POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

MIELOMA MULTIPLO

Terapia alla diagnosi

Maria Teresa Petrucci

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERA UNIVERSITARIA
POLICLINICO UMBERTO I

Disclosures of Maria Teresa Petrucci

Company name	Honoraria	Advisory board	Support for attending meetings and/or travel
Celgene- BMS	X	X	X
Janssen-Cilag	X	X	X
Takeda	X	X	X
AbbVie	X		
Amgen	X	X	X
GSK	X	X	
Menarini		X	
Sanofi	X	X	X
Oncopeptides		X	
Pfizer	X	X	

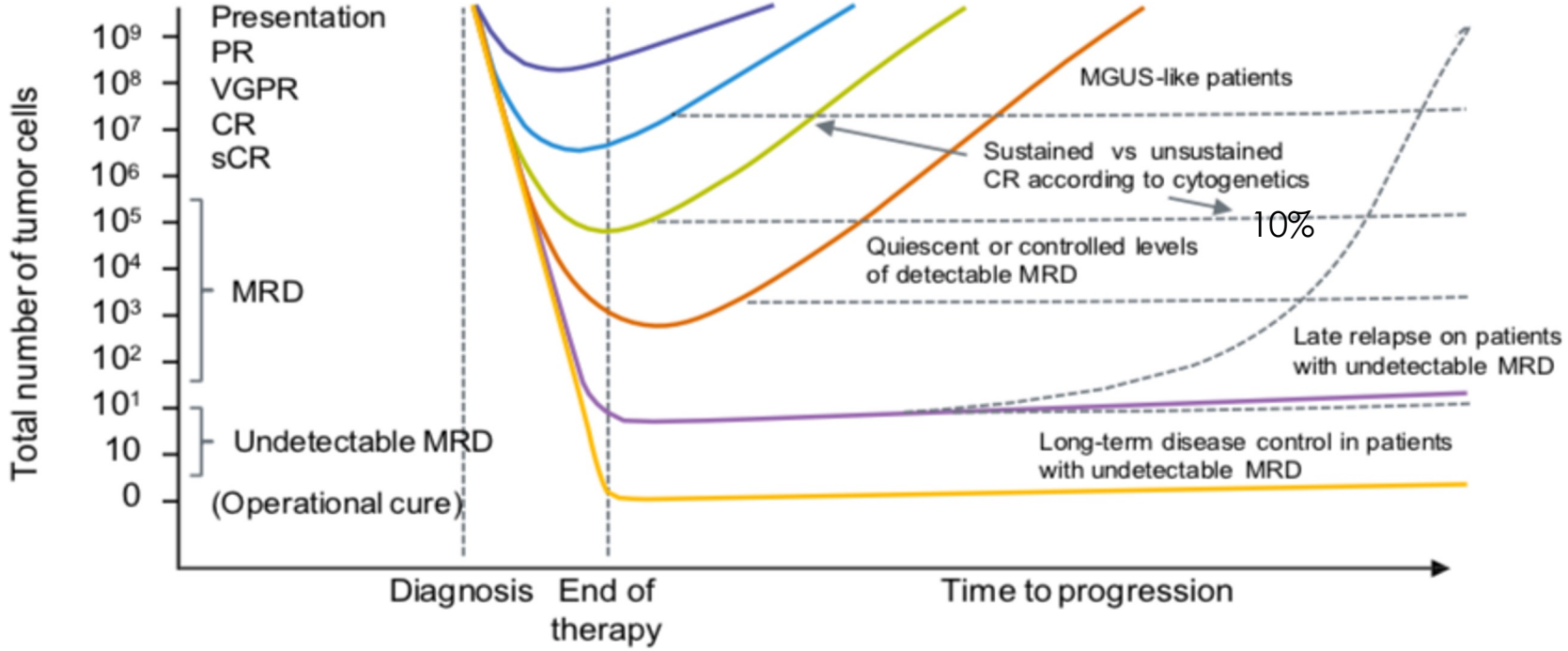
MM paradigma di trattamento

Elegibili trapianto

Induzione → Intensificazione → Consolidamento → Mantenimento

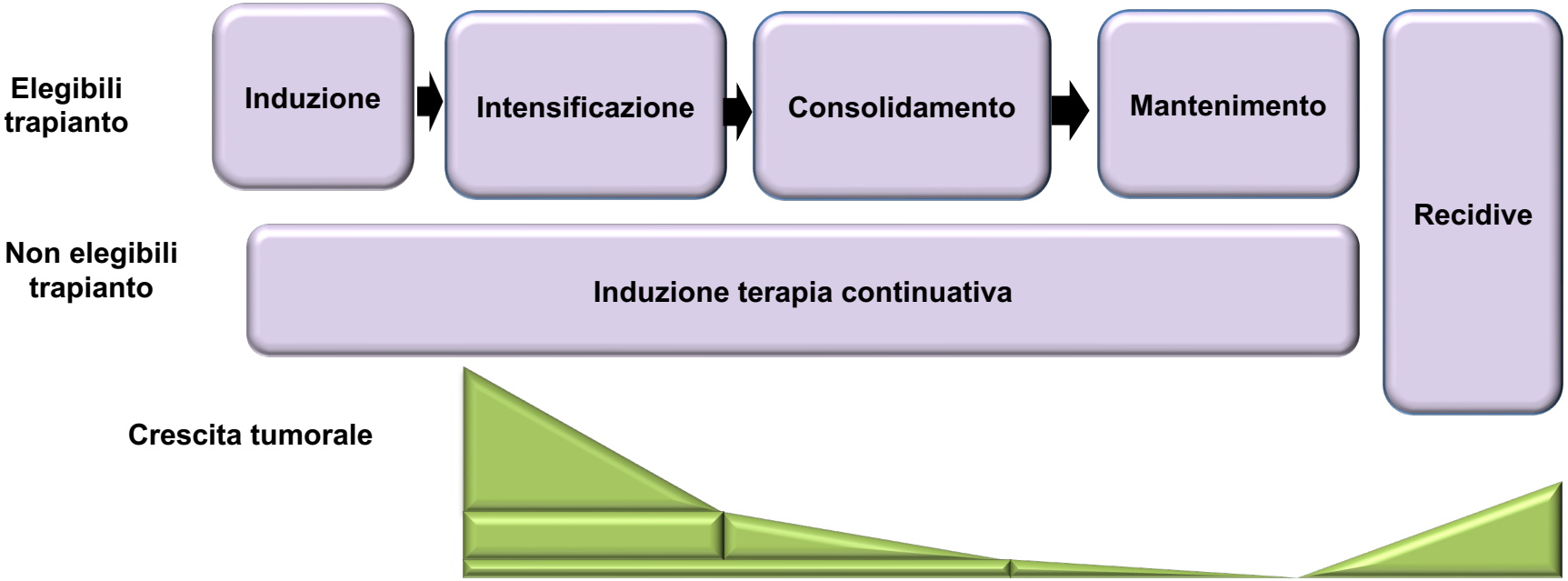
Non elegibili trapianto

Induzione terapia continuativa



Paiva et al Blood 2015

MM paradigma di trattamento



Phase 3 Randomized Study of Daratumumab + Bortezomib, Lenalidomide, and Dexamethasone (VRd) Versus VRd Alone in Patients With Newly Diagnosed Multiple Myeloma Who Are Eligible for Autologous Stem Cell Transplantation: Primary Results of the PERSEUS Trial*

*ClinicalTrials.gov Identifier: NCT03710603; sponsored by EMN in collaboration with Janssen Research & Development, LLC.

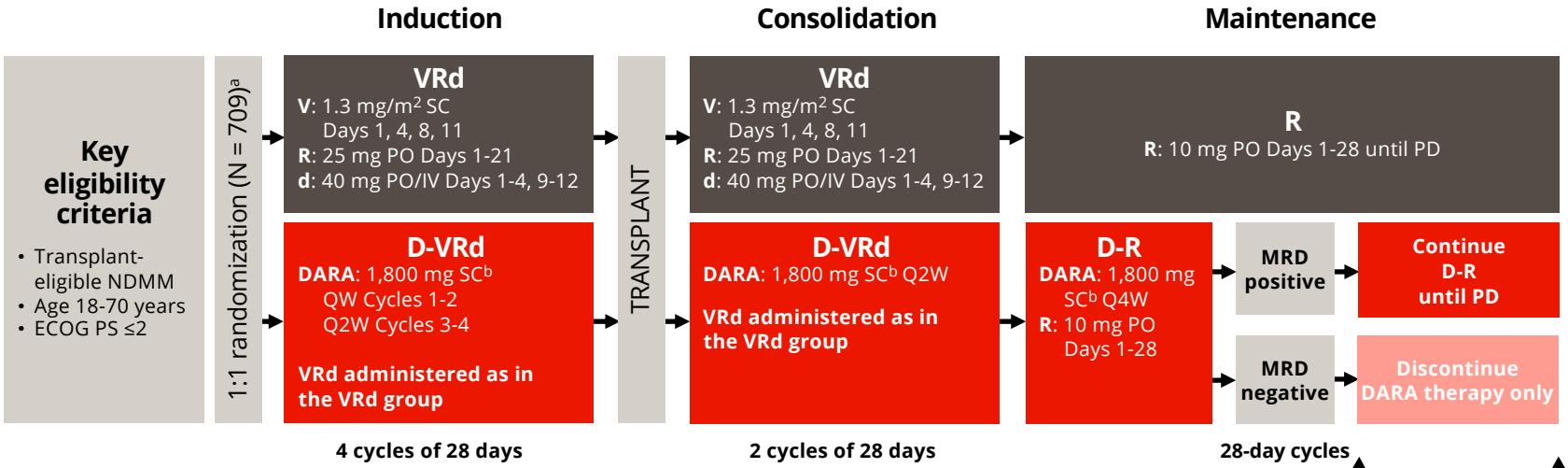
Pieter Sonneveld,[1] Meletios A. Dimopoulos,[2] Mario Boccadoro,[3] Hang Quach,[4] P. Joy Ho,[5] Meral Beksac,[6] Cyrille Hulin,[7] Elisabetta Antonioli,[8] Xavier Leleu,[9] Silvia Mangiacavalli,[10] Aurore Perrot,[11] Michele Cavo,[12] Angelo Belotti,[13] Annemiek Broijl,[1] Francesca Gay,[14] Roberto Mina,[14] Inger S. Nijhof,[15,16] Niels W.C.J. van de Donk,[15] Eirini Katodritou,[17] Fredrik Schjesvold,[18] Anna Sureda Balari,[19] Laura Rosiñol,[20] Michel Delforge,[21] Wilfried Roeloffzen,[22] Tobias Silzle,[23] Annette Vangsted,[24] Hermann Einsele,[25] Andrew Spencer,[26] Roman Hajek,[27] Artur Jurczyszyn,[28] Sarah Lonergan,[1] Tahamtan Ahmadi,[29] Yanfang Liu,[30] Jianping Wang,[30] Diego Vieyra,[30] Emilie M.J. van Brummelen,[30] Veronique Vanquickelberghe,[30] Anna Sitthi-Amorn,[30] Carla J. de Boer,[30] Robin Carson,[30] Paula Rodriguez-Otero,[31] Joan Bladé,[32] Philippe Moreau[33]

[1]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [2]National and Kapodistrian University of Athens, Athens, Greece; [3]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; [4]University of Melbourne, St Vincent's Hospital, Melbourne, Australia; [5]Institute of Haematology, Royal Prince Alfred Hospital and University of Sydney, Camperdown, NSW, Australia; [6]Ankara University, Ankara, Turkey; [7]Department of Hematology, Hôpital Haut Lévêque, University Hospital, Pessac, France; [8]Department of Hematology, Careggi Hospital and University of Florence, Firenze, Italy; [9]University of Poitiers, CHU and Inserm 1313, Poitiers, France; [10]Hematology Division, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; [11]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [12]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [13]Department of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy; [14]Division of Hematology 1, AOU Città della Salute e della Scienza di Torino, and Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy; [15]Department of Hematology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [16]Department of Hematology, St Antonius Hospital, Nieuwegein, The Netherlands; [17]Department of Hematology, Theagenion Cancer Hospital, Thessaloniki, Greece; [18]Oslo Myeloma Center, Department of Hematology, and KG Jebsen Center for B-cell Malignancies, University of Oslo, Oslo, Norway; [19]Hematology Department, Institut Català d'Oncologia - Hospitalet, IDIBELL, University of Barcelona, Barcelona, Spain; [20]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; [21]University of Leuven, Leuven, Belgium; [22]University Medical Center Groningen, Groningen, The Netherlands; [23]Department of Medical Oncology and Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [24]Department of Hematology, Rigshospitalet, Copenhagen, Denmark; [25]Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany; [26]Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne, Australia; [27]Department of Hematooncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [28]Plasma Cell Dyscrasias Center, Department of Hematology, Jagiellonian University Medical College, Kraków, Poland; [29]Genmab US, Inc., Plainsboro, NJ, USA; [30]Janssen Research & Development, LLC; [31]Department of Hematology, Cancer Center Clínica Universidad de Navarra, Pamplona, Navarra, Spain; [32]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; and GEM/PETHEMA; [33]Hematology Department, University Hospital Hôtel-Dieu, Nantes, France

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

https://www.congresshub.com/Oncology/ASH2023/Daratumumab/Sonneveld

PERSEUS: Study Design



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA). [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

PERSEUS: Baseline Demographic and Clinical Characteristics

	D-VRd (n = 355)	VRd (n = 354)
Age		
Median (range), years	61.0 (32-70)	59.0 (31-70)
Category, n (%)		
<50 years	54 (15.2)	54 (15.3)
≥50 and <65 years	207 (58.3)	213 (60.2)
≥65 years	94 (26.5)	87 (24.6)
Male, n (%)	211 (59.4)	205 (57.9)
ECOG PS,[a] n (%)		
0	221 (62.3)	230 (65.0)
1	114 (32.1)	108 (30.5)
2	19 (5.4)	16 (4.5)
3	1 (0.3)	0
MM diagnosis, n (%)		
N	354	352
CRAB criteria only[b]	125 (35.3)	113 (32.1)
Biomarkers of malignancy only	52 (14.7)	65 (18.5)
CRAB criteria and biomarkers of malignancy	177 (50.0)	174 (49.4)

	D-VRd (n = 355)	VRd (n = 354)
ISS stage,[c] n (%)		
N	355	353
I	186 (52.4)	178 (50.4)
II	114 (32.1)	125 (35.4)
III	55 (15.5)	50 (14.2)
Number of extramedullary plasmacytomas, n (%)		
0	340 (95.8)	338 (95.5)
≥1	15 (4.2)	16 (4.5)
Cytogenetic profile,[d] n (%)		
Standard risk	264 (74.4)	266 (75.1)
High risk	76 (21.4)	78 (22.0)
Indeterminate	15 (4.2)	10 (2.8)

- **D-VRd and VRd treatment arms were well balanced**

MM, multiple myeloma; CRAB, calcium, renal, anemia, bone. [a]ECOG PS is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. One patient had an ECOG PS score of 0 at randomization that worsened to a score of 3 at baseline. [b]≥1 of the CRAB criteria. [c]Based on the combination of serum β2-microglobulin and albumin levels. Higher stages indicate more advanced disease. [d]Based on fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

PERSEUS: Stem Cell Collection and Transplantation

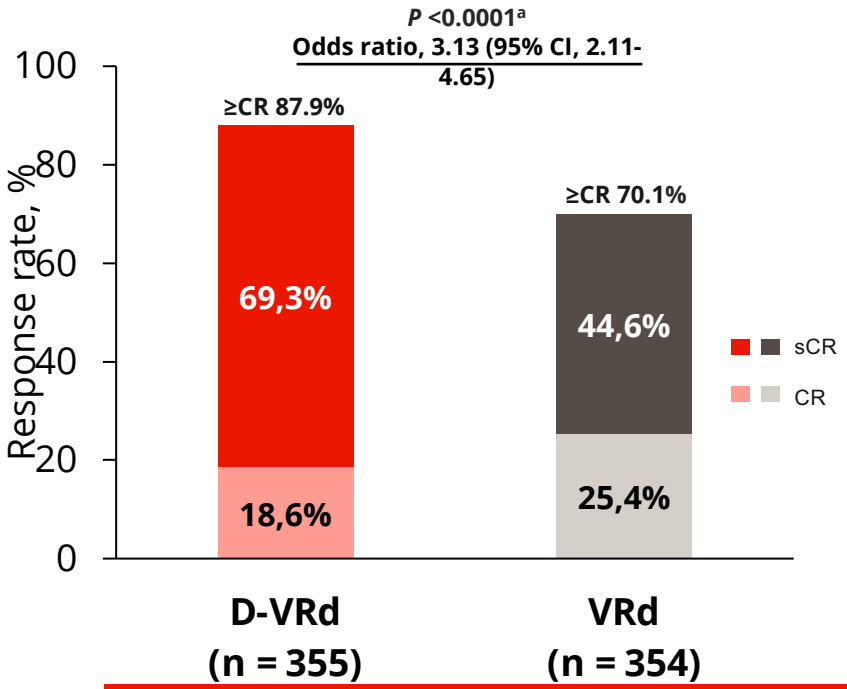
	D-VRd	VRd
Patients receiving plerixafor for mobilization, n (%)[a]	134 (40.0)	72 (22.7)
Median $CD34^+$ cells collected, 10^6/kg[b]	5.5	7.4
Patients receiving transplant, n (%)[c]	315 (89.7)	302 (87.0)
Patients achieving hematopoietic reconstitution, n (%)[d]	314 (99.7)	300 (99.3)
Median time to engraftment, days[e]	14	14

- **Stem cell mobilization and collection were feasible with D-VRd**
- **D-VRd did not impact the ability to receive transplant or engraftment**

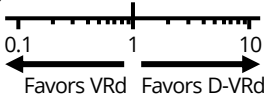
[a]Among patients who proceeded to stem cell mobilization (D-VRd, n = 335; VRd, n = 317). [b]Among patients who had stem cells collected (D-VRd, n = 326; VRd, n = 314). [c]In the safety population (D-VRd, n = 351; VRd, n = 347). [d]Among patients who proceeded to transplant (D-VRd, n = 315; VRd, n = 302). [e]Number of days from the transplant date, excluding patients whose counts did not nadir below the set threshold. The date of engraftment post-ASCT was defined as the latest date of absolute neutrophil count ≥0.5 × 10^9/L and platelet count ≥20 × 10^9/L. Patients with hematopoietic reconstitution were included (D-VRd, n = 314; VRd, n = 300).

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

PERSEUS: Overall ≥CR Rates



Subgroup	VRd no. of patients with ≥CR/total no. (%)	D-VRd no. of patients with ≥CR/total no. (%)	Odds ratio (95% CI)
Sex			
Male	143/205 (69.8)	185/211 (87.7)	3.08 (1.86-5.12)
Female	105/149 (70.5)	127/144 (88.2)	3.13 (1.69-5.80)
Age			
<65 y	186/267 (69.7)	235/261 (90.0)	3.94 (2.43-6.37)
≥65 y	62/87 (71.3)	77/94 (81.9)	1.83 (0.91-3.68)
Race			
White	226/323 (70.0)	289/330 (87.6)	3.03 (2.02-4.53)
Other	22/31 (71.0)	23/25 (92.0)	4.70 (0.91-24.25)
ISS stage			
I	129/178 (72.5)	167/186 (89.8)	3.34 (1.87-5.95)
II	84/125 (67.2)	101/114 (88.6)	3.79 (1.91-7.54)
III	34/50 (68.0)	44/55 (80.0)	1.88 (0.77-4.58)
Type of MM			
IgG	122/185 (65.9)	178/204 (87.3)	3.54 (2.12-5.90)
Non-IgG	73/96 (76.0)	72/78 (92.3)	3.78 (1.45-9.83)
Cytogenetic risk			
Standard risk	182/266 (68.4)	234/264 (88.6)	3.60 (2.27-5.70)
High risk	59/78 (75.6)	63/76 (82.9)	1.56 (0.71-3.44)
Indeterminate	7/10 (70.0)	15/15 (100)	NE (NE-NE)
ECOG PS			
0	160/230 (69.6)	195/221 (88.2)	3.28 (2.00-5.39)
≥1	88/124 (71.0)	117/134 (87.3)	2.82 (1.49-5.34)

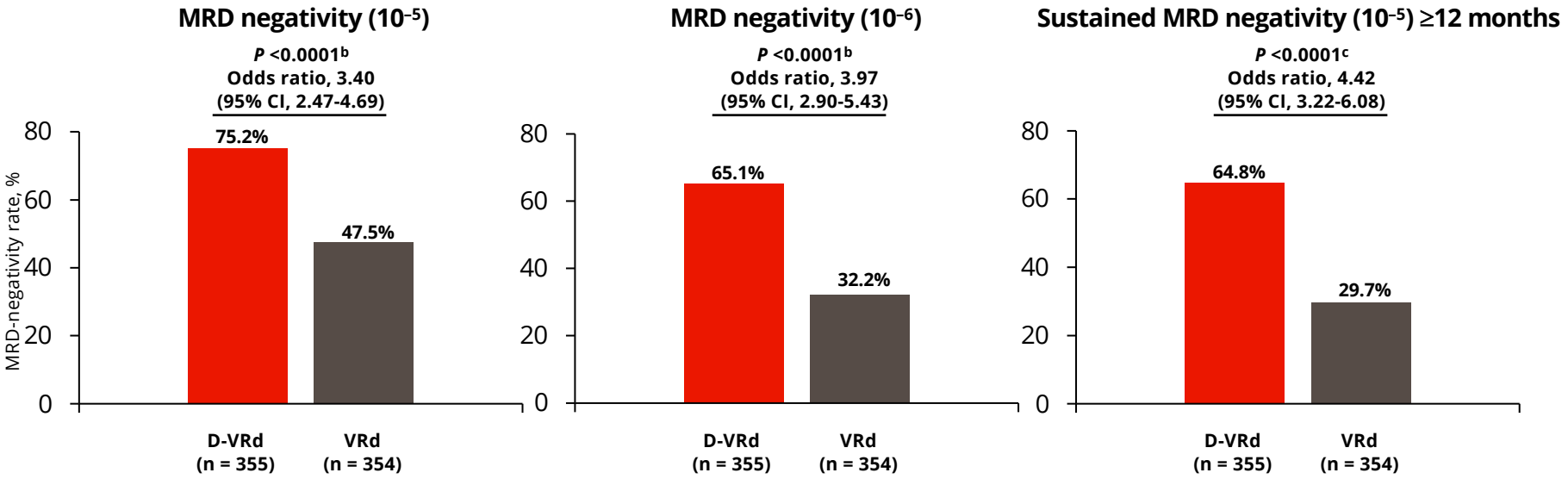


- **Overall ≥CR rate was significantly higher with D-VRd versus VRd**
- **≥CR rate was improved with D-VRd versus VRd across subgroups**

sCR, stringent complete response; NE, not estimable. [a]*P* value (2-sided) was calculated with the use of the stratified Cochran–Mantel–Haenszel chi-squared test.

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

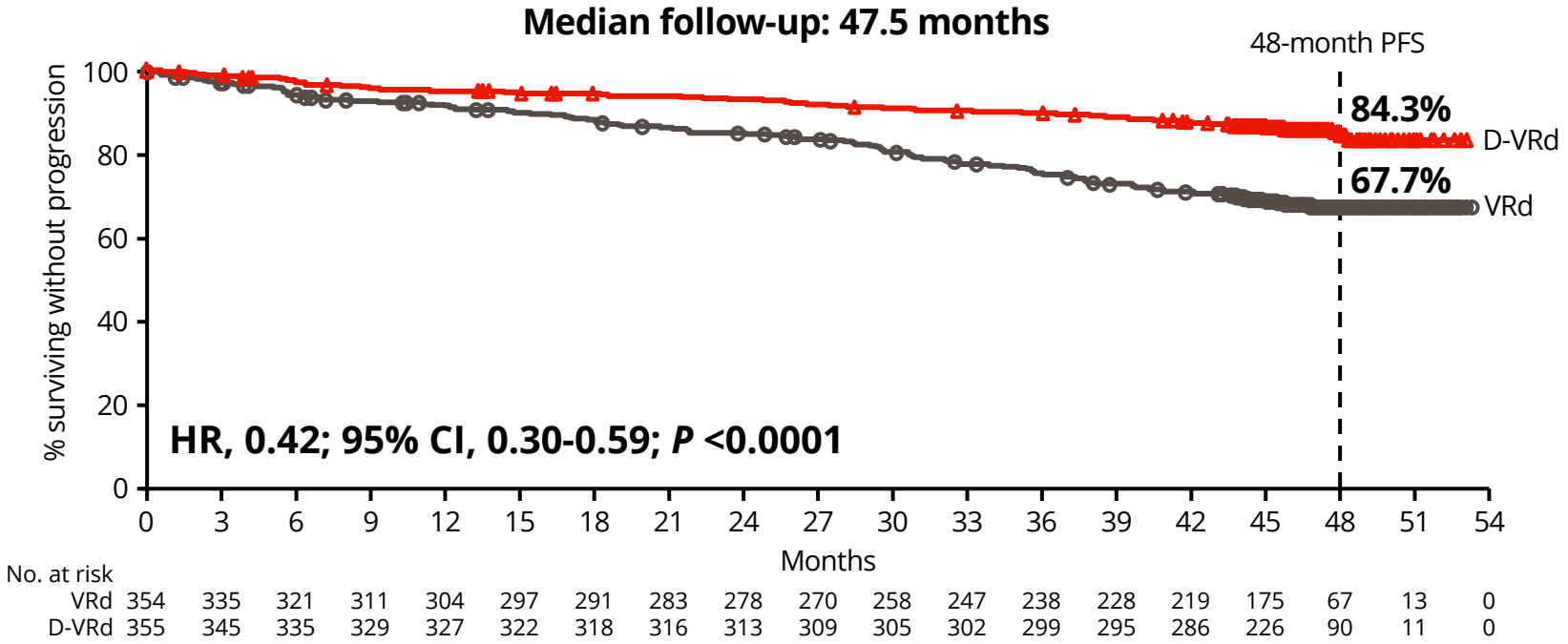
PERSEUS: Overall and Sustained MRD-negativity Rates[a]



- **Deep and durable MRD negativity was achieved with D-VRd**
- **64% (207/322) of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity per protocol[d]**

[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via next-generation sequencing (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA). [b]*P* values were calculated with the use of the stratified Cochran–Mantel–Haenszel chi-squared test. [c]*P* value was calculated with the use of Fisher's exact test. [d]After ≥24 months of maintenance therapy, DARA was discontinued in patients who achieved ≥CR and sustained MRD negativity (10^{-5}) for ≥12 months.

PERSEUS: Progression-free Survival

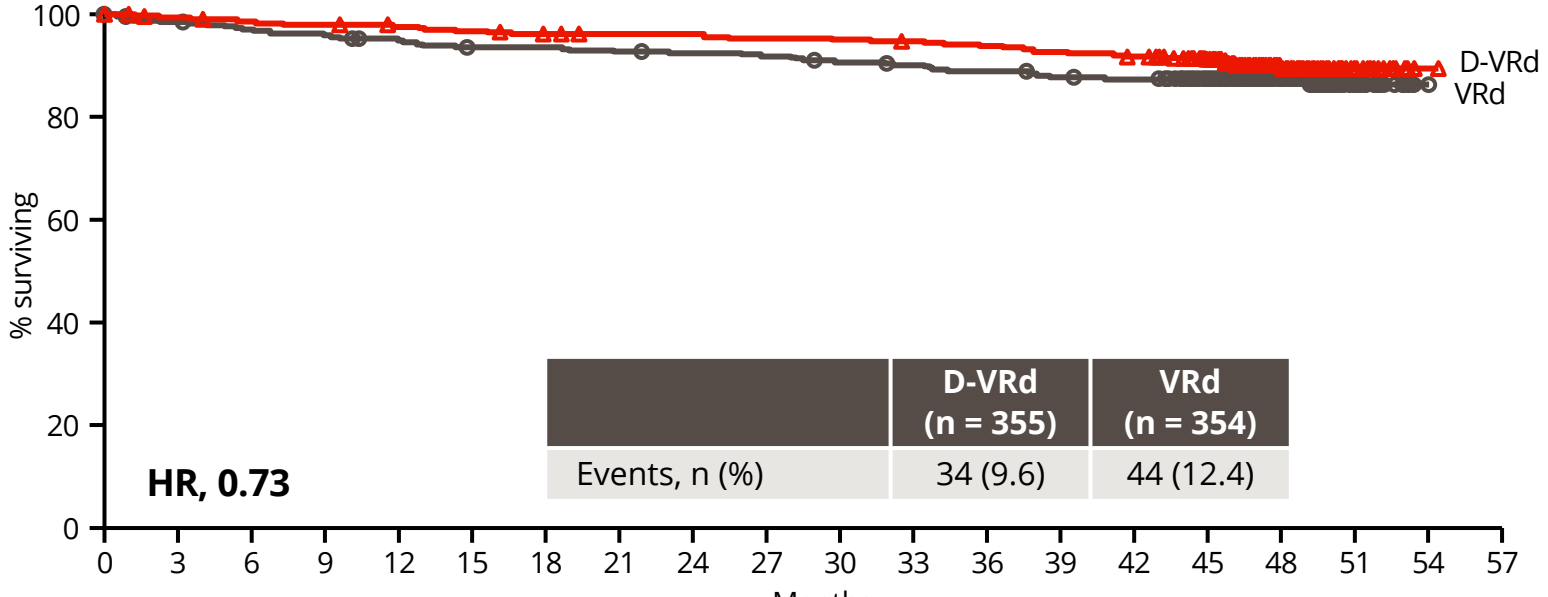


- **58% reduction in the risk of progression or death in patients receiving D-VRd**

HR, hazard ratio; CI, confidence interval.

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

PERSEUS: Overall Survival



	D-VRd (n = 355)	VRd (n = 354)
Events, n (%)	34 (9.6)	44 (12.4)

No. at risk

VRd	354	343	337	334	328	322	322	319	317	315	310	307	303	298	296	263	127	27	1	0
D-VRd	355	347	343	341	338	335	331	329	329	326	325	323	321	316	312	284	135	21	1	0

- **OS data trend favorably for D-VRd**

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

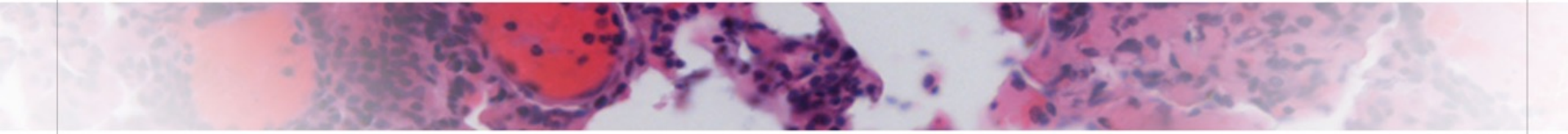
PERSEUS: Safety

Event, n (%)[a]	D-VRd (n = 351)		VRd (n = 347)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
HEMATOLOGIC				
Neutropenia	**243 (69.2)**	**218 (62.1)**	**204 (58.8)**	**177 (51.0)**
Thrombocytopenia	**170 (48.4)**	**102 (29.1)**	**119 (34.3)**	**60 (17.3)**
Anemia	78 (22.2)	21 (6.0)	72 (20.7)	22 (6.3)
Febrile neutropenia	34 (9.7)	33 (9.4)	38 (11.0)	35 (10.1)
NON-HEMATOLOGIC				
Diarrhea	214 (61.0)	37 (10.5)	188 (54.2)	27 (7.8)
Peripheral sensory neuropathy	**188 (53.6)**	**15 (4.3)**	**179 (51.6)**	**14 (4.0)**
Constipation	119 (33.9)	8 (2.3)	118 (34.0)	6 (1.7)
Pyrexia	111 (31.6)	8 (2.3)	109 (31.4)	9 (2.6)
Insomnia	95 (27.1)	8 (2.3)	61 (17.6)	6 (1.7)
Asthenia	94 (26.8)	12 (3.4)	89 (25.6)	9 (2.6)
Cough	85 (24.2)	1 (0.3)	51 (14.7)	0
Fatigue	84 (23.9)	10 (2.8)	92 (26.5)	18 (5.2)
Rash	82 (23.4)	9 (2.6)	94 (27.1)	17 (4.9)
Back pain	80 (22.8)	2 (0.6)	66 (19.0)	1 (0.3)
Peripheral edema	72 (20.5)	4 (1.1)	74 (21.3)	1 (0.3)
Nausea	71 (20.2)	2 (0.6)	58 (16.7)	2 (0.6)
Infections	**305 (86.9)**	**124 (35.3)**	**266 (76.7)**	**95 (27.4)**
COVID-19	123 (35.0)	12 (3.4)	83 (23.9)	4 (1.2)
Upper respiratory tract infection	111 (31.6)	2 (0.6)	87 (25.1)	6 (1.7)
Pneumonia	64 (18.2)	37 (10.5)	38 (11.0)	21 (6.1)

TEAE, treatment-emergent adverse event. [a]TEAEs of any grade reported in ≥20% of patients in either treatment group and grade 3 or 4 TEAEs reported in ≥10% of patients in either treatment group.

Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



EMN

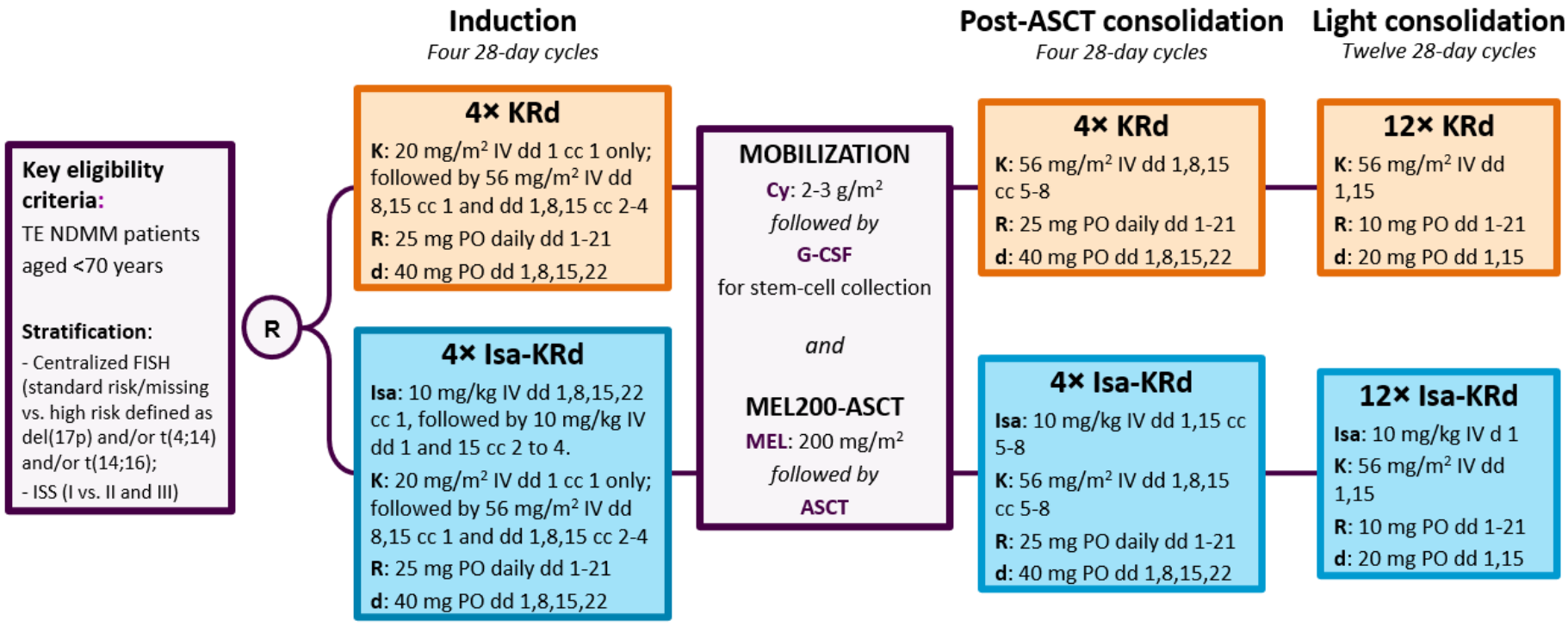
Results of the Phase III Randomized IsKia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone Vs Carfilzomib-Lenalidomide-Dexamethasone as Pre-Transplant Induction and Post-Transplant Consolidation in Newly Diagnosed Multiple Myeloma Patients

Francesca Gay, MD, PhD[1,2]; Wilfried Roeloffzen, MD, PhD[3]; Meletios Athanasios Dimopoulos, MD, PhD[4]; Laura Rosiñol, MD, PhD[5]; Marjolein van der Klift, MD, PhD[6]; Roberto Mina, MD[1,2]; Albert Oriol Rocafiguera, MD[7]; Eirini Katodritou, MD[8]; Ka Lung Wu, MD, PhD[9]; Paula Rodriguez Otero, MD, PhD[10]; Roman Hájek, MD, PhD[11,12]; Elisabetta Antonioli, MD[13]; Mark van Duin, PhD[14]; Mattia D'Agostino, MD[1,2]; Joaquín Martínez-López, MD, PhD[15]; Elena M. van Leeuwen-Segarceanu, MD, PhD[16]; Paola Tacchetti, MD, PhD[17]; Niels W.C.J. van de Donk, MD, PhD[18]; Katja Weisel, MD[19]; Luděk Pour, MD[20]; Jakub Radocha, MD, PhD[21]; Angelo Belotti, MD[22]; Fredrik Schjesvold, MD, PhD[23,24]; Joan Bladé, MD, PhD[25]; Hermann Einsele, MD, PhD[26]; Pieter Sonneveld, MD, PhD[14]; Mario Boccadoro, MD[27]; Annemiek Broijl, MD, PhD[28]

1. Division of Hematology, Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy; 2. Division of Hematology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, University of Torino, Torino, Italy; 3. Department of Hematology, University Medical Center Groningen, Groningen, the Netherlands; 4. Hematology and Medical Oncology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens, Greece; 5. Amyloidosis and Myeloma Unit, Department of Hematology, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; 6. Department of Internal Medicine, Amphia Hospital, Breda, the Netherlands; 7. Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain; 8. Department of Hematology, Theagenion Cancer Hospital, Thessaloniki, Greece; 9. ZNA Stuivenberg, Lange Beeldekenstraat 267, 2060, Antwerp, Belgium; 10. Clínica Universidad de Navarra, Pamplona, Spain; 11. Department of Haematooncology, University Hospital Ostrava, Ostrava, Czech Republic; 12. Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; 13. Hematology Unit, AOU Careggi, Florence, Italy; 14. Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands; 15. Hematology Department, Hospital Universitario 12 de Octubre, Medicine Department Complutense University, CNIO, Madrid, Spain; 16. Department of Hematology, St. Antonius Hospital, Nieuwegein, the Netherlands; 17. IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; 18. Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Hematology, Cancer Center Amsterdam, Amsterdam, the Netherlands; 19. Department of Oncology, Hematology and BMT, University Medical Center of Hamburg-Eppendorf, Germany; 20. Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Brno, Czech Republic; 21. 4th Department of Internal Medicine-Hematology, University Hospital Hradec Kralove, Charles University, Faculty of Medicine in Hradec Kralove, Hradec Kralove, Czech Republic; 22. Department of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy; 23. Oslo Myeloma Center, Department of Hematology, Oslo University Hospital, Oslo, Norway; 24. KG Jebsen Center for B cell malignancies, University of Oslo, Oslo, Norway; 25. Hematology Department, Hospital Clínic, IDIBAPS, Barcelona, Spain; 26. Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany; 27. European Myeloma Network, EMN, Italy; 28. Erasmus MC Cancer Institute, Rotterdam, Netherlands

IsKia EMN24 Study Design

42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021

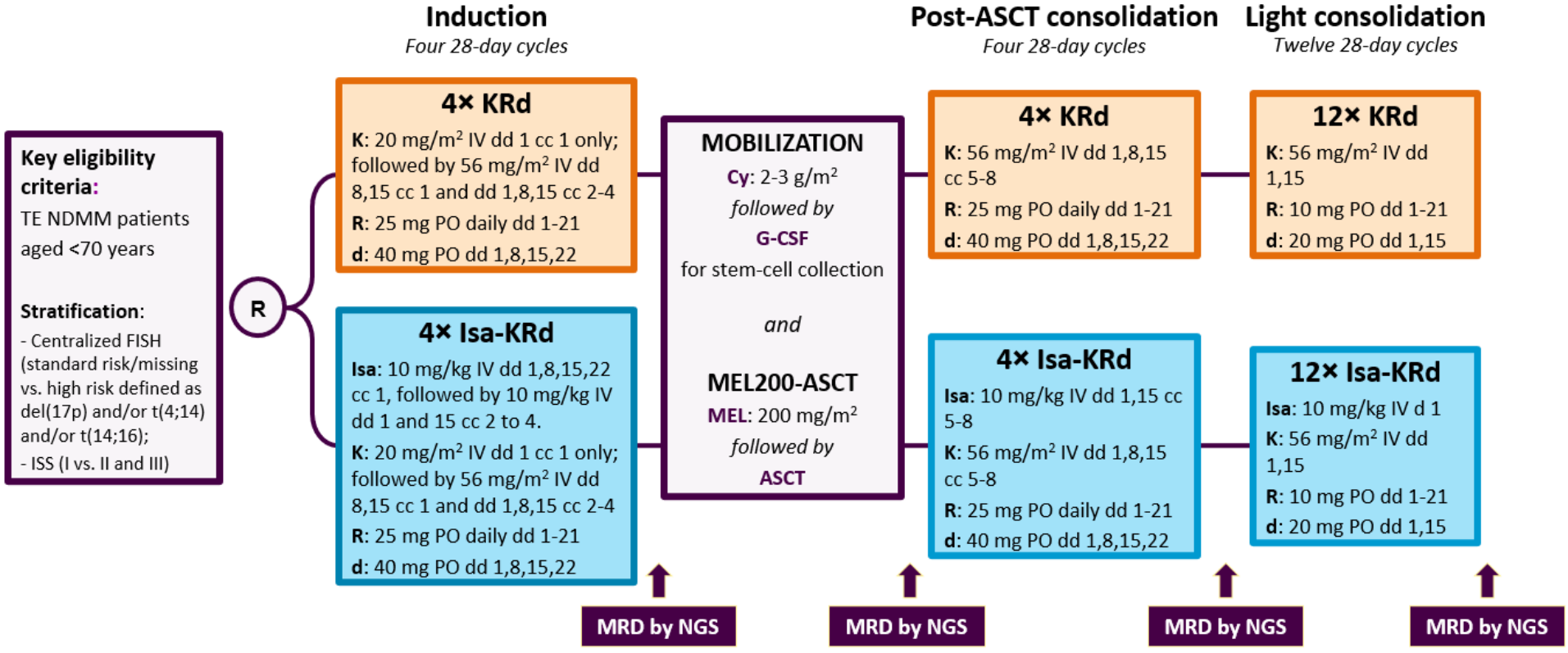


The EMN24 IsKia trial is registered with ClinicalTrials.gov: NCT04483739; it was sponsored by the European Myeloma Network (EMN).
All patients provided informed consent. This presentation includes discussion of the off-label use of a drug or drugs for the treatment of multiple myeloma.

TE, transplant-eligible; NDMM, newly diagnosed multiple myeloma; FISH, fluorescence *in situ* hybridization; del, deletion; t, translocation; ISS, International Staging System stage; R, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenous; dd, days; cc, cycles; PO, orally; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; MEL, melphalan; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; NGS, next-generation sequencing; PFS, progression-free survival.

IsKia EMN24 Study Design

42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021



TE, transplant-eligible; NDMM, newly diagnosed multiple myeloma; FISH, fluorescence *in situ* hybridization; del, deletion; t, translocation; ISS, International Staging System stage; R, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenous; dd, days; cc, cycles; PO, orally; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; MEL, melphalan; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; NGS, next-generation sequencing; PFS, progression-free survival.

IsKia EMN24 Study Design

42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021

Key eligibility criteria:
TE NDMM patients aged <70 years

Stratification:
- Centralized FISH (standard risk/missing vs. high risk defined as del(17p) and/or t(4;14) and/or t(14;16);
- ISS (I vs. II and III)

R

Induction
Four 28-day cycles

4× KRd
K: 20 mg/m² IV dd 1 cc 1 only; followed by 56 mg/m² IV dd 8,15 cc 1 and dd 1,8,15 cc 2-4
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1,8,15,22

4× Isa-KRd
Isa: 10 mg/kg IV dd 1,8,15,22 cc 1, followed by 10 mg/kg IV dd 1 and 15 cc 2 to 4.
K: 20 mg/m² IV dd 1 cc 1 only; followed by 56 mg/m² IV dd 8,15 cc 1 and dd 1,8,15 cc 2-4
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1,8,15,22

MOBILIZATION
Cy: 2-3 g/m²
followed by
G-CSF
for stem-cell collection

and

MEL200-ASCT
MEL: 200 mg/m²
followed by
ASCT

Post-ASCT consolidation

4× KRd
K: 56 mg/m² IV dd 1,8,15 cc 5-8
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1,8,15,22

4× Isa-KRd
Isa: 10 mg/kg IV dd 1,15 cc 5-8
K: 56 mg/m² IV dd 1,8,15 cc 5-8
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1,8,15,22

MRD by NGS

Primary endpoint:
MRD negativity by NGS after post-ASCT consolidation

Key secondary endpoints:
MRD negativity after induction;
PFS

Other secondary endpoints:
Sustained MRD negativity

TE, transplant-eligible; NDMM, newly diagnosed multiple myeloma; FISH, fluorescence *in situ* hybridization; del, deletion; t, translocation; ISS, International Staging System stage; R, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenous; dd, days; cc, cycles; PO, orally; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; MEL, melphalan; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; NGS, next-generation sequencing; PFS, progression-free survival.

Patient characteristics

		Isa-KRd n=151	KRd n=151
Age, years	Median (IQR)	61 (55–66)	60 (54–63)
Sex, n (%)	Female	72 (48)	67 (44)
	Male	79 (52)	84 (56)
Cytogenetic risk as per IMWG, n (%) *High risk: t(4;14), t(14;16), or del(17p)*	Standard risk	115 (82)	113 (81)
	High risk	25 (18)	26 (19)
	Missing	*11*	*12*
No. of HRCA risk: 0 vs. 1 vs. 2+ HRCA, n (%) *del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21)*	0 HRCA	78 (56)	75 (54)
	1 HRCA	49 (35)	49 (35)
	2+ HRCA	13 (9)	15 (11)
	Missing	*11*	*12*
R-ISS, n (%)	I	50 (35)	48 (34)
	II	82 (58)	85 (59)
	III	10 (7)	10 (7)
	Missing	*9*	*8*
R2-ISS, n (%)	I	34 (24)	35 (25)
	II	45 (32)	47 (34)
	III	52 (37)	51 (37)
	IV	8 (6)	6 (4)
	Missing	*12*	*12*

% are calculated on the number of patients whose data were available.; % may not total 100 because of rounding

Sonneveld P, et al. Blood. 2016 Jun 16;127(24):2955-62. doi: 10.1182/blood-2016-01-631200.

D'Agostino M et al. J Clin Oncol. 2022 Oct 10;40(29):3406-3418. doi: 10.1200/JCO.21.02614. Erratum in: J Clin Oncol. 2022 Dec 1;40(34):4032.

Palumbo A, et al. J Clin Oncol. 2015 Sep 10;33(26):2863-9. doi: 10.1200/JCO.2015.61.2267.

Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IQR, interquartile range; IMWG, International Myeloma Working Group; t, translocation; del, deletion; No., number; HRCA, high-risk cytogenetic abnormalities; amp, amplification; R-ISS, Revised International Staging System stage; R2-ISS, Second Revision of the International Staging System stage.

Patient characteristics

		Isa-KRd n=151	KRd n=151
Age, years	Median (IQR)	61 (55–66)	60 (54–63)
Sex, n (%)	Female	72 (48)	67 (44)
	Male	79 (52)	84 (56)
Cytogenetic risk as per IMWG, n (%) *High risk: t(4;14), t(14;16), or del(17p)*	Standard risk	115 (82)	113 (81)
	High risk	25 (18)	26 (19)
	Missing	*11*	*12*
No. of HRCA risk: 0 vs. 1 vs. 2+ HRCA, n (%) *del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21)*	0 HRCA	78 (56)	75 (54)
	1 HRCA	49 (35)	49 (35)
	2+ HRCA	13 (9)	15 (11)
	Missing	*11*	*12*
R-ISS, n (%)	I	50 (35)	48 (34)
	II	82 (58)	85 (59)
	III	10 (7)	10 (7)
	Missing	*9*	*8*
R2-ISS, n (%)	I	34 (24)	35 (25)
	II	45 (32)	47 (34)
	III	52 (37)	51 (37)
	IV	8 (6)	6 (4)
	Missing	*12*	*12*

% are calculated on the number of patients whose data were available.; % may not total 100 because of rounding

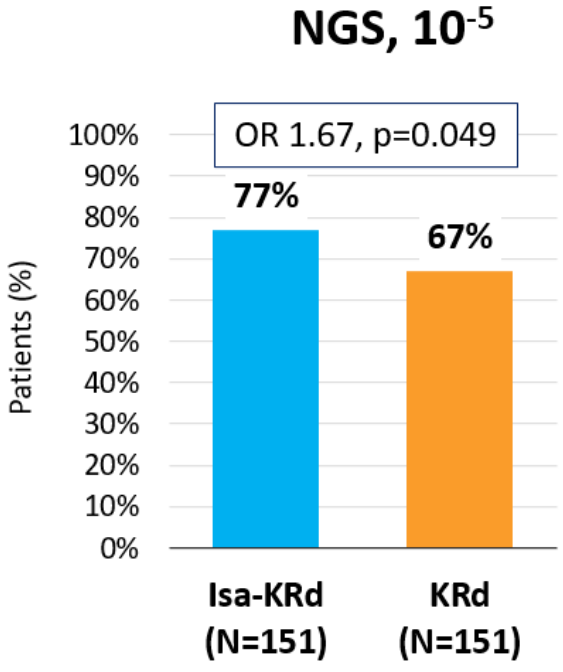
Sonneveld P, et al. Blood. 2016 Jun 16;127(24):2955-62. doi: 10.1182/blood-2016-01-631200.

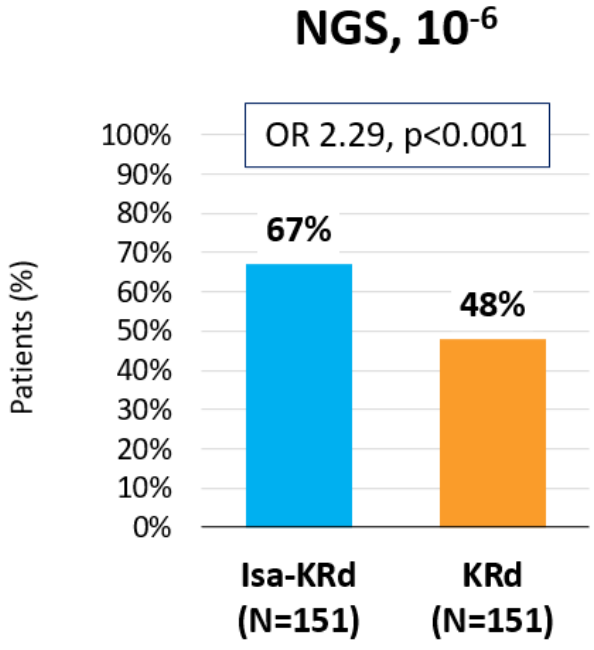
D'Agostino M et al. J Clin Oncol. 2022 Oct 10;40(29):3406-3418. doi: 10.1200/JCO.21.02614. Erratum in: J Clin Oncol. 2022 Dec 1;40(34):4032.

Palumbo A, et al. J Clin Oncol. 2015 Sep 10;33(26):2863-9. doi: 10.1200/JCO.2015.61.2267.

Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IQR, interquartile range; IMWG, International Myeloma Working Group; t, translocation; del, deletion; No., number; HRCA, high-risk cytogenetic abnormalities; amp, amplification; R-ISS, Revised International Staging System stage; R2-ISS, Second Revision of the International Staging System stage.

Primary Endpoint: Post-consolidation MRD negativity (ITT analysis)





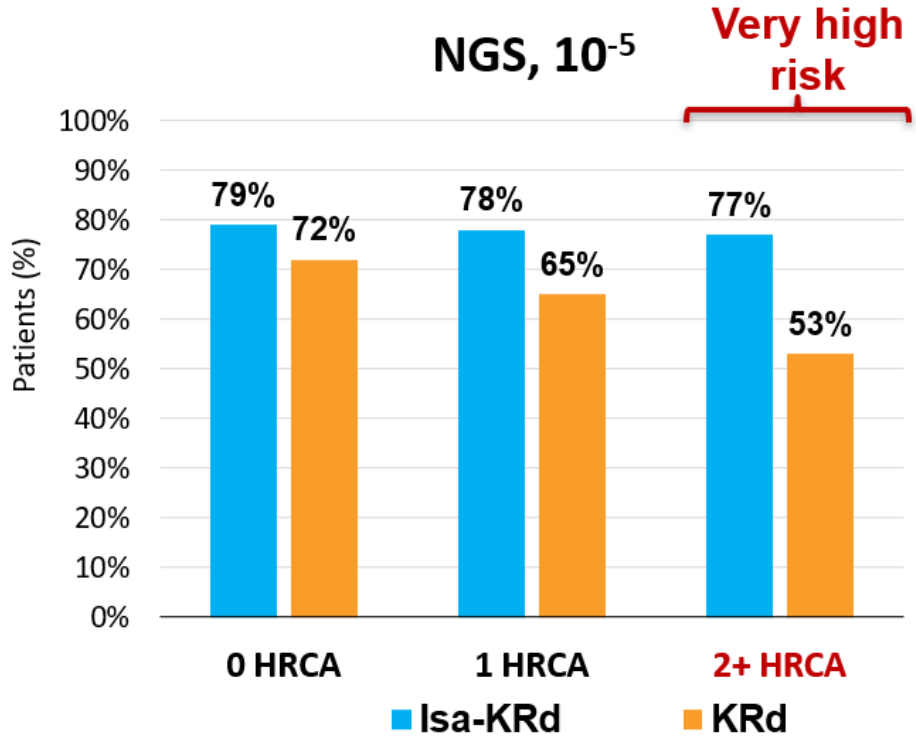
≥VGPR after consolidation was 94% in both arms; ≥CR 74% vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms.
Consistent MRD results were detected by next-generation flow

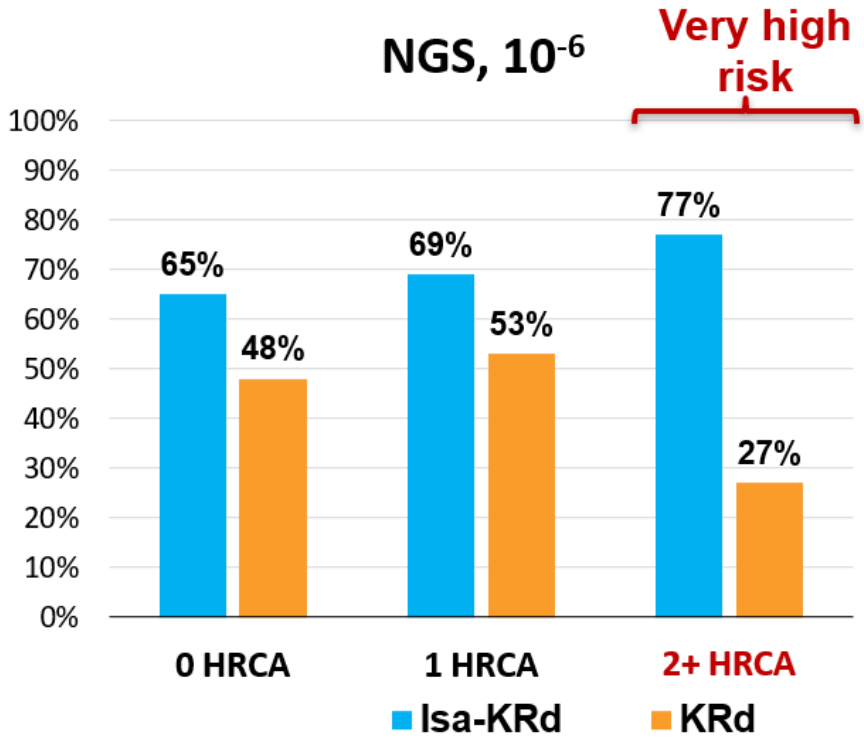
In the logistic regression analysis, ORs, 95% CIs, and p-values were adjusted for stratification factor.

MRD, minimal residual disease; ITT, intention to treat; NGS, next-generation sequencing; OR, odds ratio; p, p-value; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; CI, confidence interval.

Post-consolidation MRD negativity by NGS

Subgroup analysis by cytogenetic risk





1 HRCA was defined as the presence of one of the following high-risk cytogenetic abnormalities: del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21); 2+ HRCA was defined as the presence of at least two high-risk cytogenetic abnormalities.

MRD, minimal residual disease; NGS, next-generation sequencing; HRCA, high-risk cytogenetic abnormalities; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; del, deletion; t, translocation; amp, amplification.

Safety analysis: treatment-related adverse events

	Isa-KRd (n=151)		KRd (n=151)	
	Any grade, n (%)	Grade 3-4, n (%)	Any grade, n(%)	Grade 3-4, n (%)
Pts with ≥1 hematologic toxicity	83 (55)	61 (40)	67 (44)	46 (30)
Anemia	32 (21)	5 (3)	28 (19)	5 (3)
Neutropenia	62 (41)	55 (36)*	39 (26)	33 (22)*
Thrombocytopenia	51 (34)	22 (15)	38 (25)	25 (17)
Pts with ≥1 Non-Hematologic toxicity	136 (90)	61 (41)	129 (85)	56 (37)
Infections (excluding COVID19)	55 (36)	23 (15)	49 (32)	17 (11)
Asthenia/fatigue	37 (25)	5 (3)	40 (26)	3 (2)
Dyspnea	20 (13)	2 (1)	9 (6)	1 (<1)
Rash	33 (22)	5 (3)	40 (26)	5 (3)
Peripheral neuropathy	22 (15)	0	25 (17)	0
Infusion-related reactions	30 (20)	5 (3)	2 (1)	0
Cardiac disorders	11 (7)	1 (<1)	19 (13)	5 (3)
Vascular disorders	29 (19)	7 (5)	33 (22)	15 (10)
Hypertension	5 (3)	2 (1)	6 (4)	3 (2)
Thromboembolism	12 (8)	4 (3)	16 (11)	9 (6)
Gastrointestinal disorders	79 (52)	10 (7)	73 (48)	8 (5)
Nausea	36 (24)	4 (3)	31 (21)	2 (1)
Vomiting	18 (12)	2 (1)	12 (8)	1 (<1)
Diarrhea	41 (27)	6 (4)	37 (25)	5 (3)

SARS-CoV-2 infection

Isa-KRd (n=151)		KRd (n=151)	
Any grade, n (%)	Grade ≥3, n (%)	Any grade, n (%)	Grade ≥3, n (%)
39 (26)	3 (2)	28 (19)	2 (1)

*p-value =0.008

Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone.

Daratumumab Carfilzomib Lenalidomide and Dexamethasone induction and consolidation with tandem transplant in high-risk newly diagnosed myeloma patients: results of the phase 2 study IFM 2018-04

Cyrille Touzeau[1], Aurore Perrot[2], Cyrille Hulin[3], Salomon Manier[4], Margaret Macro[5], Marie-Lorraine Chretien[6], Lionel Karlin[7], Martine Escoffre[8], Caroline Jacquet[9], Mourad Tiab[10], Xavier Leleu[11], Hervé Avet-Loiseau[2], Alexandra Jobert[12], Lucie Planche[12], Jill Corre[2], Philippe Moreau[1]

[1] Service d'hématologie, CHU Hotel Dieu, Nantes, France. [2] CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France. [3] Service d'hématologie, Hôpital Haut-Lévêque, CHU de Bordeaux, Pessac, France. [4] Maladies du Sang, CHRU de Lille, France. [5] Service d'hématologie, CHU Caen, France. [6] Hématologie Clinique, CHU Dijon Bourgogne, France. [7] Hôpital Lyon Sud, Pierre-benite, France. [8] Service d'hématologie, CHU de Rennes, France. [9] Service d'hématologie, CHU Nancy, Vandoeuvre-lès-Nancy, France. [10] Service d'hématologie, Centre Hospitalier Departemental, La Roche sur Yon, France. [11] Service d'hématologie, CHU de Poitiers, France. [12] Département de recherche clinique, CHU Hotel Dieu, Nantes, France.

American Society *of* Hematology

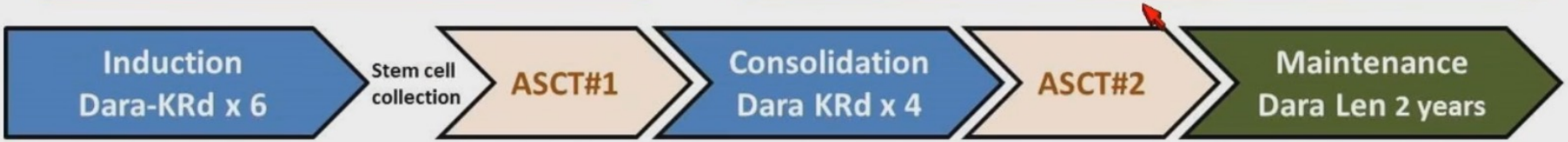
2018-04 Study design

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 :** Feasability
  primary endpoint : >70% patients receiving 2nd transplant
- **Secondary Objectives:** Safety, ORR, PFS, OS, stem-cell collection



Dara : 16 mg/kg IV D1,8,15,22 (cycle 1 and 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 cycle**	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 cycle**	**Mel 200**	**Dara :** 16 mg/kg IV every 8 weeks **Len :** 10 mg 21/28

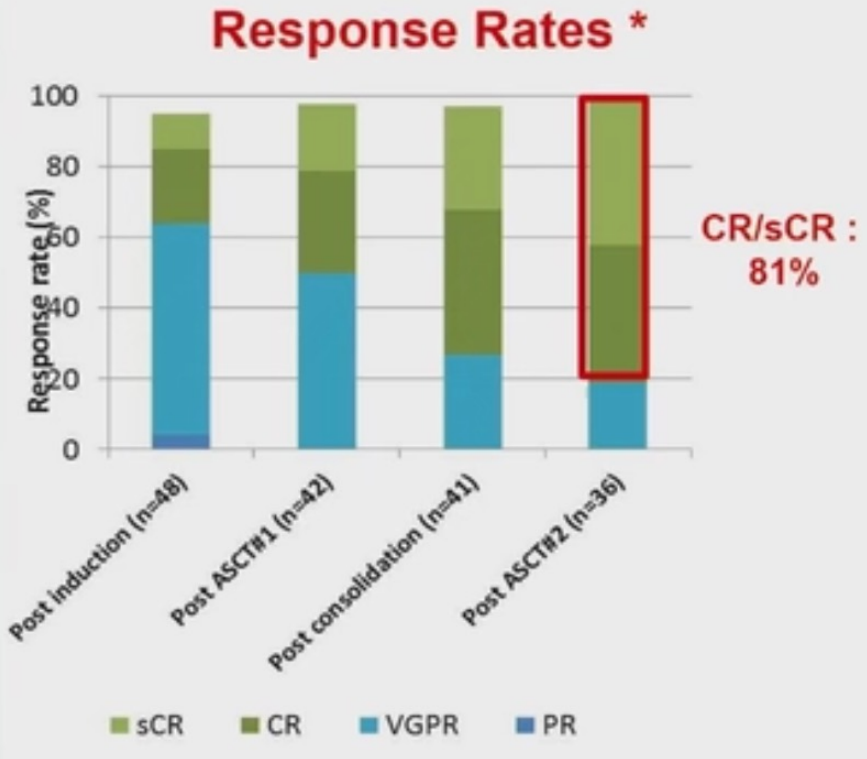
Baseline characteristics

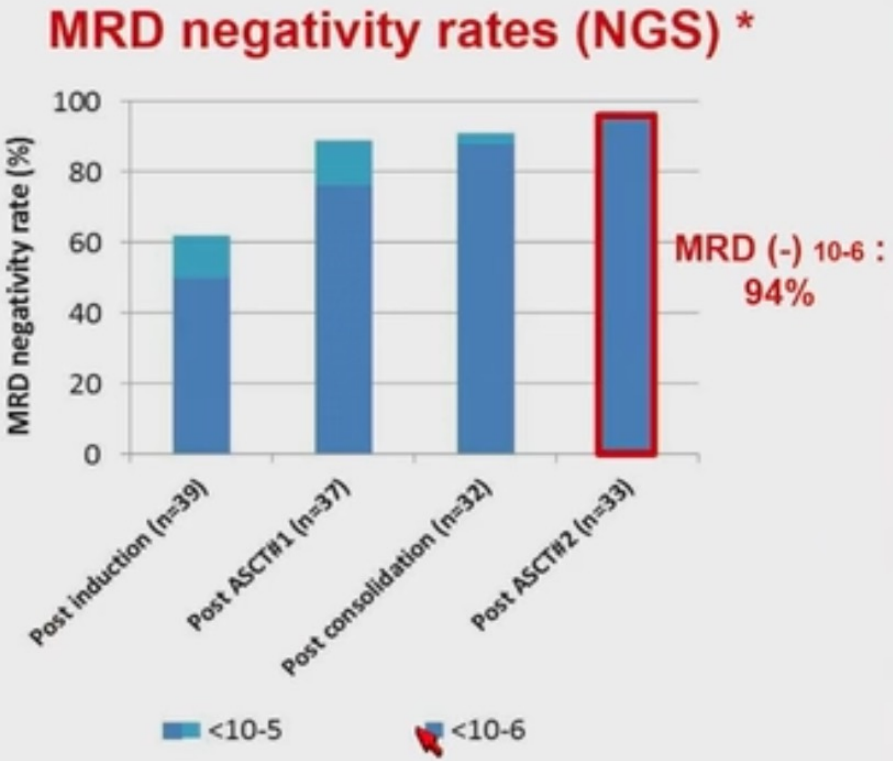
	N=50
Median age (range), years	57 (38-65)
ECOG PS	
0-1	47 (94%)
2	3 (6%)
ISS score	
stage 1	21 (42%)
stage 2	17 (34%)
stage 3	12 (24%)
R-ISS score	
stage 2	38 (76%)
stage 3	12 (24%)

	N=50
Extramedullary disease	4 (8%)
primary PCL	3 (6%)
High-risk (HR) cytogenetics	50 (100%)
del(17p)	20 (40%)
t(4;14)	26 (52%)
t(14;16)	10 (20%)
gain(1q)	25 (50%)
del(1p)	6 (12%)
≥2 HR cytogenetic abnormalities *	30 (60%)

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

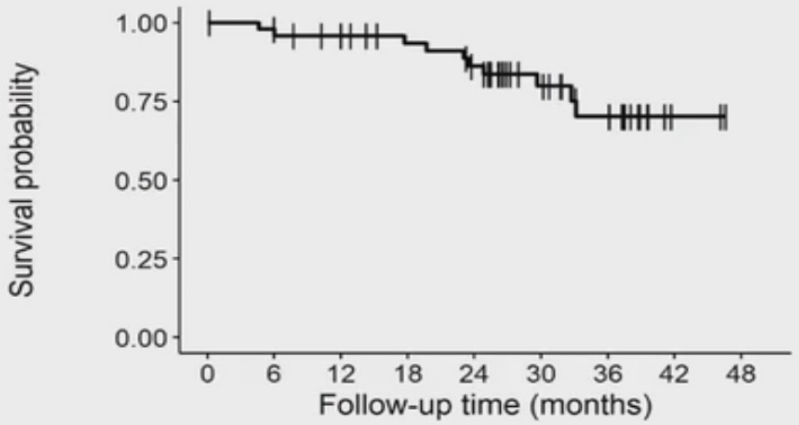
Response rates and MRD





Progression-free and Overall Survival

Progression-free survival

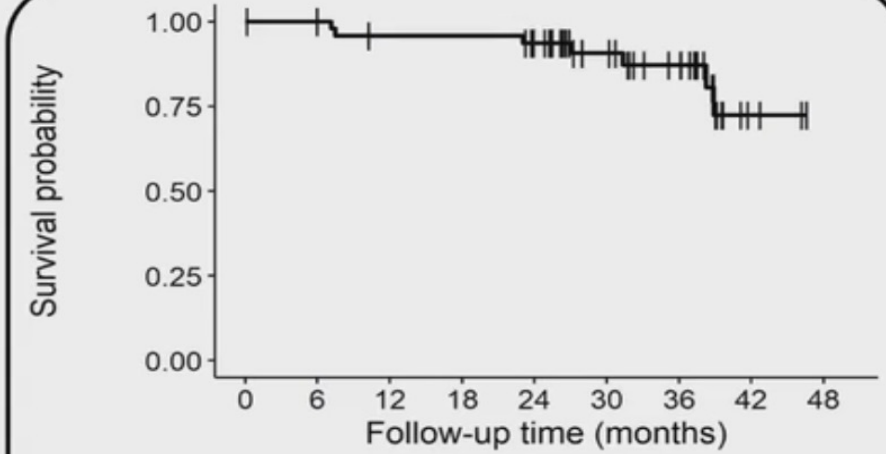


24-month PFS : 86% (77% - 97%)

30-month PFS : 80% (68% - 94%)

8 patients had disease progression

Overall Survival



24-month OS : 94% (87% - 100%)

30-month OS : 91% (82% - 100%)

7 patients died : disease prog (n=5) ; SAE (n=2)

Safety of Dara-KRd as induction/consolidation

Hematologic treatment related AE:

	Any grade n(%)	Grade 3/4 n(%)
Neutropenia	24 (48%)	22 (44%)
Anemia	17 (34%)	11 (22%)
Thrombocytopenia	18 (36%)	12 (24%)

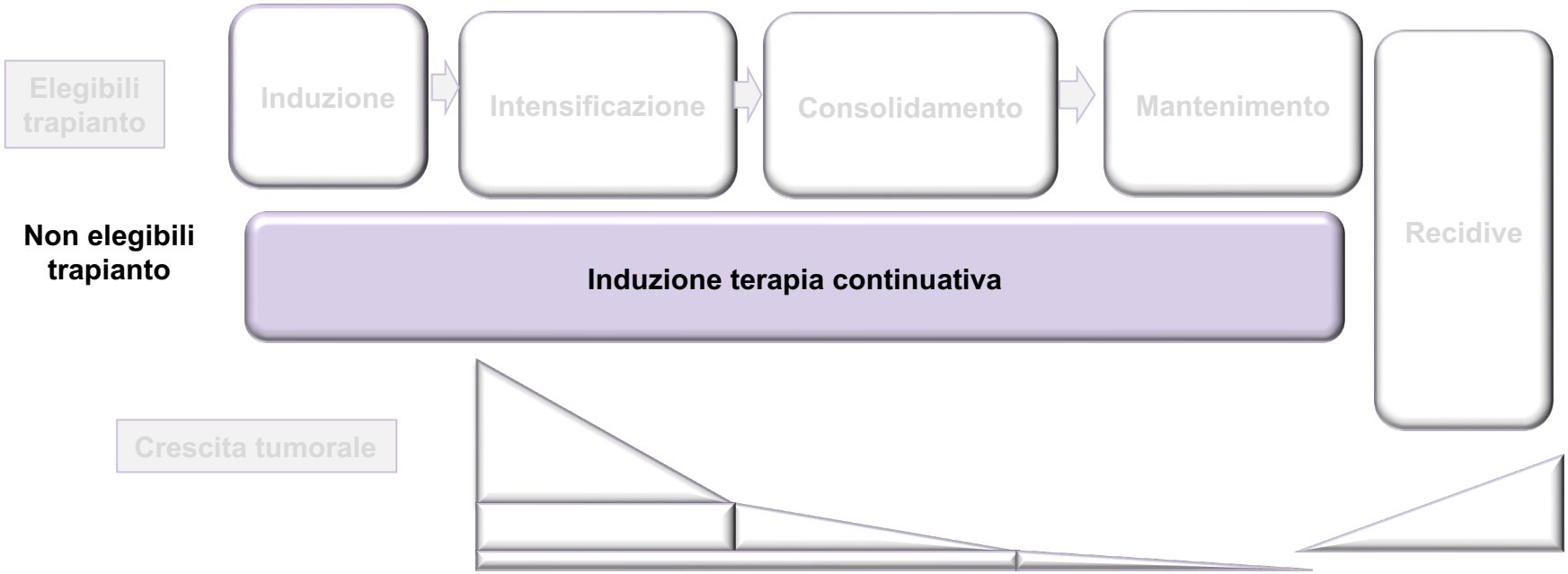
AE leading to study discontinuation (n=4):
- COVID-19 infection (n=2)
- tumor lysis syndrome (n=1)
- JC virus infection (n=1)

AE leading to death (n=2)
- Septic shock (n=1) (induction cycle 6)
- JC virus infection (n=1) (maintenance)

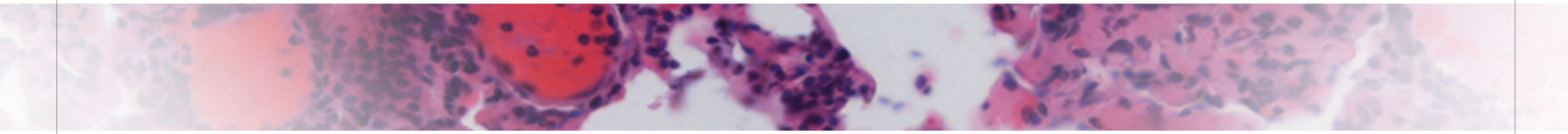
Most common non-hematologic treatment related AE:

	Any grade n(%)	Grade 3/4 n(%)
Infection	32 (64%)	7 (14%)
GI disorders	31 (62%)	5 (10%)
Skin rash	9 (18%)	0
Peripheral neuropathy	10 (20%)	0
Deep-vein thrombosis	6 (12%)	2 (4%)
Hepatic cytolysis	6 (12%)	3 (6%)
Renal failure	6 (12%)	3 (6%)
Hypertension	5 (10%)	2 (4%)
Cardiac event	2 (4%)	0

MM paradigma di trattamento



American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



Carfilzomib-Lenalidomide-Dexamethasone (KRd) Vs. Lenalidomide-Dexamethasone (Rd) in Newly Diagnosed Fit or Intermediate-Fit Multiple Myeloma Patients Not Eligible for Autologous Stem-Cell Transplantation (Phase III EMN20 Trial): Analysis of Sustained Undetectable Minimal Residual Disease (MRD)

Sara Bringhen, MD, PhD[1], Elisabetta Antonioli, MD[2], Barbara Gamberi, MD[3], Benedetto Bruno, MD, PhD[4,5], Daniele Derudas[6], Patrizia Tosi, MD[7], Francesca Fazio, MD, PhD[8], Rita Mazza, MD[9], Sonia Ronconi, MD[10], Paolo Corradini, MD[11], Flavia Lotti, MD[12], Claudia Cellini, MD, PhD[13], Antonietta Pia Falcone, MD, PhD[14], Piero Galieni, MD[15], Roberto Ria, MD[16], Angelo Belotti, MD[17], Donato Mannina, MD[18], Anna Maria Cafro, MD[19], Clotilde Cangialosi, MD[20], Iolanda Donatella Vincelli, MD[21], Alessandra Lombardo, MD[22], Alessandra Larocca, MD, PhD[1,5], Mario Boccadoro, MD[23] and Mattia D'Agostino, MD[4,5]

1. SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Department of Oncology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; 2. Hematology Unit, AOU Careggi, Florence, Italy; 3. Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Italy; 4. Division of Hematology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, University of Torino, Torino, Italy; 5. Division of Hematology, Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy; 6. SC di Ematologia e CTMO, Ospedale Oncologico di Riferimento Regionale "A. Businco", ARNAS "G. Brotzu", Cagliari, Italy; 7. UO Ematologia, Ospedale di Rimini, Rimini, Italy; 8. Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; 9. Department of Oncology and Hematology, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Italy; 10. IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; 11. University of Milan. Hematology Division, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; 12. Sezione di Ematologia e Immunologia Clinica, Ospedale Santa Maria della Misericordia, località Sant'Andrea delle Fratte, Perugia, Italy; 13. AUSL Romagna, U.O.C. Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy; 14. Hematology, IRCCS "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Italy; 15. UOC Ematologia e Terapia cellulare, Ospedale C. e G. Mazzoni, Ascoli Piceno, Italy; 16. Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro Medical School, Bari, Italy; 17. Department of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy; 18. Oncology-Hematology Department, Papardo Hospital, Messina, Italy; 19. SC Ematologia, ASST GOM Niguarda, Milano, Italy; 20. U.O.C. Ematologia, A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy; 21. Hematology Unit, Department of Hemato-Oncology and Radiotherapy, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy; 22. S.C. di Oncoematologia, A.O. Santa Maria di Terni, Terni, Italy; 23. European Myeloma Network, EMN, Italy

Study design

Randomized, multicenter, phase III EMN20 trial (NCT04096066): KRd vs. Rd

NTE NDMM
fit/intermediate-fit
patients
N=82

1:1 Randomization

Stratification for:
- ISS
- Fitness

KRd (n=42)
Carfilzomib (K):
- 20 mg/m² IV on day (D) 1 of cycle 1;
- 56 mg/m² IV on D 8, 15 of cycle 1; on D 1, 8, 15 of cycles 2–12; on D 1, 15 from cycle 13 onwards

Lenalidomide (R): PO 25 mg D 1–21
Dexamethasone (d): PO 40 mg/day* on D 1, 8, 15, 22
* 20 mg/day on D1, 8, 15, 22 for pts ≥75 years

- MRD Neg → Rd → *Until PD*
- MRD Pos → KRd for 5 years → Rd → *Until PD*

Rd (n=40)
Lenalidomide (R): PO 25 mg on days (D) 1–21
Dexamethasone (d): PO 40 mg/day* on D 1, 8, 15, 22
* 20 mg/day D1,8,15,22 for pts ≥75 years

→ *Until PD*

Screening — **After 1 yr** (MRD) — **After 2 yrs** (MRD)

NTE, transplant-ineligible; NDMM, newly diagnosed multiple myeloma; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenously; D, days; PO, orally; pts, patients; MRD, minimal residual disease; Neg, negative; Pos, positive; yr, year; PD, progressive disease.

Endpoints

- **Primary endpoints**: MRD after 2 years of treatment and PFS
  - MRD assessment: clonoSEQ®* assay, sensitivity of $\geq 10^{-5}$
  - MRD assessment performed after 1 and 2 years of study therapy in patients who achieved ≥VGPR
  - MRD negativity rate: proportion of MRD-negative patients (sensitivity of $\geq 10^{-5}$) at 2 years of treatment

- **Key secondary endpoints**: response rates, overall survival, and safety

- On Nov 23, 2021, the **protocol** was prematurely **stopped** after the introduction of frontline Dara-Rd

**Adaptive Biotechnologies, Seattle, US-WA.* MRD, minimal residual disease; PFS. progression-free survival; VGPR, very good partial response; Dara, daratumumab; R, lenalidomide; d, dexamethasone.

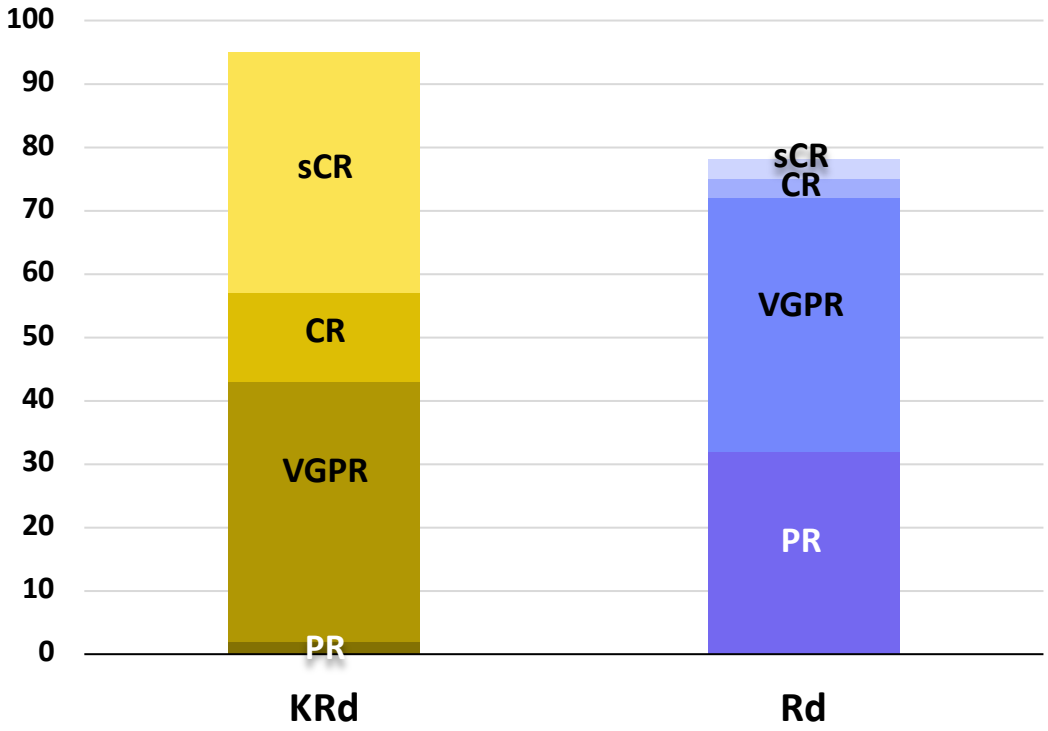
Baseline characteristics

	KRd (n=42)	Rd (n=40)
Age		
median, years (IQR)	73 (70–76)	74 (72–76)
76-80 years, n (%)	11 (26)	13 (22)
ISS stage, n (%)		
I	11 (26)	10 (25)
II	17 (40)	18 (45)
III	14 (33)	12 (30)
Cytogenetic risk, n (%)		
Standard	28 (78)	29 (78)
High*	8 (22)	8 (22)
Missing	6	3
Frailty status, n (%)		
Fit	26 (62)	22 (55)
Intermediate-fit	16 (38)	18 (45)
Frail	0	0

**Cytogenetic risk was defined as the presence of del(17p) or t(4;14) or t(14;16).*

K, carfilzomib; R, lenalidomide; d, dexamethasone; IQR, interquartile range; ISS, International Staging System; del, deletion; t, translocation.

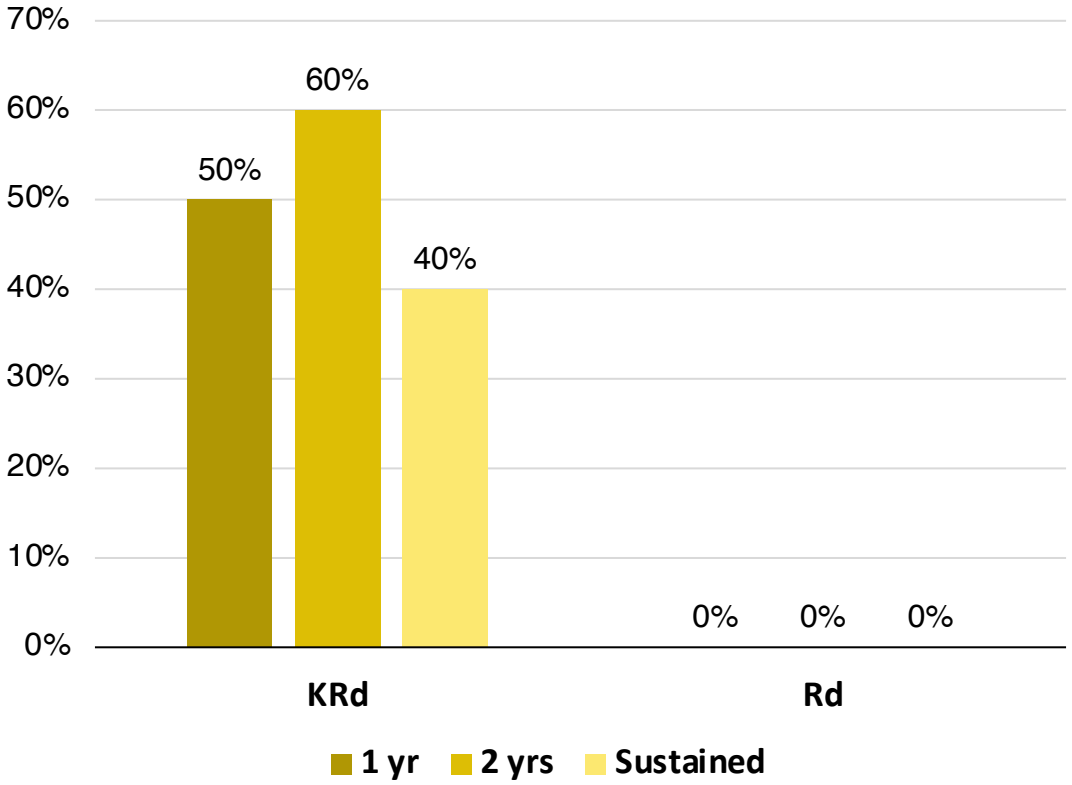
Response rates



	KRd n=42	Rd n=40	p-value
≥PR	40 (95%)	31 (78%)	0.04
≥VGPR	39 (93%)	18 (45%)	<0.0001
≥CR	22 (52%)	2 (5%)	0.0002

K, carfilzomib; R, lenalidomide; d, dexamethasone; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response.

MRD negativity rates



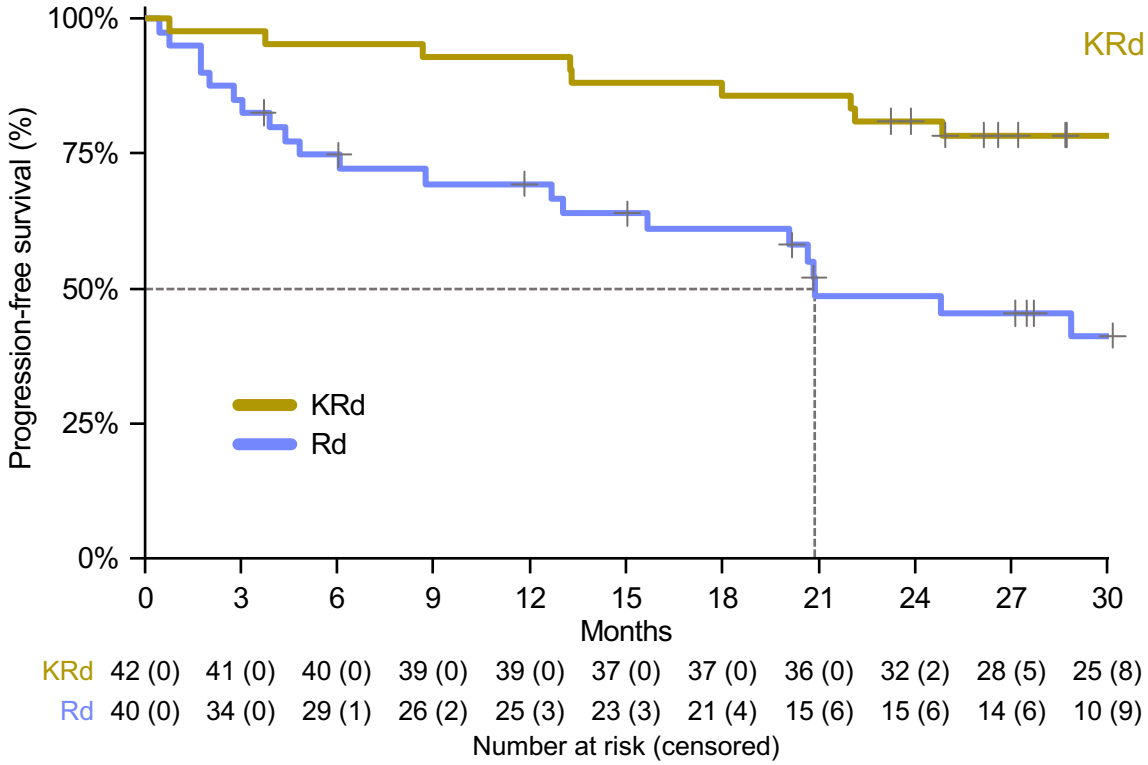
	KRd n=42	Rd n=40	p-value
At 1 year	21 (50%)	0 (0)	<0.0001
At 2 years	25 (60%)	0 (0)	<0.0001
Sustained	17 (40%)	0 (0)	<0.0001

Sustained MRD negativity was defined as 2 consecutive MRD-negative test results, the first achieved after 12 months of treatment and the second at least 12 months apart.

MRD, minimal residual disease; K, carfilzomib; R, lenalidomide; d, dexamethasone; yr, year.

Progression-free survival

Median follow-up: 31.4 months (IQR 25–34)



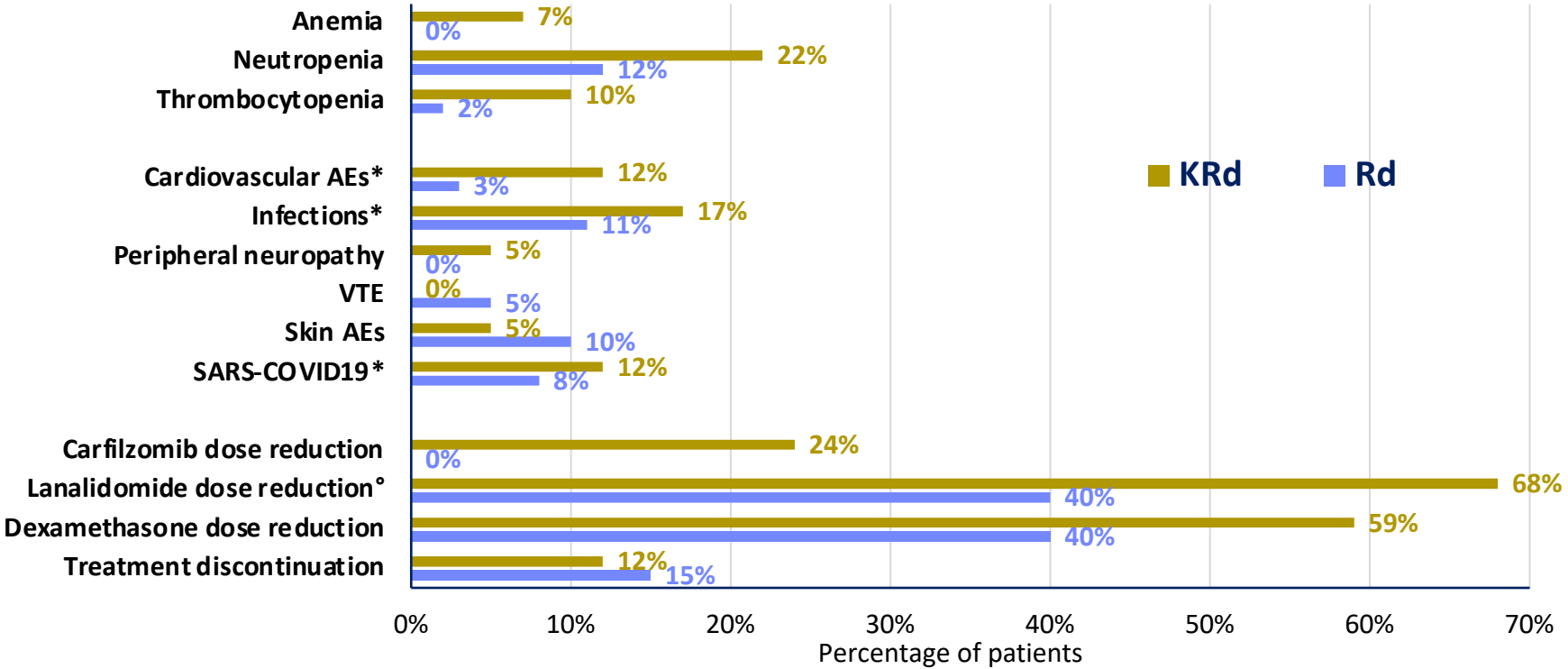
KRd vs. Rd: HR 0.28, 95% CI 0.13–0.60, p=0.0013

	KRd n=42	Rd n=40
Events	n=9	n=21
2-year PFS	81%	48%
Median PFS	Not reached	20.9 mos

IQR, interquartile range; K, carfilzomib; R, lenalidomide; d, dexamethasone; HR, hazard ratio; CI, confidence interval; p, p-value.; PFS, progression-free survival.; mos, months.

Safety

Grade 3–5 adverse events and dose modification



*KRd: 3 G5 AEs (3 due to COVID19 infection); Rd: 3 G5 AEs (1 due to cardiac AE, 1 due to COVID19 and 1 due to infection)

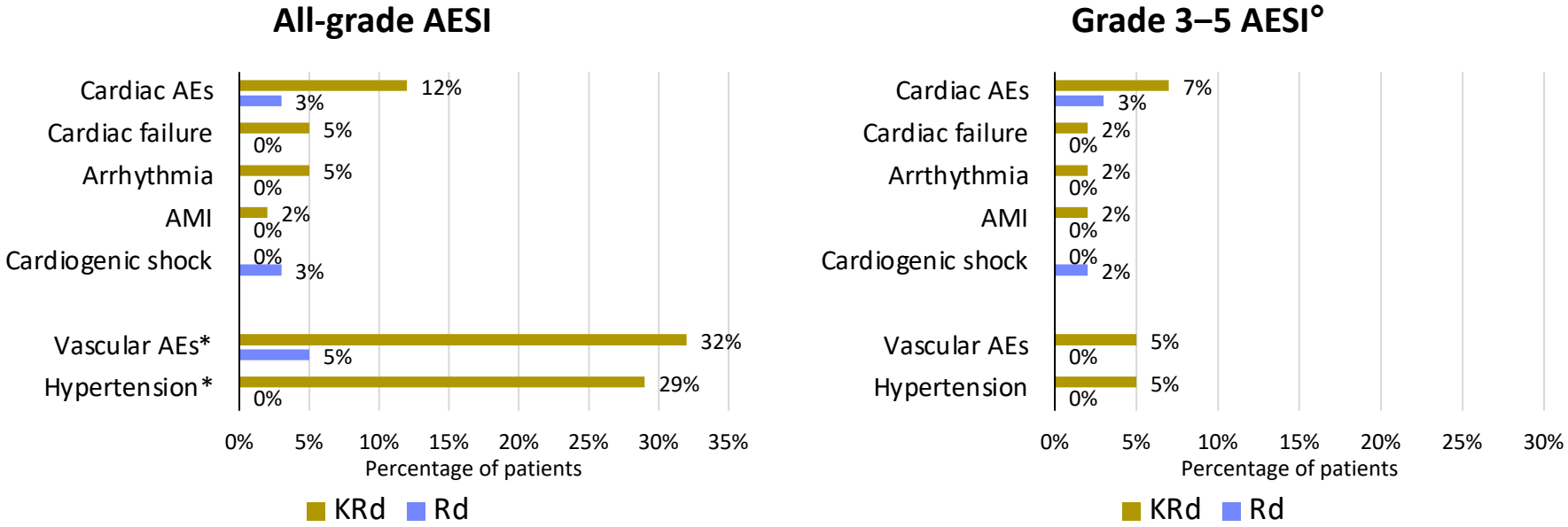
°p-value < 0.01

K, carfilzomib; R, lenalidomide; d, dexamethasone; AEs, adverse events; VTE, venous thromboembolism; G, grade.

Safety

Adverse events of special interest

Cardiovascular AEs



°1 G5 AE in the Rd group: 1 cardiogenic shock

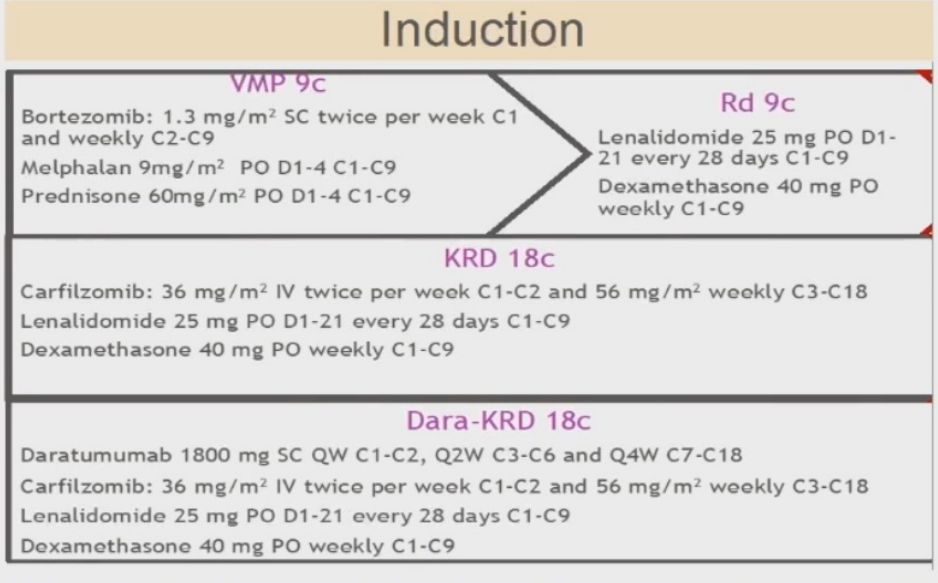
*p-value < 0.01

AEs, adverse events; AESI, AEs of special interest; AMI, acute myocardial infarction; K, carfilzomib; R, lenalidomide; d, dexamethasone; G, grade.

GEM-2017FIT: Induction therapy with VMP/Rd vs KRd or Dara-KRd 18c followed by consolidation and maintenance therapy with Dara and Len: phase III, multicenter, randomized trial for elderly FIT NDMM aged between 65 and 80 years

María-Victoria Mateos, Bruno Paiva, Teresa Cedena, Noemí Puig, Anna Sureda, Albert Oriol, Enrique-M Ocio, Laura Rosiñol, Yolanda González, Joan Bargay, Esther González, Miguel Teodoro Hernández, Angel Payer, Alexia Suarez, María-Jesús Blanchard, Sebastián Garzón, Felipe Casado, Valentín Cabañas, Jaime Pérez de Oteyza, Mercedes Gironella, Joaquín Martínez, Ana Isabel Teruel, Pilar Delgado, Elena Prieto, Juan-José Lahuerta, Joan Bladé, Jesús San Miguel

GEM2017FIT phase 3 trial: VMP-Rd 18c vs KRd or D-KRd 18c in NDMM-TIE and up to 80 years

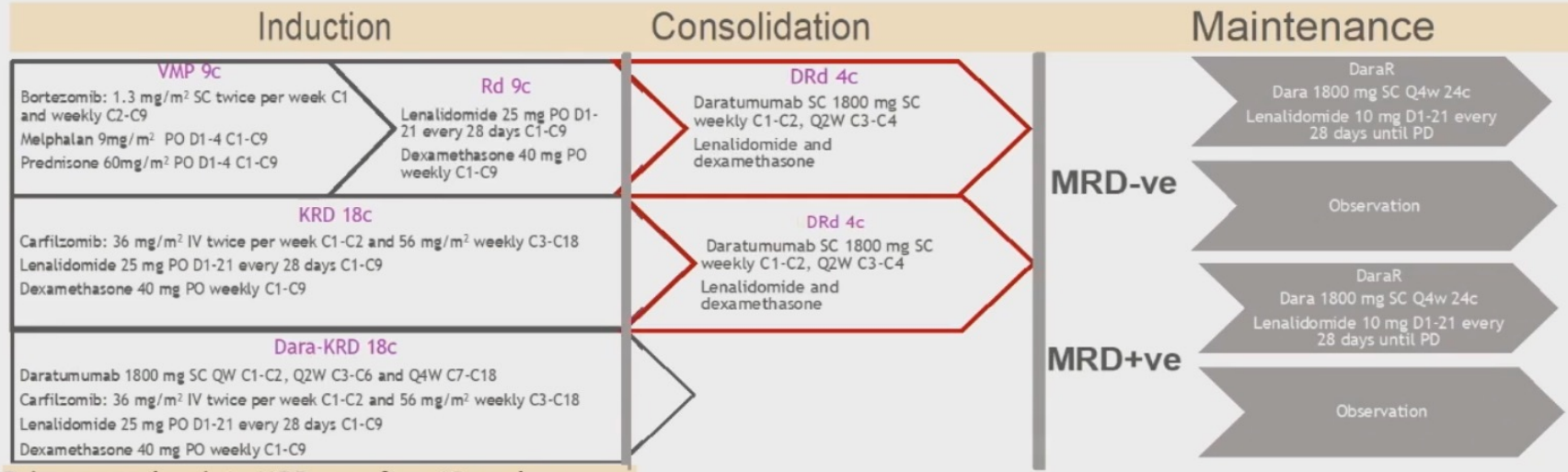


- VMP-Rd in patients younger than 80 years resulted in a MRD-ve rate of 20%
- Hypothesis was to increase the MRD-ve rate up to 35% in the two experimental arms
- Sample size required was 462 patients

Primary end-point: MRD-ve by NGF at 10^{-5} after 18 cycles comparing VMP-Rd with KRd and VMP-Rd with D-KRd

Dexamethasone 20 mg in patients older than 75 years

GEM2017FIT phase 3 trial: VMP/Rd 18c vs KRd or D-KRd 18c in NDMM-TIE and up to 80 years



Primary end-point: MRD-ve after 18 cycles

Secondary end-point: Kynetic of MRD after consolidation

Secondary end-points: Kinetic of the MRD during maintenance, PFS and OS

Safety profile

Dexamethasone 20 mg in patients older tan 75 years

*If biochemical progression does occur during the first 2 years, it is possible to crossover to DaraR maintenance

GEM2017 phase 3 trial in NDMM TIE FIT

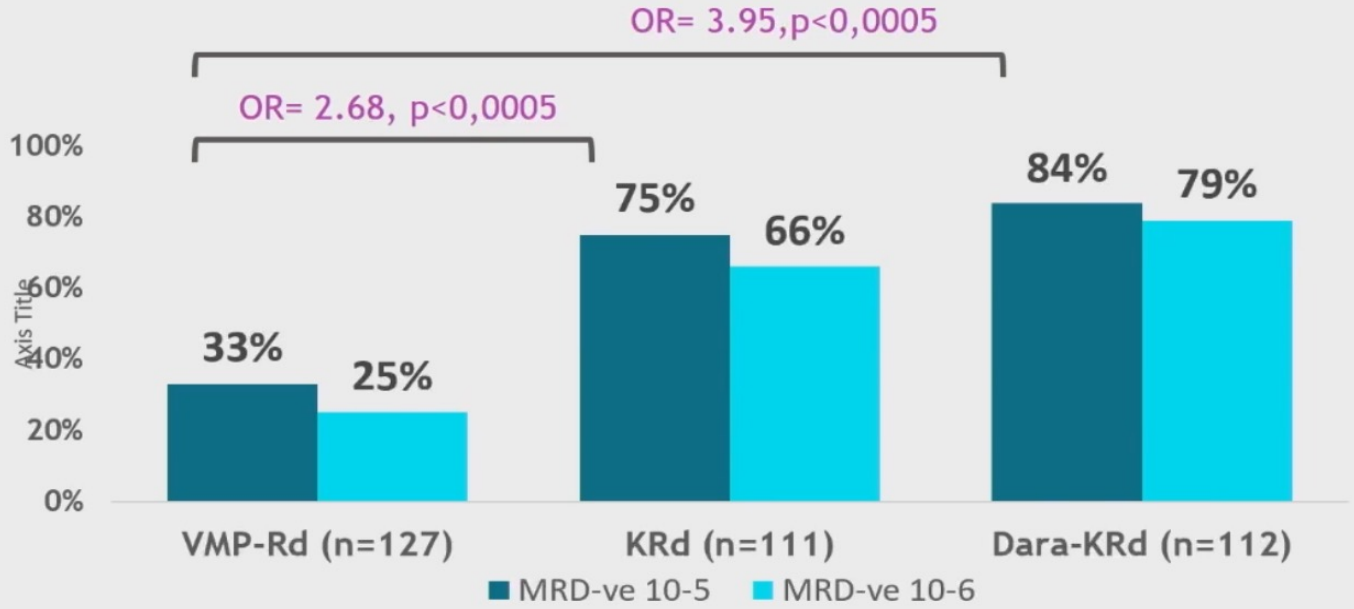
	VMP 9c-Rd 9c (n=154)	KRD (n=154)	Dara KRd (n=153)
Age, median (range) ≥ 75 years	72 (65-80) 33%	72 (65-80) 34%	73 (66-80) 35%
ISS (I-II/III), %	66/28	68/32	69/28
Extramedulary disease, n (%)	22 (14)	22 (14)	25 (16)
High-risk CA, n (%) - del17/del17p/t(4;14)/t(14;16) - del17/del17p/ t(4;14)/t(14;16)/Gain/amp1q/del1p	 12(13%) 43(47%)	 15(14%) 54(52%)	 18(18%) 53(54%)
GAH score, mean	18,25	19	19,35

GAH score betweein 0 and 42 for being FIT

GEM2017 phase 3 trial in NDMM TIE FIT: best response

Response rates, n (%)	VMP 9c-Rd 9c (n=154)	KRd 18c (n=154)	Dara KRd 18c (n=153)
ORR	119 (77%)	126 (82%)	134 (88%)
sCR/CR	59 (38%)	90 (58%) P <0.001	94 (61%) P <0.0001
VGPR	42 (27%)	25 (16%)	38 (25%)
PR	18 (12%)	11 (7%)	3 (2%)
Progressive disease	25 (16%)	11 (7%)	2 (1.3%)
Non evaluable for response	4 (7%)	8 (5%)	8 (5%)

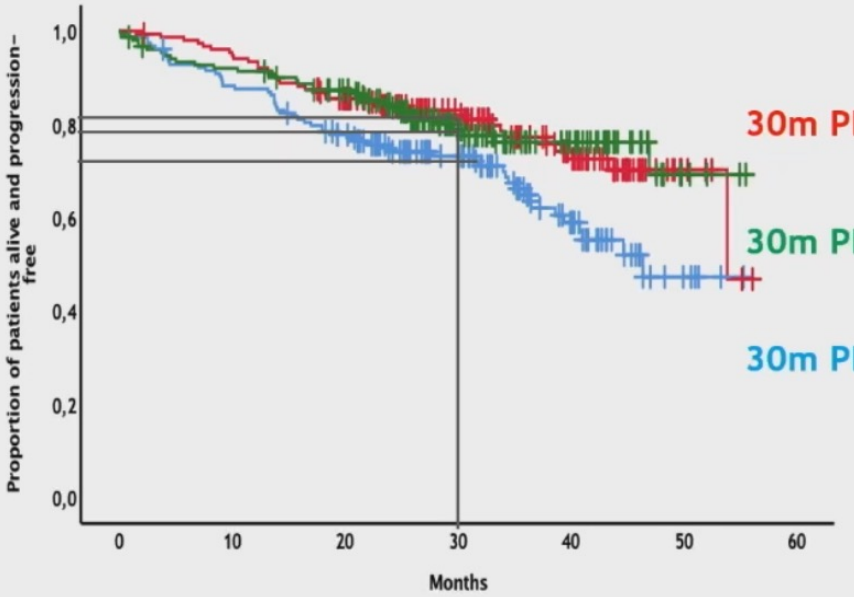
GEM2017 phase 3 trial in NDMM TIE FIT: MRD-ve rate at 10^{-5} after 18 induction cycles in the evaluable population: Primary endpoint



Evaluable population included all patients who have completed the 18 induction cycles as well as those who discontinued early because of progressive disease and the MRD was considered as positive

GEM2017 phase 3 trial in NDMM TIE FIT: Progression-free survival

Median follow-up: 33 months



30m PFS: KRd: 83%

30m PFS: D-KRd: 79%

30m PFS: VMP-Rd: 73%

HR: 0.57,
95% CI: 0.37-0.89
p=0.01

HR: 0.58,
95% CI: 0.38-0.88
p=0.01

GEM2017 phase 3 trial in NDMM TIE FIT: Safety Profile

	VMP/Rd (n=154) G3-4	KRd (n=154) G3-4	KRd-Dara (n=153) G3-4
Hematologic toxicity			
- Neutropenia	77(50%)	37(24%)	73 (47%)
- Anemia	17 (11%)	7 (5%)	16 (10%)
- Thrombocytopenia	52(34%)	24 (16%)	26(17%)
Non hematologic toxicity			
- Infusion-related reaction to Dara IV/SC	-	-	Any grade 21 (14%)/1(0.6%)
- GI symptomatology	15 (9%)	11 (7%)	19 (12%)
- Infections	19 (12%)	23 (15%)	25 (16%)
- Rash	3 (2%)	18 (12%)	9 (6%)
- Cardiovascular toxicity	8 (5%)	17 (11%)	21 (14%)
+Cardiac failure	3 (2%)	3 (2%)	7 (5%)
+Hypertension	-	8 (5%)	3 (2%)
Pts requiring reduction of any drug			
- Bortezomib	36 (23%)		
-Melphalan	20 (13%)		
-Lenalidomide	16 (10%)	41 (27%)	35 (23%)
-Dexamethasone	13 (8%)	15 (9%)	12 (8%)
-Carfilzomib		25 (16%)	18 (12%)
Daratumumab			2 pts had to discontinue

Conclusioni

Il raggiungimento della MRD negatività è fortemente associato al ritardo della recidiva di malattia anche nel MM

Una risposta rapida e profonda dopo la terapia di induzione nei pazienti eleggibili al trapianto è molto importante per l'andamento post trapianto

Gli schemi D-VRD e Isa-KRd aumentano la percentuale dei pazienti con risposte più profonde

Anche per i pazienti non eleggibili al trapianto terapie di associazione dei nuovi farmaci aumentano la percentuale di pazienti MDR negativi

Categorizzare meglio i nostri pazienti sulla base della malattia per eseguire trattamenti sempre più mirati