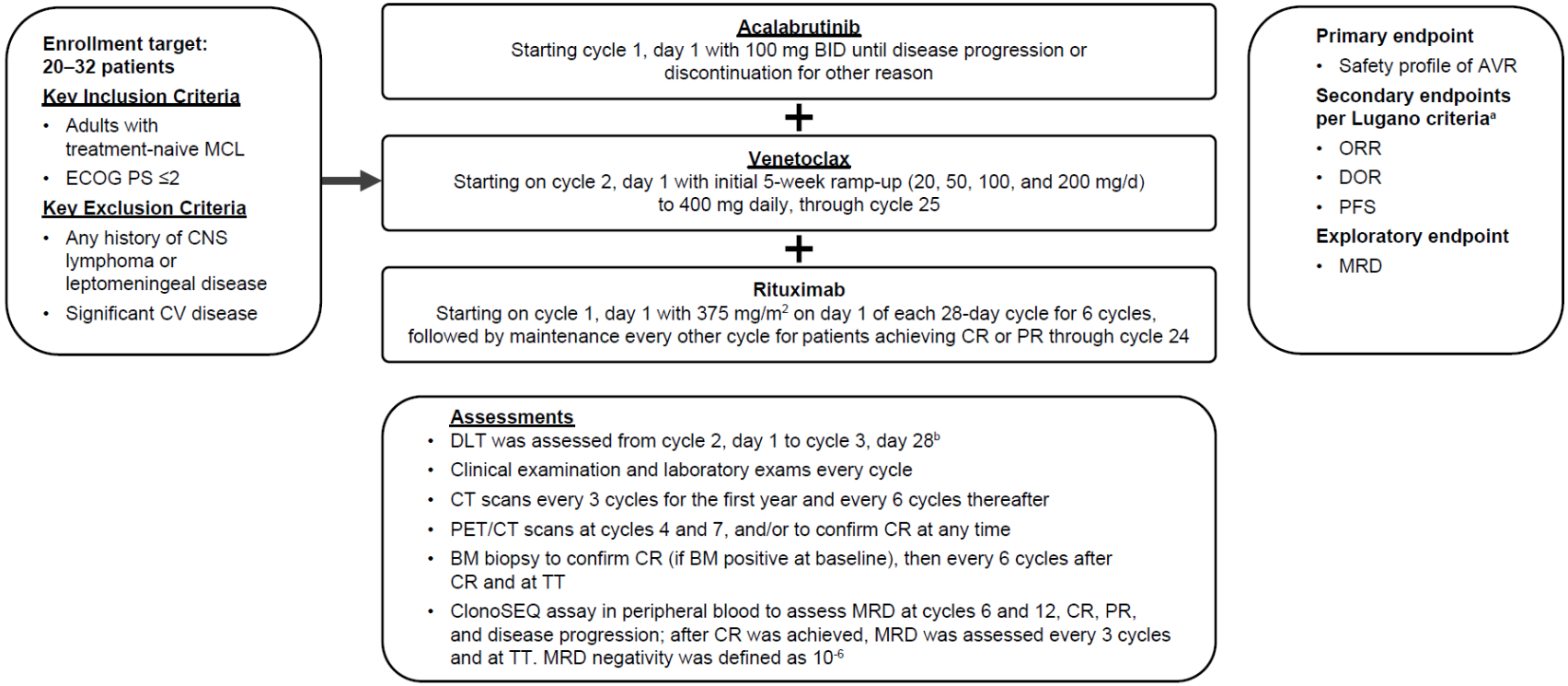
SUPPLEMENTARY APPENDIX

S1. Study design



[a]Efficacy endpoints evaluated per the Lugano classification for non-Hodgkin lymphoma, which requires PET/CT and BM biopsy confirmation of CR.
[b]The study had an initial dose-finding period in which DLT was evaluated, followed by an expansion phase. No DLTs were observed during the dose-finding period in the 6 initial patients. Therefore, the initial cohort was expanded to 21 patients, and venetoclax 400 mg daily was the dose chosen after ramp-up for triple therapy.
AVR, acalabrutinib + venetoclax + rituximab; BID, twice daily; BM, bone marrow; CNS, central nervous system; CR, complete response; CT, computed tomography; CV, cardiovascular; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MRD; minimal residual disease; ORR, overall response rate; PET/CT, positron-emission tomography/computed tomography; PFS, progression-free survival; PR, partial response; TT, treatment termination.

S2. Inclusion and exclusion criteria

Inclusion Criteria

- Men and women ≥18 years of age
- Pathologically confirmed mantle cell lymphoma (MCL), with documentation of chromosomal translocation t(11;14) (q13;q32) and/or overexpression of cyclin D1 in association with other relevant markers (eg, CD5, CD19, CD20)
- Patients with MCL requiring treatment and for whom no prior systemic therapies have been received
- Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (≥1 nodal lesion with ≥2.0 cm in the longest dimension and/or extranodal lesion >1.0 cm in the longest dimension)
- Eastern Cooperative Oncology Group performance status ≤2
- Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib, 30 days after the last dose of venetoclax, or 12 months after the last dose of rituximab, whichever is longest
- Men who are sexually active and can beget children must agree to use highly effective forms of contraception and refrain from sperm donation during the study and for 90 days after the last dose of venetoclax or rituximab, whichever is longest
- Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty

- Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations)

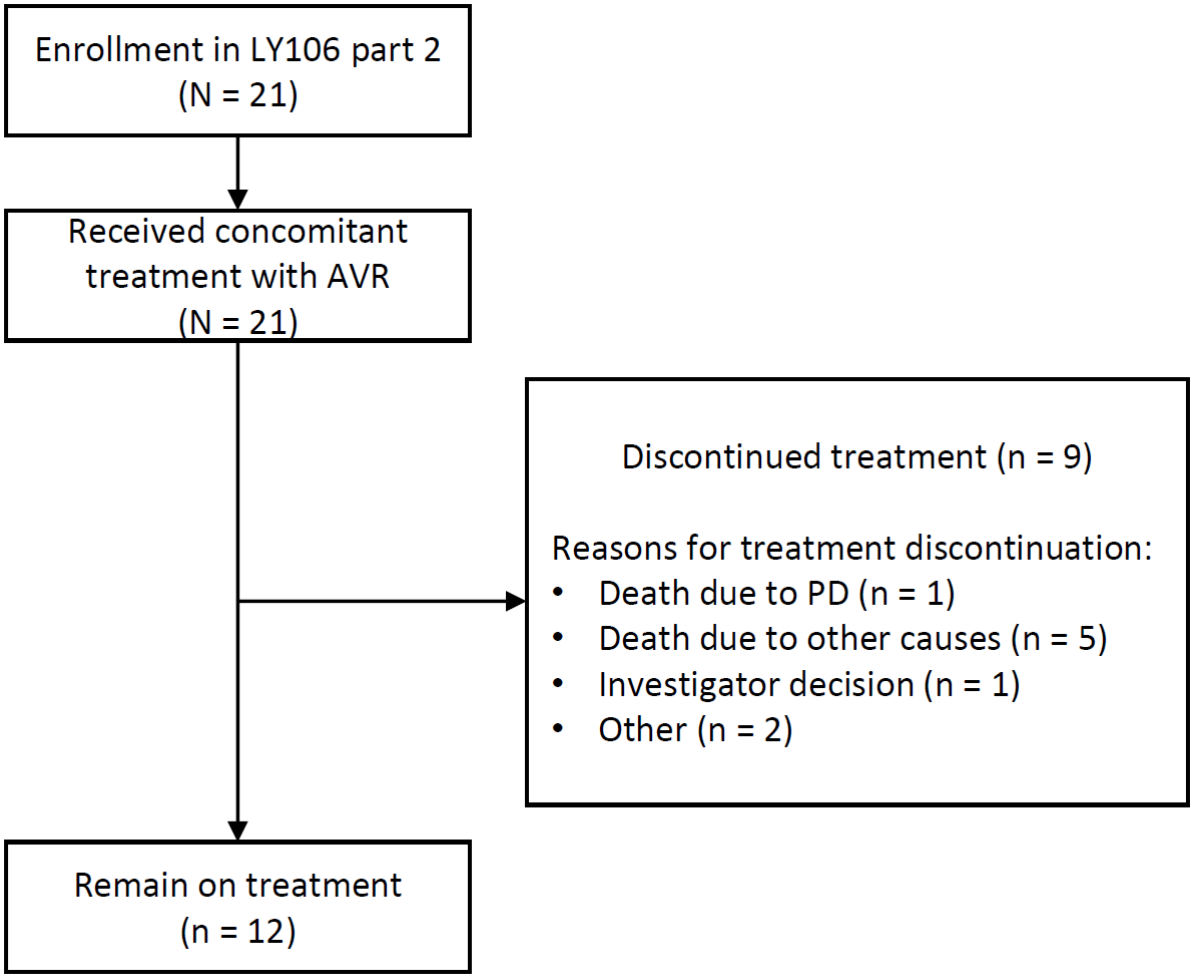
Exclusion Criteria

- History of prior malignancy except for the following:
    - Malignancy treated with curative intent and with no evidence of active disease for >2 years before screening and at low risk for recurrence
    - Localized melanoma, non-melanoma skin cancer, or carcinoma in situ adequately treated without current evidence of disease
- Indication of tumor debulking before stem cell transplant
- Any history of or ongoing central nervous system lymphoma or leptomeningeal disease
- Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura
- Major surgical procedure within 28 days of first dose of study drug
- Significant cardiovascular disease (such as uncontrolled or untreated symptomatic arrhythmias, congestive heart failure, myocardial infarction within 6 months of screening, any class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec at screening); exception: controlled, asymptomatic atrial fibrillation during screening

- Absolute neutrophil count (ANC) <1.0 x 10^9/L or platelet count <75 x 10^9/L; or ANC <0.75 x 10^9/L or platelet count <50 x 10^9/L if bone marrow involvement
- Total bilirubin >1.5 x the upper limit of normal (ULN) and aspartate aminotransferase or alanine transaminase >2.5 x ULN; or estimated creatinine clearance of <60 mL/min calculated by the Cockcroft Gault equation; or international normalized ratio >1.5 or activated partial prothrombin clotting time (in the absence of a lupus anticoagulant) >1.5 x ULN
- Malabsorption syndrome or disease or surgery significantly affecting gastrointestinal function
- Uncontrolled active systemic fungal, bacterial, viral, or other infection
- Known history of infection with human immunodeficiency virus
- Ongoing immunosuppressive therapy, including corticosteroids for treatment of MCL or other conditions within 2 weeks before first dose of study drug
- History of anaphylaxis or hypersensitivity to rituximab or allergy to uric acid–lowering agents
- Active hepatitis B or C infection
- Vaccination with a live virus within 28 days of first dose of study drug
- Stroke or intracranial hemorrhage within 6 months of first dose of study drug
- History of bleeding diathesis, presence of a gastrointestinal ulcer within 3 months of screening or need for anticoagulation therapy with warfarin or equivalent vitamin K antagonist within 7 days of first dose of study drug

- Requiring treatment with a strong CYP3A inhibitor/inducer or a proton-pump inhibitor
- Breastfeeding or pregnant
- Concurrent participation in another therapeutic clinical trial
- History of confirmed progressive multifocal leukoencephalopathy

S3. Patient disposition.



A, acalabrutinib; PD, progressive disease; V, venetoclax; R, rituximab.

S4. Treatment exposure and patient disposition by study drug

	N=21
Acalabrutinib	
Number of cycles administered, median (range)	27.0 (7.0–43.0)
Still receiving acalabrutinib, n (%)	10 (47.6)
Discontinued acalabrutinib, n (%)	11 (52.4)
Disease progression	2 (9.5)
AE	6 (28.6)
Investigator's decision	3 (14.3)
Venetoclax	
Number of cycles administered, median (range)	21.5 (5.0–24.0)
Completed study regimen, n (%)	12 (57.1)
Still receiving venetoclax, n (%)	1 (4.8)
Discontinued venetoclax, n (%)	8 (38.1)
Disease progression	2 (9.5)
AE	4 (19.0)
Investigator's decision	1 (4.8)
Other	1 (4.8)
Rituximab	
Number of cycles administered, median (range)	15.0 (6.0–16.0)
Completed rituximab treatment, n (%)	11 (52.4)
Still receiving rituximab, n (%)	3 (14.3)
Discontinued rituximab, n (%)	7 (33.3)
Disease progression	2 (9.5)
AE	4 (19.0)
Investigator's decision	1 (4.8)

AE, adverse event.

S5. Acalabrutinib, venetoclax, and rituximab discontinuation by treatment phase

Patients, n (%)	Induction With Acalabrutinib + Venetoclax + Rituximab Cycles 1–6			Maintenance With Acalabrutinib + Venetoclax ± Rituximab Cycles 7–25			Maintenance With Acalabrutinib Monotherapy >Cycle 25			Entire Study Period		
	A	V	R	A	V	R	A	V	R	A	V	R
Continued tx	21 (100)	20 (95)	20 (95)	12 (57)	2 (10)	3 (14)	10 (48)	1 (5)	3 (14)	10 (48)	1 (5)	3 (14)
Completed tx	–	0	0	–	11 (52)	11 (52)	–	1 (5)	0	–	12 (57)	11 (52)
Discontinued tx	0	1 (5)	1 (5)	9 (43)	7 (33)	6 (29)	2 (10)	0	0	11 (52)	8 (38)	7 (33)
PD	0	0	0	2 (10)	2 (10)	2 (10)	0	0	0	2 (10)	2 (10)	2 (10)
AE	0	1 (5)*	1 (5)*	4 (19)*	3 (14)*	3 (14)*	2 (10)†	0	0	6 (29)	4 (19)	4 (19)
Other	0	0	0	0	1 (5)	0	0	0	0	0	1 (5)	0
Investigator's decision	0	0	0	3 (14)	1 (5)*	1 (5)*	0	0	0	3 (14)	1 (5)	1 (5)

A, acalabrutinib; AE, adverse event; COVID-19, coronavirus disease 2019; PD, progressive disease; R, rituximab; tx, treatment; V, venetoclax.

*Discontinued due to COVID-19 infection.

†Discontinued due to AE (non–treatment-related grade 3 seizure, n=1; grade 3 COVID-19 infection, n=1).