NOVEL COMBINATION THERAPIES IN NDMM – EVIDENCE FOR QUADRUPLETS

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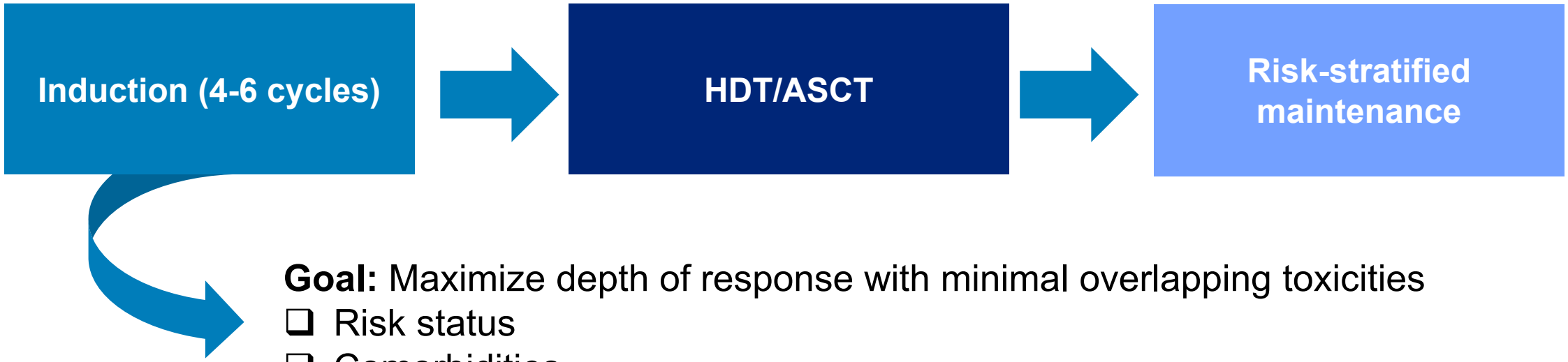
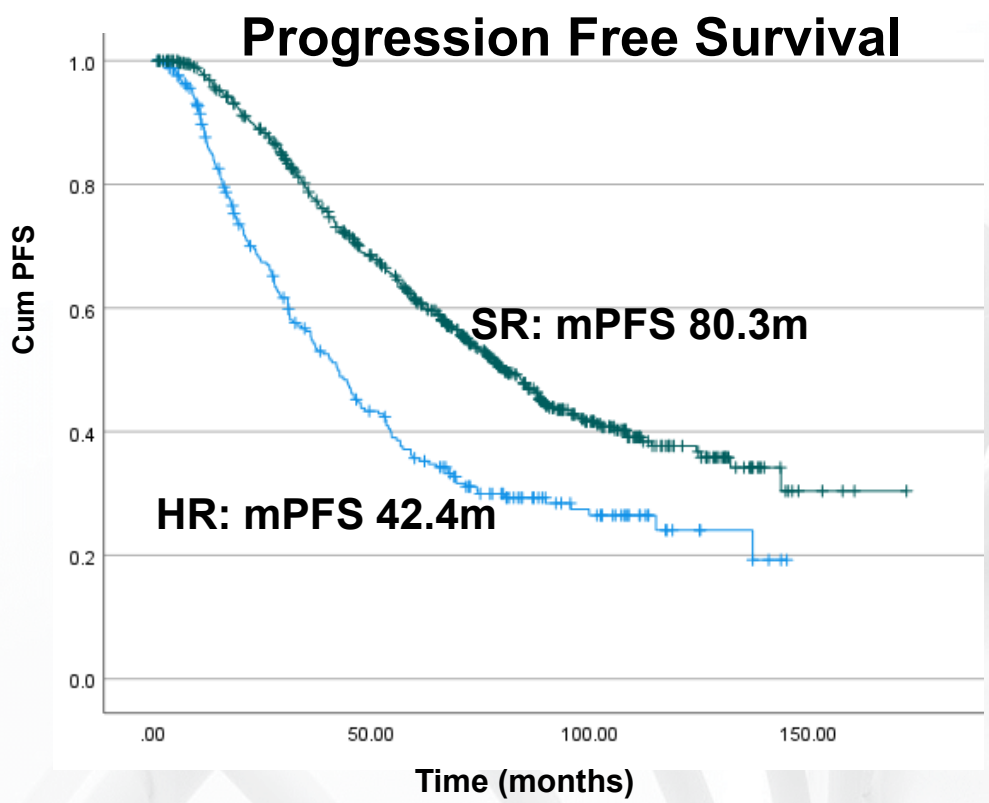
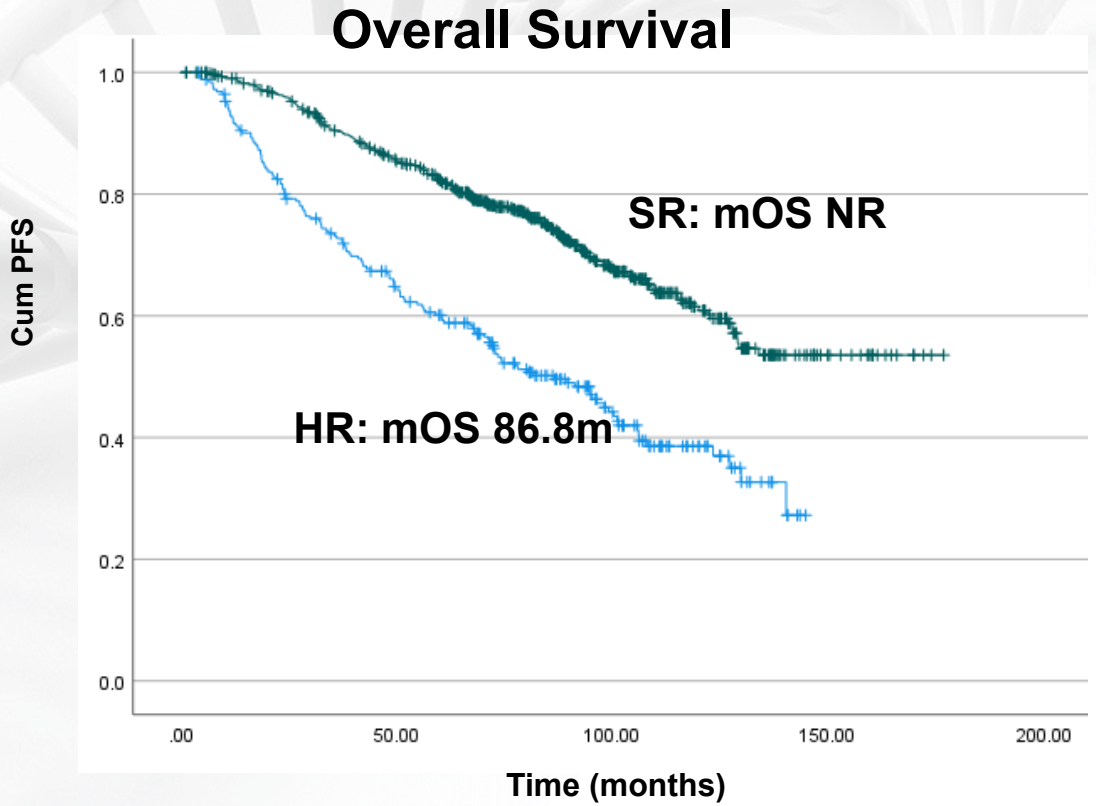
APPROACH TO NDMM: HOW DO WE OPTIMIZE DEPTH AND DURATION OF RESPONSE?



RVD 1000



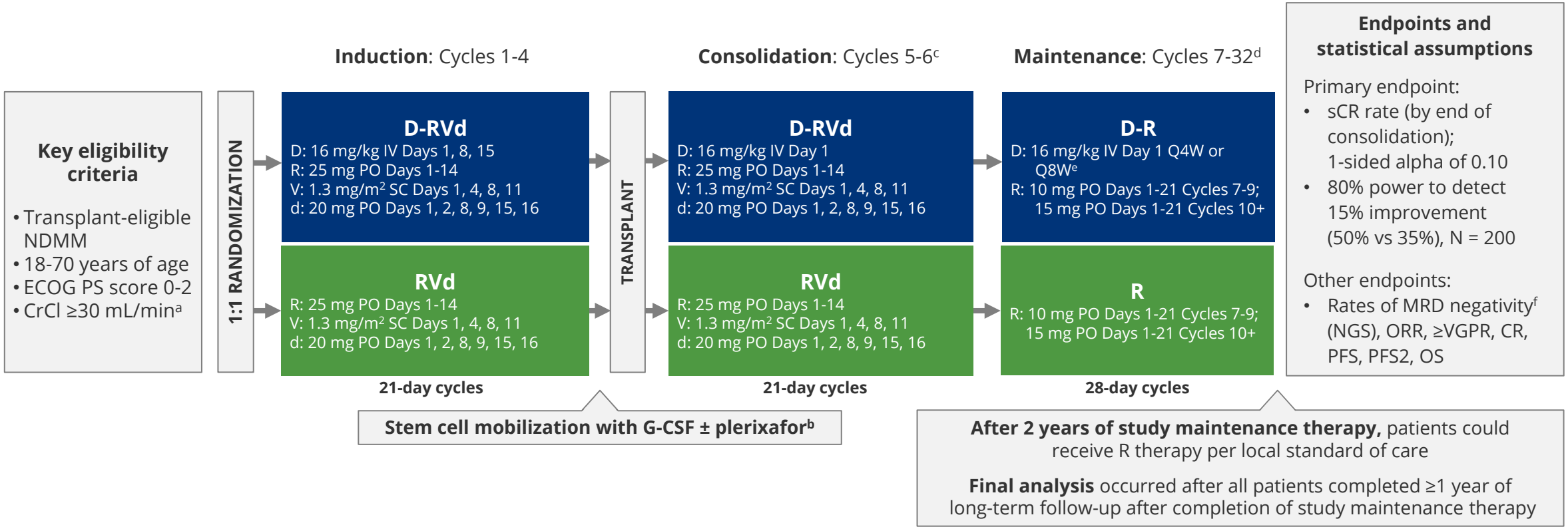


Median OS for the entire cohort was ~11 years

Parikh et al Abstract # 8061, ASCO 2022; Joseph et al JCO 2020

GRIFFIN: STUDY DESIGN

- 35 sites in the United States with enrollment between December 2016 and April 2018



ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; PO, oral; SC, subcutaneous; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab plus lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; NGS, next-generation sequencing; ORR, overall response rate; VGPR, very good partial response; CR, complete response; PFS, progression-free survival; PFS2, PFS on next subsequent line of therapy; OS, overall survival. [a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60 to 100 days post-transplant. [d]Patients who completed maintenance Cycles 7 to 32 were permitted to continue single-agent lenalidomide thereafter. [e]Protocol amendment 2 allowed for the option to dose DARA Q4W based on pharmacokinetic results from study SMM2001 (ClinicalTrials.gov Identifier: NCT02316106). [f]To measure MRD negativity at a minimum threshold of 10^{-5}, bone marrow aspirates were collected at first evidence of suspected CR or sCR (including patients with ≥VGPR and suspected DARA interference), after induction but before stem cell collection, at the post-transplant consolidation disease evaluation, and at 12 months and 24 months (±3 weeks) of maintenance therapy.

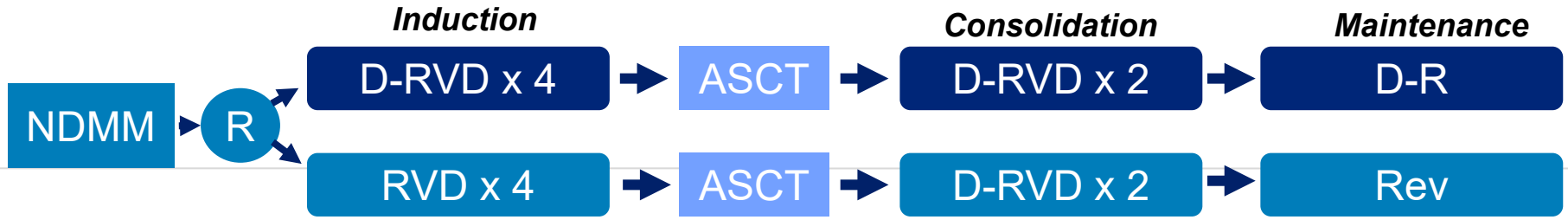
GRIFFIN: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

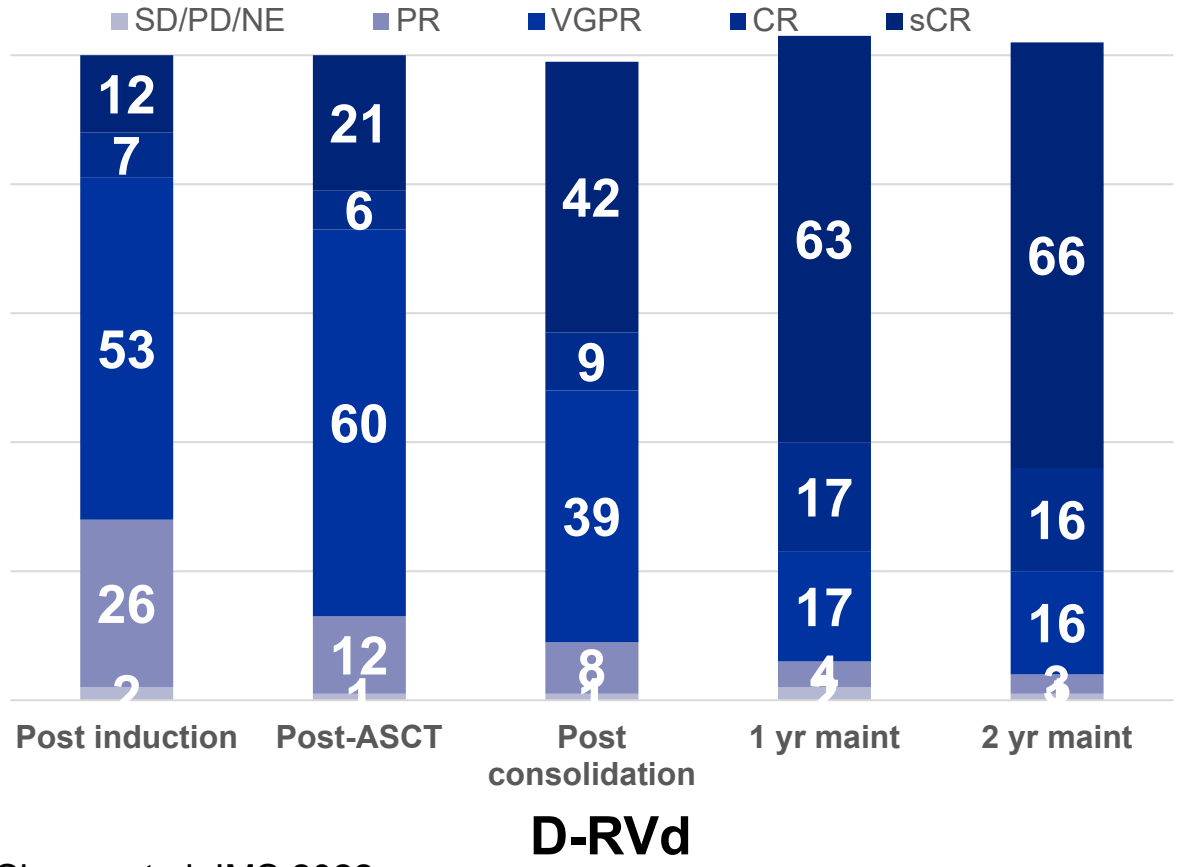
Characteristic	D-RVd (n = 104)	RVd (n = 103)
Age, years		
Median (range)	59 (29-70)	61 (40-70)
≥65, n (%)	28 (27)	28 (27)
Sex, n (%)		
Male	58 (56)	60 (58)
ECOG PS score, n (%)[a]		
0	39 (39)	40 (39)
1	51 (50)	52 (51)
2	11 (11)	10 (10)
Baseline CrCl, n (%)		
30-50 mL/min	9 (9)	9 (9)
>50 mL/min	95 (91)	94 (91)
ISS disease stage, n (%)[b]		
I	49 (47)	50 (49)
II	40 (38)	37 (36)
III	14 (13)	14 (14)
Missing	1 (1)	2 (2)

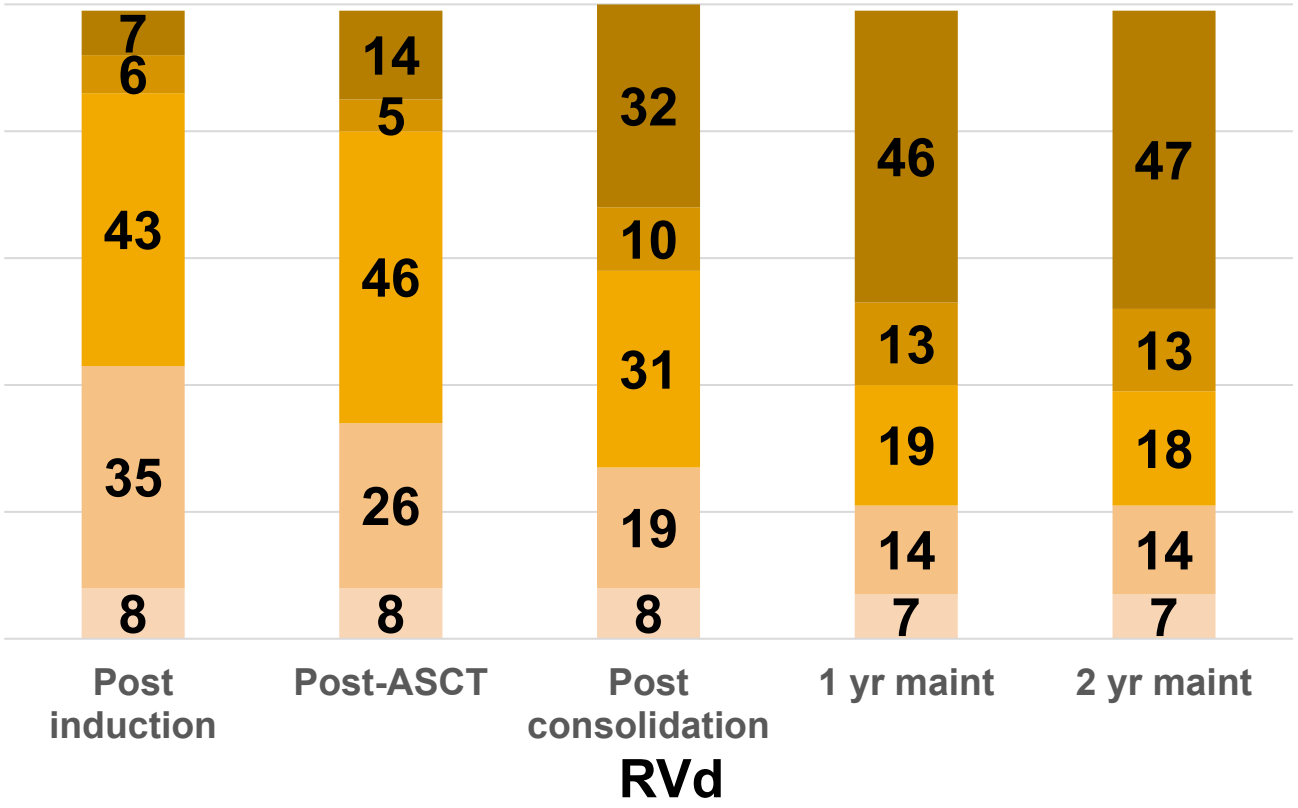
Characteristic	D-RVd (n = 104)	RVd (n = 103)
Cytogenetic risk profile, n (%)[c]		
Standard risk	82 (84)	83 (86)
High risk	16 (16)	14 (14)
del17p	8 (8)	6 (6)
t(4;14)	8 (8)	6 (6)
t(14;16)	1 (1)	3 (3)
Revised cytogenetic risk profile, n (%)[c]		
Standard risk	56 (57)	60 (62)
High risk	42 (43)	37 (38)
del17p	8 (8)	6 (6)
t(4;14)	8 (8)	6 (6)
t(14;16)	1 (1)	3 (3)
gain 1q	34 (35)	28 (29)
t(14;20)	1 (1)	1 (1)
Median time since MM diagnosis, months[d]		
Median	0.7	0.9

ITT, intent-to-treat; ISS, International Staging System; MM, multiple myeloma. [a]ECOG PS is scored on a scale from 0-5, with 0 indicating no symptoms and higher scores indicating increasing disability. Percentages based on evaluable patients (D-RVd, n = 101; RVd, n = 102). [b]The ISS disease stage is based on the combination of serum β2-microglobulin and albumin levels. Higher stages indicate more advanced disease. [c]Cytogenetic risk was assessed by fluorescence in situ hybridization (locally tested) among patients with available cytogenetic risk data among evaluable patients (D-RVd, n = 98; RVd, n = 97); high risk was defined as the presence of del17p, t(4;14), or t(14;16), while revised high risk was defined as the presence of del17p, t(4;14), t(14;16), t(14;20), or gain 1q (≥3 copies of chromosome 1q21) among those patients. [d]Data are based on evaluable patients (D-RVd, n = 103; RVd, n = 102).

GRIFFIN STUDY: RESPONSES DEEPENED OVER TIME



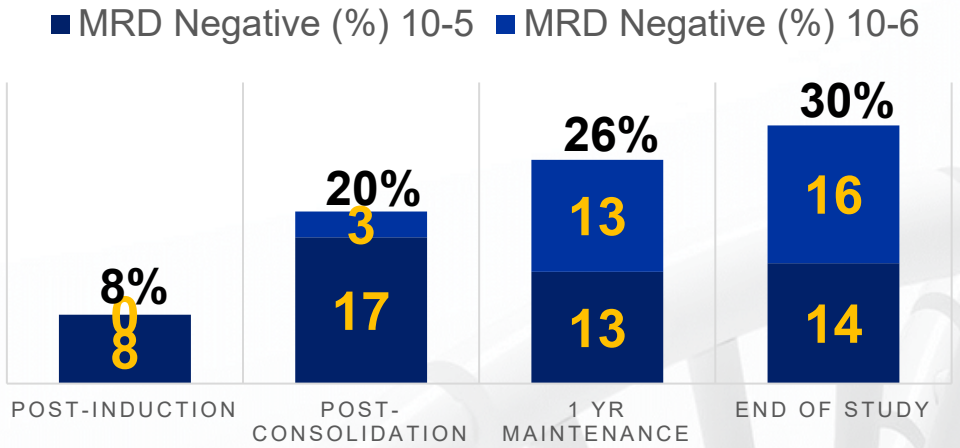




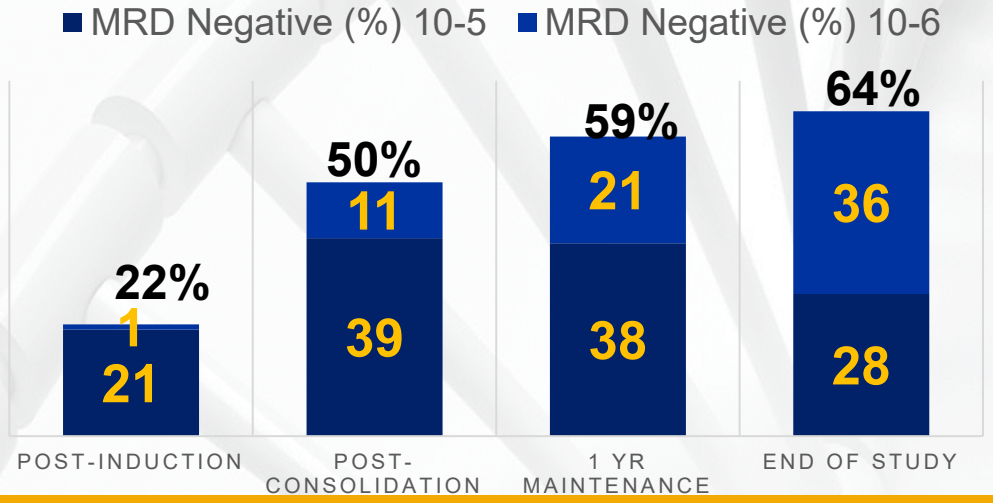
Sborov et al, IMS 2022

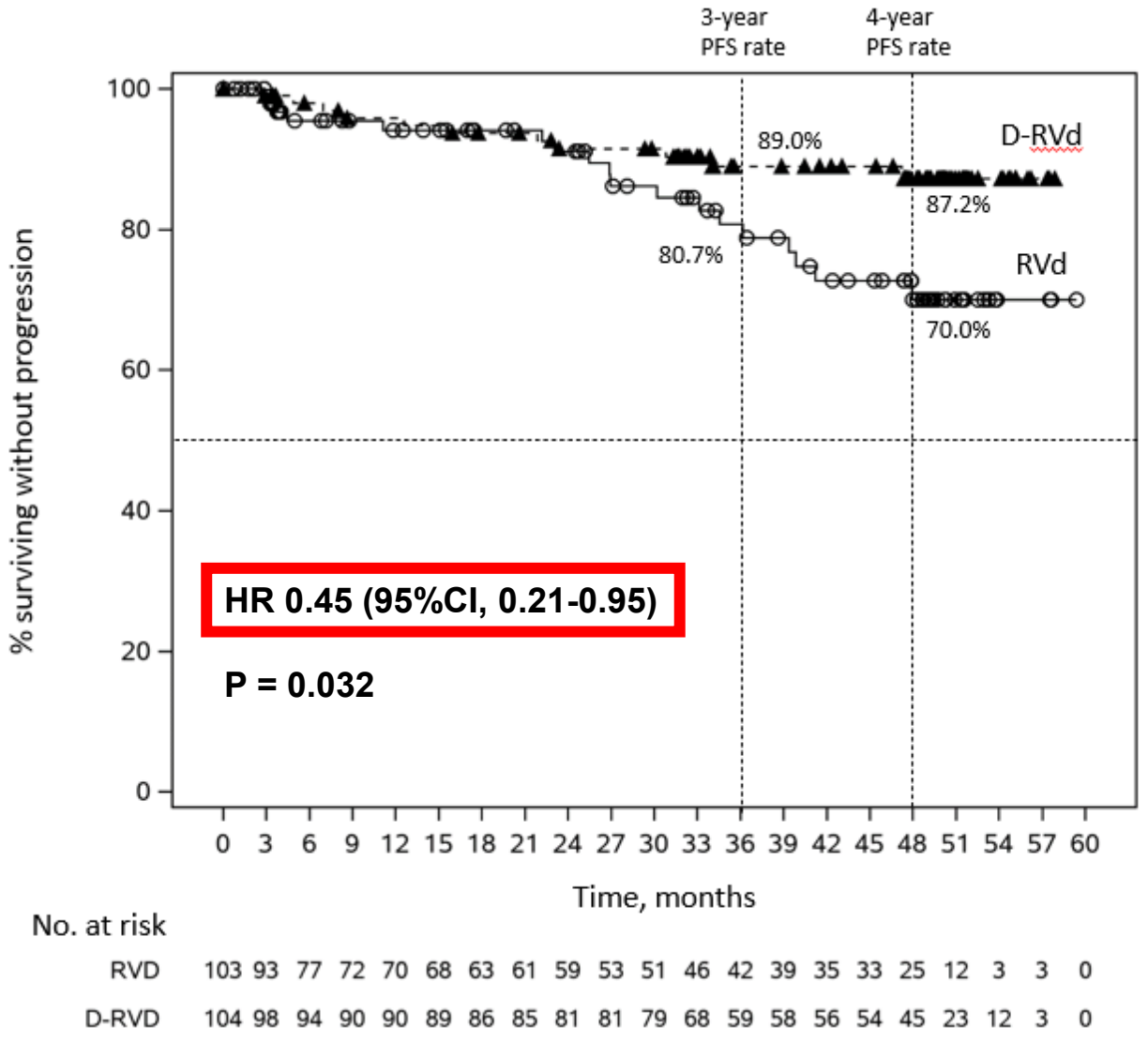
PHASE 2 GRIFFIN STUDY

RVD



D-RVD





GRIFFIN: MOST COMMON TEAES

Most common TEAEs, n (%)	D-RVd (n = 99)		RVd (n = 102)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Neutropenia	63 (64)	46 (46)	41 (40)	23 (23)
Thrombocytopenia	44 (44)	16 (16)	36 (35)	9 (9)
Leukopenia	39 (39)	17 (17)	30 (29)	8 (8)
Anemia	37 (37)	9 (9)	33 (32)	6 (6)
Lymphopenia	31 (31)	23 (23)	29 (28)	23 (23)
Nonhematologic				
Fatigue	71 (72)	7 (7)	63 (62)	6 (6)
Upper respiratory tract infection	67 (68)	4 (4)	51 (50)	2 (2)
Diarrhea	66 (67)	7 (7)	56 (55)	5 (5)
Peripheral neuropathy[b]	62 (63)	7 (7)	78 (76)	9 (9)
Cough	53 (54)	0	31 (30)	0

Most common TEAEs, n (%)	D-RVd (n = 99)		RVd (n = 102)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Nonhematologic (cont'd)				
Nausea	52 (53)	2 (2)	51 (50)	1 (1)
Constipation	51 (52)	2 (2)	42 (41)	1 (1)
Pyrexia	48 (48)	3 (3)	33 (32)	3 (3)
Insomnia	45 (45)	2 (2)	31 (30)	1 (1)
Back pain	41 (41)	2 (2)	36 (35)	3 (3)
Arthralgia	39 (39)	1 (1)	38 (37)	2 (2)
Peripheral edema	36 (36)	2 (2)	37 (36)	3 (3)
Headache	33 (33)	5 (5)	24 (24)	1 (1)
Vomiting	32 (32)	3 (3)	29 (28)	0
Muscle spasms	30 (30)	2 (2)	20 (20)	1 (1)
Dyspnea	24 (24)	2 (2)	31 (30)	5 (5)
Infusion-related reaction[c]	49 (49)	7 (7)	—	—

- Rates of TEAEs leading to treatment discontinuation were similar (D-RVd, 33%; RVd, 31%)
- TEAEs leading to death occurred in 1 patient in each group (neither related to study treatment)

TEAE, treatment-emergent adverse event. [a]Any grade TEAEs occurring in ≥30% of patients in either group are listed. The safety analysis population included all randomized patients who received ≥1 dose of the study treatment; analysis was according to treatment received. [b]Peripheral neuropathy includes the preferred terms of peripheral neuropathy and peripheral sensory neuropathy. [c]There were no grade 4 or 5 infusion-related reactions.

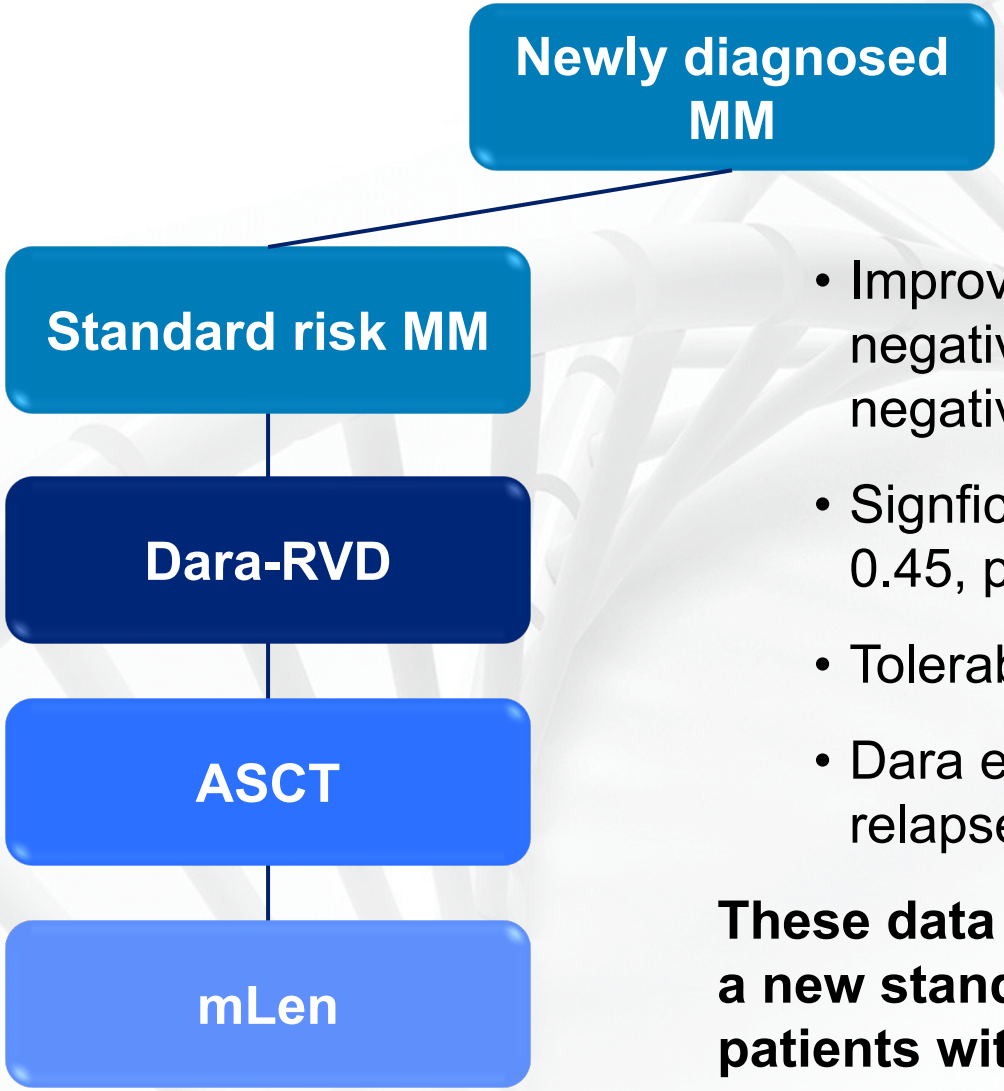
IMPROVING UPON RVD:
THE ROLE OF MONOCLONAL ANTI-CD38 AB IN NDMM

	Regimen	Depth of Response					
		Post-induction (%)		Post-ASCT (%)		Post-consolidation (%)	
		sCR	≥VGPR	sCR	≥VGPR	sCR	≥VGPR
CASSIOPEIA[1,2]	VTD	6.5%	56.1%	9.4%	67.4%	20.3%	78%
	Dara-VTD	7.4%	65%	13.4%	76.7%	29%	83.4%
GRIFFIN[3]	RVD	7%	56%	14%	66%	32%	73%
	Dara-RVD	12%	72%	21%	87%	42%	91%

		Post induction (%)				
		CR	≥VGPR	MRD (10-5) neg		
GMMG-HD7 [4]	RVD	22%	61%	36%		
	Isa-RVD	24%	77%	50%		

1. Moreau et al., Lancet, 2019;391(10192):29-38. 2. Moreau et al, Lancet 2021;10,P1378-1390; 3.Voorhees et al., Blood, 2020;136:936-945; 4. Goldschmidt et al, Lancet Hem 2022, 11, E810-821.

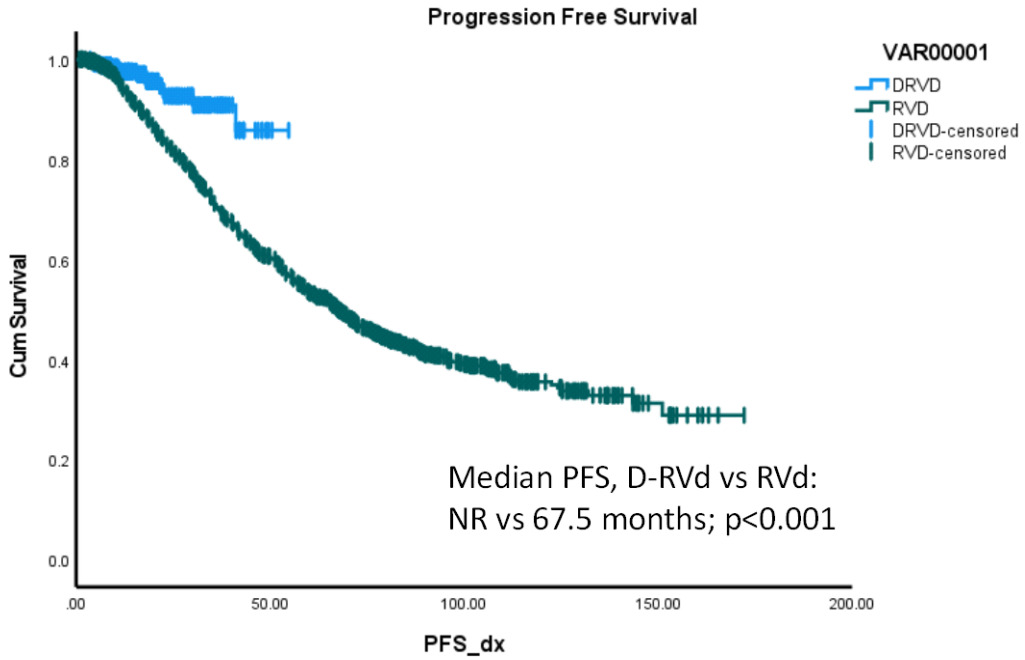
APPLYING GRIFFIN TO CLINICAL PRACTICE

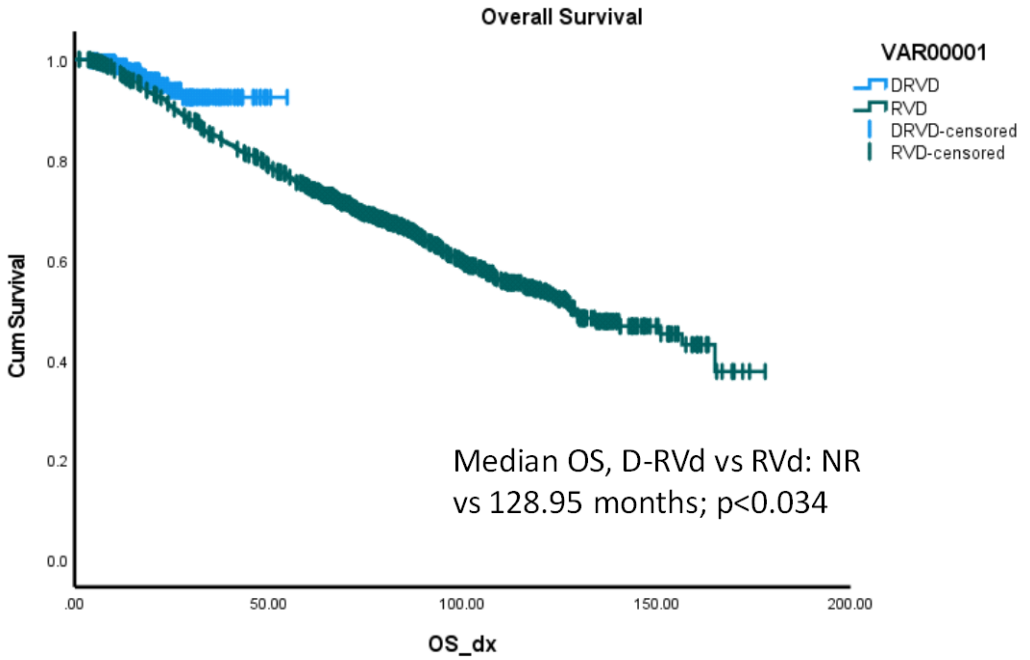


- Improved DOR and higher rates of MRD negativity favoring D-RVDTime to MRD negativity was shorter for D-RVd versus RVd
- Signficant PFS benefit at 4 year mark (HR 0.45, p=0.03)
- Tolerable AE profile
- Dara exposure does not preclude later use in relapsed disease

These data support the use D-RVd induction as a new standard of care in transplant-eligible patients with NDMM

DRVD VS RVD (EMORY)





1-year PFS, D-RVd vs RVd: 98% vs 93%
2-year PFS, D-RVd vs RVd: 93% vs 82%

1-year OS, D-RVd vs RVd: 99% vs 97%
2-year OS, D-RVd vs RVd: 94% vs 91%

Unpublished data. PLEASE DO NOT POST

2023 ASCO® ANNUAL MEETING

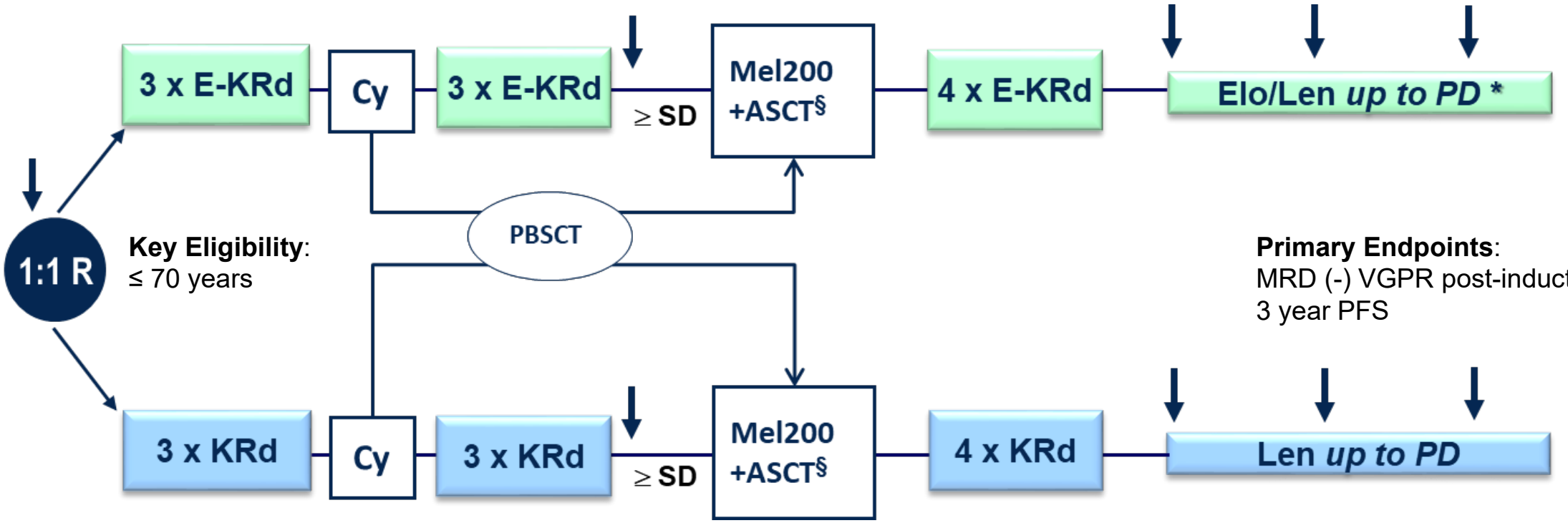
CARFILZOMIB, LENALIDOMIDE, AND DEXAMETHASONE (KRD) *VERSUS* ELOTUZUMAB AND KRD IN TRANSPLANT-ELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: POST-INDUCTION RESPONSE AND MRD RESULTS FROM AN OPEN-LABEL RANDOMIZED PHASE 3 STUDY

S Knop,[1] T Stuebig,[2] M Kull,[3] R Greil,[4] N Steiner,[5] F Bassermann,[6] A Nogai,[7] M von Lilienfeld-Toal,[8] S Janjetovic,[9] K Trautmann-Grill,[10] M Bittrich,[1] MM Engelhardt,[11] A Hoferer,[12] S Theurich,[13] M Binder,[14] N Zojer,[15] HA Duerk,[16] M Brueggemann,[17] S Held,[18] and H Einsele[1] on behalf of *Deutsche Studiengruppe Multiples Myelom*

[1]Wuerzburg University Medical Center, Wuerzburg, Germany; [2]Schleswig-Holstein University Hospital, Kiel Campus, Kiel, Germany; [3]Ulm University Hospital, Dept. of Internal Medicine 3, Ulm, Germany; [4]3rd Medical Department, Paracelsus Medical University; Salzburg Cancer Research Institute-CCCIT; Cancer Cluster Salzburg, Salzburg, Austria; [5]Medical University Innsbruck, Dept. of Internal Medicine V, Innsbruck, Austria; [6]University Hospital rechts der Isar, Munich, Germany; [7]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Medizinische Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie, Berlin, Germany; [8]Jena University Hospital, Dept. of Hematology and Oncology, Jena, Germany; [9]Helios Klinikum Berlin-Buch, Dept. of Hematology and Oncology, Berlin, Germany; [10]Department of Hematology and Oncology, Dresden University Hospital Carl Gustav Carus, Dresden, Germany; [11]University Hospital Medical Centre, Freiburg, Germany; [12]Robert Bosch Hospital, Dept. of Hematology and Oncology, Stuttgart, Germany; [13]Department of internal Medicine III, Hematology and Oncology, Gene Center, Cancer- and Immunometabolism Research Group, Ludwig-Maximilians University Munich, Mu, Munich, Germany; [14]Department of Internal Medicine IV, Oncology/Hematology, Martin-Luther-University Halle-Wittenberg, Halle, Germany; [15]Wilhelminen Cancer Research Institute, First Department of Medicine, Center for Oncology, Hematology, and Palliative Care, Clinic Ottakring, Vienna, Austria; [16]St Barbara Hospital Hamm, Dept. of Hematology and Oncology, Hamm, Germany; [17]Medical Department II, University Schleswig Holstein in the City Hospital Kiel, Kiel, Germany; [18]Clinassess GmbH, Leverkusen, Germany.

DSMM XVII Study: Elo-KRd versus KRd

Study Design; *N=576*



↓ MRD assessment by NGF (EuroFlow; 10exp-5 sensitivity) and NGS

* Elo maint. 20 mg/kg q28 days; § Tandem if no CR

Stefan Knop, MD

clinicaltrials.gov: NCT03948035

DSMM XVII STUDY: PATIENT CHARACTERISTICS

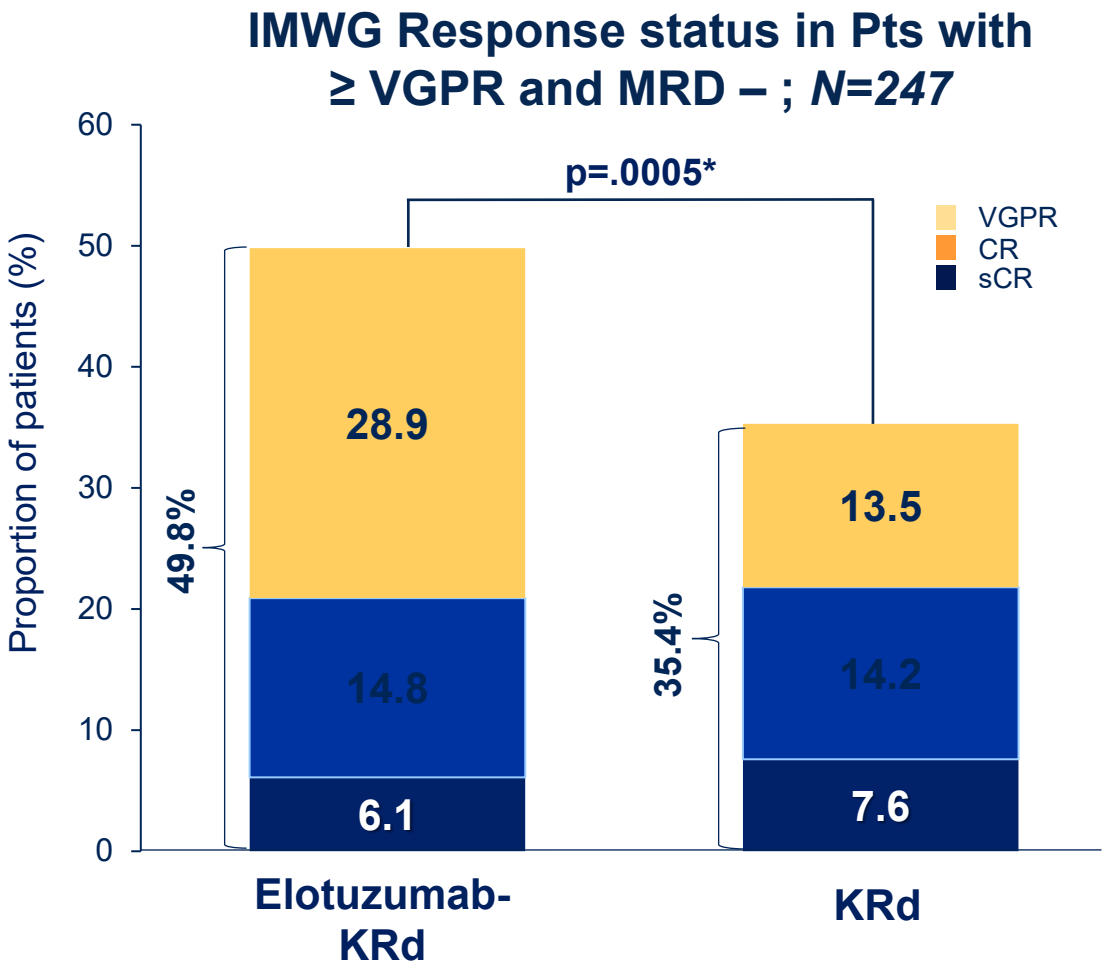
Recruitment Period: 08/2018 – 10/2021; *Data Cut-off: Jan 6, 2023*

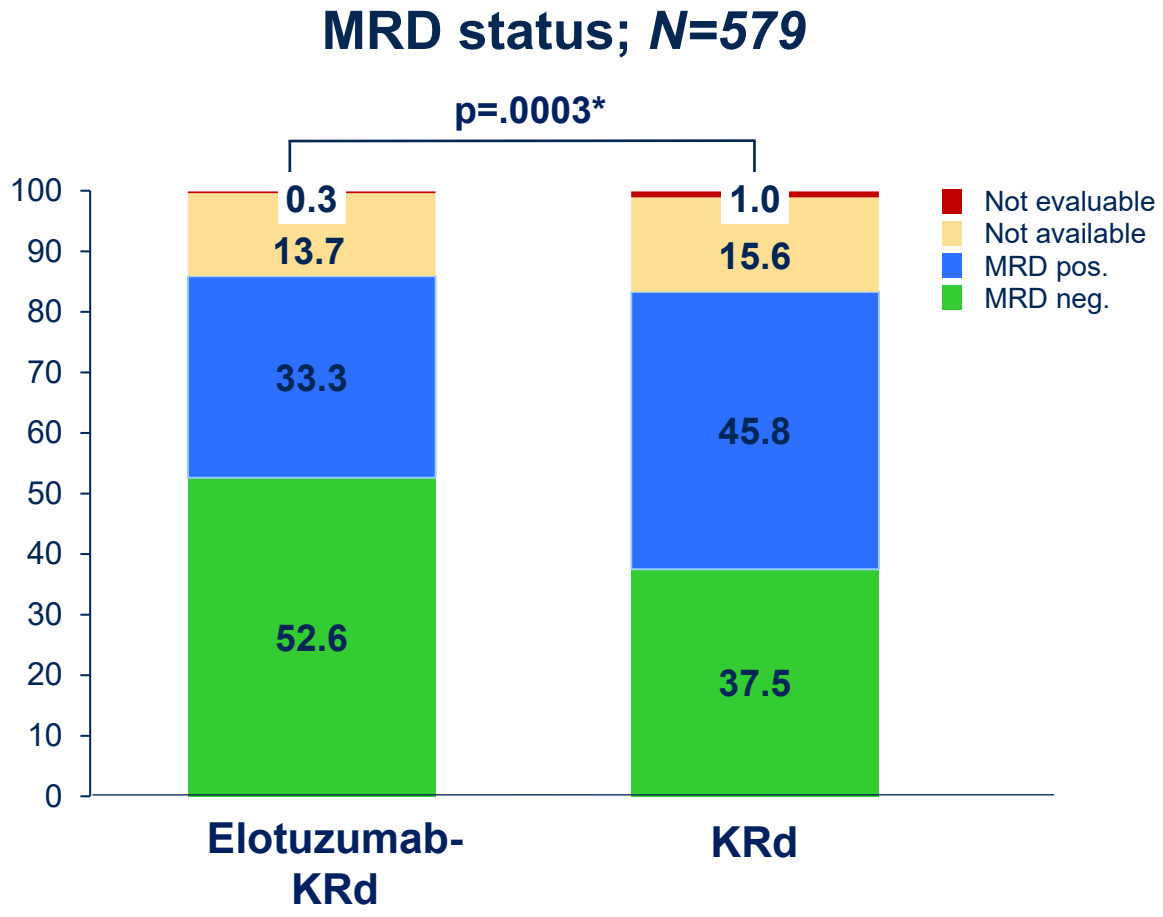
	Elo-KRd (N=291)	KRd (N=288)
Age, years		
Median (range)	58.7 (33-71)	57.9 (31-71)
Distribution, n (%)		
< 40	10 (3.4)	11 (3.8)
40 - 49	33 (11.3)	25 (12.2)
50 - 59	95 (32.6)	97 (33.3)
≥ 60	153 (52.5)	145 (50.4)
ECOG PS score[a], n (%)		
0	159 (54.6)	155 (53.8)
1	110 (37.8)	103 (35.8)
2	20 (6.9)	28 (9.7)
R-ISS Stage, n (%)		
I	96 (33.0)	89 (30.9)
II	118 (40.5)	130 (45.1)
III	25 (8.6)	27 (9.4)
n.a.	52 (17.8)	42 (14.5)

	Elo-KRd (N=291)	KRd (=288)
Type of myeloma, n (%)		
IgG	169 (58.0)	150 (52.1)
IgA	58 (19.9)	72 (24.7)
Light chain	60 (20.5)	61 (25.0)
Other	4 (1.4)	5 (1.7)
Cytogenetic profile, n/evaluable (%)		
+ 1q21	25/241 (10.4)	20/244 (8.2)
del17p	16/244 (6.5)	16/248 (6.4)
t(4;14)	21/240 (8.8)	26/248 (10.4)
t(14;16)	2/228 (0.8)	2/236 (0.7)
High-risk MM	56/227 (24.7)	52/232 (22.4)
Median interval since diagnosis (range), months	0.3 (0.0-208.7)	0.4 (0.0-102.5)

→ **91.6% of pts received all six cycles**

PRIMARY ENDPOINT: RESPONSE DETAILS





* Chi square; (2-sided, alpha=.0253)

DSMM XVII STUDY: ADVERSE EVENTS (AES)

Treatment-emergent AEs (TEAEs); Safety Population, *N=574*

	Elo-KRd, *N=288*				KRd, *N=279*			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
Any adverse event								
	78 (26.9%)	106 (36.5%)	106 (36.5%)	5 (1.7%)	102 (36.6%)	87 (31.2%)	90 (32.3%)	8 (2.8%)
Blood and lymphatic system disorders (preferred terms)								
Neutropenia	15 (5.2%)	23 (7.9%)	10 (3.4%)		20 (6.8%)	32 (8.1%)	10 (3.5%)	
Febrile neutropenia	9 (3.1%)	16 (5.5%)	2 (0.7%)		7 (2.5%)	7 (2.5%)	1 (0.4%)	
Thrombocytopenia	25 (8.6%)	32 (7.9%)	13 (4.5%)		22 (7.7%)	10 (3.5%)	20 (7.1%)	
Thrombotic microangiopathy	1 (0.3)	1 (0.3%)					1 (0.4%)	
Cardiac disorders (preferred terms)								
Myocardial infarction		1 (0.3%)	1 (0.3%)		1 (0.4%)		3 (1.1%)	
Cardiac arrest								1 (0.4%)
Cardiac failure	3 (1.0%)	5 (1.7%)			2 (0.7%)	5 (1.8%)	1 (0.4%)	
Atrial fibrillation	3 (1.0%)	4 (1.4%)			2 (0.7%)	4 (1.4%)	2 (0.7%)	
Gastrointestinal disorders (preferred terms)								
Diarrhea	66 (22.7%)	8 (2.7%)			58 (20.4%)	5 (1.8%)		
Constipation	54 (18.6%)	2 (0.7%)			47 (16.6%)			
Renal/urinary disorders (preferred terms)								
Acute kidney injury	7 (2.4%)	6 (2.1%)			3 (1.1%)	8 (2.8%)	3 (1.1%)	

TEAES; SAFETY POPULATION, *N=574*

	Elo-KRd, *N=288*				KRd, *N=279*			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
General disoders/administration site conditions (preferred terms)								
Chills	31 (10.7%)	1 (0.3%)			16 (5.7%)			
Pyrexia	114 (39.6%)	21 (7.2%)			68 (24.0%)	6 (2.1%)		
Infections and infestations (preferred terms)								
CMV reactivation	4 (1.4%)	2 (0.7%)			1 (0.4%)	1 (0.4%)		
COVID-19 infection	7 (2.4%)	5 (1.7%)		1 (0.3%)	8 (2.8%)			1 (0.4%)
Pneumonia *(various)*	8 (2.7%)	19 (6.6%)	1 (0.3%)		0	18 (6.4%)		1 (0.4%)
Sepsis/septic shock		2 (0.7%)	1 (0.3%)		1 (0.4%)	1 (0.4%)	3 (1.1%)	1 (0.4%)
Urinary tract infection *(various)*	19 (6.6%)	3 (1.0%)			7 (2.5%)	3 (1.1%)		
Metabolism and nutrition disorders (preferred terms)								
Hypophosphatemia	10 (3.4%)	11 (3.8%)	1 (0.3%)		9 (3.2%)	7 (2.5%)		
TLS	1 (0.3%)	1 (0.3%)	1 (0.3%)			1 (0.4%)	2 (0.7%)	
Nervous system disorders (preferred terms)								
Polyneurpathy	10 (3.4%)	2 (0.7%)			13 (4.6%)	1 (0.4%)		
Vascular disorders (preferred terms)								
Thrombosis *(various)*	20 (6.9%)	2 (0.7%)			12 (4.0%)	3(1.1%)		
Hypertension	22 (7.5%)	15 (5.2%)			27 (9.7%)	19 (6.7%)		
Skin and sucutaneous tissue disorders (preferred terms)								
Rash *(various)*	73 (25.3%)	16 (5.5%)			73 (26.1%)	11 (4.0%)		

Conclusions

- First positive randomized study for Elo in NDMM
- Met first co-primary endpoint : Higher ≥ VGPR + MRD negativity rate (49.8% vs 35.4%) post induction
- Manageable safety profile in fit patients up to 70 years

Is this practice changing data?

- ❑ Shows utility of quad vs triplet for NDMM induction (Dara)
- ❑ What is the optimal backbone?

IFM 2018-04 phase 2 study design

Key inclusion criteria:

- Age < 66
- **Newly diagnosed multiple myeloma**
- **Transplant-eligible**
- **High-risk FISH :** t(4;14), 17p del, t(14;16)
- ECOG 0-2

Objectives:

- **Primary Objective :**
  Feasibility (endpoint : >70% patients completed 2nd transplant)
- **Secondary Objectives:**
  Safety, ORR, PFS, OS, stem-cell collection

Induction Dara-KRd x 6	Stem cell collection	ASCT #1	Consolidation Dara KRd x 4	ASCT #2	Maintenance Dara Len 2 years
Dara : 16 mg/kg IV D1,8,15,22 (cycle 1 - 2) D1 D15 (Cycle 3 to 6) **K : (20)36 mg/m2 IV** D1-2, 8-9, 15-16 **Len : 25 mg** D1-21 **Dex : 20 mg** D1-2,8-9,15-16,22-23 **28-day cycles**	Cyclo GCSF +/- Plerix	**Mel 200**	**Dara : 16 mg/kg IV** D1 D15 **K : 56 mg/m2 IV** D1, 8, 15 **Len : 15 mg** D1-21 **Dex : 40 mg** D1, 8, 15, 22 **28-day cycles**	**Mel 200**	**Dara** : 16 mg/kg IV every 8 weeks **Len** : 10 mg 21/28

PRESENTED BY:
Cyrille Touzeau

Patient characteristics

	N=50
Median age (range), years	57 (38-65)
ECOG PS	
0-1	47 (94%)
2	3 (6%)
ISS score	
stage 1	21 (42%)
stage 2	17 (34%)
stage 3	12 (24%)
R-ISS score	
stage 2	38 (76%)
stage 3	12 (24%)

	N=50
High-risk (HR) cytogenetics	50 (100%)
17p deletion	20 (40%)
t(4;14)	26 (52%)
t(14;16)	10 (20%)
1q gain	25 (50%)
2 HR cytogenetic abnormalities *	34 (68%)

* defined by the presence of 2 HR abnormalities among 17p del, 1q gain, t(4;14), t(14;16)

Dara-KRd induction : Safety

Hematologic treatment related AE:

	Any grade N (%)	Grade 3/4 N (%)
Neutropenia	22 (44%)	20 (40%)
Anemia	14 (28%)	7 (14%)
Thrombocytopenia	13 (26%)	4 (8%)

AE leading to treatment discontinuation (n=2)
- COVID-19 infection (n=1)
- tumor lysis syndrome (n=1)

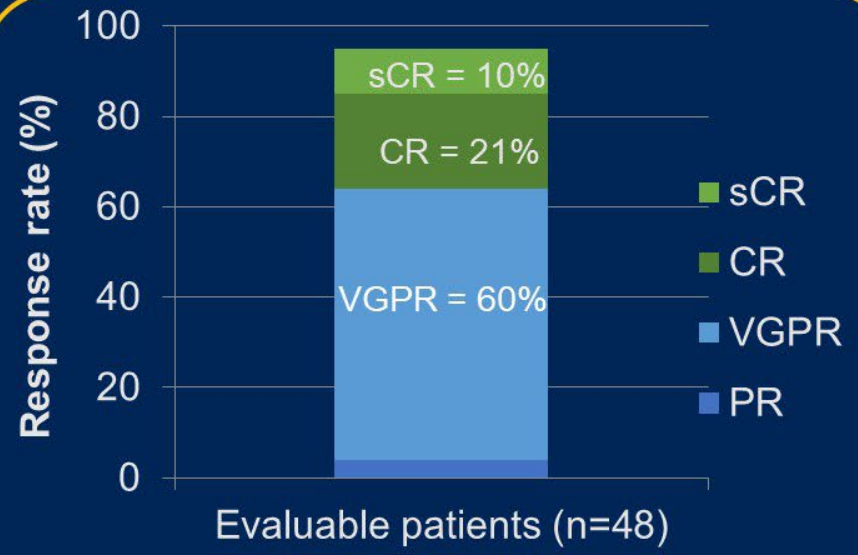
Grade 3/4 infection (n=3)
- COVID 19 infection (n=1)
- CMV infection (n=1)
- Pseudomonas aeruginosa bacteriemia (n=1)

Most common non hematologic treatment related AE:

	Any grade N (%)	Grade 3/4 N (%)
GI disorders	23 (46%)	2(4%)
Infection	20 (40%)	3 (6%)
Skin rash	8 (16%)	0
Deep-vein thrombosis	7 (14%)	3 (6%)
Peripheral neuropathy	6 (12%)	0
Hepatic cytolysis	4 (8%)	2 (4%)
Renal failure	3 (6%)	3 (6%)
Cardiac event	1 (2%)	0

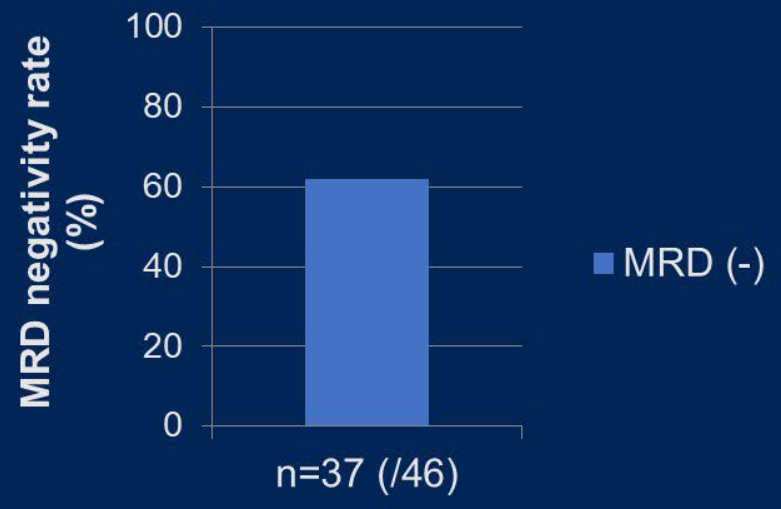
Dara-KRd induction : Response rates and MRD

Response Rate



ORR= 96%
CR/sCR rate = 31%
≥VGPR rate = 91%

MRD negativity (NGS, 10-5)



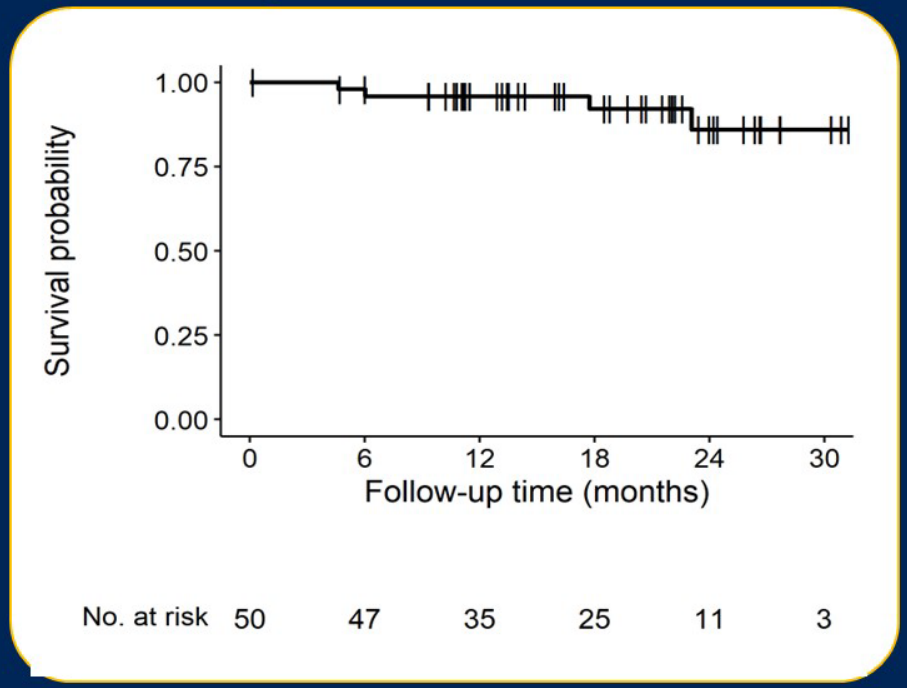
MRD negativity rate (NGS, 10-5) : 62%

Progression-free and overall survival

Median follow-up : 19.4 months

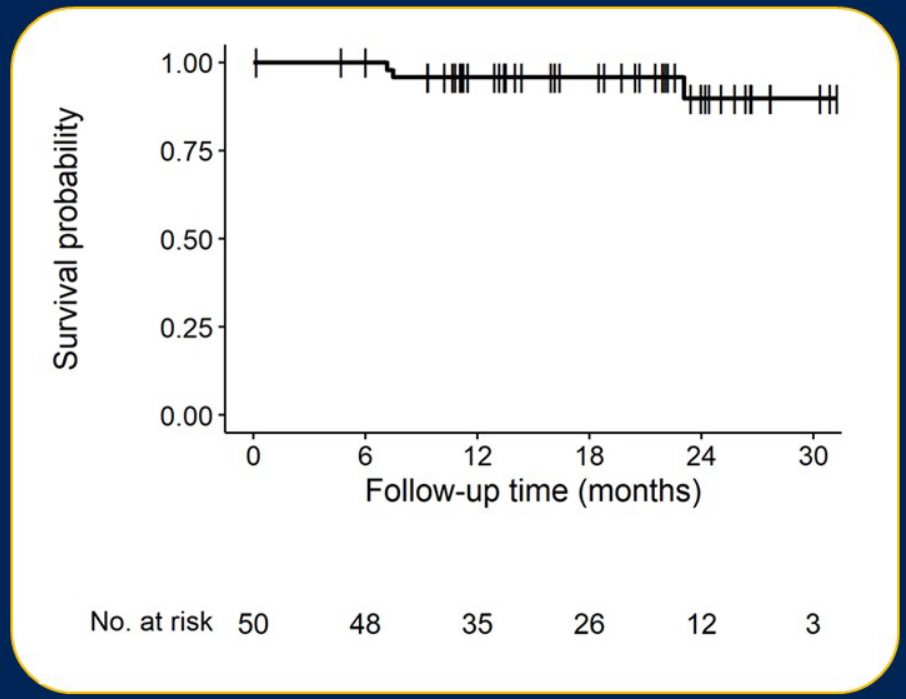
Data cut-off: april 25 2022

Progression-free survival

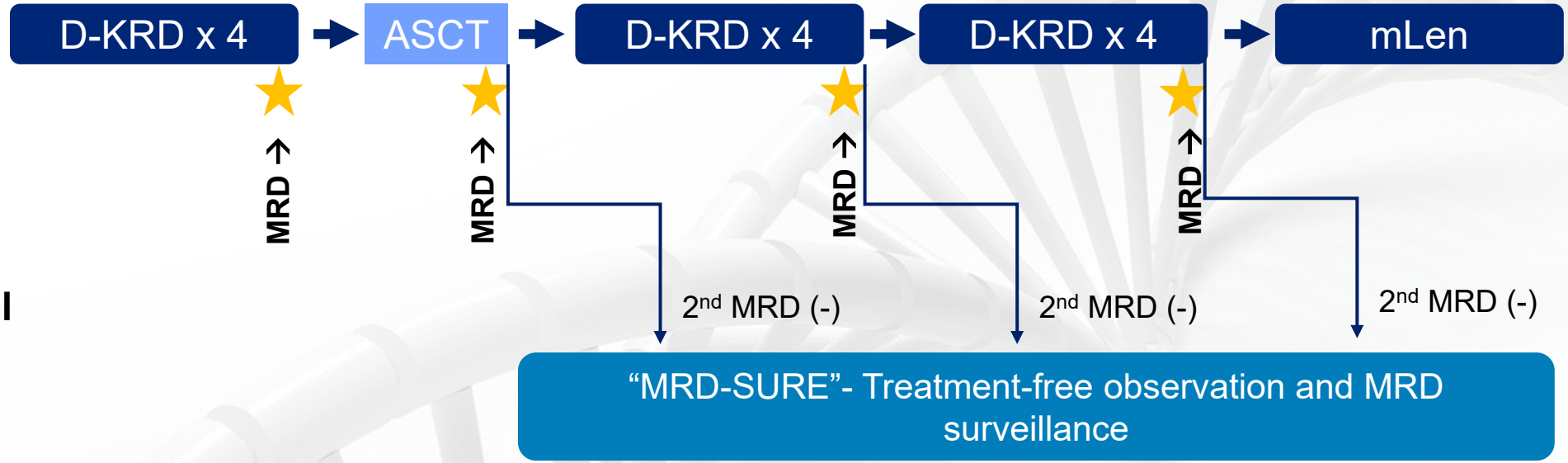


12-month PFS : 96% (90% - 100%)
18-month PFS : 92% (84% - 100%)

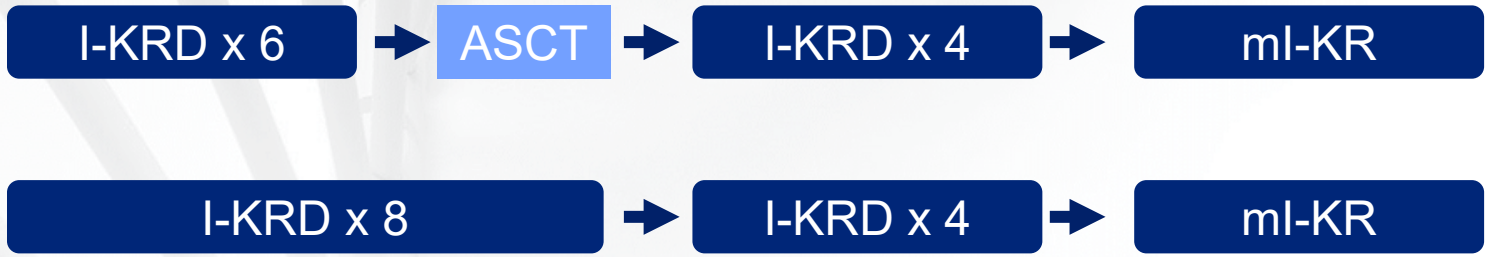
Overall Survival



12-month OS : 96% (90% - 100%)
18-month OS : 96% (90% - 100%)



MASTER trial
Costa et al.



GMMG-CONCEPT trial
Leypoldt et al.

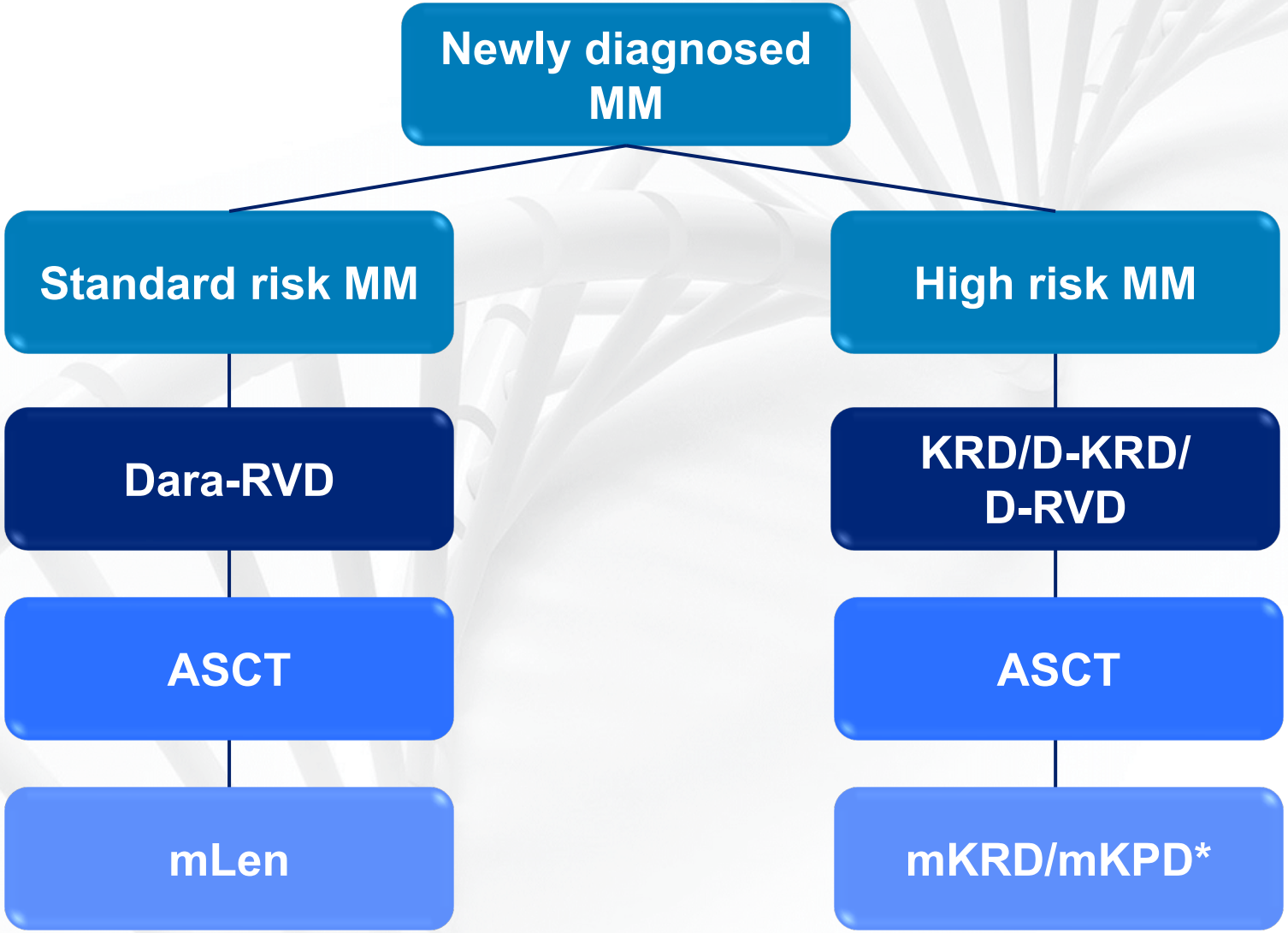
MONOCLONAL ANTIBODIES IN HIGH RISK MM

Trial	Regimen	Ph	n	mFU	Response Rates			MRD neg	PFS
					≥CR	≥VGPR	ORR		
IFM 2018-04[1]	D-KRD	2	50	19.4m	31%	91%	96%	62%	18 month PFS 92%
GMMG-CONCEPT[2]	Isa-KRD	2	50	24.9m	46%,	90%	100%	62.5%	2y PFS 75.5%
MASTER [3, 5]	D-KRD	2	70	25.1m	89%/ 71%*			79%/ 62%*	3y PFS 79%/50%*
GRIFFIN [4]	D-RVD	2	47	49.6m	79%/ 62%*			56%/ 62%*	2y PFS 94%/64%*

1. Touzeau et al, ASH 2022; 2. Leypoldt et al *Leuk* 2022; 3. Costa et al, *JCO* 2022; 4. Callander et al, ASH 2022;
5. Costa et al EHA 2023

*1 HR feature/ ≥2 HR features

TREATMENT ALGORITHM FROM TE-NDMM



Nooka et al, Leuk 2014
Nooka et al, ASCO 2023

THANK YOU!

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