GIORNATE EMATOLOGICHE VICENTINE

XI edizione

9-10 Ottobre 2025
Palazzo Bonin Longare - Vicenza

Come definisco il mieloma ad alto rischio nel 2025

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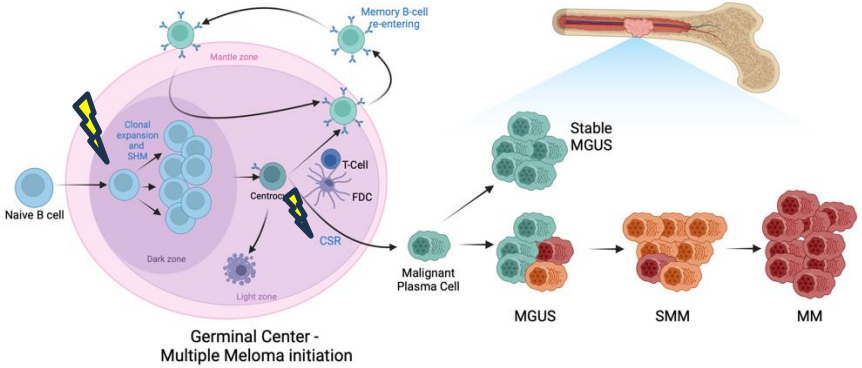
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Johnson & Johnson	x		x		x	x	
Pfizer	x				x	x	
Takeda						x	
GSK			X		X		
Sanofi					X	X	
IGI	X		X				
Menarini					X	X	

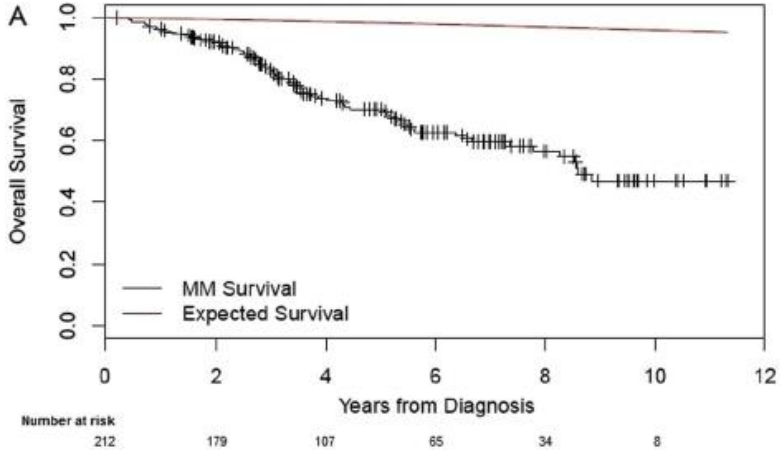
Mutiple Myeloma is a highly hetergenous disease

Biology



Adapted from Maura *et al.* – Hematol Oncol Clin N Am 2024.

Clinics



Ravi et al, BCJ, 2018

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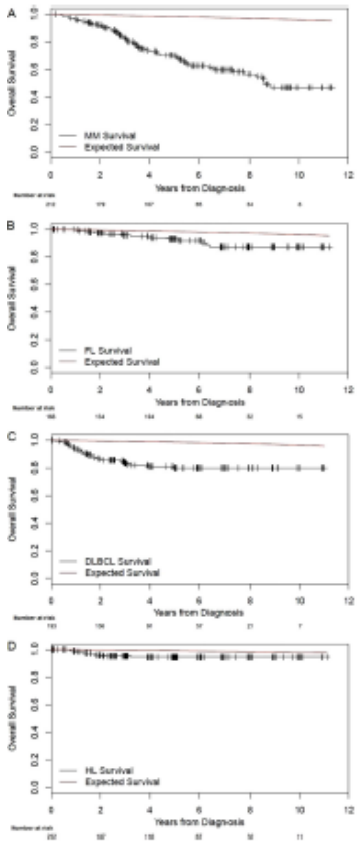

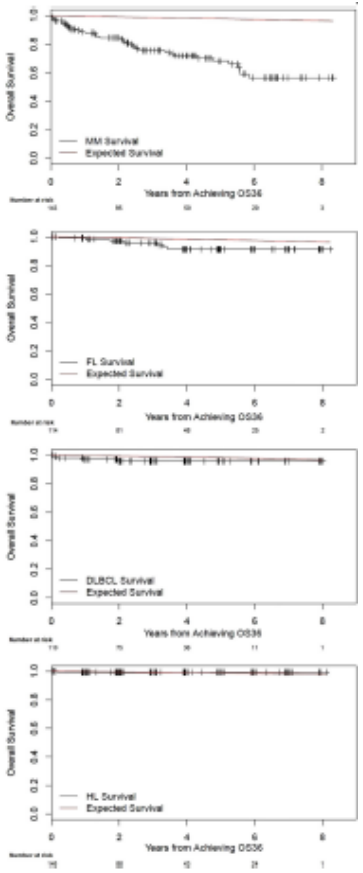

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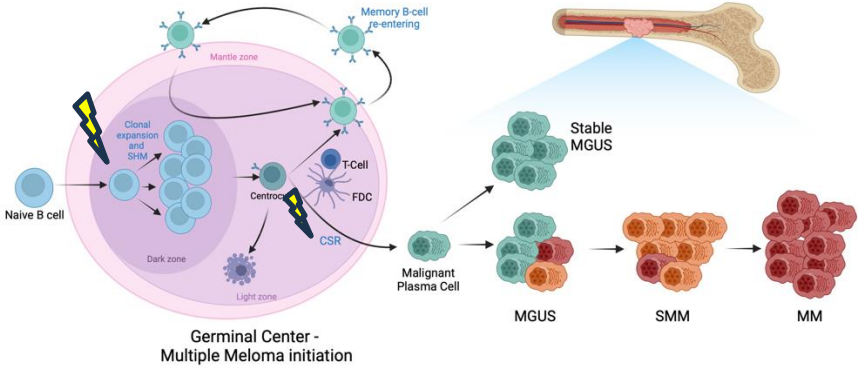

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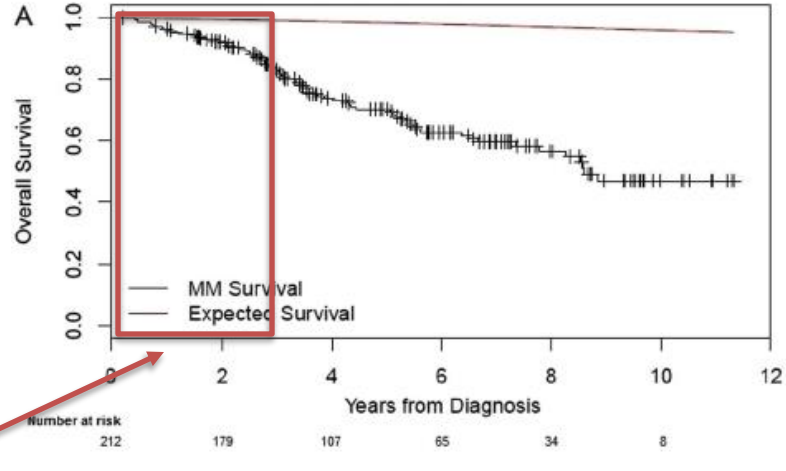

The definition of high-risk/UltraHR patients still represents unmet clinical need

Ravi et al, BCJ, 2018

Broad definition of HR Multiple Myeloma

Prognostic factors			
Patient-related	**Disease burden-related**	**Disease biology-related**	**Therapy-related**
Age	High B_2 microglobulin*	Cytogenetic abnormalities	Quality of response
Performance status	Low albumin*	GEP	Early relapse
Comorbidities	Renal impairment	Circulating PCs	
	LDH above ULN	EMD	
		High proliferation rate	

Zamagni et al., Blood 2022

Broad definition of HR Multiple Myeloma

Different strategies of risk stratification

	Serum features	Genomic features	Proposed clinical definition of high risk:	% defined as high risk	Definition of high risk	Outcomes based on risk	Additional important notes
ISS [3]	Serum β2-microglobulin Serum albumin	None	NA[a]	33.6%	ISS stage III: Serum β2-microglobulin >5.5 mg/L	Median OS (months) • Stage I: 62 • Stage II: 45 • Stage III: 29	B2-microglobulin: indicative of increased tumor burden and declining renal function Serum albumin: driven by inflammatory cytokines such as IL-6 and the bone marrow microenvironment
R-ISS [2]	LDH Serum β2-microglobulin Serum albumin	del(17p)[b] t(4;14) t(14;16)	NA[c]	10%	ISS stage III and either high-risk CA by iFISH or high LDH	5-year OS: • Stage 1: 82% • Stage 2: 62% • Stage 3: 40%	Stage 3 patients have a median PFS of 29 months and median OS of 37 months [54]
IMWG [5]	Serum β2-microglobulin Serum albumin	del(17p)[b] t(4;14) +1q21	Median OS <2 years	20%	ISS II/III and t(4;14) or 17p13 del by iFISH	Median OS: • Low risk: >10 years • Standard risk: 7 years • High risk: 2 years	High-risk group with a 4-year PFS of 12% and OS of just 35% Low-risk group consists of ISS I/II and absence of t(4;14), 17p13 del or +1q21 and age <55 years
mSMART [55]	LDH Serum β2-microglobulin Serum albumin	Ploidy status t(4;14) t(14;16) t(14;20) t(11;14) t(6/14) del(17p) and p53 deletion deletion 13 gain 1q GEP	NA[d]	20%	High-risk genetic Abnormalities • t(14;16); t(14;20); • Del17p or p53 mutation GEP: high-risk signature	Median OS: • High risk: 3 years • Intermediate risk: 4–5 years • Standard risk: 8–10 years	• Trisomies may ameliorate high-risk genetic abnormalities • High plasma cell S-phase also defines high risk: cutoffs vary • Standard risk includes all others including trisomies, t(11;14), and t(6;14) • t(4;14): re-classified as intermediate risk
EMC92/SYK92 –MMprofiler [30]	None	High-risk survival signature of 92 genes[e]	Median OS <2 years	18–20%	Two-tiered system of high and standard risk	Reduced OS with HR of 2.06 to 5.23 in validation cohorts amongst the TT2, TT3, APEX, and MRC-IX studies	In multivariate analyses, the signature was proven to be independent of the currently used prognostic factors
UAMS GEP70 or MyPRS [28]	None	High-risk survival signature of 70 genes[e]	"early disease-related death"	13–14%	Two-tiered system of high and standard risk	HR for high v standard-risk GEP: • EFS: 3.41 ($P = 0.002$) • OS: 4.75 ($P<0.001$)	Standard-risk patients with a 5-year continuous complete remission of 60% vs. 3-year rate of only 20% in those with a high-risk "Early disease-related death" definition not clear in the primary literature
CoMMpass [19]	LDH	[f]TP53 mutation λ-chain translocation IGLL5 mutation	Time to progression (TTP) of < 18 months	20.6%	TTP < 18 months: high-risk TTP >18 months: low risk	Median OS in months: • High risk: 32.8 • ISS III: 54 • Baseline high-risk CA: 65	TTP 18-month cutoff chosen because time to ASCT was ~6 months and many MM studies define early PD as relapse within 12 months from ASCT
	Serum features	**Genomic features**	**Proposed clinical definition of high risk:**	**% defined as high risk**	**Definition of high risk**	**Outcomes based on risk**	**Additional important notes**
Myeloma Genome Project [6, 17]	Serum β2-microglobulin Serum albumin	TP53 inactivation +1q amp	NA[g]	6.1%	Biallelic TP53 inactivation or amp of CKS1B (1q21) on the background of ISS stage III	High risk: • Median PFS: 15.4 months • Median OS: 20.7 months	1q amplification considered ≥ 4 copies LDH values were not universally available preventing the calculation of R-ISS thus ISS and IMWG risk criteria were used
Cytogenetics Prognostic Index [9]	None	del(17p) t(4;14) del(1p32) 1q21 gain trisomies 3, 5, and 21	NA	11–18%	Prognostic Index >1 defined high risk[h]	5-year survival: • High risk: <50% • Int risk: 50–75% • Low risk: >75%	The main objective was to develop and validate a prognostic model based on the seven cytogenetic abnormalities

Hagen et al, Blood Canc J. 2022

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Hagen et al, Blood Canc J. 2022

R2-ISS

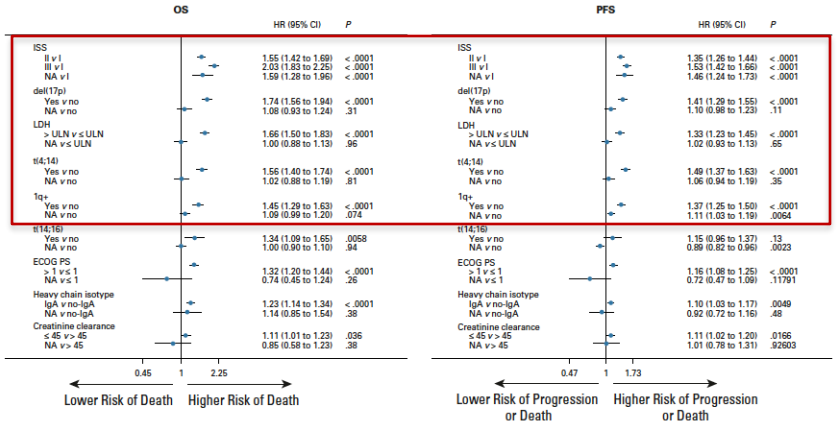
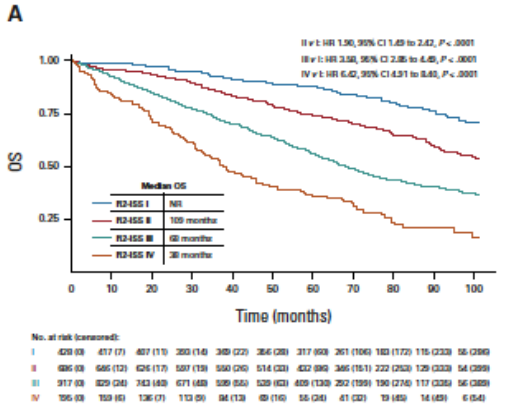
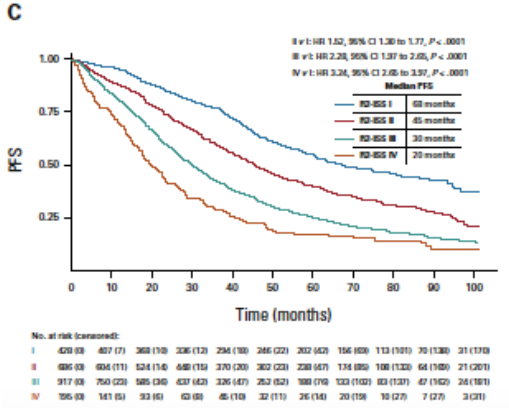


TABLE 2. R2-ISS Score Definition on the Basis of the Evaluable Patients Included in the Training Set (n = 2,226)

Risk Feature	OS HR (95% CI)	PFS HR (95% CI)	Score Value[a]
ISS II	1.75 (1.49 to 2.05)	1.43 (1.28 to 1.61)	1
ISS III	2.53 (2.13 to 3.01)	1.76 (1.54 to 2.01)	1.5
del(17p)	1.82 (1.53 to 2.17)	1.43 (1.23 to 1.65)	1
LDH high	1.60 (1.36 to 1.88)	1.37 (1.20 to 1.57)	1
t(4;14)	1.53 (1.29 to 1.81)	1.40 (1.21 to 1.62)	1
1q+	1.47 (1.29 to 1.68)	1.33 (1.20 to 1.48)	0.5

Group	No. (%)	Total Additive Score
Low (I)	428 (19)	0
Low-intermediate (II)	686 (31)	0.5-1
Intermediate-high (III)	917 (41)	1.5-2.5
High (IV)	195 (9)	3-5



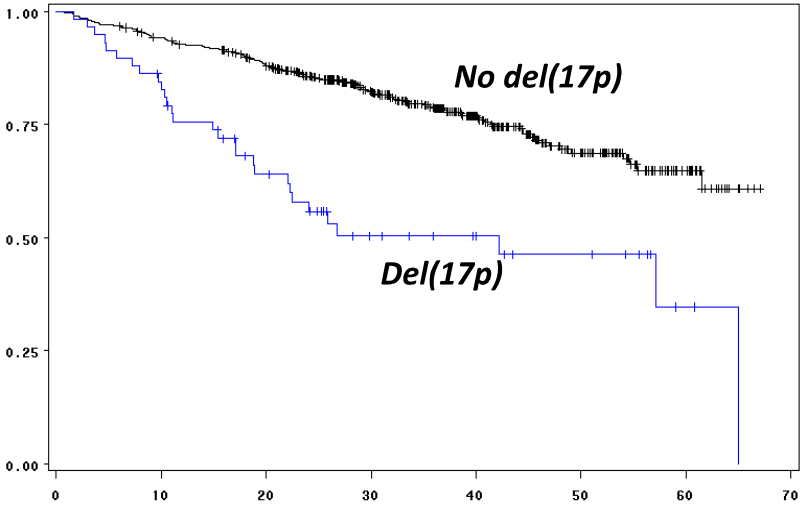


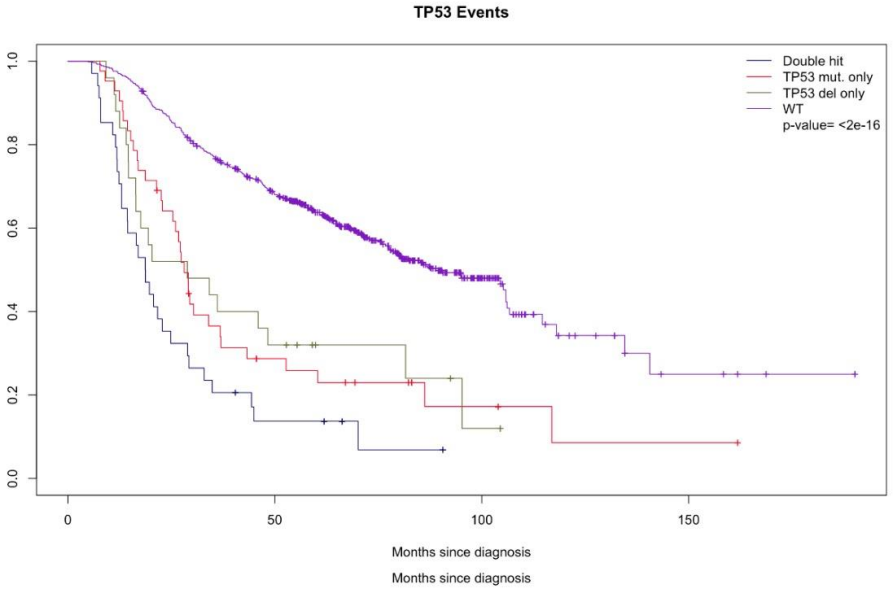
D'agostino et al., JCO, 2022

Unmet need: a consensus defition of HR myeloma

Deletion 17p and TP53 mutations

8% of newly diagnosed myeloma patients





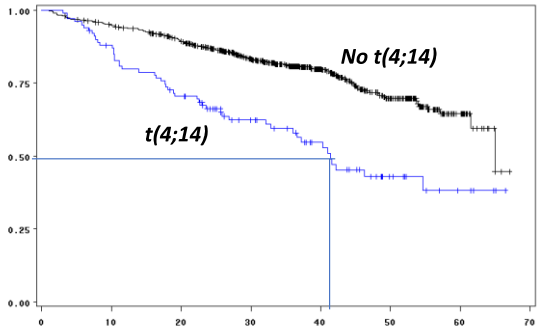
Avet-Loiseau et al., JCO, 2025

Deletion 17p and TP53 mutations

- Incidence – approx 8% each
- Isolated del17p performs poorly. In multi-variant analysis definitely an independent variable
  - Using iFISH there is a dosage response in outcome based on clonal fraction.
  - Greatest effect seen over 60% but sill significance over 20%
  - Most trials do not report the cut off values – this should be mandatory moving forward
  - Moving forward clonal fraction should be >20%
- Biallelic events perform very poorly (either deletion and mutation or both alleles deleted)
- Mutation alone also performs similar to isolated del17p
- Mutation should be included in all trials moving forward
- In R-ISS del17p is not automatically Stage III – this needs to be updated
- At relapse
  - Generally events are enriched
  - Prognosis remains poor

t(4;14), t(14;16), t(14;20)

12-15% of patients

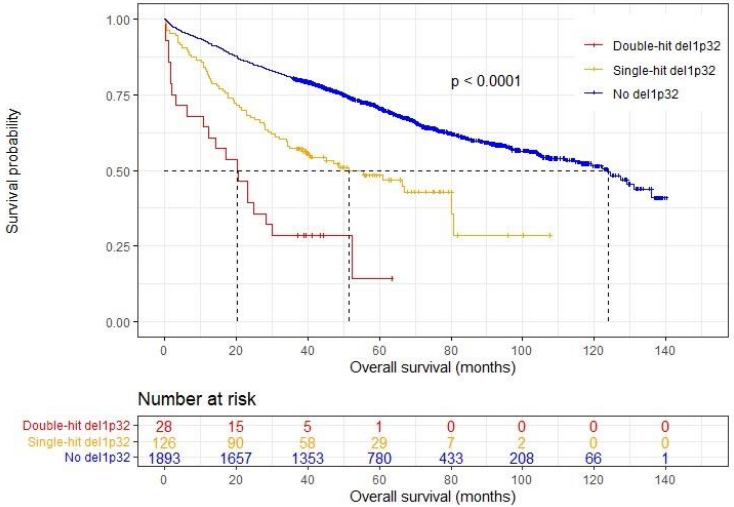


Avet-Loiseau H et al, Blood 2007

- Biology driven by the translocation is important
- Data suggests that t(4;14) on its own is not prognostic
  - About 60% of t(4;14) have another lesion (17p, 1q and 1p) and these perform poorly
  - Preliminary data suggesting the breakpoint maybe important and potentially related to the NSD2 isoform (short isoform performs worse)
- MAF and MAFB are rare -4% overall
  - High occurrence of with other abnormalities (eg 1q and 17p) and APOBEC

Deletion(1p32)

- Incidence approx 5-15% NDMM and 20% of these have bi-allelic deletion
- Cut off 10-30%
- Prognostic in many data sets. In some, only prognostic if mono-allelic is combined with other factors e.g., 1q
- Biallellic deletion definitely poor risk (CDKN2A) – but only picked up with SNP array or NGS not FISH

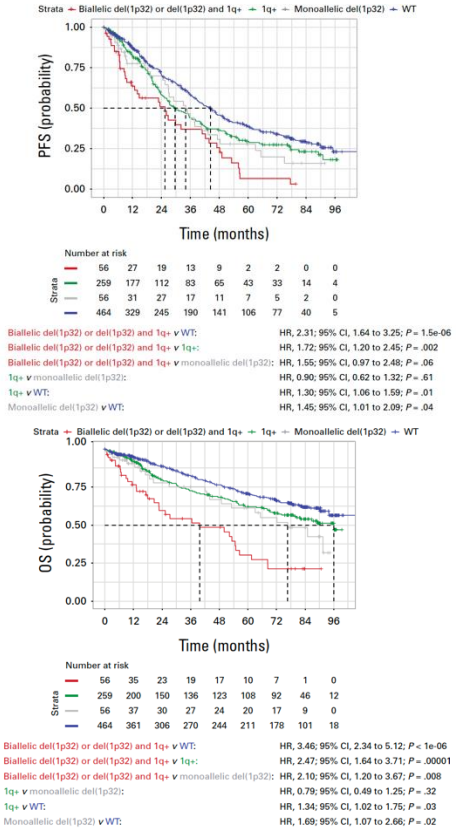


Schavgoulidze A, Blood 2022

Avet-Loiseau et al., JCO, 2025

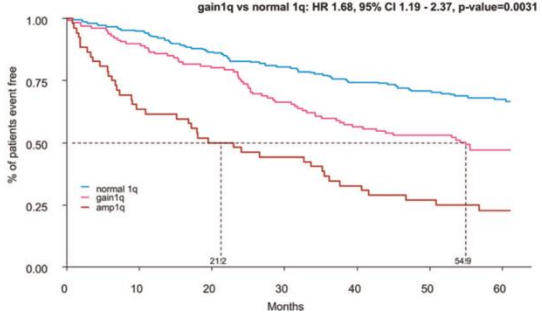
Gain / Amplification 1q

- Incidence - approx 30% NDMM
- Although patients with a 1q gain have a slightly inferior outcome in most studies, its major effect is in combination with other abnormalities.
- In some studies Amp1q alone has emerged as a high-risk abnormality and is often a sign of complex abnormalities. However, this is not consistent across studies and requires further validation.
- Therefore gain1q and amp1q is considered high-risk if in association with another abnormality

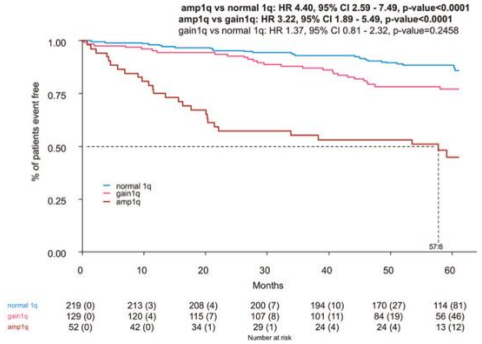


Gain / Amplification 1q

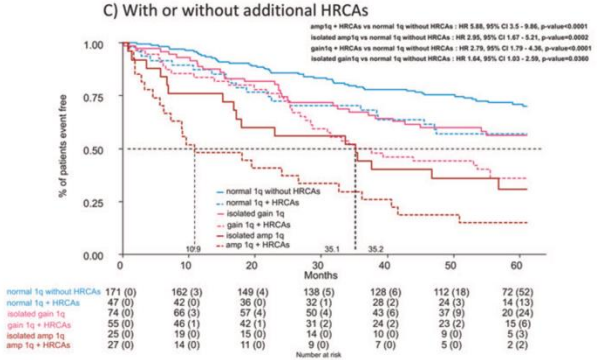
A) PFS



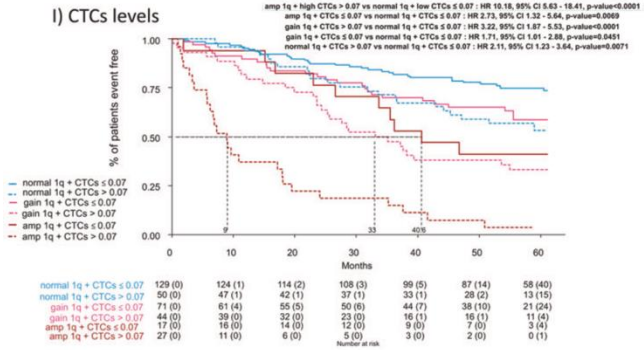
B) OS



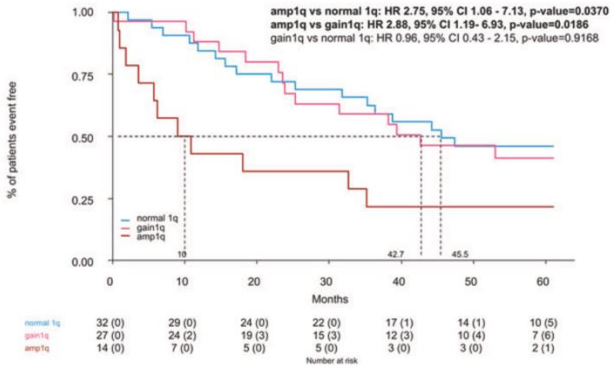
C) With or without additional HRCAs



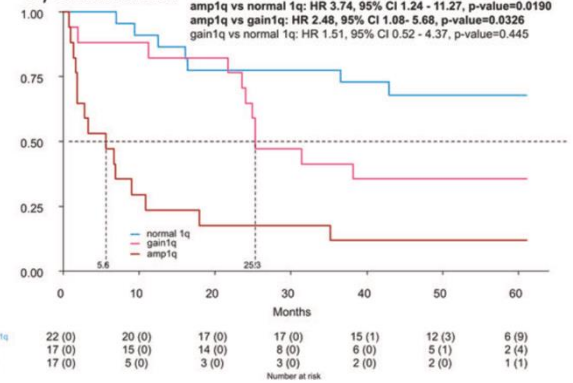
I) CTCs levels



F) ISS III



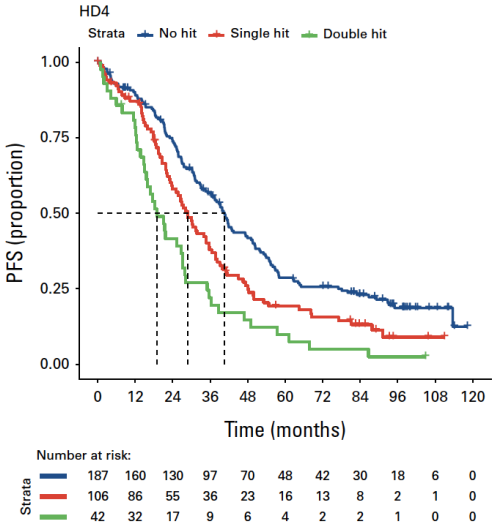
D) Elevated LDH



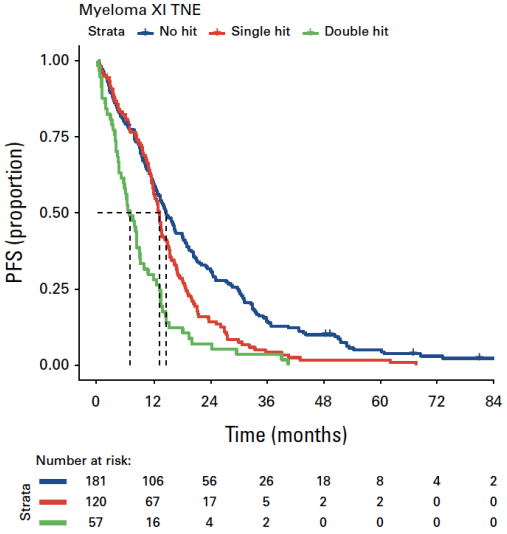
D'Agostino et al., BCJ 2024

Double/triple hit entities represents a very HR MM population with dimsal prognosis

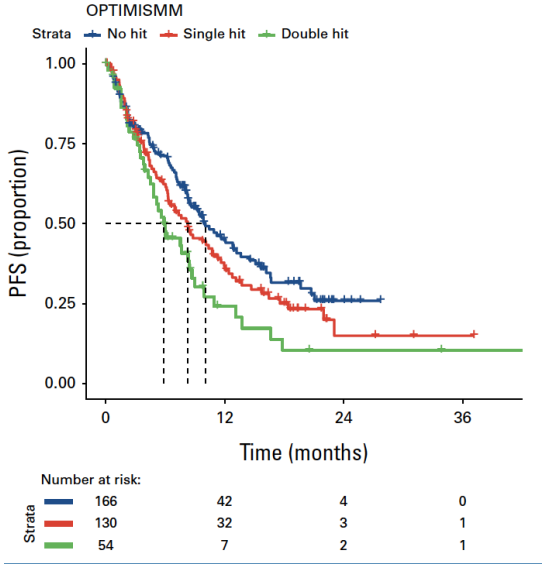
TE NDMM



NTE NDMM



RRMM



Curves separation was consistent in studies with treatment combinations with Pis, IMIDs and anti-CD38 monoclonal antibodies

Kaiser et al., JCO, 2025

Final consensus HR classification

- Del(17p) >20%
- TP53 mutation
- Biallelic del(1p32)
- t(4;14) or t(14;16) or t(14;20) AND either 1q gain/amp or monoallelic del1p32
- 1q gain/amp AND monoallelic del1p32

Avet-Loiseau et al., JCO, 2025

Final consensus HR classification

- Del(17p) >20%
- TP53 mutation

~50%

- Biallelic del(1p32)

~5%

- t(4;14) or t(14;16) or t(14;20) AND either 1q gain/amp or monoallelic del1p32
- 1q gain/amp AND monoallelic del1p32

~45%

TOT 100% HR patients

Avet-Loiseau et al., JCO, 2025

Consensus HR classification validation

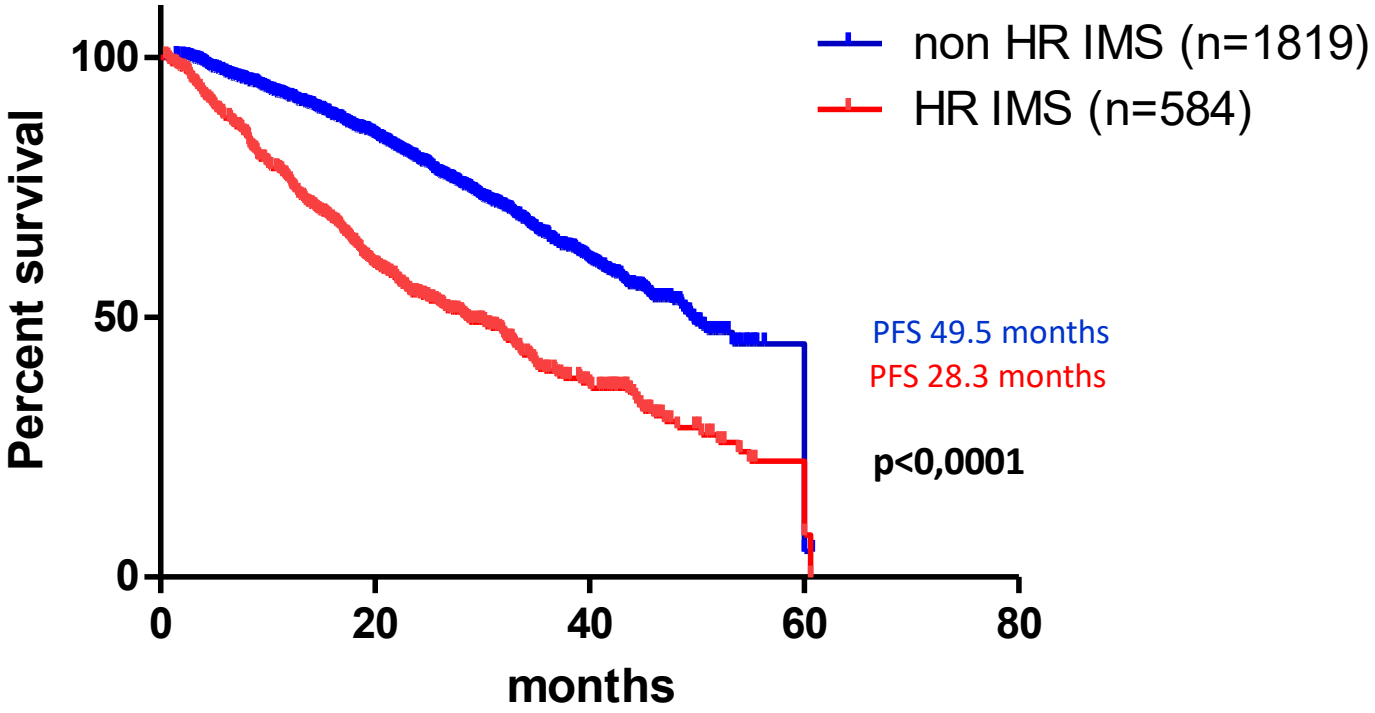
5602 NDMM with NGS
- 1250 HR IMS 22.3%
- 1117 HR IMWG 19.9%

	Non HR IMS	HR IMS	
Non HR IMWG	4161	324 (5.8%)	4485
HR IMWG	19 (3.4%)	925	1117
	4352	1250	**5602**

Conclusion: 515 patients (9.2%) reclassified
- 5.8% non HR IMWG become HR IMS
- 3.4% HR IMWG become non HR IMS

Avet-Loiseau et al., JCO, 2025

PFS according to IMS definition

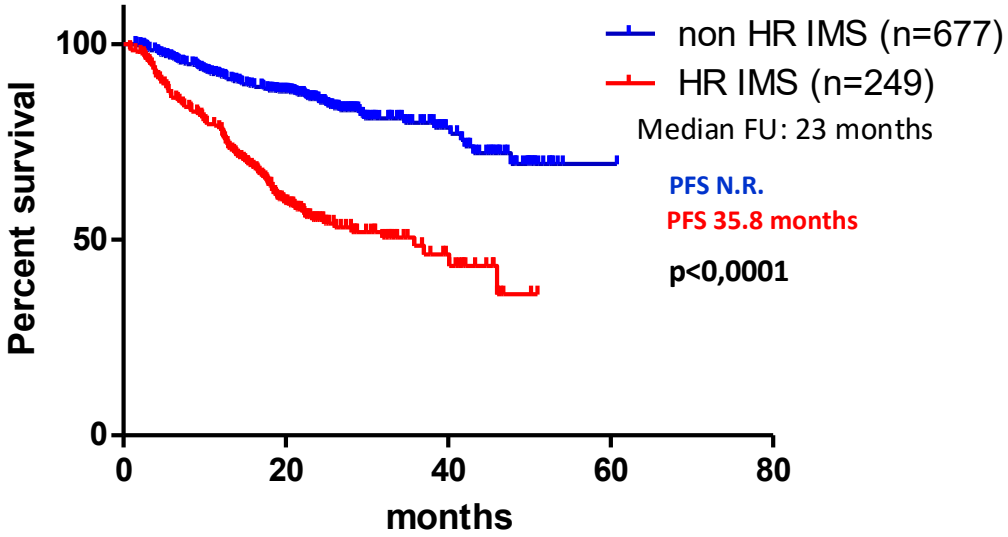


(Median FU : 31.7 months

Schavgoulidze et al., Blood, 2025

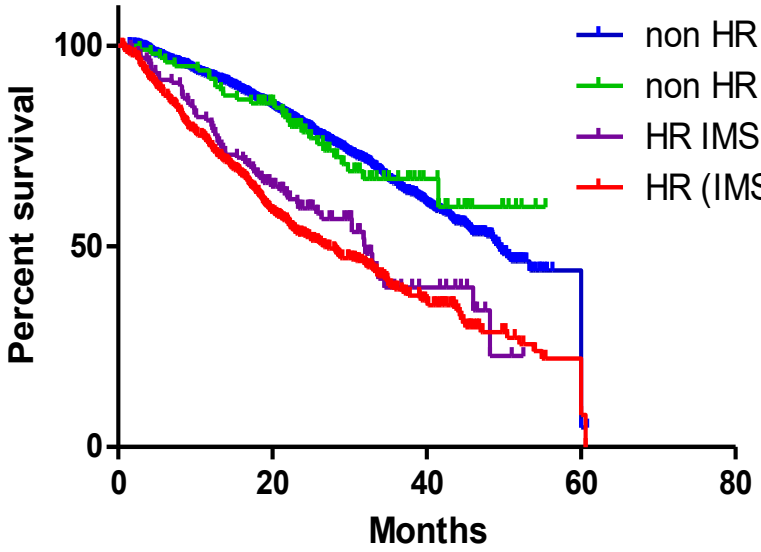
Consensus HR classification validation

PFS according to IMS in patients treated by anti-CD38



Schavgoulidze et al., Blood, 2025

PFS according to IMS and IMWG definitions



PFS 49.4 months
PFS N.R.
P=0.8

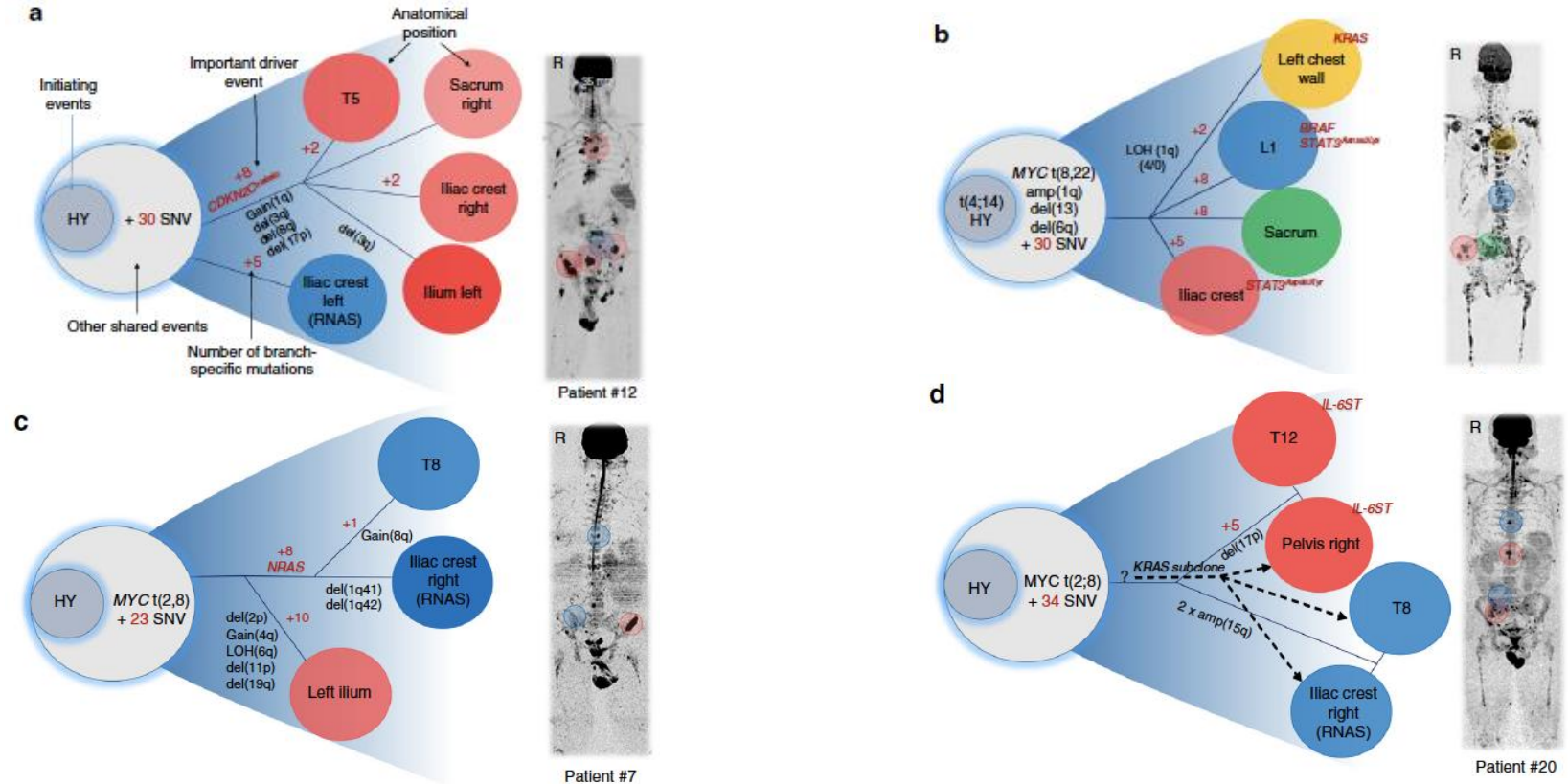
PFS 31.9 months
PFS 26.6 months
P=0.2

Schavgoulidze et al., Blood, 2025

Discussion points

- Not a definitive risk stratificaton: role of GEP, CTCs, EMD etc
- Not a molecular classification
- Likely unable to address all functional high-risk cases
- Role of beta-2 microglobulin still debatable (with normal kidney function)
- Will likely require the wide adoption of NGS
- A starting point needed to address HR in ad-hoc clinical trials, perform meta-analyses etc

Multiple Myeloma is a «patchy disease»



Rasche et al., Blood, 2025

For a better definition of HRMM we need to integrate different strategies:

- Intercept functional high risks
- Possible Biomarkers able to resolve spatial heterogeneity
- Static to dynamic evaluation

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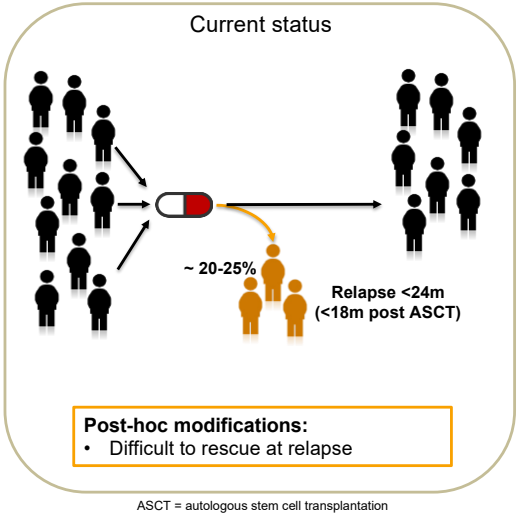
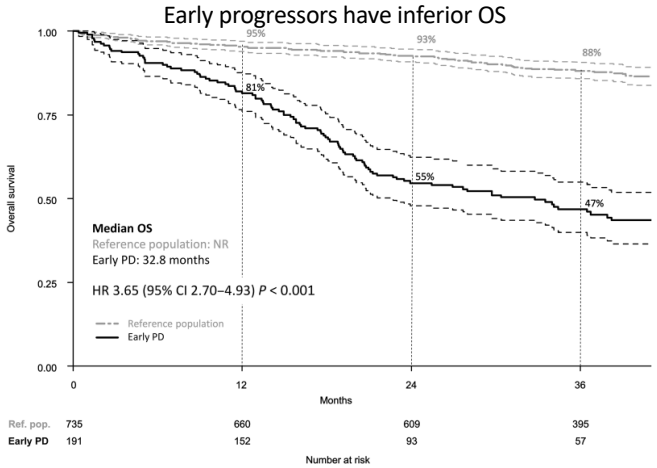
Functional High-risk MM patients

Fact: 20-25% of MM patients have poor outcome even in the era of novel treatments



ASCT = autologous stem cell transplantation

Courtesy of M. Kaiser



D'Agostino et al., Clin Can Res 2020

FHR patients are those exhibiting early progressive disease be best defined as relapse within 18 months of initiation of any first-line therapy.

A refined and integrated molecualr assessment could identify FHR patients

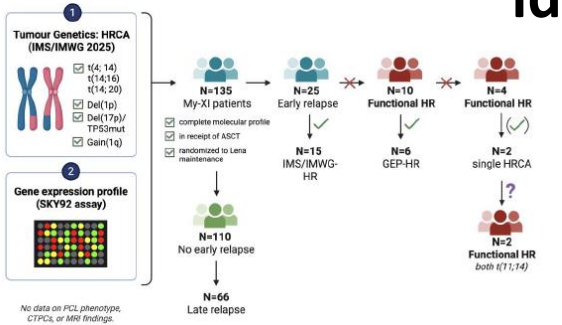
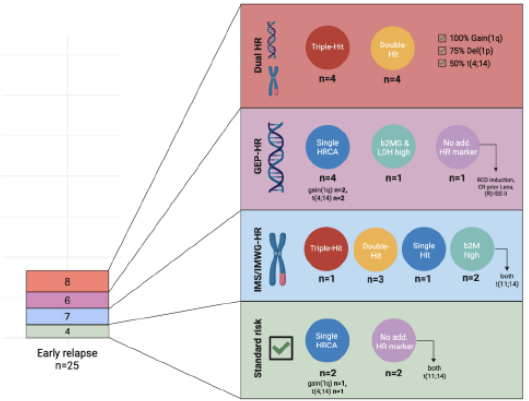
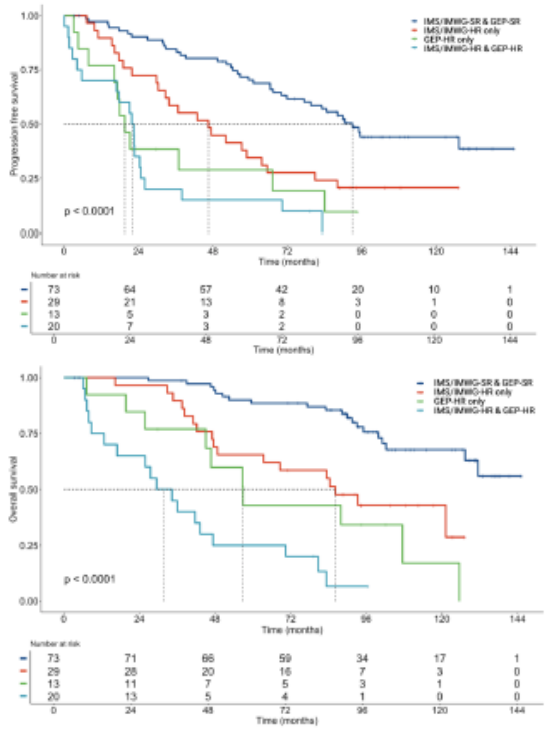


Figure 1B





Beer et al., Blood 2025

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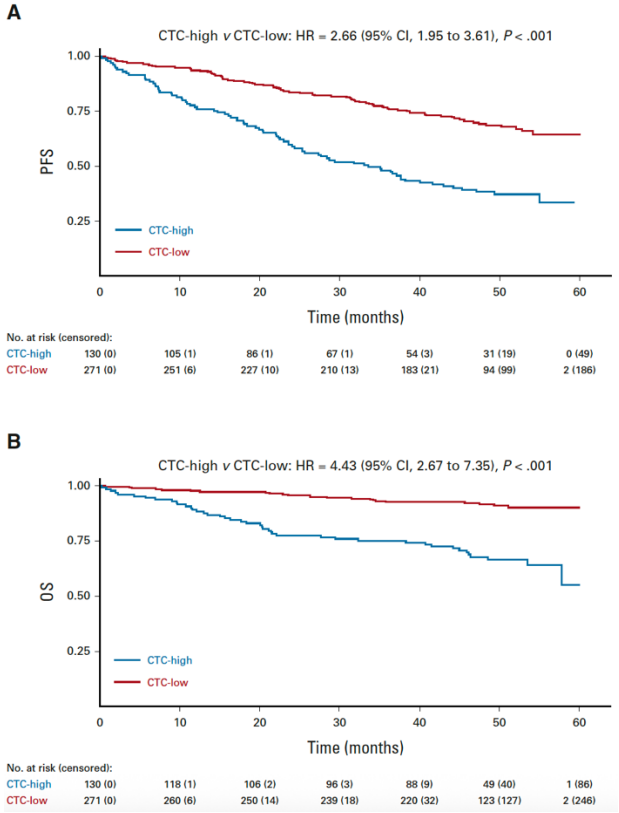
Circulating tumor cells (CTCs)



	PFS		OS	
Covariate	HR (95% CI)	P	HR (95% CI)	P
CTC cutoff				
CTC-high v CTC-low	2.11 (1.49 to 2.97)	< .001	2.61 (1.49 to 4.56)	< .001
ISS				
II/III v I	1.04 (0.74 to 1.46)	.812	1.08 (0.62 to 1.87)	.792
LDH				
High v low	2.22 (1.48 to 3.33)	< .001	4.77 (2.77 to 8.19)	< .001
CA				
High risk[a] v standard risk	1.33 (0.93 to 1.90)	.123	2.53 (1.43 to 4.48)	.001
amp(1q)				
Yes v no	2.03 (1.42 to 2.91)	< .001	1.94 (1.06 to 3.54)	.030
Depth of response				
MRD NEG v POS[b]	0.53 (0.37 to 0.75)	< .001	0.41 (0.23 to 0.73)	.002

Bertamini et al., JCO 2022
Garces et al., Hemasphere, 2025

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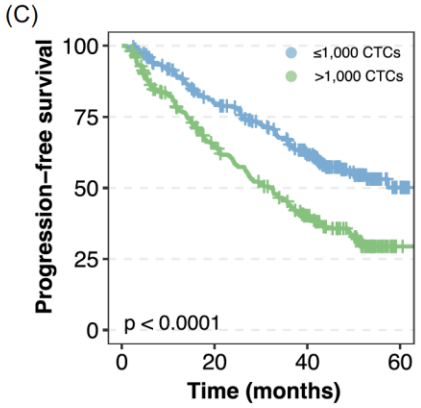
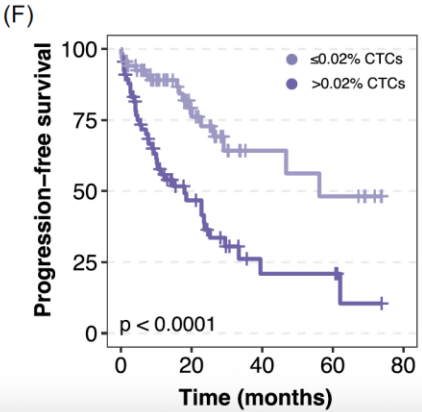
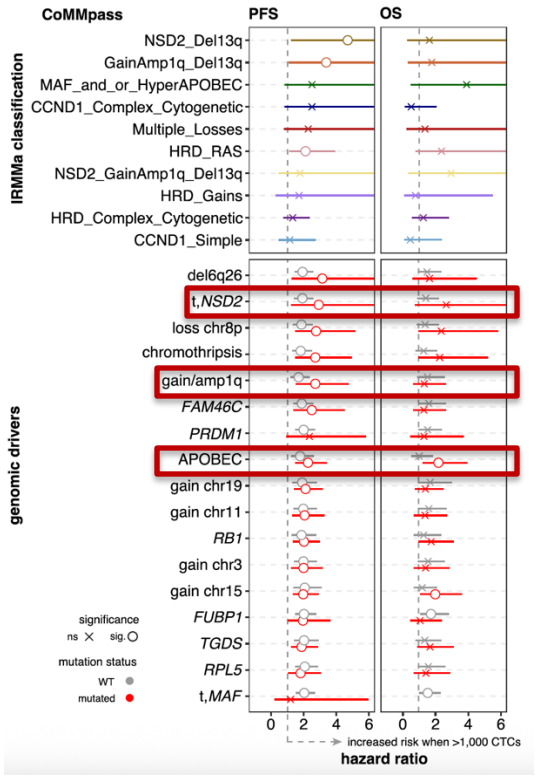
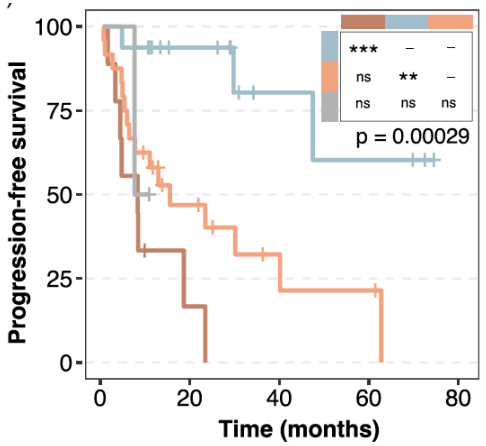
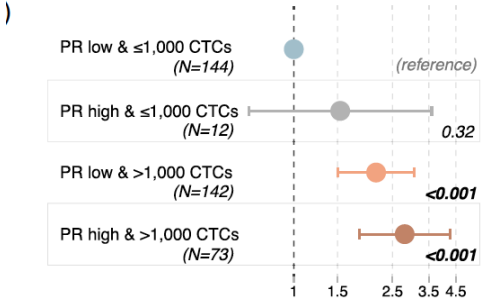




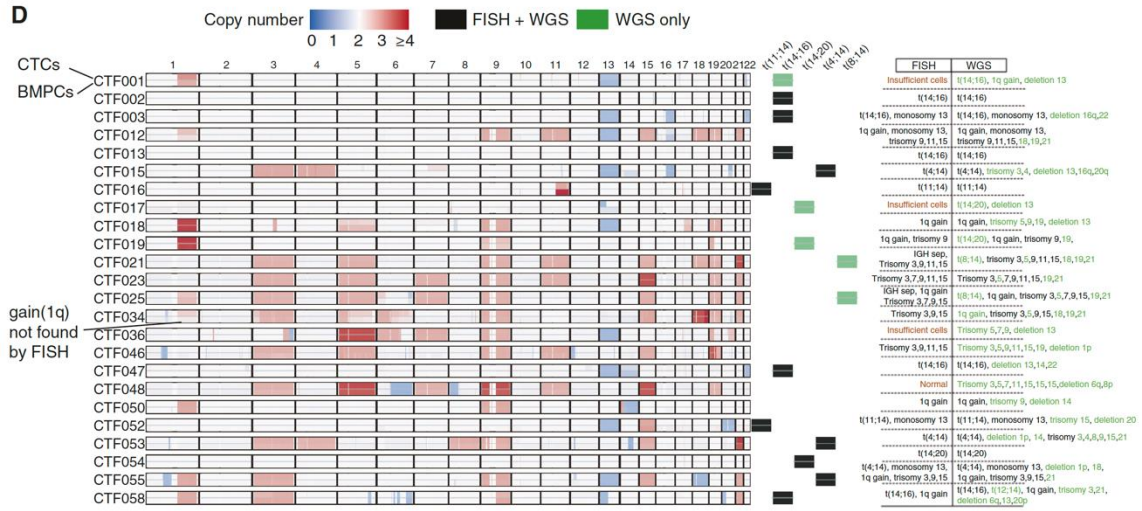


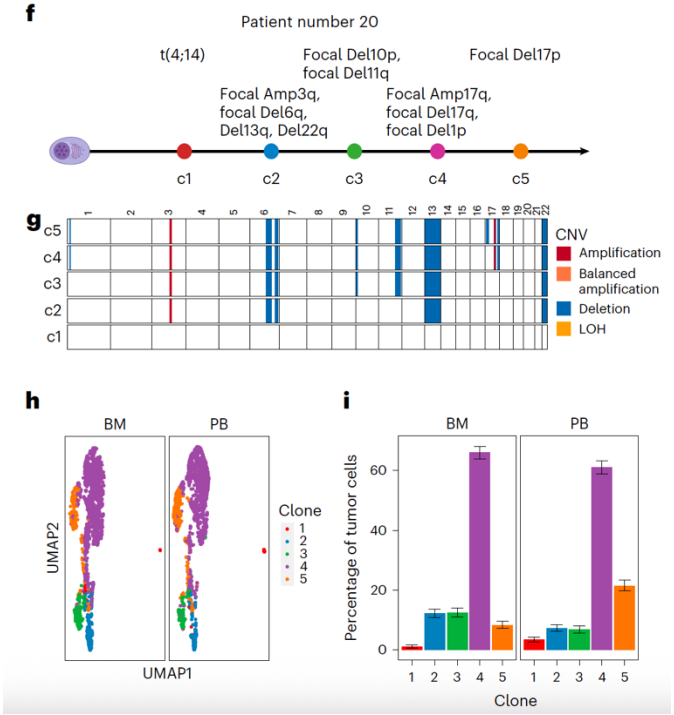




Garces et al., Hemasphere, 2025

Sequencing approches of CTCs could help to better define the ridk category of MM patients and may resolve spatial heterogeneity





Molecular approches identifies high risk clones

Dutta et al., Cancer Discovery 2022
Lightbody et al., Nat Cancer, 2025

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- Possible Biomarkers able to resolve spatial heterogeneity
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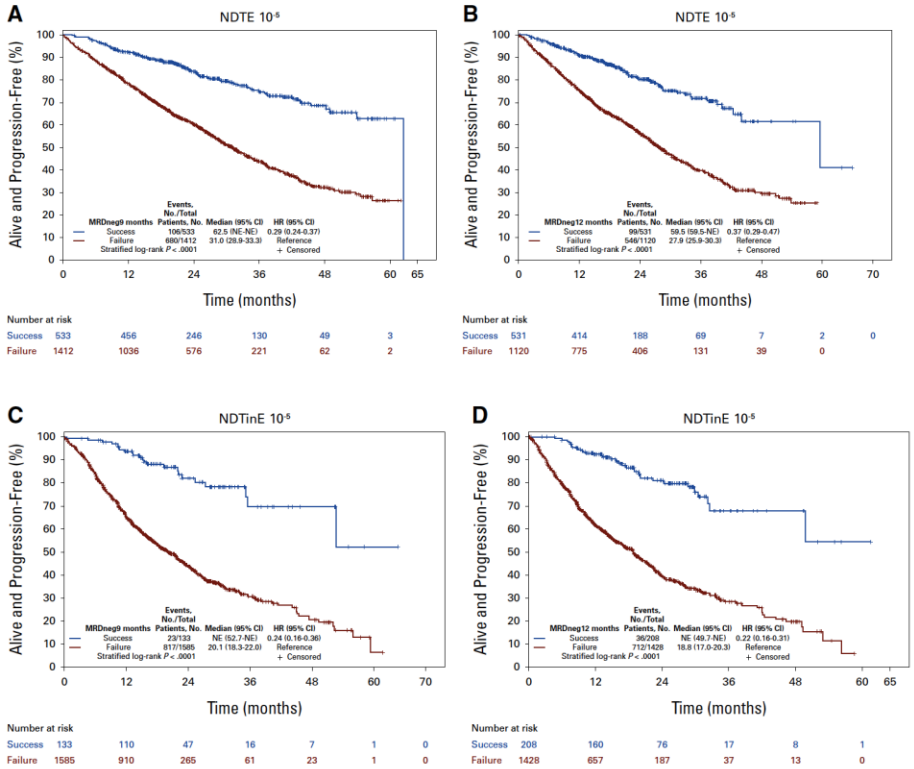
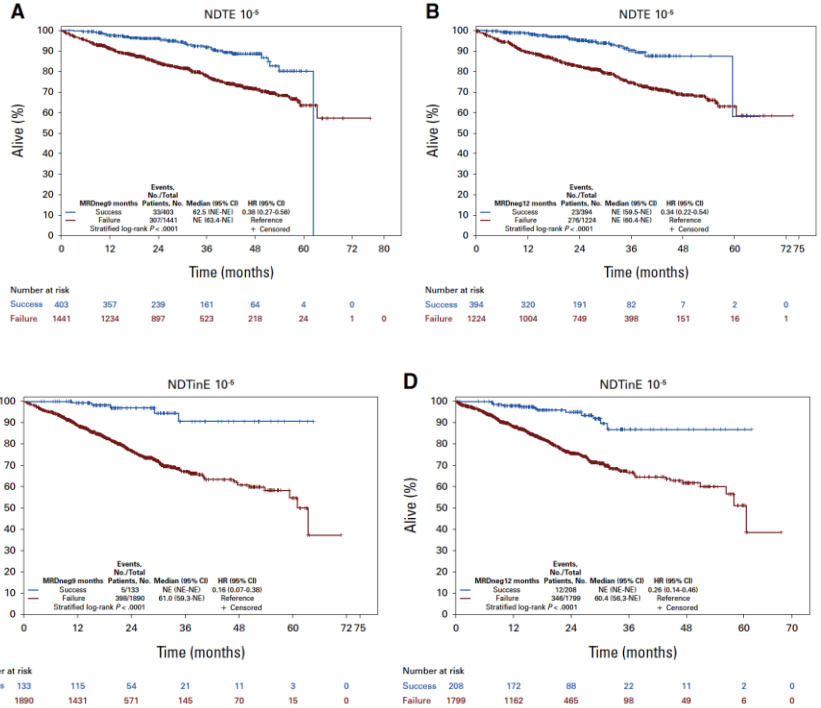
MRD negativity as surrogate of survival

PFS

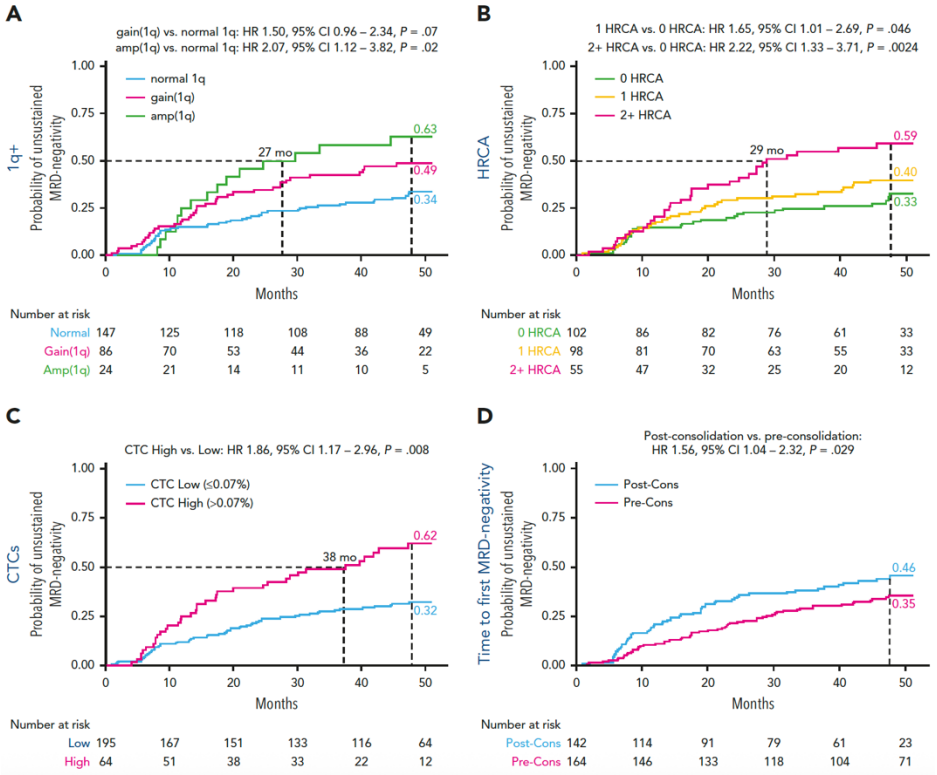


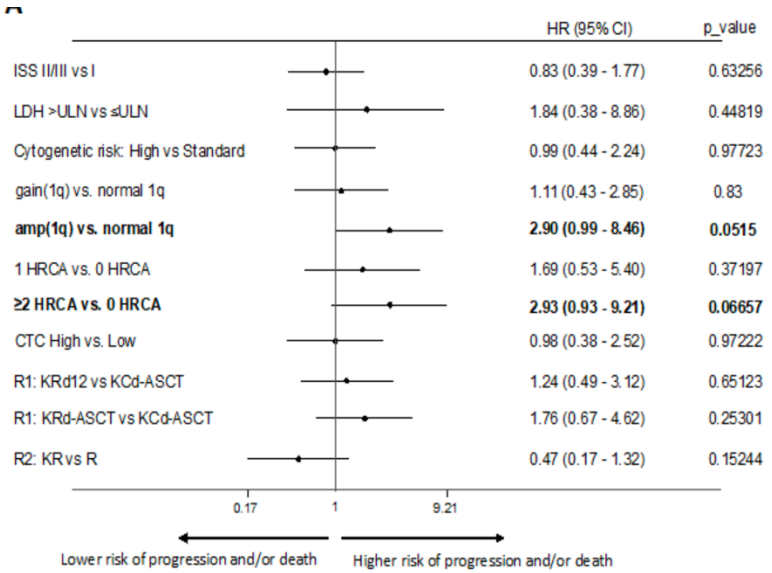
OS



Shi et al., JCO, 2025

Sustained MRD negativity and risk factors fo MRD resurgence





Patients with HRCA, high CTCs, amp1q are HR of MRD resurgence

D'Agostino et al., Blood, 2024

Conclusions:

- New IMS/IMWG consensus is a strong backbone for HR definition in Multiple Myeloma
- IMS/IMWG consensus will serve as «Trojan horse» to introduce genomics in MM clinical practice
- In the next years IMS/IMWG consensus need to be implemented for:
  Early interception of FHR
  CTCs
  Spatial heterogeity
- The static baseline evaluation need to be integrated with a longitudinal dynamic approach based on MRD assessment (NGF or NGS) for MRD-driven treatment strategies
- MRD-driven clinical trials will be the game changer for the new clinical practice in the next years

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Sistema Socio Sanitario Regione Lombardia

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Funding:

erc European Research Council

AIRC

IMS

Fondazione Umberto Veronesi

Pfizer Global Medical Grants

Johnson&Johnson Innovative Medicine

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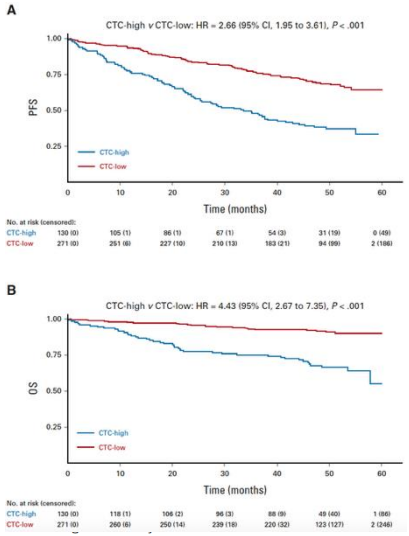

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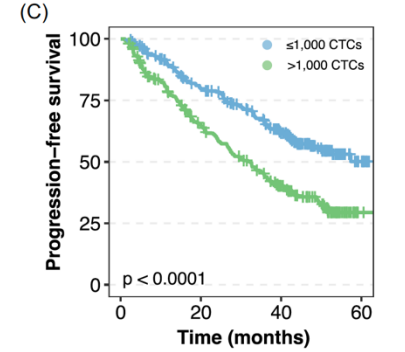

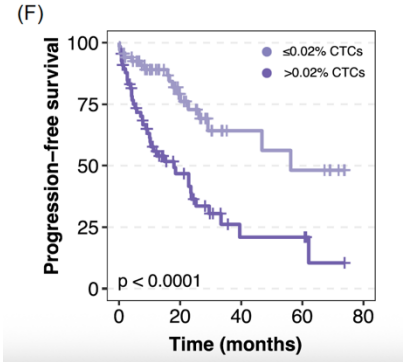

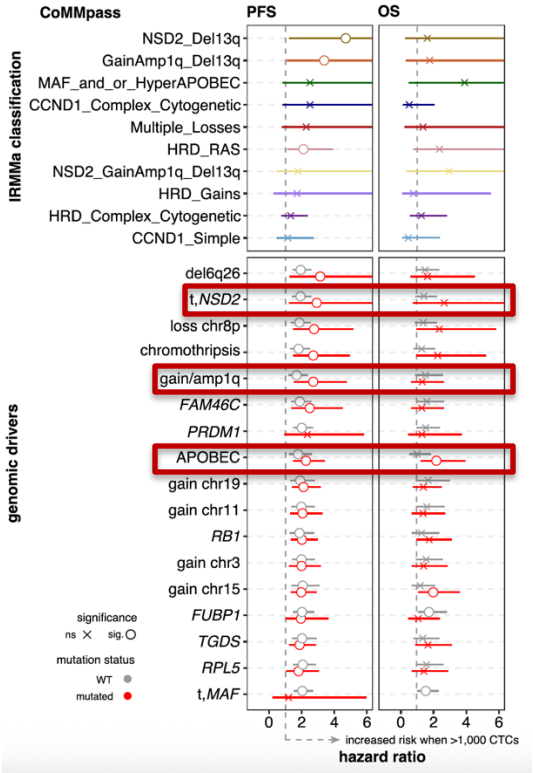

Bertamini et al., JCO 2022
Garces et al., Hemasphere, 2025

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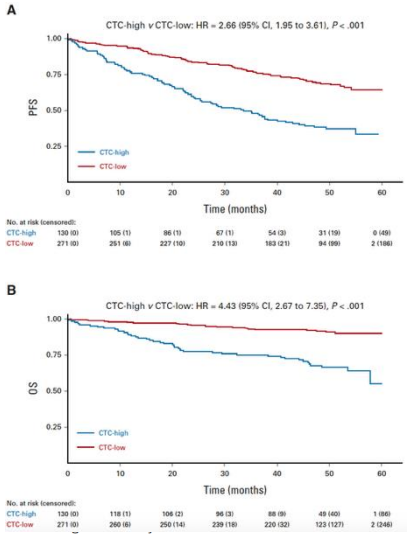

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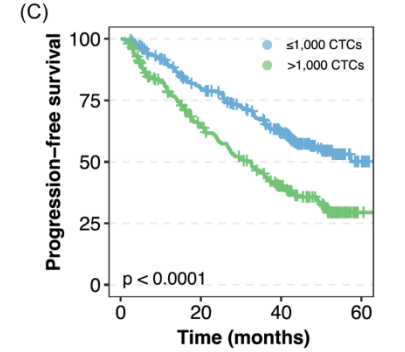

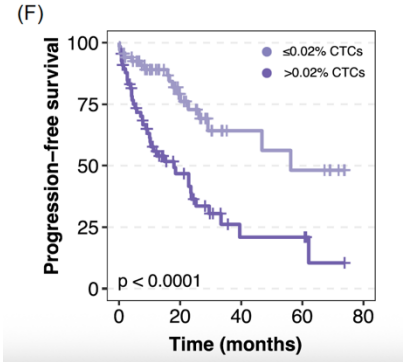

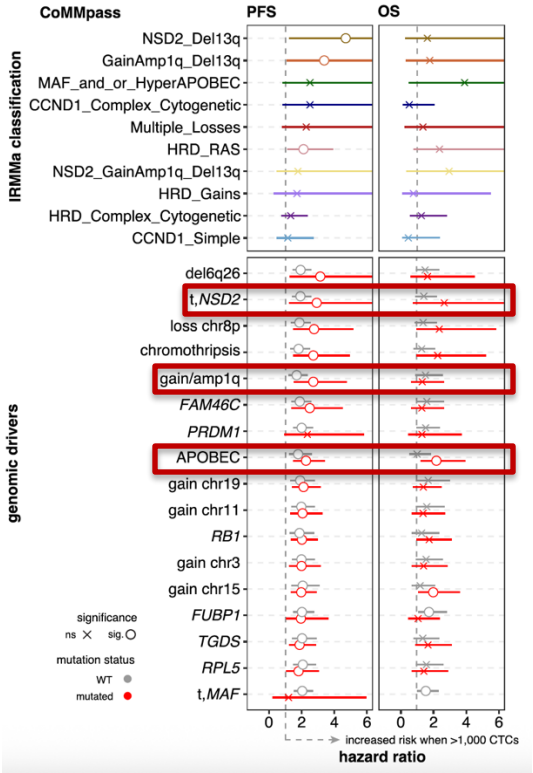

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