INTERNATIONAL MYELOMA FOUNDATION

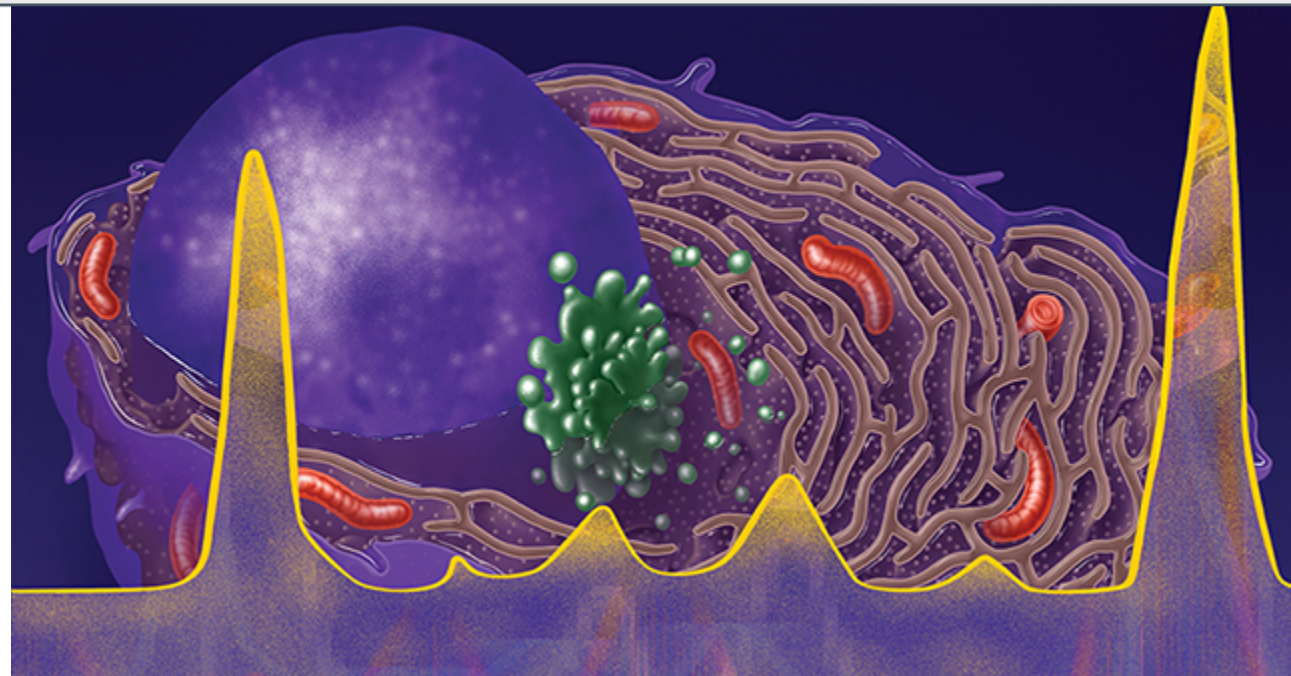
CCO LIVE

Considering the Recent Data on Transplantation, Consolidation, and Maintenance After Induction

Faculty Presenters:

Shaji Kumar, MD

Philippe Moreau, MD



This activity is supported by educational grants from AbbVie; Amgen; Bristol-Myers Squibb; Celgene Corporation; Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Takeda Oncology.

Image: Copyright©2018 DNA Illustrations. All Rights Reserved

Program Faculty

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

Shaji Kumar, MD, has disclosed that he has consulted with payment to Mayo Clinic from AbbVie, Amgen, Celgene, Dr. Reddy's Laboratory, Genentech, Janssen, Kite, MedImmune, Merck, Oncopeptides, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche-Genentech, Sanofi, and Takeda.

Program 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.

What’s next after induction?

The US Perspective

Shaji Kumar, MD

Patient Case Example

- A 53-year-old woman with no other health problems was diagnosed with myeloma when she presented with back pain and increasing fatigue

Lab Test	Result
Hemoglobin	10.8 g/dL
Serum Ca^{2+}	Normal
Serum creatinine	Normal
Serum LDH	Normal
Serum $\beta_2$microglobulin	2.8 mg/dL
Serum albumin	4.1 g/dL

- Serum protein electrophoresis: IgGK monoclonal protein of 3.2 g/dL
- 24-hour urine protein electrophoresis: 210 mg monoclonal protein, kappa light chain

Patient Case Example

- Whole-body low-dose CT showed multiple lytic lesions
- Bone marrow biopsy showed 40% plasma cell involvement, FISH showed no abnormality
- She was started on treatment with a combination of bortezomib, lenalidomide, and dexamethasone
- At the completion of 4 cycles of therapy:
  - Repeat bone marrow biopsy shows no MRD
  - Serum and urine immunofixation were both negative

What would you do next for this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	ASCT followed by RVD consolidation and lenalidomide maintenance
Shaji Kumar, MD	ASCT followed by lenalidomide maintenance
Philippe Moreau, MD	ASCT followed by RVD consolidation and lenalidomide maintenance
S. Vincent Rajkumar, MD	ASCT followed by lenalidomide maintenance
Jesús F. San-Miguel, MD, PhD	ASCT followed by RVD consolidation and lenalidomide maintenance

Patient Case Example

- A 53-year-old woman with no other health problems was diagnosed with myeloma when she presented with back pain and increasing fatigue

Lab Test	Result
Hemoglobin	10.8 g/dL
Serum Ca^{2+}	Normal
Serum creatinine	Normal
Serum LDH	**Above ULN**
Serum $\beta_2$microglobulin	**7.1 mg/dL**
Serum albumin	4.1 g/dL

- Serum protein electrophoresis: IgGK monoclonal protein of 3.2 g/dL
- 24-hour urine protein electrophoresis: 210 mg monoclonal protein, kappa light chain

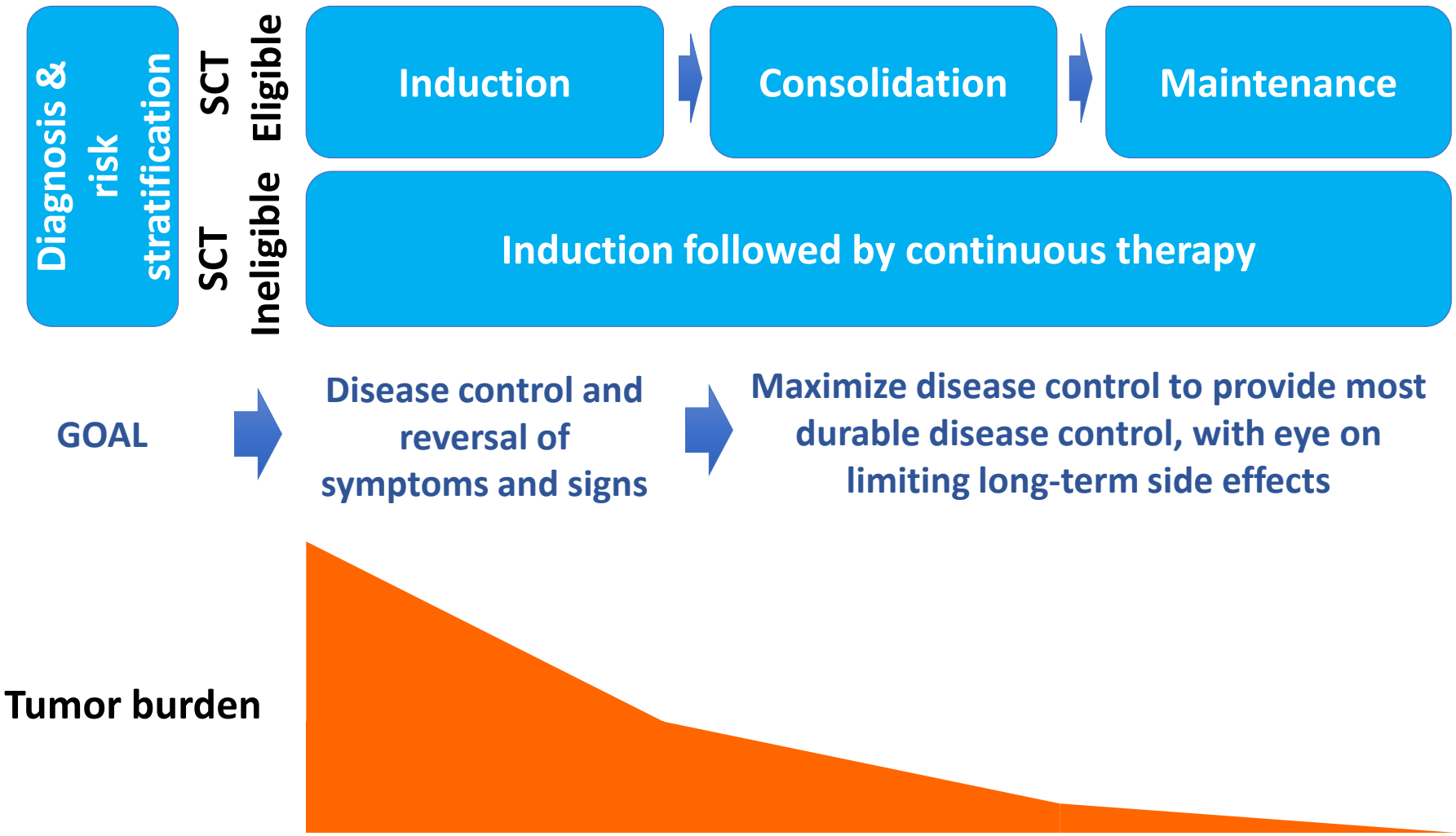
Patient Case Example

- Whole-body low-dose CT showed multiple lytic lesions
- Bone marrow biopsy showed 40% plasma cell involvement, **FISH showed 17p deletion in > 50% of tumor cells**
- She was started on treatment with a combination of bortezomib, lenalidomide and dexamethasone
- At the completion of 4 cycles of therapy:
  - Repeat bone marrow biopsy shows no MRD
  - Serum and urine immunofixation were both negative

Now, what would you do next for this patient?

Faculty	Recommendation
Brian G.M. Durie, MD	ASCT followed by RVD consolidation and PI-based maintenance
Shaji Kumar, MD	ASCT followed by PI-based maintenance
Philippe Moreau, MD	Tandem ASCT followed by RVD consolidation and PI-based maintenance
S. Vincent Rajkumar, MD	ASCT followed by PI-based maintenance
Jesús F. San-Miguel, MD, PhD	Tandem ASCT followed by RVD consolidation and lenalidomide maintenance

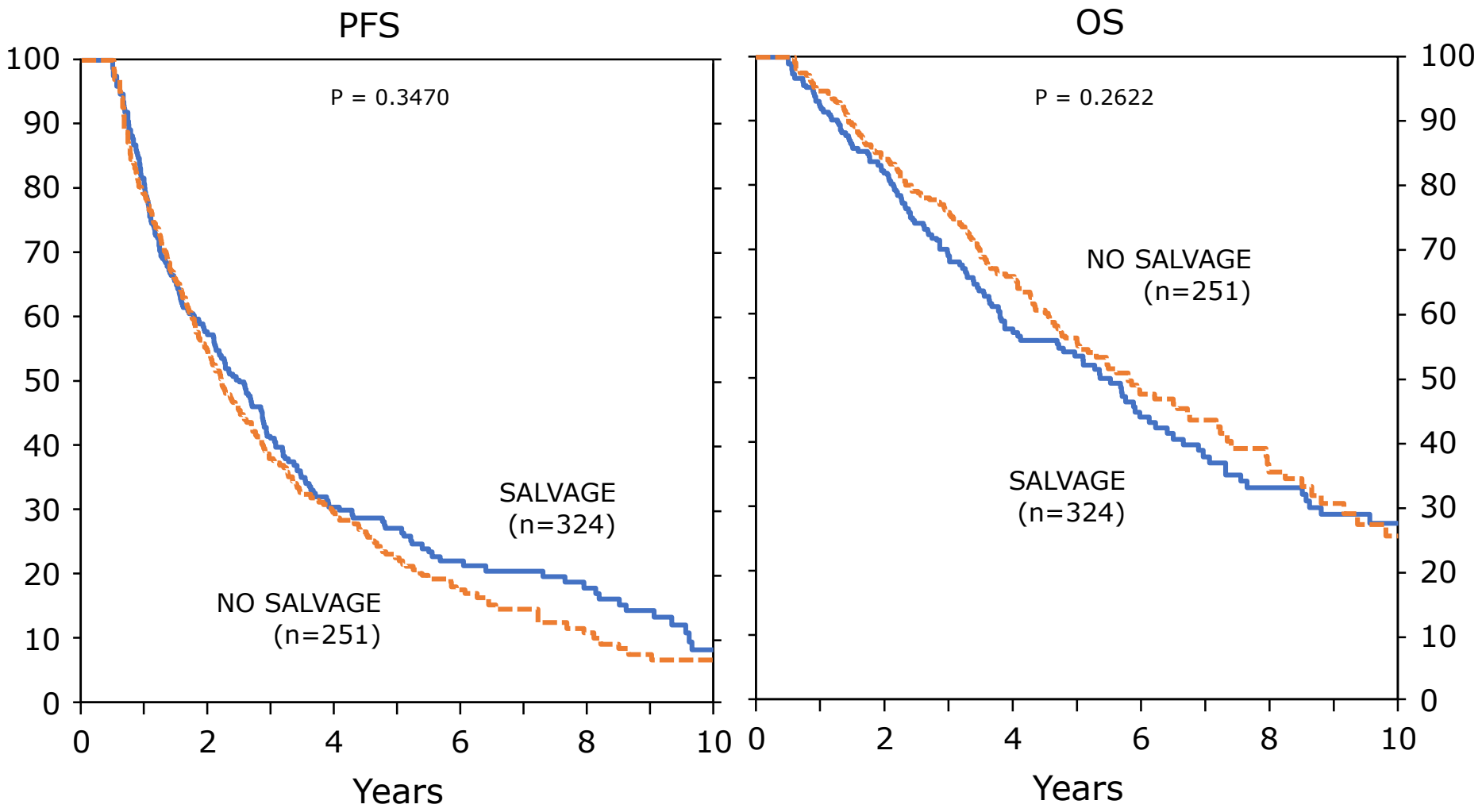
Myeloma Treatment Paradigm



Consolidation and Maintenance

- Stem cell transplantation (SCT): one or two?
- Post-transplantation consolidation?
- Post-transplantation maintenance?

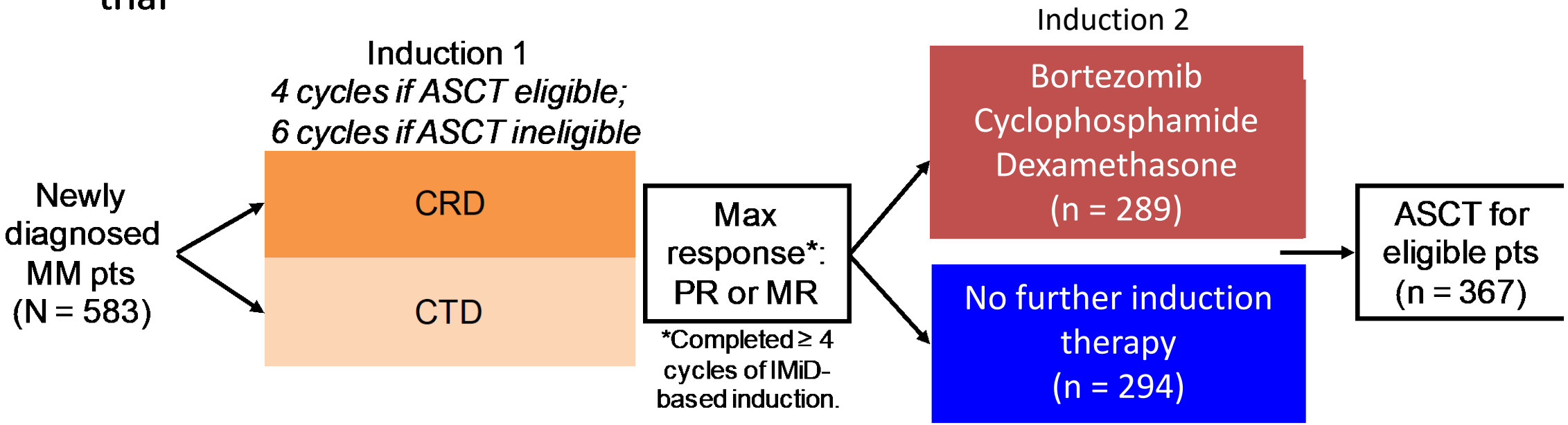
When Do You Stop Induction Therapy?



Vij R, Biol Blood Marrow Transplant. 2014.

Ideal Duration of Induction Prior to SCT?

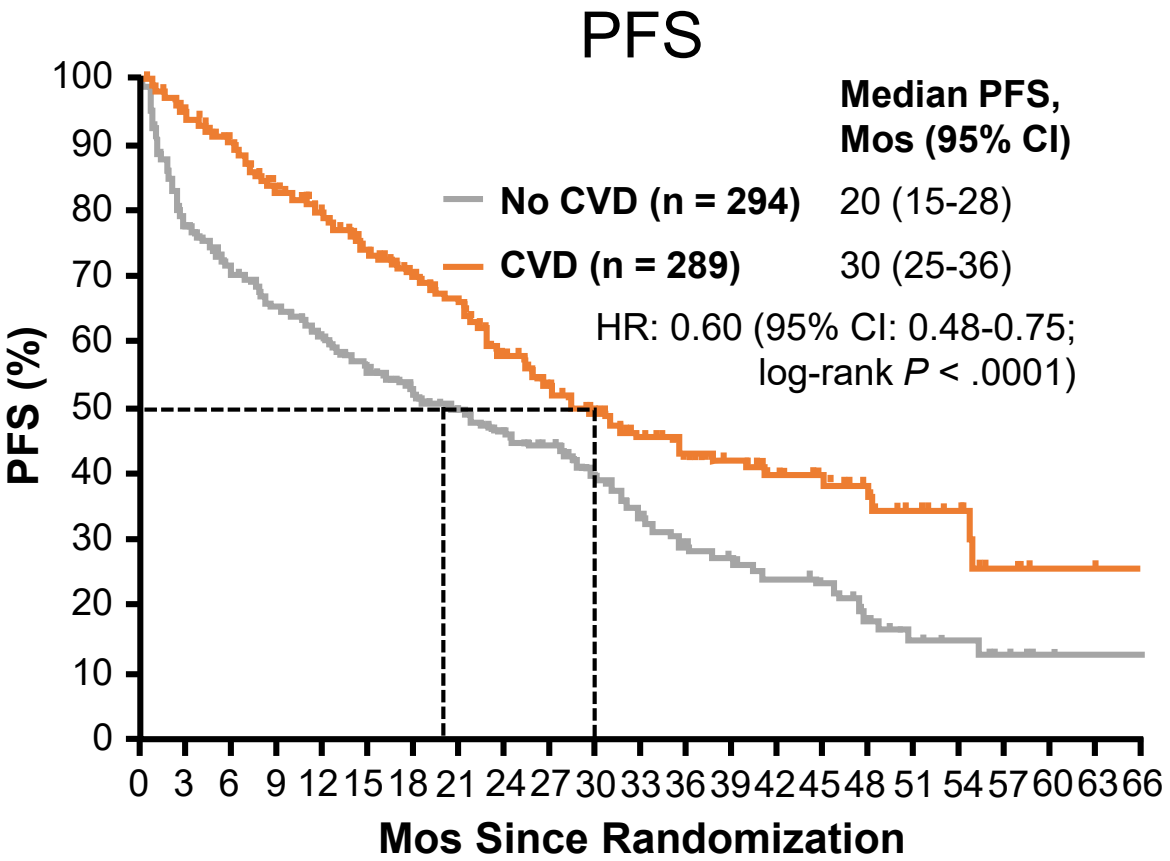
- UK-based multicenter, open-label, parallel group, randomized controlled phase III trial

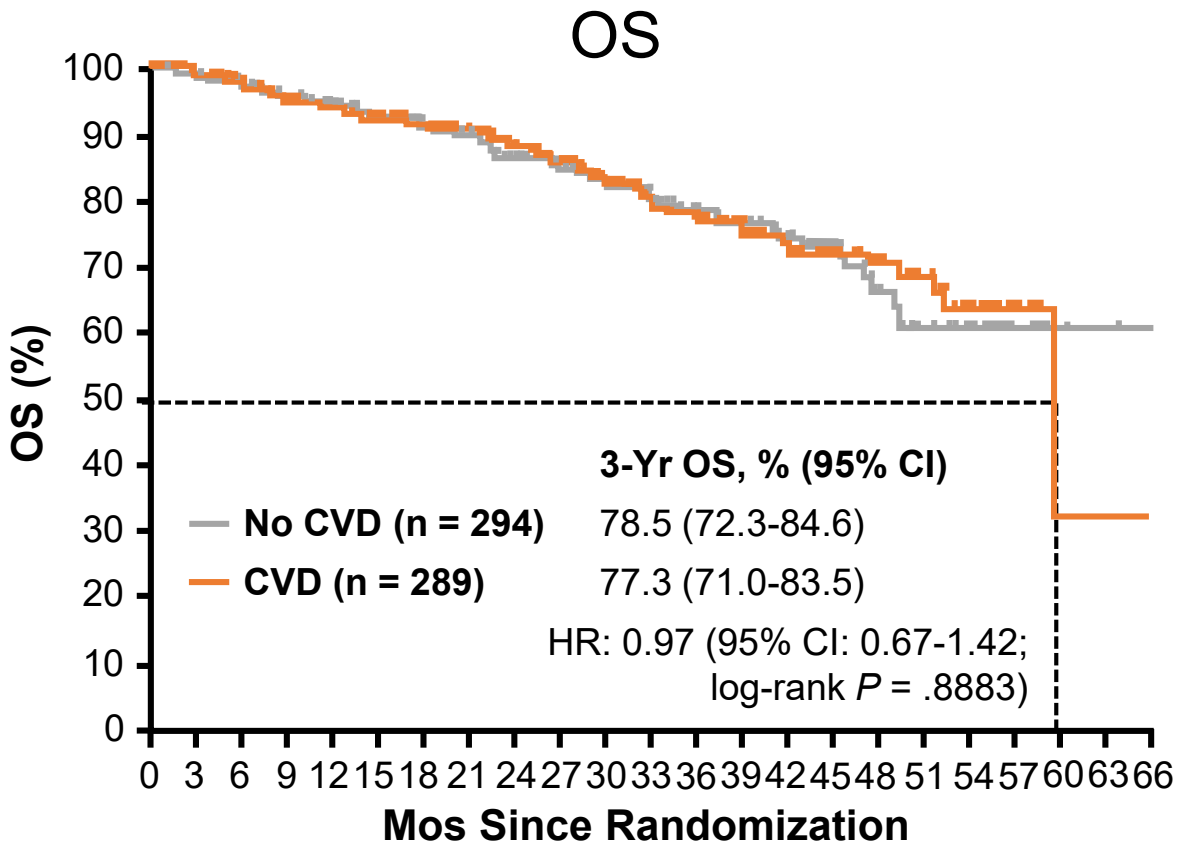


- Primary endpoints: PFS, OS
- Secondary endpoints: Improved response vs baseline, PI effect in high-risk pt group

Jackson. ASH 2016. Abstr 244.

Myeloma XI: Results

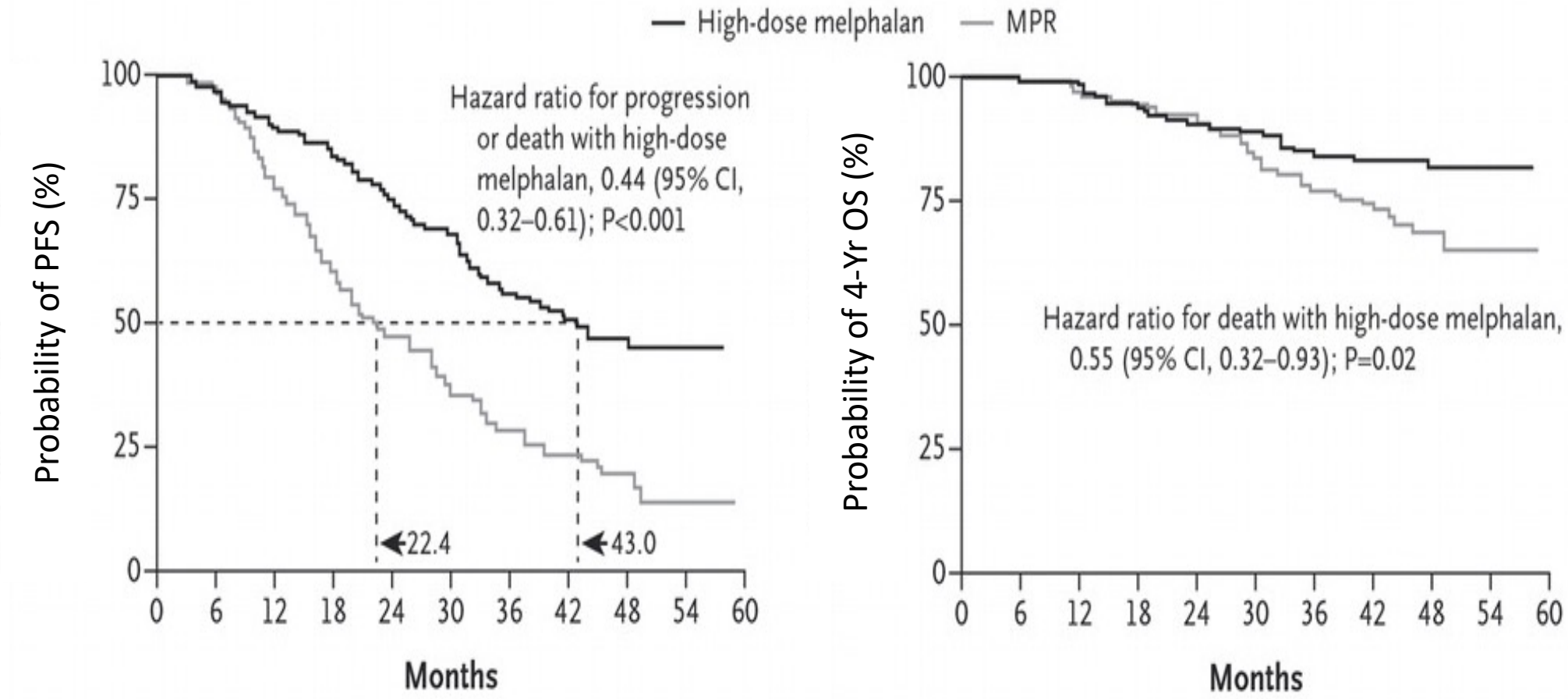




Recommendation: 4-6 cycles of induction and then transplant

Jackson. ASH 2016. Abstr 244.

Do We Still Need ASCT with Novel Drugs?



Palumbo. N Engl J Med 2014;371:895.

Do We Still Need ASCT? IFM 2009

Registration

RVD 1
Lenalidomide + Bortezomib + Dexamethasone

Randomization (stratified on ISS and FISH)

Arm A	Arm B
RVD 2 and 3	RVD 2 and 3
PBSC Collection (cyclophosphamide and G-CSF)	PBSC Collection (cyclophosphamide and G-CSF)
RVD 4 to 8	ASCT HDM 200 mg/m^2
Lenalidomide Maintenance 12 months (10-15 mg/day)	RVD 4 and 5
	Lenalidomide Maintenance 12 months (10-15 mg/day)

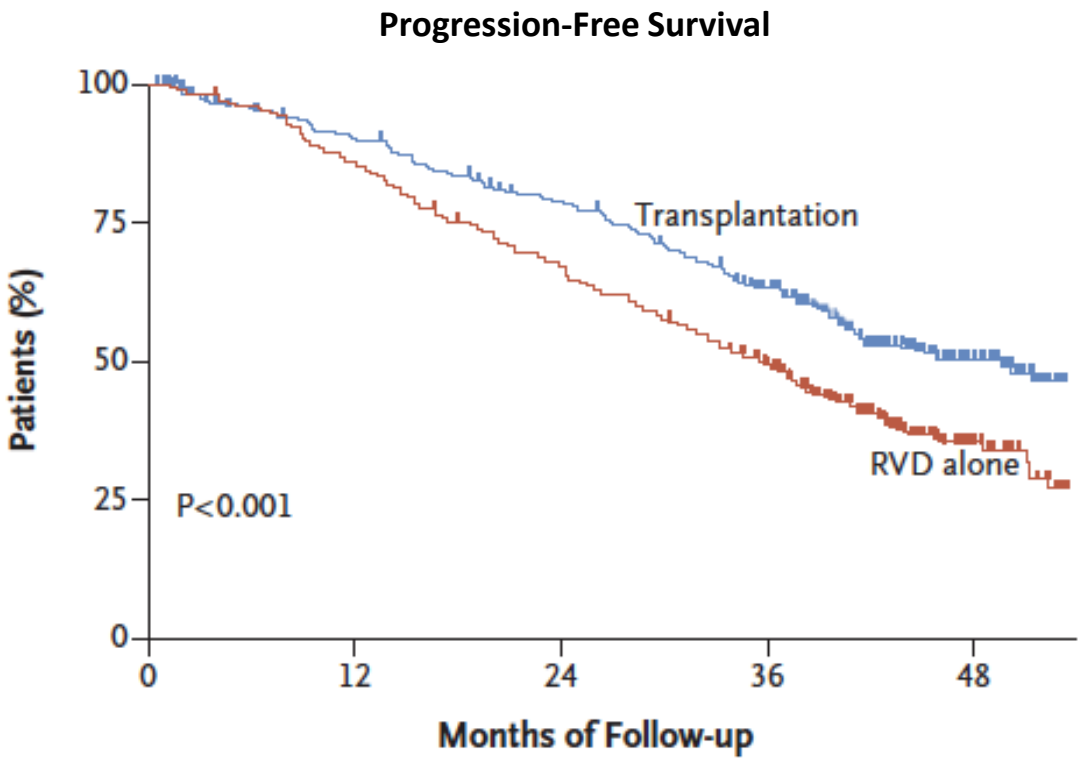
Attal. NEJM. 2017;376:1311.

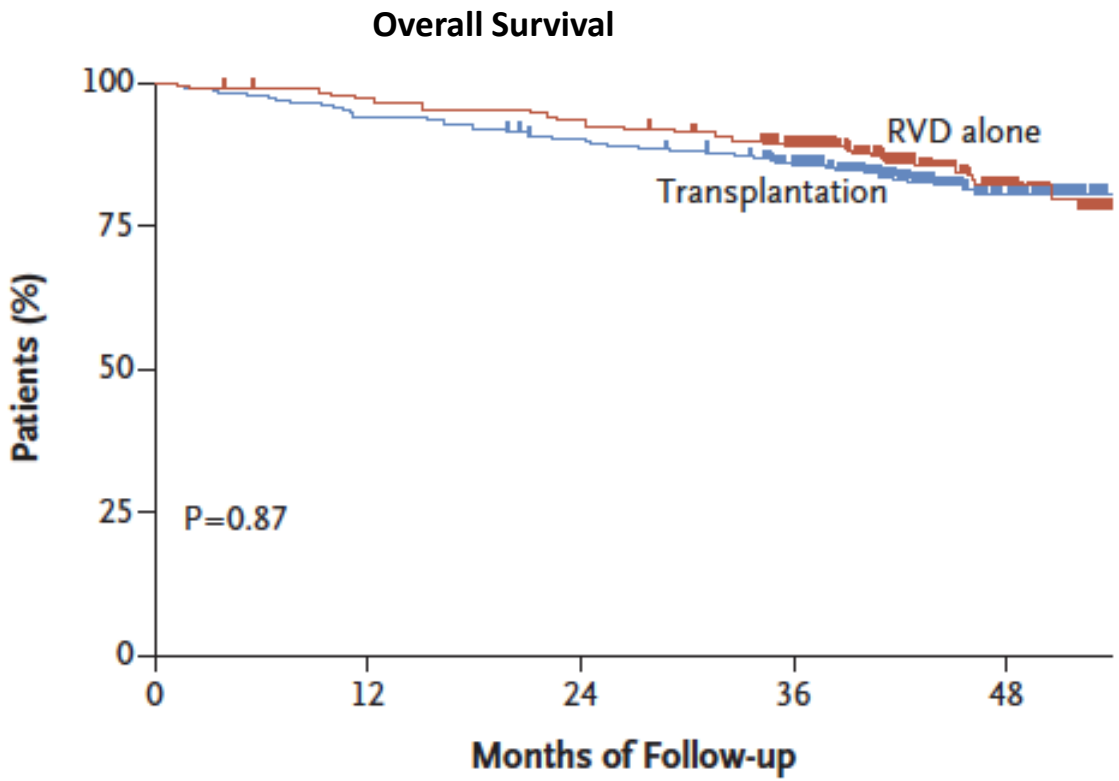
Deeper Responses With SCT

Outcome	RVD-Alone Group (N = 350)	Transplantation Group (N = 350)
Best response during the study , n (%)		
Complete response	169 (48)	205 (59)
Very good partial response	101 (29)	102 (29)
Partial response	70 (20)	37 (11)
Stable disease	10 (3)	6 (2)
Complete response, n (%)	169 (48)	205 (59)
Complete response or very good partial response, n (%)	270 (77)	307 (88)
Minimal residual disease not detected during study, n/ total n with complete or very good partial response (%)	171/265 (65)	220/278 (79)

Attal. NEJM. 2017;376:1311.

Better PFS; Comparable OS





Recommendation: upfront SCT recommended, but a delayed approach is acceptable

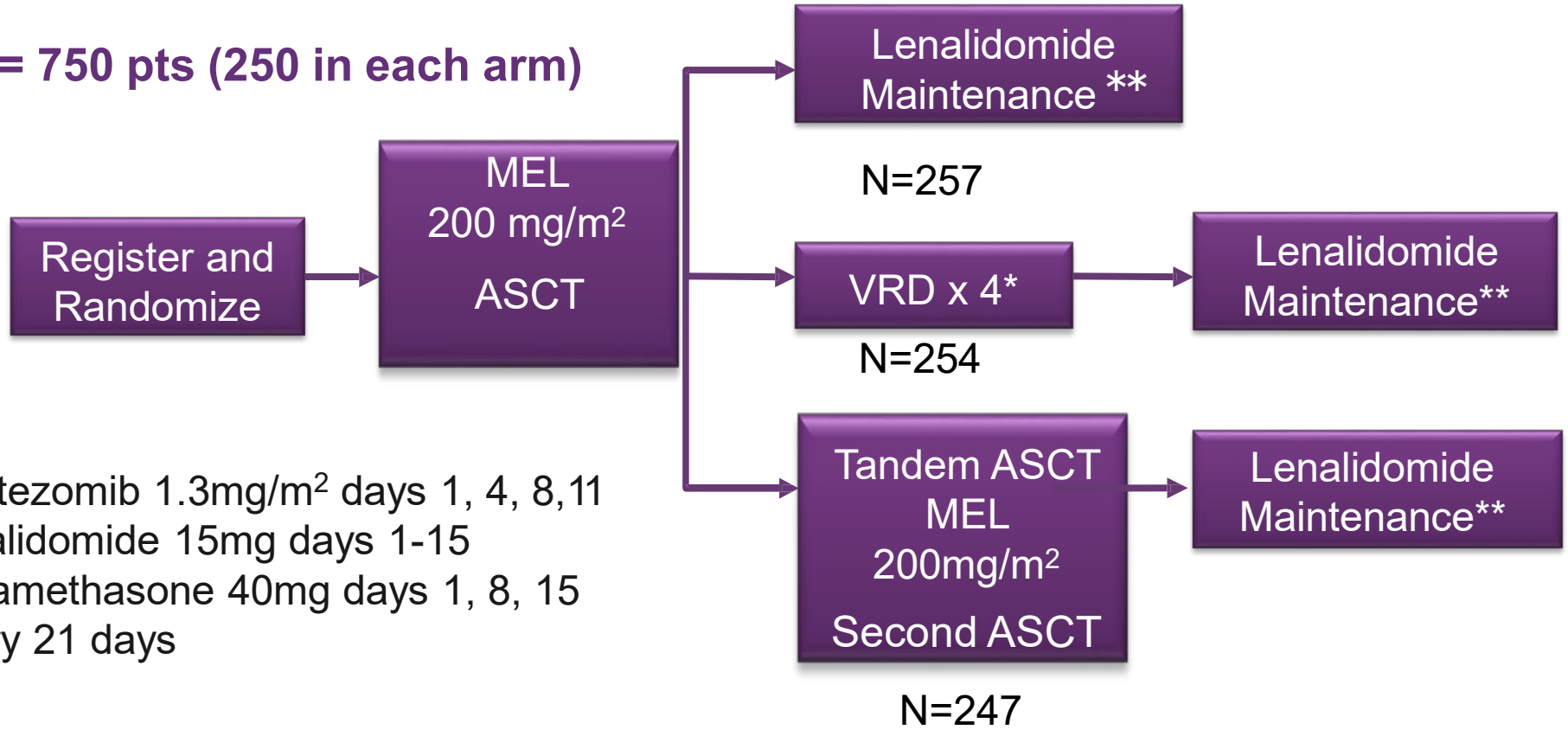
Attal. NEJM. 2017;376:1311.

What Should Be Done Post ASCT?

- Consolidation with tandem ASCT?
- Non-transplant consolidation?
- Maintenance?

STaMINA Trial: BMT CTN 0702

N = 750 pts (250 in each arm)

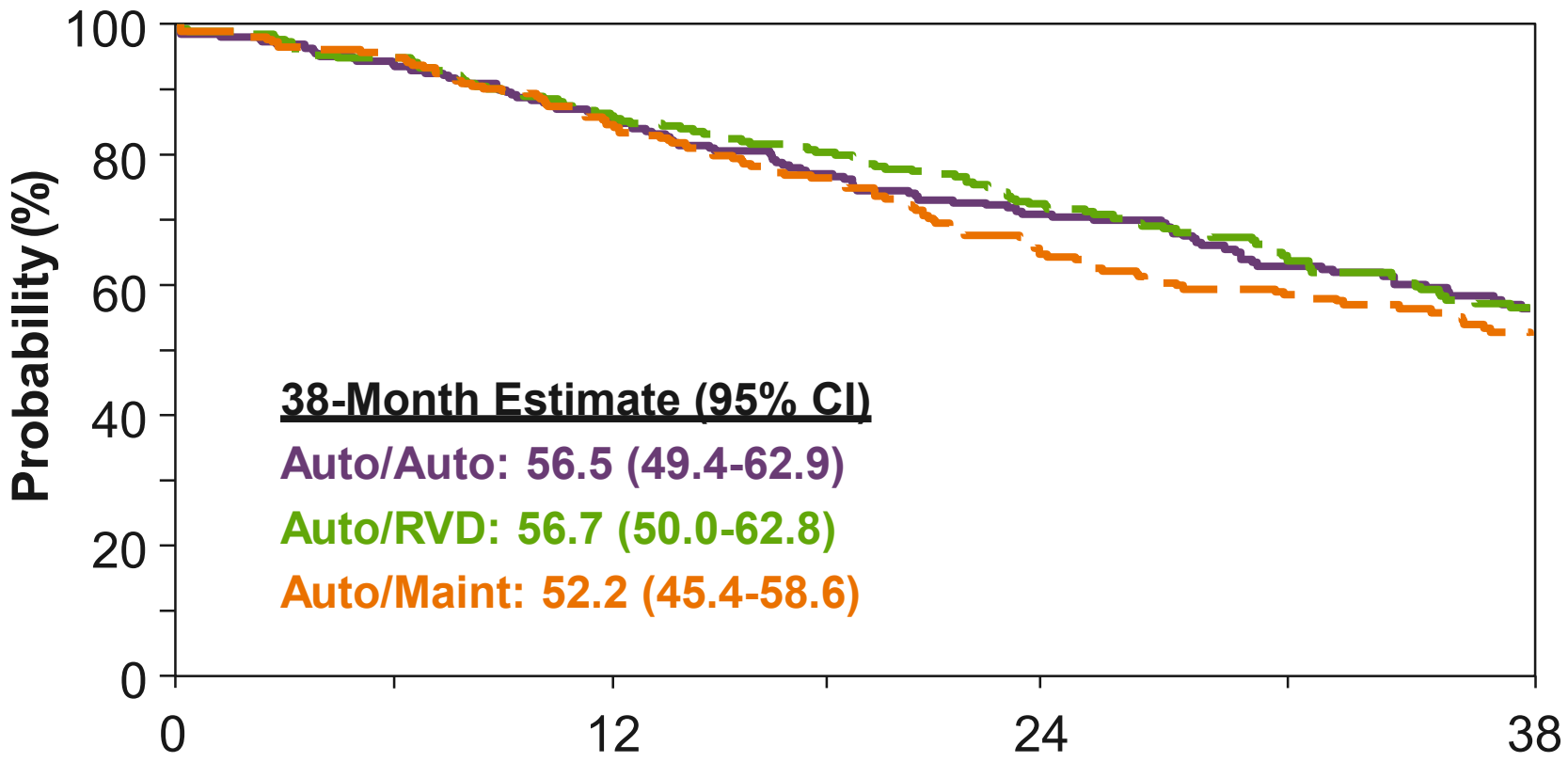


*Bortezomib 1.3mg/m^2 days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15
Every 21 days

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

Stadtmauer. ASH 2016. Abstr LBA-1.

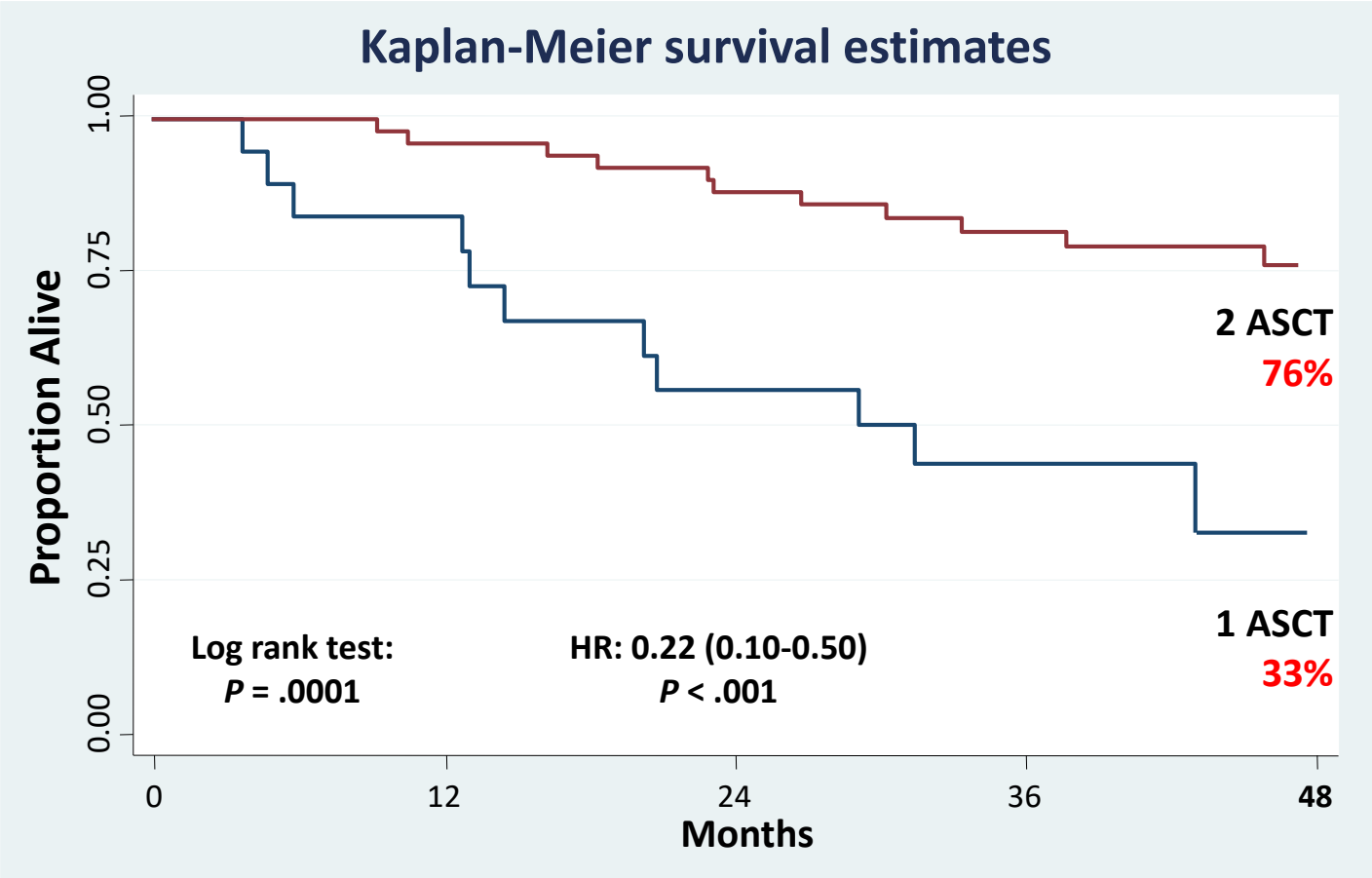
STaMINA Trial: Primary Endpoint—PFS



Recommendation: with VRd induction, no role for additional VRd consolidation

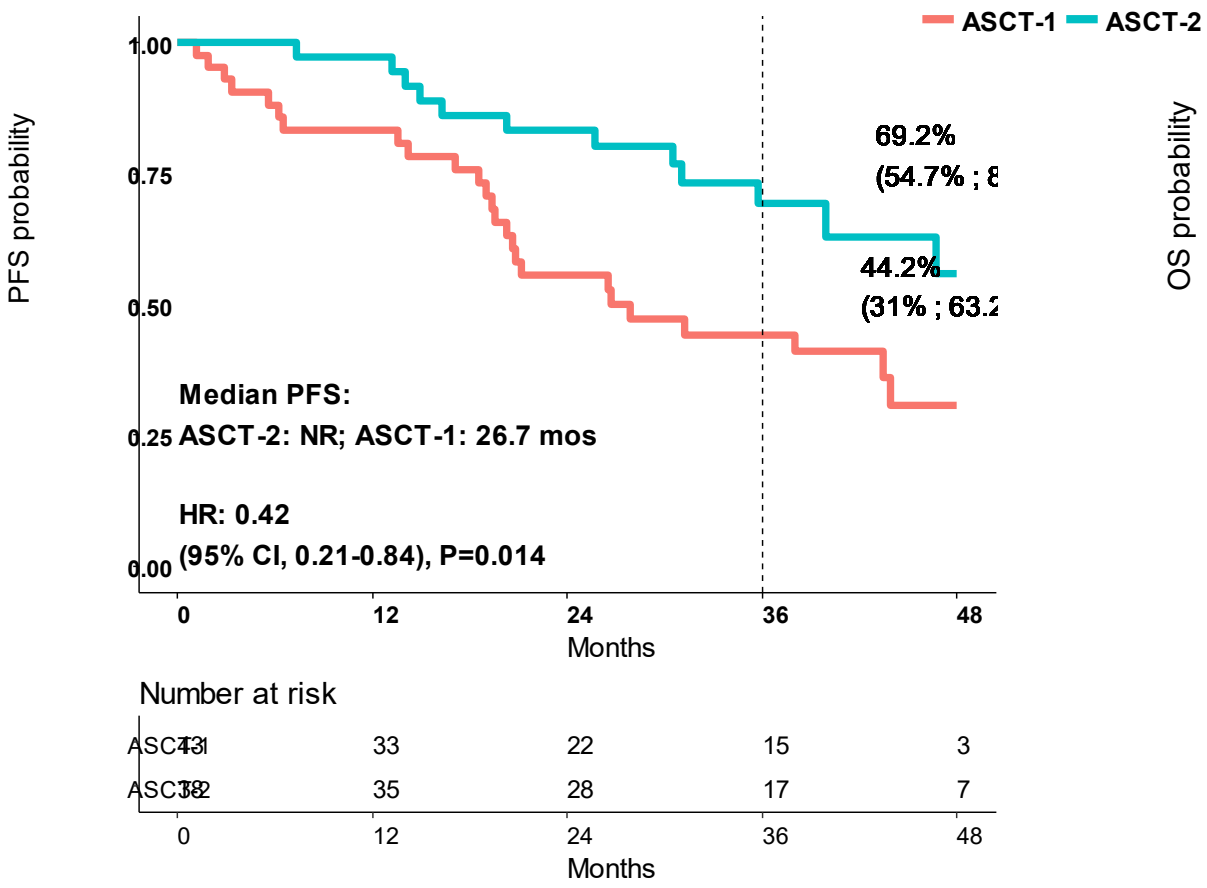
Stadtmauer. ASH 2016. Abstr LBA-1.

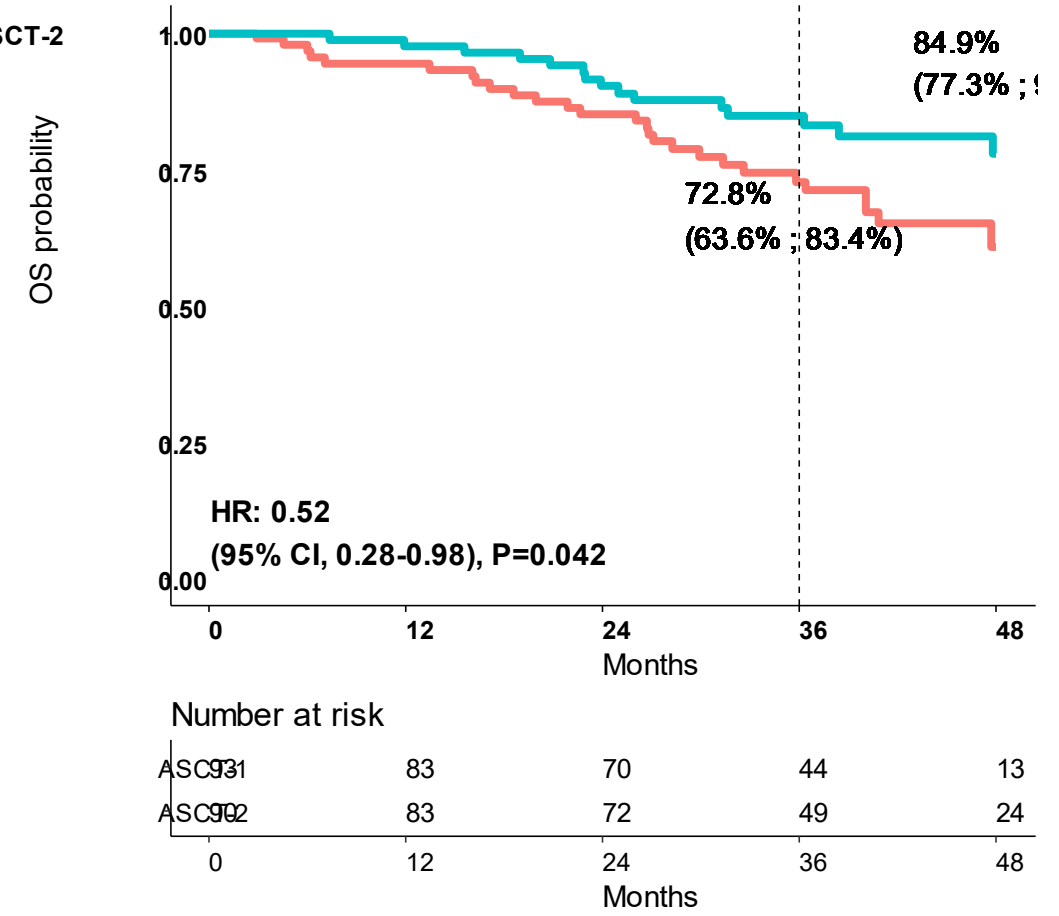
Tandem ASCT: del(17p) ± t(4;14)



Cavo. ASH 2013. Abstr 767.

EMN02: Single vs Tandem: High Risk Genetics

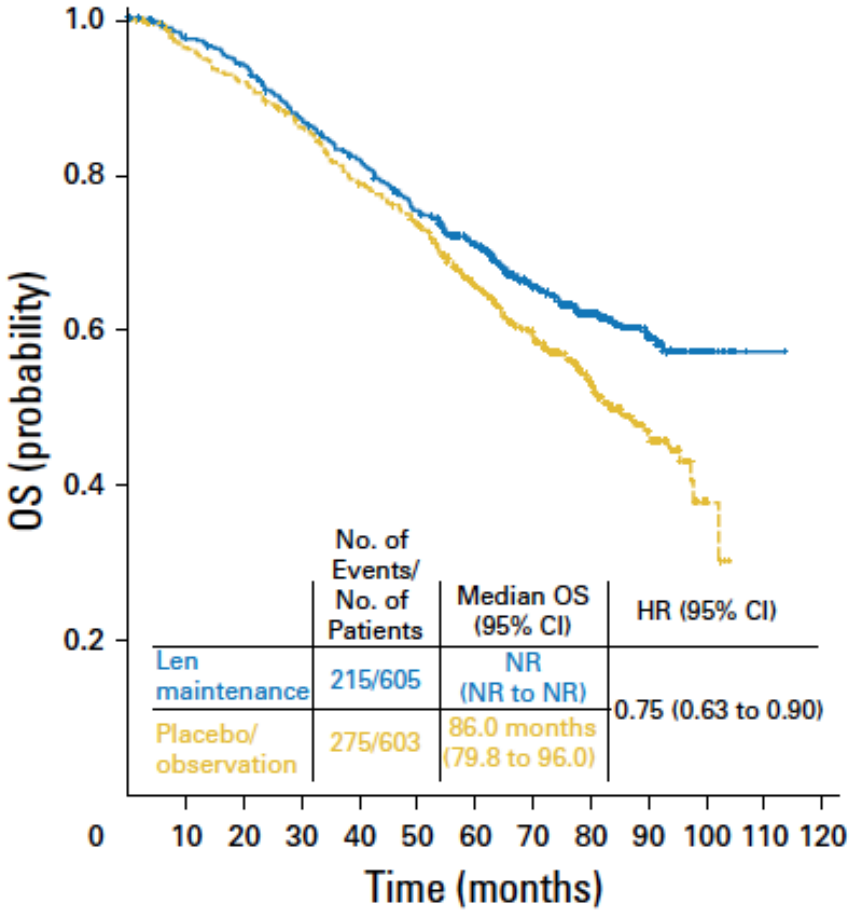


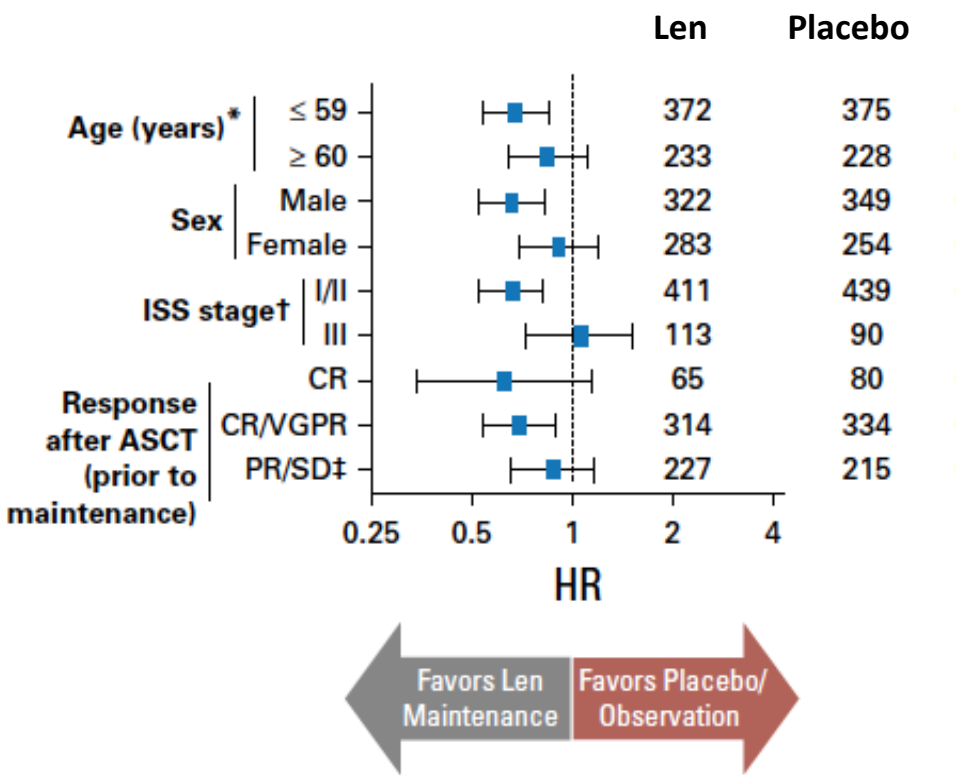


Recommendation: in high-risk patients, a discussion regarding tandem SCT is warranted

Cavo. ASH 2017. Abstr 401.

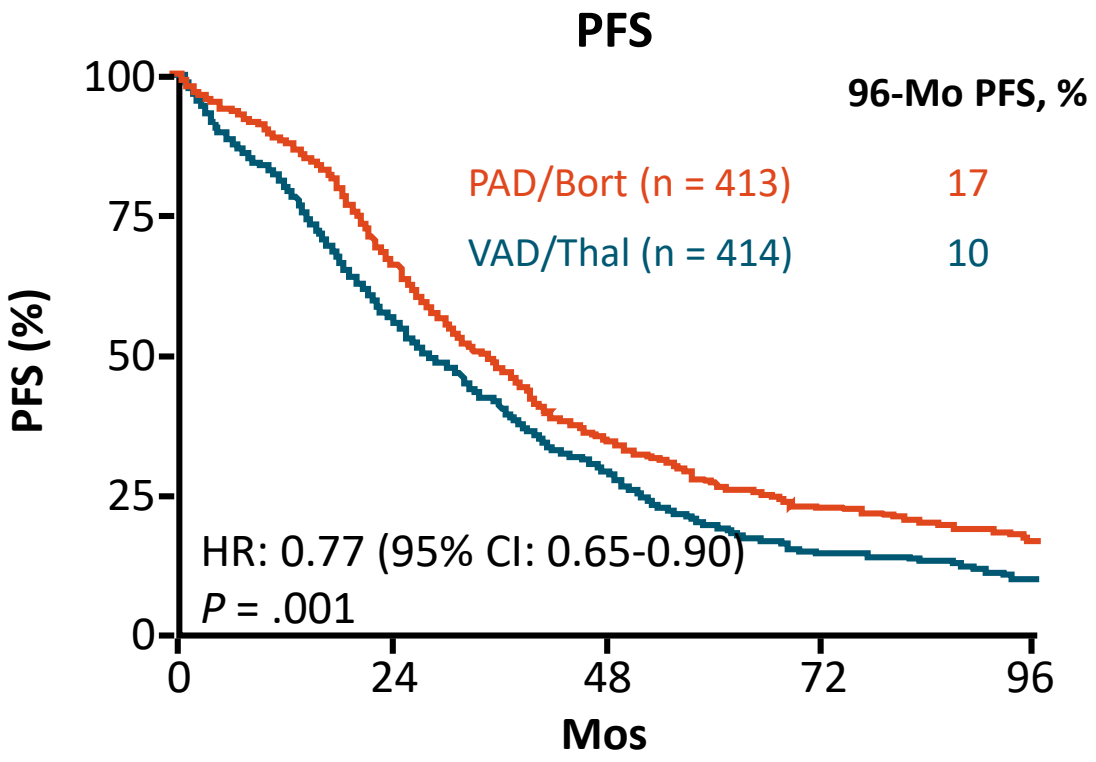
Lenalidomide Maintenance

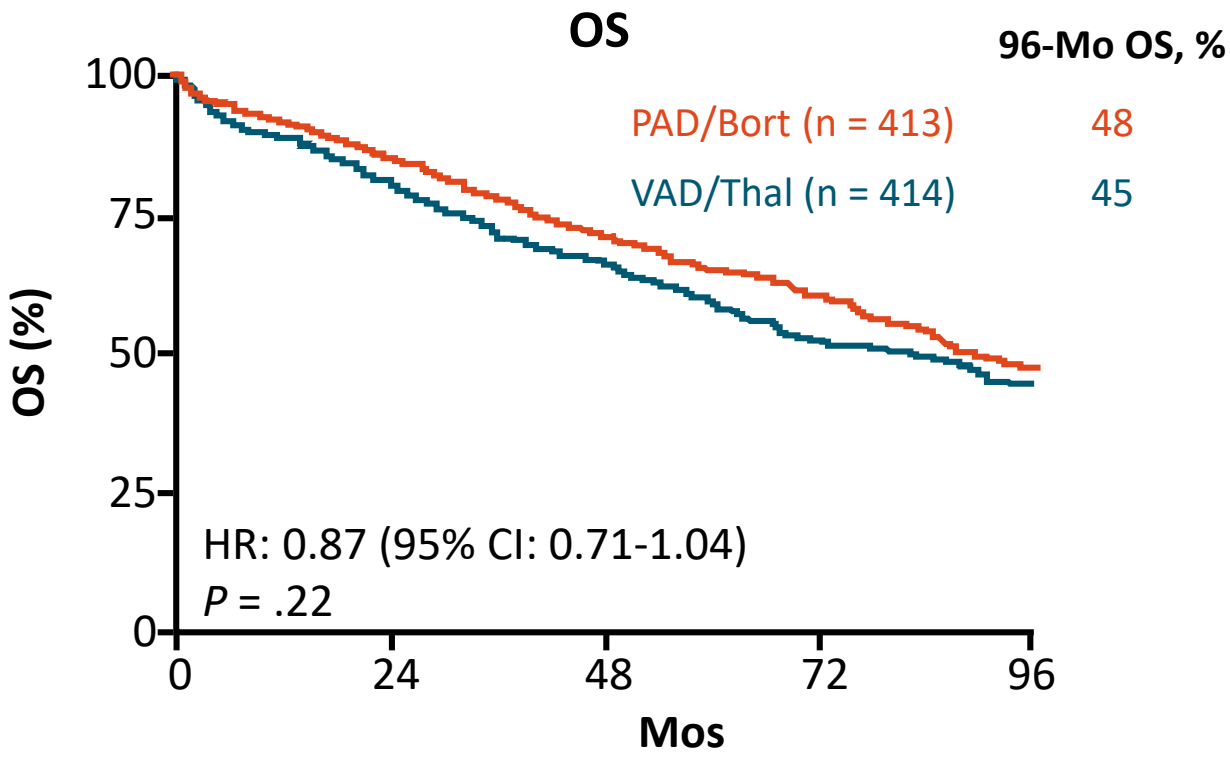




McCarthy. JCO. 2017;35:3279.

Phase III HOVON-65/GMMG-HD4 Trial: Bortezomib Maintenance



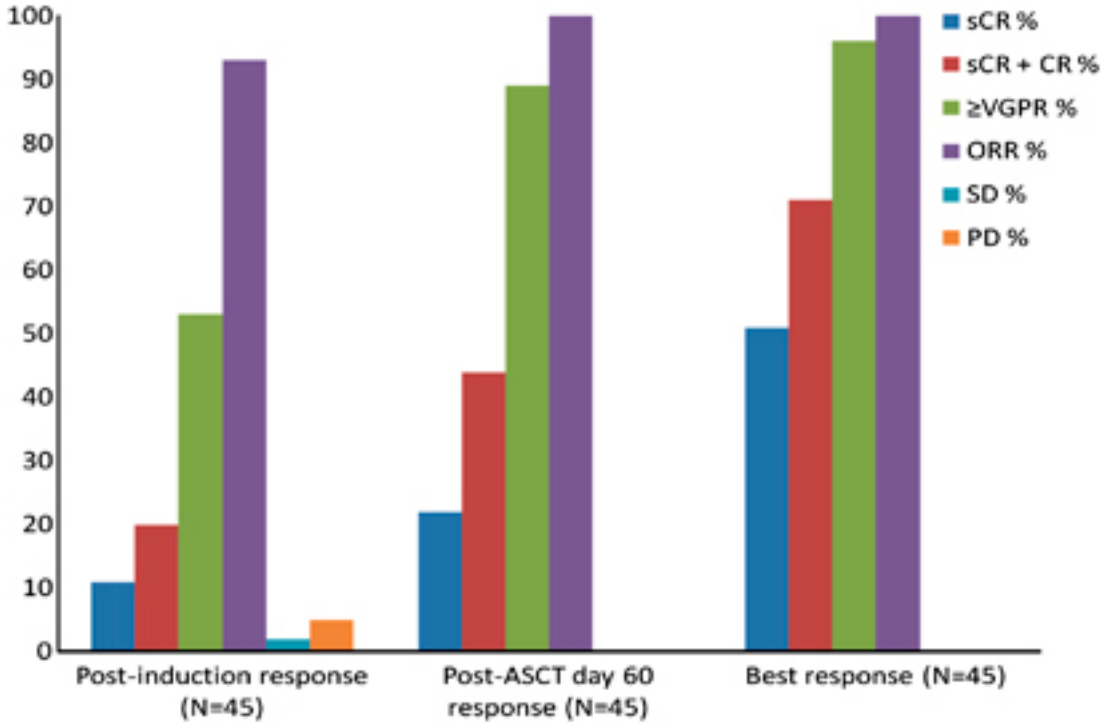


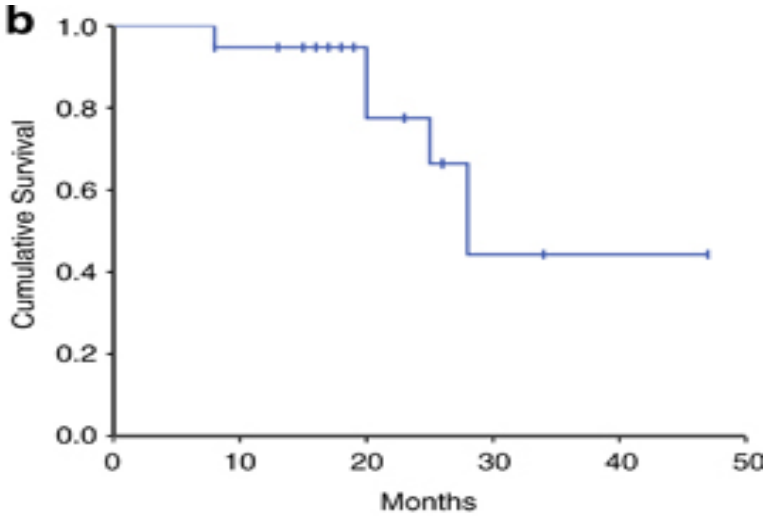
Recommendation: Lenalidomide maintenance should be considered for standard risk and bortezomib maintenance for high risk

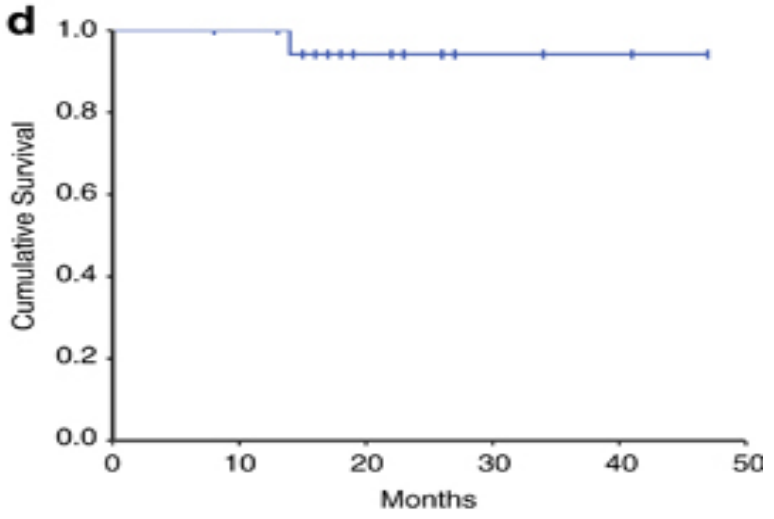
Outcome, %	PAD/Bort	VAD/Thal
CR/nCR	50	35
≥ VGPR	75	56
ORR	91	83

Goldschmidt. Leukemia. 2018;32:383.

Different strategy for HR? VRD Maintenance







Nooka. Leukemia. 2014;28:690.

Take Home Points

- In transplant-eligible patients: upfront transplant after 4-6 cycles of induction regardless of the depth of response is standard
  - Delayed SCT at first relapse is acceptable
- If VRd induction is used, additional consolidation with VRd is not recommended
- Tandem transplant is not standard approach
  - In high-risk MM, possibility of benefit should be discussed
- Lenalidomide maintenance recommended for all standard-risk MM and bortezomib based maintenance for high risk
  - del17p: VRd maintenance could be considered

MAYO CLINIC

Thank you

kumar.shaji@mayo.edu

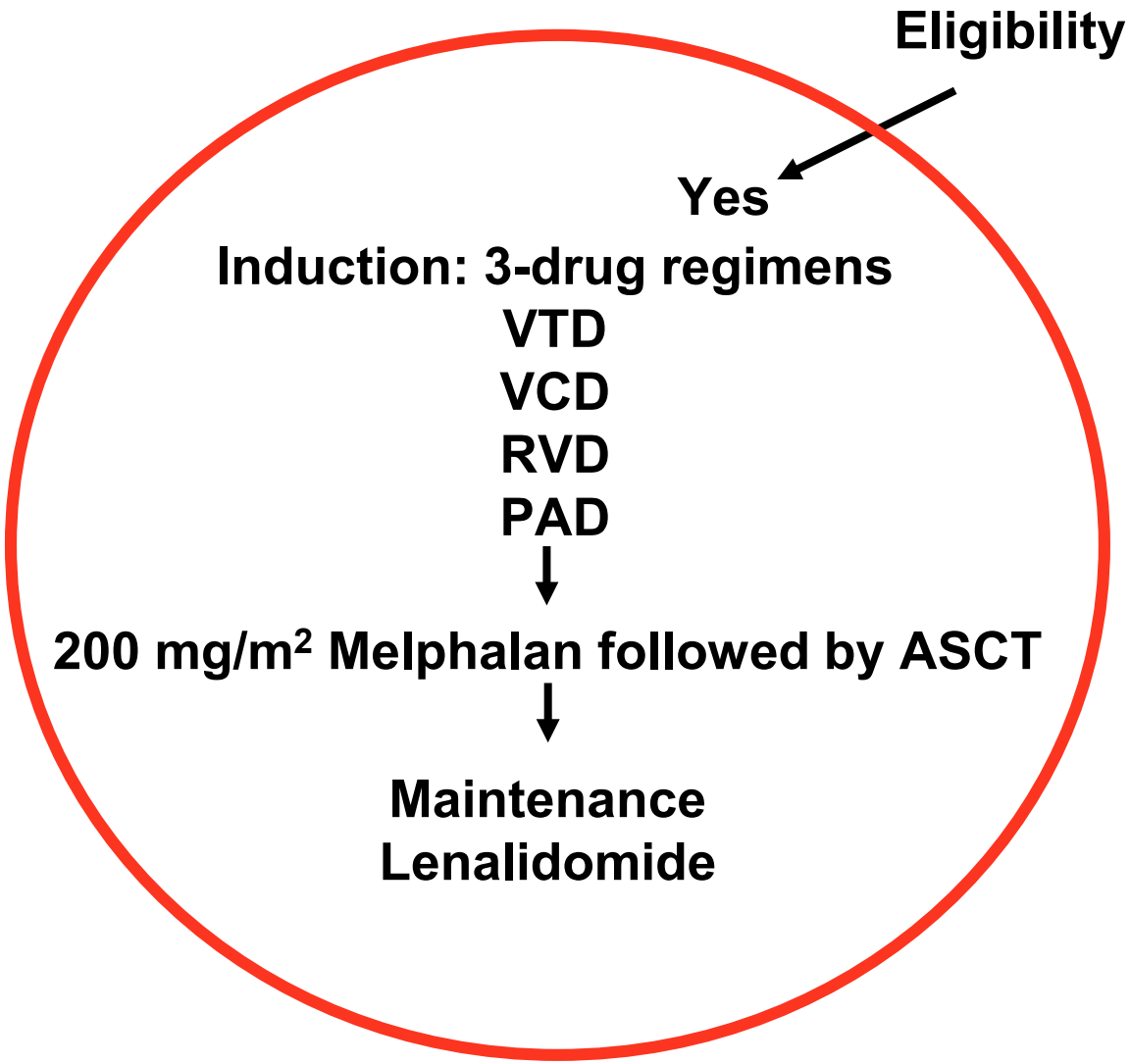
What's Next After Induction in Patients Eligible for ASCT ?

The European Perspective

Pr Philippe Moreau

University Hospital, Nantes, France

CENTRE HOSPITALIER
UNIVERSITAIRE DE NANTES



FRONTLINE THERAPY
ESMO guidelines
Moreau et al, Ann Oncol 2017

No Consolidation!

Single ASCT!

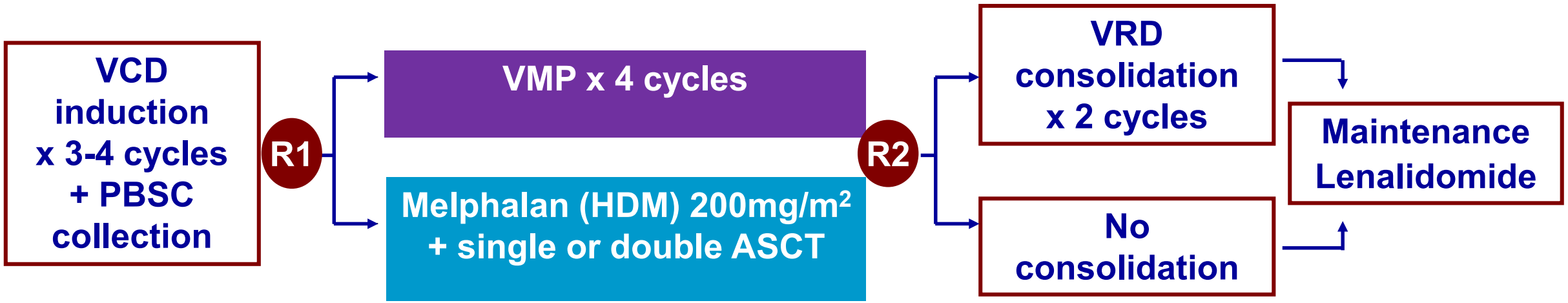
No Delayed ASCT!

≤ 65 Years or
Fit Patients ≤ 70 Years in Good Clinical Condition

In the context of novel-agent based therapy, frontline ASCT is the standard of care !

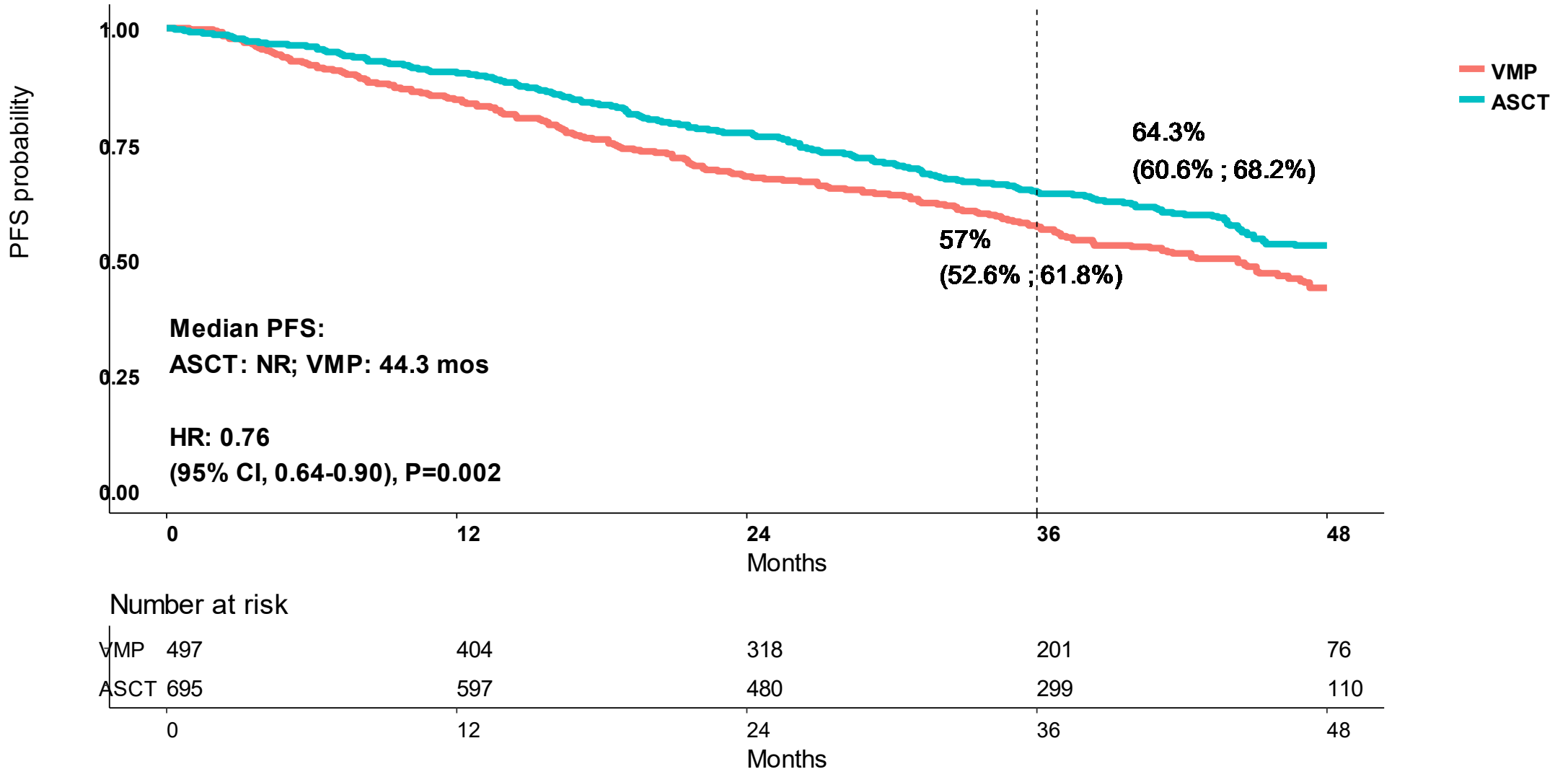
IFM 2009
EMN02

EMN02/HO95 MM Trial: Study Design



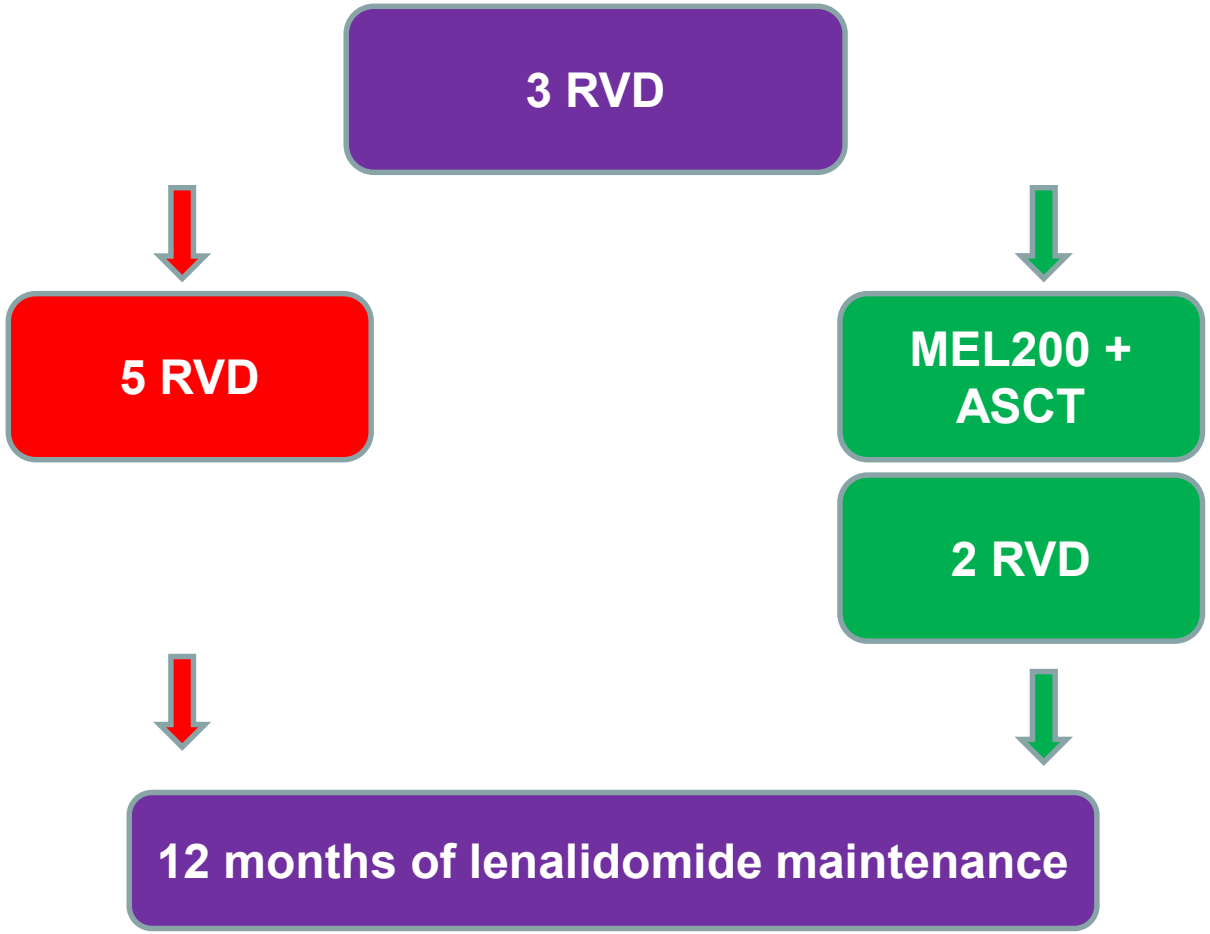
Cavo. ASH 2017. Abstr 401.

PFS by randomization (VMP *vs* ASCT)

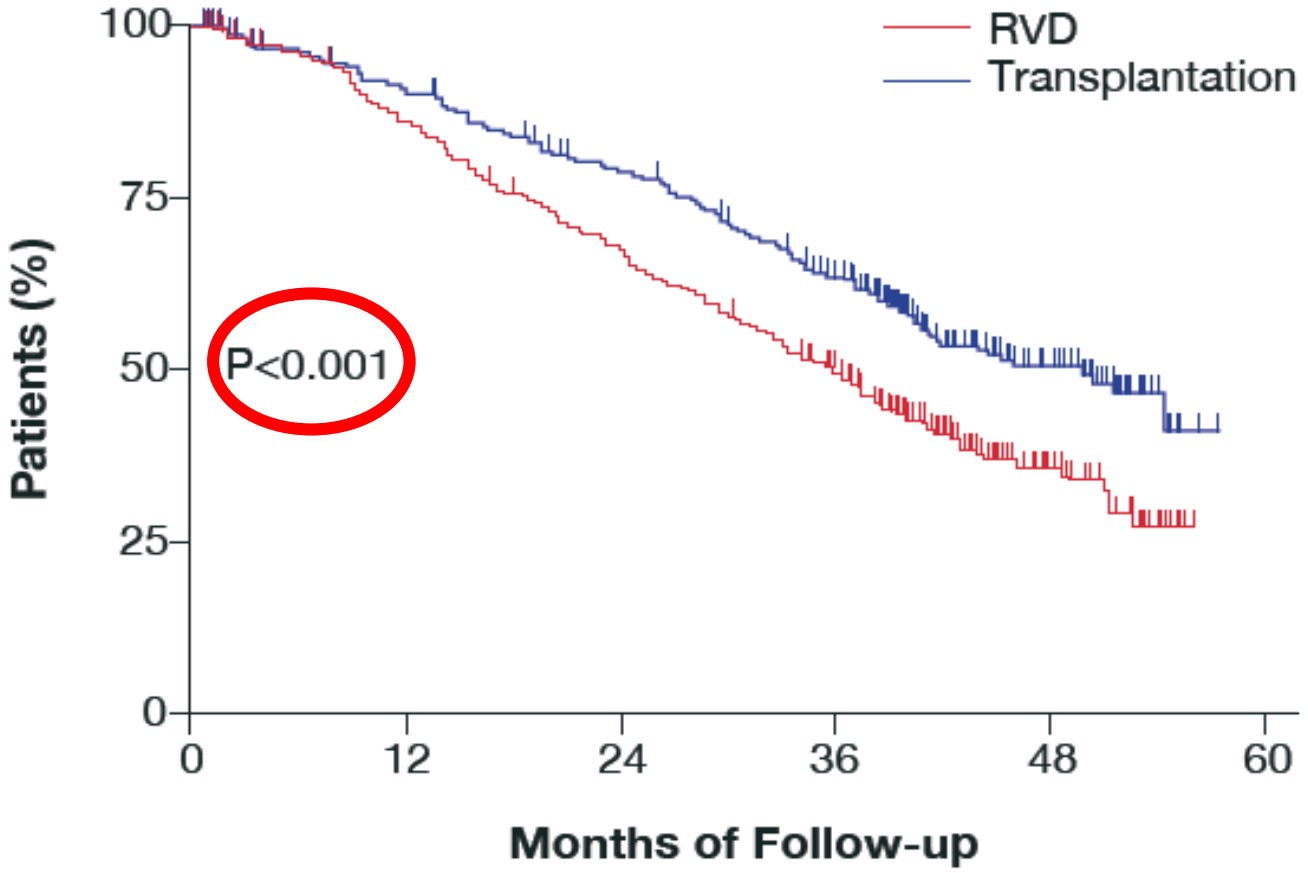


Cavo. ASH 2017. Abstr 401.

IFM DFCI 2009 Trial
700 patients < 66y,
Newly diagnosed symptomatic MM



Attal. NEJM. 2017;376:1311.



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

PROGRESSION-FREE SURVIVAL

Attal. NEJM. 2017;376:1311.

IFM 2009: PFS, Prognostic Factors

	Multivariate Analysis aHR	*P* Value
Treatment arm (B/A)	0.80	0.02
ISS II vs I III vs I	1.33 1.45	0.02 0.01
FISH (high risk/standard)	2.22	< 0.001
CR	0.58	< 0.001
MRD (FCM)	0.39	< 0.001

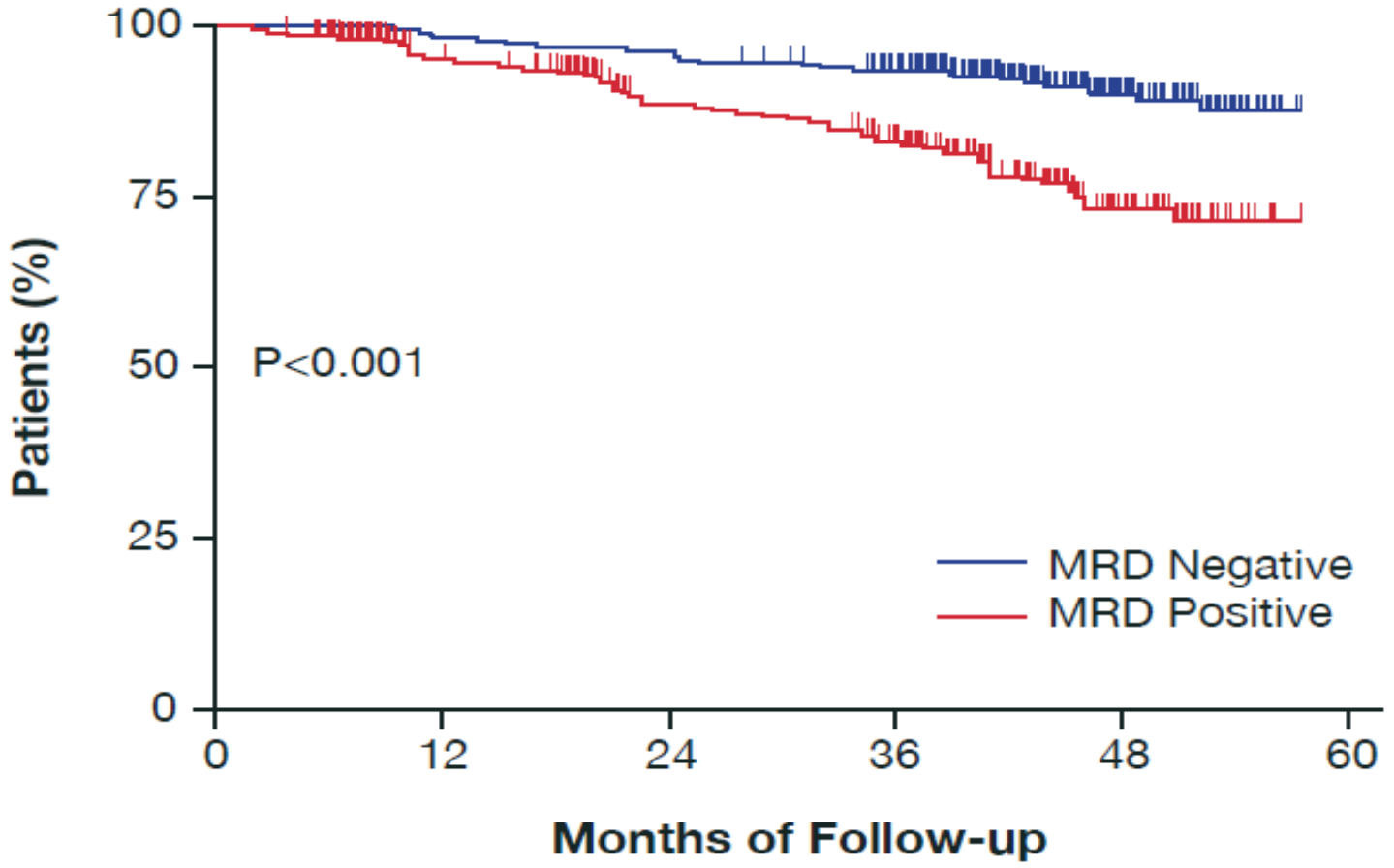
Attal. NEJM. 2017;376:1311.

IFM 2009: Best Response.

	RVD group N=350	Transplant group N=350	p-value
CR	48%	59%	
VGPR	29%	29%	0.004
PR	20%	11%	
<PR	3%	2%	
At least VGPR	77%	88%	<0.001
MRD neg by FCM , n (%)	171/265 (65%)	220/278 (80%)	<0.001

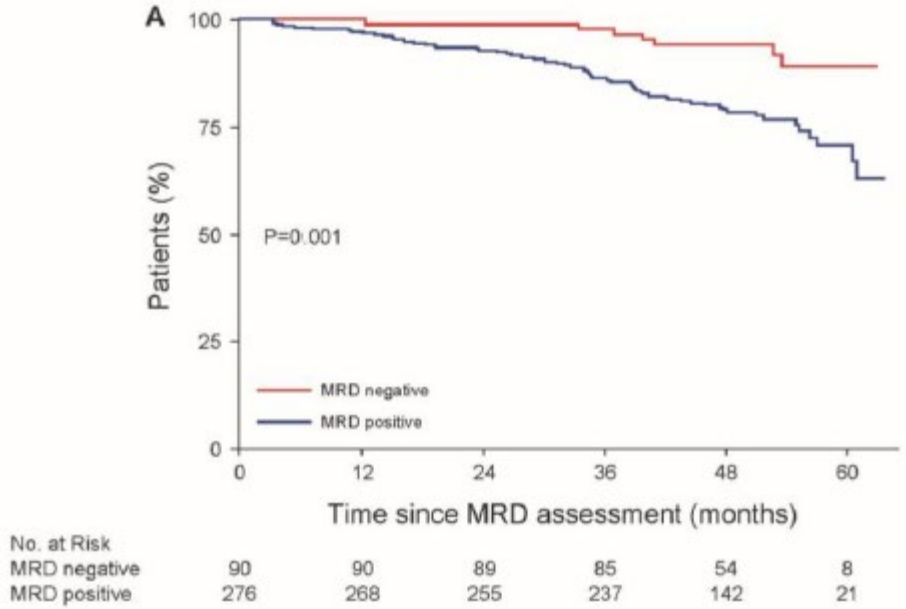
IFM/DFCI 2009: OS According to MRD (FCM) (9/2015)

S2B

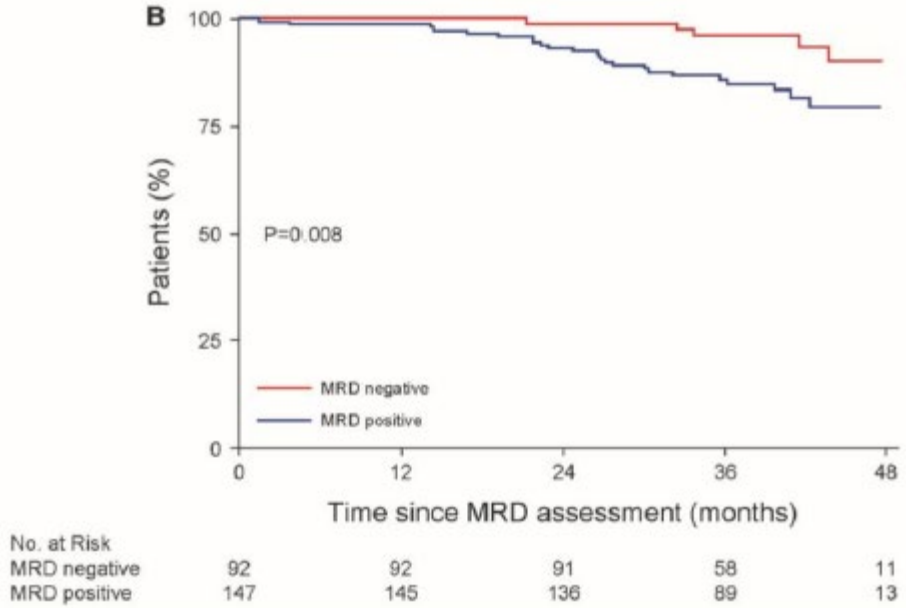


No. at Risk

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



Overall survival
at the start of maintenance
NGS, 10^{-6}



Overall survival
after 12 months of maintenance
NGS, 10^{-6}

Perrot. Blood. 2018;[Epub].

Role of Induction

- Fast control of the disease

- Achieve high response rates (MRD neg?)

- Minimal toxicity

- Allow adequate stem cell harvest

VTD and VCD are widely used in Europe

VRD in US, less toxic, as effective : future in Europe following approval of Len ?

→ easily up to 6 cycles

blood
2012 120: 1589-1596
Prepublished online July 12, 2012;
doi:10.1182/blood-2012-02-408922

Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study

Laura Rosiñol, Albert Oriol, Ana Isabel Teruel, Dolores Hernández, Javier López-Jiménez, Javier de la Rubia, Miquel Granell, Joan Besalduch, Luis Palomera, Yolanda González, Mª Asunción Etxebeste, Joaquín Díaz-Mediavilla, Miguel T. Hernández, Felipe de Arriba, Norma C. Gutiérrez, Mª Luisa Martín-Ramos, Mª Teresa Cibeira, Mª Victoria Mateos, Joaquín Martínez, Adrián Alegre, Juan José Lahuerta, Jesús San Miguel and Joan Bladé

Table 2. Response rate to induction therapy according to treatment arm

6 cycles of VTD

	QT + V, n = 129	TD, n = 127	VTD, n = 130
CR, %	21*	12*	35*
VGPR, %	15	15	25
PR, %	39	33	25
SD, %	12	12	6
PD, %	12†	23	7‡
Early deaths, %	1	1	2

60%

*VTD vs QT + V, *P* = .01; VTD vs TD, *P* = .0001. †QT + V vs TD, *P* = .02. ‡VTD vs TD, *P* = .0004.

Median number of CD34+ cells : 3.8×10^6/kg

Rosiñol. Blood. 2012;120:1589.

Pethema/GEM Phase 3 Study: VRD-GEM Induction 6 Cycles (N=455 Patients)

Response, n (%)	Overall 455 (100%)
Complete response (CR + sCR)	**176 (39)**
VGPR	**133 (29)**
MRD negative, NGF, 3 x 10^{-6}, n = 320	**35%**
PR	77 (17)
Stable disease	30 (6)
Progressive disease	30 (6)
Non-evaluable	12 (3)
Early death	7 (1.5)
Overall response rate	**386 (85)**

68%

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

Rosiñol. ASH 2017. Abstr 130.

Abstract 3245; Poster
Dec. 2, 6:00 PM
Rosinol et al

Toxicity

	VTD, n = 130 Grade 3-4 %	VRD, n= 455 Grade 3-4 %
Neutropenia	10	11
Thrombocytopenia	8	6
Peripheral neuropathy		
Grade 2	46	13
Grade 3	12	1
Grade 4	2	0
Discontinuation during induction		
Toxicity	7	2
Disease progression	7	6
Death	2	1.5

Rosiñol. Blood. 2012;120:1589. Rosiñol. ASH 2017. Abstr 130.

Kinetics of Response According to MRD, NGF/Euroflow (n=320), 10^{-6}

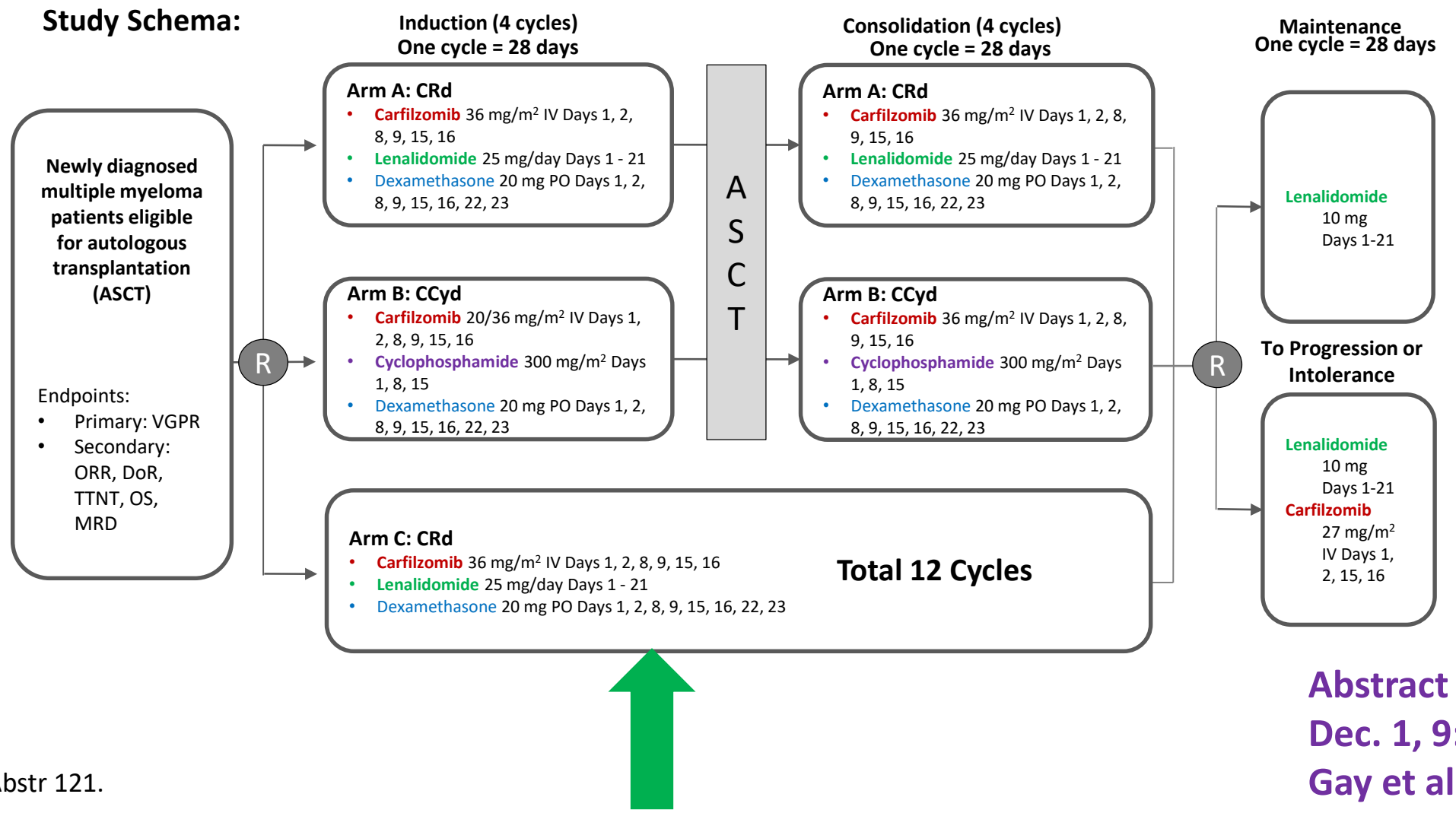
	Induction (VRDx6)	HDT/ASCT	Consolidation (VRDx2)
MRD negative	35%	54%	58%
MRD positive	65%	46%	42%

Paiva. ASH 2017. Abstr 905.

How to improve ?

Future …

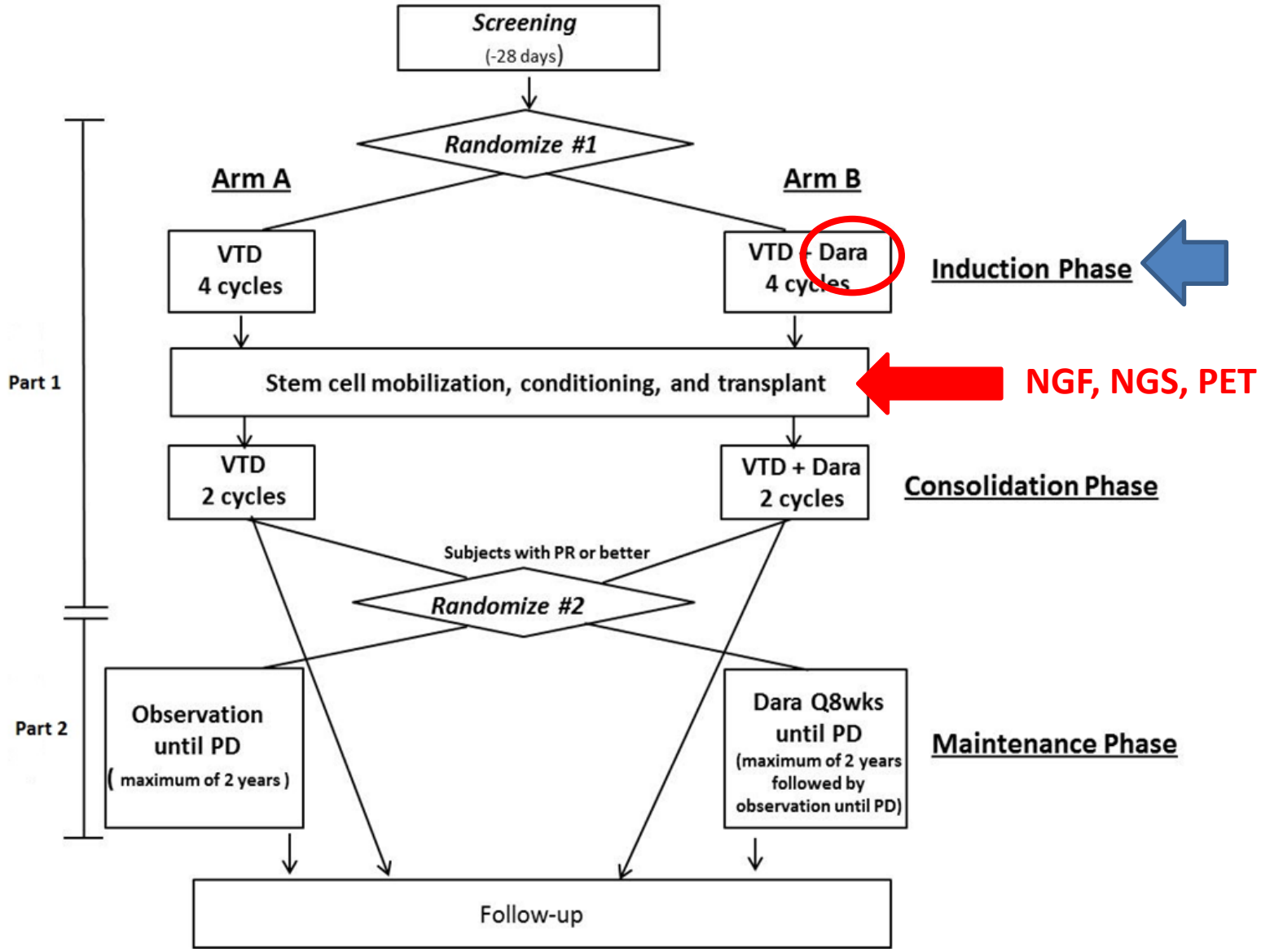
Forte: KRd Study Design (Gimema)



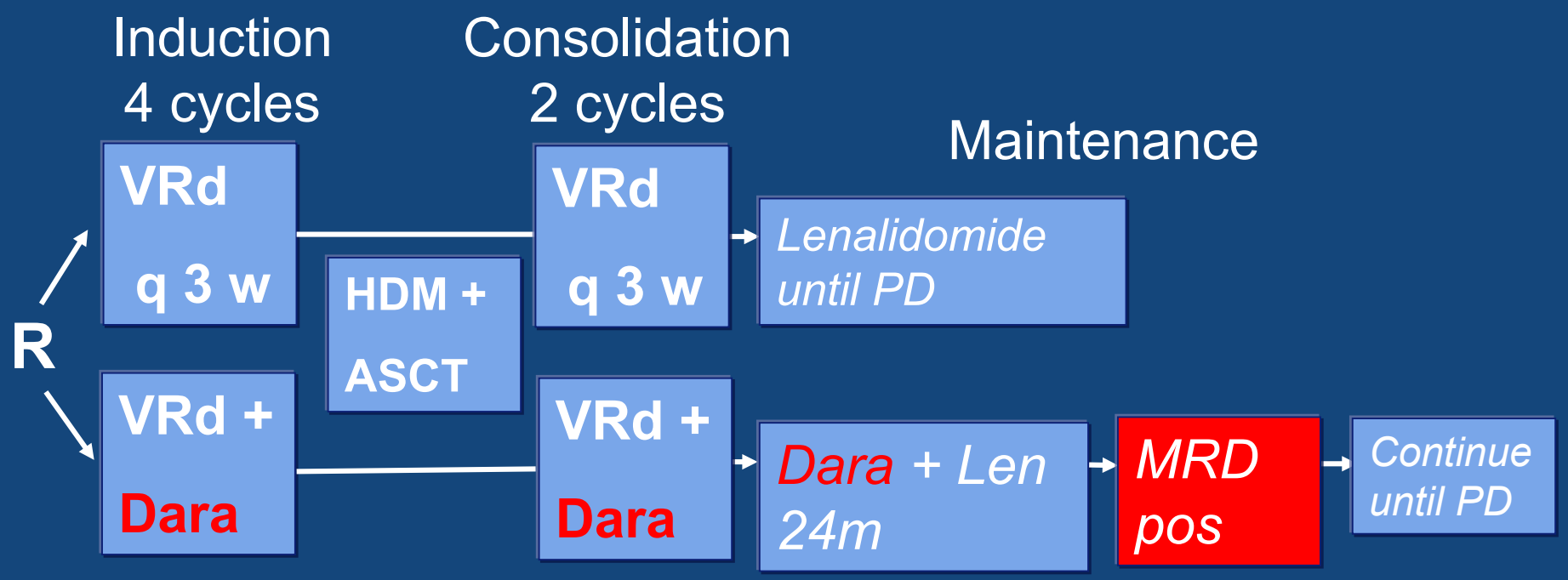
Gay. ASH 2018. Abstr 121.

Abstract 121; Oral
Dec. 1, 9:30 AM
Gay et al

CASSIOPEIA – 1080 Patients – ASCO 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

Perseus, PI, P.Sonneveld

Role of Consolidation

- Short duration after ASCT

- Increased the depth of response (MRD neg)

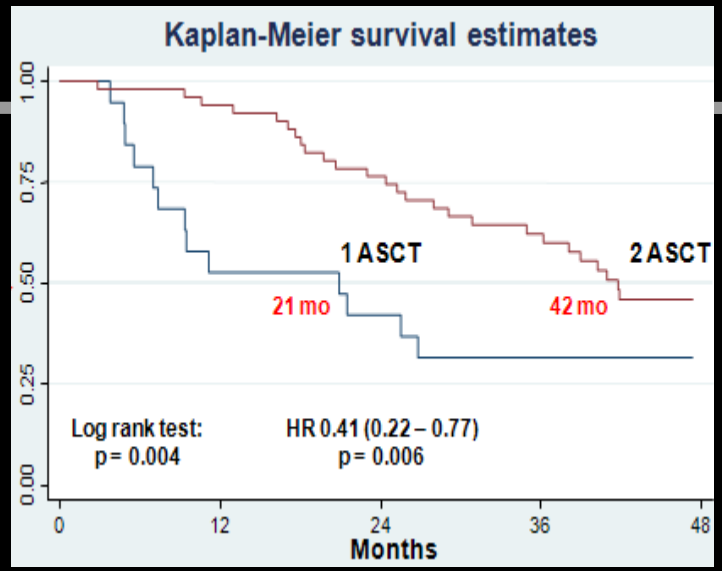
- Reduced toxicity allowing maintenance

Tools and Issues

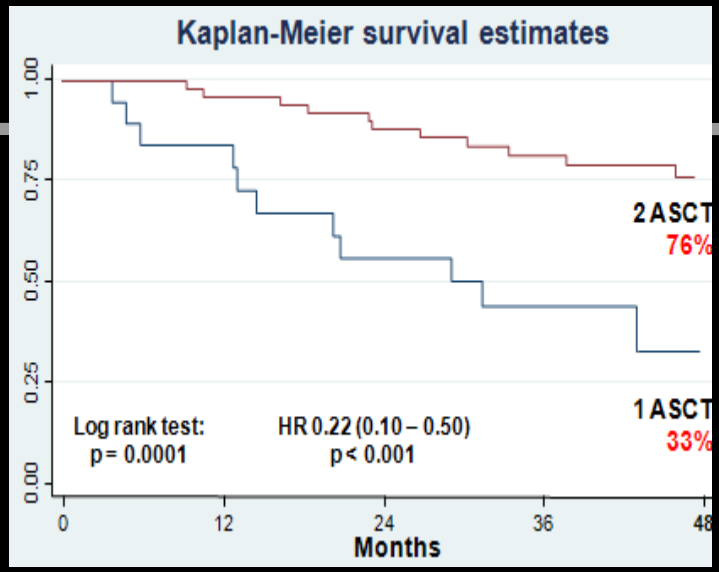
- Novel-agent based
- Second (tandem) ASCT

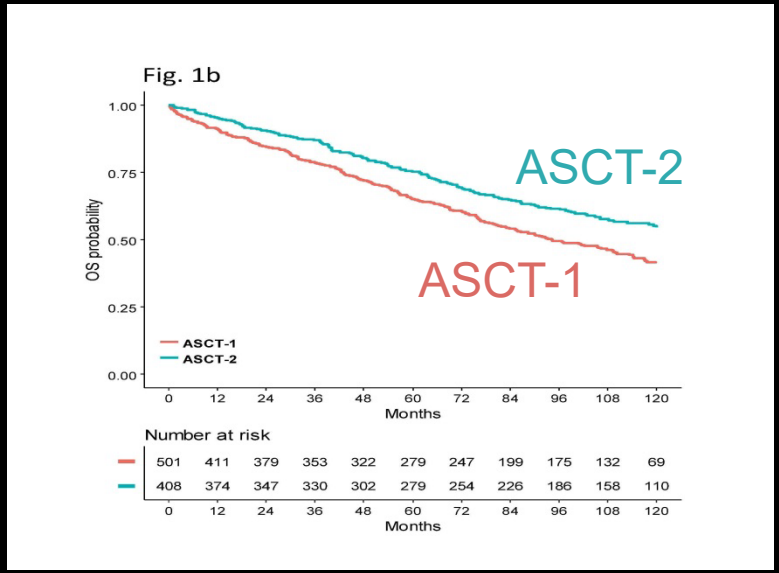
- Necessary?
- Best one?
- Optimal duration?

Double vs Single ASCT After Bortezomib-Based Induction



Cavo et al. ASH 2013
Abstract 767.

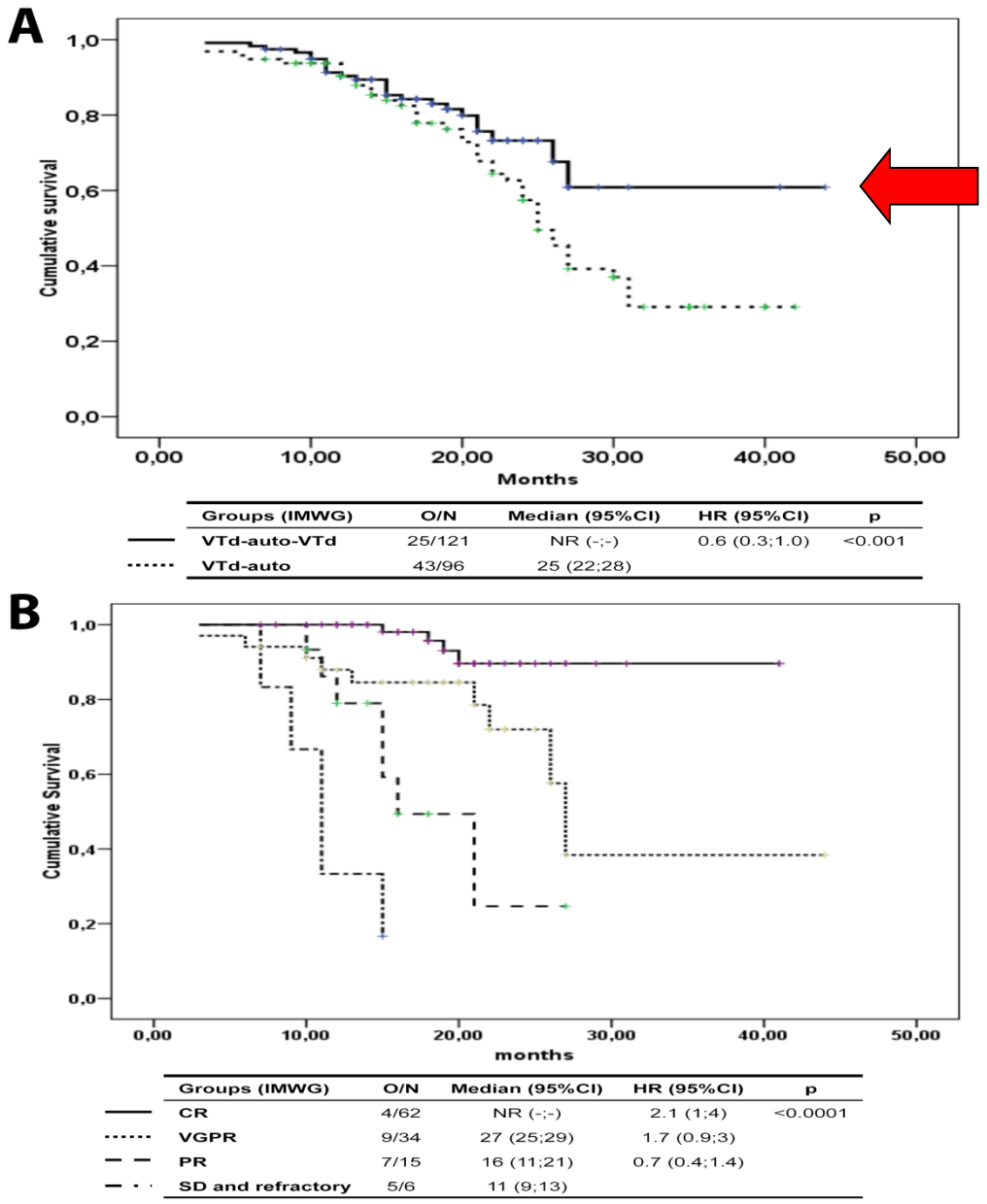




Cavo et al. ASH 2018
Abstract 124
Saturday, December 1, 2018: 9:30 AM

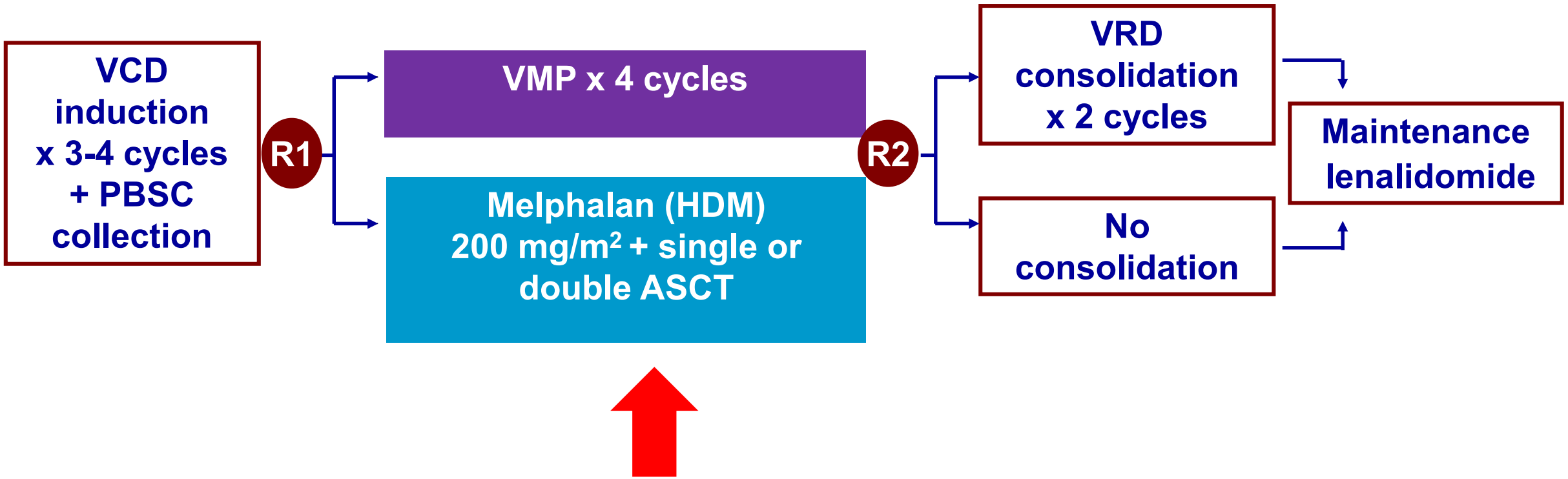
Retrospective trial
217 patients

VTD – auto
vs
VTD – auto - VTD



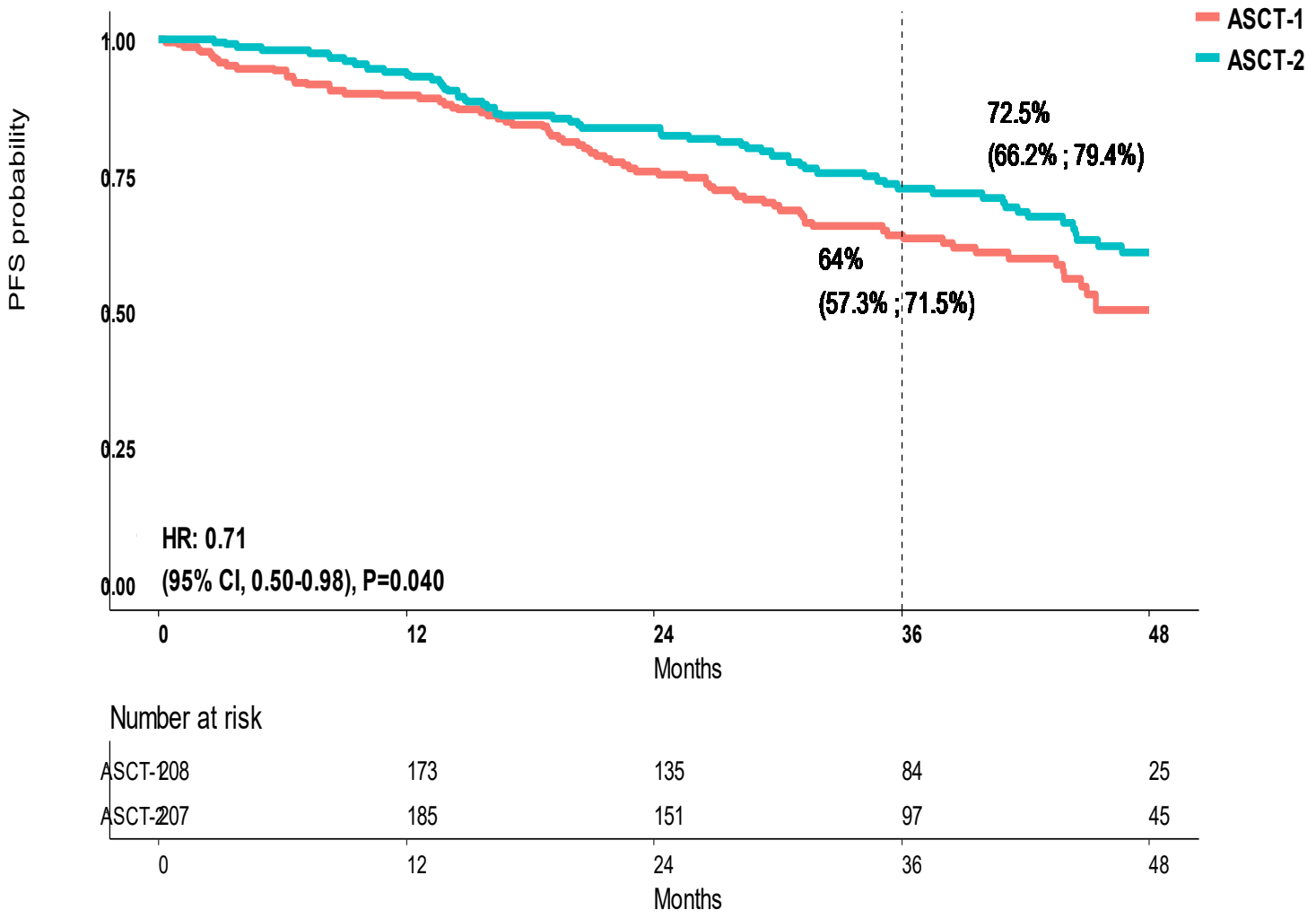
Leleu X, Moreau P. Leukemia 2013;27:2242.

EMN02/HO95 MM Trial: Study Design



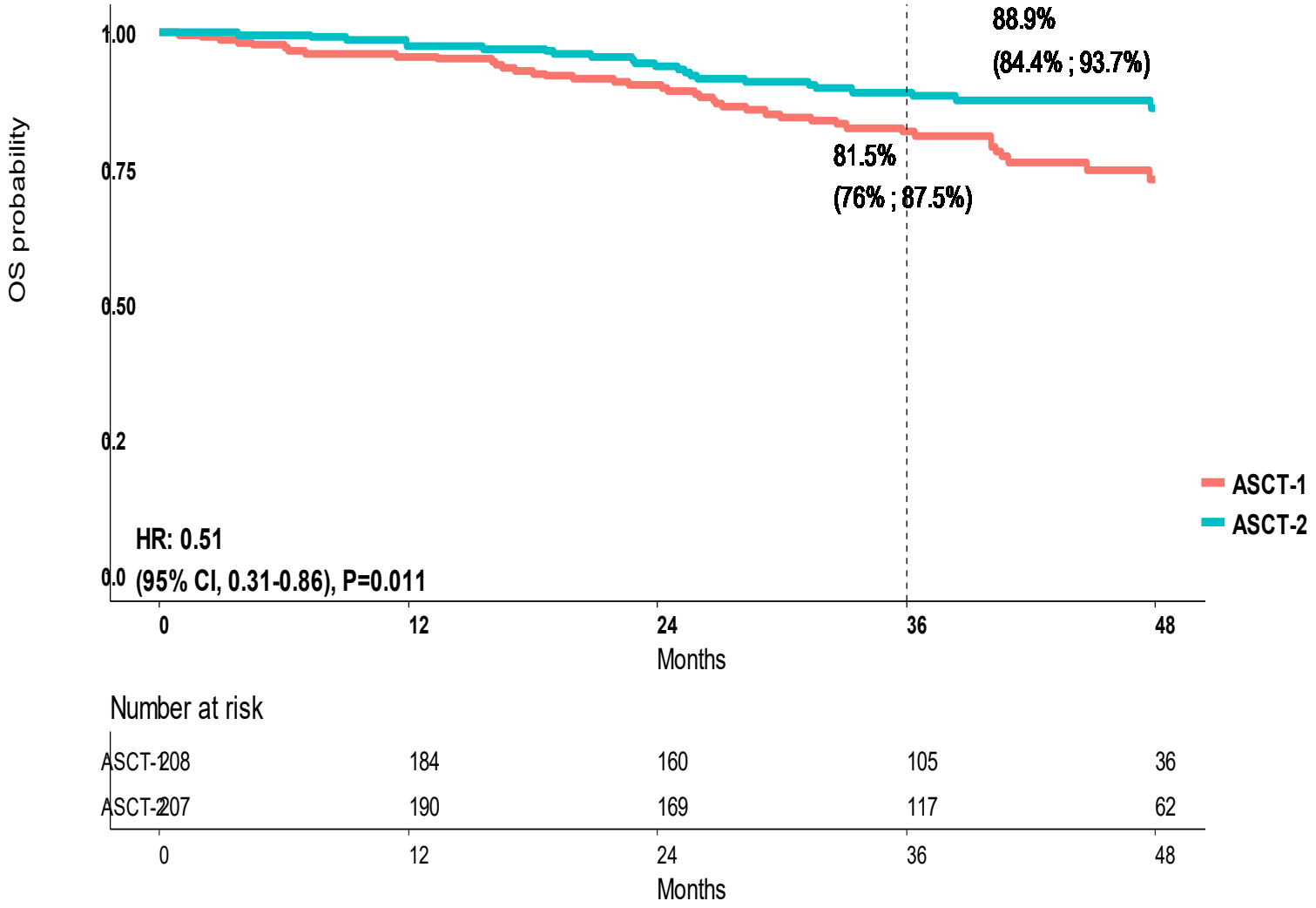
Cavo. ASH 2017. Abstr 401.

PFS by Randomization (ASCT-1 *vs* ASCT-2)



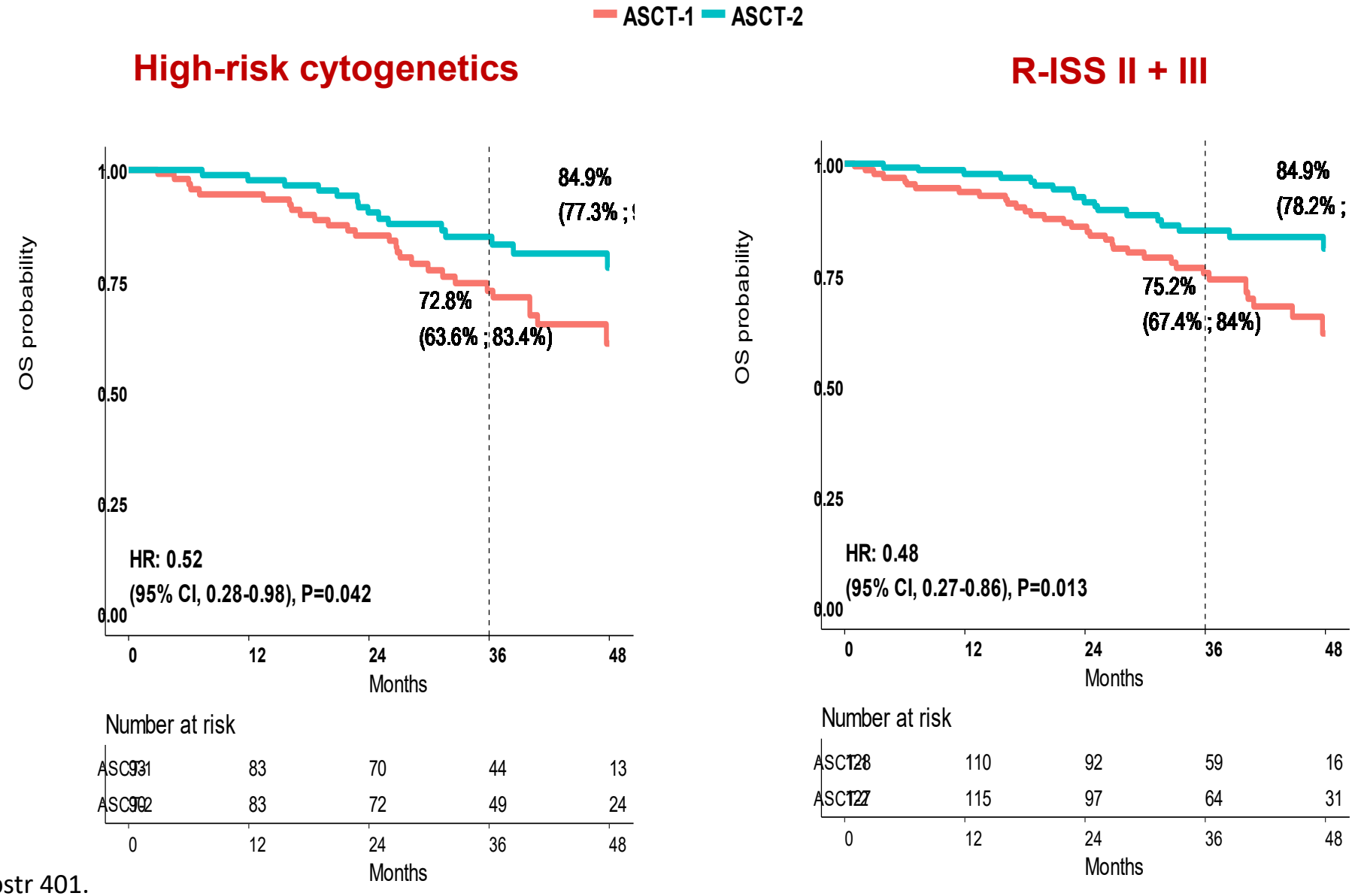
Cavo. ASH 2017. Abstr 401.

OS by Randomization (ASCT-1 *vs* ASCT-2)



Cavo. ASH 2017. Abstr 401.

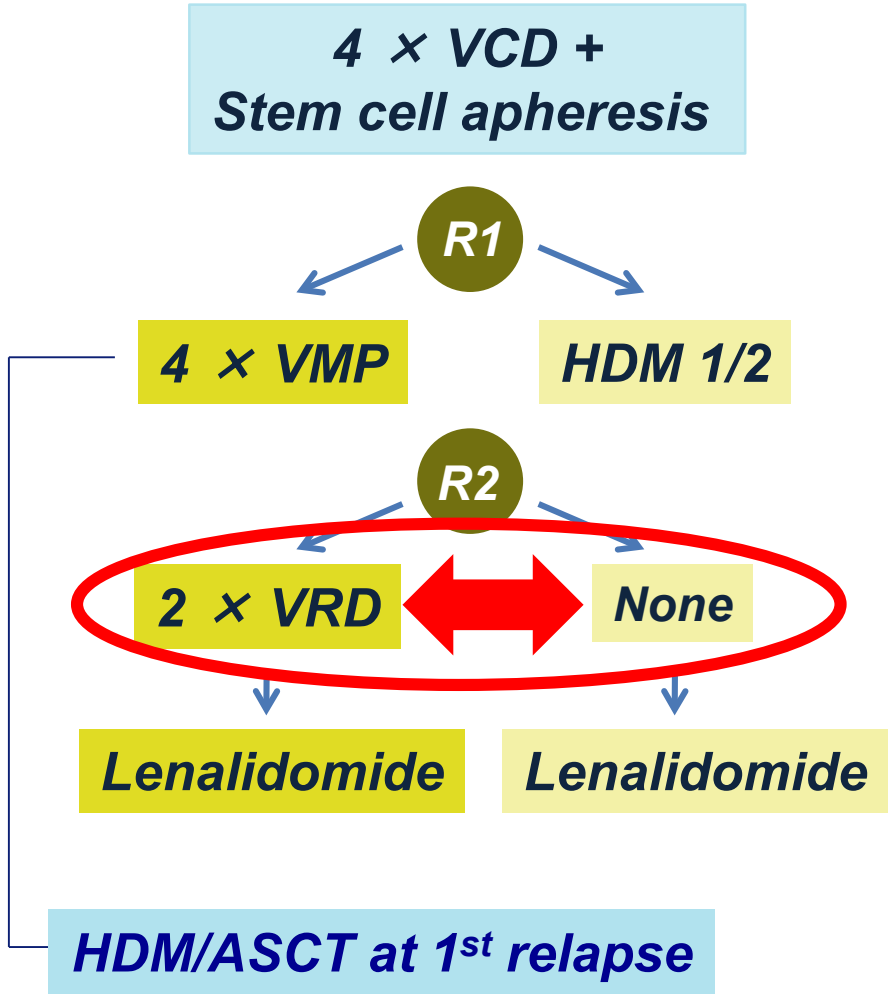
OS by Randomization in High-Risk Subgroups



Cavo. ASH 2017. Abstr 401.

Sonneveld et al. ASH 2016. Abstr 242.

Design of EMN02 Trial



Registration
Induction

Early or late ASCT, once or twice

MRD

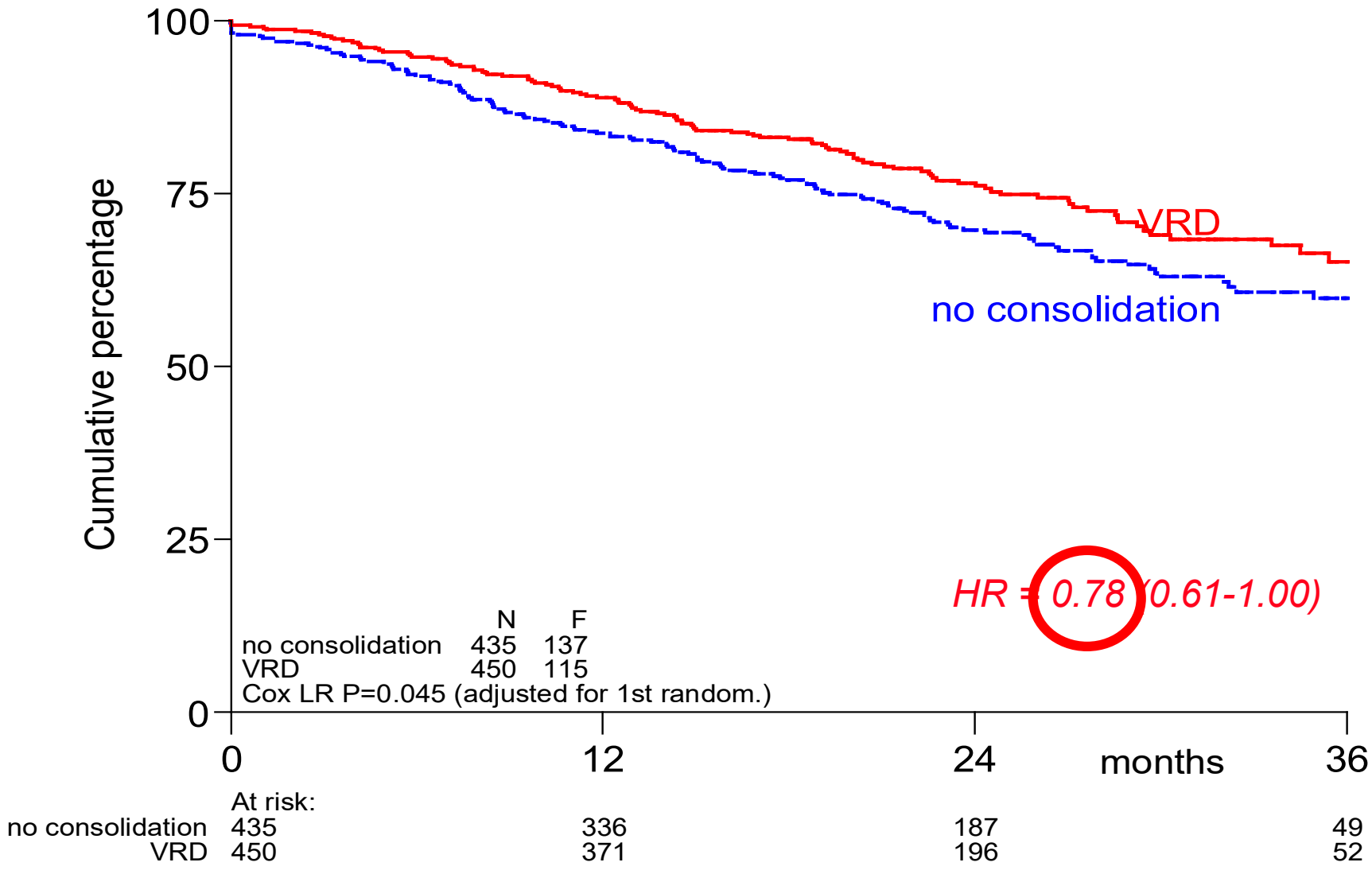
Consolidation

Maintenance until relapse

https://clinicaltrials.gov/ct2/show/NCT01208766 [Accessed March 2015]

Erasmus MC

Progression-Free Survival



EMN02 / HO95 MM

Sonneveld. ASH 2016. Abstr 242.

Kinetics of Response According to MRD, NGF/Euroflow (n=320), 10^{-6}

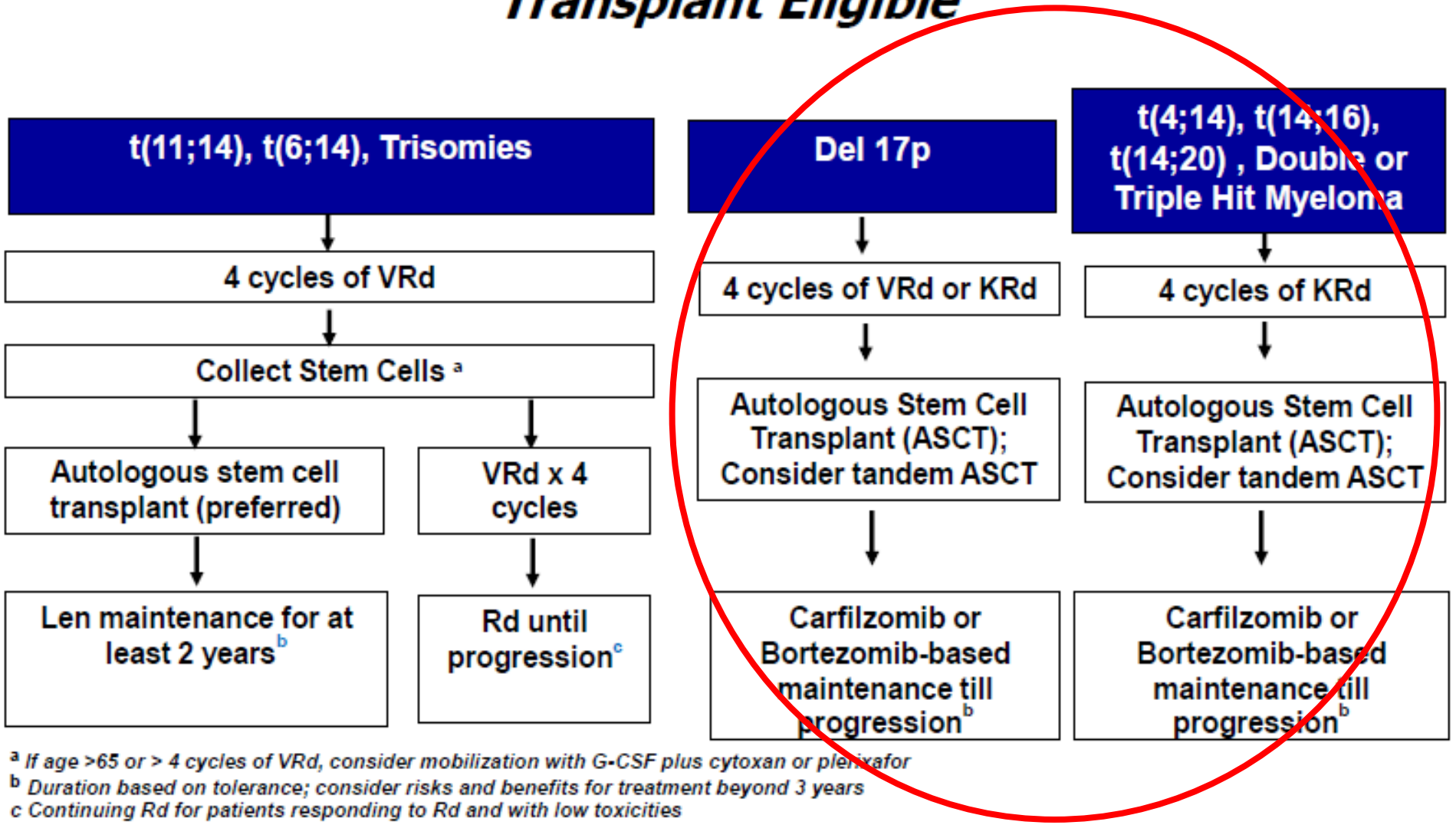
	Induction (VRDx6)	HDT/ASCT	Consolidation (VRDx2)
MRD negative	35%	54%	58%
MRD positive	65%	46%	42%

Paiva. ASH 2017. Abstr 905.

MAYO CLINIC

mSMART – Off-Study

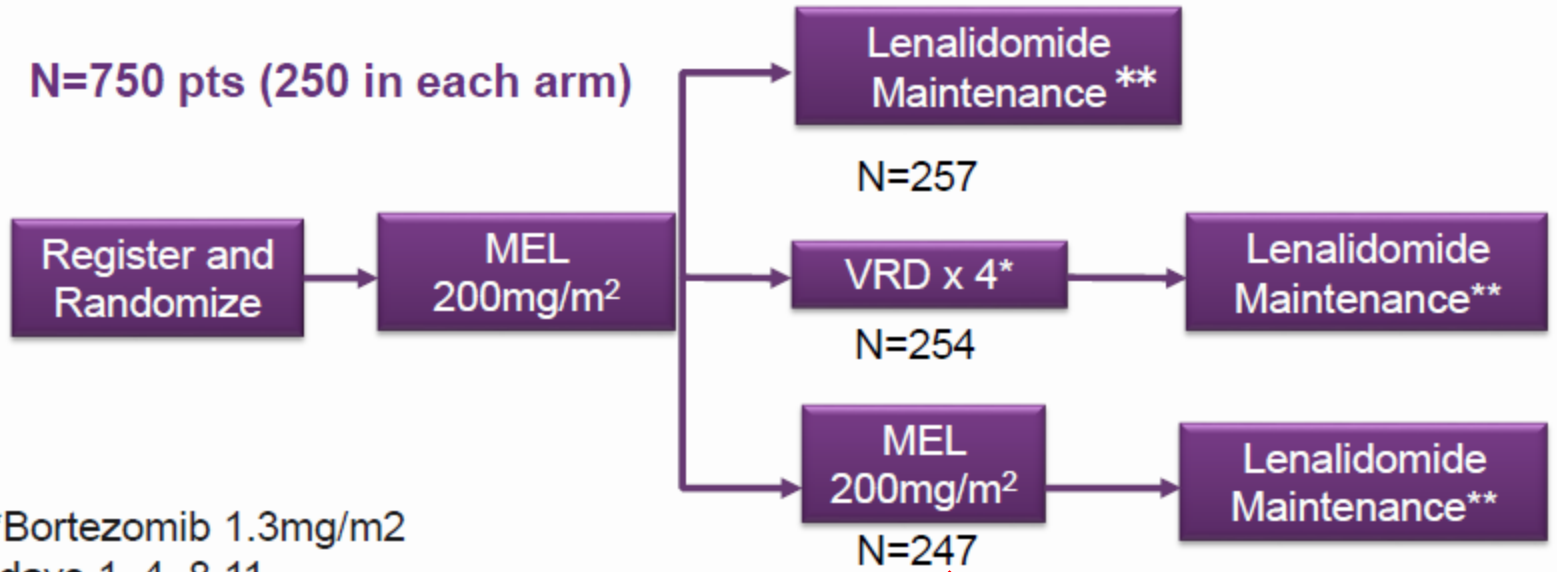
Transplant Eligible



a *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor*
b *Duration based on tolerance; consider risks and benefits for treatment beyond 3 years*
c *Continuing Rd for patients responding to Rd and with low toxicities*

Dispenzieri. 2007;82:323; Kumar. Mayo Clin Proc. 2009;84:1095; Mikhael. Mayo Clin Proc. 2013;88:360.

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. ASH 2016. Abstr LBA-1.

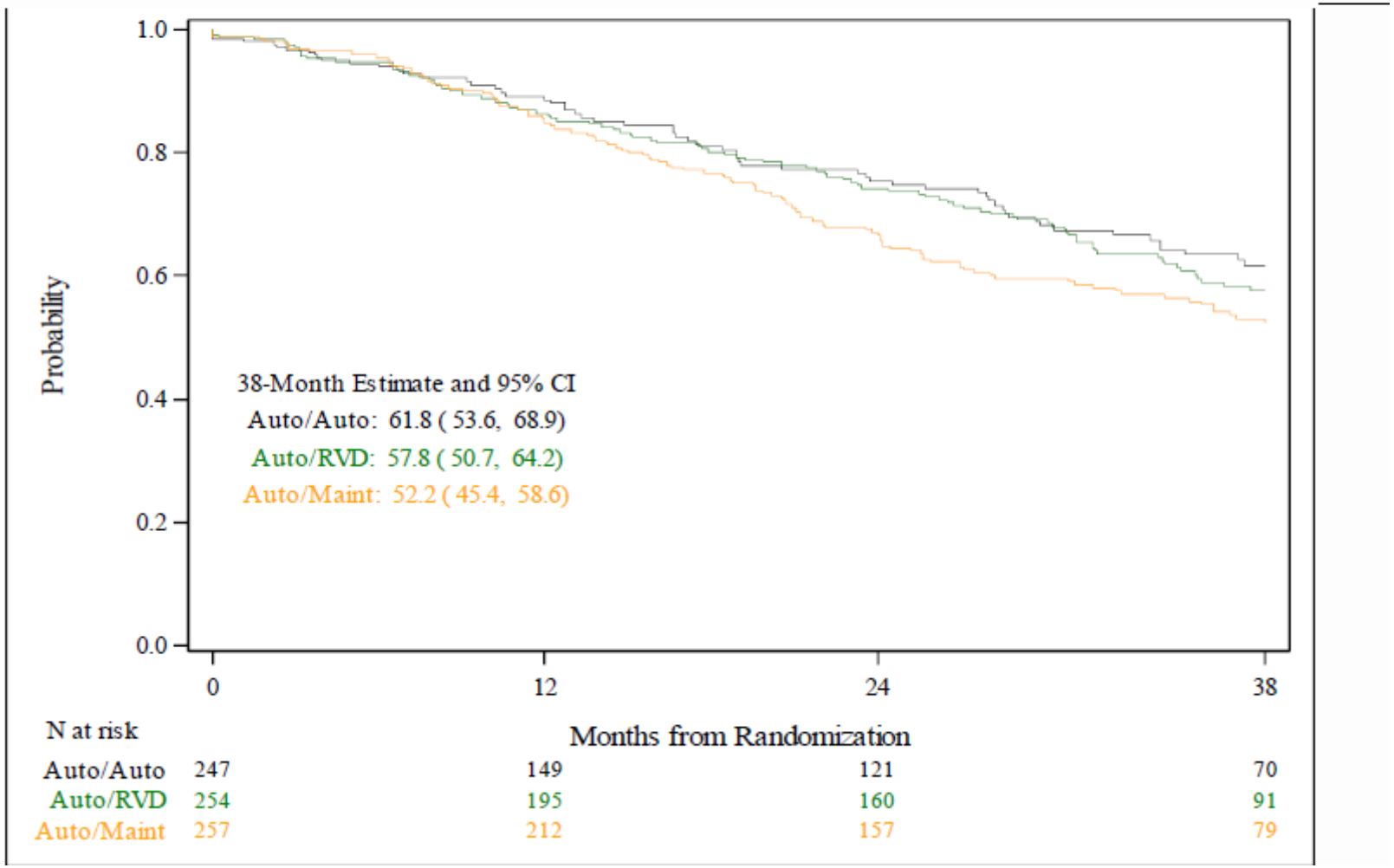
Compliance with each intervention

	Auto/Auto (N=247)		Auto/RVD (N=254)		Auto/Maint (N=257)	
	N	%	N	%	N	%
Received 2nd Intervention						
No	79	32.0	30	11.8	-	-
Yes	168	68.0	224	88.2	-	-
Started maintenance						
No	41	16.6	43	16.9	14	5.4
Yes	206	83.4	211	83.1	243	94.6

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Stadtmauer. ASH 2016. Abstr LBA-1.

Progression-Free Survival – as treated/per protocol Analysis



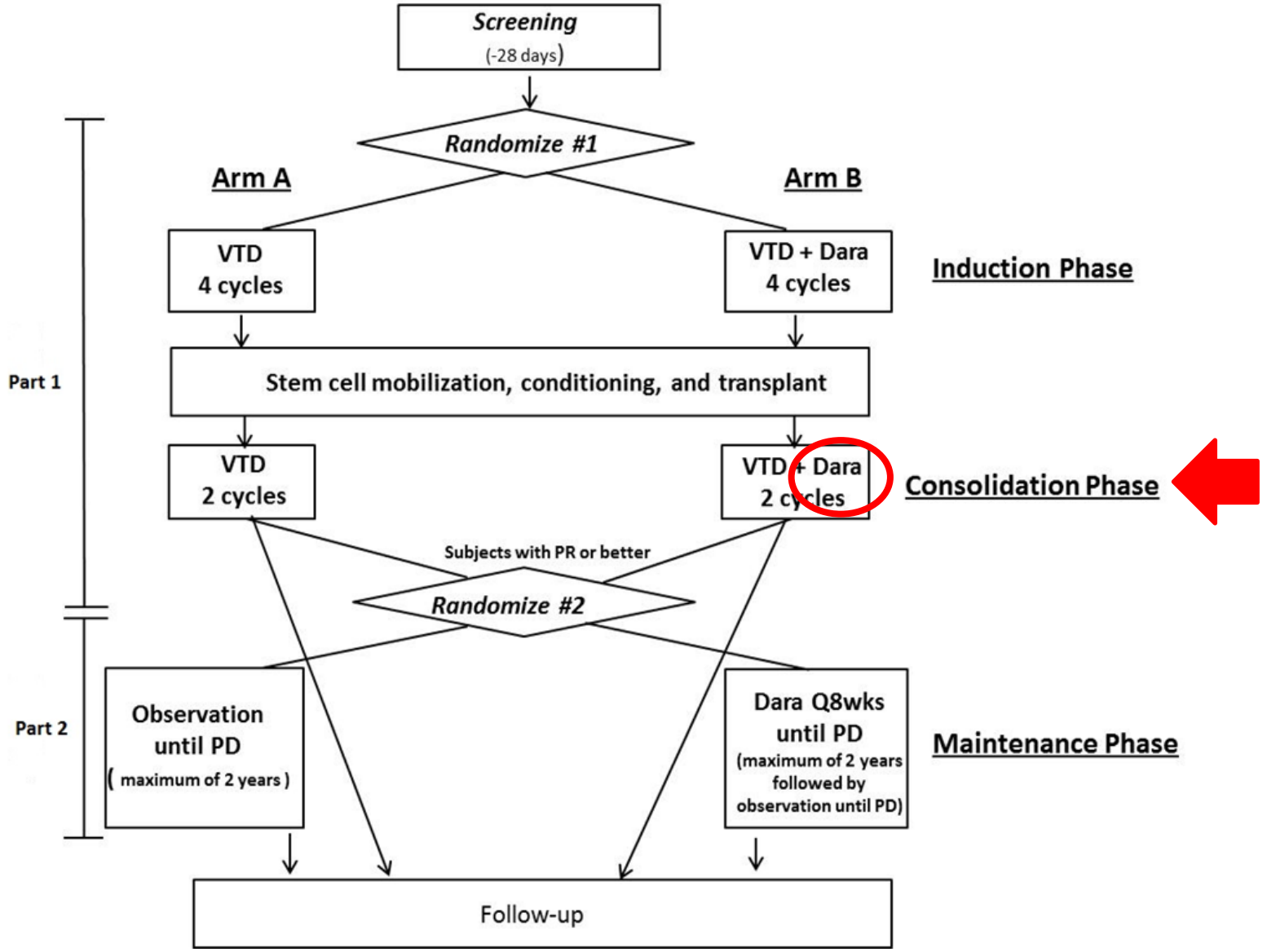
Stadtmauer. ASH 2016. Abstr LBA-1.

Consolidation

- Necessary?
- Best one?
- Optimal duration?

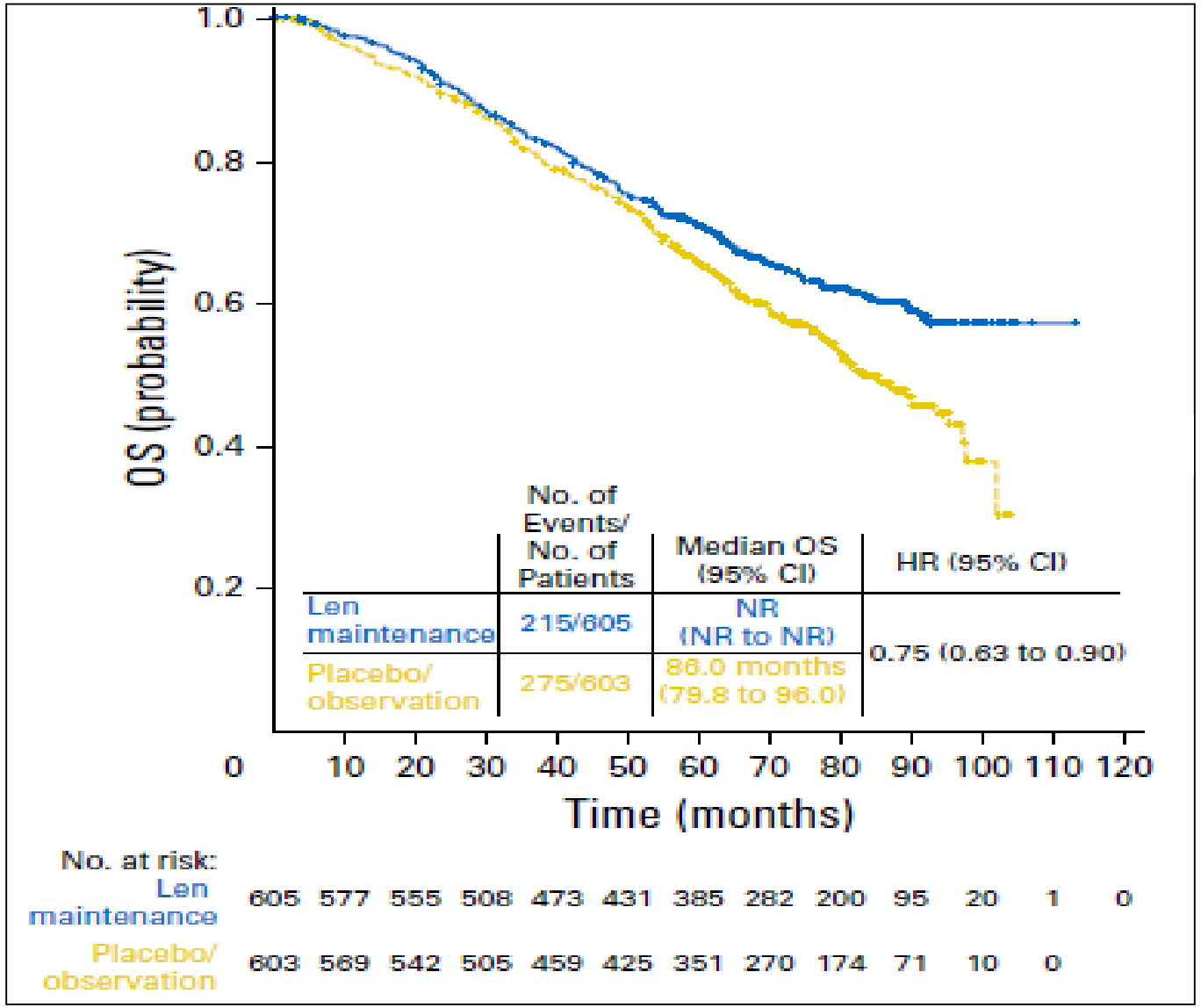
Tandem ASCT in high risk

CASSIOPEIA – 1080 Patients – ASCO 2019

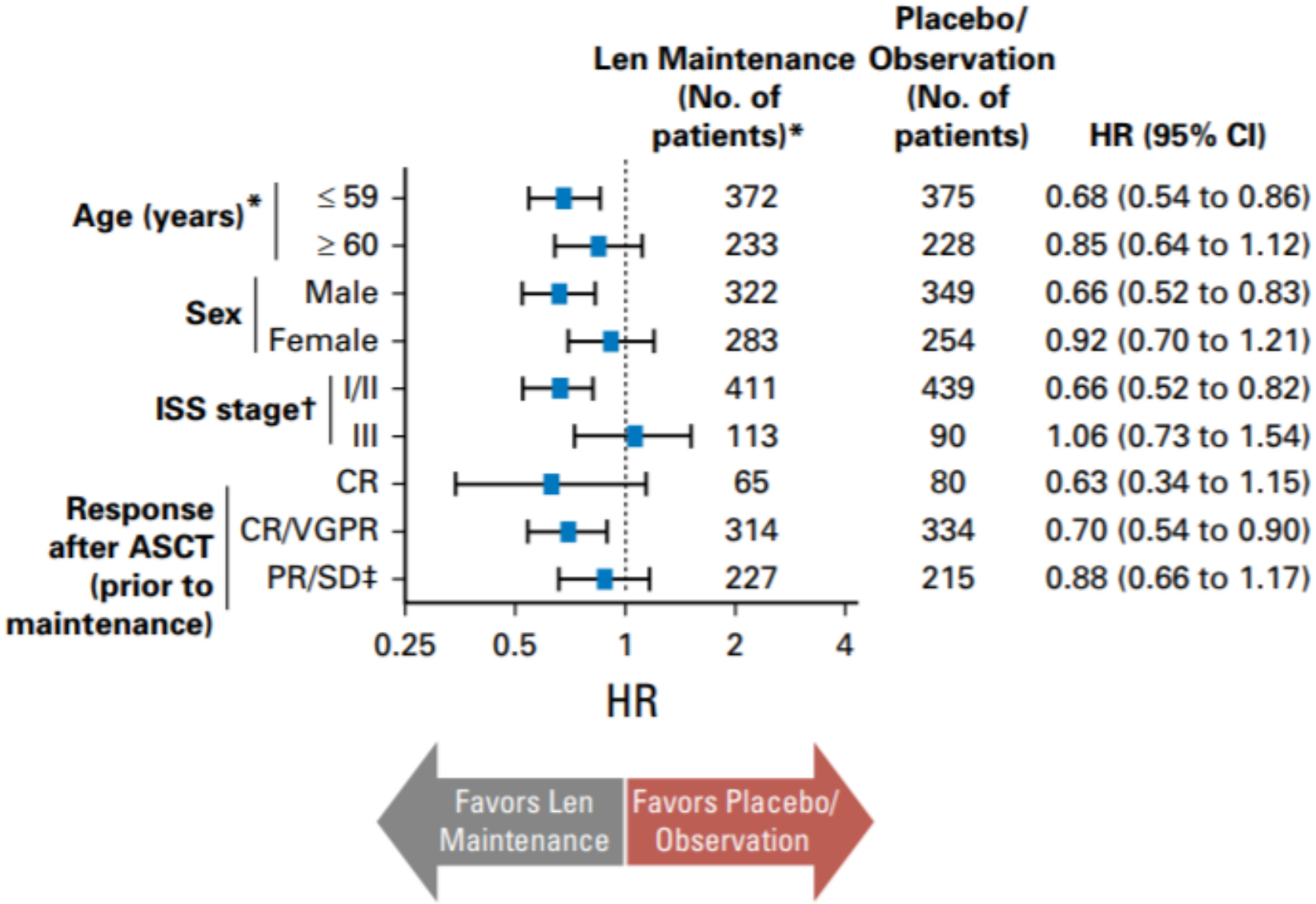


Sustained responses following ASCT are needed:

Impact of maintenance



McCarthy. J Clin Oncol. 2017;35:3279.

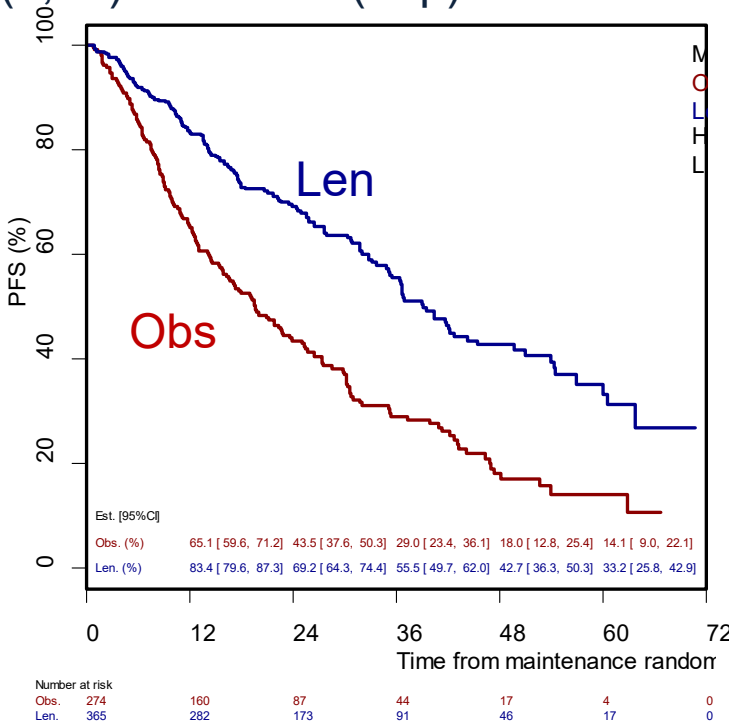


McCarthy. J Clin Oncol. 2017;35:3279.

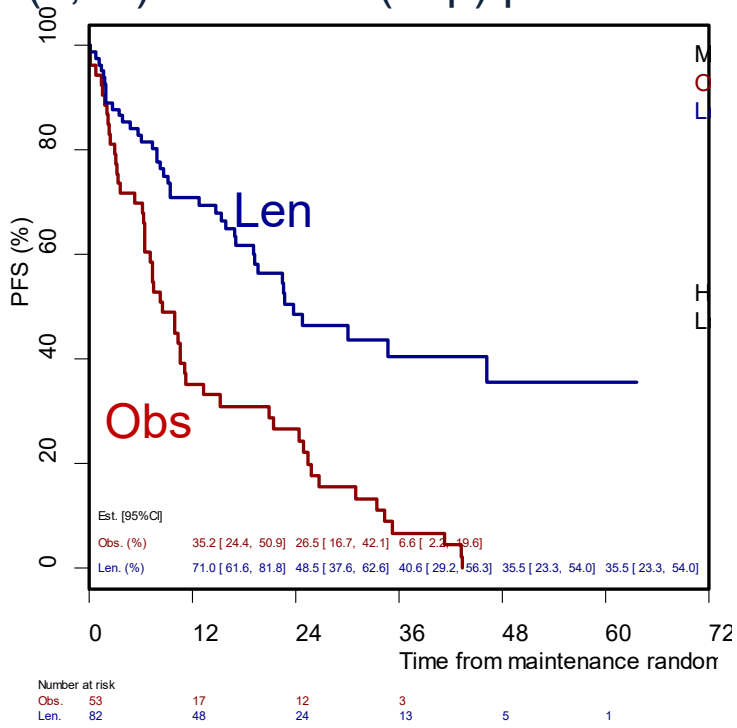
Cytogenetic risk groups

Lenalidomide improved PFS regardless of cytogenetic risk

t(4;14) and/or del(17p) absent: HR 0.50



t(4;14) and/or del(17p) present: HR 0.36

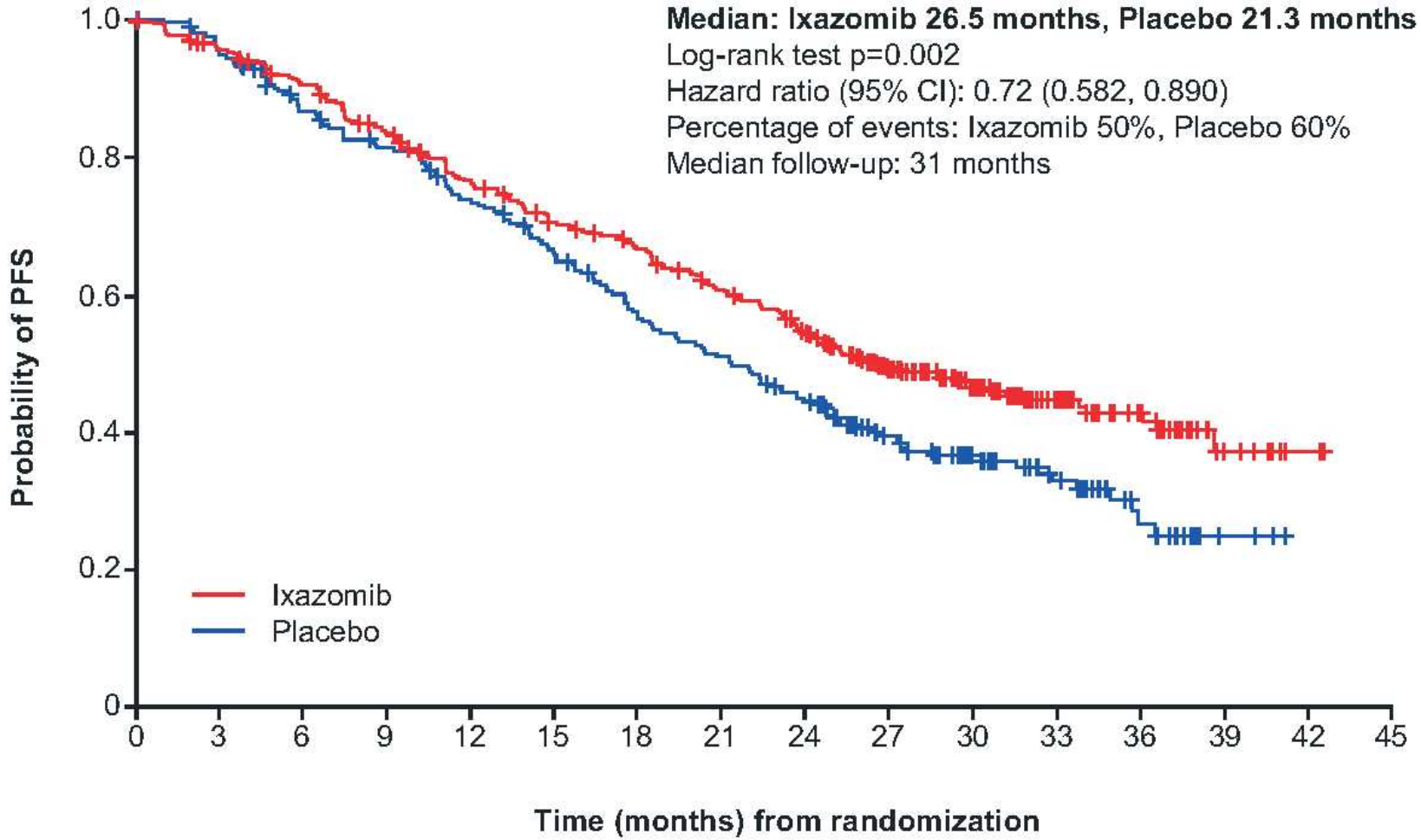


Jackson. ASH 2017. Abstr 436.

TOURMALINE MM-3

- Ixazomib vs placebo, phase 3
- In patients responding to ASCT
- Randomization 3:2
- 656 patients
- D1,8,15 in 28-day cycles
- Primary endpoint: PFS

Dimopoulos. ASH 2018. Abstr 301; NCT02181413



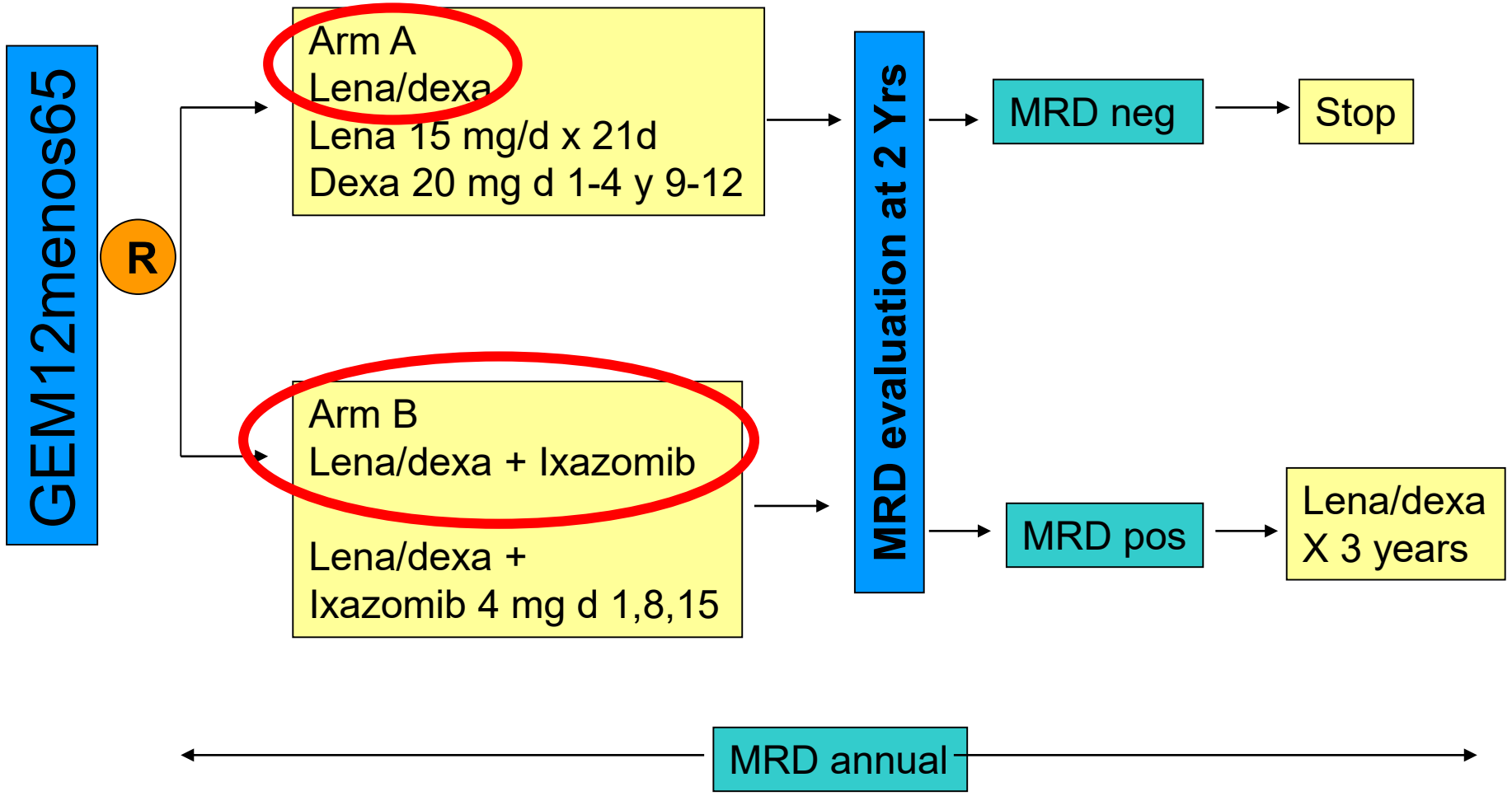
Number of patients at risk

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. ASH 2018; oral abstract 301. Sunday, December 2, 2018: 7:30 AM

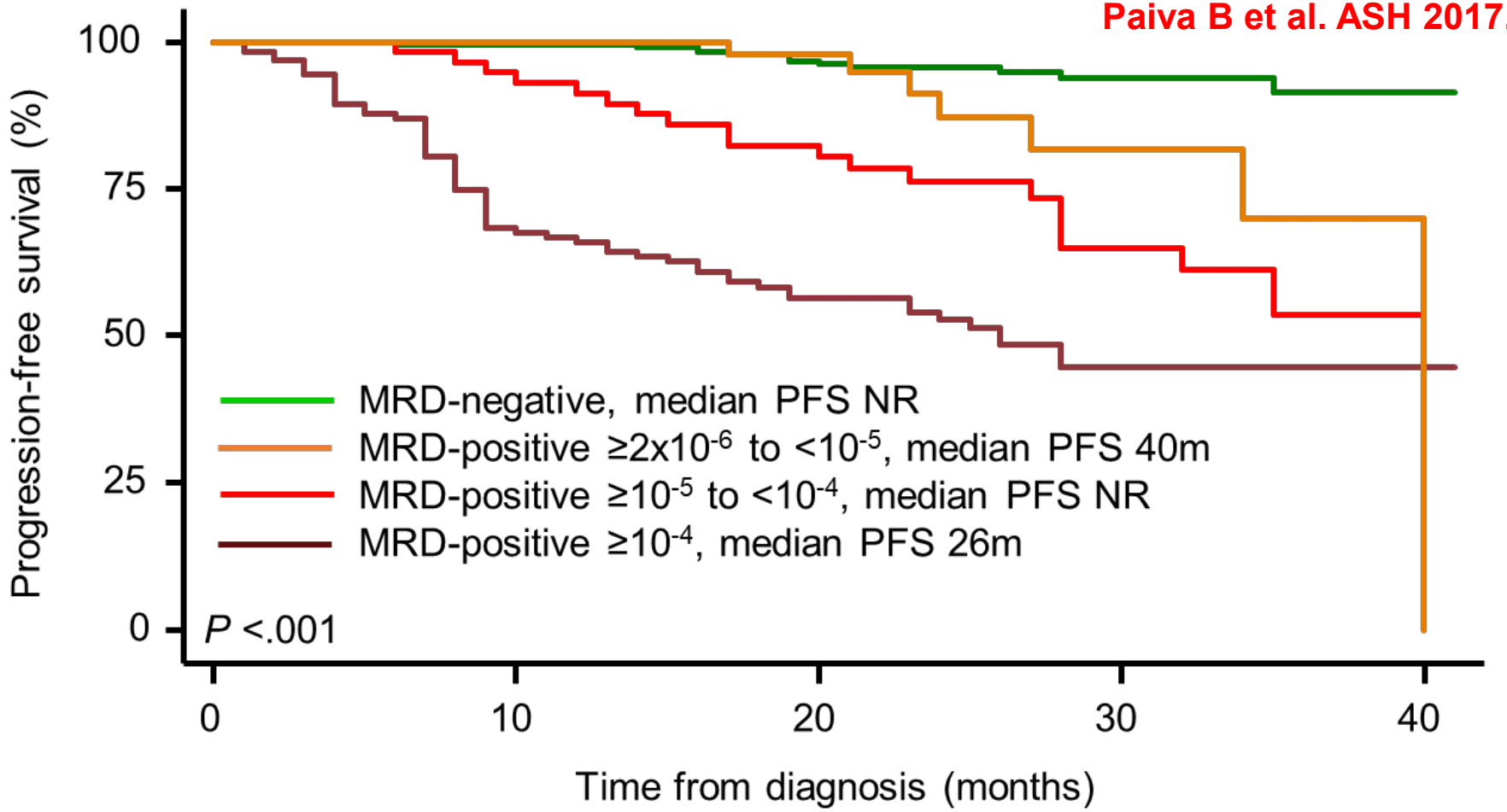
GEM14

Second trial as continuation of the previous one



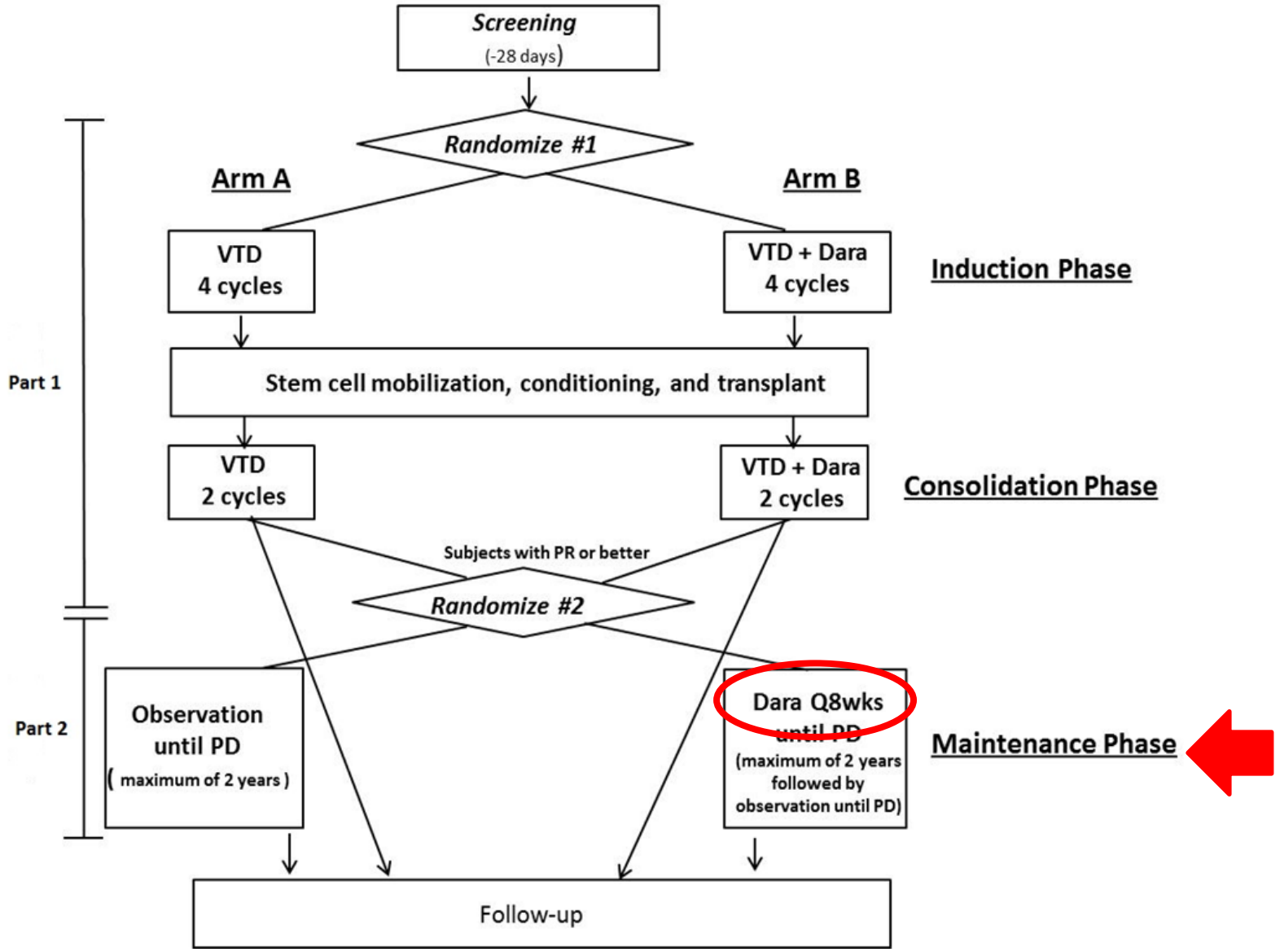
NCT02253316.

Paiva B et al. ASH 2017. Abstr 905.



Number at risk					
MRD-neg	225	224	177	86	4
MRD ≥2x10^{-6} to <10^{-5}	49	49	36	10	1
MRD ≥10^{-5} to <10^{-4}	57	54	43	20	1
MRD ≥10^{-4}	127	84	57	20	2

CASSIOPEIA – 1080 Patients – ASCO 2019



Conclusions: European Perspectives

- Frontline ASCT: standard of care

- VTD / VRD: best induction regimens prior to ASCT

- Optimal consolidation has to be defined (tandem in high risk)

- Consider the global strategy: induction/ ASCT / consolidation / maintenance

INTERNATIONAL MYELOMA FOUNDATION

Go Online for More Educational Programs on Myeloma!

On-demand Webcast of this symposium, including expert faculty commentary (IMF link below)

Downloadable slides from this symposium (IMF link below)

Interactive Decision Support Tool for myeloma, with personalized expert recommendations for your patients with myeloma

Online programs on caring for your patients with myeloma

myeloma.org/videos/new-strategies-multiple-myeloma-care-next-steps-future

clinicaloptions.com/MyelomaTool

clinicaloptions.com/oncology/topics/Multiple-Myeloma

CLINICAL CARE OPTIONS® ONCOLOGY