EMORY WINSHIP CANCER INSTITUTE

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EMORY UNIVERSITY SCHOOL OF MEDICINE

Induction Therapy and MM

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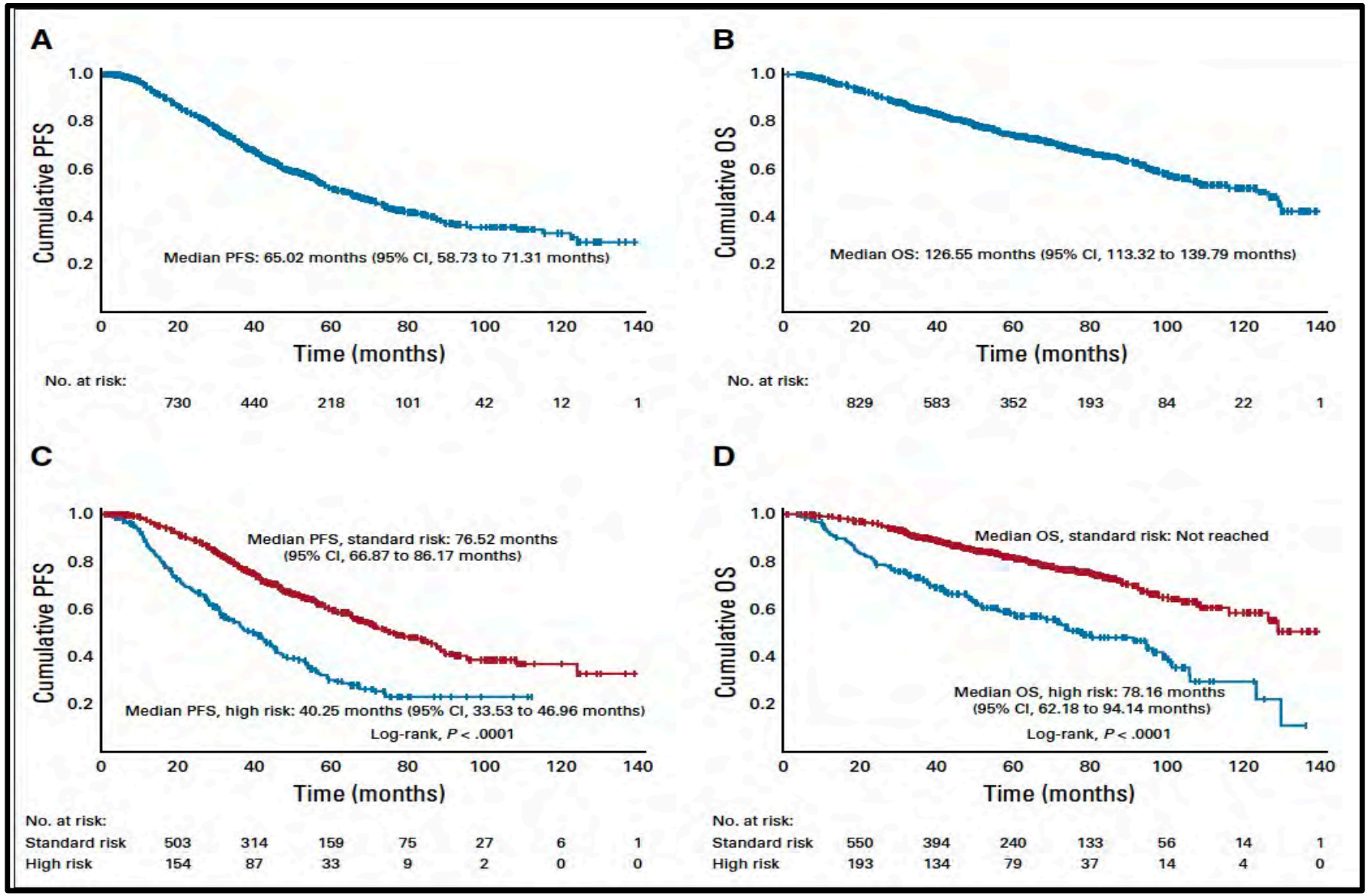
Induction Principles

- Goals are to induce a rapid and deep response
- Do above without significant toxicity

- Current standard of care is IMID+PI+Dex
- Rapidly expanding towards IMID+PI+ Dex+ CD38 Moab

Outcomes from RVD 1000 series



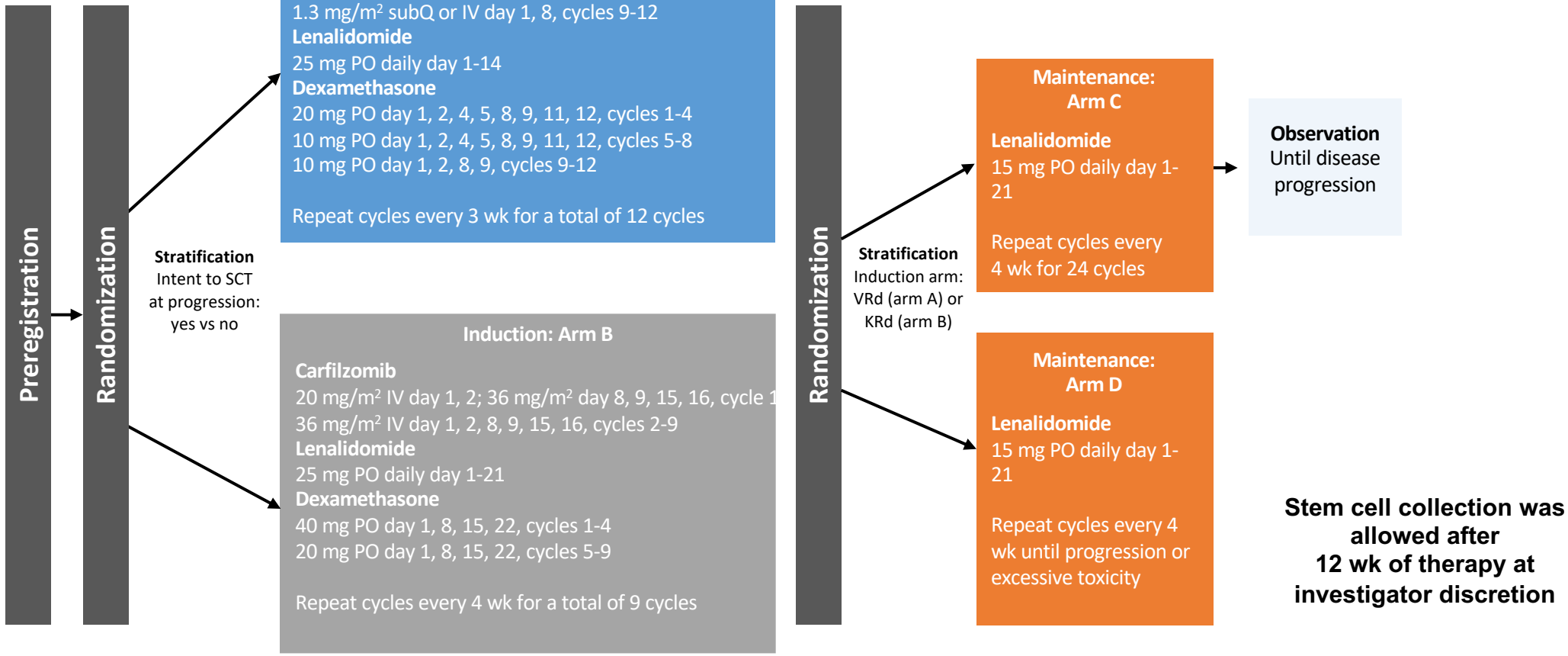
Joseph et al, JCO 2020

Phase 2 KRd Studies in NDMM

Trial	Response	Grade 3/4 AEs
Jakubowiak et al[1] (N=53)	nCR: 78% sCR: 61% 24-month PFS: 92%	Hypophosphatemia: 25% Hyperglycemia: 23% Anemia: 21% Thrombocytopenia: 17% Neutropenia: 17%
Korde et al[2] (N=45)	CR/sCR: 56% ≥nCR: 62% ≥VGPR: 89% ≥PR: 98%	Lymphopenia: 76% Anemia: 27% Neutropenia: 33% Thrombocytopenia: 24%
Zimmerman et al[3] (N=76)	VGPR: 96% CR: 73% sCR: 69%	Lymphopenia: 28% Neutropenia: 18% Infections: 8%
Gay et al[4] (N=474); FORTE trial	**KRd_ASCT_KRd vs KRd12** ≥VGPR: 89% vs 87% ≥CR: 60% vs 61% sCR: 44% vs 43%	–

- KRd12, 12 cycles of KRd; nCR, near complete response; PR, partial response.
- 1. Jakubowiak AJ, et al. *Blood*. 2012;120:1801-1809. 2. Korde N, et al. *JAMA Oncol*. 2015;1:746-754. 3. Zimmerman T, et al. ASH 2016 (abstr 675). 4. Gay F, et al. ASH 2020 (abstr 294).

Phase 3 ENDURANCE Study[1]
ECOG-ACRIN E1A11



Coprimary endpoints

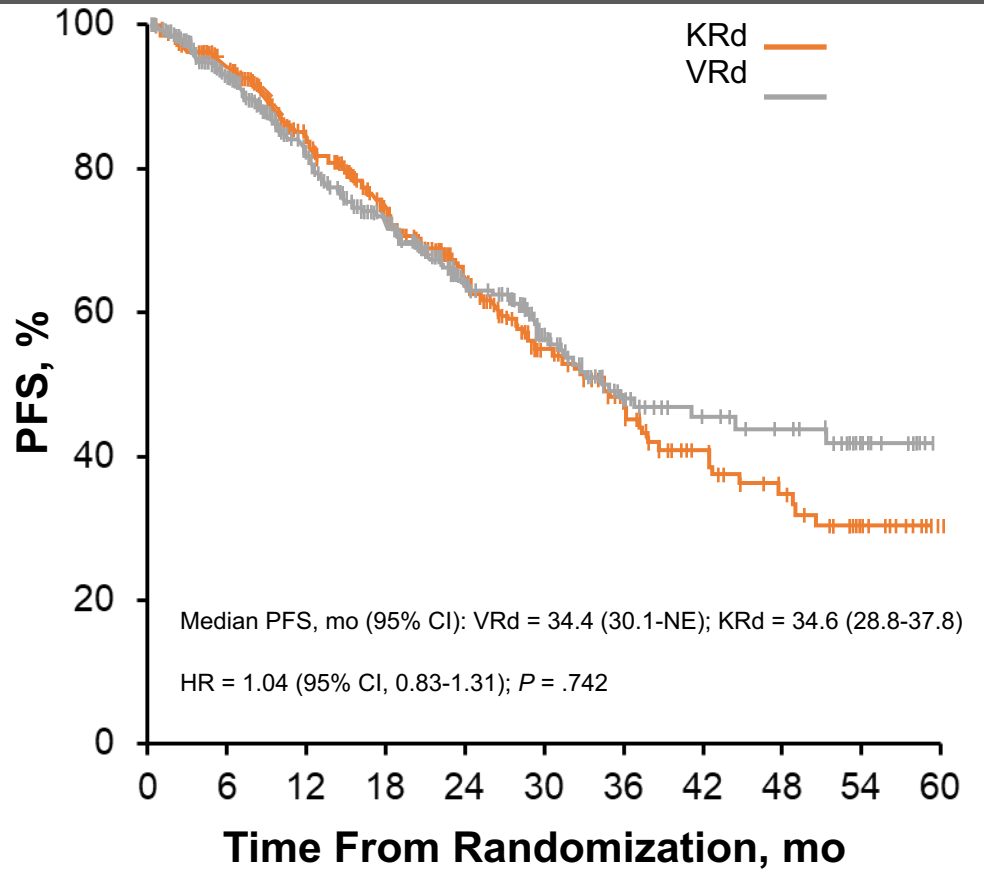
- PFS for the induction randomization
- OS for the second randomization

Stem cell collection was allowed after 12 wk of therapy at investigator discretion

1. Kumar S et al. American Society of Clinical Oncology 2020 Annual Meeting (ASCO 2020). Abstract LBA3.

ENDURANCE: PFS From Induction Randomization[1]

- Second interim analysis of PFS (January 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow-up of 15 mo (13-18)
- For patients aged ≥70 y, median PFS (95% CI) for VRd = 37 mo (29-NE) and KRd = 28 mo (24-36)
- With censoring at SCT or alternative therapy: median PFS (95% CI) for VRd = 31.7 mo (28.5-44.6) and KRd = 32.8 mo (27.2-37.5)



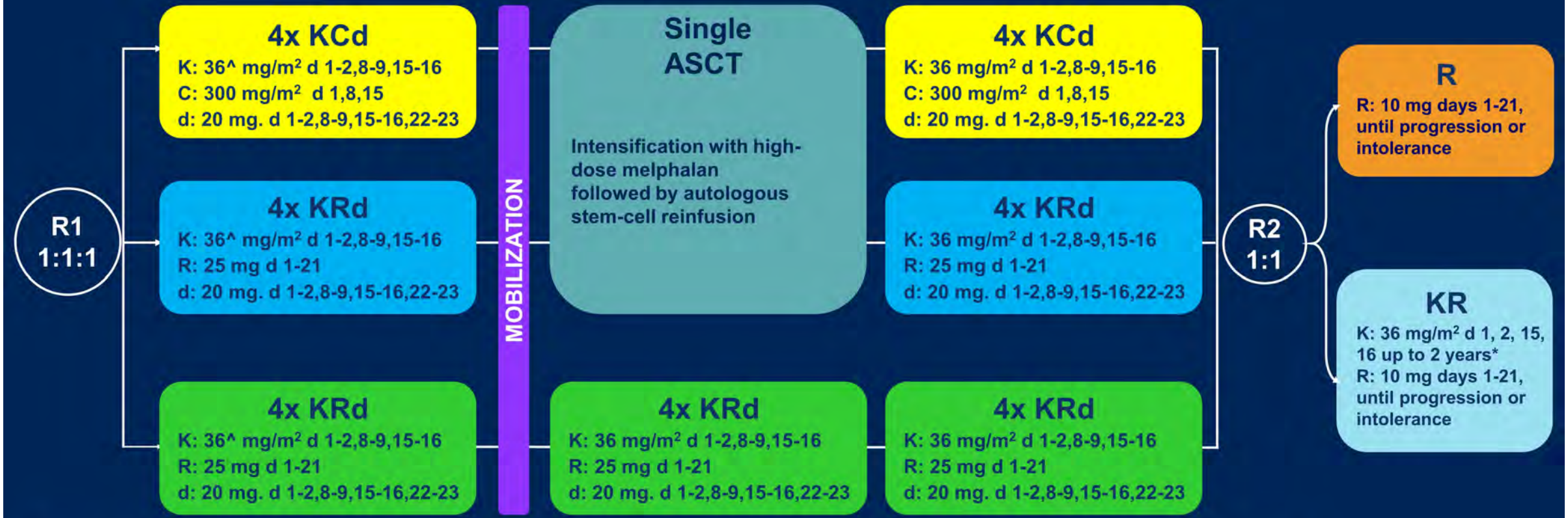
No. at Risk

KRd	545	401	252	187	127	83	59	38	25	13	3
VRd	542	377	243	183	114	73	43	31	26	14	0

1. Kumar S et al. ASCO 2020. Abstract LBA3.

Trial design

474 NDMM patients, transplant-eligible and younger than 65 years



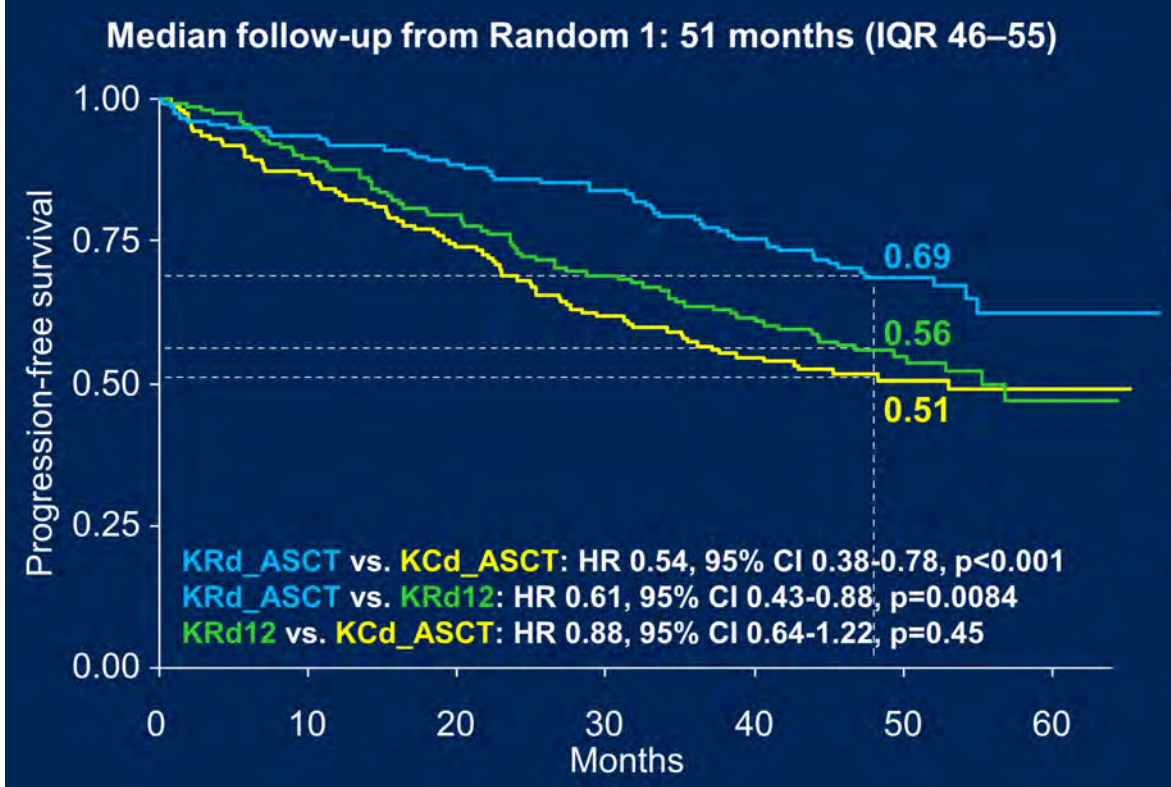
^20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.

NDMM, newly diagnosed multiple myeloma, R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); ASCT, autologous stem-cell transplantation; 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.

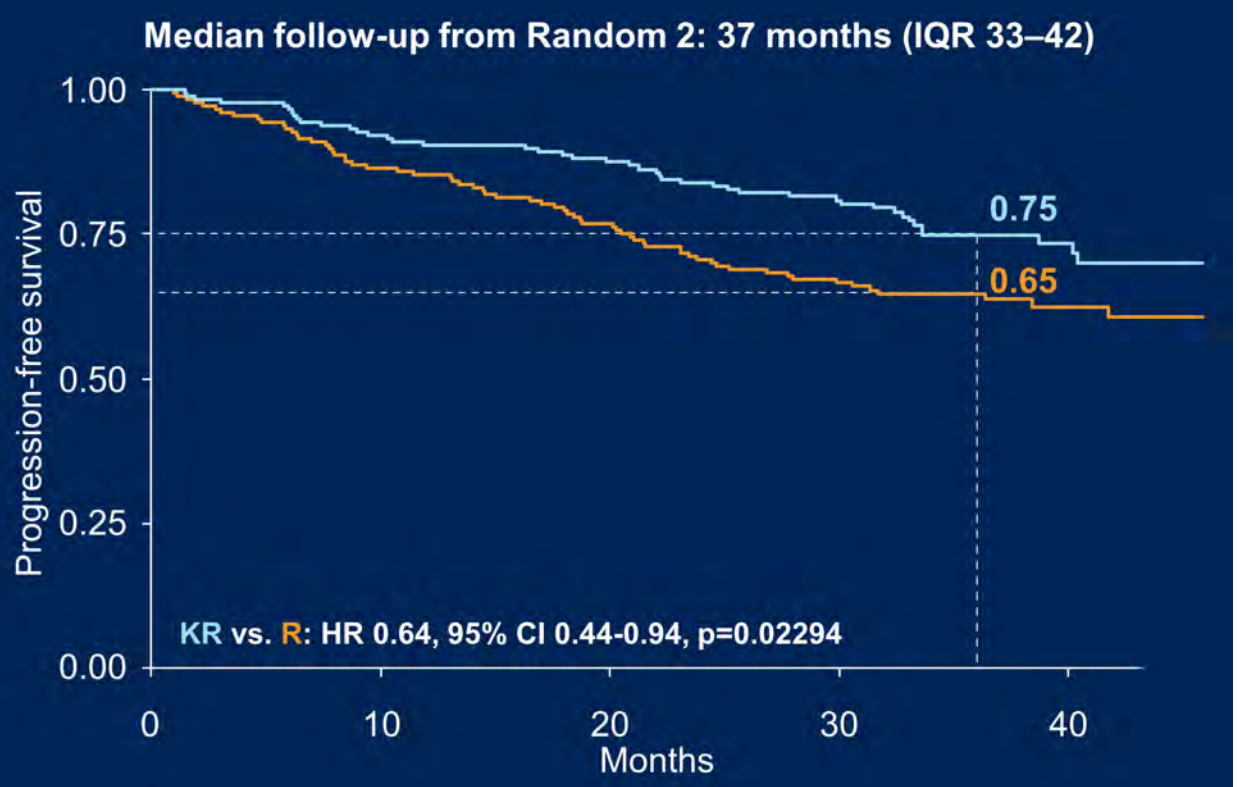
Presented by Francesca Gay

Progression-free survival

KRd_ASCT vs. KRd12 vs. KCd_ASCT



KR vs. R



3-year PFS reported in the figure. 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; Random 2, second randomization (maintenance treatment); p, p-value; HR, hazard ratio; CI, confidence interval.

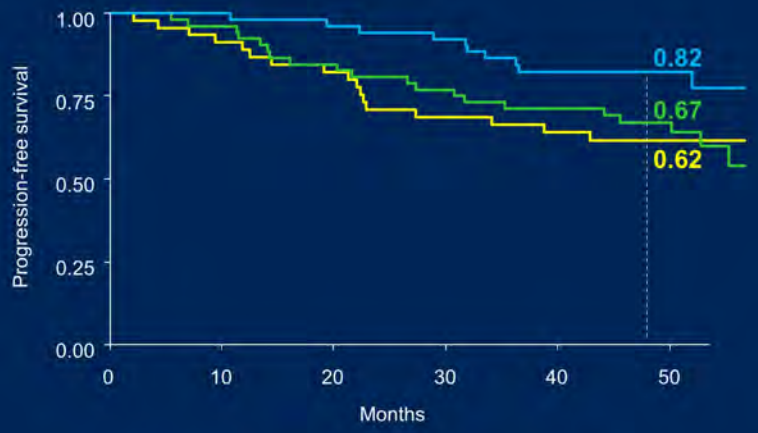
Presented by Francesca Gay

Progression-free survival: Random 1

KRd_ASCT vs. KRd12 vs. KCd_ASCT

Median follow-up from Random 1: 51 months (IQR 46-55)

Standard risk (N=153)

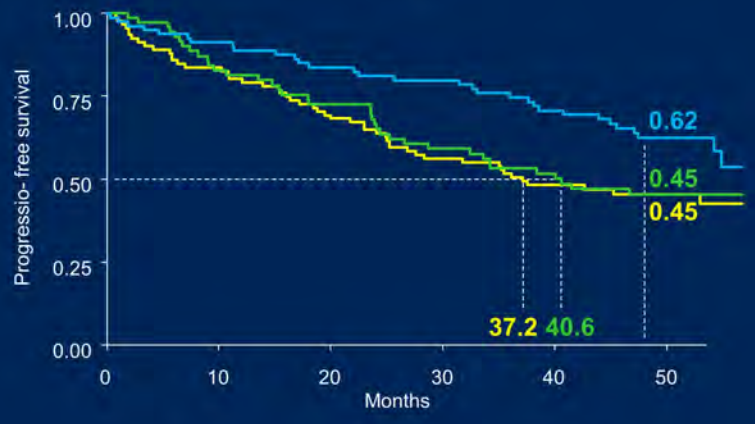


KRd_ASCT vs. KCd_ASCT: HR 0.44, p=0.04

KRd_ASCT vs. KRd12: HR 0.46, p=0.04

KRd12 vs. KCd_ASCT : HR 0.96, p=0.9

High risk (N=243)

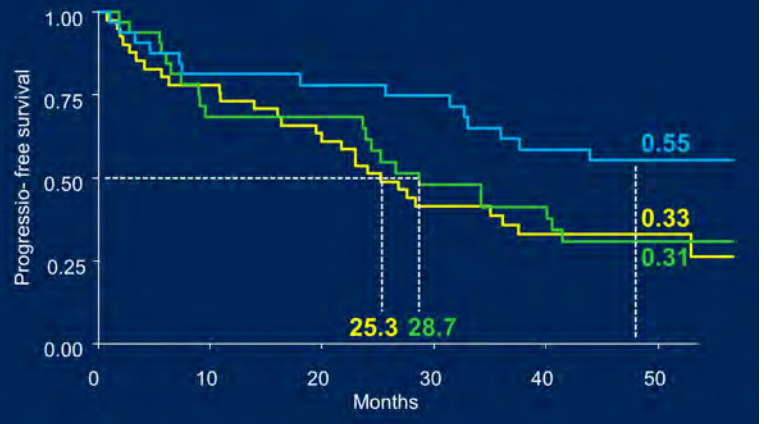


KRd_ASCT vs. KCd_ASCT: HR 0.57, p=0.01

KRd_ASCT vs. KRd12: HR 0.6, p=0.04

KRd12 vs. KCd_ASCT: HR 0.95, p=0.8

Double hit (N=105)



KRd_ASCT vs. KCd_ASCT: HR 0.49, p=0.03

KRd_ASCT vs. KRd12: HR 0.53, p=0.07

KRd12 vs. KCd_ASCT: HR 0.91, p=0.75

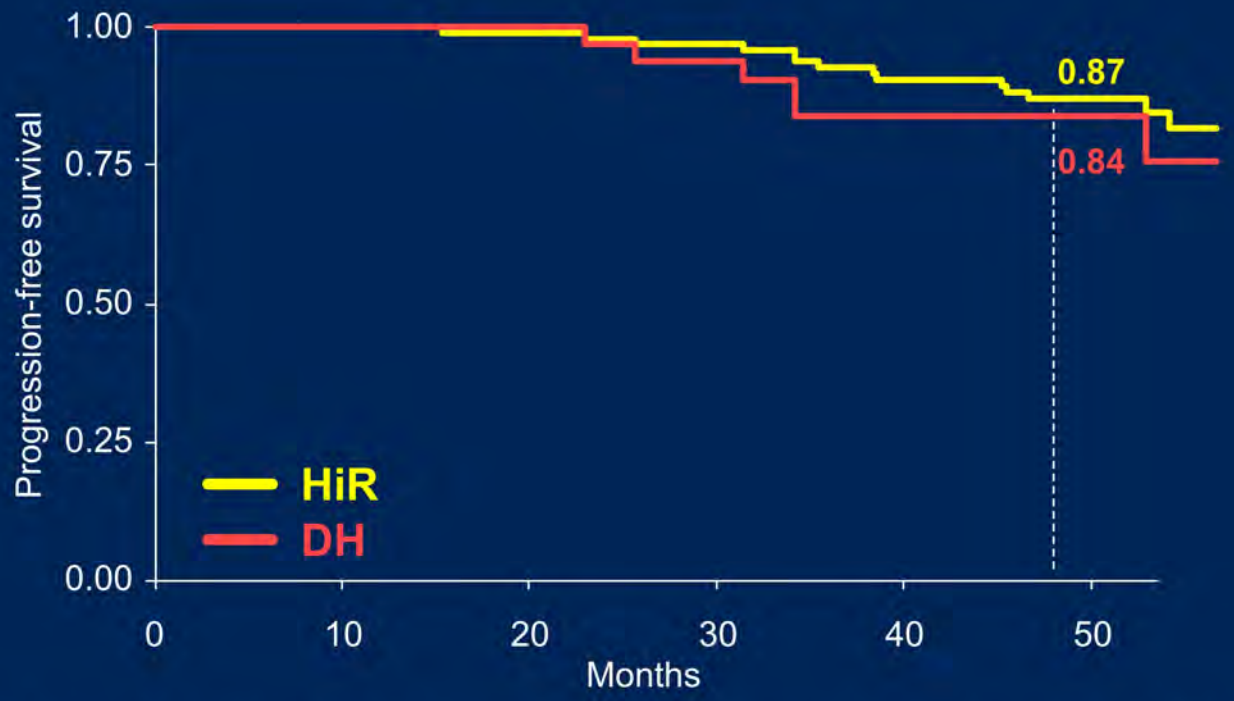
Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; HR, hazard ratio; CI, confidence interval; p, p-value; iQR, interquartile range.

Presented by Francesca Gay

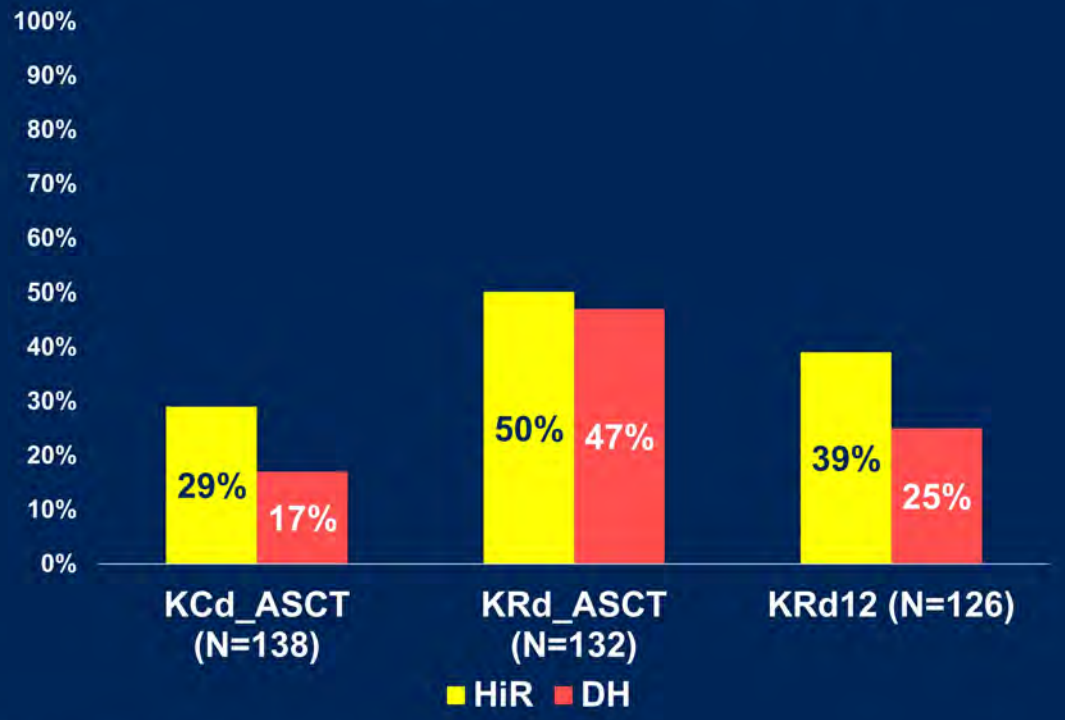
Sustained 1-year MRD negativity in High-risk patients

KRd_ASCT vs. KRd12 vs. KCd_ASCT

4-year PFS in 1-year sustained MRD-negative patients



Sustained 1-year MRD negativity



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; HiR, high risk; DH, double hit; N, number; PFS, progression-free survival.

Presented by Francesca Gay

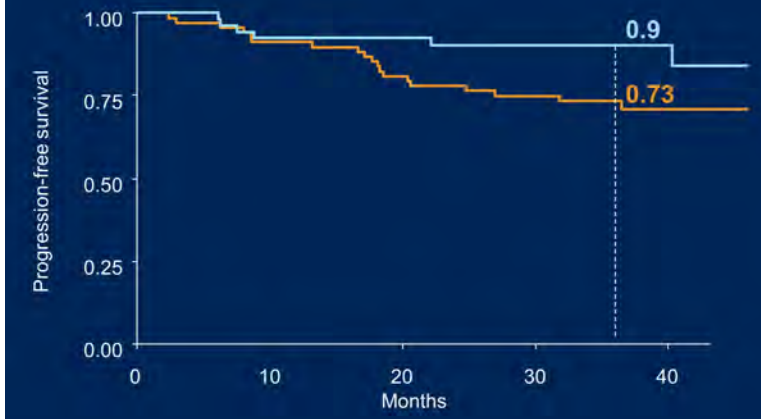
Progression-free survival: Random 2

KR vs. R

3-year progression-free survival

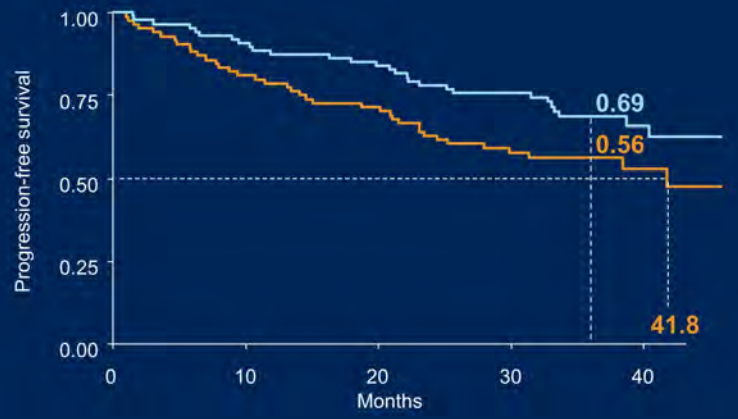
Median follow-up from Random 2: 37 months (IQR 33-42)

Standard risk (N=120)



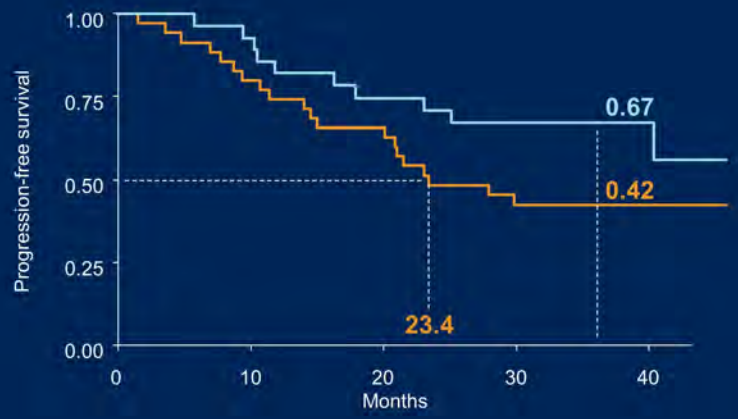
KR vs. R: HR 0.4, p=0.05

High risk (N=172)



KR vs. R: HR 0.6, p=0.04

Double hit (N=105)



KR vs. R: HR 0.53, p=0.1

Random 2, second randomization (maintenance treatment); IQR, interquartile range; K, carfilzomib; R, lenalidomide; HR, hazard ratio; CI, confidence interval; p, p-value.

Presented by Francesca Gay

IFM 2009 Study design

700 patients randomized stratified on ISS and FISH

Arm A – RVD alone	Arm B - Transplantation
3 RVD	3 RVD
PBSC collection (cyclophosphamide 3g/m^2 and GCSF 10 µg/kg/d)	
5 RVD	HD Melphalan 200 mg/m^2 + ASCT
	2 RVD

Lenalidomide maintenance 13 cycles (10-15 mg/d)

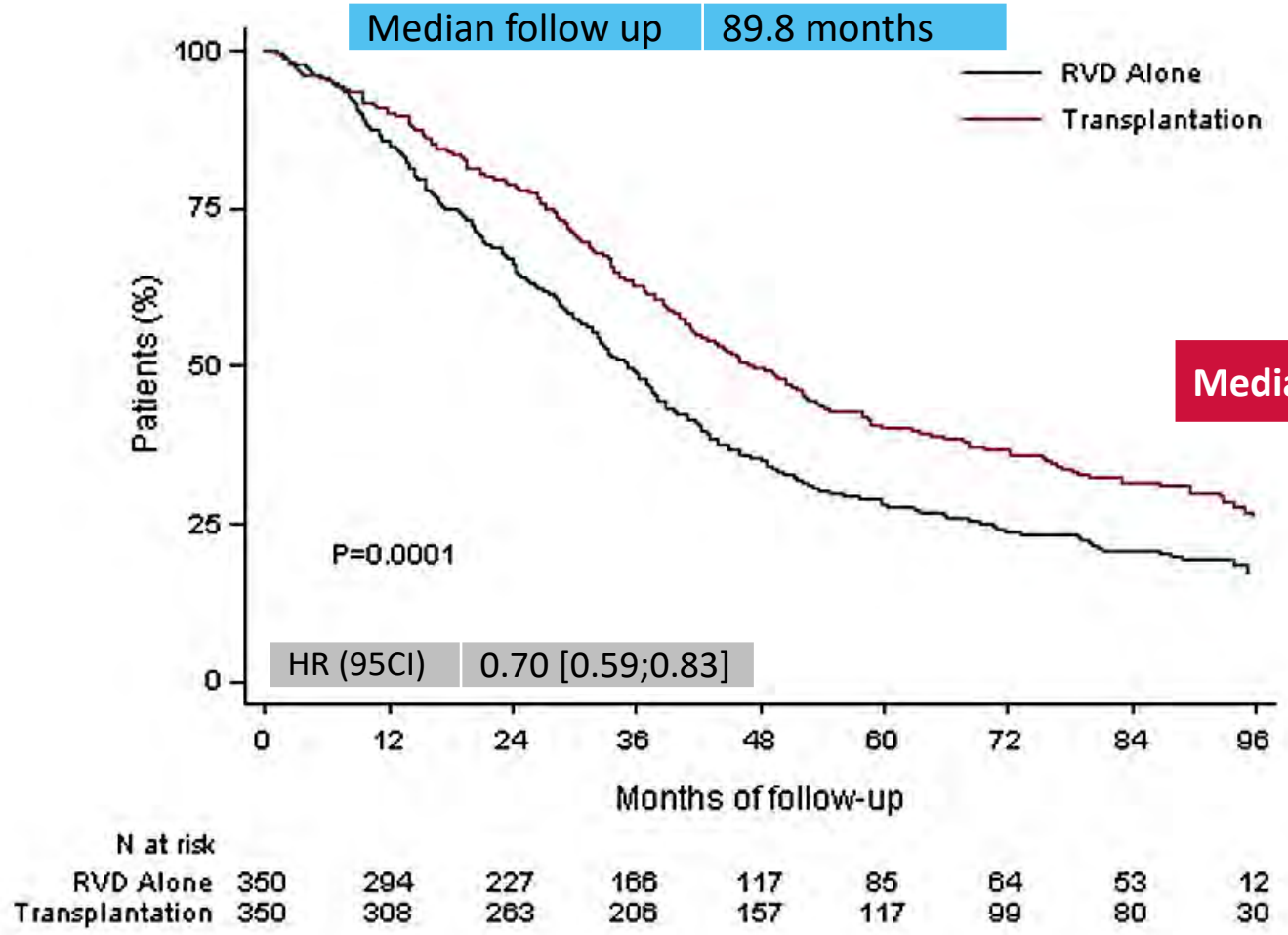
RVd 21d cycles
. Lenalidomide 25 mg/d: D1-D14
. Bortezomib 1.3 mg/m^2 D1, D4, D8, D11
. Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

Primary endpoint = PFS

Secondary endpoints
. ORR, MRD
. TTP
. OS
. Toxicity

M Attal et al, N Engl J Med 2017

Updated PFS (primary endpoint)



Median PFS 47.3 months (Transplantation, arm B)

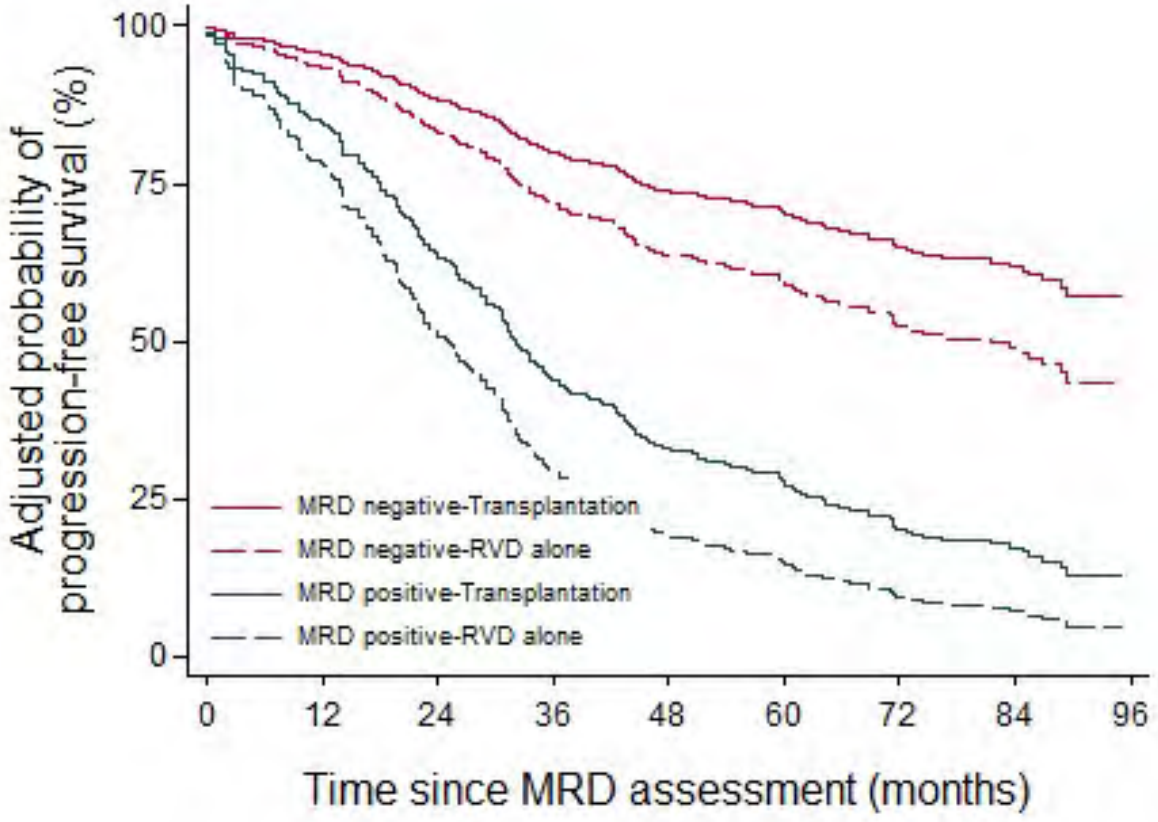
Median PFS 35 months (RVD alone, arm A)

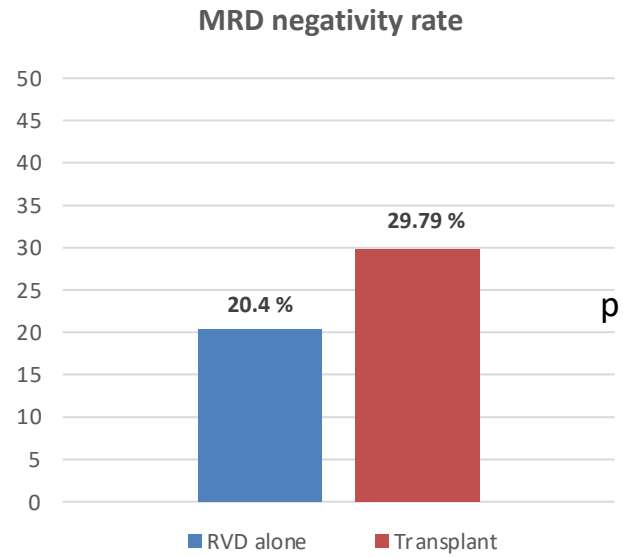
30% reduction in the risk of progression or death in patients receiving transplant

M Attal et al, N Engl J Med 2017

Subgroup analyses

Median follow up	89.8 months





p 0.01

Transplant is superior to VRD alone, even in patients who achieved undetectable MRD at 10^{-6}

M Attal et al, N Engl J Med 2017

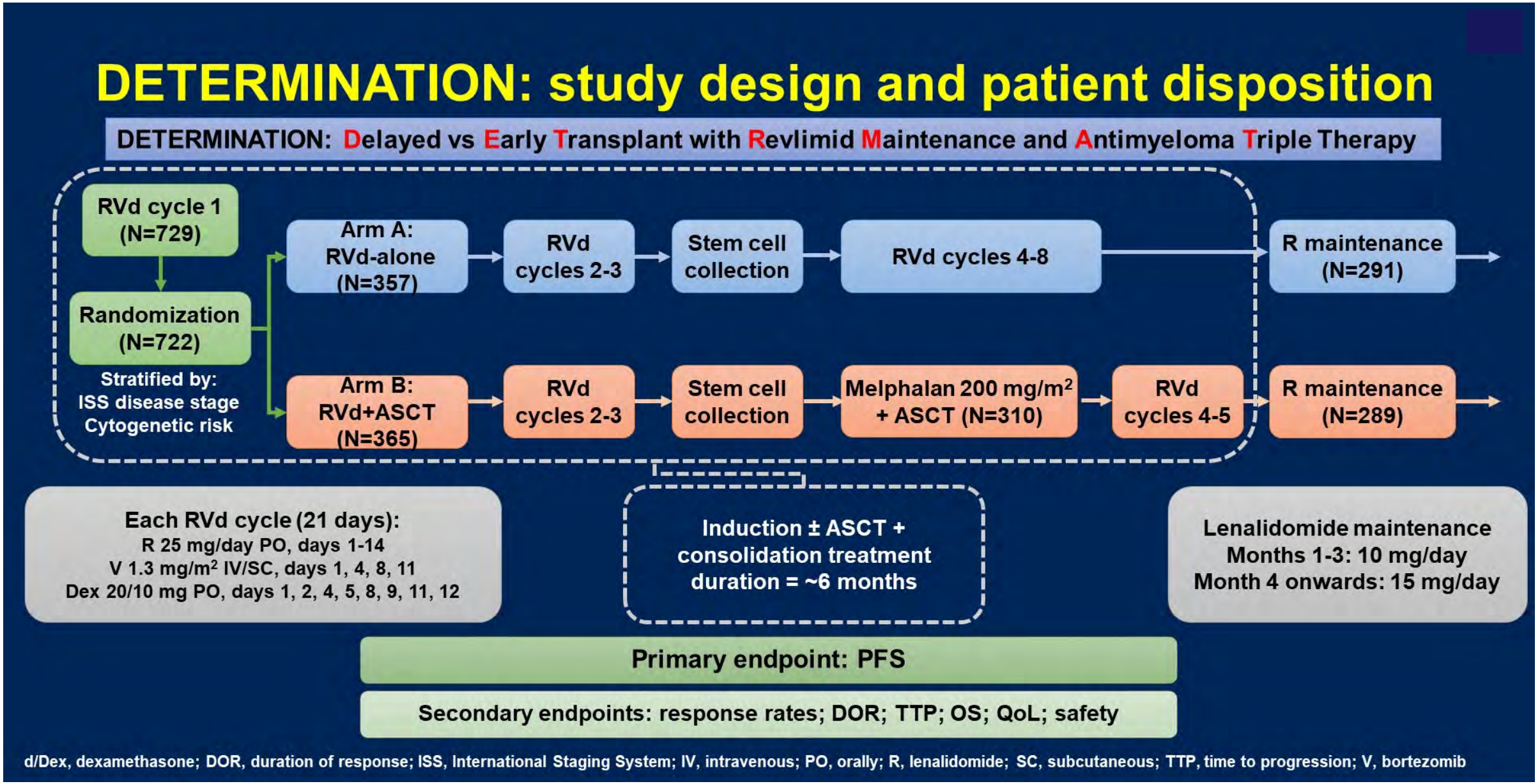
2022 ASCO® ANNUAL MEETING

RVd ± ASCT and Lenalidomide Maintenance to Progression for NDMM

The Phase 3 DETERMINATION Trial

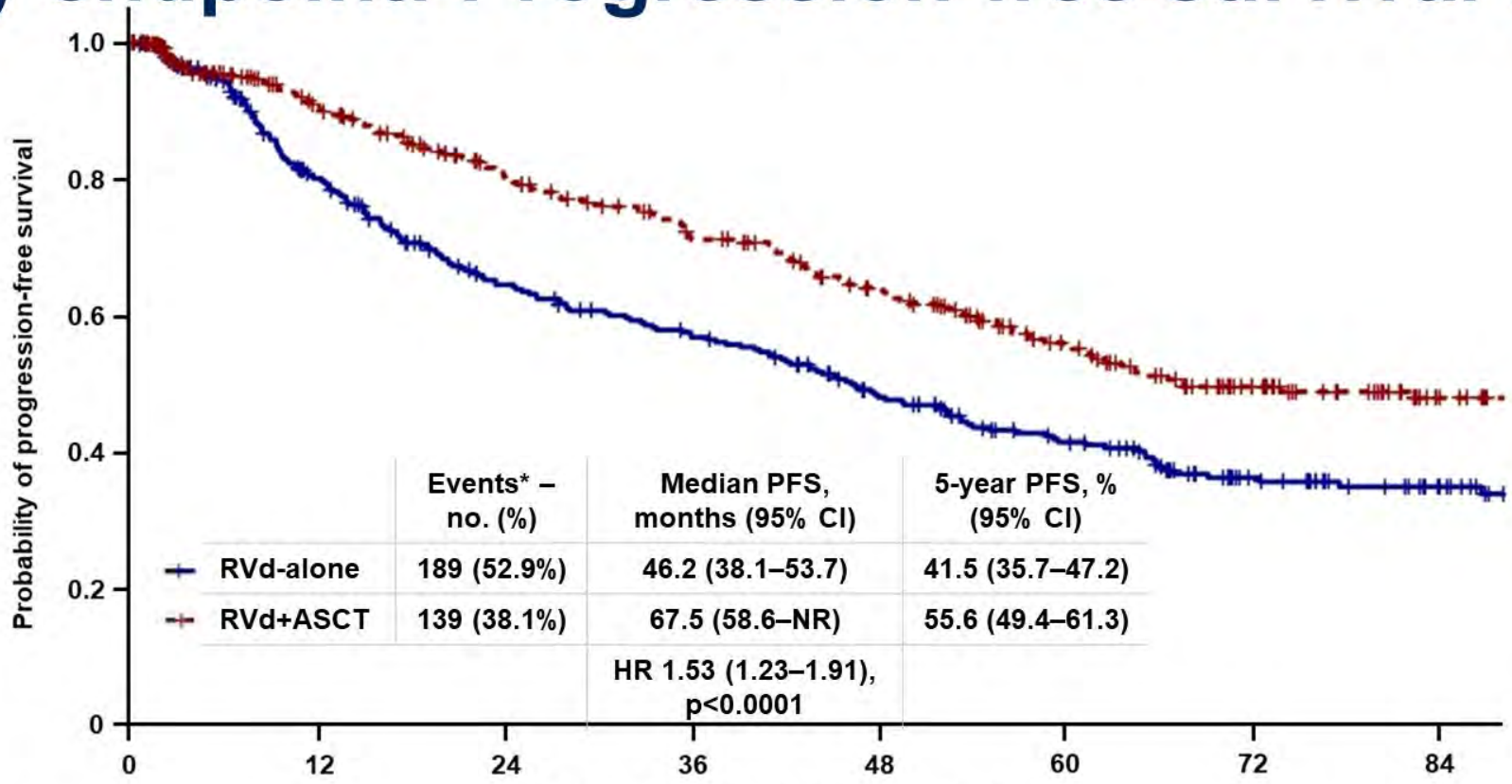
Paul G. Richardson, MD, RJ Corman Professor of Medicine, Harvard Medical School
Clinical Program Leader, Director of Clinical Research,
Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA

DETERMINATION: study design and patient disposition



d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

Primary endpoint: Progression-free survival (PFS)



Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

CI, confidence interval; HR, hazard ratio; Data cutoff: 12/10/21. *PFS events: disease progression or death.

Grade ≥3 treatment-related AEs (all treatment)

AE, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	78.2	94.2
Any hematologic	60.5	89.9
Any grade 5 (fatal) AE	0.3	1.6 *
Neutropenia	42.6	86.3
Thrombocytopenia	19.9	82.7
Leukopenia	19.6	39.7
Anemia	18.2	29.6
Lymphopenia	9.0	10.1
Febrile neutropenia	4.2	9.0
Diarrhea	3.9	4.9
Nausea	0.6	6.6
Mucositis oral	0	5.2
Fatigue	2.8	6.0
Fever	2.0	5.2
Pneumonia	5.0	9.0
Hypophosphatemia	9.5	8.2
Neuropathy	5.6	7.1

(S)AE, (serious) adverse event

- Rates of all grade ≥3 and of hematologic grade ≥3 treatment-related AEs during all treatment significantly higher with RVd + ASCT (both $p<0.001$)
  - Rates hematologic grade ≥3 treatment-related AEs during maintenance: 26.1% vs 41.9%
- Related SAEs:
  - Prior to maintenance: 40.3% vs 47.1%
  - During maintenance: 11.3% vs 16.6%

* Includes 1 death related to ASCT on Arm B identified after data cutoff; p=0.12

MRD / PFS by MRD status

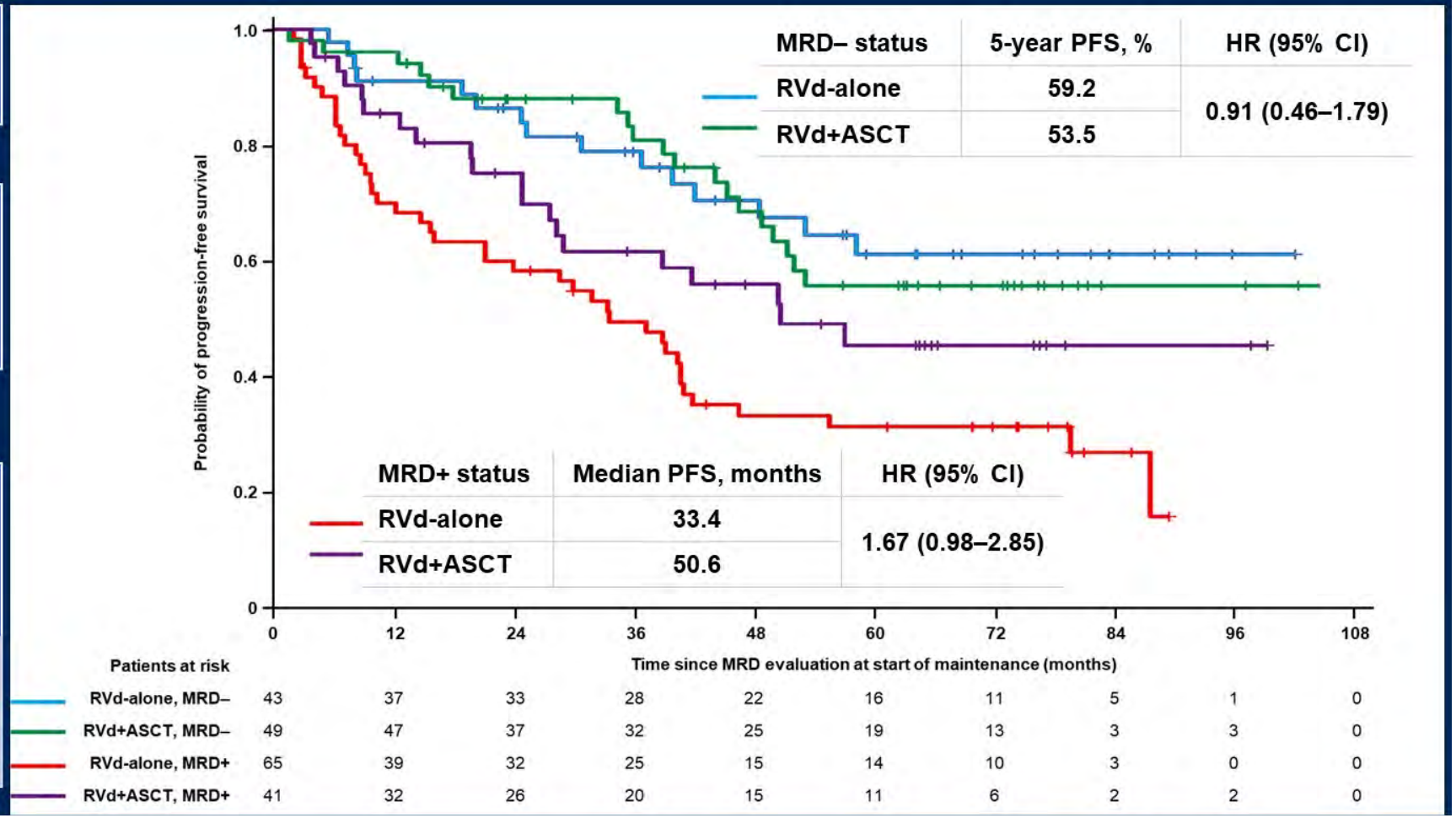
Preliminary analysis

108 RVd-alone, 90 RVd+ASCT patients with samples from start of maintenance

Rate of MRD-negative status (NGS, 10^{-5}):

39.8% vs 54.4%

Odds ratio 0.55 (unadjusted 95% CI 0.30–1.01)



Subsequent therapy and rate of ASCT in RVD-alone arm (delayed ASCT)

279 RVd-alone and 276 RVd+ASCT patients were off protocol therapy

- 222 (79.6%) and 192 (69.6%) had received subsequent therapy (table)

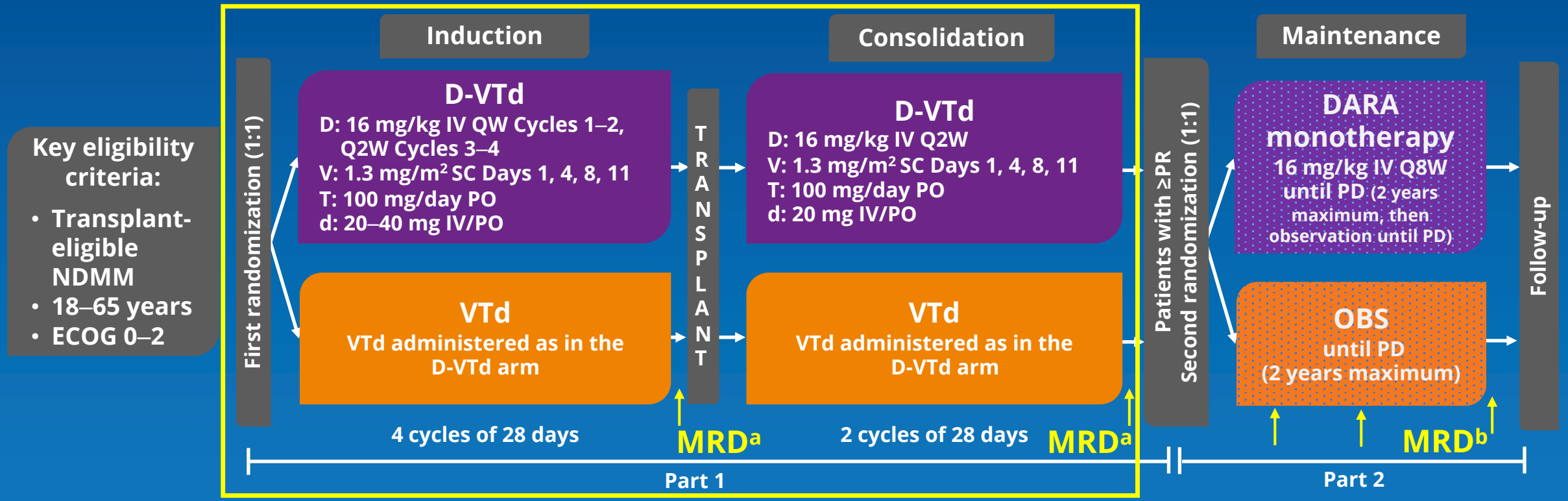
Only 78 (28.0%) of 279 RVd-alone patients had received ASCT at any time following end of study treatment

Subsequent therapy in patients off protocol therapy, %	RVd-alone (N=279)	RVd+ASCT (N=276)
Any treatment *	79.6	69.6
Subsequent therapy	n=222	n=192
Any immunomodulatory drug	55.9	58.3
Pomalidomide	30.2	29.2
Lenalidomide	25.7	29.2
Any proteasome inhibitor	55.9	50.0
Bortezomib	27.5	25.5
Carfilzomib	21.2	16.7
Ixazomib	8.1	7.8
Marizomib	0	0.5
Any monoclonal antibody	16.2	27.6
Daratumumab	11.3	21.4
Elotuzumab	4.5	6.3
Isatuximab	0.5	0

*Including IMiDs, PIs, mAbs, HDACi (panobinostat), ASCT, chemotherapy, RT, steroids, other

CASSIOPEIA: Induction/Consolidation

– Analyses in Part 1 were conducted in the ITT population (N=1085), which included all first-randomization patients



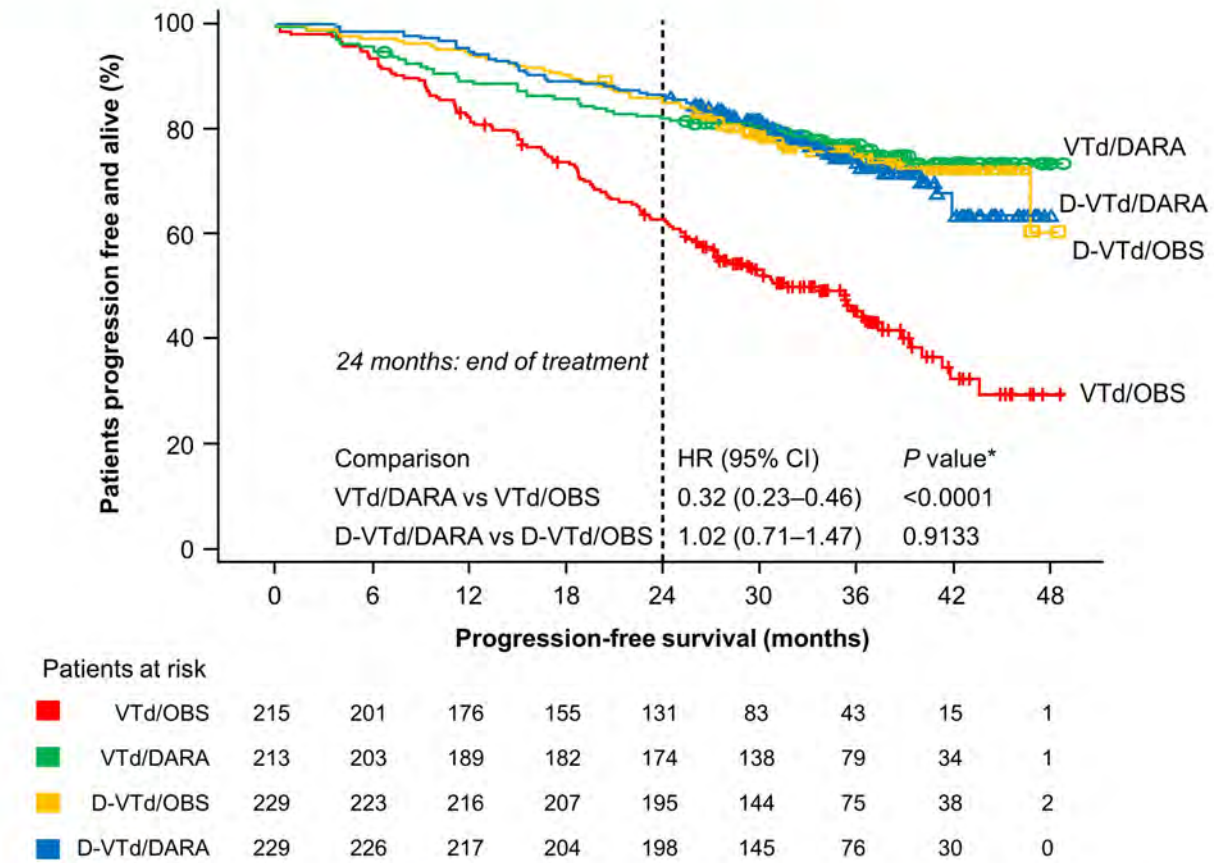
Stratification factors:
- Site affiliation (IFM or HOVON)
- ISS disease stage (I, II, or III)
- Cytogenetic risk status (high or standard/unknown risk)

Stratification factors:
- Induction treatment (D-VTd or VTd)
- Depth of response

≥PR, partial response or better; IV, intravenous; Q8W, every 8 weeks; OBS, observation; ECOG, Eastern Cooperative Oncology Group; QW, every week; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; IFM, Intergroupe Francophone du Myélome; HOVON, the Dutch-Belgian Cooperative Trial Group for Hematology-Oncology; ISS, International Staging System; PD, progressive disease; ≥VGPR, very good partial response or better.
[a]MRD analyses were performed at predefined timepoints for all patients, regardless of response. [b]MRD analyses were performed in patients with ≥VGPR at Weeks 25, 52, and 105.

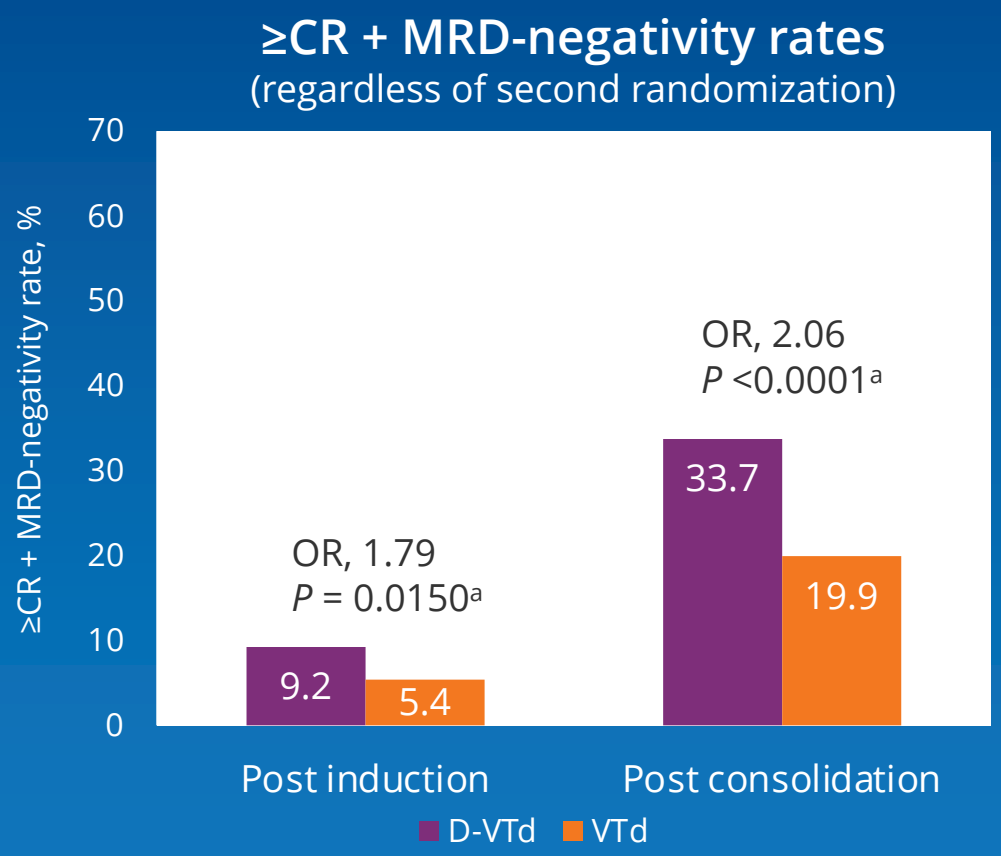
DARA Significantly Improved PFS vs OBS in Patients Treated With VTd Induction/Consolidation

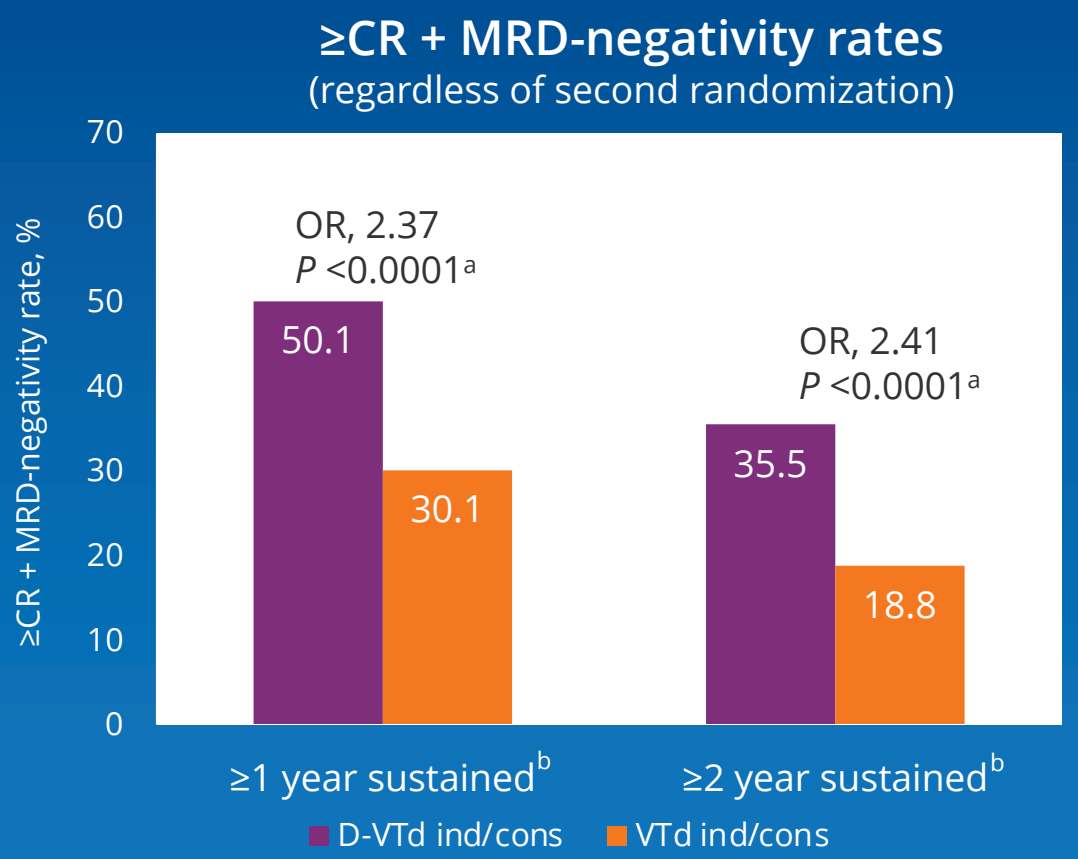
- A prespecified analysis showed significant interaction between maintenance and induction/consolidation therapy
- A PFS benefit was observed for VTd/DARA vs VTd/OBS
- PFS was not different for D-VTd/DARA vs D-VTd/OBS



*Nominal *P* value.
CI, confidence interval; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival; VTd, bortezomib, thalidomide, and dexamethasone.

CASSIOPEIA: D-VTd Improved Rates of ≥CR + MRD Negativity (MFC; 10^{-5}) Versus VTd Following Induction and Consolidation





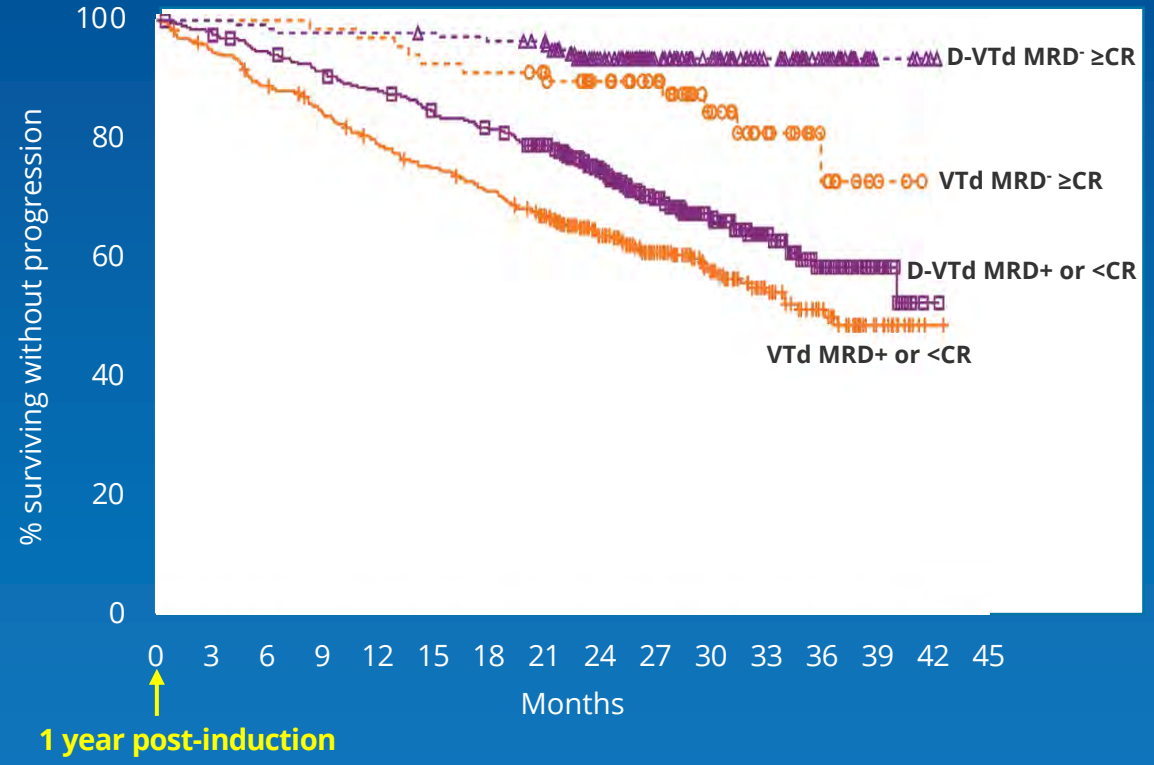
- Post-consolidation MRD-negativity rates among patients who achieved ≥CR were consistent across subgroups, including ISS disease stage and high-risk cytogenetics

MFC, multiparametric flow cytometry.

[a]Cochran-Mantel-Haenszel estimate of the common odds ratio for stratified tables was used. The stratification factors were study site affiliation, ISS disease stage, and cytogenetics. *P* value was calculated based on a stratified Cochran-Mantel-Haenszel chi-squared test.

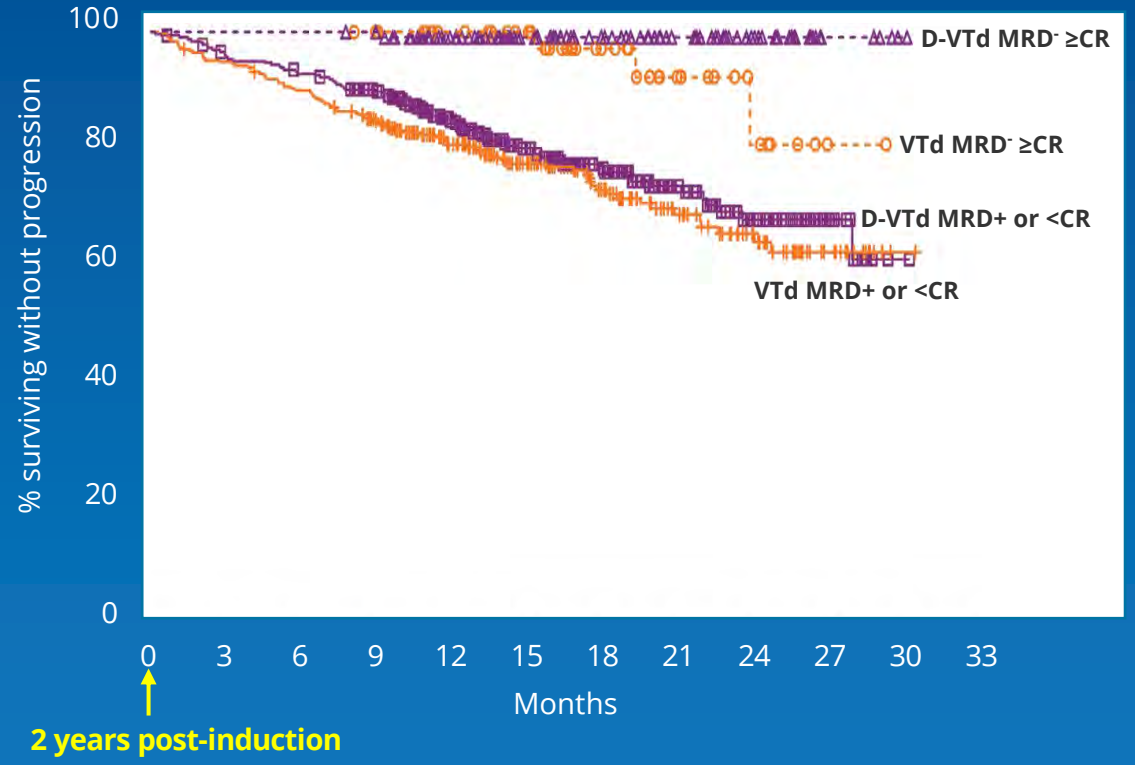
CASSIOPEIA: Landmark PFS Analysis From Post-induction ≥CR + MRD-negativity (MFC; 10^{-5}) Status By Treatment Group

1-year sustained MRD negativity
(regardless of second randomization)



No. at risk																
VTd MRD⁻ ≥CR	380	359	336	315	294	279	264	239	185	137	99	64	43	19	1	0
VTd MRD⁻ ≥CR	70	70	70	69	68	65	64	60	53	45	27	18	9	2	0	0
DVTd MRD⁺ or <CR	337	329	316	305	293	277	269	251	194	148	101	68	42	15	1	0
DVTd MRD⁺ or <CR	147	147	145	144	144	143	141	135	107	79	60	42	26	5	1	0

2-year sustained MRD negativity
(regardless of second randomization)



No. at risk												
VTd MRD⁻ ≥CR	311	294	278	252	196	145	104	68	45	20	1	0
VTd MRD⁻ ≥CR	50	50	50	48	42	37	23	14	7	1	0	0
DVTd MRD⁺ or <CR	326	309	299	280	211	159	112	72	46	15	0	0
DVTd MRD⁺ or <CR	111	111	111	108	90	68	51	38	22	5	1	0

MFC, multiparametric flow cytometry.

Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients (Pts) With Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of GRIFFIN After 24 Months of Maintenance

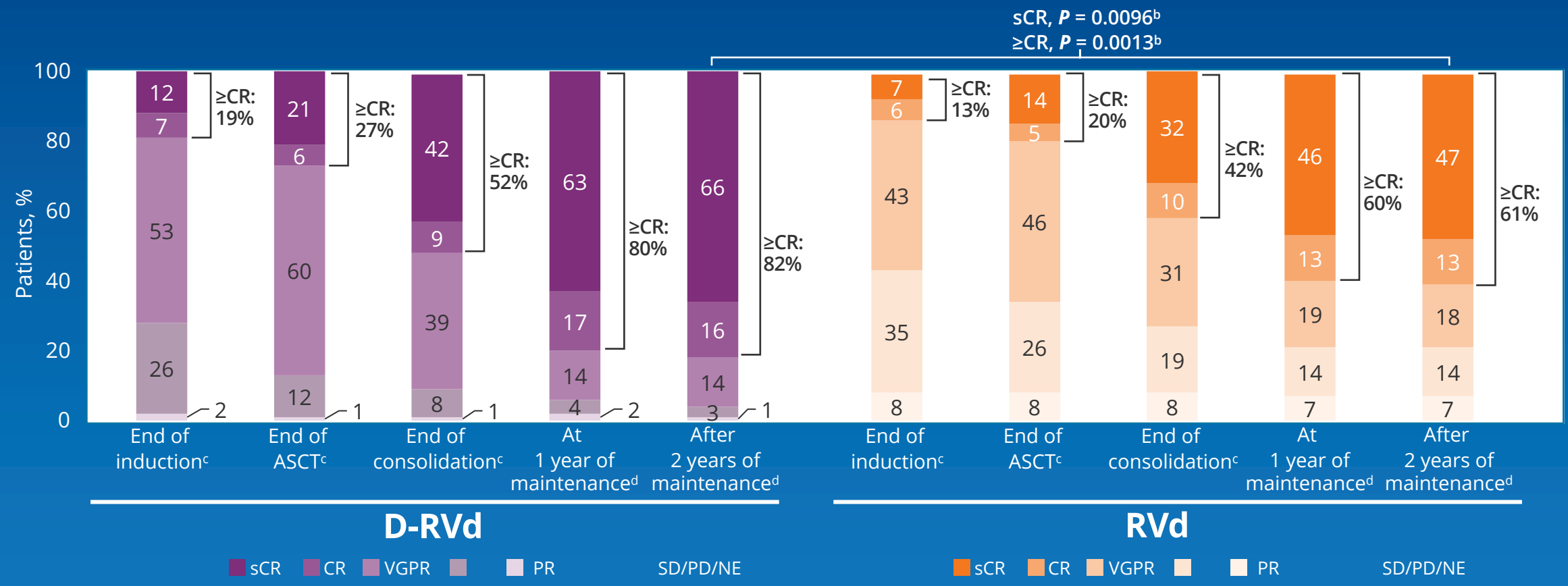
Jacob Laubach,[1,*] Jonathan L. Kaufman,[2] Douglas W. Sborov,[3] Brandi Reeves,[4] Cesar Rodriguez,[5] Ajai Chari,[6] Rebecca Silbermann,[7] Luciano J. Costa,[8] Larry D. Anderson Jr,[9] Nitya Nathwani,[10] Nina Shah,[11] Naresh Bumma,[12] Yvonne A. Efebera,[13] Sarah A. Holstein,[14] Caitlin Costello,[15] Andrzej Jakubowiak,[16] Tanya M. Wildes,[17] Robert Z. Orlowski,[18] Kenneth H. Shain,[19] Andrew J. Cowan,[20] Huiling Pei,[21] Annelore Cortoos,[22] Sharmila Patel,[22] J. Blake Bartlett,[23] Jessica Vermeulen,[24] Thomas S. Lin,[22] Paul G. Richardson,[1] Peter M. Voorhees[25]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [3]Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA; [4]University of North Carolina – Chapel Hill, Chapel Hill, NC, USA; [5]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [6]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [7]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [8]University of Alabama at Birmingham, Birmingham, AL, USA; [9]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [10]Judy and Bernard Briskin Center for Multiple Myeloma Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [11]Department of Medicine, University of California San Francisco, San Francisco, CA, USA; [12]Division of Hematology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [13]OhioHealth, Columbus, OH, USA; [14]Division of Oncology & Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA; [15]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [16]University of Chicago Medical Center, Chicago, IL, USA; [17]Cancer & Aging Research Group, St. Louis, MO, USA; [18]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [19]Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL, USA; [20]Division of Medical Oncology, University of Washington, Seattle, WA, USA; [21]Janssen Research & Development, LLC, Titusville, NJ, USA; [22]Janssen Scientific Affairs, LLC, Horsham, PA, USA; [23]Janssen Research & Development, LLC, Raritan, NJ, USA; [24]Janssen Research & Development, LLC, Leiden, The Netherlands; [25]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual

*Presenting author.

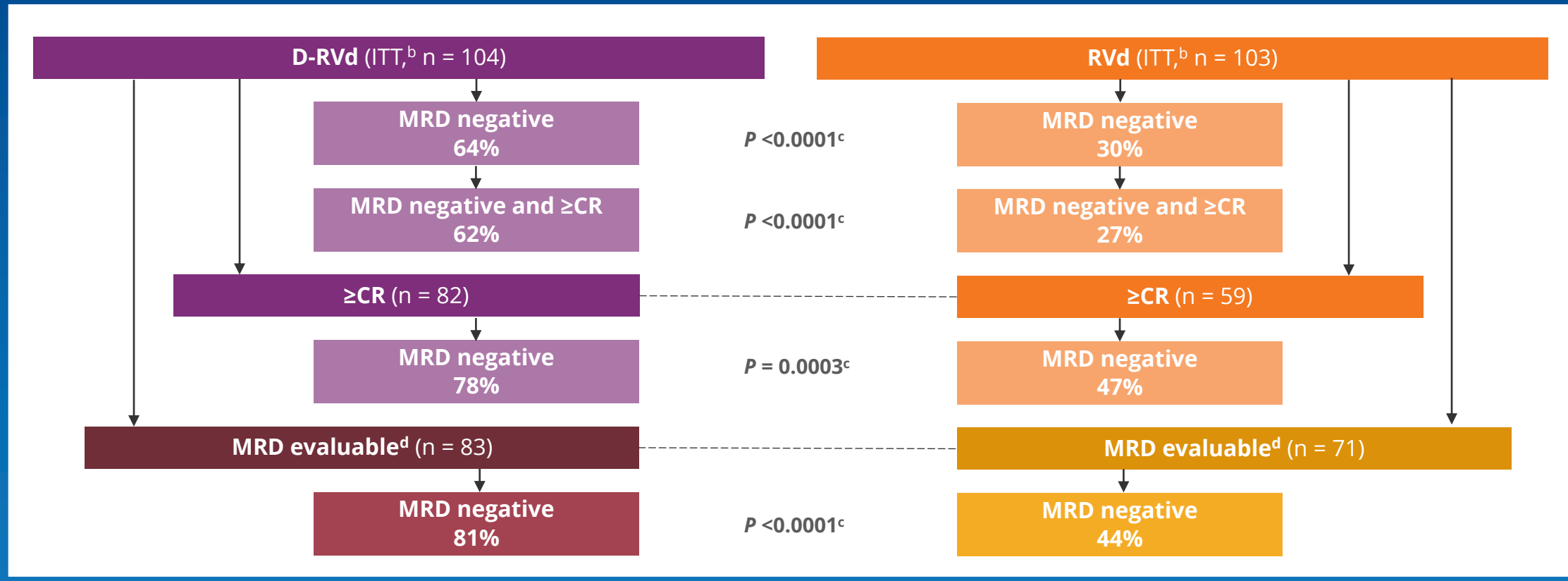
GRIFFIN: Responses Deepened Over Time[a]



- Response rates for sCR and ≥CR were greater for D-RVd versus RVd at all time points, with the deepest responses occurring after 2 years of maintenance therapy

PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test. [c]Response rates are from the primary analysis cutoff (median follow-up: 13.5 mo), and the response-evaluable population included 196 patients (D-RVd, n = 99; RVd, n = 97). [d]Response rates for the maintenance phase have longer follow-up (median: 38.6 mo), and the response-evaluable population included 197 patients (D-RVd, n = 100; RVd, n = 97). Percentages may not add up due to rounding.

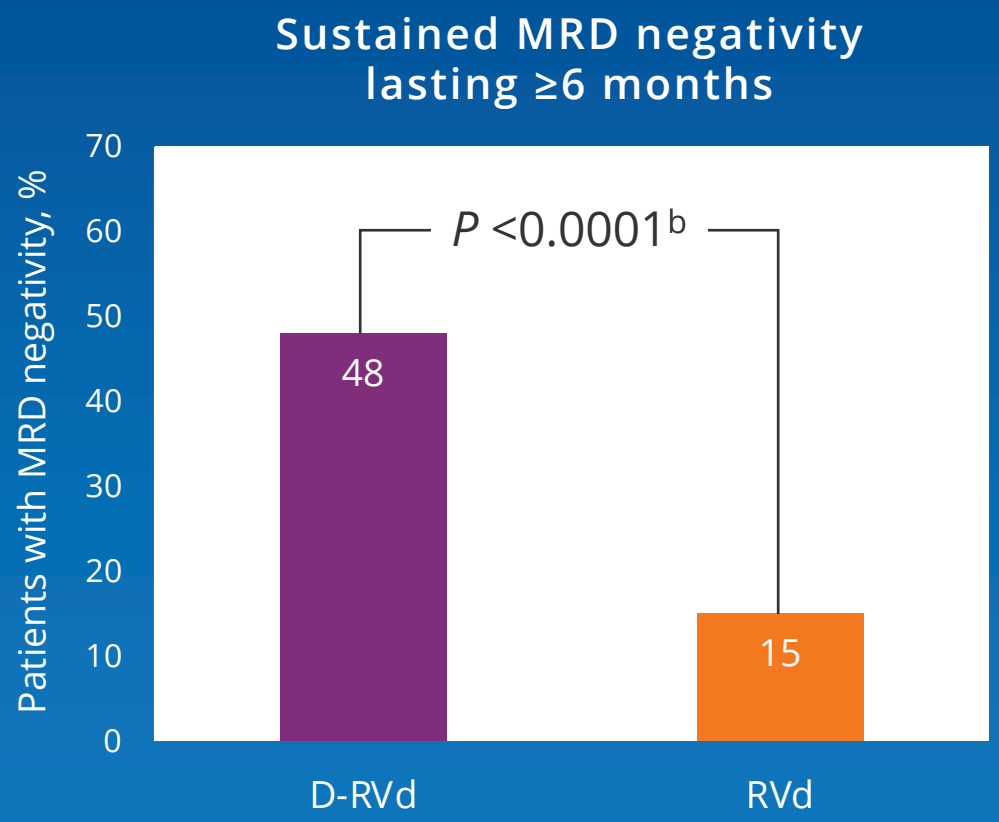
GRIFFIN: MRD Negativity[a] (10^{-5}) After 2 Years of Maintenance Therapy

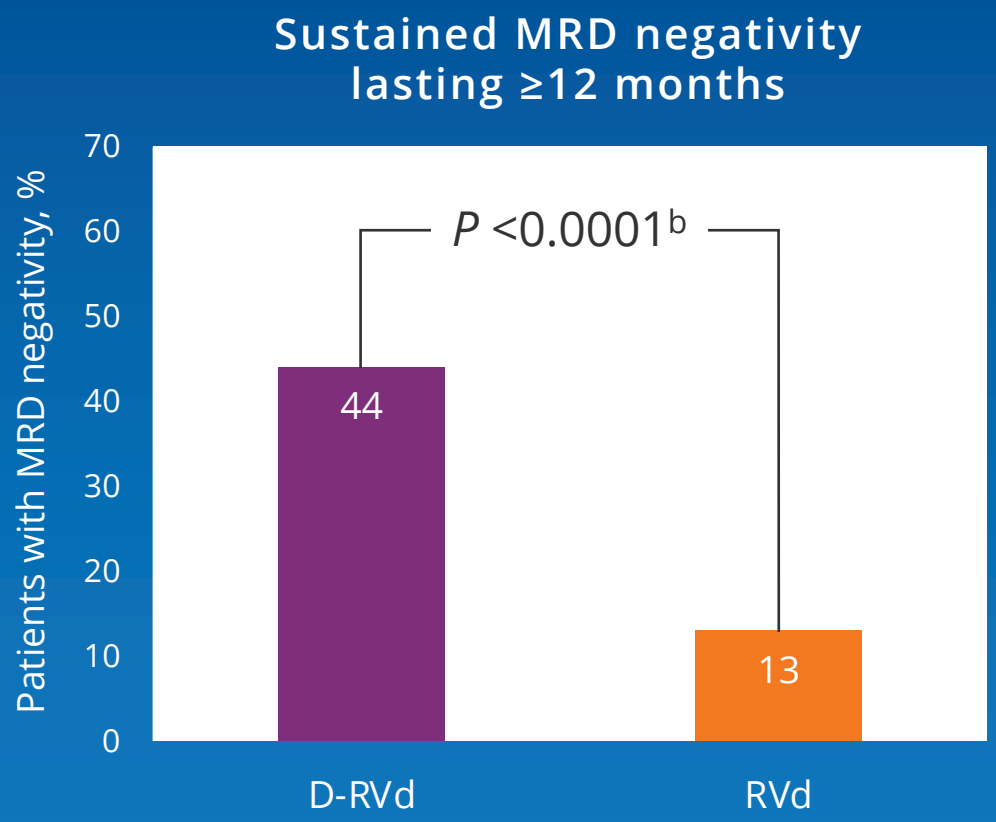


- Similarly, MRD-negativity (10^{-6}) rates favored D-RVd versus RVd in the ITT population (36% vs 15%, respectively; *P* = 0.0007), as well as among patients who achieved ≥CR (43% vs 22%; *P* = 0.0121)

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 38.6 months. [b]For the ITT population, patients with a missing or inconclusive assessment were considered MRD positive. [c]*P* values were calculated using the Fisher's exact test. [d]The MRD-evaluable population includes patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken.

GRIFFIN: D-RVd Improved Rates of Durable MRD Negativity[a] (10^{-5}) Lasting ≥6 Months or ≥12 Months Versus RVd

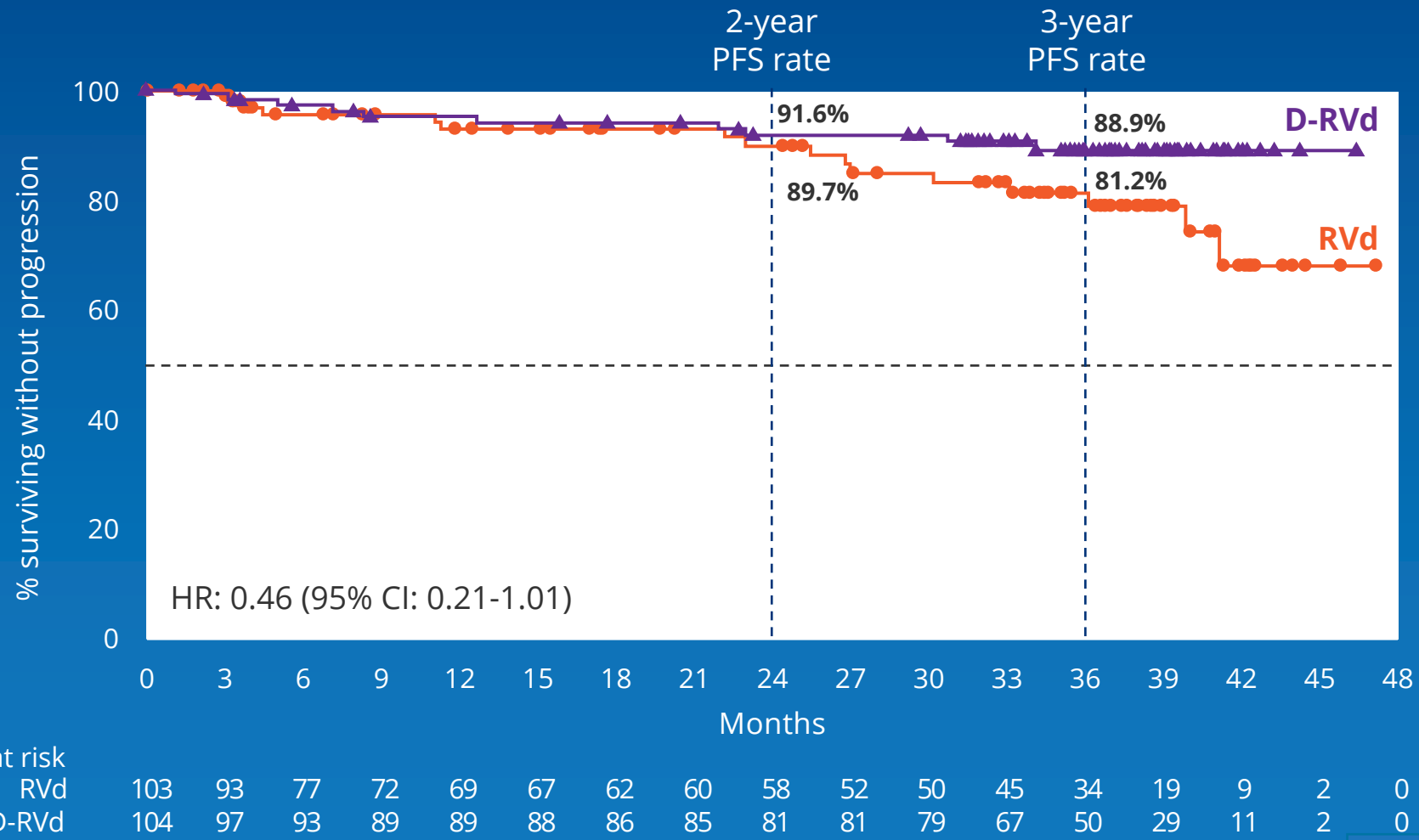




[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 38.6 months, and MRD-negativity rates are among the ITT population (D-RVd, n = 104; RVd, n = 103). Bone marrow aspirates were assessed at baseline, at first evidence of suspected CR or sCR (including patients with VGPR or better and suspected DARA interference), at the end of induction and consolidation, and after 1 and 2 years of maintenance, regardless of response. [b]*P* values were calculated using the Fisher's exact test.

GRIFFIN: PFS in the ITT Population

- Median follow-up: 38.6 months
- Median PFS was not reached in either group
- There is a positive trend toward improved PFS for D-RVd/DR versus RVd/R
- The separation of the PFS curves begins beyond 1 year of maintenance and suggests a benefit of prolonged DR therapy



HR, hazard ratio.

Addition of Isatuximab to Lenalidomide, Bortezomib and Dexamethasone as Induction Therapy for Newly-Diagnosed, Transplant-Eligible Multiple Myeloma: The Phase III GMMG-HD7 Trial

Hartmut Goldschmidt[1,2], Elias K. Mai[1], Eva Nievergall[1], Roland Fenk[3], Uta Bertsch[1,2], Diana Tichy[4], Britta Besemer[5], Jan Dürig[6], Roland Schroers[7], Ivana von Metzler[8], Mathias Hänel[9], Christoph Mann[10], Anne Marie Asemissen[11], Bernhard Heilmeier[12], Stefanie Huhn[1], Katharina Kriegsmann[1], Niels Weinhold[1], Steffen Luntz[13], Tobias A. W. Holderried[14], Karolin Trautmann-Grill[15], Deniz Gezer[16], Maika Klaiber-Hakimi[17], Martin Müller[18], Cyrus Khandanpour[19], Wolfgang Knauf[20], Markus Munder[21], Thomas Geer[22], Hendrik Riesenberg[23], Jörg Thomalla[24], Martin Hoffmann[25], Marc-Steffen Raab[1], Hans J. Salwender[26], Katja C. Weisel[11] for the German-speaking Myeloma Multicenter Group (GMMG)

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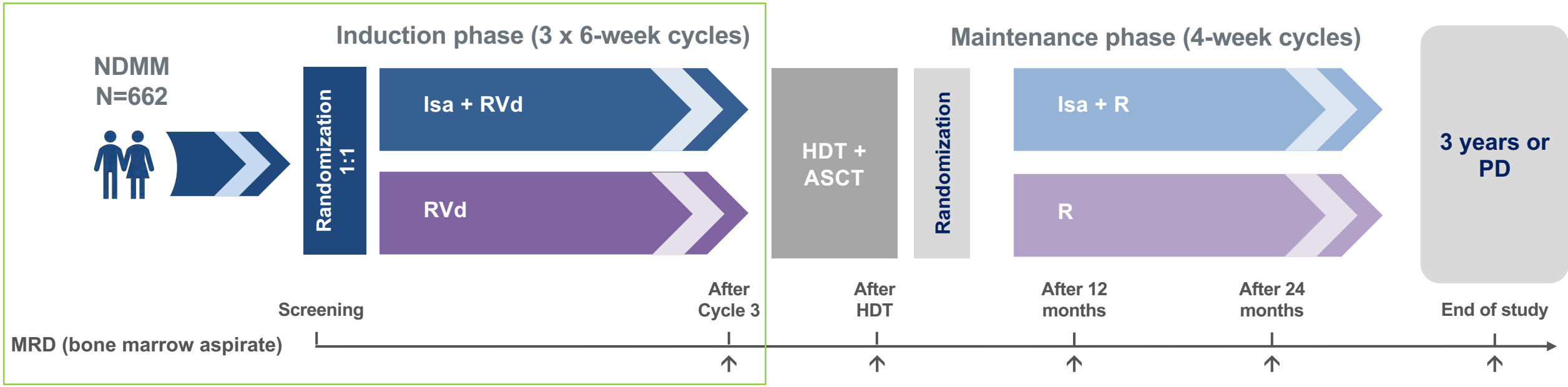
ASH 2021; Final Abstract Code: 463

HD7

Primary endpoint: MRD negativity at the end of induction phase



Primary endpoint:
- MRD negativity at the end of induction treatment (NGF, sensitivity 10^{-5}) stratified according to R-ISS

Secondary endpoints:
- CR after induction
- Safety

Data cut-off:
- April 2021

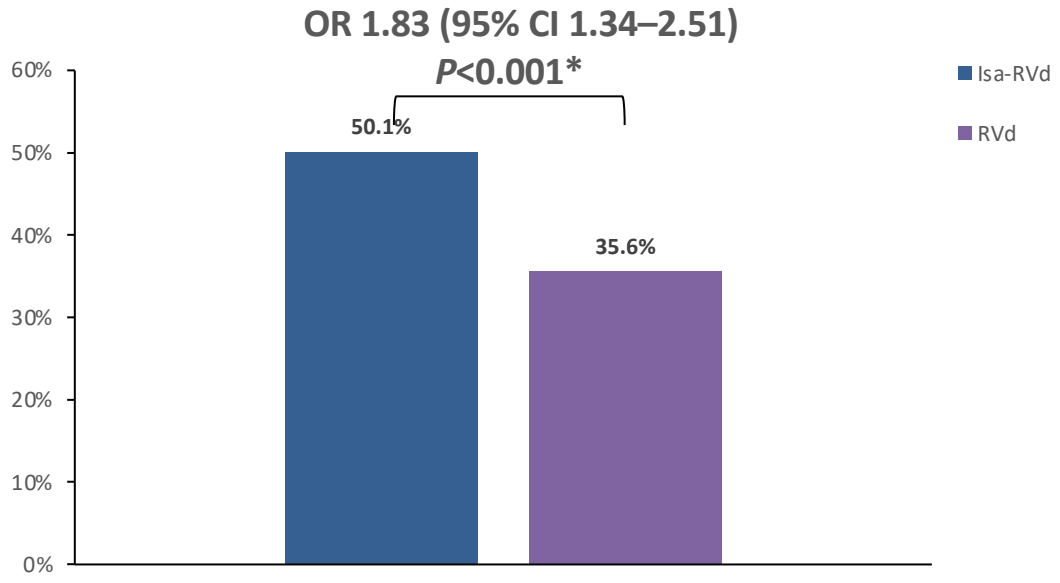
ASCT, autologous stem cell transplant; CR, complete response; d, dexamethasone; HDT, high-dose therapy; Isa, isatuximab; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGF, next-generation flow; PD, progressive disease; R, lenalidomide; R-ISS, Revised International Staging System; Te, transplant eligible; V, bortezomib

1. ClinicalTrials.gov: NCT03617731

HD7

First primary endpoint, end of induction MRD negativity by NGF (10^{-5}), was met in ITT analysis

Patients with MRD negativity at the end of induction therapy



Low number of not assessable/missing† MRD status: Isa-RVd (10.6%) and RVd (15.2%)

Isa-RVd is the first regimen to demonstrate a rapid and statistically significant benefit from treatment by reaching a MRD negativity of 50.1% at the end of induction and to show superiority vs. RVd in a Phase 3 trial

P value derived from stratified conditional logistic regression analysis
†Missing NGF-MRD values were due to either patients' loss to follow-up during induction therapy or to missing bone marrow samples or technical failures in measurement counted as non-responders, i.e. NGF-MRD positive
CI, confidence interval; d, dexamethasone; Isa, isatuximab; ITT, intent-to-treat; MRD, minimal residual disease; NGF, next-generation flow; OR, odds ratio; R, lenalidomide; V, bortezomib

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Knowledge that will change your world

Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), Autologous Transplantation and MRD Response-Adapted Consolidation and Treatment Cessation-Final Primary Endpoint Analysis of the MASTER Trial

Luciano J. Costa[1], Saurabh Chhabra[2], Natalie S. Callander, MD[3] , Eva Medvedova[4], Bhagirathbhai Dholaria[5], Rebecca Silbermann[4], Kelly Godby[1], Binod Dhakal[2], Susan Bal[1], Smith Giri[1], Anita D'Souza[2], Timothy Schmidt[3], Aric Hall[3], Pamela Hardwick[1], Robert F. Cornell[5], Parameswaran Hari[2]

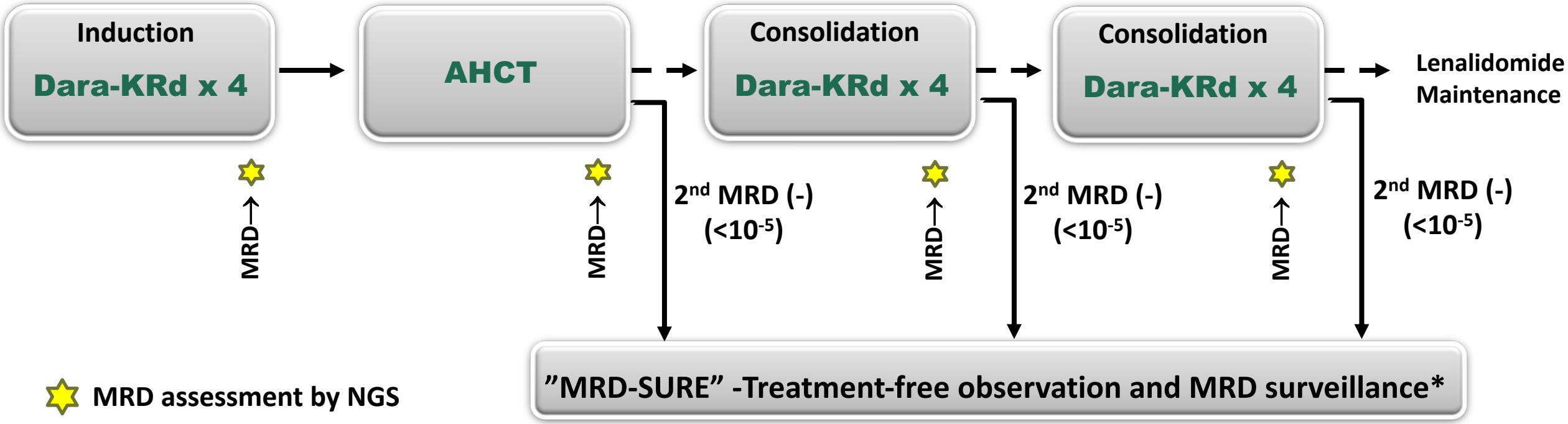
1- University of Alabama at Birmingham; 2- Medical College of Wisconsin; 3- University of Wisconsin at Madison;
4- Oregon Health and Science University; 5- Vanderbilt University

COMMIT- Academic Consortium to Overcome Multiple Myeloma through Innovative Trials

Treatment

Dara-KRd

- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



*24 and 72 weeks after completion of therapy

MASTER trial

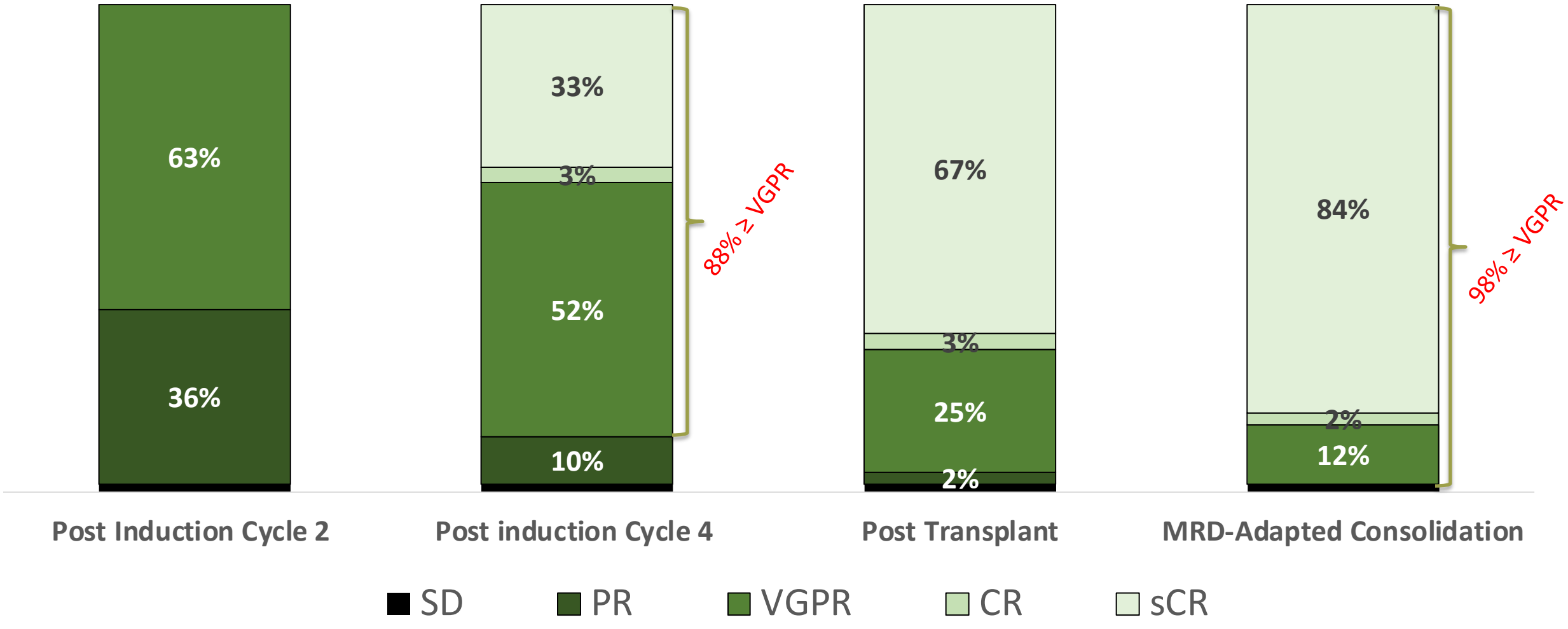
Patients

- 123 patients enrolled across 5 sites
- 118 (96%) with MRD trackable by ClonoSEQ®
- Median follow-up of 23.8 months

Characteristic	Standard-risk 0 HRCA N=53 (43%)	High-risk 1 HRCA N=46 (37%)	Ultra high-risk 2+ HRCA N=24 (20%)	Total N=123
Gender				
Male	33 (62%)	24 (52%)	13 (54%)	70 (57%)
Female	20 (38%)	22 (48%)	11 (46%)	53 (43%)
Age				
Median (range)	60 (36-79)	61 (35-77)	60 (41-72)	60 (35-79)
Age ≥ 70	12 (23%)	10 (22%)	2 (8%)	24 (20%)
Race/ethnicity				
Whites	42 (79%)	33 (72%)	19 (79%)	94 (76%)
Racial/ethnic minorities	11 (21%)	13 (28%)	5(21%)	29 (23%)
ECOG				
0-1	42 (79%)	40 (87%)	17 (71%)	99 (80%)
2	11 (21%)	6 (13%)	7 (29%)	24 (20%)

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

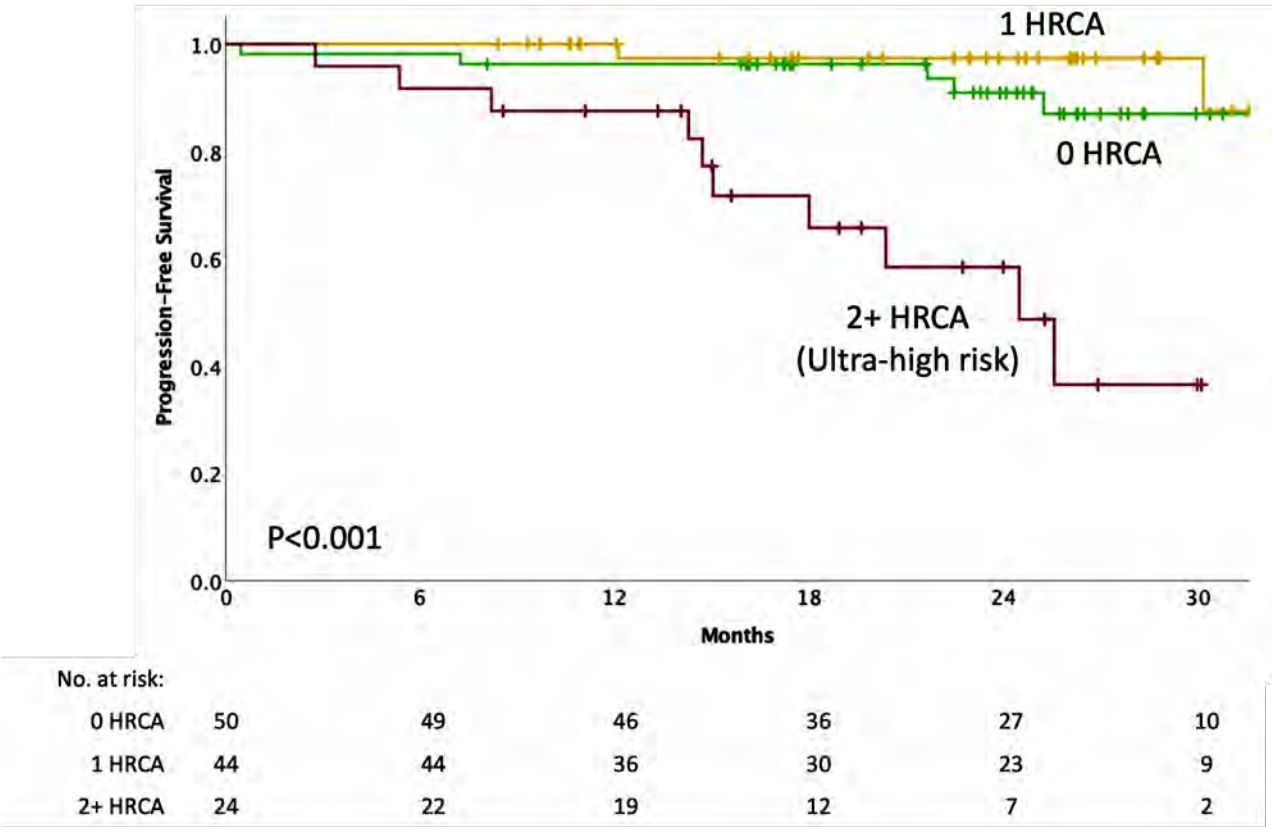
Best IMWG response by phase of therapy (ITT)



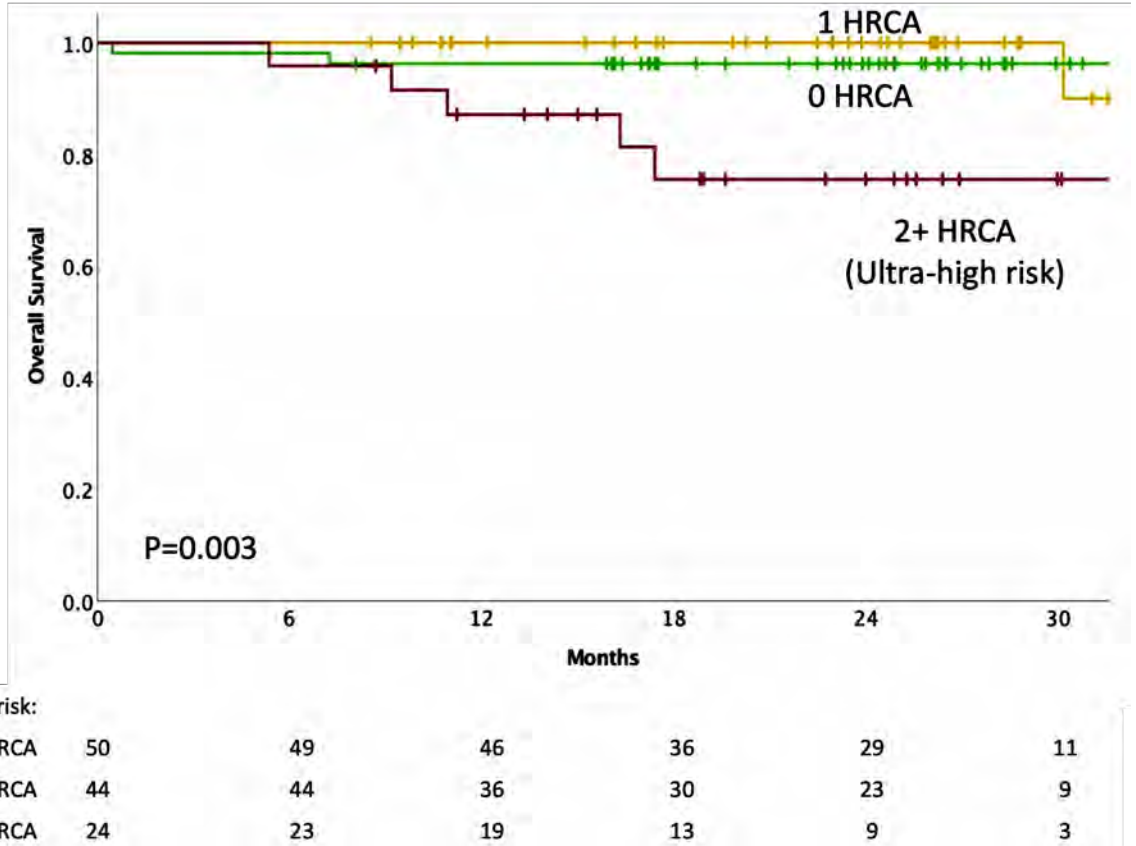
N=123

MASTER trial

Progression-Free and Overall Survival



No. at risk:						
0 HRCA	50	49	46	36	27	10
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	22	19	12	7	2



No. at risk:						
0 HRCA	50	49	46	36	29	11
1 HRCA	44	44	36	30	23	9
2+ HRCA	24	23	19	13	9	3

2-year PFS

0 HRCA	91%
1 HRCA	97%
2+ HRCA	58%

2-year OS

0 HRCA	96%
1 HRCA	100%
2+ HRCA	76%

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

MASTER trial

2022 ASCO® ANNUAL MEETING

THE UNIVERSITY OF CHICAGO

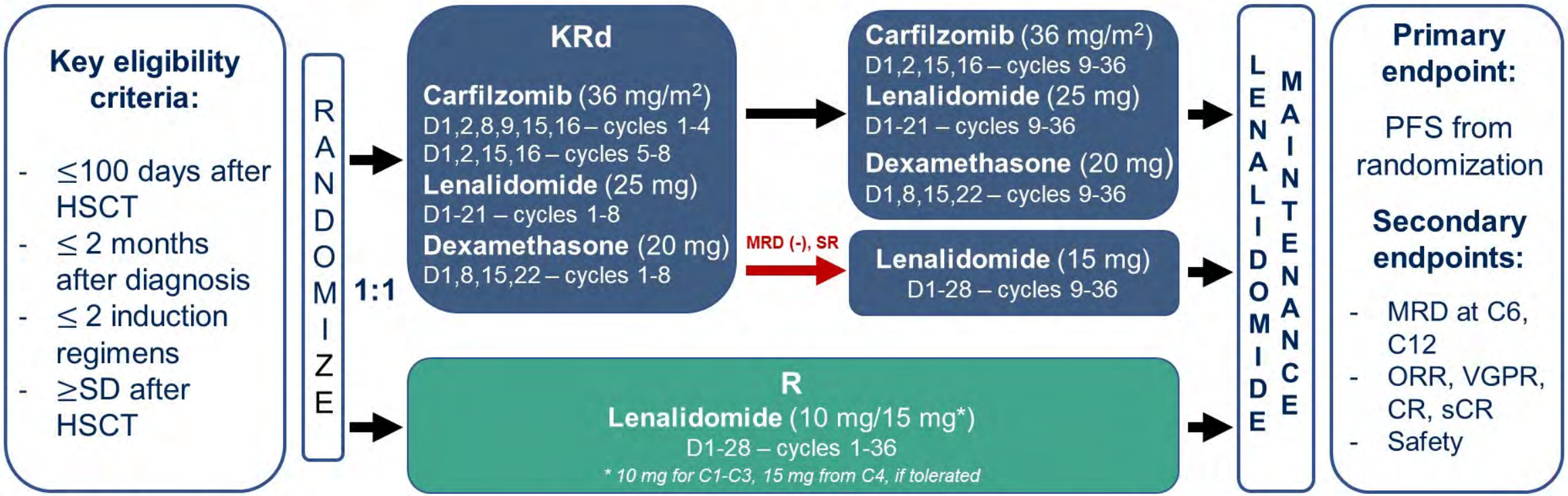
Polish Myeloma Consortium

ATLAS: A Phase 3 Randomized Trial of Carfilzomib, Lenalidomide, and Dexamethasone Versus Lenalidomide Alone After Stem-cell Transplant for Multiple Myeloma

Dominik Dytfeld, Tomasz Wrobel, Krzysztof Jamroziak, Tadeusz Kubicki, Pawel Robak, Jaroslaw Czyz, Agata Tyczyńska, Agnieszka Druzd-Sitek, Krzysztof Giannopoulos, Adam Nowicki, Anna Łojko-Dankowska, Magdalena Matuszak, Lidia Gil, Bartosz Puła, Justyna Rybka, Lidia Usnarska-Zubkiewicz, Olga Czabak, Andrew T Stefka, Benjamin A Derman, Andrzej J Jakubowiak

Study Design

Multicenter, randomized, open-label, phase 3 study



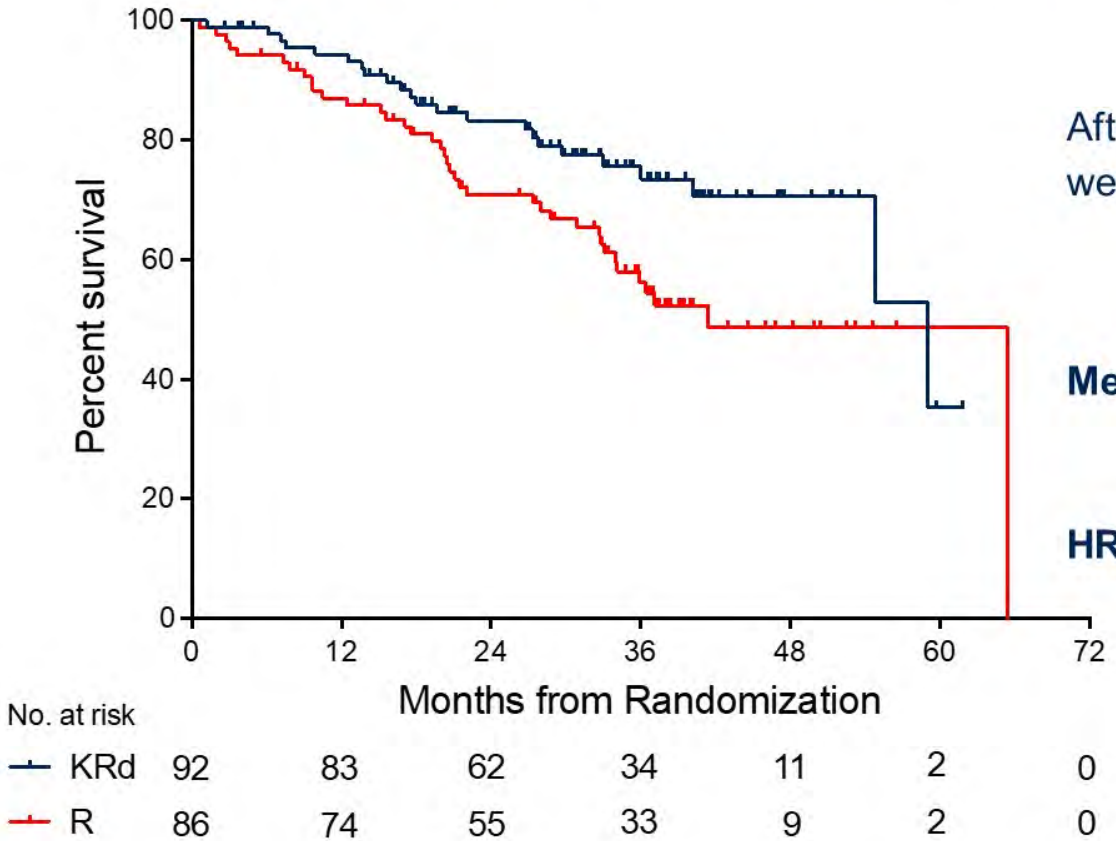
Stratification factors:

- post-transplant response (≥VGPR vs <VGPR)
- standard (SR) vs high risk (HR) cytogenetics

KRd pts with SR cytogenetics having reached IMWG MRD negativity[1] after C6 converted to R alone after C8

[1]*Kumar et al, Lancet Oncol 2016; 17:e328-46*

Progression Free Survival



After median follow-up of 33.8 months there were **61 PFS events:**

- **23 in the KRd arm**
- **38 in the R arm**

Median PFS:

KRd 59.0 months (95% CI 52.5-NR)

R 41.1 months (95% CI 33.4-65.4)

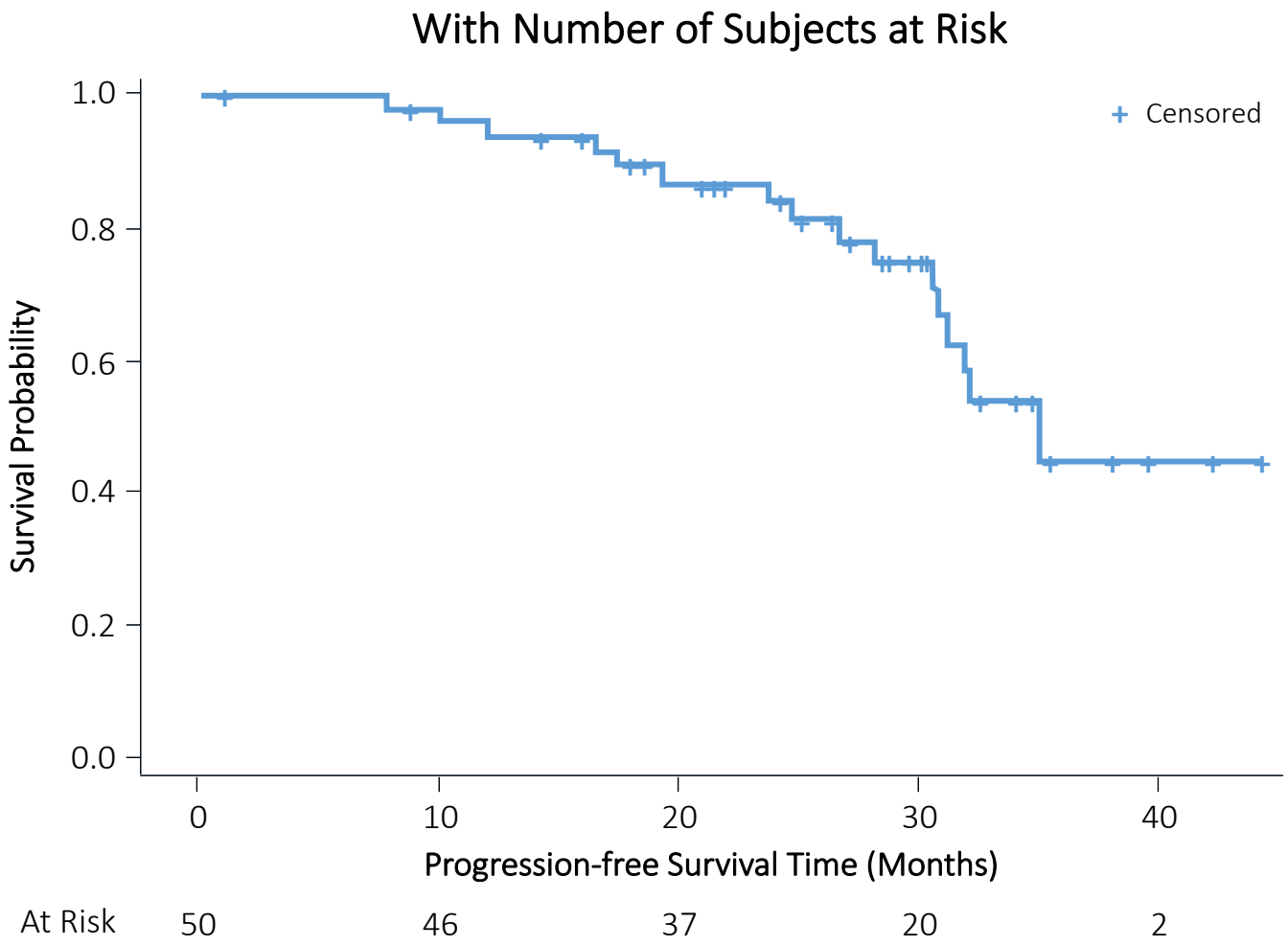
HR 0.56 (95% CI 0.34-0.93); **p=0.026**

HR – hazard ratio (log rank)

This early analysis was at 60% of expected 105 events for primary analysis, for which the p-value criterion for significance (p=0.05) was not adjusted for the interim nature of the comparison. Patients will be followed up until the primary analysis which will be adjusted accordingly.

RVd-Lite

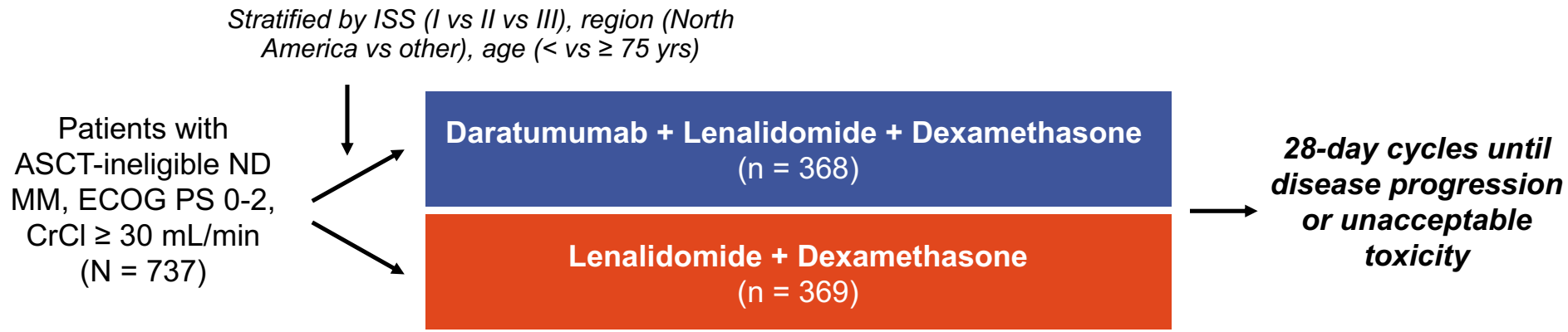
- Regimen (N=53)
  - Lenalidomide: 15 mg po days 1 to 21
  - Bortezomib: 1.3 mg/m2 SC 1× weekly on days 1, 8, 15, 22
  - Dexamethasone
    - If ≤75 years, 20 mg 2× weekly
    - If >75 years, 20 mg 1× weekly
- Results
  - 86% ORR
  - 66% ≥VGPR
  - Median PFS: 35.1 months
  - Median OS: NR
  - Median follow-up: 30 months
  - Median age: 73 years (range: 65-91)
  - PN: 62%
  - Only 1 patient had grade 3 symptoms



- PN, peripheral neuropathy.
- O'Donnell et al. *Br J Haematol*. 2018;182:222-230.

MAIA: Study Design

- Multicenter, open-label, randomized phase III trial

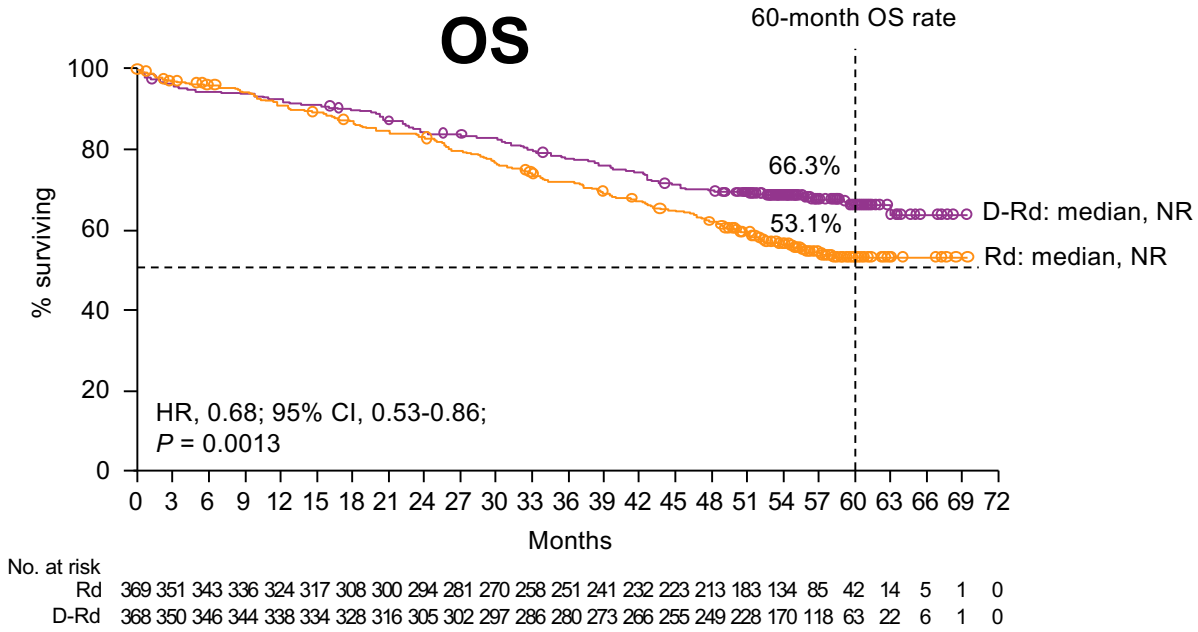


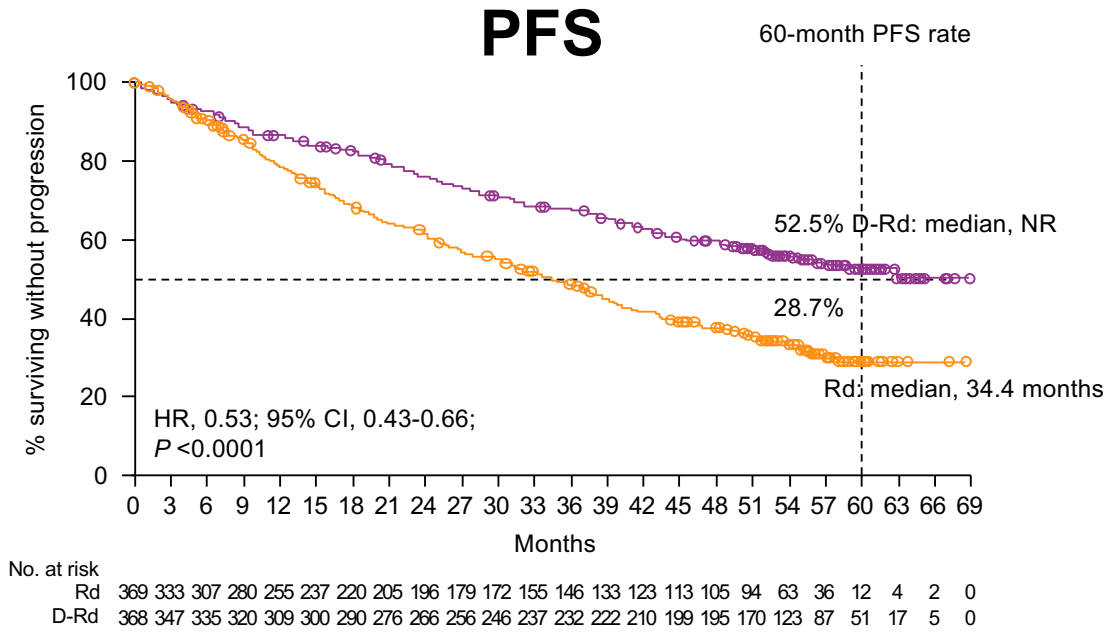
Dosing: daratumumab, 16 mg/kg IV (QW cycles 1-2, Q2W cycles 3-6, Q4W cycle 7+); lenalidomide, 25 mg QD PO on Days 1-21; dexamethasone 40 mg QW PO or IV.

- Primary endpoint: PFS
- Secondary endpoints: TTP, CR/sCR, MRD by NGS (10^{-5}), PFS2, OS, ORR, safety

Facon T, et al. EHA (abstr LB1901)

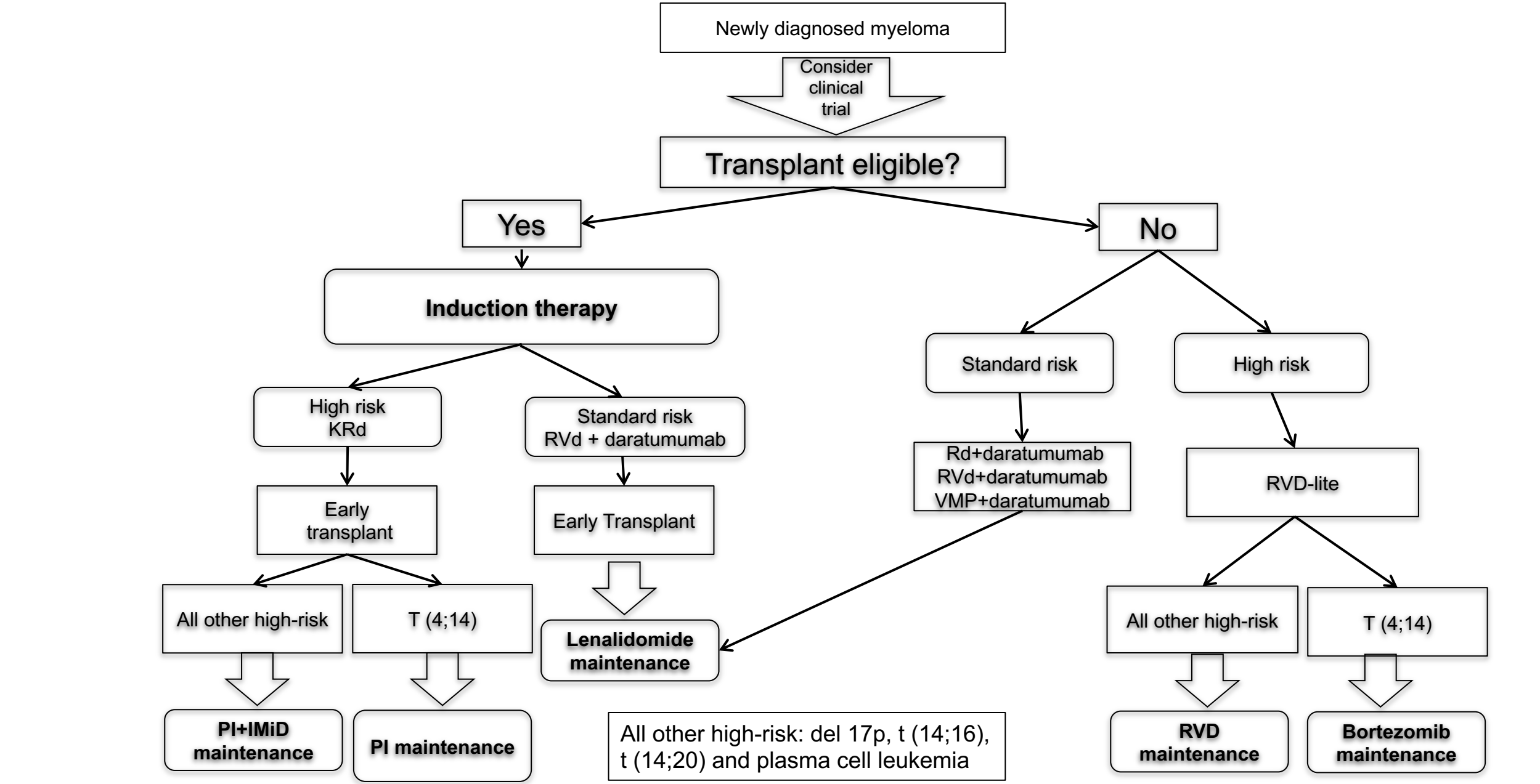
MAIA: OS and PFS with D-Rd and Rd





D-Rd, daratumumab plus lenalidomide and Dexamethasone; Rd, lenalidomide and Dexamethasone; HR, hazard ration; CI, confidence interval; NR, not reached.

Facon T, et al. EHA (abstr LB1901)



Emory Algorithm for newly diagnosed patients

VD: bortezomib/dexamethasone, Rd: lenalidomide/dexamethasone
RVD: bortezomib/lenalidomide/dexamethasone, RVD-lite: modified RVD
VMP: bortezomib/melphalan/prednisone

Conclusions

- CD38 based induction clearly adds value in the induction setting
- Role in the maintenance setting remains unclear given the very long outcomes for standard risk with len alone
- May be more exciting if addition of a second agent to Len allows one to shorten maintenance duration
- **Do Not** yet use MRD to define duration of maintenance

Patients and Families

Thanks to:

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Vikas Gupta
Nisha Joseph
Leon Bernal
Charise Gleason
Donald Harvey
Colleen Lewis
Amelia Langston
Y. Gu
S-Y Sun
Jing Chen
Mala Shanmugan
Larry Boise
Cathy Sharp

And the Clinical Research Team

IMS

Golfers Against Cancer
T.J. Martell Foundation

And Many Others who are part of the B-cell Team

sloni01@emory.edu