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

Turin, September 13-14th 2018

How I treat elderly high risk Multiple Myeloma

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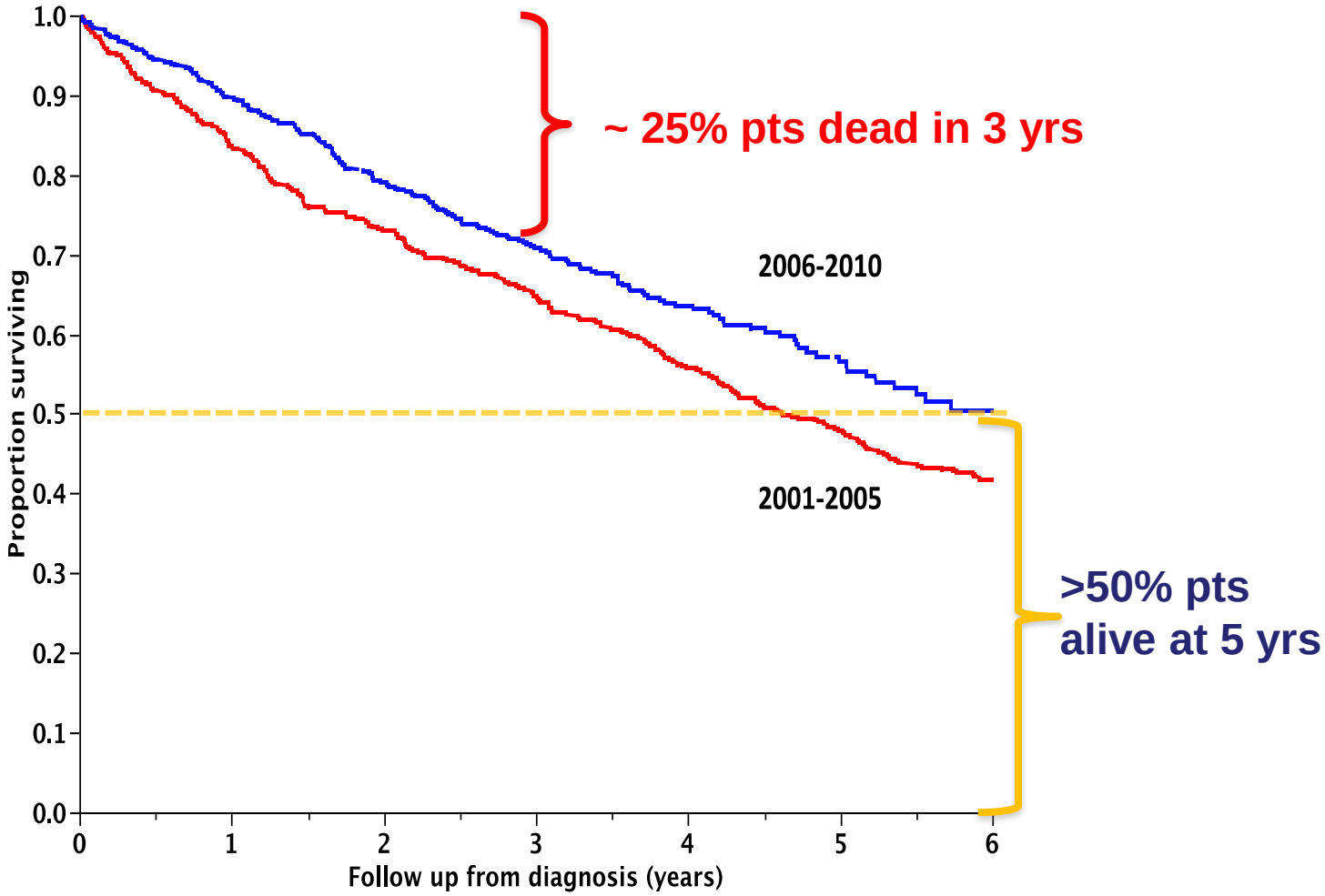
Scientific Advisory Board	BMS

Presentation includes discussion of the off-label use of a drug or drugs

Introduction of novel agents has improved OS in MM

Myeloma Is Not One Disease



The improvement was primarily seen among patients over 65 years
6-year OS improved from 31% to 56%; P<0.001

Median follow-up 5.9 years

Kumar SK, et al. Leukemia. 2014;28:1122-1128

Prognostic factors in MM

Patient-related

- Age
- Performance status
- Frailty Status

Disease-related

- High β_2 microglobulin
- Low albumin
- Renal impairment
- LDH above the upper limit
- Cytogenetic abnormalities
- Gene expression profile (GEP)
- Circulating plasma cells
- Extramedullary disease
- High proliferation rate

ISS

Disease burden

Disease biology

At diagnosis

Therapy-related

- Quality of response
- Early relapse/Primary refractory MM/No response PI/IMiD

(Elderly) High Risk MM

- High-risk (HR) cytogenetics
- ISS and R-ISS stage III
- Renal impairment

- Age and frailty

- Plasma cell Leukemia (PCL)
- Extra-medullary (EM) disease

- No response PI/IMiD, primary refractory disease

(Elderly) High Risk MM

- **High-risk (HR) cytogenetics**
- ISS and R-ISS stage III
- Renal impairment

- **Age and frailty**

- **Plasma cell Leukemia (PCL)**
- **Extra-medullary (EM) disease**

- **No response PI/IMiD, primary refractory disease**

Characteristics
(Elderly) High-risk 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**

Open issues
Elderly High-risk MM

- Improvements in outcomes have not been as great as in TE patients
- No treatment regimen has demonstrated sustained and consistent survival benefit
- Relatively **small number of elderly HR MM** enrolled in clinical trials
- There is a **lack of prospective randomized trials**, which might strongly support choices of therapy in this setting (meta/pooled analysis or subgroup analysis)

Summary of cytogenetic risk features

	High-risk	Standard-risk
Cytogenetic abnormality	FISH: t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q) Non hyperdiploid Karyotipe Karyotype del(13) GEP: high-risk signature	All others including: FISH: t(11;14), t(6;14)

- Cytogenetic **abnormalities by FISH** currently are clinically relevant prognostic factors in MM.
- The IMWG consensus panel on FISH advises to test for the presence of **del(17p), t(4;14), and possibly t(14;16).**
- An extended panel, which may be incorporated in clinical trials, includes t(11;14), t(14;20), gain(1q), del(1p), del(13q), and ploidy status.

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

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 novel therapies, such as MPV or Rd**

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

Revised ISS staging system

A total of **3,060 pts** with **NDMM** enrolled onto 11 international, multicenter clinical trials
All patients received new drugs (IMIDs or PIs)

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 < upper limit of normal
	High	Serum LDH > upper limit of normal
A new model for risk stratification for MM		
R-ISS stage	I	ISS stage I, 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

CA, chromosomal abnormalities; iFISH, interphase fluorescent *in situ* hybridisation; ISS, International Staging System; R-ISS, Revised International Staging System.

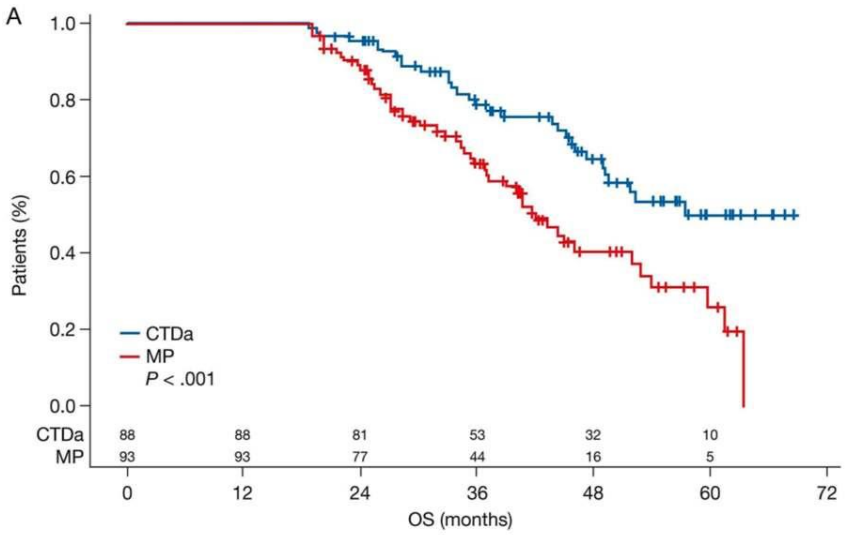
Palumbo A, et al. J Clin Oncol 2015;33:2863–9.

Why risk stratification?

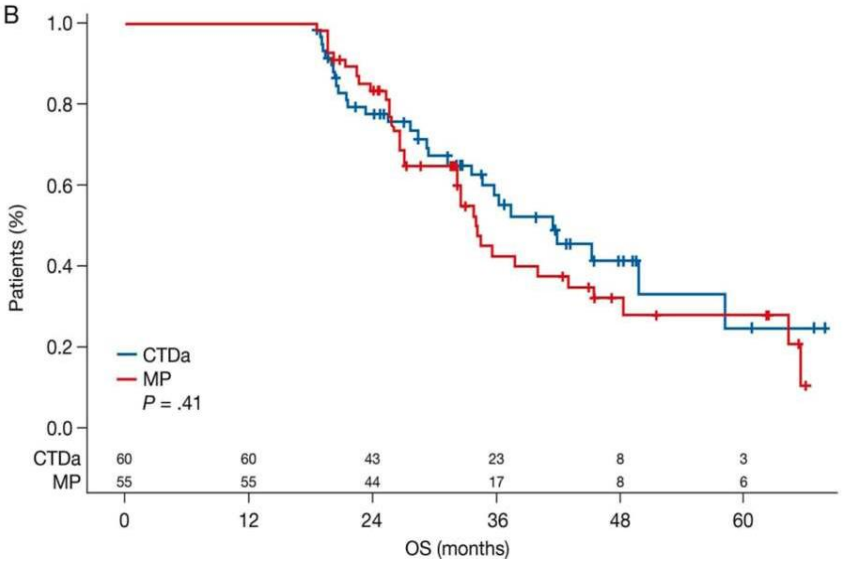
- ***Two important goals***
  - ***Counsel:*** Need to provide patient with realistic expectations based on the currently available treatments
  - ***Therapy:*** Decide if particular therapies can be chosen based on their differential effects on the high-risk and standard-risk disease

Thalidomide-based treatments

Favorable cytogenetic profiles



Adverse cytogenetic profiles



Inability of Thalidomide to either improve or overcome the adverse prognosis of high-risk cytogenetics

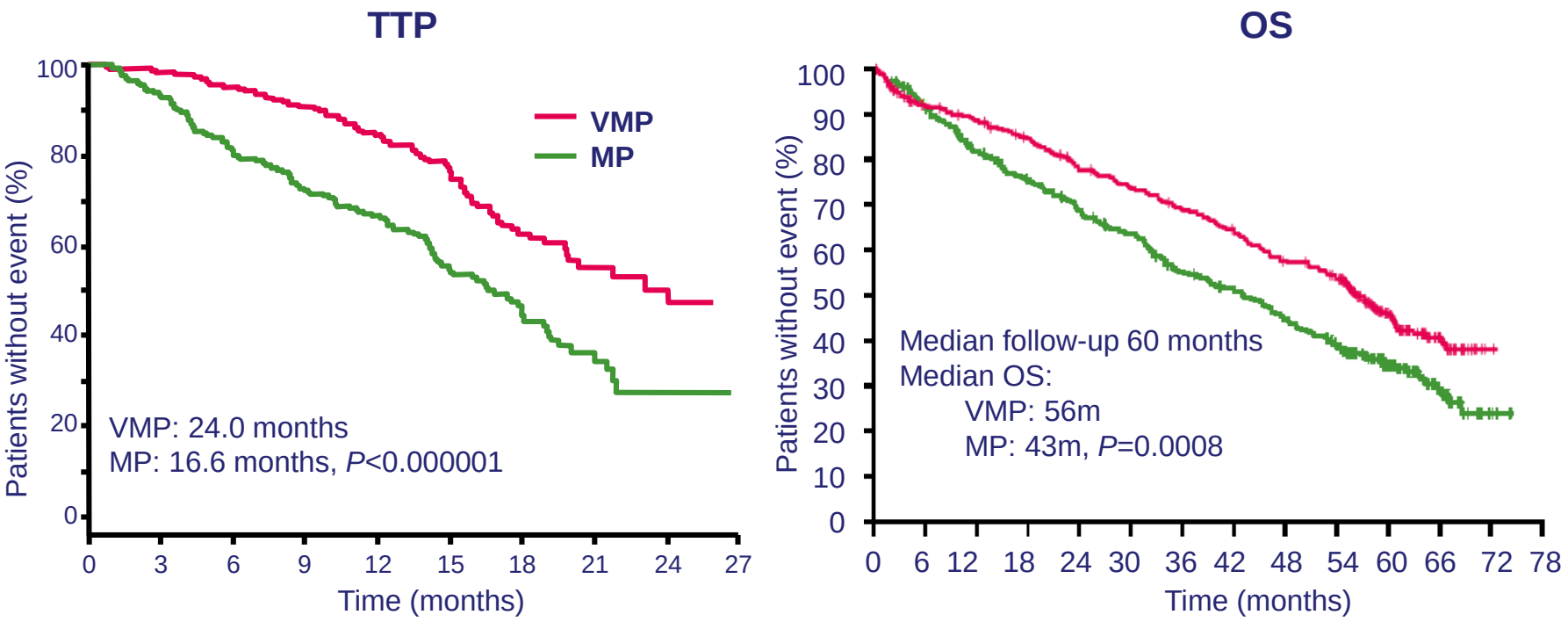
Sonneveld P, et al.. Blood 2016; 127:2955-2962

Morgan G et al. Blood 2011

Bortezomib-melphalan- prednisone (VMP) vs Melphalan-prednisone (MP): VISTA trial

CR 30% vs 4%

Median OS benefit: 13.3 mo



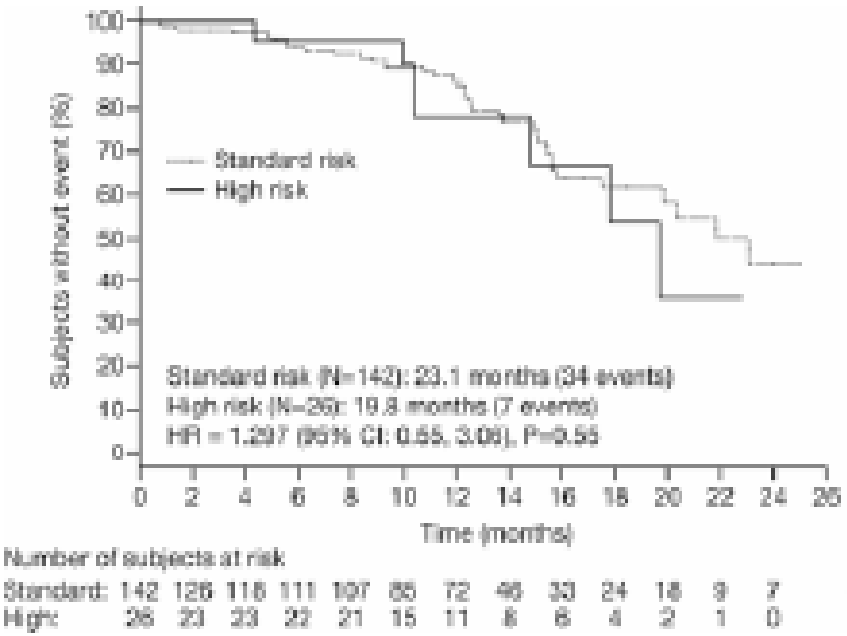
G3-4 AEs: GI (19%), PN (13%), Varicella Virus Zoster reactivation (3%)

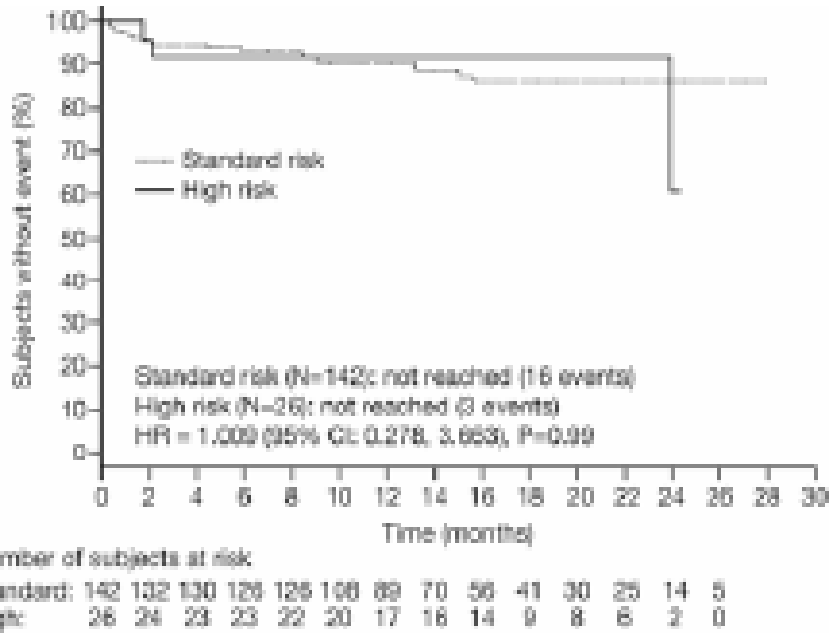
VMP is one standard of care

9 cycles: bortezomib twice weekly x 4 cycles weekly x 5cycles

San Miguel et al. JCO 2013; 31(4):448-55

Bortezomib-melphalan- prednisone (VMP) vs Melphalan-prednisone (MP): VISTA trial





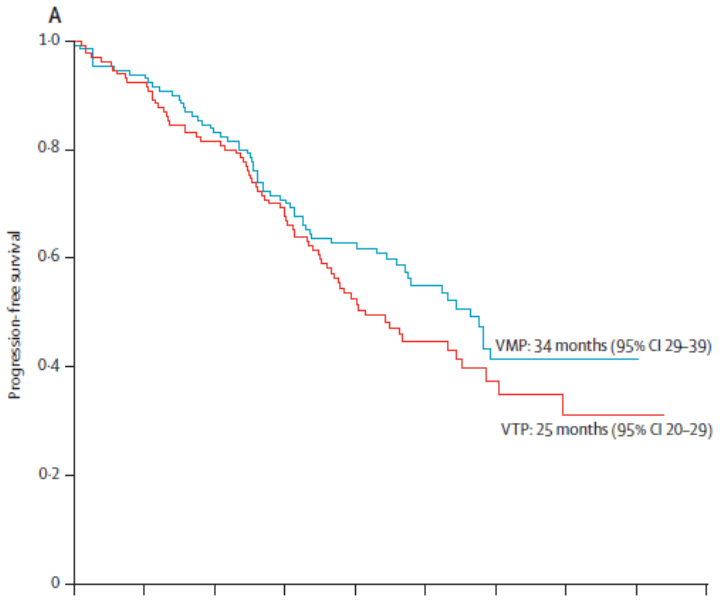
26 patients with HR and 142 patients with standard cytogenetic profiles within the VMP arm, had the same rate of CR (28%), with similar TTP (P = 0.55) and OS (P = 0.99).

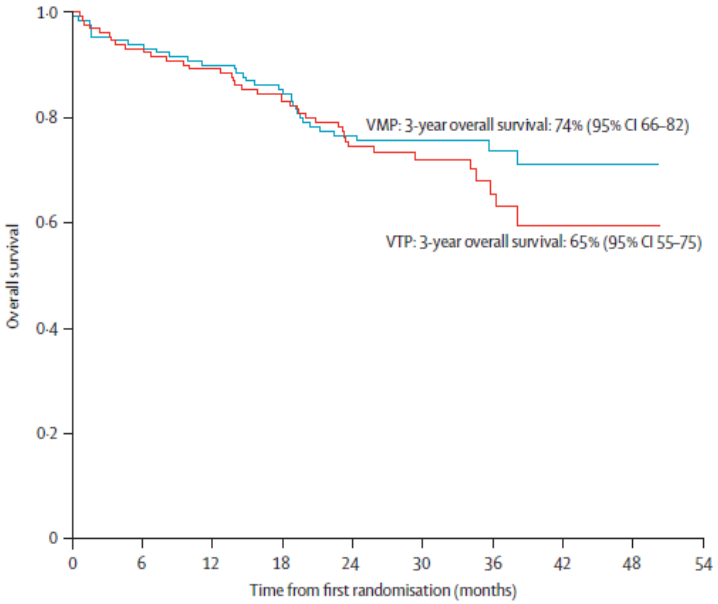
HR cytogenetics did not influence outcome when compared with SR

9 cycles: bortezomib twice weekly x 4 cycles weekly x 5cycles

San Miguel et al. JCO 2013; 31(4):448-55

VMP vs VTP induction cycles* followed by maintenance VT vs VP: PETHEMA TRIAL





- **44 High Risk** vs 187 SR patients.
- HR patients had shorter PFS (24 *vs* 33 mo, HR 0·6) and shorter OS (3-year OS 55% *vs* 77%, HR 0·4, p=0·001) than SR patients .

These regimens did not overcome the negative prognosis of HR cytogenetics. However, few patients were analyzed.

*6 cycles: bortezomib twice weekly for the first cycle, followed by once weekly for 5 cycles

Mateos M et al. Lancet Oncol 2010; 11: 934–41

Perspectives

blood

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

Consensus statement transplant ineligible patients

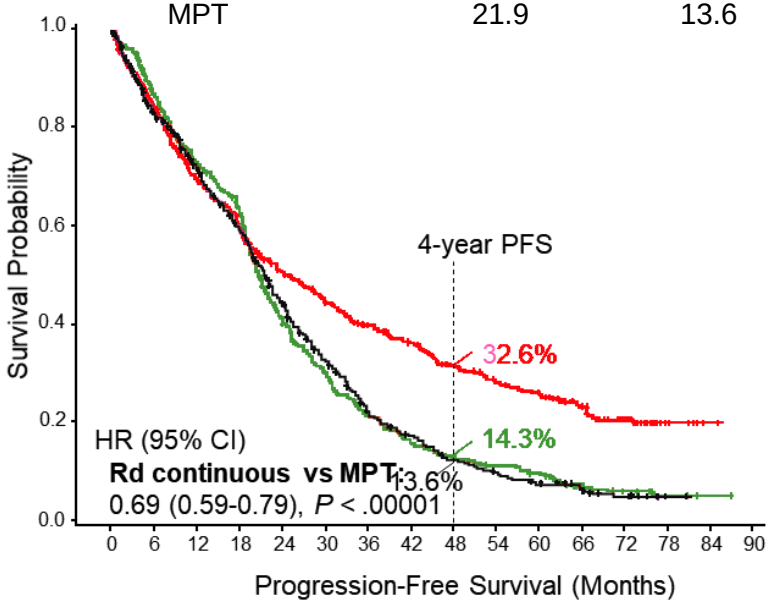
- Data in non TE patients are scarce.
- VMP may partly restore PFS in HR cytogenetics

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

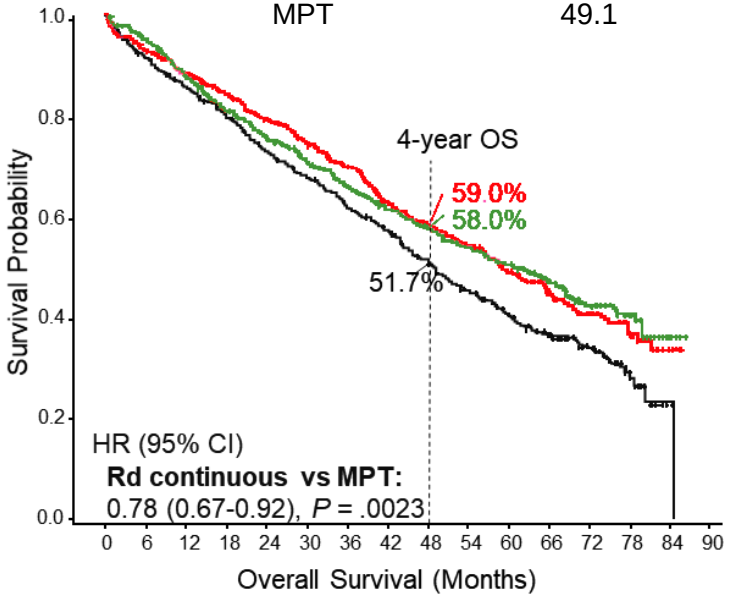
Melphalan-prednisone-thalidomide (MPT) vs lenalidomide-dexamethasone (Rd18) vs continuous Rd: FIRST trial

Rd continuous significantly extended PFS and OS vs MPT

	Median PFS, mos	4-year PFS, %
Rd continuous	26.0	32.6
Rd18	21.0	14.3
MPT	21.9	13.6



	Median OS, mos	4-yr OS, %
Rd continuous	59.1	59.0
Rd18	62.3	58.0
MPT	49.1	51.7



Rd is one standard of care

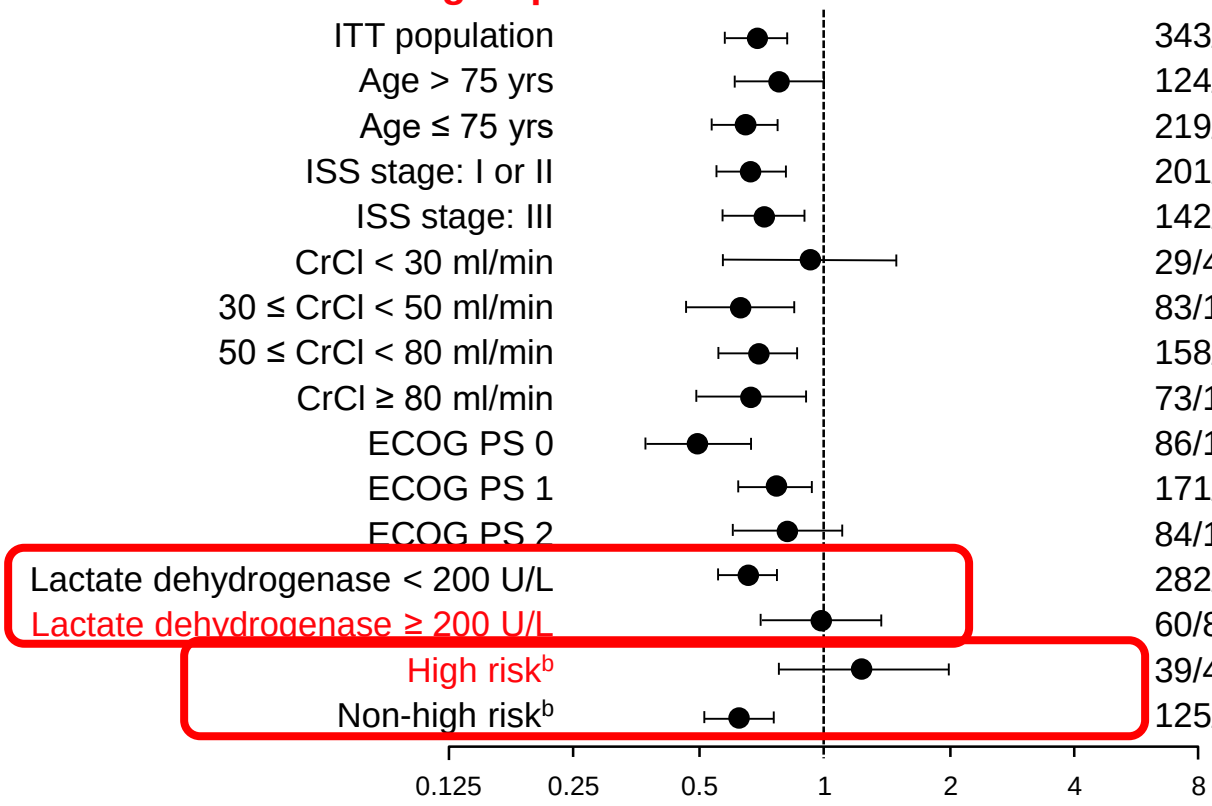
[a] PFS is based on investigator assessment of IMWG criteria; Data cutoff: January 21, 2016.
HR, hazard ratio; IMWG, International Myeloma Working Group; MPT, melphalan, prednisone, thalidomide; PFS, progression-free survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Facon T et al. ASH 2016, oral presentation.

FIRST trial

Effect of subgroup on progression-free survival

PFS favored Rd continuous over MPT in the majority of subgroups analyzed



Subgroup	Rd Cont[a]	MPT[a]	HR (95% CI)
ITT population	343/535	387/547	0.69 (0.59, 0.79)
Age > 75 yrs	124/186	127/188	0.78 (0.60, 0.99)
Age ≤ 75 yrs	219/349	260/359	0.64 (0.54, 0.77)
ISS stage: I or II	201/319	228/323	0.67 (0.55, 0.81)
ISS stage: III	142/216	159/224	0.71 (0.57, 0.90)
CrCl < 30 ml/min	29/45	40/55	0.93 (0.57, 1.51)
30 ≤ CrCl < 50 ml/min	83/126	91/126	0.63 (0.47, 0.85)
50 ≤ CrCl < 80 ml/min	158/241	158/222	0.69 (0.55, 0.87)
CrCl ≥ 80 ml/min	73/123	98/144	0.67 (0.49, 0.91)
ECOG PS 0	86/155	104/156	0.50 (0.37, 0.66)
ECOG PS 1	171/257	197/275	0.76 (0.62, 0.94)
ECOG PS 2	84/119	82/111	0.82 (0.60, 1.11)
Lactate dehydrogenase < 200 U/L	282/448	309/434	0.65 (0.55, 0.77)
Lactate dehydrogenase ≥ 200 U/L	60/86	77/112	0.98 (0.70, 1.38)
High risk[b]	39/43	37/47	1.27 (0.81, 2.01)
Non-high risk[b]	125/205	147/206	0.66 (0.52, 0.84)

[a] Number of events/number of patients.

[b] Complete cytogenetics profile for 501 patients (248 in Rd continuous and 253 in MPT); high-risk cytogenetics included t(4;14), t(14;16), and del(17p).

CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; HR, hazard ratio; ISS, International Staging System; ITT, intent to treat; MPT, melphalan, prednisone, thalidomide; PFS, progression-free survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression.

Facon T, et al. Final Analysis of Overall Survival From the FIRST Trial. *ASH 2016, abstract 241*.

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 Rd may improve outcome with HR cytogenetics

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

VRd vs continuous Rd: SWOG trial

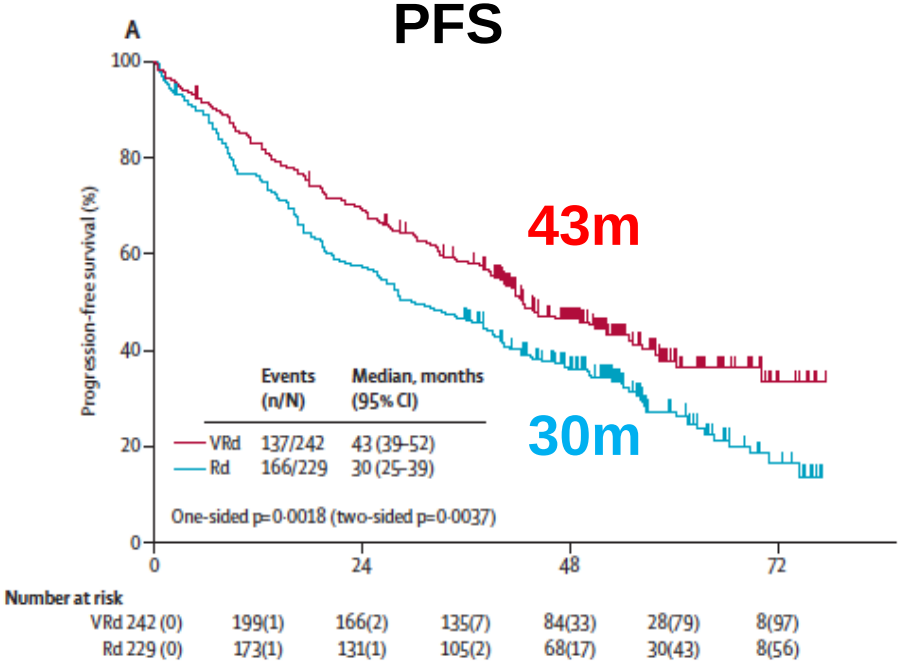
The study included both younger and elderly patients (median age was 63 years and 43% were ≥65 years)

ORR: 81% vs 71%

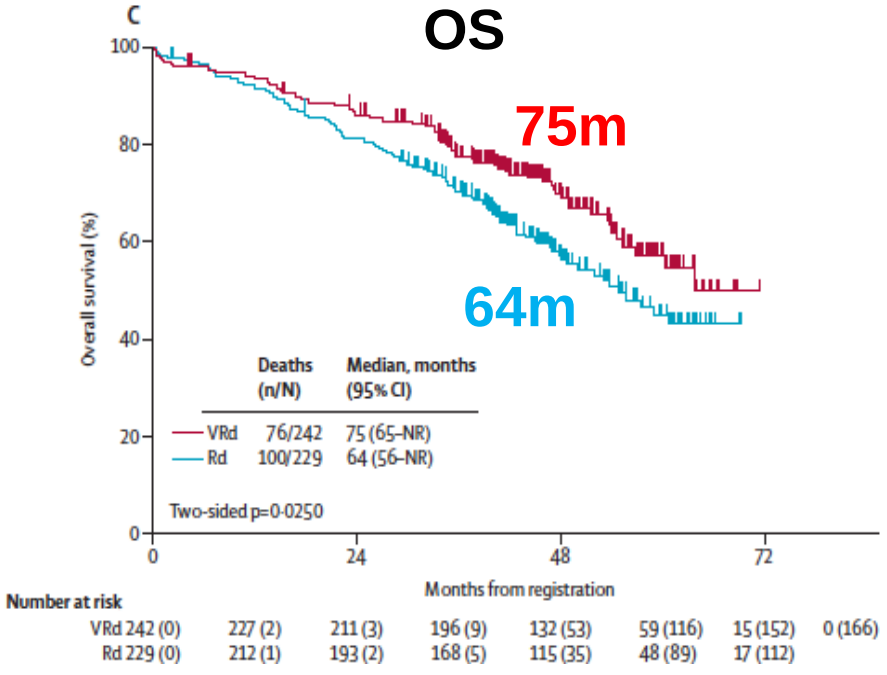
CR 16% vs 8 %

G3-4 AEs: PN 33%

PFS



OS

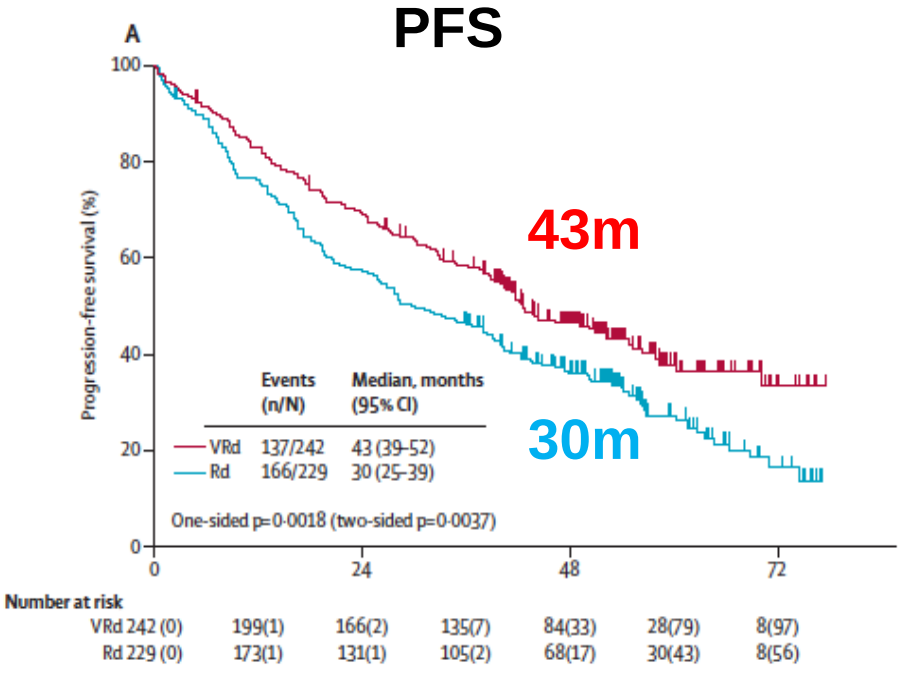


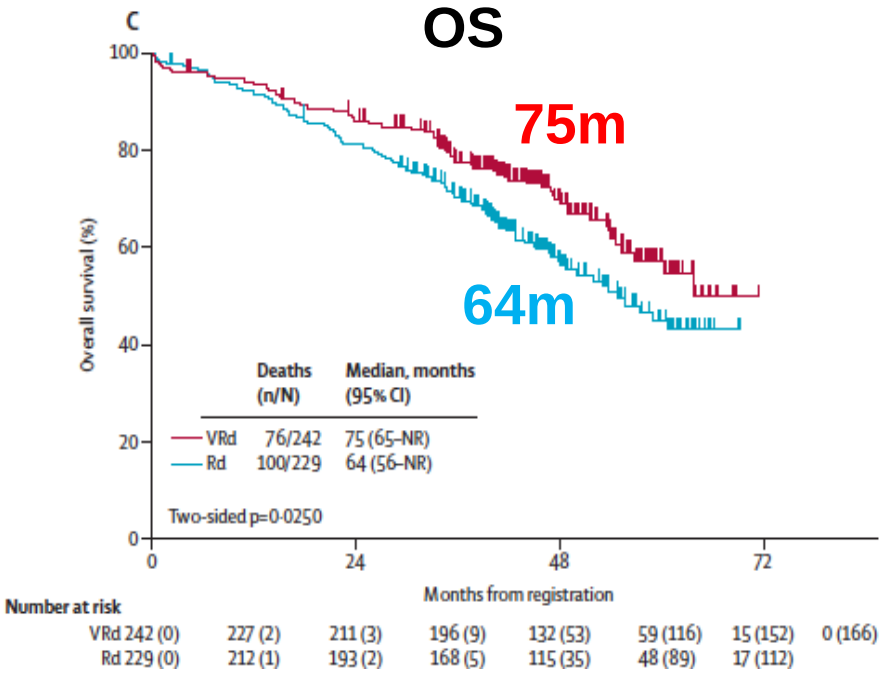
Bortezomib twice a week IV x 8 cycles

Durie B et al. Lancet 2017

VRd-Rd vs continuous Rd: SWOG trial

- **Evaluable high risk cytogenetic patients n=44 (cut-off values 5%).**
- **Median PFS was 16 vs 38 months with Rd vs VRd in 44 HR patients, and 15 vs 34 months in17 patients with t(4;14) by FISH, respectively.**
- **These differences were not significant (p=0.19 and 0.96, respectively).**



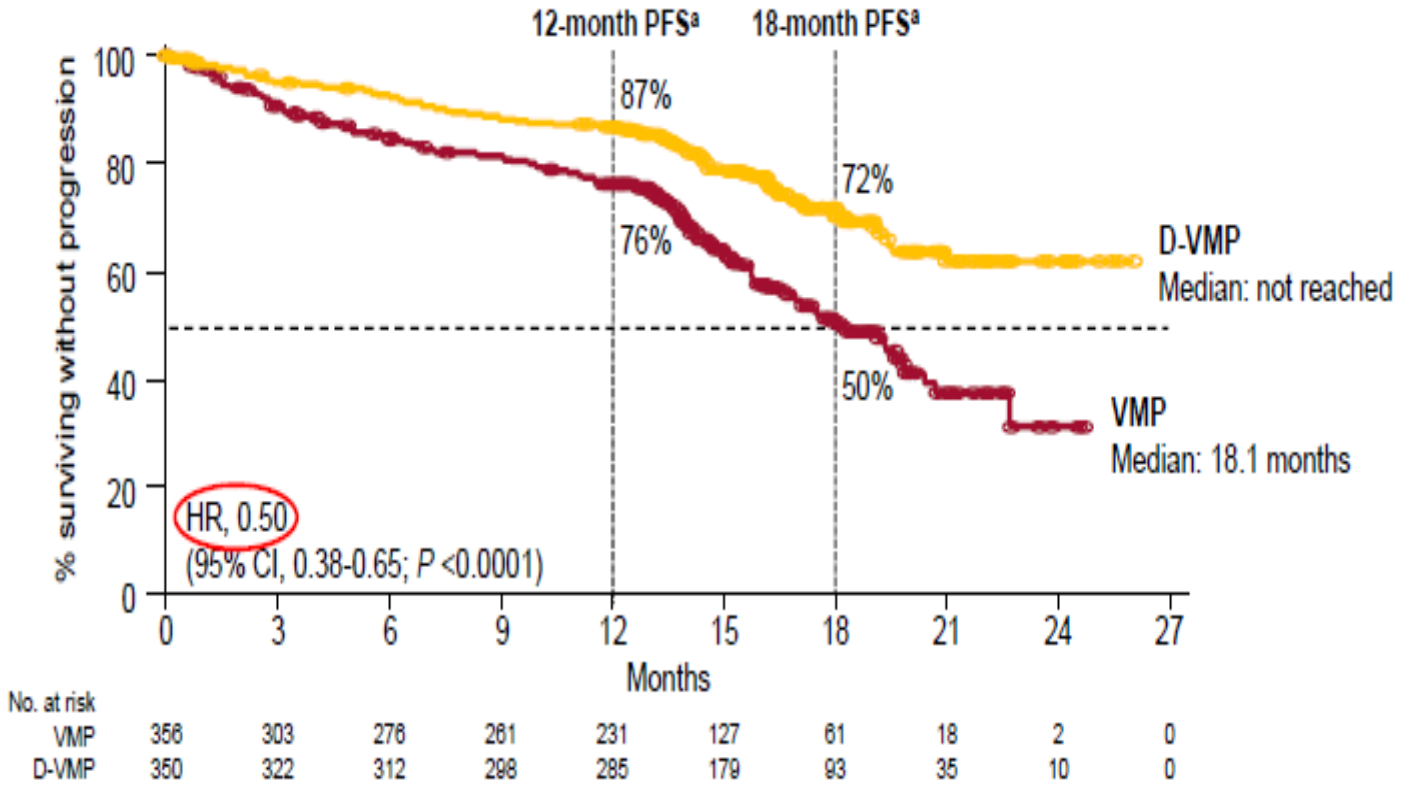


Bortezomib twice a week IV x 8 cycles

Durie B et al. Lancet 2017

Daratumumab-VMP vs VMP: Alcyone trial

- Median (range) follow-up: 16.5 (0.1-28.1) months



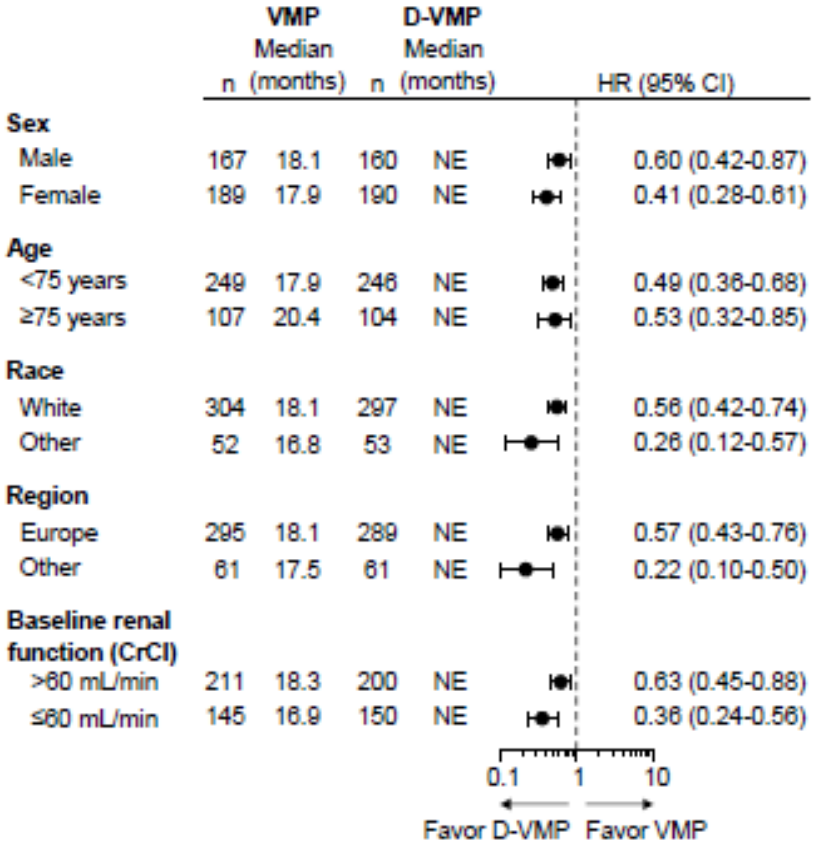
50% reduction in the risk of progression or death in patients receiving D-VMP

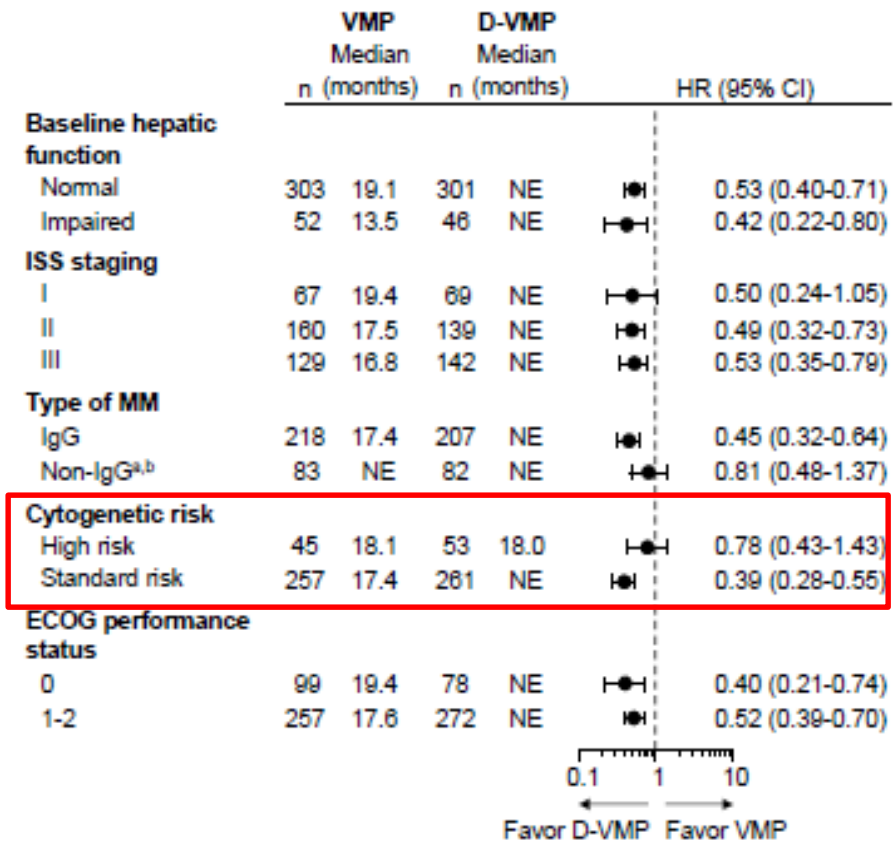
47% reduction in ≥75 years age group

*9 cycles: bortezomib twice weekly for the first cycle, followed by once weekly

Mateos MV et al. NEJM 2017

Daratumumab-VMP vs VMP: Alcyone trial





D-VMP prolonged PFS across all subgroups analyzed

The hazard ratio for progression or death in the daratumumab group was higher among patients with HR cytogenetic profile (0.78) than standard-risk (0.39). Few patients were analyzed.

Mateos MV et al. NEJM 2017

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/m^2, d 1,4,8,11,22,25,29,32 (cy 1-4); d 1,8,22,29 (cy 5-9)
M: 9 mg/m^2, d 1-4
P: 60 mg/m^2, d 1-4

VMPT
Nine 6-wk courses
V: 1.3 mg/m^2, d 1,4,8,11,22,25,29,32 (cy 1-4); d 1,8,22,29 (cy 5-9)
M: 9 mg/m^2, d 1-4
P: 60 mg/m^2, d 1-4
T: 50 mg/d

VT MAINTENANCE
For 2 yr/ until progression/relapse
V: 1.3 mg/m^2 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.

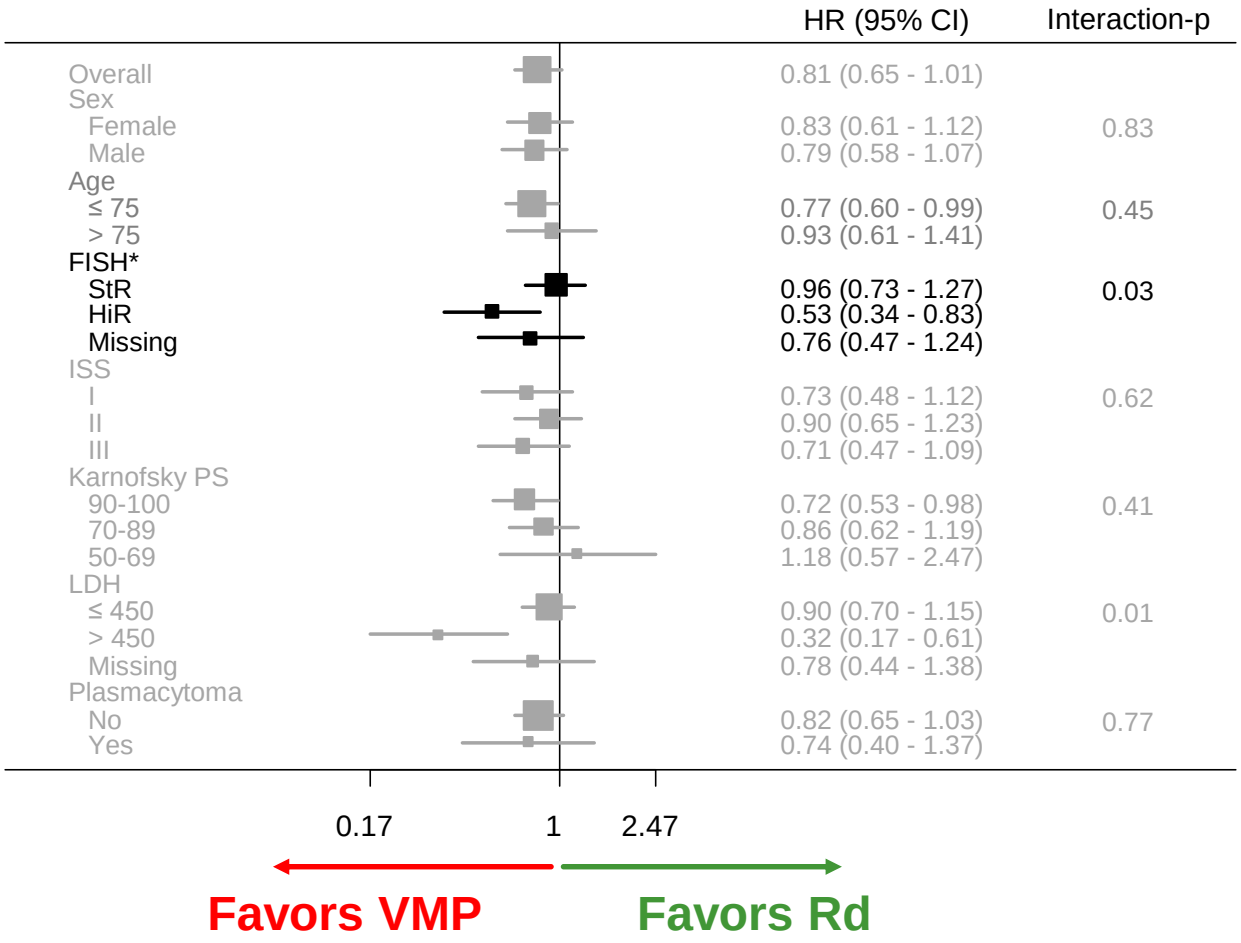
Palumbo A et al, JCO 2010 and 2014; Magarotto V et al, Blood 2015

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

	VMP (N=257)	Rd (N=217)	P
Median age (IQR)	71 (69-75)	73 (70-77)	0.001
Chromosomal Abnormalities (%)			
Standard risk	53%	63%	1.00
High risk*	19%	22%	
Missing	28%	15%	

Palumbo A et al, JCO 2010 and 2014; Magarotto V et al, Blood 2015

VMP versus Rd
PFS Subgroup Analysis

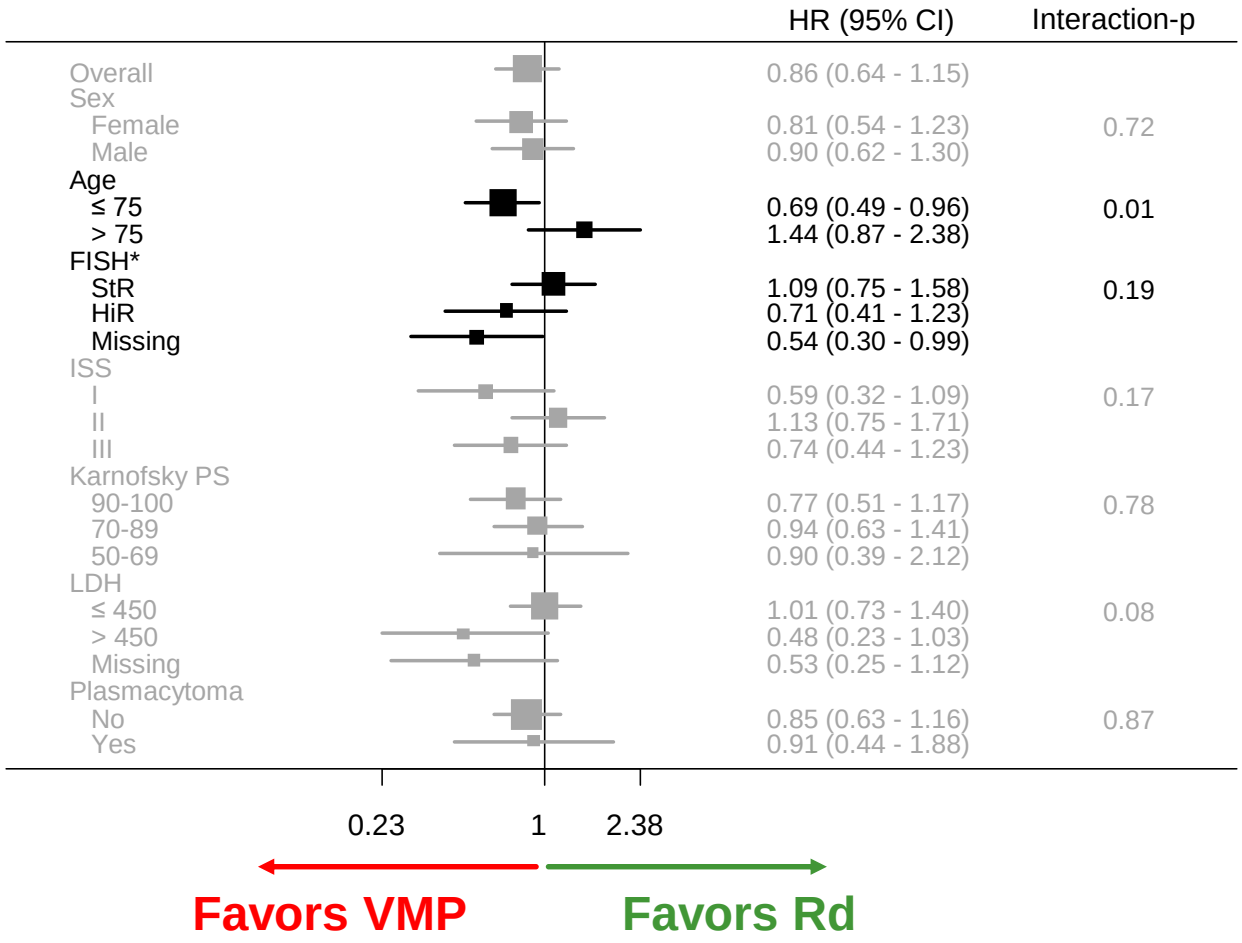


***Interaction-p between StR and HiR FISH**

PFS, progression-free survival; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone

Larocca A et al ASH 2018

VMP versus Rd
OS Subgroup Analysis



***Interaction-p between StR and HiR FISH**

OS, overall survival; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone

Larocca A et al ASH 2018

Perspectives

blood

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

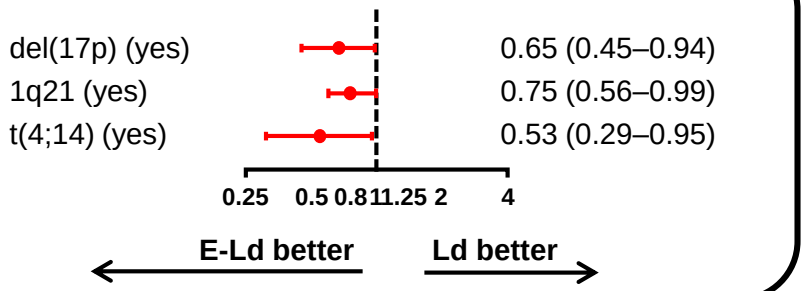
Consensus statement transplant-ineligible patients

- 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.**

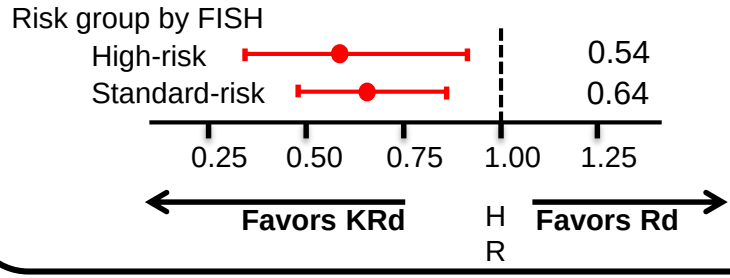
Sonneveld P, et al.. Blood 2016; 127:2955-2962

High risk versus standard risk cytogenetics in relapsed/refractory MM

Elotuzumab-Rd vs Rd

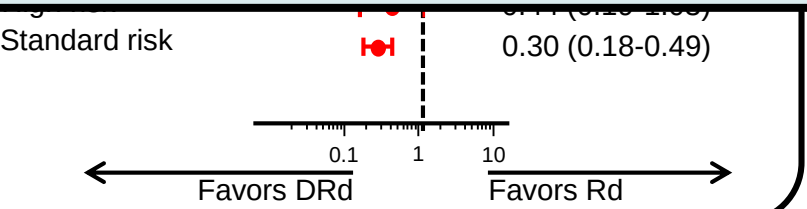


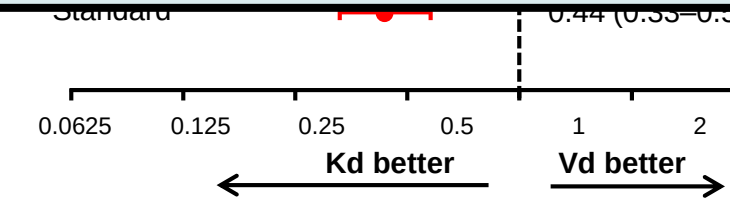
Ixazomib-Rd vs Rd



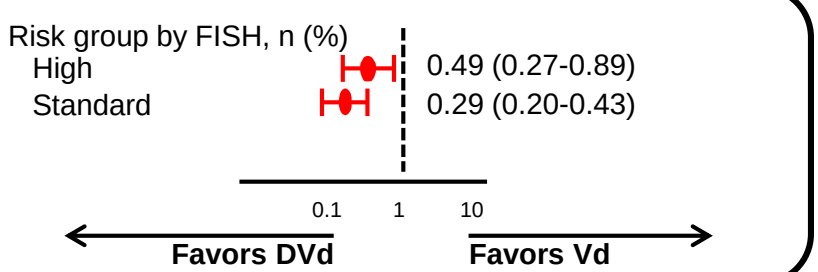
Median age 64-66 years

Patients ≥75 years 11-20%

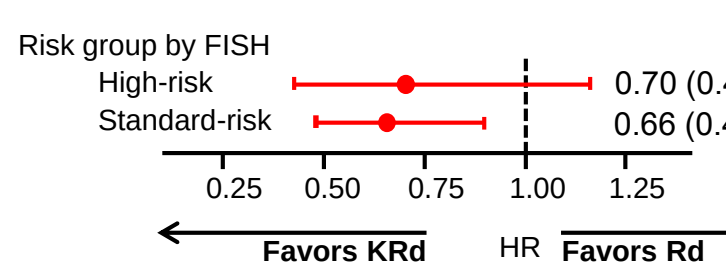




Daratumumab-Vd vs Vd

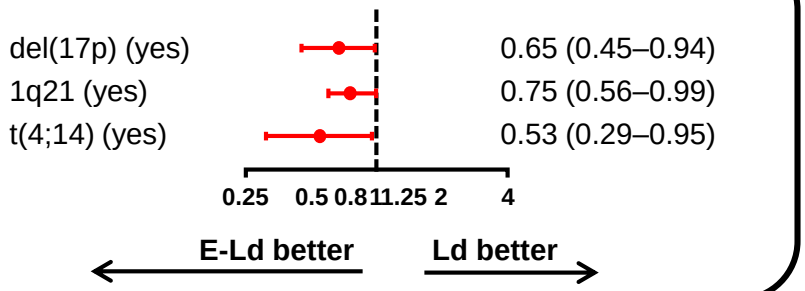


Carfilzomib (K)Rd vs Rd

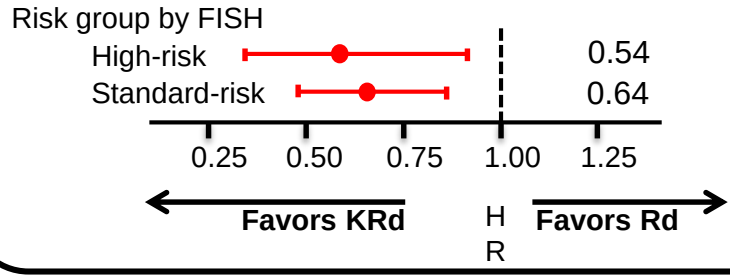


High risk versus standard risk cytogenetics in relapsed/refractory MM

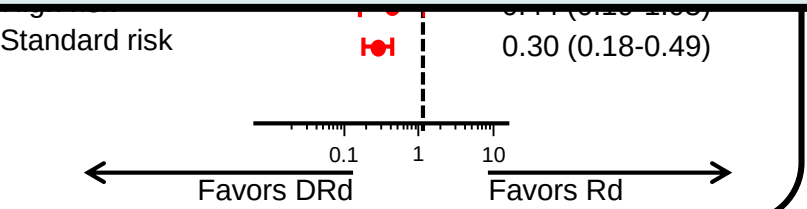
Elotuzumab-Rd vs Rd

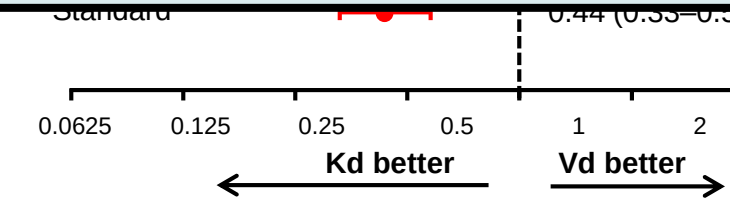


Ixazomib-Rd vs Rd

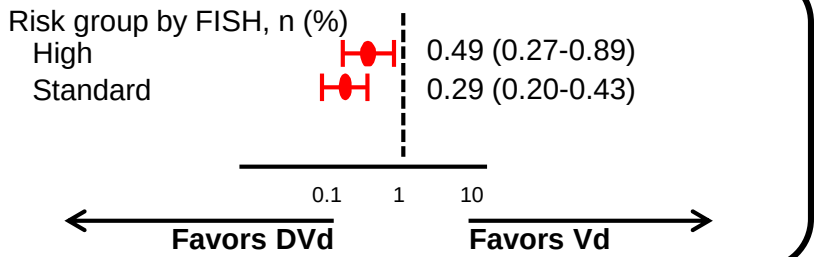


Novel combos improve but not overcome HR Cytogenetic profile

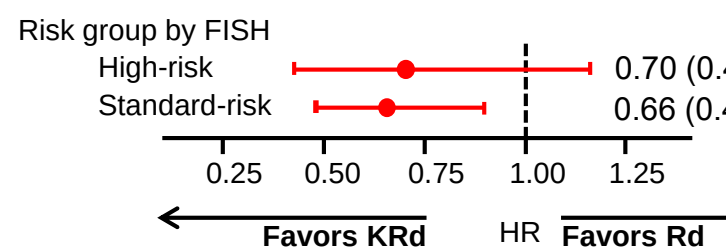




Daratumumab-Vd vs Vd



Carfilzomib (K)Rd vs Rd



How I treat elderly HR cytogenetics NDMM

- FISH analysis in all NDMM patients for risk stratification
- Suboptimal results with doublets (Rd or Vd) (median PFS 8-19 vs 21-37 months in SR patients).
- Median PFS with triplets (VMP, VRD) 12-38 vs 32-33 months reported in SR patients
- **The longest PFS in HR patients was 38 months with VRD**

Triplet regimen (VMP) for High-risk NDMM patients ineligible for transplant

In Standard-risk patients, choice of treatment according to comorbidities (PNP, RI), fitness/age, compliance and patient preference

In the future better treatment options (VRD, PI-IMiDs combo, plus MoAb) and newer combination in high-risk cytogenetics patients are needed

High Risk NDMM
Age and Frailty

All elderly patients are not equal
Fit or Frail?

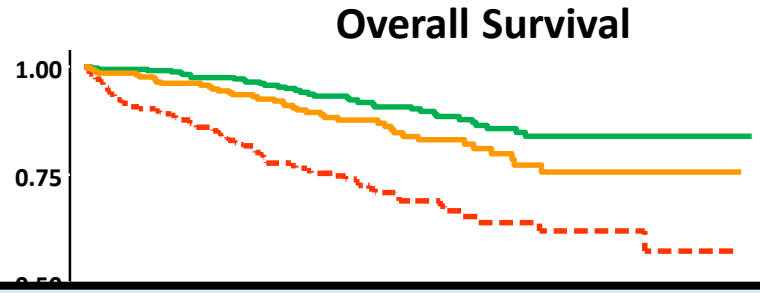
IMWG Frailty Score

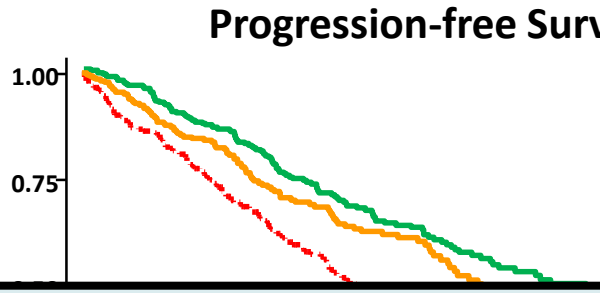
Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.13 (0.76-1.69)	0.549	1
	Age >80 years	2.40 (1.56-3.71)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.37 (0.92-2.05)	0.125	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.67 (1.08-2.56)	0.02	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.43 (0.96-2.14)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

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

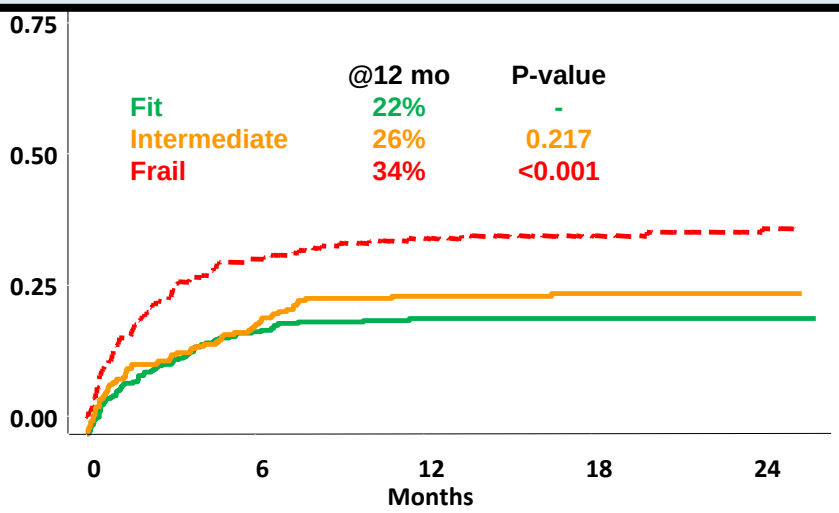
Palumbo A et al, Blood 25(13):2068-74, 2015

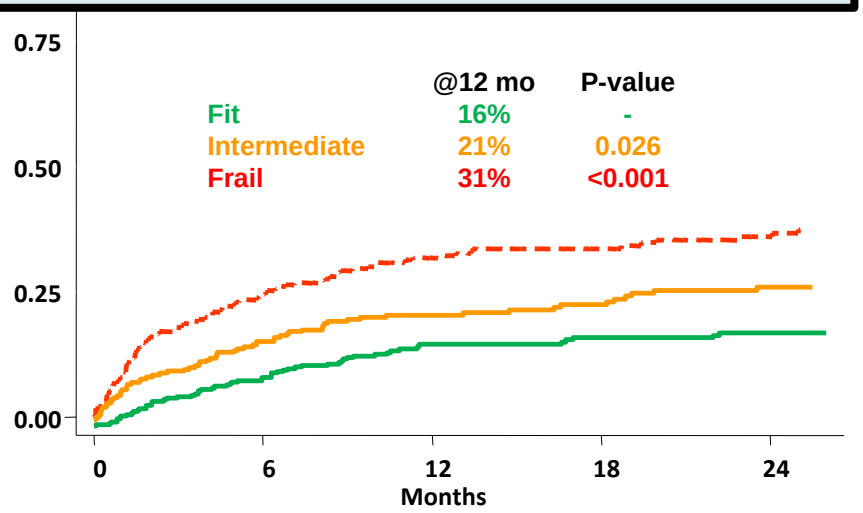
IMWG Frailty Score: long-term outcome





Frail patients
have an increased risk of death, progression, non-hematologic AEs, and treatment discontinuation, regardless of ISS stage, cytogenetics, and type of treatment.





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

How to select the appropriate therapy Elderly Frail Patients?

No evidence-based medicine in frail patients:

- **No randomized phase III trials**
- **No randomized phase II trials**
- **No meta-analysis**

How I treat Elderly Frail MM patients

Treatment algorithm for elderly MM patients based on balancing safety and efficacy

PATIENT STATUS ASSESSMENT

Age (score 0 – 1 – 2) Charlson (score 0 – 1)

ADL (score 0 – 1) IADL (score 0 – 1)

FIT	INTERMEDIATE	FRAIL
Full dose	Full dose/Reduced	Reduced dose
ASCT TRIPLET REGIMENS VMP (VRD) DOUBLET REGIMENS Rd	DOUBLET REGIMENS Rd Vd Reduced-dose triplet	Doublet regimens Rd Vd Palliative

Larocca A et al, Leukemia 2018

High-risk disease

Capacity to spread outside the bone marrow

Extramedullary Myeloma (EMD)

Incidence ranging from 1,7% to 4,5% at diagnosis

and from 3,4% to 24% at relapse

Plasma cell leukemia (PCL)

More than 20% PCs in PB and/or
Absolute PC count > $2x10^9$/L
Incidence ranging from 2% to 4% of pts with MM

Treatment of EM

Treatment is challenging.

Thalidomide → ineffective

Lenalidomide → anecdotal reports of efficacy

Pomalidomide → ~ 30% of responses and cross BBB

Bortezomib → anecdotal reports of efficacy

Carfilzomib → no data available

Ixazomib → no data available

Daratumuab single agent → ~ 21% of responses

Bladè et al. BJH 2001
Calvo-Villas et al. European J Haematology 2011
Short et al. Leukemia 2011
Mussetti et al. Leuk Lymphoma 2013
Lonial et al. Lancet 2016

Still an unmet clinical need!

.... Aggressive approach with novel agents plus chtp

High-risk disease
Primary refractory MM

Non-responsive disease in patients who have never achieved minimal response or better with any therapy

				Primary Refractory.		
FIRST Study[1]		***n***	**ORR**	**SD + PD =**		**Overall**
• Len + Dex contin	(Rd)	(535)	81%	12%	2%	**14%**
• Len + Dex 18m	(Rd)	(541)	79%	15%	1%	**16%**
• Mel + Thal + Pred	(MPT)	(547)	67%	21%	3%	**24%**
SWOG Study[2]						
• Len + Dex	(Rd)	(214)	71.5%	24%	4%	**28%**
• Len + Bort + Dex	(RVd)	(216)	81.5%.	16%	3%	**19%**
IFM 2009 Study[3]						
• RVd		(350)	97%	3%	0%	**3%**
• RVd + Auto		(350)	98%	2%	0%	**2%**
Mayo + PMH						
• CyBORD[4]	(VCD).	(33)	88%	-	-	**12%**

Hulin C, et al. JCO 2016:34:3609-17, [2]Durie B, et al. Lancet 2017:389:519-27, [3]Attal M, et al. N Engl J Med 2017: 376(14): 1311, [4]Reeder CB, et al. Leukemia 2009:23:12337

Many novel agents are being tested in NDMM
→ Future incidence of Primary Refractory MM is unknown

Majithia N. et al. American Journal of Hematology, Vol. 90, No. 11, 2015

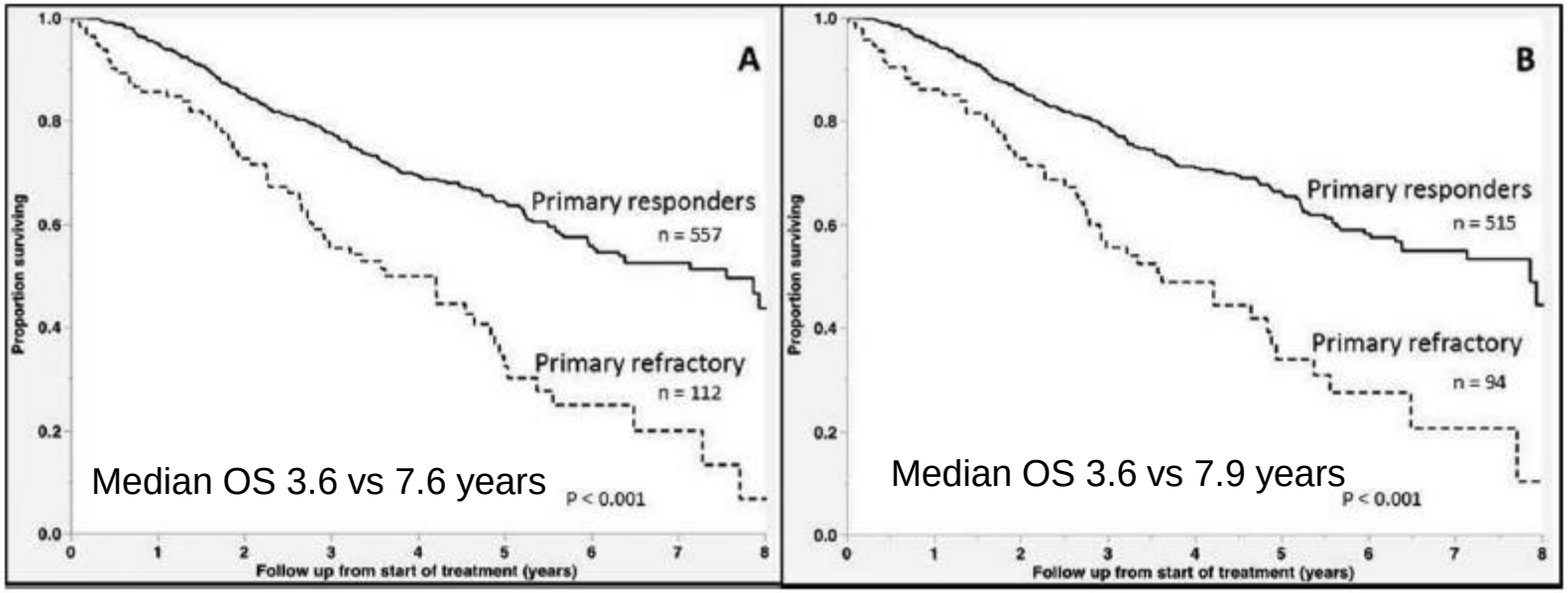
Primary Refractory MM
Overall Survival from start of therapy

816 NDMM patients treated at Mayo Clinic 2006-2014
Retrospective review

112 Primary Refractory MM (17%)

OS in the entire cohort

OS excluding patients who did not receive a novel agent with induction



Majithia N. et al. American Journal of Hematology, Vol. 90, No. 11, 2015

Primary Refractory MM
Prognostic factors for OS

816 NDMM patients treated at Mayo Clinic 2006-2014
Retrospective review

	Univariable analysis		Multivariable analysis[a]	
Prognostic factor	HR	*P*	HR	*P*
Older than 65 years	2.0	<0.001	2.1	<0.001
Serum creatinine at least 2 mg/dL	1.9	0.001	1.9	0.14
ISS Stage 3	2.2	<0.001	1.4	0.25
LDH over upper limit of normal	1.8	<0.001	1.9	0.02
PCLI at least 1%	1.5	0.006	1.3	0.34
BMPC at least 60%	1.4	0.02	0.9	0.63
High-risk FISH	1.8	0.002	1.5	0.13
Primary refractory MM	2.3	<0.001	3.2	<0.001

Primary refractoriness carried the strongest hazard of death, underscoring the prognostic significance of response in the current era.

Majithia N. et al. American Journal of Hematology, Vol. 90, No. 11, 2015

Primary Refractory MM/Extra-medullary and PCL How I treat?

Limited data and few prospective clinical trials in elderly patients!

- Salvage therapies (novel agents, intensive chemotherapy)

- Maintenance therapy

- Palliative care

Can we identify these patients prospectively?
Incidence may decrease with future novel agents!
More clinical trials nedeed

Treatment Decision Process in Elderly (High Risk) Multiple Myeloma

Patients
- Frailty/fitness
- Hospitalization
- Medications
- Social Support

Multiple Myeloma
- **Cytogenetics**
- **Stage**
- **Tumor burden**

Goals of Care
- **CR vs Disease Control**
- **Balance safety and efficacy**
- **QoL**
- Expectations

Newer Drugs
Comorbidities: cardiovascular
pulmonary
renal functions
Compliance to treatment
Toxicities Neuropathy
DVT/PE
Cardiac toxicity

Conclusions

- No treatment regimen showed to consistently improve outcomes in high risk MM
- Future investigations including emerging agents may benefit these patients
- Future risk stratified treatments (cytogenetics)

Acknowledgments

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