Poster #:

XXI IWCLL International Workshop on CLL

MYD88 Mutations in Chronic Lymphocytic Leukemia Exhibit Distinct Biological Behaviors and Prognostic Implications

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OBJECTIVES

• We analyzed a large cohort of CLL patients from China to clarify the clinical and biological profile of MYD88-mutant CLL and its prognostic significance under different treatment modalities. By comparing 139 MYD88-mutated cases to 942 MYD88 wild-type cases, we delineated the unique characteristics of this subgroup.

CONCLUSIONS

• Our study establishes that CLL patients harbouring MYD88 mutations represent a unique subset with distinct biology. These patients are typically IGHV-mutated males with atypical CLL immunophenotype, lower-risk genetic features, and a higher prevalence of an IgG paraprotein.
• The presence of a MYD88 mutation, especially a non-L265P variant, could be considered an extremely positive prognostic marker in CLL.
• While BTKi are highly effective in CLL generally, our data suggest that MYD88-mutant patients may do just as well with less intensive therapies.
• Further research is warranted to unravel why MYD88 mutations confer such indolence. Understanding this could shed light on CLL pathogenesis and reveal new insight on personalized treatment decisions.

INTRODUCTION

• Chronic lymphocytic leukaemia (CLL) shows marked geographic heterogeneity in the frequency and clinical impact of MYD88 mutations. Western cohorts report a low incidence of MYD88 mutation with 0.5%-3%, whereas studies from Asia report a much higher rates of 10%–28%. However, the clinical significance of MYD88 mutations in CLL remains incompletely defined, with conflicting reports.

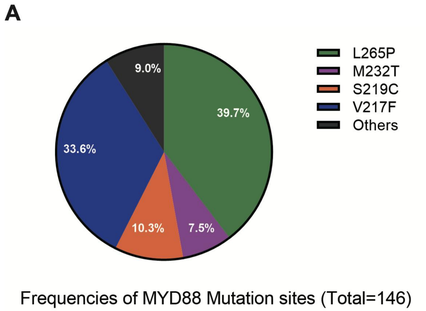
METHODS

• We analyzed clinical data from 1081 CLL patients diagnosed between 2000 and 2024, all of whom underwent MYD88 genotyping by next-generation or Sanger sequencing. We present the largest series of 139 MYD88-mutated CLL and demonstrate that MYD88-mutated CLL constitutes a distinct clinical entity.

RESULTS

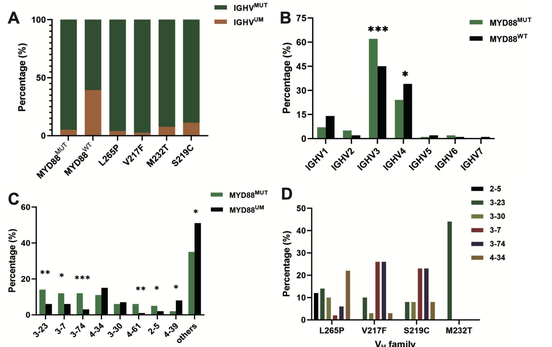
• These patients were predominantly male and almost uniformly carried mutated IGHV genes, while high-risk cytogenetic lesions (del17p/del11q) were comparatively infrequent. Relative to MYD88 wild-type disease, MYD88-mutated CLL showed a significantly longer time-to-first treatment and superior overall survival, which was persisted even within the IGHV-mutated subset. Unlike wild-type CLL, MYD88-mutated cases derived comparable long-term benefit from either chemo-immunotherapy or BTK inhibitor therapy. Moreover, different MYD88 mutation hotspots exhibited subtle phenotypic differences. The canonical L265P variant was associated with shorter treatment-free survival than V217F or S219C.

Figure 1. The frequencies of MYD88 mutation sites in our series.



Frequencies of MYD88 Mutation sites (Total=146)

Figure 2. IGHV gene usage in MYD88-mutated vs wild-type CLL



A.The distribution of IGHV-mutated and IGHV-unmutated CLL in patients according to MYD88 mutational status; B. The usage of IGHV segment in MYD88WT and MYD88MUT patients; C. The distribution of IGHV segments usage in MYD88WT and MYD88MUT patients. D. The distribution of IGHVsegments usage among different MYD88 mutational subgroups.

Figure 3. Co-mutation landscape in MYD88-mutant and MYD88 wild-type CLL.

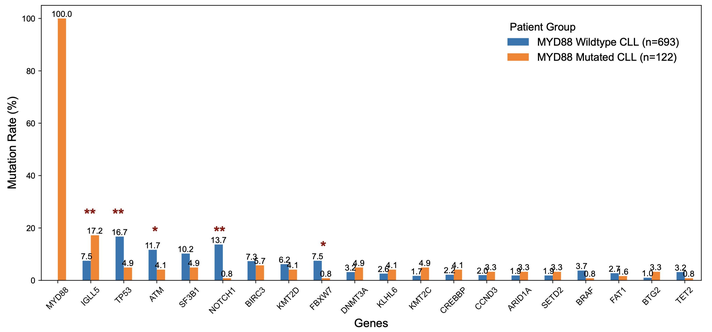


Figure 4. Kaplan-Meier curves for OS by MYD88

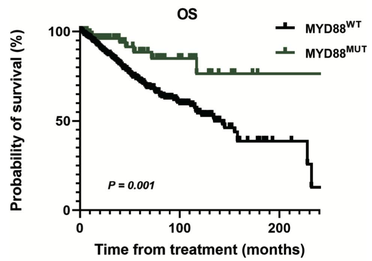


Figure 5. Kaplan-Meier curves for TTFT, PFS, OS by MYD88 and IGHV status.

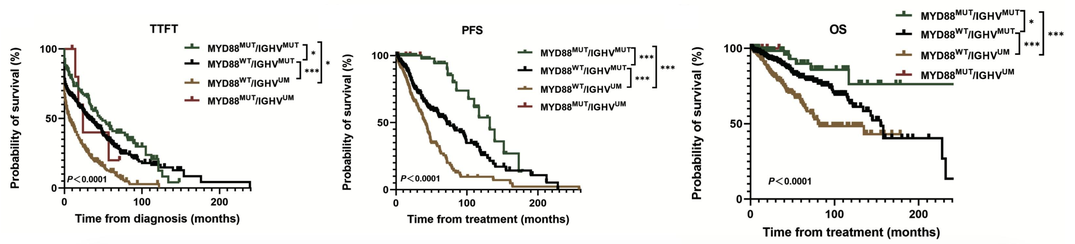
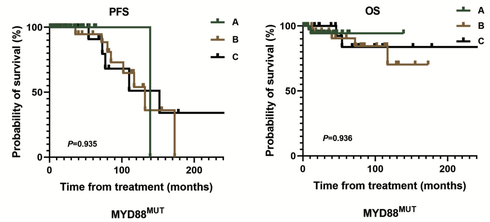


Figure 6. First-line treatment outcomes in MYD88-WT CLL.



- BTK inhibitor (Group A, green)
- Chemoimmunotherapy (Group B, brown)
- Chemotherapy (Group C, black)

While BTKi are highly effective in CLL generally, our data suggest that MYD88-mutant patients may do just as well with less intensive therapies.