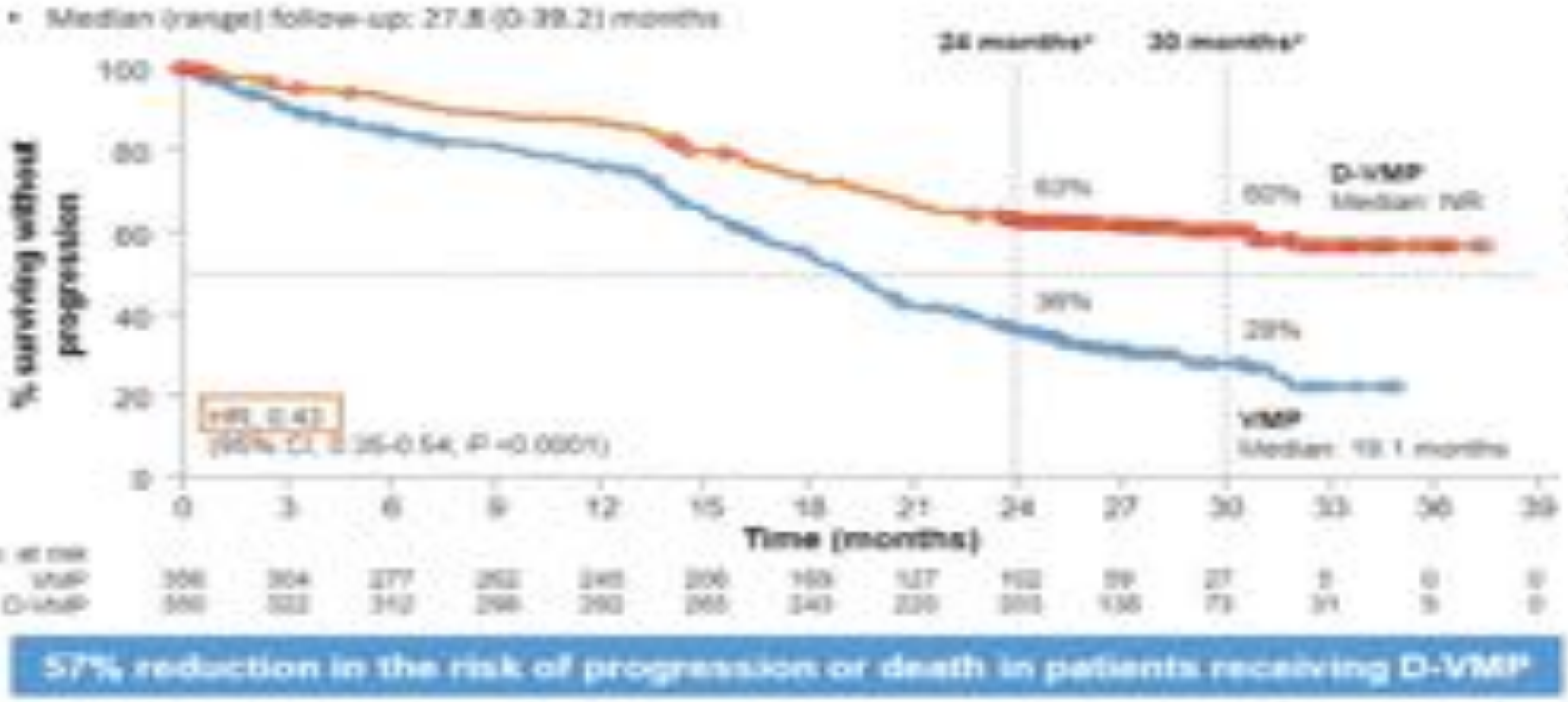
Highlights from IMW 2019

Francesco Di Raimondo

Terapia di prima linea senza trapianto autologo del paziente fit con regimi comprensivi di anticorpi monoclonali

Overview of mPFS in recent phase 3 trials in transplant-ineligible NDMM

ALCYONE D-VMP versus VMP efficacy: PFS



Grade 3/4 AEs of interest with D-VMP*

- Neutropenia (40%), thrombocytopenia (34%), anaemia (16%), infections (23%)

57% reduction in the risk of progression or death in patients receiving D-VMP*

*Kaplan-Meier estimate

Dimopoulos M, et al. Blood. 2019;133:106. Presented at ASH 2018.
Mateos MV, et al. New Engl J Med. 2018;378:518-28.

MAIA: DRd vs Rd efficacy: PFS

Grade 3/4 AEs of interest with D-Rd
- Neutropenia (50%), leukopenia (13%), anaemia (12%), lymphopenia (15%), infections (32%)

45% reduction in the risk of progression or death in patients receiving D-Rd

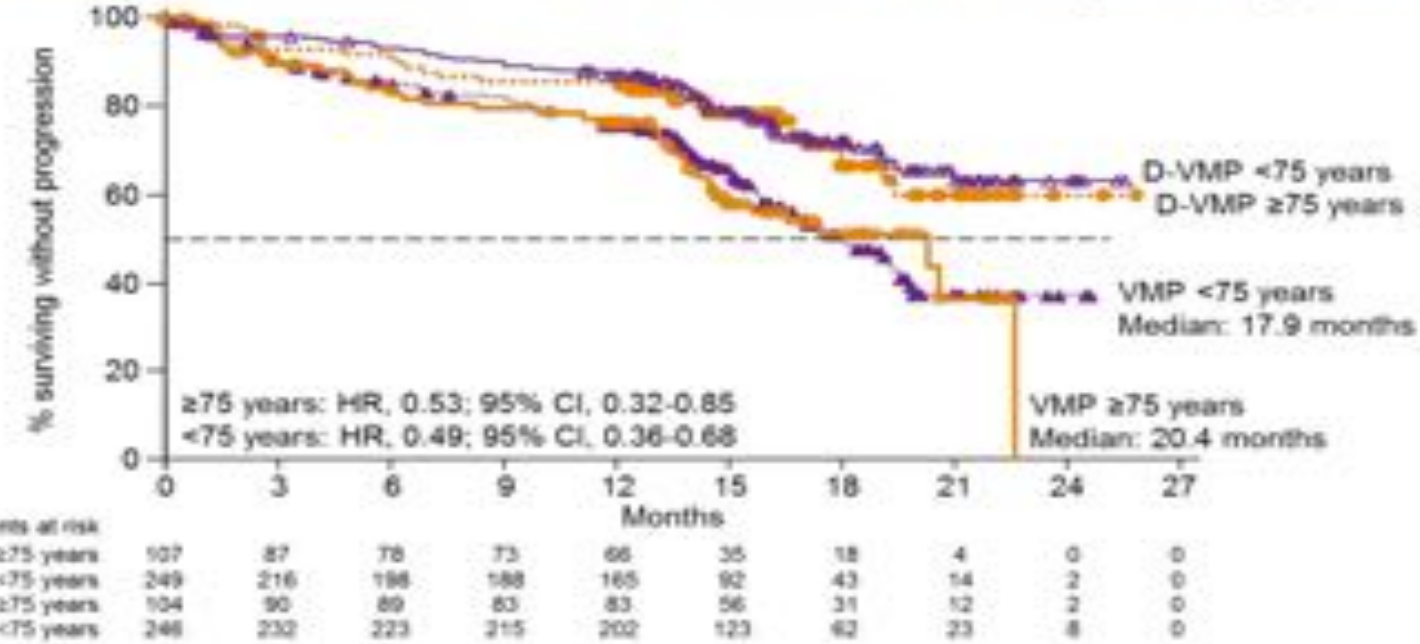
*Kaplan-Meier estimate

Facon T, et al. Blood. 2019;133(Libl.1. Presented at ASH 2018.
Facon T, et al. N Engl J Med. 2019;380:2104-15.

Also in a 75-year old patient

ALCYONE Study

Also in the MAIA study no impact of age was observed



18-month PFS, %[a]	D-VMP	VMP
≥75 years	71	51
<75 years	72	50

Mateos MV et al. N Engl J Med 2018;378:518-28
Usmani SZ, et al., ASCO 2019; abstract 8035, oral presentation

CI, confidence interval; D, daratumumab; HR, hazard ratio; PFS, progression-free survival; VMP, bortezomib-melphalan-prednisone.

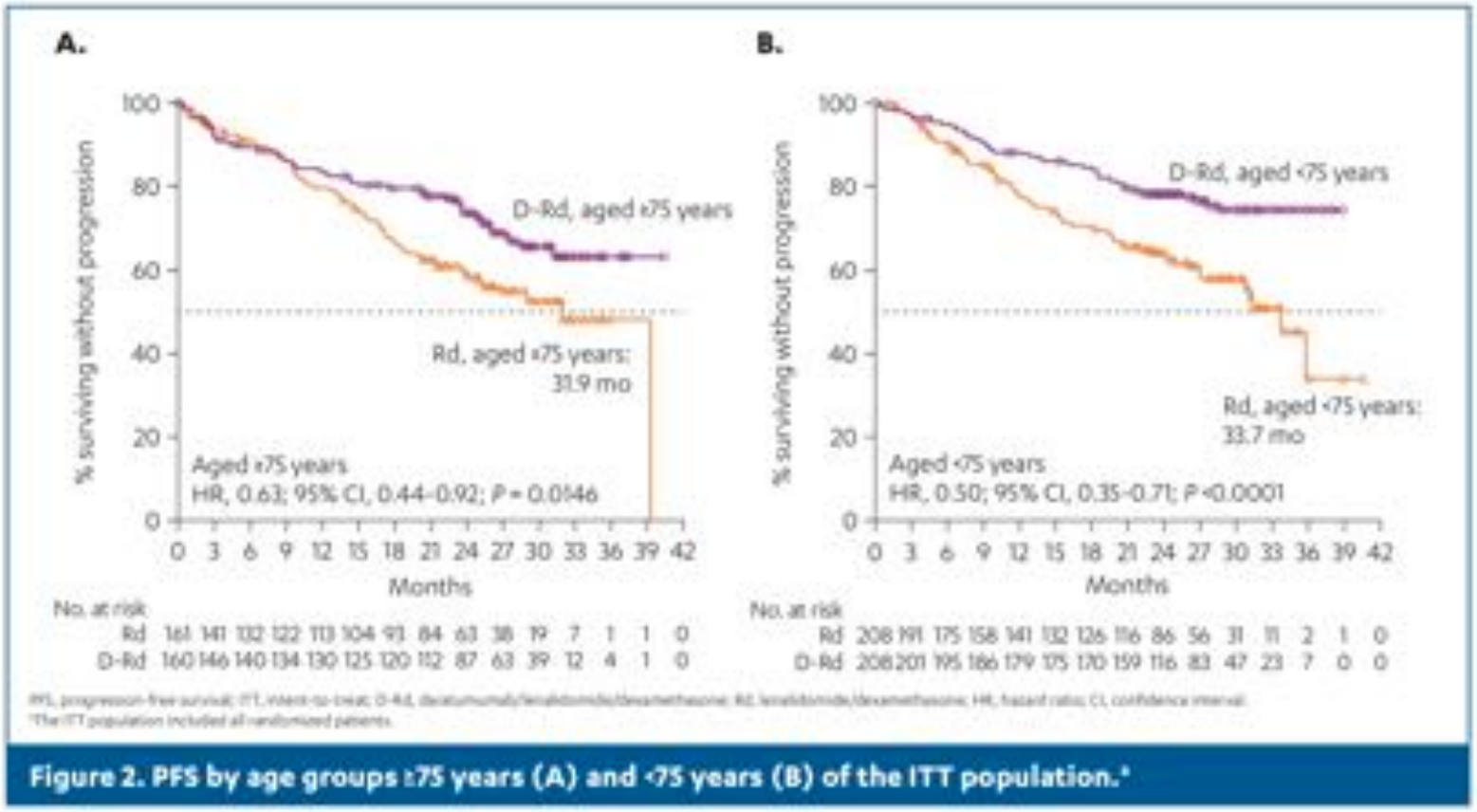


Figure 2. PFS by age groups ≥75 years (A) and <75 years (B) of the ITT population.[a]

Hulin C, EHA. 2019

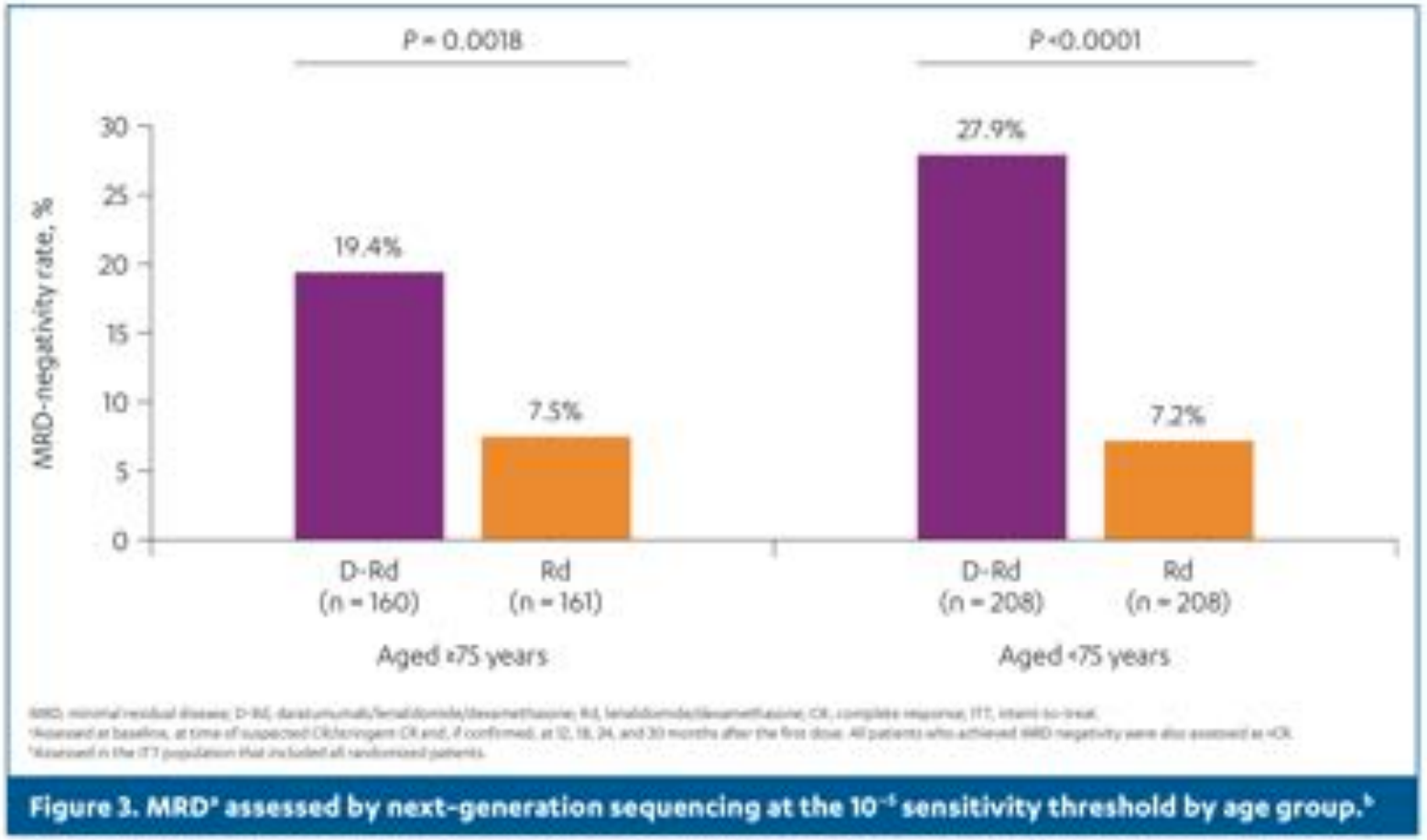
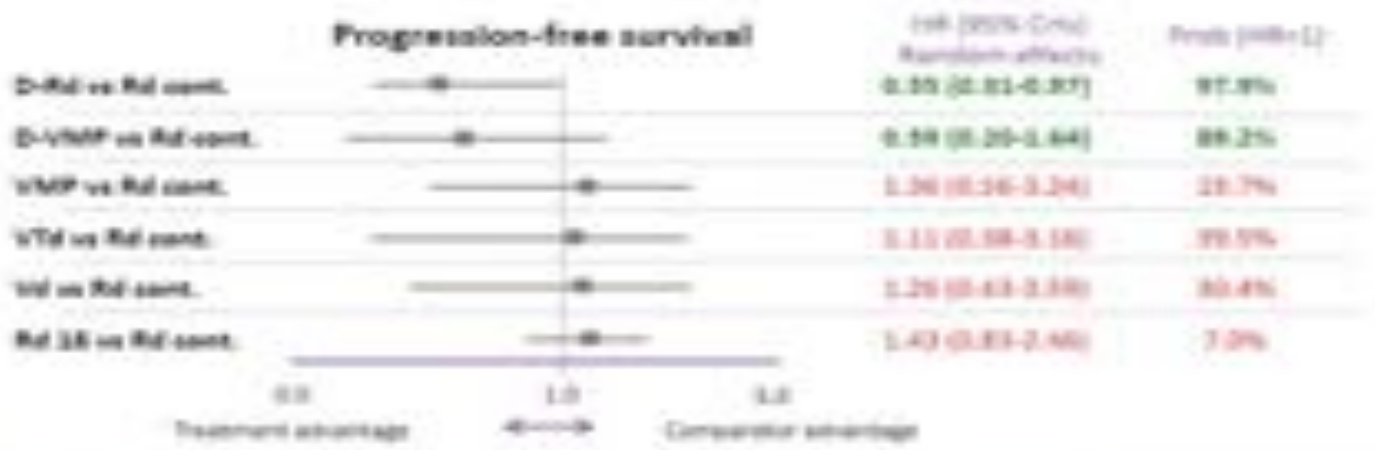


Figure 3. MRD[a] assessed by next-generation sequencing at the 10^{-5} sensitivity threshold by age group.[b]

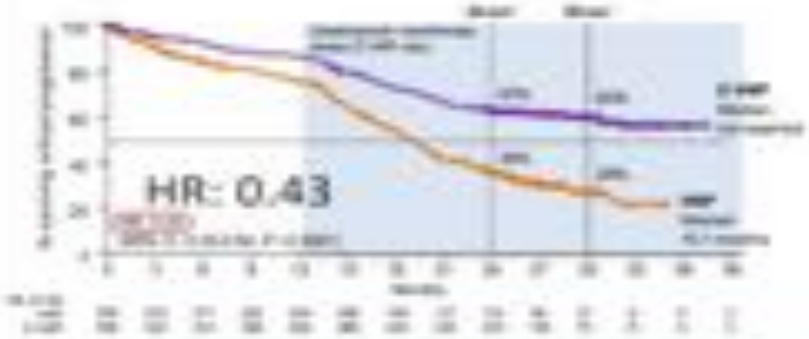
Hulin C, EHA. 2019

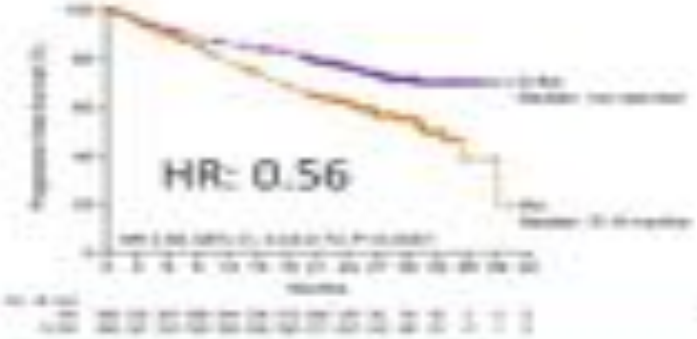
Frontline Therapies for Patients Non-Eligible for ASCT
Results from Network Meta-analysis

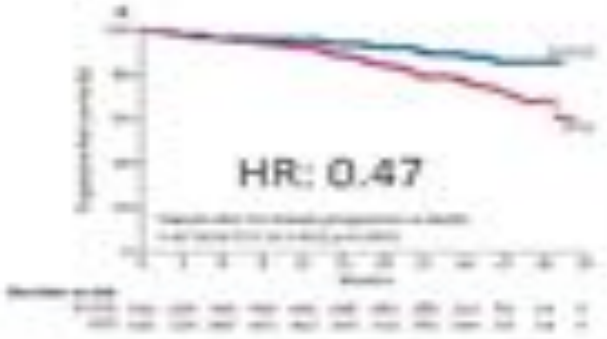


- D-Rd and D-VMP reduce the risk of progression vs Rd by 45% and 41%, respectively
- Probability of D-Rd & D-VMP demonstrating better PFS to Rd continuous is 98% and 89%, respectively
- D-Rd has the highest probability of being ranked first followed by D-VMP

Addition of MoAbs to standard therapy: what are the data?





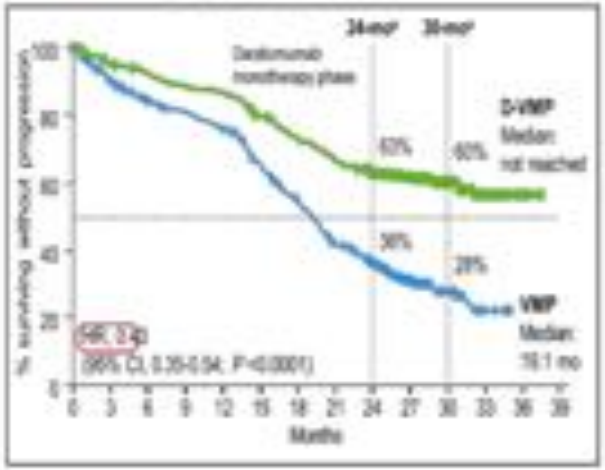


	D-VMP vs VMP	D-Rd vs Rd	D-VTD vs VTD
HR (PFS)	0.43	0.56	0.47
MRD(-) %	27% vs 7%	24% vs 7%	64% vs 44%
Treatment failure (SD or PD)	9% vs 26%	7% vs 19%	6% vs 8%

Mateos MV et al N Engl J Med 2018;378:518-28.
Dimopoulos MA et al ASH 2018 Abstract 156.
Facon T et al N Engl J Med 2019;380:2104-15.
Moreau P et al Lancet. 2019 Jul 6;394(10192):29-38.

New drug-based combinations

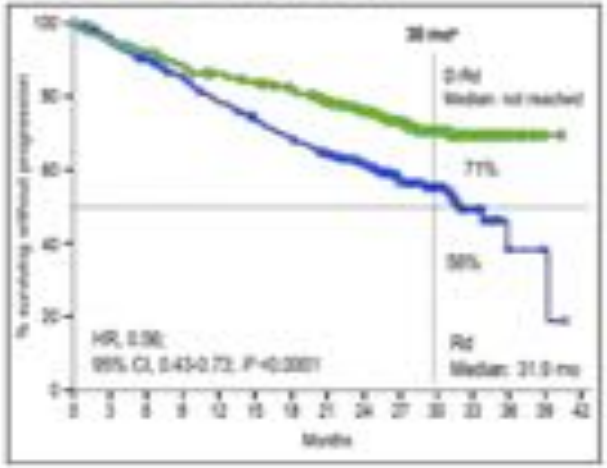
Dara-VMP[1]



MRD neg 27% vs 7%

30-mo PFS: 60% vs 28%

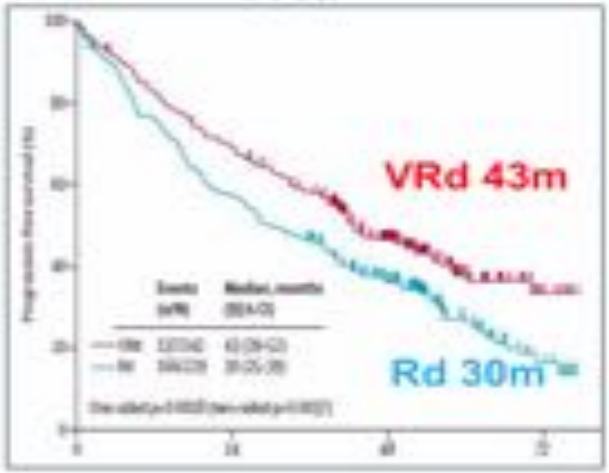
Dara-Rd[2]



MRD neg 24% vs 7%

30-mo PFS: 71% vs 56%

VRd[3]

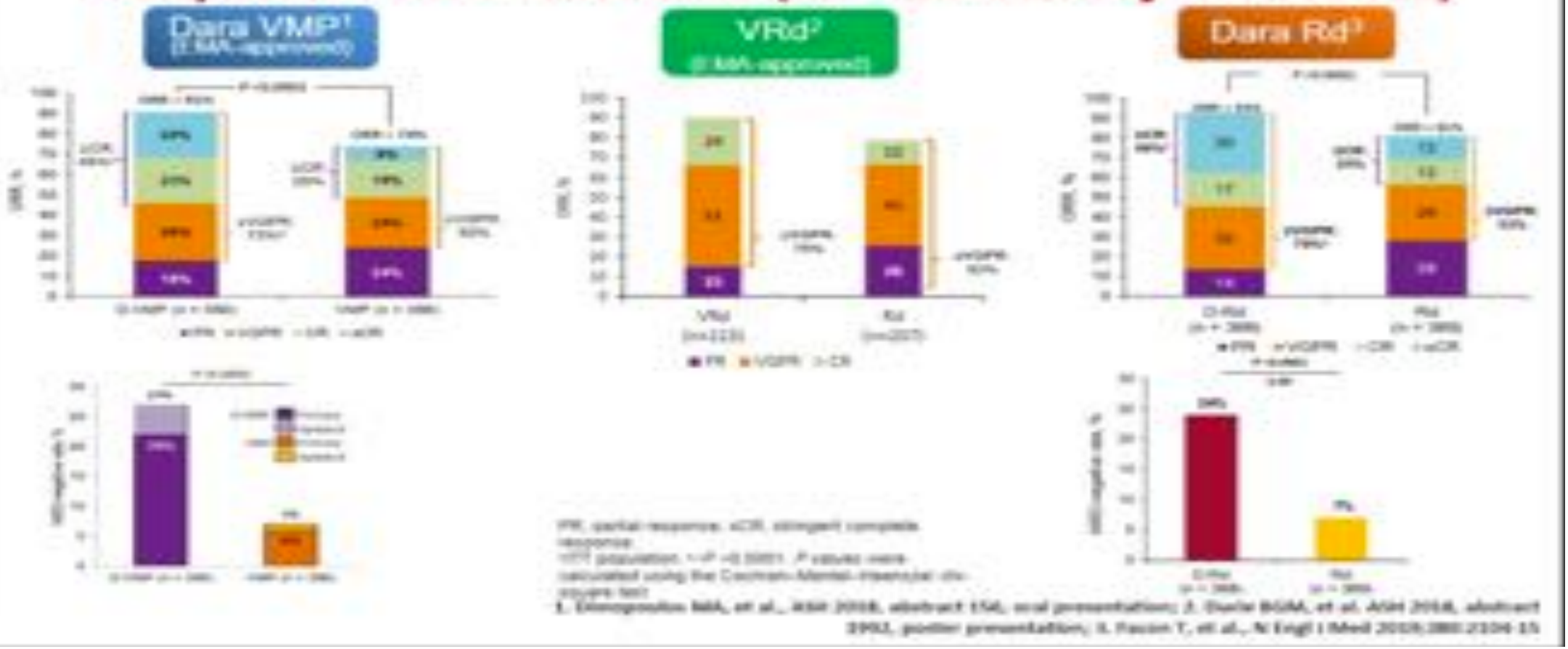


Median PFS

34 vs 24 months (≥65 yrs)

- New standards of care: Dara-VMP, Dara-Rd, VRd
- New potential future treatments: Elotuzumab-Rd, Ixazomib-Rd, Carfilzomib-Rd, Dara-KRd, Isatuximab-VRd

Response: ORR[a] and MRD (10^{-5} Sensitivity Threshold)



PR, partial response; sCR, stringent complete response
[a]ITT population; [b]P values were calculated using the Cochran-Mantel-Haenszel chi-square test

1. Dimopoulos MA, et al., ASH 2018, abstract 156, oral presentation; 2. Durie BGM, et al. ASH 2018, abstract 2952, poster presentation; 3. Facon T, et al., N Engl J Med 2019;380:2104-15

Is addition of MoAbs increasing toxicity?

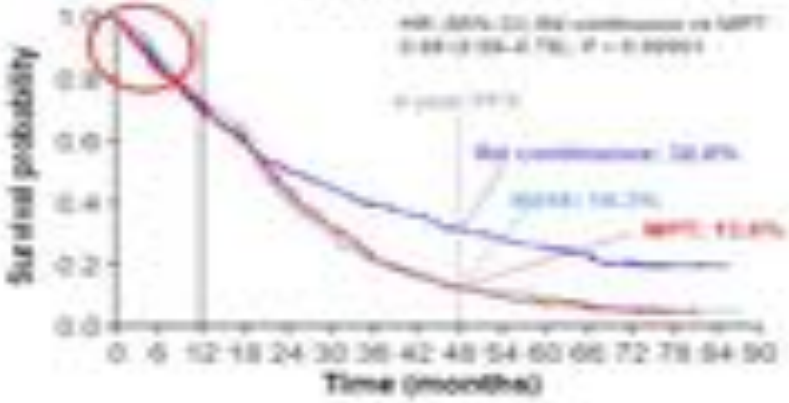
	MAIA (DRd vs Rd)	ALCYONE (D-VMP vs VMP)	CASSIOPEIA (D-VTD vs VTD)
Grade 5 events	6.9% vs 6.3%	4% vs 4.5%	0.2% vs 1.6%
D/C due to toxicity	7.1% vs 15.9%	4.9% vs 9%	7% vs 8%
Infections ≥Gr3	32.1% vs 23.3%	23.1% vs 14.7%	22% vs 20%

Mateos MV et al N Engl J Med 2018;378:518-19. Facon T et al N Engl J Med 2019;380:2104-15. Moreau P et al Lancet. 2019 Jul 6;394(10192):29-38.

What is the best option for frail and elderly patients?

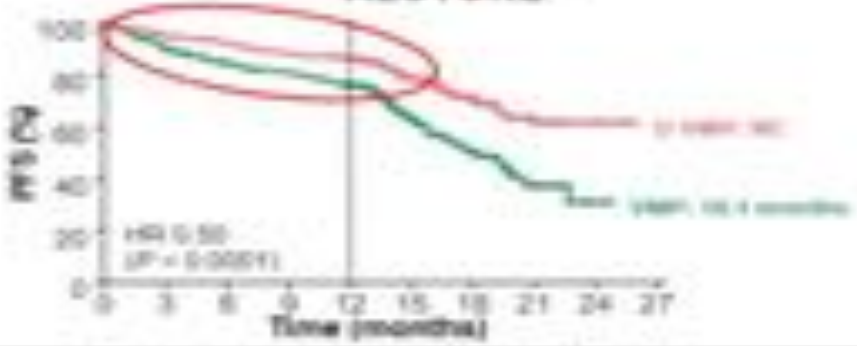
About 20% of elderly patients have treatment failure within the first year

FIRST/MM-020[1]



MAIA[1] **≥75 years**

ALCYONE[2]



Use of ImiDs, PIs, CD38 in NDMM TNE Patients ...accross various regimens and fitness levels

Frail — no ASCT.....more ASCT — **Fit**

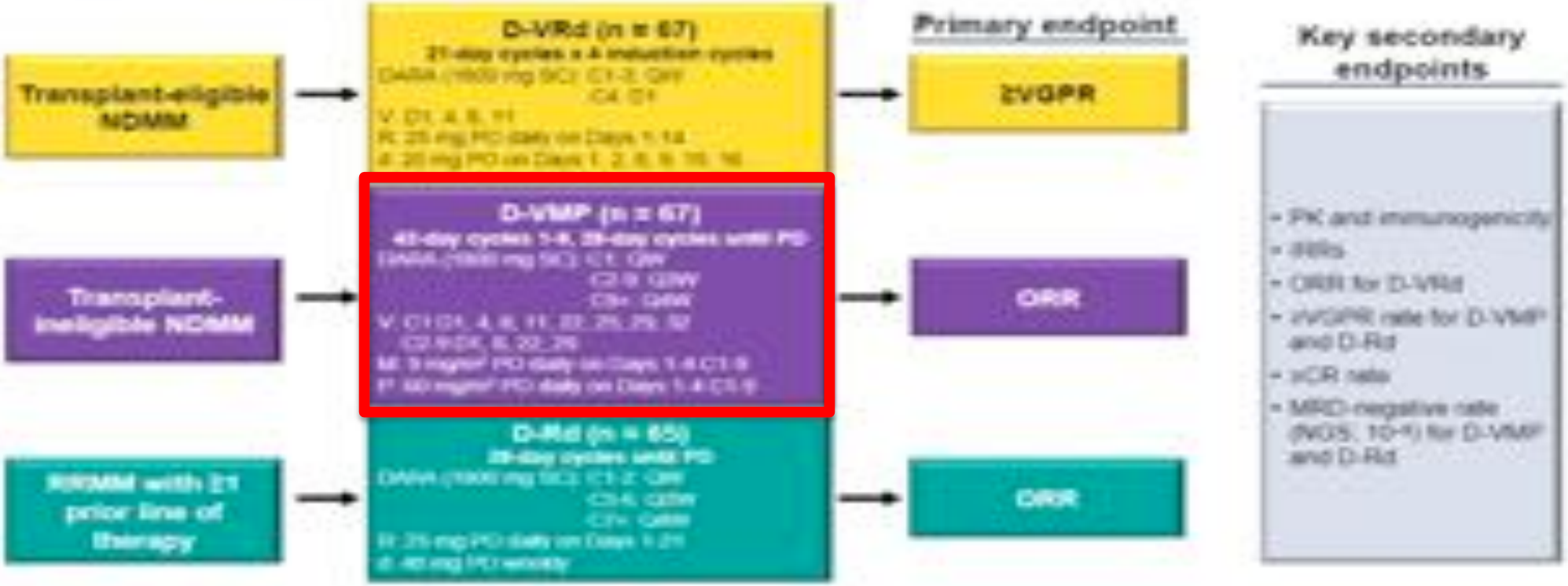
R-DARA → DRd → (VRD/VRD lite) → D-VRD lite → D-VRD/KRD

(No/few Dex)

Continuous Len...before continuous Len and CD38
SC Dara for all patients, other CD38 ?
Iberdomide to replace Lenalidomide ?

PLEIADES (MMY2040) Study Design

- Phase 2 study of DARA SC in combination with standard treatment regimens (N = 199)



Chari A

Baseline Demographic and Clinical Characteristics

	D-VRd (n = 67) Transplant-eligible NDMM	D-VMP (n = 67) Transplant-ineligible NDMM	D-Rd (n = 65) NDMM with ≥ 1 prior line of therapy
Age			
Median (range), years	59 (33-78)	75 (56-86)	69 (33-82)
Male, n (%)	48 (71.6)	31 (46.3)	45 (69.2)
Median (range) body weight, kg	77.0 (43.6-147.6)	66.0 (45.0-100.0)	80.6 (53.6-142.9)
Race, n (%)			
White	38 (56.7)	46 (68.7)	45 (69.2)
Baseline ECOG PS score, n (%)			
0	40 (59.7)	25 (37.3)	36 (55.4)
1	26 (38.8)	38 (56.7)	29 (44.6)
2	1 (1.5)	4 (6.0)	0
Median (range) number of prior lines of therapy, n	NA	NA	1 (1-5)
ISS staging,* n (%)			
I	30 (44.8)	22 (32.8)	27 (42.2)†
II	23 (34.3)	30 (44.8)	19 (29.7)†
III	14 (20.9)	15 (22.4)	18 (28.1)†
Cytogenetic risk‡			
N	53	41	31
Standard risk, n (%)	40 (75.5)	33 (80.5)	20 (64.5)
High risk, n (%)	13 (24.5)	8 (19.5)	11 (35.5)

Baseline patient characteristics were consistent with DARA IV studies

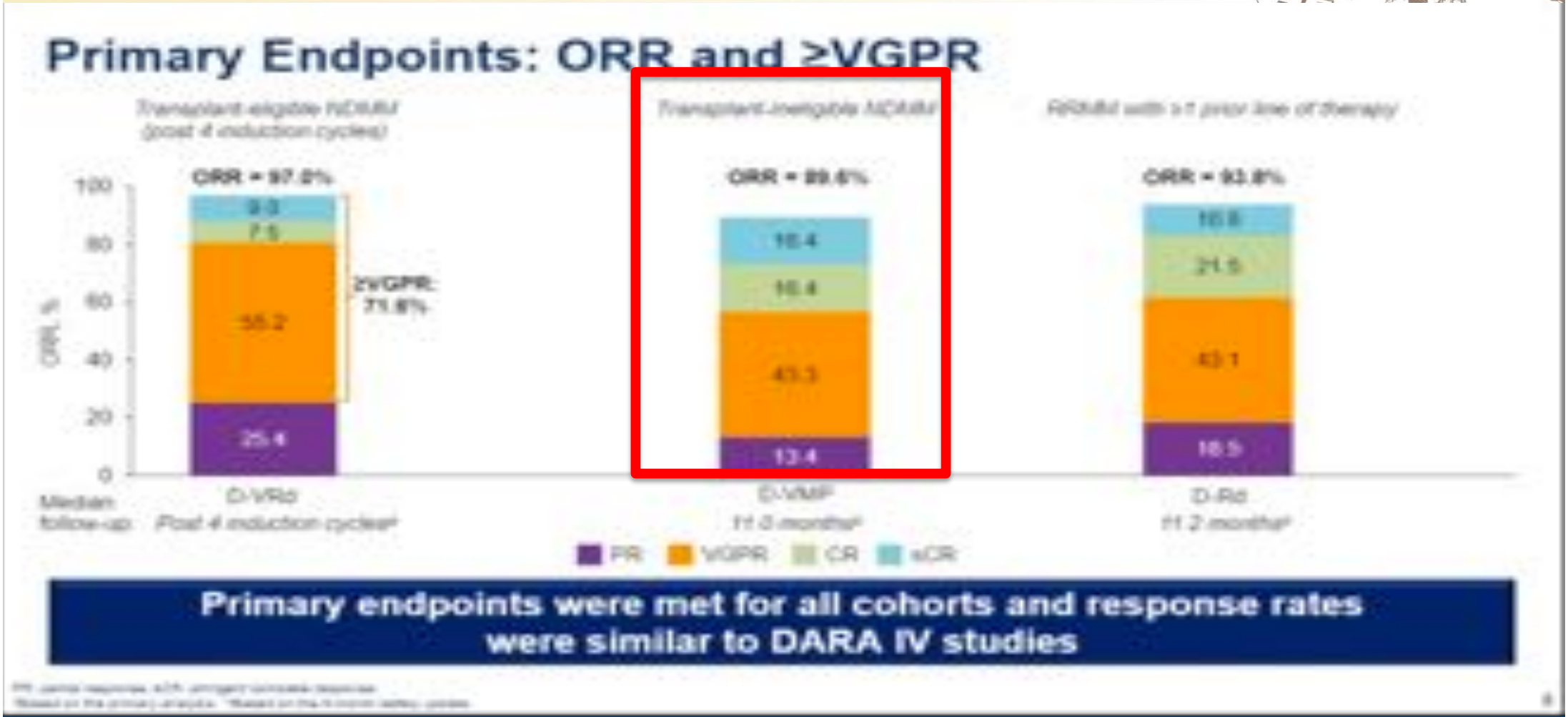
Patient Disposition and Exposure

- All patients in the D-VRd cohort have either completed (97.0%) or discontinued (3.0%) treatment
- 10.4% of patients in D-VMP and 20.0% in D-Rd cohorts discontinued treatment as of the clinical cutoff[a]

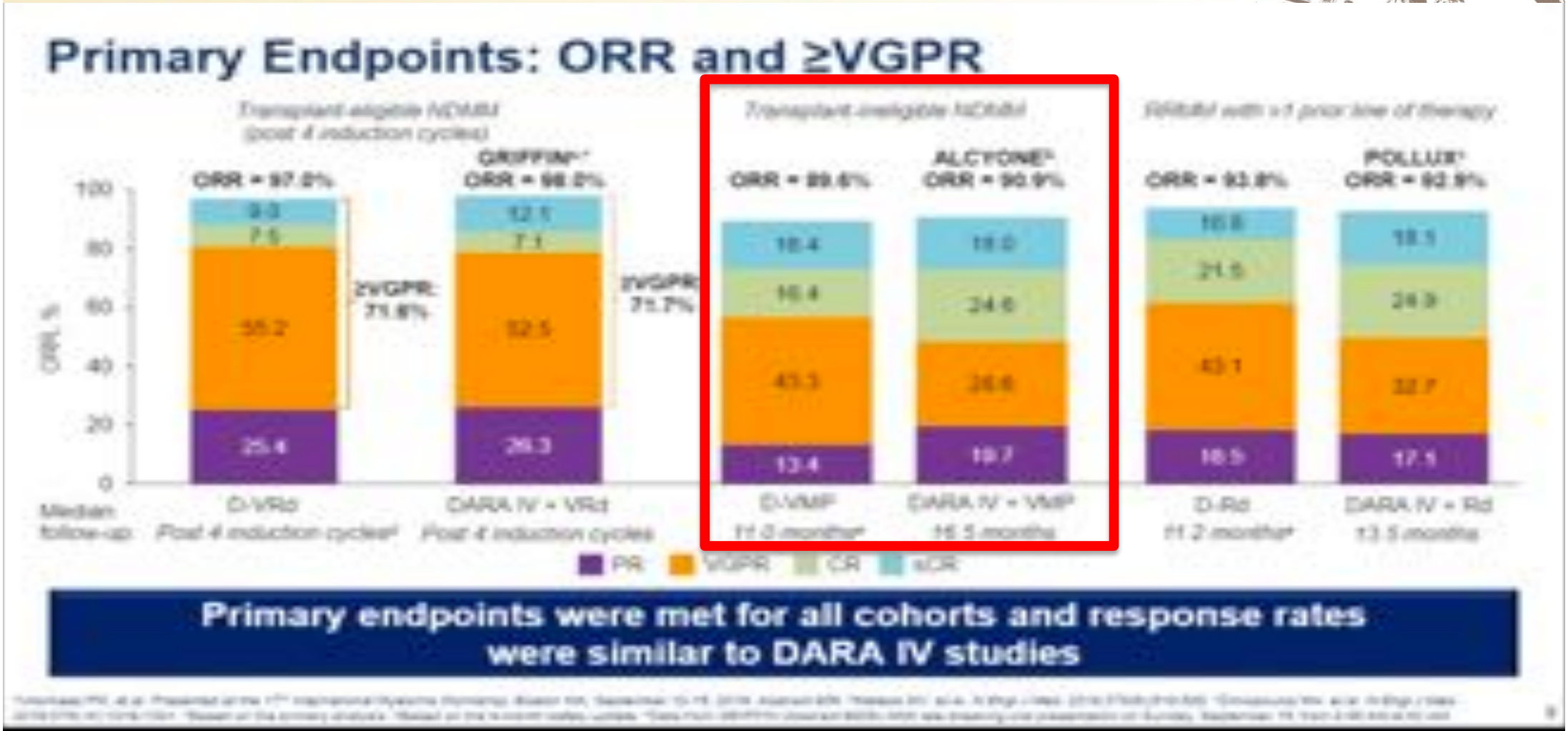
	D-VRd (n = 67)	D-VMP (n = 67)	D-Rd (n = 65)
	Transplant-eligible NDMM	Transplant-ineligible NDMM	NDMM with ≥ 1 prior line of therapy
Median (range) number of treatment cycles	4.0 (1-4)	8.0 (1-10)	12.0 (1-15)
Median (range) duration of treatment, months	2.6 (0-4)	10.8 (0-13)	11.1 (0-18)
Median (range) duration of follow-up, months	7.1 (0.5-10.7)	11.0 (0.6-13.3)	11.2 (0.7-12.9)
Relative dose intensity, median %			
DARA SC	100.0	100.0	100.0
Bortezomib	97.9	96.7	–
Melphalan	–	97.5	–
Prednisone	–	96.3	–
Lenalidomide	100.0	–	96.5
Dexamethasone	100.0	–	73.3

- **Median administration of DARA SC was 5 minutes**
- **Relative dose intensities of DARA SC combination therapies are consistent with those previously reported with DARA IV**

Chari A


Primary Endpoints: ORR and ≥VGPR
ORR = 97.8%
9.3
7.5
55.2
25.4
≥VGPR: 71.8%
ORR = 89.6%
16.4
16.4
43.3
13.4
ORR = 93.8%
16.8
21.5
43.1
16.5
100
80
60
40
20
0
ORR, %
Median follow-up:
D-VRd
Post 4 induction cycles
D-Rd
PR
VGPR
CR
sCR
Primary endpoints were met for all cohorts and response rates were similar to DARA IV studies

Chari A


Primary Endpoints: ORR and ≥VGPR
Transplant-eligible NDMM
(post 4 induction cycles)
ORR = 97.0%
GRIFFIN[1,2]
ORR = 98.0%
≥VGPR: 71.8%
≥VGPR: 71.7%
Transplant-ineligible NDMM
ORR = 89.6%
ALCYONE[3]
ORR = 90.9%
Relapsed with ≥1 prior line of therapy
ORR = 93.8%
POLLUX[4]
ORR = 92.9%
100
80
60
40
20
0
ORR, %
9.3
7.5
55.2
25.4
12.5
7.1
52.5
26.3
18.4
16.4
43.3
13.4
18.0
24.6
26.6
19.7
16.8
21.5
43.1
18.5
18.1
24.9
32.7
17.1
Median follow-up:
D-VRd
Post 4 induction cycles[1]
DARA IV + VRd
Post 4 induction cycles
D-VMP
11.3 months[4]
DARA IV + VMP
16.5 months
D-Rd
11.2 months[4]
DARA IV + Rd
13.5 months
PR
VGPR
CR
sCR
Primary endpoints were met for all cohorts and response rates were similar to DARA IV studies

Safety Summary

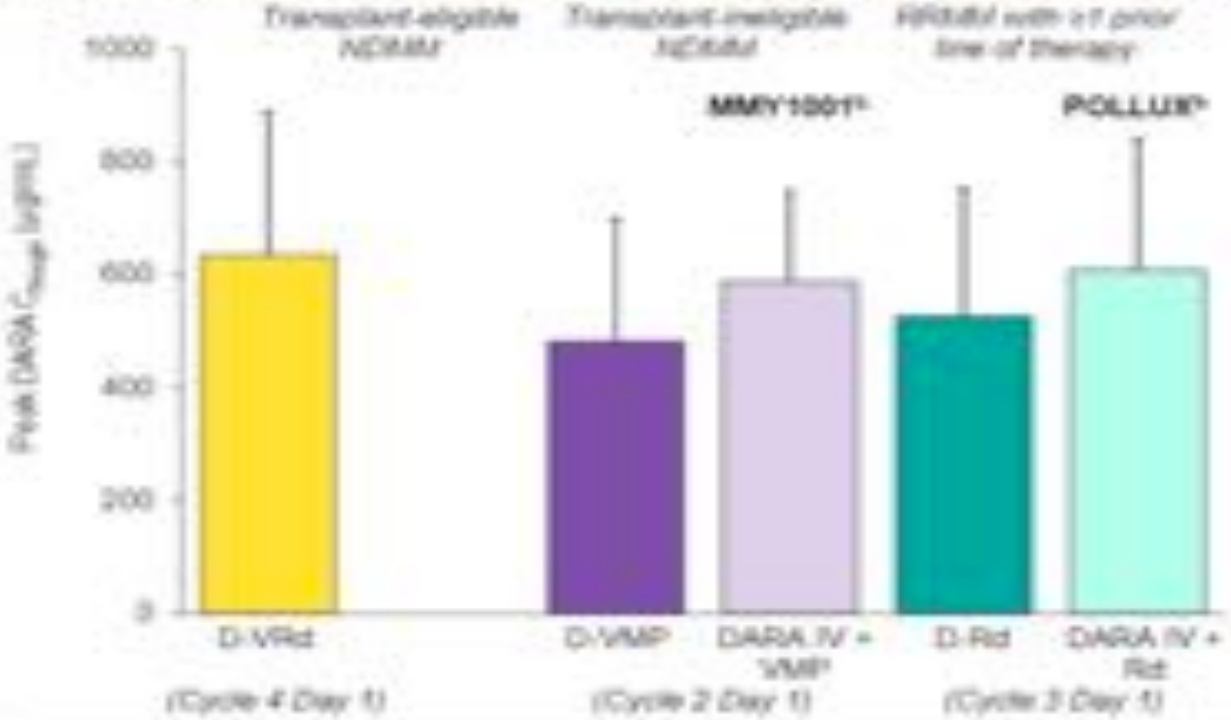
	D-VRd (n = 67)	D-VMP (n = 67)	D-Rd (n = 65)
	Transplant-eligible NDMM	Transplant-ineligible NDMM	Ineligible with ≥ 1 prior line of therapy
Any TEAE, n (%)	67 (100.0)	67 (100.0)	65 (100.0)
Serious TEAE, n (%)	19 (28.4)	26 (38.8)	31 (47.7)
Grade 3/4 TEAE, n (%)	38 (56.7)	46 (68.7)	54 (83.1)
TEAEs leading to treatment discontinuation, n (%)	1 (1.5)	2 (3.0)	5 (7.7)
Fatal TEAE, n (%)	1 (1.5)	2 (3.0)	2 (3.1)

- IRRs occurred in 7.5% (15/199) of patients across all cohorts
  - 93.3% (14/15) of patients with IRRs experienced them on the first administration
  - IRRs were mild (grade 1/2) in 93.3% (14/15) of patients; 1 patient had a grade 3 IRR leading to discontinuation of DARA SC, and no patient had a grade 4 IRR
- Median time to onset of IRRs was 3.3 hours
  - Patients were not required to stay for observation beyond the first administration of DARA SC
- Local injection-site reactions occurred in 7.5% (15/199) of patients across all cohorts (all grade 1/2)

DARA SC combination therapy safety profiles were consistent with DARA IV, with lower rates of IRRs

Chari A

PK and Immunogenicity Summary[a]



- Peak C_{trough} values were consistent with historical data
- C_{max} after 1st dose:[c]
  - D-VRd: 100 ± 48.5 µg/mL
  - D-VMP: 98.6 ± 51.6 µg/mL
  - D-Rd: 108 ± 49.9 µg/mL
- 10 patients developed rHuPH20 antibodies, all were non-neutralizing
- No patients developed anti-DARA antibodies

PK and immunogenicity were comparable to previous reports

Conclusions

- DARA SC in combination with standard of care demonstrated comparable clinical activity and safety to corresponding DARA IV-containing regimens
- IRRs were infrequent and mild
- Administration time was 5 minutes, substantially reducing infusion time versus IV formulations
- DARA SC is currently under review by health authorities

These results support the use of flat-dose 1800 mg DARA SC in combination with standard treatment regimens

Can improvement be reached in fit patients?

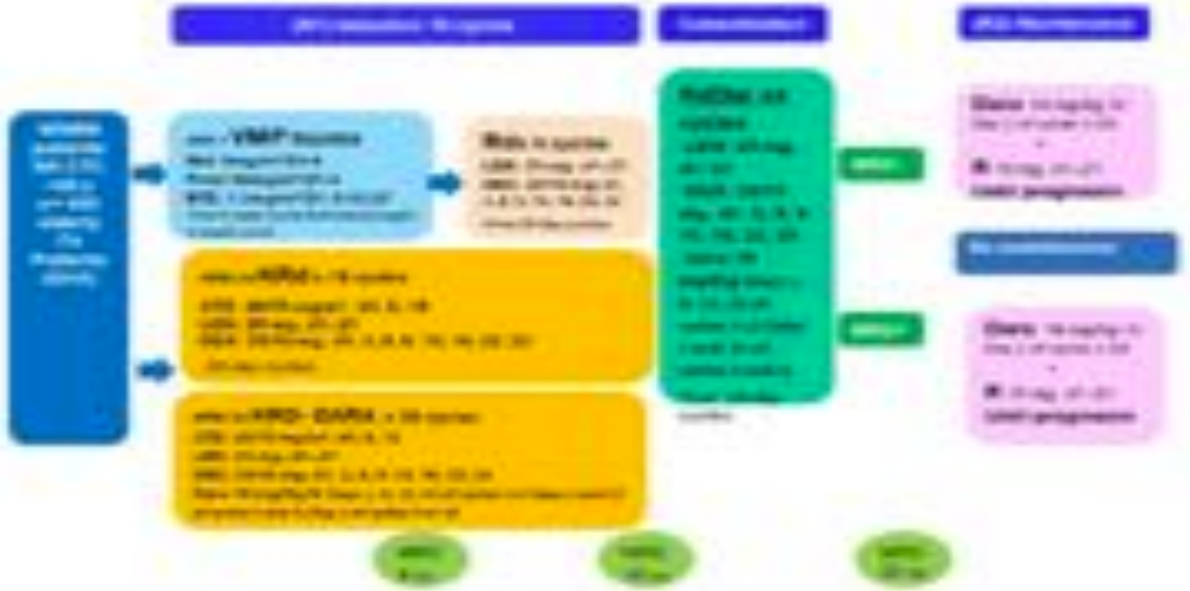
Intensive treatment

GEM2017FIT
462 patients

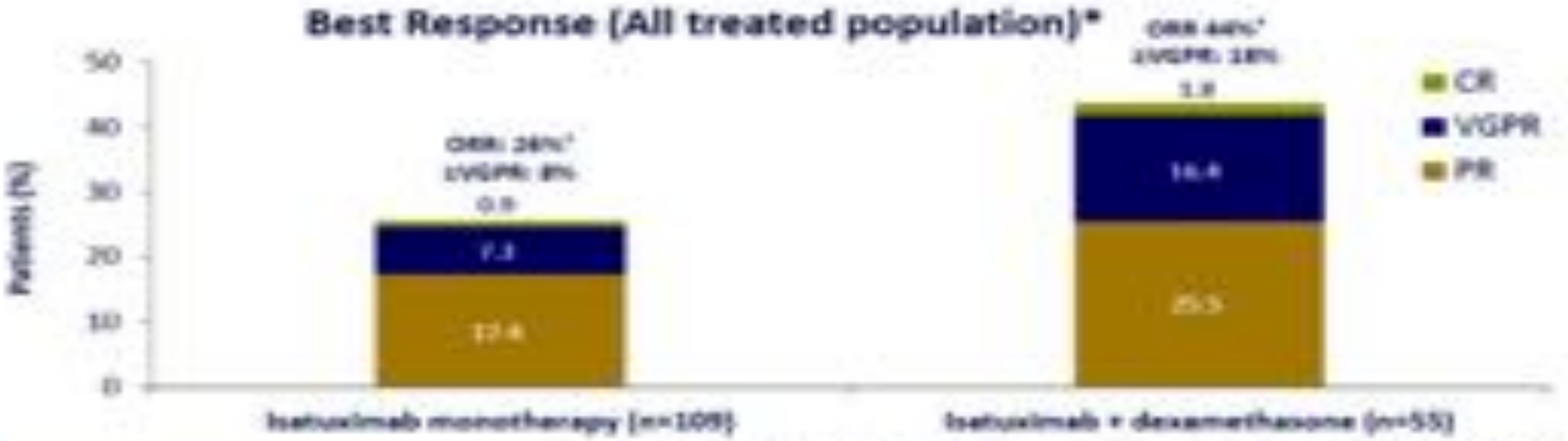
Primary endpoint – MRD negativity and PFS

Hypothesis

- MRD negativity at 18 months in experimental arms superior (35%) over VMP/Rd (20%)
- PFS in experimental arms superior (51 months) over VMP/Rd (34 months)

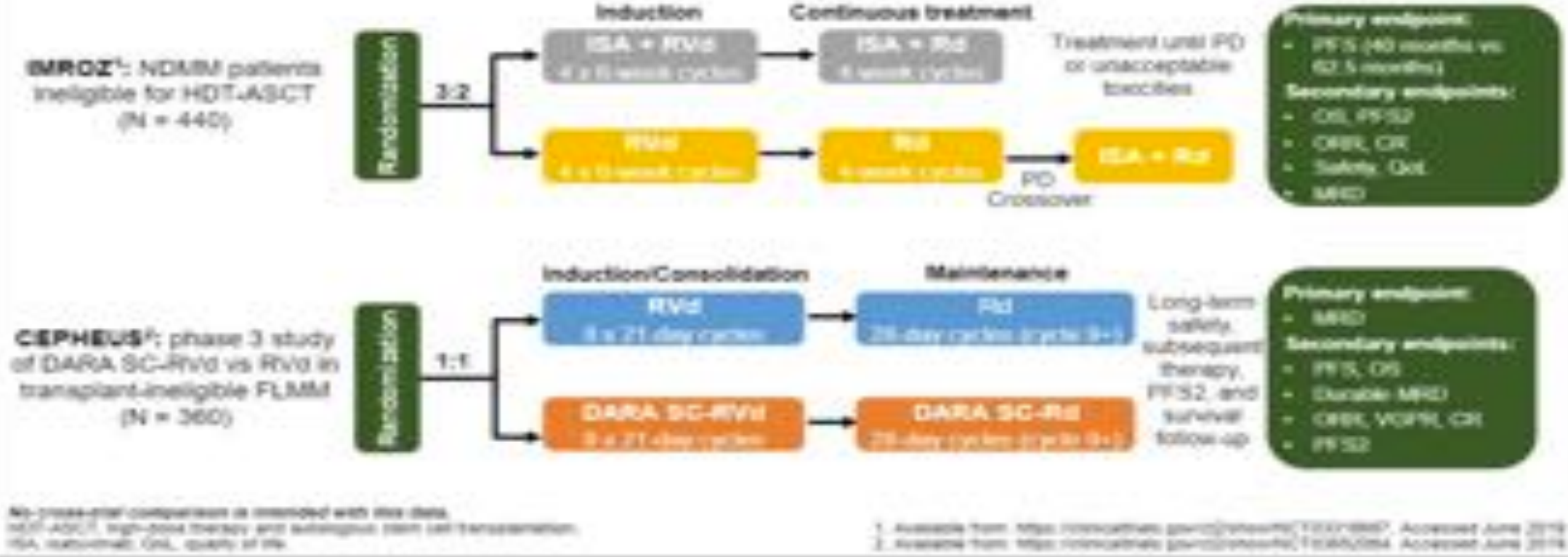


Isatuximab: another anti-CD38 MAb
Results of phase 2 study (Isa +/- Dexa)



	Isatuximab monotherapy (n=109)	Isatuximab + dexamethasone (n=55)
Time to first response in months, median (range)	1.0 (1–6)	1.2 (1–4)
Time to best response in months, median (range)	1.9 (1–9)	1.9 (1–7)
Duration of response in months, median (range)	7.2 (2–19)	9.2 (1–16)

IMROZ (EFC12522) and CEPHEUS (MMY3019): study designs



No cross-trial comparison is intended with this data.
HDT-ASCT, high-dose therapy and autologous stem cell transplantation; ISA, isatuximab; QoL, quality of life

1. Available from: https://clinicaltrials.gov/ct2/show/NCT03319667. Accessed June 2019.
2. Available from: https://clinicaltrials.gov/ct2/show/NCT03652064. Accessed June 2019.

Preliminary results from a Phase I study of isatuximab in combination with bortezomib, lenalidomide, dexamethasone in patients with newly diagnosed multiple myeloma non-eligible for transplant

Enrique M. Ocio,[1] Paula Rodriguez-Otero,[2] Sara Bringhen,[3] Stefania Oliva,[3] Axel Nogai,[4] Michel Attal,[5] Philippe Moreau,[6] Dheepak Kanagavel,[7] Thomas Fitzmaurice,[8] Junlong Wu,[9] Joaquin Martinez-Lopez[10]

[1]University Hospital Marqués de Valdecilla (IDIVAL), University of Cantabria, Santander, Spain and University Hospital of Salamanca (IBSAL) - Cancer Research Center (IBMCC-CSIC-USAL), Salamanca, Spain; [2]University Clinic of Navarra, Center for Applied Medical Research (CIMA), IDISNA, Pamplona, Spain; [3]Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy; [4]Charité Berlin, Hematology/Oncology, Centrum 14, Berlin, Germany; [5]Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France; [6]University Hospital, Nantes, France; [redacted]; [10]Hematology, Hospital Universitario 12 de Octubre, CNIO, Complutense, Madrid, Spain

Phase I Study: Design and Eligibility

Key eligibility criteria:
- ✓ Adults with NDMM
- ✓ Patients non-eligible for transplantation
- ✓ Adequate bone marrow reserve and organ function

Primary Objective
- CR rate (according to IMWG criteria[1])

Secondary Objectives
- Safety, ORR, DOR, PFS, PK

Exploratory Objective
- MRD negativity in patients achieving ≥VGPR

Induction phase (4 x 6-week cycles)

Bortezomib *1.3 mg/m² s.c*	D1, 4, 8, 11 D22, 25, 29, 32
Lenalidomide *25 mg/d p.o.*	D1-14 D22-35
Dexamethasone *20 mg/d IV/p.o*	D1-2, 4-5, 8-9, 11-12, 15 D22-23, 25-26, 29-30, 32-33
Isatuximab *10 mg/kg IV*	QW C1, Q2W C2–4

Maintenance phase (4-week cycles)

Lenalidomide *25 mg/d p.o.*	D1-21
Dexamethasone *40 mg/d IV/p.o**	D1, 8, 15, 22
Isatuximab *10 mg/kg IV*	D1, 15

- PD
- Unacceptable toxicity
- Any other reasons

Target population N=27

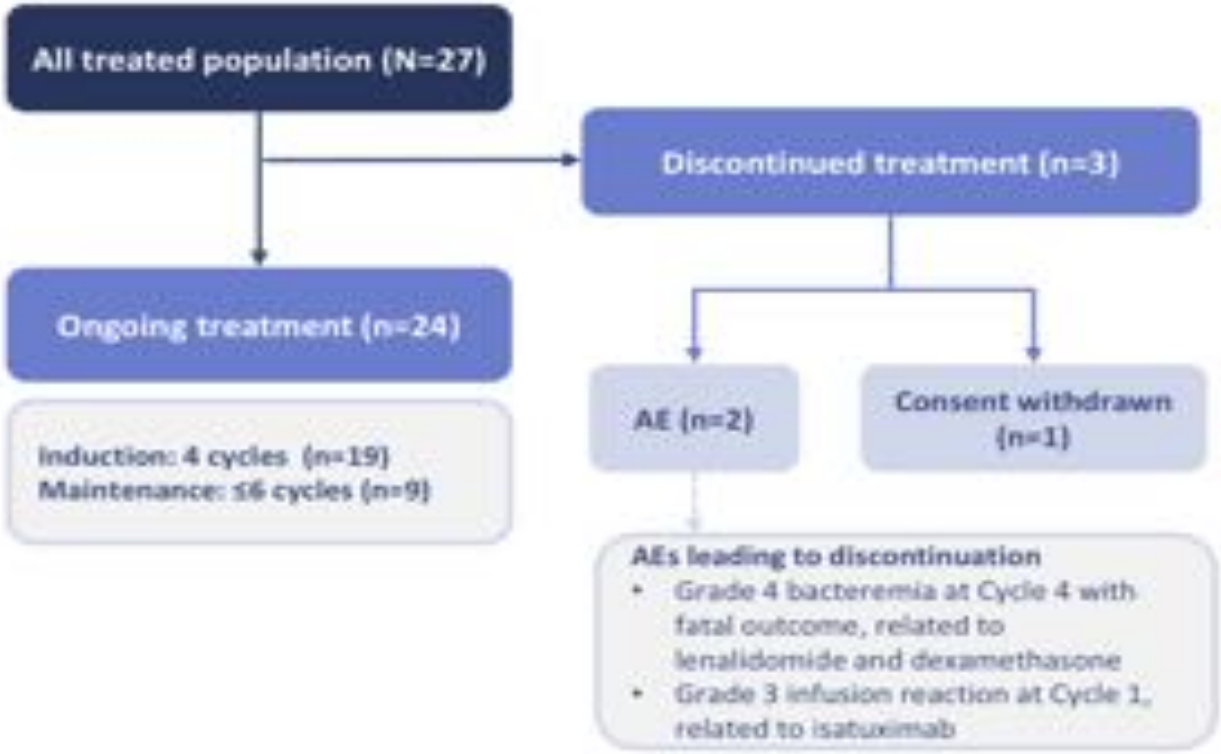
Data cut-off: September 3, 2018; *20 mg/day in patients >75 years old

1. Palumbo A, et al. J Clin Oncol 2014;32:587–600

Patient Demographics and Clinical Characteristics

	All patients (N=27)
Age in years, median (range)	71 (63, 77)
Weeks since initial diagnosis, median (range)	7.9 (0.9, 640.1)
Type of myeloma at diagnosis, n (%)	
Light chain only	1 (3.7)
IgA	5 (18.5)
IgG	21 (77.8)
Light chain (kappa)	16 (59.3)
Light chain (lambda)	5 (18.5)
ISS stage at baseline, n (%)	
Stage I	14 (51.9)
Stage II	11 (40.7)
Stage III	2 (7.4)
CrCl <60 mL/min, n (%)	6 (22.2)
High-risk cytogenetics*, n/N (%)	3/23† (13.0)

Preliminary Analysis: Patient Disposition and Drug Exposure

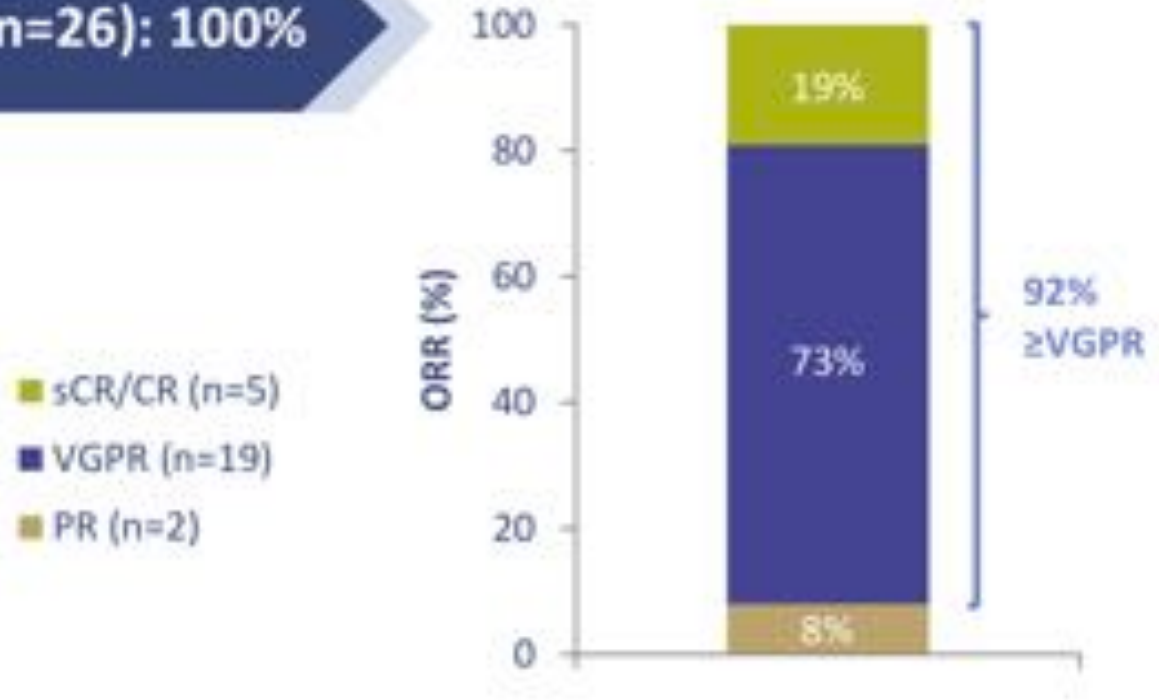


Drug exposure	All patients (N=27)
Median number of cycles, n (range)	6.0 (1, 15)
Median duration of exposure, months (range)	7.2 (0.2, 16.1)
Median relative dose intensity (%)	
Isatuximab	95.7
Bortezomib	95.6
Lenalidomide	92.8
Dexamethasone	100.8

AE, adverse event; Data cut-off: September 3, 2018; Last patient in: 30 April 2018
Median duration of follow-up: 6.8 months (range 2.8–15.7)

Response Summary (IMWG Criteria): Efficacy-Evaluable Patients

ORR (n=26): 100%

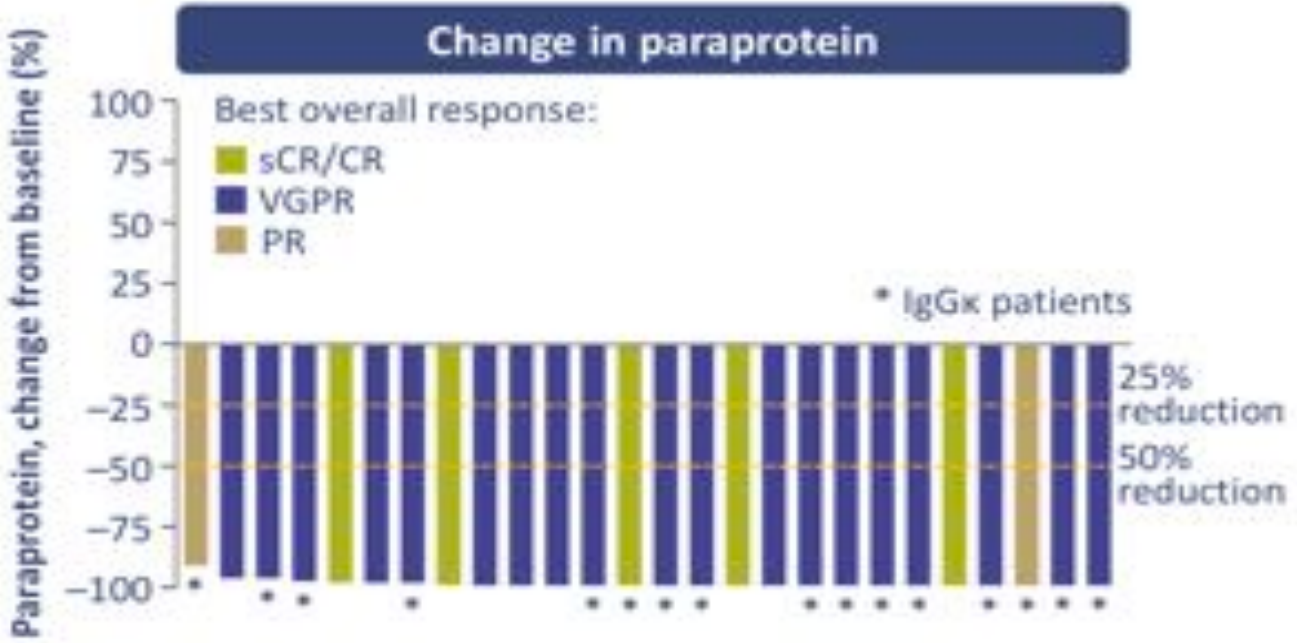


- No patients experienced PD
- 92% of patients achieved ≥VGPR* including the three patients with high-risk cytogenetics (among these one patient achieved CR)
- 13 of 19 patients with VGPR had IgG kappa disease at baseline

Time to Response and Maximum Change in Paraprotein

Time to response*	All patients (N=27)
Time to first response in months, median (range)	1.4 (1.1, 7.6)
Time to best response in months, median (range)	2.8 (1.2, 13.2)

Median duration of follow-up: 6.8 months (range 2.8–15.7 months)

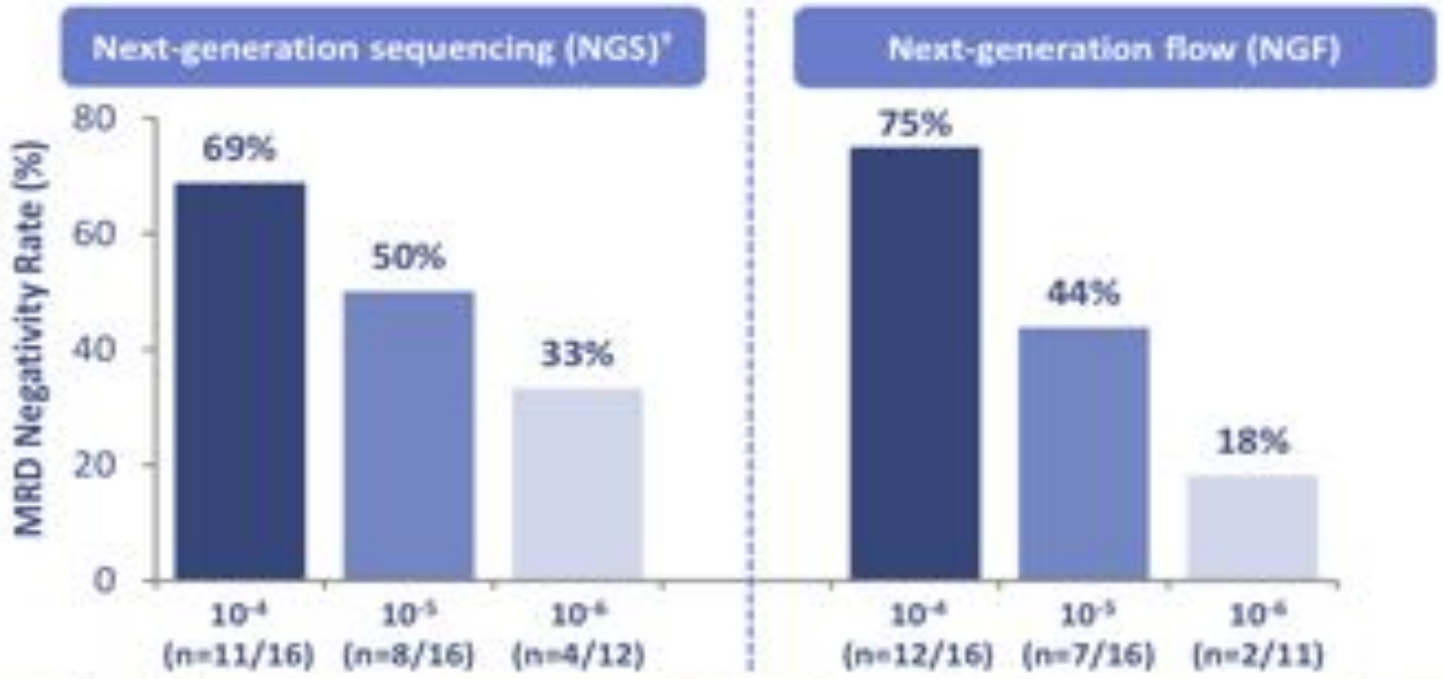


The majority of patients achieved a 100% reduction in paraprotein

IFE, immunofixation electrophoresis; Median follow-up duration: 6.8 months (range 2.8, 15.7)
*First disease assessment was performed at the end of Cycle 1 (Week 6)

Ocio E

Minimal Residual Disease Evaluation*



The high MRD negativity rate achieved by NGS and NGF is concordant
7/16 evaluable patients (44%) achieved MRD negativity by NGS and/or NGF at 10^{-5} sensitivity level

*Of 18 efficacy-evaluable patients with BMA samples collected at MRD cut-off (all ≥VGPR), 2 patients had bone marrow aspirate (BMA) samples not evaluable by NGS or NGF at 10^{-4} or 10^{-5} sensitivity levels, and some patients had BMA samples that did not reach the standard limit of detection (10^{-6}) for NGS (4 patients) and NGF (5 patients)
†Overestimation of MRD negativity rate by NGS may be due to hemodilution of BMA samples from 2 patients

Treatment Emergent Adverse Events* and Hematologic Laboratory Abnormalities for all Patients (N=27)

TEAEs	All grades	Grade ≥3
Any TEAE (%)	100	63.0
Peripheral sensory neuropathy†	70.3	3.7
Infusion-related reaction	63.0	3.7
Edema peripheral	63.0	3.7
Constipation	59.3	0
Diarrhea	51.9	7.4
Asthenia	44.4	3.7
Hypotension	40.7	3.7
Fatigue	40.7	3.7
Cough	25.9	0
Muscoskeletal pain	25.9	0
Dizziness	25.9	0
Back pain	22.2	7.4
Dyspnea	22.2	7.4

Grade ≥3 infections were reported in 7 patients (25.9%)

Hematologic laboratory abnormalities (%)	All grades	Grade 3	Grade 4
Thrombocytopenia	100	25.9	7.4
Anemia	96.3	7.4	0
Neutropenia	70.4	51.9	0
Lymphopenia	100	51.9	22.2

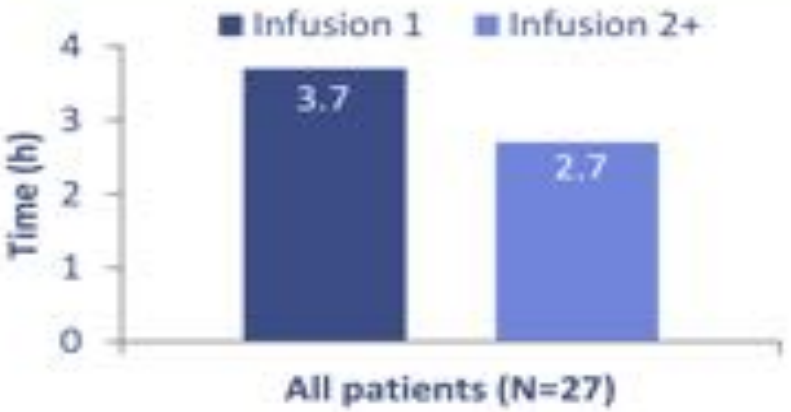
Discontinuations due to TEAEs:
Bortezomib, 6 (22.2%) patients
Lenalidomide, 2 (7.4%) patients

No new safety signals were observed

TEAE, treatment emergent adverse event; *TEAEs in ≥25% of patients (all grades) or ≥5% (Grade 3/4)
†Grade 1 = 29.6%; Grade 2 = 37.0%; Grade 3 = 3.7%

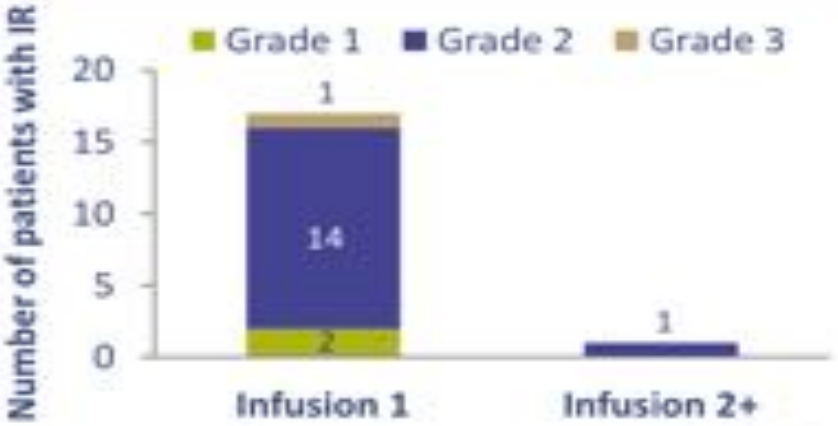
Isatuximab Administration and IRs

Isatuximab median infusion duration



Starting infusion rate was 175 mg/h

IRs in 17 patients (63%)



Mandatory pre-treatment prophylaxis*

Discontinuation due to Grade 3 IR occurred in 1 patient

IRs predominantly occurred during the first infusion†

*Prophylaxis: Dexamethasone 40 mg (or 20 mg for patients ≥75 years old) IV/PO, diphenhydramine 25–50 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent), and acetaminophen 650–1000 mg PO 15–30 minutes (but ≤60 minutes) prior to isatuximab infusion

†One patient experienced two IRs (Grade 2)

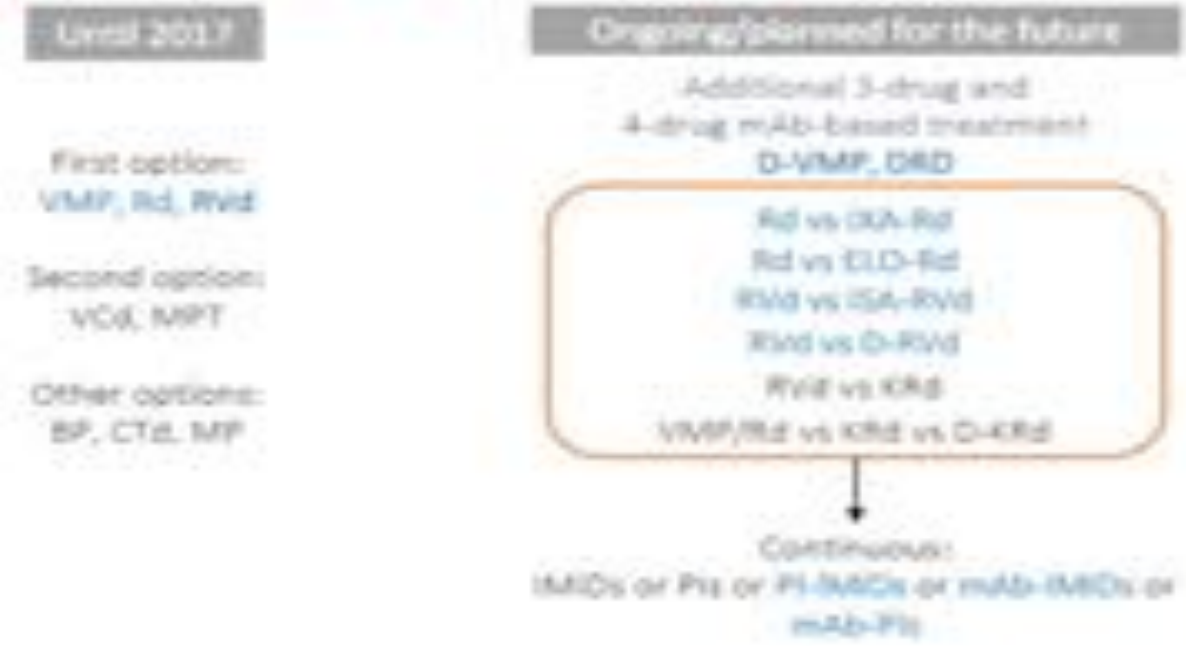
Conclusions

- Encouraging clinical activity of isatuximab combined with VRd as induction, followed by isatuximab with Rd as maintenance therapy in NDMM
- ORR confirmed as 100% in efficacy-evaluable patients: ≥VGPR was achieved in 92%
- Overall, 7/16 MRD-evaluable patients (44%) achieved MRD negativity by NGS and/or NGF at the 10^{-5} sensitivity level
- The isatuximab regimen was well tolerated with a manageable safety profile; AEs with this combination were generally consistent with the known safety profiles of the individual agents
- IRs were generally Grade 1/2 in severity (one Grade 3 reaction), and predominantly occurred during the first infusion
- Median infusion duration for isatuximab was 3.7 h for 1st infusion and 2.7 h for subsequent infusions

Two Phase III isatuximab plus VRd backbone studies are ongoing in NDMM
GMMG HD-7 (NCT03617731): transplant eligible patients[1]
IMROZ (NCT03319667): transplant ineligible patients[2]

IMROZ

Current and potential future treatment algorithms for transplant-ineligible MM patients



Highlights from IMW 2019

19-20 novembre 2019 Bologna