# **CLL18/MOIRAI** international phase-III trial: aiming to establish **m**easurement **o**f **i**ndividual **r**esidual disease for **a**djustment of treatment duration to **i**mprove outcomes in first-line treatment of CLL/SLL

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## BACKGROUND

The two major treatment options chronic lymphocytic leukemia (CLL) are continuous BTK inhibitor until progression, or a venetoclax-based fixed-duration treatment, such as venetoclax plus obinutuzumab (Ven-Obi, 12 cycles) or venetoclax plus ibrutinib or acalabrutinib with/without obinutuzumab.
The time-limited combination therapies are more intense compared to monotherapies, but usually lead to deep responses and a treatment-free interval of several years, which carries advantages in terms of quality of life, safety and costs.

## AIMS

To evaluate if a more individualized approach is beneficial, we have designed this, phase III trial with three arms - two evaluating a fixed-duration regimen and one evaluating a treatment duration based on measurable residual disease (MRD).

## METHODS

Standard arm A is the established combination of Ven-Obi, while arm B evaluates venetoclax- pirtobrutinib (Ven-Pirto) for 15 cycles. In arm C, Ven-Pirto will be administered for at least 15 and up to 36 cycles until achievement of undetectable MRD (uMRD).
To stop treatment, two assessments with an interval of 12 weeks documenting uMRD in peripheral blood are needed, followed by an additional 12 weeks consolidation treatment after the second uMRD result.

813 previously untreated CLL/SLL patients will be recruited 1:1:1 to the three arms with stratification according to TP53 deletion and/or mutation, IGHV mutational status, type of disease (CLL vs. SLL), and age. Primary endpoint is the investigator-assessed progression-free survival (PFS). The trial is designed to show both superiority of MRD-guided Ven-Pirto over Ven-Obi and over fixed duration Ven-Pirto.
Secondary endpoints include iwCLL response, MRD, overall survival and safety parameters.

## RESULTS

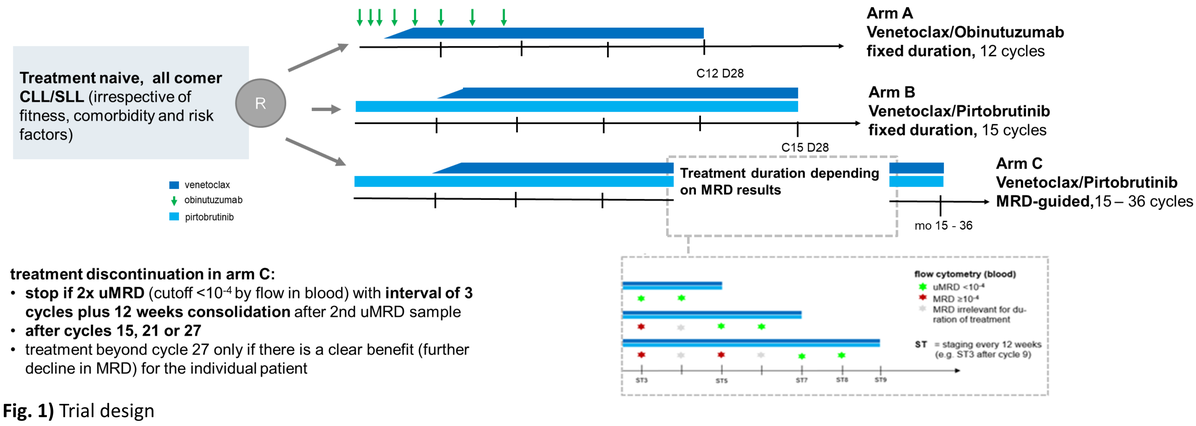
The recruitment for CLL18/MOIRAI started in June 2025. The first patient was enrolled on June 30th 2025. Estimated recruitment time of the 813 pts in approx. 160 sites in 16 countries is 20 months. Approx. 41 months after start of recruitment, a sufficient number of PFS events shall be reached for the primary endpoint analysis.

## CONCLUSION

The CLL18/MOIRAI trial will address the question if an individualized, MRD-guided first-line treatment with pirtobrutinib and venetoclax improves the outcome of patients with CLL/SLL compared to fixed-duration venetoclax with either obinutuzumab or pirtobrutinib.

## CONTACT INFORMATION

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**treatment discontinuation in arm C:**
- **stop if 2x uMRD** (cutoff $<10^{-4}$ by flow in blood) with **interval of 3 cycles plus 12 weeks consolidation** after 2nd uMRD sample
- **after cycles 15, 21 or 27**
- treatment beyond cycle 27 only if there is a clear benefit (further decline in MRD) for the individual patient

**Fig. 1)** Trial design