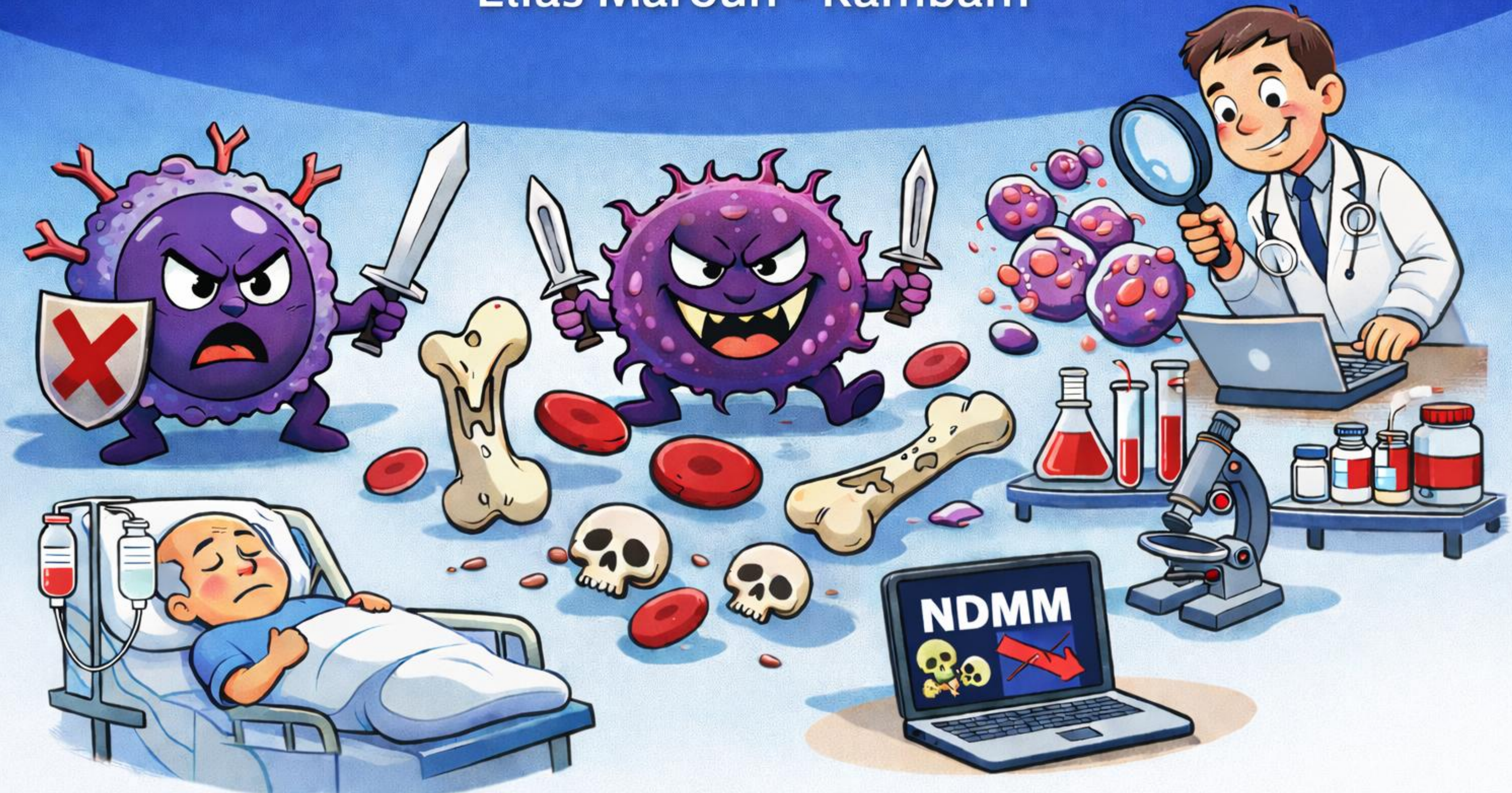
NDMM (without Immunotherapy)

Elias Maroun - Rambam



Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma results of the randomized phase III COBRA trial

Dominik Dytfeld, Tadeusz Kubicki, Agata Tyczyńska, Marcin Rymko, Krzysztof Jamroziak, Fredrik Schjesvold, Jaroslaw Piszcz, Tomasz Wróbel, Krzysztof Giannopoulos, Bartosz Pula, Agnieszka Końska, Pawel Steckiewicz, Juha Lievonen, Mateusz Ziarkiewicz, Pawel Bernatowicz, Lidia Gil, Anna Lojko-Dankowska, Magdalena Matuszak, Jan Zaucha, Maria Czyżewska, Kamil Wiśniewski, Magdalena Olszewska-Szopa, Anna Puła, Frank Wen, Frida Bugge Askeland, Valdas Peceliunas, Jennifer Cooperrider, Ken Jiang, Theodore Karrison, Benjamin Derman, Andrzej Jakubowiak

Presented by Dominik Dytfeld at the 67th American Society of Hematology Annual Meeting and Exposition

Background

- **VRd** has been the established frontline triplet in **NDMM** for many years
- No other triplet has shown **superiority over VRd** in randomized trials
- **KRd** is highly active, but **ENDURANCE** found **no PFS difference vs VRd** in NDMM without high-risk features
- Uncertainty remains regarding KRd vs VRd in:
  - ASCT- eligible patients
  - high-risk cytogenetics
- **COBRA** is a randomized phase III trial comparing **KRd vs VRd** across the entire **NDMM** population regardless of the cytogenetic risk and transplant eligibility
- We present the **pre-specified interim analysis** of COBRA

Kumar S.K., Lancet Oncol. 2020
Jakubowiak A.J. Blood. 2012
Jasielec J., Leukemia. 2020

COBRA

Multicenter, randomized, open-label, phase 3 study

THE UNIVERSITY OF CHICAGO
Polish Myeloma Consortium

Key eligibility criteria:

- Newly diagnosed multiple myeloma
- IMWG Frailty Score <2

R A N D O M I Z A T I O N 1:1
n=250

KRd
28-day cycles x 24

Carfilzomib 56 mg/m^2 (20mg C1D1)
D1, 8 and 15– cycles 1-12
D1 and 15 – cycles 13-24
Lenalidomide 25 mg
D1-21 – cycles 1-24
Dexamethasone
40 mg D1,8,15,22 cycles 1-12 and 20mg D1,8, 15, 22 cycles 13-24

R
until progression
Lenalidomide 15 mg

Stem cell collection after cycle 4 (TE)

VRd
21-day cycles x 8

Bortezomib 1.3mg/m^2
D1, 4, 8, 11
Lenalidomide 25 mg
D1-14
Dexamethasone 20 mg
D1, 2, 4, 5, 8, 9, 11, 12

RD
28-day cycles x 18

Lenalidomide 25 mg
D1-21– cycles
Dexamethasone 20 mg
D1, 8, 15, 22

R
until progression
Lenalidomide 15 mg

Co-primary endpoints*

≥ CR + MRD (-) 10^{-5} at 12 months

PFS**

Secondary endpoints

MRD (-)
sMRD (-)
ORR
OS
Safety

*A p-value of 0.025 is needed for statistical significance.

**At this interim analysis, 86 of a projected 106 PFS events have occurred (81%). Based on O'Brien-Fleming type error-spending, the required p-value for this analysis is 0.011

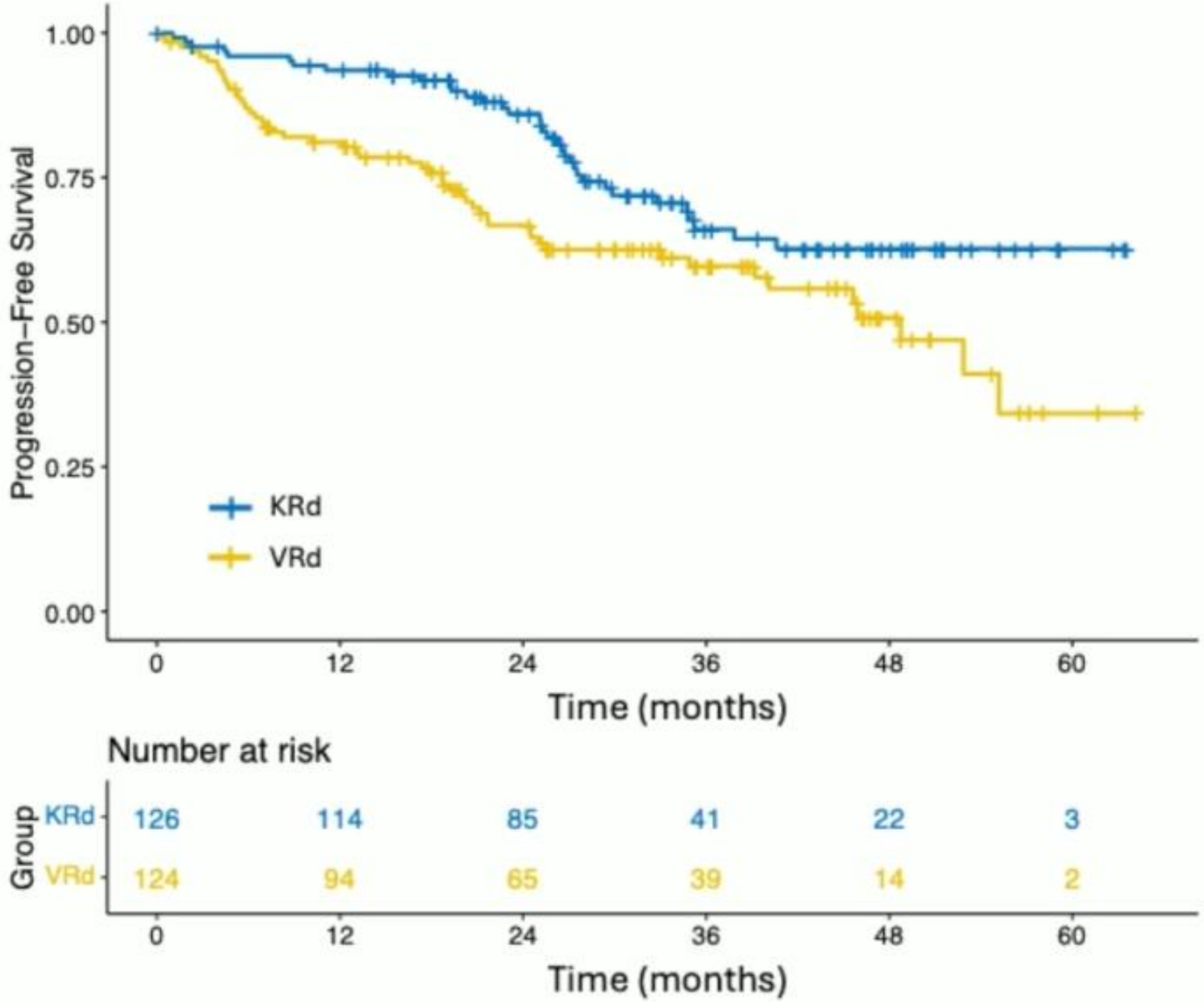
Stratification factors:
– standard vs high risk cytogenetics t(4;14) or t(14;16) or del17p
– TE vs TNE (n=210 after 1st protocol amendment)

Baseline Patient Characteristics

	KRd n=126	VRd n=124
age median (range)	66 (33-78)	67 (31-80)
female/male	70 (56%) / 56 (44%)	73 (59%) / 51 (41%)
white/black/asian/other	117 (93%) / 3 (2%) / 2 (2%) / 4 (3%)	120 (97%) / 3 (2%) / 0 / 1 (1%)
TE/TNE (n=210)*	65 (59%) / 40 (41%)	65 (59%) / 40 (41%)
ECOG 0/1/2	31 (25%) / 89 (70%) / 6 (5%)	31 (25%) / 91 (74%) / 2 (1%)
ISS I/II/III	43 (35%) / 47 (38%) / 33 (27%)	50 (40%) / 47 (38%) / 27 (22%)
standard risk	97 (77%)	96 (77%)
high risk del17p/t (4;14)/t (14;16)/more than 1	29 (23%) 14 (48%) / 15 (51%) / 8 (27%) / 8 (27%)	28 (23%) 15 (53%) / 11 (39%) / 4 (14%) / 2 (7%)

*Data collected after 1st amendment

Progression Free Survival



intent-to-treat

Median follow up: 53 months
HR 0.57 (95% CI: 0.37-0.88) p=0.0095

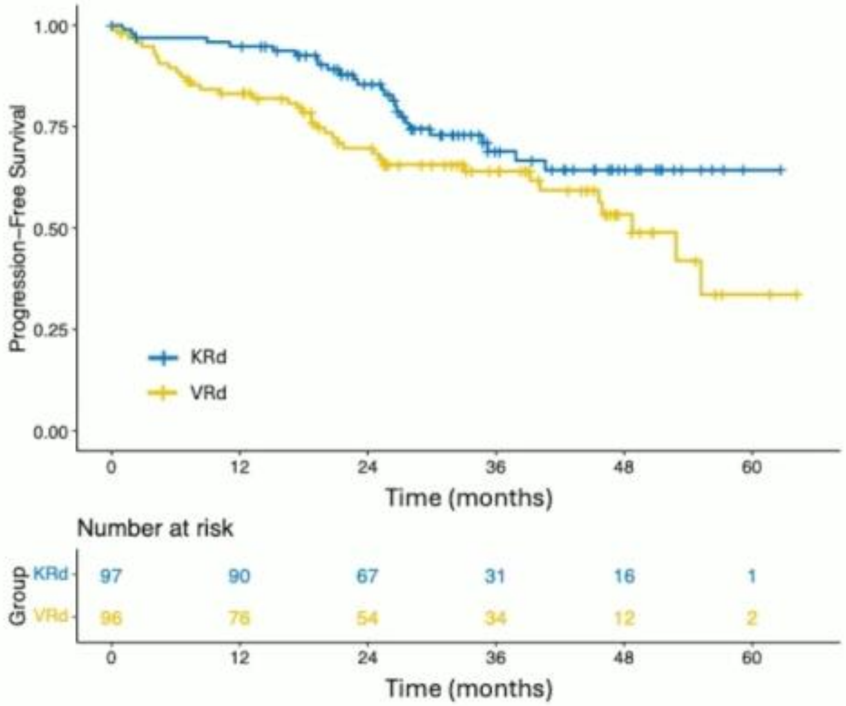
Progression or death **KRd 35 (28%)**
Median PFS **KRd: NR**

Progression or death **VRd 51 (41%)**
Median PFS **VRd: 48.8 m**

Presented by Dominik Dytfeld at the 67th American Society of Hematology Annual Meeting and Exposition

Progression Free Survival

Standard risk

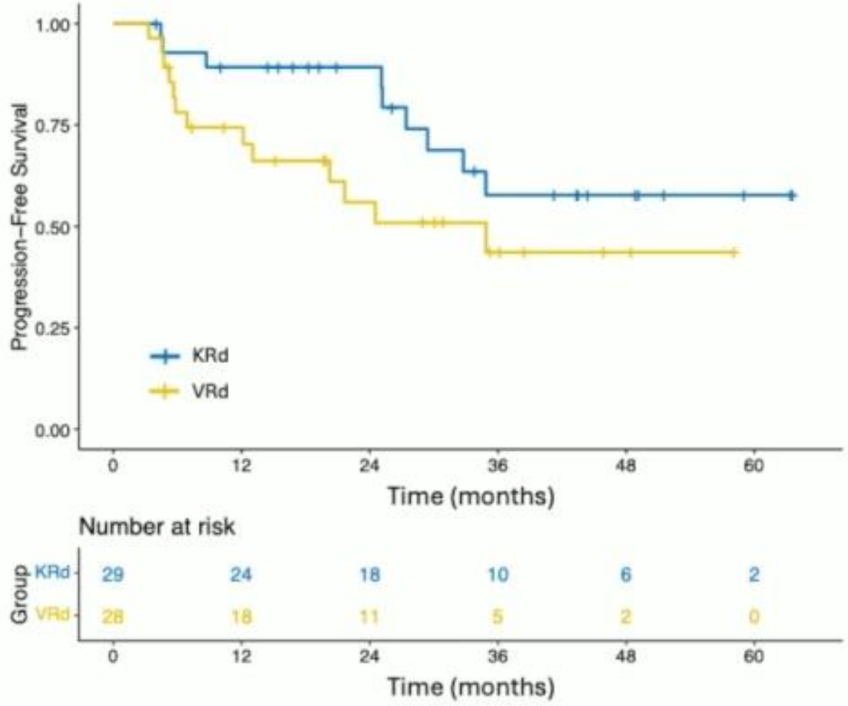


HR 0.59 (95% CI: 0.36-0.98) p=0.04

Progression or death KRd 26 (27%)
Median PFS KRd: NR

Progression or death VRd 38 (40%)
Median PFS VRd: 48.8 m

High risk



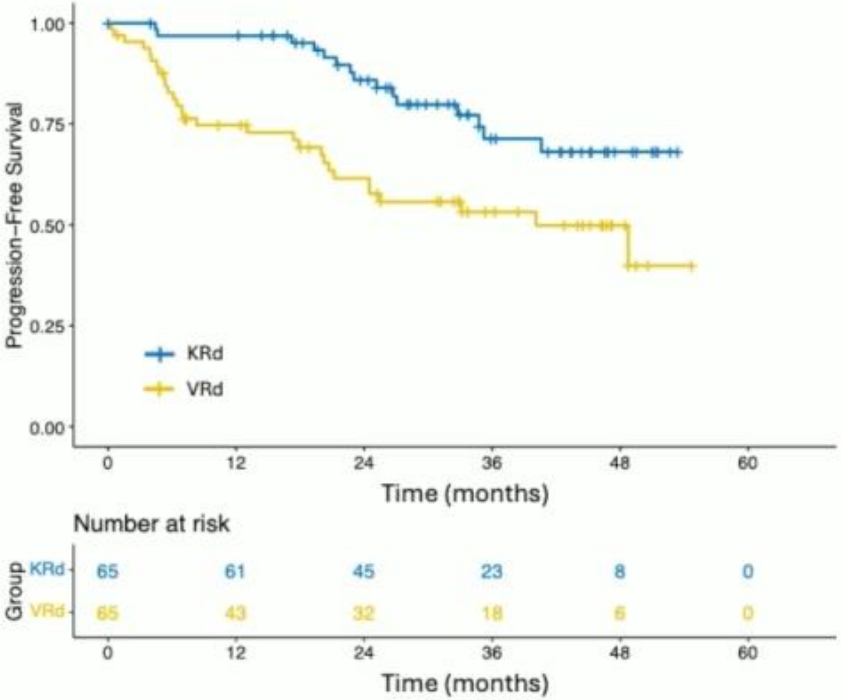
HR 0.52 (95% CI: 0.22-1.22) p=0.12

Progression or death KRd 9 (31%)
Median PFS KRd: NR

Progression or death VRd 13 (48%)
Median PFS VRd: 34.9 m

Progression Free Survival

Transplant eligible

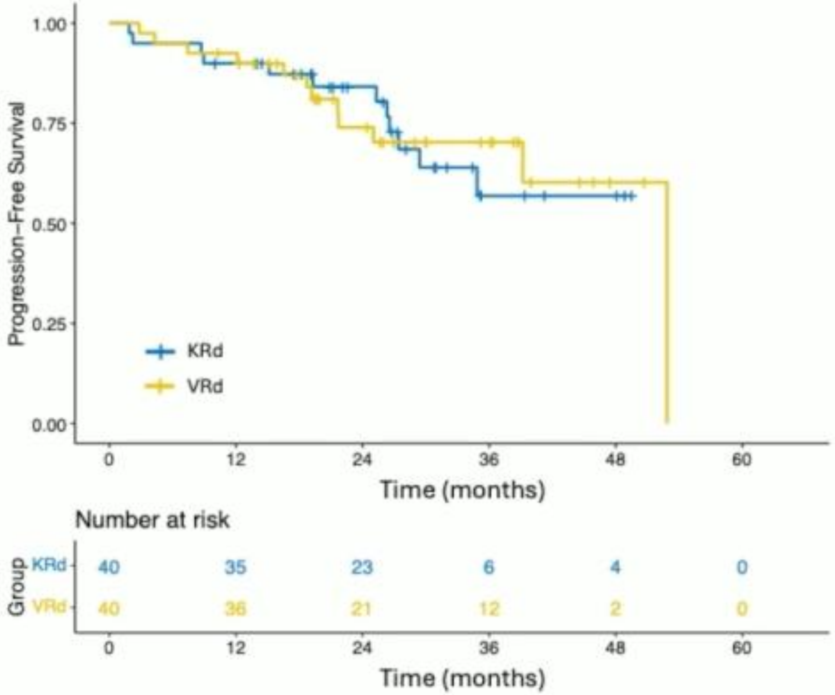


HR 0.40 (95% CI: 0.21-0.75) p=0.003

Progression or death KRd 15 (23%)
Median PFS KRd: NR

Progression or death VRd 29 (45%)
Median PFS VRd: 40.1 m

Transplant not eligible



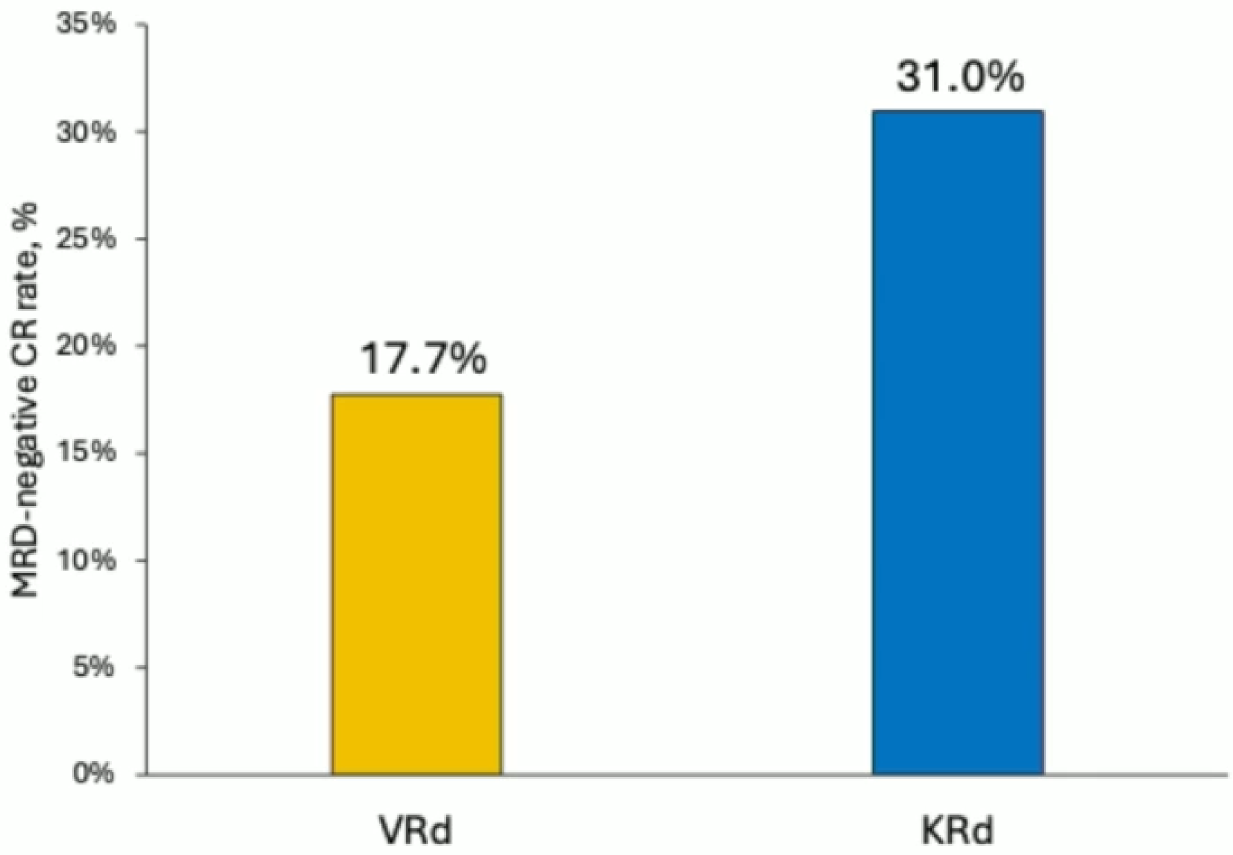
HR 1.06 (95% CI: 0.21-0.75) p=0.87

Progression or death KRd 12 (30%)
Median PFS KRd: NR

Progression or death VRd 12 (30%)
Median PFS VRd: 52.9 m

Minimal Residual Disease – 10^{-5}

THE UNIVERSITY OF CHICAGO
Polish Myeloma Consortium

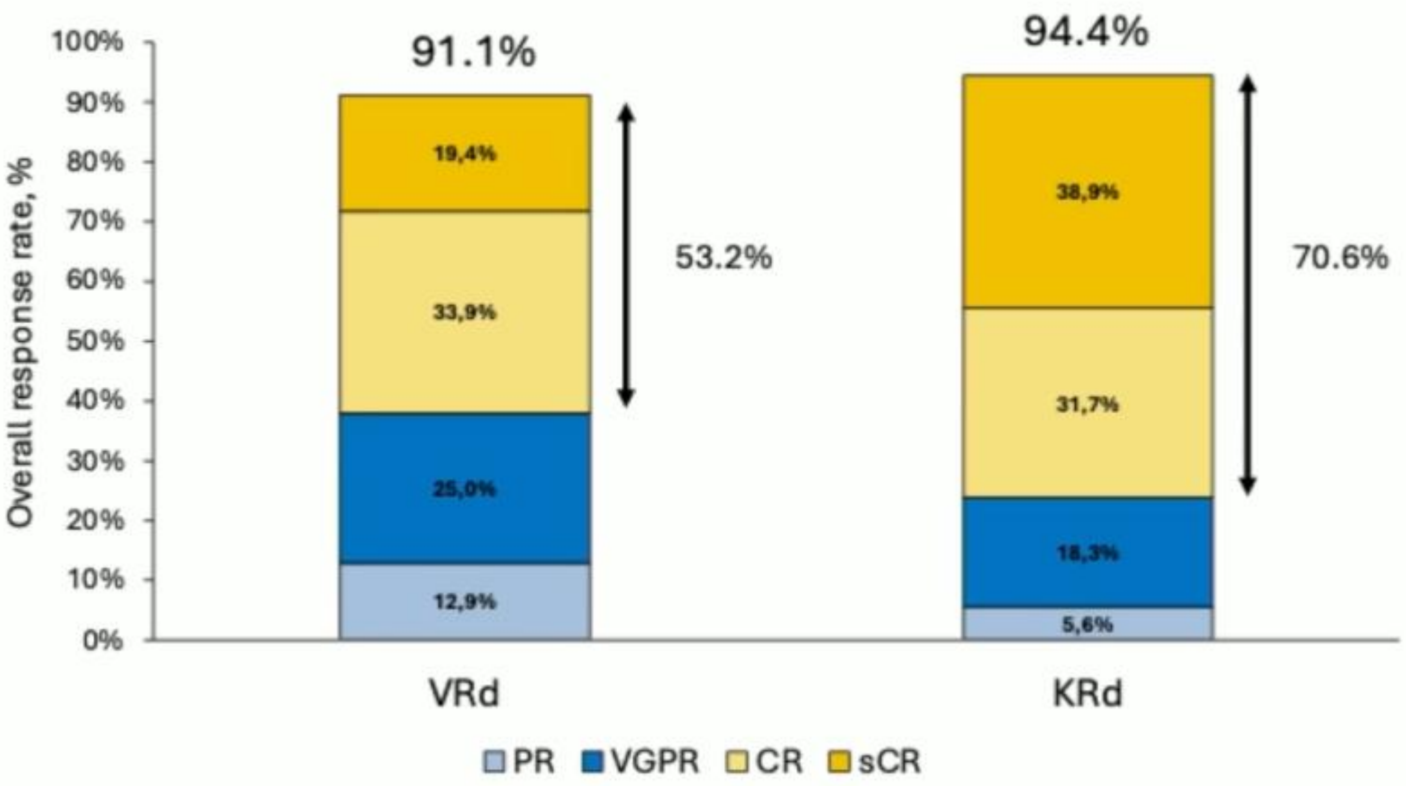


OR=2.08
95%CI: 1.15-3.77; p = 0.016

intent-to-treat

at 12 months
≥ CR + MRD (-) NGS 10^{-5}

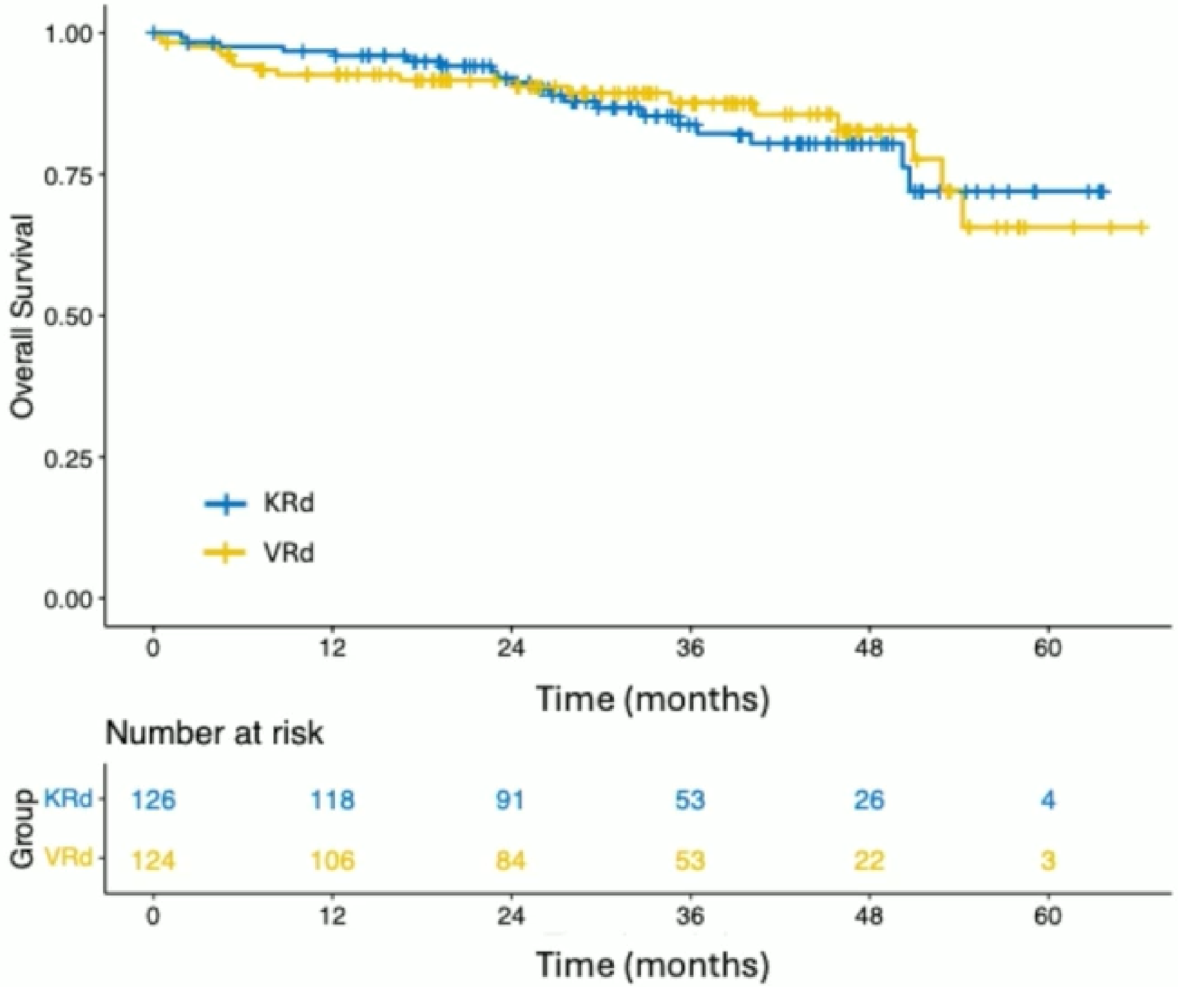
Overall Response Rate



CR%
OR = 2.11
95% CI: 1.26–3.56; p= 0.005

intent-to-treat

Overall Survival



intent-to-treat

Median follow up: 53 months

HR 1.05 (95% CI: 0.56-2.00) p=0.87

Deaths KRd 20 (16%)
Median PFS KRd: NR

Deaths VRd 18 (15%)
Median PFS VRd: NR

Safety

	KRd n=126	VRd n=124
any AEs grade/≥G3	96% / 73%	94% / 62%
any AE s leading to treatment discontinuation	11%	8%
any AEs grade 5*	5 (4%)	7 (6%)
neutropenia any grade/≥G3	29% / 21%	17% / 11%
neuropathy any grade/≥G3	17% / 2%	56% / 2%
cardiac any grade/≥G3	18% / 6%	10% / 2%
infection any grade/≥G3	75% / 25%	60% / 23%

* KRd: 1 x COVID, 1 x stroke , 1 x pneumonia, 1 x sepsis, 1 x acute kidney failure
VRd - 3 x COVID, 1 x pneumonia, 1 x respiratory failure, 2 x unknown

Conclusions

- COBRA showed superior efficacy of KRd vs VRd in NDMM, achieving both co-primary endpoints of MRD-negative CR at 12 months and progression-free survival
- The PFS benefit of KRd was observed regardless of cytogenetic risk
- KRd produced deeper responses, with higher rates of ≥CR and MRD-negativity
- KRd demonstrated anticipated toxicity profiles with higher rates of neutropenia and cardiac events, but less neuropathy
- COBRA results support further evaluation of KRd-based induction regimens in NDMM

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

ABSTRACT #370

Role of bortezomib maintenance therapy in the anti-CD38 antibody era: Interim analysis results of a randomized Phase III study for transplant-ineligible newly diagnosed multiple myeloma (JCOG1911/B-DASH Study)

Tomotaka Suzuki, Ryunosuke Machida, Yusuke Sano, Kazuyuki Shimada, Shinsuke Iida, Nobuhiko Yamauchi, Nobuhiko Nakamura, Hiroshi Handa, Yoshikazu Hori, Yasuhiro Suzuki, Daisuke Ogiya, Keisuke Kataoka, Eiji Negoro, Hiroyuki Takahashi, Junya Kuroda, Junya Makiyama, Ichiro Hanamura, Kaname Miyashita, Satoshi Ito, Hideki Uryu, Shigeru Kusumoto, Masahiro Takeuchi, Yasuhiro Harada, Takahiro Kumode, Ritsuro Suzuki, Isao Yoshida, Naoko Harada, Wataru Munakata, Hirokazu Nagai, Dai Maruyama
On behalf of the Lymphoma Study Group of Japan Clinical Oncology Group (JCOG-LSG)

Background

- Based on the previous JCOG study (JCOG1105, a randomized phase II trial to determine the optimal MPB (melphalan, prednisolone, bortezomib) regimen for Japanese patients [1]) and the ALCYONE trial [2], the JCOG Lymphoma Study Group has established daratumumab (Dara) –MPB (D-MPB) as the standard treatment.

- The addition of Dara to MPB significantly improved both PFS and OS [2]; however, a decline in PFS was observed during the Dara maintenance phase, highlighting the need for improved maintenance strategies.

- Although the potential benefit of bortezomib (Bor) maintenance therapy has been suggested [3,4], it has not yet been validated in a randomized controlled trial.

1) Maruyama D et al. Br J Haematol 2021;192:531
2) Mateos MV et al. NEJM 2018; 378: 518
3) Sonneveld P et al. J Clin Oncol 2012; 30: 2946
4) Palumbo A et al. J Clin Oncol 2014; 32: 634

Aim of this study

- To confirm the superiority of Bor and Dara maintenance therapy over Dara maintenance therapy in patients with transplant ineligible newly diagnosed multiple myeloma (NDMM), who responded to D-MPB in terms of PFS.

- In this presentation, we will report the updated results beyond those included in the abstract prepared from the interim analysis.

JCOG1911 study design

Multicenter, randomized (1:1), phase III study

1st registration

2nd registration

Arm A:
Dara 1800 mg/body sc.

Observation until PD

1st registration

- **Newly diagnosed multiple myeloma (IMWG2014[1])**
- **Age:** ≥ 65 or 20–64 years old, who refused HDT/ASCT
- **ECOG PS:** 0-2, or 3 due to osteolytic lesions
- **Measurable paraprotein of**
  - ≥ 1 g/dL of IgG,
  - ≥ 0.5 g/dL of IgA, or IgD
  - ≥ 0.2 g/24 hrs of Bence Jones protein
- Neither cardiac nor gastrointestinal amyloidosis
- **Peripheral neuropathy (PN):** ≤ Grade 1 without neuralgia

2nd registration

- **Response to induction therapy: (i) or (ii)**
  - (i) Completed 18 courses of D-MPB and achieved **PR or better**
  - (ii) Received 12–17 courses with **PR or better** if:
    - (a) Patient elects to discontinue D-MPB, or
    - (b) Discontinuation required due to AEs unrelated to Dara or Bor, or
    - (c) Melphalan discontinued per dose-modification criteria.
- **ECOG PS: 0–2**
- **PN: (i) or (ii)**
  - (i) PN ≤ Grade 2 without neuralgia
  - (ii) PN ≤ Grade 1 with neuralgia ≤ Grade 2

Adj
① Ir
② A
③ R
④ C

Observation until PD

n-f

istration

Sample size

We assumed the 2-year PFS (from randomization) of arm A as 65% and expected 11% increase in the 2-year PFS in arm B.
The sample size was set at 83 patients per arm with a one-sided alpha of 5%, and power of 70%.

Endpoints

Primary endpoint： PFS from 2^{nd} registration

Key secondary endpoints

- Overall survival (OS) from first/second registration
- PFS from first registration
- Adverse events (AEs) / severe AEs
- Completion of maintenance therapy
- Time to next treatment (TNT) from first/second registration
- Response rate of induction therapy
- Completion of induction therapy

Patient characteristics at 1st registration

	ALL (N = 224)
Median age, years (range)	74 (62-86)
Male	50.9%
Performance Status	
･0 / 1	43.8% / 35.7%
･2	12.9%
･3	7.6%
IMWG frailty [1)]	
･Fit	53.1%
･Intermediate	26.3%
･Frail	20.5%
M protein subtype	
･IgG	64.7%
･IgA	23.7%
･BJP	11.2%

	ALL (N = 224)
ISS	
･I	21.9%
･II	52.7%
･III	25.4%
Cytogenetic risk¶	
･Standard	73.7%
･High	23.2%
･Unknown	3.1%

¶ High-risk cytogenetic abnormalities were defined as the presence of at least one of the following: del(17p), t(11;14), or t(14;16)

1) Palumbo A et al. Blood. 2015;125 :2068

Characteristics of randomized patients

Characteristics at 1st registration	Arm A (n = 73)	Arm B (n = 70)
Median age, years (range)	74 (65-85)	73 (64-86)
・≥75 years	37.0%	34.3%
Male	56.2%	42.9%
M protein type		
・IgG	68.5%	67.1%
・IgA	19.2%	22.9%
・BJP	12.3%	10.0%
ISS		
・I	27.4%	15.7%
・II	56.2%	58.6%
・III	16.4%	25.7%
Cytogenetic high risk	19.2%	22.9%

Characteristics at 2nd registration	Arm A (n = 73)	Arm B (n = 70)
Response to D-MPB		
・PR	21.9%	21.4%
・VGPR	27.4%	22.9%
・CR or better	50.7%	55.7%
MRD negative during induction therapy¶	34.2%	34.3%
IMWG frailty		
・Fit	64.4%	52.9%
・Intermediate	24.7%	24.3%
・Frail	11.0%	22.9%

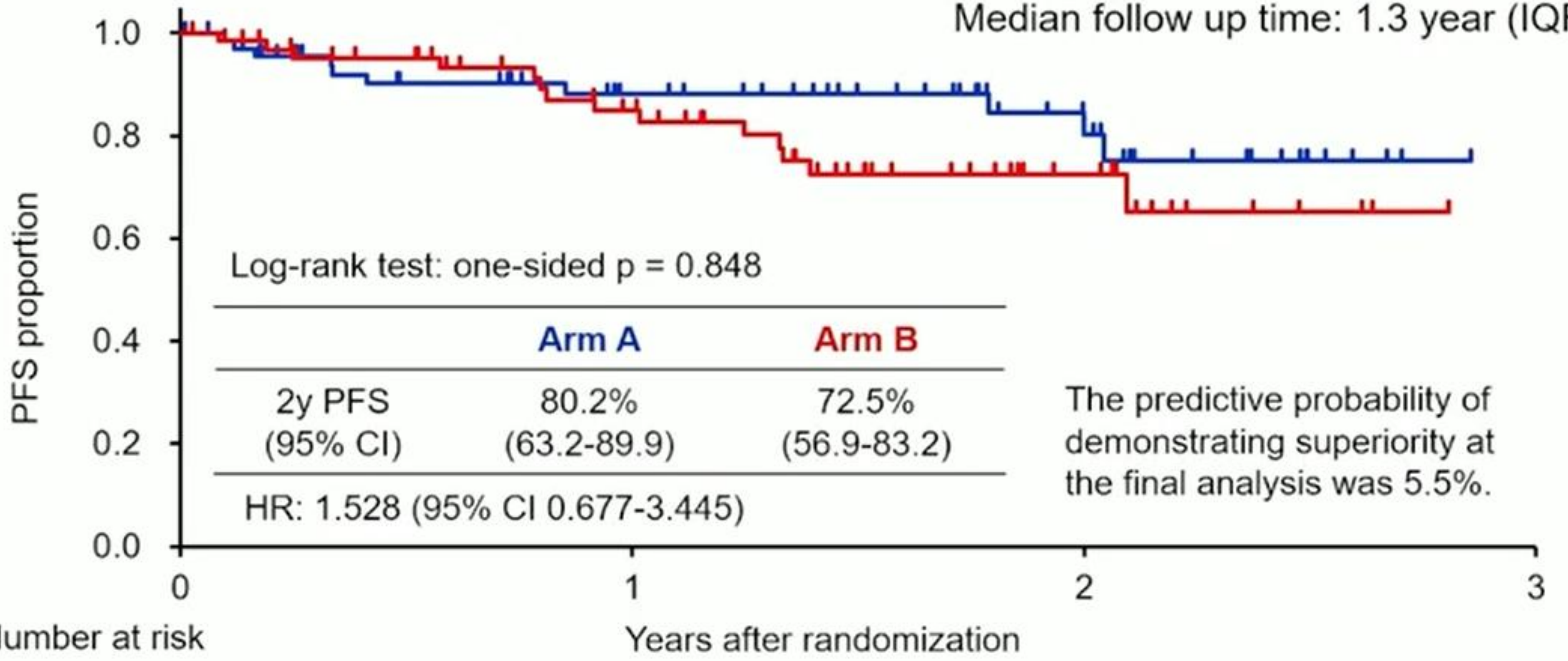
: Adjustment factors

¶MRD was assessed by multiparameter FCM of bone marrow samples, using a sensitivity threshold of 10^{-5}.

PFS from randomization (interim analysis)

Data cutoff: Nov 2024

Median follow up time: 1.3 year (IQR: 0.5-2.0)



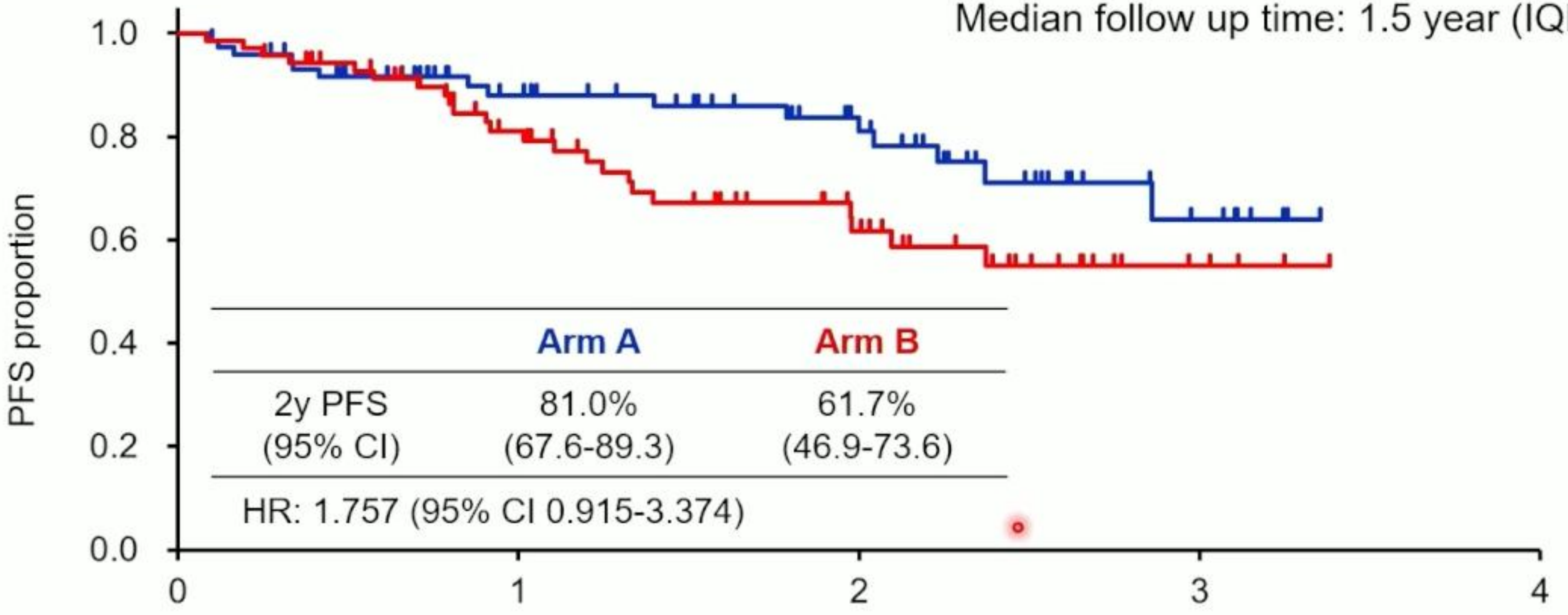
Number at risk				
Arm A	69	40	19	0
Arm B	66	39	13	0

In March 2025, the JCOG Data and Safety Monitoring Committee recommended early termination of the study.

PFS from randomization (updated analysis)

Data cutoff: Jun 2025

Median follow up time: 1.5 year (IQR: 0.9-2.3)



	Arm A	Arm B
2y PFS (95% CI)	81.0% (67.6-89.3)	61.7% (46.9-73.6)

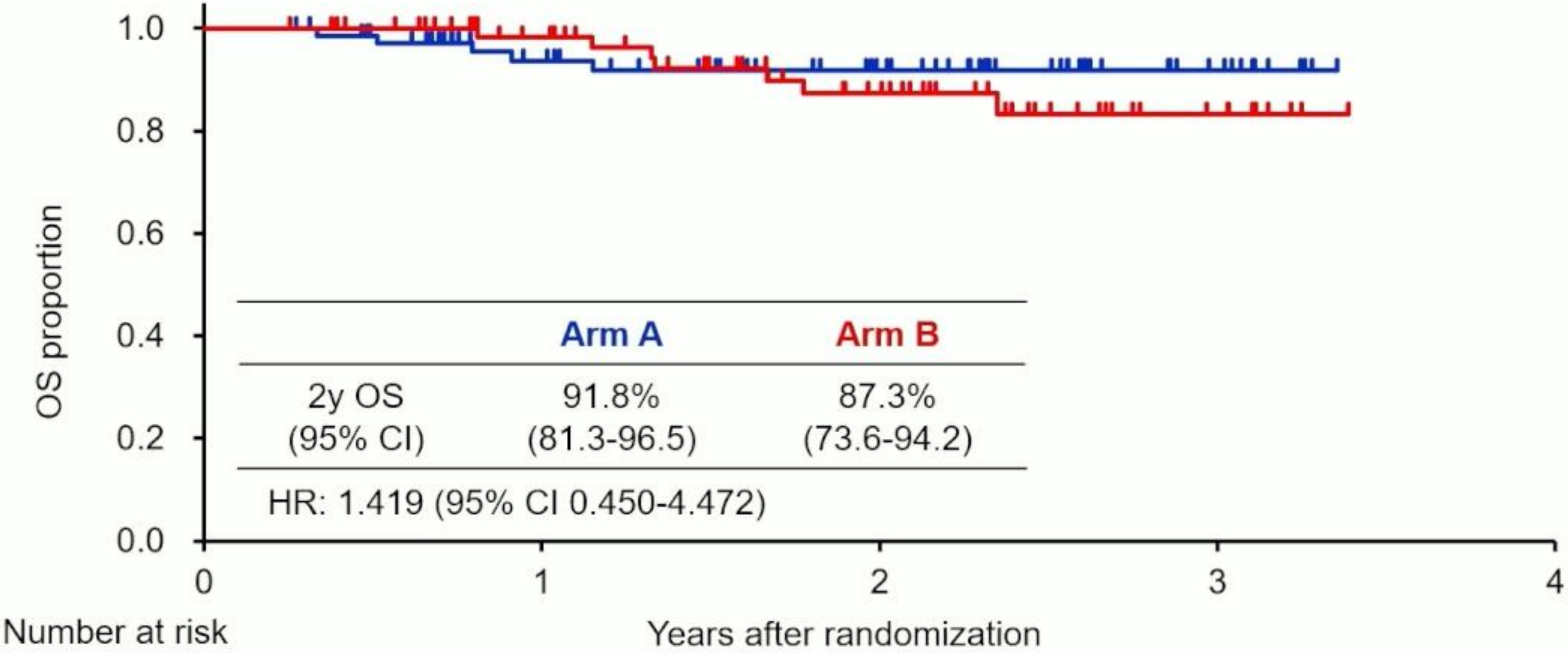
HR: 1.757 (95% CI 0.915-3.374)

Number at risk

	0	1	2	3	4
Arm A	73	49	30	7	0
Arm B	70	45	23	4	0

OS from randomization (updated analysis)

Data cutoff: Jun 2025



Number at risk	0	1	2	3	4
Arm A	73	53	36	10	0
Arm B	70	55	31	8	0

There was no apparent difference in OS between arms.

Summary of safety and maintenance therapy administration

	Arm A (n = 73)	Arm B (n = 70)
Maintenance therapy status §		
・Median number of courses (IQR)	19 (6-24)	12 (7-21)
Treatment discontinuation, n(%)		
・Due to AEs	4 (5.5)	3 (4.3)
・Due to patient refusal	0 (0)	9 (12.9) ¶
Any treatment emergent AEs, n (%) ṫ		
・Grade ≥2	29 (41.4)	40 (60.0)
・Grade ≥3	6 (8.6)	8 (12.3)

§ Data cutoff, Mar 2025

¶ All were considered to be associated with treatment emergent AEs.

ṫ Information of safety population (n = 70 and 65 in Arm A and Arm B, respectively)

Common AEs during maintenance therapy in the safety population

	Arm A (n = 70)		Arm B (n = 65)	
	Grade ≥2	Grade ≥3	Grade ≥2	Grade ≥3
Hematological				
・Neutropenia	11.4%	0%	15.4%	3.1%
・Lymphocytopenia	27.1%	15.7%	38.5%	12.3%
・Thrombocytopenia	2.9%	1.4%	3.1%	3.1%
Non-hematological				
・Lung or upper respiratory infection	10.0%	2.9%	10.8%	3.1%
・Peripheral neuropathy (sensory or motor)	8.6%	0%	18.5%	0%
・Nausea or appetite loss	1.4%	0%	9.2%	3.1%
・Diarrhea	0%	0%	6.2%	0%

In Arm B, the proportions of hematologic toxicity, peripheral neuropathy, and gastrointestinal toxicity were higher, although the majority of events were grade ≤2.

Discussion

<u>Why did Arm B (Bor-containing arm) fail to show PFS superiority?</u>

- Although AE-related discontinuation was more frequent in Arm B, it did not clearly account for the increased PFS events in Arm B.

- Arm B had a higher proportion of patients with ISS stage III or frail.

- Arm A demonstrated better-than-expected PFS (2-year PFS: 65% assumed vs. 81% observed).

- The exact reason why Arm B failed to demonstrate superiority in PFS remains unclear at this time: further evaluations, including detailed subgroup analyses and ancillary studies (genomic profiling by NGS at baseline and at progression) are underway to investigate this finding.

Conclusion

- This phase III study revealed that adding Bor to Dara maintenance therapy did not improve PFS and was associated with increased toxicities in patients with transplant ineligible NDMM.


תודה
על ההקשבה
NDMM