XIX CONGRESSO NAZIONALE SIES 2026

UNIVERSITÀ DI TORINO

PRDM1 and *TNFAIP-3* copy number losses predict a shorter time to first treatment in IgM gammopathies: new insights from the FIL "BIO-WM" trial

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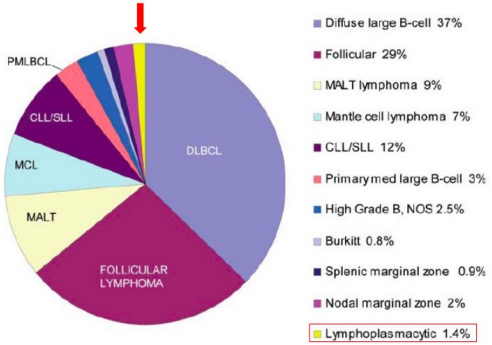
Palazzo degli Affari

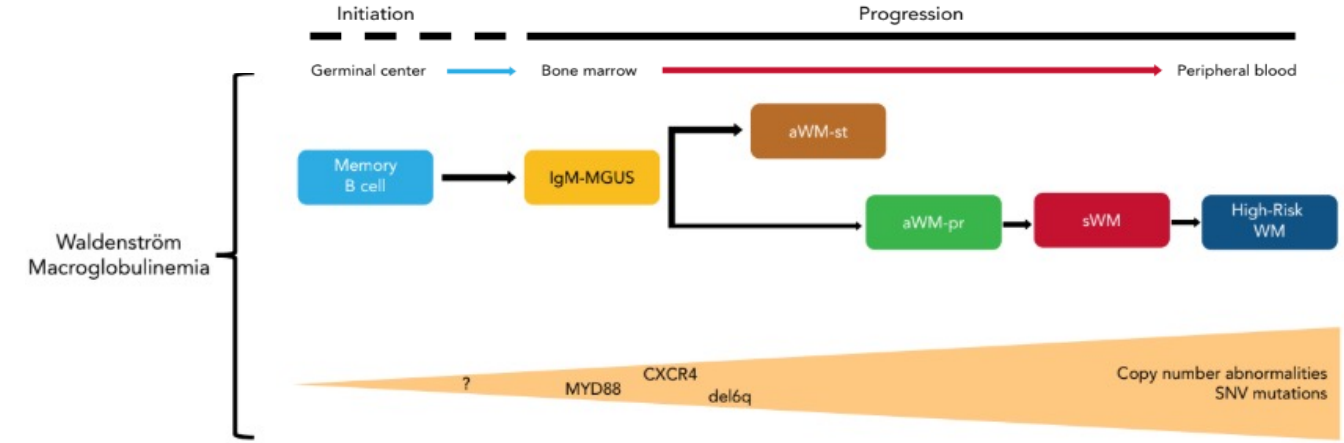
FONDAZIONE ITALIANA LINFOMI

Disclosures of Mariapia Pironti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

The 2008 WHO classification of lymphoid neoplasms





Comment on Bagratuni et al, 3086, Blood

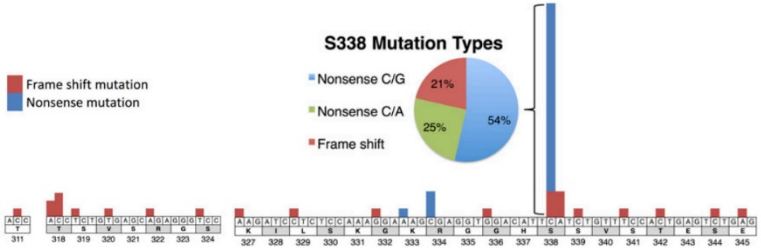
MYD88L265P MUTATION

Marker highly characteristic of WM and IgM-MGUS and post-GC LPDs

Disease categories	Mutation frequency by (AS-PCR)
WM	**79–100%**
IgM-MGUS	50–80%
non-GC DLBCL	19%
MZL, MALT	<10%
CLL, FL	<5%
MM, HCL, MCL IgA/IgG MGUS	0%
HEALTHY	0%

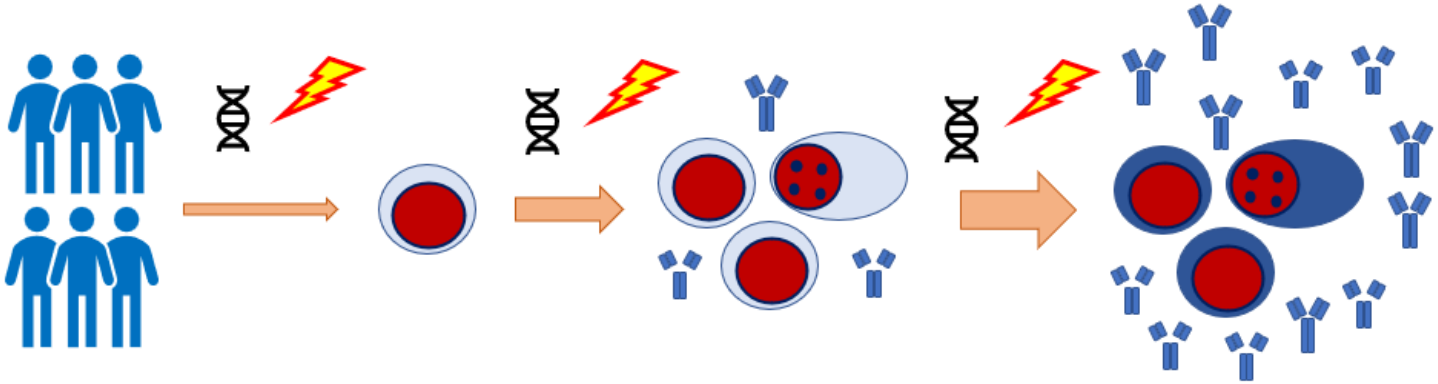
Xu et al. Blood 2013

CXCR4 WHIM-like MUTATIONS



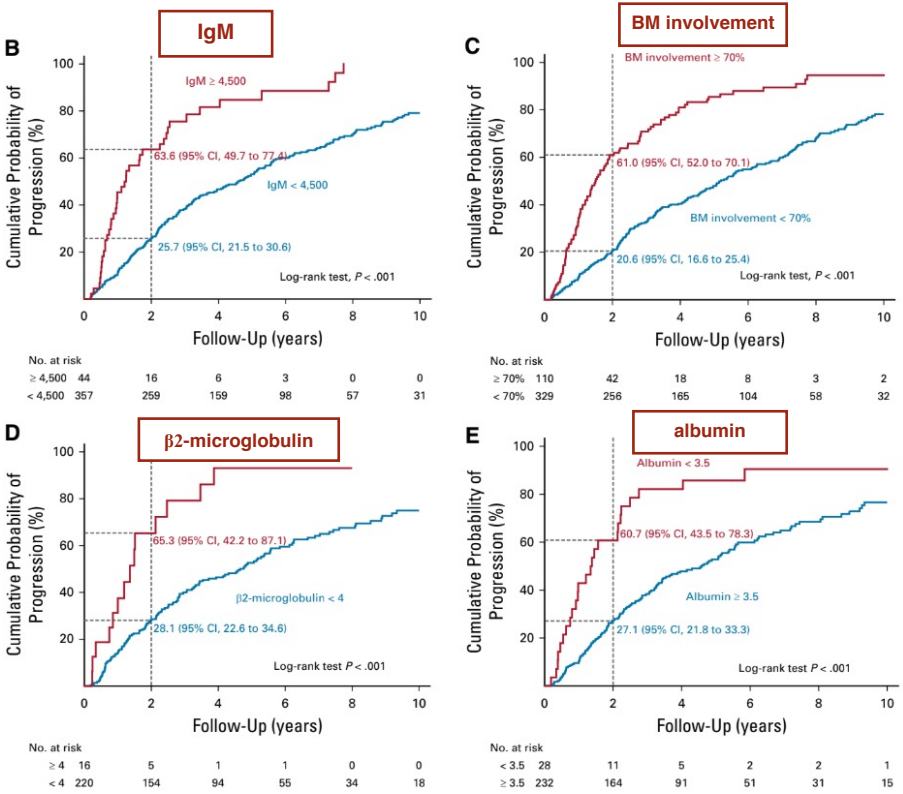
Hunter et al, Blood 2014; 123: 1637-1745

The biological mechanisms driving the progression of the pre-malignant IgM-MGUS clone to sWM or even transformed disease are still unknown

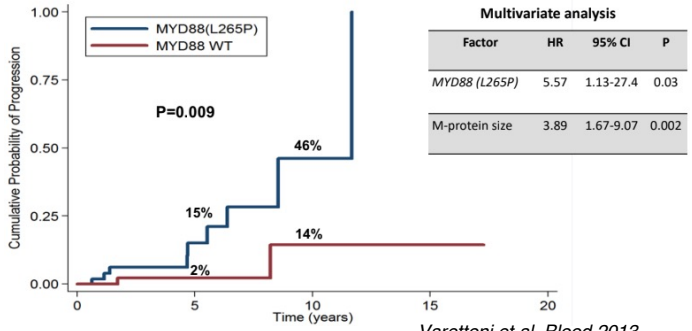


The risk of progression from IgM MGUS to cancer is 2% per year in the first 10 years after diagnosis and 1% per year thereafter. **Overall, the 20 years risk of progression varies from 19% to 55%,** according to patient's risk factors.

Kyle, R. A. et al. Blood 2012 and N. Engl. J. Med. 2018



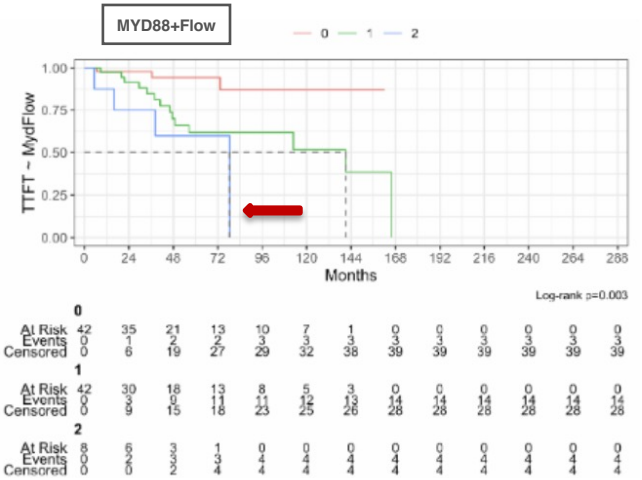
Bustoros M. et al, JCO Apr 2019



Multivariate analysis

Factor	HR	95% CI	P
MYD88 (L265P)	5.57	1.13-27.4	0.03
M-protein size	3.89	1.67-9.07	0.002

Varettoni et al, Blood 2013,



Dogliotti I. et al, Blood ADV 2026, in press

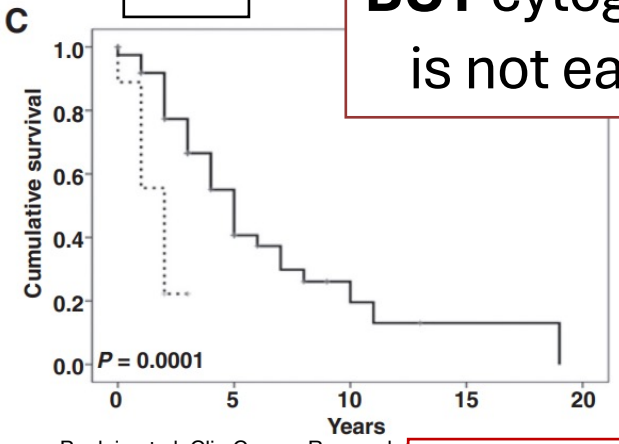
	Time to first treatment		
	HR	*IC 95%*	*P*
B2M	2.27	1.11-4.6	0.02
CXCR4 mutations	-	-	NS

Krzisch D et al, Am J Hematol. 2021

Cytogenetic and molecular abnormalities were not icantly associated with nly **a trend for shorter** as observed **in tri12** and **del6q** patients

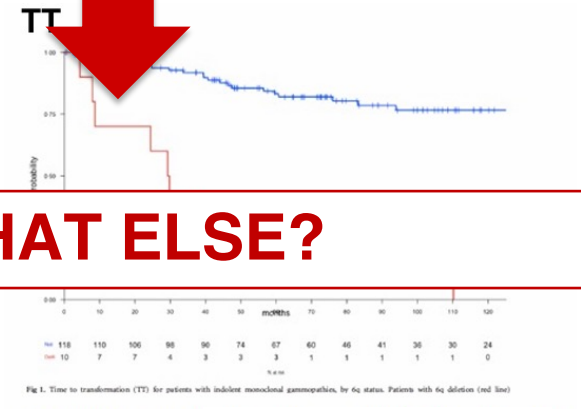
BUT cytogenetic analysis for del6q detection is not easily affordable in clinical practice

TP53mut



Poulain et al, Clin Cancer Research

TT



García-Sanz R. et al, Br J Haematol. 2021

WHAT ELSE?

FIL_BIOWM

Non-invasive diagnostics and monitoring of minimal residual disease and clonal evolution in WM and in IgM-MGUS patients

IWMF SUPPORT • EDUCATION • RESEARCH
International Waldenstrom's Macroglobulinemia Foundation

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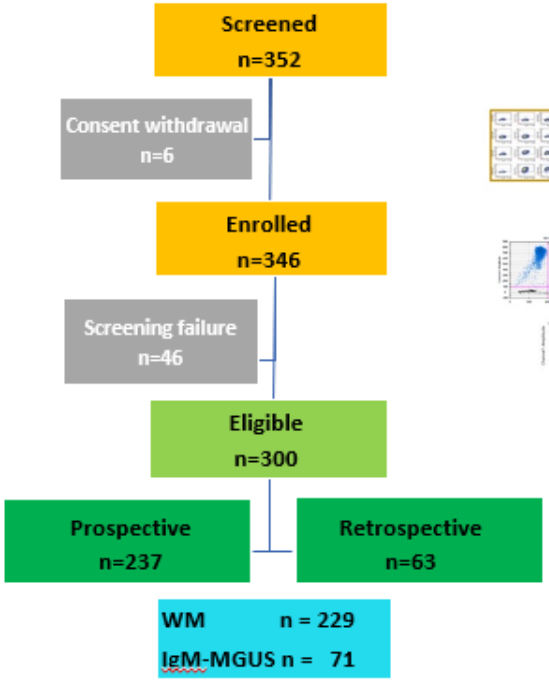
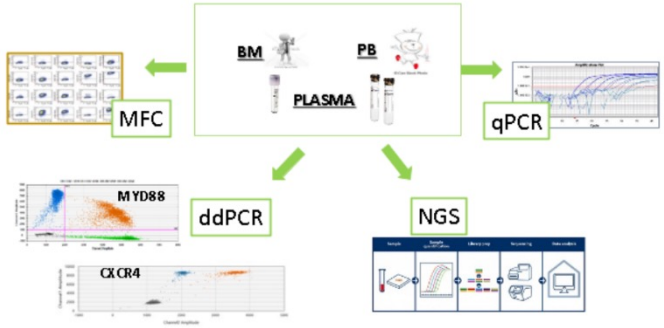
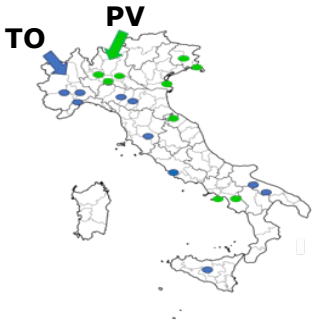
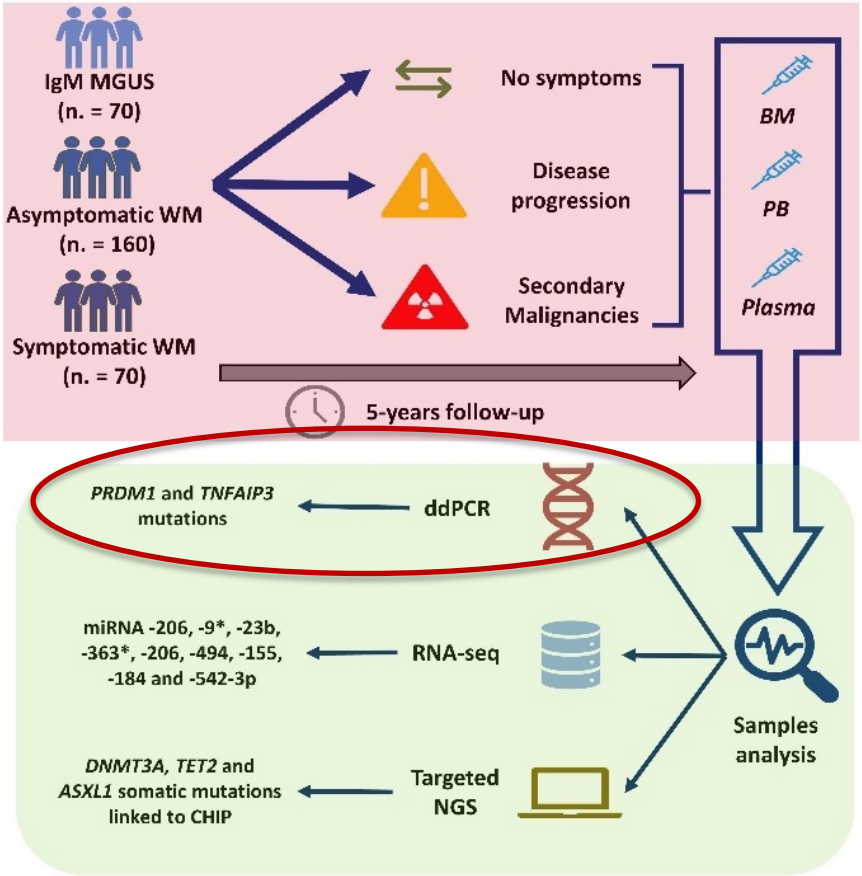
Ramon Garcia-Sanz





Marzia Varettoni





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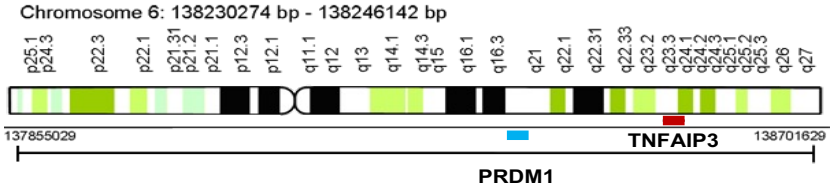
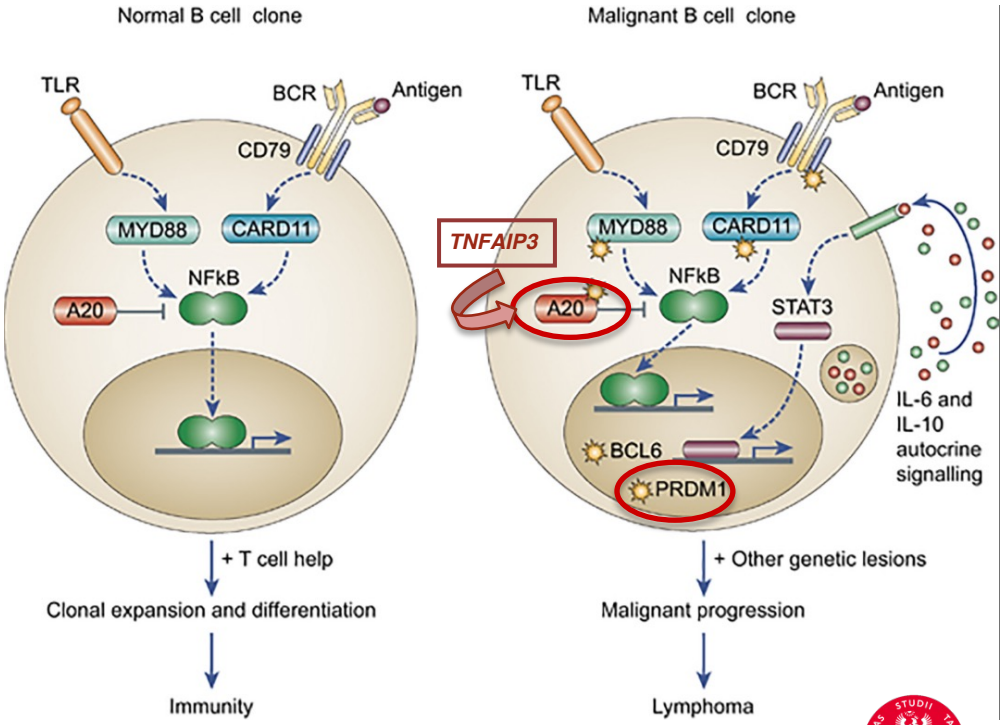
PRDM1 and *TNFAIP3*





Inactivation/deletions of these two candidate oncosoppressor genes were analyzed by ***ddPCR*** on **unsorted BM leftovers**

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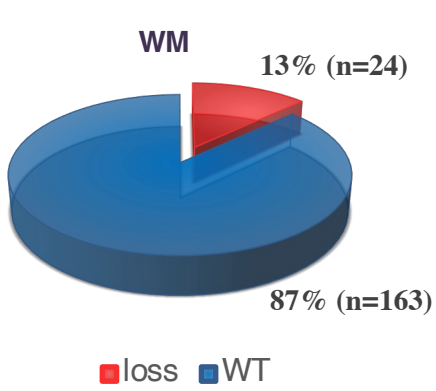
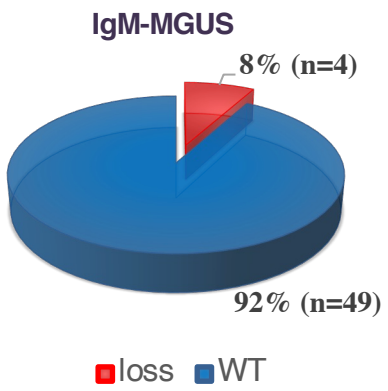
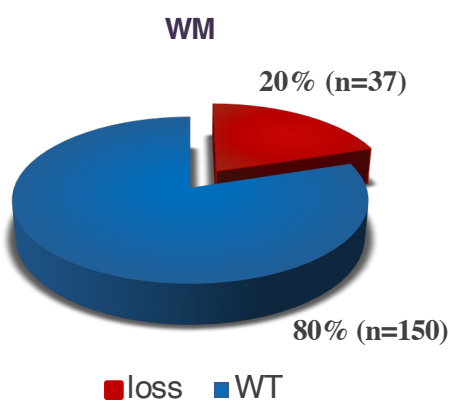
CNVs rate in WM and IgM-MGUS (n=239)

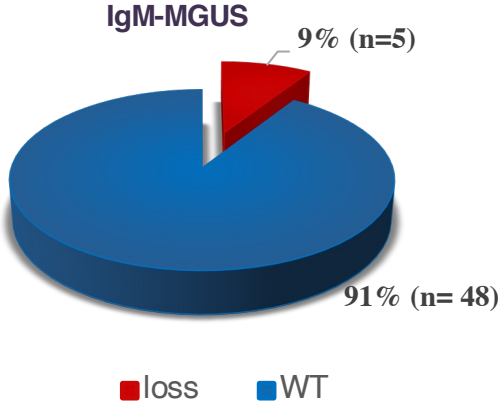
TNFAIP-3





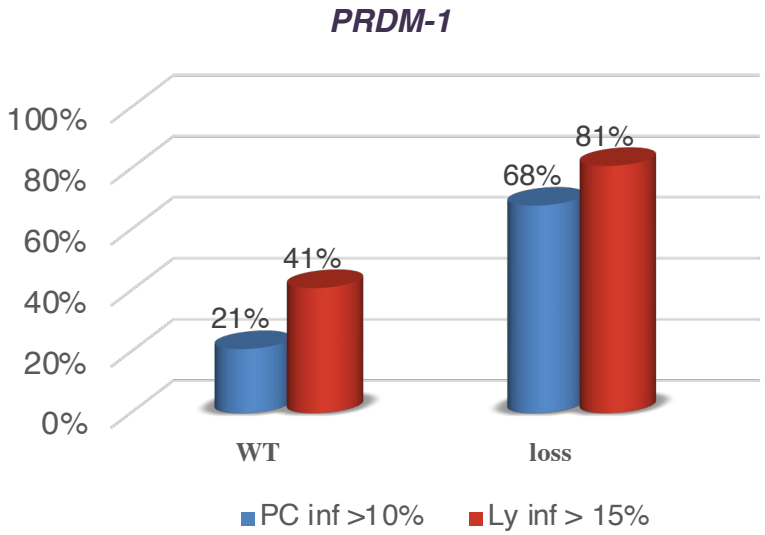
PRDM-1

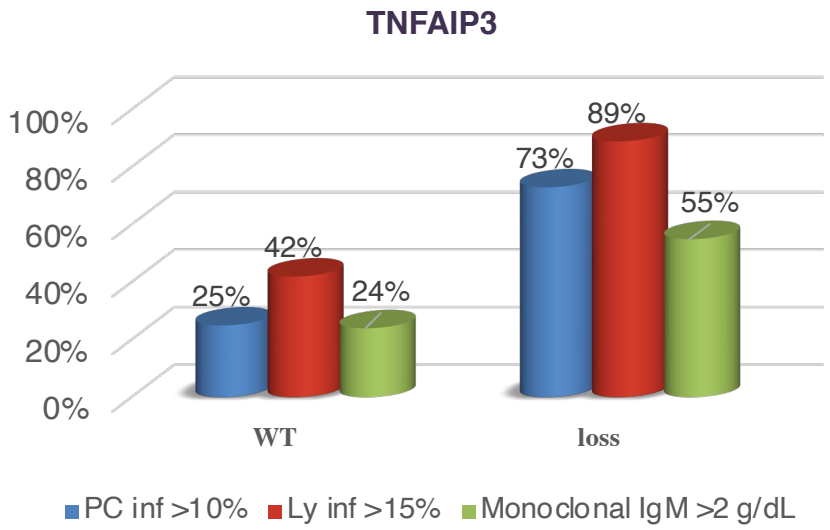




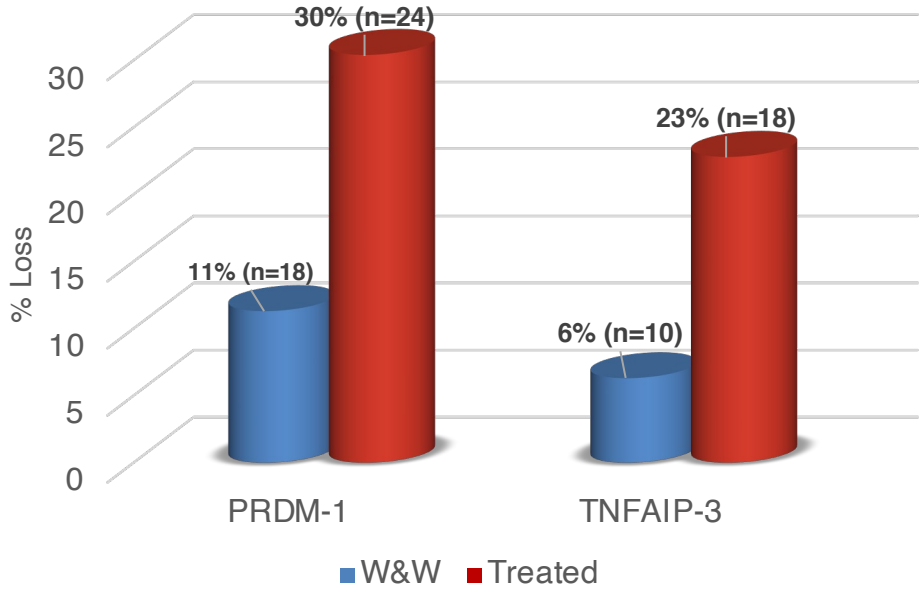
CNVs and clinical features

Factor		PRDM1, n (%)		TNFAIP3, n (%)		p-value	
		WT	Loss	WT	Loss		
Plasma cell inf. [n=123]	>10%	21 (21)	17 (68)	27 (25)	11 (73)	<0.001	
Lymphocyte infiltr. [n=122]	>15%	39 (41)	21 (81)	44 (42)	16 (89)	<0.001	
Monoclonal IgM [n=186]	>2 g/dL	39 (26)	13 (38)	40 (24)	12 (55)	0.145	0.005





Need for treatment at baseline or during FU (n=239)

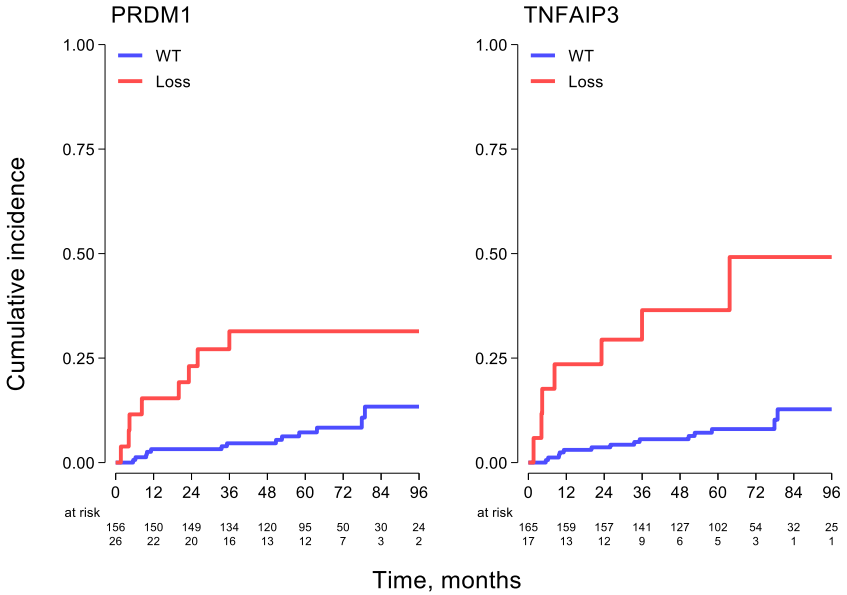


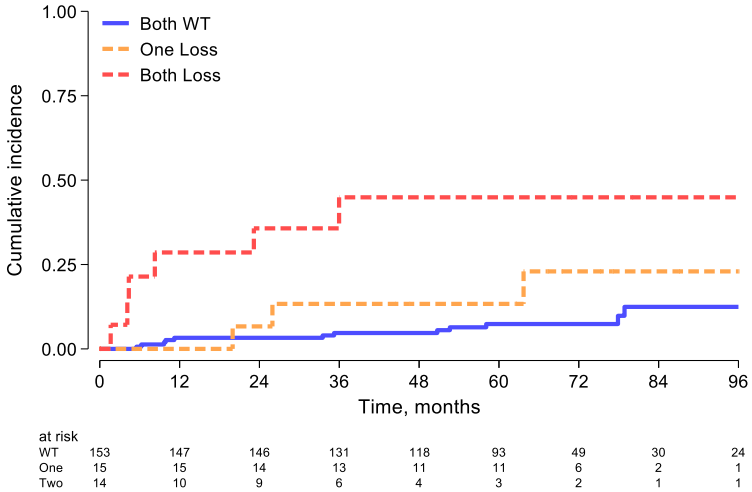
Time to first treatment (TTFT)

PRDM1	3-yr CIF% (95%CI)	Logrank test
WT	4.6 (2.2-9.4)	<0.001
Loss	31 (17-53)	

TNFAIP3	3-yr CIF% (95%CI)	Logrank test
WT	5.6 (2.9-10)	<0.001
Loss	36 (18-64)	

Loss	3-yr CumInc % (95%CI)	Logrank test
		Overall p<0.001
WT	4.7 (2.2-9.6)	wt vs one 0.161
One	13 (3.5-44)	wt vs two <0.001
Both	44.5 (23-74)	two vs one 0.098





CONCLUSIONS:

- We studied *PRDM1* and *TNFAIP3* CNVs in the context of FIL «BIO-WM trial»;
- *PRDM1* and *TNFAIP3* oncogenes losses were detected in 12-18% of this IgM gammopathies **prospective** series;
- the co-occurrence of both losses was associated to a **higher baseline tumor burden** and **shorter TTFT**

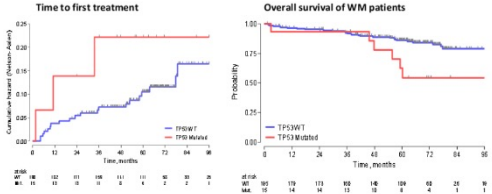
Future perspectives?

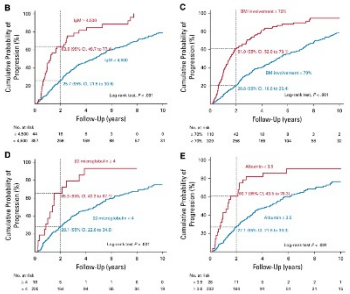
…future perspectives

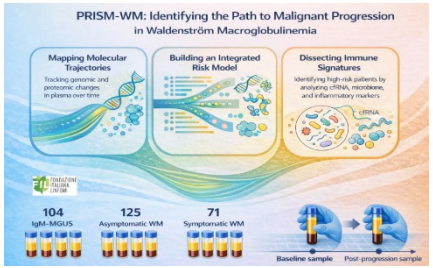
- Integrating these CNVs into the «BIO-WM» mutational study (ASH 2025);

- Integrating these CNVs with published prognostic score (Bustoros et al., Dogliotti et al.);

- Analyzing leftover samples to identify new biomarkers (e.g, microbiome and WES)







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FIL "BIO-WM" team