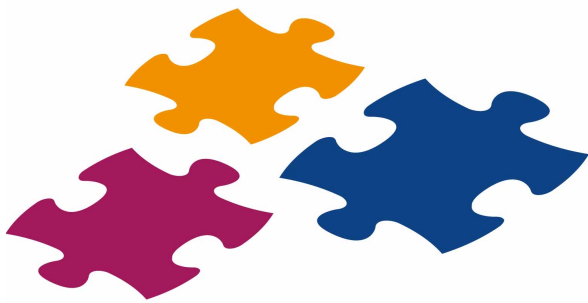


UPDATE IN EMATOLOGIA



Mercoledì 15 Dicembre 2021

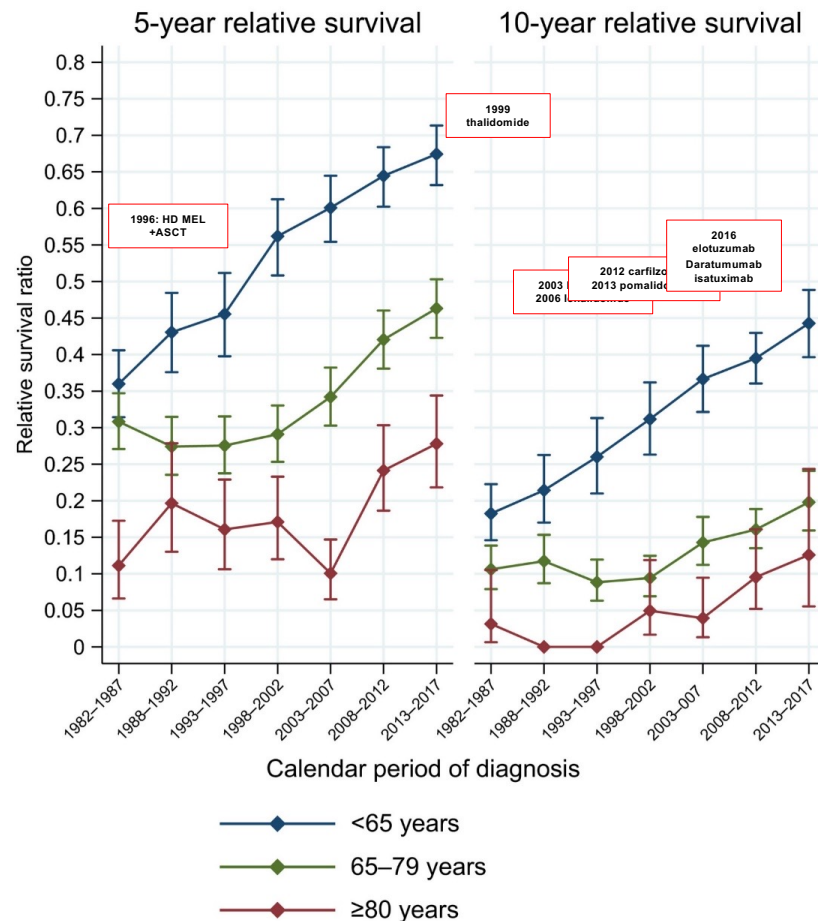
GENOVA

Starhotels President

Antonella Laudisi

TRATTAMENTO DEL MIELOMA MULTIPLO AD ALTO RISCHIO

MM survival over time



- The overall survival (OS) of patients with multiple myeloma (MM) has significantly improved over the last decade and is currently close to a median of 10 years for newly diagnosed (ND) fit patients.
- However, the improvement has not been uniform, and 15-20% of all patients have a predicted OS below 3 years.
- This subgroup is identified as having high-risk (HR) MM, and represents a challenge to diagnosis and to treat, due to the unsatisfactory disease control and early relapse, even with the newest therapies

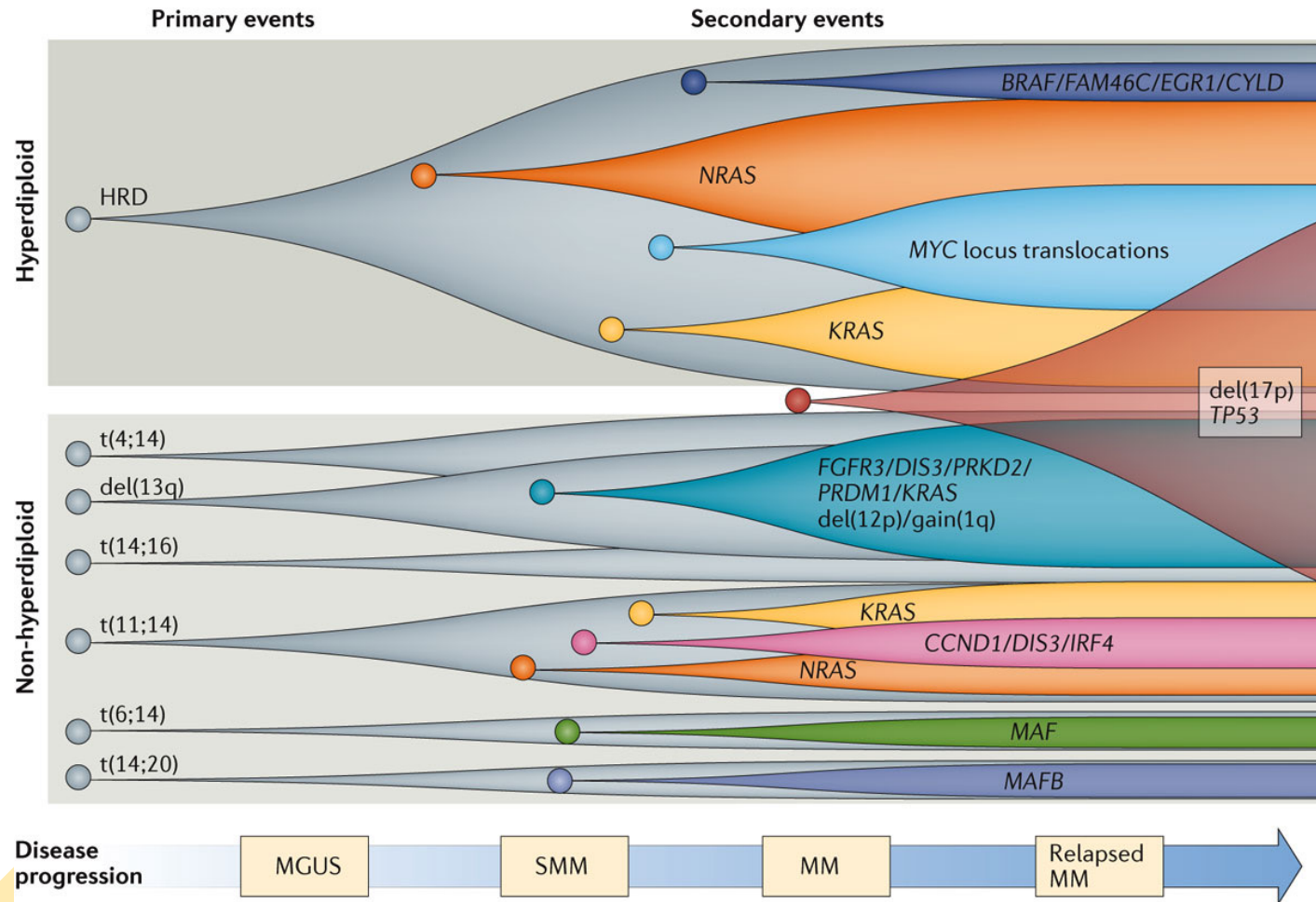
Multiple prognostic factors in MM

Patient-related	Disease burden-related	Disease biology-related	Therapy related
Age	High B2 microglobulin	Cytogenetic abnormalities	Quality of response
Performance status	Low albumin	GEP	Early relapse
Comorbidities	Renal impairment	Circulating PC	
	LDH above ULN	EMD	
		High proliferative rate	

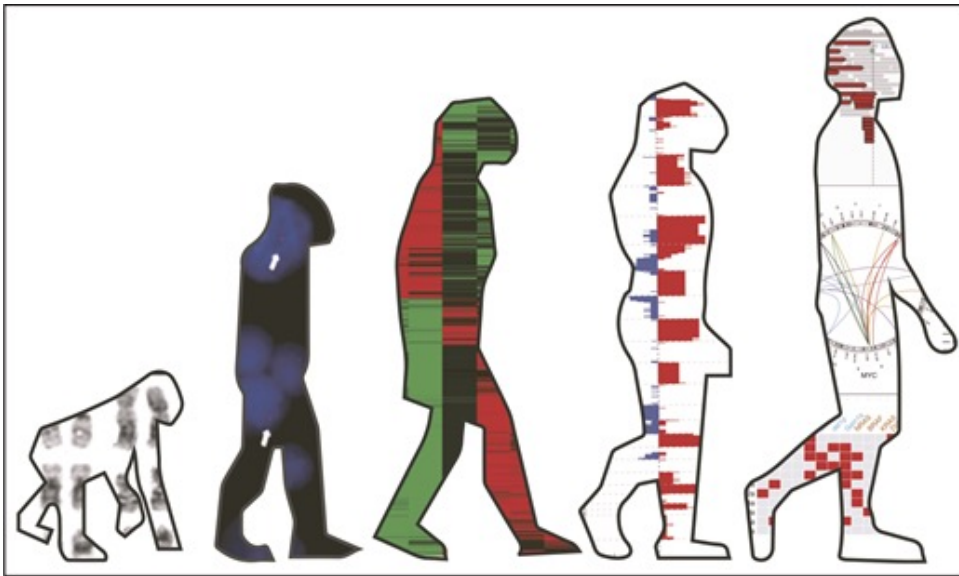
WJ Chng, et al. Leukemia, 2014)
 C Pawlyn, et al. Leukemia, 2020
 A Palumbo, et al. N Engl J Med, 2011
 SK Kumar, et al. Leuk Lymphoma, 2014
 JR Mikhael, et al., Mayo Clin Proc, 2013
 SZ Usmani, et al. Haematologica, 2012
 J Bladé, et al. Haematologica, 2012



MM is complex and heterogeneous disease for genetic abnormalities.



Prognostic cytogenetic abnormalities



- G-band karyotyping
- FISH
- GEP
- SNP array
- NGS

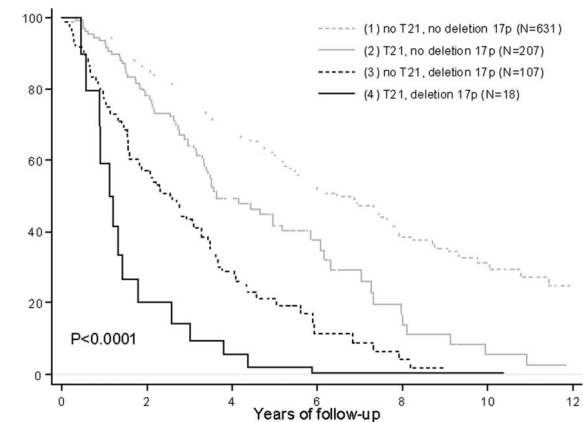
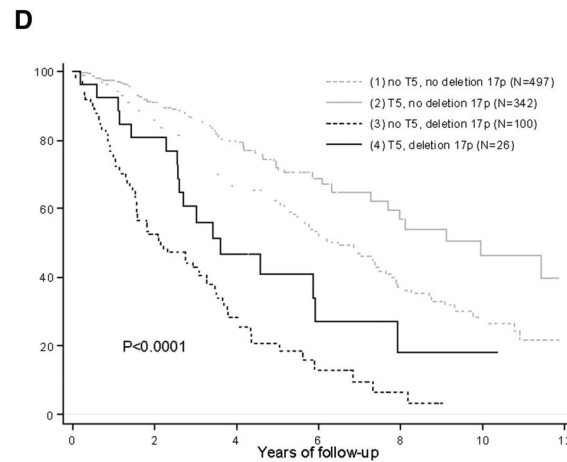
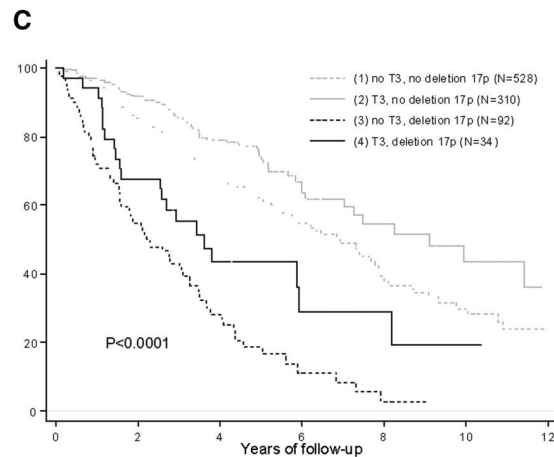


FISH PC→ is the preferred and routinely used method to detect recurrent chromosomal abnormalities. It can reveal abnormalities in approximately 90% of patients

Prognostic cytogenetic abnormalities

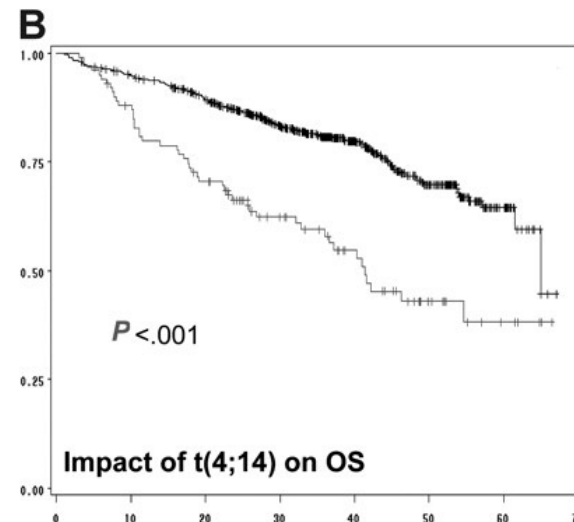
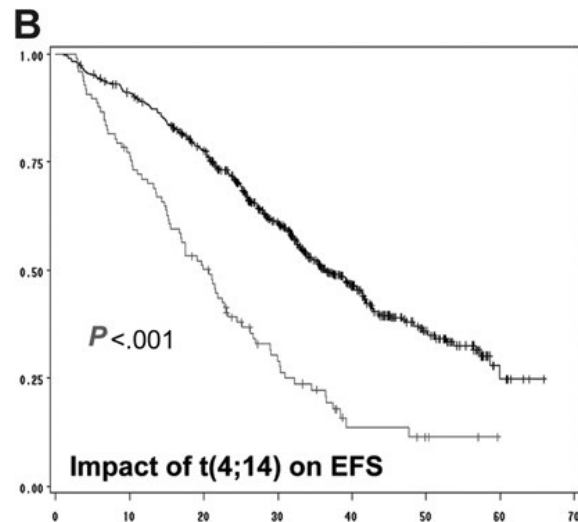
The most common cytogenetic abnormality is **hyperdiploidy**, which is present in 55% of patients.

The trisomies, preferentially affecting the odd chromosomes (3, 5, 7, 9, 11, 15, 19, and 21), are generally associated with a rather **favorable prognosis**, but the reality is more complex and depends on the exact chromosomes involved:



Impact of genomic aberrations on MM patients survival

t(4;14)



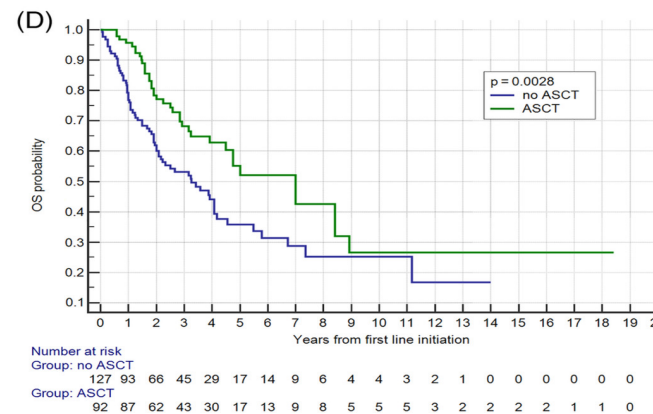
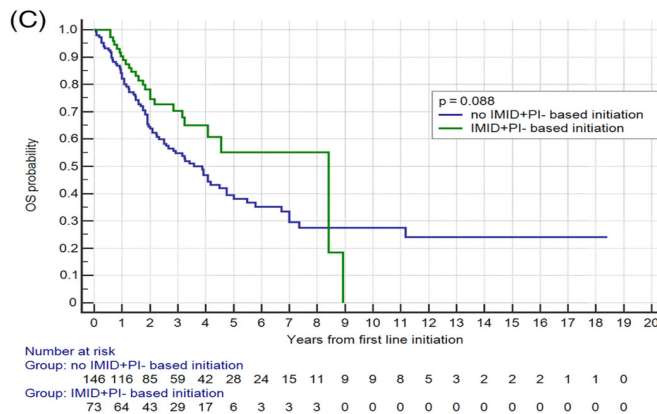
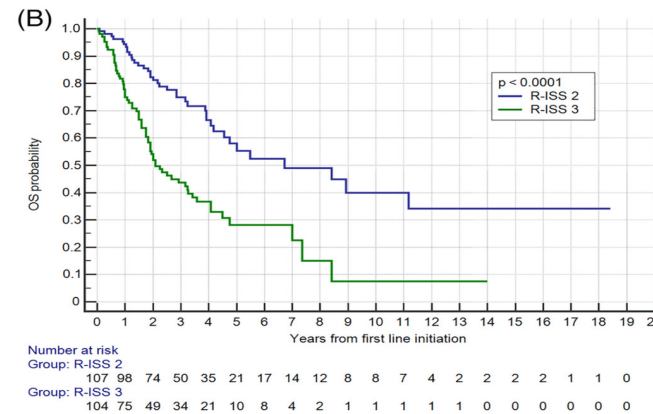
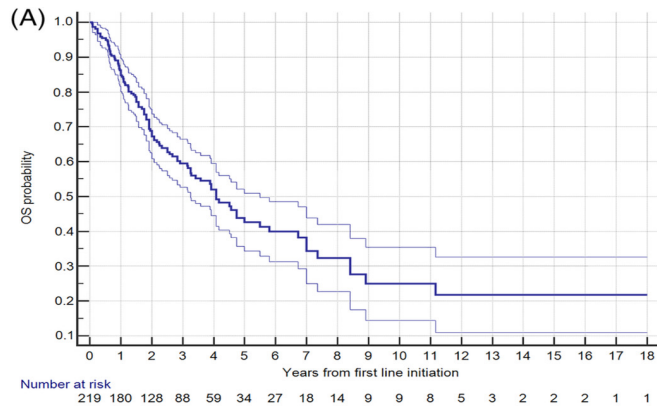
Hervé Avet-Loiseau et al. Blood, 2007

- It is observed in 12-15 % of patients
- it deregulates FGFR3
- It is sensitive to bortezomib-based therapies
- it is a very heterogenous entity (some HR, others SR)
- ongoing studies on breakpoints locations



Impact of genomic aberrations on MM patients survival

t(14;16)

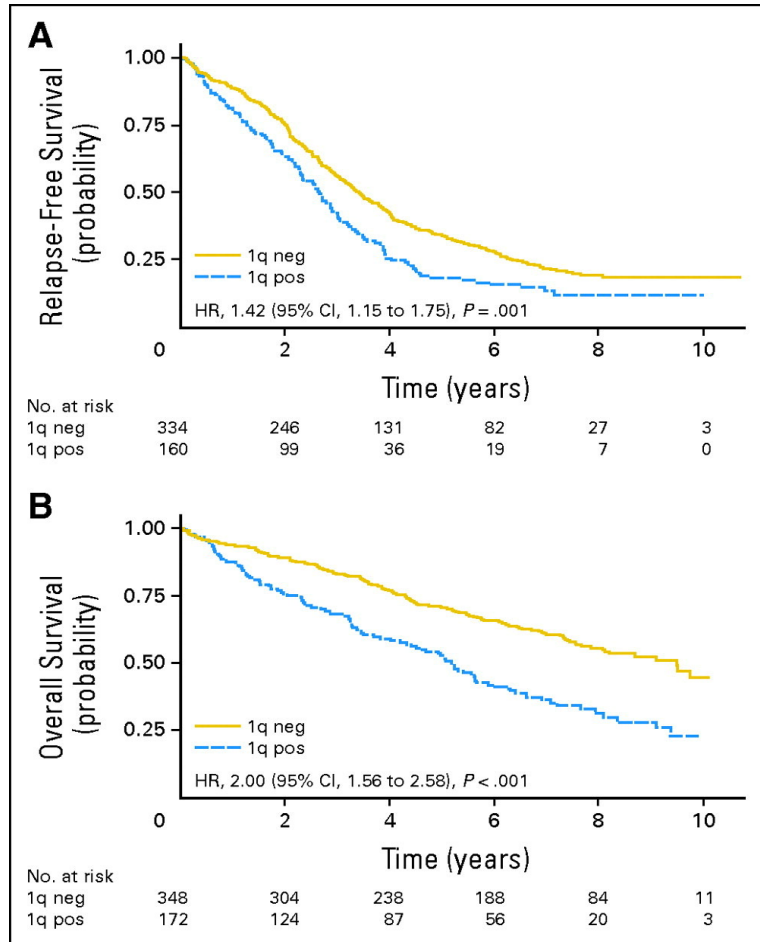


- Early event
- Rare entity (3-5%)
- Really independent prognostic value?

Hervé Avet-Loiseau et al. Blood, 2008
Goldman-Mazur et al. Am J Hematol 2020

Impact of genomic aberrations on MM patients survival

1q gain

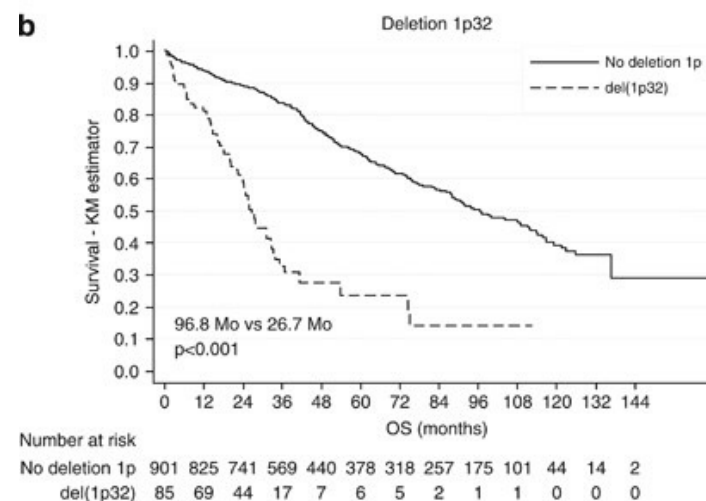
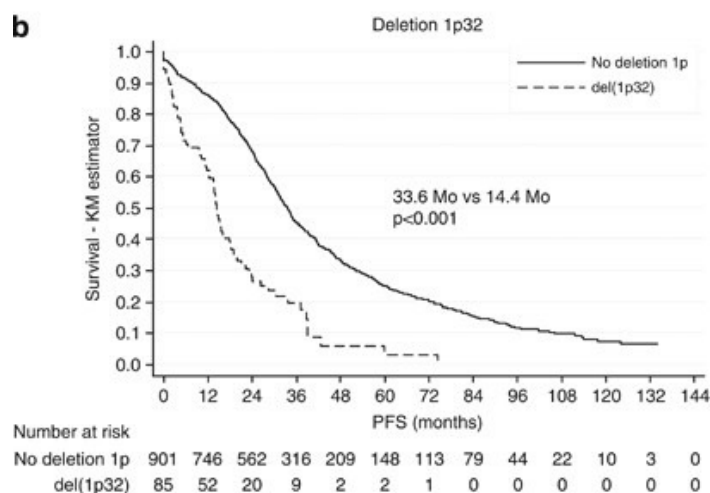


- Observed in 35% of MM patients
- It deregulates CKS1B
- More data are needed to better define its prognostic role: only an amplification (>3 copies) would be of high risk.



Impact of genomic aberrations on MM patients survival

Del 1p32



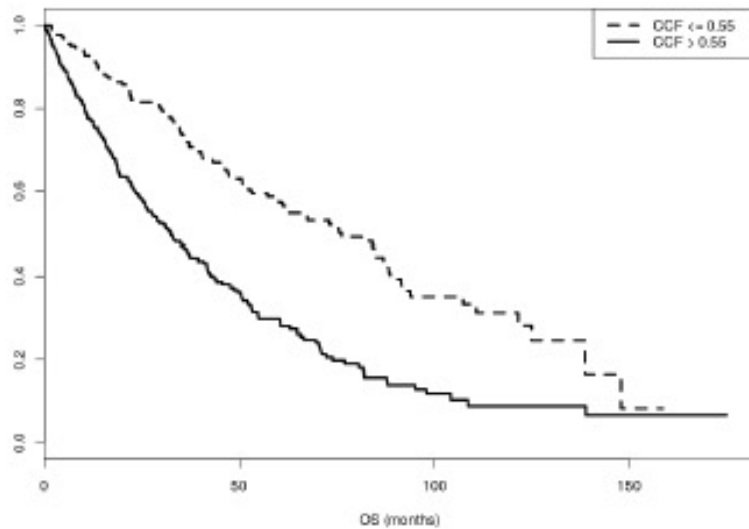
- Observed in 8-10 % of MM patients
- It targets CDKN2C and FAF1
- More data are need to better define its poor prognostic role



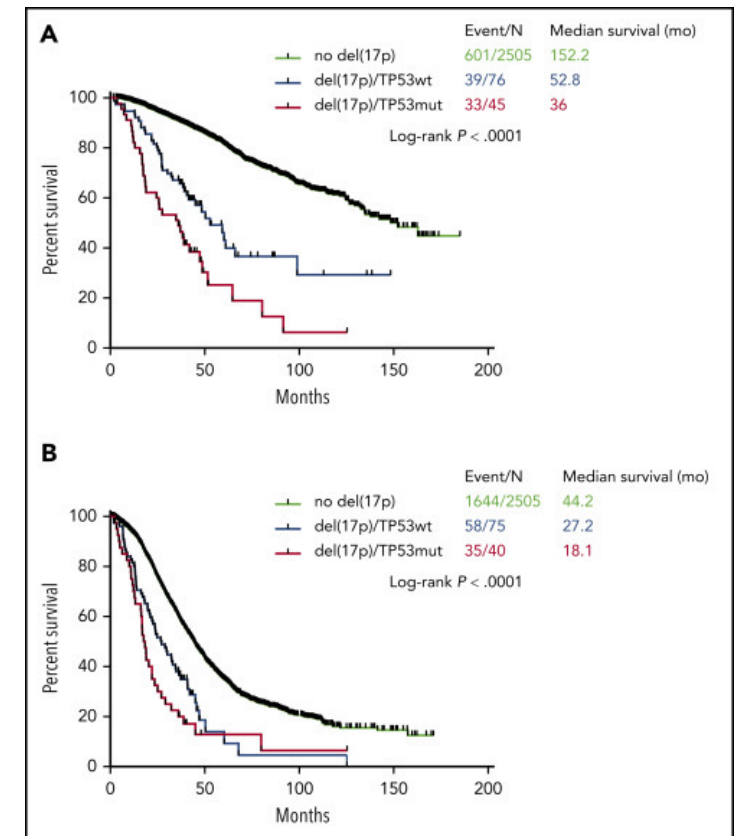
Impact of genomic aberrations on MM patients survival

Del 17p

Prognostic threshold for clone size: 55-60%
(observed in 8% of NDMM)



Takurta et al. Blood 2018



Double hit < del17p < standard risk

Corre J. et al. Blood, 2021

Summary of cytogenetic classification of MM

Chromosome/region (frequency)	Gene involved/effect	Prognostic implication
14q32 (locus IGH) (45-50%)		
t(11;14) (20%)	Cyclin D1 hyperexpression	Neutral
t(4;14) (10-15%)	FGFR3 and MMSET deregulated	Unfavorable (worsened by chromosome 1 alterations, improved by trisomy 5)
t(14;16) (<5%)	cMAF	Doubt, mainly unfavorable
t(14;20) (<5%)	UK	Doubt, mainly unfavorable
1q21 acquisition (30%)	CKS1B, MCL1	
Gain		Partially unfavorable
Amplification (≥ 3)		Unfavorable
1p32 deletion (10%)	FAF1/CDKN2C	Unfavorable
17p deletion (8-15% according to PCs cutoff)	TP53 and UK	
Single hit	Deletion	Unfavorable
Double hit	Bi-allelic inactivation (del+mut)	Very unfavorable

International Staging System (ISS)

Table 2.

New International Staging System

Stage	Criteria	Median Survival (months)
I	Serum β_2 -microglobulin < 3.5 mg/L Serum albumin \geq 3.5 g/dL	62
II	Not stage I or III*	44
III	Serum β_2 -microglobulin \geq 5.5 mg/L	29

*There are two categories for stage II: serum β_2 -microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2 -microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

Greipp et al JCO. 2005;23(15):3412-20

Limitations:

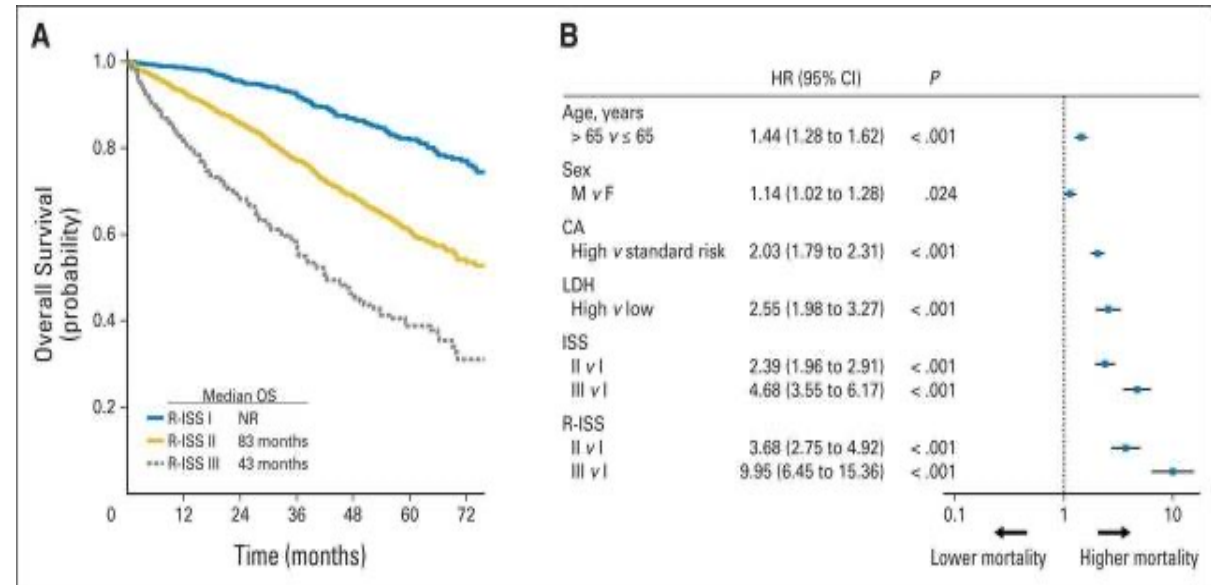
- Patients studied were treated with old combinations, not representative of current standard of care
- Lack of inclusion of genomic-proliferation related aspects
- Wide heterogeneity within groups

Revised International Staging System (R-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 \geq 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2 -microglobulin \geq 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 et al. JCO 2015

.....however this definition now seems oversimplified and too restrictive, and it may lead to misclassification because it is only based on 3 unweighted cytogenetic abnormalities, mixed with biochemical factors.

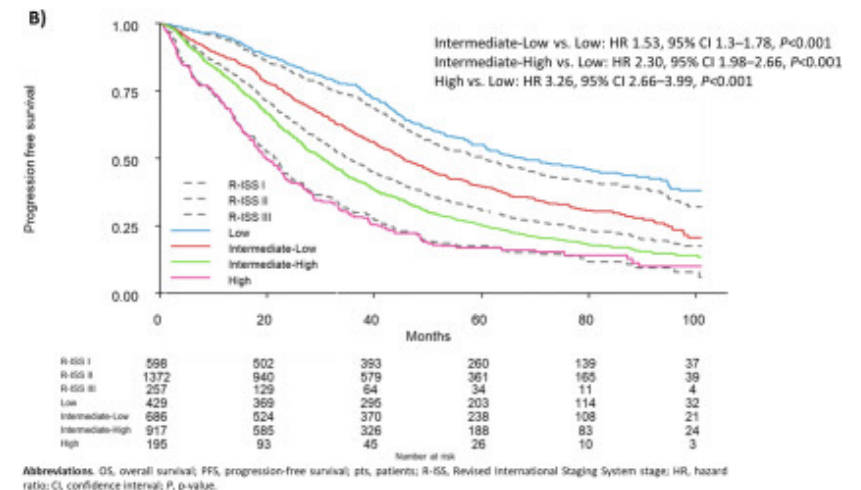
Development and Validation of a Cytogenetic Prognostic Index Predicting Survival in Multiple Myeloma (EMN model: R2-ISS)

Risk feature	OS Hazard ratio*	PFS Hazard ratio*	Score value**
ISS II	1.55 (1.42-1.69)	1.35 (1.26-1.44)	1
ISS III	2.02 (1.83-2.24)	1.53 (1.42-1.66)	1.5
del(17p)	1.74 (1.56-1.94)	1.41 (1.29-1.55)	1
High LDH	1.65 (1.50-1.83)	1.33 (1.23-1.45)	1
t(4;14)	1.56 (1.40-1.74)	1.49 (1.36-1.63)	1
1q CNAs	1.45 (1.29-1.63)	1.37 (1.25-1.50)	0.5
Group	Number of patients (%)		Total additive score
Low	429 (19.3%)		0
Low-Intermediate	686 (30.8%)		0.5-1
Intermediate-High	917 (41.2%)		1.5-2.5
High	195 (8.8%)		3-5

*Cox model adjusted for age, sex, therapy, performance status, isotype, t(14;16) and renal function.

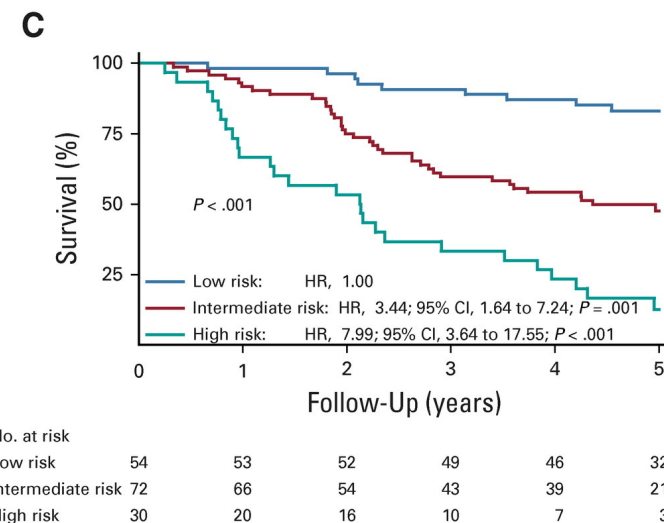
**Calculated on the risk of death in patients with complete data only (n=2227), value rounded at the nearest 0.5 with ISS II vs. I comparison as reference (score = 1).

Abbreviations. OS, overall survival; PFS, progression-free survival; pts, patients; ISS, International Staging System stage; LDH, lactate dehydrogenase; CNAs, copy-number abnormalities.



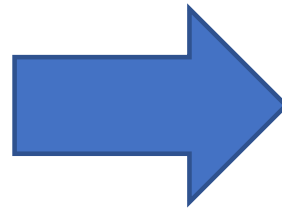
Development and Validation of a Cytogenetic Prognostic Index Predicting Survival in Multiple Myeloma (IFM model)

Cytogenetic factor	Coefficient
Trisomy 5	-0.3
Trisomy 21	0.3
t(4;14)	0.4
Gain 1q	0.5
del(1p32)	0.8
del(17p)	1.2
Risk(score=sum of coefficient) Low Intermediate High	≤0 >0 and ≤1 >1



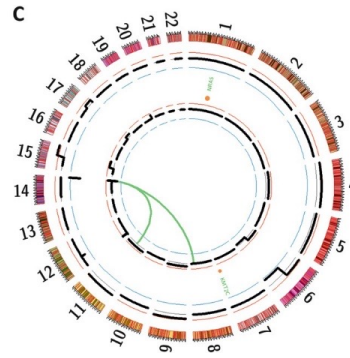
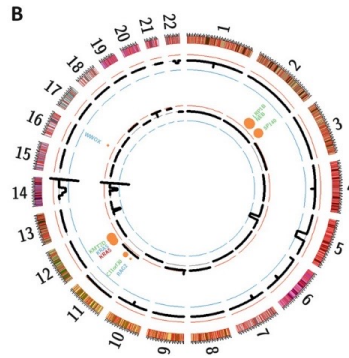
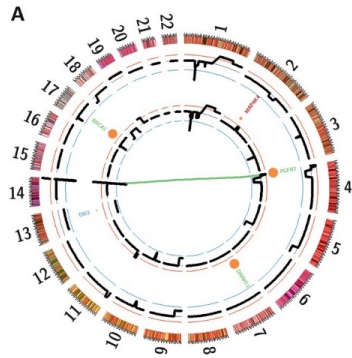
Who are the real high-risk MM patients in 2021?

Mainly based on genetic abnormalities IMWG:
del(17p), t(4;14) or t(14;16)



Del17p
TP53mut
trisomy 21
t(4;14) del1p32
trisomy 5
gain1q

Corre J, et al. Blood 2021

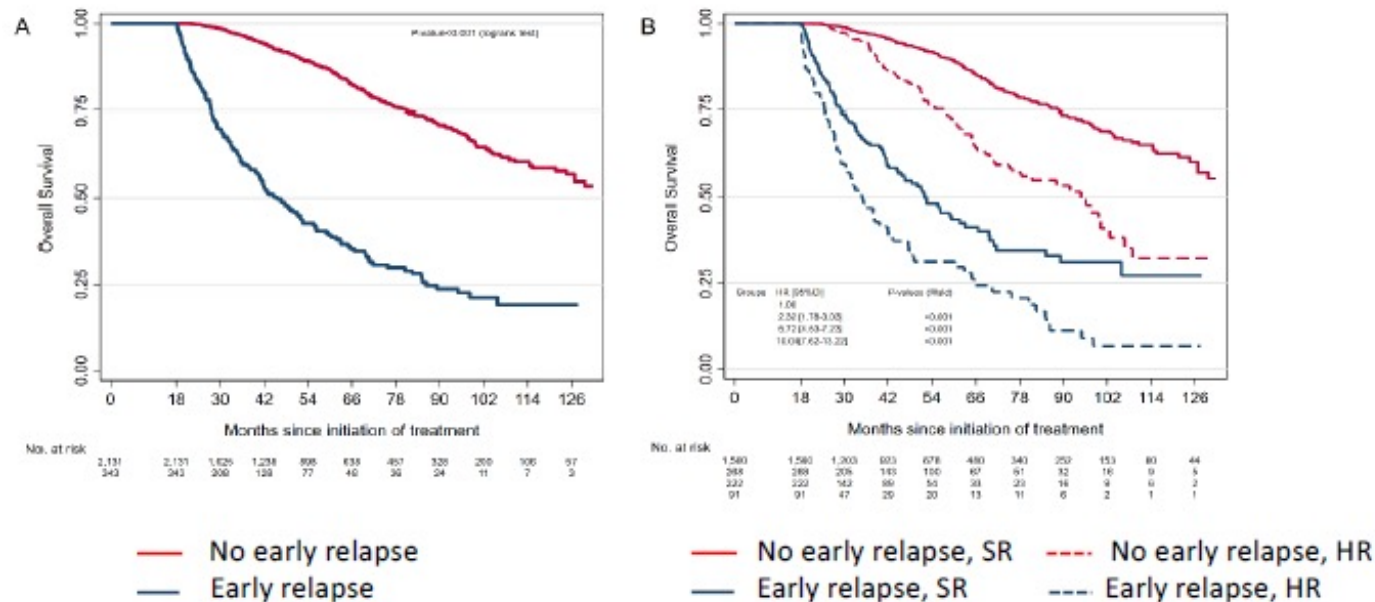


Not only at diagnosis

Dynamic risk assessment: early relapse

Response to treatment is a major prognostic factor for MM. Indeed, an early relapse (<18 months from starting treatment or < 12 months from ASCT) negatively impacts survival regardless of cytogenetic abnormalities.

Approximately two thirds of early relapsing patients were not initially considered HR

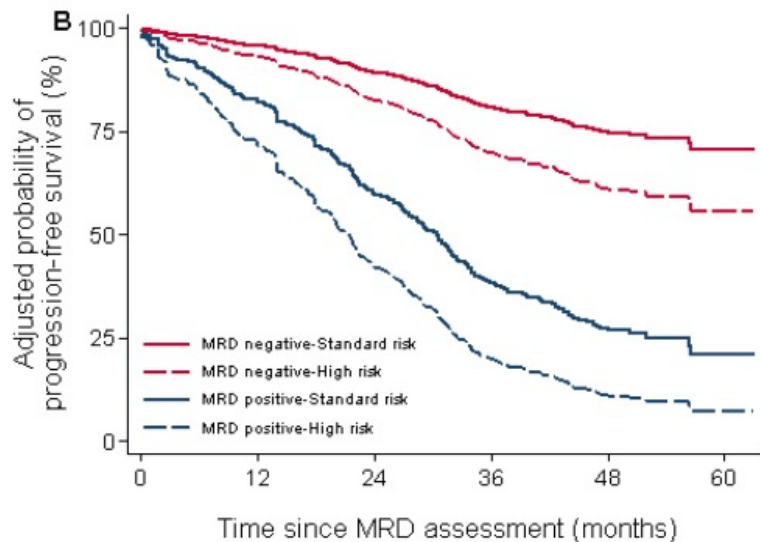


Dynamic risk assessment: MRD

Significant progress has recently been made in assessing the depth of response thanks to the development of sensitive techniques to determine the level of minimal residual disease (MRD).

Next-generation flow and NGS permit achievement of the unprecedented sensitivity threshold of 1 tumor plasma cell in 1 million (10^{-6}) analyzed bone marrow cells.

Achieving an undetectable MRD is associated with significantly longer progression-free and overall survival, whether in the first line or at relapse.



.....risk is a dynamic concept

Definition of prognosis risk in MM patients

High risk patients:

del(17p) >15% plasma cells
t(4;14)

Amp (1q21) >3 copies

some mutations (TP53? BRAF?)

poor responders (MRD positivity)

early relapses

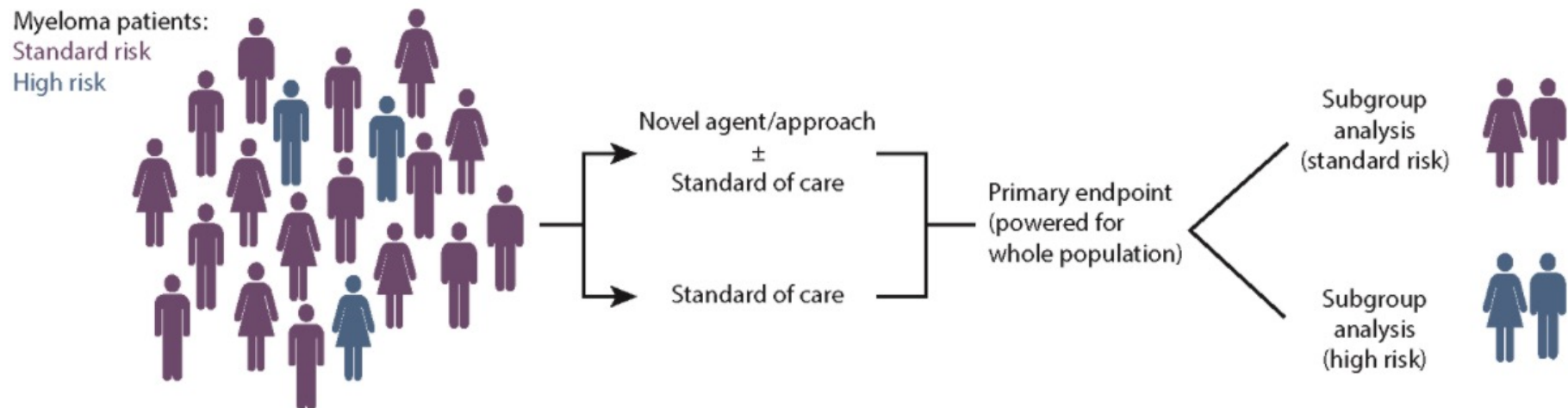
Standard risk patients:

All others

Treatment of HRMM

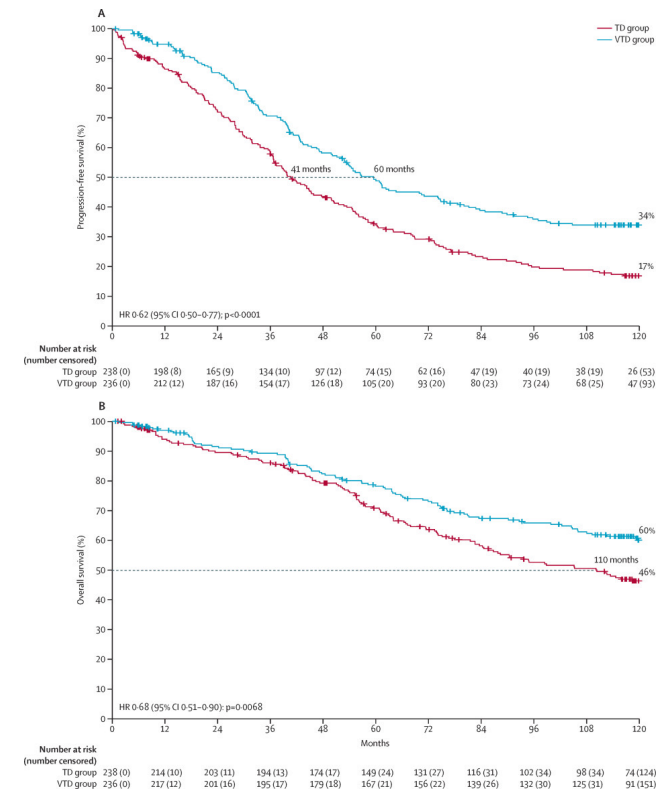
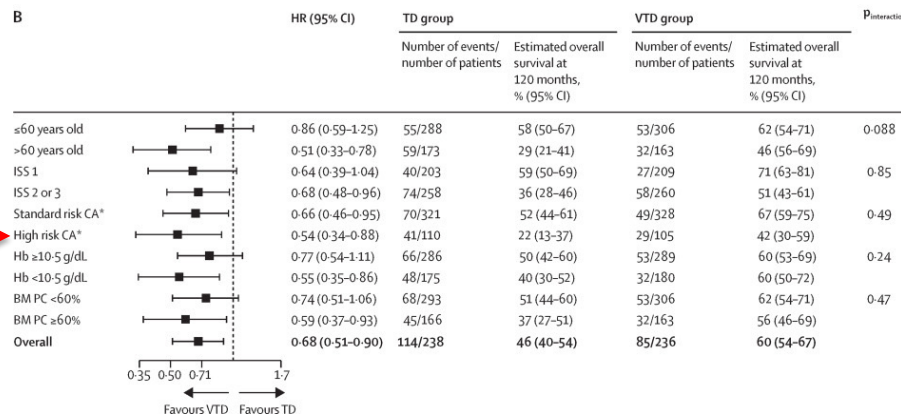
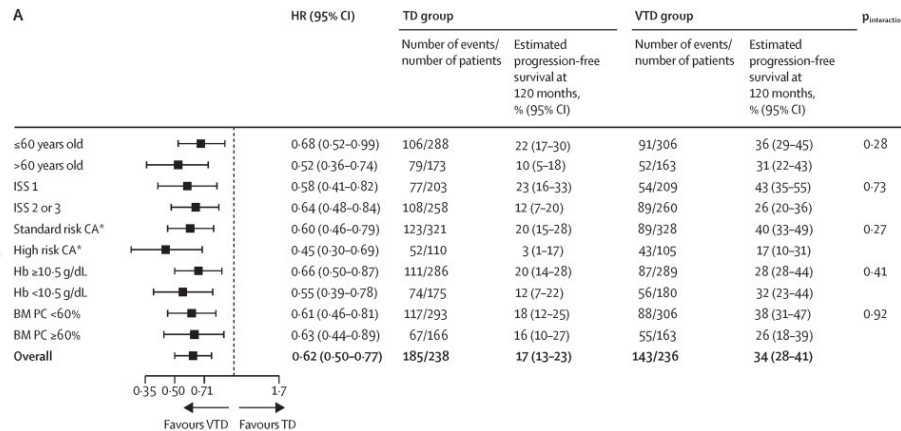
Therapeutic approaches to MM have traditionally been tailored on patient's age, frailty or comorbidities, but very rarely on the biology of the disease, mainly because of the lack of homogeneous criteria for defining HR disease and lack of prospective and risk-adapted clinical trials.

Available data on the outcomes of HR patients are mostly biased by post-hoc nature of the analyses and reduced statistical power due to the limited sample size of HR subgroups



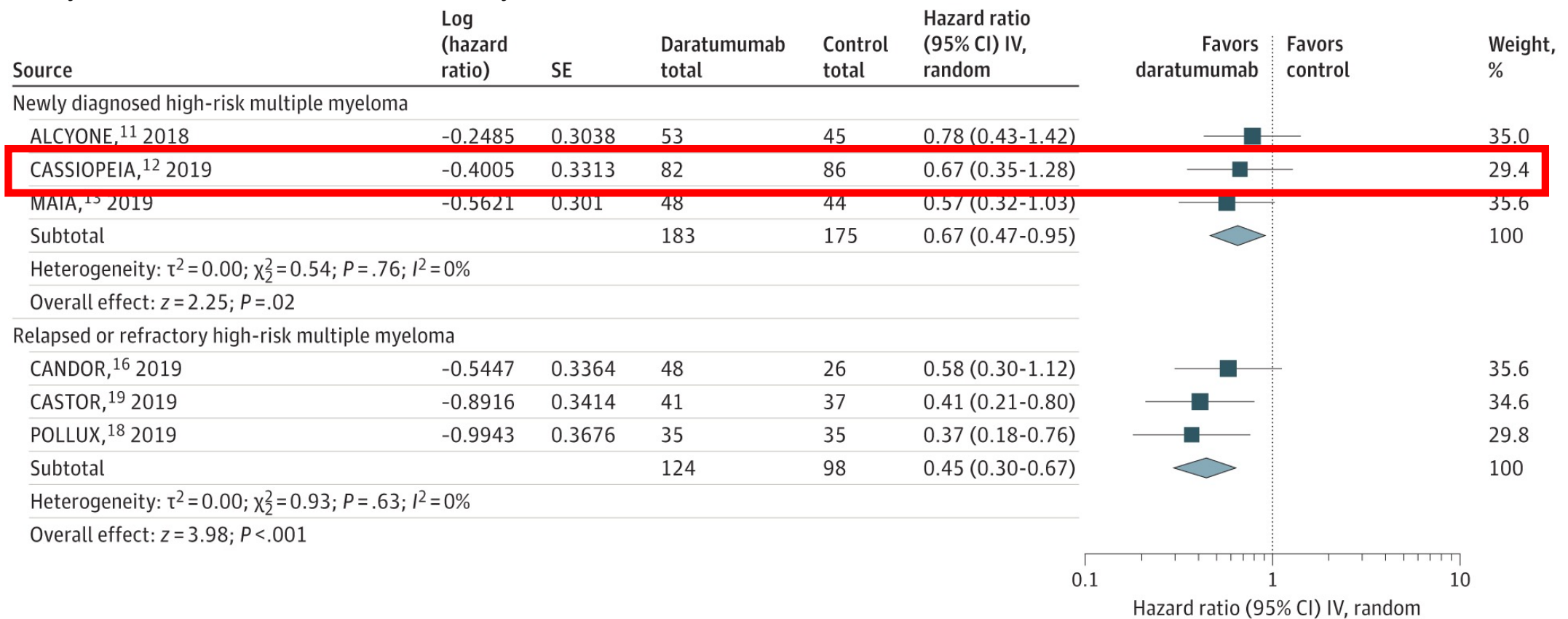
Therapeutic strategy for HR patients in TE NDMM (induction regimes)

Regimen containing: PI + IMiD + dexamethasone (4-6 cycles)

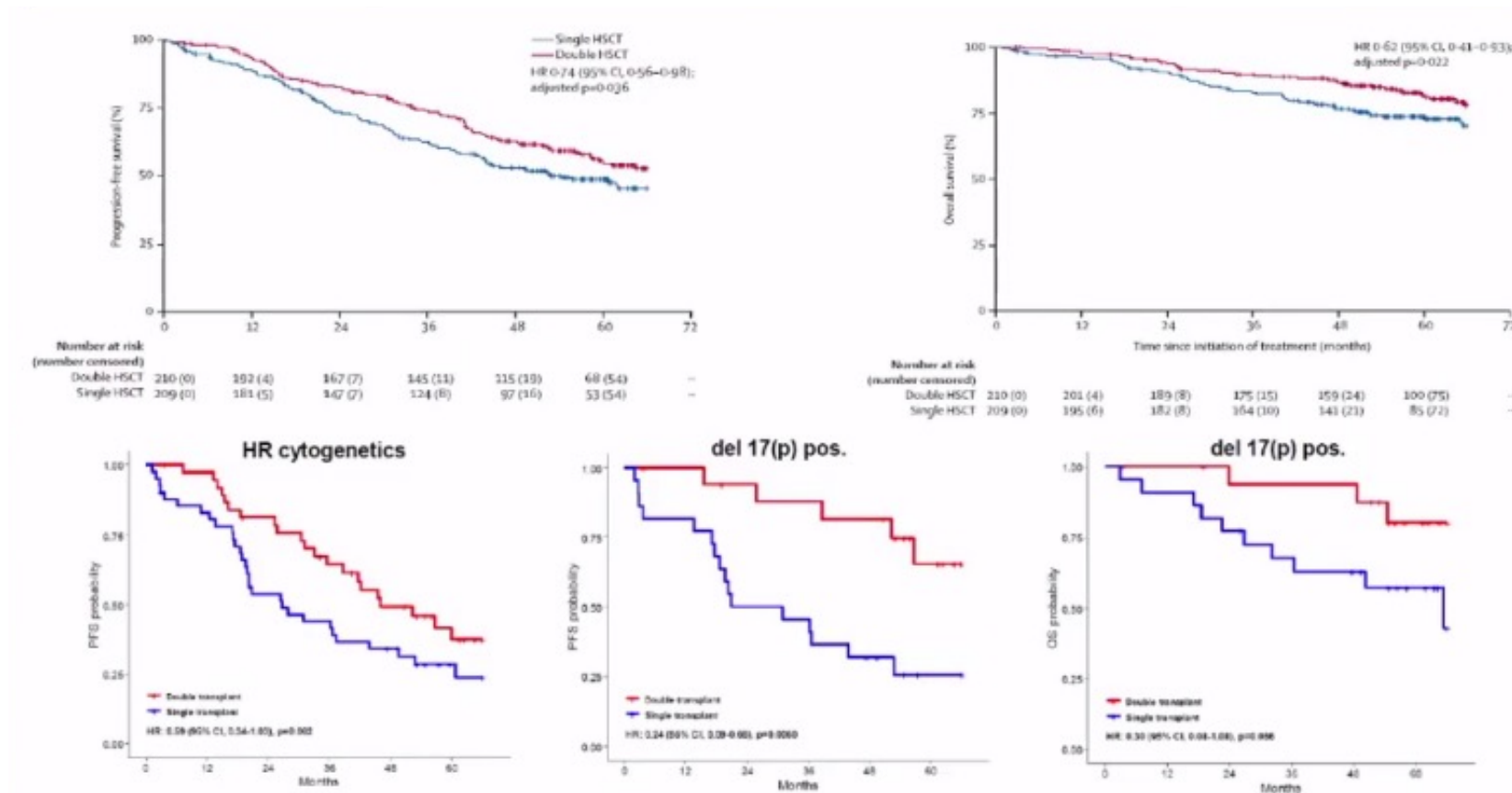


Therapeutic strategy for HR patients in TE NDMM (induction regimes)

Evaluation of Daratumumab for the Treatment of Multiple Myeloma in Patients With High-risk Cytogenetic Factors: A Systematic Review and Meta-analysis

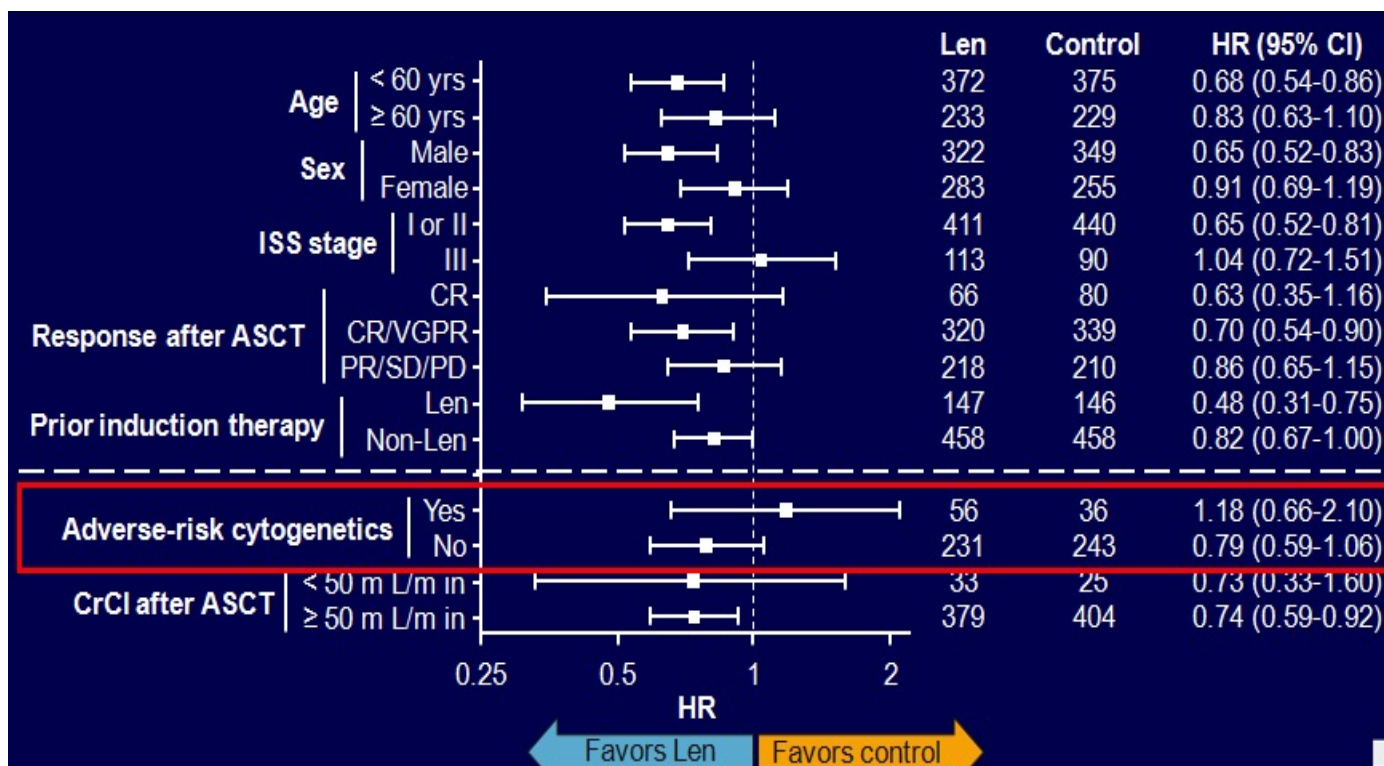


Therapeutic strategy for HR patients in TE NDMM (single vs double ASCT)



Therapeutic strategy for HR patients in TE NDMM (Maintenance regimen)

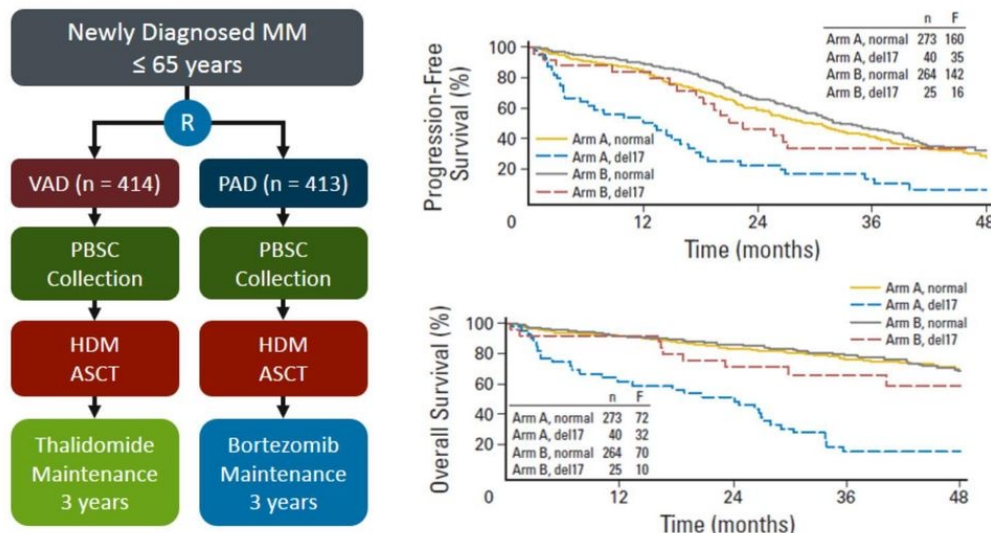
In the meta-analysis of lenalidomide maintenance , patients with adverse risk cytogenetics did not benefit (HR = 1.17)



Therapeutic strategy for HR patients in TE NDMM (Maintenance regimen)

Patients with high risk cytogenetics may benefit from including a proteasome inhibitor in their maintenance therapy

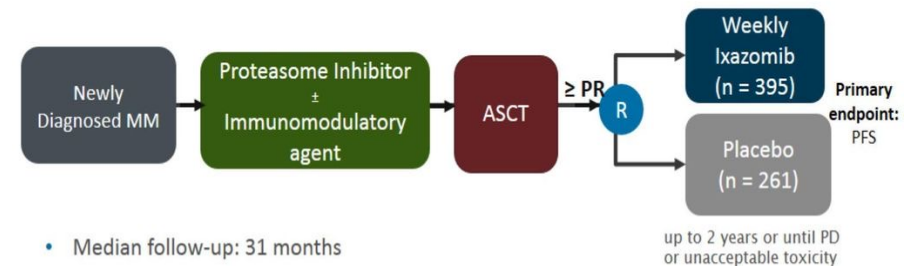
HOVON-65/GMMG-HD4: Bortezomib Induction and Maintenance by Cytogenetic Risk



Sonneveld P, et al. *J Clin Oncol*. 2012;30:2946-2955. Reprinted with permission.
© 2012 American Society of Clinical Oncology. All rights reserved.

Sonneveld P, et al. *J Clin Oncol*. 2012;30:2946-2955.

Ixazomib vs Placebo Following ASCT in Newly Diagnosed MM, Phase 3 Tourmaline-MM3 Trial

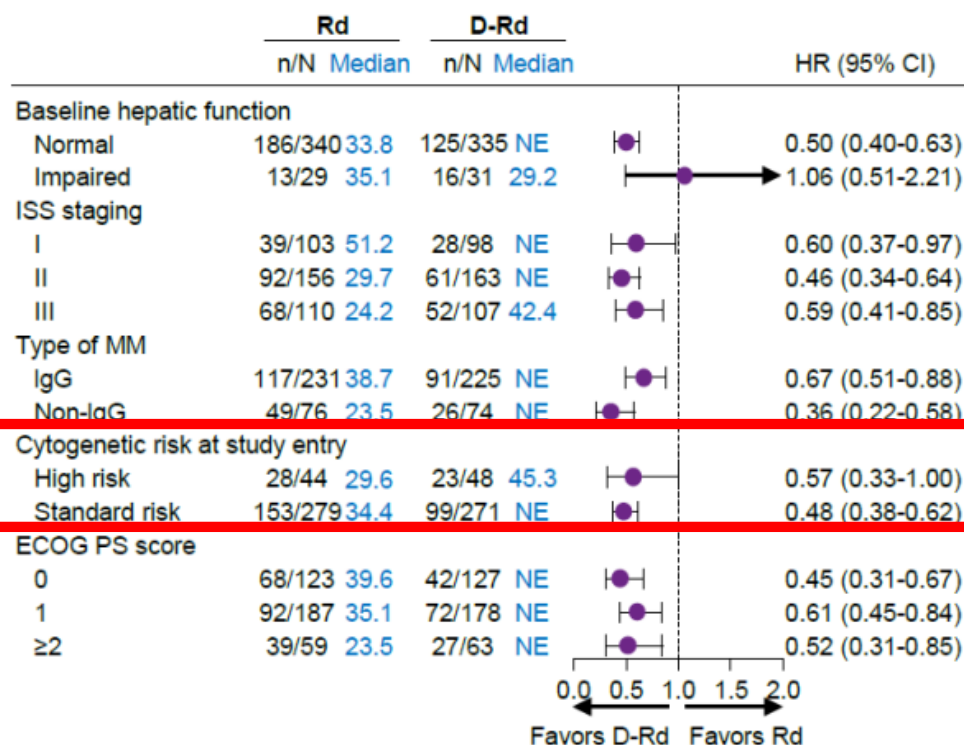


- Median follow-up: 31 months
- Median PFS 26.5 mo vs 21.3 mo; HR = 0.72, $P = .002$
- Landmark analysis from ASCT, median PFS: 30.7 vs 24.9 mo; HR = 0.684; $P < .001$
- PFS benefit across subgroups, including ISS III (HR, 0.661), PI-exposed (HR, 0.750), PI-naïve (HR, 0.497), and patients with high-risk cytogenetics (HR, 0.625)
- Discontinuation due to AEs was low (7% ixazomib vs 5% placebo)
- Global Quality of Life scores (EORTC QLQ-C30) on ixazomib were similar to placebo

Dimopoulos MA, et al. ASH Annual Meeting. 2018: Abstract 301.

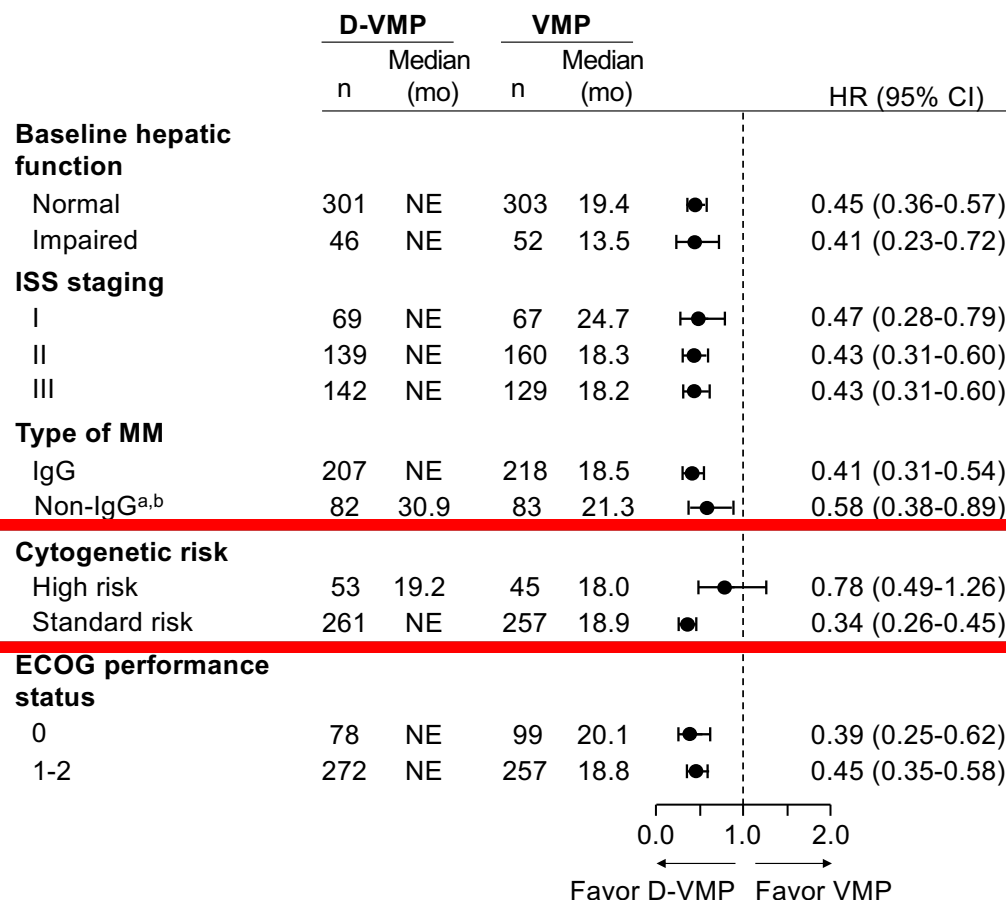
Results of selected clinical trials for NDMM NTE carrying high risk features

MAIA



Facon et al, NEJM 2020

ALCYONE



Mateos MV et al., Lancet 2020

Current approved triplet combination for R/R MM in HR patients

Trial	Regimen	Study Design (Primary Endpoint)	Study definition of HR	N. ofHR patients (%)	PFS rates	MRD neg (%)
CANDOR	D-Kd vs Kd	Randomized, open-label, controled, phase III, RRMM (PFS)	t(4;14), t(14;16) or del(17p)	74 (16)	Median PFS: NE (D-Kd) vs 15.8 mos (Kd)	-
ELOQUENT-3	Elo-Pd vs Pd	Randomized, open-label, controled, phase II, RRMM (PFS)	ISS stage II or III and del(17p), t(4;14), t(4;16)	27 (23)	Median PFS: 6.2 mos (HR) vs 10.3 mos (SR) (Elo-Pd) 2.2 mos (HR) vs 5.2 mos (SR) (Pd)	-
CASTOR	D-Vd vs Vd	Randomized, open-label, controled, phase III, RRMM (PFS)	del(17p), t(4;14), t(14;16)	91 (18)	Median PFS: 12.6 mos (HR) vs 16.6 mos (SR) (D-Vd) 6.2 mos (HR) vs 6.6 mos (SR) (Vd)	15%(HR) vs 13% (SR) (D-Vd) 0 (HR) vs3% (SR) (Vd)
OPTIMISMM	PVd vs Vd	Randomized, open-label, controled, phase III, RRMM (PFS)	del(17p), t(4;14), t(14;16)	110 (20)	Median PFS: 8.44mos (HR) vs 11.2 mos (ITT) (PVd) 5.32 mos (HR) vs 7-1 (ITT) (Vd)	-
POLLUX	D-Rd vs Rd	Randomized, open-label, controled, phase III, RRMM (PFS)	del(17p), t(4;14), t(14;16)	65 (11)	Median PFS: 26.8 mos (HR) vs 52.0 mos (SR) (D-Rd) 8.3 mos (HR) vs 18.6 mos (SR) (Rd)	29% (HR) vs35% (SR) (D-Rd) 3% (HR) vs 9% (SR) (Rd)
ASPIRE	KRd vs Rd	Randomized, open-label, controled, phase III, RRMM (PFS)	del(17p), t(4;14), t(14;16)	100 (13)	Median PFS: 23.1 mos (HR) vs 29.6 mos (SR) (KRd) 13.9 (HR) vs 19.5 (SR) (Rd)	-
ENDEAVOR	Kd vs Vd	Randomized, open-label, controled, phase III, RRMM (PFS)	del(17p), t(4;14), t(14;16)	210 (23)	Median PFS: 8.8 mos (HR) vs NE (SR) (Kd) 6.0 mos (HR) vs 10.2 mos (SR) (Vd)	-

Management of patients with HR MM

	Suggested treatment
Transplant eligible	<ul style="list-style-type: none"> • Quadruplet induction (MoAb + PI + IMiD + dex)/ Pis –based regimen • Double ASCT • PI-based maintenance \pm MoAbs until PD or toxicity
Transplant ineligible	<ul style="list-style-type: none"> • Fit patients: Quadruplet/triplet induction (MoAb + PI + IMiD + dex) until PD or toxicity • Frail patients: dose-adjusted triplet or doublets
Relapsed/refractory	<ul style="list-style-type: none"> • Triplets (MoAb \pm PI + IMiD) and/or novel drugs (BiTEs, CAR-T)

Adapted from Zamagni E. et al. Blood 2021

Clinical trials specifically dedicated to HR NDMM

Trial	RegIFM 2018-04imen	Study Design	Study Definition of HR	Results
OPTIMUM	Dara-CVRd vs VRd	Phase IIb, first line TE and TNE NDMM (MRD 100 days post-ASCT and PFS)	Two or more of: t(4;14), or t(4;14), t(14;20), del(1p32) gain(1q) or del(17p), HR-GEP, PCL (>20%cPCs)	93% ORR, 52% CRs, 35% VGPR, 5% PR MRD 50%
UK-MRA Myeloma XV (RADAR) (EudraCT: 2019-001258-25)	Cy-PI-RD + ASCT followed by Len +/- PI +/- Isa / 12 mos Isa	Phase II, first line TE and TNE NDMM (MRD & Response)	t(4;14), t(14;16), t(14;20), del(17p), gain(1q)	Ongoing study
GMMG-CONCEPT	Isa-KRd in induction, consolidation and maintenance +/- ASCT	Phase II, TE (Arm A) and TNE (ArmB) NDMM (MRD-neg 10^{-5} post-consolidation)	del(17p) or t(4;14) or t(14;16) or > 3 copies 1q21 and ISS2 or 3 stage disease	Interim analysis on 50 pts: 46(A), 4(B) ORR, ≥ PR:100%, ≥ VGPR: 90%, CR/sCR: 46% MRD-pos: 20/33 (61%), MRD-neg: 11/33 (33%)
IRD Study (Nordic Myeloma Study Group) (HR-Maintenance Arm)	Ird induction and consolidation followed by IR maintenancr (HR Arm)	Phase II, TE NDMM (MRD < 0.01%)	t(4;14), del(17p) (60%), t(14;16), t(14;20), gain(1q)	Ongoing study
ANTARES EMN19 (NCT04166565)	CyBorD +/- ASCT	Phase II, NDMM or 1 relapse MM with EMD (≥CR)	EMD associated with high LDH level, del(17p) and HR-GEP	Ongoing study
IFM 2018-04 (NCT03606577)	Dara-KRd for induction and consolidation + double ASCT	Phase II, non randomized, NDMM TE	del(17p), or t(14;16) or t(4;14)	Ongoing study

Conclusions

- Despite the considerable enrichment of the therapeutic arsenal, high-risk MM still constitutes an unmet medical need also in 2021.
- The time has come to readdress the risk stratification: the use of a multiparametric cytogenetic score, such as the IFM and R2-ISS, represent valuable options to comprehensive evaluate risk assessment in MM patient in clinical practice
- Considering that risk evolves over the course of the disease, risk factors may co-occur at the same time altering each other as well, the preferred therapeutic option for HR patients includes specific strategies such as double ASCT and newer drugs for specific subsets
- Also, evaluation of the MRD constitutes an additional tool to better stratify HR patients allowing therapeutic adjustments if necessary.

GRAZIE PER L'ATTENZIONE