCHBV](#))

PREMEDICATIONS:

- Cycle 1 to 6: Antiemetic protocol for moderately emetogenic chemotherapy (see protocol [SCNAUSEA](#))
- Cycle 7 onward: Antiemetics usually not required

For ritUXimab Portion:

- For intravenous infusion:
diphenhydramINE 50 mg PO prior to ritUXimab IV and then q4h during the IV infusion, if the infusion exceeds 4 hours
acetaminophen 650 to 975 mg PO prior to ritUXimab IV and then q4h during the IV infusion, if the infusion exceeds 4 hours
- For subcutaneous injection:
diphenhydramINE 50 mg PO prior to ritUXimab subcutaneous
acetaminophen 650 to 975 mg PO prior to ritUXimab subcutaneous

SUPPORTIVE MEDICATIONS:

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Activated: 1 Oct 2026 Revised:

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- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

TREATMENT:

Cycles 1 to 5:

Drug	Dose	BC Cancer Administration Guideline
acalabrutinib	100 mg twice daily continuously	PO
bendamustine	90 mg/m ² on Days 1 and 2	IV in 250 to 500 mL NS over 60 minutes
riTUXimab***†	375 mg/m ² * on Day 1 or 2 whenever possible, but not later than 72 hours after Day 1 of bendamustine	IV in 250 to 500 mL NS over 90 minutes to 8 hours**
	If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration	
	1400 mg (fixed dose in 11.7 mL) on Day 1 or 2 whenever possible but not later than 72 hours after Day 1 of bendamustine	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration

- Repeat every 4 weeks (i.e. 28 days) for 5 cycles, then proceed to Cycle 6

Cycle 6:

Drug	Dose	BC Cancer Administration Guideline
acalabrutinib	100 mg twice daily continuously	PO
bendamustine	90 mg/m ² on Days 1 and 2	IV in 250 to 500 mL NS over 60 minutes
riTUXimab***†	375 mg/m ² * on Day 1 or 2 whenever possible, but not later than 72 hours after Day 1 of bendamustine	IV in 250 to 500 mL NS over 90 minutes to 8 hours**
	If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration	
	1400 mg (fixed dose in 11.7 mL) on Day 1 or 2 whenever possible but not later than 72 hours after Day 1 of bendamustine	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration

- Cycle 6 duration = 12 weeks (i.e. 84 days). After 12 weeks, proceed to Cycle 7

Cycles 7 to 14:

Drug	Dose	BC Cancer Administration Guideline
acalabrutinib	100 mg twice daily continuously	PO
riTUXimab***†	375 mg/m ² * on Day 1	IV in 250 to 500 mL NS over 90 minutes to 8 hours**
	If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration	
	1400 mg (fixed dose in 11.7 mL) on Day 1	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration

* Select dose per Dose Banding Table (appendix)

**Start the (first dose) initial infusion at 50 mg/h and, after 1 hour, increase by 50 mg/h every 30 minutes until a rate of 400 mg/h is reached. For all subsequent treatments, infuse 50 mL (or 100 mL) of the dose over 30 minutes then infuse the remaining 200 mL (or 400 mL) over 60 minutes (total infusion time = 90 minutes). Development of an allergic reaction may require a slower infusion rate. See hypersensitivity below.

***The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than 30 to 50 x 10⁹ /L. While there is no requirement to withhold riTUXimab based on lymphocyte count, clinicians may wish to pre-medicate patients with high tumour burden with steroids prior to riTUXimab infusion or omit the riTUXimab from the first cycle of treatment.

†Patients must receive first dose by IV infusion (using the IV formulation) because the risk of reactions is highest with the first infusion. IV administration allows for better management of reactions by slowing or stopping the infusion. IV first dose should also be given to patients previously treated more than 6 months ago.

‡During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible. If restarting more than 6 months from prior subcutaneous rituximab, give first dose by IV infusion (using the IV formulation).

- Repeat every 12 weeks (i.e. 84 days) for 8 Cycles (i.e. Cycles 7 to 14), then proceed to Cycle 15

Cycle 15 onward:

Drug	Dose	BC Cancer Administration Guideline
acalabrutinib	100 mg twice daily continuously	PO

- Continue treatment until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Toxicity Occurrence	Dose Modifications After Recovery		
	bendamustine	acalabrutinib	riTUXimab
1 st	70 mg/m ²	100 mg twice daily	No specific dose modifications. Toxicity is managed by treatment delay or other measures.
2 nd	Discontinue	100 mg once daily	
3 rd		100 mg once daily	
4 th		Discontinue	

1. Hematological:

Neutropenia:

ANC (x10 ⁹ /L)	bendamustine	acalabrutinib
Greater than or equal to 1.0	100%	100%
0.5 to less than 1.0	Withhold bendamustine. Once ANC recovers to greater than or equal to 1.0 or baseline, resume bendamustine at dose level indicated above.	100%
Less than 0.5	Withhold bendamustine. Once ANC recovers to greater than or equal to 1.0 or baseline, resume bendamustine at dose level indicated above.	Withhold acalabrutinib if ANC less than 0.5 lasts longer than 7 days. Once ANC recovers to greater than or equal to 1.0 or baseline, resume acalabrutinib at dose level indicated above.

Thrombocytopenia:

Platelets (x10 ⁹ /L)	bendamustine	acalabrutinib
Greater than or equal to 50	100%	100%
25 to less than 50	Withhold bendamustine. Once platelets recover to greater than or equal to 50 or baseline, resume bendamustine at dose level indicated above.	Withhold acalabrutinib if there is presence of significant bleeding. Once platelets recover to greater than or equal to 50 or baseline, resume acalabrutinib at dose level indicated above.
Less than 25	Withhold bendamustine. Once platelets recover to greater than or equal to 50 or baseline, resume bendamustine at dose level indicated above.	Withhold acalabrutinib. Once platelets recover to greater than or equal to 50 or baseline, resume acalabrutinib at dose level indicated above.

Other Hematologic Toxicity:

Severity	bendamustine	acalabrutinib
Unmanageable Grade 3 OR Grade 4 ^β	Withhold bendamustine. Once toxicity resolves to less than or equal to Grade 2 or baseline, resume bendamustine at dose level indicated above.	Withhold acalabrutinib. Once toxicity resolves to less than or equal to Grade 2 or baseline, resume acalabrutinib at indicated above

^β Grade 4 lymphopenia is an expected effect of bendamustine and ritUXimab treatment. Dose modification is usually reserved for cases where lymphopenia is considered clinically important, e.g. associated recurrent infections.

2. Non-Hematologic Toxicities:

Severity	bendamustine	acalabrutinib
Grade 3 OR Grade 4	Withhold bendamustine. Once toxicity resolves to less than or equal to Grade 1 or baseline, resume bendamustine at dose level indicated above.	Withhold acalabrutinib. Once toxicity resolves to less than or equal to Grade 2 or baseline, resume acalabrutinib at indicated above

PRECAUTIONS:

- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- Thrombocytopenia:** Support with platelet transfusion may be required.
- Hepatitis B Reactivation:** See SCHBV protocol for more details.
- Bendamustine Infusion Reactions and Hypersensitivity:** Bendamustine can cause allergic type reactions during the IV infusion such as fever, chills, pruritus and rash. Severe anaphylactic and anaphylactoid reactions have occurred rarely, particularly in the second and subsequent cycles of therapy. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. Consider pre-treatment with antihistamines, antipyretics and corticosteroids for patients experiencing Grade 1 or 2 infusion reactions; consider discontinuing treatment for patients experiencing Grade 3 or 4 infusion reactions. See BC Cancer Hypersensitivity Guidelines.
- ritUXimab Hypersensitivity:** Refer to BC Cancer Hypersensitivity Guidelines. ritUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, alarm, pruritus, sneezing, cough, fever or faintness. For the first dose, patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion is completed. For all subsequent doses, constant visual observation is not required. Vital signs are not required unless symptomatic. Because transient hypotension may occur during infusion, consider withholding antihypertensive medications 12 hours prior to ritUXimab infusion. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. A reasonable guideline is as follows. After recovery of symptoms, restart ritUXimab infusion at one infusion rate below the rate at which the reaction occurred and continue with escalation of infusion rates on the appropriate schedule above. If the infusion must be stopped a second time, restart after clearance of symptoms, at one infusion rate lower and continue at that rate without further escalation. Fatal cytokine release syndrome can occur (see below).
- Tumour Lysis Syndrome:** Tumor lysis syndrome has been associated with bendamustine, possibly leading to acute renal failure and death. Usual onset occurs during the first cycle. Maintain adequate volume status and monitor blood chemistry, including potassium and uric acid levels. Allopurinol has been used, but the concomitant use of bendamustine and allopurinol can cause increased risk of severe skin toxicity.
- Drug Interactions:**
 - bendamustine:** CYP1A2 inhibitors can potentially decrease plasma concentration of bendamustine. CYP1A2 inducers can potentially increase plasma concentration of bendamustine.

- **acalabrutinib:** acalabrutinib is a CYP3A4 substrate. Concomitant therapy with strong or moderate CYP 3A inhibitors may increase acalabrutinib exposure; avoid if possible. Concomitant use of acalabrutinib with strong CYP 3A inducer may decrease acalabrutinib exposure; avoid if possible. If concomitant use cannot be avoided, dose modification may be required.
- 8. **Skin Reactions:** Rash, toxic skin reactions and bullous exanthema have been reported with bendamustine. They may be progressive and increase in severity with further treatment. Monitor closely. If skin reactions are severe or progressive, consider withholding or discontinuing bendamustine.
- 9. **Fatal Cytokine Release Syndrome** has been reported with ritUXimab. It usually occurs within 1-2 hours of initiating the first ritUXimab infusion. Initially, it is characterised by severe dyspnea (often with bronchospasm and hypoxia) in addition to fever, chills, rigors, urticaria and angioedema. Pulmonary interstitial infiltrates or edema visible on chest x-ray may accompany acute respiratory failure. There may be features of tumour lysis syndrome such as hyperuricemia, hypocalcemia, acute renal failure and elevated LDH. For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized. The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than $30\text{-}50 \times 10^9/\text{L}$. While there is no requirement to withhold ritUXimab based on lymphocyte count, clinicians may wish to pre-medicate patients with high tumour burden with steroids prior to ritUXimab infusion or omit the ritUXimab from the first cycle of treatment.
- 10. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported with ritUXimab. If such a reaction occurs, ritUXimab should be discontinued.
- 11. **Gastrointestinal Obstruction or Perforation:** There have been rare reports of gastrointestinal obstruction or perforation, sometimes fatal, when ritUXimab is given in combination with other chemotherapy, occurring 1 to 12 weeks after treatment. Symptoms possibly indicative of such complications should be carefully investigated and appropriately treated.
- 12. **Medication Safety:** ritUXimab is formulated differently for IV versus subcutaneous administration. Use caution during prescribing, product selection, preparation and administration. IV formulation is supplied as 10 mg/mL solution which must be diluted prior to administration. Subcutaneous formulation is supplied as a fixed dose 1600mg/13.4mL ready-to-use solution which contains hyaluronidase to facilitate injection.
- 13. **Increased drug absorption by hyaluronidase:** other subcutaneous medications should not be injected at the same site as subcutaneous ritUXimab. Increased systemic effects are unlikely to be clinically significant with topical applications of EMLA, hydrocortisone, or diphenhydramine.
- 14. **Hemorrhagic events:** Minor hemorrhagic events including bruising, epistaxis and petechiae occur in approximately half of the patients treated with acalabrutinib. Major hemorrhagic events (serious or Grade 3 or higher bleeding) occur in 3% of patients. Use with caution in patients taking anticoagulants or medications that inhibit platelet function. Hold treatment for 3 to 7 days pre- and post-surgery; reinstitute post-surgery based on the risk of bleeding.

Contact the LY Systemic Therapy physician at your regional cancer centre or the LY Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Wang M, Salek D, Belada D et al. Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma. *J Clin Oncol* 2025 Jul 10; 43(20): 2276-2284.
2. Acalabrutinib (Calquence) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. *Canadian Journal of Health Technologies* Oct 2025; 5(10): 1-21.

Appendix. Dose Bands

riTUXimab DOSE BANDING TABLE

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 364		Pharmacy prepares specific dose
364	442.49	400
442.5	480.49	460
480.5	554.49	500
554.5	665.49	600
665.5	776.49	700
776.5	887.49	800
887.5	999.49	900
999.5	1099.49	1000
1099.5	1199.49	1100
1199.5	1299.49	1200
1299.5	1399.49	1300
1399.5	1499.49	1400
1499.5	1599.49	1500
More than 1599.49		Pharmacy prepares specific dose