MAVRiC: A Phase 2 Study of Mutation-Guided Finite-Duration Acalabrutinib Plus Venetoclax for Relapse After Frontline Finite-Duration Covalent Bruton Tyrosine Kinase Inhibitor Plus Venetoclax–Based Combination Therapy in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Plain language summary

Why will we perform this research?
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a blood cancer for which there is no definitive cure. Although the combination of targeted therapies like Bruton tyrosine kinase inhibitors (BTKis) and BCL-2 inhibitors (BCL-2is) have improved outcomes for many patients with CLL/SLL, disease progression may eventually occur. It is also unknown whether patients who were previously treated with these types of drugs can benefit from retreatment with them after disease progression occurs.

Who will participate in this study?
Adult patients (aged ≥18 years) with CLL/SLL who previously responded to prior first-line treatment with a finite-duration covalent BTKi and BCL-2i with or without another drug called obinutuzumab for at least 2 years after completion of treatment who later relapsed will be eligible to participate in this study.

How will we perform this research?
Patients participating in this study will receive a combination of a covalent BTKi called acalabrutinib and a BCL-2i called venetoclax. Patients with high-risk CLL/SLL, defined as genetic characteristics that are indicative of poor prognosis (unmutated IGHV, *TP53* mutation, and del(17p)) will receive 24 cycles (28 days each) of treatment, and patients without these high-risk disease genetic characteristics will receive 14 cycles of treatment. Patients will be followed for 3 or 4 years after treatment, depending on their treatment group.

Where can I access more information?
More information on this trial can be found on ClinicalTrials.gov, using the trial number NCT07024706.

The MAVRiC trial is funded by AstraZeneca. AstraZeneca, Genentech/Roche, and AbbVie are supplying the study drugs
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Background

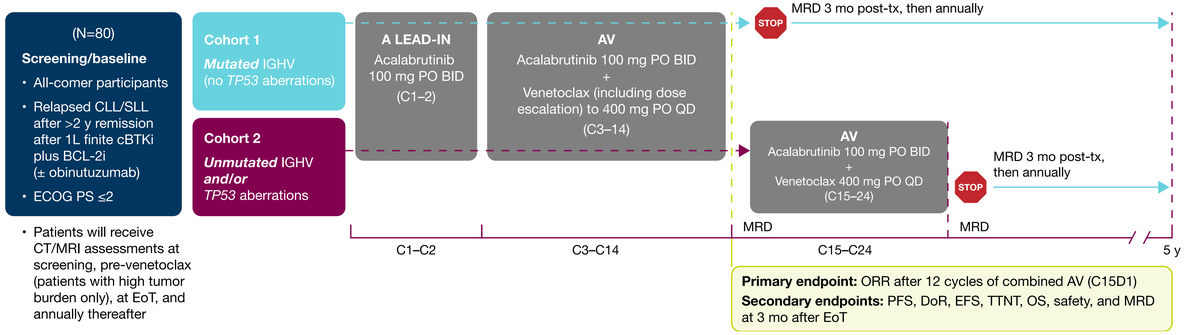
- CLL/SLL is a persistent disease for which there is no definitive cure[1]
- Fixed-duration treatment with a cBTKi and a BCL-2i is now a 1L treatment option for patients with CLL/SLL[2-4]
  - EU approvals for fixed-duration acalabrutinib plus venetoclax (± obinutuzumab) and ibrutinib plus venetoclax were based on results demonstrating significant improvements in PFS vs chemoimmunotherapy from the phase 3 AMPLIFY and GLOW studies, respectively[3-6]
- However, a significant proportion of patients experience disease progression following fixed-duration 1L treatment and will need subsequent lines of therapy or retreatment[5,6]
- Furthermore, as seen in prior studies of cBTKi plus BCL-2i, patients with unmutated IGHV were more likely to achieve uMRD compared with those with mutated IGHV yet were also more likely to relapse sooner[5,6]
- More prospective data in a clinical trial setting are needed to better understand whether patients can be effectively retreated with finite-duration (total 14 cycles or 24 cycles) cBTKi plus BCL-2i at relapse, as there is limited published evidence assessing retreatment with a BTKi plus BCL-2i[7,8]

Rationale

- This study (**Figure 1**) is the first to evaluate the efficacy of acalabrutinib plus venetoclax–based retreatment in patients with CLL/SLL with disease relapse after cBTKi plus BCL-2i 1L therapy
- Whether longer treatment duration for patients with higher–genetic-risk CLL/SLL may lead to longer remissions will also be evaluated

Figure 1. Study Design: MAVRiC (*M*utation-Guided Finite-Duration ***AV*** for ***R***elapse *in* **C**LL/SLL; NCT07024706)

Phase 2, Open-Label, Multicenter, Single-Arm, Global Study Assessing the Efficacy and Safety of IGHV- and *TP53*-Mutation Risk-Guided, Finite-Duration AV-Based Combination Therapy After Prior Finite-Duration cBTKi Plus BCL-2i Treatment



Cycle=28 days.
Clonality and MRD (10^{-5}) by clonoSEQ® from PB (also by BM for SLL).
Patients with PD will come off study treatment and enter follow-up.

Summary

- MAVRiC (NCT07024706) is a phase 2, open-label, multicenter, single-arm, global study assessing the efficacy and safety of IGHV- and *TP53*-mutation risk-guided, finite-duration acalabrutinib plus venetoclax after prior finite-duration cBTKi plus BCL-2i treatment in patients with CLL/SLL
- Global enrollment is planned for 80 patients

Key inclusion criteria

All patients

- Age ≥18 years
- Diagnosis of CLL/SLL per iwCLL 2018 criteria[9]
- Prior 1L treatment with finite-duration cBTKi plus BCL-2i ± obinutuzumab with a response of PR or better for ≥2 years after the end of prior 1L treatment with subsequent relapse
- ECOG PS ≤2
- Adequate organ function

Cohort 1

- Mutated IGHV and no *TP53* aberrations

Cohort 2

- Unmutated IGHV and/or *TP53* aberrations

Key exclusion criteria

All patients

- Clinically significant cardiovascular disease within 6 months of enrollment
- Active central nervous system involvement
- Richter transformation
- Active significant infection
- Renal dysfunction or impairment

Study endpoints

1° Efficacy
- ORR, defined as percentage of patients who have a best response of CR, CRi, nPR, or PR, per iwCLL 2018 criteria[9] as assessed by the investigator after C14

2° Efficacy
- PFS and DoR by investigator and per iwCLL 2018 criteria,[9] EFS, TTNT, OS, safety/tolerability, and uMRD ($<10^{-5}$; clonoSEQ) in peripheral blood at 3 months after the end of treatment

Safety
- AEs, SAEs, AEs leading to treatment discontinuation, ECIs, and relevant clinical laboratory results

Poster

Supplementary material

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Abbreviations

1L, first line; A, acalabrutinib; AE, adverse event; AV, acalabrutinib plus venetoclax; BCL-2i, B-cell lymphoma-2 inhibitor; BID, twice daily; BM, bone marrow; BTKi, Bruton tyrosine kinase inhibitor; C, cycle; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete remission; CRi, complete remission with incomplete bone marrow recovery; CT, computed tomography; D, day; DoR, duration of response; ECI, event of clinical interest; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; EoT, end of treatment; EU, European Union; IGHV, immunoglobulin heavy chain variable region genes; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mo, months; MRD, minimal residual disease; MRI, magnetic resonance imaging; nPR, nodular partial remission; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; PO, oral; PR, partial remission; QD, once daily; SAE, serious adverse event; SLL, small lymphocytic lymphoma; TTNT, time to next treatment; tx, treatment; uMRD, undetectable minimal residual disease; y, years

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