How Do I Choose?
Treatment Decisions After Multiple Lines of Therapy

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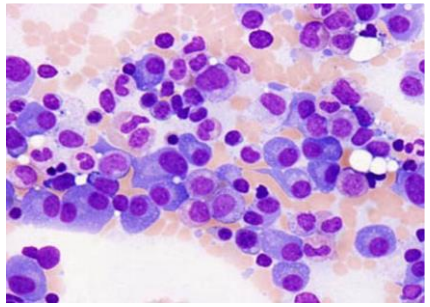
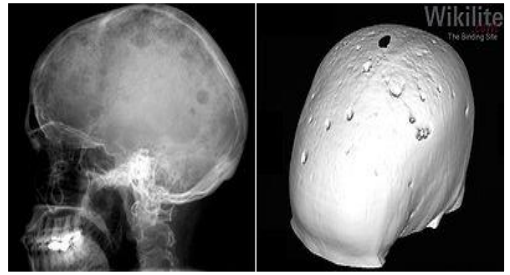
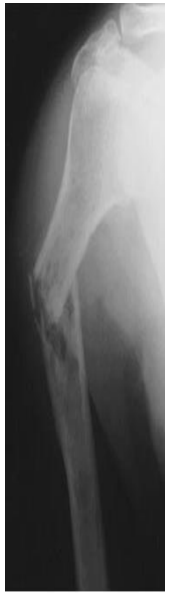
Management of Relapsed Myeloma

- **Despite progress in the management of newly diagnosed patients with myeloma, virtually all patients eventually relapse**
- **Relapses vary clinically and may**
  - **Be biochemical only**
  - **Involve light chain escape or nonsecretory pattern**
  - **Involve extramedullary sites**
- **Optimal management still depends on judicious use of sequential regimens**







Treatment of Relapsed Myeloma
Considerations

- Previously, many patients received fixed-duration bortezomib-based regimens, or, as part of first-line therapy
  - VTD, RVD, or CyBorD induction followed by ASCT if younger and fit
  - Rd or VMP if transplant-ineligible
- In the United States, initial therapy often consists of RVD
  - Some younger transplant-eligible patients may have deferred ASCT
- More patients are progressing while on continuous therapy
  - Lenalidomide maintenance after ASCT is standard of care
  - Wider availability of lenalidomide + dexamethasone for elderly patients
  - Bortezomib maintenance used in selected settings
  - Lenalidomide or proteasome inhibitor-based therapies are used continuously in relapsed/refractory myeloma

ASCT, autologous stem cell transplant; CyBorD, cyclophosphamide + bortezomib + dexamethasone; Rd, lenalidomide + low-dose dexamethasone; RVD, lenalidomide + bortezomib + dexamethasone; VMP, bortezomib + melphalan + prednisone; VTD, bortezomib + thalidomide + dexamethasone

Patient Case

- 65-year-old man with anemia and extensive lytic bone in disease in 2014
  - IgG lambda myeloma with 35% marrow plasma cells
  - FISH cytogenetics positive only for del 13q but LDH was high → R-ISS II
  - Treated with VTD induction (4 cycles), ASCT and lenalidomide maintenance (10 mg/d)
  - CR achieved 4 months after starting maintenance therapy, but MRD (+)
- M-protein reappeared 1½ years later and increased slowly without detectable myeloma-related organ damage
  - After a discussion of observation versus active therapy, patient wishes to defer therapy as long as possible
  - 3 months later, he becomes concerned from the monthly continuous increase (from 7 g/L to 11 g/L and 13 g/L) and decided to receive Rd (no Rd-based therapies were available in 2016)
  - Patient achieved a PR after 3 cycles of therapy and continued on Rd
- Clinical relapse with anemia developed 19 months later; M-protein 32 g/L

Patient case: What treatment would you advise for this patient?

1. **Add a third drug to Rd**
2. **Bortezomib plus dexamethasone (VD)**
3. **Carfilzomib + dexamethasone (K56d)**
4. **Pomalidomide + low dose dexamethasone**
5. **Daratumumab + bortezomib + dexamethasone (DaraVd)**
6. **Cyclophosphamide, thalidomide, dexamethasone (CTD)**

Factors in Choice of Treatment

Patient-Related	Disease-Related	Treatment-Related
• Age • Comorbidities – Peripheral neuropathy – Renal insufficiency – Diabetes • Bone marrow reserve • Frailty • Mobility • Social factors • Patient preference • Drug availability	• Biology of myeloma – Cytogenetics – ? Mutational profile • Extramedullary disease • Pace of relapse – Biochemical only – Indolent – Aggressive • Site of relapse	• Initial therapy • Toxicity profile • Refractoriness • Dosing schedule • Route of administration

Treatment of Relapsed Myeloma

Progress in Therapeutic Options

- **FDA has approved 5 new drugs for relapsed myeloma**
  - **2 proteasome inhibitors: Carfilzomib and ixazomib**
  - **2 monoclonal antibodies: Daratumumab and elotuzumab**
  - **1 HDAC inhibitor: Panobinostat**

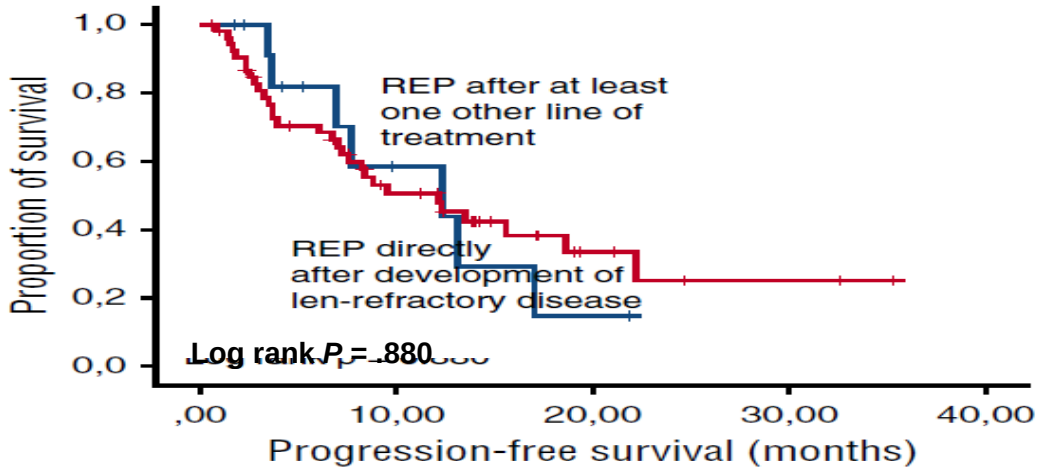
New/oral proteasome inhibitors	Monoclonal antibodies	Kinase inhibitors	HDAC inhibitors	Novel mechanisms	Immunotherapies
• Carfilzomib • Ixazomib • Oprozomib	• Elotuzumab • Daratumumab • Isatuximab	• Vemurafenib • Afuresertib • Dinaciclib • PIM (LGH447) • Trametinib	• Panobinostat • Ricolinostat	• Venetoclax • Selinexor • Nutlins • TTI-621-01 • MCL-1 inhibitor	• Pembrolizumab • Nivolumab • Durvalumab • CAR T cells • BITEs

HDAC, histone deacetylase

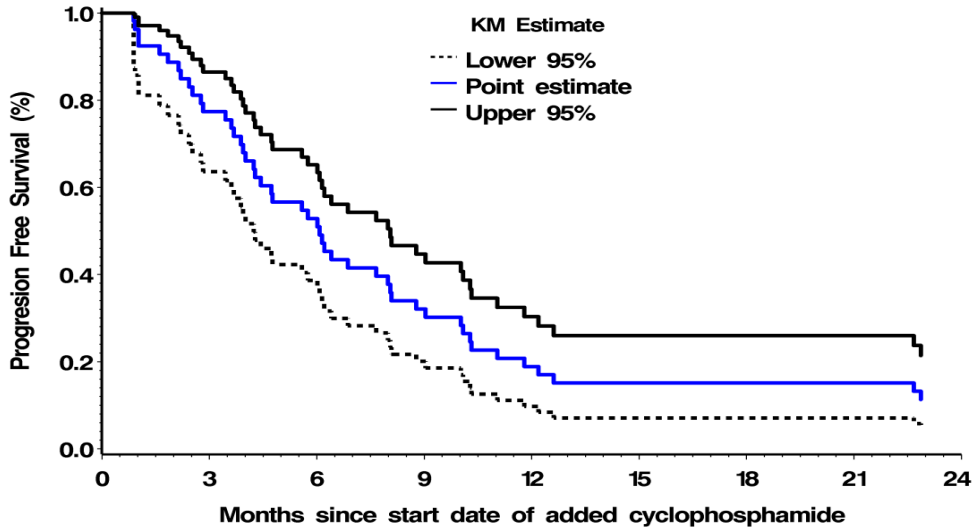
Slide courtesy of Stewart AK.

Addition of 3rd Agent to Lenalidomide at the Time of Progression While on Rd

- **Addition of low-dose cyclophosphamide to len + steroids at the time of next relapse**
  - **PFS 12 months when 50 mg daily added (prospective Dutch trial)[1]**
  - **PFS 7 months when 500 mg weekly added (retrospective PMCC study)**



Dutch Trial[1]



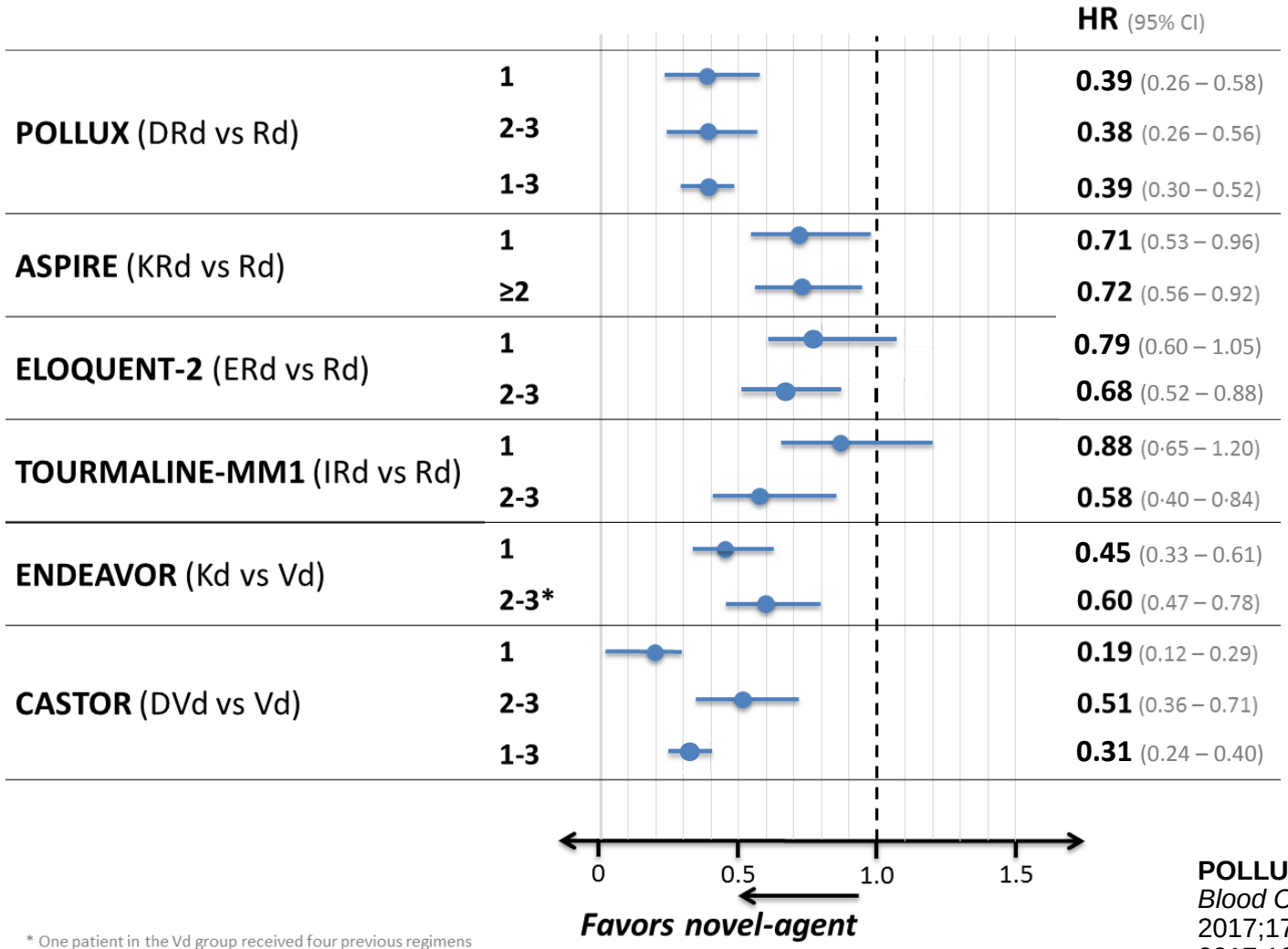
Princess Margaret Cancer Centre Data[2]

- **Addition of clarithromycin extended PFS by 5 months in another PMCC study[3]**

PFS, progression-free survival; PMCC, Princess Margaret Cancer Centre; REP, lenalidomide + cyclophosphamide + prednisone

1. Nijhof IS, et al. *Blood*. 2016;128(19):2297-2306. 2. Alahmadi M, et al. *Blood*. 2015;126: Abstract 1842. 3. Kaedbey R, et al. *Blood*. 2015;15(Suppl 3):e298.

Novel Agents-Based Therapies: PFS According to Previous Lines of Therapy



* One patient in the Vd group received four previous regimens

Conclusions cannot be drawn from cross trial comparisons as aspects of the study designs and patient populations may be different

POLLUX: Moreau P, et al. *Blood.* 2017;130: Abstract 1883. **ASPIRE:** Dimopoulos MA, et al. *Blood Cancer J.* 2017;7(4):e554. **ELOQUENT-2:** Dimopoulos MA, et al. *Br J Haematol.* 2017;178(6):896-905. **TOURMALINE-MM1:** Mateos MV, et al. *Haematologica.* 2017;102(10):1767-1775. **ENDEAVOR**: Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38. **CASTOR**: Spencer A, et al. *Blood*. 2017;130: Abstract 3145.

Regimens for R/R MM After 1-3 Prior Lines

Based on previous exposure or refractoriness to bortezomib or lenalidomide (according to inclusion/exclusion criteria of respective studies)

		KRD	KD	Elo-RD	IRD	DRd	DVd	Pano-VD
Bortezomib	Exposure	+	+	+	+	+	+	+
	Refractoriness	-	-	+	-	+	-	-
Lenalidomide	Exposure	+	+	+	+	+	+	+
	Refractoriness	-	+	-	-	-	+	+

R/R MM, relapsed/refractory multiple myeloma

ENDEAVOR: Progression-Free Survival By Prior Bortezomib and Lenalidomide

	Prior Bortezomib Exposure		Prior Lenalidomide Exposure		Lenalidomide-Refractory	
	Kd (n = 250)	Vd (n = 252)	Kd (n = 177)	Vd (n = 177)	Kd (n = 113)	Vd (n = 122)
Median follow-up in ITT, months	11.9	11.1	11.9	11.1	11.9	11.1
Median PFS, months	15.6	8.1	12.9	7.3	8.6	6.6
Hazard ratio (95% CI)	0.56 (0.44–0.73; *P*<.0001)		0.69 (0.52–0.92; *P* = .0052)		0.80 (0.57–1.11)	

ITT, intention-to-treat; Kd, carfilzomib and dexamethasone; Vd, bortezomib and dexamethasone

Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38. Moreau P, et al. *Leukemia*. 2017;31(1):115-122.

CASTOR: Progression-Free Survival By Prior Treatment Exposure

	Prior Bortezomib Exposure		Lenalidomide-Refractory	
	DVd (n = 162)	Vd (n = 164)	DVd (n = 45)	Vd (n = 60)
Median follow-up in ITT, months	13.0		13.0	
Median PFS, months	12.3	6.7	10.3	4.4
Hazard ratio (95% CI)	0.46 (0.32–0.66; *P*<.0001)		0.37 (0.21–0.65; *P* = .0004)	

DVd, daratumumab + bortezomib + dexamethasone

Chanan-Khan AA, et al. *Blood.* 2016;128: Abstract 3313.

Retreatment With IMiDs: TTP

Retrospective study

- Median of 2 treatments prior to IMiD based salvage therapy
- Median time from diagnosis to repeat exposure to IMiD: 28 months

N = 140	Len → Len n = 48	Len → Thal n = 11	Thal → Len n = 58	Thal → Thal n = 23
ORR (≥PR) to repeat IMiD therapy	54%	20%	48%	30%

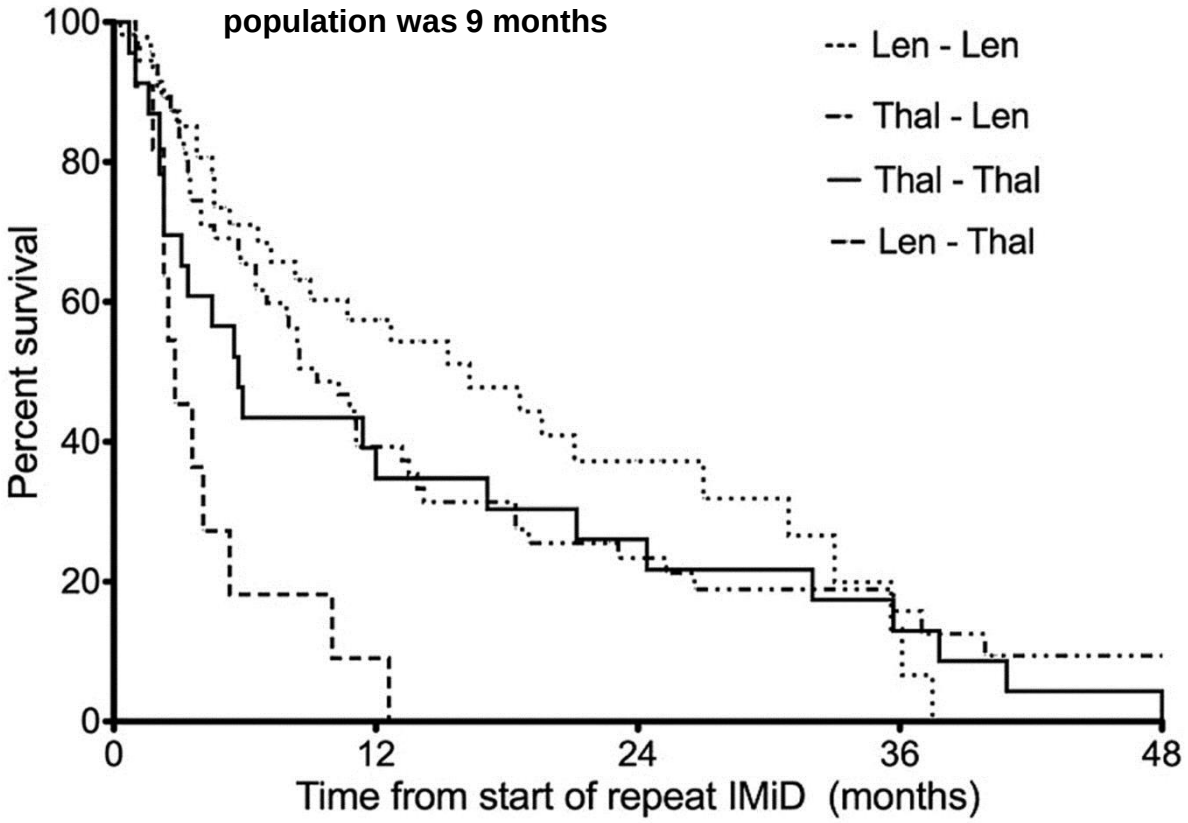
- Repeat therapy with IMiDs feasible
- Response rates with lenalidomide retreatment higher than with repeat thalidomide administration

IMiD, immunomodulatory drug; Len, lenalidomide; ORR, overall response rate; PR, partial response; Thal, thalidomide; TTP, time to progression

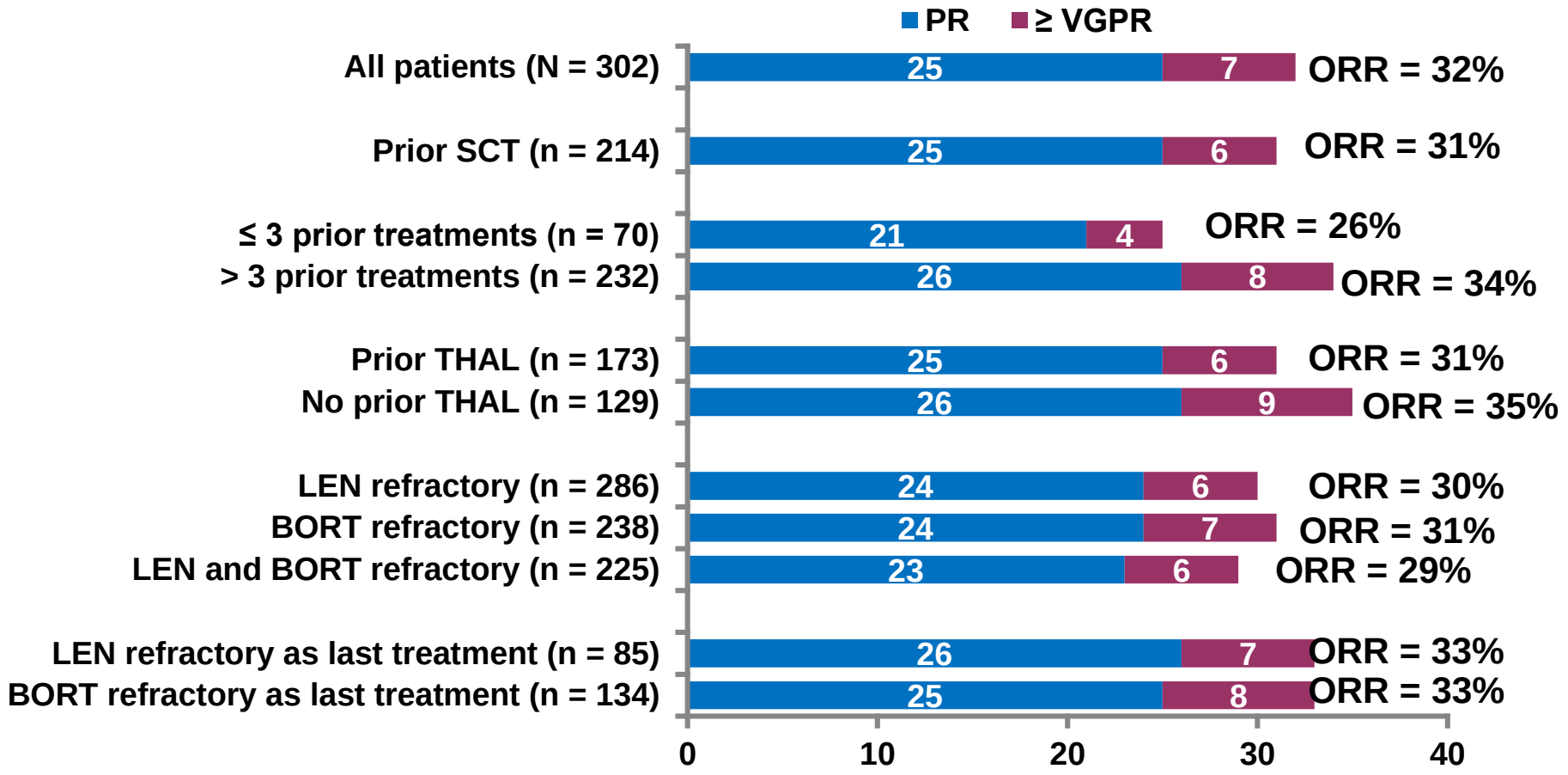
Madan S, et al. *Blood.* 2011;118(7):1763-1765.

Lenalidomide followed by lenalidomide = 16 months, thalidomide followed by lenalidomide = 9 months, thalidomide followed by thalidomide = 6 months, and lenalidomide followed by thalidomide = 3 months

Overall, the median time to progression for the entire study population was 9 months



MM-003: Response By Prior Treatment in the POM + LoDEX Arm

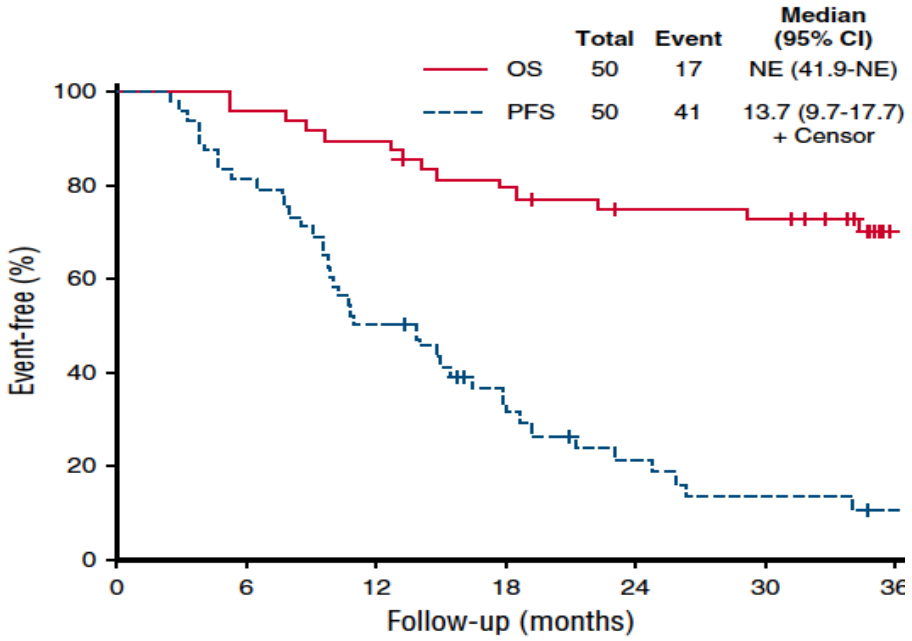


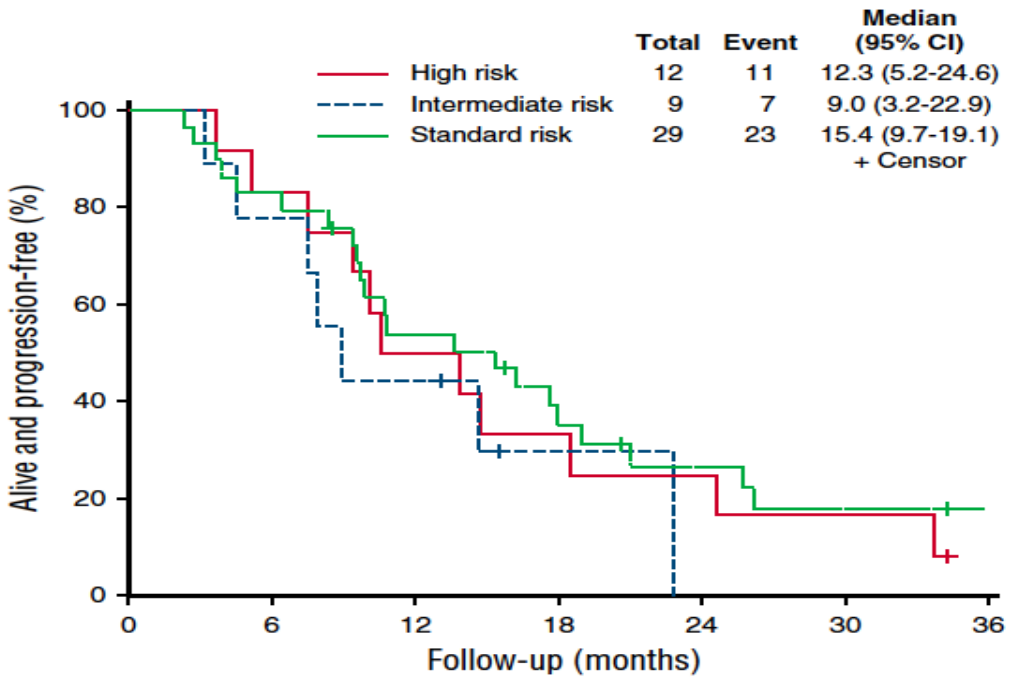
San Miguel JF, et al. *Haematologica.* 2015;100(10):1334-1339.

Pomalidomide Plus Bortezomib and Dexamethasone

Pom: 4 mg/d, **days 1-21** **Bor:** 1.3 mg/m (IV or SC) weekly **Dexa**: 40 mg weekly
After 8 cycles, maintenance with Pom single-agent

- 50 patients with relapsed, lenalidomide refractory multiple myeloma. Median prior lines of therapy: 2 (1-5)
- 26% were len-refractory as last line of therapy
- **ORR: 86%, including 22% sCR/CR and 28% of VGPR**
- **ORR of 100% in patients with del17p**



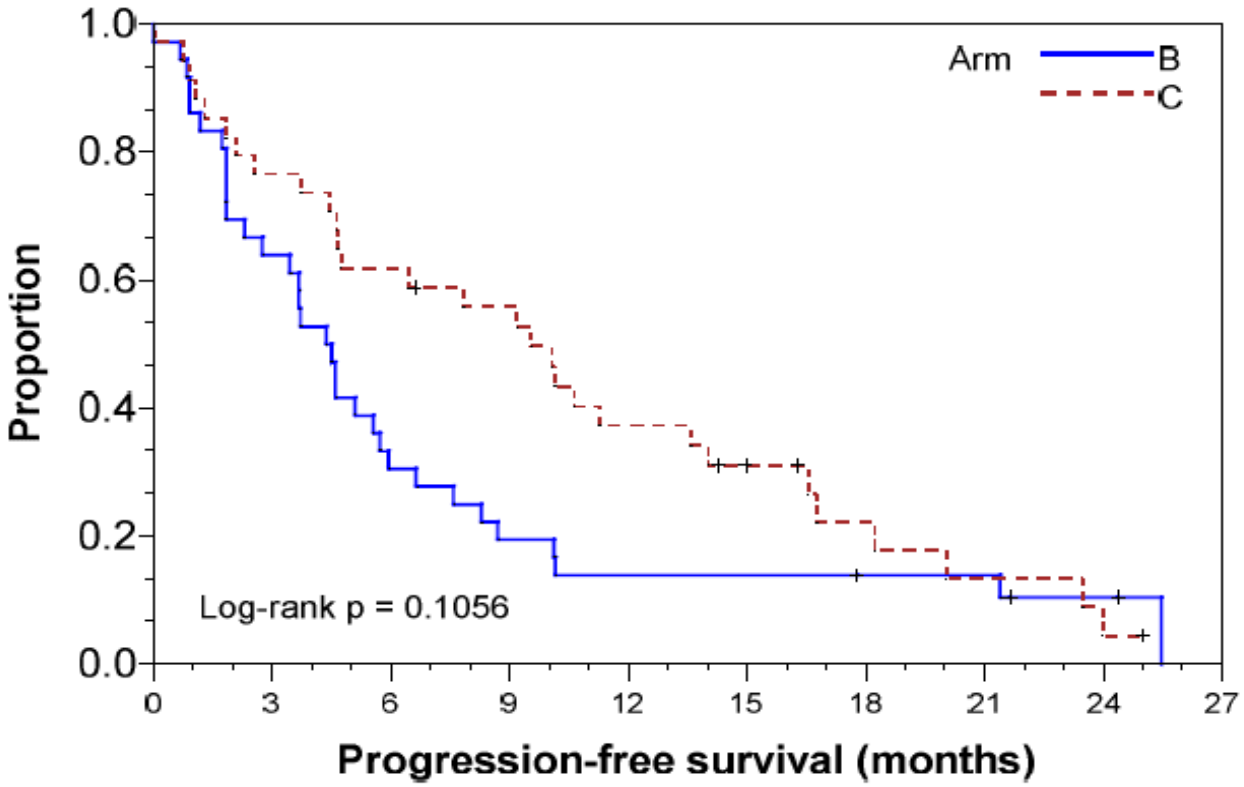


Safety profile: ≥G3 neutropenia (70%), lung infection (10%), and PN (4%)

Rationale for a phase III trial OPTIMISMM: Vd +/- Pomalidomide

Paludo J, et al. *Blood.* 2017;130(10):1198-1204.

A Phase II Study of Pom/Cyclo/Dex vs Pom/Dex for R/R MM

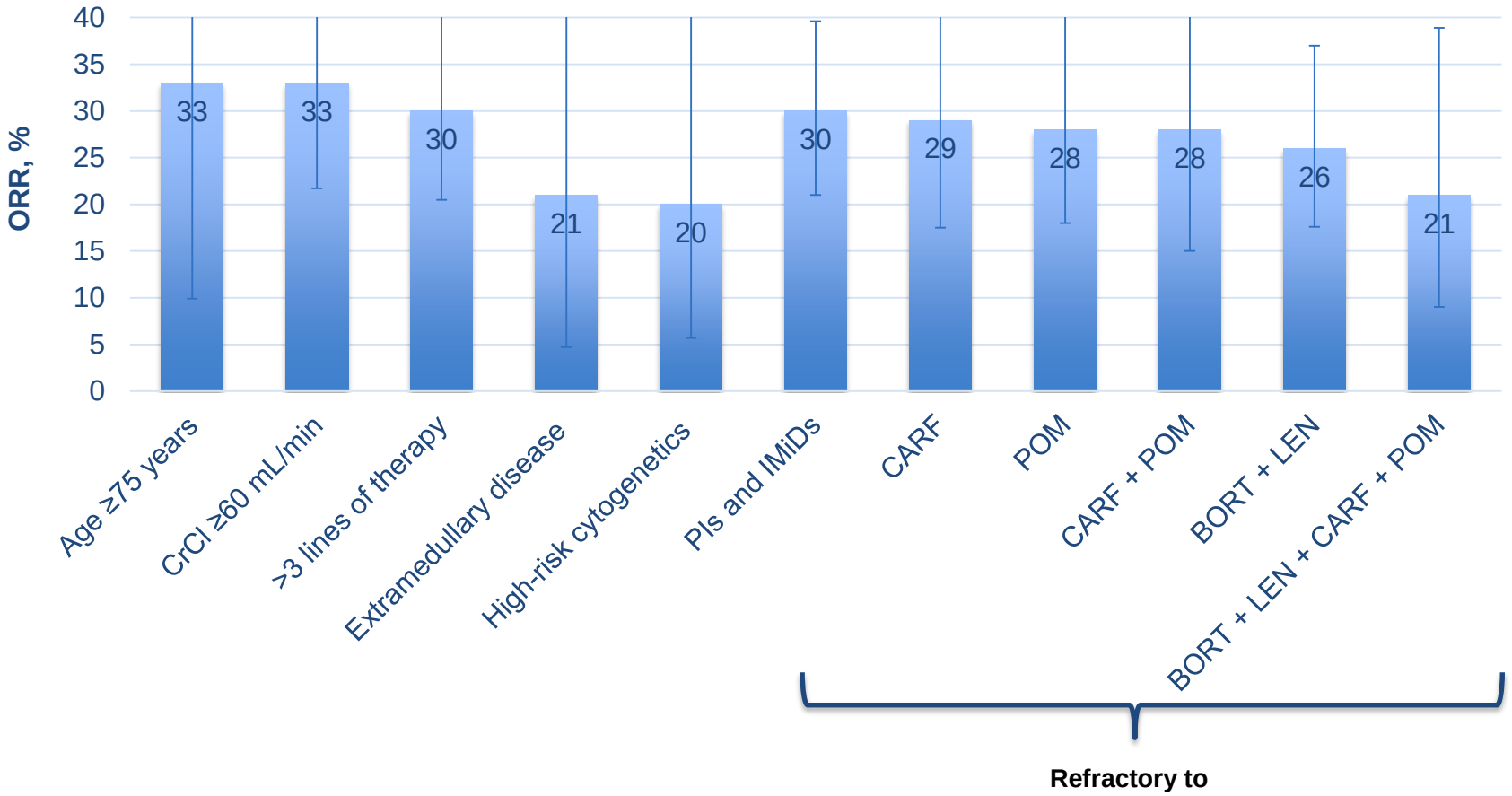


Arm	N	Event	Censored	Median (95% CI)
B	36	33 (92%)	3 (8%)	4.4(2.3, 5.7)
C	34	29 (85%)	5 (15%)	9.5(4.6, 14.0)

Arm B: Pom/LowDexa; Arm C: Pom/LowDexa +Cyclo (400 mg PO day 1, 8, 15)

Baz RC, et al. *Blood.* 2016;127(21):2561-2568.

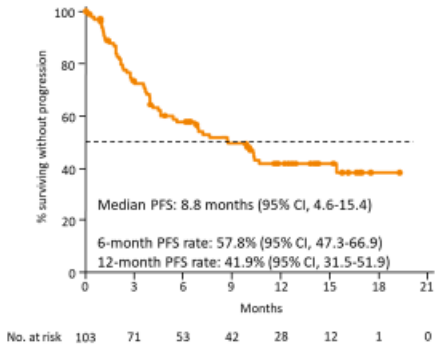
Daratumumab Monotherapy ORR By Subgroup: Sirius Trial

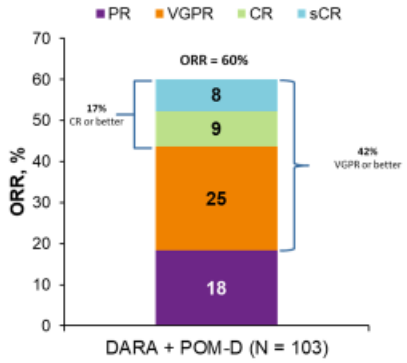


Lonial S, et al. *Lancet.* 2016;387(10027):1551-60.

Pomalidomide + Daratumumab + Dex

MMY1001 phase 1b study: daratumumab + POM-D in RRMM: PFS and ORR

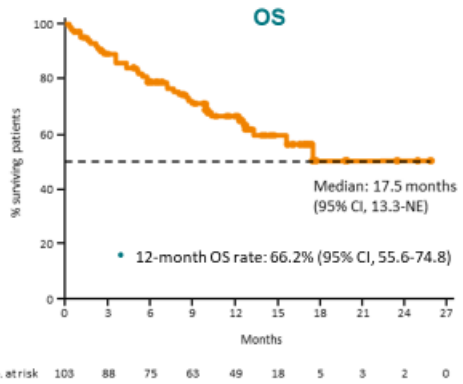


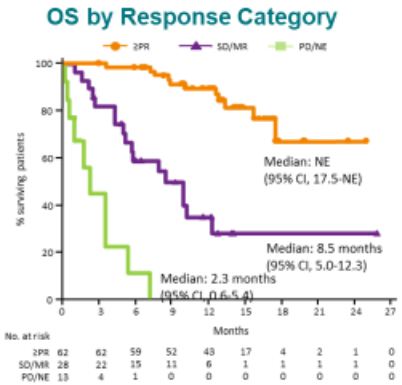


- Among patients with CR or better, the MRD negative rate at:
  - 10^{-4} threshold = 6/17 (35%)
  - 10^{-5} threshold = 5/17 (29%)
  - 10^{-6} threshold = 1/17 (6%)

~40% of patients maintain PFS after 1 year
Deep responses were observed with DARA + POM-D

MMY1001: daratumumab + POM-D: OS





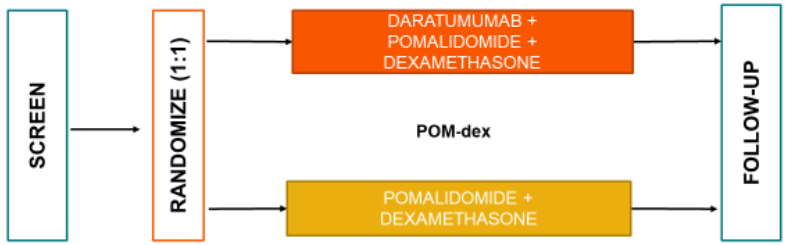
Patients with SD/MR derive survival benefit with DARA + POM-D

16 June 2017: FDA approved DARA+POM-D for MM patients with ≥ 2 prior lines of therapy including a PI & LEN

- Patients: RRMM, **≥1 prior line of therapy** (IMiD and PI; len-refractory if only 1 prior regimen), ≥PR on prior therapy, PD on/after last regimen
- Exclusion criteria included prior anti-CD38 mAb or pomalidomide
- Primary endpoint: PFS

N=354

APOLLO STUDY



Cycle length = 28 days
Treatment until progression or unacceptable toxicity

Usmani SZ, et al. *Haematologica*. 2017;102(s2): Abstract P676. Chari A, et al. *Blood*. 2017;130:974-981. National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT03180736. Accessed: April 17, 2018.

Pomalidomide + Elotuzumab + Dex
ELO-3: Phase II Study Design

RANDOMIZATION

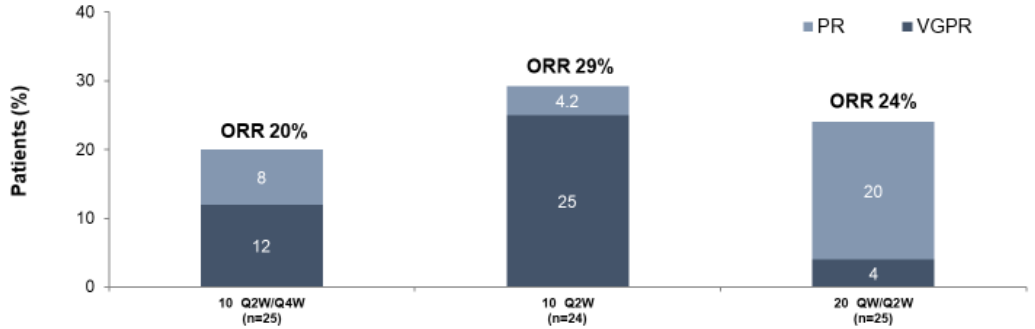
	Cycle 1 and 2	Cycle 3 and Beyond
Control Arm	**Pomalidomide:** 4 mg PO daily (days 1-21) of each cycle **Dexamethasone:** • 40 mg PO per day (days 1, 8, 15, 22) of each cycle (subjects ≤75 years old) • 20 mg PO per day (days 1, 8, 15, 22) of each cycle (subjects >75 years old)	**Pomalidomide:** 4 mg PO daily (days 1-21) of each cycle **Dexamethasone:** • 40 mg PO per day (days 1, 8, 15, 22) of each cycle (subjects ≤75 years old) • 20 mg PO per day (days 1, 8, 15, 22) of each cycle (subjects >75 years old)
Elotuzumab Arm	**Elotuzumab:** 10 mg/kg IV (days 1, 8, 15, 22) of each cycle **Pomalidomide:** 4 mg PO daily (days 1-21) of each cycle **Dexamethasone:** • 28 mg PO + 8 mg IV on days of elotuzumab dosing (subjects ≤75 years old) • 8 mg PO + 8 mg IV on days of elotuzumab dosing (subjects >75 years old)	**Elotuzumab:** 20 mg/kg IV day 1 of each cycle **Pomalidomide:** 4 mg PO daily (days 1-21) of each cycle **Dexamethasone (weeks with elotuzumab dosing):** • 28 mg PO + 8 mg IV on day of elotuzumab dosing (subjects ≤75 years old) • 8 mg PO + 8 mg IV on day of elotuzumab dosing (subjects >75 years old) **Dexamethasone (weeks without elotuzumab dosing):** • 40 mg PO per week (subjects ≤75 years old) • 20 mg PO per week (subjects >75 years old)

Follow-Up
Follow-up every 4 weeks for tumor response until PD; then survival follow-up every 12 weeks or more frequently

National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT03030261. Accessed: April 17, 2018.

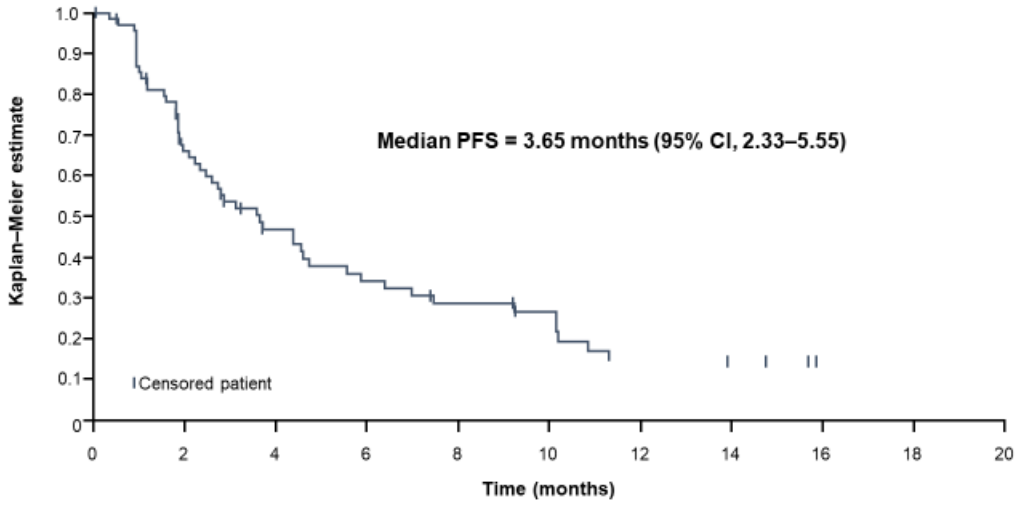
Other Novel Regimens

Updated data from a dose-finding phase II trial of single agent isatuximab (anti-CD38 mAb) in relapsed/refractory multiple myeloma

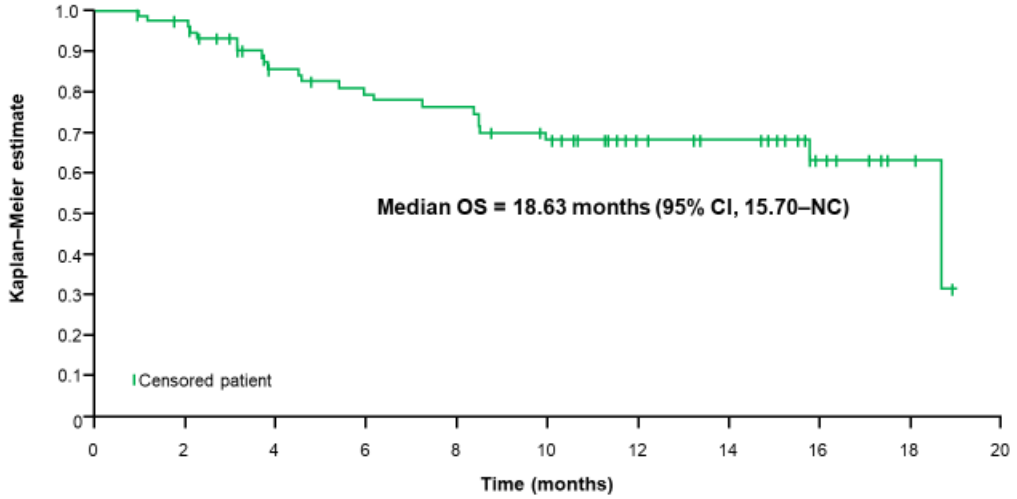


Median time to first response, mo	2 (0.8–2.1)	0.9 (0.9–1)	1.35 (0.9–2.8)
Median time to best response, mo	3 (0.9–12.9)	4.6 (0.9–12.9)	1.35 (0.9–2.8)

PFS at ≥10 mg/kg



OS at ≥10 mg/kg



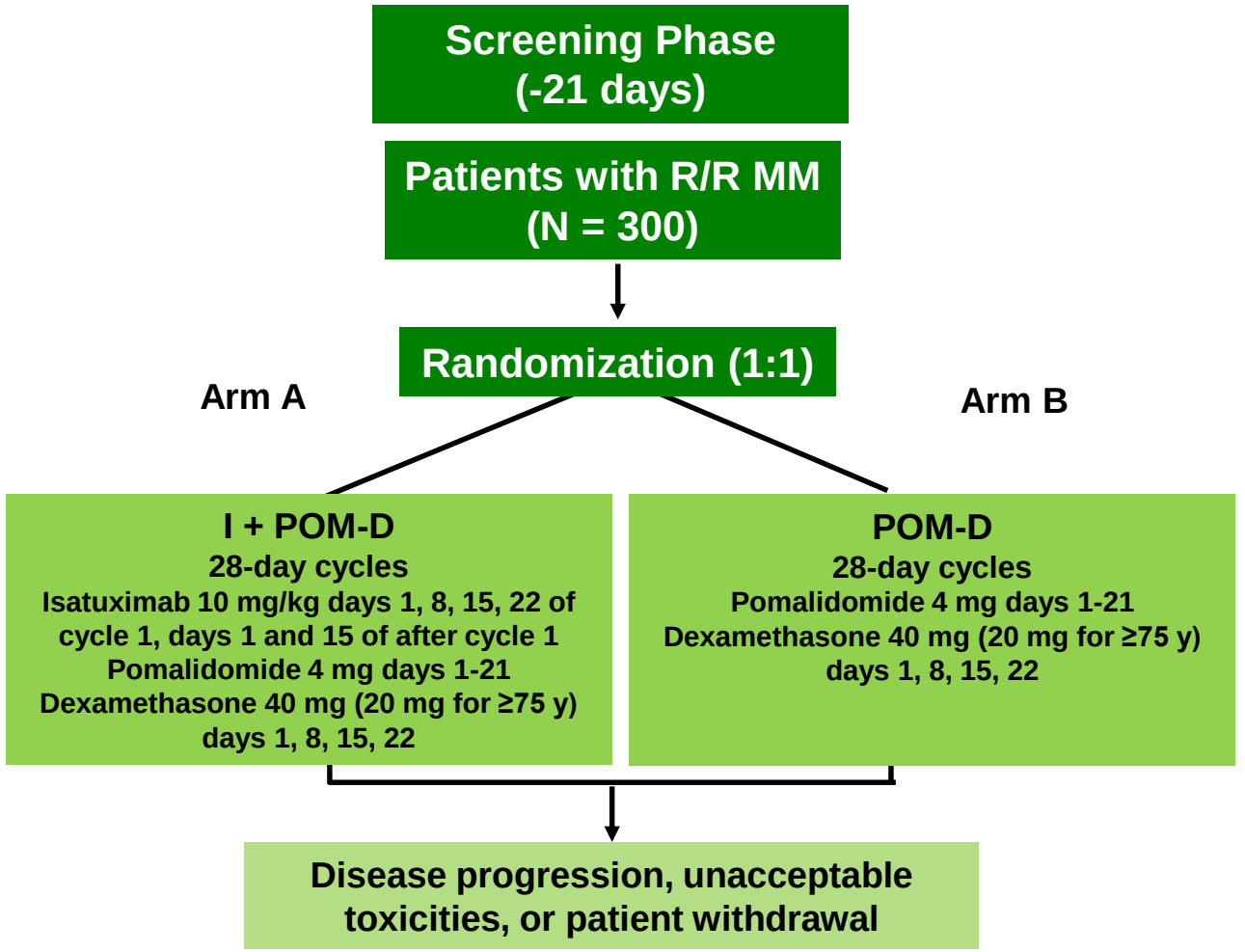
OS, overall survival

Martin T, et al. *Blood.* 2016;128: Abstract 509.

Data cut-off: Feb, 2016

Isatuximab Plus Pomalidomide and Dexamethasone

- Patients:
  - ≥2 prior lines of therapy
  - Failed treatment with lenalidomide and a PI alone or combination
  - Refractory to last line of treatment
  - Pomalidomide naive
- Primary endpoint: PFS
- Secondary endpoints include:
  - ORR, OS, TTP, PFS in high risk cytogenetic population, DoR, Safety, QoL



DoR, duration of response; QoL, quality of life

Richardson P, et al. Presented at: International Myeloma Workshop 2017; March 1-4, 2017: New Delhi, India. Abstract PS-249.

STORM Study: Selinexor Plus Dex in Patients With R/R MM

- **78 patients after a median of 7 prior lines of therapy: 48 patients quad refractory (bor, carf, len, & pom) and 30 penta refractory (bor, carf, len, pom, & CD38 mAbs)**

Category	N*	ORR (%)	CBR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)	NE (%)
Overall	**78**	**16 (21%)**	**26 (33%)**	**4 (5%)**	**12 (15%)**	**10 (13%)**	**27 (35%)**	**9 (12%)**	**16 (21%)**
Quad Refractory	**48**	**10 (21%)**	**14 (29%)**	**2 (4%)**	**8 (17%)**	**4 (8%)**	**21 (44%)**	**4 (8%)**	**9 (19%)**
Penta Refractory	**30**	**6 (20%)**	**12 (40%)**	**2 (7%)**	**4 (13%)**	**6 (20%)**	**6 (20%)**	**5 (17%)**	**7 (23%)**
6 Doses/ Month	**51**	**10 (20%)**	**15 (29%)**	**3 (6%)**	**7 (14%)**	**5 (10%)**	**21 (41%)**	**4 (8%)**	**11 (22%)**
8 Doses/ Month	**27**	**6 (22%)**	**11 (41%)**	**1 (4%)**	**5 (19%)**	**5 (19%)**	**6 (22%)**	**5 (19%)**	**5 (19%)**

Median DoR: 5 months; Median PFS: 2.3 months; Median OS: 9.3 months

Main toxicities are thrombocytopenia (59% grade 3/4) and neutropenia (17% grade 3/4), anemia (28% grade 3/4), fatigue (15% grade 3/4), which are manageable with dose modifications

*1 patient did not have measurable disease at baseline. Selinexir 80 mg oral + Dex 20 mg, twice daily

Vogl DT, et al. *Blood.* 2016:128: Abstract 491.

Phase I Study of Selinexor + Bortezomib + Dex

100 mg oral q w + 1.3 mg/m² SC q w x 4 / 5 + 40 mg q w

- **44 patients: 22 in the dose escalation and 20 in the expansion cohort. Median PL: 3 (1-11)**
- **R/R MM after at least 1PL: Prior PI exposure allowed, but no bz refractory in the last line of therapy**

Best Responses† in Evaluable SVd Patients as of November 15th, 2017

Category	N*	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR‡ (%)	MR (%)	SD (%)	PD (%)
PI Relapsed or Naïve	19	**16 (84%)**	**16 (95%)**	2 (11%)	5 (26%)	9 (47%)	2 (11%)	1 (5%)	--
PI Refractory	21	**9 (43%)**	**14 (67%)**	1 (5%)	4 (19%)	4 (19%)	5 (24%)	6 (29%)	1 (5%)
PI Relapsed or Naïve, ≤ 3 Prior Treatments (BOSTON**)	18	**15 (83%)**	**16 (89%)**	2 (11%)	6 (33%)	7 (39%)	1 (6%)	2 (11%)	--

- **ORR of 83% in PI relapsed or naïve MM with 1-3PL** compares favorably to the ORR of 63% reported for VD in previous trials
- In patients with **PI refractory MM, ORR of 43% and CBR of 67%** support preclinical findings that selinexor resensitizes and overcomes PI-resistance
- AEs were manageable (mostly grade 1/2) and included nausea, fatigue, anorexia, and thrombocytopenia. PN in only 6 patients
- Grade 3/4 AEs: Thrombocytopenia (40%), neutropenia (19%), and anemia (12%)

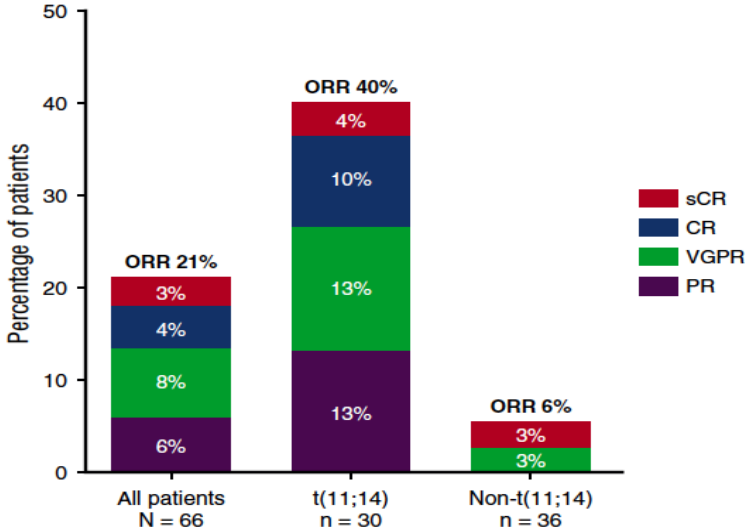
Rationale for the BOSTON, phase III trial: Vd +/- Selinexor

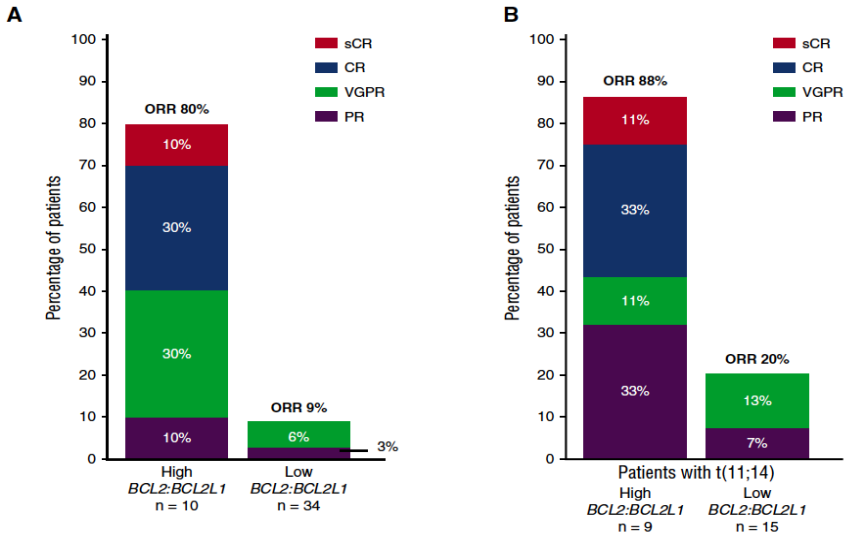
Bahlis NJ, et al. *Blood.* 2017;130: Abstract 3135.

Venetoclax Monotherapy: Phase I in Patients With R/R MM (for t11;14 Patients)

30 mg to 1200 mg oral admin (MTD: 1200 mg)

- **66 patients after a median of 5 prior lines of therapy: 79% refractory to last line of therapy; 61% double refractory to bor and len**





Main toxicities are thrombocytopenia (26% grade 3/4) and neutropenia (21% grade 3/4); serious AEs: Pneumoniae (8%) and sepsis (5%)

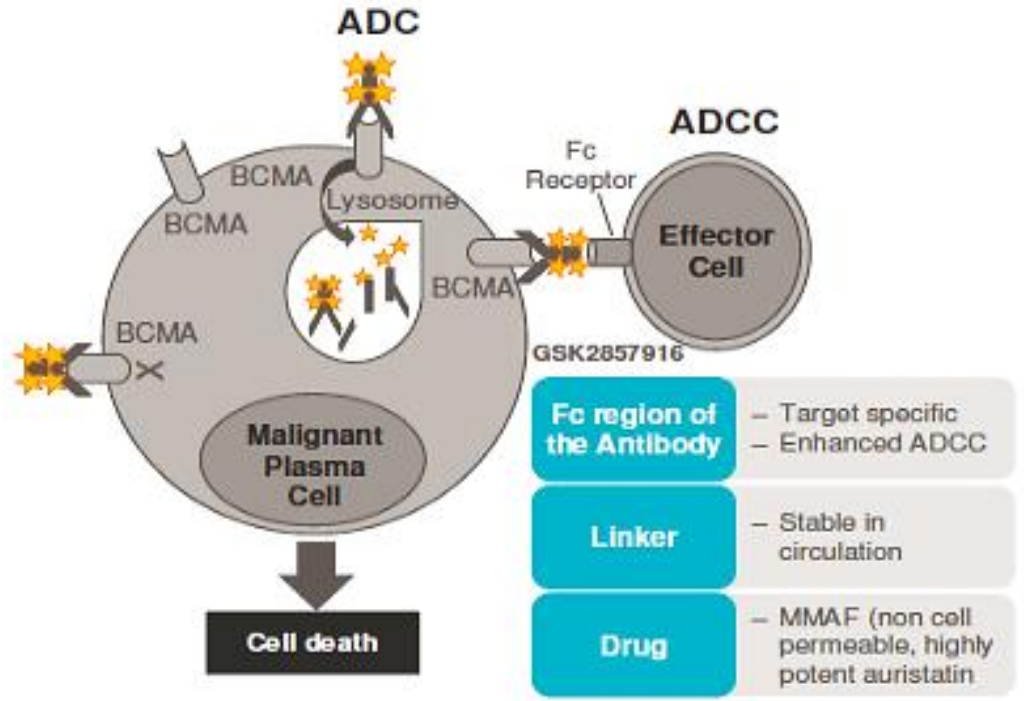
Higher ORR (88% vs 20%) were seen in patients with a high BCL2:BCL2L1 ratio regardless of t(11;14)

- **20 patients with t(11;14) after a median of 3 prior lines of therapy received venetoclax at dose of 800 mg daily plus dexamethasone 40 mg weekly. The ORR was 65% including 7 patients in VGPR and 6 patients in PR**
- **The 6-month TTP was 64%**

Kumar S, et al. *Blood*. 2017;130(22):2401-2409.

GSK2857916: BCMA-ADC in MM (1)

- **Humanized IgG1 anti-BCMA antibody conjugated to monomethyl auristatine-F**
- **BCMA is restricted to B cells at later stages of differentiation, broadly expressed on malignant PC**



Mechanisms of Action:
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signalling inhibition

N = 30 patients with MM at escalating doses
At high doses ≥3.4 mg/kg (n = 10) **ORR 67%**

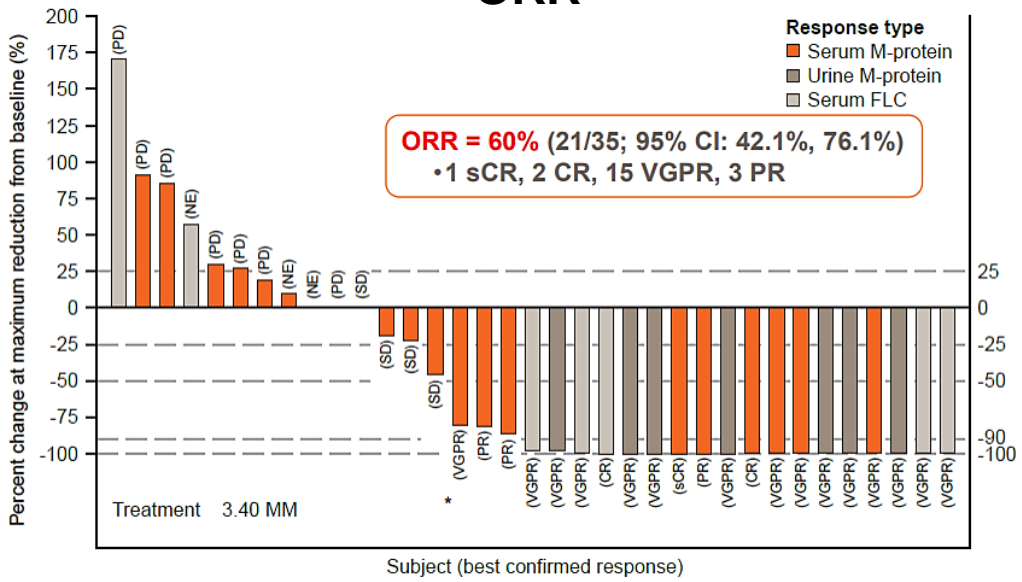
70% ≥5 prior lines

Cohen AD, et al. *Blood.* 2016;128(22):1148.

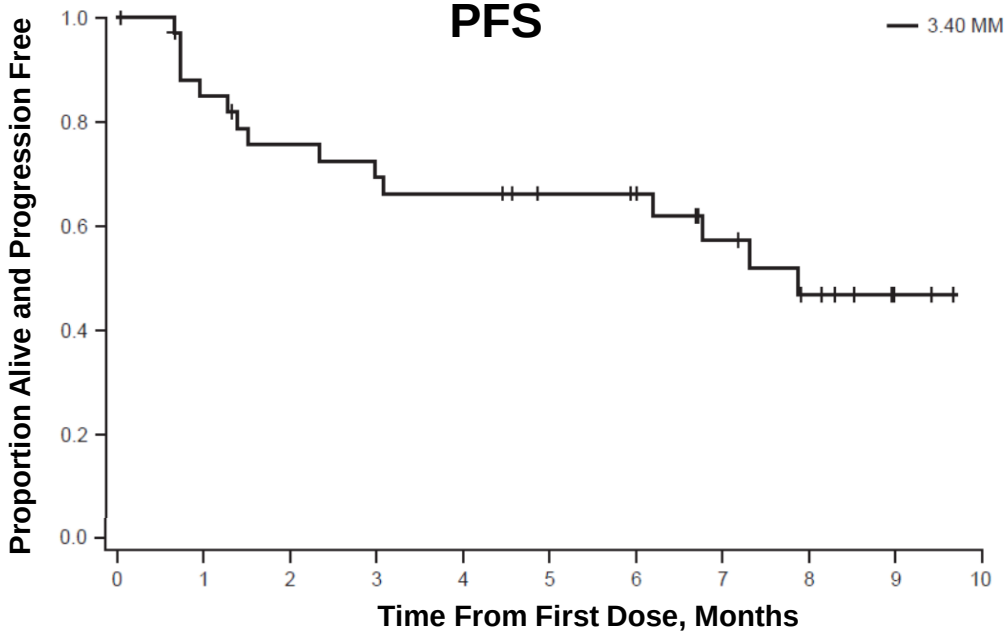
GSK2857916: BCMA-ADC in MM (2)

- **35 patients received the BCMA-ADC at dose of 3.4 mg/kg IV in 1-hour infusion without premedication and every 3 weeks**
- **57% of them had received at least 5 PL of therapy**
  - **97% PI refractory**
  - **91% IMiD refractory**
  - **30% Dara refractory**

ORR



PFS



Number of subjects	**35**
Progressed or died	15 (43%)
Censored, f/u ended	3 (9%)
Censored, f/u ongoing	17 (49%)

Progression-free survival, months

Q1 (95% CI)	2.3 (0.7, 6.8)
Median (95% CI)	**7.9 (3.1, -)**
Q3 (95% CI)	N/A

- **Response sustained in the different subgroups of patients**
- **Dara-treated, ORR of 43%**
- **Safety profile: Corneal events in 63% grade 1/2, thrombocytopenia in 34%**

Trudel S, et al. *Blood.* 2017:130: Abstract 741.

Patient Case

- **65-year-old man with anemia and extensive lytic bone in disease in 2014**
  - **IgG lambda myeloma with 35% marrow plasma cells**
  - **FISH cytogenetics positive only for del 13q but LDH was high → R-ISS II**
  - **Treated with VTD induction (4 cycles), ASCT, and lenalidomide maintenance (10 mg/d)**
  - **CR achieved 4 months after starting maintenance therapy, but MRD-positive**
- **M-protein reappeared 1½ years later and increased slowly without detectable myeloma-related organ damage**
  - **After a discussion of observation versus active therapy, the patient wishes to defer therapy as long as possible**
  - **3 months later, he becomes concerned from the monthly continuous increase (from 7 g/L to 11 g/L and 13 g/L) and decided to receive Rd (no Rd-based therapies were available in 2016)**
  - **Patient achieved a PR after 3 cycles of therapy and continued on Rd**
- **Clinical relapse with anemia developed 19 months later; M-protein 32 g/L**

Patient case: What treatment would you advise for this patient?

1. **Add a third drug to Rd**
2. **Bortezomib plus dexamethasone (VD)**
3. **Carfilzomib + dexamethasone (K56d)**
4. **Pomalidomide + low dose dexamethasone**
5. **Daratumumab + bortezomib + dexamethasone (DaraVd)**
6. **Cyclophosphamide, thalidomide, dexamethasone (CTD)**

Patient Case

- **65-year-old man with relapsed myeloma**
  - **Intensification with lenalidomide could be an option for biochemical relapsing patients while on lenalidomide maintenance but phase III data are missing; our patient had a clinical relapse**
  - **Bortezomib retreatment is inferior to K56d**
  - **K56d: A suitable option for lenalidomide refractory patients, although best results are shown at second line**
  - **PomDex: Good results in lenalidomide refractory patients; possibly a third agent is needed for best results in this young and fit patient**
  - **DaraVd: A suitable option for lenalidomide refractory patients with PFS advantage over Vd**
  - **CTD: Very poor results after lenalidomide failure**
  - **However, both K56d and DaraVd have shown inferior results in patients who are lenalidomide-refractory compared to the whole population in ENDEAVOR and CASTOR studies**

Relapsed Myeloma
Summary and Conclusions

- **Challenges**
  - **Patients and myeloma biology are heterogeneous**
  - **Choices in many countries may be limited by availability**
- **Choice of treatment in patients who have been exposed to both bortezomib and lenalidomide and mainly in those refractory to those agents remain a challenge**
- **Triplet regimens are generally preferred in this high-risk population, although results from phase III are limited**
  - **Exceptions may include elderly, frail patients**
  - **Certain patients do well with the pom + dex doublet only, and future efforts to identify them are desirable**
  - **The strategy of adding a 3rd agent only "on demand" is of interest but has not been tested in phase III studies**

Relapsed Myeloma
Summary and Conclusions

- **Efforts to improve quality of life of patients on these newer regimens are ongoing**
  - **Weekly carfilzomib**
  - **Subcutaneous daratumumab**
- **The field will change again with the maturity of the next phase III studies, as the newer triplets are being evaluated in the following settings:**
  - **As first-line therapy**
  - **With pomalidomide rather than lenalidomide**

Relapsed Myeloma
Summary and Conclusions

- **Future directions for relapsed myeloma include**
  - **Targeted therapy**
    - **Venetoclax for t(11;14)**
    - **FGFR3 inhibitors for t(4;14)**
    - **Nutlins for del 17p**
  - **New drug classes (eg, selinexor)**

- **Immunotherapy will have a large impact on patient management**
  - **Integration of immunotherapy into all phases of therapy is likely**
    - **Conjugated monoclonal antibodies**
    - **Optimal use of checkpoint inhibitors**
    - **BITEs**
    - **CAR T cells**

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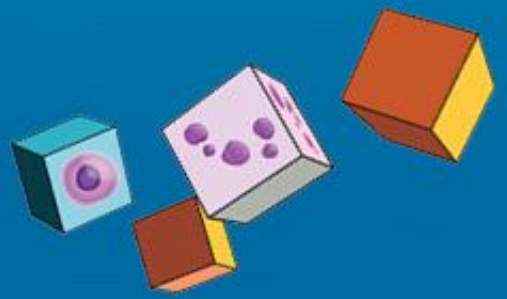
Treatment Decisions for Relapsed/Refractory Multiple Myeloma:



Fitting the Pieces Together