Real-World Overall Survival, Richter's Transformation, and Secondary Primary Malignancy Rates in CLL: Fixed-Duration Venetoclax-Based Therapy vs. Indefinite BTK Inhibitor Monotherapy: A TriNetX Propensity-Matched Analysis

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INTRODUCTION

- The CLL treatment landscape is defined by two dominant targeted therapy paradigms: fixed-duration venetoclax-based combinations (venetoclax + obinutuzumab or ofatumumab; Ven-O/Ofa) and indefinite BTK inhibitor (BTKi) monotherapy (ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib).
- Real-world comparative data on overall survival (OS), Richter's transformation (RT), and secondary primary malignancy (SPM) rates across both paradigms remain limited.

METHOD

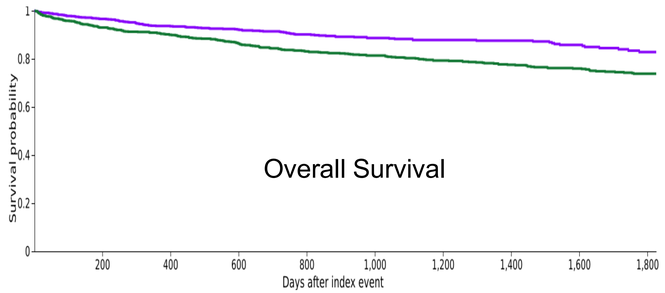
- Using the TriNetX federated research network (112 healthcare organizations), we identified adults with CLL (ICD-10: C91.1; diagnosed January 1990–May 2026) treated with Ven-O/Ofa without BTKi exposure (Cohort 1; n=1,276) or BTKi monotherapy without venetoclax or anti-CD20 therapy (Cohort 2; n=11,549).
- The index event was initiation of the qualifying regimen. Outcomes were analyzed over 5 years from index.
- Propensity score matching (1:1) was performed on age, sex, race, diabetes, hyperlipidemia, hypertension, ischemic heart disease, cerebrovascular disease, CKD, liver cirrhosis, and chronic lower respiratory disease, yielding 1,273 patients per arm.
- Primary outcome was OS by Kaplan-Meier analysis with Cox regression. Secondary outcomes included RT (C83.3x, C85.1x, C85.2x, C85.8x, C88.0) and SPM rates; ie. MDS/AML, lung, prostate, and skin cancer (BCC/SCC), excluding patients with prior SPM.

CONCLUSIONS

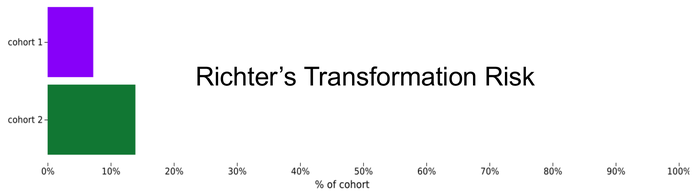
- In this propensity-matched real-world analysis of 2,546 CLL patients, fixed-duration venetoclax-based therapy was associated with improved 5-year OS and lower Richter's transformation rates vs. indefinite BTKi monotherapy.
- SPM rates were largely comparable, though higher skin cancer incidence with Ven-O/Ofa warrants further investigation and highlights the importance of dermatologic surveillance in this population.

RESULTS

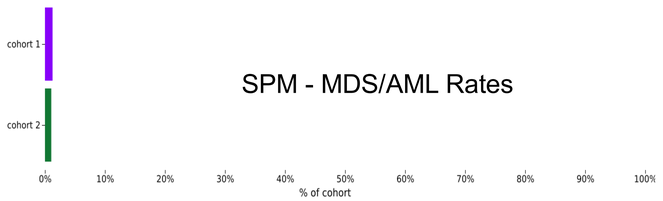
- Cohorts were well-balanced post-PSM (all standardized mean differences <0.11).
- Mortality risk was significantly lower with Ven-O/Ofa (9.7% vs. 18.8%; RR 0.52, 95% CI 0.42–0.64).
- Five-year survival was 82.8% vs. 73.8% (p<0.001; HR 0.58, 95% CI 0.46–0.72).
- RT risk was lower with Ven-O/Ofa (7.2% vs. 13.9%; RR 0.52, 95% CI 0.41–0.66; p<0.001).
- SPM rates were comparable for MDS/AML (1.3% vs. 1.1%; p=0.614), lung (1.7% vs. 2.2%; p=0.308), and prostate cancer (1.7% vs. 2.5%; p=0.143).
- Skin cancer (BCC/SCC) was significantly higher with Ven-O/Ofa (3.2% vs. 1.7%; RR 1.87, 95% CI 1.10–3.15; p=0.018).



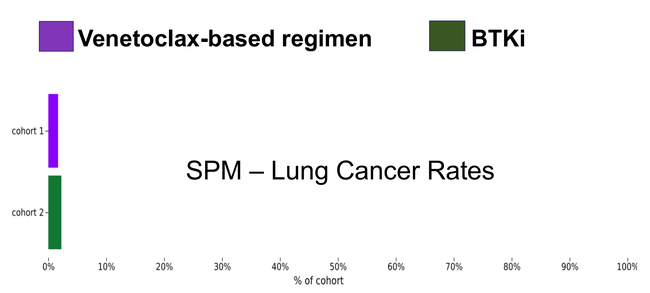
Overall Survival



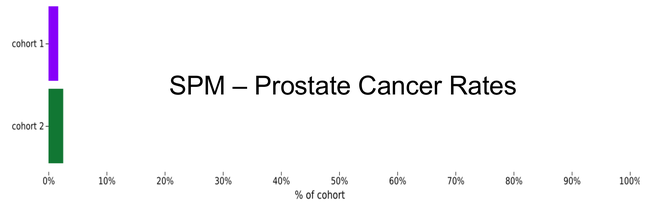
Richter's Transformation Risk



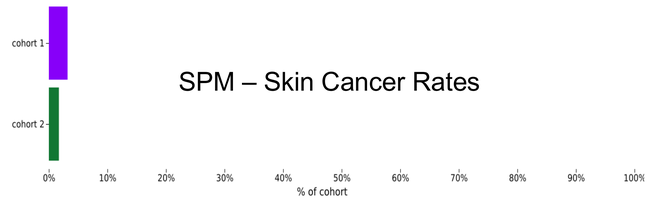
SPM - MDS/AML Rates



SPM – Lung Cancer Rates



SPM – Prostate Cancer Rates



SPM – Skin Cancer Rates

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