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# PB1909 LOW-BURDEN *TP53* MUTATIONS REPRESENT FREQUENT GENETIC EVENTS IN CLL WITH AN INCREASED RISK FOR TREATMENT INITIATION

**Topic:** 5. Chronic lymphocytic leukemia and related disorders - Biology & Translational Research

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**Background:**

Presence of *TP53* mutations and/or deletions of chromosomal region 17p (del(17p)) represent established prognostic and predictive biomarkers for chronic lymphocytic leukemia (CLL). However, the clinical significance of low-burden *TP53* variants (variant allele frequency: <10%) is still a matter of debate, with some studies suggesting a reporting threshold below 10%.

**Aims:**

In this study, we aimed to scrutinize the subclonal architecture and clinical impact of *TP53* mutations using a sensitive, next-generation sequencing-based (NGS) mutation analysis in a 'real-world' cohort of Hungarian CLL patients.

**Methods:**

Peripheral blood samples from 901 patients with CLL were collected from 20 oncohematological centers in Hungary. *TP53* mutations were screened using Multiplicom SureMASTR *TP53* Panel (Agilent, Santa Clara, CA, USA) covering the whole coding sequence of the *TP53* gene. All *TP53* variants below the 10% cut-off value were validated by either an alternative *TP53* NGS panel (CleanPlex, Paragon Genomics, CA, USA) or by droplet digital polimerase chain reaction (ddPCR). The del(17p) status was screened as part of the routine diagnostic characterization by interphase fluorescence in situ hybridisation (FISH). Kaplan-Meier-survival curves and log



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rank tests were performed to compare survival times between different patient subgroups.

**Results:**

In 17.6% (159/901) of the patients we identified 226 *TP53* mutations, with 49% (n=110) of those being high-burden variants, and 51% (n=116) representing low-burden mutations. Low-burden *TP53* mutations as sole alterations were identified in 39% (n=62) of all mutated cases with 82.3% (51/62) of these being represented by a single low-burden *TP53* mutation. While both high- and low-burden *TP53* mutations appeared in most cases as sole alterations (39.6%, (63/159) and 32.1% (51/159) respectively), multiple mutations could be detected in 28.3% (45/159) of *TP53* mutated cases showing heterogenous subclonal composition. As for the the entire patient cohort, 67.7% (153/226) of the detected *TP53* mutations were validated by either NGS or ddPCR. All low-burden mutations examined between 5-10% variant allele frequency were successfully validated (n=38), while 74.3% (78/105) of the *TP53* mutations with variant allele frequencies between 1-5% could be confirmed. Considering samples collected exclusively prior to first treatment initiation, we found significant differences in time to first treatment (TTFT) between patients harbouring either high-burden or low-burden *TP53* mutations versus wild-type patients (high-burden vs wild type *TP53*: $p<0.0001$; low-burden vs wild type *TP53*: $p=0.0031$). Considering IGHV mutational status, patients with unmutated IGHV harbouring *TP53* mutation showed significantly lower TTFT compared to patients with wild-type *TP53* regardless of the IGHV status.

**Summary/Conclusion:**

In this study, we explored the repertoire and clinical impact of low-burden *TP53* mutations in a nation-wide, 'real world' Hungarian patient cohort. Our results demonstrate that patients with sole low-burden *TP53* mutations represent more than one third of patients with *TP53* mutations, having significantly increased risk for treatment initiation. Furthermore, our data demonstrates that *TP53* variants between the 5-10% variant allele frequency range can be reliably detected by NGS, hence the 10% cut-off value for *TP53* variant reporting in routine diagnostics might be worth reconsidering.