HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

University of Salamanca

Avanzando en el tratamiento del Mieloma Múltiple

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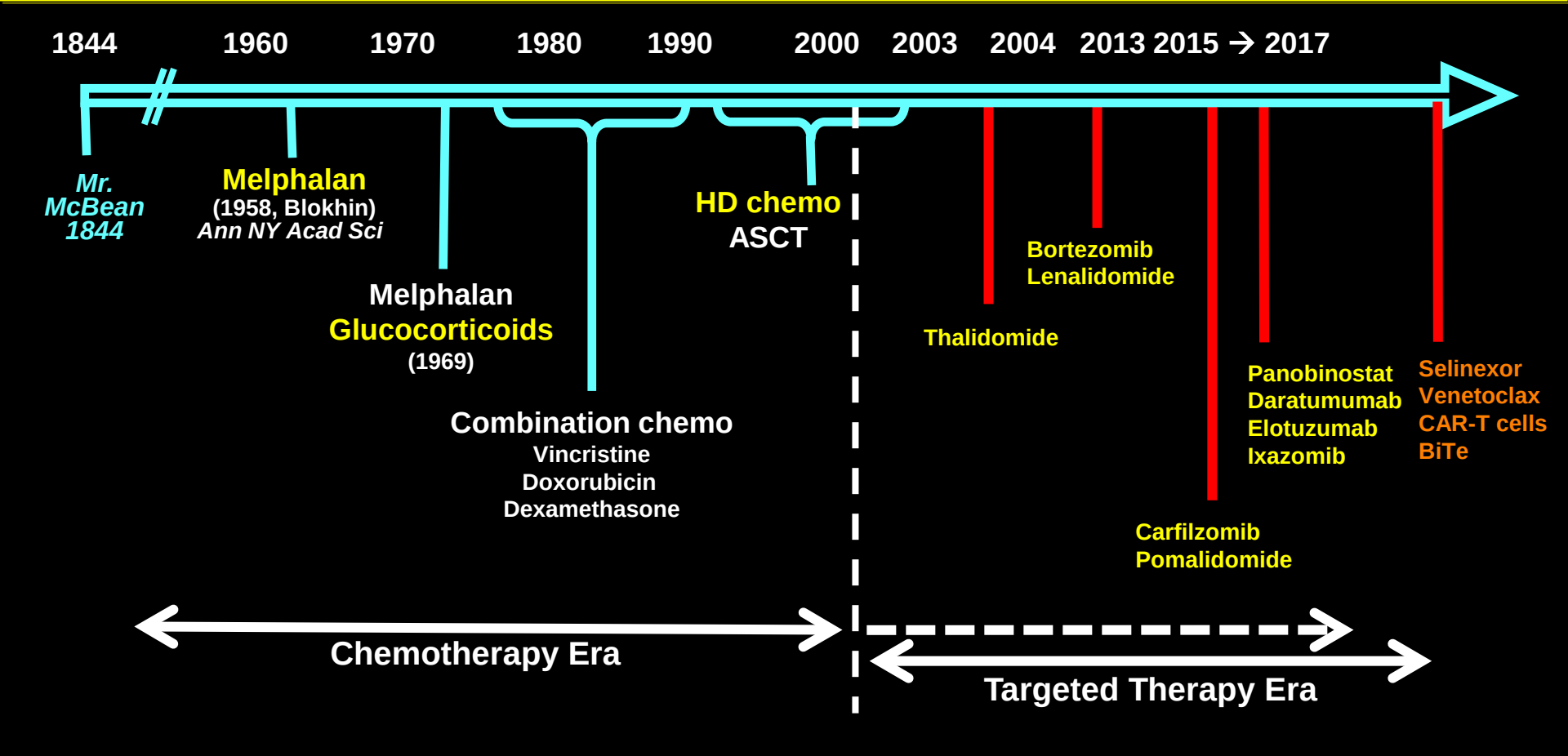
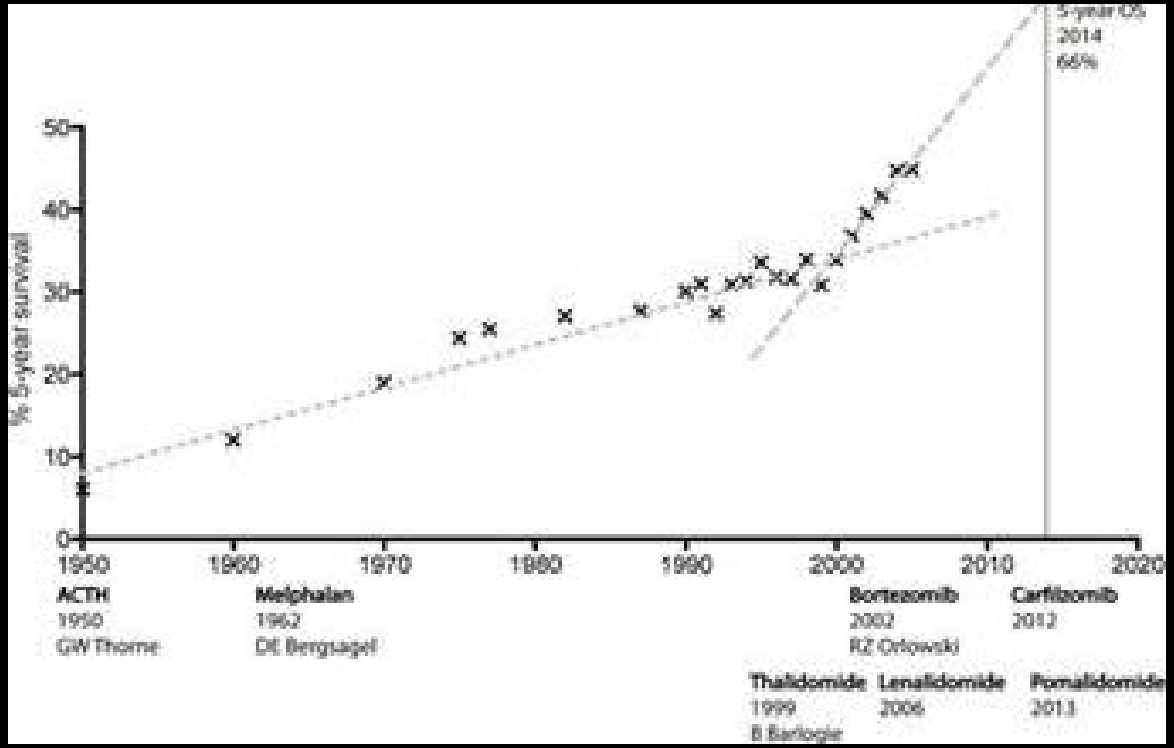
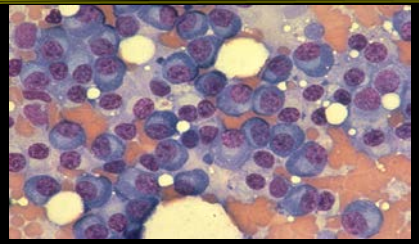
Treatment of MM

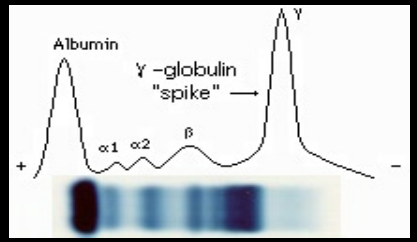


Significant improvement on OS

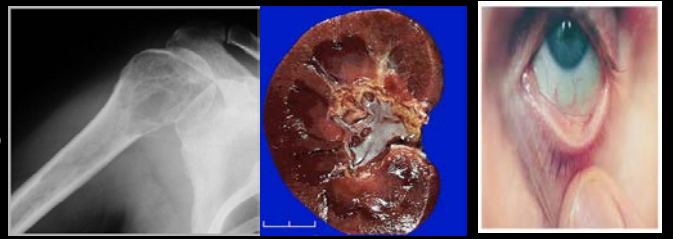


Introduction



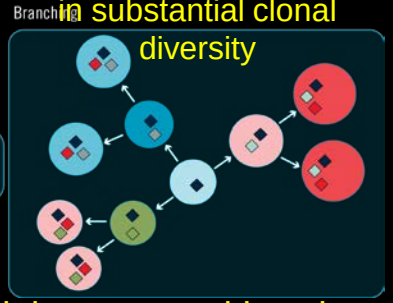


Myeloma-defining events

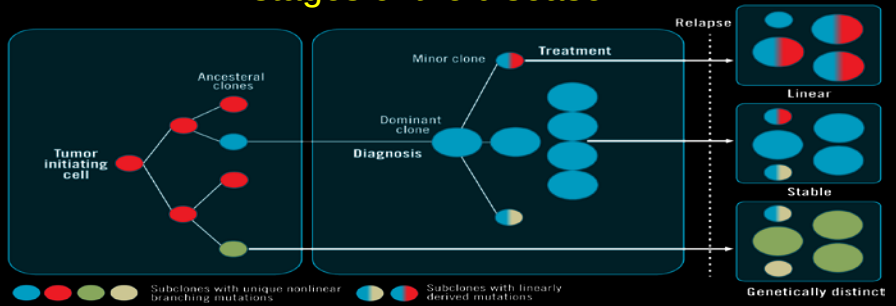


Malignant PCs may not evolve in a linnear manner

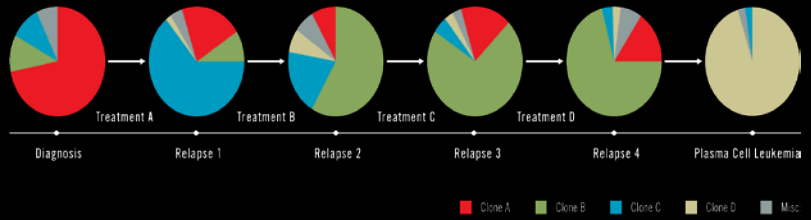
Branching model, resulting in substantial clonal diversity

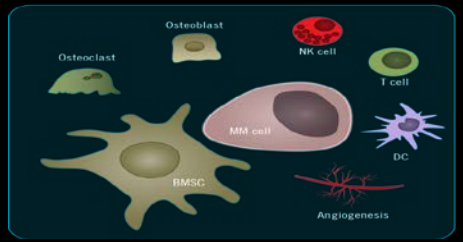


Subclonal heterogeneity is also present at all different stages of the disease



Treatment may control an indolent or sensitive clone, allowing a more aggressive clone to expand

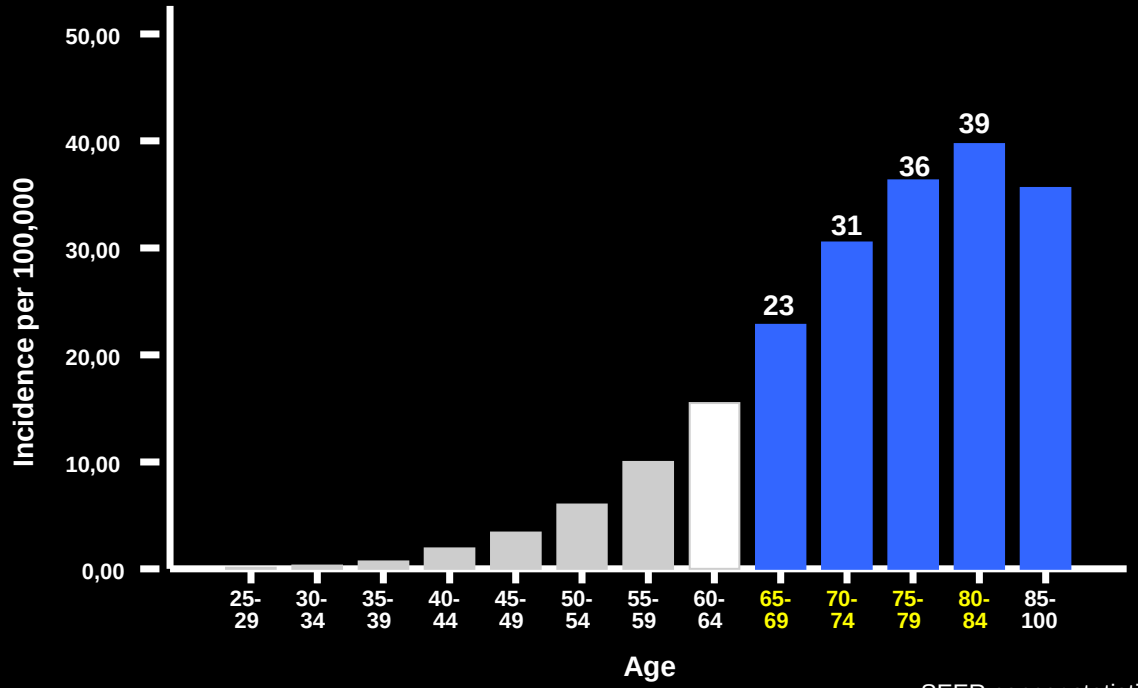




In addition, cellular and noncellular components are important for MM pathogenesis

Introduction

- Multiple Myeloma is the second most frequent haematological neoplastic disease
- It usually affects the elderly population: median age at diagnosis 69 years



SEER cancer statistics review 1975-2010

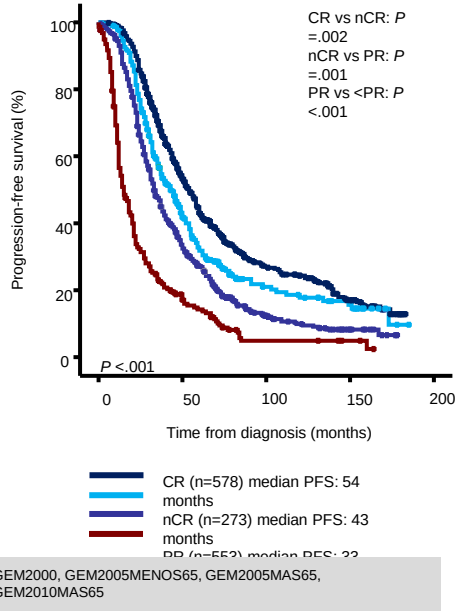
What are the optimal treatment goals for MM patients?

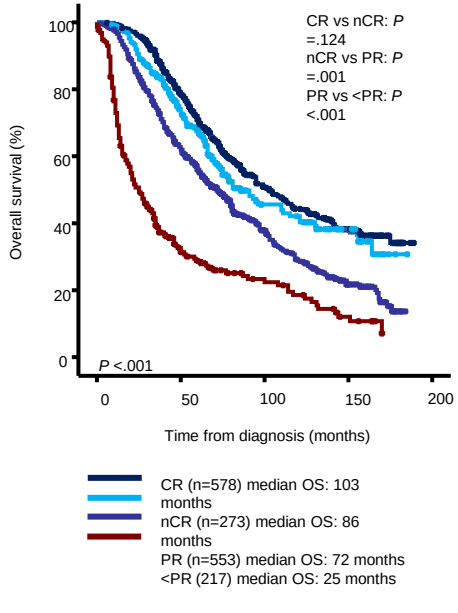
- To achieve cure or at least long-term suvival (>10–20 years) with good quality of life.
- Prolong survival
- Delay disease progression
- Ensure good quality of life

To achieve these goals..... erradication or at least major reduction of the tumor clone is required

Pooled analysis of three GEM clinical trials

CR is a typical endpoint and one of the most powerful prognostic markers in MM



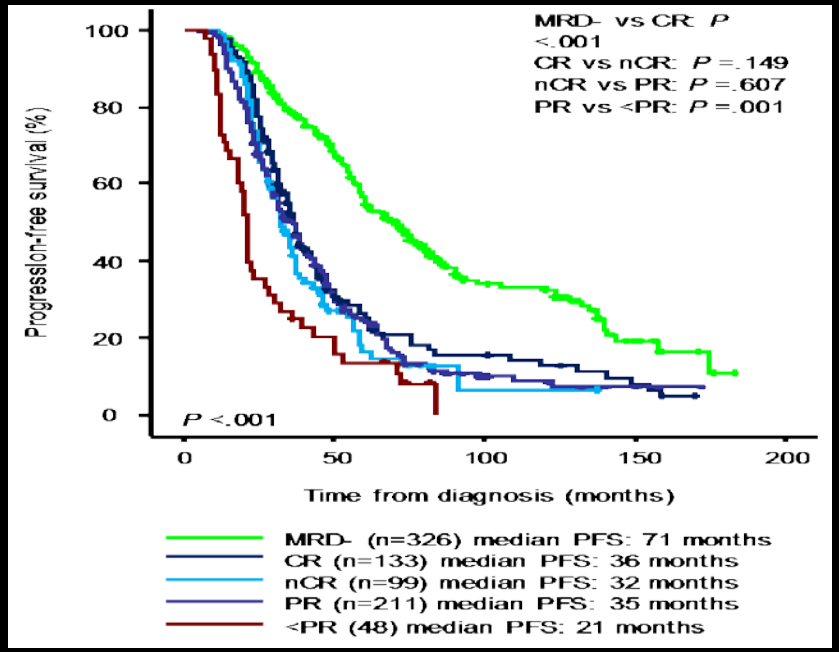


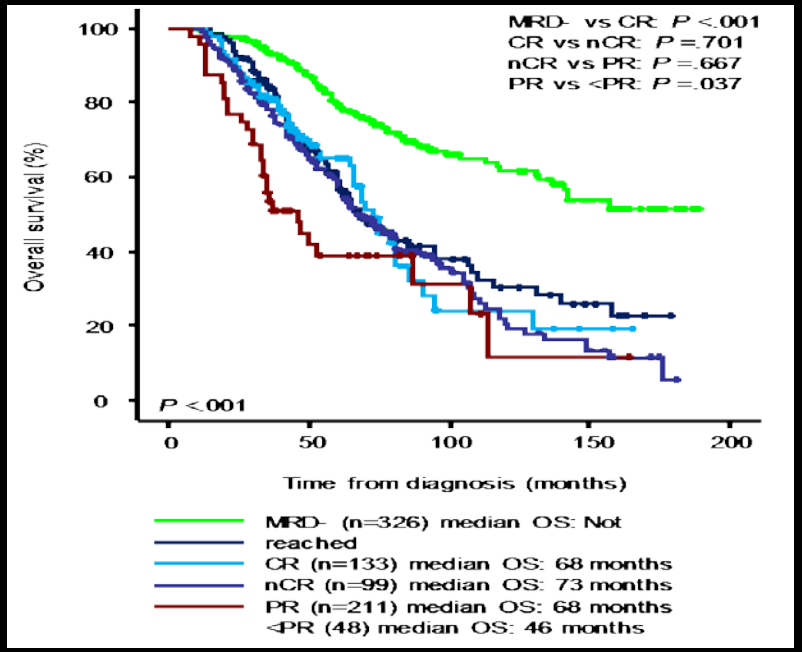
Lahuerta JJ et al. JCO 2017: Epub ahead of prin

Pooled analysis of three GEM clinical trials

The true value of CR relies in the MRD status, and CR without MRD is no better than PR

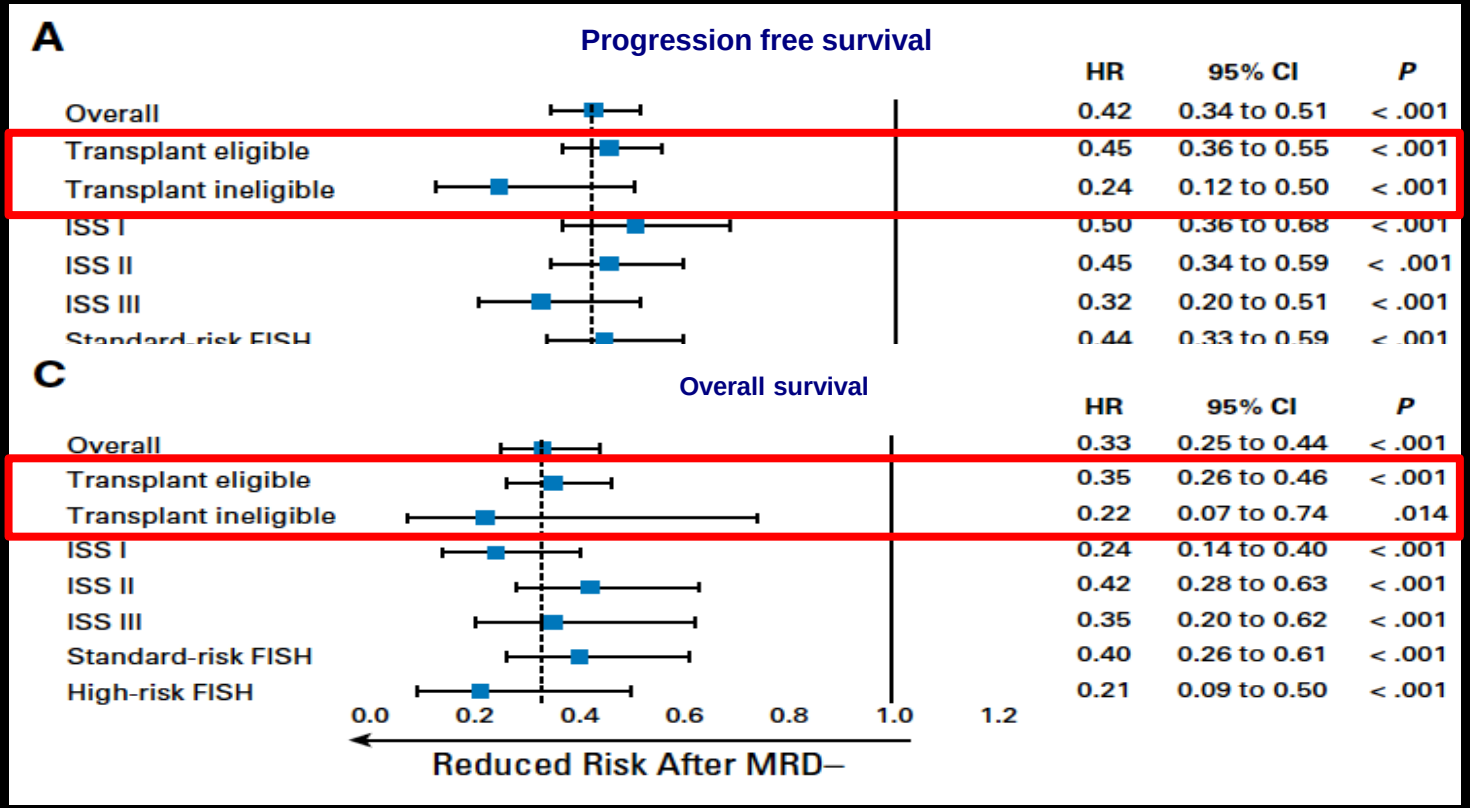
MRD evaluated by flow-cytometry





Lahuerta JJ et al. JCO 2017: Epub ahead of print

MRD as predictor across MM patients subgroups

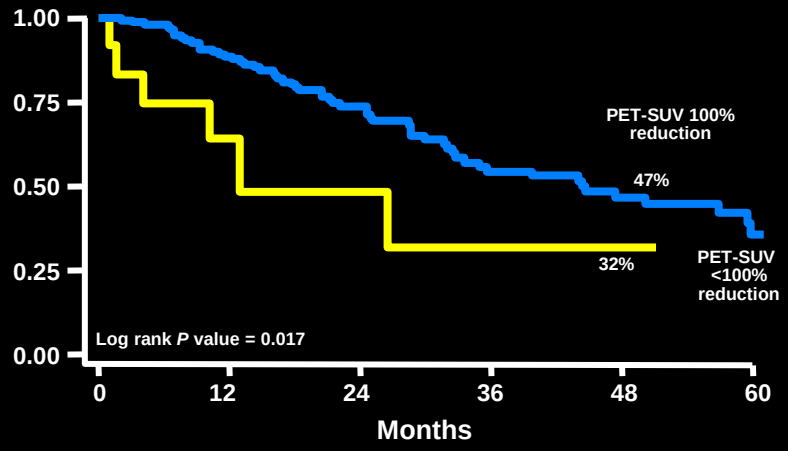


Lahuerta JJ et al. JCO 2017: Epub ahead of print

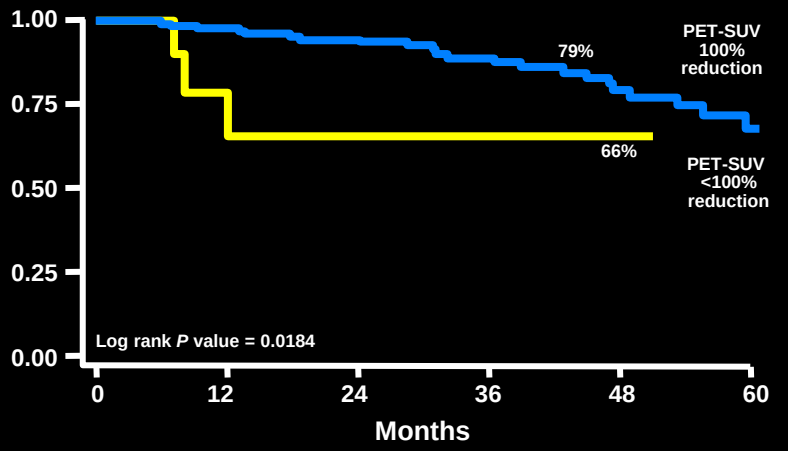
Impact of PET-CT Negativity on Clinical Outcomes

PET-CT is a reliable technique for predicting long-term outcomes.

PFS according to PET-SUV post-ASCT PET-CT



OS according to PET-SUV post ASCT PET-CT



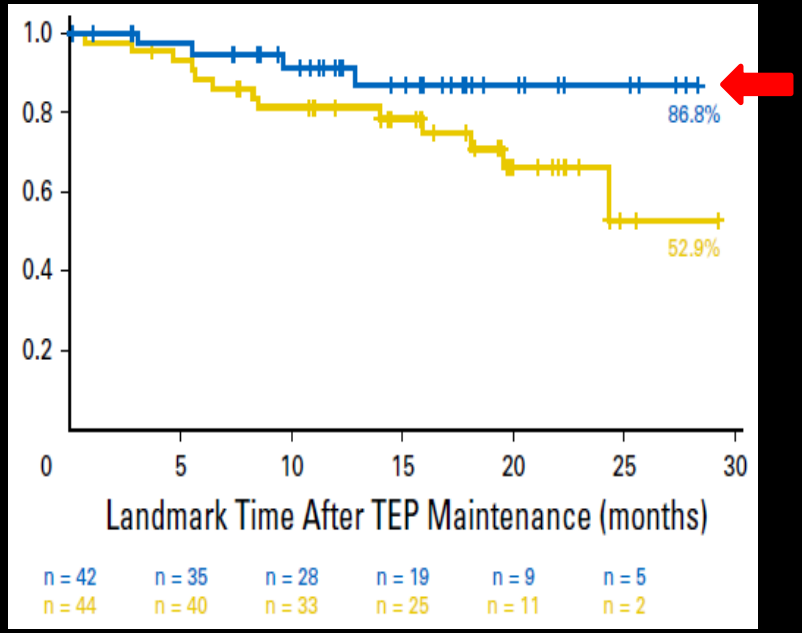
PET-CT, positron emission tomography–computed tomography; SUV, standardized uptake value

Zamagni E et al. *Blood*. 2011;118:5989.

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

New response criteria: IMWG 2016

lard IMWG Response criteria[6]	***sCR (stringent complete response)***	CR as defined below PLUS Normal FLC ratio[10] AND Absence of clonal cells in bone marrow biopsies by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 PCs)[7]
	CR (complete response)	Negative immunofixation on the serum AND urine AND[11] Disappearance of any soft tissue plasmacytomas AND <5% plasma cells in bone marrow aspirates (If cellular MRD is to be performed, the first BM aspirate should be sent to MRD and morphological evaluation is not mandatory)
Respons[illegible]tegory		**Response criteria [1]**
IMWG MRD negativity criteria (Requires CR as defined below)	***Sustained MRD negative***	MRD negative in the marrow (Next-generation flow or Next-generation sequencing) and by imaging as defined below, confirmed one year apart.[2] Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry[4] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD negative	Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[5] or higher
	Imaging+ MRD-negative	MRD negative as defined by Next-generation flow or Next-generation sequencing PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT[3]

These response criteria apply to all MM patients

Kumar S et al. Lancet Oncology 2016; 17: e328–46

Individualizing Treatment in the Era of Novel Agents

Stratification

- Biological Age, Performance status, Comorbidities
- Myeloma Comorbidity Index

Transplant

or

Non-transplant candidate

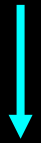
Risk Factors

- *Cytogenetics*
- *ISS, R-ISS*
- *Renal function*
- *LDH*
- *Extramedullary disease*

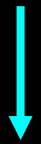
Standard vs High Risk

Management of MM in the transplant candidate ND patient

Induction



ASCT



Maintenance

According to the ESMO & NCCN guidelines

Management of MM in the transplant candidate ND patient

Induction

Three-drug based combon:
- *VTD*
- *VRD*
- *VCD*
- *PAD*

- **VTD is the standard of care outside US**
- **RVD in US and 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

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

Management of MM in the non- transplant candidate ND patient

Alkylators-based regimens

MP → VMP

One randomized trial:
PFS: 21 months
OS: 56 months

San Miguel . J Clin Oncol. 2013; 31: 448-55

Alkylators-free regimens

IMiD's → Len-dex

One randomized trial:
PFS: 26 months
OS: 59 months

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

Other combos

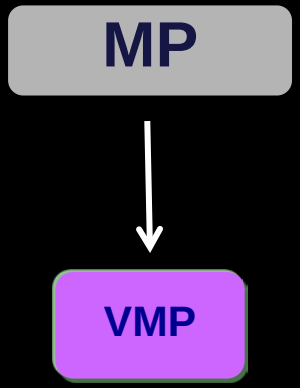
PI's/IMiD's → VRD
VMP->RD

PFS: 40 m/32m
OS: 74 m/60 m

Durie B. Lancet 2017
Mateos MV. EHA 2017

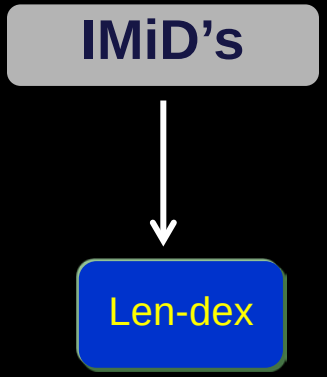
Management of MM in the non- transplant candidate ND patient

Alkylators-based regimens



VMP-Dara

Alkylators-free regimens

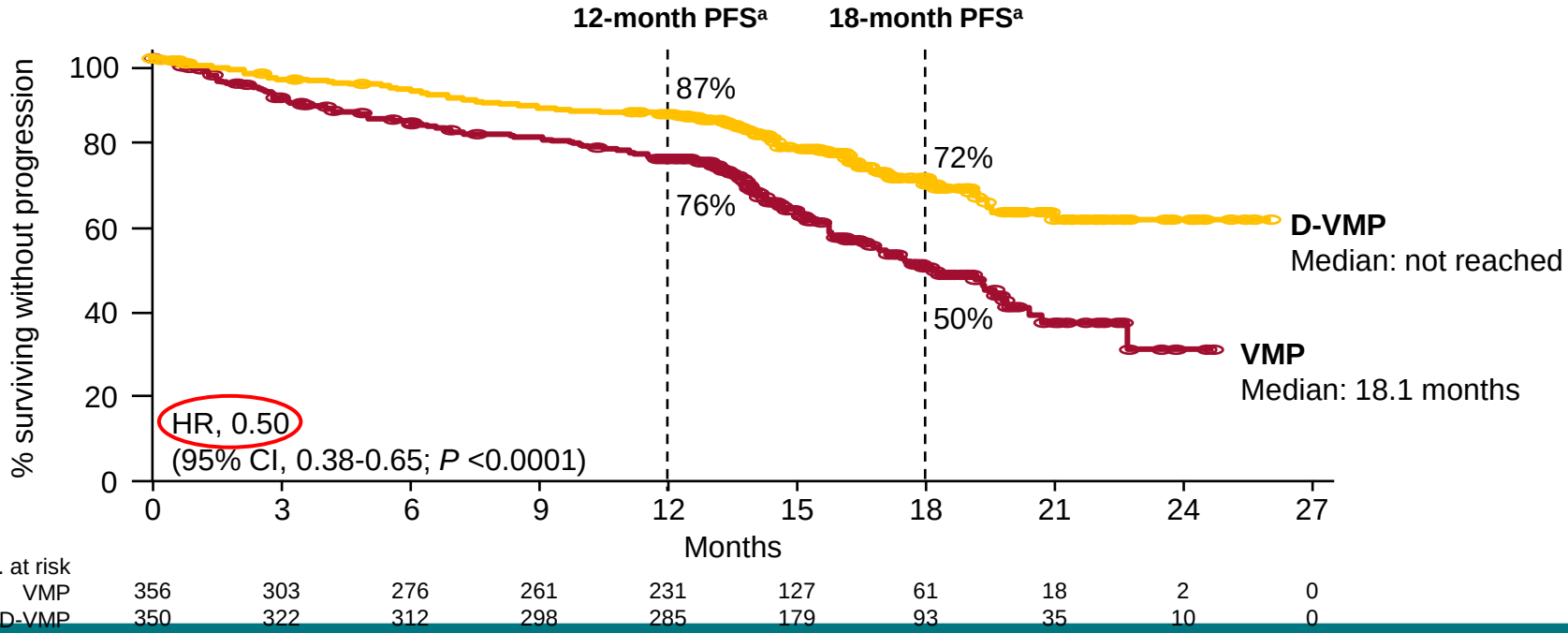


New potential standards

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

Efficacy: PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months

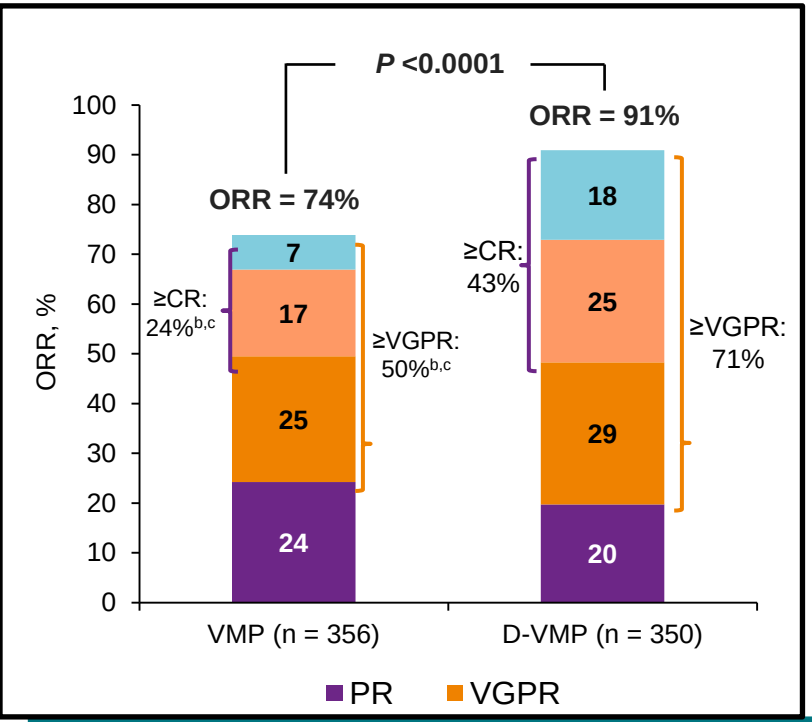


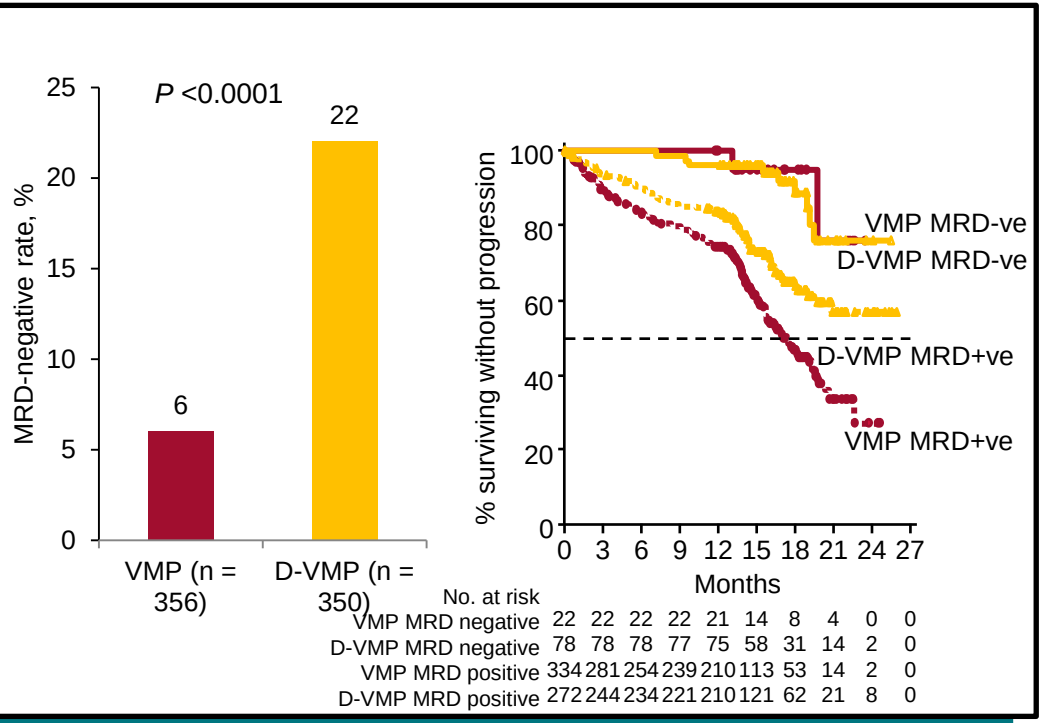
50% reduction in the risk of progression or death in patients receiving D-VMP
PFS benefit sustained in all subgroups of patients

PFS, progression-free survival; VMP, bortezomib/melphalan/prednisone; D, daratumumab; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Mateos MV, et al. Presented at ASH 2017 (Abstract LBA-4), oral presentation.

Efficacy: ORR[a] and MRD evaluation



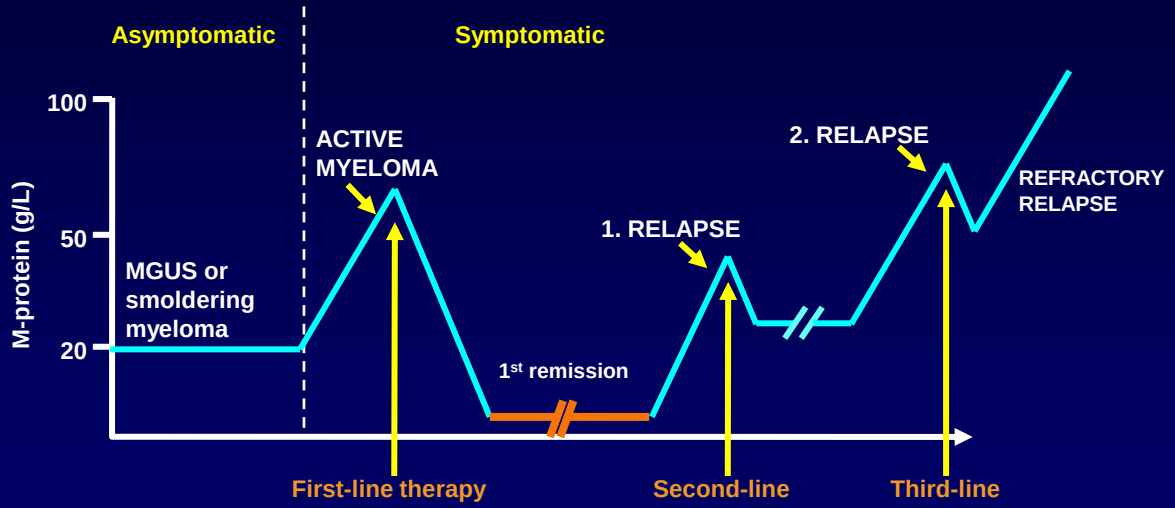


Significantly higher ORR, ≥VGPR rate, and ≥CR rate with D-VMP;
>3-fold higher MRD-negativity rate with D-VMP;
Lower risk of progression or death in all MRD-negative patients

ORR, overall response rate; VMP, bortezomib/melphalan/prednisone; D, daratumumab; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response.
[a]Intent-to-treat population. [b]*P* value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test.
[c]*P* <0.0001. [d]Responders in response-evaluable population.

Mateos MV, et al. Presented at ASH 2017 (Abstract LBA-4), oral presentation.

Natural History of MM



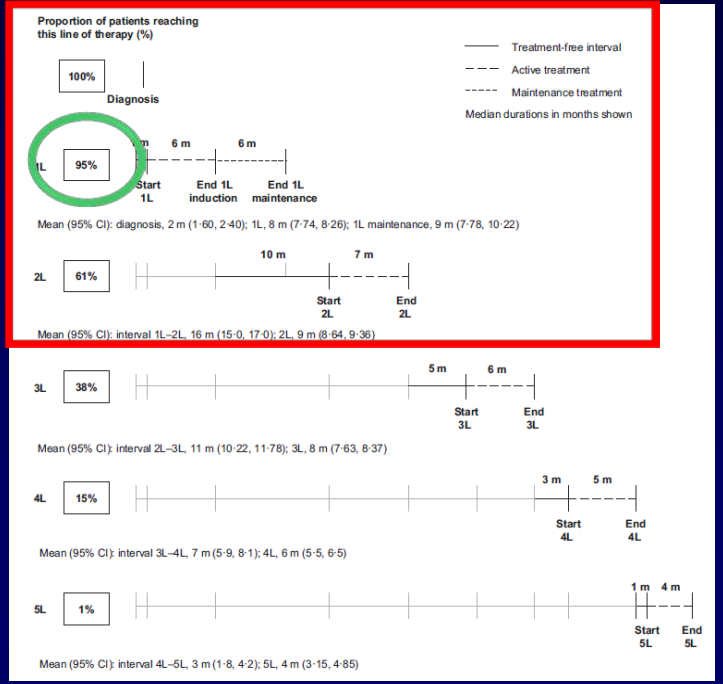
- The second line of treatment will arrive later than in the past
- How many patients will arrive to the second line?

MGUS=monoclonal gammopathy of undetermined significance

Kurtin et al. Clin J Oncol Nurs. 2013;17 Suppl:7-11

Real-world duration of therapy: Limited feasibility of continuous treatment

- Retrospective chart review of ~5000 patients in Belgium, France, Germany, Italy, Spain, Switzerland, and UK
- Real-world data show:
  - Median 6 months duration of first-line therapy
  - Followed by median 10 months treatment-free interval
  - General decrease in duration of subsequent lines of therapy and duration of treatment-free intervals



Yong K, et al. Br J Haematol 2016;175(2):252-64.

Strategies at Relapse :
How to Make the Right Choice

Type of relapse

Efficacy of previous treatments

Toxicity of previous treatments

Further options

Strategies at Relapse: How to Make the Right Choice

- **Early relapse (<1 year post induction/ASCT)----------5-10%**
  - ***"Overcome drug resistance"***
  - **Combination of non-cross-resistant agents**
    - **VTD-PACE or KRD/DaraRd→ RIC-Allo**

- **Intermediate relapse (1-3 years post ASCT)----------80%**
  - **"*Prolong survival until curative treatments are developed"***

- **Late relapse (>2-3 years post first line) ----------10%**
  - **Reinduction + 2nd ASCT/Retreatment with the same backbone**

San Miguel J, et al. JCO 2013; 31:448-455

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance (~~Len~~)

Induction Bortezomib-based combo

~~Lenalidomide-dex~~

1st relapse

Rd
Continuous therapy as backbone

Carfilzomib plus Rd
PFS: 26.3m, HR: 0.69

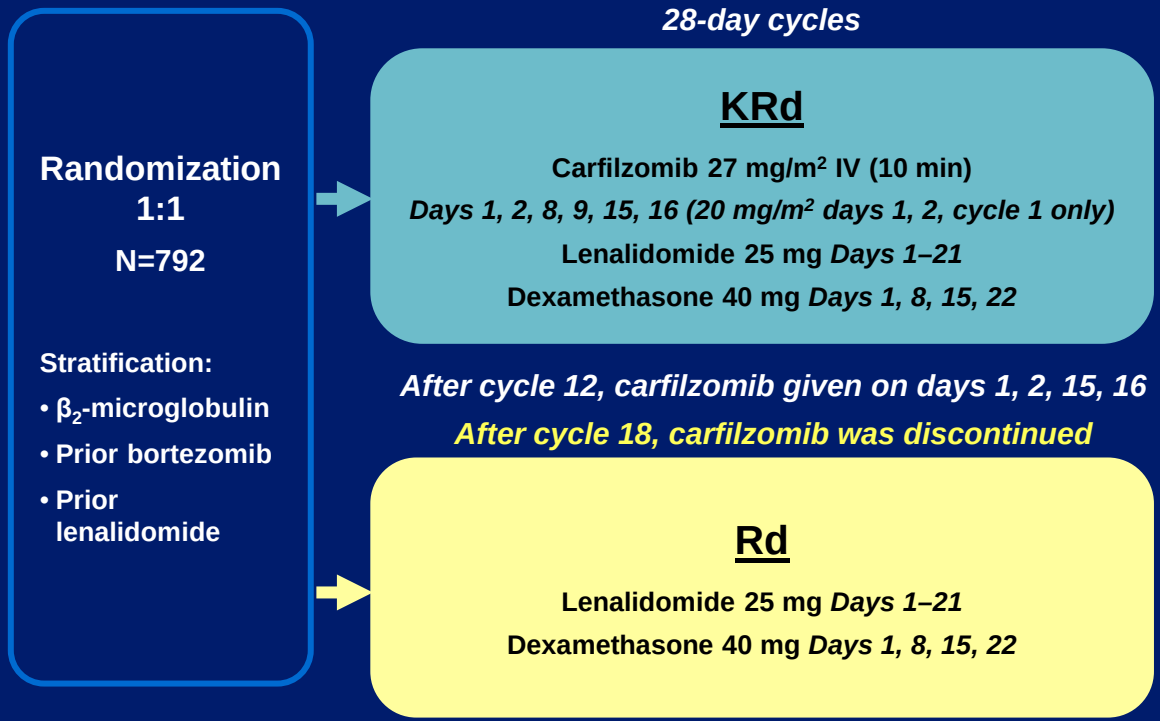
Elotuzumab plus Rd
PFS: 19m, HR: 0.73

Daratumumab plus Rd
PFS: NR, HR: 0.37

Ixazomib plus Rd
PFS: 20.6m, HR: 0.74

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. Dimopoulos N Engl J Med 2016; 4. Moreau P et al. NEJM 2016;374(17):1621-34.

ASPIRE: Study Design

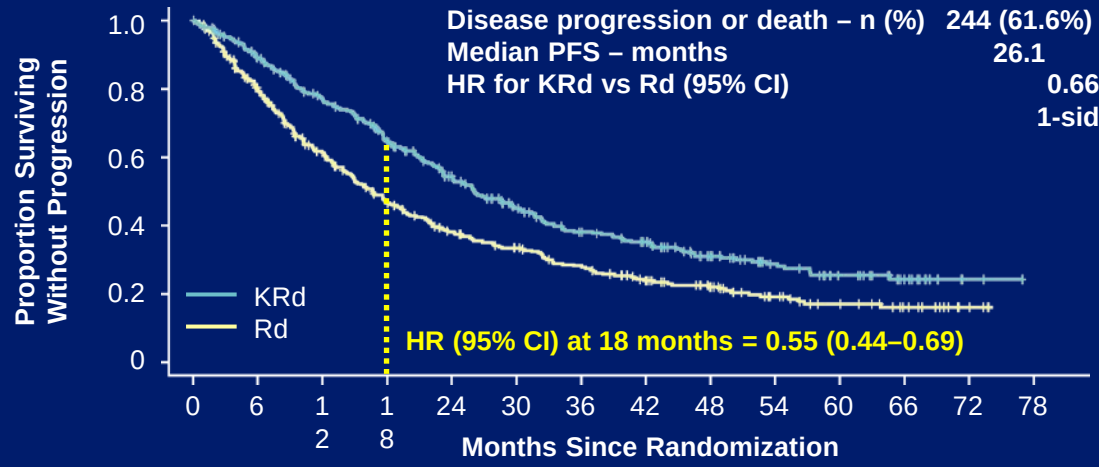


Stewart AK, et al. Presented at ASH 2017 (Abstract 743), oral presentation

Updated Investigator-Assessed Progression-Free Survival

ITT Population (N=792): 9.5-month Improvement

	KRd (n=396)	Rd (n=396)
Disease progression or death – n (%)	244 (61.6%)	272 (68.7)
Median PFS – months	26.1	16.6
HR for KRd vs Rd (95% CI)	0.66 (0.55–0.78)	
	1-sided *P*<0.0001	



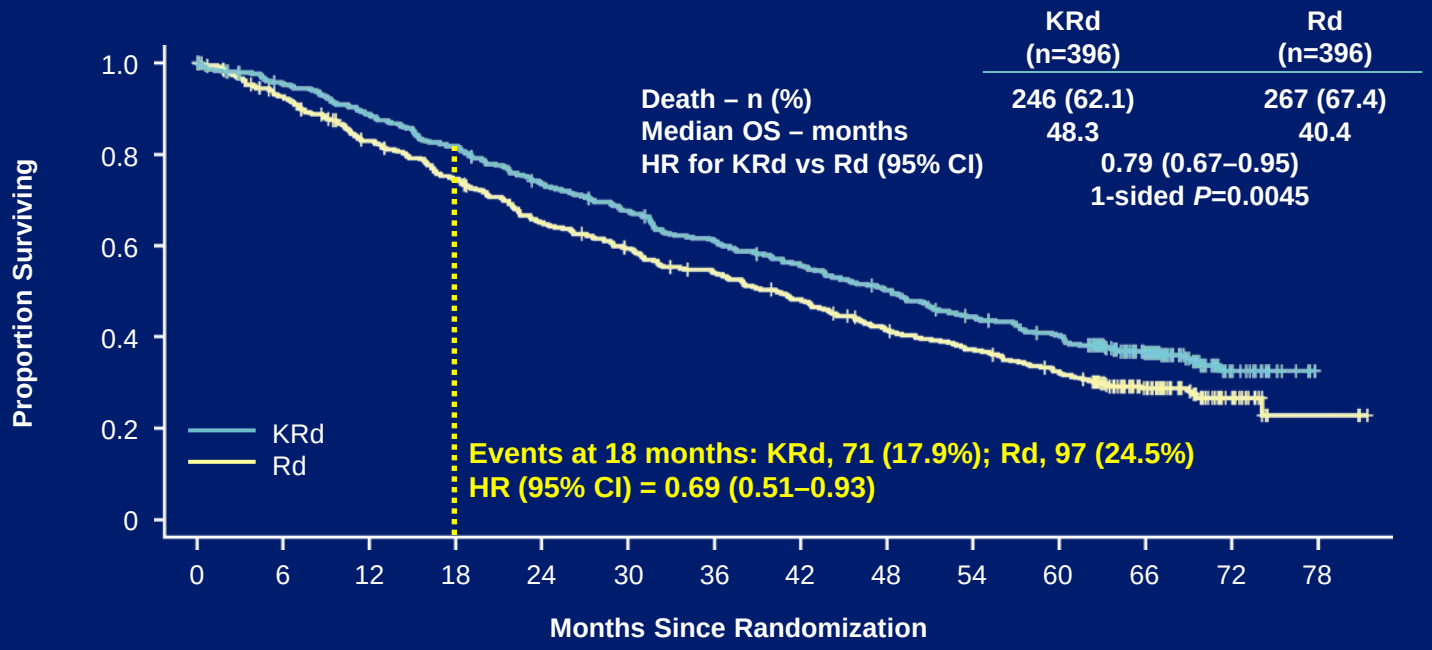
Number of patients at risk:

KRd	396	337	282	227	178	136	109	94	65	45	32	17	2	0
Rd	396	291	211	154	118	99	81	61	45	30	21	13	4	0

- **Data cutoff date: April 28, 2017; Median follow-up: 48.8 (KRd) and 48.0 (Rd) months**
- **Carfilzomib discontinued after 18 cycles**

Stewart AK, et al. Presented at ASH 2017 (Abstract 743), oral presentation

Overall Survival: 7.9-month Median Improvement



Number of patients at risk:

KRd	396	369	343	316	282	259	232	211	190	166	149	88	22	0
Rd	396	356	313	281	243	220	199	176	149	133	113	69	20	3

Stewart AK, et al. Presented at ASH 2017 (Abstract 743), oral presentation

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ASCT (melphalan 200)

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Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

1st relapse

Rd
Continuous therapy as backbone

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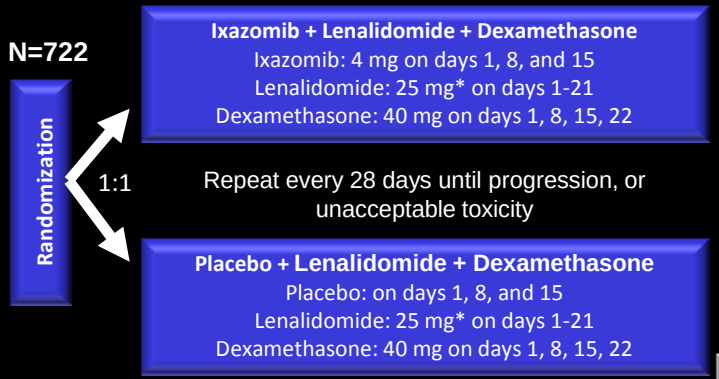
1. Stewart AK, et al. N Engl J Med 2015;372:142-52; 2. Lonial S, et al. N Engl J Med 2015; 373(7):621–31;
3. Dimopoulos N Engl J Med 2016; 4. Moreau P et al. NEJM 2016;374(17):1621-34.

TOURMALINE-MM1: Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design



Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Response and progression (IMWG 2011 criteria[1]) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

Primary endpoint:
- PFS

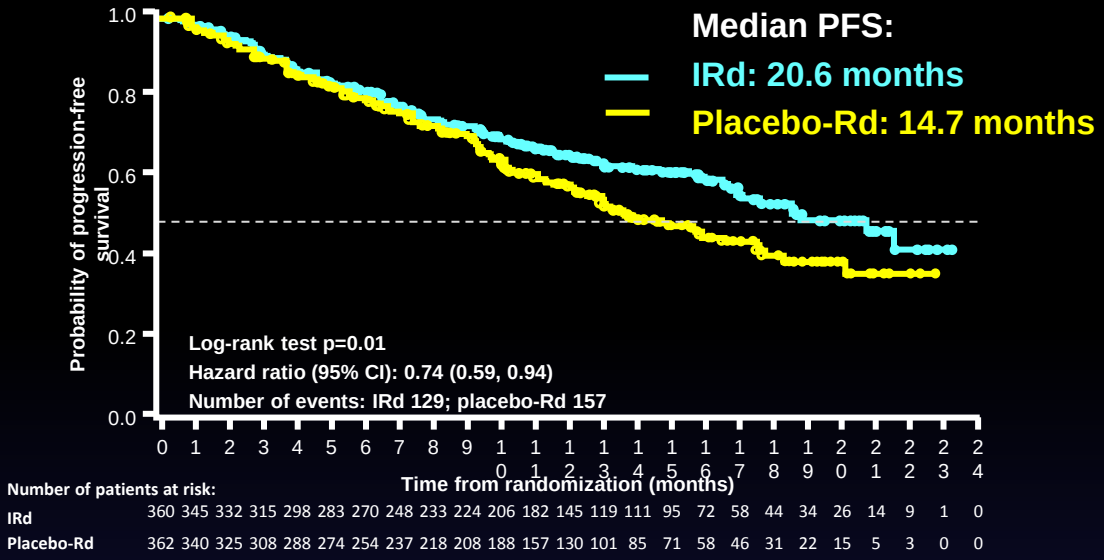
Key secondary endpoints:
- OS
- OS in patients with del(17p)

Exploratory study objective
- Evaluate potential relationships between treatment outcomes and tumor gene expression patterns by RNA-seq

*10 mg for patients with a creatinine clearance of ≤60 or ≤50 ml/min/1.73 m^2, with the cutoff point determined according to the local prescribing information

Moreau P et al. NEJM 2016;374(17):1621-34

Final PFS analysis: A significant, 35% improvement in PFS with IRd vs placebo-Rd



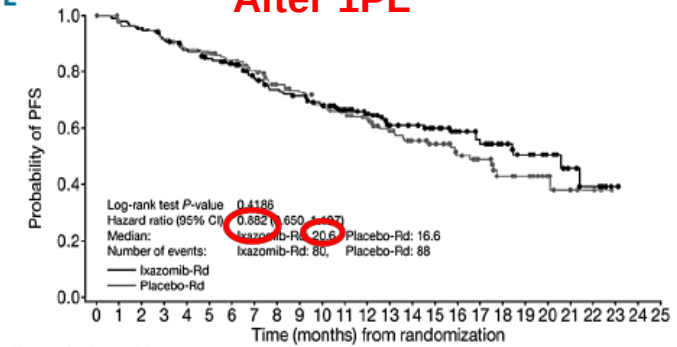
- Median follow-up: 14.8 months in the IRd group and 14.6 months in the placebo-Rd group

Moreau P et al. NEJM 2016;374(17):1621-34

TOURMALINE-MM1: PFS according to the number of prior lines of therapy

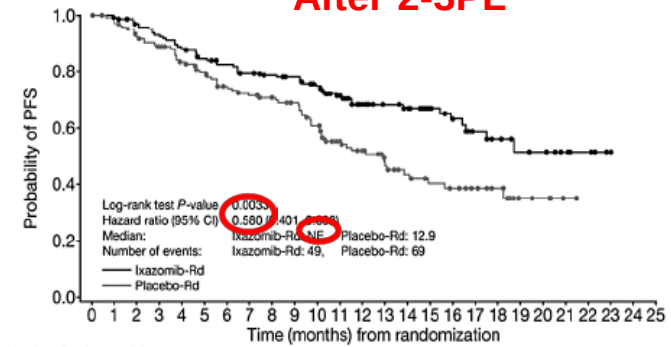
E

After 1PL



F

After 2-3PL



B

Variable	Median PFS, months (events/n) Ixazomib-Rd	Placebo-Rd	HR	95% CI
1 prior therapy	20.6 (80/212)	16.6 (88/213)	0.882	(0.650, 1.197)
High risk	18.5 (18/45)	9.7 (19/34)	0.642	(0.325, 1.271)
Standard risk	20.6 (37/111)	17.5 (48/124)	0.807	(0.521, 1.251)
Immunomodulatory drug-naive	18.5 (47/119)	13.6 (48/111)	0.807	(0.533, 1.221)
Immunomodulatory drug-exposed	NE (33/93)	20.1 (40/102)	0.902	(0.562, 1.446)
PI-naive	NE (25/75)	17.5 (30/74)	0.823	(0.483, 1.401)
PI-exposed	18.4 (55/137)	15.9 (58/139)	0.912	(0.628, 1.325)
Transplant	20.6 (50/126)	20.1 (38/118)	1.232	(0.805, 1.885)
No transplant	18.4 (30/86)	12.3 (50/95)	0.604	(0.380, 0.959)
No transplant but prior melphalan treatment	NE (11/44)	13.2 (25/47)	0.509	(0.245, 1.058)

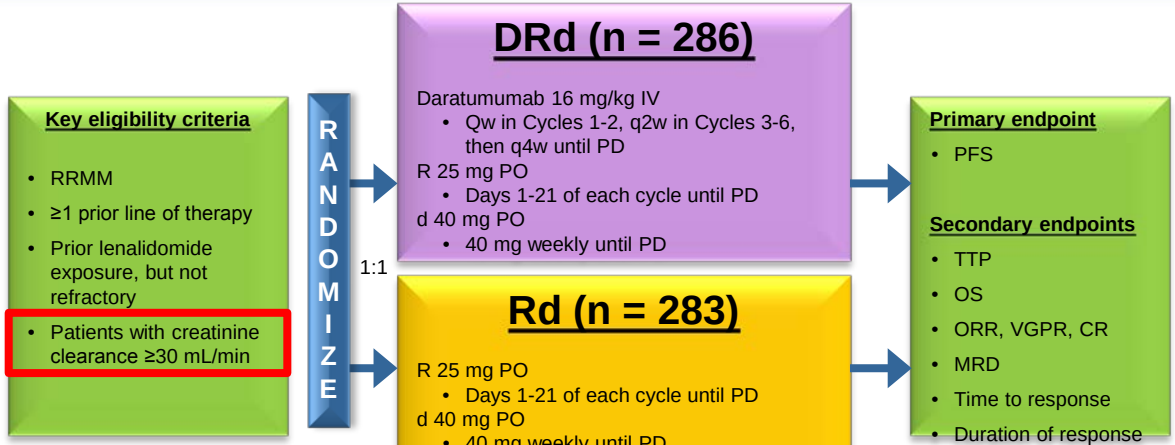
Variable	Median PFS, months (events/n) Ixazomib-Rd	Placebo-Rd	HR	95% CI
2-3 prior therapies	NE (49/148)	12.9 (69/149)	0.580	(0.401, 0.838)
High risk	NE (8/30)	11.1 (16/28)	0.421	(0.180, 0.987)
Standard risk	NE (26/88)	11.5 (43/92)	0.486	(0.298, 0.793)
Immunomodulatory drug-naive	NE (13/48)	11.1 (23/47)	0.473	(0.235, 0.951)
Immunomodulatory drug-exposed	18.7 (36/100)	13.0 (46/102)	0.627	(0.399, 0.984)
PI-naive	NE (11/35)	14.9 (13/35)	0.601	(0.265, 1.359)
PI-exposed	18.7 (38/113)	11.1 (56/114)	0.575	(0.380, 0.869)
Transplant	18.7 (30/86)	13.0 (36/81)	0.730	(0.444, 1.20)
No transplant	NE (19/62)	10.2 (33/68)	0.454	(0.252, 0.81)
No transplant but prior melphalan treatment	NE (13/46)	10.2 (24/52)	0.441	(0.219, 0.88)

Pts with 2 or 3 PL or 1PL without trx seemed to have greater benefit than pts after 1PL and trx

Mateos MV et al. Haematologica. 2017 Oct;102(10):1767-1775.

POLLUX: Study Design

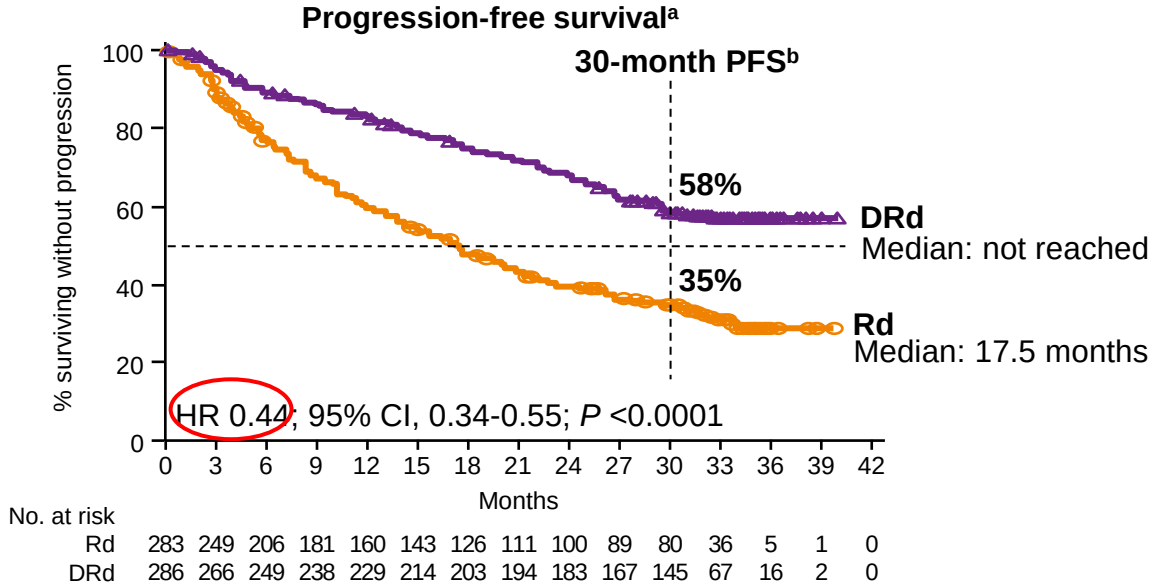
Multicenter, randomized (1:1), open-label, active-controlled phase 3 study



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 updated analysis: PFS



Median follow-up: 32.9 months (range, 0 - 40.0 months)

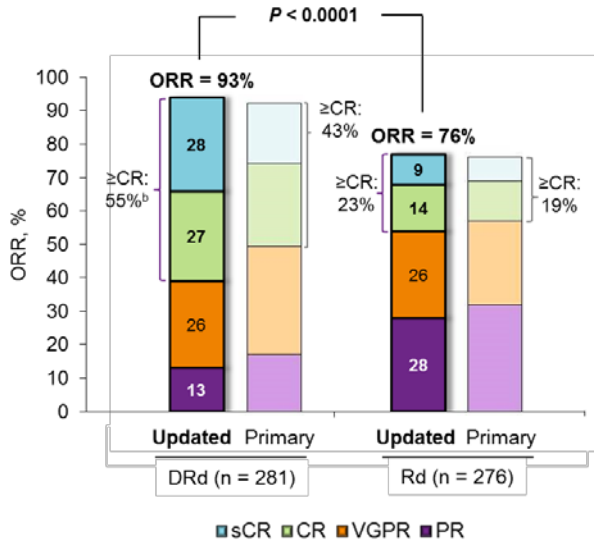
56% reduction in risk of progression/death for DRd versus Rd

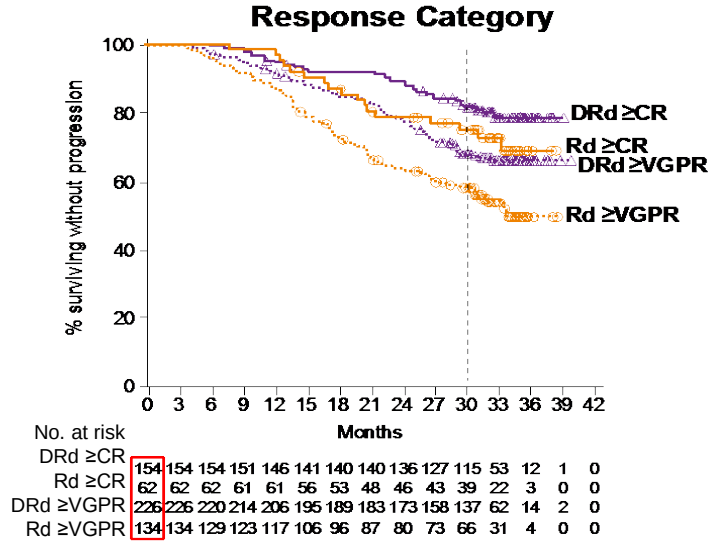
HR, hazard ratio; CI, confidence interval.
[a]Exploratory analyses based on clinical cut-off date of October 23, 2017; [b]Kaplan-Meier estimate.

Dimopoulos MA, et al. Presented at ASH 2017 (Abstract 739), oral presentation.

POLLUX updated analysis: ORR and MRD-negative Rates[a]

- Median follow-up: 32.9 months (range, 0 - 40.0 months)



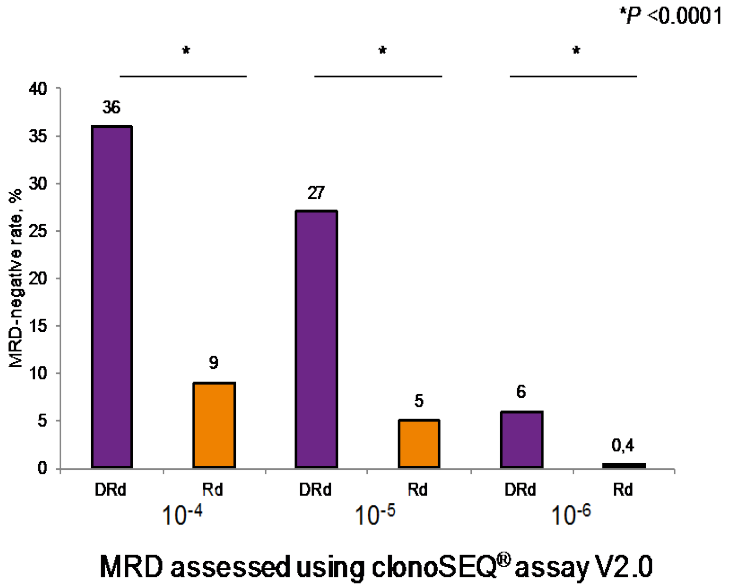


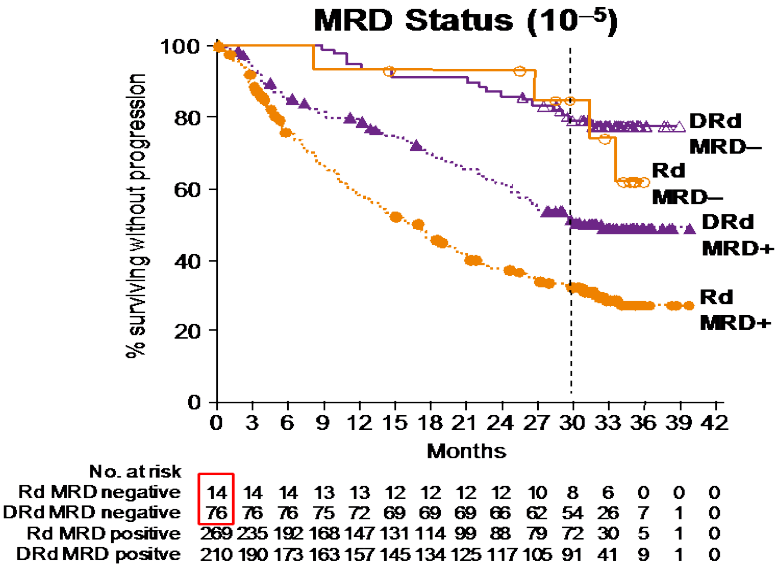
Responses continued to deepen in the DRd group and deeper responses associated with longer PFS

sCR, stringent complete response; PR, partial response.
Primary analysis reported in Dimopoulos MA, et al. *N Engl J Med.* 2016;375(14):1319-1331.
[a]Exploratory analyses based on clinical cutoff date of October 23, 2017; [b]*P* <0.0001 for DRd versus Rd.

Dimopoulos MA, et al. Presented at ASH 2017 (Abstract 739), oral presentation.

POLLUX: PFS by Depth of Response

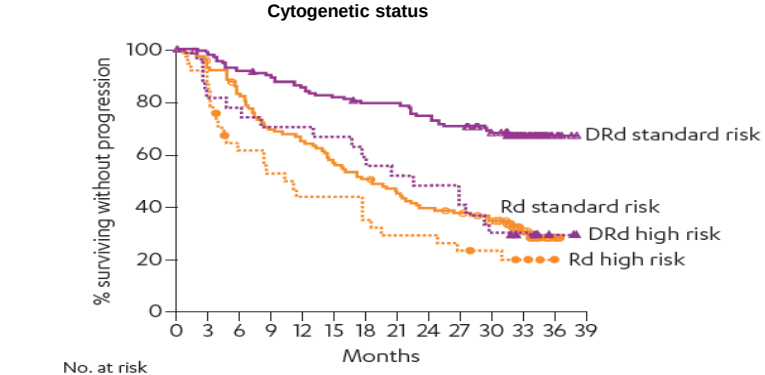




Deeper responses were more common on DRd:Significantly higher (>3-fold) MRD-negative rates for DRd versus Rd
MRD negativity was associated with longer PFS

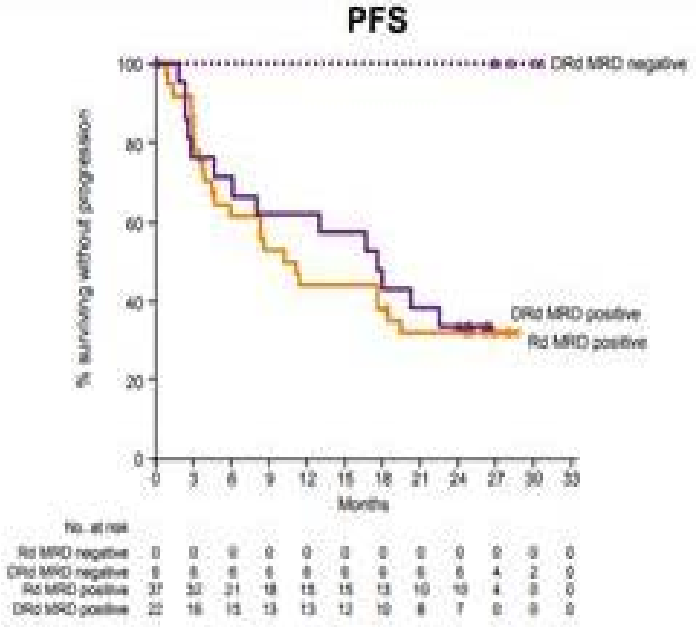
Dimopoulos MA, et al. Presented at ASH 2017 (Abstract 739), oral presentation.

Phase 3 POLLUX study: DRd vs Rd in RRMM
Subgroup analyses: cytogenetic abnormalities



High risk	DRd n = 28	Rd n = 37
mPFS, mo	22.6	10.2
HR (95% CI)	0.64 (0.33-1.27)	
P value	0.1955	

Standard risk	DRd n = 133	Rd n = 113
mPFS, mo	NR	18.5
HR (95% CI)	0.28 (0.19-0.43)	
P value	<0.0001	

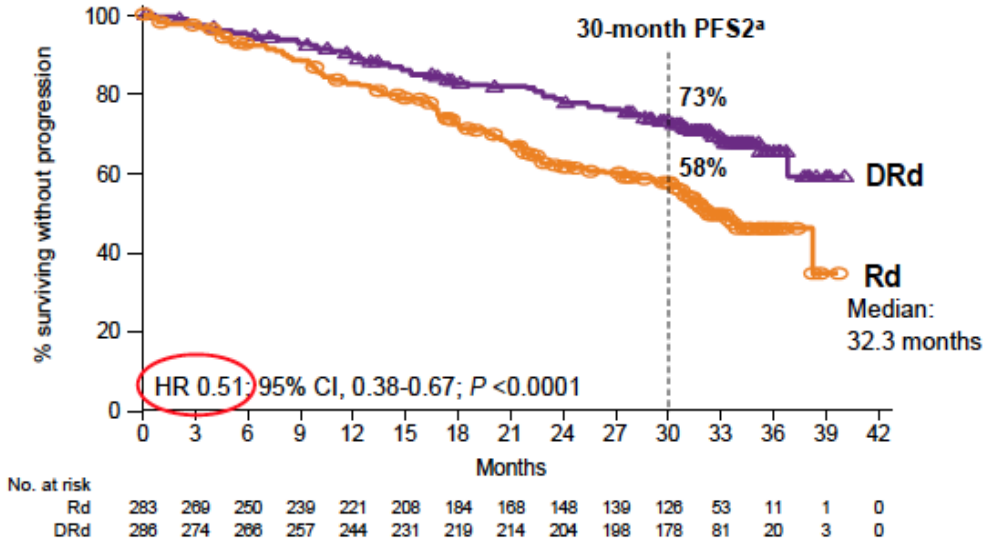


In pts with high-risk CA, Rd did not result in any MRD-ve whilst DRd patients achieved MRD-ve

Moreau P, et al. Presented at ASH 2017 (Abstract 1883), poster presentation

Phase 3 POLLUX study

PFS With Subsequent Line of Therapy (PFS2)



DRd does not negatively impact outcomes of subsequent therapy

Dimopoulos MA, et al. Presented at ASH 2017 (Abstract 739), oral presentation

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

Second ASCT/Allo-RIC

1st relapse

Retreatment with bz-based

Rd
Continuous therapy as backbone

Carfilzomib plus Rd
PFS: 26.3m, HR: 0.69

Elotuzumab plus Rd
PFS: 19m, HR: 0.73

Daratumumab plus Rd
PFS: NR, HR: 0.37

Ixazomib plus Rd
PFS: 20.6m, HR: 0.74

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. Dimopoulos MA: N Engl J Med 2016; 4. Moreau P et al. NEJM 2016;374(17):1621-34.

Comparison among the different three-drug based combinations based on Rd plus a third agent

Efficacy&Toxicity

vs. Rd
(at least 1PL)

Hazard ratio for progression

Secondary end points

	median PFS	CR	MRD
DRd[1]	NE (>30m)	55%	27%
KRd[2]	26.3m	31.8%	-
ERd[3]	18.5m	4.4%	-
IRd[4]	20.0m	14.2%	-

Combination (N)	Adverse event	Experimental arm, n (%)
		Grade ≥3
Rd + Carfilzomib (392)	Hypertension Cardiac failure Acute renal failure	17 (4.3) 15 (3.8) 13 (3.3)
Rd + Elotuzumab (318)	Infusion reaction	(1)
Rd + Ixazomib (361)	Rash	18 (5)
Rd + Daratumumab (283)	Infusion reaction	15 (5.3)

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)

How are we going to proceed in order to do the right choice concerning IMiD's-based combinations?

- Type of relapse: biochemical, aggressive,…KRd/DaraRd
- Age: elderly patients tolerate well mAbs
- Number of prior lines of therapy
  - Dara-Rd continues being the most effective rescue therapy regardless the number of prior lines.
- Patients preferences, convenience....
  - Combinations of oral admon like IRd
- Cytogenetic abnormalities,....
  - KRd vs DaraRd: KRd seems to be of benefit for this patients' population.

The main challenge for these combinations is that the population in which these trials was done is dissapearing with the use of R in the first line of therapy

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance Len

Induction Bortezomib-based combo

Lenalidomide-dex

Second ASCT/Allo-RIC

1st relapse

Retreatment with bz-based

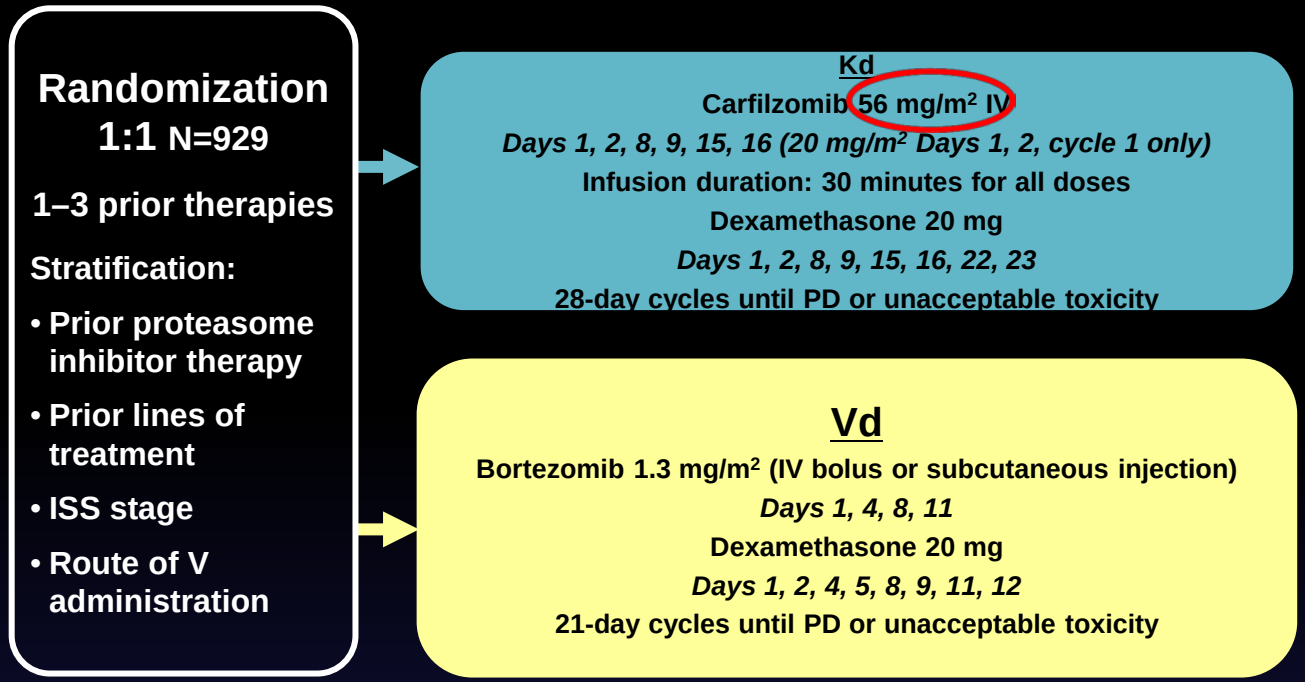
PIs-based combinations

- **Kd** HR:0.53 PFS: 18.7 m
- **VD + Daratumumab** HR:0.32 PFS: 16.7m
- ~~**Panobinostat-bz/cz** HR:0.63 PFS: 12 months~~
- ~~**Elo-Bd** HR: 0.72 PFS: 9.7 m~~

Rd
Continuous therapy as backbone

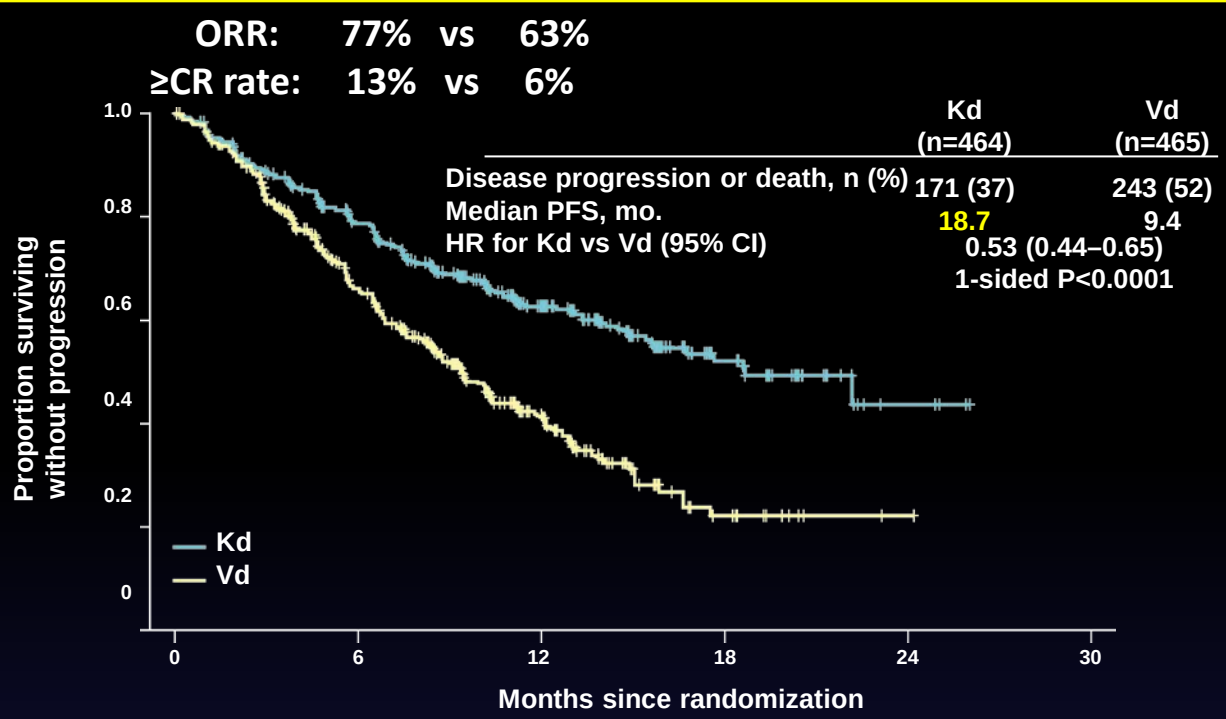
- **Carfilzomib plus Rd** PFS: 26.3m, HR: 0.69
- **Elotuzumab plus Rd** PFS: 19m, HR: 0.73
- **Daratumumab plus Rd** PFS: NR, HR: 0.37
- **Ixazomib plus Rd** PFS: 20.6m, HR: 0.74

ENDEAVOR study design



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

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

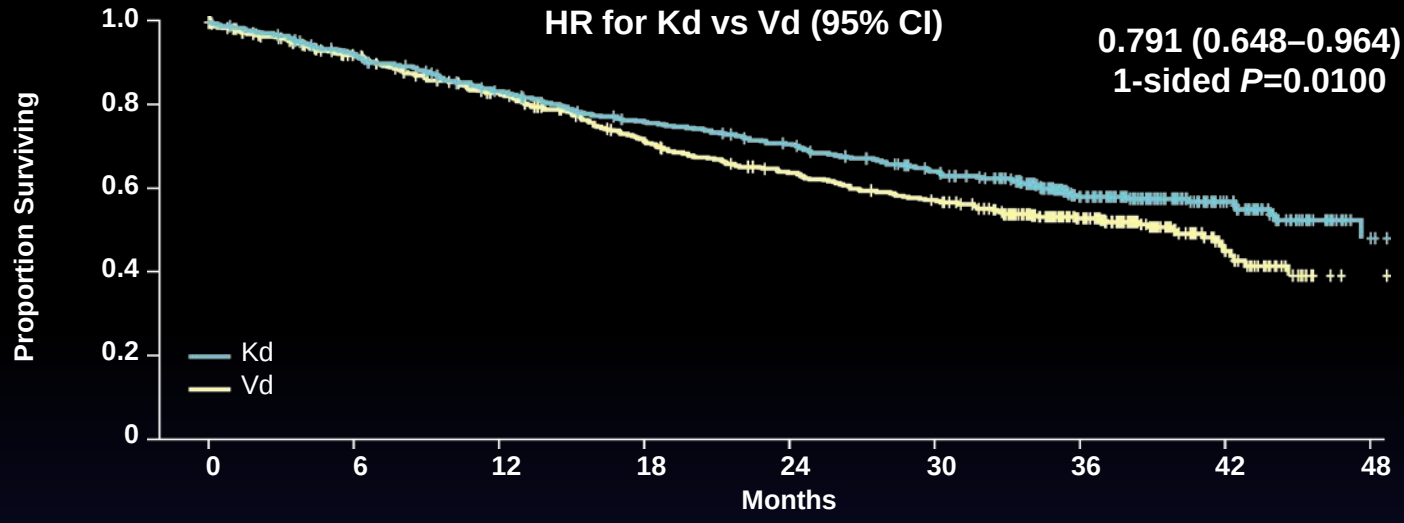


- **Significant prolongation of the Overall survival: 47 vs 40 months**

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

Endeavor: Overall Survival

	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)	
	1-sided *P*=0.0100	



Number at risk:

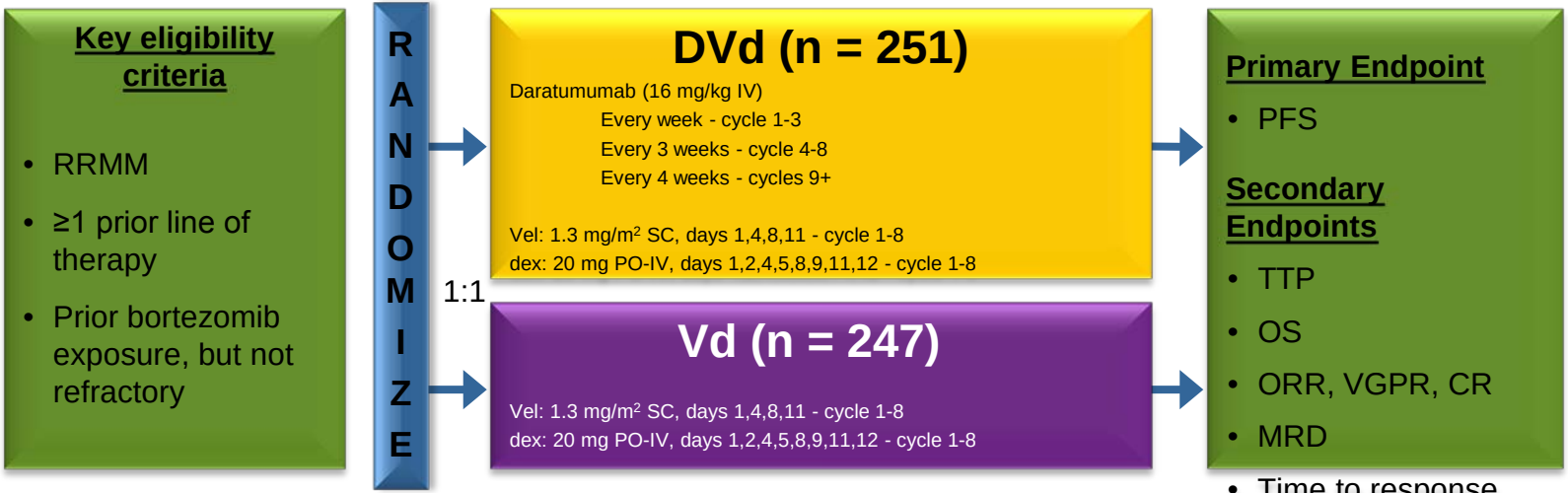
Kd	464	423	373	335	308	270	162	66	10
Vd	465	402	351	293	256	228	140	39	5

Dimopoulos MA, et al. Presented at: 16th International Myeloma Workshop; March 1-4, 2017; New Delhi, India.

Dimopoulos MA et al. Lancet Oncology 2017

CASTOR: Study Design

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



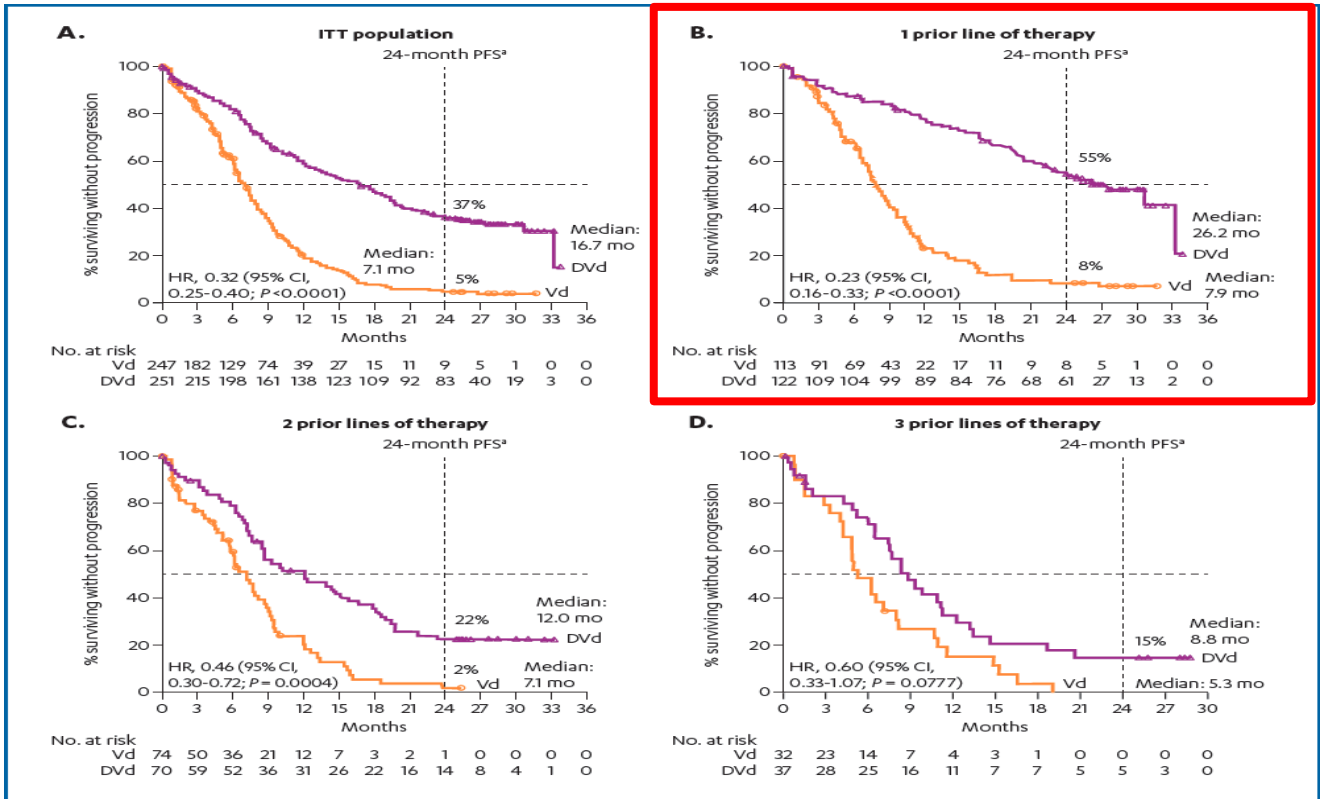
- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

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: Updated efficacy

Median f/u: 26.9 months



1. Lentzsch S, et al. Presented at ASH 2017 (Abstract 1852), poster presentation;
2. Spencer A, et al. Presented at ASH 2017 (Abstract 3145), poster presentation

CASTOR: DVd vs Vd: update of Response Rates

Table 2. Response and MRD-negative Rates of DVd Based on the Number of Prior Lines of Therapy

	Study population		1 prior line of therapy		2 prior lines of therapy		3 prior lines of therapy		1 to 3 prior lines of therapy	
	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Vd
ORR[a]										
N	240	234	119	109	64	71	35	29	218	209
%	**85**	**63**	**92**	**74**	**84**	**65**	**69**	**41**	**86**	**67**
P value	<0.0001		0.0007		0.0563		0.0487		<0.0001	
≥VGPR, %	63	29	77	42	61	18	34	28	65	32
P value	<0.0001		<0.0001		<0.0001		0.6999		<0.0001	
≥CR, %	30	10	43	15	25	9	11	3	33	11
P value	<0.0001		<0.0001		0.0118		0.3009		<0.0001	
sCR, %	10	3	14	5	6	1	6	0	11	3
MRD-negative rate (10^{-5})[b]										
N	251	247	122	113	70	74	37	32	229	219
%	**12**	**2**	**16**	**3**	**11**	**0**	**5**	**3**	**13**	**2**
P value	<0.0001		0.0002		0.0005		0.64		<0.0001	

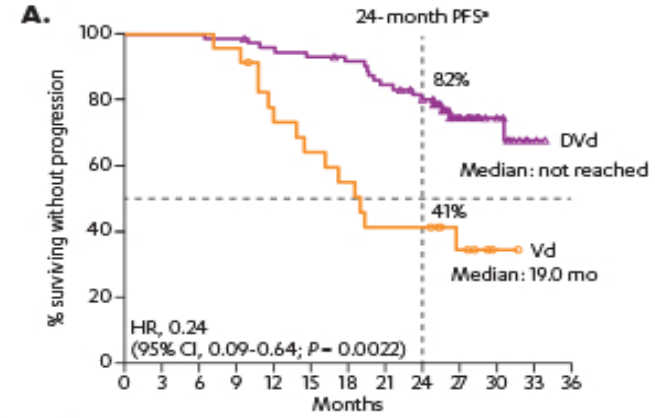
MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; ITT, intent-to-treat; Vd, bortezomib/dexamethasone; ORR, overall response rate; VGPR, very good partial response; CR, complete response; sCR, stringent complete response.
[a]Response-evaluable population.
[b]ITT population.

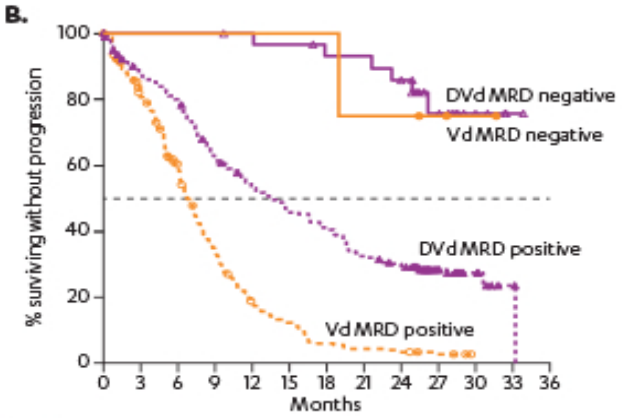
1. Lentzsch S, et al. Presented at ASH 2017 (Abstract 1852), poster presentation;
2. Spencer A, et al. Presented at ASH 2017 (Abstract 3145), poster presentation

CASTOR: DVd vs Vd in RRMM by responses

Patients achieving CR

Patients achieving MRD -ve



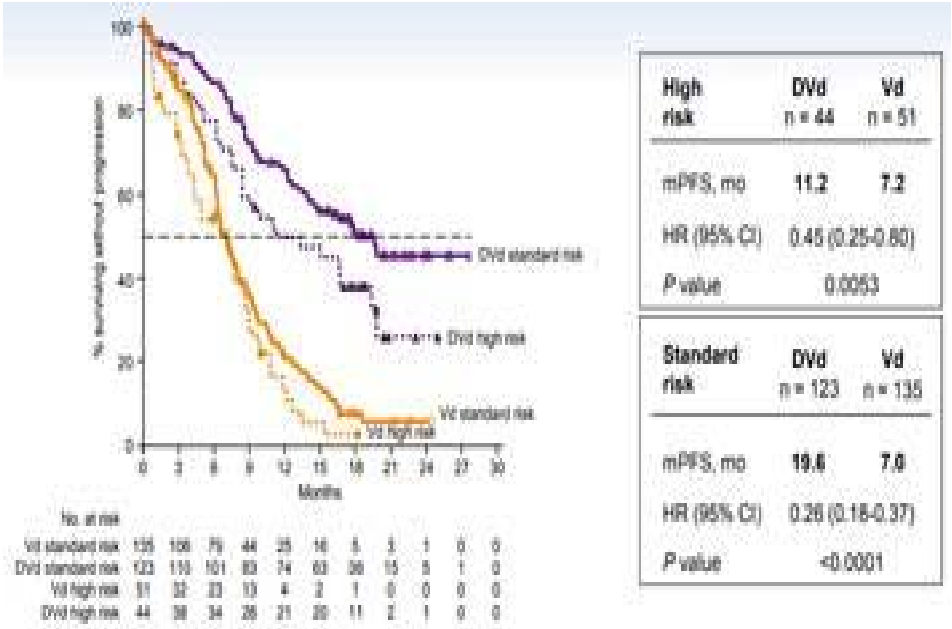


PFS, progression-free survival; CR, complete response; MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Figure 3. PFS in patients who achieved (A) ≥CR and (B) MRD negativity at 10^{-5}.

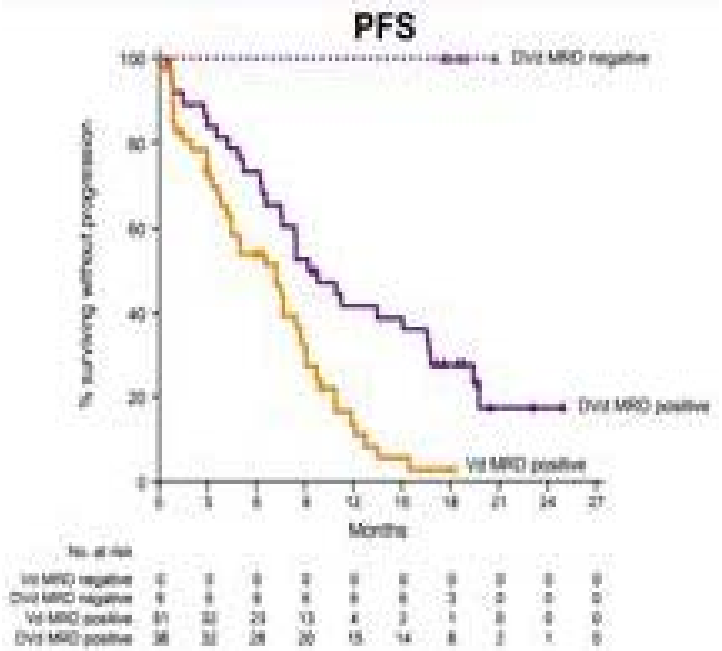
1. Lentzsch S, et al. Presented at ASH 2017 (Abstract 1852), poster presentation;
2. Spencer A, et al. Presented at ASH 2017 (Abstract 3145), poster presentation

Castor: DVd vs Vd in patients with high-risk cytogenetic abnormalities



High risk	DVd n = 44	Vd n = 51
mPFS, mo	11.2	7.2
HR (95% CI)	0.45 (0.25-0.80)	
P value	0.0053	

Standard risk	DVd n = 123	Vd n = 135
mPFS, mo	19.6	7.9
HR (95% CI)	0.26 (0.18-0.37)	
P value	<0.0001	

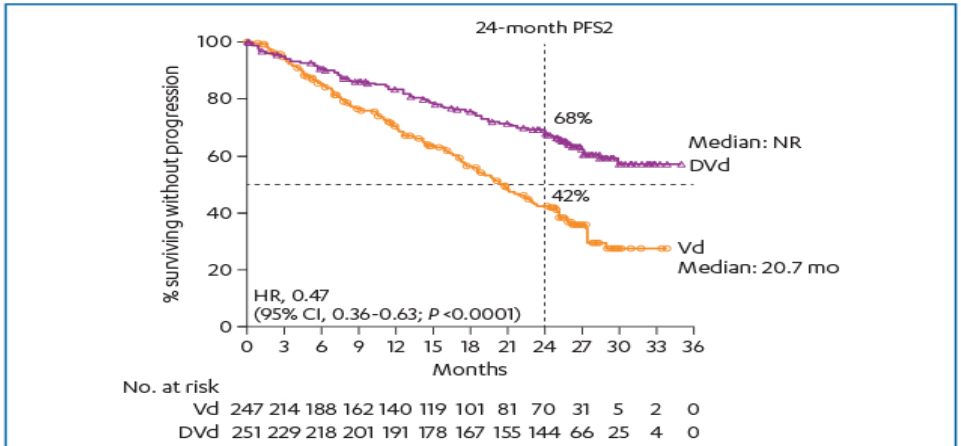


Patients with HR CA only achieve MRD-ve When received DVd

CASTOR: PFS2 as surrogate marker for OS

PFS2 in ITT and Subgroup Populations

- In the ITT population, PFS2 was significantly prolonged with DVd compared with Vd (median not reached [NR] vs 20.7 months; HR, 0.47; 95% CI, 0.36-0.63; *P* <0.0001; **Figure 2**)



PFS2, progression-free survival with subsequent line of therapy; ITT, intent-to-treat; NR, not reached; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.

Figure 2. PFS2 in the ITT population.

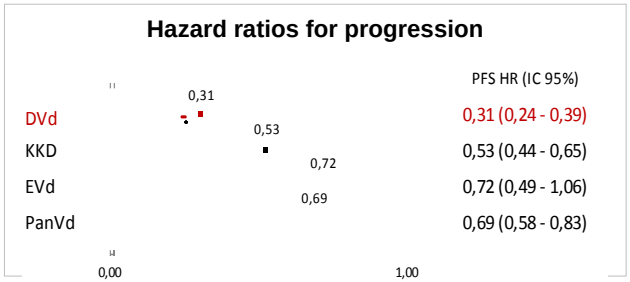
- PFS2 subgroup analyses demonstrated superiority of DVd versus Vd among patients:

1. Lentzsch S, et al. Presented at ASH 2017 (Abstract 1852), poster presentation;
2. Spencer A, et al. Presented at ASH 2017 (Abstract 3145), poster presentation

Comparison among the different PIs-based combinations

Efficacy&Toxicity

vs. Vd
(after at least 1PL)



Secondary end points

	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%*	-

Combo (N)	Adverse event	Experimental arm, n (%)	
		Grade 3	Grade 4
Kd (463)	Hypertension Dyspnea Cardiac failure	41 (9) 25 (5) 17 (4)	0 0 3 (<1)
		Grade 3	Grade 4
Vd + Dara (243)	Infusion reaction	21 (8.6)	0
	Hypertension	16 (6.6)	

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

How are we going to proceed in the clinical practice?

- Type of relapse: aggressive, early relapses occurring within the first 12 m after the last line of therapy: most effective combinations
- Age of the patients:
- Sensitivity/Refractoriness to the previous drugs
- Cumulative toxicity
- Comorbidities
- Number and type of prior lines of therapy: DVd in first relapse

The main challenge is that we have to select these combinations more and more because lenalidomide is moving to the first line of therapy

New combinations on the PI-based regimens or with second generation IMiD's after 1PL?

Sequencing treatment for MM patients

Transplant Candidate

Induction Bortezomib-based combination

▼

ASCT (melphalan 200)

▼

Lenalidomide

Non Transplant Candidate

MPV / VCD /

LD

Second ASCT/Allo-RIC

1st relapse

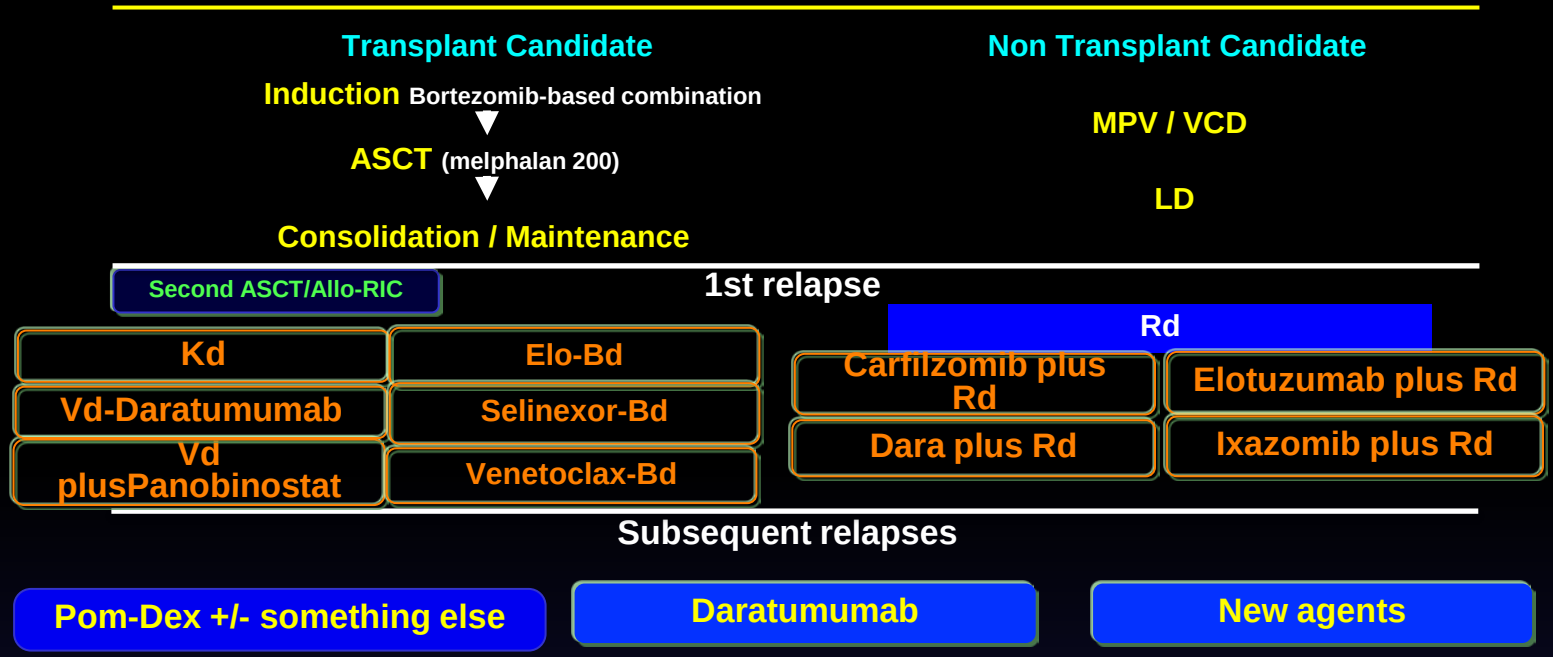
PI's based combinations

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

IMiD's based combinations

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

Treatment Possibilities at 2nd + relapse



Phase 3: Pomalidomide + low-dose dex versus high-dose dex in rel/ref MM (MM-003)

Analysis of pts (n=456) double refractory to bortezomib and lenalidomide after a median number of 5 lines

Updated PFS and OS results

median follow-up 15.4 months

	POM + LoDex (n=302)	HiDex (n=153)	P
Median PFS	4.0 months	1.9 months	< 0.001
Median OS	13.1 months	8.1 months	0.009

Approval in EU for patients who have previously received at least two prior therapies including bz and len and have demonstrated disease progression on their last line of therapy

Dimopoulos et al. ASH 2013 (Abstract 408), oral presentation

Comparison of Pom-Dex trials (& combinations)

	MM-003[1]	STRATUS (MM-010)[2]	Pom-Dex vs Pom-Cyclo-Dex[3*]	
Treatment	**PD**	**PD**	**PD**	**PCD**
n	*302*	*604*	*36*	*34*
Population	*Failed Bort & Len & refr to last line*		*At least 2 prior lines & Len-refractory*	
ORR, %	**31**	**35**	**39**	**65**
≥ VGPR, %			**14**	**12**
PFS, months	**4.0**	**4.2**	**4.4**	**9.5**
OS, months	**13.1**	**11.9**	**16.8**	**NR**

*94% EFS at 12 months

1. San Miguel, Lancet Oncology 2013

2. Dimopoulos MA, et al. ASH 2014. Abstract 80

3. Baz et al. ASH 2014. Abstract 303

*** Indicación de combinaciones con tercer fármaco no aprobada en algunos países**

Other available combinations: Pom/dex combinations

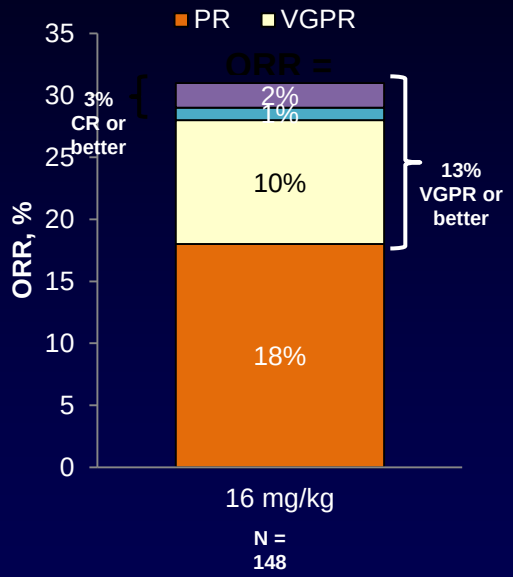
	POM + Vd[1]	K + POMdex[2]	Ixa + POMdex[3]	Dara + POMdex[4]	Isa+ POMdex	MOR202+ POMdex
Regimen	POM 1–4 mg PO D1–14 + BORT 1 mg/m² IV or 1.3 mg/m² IV or SC C1-8: D1,4,8,11; C9+: D1,8 + LoDex 20 mg (>75 y: 10 mg) C1-8: D1,2,4,5,8,9,11,12; C9+: D1,2,8,9 (n=34) †	Carfilzomib 20/27/36 mg/m² D1,2,15,16 + POM 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 P 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

Daratumumab single agent: Efficacy in Combined Analysis

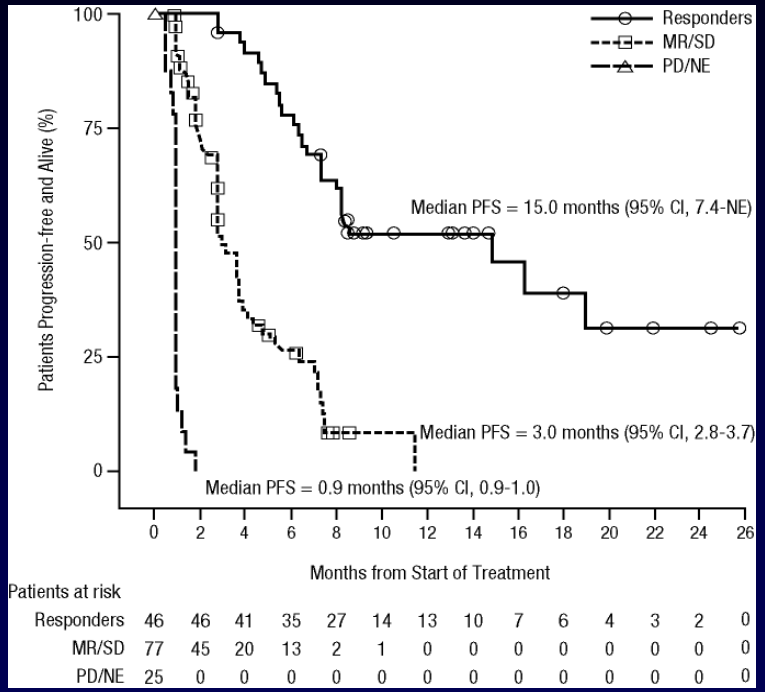
	16 mg/kg (N = 148)	
	n (%)	95% CI
Overall response rate (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR+VGPR)	19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



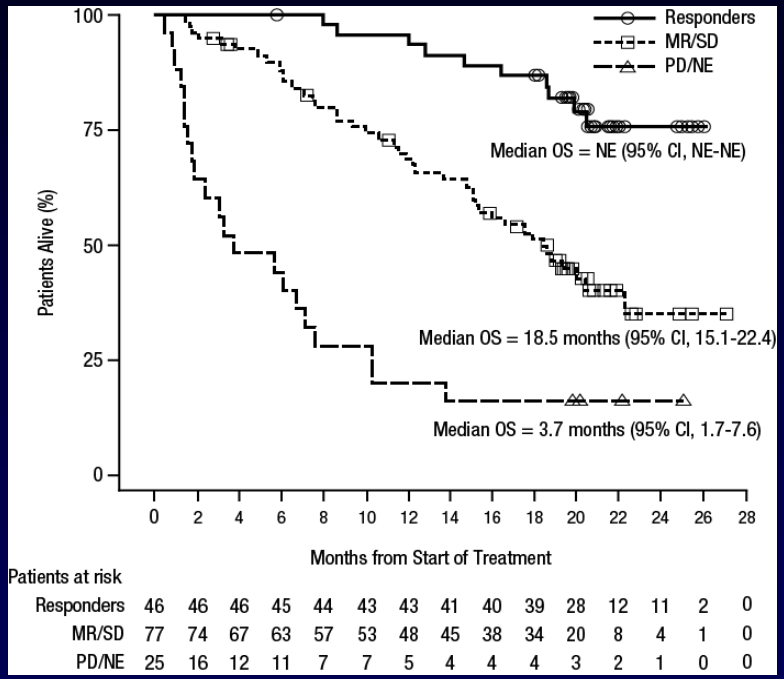
- **ORR = 31%**
- **Disease control rate was obtained in 84% of the patients**

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

GEN501 and SIRIUS (MMY2002) Combined Analysis: PFS/OS



Median PFS: 4 m



Median OS: 20 m

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

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Nothing/Consolidation/Maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

Second ASCT/Allo-RIC

1st relapse

Retreatment with bz-based

PIs-based combinations

- **Kd** — HR:0.53 PFS: 18.7 months
- **VD + Daratumumab** — HR:0.39 PFS: NR
- **Kd + Dara**
- **Kd + Cyclo**
- **Vd + Selinexor**
- **Vd + Venetoclax**

Rd
Continuous therapy as backbone

- **Carfilzomib plus Rd** — PFS: 26.3m, HR: 0.69
- **Elotuzumab plus Rd** — PFS: 19m, HR: 0.73
- **Daratumumab plus Rd** — PFS: NR, HR: 0.37
- **Ixazomib plus Rd** — PFS: 20.6m, HR: 0.74

PIs-based combinations will be more and more important but we have to wait to know the results of the Phase 3 trials

Comparisons among the different combinations no feasible because pts populations are different

Options of therapy for RRMM patients

Induction Bortezomib-based combination

↓

ASCT (melphalan 200)

↓

Lena as maintenance

Induction Bortezomib-based combo

Lenalidomide-dex

Second ASCT/Allo-RIC

1st relapse

PIs-based combinations

- **Kd** HR:0.53 PFS: 18.7 months
- **VD + Daratumumab** HR:0.39 PFS: NR
- Kd + Dara
- Kd + Cyclo
- Vd + Selinexor
- Vd + Venetoclax

Rd
Continuous therapy as backbone

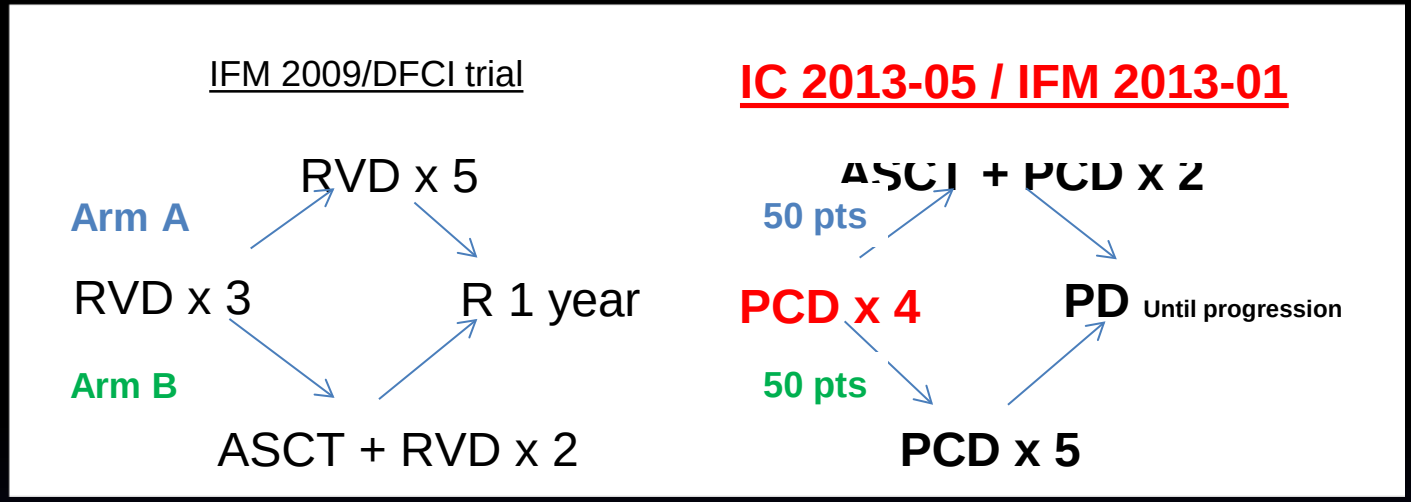
- **Carfilzomib plus Rd** PFS: 26.3m, HR: 0.69
- **Elotuzumab plus Rd** PFS: 19m, HR: 0.73
- **Daratumumab plus Rd** PFS: NR, HR: 0.37
- **Ixazomib plus Rd** PFS: 20.6m, HR: 0.74

Pom-dex based combos

- Pomalidomide +Vd
- Pom+Cy+Dex
- Pom-dex-Dara*

Pomalidomide plus cyclophosphamide and dexamethasone

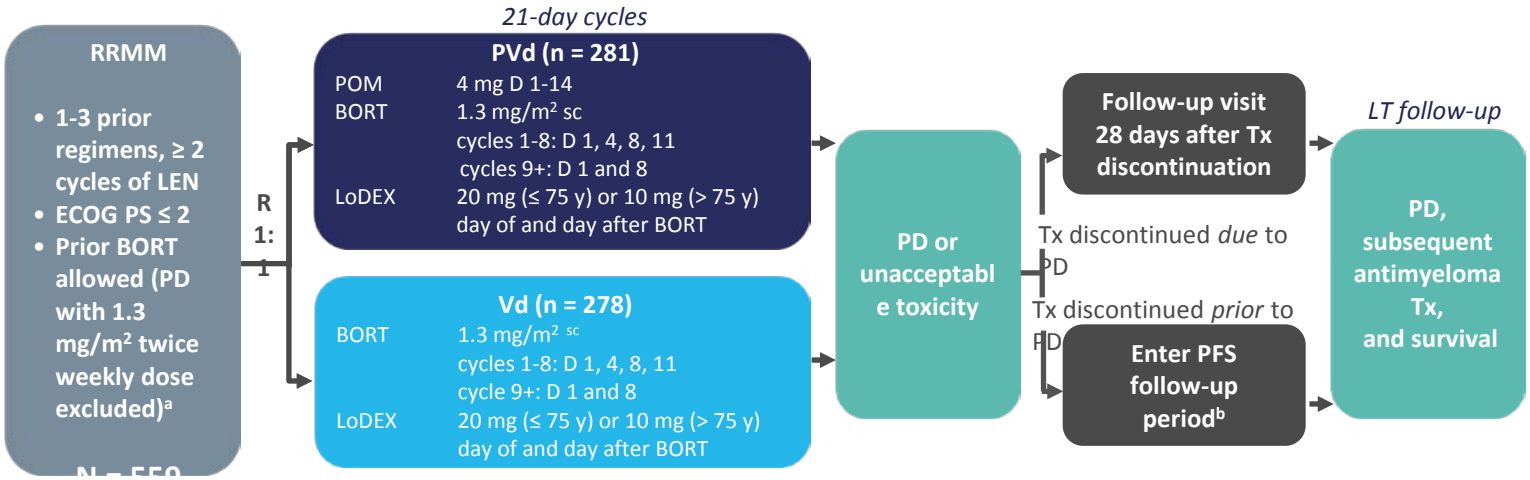
4 mg/d, días 1-21 | 300 mg weekly | 40 mg D1-4 and D15-18



- 97 pts evaluable for efficacy
- **ORR: 85%, including 1% CR and 34% of >VGPR**
- **No differences between patiens that had received or not ASCT**
- **94% of naïve transplant patients could proceed to ASCT after PCD as rescue regimen**
- Safety profile: ≥ G3 neutropenia (51%), infection (9%)

Garderet L et al. ASH 2017: oral presentation abstract 837

PHASE 3 OPTIMISMM STUDY DESIGN



- **Stratification**
  - Age (≤ 75 y vs > 75 y)
  - Prior regimens (1 vs > 1)
  - β2-microglobulin at screening (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L)

- **Study endpoints**
  - Primary: PFS
  - Secondary: OS, ORR by IMWG criteria, DOR, safety
  - Key exploratory: TTR, PFS2, efficacy analysis in subgroups

- **Data cutoff:** October 26, 2017

[a] Patients with PD during therapy or within 60 days of the last dose of a BORT-containing therapy under the approved dosing schedule of 1.3 mg/m² twice weekly were excluded.
[b] Efficacy evaluated every 21 days (± 3 days) until PD.

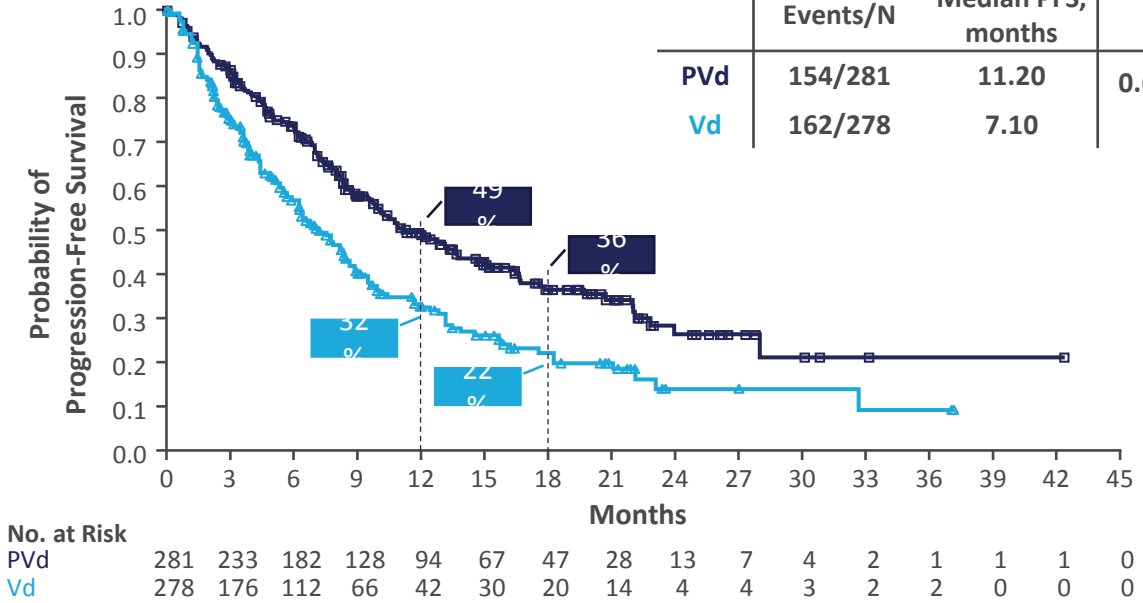
DOR, duration of response; LT, long-term; PFS2, progression-free survival after next line of therapy; TTR, time to response.

NCT01734928

Abstract 8001: OPTIMISMM—Paul Richardson, MD

PROGRESSION-FREE SURVIVAL (ITT)

- PVd reduced the risk of progression and death by 39% compared with Vd



	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	154/281	11.20	0.61 (0.49-0.77)
Vd	162/278	7.10	< .0001

Abstract 8001: OPTIMISMM—Paul Richardson, MD

PROGRESSION-FREE SURVIVAL BY LEN REFRACTORINESS

- PFS was improved with PVd regardless of LEN refractoriness

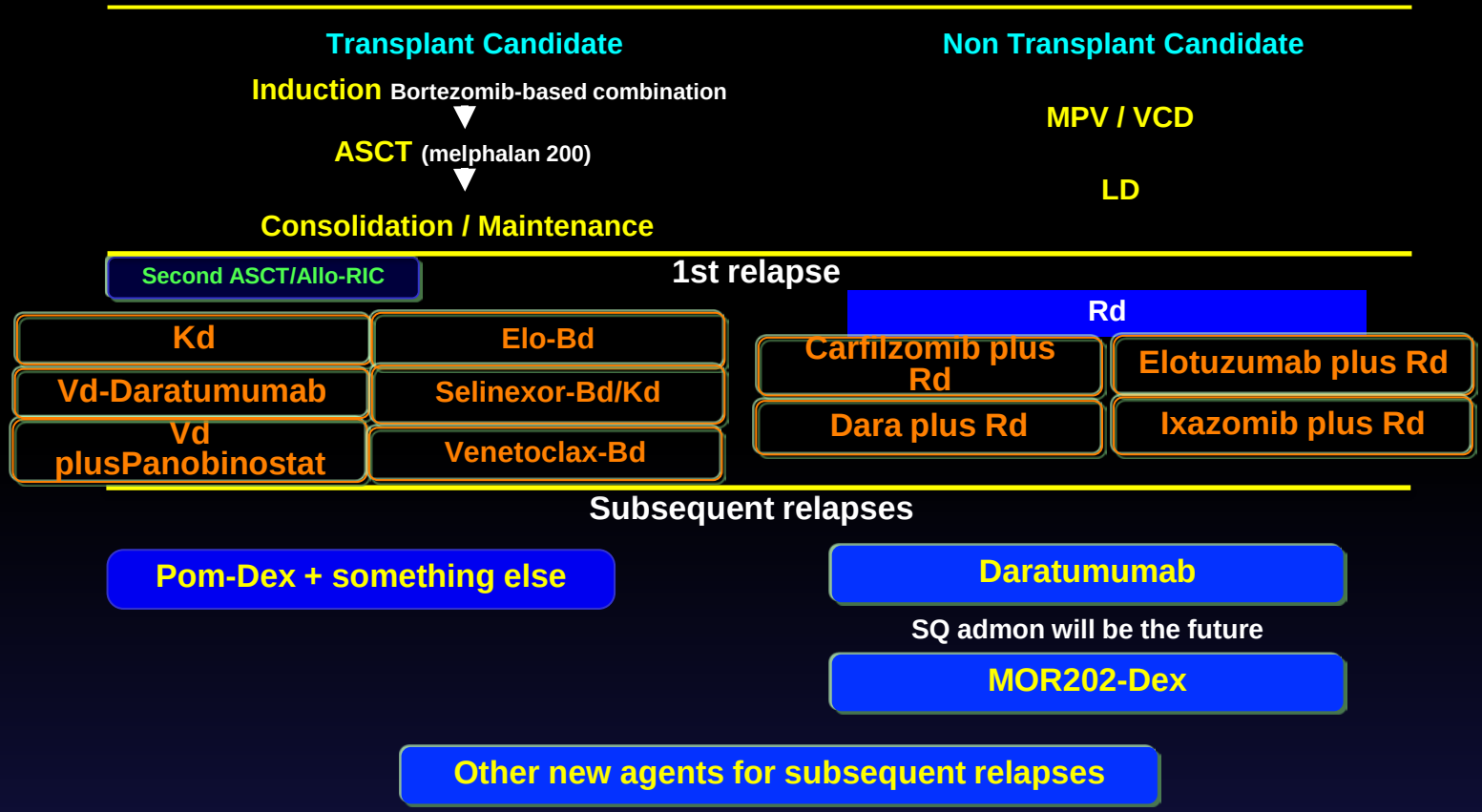
Subgroup	PFS	PVd	Vd
LEN-refractory[a]	n/N	120/200	118/191
	Median, months	9.53	5.59
	HR (95% CI) *P* Value	0.65 (0.50-0.84) < .001	
LEN-nonrefractory	n/N	34/81	44/87
	Median, months	22.01	11.63
	HR (95% CI) *P* Value	0.48 (0.30-0.75) .001	

PFS in patients lenalidomide refractory as part of the first line of therapy and receiving PVd at first relapse is 17.5 months

[a] Refractory: failure to achieve minimal response or development of progressive disease during therapy, or progression within 60 days of last dose, inclusive.

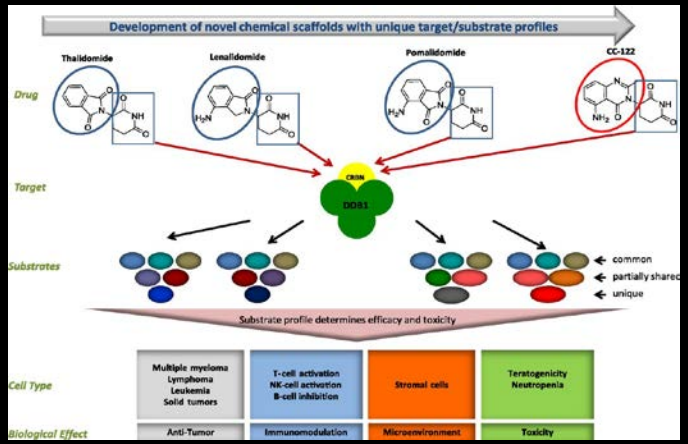
LEN-refractory: refractoriness to the last LEN-containing regimen, LEN-nonrefractory: nonrefractory to LEN in last LEN-containing regimen

Treatment Possibilities at 2nd + relapse

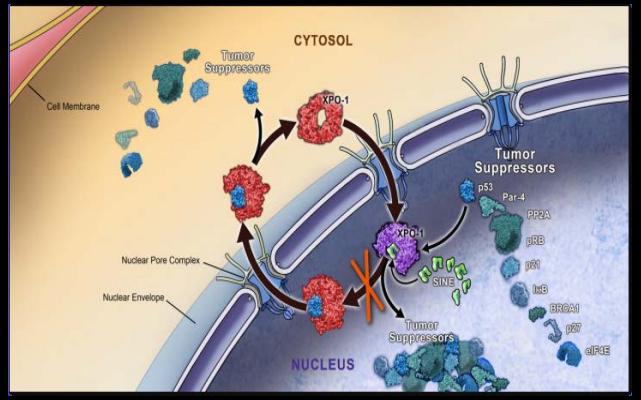


New agents

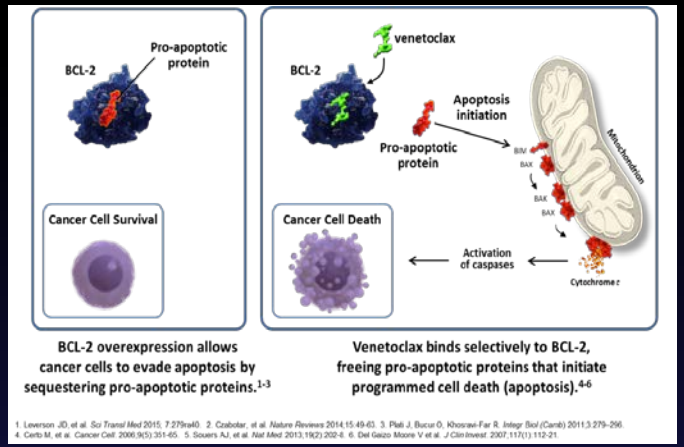
New IMiD's



Selinexor: Xpo-1 inhibitor

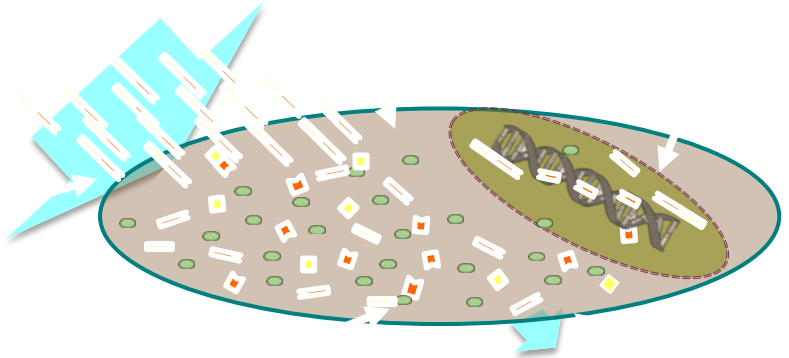


Venetoclax



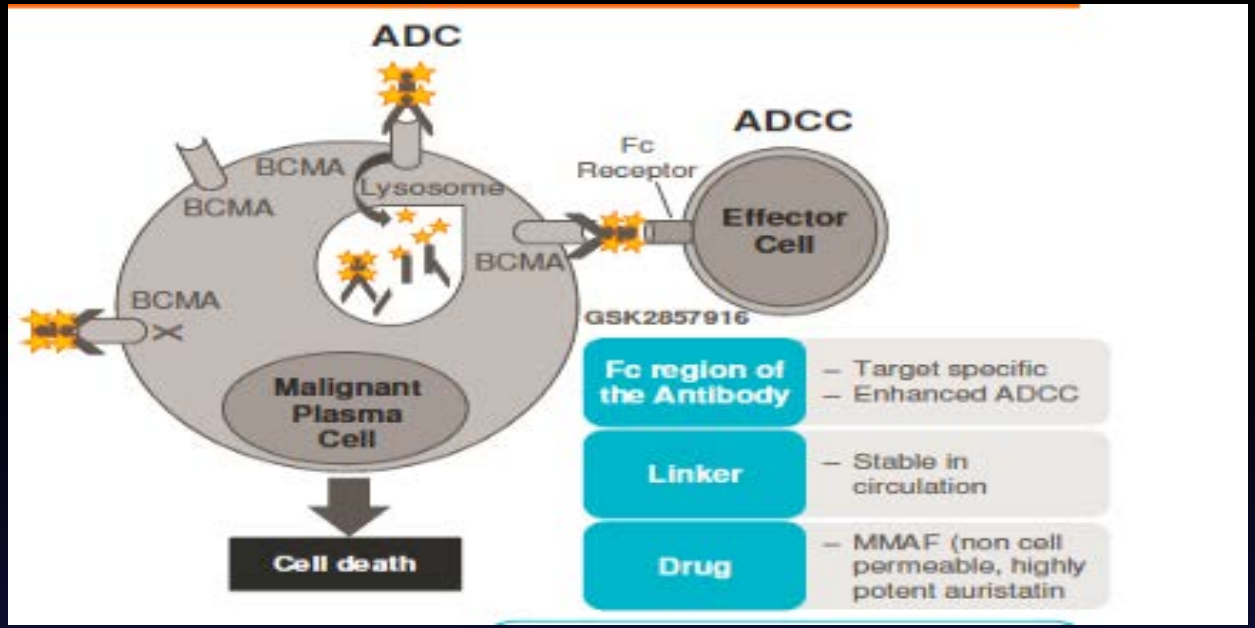
1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279-296. 4. Certo M, et al. *Cancer Cell* 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med* 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest* 2007;117(1):112-21.

Melflufen is a new alkylator



New agents

Bispecific/Conjugated MoAbs

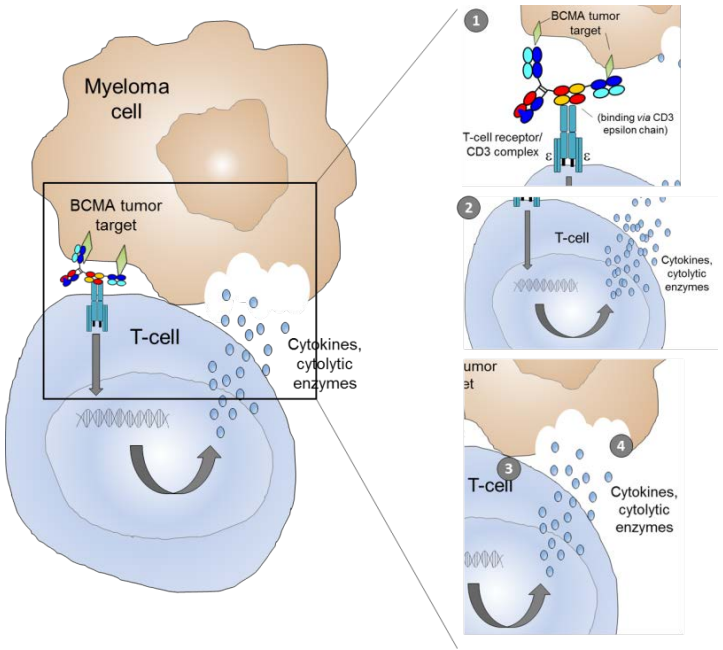


BCMA bispecific antibodies in myeloma

- **Potential to overcome the limitations of immunosuppressive tumor microenvironment by redirecting T cells to kill tumor target cells**
- BCMA (B-cell maturation antigen, CD269)
- **IgG-like bispecific antibody** (long serum half-life, retain Fc function):[1–3]
  - Anti-BCMAxCD3 (Pfizer)[4]
  - Ab-957 (GenmabDuoBody/Janssen)[1]
  - CC-93269 (EngMab/Celgene)[2,3]
  - Bi-Fab[5]
- **Non-IgG** like BiTE® (better tissue penetrance, access to epitopes):
  - BI 836909 (Boehringer Ingelheim; AMG420, Amgen)[6]

BCMA, B cell maturation antigen; CTL, cytotoxic T cell; Ig, immunoglobulin; TCB, T-cell bispecific.

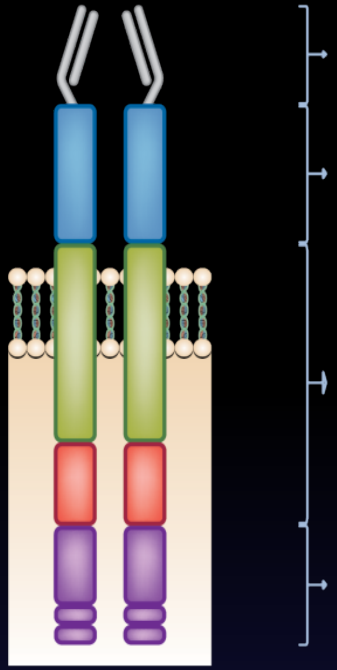
Mechanism of action of CC-93269 BCMA-TCB



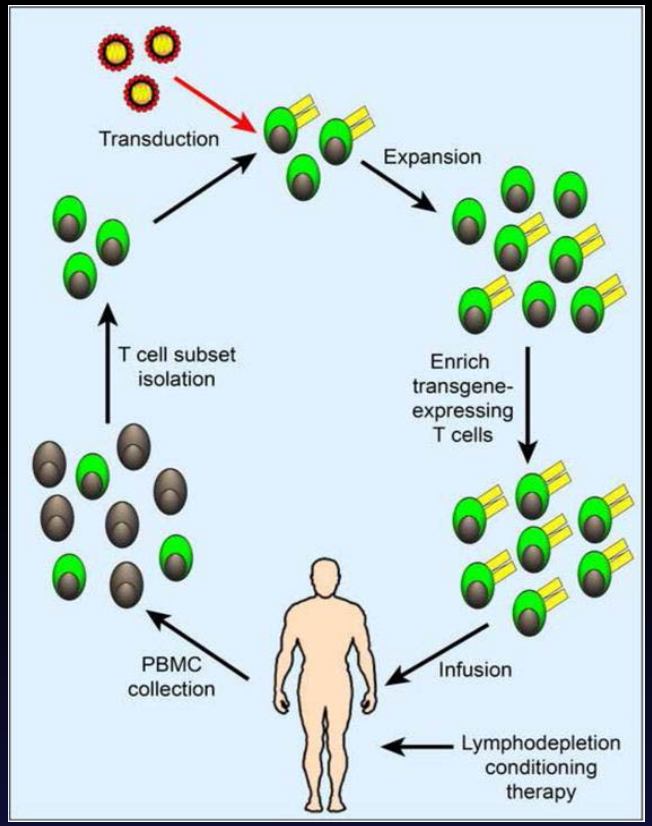
α-BCMA: bivalent high affinity binding
α-CD3ε chain: monovalent low affinity binding

1.Pillarisetti K, *et al.* Abstract 2116; Presented at ASH 2016; San Diego, California; 2. Seckinger A, *et al. Cancer Cell* 2017;**31**:396–410; 3. Cho S-F, *et al. Front Immunol* 2018;**9**:1821; 4 Panowski SH, *et al.* Abstract 383; Presented at ASH 2016; San Diego, California; 5. Ramadoss NS, *et al. J Am Chem Soc* 2015;**137**:5288–91; 6. Hipp S, *et al. Leukemia* 2017;**31**:1743–51.

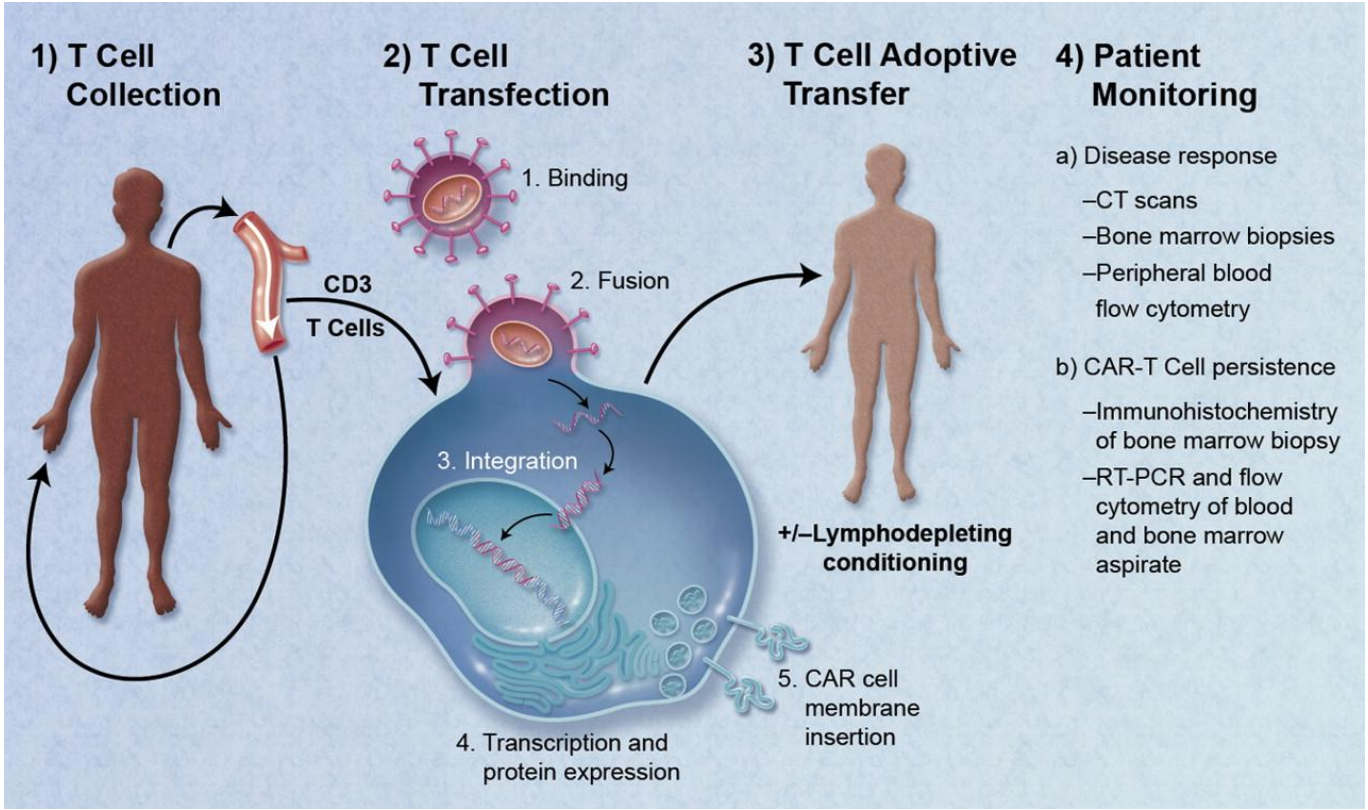
New agents



CAR-T cells



How are CAR T cells manufactured?



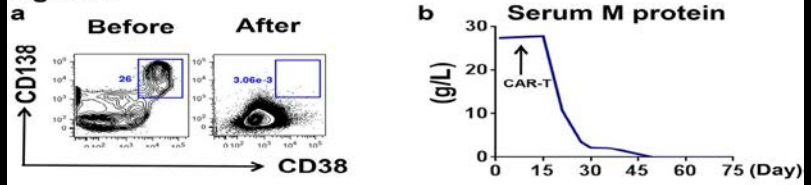
CAR, chimeric antigen receptor; CT, computed tomography; RT-PCR, reverse transcriptase polymerase chain reaction.

Jacobson CA and Ritz J. *Blood* 2011; **118**:4761–4762.

CAR-T cell for MM: LCAR-B38M

LCAR-B38M **3 smaller infusions rather than a single-one** **Targets two regions of the BCMA antigen**	Two patients had extramedullarry disease, on the forehead in one of them and on the jaw in the other.

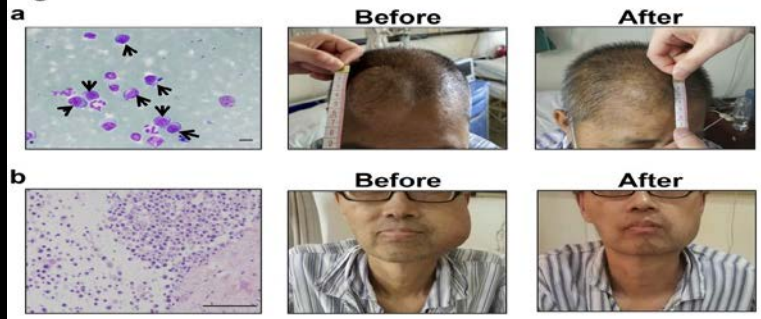
Figure 1



(a) Flow cytometry detection of bone marrow MRD before and two months after CAR-T therapy.

(b) (b) The change of plasma M protein concentration after CAR-T infusion. The final assessment was on day 65 post CAR-T.

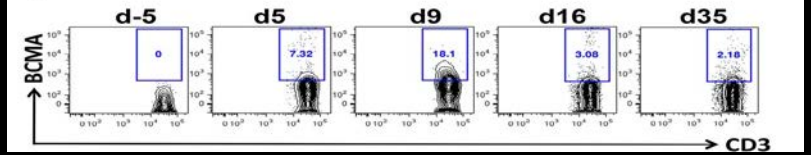
Figure 2



(a) Plasma cells were detected in the EMD. On day 20 post CAR-T infusion, the plasmacytoma on the forehead was remarkably reduced.

(b) (b) The histopathology reveals that the mass of the lower jaw was a plasmacytoma, which was largely reduced on day 23 post CAR-T.

Figure 3



Flow cytometry shows the percentage of BCMA specific CAR-T cells in CD3 positive peripheral T cells at least 35 days after CAR-T infusion.

Management of patients with MM: Summary