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Lymphomas

GENOMIC ANALYSES OF PATIENTS WITH MANTLE CELL LYMPHOMA THAT WERE REFRACTORY OR RELAPSED AFTER INDUCTION THERAPY: RESULTS FROM THE FIL_MANTLE-FIRST BIO STUDY

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MANTLE-FIRST BIO is a retrospective and multicenter study of Fondazione Italiana Linfomi (FIL) enrolling mantle cell lymphoma (MCL) patients, aged 18-80 years, who experienced first relapse or were refractory (R/R) to frontline chemo-immunotherapy (CIT).

We identified single-nucleotide variants (SNVs) and copy-number variations (CNVs) associated with different time to first progression of disease (time to POD) in a cohort of 81 diagnostic samples by targeted Next Generation sequencing (t-NGS) with a customized panel of 37 genes.

The primary endpoint of the study was the association of time to first progression of disease (POD) with the clinical and molecular features. Specifically, the previously defined threshold of 24 months since MCL diagnosis was used to classify patients as early- or late-POD.

The recurrent SNVs identified in our cohort were *ATM* (42%), followed by *NOTCH1* (32%), *SMARCA4* (30%), *TP53* (29%), and *KMT2D* (26%). Additionally, Fisher's exact test identified *TP53* (p=0.005) as prevalently associated with early-POD (Figure 1).

Among all the SNVs and CNVs detected, *TP53* (p=0.004, HR = 1.97), *NFKBIE* (p = 0.01, HR = 2.63), *STAT3* (p = 0.02, HR = 2.44), and Del 9p21.3 (*CDKN2A*, p = 0.005, HR = 2.19) were significantly associated with shorter time to POD in univariate analysis. Multivariable analysis proved the prognostic impact of the molecular alterations of *TP53* (p=0.013, HR=2.15), *NFKBIE* (p=0.04, HR=2.64), Del 9p21.3 (*CDKN2A*, p=0.009, HR=2.65), and also confirmed the association of a high-MIPI score (vs intermediate and low, p=0.001, HR=3.59) with shorter time to POD.

Unsupervised analysis identified three well-defined molecular clusters with significantly different time to POD (p=0.012). The Cluster A (C_A) was enriched for alterations in well-established MCL driver genes, encompassing *TP53*, *NFKBIE*, and Del 9p21.3 (*CDKN2A*), while the Cluster C (C_C) presented secondary mutations such as the mutations of *BCL6* and *SETD2*. Their comparison resulted highly significant (p=0.006), with the C_A associated with the shortest time to POD.

In conclusion, high-MIPI retained its prognostic significance, while *TP53* mutation and Del 9p21.3 (*CDKN2A*) emerged as independent molecular factors associated with shorter time to POD. Furthermore, the molecular stratification emphasized high genetic complexity driving clinical heterogeneous behaviors and its association with the first time to POD.

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LYMPHOMAS

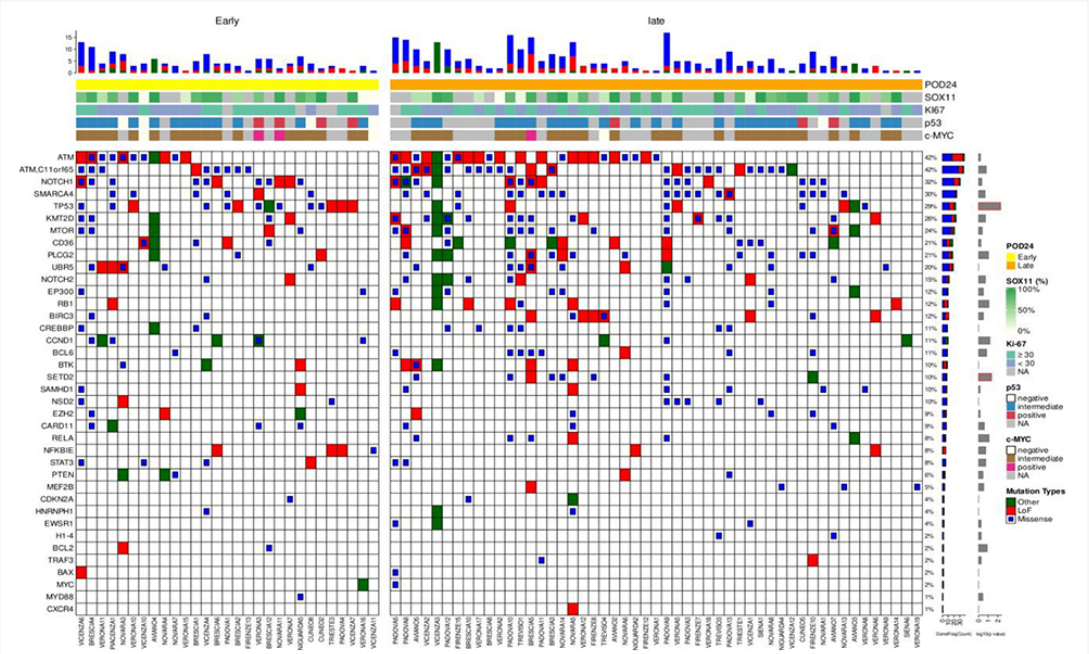

Figure 1. Mutation signatures of MCL patients divided into early- and late-POD. Recurrent somatic mutations (rows) were identified following targeted sequencing analysis of 81 diagnostic samples (columns) obtained from MCL patients (29 early- and 52 late-POD). Samples were annotated for SOX11 expression level, Ki-67, p53 and c-MYC evaluated by immunohistochemistry, when available. Right: percentage of samples mutated. Top: total number of genetic alterations across the cohort. On the right, gray bars with red border indicate *TP53* and *SETD2* as differently mutated genes in early- *versus* late-POD patients ($p<0.005$ and $p<0.04$, respectively).