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Lymphomas

SECONDARY GENETIC EVENTS AND THEIR RELATIONSHIP TO *TP53* MUTATION IN MANTLE CELL LYMPHOMA A SUB-STUDY FROM THE FIL_MANTLE-FIRST BIO

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Mantle Cell Lymphoma (MCL) is an aggressive malignancy with variable clinical behavior, largely reflecting the underlying molecular heterogeneity. The genomic landscape of MCL encompasses gene mutations with strong prognostic implications (such as *TP53*, *NOTCH1*, KTDM2D, etc) and secondary genetic events, such as copy number variations (CNVs), also implicated in the pathogenesis and prognosis of MCL.

We extracted and analyzed, by targeted Next Generation Sequencing (tNGS) with a customized panel of 37 genes, the genomic DNA (gDNA) of 73 diagnostic samples of patients with relapsed/refractory MCL that were enrolled in the Fondazione Italiana Linfomi (FIL) Mantle First-BIO study (NCT04882475). CNVs were annotated with CNVkit, while the *TP53* mutation was annotated with MuTec2 and validated through Integrative Genomics Viewer (IGV). The statistical analysis was conducted on R v4.1.2, adopting the time to first relapse or progression of disease (POD) as the primary outcome measure, which was previously defined as a threshold of 24 months since MCL diagnosis, enabling us to divide the cohort into early-POD24 and late-POD24. All patients also had available data for correlating CNVs with the presence of *TP53* mutation.

We detected 18 different alterations (11 amplifications and 7 deletions) associated with MCL. The most recurrent CNVs were Amp 3q26-q28 (*BCL6*, 49%), followed by Amp 5q35.3 (*HNRNPH1*, 45%), Del13q14 (*RB1*, 34%), and Del 11q22.3-q23.2 (32%).

When comparing early and late POD groups, Fisher's exact test identified Del 13q14 (*RB1*, p= 0.02, 52% early vs 24% late), Del 6q (p= 0.01, 37% early vs 11% late), and Del 9p21.3 (*CDKN2A*, p= 0.02, 33% early vs 11% late) more prevalently associated with early POD. Among these, the Del 9p21.3 (*CDKN2A*) resulted as the stronger predictor of shorter time to POD (p=0.01), independently of *TP53* mutation in multivariable analysis. Unsupervised clustering identified molecularly defined clusters associated with significantly different time to POD (p= 0.01). Pairwise log-rank tests confirmed *TP53* (mutated vs wild-type) as the strongest prognostic factor, with cluster assessment that improved the prognostic predictivity among patients: clusters *TP53*-mut vs *TP53*-WT, p= 0.001, HR=3.92; and p= 0.014, HR= 2.23, respectively (Figure 1).

In conclusion, CNV-based molecular clusters might represent a novel approach to identify patients at higher risk of treatment failure, contributing to the prognostic predictivity of *TP53* mutation.

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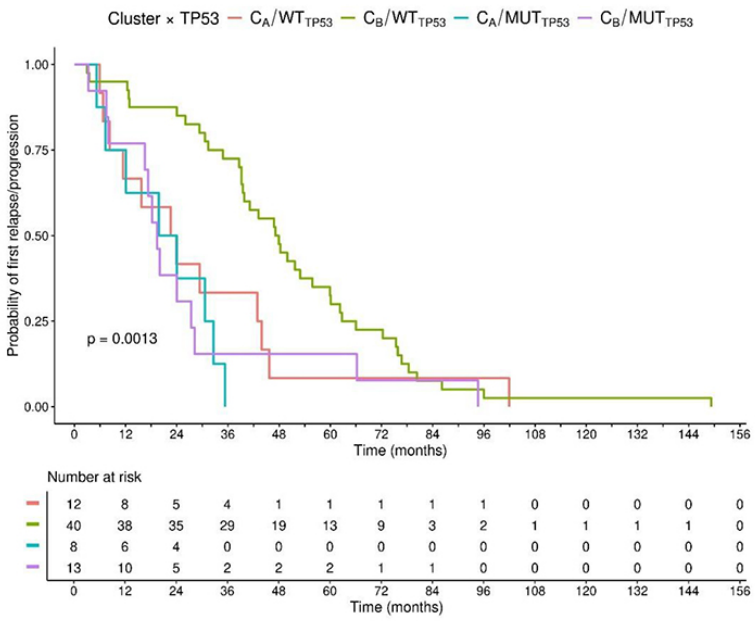

Figure 1: Kaplan Meier plots associated with C_A/TP53-WT (red) vs C_A/*TP53*-mut (blue) vs C_B/*TP53*-WT (green) vs C_B/*TP53*-mut (purple). The curves were also representative of the four molecular clusters obtained by stratifying for *TP53*, the two clusters (C_A and C_B) derived from the unbiased analysis (Non-negative matrix factorization), which use binary data (presence/absence) of the CNVs annotated in the cohort.