Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Lucia Pantani
IRCCS Azienda Ospedaliero-Universitaria di Bologna
Istituto di Ematologia "Seràgnoli"

Terapia di prima linea del paziente candidato ad ASCT

Di mantenimento
- Con 2 o 3 farmaci

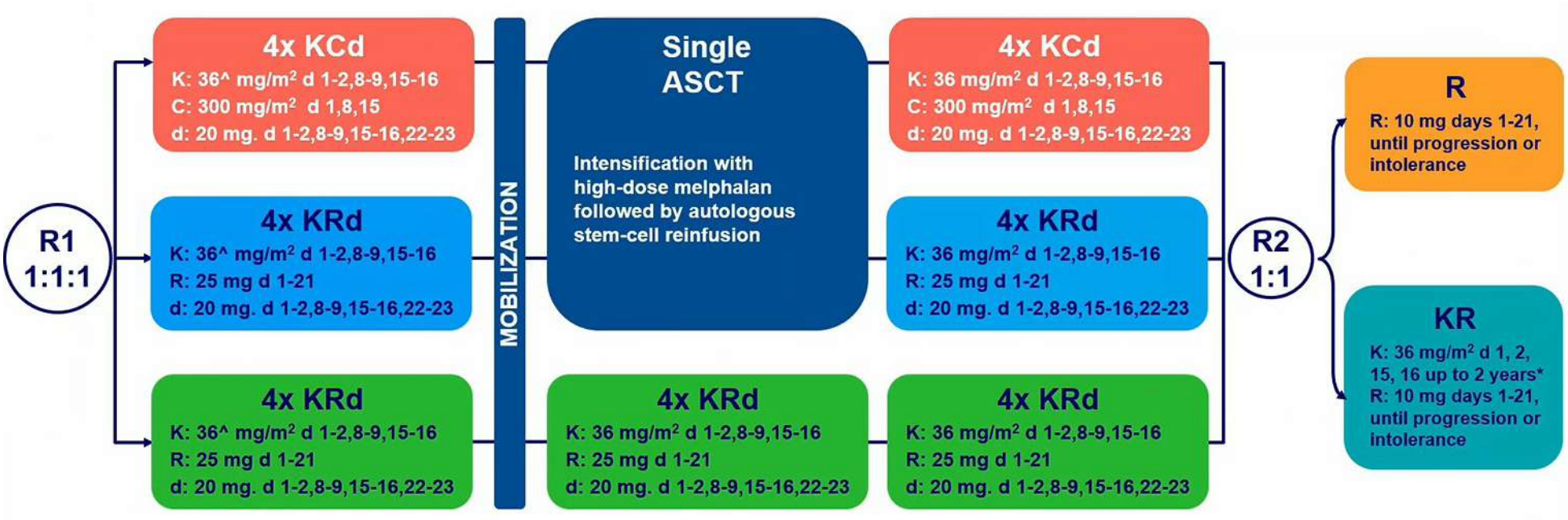
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Honoraria
Janssen							x
Sanofi							x
Amgen							x
GlaxoSmithKline							x

IMMUNOMODULATORY AGENTS

+ PROTEASOME INHIBITORS

FORTE ph.II trial: study design

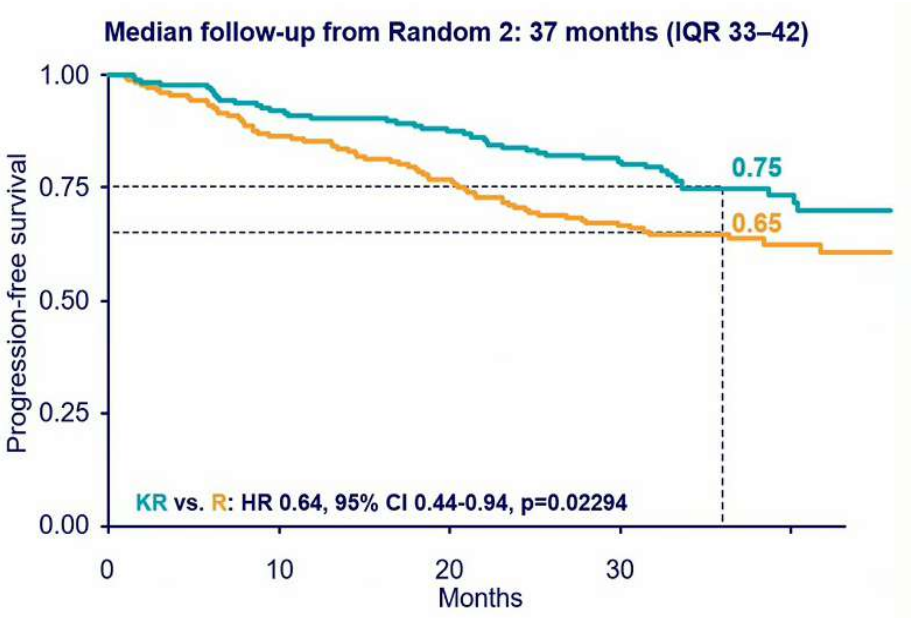


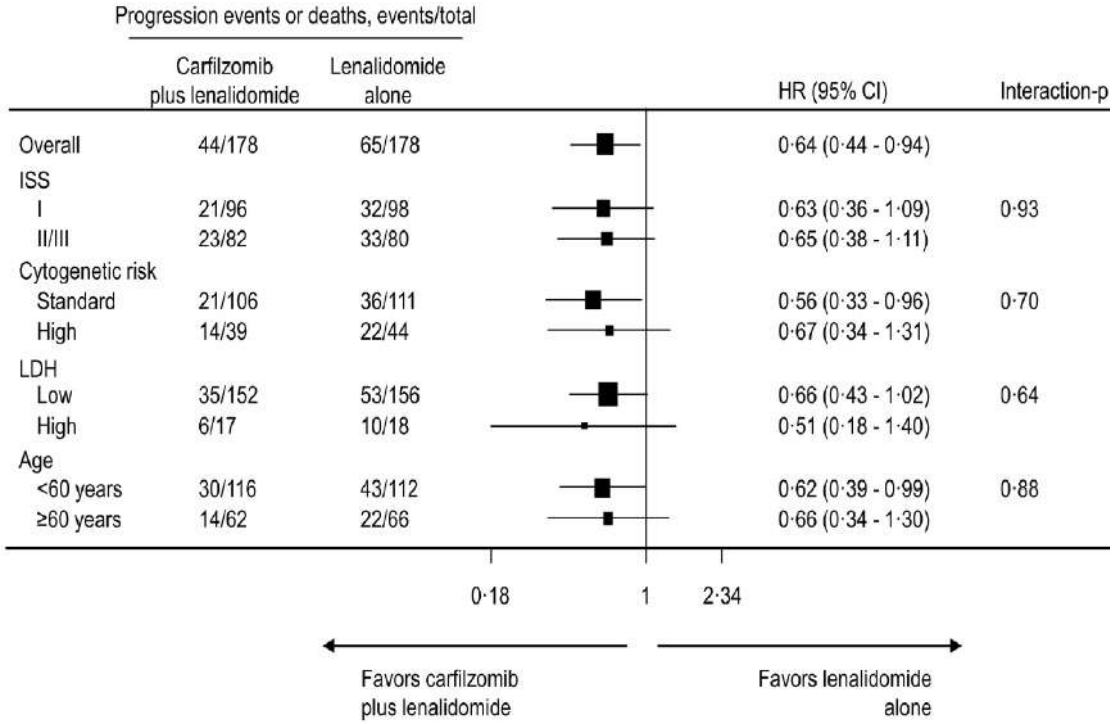
^20 mg/m2 on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m2 days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards

Primary endpoints: rate of at least VGPR post induction with KRd vs KCd
PFS from R2 with KR vs R as maintenance therapy

Mina R. IMW 2021, oral presentation
Gay F. et al. Lancet Oncol 2021; 22: 1705–20

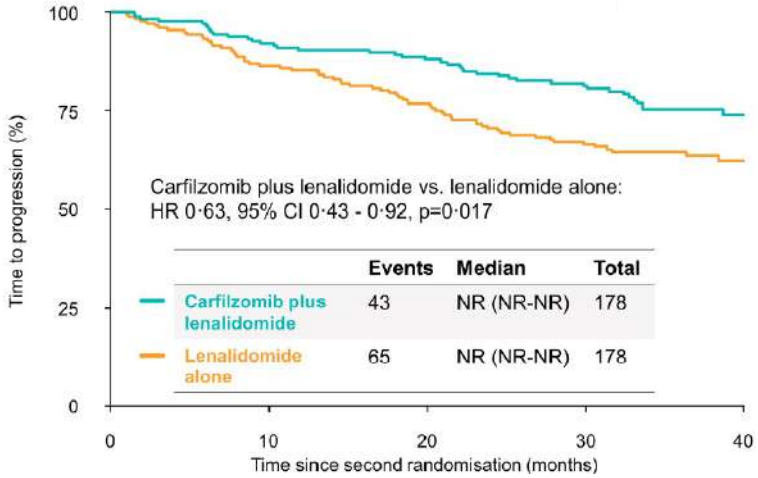
KR vs. R

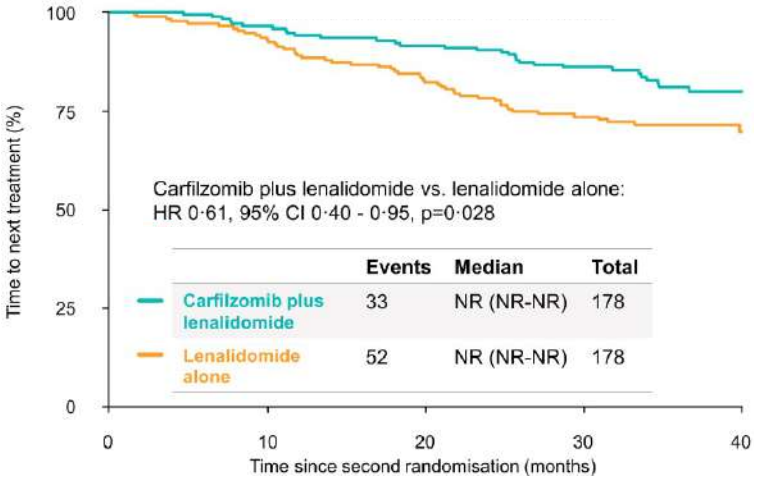

Median follow-up from Random 2: 37 months (IQR 33–42)
Progression-free survival
1.00
0.75
0.50
0.25
0.00
0.75
0.65
KR vs. R: HR 0.64, 95% CI 0.44-0.94, p=0.02294
0
10
20
30
Months

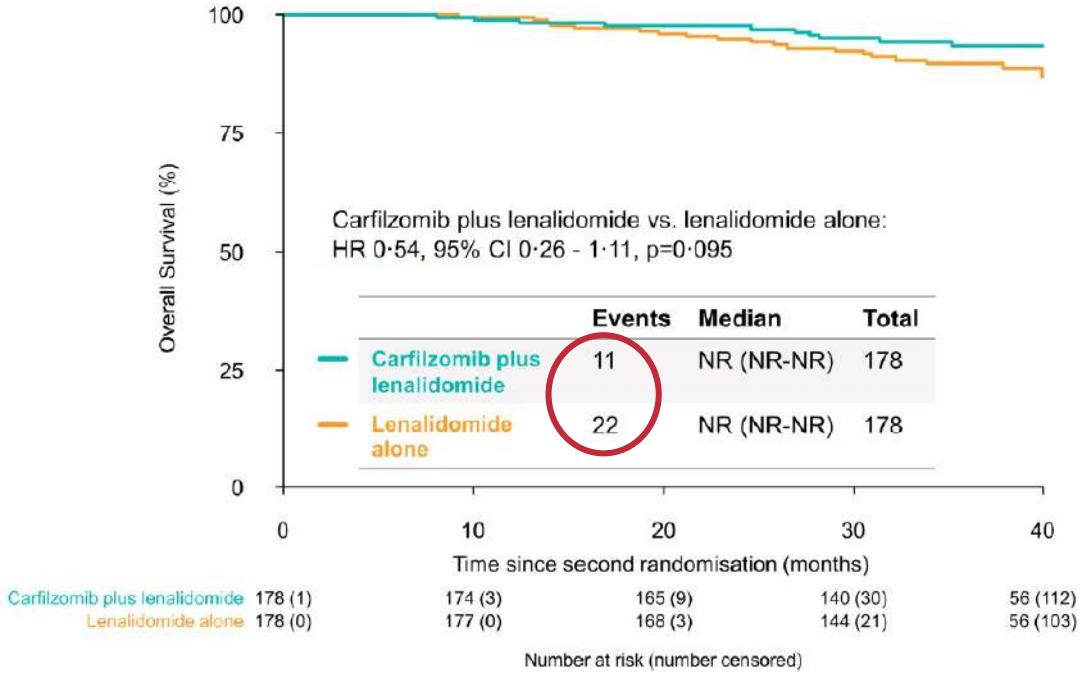

Progression events or deaths, events/total
Carfilzomib plus lenalidomide
Lenalidomide alone
HR (95% CI)
Interaction-p
Overall 44/178 65/178 0·64 (0·44 - 0·94)
ISS
I 21/96 32/98 0·63 (0·36 - 1·09) 0·93
II/III 23/82 33/80 0·65 (0·38 - 1·11)
Cytogenetic risk
Standard 21/106 36/111 0·56 (0·33 - 0·96) 0·70
High 14/39 22/44 0·67 (0·34 - 1·31)
LDH
Low 35/152 53/156 0·66 (0·43 - 1·02) 0·64
High 6/17 10/18 0·51 (0·18 - 1·40)
Age
<60 years 30/116 43/112 0·62 (0·39 - 0·99) 0·88
≥60 years 14/62 22/66 0·66 (0·34 - 1·30)
0·18
1
2·34
Favors carfilzomib plus lenalidomide
Favors lenalidomide alone

Highlights from IMW 2021

1-2 Febbraio 2022
Bologna
Royal Hotel Carlton







Conversion from MRD+ to MRD- during maintenance*:

29/63 pts with KR vs 18/60 with R (p=0.046) (flow)
14/25 pts with KR vs 7/23 with R (p=0.046) (NGS)

*pts MRD+ before maintenance who had a second sample available within 2 ys of treatment

	KR (N=140)	R (N=152)
Age		
Median (IQR)	57 (52-61)	57 (51-61)
ISS Stage		
I	70 (50)	79 (52)
II	44 (31)	57 (38)
III	26 (19)	16 (11)
LDH		
>upper limit of normal*	14 (11)	18 (12)
Chromosomal abnormalities (FISH)		
t(4;14)	17 (12)	19 (12)
t(14;16)	10 (7)	6 (4)
del(17p)	14 (10)	21 (14)
gain(1q)	45 (32)	52 (35)
amp(1q)	15 (11)	11 (7)
del(1p)	16 (11)	14 (9)
FISH status**		
Standard risk	52 (37)	68 (45)
High risk	88 (63)	84 (55)
Double hit	28 (20)	35 (23)

Subgroup analysis: efficacy by cytogenetic risk

Standard risk

Absence of any chromosomal abnormalities

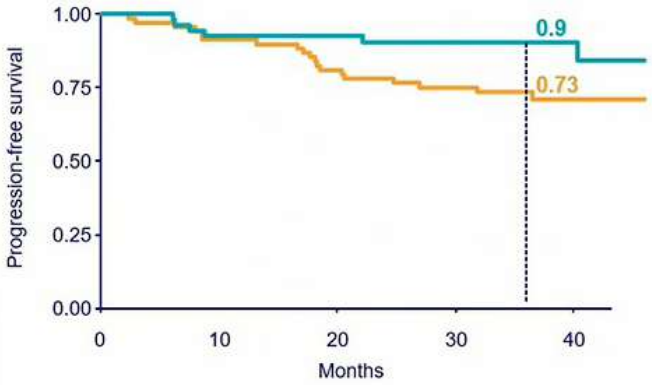
High risk

≥1 chromosomal abnormalities

Double hit

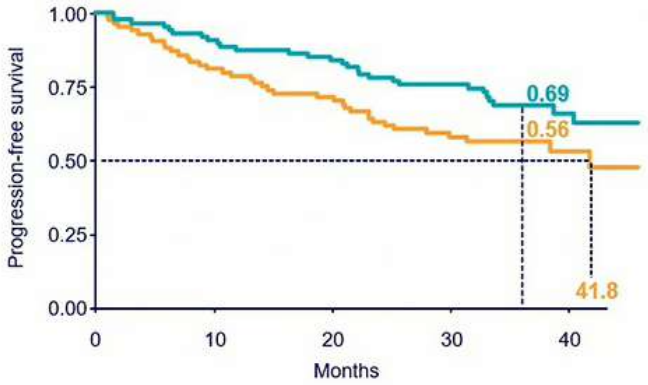
≥2 chromosomal abnormalities

Standard risk (N=120)



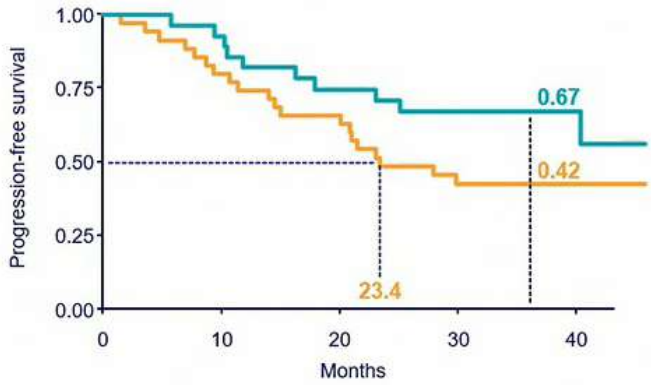
KR vs. R: HR 0.40, p=0.055

High risk (N=172)



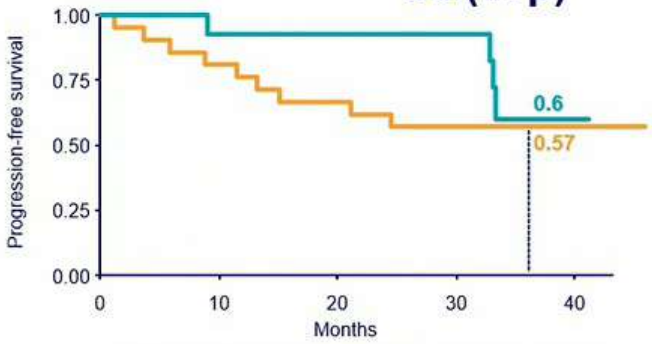
KR vs. R: HR 0.58, p=0.033

Double hit (N=105)



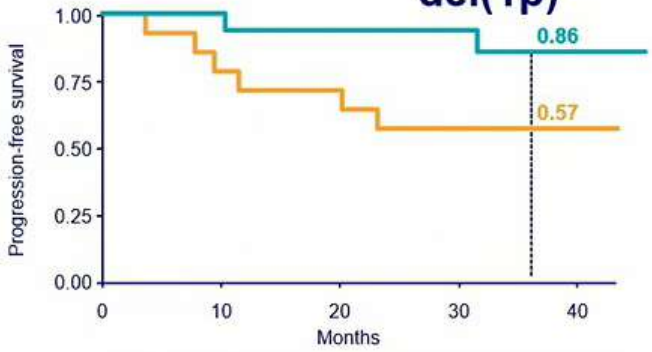
KR vs. R: HR 0.47, p=0.070

del(17p)



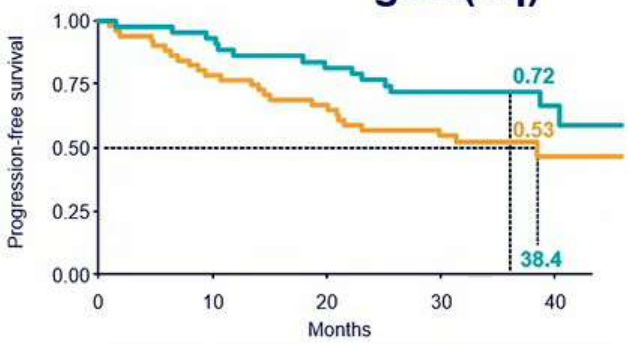
KR vs. R: HR 0.65 95% CI (0.2-2.13)

del(1p)



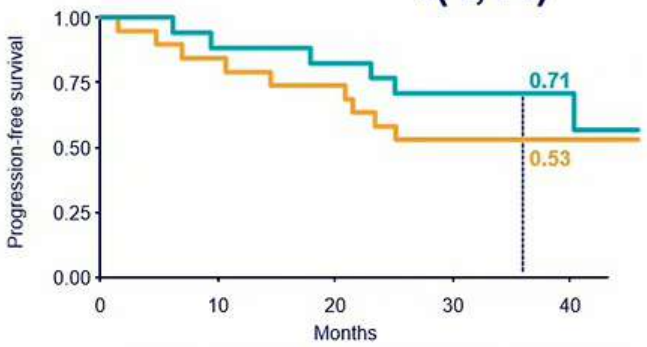
KR vs. R: HR 0.20 95% CI (0.04-0.98)

gain(1q)



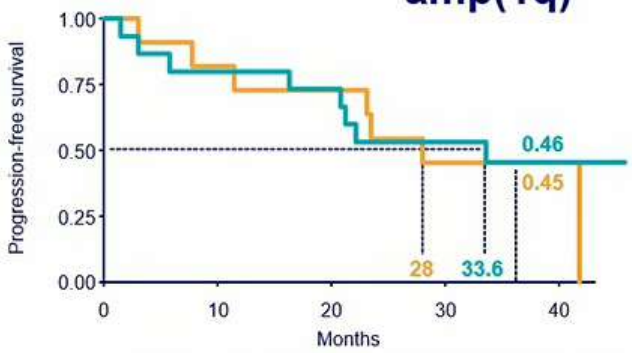
KR vs. R: HR 0.54 95% CI (0.28-1.05)

t(4;14)



KR vs. R: HR 0.69 95% CI (0.24-1.96)

amp(1q)



KR vs. R: HR 0.72 95% CI (0.25-2.04)

KR prolongs PFS in all CA subgroups, except…

in patients with amp(1q)

Safety profile

	Carfilzomib + lenalidomide (n=173)		Lenalidomide alone (n=177)	
AEs	Gr.3	Gr.4	Gr.3	Gr.4
Overall	64 (37%)	20 (12%)	56 (32%)	12 (7%)
Haematological	29 (17%)	15 (9%)	35 (20%)	11 (6%)
- neutropenia	26 (15%)	9 (5%)	32 (18%)	9 (5%)
Non-haematological	42 (24%)	6 (3%)	24 (14%)	1 (1%)
- infections	8 (5%)	-	13 (7%)	-
- cardiac	5 (3%)	-	-	1 (1%)
- vascular	8 (5%)	4 (2%)	1 (1%)	-
Treatment-emergent serious AEs	24 (14%)		15 (8%)	
Treatment discontinuation due to AEs	**20 (12%)**		**22 (12%)**	
Carfilzomib discontinuation	41 (24%)		-	
Carfilzomib dose reduction	34 (20%)		-	
Lenalidomide discontinuation	33 (19%)		22 (12%)	
Lenalidomide dose reduction	40 (23%)		52 (29%)	

GEM12MENOS65 trial

Induction
VRd-GEM (6 cycles)

R

Mel-200 | Bu-Mel

Consolidation
VRd-GEM (2 cycles)

≥ SD

R

GEM2014MAIN trial

Ixazomib 4 mg/day, D 1,8,15
Lenalidomide 15 mg/day, D 1-21
Dexamethasone 20 mg/day, D 1-4, 9-12
(n = 171)

Lenalidomide 15 mg/day, D 1-21
Dexamethasone 20 mg/day, D 1-4, 9-12
(n = 161)

MRD assessment at 2 yrs

MRD neg → Stop Maintenance

MRD pos → Lena/Dex for 3 years

*VRd-GEM: bortezomib 1.3 mg/m² SC on Days 1, 4, 8, 11;
lenalidomide 25 mg PO on D1-21;
dexamethasone 40 mg PO on Days 1-4, 9-12 in 28-day cycles.

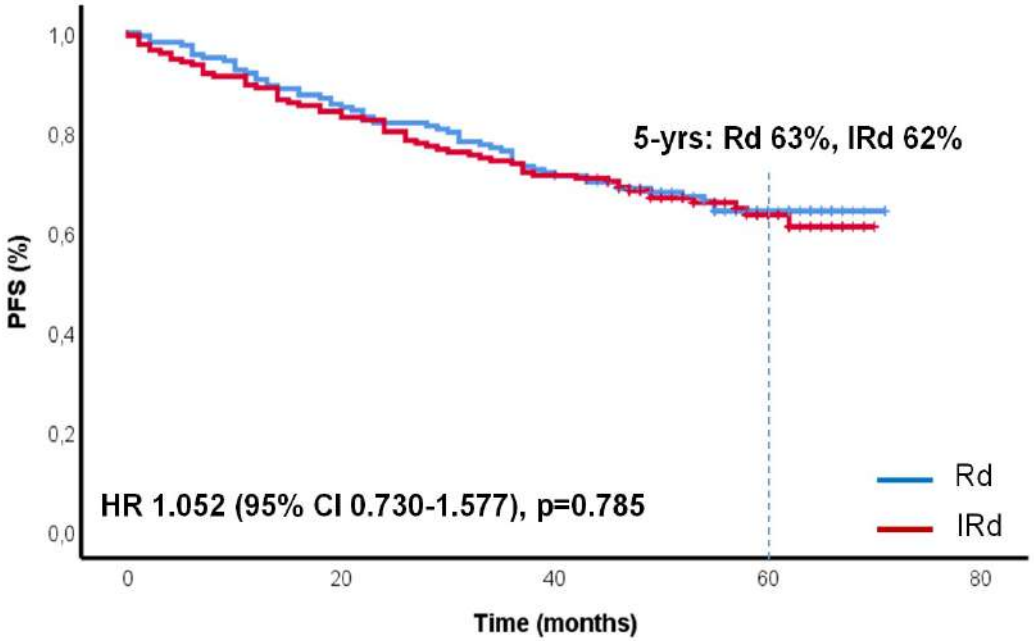
Annual MRD

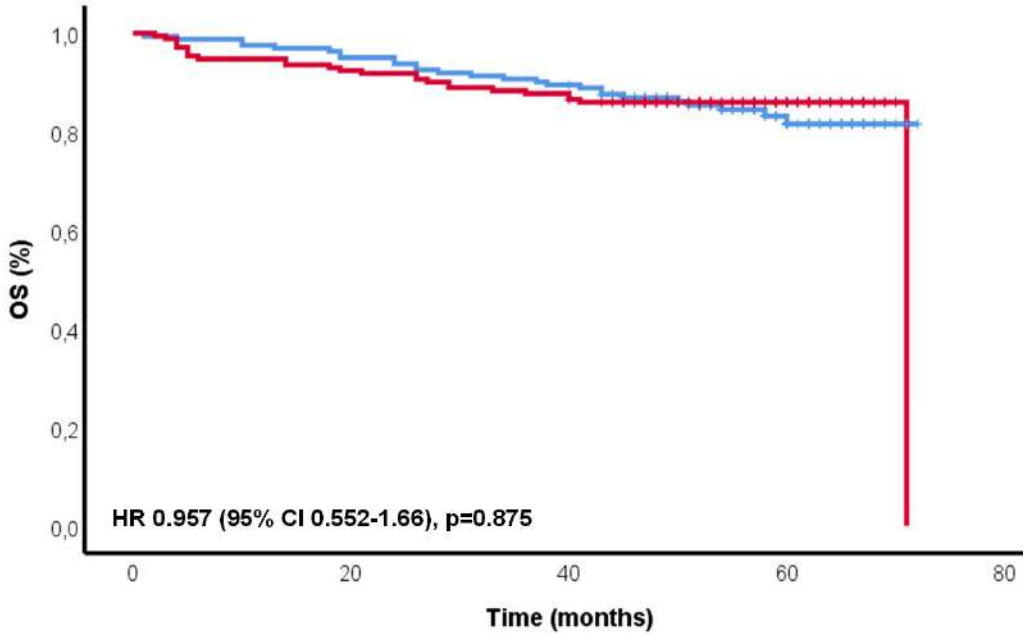
measured with NGF: sensitivity 3 x 10^{-6}

Primary endpoint: PFS

Rosiñol L. ASH 2021. Abstr 466, oral presentation

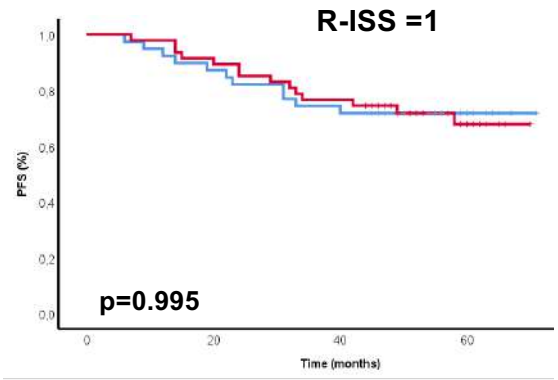
Survival from maintenance: Rd vs IRd

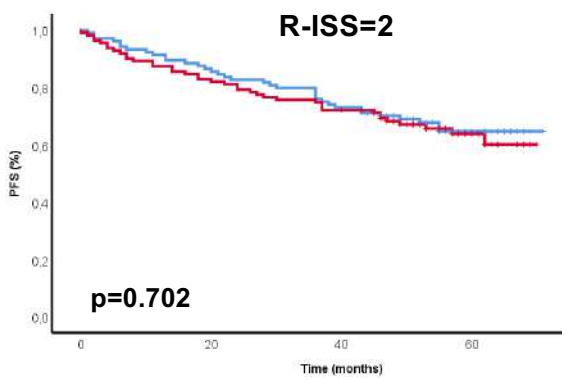


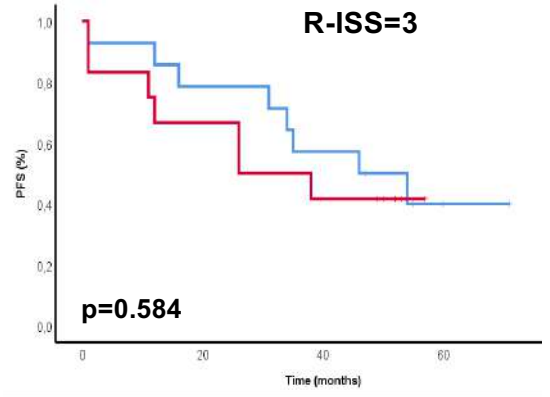


Median follow-up: 56 months

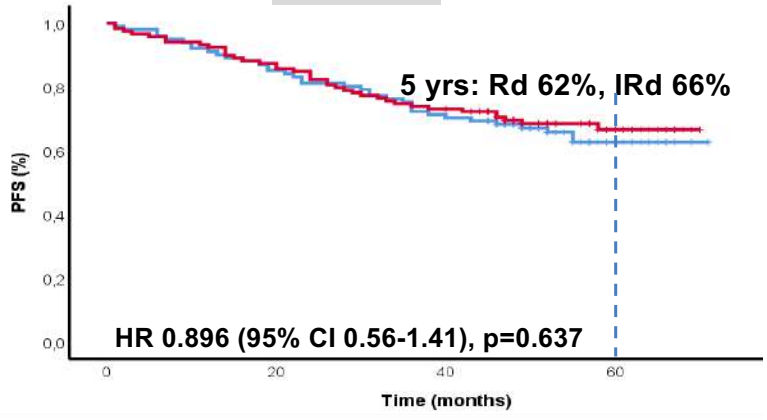
PFS according to R-ISS and cytogenetics: Rd vs IRd

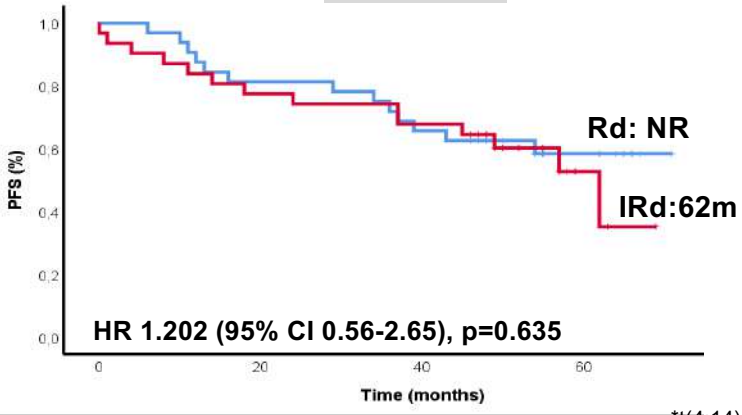






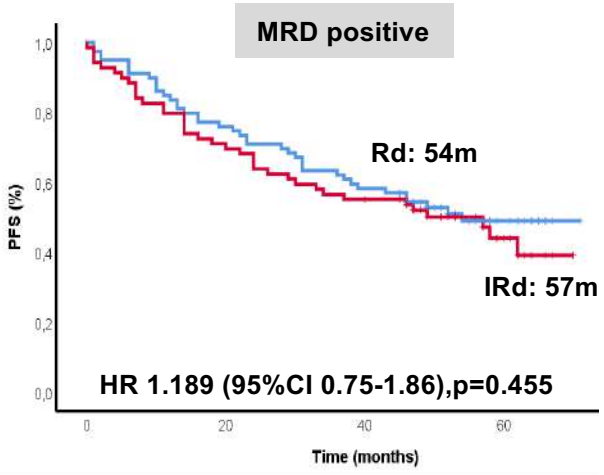
Rd
IRd

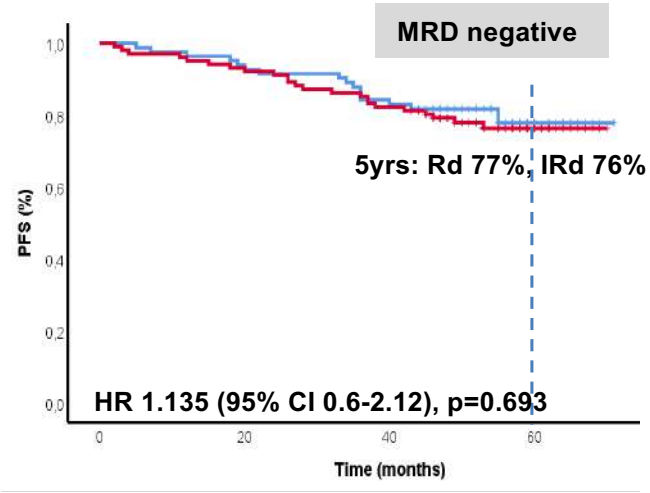




*t(4;14); t(14;16); del(17p)

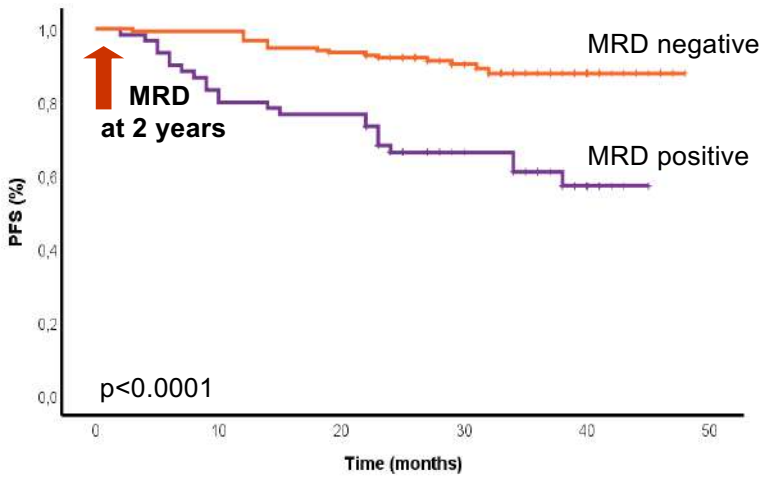
PFS according to MRD at screening: Rd vs IRd





PFS from MRD at 2 years

MRD at 2 years:
- negative: stop maintenance
- positive: Rd for 3 additional years



PFS significantly prolonged for pts MRD negative at 2 years regardless of assigned maintenance

Safety profile

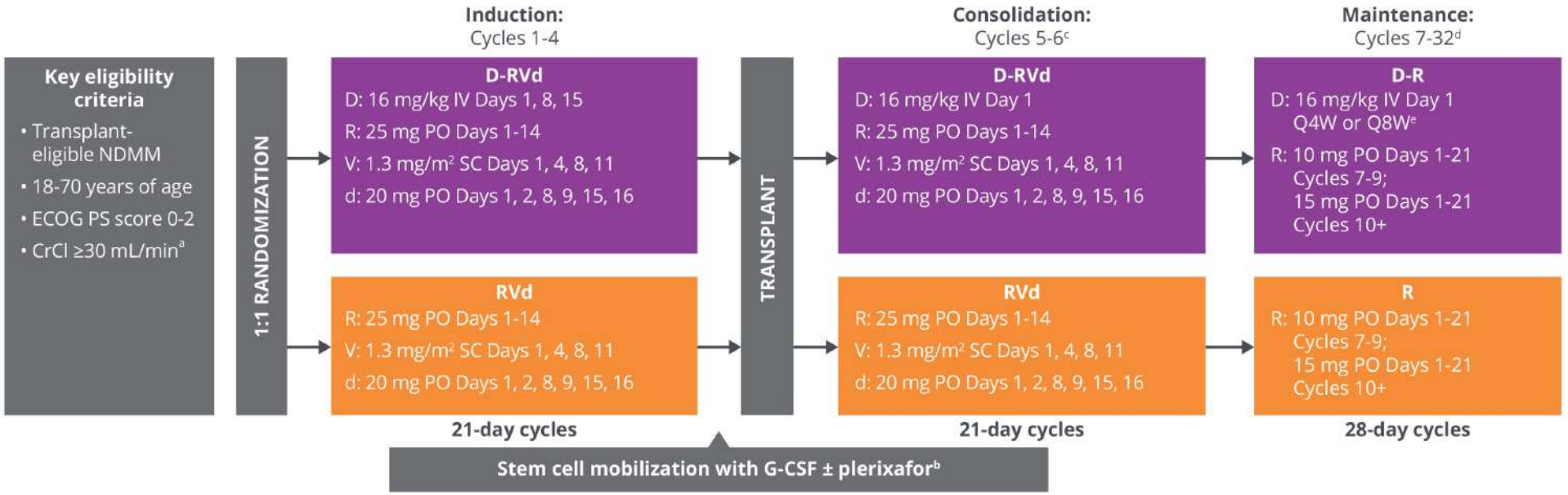
Event, n (%)	IRd (n = 171)	Rd (n = 161)
Grade 3/4 adverse event		
• Neutropenia	64 (37.4)	64 (39.7)
• Thrombocytopenia	28 (16.3)*	12 (7.4)
• Gastrointestinal	27 (15.7)†	4 (2.4)
• Cutaneous	7 (4.1)	3 (1.8)
Dose reduction		
• Ixazomib	53 (30.9)	--
• Lenalidomide	51 (29.8)	34 (21.1)
• Dexamethasone	37 (21.6)	35 (21.7)
Discontinuation		
• Ixazomib	16 (9.3)	--
• Lenalidomide	1	1
• Dexamethasone	7 (5.2)	13 (8)

*P = .011 vs Rd. †P <.0001 vs Rd.

IMMUNOMODULATORY AGENTS

+ MONOCLONAL ABs

Daratumumab + RVd in NDMM: Updated analysis of GRIFFIN after 24 months of Maintenance



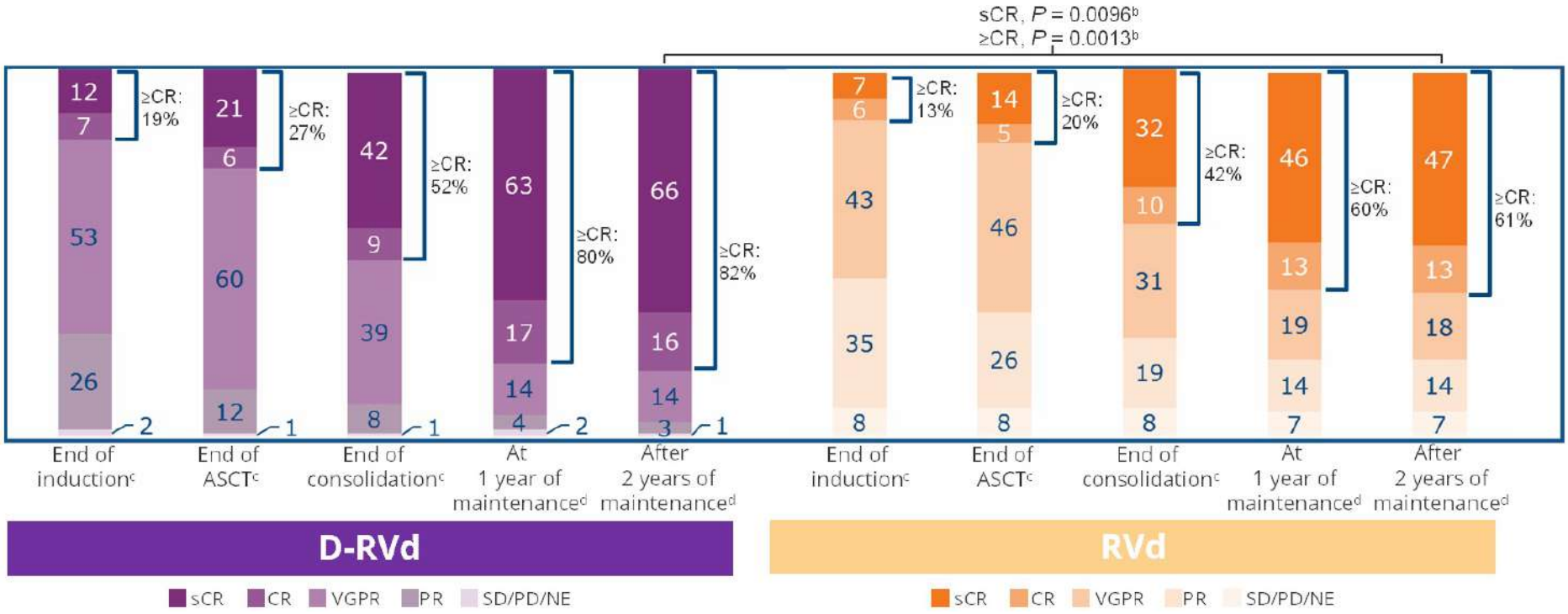
Primary endpoint: sCR by end of consolidation with 1-sided α = 0.1
Key secondary endpoints: rates of MRD negativity, ORR, ≥VGPR, CR, PFS, OS

Median follow-up 38.6 mos

Jacob Laubach et al. ASH 2021, abs 79, oral presentation
Larry D. Anderson Jr. et al. ASH 2021, poster 2723

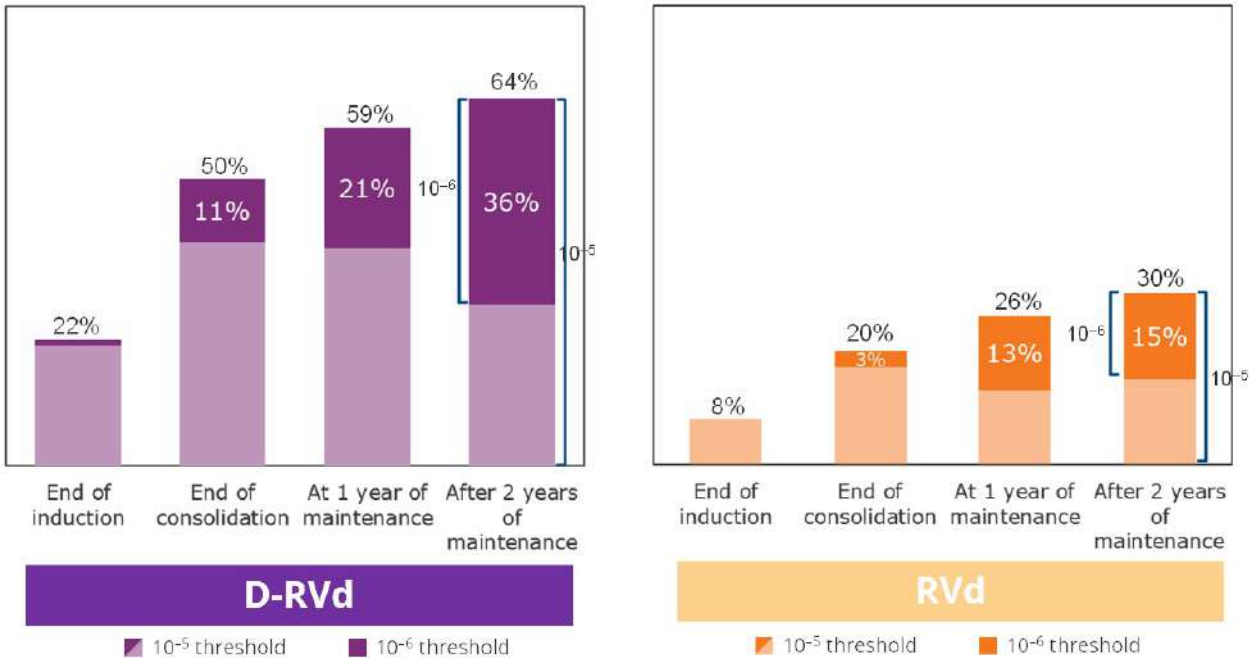
Responses Deepened Over Time:

Response rates for sCR and ≥CR were greater for D-RVd versus RVd at all time points, with the deepest responses occurring after 2 years of maintenance therapy

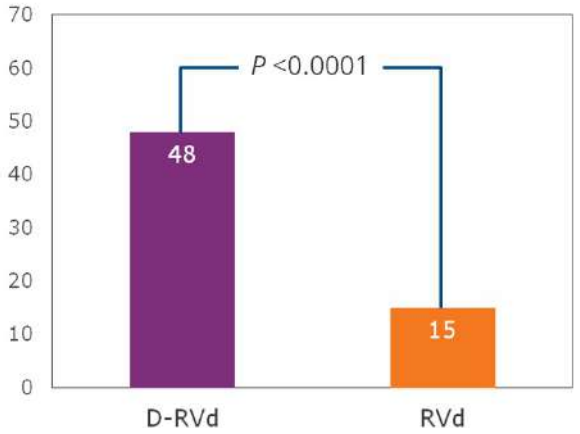


PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test. [c]Response rates are from the primary analysis cutoff (median follow-up: 13.5 mo), and the response-evaluable population included 196 patients (D-RVd, n = 99;

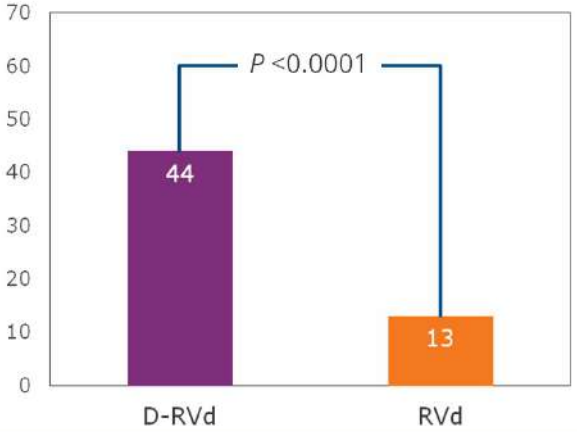
MRD-negativity Rates



Sustained MRD negativity lasting ≥6 months



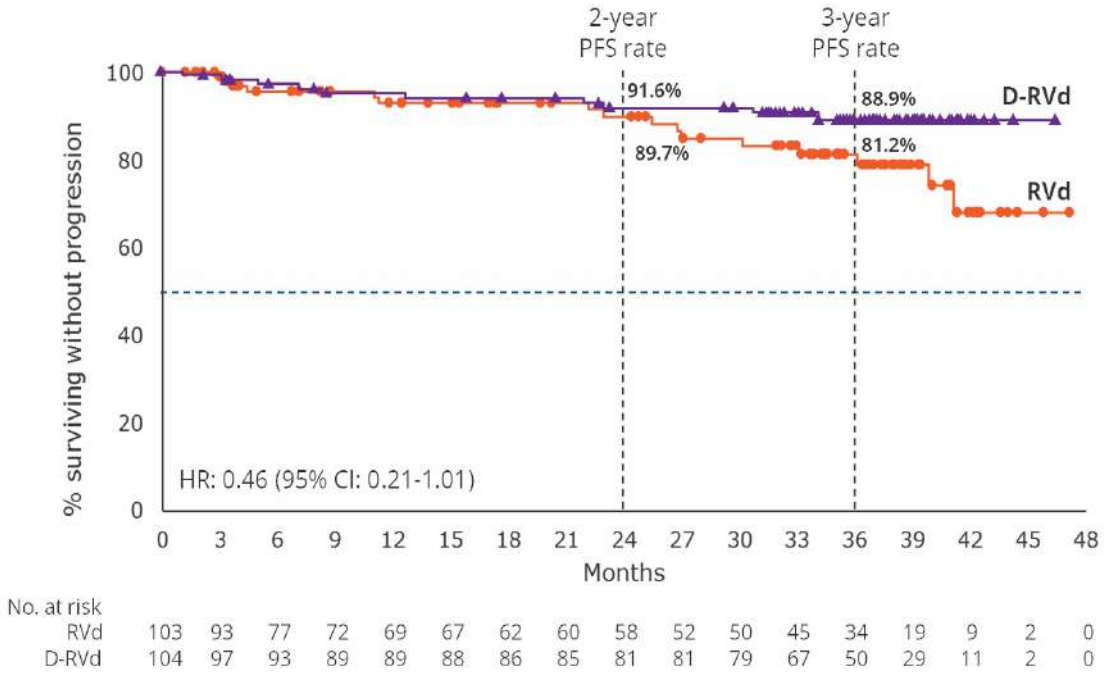
Sustained MRD negativity lasting ≥12 months



MRD-negative (10^{-5}) conversion rate

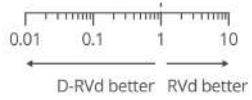
29% (15/52) of D-RVd pts and 12% (10/82) of RVd pts MRD positive at the end of consolidation became MRD negative after 2 years of DR or R maintenance

PFS in the ITT Population



Updated PFS after 24 months of maintenance therapy.

	Hazard ratio[a] (95% CI)	RVd n/N	RVd Median PFS (mo)	D-RVd n/N	D-RVd Median PFS (mo)	Hazard ratio[a] (95% CI)
Overall (ITT)		16/103	NR	10/104	NR	0.46 (0.21-1.01)
Age						
<65 years		11/75	NR	9/76	NR	0.63 (0.26-1.52)
≥65 years		5/28	NR	1/28	NR	0.14 (0.02-1.23)
ISS disease stage						
I		5/50	NR	5/49	NR	0.74 (0.21-2.57)
II		5/37	NR	4/40	NR	0.61 (0.16-2.27)
III		6/14	33.1	1/14	NR	0.13 (0.02-1.07)
Cytogenetic risk						
High risk		5/14	36.1	5/16	NR	0.59 (0.17-2.05)
Standard risk		10/83	NR	4/82	NR	0.32 (0.10-1.04)
Revised cytogenetic risk						
High risk		8/37	41.1	7/42	NR	0.55 (0.20-1.53)
Standard risk		7/60	NR	2/56	NR	0.25 (0.05-1.19)



The separation of the PFS curves begins beyond 1 year of maintenance and suggests a benefit of prolonged DR therapy

Safety profile and treatment discontinuation

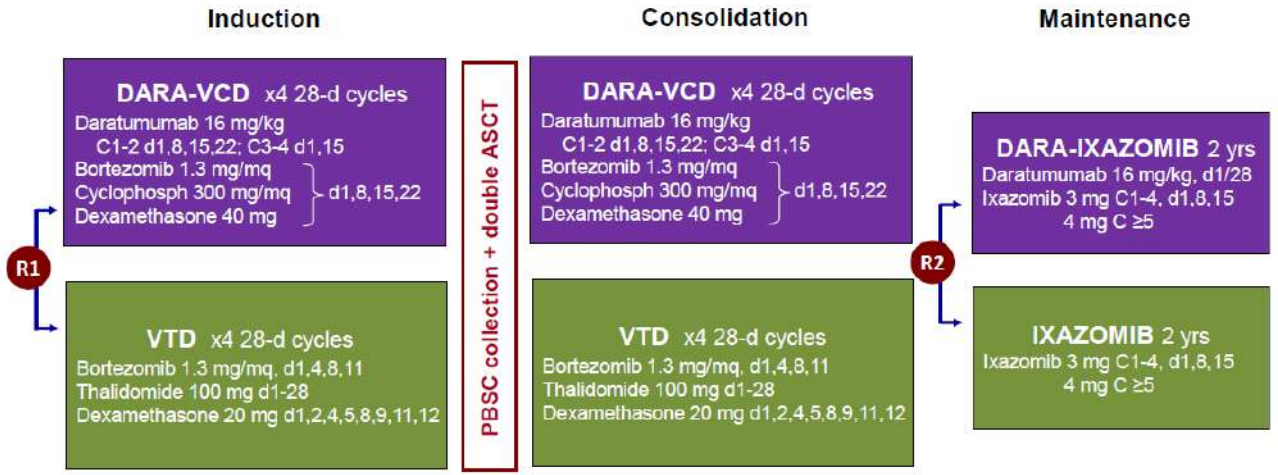
Patients, n (%)	D-RVd (n = 104)	RVd (n = 103)
Treated with maintenance therapy	90 (87)	70 (68)
Completed maintenance therapy	67 (64)	44 (43)
Discontinued maintenance therapy	**21 (20)**	**21 (20)**
Adverse event	8 (8)	7 (7)
Progressive disease	3 (3)	7 (7)
Patient withdrawal	2 (2)	4 (4)
Lost to follow-up	2 (2)	0
Death	1 (1)	1 (1)
Other	5 (5)	2 (2)

Infections and SPMs with first onset during maintenance

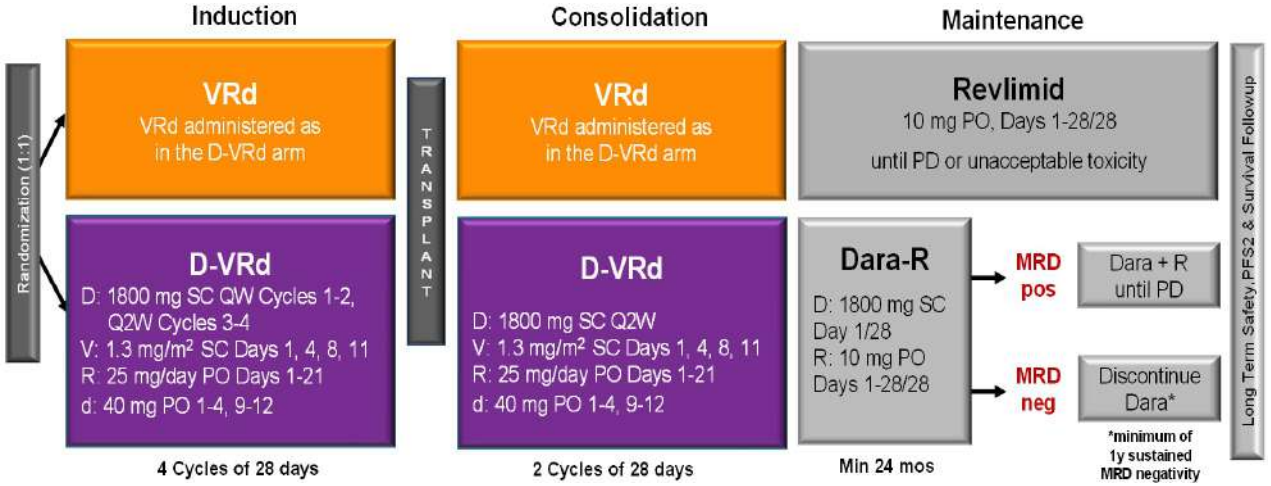
	D-VRd (n = 99)		VRd (n = 102)	
TEAE, % during maintenance	Any	Gr 3/4	Any	Gr 3/4
Overall infections	36	18	32	21
Most common infections				
- upper respiratory tract infection	53	2	41	3
- pneumonia	16	7	15	13
- urinary tract infection	11	0	3	0
- sinusitis	10	0	10	0
- influenza	10	0	7	0
- nasopharyngitis	10	0	3	0
- bronchitis	8	1	7	1
- cellulitis	8	1	3	1
Second primary malignancies	4	-	3	-
- squamous cell carcinoma (skin)	4		0	
- basal cell carcinoma	2		0	
- nasal cavity cancer	1		0	
- breast cancer	1		0	
- malignant melanoma in situ	0		1	
- nodular melanoma	0		1	
- uterine cancer	0		1	

ONGOING TRIALS

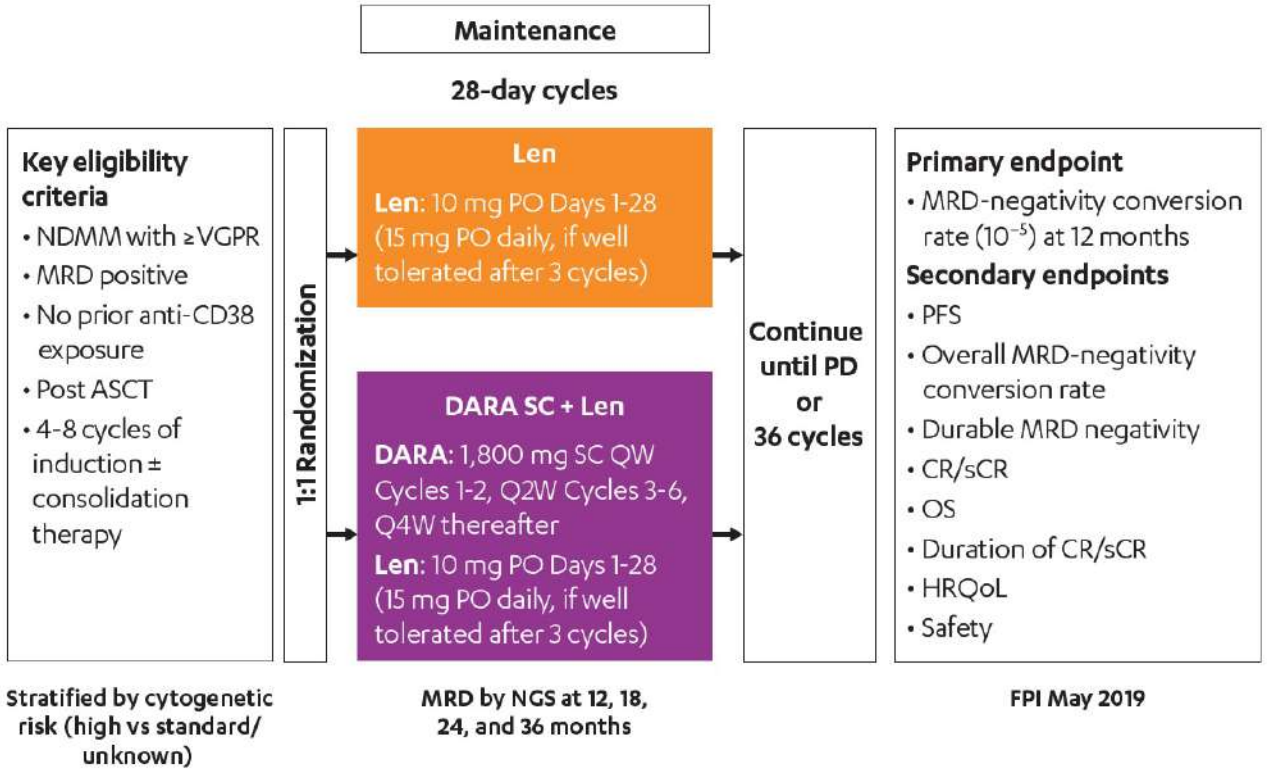
EMN18 phase 3 trial
(NCT03896737)



PERSEUS phase 3 trial
(NCT03710603)



AURIGA phase 3 trial
(NCT03901963)



Objective: to evaluate the conversion rate to MRD negativity after maintenance treatment with DARA SC plus len vs len alone in patients with NDMM who are MRD positive after ASCT

Shah et al., ASH 2019; abstract 1829

CLOSING REMARKS

- Improved PFS with carfilzomib-lenalidomide combination as maintenance treatment, but higher frequency of vascular/cardiac events; need for intravenous infusion
- Convenience of an all oral regimen, but no PFS benefits with IRd treatment, probably due to higher toxicity, leading to dose reductions or discontinuation of ixazomib
- Improved rate and depth of response for Dara-len combination, translating into prolonged PFS, but no data available from randomized trial
- Awaited results from ongoing trials