Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Alessandro Corso

Terapia di I linea senza trapianto autolog
del paziente *fit*
Con regimi privi di anticorpi monoclonali

Disclosures

Honoraria for lectures and advisory boards from Janssen, Celgene, Amgen and Takeda

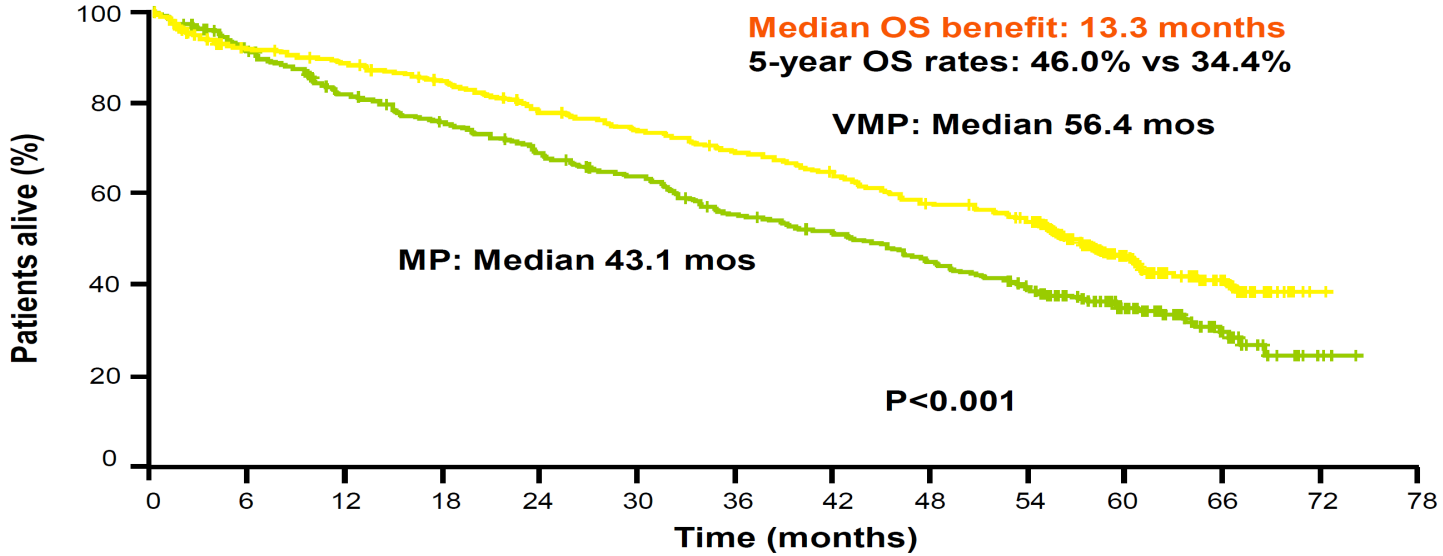
Options available today in MM *fit* patients not eligible to transplant

VMP vs Rd

Bortezomib-MP vs MP (VISTA study): final updated OS analysis

31% reduced risk of death with VMP vs MP

- Median follow-up 60.1 months

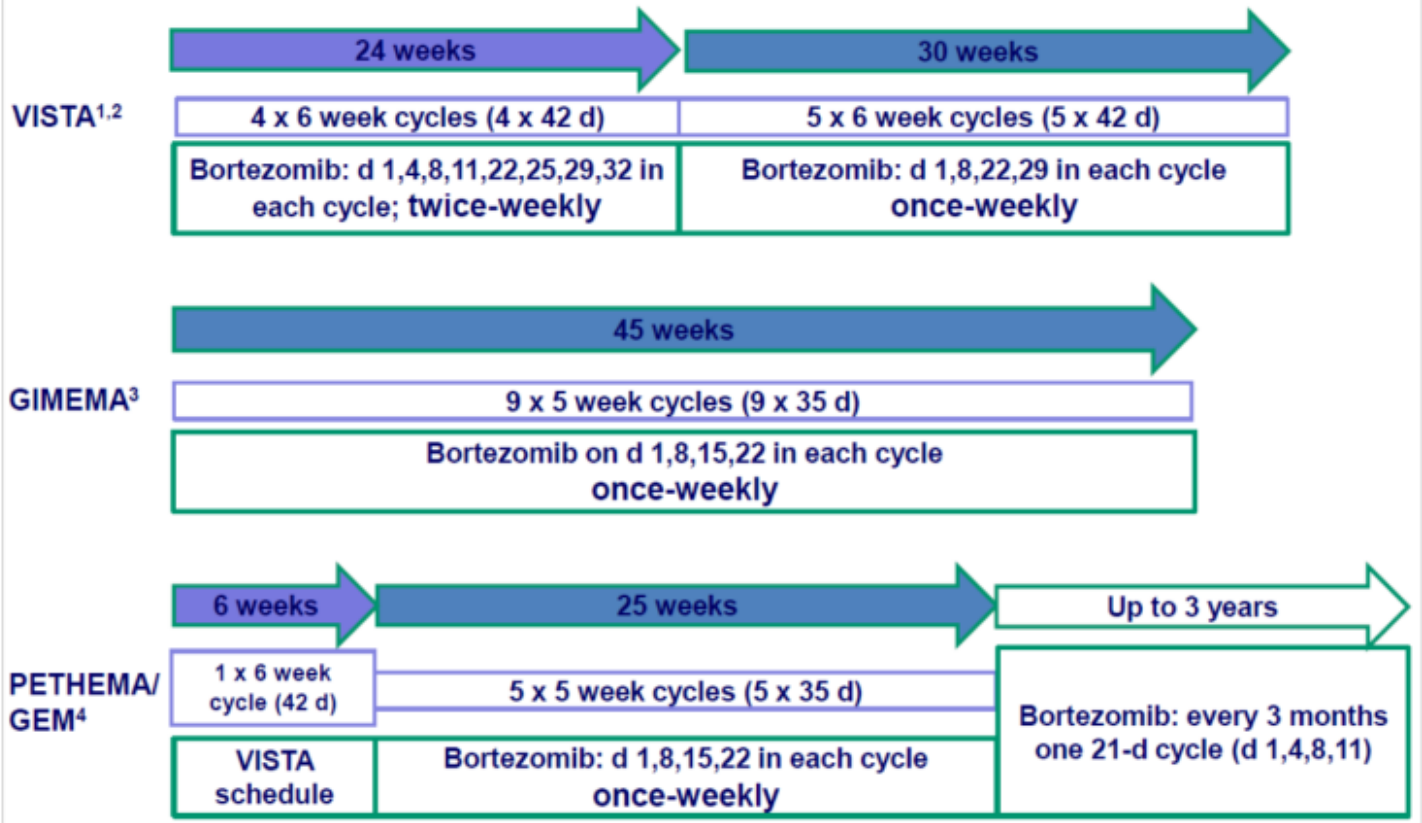


- Benefits on OS with VMP were also seen for patients ≥75 years of age

MP, melphalan and prednisone; VMP, bortezomib, melphalan and prednisone

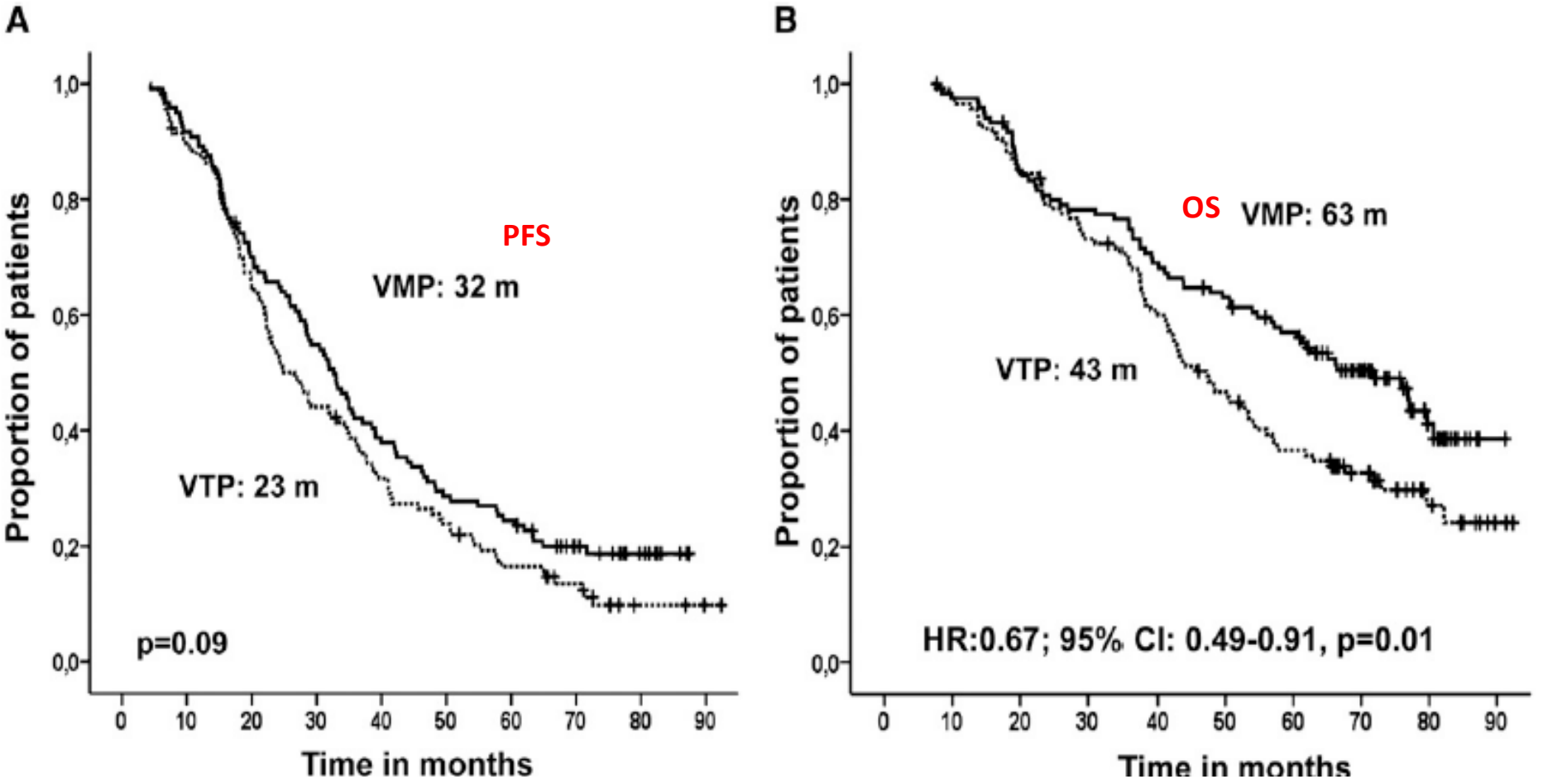
San Miguel et al. J Clin Oncol 2013;31(4):448-55

Overview of VMP schedules in phase III trials



[1]*San Miguel et al. NEJM 2008; 359: 906-917*
[2]*Mateos et al. J Clin Oncol 2010; 28: 2259-2266*
[3]*Palumbo et al. J Clin Oncol 2010; 28: 5101-5109*
[4]*Mateos et al. Lancet Oncol 2010; 11: 934-941*

GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators?



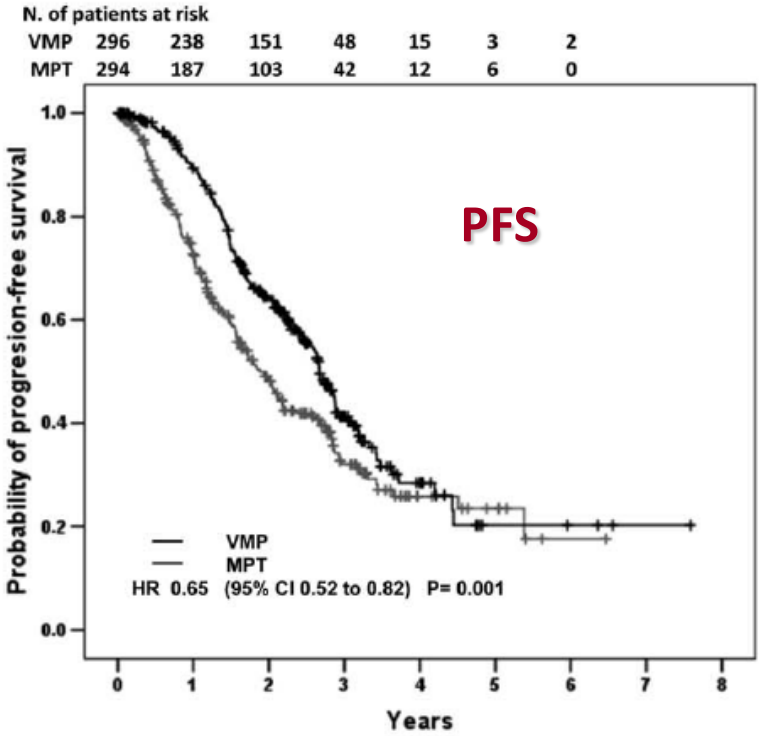
Mateos et al, Blood 2014

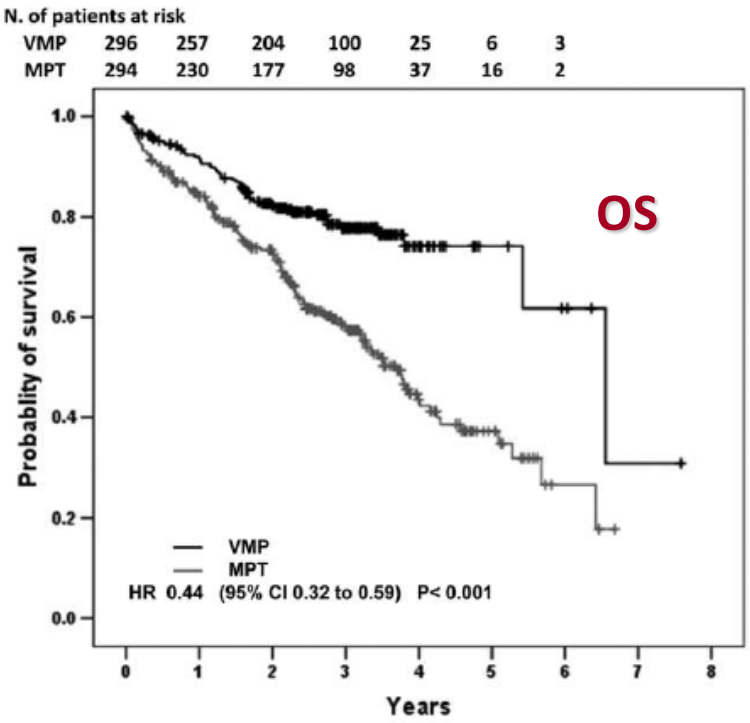
Bortezomib, melphalan, prednisone (VMP) versus melphalan, prednisone, thalidomide (MPT) in elderly newly diagnosed multiple myeloma patients: A retrospective case-matched study

Fortunato Morabito,[1*] Sara Bringhen,[2] Alessandra Larocca,[2] Pierre Wijermans,[3] Maria Victoria Mateos,[4] Peter Gimsing,[5] Carla Mazzone,[1] Daniela Gottardi,[6] Paola Omedè,[2] Sonja Zweegman,[7] Juan José Lahuerta,[8] Renato Zambello,[9] Pellegrino Musto,[10] Valeria Magarotto,[2] Martijn Schaafsma,[11] Albert Oriol,[12] Gunnar Juliusson,[13] Chiara Cerrato,[2] Lucio Catalano,[14] Massimo Gentile,[1] Ana Isabel Turel,[15] Anna Marina Liberati,[16] Maide Cavalli,[17] Davide Rossi,[18] Roberto Passera,[19] Stefano Rosso,[20] Meral Beksac,[21] Michele Cavo,[22] Anders Waage,[23] Jesus San Miguel,[24] Mario Boccadoro,[2] Pieter Sonneveld,[25] Antonio Palumbo,[2] and Massimo Offidani[26]

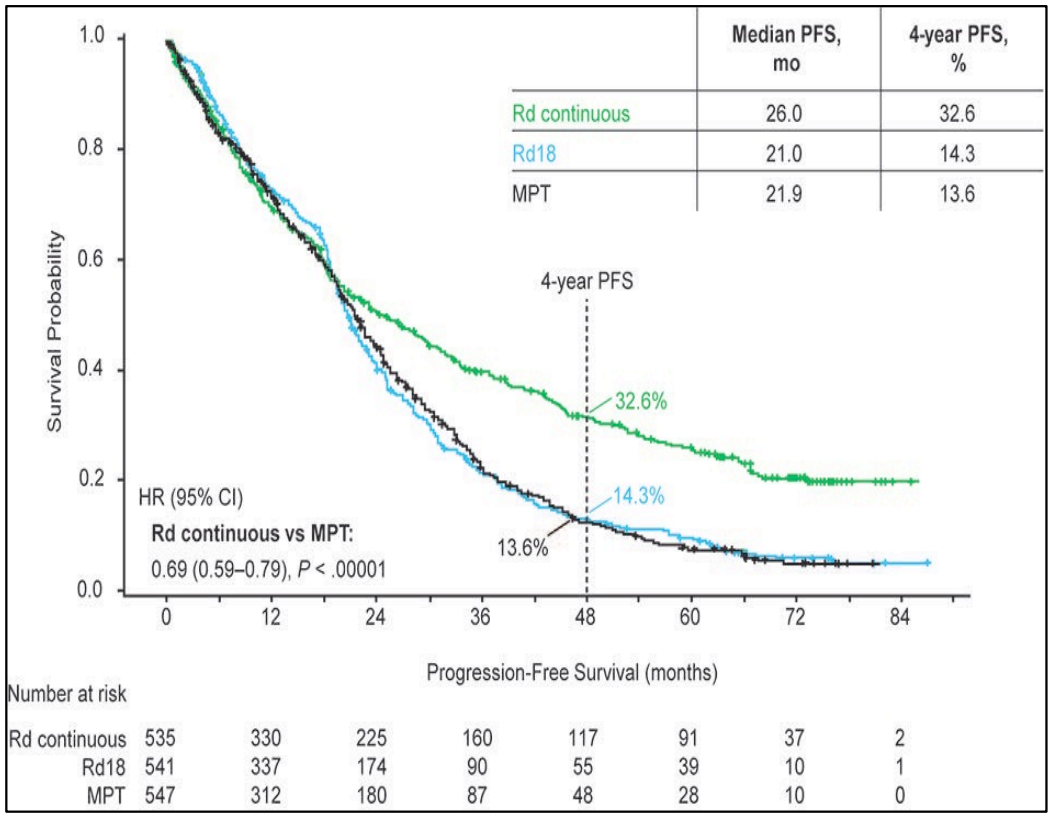
AJH

Aprile 2014



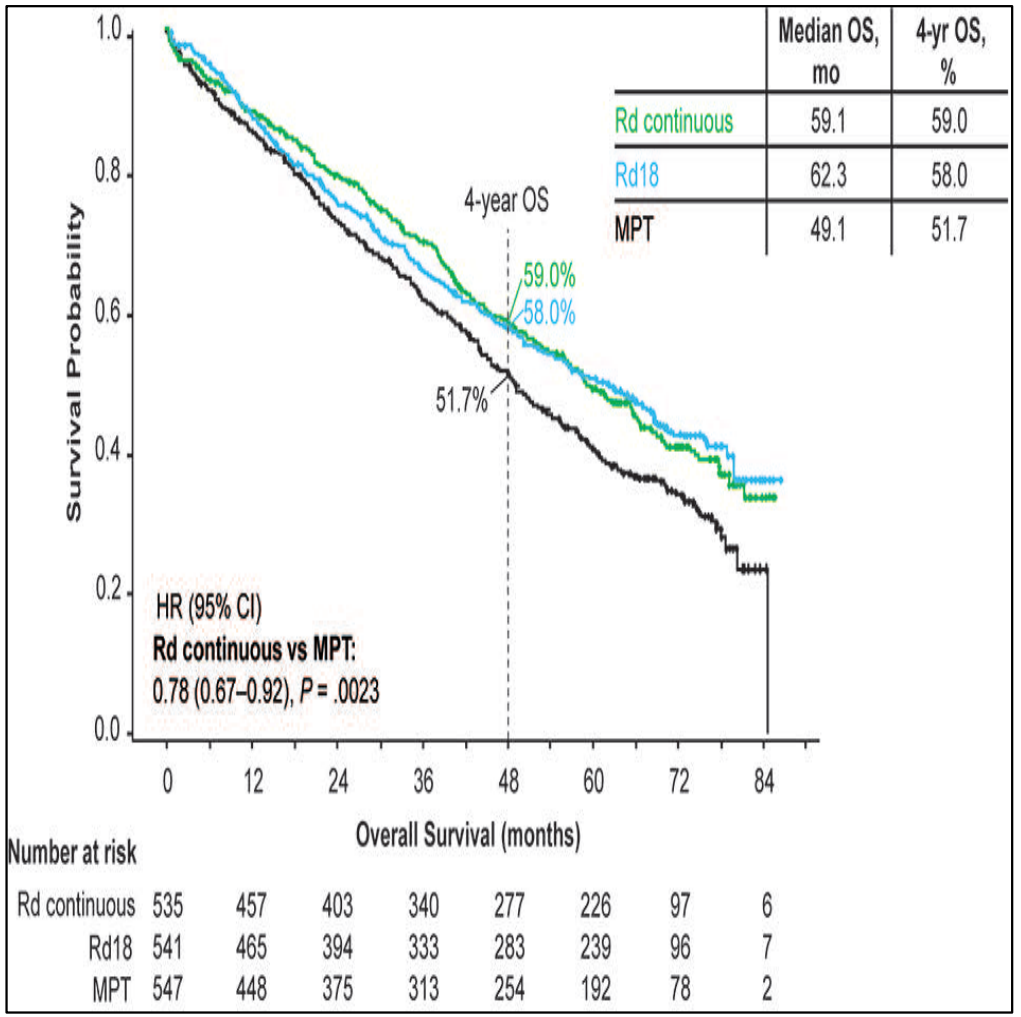


FINAL ANALYSIS OF SURVIVAL OUTCOMES FROM FIRST



CR pts	4yPFS%	Median (mo)
Rd cont	74.9	60
Rd18	39.8	41
MPT	37.5	41

≥VGPR	4yPFS%	Median (mo)
Rd cont	54.7	50.9
Rd18	22.6	30
MPT	23	31.8



Facon et al, Blood 2017 Bahlis et al, Leukemia 2017

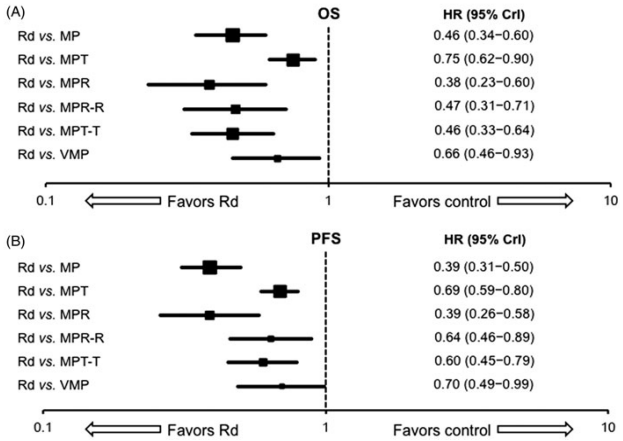


Figure 3. Mixed treatment comparison survival data: fixed-effects analyses with Rd as reference. (A) overall survival (OS); (B) progression free survival (PFS). CrI: credible interval; HR: hazard ratio; MP: melphalan and prednisone; MPR: melphalan and prednisone with lenalidomide; MPR-R: melphalan and prednisone with lenalidomide followed by lenalidomide maintenance; MPT: melphalan and prednisone with thalidomide; MPT-T: melphalan and prednisone with thalidomide followed by thalidomide maintenance; Rd: lenalidomide and low-dose dexamethasone; VMP: melphalan and prednisone with bortezomib.

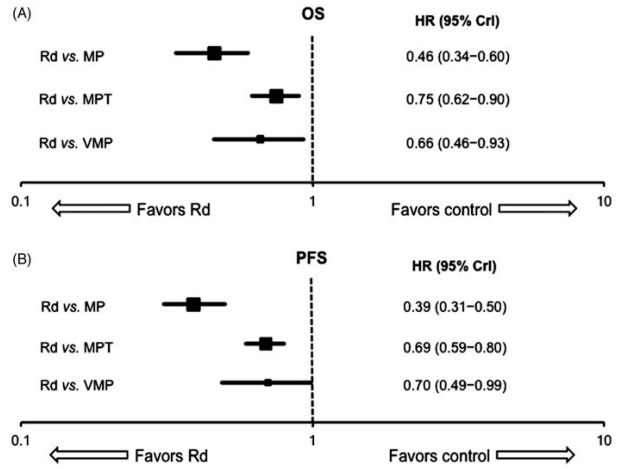


Figure 2. Mixed treatment comparison survival data: fixed effects analyses with Rd as reference. (A) overall survival (OS); (B) progression free survival (PFS). CrI: credible interval; HR: hazard ratio; MP: melphalan and prednisone; MPT: melphalan and prednisone with thalidomide; Rd: lenalidomide and low-dose dexamethasone; VMP: melphalan and prednisone with bortezomib.

A systematic literature review and network meta-analysis of treatments for patients with untreated multiple myeloma not eligible for stem cell transplantation

The present NMA results indicate that the **Rd** regimen is a more effective treatment option for ndMM patients ineligible for transplantation compared with melphalan-containing regimens **VMP, MPT and MP**. These results reinforce the improved OS and PFS benefit reported for Rd directly compared with MPT.

Although no NMA was conducted on safety outcomes, the proportion of patients discontinuing treatment due to AEs and the reported grade 3/4 AEs from the 11 studies included in the sensitivity analysis was overall higher in triplet combinations compared with doublets.

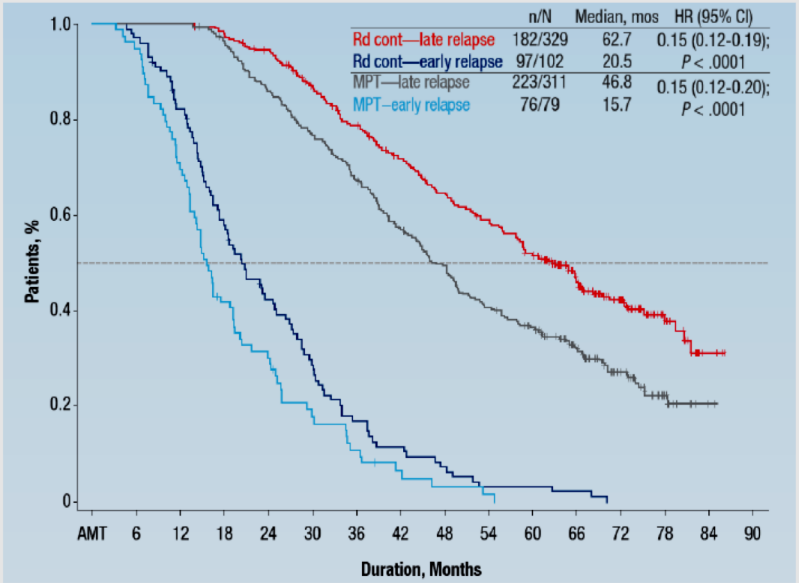
In addition to favorable efficacy and safety parameters,[5] the Rd regimen has shown significant improvements in clinically relevant quality of life measurements,[43] which is of considerable value in the context of elderly patients with an incurable disease such as MM.

Katja Weisel et al LEUKEMIA & LYMPHOMA, 2016

Impact of early vs late relapse in transplant newly diagnosed multiple myeloma: a subanalysis of the phase 3 FIRST trial Facon T. et al. Poster 617

PROGRESSION-FREE SURVIVAL 2

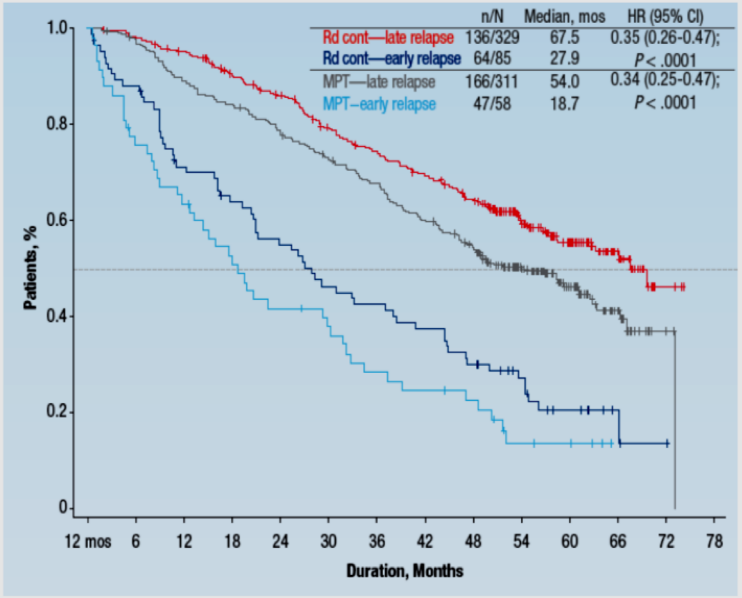
- Late relapses with Rd continuous were associated with a 42.2-month improvement in median PFS2 from randomization vs early relapses ($P < .0001$)



Facon T, et al. EHA 2019 [abstract PF617].

OS AFTER 12-MONTH LANDMARK

- In patients who received Rd continuous, median OS from the 12-month landmark was 39.6 months longer among patients with late relapse vs those with early relapse ($P < .0001$)



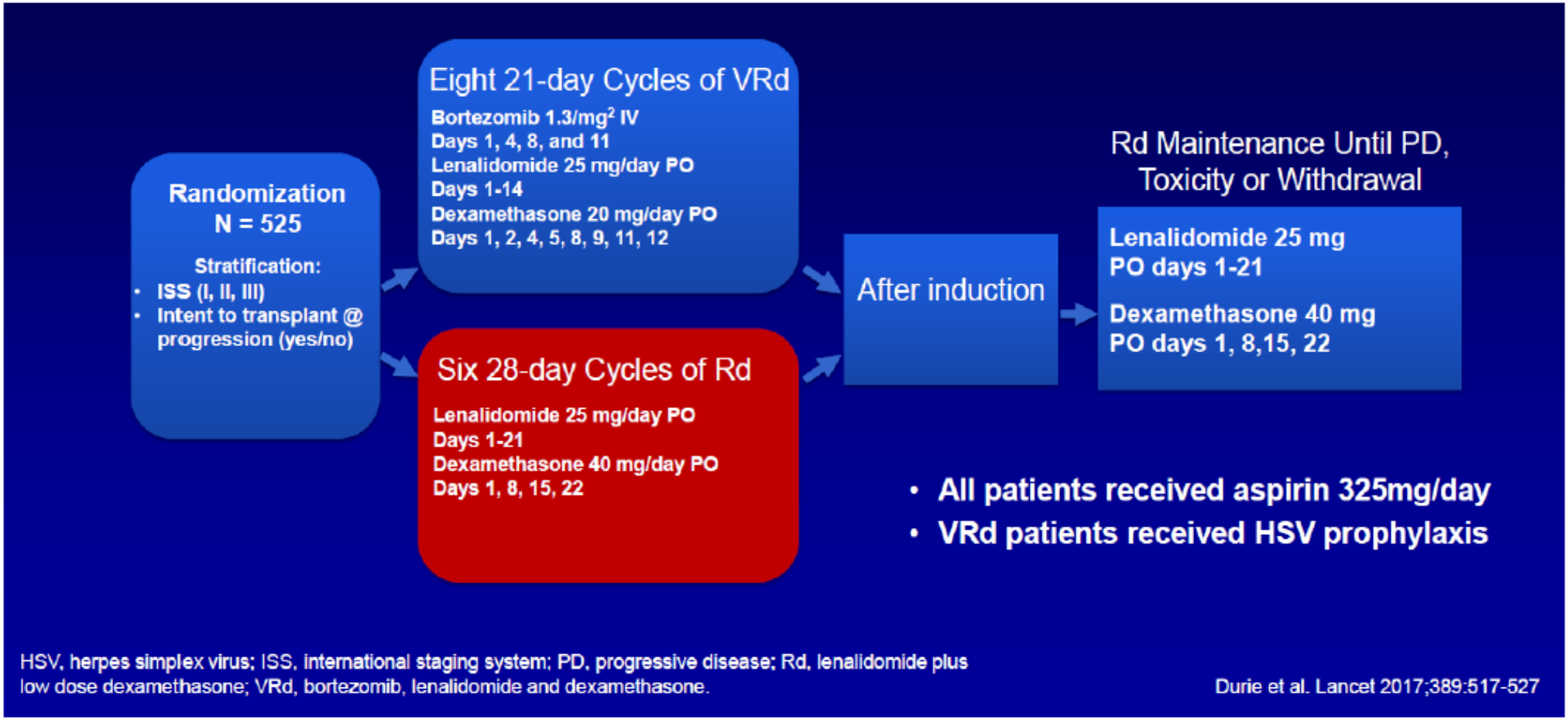
Facon T, et al. EHA 2019 [abstract PF617].

Patients with early relapse were more commonly R-ISS III vs those with late relapse (12.6% in the ITT population, 19.6% in relapse <12 mos and 8.5% in relapse ≥12 mos)

Post-Authorization Safety Study (PASS) of Lenalidomide-Based vs Non–Lenalidomide- Based Treatment in Transplant-Ineligible Newly Diagnosed Multiple Myeloma Cavo et al.

- Ongoing observational, non-interventional post-authorization safety study
- Primary endpoint incidence of cardiovascular events, secondary endpoints renal impairment, infections, and SPMs in Len vs non-LEN cohorts
- As of 12 April 2019, 165 and 162 pts were enrolled in the LEN and non-LEN cohorts. Median age was 79.0 vs 76.0 yrs.
- 11 cardiovascular events in the LEN cohort and 12 in the non-LEN cohort mainly cardiac failures.
- Similar percentages of ≥1 grade 3/4 AE (42.4% vs 47.5%); neutropenia (5.5%vs7.4%), anemia (6.7%vs 4.9%), and thrombocytopenia (3.0%vs7.4%). Discontinuations and reductions/interruptions due to ≥ 1 AE occurred in 18 (10.9%) vs 74 pts (44.8%), 3 vs 4 SPMs

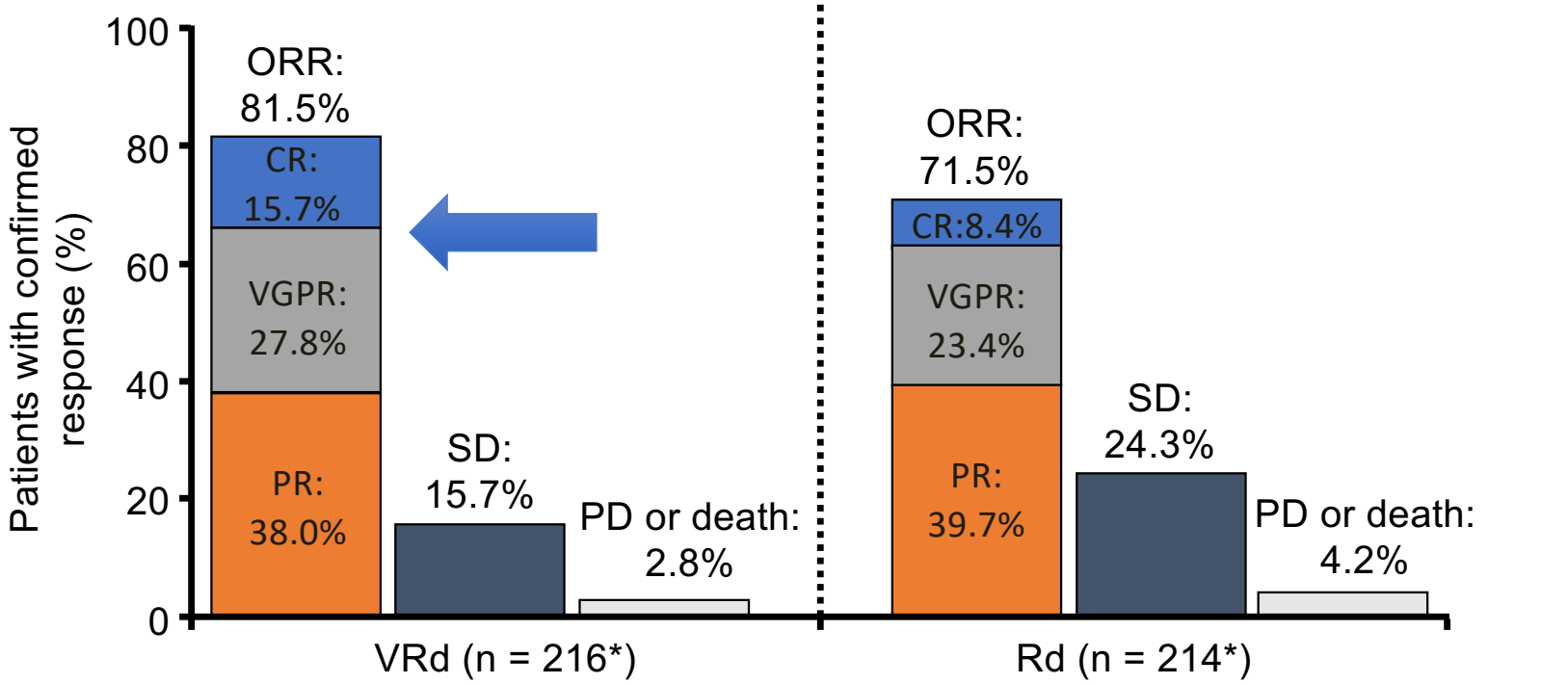
VRd vs Rd SWOG S0777: Study Design



HSV, herpes simplex virus; ISS, international staging system; PD, progressive disease; Rd, lenalidomide plus low dose dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone.

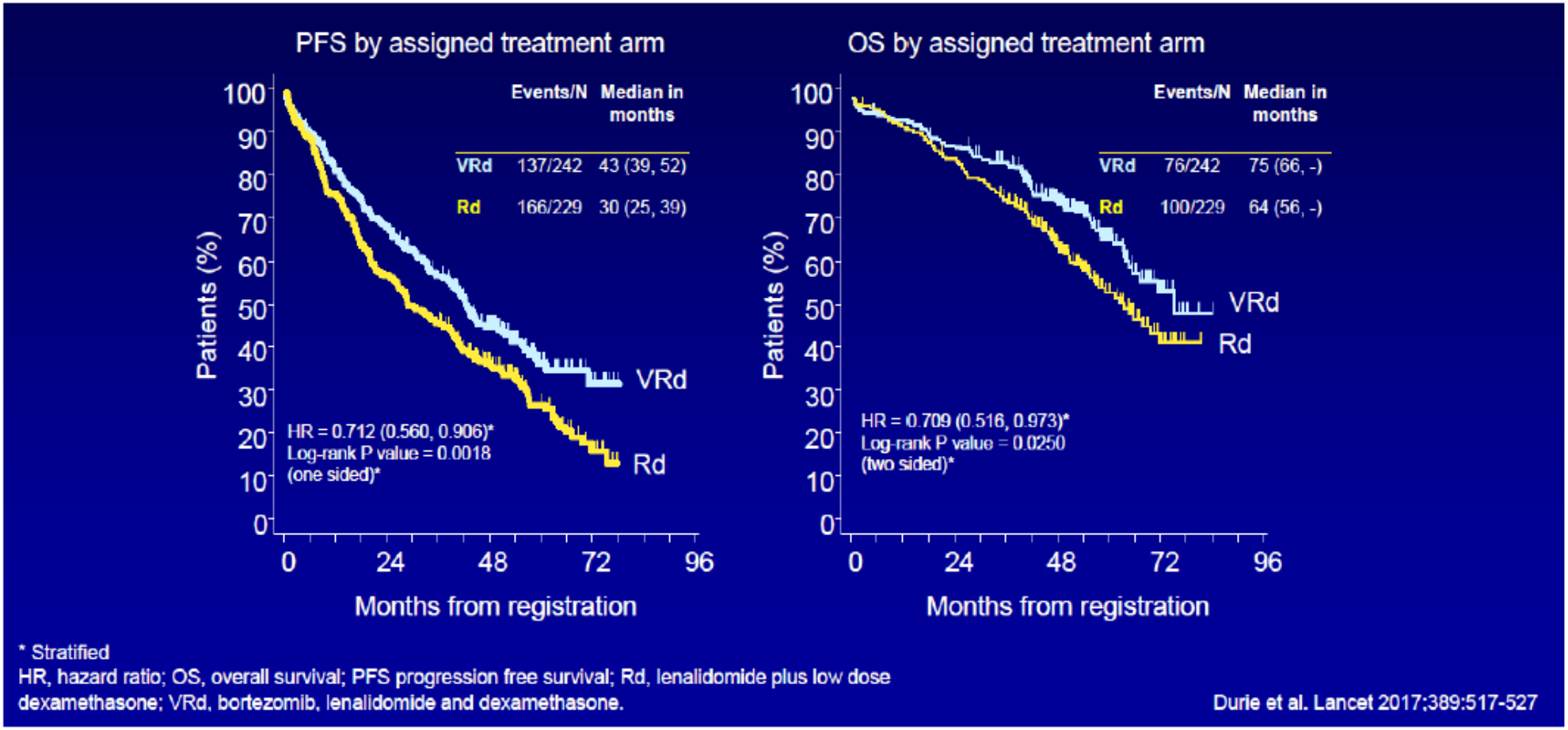
Durie et al. Lancet 2017;389:517-527

SWOG S0777 Study Design



*Assessable.

VRd vs Rd SWOG S0777 : PFS and OS by Assigned Treatment Arm



* Stratified

HR, hazard ratio; OS, overall survival; PFS progression free survival; Rd, lenalidomide plus low dose dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone.

Durie et al. Lancet 2017;389:517-527

A Phase 2 Study of Modified Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Ineligible Multiple Myeloma

Induction (cycles 1-9)
Repeat q35 days × 9 cycles

Lenalidomide 15 mg po days 1-21
Bortezomib 1.3 mg/m^2 sc* days 1, 8, 15, 22
Dexamethasone 20 mg po days 1, 2, 8, 9, 15, 16, 22, 23 (patients ≤75 years)
Dexamethasone 20 mg po days 1, 8, 15, 22 (patients >75 years old)

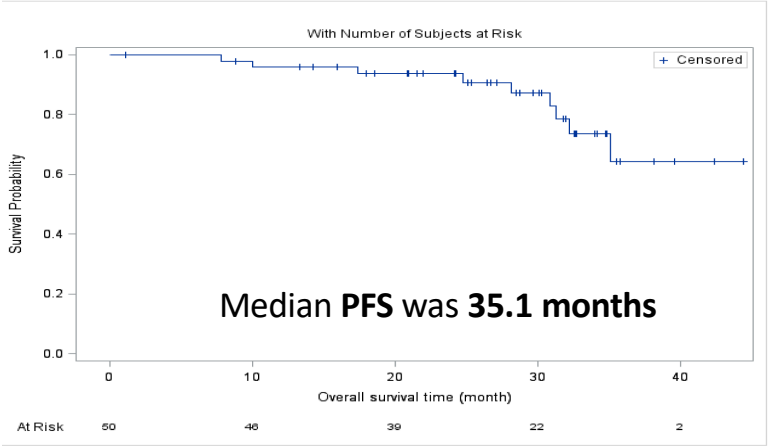
Consolidation (cycles 10-15)
Repeat q28 days × 6 cycles

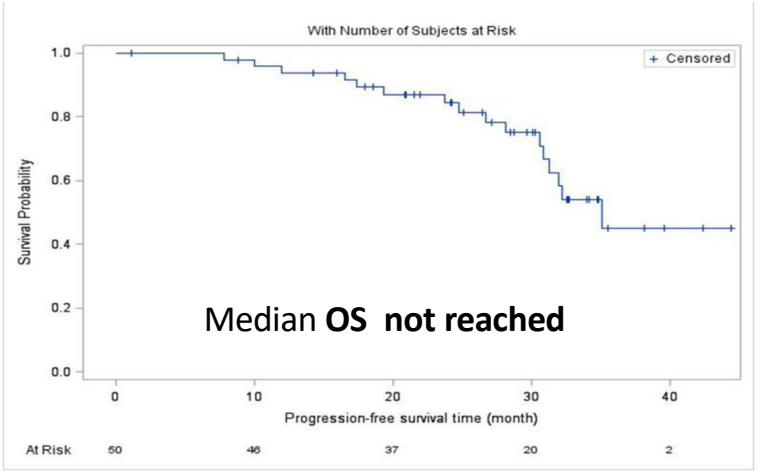
Lenalidomide 15 po days 1-21 (or last tolerated dose as of cycle 9)
Bortezomib 1.3 mg/m^2 sc days 1, 15 (or last tolerated dose as of cycle 9)

Best Overall Response	N=50	%
Stringent Complete Response	6	12
Complete Response	16	32
Very Good Partial Response	11	22
Partial Response	10	20
Minimal Response	1	2
Stable Disease	3	6
Not Evaluable[1]	3	6
ORR	43	86
VGPR or better	33	66

[1] Received less than 4 cycles of therapy

median time to response was 1.1 months.





O'Donnel E et al., Br J Haematol. 2018

Comparative effectiveness of lenalidomide, bortezomib, and their combination as first line treatment of older patients with myeloma

Adam Olszewski et al.

- Population-based data to compare through a propensity score analysis older patients receiving as first-line therapy RD, VD or RVD regimens between 2007-2015
- OS and TTF (time to treatment failure)
- 4,104 patients (76 years), RD increased from 18% to 25% (1,541 pts), VD from 17% to 26% (1,672 pts), and RVD from 1% to 26% (891 pts).
- RVD vs doublets, better TTF (median 1.7 vs 0.8y; HR 0.68) and OS (median 3.4 vs 2.7y; HR, 0.83), at the expense of higher toxicity
- RD vs VD better TTF (median 1.0 vs 0.6y; HR, 0.74) and OS (median 2.7 vs 2.3y; HR 0.91). RD more frequent thromboembolism, but less neuropathy, without significant difference in the rates of hospitalization or anemia

Treatment Pattern and Overall Survival in Newly Diagnosed Multiple Myeloma Patients who are not Eligible for Autologous Stem Cell Transplantation

Jianming He et al.

- 20,452 out of 125,832 MM patients not eligible to transplant were extracted from the US SEER-Medicare Optum databases between Jan 2007 and Sep 2018
- Baseline characteristics and OS of VRd, Rd, Vd and CyBorD groups were compared
- Mean age was 71.3 (SD 9.66) years at index diagnosis
- Bortezomib and Lenalidomide-based combinations were the most common treatment modalities. Compared to 31.7% of the overall group, 43.2% of patients treated with Bortezomib containing regimens had renal failure.
- Patients receiving VRd were younger and showed better over survival compared to Rd, Vd and CyBorD groups

Cross-trial Comparisons: Transplant-ineli

	VISTA		FIRST		SWOG S0777		VRd-Lite
	VMP	MP	Rd	MPT	VRd	Rd	VRd-Lite
mFU, months	16.3		45		84		30
mPFS, months	18	14	26	22	41	30	35
PFS HR (95% CI) p-value	0.61 (0.49-0.76) p=0.00001		0.69 (0.59-0.80) p<0.001		0.71 (0.56-0.91)[d] p=0.0018		NA
ORR, %	74	39	81	67	90	72	86
≥VGPR	41	8	48	30	75	32	66
≥ CR	33	4	21	12	24	8	44
MRD-neg rate (10^{-5}), %	NA	NA	NA	NA	NA	NA	NA
mOS, months	56.4[f]	43.1	59.1	49.1	NR	64	NR
OS HR (95% IC) P value	0.69 P = 0.0004		0.78 (0.67-0.92) p=0.0023		0.70 (0.52-0.96) p=0.01		NA

CLARION: Phase 3 Carfilzomib, Melphalan, Prednisone (KMP) vs. Bortezomib, Melphalan, Prednisone (VMP) in Newly Diagnosed MM

Study Population

Newly Diagnosed MM (N = 882)

Transplant-ineligible

≥ 18 years of age

LVEF ≥ 40%

1:1

KMP*
Carfilzomib
20/36 mg/m2 IV D1, 2, 8, 9, 22, 23, 29, 30**
Melphalan
9 mg/m2 D1-4
Prednisone
60 mg/m2 D1-4

Nine 42-day Cycles

VMP
Bortezomib
1.3 mg/m2 D1, 4, 8, 11, 22, 25, 29, 32
Cycles 1-4 then D1, 8, 22, 29 Cycles 5-9
Melphalan
9 mg/m2 D1-4
Prednisone
60 mg/m2 D1-4

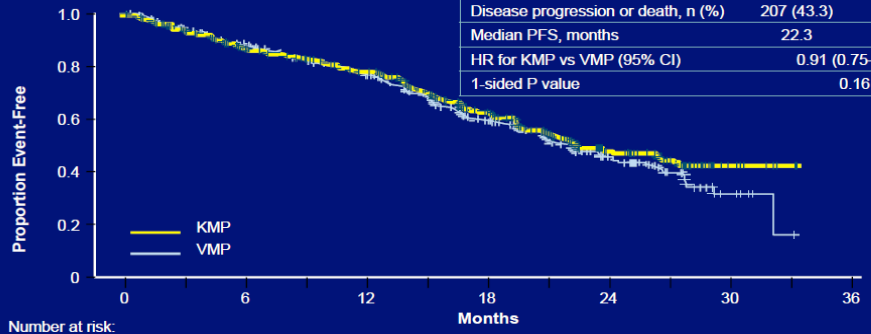
Primary endpoint: PFS
Secondary endpoint: OS, ORR, DOR, safety, HR-QOL

*Dexamethasone 4 mg given on Days 8, 9, 22, 23, 29, 30 in Cycle 1
* * 20 mg/m2 on Day 1, 2 of Cycle 1; then 36 mg/m2 on all subsequent days and cycles
Available at www.clinicaltrials.gov NCT01818752

CLARION STUDY
Primary Endpoint: Progression-Free Survival

- Median follow-up time: 22.2 months for KMP and 21.6 months for VMP
- The absence of PFS difference was consistent across subgroups

	KMP (n = 478)	VMP (n = 477)
Disease progression or death, n (%)	207 (43.3)	214 (44.9)
Median PFS, months	22.3	22.1
HR for KMP vs VMP (95% CI)	0.91 (0.75–1.10)	
1-sided P value	0.16	



Number at risk:

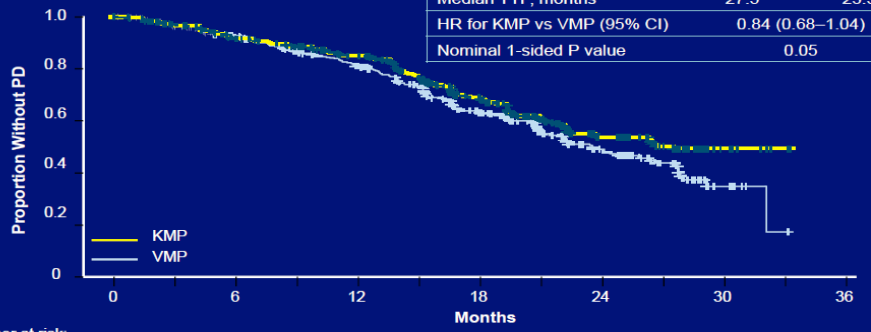
KMP	478	384	327	217	85	15	0
VMP	477	367	309	202	77	9	0

CI, confidence interval; HR, hazard ratio; KMP, carfilzomib, melphalan, prednisone; PFS, progression-free survival; VMP, bortezomib, melphalan, prednisone

Facon T, et al. Presented at: 16th International Myeloma Workshop; New Delhi, India; March 1-4, 2017.

CLARION STUDY
Time to Progression

	KMP (n = 478)	VMP (n = 477)
Disease progression, n (%)	162 (33.9)	185 (38.8)
Median TTP, months	27.5	23.5
HR for KMP vs VMP (95% CI)	0.84 (0.68–1.04)	
Nominal 1-sided P value	0.05	



Number at risk:

KMP	478	380	326	216	84	15	0
VMP	477	367	308	202	77	9	0

CI, confidence interval; HR, hazard ratio; KMP, carfilzomib, melphalan, prednisone; PD, progressive disease; TTP, time to progression; VMP, bortezomib, melphalan, prednisone

Facon T, et al. Presented at: 16th International Myeloma Workshop; New Delhi, India; March 1-4, 2017.

CLARION STUDY
AEs of Interest

	KMP (n = 474)		VMP (n = 470)	
AE, %	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Acute renal failure[a]	13.9	7.4	6.2	2.1
Cardiac failure[a]	10.8	8.2	4.3	2.8
Ischemic heart disease[a]	3.0	2.1	1.9	1.3
Hypertension[a]	24.7	10.1	8.1	3.6
Dyspnea[b]	18.1	3.6	8.5	0.6
Grade 5 AE	6.5		4.3	
Leading to treatment discontinuation	17.5		15.5	

[a]Standardized MedDRA Queries Narrow Search. [b]High-level term.
AE, adverse event; KMP, carfilzomib, melphalan, prednisone; MedDRA, Medical Dictionary for Regulatory Activities; VMP, bortezomib, melphalan, prednisone

Facon T, et al. Presented at: 16th International Myeloma Workshop; New Delhi, India; March 1-4, 2017.

A phase 1b study of once-weekly carfilzomib combined with lenalidomide and dexamethasone (wKRd) in patients (pts) with NDMM

Melissa Alsina et al.

- Treatment was given in 28-day (D) cycles (C) for up to 18 C. Carfilzomib D1, 8, and 15; lenalidomide 25 mg on D1–21; and dexamethasone 40 mg on D1, 8, and 15 (also D22 for C1–8). Initially carfilzomib was administered at 20/70 mg/m2 (20 mg/m2on C1D1; 70 mg/m2 thereafter) but after serious adverse events occurred in 2 of the first 4 pts, protocol was amended to a 2-step-up KRd dosing schedule (20 mg/m2 on C1D1; 56 mg/m2 on C1D8/C1D15; 70 mg/m2 thereafter), and after a further evaluation by a safety review committee dose was reduced to 20/56 (20 mg/m2 on C1D1; 56 mg/m2 thereafter).
- 51 enrolled between March 2016 and October 2017, but results are presented for pts who received weekly carfilzomib 56 mg/m2 (n=33)
- Twenty-five pts underwent stem cell collection; 19 to autologous SCT (allowed after C4)
- Incidence of grade ≥3 treatment-emergent AEs was 60.6%: anemia (12.1%), hyponatremia (12.1%), and increased ALT (9.1%). There were no fatal TEAEs.
- Median PFS was not reached. By C4 the overall response rate (ORR) in the safety population (n=33) was 97.0% (VGPR or better 69.7%; CR or better 3.0%)
- Among pts who did not receive autologous SCT (n=14), best overall responses at any time were 78.6% (≥VGPR) and 50.0% (≥CR); ORR was 92.9%

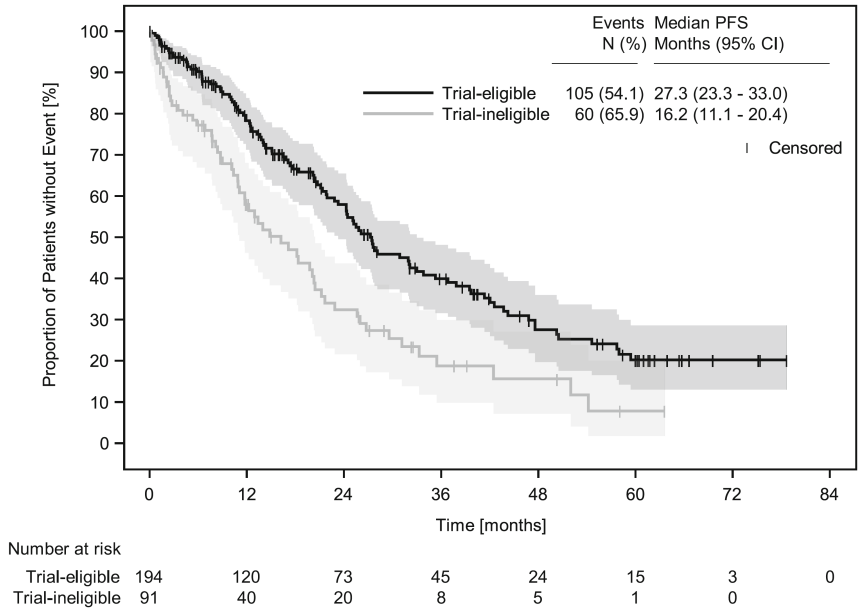
The Characteristics, Treatment Patterns, and Outcomes of Older Adults with Multiple Myeloma

Nicole C. Foley et al.

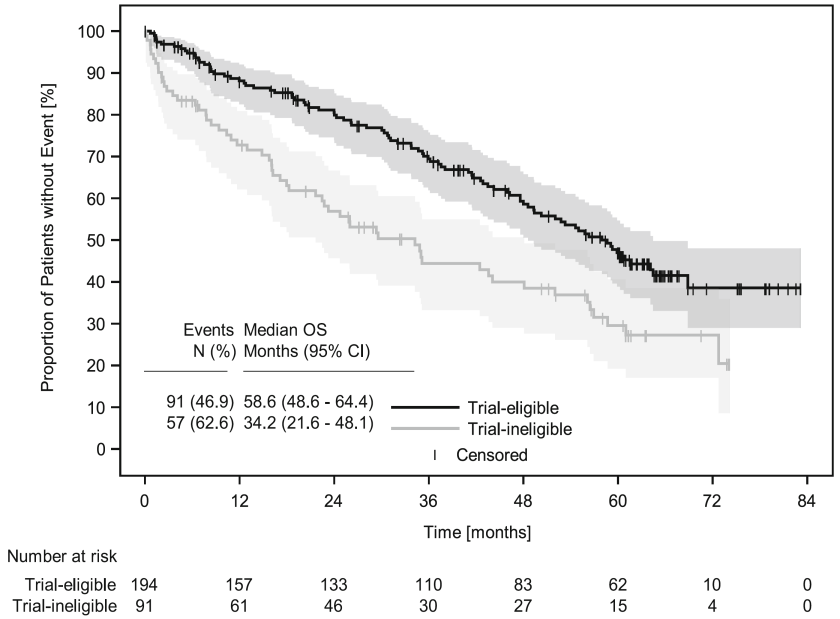
- MM pts 80 yrs or older (SEER)-Medicare Database from 2007-2013 compared with similar patients 70-79 yrs
- OS for patients 80+ was 13.4 months, in details OS in pts receiving systemic treatment 51%) 21.4 months vs 6.4 months ($p < 0.0001$) for the others
- Outcomes improved through the years; the hazard for death decreased by 3% ($p = 0.0096$) each year 2007-2013, in conjunction with increasing treatment rates, from 41% in 2007 to 61% in 2013
- After controlling for MM treatment, the year of diagnosis was no longer a significant predictor of survival
- Patients 80+ at MM diagnosis who received systemic treatment obtain proportional benefit to those age 70-79, relative to the untreated patients in the same age group indicating that, regardless of age, treatment with novel agents improves survival

Survival of potentially trial-eligible patients compared to trial-ineligible patients

a Progression-free survival (PFS)



b Overall survival (OS)



Knauff W et al., Ann Hematol 2018

CONCLUSIONS

- ✓ VMP and Rd are still the two milestones of the first line treatment of MM patients not eligible to transplant
- ✓ Although a frailty evaluation balancing the efficacy and tolerability is crucial in the treatment choice in this setting this do not justify a forgoing attitude in elderly patients
- ✓ VRD seems to be the best choice in fit elderly patients giving very good results with an acceptable toxicity
- ✓ Carfilzomib based schemes can be adopted in fit elderly patients with caution adjusting doses and schedules
- ✓ ***Respice senectute***