Induction therapy and Myeloma

Sagar Lonial, MD
Professor and Chair
Department of Hematology and Medical Oncology
Anne and Bernard Gray Professor in Cancer
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

Scope of the Problem

- In 2022, 34,470 new cases will be diagnosed (19,100 in men and 15,370 in women) and
  12,640 deaths are expected to occur (7090 in men and 5550 in women)[a]
- In 2019, there were an estimated 159,787 people living with myeloma in the United States[b]
  (5-year survival rate 57.9%, median age at diagnosis: 69 years and median age of death is 75 years[b])
- Prognosis has significantly improved, with median survival estimated at 12 years[c,d]
- Disease is sensitive to treatment, but curable only in a small subset

- a. American Cancer Society. Accessed August 19, 2022. www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html;
  b. SEER 12. Accessed August 19, 2022. https://seer.cancer.gov/statfacts/html/mulmy.html; c. Parikh R, et al. J Clin Oncol. 2022;40(16_suppl):8061; d. Joseph NS, et al. J Clin Oncol. 2020;38:1928-1937.

Risk Stratification

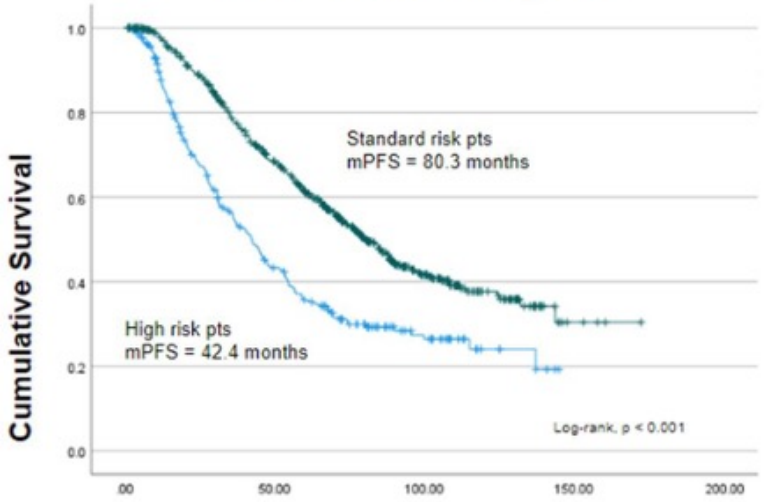
- High risk
  - Deletion 17p ≥20% and/or p53 mutation
  - Deletion 1p and +1q (1 extra copy of 1q not high risk alone)
  - High risk 14q32 trans and (+1q or deletion 1p)

- Standard risk
  - Hyperdiploidy
  - t(11;14)

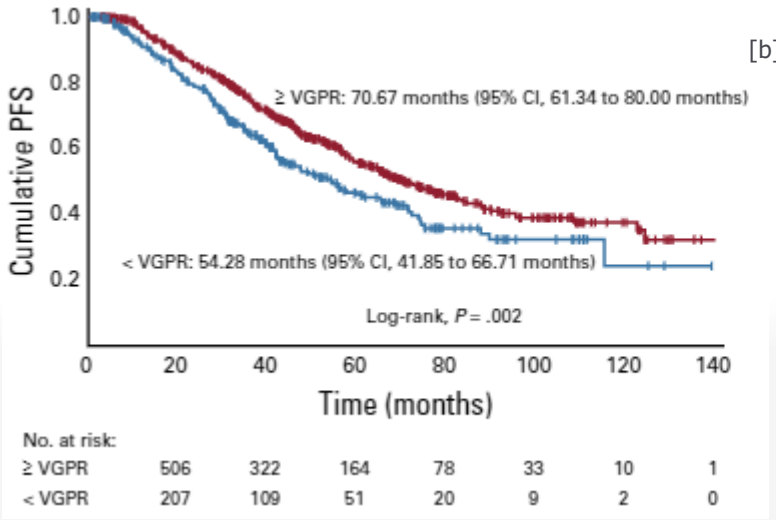
NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma (Version 1.2020).
Palumbo A. *N Engl J Med.* 2011;364:1046-1060.

Current: RVD Induction Therapy (N = 1000 Patients)

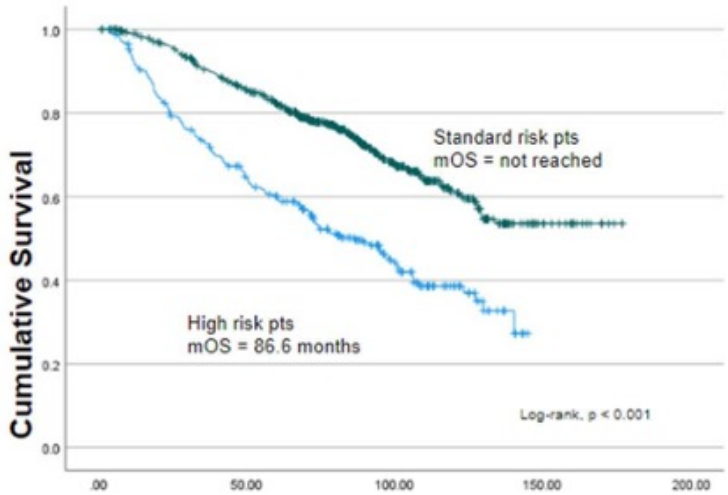
PFS for standard v high risk [a]



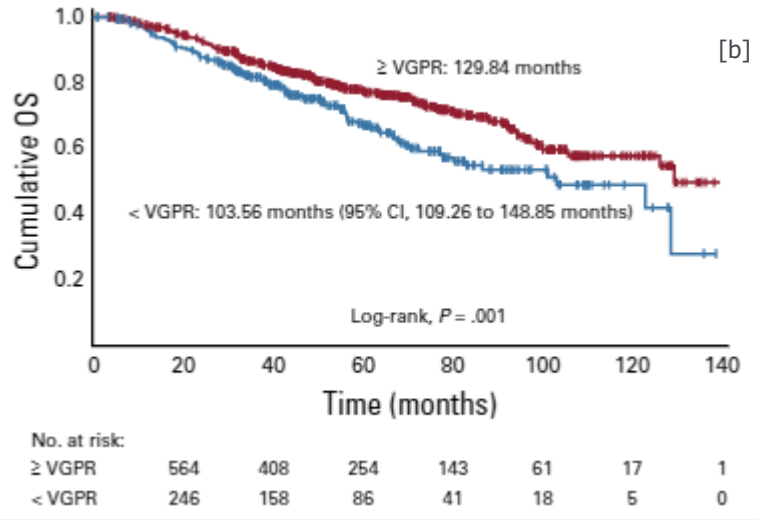
[b]



OS for standard v high risk [a]

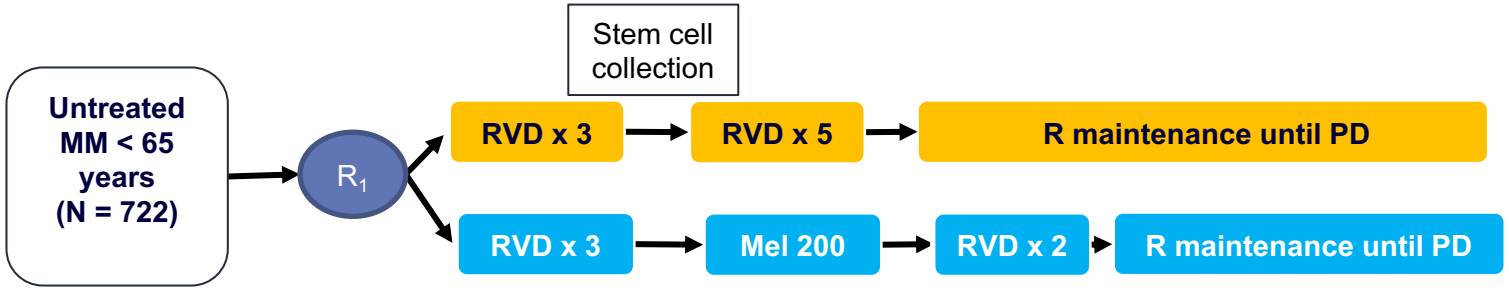


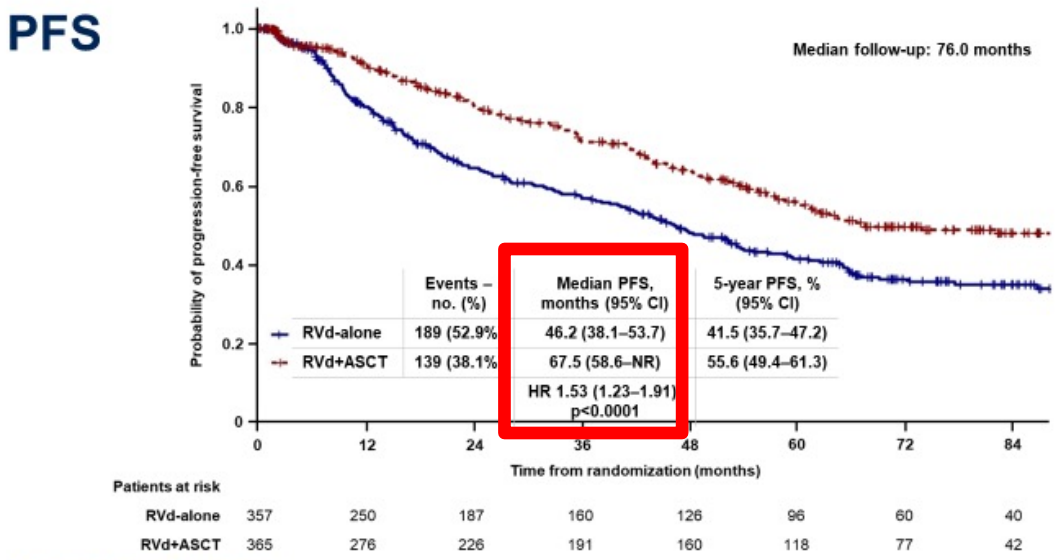
[b]

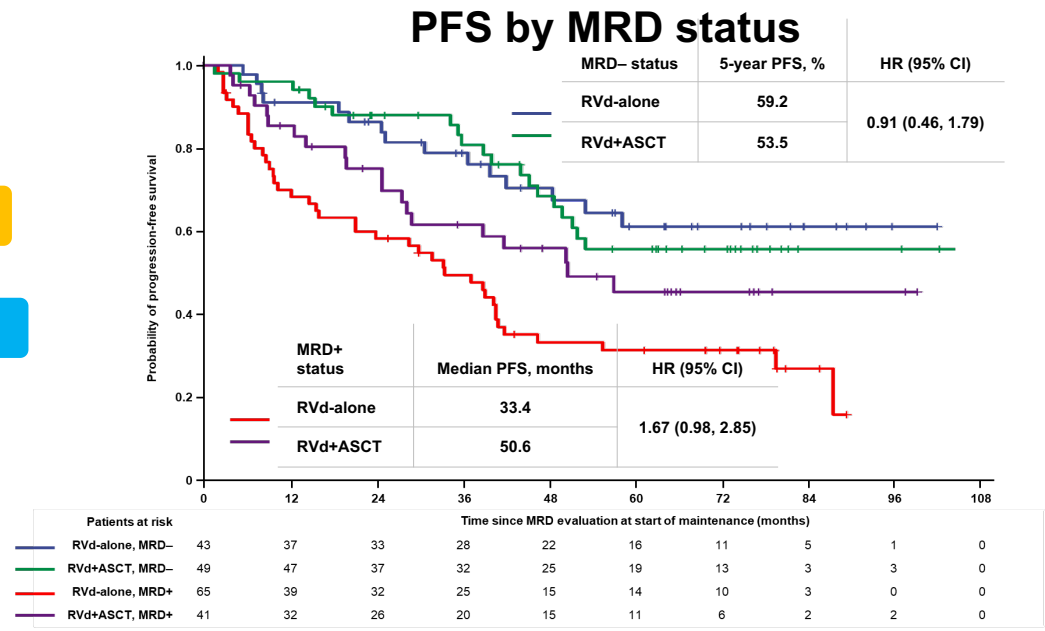


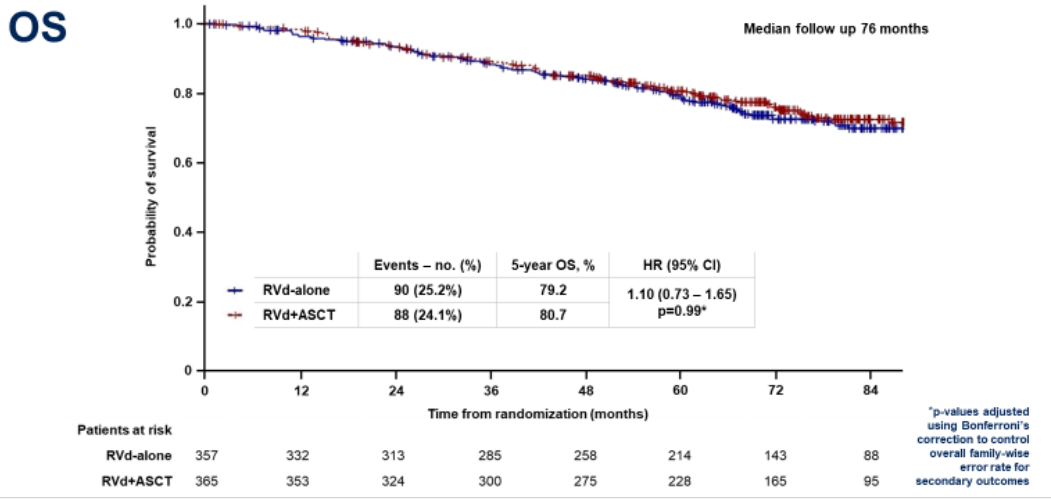
- a. Parikh R, et al. J Clin Oncol. 2022;40(16_suppl):8061; b. Joseph NS, et al. J Clin Oncol. 2020;38:1928-1937.

DETERMINATION (N = 722)





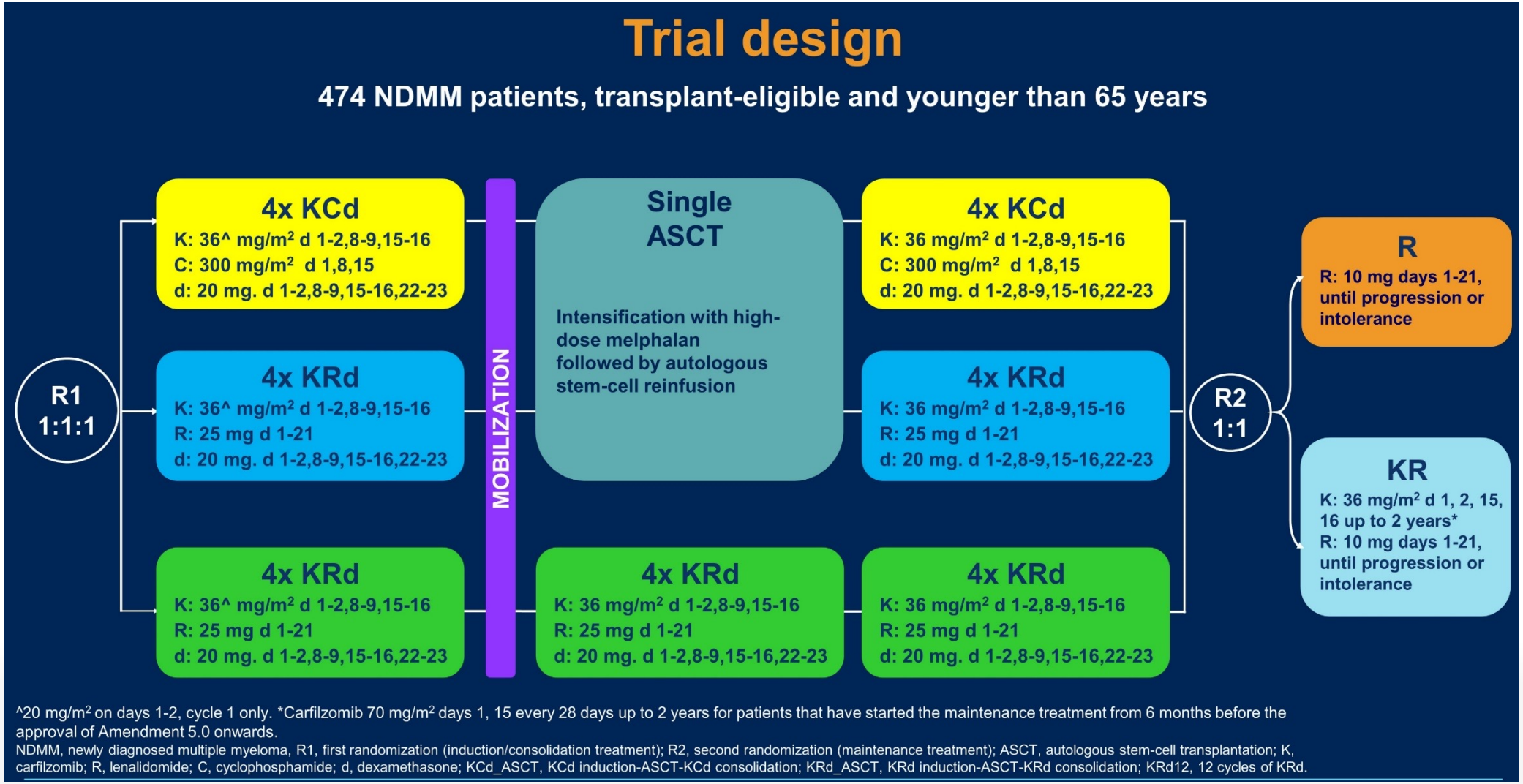




- ASCT, autologous stem cell transplant.

Richardson P, et al. J Clin Oncol. 2022;40(17_suppl): LBA4.

FORTE Trial (N = 474)

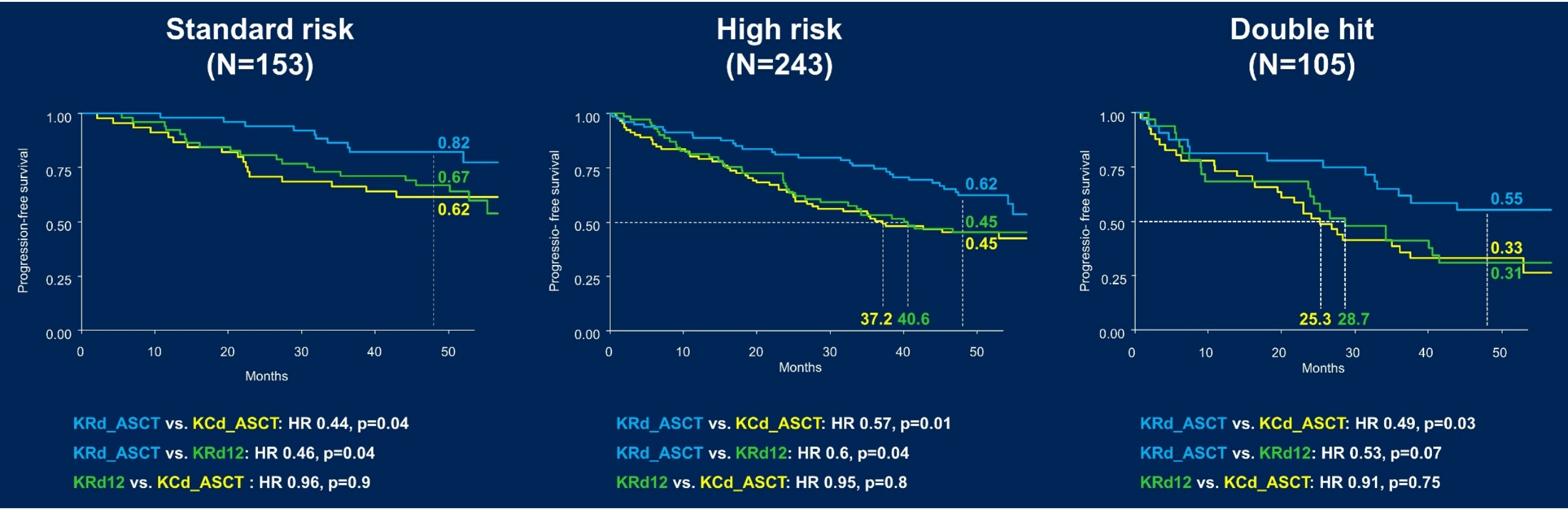


- NDMM, newly diagnosed multiple myeloma; R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment).
Gay F, et al. J Clin Oncol. 2021;39(suppl 15):8002.

After R1: PFS Benefit With KRd/ASCT

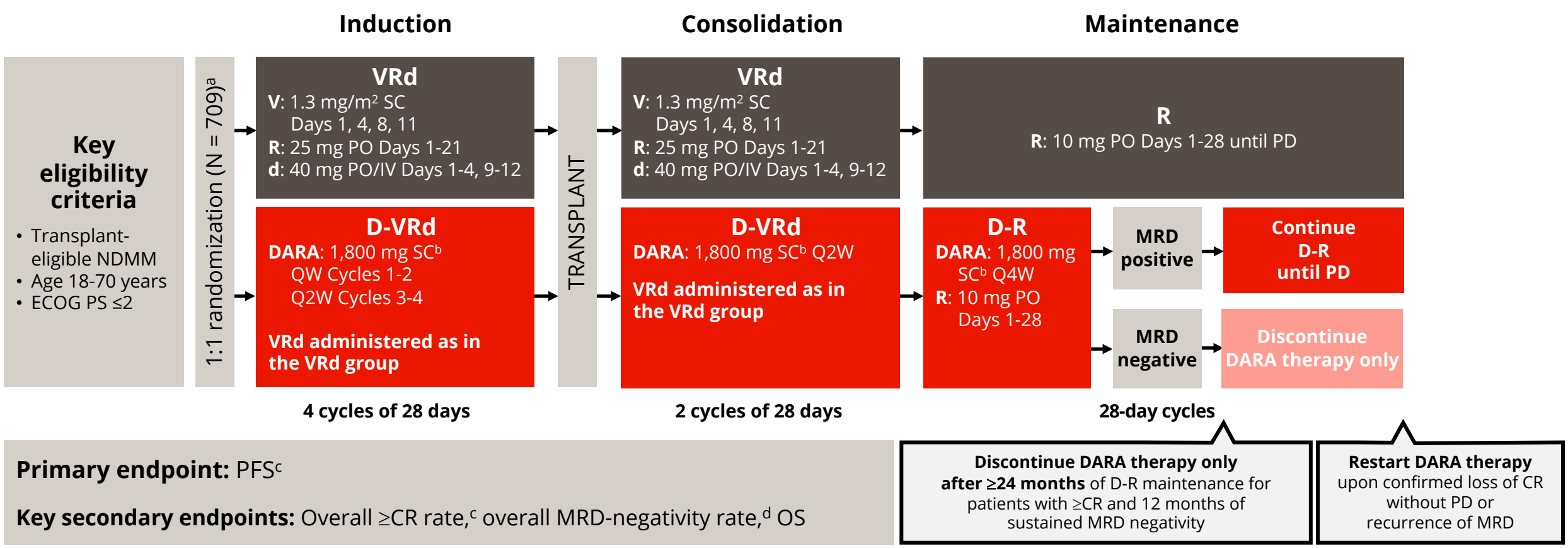
- **PFS benefit observed with KRd/ASCT vs KCd/ASCT or KCd12**

- Median follow-up from R1: 51 months



- Gay F, et al. J Clin Oncol. 2021;39(suppl 15):8002.

PERSEUS: Study Design



Primary endpoint: PFS[c]

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

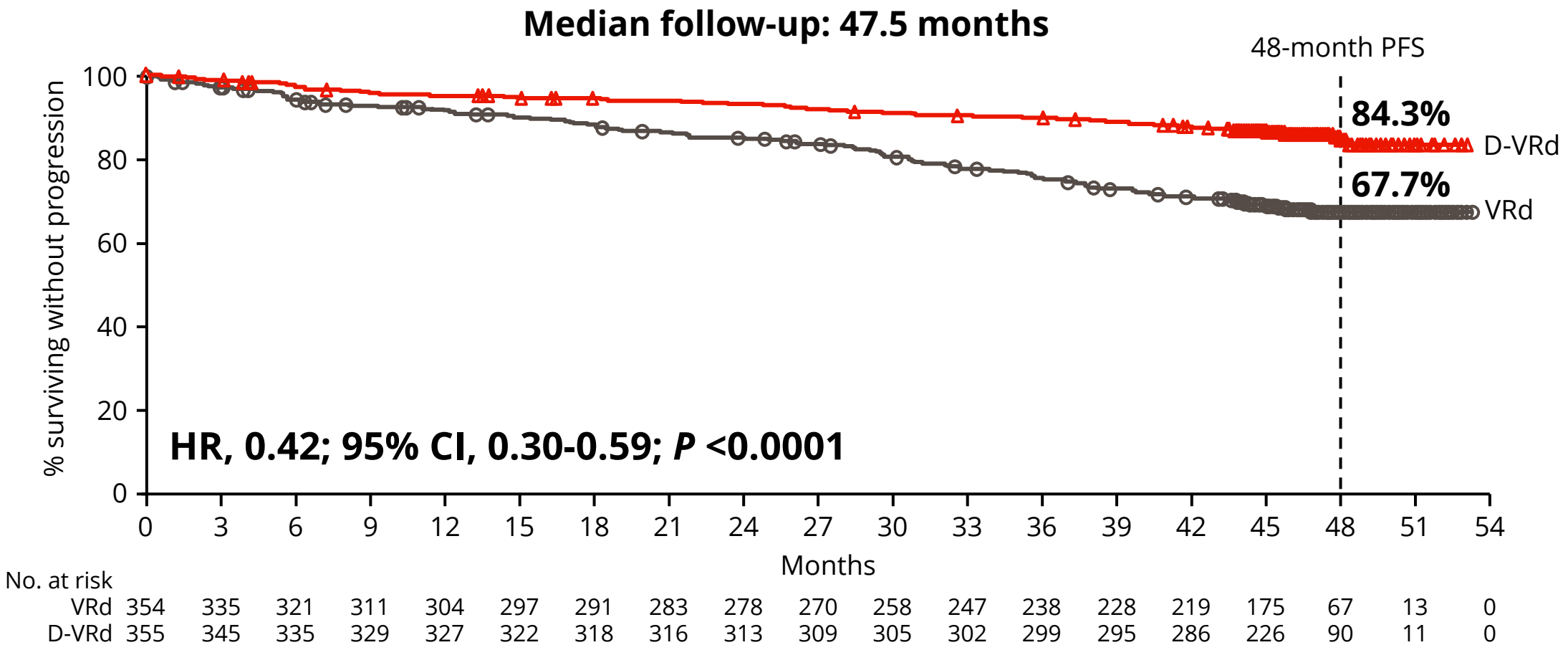
Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

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: Progression-free Survival

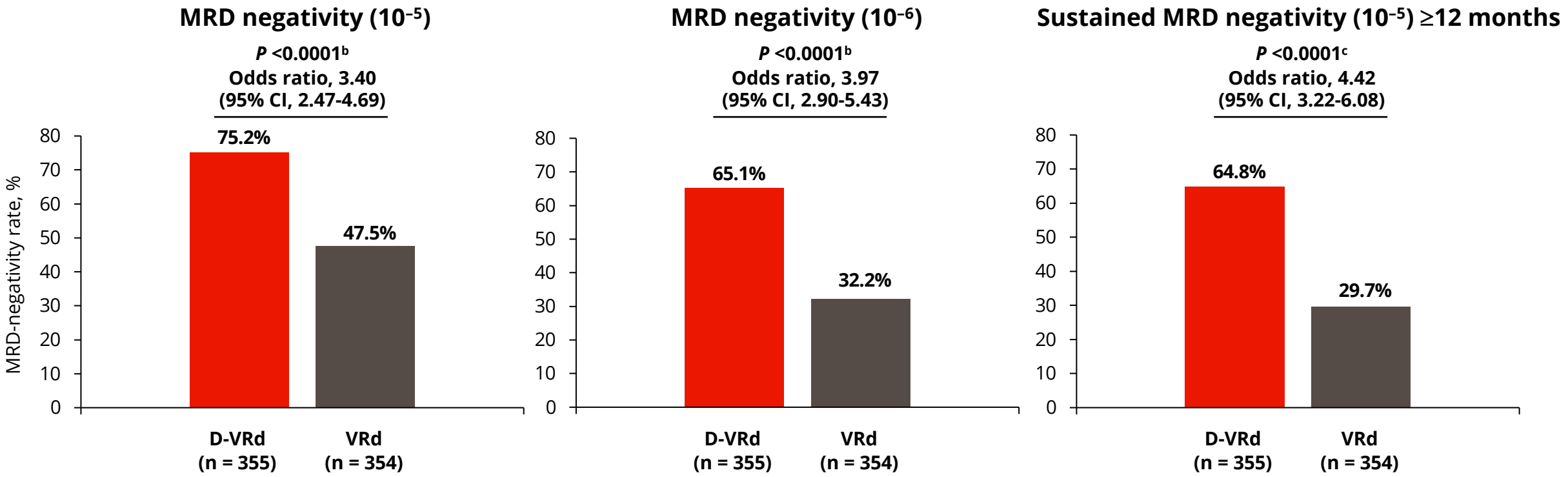


- **58% reduction in the risk of progression or death in patients receiving D-VRd**

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 and Sustained MRD-negativity Rates[a]

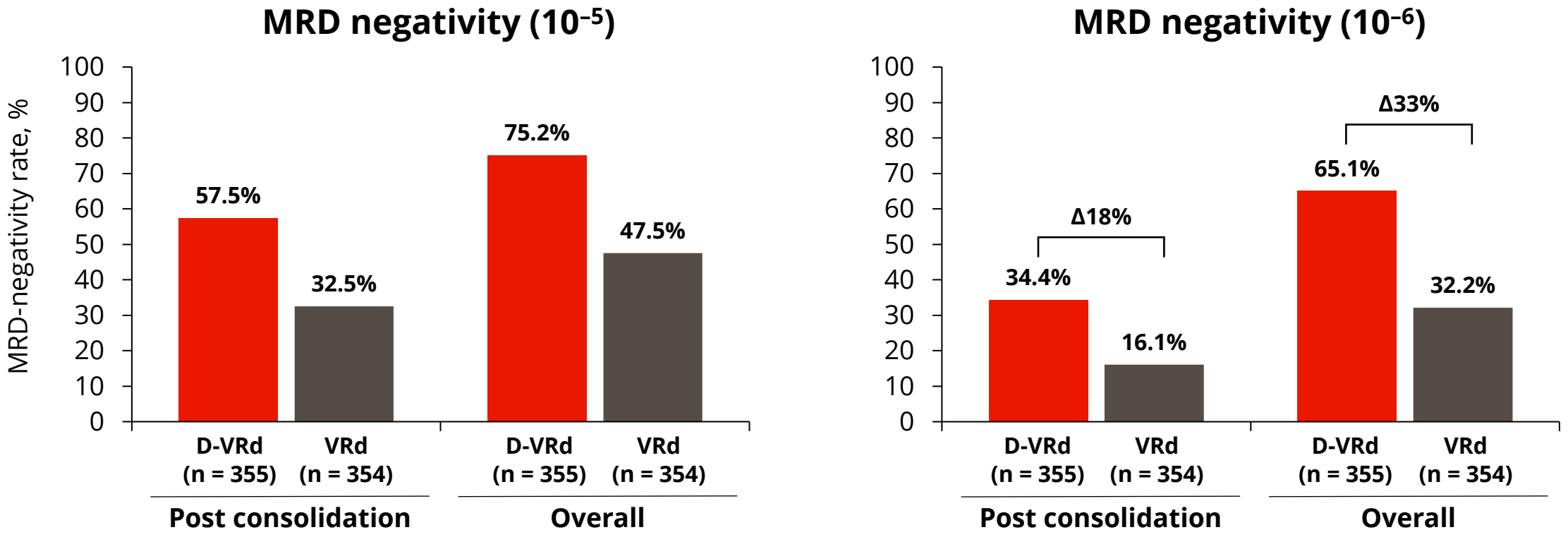


- **Deep and durable MRD negativity was achieved with D-VRd**
- **64% (207/322) of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity per protocol[d]**

[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.

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

PERSEUS: MRD-negativity Rates[a] Over Time



- **Rates of MRD negativity improved during maintenance**
- **The absolute difference between D-VRd and VRd widened over time and is most evident at the deeper threshold of 10^{-6}**

[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).

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

Iskea 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/m^2 IV dd 1 cc 1 only; followed by 56 mg/m^2 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/m^2 IV dd 1 cc 1 only; followed by 56 mg/m^2 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/m^2

followed by

G-CSF

for stem-cell collection

and

MEL200-ASCT

MEL: 200 mg/m^2

followed by

ASCT

Post-ASCT consolidation

4× KRd

K: 56 mg/m^2 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/m^2 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:

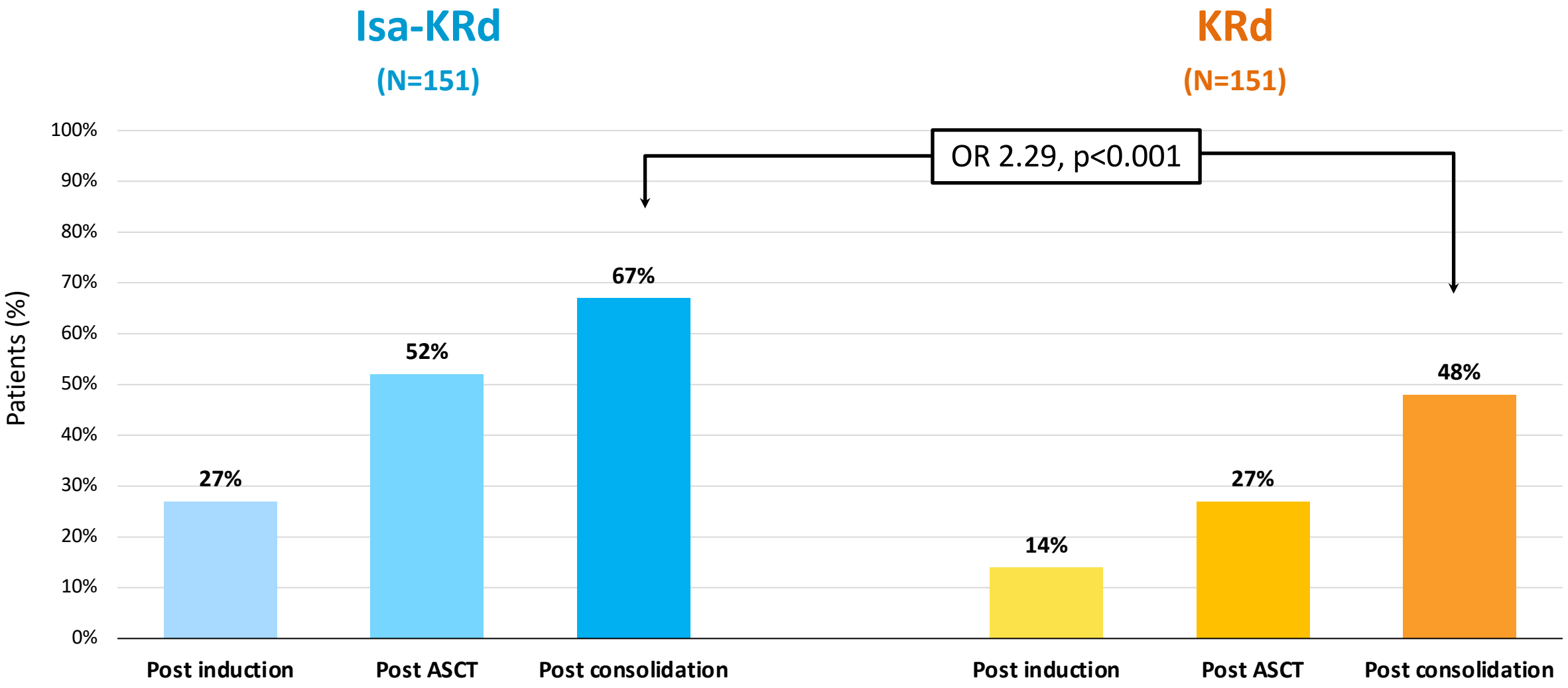
MRD negativity after induction;
PFS

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.

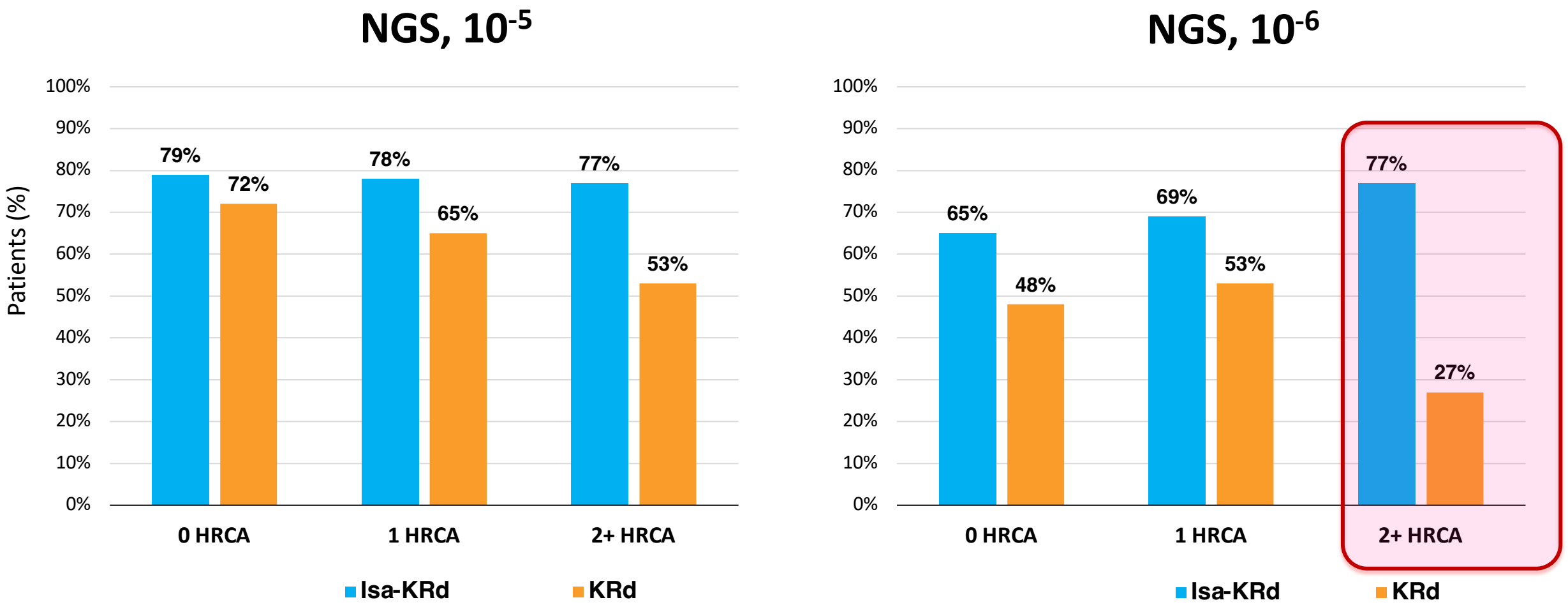
MRD negativity rates improved over time (10^{-6})



MRD, minimal residual disease; p, p-value; ASCT, autologous stem-cell transplantation.

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.

STUDY DESIGN

No consolidation
Risk-stratified maintenance approach
No Dara-based maintenance

Key eligibility criteria:

- Transplant-eligible newly diagnosed standard risk or high risk multiple myeloma
- Received either RVd or D-RVd induction

RVd

- Len: 25 mg on days 1-14/21 days
- Bort: 1.3 mg/m^2 on days 1,4,8,11/21 days
- Dexamethasone 40 mg days 1,8,15/21 days

D-RVd

- Dara: IV or SQ on days 1,8,15/21 days for C1-4 and day 1 only if C5-6 given
- Len: 25 mg on days 1-14/21 days
- Bort: 1.3 mg/m^2 on days 1,4,8,11/21 days
- Dexamethasone 40 mg days 1,8,15/28 days

ASCT

Standard-risk:
Lenalidomide maintenance until PD

High-risk*:
PI/IMiD maintenance x 3 years or PD

Primary end-point:

- ≥Complete Response Rate (≥CR rate)

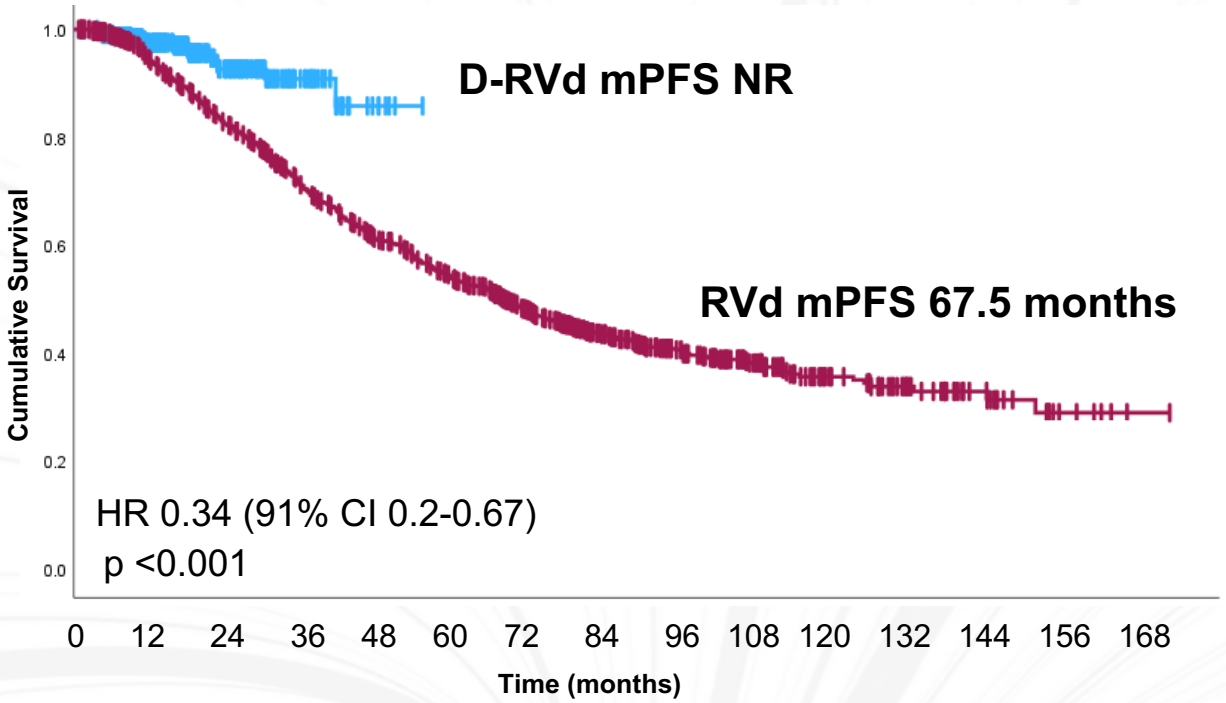
Secondary end-points:

- ≥VGPR
- PFS
- OS
- MRD (-) rate**

* High risk defined as presence of del(17p), t(4;14), t(14;16) or complex karyotype at diagnosis
** MRD assessment in progress
RVd: lenalidomide, bortezomib, dexamethasone; D-RVd: daratumumab, lenalidomide, bortezomib, dexamethasone; ASCT: Autologous Stem Cell Transplant; PFS: Progression Free Survival; ≥VGPR: Greater than Very Good Partial Response; CR: Complete Response, ORR: overall response rate;OS: overall Survival, Dara: daratumumab, Len: lenalidomide; Bort: bortezomib; Dex: Dexamethasone; IV: intravenous; SQ: subcutaneous; PD: disease progression

SURVIVAL OUTCOMES: OVERALL COHORT

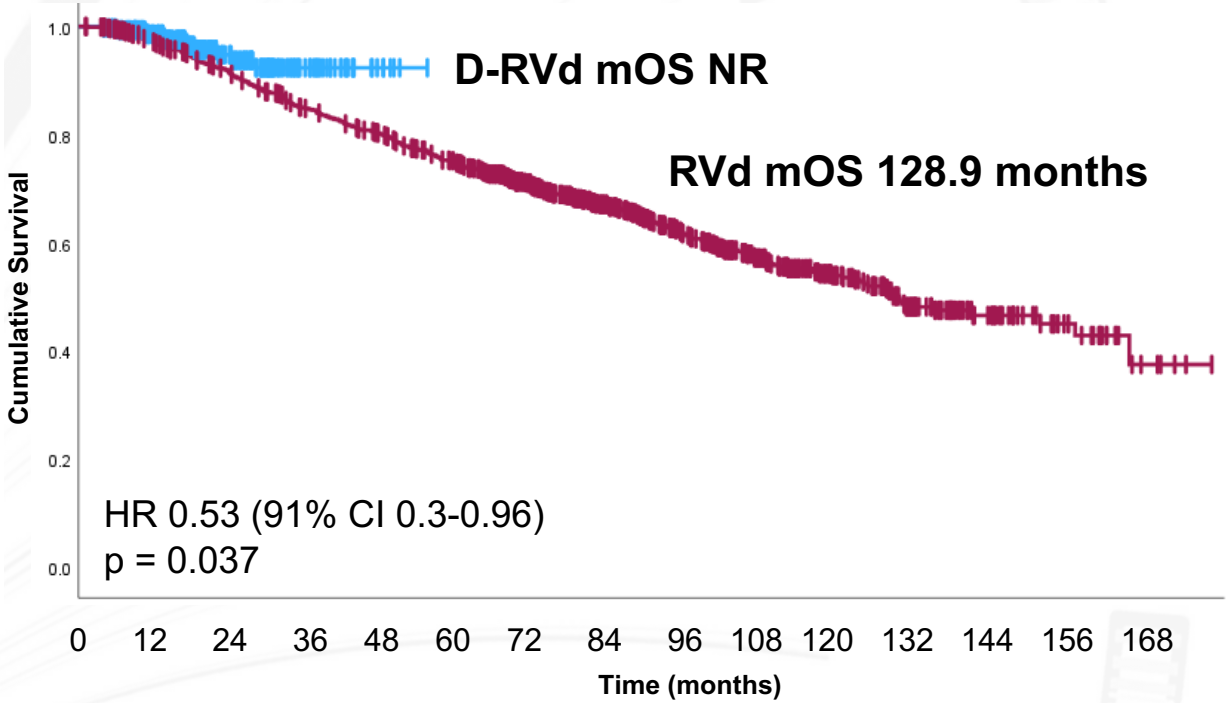
Progression Free Survival



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

Median follow up DRVd: 18 months, RVd: 87 months

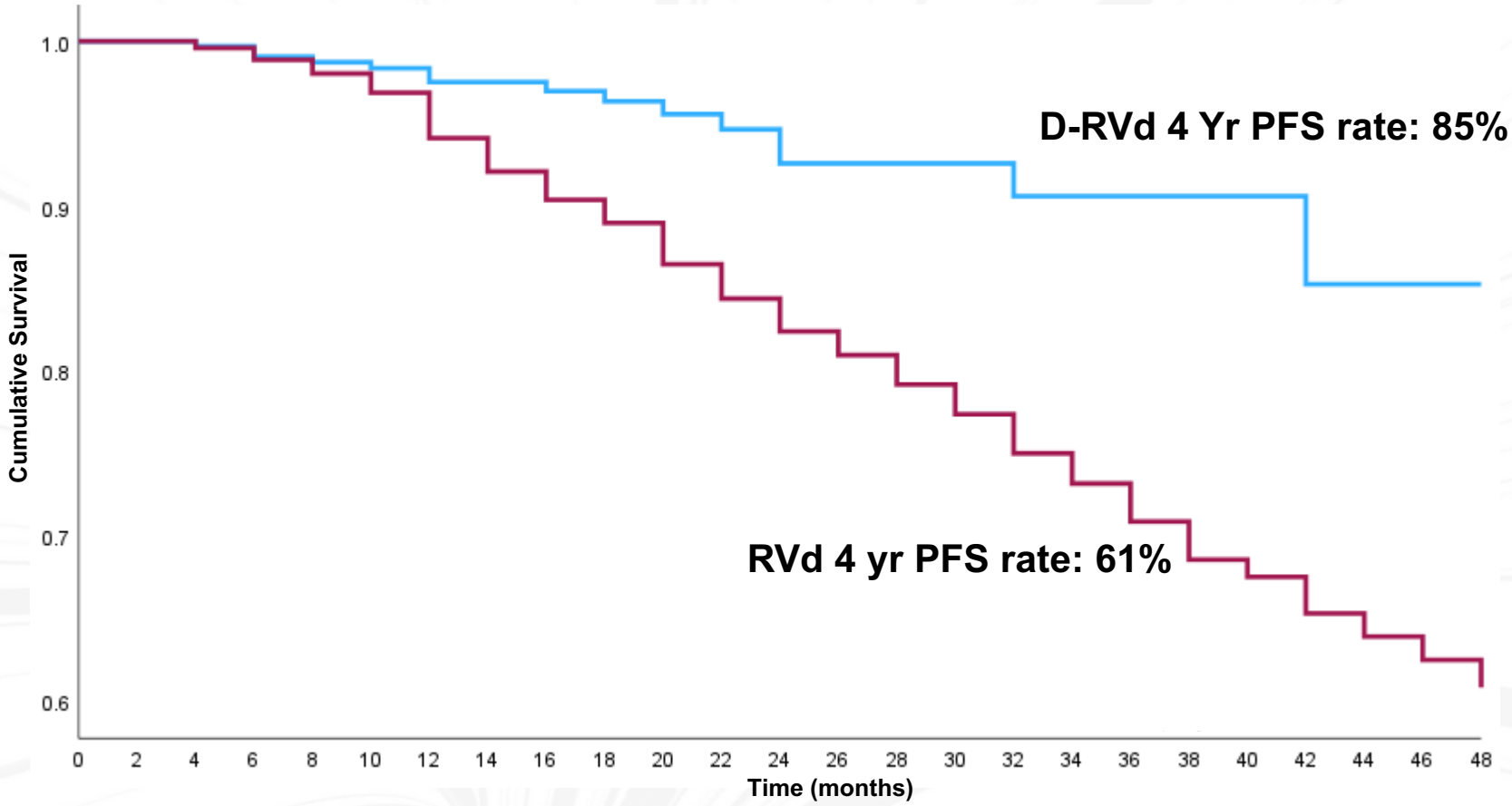
Overall Survival



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

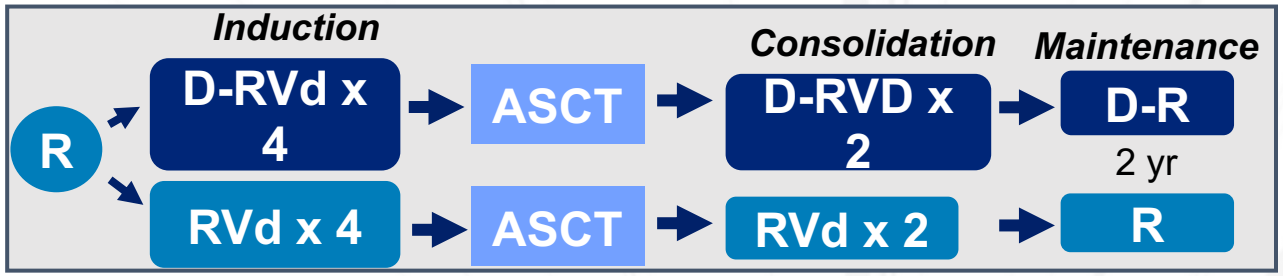
Median follow up DRVd: 18 months, RVD: 96 months

4 YEAR PFS RATE, BY TREATMENT ARM

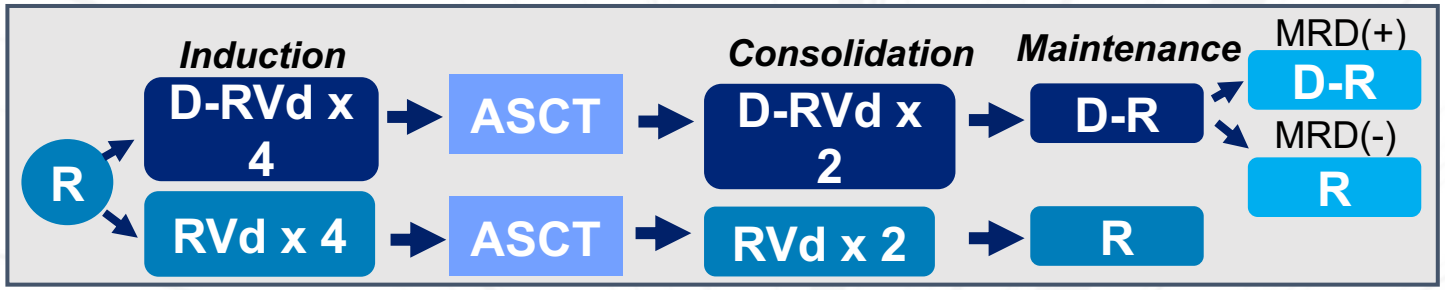


Rate*	D-RVd	RVd
1-year PFS	98%	93%
2-year PFS	93%	82%
3-year PFS	91%	69%
4-year PFS	85%	61%

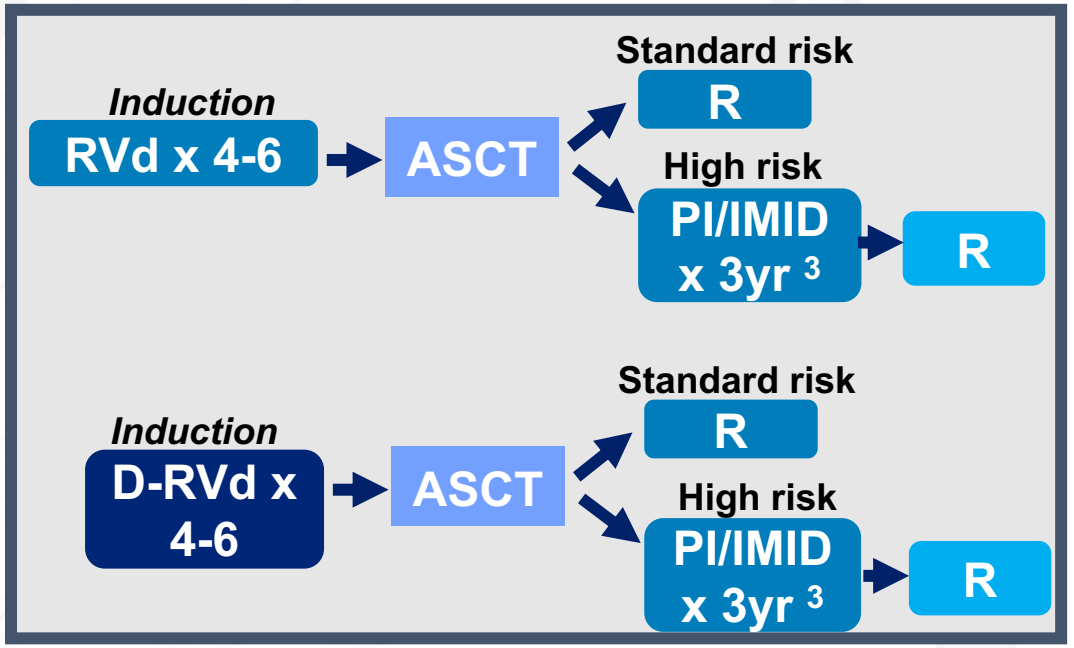
* All p values <0.001



GRIFFIN [1]



PERSEUS [2]

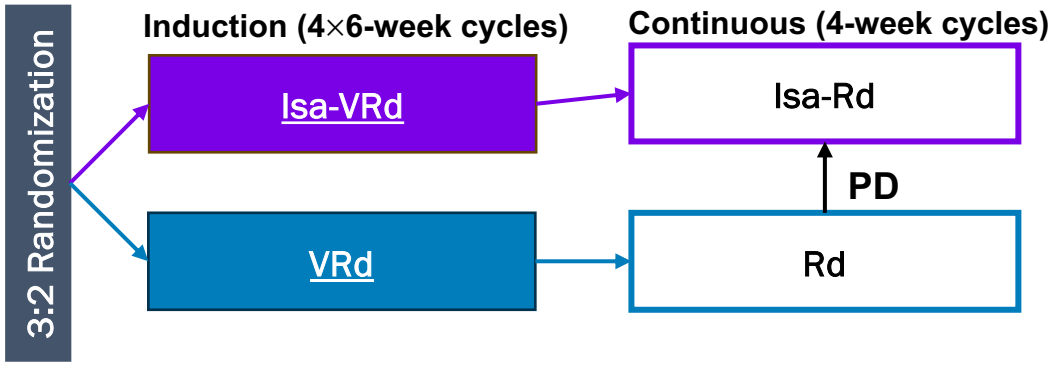


	4 year PFS	
	RVD	**D-RVD**
GRIFFIN [1]	70%	87%
PERSEUS [2]	67.7%	84.3%
Emory experience	61%	85%

1. Voorhees et al, *Lancet Hem*, 2023; 2. Sonneveld et al, ASH 2023, LBA-1; 3. Nooka et al, *Leukemia* 2014

IMROZ PHASE 3 TRIAL OF ISA-VRD VS VRD IN TRANSPLANT-INELIGIBLE NDMM: STUDY DESIGN AND PATIENTS

Key Eligibility Criteria
- Transplant-ineligible NDMM (TI due to age or comorbidities)
- Age ≤80 years



Induction	Isa 10 mg/kg IV; days 1, 8, 15, 22, 29 of cycle 1; days 1, 15, 29 of cycles 2-4 Bort 1.3 m/m^2 SUBQ; days 1, 4, 8, 11, 22, 25, 29, 32 Len 25 mg/day PO, days 1-14, 22-35 (10 mg/day if eGFR 30 to <60 mL/min/1.73 m^2) dex 20 mg IV/PO; days 1-2, 4-5, 8-9, 11-12, 15, 22-23, 25-26, 29-30, 32-33 (age ≥75 years: days 1, 4, 8, 11, 15, 22, 25, 29, 32)
Cont.	Isa 10 mg/kg IV; days 1, 15 of cycles 5-17; day 1 of cycles 18+ Len 25 mg/day PO, days 1-21 (10 mg/day if eGFR 30 to <60 mL/min/1.73 m^2) dex 20 mg IV/PO; days 1, 8, 15, 22

Primary endpoint: PFS
Key secondary endpoints: CR, MRD-neg CR (10^{-5}), ≥VGPR, OS

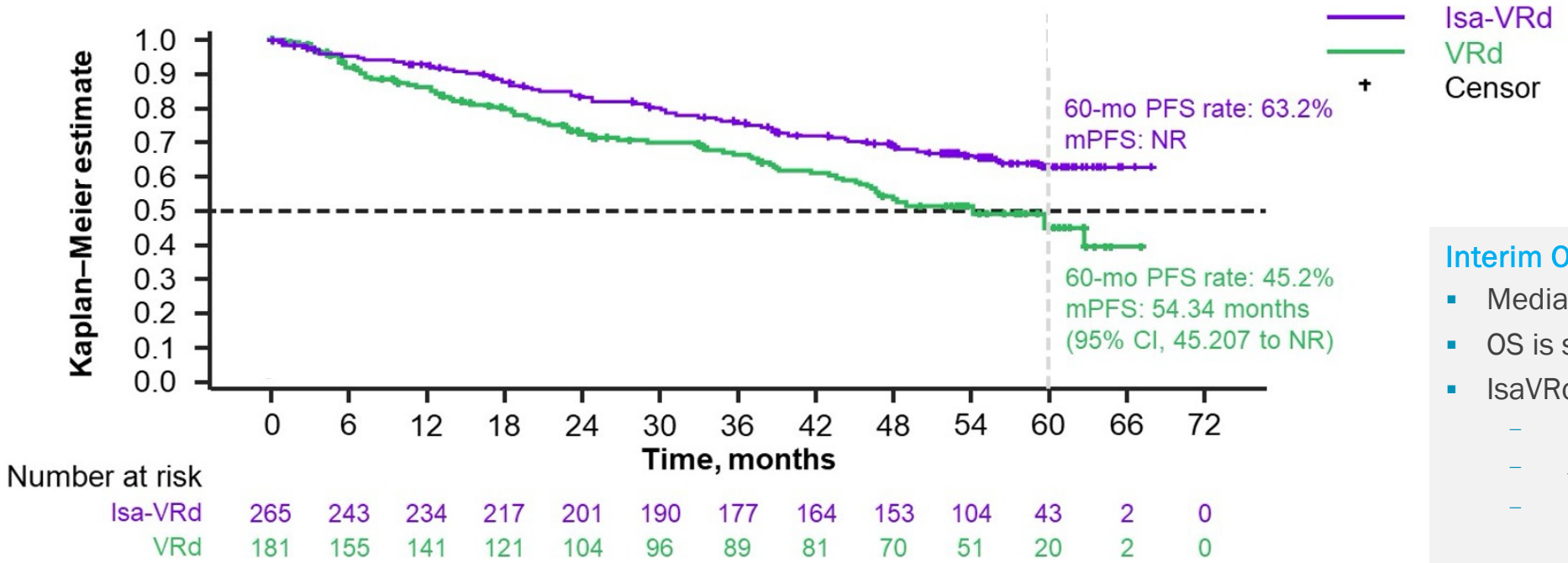
Patient Characteristics (ITT)		Isa-VRd (n=265)	VRd (n=181)
Median age (range), years		72.0 (60-80)	72.0 (55-80)
Age ≥75 years, n (%)		69 (26.0)	57 (31.5)
ECOG PS, n (%)	0	123 (46.4)	79 (43.6)
	1	112 (42.3)	83 (45.9)
	2	29 (10.9)	19 (10.5)
eGFR <60 mL/min/1.73 m^2, n (%)		66 (24.9)	62 (34.3)
R-ISS stage, n (%)	I or II	234 (88.3)	157 (86.7)
	III	29 (10.9)	21 (11.6)
	Not classified	2 (0.8)	3 (1.7)
Cytogenic risk, n (%)	Standard	207 (78.1)	140 (77.3)
	High[a]	40 (15.1)	34 (18.8)
	High and 1q21+[b]	19 (7.2)	15 (8.3)
1q21+[b], n (%)		95 (35.8)	70 (38.7)
Amplification 1q21[b], n (%)		32 (12.1)	23 (12.7)
Del(17p) (50% cutoff), n (%)		15 (5.7)	9 (5.0)
Extramedullary disease (per IRC), n (%)		18 (6.8)	6 (3.3)

[a] High risk: del(17p) and/or t(4;14) and/or t(14;16). [b]1q21+ ≥3 copies of 1q21; amplification 1q21 ≥4 copies of 1q21.

Facon T, et al. ASCO 2024. Abstract 7500. Facon T, et al. EHA 2024. Abstract S100.

IMROZ PHASE 3 TRIAL OF ISA-VRD VS VRD IN TRANSPLANT-INELIGIBLE NDMM: PFS AND OS

PFS (IRC)



Interim OS (ITT)

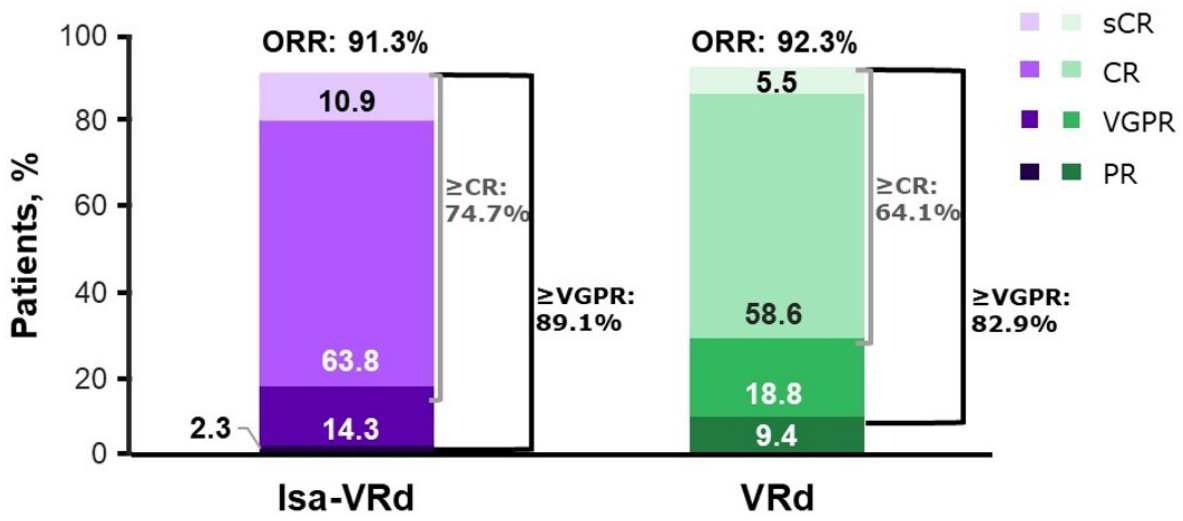
- Median follow-up: 5 years
- OS is still immature
- IsaVRd vs VRd
  - Events: 69 (26.0%) vs 59 (32.6%)
  - 5-year OS: 72.3% vs 66.3%
  - HR 0.776 (95% CI, 0.407-1.48)

PFS	Isa-VRd (n=265)	VRd (n=181)
Events, n (%)	84 (31.7)	78 (43.1)
60-month PFS, %	63.2	45.2
Median PFS (95% CI), months	NR	54.34 (45.207-NR)
HR (98.5% CI); *P* value	0.596 (0.406-0.876); 0.0005	

Facon T, et al. ASCO 2024. Abstract 7500. Facon T, et al. EHA 2024. Abstract S100.

IMROZ PHASE 3 TRIAL OF ISA-VRD VS VRD IN TRANSPLANT-INELIGIBLE NDMM: ORR AND MRD

ORR



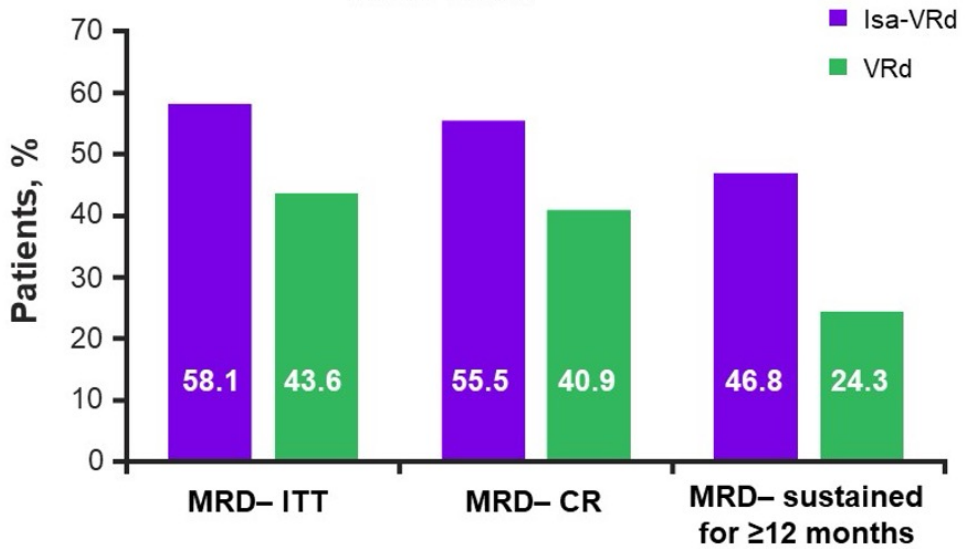
IsaVRd vs VRd

- ≥CR rate: *P*=0.01
- ≥VGPR rate: OR 1.729 (95% CI, 0.994-3.008)

Median time to MRD- (95% CI), months

- IsaVRd: 14.72 (11.53-24.08) months vs VRd: 32.79 (17.51-45.11) months

MRD Rate (NGS, 10^{-5})

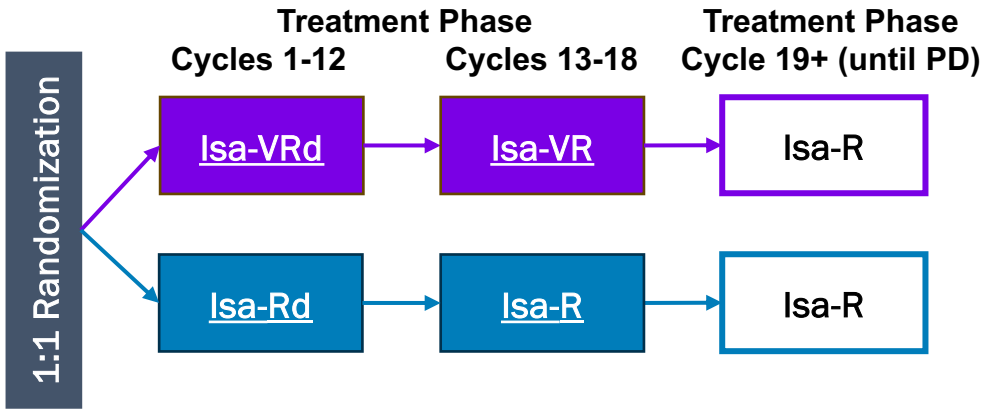


MRD	MRD– ITT	MRD– CR	MRD– for ≥12 months
OR	1.791	1.803	2.729
(95% CI)	(1.221-2.627)	(1.229-2.646)	1.799-4.141
P value	–	0.003	–

Facon T, et al. ASCO 2024. Abstract 7500. Facon T, et al. EHA 2024. Abstract S100.

BENEFIT (IFM 2020-05) PHASE 3 TRIAL OF ISA-VRD VS ISA-RD IN TRANSPLANT-INELIGIBLE NDMM: STUDY DESIGN AND PATIENTS

Key Eligibility Criteria
- Transplant ineligible NDMM, age 65-79 years
- ECOG PS 0-2



Treatment (4-week cycles)
Isa 10 mg/kg IV; days 1, 8[a], 15, 22[a] cycles 1-12; day 1, cycles 13-18 and cycle 19+
Bort 1.3 m/m^2 SUBQ; days 1, 8, 15 cycles 1-12; days 1, 15 cycles 13-18
Len 25 mg/day PO, days 1-21 cycles 1-19+
dex 20 mg IV, days 1, 8, 15, 22 cycles 1-12

Primary endpoint: MRD
Secondary endpoints: CR, MRD-neg CR (NGS, 10^{-5}), ≥VGPR, PFS, OS, AEs

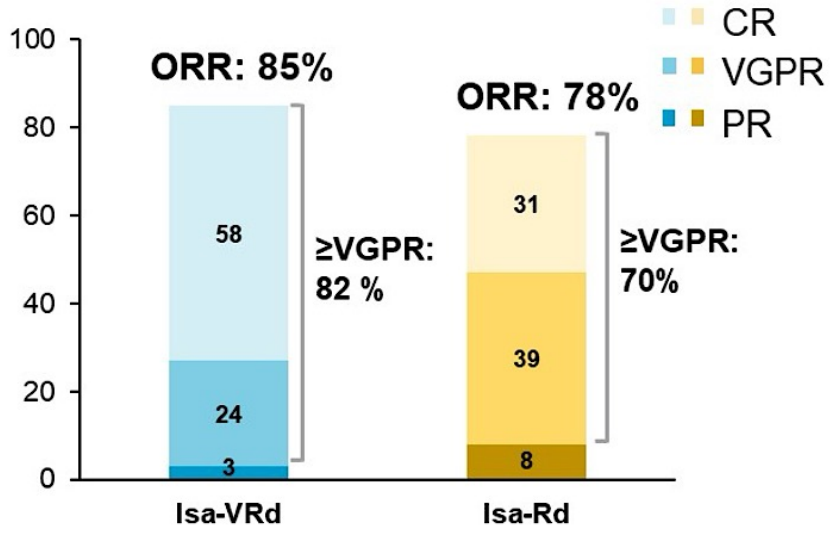
[a] Cycle 1 only.

Patient Characteristics		Isa-VRd (n=135)	Isa-Rd (n=135)
Median age (IQR), years		73.2 (71-76)	73.6 (71-76)
Age ≥75 years, n (%)		42 (31)	48 (36)
ECOG PS, n (%)	0 or 1	125 (93)	119 (88)
	>1	10 (7)	16 (12)
eGFR <60 ml/min/1.73 m^2, n (%)		19 (14)	28 (21)
ISS stage, n (%)	I/II	114 (84)	108 (80)
	III	21 (16)	27 (20)
R-ISS stage, n (%)	I	32 (24)	35 (26)
	II	92 (68)	89 (66)
	III	11 (8)	11 (8)
Cytogenetic risk, n (%)	Standard	68 (53)	75 (60)
	Intermediate	48 (37)	41 (33)
	High	13 (10)	10 (8)

ClinicalTrials.gov: NCT04751877 (accessed 12 June 2024).
Leleu XP, et al. ASCO 2024. Abstract 7501. Leleu XP, et al. EHA 2024. Abstract S203.

BENEFIT (IFM 2020-05) PHASE 3 TRIAL OF ISA-VRD VS ISA-RD IN TRANSPLANT-INELIGIBLE NDMM: ORR, PFS, AND OS

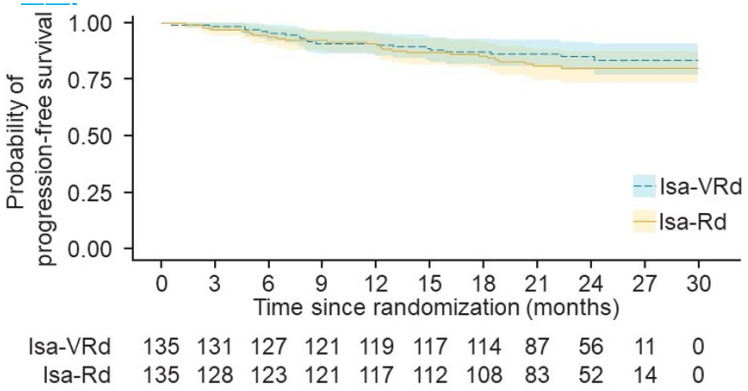
ORR



Isa-VRd vs Isa-Rd

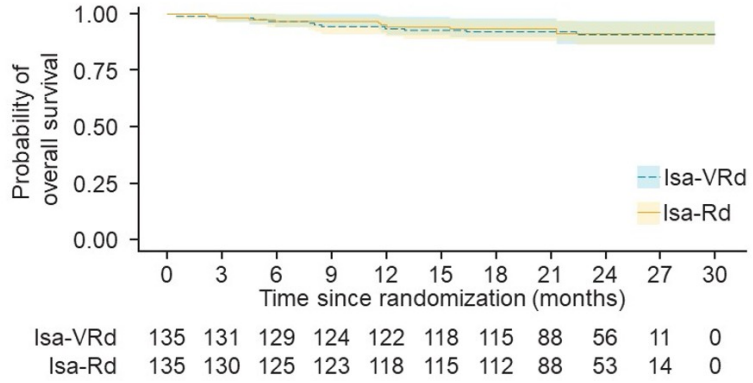
- **≥CR rate**: 58% vs 31%
  OR 2.97 (95% CI, 2-5); *P*<0.0001
- **≥VGPR rate**
  HR 1.65 (95% CI, 1.27-2.14); *P*=0.0002
- **Median months to first VGPR**
  2.1 (95% CI, 1.9-2.9) vs 3.7 (95% CI, 3-4.9)

PFS (IRC in



Estimated 24-month PFS, % (95% CI)	Isa-VRd (n=135)	Isa-Rd (n=135)
	85.2 (79.2-91.7)	80.0 (73.3-87.4)

OS (IRC in ITT)

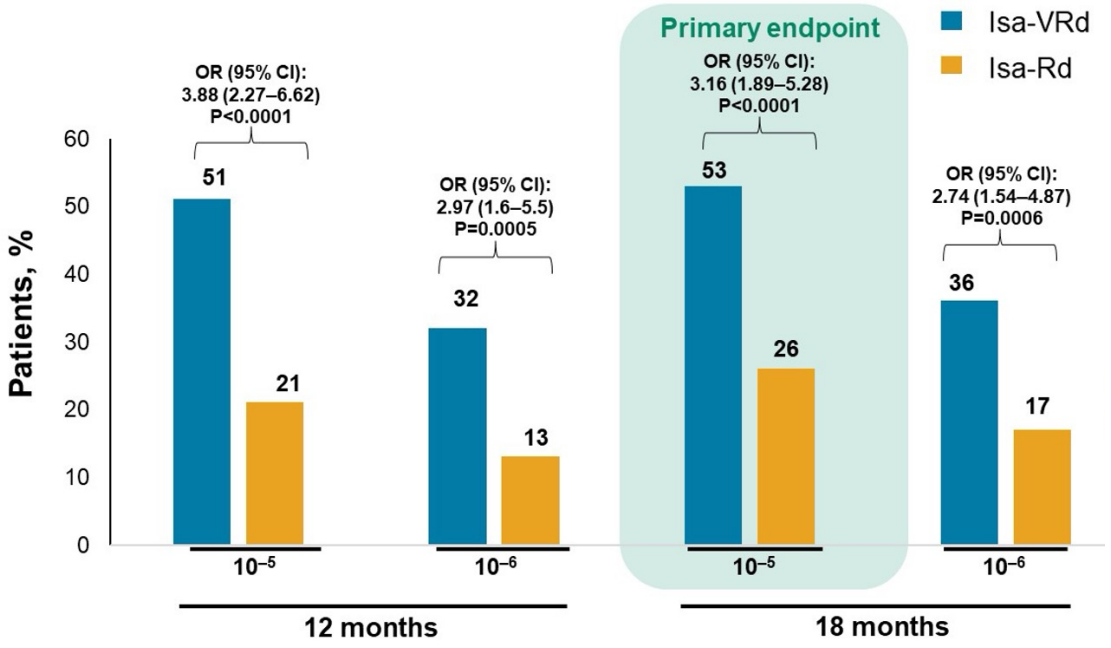


Estimated 24-month OS, % (95% CI)	Isa-VRd (n=135)	Isa-Rd (n=135)
	91.1 (86.1-96.4)	91.5 (86.5-96.8)

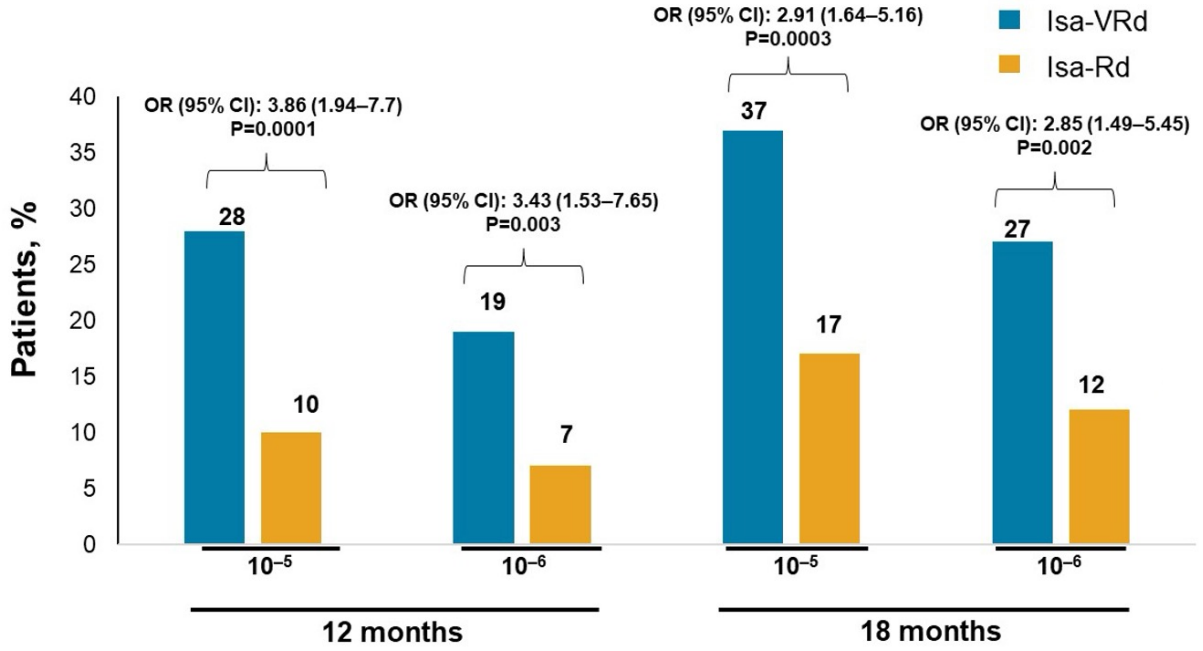
Leleu XP, et al. ASCO 2024. Abstract 7501. Leleu XP, et al. EHA 2024. Abstract S203.

BENEFIT (IFM 2020-05) PHASE 3 TRIAL OF ISA-VRD VS ISA-RD IN TRANSPLANT-INELIGIBLE NDMM: MRD

MRD-Negative Rate at 18 Months (ITT)



MRD-Negative CR Rate at 18 Months (ITT)



Leleu XP, et al. ASCO 2024. Abstract 7501. Leleu XP, et al. EHA 2024. Abstract S203.

CONCLUSION

- Myeloma induction has evolved to a 4 drug regimen. PI/IMID/CD38/Dex
- Transplant continues to play an important role for suitable candidates and improves duration of first remission substantially
- Risk adapted maintenance is an important goal
- New definitions of high risk coming soon from the IMS
- Novel consolidations including CART or TCE will hopefully begin to open to the door to limited duration therapy

Patients and Families

Thanks to:

Jonathan Kaufman
Ajay Nooka
Craig Hofmeister
Madhav Dhodapkar
L.T. Heffner
Vikas Gupta
Nisha Joseph
Leon Bernal
Charise Gleason
Danielle Roberts
Donald Harvey
Amelia Langston
Y. Gu
S-Y Sun
Jing Chen
Mala Shanmugan
Larry Boise
Bryan Burton
Sam Gagnon

IMS

Golfers Against Cancer
T.J. Martell Foundation

And Many Others who
are part of the Myeloma clinical and
research tam

sloni01@emory.edu