Provided by Purdue University and developed in partnership with Clinical Care Options, LLC and the International Myeloma Foundation.

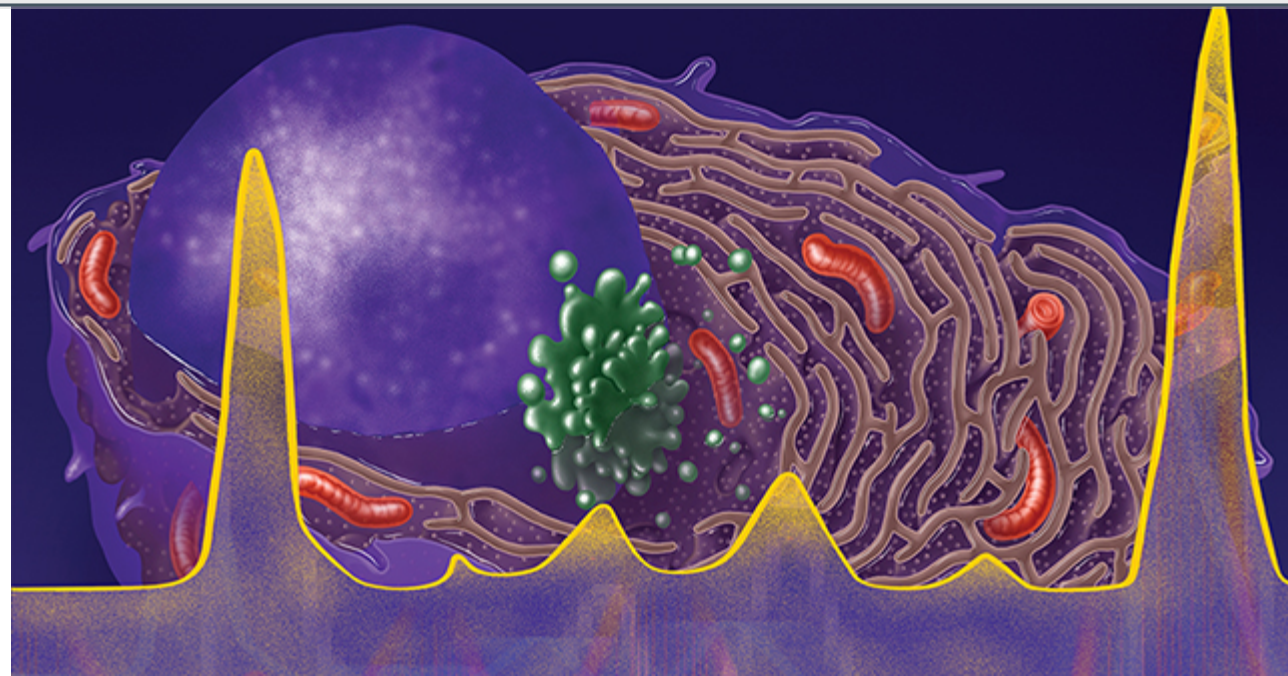
PURDUE UNIVERSITY

INTERNATIONAL MYELOMA FOUNDATION

CCO LIVE

Approaches To Achieve the Best Possible Outcomes in Myeloma

Friday, December 6, 2019
1:00 PM – 4:00 PM
Orlando, Florida



Supported by educational grants from Celgene Corporation, Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, Karyopharm Therapeutics Inc., Oncopeptides, Takeda Oncology, and The Binding Site.

Friday Satellite Symposium preceding the 61st ASH Annual Meeting & Exposition.

Program Chair and Moderator

Brian G.M. Durie, MD
Medical Director, AMyC
Co-Chair Myeloma Committee, SWOG
Chairman, International Myeloma Foundation
Specialist in Multiple Myeloma and Related Disorders
Cedars-Sinai Outpatient Cancer Center
Los Angeles, California

Brian G.M. Durie, MD, has disclosed that he has received consulting fees from Amgen, Celgene, Johnson & Johnson, and Takeda.

Faculty

Shaji Kumar, MD
Department of Hematology
Mayo Clinic
Rochester, Minnesota

Shaji Kumar, MD, has disclosed that he has received consulting fees paid to his institution from AbbVie, Amgen, Celgene, Genentech, Janssen, Kite, MedImmune, Merck, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche/Genentech, Sanofi, and Takeda.

Faculty

Thomas G. Martin, MD
Clinical Professor of Medicine
Associate Director, Myeloma Program
University of California, San Francisco Medical Center
San Francisco, California

Thomas G. Martin, MD has disclosed that he has received consulting fees from Legend Biotech and funds for research support from Amgen, Johnson & Johnson – Janssen, Sanofi, and Seattle Genetics.

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 Takeda.

Faculty

S. Vincent Rajkumar, MD
Edward W. and Betty Knight Scripps Professor of Medicine
Mayo Clinic
Rochester, Minnesota

S. Vincent Rajkumar, MD, has no real or apparent conflicts of interest to disclose.

Faculty

Jesús F. San-Miguel, MD, PhD
Director of Clinical and Translational Medicine
Universidad de Navarra
Pamplona, Spain

Jesús F. San-Miguel, MD, PhD, has disclosed that he has received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Takeda.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Initiate treatment for appropriate patients based on an accurate diagnosis of monoclonal gammopathy of undetermined significance, smoldering MM, or active MM
- Create individualized treatment strategies for patients with newly diagnosed MM through consideration of the available clinical data as well as risk assessment, age, comorbidities, and patient preferences
- Select safe and effective maintenance therapy for patients with MM based on risk and response to induction therapy
- Evaluate the efficacy and safety of combination regimens to individualize therapeutic strategies for patients with MM at first relapse
- Plan appropriate treatment strategies using all available agents and classes to provide efficacious combination therapies to heavily pretreated patients with relapsed/refractory MM
- Employ novel agents and clinical trial participation as part of clinical care strategies for MM

Agenda

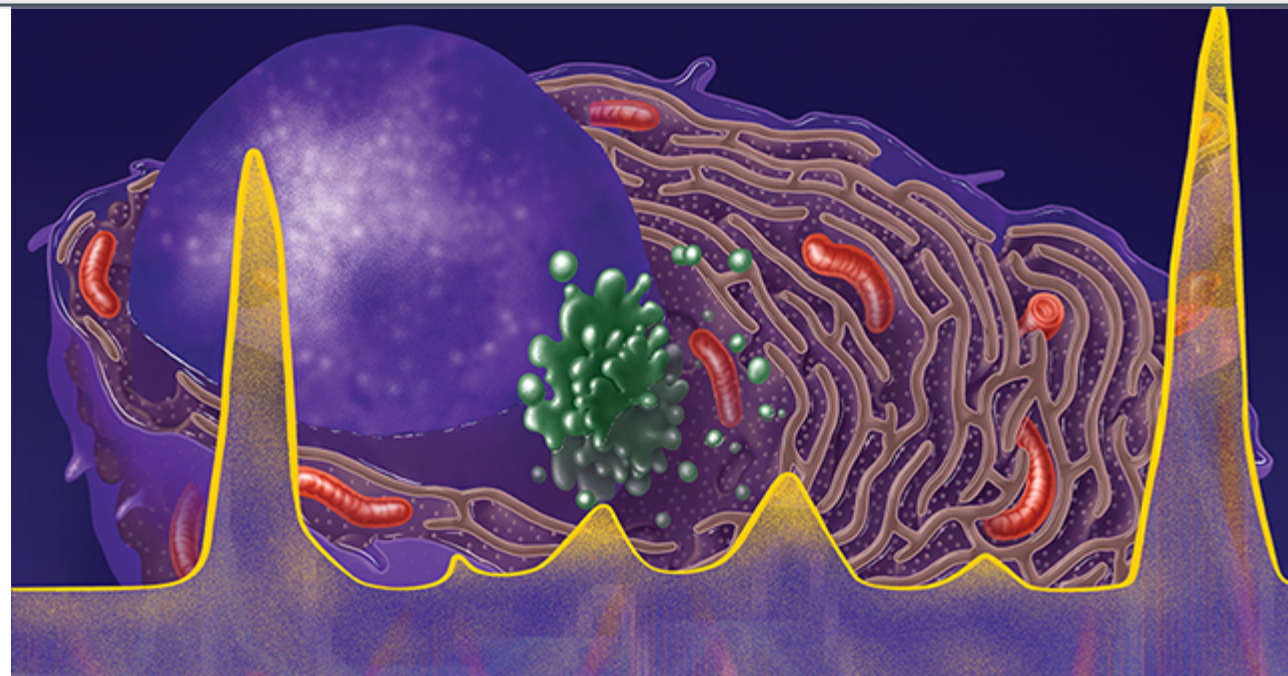
- Diagnosis and Risk Stratification of Plasma Cell Disorders - ***Jesús F. San-Miguel, MD, PhD***
- Evolution of Upfront Therapy for the Transplantation-Ineligible Patient - ***Shaji Kumar, MD***
- Upfront Therapy for the ASCT-Eligible Patient: Advances in Induction, ASCT, Consolidation, and Maintenance Therapy - ***Philippe Moreau, MD***
- The Current Therapeutic Landscape for Relapsed or Refractory MM: Which Combinations to Use and When? - S***. Vincent Rajkumar, MD***
- Future Directions: A New Era of Promising Treatments for MM - ***Thomas G. Martin, MD***
- Proposed 2020 treatment algorithms for MM

INTERNATIONAL MYELOMA FOUNDATION

CCO LIVE

Case Discussion 3 — Upfront Therapy for the ASCT-Eligible Patient: Advances in Induction, ASCT, Consolidation, and Maintenance Therapy

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 Takeda.

Patient Case Example

- A 63-year-old male presented in the clinic with bone pain
- Initial exam showed:
  - Anemia with Hb of 10.2 g/dL
  - Serum electrophoresis showed M-spike of 4.2 g/dL, IF: IgG kappa
  - Bone marrow aspirate: 30% plasma cells
  - Cytogenetics (FISH): t(11;14)
- Low-dose whole-body CT showed diffuse bone lesions, spine
- Creatinine: 80 mM/L; β_2-microglobulin: 2.5 mg/L; albumin 3.8 g/dL, LDH < normal
- He was diagnosed with symptomatic multiple myeloma, ISS1, R-ISS1

In your clinical practice, how would you treat this patient?

Expert Recommendations	
Brian G.M. Durie, MD	VRD x 4-6; single ASCT; lenalidomide maintenance until PD
Shaji Kumar, MD	VRD x 4-6; single ASCT; lenalidomide maintenance until PD
Thomas G. Martin, MD	VRD x 4-6; single ASCT; lenalidomide maintenance until PD *(until dara is available)*
Philippe Moreau, MD	VRD x 4-6; single ASCT; lenalidomide maintenance until PD
S. Vincent Rajkumar, MD	VRD x 4-6; single ASCT; lenalidomide maintenance until PD
Jesus San-Miguel, MD	*(Ideal world)* VRD-dara x 4; single ASCT; VRD-dara x 2 consolidation → len/dara maintenance 2 years *(Current practice)* VRD x 4-6; single ASCT; len maintenance until PD

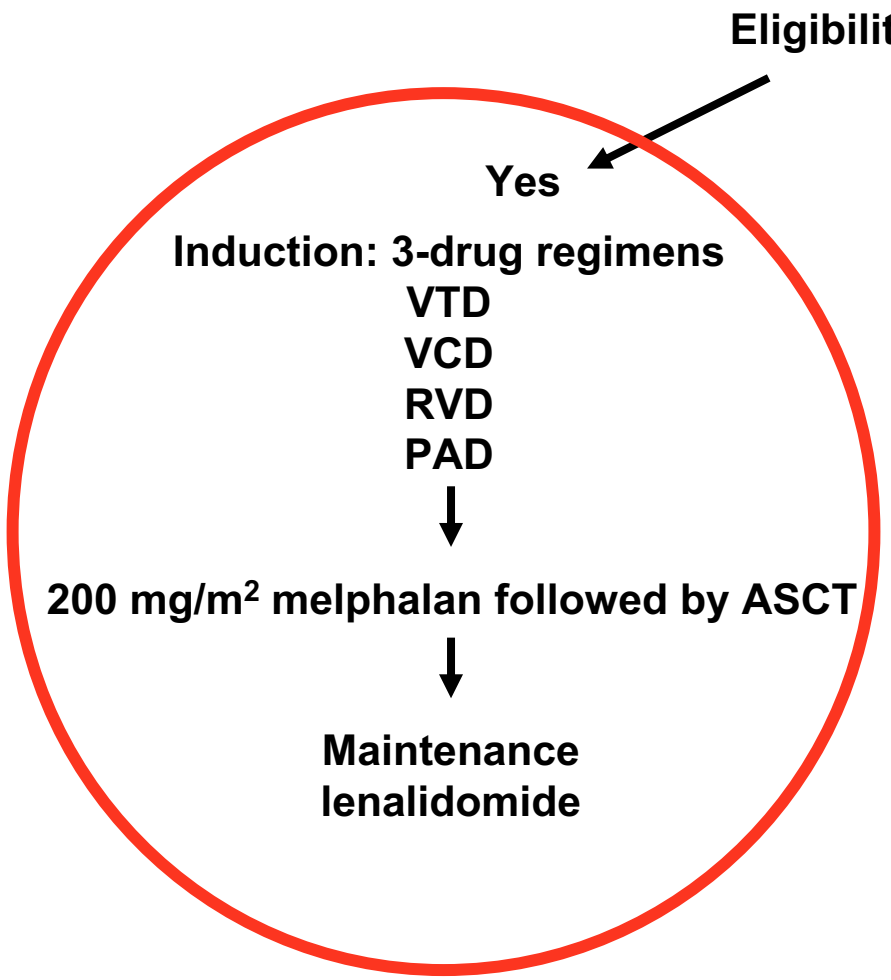
Slide credit: clinicaloptions.com

“Frontline Therapy for Patients Eligible for ASCT”

Pr Philippe Moreau

University Hospital, Nantes, France

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES



First option: VMP, Rd, VRD

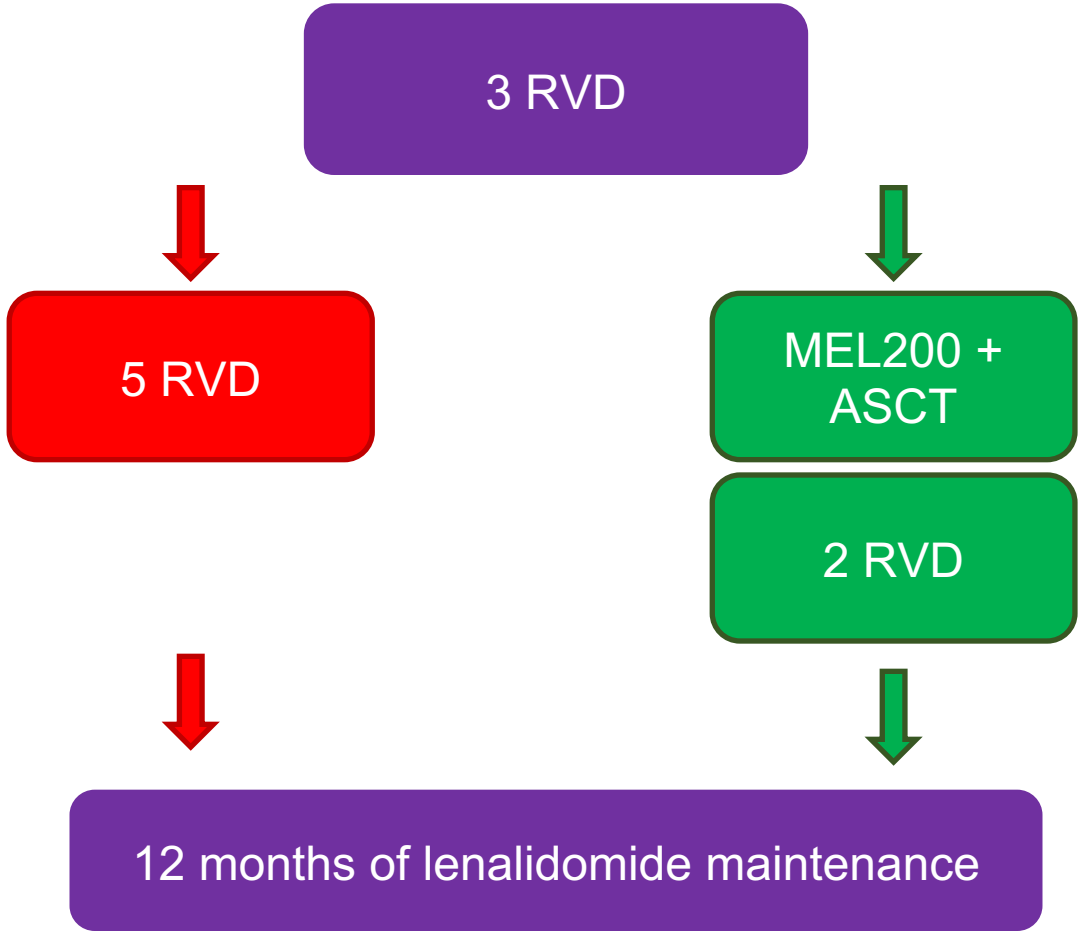
Second option: VCD, MPT

Other options: BP, CTD, MP

...”< 65 years
Or
fit patients < 70 years in good clinical condition”…

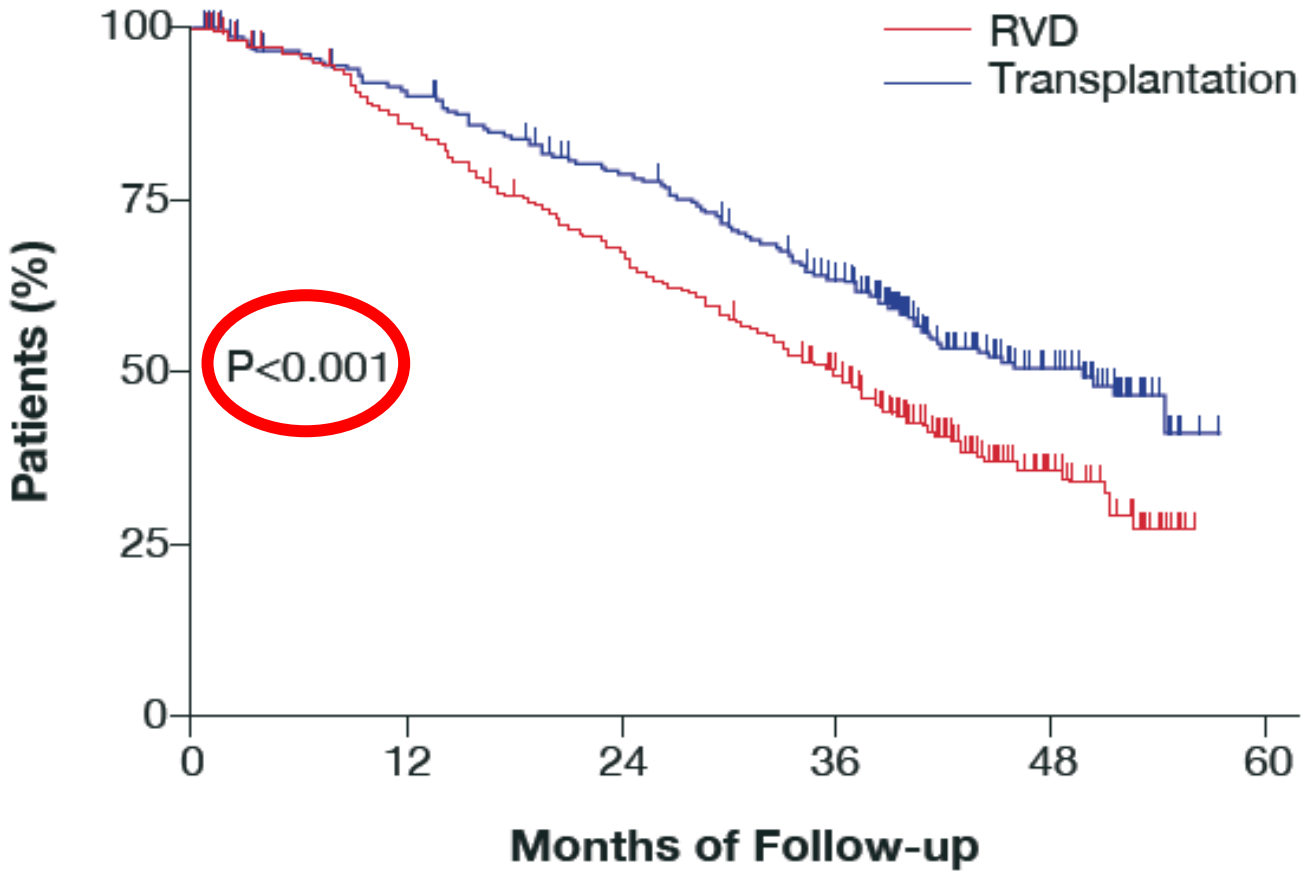
FRONTLINE THERAPY
ESMO guidelines
Moreau et al, Ann Oncol 2017

IFM DFCI 2009 trial
700 patients ≤ 65 y,
newly diagnosed symptomatic MM



Attal et al, N Engl J Med 2017

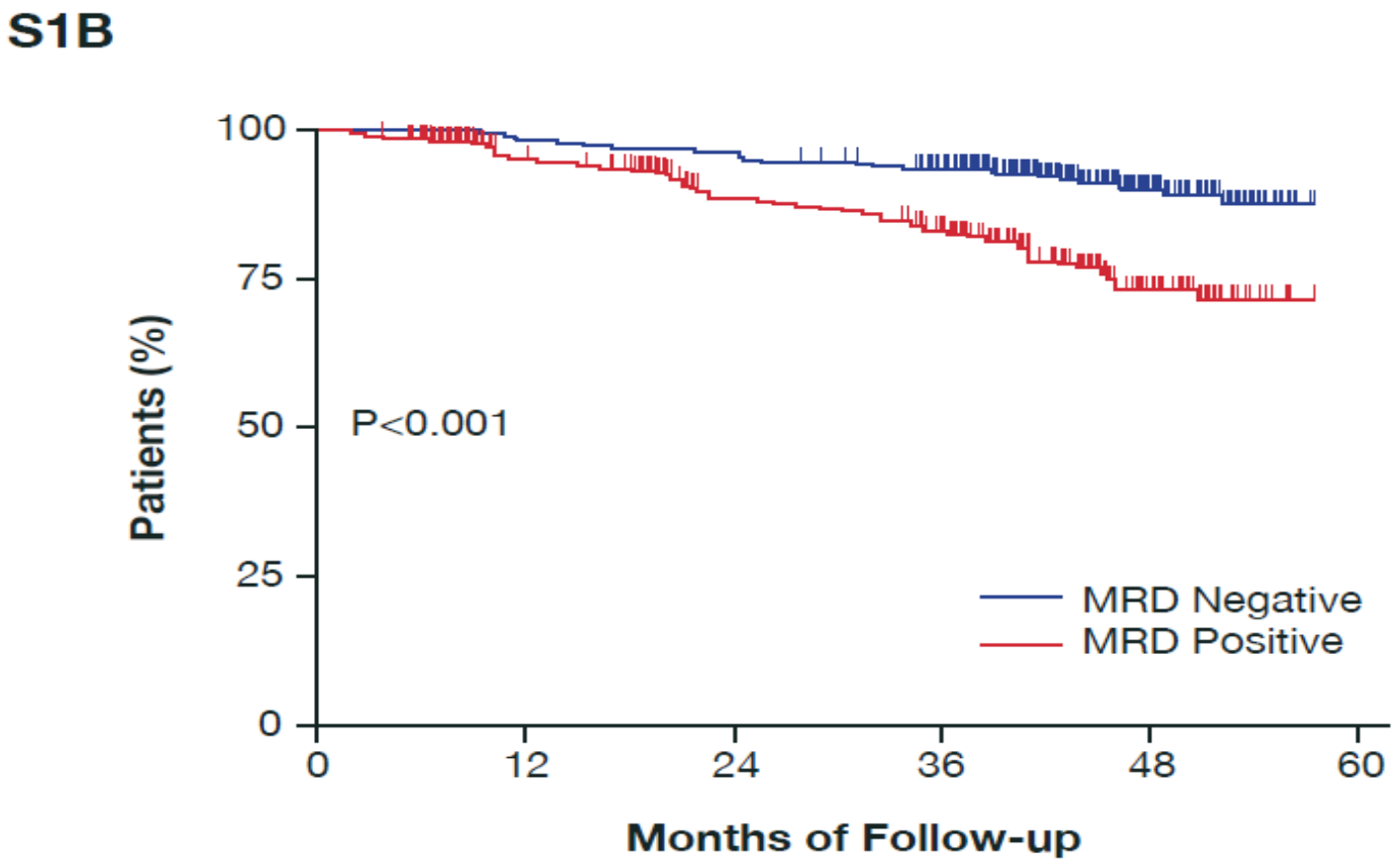
PROGRESSION-FREE SURVIVAL



No. at Risk						
RVD	350	294	228	157	32	0
Transplantation	350	308	264	196	50	0

Attal et al, N Engl J Med 2017

IFM/DFCI 2009: OS According to Minimal Residual Disease (7-Color Flow)



No. at Risk

MRD Negative	0	311	379	347	119	0
MRD Positive	700	358	259	227	65	0

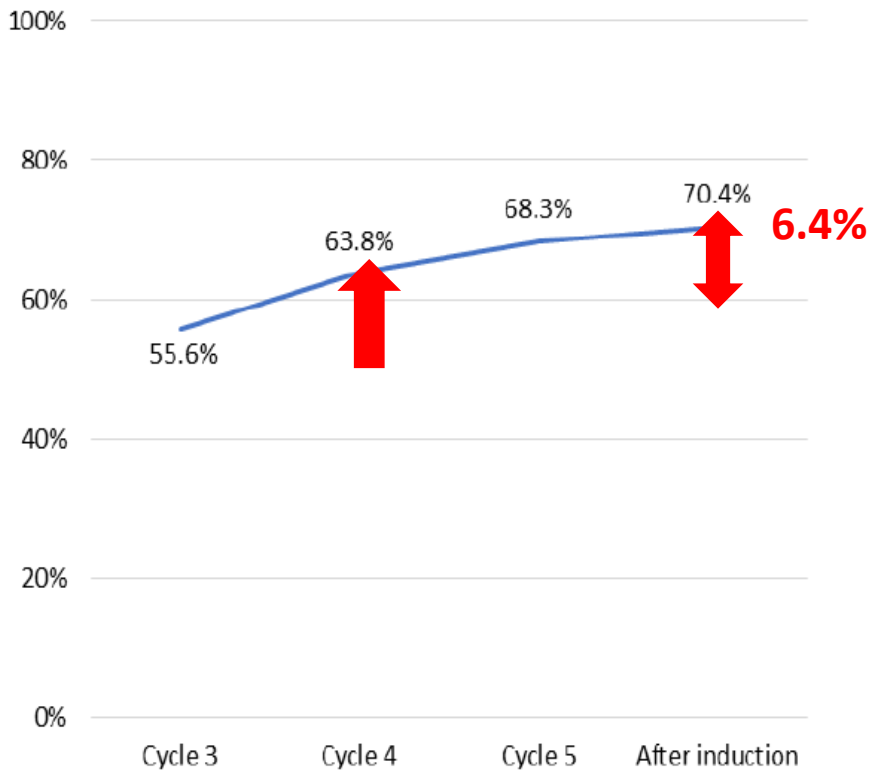
Attal et al, N Engl J Med 2017

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

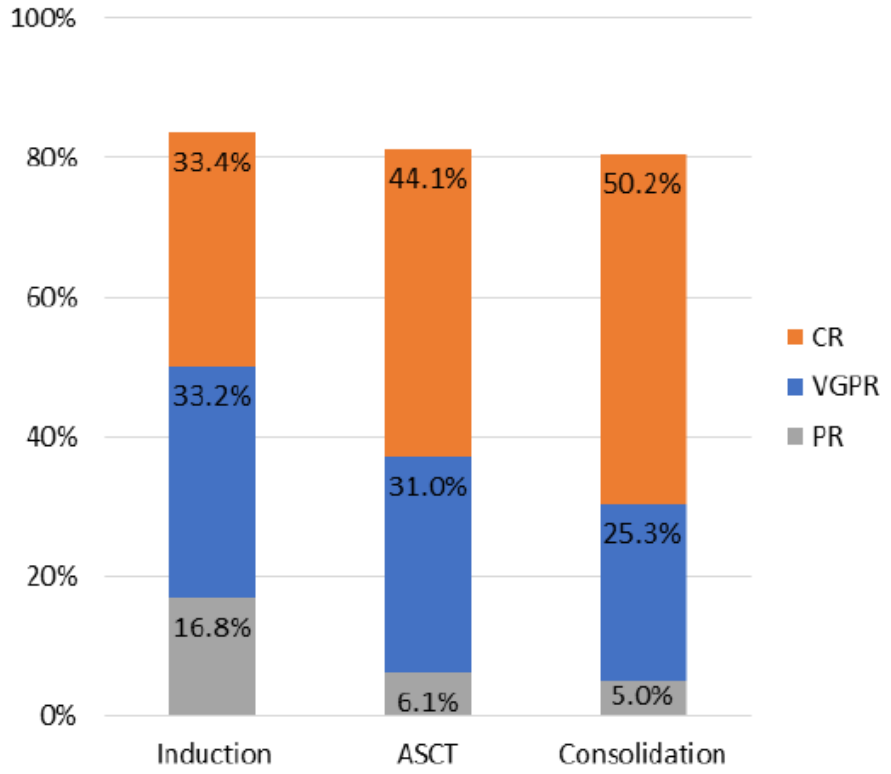
VRD x 6, 458 Patients

GEM2012 trial

VGPR or Better in 426 Patients Who Initiated Cycle 6



Response Rates in ITT N = 458



Median number of CD34+ cells (3 cycles) : 4.66 x10^6 kg

Rosinol et al. Blood 2019, prepublished online sep 4

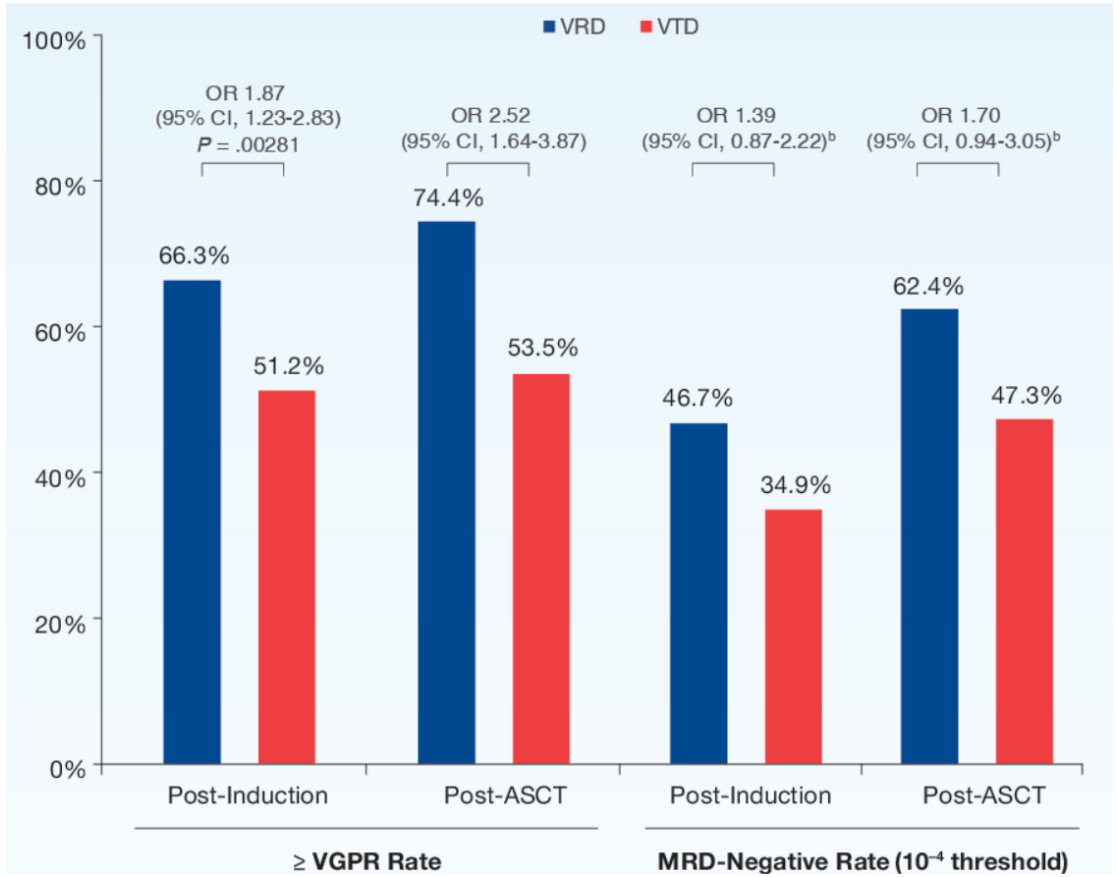
Toxicity

Adverse Events, %	VTD x 6 (n = 130)	VRD (n = 458)
Grade 3/4 neutropenia	10	12.9
Grade 3/4 thrombocytopenia	8	6
Peripheral neuropathy		
Grade 2	46	13
Grade 3	12	3.7
Grade 4	2	0.2
Discontinuation during induction		
Toxicity	7	2
Disease progression	7	13
Death	2	1

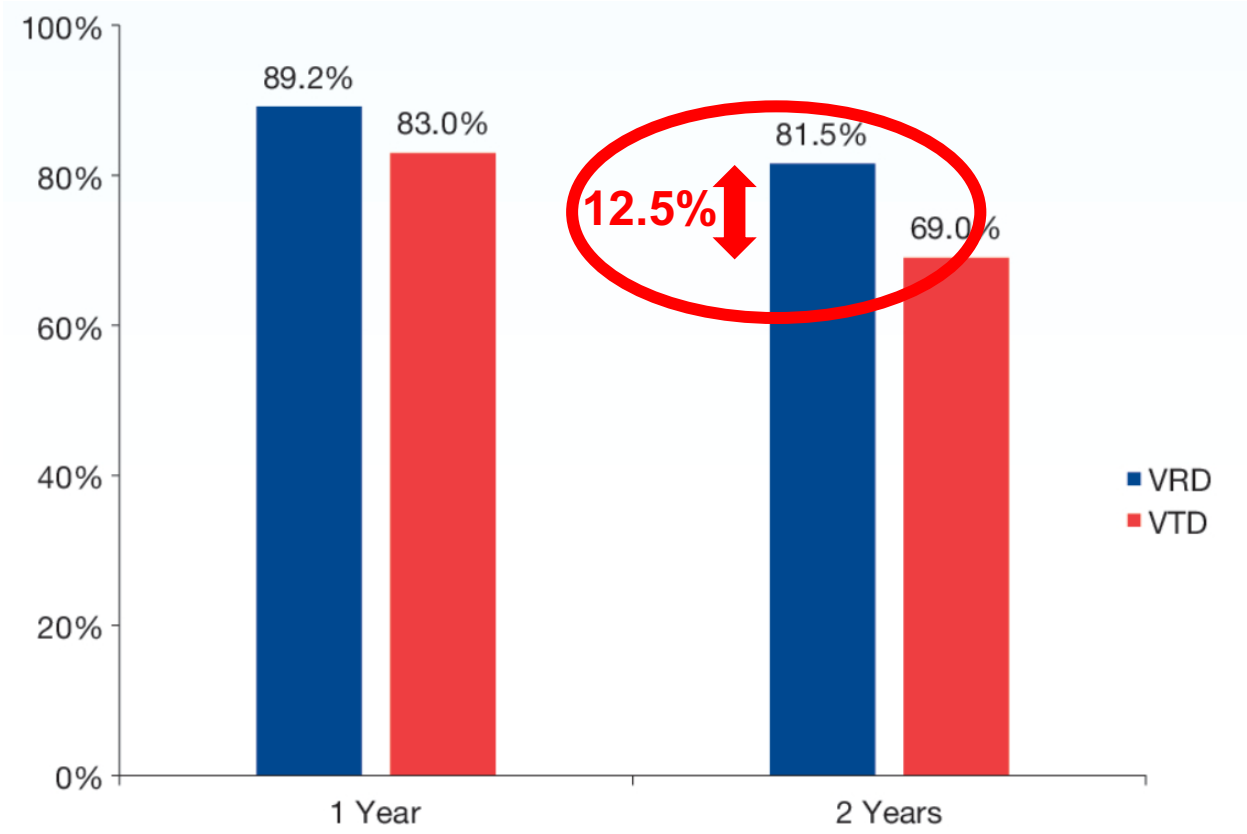
Rosinol et al. Blood 2019, prepublished online sep 4
Rosinol et al. Blood. 2012;120(8):1589-96.

Bortezomib-Lenalidomide-Dexamethasone vs Bortezomib-Thalidomide-Dexamethasone Induction: Integrated Analysis of Randomized Controlled Trials in Transplant-Eligible Newly Diagnosed Multiple Myeloma

≥ VGPR and MRD-Negative Rates After Induction and ASCT



Event-Free PFS in the GEM Studies



Rosinol et al. EHA 2019. Abstr PF594.

Kinetics of Response According to MRD, NGF/Euroflow, VRD x 6

Table 4. Minimal residual disease in the ITT population (N = 458)

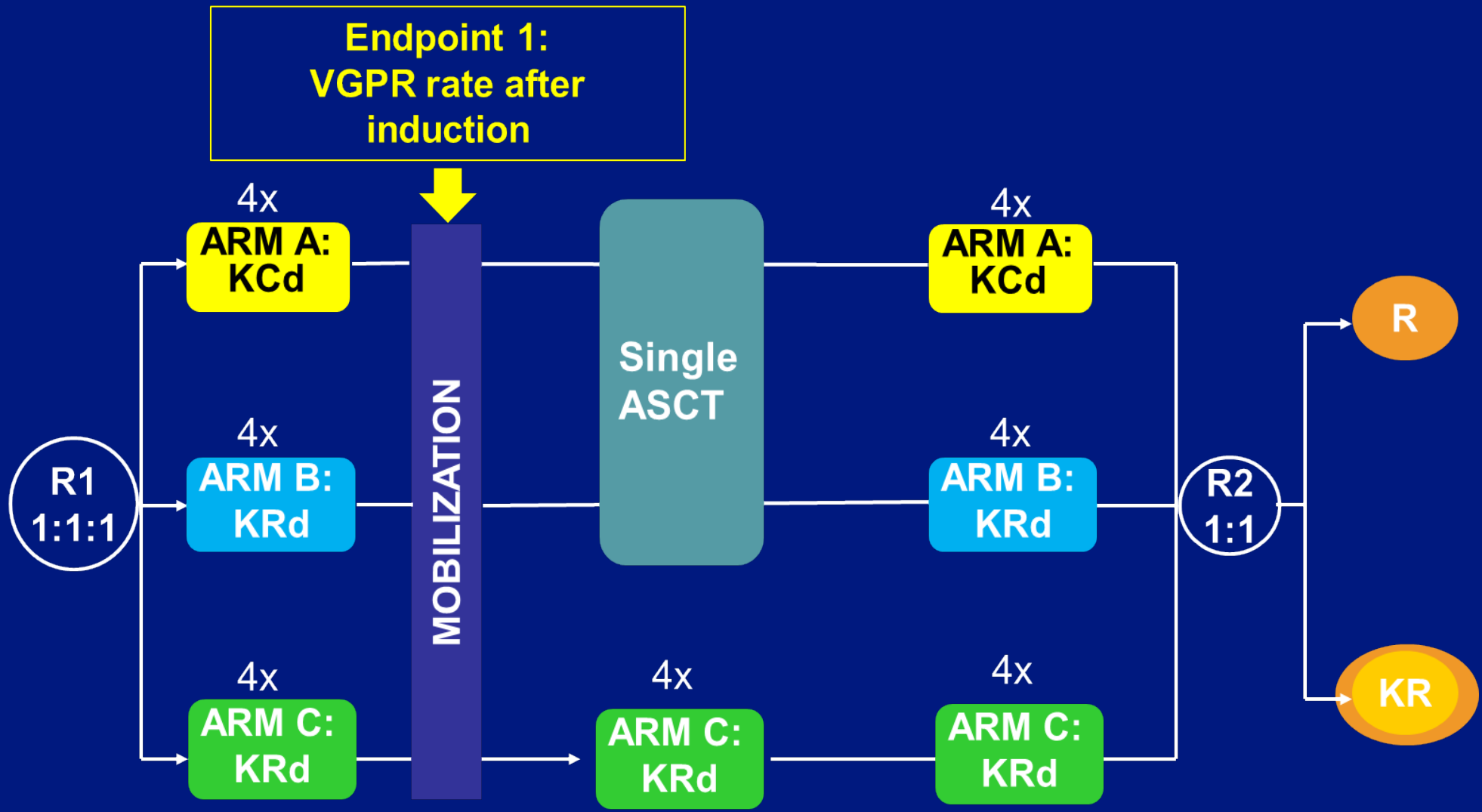
	After Induction	After ASCT	After Consolidation
Median 3 × 10^{-6} sensitivity, n (%)			
MRD undetectable	132 (28.8)	193 (42.1)	207 (45.2)
MRD positive	264 (57.6)	167 (36.5)	157 (34.3)
Missing*	62 (13.5)	98 (21.4)	94 (20.5)

*Most missing data due to patient discontinuation

Rosinol et al. Blood 2019, prepublished online sep 4 .

FORTE Trial Design

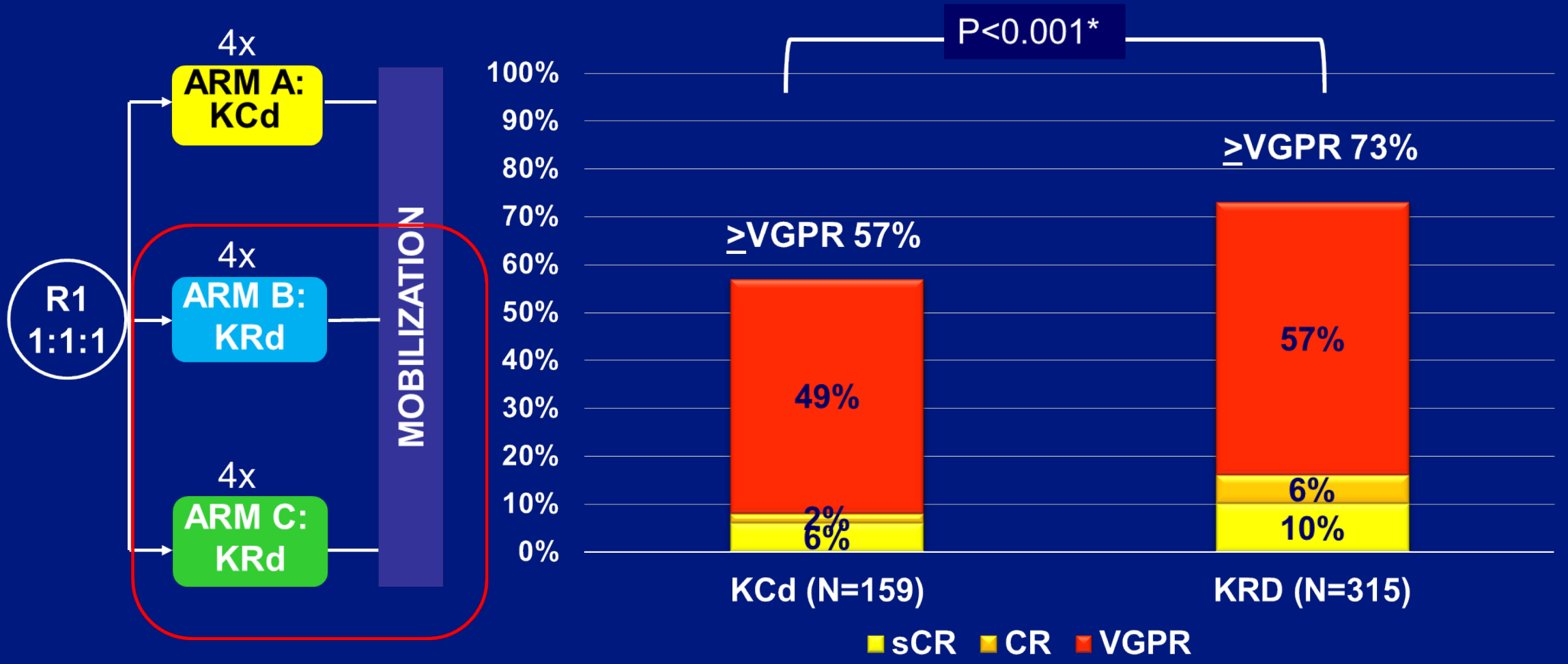
- NDMM patients, transplant eligible and younger than 65 years



Gay et al. ASCO 2019. Abstract 8002.

Induction Phase

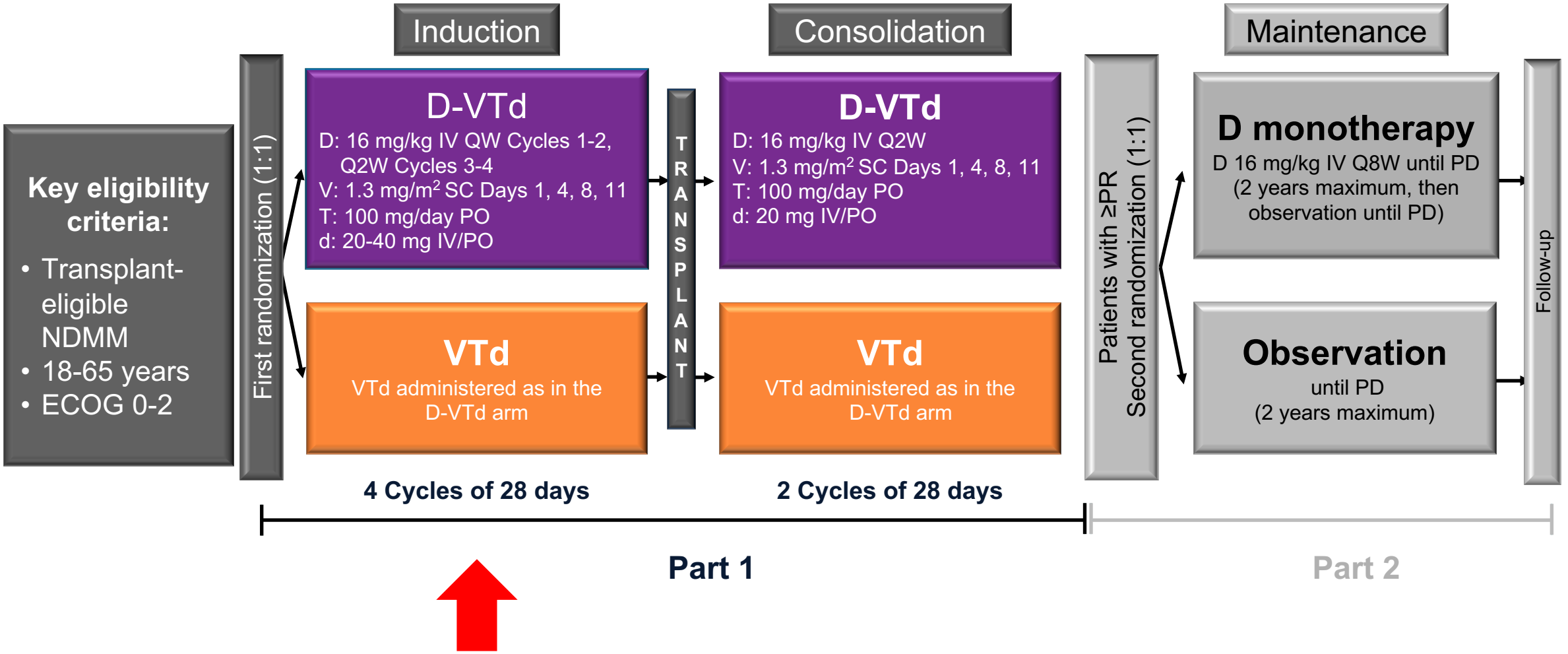
Endpoint 1: VGPR rate with KRd vs KCd induction
ITT analysis



Gay et al. ASCO 2019. Abstract 8002.

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 et al. Lancet;2019

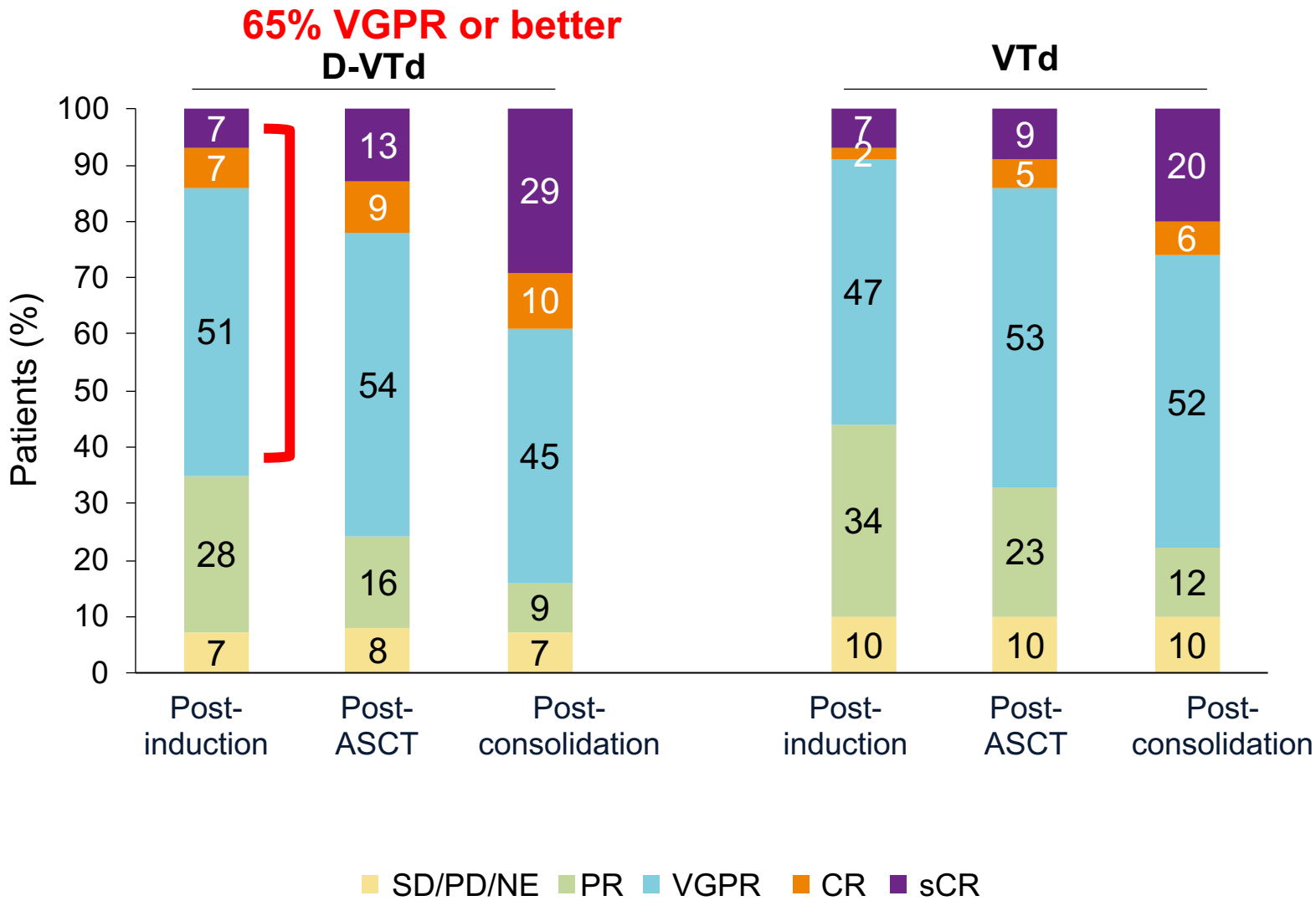
Patient Disposition

- Median follow-up: 18.8 months
- Completed induction and consolidation:
  - **85% D-VTd**
  - **81% VTd**
- Underwent ASCT:
  - **90% D-VTd**
  - **89% VTd**

	D-VTd (n = 543)	VTd (n = 542)
Patients who discontinued study treatment, n (%)	75 (14)	101 (19)
Reason for discontinuation, n (%)[a]		
Adverse event/serious adverse event	49 (9)	55 (10)
Progressive disease	19 (4)	21 (4)
Physician decision	4 (1)	12 (2)
Withdrawal by patient	3 (1)	1 (<1)
Treatment stopped by sponsor	3 (1)	2 (<1)
Lost to follow-up	1 (<1)	0
Treatment delay for toxicity (>6 weeks)	2 (<1)	1 (<1)
Patient decision	0	8 (2)
Death	0	7 (1)
Prohibited medication	0	1 (<1)

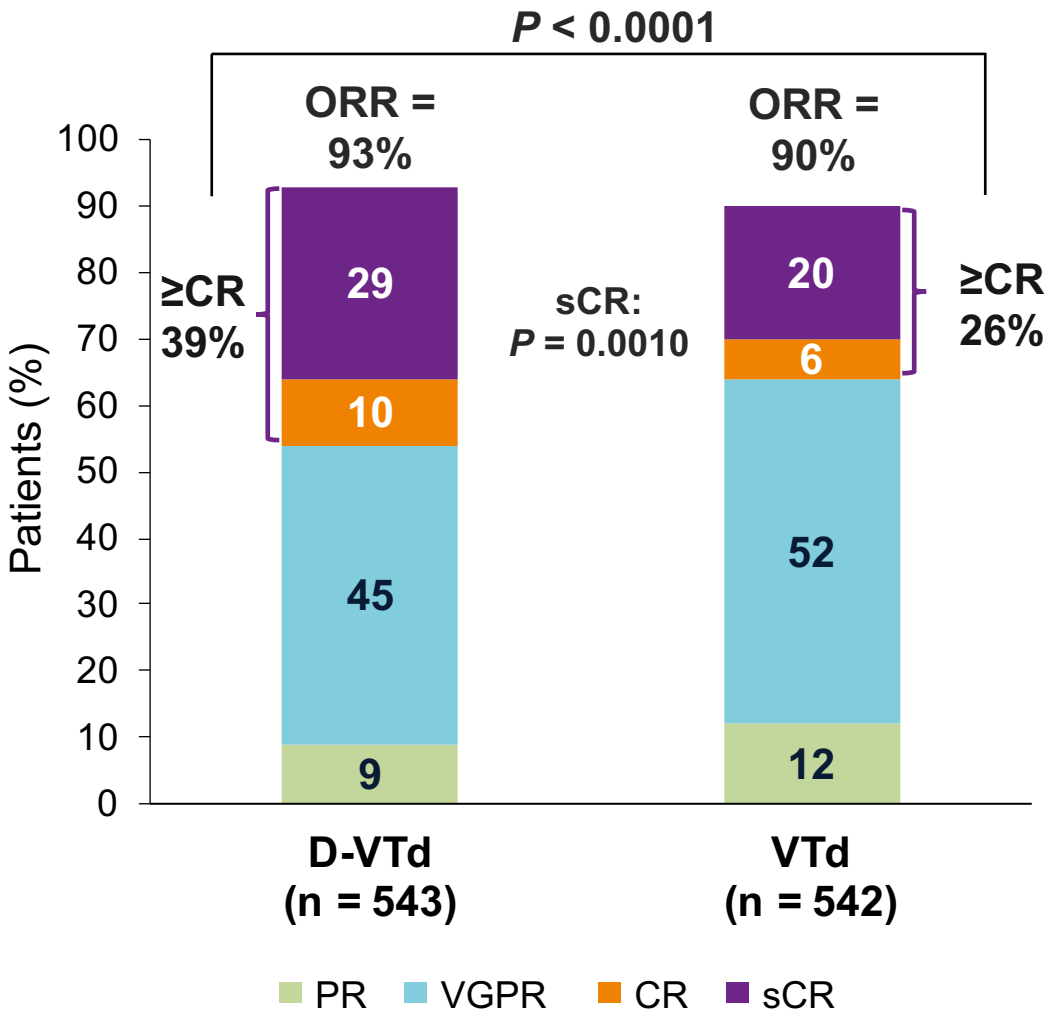
Moreau et al. ASCO 2019. Abstr 8003. Moreau et al. Lancet; 2019.

Efficacy: Response Rates Over Time



Moreau et al. ASCO 2019. Abstr 8003. Moreau et al. Lancet; 2019.

Efficacy: Post-Consolidation Depth of Response



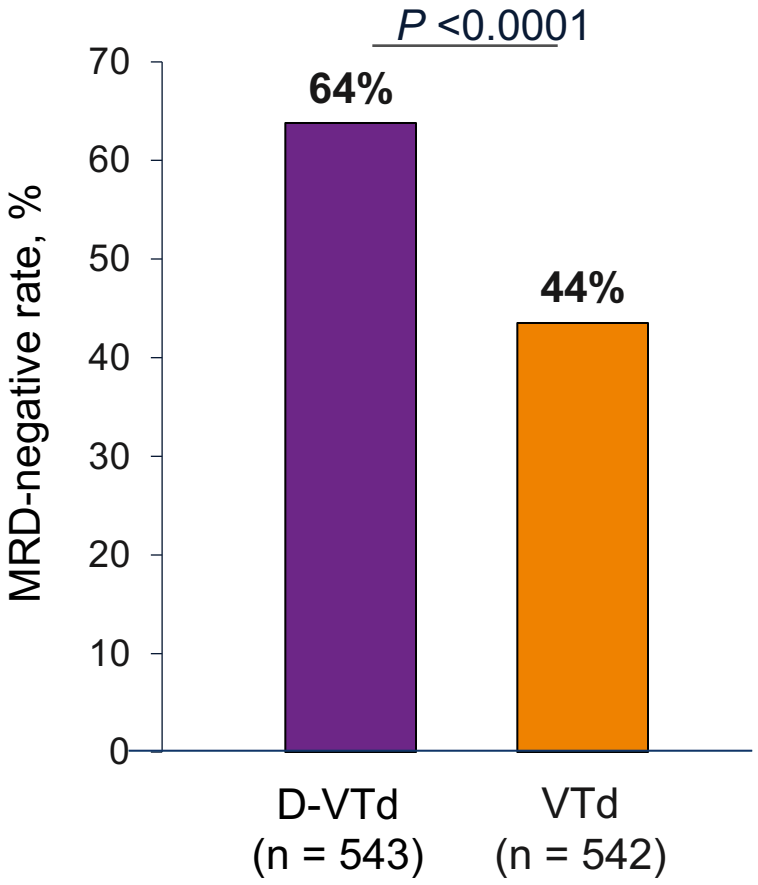
- **Primary endpoint**
  - **Post-consolidation sCR**
    - **29% D-VTd vs 20% VTd**
    - **Odds ratio, 1.60; 95% CI, 1.21-2.12; *P* = 0.0010**

- 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

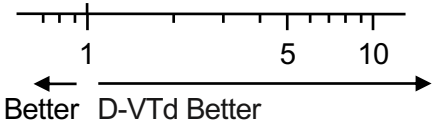
Moreau et al. ASCO 2019. Abstr 8003. Moreau et al. Lancet;2019.

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



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

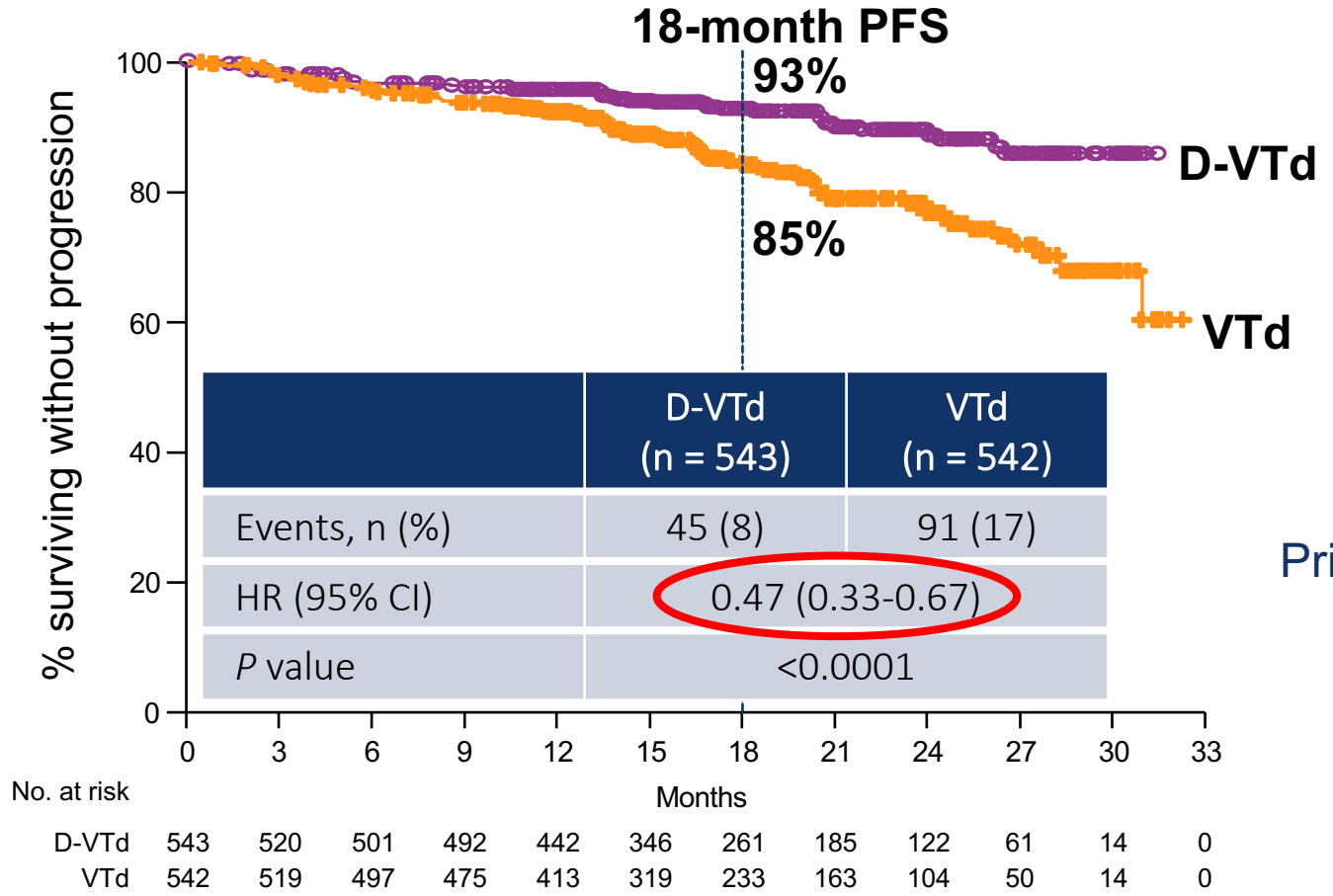
Subgroup	VTd	D-VTd	Odds Ratio (95% CI)
	minimal residual disease negative, n (%)		
Sex			
Male	131 (41)	192 (61)	2.22 (1.62–3.05)
Female	105 (47)	154 (68)	2.37 (1.62–3.48)
Age			
<50 years	38 (42)	56 (68)	2.84 (1.53–5.28)
≥50 years	198 (44)	290 (63)	2.19 (1.68–2.85)
Site			
IFM	204 (45)	287 (64)	2.16 (1.65–2.81)
HOVON	32 (38)	59 (65)	3.05 (1.65–5.65)
ISS disease stage			
I	103 (45)	137 (67)	2.48 (1.68–3.67)
II	96 (41)	155 (61)	2.21 (1.54–3.18)
III	37 (46)	54 (64)	2.14 (1.15–4.00)
Cytogenetic profile at trial entry			
High risk	38 (44)	49 (60)	1.88 (1.02–3.46)
Standard risk	197 (43)	296 (64)	2.35 (1.80–3.07)
Baseline creatinine clearance			
>90 mL/min	139 (44)	205 (62)	2.07 (1.51–2.84)
≤90 mL/min	97 (43)	141 (67)	2.64 (1.79–3.89)
Baseline hepatic function			
Normal	216 (43)	310 (65)	2.40 (1.85–3.10)
Impaired	20 (48)	36 (57)	1.47 (0.67–3.21)
Type of multiple myeloma			
IgG	122 (39)	201 (61)	2.43 (1.77–3.34)
Non-IgG	59 (49)	61 (66)	2.00 (1.15–3.50)
ECOG performance status			
0	112 (44)	172 (65)	2.39 (1.68–3.41)
≥1	124 (44)	174 (63)	2.17 (1.55–3.04)



Moreau et al. ASCO 2019. Abstr 8003. Moreau et al. Lancet;2019.

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	

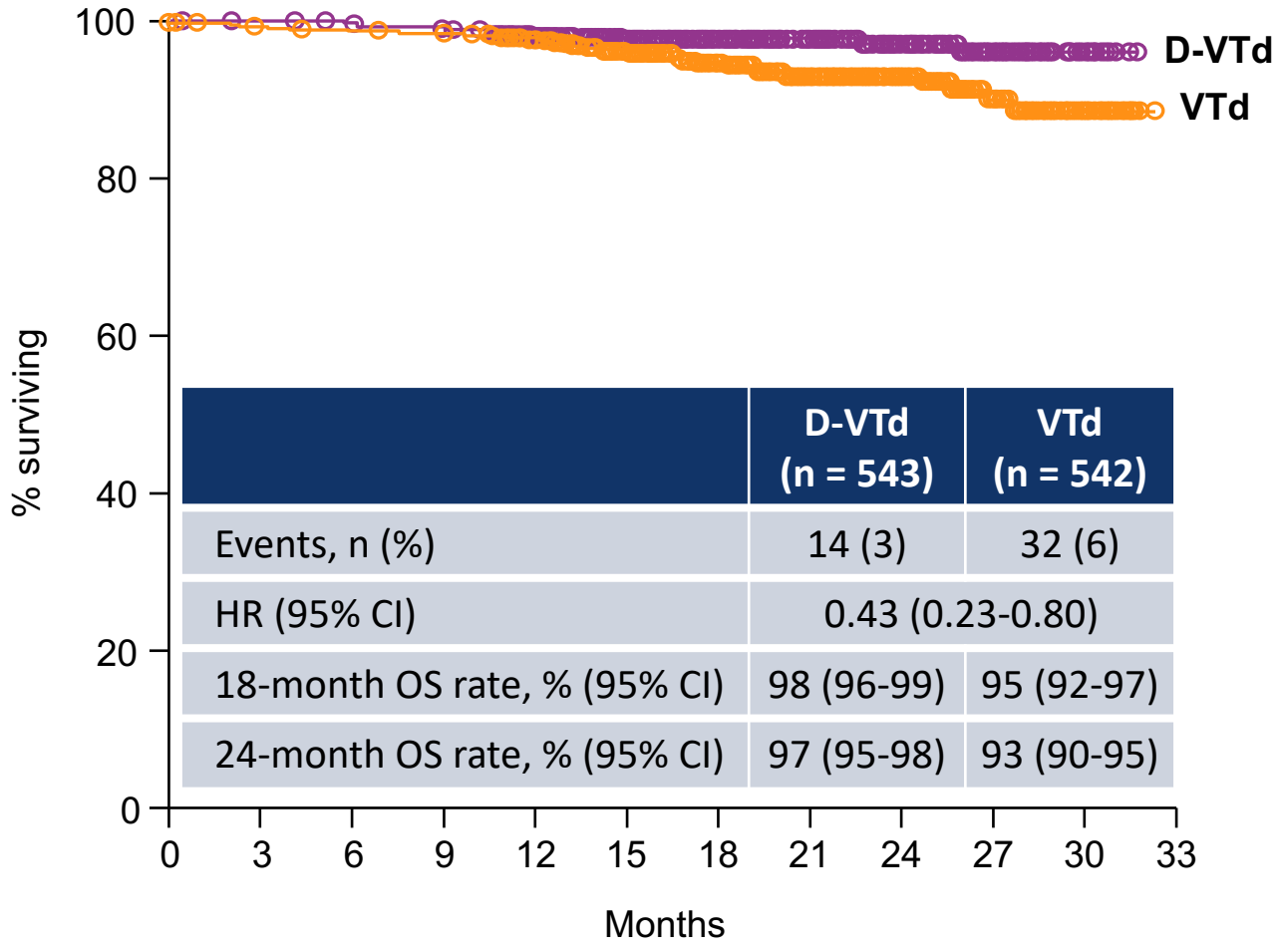
Primary and final PFS analysis of Part 1

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

Moreau et al. ASCO 2019. Abstr 8003. Moreau et al. Lancet;2019.

Efficacy: OS

- Median OS was not reached in either treatment arm



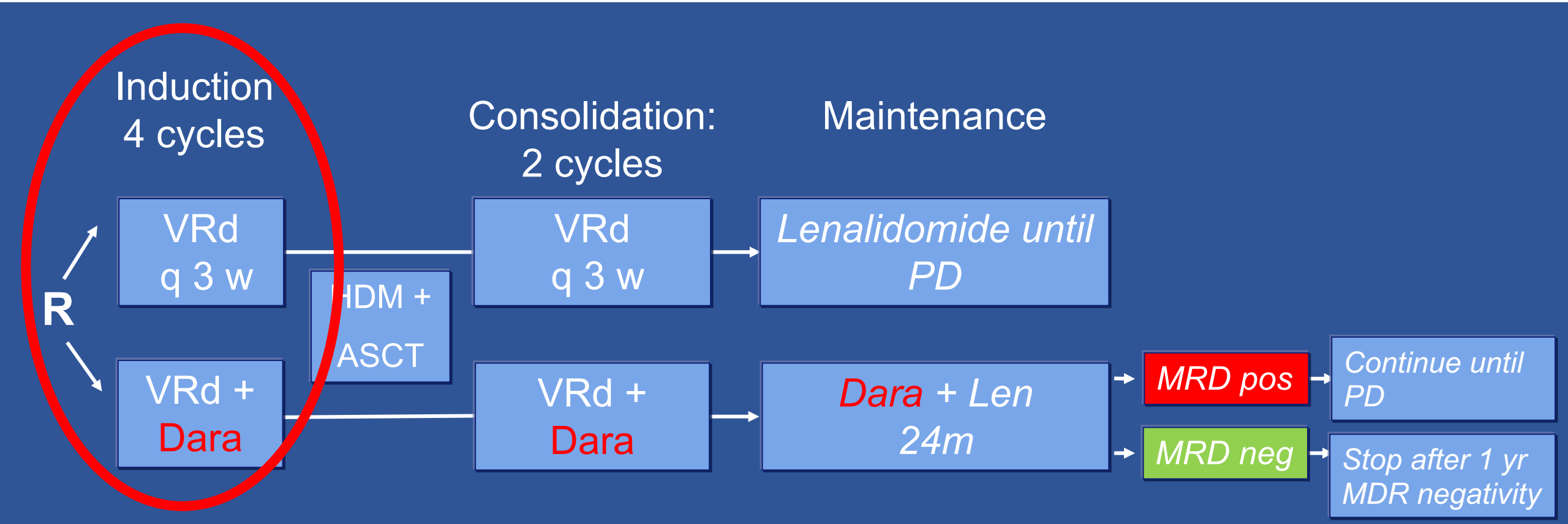
	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	14 (3)	32 (6)
HR (95% CI)	0.43 (0.23-0.80)	
18-month OS rate, % (95% CI)	98 (96-99)	95 (92-97)
24-month OS rate, % (95% CI)	97 (95-98)	93 (90-95)

No. at risk												
VTd	542	535	531	528	480	371	283	206	131	71	17	0
D-VTd	543	539	535	532	485	388	292	212	137	75	17	0

OS data are immature after median follow-up of 18.8 months

Moreau et al. ASCO 2019. Abstr 8003.
Moreau et al. Lancet;2019.

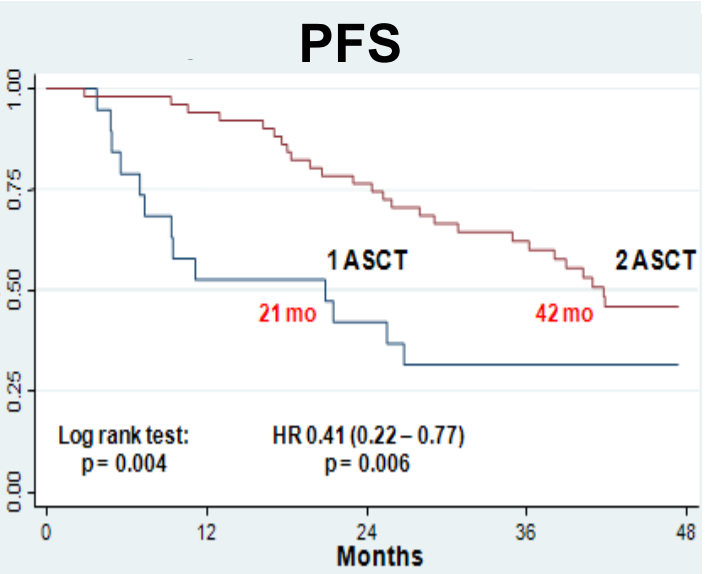
Daratumumab-VRd Trial in Transplant Eligible NDMM
EMN017/HOVON158/MMY3014 Registration Trial



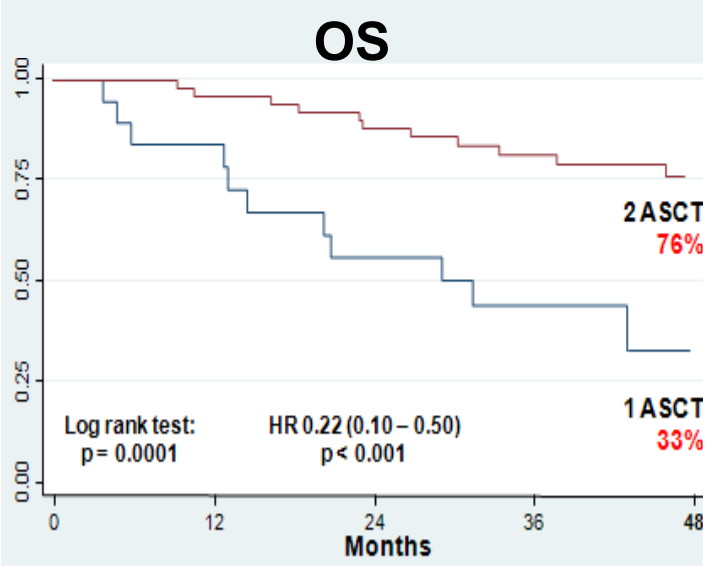
Primary endpoint: PFS
Secondary endpoint: MRD 10^{-5} by NGS after consolidation
Patients: NDMM, 18-70 yr, n=640

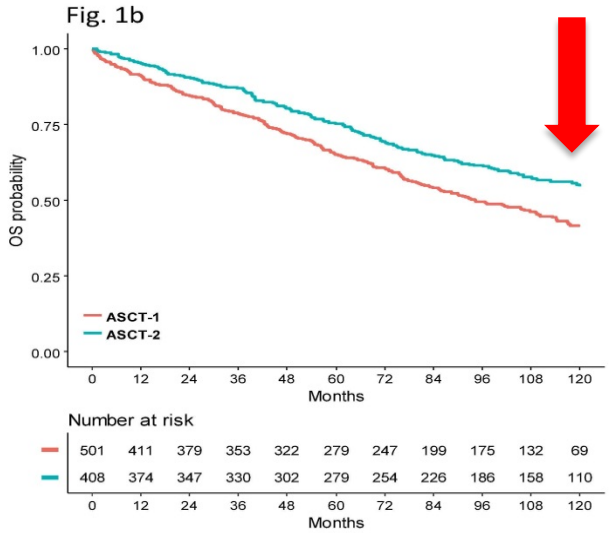
PERSEUS, PI, P.Sonneveld. ASCO 2019. Abstr TPS8055.

Double vs Single ASCT After Bortezomib-Based Induction



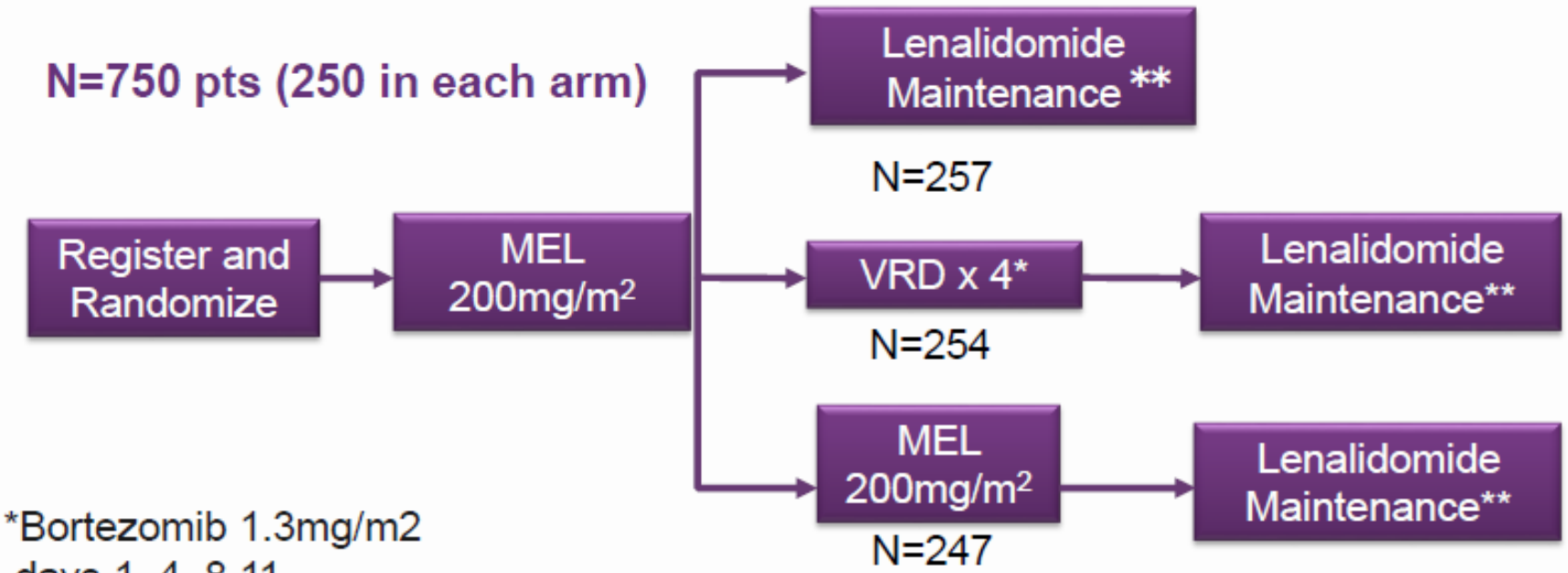
Cavo et al. ASH 2013.
Abstract 767,
oral presentation





Cavo et al. ASH 2018
Abstract 124

BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA



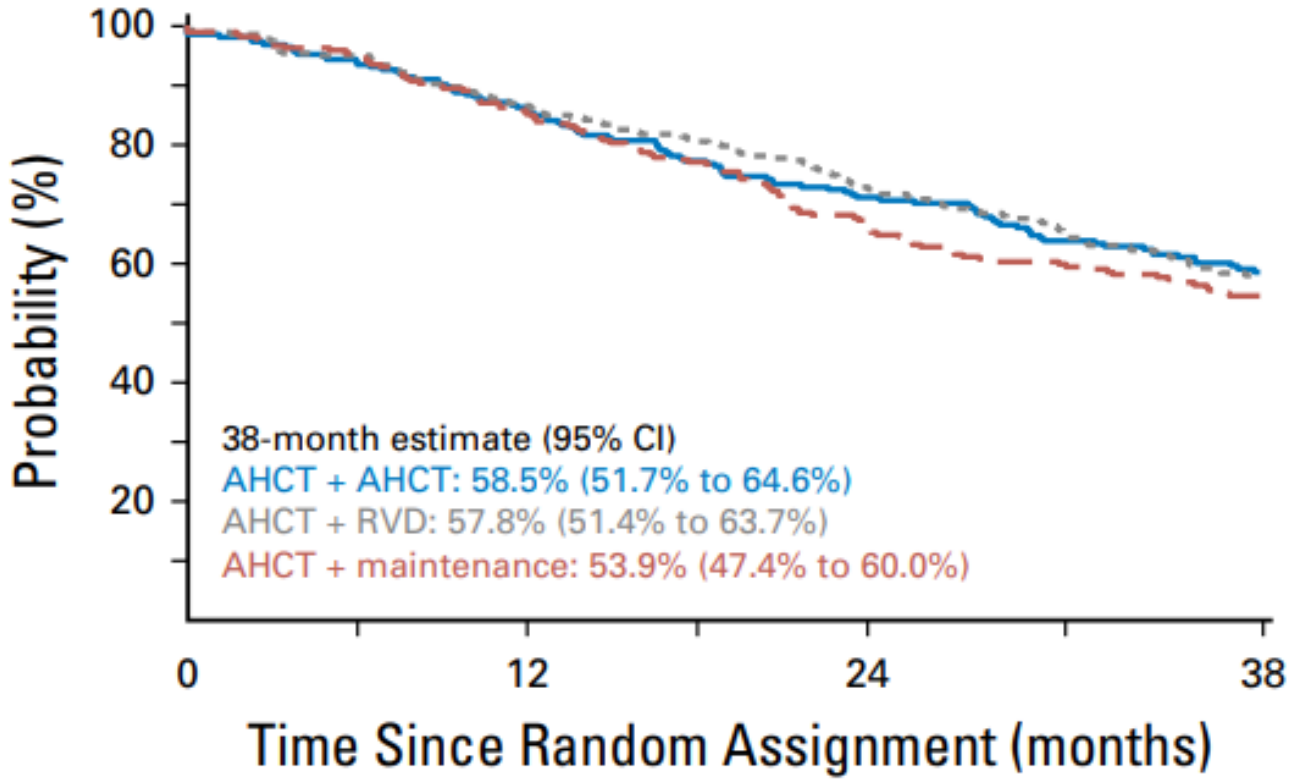
*Bortezomib 1.3mg/m2
days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15
Every 21 days

**Lenalidomide x 3years :
10mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Stadtmauer et al. J Clin Oncol 2019.

Progression-Free Survival

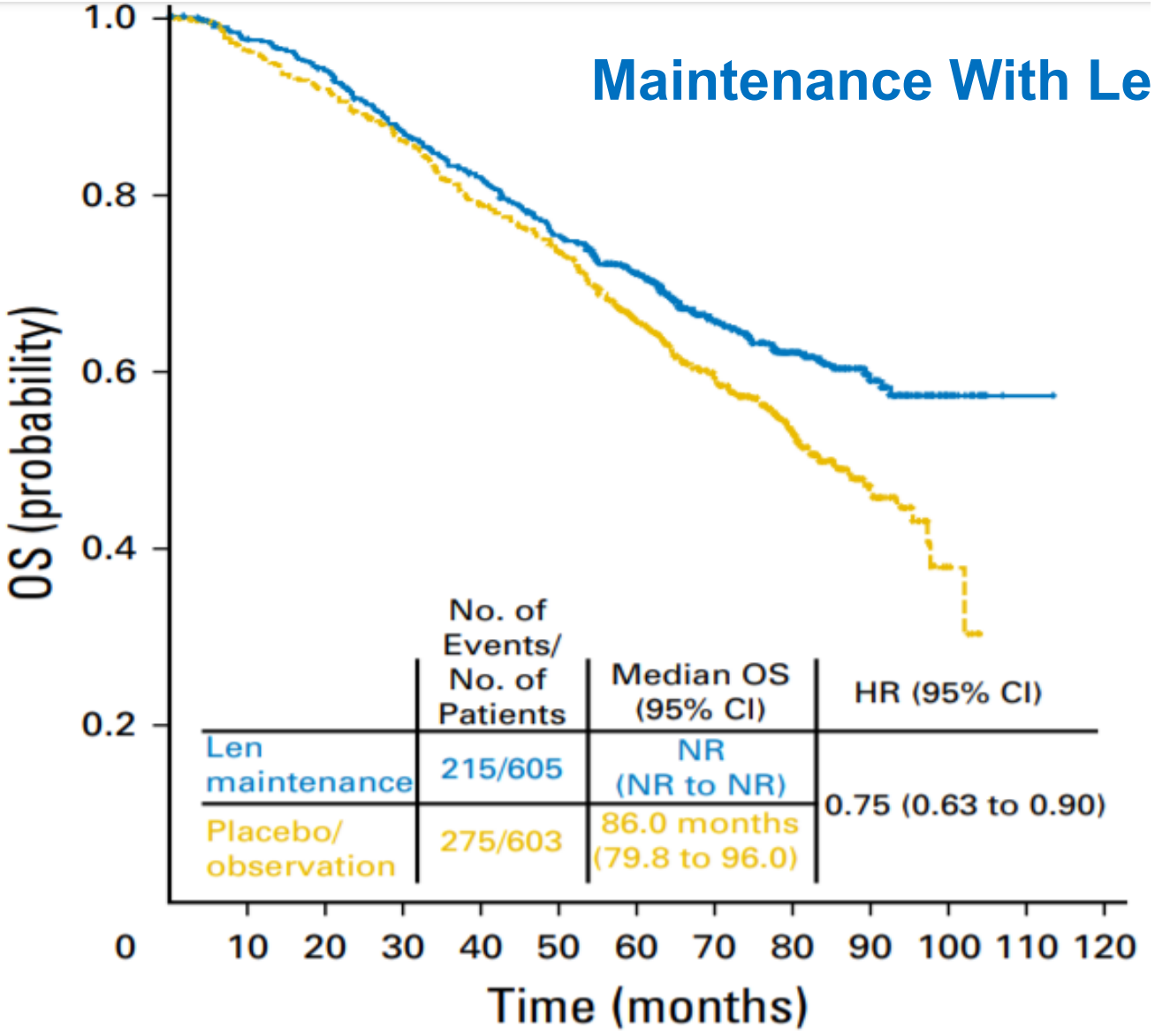


No. at risk:

AHCT + AHCT	247	200	158	117
AHCT + RVD	254	216	179	130
AHCT + maintenance	257	214	164	111

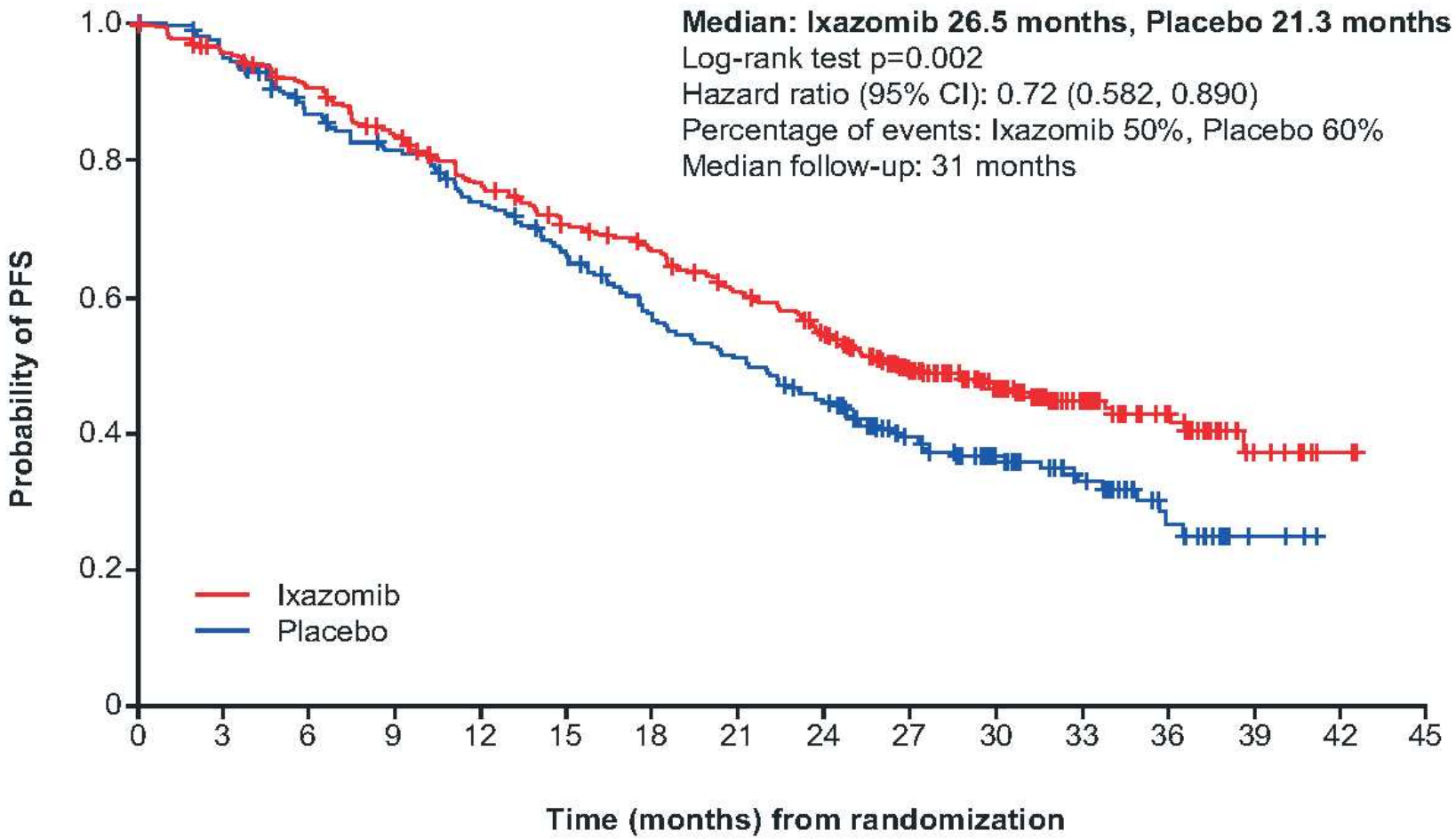
Stadtmauer et al. J Clin Oncol 2019.

Maintenance With Lenalidomide



McCarthy et al. J Clin Oncol 2017.

Oral Ixazomib Maintenance Following Autologous Stem Cell Transplantation (TOURMALINE-MM3): A Double-Blind, Randomized, Placebo-Controlled Phase 3 Trial



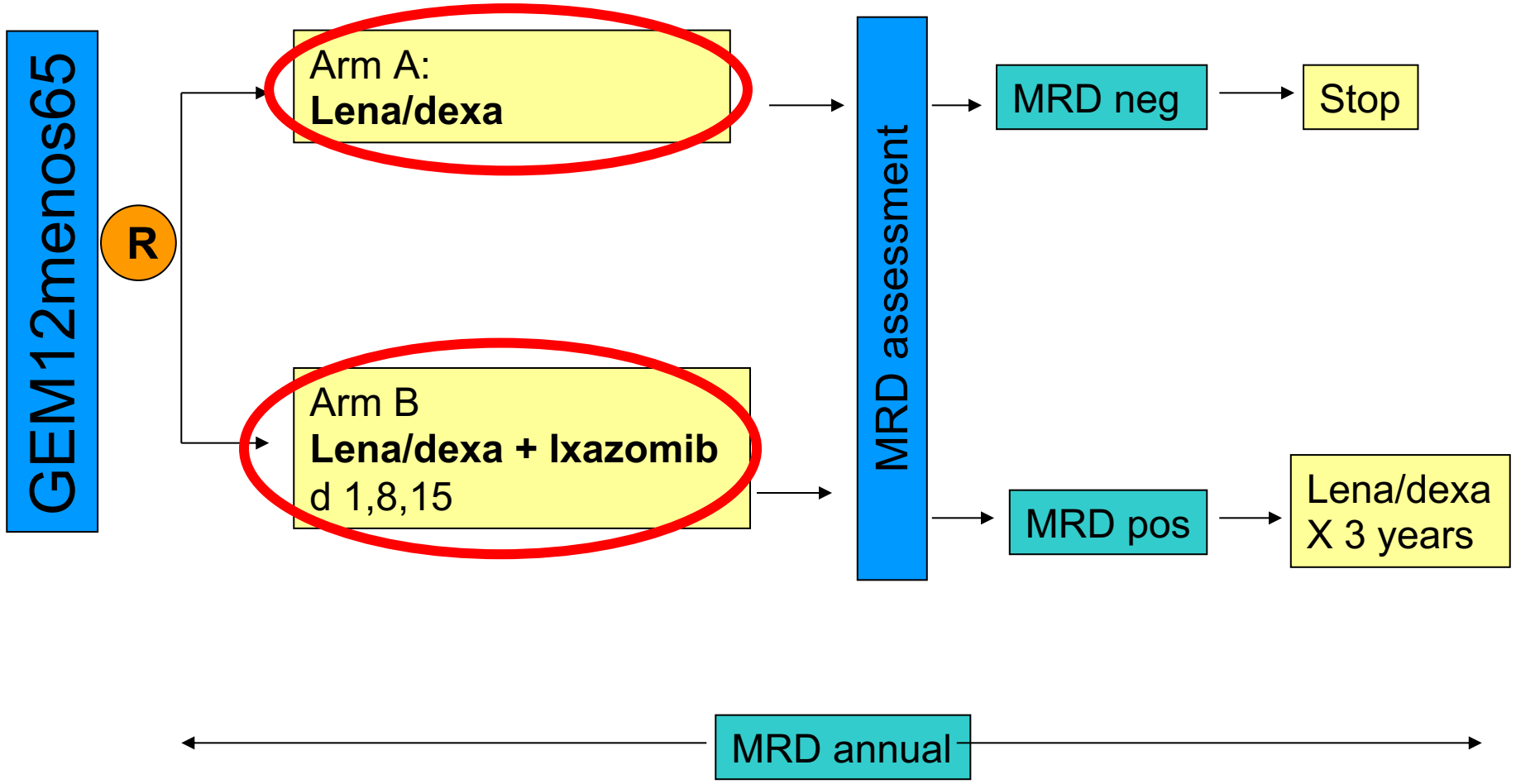
Number of patients at risk

Ixazomib	395	363	340	311	279	255	238	213	187	135	93	56	35	9	3	0
Placebo	261	238	210	195	174	153	130	117	100	69	46	32	15	3	0	0

Dimopoulos et al. Lancet 2019; 393:253-264

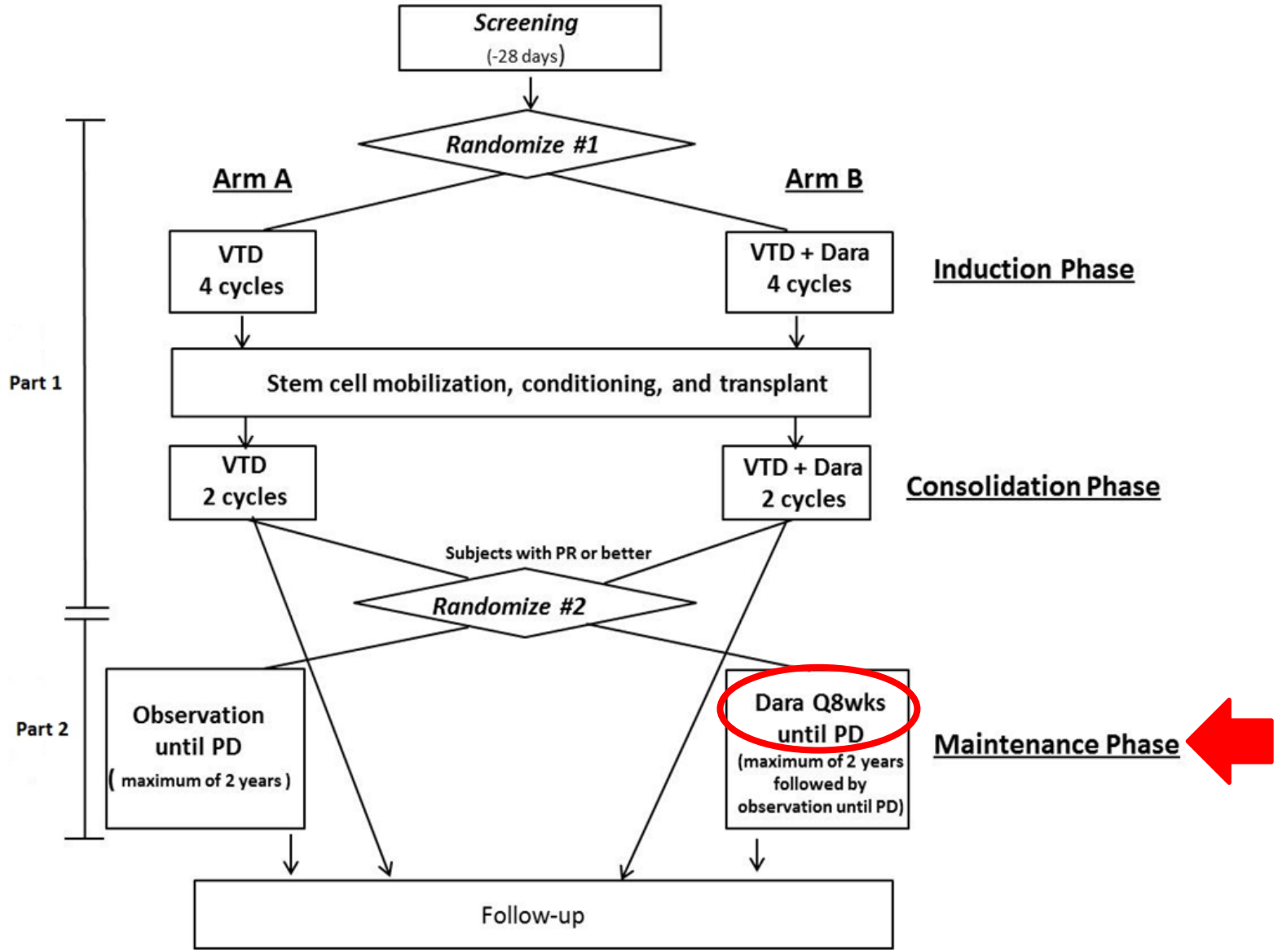
GEM14

Maintenance trial after ASCT

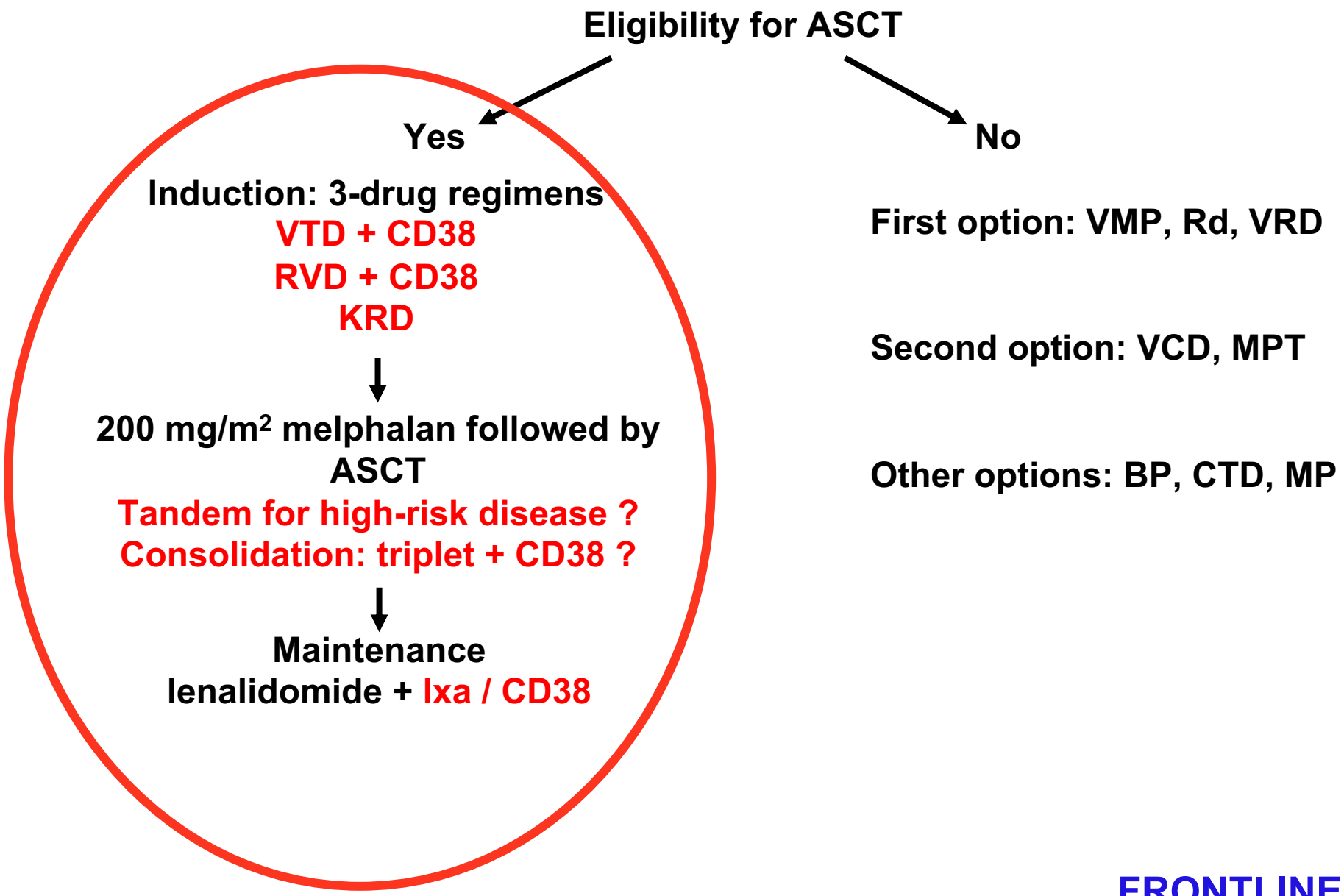


NCT02406144

CASSIOPEIA – 1080 Patients



Moreau et al. Lancet;2019



FRONTLINE THERAPY
ESMO guidelines, 2020 ?

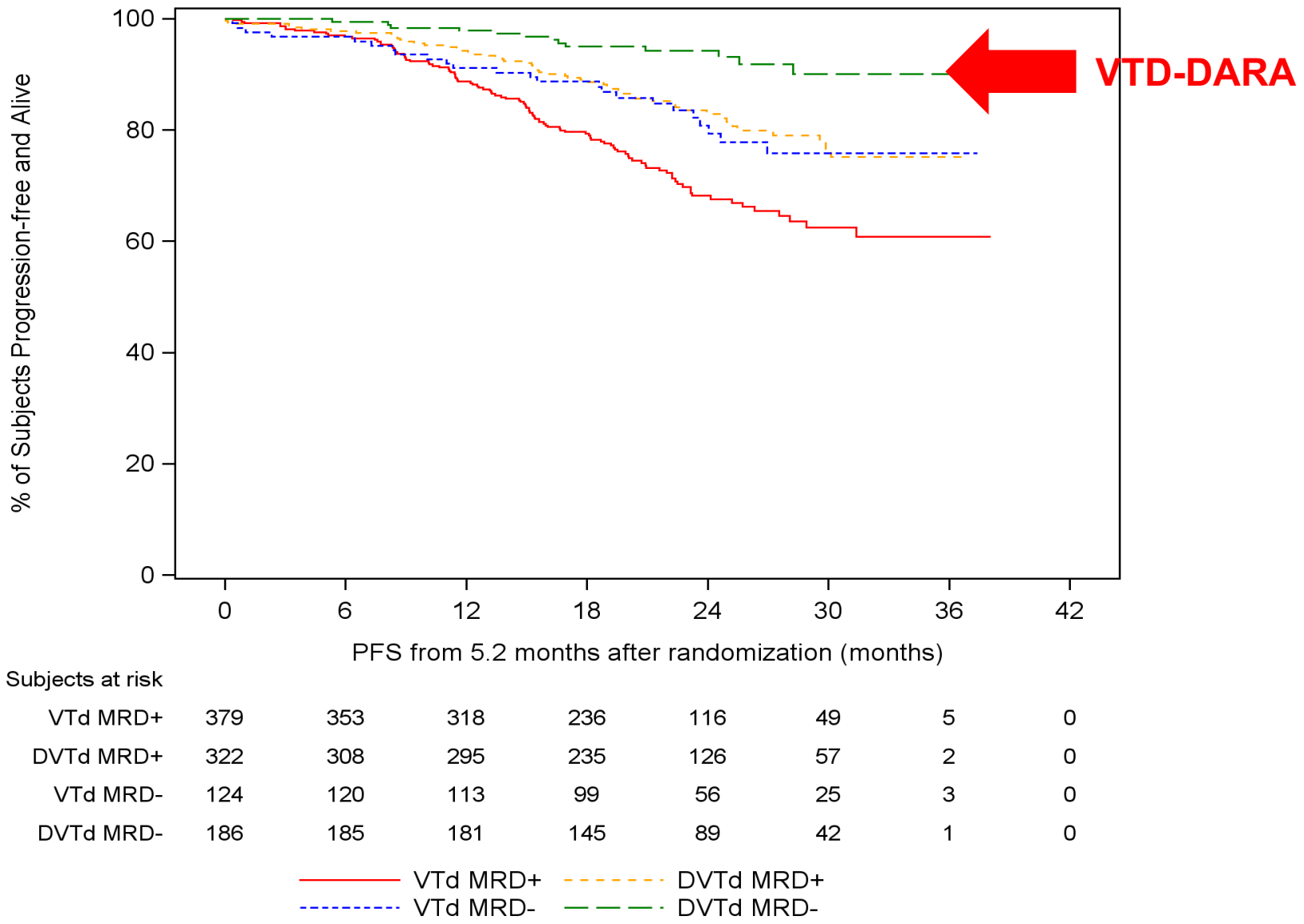
Multivariate Cox Proportional Hazards Regressions for PFS

Minimal Residual Disease by Flow Cytometry at 10^{-5} and Interaction With Treatment

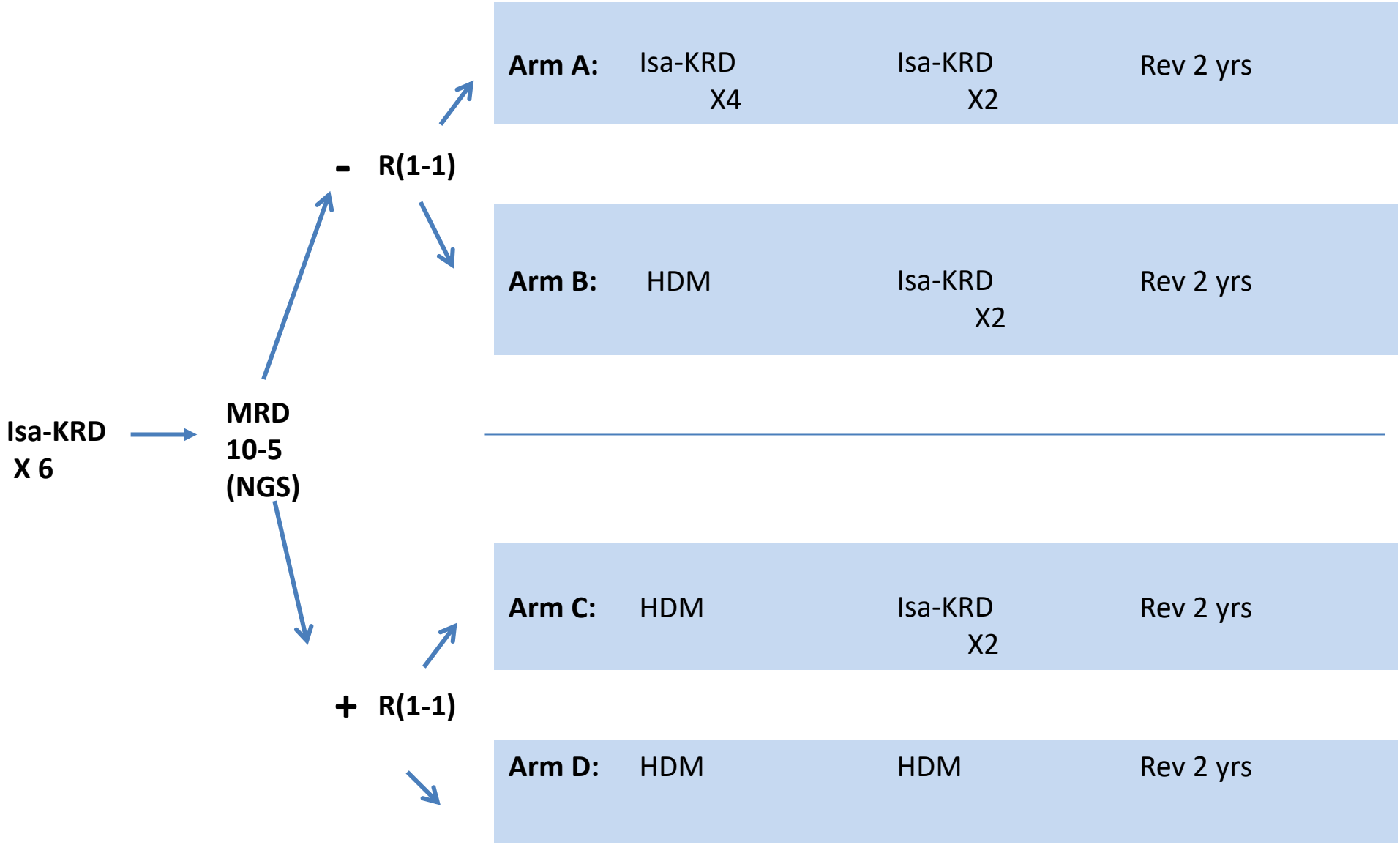
Intent-to-Treat Analysis Set

	Hazard Ratio (95% CI)	*P* Value
First landmark analysis **at post-induction** (N=1006)		
MRD (negative vs positive)	0.52 (0.28, 0.97)	**0.0408**
Treatment group (DVTd vs VTd)	0.43 (0.27, 0.70)	0.0006

Landmark Analysis: Kaplan-Meier Plot for PFS by Post-Induction MRD Status by Flow Cytometry at 10^{-5} and Treatment Group Intent-to-Treat Analysis Set



IFM 2020. Patients < 65 Years



NCT03104842