GIORNATE EMATOLOGICHE VICENTINE

X edizione

12-13 Ottobre 2023
Palazzo Bonin Longare - Vicenza

Marcatori prognostici clinici e di laboratorio

Niccolò Bolli
Università di Milano – Ospedale Maggiore Policlinico di Milano

UNIVERSITÀ DEGLI STUDI DI MILANO

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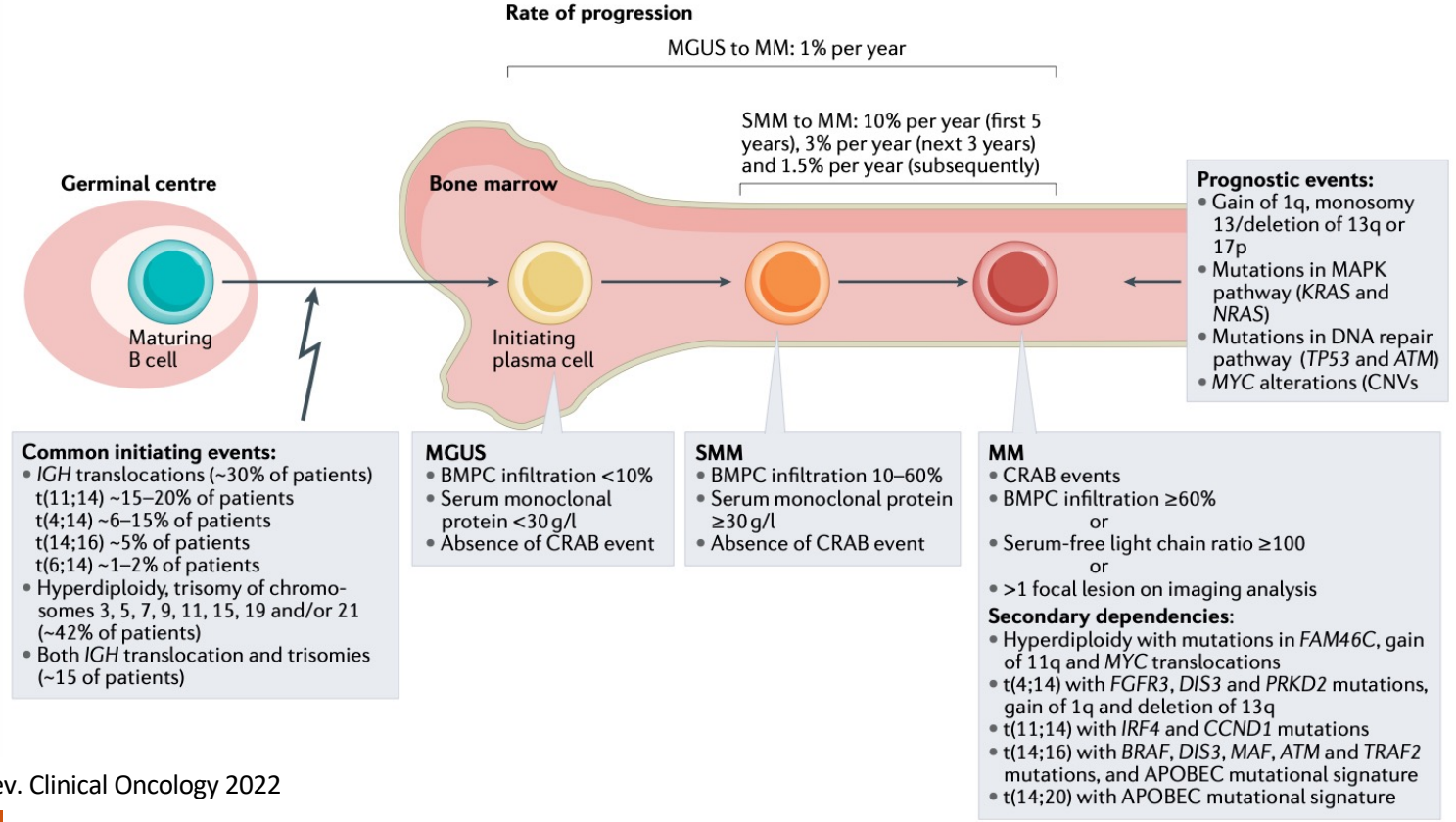
Jazz					X		
Pfizer					X	X	
Amgen					X		
GSK					X	X	
BMS/Celgene						X	

Clinical and biological evolution of myeloma is a continuum



Dutta et al, Nat. Rev. Clinical Oncology 2022

How do we go from

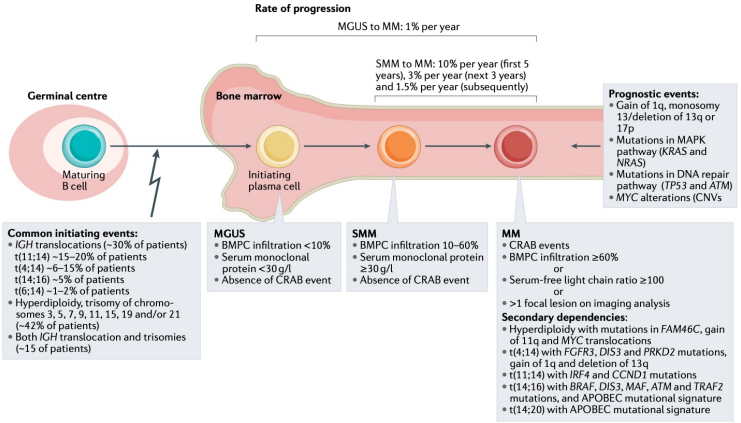
ICC classification

- Plasma cell neoplasms
  - Non-IgM MGUS
  - Multiple myeloma (plasma cell myeloma)*
    - Multiple myeloma, NOS
    - Multiple myeloma with recurrent genetic abnormality
      - Multiple myeloma with *CCND* family translocation
      - Multiple myeloma with *MAF* family translocation
      - Multiple myeloma with *NSD2* translocation
      - Multiple myeloma with hyperdiploidy
  - Solitary plasmacytoma of bone
  - Extraosseous plasmacytoma

Campo et al, Blood 2022

to

Biological classification



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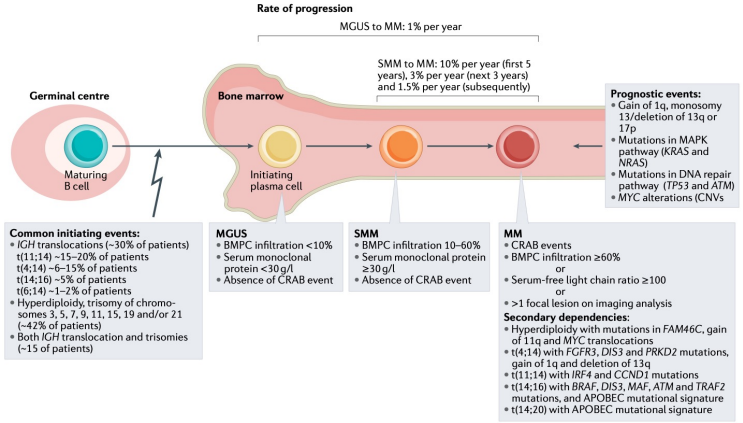


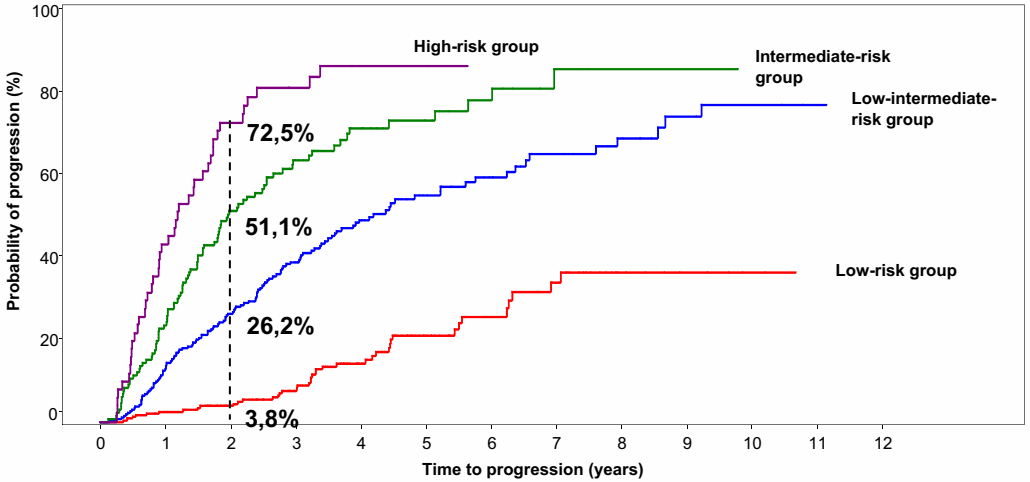
Dutta et al, Nat. Rev. Clinical Oncology 2022

Can we integrate variables (clinical, laboratory etc) to classify myeloma in
- biologically meaningful categories
- clinically useful categories

IMWG model for risk stratification of SMM incorporating FISH

Risk factor	Coefficient	Odds ratio (95% CI)	*p* value	Score
FLC IU				
0–10 (reference)	–	–	–	0
>10–25	0.69	1.99 (1.15, 3.45)	0.014	2
>25–40	0.96	2.61 (1.36, 4.99)	0.004	3
>40	1.56	4.73 (2.88, 7.77)	<0.0001	5
M-protein				
0–1.5 (reference)	–	–	–	0
>1.5–3	0.95	2.59 (1.56, 4.31)	0.0002	3
>3	1.3	3.65 (2.02, 6.61)	<0.0001	4
BMPC				
0–15 (reference)	–	–	–	0
>15–20	0.57	1.77 (1.03, 3.06)	0.04	2
>20–30	1.01	2.74 (1.6, 4.68)	0.0002	3
>30–40	1.57	4.82 (2.5, 9.28)	<0.0001	5
>40	2	7.42 (3.23, 17.02)	<0.0001	6
FISH abnormality *	0.83	2.28 (1.53, 3.42)	<0.0001	2

*t(4;14), t(14;16), del(13), +(1q)



Risk Stratification groups	Total risk score	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low	0-4	Reference	3.8%	241 (35.0%)
Low-intermediate	5-8	7.56 (3.77 – 15.2)	26.2%	264 (38.3%)
Intermediate	9-12	17.3 (8.63 – 34.8)	51.1%	133 (19.3%)
High	>12	31.9 (15.4 – 66.3)	72.5%	51 (7.4%)

Mateos MV, et al. Blood Cancer J. 2020

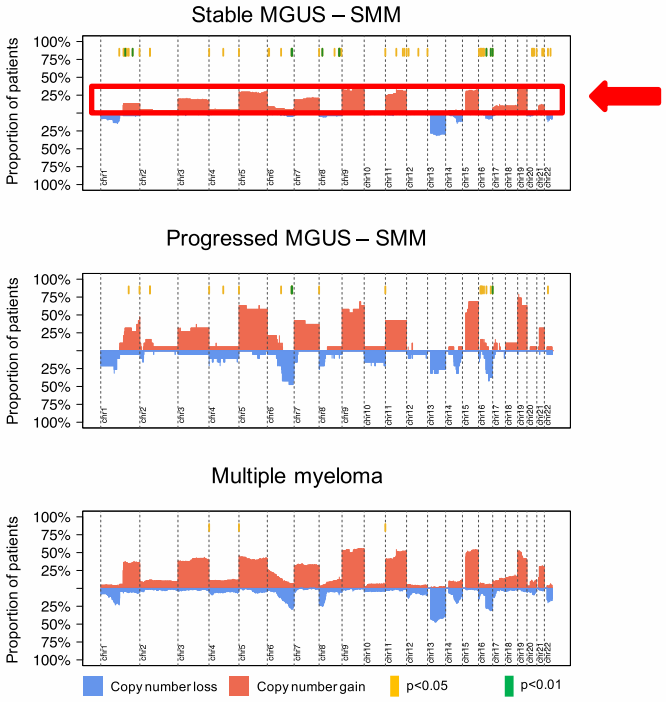
Genomic features can help prognostication in SMM

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

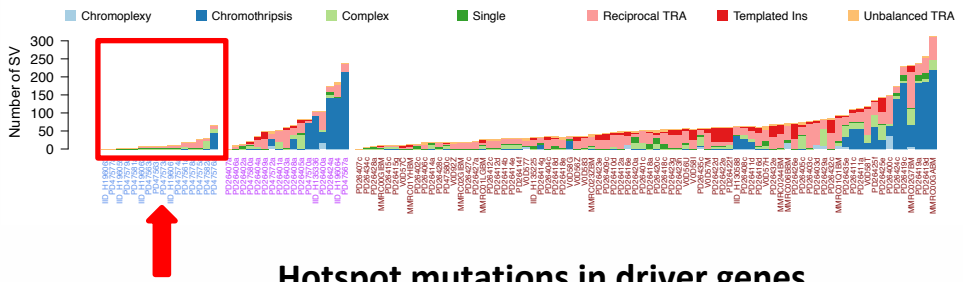
Bustoros et al, JCO 2020

Whole-genome sequencing dissects features of non-progressive cases

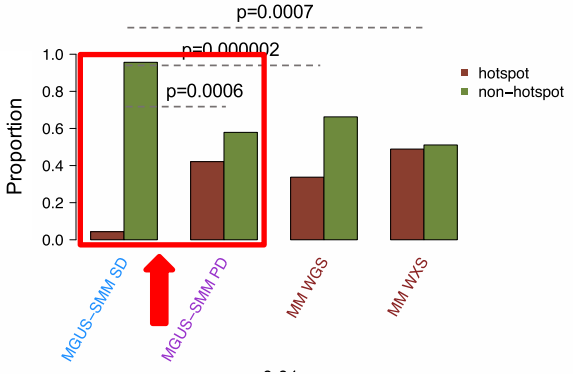
Fewer deletions



Fewer complex rearrangements



Hotspot mutations in driver genes



Oben et al, Nat Comms 2021

SMM has stage-specific prognostic markers of progression, not shared by NDMM

RAS mutations, TS deletions, MYC translocations etc

1st take home message

High-risk clinical features of NDMM

Focal Myeloma Lesions: Discrete areas of plasma cell (PC) accumulations on both PET-TCT and MRI that can predict PFS and OS

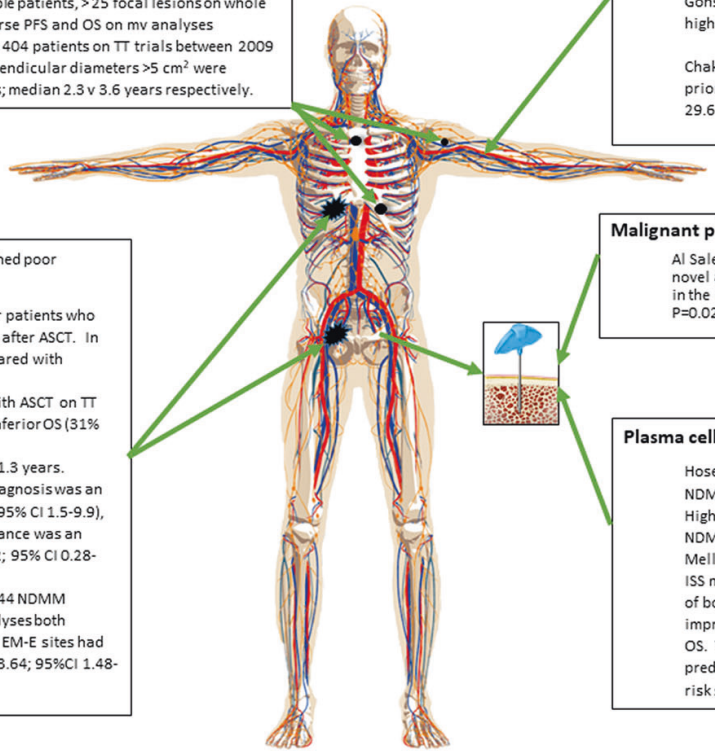
Usmani BLOOD 2013[86]: 302 patients treated on the Total Therapy 3 trials for NDMM, on mv analyses >3 focal lesions on PET-CT imparted inferior OS and PFS
Mai Haematologica 2015[87]: 161 transplant eligible patients, >25 focal lesions on whole body MRI or > 7 on axial MRI associated with worse PFS and OS on mv analyses
Rasche Nat Com 2017[88]; Rasche BLOOD 2018[89*]: 404 patients on TT trials between 2009 and 2015. 3 large FLs with a product of the perpendicular diameters >5 cm^2 were associated with poor PFS and OS on mv analyses; median 2.3 v 3.6 years respectively.

Circulating malignant plasma cells (CPCs) in the peripheral blood:

Vagoni BJH 2015[95]: Cohort of 566 patients, elevated CPCs adversely affected PFS in patients with standard but not high risk cytogenetics

Gonsalves ASCO 2019[96]: Addition of CPCs to R-ISS staging identified a high risk cohort of stage I and II patients.

Chakraborty BCJ 2016[97]: 840 patients who had an assessment of CPCs prior to ASCT. Presence of CPCs predicted poorer PFS (median 15.1 v 29.6 months; p<0.001) and OS (median 41.0 v NR months; p<0.001)



Extramedullary Myeloma (EMM): Well-established poor prognostic feature; includes both EME and EMB

Poor prognosis with a median OS of <1 year for patients who are refractory to standard therapies or relapse after ASCT. In general, the prognosis for EM-E is worse compared with EM-B[90].
Usmani Haem 2012[91]: 1965 patients treated with ASCT on TT and non-TT protocols. EME had significantly inferior OS (31% vs. 59%, p 0.001)
Weinstock BJH 2015[92]: Median OS in EME just 1.3 years.
Moreau JCO 2017[93]: IFM-2009 trial, EMM at diagnosis was an independent prognostic factor for OS (HR 3.9; 95% CI 1.5-9.9), whereas PET-CT normalization before maintenance was an independent prognostic factor for PFS (HR 0.42; 95% CI 0.28-0.62)
Gagelmann Haem 2018[94]: EBMT evaluating 3744 NDMM patients undergoing up front ASCT, on mv analyses both patients with one EM-E site and those with ≥ 2 EM-E sites had inferior OS (HRs of 2.30; 95% CI 1.43-3.70 and 3.64; 95%CI 1.48-8.94)**

Malignant plasma cells in the BM:

Al Saleh CLML 2020[98]: 1426 NDMM patients treated with primarily novel agents. Controlling for FISH and ISS/R-ISS, plasma cells >60% in the BM lead to worse PFS (HR, 1.23; P=0.015) and OS (HR, 1.24; P=0.02).

Plasma cell proliferation index (PCPI):

Hose Haem 2011[99]: High PCPI associated with inferior survival in NDMM
High PCPI: incorporated into some risk stratification systems for NDMM[55]
Mellors BLD ADV 2020[100]: In mv analyses controlling for CAs, age, R-ISS metaphase cytogenetics, and standard FISH, PCLI was predictive of both PFS and OS. The addition of PCLI to the R-ISS did not improve risk discrimination of Kaplan-Meier estimates for PFS and OS. Thus, similar to previous studies, PCLI has independent predictive value for PFS and OS but does not appear to improve the risk stratification of the newer R-ISS risk modeling.

Hagen et al, Blood Canc J. 2022

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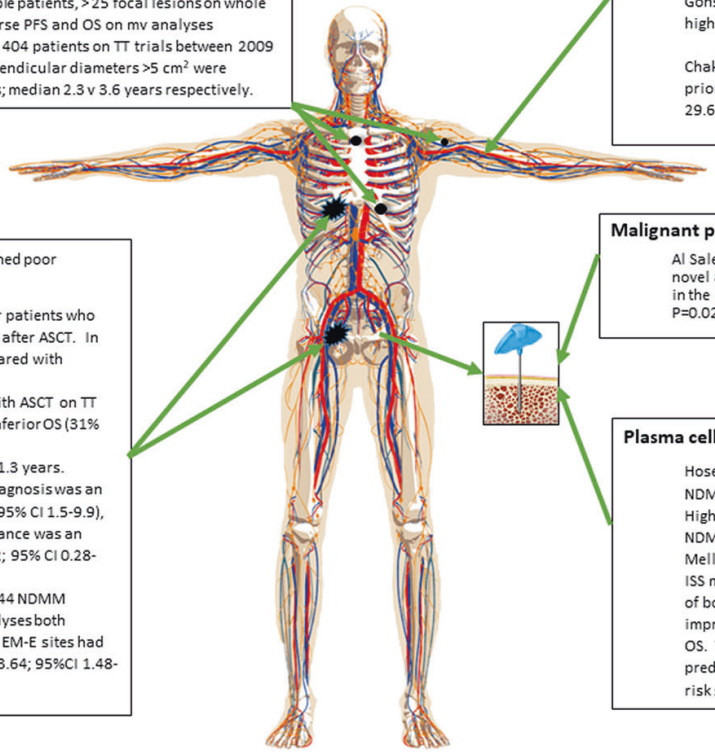

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Today we only look at this
(DNA only)

Hagen et al, Blood Canc J. 2022

Different strategies of risk stratification

Hagen et al, Blood Canc J. 2022

	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

Risk stratification according to R2-ISS

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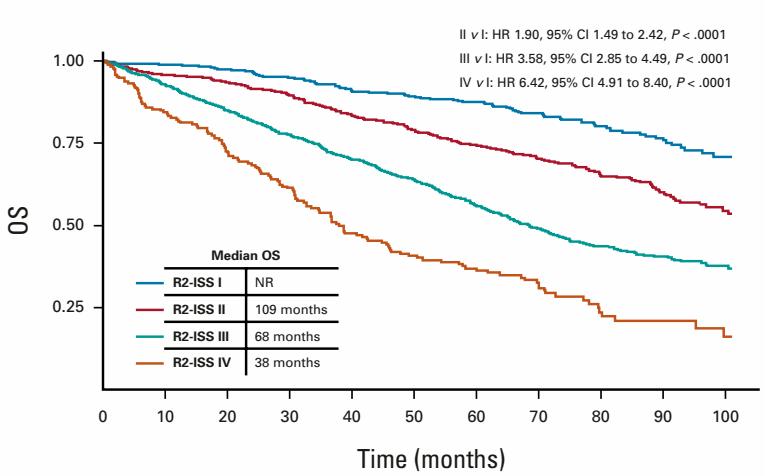

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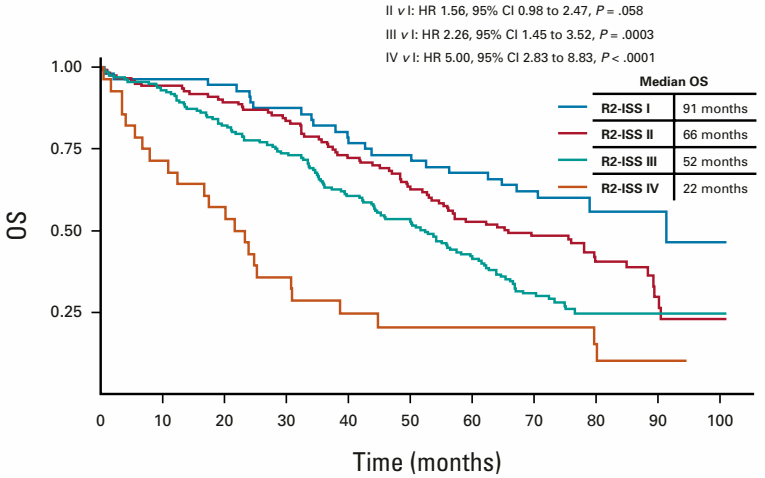


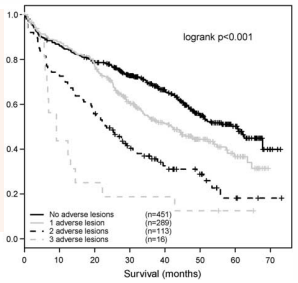
Risk Feature	OS HR (95% CI)	PFS HR (95% CI)	Score Value[a]
ISS II	1.75 (1.49 to 2.05)	1.43 (1.28 to 1.61)	1
ISS III	2.53 (2.13 to 3.01)	1.76 (1.54 to 2.01)	1.5
del(17p)	1.82 (1.53 to 2.17)	1.43 (1.23 to 1.65)	1
LDH high	1.60 (1.36 to 1.88)	1.37 (1.20 to 1.57)	1
t(4;14)	1.53 (1.29 to 1.81)	1.40 (1.21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

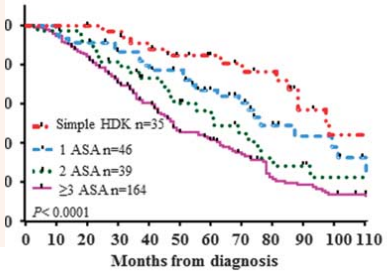
Increasing genomic complexity correlates with prognosis in NDMM

n. *3* lesions:
- del(17p)
- amp(1q)
- adverse IGH transl.



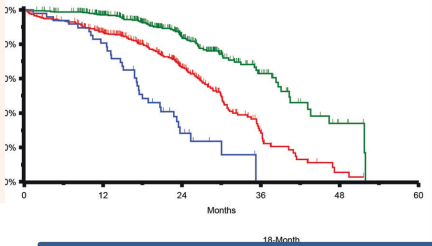
Boyd, Leukemia 2012

HD pts only
- Karyotype
- del(1p) amp (1q)
- t(11;14)
- del(13q)
- del(17p)



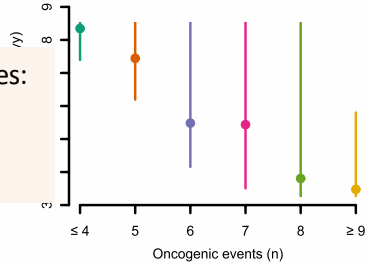
Carballo-Zarate et al, Mod Path 2017

Either:
- *TP53* inactivation (bi-allelic)
- ISS III plus *CSK1B* amplification (>= 4 copies)



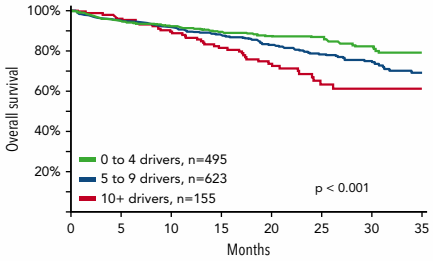
Walker et al, Leukemia 2018

n. *197* features:
- mutations
- CNAs
- karyotype



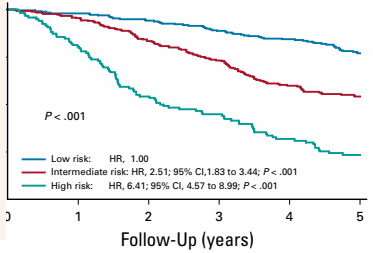
Bolli, Leukemia 2018

Whole exome



Walker, Blood 2018

Trisomy 5
Trisomy 21
t(4;14)
1q gain
del(1p32)
del(17p)



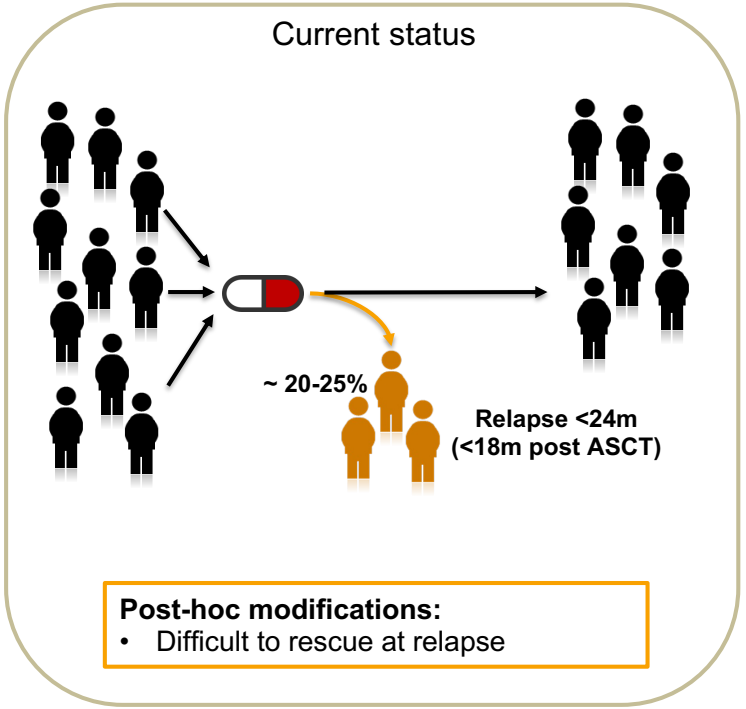
Perrot, JCO 2019

Consensus is lacking for the definition of HR myeloma

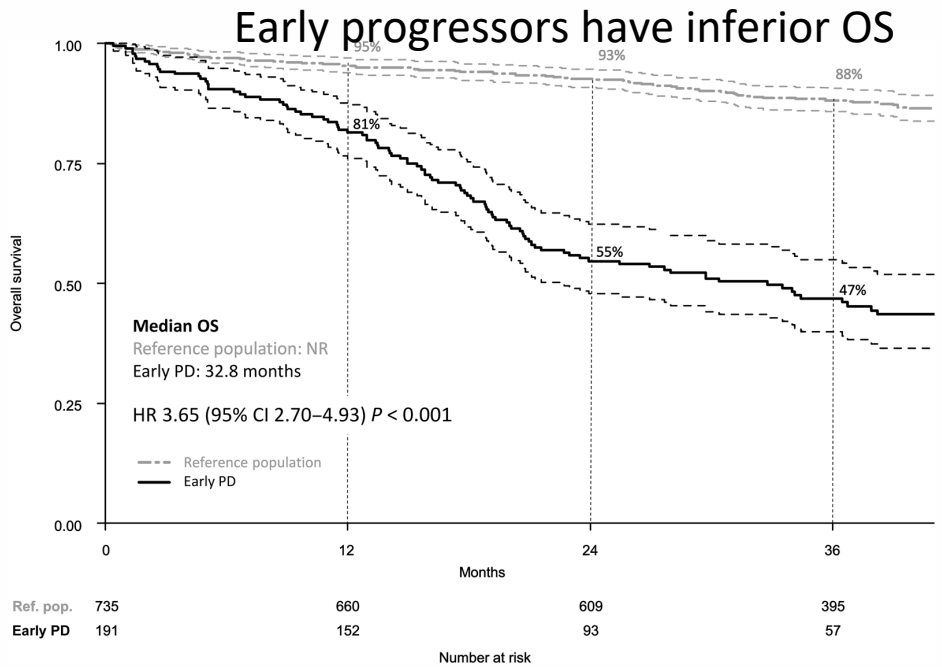
2nd take home message

How do we deal with HR disease?

- 1st approach: we deal with it ex-post

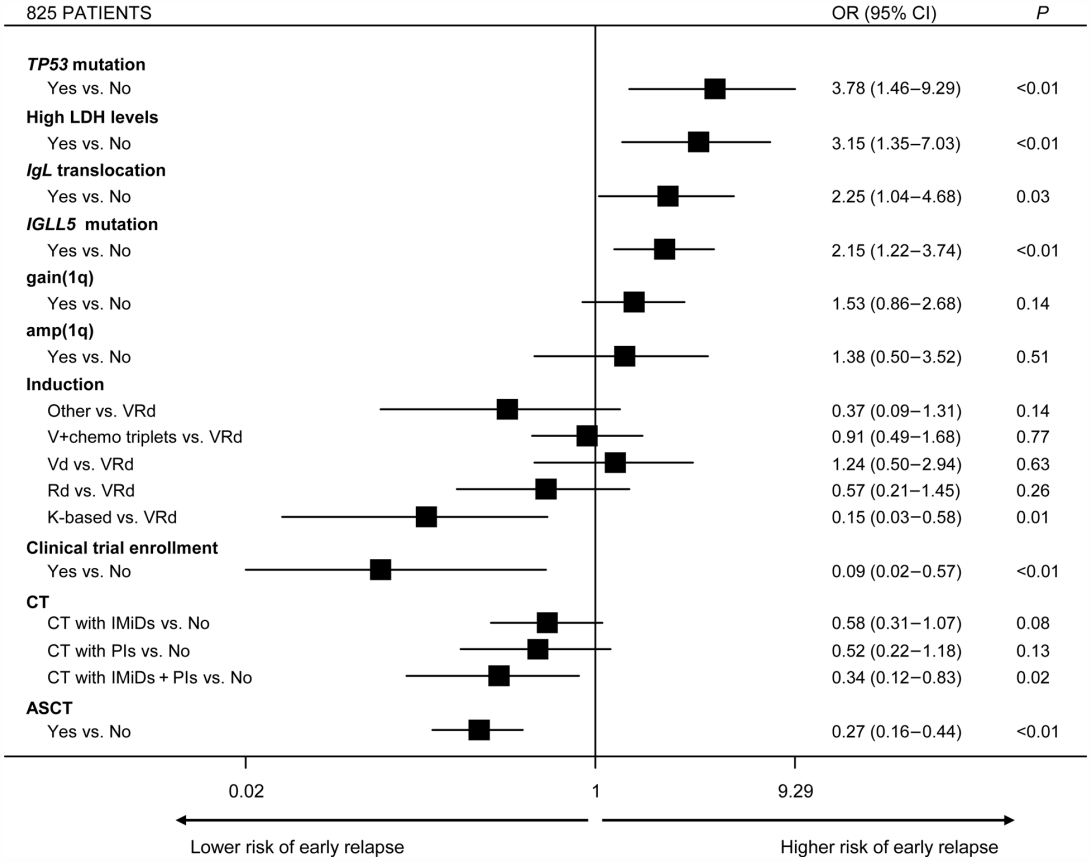


ASCT = autologous stem cell transplantation



D'Agostino et al., CCR 2020

Predictors of early relapse at diagnosis mandate a comprehensive genetic analysis

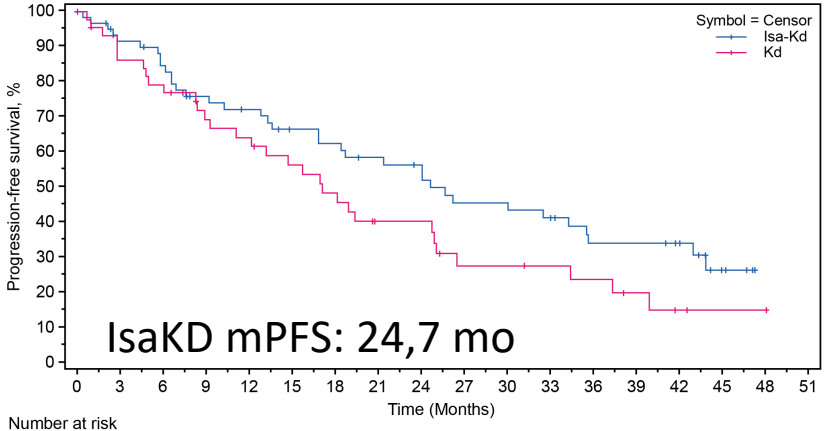


D'Agostino M et al, Clin Cancer Res 2020

Impact of early relapse (functional HR) on IKEMA outcomes

EARLY

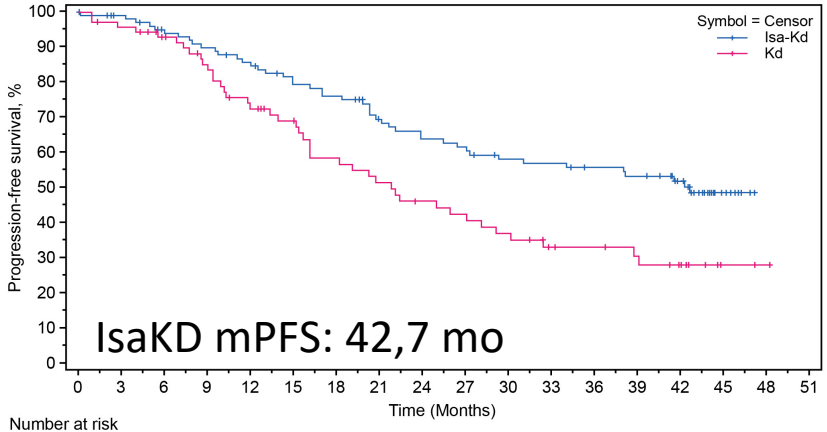
Figure 1. Kaplan-Meier estimate of progression-free survival for early relapse patients



d, dexamethasone; Isa, isatuximab; K, carfilzomib. Cut-off date: January 14, 2022. Median follow-up time: 44.19 months.

LATE

Figure 2. Kaplan-Meier estimate of progression-free survival for late relapse patients

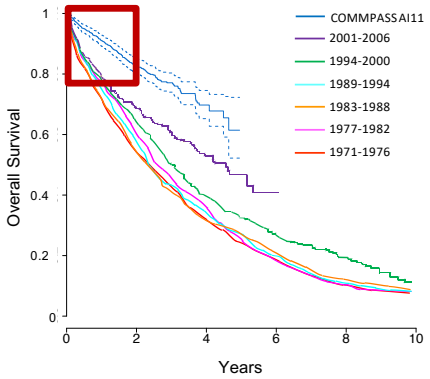


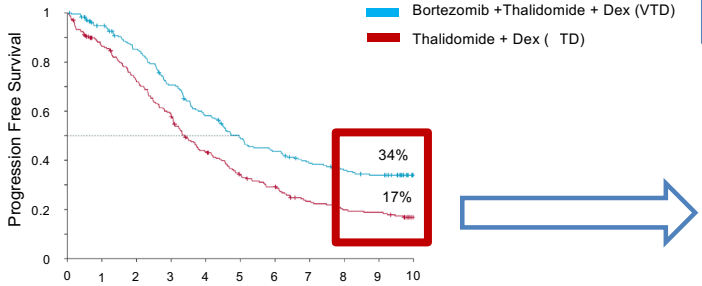
d, dexamethasone; Isa, isatuximab; K, carfilzomib. Cut-off date: January 14, 2022. Median follow-up time: 43.83 months.

Early relapse: <12 mo from initiation of the most recent LOT for pts with ≥2 prior LOT, <18 mo for pts with 1 prior LOT, and <12 mo from autologous stem-cell transplantation (ASCT).

Facon et al, ASH 2022

Functional definition of high-risk and low-risk myeloma





The advent of novel drugs in patients with newly diagnosed and relapsed/refractory multiple myeloma has resulted in improved overall survival

However, a subset of newly diagnosed multiple myeloma patients have not benefited from newer therapies, reflected in persisting poor clinical outcomes

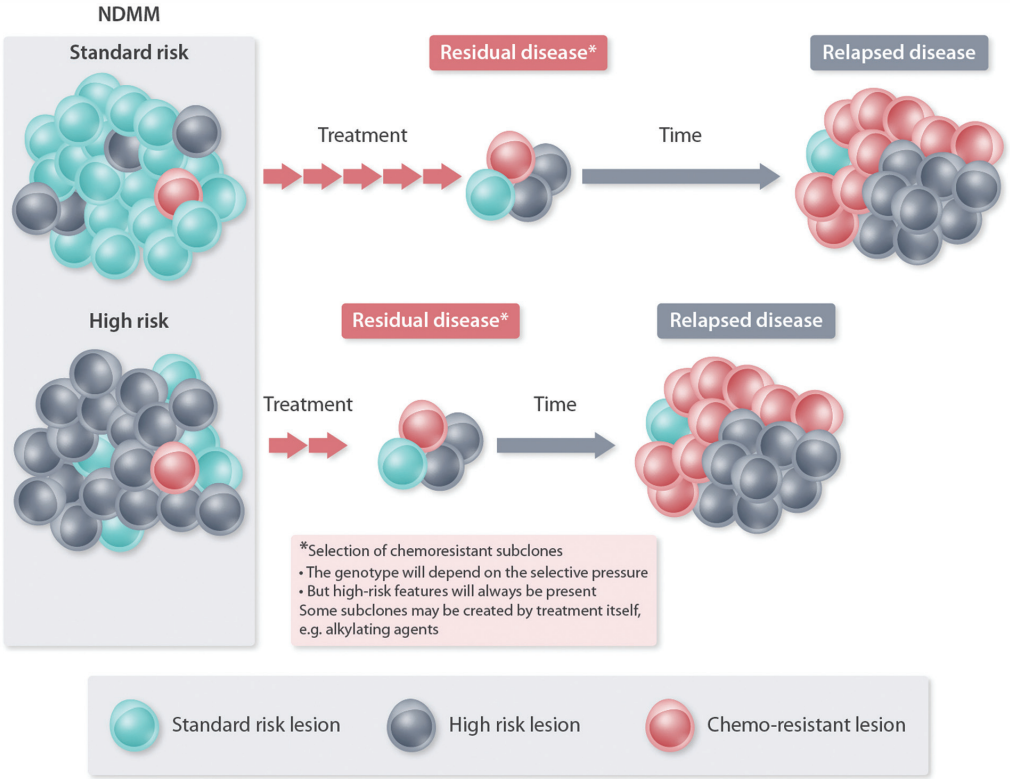
Conversely, another subset of multiple myeloma patients have excellent outcomes despite limited therapy

A) Adapted from: Kumar et al. Leukemia 2014 B) Tacchetti et al. Lancet Hem 2020

Absolute prediction of HR risk is not possible today. Sometimes we only know *ex post*

3rd take home message

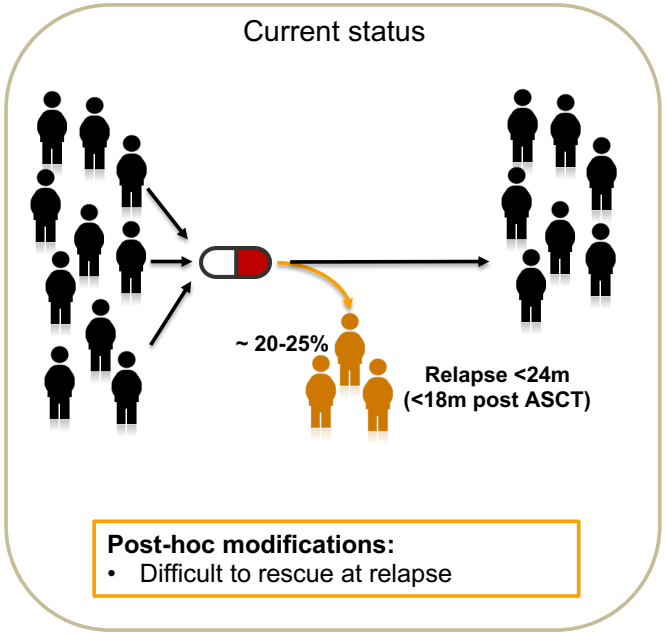
Evolutionary-convergent view of risk in myeloma

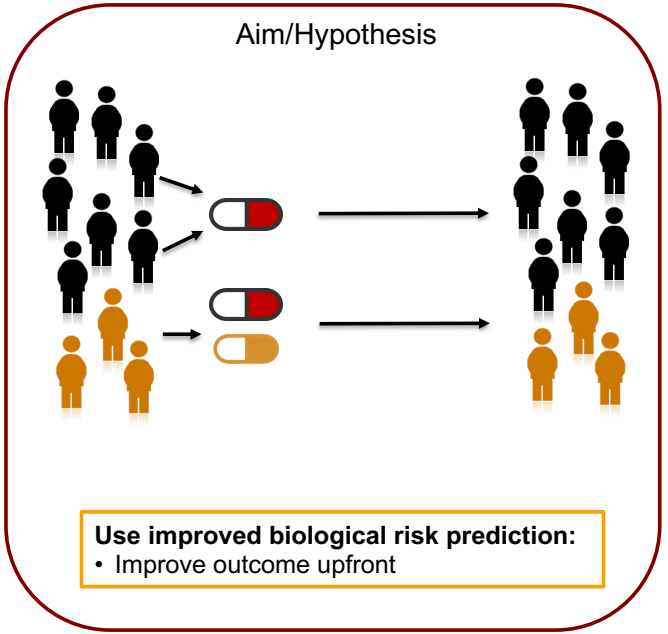


Da Và et al, Hemasphere, 2020

How do we deal with HR disease?

- 2nd approach: we identify patients prospectively and treat accordingly





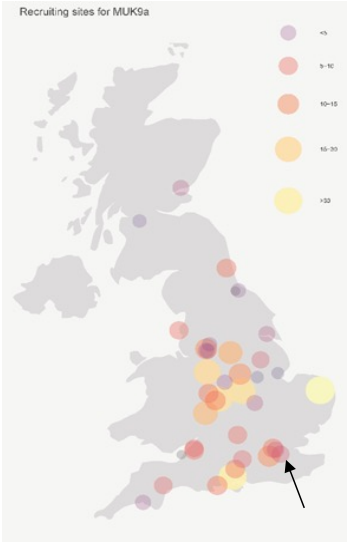
ASCT = autologous stem cell transplantation

Currently no uniform treatment standard

Presented by: Martin Kaiser, MD, FRCP, FRCPath
@MyMKaiser

UK multi-centre phase 2 trial for UHiR MM and PCL - Screening protocol

39 NHS hospitals
Mostly community (DGH)
Sep 2017 – Jul 2019



Suspected or confirmed NDMM/PCL
Recruited to OPTIMUM Screening (n=472)

Enrollment

Did not have a symptomatic Multiple Myeloma or PCL diagnosis (n=60)
- Asymptomatic Myeloma (n=22)
- MGUS (n=14)
- Other (n=16)
- No confirmed diagnosis (n=8)

Central sample

Multiple Myeloma or PCL diagnosis (n=412)

Genetic & GEP Risk screening

87% complete screening result

Risk screening result (n=412)
- **Ultra High risk (n=138)**
- Non-high risk (n=221)
- Partial result (n=24)
- Missing risk result (n=29)

Recruitment 10 months ahead of projection

Remained in OPTIMUM Screening
(n=305; including 30 high risk patients)
- Standard of Care therapy – Data collection

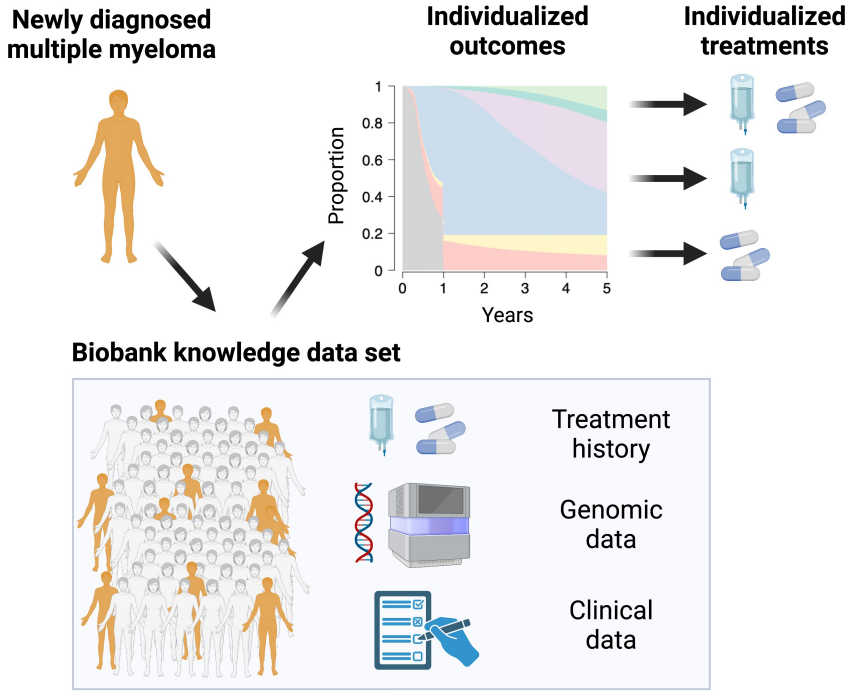
Registered and eligible for OPTIMUM Treatment Trial (n=107)

Presented by: **Martin Kaiser, MD, FRCP, FRCPath**
@MyMKaiser

Individualized Risk Model for Myeloma (IRMM)

- MMRF, N=1062
- Moffitt, N=177
- MPG, N=492
- MSKCC, N=109
- UAMS, N=93

- Clinical
- Demographic
- Ethnic
- Treatment
- Genomics (WES/WGS)



Model is driven by Deep Neural Networks

Arjun Raj Rajanna

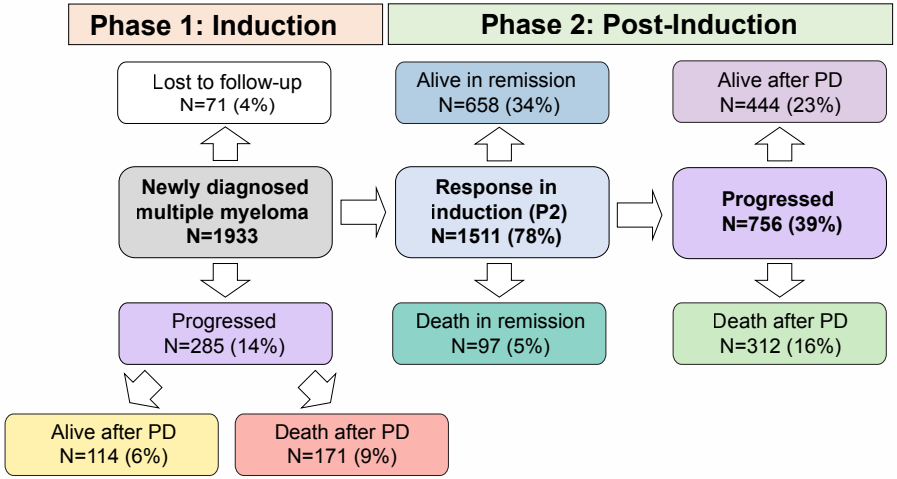
Andriy Derkach

Bachisio Ziccheddu

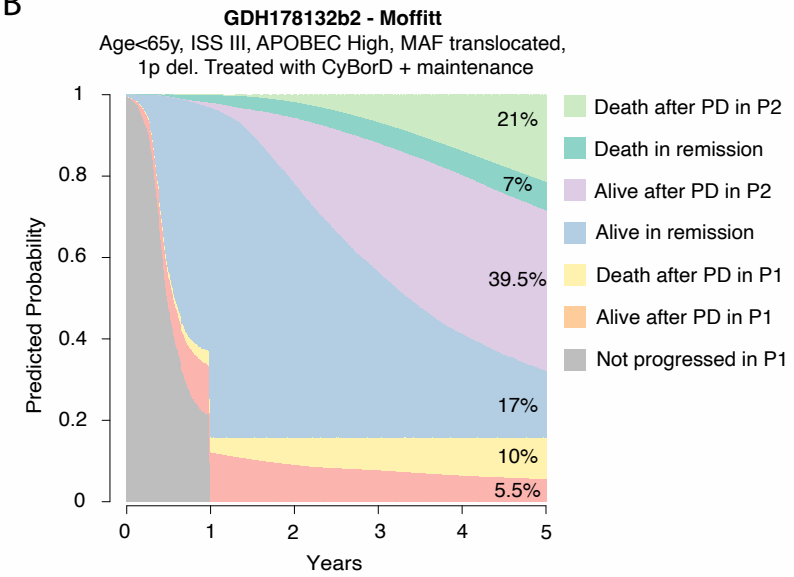
Courtesy of Francesco Maura (U. of Miami)

Personalized survival prediction in MM

A



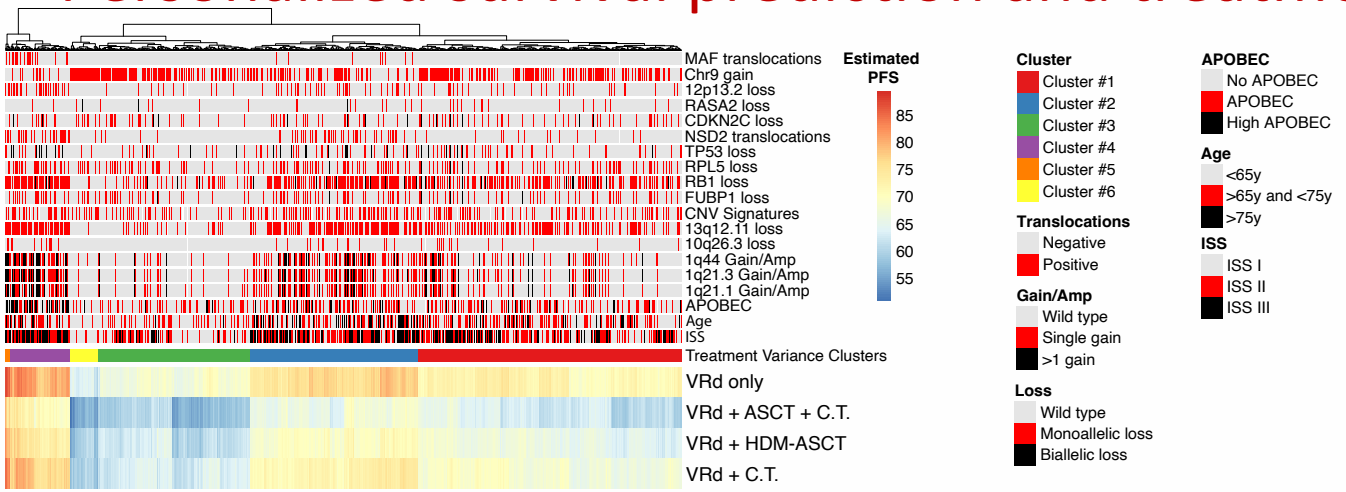
B



Maura et al, 2023 submitted

Personalized survival prediction and treatment variance

A



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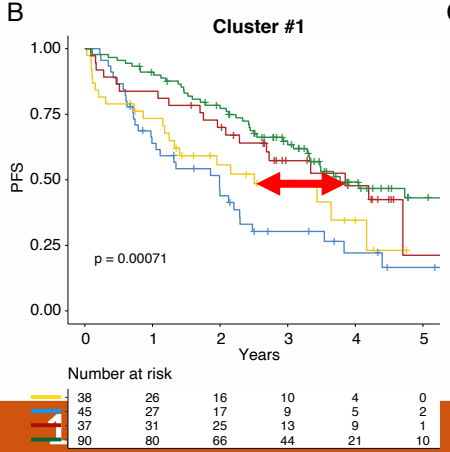
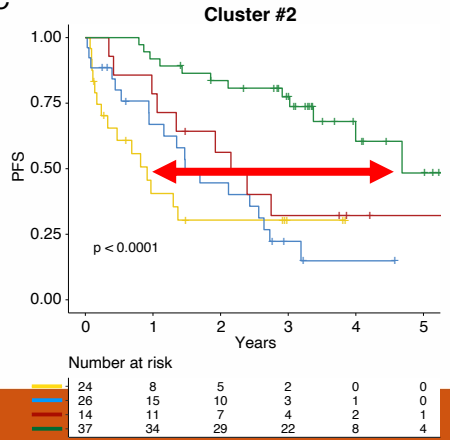
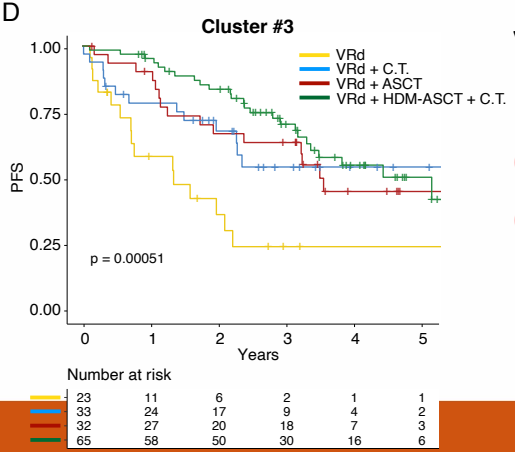


C



D



VRd+ASCT+maint vs VRd

Cluster 1: PFS 1.5x

Cluster 2: PFS 4.7x

Maura et al, 2023 submitted

Conclusions

- In SMM, genomic prognostication may soon complement laboratory data
- In NDMM consensus on HR disease definition is lacking
  - 2 HR lesions, 1 + HR transcriptome, CTCs?
  - Radiology?
- Current risk prediction strategies are are imperfect for
  - Accuracy
  - Prediction of Tx effect
- Promise of large knowledge banks for prospective identification of patients
- Need for ad-hoc studies in HR even as we learn how to define and predict HR
- Future IMS risk stratification will mandate extended genotyping, preferrably by NGS

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