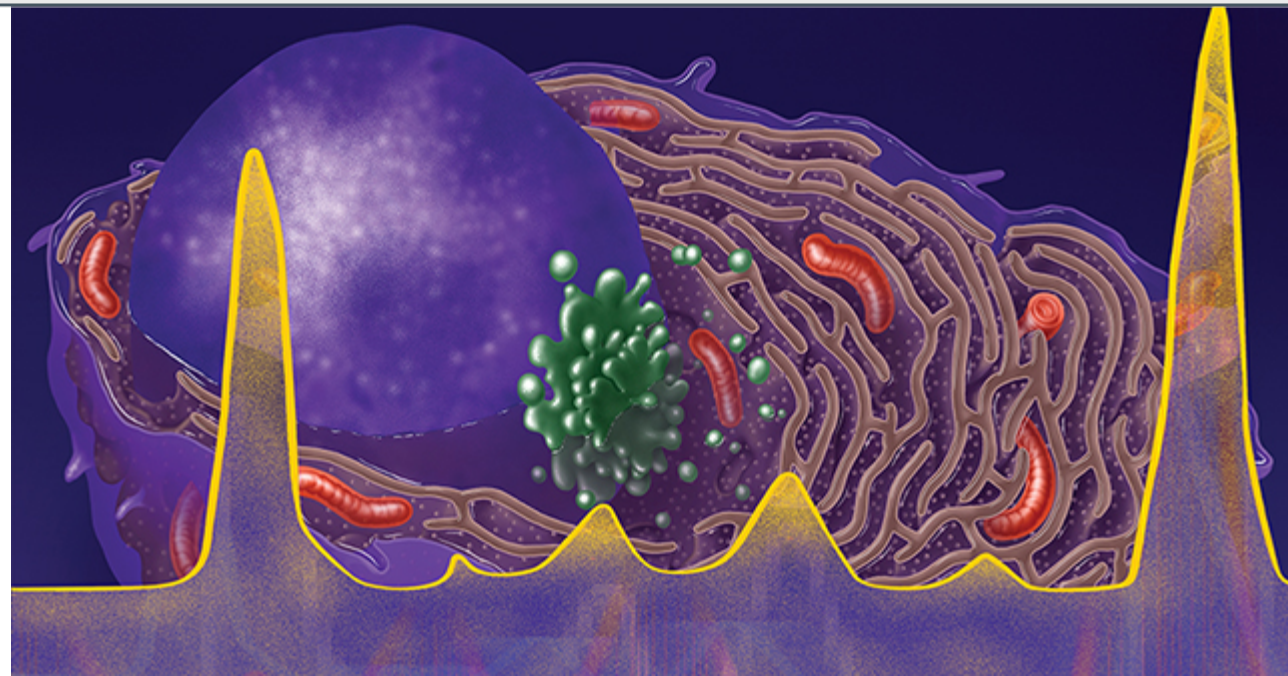
This activity is provided by the Annenberg Center for Health Sciences at Eisenhower and developed in partnership with Clinical Care Options, LLC and the International Myeloma Foundation.

Individualized Approaches to Frontline Treatment Selection

Philippe Moreau, MD
Professor of Clinical Hematology
Head, Hematology Department
University Hospital Hôtel-Dieu
Nantes, France



Faculty

Philippe Moreau, MD
Professor of Clinical Hematology
Head, Hematology Department
University Hospital Hôtel-Dieu
Nantes, France

Philippe Moreau, MD, has disclosed that he has received consulting fees from AbbVie, Amgen, Celgene, Janssen, and Sanofi.

Agenda

- What patient and disease factors guide therapy decisions?
  - Impact of age, performance status, and comorbidities on therapy selections
  - When to use 3-drug vs 4-drug regimens?
- Current therapeutic options for transplant eligible and ineligible patients
  - Triplet therapies
  - Quad therapies
- New therapeutic strategies for transplantation, consolidation, and maintenance

Patient Case Example: 73-Year-Old Male

Presents with:

- Bone pain
- Anemia Hb: 10.2 g/dL
- Serum electrophoresis: M-spike: 4.2 g/dL; IF: IgG K
- Bone marrow aspirate: 30% plasma cells
- Cytogenetics (FISH): **t(11;14)**
- Low-dose whole-body CT: diffuse bone lesions, spine

- Creatinine: 0.9 mg/dL; **β2-M: 2.5 mg/L**, albumin 3.8 g/dL, LDH < normal

→ symptomatic multiple myeloma, **ISS1, R-ISS1**

Presurvey 2: In your current clinical practice, what would you recommend for this patient?

1. Rd until progression
2. VRD x 8 followed by Rd until PD
3. VRD lite followed by R until PD
4. VMP-daratumumab x 9 followed by daratumumab until PD
5. Rd + daratumumab, until PD
6. VRD x 4 → ASCT prepared by mel 200 → len maintenance until PD
7. Uncertain

Expert Recommendations

Expert Recommendations	
Brian G.M. Durie, MD	Rd + daratumumab, until PD
Shaji Kumar, MD	Rd + daratumumab, until PD
Thomas G. Martin, MD	RVd x 4 → ASCT → Len maintenance
Philippe Moreau, MD	Rd + daratumumab, until PD
S. Vincent Rajkumar, MD	VRD x 8 → Rd until PD
Jesús San-Miguel, MD	Rd + daratumumab, until PD Dara + VMP with bortez maintenance

Phase III Trials in NDMM Not Eligible for ASCT

Trial	Regimen	n	mPFS	mOS
Vista[1]	VMP	344	24 (TTP)	56.4

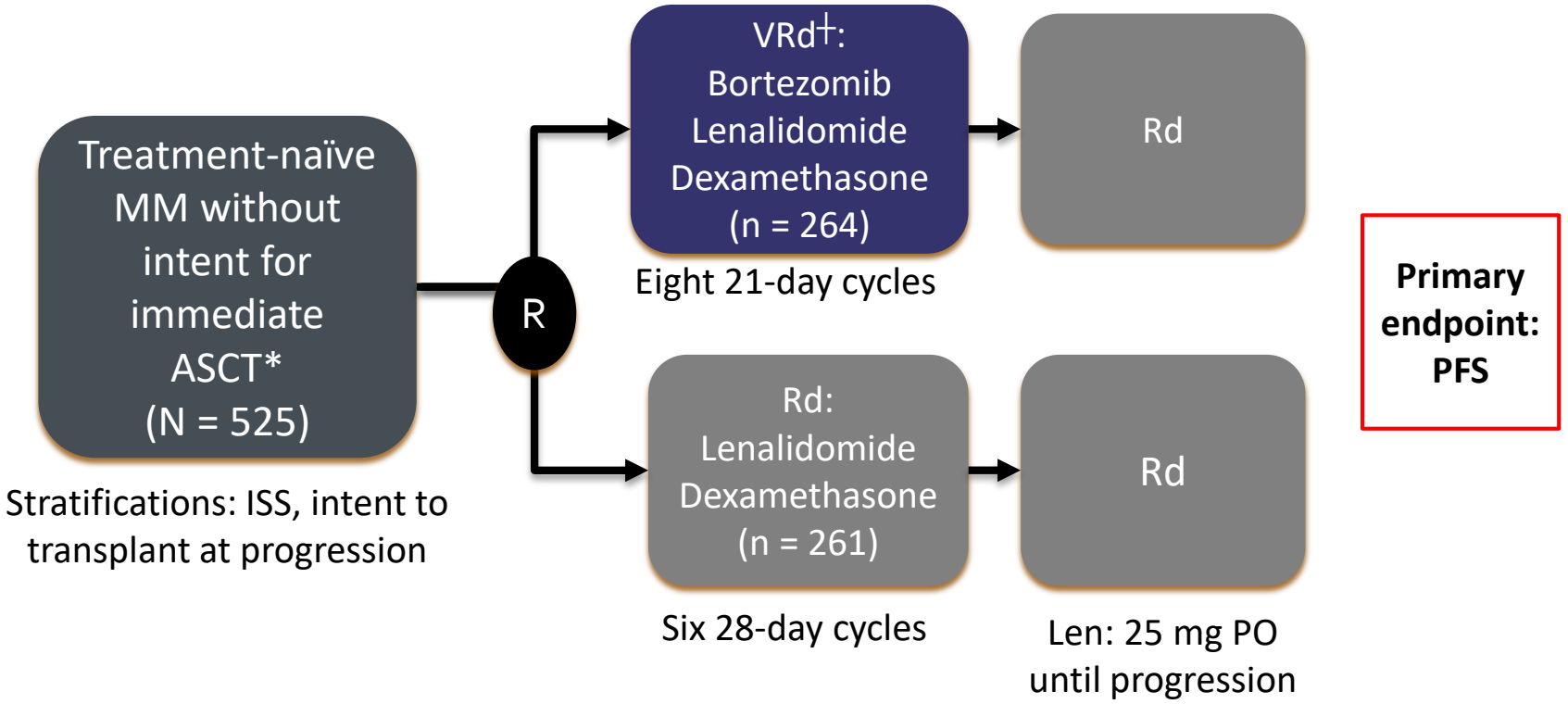
1. San Miguel. ASH. 2011. Abstr. 476

Phase III Trials in NDMM Not Eligible for ASCT

Trial	Regimen	n	mPFS	mOS
Vista[1]	VMP	344	24 (TTP)	56.4
FIRST[2]	Rd cont	535	26	59.1

1. San Miguel. ASH. 2011. Abstr. 476. 2. Facon. Blood. 2018;131:301.

SWOG 0777 Trial



*All high-risk patients received aspirin (325 mg/d. †Patients received HSV prophylaxis. ‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.

Durie BG, et al. Lancet. 2017;389:519-527.

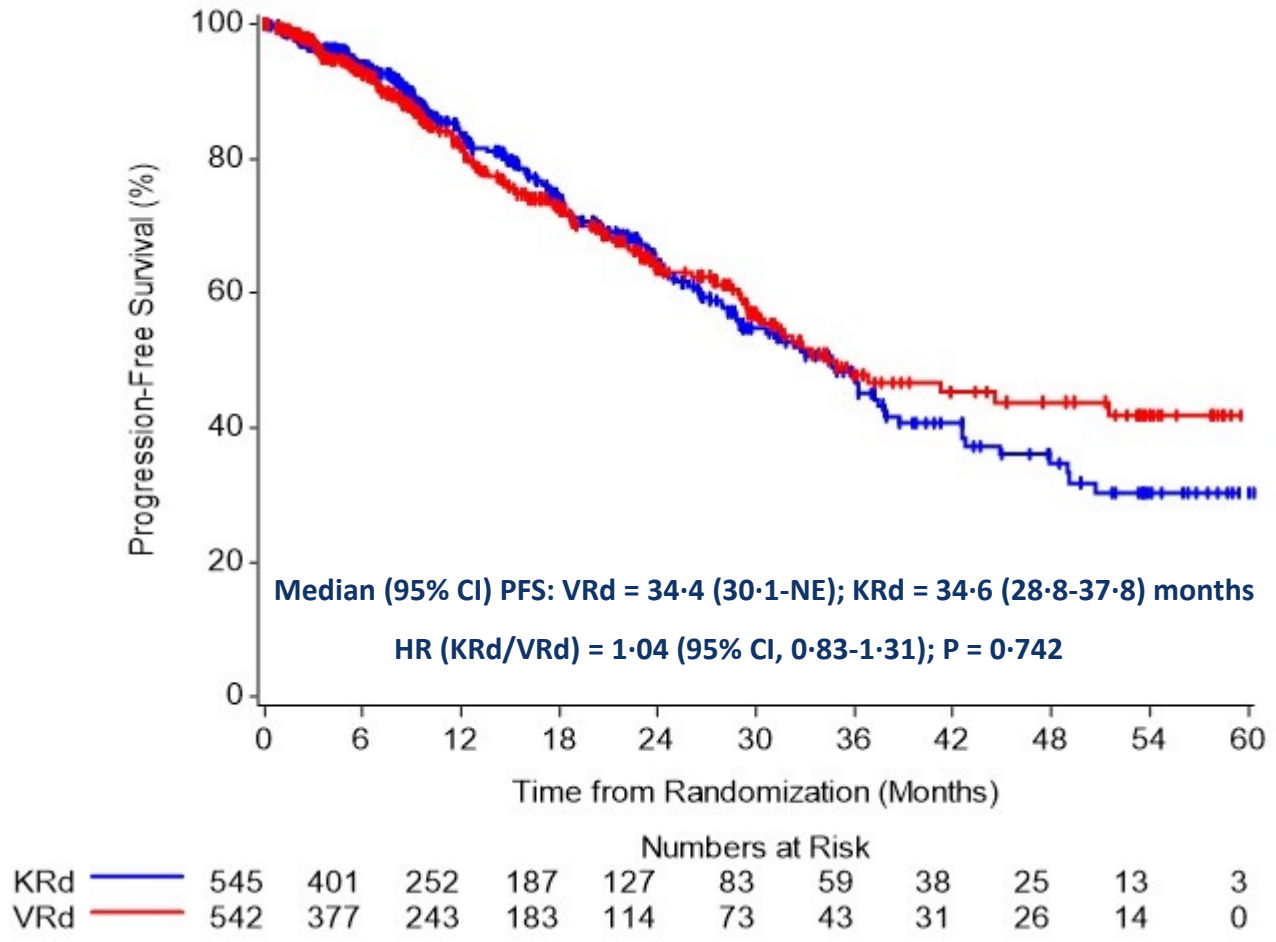
ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma: results of ENDURANCE (E1A11) phase 3 trial

Shaji K. Kumar, Susanna J. Jacobus, Adam D. Cohen, Matthias Weiss, Natalie Scott Callander, Avina A. Singh, Terri L. Parker, Alexander Menter, Alex Yang, Benjamin Marshall Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Seth Rosenberg, Jeffrey A. Zonder, Edward Anthony Faber, Sagar Lonial, Paul G. Richardson, Robert Z. Orlowski, Lynne I. Wagner, S. Vincent Rajkumar

Federally Funded Research

EDURANCE: PFS from Induction Randomization



- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients ≥ 70 years, median PFS (95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31·7 (28·5-44·6) and KRd = 32·8 (27·2-37·5) months

Kumar. ASCO 2020 Abstr LBA3.

Phase III Trials in NDMM Not Eligible for ASCT

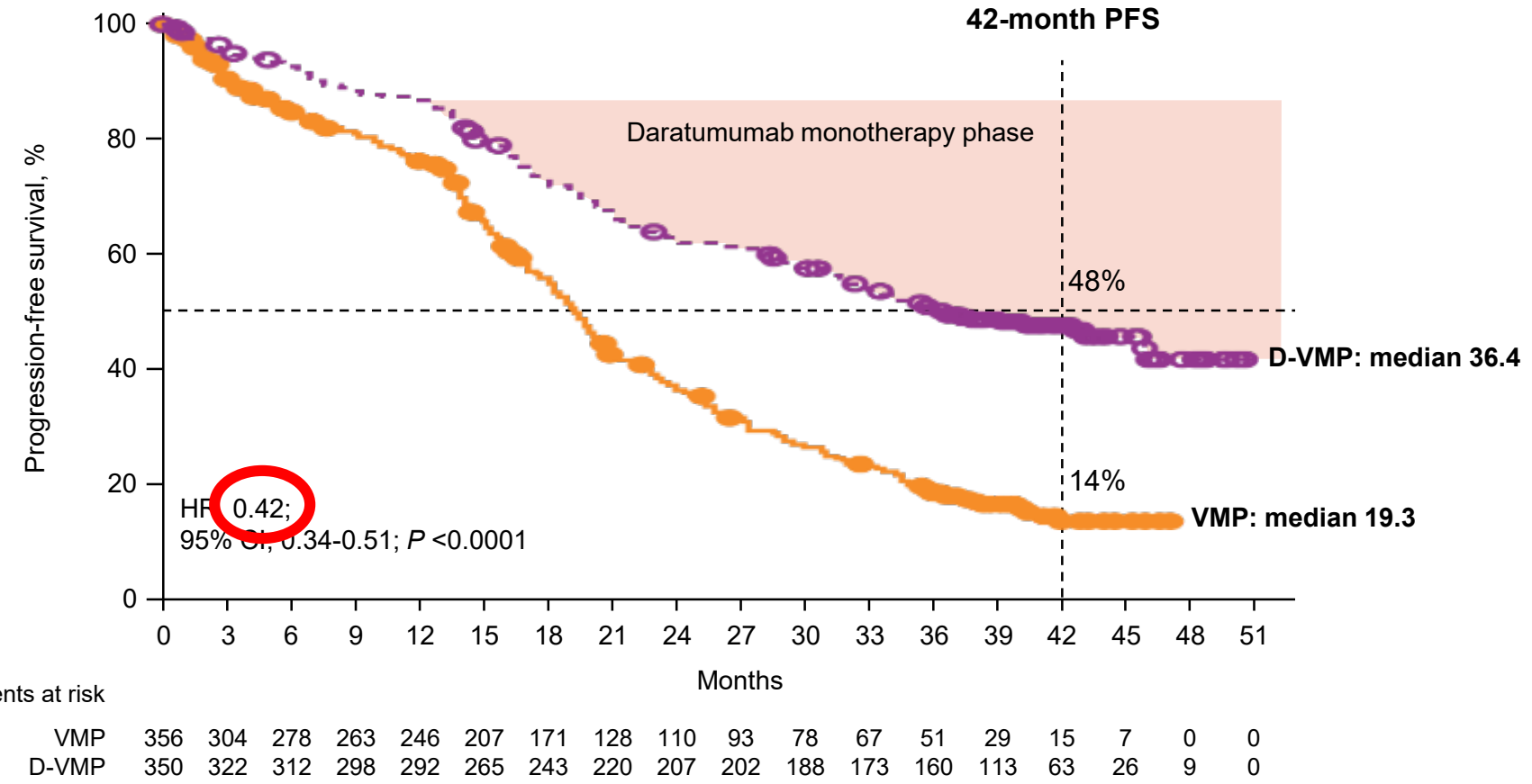
Trial	Regimen	n	mPFS	mOS
Vista[1]	VMP	344	24 (TTP)	56.4
FIRST[2]	Rd cont	535	26	59.1
SWOG777[3]	VRD	242* 91**	43 34	75 65
Endurance[4]	VRD	542 # 167 ##	34.4 37	3-year:84% NA

*: median age: 64; ** > 65 years; # median age 65; ## > 70 years

1. San Miguel. ASH. 2011. Abstr. 476. 2. Facon. Blood. 2018;131:301. 3. Durie. Lancet. 2017;389:519. 4. Kumar. ASCO 2020 Abstr LBA3.

Phase III ALCYONE Trial: PFS with Dara + VMP vs VMP in NDMM

- Median (range) follow-up: 40.1 (0-52.1) months



D-VMP continued to demonstrate a significant PFS benefit with extended follow up

Mateos. Lancet. 2020;395:132. Mateos. ASH 2019. Abstr 859.

Phase III Trials in NDMM Not Eligible for ASCT

Trial	Regimen	n	mPFS	mOS
Vista[1]	VMP	344	24 (TTP)	56.4
FIRST[2]	Rd cont	535	26	59.1
SWOG777[3]	VRD	242* 91**	43 34	75 65
Endurance[4]	VRD	542 # 167 ##	34.4 37	3-year: 84% NA
Alcyone[5]	VMP-Dara	356	36.4	42-Mo: 75%

*: median age: 64; ** > 65 years; # median age 65; ## > 70 years

1. San Miguel. ASH. 2011. Abstr. 476. 2. Facon. Blood. 2018;131:301. 3. Durie. Lancet. 2017;389:519. 4. Kumar. ASCO 2020 Abstr LBA3. 5. Mateos. ASH 2019. Abstr 859.

Phase III Trials in NDMM Not Eligible for ASCT

Trial	Regimen	n	mPFS	mOS
Vista[1]	VMP	344	24 (TTP)	56.4
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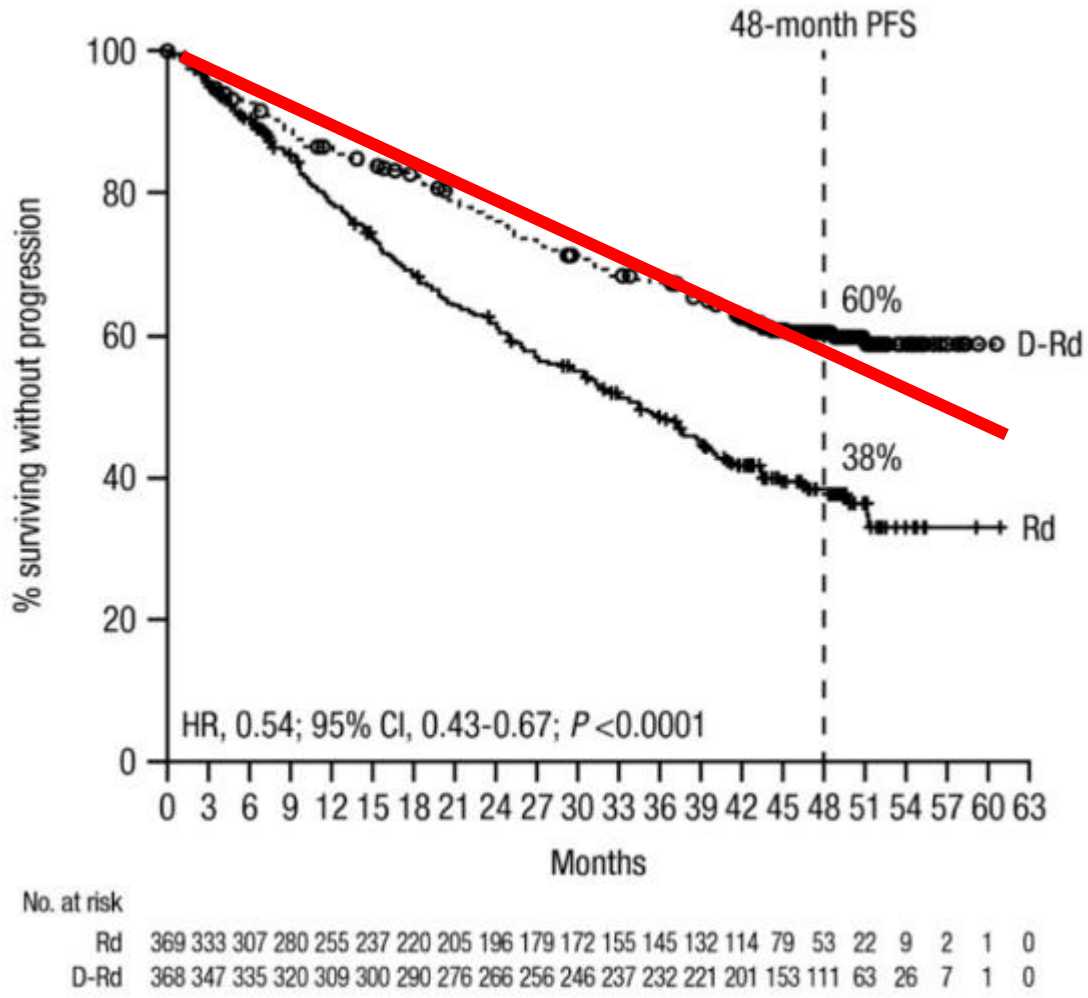
Endurance[4]	VRD	542 # 167 ##	34.4 37	3-year: 84% NA
Alcyone[5]	VMP-Dara	356	36.4	42-Mo: 75%
MAIA[6]	Rd-Dara	368	30-Mo: 71%	Immature

*: median age: 64; ** > 65 years; # median age 65; ## > 70 years

1. San Miguel. ASH. 2011. Abstr. 476. 2. Facon. Blood. 2018;131:301. 3. Durie. Lancet. 2017;389:519. 4. Kumar. ASCO 2020 Abstr LBA3. 5. Mateos. ASH 2019. Abstr 859. 6. Facon. NEJM. 2019;380:2104.

ASH2020 – Kumar et al – MAIA Follow-up : 4 years

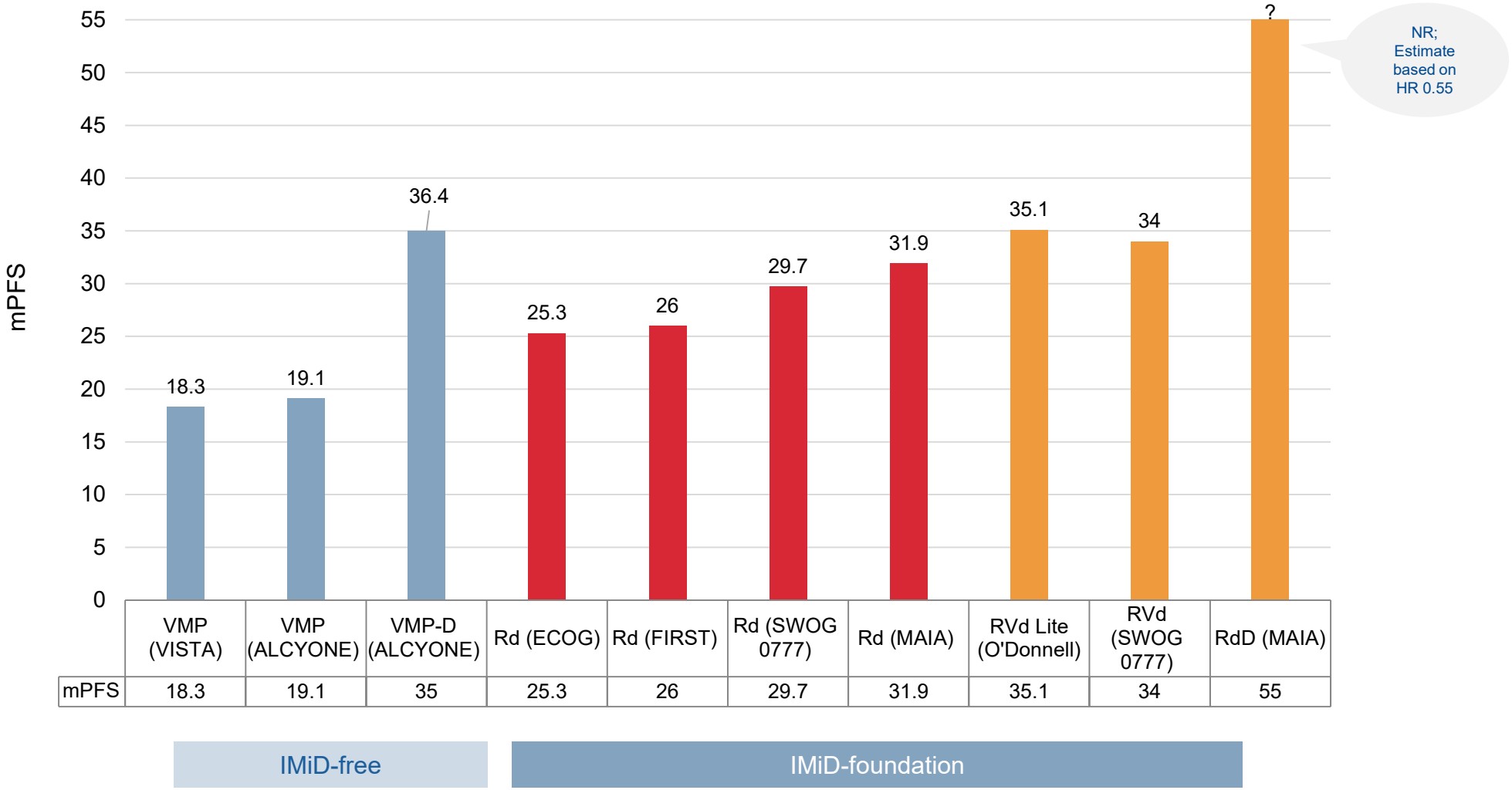
Figure. Updated progression-free survival with D-Rd and Rd in MAIA.



Median NR (55+ ?) vs 34 mos

Kumar. ASH 2020. Abstr 2276.

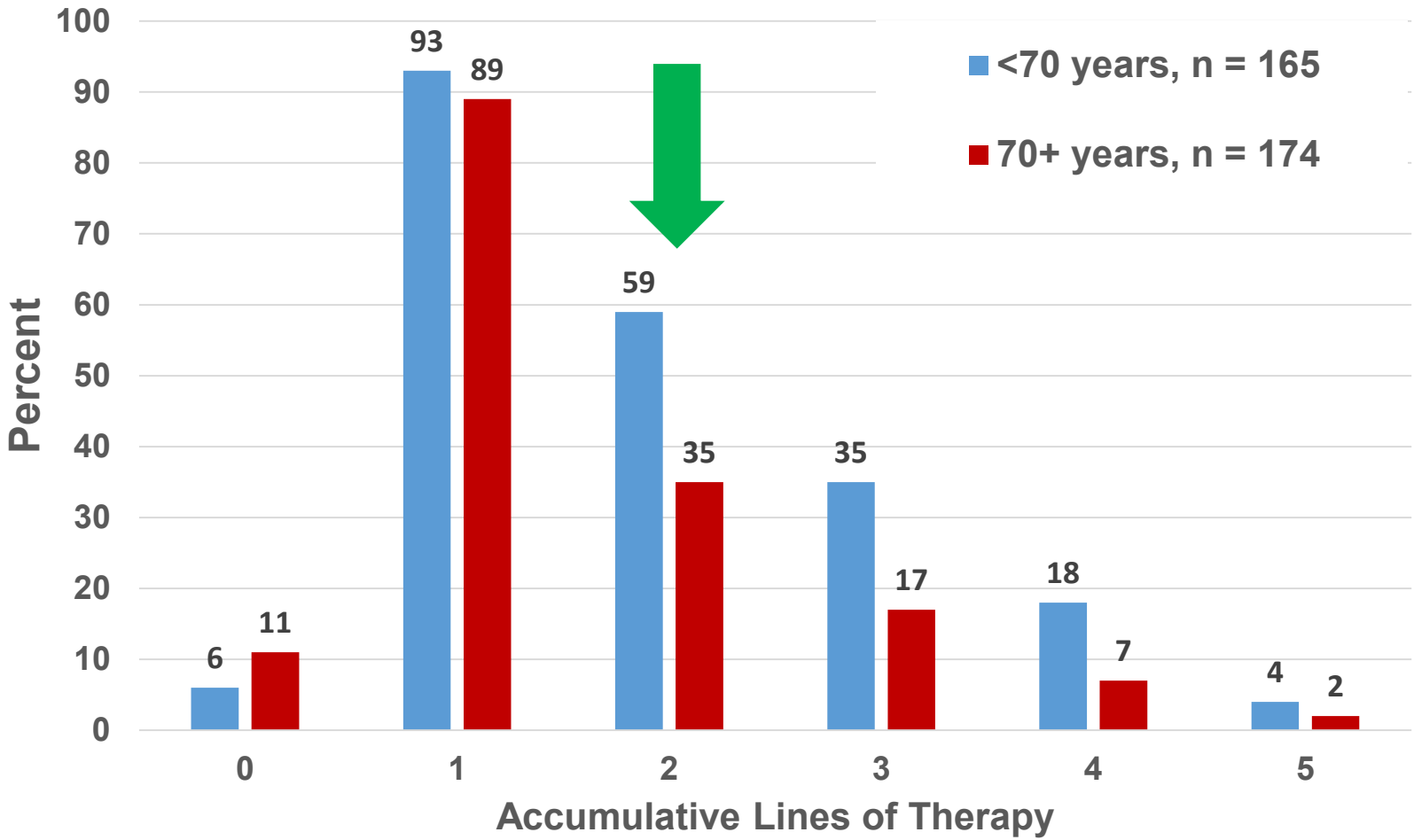
Overview of Median PFS in Recent Phase III Trials in Patients Not Eligible for ASCT



1. San Miguel. ASH. 2011. Abstr. 476. 2. Dimopoulos. ASH 2018. Abstr 156. 3. Rajkumar. Lancet Oncol. 2010;11:29.
4. Facon. Blood.2018;131:301. 5. Durie. Lancet. 2017;389:519. 6. Facon. ASH 2018. Abstr LBA-2. 7. O'Donnell. Br J Haematol. 2018;182:222.

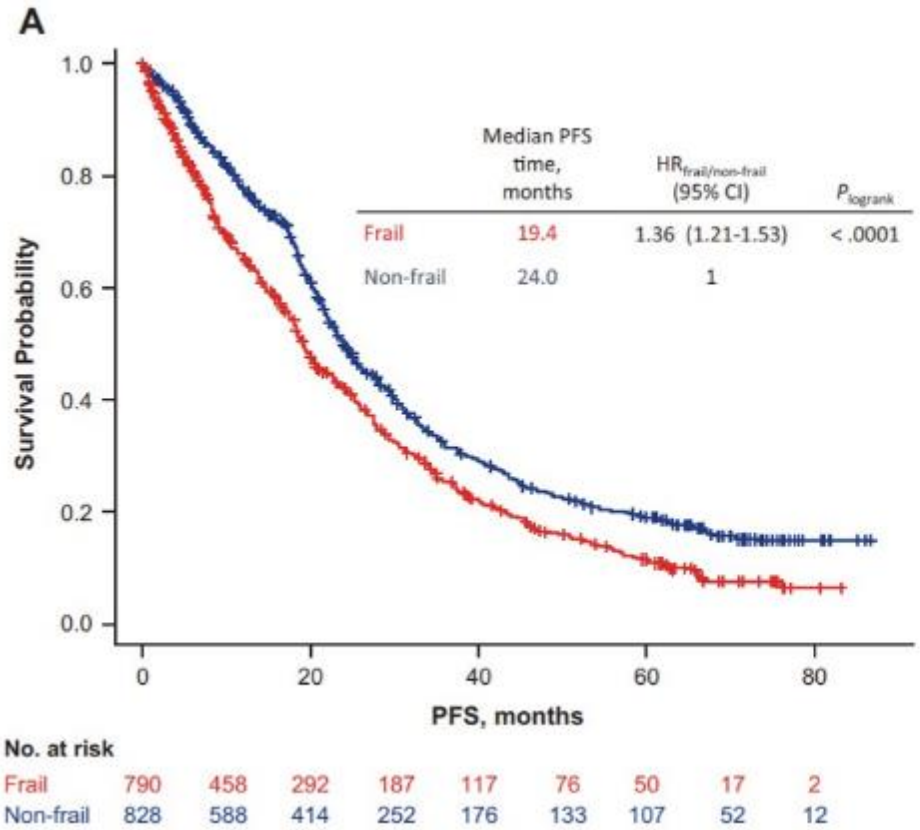
Direct comparison between trials is not intended and should not be inferred. HR, hazard ratio; NR, not reached; NSCT, non-stem cell transplant; PFS, progression-free survival; Rd, lenalidomide, low-dose dexamethasone; RdD, daratumumab, lenalidomide, dexamethasone; RVd, lenalidomide, bortezomib and dexamethasone; VMP; bortezomib, melphalan, prednisone.

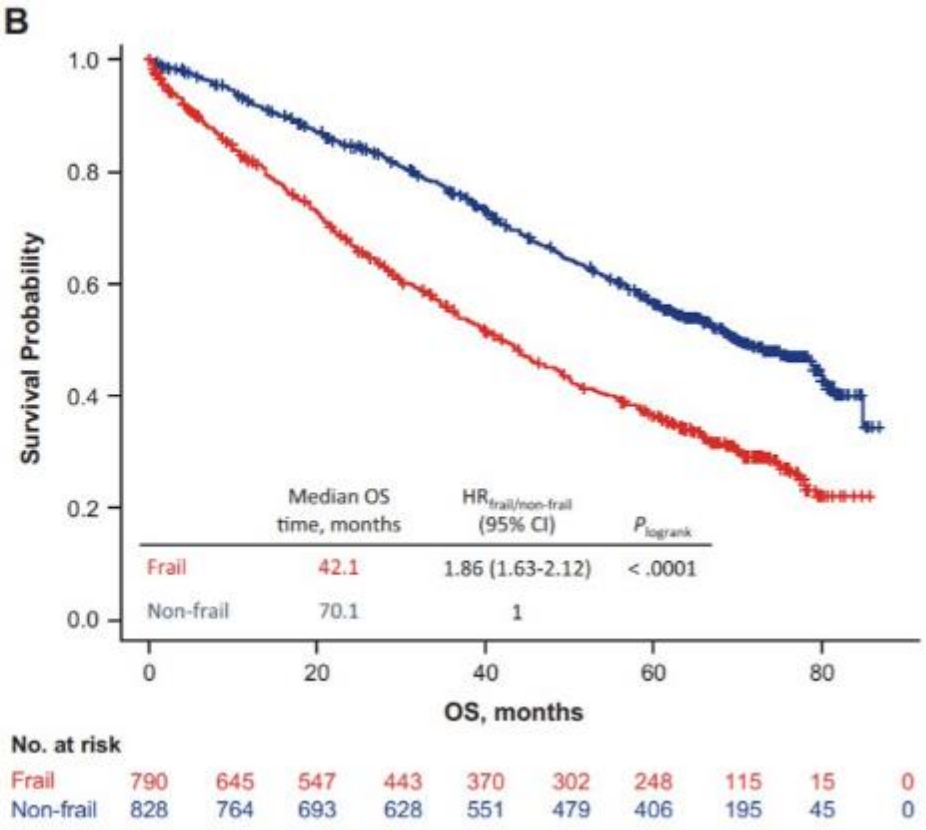
Accumulative Lines of Therapy Received by Age at Diagnosis : Best Therapy Should Be Used Upfront in Elderly Patients



Courtesy of A Spencer

PFS and OS by Frailty Level in the FIRST Study

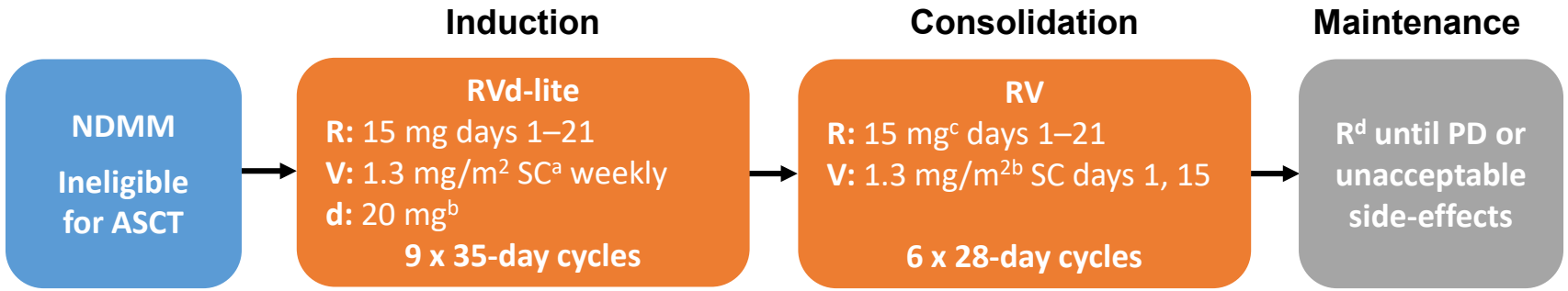




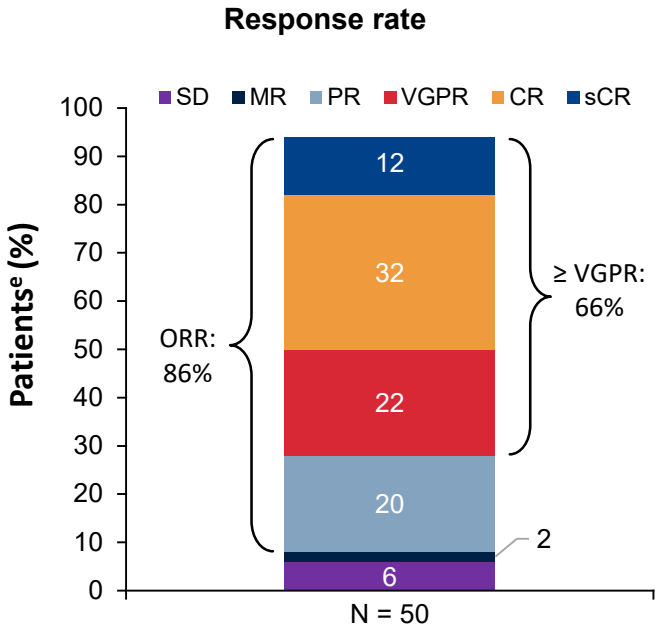
Category	Score
Age	
• ≤ 75 years	0
• 76-80 years	1
• > 80 years	2
Charlson Comorbidity Index	
• ≤ 1	0
• > 1	1
ECOG PS	
• 0	0
• 1	1
• ≥ 2	2
Sum of scores	
• Non-frail	0-1
• Frail	≥ 2

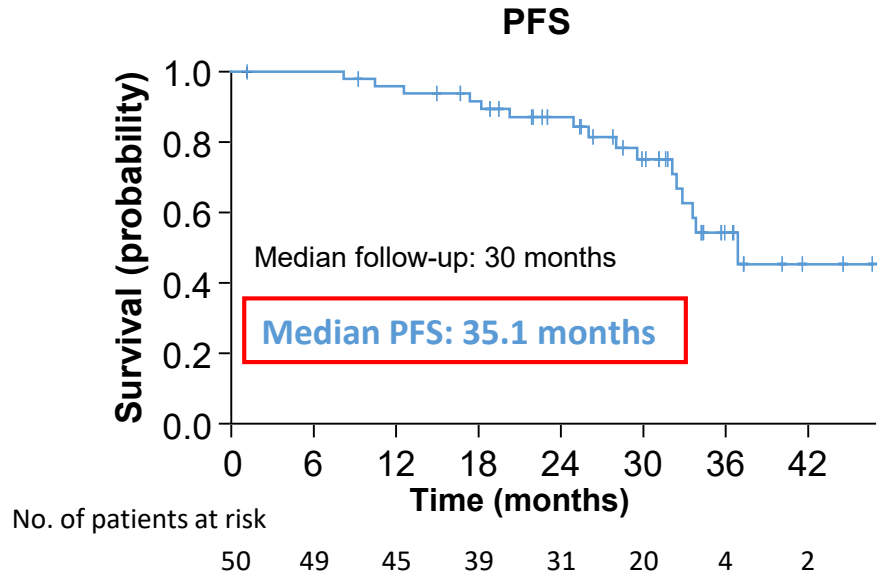
Facon. Leukemia. 2020;34:224.

Modified RVd (RVd-lite) in Transplant-Ineligible MM



Baseline characteristics, %	N = 50
Median age (range), years	73 (65–91)
ISS stage at diagnosis	
I	38
II	34
III	28
ECOG PS score	
0	50
1	36
2	14

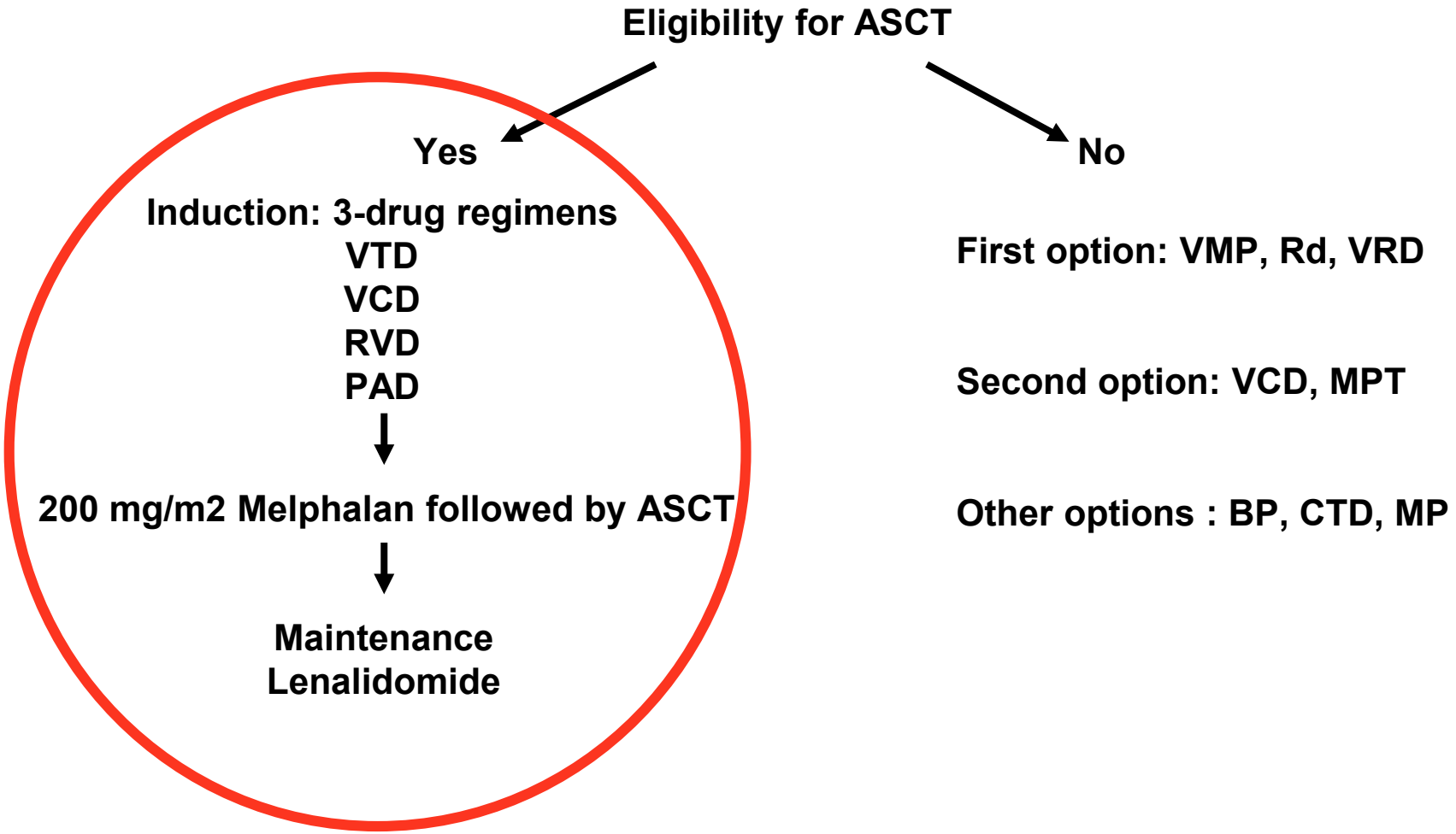




- ≥ CR was 44% (ITT population, N = 50)
- ORR was 86%, ≥ VGPR was 66% for patients evaluable for response[a] after 4 cycles (n = 46)
- Median TTR was 1.1 months
- Grade 3/4 peripheral neuropathy was 2%, neutropenia was 14%

[a] The first 10 patients received BORT IV for cycle 1 only followed by SC administration. Subsequent patients received BORT SC. [b] Days 1, 2, 8, 9, 15, 16, 22, 23 for patients ≤ 75 years; days 1, 8, 15, 22 for patients > 75 years. [c] Or last tolerated dose as of cycle 9. [d] Optional. [e] 6% of patients received < 4 cycles of therapy and were therefore not evaluable. MR, minimal response; TTR, time to response.

O'Donnell. Br J Haematol. 2018;182:222.



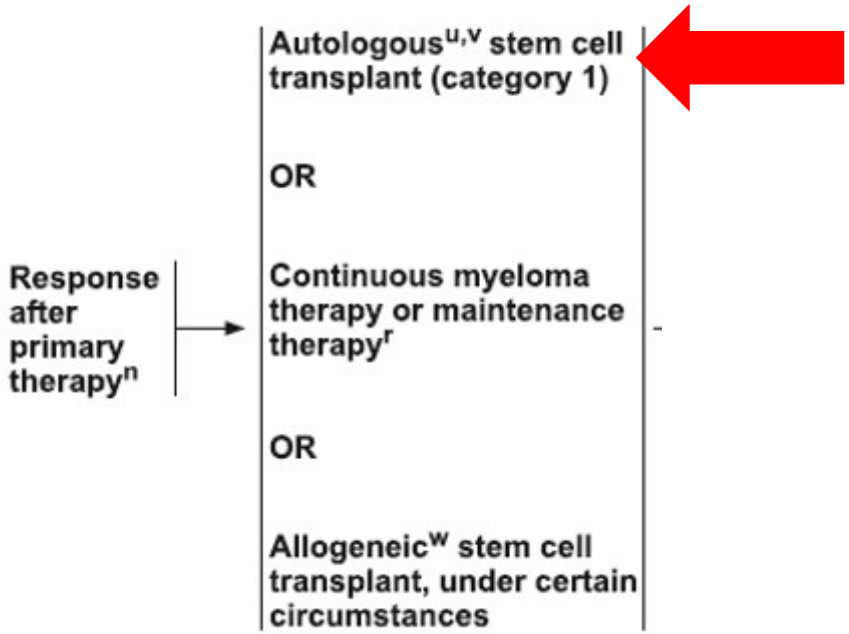
...”< 66 years *Or*
fit patients < 70 years in good clinical condition”…

FRONTLINE THERAPY
ESMO guidelines
Moreau et al, Ann Oncol 2017

Multiple Myeloma, Version 1.2020

Featured Updates to the NCCN Guidelines

Shaji K. Kumar, MD[1,*]; Natalie S. Callander, MD[2,*]; Jens Hillengass, MD[3,*]; Michaela Liedtke, MD[4,*]; Muhamed Baljevic, MD[5]; Erica Campagnaro, MD[6]; Jorge J. Castillo, MD[7]; Jason C. Chandler, MD[8]; Robert F. Cornell, MD, MPH[9]; Caitlin Costello, MD[10]; Yvonne Efebera, MD, MPH[11]; Matthew Faiman, MD[12]; Alfred Garfall, MD[13]; Kelly Godby, MD[14]; Leona Holmberg, MD, PhD[15]; Myo Htut, MD[16]; Carol Ann Huff, MD[17]; Yubin Kang, MD[18]; Ola Landgren, MD, PhD[19]; Ehsan Malek, MD[12]; Thomas Martin, MD[20]; James Omel, MD[21]; Noopur Raje, MD[22]; Douglas Sborov, MD, MSc[23]; Seema Singhal, MD[24]; Keith Stockerl-Goldstein, MD[25]; Carlyn Tan, MD[26]; Donna Weber, MD[27]; Alyse Johnson-Chilla, MS[28,*]; Jennifer Keller, MSS[28,*]; and Rashmi Kumar, PhD[28,*]



JNCCN.org | Volume 17 Issue 10 October 2019

INDUCTION

↓

ASCT prepared by melphalan 200 mg/m^2

↓

(Consolidation)

↓

Maintenance

VRD x 6, 458 patients

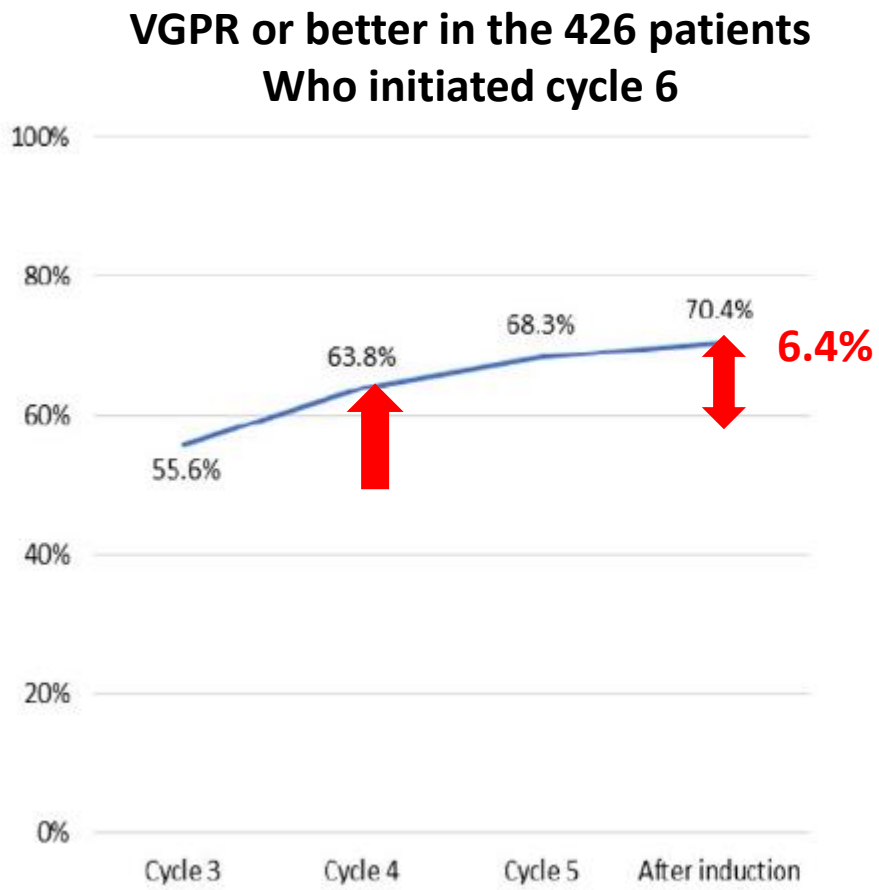
GEM2012 trial

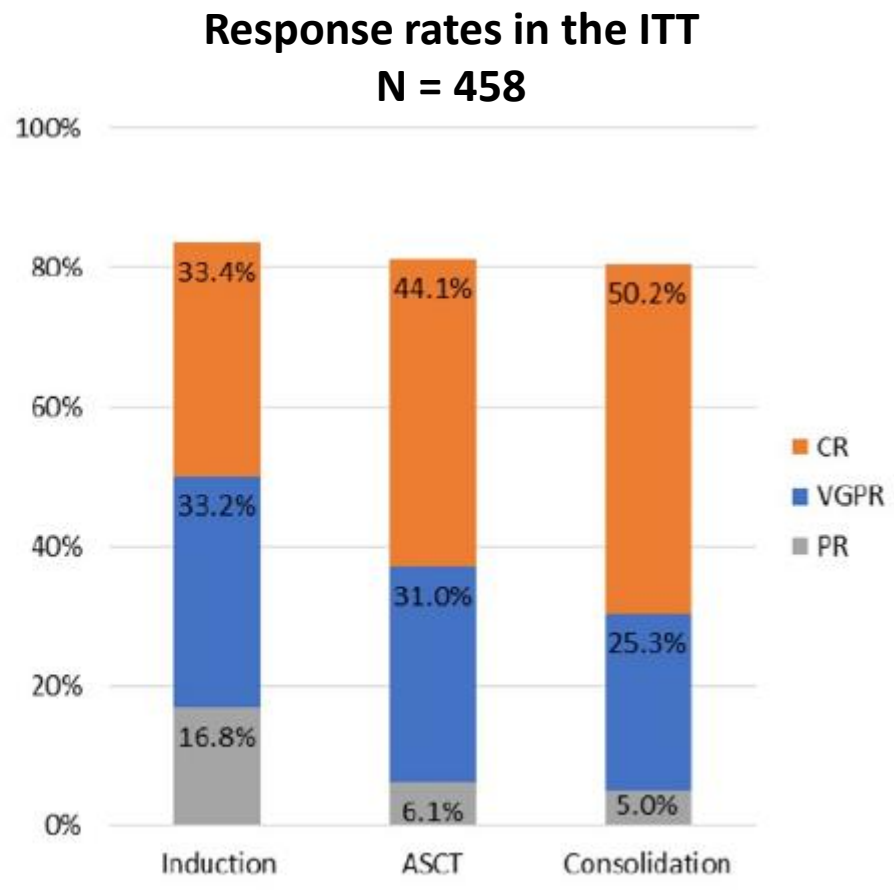
blood®

Prepublished online September 4, 2019;
doi:10.1182/blood.2019000241

Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplantation in multiple myeloma

Laura Rosiñol, Albert Oriol, Rafael Rios, Anna Sureda, María-Jesús Blanchard, Miguel Teodoro Hernández, Rafael Martínez-Martínez, Jose M Moraleda, Isidro Jarque, Juan Bargay, Mercedes Gironella, Felipe de Arriba, Luis Palomera, Yolanda Gonzalez-Montes, Josep Marti, Isabel Krsnik, Jose M Arguiñano, Maria-Esther Gonzalez, Ana Pilar Gonzalez, Luis Felipe Casado, Lucia Lopez-Anglada, Bruno Paiva, Maria-Victoria Mateos, Jesus San Miguel, Juan-José Lahuerta and Joan Bladé



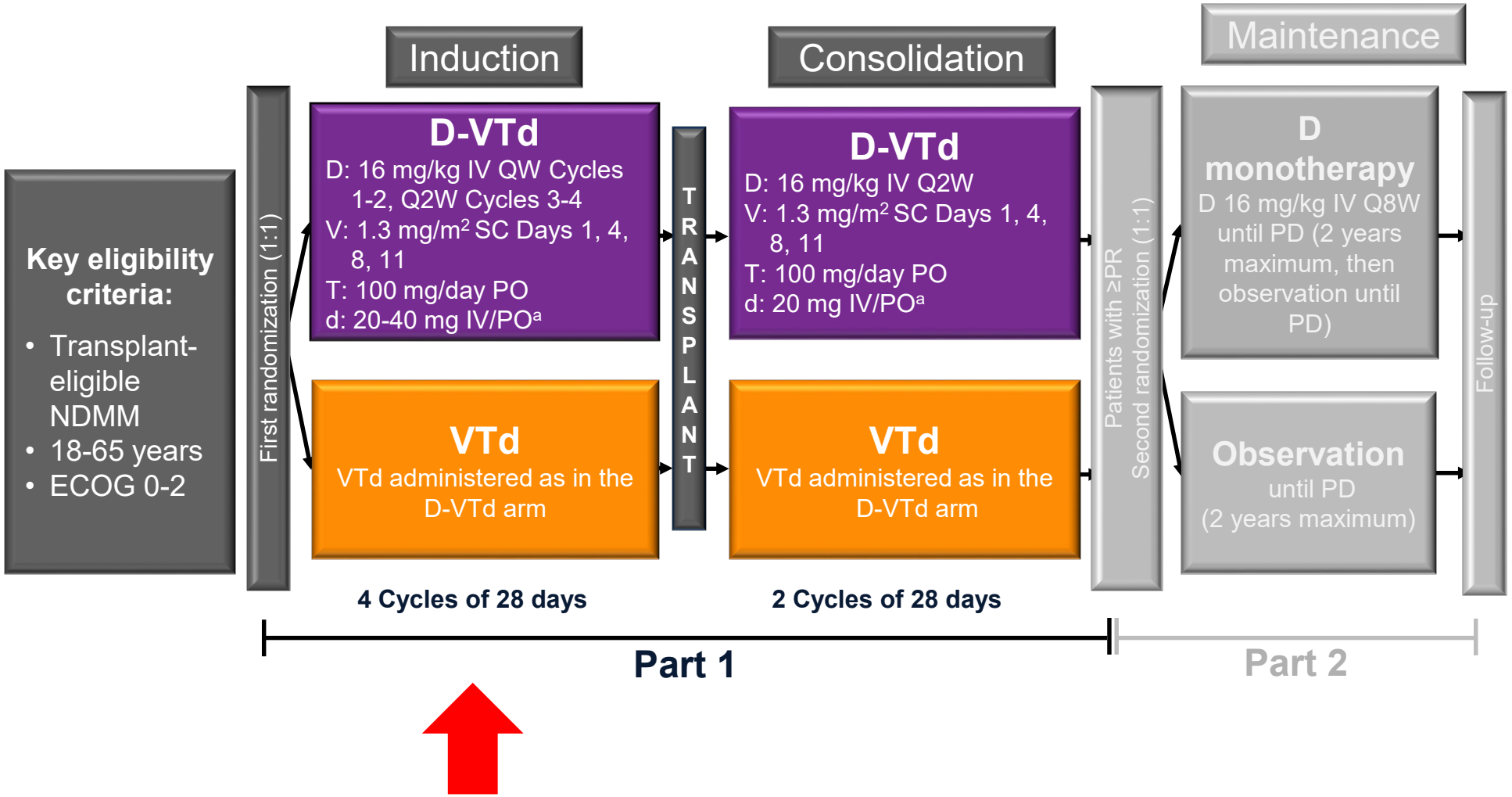


Median number of CD34+ cells (3 cycles) : 4.66 10_6/kg

Rosinol. Blood 2019;134:1337.

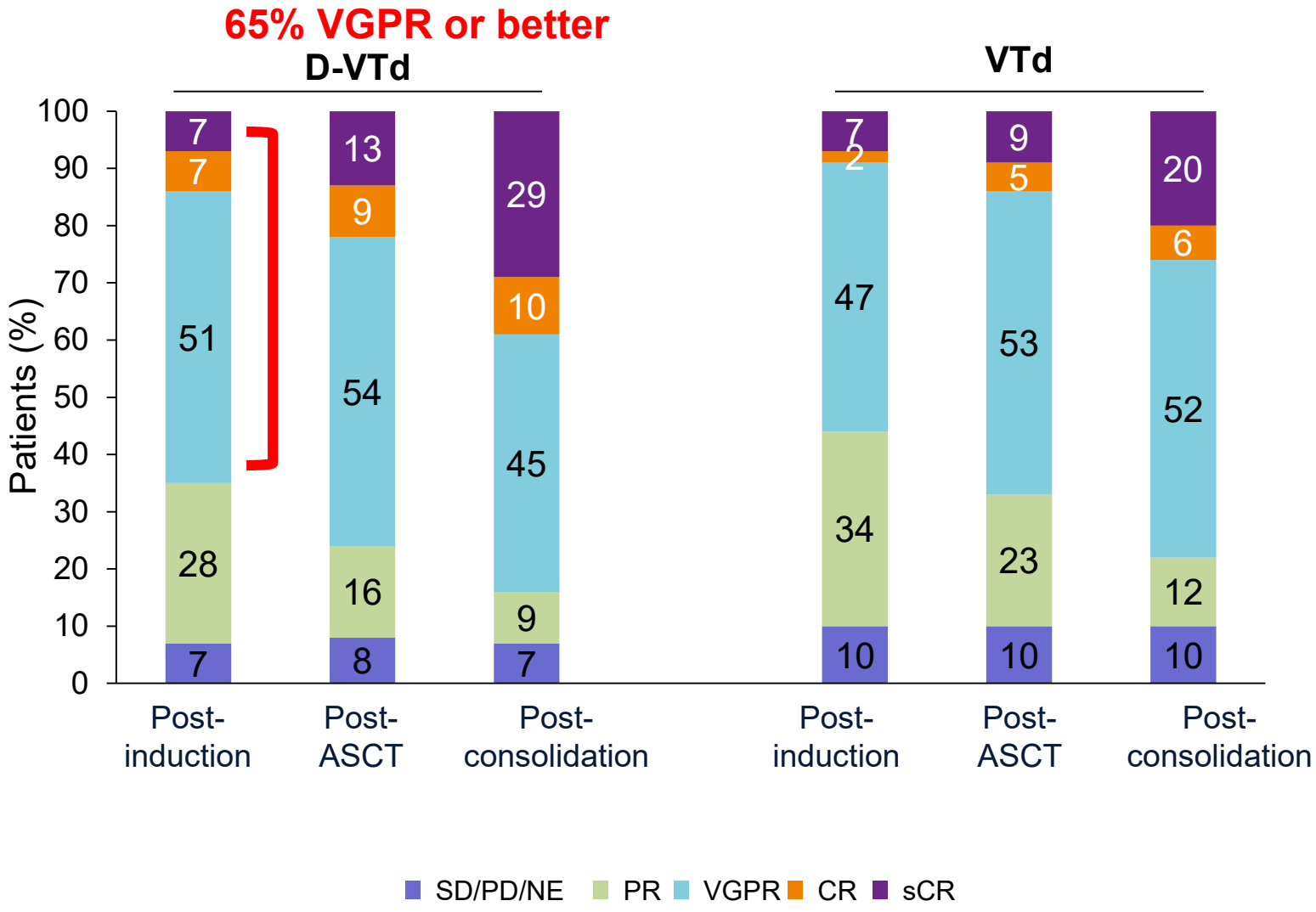
CASSIOPEIA Study Design

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



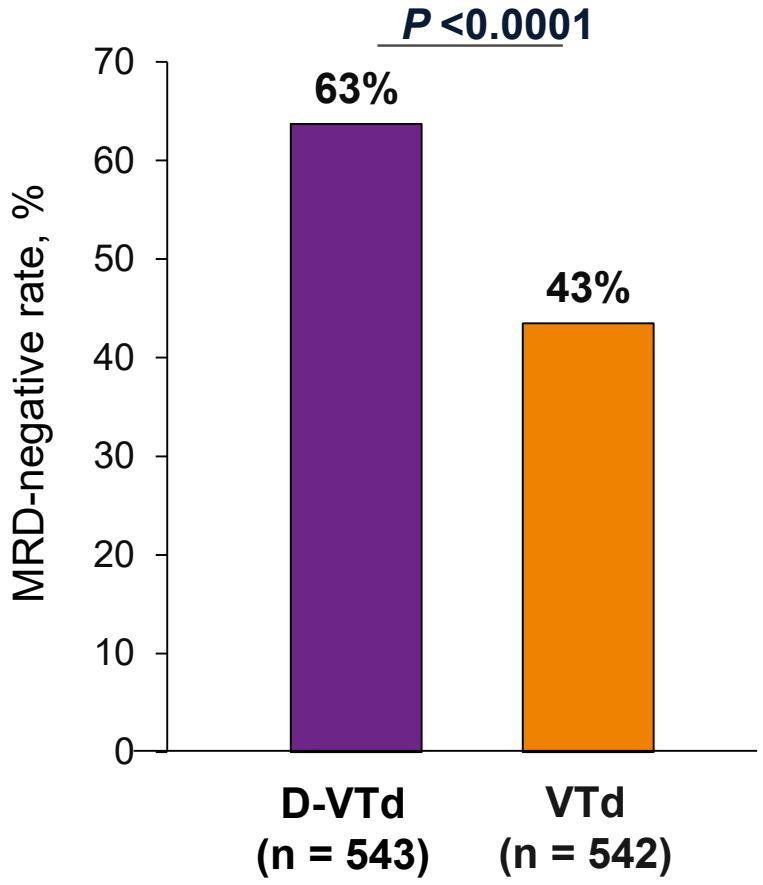
Moreau. The Lancet. 2019 Jul 6;394:29.

Efficacy: Response Rates Over Time

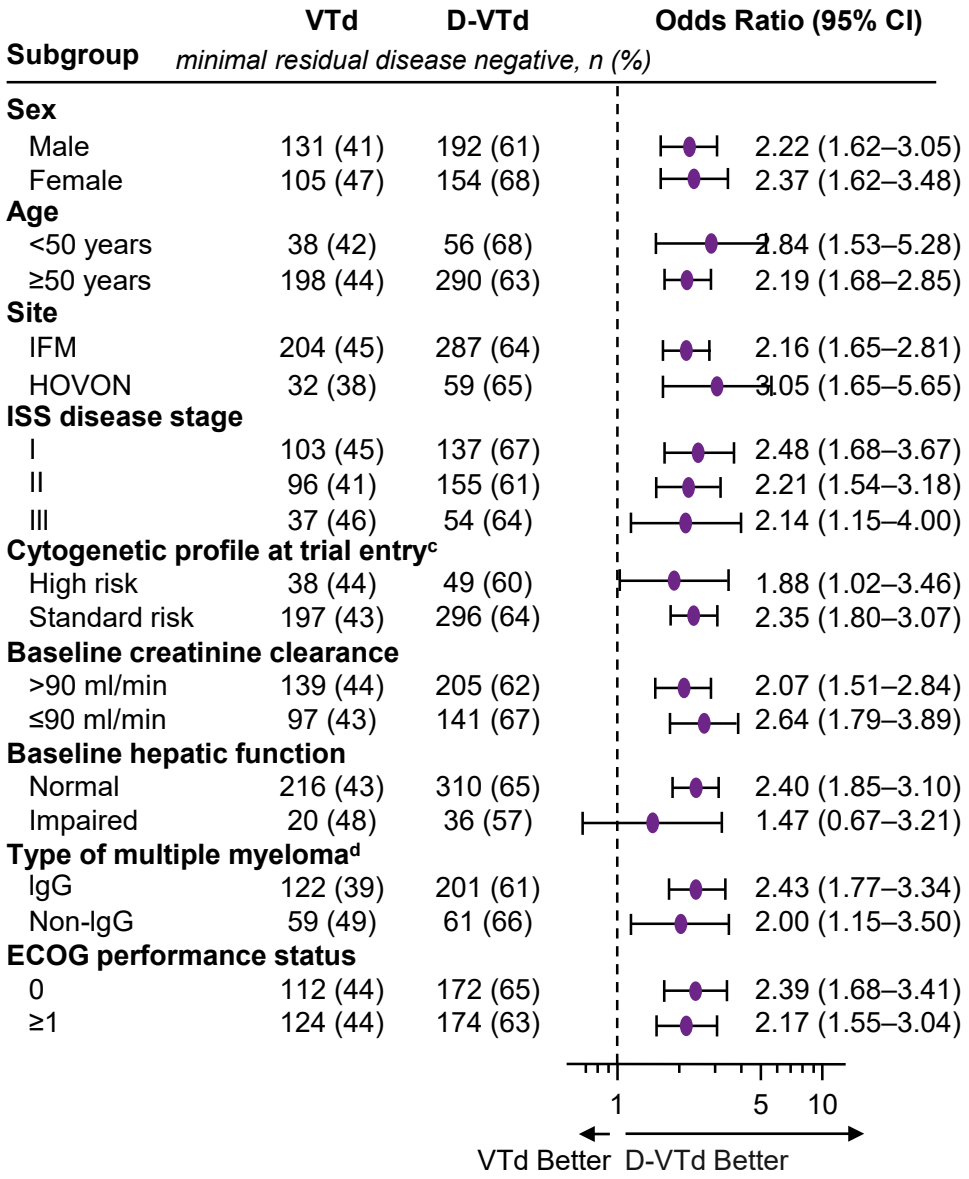


Moreau. The Lancet. 2019 Jul 6;394:29.

Efficacy: MRD (Flow Cytometry; 10^{-5})



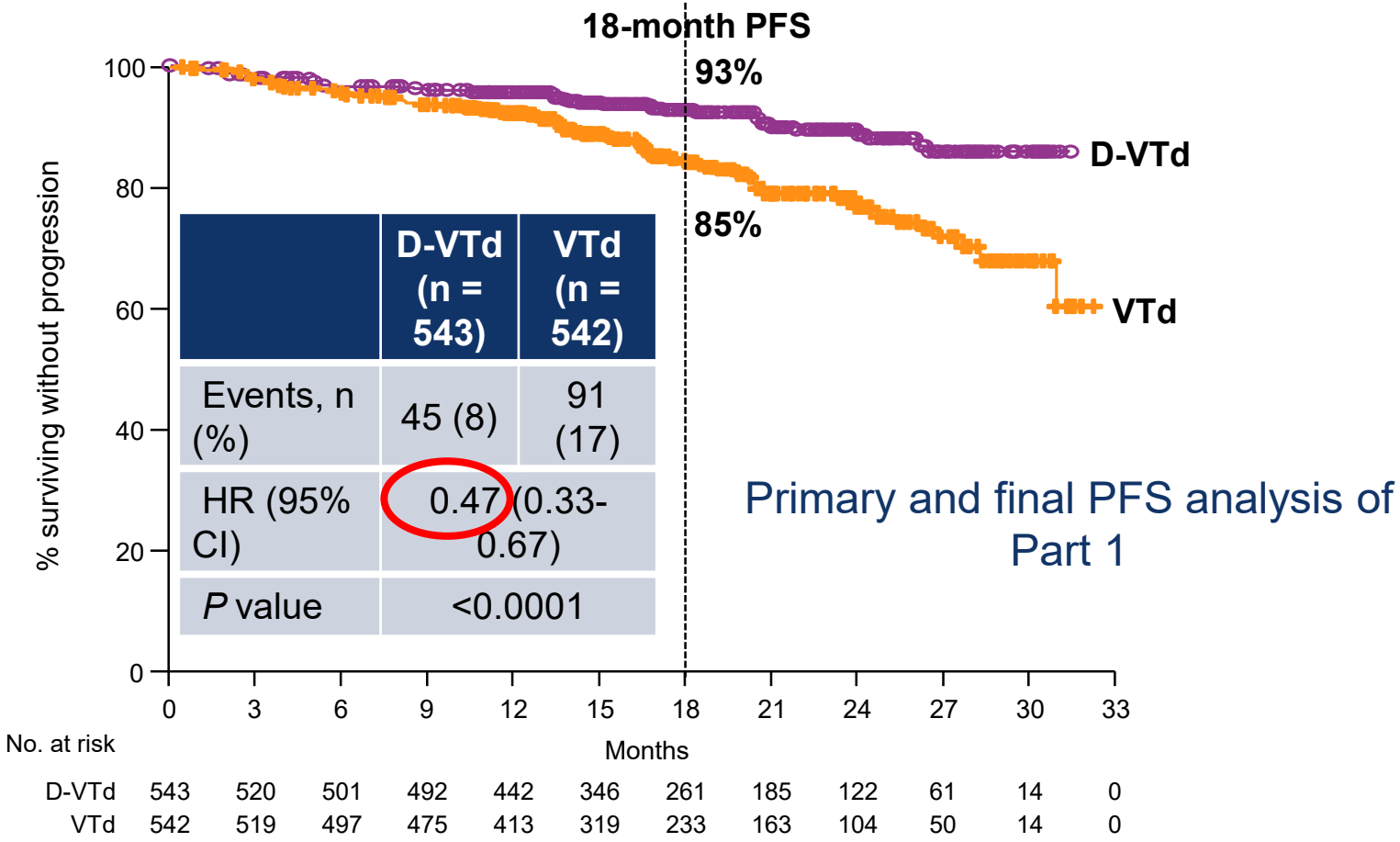
D-VTd superior across all subgroups including high-risk cytogenetics and ISS stage III



Moreau. The Lancet. 2019 Jul 6;394:29.

Efficacy: PFS From First Randomization

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



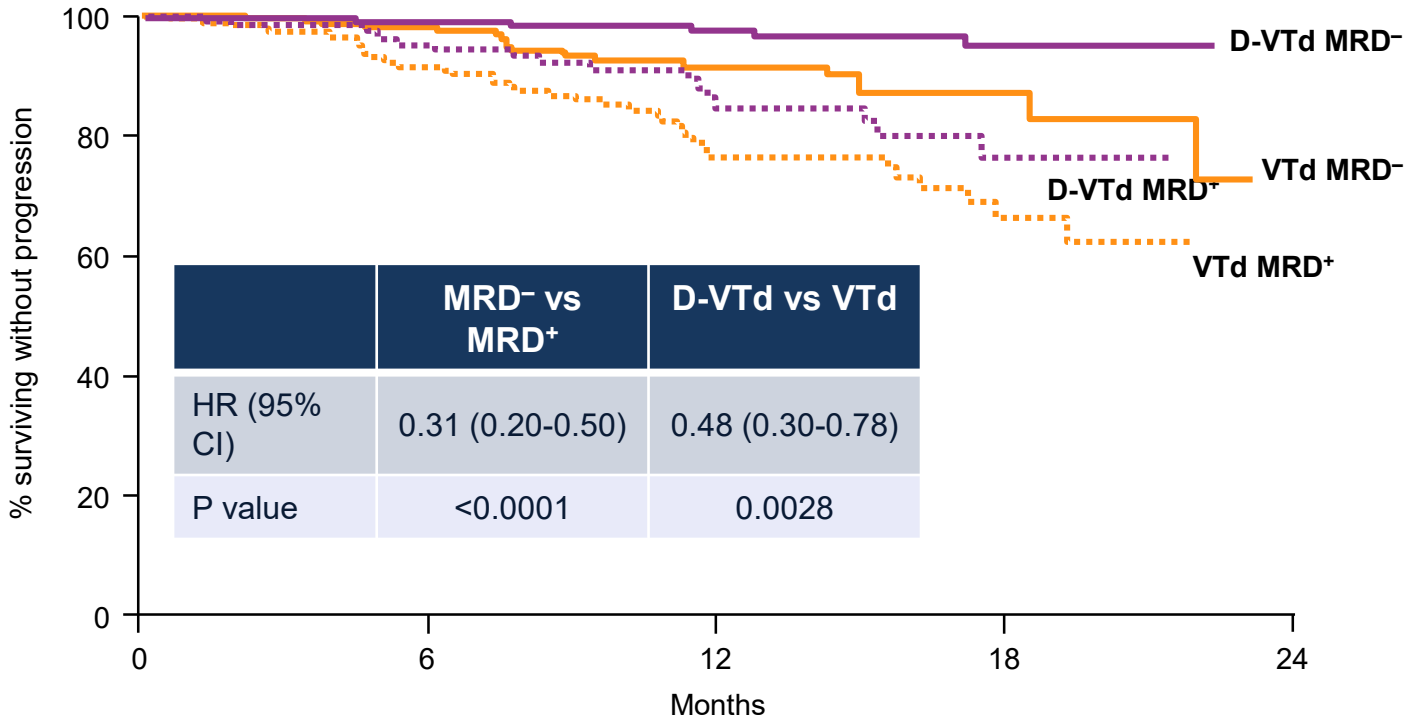
	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	45 (8)	91 (17)
HR (95% CI)	0.47 (0.33-0.67)	
P value	<0.0001	

Primary and final PFS analysis of Part 1

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

Moreau. The Lancet. 2019 Jul 6;394:29.

Post-consolidation PFS by MRD Status (MFC; 10^{-5})



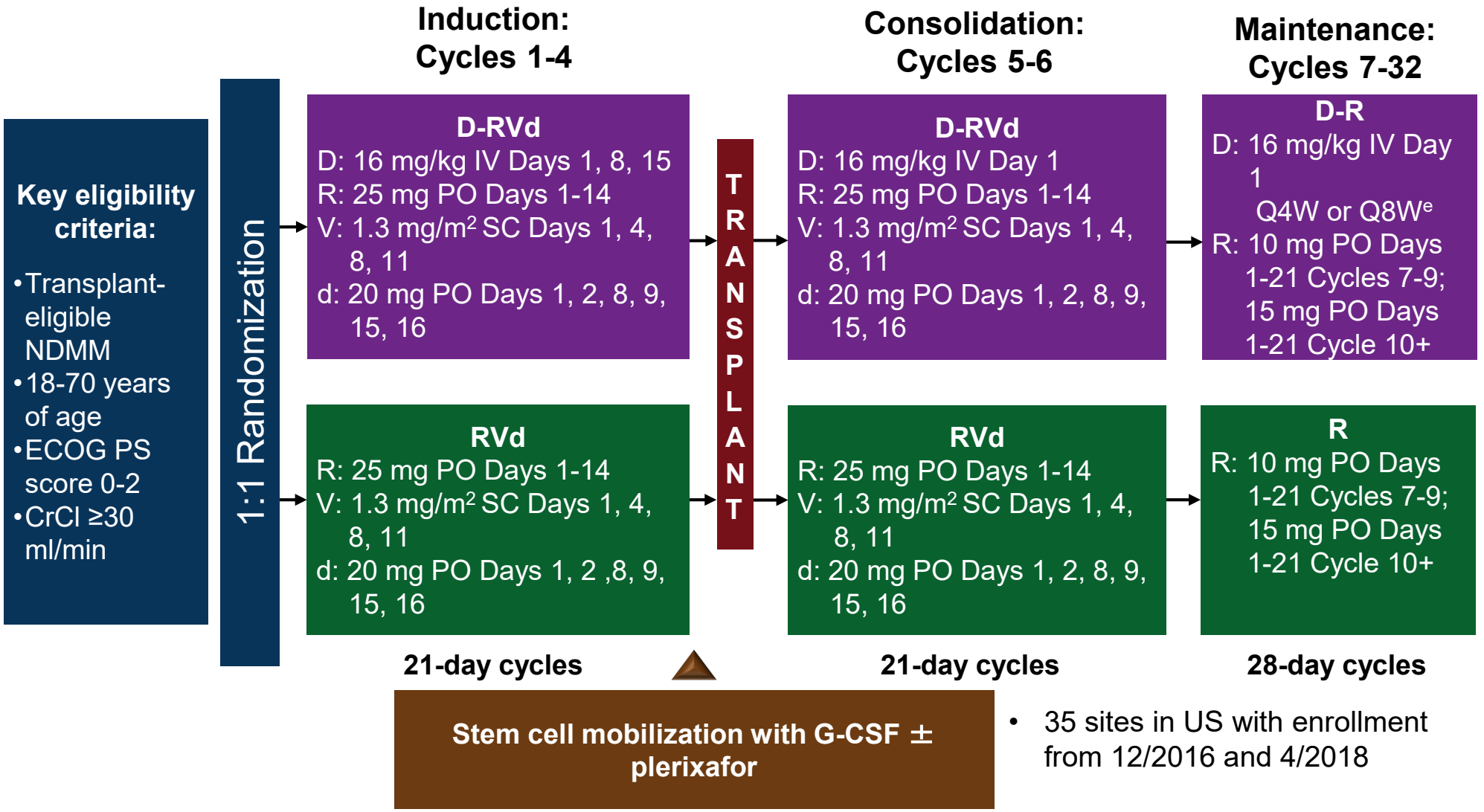
	MRD⁻ vs MRD⁺	D-VTd vs VTd
HR (95% CI)	0.31 (0.20-0.50)	0.48 (0.30-0.78)
P value	<0.0001	0.0028

No. at risk					
D-VTd MRD⁻	344	241	132	44	0
VTd MRD⁻	232	167	88	27	0
D-VTd MRD⁺	148	105	53	17	0
VTd MRD⁺	243	152	75	23	0

PFS benefit for D-VTd versus VTd in patients achieving MRD negativity

Avet-Loiseau et al. EHA 2019

Randomized Phase 2 GRIFFIN Study: RVd + Daratumumab in ASCT-Eligible Patients[1]



- 35 sites in US with enrollment from 12/2016 and 4/2018

Endpoints & statistical assumptions

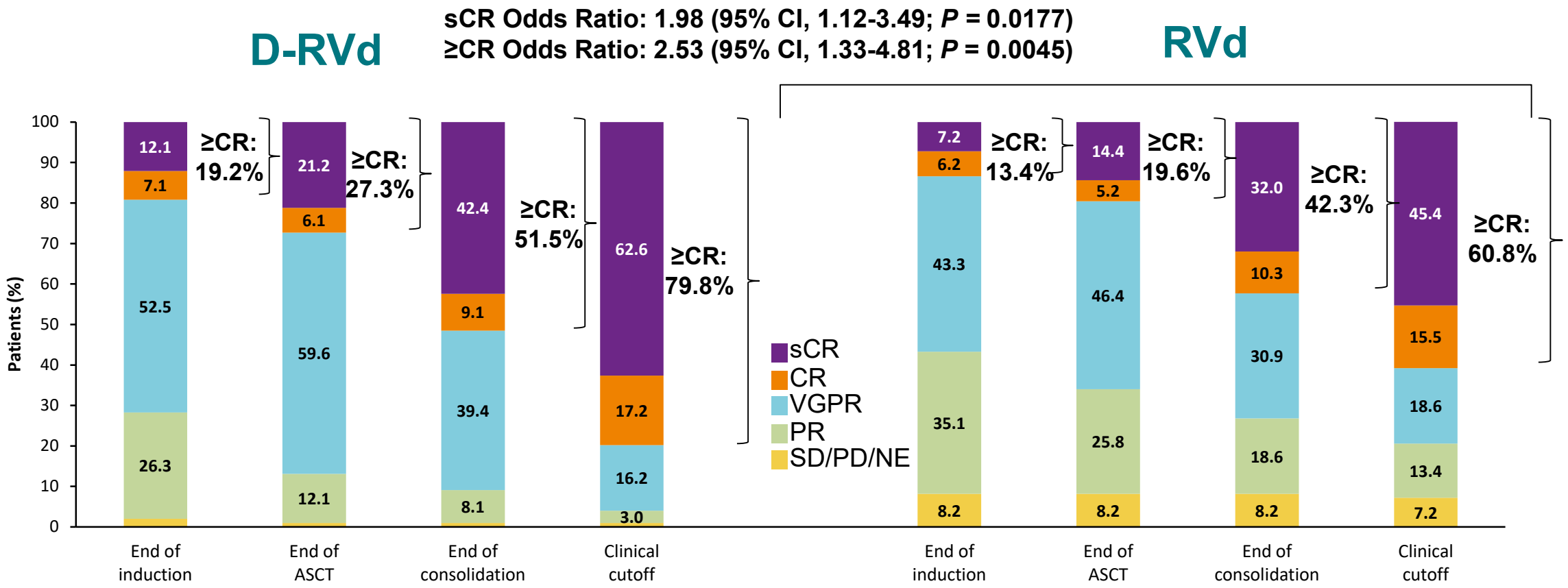
Primary endpoint:
sCR rate (by end of consolidation);
1-sided alpha of 0.1

80% power to detect 15% improvement (50% vs 35%), N = 200

Secondary endpoints:
rates of MRD negativity (measured by clonoSEQ; NGS 10^{-5}), CR, ORR, ≥VGPR

Voorhees. Blood. 2020;136:936.

GRIFFIN: Responses Deepened Over Time



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

Voorhees. Blood. 2020;136:936.

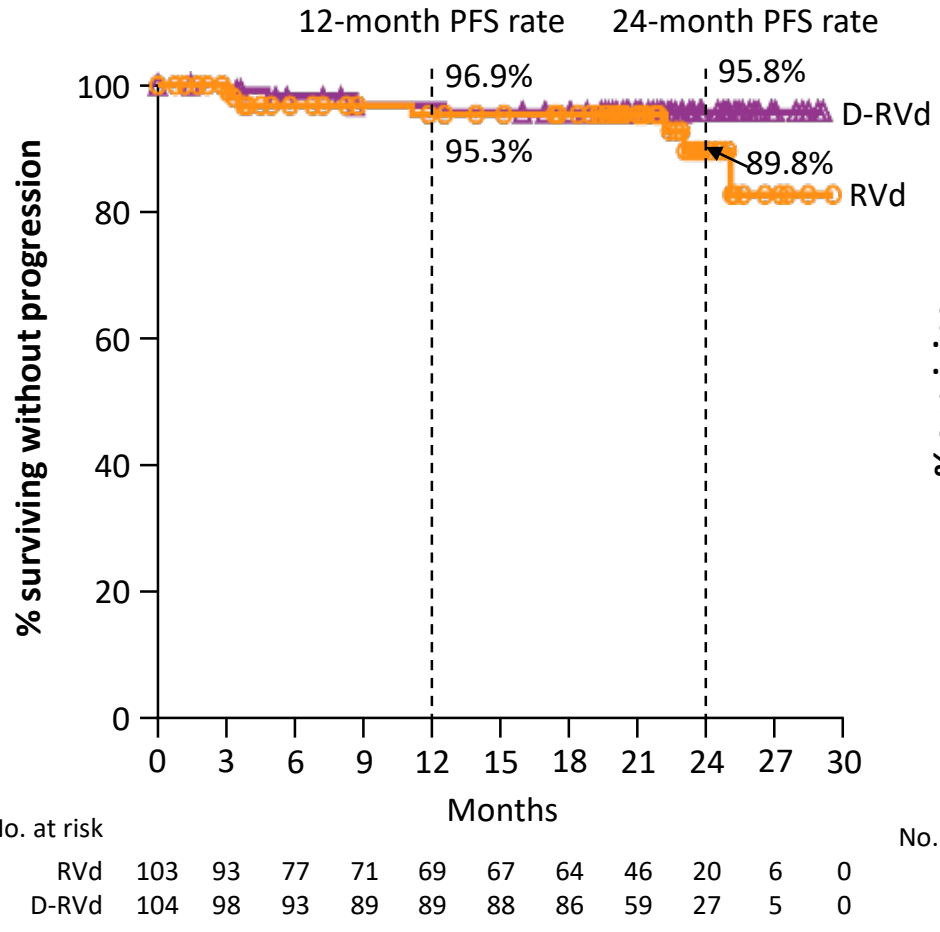
Post-Consolidation MRD Negativity

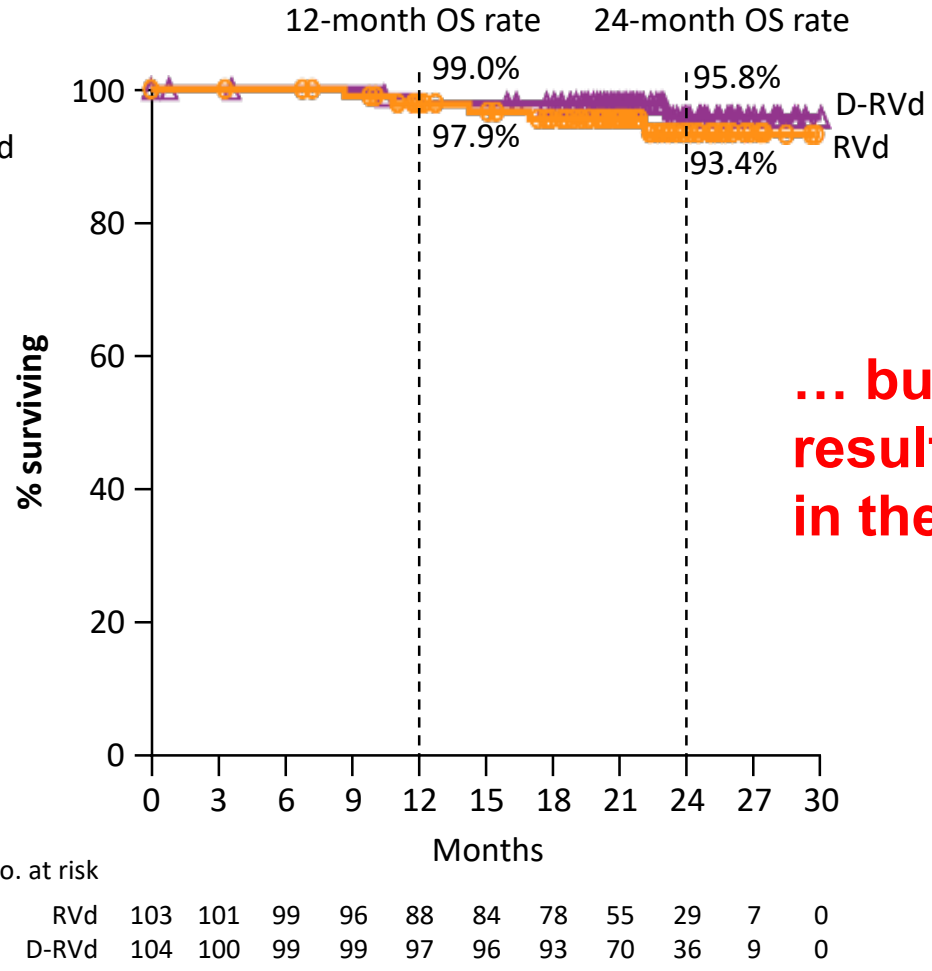
MRD-Negative Status (10^{-5}),[a] n (%)	D-RVd	RVd	Odds Ratio (95% CI)	*P* value[b]
In ITT population				
MRD negative regardless of response	46/104 (**44.2**)	15/103 (**14.6**)	4.70 (2.38-9.28)	<0.0001
MRD negative with CR or better	30/104 (**28.8**)	10/103 (**9.7**)	3.73 (1.71-8.16)	0.0007
In patients 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

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.

D-RVd: Estimated PFS and OS (>95%) at 2 Years…



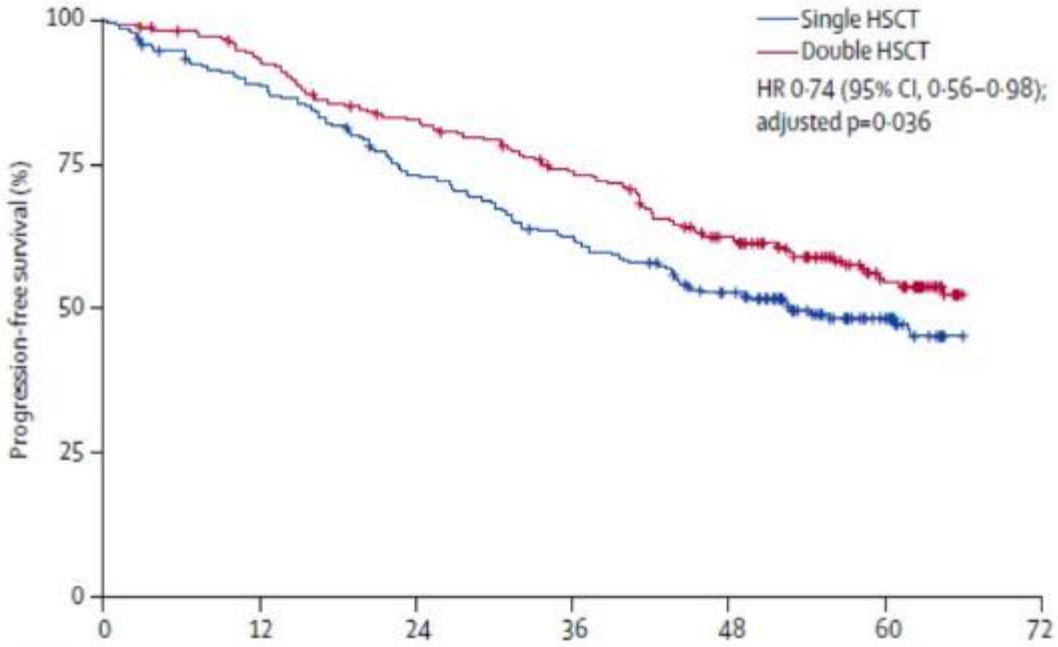


… but impressive results also achieved in the RVd arm !!

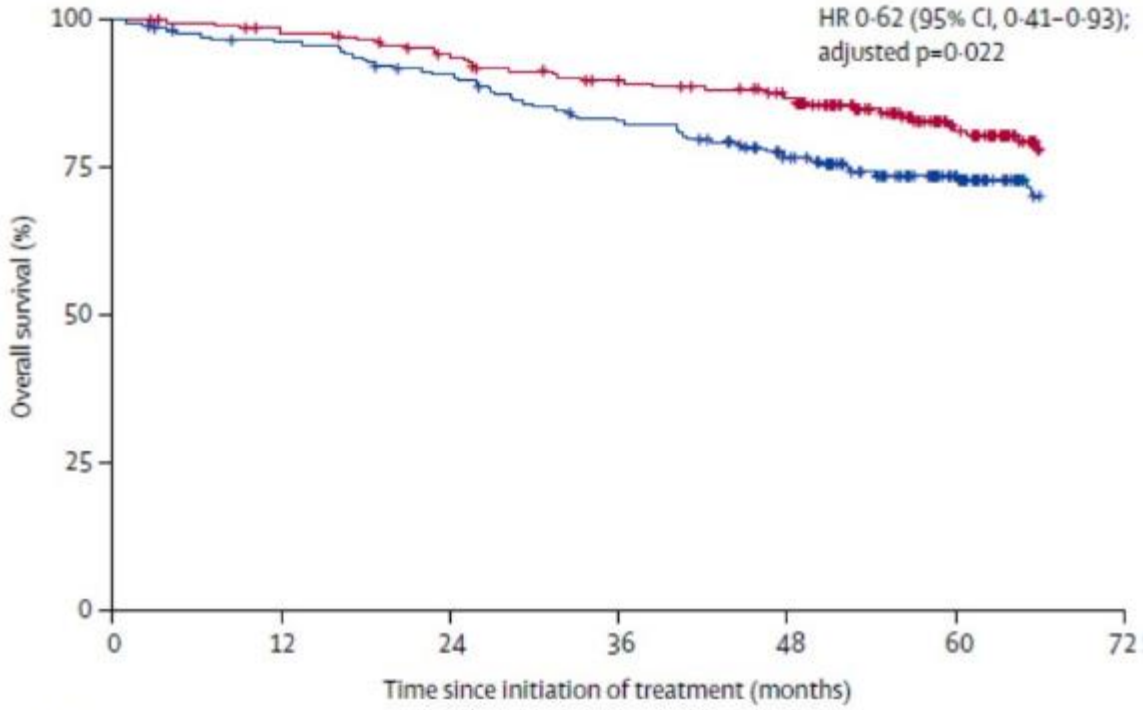
- **Median follow-up = 22.1 months**

Voorhees. Blood. 2020;136:936. Voorhees ASH 2019. Abstr 691.

Role of tandem ASCT



Number at risk (number censored)							
Double HSCT	210 (0)	192 (4)	167 (7)	145 (11)	115 (19)	68 (54)	..
Single HSCT	209 (0)	181 (5)	147 (7)	124 (8)	97 (16)	53 (54)	..



Number at risk (number censored)							
Double HSCT	210 (0)	201 (4)	189 (8)	175 (15)	159 (24)	100 (75)	..
Single HSCT	209 (0)	195 (6)	182 (8)	164 (10)	141 (21)	85 (72)	..

5-year PFS
53.5% vs 44.9%

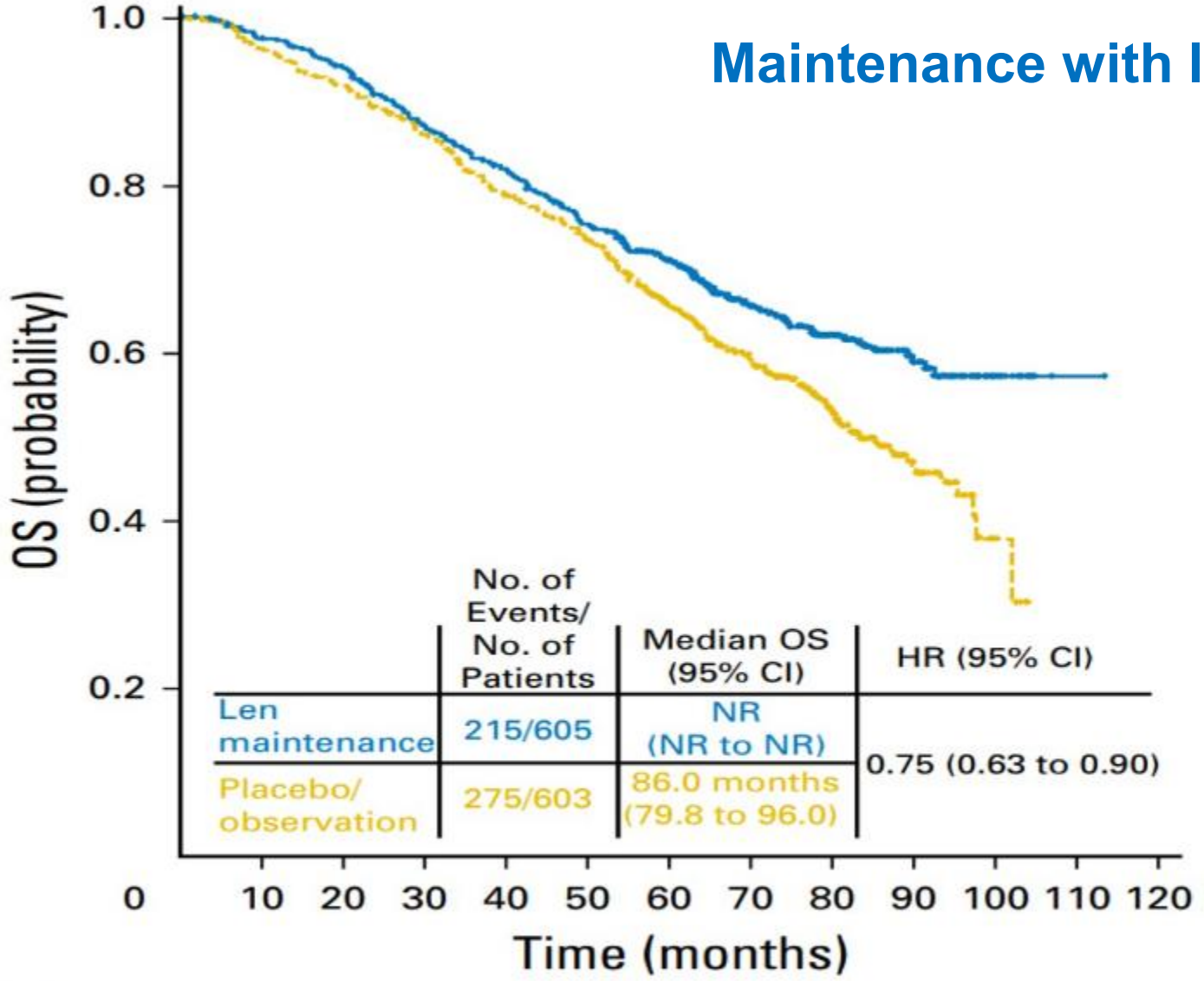
5-year OS
83.3% vs 72.6%

Lancet Haematol 2020;
7: e456–68

Published Online
April 30, 2020

Cavo et al. EMN02 study

Maintenance with lenalidomide



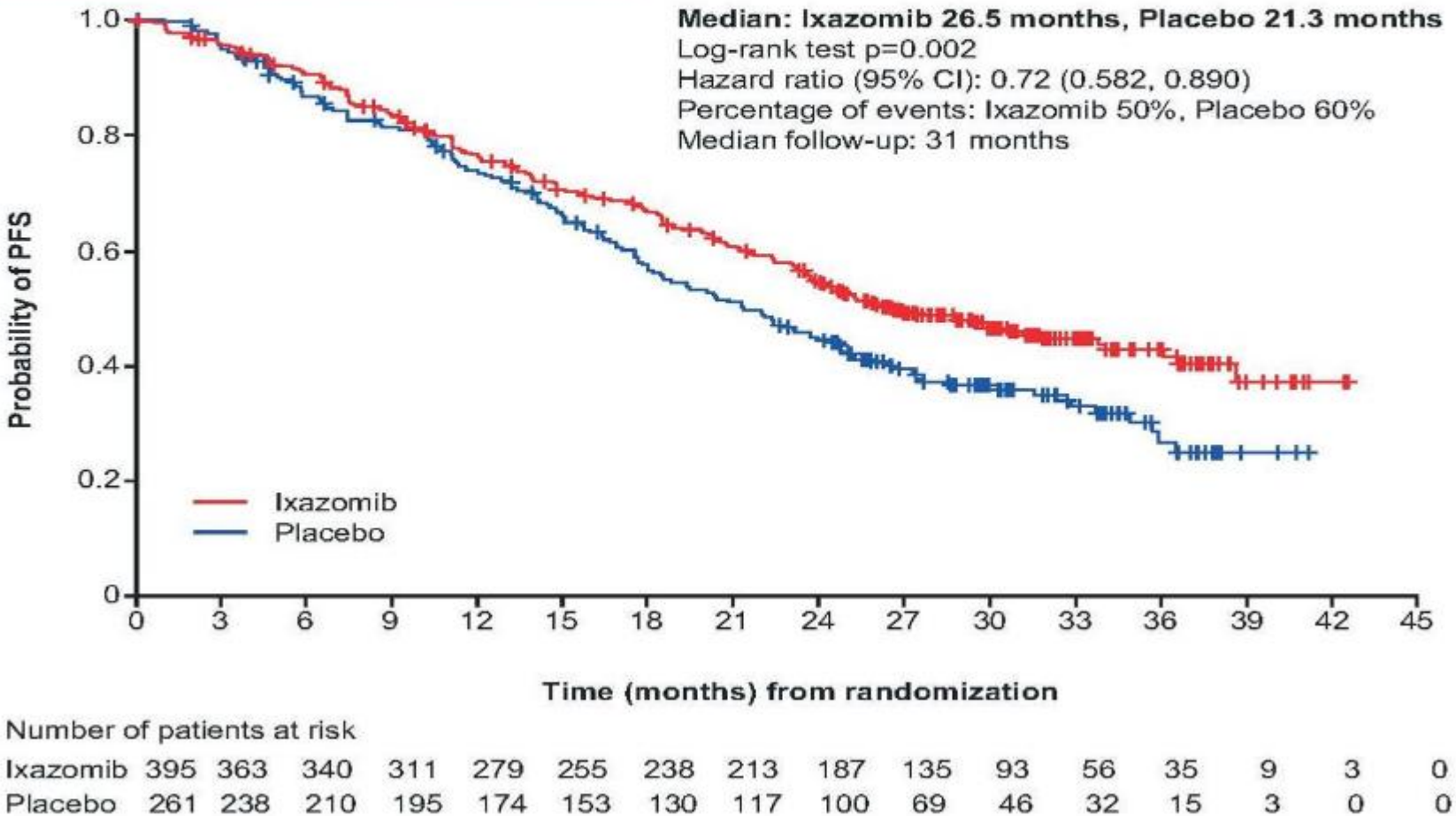
No. at risk:

Len maintenance	605	577	555	508	473	431	385	282	200	95	20	1	0
Placebo/ observation	603	569	542	505	459	425	351	270	174	71	10	0	

McCarthy. JCO. 2017;35:3279.

Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial

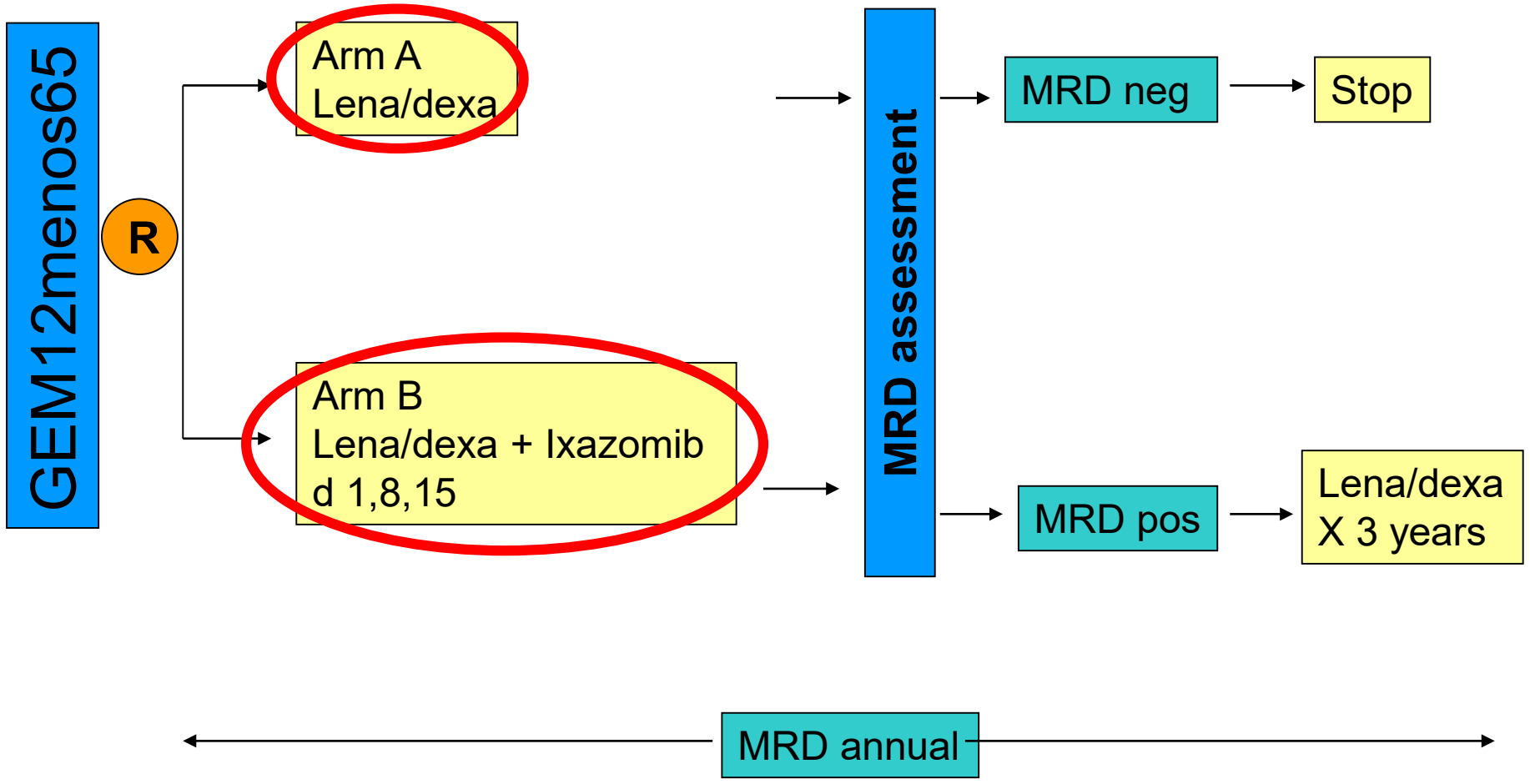
*Meletios A Dimopoulos, Francesca Gay, Fredrik Schjesvold, Meral Beksac, Roman Hajek, Katja Christina Weisel, Hartmut Goldschmidt, Vladimir Maisnar, Philippe Moreau, Chang Ki Min, Agnieszka Pluta, Wee-Joo Chng, Martin Kaiser, Sonja Zweegman, Maria-Victoria Mateos, Andrew Spencer, Shinsuke Iida, Gareth Morgan, Kaveri Suryanarayan, Zhaoyang Teng, Tomas Skacel, Antonio Palumbo, Ajeeta B Dash, Neeraj Gupta, Richard Labotka, S Vincent Rajkumar, on behalf of the TOURMALINE-MM3 study group**



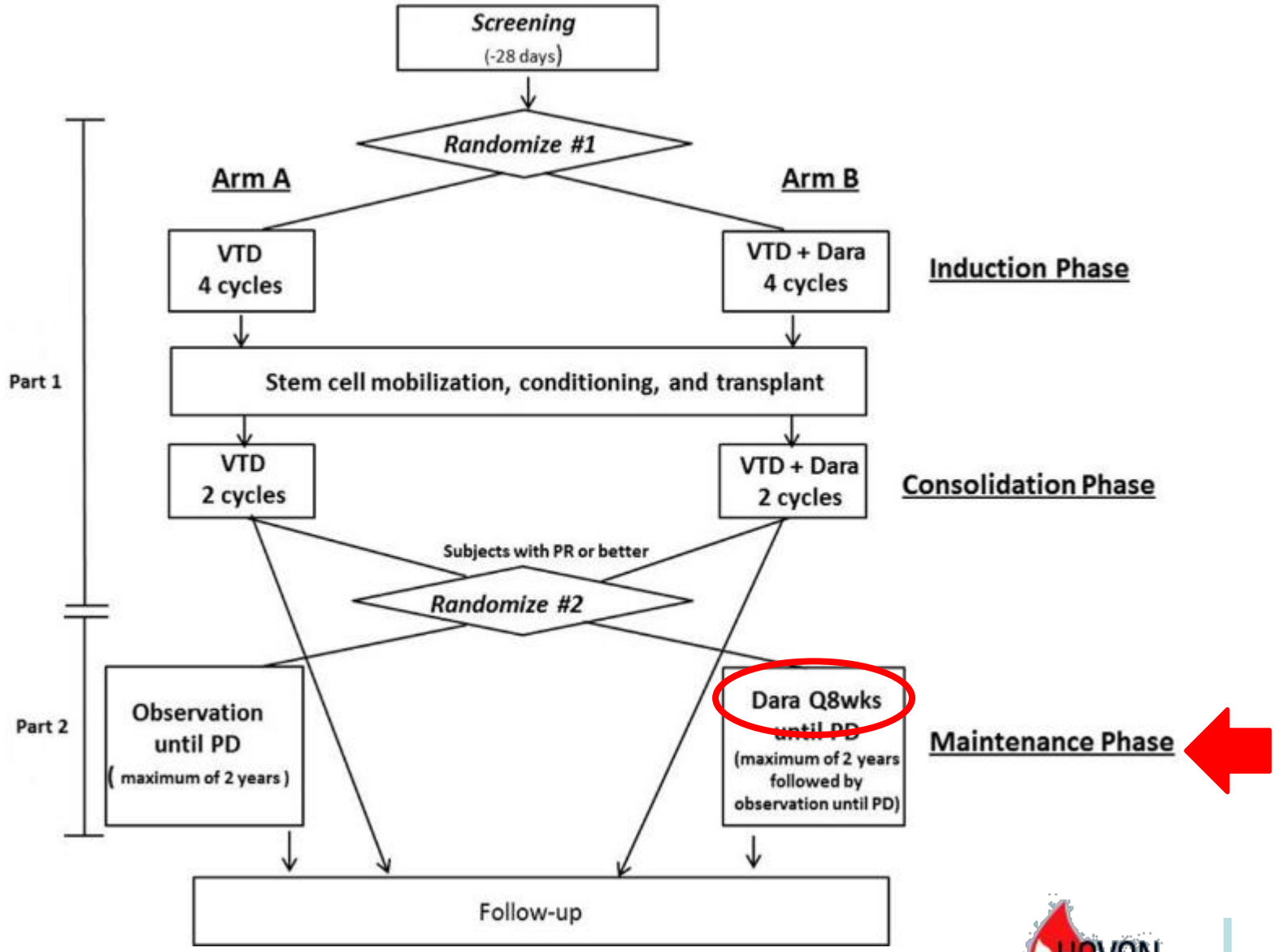
Dimopoulos et al. The Lancet 2019;393:253.

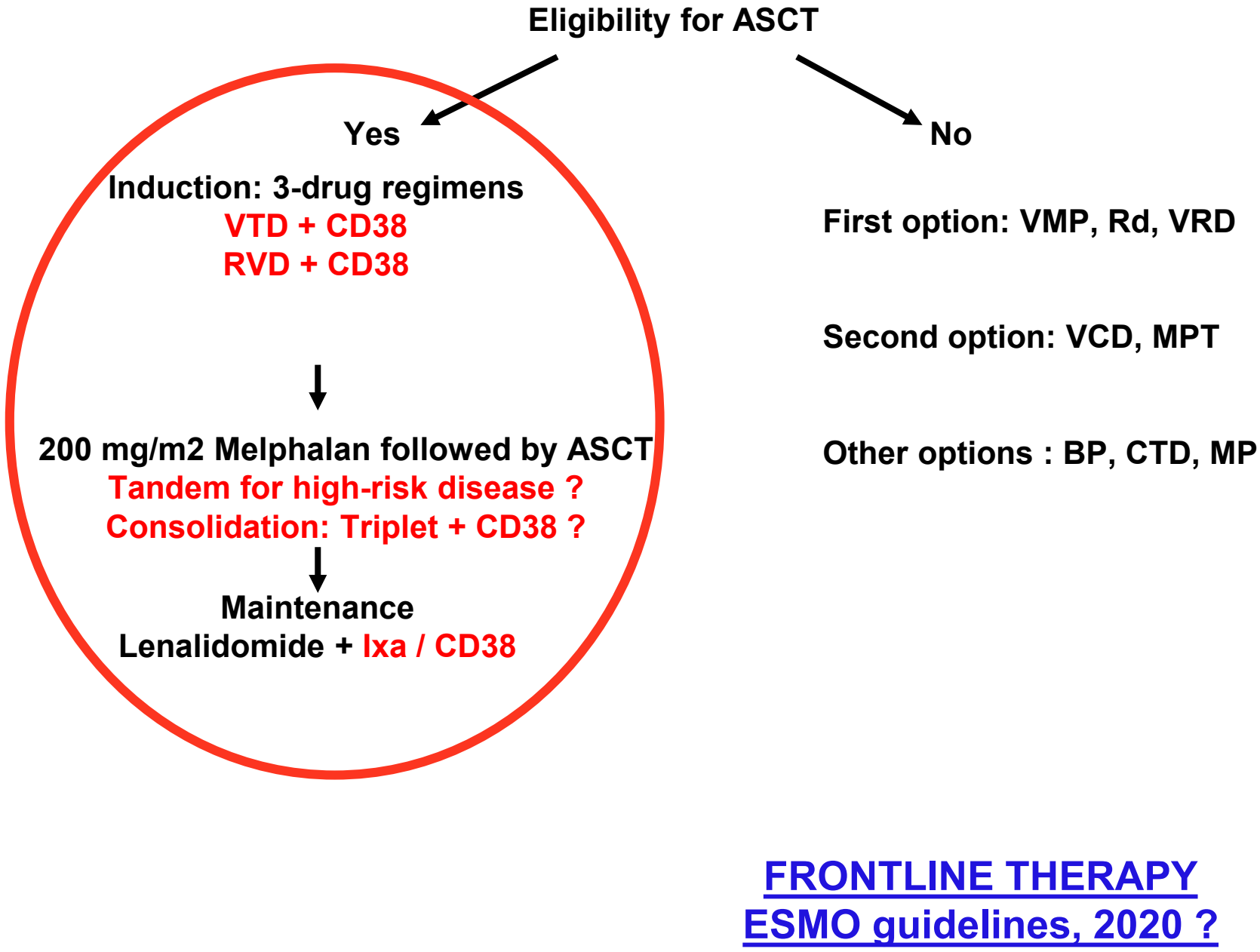
GEM14

Maintenance trial after ASCT



CASSIOPEIA – 1080 patients – ASCO 2019





FRONTLINE THERAPY
ESMO guidelines, 2020 ?

Now, let’s return to our patient case

INTERNATIONAL
MYELOMA
FOUNDATION

Patient Case Example: 73-Year-Old Male

Presents with:

- Bone pain
- Anemia Hb: 10.2 g/dL
- Serum electrophoresis: M-spike: 4.2 g/dL; IF: IgG K
- Bone marrow aspirate: 30% plasma cells
- Cytogenetics (FISH): **t(11;14)**
- Low-dose whole-body CT: diffuse bone lesions, spine

- Creatinine: 0.9 mg/dL; **β2-M: 2.5 mg/L**, albumin 3.8 g/dL, LDH < normal

→ symptomatic multiple myeloma, **ISS1, R-ISS1**

Assessment 2: Now, what would you recommend for this patient?

1. Rd until progression
2. VRD x 8 followed by Rd until PD
3. VRD lite followed by R until PD
4. VMP-daratumumab x 9 followed by daratumumab until PD
5. Rd + daratumumab, until PD
6. VRD x 4 → ASCT prepared by mel 200 → len maintenance until PD
7. Uncertain

Panel Discussion:
Individualized Approaches to Frontline Treatment Selection

INTERNATIONAL MYELOMA FOUNDATION