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A Refined Continuous Individualized Risk Index (CIRI2-CLL) for Accurately Predicting Outcomes after Limited-Duration CLL Therapy

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OBJECTIVES

- The aim of this study was to validate and refine CIRI models for CLL in the context of modern, standard of care fixed-duration targeted therapy, and to benchmark performance against other established indices.

CONCLUSIONS

- Our results validate CIRI2-CLL in the context of limited-duration CLL therapy (CIT and targeted fixed-duration therapy), and suggest adaptability with emerging additional longitudinal outcome data.
- CIRI2-CLL enables identification of patients with increased risk for disease progression after Ven-Obi, supporting risk-based clinical-decision making and informing future risk-adapted CLL trials.

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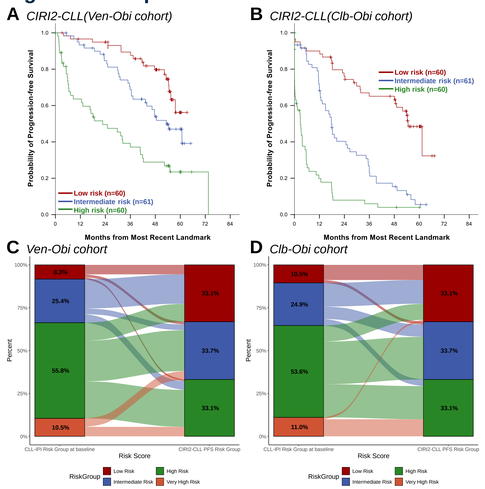
INTRODUCTION

- Measurable residual disease (MRD) status after limited-duration treatment for patients with CLL is an established prognostic factor for survival times, but most prognostic indices such as CLL-IPI rely solely on pre-treatment features.
- To incorporate dynamic MRD data in prognostic models across diverse cancer types including CLL, the continuous individualized risk index was previously proposed (CIRI, Kurtz et al. 2019). CIRI dynamically determines outcome probabilities for individual patients by integrating diverse factors over time, including treatment modality and serial MRD measurements on and post-treatment.
- Since developed in the context of chemoimmunotherapy (CIT) we here propose a refined version of CIRI, CIRI2-CLL, in the context of fixed-duration targeted therapy, which includes MRD status on-treatment (interim), at end-of-treatment (EoT) and in addition at 12-month post-EoT (FU12).

METHODS

- Patient level data of the CLL8/10/11 (FC [±rituximab (R)], BR, Clb [±R/Obi], n=614) and MURANO (venetoclax (Ven)-R vs BR, n=299) trials was used to infer model parameters.
- For previously established factors, including CLL-IPI (age, IGHV, *TP53*del/mut, Binet/Rai and ß2M), therapy effect (chemo- and CIT), and MRD status (interim and EoT), an updated development set from CLL8/10/11 was used.
- For the therapeutic effect of Ven and MRD status at FU12, the MURANO trial data was used.
- This refined model CIRI2-CLL was applied to an independent validation set from the CLL14 study (Ven-Obi vs Clb-Obi, n=381) to predict progression-free survival (PFS) and overall survival (OS). To capture the nonuniform change in PFS following therapy coinciding with end of fixed-duration targeted therapy, a piecewise proportional hazards modelling was used with a single change-point at 18 months in a modified Bayesian model.
- Finally, model calibration, stratification and performance were assessed and compared to individual indices.

Figure 2. Comparison of CIRI2-CLL to CLL-IPI



RESULTS

- **CLL-IPI in Ven-Obi**: In CLL14 patients, very high vs low CLL-IPI risk was associated with significantly shorter PFS (p<0.001, Fig 1A), while differences between adjacent risk groups were not significant.
- **CIRI2-CLL vs CLL-IPI**: In the full CLL14 validation set, CIRI2-CLL showed adequate calibration (<5% difference observed vs predicted; Fig 1B) and 21–31% higher C-statistics vs CLL-IPI from 1–5 years (p<0.001), outperforming MRD and other single-factor indices (Fig 1C). Performance was consistent in Ven-Obi patients (Fig 1D,E).
- **Risk stratification by CIRI2-CLL**: Low (n=17), intermediate (n=140), and high (n=24) risk groups had 3-year PFS rates of 100.0%, 70.2%, and 10.8% respectively (Fig 1F). When grouping into tertiles by predicted risk, 3-year PFS in Ven-Obi was 89.4%, 68.8%, 37.1%; in Clb-Obi, 65.1%, 23.0%, 5.9% (Fig 2A,B).
- **MRD status and CIRI2-CLL**: ~16–20% of patients were reclassified to higher or lower risk by CIRI2-CLL vs CLL-IPI (Fig 2C,D). MRD status alone missed substantial risk heterogeneity (e.g., 45.5% of Ven-Obi patients with uMRD had intermediate CIRI2-CLL risk).
- **Overall survival:** CIRI2-CLL outperformed individual indices for OS prediction (C-statistic 0.77–0.99; p<0.001) with adequate calibration and clear separation into low, intermediate, and high OS risk (3-year OS in Ven-Obi: 92.7%, 58.1%, 0%; Fig 3A–C).

Figure 3. CIRI2-CLL for Overall Survival

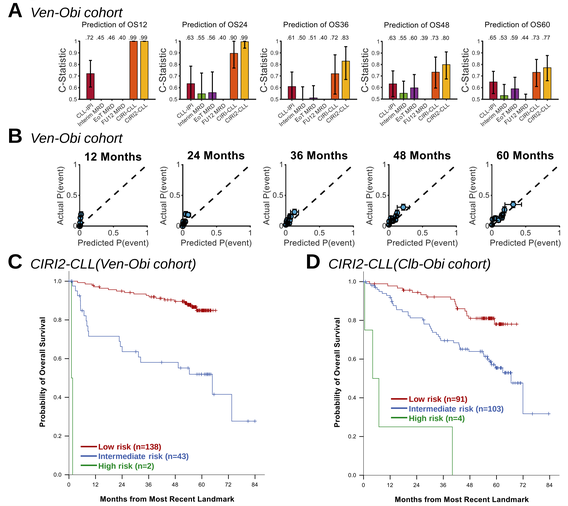
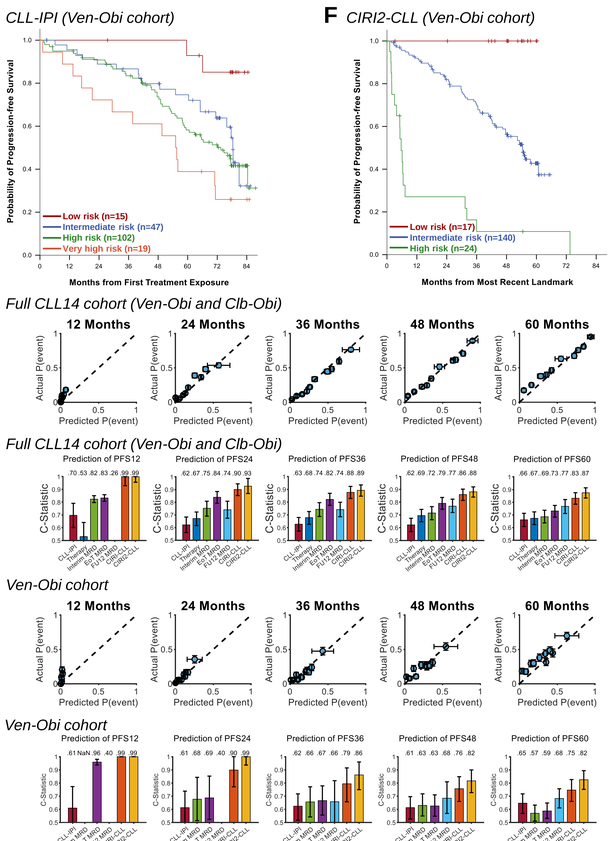


Figure 1. CIRI2-CLL for Progression-free Survival



Footnote

- Figure 1F. Kaplan-Meier estimate in the Ven-Obi treated cohort shows the PFS for patients stratified by CIRI2-CLL risk prediction of PFS36 split into three groups based on the optimal two cut-offs after integration of all information (i.e. after FU12 MRD assessment when it was not missing). To guard against guaranteed time bias, patients with PFS-event (disease progression or death) prior to FU12 MRD assessment (n=2 [1.1%] in the Ven-Obi treated cohort) were excluded.
- Figure 2A/B. Kaplan-Meier estimates in the Ven-Obi treated (Figure 2A) and Clb-Obi treated (Figure 2B) cohort show the PFS for patients stratified by CIRI2-CLL risk prediction of PFS36 split into three groups based on the 3-quantiles cut-offs respectively after integration of all information (i.e. after FU12 MRD assessment when it was not missing). To guard against guaranteed time bias, patients with PFS-event (disease progression or death) prior to FU12 MRD assessment (n=2 [1.1%] in the Ven-Obi treated cohort, n=17 [8.6%] in the Clb-Obi treated cohort) were excluded.
- Figure 3C/D. Kaplan-Meier estimates in the Ven-Obi treated (Figure 3C) and Clb-Obi treated (Figure 3D) cohort show the OS for patients stratified by CIRI2-CLL risk prediction of OS36 split into three groups based on the optimal two cut-offs respectively after integration of all information (i.e. after FU12 MRD assessment when it was not missing).

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