4th edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, March 26-27, 2026

Starhotels Majestic

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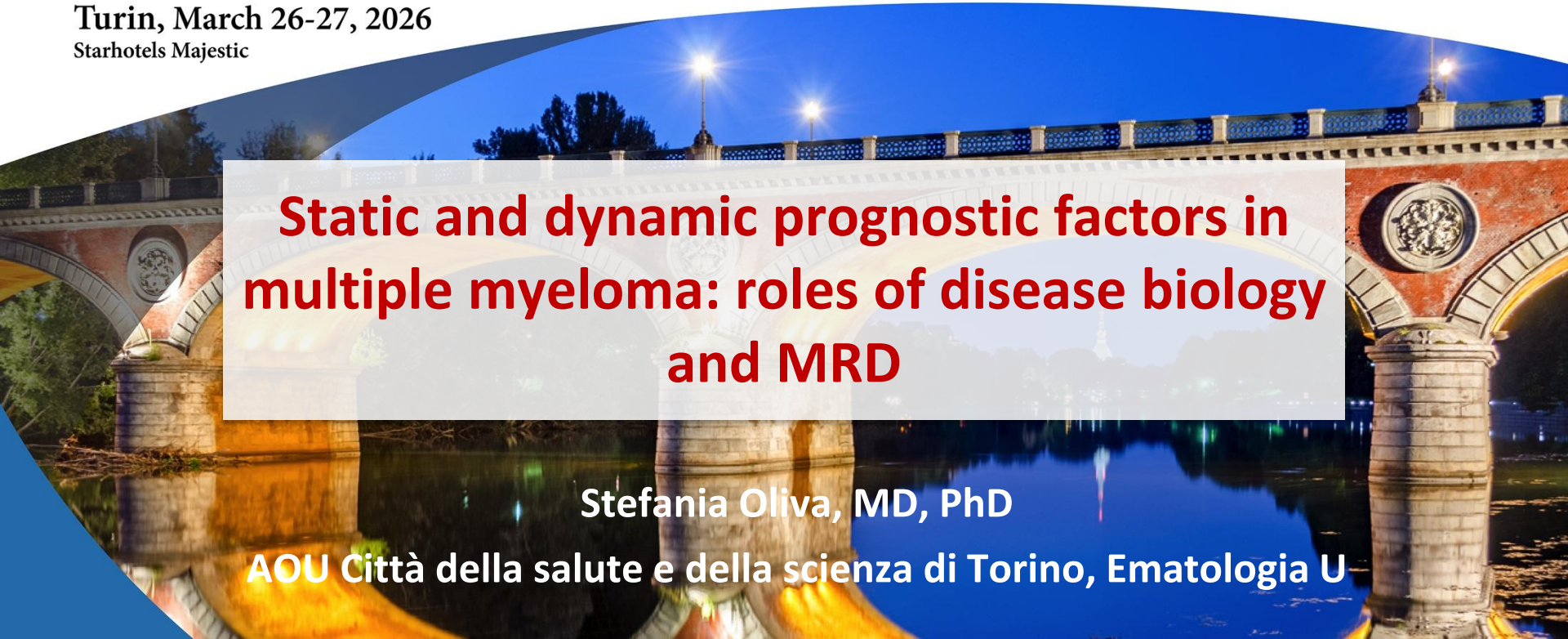

Static and dynamic prognostic factors in multiple myeloma: roles of disease biology and MRD

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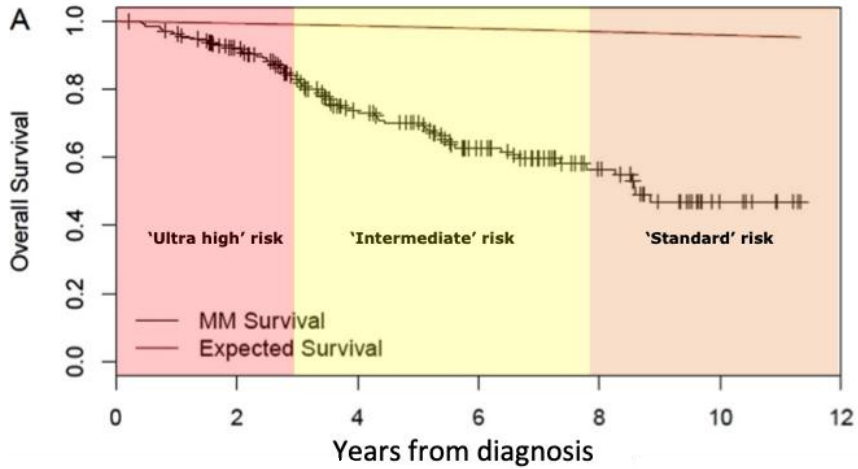
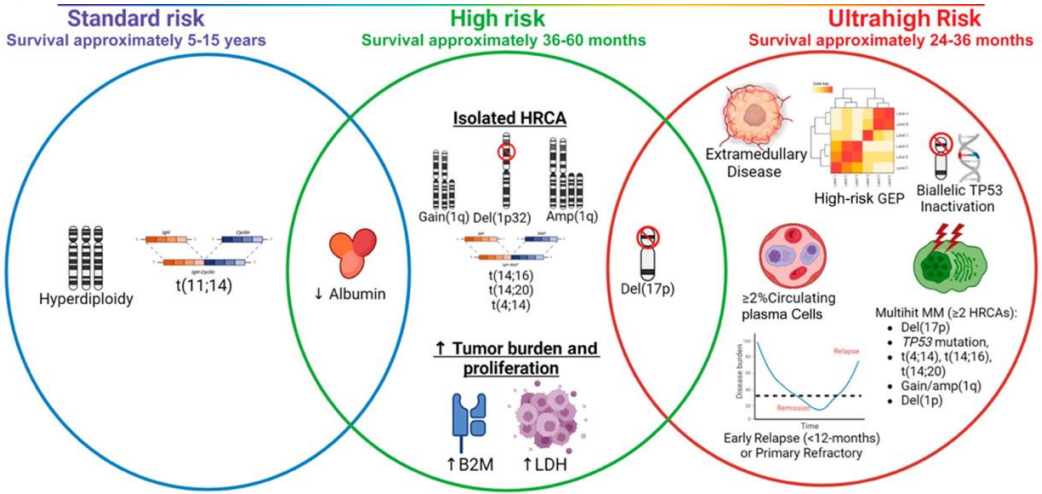
Disclosures of Stefania Oliva

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						x	
Celgene/Bristol Myers						x	
Janssen			x			x	
Sanofi						x	
Pfizer						x	
Takeda						x	
Adaptive Biotchnologies						x	

Multiple myeloma outcome is heterogeneous



The importance of risk stratifcation for a static prognostication



Adapted from Ravi P, et al. 2018.

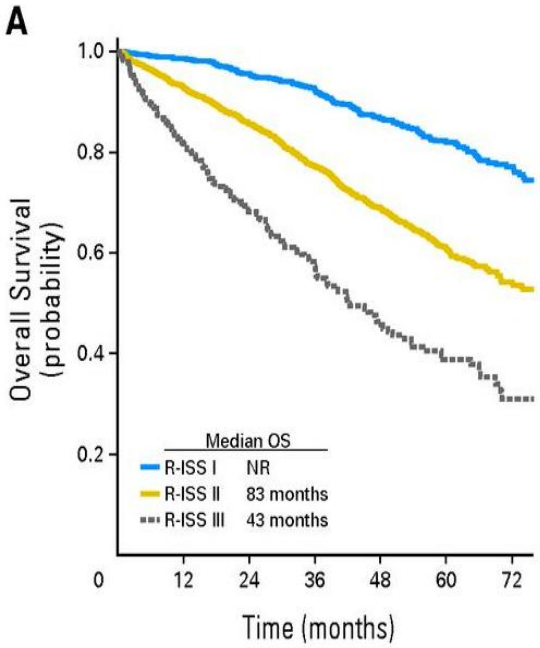
Rees MJ, Am Soc Clin Oncol Educ Book. 2024 Jun; 44(3).

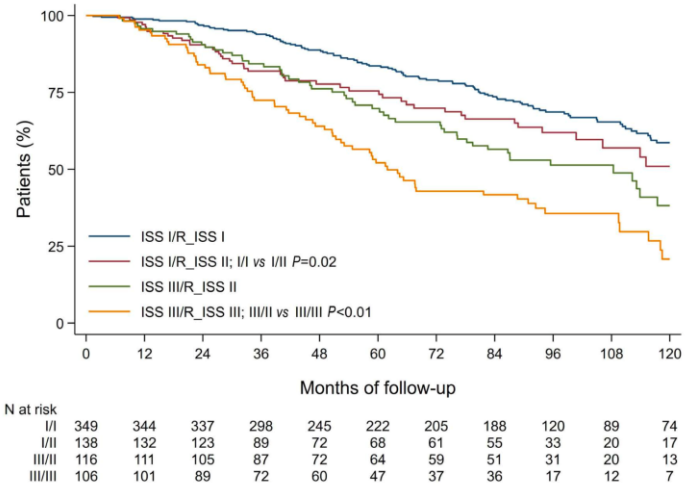
From R-ISS to R2-ISS

Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

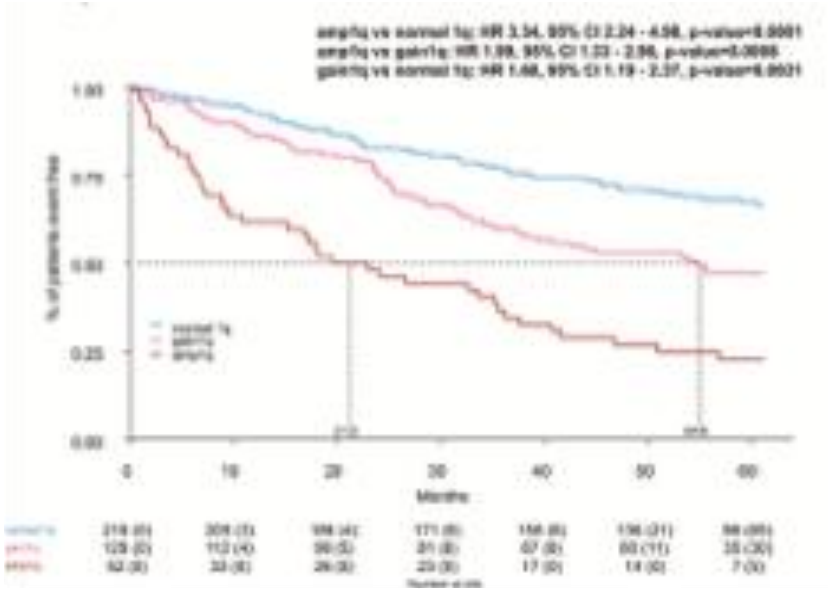


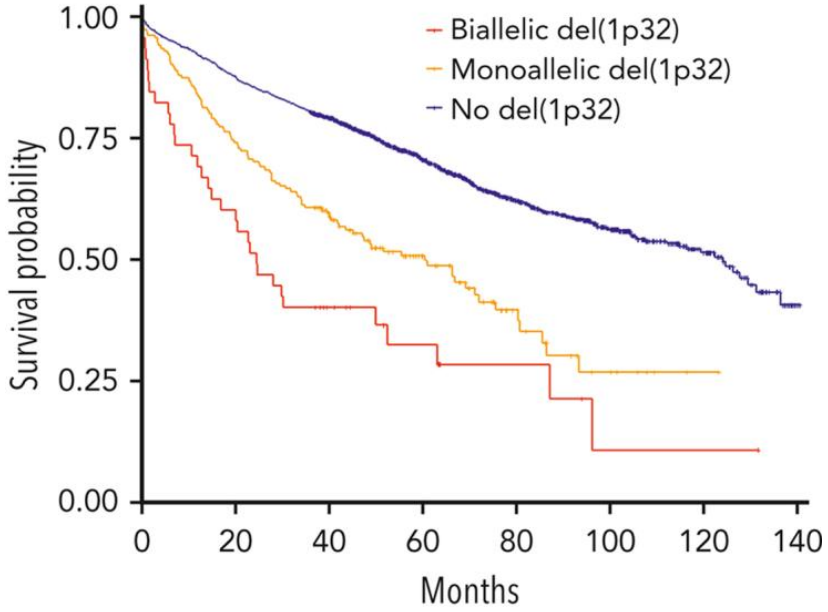


Palumbo A et al. JCO doi:10.1200/JCO.2015.61.2267. Schavgoulidze A et al Haematologica doi.org/10.3324/haematol.2021.280566

From R-ISS to R2-ISS

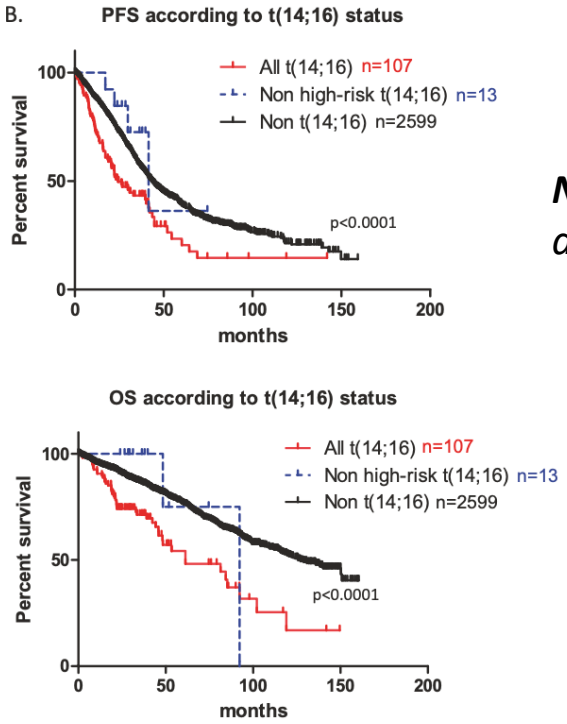
The importance of CHR1 abnormalities





D'Agostino M et al BCJ 2024; Schavgoulidze et al, Blood. 2023 Mar 16;141(11):1308-1315

From R-ISS to R2-ISS



What about t (14;16)?

Non-High risk t(14;16): *patients with t(14;16) but without deletion 17p, TP53 mutation, gain/amp 1q, deletion 1p32*

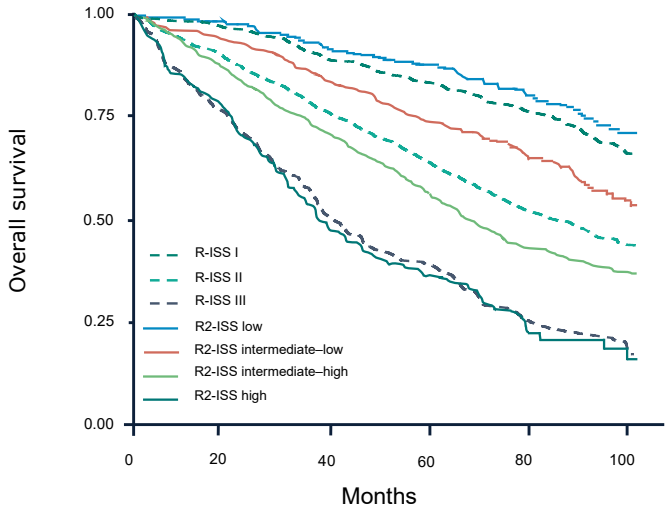
Only the interaction of t(14;16) with other high risk lesions can lead a particular aggressive disease

Avet-Loiseau, H Blood 2011, 117, 2009–2011. Mina, R.; Blood Cancer J. 2020, 10, 1–4;

Schavgoulidze A, *Blood Cancer J.* **13**, 160 (2023). https://doi.org/10.1038/s41408-023-00933-4

From R-ISS to R2-ISS

Overall survival according to the R2-ISS, with superimposed R-ISS in the same patient population



R2-ISS intermediate–low vs. R2-ISS low HR 1.91 (1.5–2.44)
R2-ISS intermediate–high vs. R2-ISS low HR 3.60 (2.87–4.51)
R2-ISS high vs. R2-ISS low HR 6.46 (4.93–8.45)

High-risk factors (score value):

- ISS II (1)
- ISS III (1.5)
- del(17p) (1)
- High LDH (1)
- t(4;14) (1)
- **gain(1q) (0.5)**

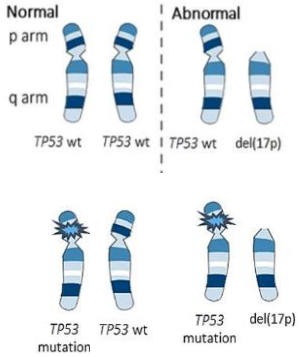
Risk groups (score):

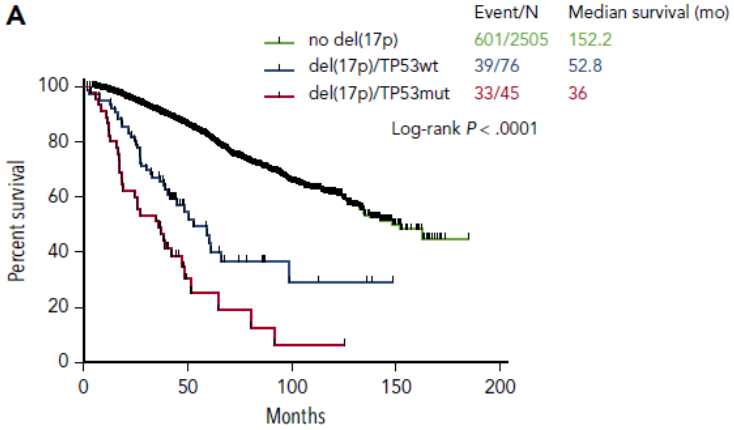
- Low (0)
- Low–intermediate (0.5–1)
- Intermediate–high (1.5–2.5)
- High (>2.5)

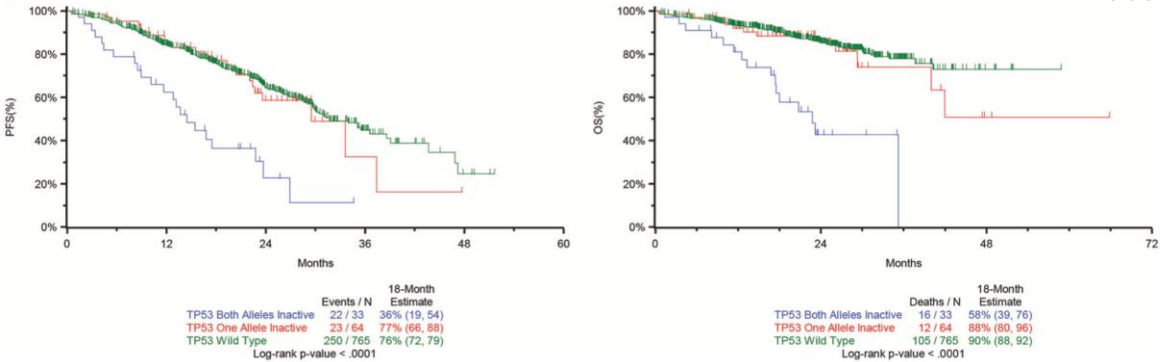
Del(17p), t(4;14) and 1q+ detected by **iFISH** were considered high-risk CA

D'Agostino M, JCO. 2022, 40:3406-3418.

Chr 17p deletion and TP53 mutation







Bi-allelic inactivation of TP53 is the crucial driver of Prognosis when compared to wild-type or mono-allelic inactivation

Corre et al. Blood 2021

From R2-ISS to CGS high risk definitions

	Comments
del(17p) and/or TP53 mutation	• For del 17p by FISH: CCF must be ≥20%, by analyses conducted on CD138-positive/purified cells. • TP53 mutation must be assessed using an NGS-based method.
One of translocations t(4;14) or t(14;16) or t(14;20) co-occurring with 1q+ and/or del(1p32)	
Monoallelic del(1p32) along with 1q+, or biallelic del(1p32)	• biallelic del(1p32) must be assessed using an NGS-based method.
High b2M (≥5.5 mg/L) with normal creatinine (<1.2 mg/dL)	

Abbreviations: 1q21, gain (three copies) or amplification (≥4 copies) of the long arm of chromosome 1; b2M, b2 microglobulin; CCF, cancer clonal fraction; HRMM, high-risk multiple myeloma; NGS, next generation sequencing.

Avet-Loiseau H et al J Clin Oncol 2025 ; 43:2739-2751

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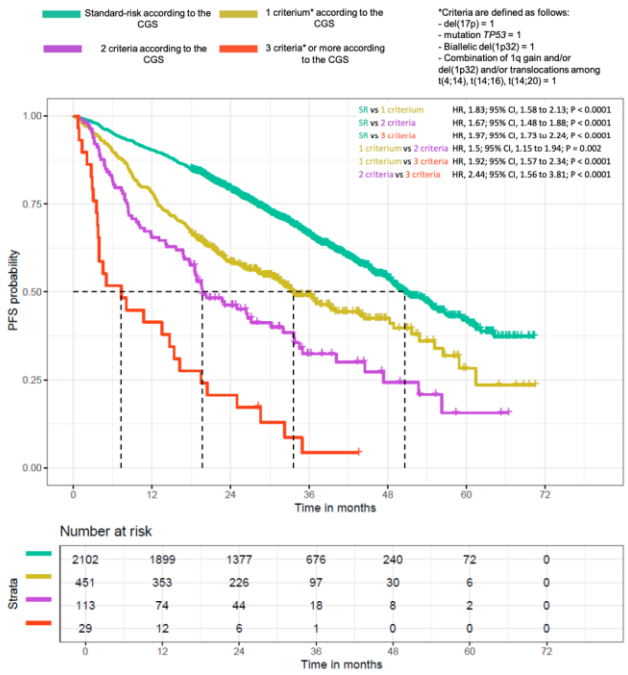
Avet-Loiseau H et al J Clin Oncol 2025 ; 43:2739-2751

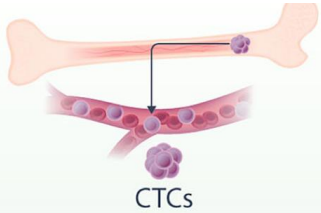
"Double-hit" and ultra high risk patients



The culmination of several HR genomic criteria had an even
worse prognosis (1 criterion vs 2 criteria vs 3 or more criteria
had a median PFS of 34, 20, and 7 months

Schavgoulidze A et al Blood 2026

Eleveted Circulating tumour cells (CTCs) in MM



Study design

CoMMPass cohort
CellSearch
n = 540

patients with CTC enumeration

Ostrava cohort
NGF cytometry
n = 135

WGS/WES

RNAseq

Elevated CTCs associated with:

Worse prognostic
and advanced disease stages

Complex genomics
gain/amp1q, APOBEC, chromothripsis

Proliferative profile
enrichment in cell cycle and proliferation

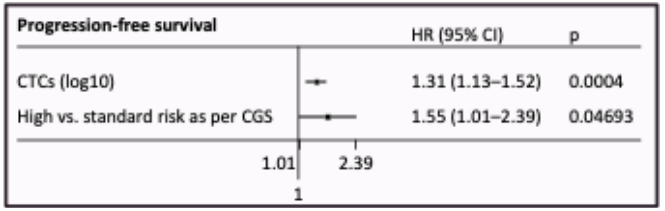
Elevated CTCs reflect aggressive biological features and outperform prognostic markers such as proliferation signatures

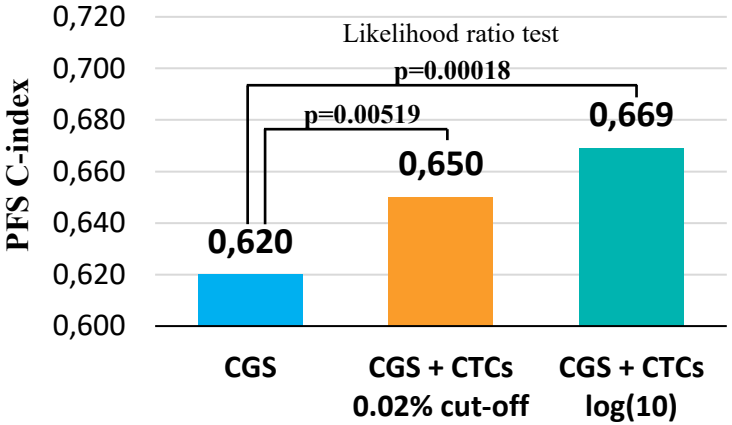
❖ Not a single optimal threshold →

for easiness of clinical implementation: 0.02% for dichotomized stratification and 2% for "hidden" PCL.[6]

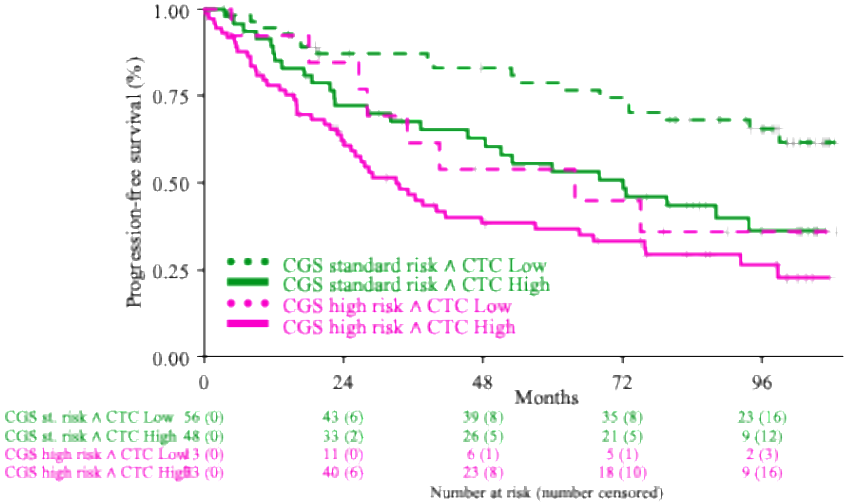
Garces JJ et al et al Hemasphere 2025, Bertamini L, et al, HemaSphere 2025;9(S1):230 [Abstract #S199, EHA 2025 30th meeting].

CTCS improve risk stratification





Multivariate Cox model adjusted for center, transplant eligibility, treatment regimen, and age



Median PFS – CGS standard risk ∧ CTC Low: not reached
Median PFS – CGS standard risk ∧ CTC High: 72 months

Median PFS – CGS high risk ∧ CTC Low: 64 months
Median PFS – CGS high risk ∧ CTC High: 33 months

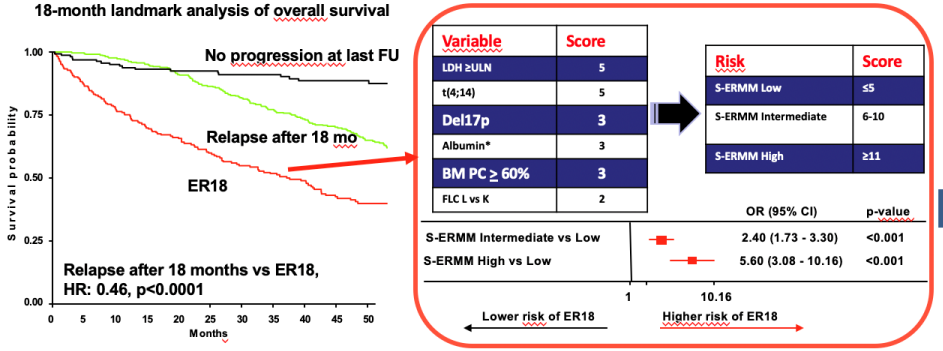
High risk as per CGS was defined as the presence of ≥1 of these abnormalities: (1) del(17p), with a cutoff of >20% clonal fraction, and/or TP53 mutation; (2) an IgH translocation including t(4;14), t(14;16), or t(14;20) along with 1q+ and/or del(1p32); (3) monoallelic del(1p32) along with 1q+ or biallelic del(1p32); or (4) β2 microglobulin ≥5.5 mg/L with normal creatinine (<1.2 mg/dL). Avet-Loiseau H, et al. J Clin Oncol. 2025 Aug 20;43(24):2739-2751. doi: 10.1200/JCO-24-01893; err. 10.1200/JCO-25-01367.

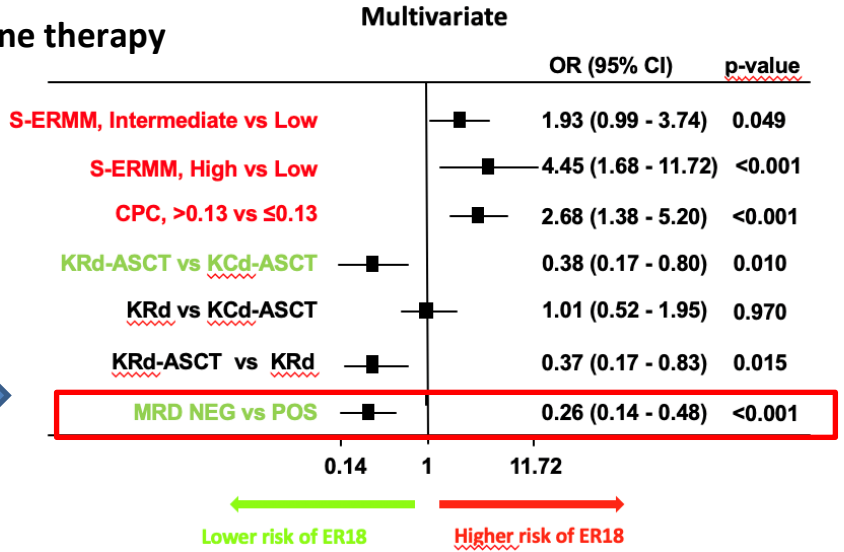
D'agostino M et al et al ASH 2025, oral presemntation

Determinants of functional high risk (FHR) : baseline + MRD response

Baseline genetic and disease-related features, response to first line therapy

MRD is the new endpoint of response able to reduce the risk of ER





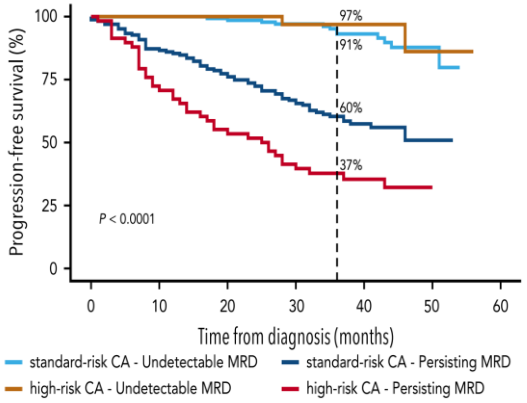
MM, multiple myeloma; FU, follow-up; ER18, early relapse ≤18 months from diagnosis; LDH, lactate dehydrogenase; ULN, upper limit of normal; BMPC, bone marrow plasma cells; FLC, free light chain.; CI, confidence interval.CPC: circulating plasma cells, K: carfilzomib R: lenalidomide D:dexamethasone, ASCT: autologous stem cell trasnplant, C: cyclophophamide

Zaccaria GM, et al. Clin Cancer Res. 2021 Jul 1;27(13):3695-3703. doi: 10.1158/1078-0432. Beksac M, et al. Bone Marrow Transplant. 2023;58(8):916-923.
Charalampous C, et al.. Blood Adv. 2023;7:4371-4380, Majithia N, et al. Am J Hematol. 2015;90(11):981-985.

The importance to achieve and mantain MRD negativity

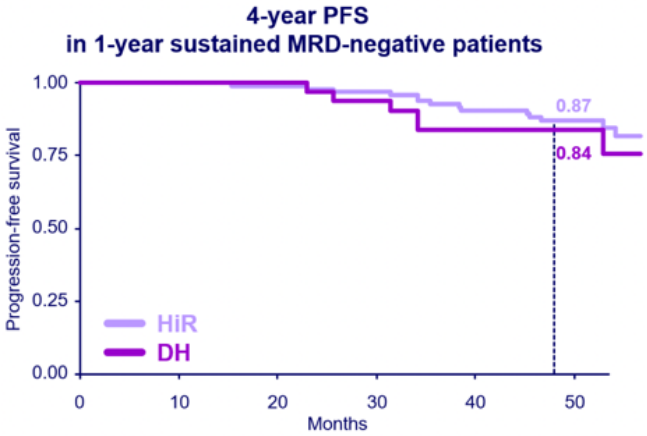
GEM2012MENOS65 trial (10^{-6})

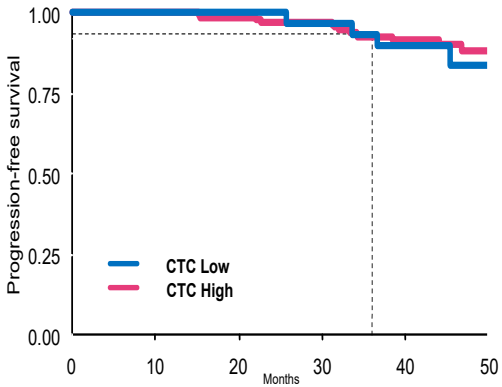
3-year PFS
In MRD negative patients



FORTE trial (10^{-5})

3-year PFS
in 1-year sustained-MRD negative patients

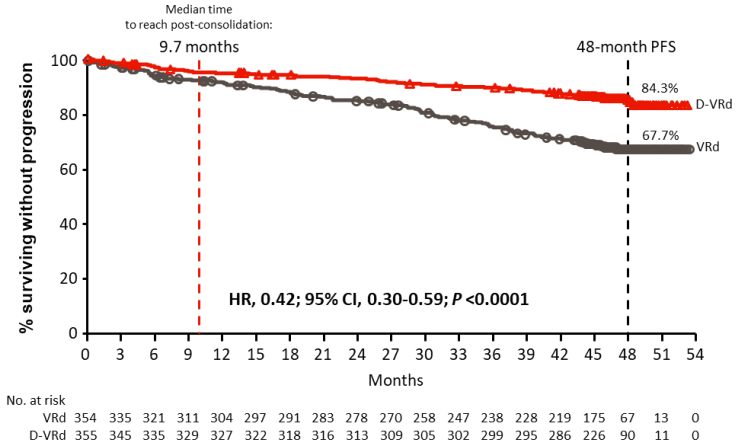




Goicoechea I et al. Blood 2021;137(1):49-60; Mina R et al Lancet Hematol 2022; Bertamini L. et al, JCO 2022.

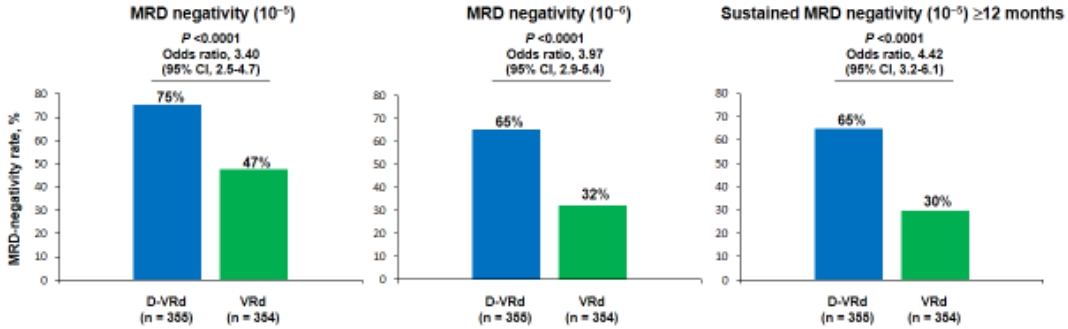
CA, cytogenetic abnormalities; MM, multiple myeloma; MRD, minimal residual disease.; HiR, high risk; DH, double hit, CTC: circulating tumour cells

The importance to achieve and mantain MRD negativity



58% reduction in the risk of progression or death in patients receiving D-VRd

PERSEUS: Overall and Sustained MRD-negativity rates



64% (207/322) patients receiving Dara-Rev maintenance discontinued Dara after 24 months (≥CR and sustained MRD negativity [10^{-5}] for ≥12 months)

MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via next-generation sequencing.

Courtesy of P Sonneveld; presented at ASH 2023

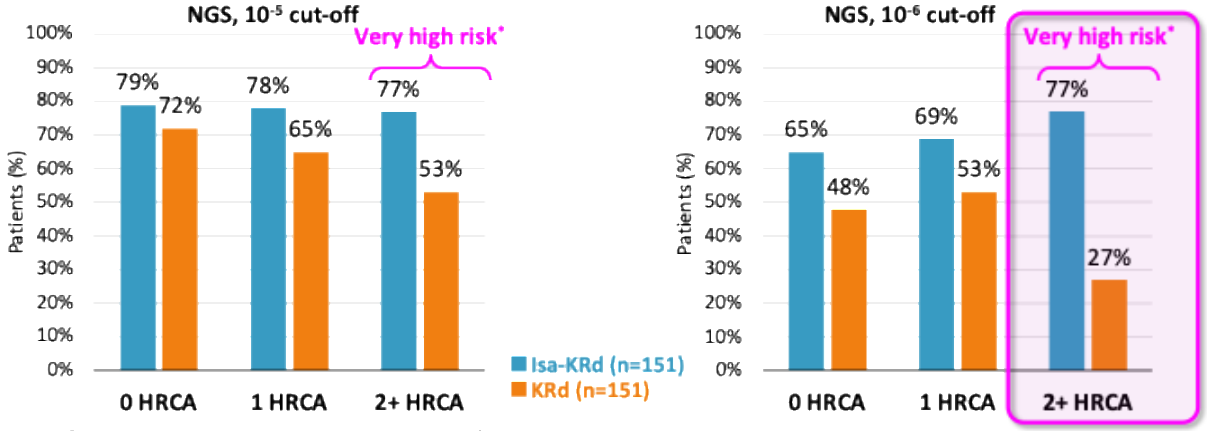
Rates of MRD negativity improved during maintenance

The absolute difference between D-VRd and VRd widened over time and is most evident at the deeper threshold of 10^{-6}

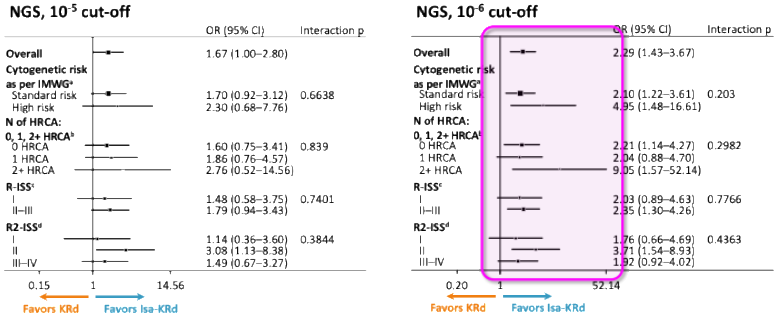
Sonneveld P et al ASH 2023 oral presentation, Sonneveld P et al N. Eng J Med 2024

Rodriguez-Otero P et al. ASCO 2024

How to mitigate »*the very high risk*«



ISKIA: Isa-KRd vs KRd



Post-consolidation MRD negativity by NGS
Subgroup analysis by cytogenetic risk

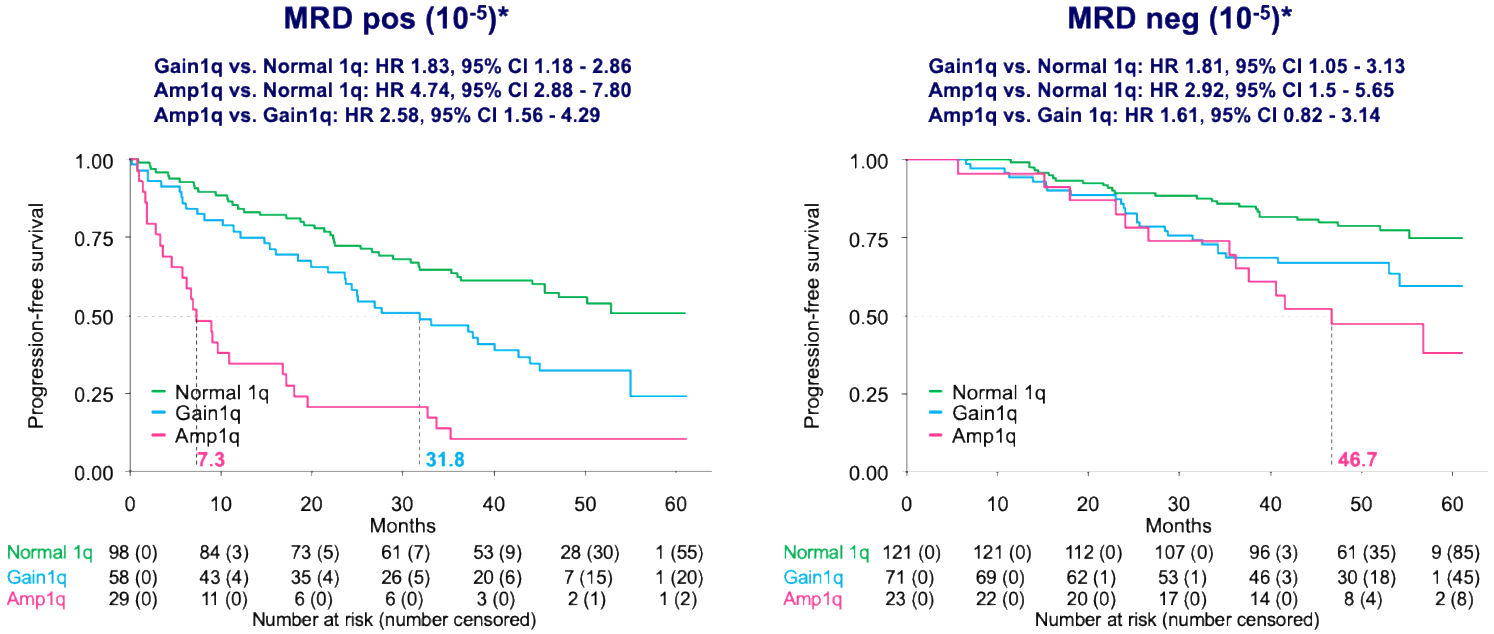
But is it corraleted with PFS and OS?

**1 HRCA was defined as the presence of one of the following high-risk cytogenetic abnormalities (CA): del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21); 2+ HRCA was defined as the presence of at least two high-risk CA.*

MRD, measurable residual disease; NGS, next-generation sequencing; HRCA, high-risk cytogenetic abnormalities; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; del, deletion; t, translocation; amp, amplification.

Gay F et al ASH 2023

MRD alone or MRD + baseline risk stratification?



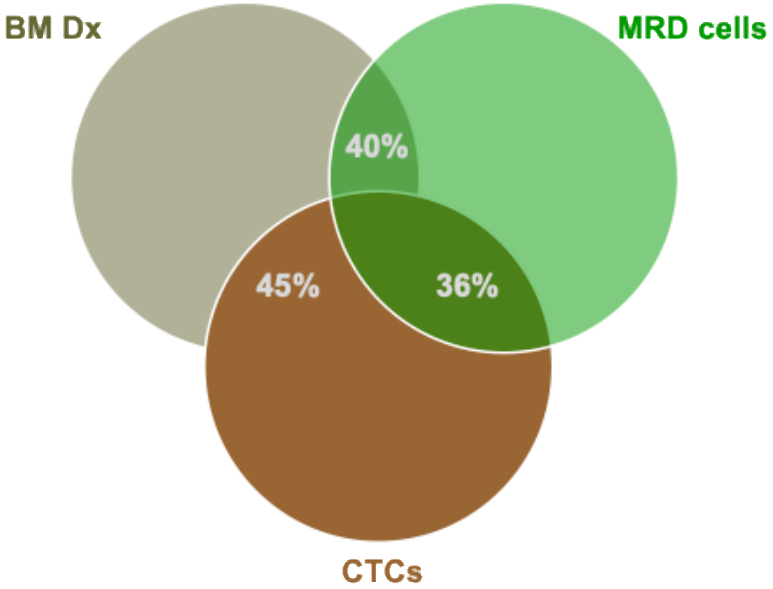
Analysis performed by multiparameter flow cytometry (MFC) before maintenance in the intention-to-treat population.

D'Agostino M. et al BCJ 2024

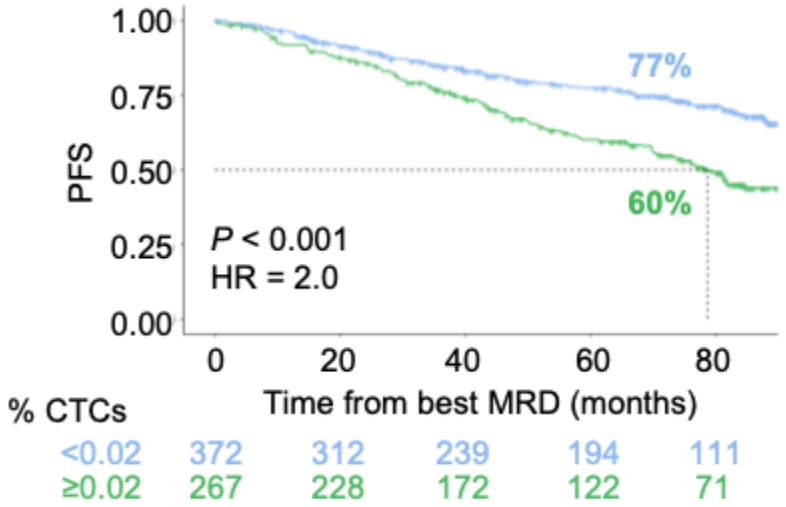
PFS: progression-free survival; HR, hazard ratio; MRD: minimal residual disease, POS, positivity; NEG, negativity.

Combined Assessment of CTCs and MRD for dynamic risk assessment

CTCs and MRD show the lowest genomic similarity



MRD neg patients

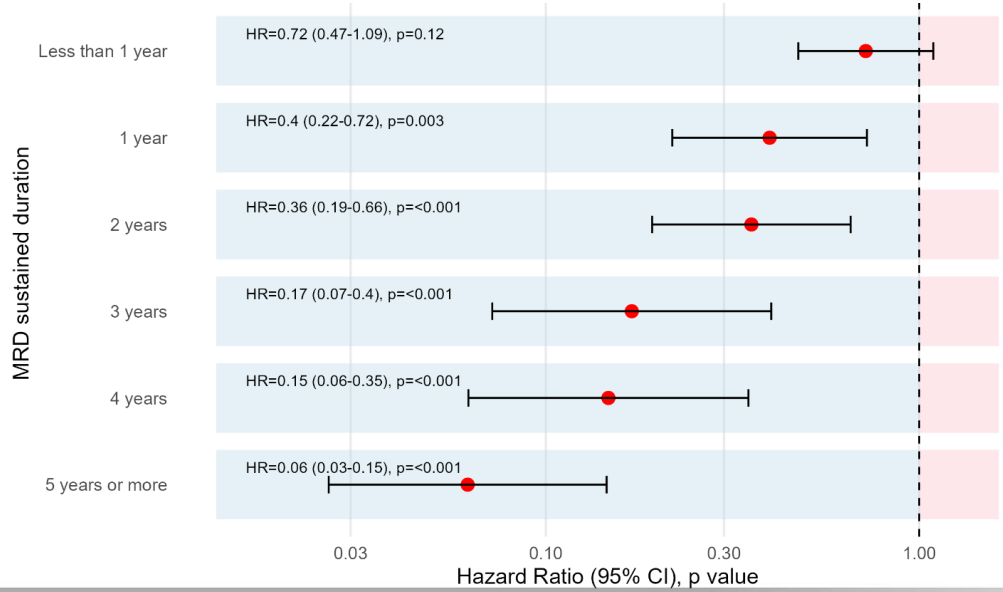


SNV: ≥2 callers (Seurat, Strelka and Mutect), AF <2% in T cells, >5% in the tumor sample, filter false-positives
CNV: Log2 < -0.5 (deletion) and > 0.5 (amplification); filter X and Y chromosomes

Paiva B et al ASH 2025, oral presentation

Sustained MRD negativity is clinically relavant: How many years of Sustained MRD negativity?

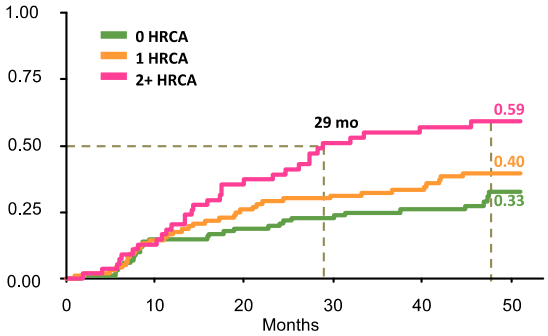
FORTE trial long term follow-up

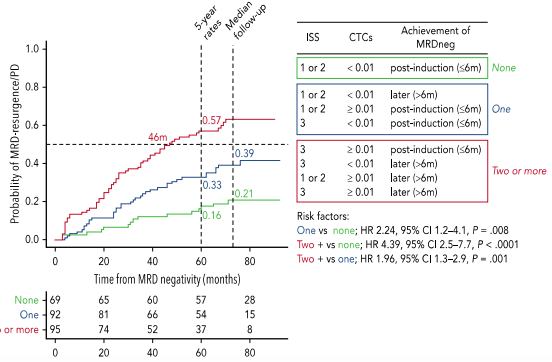


Manuscript in preparation

Risk of losing MRD negativity over time

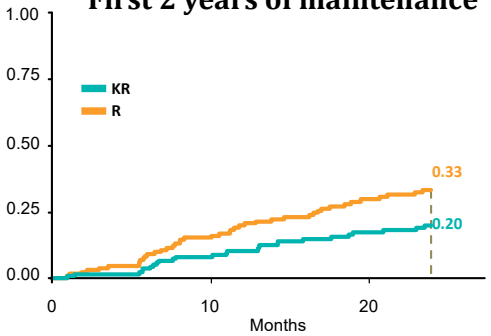
MRD resurgence from first MRD negativity

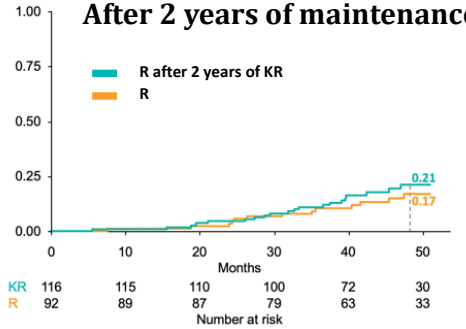




D'Agostino M et al, Blood 2024; Guerrero C et al, Blood 2024.
Abbreviatons R; lenalidomide; K carfilzomib; HRCA: high-risk chromosomal abnormalities

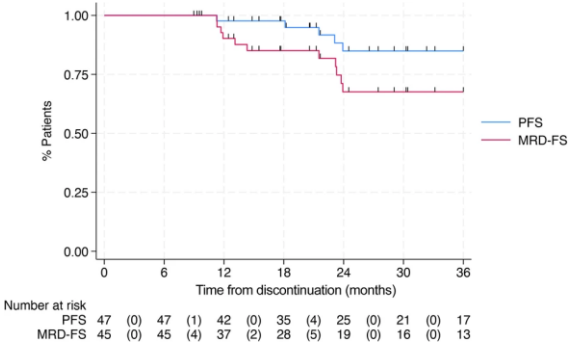
FORTE trial: KR vs R maintenance



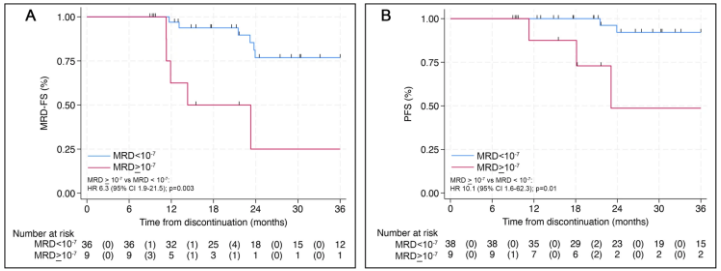


MRD adapted treatment discontinuation

MRD2stop study: maintenance cessation based on MRD



Exploratory endpoint: MRD 10-7



Greek Discontinuation Study (n=52)

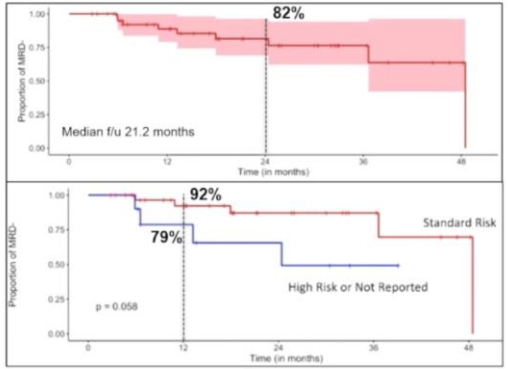
- Post-ASCT
- 3+ years of: maintenance lenalidomide, sustained MRD <10^{-6} (NGF) & PET negativity
- Restart lenalidomide if MRD (+)

23% MRD 10^{-6} resurgence

Conclusion: Maintenance cessation with 3+ year-sustained MRD negativity at 10^{-5} or 10^{-6} associated with similarly excellent outcomes (esp. standard-risk myeloma)

MSK Discontinuation Study (n=43)

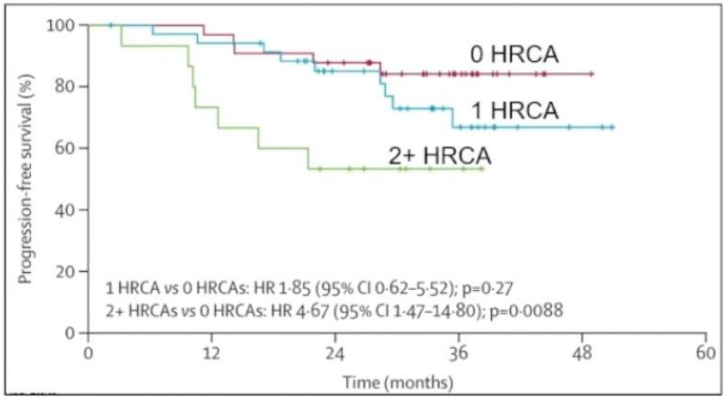
- 3+ years of sustained MRD <10^{-5} (flow) during maintenance
- Optional: Restart lenalidomide if MRD (+)



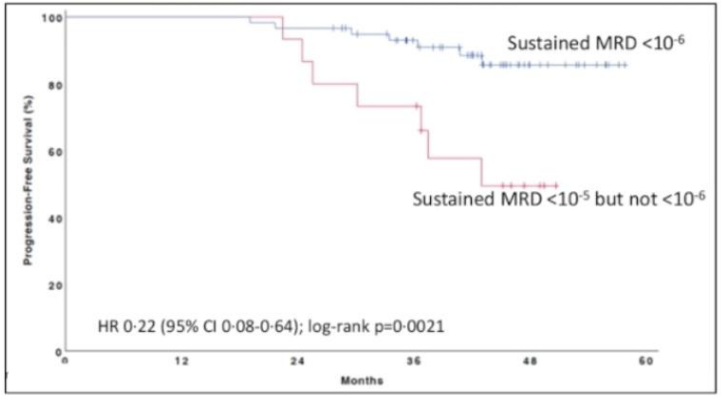
Derman B A et al BCJ 2024, Terpos E A et al Blood 2025, Korde et al IMS 2024

MRD adapted treatment discontinuation: Master Trial (daraKRD + ASCT)

Stop therapy after 2 consecutive MRD<10^{-5}
71% proceeded with active surveillance



Patients with 0 high-risk abnormalities do well despite no maintenance therapy
2-year PFS from discontinuation = 88%



Patients with sustained MRD <10^{-6} have better outcomes than sustained MRD <10^{-5} only
4-year PFS from randomization = ~90%

Costa et al The lancet Hematology 2023

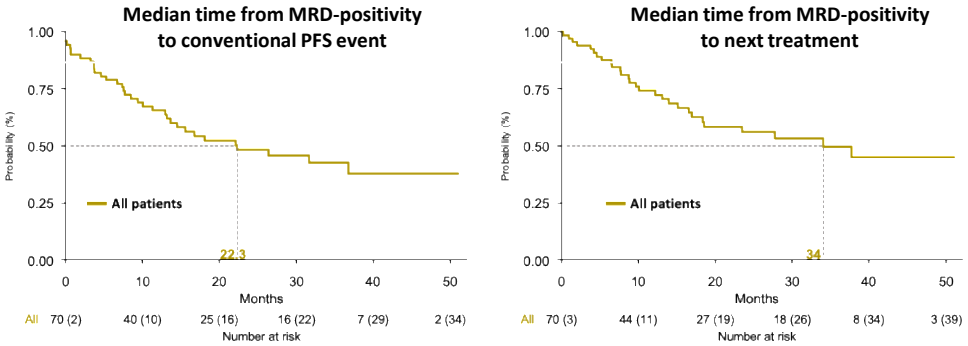
MRD adapted treatment intensification

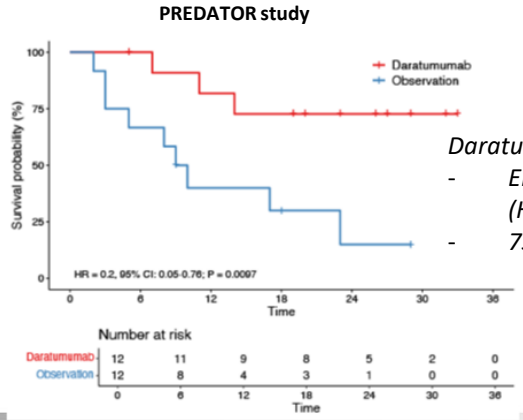
Before MRD era: treatment at biochemical vs clinical progression

Study	endpoint	BP(months)	CP (months)
Mayo clinic	OS from relapse	59.4	26.2
Mayo clinic	TTNT	17	9.6
Greek group	PFS	24	13.2

→ *Early treatment: nearly doubled survival and 37% lower risk of progression or death.*

MRD resurgence: what to do?

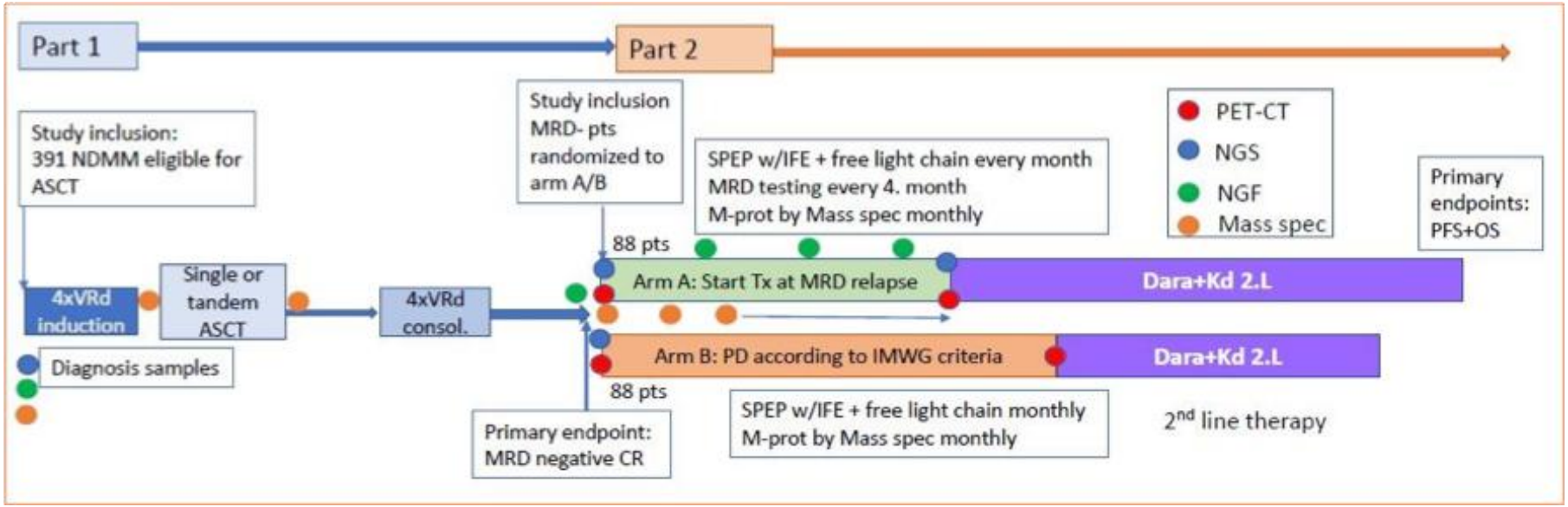




Daratumumab vs observation:
- *EFS not reached vs 9.5 months (HR≈0.20; ~80% risk reduction)*
- *75% MRD negativity regained*

Katodritou e et al Annals of hematology 2018 , Goldman-Mazur S et al Blood advances 2023, D'Agostino M et al Blood 2024

MRD adapted treatment intensification: the Remnant study



ClinicalTrials.gov Identifier: NCT04513639

Rasmussen A. et al., *Hemato* 2020, *1*(2), 36-48

Conclusions

- Current new risk stratification models to evaluate static prognosticators in 2026: the role of NGS + FISH

- The best way to stratify MM patients is to combine the different prognostic factors, creating a more comprehensive and powerful score (NGS, FISH analyses, CTCs, MRD..)

- MRD should be used as dynamic tool to monitor FHR, to modulate static risk and MM therapies (de-intensification and intensification)

Future perspectives

- Development of risk-tailored treatment strategies based on both baseline and dynamic risk factors, combination with CTCs
- Randomized clinical trials to compare different treatment strategies specifically designed for high-risk disease (many phase II single arm trials so far)

Thank you for the attention

Aknowledgements

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Transplant Unit
Nurses
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Statisticians

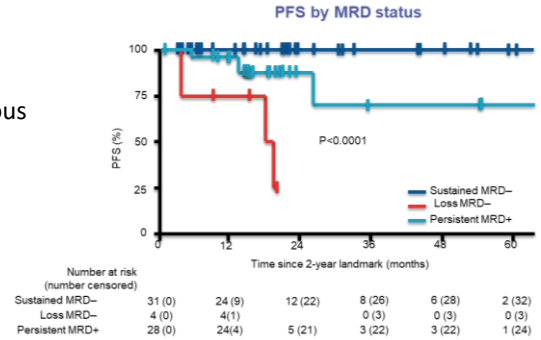
Back up

How to use the kinetics of MRD to guide treatments

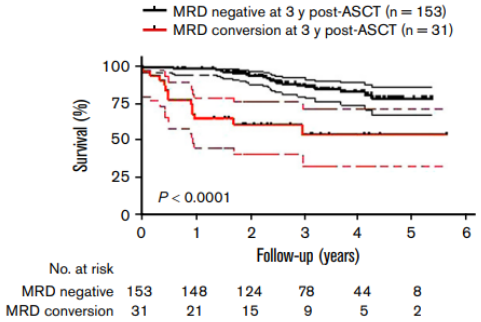
Potential MRD-adapted strategies in MM

Scenario	Information learned	Potential intervention
Sustained MRD negativity	Deep/durable responders	Single-agent maintenance: discontinue Multi-agent maintenance: de-escalate
MRD (+) to MRD (-)	Benefit conferred by intervention (ie, ASCT, maintenance)	De-escalation of intensive therapy
MRD (+) to MRD (+)	Signifies persistent disease	Careful monitoring for disease progression Early intervention before progression
MRD (-) to MRD (+)	Harbinger of progression	Early intervention before progression

5 years continuous single Len maintenance approach

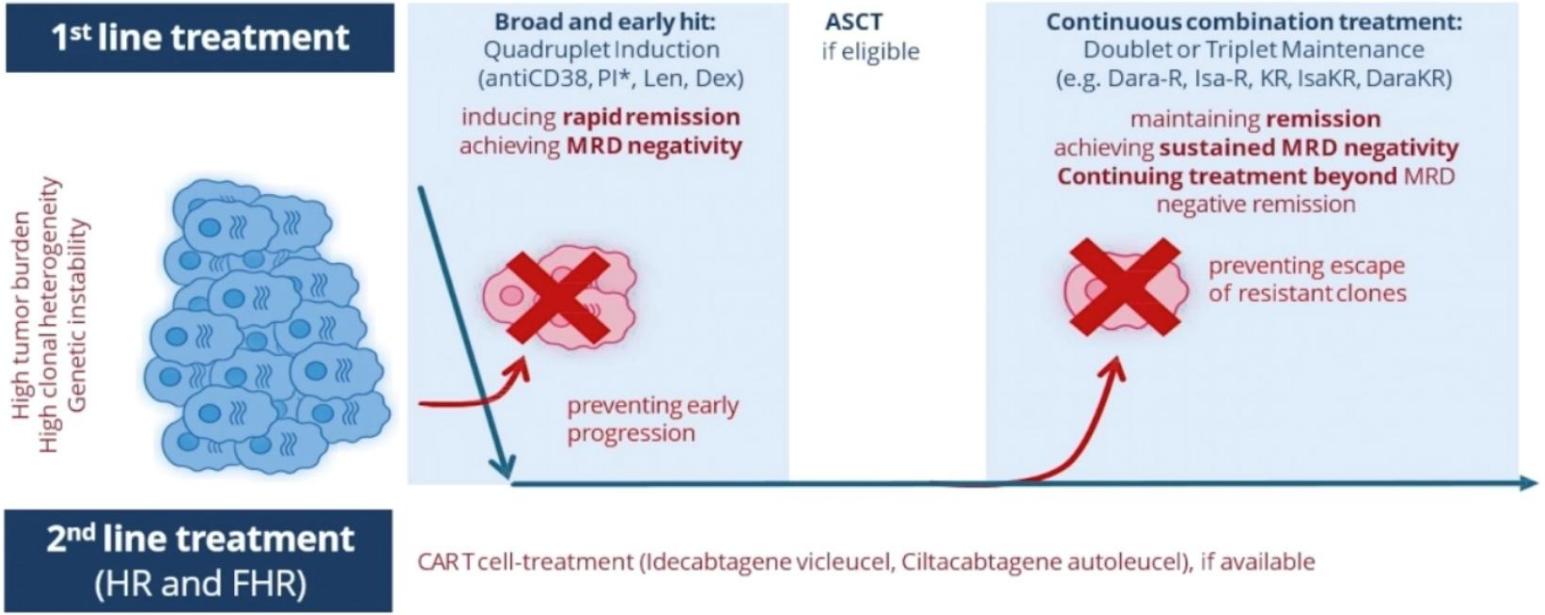


2 years continuous Len+PI maintenance approach



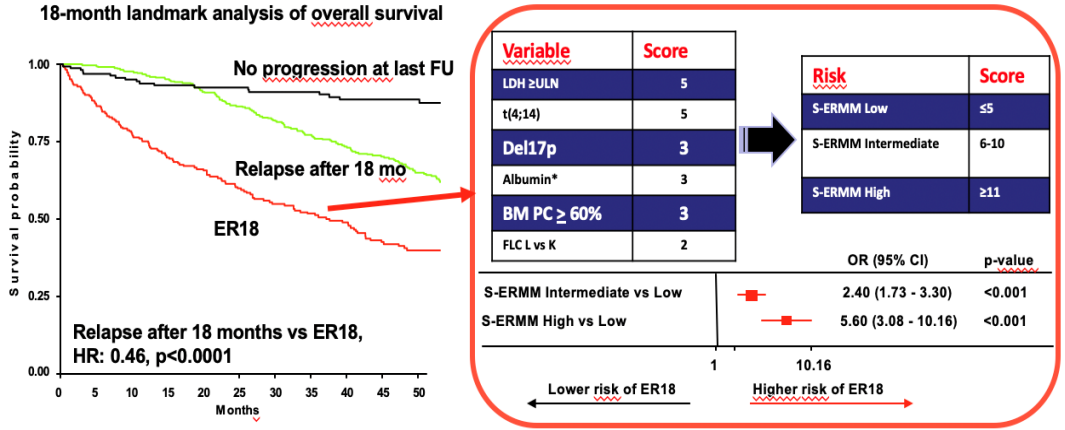
Derman B A et al Hematol Oncol Clin N Am, 2023 Diamond B, et al. Lancet Haematol 2021;8:e422–32, Mohan M, et al. Blood advances 2022;8:e808–17

Paradigm of treating HR patients



Determinants of FHR

Baseline genetic and disease-related features



Variable	Score
LDH ≥ULN	5
t(4;14)	5
Del17p	3
Albumin*	3
BM PC ≥ 60%	3
FLC L vs K	2

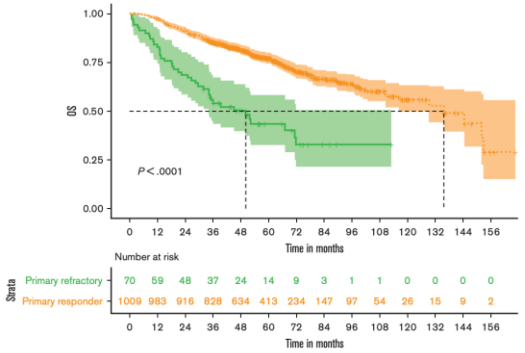
Risk	Score
S-ERMM Low	≤5
S-ERMM Intermediate	6-10
S-ERMM High	≥11

	OR (95% CI)	p-value
S-ERMM Intermediate vs Low	2.40 (1.73 - 3.30)	<0.001
S-ERMM High vs Low	5.60 (3.08 - 10.16)	<0.001

1 — 10.16

Lower risk of ER18 — Higher risk of ER18

Response to first line therapy



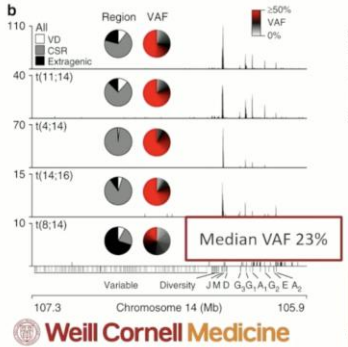
Variable		N	Events	Hazard ratio	HR (95% CI)	P
Age		751			1.26 (1.06, 1.50)	.008
ISS	1	291	54		Reference	
	2	263	60		1.04 (0.71, 1.51)	.845
	3	197	79		1.57 (1.07, 2.31)	.022
Type of induction	Quadruplets	76	9		Reference	
	Triplets	675	184		1.93 (0.98, 3.80)	.056
ECOG	0-1	365	69		Reference	
	2-4	386	124		1.72 (1.27, 2.33)	<.001
FISH	Standard-Risk	415	74		Reference	
	High-Risk	247	75		2.11 (1.52, 2.92)	<.001
	Double-Hit	89	44		4.36 (2.97, 6.41)	<.001
Response at induction	Primary responder	718	174		Reference	
	Primary refractory	33	19		4.26 (2.61, 6.94)	<.001
Plasma cells in the BM	Less than 60%	473	100		Reference	
	More than 60%	278	93		1.36 (1.00, 1.87)	.051

Zaccaria GM, et al. Clin Cancer Res. 2021 Jul 1;27(13):3695-3703. doi: 10.1158/1078-0432. Beksac M, et al. Bone Marrow Transplant. 2023;58(8):916-923.
Charalampous C, et al.. Blood Adv. 2023;7:4371-4380, Majithia N, et al. Am J Hematol. 2015;90(11):981-985.

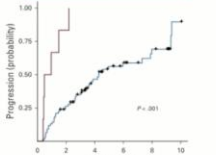
MYC rearrangements

CoMMpass: *MYC*-r Are Present at Myeloma Diagnosis

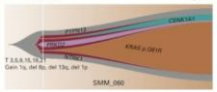
MYC::IGH are Sub-clonal Events



MYC alterations are associated with SMM progression



At MM Diagnosis, the predominant clone was already present at SMM diagnosis



MYC-r were present at diagnosis in 22/24 patients with >1 sample

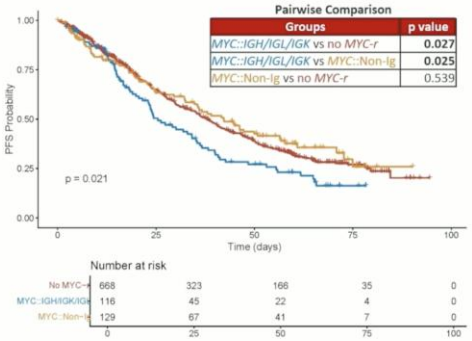
Patients with serial Samples	N = 147
Always *MYC*-r neg	123 (84%)
MYC-r pos in first sample	22 (15%)
MYC-r neg → pos	2 (1.4%)

Misund, K., et al. *Leukemia*, *34*(1), 322–326.
Boyle, E. M., et al. *Nature Communications*, *12*(1), 293.
Misund, K., et al. *Leukemia*, *34*(1), 322–326.
Barwick, B. G., et al. *Nature Communications*, *10*(1), 1911.
Bustoros, M et al. *Journal of Clinical Oncology*, 38(21), 2380–2389.

Weill Cornell Medicine

9

CoMMpass: *MYC*-r are Associated with Inferior PFS



Weill Cornell Medicine

Multivariable Cox - PFS		
Characteristic	**HR (95% CI)**	**p-value**
***MYC-R* status**		0.040
No *MYC* alteration	—	
MYC::Non-Ig	1.08 (0.83 - 1.40)	0.54
MYC::IGH/IGL/IGK	**1.40 (1.09 – 1.80)**	0.008
Age at Diagnosis		**0.029**
Age < 65	—	
Age >= 65	1.23 (1.02 - 1.48)	
AutoSCT 1st line		**<0.001**
No AutoSCT	—	
AutoSCT	0.43 (0.35 - 0.53)	
First Line		
Doublet	—	0.38
Triplet	0.91 (0.75 - 1.12)	
Del17p Present	1.35 (1.02 - 1.77)	**0.040**
Gain1q21 Present	1.32 (1.10 - 1.58)	**0.003**
Del1p22 Present	1.26 (1.03 - 1.55)	**0.029**
t(4;14) Present	1.07 (0.82 – 1.41)	0.61

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

10

Saldarriaga MM et al et al ASH 2025, oral presentation

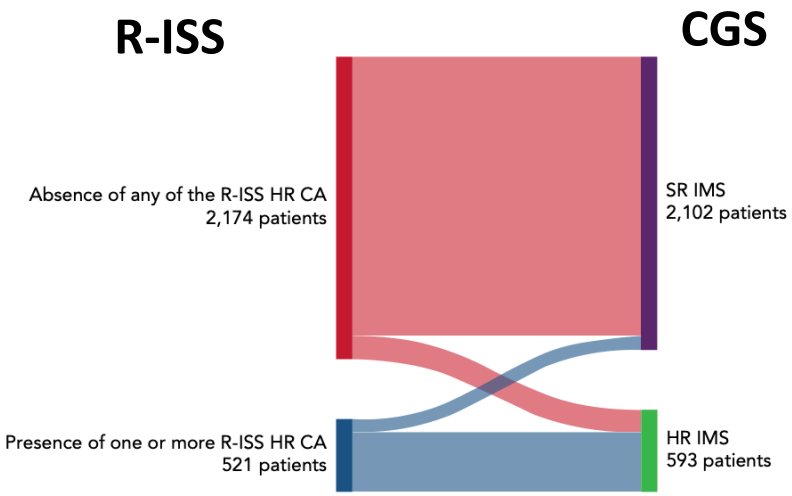
Ultra High risk MM

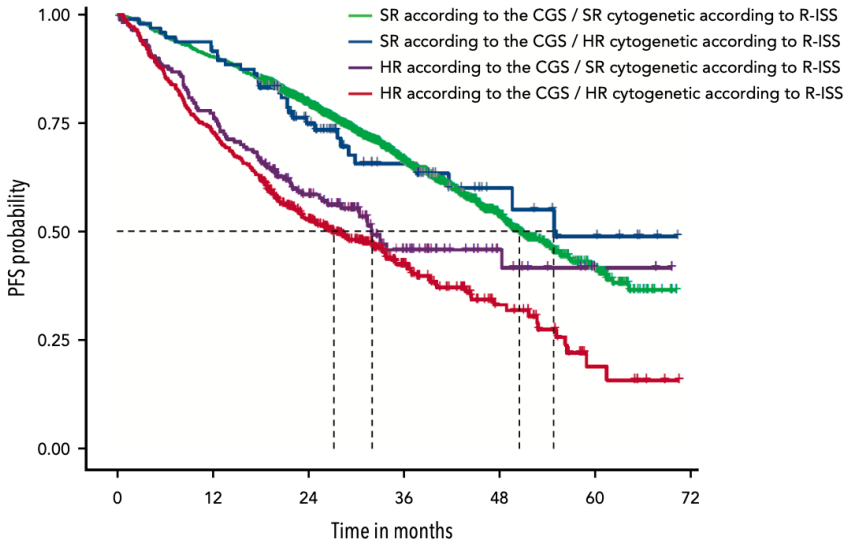
Ultra HR MM is not defined in a consensus approach, however used for MM leading to death in 24-36 months with following features[1]:

- Biallelic TP53 inactivation
- ≥2 HRCAs: del(17p), TP53 mutation, t(4;14), t(14;16), t(14;20), gain(1q), amp(1q), del(1p32)
- High-risk GEP signature
- Extramedullary disease
- ≥2% circulating plasma cells

Rees MJ, Am Soc Clin Oncol Educ Book. 2024 Jun; 44(3).

Reclassification of patients





18.2% R-ISS were reclassified SR CGS, **7.8%** with SR R- ISS were reclassified HR-CGS

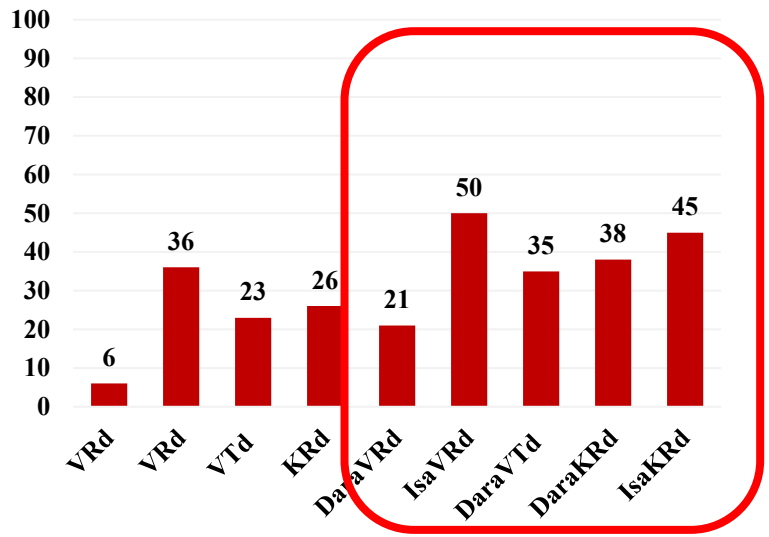
The HR CA criteria from the R-ISS classification were not able to discriminate between patients in the HR and SR CGS subgroups

Schavgoulidze A et al Blood 2026

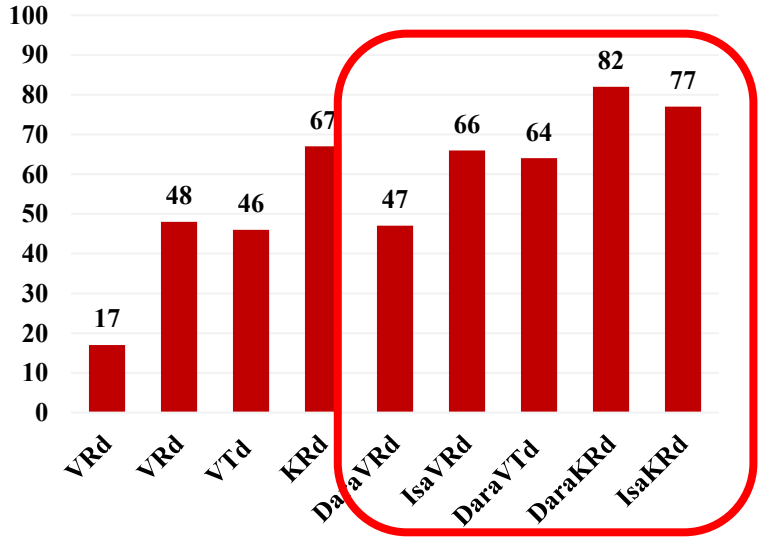
The importance to achieve and mantain MRD negativity

Triplets vs quadruplets as induction and consolidation in transplant eligible patients: the more, the deeper

Post-induction MRD negativity rates (%, 10^{-5})



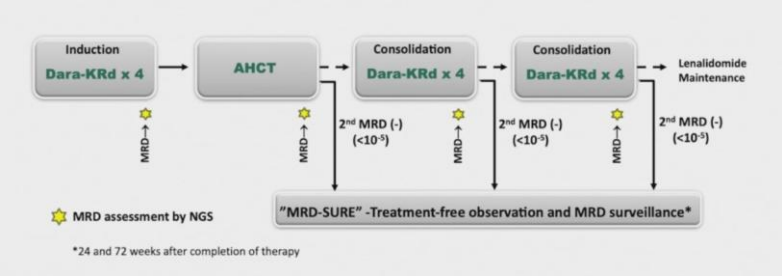
Post-consolidation MRD negativity rates (%; 10^{-5})

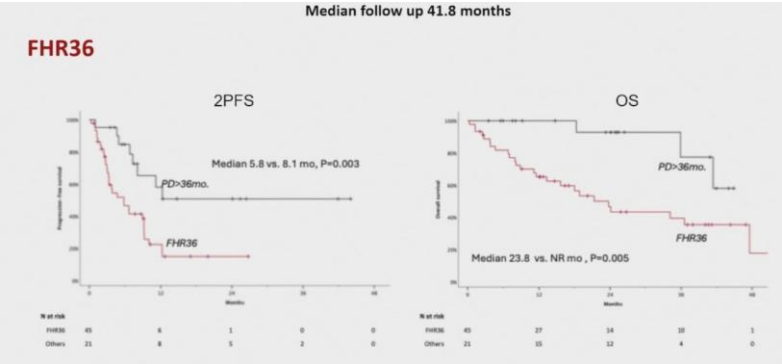


Despite the use of quadruplets, 1/4 to 1/3 patients will be MRD positive before starting maintenance

Voorhees et al Blood 2020, Goldschmidt H et al Lancet haem 2022; Gay F et al ASH 2023; Costa L et al JCO 2022; Moreau P et al The Lancet 2019, Avet Loiseau H et al ASCO 2019

Functional High risk 36 after quadruplets and ASCT





Cox Regression Model

ORR	OR	95% C.I	P
FHR36	0.25	0.07-0.90	0.03
TCRT in second line therapy	8.98	0.94-85.58	0.06
IMS/IMWG high risk	0.28	0.09-0.88	0.03
2PFS	**HR**	**95% C.I**	**P**
FHR36	2.39	1.09-5.27	0.03
TCRT in second line therapy	0.17	0.04-0.71	0.02
IMS/IMWG high risk	0.97	0.52-1.82	0.93
OS	**HR**	**95% C.I**	**P**
FHR36	4.20	1.25-14.16	0.02
TCRT in second line therapy	0.36	0.05-2.74	0.33
IMS/IMWG high risk	1.77	0.80-3.93	0.16

FHR36= functional high risk with progression in the first 36 months from onset of first line therapy; TCRT= T-cell redirecting threrapy; ORR= overall response rate; 2PFS= second progression free survival; OS= Overall survival

TCRT in 2° line is associated with improved 2PFS

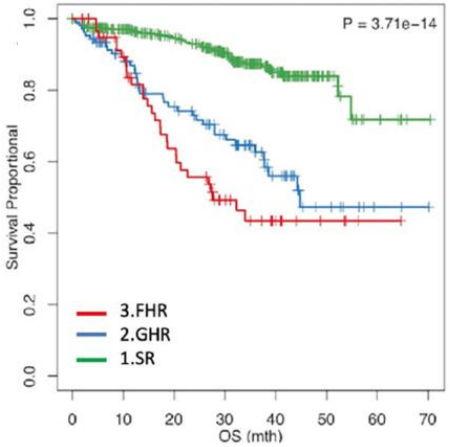
Costa LJ et al ASH 2025, oral presentation

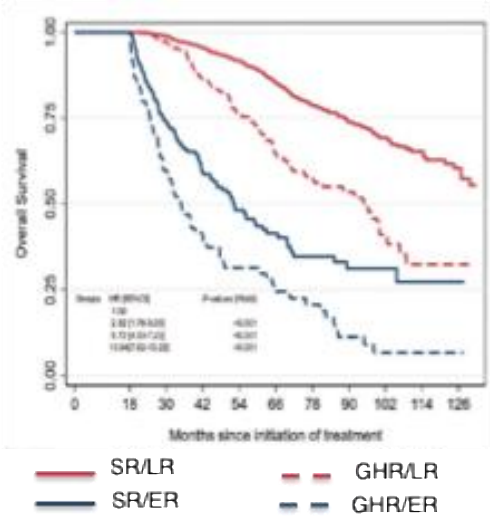
Functional high risk (FHR)

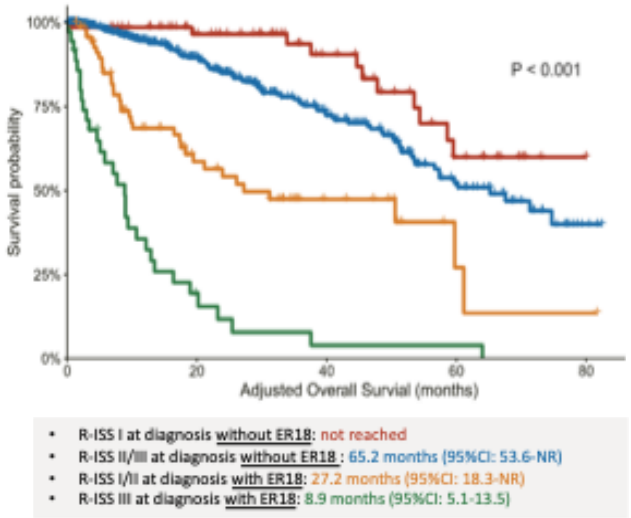
DINAMIC DEFINITION:

Patients with no apparent/not necessarily high-risk features at diagnosis ***who progress within 12 to 18 months from treatment initiation*** despite an optimal initial therapy

ISS-I was reported in 12-22% of ER, Standard risk cytogenetics in 12-40% of ER



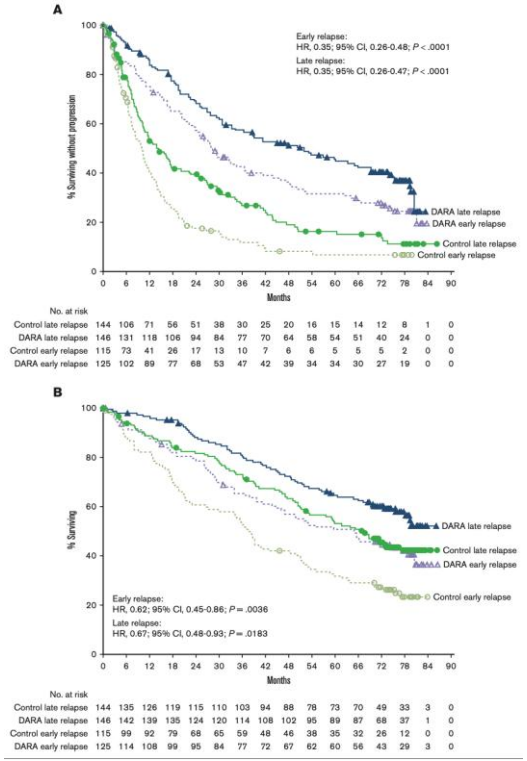




ISS, International Staging System; ER, ealy relapse, SR, standard risk; GHR, genomic high risk; FHR, functional high risk; LR, late relapse, R-ISS, Revised International Staging system

Bygrave C, et al., Br J Haematol. 2021; Corre J et al., *Haematologica*. 2020; Yan et al., Cancer 2023; Spencer A, et al. Blood. 2019; Kastritis E, et al. Clin Lymphoma, Myeloma Leuk 2020; D'Agostino M, et al. Clin Cancer Res. 2020; Soekojo et al., Blood Cancer J. 2022, Kumar SK, Leukemia. 2018; Gopalakrishnan S et al., Biol Blood Marrow Transplant. 2019

Strategies to improve FHR and MRD



24-Months cut-off in post-hoc analysis of Castor and Pollux trials

Table 2. Response rates and MRD-negativity rates according to the relapse subgroup

	Early relapse (<24 mos)			Late relapse (≥24 mos)		
	DARA	Control	P	DARA	Control	P
Response, n (%)*						
Patients evaluated, n	121	110		145	141	
ORR	110 (90.9)	81 (73.6)	.0004†	136 (93.8)	114 (80.9)	.0010‡
≥CR	56 (46.3)	15 (13.6)	<.0001†	83 (57.2)	42 (29.8)	<.0001†
sCR	20 (16.5)	2 (1.8)		44 (30.3)	21 (14.9)	
CR	36 (29.8)	13 (11.8)		39 (26.9)	21 (14.9)	
≥VGPR	94 (77.7)	43 (39.1)	<.0001†	114 (78.6)	83 (58.9)	.0003†
VGPR	38 (31.4)	28 (25.5)		31 (21.4)	41 (29.1)	
PR	16 (13.2)	38 (34.5)		22 (15.2)	31 (22.0)	
MR	3 (2.5)	10 (9.1)		2 (1.4)	7 (5.0)	
SD	4 (3.3)	15 (13.6)		6 (4.1)	18 (12.8)	
PD	4 (3.3)	3 (2.7)		0	2 (1.4)	
NE	0	1 (0.9)		1 (0.7)	0	
MRD (10^{-5}) ‡						
Patients evaluated, n	125	115		146	144	
MRD negative, n (%)	28 (22.4)	3 (2.6)	<.0001§	46 (31.5)	15 (10.4)	<.0001§

…still there is a gap for early progressors

Spencer A et al Blood Advances 2023

Strategies to improve FHR and MRD

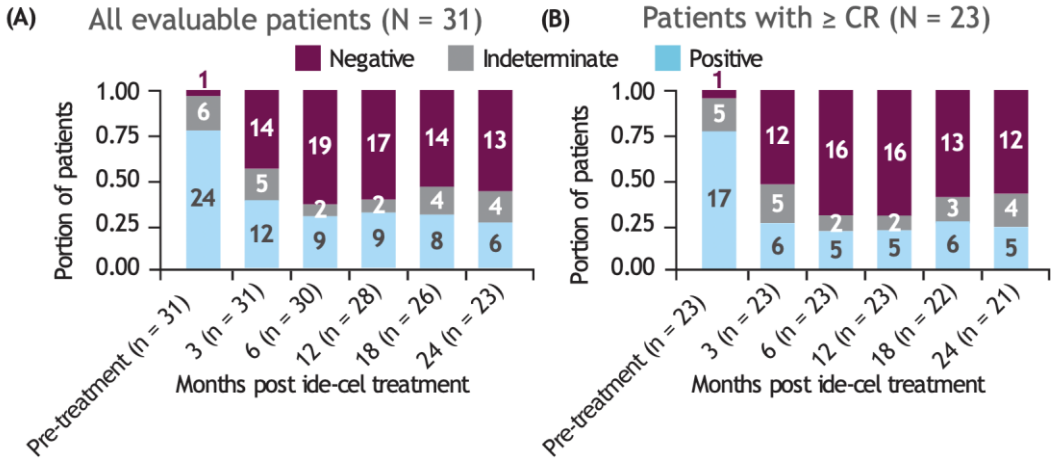
Early immunotherapy: suboptimal response to first line

KarMMa-2 Cohort 2C:
Clinical High-Risk MM due to inadequate response to frontline ASCT (n=31)

Median follow-up 27.9 months

Efficacy outcome	N =31
ORR	87% (≥CR 74%)
24 months PFS	83%
24 months OS rate	100%

MRD negativity at 10^{-5}

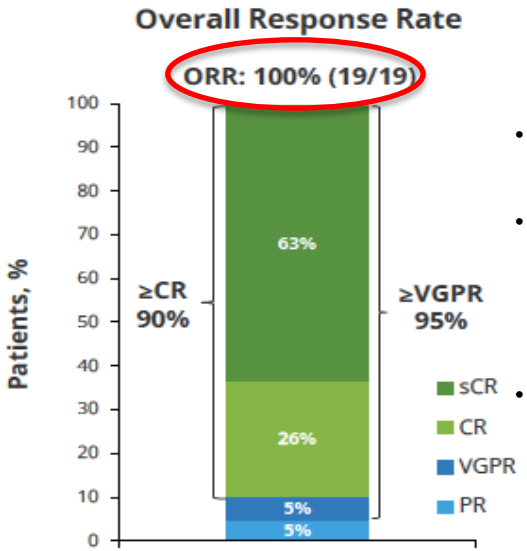


ASCT: autologous stem cell transplant, ORR: overall response rate, PFS: progression free survival, MRD: minimal residual disease, CR: complete response

Alsina et al., Poster P871 EHA 2023, updated data at ASH 2023 n 2101, Dec 9 2023

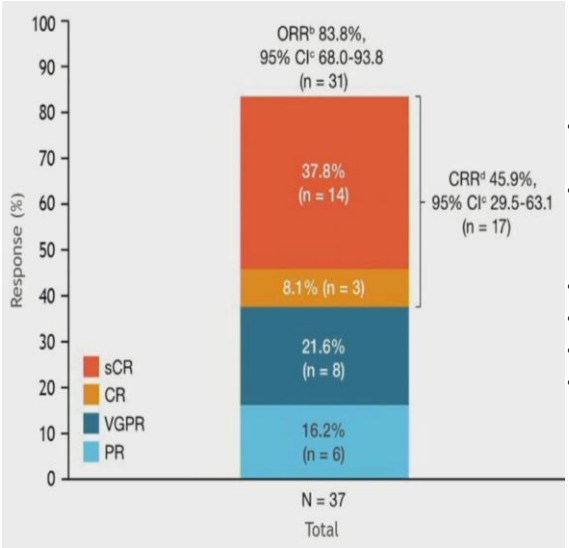
Strategies to improve FHR and MRD

CARTITUDE-2 Cohort B:
Cilta-cel in patients with early relapse after initial therapy (n=19)
Progression ≤12 months from ASCT or induction therapy.



- Median duration of response was not reached
- Of the 15 patients with MRD-evaluable samples at 10-5, 14 (93.3%) were MRD negative
- 12-month PFS rate was 89.5%

KarMMa-2:
Cohort 2a – Ide-cel for patients with an early relapse (18 months) after ASCT



- Median duration of response in responding patients: 15.7 months
- Median duration of response in patients achieving a ≥CR: 23.5 months
- MRD negativity status (<10-5)
- In patients who achieved ≥ CR
- 12 months post infusion: 70%
- Median PFS: 11.4 months

ASCT: autologous stem cell transplant, ORR: overall response rate, sCR: stringent complete response, CR: complete response, VGPR: very good partial response, PR: partial response,, MRD: minimal residual disease, PFS: progression free survival

van de Donk N et al. ASH 2022; abstract 3354 (poster presentation); updated data presented at ASH 2023 Abstrc1021, Dec 11 2023, Usmani T et al, oral abstract 361 ASH 2022

Strategies to improve FHR and MRD

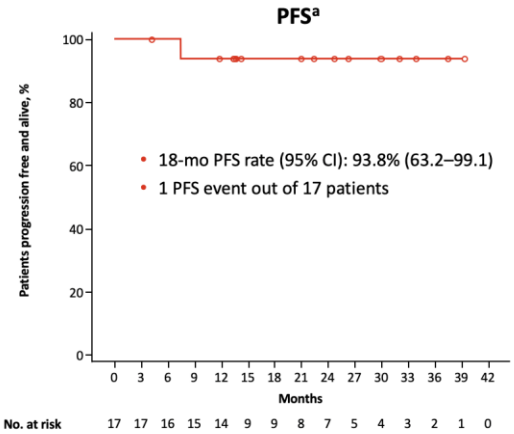
Early immunotherapy: suboptimal response to first line

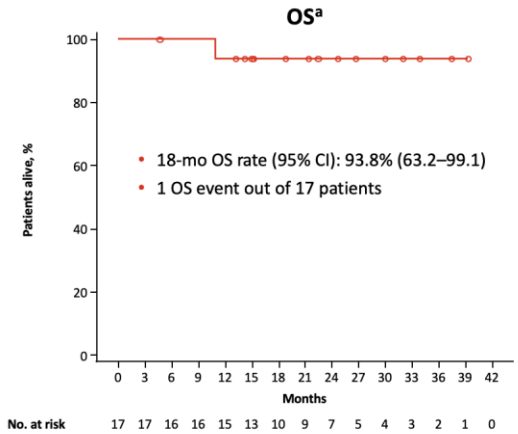
CARTITUDE-2, cohort D
Clinical High-Risk MM due to inadequate response (>CR)to frontline ASCT (n=17)

Median follow-up 22.4 months

Efficacy outcome	N =17
ORR	94% (≥CR 94%)
18 months PFS	94%
18 months OS rate	94%

MRD negativity at 10^{-5} = 71%



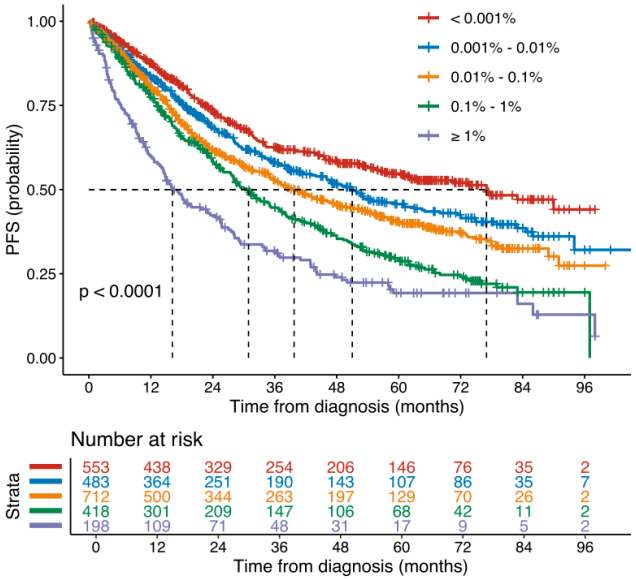


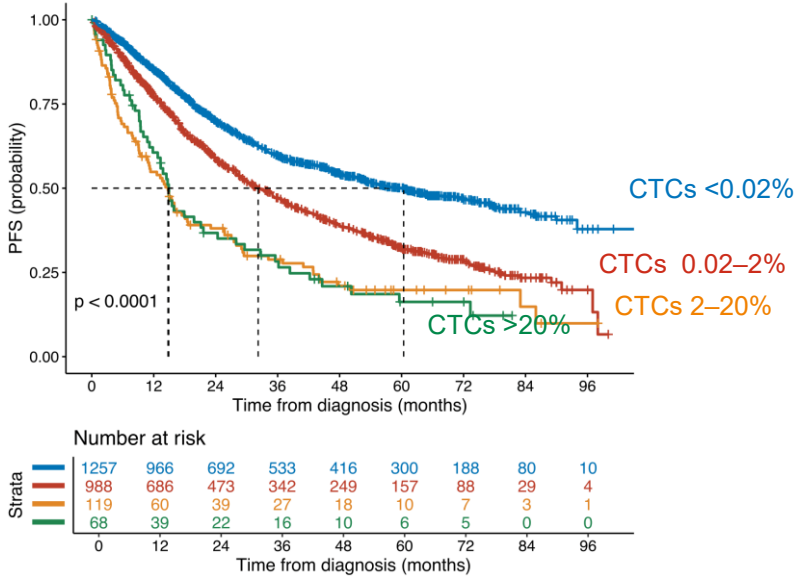
CR: complete response , ASCT: autologous stem cell transplant, ORR: overall response rate, PFS: progression free survival, OS: overall survival, CI: confidence interval, MRD: minimal residual disease

Arnulf B. et al EHA24

CTCs in multiple myeloma

- CTCs detected by flow cytometry are a **common feature in multiple myeloma** (MM) and in MM precursors.[1]
- **CTCs have an independent prognostic impact** in NDMM patients.[2-5]
- Not a single optimal threshold → for easiness of clinical implementation: 0.02% for dichotomized stratification and 2% for "hidden" PCL.[6]



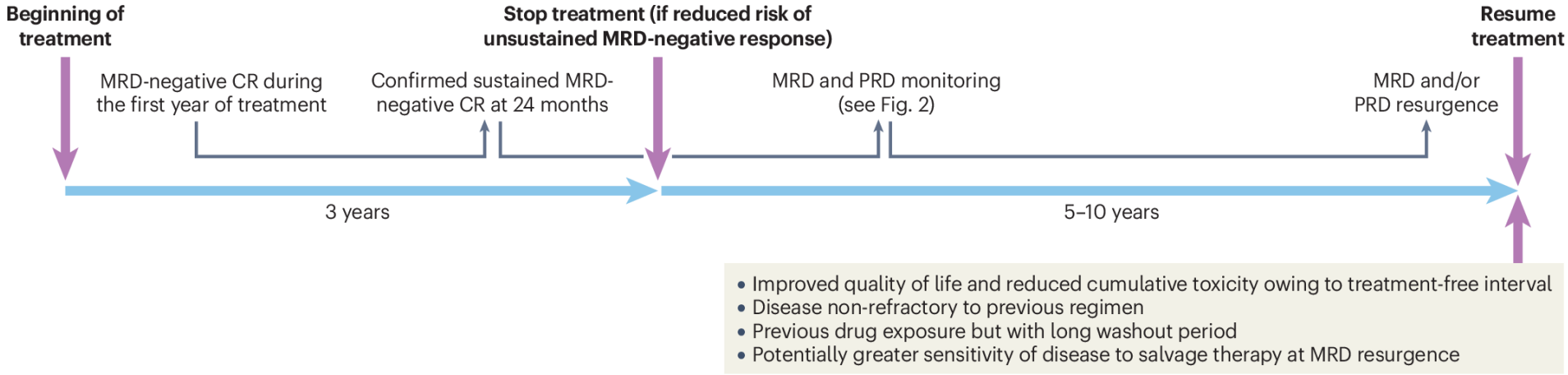


CTCs: circulating tumour cells

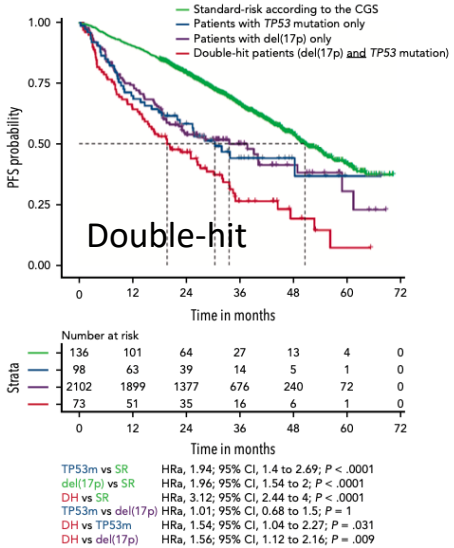
1. Sanoja-Flores L, et al. Blood Cancer J. 2018 Nov 19;8(12):117. doi: 10.1038/s41408-018-0153-9. 2. Bertamini L, et al. J Clin Oncol. 2022 Sep 20;40(27):3120-3131. doi: 10.1200/JCO.21.01393.
3. Garcés JJ, et al. J Clin Oncol. 2022 Sep 20;40(27):3151-3161. doi: 10.1200/JCO.21.01365. 4. Jelinek T, et al. J Clin Oncol. 2023 Mar 1;41(7):1383-1392. doi: 10.1200/JCO.22.01226
5. Kostopoulos I, et al. J Clin Oncol. 2023 Jan 20;41(3):708-710. doi:10.1200/JCO.22.01606. 6. Bertamini L, et al, HemaSphere 2025;9(S1):230 [Abstract #S199, EHA 2025 30th meeting].

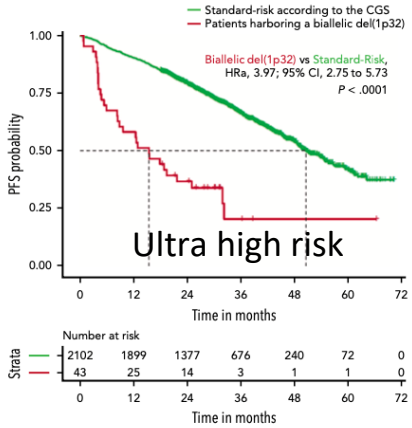
Conclusion from ASH

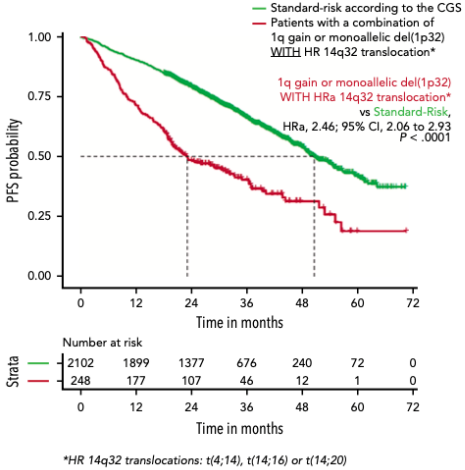
Hypothetical scenario of fixed treatment duration in patients with sustained MRD-negative CR

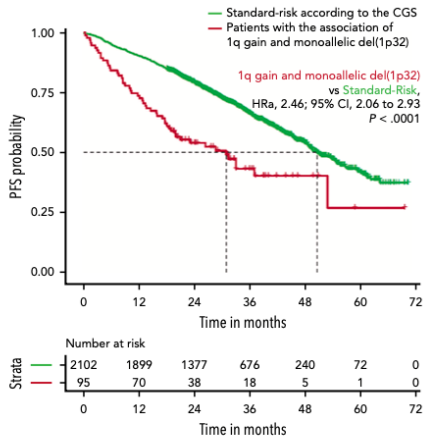


"Double-hit" and ultra high-risk patients









the mutual association of 1q gain or monoallelic del1p + HR14q translocations or monoallelic del1p led to a PFS of less than 30 months

Schavgoulidze A et al Blood 2026

Is it FISH still the gold standard for prognostication?

	FISH	Targeted panel	WGS
Canonical translocations	Yes	Yes, if covered	Yes
Copy Number Variants	Limited	Yes	Yes
Focal Copy Number Variants	Limited	Limited	Yes
Copy Neutral LOH	No	Limited	Yes
Single nucleotide variants and indels	No	Yes, if covered	Yes
Structural variants	No	Limited	Yes

- **CCF** (> 20% for del17p in new criteria) is more accurately caputerd with NGS vs FISH
- **SNVs,** small insertion/deletions at low allele variants frequencies reflects tumour sub-clones hidden by fish
- **copy-neutral loss of heterozygosity (CN-LOH)**: in MM, for instance, regions such as 1p or 17p may appear diploid yet are homozygous due to the deletion of 1 allele and duplication of the other, analysis of the minor allele to identify CN-LOH should be incorporated.

Garces JJ et al Blood 2026