MRD-GUIDED VS FIXED-DURATION TARGETED THERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROGRESSION-FREE SURVIVAL AND DEPTH OF RESPONSE

Authors: SAMEER BHIMANI, M.D[1]; AMBER SOBUTO, D.O[2]; RAMSHA KHAN, D.O[1]; DOUGLAS KLAMP, M.D[1]; SIMRAN BHIMANI, M.D[1]; MUHAMMAD UMAIR ANJUM, MD[1].

1. THE WRIGHT CENTER FOR GRADUATE MEDICAL EDUCATION, SCRANTON, PA, USA.
2. HEMATOLOGY AND ONCOLOGY ASSOCIATES OF NORTHEASTERN PENNSYLVANIA, DUNMORE, PA, USA.

CONTACT INFORMATION: **sameerbhimani94@gmail.com**

INTRODUCTION

- Targeted therapies have transformed the treatment landscape of chronic lymphocytic leukemia (CLL).
- Fixed-duration venetoclax-based regimens achieve durable remissions while limiting treatment exposure.
- Minimal residual disease (MRD) is increasingly used to individualize treatment duration.
- Whether MRD-guided treatment improves clinical outcomes compared with conventional fixed-duration therapy remains uncertain.

AIM

To compare progression-free survival (PFS) and rates of undetectable MRD (uMRD) among fixed-duration, MRD-guided, and intensified targeted therapy strategies in CLL.

METHOD

Study Design
- Systematic review and meta-analysis
- Prospective clinical trials
- Targeted therapies in CLL

Primary Outcome
- Progression-free survival (hazard ratio)

Secondary Outcome
- Undetectable MRD (uMRD)

Statistical Analysis
- Random-effects inverse variance model
- REML estimator
- Hartung-Knapp adjustment
- Logit-transformed proportions for MRD
- Prespecified subgroup analyses

CONCLUSIONS

- Targeted therapies significantly improve progression-free survival in CLL.
- Intensified regimens achieve the deepest MRD responses.
- Higher MRD negativity did not translate into proportional improvements in PFS.
- Fixed-duration therapy remains an effective and clinically meaningful treatment strategy.
- Additional prospective studies are needed to better define the role of MRD-guided treatment discontinuation.

RESULTS

Pooled Meta-analysis Results

Outcome	Estimate	95% CI	Interpretation
Progression-free survival	HR 0.28	0.19–0.40	✓ Significant benefit
Sensitivity analysis	HR 0.31	0.26–0.37	✓ Robust findings
Overall pooled uMRD	65%	62%–68%	✓ High depth of response

Eight prospective trials • Twelve treatment comparisons • Seven MRD treatment arms

- **Eight prospective clinical trials comprising 12 treatment comparisons** were included in the quantitative synthesis.
- Targeted therapy was associated with a **significant improvement in progression-free survival (PFS)**, with a pooled hazard ratio (HR) of **0.28 (95% CI, 0.19–0.40; I^2 = 86%)**.
- Sensitivity analysis confirmed the robustness of the findings (**HR, 0.31; 95% CI, 0.26–0.37**).
- Seven treatment arms from five trials contributed to the MRD analysis, demonstrating an **overall pooled undetectable MRD (uMRD) rate of 65% (95% CI, 62%–68%; I^2 = 95%)**.
- **Intensified combination regimens** achieved the highest pooled uMRD rate (**74%**), followed by **fixed-duration therapy (62%)** and **MRD-guided strategies (54%)**.
- Despite deeper MRD responses with intensified regimens, **these did not translate into proportional improvements in progression-free survival.**