Evoluzione Genomica delle Discrasie Plasmacellulari

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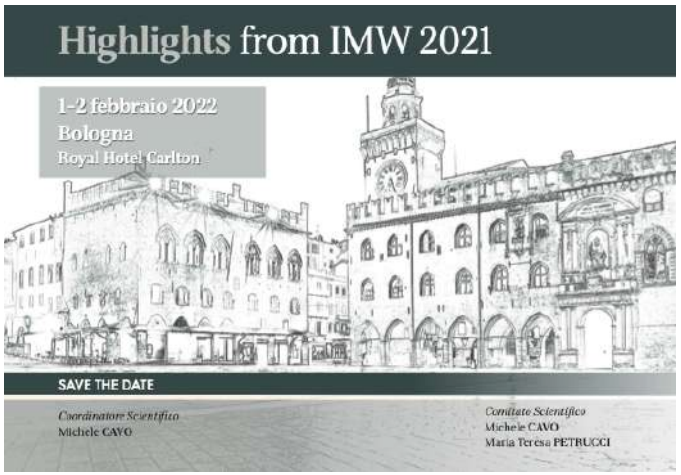

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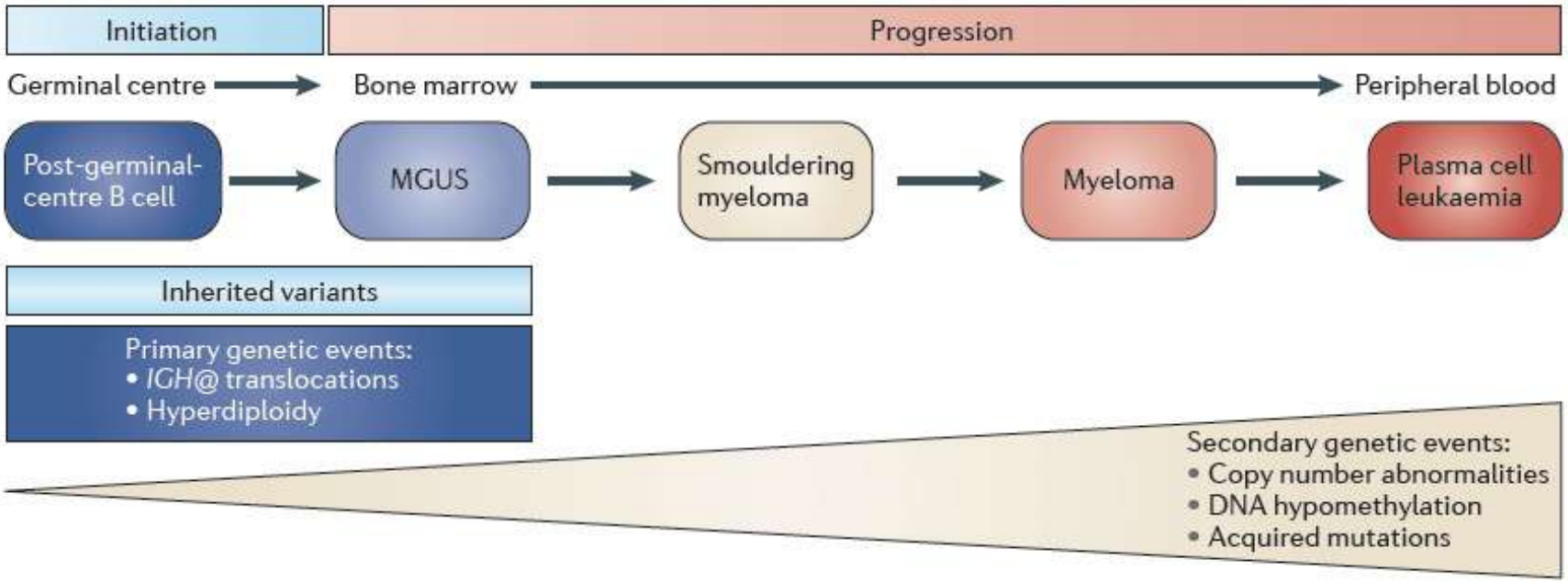
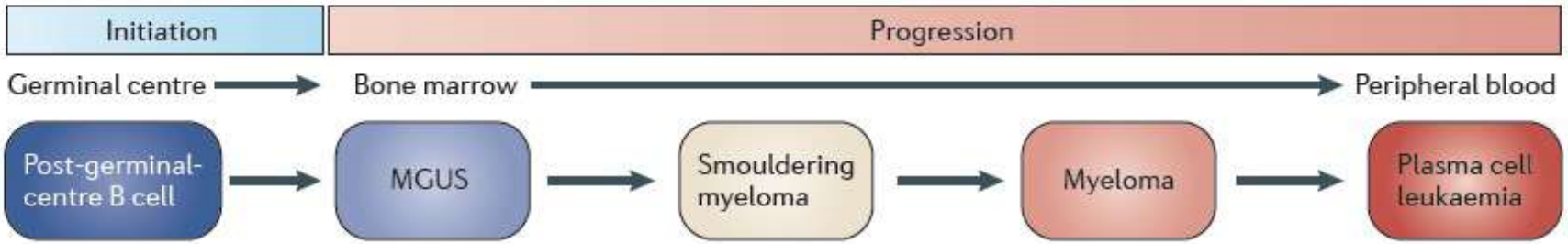
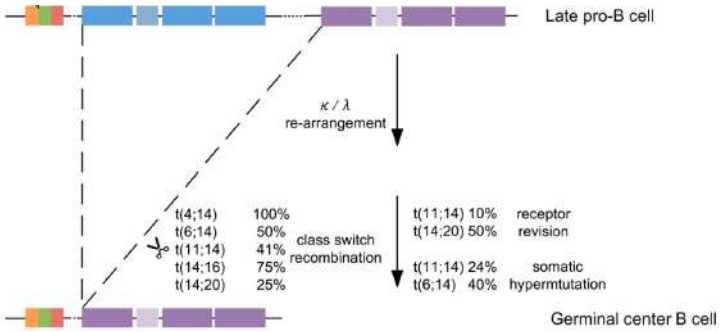
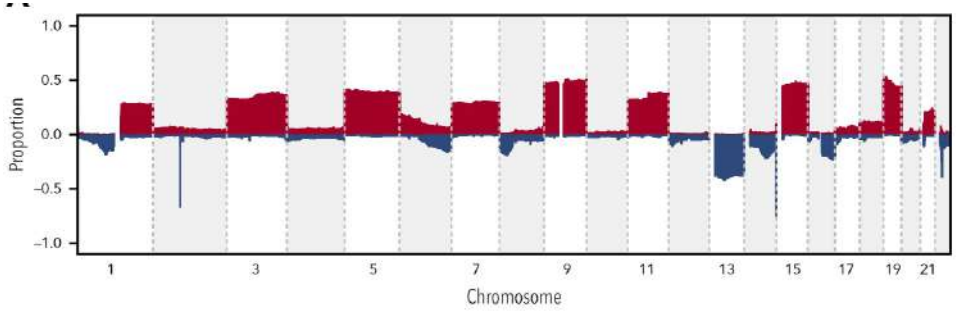
Outline of clonal PC evolution

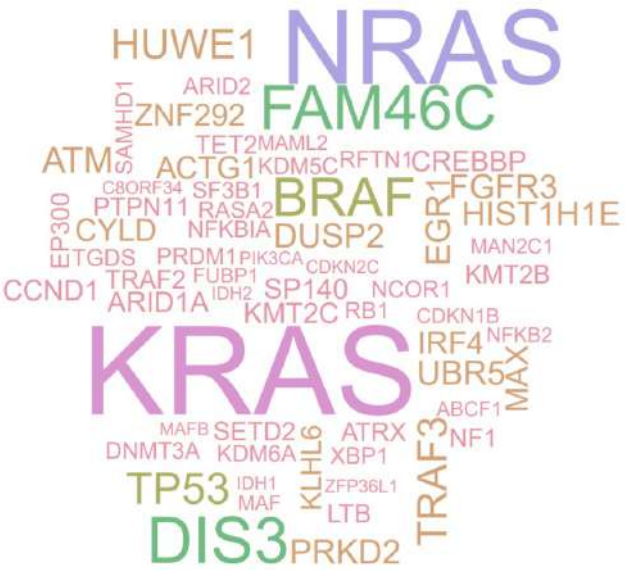


Morgan, Walker & Davies *Nat Rev Cancer* 2012 **12**:335









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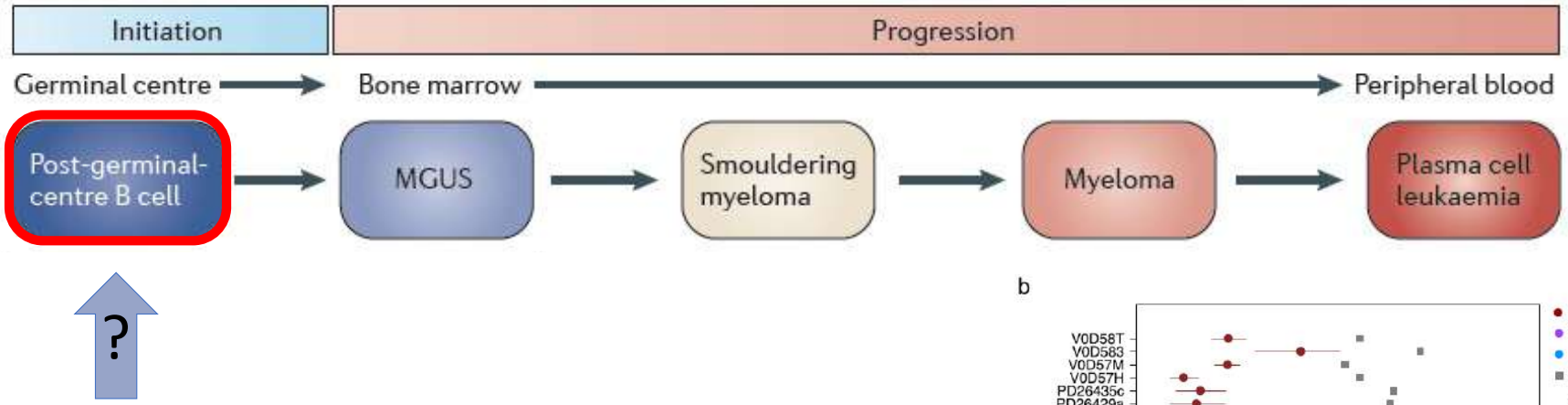
Clonal PCs arise decades before diagnosis

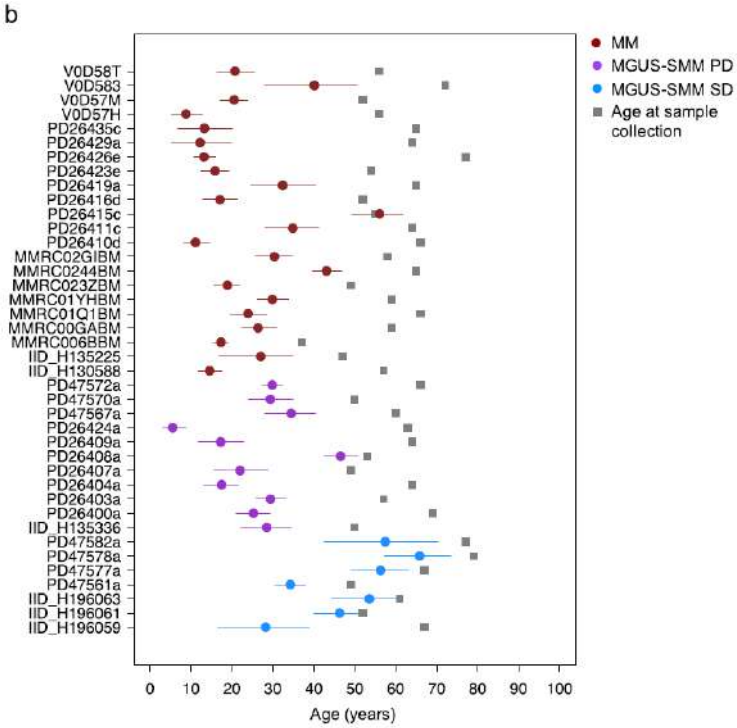


When does MGUS start?

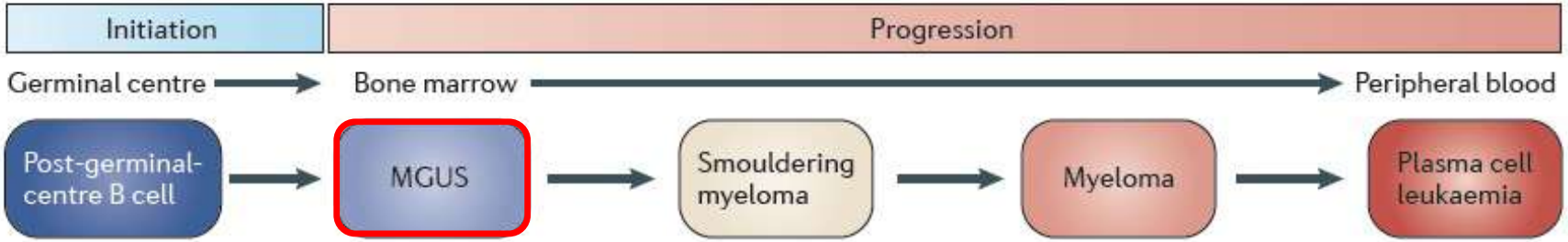
Examine mutation rates

Clock-like mutations correlate with age

Myeloma initiation at 20-30 years of age



Rustad et al. *Nat Commun 2020*
Oben et al. *Nat Commun 2021*



IGH translocations are present

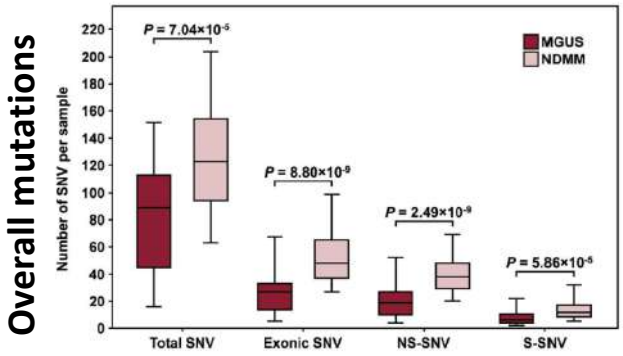
100% of patients have mutations by WGS

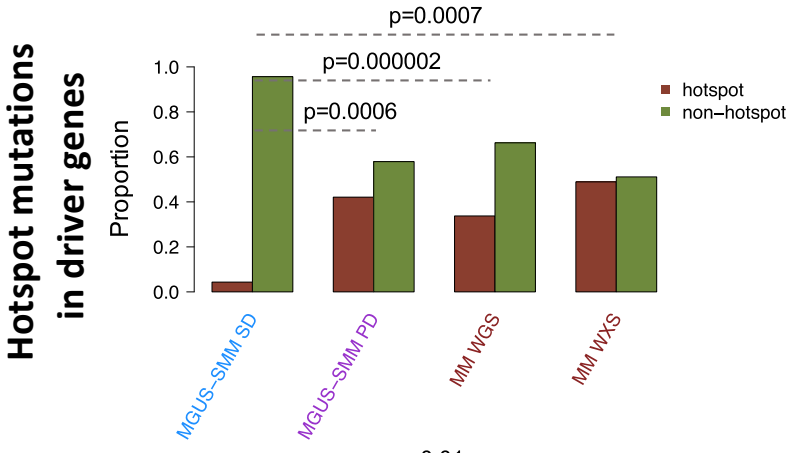
CNAs: amplifications >> deletions

Distinct profile of progressive and non-progressive cases

No biallelic deletions in TSGs.
CDKN2C, TP53, CYLD, BIRC2/3

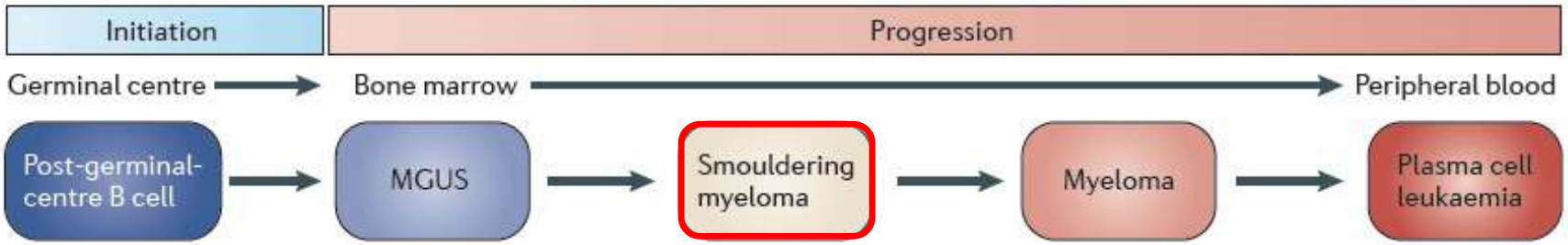
No *TP53* mutations or *MYC* abnormalities

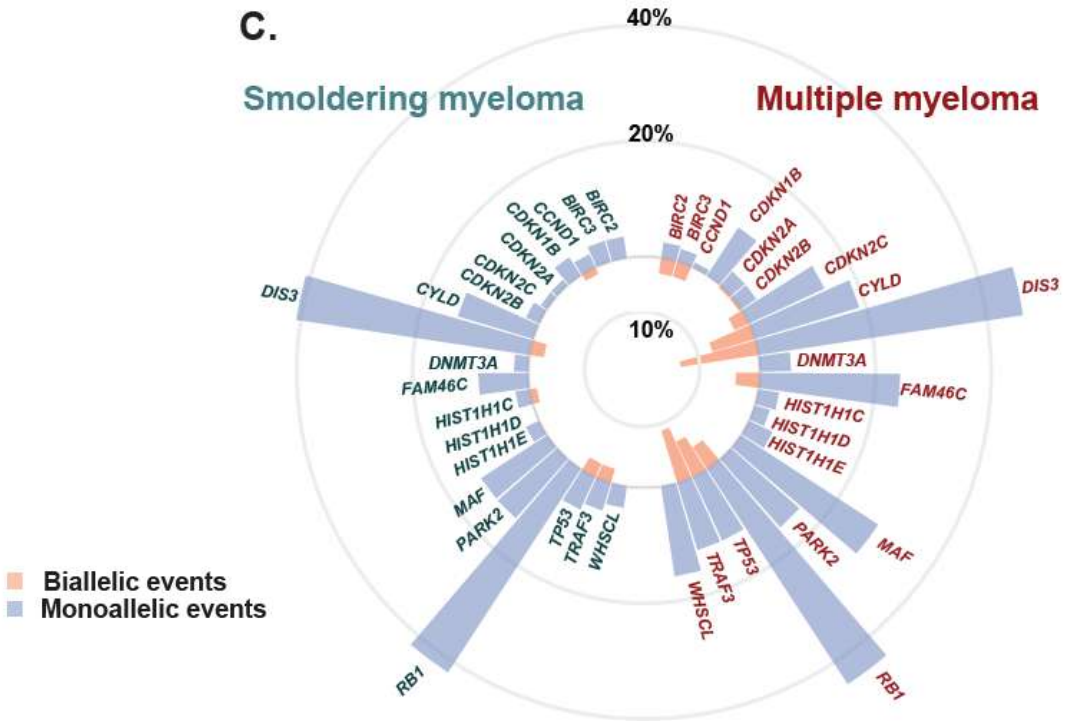




Mikulasova et al. Haematologica 2017
Oben et al, Nature Comms 2021

Distinct mutational profile of SMM and MM

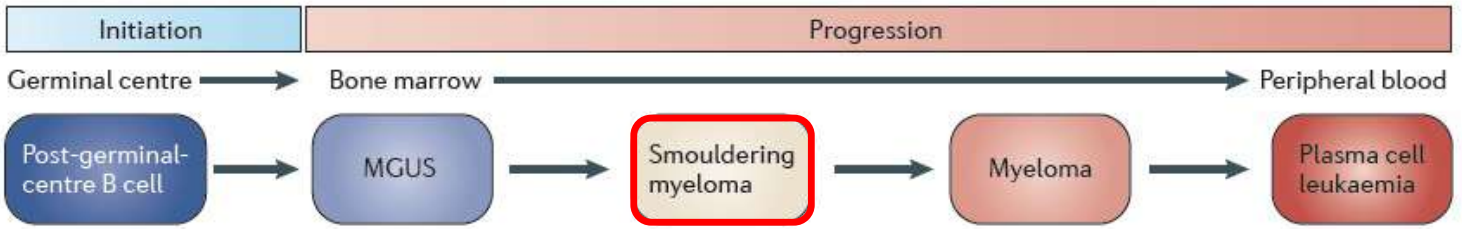


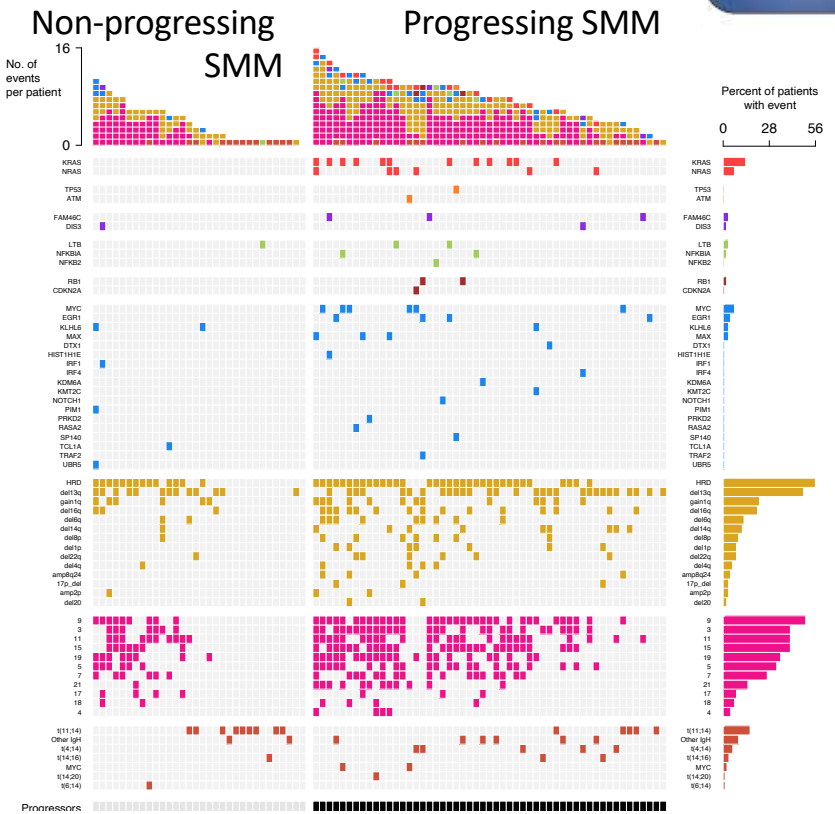


- Total of 103 (64/223 pts) biallelic events identified in MM, compared to 8 (8/82 pts) in SMM, χ^2=10.9, p=0.001
- 1.2% SMM patients with Biallelic *TP53*, compared to 8.1% in MM
- 2% SMM with Biallelic *DIS3*, compared to 5% in MM
- Biallelic inactivation may be a hallmark mechanism in the transition to MM

Boyle, Walker et al. Nature Commun. 2021

Genomic features can help prognostication in SMM

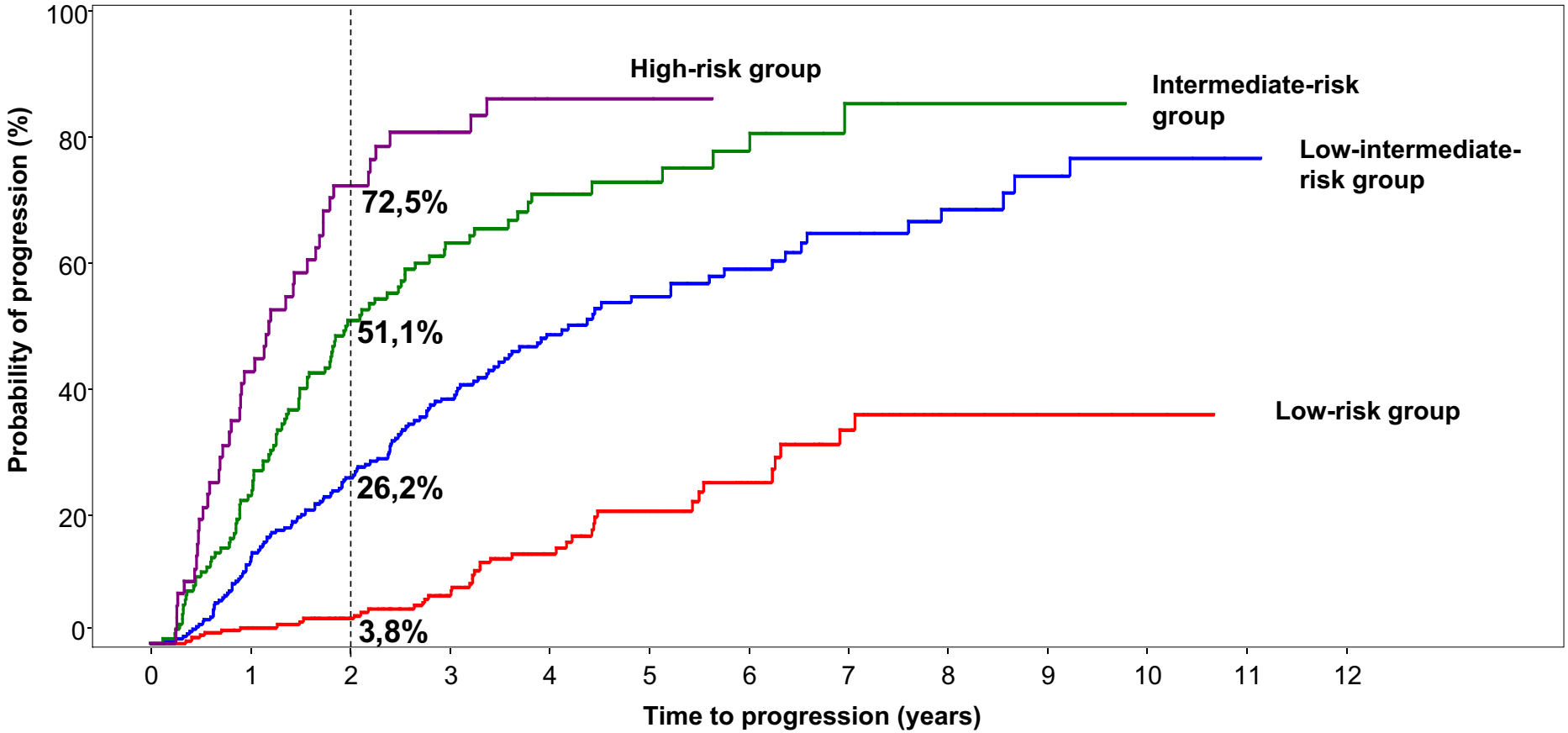




Term	No. (%)	Estimate (95% CI)	*P*
DNA repair pathway			
Wild type	80 (94)	Reference	
Mutation	5 (6)	5.54 (1.96 to 15.64)	.001
MYC			
Wild type	79 (93)	Reference	
Mutation	6 (7)	4.53 (1.74 to 11.82)	.002
MAPK pathway			
Wild type	70 (82)	Reference	
Mutation	15 (18)	3.84 (1.90 to 7.74)	< .001
t(4;14)			
Wild type	80 (94)	Reference	
Mutation	5 (6)	2.58 (0.92 to 7.27)	.072
Mayo 2018			
Low	23 (27)	Reference	
Intermediate	22 (26)	1.91 (0.66 to 5.47)	.23
High	40 (47)	4.47 (1.63 to 12.26)	.004

Bustoros et al, JCO 2020

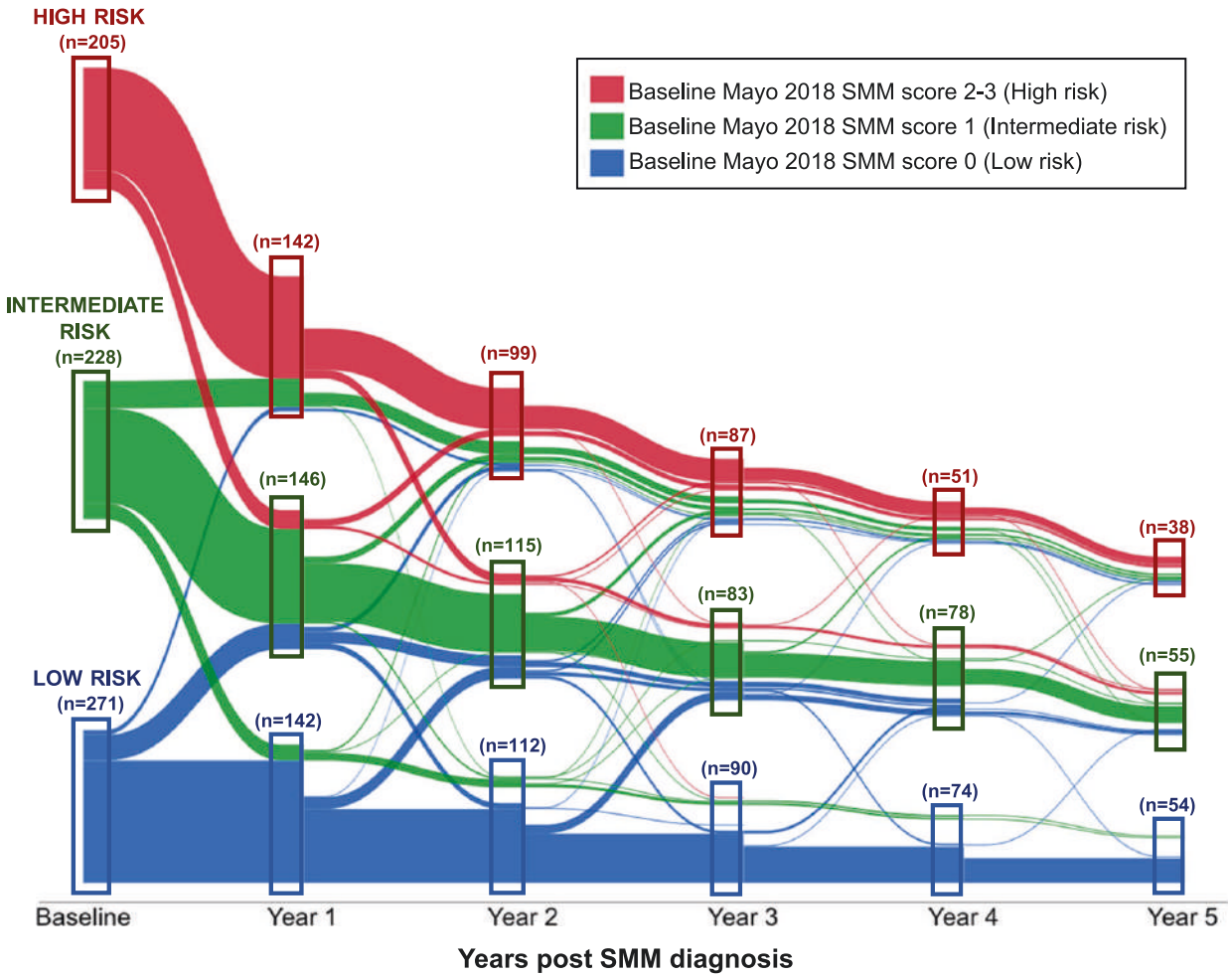
IMWG model for risk stratification of SMM incorporating FISH



Mateos MV, et al. Blood Cancer J. 2020;10(10):102.

Possible added value of dynamic risk-stratification in SMM

Replacing invasive by minimally invasive tumor burden assessment in the model?



1. Visram A, et al. Blood Cancer Journal 2021

Aims of the iMMunocell study group

- Compare the prognostic value of PC quantification in bone marrow (BM) vs the evaluation of circulating tumor cells (CTCs) in peripheral blood (PB) of SMM patients

- Define immune signatures predictive of time-to progression (TTP) in SMM to identify patients with stable tumor burden, but at risk of progression due to lost immune surveillance

Termini et al., IMS 2021

Conclusions

- MM initiation decades before diagnosis
- Continuum of genomic features – more studies needed for classification and prognosis
- CTC numbers may have greater prognostic value than BM PC counts
  - Rationale for future dynamic models
- Tumor microenvironment is a key player in disease progression

Evviva i meetings in presenza!