Update on options for relapsed MM in 2019

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Disclosures

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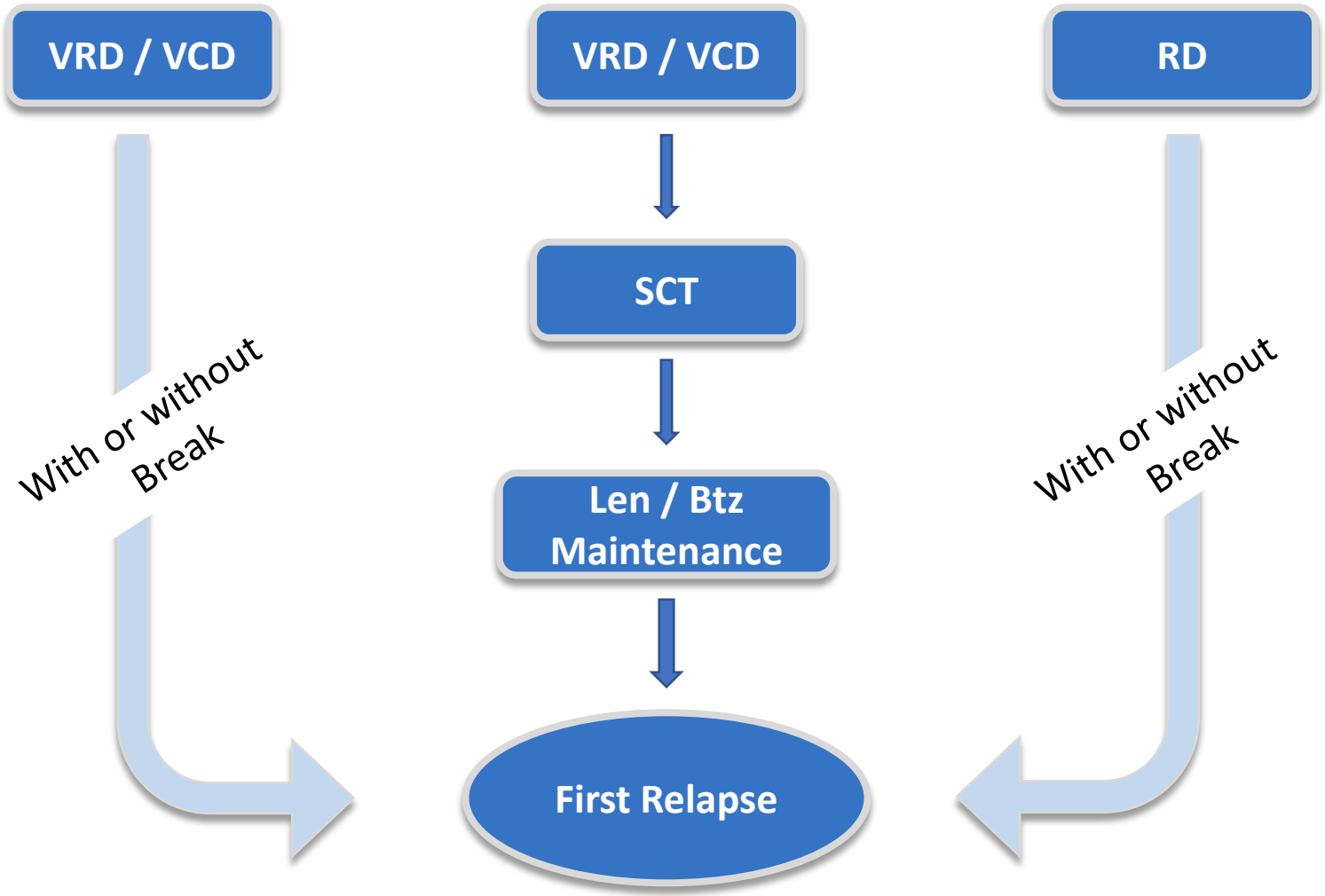
Summary Initial Therapy of MM in 2019

- Transplant Based –
  - Still Standard of Care
  - Induction – Triplet RVD (CyBorD Start in some cases)
  - Dara CyBorD or KCD if NOT prohibited by insurance
  - Goal MRD Neg ***esp. if High Risk patient or Choosing delayed transplant***
- High Risk Disease
  - Trials
  - MRD Negativity Goal
- Coming soon:
  - Response adapted induction
  - Immunotherapy in early therapy

RELAPSED DISEASE

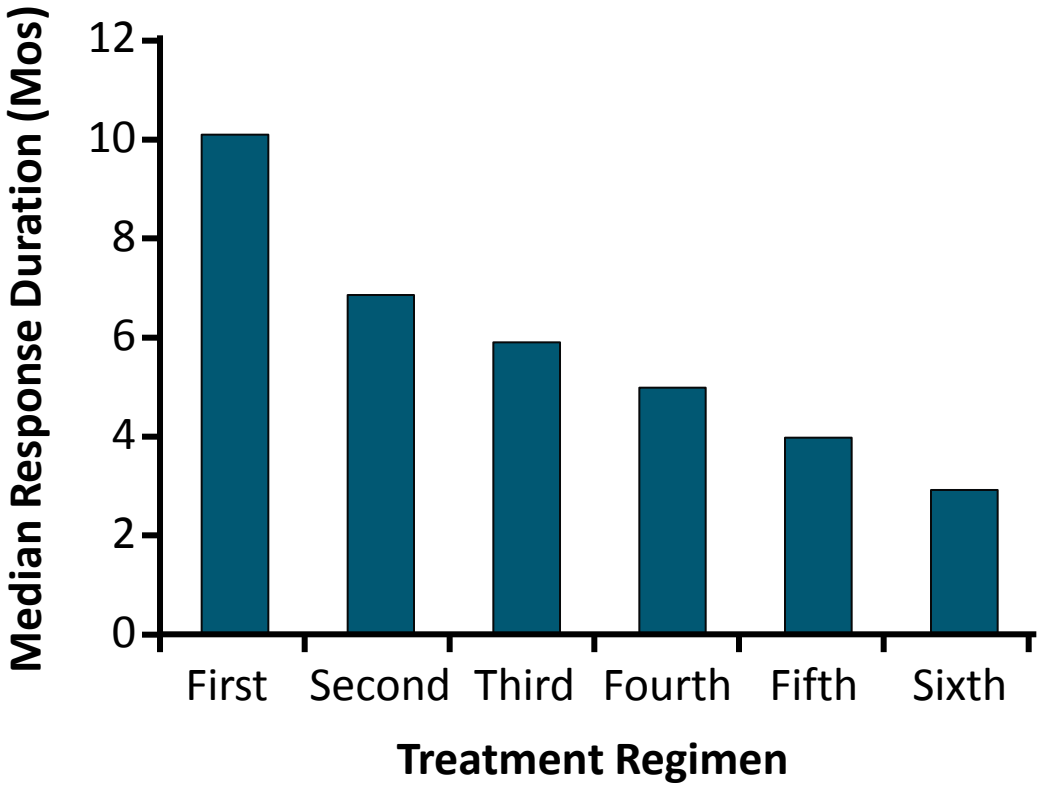
The Landscape of Relapsed MM today



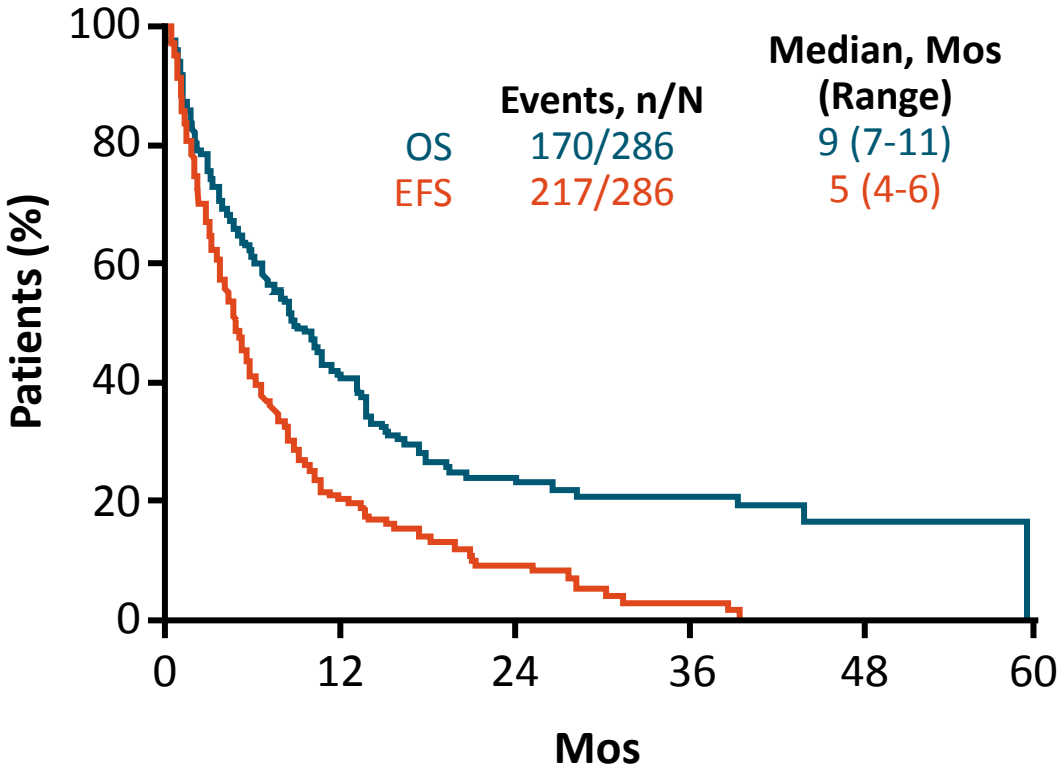
VRD (or VRd)=bortezomib + lenalidomide + dexamethasone; VCD=bortezomib + cyclophosphamide + dexamethasone; RD (or Rd)=lenalidomide + dexamethasone; SCT=stem cell transplantation; Len=lenalidomide; Btz=bortezomib

Confronting Disease Relapse in Myeloma

Response Duration With Increasing Treatment[1]



Survival Outcomes[2]



1. Kumar. Mayo Clin Proc. 2004;79:867. 2. Kumar. Leukemia. 2012;26:149.

Definition of Relapsed and Refractory Myeloma

- Relapsed/refractory myeloma[1,2]
  - Meets IMWG criteria for PD[3]
  - RR MM: progression on therapy in patients who obtain ≥ minor response or progress within 60 days of most recent therapy
  - Primary refractory MM: progression on therapy without having achieved at least minor response
  - Relapsed MM: meets IMWG criteria for PD but does not fit definition of RR or primary refractory MM

IMWG Criteria for PD[3]

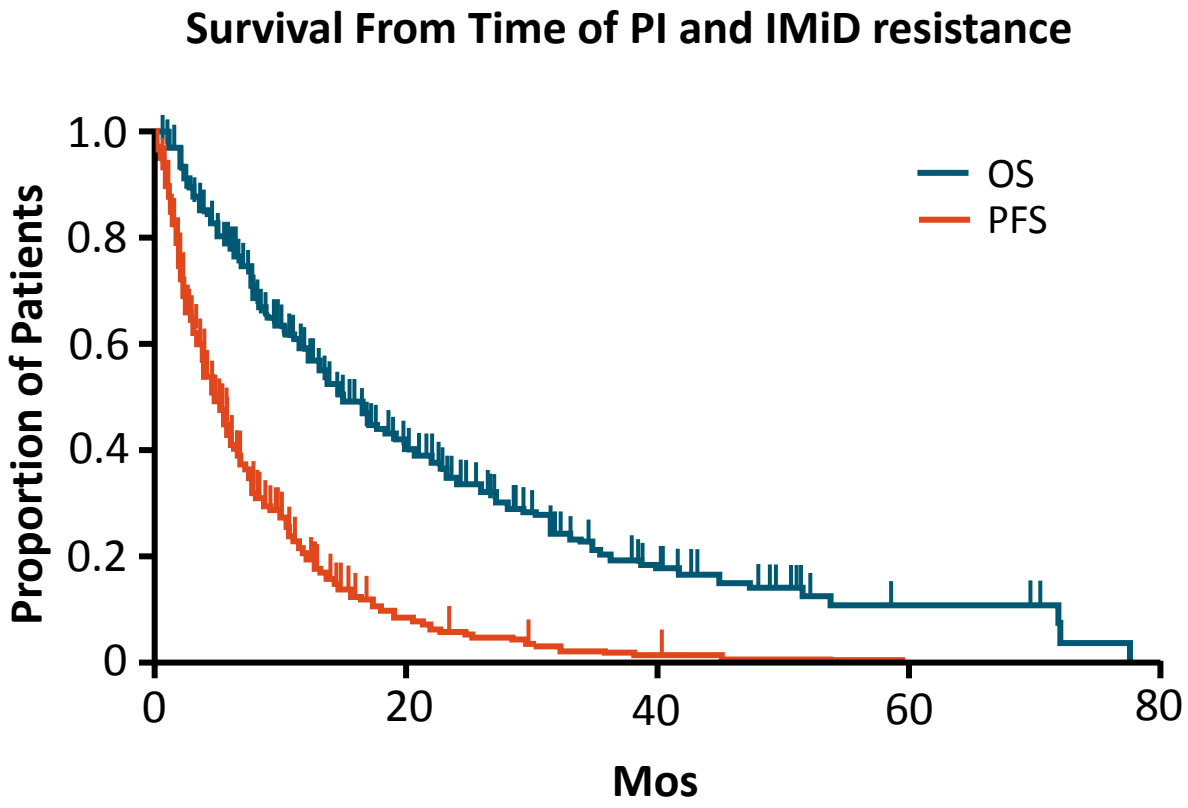
≥ 25% increase from nadir in:

- Serum or urine M-protein (absolute increase ≥ 0.5 g/dL* and ≥ 200 mg/24 hrs, respectively), *or*
- Difference between involved and uninvolved FLC levels† (absolute increase > 100 mg/L), *or*
- Bone marrow plasma cells‡ (absolute increase ≥ 10%), *or*
- New lesions (≥ 50% increase in SPD of > 1 lesion or longest diameter of previous lesion > 1 cm in short axis), *or*
- Circulating plasma cells (≥ 50% increase [minimum 200 cells/μL] if only measure of disease)

*If lowest M component ≥ 5 g/dL, increase must be ≥ 1 g/dL.
†In patients without measurable serum/urine M-protein.
‡In patients without measurable serum/urine M-protein or involved FLC.

1. Nooka. Blood. 2015;125:3085. 2. Rajkumar. Blood. 2011;117:4691. 3. Kumar. Lancet Oncol. 2016;17:e328.

IMWG Study on Refractory Myeloma: Scope of the Problem

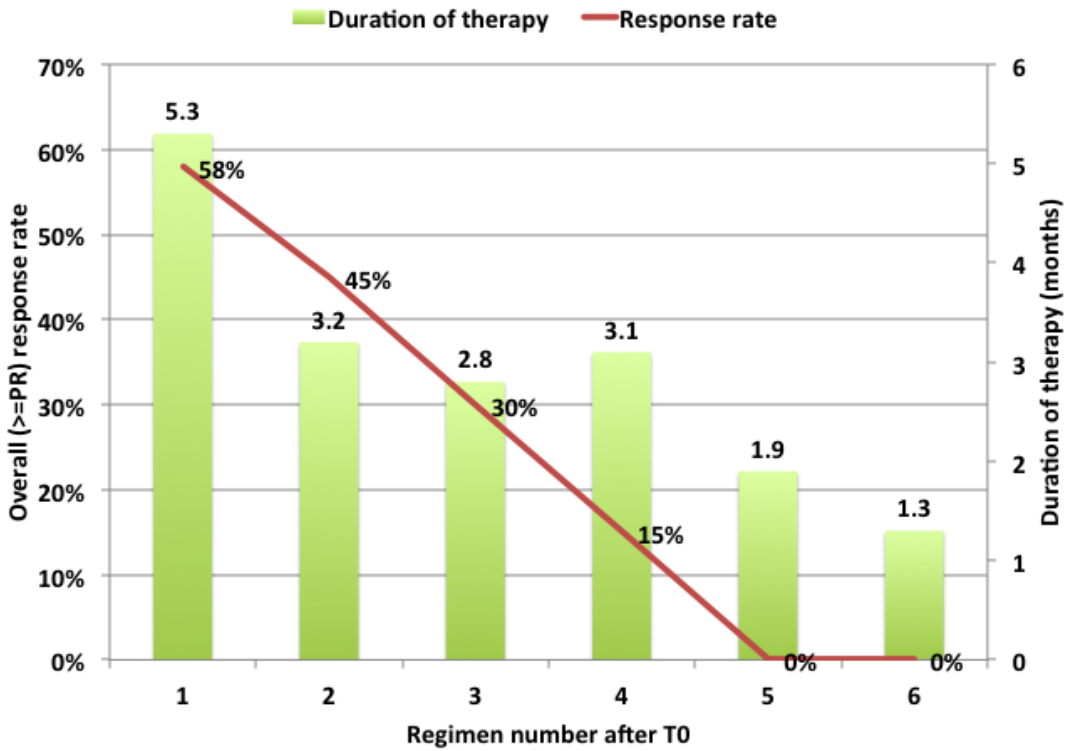


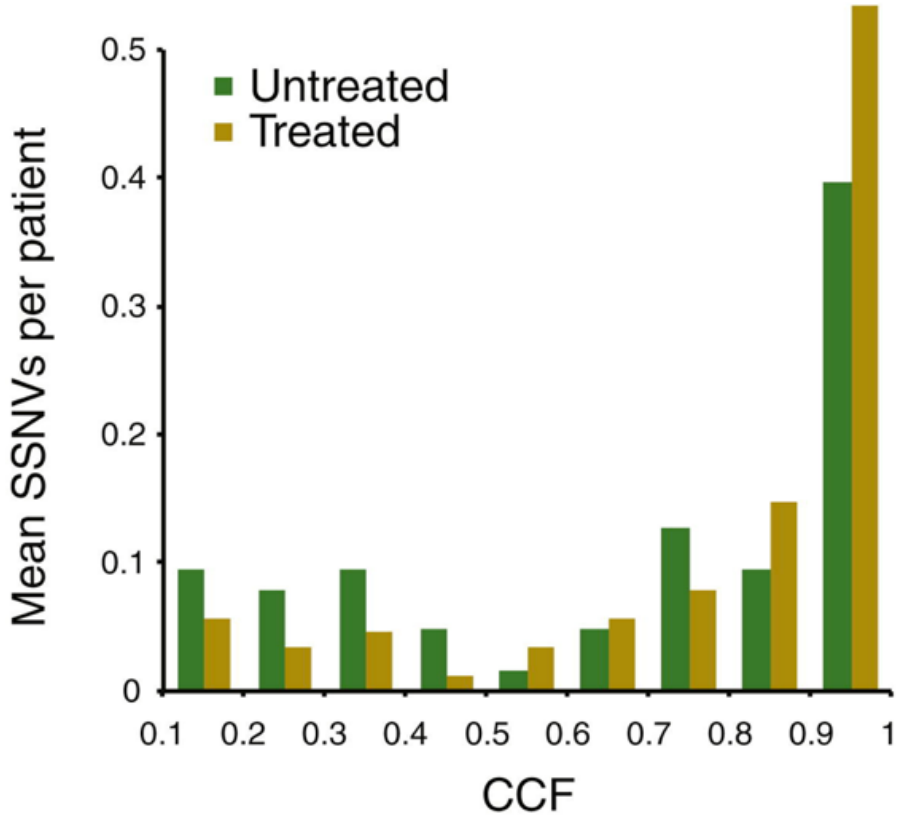
Kumar. Leukemia. 2017;31:2443.

Questions to Ask before treatment

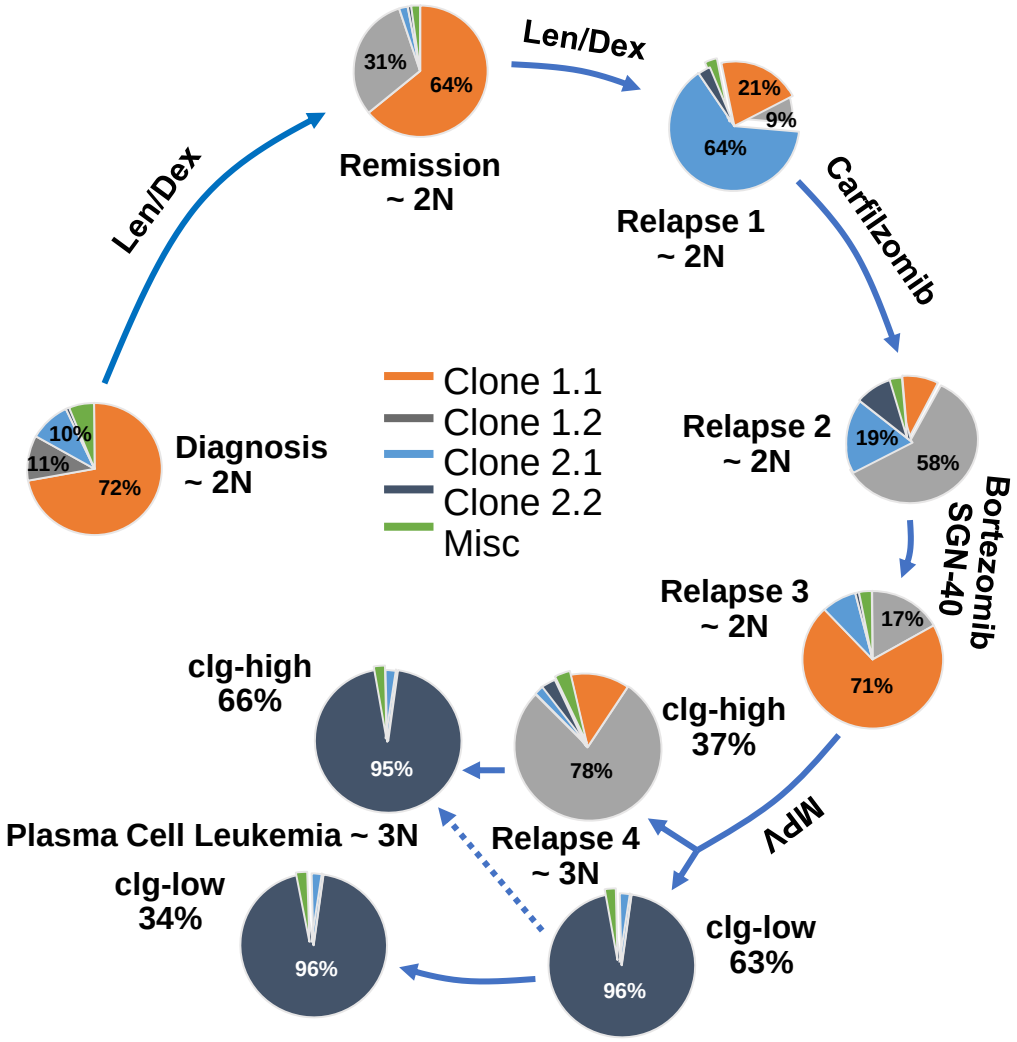
- Do I really need to treat this patient?
- Does the patient have new high-risk features? Marrow?
- What drugs have been used so far?
- Response to previous treatments (eg, efficacy, duration of response, toxicity)?
- How well is the patient (PS, marrow reserve)?
- What are the patient's goals/preferences?

Development of Resistance





Kumar SK, et al. Unpublished data; Lohr JG, et al. *Cancer Cell*. 2014;25(1):91–101.



- Multiple clones may be present at the time of diagnosis
- The predominant clone may change over time, especially after sequential treatment rounds
- Relapse can occur when:
  - Existing clone no longer has to compete for space with the formerly dominant clone
  - Acquires additional mutation(s) providing a growth and/or survival advantage
- **Combination chemotherapy needed for optimal disease control**
- **Different clones may emerge at different bone/EMD sites**

Keats JJ, et al. *Blood*. 2012;120:1067-1076.

Why Care About Sequencing of drugs?

1. Need to treat multiple relapses
2. Better understanding of disease biology
3. Increasing drug/combination choices: Evidence-based using emerging phase 3 data
4. Adapting treatment to individual patients: disease heterogeneity
5. Need to optimize efficacy, while minimizing toxicity

General Principles

- Duration of initial response defines biology
- Triplet (two active classes + dex) preferred over doublet
  - At least one drug from a non-refractory class
- Consider PS, age and comorbidities when selecting drug/doses
- Take into account prior toxicities/residual toxicities
- Treat to maximum response and maintain on one drug until progression or tolerability

Risk Stratification of Relapsed disease

- Duration of initial response/ primary refractory disease
- Acquisition of new abnormalities (1qamp, del17p)
- ISS/RISS
- Performance status
- Presence of EMD
- Circulating plasma cells

Factors in Selecting Relapsed Therapy

Patient	Disease	Treatment

• Age
• Performance status
• Renal insufficiency
• Poor marrow reserve
• Neuropathy
• Comorbidities
  • Cardiac disease
  • Diabetes
	• Risk Status
	• Cytogenetics
	• del [17p], t(4;14), t(14;16)
	• Rapidity of relapse
	  • Rate of rise
	  • Organ damage
	  • Extramedullary disease
	  • Plasma cell leukemia
		• Previous therapy
		  • Depth
		  • Duration
		• Route of administration
		• Single or combination
		• Cost
		• Toxicity
		  • Myelosuppression
		  • Neuropathy
		  • Thrombosis
		• Risk of SPM

SPM: secondary primary malignancy

Dimopoulos MA, et al. *Nat Rev Clin Oncol.* 2015;12(1):42-54.; Baz R, et al. *Support Care Cancer.* 2015;23(9):2789-2797.

Can I Use Previous Regimen Again as Salvage?

- Depth of response
  - How rapidly and successfully did it work?[1]
    - CR, VGPR, PR, MR, SD

- Duration of response[2]
  - How long did it last?

- Are there better options for my patient that give better depth and duration of response?

- If depth and duration (minimum 18 months) reasonable, consider re-treating with same regimen—knowing it will likely be less effective.

CR=complete response, PR=partial response, MR=minimal response, SD=stable disease

1. Niesvizky R, et al. *Br J Haematol*. 2008;143(1):46-53. 2. Agarwal A, et al. *Clin Lymphoma Myeloma Leuk* .2016; 7(2):69-77.

Drug Options for MM in 1st Relapse

Immunomodulatory drugs	Proteasome inhibitors	Traditional chemotherapy	Monoclonal antibodies
• Thalidomide • Lenalidomide	• Bortezomib • Carfilzomib • Ixazomib	• Cyclophosphamide • Adriamycin/doxil	• Daratumumab • Elotuzumab

Most Recent Approved Agents and Regimens for Relapsed/Refractory Myeloma

Treatment	Previous Lines of Therapy
Carfilzomib (IV proteasome inhibitor) monotherapy	≥ 1
Carfilzomib (IV proteasome inhibitor) + dexamethasone ± lenalidomide	1-3
Daratumumab (IV CD38-targeted antibody) monotherapy	≥ 3
Daratumumab (IV CD38-targeted antibody) + dexamethasone + lenalidomide or bortezomib	≥ 1
Daratumumab (IV CD38-targeted antibody) + pomalidomide + dexamethasone	≥ 2
Elotuzumab (IV SLAMF7-targeted antibody) + lenalidomide + dexamethasone	1-3
Elotuzumab (IV SLAMF7-targeted antibody) + pomalidomide + dexamethasone	≥ 2
Ixazomib (PO proteasome inhibitor) + lenalidomide + dexamethasone	≥ 1
Panobinostat (PO HDAC inhibitor) + bortezomib + dexamethasone	≥ 2

Carfilzomib [PI]. Daratumumab [PI]. Elotuzumab [PI]. Ixazomib [PI]. Panobinostat [PI].

Phase III Lenalidomide-Based Therapy for R/R Myeloma

Trial	ORR, %	≥ CR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos	Median F/u (OS), Mos
ASPIRE: KRd vs Rd[1]	87 vs 67	32 vs 9	70 vs 40	26.3 vs 16.6 HR: 0.69	48.3 vs 40.4 HR: 0.79	67.0
TOURMALINE-MM1: IxaRd vs Rd[2]	78 vs 72	14 vs 7	48 vs 39	20.6 vs 14.7 HR: 0.74	NR	23.0
POLLUX: DRd vs Rd[3-5]	93 vs 76	57 vs 23	80 vs 49	44.5 vs 17.5 HR: 0.44	NR vs NR HR: 0.63	36.0
ELOQUENT-2: ERd vs Rd[6,7]	79 vs 66	5 vs 9	36 vs 30	19.4 vs 14.9 HR: 0.73	48.3 vs 39.6 HR: 0.78	60.5

1. Stewart. ASH 2017. Abstr 743. 2. Moreau. NEJM. 2016;374:1621. 3. Dimopoulos. NEJM. 2016;375:1319.
4. Dimopoulos. ASH 2017. Abstr 739. 5. Bahlis. ASH 2018. Abstr 1996. 6. Dimopoulos. EHA 2017. Abstr S456.
7. Lonial. ASCO 2018. Abstr 8040.

Phase III PI-Based Therapy for R/R Myeloma

Trial	ORR, %	≥ CR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos	Median F/u (OS), Mos
ENDEAVOR: Kd vs Vd[1]	77 vs 63	13 vs 6	54 vs 29	18.7 vs 9.4 HR: 0.53	NR vs 24.3 HR: 0.79	12.5
CASTOR: DVd vs Vd[2,3]	84 vs 63	29 vs 10	62 vs 29	16.7 vs 7.1 HR: 0.31	NR HR 0.63	19.4
PANORAMA-1: PanoVd vs Vd[4,5]	61 vs 55	11 vs 6	28 vs 16	12.0 vs 8.1 HR: 0.63	40 vs 36 HR: 0.94	--
Elotuzumab (*phase II*) EVd vs Vd[6]	66 vs 63	4 vs 4	36 vs 27	9.7 vs 6.9 HR: 0.72	NR HR: 0.61	16.0
MMY1001 (*phase I*)**:** DKd vs Kd[7]	84	27	71	NR (1-yr PFS: 71%)	NR (1-yr OS: 82%)	12.0

1. Dimopoulos. Lancet Oncol. 2016;17:27. 2. Palumbo. NEJM. 2016;375:754. 3. Lentzsch. ASCO 2017. Abstr 8036. 4. San-Miguel. Lancet Oncol. 2014;15:1195. 5. San-Miguel. ASH 2015. Abstr 3026. 6. Jakubowiak. Blood. 2016;127:2833. 7. Chari. ASCO 2018. Abstr 8002.

Pomalidomide-Based Salvage Therapy for R/R Myeloma

Trial	Patient Population	Primary Endpoint	ORR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos
Pom/Dex (N = 302)[1] Phase III trial vs HD Dex	R/R; ≥ 2 lines of tx including len and btz	PFS	31 vs 10	6 vs < 1	4.0 vs 1.9	12.7 vs 8.1
Bortezomib + Pom/Dex (N = 559)[2] Phase III trial vs Vd	1-3 lines of tx with len exposure; prior PI ok	PFS	82 vs 50	53 vs 18	11 vs 7	NR
Carfilzomib + Pom/Dex (N = 57)[3]	R/R to most recent tx; 1-3 lines of tx; len refractory	MTD, PR rate	62	23	10.3	NR (1 yr: 67%)
Daratumumab + Pom/Dex (N = 103)[4]	R/R; ≥ 2 lines of tx, including len and btz	MTD	60	42	8.8	17.5
Ixazomib + Pom/Dex (N = 32)[5]	1-5 lines of tx, including len and PI; len refractory	MTD activity	48; high risk: 58	20	--	--
Elotuzumab + Pom/Dex (N = 60)[6] Phase II trial vs Pom/Dex	≥ 2 lines of tx including IMiD and PI; refractory to last tx	PFS	53 vs 26	20	10.3 vs 4.8	--

1. San Miguel. Lancet Oncol. 2013;14:1055. 2. Richardson. ASCO 2018. Abstr 8001. 3. Bringhen. Leukemia. 2018;32:1803.
4. Chari. Blood. 2017;130:974. 5. Krishnan. Leukemia. 2017;[Epub]. 6. Dimopoulos. EHA 2018. Abstr LBA2606.

How to Make the Best Choice for Therapy

PD While Not on Lenalidomide Maintenance	*PD On Lenalidomide Maintenance (Len-Refractory)*
Triplets (with Rd as backbone)	**Triplets (with other backbones)**
Daratumumab + Rd	**Daratumumab + Vd**
Carfilzomib + Rd	**Daratumumab + PomD**
Ixazomib + Rd	**Daratumumab + KD**
Elotuzumab + Rd	**Carfilzomib + PomD**
	Ixazomib + PomD
	Elotuzumab + PomD

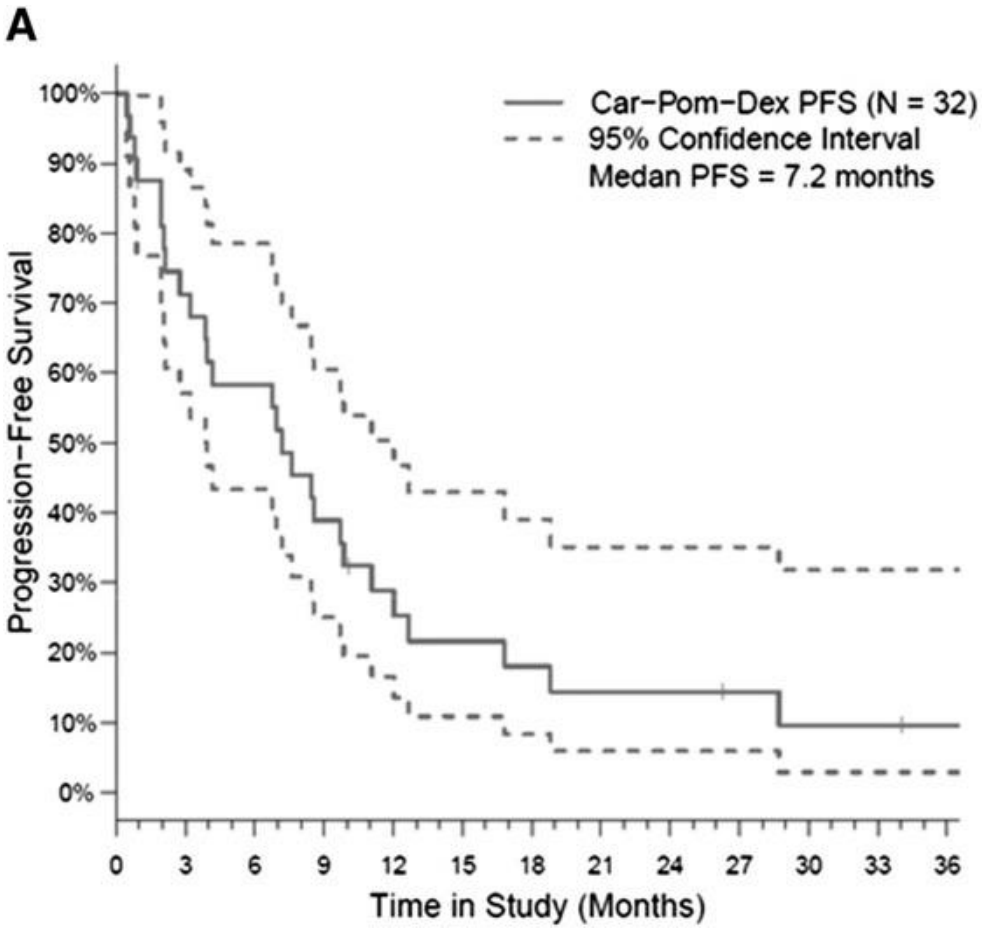
Other options: Kd, PomD, clinical trial (!)

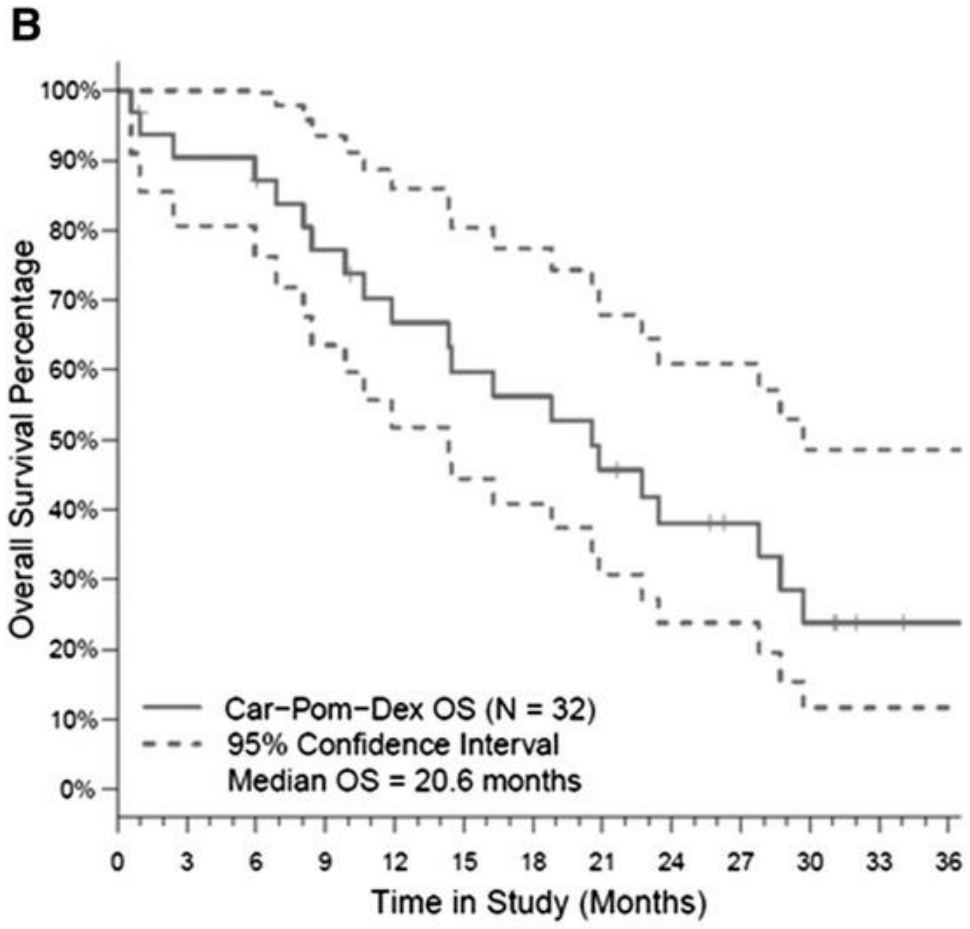
Continue with triplet combinations with ≥ 1 new agent at each relapse

How do we choose – A case

- 73-yr-old man with relapsed MM who presents for follow-up with new onset bone pain and anemia
- History:
  - ISS stage II myeloma (Dx 2010): lenalidomide/bortezomib/ dexamethasone x 4 cycles, then single ASCT (VGPR)
  - Lenalidomide maintenance (CR x 4 yrs followed by symptomatic relapse with new del[17p])
  - Carfilzomib/dexamethasone (VGPR) followed by second ASCT and lenalidomide maintenance (VGPR x 18 mos who has now developed symptomatic relapse)

Carfilzomib-Pomalidomide-Dex (KPd)

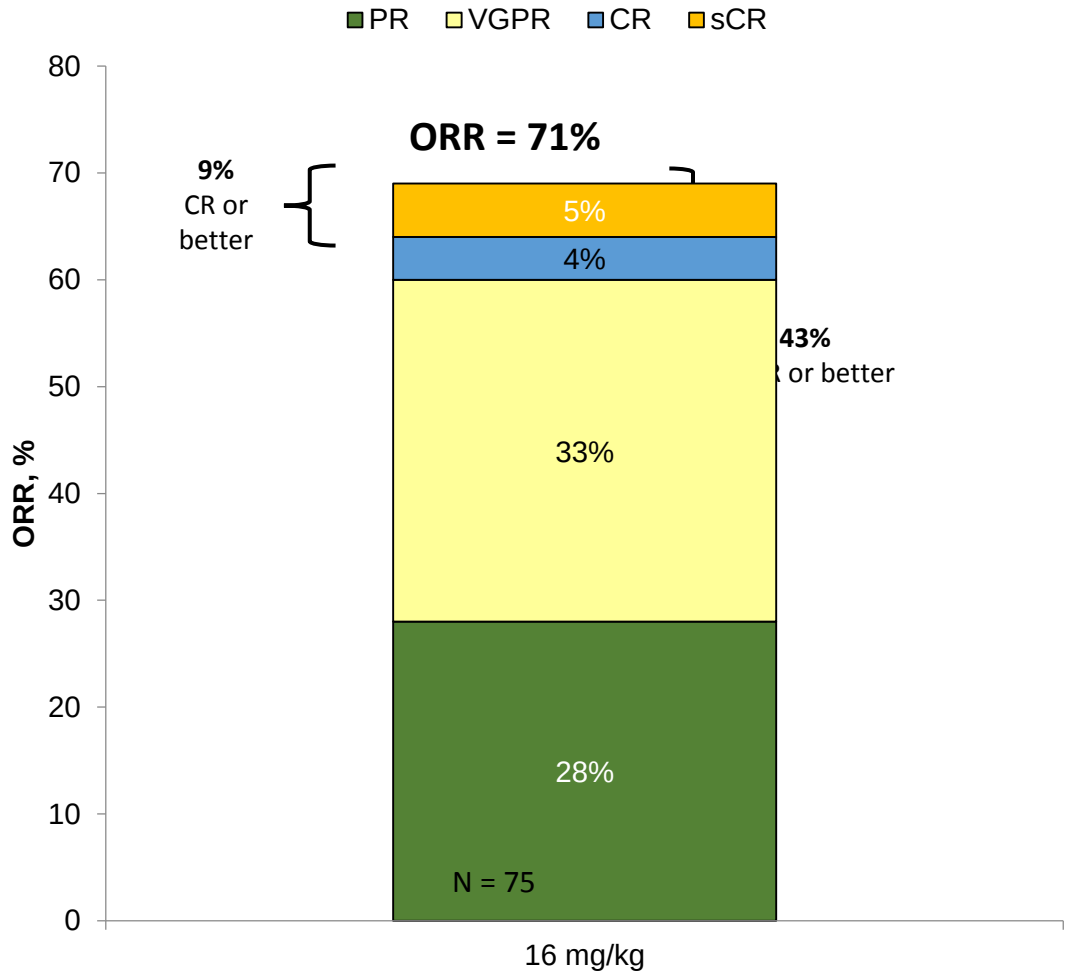




ORR	**50%**
>=VGPR	**16%**

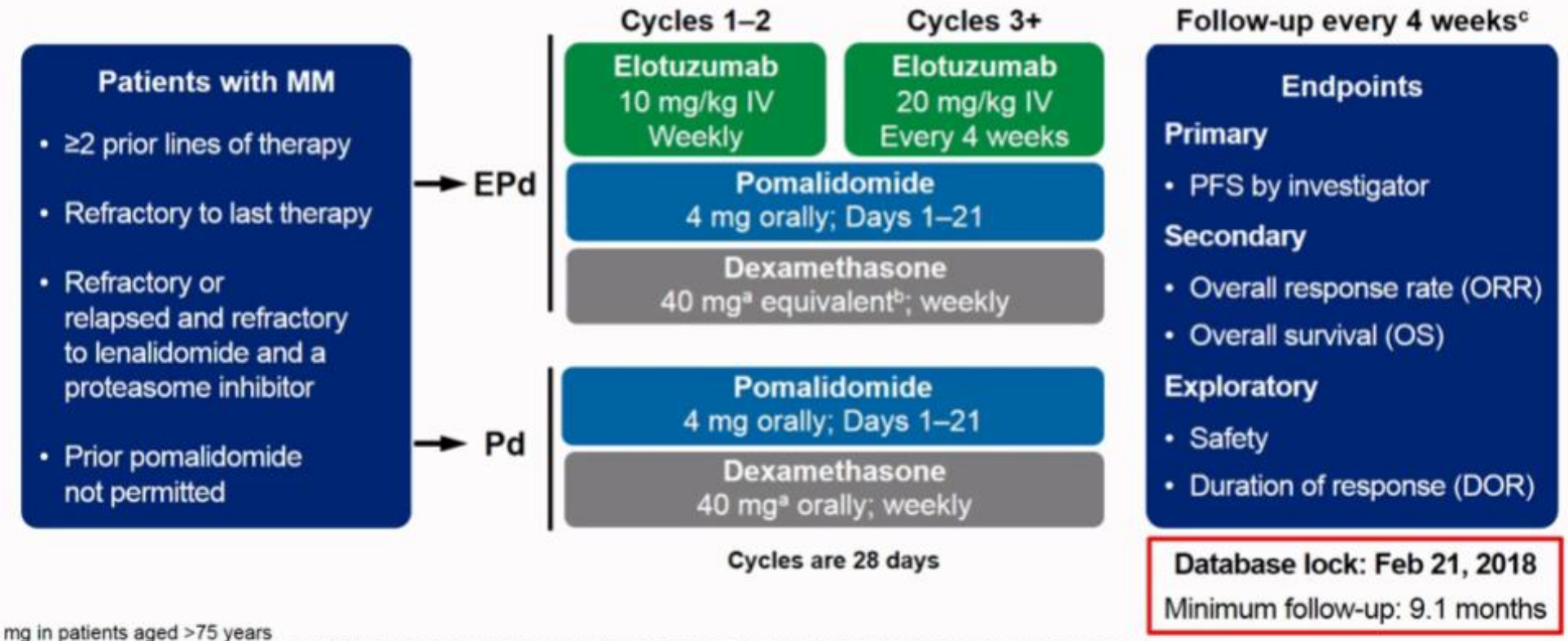
Daratumumab-Pomalidomide-Dex (DPd)

	DARA + POM-D (N = 75)	
	n (%)	**95% CI**
Overall response rate (sCR+CR+VGPR+PR)	**53 (71)**	**59.0-80.6**
Best response		
sCR	4 (5)	1.5-13.1
CR	3 (4)	0.8-11.2
VGPR	25 (33)	22.9-45.2
PR	21 (28)	18.2-39.6
MR	2 (3)	0.3-9.3
SD	17 (23)	13.8-33.8
PD	3 (4)	0.8-11.2
VGPR or better (sCR+CR+VGPR)	32 (43)	31.3-54.6
CR or better (sCR+CR)	7 (9)	3.8-18.3



ELOQUENT-3: Study design

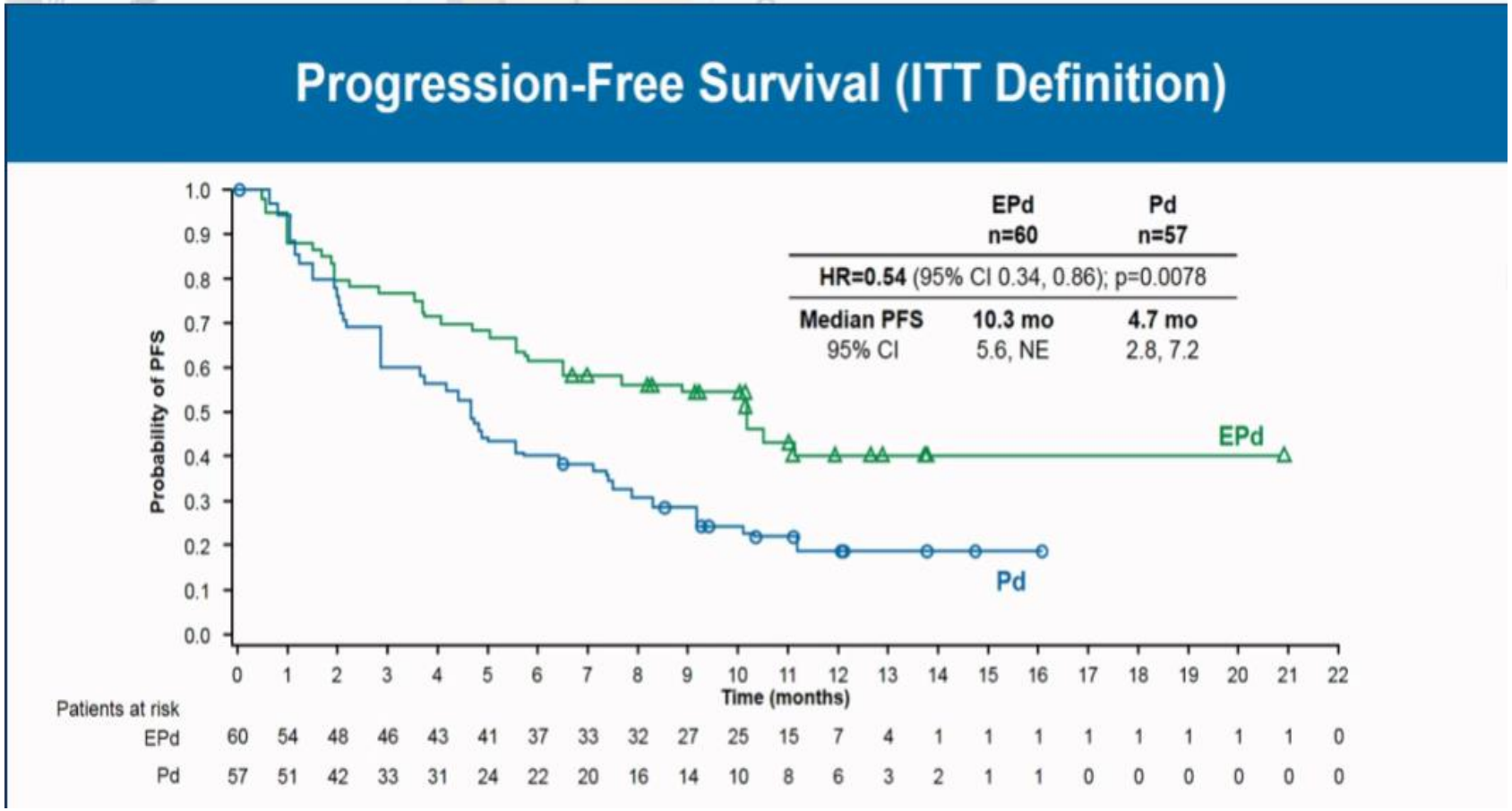
An international, open-label, randomized, phase 2 trial (NCT02654132), with a 2-sided α=0.2 and 85% power to detect a true HR of 0.57



[a]20 mg in patients aged >75 years
[b]Dexamethasone was split between oral (28 or 8 mg in patients aged ≤75 or >75 years) and IV (8 mg) doses on days with elotuzumab
[c]Follow-up continued until disease progression; follow-up for survival occurred at least every 12 weeks
HR, hazard ratio

Dimopoulos et al. Presented at EHA 2018. Abstract LB2606

ELOQUENT-3: Results



- 46% reduction in risk of progression or death for EPd vs Pd
- Safety consistent with previous reports of elo and pom

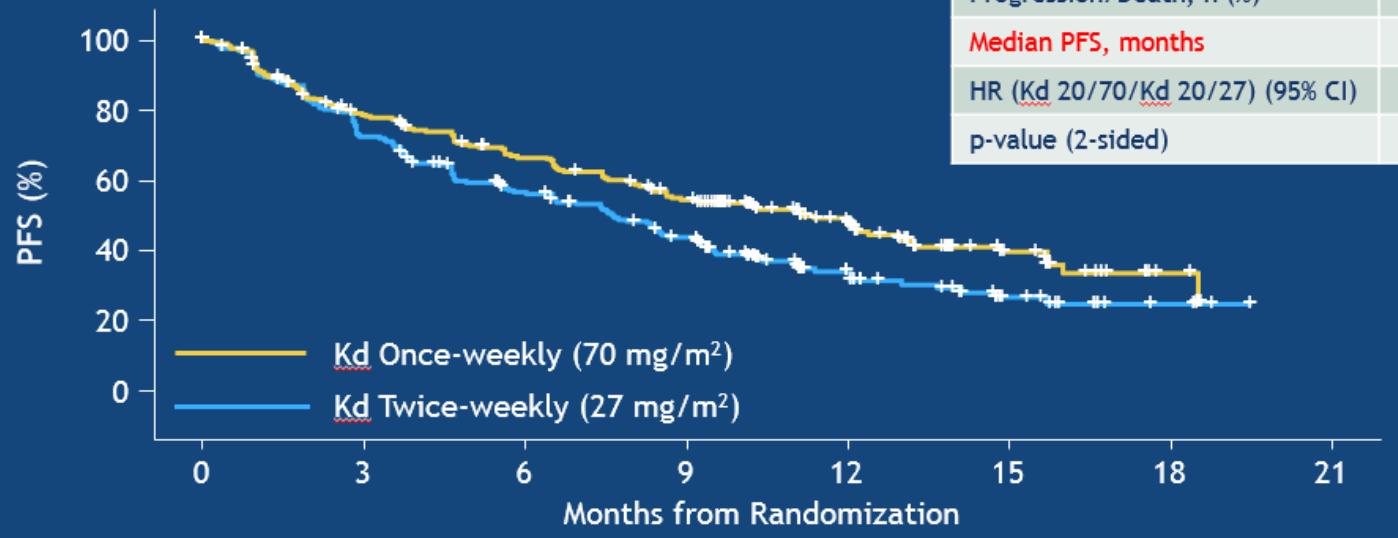
EPd, elotuzumab, pomalidomide, dexamethasone; Pd, pomalidomide, dexamethasone

Dimopoulos et al. Presented at EHA 2018. Abstract LB2606

A.R.R.O.W. Study

Primary Endpoint: PFS

	Once-weekly Kd 20/70 mg/m² (n=240)	Twice-weekly Kd 20/27 mg/m² (n=238)
Progression/Death, n (%)	126 (53%)	148 (62%)
Median PFS, months	11.2	7.6
HR (Kd 20/70/Kd 20/27) (95% CI)	0.693 (0.544, 0.883)	
p-value (2-sided)	0.0029	



Number of Patients at Risk:

Kd 20/70	240	178	145	114	69	24	5	0
Kd 20/27	238	164	119	86	41	15	4	0

Data cutoff date: June 15, 2017; Median follow-up: 12.6 (once-weekly) and 12.0 (twice-weekly) months

CI, confidence interval; HR, hazard ratio

Should I Consider a Second ASCT?

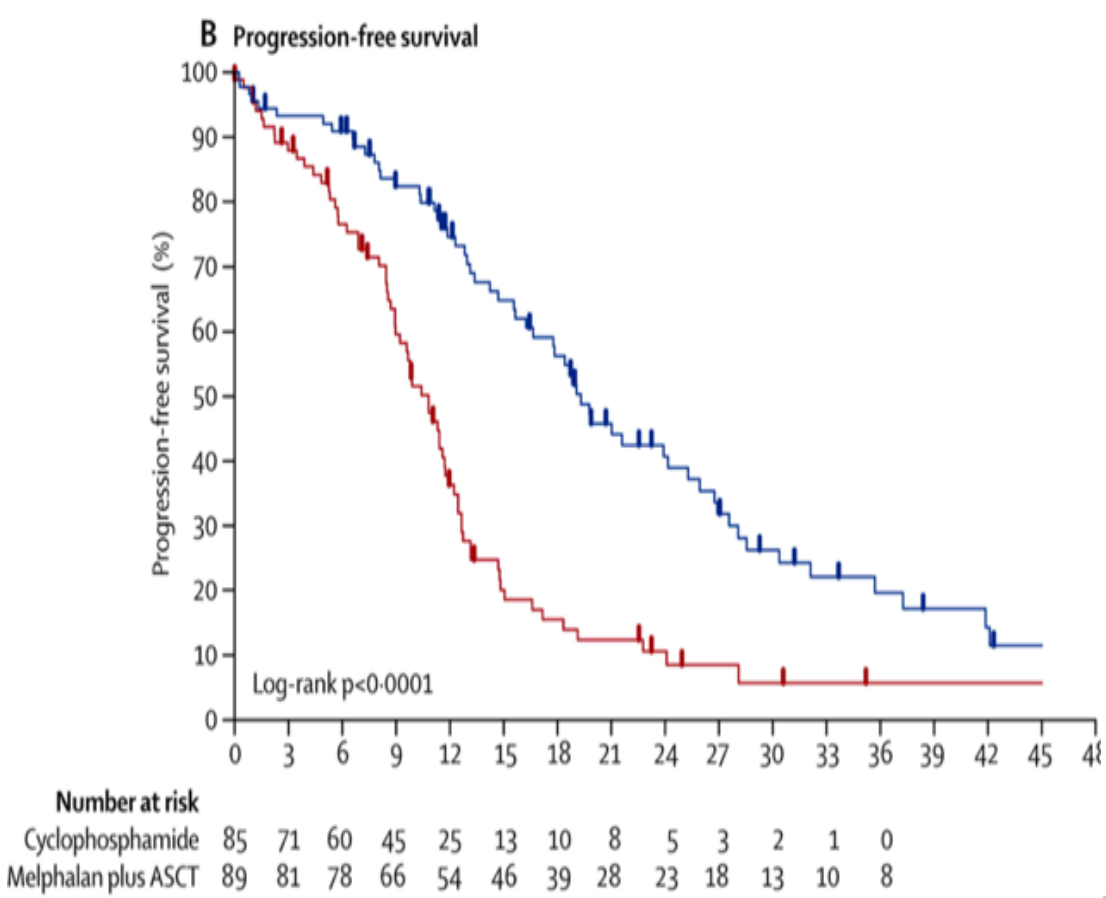
1. • Did the patient tolerate the first ASCT well?

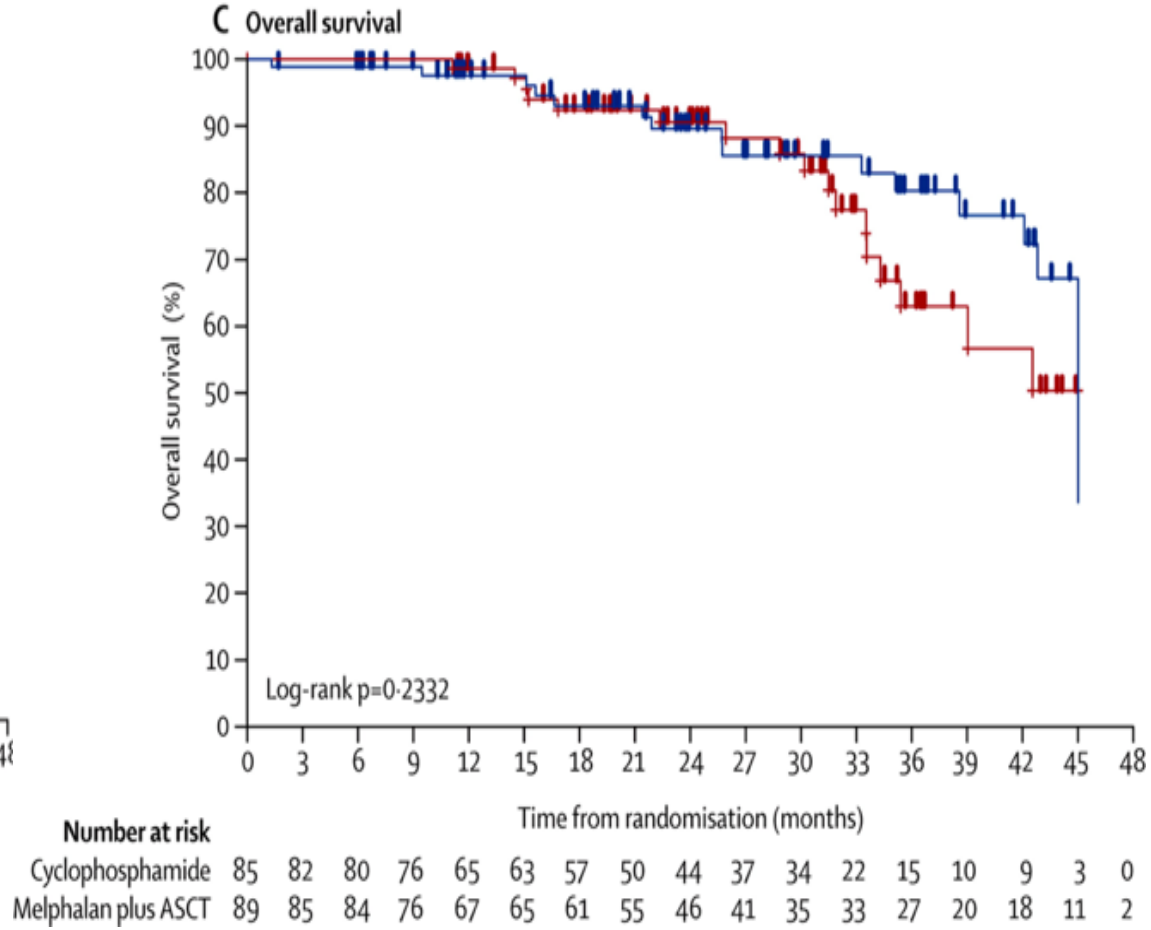
2. • Did the patient have 18+ months of PFS benefit after the first ASCT (in absence of maintenance)?

3. • Did the patient have a minimum of 24+ months PFS after the first ASCT followed by maintenance?

Note: Expect only 50% to 70% of PFS with second ASCT

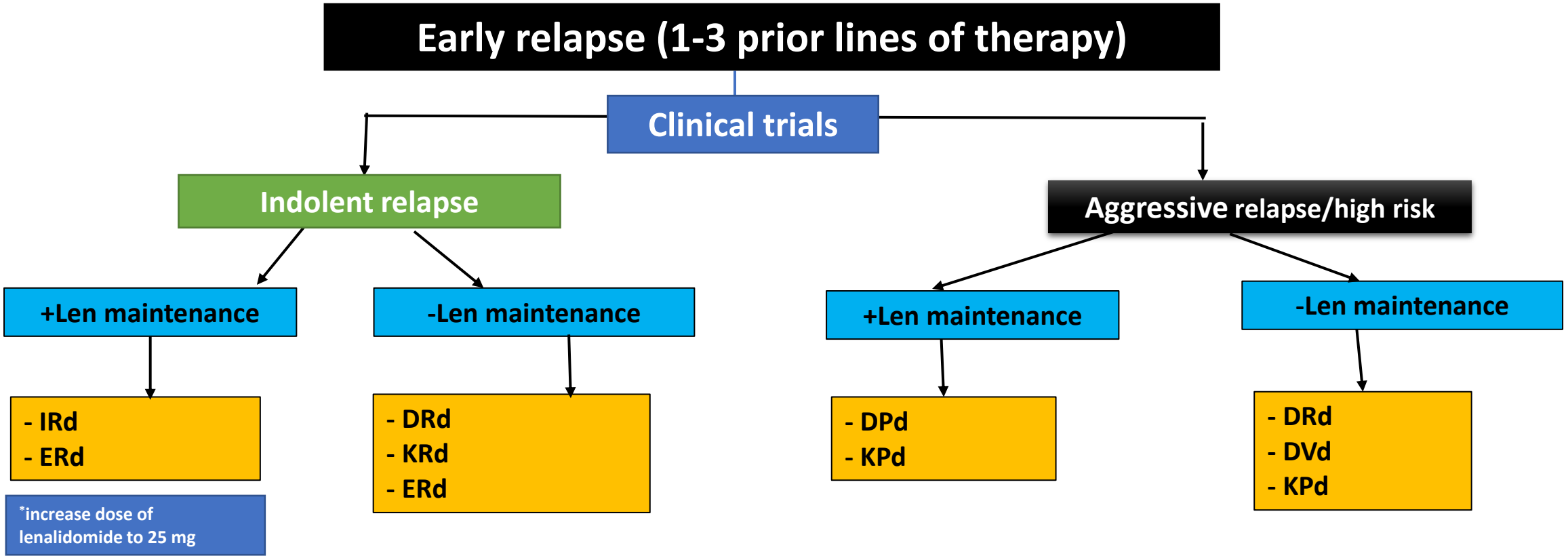
Salvage High-Dose Chemotherapy (HDT)





New Agents and Clinical Trials

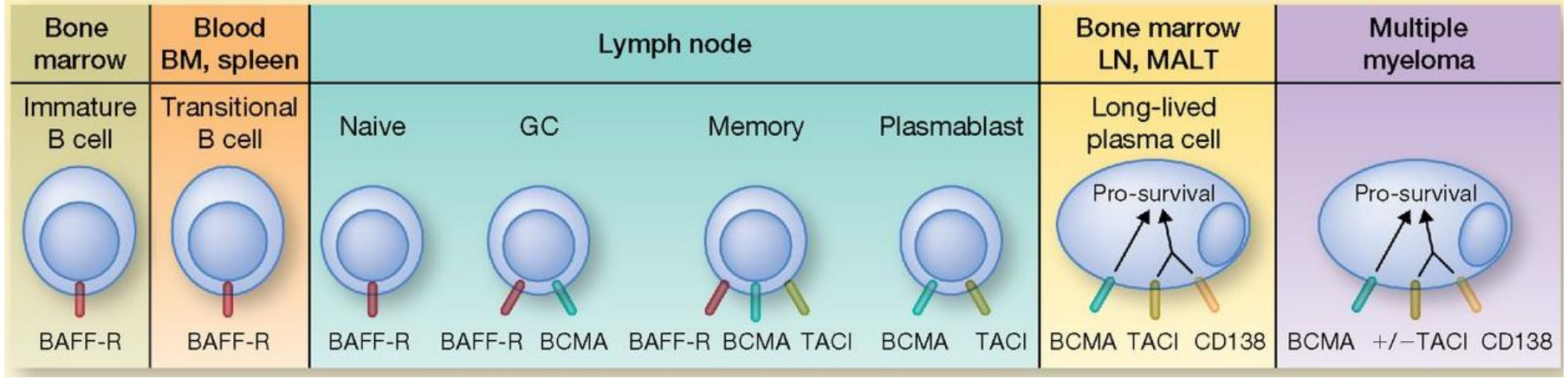
Approach to Initial Relapse (<3 lines)

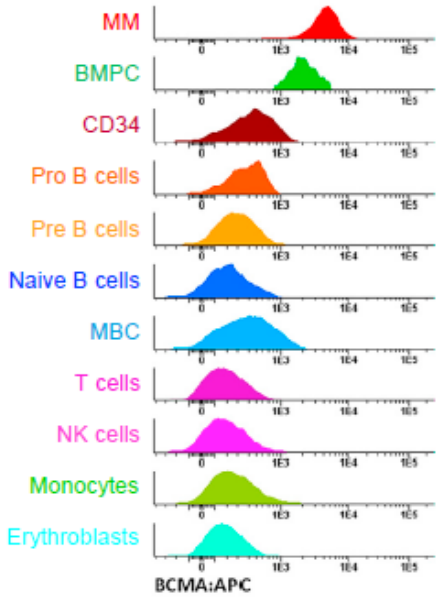


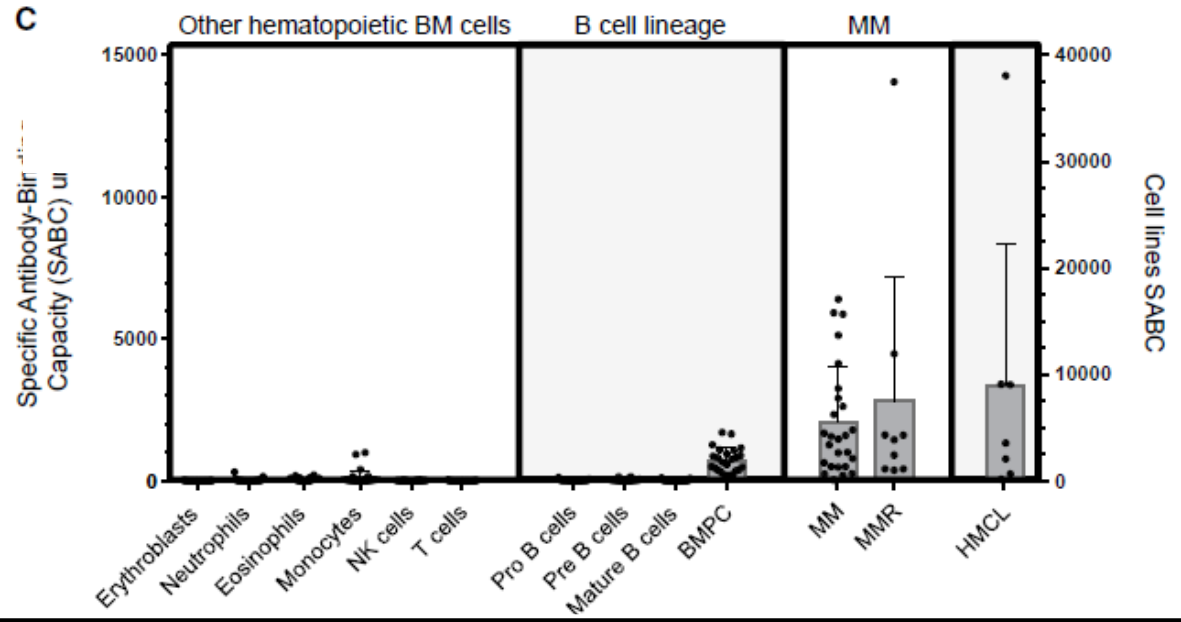
I – Ixazomib
E – Elotuzumab
D – Daratumumab
K – Carfilzomib
R - Lenalidomide

V - Bortezomib
P - Pomalidomide
Len - Lenalidomide

B-Cell Maturation Antigen (BCMA), a near perfect target







- **BCMA expressed on normal and malignant plasma cells**
  - Promotes MM cell survival

Seckinger A. Cancer Cell 31:1, 2017

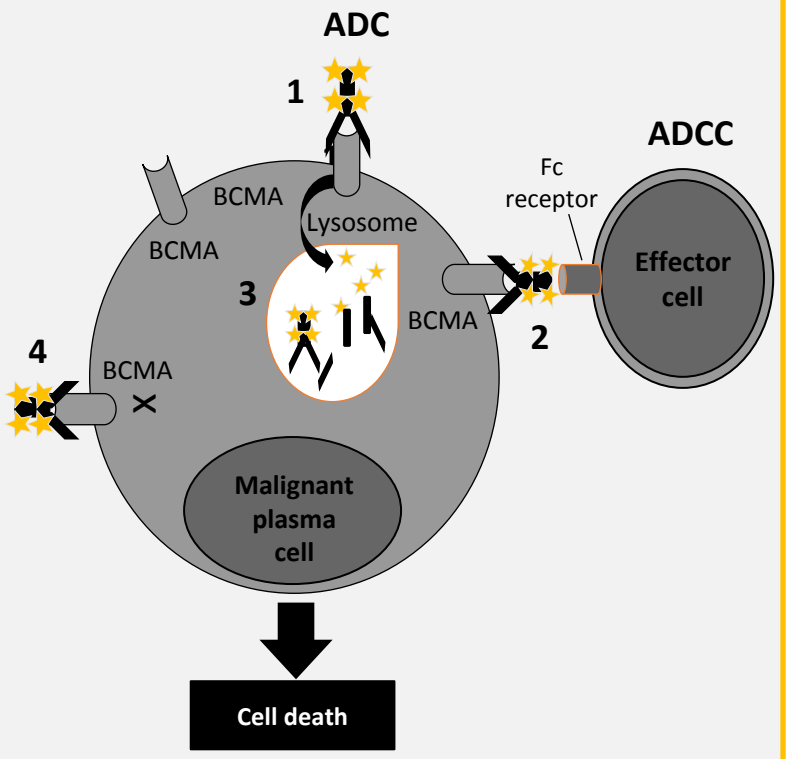
GSK 7916 – One way to target BCMA

- **GSK2857916:** humanized, afucosylated IgG1 **anti-BCMA antibody;** neutralization of soluble BCMA
  - Preclinical studies demonstrate selective and potent activity[1]

Cytotoxic agent	MMAF (non-cell permeable, highly potent auristatin
Afucosylation	Enhanced ADCC
Linker	Stable in circulation

Four mechanisms of action:

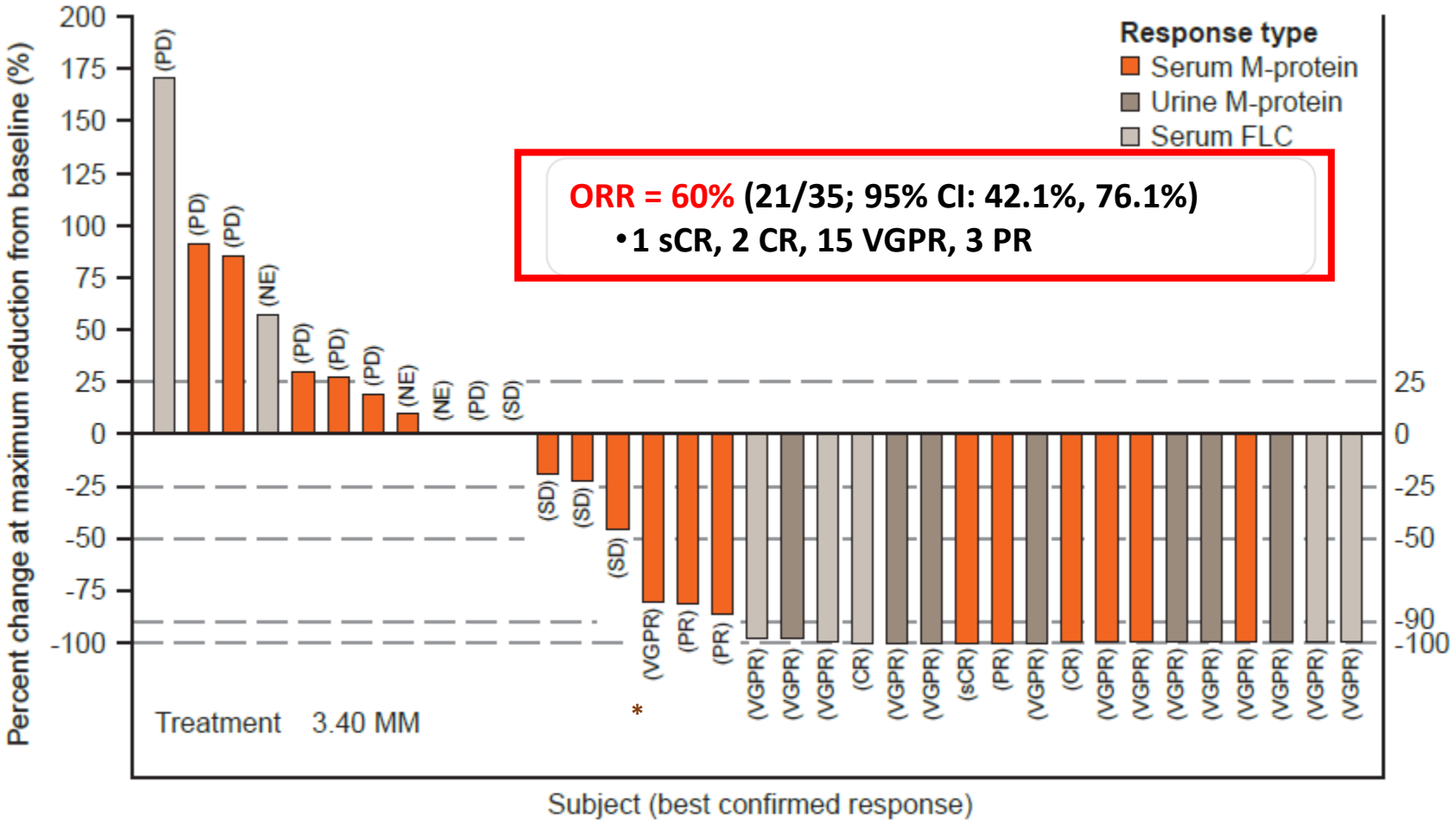
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signalling inhibition



ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F

[1]Tai YT, et al. Blood 2014;123(20):3128-38.

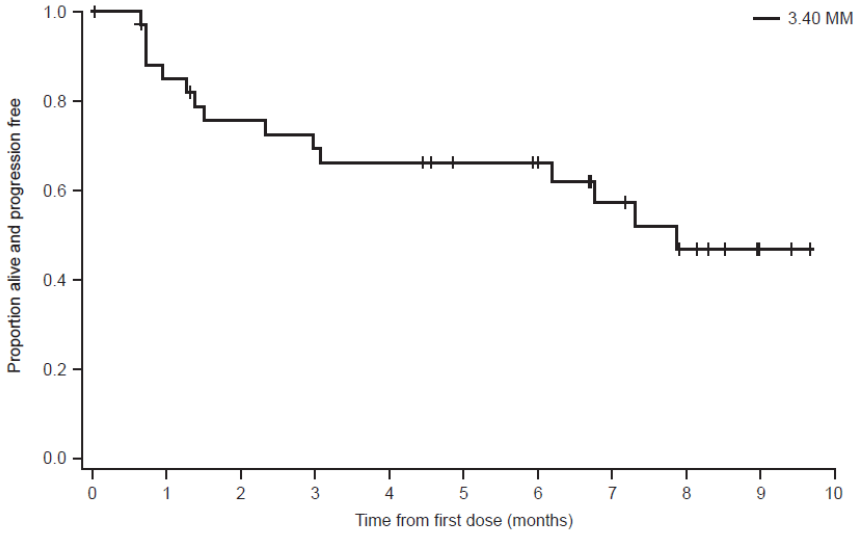
DREAMM-1 Part 2: Maximum % Reduction in M-Protein or Free Light Chain from Baseline

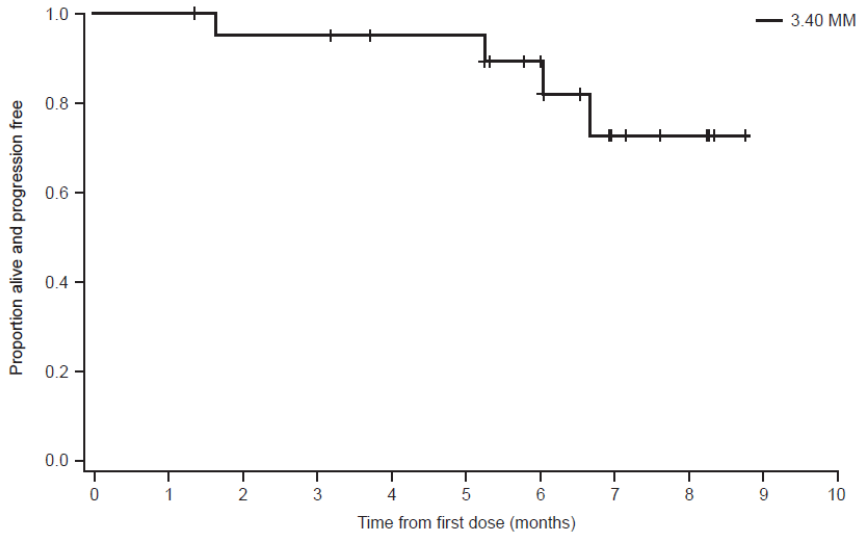


*One patient with a VGPR had a <90% reduction in serum M-protein due to missing laboratory data, which was confirmed by investigators as too small to quantify after the data cut-off

CI, confidence interval; CR, complete response; FLC, free light chain; M-protein, myeloma protein; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

DREAMM-1 Part 2: Efficacy – Progression-free Survival and duration of response





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

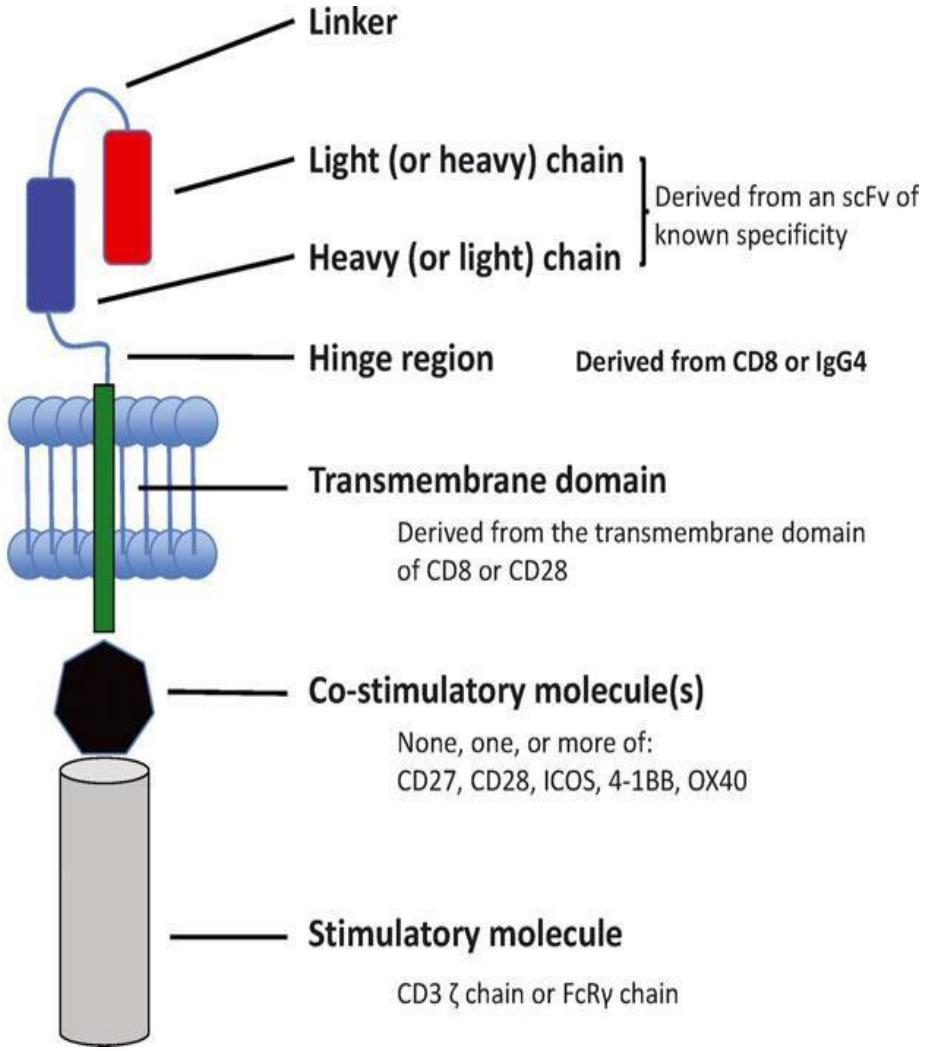
Number of subjects	**21**
Progressed or died	4 (19%)
Censored, f/u ended	0
Censored, f/u ongoing	17 (81%)

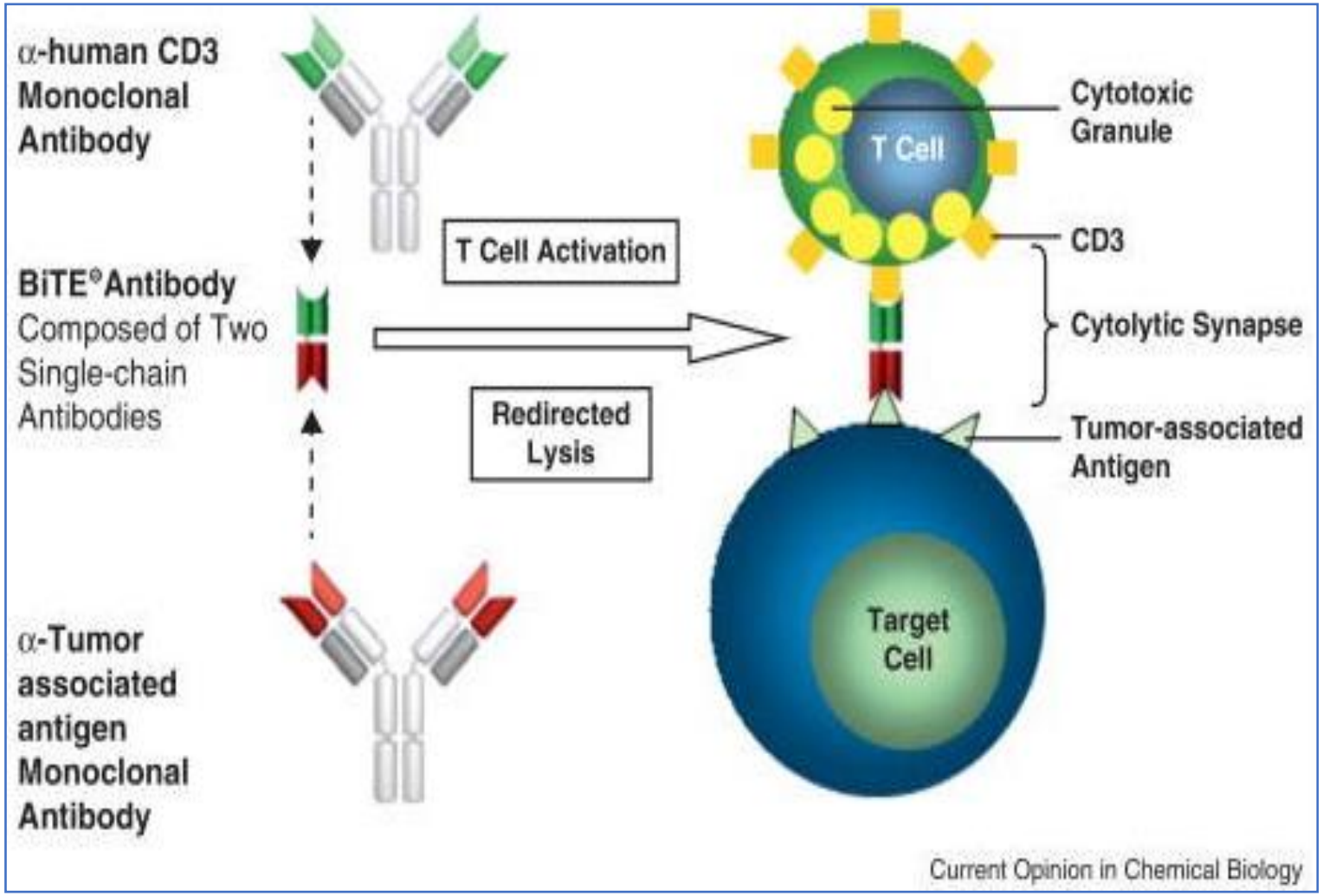
Progression-free survival (months)	
Q1 (95% CI)	2.3 (0.7, 6.8)
Median (95% CI)	**7.9 (3.1, -)**
Q3 (95% CI)	N/A

Duration of response (months)	
Q1 (95% CI)	6.7 (1.6, -)
Median (95% CI)	**N/A (6.7, -)**
Q3 (95% CI)	N/A

CI, confidence interval; f/u, follow-up; N/A, not available; Q, quartile

2 other major ways to target BCMA

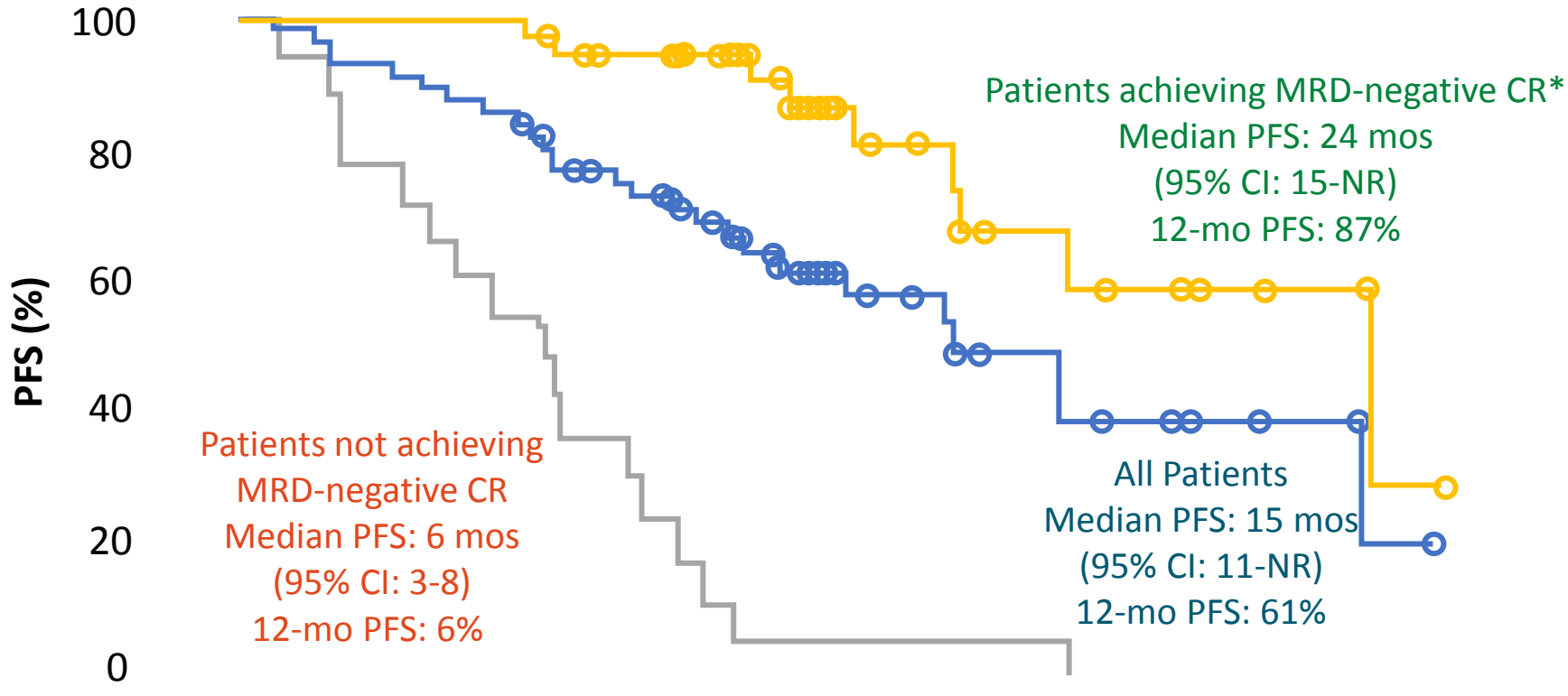




ASH 2018

	Juno JCARH125	CARsgen CT053	Bluebird bb21217	Legend/Janssen LCAR-B38M
ASH 2018 Abstract	Mailankody et al. Abstract #957	Jiang et al. Abstract #960	Shah et al. Abstract #488	Zhao et al. Abstract #955
Enrollment	8 evaluable	13 evaluable	7	57
Median Prior Lines	10 (4-15)	4 (2-10)	9 (4-17)	3 (1-9)
High-Risk Cyto	50%	NR	50%	NR
Response Rate	**ORR: 8 (100%) CR/sCR: 3**	**ORR 13 (100%) CR: 2**	**ORR: 6 (86%) CR/sCR: 1 MRD-neg: 3/3**	**ORR 50 (88%) CR: 42 MRD-neg:39**
Median F/U	1.25 months	2 months	4 months	12 months (CR: 22 mos.)
Median PFS	-	-	-	15 months (CR: 24 mos.)
Median OS	-	-	-	NR

LEGEND-2 Updated Analysis: PFS



Patients at Risk, n									
All patients	57	53	48	37	21	11	7	4	1	0
Patients achieving MRD-negative CR	39	39	38	33	20	10	7	4	1	0
Patients not achieving MRD-negative CR	18	14	10	4	1	1	0	0	0	0

*30/39 patients still in remission

Zhao. ASH 2018. Abstr 955.

A Legendary problem….

Nanjing Legend's developing LCAR-B38M dataset (NCT03090659)					
Presented at	Asco 2017	Ash 2017			Ash 2018
Data cut	Feb 2017	Aug 2017			Jun 2018
Patient n	35	11			57
Hospital (n)	Xi'an Jiaotong (35)	RM (6)	RJ (3)	CZ (2)	Xi'an Jiaotong (57)
Best ORR	100%	100%			88%
CR	15 (43%)	5 (83%)	2 (67%)	1 (50%)	42 (74%)
PR	20	1	1	1	8
No response	0	0	0	0	7
Notes	2 relapses	Further 6 pts treated			14 relapses

RM=Renji Hosp; RJ=Jiangsu Provincial Hosp; CZ=Shanghai Changzheng Hosp.

Second Affiliated Hospital of Xi'an Jiaotong University, 57 subjects treated.

Three other hospitals taking part in the trial:
Ruijin Hospital; Jiangsu Provincial and Shanghai Changzheng (17 additional pts)

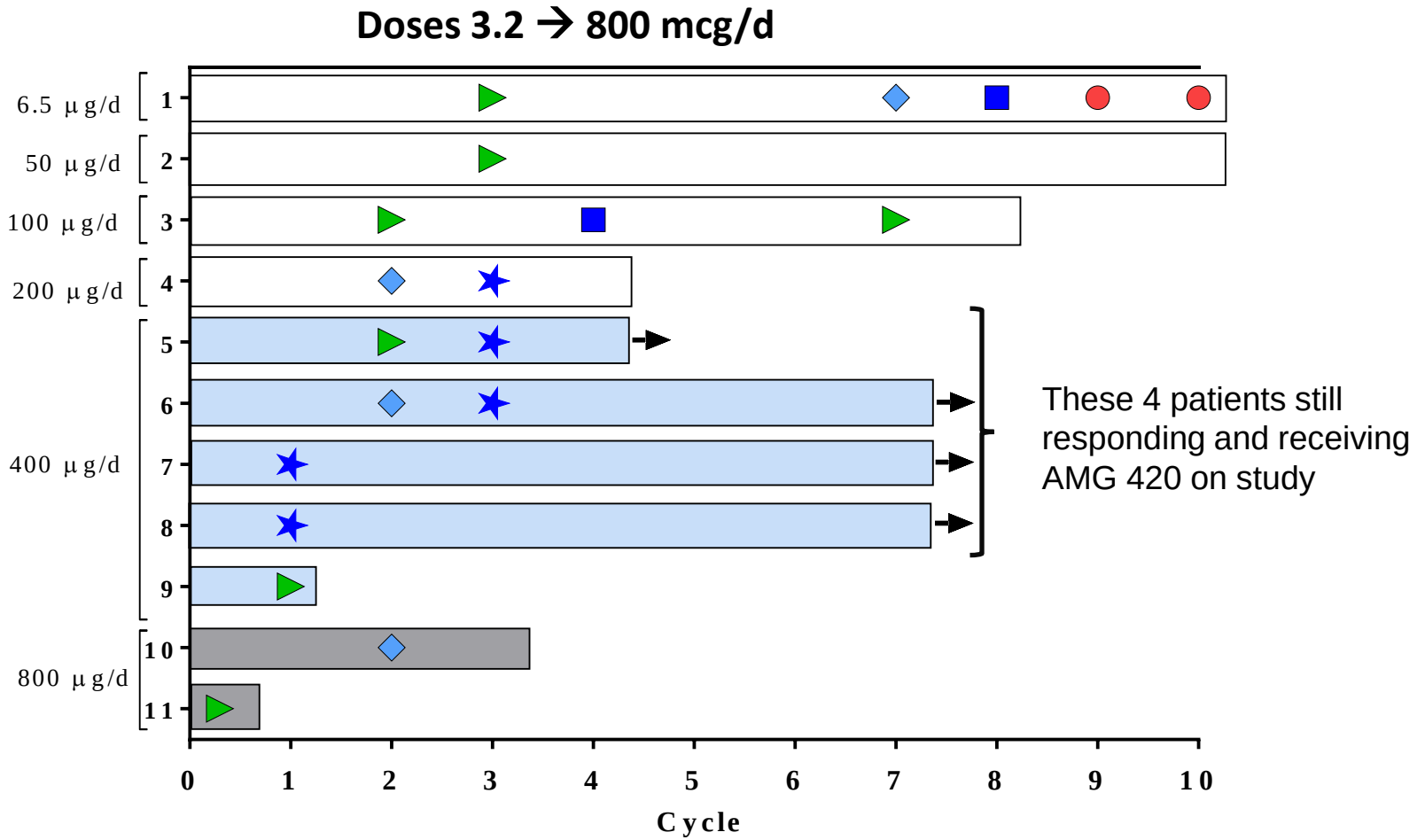
At least 1-3 TRM ? (17 deaths – 14 PD)

Other COD – suicide after PD; esophagitis; PE? SOB?

No Intent to treat data

Much less advanced pts than US BCMA targeted trials

The BiTEs are catching up…AMG 420 phase 1 study



Progressive Disease Partial Response (PR) Very Good PR Complete Response (CR) / stringent CR MRD neg/sCR

Only patients with data available at datacut are included in this graph.

CRS AEs and Serious AEs (SAEs)

		N=42	# Gr 1	# Gr 2	# Gr 3	# Gr 4	# Gr 5
CRS	All treatment-related	16 (38%)	13	2	1	-	-
SAEs in ≥2 patients	Infections	12 (29%)	-	3	7	-	2*
	Peripheral polyneuropathy	2 (5%)	-	-	2	-	-
Treatment-related SAEs	Peripheral polyneuropathy	2 (5%)	-	-	2	-	-
	Edema	1 (2%)	-	-	1	-	-

*One patient died of aspergillus / flu and one of liver failure secondary to adenovirus infection.

- Of those with serious AEs (n=20, 48%), 17 patients were hospitalized and 4 had prolonged hospitalization (one patient had both on separate occasions).
- No grade 3 or 4 central nervous system toxicities were observed.
- Regarding any nervous system AEs, except for 1 case of worsening asthenia and 2 of peripheral polyneuropathy, all AEs were grade 1 and 2 and were generally nonspecific (eg, headache, fatigue).

Finally … More New Drugs

- Selinexor
- Venetoclax
- Oprozomib
- Melflufen

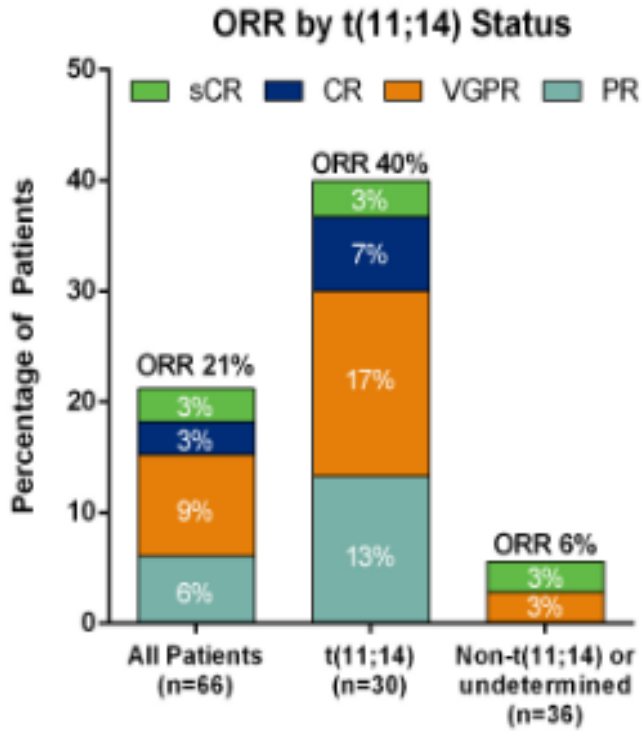
Venetoclax therapy - t(11:14) Myeloma

Design: Phase II, open label, study of venetoclax plus DEX

Dosing & Schedule:
VEN: initial 2 week lead in period with weekly dose-escalation
- Final doses: daily at 800 mg plus DEX 40 mg weekly
- *Median 3 prior lines*

- ***RESULTS:***
- ***Overall Responses – 65%***
- ***Len Refractory – 71% ; BORT Refractory – 82%***
- ***6mo freedom from Progression – 64%***

- **Median time on VEN: 2.5 mo (0.2-23); 26% received VEN + dex for a median of 1.4 mo (0.1-11)**



venetoclax monotherapy

Safety, n (%)	Venetoclax
Gr 3/4 (≥10%)	Thrombocytopenia (26%), neutropenia (20%), lymphopenia (15%), anemia (14%), and decreased white blood cells (12%)
SAEs ≥2 pts	Pneumonia (n=5), sepsis (3), pain, pyrexia, cough, and hypotension (2 each)
Deaths	8 (all considered unrelated to VEN)

Kumar S, et al. ASH 2016. Abstract 488.
Kaufman J, et al ASH 2017 Abstract 3131

Carfilzomib + Venetoclax

Key eligibility criteria:

- Pts with RRMM and no prior carfilzomib exposure

VenKd on 28-d cycles in 4 cohorts:

- **1: (n=4)** Ven 400 mg/d + **K 27 mg/m²** Days 1, 2, 8, 9, 15, 16 + dex 40 mg QW
- **2: (n=3)** Same as 1) but Ven 800 mg/d
- **3: (n=6 + 22[a])** Ven 800 mg/day + **K 70 mg/m²** Days 1, 8, 15 + dex 40 mg QW
- **4: (n=7)** Ven 800 mg + **K 56 mg/m²** Days 1, 2, 8, 9, 15, 16 + dex 20 mg Days 1, 2, 8, 9, 15, 16, 22, 23

Treatment continued until progressive disease or unacceptable toxicity

Efficacy	N	ORR, %	≥CR, %
All patients	42	79	38
PI refractory	21	76	43
IMiD refractory	26	77	23
Double refractory (PI & IMiD)	14	71	29
t(11;14) positive	8	100	63
High-risk cytogenetics	12	83	33
Standard-risk cytogenetics	29	76	38

Key Conclusions:

- MTD was not reached. Ven 800 mg/day + K 70 mg/m² QW was selected for expansion
- Ven + Kd appears tolerable with no new safety signals or changes in Ven pharmacokinetics
- Response rates were comparable in all high-risk subgroups; the subset with t(11;14) had the highest response

SINE COMPOUNDS: Selinexor + Dex (N=79)

XPO1 (Exportin 1)

increases the nuclear export / inactivation of tumor suppressor proteins (e.g. p53, IkB, p21, FOXO) export / translation of eIF4E-bound oncoprotein mRNAs (e.g. c-MYC, BCL-2, Cyclin D).

Design: Phase II study of Sd

Study Population: RRMM
- 48 pts refractory to REV, POM, V, K (Quad)
- 33 pts refractory to above + anti-CD38 mAbs (Penta)

Dosing & Schedule:
S: 80 mg BIW for 6 or 8 doses of a 28 d cycle
D: 20 mg BIW
Median age: 68 yrs

Efficacy	All	Quad	Penta
ORR	21%	21%	20%
CBR	32%	29%	37%

Efficacy	ORR, n (%)
Standard Risk	4 (17)
High Risk	6 (33)
(17p13)	3 (38)
t(14;16)	1 (100)
t(4;14)	2 (50)

Safety, n (%) Gr 3/4 (≥10%)	All patients
Thrombocytopenia	58
Neutropenia	21
Anemia	25
Fatigue	14
Hyponatremia	20

Efficacy	All	Responders	Non-responders
mOS	9.3 mo	NR (>11 mo)	5.7 mo
PFS	2.1 mo		
DOR		5 mo	

- **Most quad patients (83%) received 6 doses/cycle; penta patients (65%) received 8 doses/cycle**

Vogl DT, et al. ASH 2016. Abstract 491.

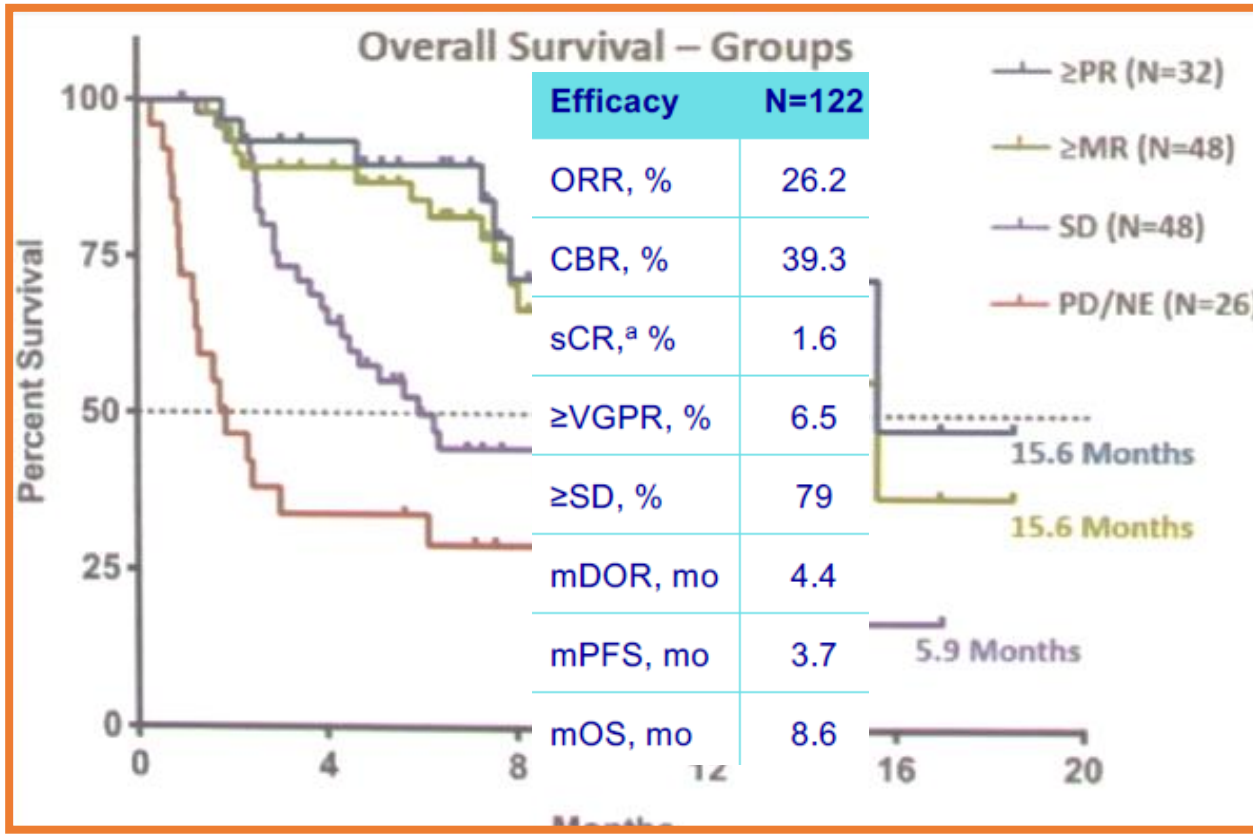
Selinexor (STORM)

Key eligibility criteria:

- Patients with penta-refractory RRMM (BORT, CAR, LEN, POM, DARA and alkylator [including last therapy])
- ANC ≥1000 mm^3
- Platelets ≥50k/mm^3 (≥75k if marrow plasma <50%)
- Creatinine clearance ≥20 mL/min
- Hemoglobin ≥8.5 g/dL

Selinexor + dexamethasone (Sd)
(N=123)
80 mg selinexor + 20 mg dexamethasone 2QW

(eg, Monday and Wednesday or
Tuesday and Thursday, etc)



Efficacy	N=122
ORR, %	26.2
CBR, %	39.3
sCR,[a] %	1.6
≥VGPR, %	6.5
≥SD, %	79
mDOR, mo	4.4
mPFS, mo	3.7
mOS, mo	8.6

- 32.2% of patients discontinued treatment due to AEs.
- There were 4 deaths on treatment: sepsis, respiratory failure, PE, and an unrelated, unspecified cardiac event

Allogeneic SCT

- Graft-vs-myeloma effect
- Can potentially provide sustained disease control (ie, cure)
- High treatment-related mortality
- Morbidity from GVHD
- No definite OS advantage vs autologous SCT
- Should be offered to high-risk patients in trials

Dhakal. Bone Marrow Transplant. 2016;51:492.

Summary - Relapse

- Early Relapse
  - Choice of Triplets
  - KRD with OS data now
  - Dara –RD
  - POM for R in the post maintenance setting
- Refractory Relapse
  - Variety of New Compounds
- **CAR-T vs. Other**
  - **Waiting in line for CAR-T vs. Trying something else?**