Highlights from
IMS 20th meeting 2023

Maria Teresa Petrucci

Terapia di induzione a quattro farmaci: per tutti i pazienti?

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

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	

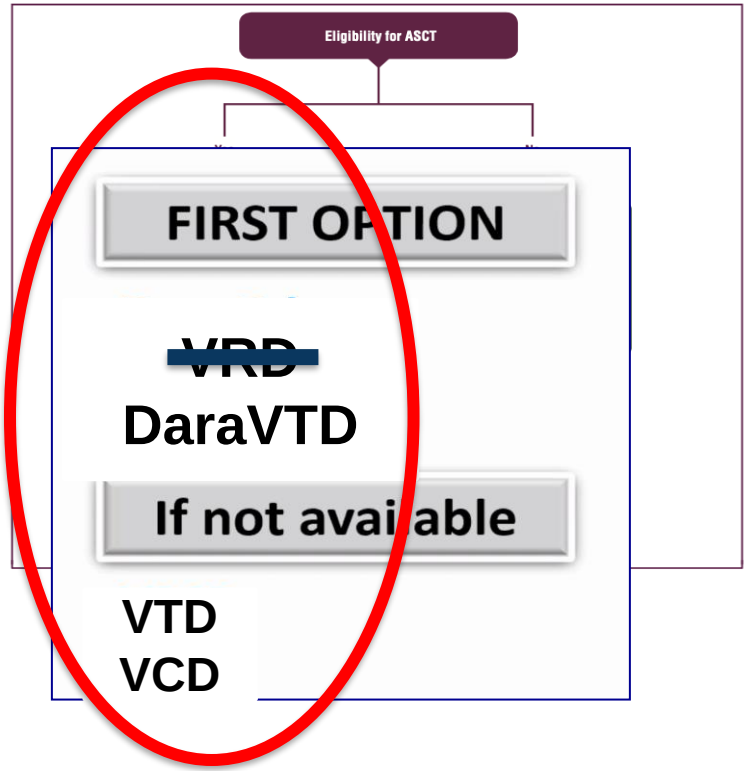
Mieloma Multiplo: Malattia Complessa

L’eterogeneità della malattia complica la scelta terapeutica

Non esiste una terapia standard basata sulle

caratteristiche del paziente e della patologia

Linee guida ESMO 2021



…ultimo approccio: terapia continuativa

Combination regimens

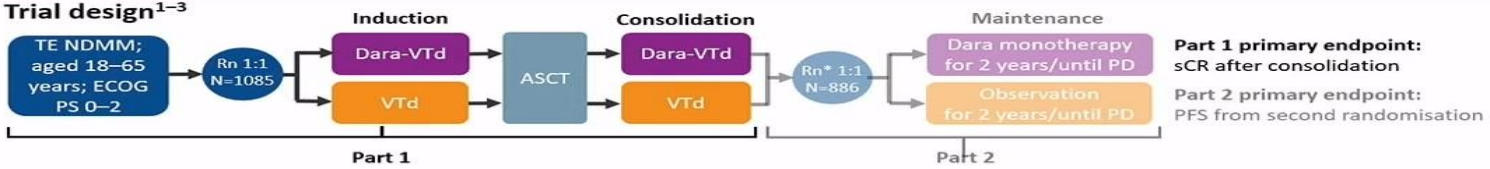
- Faster and deeper response
- Different mechanisms target multiple clones simultaneously
- Prevention of drug-resistant subclones emergence
- Eradication of all clones

Cavo M et al. Blood 2011;117(23):6063-73;
Cavo et al. Blood 2012;120(1):9-19;
Kumar S, et al. Lancet Oncology 2016;17:e328-46

Dimopoulos et al, Annals of Oncology 2021

Dara-VTd (CASSIOPEIA)

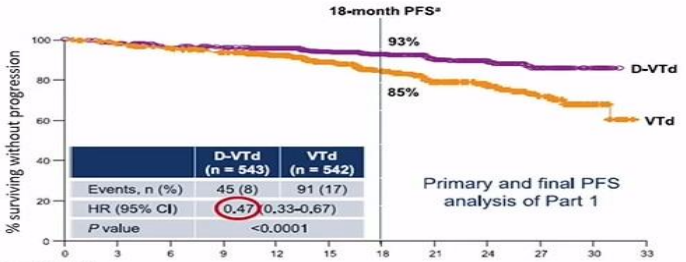
Trial design[1–3]



Part 1 primary endpoint: sCR after consolidation

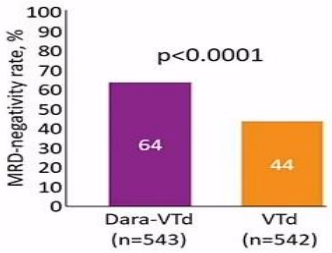
Part 2 primary endpoint: PFS from second randomisation

PFS with a median follow-up of 18.8 months (part 1)[3]



	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	45 (8)	91 (17)
HR (95% CI)	0.47 (0.33–0.67)	
P value	<0.0001	

MRD-negativity rates (part 1)[1]



TEAEs of interest (part 1)[1]

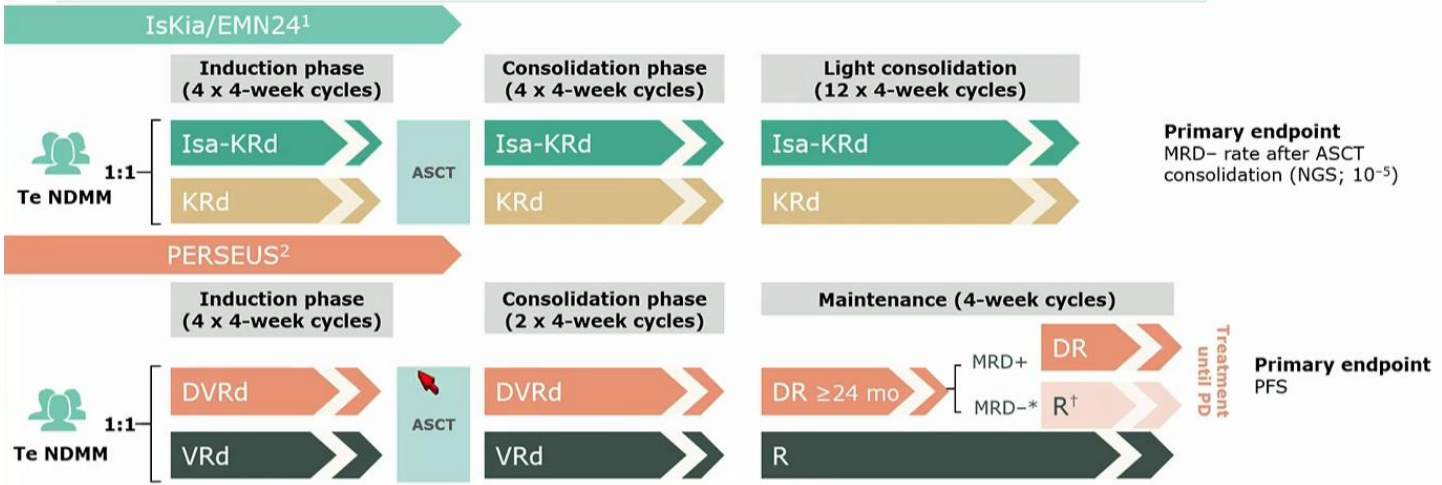
n (%)	D-VTd (n=536)	VTd (n=538)
Infusion-related reactions		
Any grade	190 (35)	NA
Grade 3/4	19 (4)	NA
Infections		
Any grade	351 (65)	306 (57)
Grade 3/4	118 (22)	105 (20)
Most common serious infection		
Pneumonia	19 (4)	9 (2)
Second primary malignancies	10 (2)	12 (2)
Peripheral sensory neuropathy		
Any grade	314 (59)	340 (63)
Grade 3/4	47 (9)	46 (9)

*Patients with ≥PR.

ASCT, autologous stem cell transplant; CI, confidence interval; CR, complete response; d, dexamethasone; D/Dara, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NA, not applicable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Rn, randomisation; sCR, stringent complete response; T, thalidomide; TE, transplant-eligible; TEAE, treatment-emergent adverse event; V, bortezomib; VGPR, very good partial response.

1. Moreau P, et al. Lancet 2019;394:29–38; 2. Moreau P, et al. Lancet Oncol 2021;22:1378–1390; 3. Moreau P, et al. EHA 2019 (Abstract No. S874 – presentation).

Ongoing Phase III trials will provide further insights on the role of quadruplets with both V- and K-based backbones in **Te NDMM**



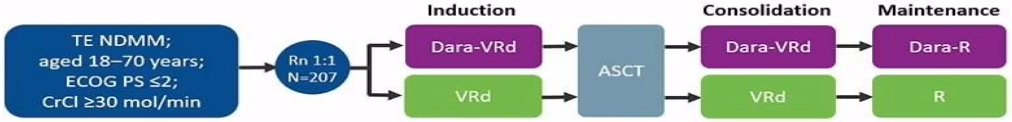
Evaluation of quadruplets with different PI backbones may offer physicians greater choice in tailoring treatment to patients

*≥12 month sustained; at 10^{-5} by NGS
†Opportunity to restart D upon loss of CR or MRD–
ASCT, autologous stem cell transplant; D, daratumumab, d, dexamethasone; K, carfilzomib; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; R, lenalidomide; Te, transplant eligible; V, bortezomib

1. Clinicaltrials.gov NCT04483739;
2. Clinicaltrials.gov NCT03710603

Dara-VRd (GRIFFIN[1] and PERSEUS[2])

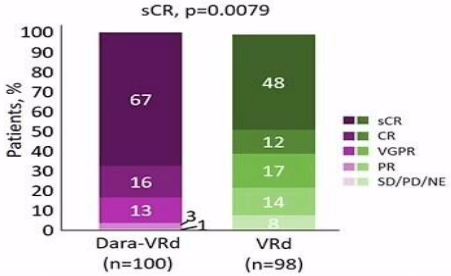
GRIFFIN trial design (Phase II)[1]



Primary endpoint: sCR rate (by end of consolidation)

Rates of TEAEs leading to treatment discontinuation[1]	**TEAEs leading to death*[1]**
Dara-VRd: 33% (n=33), VRd: 31% (n=32)	Dara-VRd: n=1, VRd: n=1

End-of-study response rates†[1]



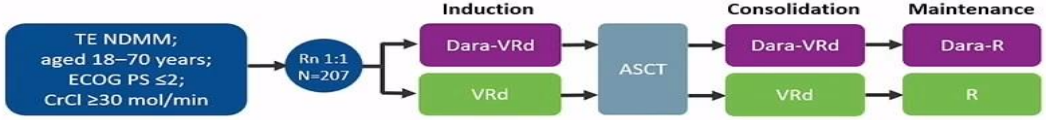
*The TEAE leading to death was bronchopneumonia in the Dara-VRd group and unknown in the VRd group. Neither was related to study treatment;[3] †49.6 month follow-up.

ASCT, autologous stem cell transplant; CR, complete response; CrCl, creatinine clearance; d, dexamethasone; Dara, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; NDMM, newly diagnosed multiple myeloma; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, lenalidomide; Rn, randomisation; sCR, stringent complete response; SD, stable disease; TE, transplant-eligible; TEAE, treatment-emergent adverse event; V, bortezomib; VGPR, very good partial response.

1. Voorhees PM, et al. Lancet Haematol 2023; doi: 10.1016/S2352-3026(23)00217-X. Online ahead of print; 2. Sonneveld P, et al. ASCO 2019 (Abstract No. TPS8055 – poster).

Dara-VRd (GRIFFIN[1] and PERSEUS[2])

GRIFFIN trial design (Phase II)[1]

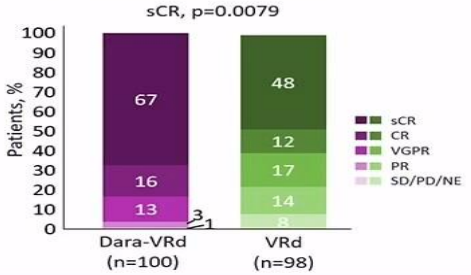


Primary endpoint: sCR rate (by end of consolidation)

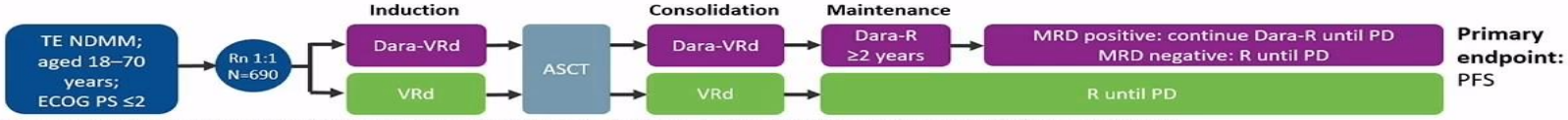
Rates of TEAEs leading to treatment discontinuation[1]
Dara-VRd: 33% (n=33), VRd: 31% (n=32)

TEAEs leading to death*[1]
Dara-VRd: n=1, VRd: n=1

End-of-study response rates†[1]



PERSEUS trial design (ongoing; Phase III)[2]



*The TEAE leading to death was bronchopneumonia in the Dara-VRd group and unknown in the VRd group. Neither was related to study treatment;[3] †49.6 month follow-up.

ASCT, autologous stem cell transplant; CR, complete response; CrCl, creatinine clearance; d, dexamethasone; Dara, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; NDMM, newly diagnosed multiple myeloma; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, lenalidomide; Rn, randomisation; sCR, stringent complete response; SD, stable disease; TE, transplant-eligible; TEAE, treatment-emergent adverse event; V, bortezomib; VGPR, very good partial response.

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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).

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

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).

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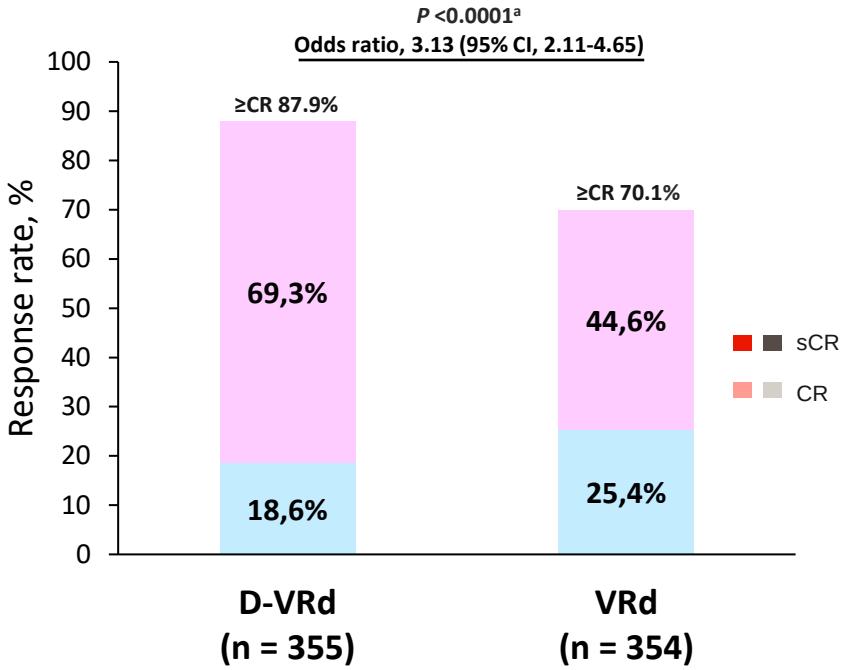
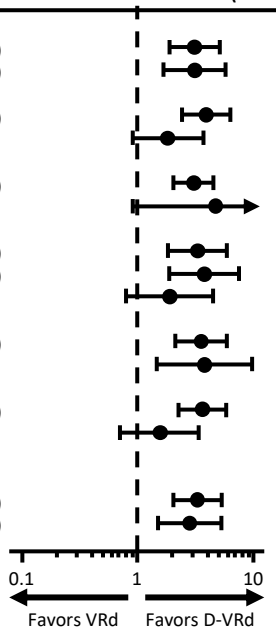
PERSEUS: Overall ≥CR Rates



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.

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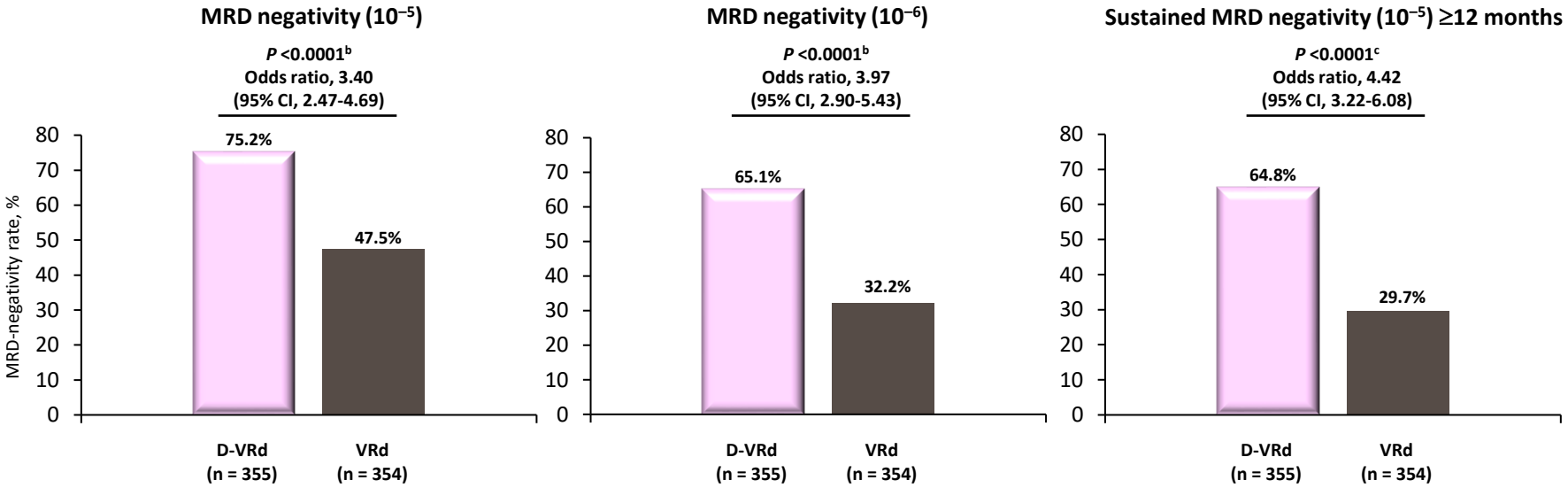
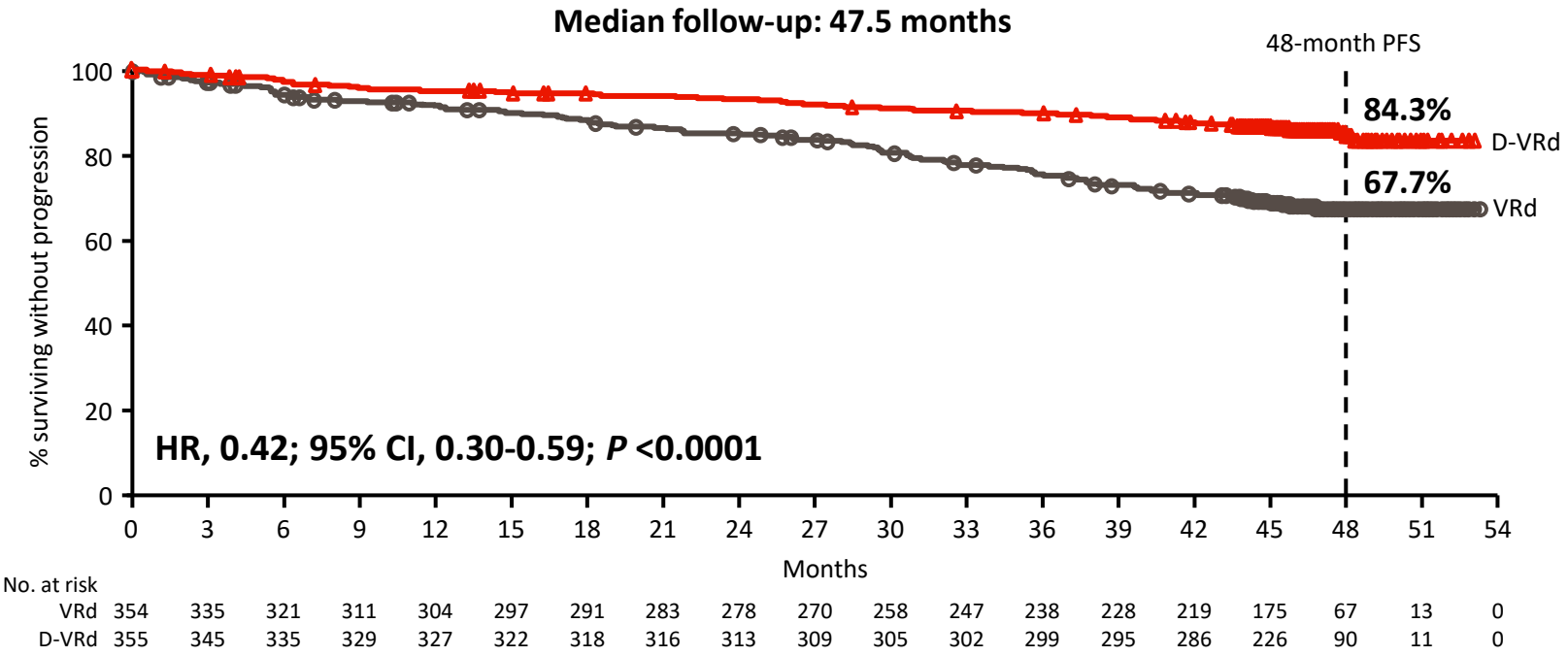
PERSEUS: Overall and Sustained MRD-negativity Rates[a]



- **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.

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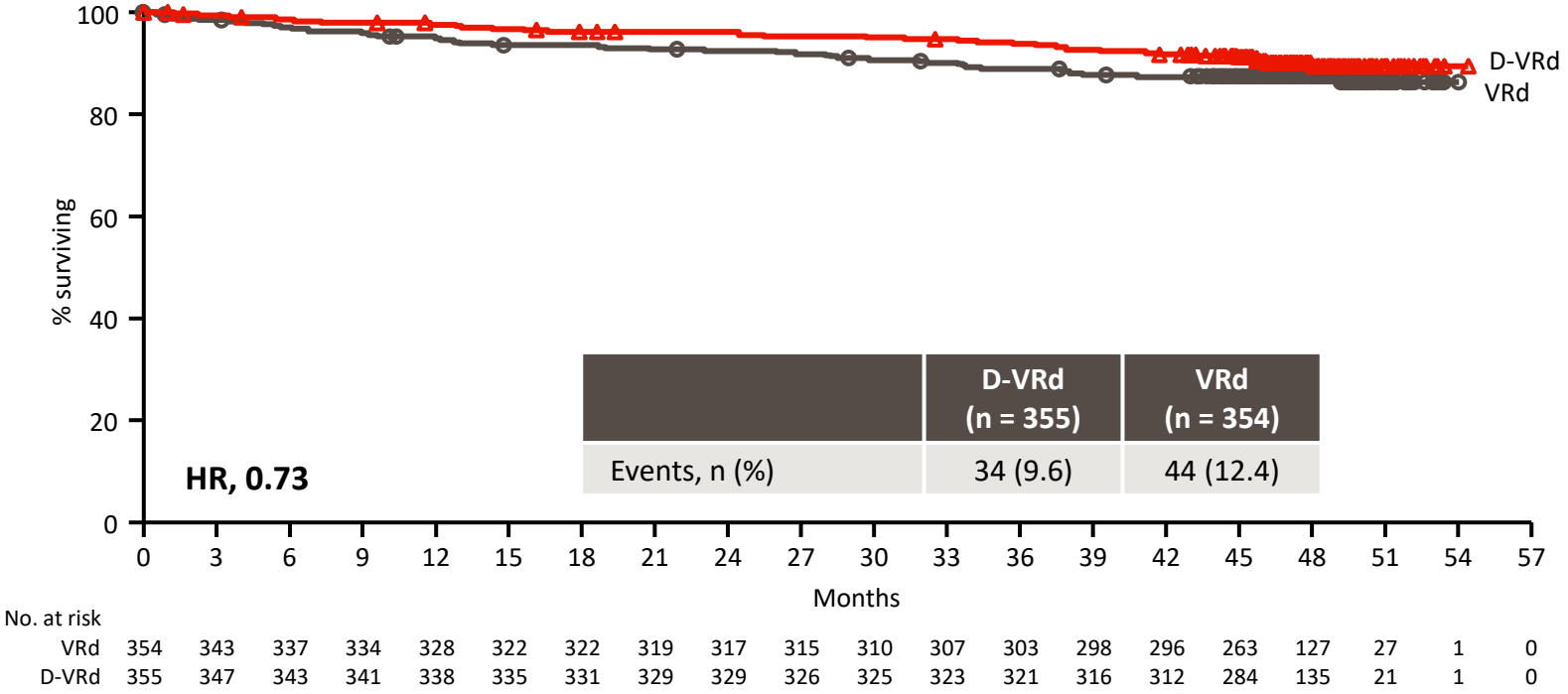
PERSEUS: Overall Survival



	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**

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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.

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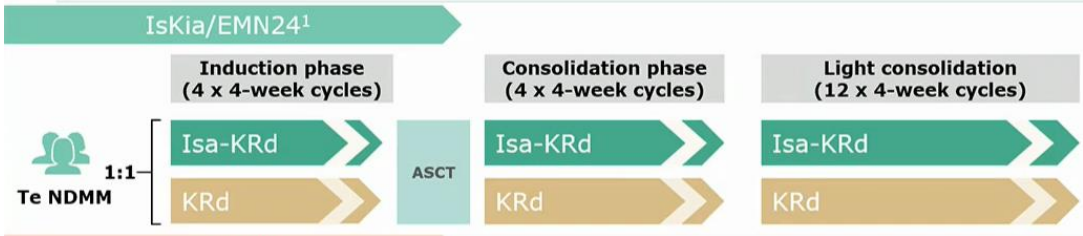
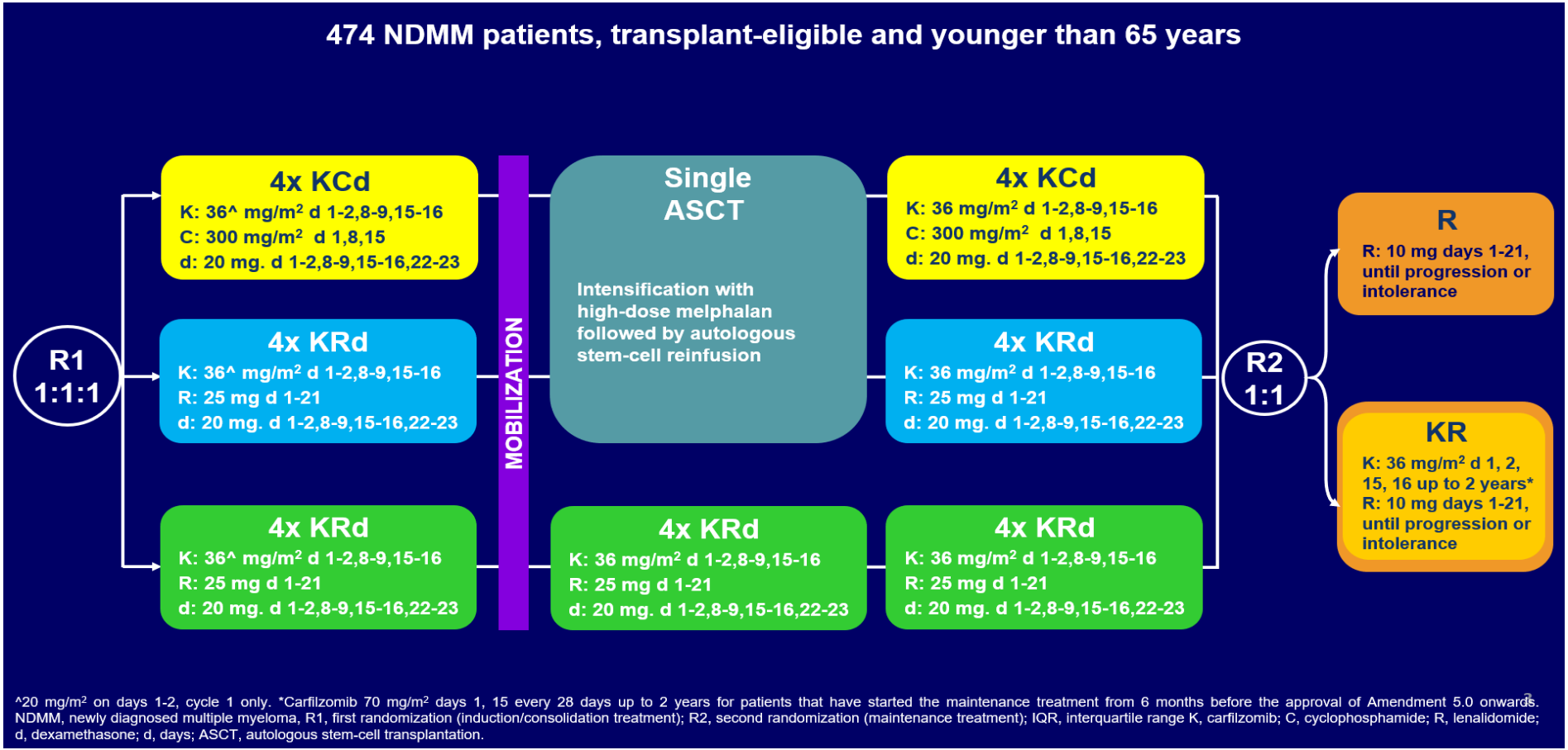


Primary endpoint
MRD– rate after ASCT consolidation (NGS; 10^{-5})

*≥12 month sustained; at 10^{-5} by NGS
†Opportunity to restart D upon loss of CR or MRD–
ASCT, autologous stem cell transplant; D, daratumumab, d, dexamethasone; K, carfilzomib; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; R, lenalidomide; Te, transplant eligible; V, bortezomib

1. Clinicaltrials.gov NCT04483739;
2. Clinicaltrials.gov NCT03710603

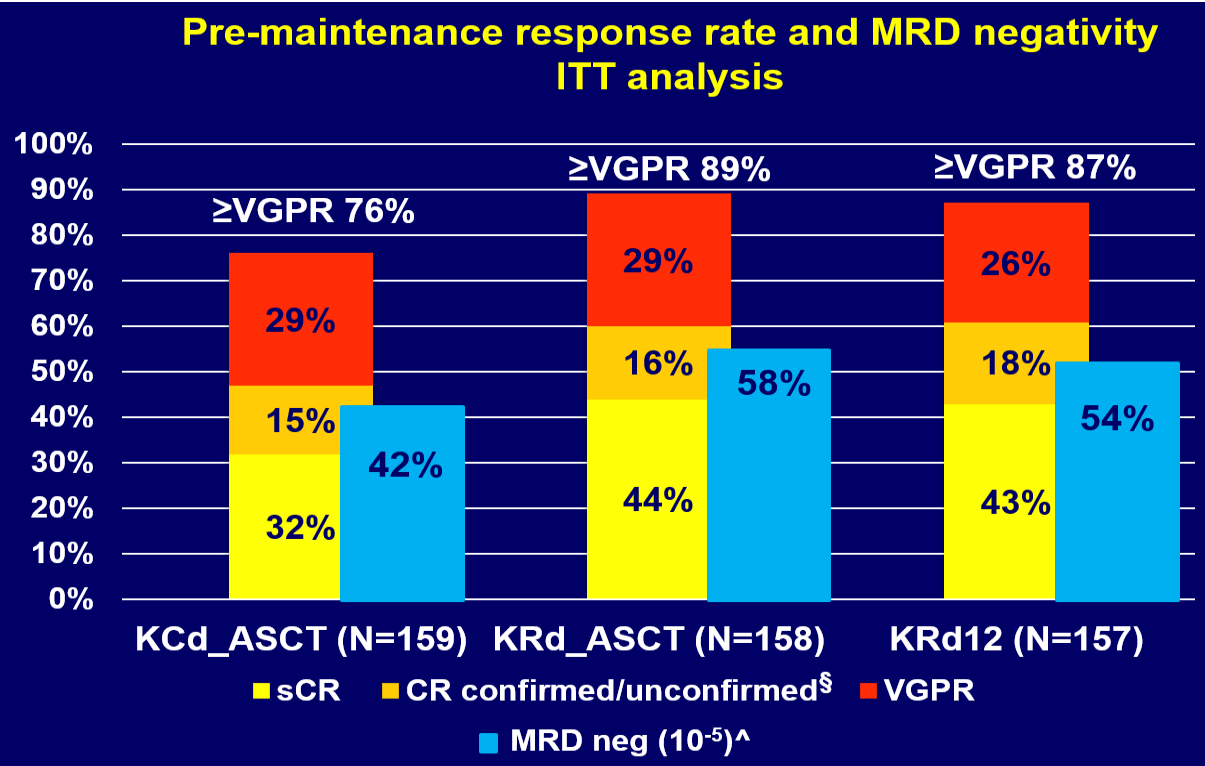
FORTE Study: Trial design



^20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards. NDMM, newly diagnosed multiple myeloma, R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.

Gay F. Lancet Oncol 2021

KRd_ASCT vs KRd12 vs KCd_ASCT: Efficacy



	OR	p-value*
≥VGPR		
KRd_ASCT vs KCd_ASCT	2.53	0.004
KRd12 vs KCd_ASCT	2.11	0.015
sCR		
KRd_ASCT vs KCd_ASCT	1.65	0.035
KRd12 vs KCd_ASCT	1.60	0.048

MRD neg (10^{-5})	OR	p-value*
KRd_ASCT vs KCd_ASCT	2.02	0.009
KRd12 vs KCd_ASCT	1.73	0.042

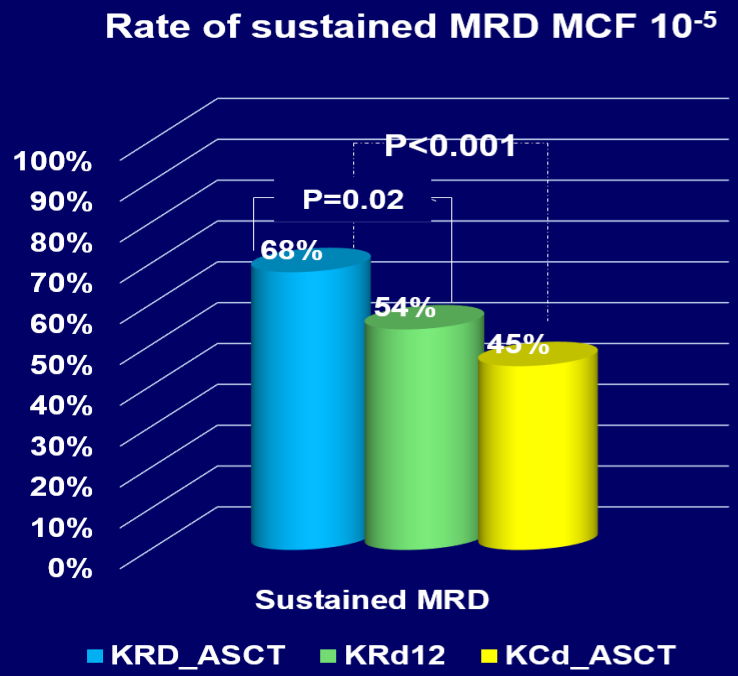
^Patients whose samples were not available (~10%) were considered as positive. *Adjusted for ISS, Age, FISH, LDH.
§ Unconfirmed CR/sCR: patients missing immunofixation/sFLC analysis needed to confirm CR/sCR (6% in KCd_ASCT_KCd; 8% in KRd_ASCT_KRd; 6% KRd_12).
ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; MRD, minimal residual disease; neg, negativity; ITT, intention to treat; sCR, stringent complete response; CR: complete response; VGPR: very good partial response; OR: odds ratio; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; FLC, free light chain, ISS, International Staging System.

Gay F. Lancet Oncol 2021

Progression-free survival: Random 1

Progression-free survival: Random 1

Median follow-up from Random 1: 45 months (40-49 months)



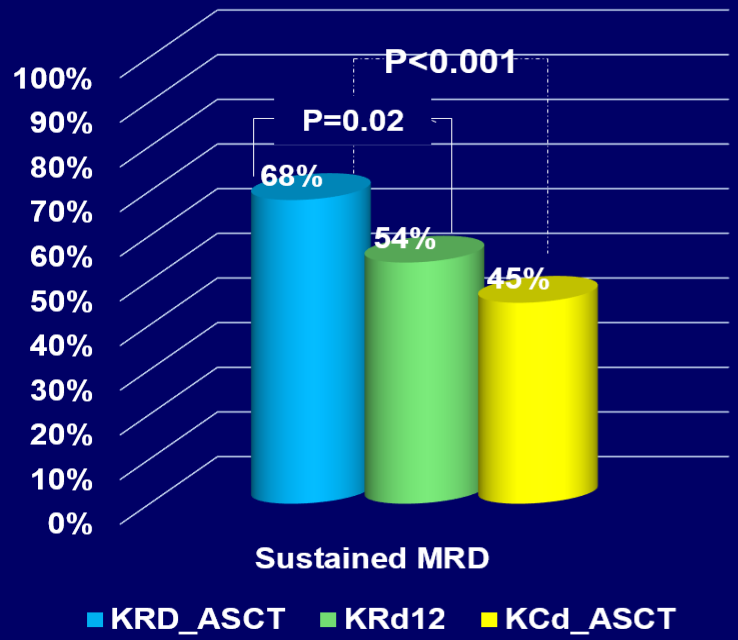
Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, p-value; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; MFC, multiparameter flow cytometry; 3-year PFS reported in the figure.

Gay F. Lancet Oncol 2021

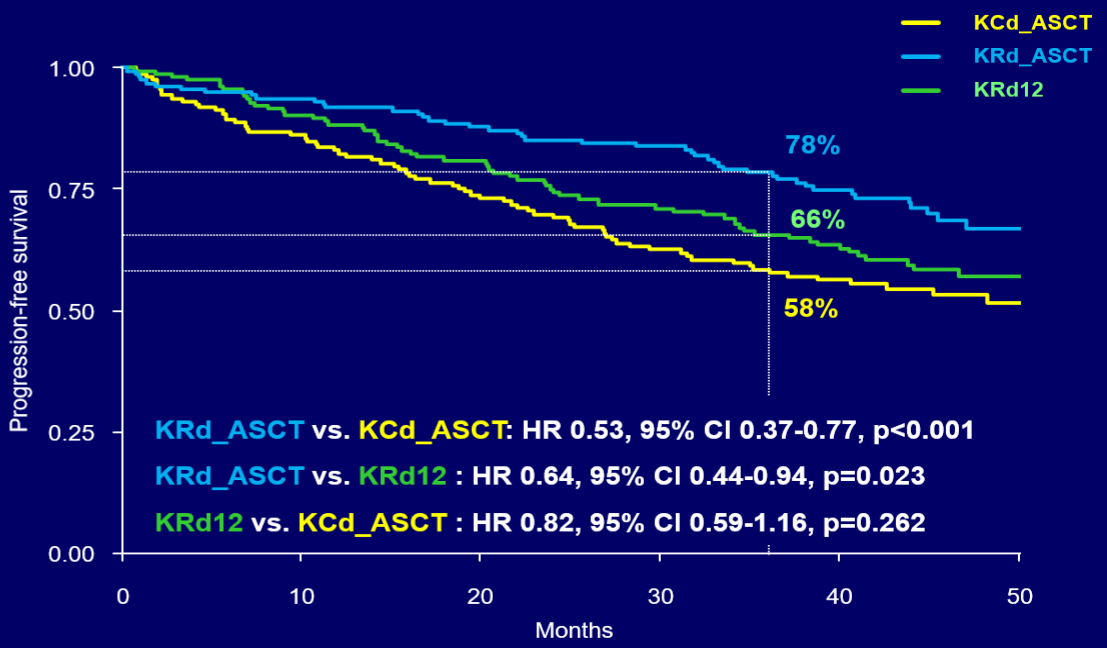
Progression-free survival: Random 1

Median follow-up from Random 1: 45 months (40-49 months)

Rate of sustained MRD MCF 10^{-5}



Progression-free survival

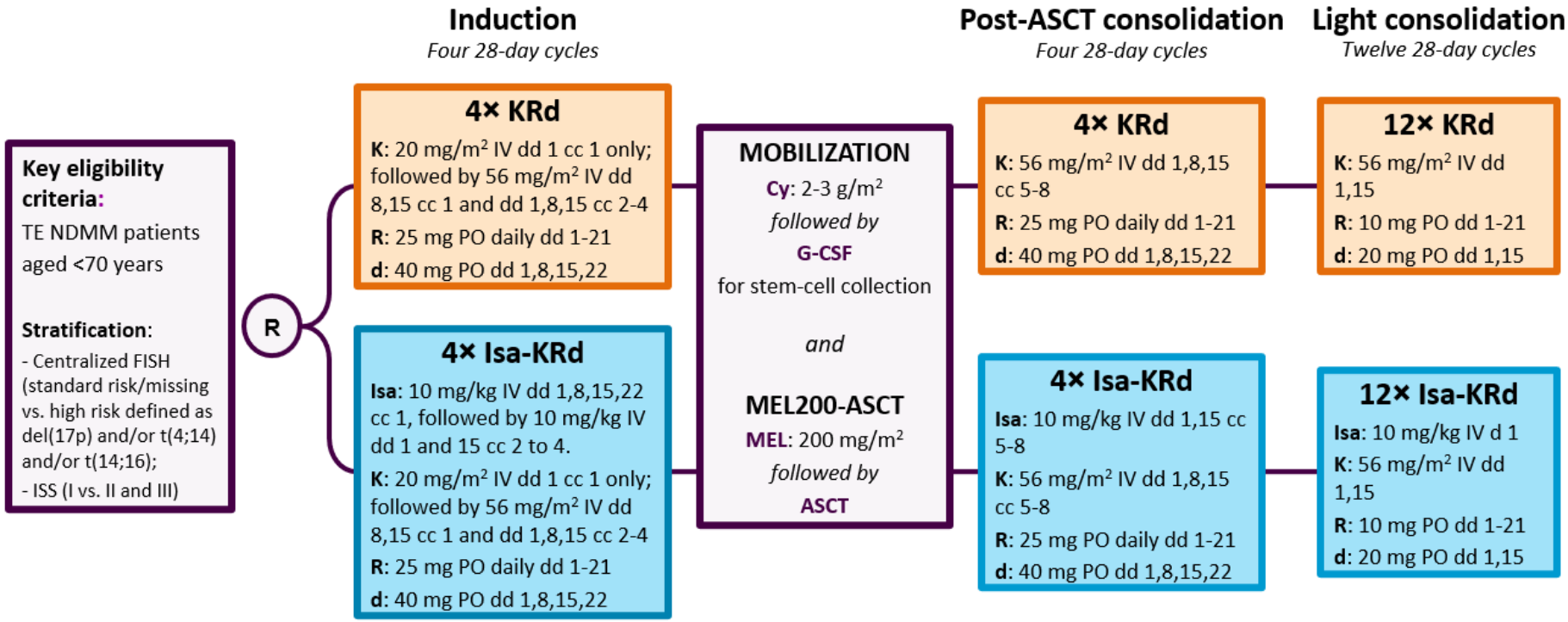


Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, p-value; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; MFC, multiparameter flow cytometry; 3-year PFS reported in the figure.

Gay F. Lancet Oncol 2021

IsKia EMN24 Study Design

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

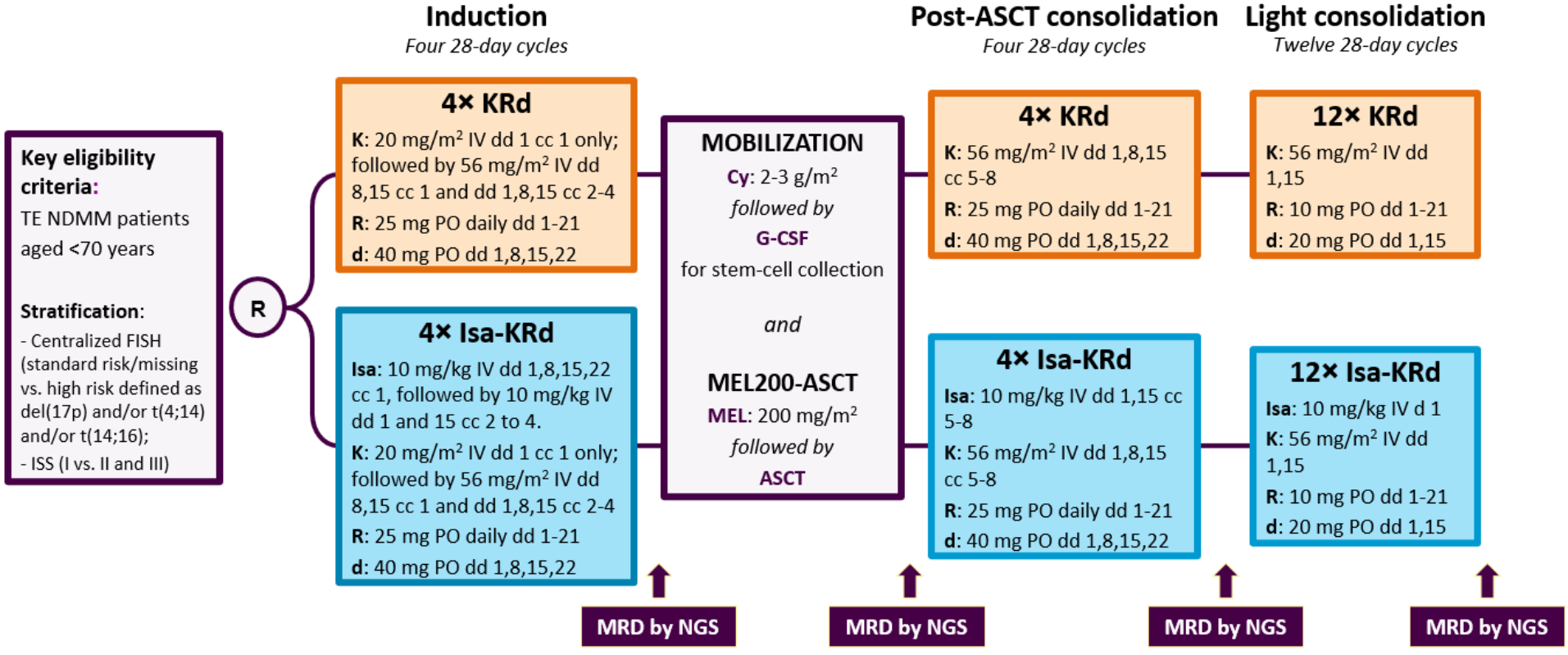


The EMN24 IsKia trial is registered with ClinicalTrials.gov: NCT04483739; it was sponsored by the European Myeloma Network (EMN).
All patients provided informed consent. This presentation includes discussion of the off-label use of a drug or drugs for the treatment of multiple myeloma.

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

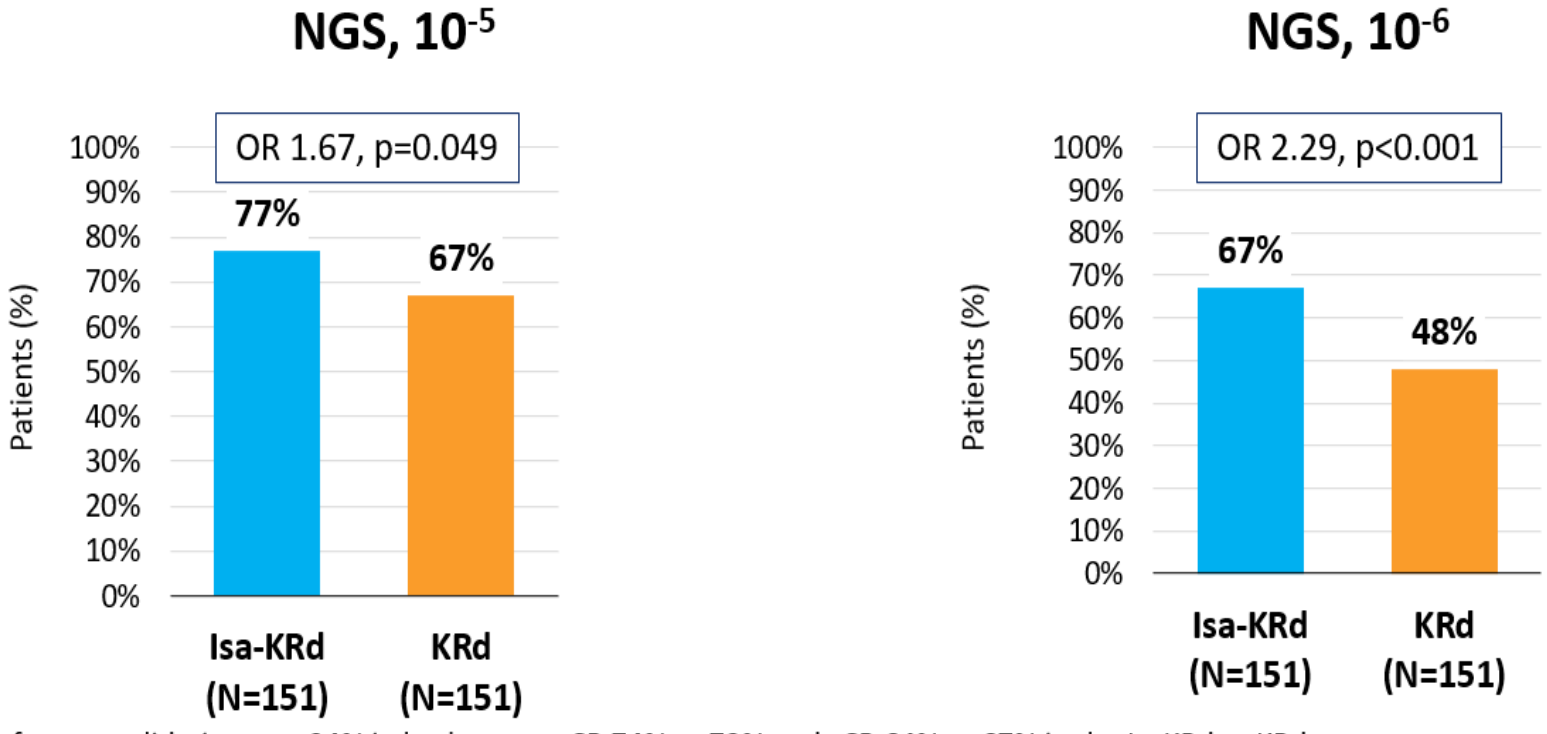
Sonneveld P, et al. Blood. 2016 Jun 16;127(24):2955-62. doi: 10.1182/blood-2016-01-631200.

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.

Primary Endpoint: Post consolidation MRD negativity (ITT alalysis)



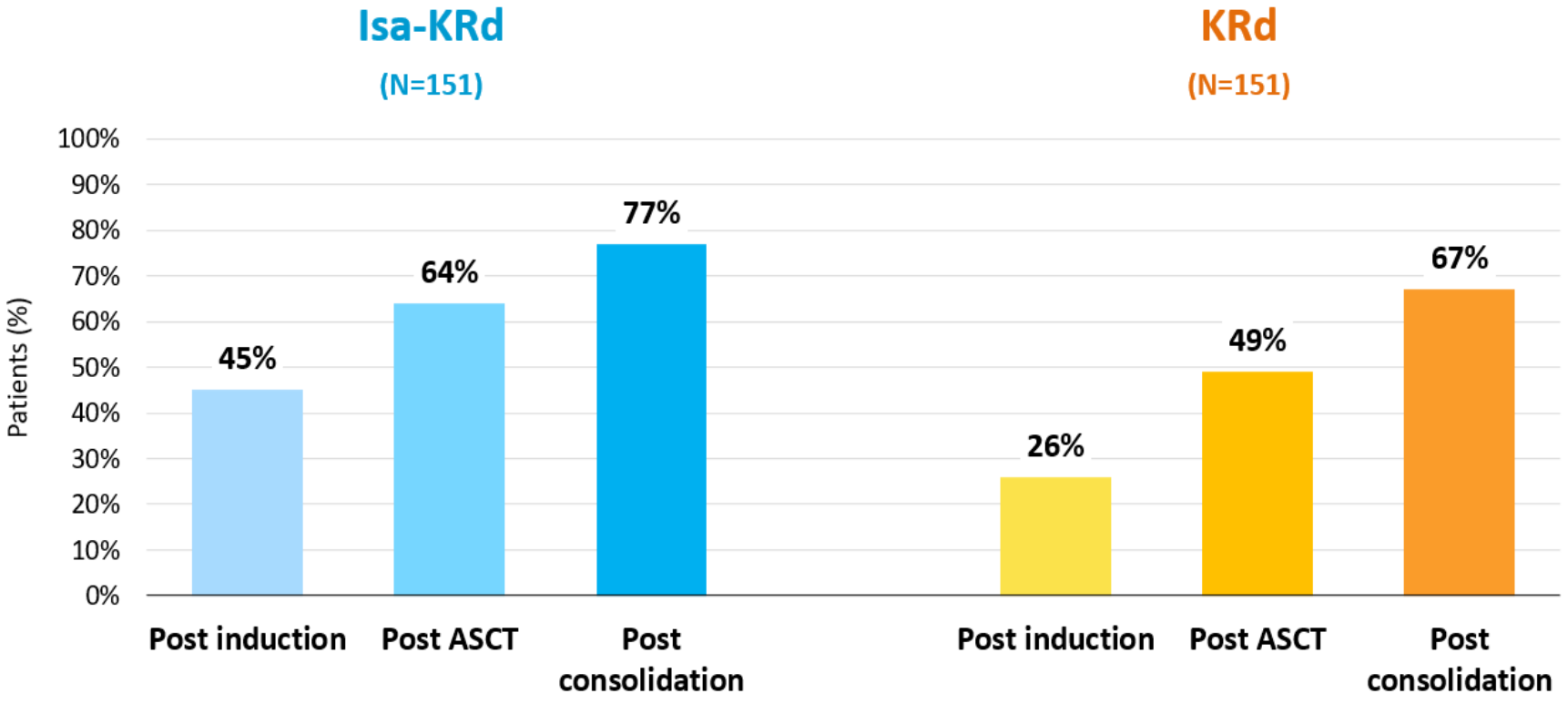
≥VGPR after consolidation was 94% in both arms; ≥CR 74% vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms.

Consistent MRD results were detected by next-generation flow

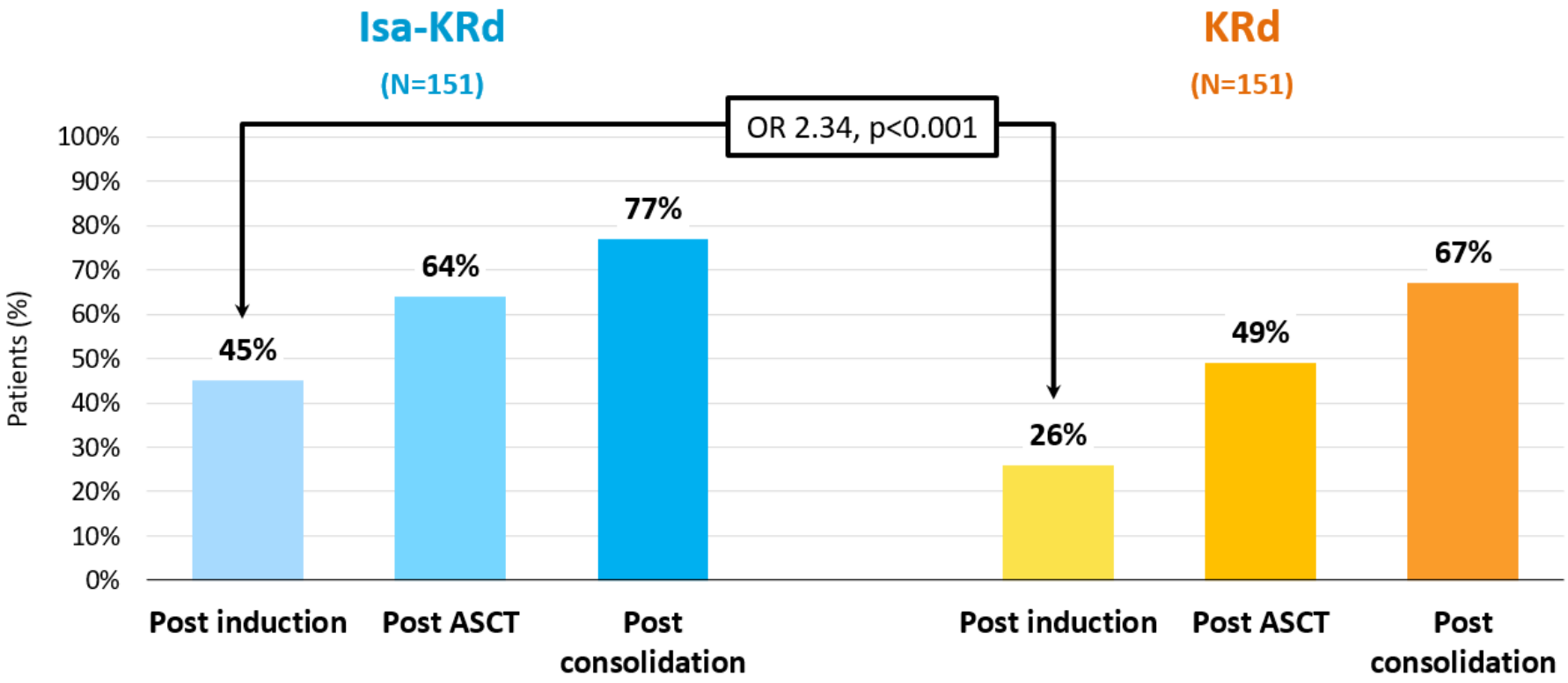
In the logistic regression analysis, ORs, 95% CIs, and p-values were adjusted for stratification factor.

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.

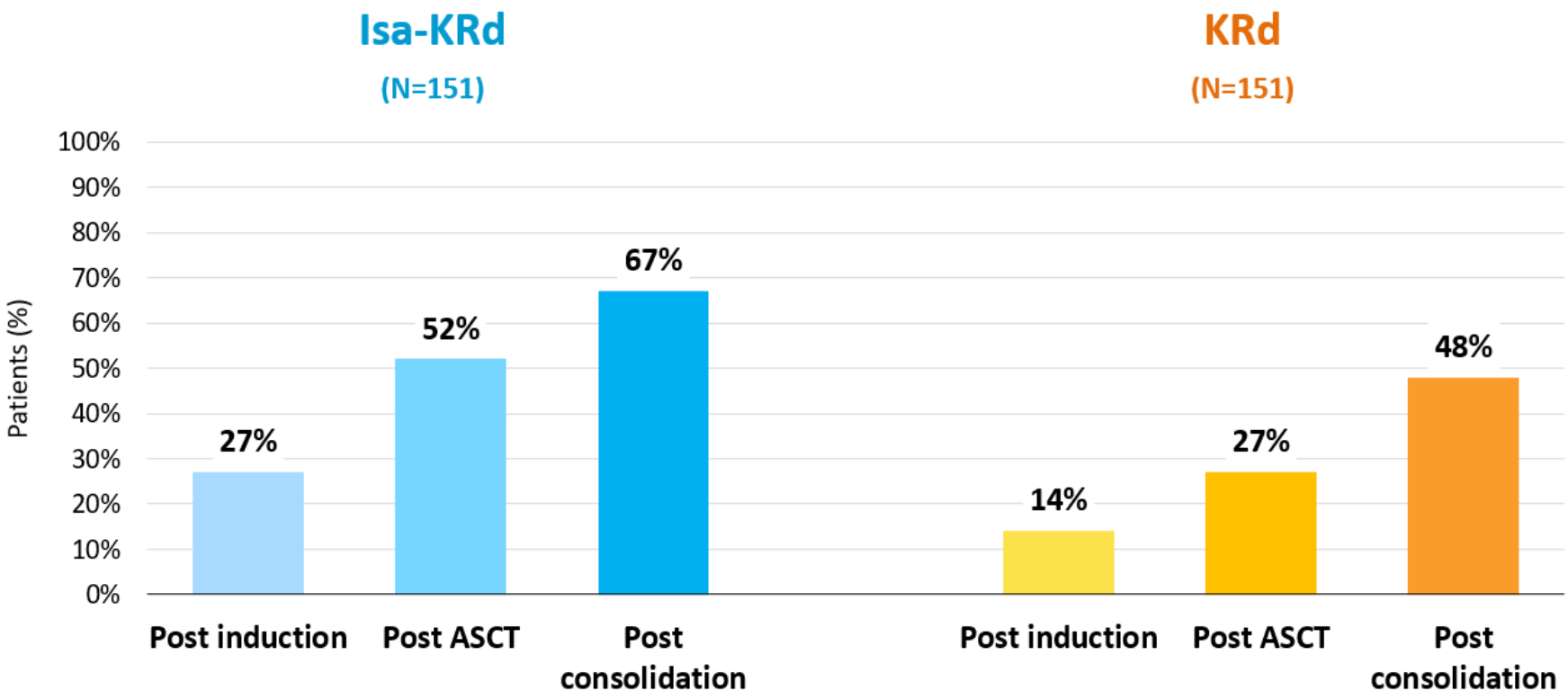
MRD negativity rates improved over time (10^{-5})



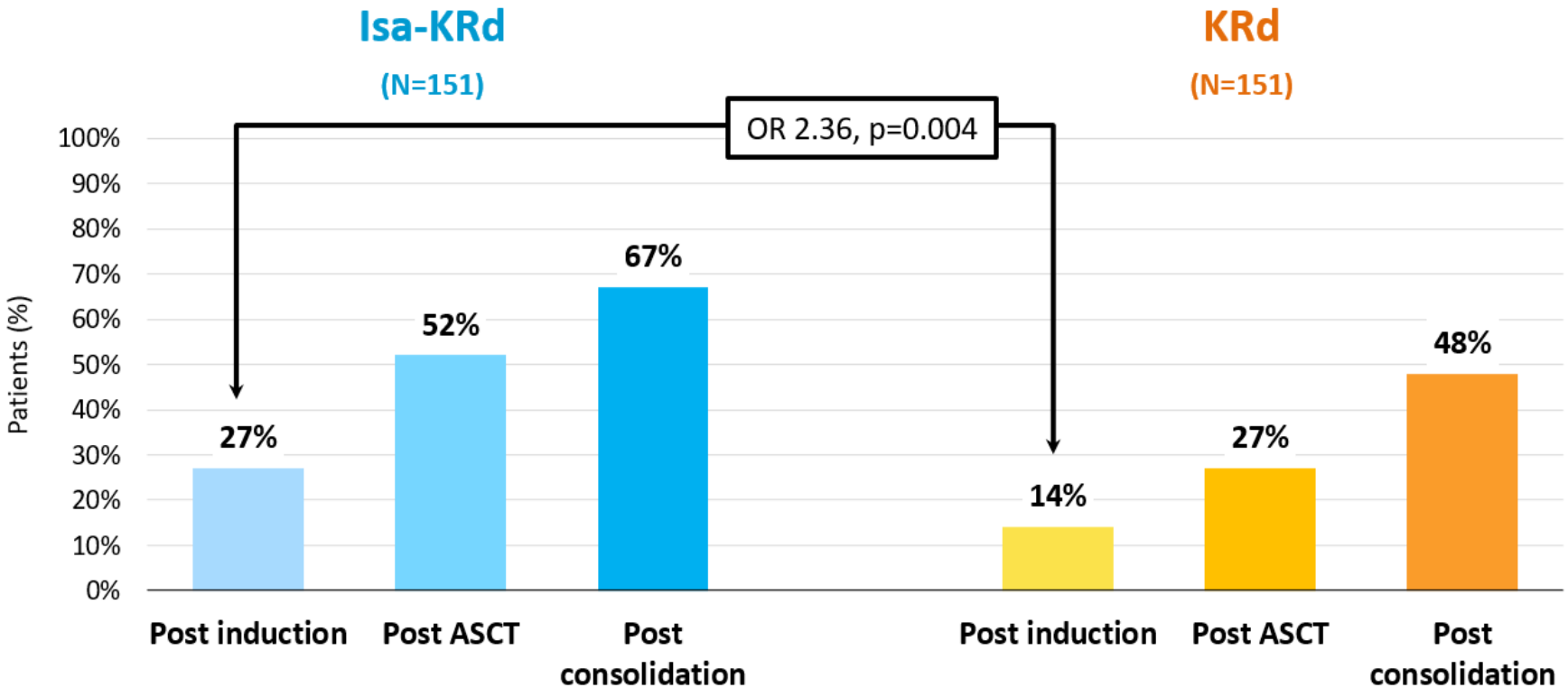
MRD negativity rates improved over time (10^{-5})



MRD negativity rates improved over time (10^{-6})



MRD negativity rates improved over time (10^{-6})



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*

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)
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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)

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Safety analysis: treatment-related adverse events

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	Any grade, n (%)	Grade 3-4, n (%)	Any grade, n(%)	Grade 3-4, n (%)
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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*

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Infections (excluding COVID19)	55 (36)	23 (15)	49 (32)	17 (11)
Asthenia/fatigue	37 (25)	5 (3)	40 (26)	3 (2)
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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)
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Diarrhea	41 (27)	6 (4)	37 (25)	5 (3)

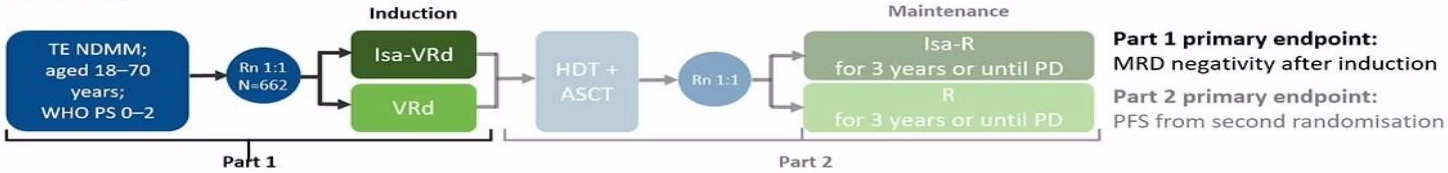
SARS-CoV-2 infection

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-VRd (GMMG HD7)

Trial design[1,2]



Part 1 primary endpoint: MRD negativity after induction

Part 2 primary endpoint: PFS from second randomisation

MRD-negativity rates after induction (part 1)[1]

OR, 1.82; 95% CI, 1.33–2.48; p=0.00017

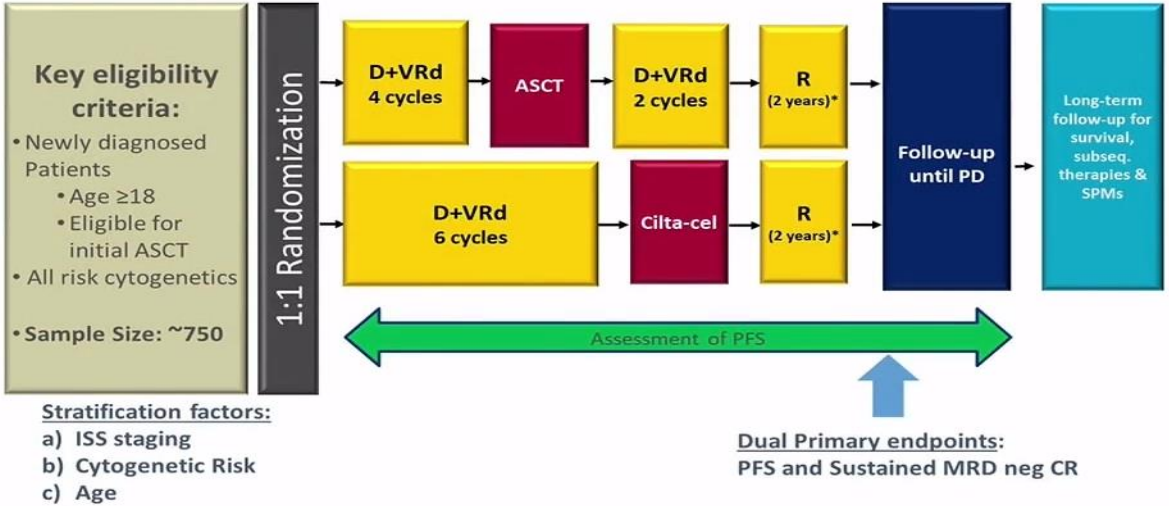
Safety (part 1)[1]

	Isa-VRd (n=330)	VRd (n=328)
Peripheral sensory neuropathy, n (%)		
Grade 1 or 2	68 (21)	80 (24)
Grade 3 or 4	22 (7)	25 (8)
Infections, n (%)		
Grade 1 or 2	44 (13)	43 (13)
Grade 3 or 4	40 (12)	32 (10)
Grade 3 or 4 AE, n (%)	208 (63)	199 (61)
Any serious grade 3 or 4 AE, n (%)	92 (28)	93 (28)
Deaths, n (%)	4 (1)	8 (2)

AE, adverse event; ASCT, autologous stem cell transplant; CI, confidence interval; d, dexamethasone; HDT, high-dose therapy; Isa, isatuximab; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OR, odds ratio; PD, progressive disease; PFS, progression-free survival; R, lenalidomide; Rn, randomisation; TE, transplant-eligible; V, bortezomib; WHO PS, World Health Organisation performance status.

1. Goldschmidt H, et al. Lancet Haematol 2022;9:e810-21; 2. Goldschmidt H, et al. ASH 2021 (Abstract No. 463 – presentation).

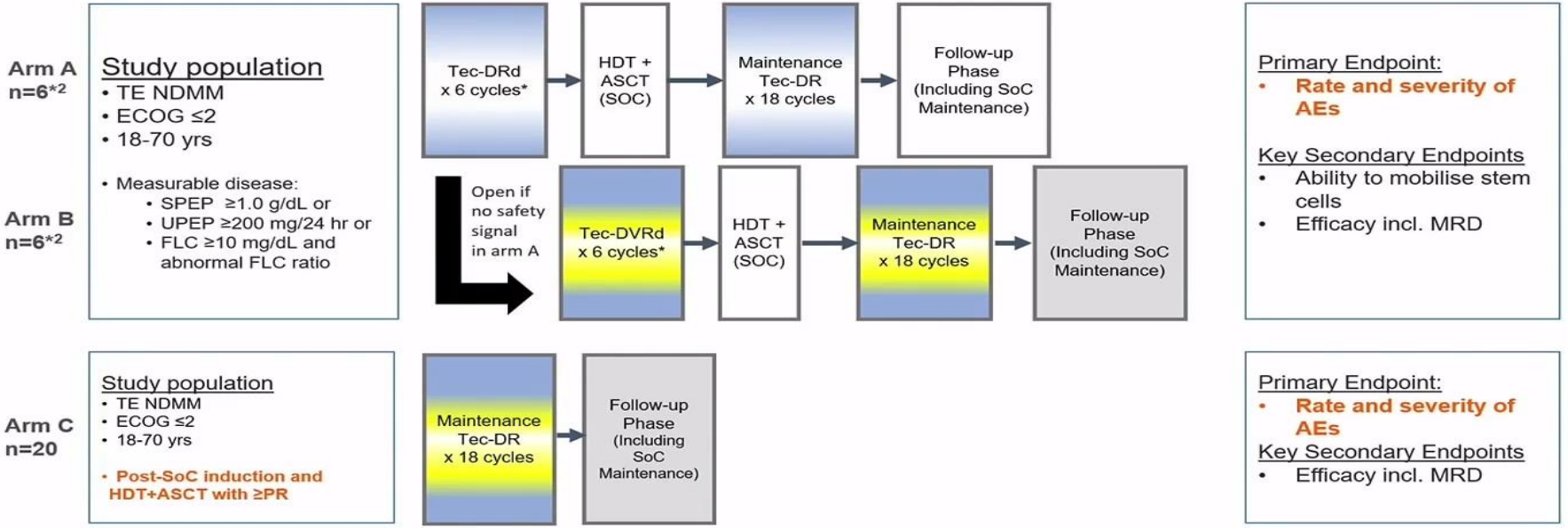
CARTITUDE-6: Randomised Phase III study in newly diagnosed, transplant-eligible patients[1]



*Participants benefitting from therapy have the option to continue lenalidomide therapy until PD per investigator's discretion after benefit-risk assessment and review by the medical monitor.
ASCT, autologous stem cell transplant; CR, complete response; D, daratumumab; d, dexamethasone; ISS, international staging system; MRD, minmal residual disease; neg, negativity; PD, progressive disease; PFS, progression-free survival; SPM, second primary malignancies; R, lenalidomide; V, bortezomib.

1. Boccadoro M, et al. ASH 2022 (Abstract No. – presentation).

Phase II MajesTEC-5 study design – overview[1,2]



*Arm A or B will be expanded to 20 patients depending on safety data.[2]

AE, adverse event; ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; D, daratumumab; d, dexamethaone; ECOG, Eastern Cooperative Oncology Group; FLC, free light chain; HDT, high-dose therapy; Len, lenalidomoide; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PI, principal investigator; PR, partial response; R, lenalidomide; SoC, standard of care; SPEP, Serum Protein Electrophoresis; TE, transplant eligble; Tec, teclistamab; UPEP, Urine Protein Electrophoresis; V, bortezomib.

1. NCT05695508. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05695508 (last accessed September 2023); 2. Personal communication by Rasche L.

Co-PIs Raab/Rasche

CONCLUSIONI

- **Importante ottenere risposte profonde dopo la terapia di induzione**
- **Evidenza di prognosi migliore per i pazienti con ottime risposte con il primo trattamento di induzione**
- **Gli anticorpi monoclonale anti-CD38 in aggiunta alla tripletta inducono una maggiore profondità della risposta che si traduce in più lunghe PFS**
- **Per cui, al momento, per i pazienti con mieloma multiplo eleggibili al trapianto di cellule staminali il trattamento più indicato è un regine a 4 farmaci considerando anche come la tossicità dell'aggiunta degli anticorpi monoclonale è minima e ben gestibile**