2nd edition

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

Turin, September 13-14, 2021

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How I treat elderly high risk Multiple Myeloma

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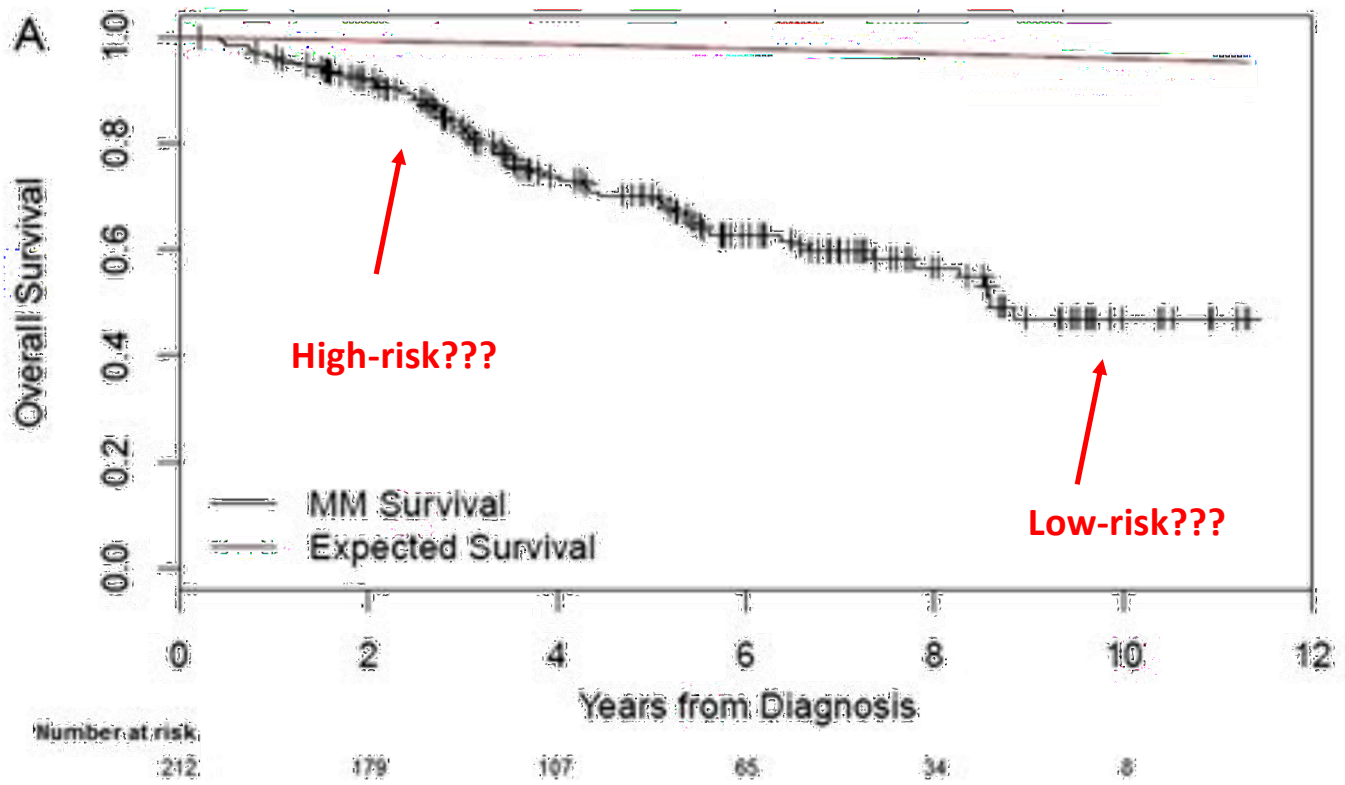
Introduction of novel agents has improved OS in MM

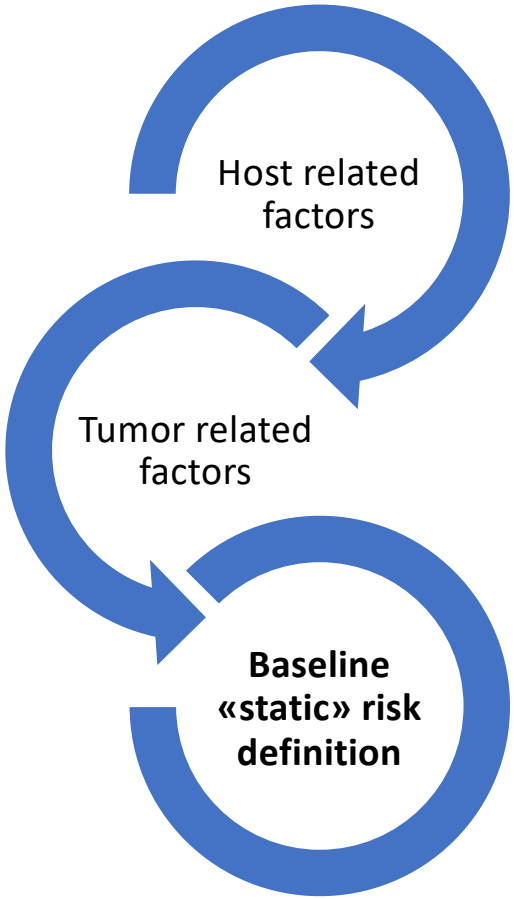


Multiple myeloma is a heterogeneous disease and so the prognosis of affected patients

Ravi P, et al., *Blood Cancer Journal* 2018;8:26.

Prognostic Factors

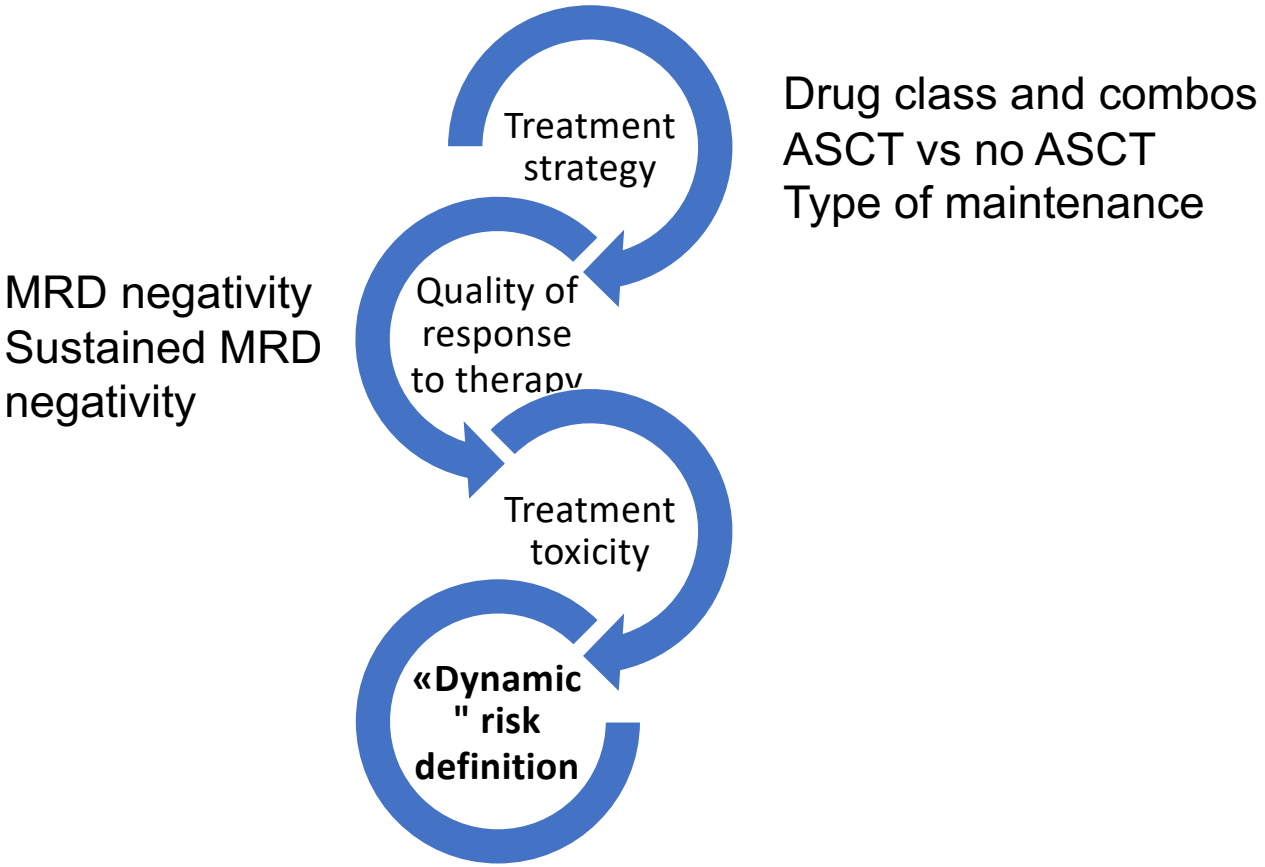
Risk stratification in MM comes from the interaction of several factors



Frailty/fitness
Organ function (renal function)

Genetic lesions
Tumor burden
Circulating Plasmacells
Extramedullary disease
Number of PET/MRI lesions

Prognostic Factors



Prognostic Factors

Disease-related Factors

- R-ISS
- Chromosomal abnormalities
- Circulating Plasma Cells
- Plasma cell Leukemia
- Extramedullary disease
- Early relapse

Patient-related Factors

- Frailty
- Performance Status
- Age
- Renal Failure
- Co-morbidities
- Organ Function

Prognostic Factors

Disease-related Factors

- R-ISS
- Chromosomal abnormalities
- Circulating Plasma Cells
- Plasma cell Leukemia
- Extramedullary disease
- Early relapse

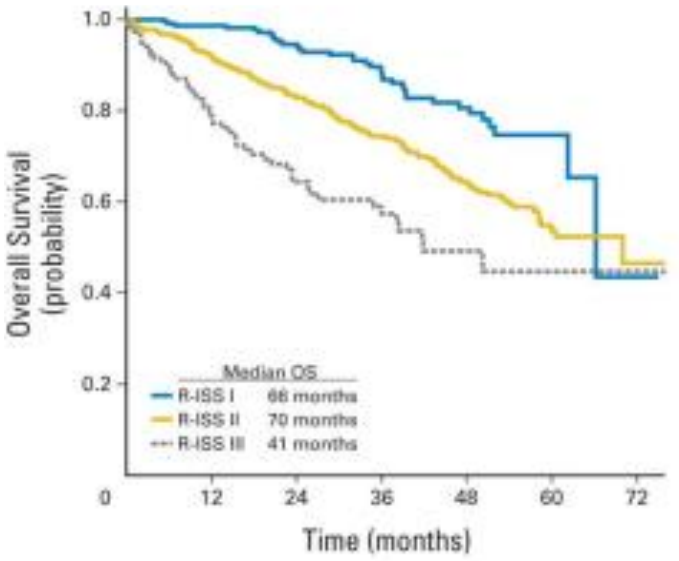
Revised International Staging System (R-ISS)

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 below the upper limit of normal
High	Serum LDH above 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

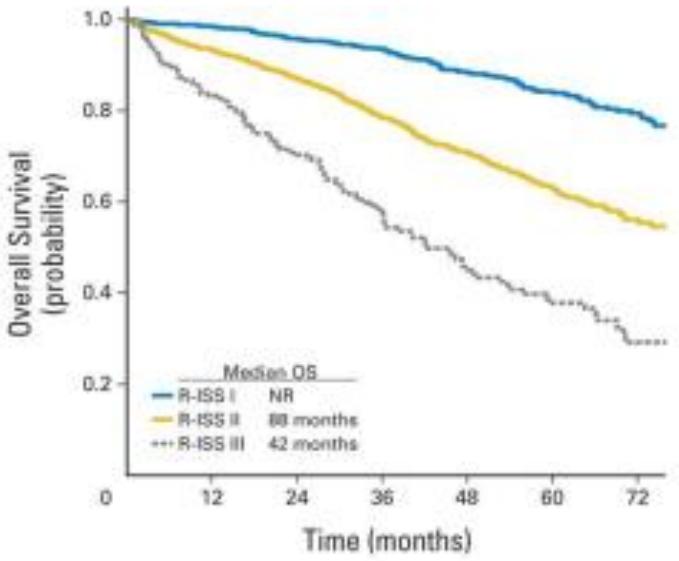
Palumbo et al, J Clin Oncol. 2015 Sep 10;33(26): 2863-9

Revised International Staging System (R-ISS)

Nontransplant eligible patients



Transplant eligible patients



The main limitation is that the intermediate group accounts for 60% of all patients, possibly including patients with a different prognosis.

Palumbo et al, J Clin Oncol. 2015 Sep 10;33(26): 2863-9

Chromosomal abnormalities in MM

R-ISS included chromosomal abnormalities

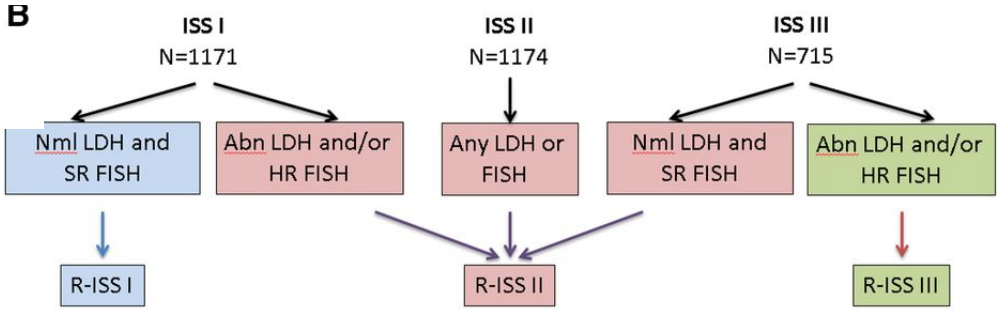
- t(14;16)
- t(4;14)
- del17p

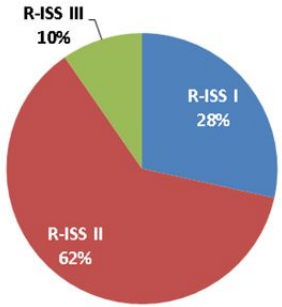
Other recurrent chromosomal abnormalities

- t(14;20)
- del13q
- del1p
- 1q amp/gain
- MYC
- t(11;14)

Revised International Staging System (R-ISS)

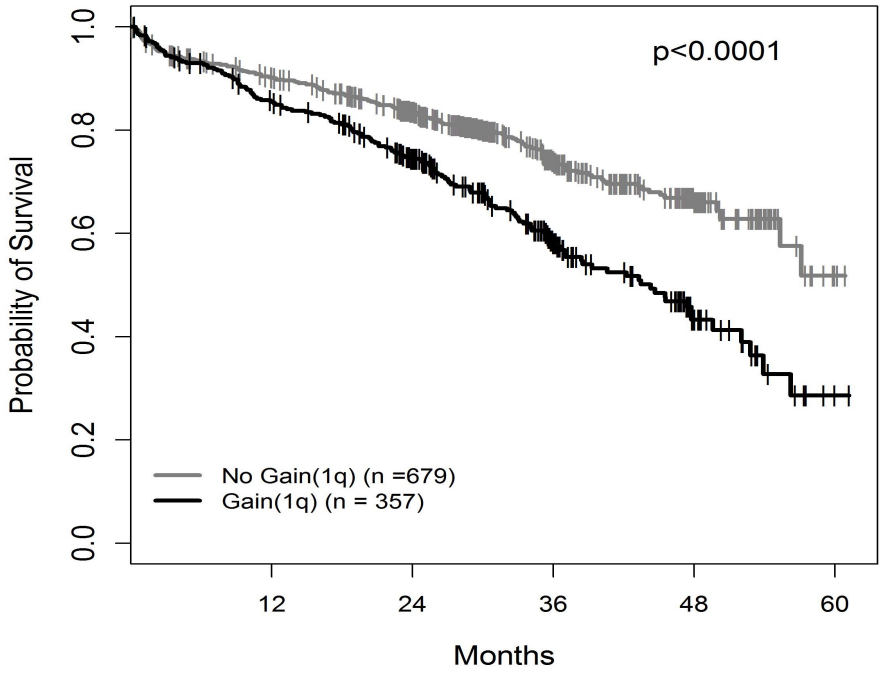
R-ISS is the standard risk stratification in NDMM[1]





	R-ISS I (N=871)	R-ISS II (n=1894)	R-ISS III (n=295)
5-year PFS, % (n=3060)	54	36	22
5-year OS, %			
All (n=3060)	81	60	40
ASCT (n=1998)	83	62	39
No ASCT (n=1062)	75	52	47

1q CNA is a poor prognostic factor in NDMM[2]

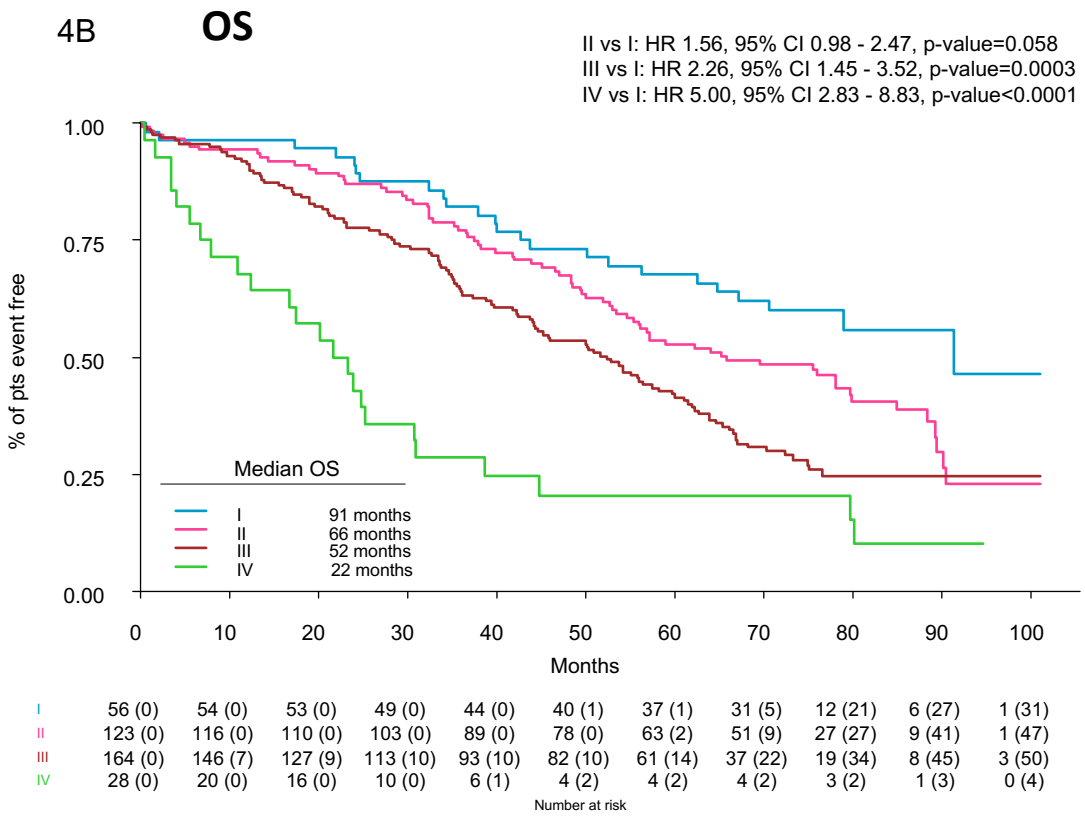


Abbreviations. R-ISS: Revised International Staging System; NDMM: Newly Diagnosed Multiple Myeloma; CNA: Copy Number Alteration; Abn: abnormal; Nml: normal; HR-FISH: del(17p) and/or t(4;14) and/or t(14:16) by fluorescence-in-situ hybridization.

Figure adapted from Dispenzieri et al ASH 2016. 1. Palumbo et al JCO 2015 Sep 10;33(26):2863-9; 2. Shah et al Leukemia 32, 102–110 (2018)

A new R2-ISS: adding 1q to R-ISS

Newly diagnosed MM non-transplant eligible

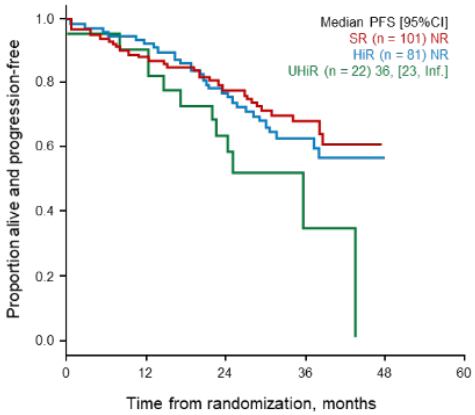


The **inclusion of 1q copy number alterations (CNA)** in the R-ISS generate a ***new scoring system R2-ISS*** that better discriminate intermediate risk patients into different risk groups

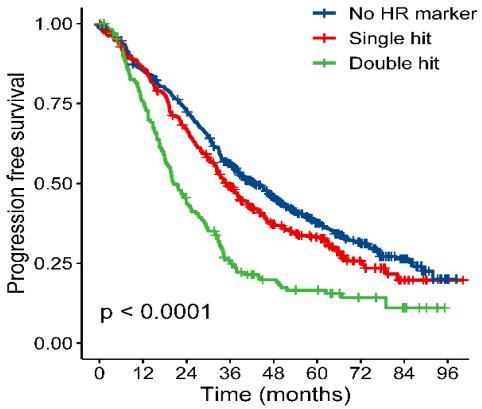
D'Agostino et al, ASH 2020.

Number of genetic lesions matters: standard risk vs high-risk vs ultra high-risk

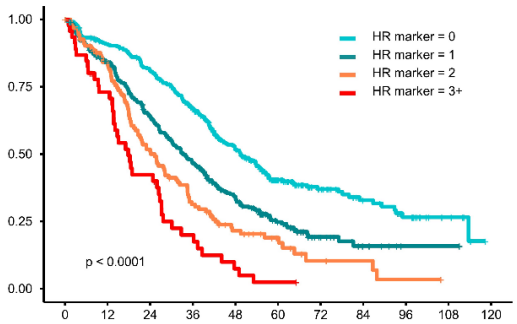
KCRD Myeloma XI



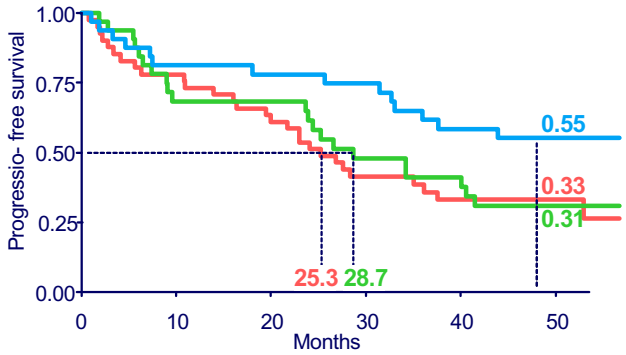
CRD/CTD Myeloma IX-XI



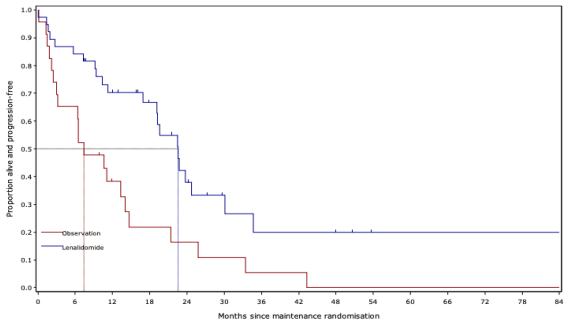
Bortezomib (GMMG-HD4/MM5)



KRd-ASCT vs KRD12 vs KCd-ASCT FORTE



R maintenance Myeloma XI



Shah V, et al., Blood 2018, Pawlyn C, et al., ASH 2019, Weinhold et al., Haematologica in print, Mina et al, et al., EHA 2021, Croft J, et al., ASH 2019; G. Jackson GH. Et al, Lancet Oncol. 2019 Jan;20(1):57-73.

Characteristics (Elderly) High-risk (HR) MM

- Disease with adverse clinical and biological features that lead to **early progression**
- Can present similarly to **standard-risk or alternatively with an aggressive clinical course**
- Risk profile may change **from diagnosis to subsequent relapses**
- Relatively **small number** of elderly HR MM enrolled in clinical trials
- **Lack of prospective randomized trials**, which might support choices of therapy in this setting (meta/pooled analysis or subgroup analysis)

VOLUME 31 · NUMBER 22 · AUGUST 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chromosomal Abnormalities Are Major Prognostic Factors in Elderly Patients With Multiple Myeloma: The Intergroupe Francophone du Myélome Experience

Hervé Avet-Loiseau, Cyrille Hulin, Loic Campion, Philippe Rodon, Gerald Marit, Michel Attal, Bruno Royer, Mamoun Dib, Laurent Voillat, Didier Bouscary, Denis Caillot, Marc Wetterwald, Brigitte Pegourie, Gerard Lepeu, Bernadette Corront, Lionel Karlin, Anne-Marie Stoppa, Jean-Gabriel Fuzibet, Xavier Delbrel, Francois Guilhot, Brigitte Kolb, Olivier Decaux, Thierry Lamy, Laurent Garderet, Olivier Allangba, Francois Lifermann, Bruno Anglaret, Philippe Moreau, Jean-Luc Harousseau, and Thierry Facon

- Retrospective analysis of **1,890 patients** (median age 72 ys; 66-94 ys)
- The incidence of **t(4;14)** was not uniform over age, with a **marked decrease in the oldest patients**
- **t(4;14) and del(17p) are major prognostic factors in elderly patients** with MM, both for PFS and OS, indicating that these two abnormalities should be investigated at diagnosis of MM, regardless of age.
- The prognostic value of t(4;14) and del(17p) was retained in patients treated with **therapies, such as VMP or Rd**

Avet-Loiseau H, et al. J Clin Oncol. 2013;31(22)2806-2809

VMP (bort twice or once weekly) or modified-Rd Impact on High Risk Cytogenetic Transplant-Ineligible Patients with Newly Diagnosed MM

GIMEMA-MM-03-05 (BORT-based)

Median follow-up 72.3 months

1° RANDOMIZATION

VMP
Nine 6-wk courses
V: 1.3 mg/m², d 1,4,8,11,22,25,29,32 (cy 1-4); d 1,8,22,29 (cy 5-9)
M: 9 mg/m², d 1-4
P: 60 mg/m², d 1-4

VMPT
Nine 6-wk courses
V: 1.3 mg/m², d 1,4,8,11,22,25,29,32 (cy 1-4); d 1,8,22,29 (cy 5-9)
M: 9 mg/m², d 1-4
P: 60 mg/m², d 1-4
T: 50 mg/d

VT MAINTENANCE
For 2 yr/ until progression/relapse
V: 1.3 mg/m² every 14 d
T: 50 mg/d

EMN01 (LEN-based)

Median follow-up 65.8 months

1° RANDOMIZATION

Rd
Nine 28-d courses
R: 25 mg, d 1-21
d: 40 mg, d 1,8,15,22

MPR
Nine 28-d courses
M: 0.18 mg/kg, d 1-4
P: 1.5 mg/kg, d 1-4
R: 10 mg, d1-21

CPR
Nine 28-d courses
C: 50 mg, d1-21
P: 25 mg, 3 times wk
R: 25 mg, d1-21

2° RANDOMIZATION

R MAINTENANCE
28-d courses until relapse
R: 10 mg/d, d 1-21

RP MAINTENANCE
28-d course until relapse
R: 10 mg/d, d 1-21
P: 25 mg; 3 times wk

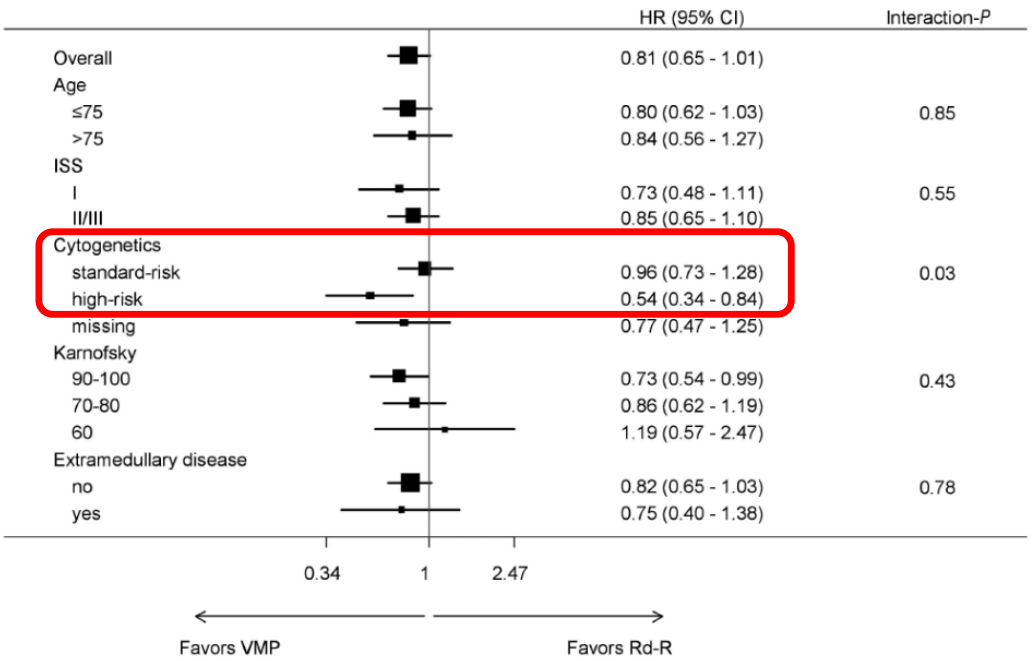
VMP, bortezomib-melphalan-prednisone; VMPT, bortezomib-melphalan-prednisone-thalidomide; VT, bortezomib-thalidomide; Rd, lenalidomide-dexamethasone; MPR, melphalan-prednisone-lenalidomide; CPR, cyclophosphamide-prednisone-lenalidomide; R, lenalidomide; RP, lenalidomide-prednisone; d, day; wk, week; yr, year.

Larocca A, et al. Haematologica 2020 Volume 105(4):1074-1080. Palumbo A et al, JCO 2010 and 2014; Magarotto V et al, Blood 2015

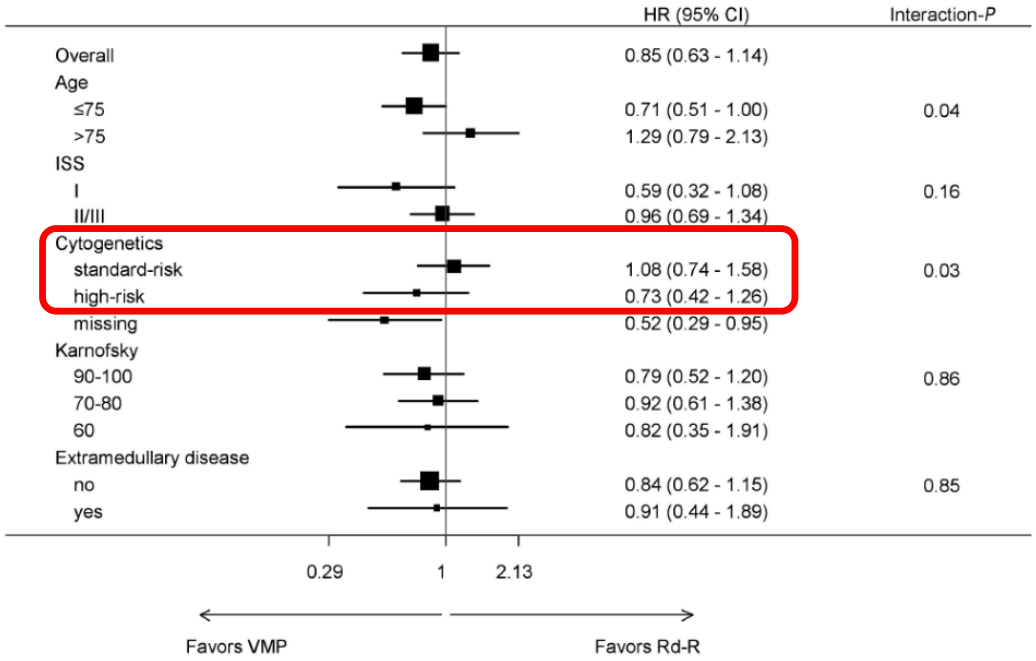
VMP (bort twice or once weekly) or modified-Rd Impact on High Risk Cytogenetic Transplant-Ineligible Patients with Newly Diagnosed MM

Subgroup analysis of PFS and OS in the intention-to-treat population for patients treated with VMP or Rd-R.

PFS



OS



No differences were observed between SR patients treated with VMP or Rd-R, whereas among the HR patients, the probabilities of progression and death were lower with VMP than with Rd-R.

VMP: bortezomib-melphalanprednisone; Rd-R: lenalidomide-dexamethasone followed by lenalidomide maintenance; HR: hazard ratio; 95% CI: 95% confidence interval; ISS: International Staging System.

Larocca A, et al. Haematologica 2020 Volume 105(4):1074-1080. Palumbo A et al, JCO 2010 and 2014; Magarotto V et al, Blood 2015

Perspectives

blood

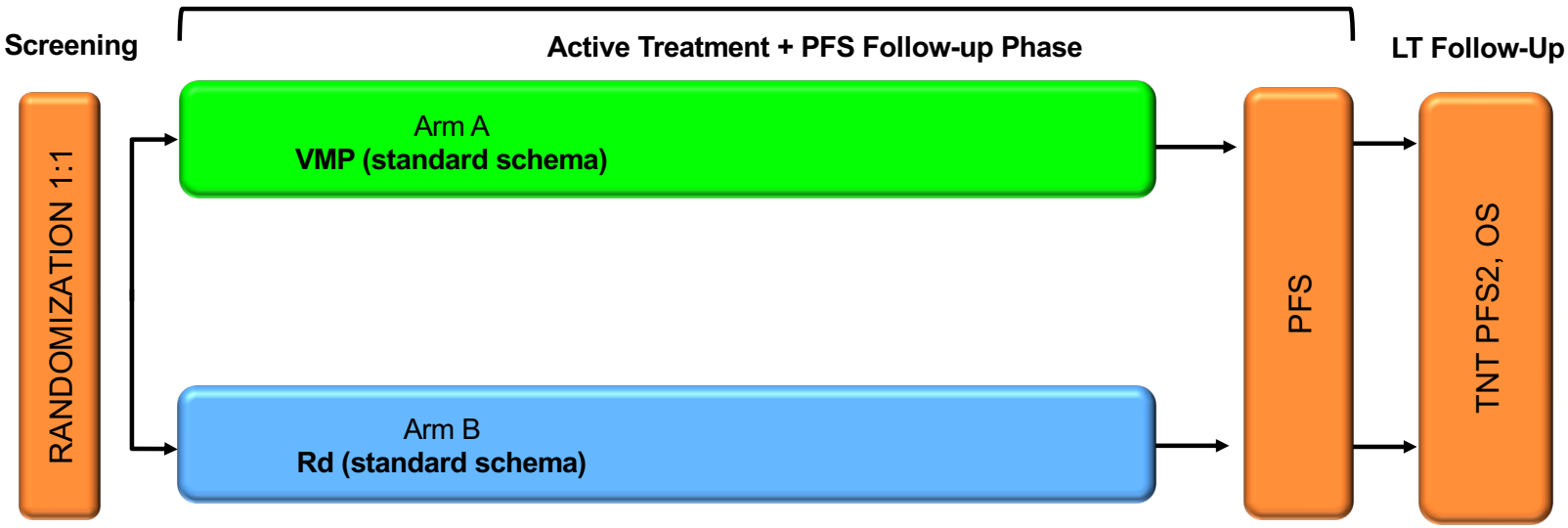
Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group

Consensus statement transplant-ineligible patients

- Data in non TE patients are scarce.
- VMP may partly restore PFS in HR cytogenetics
- There are no data suggesting that lenalidomide may improve outcome with HR cytogenetics
- **The IMWG group advises treating NDMM patients with HR cytogenetics with the combination of a proteasome inhibitor with lenalidomide and dexamethasone.**

Sonneveld P, et al.. Blood 2016; 127:2955-2962

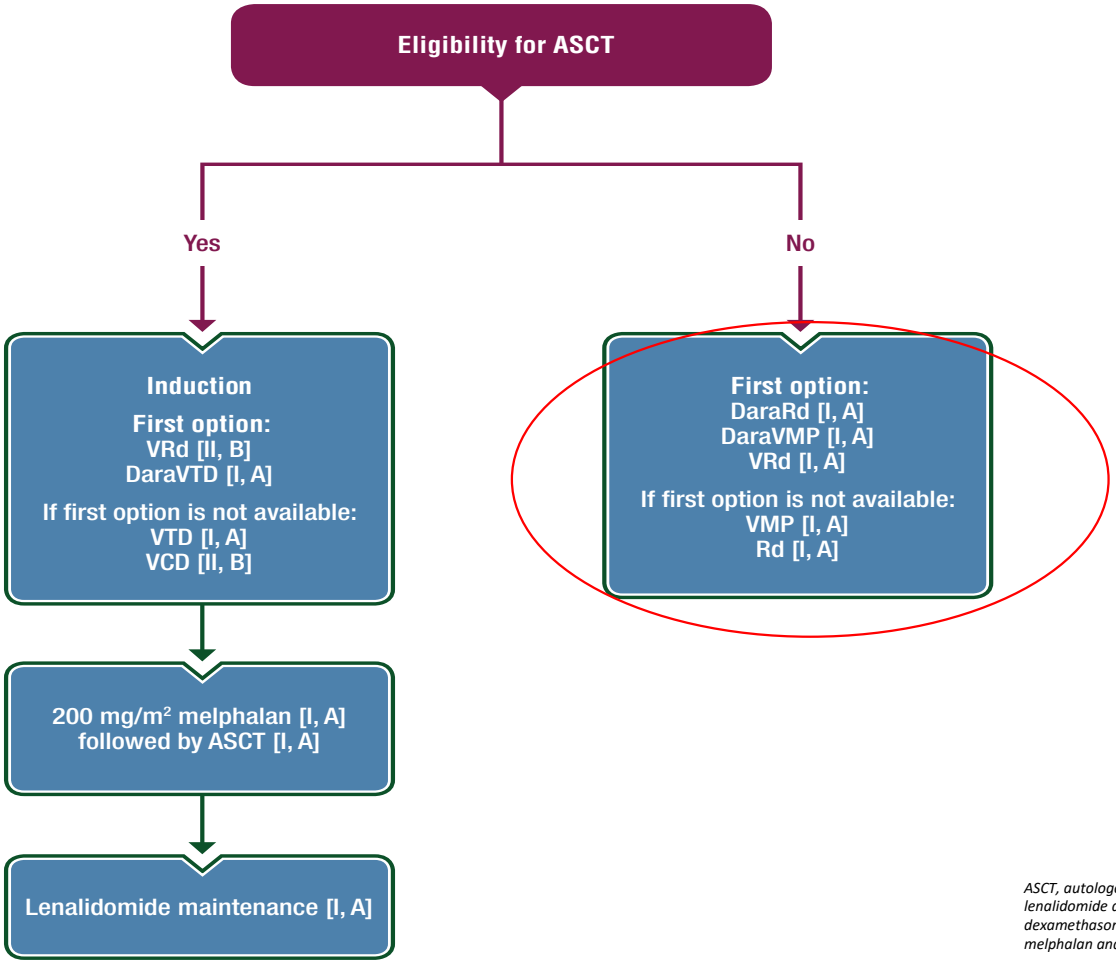
Real-MM Study



Primary objective: -PFS

Secondary objectives: - OS, TTP, TNT, PFS2
- Safety
- Validation of frailty score in a community population
- Healt related costs
- Efficacy in specific subgroups (e.g. FISH, Frailty score)

Multiple myeloma: EHA-ESMO Clinical Practice Guidelines
Treatment of Newly diagnosed Multiple Myeloma

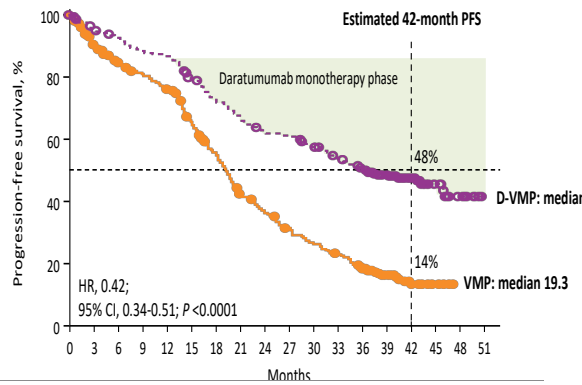


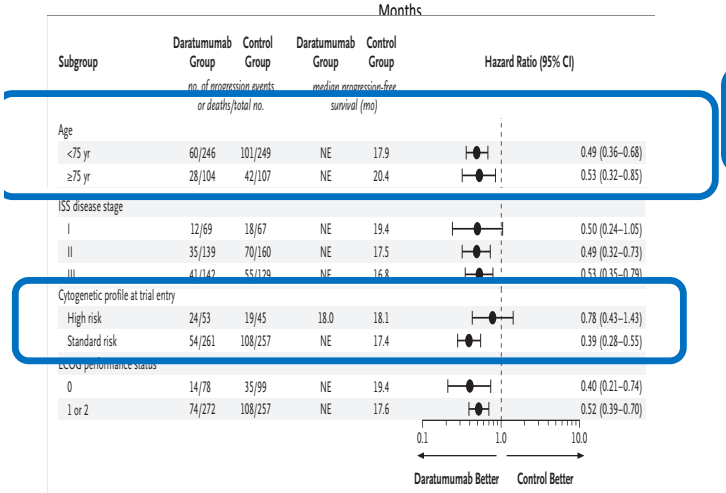
ASCT, autologous stem cell transplantation; Dara, daratumumab; PI, proteasome inhibitor; Rd, lenalidomide and low-dose dexamethasone; VRD, bortezomib, lenalidomide, and dexamethasone; VCD, Bortezomib, cyclophosphamide and dexamethasone; VMP, bortezomib, melphalan and prednisone; VTD, Bortezomib, thalidomide and dexamethasone.

Dimopoulos MA, et al. Ann Oncol. 2021;32(3):309-322.

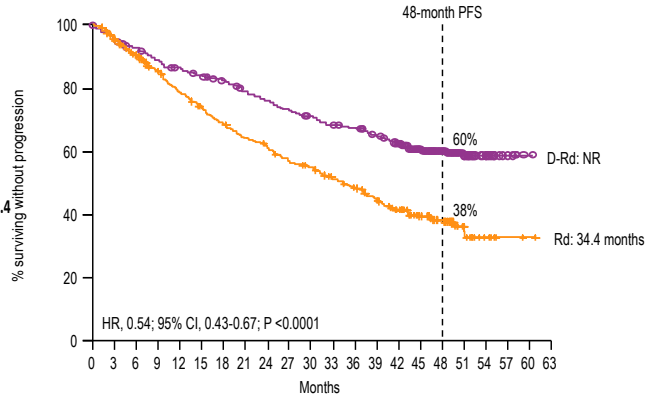
Current standard treatment for transplant ineligible MM

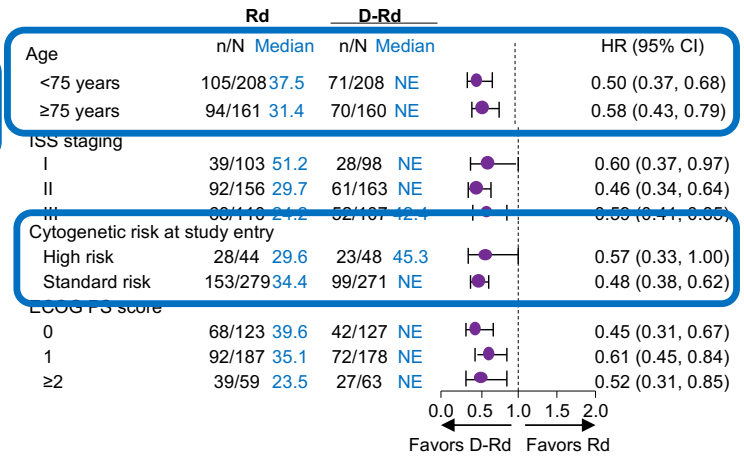
Dara-VMP[1,2]



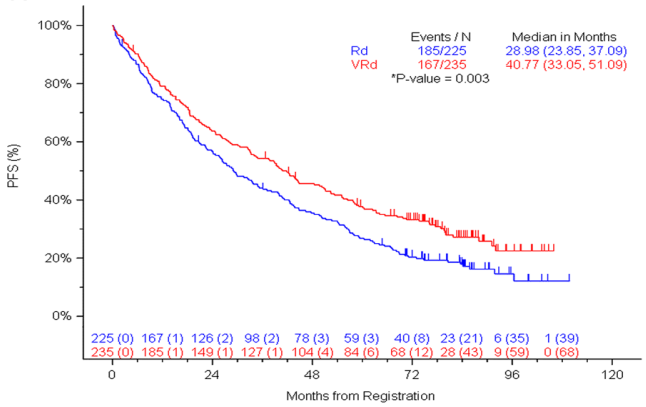


Dara-Rd[3]





VRd[4]



	Patients (N=471)*	Progression-free survival		Overall survival	
		HR (95% CI)	p value	HR (95% CI)	p value
Patients given bortezomib with lenalidomide and dexamethasone (VRd group)	242 (51%)	0·73 (0·58–0·92)	0·007	0·74 (0·55–1·00)	0·048
International Staging System stage III	157 (33%)	1·58 (1·16–2·13)	0·003	2·16 (1·43–3·25)	0·0003
International Staging System stage II	184 (39%)	1·16 (0·86–1·57)	0·322	1·18 (0·77–1·81)	0·447
Intent to transplant	324 (69%)	0·98 (0·74–1·28)	0·866	0·86 (0·61–1·20)	0·371
Age ≥65 years	202 (43%)	1·32 (1·03–1·71)	0·031	1·88 (1·34–2·62)	0·0002

Data are n (%) unless otherwise stated. *N=471 patients with valid data for factor.

Table 2: **Multivariate age-adjusted progression-free survival and overall survival**

In both trials no impact of age was observed

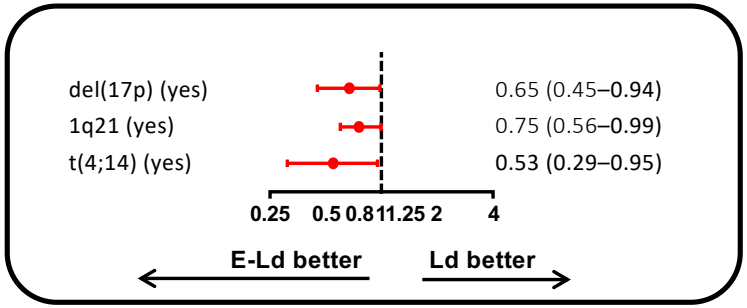
Median PFS 16 months for Rd and 38 months for VRd in high risk by FISH

Dara, daratumumab; V, bortezomib; M, melphalan; P, prednisone; R, lenalidomide; K, carfilzomib; MRD neg, minimal residual disease; MRD neg, MRD negative; PFS, progression-free survival; yrs, years.

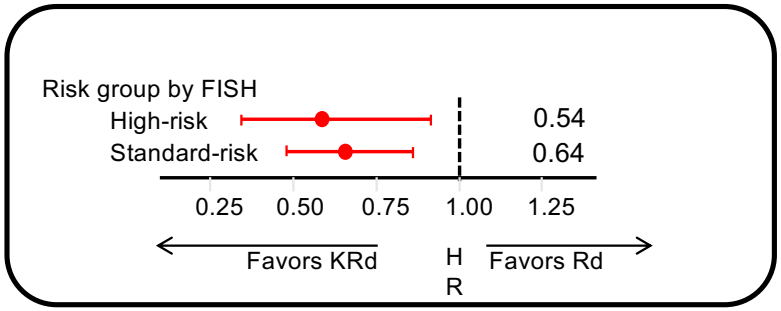
1. Mateos MV et al., ASH 2019; 2. Mateos MV et al, NEJM 2018; 3. Kumar S. et al., ASH 2020; 4. Durie B, et al. Blood Cancer J 2020. 5. Durie B, ASH 2018; 6. Durie Lancet 2017 389: 519–27

High risk versus standard risk cytogenetics in relapsed/refractory MM

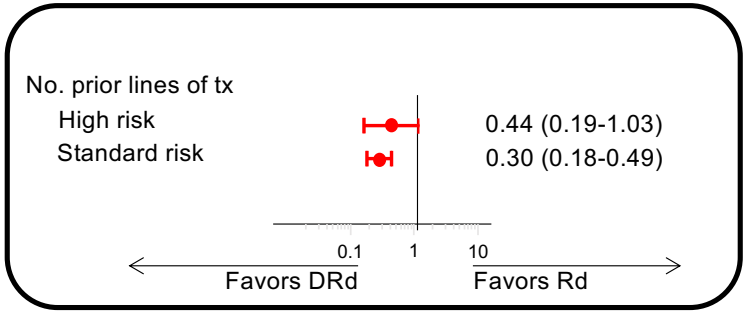
Elotuzumab-Rd vs Rd



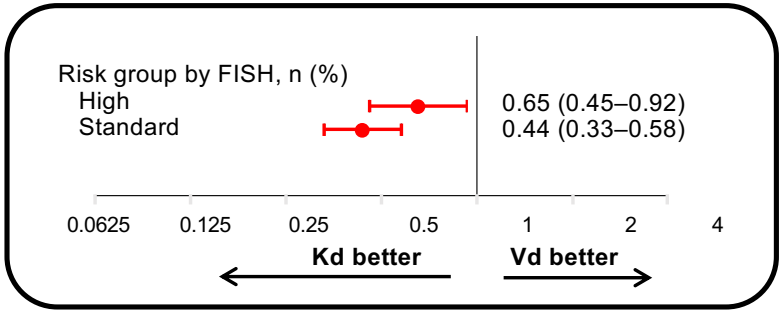
Ixazomib-Rd vs Rd



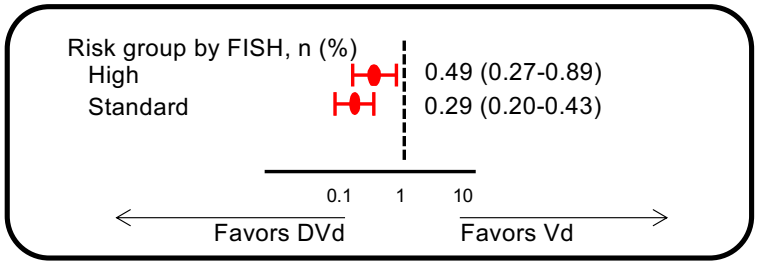
Daratumumab-Rd vs Rd



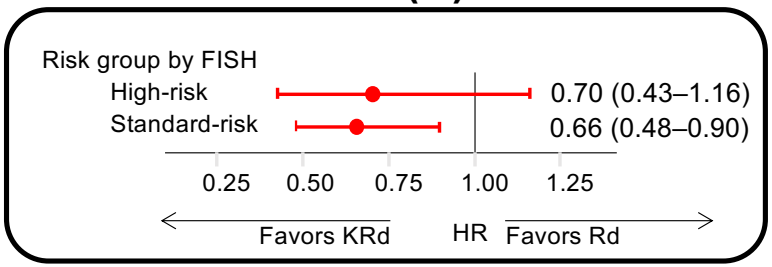
Carfilzomib (K)d vs Vd



Daratumumab-Vd vs Vd

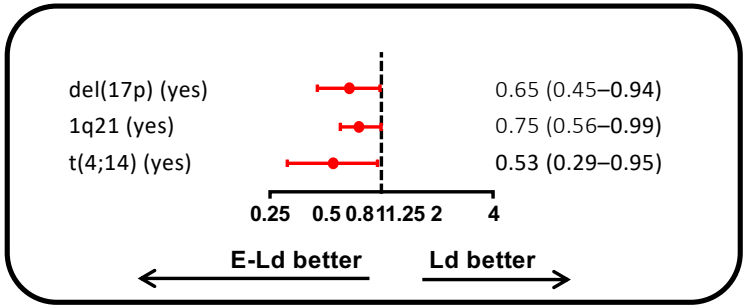


Carfilzomib (K)Rd vs Rd

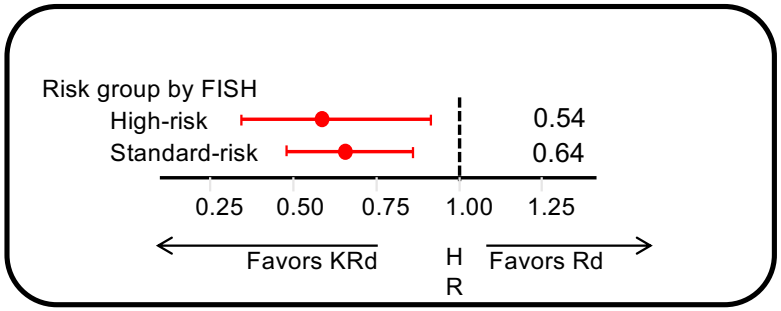


High risk versus standard risk cytogenetics in relapsed/refractory MM

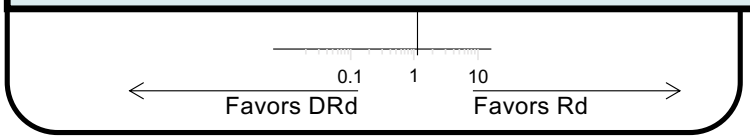
Elotuzumab-Rd vs Rd



Ixazomib-Rd vs Rd

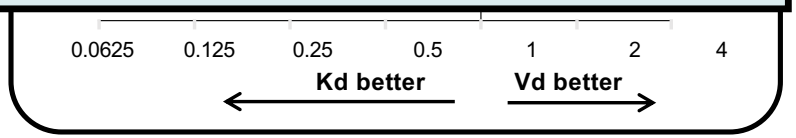


Daratumumab-Rd vs Rd

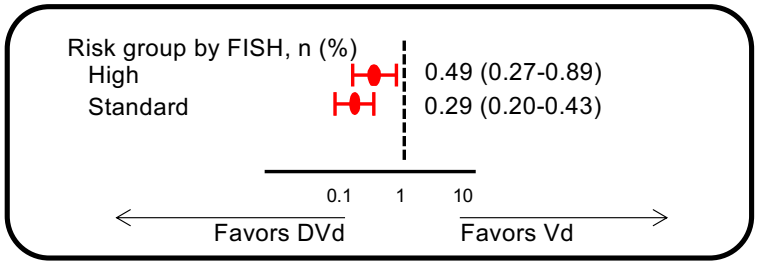


Carfilzomib (K)d vs Vd

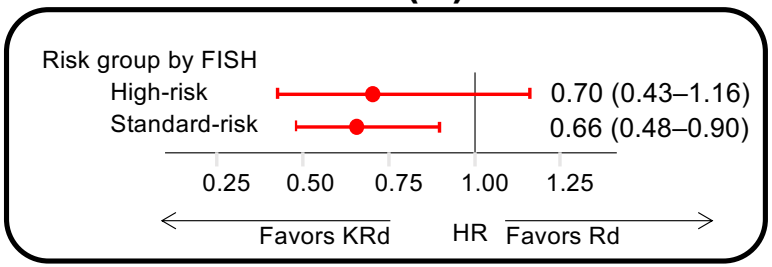
Median age 64-66 years
Patients ≥75 years 11-20%



Daratumumab-Vd vs Vd

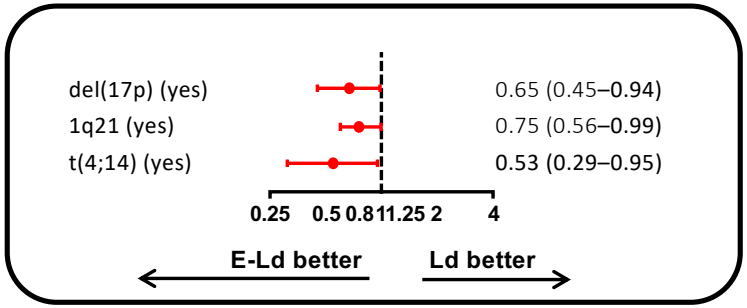


Carfilzomib (K)Rd vs Rd

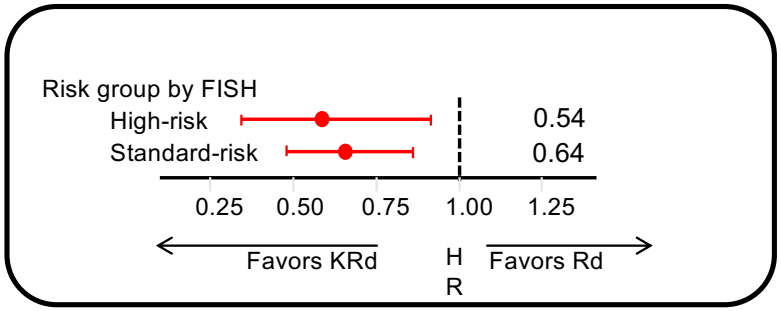


High risk versus standard risk cytogenetics in relapsed/refractory MM

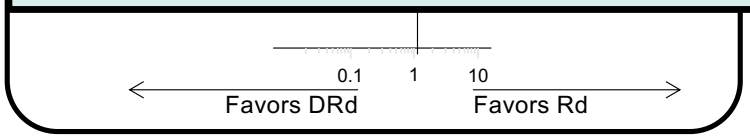
Elotuzumab-Rd vs Rd



Ixazomib-Rd vs Rd

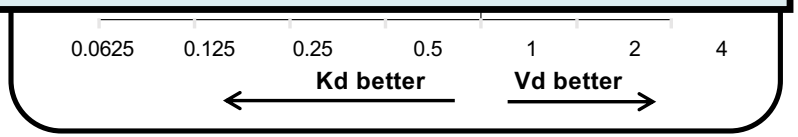


Daratumumab-Rd vs Rd

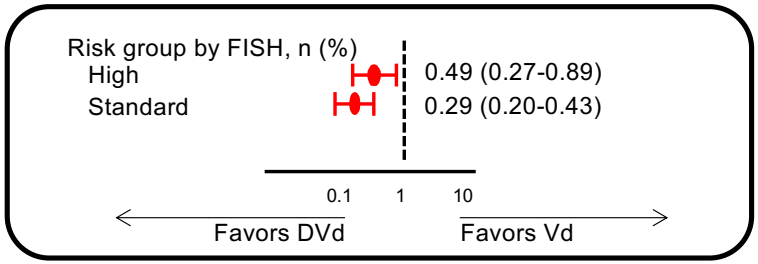


Carfilzomib (K)d vs Vd

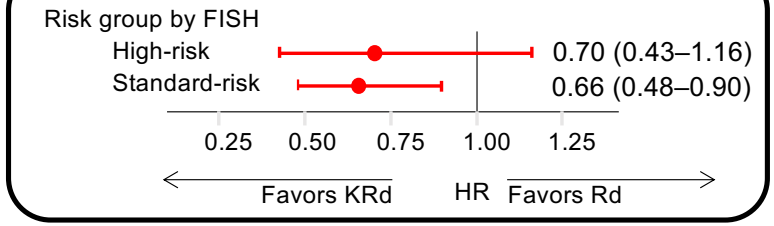
Novel combos improve but not overcome
High Risk Cytogenetic profile



Daratumumab-Vd vs Vd



Carfilzomib (K)Rd vs Rd



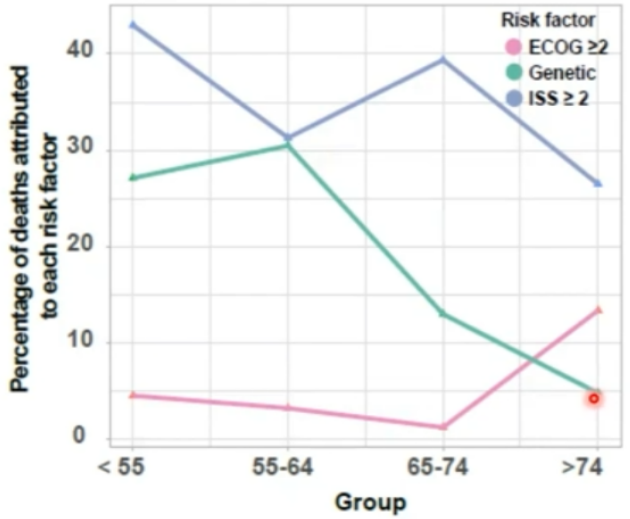
Differences in the genetic make-up of Myeloma by age

Contribution of genetics to outcome

Event	<66 (%)	66-77 (%)	>75 (%)	p-value
del(13)	45	43.6	37	.004
t(4;14)	14.3	10.9	8.3	.001
del(17p)	6	5.9	6.1	NS

- The percentage of deaths attributed to genetics [del(1p), gain(1q), del(17p) and t(4;14)] goes down with age in favor of factors such as Performance Status and ISS

- Suggesting the contribution of conventional genetic studies to outcome in elderly patients is less important in favor of clinical features



Boyle et al Leukemia *in press*

NYU Langone Health

Prognostic Factors

The current risk stratification model does not take into account all the risk factors

Patient-related Factors

- **Frailty**
- **Performance Status**
- **Age**
- **Renal Failure**
- **Co-morbidities**
- **Organ Function**

Elderly MM patients

Heterogeneous population
Variety of disease- and host-related factors

Fit patients ASCT Eligible

Based on
Age
Performance status (PS)
Comorbidities
(R-MCI score, HCT-CI) and organ function

Fit patients No ASCT Eligible

Active, independent, who exercise regularly

Unfit

Can perform limited activities but they don't need any help

Frail

Help for household tasks
Dependent on other people
Partial help for their personal care

Fit, Intermediate (Unfit) and Frail

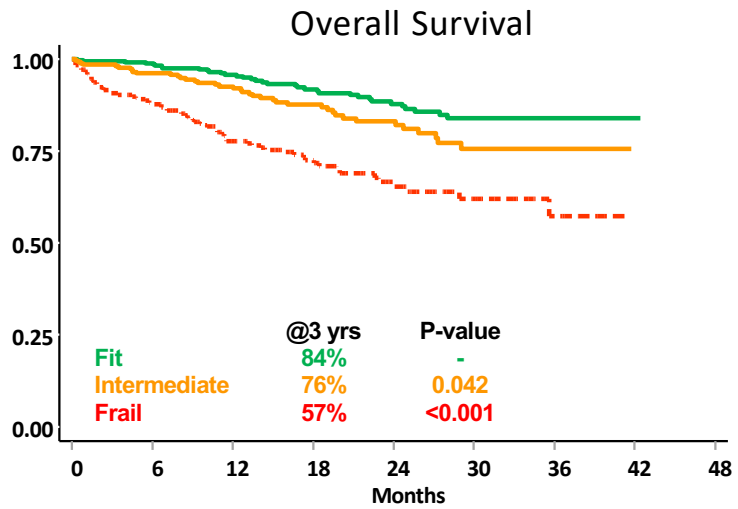
IMWG Frailty Score

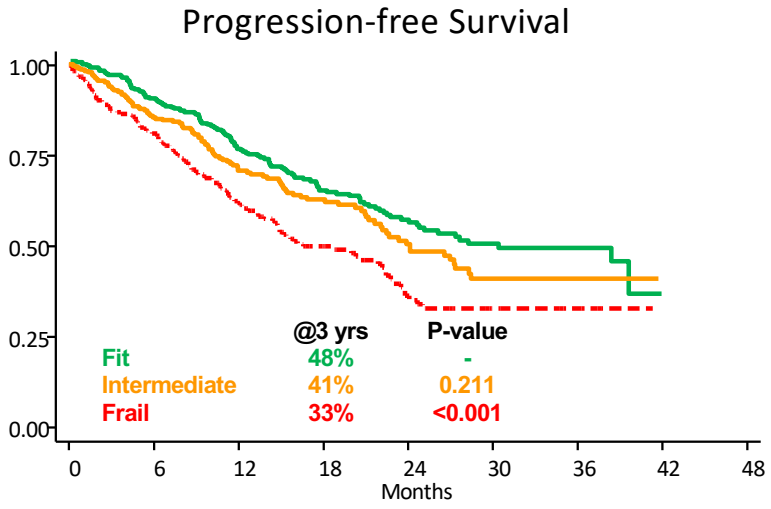
Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.13 (0.76-1.69)	0.549	1
	Age >80 years	2.40 (1.56-3.71)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.37 (0.92-2.05)	0.125	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.67 (1.08-2.56)	0.02	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.43 (0.96-2.14)	0.078	1

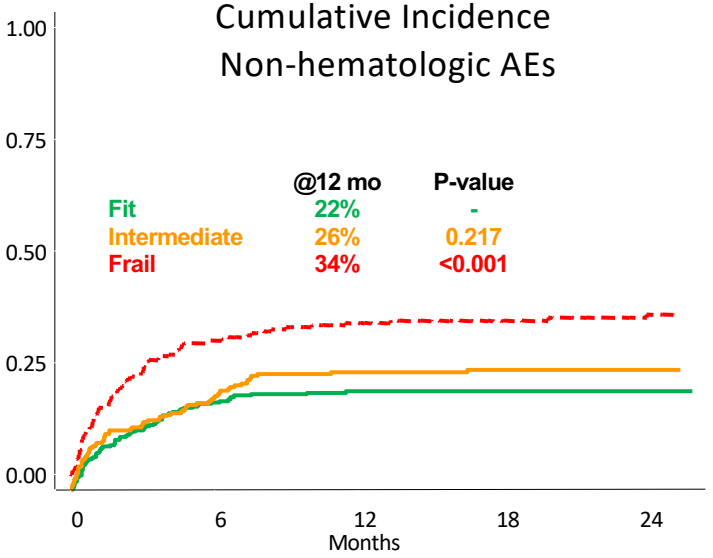
ADDITIVE TOTAL SCORE	PATIENT STATUS
0	FIT
1	INTERMEDIATE/UNFIT
≥2	FRAIL

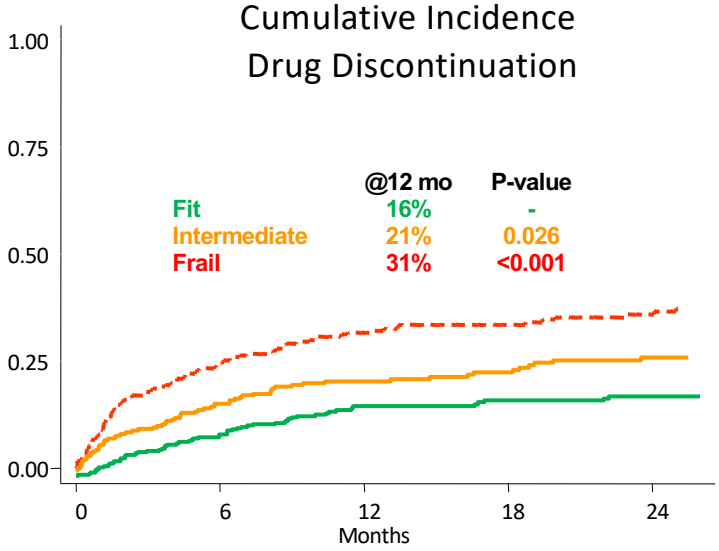
Palumbo A et al, Blood 25(13):2068-74, 2015

IMWG Frailty Score: long-term outcome



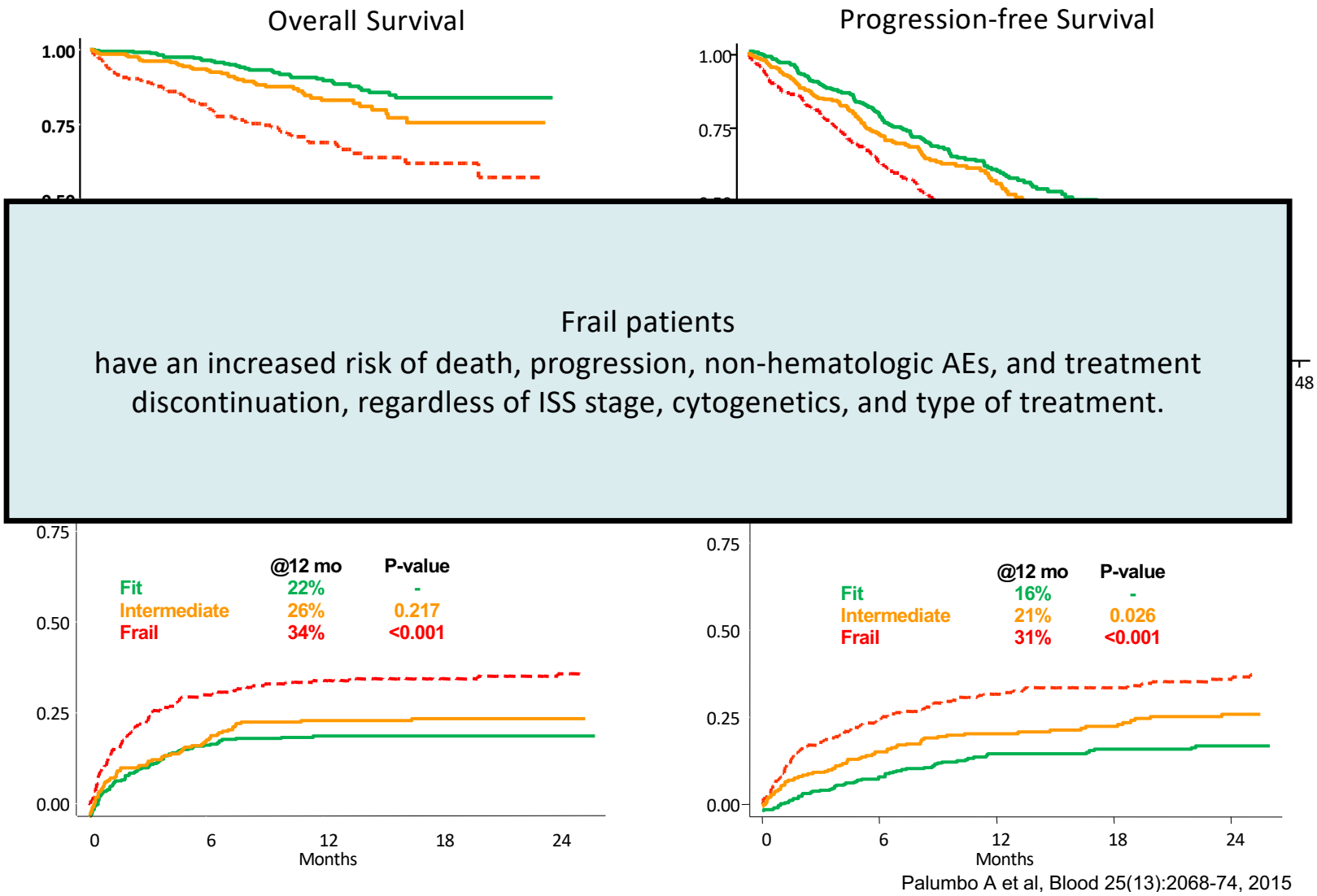






Palumbo A et al, Blood 25(13):2068-74, 2015

IMWG Frailty Score: long-term outcome



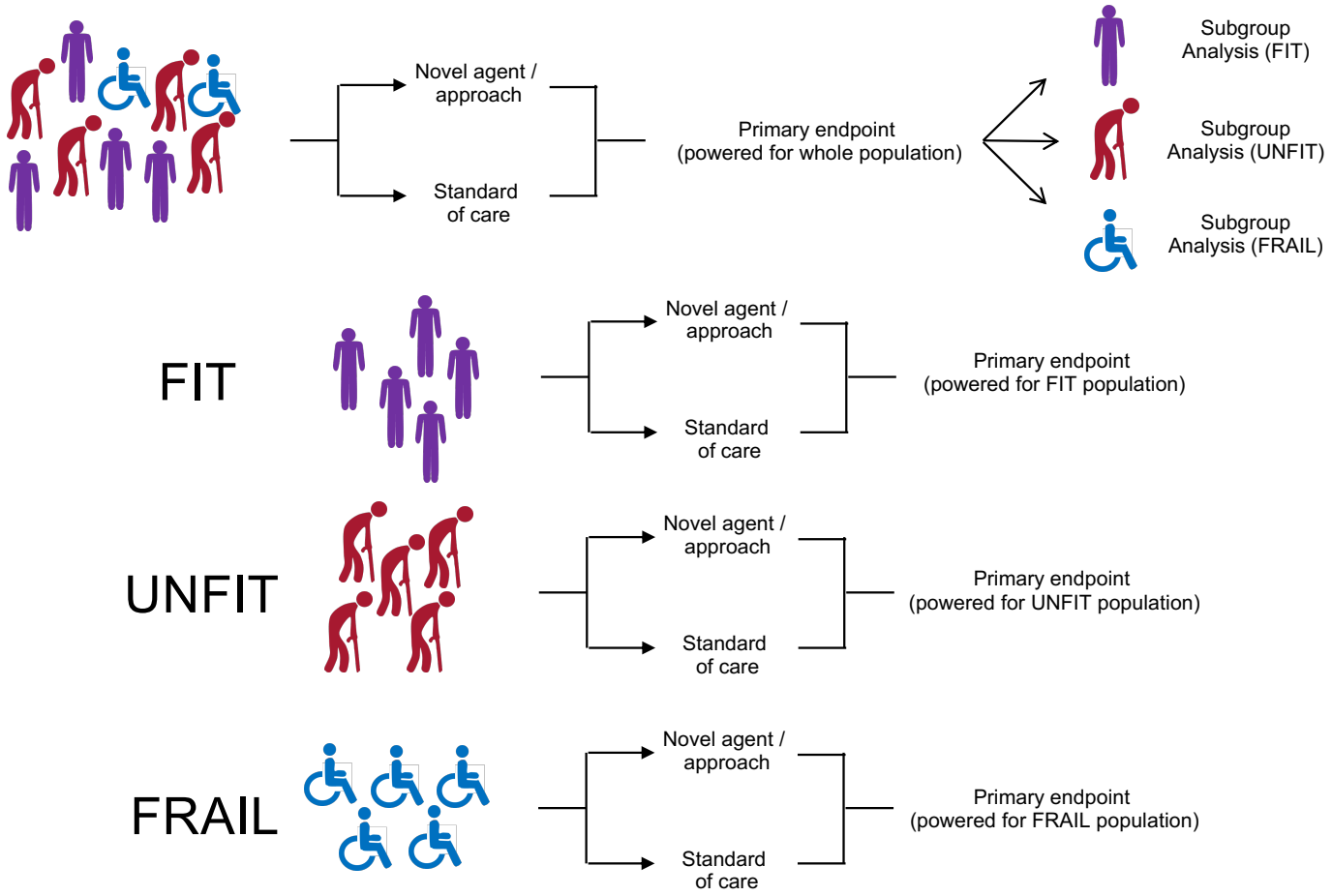
Palumbo A et al, Blood 25(13):2068-74, 2015

How I treat elderly MM patients

FRAILTY ASSESSMENT IMWG Frailty Score or RMC-Index		
FIT PATIENTS	**INTERMEDIATE-FIT PATIENTS**	**FRAIL PATIENTS**
		
age ≤75 + ADL >4 + IADL >5 +CCI≤1	age 76-80 or ADL ≤4 or IADL ≤5 +CCI >1	age >80; age 76-80 + ADL ≤4 or IADL ≤5 or CCI >1; age ≤75 + at least 2 ADL ≤4 or IADL ≤5 or CCI >1
Goal: efficacy	*Goal: efficacy/safety*	*Goal: safety/QoL*
APPROVED REGIMENS		
Daratumumab-VMP Daratumumab-Rd VRd ASCT in pts ≤70 years old	Daratumumab-VMP, weekly V Daratumumab-Rd VRd-lite Vd	Dose-adjusted Rd ± daratumumab Dose-adjusted Vd or VMP Palliative treatment
EXPERIMENTAL REGIMENS with monoclonal antibodies		
Daratumumab-VRd (NCT03652064) Isatuximab-VRd (NCT03319667) Isatuximab-VCd (NCT02513186) Belantamab-VRd (NCT04091126)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-VRd lite (NCT04052880)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-R (NCT03993912)

Bonello F et al. Pharmaceuticals 2020

Improving outcomes for older patients in clinical trials



Identify patients upfront and adapt therapy based on frailty

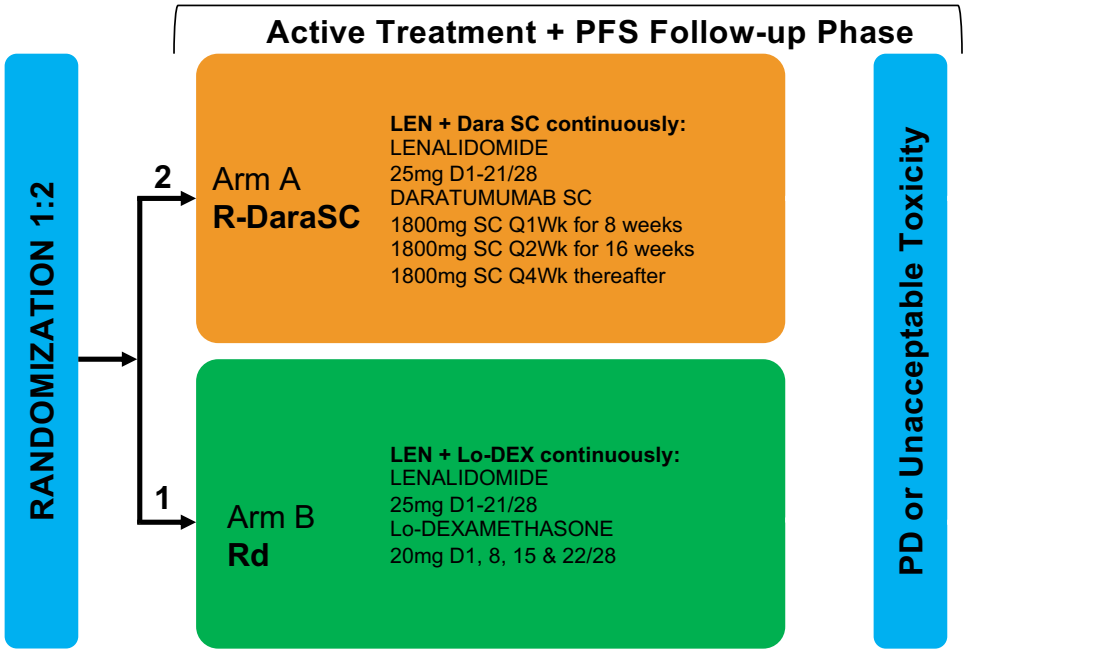
Courtesy by Charlotte Pawlyn

Frailty-adjusted treatments

IFM 2017-03

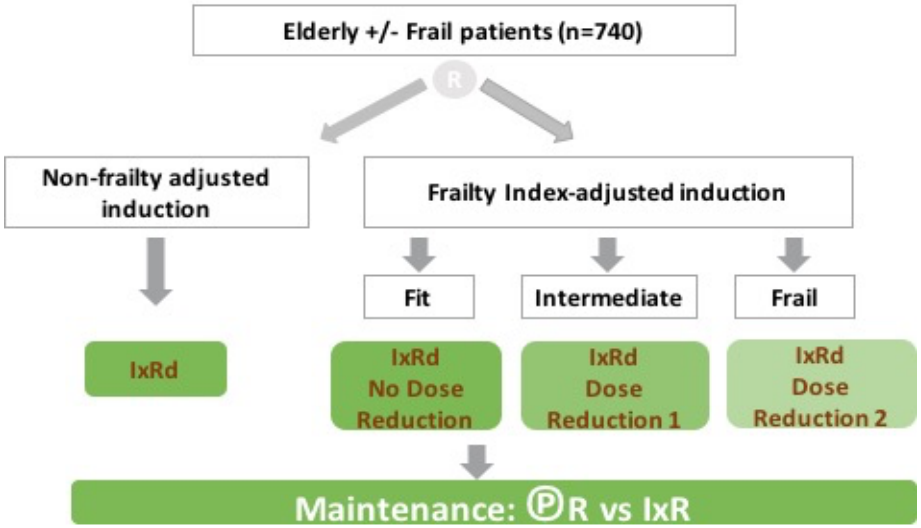
340 patients (frail)

Primary endpoint - PFS



UK-MRA FitNEss trial

Concept of frailty-adjusted dosing

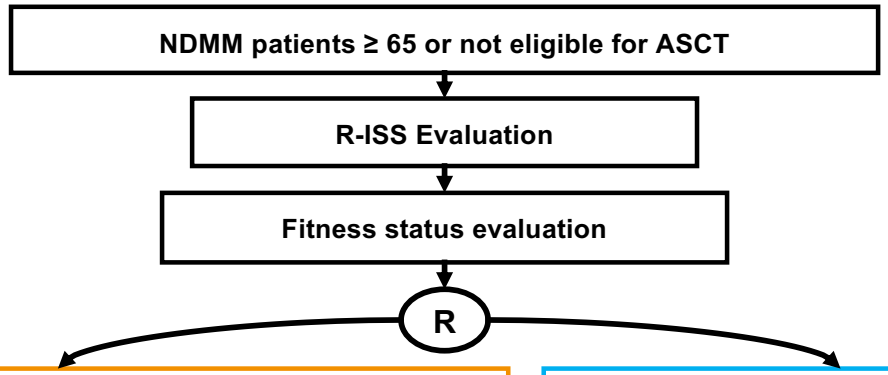


Randomization will be stratified by International Staging System (I vs II vs III) and age (<80 vs ≥80)
In Arm A Low Dose Dex (20mg/week) during Cycle 1 and 2 then Methylprednisolone (with SC Dara)

www.clincaltrials.gov identifier: NCT03993912
Fitness trial - NCT03720041

Frailty and MRD adapted treatments

Phase III EMN20: KRd vs Rd in NDMM ASCT-ineligible fit and intermediate patients



ARM A: KRd until PD or intolerance*

Carfilzomib (K):

- 20 mg/m^2 IV on day 1 of cycle 1;
- 56 mg/m^2 IV on days 8 and 15 in cycle 1; on days 1, 8 and 15 in cycles 2-12; on days 1 and 15 from cycle 13 and onwards.

Lenalidomide (R):

- 25 mg orally on days 1-21

Dexamethasone (d):

-40 mg orally on days 1, 8, 15 and 22

Each cycle is a 28-day cycle.

ARM B: Rd until PD or intolerance

Lenalidomide (R):

- 25 mg orally on days 1-21

Dexamethasone (d):

-40 mg orally on days 1, 8, 15 and 22.

Each cycle is a 28-day cycle.

*VGPR patients in sustained MRD negativity (MRD negative at least at 10^{-5} after 1 and 2 years of therapy) will stop carfilzomib after 2 years of treatment, and will continue with lenalidomide and dexamethasone.

K, Carfilzomib; R, Lenalidomide; Dex, dexamethasone; NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem cell transplattaion; MRD, minimal residual disease

Summary

- Current risk stratification models (R-ISS) do not entirely define each patient's risk, in particular for elderly patients

- Risk status requires a comprehensive evaluation of **disease** and **host-related factors**: tumor burden, cytogenetic/molecular lesions, clinical presentation (circulating plasmacells, extramedullary disease, renal failure), age, comorbidities and fitness

- **Continuous assessment of risk status** as it may change according to both biological (accumulating lesions, evolution to sPCL, development of EMD) and clinical factors (early relapse)

- **Baseline risk status modulation by treatment and response is also possible in elderly patients**
  - The achievement of MRD negativity and a sustained MRD negativity could be the key to overcome baseline high-risk factors such as chromosomal abnormalities, ISS and CPC

Conclusions

- **New combos** (Dara-VMP, Dara-Rd, VRd**) significantly improve outcome both in high risk and standard risk patients**
- **No treatment regimen showed to consistently overcome high risk cytogenetic profile**
- Future investigations including **emerging agents** may benefit these patients
- Future **risk-stratified treatments** (cytogenetics, frailty) should be investigated (risk-tailored treatment strategies based on both baseline patient and disease and dynamic risk factors)
- In the choice of treatment consider not only the biologic high risk disease but also **frailty status of patients**

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