Up-Front Management of Multiple Myeloma

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Disclosures

Consulting Agreements	Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Janssen Biotech Inc, Merck, Takeda Oncology
Contracted Research	AstraZeneca Pharmaceuticals LP

Case Presentation: Dr Peswani

70-year-old woman

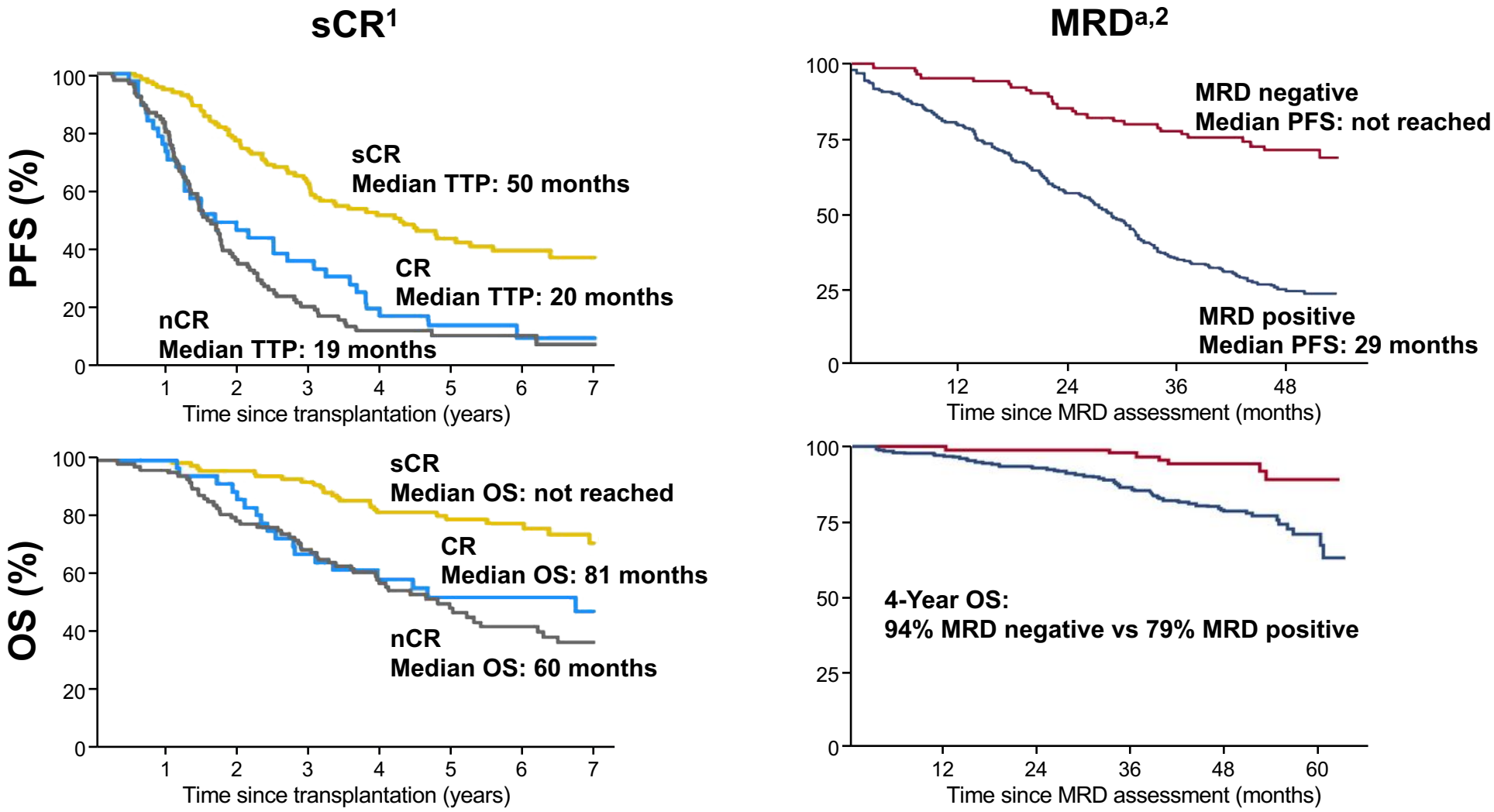
- Diagnosis: Stage II t(4;14) multiple myeloma
- Bortezomib/lenalidomide/dexamethasone (VRD), with VGPR
- Patient is willing to receive maintenance therapy but not yet ASCT

Case Presentation: Dr Khan

84-year-old woman

- Presents with chronic kidney disease and a recent decline in renal function
- Diagnosis: IgG-lambda multiple myeloma, no significant bone disease
- Good performance status, GFR <40

sCR and MRD as a Surrogate Endpoint for PFS and OS



- **Achievement of sCR and MRD negativity after ASCT are associated with better PFS and OS**

sCR, stringent complete response; MRD, minimal residual disease: OS, overall survival; TTP, time to progression; CR, complete response; nCR, near complete response; ASCT, autologous stem cell transplantation.
[a]According to MRD status at the start of maintenance therapy.

1. Kapoor P, et al. *J Clin Oncol*. 2013;31(36):4529-4535. 2. Perrot A, et al. *Blood.* 2018;132(23):2456-2464.

THE LANCET

Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study

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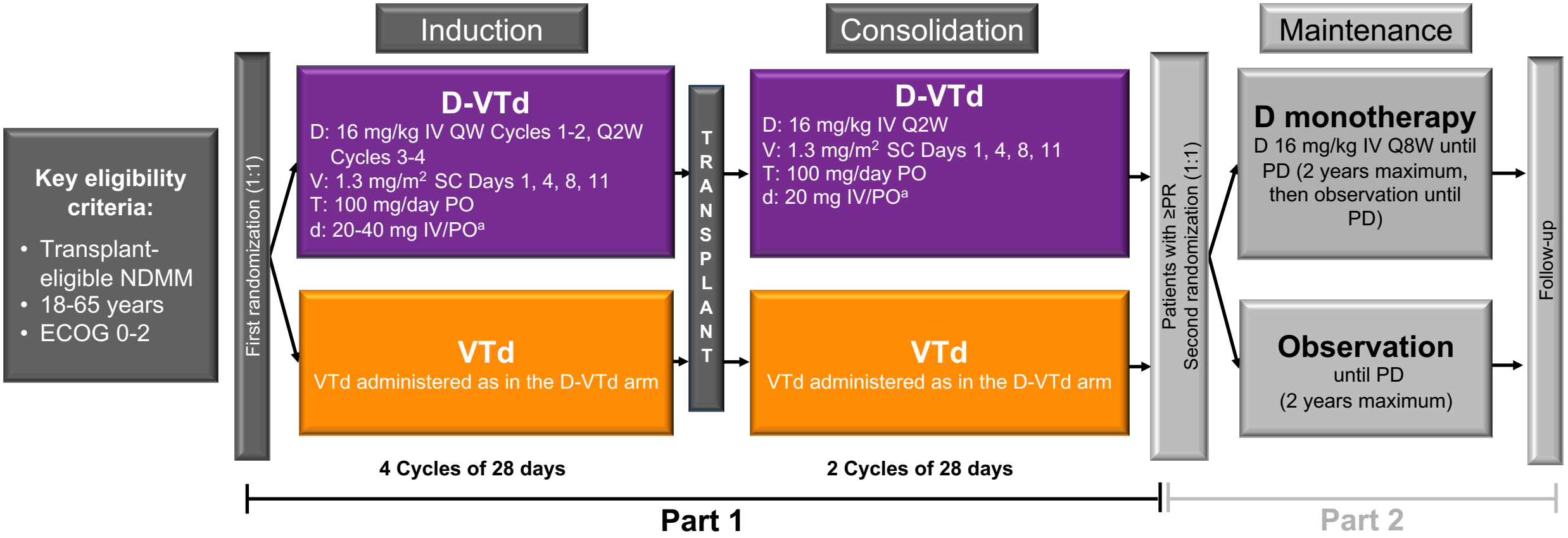
Philippe Moreau, Michel Attal, Cyrille Hulin, Bertrand Arnulf, Karim Belhadj, Lotfi Benboubker, Marie C Béné, Annemiek Broijl, Hélène Caillon, Denis Caillot, Jill Corre, Michel Delforge, Thomas Dejoie, Chantal Doyen, Thierry Facon, Cécile Sonntag, Jean Fontan, Laurent Garderet, Kon-Siong Jie, Lionel Karlin, Frédérique Kuhnowski, Jérôme Lambert, Xavier Leleu, Pascal Lenain, Margaret Macro, Claire Mathiot, Frédérique Orsini-Piocelle, Aurore Perrot, Anne-Marie Stoppa, Niels WCJ van de Donk, Soraya Wuilleme, Sonja Zweegman, Brigitte Kolb, Cyrille Touzeau, Murielle Roussel, Mourad Tiab, Jean-Pierre Marolleau, Nathalie Meuleman, Marie-Christiane Vekemans, Matthijs Westerman, Saskia K Klein, Mark-David Levin, Jean Paul Fermand, Martine Escoffre-Barbe, Jean-Richard Eveillard, Reda Garidi, Tahamtan Ahmadi, Sen Zhuang, Christopher Chiu, Lixia Pei, Carla de Boer, Elena Smith, William Deraedt, Tobias Kampfenkel, Jordan Schecter, Jessica Vermeulen, Hervé Avet-Loiseau, Pieter Sonneveld

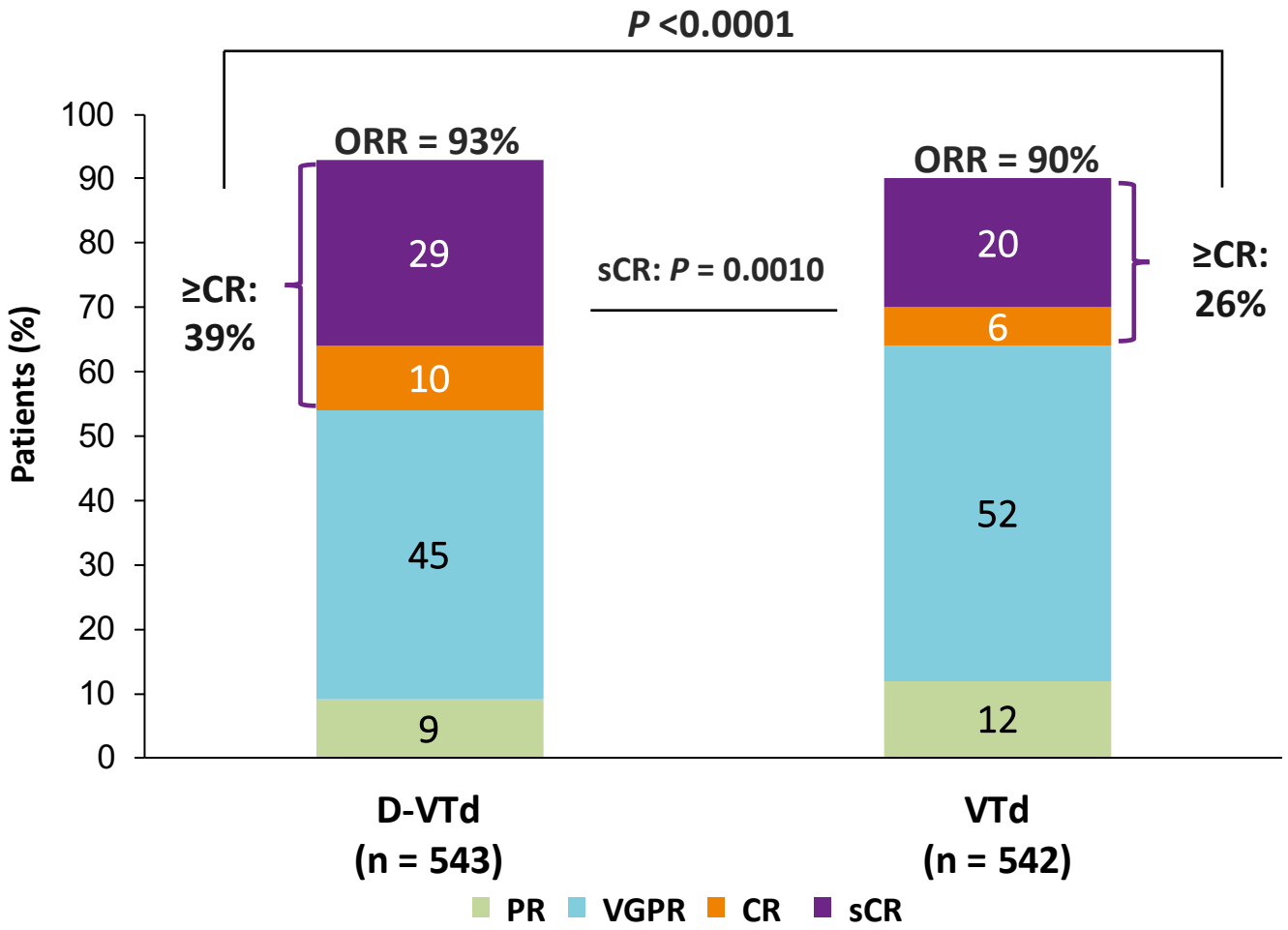
CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017



D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease; sCR, stringent complete response; PFS, progression-free survival; MRD, minimal residual disease; CR, complete response; OS, overall survival.
[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

CASSIOPEIA: Post-consolidation Depth of Response



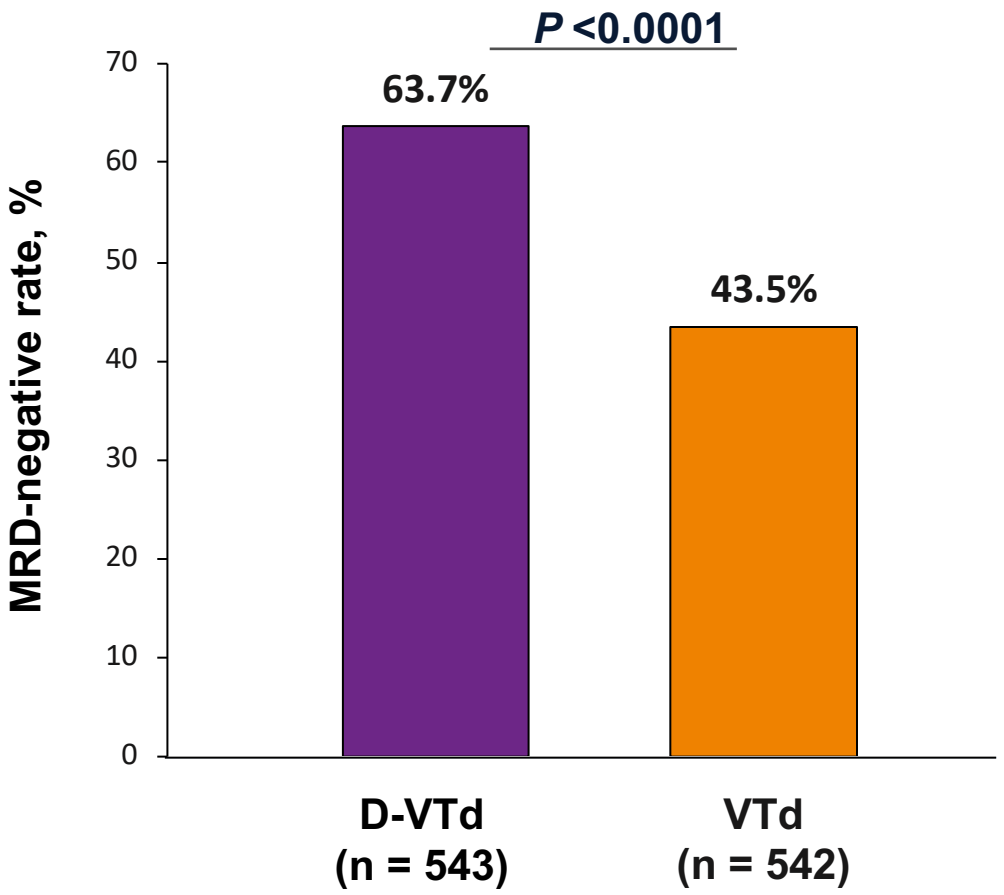
- Primary endpoint
  - Post-consolidation sCR
    - 29% D-VTd vs 20% VTd
    - Odds ratio, 1.60; 95% CI, 1.21-2.12; *P* = 0.0010

- sCR definition
  - All required
    - SIFE negative
    - UIFE negative
    - <5% plasma cells in the BM
    - Four-color flow negativity
    - Normal FLC ratio
    - Disappearance of all plasmacytomas

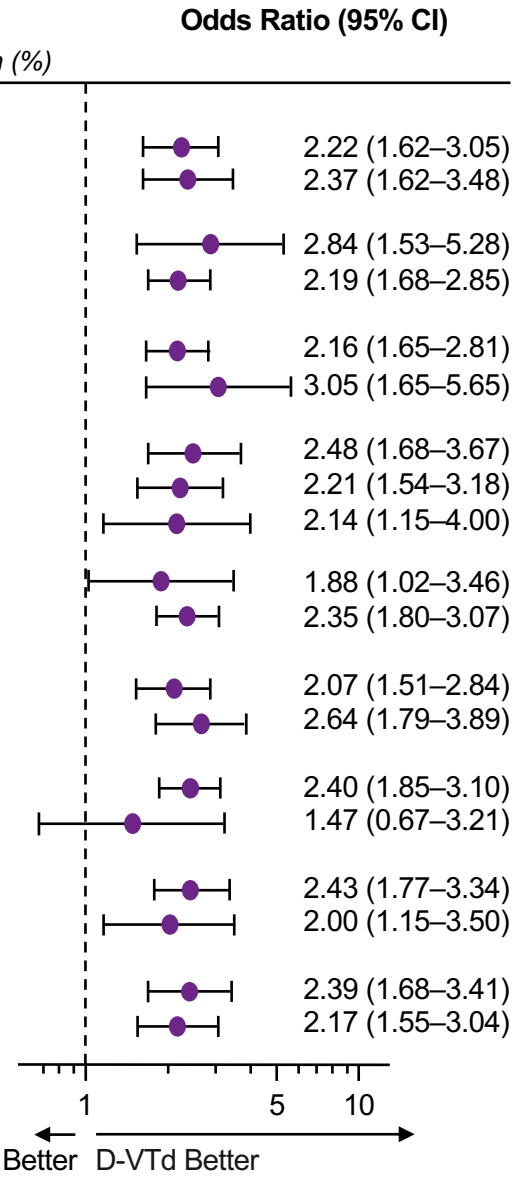
The addition of daratumumab to VTd improved depth of response

Moreau P et al. Lancet 2019 Jul 6;394(10192):29-38. Moreau P et al. Proc ASCO 2019; Abstract 8003.

CASSIOPEIA: MRD (Flow Cytometry; 10^{-5})[a,b]



Subgroup	VTd	D-VTd
	Minimal residual disease negative, n (%)	
Sex		
Male	131 (41)	192 (61)
Female	105 (47)	154 (68)
Age		
<50 years	38 (42)	56 (68)
≥50 years	198 (44)	290 (63)
Site		
IFM	204 (45)	287 (64)
HOVON	32 (38)	59 (65)
ISS disease stage		
I	103 (45)	137 (67)
II	96 (41)	155 (61)
III	37 (46)	54 (64)
Cytogenetic profile at trial entry[c]		
High risk	38 (44)	49 (60)
Standard risk	197 (43)	296 (64)
Baseline creatinine clearance		
>90 ml/min	139 (44)	205 (62)
≤90 ml/min	97 (43)	141 (67)
Baseline hepatic function		
Normal	216 (43)	310 (65)
Impaired	20 (48)	36 (57)
Type of multiple myeloma[d]		
IgG	122 (39)	201 (61)
Non-IgG	59 (49)	61 (66)
ECOG performance status		
0	112 (44)	172 (65)
≥1	124 (44)	174 (63)

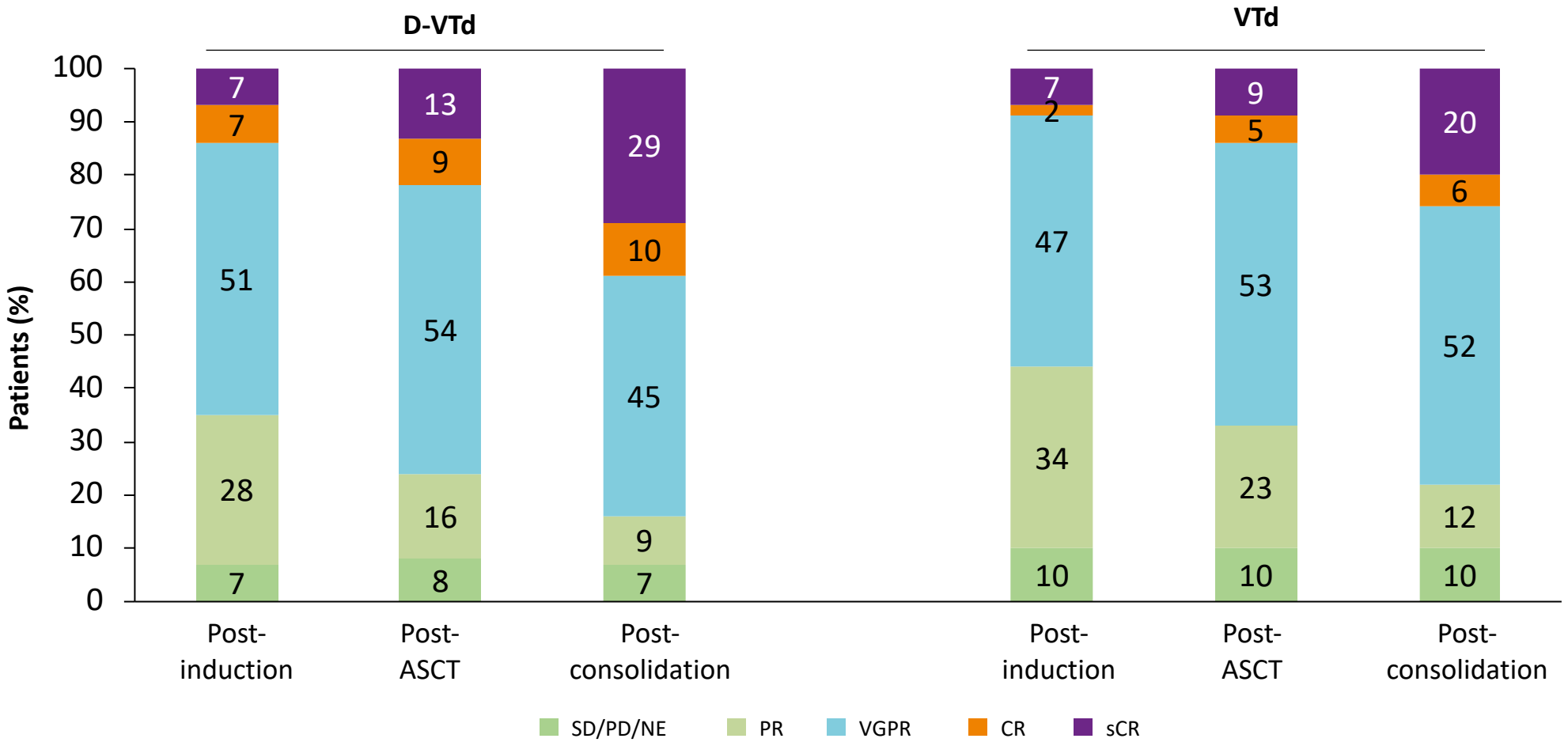


D-VTd superior across all subgroups including high-risk cytogenetics and ISS stage III

Moreau P et al. Proc ASCO 2019; Abstract 8003.

[a]Post-consolidation. [b]Additional MRD results will be presented during tomorrow's Poster Discussion session: Avet-Loiseau H, et al. ASCO 2019. Abstract 8017.
[c]Based on patients with available cytogenetics results. [d]Based on patients with available serum heavy chain disease type only.

CASSIOPEIA: Response Rates Over Time

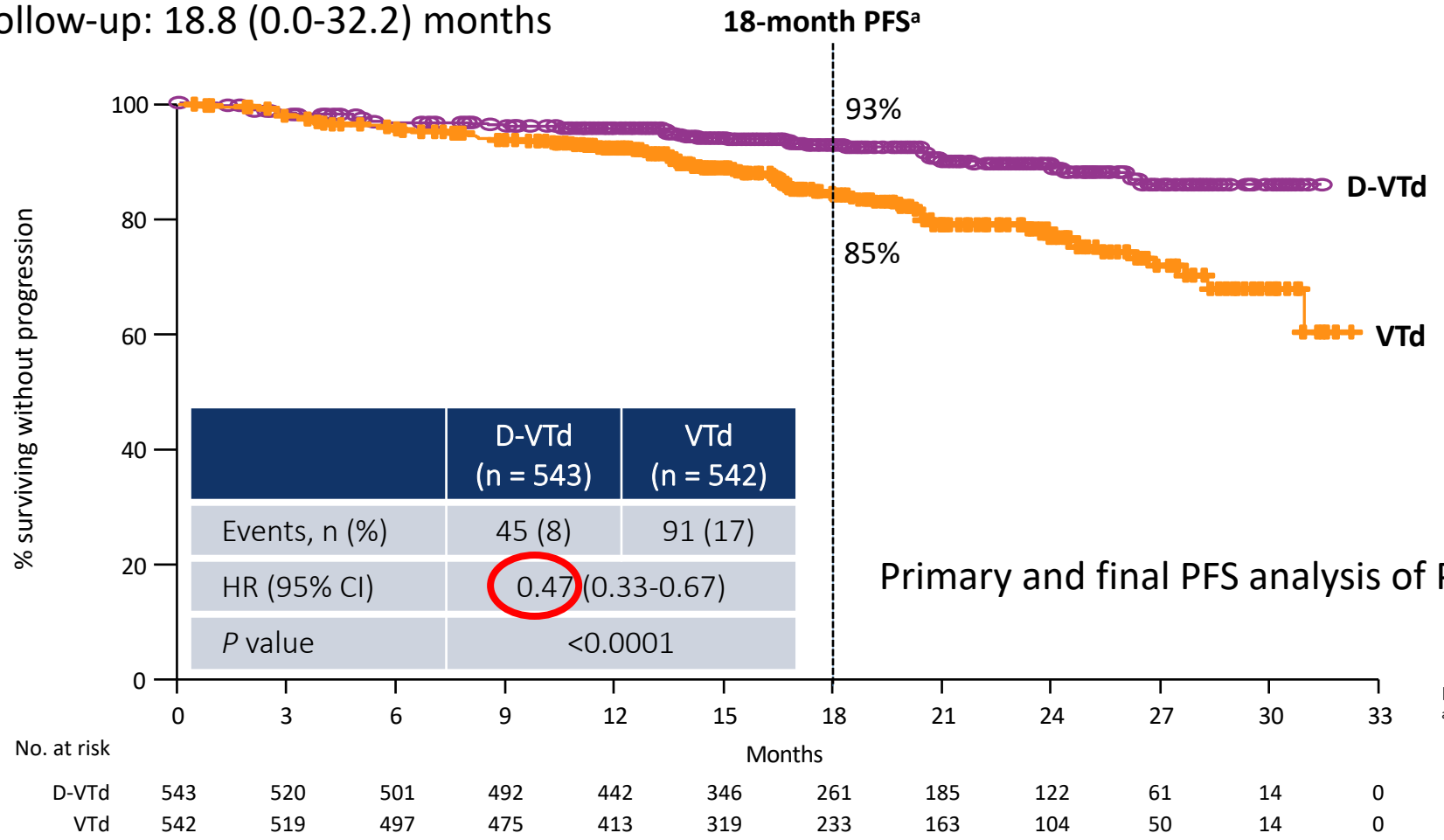


Responses deepened over time

Moreau P et al. Lancet 2019 Jul 6;394(10192):29-38. Moreau P et al. Proc ASCO 2019; Abstract 8003.

CASSIOPEIA: PFS From First Randomization

- Median (range) follow-up: 18.8 (0.0-32.2) months



	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	

Primary and final PFS analysis of Part 1

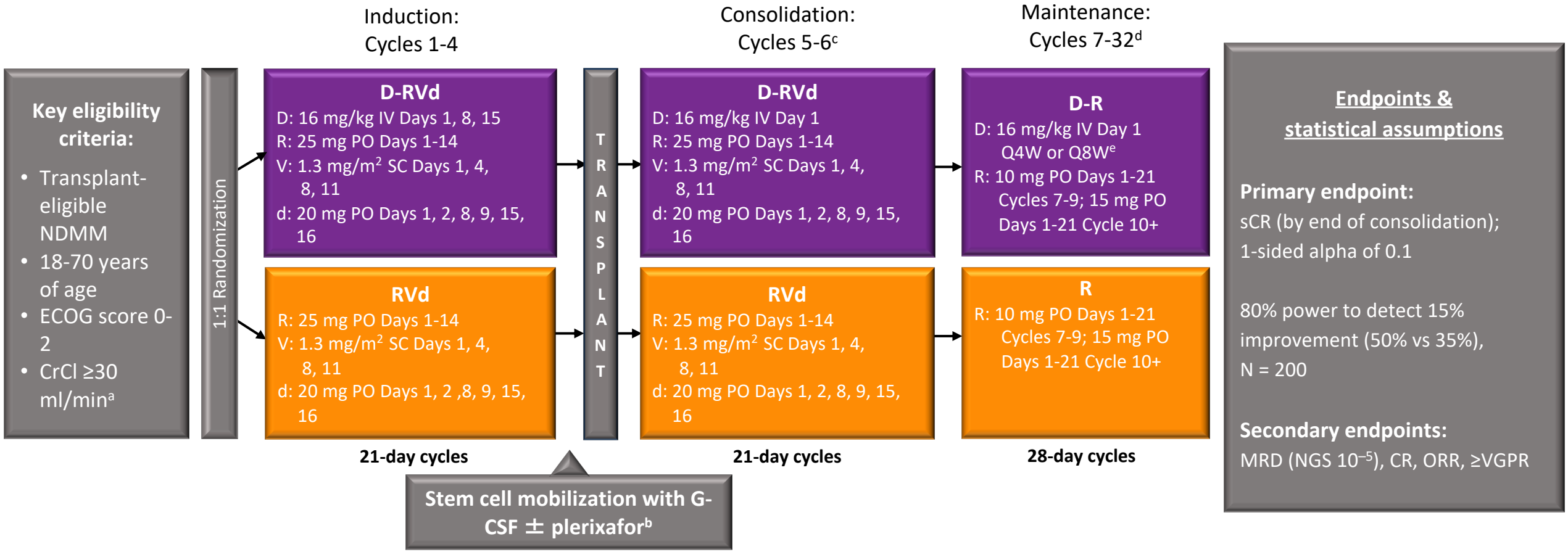
HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

53% reduction in the risk of progression or death in the D-VTd arm

Moreau P et al. Lancet 2019 Jul 6;394(10192):29-38. Moreau P et al. Proc ASCO 2019; Abstract 8003.

GRIFFIN (NCT02874742): Randomized Phase 2 study

- D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 to 4/2018

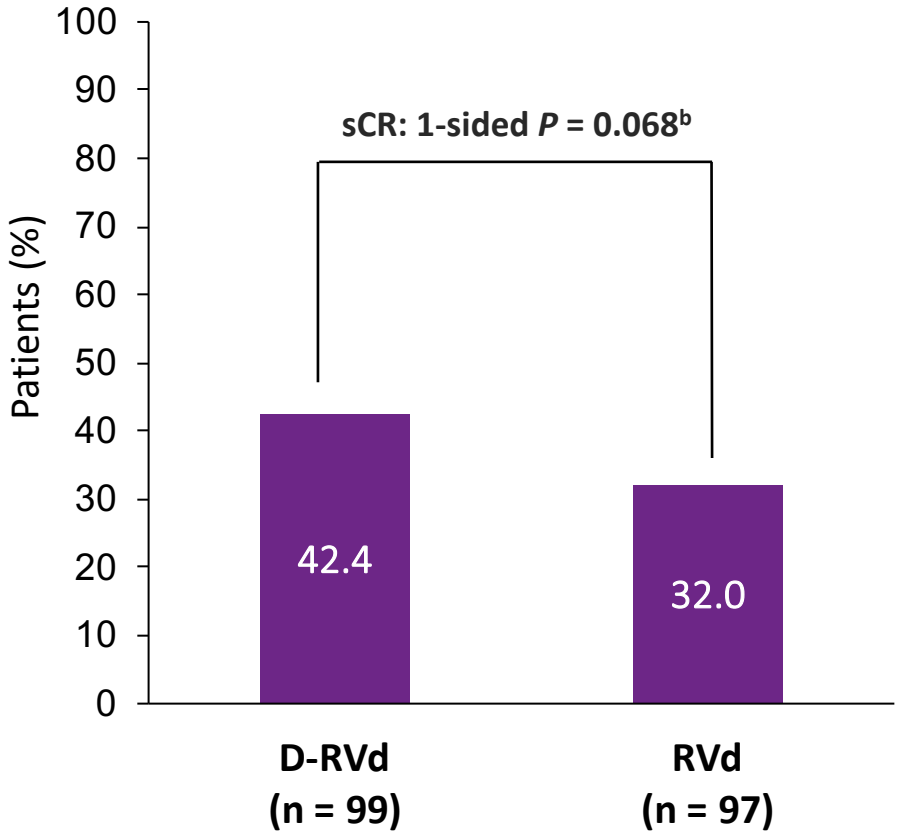


D-RVd, daratumumab-lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; US, United States; ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab-lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; CR, complete response; ORR, overall response rate; VGPR, very good partial response.

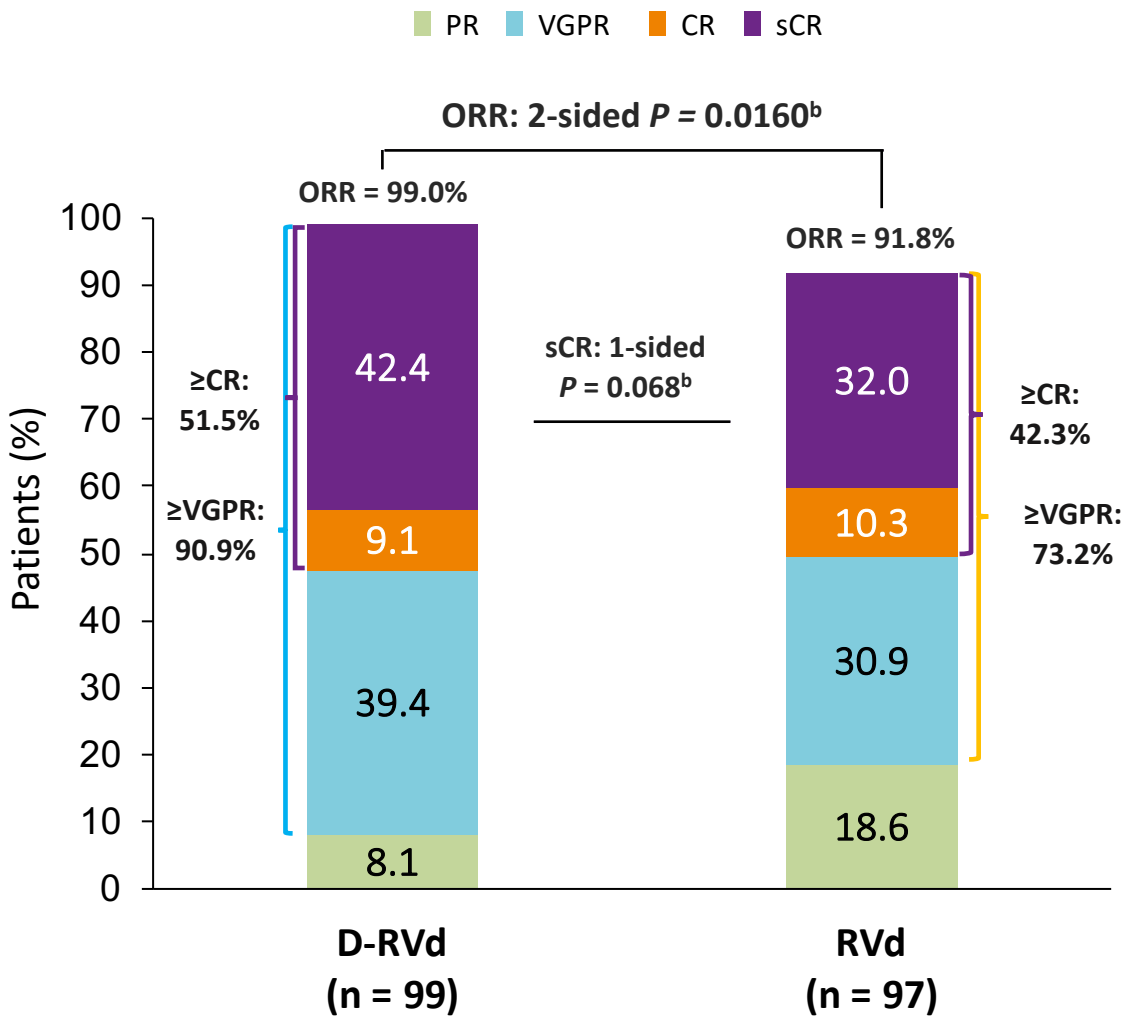
[a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60-100 days post transplant. [d]Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).

GRIFFIN Primary Endpoint: sCR by the End of Consolidation[a]

- **Primary endpoint met at pre-set 1-sided alpha of 0.1**
  - sCR by end of consolidation
    - 42.4% D-RVd vs 32.0% RVd
    - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = 0.068[b]



Post-consolidation depth of response[a]



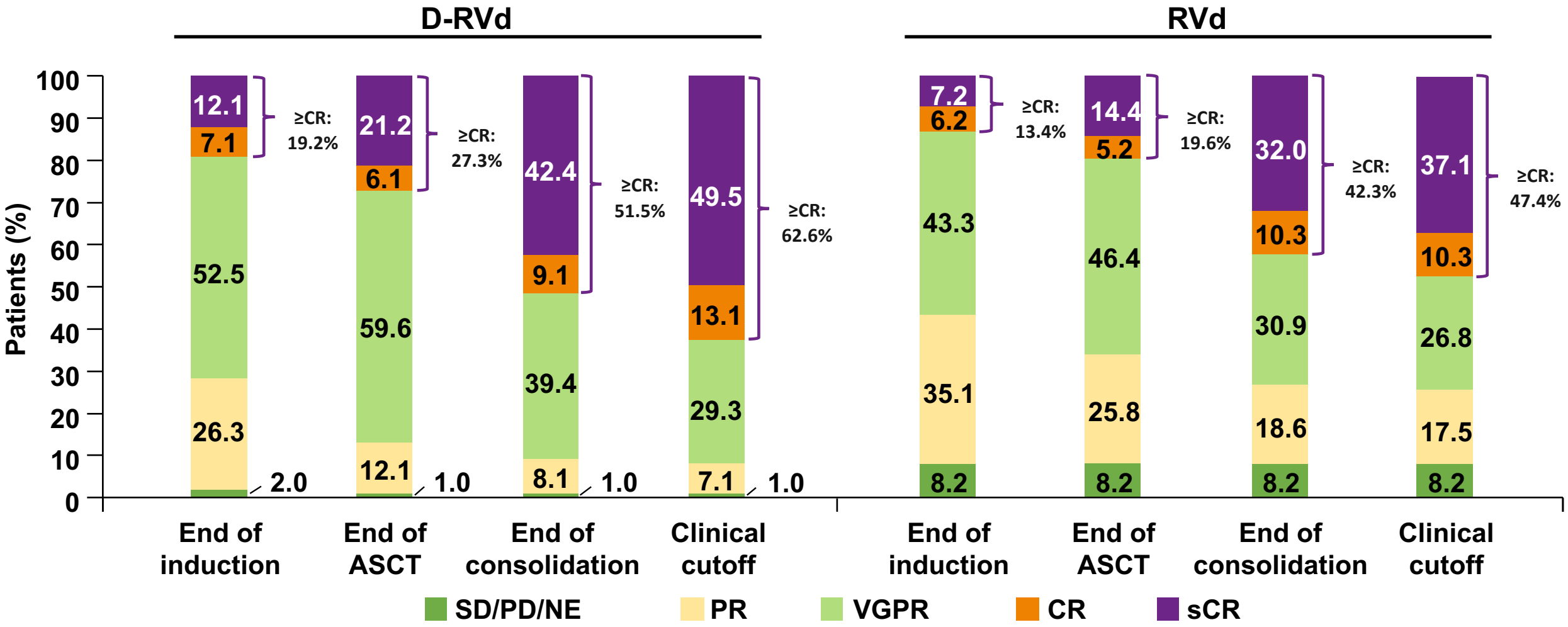
Voorhees P et al. Proc IMW 2019; Abstract 906.

PR, partial response.

[a]Included patients in the response-evaluable population (all randomized patients with a confirmed diagnoses of MM, measurable disease at baseline, received ≥1 dose of study treatment, and had ≥1 post-baseline disease assessment).

[b]*P* values were calculated with the use of the Cochran–Mantel–Haenszel chi-square test. A 1-sided *P* value is reported for sCR; for all other responses, 2-sided *P* values not adjusted for multiplicity are reported.

GRIFFIN: Responses Deepened Over Time



Response rates and depths were greater for D-RVd at all time points

SD, stable disease; PD, progressive disease; NE, not evaluable.

Voorhees P et al. Proc IMW 2019; Abstract 906.

GRIFFIN: Post-Consolidation MRD Negativity

MRD-Negative Status (10^{-5}),[a] n (%)	D-RVd	RVd	Odds Ratio (95% CI)	*P* value[b]
In ITT population				
MRD negative regardless of response	46/104 (**44.2**)	15/103 (**14.6**)	4.70 (2.38-9.28)	<0.0001
MRD negative with CR or better	30/104 (**28.8**)	10/103 (**9.7**)	3.73 (1.71-8.16)	0.0007
In patients achieving CR or better	30/51 (**58.8**)	10/41 (**24.4**)	4.65 (1.76-12.28)	0.0014
In patients who received ASCT	45/94 (**47.9**)	14/78 (**17.9**)	4.31 (2.10-8.85)	<0.0001

Voorhees P et al. Proc IMW 2019; Abstract 906.

D-RVd improved MRD-negativity (10^{-5}) rates at the end of consolidation

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on assessment of bone marrow aspirates by next-generation sequencing in accordance with International Myeloma Working Group criteria. MRD assessments occurred in patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken (D-RVd, n = 71; RVd, n = 55). Patients with a missing or inconclusive assessment were considered MRD positive. [b]*P* values were calculated from the Fisher's exact test.

Ongoing Phase III Studies of Daratumumab Combined with VRd Induction Therapy

- ***PERSEUS*** (NCT03710603): D-VRd vs VRd in Subjects With Previously Untreated Multiple Myeloma Who Are Eligible for High-dose Therapy (Target N = 690)
- ***CEPHEUS*** (NCT03652064): D-VRd vs VRd in Subjects With Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy (Target N = 395)

Clinicaltrials.gov, Accessed December 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

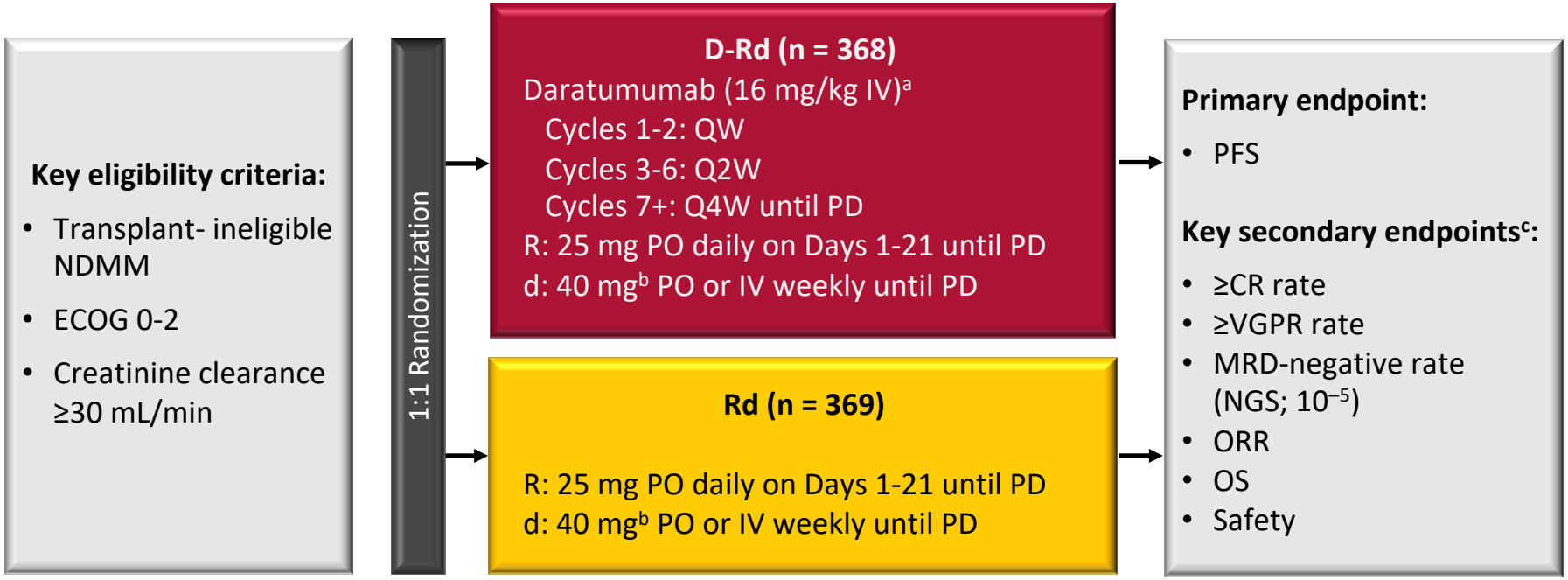
Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma

T. Facon, S. Kumar, T. Plesner, R.Z. Orlowski, P. Moreau, N. Bahlis, S. Basu, H. Nahi, C. Hulin, H. Quach, H. Goldschmidt, M. O'Dwyer, A. Perrot, C.P. Venner, K. Weisel, J.R. Mace, N. Raje, M. Attal, M. Tiab, M. Macro, L. Frenzel, X. Leleu, T. Ahmadi, C. Chiu, J. Wang, R. Van Rampelbergh, C.M. Uhlar, R. Kobos, M. Qi, and S.Z. Usmani, for the MAIA Trial Investigators*

N Engl J Med 2019;380:2104-15

MAIA Study Design

- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)



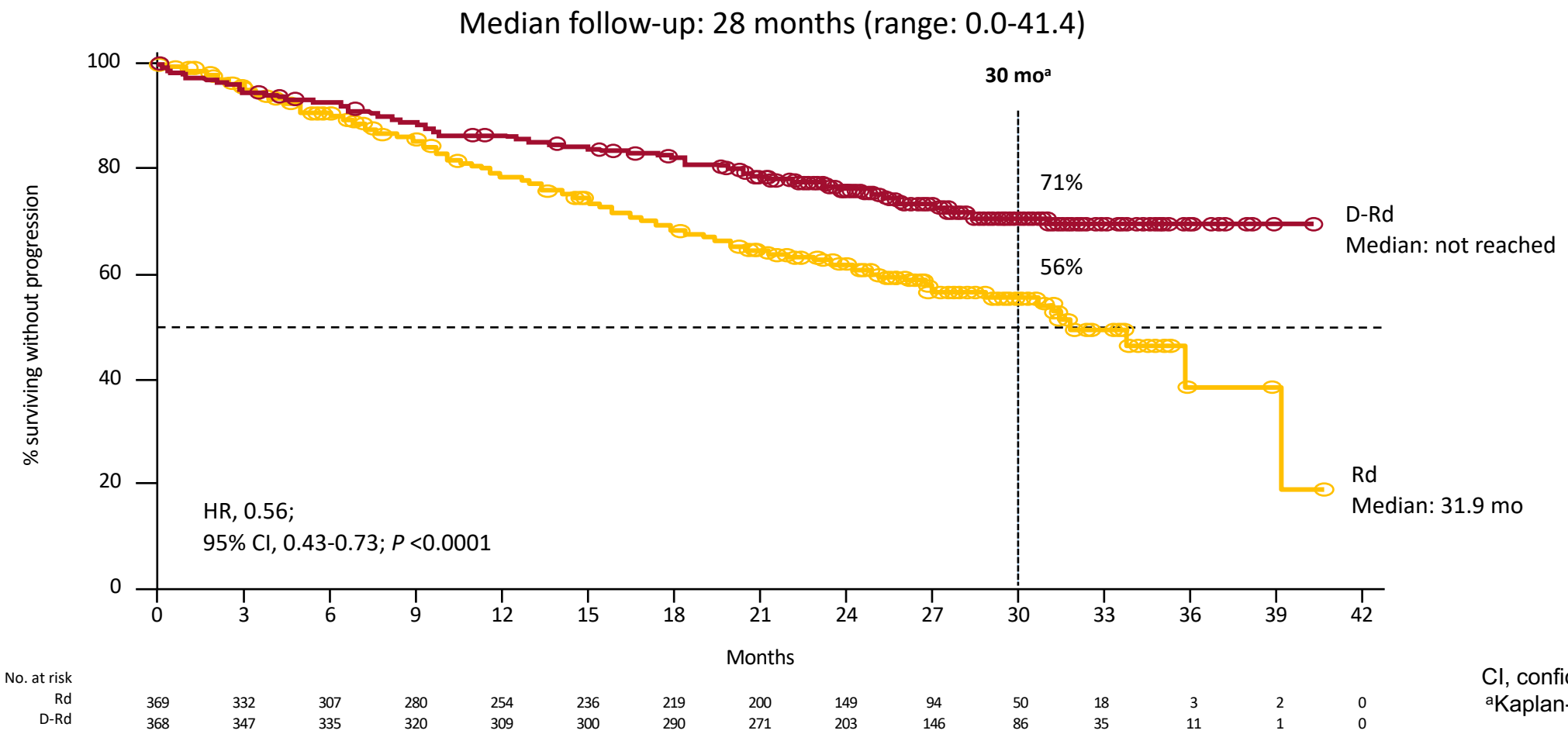
Stratification factors
- ISS (I vs II vs III)
- Region (NA vs other)
- Age (<75 vs ≥75 years)

Cycle: 28 days

[a]On days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.
[b]For patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.
[c]Efficacy endpoints were sequentially tested in the order shown.

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; NA, North America; IV, intravenously; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, orally; CR, complete response; VGPR, very good partial response; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; BMI, body mass index.

MAIA Primary Endpoint: PFS

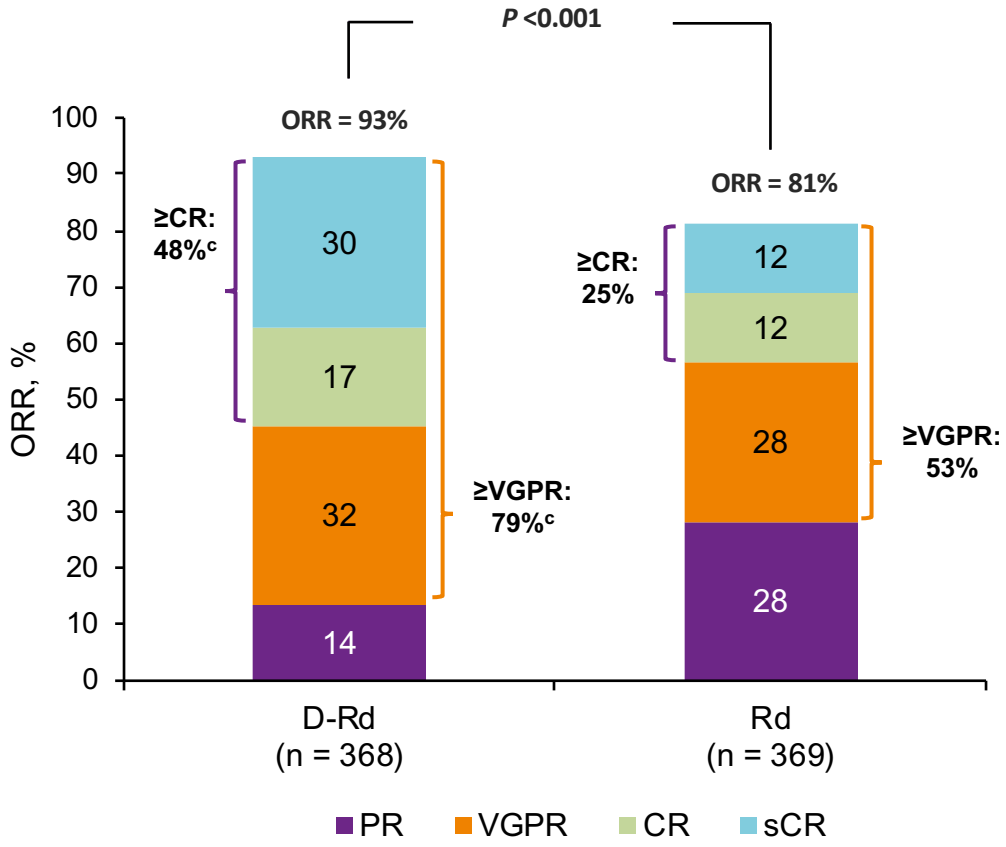


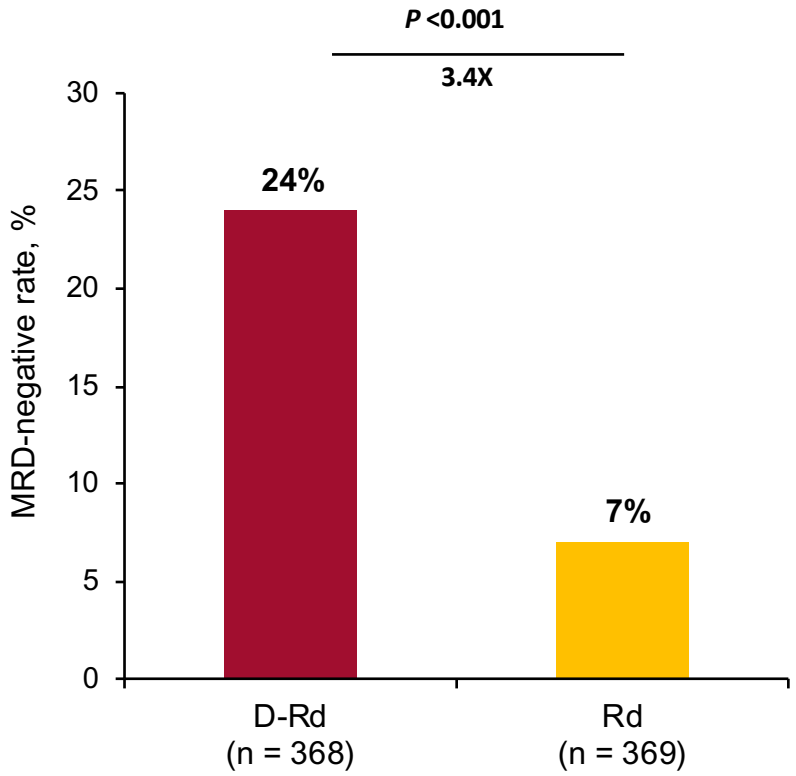
CI, confidence interval.
[a]Kaplan-Meier estimate.

44% reduction in the risk of progression or death in patients receiving D-Rd

Facon T et al. N Engl J Med 2019;380:2104-15.

MAIA: ORR[a] and MRD[b] (NGS; 10^{-5} Sensitivity Threshold)





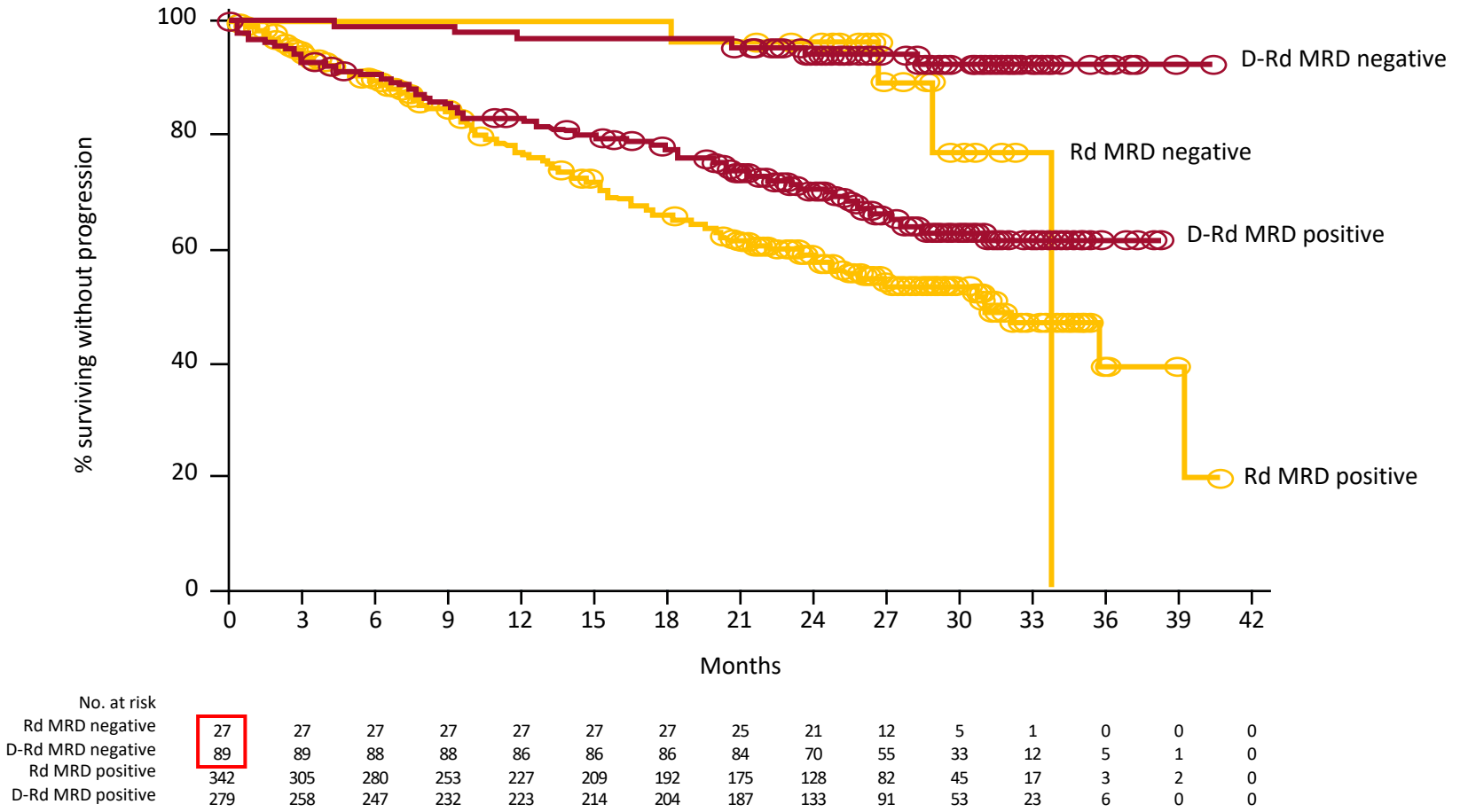
Significantly higher ORR, ≥CR rate, ≥VGPR rate, and MRD-negative rate with D-Rd

PR, partial response; sCR, stringent complete response.

[a]ITT population. [b]Assessed at time of suspected CR/sCR; and if confirmed, at 12, 18, 24, and 30 months after first dose. [c]*P* <0.0001; *P* values were calculated using the Cochran–Mantel–Haenszel chi-square test.

Facon T et al. N Engl J Med 2019;380:2104-15.

MAIA: PFS by MRD Status



- **>3-fold higher MRD negativity achieved with D-Rd**
- **Lower risk of progression or death with MRD negativity**

Facon T et al. N Engl J Med 2019;380:2104-15.