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Do TP53 mutation impact outcome in WM?

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Introduction. TP53 is a tumor suppressor gene that functions as regulator influencing cellular responses to DNA damage. *TP53* alteration are associated to pejorative outcome in most of B lymphoid disorders but little is known regarding *TP53* alteration in Waldenstrom's Macroglobulinemia (WM).

Material and methods. We have explored the incidence of *TP53* alteration using sanger sequencing and ultra-deep targeted sequencing in 125 WM and 10 IgM MGUS, along with the clinical features and the associated genomic landscape using SNP array and mutational landscape in an integrative study.

Results. Overall, we have identified alteration of *TP53* locus including mutation, deletion and copy neutral loss of heterozygosity in 11,2% of WM. *TP53* mutation was acquired in 7,3% of WM patients at diagnosis, being absent in IgM MGUS. No correlation with *CXCR4* mutations was found. A high correlation between *TP53* mutation and deletion 17p ($p<0.001$) was observed. Patients with *TP53* alteration had a greater number of genomic abnormalities using SNP arrays. Importantly, WM with *TP53* alteration had a significantly shorter overall survival, particularly in symptomatic WM, and independently of IPSSWM score. Specific treatment for WM with *TP53* may have to be studied. Ibrutinib is a BTK inhibitor that showed activity in WM. The effect of ibrutinib was assessed using primary WM cells, along with cell lines. Nutlin-3a-targeted p53 signalling induced cytotoxicity preclinically, along with new compounds such as ibrutinib, Prima^{Met} or CP31398 that bypass p53 pathway in WM, paving the path for future treatment tailored options.

Conclusion. Our results highlight the clinical significance of detection of *TP53* alteration in WM to determine the prognosis of WM and guide the treatment choice. New compound such as ibrutinib or p53 reactivator may bypass *TP53* mutation also identified as a new potential genomic subgroup of WM with poor prognosis.