



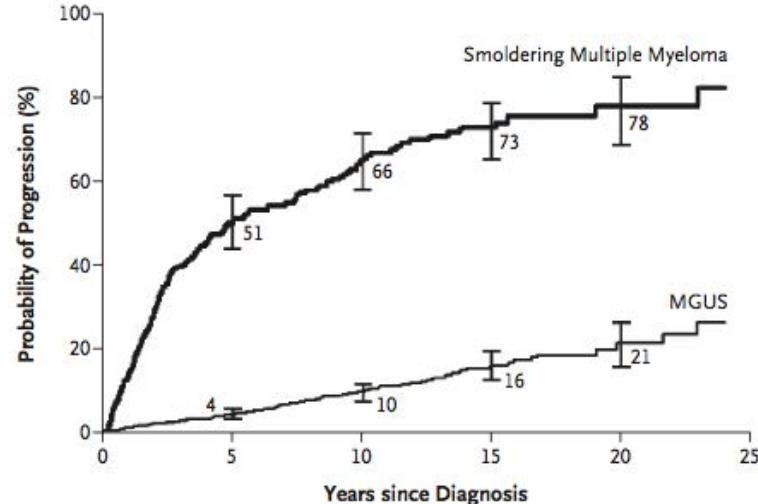
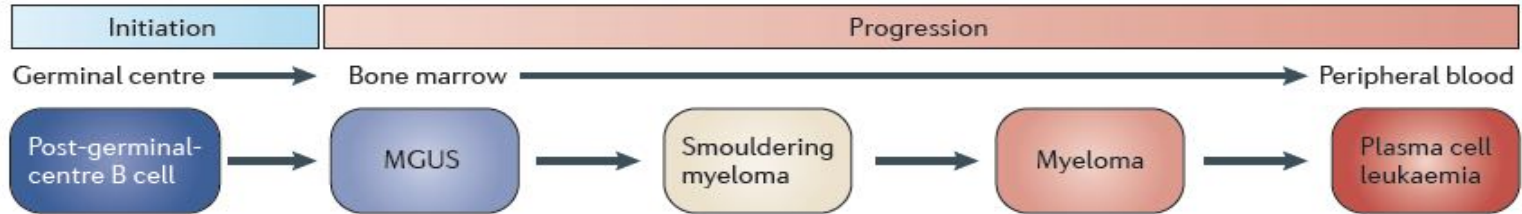
Evolution clonale MGUS-SMM-MM

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MCU-PH, Service d'Hématologie CHU Lille
Unité CANTHER, INSERM UMR-S1277 et CNRS UMR9020

Novembre 2021



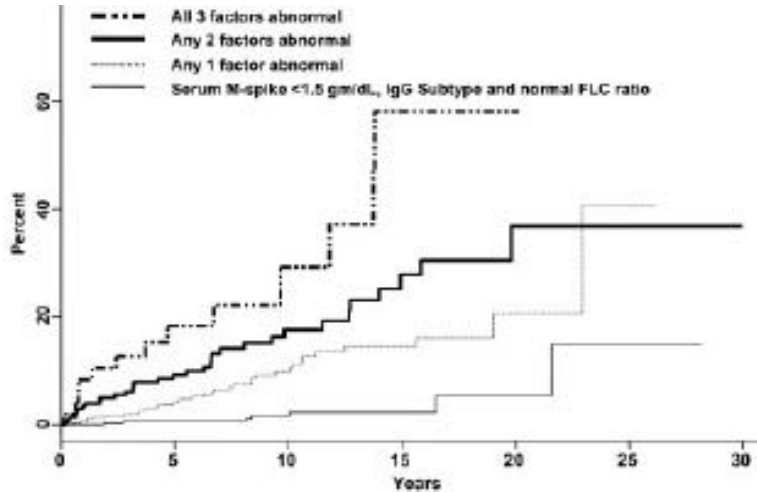
Continuum of MGUS/SMM/MM



Prognostic markers of SMM

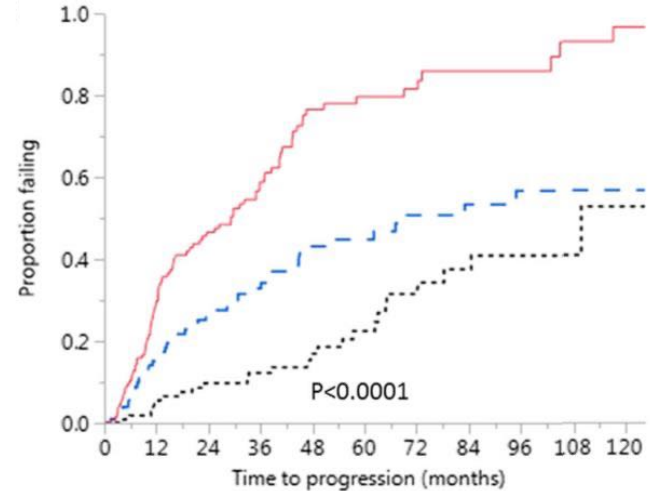
MGUS - Mayo clinic

Non-IgG
M-spike $\geq 15\text{g/L}$
SFLCr abnormal

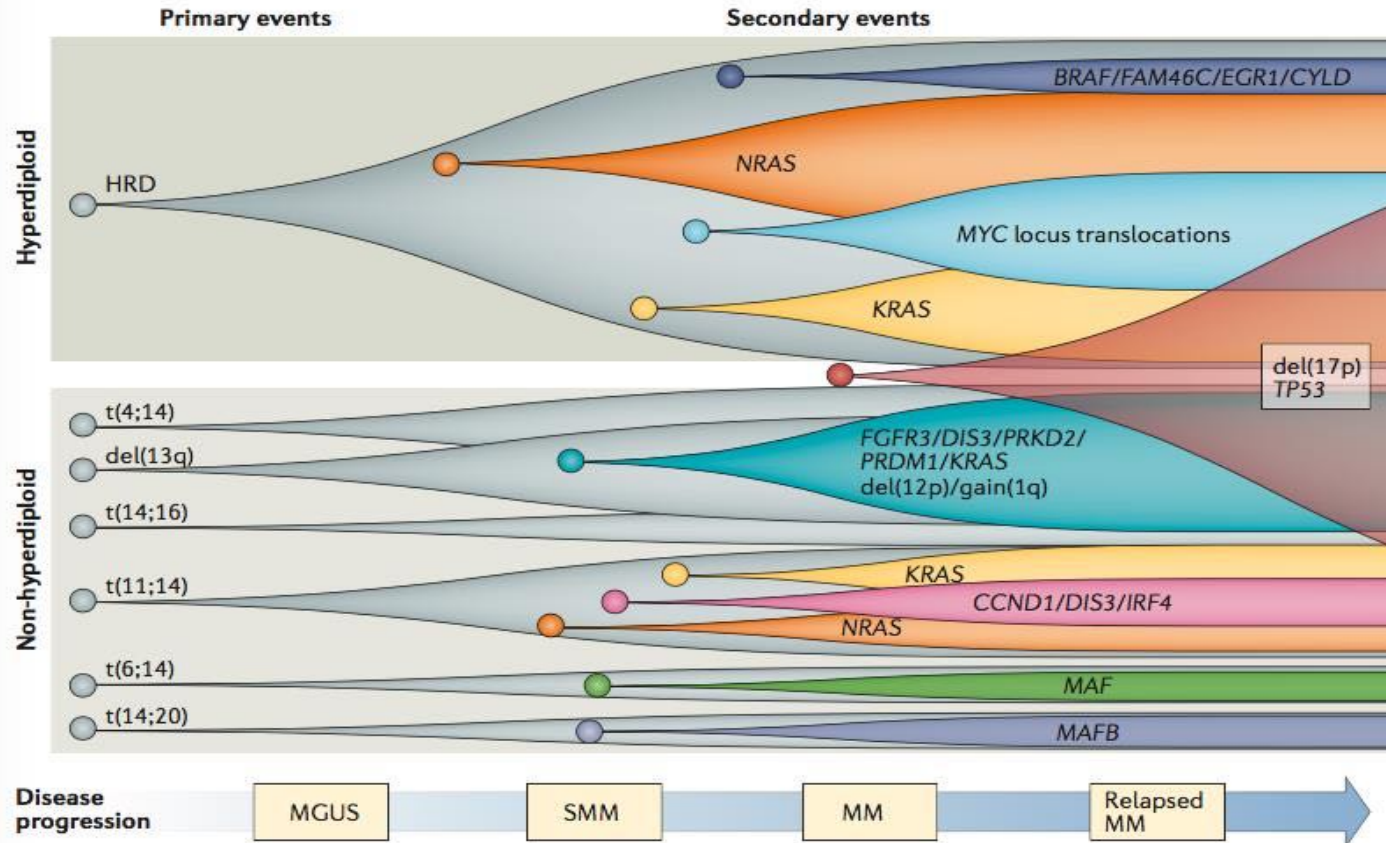


SMM - IMWG 2-20-20

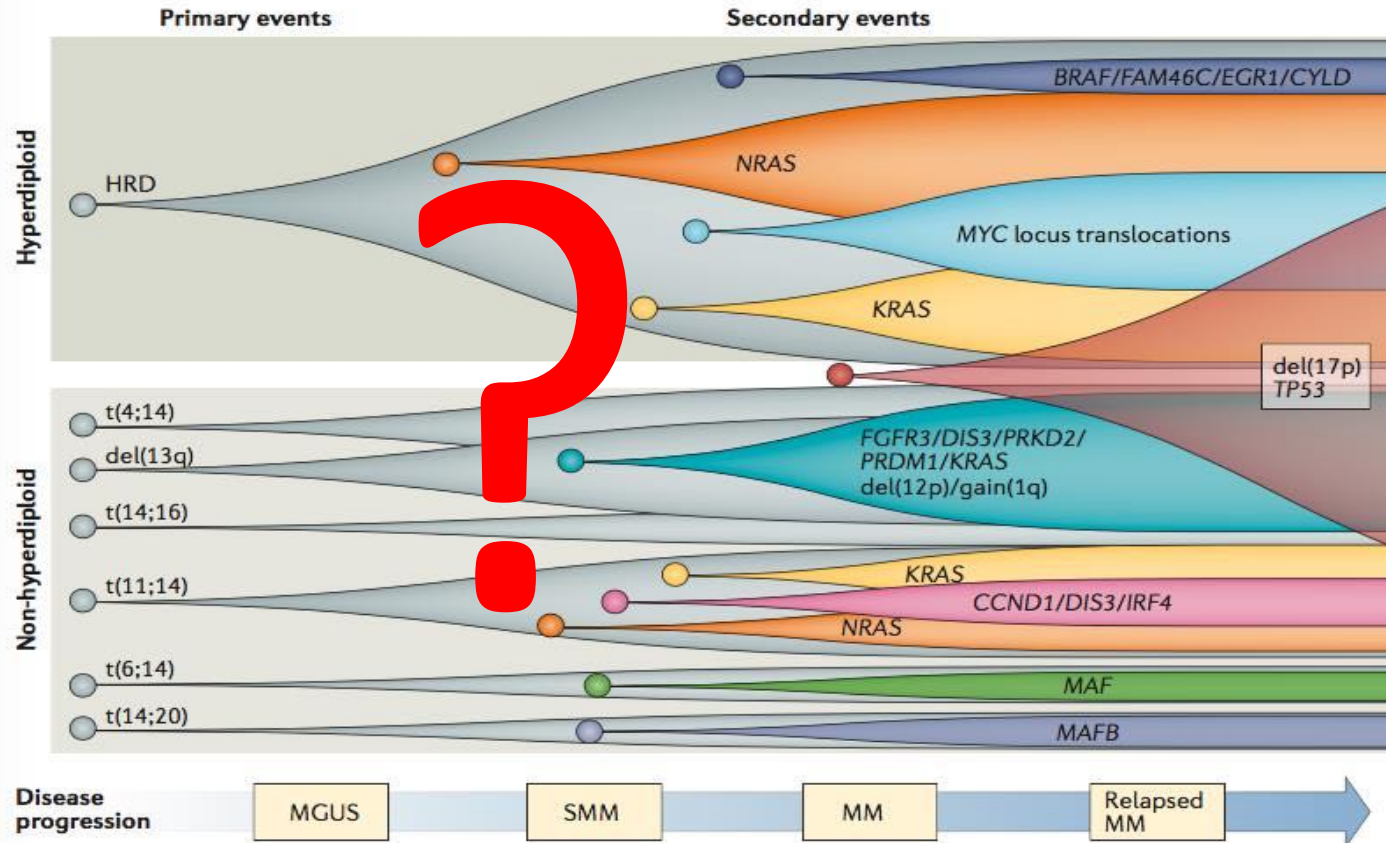
BMPC $> 20\%$,
M-spike $> 2\text{ g/dL}$,
SFLCr > 20



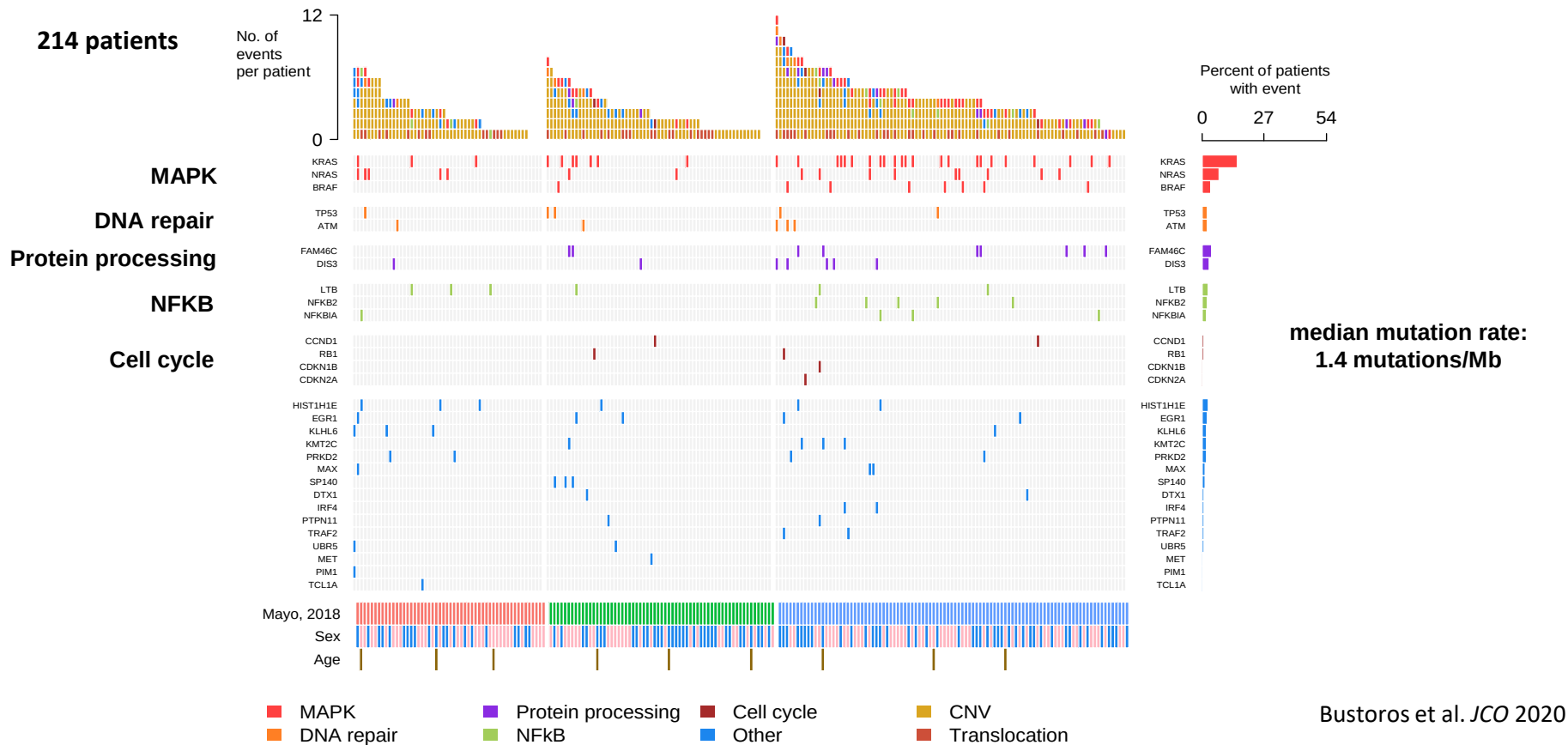
Genomic of MM



Genomic of MM



Genomic landscape of SMM



Genomic landscape of SMM

214 patients

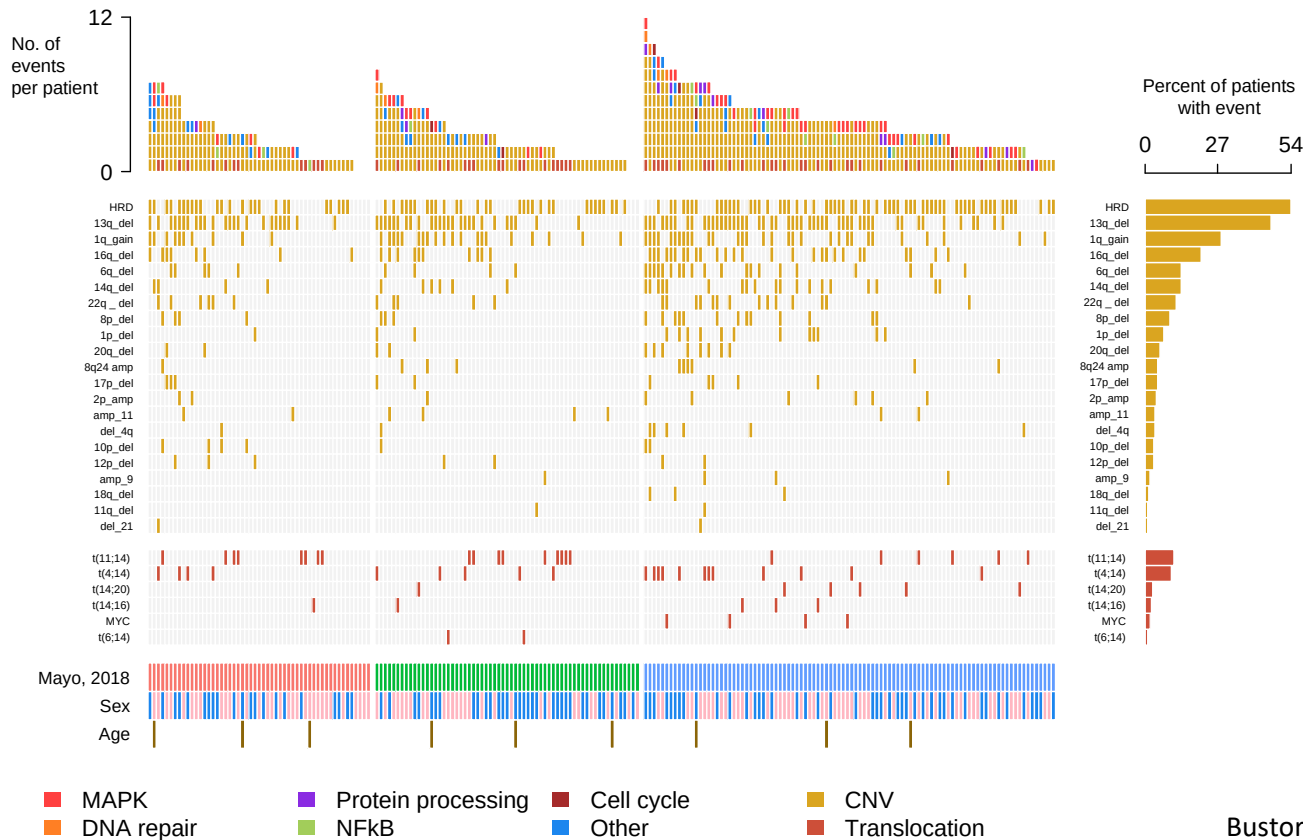
HDR 54%

del13q 50%

gain1q 30%

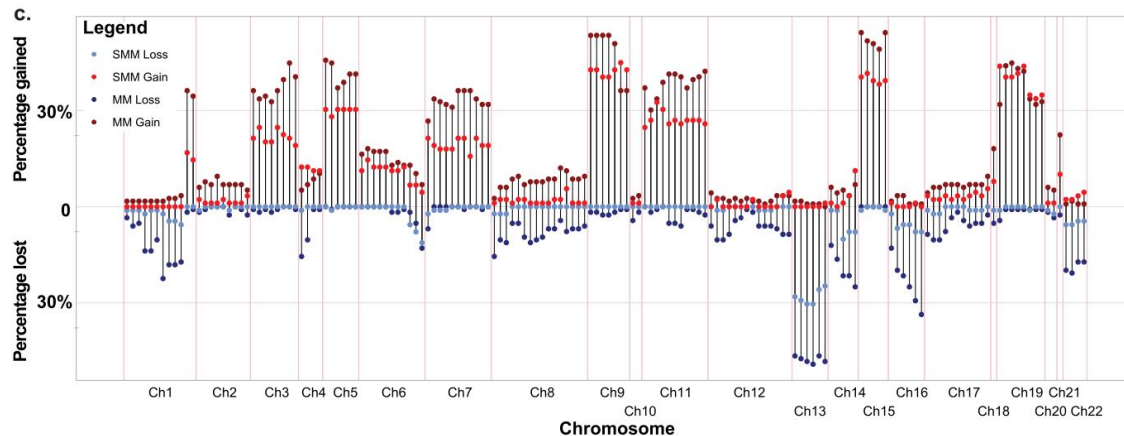
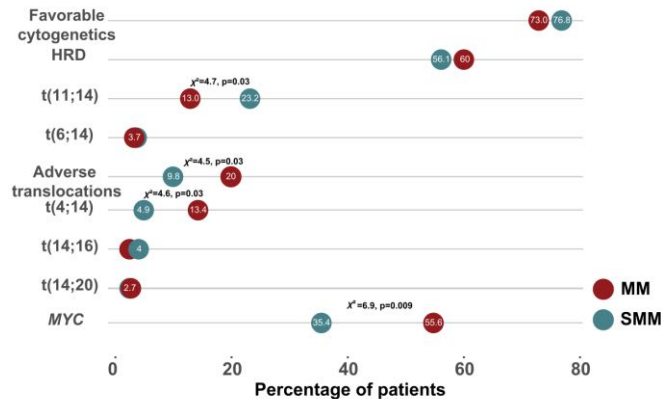
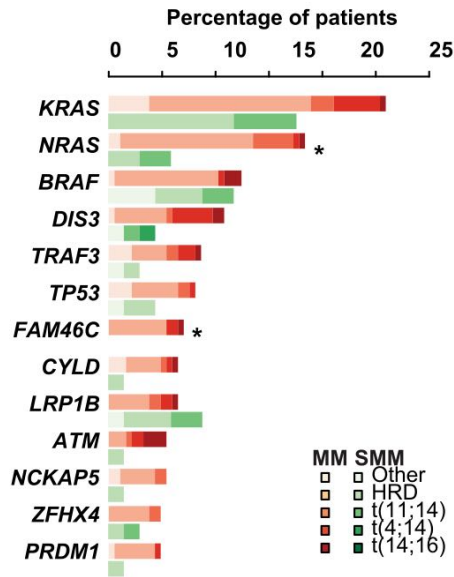
t(11;14) 11%

t(4;14) 10%



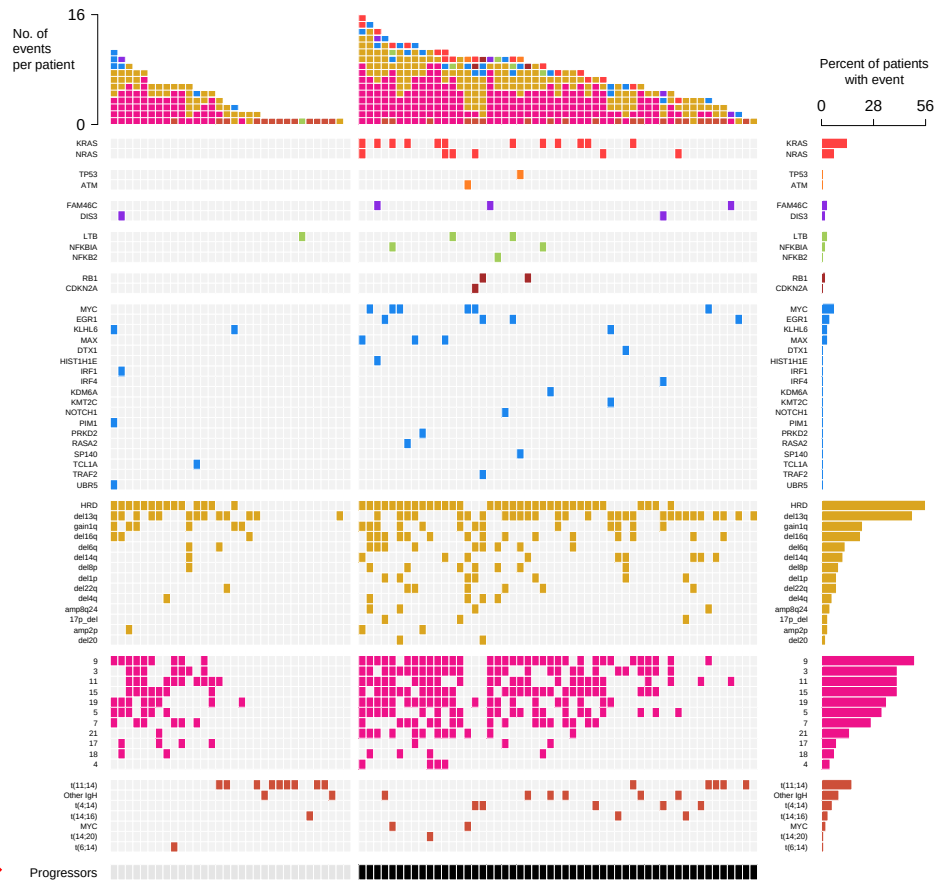
Genomic landscape of SMM

82 SMM vs. 223 MM



Genomic prognostication of SMM

85 untreated patients



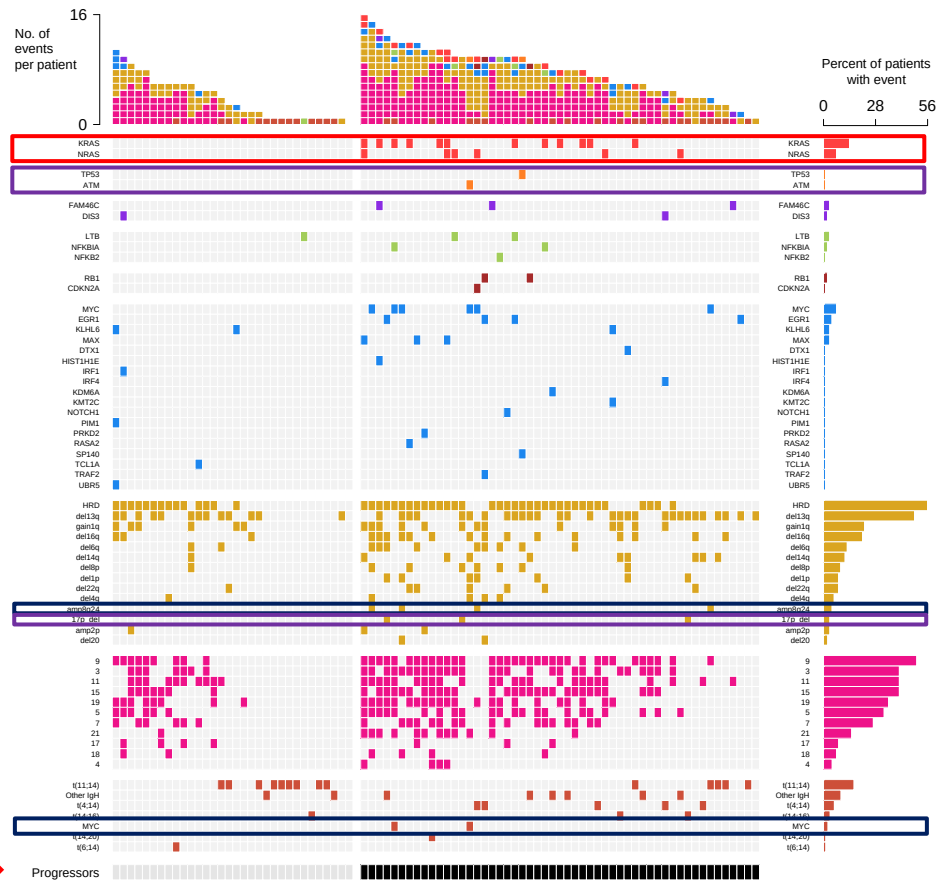
Genomic prognostication of SMM

85 untreated patients

MAPK alterations

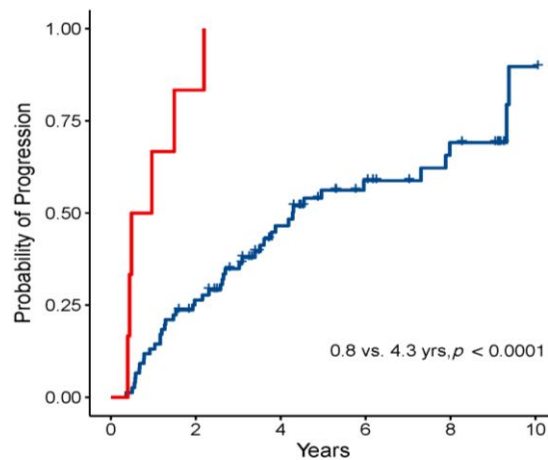
DNA repair alterations

MYC alterations



Genomic prognostication of SMM

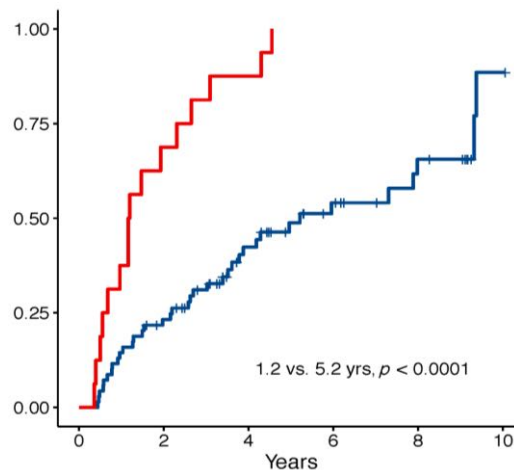
MYC alterations



Number at risk

0	76	54	30	16	9	1
1	6	1	0	0	0	0

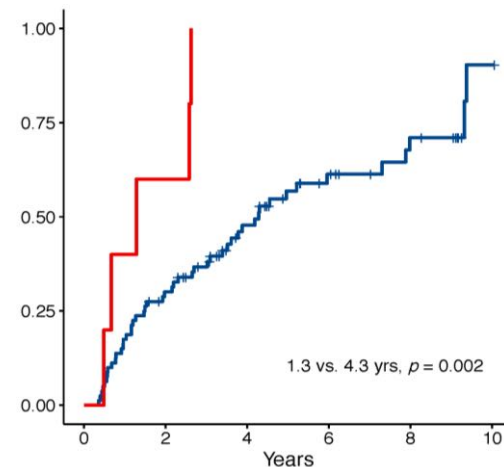
MAPK pathway mutations



Number at risk

WT	69	51	29	16	9	1
Mut	16	5	2	0	0	0

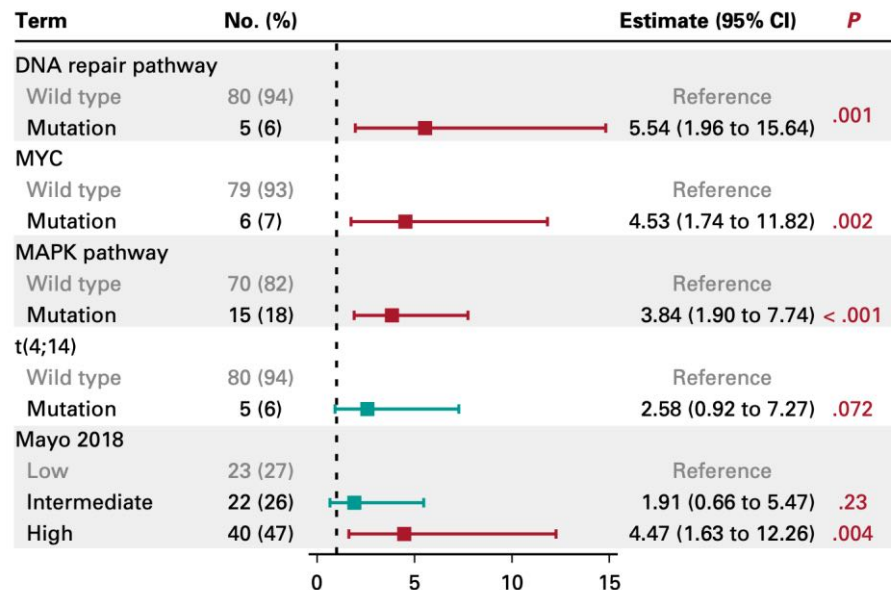
DNA repair alterations



Number at risk

0	80	54	31	16	9	1
1	5	2	0	0	0	0

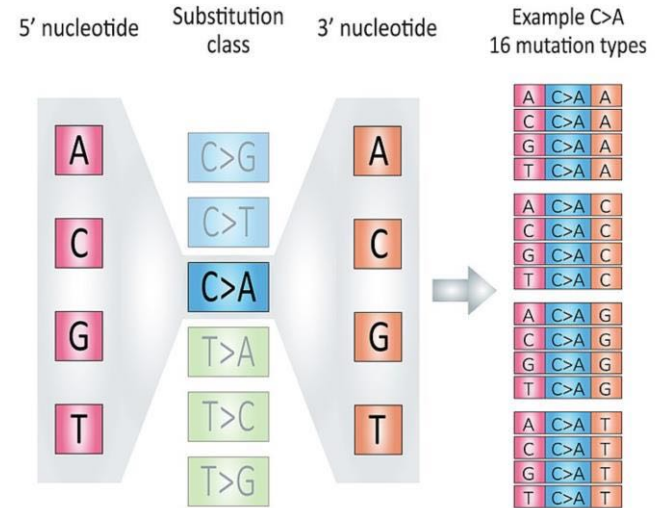
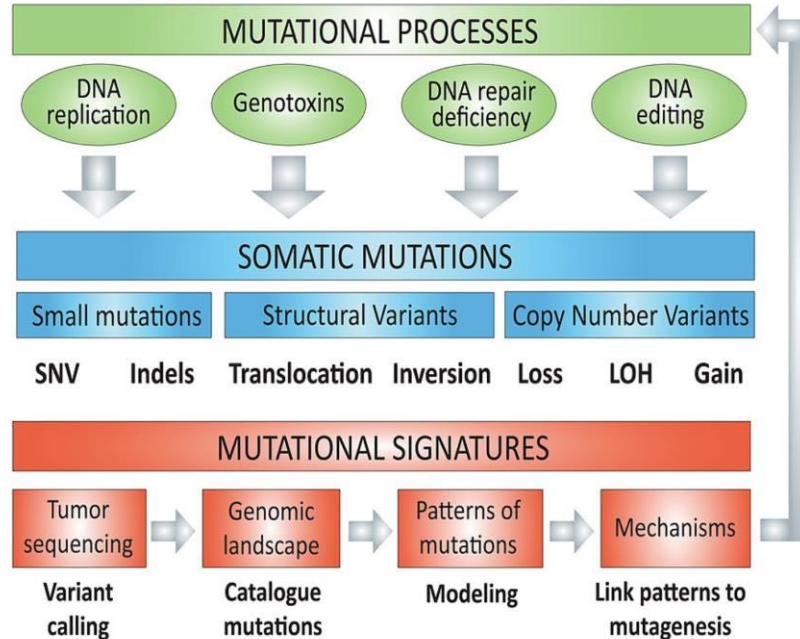
Genomic prognostication of SMM



	Likelihood Ratio		
Model	Test Statistic	χ^2 P	C-Statistic (95% CI)
Primary cohort			
Mayo 2008	32.02	< .001	0.66 (0.57 to 0.74)
Mayo 2008 + genetic model			0.75 (0.65 to 0.86)
Mayo 2018	20.46	< .001	0.72 (0.64 to 0.80)
Mayo 2018 + genetic model			0.77 (0.70 to 0.85)
Validation cohort			
Mayo 2008	12.62	< .001	0.57 (0.47 to 0.67)
Mayo 2008 + genetic model			0.66 (0.56 to 0.76)
Mayo 2018	10.19	.001	0.61 (0.49 to 0.74)
Mayo 2018 + genetic model			0.67 (0.56 to 0.77)

Mutational signatures

IDENTIFICATION OF MUTATIONAL SIGNATURES



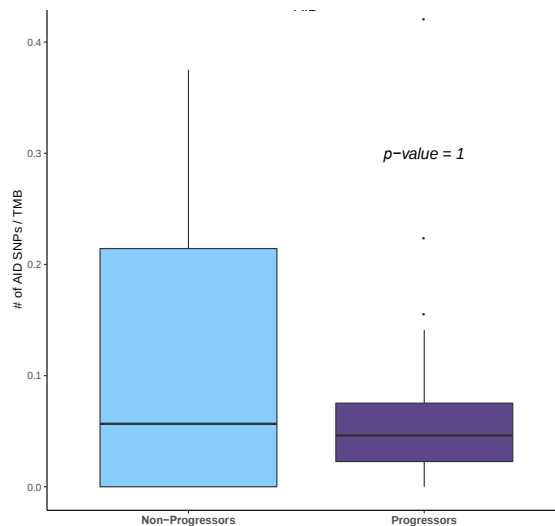
Myeloma :

- aging
- AID
- APOBEC

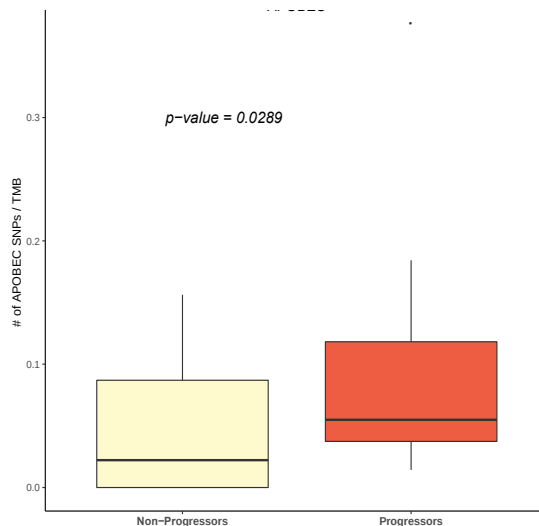
The impact of mutational signatures in SMM

Mutational signatures

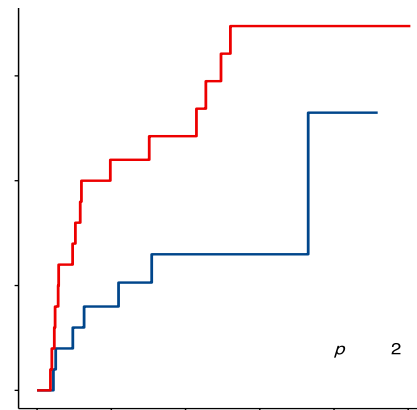
AID mutational signatures



APOBEC mutational signatures

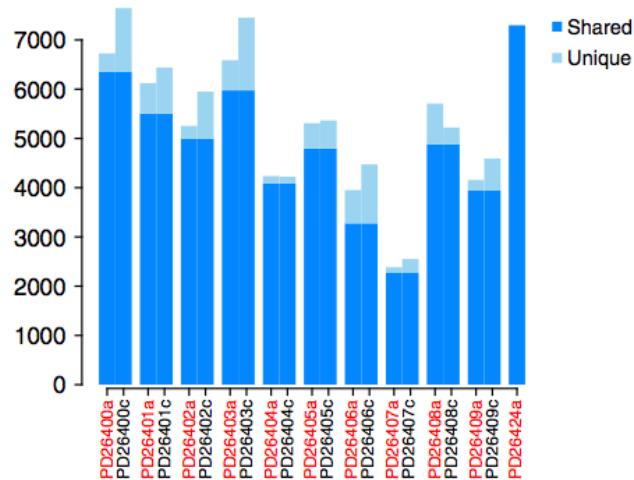


APOBEC mutational signatures

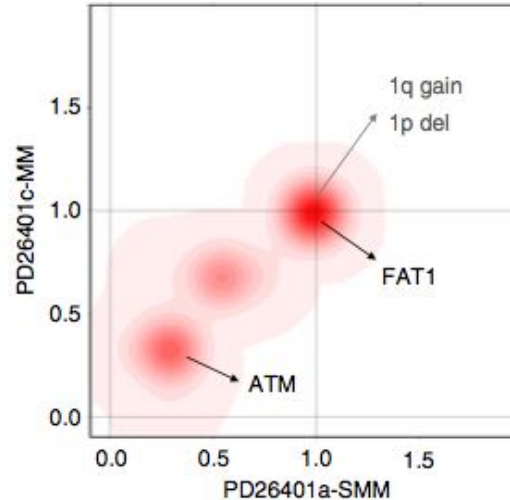


Clonal evolution of SMM

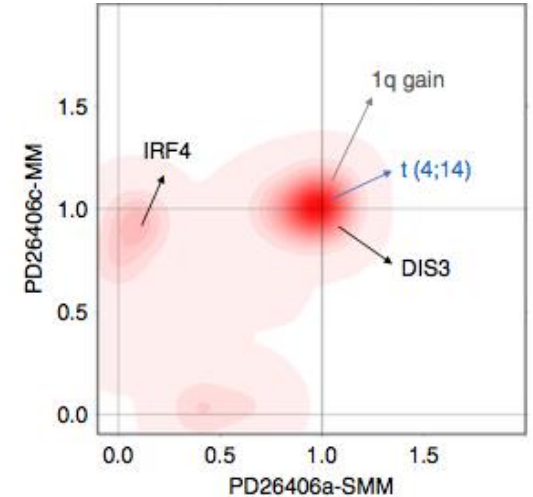
10 sequential WGS – SMM/MM



4/10 cases: linear evolution
mTTP = 5.5 months

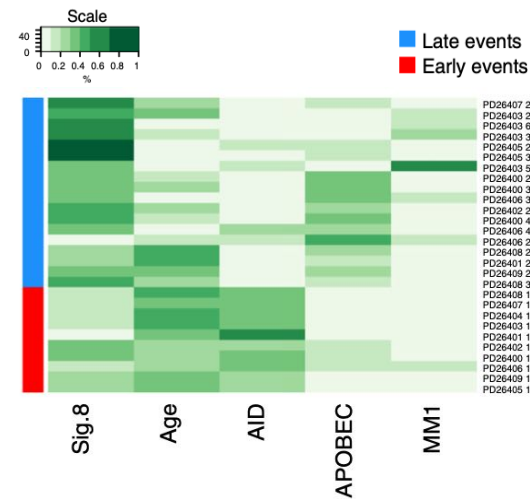
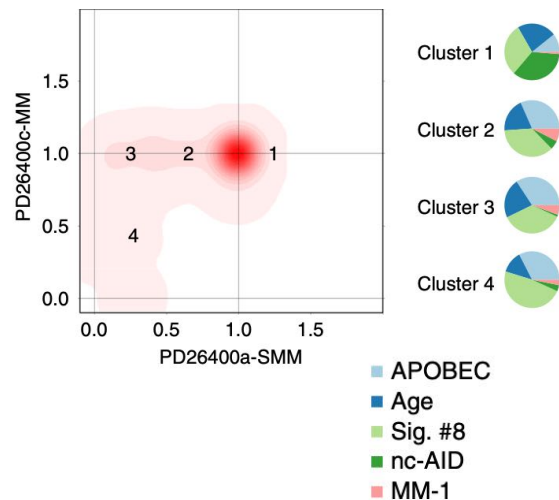
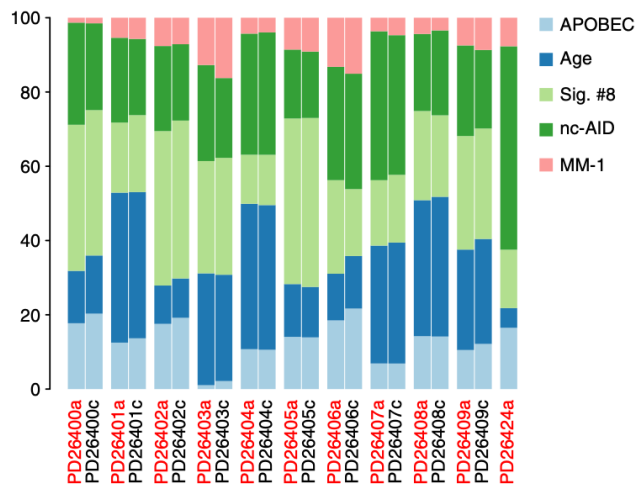


6/10 cases: branched evolution
mTTP = 23 months

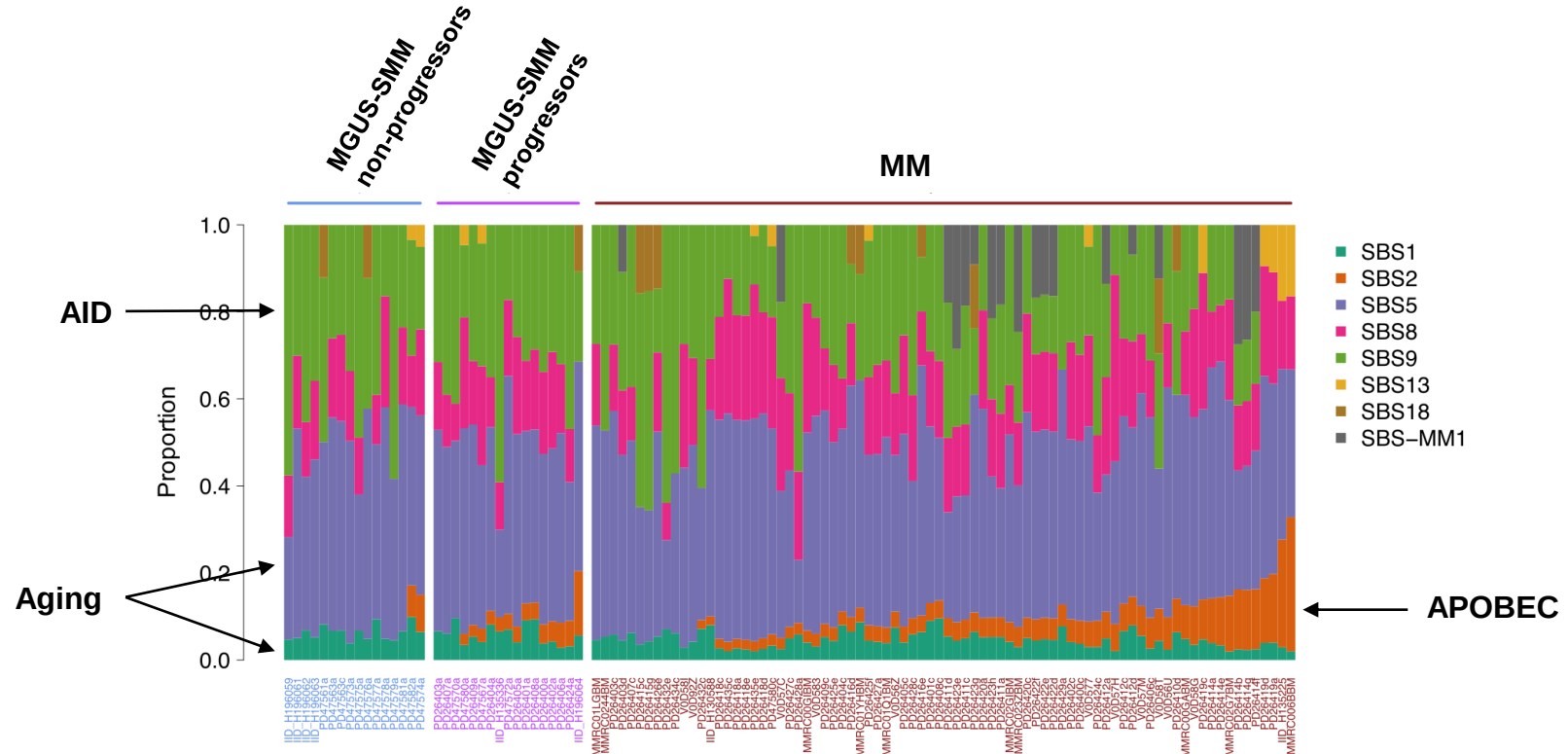


Clonal evolution of SMM

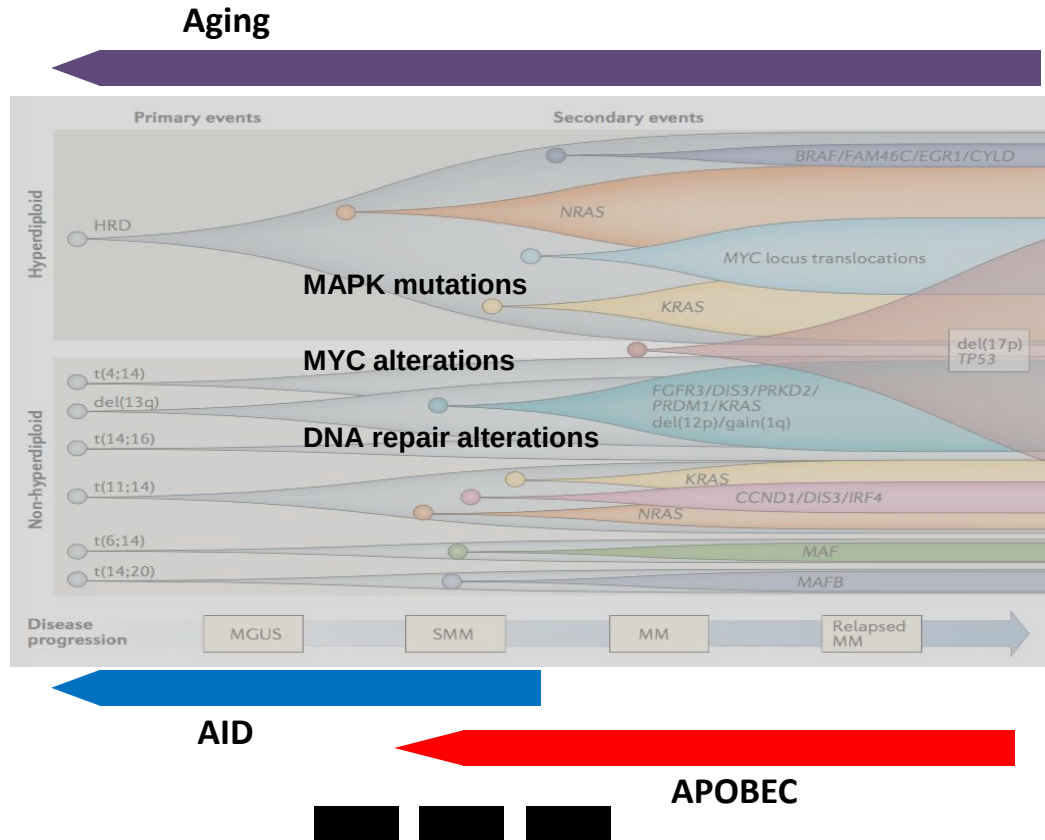
10 sequential WGS – SMM/MM Evolution of mutational signatures



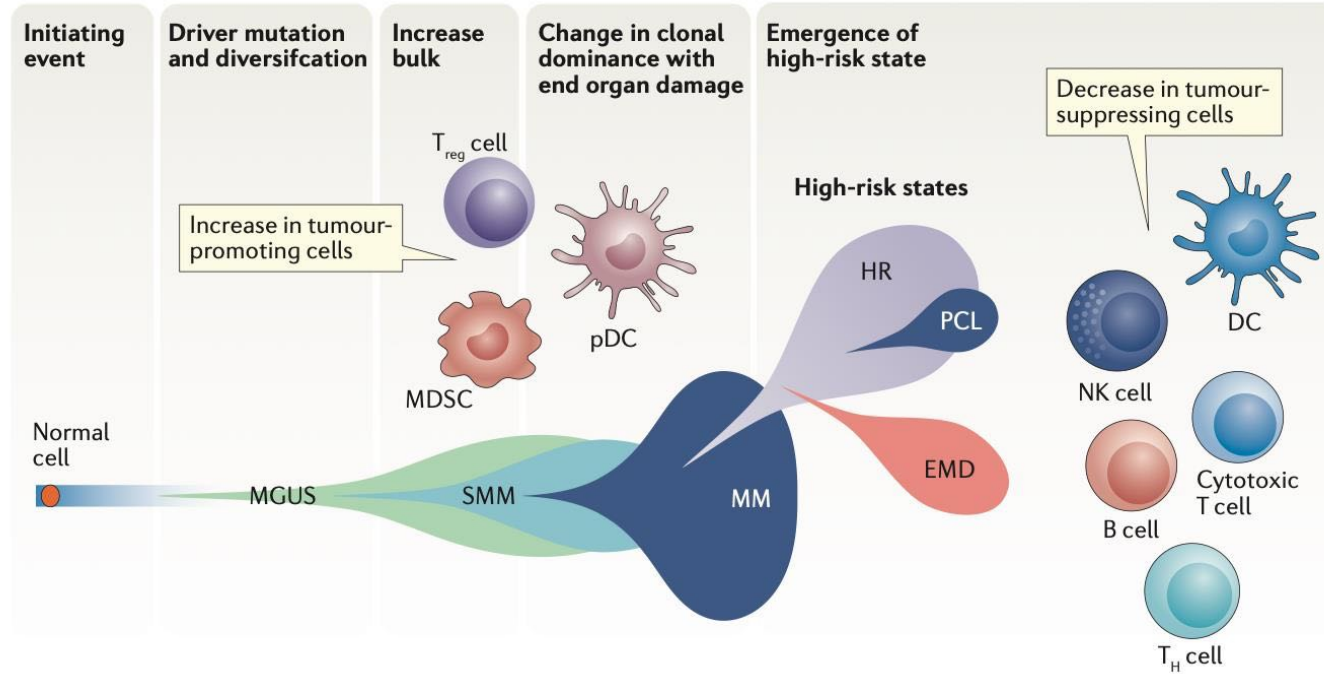
The impact of mutational signatures in SMM



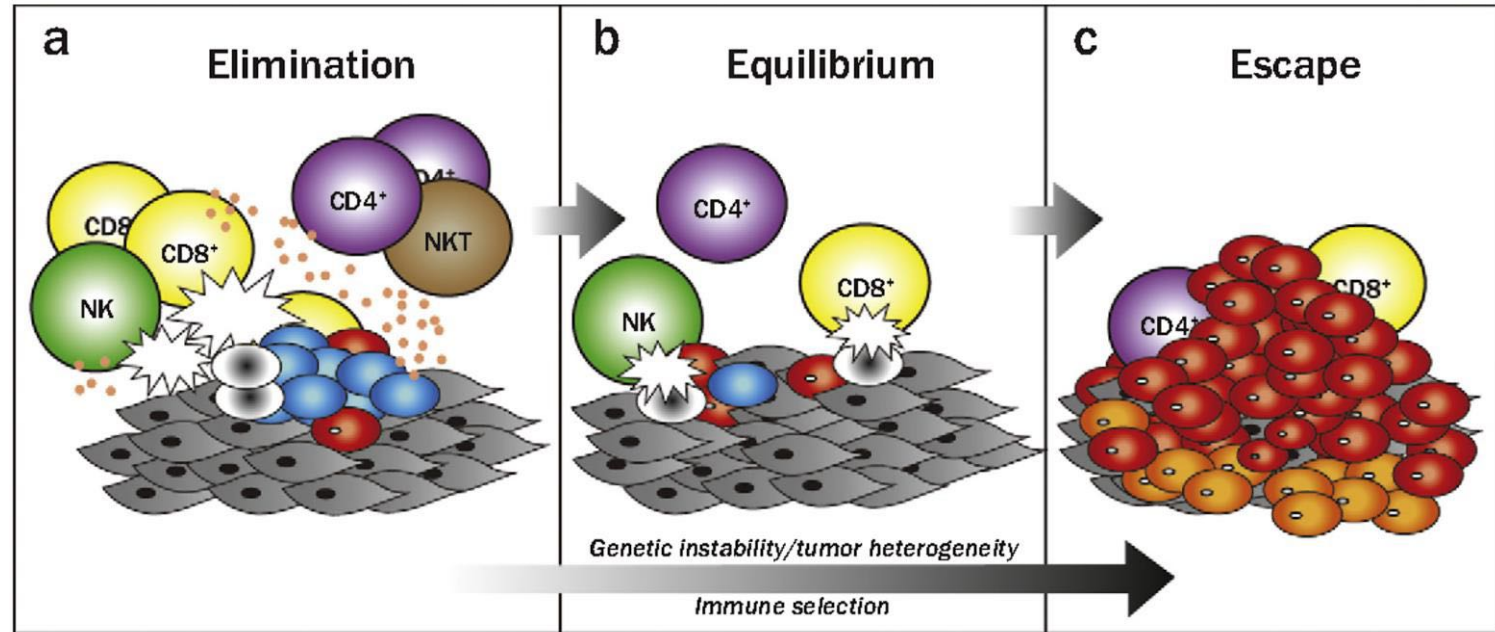
Genomic landscape of SMM



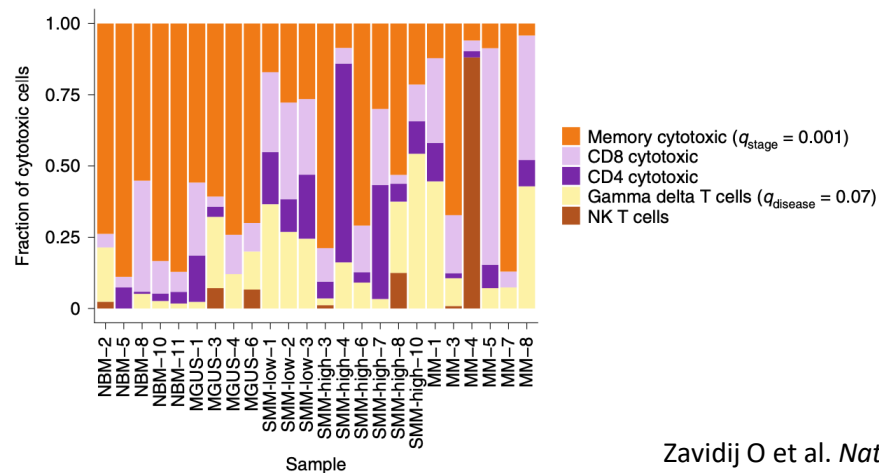
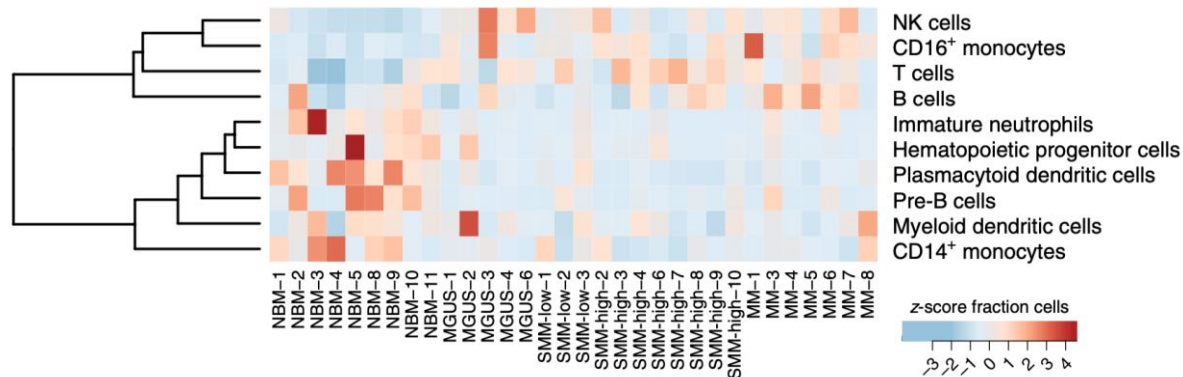
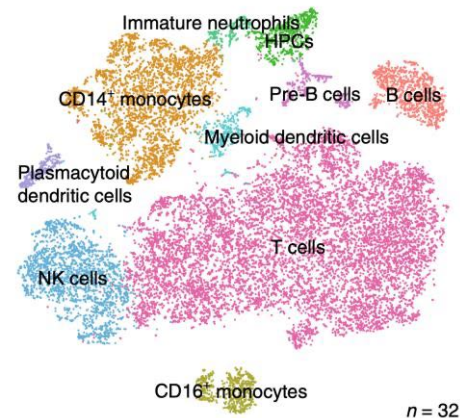
Immune evolution in MM



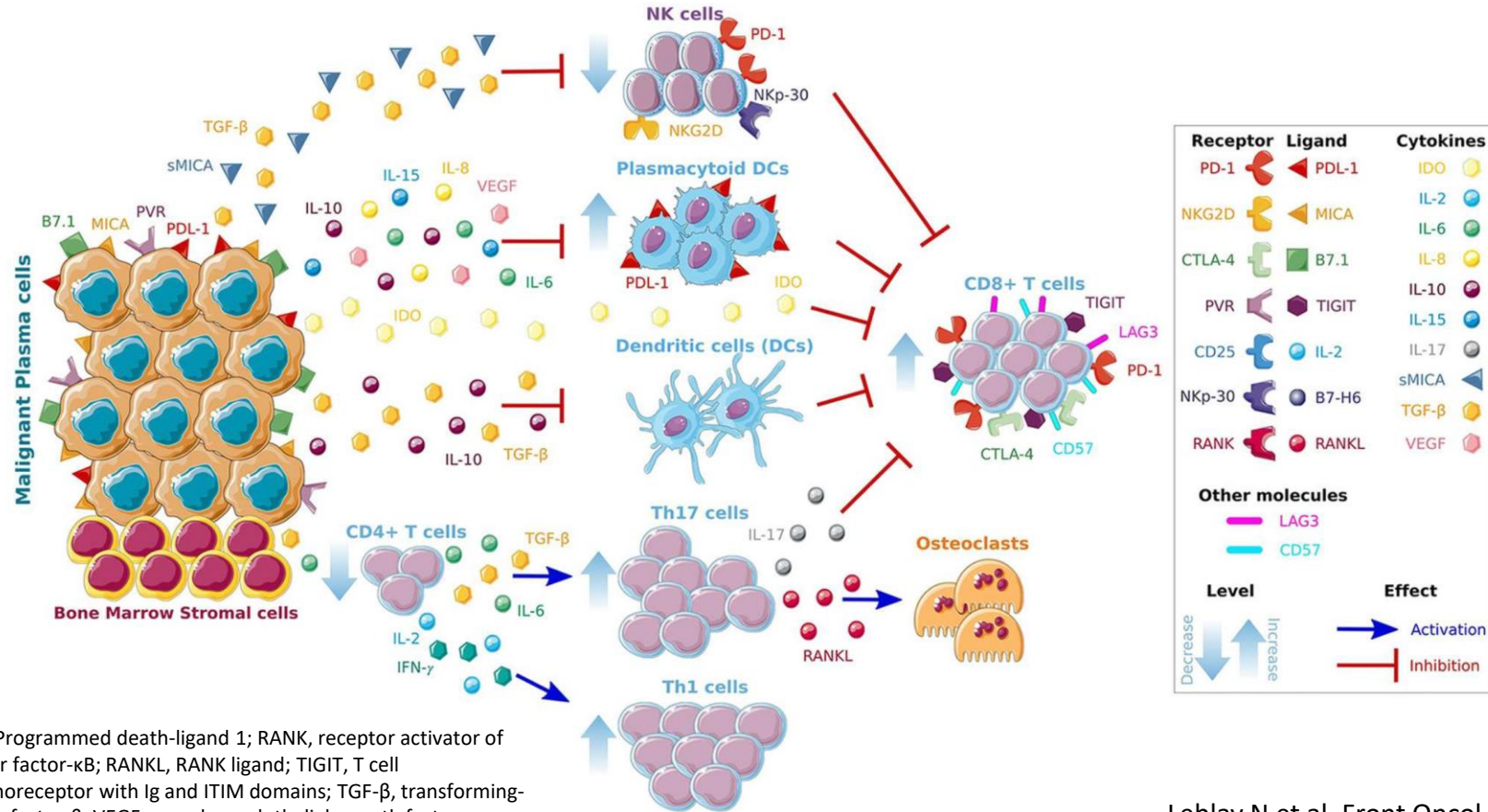
Mechanism of immune escape in cancer



Modification of immune microenvironment in MM

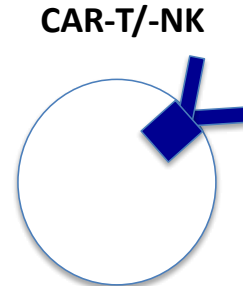
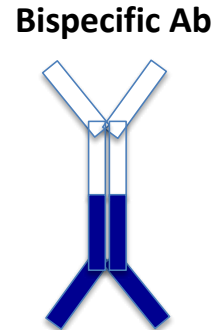
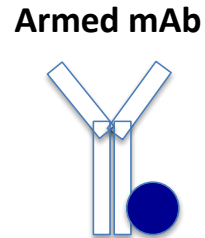
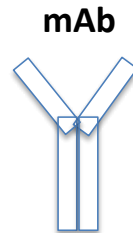
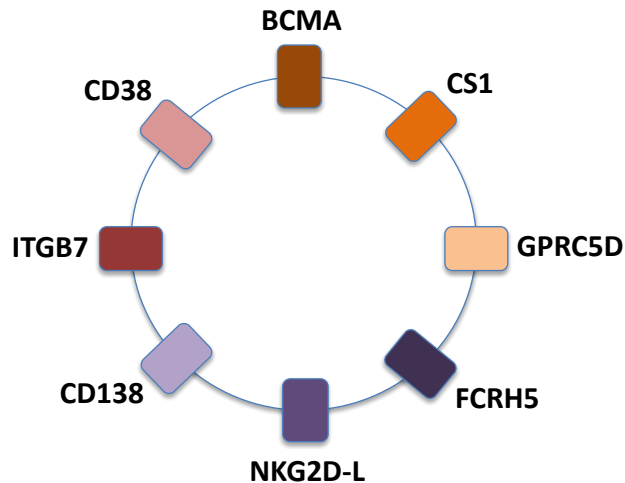


Immune deregulation in MM



PD-1, Programmed death-ligand 1; RANK, receptor activator of nuclear factor- κ B; RANKL, RANK ligand; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TGF- β , transforming-growth factor- β ; VEGF, vascular endothelial growth factor

Immunotherapies in MM



- **ADC :** Belantamab
MEDI2228

- **Bispecifics:** AMG420, AMG701
Teclistamab
Talquetamab
Elranatamab
REGN5458
TNB-383B
CC-93269
BFCR4350A

- **CAR-T:** ide-cel
cilta-cel
orva-cel
bb21217
p-BCMA-101
CT053
ALLO715

Conclusions

- Myeloma oncogenesis:
 - Primary events (HRD & IGH transloc)
 - Secondary events (MAPK, MYC, DNA repair)
 - Aging and AID mutational processes are implicated in early genomic events
 - APOBEC deregulations participate to the rise of subclones driving progression
 - Modification of the immune micro-environnement during myeloma evolution leading to a decrease ratio of memory cytotoxic T cells
-
- **Implication to scoring system ?**
 - **Early intervention to prevent progression ?**