Disclosures for Palumbo Antonio, MD

Research Support/P.I.	No relevant conflicts of interest to declare
Employee	No relevant conflicts of interest to declare
Consultant	Amgen, Bristol-Myers Squibb, Celgene, Janssen, Millenium, Onyx
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	Amgen, Bristol-Myers Squibb, Celgene, Janssen, Millenium, Onyx
Scientific Advisory Board	No relevant conflicts of interest to declare

Presentation includes discussion of the off-label use of a drug or drugs

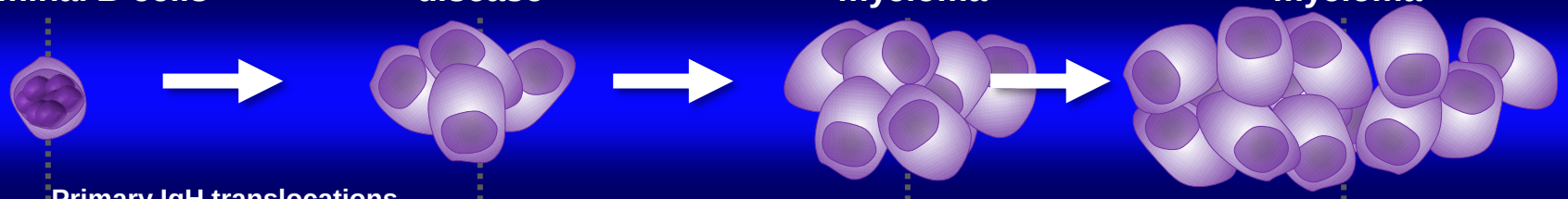
Status of the art of treatment

Antonio Palumbo, MD
University of Torino
Torino, Italy

Biological events

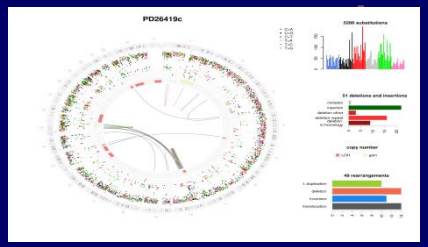
Clinical Phase

Normal Pregerminal B cells → Precursor disease → Multiple myeloma → Extramedullary myeloma

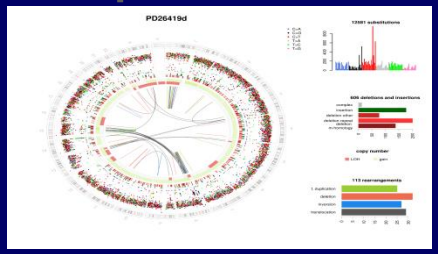


- Primary IgH translocations
- Hyperdiploidy
- Cyclin D gene dysregulation
- Deletion of chromosome 13
- *NRAS* mutation
- *KRAS* and *FGFR3* mutations
- *MYC* up-regulation
- *MYC* rearrangement
- p18, p53 and Rb gene inactivation

NDMM: 5286 substitutions



RRMM: 12581 substitutions



Korde N, et al. Blood. 2011;117: 5573-81.

Early or late intervention

Increasing genetic and epigenetic abnormalities[1]

Normal pre-germinal B cells → **Precursor disease** → **Multiple myeloma** → **Extramedullary myeloma**

Sensitive disease

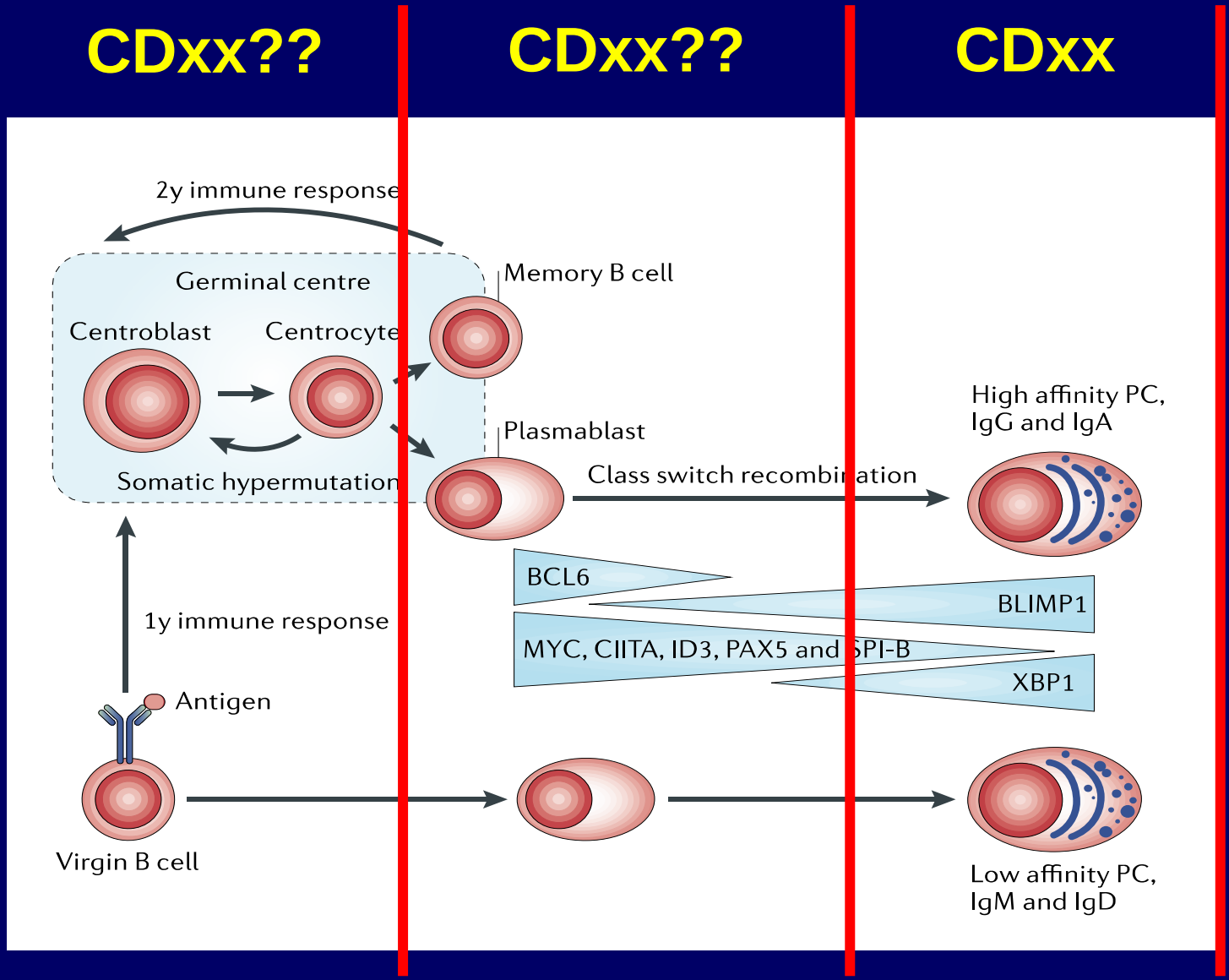
- 5-year PFS: 67%
- 5-year OS: 73%

Resistant disease

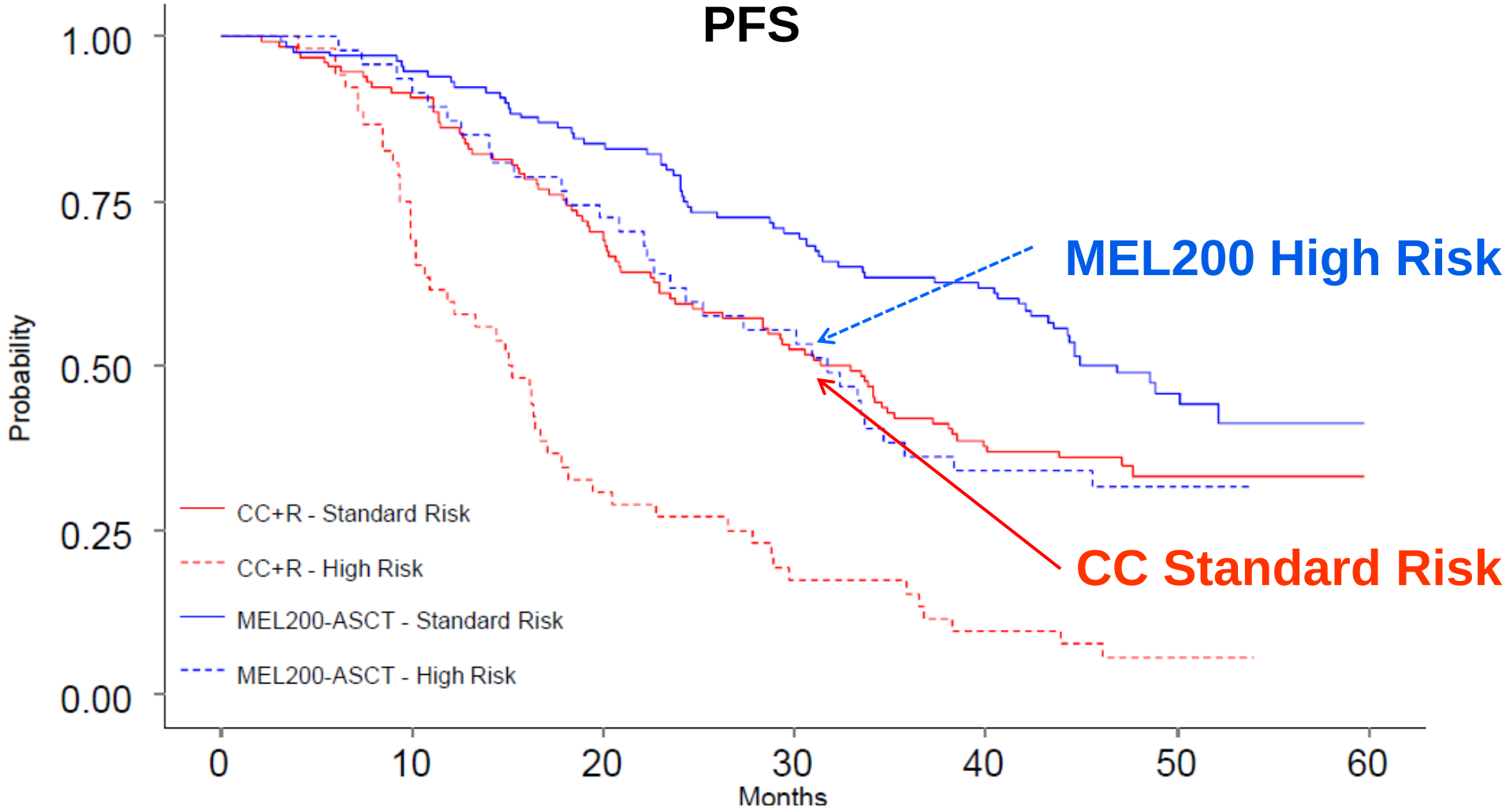
- Median PFS: 5 mo
- Median OS: 9 mo

- **1st Tx 100; - 2nd Tx 60; - 3rd Tx 35; - 4th Tx 20; - 5th Tx 10**

Progenitors Cells - Antigen Escape

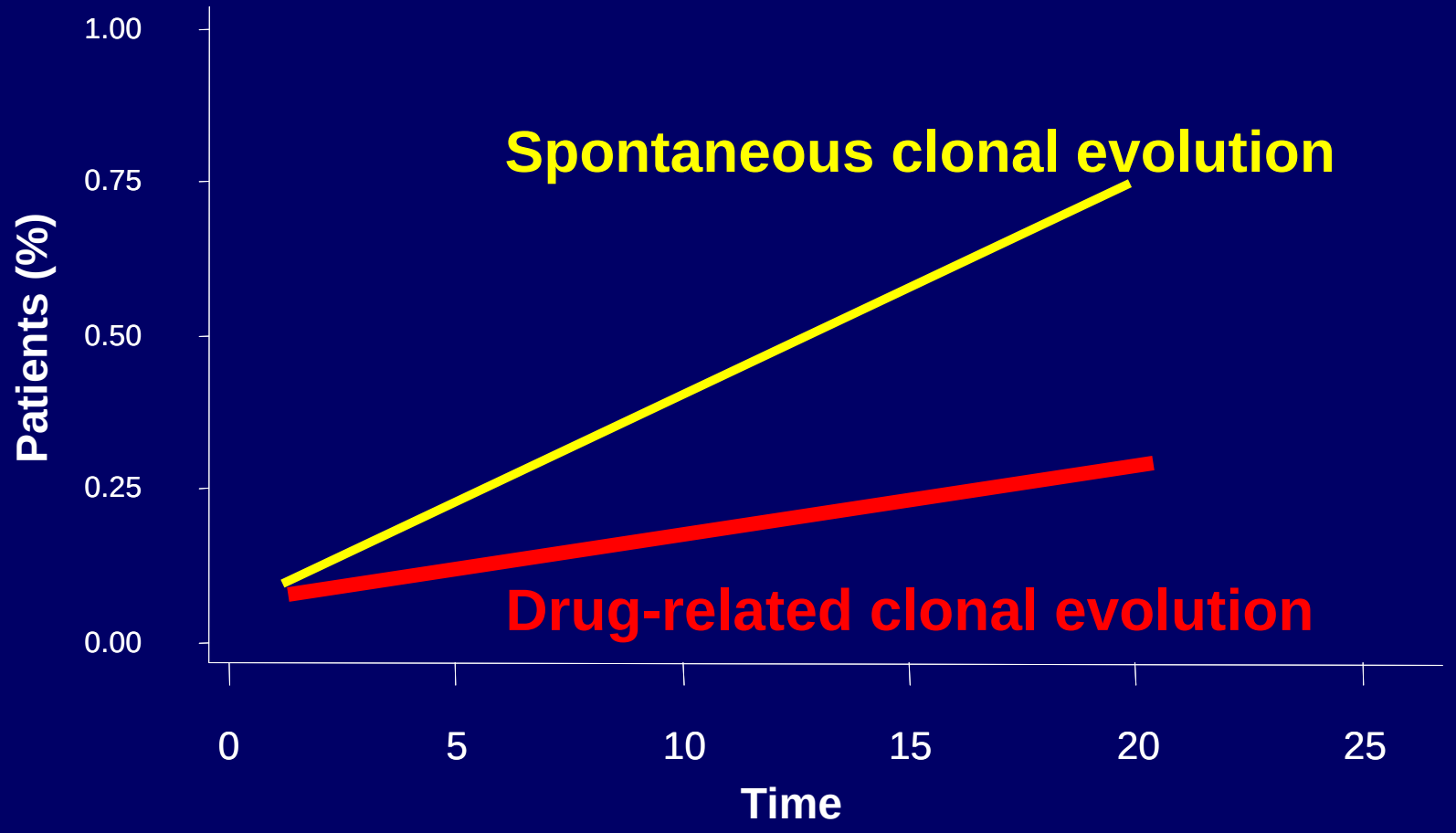


Early vs Late ASCT
791 patients



Gay F. et al manuscript in preparation

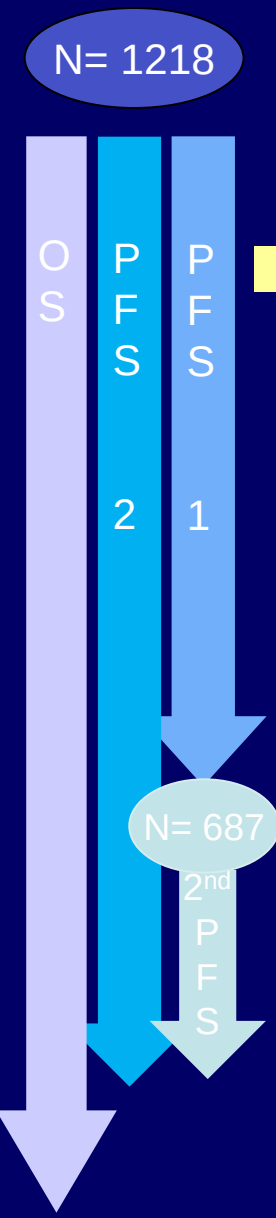
Clonal evolution

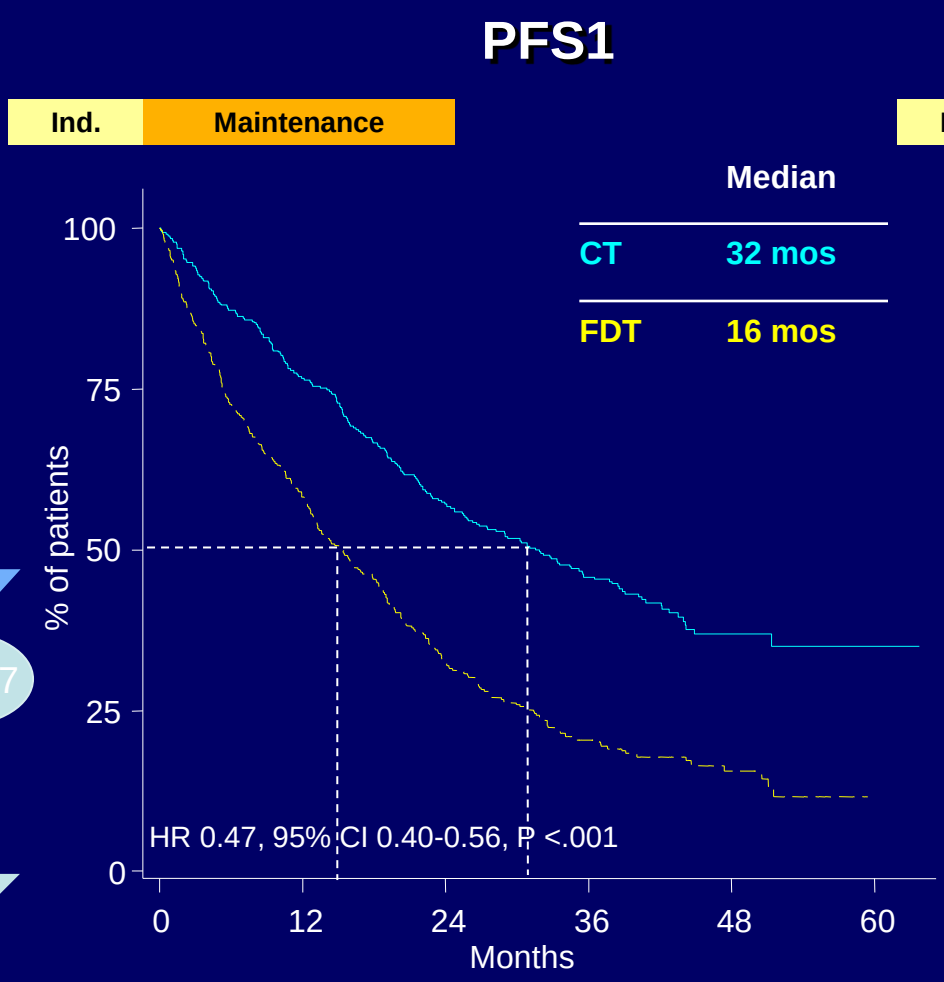


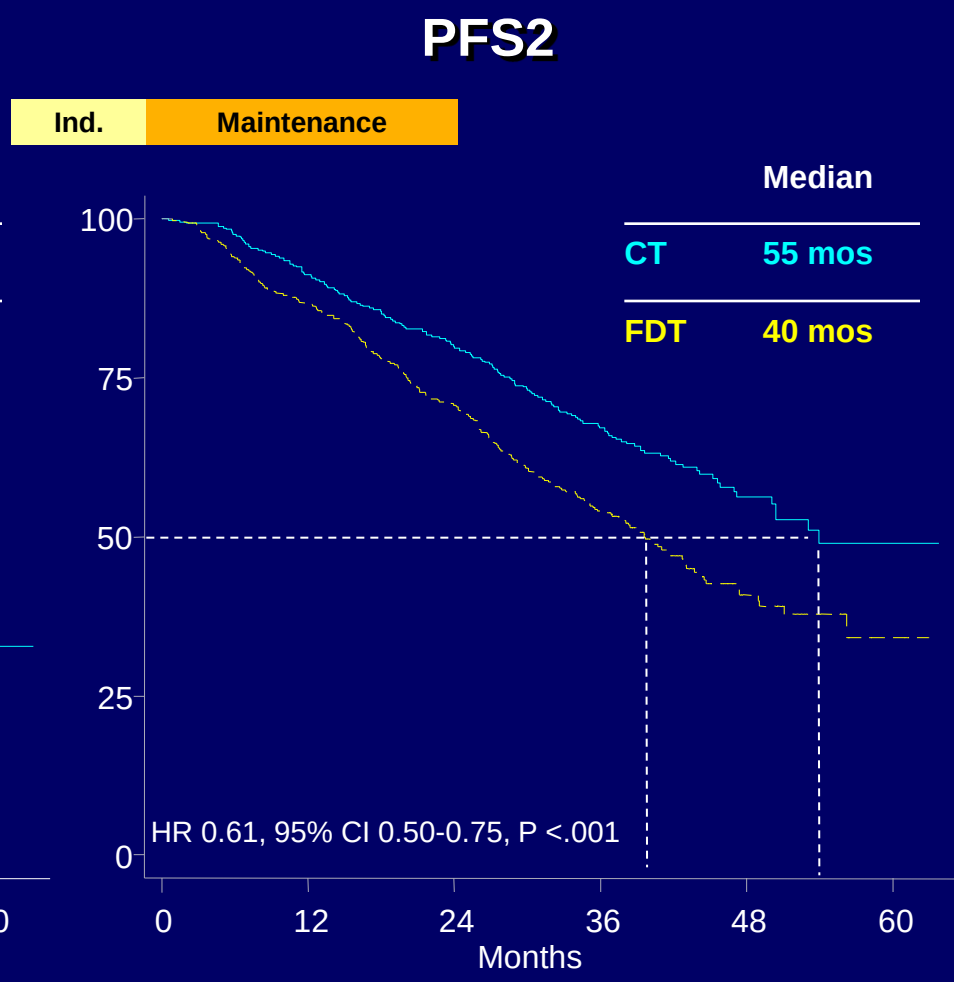
Continuous vs Fix duration

Meta-analysis of 3 studies: 1218 patients

1-year Landmark analysis







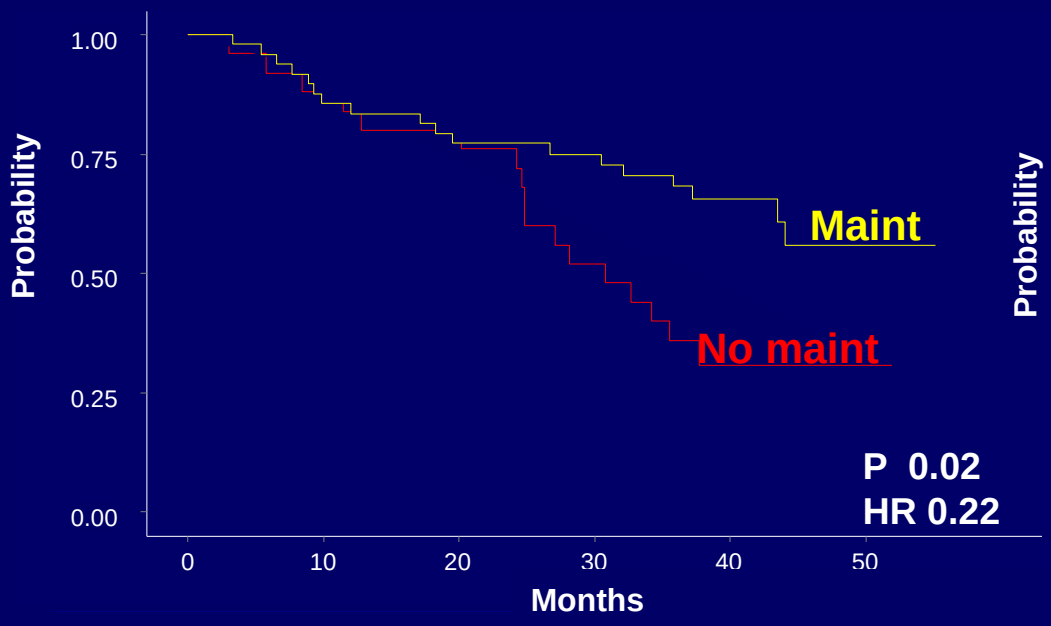
CT, continuous therapy; FDT, fixed duration of therapy; PFS, progression-free survival; mos, months.

Palumbo A, et al. JCO 2015 in Press

Maintenance vs no Maintenance in 1964 CR patients

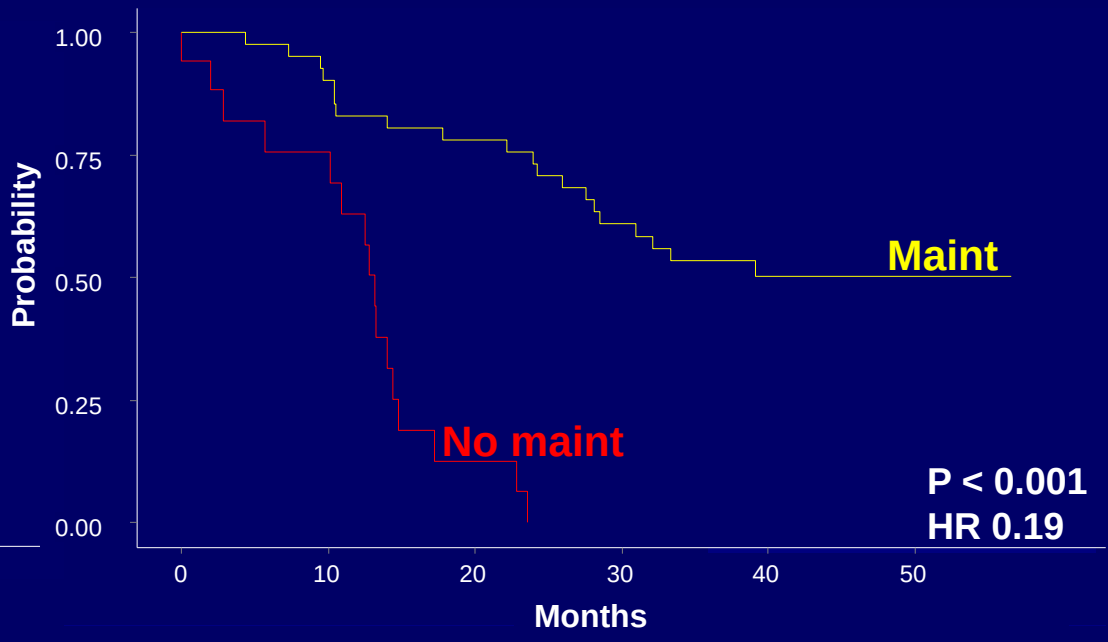
Progression-free survial
12-months landmark analysis

- **Young patients treated with ASCT**



MEDIAN PFS: NA vs 30.8 months

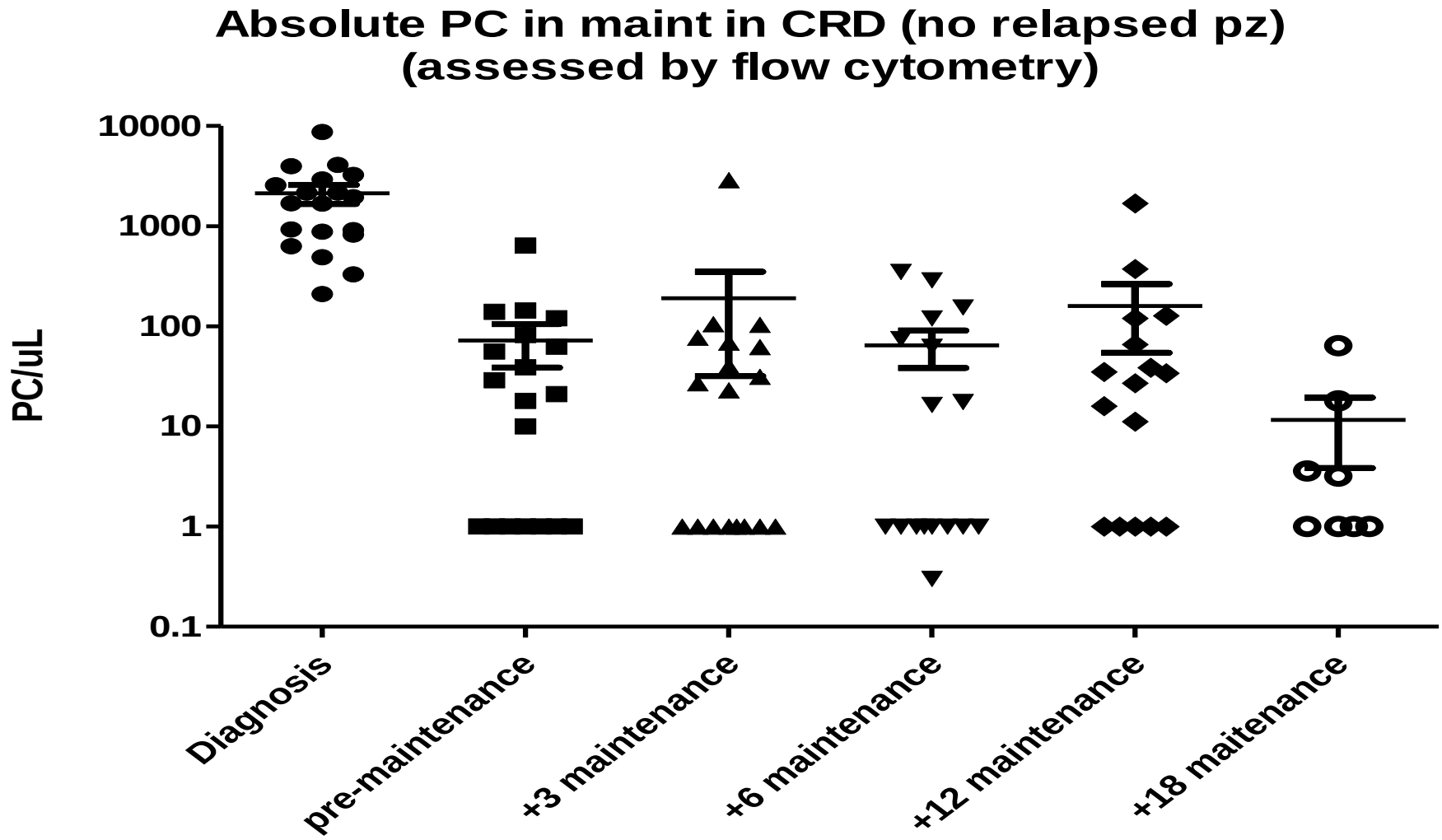
- **Young patients treated with CC**



MEDIAN PFS: NA vs 13.2 months

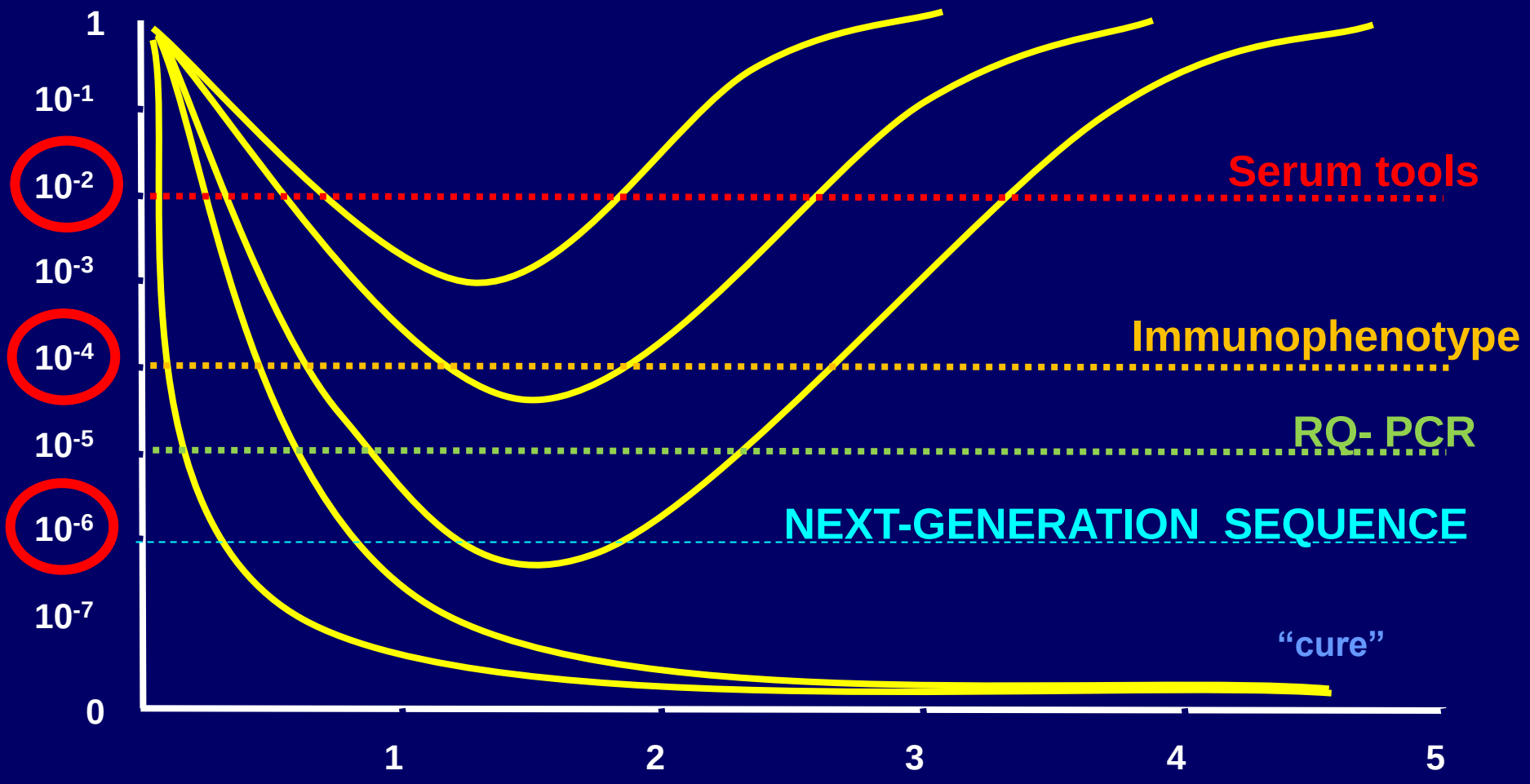
Cerrato C et al AH 2015

Tumor load during maintenance according to mainteneance (no relapsed patients included)



Complete Response

MRD sensitivity



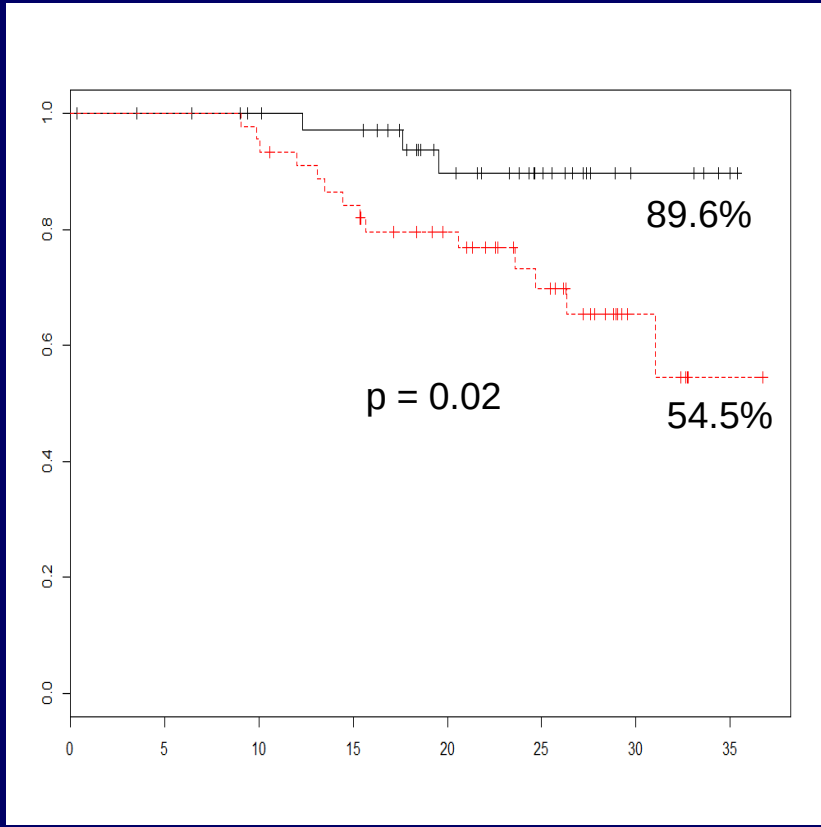
MRD: bone marrow only? NO

- CT/PET positive in 29% of CR patients

- PET/CT sensitivity of 50.0 %
  specificity of 85.7 %,
  overall accuracy of 74.2 %.

- MRI sensitivity of 80.0 %,
  specificity of 38.1 %,
  overall accuracy of 51.6 %.

PFS: VRD vs MEL200
negative PET-CT and MRD
(47.7% of patients)



Zamagni E. et al, Clin Cancer Res. 2015;21(19):4384

Moreau et al – ASH2015

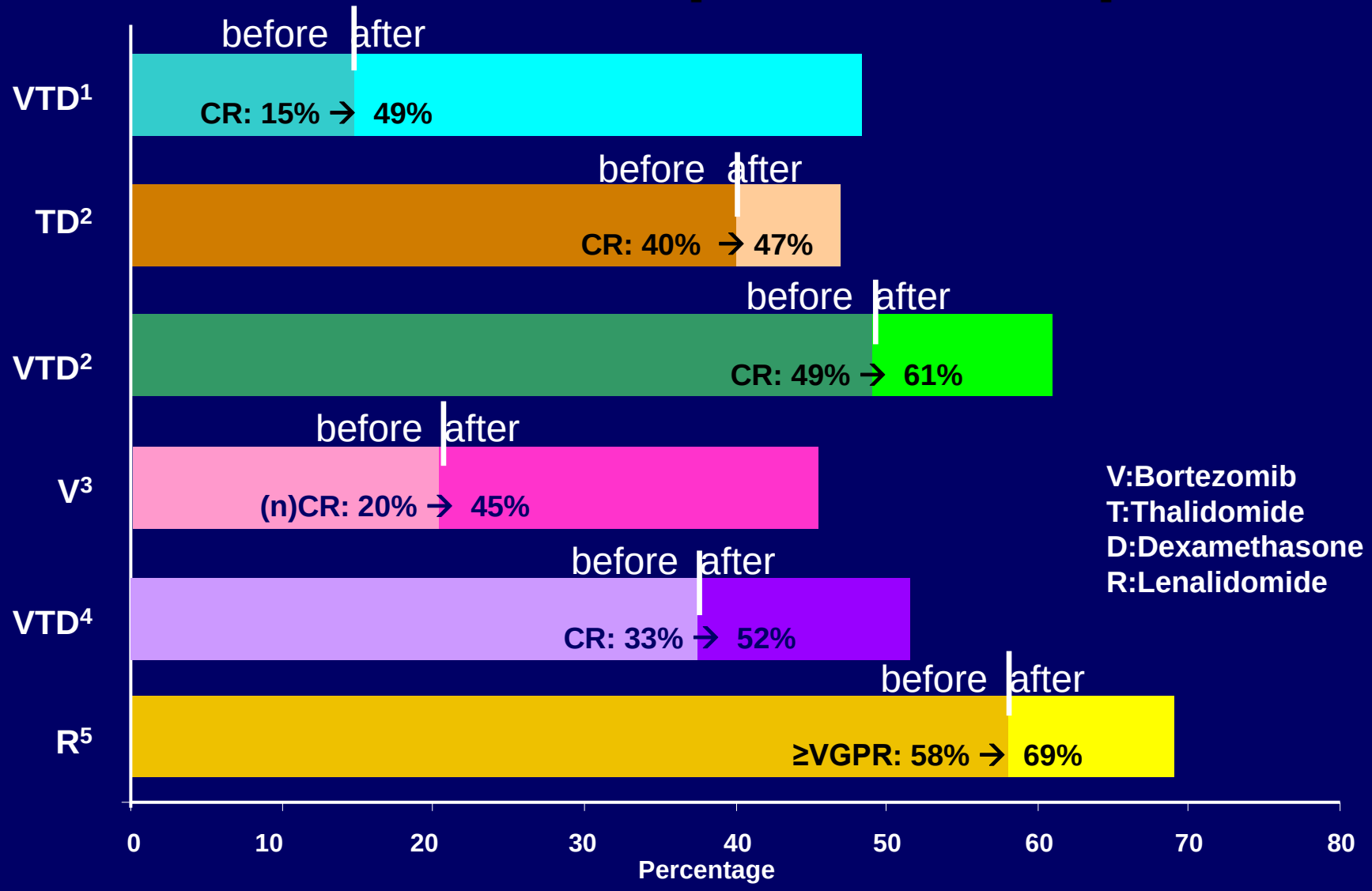
Young patients

Three Drug Regimens

Induction regimen	Schedule
Bortezomib-Cylophosphamide-Dexamethasone[2]	28-day cycles Bor: 1.3 mg/m^2 d 1-4-8-11 Cycl: 300 mg/m^2 d 1-8-15-(22) Dex: 40 mg d 1, 8, 15, 22
Bortezomib-Doxorubicin-Dexamethasone[3]	28-day cycles Bor: 1.3 mg/m^2 d 1-4-8-11 Dox: 9 mg/m2 d 1-4 Dex. 40 mg d 1, 8, 15, 22
Bortezomib-Thalidomide-Dexamethasone[4]	21-day cycles Bor: 1.3 mg/m^2 d 1-4-8-11 Thal: 100 - 200 mg/d Dex: 40 mg, d 1-4, 9-12
Bortezomib-Lenalidomide-Dexamethasone[5]	28-day cycles Bor: 1.3 or 1 mg/m^2 d 1-4-8-11 Len: 15 or 25 mg d 1-21 Dex: 40 mg d 1, 8, 15, 22

[2]Khan ML, et al. Br J Haematol. 2012;156(3):326-333; [3]Sonneveld P, et al. J Clin Oncol. 2012;30(24):2946-5295; [4]Cavo M, et al. Lancet. 2010;376(9758):2075-2085; [5]Richardson PG, et al. Blood 2010; 116(5):679-686.

Consolidation Improves Response



1 Ladetto M, et al. J Clin Oncol. 2010;28(12):2077-2084. 2 Cavo M, et al. Blood. 2012;120(1):9-19. 3. Mellqvist UH, et al. Blood. 2013;121(23):4647-4651; 4. Leleu X, et al. Leukemia. 2013;27(11):2242-2244 5 Attal M, et al. N Eng J Med 2012;366(19):1782-1791

Sequential treatment

VCD

Four 21-day courses

V: 1.3g/m^2, d 1,4,8,11
C: 500 mg/m^2, d 1,8
D: 40 mg, d 1,4,8,11

TRANSPLANTATION

MEL200

Two courses

M: 200 mg/m^2 day -2
Stem cell support day 0

CONSOLIDATION

VRD

Four 28-day course

V: 1.3 mg/m^2 d 1,4,8,11
R: 25 mg/day, d 1-21
D: 40 mg, d 1,4,8,11

MAINTENANCE

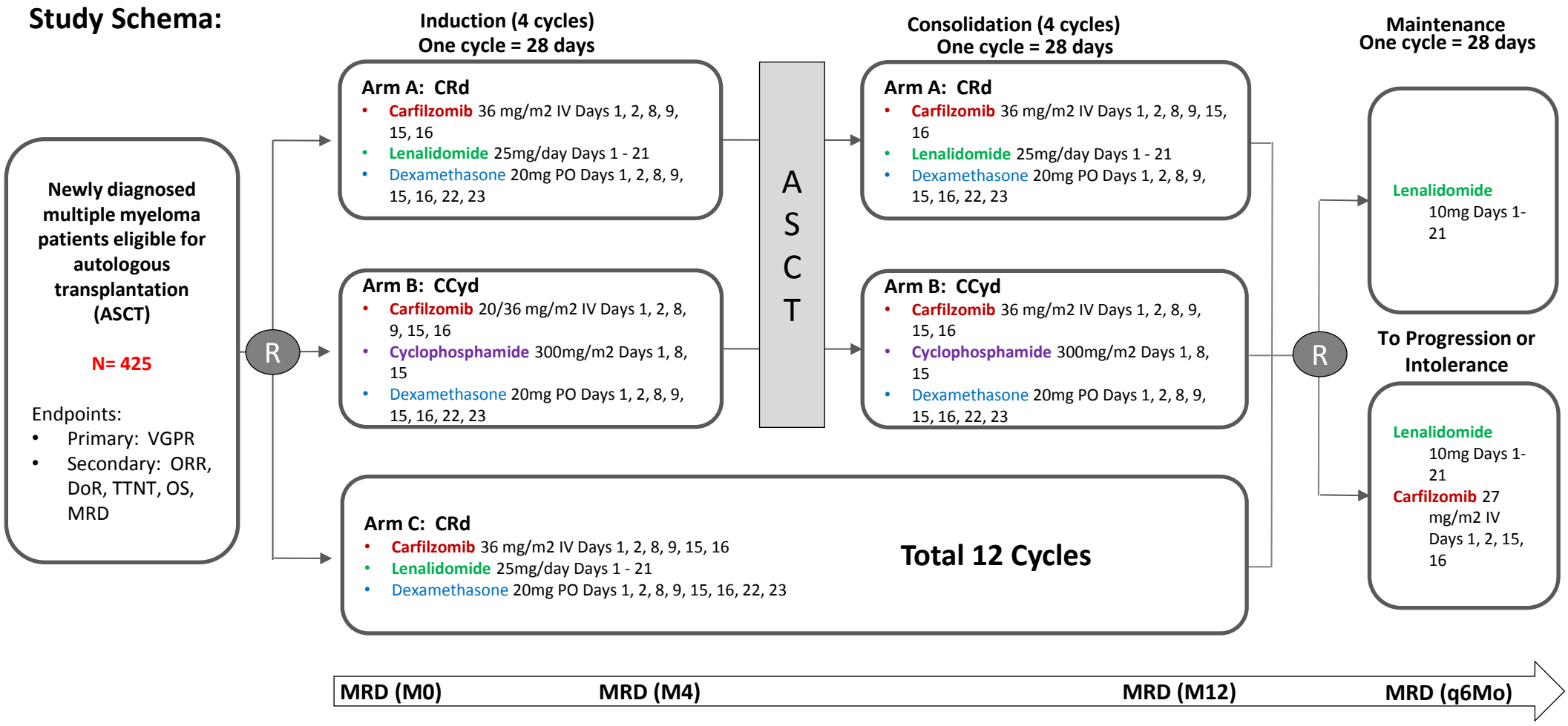
R

Maintenance

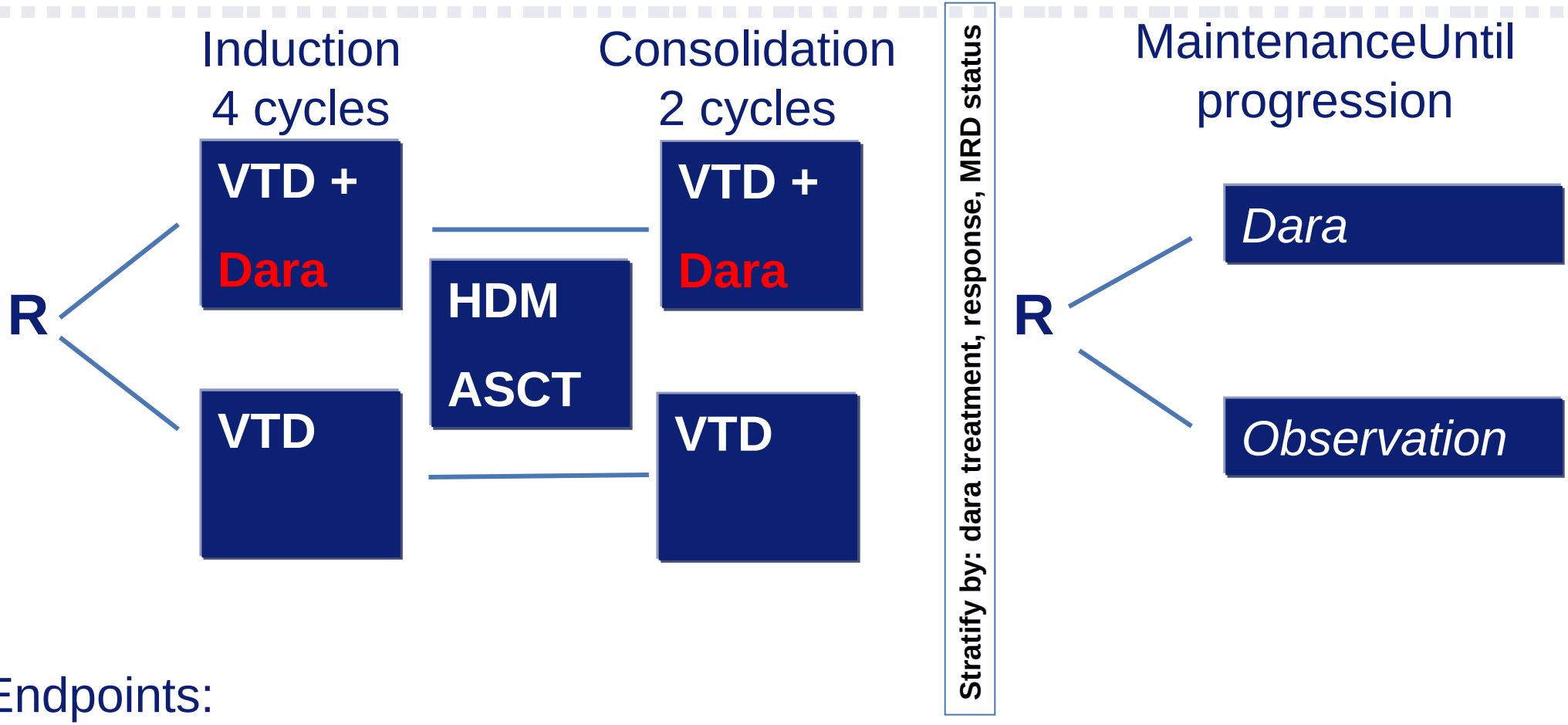
L: 10 mg/day on days 1-21

V, bortezomib; C, cyclophosphamide; D, dexamethasone; MEL200, melphalan 200 mg/m^2 ; R, lenalidomide

Italian KRd study design



Daratumumab trial in transplant eligible NDMM Hovon/IFM



Endpoints:

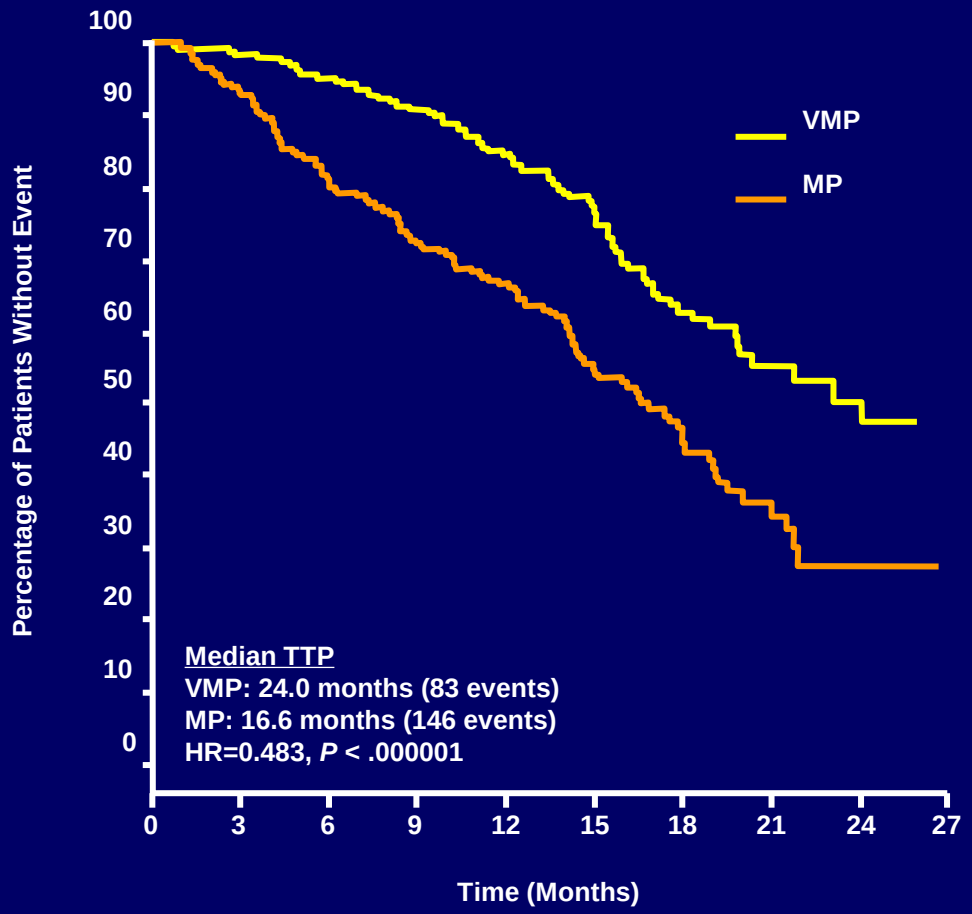
- sCR
- PFS, OS

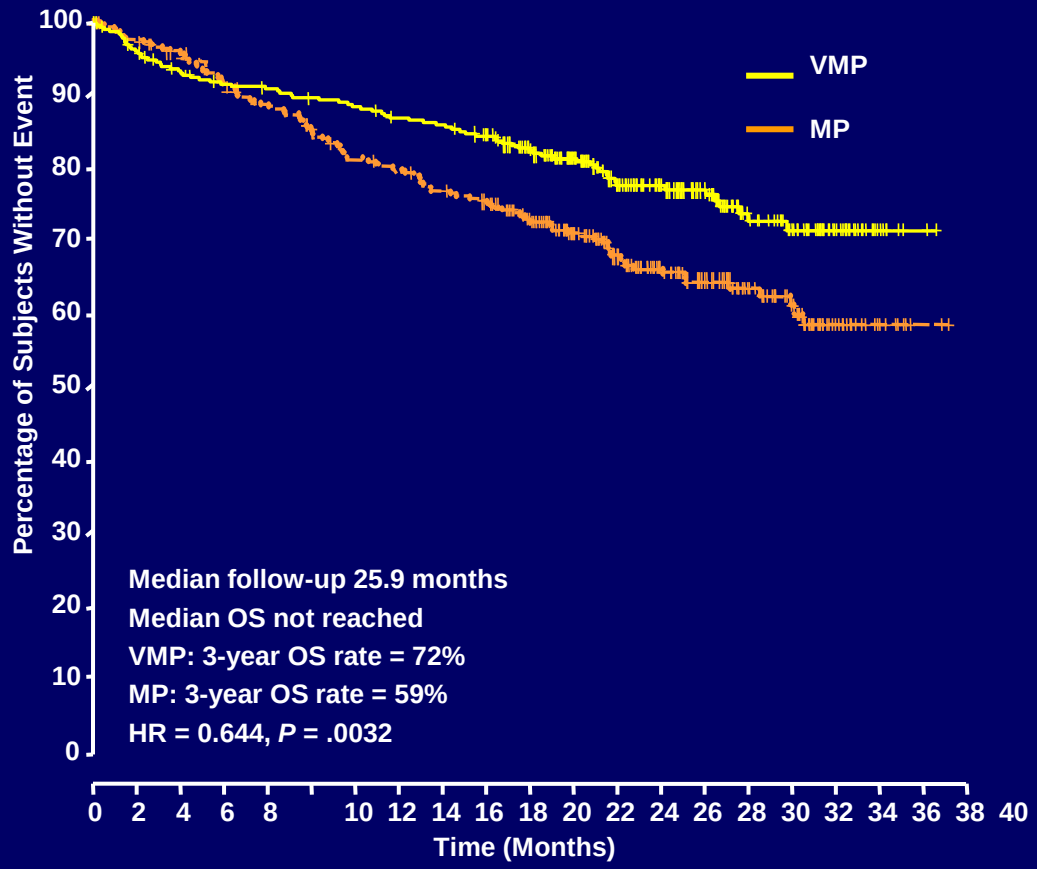
Courtesy P Sonneveld

Elderly patients

VMP (Bortezomib/Melphalan/Prednisone) Current Standard of Care

~52% reduced risk of progression
~36% reduced risk of death



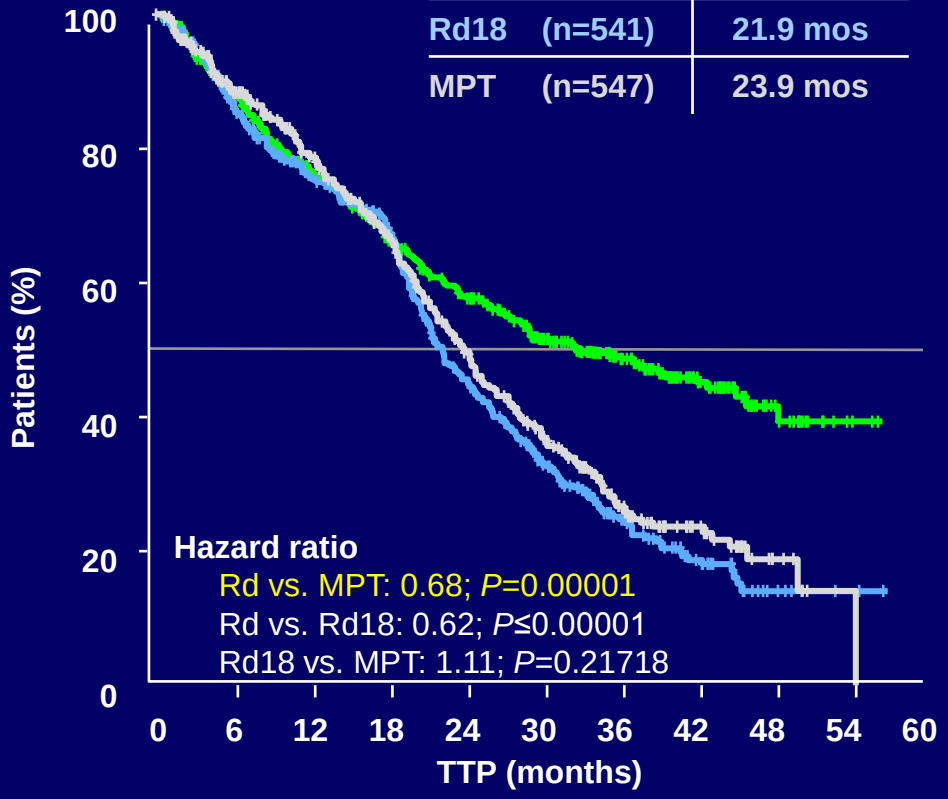


San Miguel JF, et al. ASH 2008. Abstract 650.

FIRST Trial: TTP and Time to 2nd Anti-myeloma Therapy

e to Progression

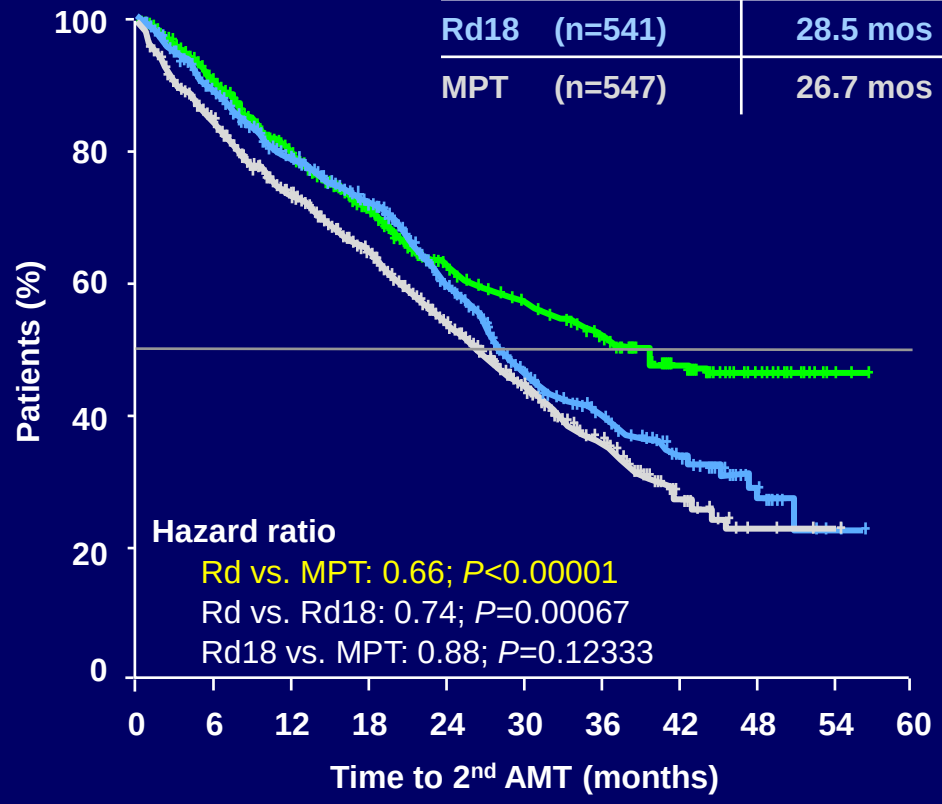
		Median TTP
Rd	(n=535)	32.5 mos
Rd18	(n=541)	21.9 mos
MPT	(n=547)	23.9 mos



Rd	535	398	318	263	218	167	105	55	19	2	0
Rd18	541	389	317	265	167	108	56	30	7	2	0
MPT	547	379	303	242	169	115	58	28	6	1	0

Time to 2nd AMT

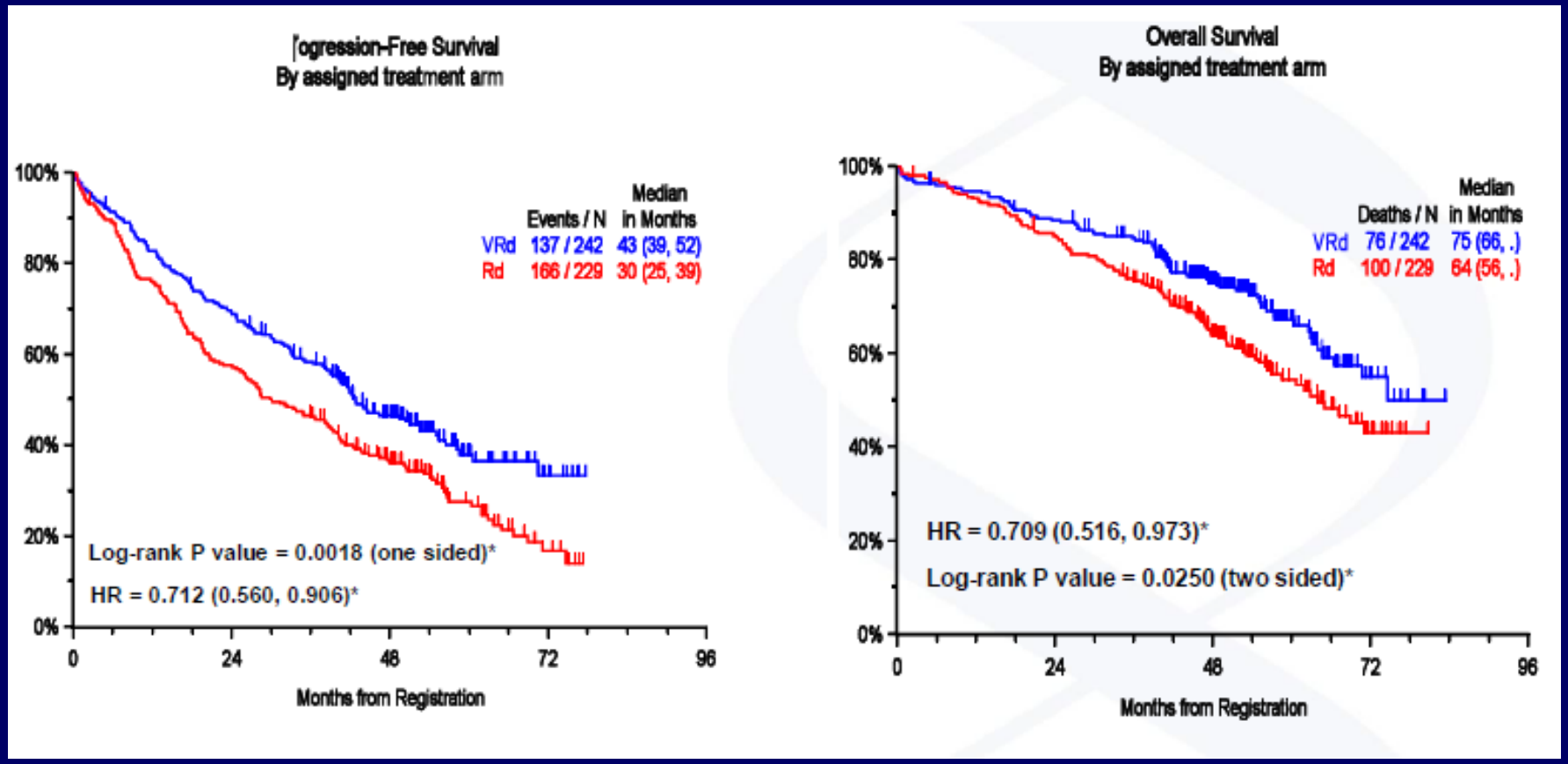
		Median Time to 2nd AMT
Rd	(n=535)	39.1 mos
Rd18	(n=541)	28.5 mos
MPT	(n=547)	26.7 mos



Rd	535	445	371	319	275	224	142	77	28	3	0
Rd18	541	451	375	331	266	181	111	61	16	2	0
MPT	547	422	351	293	239	177	101	42	9	1	0

Facon T, et al. Blood. 2013;122:abstract 2.

VRd vs Rd in NDMM



Durie et al ASH 2015

Salvage therapy

Two Drug Regimens

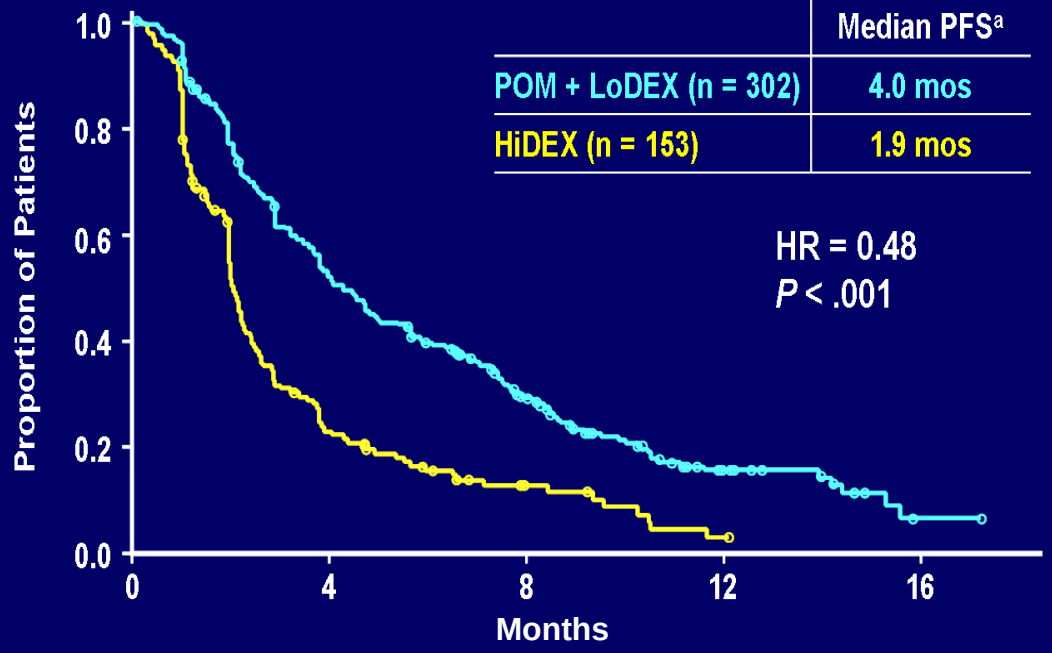
regimen	Schedule
Bortezomib-Dexamethasone[1]	**21-day cycles** **Bor: 1.3 mg/m^2 , d 1-4-8-11** **Dex: 40 mg, d 1-4, 9-12**
Lenalidomide-Dexamethasone[6]	**28-day cycles** **Len: 25 mg d 1-21** **Dex: 40 mg d 1, 8, 15, 22**

[1]Harousseau JL, et al. J Clin Oncol. 2010;28(30):4621-4629; [6]Rajkumar V, et al. Lancet Oncol 2011; 116(5):679-686.

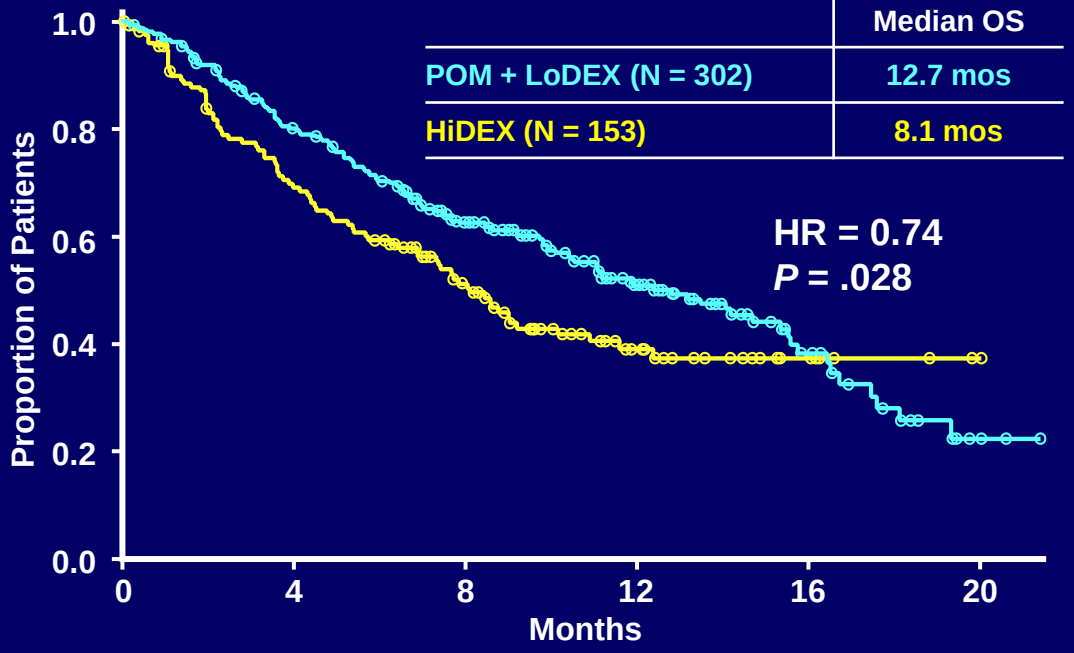
3: POM-Dex vs Dex in Relapsed MM

Pomalidomide 4 mg orally d 1–21 of 28-day cycels
Dexamethasone 40 mg d 1, 8, 15, 22

Progression-free survival



Overall survival



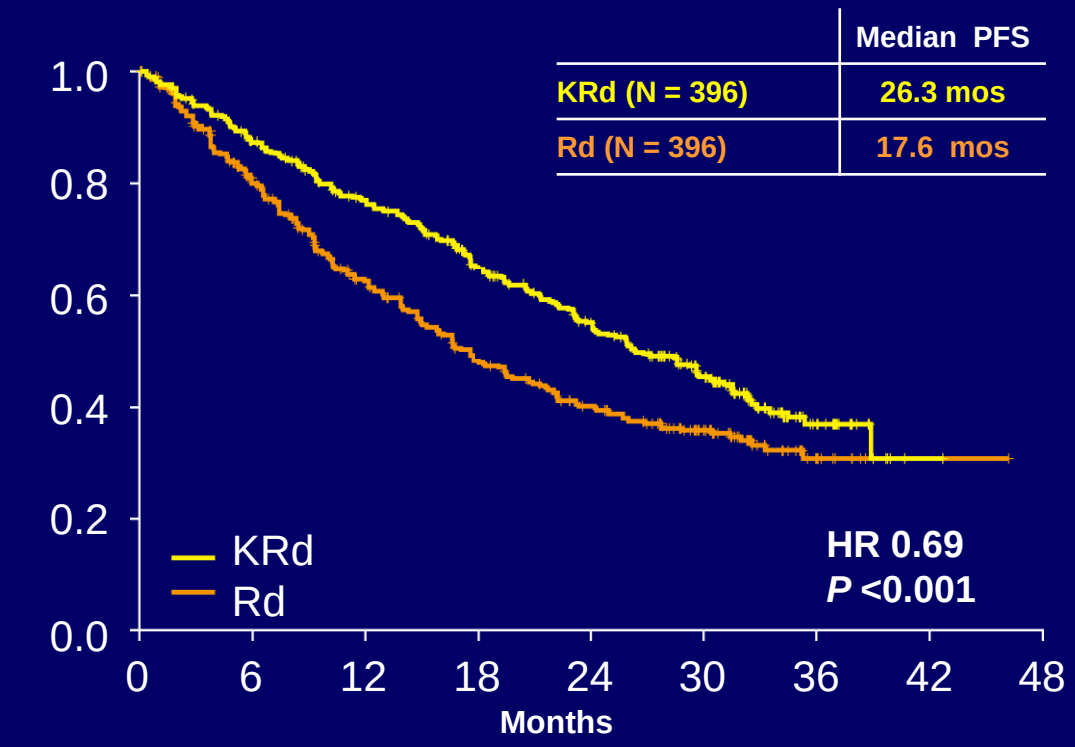
[a] Based on IMWG criteria.

San-Miguel JF, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 8510.

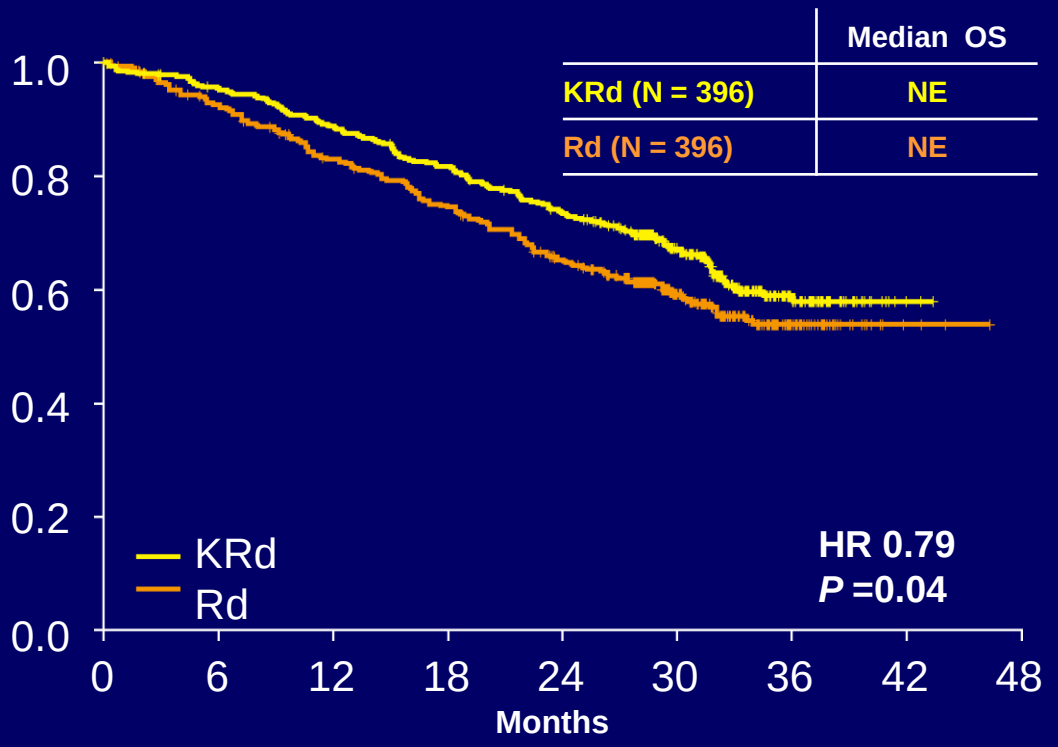
Carf-Len-Dex vs Len-Dex in Relapsed MM

omib 27 mg/m2 IV d 1,2,8,9,15,16 (20 mg/m2 d 1,2 cycle 1)
Lenalidomide 25 mg d 1-21
Dexamethasone 40 mg d 1, 8, 15, 22

Progression-free survival



Overall survival

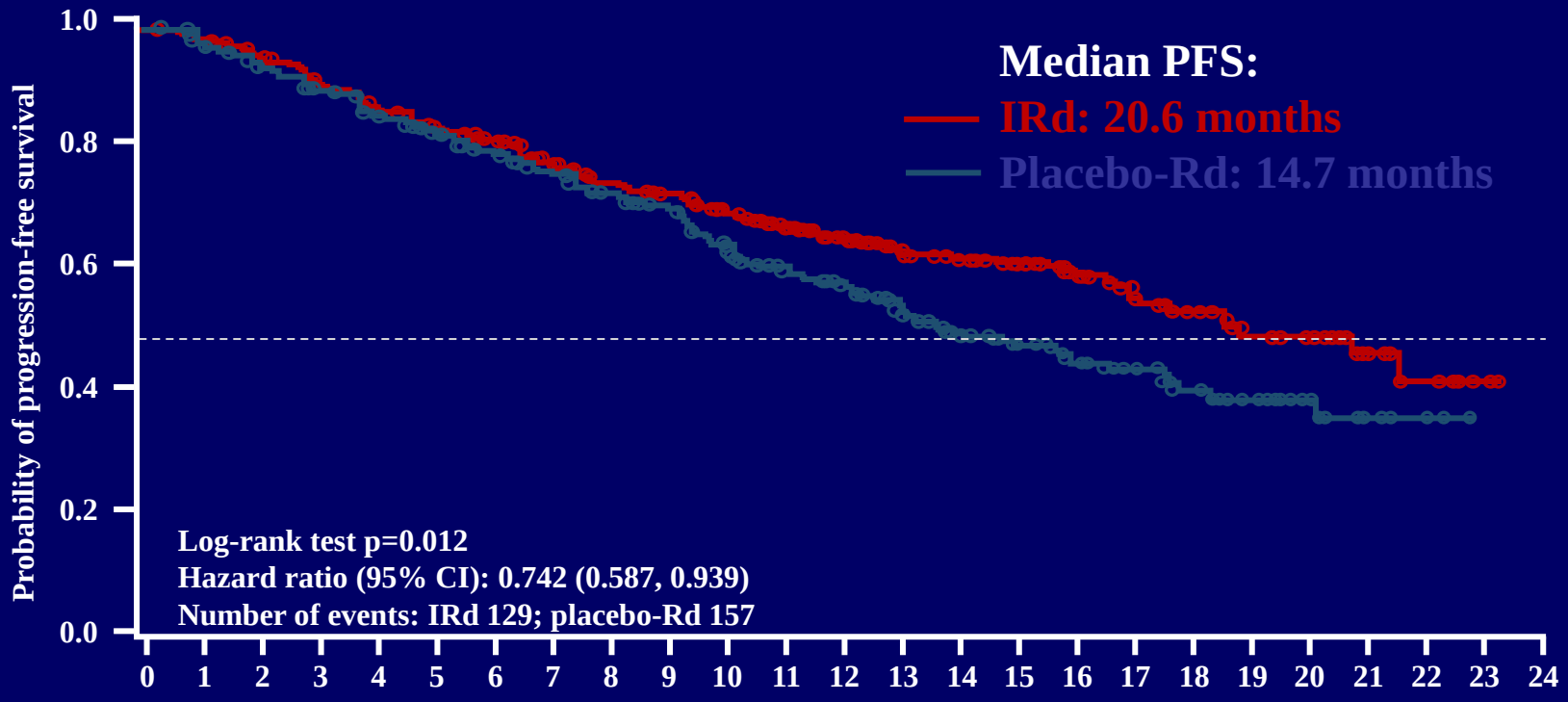


KRd, carfilzomib-lenalidomide-dexamethasone; Rd, lenalidomide-dexamethasone; NE, not estimable; PFS, progression-free survival; OS, overall survival

Stewart KA, et al. *NEJM.* 2015;372:142

ib, Lenalidomide Dexamethasone (Ird) in RRMM myeloma

Ixazomib: 4 mg on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22



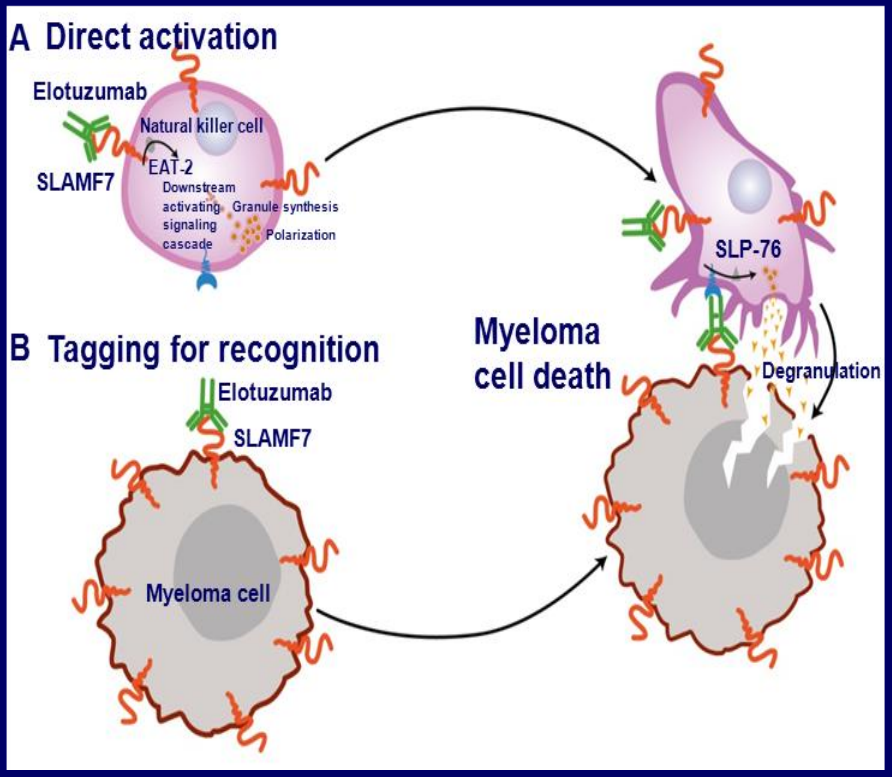
Number of patients at risk:																									
IRd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo-Rd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Median follow-up: ~15 months

Moreau et al ASH 2015

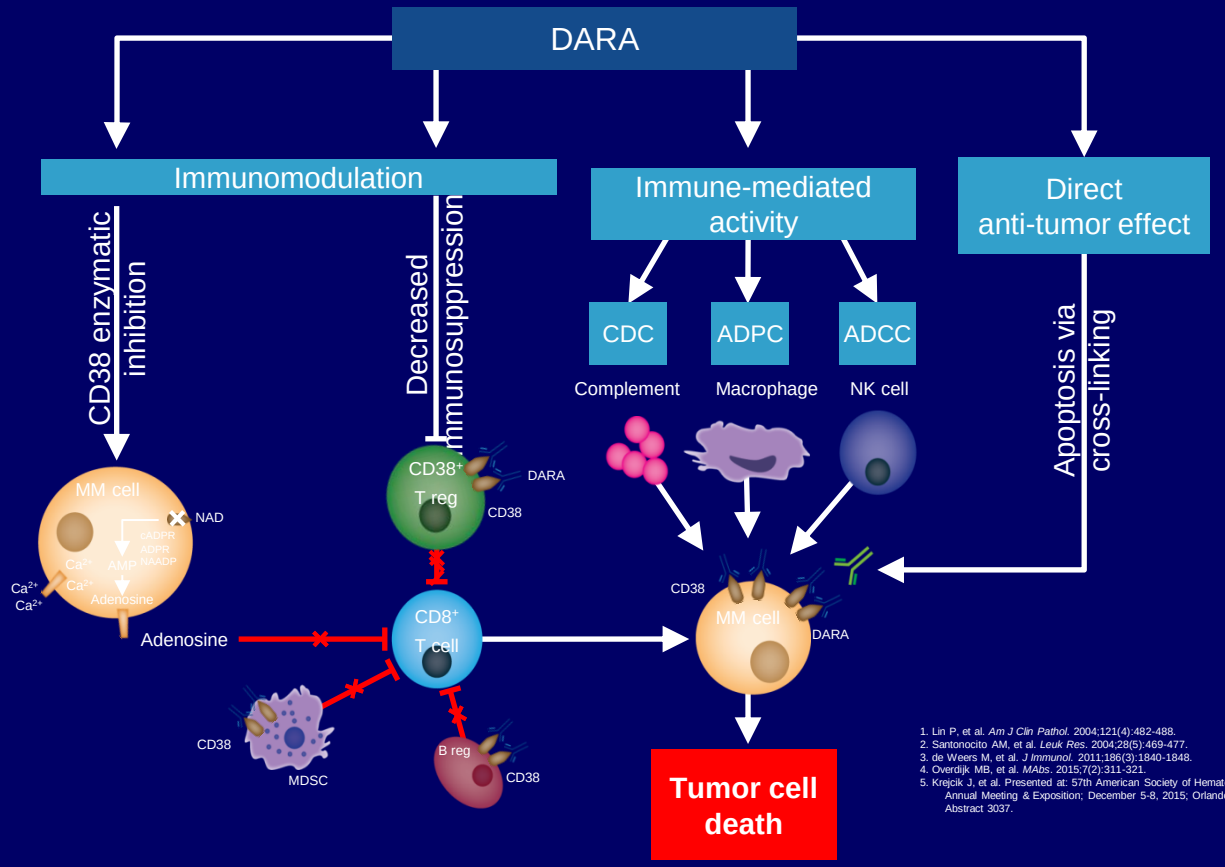
mmuno oncology agents

Elotuzumab: Mechanism of Action



1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84
2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9
3. Guo H et al. *Mol Cell Biol* 2015;35:41–51

Darartumumab: Mechanism of Action



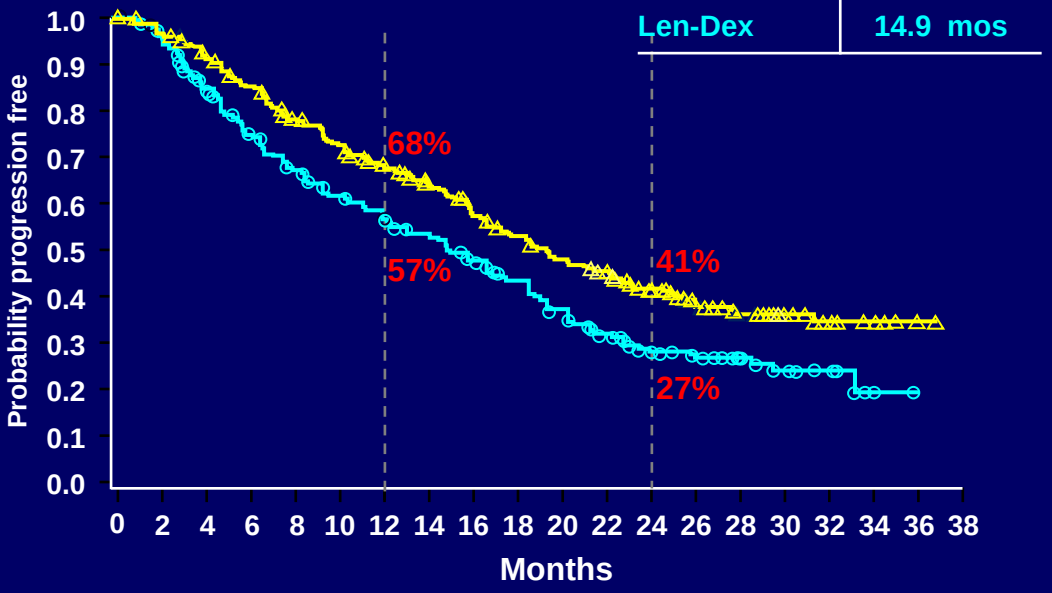
1. Lin P, et al. *Am J Clin Pathol*. 2004;121(4):482-488.
2. Santonocito AM, et al. *Leuk Res*. 2004;28(5):469-477.
3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
5. Krejcik J, et al. Presented at: 57th American Society of Hematology Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 3037.

ENT-2: Elo-Len-Dex vs Len-Dex in Relapsed/Refractory MM

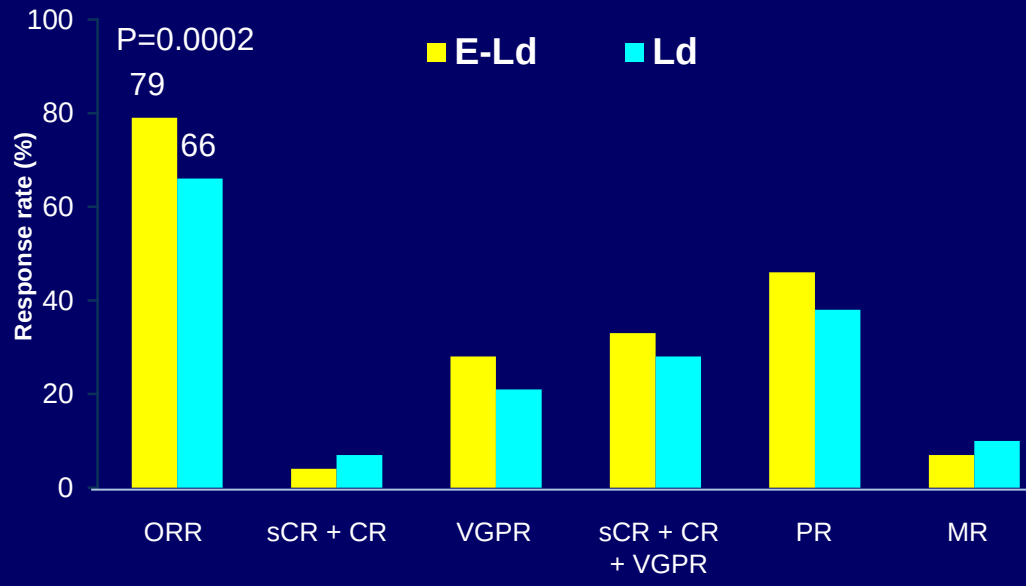
Elotuzumab 10 mg/kg IV d 1,8,15,22 (cycle 1,2); d 1,15 (cycles 3+)
Lenalidomide 25 mg orally d 1-21
Dexamethasone 40 mg d 1,8,15,22 in 28-day cycles

Progression-free survival

	Median PFS
Elo-Len-Dex	19.4 mos
Len-Dex	14.9 mos



Overall response rate



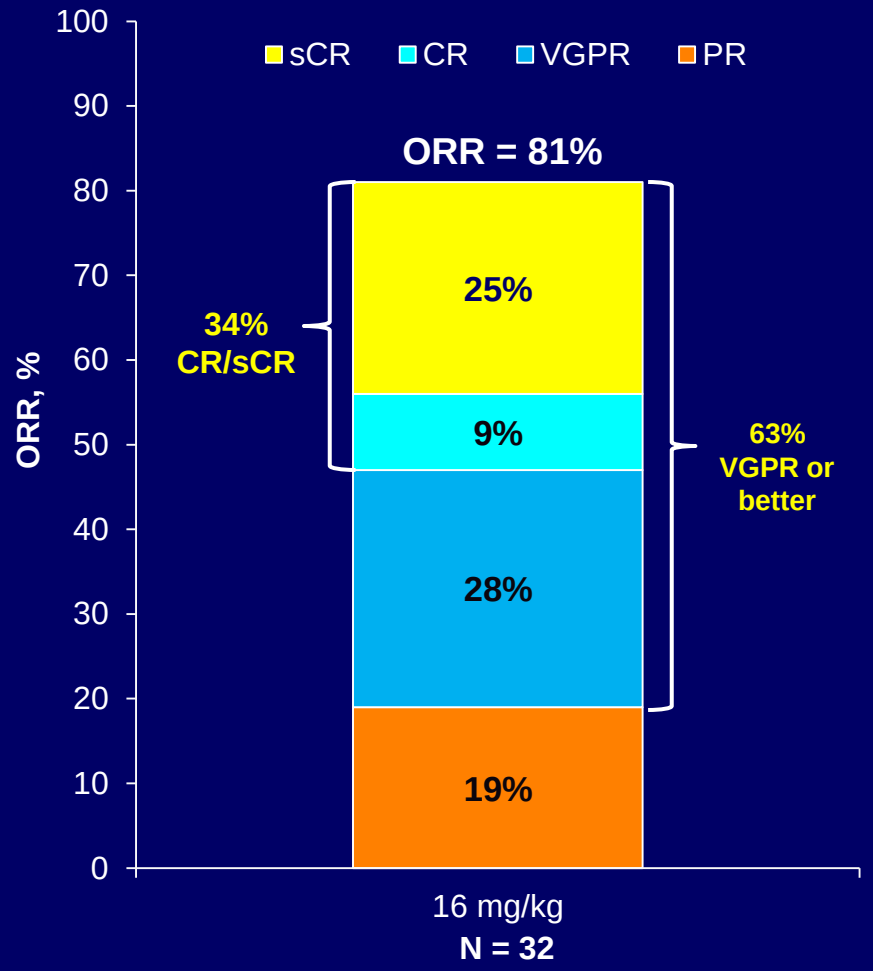
Elo, elotuzumab; Len, lenalidomide; Dex, dexamethasone; ORR, overall response rate; CR, complete response; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; PFS, progression-free survival.

Lonial S, et al. *ASCO.* 2015; abstract 8508.

...b Lenaldomide Dexamethasone in RRMM

Response Rate

	N = 32	
	n (%)	**95% CI**
Overall response rate (sCR+CR+VGPR+PR)	**26 (81)**	**63.6-92.8**
Best response		
sCR	8 (25)	11.5-43.4
CR	3 (9)	2.0-25.0
VGPR	9 (28)	13.7-46.7
PR	6 (19)	7.2-36.4
VGPR or better (sCR+CR+VGPR)	20 (63)	43.7-78.9
CR or better (sCR+CR)	11 (34)	18.6-53.2

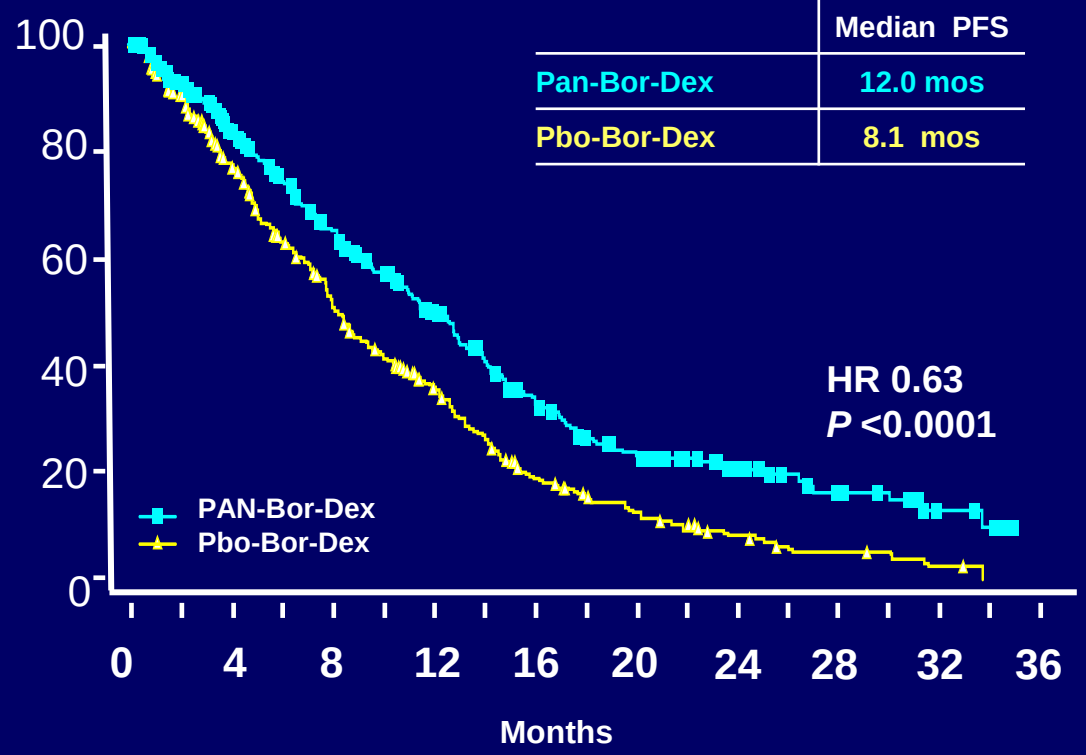


- **ORR = 81%**
- **Clinical benefit rate (ORR + minimal response) = 88%**

AMA: Pan-Bor-Dex in Relapsed MM

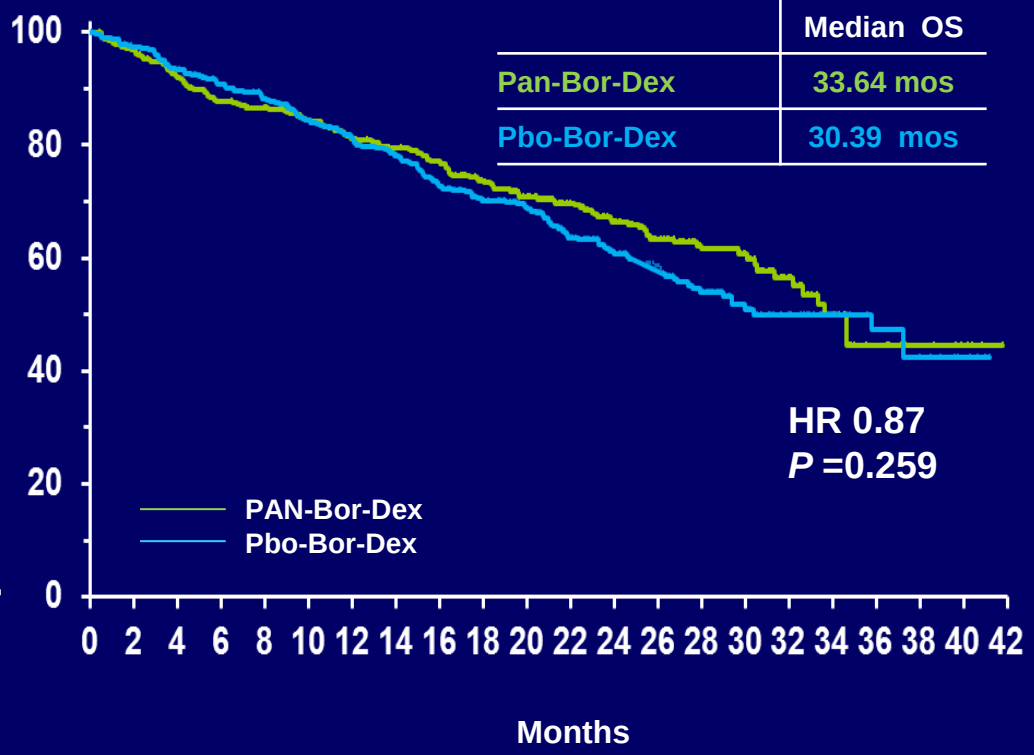
Panobinostat 20 mg orally d 1,3,5,8,12 in 21-day cycles
Bortezomib 1.3mg/m2
Dexamethasone 20 mg

Progression-free survival



	Median PFS
Pan-Bor-Dex	12.0 mos
Pbo-Bor-Dex	8.1 mos

Overall survival



	Median OS
Pan-Bor-Dex	33.64 mos
Pbo-Bor-Dex	30.39 mos

Pan, panobinostat; Bor, bortezomib; Dex, dexamethasone; Pbo, placebo; PFS, progression-free survival; OS, overall survival

San-Miguel JF, et al. *Blood.* 2014;124: Abstract 4742.

Future Therapeutic Algorithm

	Young	Fit Elderly	Frail Elderly
Diagnosis	VRD/VCD – ASCT	VRD/VCD	Rd
PI based Therapy	Carf-Rd	Carf-Rd	Ixa-Rd
MoAb Therapy	Dara-R/Vd	Dara-R/Vd	Elo-R/Id
Len→Pom Therapy	Pom-Vd	Pom-Vd	Pom-Id
HDAC Therapy	Panob-Vd	Panob-Vd	Panob-Vd

ASCT, autologous stem cell transplant; BTZ, bortezomib; CARF, carfilzomib; CY, cyclophosphamide; D, dexamathasone; R, lenalidomide; V, bortezomib; MPV, melphalan+prednisone+thalidomide; POM, pomalidomide; Rd, lenalidomide +dexamethasone; VTD, bortezomib+thalidomide+dexamethasone; Panob, panobinostat.

Conclusion

- NDMM: Early intervention, CR rate, continuous therapy
  - Young patients → ASCT
  - Elderly fit patients → three drug combo
  - Elderly frail patients → two drug combo
- RRMM: Previous drug sensitivity, co-morbidities
  - Fit: three drug regimen
  - Frail: two drug regimen
- New comers
  - Carfilzomib, Ixazomib
  - Daratunumab, Elotuzumab,
  - Panobinostat,