Update In Myeloma: Diagnosis, staging and Initial Treatment

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Updated IMWG Criteria for Diagnosis of Multiple Myeloma

MGUS

- M-protein < 3 g/dL
- Clonal plasma cells in BM < 10%
- No myeloma defining events

Smoldering Myeloma

- M-protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
- Clonal plasma cells in BM ≥ 10% - 60%
- No myeloma defining events

Multiple Myeloma

- Underlying plasma cell proliferative disorder

AND

- 1 or more myeloma defining events including either:

✓≥ 1 **CRAB** feature(s)

OR

✓≥ 1 **Biomarker Driven**

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

Biomarker driven **(1)** Sixty-percent (≥60%) clonal PCs by BM; **(2)** serum free Light chain ratio involved:uninvolved ≥100; **(3)** >1 focal lesion detected by MRI

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Rajkumar SV, et al. *Lancet Oncol*. 2014;15:e538-e548.

Revised ISS staging

Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

Palumbo et al, *JCO* 2015

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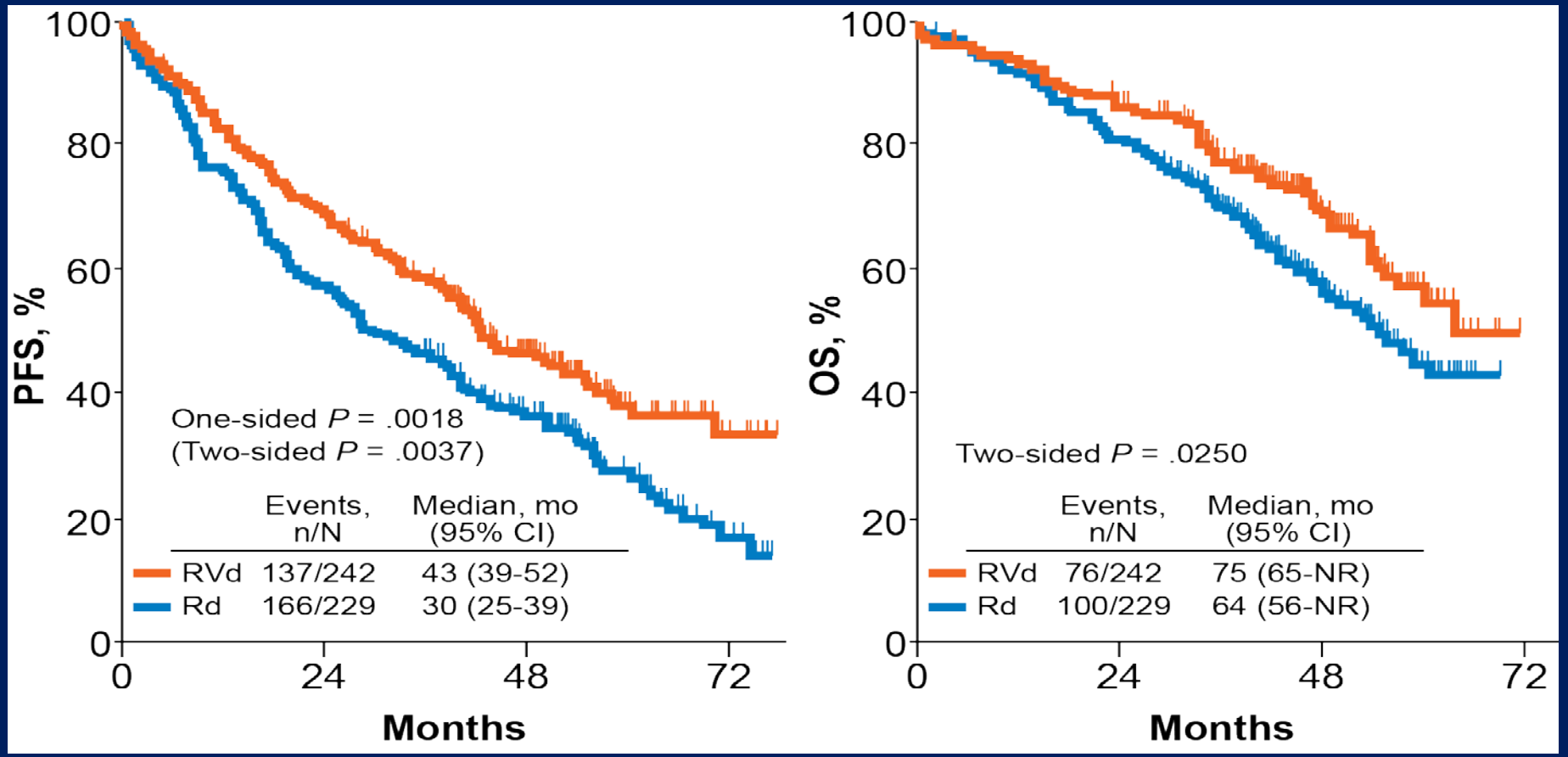
What Is the Current State of the Art?

- Induction for younger patients
  - 3-drug induction followed by auto-transplant in first response
  - Maximize response post-transplant?
  - Maintenance therapy after auto-transplant
  - Intensified maintenance in high risk?
  - Goals of treatment now include trying to achieve MRD negativity

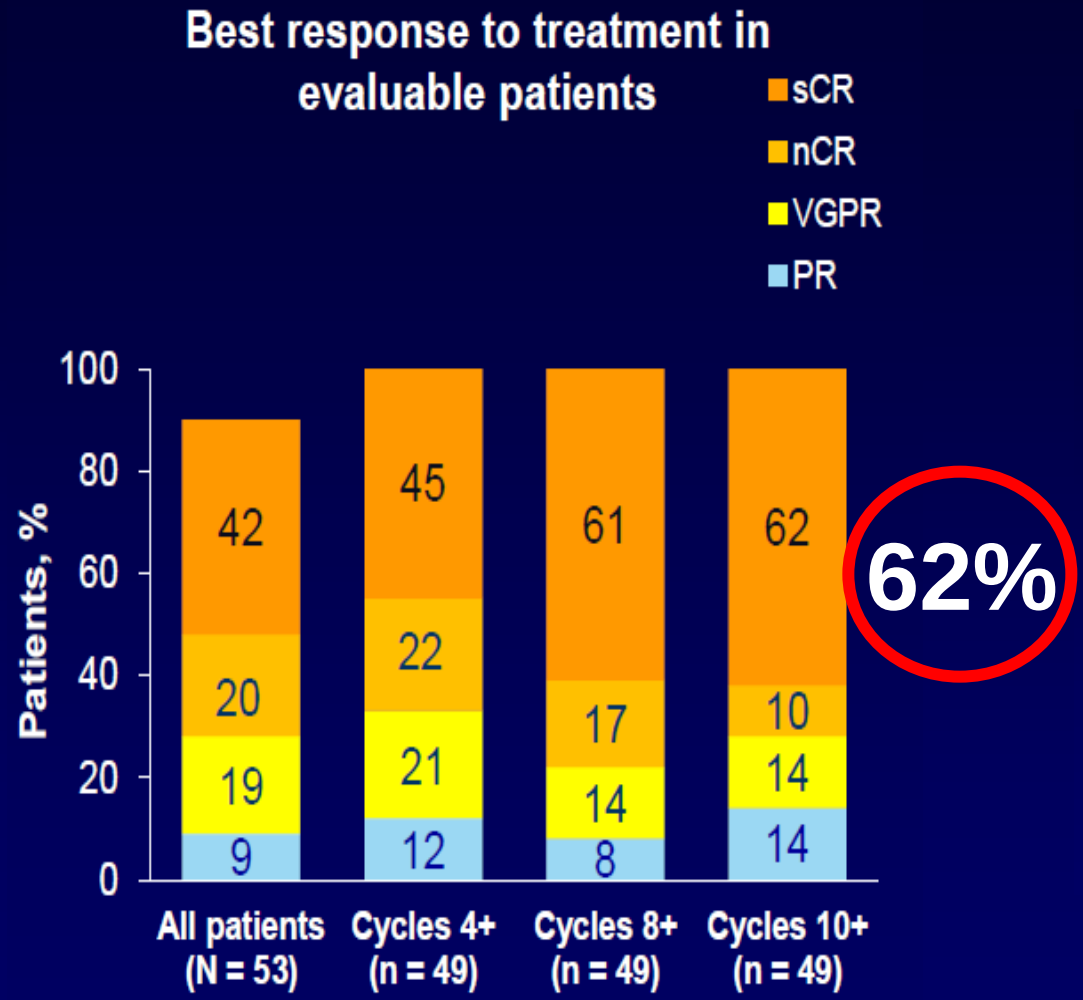
SWOG S0777 (N = 525): RVd Versus Rd[1]

- **Initial therapy:** RVd for eight 21-day cycles vs Rd for six 28-day cycles in patients not intending to proceed to transplant, followed by Rd in both arms

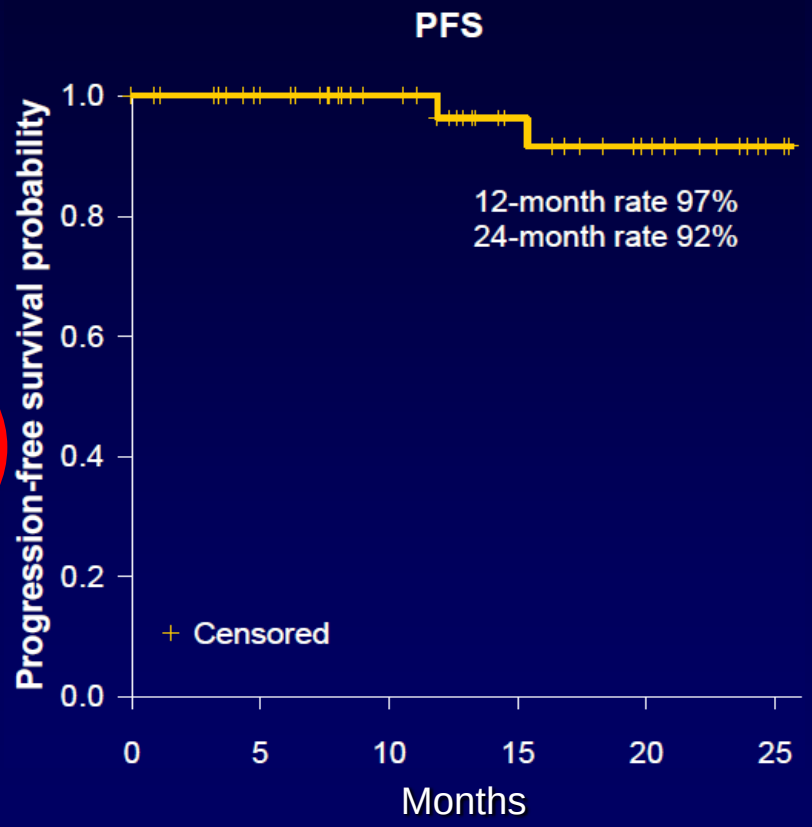


1. Durie B et al. *Lancet*. 2017;389:519-527.

Phase I/II KRd in Newly Diagnosed MM

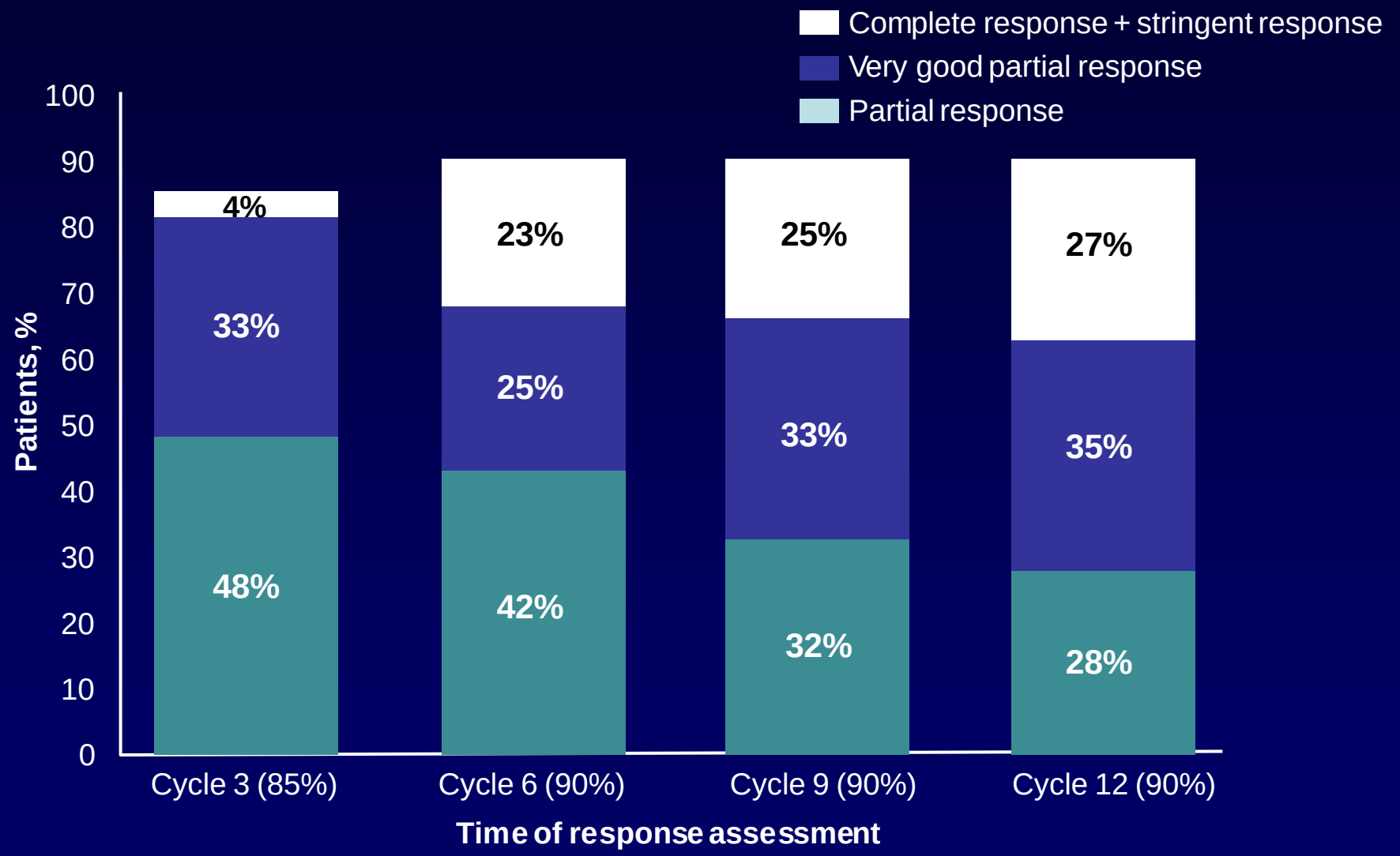


62%



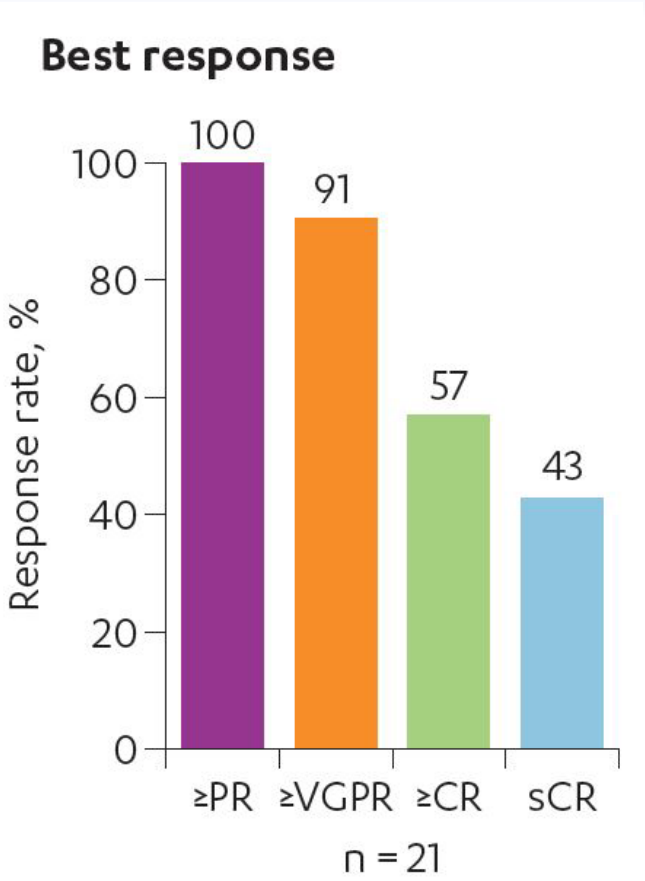
Jakubowiak AJ, et al. *Blood*. 2012;120:1801-1809.

Ixazomib, Lenalidomide, and Dexamethasone in Newly Diagnosed MM[1]



1. Kumar SK, et al. *Lancet Oncol*. 2014;15:1503-1512.

KRD-Dara ORR[a,b]

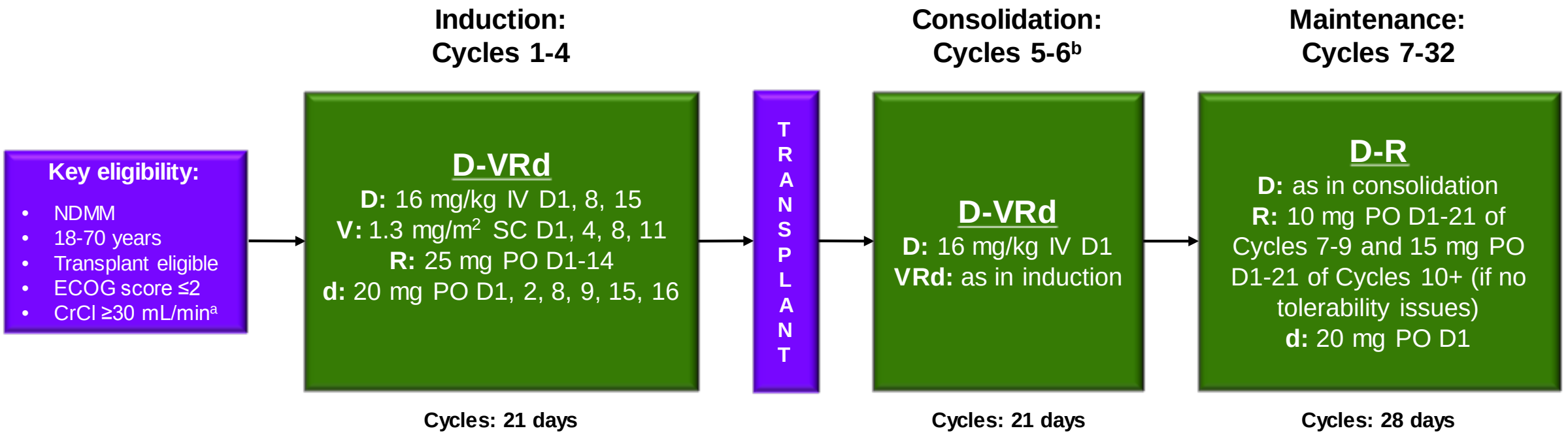


ORR, overall response rate; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response.
[a]Response-evaluable population.
[b]ORR includes all responses ≥PR.

- After a median follow-up of 16 months, the ORR was 100%, including 57% ≥CR and 91% ≥VGPR (**Figure**)

Chari et al, ASH 2017

GRIFFIN: Safety Run-in Phase (N = 16)



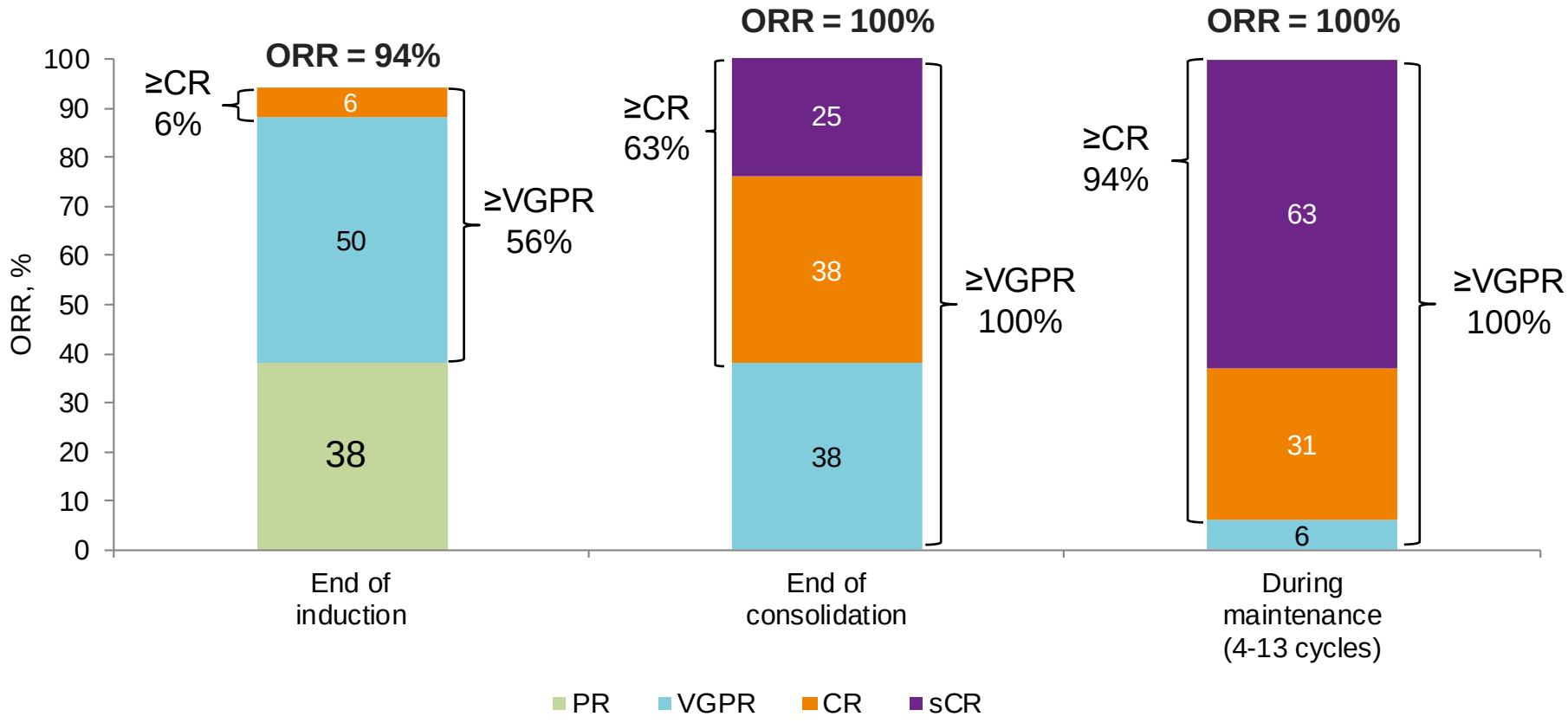
- Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter

Safety run-in phase in 16 patients to assess dose-limiting toxicities during 1 Cycle of D-VRd

ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; D, daratumumab; IV, intravenously; D, day; V, bortezomib; SC, subcutaneously; PO, orally; d, dexamethasone; D-R, daratumumab/lenalidomide; R, lenalidomide.

Efficacy: Investigator-assessed Response Rate

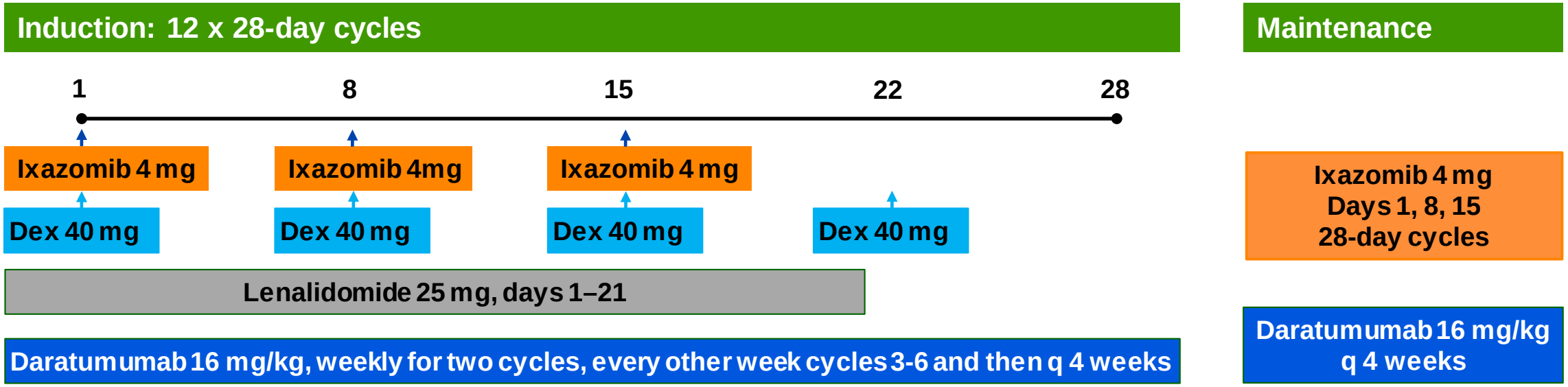
- Median (range) follow-up: 16.8 (15.9-18.7) months



Responses continued to deepen over time

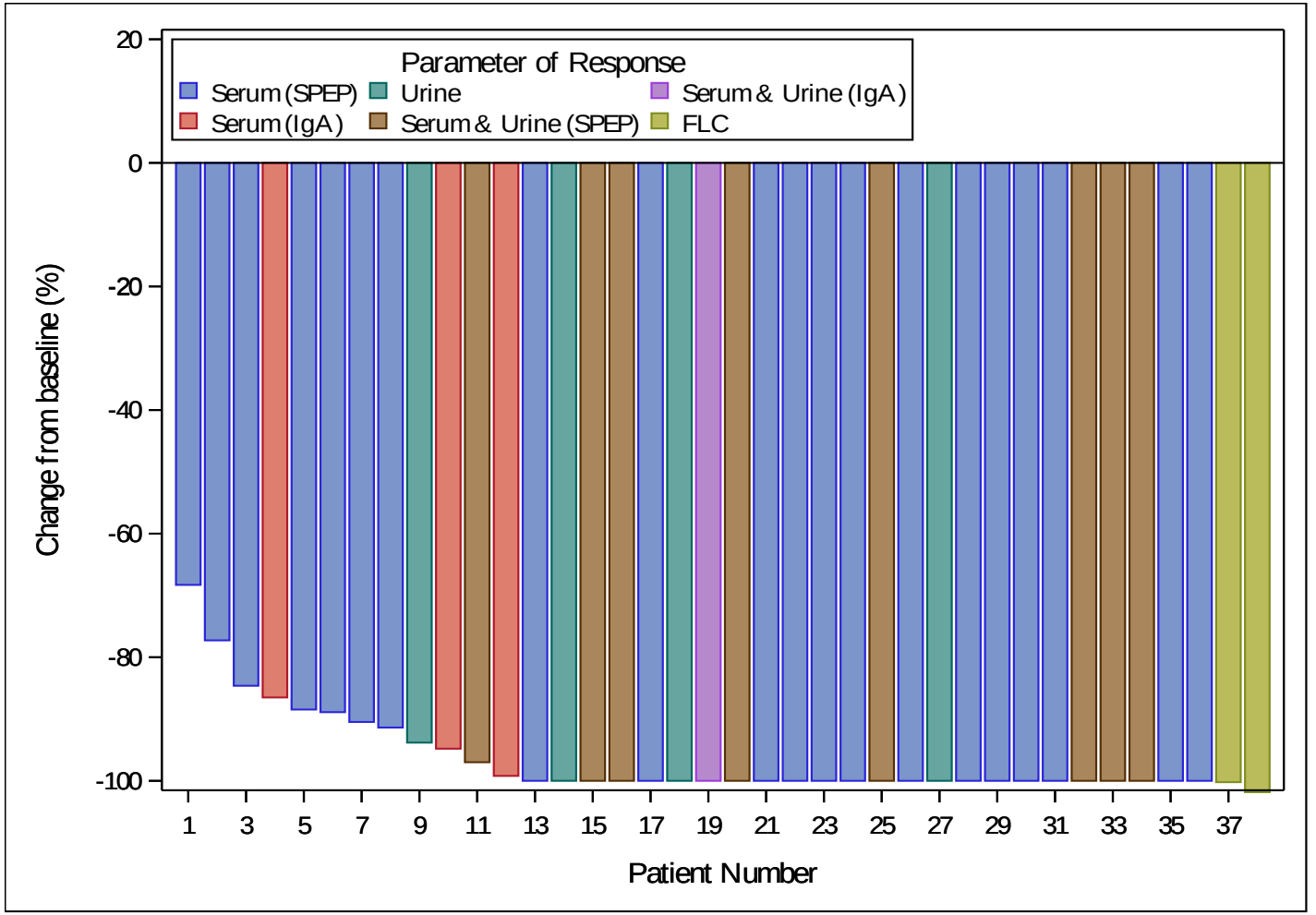
ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response

IRD-Dara Treatment schedule



- Standard infectious disease, bone, and thrombosis prophylaxis
- Treatment till progression or unacceptable toxicity or to a maximum of 3 years
- Stem cells could be collected after 4 cycles if SCT eligible

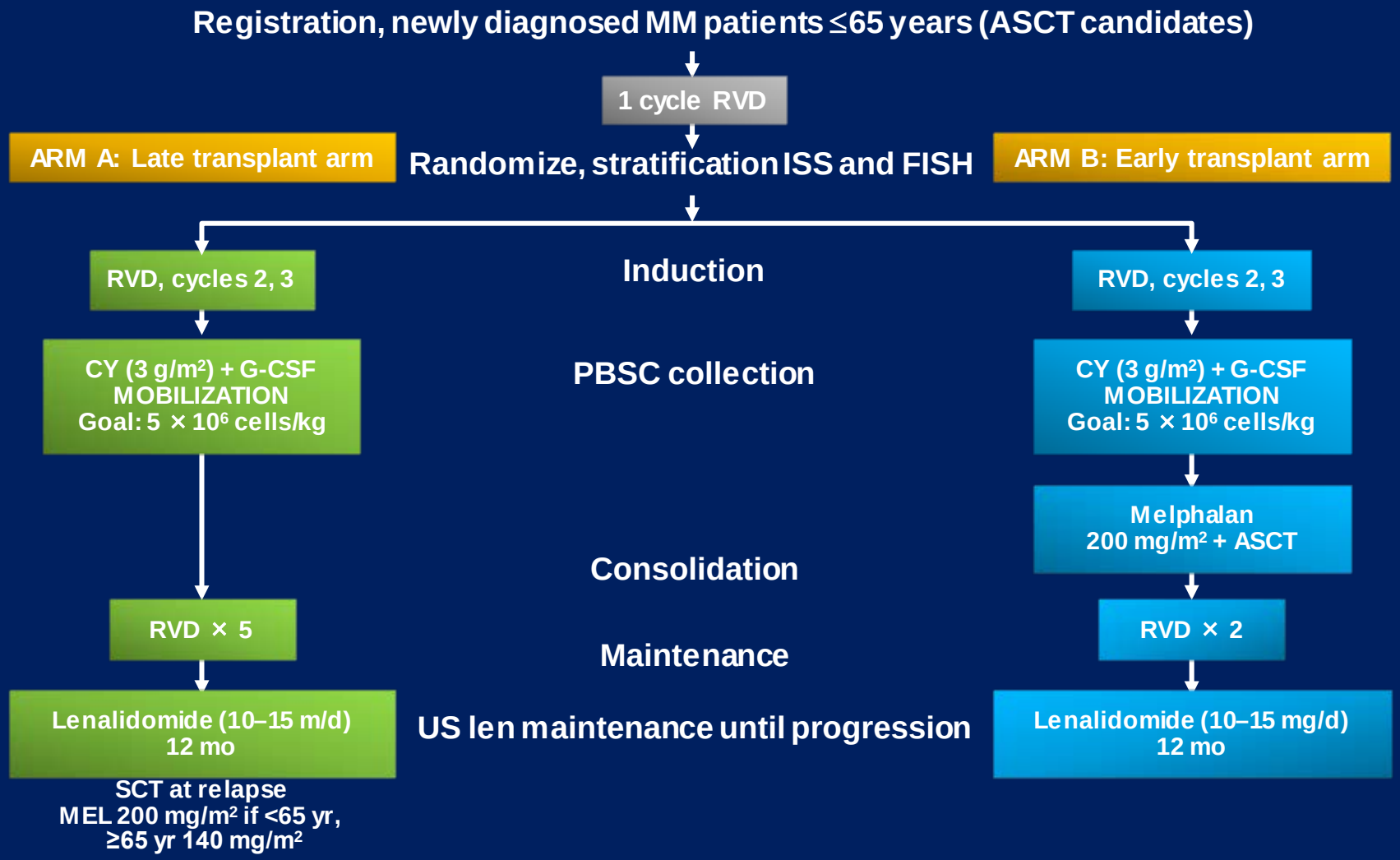
IRD-Dara Depth of response



Aggressive Induction

- PI/IMID is standard
- Role of MOAB is emerging for newly diagnosed MM
- Choice of PI remains unclear, and may vary based on co-morbid illness or ability to tolerate side effects
- Additional data on role of MOAB in younger patients in progress
- What remains the role of HDT?

Role of Transplant in 2019



Attal M, et al. *Blood*. 2015;126: abstract 391.

IFM 2009: Response Increase

	RVD Arm N = 350	Transplant Arm N = 350	*P* Value
Post-induction, %	47	50	NS
Post-transplant or at C4, %	55	73	<.0001
Post-consolidation, %	71	81	<.006
Post-maintenance, %	78	88	<.001

Attal M, et al. *Blood*. 2015;126: abstract 391.

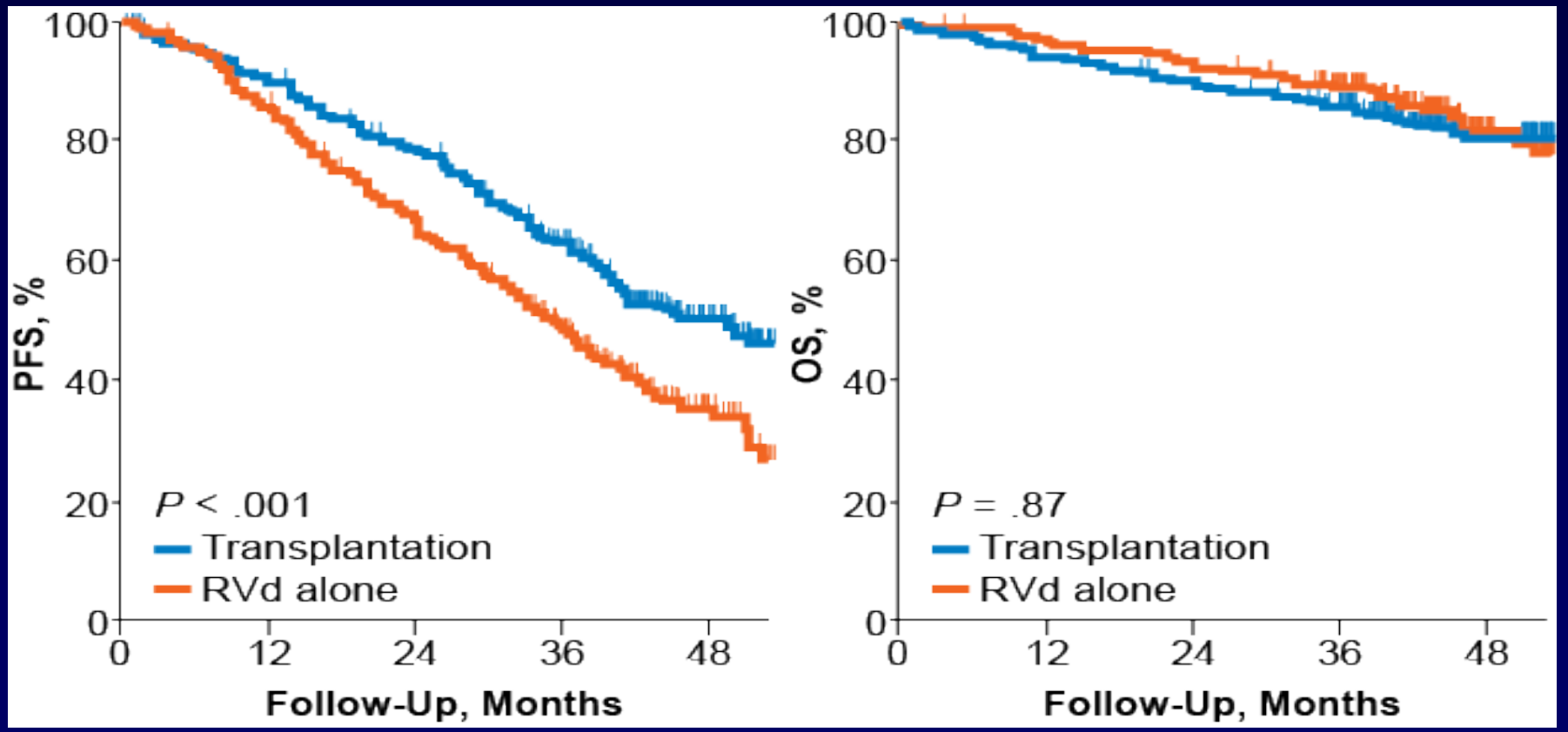
IFM2009: RVd Alone Vs RVd + ASCT[1]

RVd 1

RVd 2-3 → PBSC collection → RVd 4-8

RVd 2-3 → PBSC collection → ASCT → RVd 4-5

Lenalidomide
12 mo



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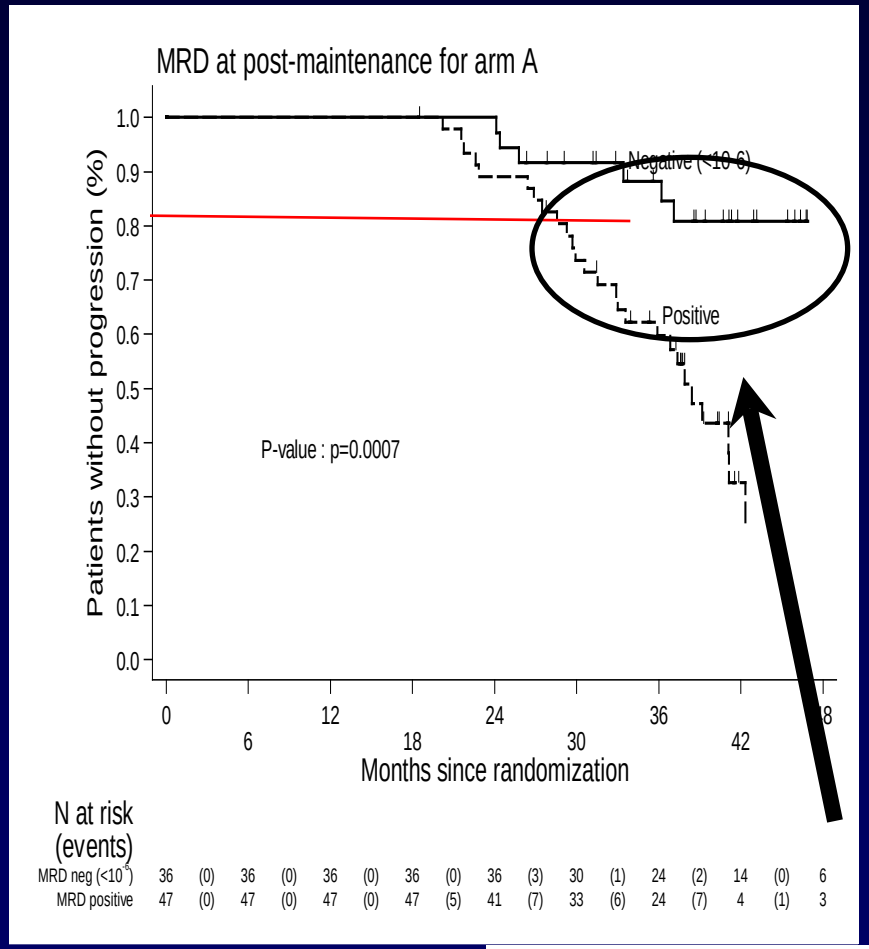
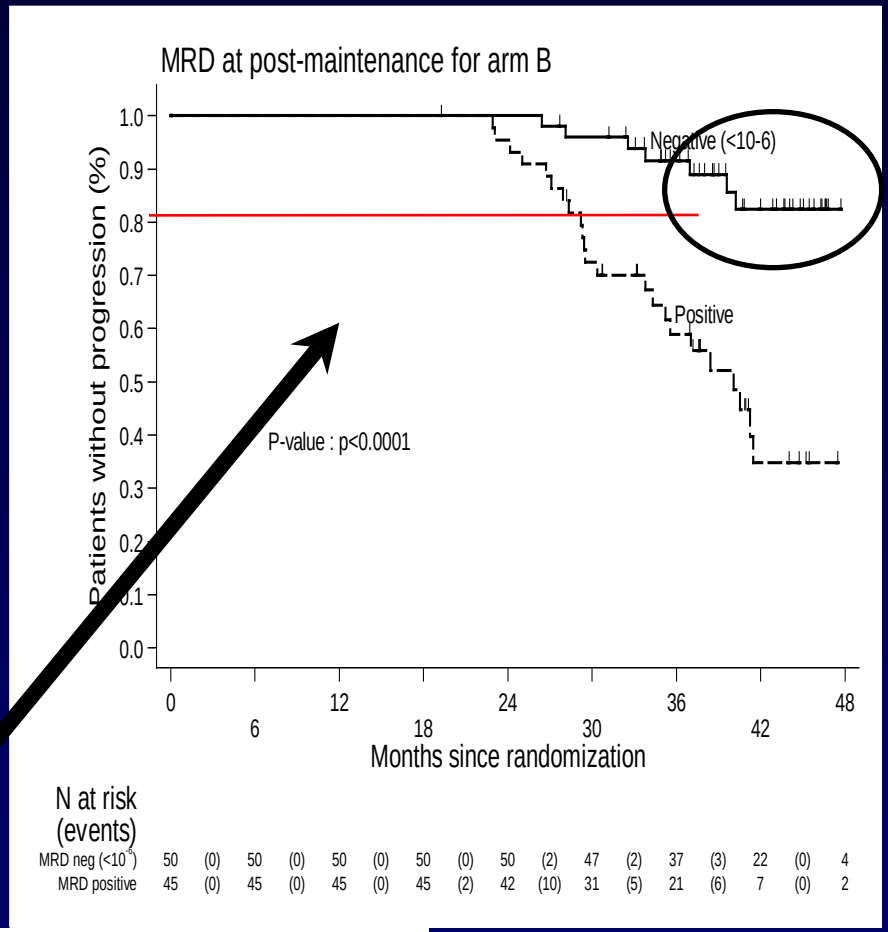
1. Attal M et al. *N Engl J Med*. 2017;376:1311-1320.

Depth of response is more important than how you got there, but odds are better if you Transplant





Same depth of response resulted in same outcome regardless of treatment arm

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Carfilzomib-Lenalidomide-Dexamethasone (KRd) Induction-Autologous Transplant (ASCT)-KRd Consolidation vs KRd 12 Cycles vs Carfilzomib-Cyclophosphamide-Dexamethasone (KCd) Induction-ASCT-KCd consolidation: Analysis of the Randomized FORTE Trial in Newly Diagnosed Multiple Myeloma (NDMM)

Francesca Gay[1], Chiara Cerrato[1], Delia Rota Scalabrini[1], Monica Galli[1], Angelo Belotti[1], Elena Zamagni[1], Antonio Ledda[1], Mariella Grasso[1], Emanuele Angelucci[1], Anna Marina Liberati[1], Patrizia Tosi[1], Francesco Pisani[1], Stefano Spada[1], Ombretta Annibali[1], Anna Baraldi[1], Paola Omedé[1], Piero Galieni[1], Rita Rizzi[1], Norbert Pescosta[1], Sonia Ronconi[1], Donatella Vincelli[1], Anna Maria Cafro[1], Massimo Offidani[1], Antonio Palumbo[2], Pellegrino Musto[1], Michele Cavo[1], Mario Boccadoro[1].

1 GIMEMA / European Myeloma Network, Italy; 2 University of Torino - Currently Takeda Pharmaceuticals Co.

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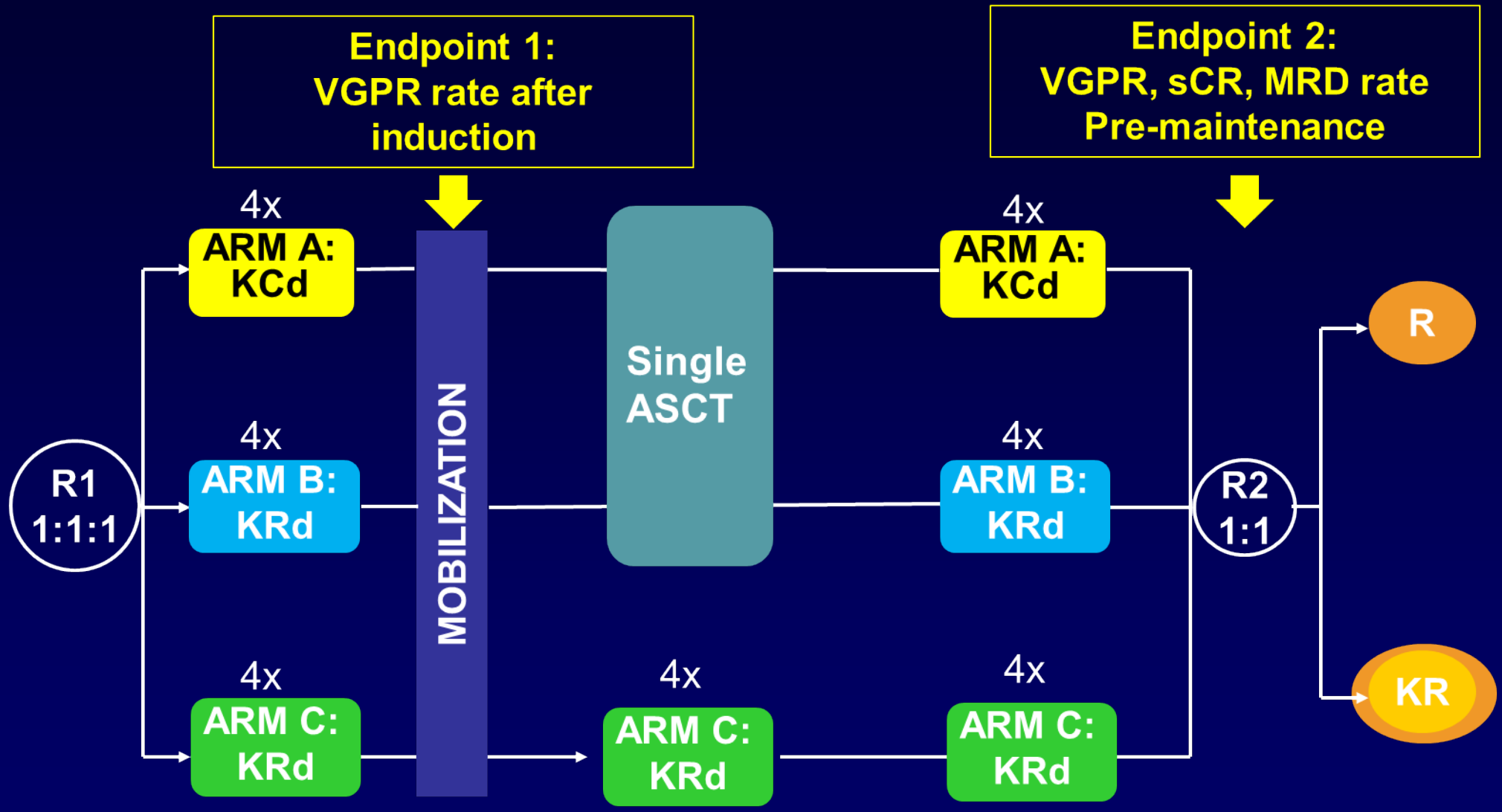
Trial Design

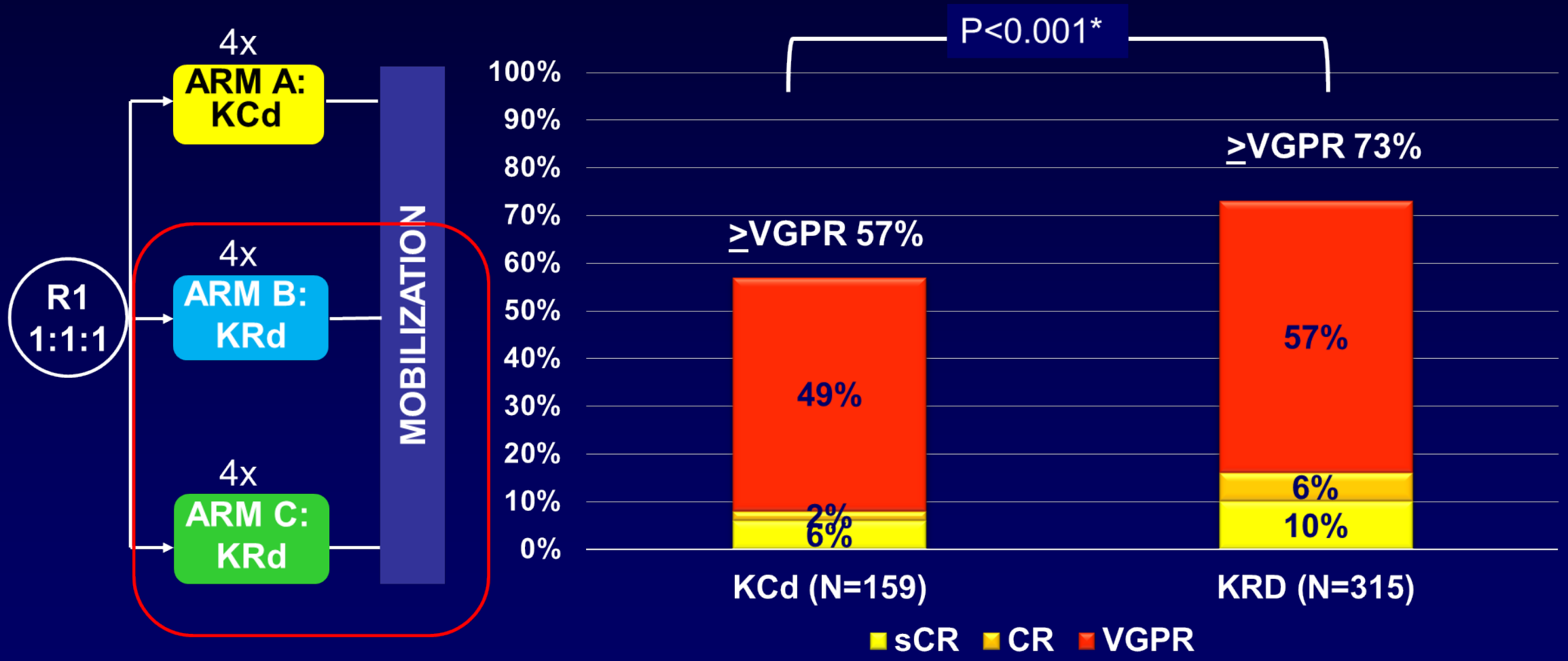
- NDMM patients, transplant eligible and younger than 65 years



R1: randomization1; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; ASCT: Autologous Stem Cell Transplant; R2: randomization2; R: Lenalidomide; KR: Carfilzomib, Lenalidomide. NDMM, newly diagnosed multiple myeloma; ; VGPR: very good partial response; sCR, stringent complete response; MRD, minimal residual disease.

Induction Phase

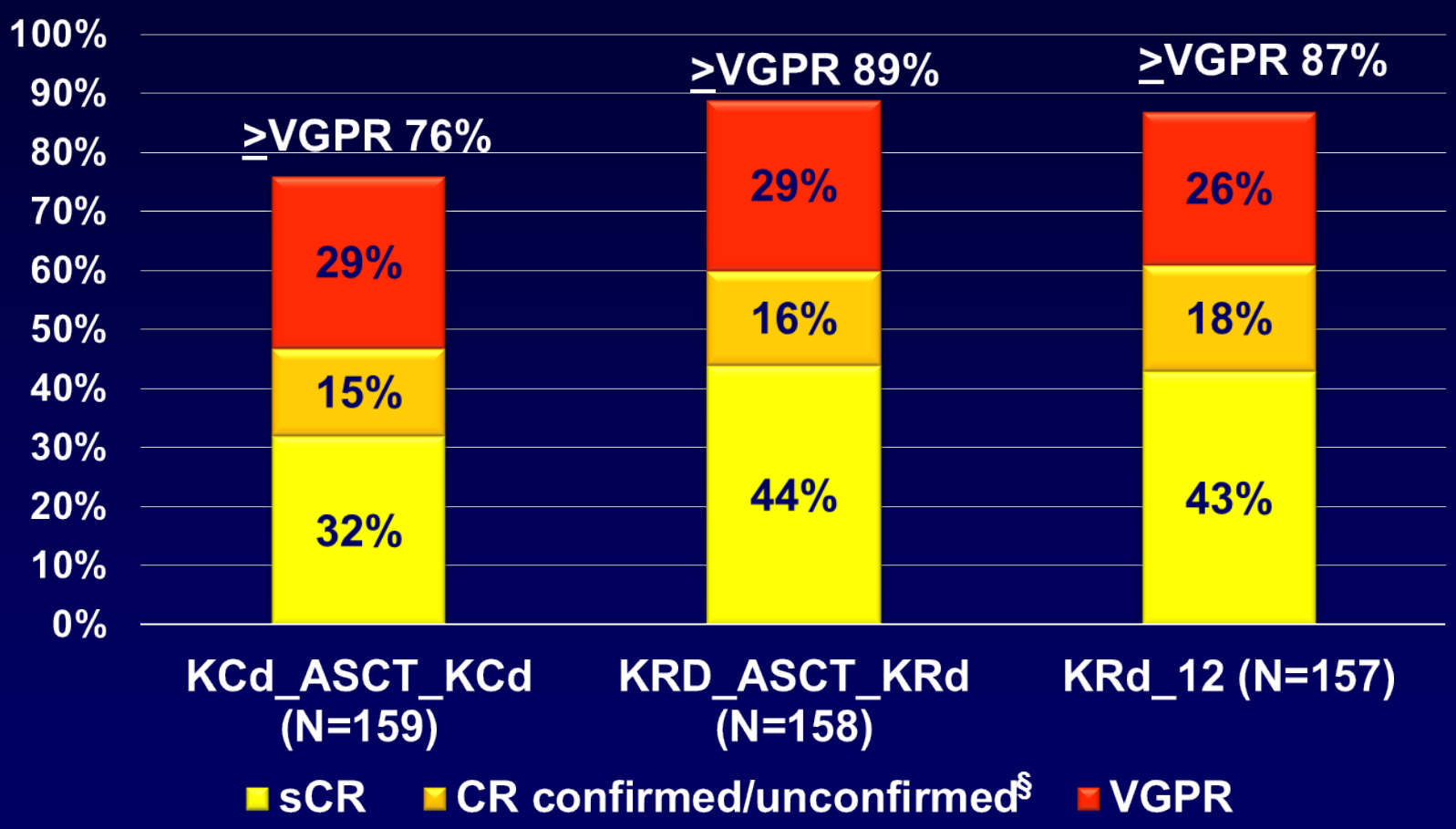
Endpoint 1: VGPR rate with KRd vs KCd induction
ITT analysis



R1: randomization1; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; *adjusted for International Staging System Stage, FISH analysis and age

Response Rate pre-maintenance

ITT analysis

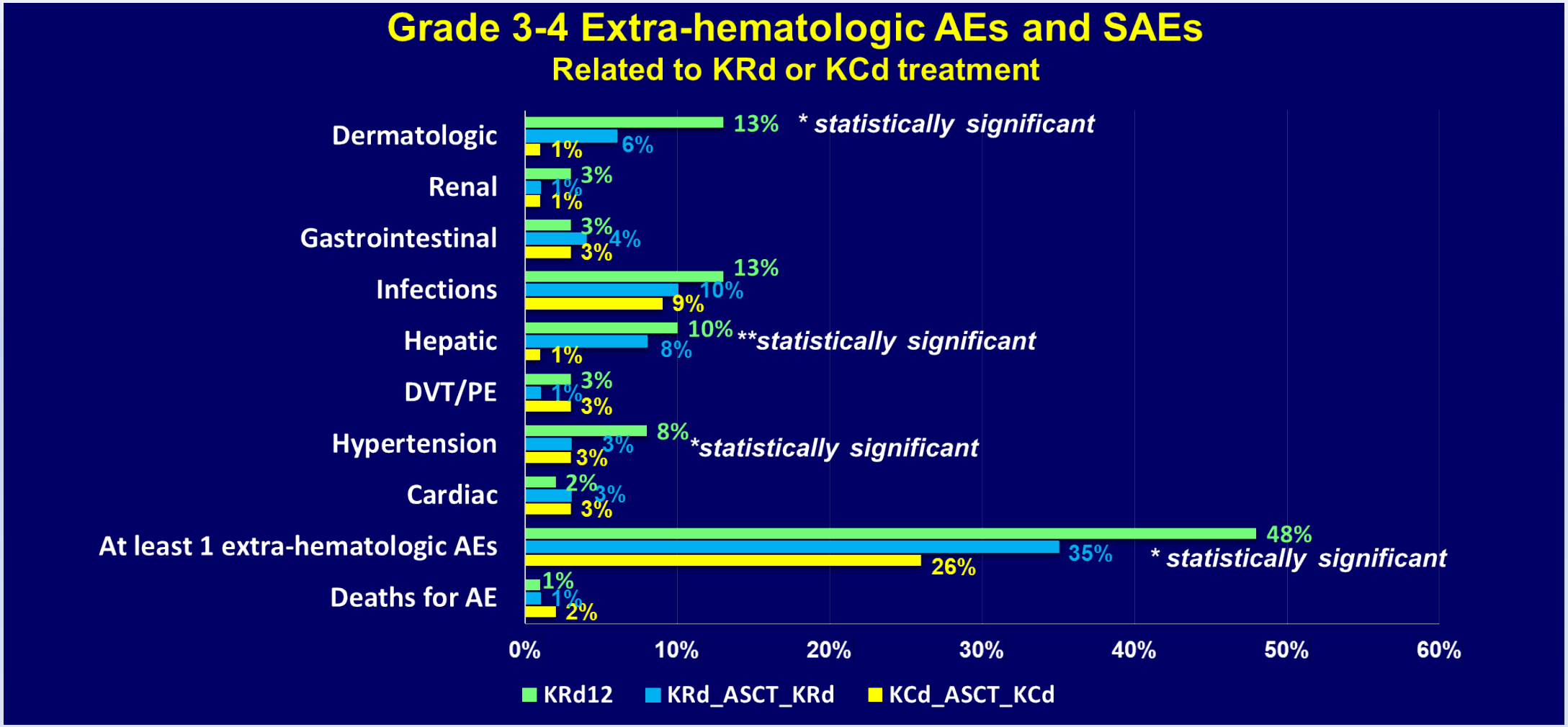


	OR	P value*
≥VGPR		
KRd-ASCT-KRd vs KCd-ASCT-KCd	2.53	0.004
KRd12 vs KCd-ASCT-KCd	2.11	0.015

§Unconfirmed CR/sCR: patients missing immunofixation/sFLC analysis needed to confirm CR/sCR (6% in KCd_ASCT_KCd; 8% in KRd_ASCT_KRd; 6% KRd_12)

KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; ASCT, Autologous Stem Cell Trasplant; sCR: stringent Complete Response; CR: Complete Response; VGPR: Very Good Partial Response; ITT: intention to treat; OR: Odds Ratio; * Adjusted for ISS, Age, FISH, LDH.

Safety



****P**-value for comparison KRd_ASCT_KRd vs KCd_ASCT_KCd and *P*-value for comparison KRd12 vs KCd_ASCT_KCd<.05; **P* value for comparison KRd12 vs KCd_ASCT_KCd<.05.

AE, adverse events; DVT, deep vein thrombosis; PE, pulmonary embolism; SAEs, serious AE

Gay F, et al. *Blood.* 2018;132: Abstract 121.

Induction and Transplant

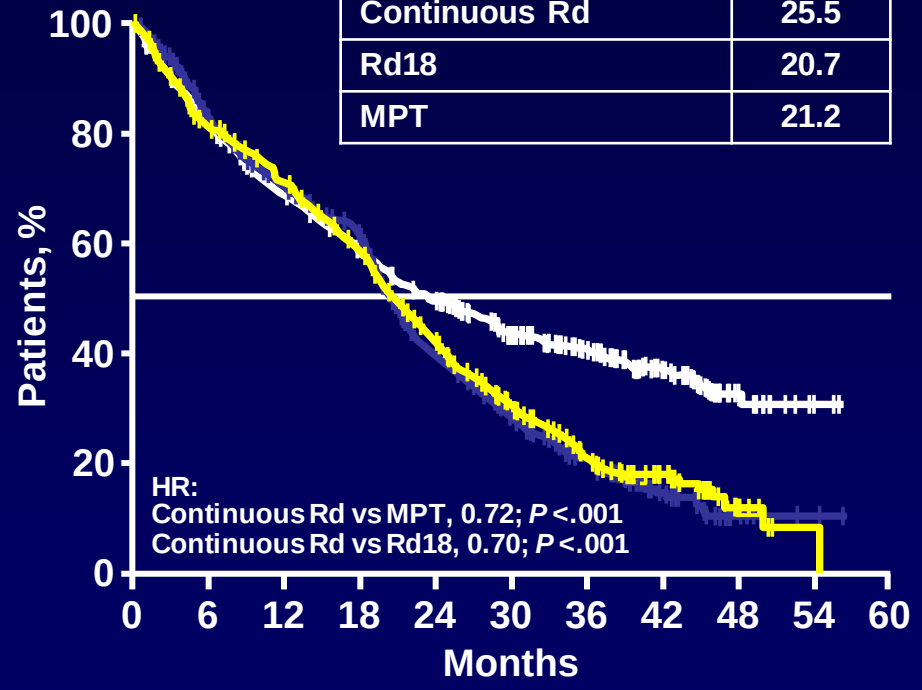
- Three drugs are the standard
- PI/IMiD/Dex is the standard (B vs C vs I)
- Addition of a fourth drug for limited duration is a goal; will most likely be mAb (Dara, Elo, etc)
- Transplant continues to improved outcomes
- Maintenance is advised
- CR/MRD is a goal

FIRST Trial: Progression-Free Survival and Overall Survival Best With Continuous Therapy

Median follow-up of 67 months as of 21 January 2016

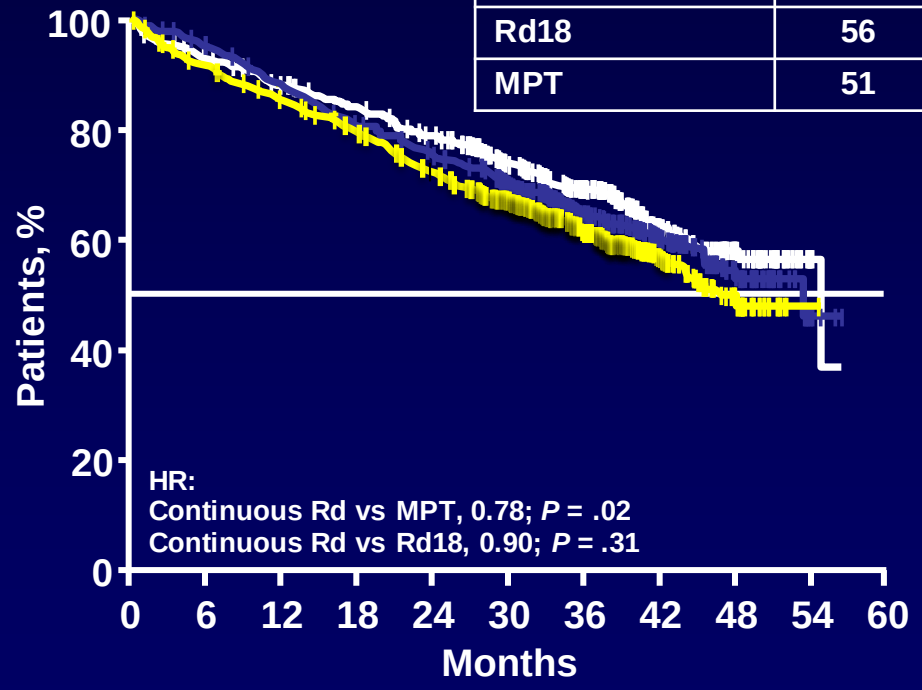
PFS

	Median, mo
Continuous Rd	25.5
Rd18	20.7
MPT	21.2



OS

	4-Yr, %
Continuous Rd	59
Rd18	56
MPT	51



Continuous Rd (N = 535) Rd18 (N = 541) MPT (N = 547)

MPT, melphalan, prednisone, thalidomide; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Benboubker L, et al. *N Engl J Med.* 2014;371:906-917.

Efficacy and Feasibility of Dose/Schedule-Adjusted Rd-R Vs. Continuous Rd in Elderly and Intermediate-Fit Newly Diagnosed Multiple Myeloma (NDMM) Patients: RV-MM-PI-0752 Phase III Randomized Study

Alessandra Larocca,1 Marco Salvini,1 Lorenzo De Paoli,1 Nicola Cascavilla,1 Giulia Benevolo,1 Monica Galli,1 Vittorio Montefusco,1 Tommaso Caravita di Toritto,1 Anna Baraldi,1 Stefano Spada,1 Nicola Giuliani,1 Chiara Pautasso,1 Stefano Pulini,1 Sonia Ronconi,1 Norbert Pescosta,1 Anna Marina Liberati,1 Francesca Patriarca,1 Claudia Cellini,1 Patrizia Tosi,1 Massimo Offidani,1 Michele Cavo,1 Antonio Palumbo,2 Mario Boccadoro,1 Sara Bringhen.1

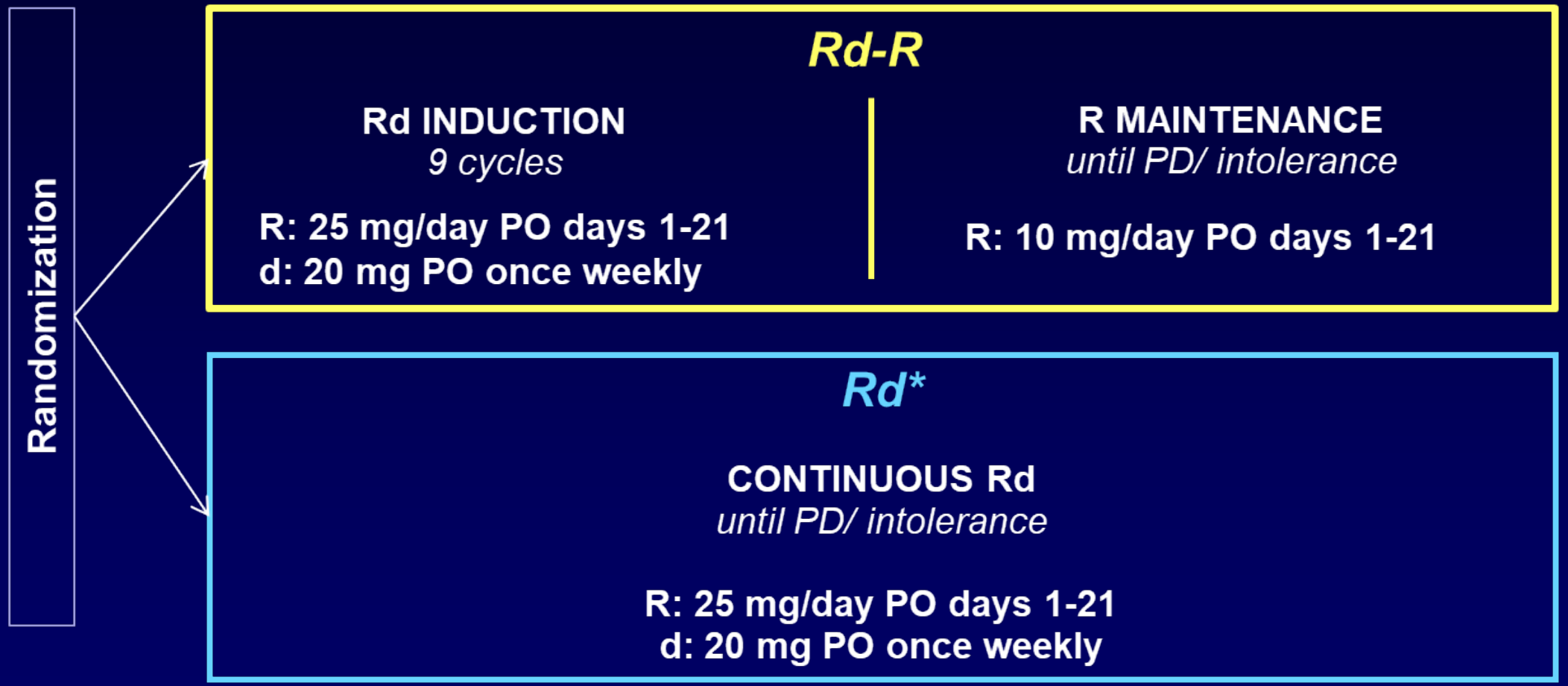
On behalf of Co-Investigators

1 GIMEMA / European Myeloma Network, Italy; 2 University of Torino - Currently Takeda Pharmaceuticals Co.

Correspondence: alelarocca@hotmail.com

Study design

199 intermediate-fit patients have been enrolled and could be evaluated

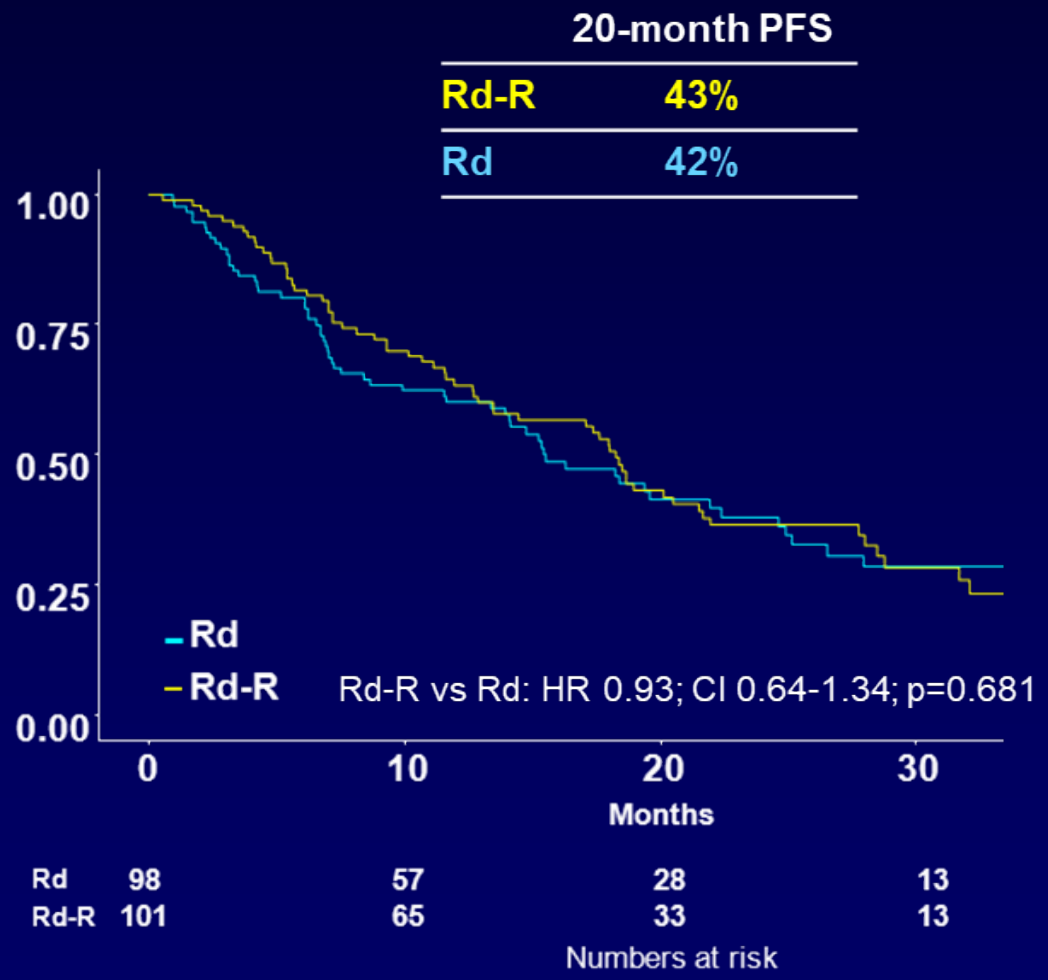


*The dose and schedule of continuous Rd was the one adopted in patients >75 years in the FIRST trial (Hulin C et al. JCO 2016)

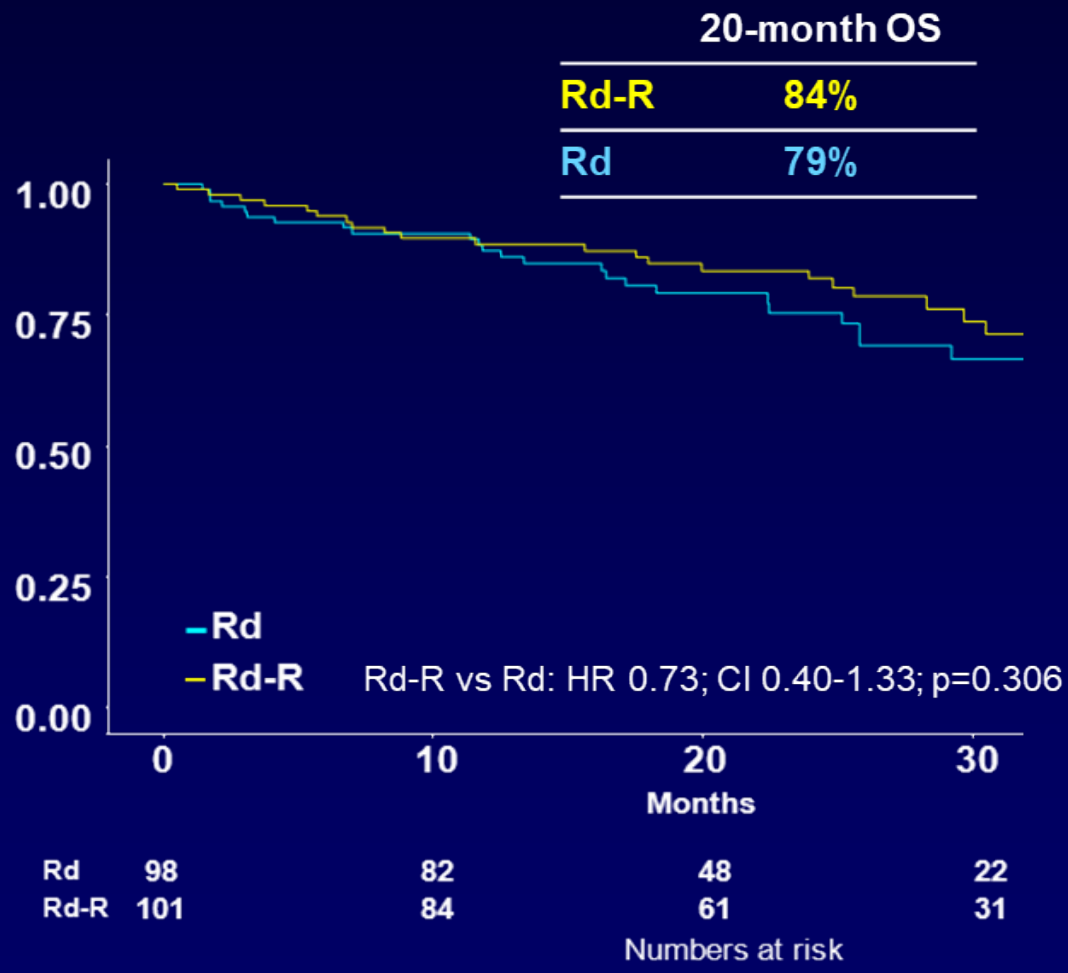
R, lenalidomide; d, dexamethasone; PO, orally; PD, progressive disease

Rd-R vs Rd

Progression-free survival



Overall survival

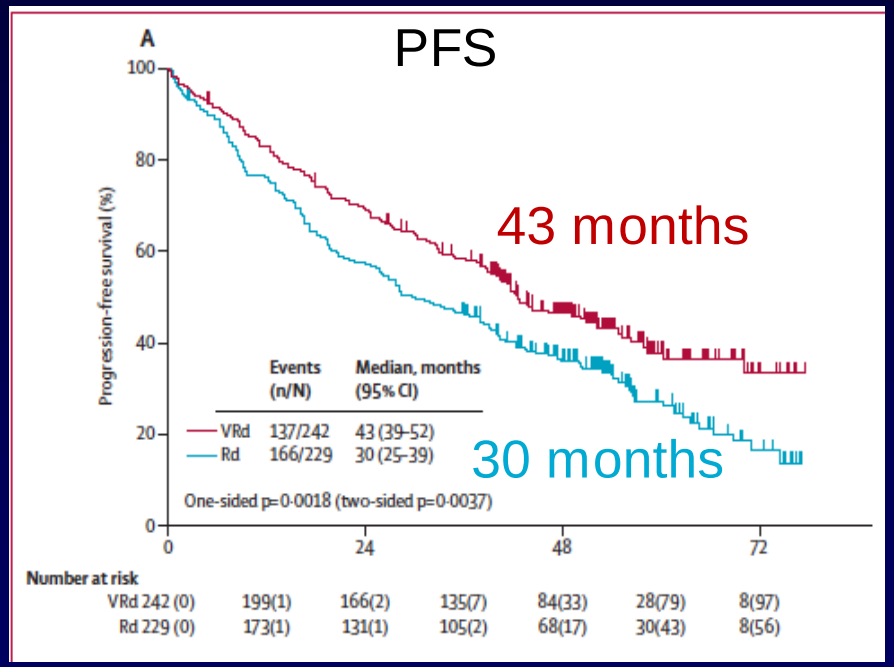


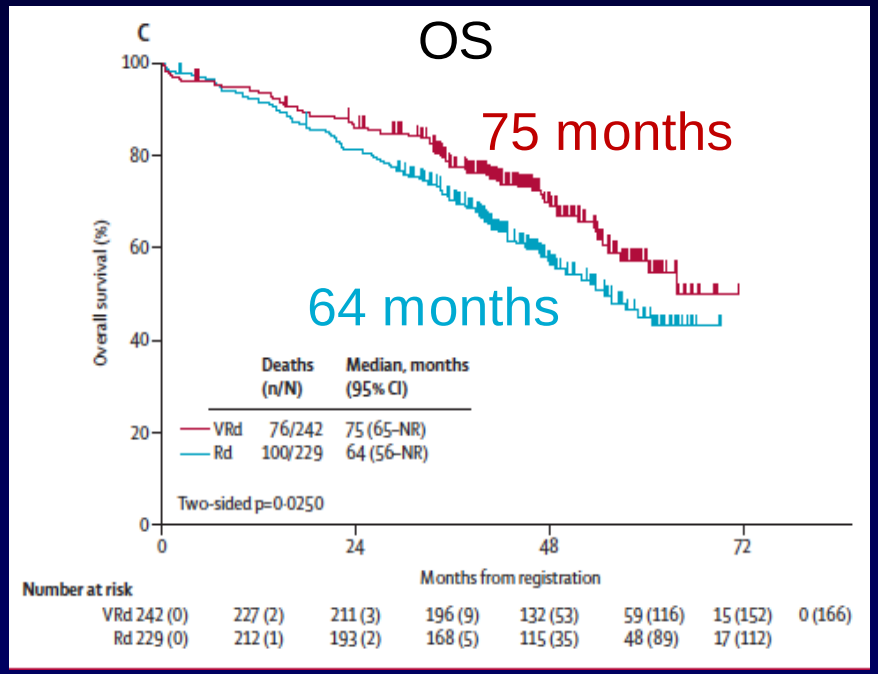
R, Lenalidomide; d, dexamethasone; PFS, progression-free survival, OS, overall survival.

VRd vs Rd Followed by Rd Maintenance: SWOG S0777 Study

VRd (8 cycles) or Rd (6 cycles) induction, followed by Rd maintenance until PD, bortezomib twice a week IV x 8 cycles

ORR (CR) (%): 82 (16) vs 72 (8)





SWOG study was not specifically conducted in elderly patients with newly diagnosed MM

AE: 82% vs 75%; discontinuations: 23% vs 10%

Peripheral neuropathy (33%)

Median (range) age = 63 (28 to 87) years Age ≥65 years = 43%
ISS stage III = 33%; creatinine ≥2 mg/dL = 5%

Multivariate analysis: VRd, stage III, and >65 years

>65 years; PFS: 36.9 months vs 25.9 months;
OS: 74.6 months vs 58.4 months
ORR: 74% vs 69%% VGPR: 57% vs 34%

Durie BG, et al. *Lancet.* 2017;389(10068):519-527.

RVD-Lite[1]

35-day cycle of

Lenalidomide
- 15 mg/day on days 1–21

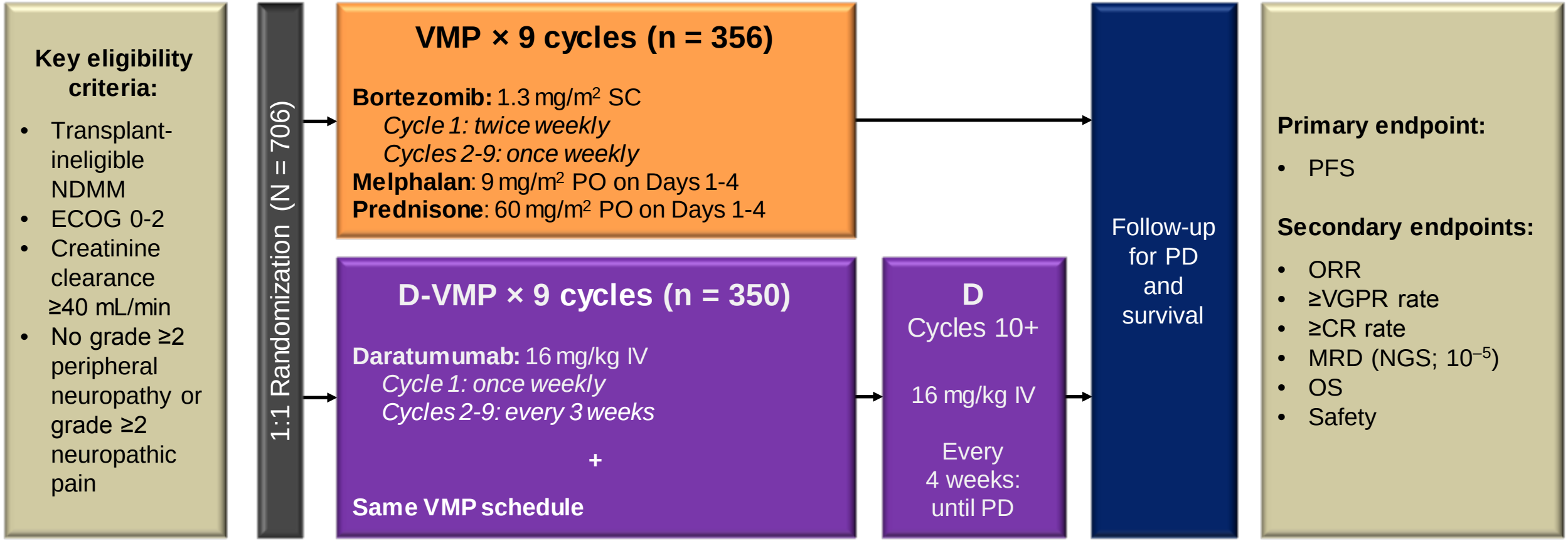
Bortezomib
- 1.3 mg/m^2 once weekly SC on days 1, 8, 15, and 22; and

Dexamethasone
- 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 for patients ≤75 years, and days 1, 8, 15, and 22 for patients older than 75 years

Response After 4 Cycles (N = 30)	N (%)
ORR (≥PR)	**27 (90.0)**
CR	5 (16.7)
VGPR	11 (36.7)
PR	11 (36.7)
SD	3 (10.0)
≥VGPR	16 (53.3)

1. O'Donnell EK, et al. ASH 2014. Abstract 4217.

ALCYONE Study Design



Stratification factors

- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

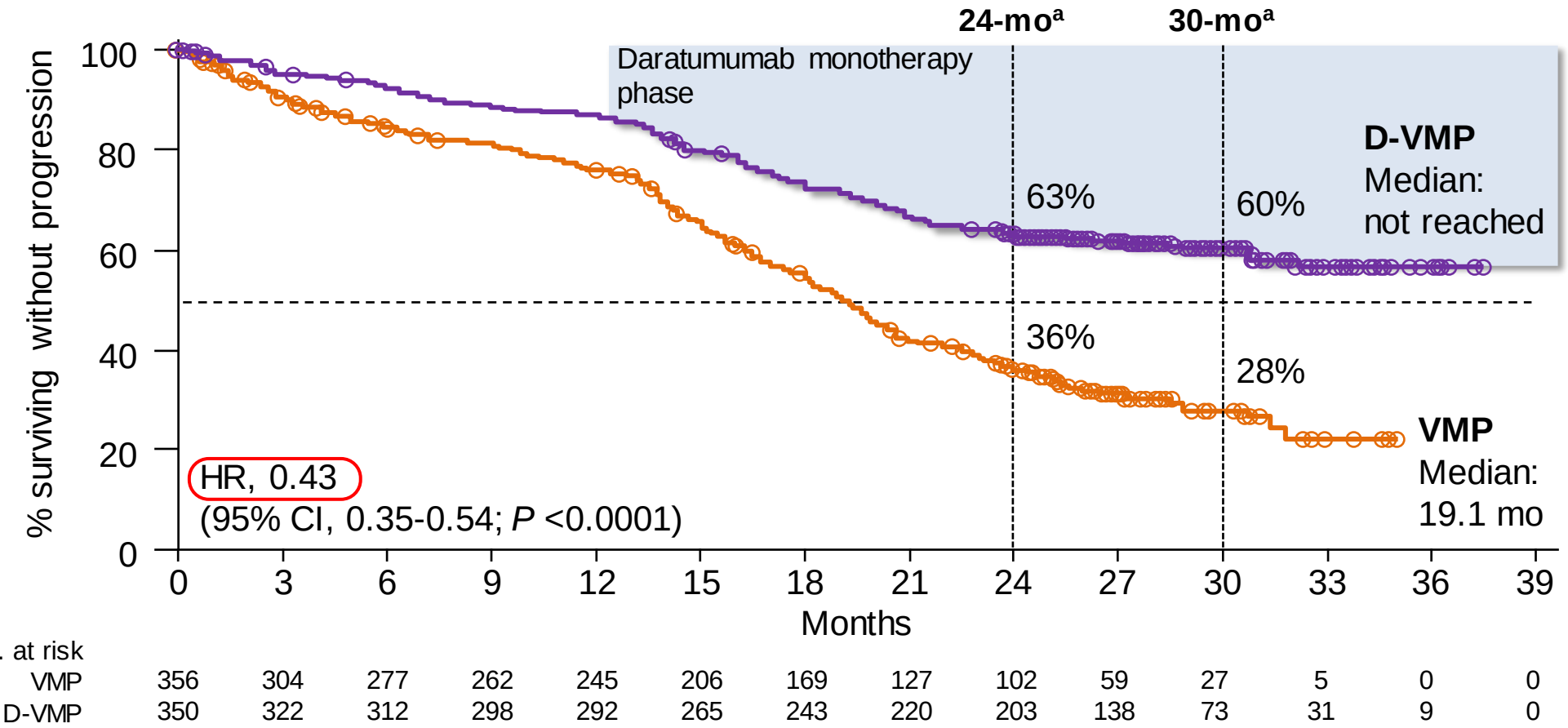
Statistical analyses

- 360 PFS events: 85% power for 8-month PFS improvement[a]

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; SC, subcutaneously; PO, orally; IV, intravenously; D, daratumumab; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.
[a]8-month PFS improvement over 21-month median PFS of VMP.

Efficacy: PFS

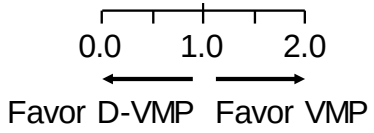
- Median (range) follow-up: 27.8 (0-39.2) months

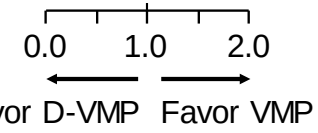


HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Efficacy: PFS in Prespecified Subgroups

	D-VMP n	D-VMP Median (months)	VMP n	VMP Median (months)	HR (95% CI)
Sex					
Male	160	30.9	167	18.9	0.50 (0.37-0.68)
Female	190	NE	189	19.8	0.38 (0.28-0.52)
Age					
<75 years	246	NE	249	19.0	0.41 (0.32-0.53)
≥75 years	104	32.2	107	20.1	0.51 (0.34-0.75)
Race					
White	297	NE	304	19.3	0.46 (0.37-0.58)
Other	53	NE	52	18.9	0.32 (0.17-0.58)
Region					
Europe	289	NE	295	19.1	0.47 (0.38-0.60)
Other	61	NE	61	19.0	0.28 (0.15-0.52)
Baseline renal function (CrCl)					
>60 mL/min	200	NE	211	19.1	0.45 (0.34-0.60)
≤60 mL/min	150	NE	145	18.9	0.42 (0.30-0.59)
Baseline hepatic function					
Normal	301	NE	303	19.4	0.45 (0.36-0.57)
Impaired	46	NE	52	13.5	0.41 (0.23-0.72)
ISS staging					
I	69	NE	67	24.7	0.47 (0.28-0.79)
II	139	NE	160	18.3	0.43 (0.31-0.60)
III	142	NE	129	18.2	0.43 (0.31-0.60)
Type of MM					
IgG	207	NE	218	18.5	0.41 (0.31-0.54)
Non-IgG[a,b]	82	30.9	83	21.3	0.58 (0.38-0.89)
Cytogenetic risk					
High risk	53	19.2	45	18.0	0.78 (0.49-1.26)
Standard risk	261	NE	257	18.9	0.34 (0.26-0.45)
ECOG performance status					
0	78	NE	99	20.1	0.39 (0.25-0.62)
1-2	272	NE	257	18.8	0.45 (0.35-0.58)



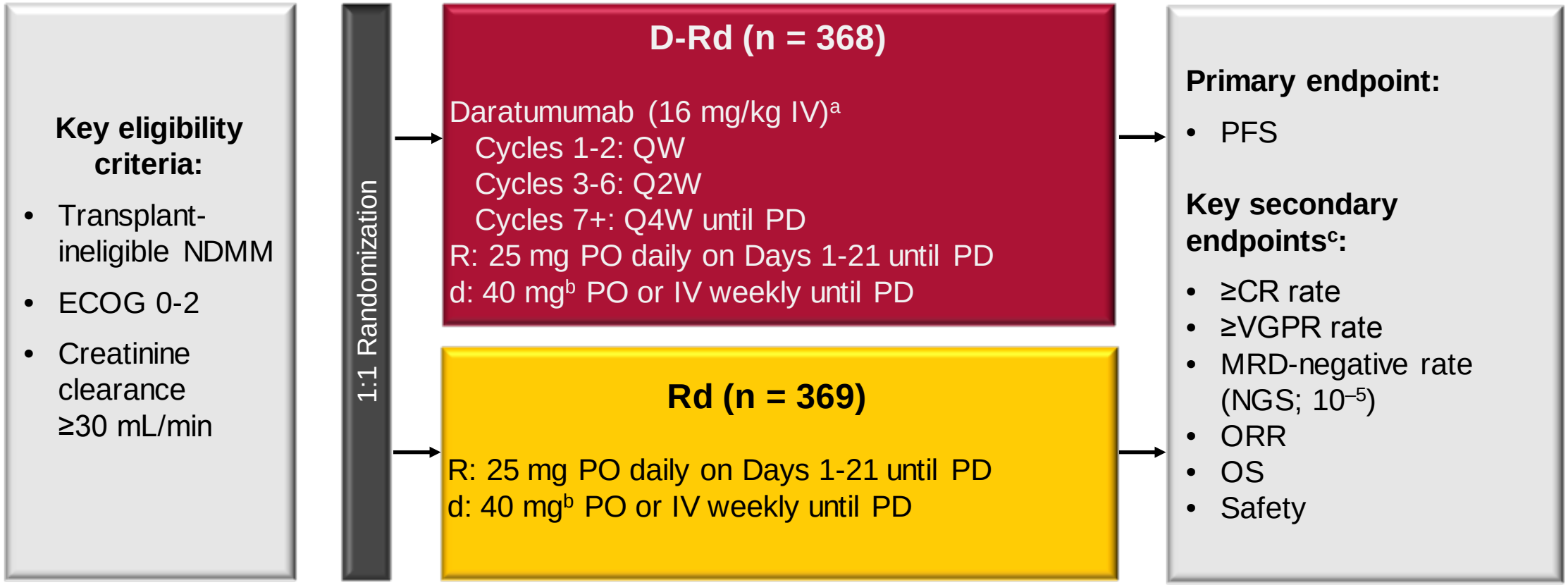


[a]Patients with measurable disease in serum. [b]95% of non-IgG patients were IgA.
NE, not evaluable; CrCl, creatinine clearance

Dimopoulos MA, et al. *Blood.* 2018;132: Abstract 156.

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)

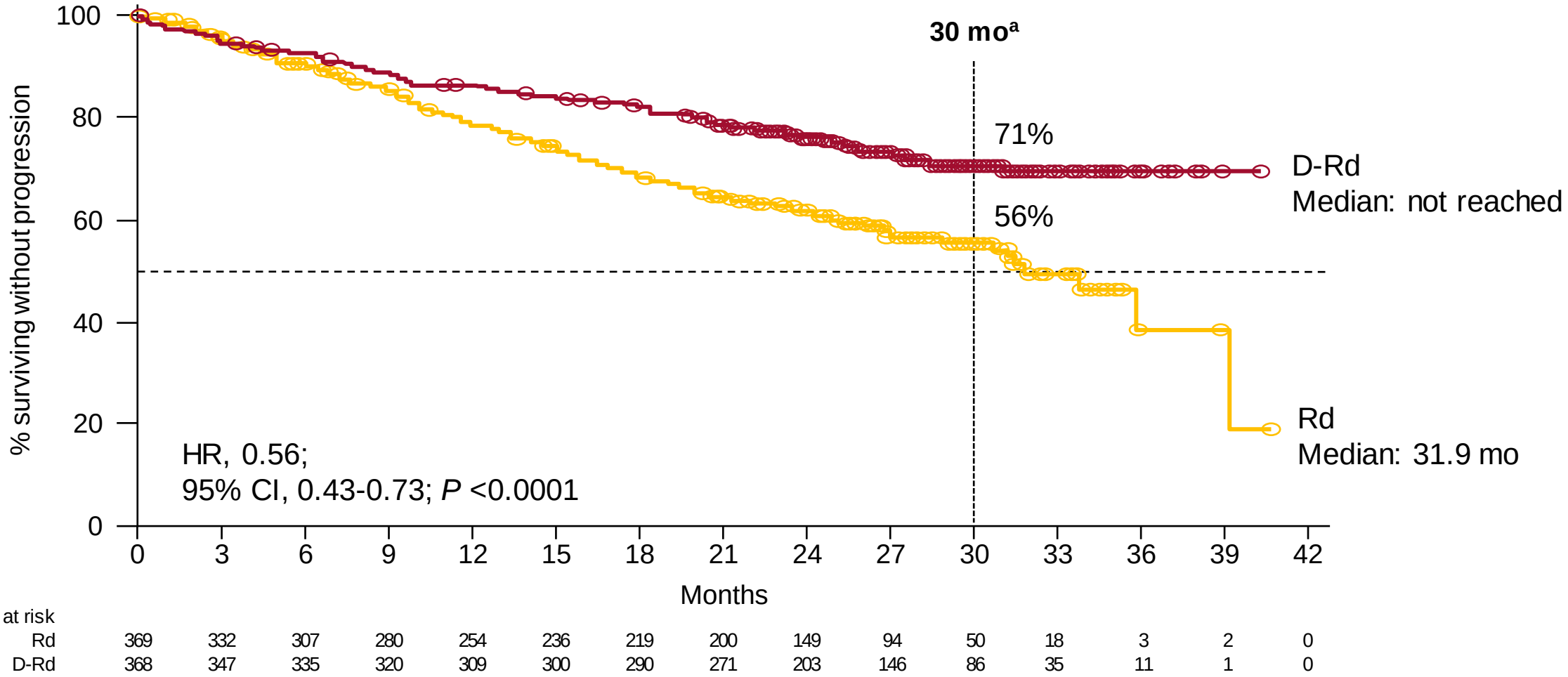
Cycle: 28 days

[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.

Efficacy: PFS

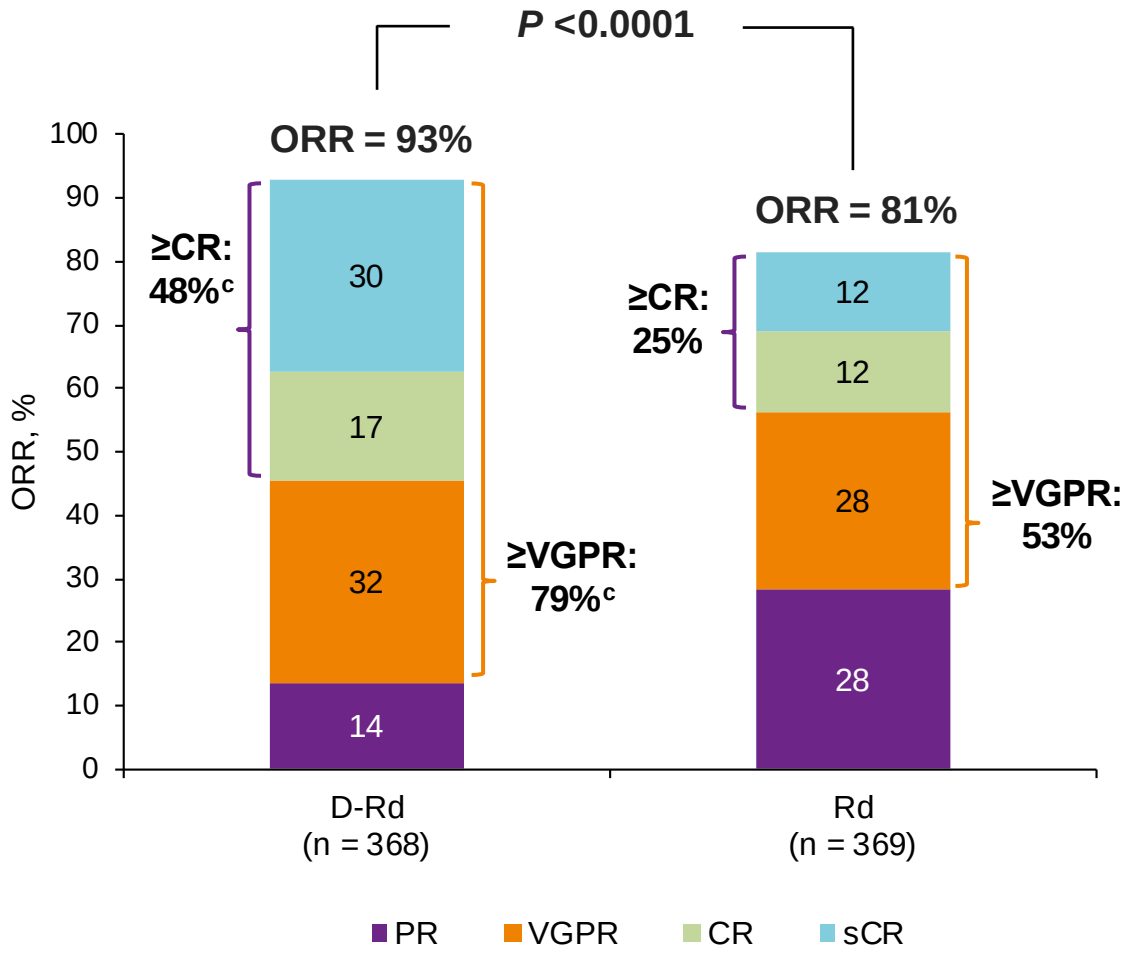
Median follow-up: 28 months (range: 0.0-41.4)

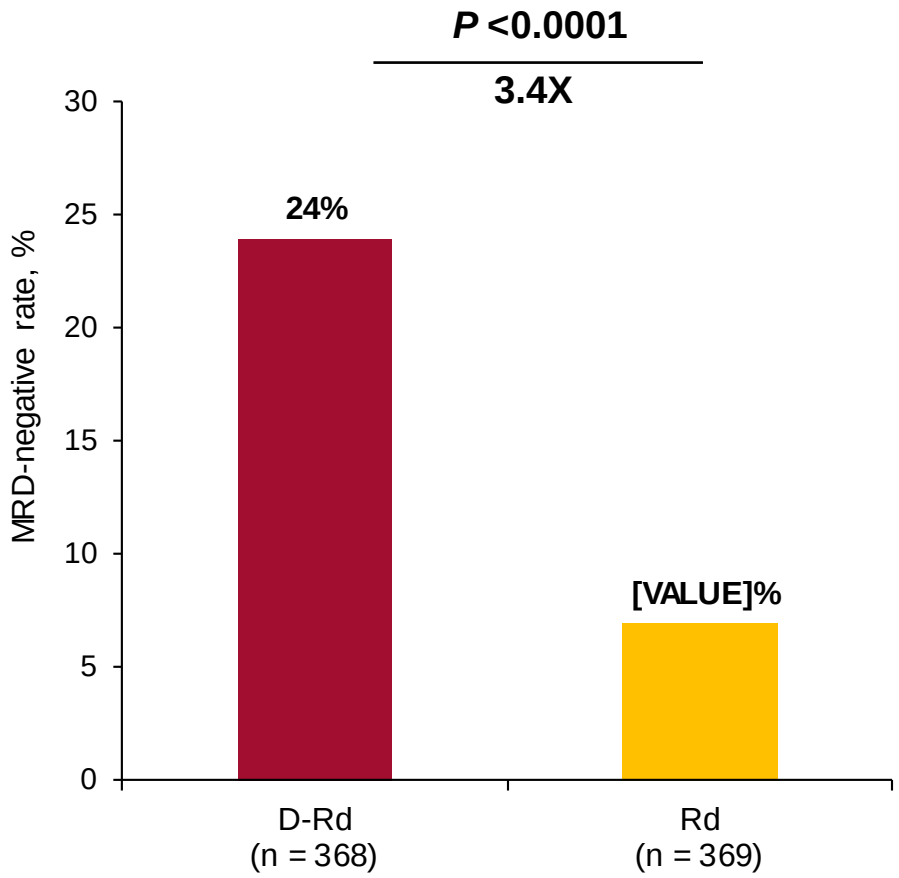


44% reduction in the risk of progression or death in patients receiving D-Rd

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

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

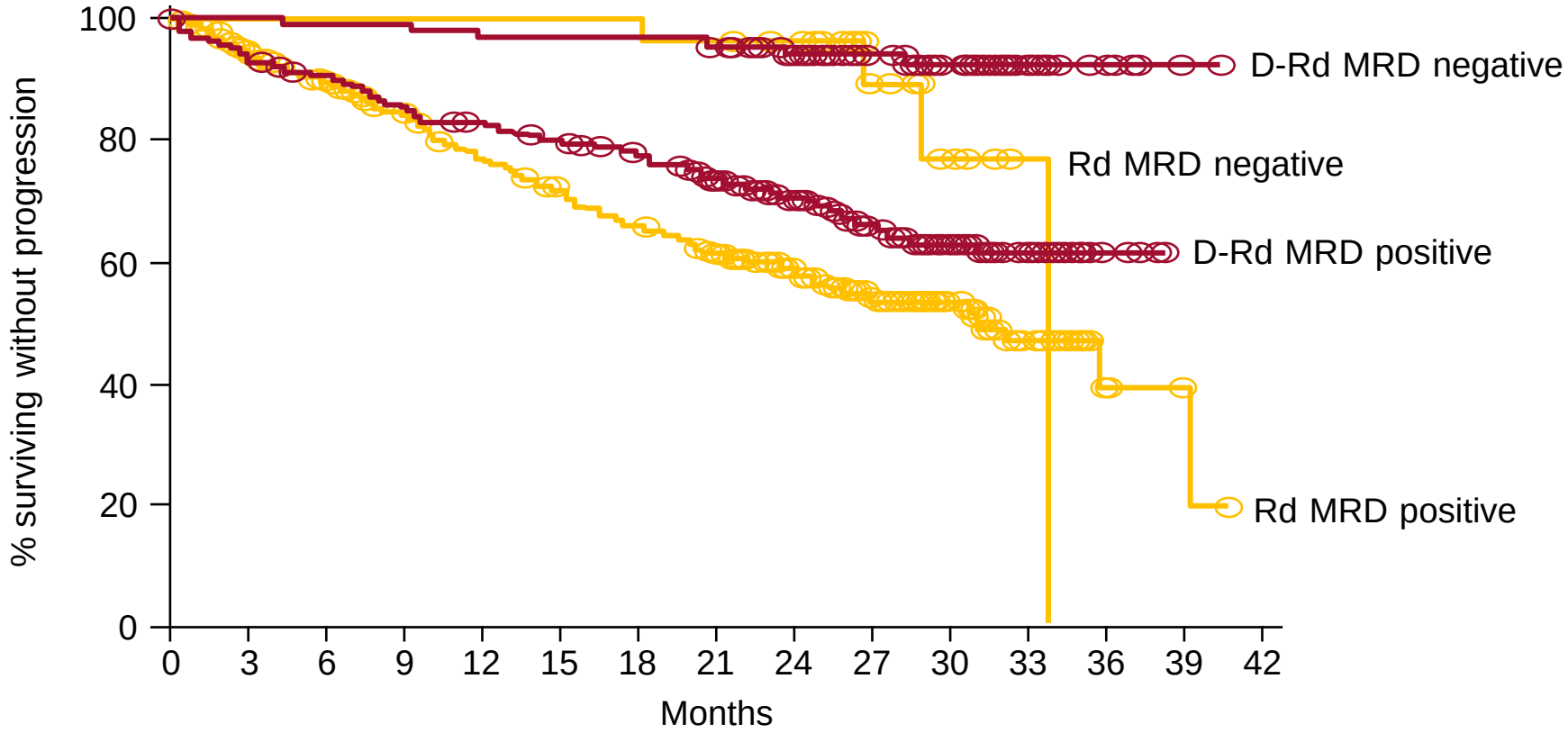




Significantly higher ORR, ≥CR rate, ≥VGPR rate, and MRD-negative rate with D-Rd

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.

Efficacy: PFS by MRD Status

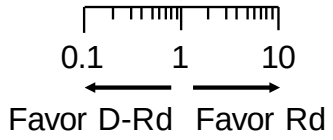


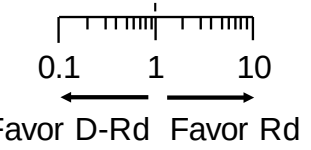
No. at risk															
Rd MRD negative	27	27	27	27	27	27	27	25	21	12	5	1	0	0	0
D-Rd MRD negative	89	89	88	88	86	86	86	84	70	55	33	12	5	1	0
Rd MRD positive	342	305	280	253	227	209	192	175	128	82	45	17	3	2	0
D-Rd MRD positive	279	258	247	232	223	214	204	187	133	91	53	23	6	0	0

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

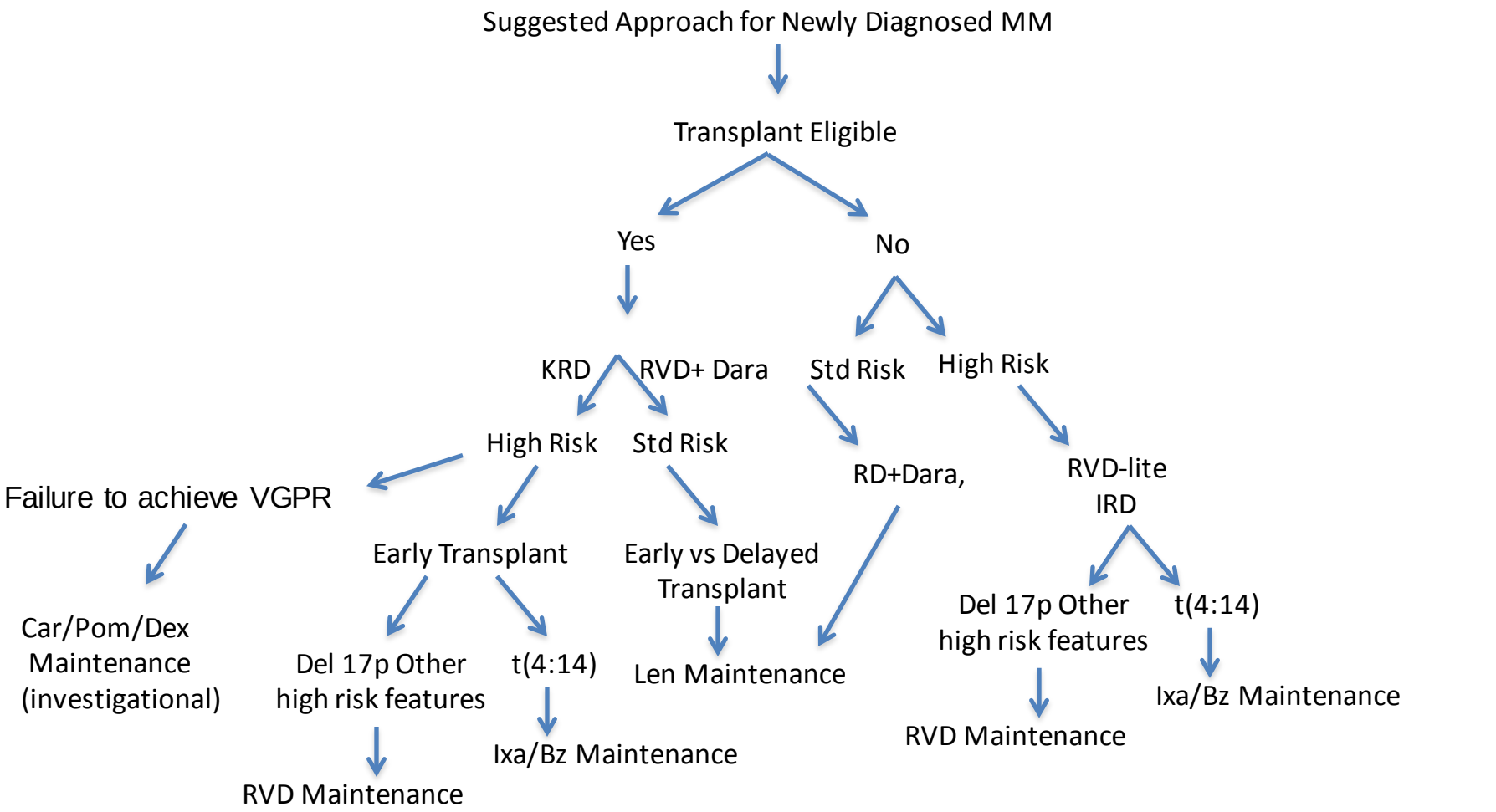
Efficacy: PFS in Prespecified Subgroups

	D-Rd N	Rd N	HR (95% CI)
Sex			
Male	189	195	0.65 (0.46-0.93)
Female	179	174	0.47 (0.32-0.69)
Age			
<75 years	208	208	0.50 (0.35-0.71)
≥75 years	160	161	0.63 (0.44-0.92)
Race			
White	336	339	0.55 (0.42-0.72)
Other	32	30	0.68 (0.31-1.49)
Region			
North America	101	102	0.65 (0.41-1.04)
Other	267	267	0.52 (0.38-0.71)
ISS staging			
I	98	103	0.59 (0.31-1.11)
II	163	156	0.43 (0.29-0.64)
III	107	110	0.72 (0.48-1.09)
Baseline CrCl			
>60 mL/min	206	227	0.52 (0.36-0.74)
≤60 mL/min	162	142	0.60 (0.41-0.87)
Type of MM			
IgG	225	231	0.74 (0.53-1.03)
Non-IgG	74	76	0.32 (0.18-0.55)
Cytogenetic risk			
High risk	48	44	0.85 (0.44-1.65)
Standard risk	271	279	0.49 (0.36-0.67)
Baseline hepatic			
Normal	335	340	0.51 (0.39-0.68)
Impaired	31	29	1.08 (0.49-2.38)
ECOG score			
0	127	123	0.49 (0.29-0.81)
1	178	187	0.63 (0.44-0.90)
≥2	63	59	0.51 (0.29-0.89)





Facon T, et al. ***Blood.*** **2018;132: Abstract LBA-2.**



Nooka et al, *JOP* 2016
Modified.