HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

University of Salamanca

Avances en el tratamiento del Mieloma Múltiple

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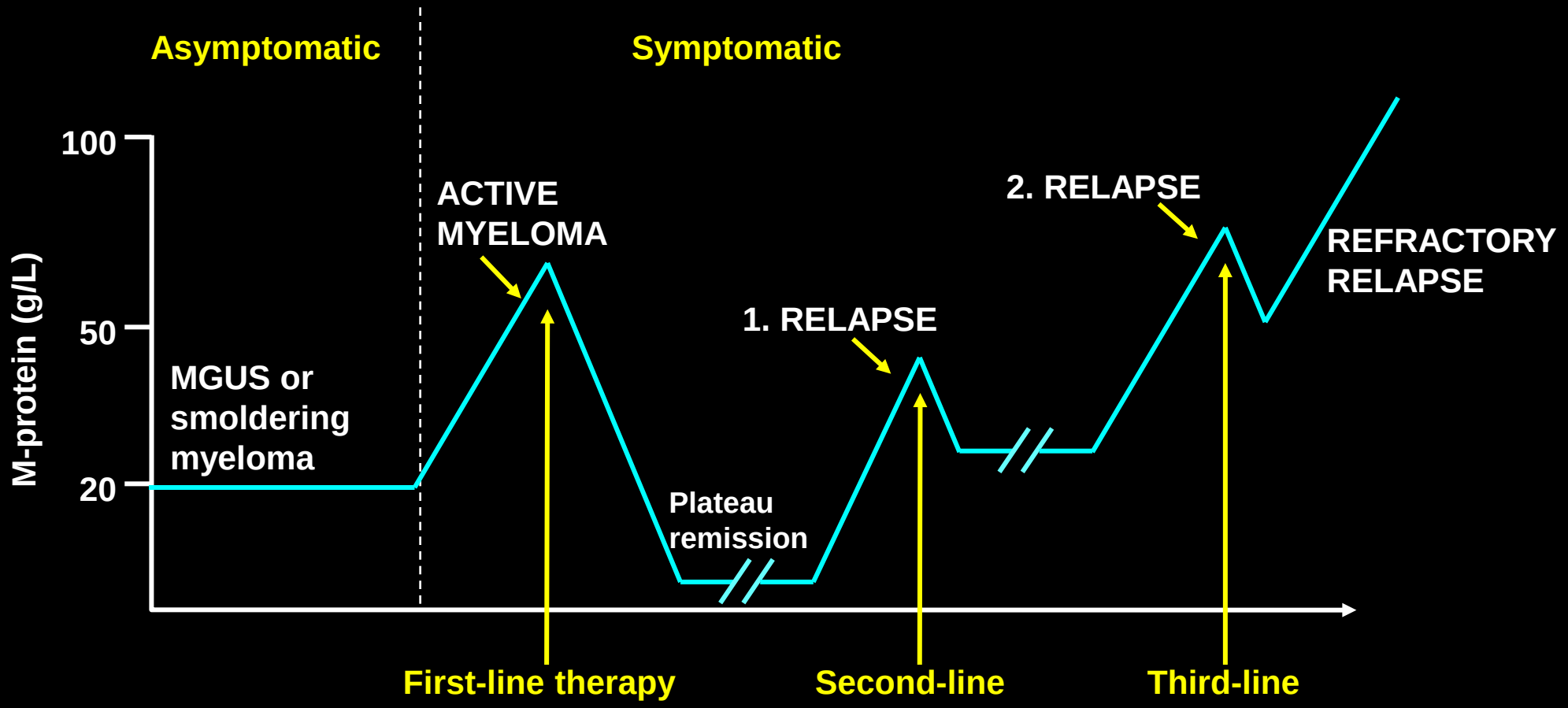
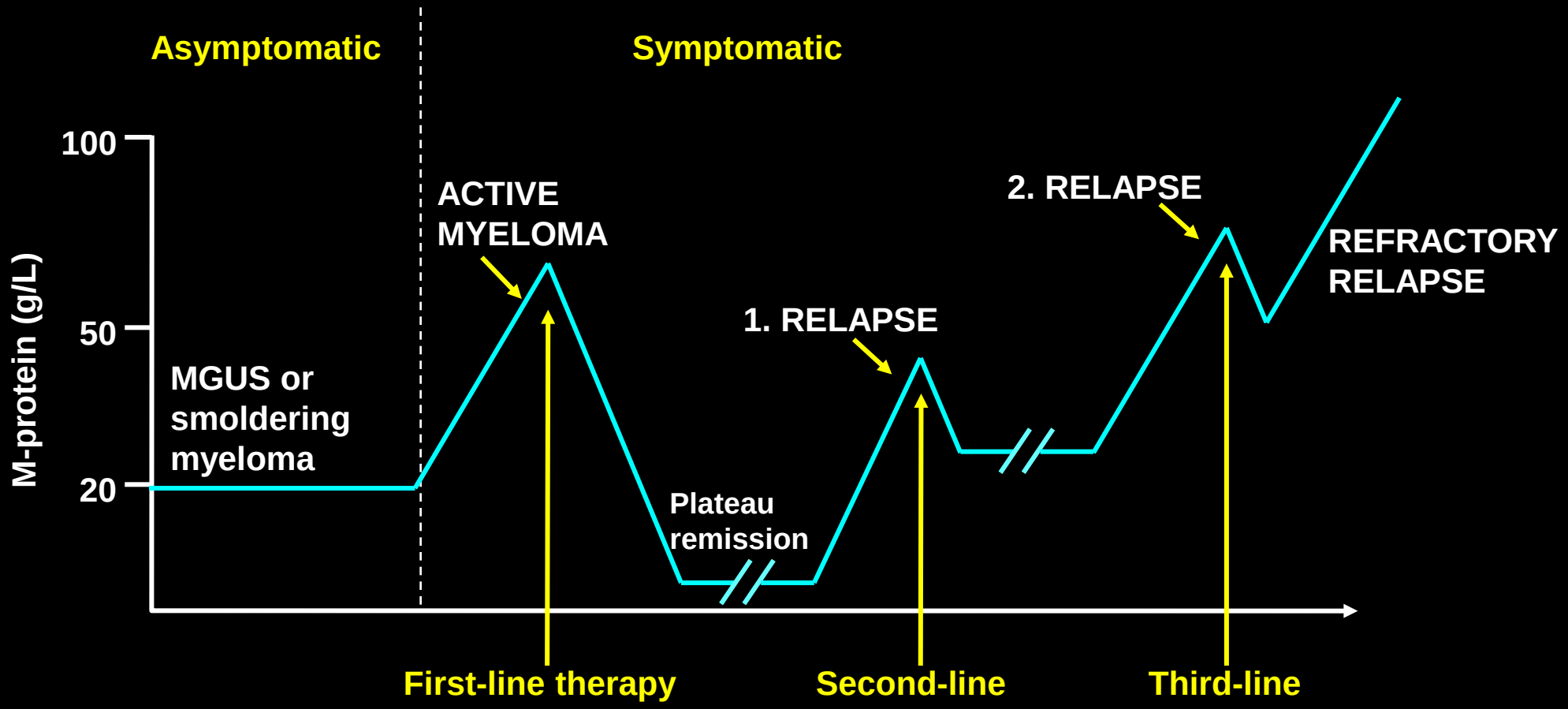
Natural History of Multiple Myeloma



MGUS=monoclonal gammopathy of undetermined significance.

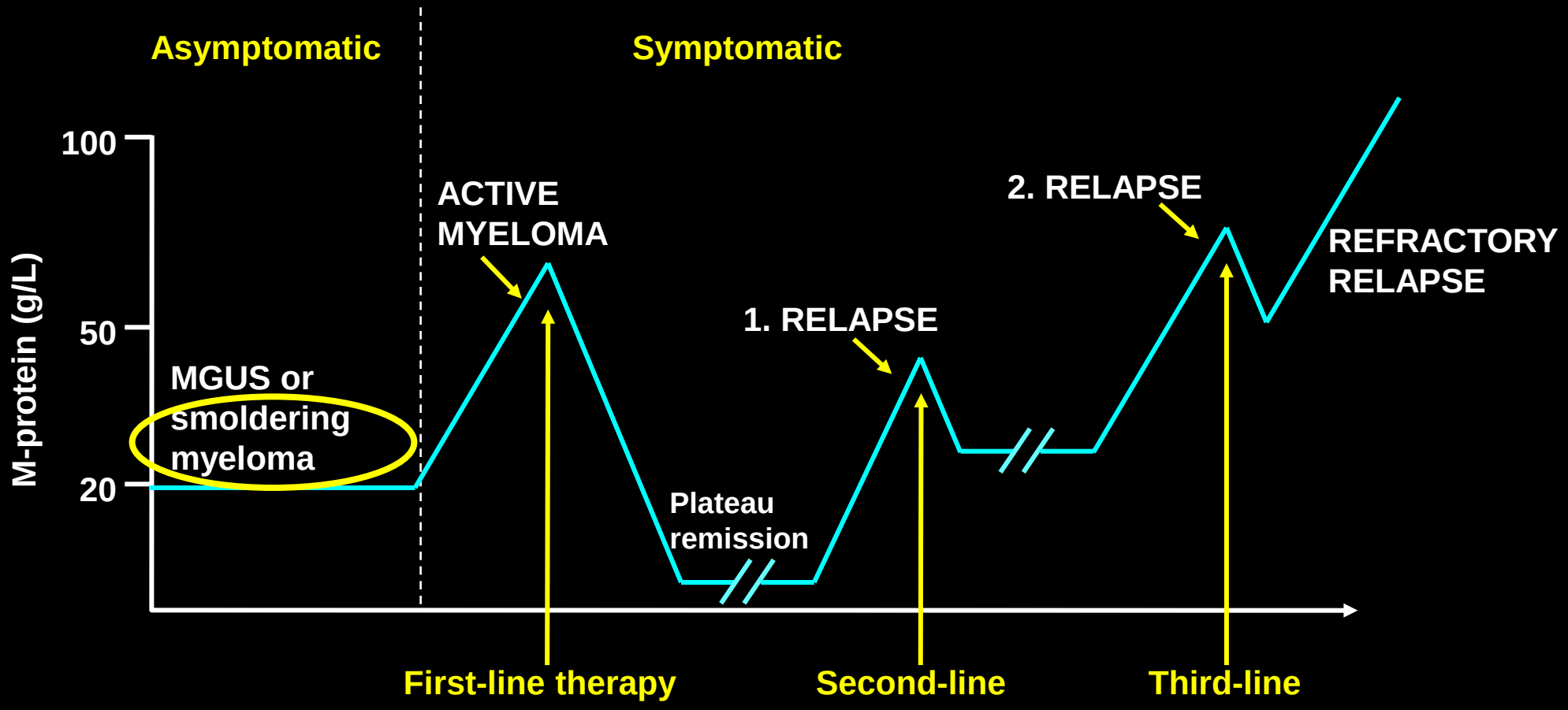
Natural History of Multiple Myeloma



To change this natural history and converts MM into a curable disease

MGUS=monoclonal gammopathy of undetermined significance.

Natural History of Multiple Myeloma



To change this natural history and converts MM into a curable disease

MGUS=monoclonal gammopathy of undetermined significance.

Smouldering Multiple Mieloma: Classical definition

Monoclonal component	**≥ 3 g/dL serum**
	AND/OR
Bone Marrow Plasma Cells (%)	**10-60%**
	AND
Myeloma-defining event	**Absent**

Myeloma-defining events:

End-organ damage

Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)

Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)

Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L

Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡

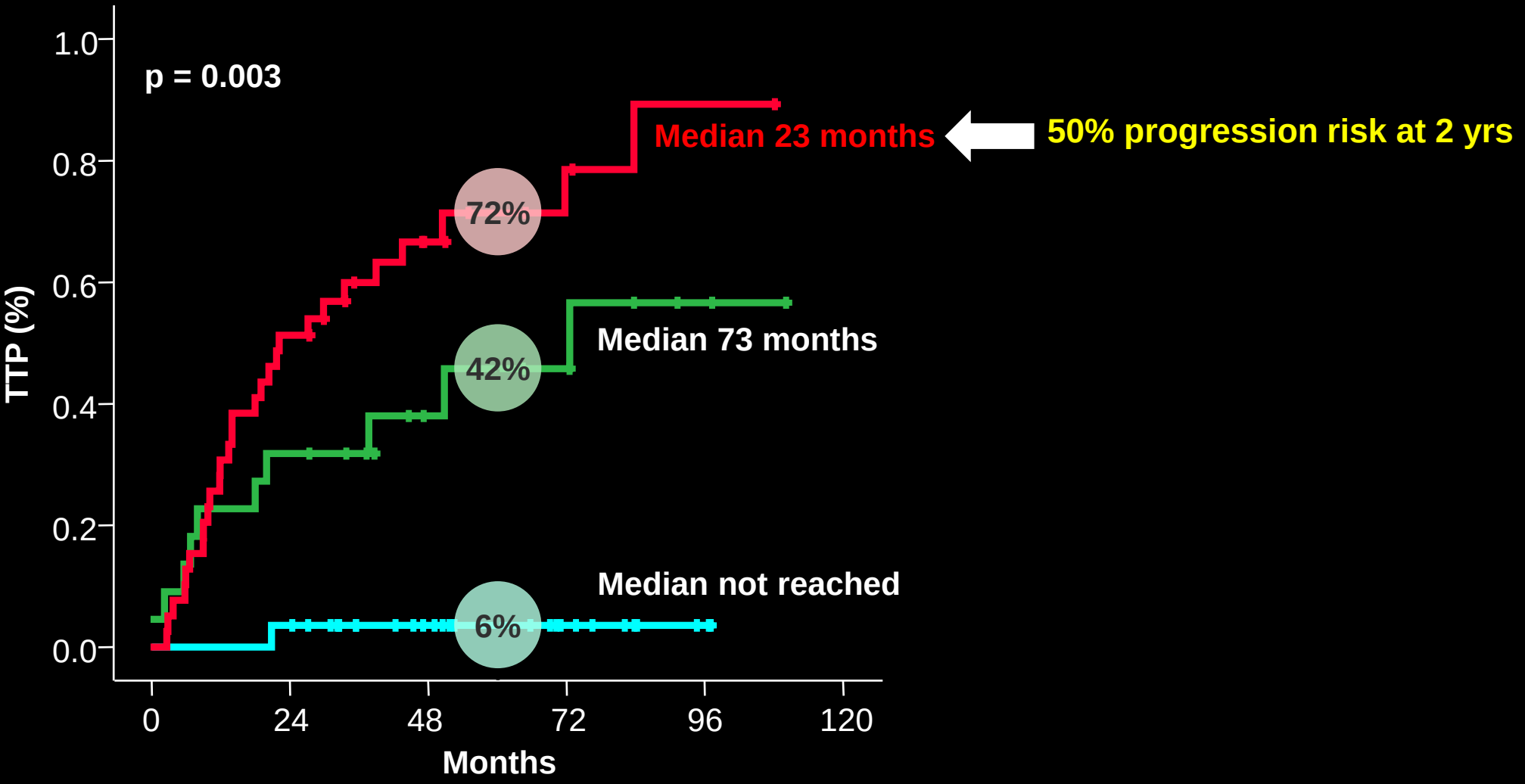
Any one or more of the biomarkers

- Clonal bone marrow plasma cell infiltration ≥ 60%
- Involved:uninvolved sFLC ratio ≥ 100
- >1 focal lesions in MRI

IMWG Br J Haematol 2003; 21:749-57

Kyle R. N Engl J Med 2007; 356:2582-90

Smoldering Multiple Myeloma

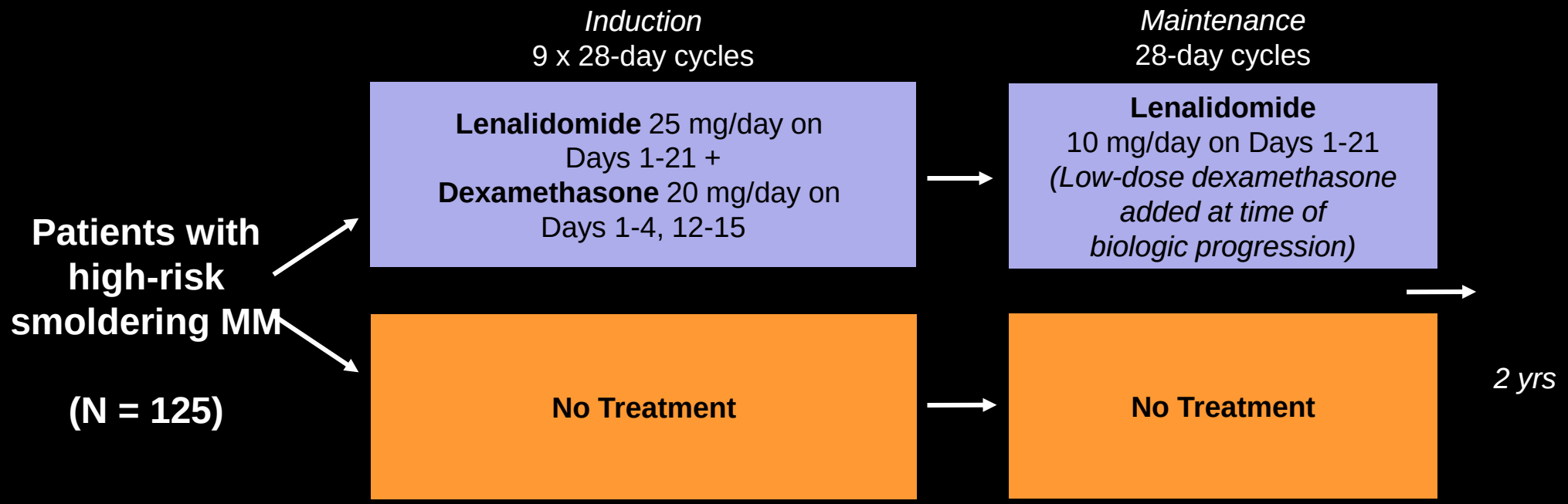


Kyle R. N Engl J Med 2007; 356:2582-90
Perez-Persona E, et al. Blood. 2007;110:2586-92.
Dispenzieri A. Blood 2008; 111:785-9

Hillengass J et al. J Clin Oncol 2010; 28: 1606-10
Hillengass et al. ASH 2012 (Abstract 2911), poster
Neben et al. ASH 2012 (Abstract 1806), poster

QuiRedex: Study Design

- Multicenter, open-label, randomized phase III trial



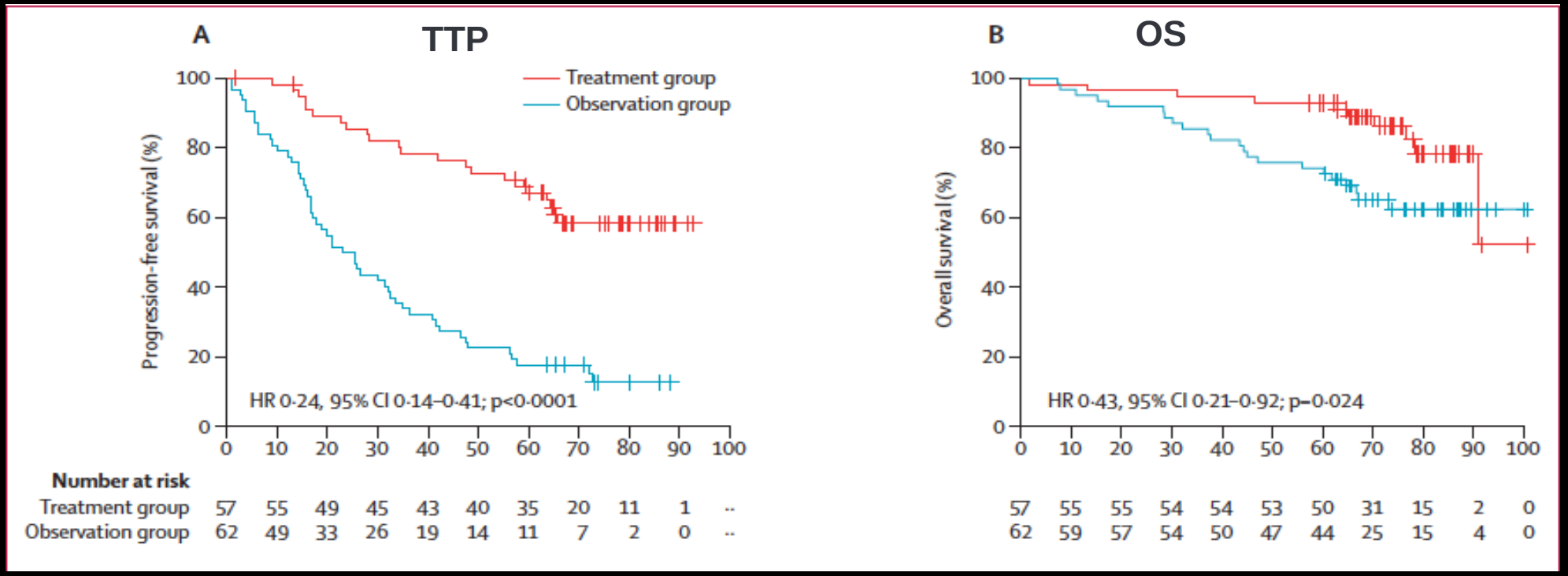
In both arms, blood counts, biochemical analysis (including creatinine and calcium) and serum/urine levels of MC were performed monthly. Skeletal survey was performed during the screening phase and thereafter only if clinical symptoms emerged.

Amendment in August 2011: Stop treatment after 2 years

Mateos MV, et al. NEJM 2013; 369:438-47

QuiRedex Phase 3 trial:
Len-dex vs no treatment (n = 119)

Median follow-up: 75 m

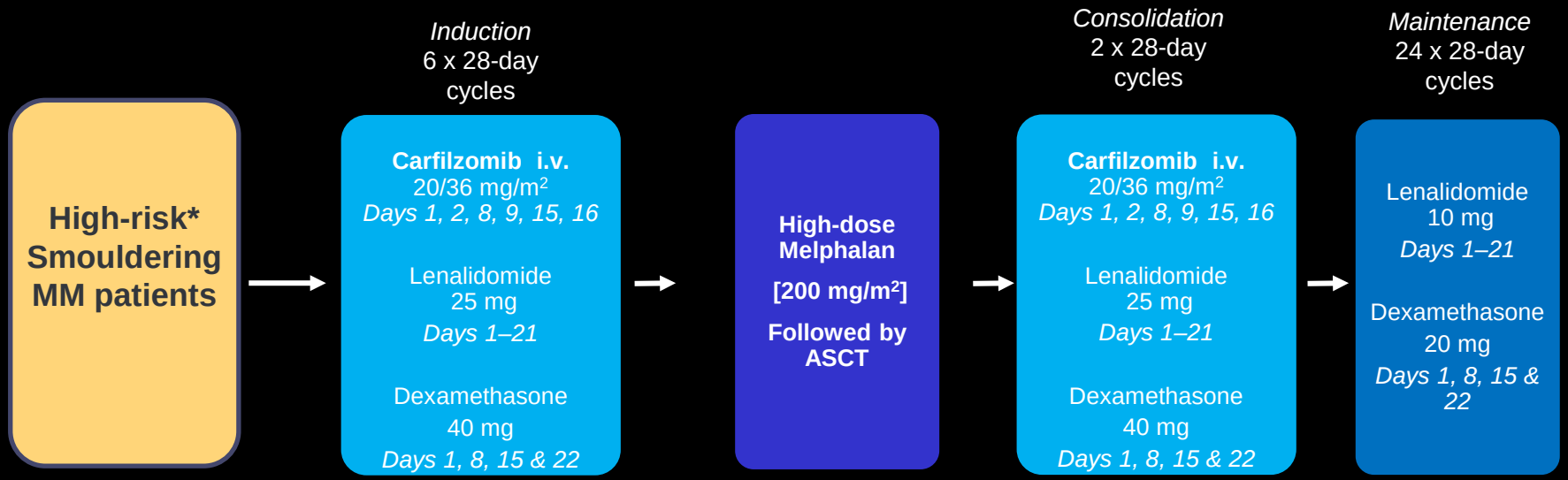


Early treatment with Rd significantly delayed the TTP to Myeloma with a benefit in OS

Mateos MV, et al. NEJM 2013
Mateos MV, et al. Lancet Oncology 2016

GEM-CESAR: Study Design

- Multicenter, open-label, randomized phase II trial



High-risk was defined according to the Mayo and/or Spanish models

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening and if bone disease was detected in the CT or PET-CT, patients were excluded

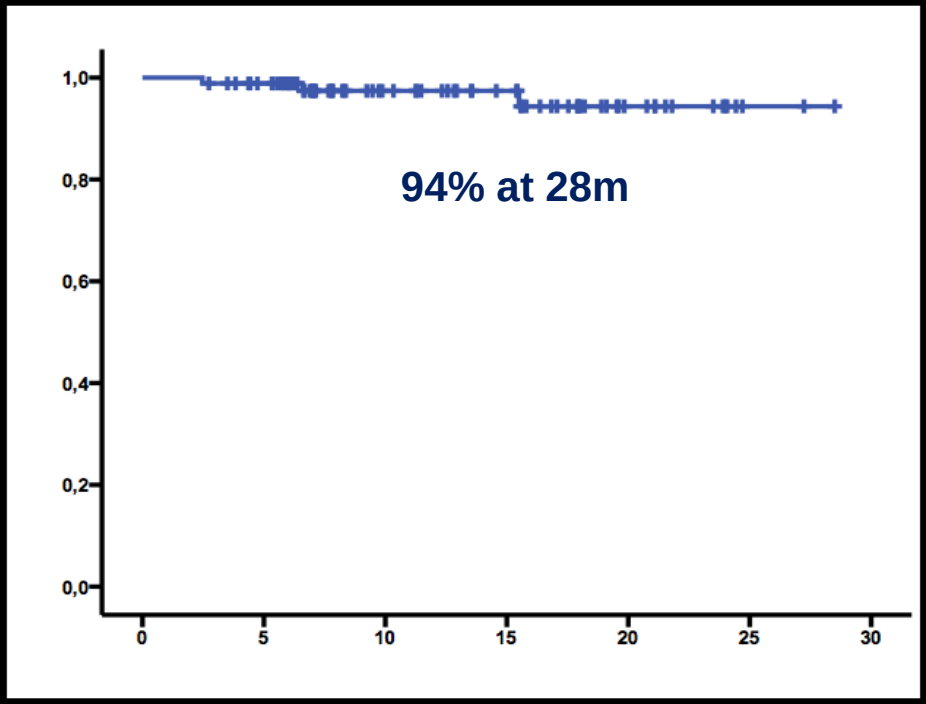
GEM-CESAR: Efficacy

Response category	Induction (n=71)	HDT-ASCT (n=42)	Consolidation (n=35)	Maintenance (n=29)
ORR	**69 (98%)**	**42 (100%)**	**35 (100%)**	**29 (100%)**
sCR	21 (**30%**)	22 (**52%**)	24 (**69%**)	24 (**83%**)
CR	9 (**13%**)	2 (**5%**)	2 (**6%**)	2 (**7%**)
VGPR	27 (38%)	12 (29%)	7 (20%)	2 (7%)
PR	12 (17%)	6 (14%)	2 (6%)	1 (3%)
SD				
Biological progression	2 (3%)	-	-	-
Clinical progression	-			-

GEM-CESAR Outcomes

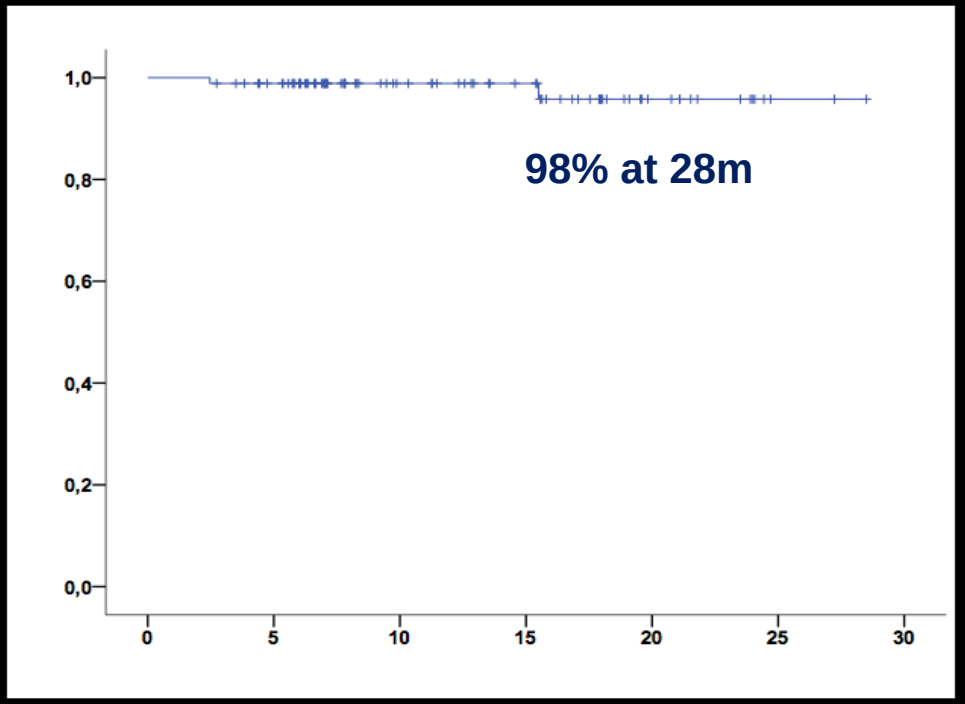
Median follow-up: 10 (1-28)

PFS



Two patients experienced biological relapse at the end of induction and they proceeded to subsequent therapy

OS

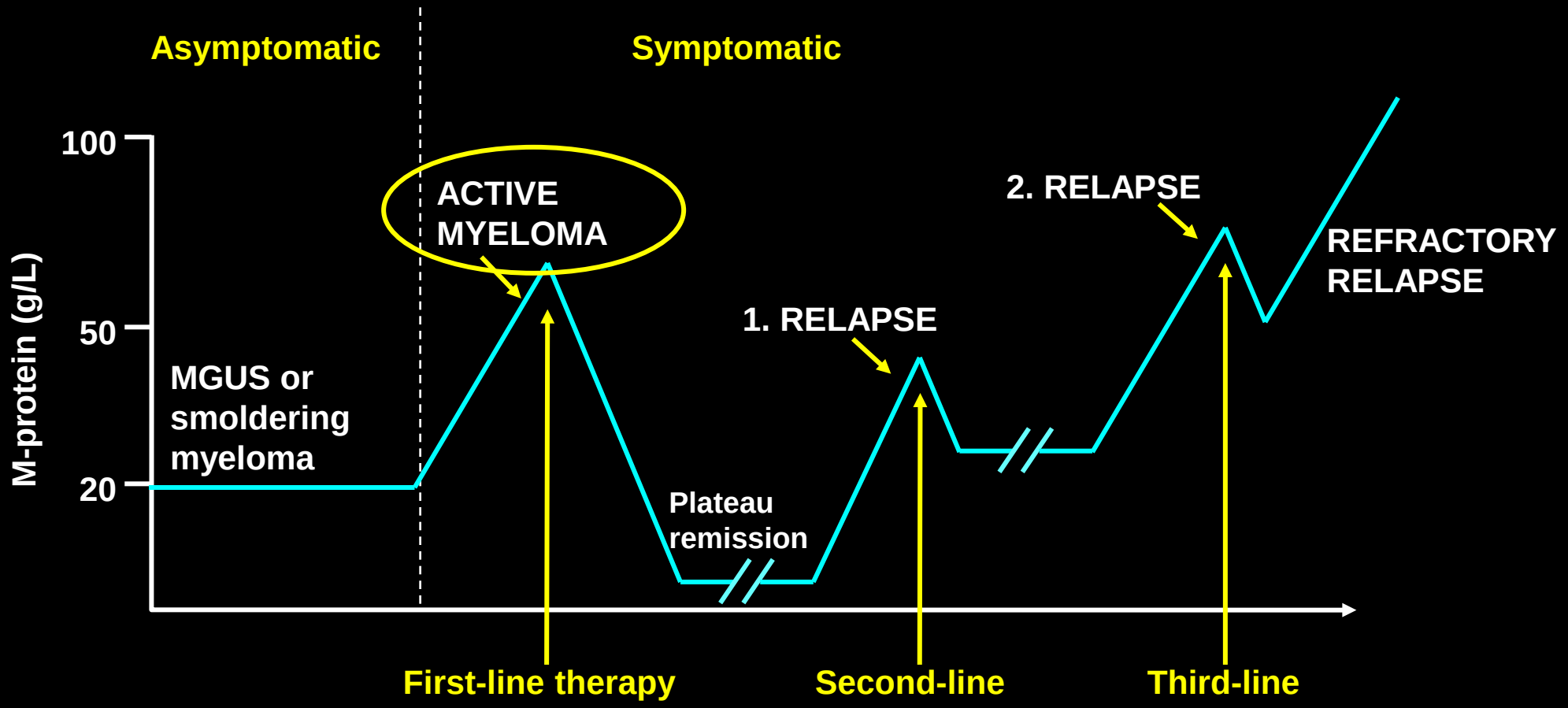


Two patients died: one patient who progressed and was refractory and died due to disease progression; other patient due to massive stroke during induction

What is the future in the management of MM patients?

- Early treatment for selected asymptomatic myeloma patients to be cured

Natural History of Multiple Myeloma



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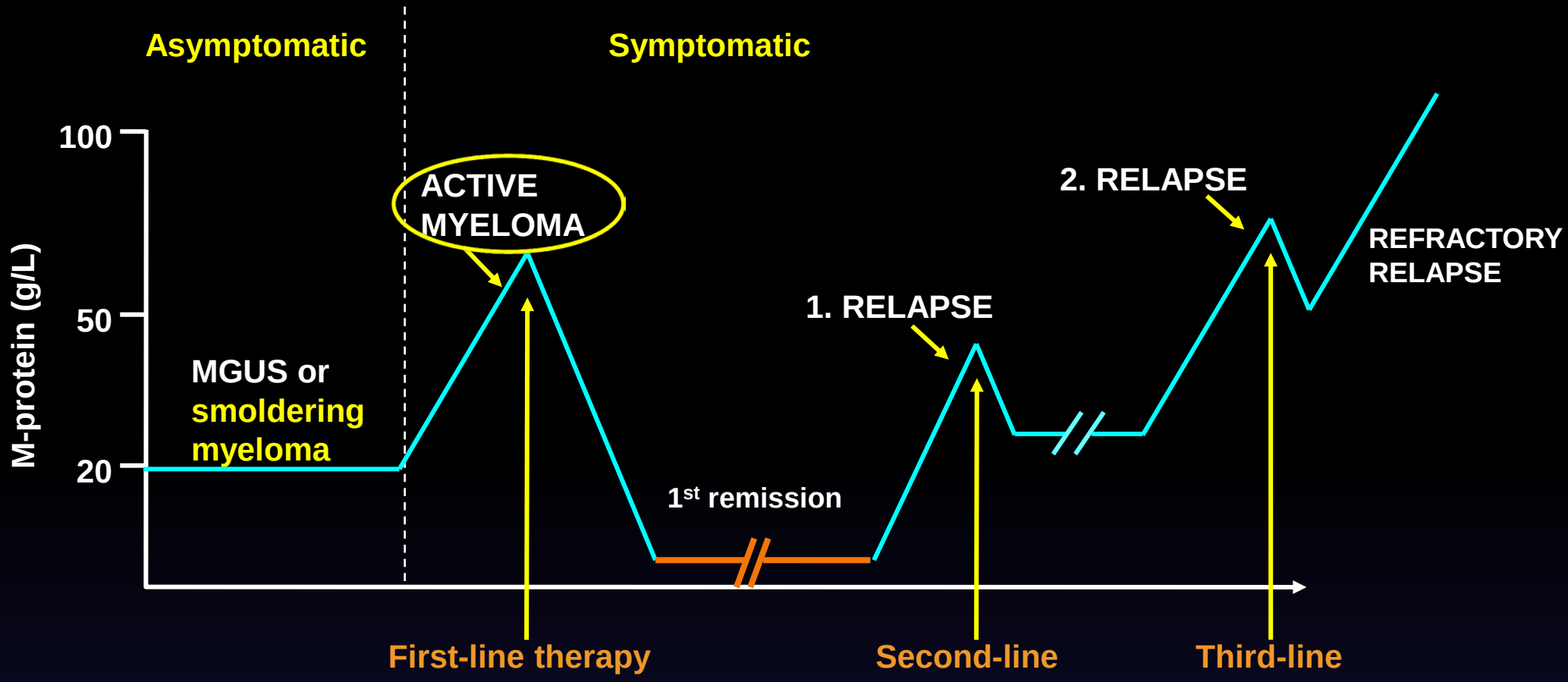
Natural History of MM



MGUS, monoclonal gammopathy of undetermined significance

Management of MM in the transplant candidate ND patient

Induction

Three-drug based combon:

- *VTD*
- *VRD*
- *VCD*
- *PAD*

- **RVD is the standard of care in US**
- **It is becoming the new standard of care in the non-US countries.**
- **CyBorD can be also used as induction regimen**
- **Number of cycles: 4-6**

ASCT MEL200

- **MEL200 is the standard conditioning regimen**

Maintenance Len
Bortezomib

- **Len single agent as continuous treatment until DP**
- **Bor in patients with high risk CA after tandem ASCT**

According to the ESMO & NCCN guidelines

Management of MM in the transplant candidate ND patient

Induction regimens

Induction Regimen	Number of Cycles	Phase	Study Details	Response Postinduction (%) CR	Response Postinduction (%) ≥VGPR
VTD vs TD[2]	6	3	VBMCP/VBAD + V vs TD vs VTD induction + α-IFN, thalidomide, or thalidomide/bortezomib maintenance	35 14	60 29
RVD[6]	6	Pethema Group 455 pts	Phase 3: RVd induction in 458 NDMM	39	87

Toxicity profile of RVD is better than VTD and is becoming our new standard induction regimen

1. Cavo M et al. *Lancet.* 2010;376:2075.
2. Rosinol L et al. *Blood.* 2012;120:1589.
3. Richardson PG et al. *Blood.* 2010;116:679.
4. Roussel M et al. *J Clin Oncol.* 2014; 32:2712
5.Attal M. NEJM 2017
6.Rosiñol L et al. ASH 2017

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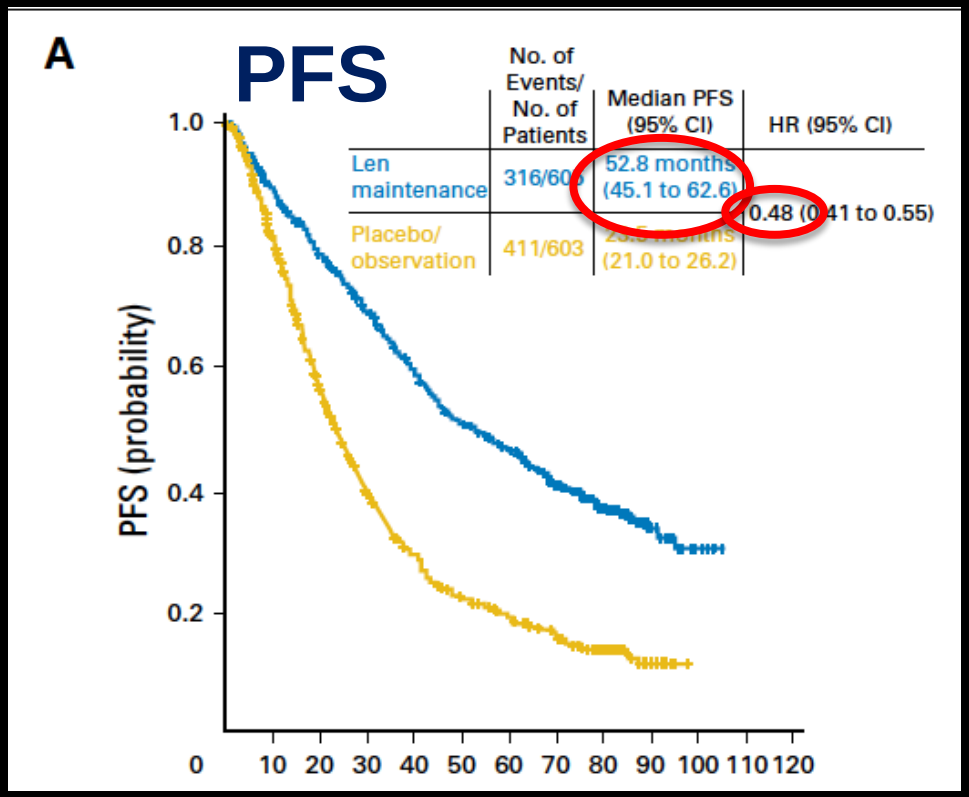
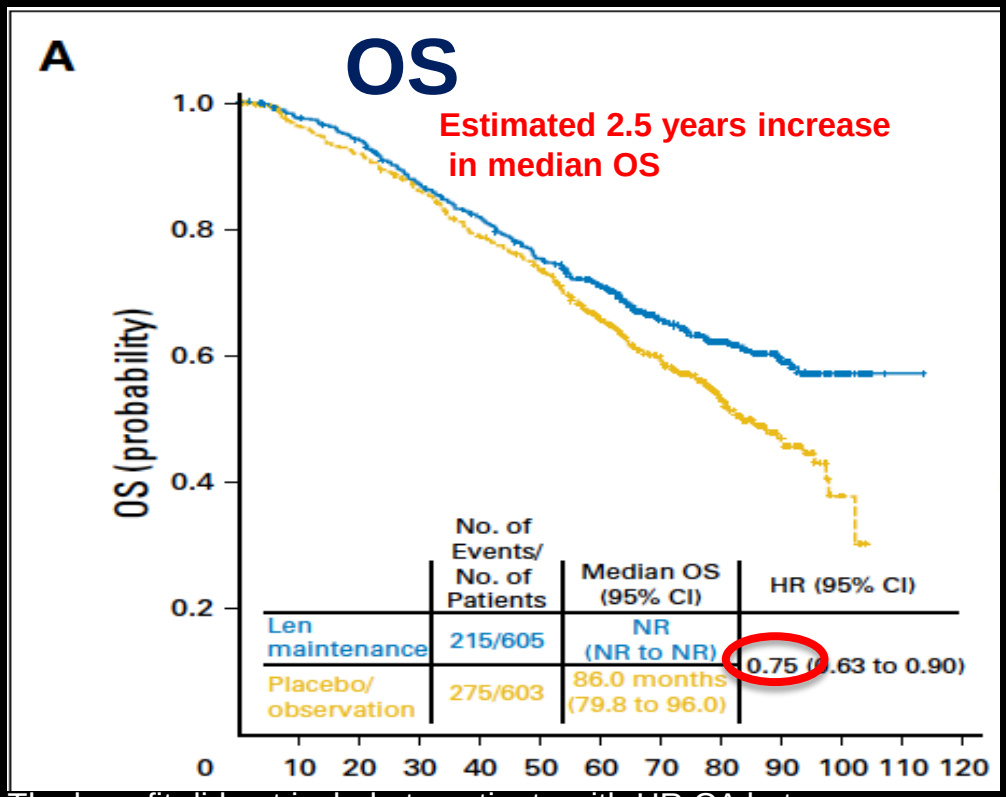
Management of MM in the transplant candidate ND patient

Maintenance after HDM-ASCT: metaanalysis of CALGB, IFM and GIMEMA trials



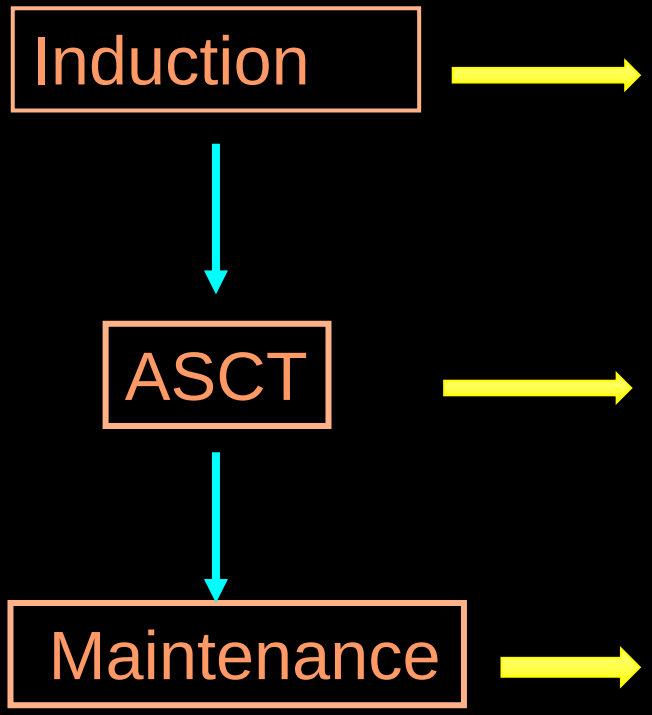
The benefit included also to patients with HR CA but many patients had not the cytogenetic information



The benefit did not include to patients with HR CA but many patients had not the cytogenetic information

McArthy P et al. JCO 2017

Management of MM in the transplant candidate ND patient: future



Three-drug based combinations:
- *Second generation PIs:* KRd, KTd, IRd

Three-drug based combinations plus mAb
- VTD plus/minus Daratumumab
- RVD plus/minus Elotuzumab
- RVD plus Isatuximab

MEL200 vs BuMel: BuMel superior
MEL200 plus/minus Bz: no superiority

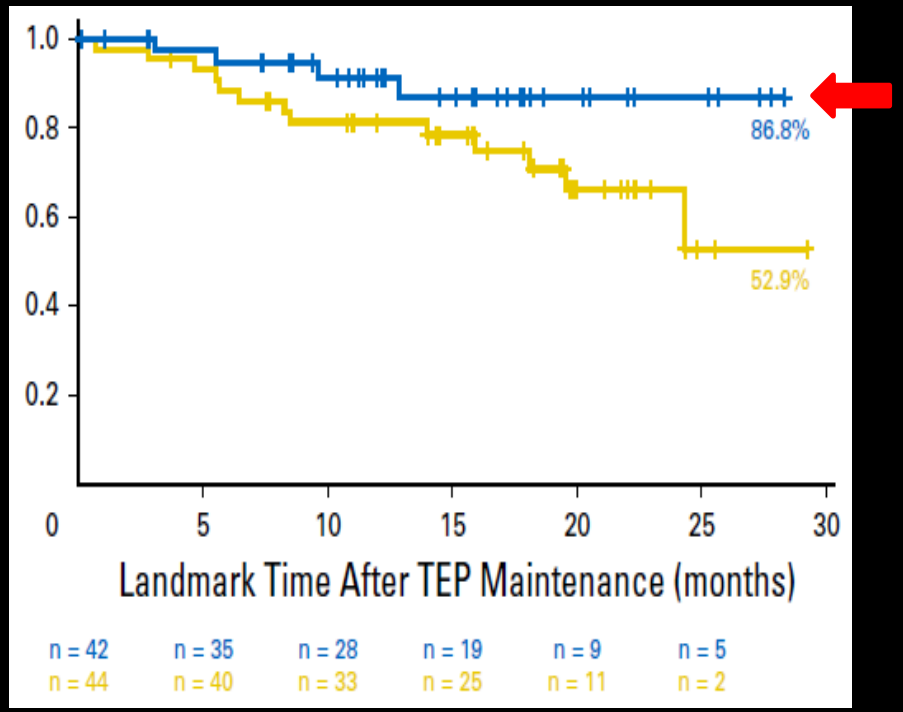
Many trials evaluating:
i) continuous vs fixed duration
ii) duration driven by MRD status
iii) Ixazomib as oral PI
iv) monoclonal antibodies

Would be also possible to reserve the ASCT at relapse in selected patients achieving minimal residual disease negative at high sensitivity level after induction

Impact of MRD –ve inside and outside of the bone marrow

PFS for patients with negative PET-CT and negative MRD by flow

VRD as induction followed by HDT-ASCT/VRD consolidation and len maintenance



Moreau et al. J Clin Oncol 2017

What is the future in the management of MM patients?

- **Early treatment** for selected asymptomatic myeloma patients to be cured
- **Young NDMM patients:**

  - Near future: RVD→ASCT—>Maintenance with Len

  - Future: Second generation PIs and Mabs as part of induction, better conditioning regimen before ASCT and optimization of maintenance. Optimal sequencing guided by MRD evaluation

Management of MM in the non-transplant candidate ND patient

- Alkylators-based induction regimens
- Non-alkylators-based induction regimens

Elderly MM patients are an heterogeneous group

Moderately fit:

Not regularly active but Routinely walking

Very fit:

active, who exercise regularly

Severely frail:

Dependent on other people

Mildly frail:

Help for household tasks

Moderately frail:

Partial help for their personal care

Vulnerable:

Can perform limited activities but they don't need any help

Palumbo A. Blood 2011; 118:4519-29

New standards of care for elderly MM patients

Alkylators-based regimens

MP → VMP

One randomized trial:
Benefit in PFS...8m
OS...13m

Alkylators-free regimens

IMiD's → Len-dex

One randomized trial:
Benefit in PFS&OS vs MPT

Is it possible to combine Bortezomib and Len in elderly?

San Miguel. N Engl J Med 2008;359:906-17
San Miguel . J Clin Oncol. 2013; 31: 448-55

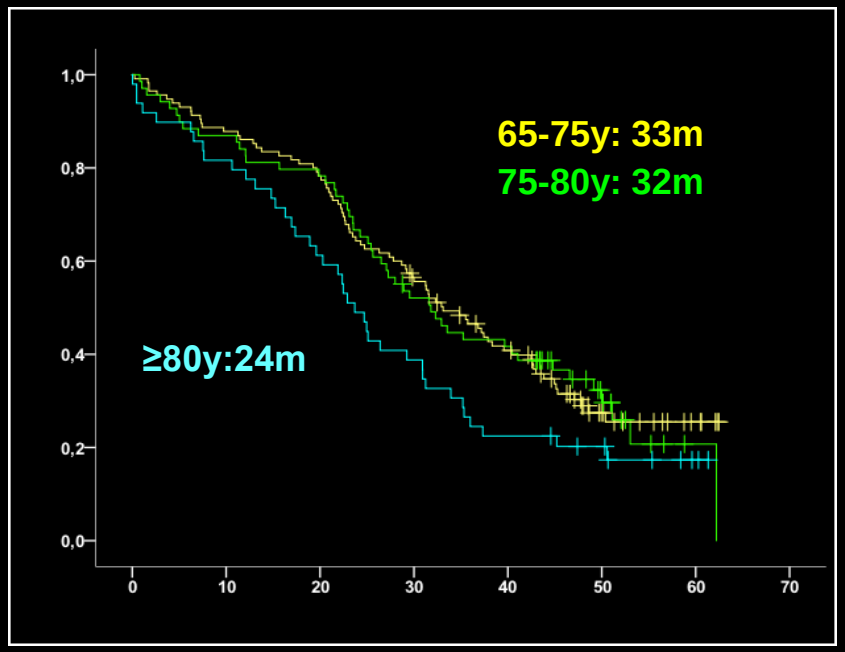
Benboubker L, et al. NEJM 2014; 371: 906-17

GEM2010 trial: VMP-Rd x 18 cycles in alternating/sequential approach (n=233)

ORR: 80% with 49% CR rate in the group between 65-75 years

Median follow-up: 51m (29-64)

PFS

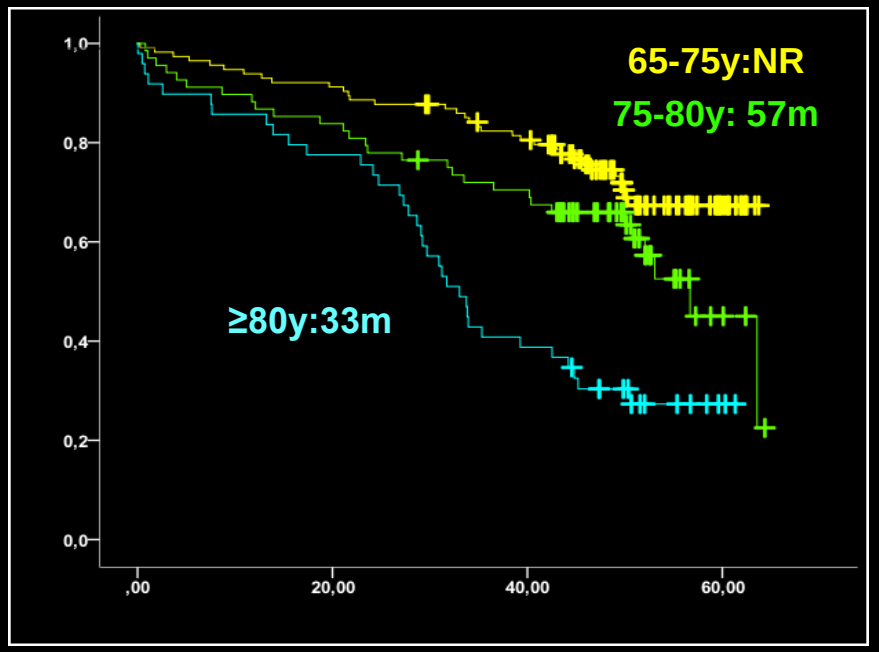


65-75 vs 75-80→ p= 0.9

65-75 vs ≥ 80→ p= 0.03

75-80 vs ≥ 80→ p= 0.07

OS



65-75 vs 75-80→ p= 0.05

65-75 vs ≥ 80→ p< 0.0001

75-80 vs ≥ 80→ p= 0.002

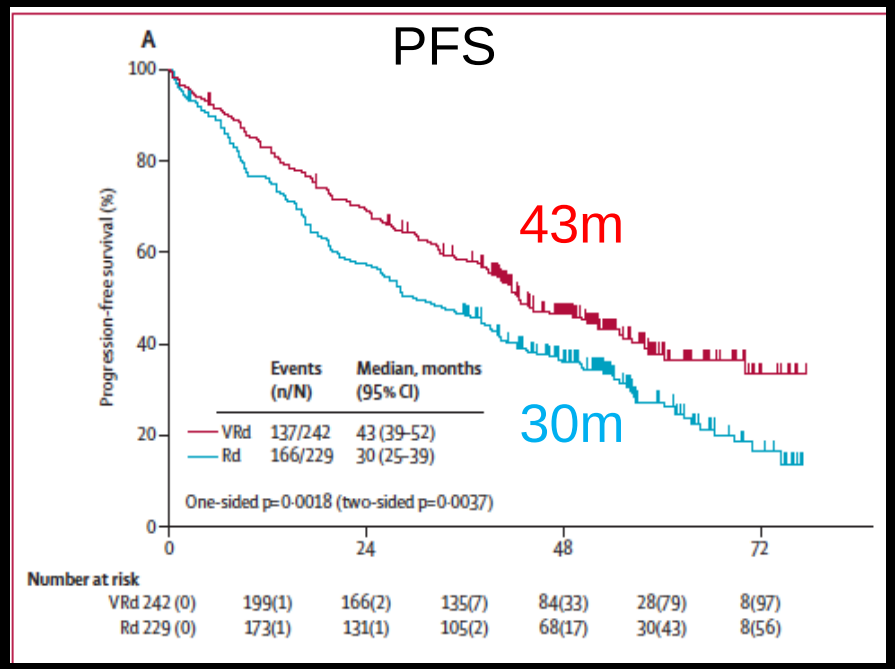
AEs: 4% of Grade 3-4 PN

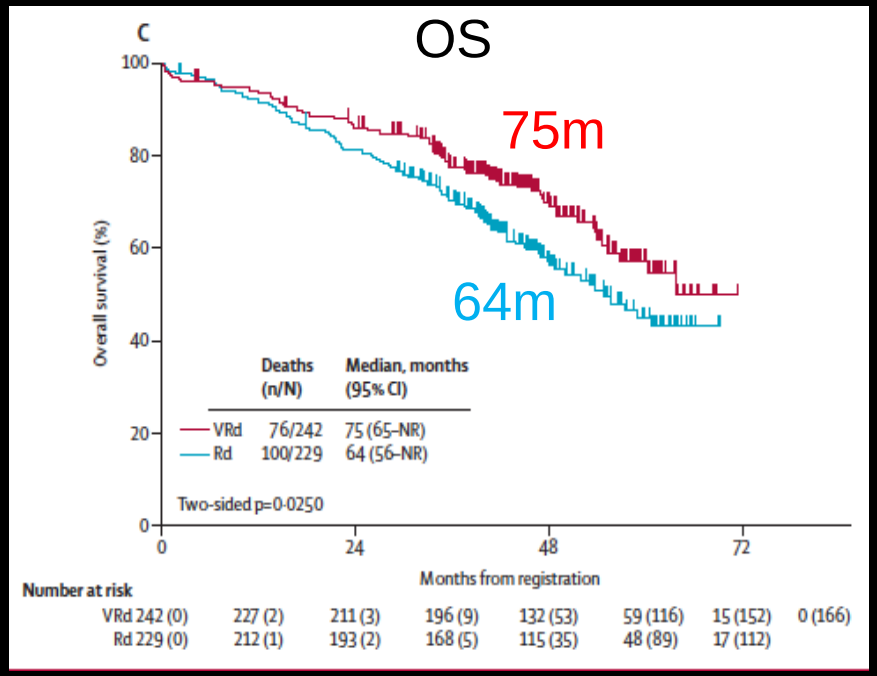
Mateos MV EHA 2017

VRd-->Rd vs continuous Rd: SWOG

Bortezomib twice a week IV x 8 cycles

ORR (CR) (%): 81(16) vs 71(8)





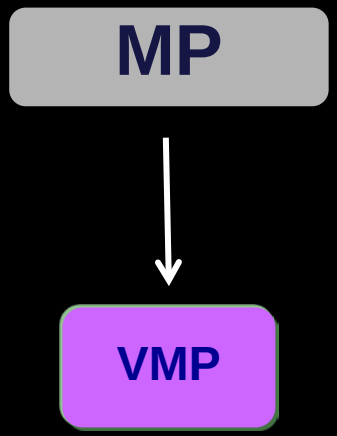
SWOG study was not specifically conducted in elderly patients with newly diagnosed MM

G3-4 AEs: PN (33%)

Durie B et al. Lancet 2017

New standards of care for elderly MM patients: future

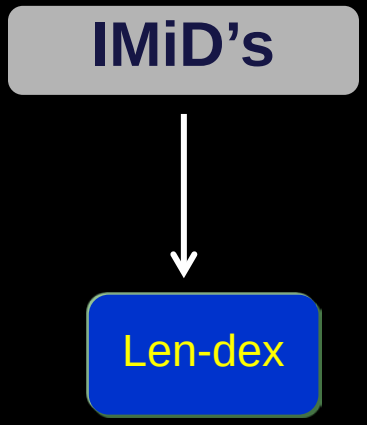
Alkylators-based regimens



New potential new standards

- KMP = VMP
- CyBorD-Isatuximab
- VMP-Dara vs VMP→LBA

Alkylators-free regimens



New potential new standards

- Len-dex + Elotuzumab
- Len-dex + Ixazomib
- Len-dex + Daratumumab
- Len-dex + Carfilzomib
- Len-dex + Carfilzomib + Dara
- Len-dex + Bortezomib + Isa
- Len-dex + Bortezomib

What is the future in the management of MM patients?

- **Early treatment** for selected asymptomatic myeloma patients to be cured
- **Young NDMM patients:**
  - **Near future:** RVD→ASCT—>Maintenance with Len
  - **Future:** Second generation PIs and Mabs as part of induction, better conditioning regimen before ASCT and optimization of maintenance. Optimal sequencing guided by MRD evaluation
- **Elderly NDMM patients:**
  - **Near future:** VMP->Rd/R as continuous or RVD
  - **Future:** VMP plus Dara and all Rd-based combinations with especial emphasis on Rd plus Daratumumab or KRd-Daratumumab

GEM2017FIT

(R1) Induction 18 cycles

Consolidation

(R2) Maintenance

NDMM patients NS CTC >65 y n= 462 elderly Fit Patients (GHA)

Rd

LEN: 25 mg, d1–21
DEX: 20/10 mg, d1, 2, 8, 9, 15, 16, 22, 23

Nine 28-day cycles

MRD+

No maintenance

MRD-

No maintenance

Directly to the R2 maintenance fase

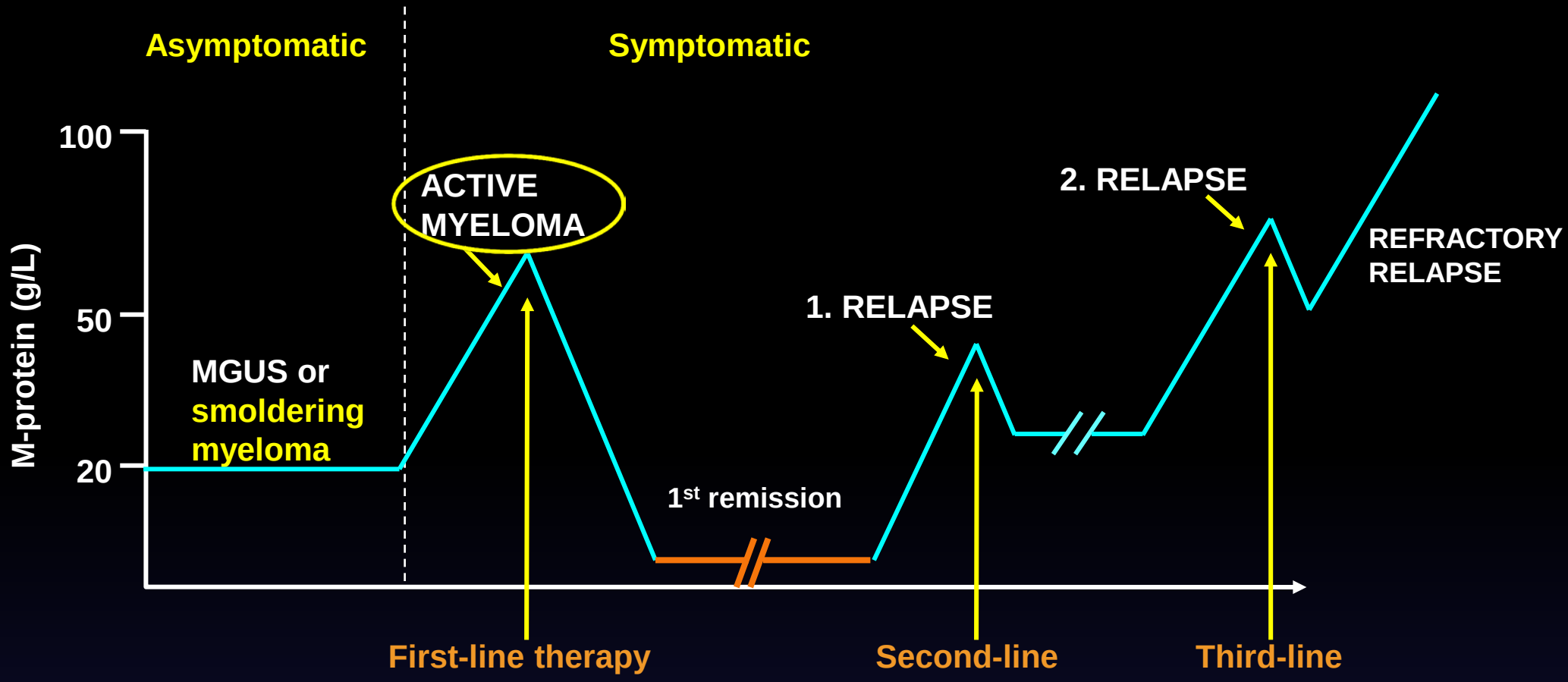
MRD 9 cy

MRD 18 cy

MRD 22 cy

[a]During the first cycle (6 weeks), bortezomib is given on D1, 4, 8, 11, 22, 25, 29, and 32.; GAH: J Geriatr Oncol.

Natural History of MM



The first remission is now longer than in the past and we can potentially cure some standard risk patients at this stage but……. Most patients will finally relapse so new options are necessary

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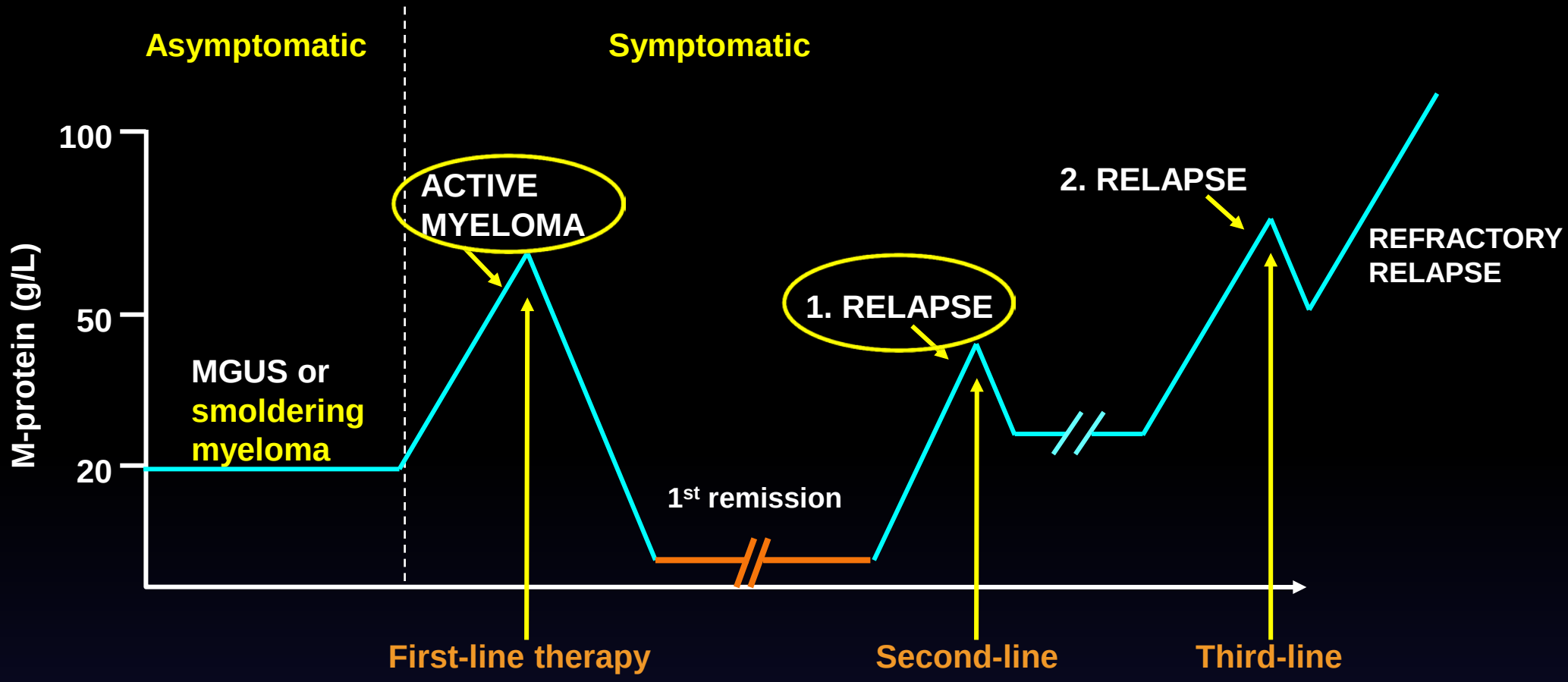

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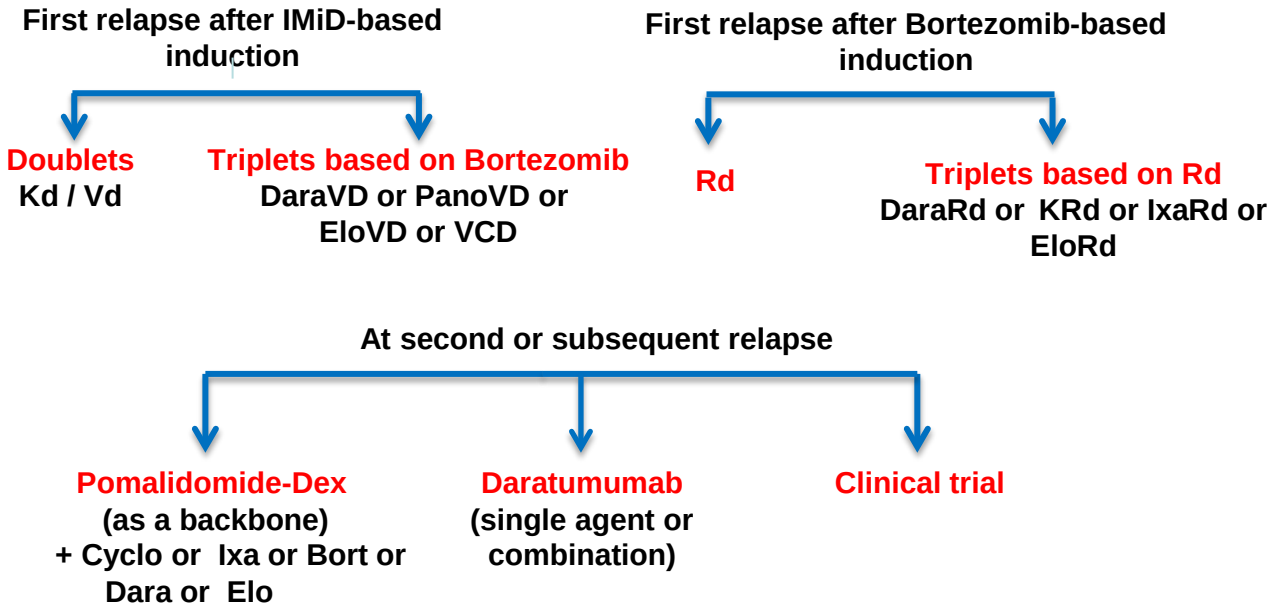
RELAPSE / REFRACTORY MULTIPLE MYELOMA
ESMO guidelines 2017



Moreau P, et al. Ann Oncol 2017;28(suppl_4):iv52-iv61.

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

1st relapse

Rd
Continuous therapy as backbone

- Carfilzomib plus Rd
- Elotuzumab plus Rd
- Daratumumab plus Rd
- Ixazomib plus Rd

1. Stewart AK, et al. N Engl J Med 2015;372:142-52; 2. Lonial S, et al. N Engl J Med 2015; 373(7):621–31;
3. Plesner T et al. presented at ASH 2015 (Abstract 507), oral presentation; 4. Moreau P et al. NEJM 2016;374(17):1621-34.

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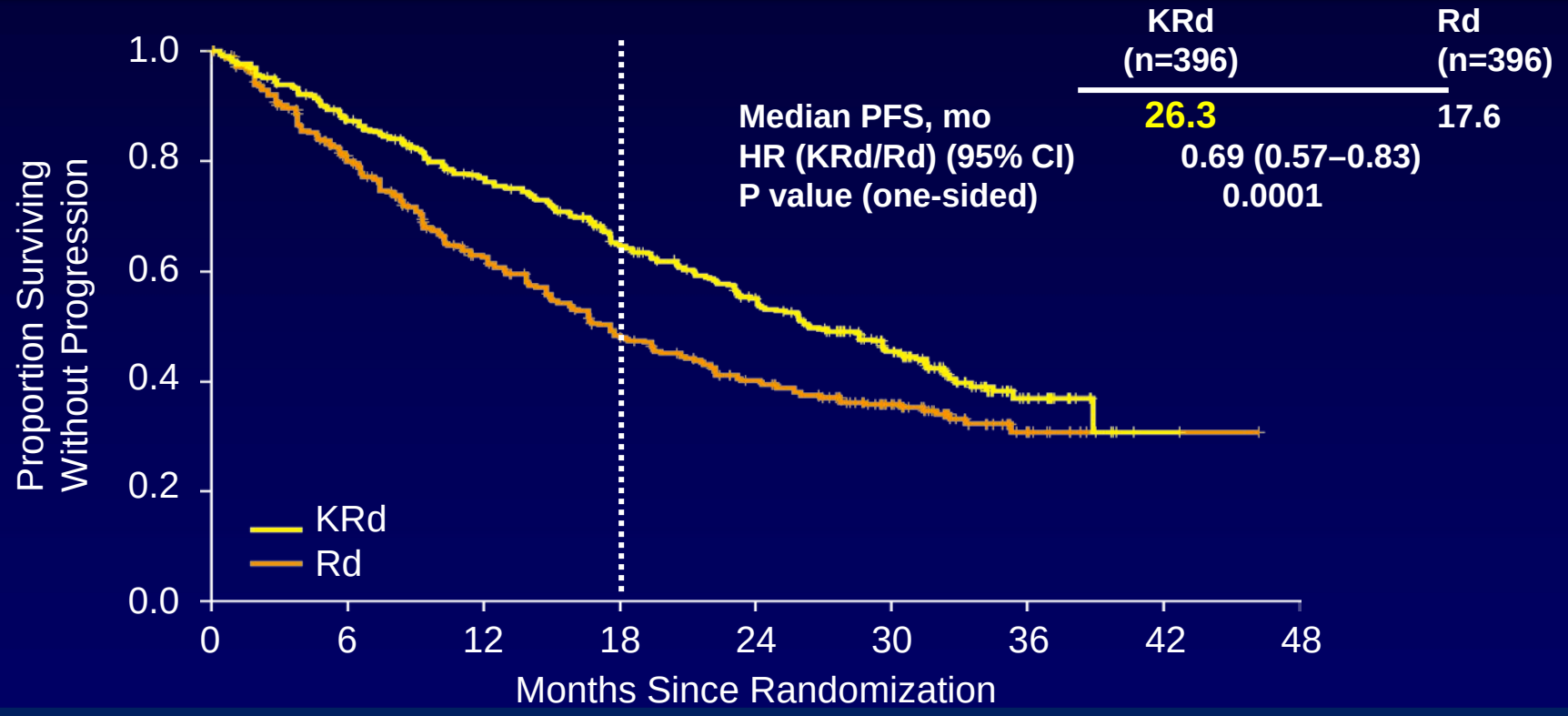
ASPIRE: KRd vs Rd *(N=792)*

ORR: 87% vs 66%
≥CR rate: 32% vs 9%



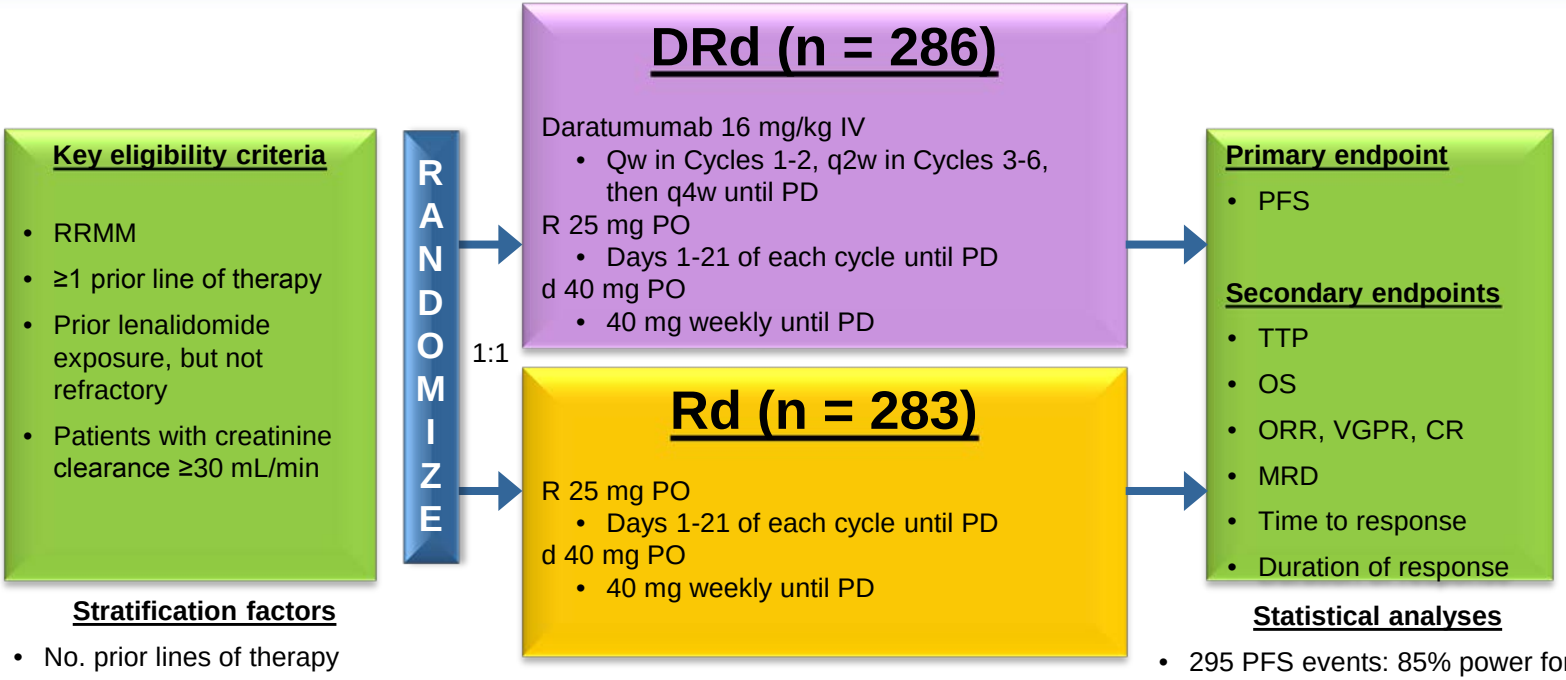
Median follow-up was 32.3 months for KRd and 31.5 months for Rd

KRd-treated patients had a 31% reduction in the risk of disease progression or death in comparison with Rd

Stewart AK, et al. N Engl J Med 2015;372:142-52

POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study



Stratification factors

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

Cycles: 28 days

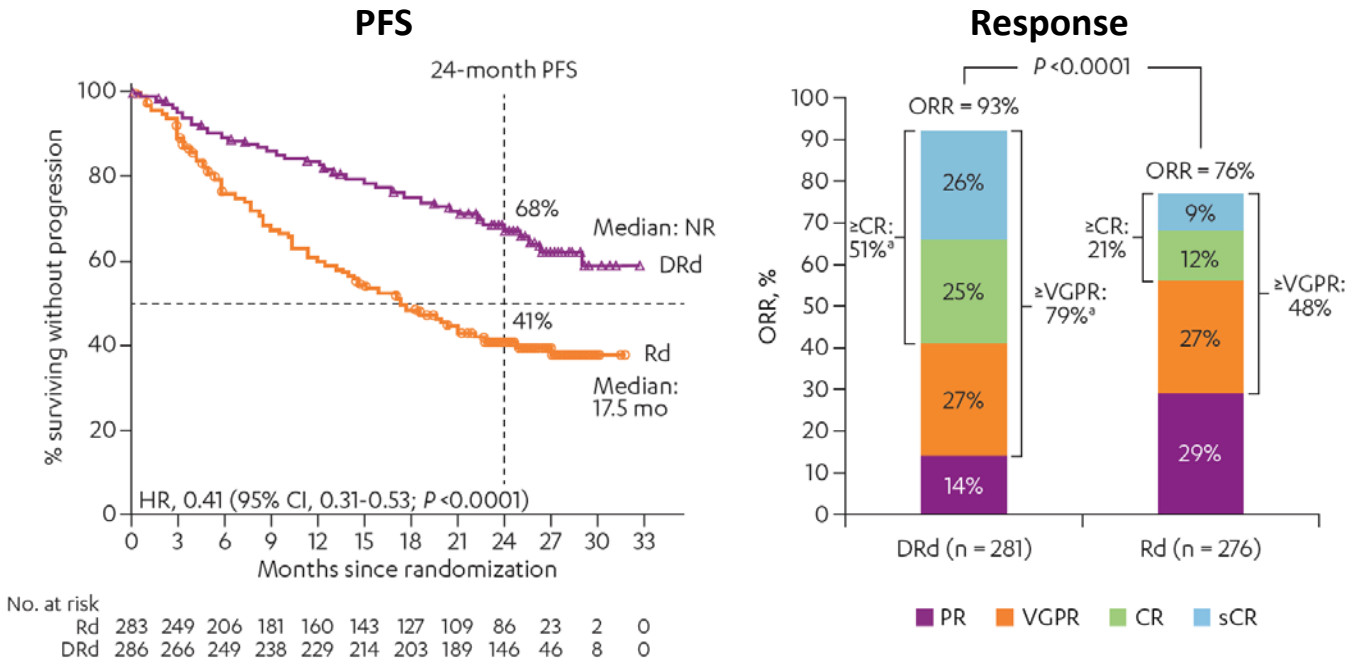
Statistical analyses

- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.

POLLUX update: Dara-Rd vs Rd

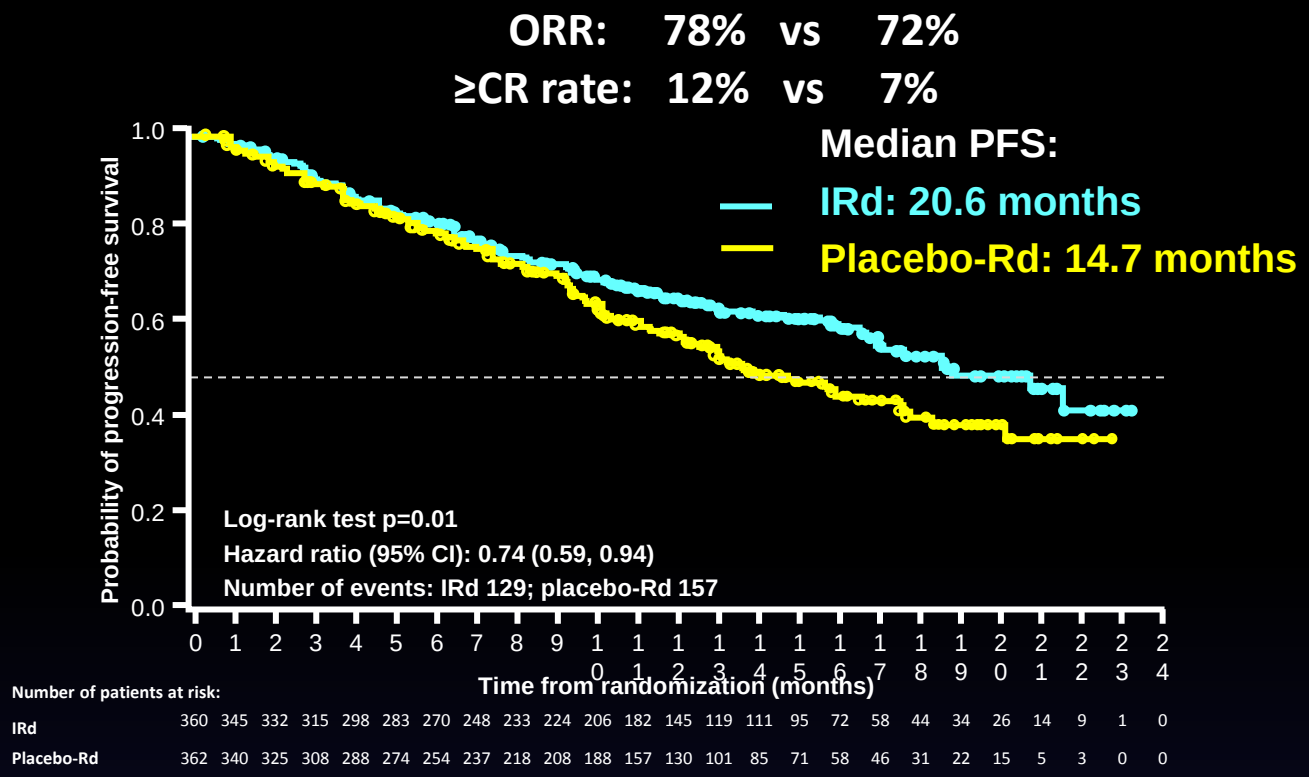


- Median follow-up of 25.4 months

DRd-treated patients had a 59% reduction in the risk of progression or death vs Rd
Deep responses continue in the DRd group with longer follow-up

Bahlis NJ, et al. Poster presentation at ASCO 2017. Abstract 8025.

Tourmaline-MM1: IRd vs placebo-Rd: three-drug based regimen of oral administration



- Median follow-up: 14.8 months in the IRd group and 14.6 months in the placebo-Rd group

26% reduction in the risk of progression of death

Moreau P et al. N Engl J Med 2016;374(17):1621-34

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

1st relapse

Rd
Continuous therapy as backbone

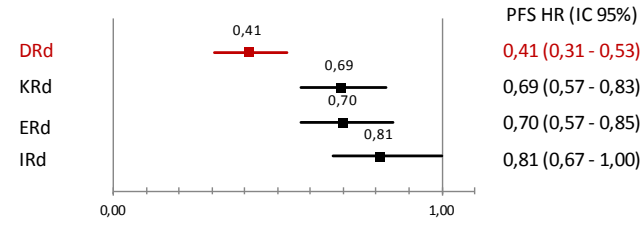
- Carfilzomib plus Rd
- ~~Elotuzumab plus Rd~~
- Daratumumab plus Rd
- Ixazomib plus Rd

1. Stewart AK, et al. N Engl J Med 2015;372:142-52; 2. Lonial S, et al. N Engl J Med 2015; 373(7):621–31;
3. Plesner T et al. presented at ASH 2015 (Abstract 507), oral presentation; 4. Moreau P et al. NEJM 2016;374(17):1621-34.

If we would have all available combinations…..
How to choose if we consider the efficacy?

vs. Rd
(after at least 1PL)

Hazard ratios for PFS



Secondary end-points: CR rates and MRD

	median PFS	CR	MRD
DRd[1]	NR (>30m)	51.3%	33.9%
KRd[2]	26.3m	31.8%	-
ERd[3]	18.5m	4.4%	-
IRd[4]	20.0m	14.2%	-

1 POLLUX update analysis ASCO 2017 "*data on file*" I 2 EPAR KYPROLIS EMEA/H/C/003790/0000 I 3 EPAR EMPLICITY EMEA/H/C/003967/0000 I 4 EPAR NINLARO EMEA/H/C/003844/0000 (data cut-off 12 July 2015)

Adverse events of interest

Study	Combination (N)	Adverse event	Experimental arm, n (%)	
			Any grade	Grade ≥3
ASPIRE[1]	Rd + Carfilzomib (392)	**Hypertension** **Cardiac failure** **Acute renal failure**	56 (14.3) 25 (6.4) 33 (8.4)	17 (4.3) 15 (3.8) 13 (3.3)
ELOQUENT-2[2]	Rd + Elotuzumab (318)	**Infusion reaction**	33 (10)	(1)
TOURMALINE[3]	Rd + Ixazomib (361)	**Rash**	131 (36)	18 (5)
POLLUX[4]	Rd + Daratumumab (283)	**Infusion reaction**	135 (47.7)	15 (5.3)

1. Stewart AK, et al. N Engl J Med. 2015;372(2):142-152.
2. Dimopoulos MA et al. Br J Haematol 2017, Epub ahead of print.
3. Moreau P, et al. N Engl J Med. 2016;374(17):1621-1634.
4. Dimopoulos MA et al. N Engl J Med 2016;375:1319-31

Options of therapy for RRMM patients

Induction Bortezomib-based combination → **ASCT** (melphalan 200) → **Nothing/Consolidation/Maintenance**

Lenalidomide

Induction Bortezomib-based combo

Lenalidomide-dex

Lenalidomide

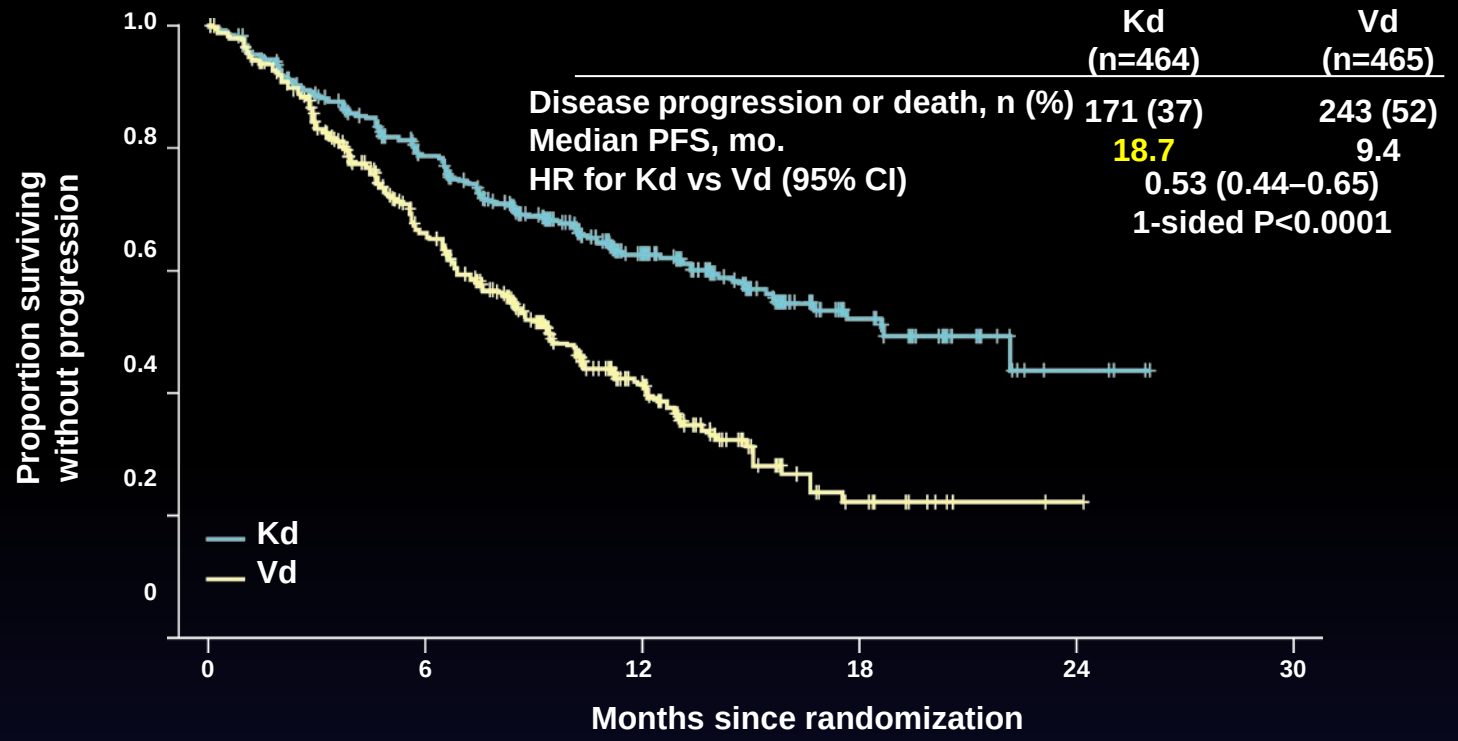
1st relapse

PI's based combinations		IMiD's based combinations	
Kd HR:0.53 PFS: 18.7 months[1]	**VD + Daratumumab** HR:0.33 PFS: NR[7]	**Carfilzomib plus Rd** PFS: 26.3m, HR: 0.69[2]	**Elotuzumab plus Rd** PFS: 19.4m, HR: 0.73[3]
~~**Panobinostat-bz/cz**~~ ~~HR:0.63 PFS: 12 months[6]~~	~~**Elo-Rd**~~ ~~HR: 0.72 PFS: 9.7 m[8]~~	**Daratumumab plus Rd** PFS: NR, HR: 0.37[4]	**Ixazomib plus Rd** PFS: 20.6m, HR: 0.74[5]

1. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38 ; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Dimopoulos MA et al. presented at ASH 2015 (Abstract 28), oral presentation; 4. Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral presentation; 5. Moreau P et al. N Engl J Med 2016;374(17):1621-34; 6. San Miguel JF, et al. Lancet Oncol. 2014;15(11):1195-1206; 7. Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation; 8. Jakubowiak A et al. Blood 2016: 127(23):2833-40

Endeavor trial: Kd at double dose (56 mg/m^2) vs Vd *(N=929)*

ORR: 77% vs 63%
≥CR rate: 13% vs 6%



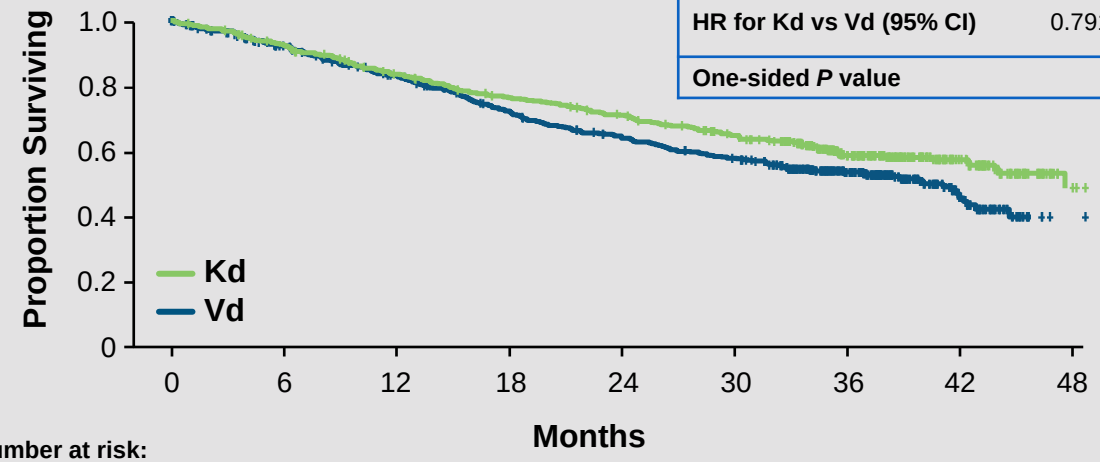
- **Significant prolongation of the Overall survival: 47 vs 40 months**

Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38

Overall Survival

Median follow-up: 37.5 months (carfilzomib), 36.9 months (bortezomib)

	Kd (n = 464)	Vd (n = 465)
Death, n (%)	189 (40.7)	209 (44.9)
Median OS, months	47.6	40.0
HR for Kd vs Vd (95% CI)	0.791 (0.648–0.964)	
One-sided *P* value	0.0100	



Number at risk:
(number censored)

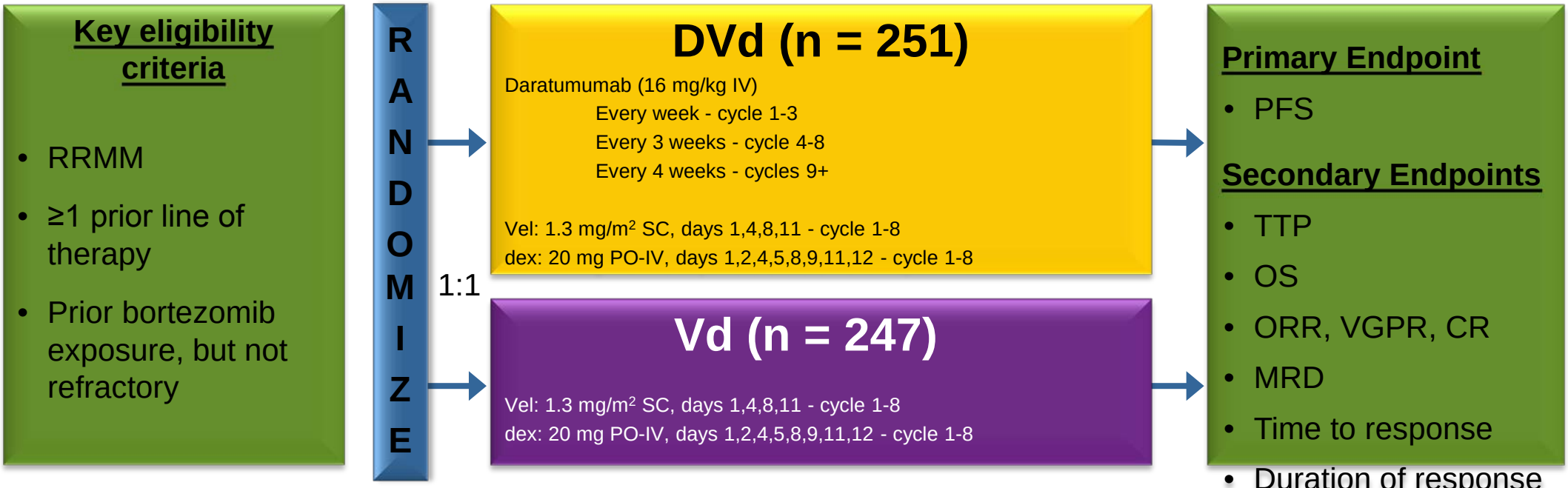
Kd	464 (0)	423 (7)	373 (16)	335 (21)	308 (25)	270 (35)	162 (121)	66 (215)	10 (266)
Vd	465 (0)	402 (28)	351 (40)	293 (50)	256 (56)	228 (58)	140 (130)	39 (221)	5 (251)

CI = confidence interval; HR = hazard ratio; Kd = carfilzomib and dexamethasone; OS = overall survival; Vd = bortezomib and dexamethasone.

Dimopoulos MA, et al. *Lancet Oncol.* Published Online August 23, 2017 as doi:10.1016/S1470-2045(17)30578-8.

CASTOR: Study Design

Multicenter, randomized, open-label, active-controlled phase 3 study



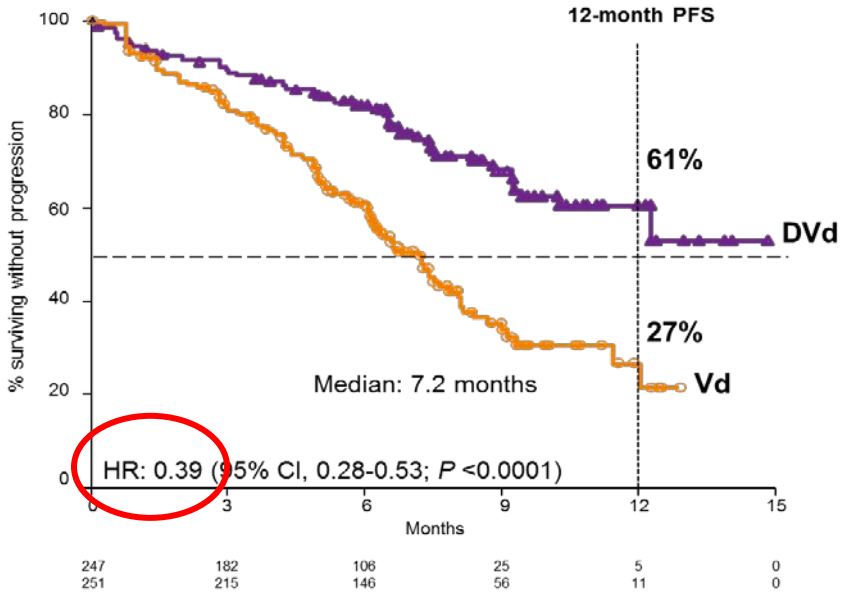
- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

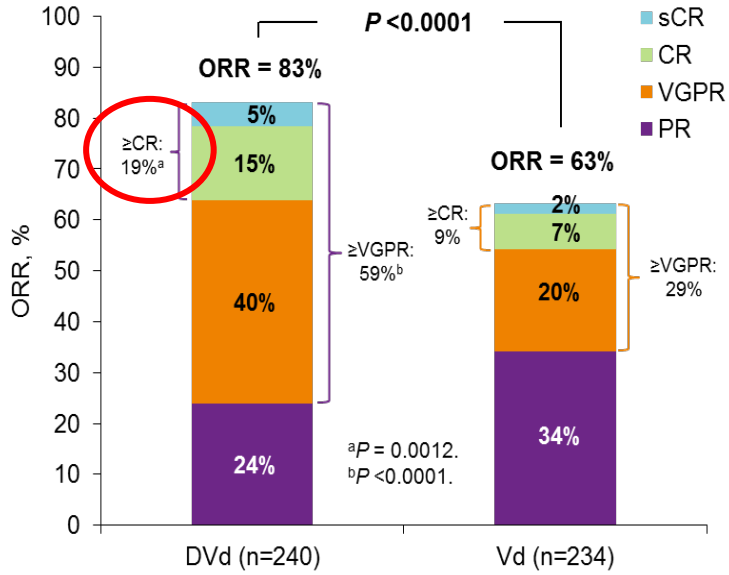
Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

CASTOR: Primary Analysis Results[1]

Median follow-up: 7.4 months





- **Hazard ratio (HR): 0.39; 61% reduction in the risk of progression or death with DVd versus Vd**

CI, confidence interval; sCR, stringent complete response; PR, partial response.

1. Palumbo A, et al. *N Engl J Med.* 2016;375(8):754-766.

Options of therapy for RRMM patients

Induction Bortezomib-based combination → **ASCT** (melphalan 200) → **Nothing/Consolidation/Maintenance**

Lenalidomide

Induction Bortezomib-based combo

Lenalidomide-dex

Lenalidomide

1st relapse

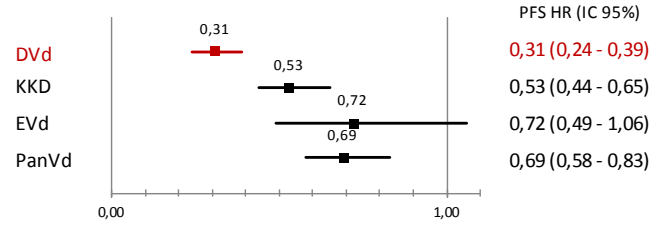
PI's based combinations		IMiD's based combinations	
Kd HR:0.53 PFS: 18.7 months[1]	**VD + Daratumumab** HR:0.33 PFS: NR[7]	**Carfilzomib plus Rd** PFS: 26.3m, HR: 0.69[2]	**Elotuzumab plus Rd** PFS: 19.4m, HR: 0.73[3]
~~**Panobinostat-bz/cz**~~ ~~HR:0.63 PFS: 12 months[6]~~	~~**Elo-Rd**~~ ~~HR: 0.72 PFS: 9.7 m[8]~~	**Daratumumab plus Rd** PFS: NR, HR: 0.37[4]	**Ixazomib plus Rd** PFS: 20.6m, HR: 0.74[5]

1. Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38 ; 2. Stewart AK, et al. N Engl J Med 2015;372:142-52; 3. Dimopoulos MA et al. presented at ASH 2015 (Abstract 28), oral presentation; 4. Usmani SZ, et al. Presented at ASH 2016 (Abstract 1151), oral presentation; 5. Moreau P et al. N Engl J Med 2016;374(17):1621-34; 6. San Miguel JF, et al. Lancet Oncol. 2014;15(11):1195-1206; 7. Mateos M, et al. Presented at ASH 2016 (Abstract 1150), oral presentation; 8. Jakubowiak A et al. Blood 2016: 127(23):2833-40

How to choose if we consider the efficacy?

vs. Vd
(after at least 1PL)

Hazard ratios for PFS



Secondary endpoints

	median PFS	CR	MRD
DVd[2]	16.7m	28.8%	18.7%
KKd[3]	**17.6m**	12.5%	-
Evd[1]	9.7m	3.9%	-
PanVd[4]	9.9m	14.2%*	-

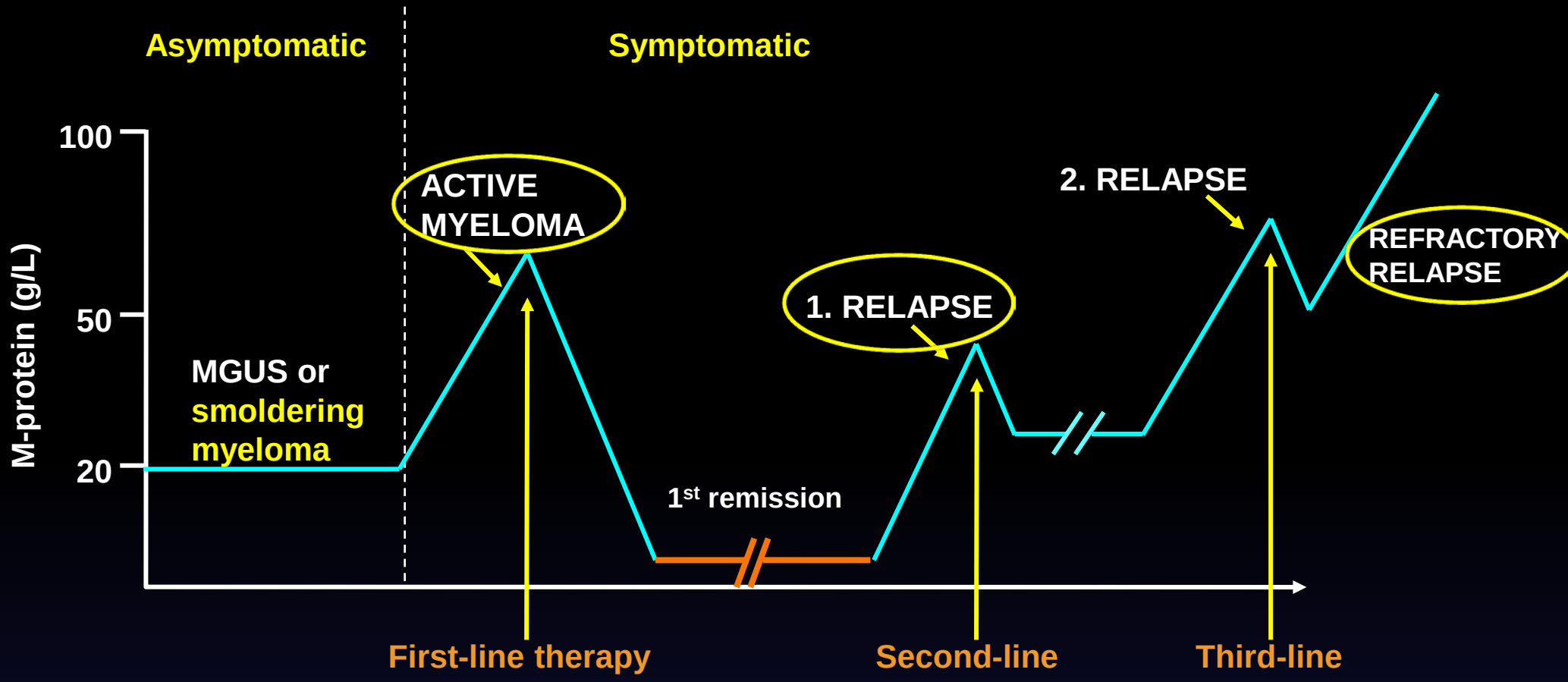
1 EPAR EMPLICITY EMEA/H/C/003967/0000 l 2 CASTOR update analysis ASCO 2017 l 3 Siegel et al, EHA 2017 l 4 FARIDAK EMEA/H/C/003725/0000 *INVESTIGATOR ASSESMENT

Adverse events of interest

Study	Combination (N)	Adverse event	Experimental arm, n (%)		
			Any grade	Grade 3	Grade 4
PANORAMA[1]	Vd + Panobinostat (381)	Diarrhea Fatigue Vomiting	260 (68) 217 (57) 98 (26)	92 (24) 86 (23) 25 (7)	5 (1) 5 (1) 3 (<1)
			Grade 1-2	**Grade 3**	**Grade 4**
ENDEAVOR[2]	Kd (463)	**Hypertension** **Dyspnea** **Cardiac failure**	74 (16) 107 (23) 16 (3)	41 (9) 25 (5) 17 (4)	0 0 3 (<1)
			Any grade	**Grade 3**	**Grade 4**
CASTOR[3]	Vd + Daratumumab (243)	**Infusion reaction**	110 (45.3)	21 (8.6)	0
		Hypertension	21 (8.6)	16 (6.6)	

1. San Miguel J, et al. Lancet Oncol. 2014 Oct;15(11):1195-206.
2. Dimopoulos MA, et al. Lancet Oncol 2016; 17: 27–38.
3. Palumbo A, et al. N Engl J Med 2016;375:754-66.

Natural History of MM



The first remission is now longer than in the past and we can potentially cure some standard risk patients at this stage but……. Most patients will finally relapse so new options are necessary

MGUS, monoclonal gammopathy of undetermined significance

Treatment Possibilities at 2nd + relapse

Induction Bortezomib-based combination
Lenalidomide

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance
Lenalidomide

Induction Bortezomib-based combo
Lenalidomide-dex

1st relapse

PI's based combinations

- Kd
- Vd-Daratumumab
- Vd plusPanobinostat
- Elo-Bd
- Selinexor-Bd
- Venetoclax-Bd

IMiD's based combinations

- Carfilzomib plus Rd
- Dara plus Rd
- Elotuzumab plus Rd
- Ixazomib plus Rd

Subsequent relapses

- Pom-Dex
- Daratumumab

How are we going to proceed in the clinical practice?

Comparison of Pom-Dex trials (& combinations)

	MM-003[1]	STRATUS (MM-010)[2]	Pom-Dex vs Pom-Cyclo-Dex[3]		Pom-Btz-Dex[4]
Treatment	**PD**	**PD**	**PD**	**PCD**	**PVD**
n	***302***	***682***	***36***	***34***	***47***
Population	***Failed Bort & Len & refr to last line***		***At least 2 prior lines & Len-refractory***		***1-4 prior lines & Len-refractory***
ORR, %	**31**	**32.6**	**39**	**65**	**85**
≥ VGPR, %			**14**	**12**	**45**
PFS, months	**4.0**	**4.6**	**4.4**	**9.5**	**10.7**
OS, months	**12.7**	**11.9**	**16.8**	**NR**	**94***

***EFS at 12 months**

1. San Miguel J, et al. Lancet Oncology 2013;14(11):1055-66.
2. Dimopoulos MA, et al. Blood 2016;128(4):497-503.
3. Baz RC, et al. Blood 2016;127:2561-2568
4. Lacy et al. ASH 2014. Abstract 304

The future: Pom/dex combinations

	POM + Vd[1]	K + POMdex[2]	Ixa + POMdex[3]	Dara + POMdex[4]	Isa+ POMdex	MOR202+ POMdex
Regimen	POM 1–4 mg PO D1–14 + BORT 1 mg/m² IV or 1.3 mg/m² IV or SC C1-8: D1,4,8,11; C9+: D1,8 + LoDex 20 mg (>75 y: 10 mg) C1-8: D1,2,4,5,8,9,11,12; C9+: D1,2,8,9 (n=34) †	Carfilzomib 20/27/36 mg/m² D1,2,15,16 + POM 3 or 4 mg/day D1–21 + Dex QW 40 mg C1–4 (20 mg C5–8) (n=46)‡ The same combination but K weekly (n=57)	Ixazomib 3 or 4 mg D1,8,15 + POM 4 mg/day D1–21 + Dex 40 mg D1,8,15,22 (>75 y: 20 mg) (All, n=32; Ixa 4 mg, n=25)	Daratumumab 16 mg/kg C1–2 QW; C3–6 Q2W; C7–13 or until PD Q4W + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (n=98)	Isatuximab 10 mg/Kg IV C1 QW; Q2W thereafter + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (m=14)	MOR202 at dose of 4, 8, 16 mg/kg QW + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (n=9=
Study phase	1	1/2	1/2	1	1/2	1/2
Prior lines of therapy, n	1–4		1–5 including PI and Len	≥2 (2–13)	4.5 (3-11)	2
Refractory to Len, n (%)	All patients were Len-refractory	40 (87)/41(72)	32 (100); 25 (100)	87 (89)	15(75)	9 (100)
Refractory to PI, n (%)	All pts were PI-exposed (but not refractory)	NR	20 (63); 15 (60)*	74 (76)	-	-
ORR, %	65	64/64	44	71	64	78
Median (range) DOR	7.4 (4.4–9.6) months	NR	56 (28-160) months	NR	4 months	-
Median PFS, months	NR	12.9/9.2	NR	6-m rate = 66%	-	-

D, day; Dex, dexamethasone; DOR, duration of response; IMiD, Immunomodulatory drug; Len, lenalidomide; NR, not reported; ORR, overall response rate; PI, proteasome inhibitor; PFS, progression-free survival

1.Richardson et al. Presented at EHA 2016; P653; 2. Rosenbaum et al. Presented at ASH 2015 (Abstract 8007); 3. Krishnan et al. Presented at ASCO 2016 (Abstract 8008), oral presentation; 4. Chari et al. Presented at ASH 2015 (Abstract 508), oral presentation

Treatment Possibilities at 2nd + relapse

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↓

ASCT (melphalan 200)

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Lenalidomide-dex

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- Vd plusPanobinostat
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IMiD's based combinations

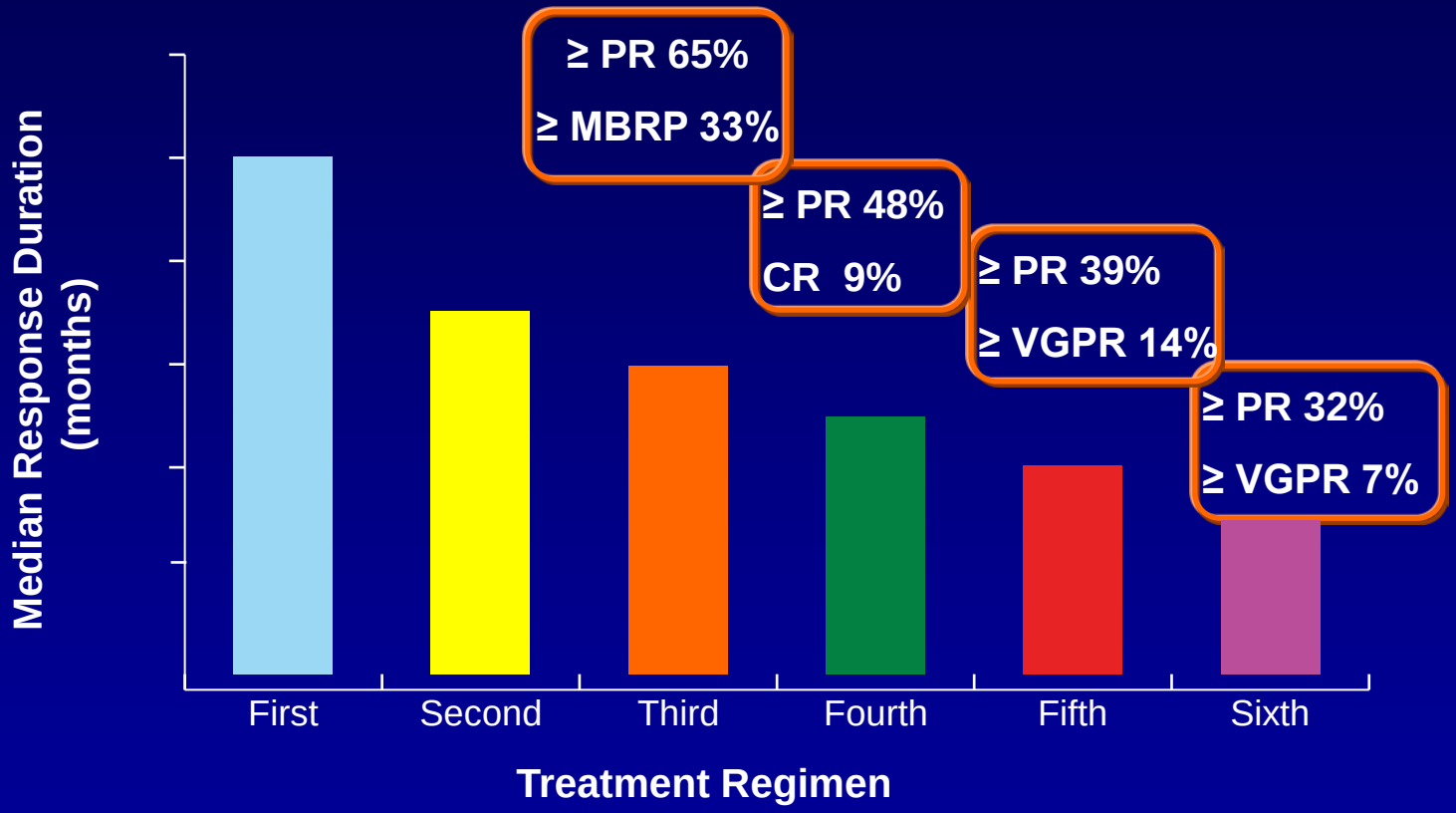
- Carfilzomib plus Rd
- Elotuzumab plus Rd
- Dara plus Rd
- Ixazomib plus Rd

Subsequent relapses

- Pom-Dex +/- something else
- Daratumumab

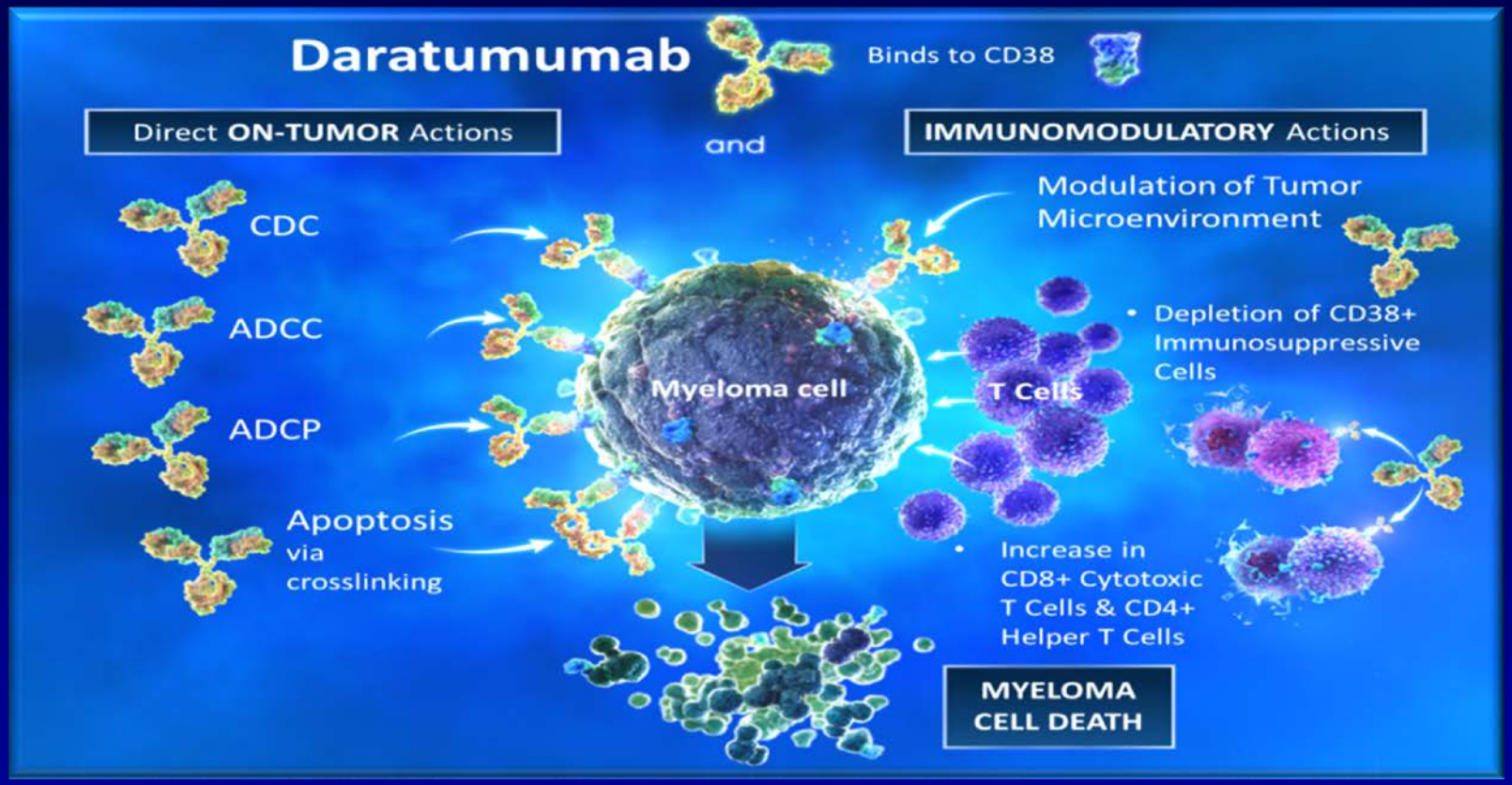
To move it earlier on

Optimizing Pomalidomide: The sooner, the better responses



Kumar S, et al. *Mayo Clin Proc*. 2004;79:867-74.

Daratumumab: Mechanisms of action



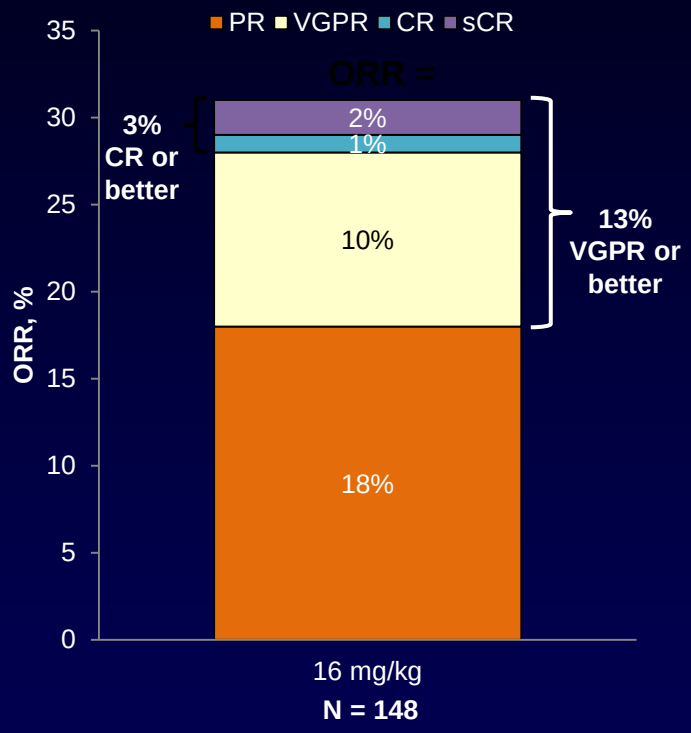
Daratumumab is a fully human monoclonal antibody that targets CD38

Direct on-tumor and immunomodulatory mechanisms of action[1-5]

Lammerts van Bueren J, et al. Blood. 2014;124. Abstract 3474; 2. Overdijk MB, et al. J Immunol. 2016;197(3):807-813; 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. Blood. 2016;128(3):384-394.

Efficacy in Combined Analysis

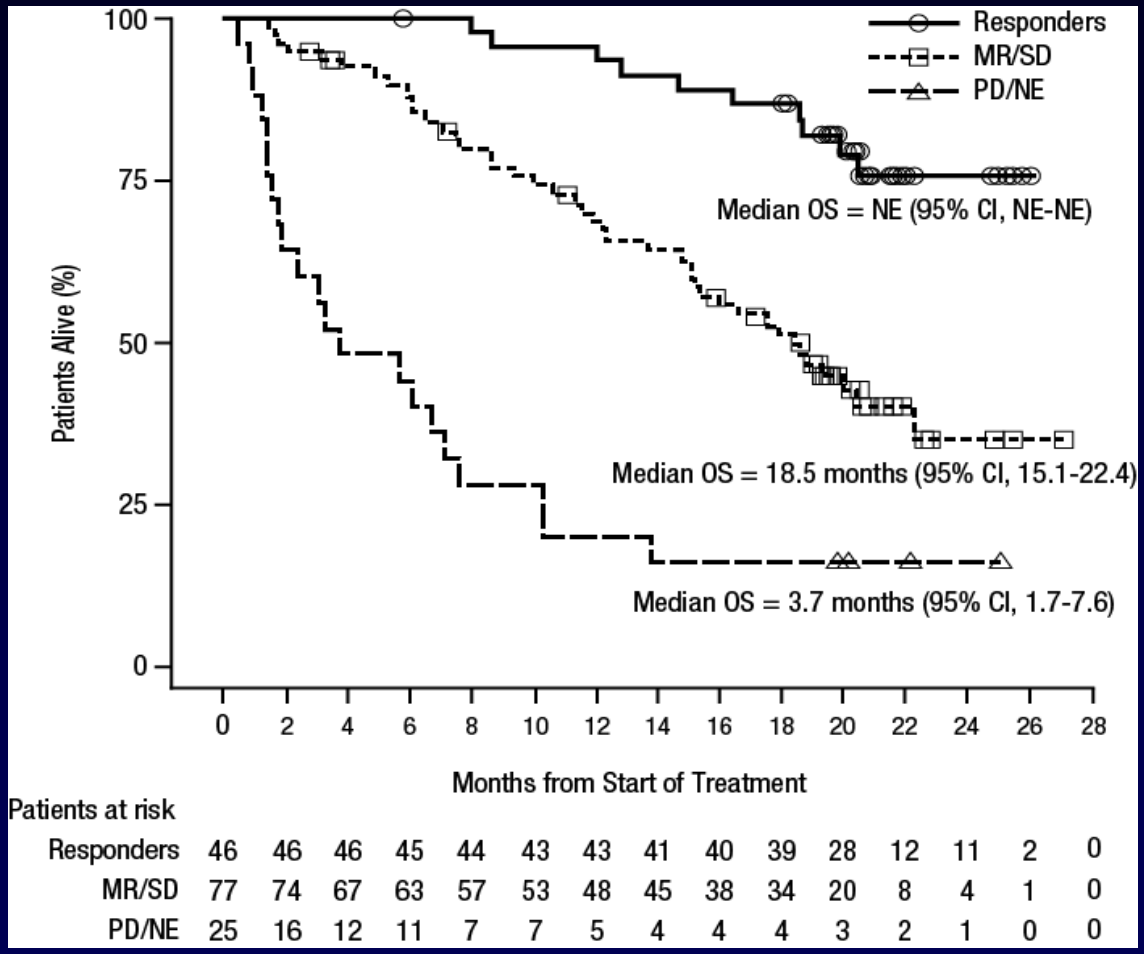
	16 mg/kg (N = 148)	
	n (%)	95% CI
Overall response rate (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR+VGPR)	19 (13)	7.9-19.3
CR or better (sCR+CR)	5 (3)	1.1-7.7



- **ORR = 31%**
- **Disease control rate was obtained in 84% of the patients**

Usmani, SZ et al. Blood 2016; 128 (1):37-44

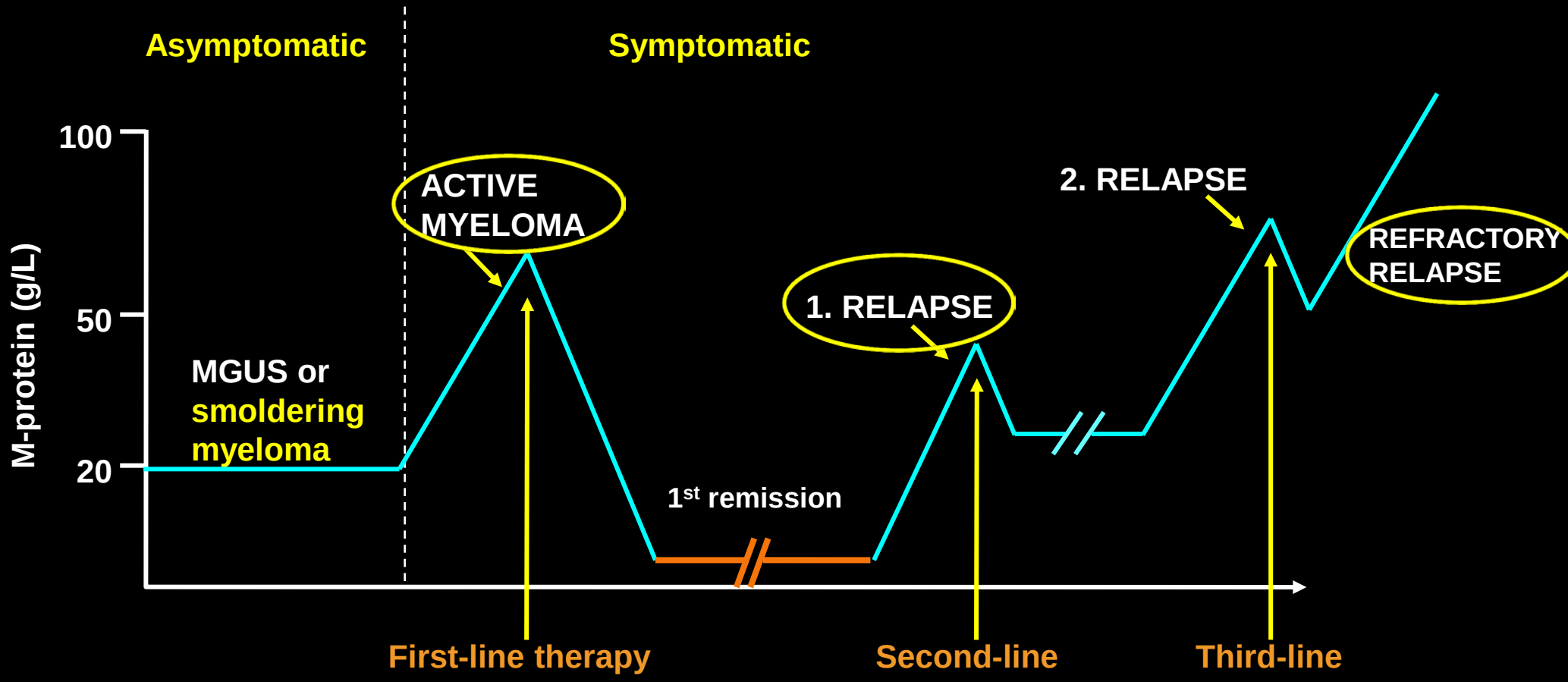
GEN501 and SIRIUS (MMY2002) Combined Analysis: OS by response category



Patients at risk															
Responders	46	46	46	45	44	43	43	41	40	39	28	12	11	2	0
MR/SD	77	74	67	63	57	53	48	45	38	34	20	8	4	1	0
PD/NE	25	16	12	11	7	7	5	4	4	4	3	2	1	0	0

Usmani S, et al. Blood 2016. May 23 [Epub ahead of print].

Natural History of MM



The first remission is now longer than in the past and we can potentially cure some standard risk patients at this stage but……. Most patients will finally relapse so new options are necessary

MGUS, monoclonal gammopathy of undetermined significance

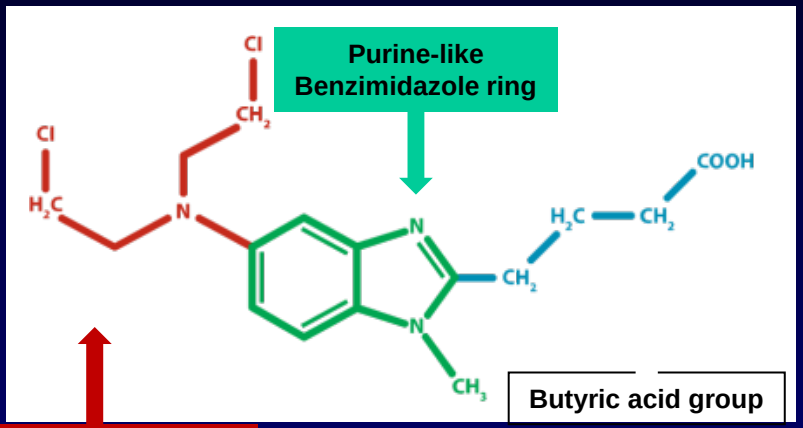
Bendamustine in R/R MM

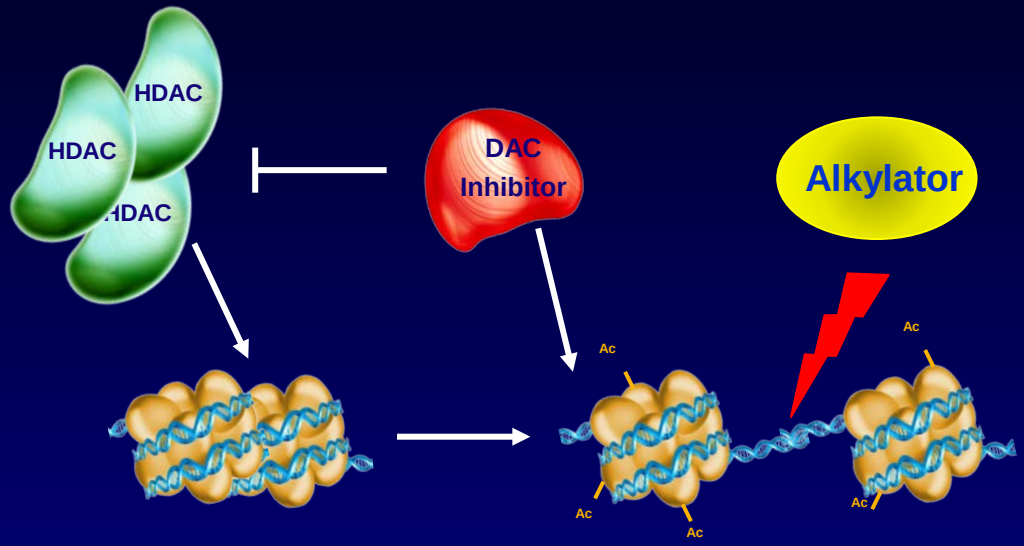
Single agent[1] (31 patients relapsing HDT)	ORR: 31% (7% CR, 24% PR); PFS: 6m
Benda-Bort[2] (40 patients *6 prior lines*)	ORR: 27% (2% CR, 5% VGPR, 21%PR)
Benda-Bortz-Dex[3] (40 patients *4 prior lines*)	ORR: 72% (25% VGPR, 47%PR)
Benda-Bort-Dex[4] (79 patients *2 prior lines*)	ORR: 61% (15% CR, 20% VGPR, 25% PR)
Benda-Bort-Dex[5] (73 patients *elderly 1st rel.*)	ORR: 70% (14% CR, 16% VGPR, 40% PR)
Benda-Bort-Dex[6] (75 patients *1 prior line*)	ORR: 72% (16% CR, 19% VGPR, 37% PR)
Benda-Bort-Pred[7] (78 patients *2 prior lines*)	ORR: 69% (17% nCR,13% VGPR, 40% PR)
Benda-Thal-Pred[8] (28 patients *2 prior lines*)	ORR: 86% (14% CR, 18% VGPR, 50% PR)
Benda-Thal-Dex[9] (23 patients *5 prior lines*)	ORR: 26% (4% CR, 22% PR)
Benda-Thal-Dex[10] (66 patients *84% >2 prior lines*)	ORR: 46%
Benda-Len-Dex[11] (29 patients *3 prior lines*)	ORR: 52% (24% VGPR, 28% PR)
Benda-Len-Dex[12] (41 patients *3 prior lines*)	ORR: 50% (11% CR, 7% VGPR, 32% PR)

1. Knop et al. Hematologica 2005, 90:1287
2. Berenson. BJH 2013
3. Hrusowsky et al ASH 2007 Abstract 4851
4. Ludwig H. Blood 2013
5. Rodon, ASH 2013. Abstract 1971
6. Offidani, Blood Cancer J 2013
7. Pönisch et al. J Cancer Res Clin Oncol 2013
8. Pönisch et al. BJH 2008,
9. Grey-Davies E. BJH 2012
10. Schey, ASH 2013. Abstract 286
11. Lentzsch. S. Blood 2012
12. Pozzi, ASH 2013. Abstract 3222

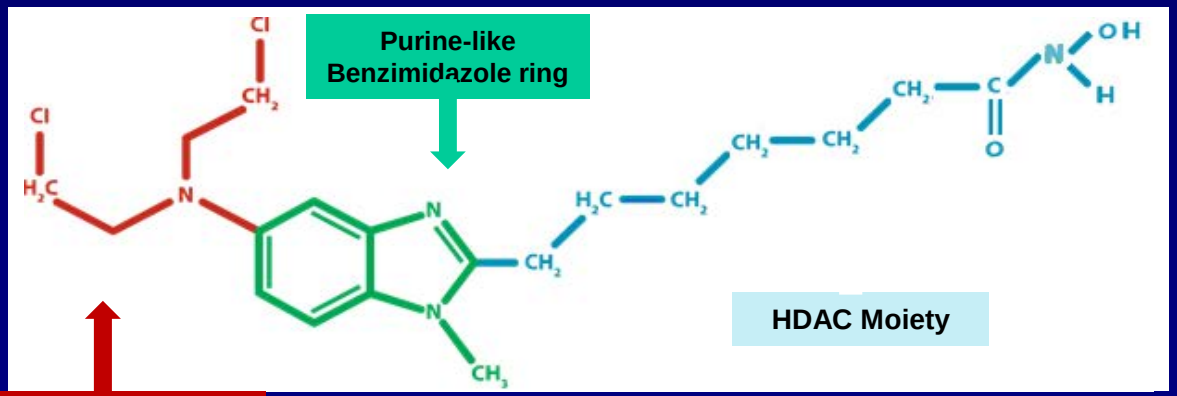
EDO-S101: bendamustine derivative

Bendamustine



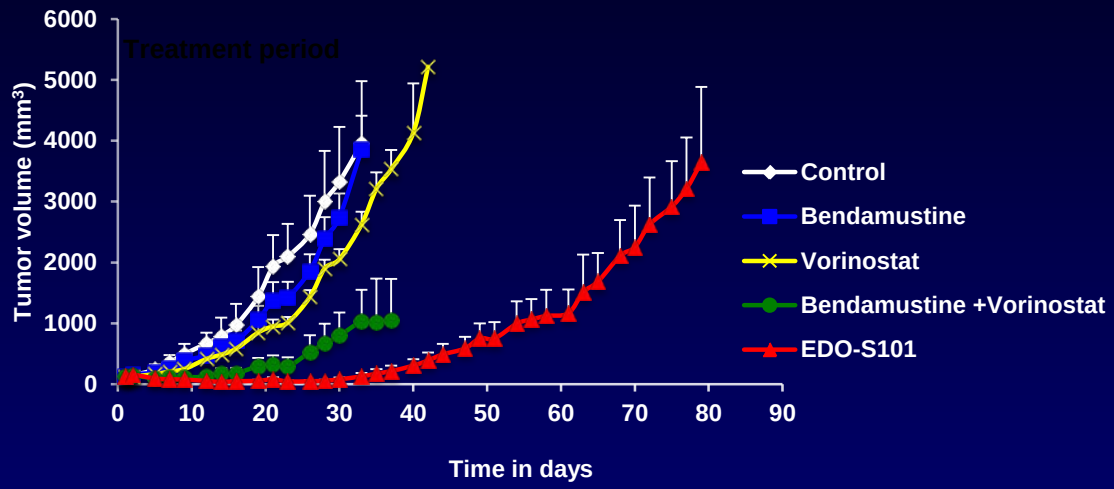


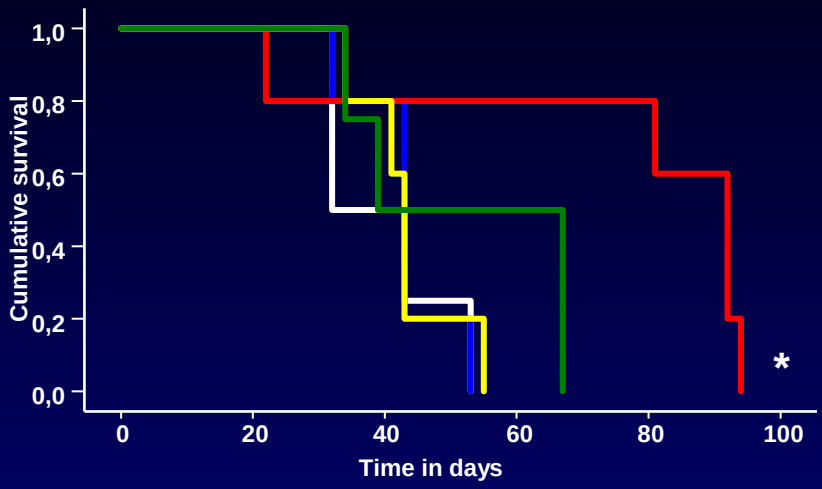
EDO-S101



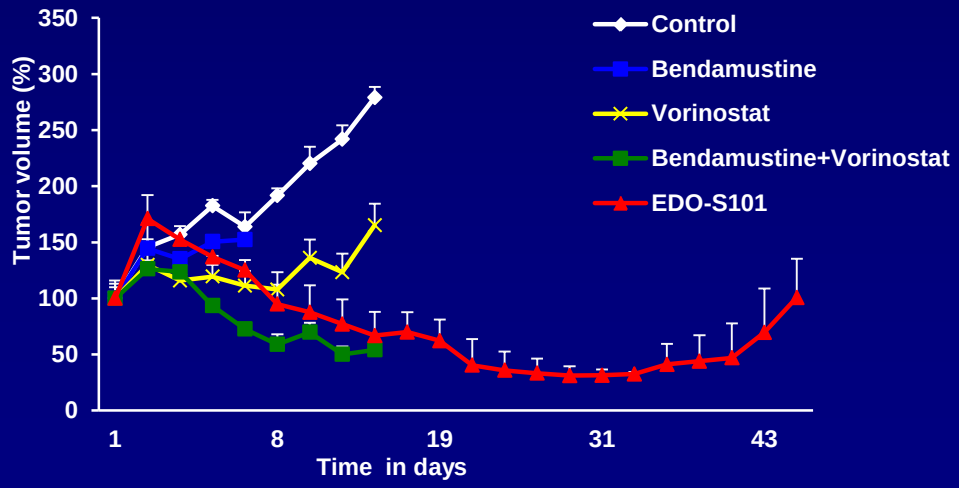
In vivo activity of EDO-S101

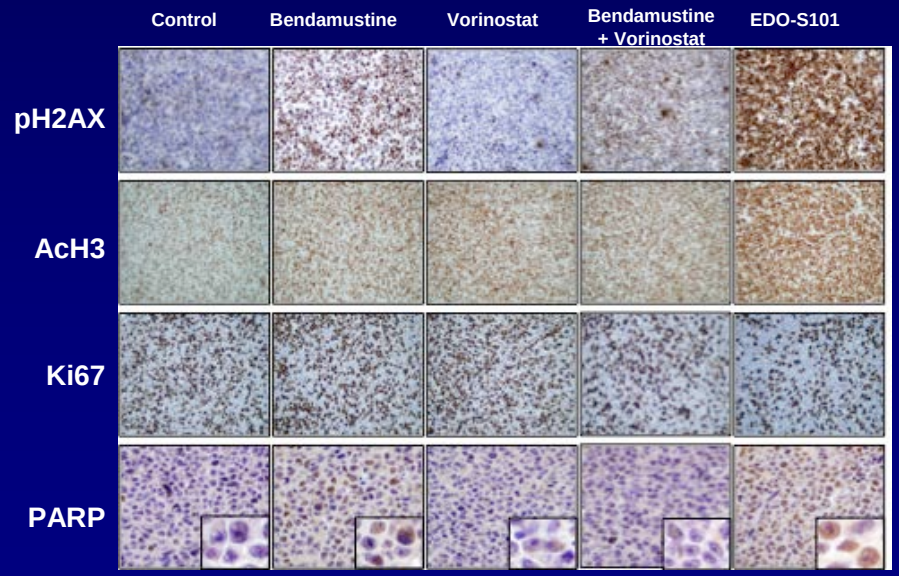
Small tumors





Big tumors

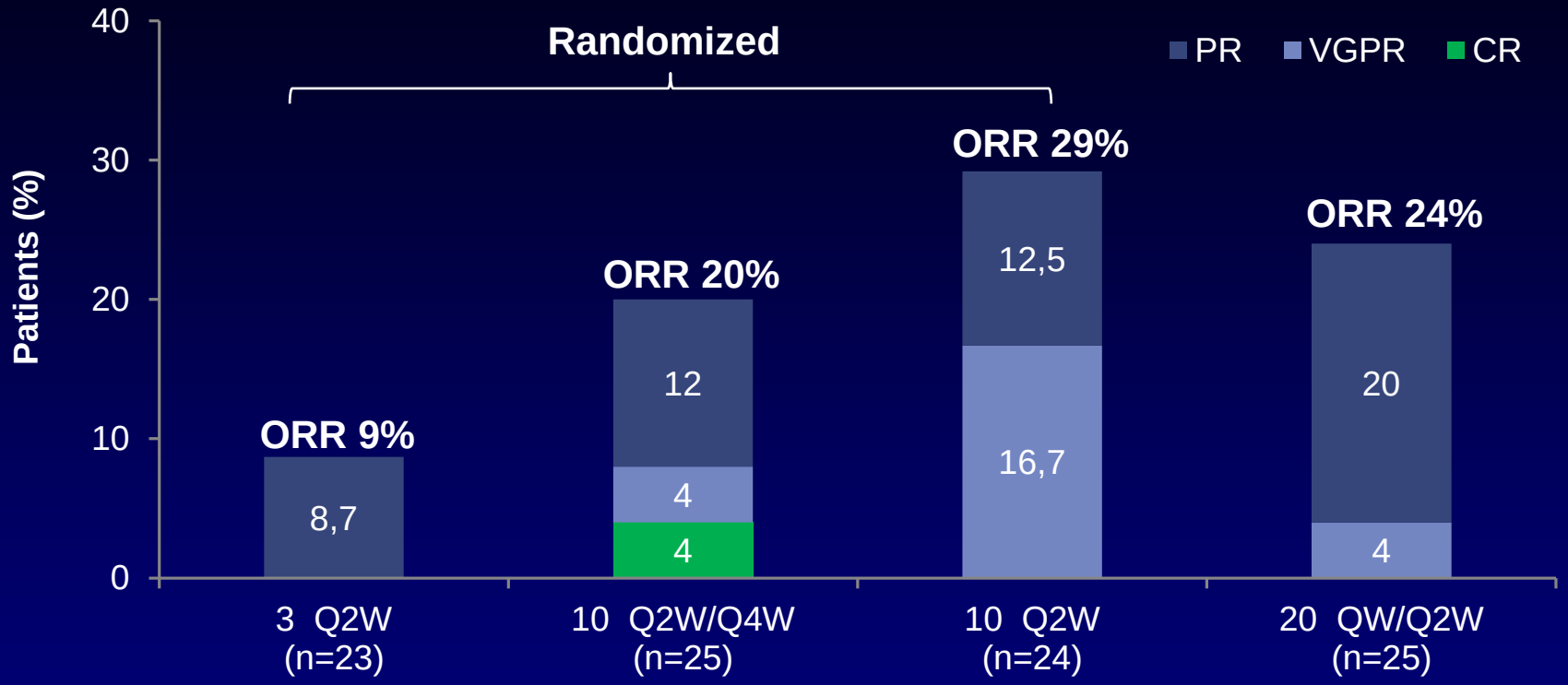




Lopez Iglesias et al, Submitted

TED10893

Efficacy of Isatuximab



Time to first response, mo	2.4 (0.9–3.9)	2.0 (0.8– 2.0)	0.9 (0.9–3.7)	1.4 (0.9–2.8)

- Follow-up ongoing (22 patients remain on treatment)

Interim analysis results. Data cut-off: Nov 6, 2015.
***Response defined according to IMWG criteria for all treated patients**
mo, months; VGPR, very good partial response

Martin T, ASH 2015 Abst 509

Isatuximab combinations in RRMM

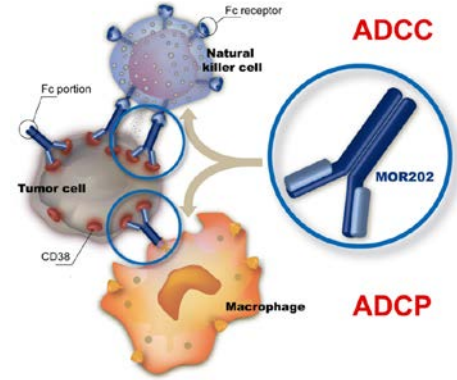
- **+ Pom - Dex**
  - **n= 20** **Median (range) prior lines: 4.5 (3-11); 75% refr. to IMiD**
  - **ORR 64% (1 CR, 4 VGPR, and 4 PR) Median (range) DOR: 19.71 (8-45) weeks**
  - **No new safety signals**
  - **MTD not reached; Isatuximab 10 mg/kg selected for expansion cohort**
  - **Phase III study of isatuximab plus Pom/Dex was planned to start in 2017**

Richardson, P et al. ASH 2016. Abst. 2123

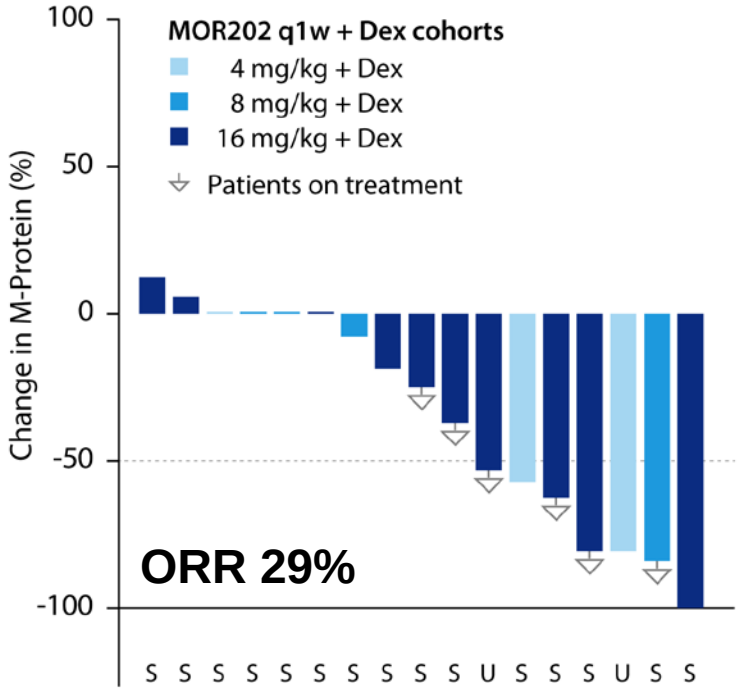
- **+ Cfz - Dex**
  - **n= 12** **Median (range) prior lines: 3.5 (2-8); 75% refr. to IMiD &PI; 65% refr. to Cfz**
  - **ORR 66.7% (2 VGPR, 6 PR, and 2 MR)**
  - **No new safety signals**
  - **MTD not reached; 21 patients to be enrolled into expansion phase**

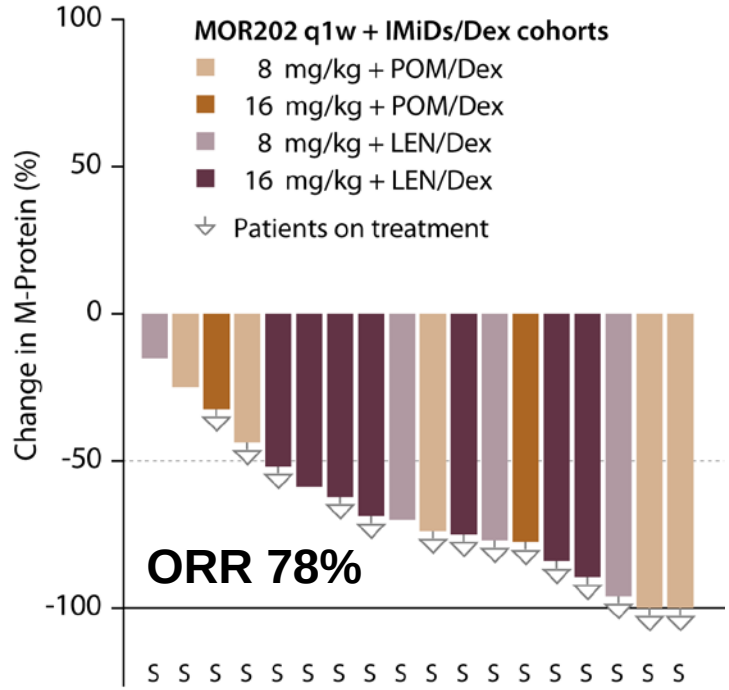
Martin, T et al. ASH 2016. Abst. 2111

Anti-CD38 MoAb: MOR202



Efficacy: Best Maximum Change in M-Protein





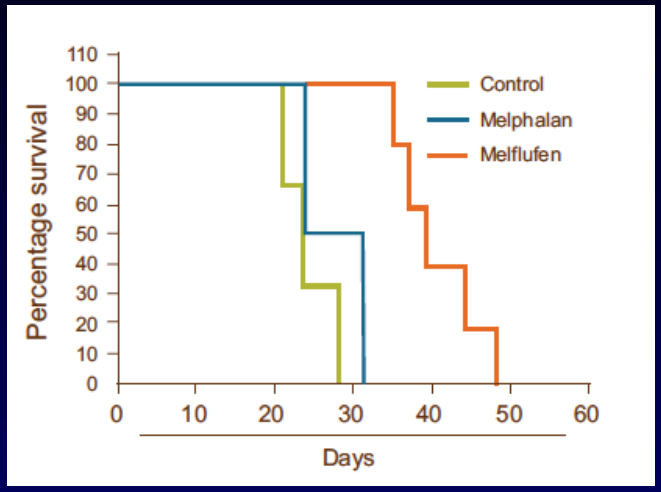
Data from 35 response-evaluable patients treated with clinically relevant dose regimens who received > 1 treatment cycle

S, serum; U, urine

Raab et al. ASH 2016 Abst 1152

Melflufen

- Melflufen is a highly lipophilic alkylator, consisting of **melphalan + 4-fluoro-L-phenylalanine**.
- **Intracellular peptidases** that are overexpressed in most malignant cells, will rapidly **cleave melflufen releasing the hydrophilic, active metabolite melphalan**.
- In vitro, equimolar treatment of tumor cells with melphalan and melflufen, results in a 10-20 fold higher intracellular concentration of melphalan.



Chauhan Clin Cancer Res 2013 & Wickström Invest New Drugs 2008

Phase I/II

Phase I: 4/6 @ 55 mg had DLTs (hem.) → MTD 40 mg /3w

Phase II: n=31. 4 (2-9) prior lines. 97% IMiD and 90% PI; 77% melphalan & 71% ASCT

ORR @ MTD 48% ..... 1 VGPR & 10 PR 62% in Alkylator refr. Pts PFS: 7.6 m

G3/4 rel. TEAEs: Thromboc. (68%), Neutropenia (55%), Anemia: 42%

Paba-Praba C. ASH 2014

Voorhees P. ASH 2015

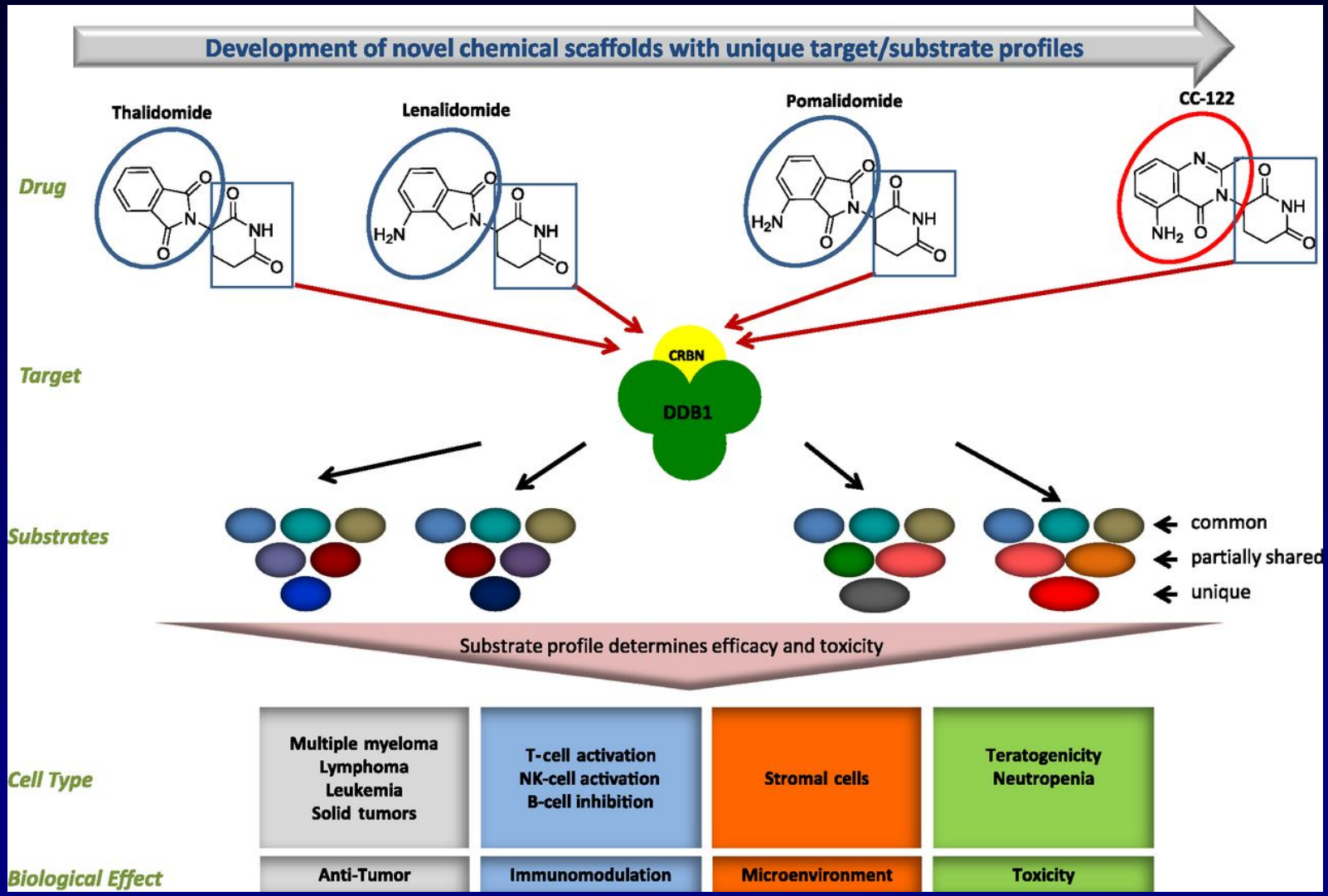
+ Dex

n=9 patients with a median of 5.2 (range 3-10) lines of therapy.

Mellqvist P. EHA 2016

Grade 3/4 TRAE: G3 thrombocytopenia, G3 pneumonia, G4 febrile neutropenia, G3 nausea and G3 neutropenia.

Next-generation IMIDs, CELMoDs™ (Cereblon E3 Ligase Modulation Drugs) in Multiple Mieloma



CC-122

Pleiotropic Pathway Modifier

CC-220

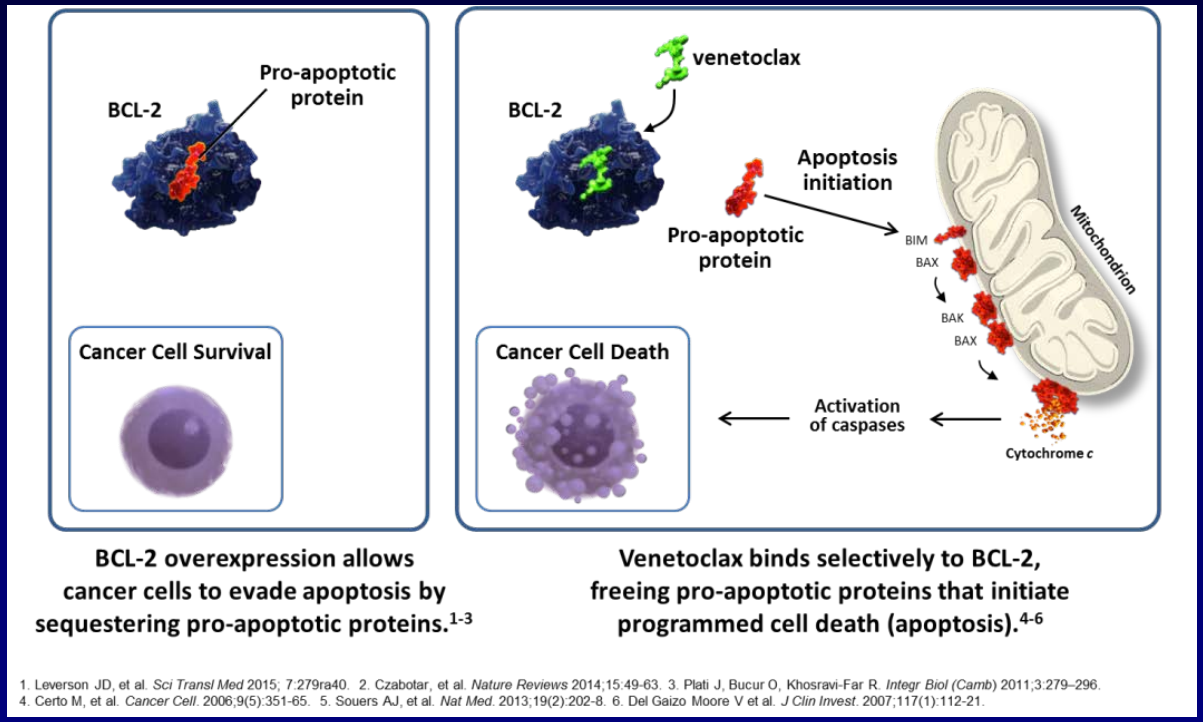
Blood 2015

Venetoclax (Bcl-2 inhibitor)

- Venetoclax (ABT-199 / GDC-0199) is a potent, selective, orally bioavailable, small-molecule, BCL-2 inhibitor[1]

- Anti-apoptotic proteins BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival[2]

- Venetoclax induces cell death in multiple myeloma (MM) cell lines and primary samples, particularly those positive for the translocation t(11;14), which correlates with higher ratios of BCL2 to MCL1 and BCL2 to BCL2L1 ($BCL\text{-}X_L$) mRNA[2,3]



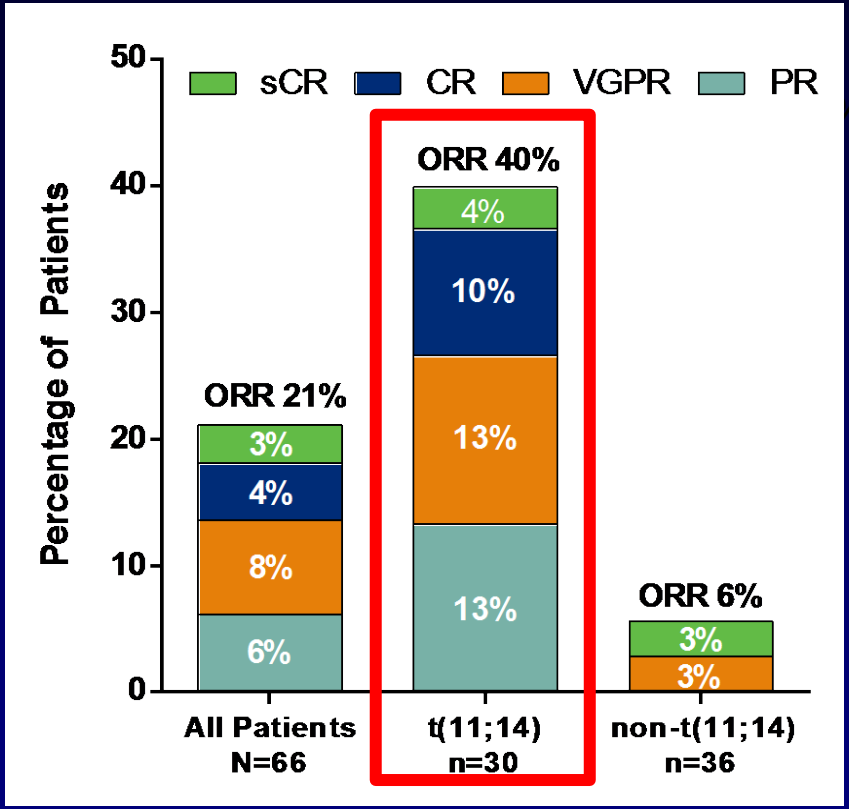
1. Souers AJ, et al. Nat Med. 2013; 19(2): 202-208.

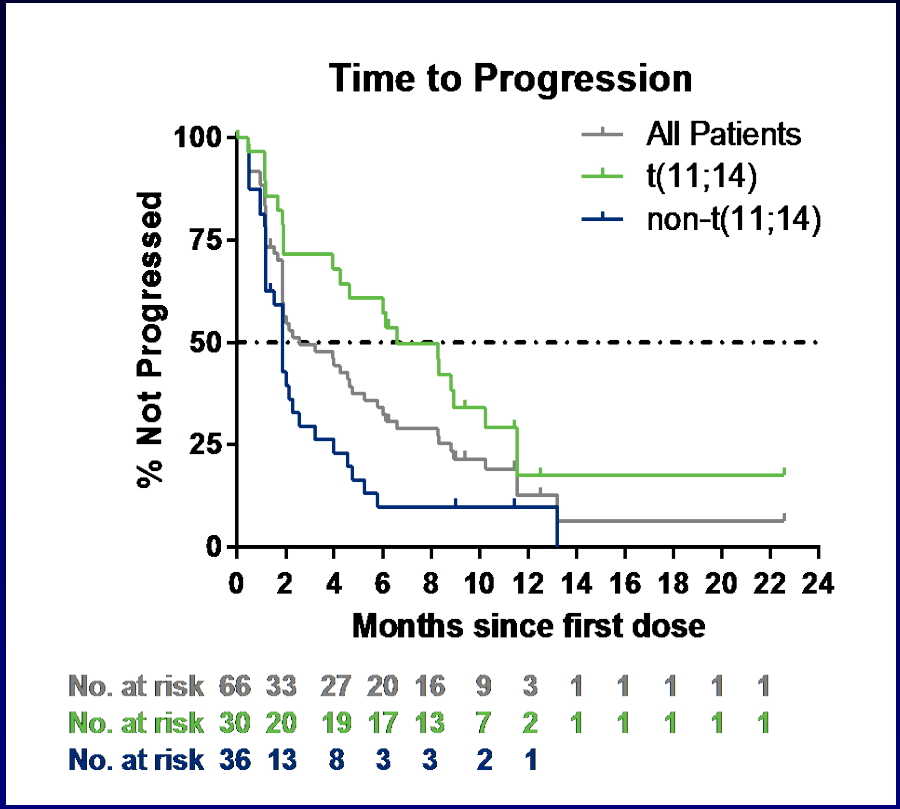
2. Touzeau C, et al. Leukemia. 2014; 28(1): 210-212.

3. Punnoose E et al. Mol Cancer Ther 2016

Venetoclax monotherapy

n= 66 pts. Median of 5 prior lines. 79% refractory to last line; 61% double refractory to Btz & Len





Higher ORR (88% vs 20%) in t(11;14) with a high BCL2:BCL2L1 ratio

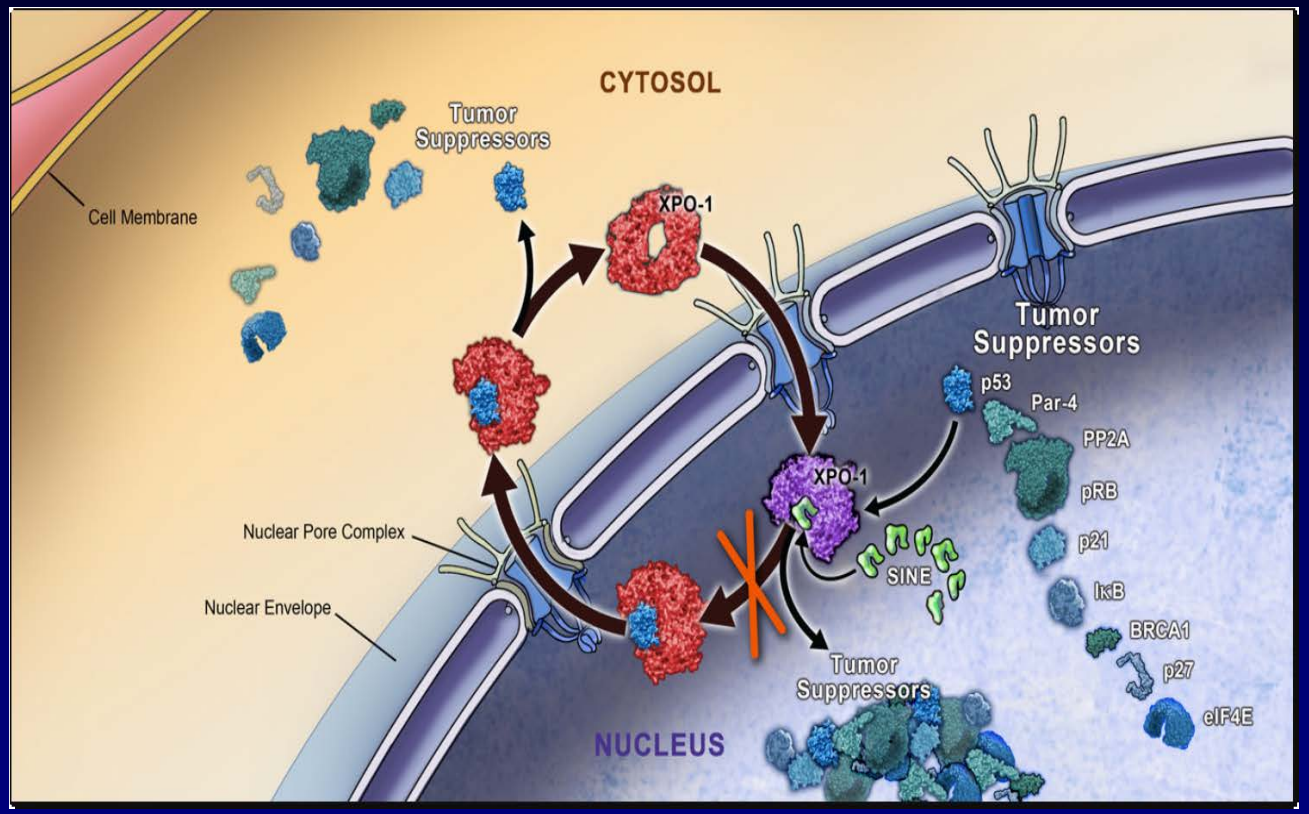
Main toxicities are thrombocytopenia (26% G3-4) and neutropenia (21% G3-4)

Serious AEs: pneumoniae (8%) and sepsis (5%)

30-1200 mg oral admon (MTD: 1200 mg)

Kumar, et al. Presented at ASH 2016 (Abstract 977), oral presentation

XPO1-Inhibitors: Selinexor



- Exportin 1 (XPO1) is the nuclear exporter for the **majority of tumor suppressor proteins** (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs
- **Selinexor** is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression.

Tai et al. Leukemia 2014

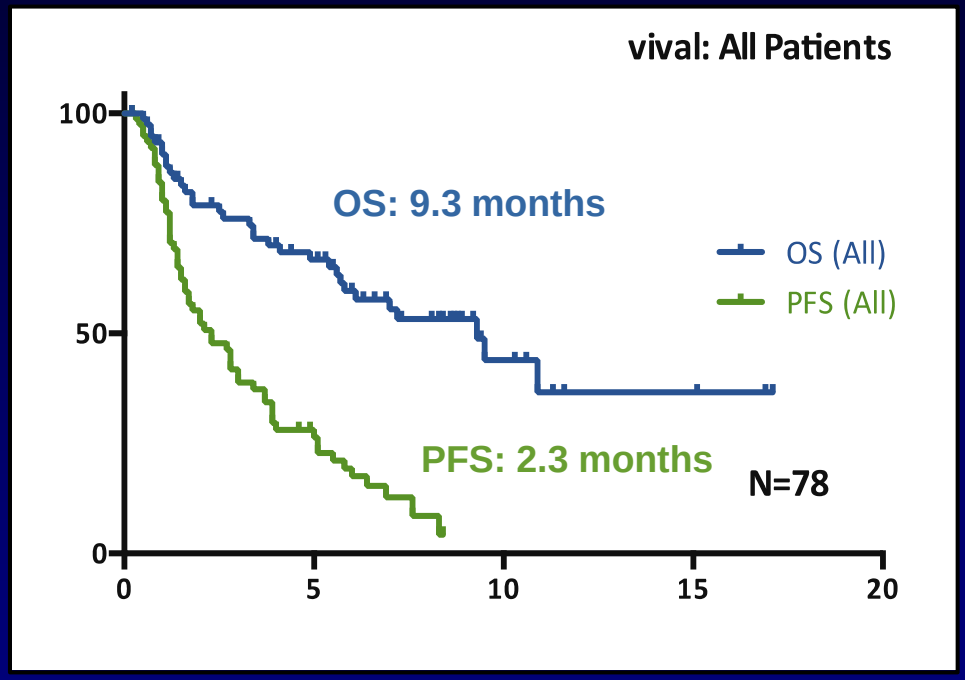
Selinexor plus dex (STORM study)

n=78 pts median of 7 prior lines of therapy:

48 pts quad refractory (bor, carf, len & pom) & 30 penta refractory (bor,carf, len, pom & CD38 mAbs)

	N*	ORR (%)	CBR (%)	VGPR (%)	PR (%)	MR (%)
Overall	78	16 (21%)	26 (33%)	4 (5%)	12 (15%)	10 (13%)
Quad Refractory	48	10 (21%)	14 (29%)	2 (4%)	8 (17%)	4 (8%)
Penta Refractory	30	6 (20%)	12 (40%)	2 (7%)	4 (13%)	6 (20%)

Median DOR: 5 months



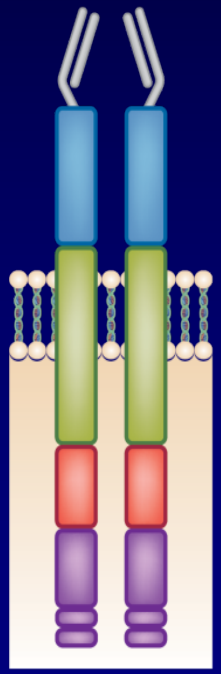
Main toxicities are thrombocytopenia (59% G3-4) and neutropenia (17% G3-4), anemia (28% G3-4), fatigue (15% G3-4), which are manageable with dose modifications

Vogl , et al. ASH 2016. Abst. 977

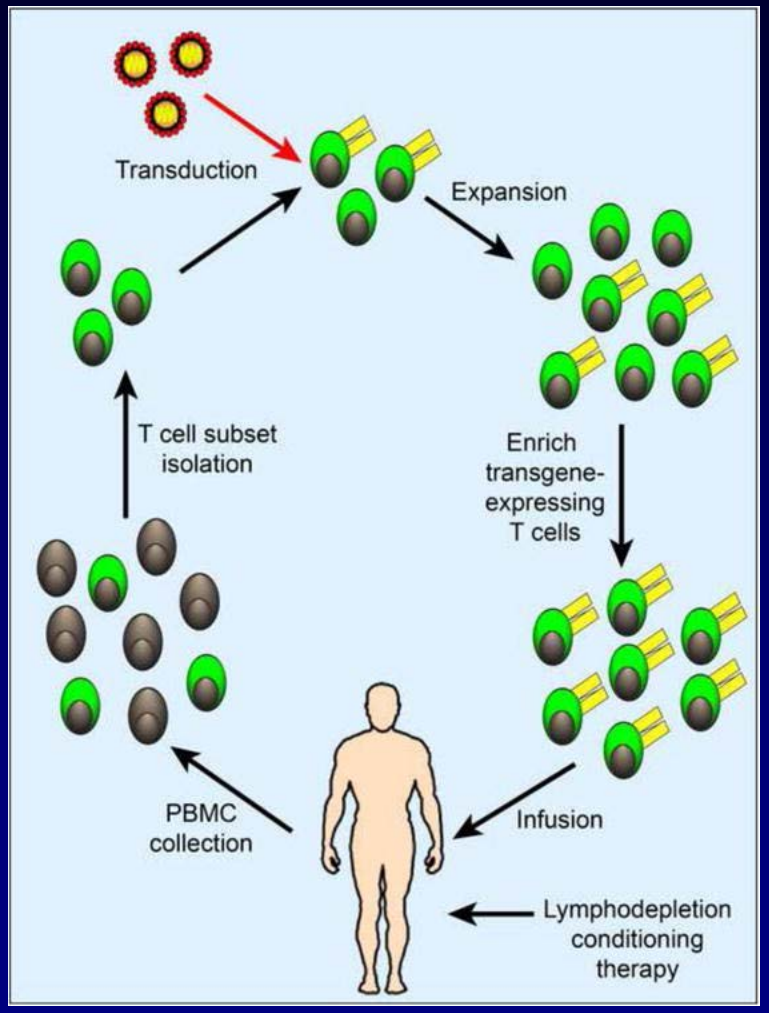
Adoptive T cell therapy: CAR-T cells

- CAR T or NK cells are engineered anti-tumor immune cells with high affinity chimeric antigen receptors specific for tumor antigens[1]

Chimeric Antigen Receptor Structure[1]



- Single-chain antibody able to recognize tumor-associated antigens in a non-MHC–specific manner
- Molecular hinge region derived from CD8 to provide flexibility to allow reorientation to bind antigen
- Cytoplasmic domain of CD28 and additional signaling domains, including CD137, were added to later generation CARs to enhance cytokine secretion and tumor growth inhibition
- Cytoplasmic signaling domain of CD3ζ



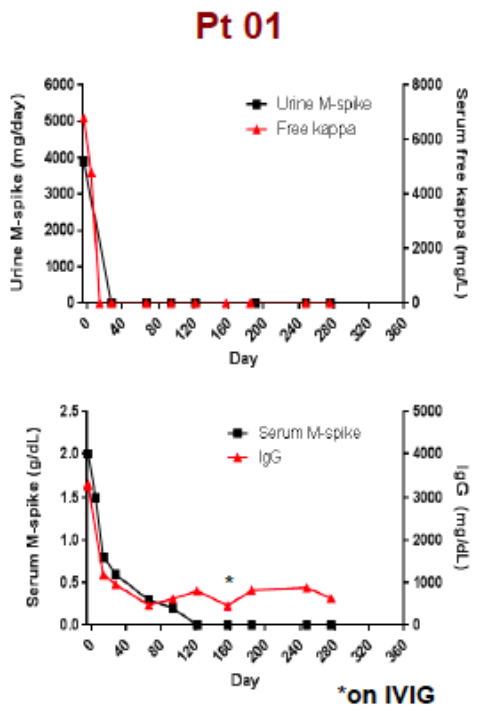
1. Kershaw MH et al. Nat Rev Cancer. 2013;13:525-541.

Turtle CJ, Hudecek M, Curr Opin Immunol, 2012

BCMA-CAR-T in MM

Clinical responses

Pt	BM PC %	Cytogenetics	CART dose received (% of planned)	CRS grade	Time to 1st response (days)	Best Heme response	PFS (mos.)
01	70	+11 -17p -16q	2 x 10e8 (40%)	3 (toci)	14	sCR*	12+
02	60	+1q +4p -17p	5 x 10e8 (100%)	1	14	MR	2
03	95	+1q t(4;14) -16q	2 x 10e8 (40%)	3 (toci)	15	VGPR*	5
09	15	t(11;14)-16q -17p	5 x 10e8 (100%)	2	-	SD	2
10	95	+1q t(11;14)	1.8 x 10e8 (100%)	-	-	PD	0.5
11	80	+1q t(4;14) -17p	5 x 10e8 (100%)	2	25	MR	2.5
07	15	+1q, +11, -4, -14, -16	5 x 10e8 (100%)	2	14	uPR**	1.5
08	80	-1p +1q, -4 -17p	5 x 10e8 (100%)	4 (toci)	-	PD	0.5
15	90	+1q, t(11;14)	5 x 10e8 (100%)	2 (toci)	14	VGPR*	2+



*No MM by flow
**unconfirmed; 24 hour UPEP not repeated

the cure is within
ABRAMSON CANCER CENTER

Cohen et al. ASH 2016 Abstract 1147

FDA Grants BCMA CAR T-Cell Therapy Breakthrough Designation in Myeloma

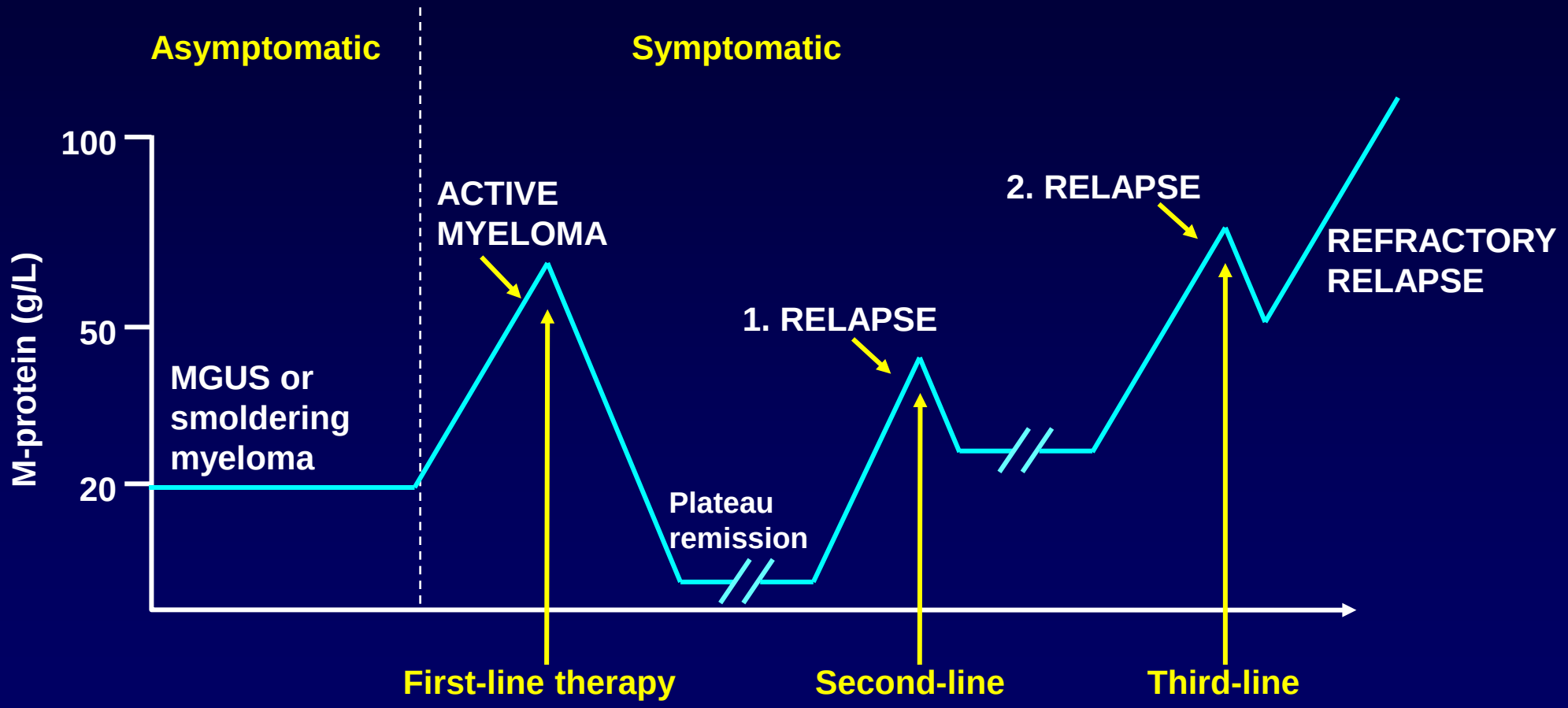
Jason Harris

Published Online: Thursday, Nov 16, 2017

The FDA has granted bb2121 a breakthrough therapy designation for previously treated patients with relapsed/refractory multiple myeloma, according to Celgene Corporation and bluebird bio, the companies developing the anti–B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T-cell therapy.

In a press release, the companies reported that the investigational agent had also been awarded PRIority MEdicines (PRIME) eligibility by the European Medicines Agency (EMA). The FDA and EMA took action based on preliminary clinical data from the ongoing phase I CRB-401 study. The companies did not release any data, but noted that updating findings would be presented in December at the 2017 ASH Annual Meeting.

Natural History of Multiple Myeloma



MGUS=monoclonal gammopathy of undetermined significance.