A Phase 2 Study of Minimal Residual Disease-Guided, Time-Limited, First-Line Therapy of Chronic Lymphocytic Leukemia with Pirtobrutinib and Venetoclax (MIRACLE)

Yucai Wang, MD, PhD[1], Wei Ding, MBBS, PhD[1], Betsy R. LaPlant, MS[2], Paul J. Hampel, MD[1], Saad S. Kenderian, MB, ChB[1], Eli Muchtar, MD[1], Min Shi, MD, PhD[3], Amber B. Koehler, PA-C, MS[1], Amy L. Behnken, APRN, CNP, MS[1], Casey N. Aitken, CCRP[1], Chandra R. Hutchens, MA, MBA[1], Rachel J. Bubik, PharmD[1], Neil E. Kay, MD[1], Sameer A. Parikh, MBBS[1]

[1]Division of Hematology, [2]Division of Clinical Trials and Biostatistics, and [3]Division of Hematopathology, Mayo Clinic, Rochester, MN, USA

BACKGROUND

- The current standard of care for first-line therapy of chronic lymphocytic leukemia (CLL) is continuous therapy with a covalent Bruton's tyrosine kinase inhibitor (BTKi), with or without an anti-CD20 monoclonal antibody, or fixed-duration therapy with venetoclax plus obinutuzumab.
- Indefinite therapy with a BTKi comes with long-term toxicities and inevitable development of resistance, while fixed-duration venetoclax-based therapy might be insufficient for a subset of high-risk diseases (e.g., with *TP53* deletion or mutation).
- Combination therapy with a covalent BTKi and venetoclax is being studied in several clinical trials, but the optimal strategy, especially the optimal duration of therapy, remains unclear.
- Pirtobrutinib is an orally available, highly selective, noncovalent, reversible inhibitor of BTK, which has demonstrated excellent efficacy and safety in CLL and mantle cell lymphoma, including in patients with prior covalent BTKi exposure and BTK C481 mutation, a key mechanism of resistance to covalent BTKi in CLL.

STUDY DESIGN

- We developed an investigator-initiated, single center, open label, phase 2 study to evaluate time-limited first-line CLL therapy with pirtobrutinib and venetoclax, in which the duration of therapy will be guided by minimal residual disease (MRD) results by ClonoSEQ (NCT05677919).
- The rationale for combining pirtobrutinib and venetoclax include their distinct mechanisms of action, potential synergy, significant single-agent activities, and the potential for achieving undetectable MRD (uMRD) with time-limited therapy.
- The rationale for MRD-guided therapy include:

  (1) MRD status is prognostic for progression-free survival (PFS) and overall survival (OS) in CLL, and achieving uMRD is an important milestone in CLL treatment;

  (2) The MRD-guided approach can tailor individualized duration of therapy based on the depth of response and may result in less toxicities and longer remissions.
- Treatment consists of a 3-cycle lead-in with pirtobrutinib alone, followed by 12-24 cycles of pirtobrutinib-venetoclax combination therapy (Fig 1). Duration of therapy is determined by MRD results (Fig 2).

STUDY DESIGN (Cont.)

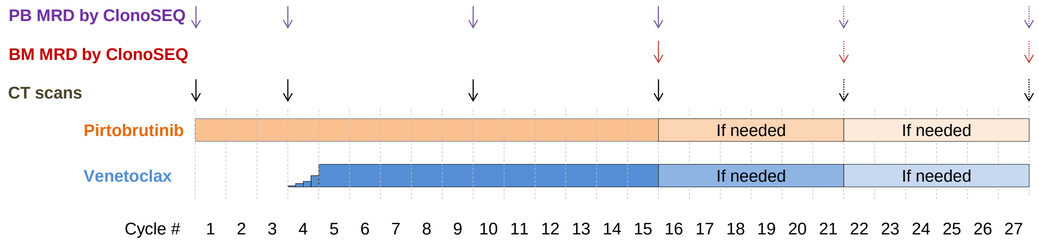

Fig 1. Trial Schema including Treatment Cycles and Response Assessment Schedule

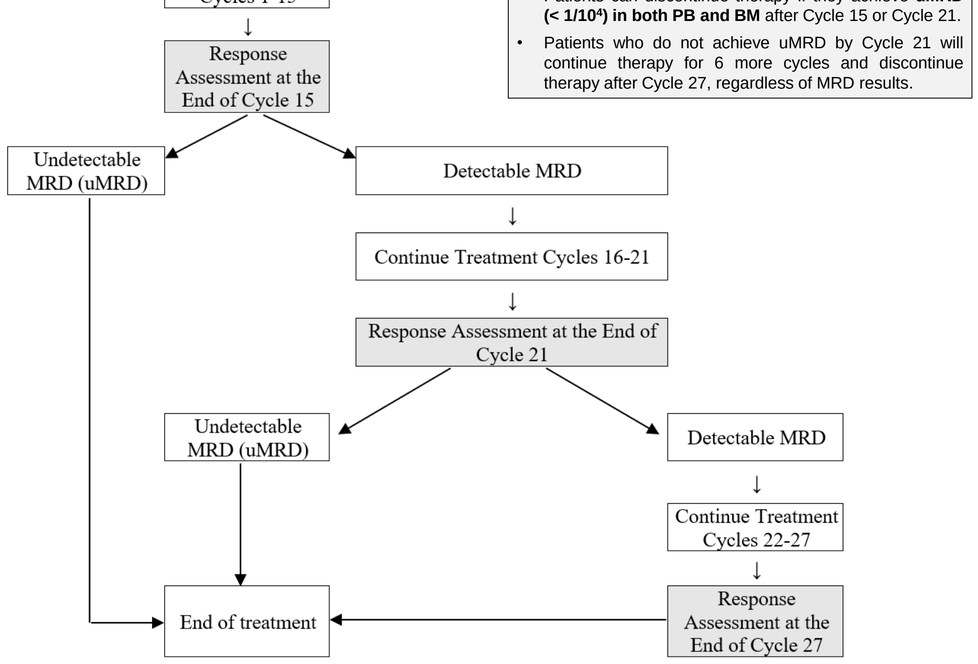

Fig 2. MRD-Guided Decision on Duration of Treatment

STUDY ENDPOINTS

Primary Endpoint:
- Rate of uMRD in both PB and BM after Cycle 15

Secondary Endpoints:
- PB uMRD rate, BM uMRD rate
- Complete response rate, Objective response rate
- Duration of response, PFS, Time to next treatment, OS
- Adverse event incidences

ELIGIBILITY CRITERIA

Main Inclusion Criteria:
- Confirmed diagnosis of CLL or SLL, with an indication to treat according to iwCLL 2018 guidelines
- ECOG PS 0-2
- Adequate blood counts (ANC ≥ 0.75, Plt ≥ 50, Hb ≥ 8)
- Adequate hepatic and renal function (ALT/AST ≤ 3 × ULN, total bilirubin ≤ 1.5 × ULN, CrCl ≥ 40 ml/min).

Main Exclusion Criteria:
- Prior CLL/SLL-directed therapy
- Richter transformation
- CNS involvement
- Major comorbidities (e.g., cardiovascular, pulmonary, infectious, malabsorption, bleeding disorder, etc)
- Other active malignancy requiring treatment or limiting expected survival to ≤ 2 years

STATISTICAL DESIGN

- With a one-stage binomial design, a sample size of 41 evaluable patients will have 10% Type I error and 90% power to detect an effective treatment, if the true proportion of patients who achieve uMRD in both PB and BM after Cycle 15 is at least 60% versus the null hypothesis that the true proportion is at most 40%.
- Four additional patients will be enrolled to account for ineligibility or drop out, for a total sample size of 45.

CONTACT

- MIRACLE (NCT05677919) is actively enrolling and is anticipated to complete accrual in Q1 of 2024.
- **PI:** Yucai Wang, MD, PhD, Email: Wang.Yucai@mayo.edu
- **Lead study coordinator:** Casey N. Aitken, CCRP, Email: Aitken.Casey@mayo.edu