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INTERNATIONAL MYELOMA FOUNDATION

CCO LIVE

How to Treat Relapsed/Refractory Multiple Myeloma in 2020

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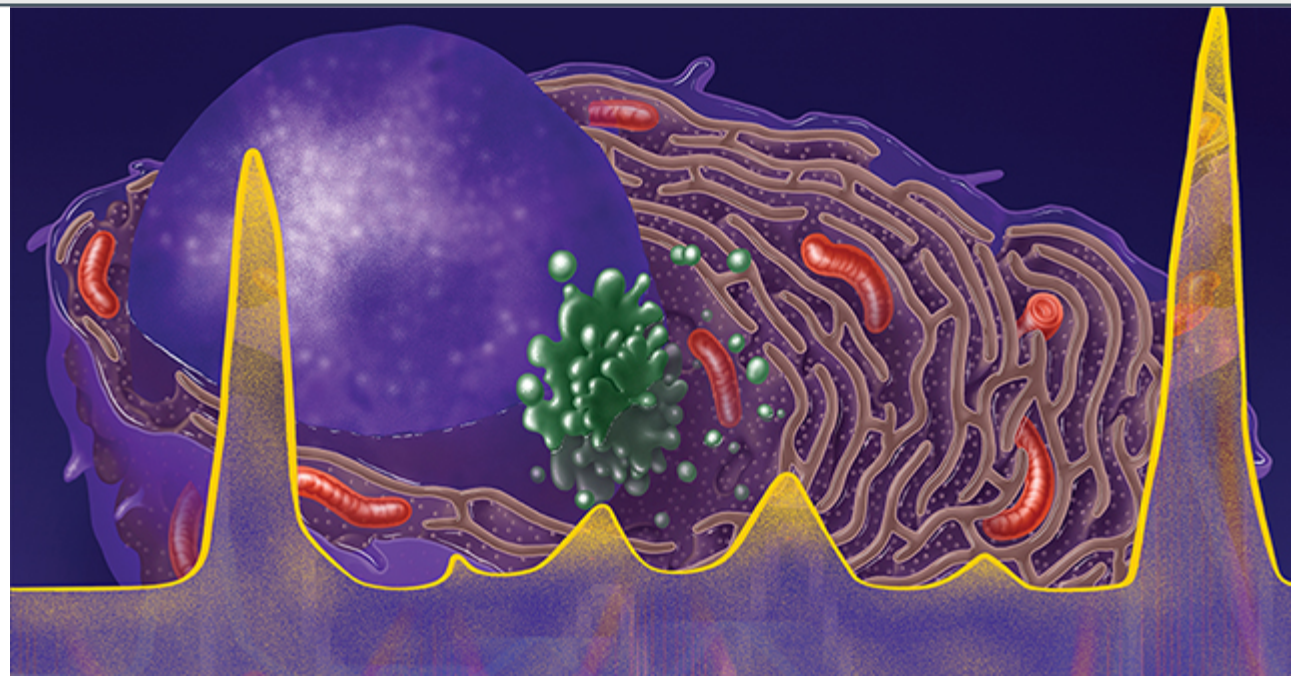

Disclosures

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

Case Discussion 3:
Managing a patient with relapsed disease after ≥ 1 line of therapy

Patient Case Example

- A 66-year-old man was diagnosed with IgA lambda **R-ISS Stage-III** myeloma
  - BM showed 60% PC with **t (4;14) plus 1q gain**
  - MC: 25 g/L; **Hb: 10 g/dL**, creatinine: 1.2 mg/dL; calcium: 9.2 mg/dL
  - Extensive bony disease
- He received **Dara-VTD + ASCT** achieving **sCR but MRD+,** planned **maintenance with lenalidomide for 2 years**
- **After 23 months,** he relapsed (18 months from ASCT)

Presurvey 3: In your current clinical practice, how would you treat this patient?

1. PI / lenalidomide / dexamethasone
2. PI / pomalidomide / dexamethasone
3. Anti-CD38 mAb / lenalidomide / dexamethasone
4. Anti-CD38 mAb / pomalidomide / dexamethasone
5. Anti-CD38 mAb / PI / dexamethasone
6. Rescue treatment followed by second ASCT
7. Uncertain

Expert Recommendations

Expert Recommendations	
Brian G.M. Durie, MD	Anti-CD38 mAb / pomalidomide / dexamethasone
Shaji Kumar, MD	Anti-CD38 mAb / PI / dexamethasone
Thomas G. Martin, MD	Anti-CD38 mAb / PI / dexamethasone
Philippe Moreau, MD	Anti-CD38 mAb / PI / dexamethasone
S. Vincent Rajkumar, MD	Anti-CD38 mAb / PI / dexamethasone
Jesús San-Miguel, MD	Anti-CD38 mAb / pomalidomide / dexamethasone

Patient Case Example, Continued

- He was treated with **Dara-Vd x 8 cycles** and **achieved VGPR**
- **He progressed 3 months later**

Presurvey 4: In your current clinical practice, what approach would you recommend for this patient now?

1. PI / pomalidomide / dexamethasone
2. Anti-CD38 mAb or elotuzumab / pomalidomide / dexamethasone
3. Anti-CD38 mAb / carfilzomib / dexamethasone
4. Selinexor or selinexor combinations
5. Belantamab or belantamab combinations
6. Venetoclax or venetoclax combinations
7. Melflufen or melflufen combinations
8. Bispecific antibodies or CAR T-cell therapy

Expert Recommendations

Expert Recommendations	
Brian G.M. Durie, MD	Bispecific antibodies or CAR T-cell therapy
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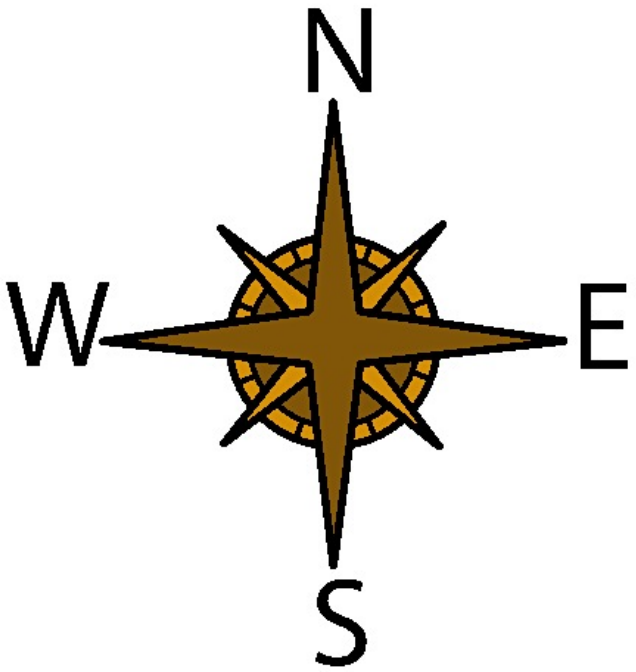
Thomas G. Martin, MD	Bispecific antibodies or CAR T-cell therapy
Philippe Moreau, MD	Bispecific antibodies or CAR T-cell therapy
S. Vincent Rajkumar, MD	PI / pomalidomide / dexamethasone
Jesús San-Miguel, MD	Bispecific antibodies or CAR T-cell therapy

Strategies at Relapse: How to Make the RIGHT CHOICE?

Disease-related Factors

Type of relapse, cytogenetic risk, extramedullary disease

Efficacy and Toxicity of previous treatments



Patient-related factors

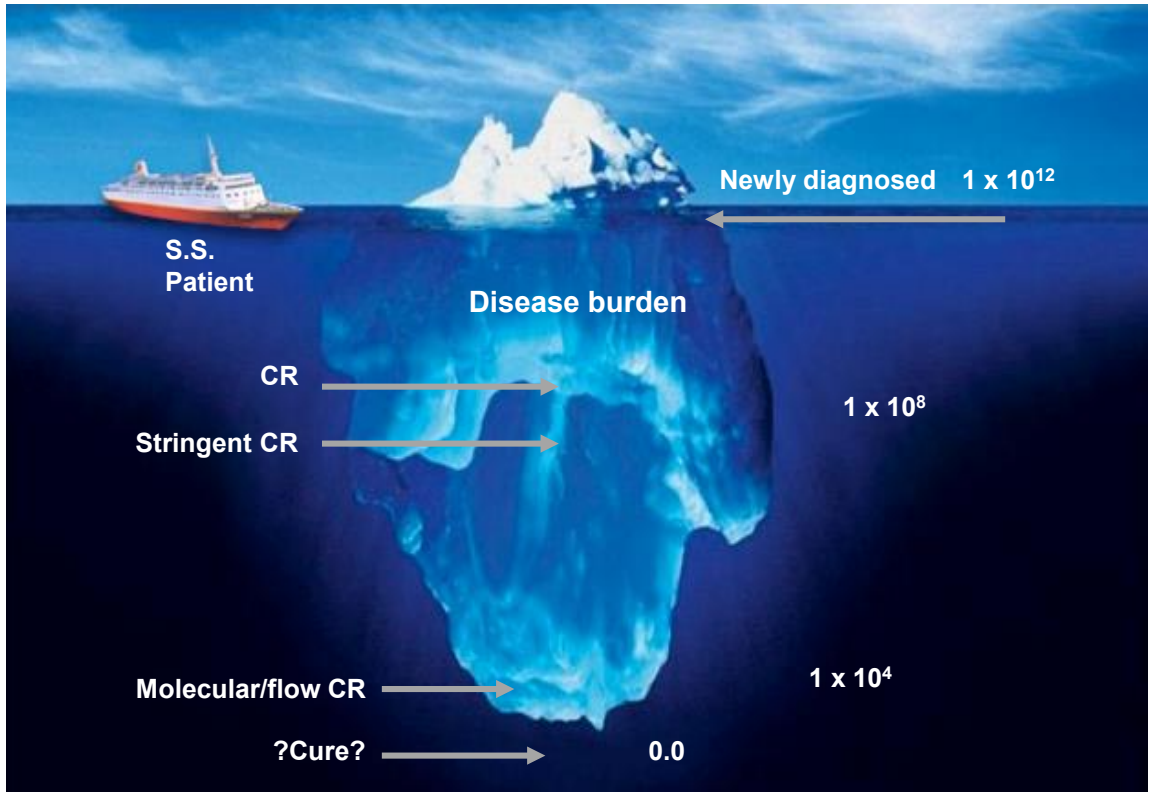
Age (Trx eligibility), comorbidities, frailty

Further options

Response to Therapy is the Key Element to Evaluate Treatment Efficacy and Critical For Survival

The definition of CR is suboptimal: ……***The term CR is confusing for the patient***

Who wouldn't want to know with precision the quality of patients' response to therapy?

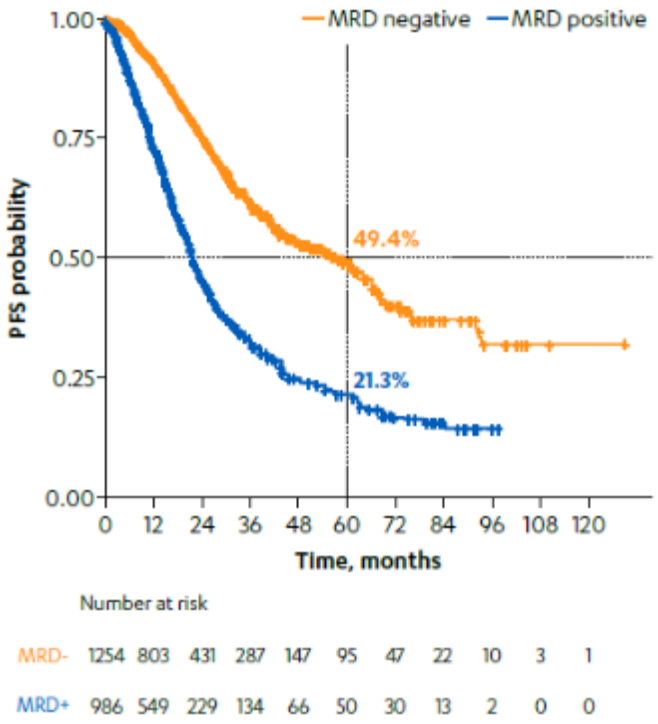


Is MRD relevant in the relapse setting ?

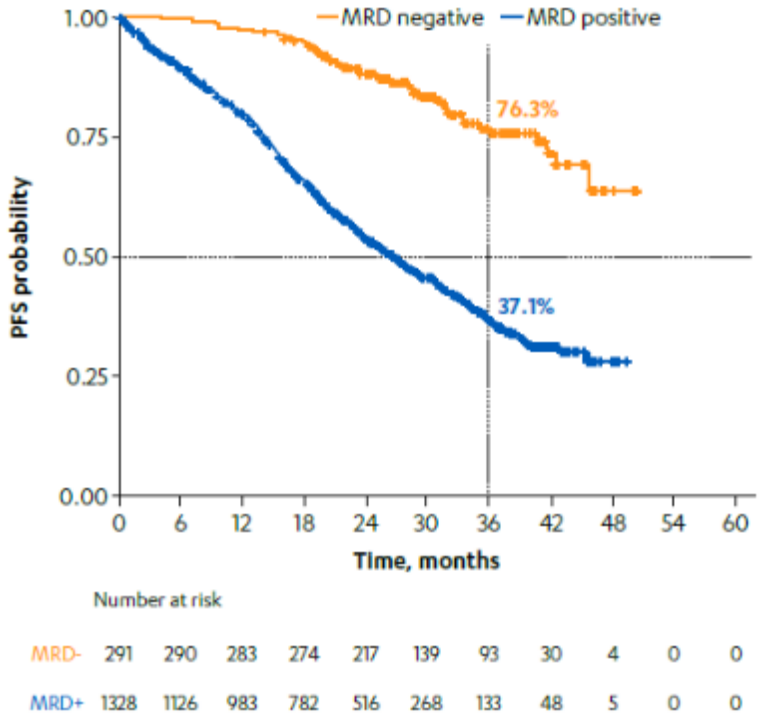
Positive vs Negative MRD: Two Different Myelomas

Results from an expanded meta-analysis (8,114 patients)

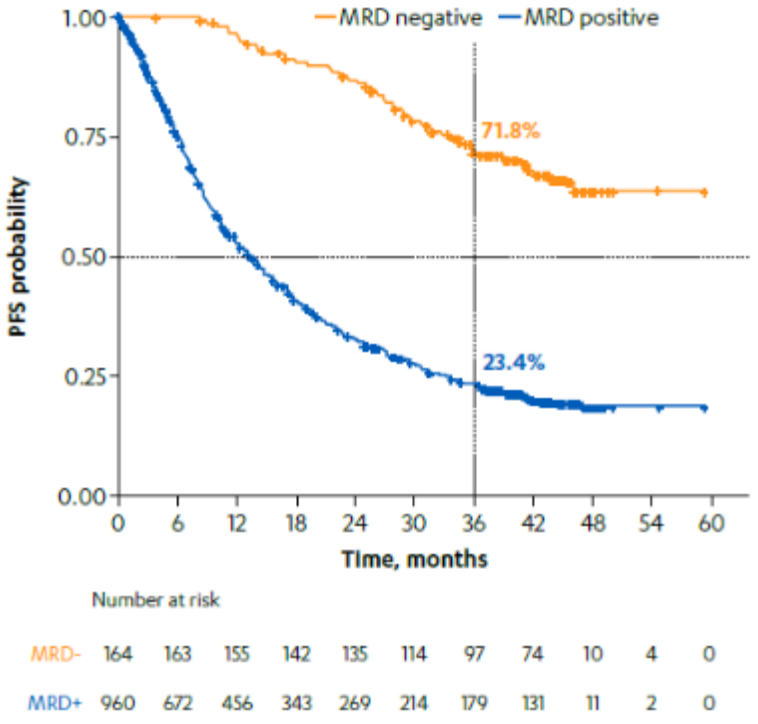
NDMM (transplant-eligible)



NDMM (transplant-ineligible)



RR MM

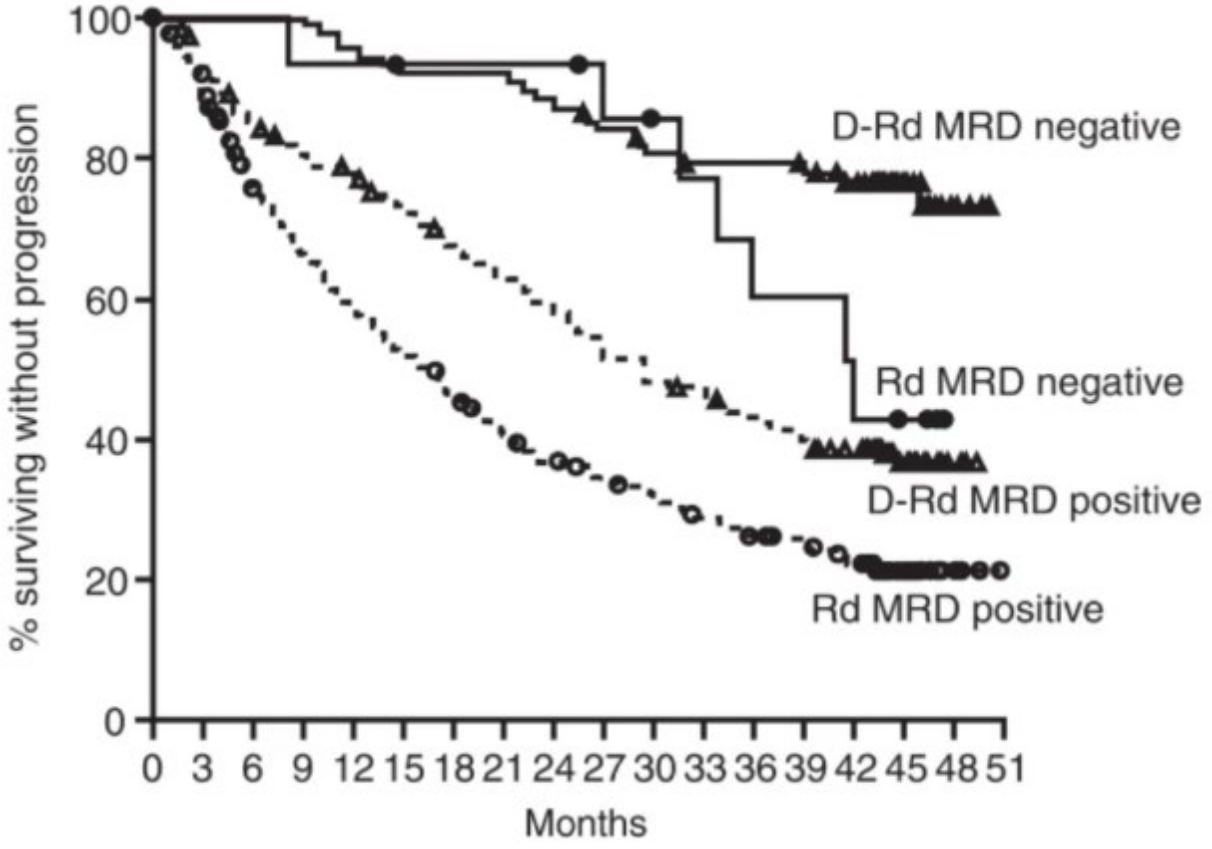


Progressive improvement in MRD technologies

Munshi. ASH 2019. Abstr 4742.

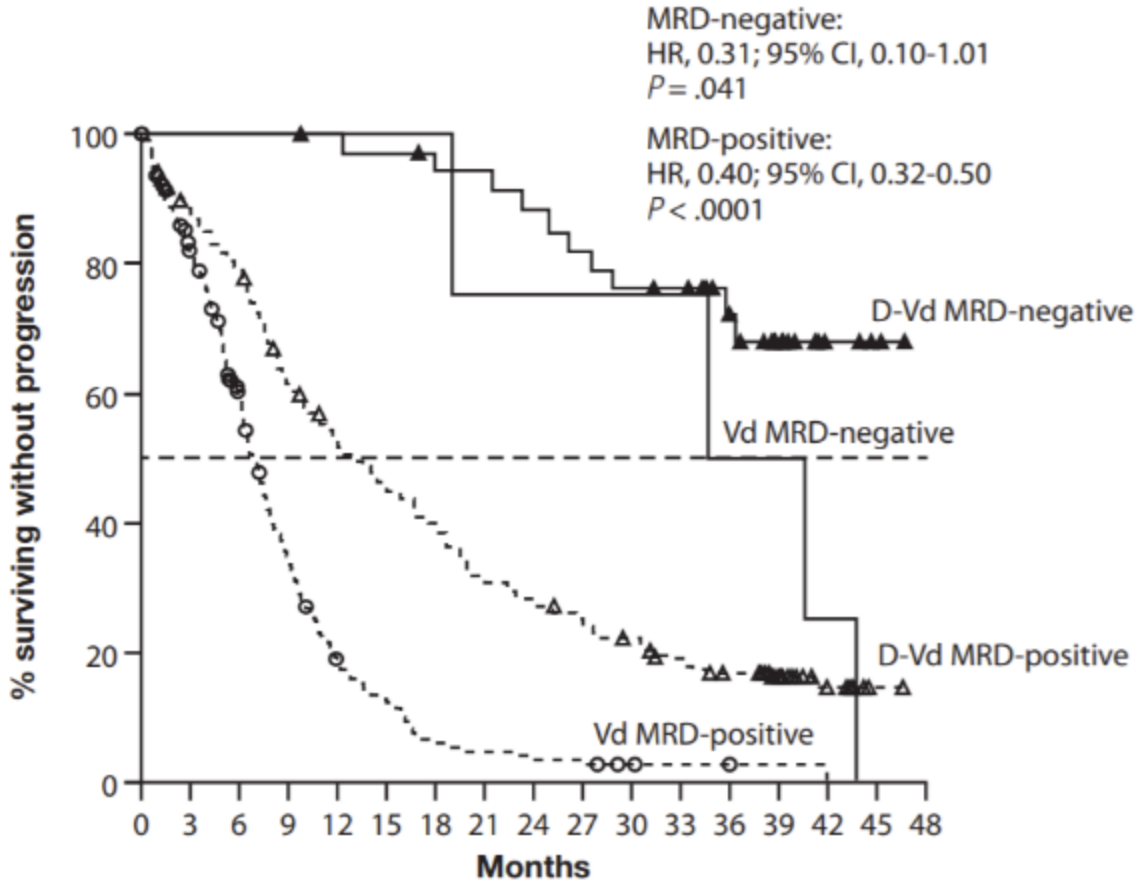
MRD Assessment in Pollux and Castor: Impact of Achieving MRD-Negativity (10^{-5})

Pollux (Rd +/- Dara)



Bahlis. Leukemia. 2020;34:1875.

Castor (Vd +/- Dara)



Mateos. Clin Lymphoma Myeloma Leuk. 2020;20:509.

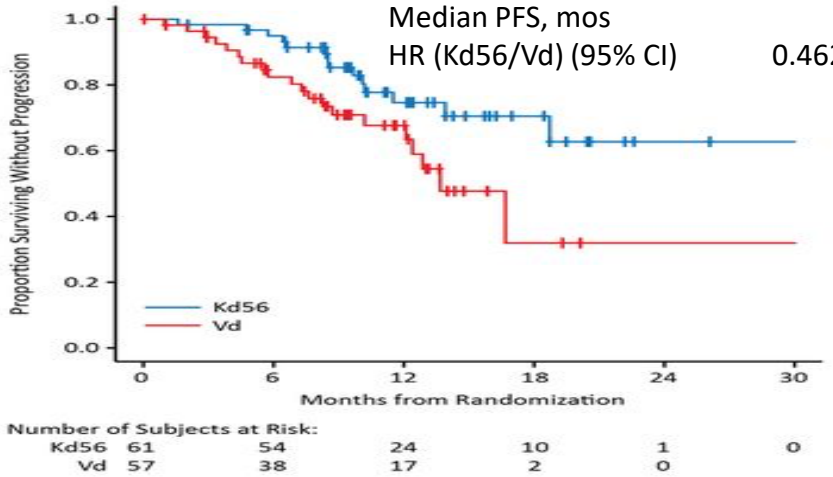
Should We Treat Biochemical Relapses?

PFS and OS According to Biochemical vs Clinical Relapses
Endeavor study (n = 211 relapsing after ASCT)

Biochemical Relapse

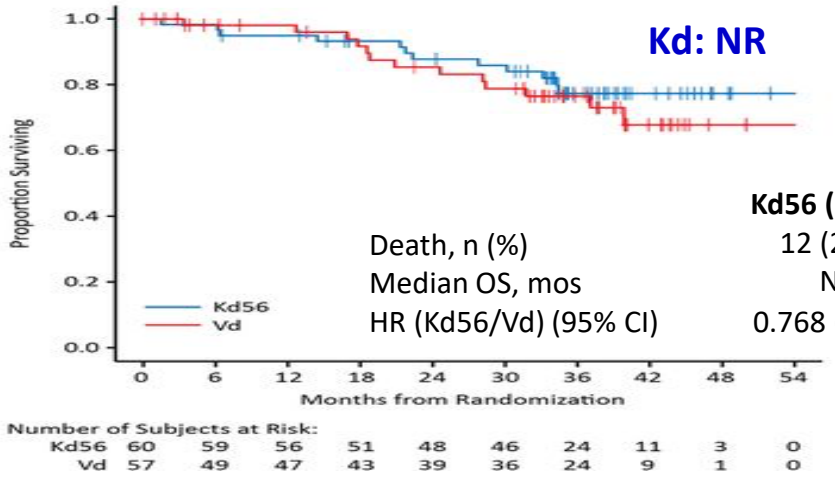
PFS

	Kd56 (n = 61)	Vd (n = 57)
Progression/Death, n (%)	14 (23.0)	20 (35.1)
Median PFS, mos	NE	13.7
HR (Kd56/Vd) (95% CI)	0.462 (0.232-0.922)	



Kd: NR

OS

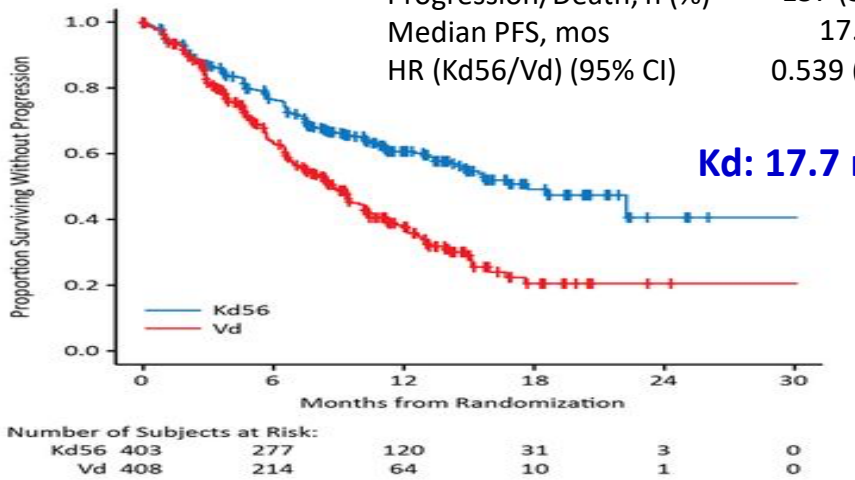


Kd: NR

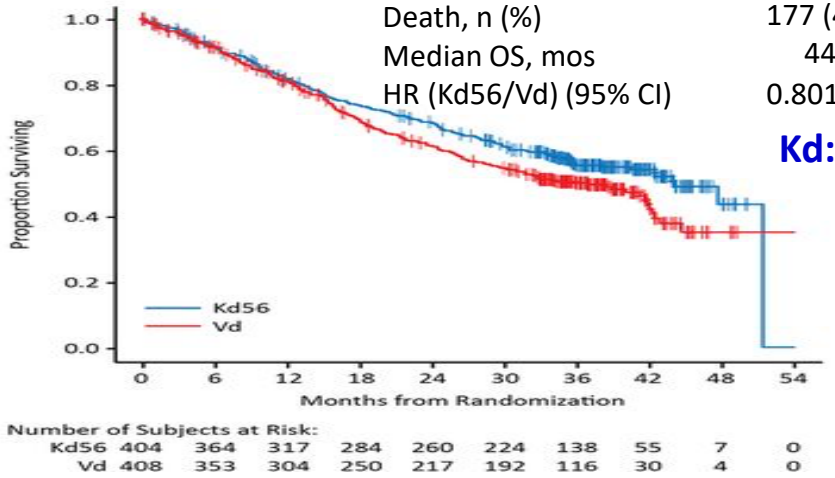
	Kd56 (n = 60)	Vd (n = 57)
Death, n (%)	12 (20.0)	13 (22.8)
Median OS, mos	NE	NE
HR (Kd56/Vd) (95% CI)	0.768 (0.350-1.683)	

Clinical Relapse

	Kd56 (n = 403)	Vd (n = 408)
Progression/Death, n (%)	157 (39.0)	223 (54.7)
Median PFS, mos	17.7	8.8
HR (Kd56/Vd) (95% CI)	0.539 (0.439-0.662)	



Kd: 17.7 m



	Kd56 (n = 404)	Vd (n = 57)
Death, n (%)	177 (43.8)	196 (48.0)
Median OS, mos	44.0	36.8
HR (Kd56/Vd) (95% CI)	0.801 (0.653-0.982)	

Kd: 44 m

Moreau. ASH 2018. Abstr 3243.

Should We Perform a Second ASCT at Relapse ?

66-Year-Old Man Relapsing after VTD + ASCT + Len x 2y:

Decisions based on the **duration of the previous response**

Late relapse (> 3-4 years post ASCT)

- ***Aggressive relapse:*** **Reinduction (VRD/KRD +/- Dara) + 2nd ASCT**
- ***Biochemical Relapse*****: Repeat the initial approach or same as above**

Early relapse (< 1 year post ASCT)

"Overcome drug resistance"

Combination of non cross-resistant agents

VRD (KRD)-PACE + Dara → RIC-Allo/CAR-T

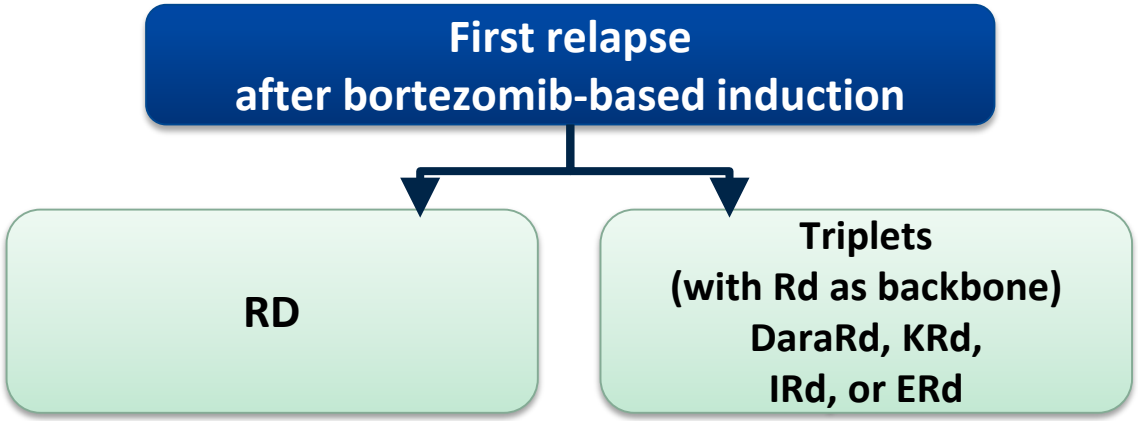
Intermediate relapse (2-3 years post ASCT)

"Prolong survival until curative treatments are developed"

Sequential novel agent combinations: Dara + PomDex…..KRD…

1st Relapse After Bortezomib-Based Induction (Len Naive or Exposed but Not Refractory)

Lenalidomide-Based Regimens: Efficacy (Rd vs triplets with Rd backbone)



Efficacy	POLLUX[1] (N = 569) DaraRd vs Rd	ASPIRE[2] (N = 792) KRd vs Rd	ELOQUENT-2[3] (N = 646) ERd vs Rd	TOURMALINE-MM1[4] (N = 722) IRd vs Rd
PFS HR (▲m)	**0.44** (▲ 27 mos) **44.5 mos** vs 17.5 mos	**0.66** (▲ 9.5 mos) **26.1 mos** vs 16.6 mos	**0.72** (▲ 4.5 mos) **19.4 mos** vs 14.9 mos	**0.74** (▲ 5.9 mos) **20.6 mos** vs. 14.7 mos

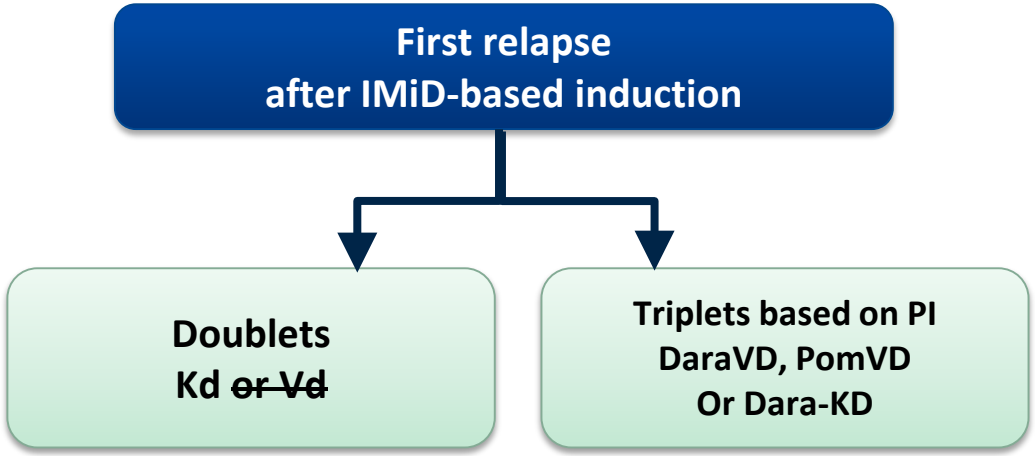
***Economical constrains**: RD + Cyclophosphamide , VTD (if TFI > 12 mos)*

This table is provided for ease of viewing information from multiple trials with different patient populations. Direct comparison across trials is not intended and should not be inferred.

1. Bahlis. Leukemia. 2020;34:1875. 2. Seigel. JCO. 2018;36:728. 3. Dimopoulos. Blood Cancer J. 2020;10:91. 4. Moreau. NEJM. 2016;374:1621.

1st Relapse Following Continuous Lenalidomide/Dex, Len Maintenance, VRD-Rd ... will be considered Len-Refrac

Proteasome Inhibitors-Based Regimens: Efficacy



Efficacy	ENDEAVOR (N = 929) Kd vs Vd[1,2]	KCyDex (N = 198) KCd vs Kd[3]	CASTOR (N = 498) DaraVd vs Vd[4]	CANDOR (N = 466) DKd vs Kd[5]	IKEMA (N = 302) IKd vs Kd[6]
PFS HR (▲mos)	0.53 (▲ 9) 18.7 vs 9.4 mos	1 (▲ 5) 20.7 vs 15.2 mos	0.31 (▲ 9) 16.7 vs 7.1 mos	0.63 (▲ NE) NE vs 15.8 mos	0.53 (▲NE) NE vs 19.2 mos
Len Refract, experimental arm, % (mPFS)	24% (8.6 mos)	36% (26 mos)	18% (9.3 mos)	31.7% (NA)	32% (NA)

***PANORAMA-1 PanoVD vs VD (n=768)[7]: mPFS **12 mos vs 8 mos** (HR: **0.63** (▲ 4 m) ; 27.6% CR rate; Only 19% Lena Refractory*

***Economical Constrains.** VMP/VCD (16 m; 83% at 1 Yr)[8]*

1. Dimopoulos. Lancet Oncol. 2016;17:P27. 2. Moreau. Leukemia. 2017;31:115. 3. Mateos. ASH 2020. Abstr 415. 4. Spencer. Haematologica. 2018;103:2079. 5. Dimopoulos. Lancet. 2020;396:186. 6. Moreau. EHA 2020. Abstr LB2603.. 7. San-Miguel. Lancet Oncol. 2014;15:1195. 8. Reece. JCO. 2008;26:4777.

Relapse/Refractory to Lenalidomide: Pomalidomide-based Regimens

Efficacy	OPTIMISM (N = 559) PVd vs Vd[1]	ICARIA (N = 307) IsaPd vs Pd[2]	ELOQUENT (N = 117) EloPd vs Pd[3]	APOLLO (N= 304) DPd vs Pd[4]
PFS HR (▲mos)	**0.61 (▲ 4.1) 11.2* vs 7.1m**	**0.59 (▲ 5.0) 11.5 vs 6.5m**	**0.54 (▲ 5.6) 10.3 vs 4.7m**	**0.63 (▲ 5.5) 12.4 vs 6.9m**
ORR, %	**82 vs 50**	**60 vs 35**	**53 vs 26**	**51 vs 19.6** ≥ VGPR

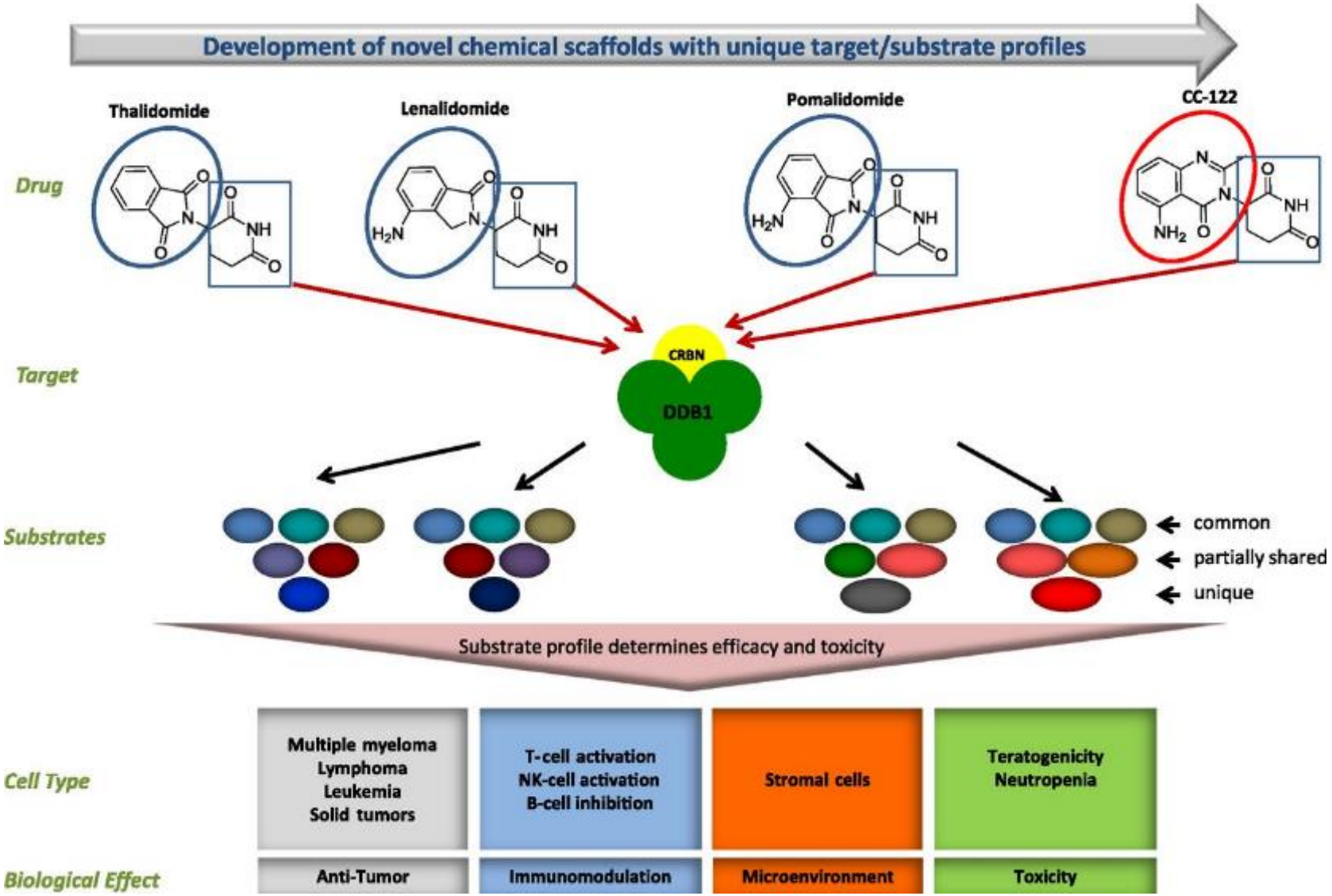
17.8 m in Len-Ref 1st

- ***PomCyDex (n = 100): mPFS 7.6 m (10.4 m in PR)[5]***
- ***KPomDex (EMN-011; n= 60): mPFS 18 m[6]***

- ***Dara-Kd*** *(CANDOR)* ***in Lena Ref HR 0.45[7]***
- ***Isa-Kd*** *(IKEMA)* ***in Lena Ref HR 0.59[8]***

1. Richardson. Lancet Oncol. 2019;20:781. 2. Attal. Lancet. 2019;394:2096. 3. Dimopoulos NEJM. 2018;379:1811. 4. Dimopoulos. ASH 2020. Abstr 412. 5. Otero. EHA 2020. Abstract EP982. 6. Sonneveld. ASH 2018. Abstract 801. 7. Dimopoulos. Lancet. 2020;396:186. 8. Moreau. EHA 2020. Abstr LBA2603.

Next-generation IMiDs, CELMoDs™ (Cereblon E3 Ligase Modulation Drugs) in Multiple Myeloma



CC-220 (iberdomide)…ORR:32%[1]

CC-92480……ORR: 54%[2]

Iber combinations:[3]

+ Dara (65% Dara Ref)….35% ORR
+ Btz (100% Btz Ref)….50% ORR

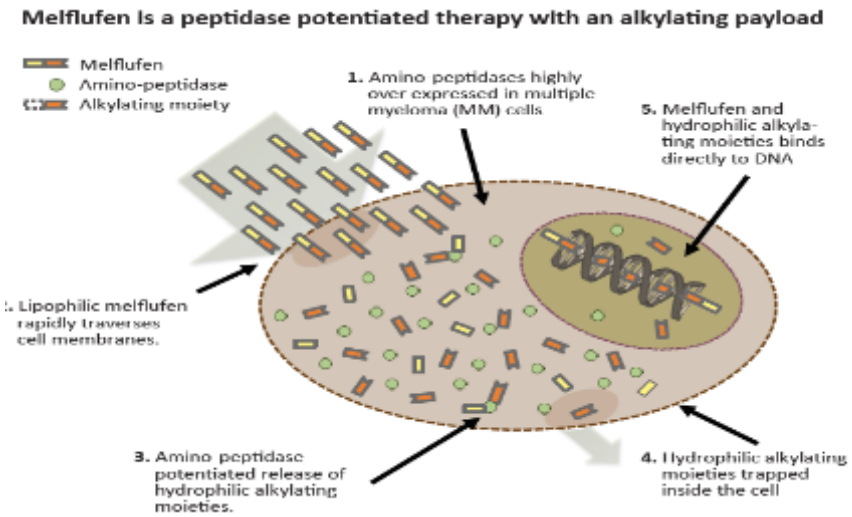
1. Lonial. ASH 2019. Abstr 3119.
2. Richardson. ASCO 2020. Abstr 8500.
3. Van de Donk. ASH 2020. Abstr 724.

Nowakowski. Blood. 2015;126:698.

Management of Patients > 3 line - Novel Drugs Under Development

Novel Alkylators: Melflufen

- Melflufen is a highly lipophilic alkylating peptide, belonging to the novel class of Peptidase Enhanced Compounds
- Intracellular amino-peptidases that are overexpressed in most malignant cells, will rapidly cleave melflufen releasing the hydrophilic, active alkylating metabolite
- In vitro, treatment of tumor cells with melflufen results in 50-fold higher intracellular concentration of alkylating metabolite than those treated with equimolar melphalan alone. In vivo, human xenograft mouse models treated with melflufen showed prolonged survival.



Melflufen 40 mg iv every 28 days + Dex 40 mg weekly

Phase II O-12-M1 trial

RR MM pts ≥ 2 lines and refr. to last line.
N = 45 in combination cohort.
Median 4 (2-14) lines; 64% double refr.; 53% Alkylator refr.

ORR 31% ..... 5 VGPR & 9 PR patients
PFS: 5.7m .....DOR 8.4m; OS: 20.7m

G3/4 AEs: Thromboc. (62%), Neutrop. (58%), Anemia: 42%

Richardson. Lancet Haematology. 2020;7:E395.

Phase II Horizon trial

- **125 RRMM pts. Median 5 (2-12) prior lines; 38% patients had high-risk cytogenetics; 88% double refr ; 71% triple refractory (PI + IMiD + anti-CD38)**

ORR 29% .
PFS: 4.2 mos. OS: 11.6 mos

G3/4AEs: Neutropenia (66%), Thromboc. (69%), Anemia: (37%)

Mateos. ASH 2019. Abstr 1883. Richardson. EHA 2020. Abstr S1605.

Anchor Trial…ORR for (Melf-Dex) + Dara: 70%; PFS: 11.5 mos…….+ Btz: 60%

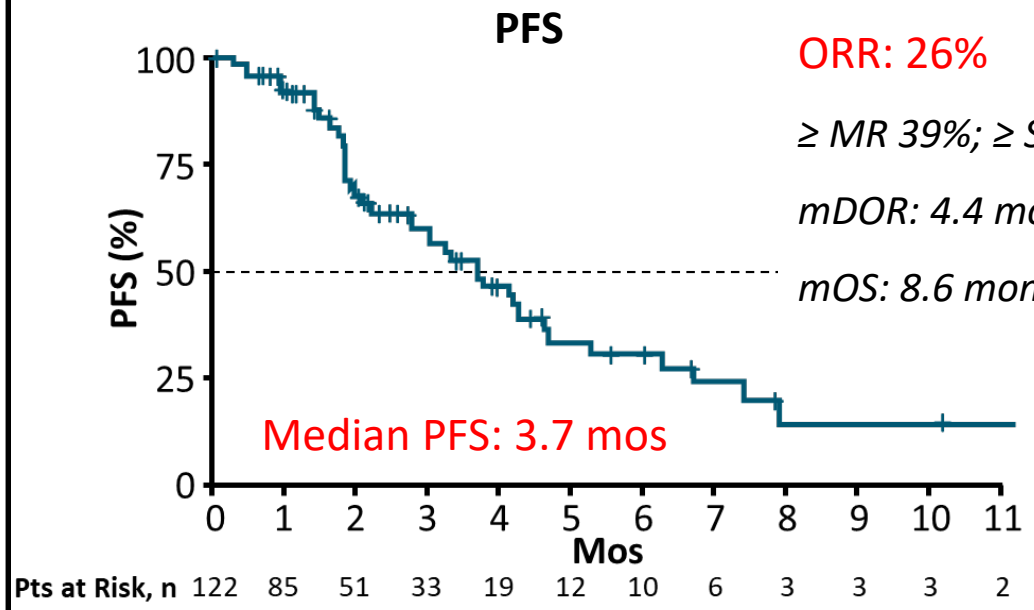
Ocio. ASH 2020. Abstr 417.

Selinexor Combination in Relapsed/Refractory MM

- ***Exportin 1 (XPO1) is the major nuclear export protein for** Tumor suppressor proteins (TSPs, e.g., p53, IkB and FOXO). **XPO1 is overexpressed in MM***
- ***Selinexor is an oral selective XPO1 inhibitor***

Phase IIb STORM Trial: **Selinexor + Dex** (N = 122)[1]

- 7 median prior lines of therapy (range: 3-18)
- 96% refractory to Btz, Len, carf, pom, dara



ORR: 26%

≥ MR 39%; ≥ SD 79%

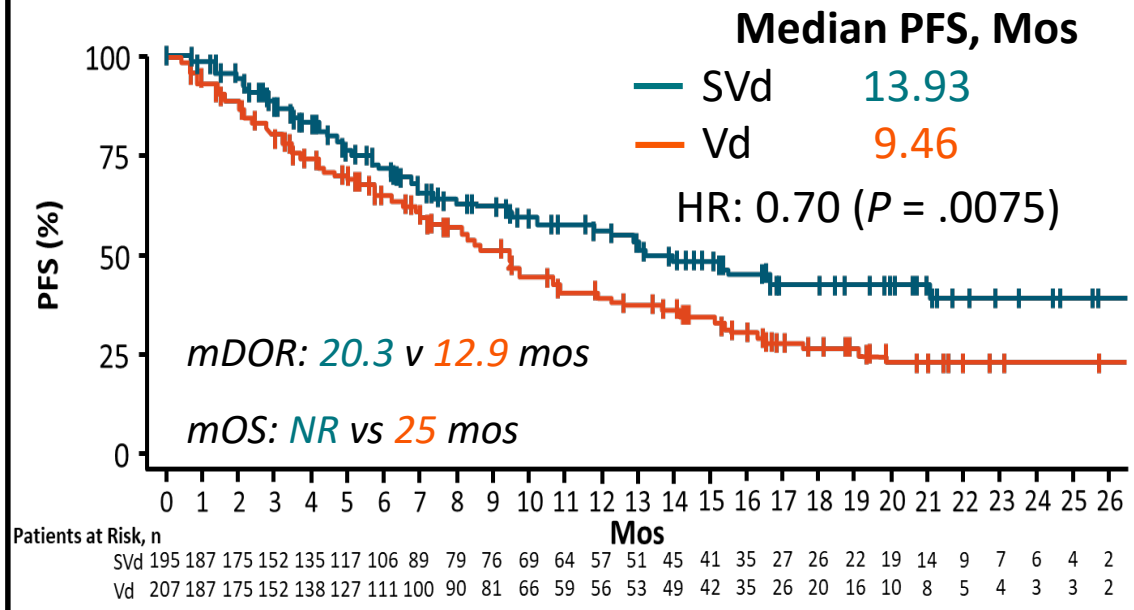
mDOR: 4.4 months

mOS: 8.6 months

***AEs:** thrombocytopenia (73%, 58% G3-4), anemia (67%, 44% G3-4), fatigue (73%; 25% G3-4); GI: nausea (72%, 10% G3/4), anorexia (56%; 5% G3/4), weight loss (50%; 1% G3/4)*

Phase III BOSTON Trial: **Selinexor + Vd** (N = 402)[2]

- 1-3 prior lines of therapy (median: 2; 19% had 3 lines)
- 76% exposed to prior PI, 38% prior len



ORR: 76% vs 62% *(28% VGPR (17% sCR/CR))*

PN G ≥ 2: 21% vs 34%, p=0.001

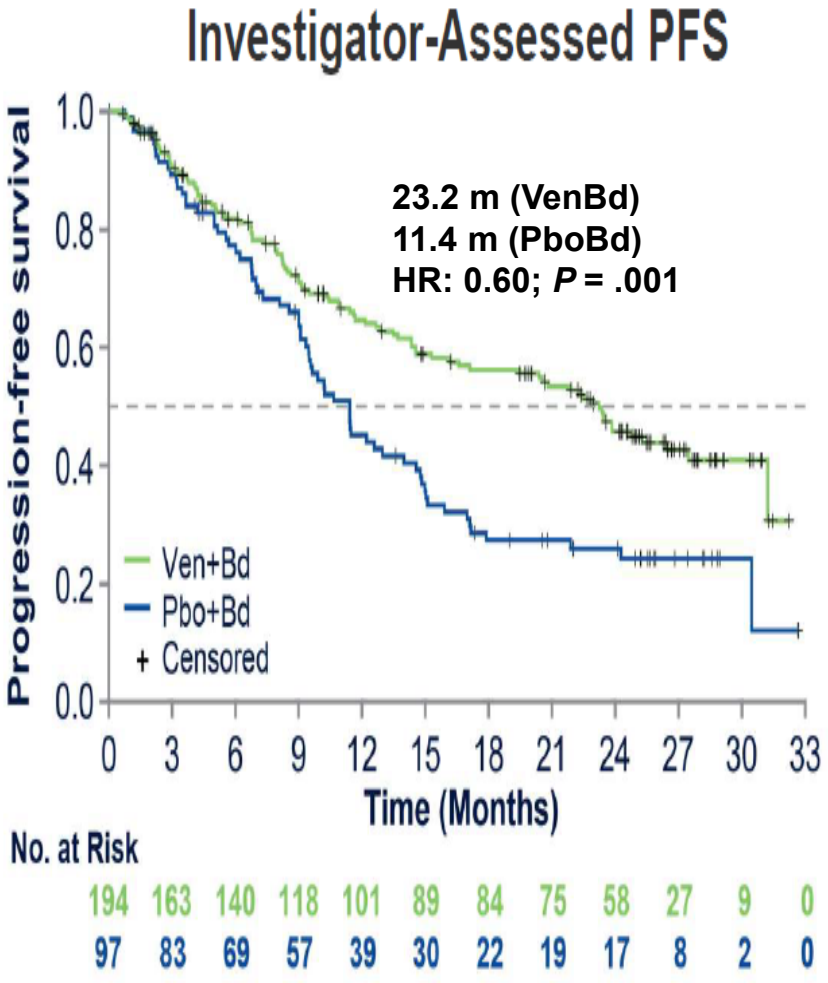
Seli-Pd (STOMP): *52 Pts: 58% ORR; 12m PFS.* *Chen. ASH 2020. Abs 726.*

1. Chari. NEJM. 2019;381:727. 2. Grosicki. Lancet. 2020;396:1563.

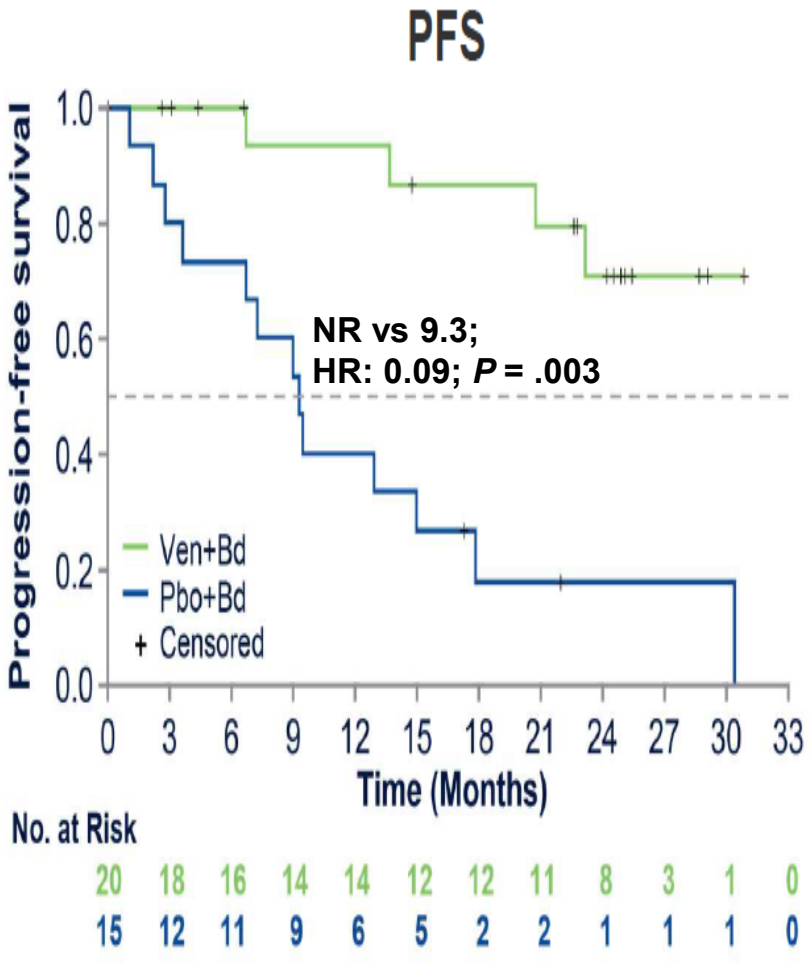
VENETOCLAX+ BortDex vs BortDex (291 patients, 2:1 random) BELLINI Study

Venetoclax is a small molecule BCL-2 inhibitor[1], induces cell death in MM cell, particularly t(11;14) & high *BCL2*....*ORR: 21%...60%*

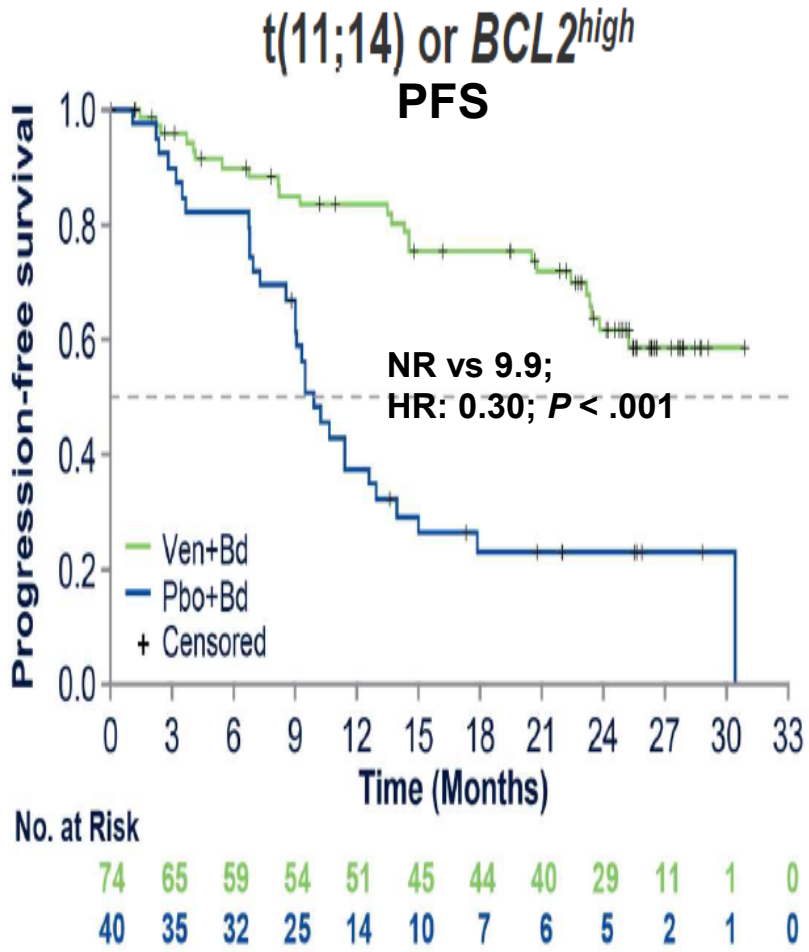
PFS in all patients



PFS in patients with t(11;14)



PFS by t(11;14) and *BCL2* status



Venetoclax: 800mg QD; BtzDex: C1-8 /21d....C9/35d ....until progression

Harrison. ASH 2019. Abstr 142.

Belantamab Mafodotin (DREAMM-2 Study) in Refractory MM

- ***Belantamab mafodotin (GSK2857916): humanized, afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA***

N = 196 after ≥ 3 prior lines of therapy; refractory or intolerant to IMiDs, PIs, and CD38 antibodies

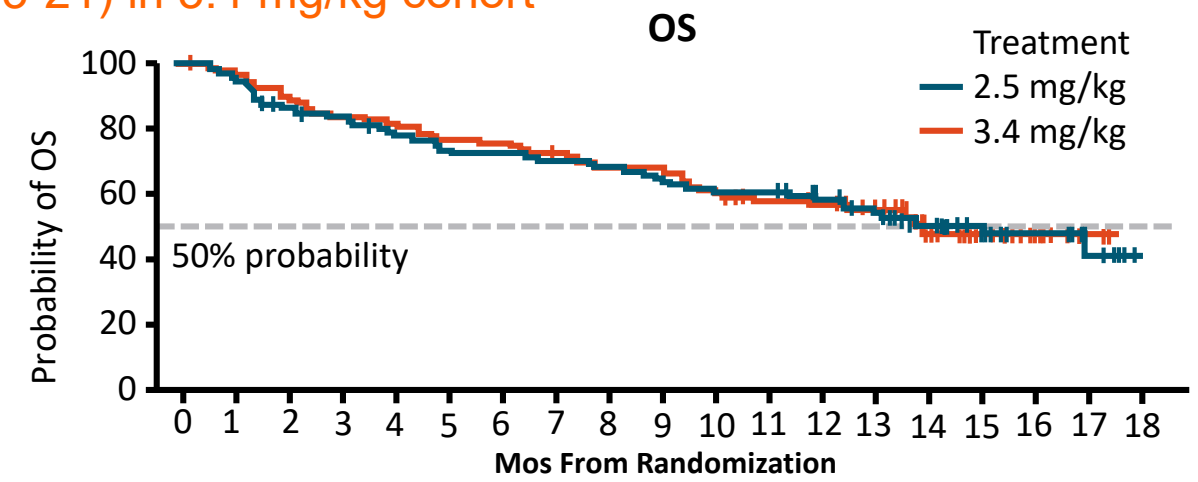
Median 7 (3-21) prior lines in 2.5 mg/kg cohort and 6 (3-21) in 3.4 mg/kg cohort

ORR: 32-35% (by dose)

18% VGPR, 5% CR or sCR at 3.4 mg/kg

≥ MR 40%; ≥ SD 57% at 3.4 mg/kg

Median DOR: 6.2 months



Median, Mos (95% CI)	Bela maf 2.5 mg/kg (n = 97)	Bela maf 3.4 mg/kg (n = 99)
OS	14.9 (9.9-NR)	14.0 (10.0-NR)
PFS	2.8 (1.6-3.6)	3.9 (2.0-5.8)

Main AEs: Corneal events: 72% to 77%; Thrombocytopenia: 36% to 57%; Infusion-related reaction: 16% to 21%

Lonial. ASCO 2020. Abstr 8536.

DREAMM-6: Bela Maf + Vd (ORR: 78%) *Nooka. ASCO 2020. Abstr 8502.*

DREAMM-5: Bela Maf Combinations *NCT04126200*

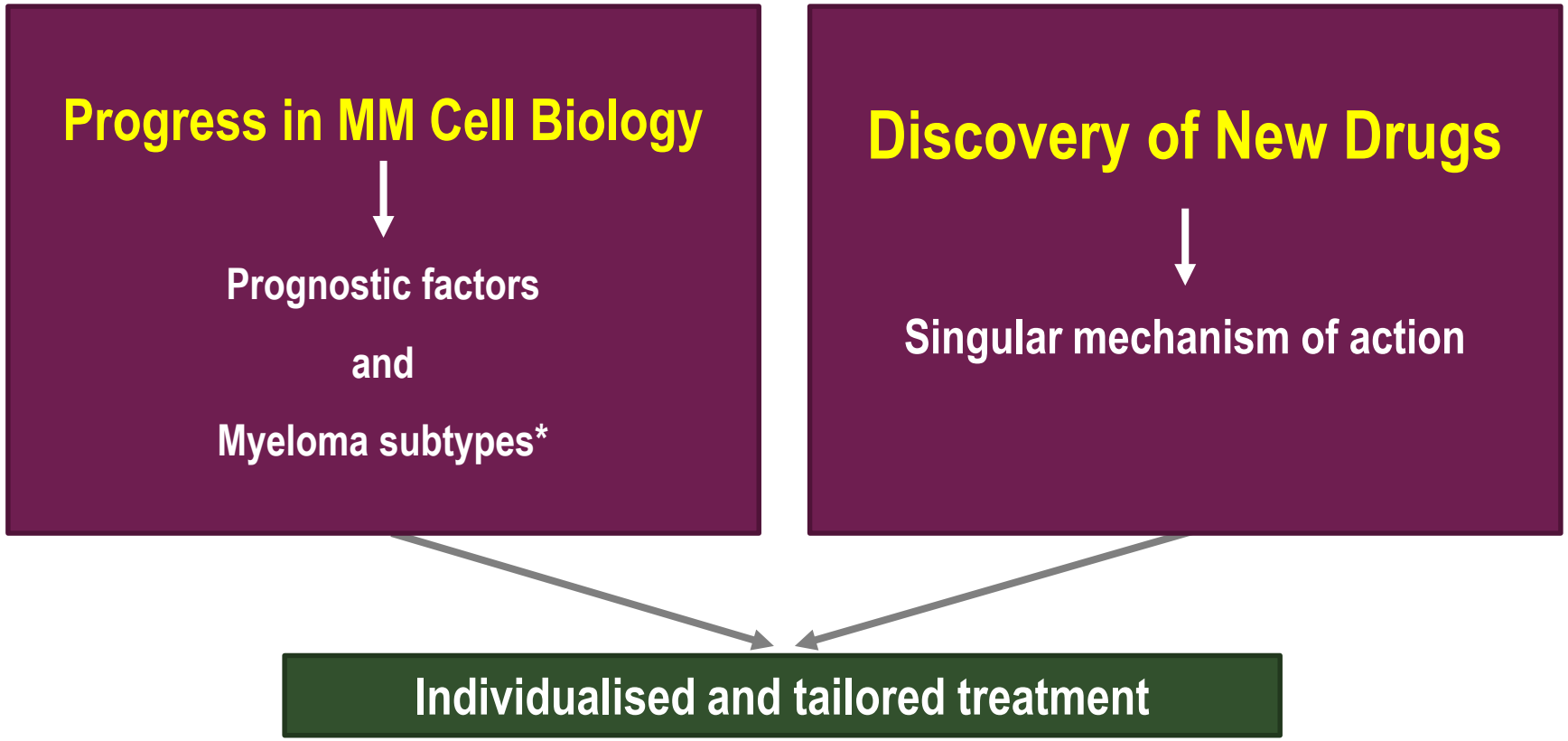
DREAMM-8: Bela Maf + Pd *NCT04484623* 29 Pts (penta Ref)….86% ORR *(Trudel. ASH 2020. Abs 725)*

DREAMM-7: Bela Maf + Vd vs DaraVd *NCT04246047*

DREAMM-9: Bela Maf + SoC in ND MM *NCT04091126*

MULTIPLE MYELOMA

A model for scientific and clinical progress from biology to therapeutics



*MM should not be considered a single entity.

Now, let’s return to our patient case

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MYELOMA
FOUNDATION

Patient Case Example

- A 66-year-old man was diagnosed with IgA lambda **R-ISS Stage-III** myeloma
  - BM showed 60% PC with **t (4;14) plus 1q gain**
  - MC: 25 g/L; **Hb: 10 g/dL**, creatinine: 1.2 mg/dL; calcium: 9.2 mg/dL
  - Extensive bony disease
- He received **Dara-VTD + ASCT** achieving **sCR but MRD+,** planned **maintenance with lenalidomide for 2 years**
- **After 23 months,** he relapsed (18 months from ASCT)

Assessment 3: Now, how would you treat this patient?

1. PI / lenalidomide / dexamethasone
2. PI / pomalidomide / dexamethasone
3. Anti-CD38 mAb / lenalidomide / dexamethasone
4. Anti-CD38 mAb / pomalidomide / dexamethasone
5. Anti-CD38 mAb / PI / dexamethasone
6. Rescue treatment followed by second ASCT
7. Uncertain

Patient Case Example, Continued

- He was treated with **Dara-Vd x 8 cycles** and **achieved VGPR**
- **He progressed 3 months later**

Assessment 4: What approach would you recommend for this patient now?

1. PI / pomalidomide / dexamethasone
2. Anti-CD38 mAb or elotuzumab / pomalidomide / dexamethasone
3. Anti-CD38 mAb / carfilzomib / dexamethasone
4. Selinexor or selinexor combinations
5. Belantamab or belantamab combinations
6. Venetoclax or venetoclax combinations
7. Melflufen or melflufen combinations
8. Bispecific antibodies or CAR T-cell therapy

Panel Discussion:
Managing patients with relapsed disease after ≥ 1 line of therapy

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