Lymphomas

PRDM1 AND TNFAIP-3 COPY NUMBER LOSSES PREDICT A SHORTER TIME TO FIRST TREATMENT IN IGM GAMMOPATHIES: NEW INSIGHTS FROM THE FONDAZIONE ITALIANA LINFOMI "BIO-WM" TRIAL

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Introduction: Deletion of the long arm of chromosome 6 (del6q) occurs in approximately 50% of Waldenstrom Macroglobulinemia (WM) patients (pts) and is associated with need for treatment, and poor clinical outcome. Cytogenetic analysis for del6q detection is not easily affordable in clinical practice, since it is time consuming and requires selection of CD19+ cells. On the other hand, *PRDM1* and *TNFAIP3* genes located on 6q21 and 6q23.3, respectively, could be more easily investigated by molecular methods. Indeed, loss of the TNFAIP3 tumor suppressor, when combined with a MYD88L265P mutation, may further lead to deregulated NF-κB activation. Similarly, PRDM1 acts as "master regulator" of B cell and plasma cell differentiation. Therefore, we evaluated the pattern and extent of PRDM1 and TNFAIP3 losses in IgM-MGUS and WM pts, investigating possible correlations with clinical outcome.

Methods: PRDM1 and TNFAIP3 copy number variations (CNVs) were investigated by ddPCR in baseline bone marrow (BM) samples collected in the prospective, observational FIL "BIO-WM" clinical trial (NCT03521596), enrolling both newly diagnosed WM and IgM-MGUS pts in 14 Italian and 3 Spanish centers (46 samples from healthy subjects were used as control for cut-off definition).

Results: Overall, 240/300 (80%) BM samples were analyzed, 187 from WM (78%) and 53 from IgM-MGUS pts (22%). The prevalence of PRDM1 and TNFAIP3 losses was 12% and 18%, respectively, slightly superior among WM cases (13% and 20%, respectively) than among IgM-MGUS (8% and 9%, respectively); of these, 22 pts (9%) carried only one loss while 24 (10%) carried both losses. Of note, the CNVs frequencies were even higher among 47 pts studied in CD19-selected BM cells (TNFAIP3 36% and PRDM1 40%). Pts carrying at least one CNV were characterized by a higher tumor mass (BM infiltration): moreover, TNFAIP3 loss was associated to higher IgM levels (IgM > 2000: 55% vs 24%, $p=0.005$) and altered LDH (30% vs 13%, $p=0.038$). In addition, a trend towards higher prevalence of CXCR4 mutations among pts carrying both CNVs losses was observed (36% vs 19%, $p=0.082$). Overall, both PRDM1 and TNFAIP3 losses were associated to a higher risk of treatment initiation at baseline or during follow-up (PRDM1: 30% vs 11% in WT, $p=0.011$; TNFAIP3: 23 vs 6% in WT, $p=0.001$). Interestingly, time to first treatment (TTFT) was shorter for pts with both CNVs losses: the 3-years risk of receiving treatment, from study inclusion, increased from 5% in double WT to 13% in single CNV, to 45% in pts with both losses ($p<0.001$) (Figure 1). Nonetheless, among treated patients, neither of these CNVs was significantly associated to PFS or OS. Of note, only 3 pts progressed during the first-line treatment two of them carrying both PRDM1 and TNFAIP3 losses.

Conclusions: PRDM1 and TNFAIP3 losses were detected in 12-18% of this IgM gammopathies prospective series: particularly the co-occurrence of both losses was associated to a higher baseline tumor burden and shorter TTFT.

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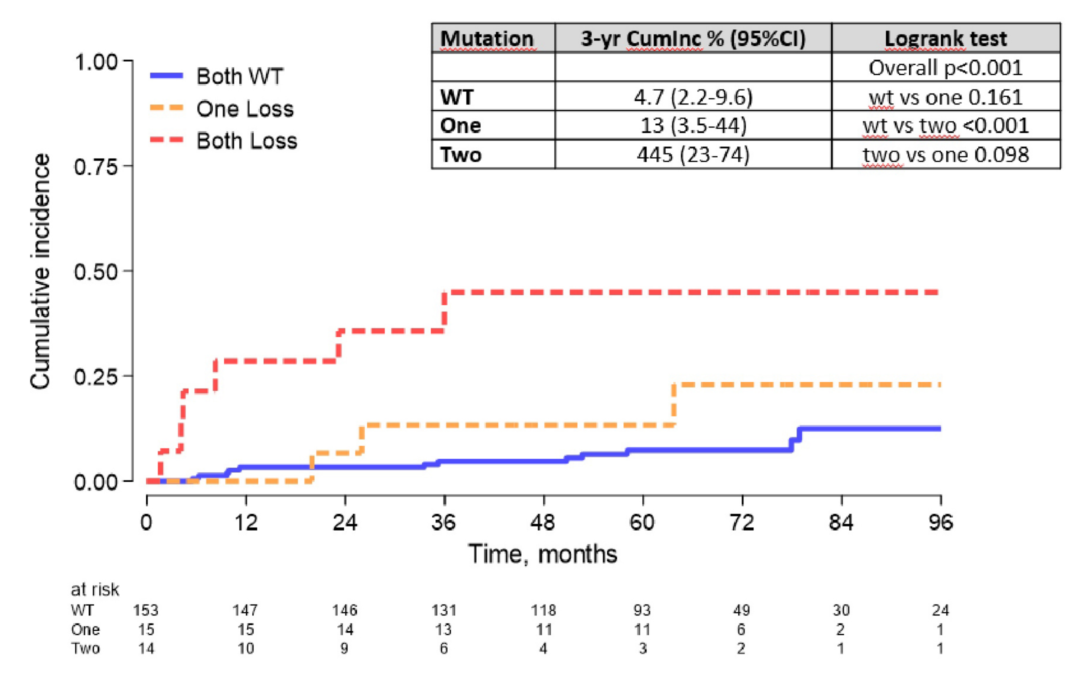

Figure1. Cumulative incidence of time to first treatment by CNV status