Therapy for Relapsed/Refractory Multiple Myeloma

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Who am I?

Who am I?

Disclosures for
Dr. Michael Green

Research Support / P.I.	No relevant conflicts of interest to declare
Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	No relevant conflicts of interest to declare
Scientific Advisory Board	No relevant conflicts of interest to declare

Presentation does NOT include discussion of the off-label use of a drug or medical device

Treatment options in relapsed/refractory MM

- Proteasome inhibitors
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- Immunomodulators
  - Lenalidomide
  - Pomalidomide
  - Thalidomide
- Monoclonal Antibodies
  - Daratumumab
  - Elotuzumab
- HDAC Inhibitors
  - Panobinostat
- Alkylating Agents
  - Cyclophosphamide
  - Bendamustine
  - Melphalan
- Cytotoxics
  - Vincristine
  - Doxorubicin
  - Cisplatin
  - Etoposide
- Steroids
- *** Selective Inhibitors of Nuclear Export
  - Sellinexor

MYELOMA THERAPY[a-d,m]

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[n]	
Preferred Regimens	
• Bortezomib/lenalidomide/dexamethasone	• Daratumumab[p]/bortezomib/dexamethasone (category 1)
• Carfilzomib (twice weekly)[h]/dexamethasone (category 1)[i]	• Daratumumab[p]/lenalidomide/dexamethasone (category 1)
• Carfilzomib (weekly)[h]/dexamethasone[i]	• Elotuzumab[q]/lenalidomide/dexamethasone (category 1)[o]
• Carfilzomib[h]/lenalidomide/dexamethasone (category 1)[o]	• Ixazomib[s]/lenalidomide/dexamethasone (category 1)[o]
Other Recommended Regimens	
• Bendamustine/bortezomib/dexamethasone	• Ixazomib[s]/dexamethasone[i]
• Bendamustine/lenalidomide/dexamethasone	• Ixazomib/pomalidomide[w]/dexamethasone
• Bortezomib/liposomal doxorubicin/dexamethasone (category 1)	• Lenalidomide/dexamethasone[t] (category 1)[i]
• Bortezomib/cyclophosphamide/dexamethasone	• Panobinostat[u]/bortezomib/dexamethasone (category 1)
• Carfilzomib[h]/cyclophosphamide/dexamethasone	• Panobinostat[u]/carfilzomib[h,i]
• Cyclophosphamide/lenalidomide/dexamethasone	• Panobinostat[u]/lenalidomide/dexamethasone
• Bortezomib/dexamethasone (category 1)[i]	• Pomalidomide[w]/cyclophosphamide/dexamethasone
• Daratumumab[p,r]	• Pomalidomide[w]/dexamethasone[t] (category 1)[i]
• Daratumumab[p]/pomalidomide[v]/dexamethasone	• Pomalidomide[w]/bortezomib/dexamethasone
• Elotuzumab/bortezomib/dexamethasone	• Pomalidomide[w]/carfilzomib[h]/dexamethasone
• Elotuzumab/pomalidomide/dexamethasone[v]	
Useful In Certain Circumstances	
• Bendamustine	• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[x] ± bortezomib (VTD-PACE)[x]
• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[x]	• High-dose cyclophosphamide


MEGA
IMID
PI

Factors to consider for treatment selection

- Disease related factors
  - Nature of relapse: Indolent vs. aggressive
  - Risk stratification: Cytogenetic abnormalities
  - Disease burden
- Patient related factors
  - Renal insufficiency
  - Neuropathy
  - Heart Disease
  - Patient preference: convenience, travel, insurance, cost

Factors to consider for treatment selection

- Previous therapy
  - Progression
  - Intolerance
  - Maintenance dosing
  - Depth and duration of response
- Treatment toxicity
  - Performance Status
  - Neuropathy: bortezomib, thalidomide
  - Cardiac issues: carfilzomib
  - COPD: daratumumab
  - DVT/PE: IMIDs
  - Financial

Clinical Trial Review Cheat Sheet

- Phase of study
- Location of study
- Patient Population: Newly Diagnosed, Early Relapse, Late Relapse, and Heavily Pretreated
- End points: Surrogate Markers versus Patient Oriented
- Toxicities

Vincent Rajkumar
@VincentRK

So today I called for Progression Free Survival (PFS) to be renamed as Progression Free Duration (PFD) because "improved PFS" incorrectly sends out a signal to patients that survival is prolonged— when in reality it may or may not be prolonged & can even be worse. @TheLancetOncol

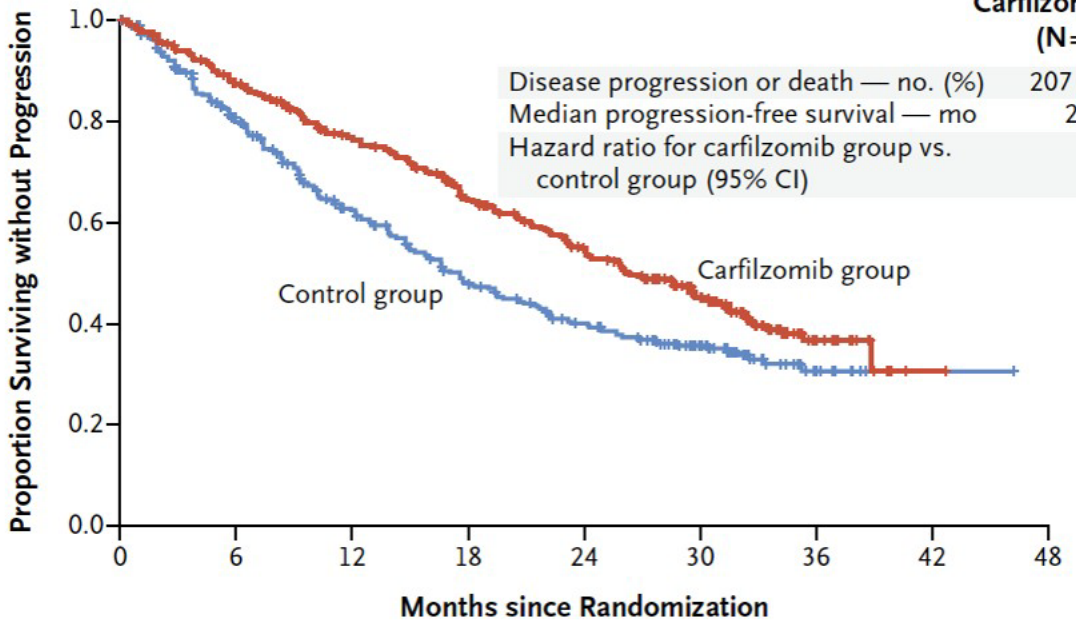
4:54 PM · Sep 20, 2019 · Twitter for iPhone

Early Relapse

Triplet regimens vs. lenalidomide-dexamethasone

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

A



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	

P=0.0001

No. at Risk								
Carfilzomib group	396	332	279	222	179	112	24	1
Control group	396	287	206	151	117	72	18	1

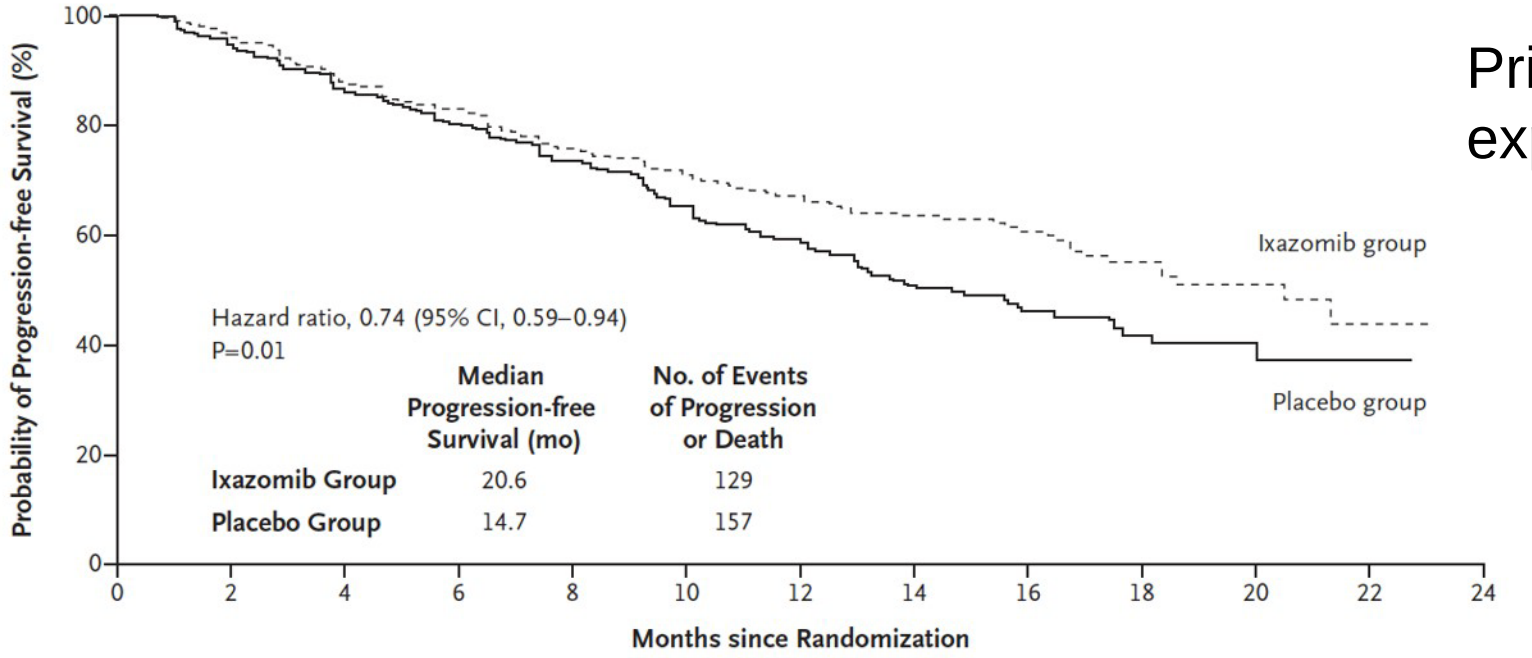
Prior lenalidomide exposure: 20%

Stewart et al. N Engl J Med 2017

Triplet regimens vs. lenalidomide-dexamethasone

Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

A Progression-free Survival in the Intention-to-Treat Population

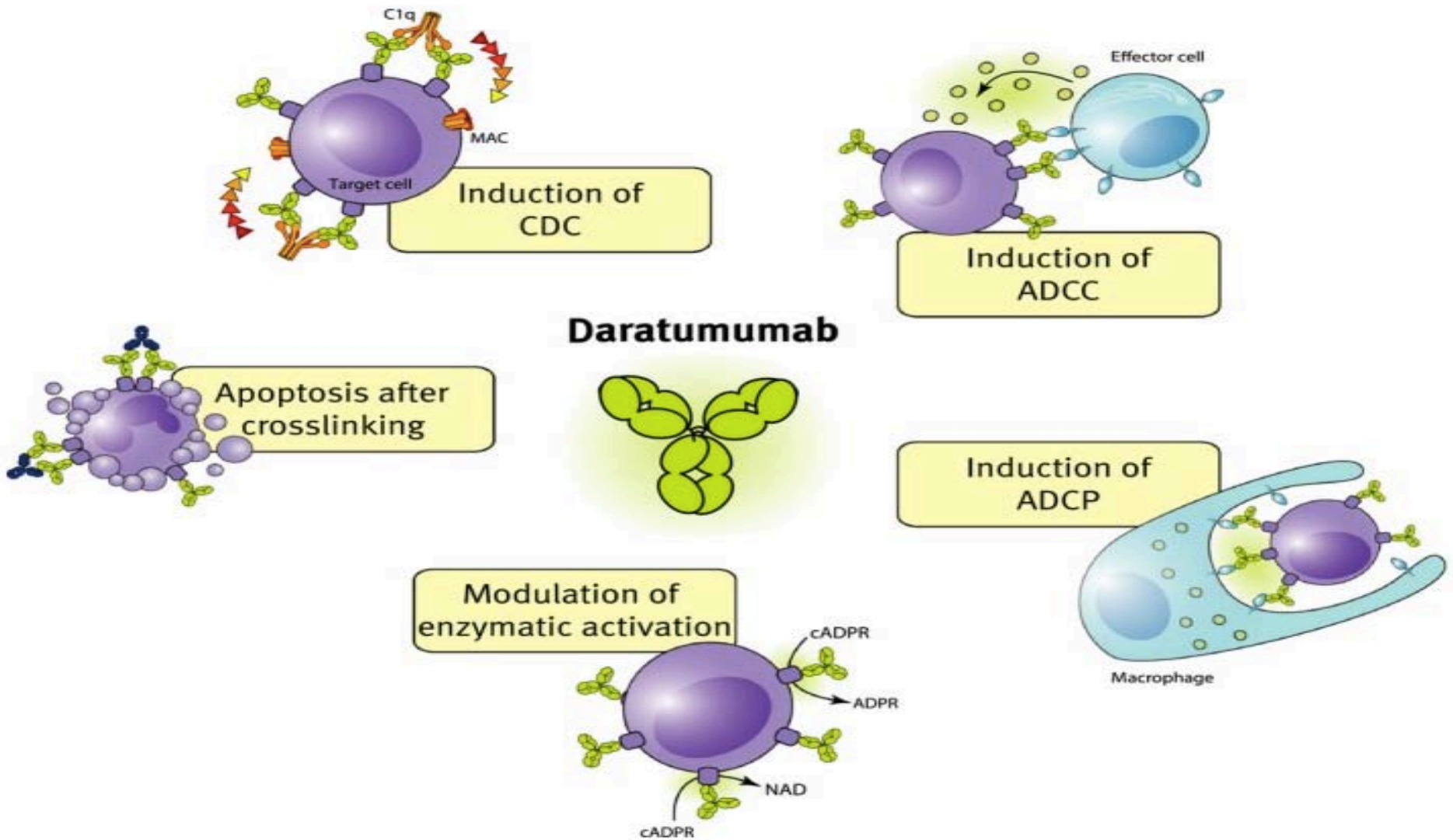


No. at Risk

Ixazomib group	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo group	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Prior lenalidomide exposure: 12%

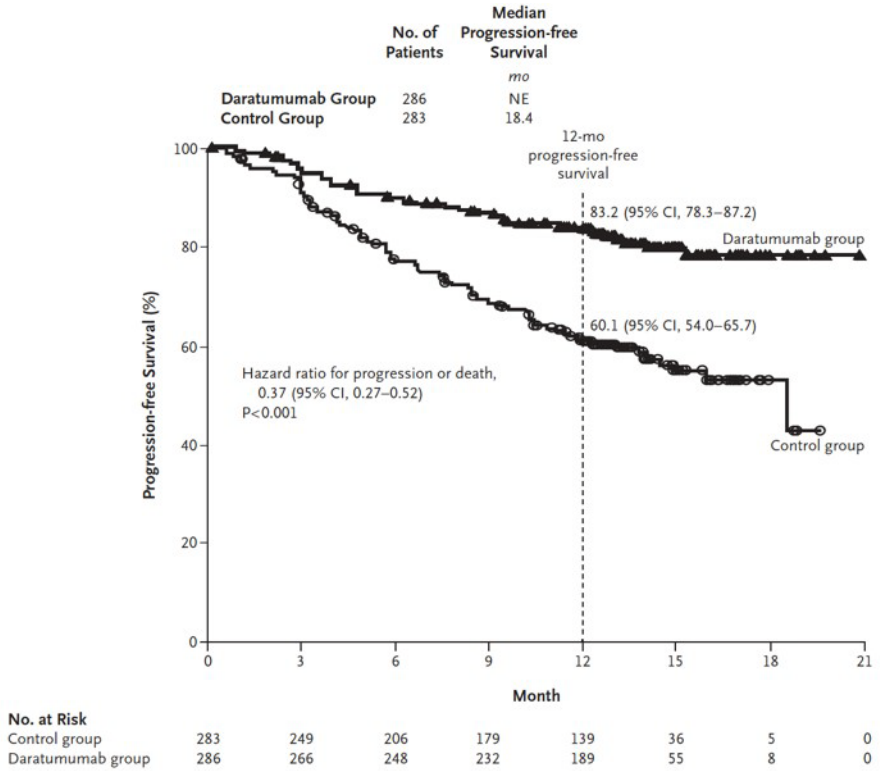
Moreau et al. N Engl J Med 2016



Van de Donk, *Immunol Rev*

Triplet regimens vs. lenalidomide-dexamethasone

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma



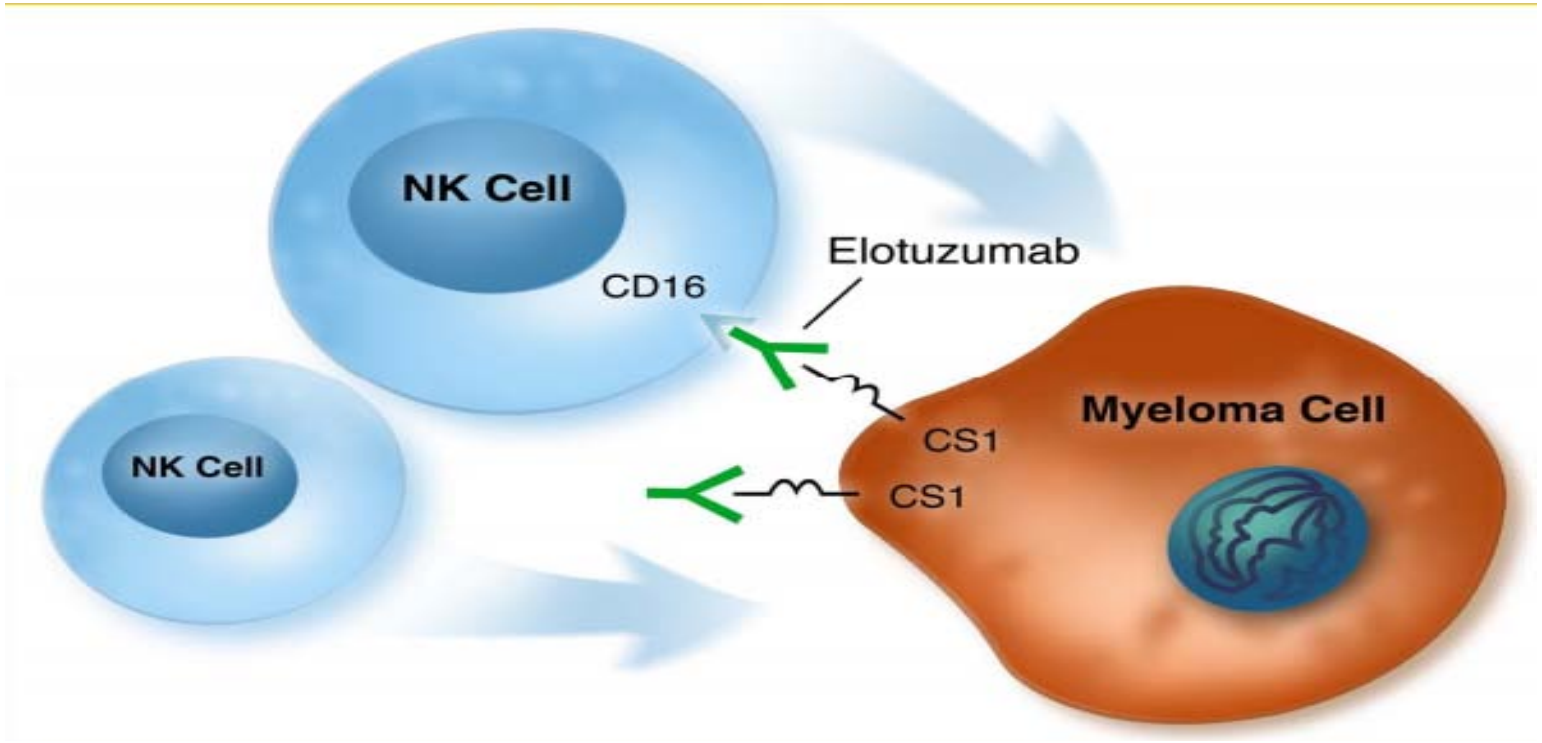
Median PFS
RD 17.5 months
Dara-RD Not reached

Prior lenalidomide exposure: 18%

Dimopoulos et al. N Engl J Med 2016

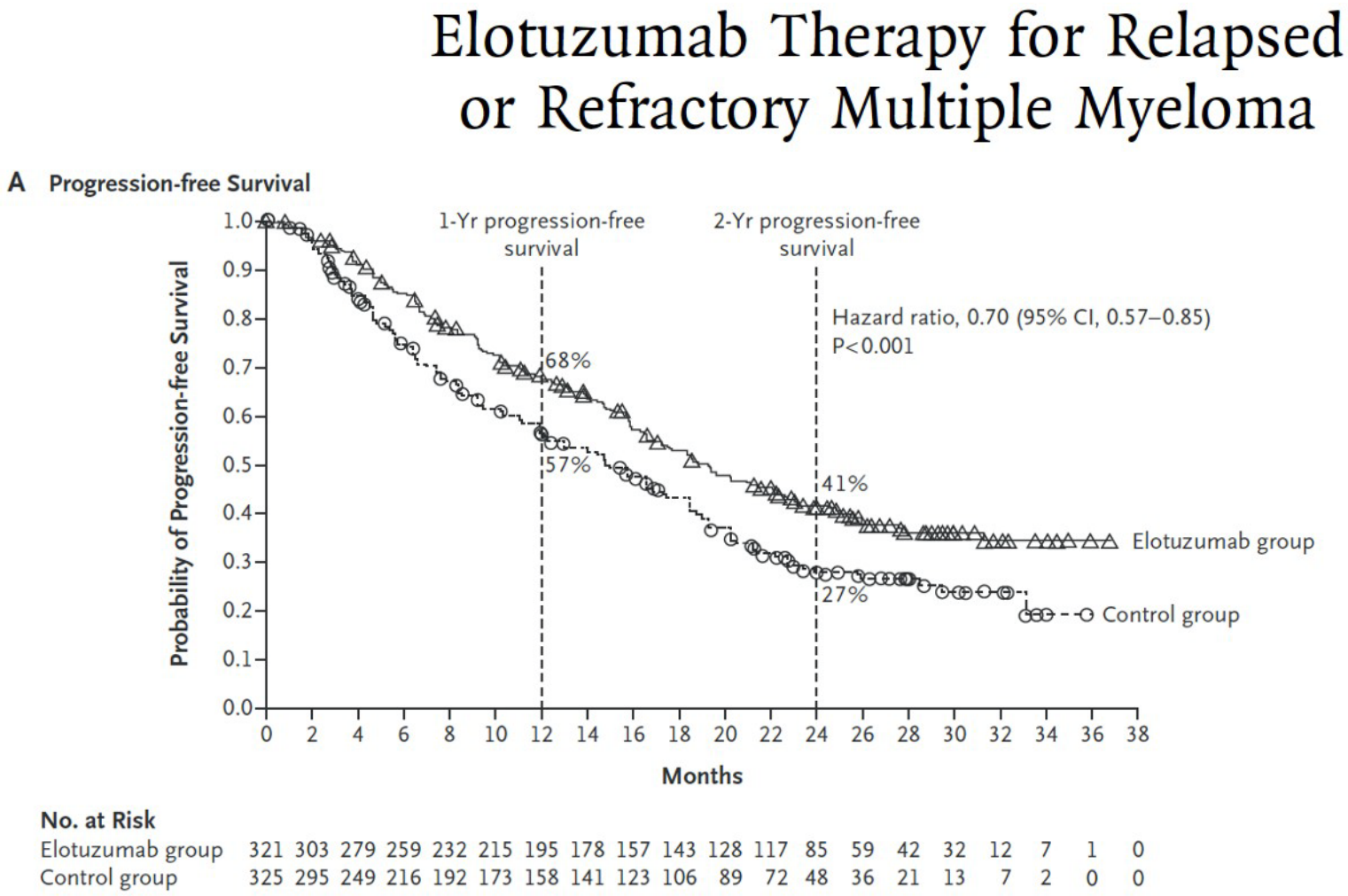
Elotuzumab

- Binds SLAMF7/CS1 on MM, inducing ADCC
- Also binds same receptor on NK cells, stimulating activity



Hsi ED, *Clin Can Res* 2008

Triplet regimens vs. lenalidomide-dexamethasone



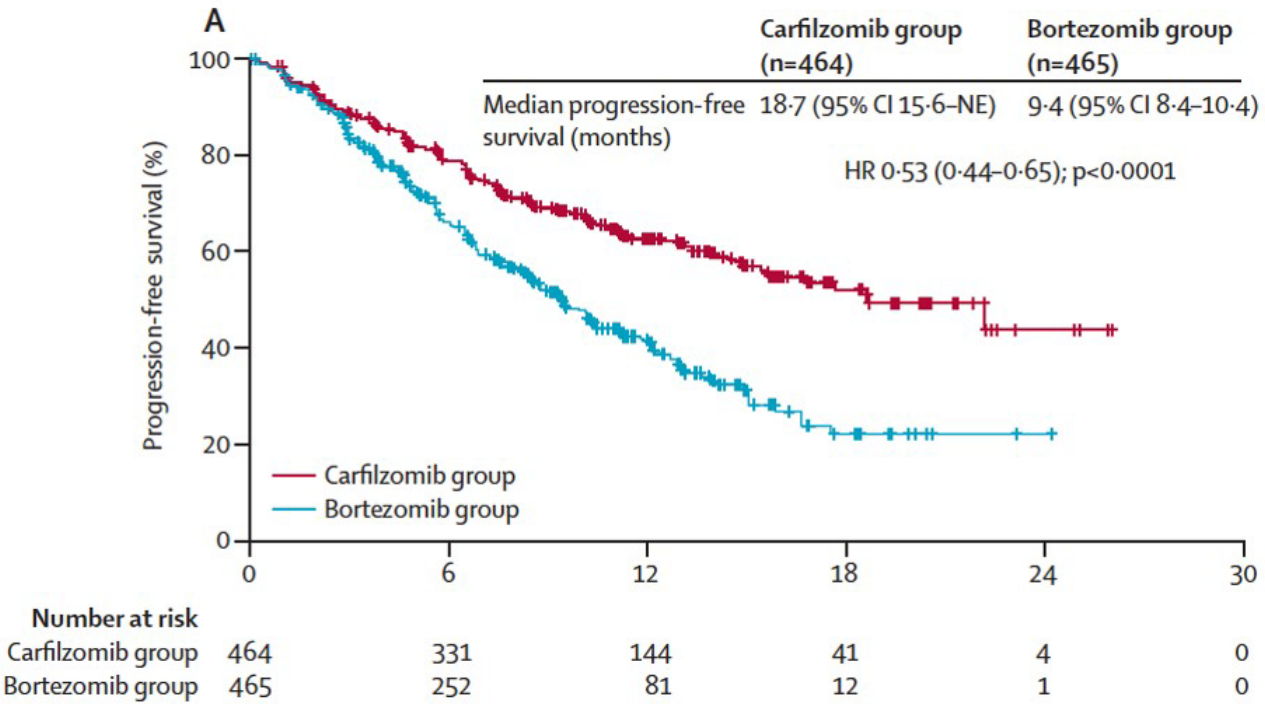
Median PFS
RD 14.9 months
Elo-RD 19.4 months

Prior lenalidomide exposure: 6%

Lonial et al.
N Engl J Med 2016

Vs. bortezomib-dexamethasone

Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study

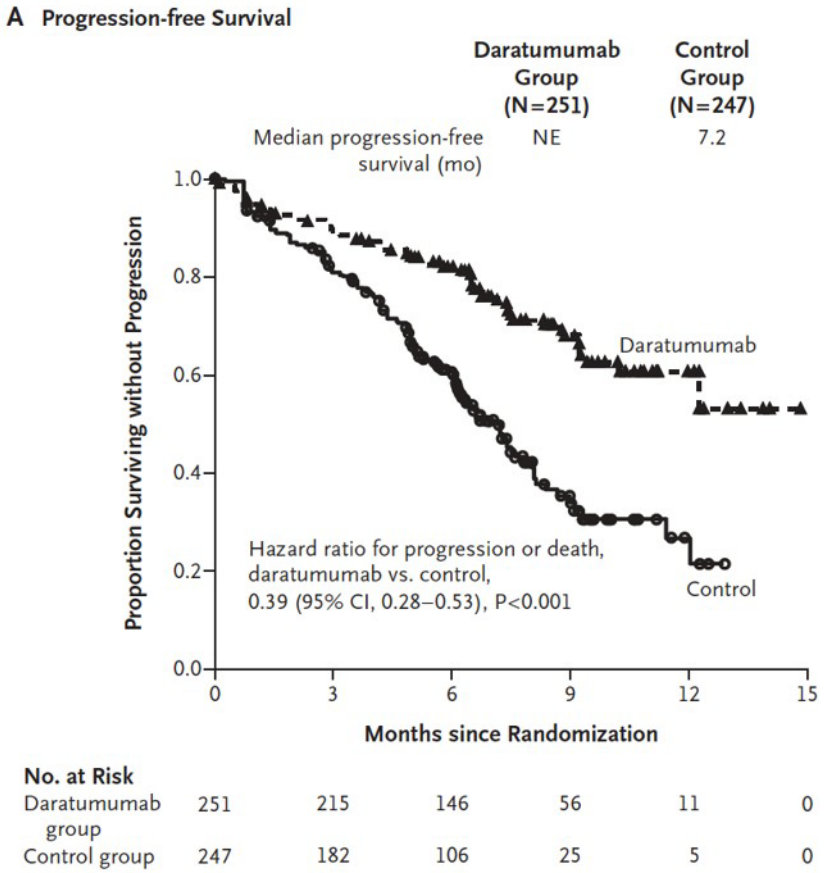


Prior lenalidomide exposure: 38%

Dimopoulos et al. Lancet Oncol 2016

Triplet regimens vs. bortezomib-dexamethasone

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma



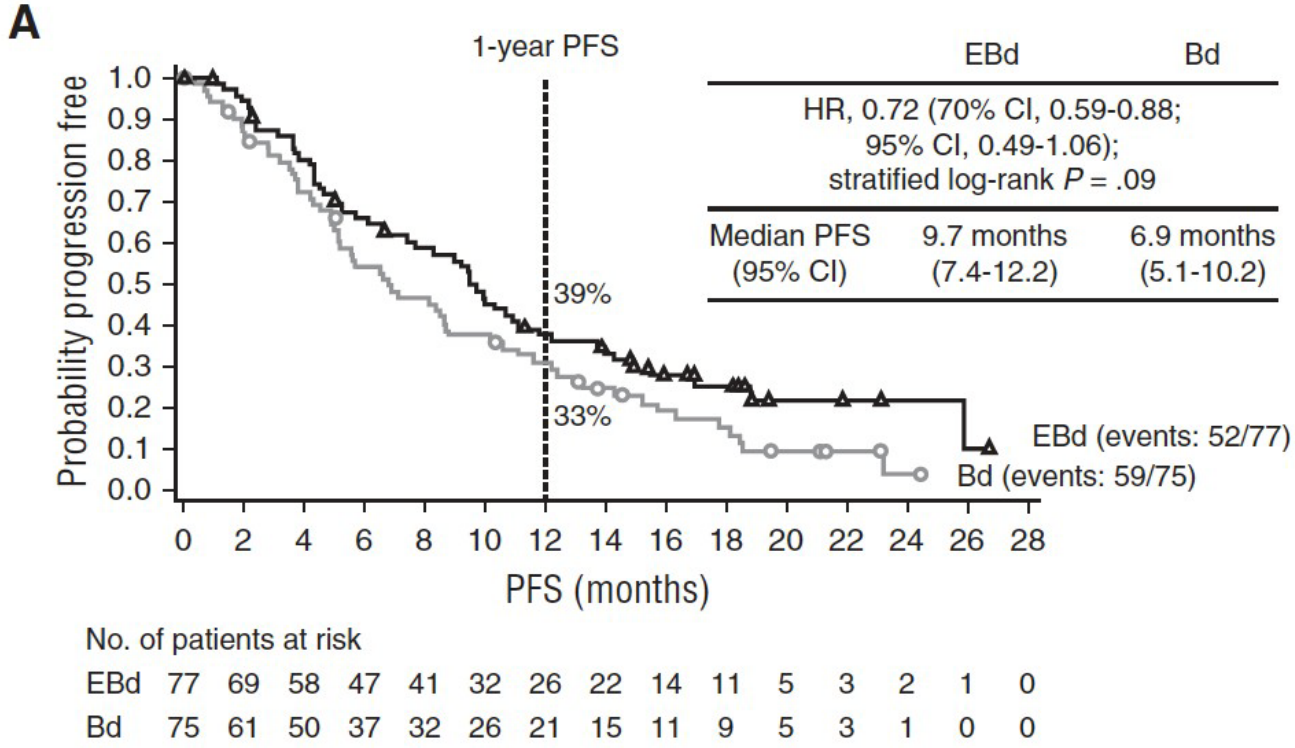
Prior lenalidomide exposure: 68%

Palumbo et al. N Engl J Med 2016

Triplet regimens vs. bortezomib-dexamethasone

CLINICAL TRIALS AND OBSERVATIONS

Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM



Prior lenalidomide exposure: 75%

Jakubowiak et al. Blood 2016

Selected toxicity of new combinations

TRIAL	ASPIRE (KRd)	TOURMALINE-MM1 (IRd)	ELOQUENT-2 (EloRd)	POLLUX (DRd)	ENDEAVOR (Kd)	CASTOR (DVd)
Peripheral neuropathy	3%	2%	NA	NA	2%	5%
Acute renal failure	3%	3%	NA	NA	5%	NA
Cardiac toxicity	7%	6%	NA	NA	8%	NA
Pneumonia/infections	2%	1%	NA	10%	8%	11%
Diarrhea	4%	6%	5%	5%	3%	4%

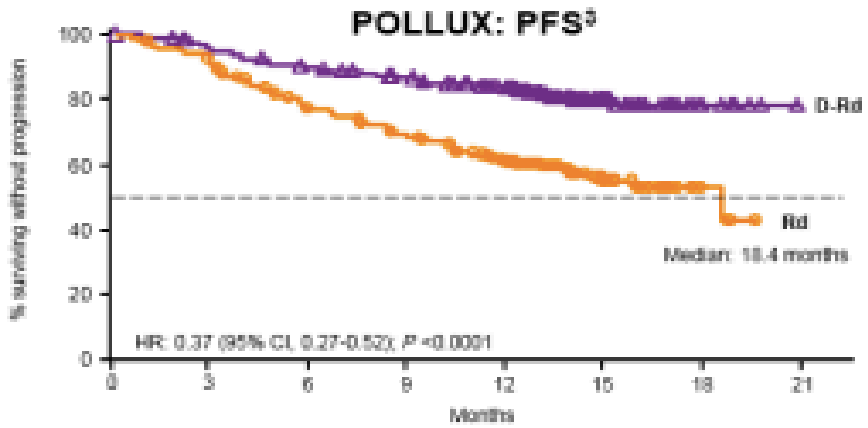
Phase III Studies: Early Relapse Disease

- >10 Randomized Trials
  - Many options – "dealer's choice"

Trial	Regimen	Prior Therapies	N	Median PFS,* mo
ASPIRE[a]	KRd vs Rd	1 to 3	792	**26.3** vs 17.6 HR = 0.69 (*P* = .0001)
ENDEAVOR[b]	Kd vs Vd	1 to 3	929	**18.7** vs 9.4 HR = 0.53 (*P* < .0001)
TOURMALINE-MM1[c]	IRd vs Rd	1 to 3	722	**20.6** vs 14.7 HR = 0.74 (*P* = .01)
ELOQUENT-2[d]	ERd vs Rd	1 to 3 10% prior len	646	**19.4** vs 14.9 HR = 0.70 (*P* < .001)
POLLUX[e]	DRd vs Rd	≥ 1	569	**>32** vs 18.4 HR = 0.37 (*P* < .001)
CASTOR[f]	DVd vs VD	≥ 1	498	**16.7** vs 7.2 HR = 0.39 (*P* < .001)

a. Stewart AK, et al. *N Engl J Med*. 2015;372:142-152; b. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27-38; c. Moreau P, et al. *N Engl J Med*. 2016;374:1621-1634; d. Lonial S, et al. *N Engl J Med*. 2015;373:621-631; e. Dimopoulos MA, et al. *N Engl J Med*. 2016;375:1319-1331; f. Palumbo A, et al. *N Engl J Med*. 2016;375:754-766; g. San Miguel JF, et al. *Lancet Oncol*. 2014;15:1195-1206.

- ASH 2018 Update:
  - Pollux Study in RRMM
  - PFS D-Rd 44.5 m vs Rd 17.5 m

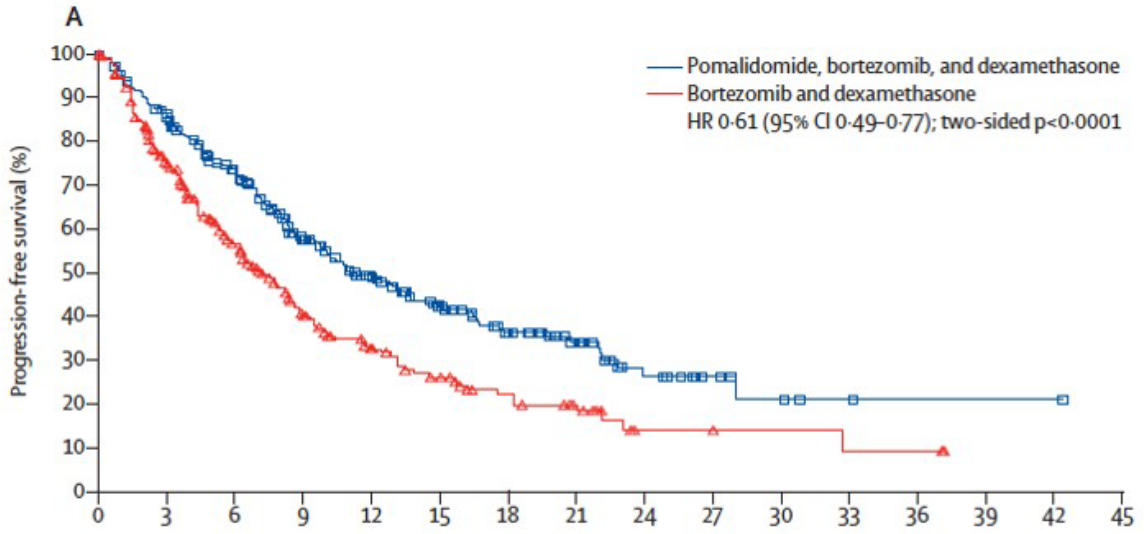


1. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331;
2. 2. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.

Late Relapse

Pomalidomide-based regimens

Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial

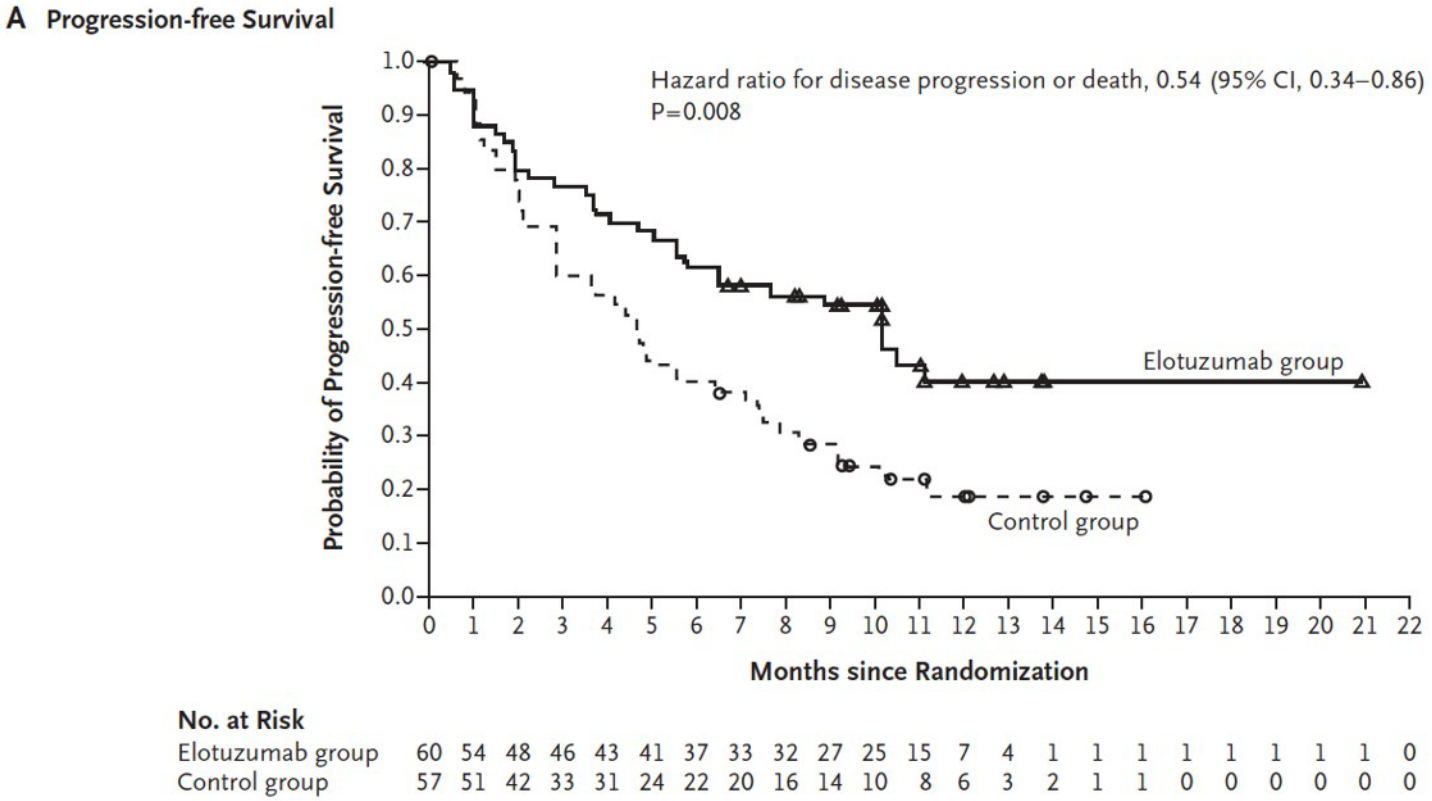


Number at risk (number censored)																
Pomalidomide, bortezomib, and dexamethasone	281 (0)	233 (11)	182 (28)	128 (46)	94 (62)	67 (76)	47 (88)	28 (105)	13 (115)	7 (121)	4 (123)	2 (125)	1 (126)	1 (126)	1 (126)	0 (127)
Bortezomib and dexamethasone	278 (0)	176 (39)	112 (63)	66 (79)	42 (92)	30 (96)	20 (102)	14 (106)	4 (113)	4 (113)	3 (114)	2 (114)	2 (114)	0 (116)	0 (116)	0 (116)

Richardson et al.
Lancet Oncol 2019

Pomalidomide-based regimens

Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma

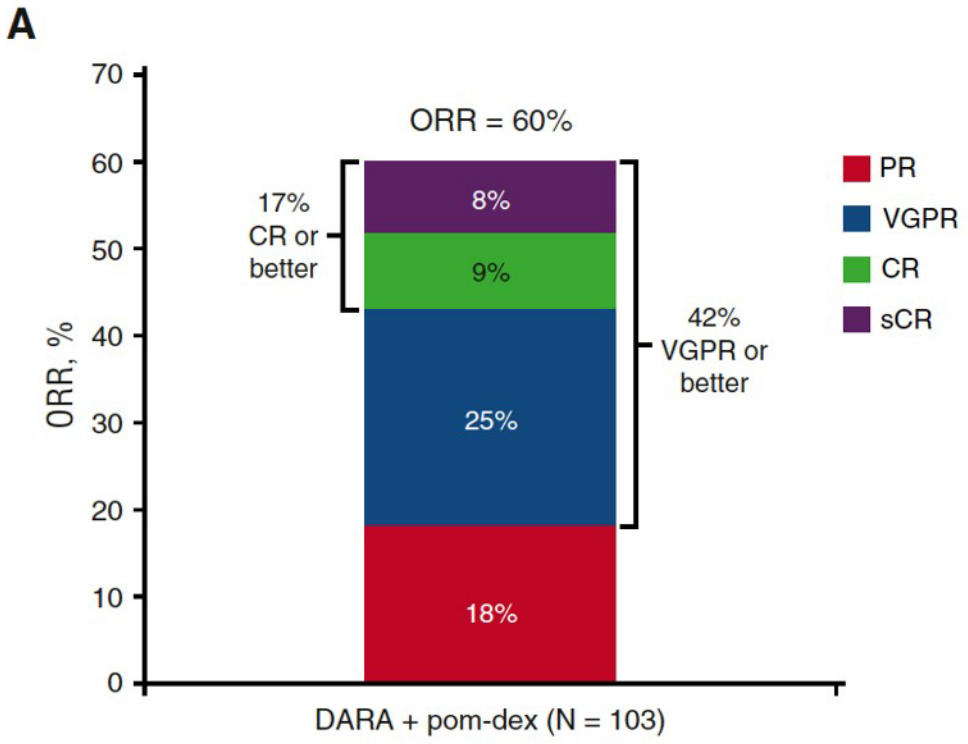


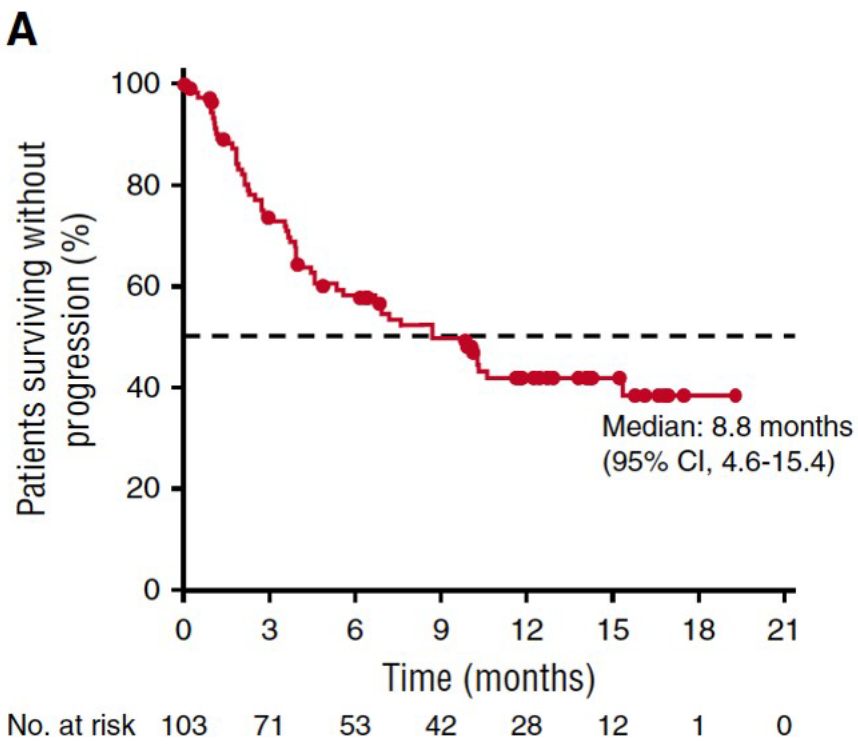
Dimopoulos et al.
N Engl J Med 2018

Pomalidomide-based regimens

CLINICAL TRIALS AND OBSERVATIONS

Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma





98% previously exposed to len + bort

71% refractory to len + bort

Chari et al. Blood 2017

Pomalidomide-based regimens

Carfilzomib, Pomalidomide, Dexamethasone Feasible in Patients With Relapsed/ Refractory MM

- KPd demonstrated favorable outcomes in mostly lenalidomide-refractory and PI-naive/sensitive relapsed/refractory MM
- 84% of pts achieved PR or better
- Median PFS 12.9 months, with OS not yet reached

Rosenbaum et al. ASCO 2016: 8007

Heavily Pretreated/Multiply Relapsed

Vincent Rajkumar Retweeted

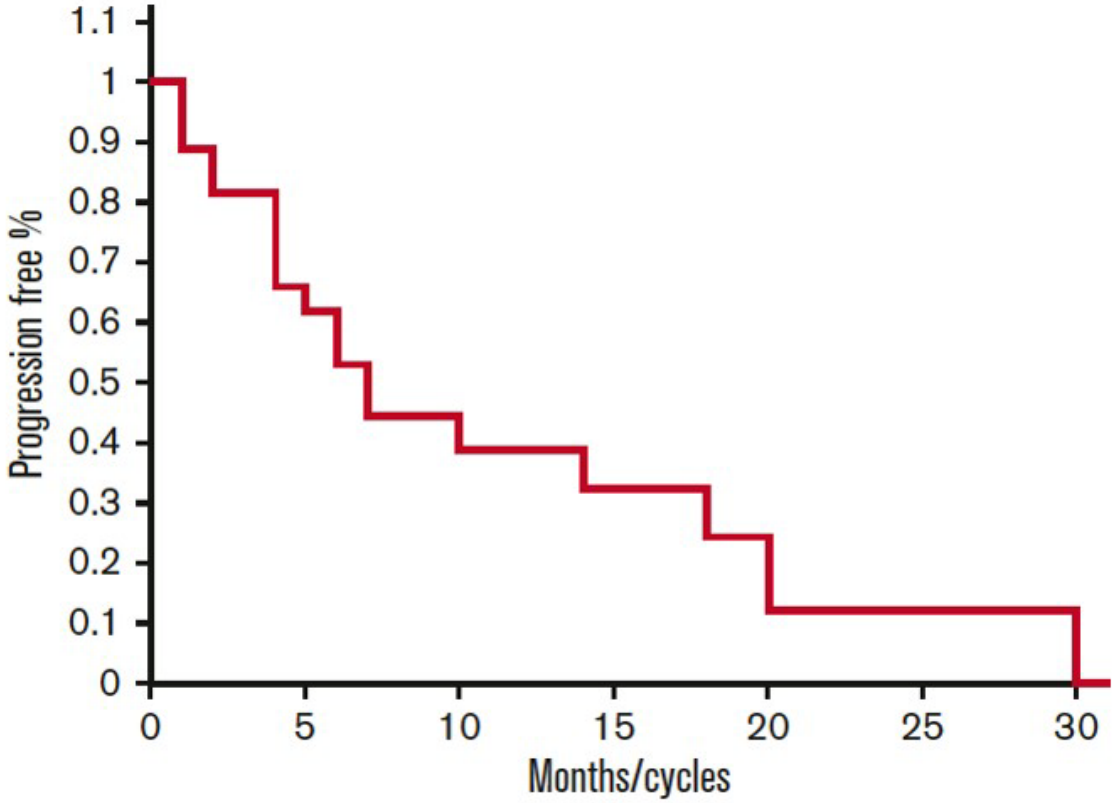
Vincent Rajkumar
@VincentRK

At present the playing field is not level. New drugs that are incremental improvements over existing drugs command high prices on par with truly innovative drugs that deliver landmark benefits. So why take risk innovating when incremental tinkering can deliver handsome rewards?

10:13 AM · Oct 12, 2019 · Twitter for iPhone

Panobinostat-based regimens

A phase 2 study of panobinostat with lenalidomide and weekly dexamethasone in myeloma



n=27

81% refractory to lenalidomide
52% refractory to bortezomib

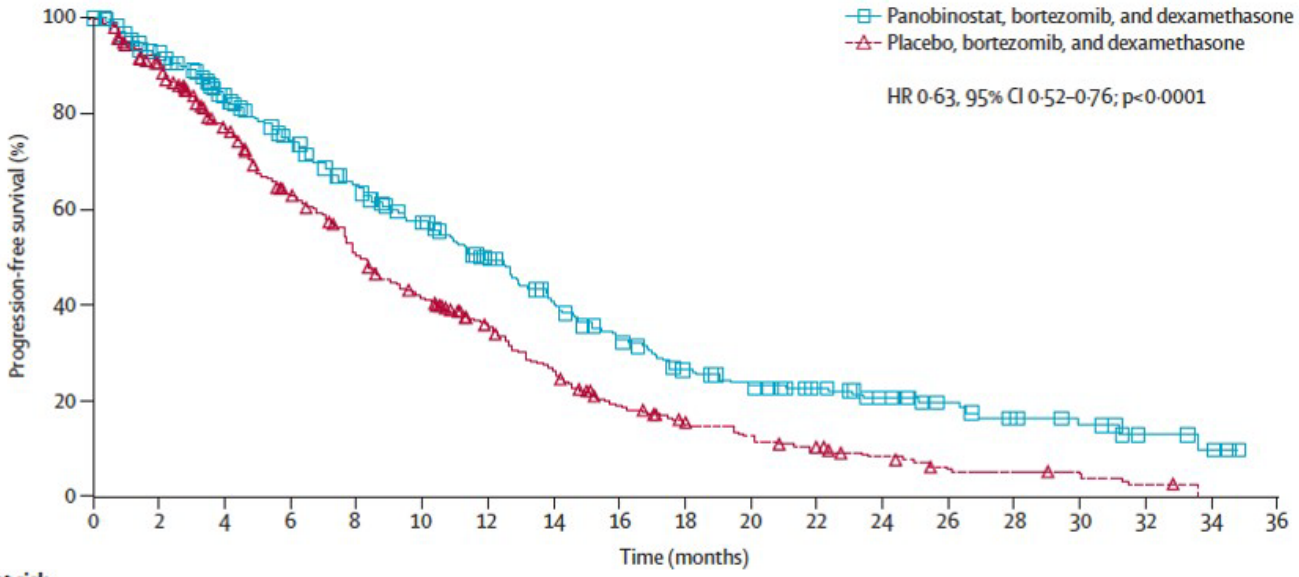
ORR 41%
CBR 74%

Median PFS: 7.1 months

Chari et al. Blood Adv 2017

Panobinostat-based regimens

Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial

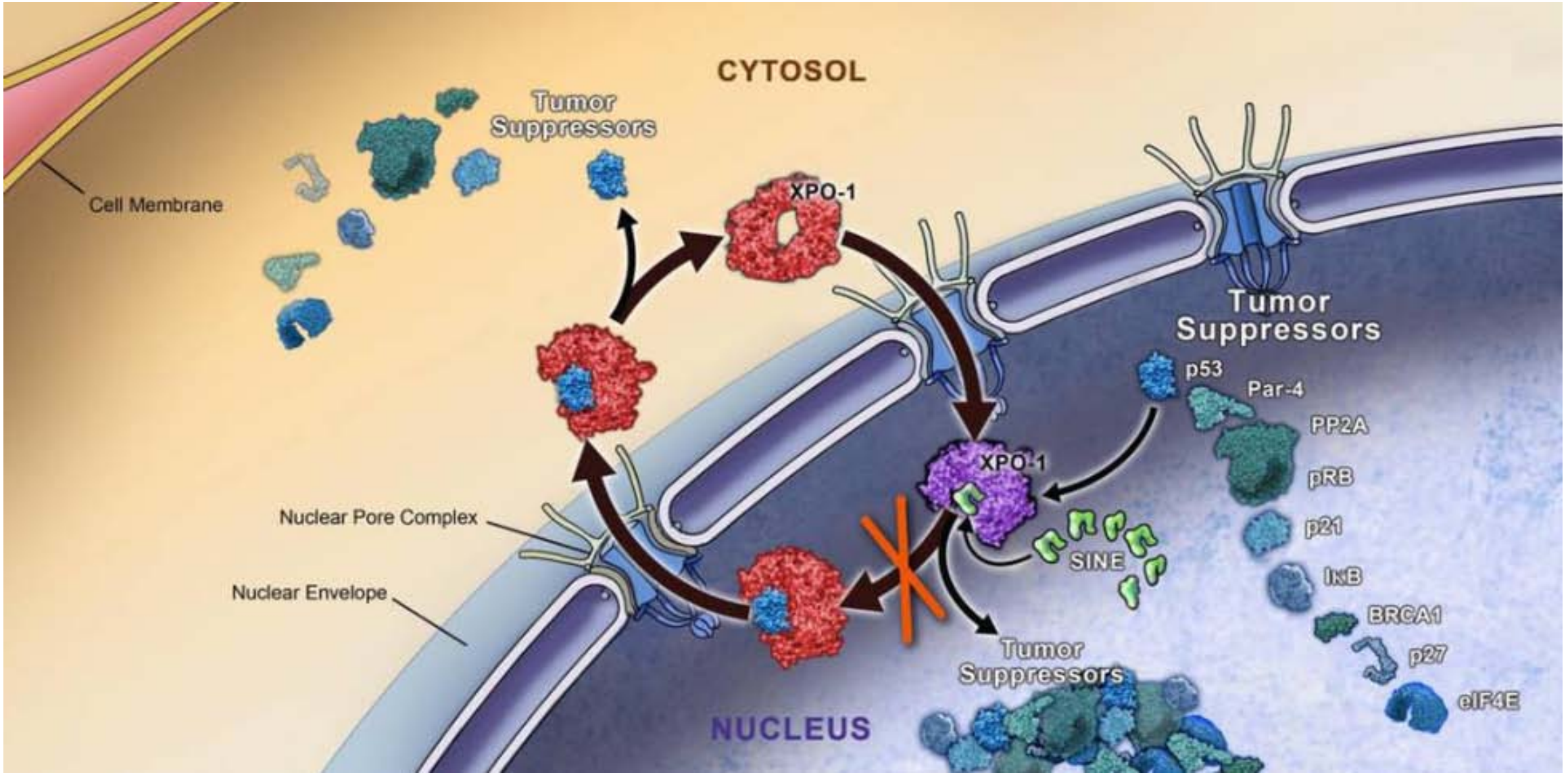


Number at risk																			
Panobinostat, bortezomib, and dexamethasone	387	288	241	202	171	143	113	89	69	52	44	35	26	18	13	10	5	3	0
Placebo, bortezomib, and dexamethasone	381	296	235	185	143	114	89	64	42	32	24	18	12	5	5	3	2	0	0

Median PFS
VD 8.1 months
Pano-VD 12 months

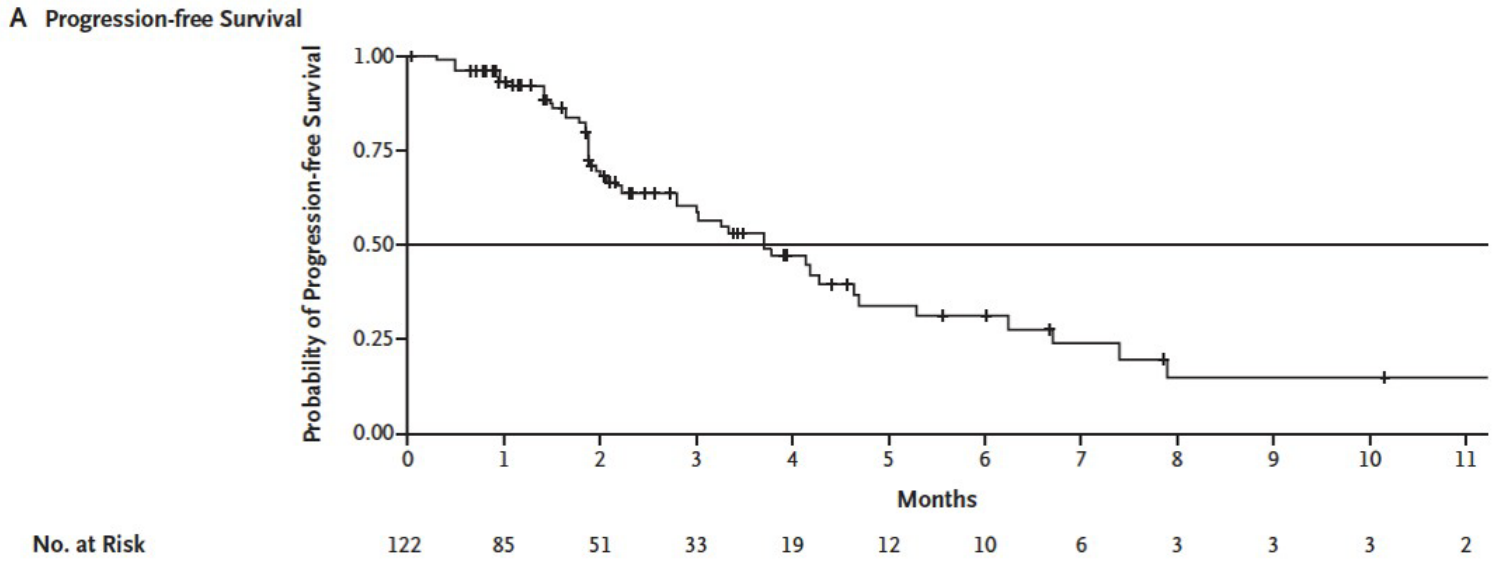
Prior lenalidomide exposure: 20%

San Miguel et al.
Lancet Oncol 2014



https://www.myelomacrowd.org/wp-content/uploads/2015/09/seli.jpg

Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma



N=122

100% refractory to ≥1 IMID, ≥1 PI and daratumumab

53% had high risk cytogenetics
- del17p
- t(4;14)
- t(14;16)
- gain1q

Grade ≥3 adverse events

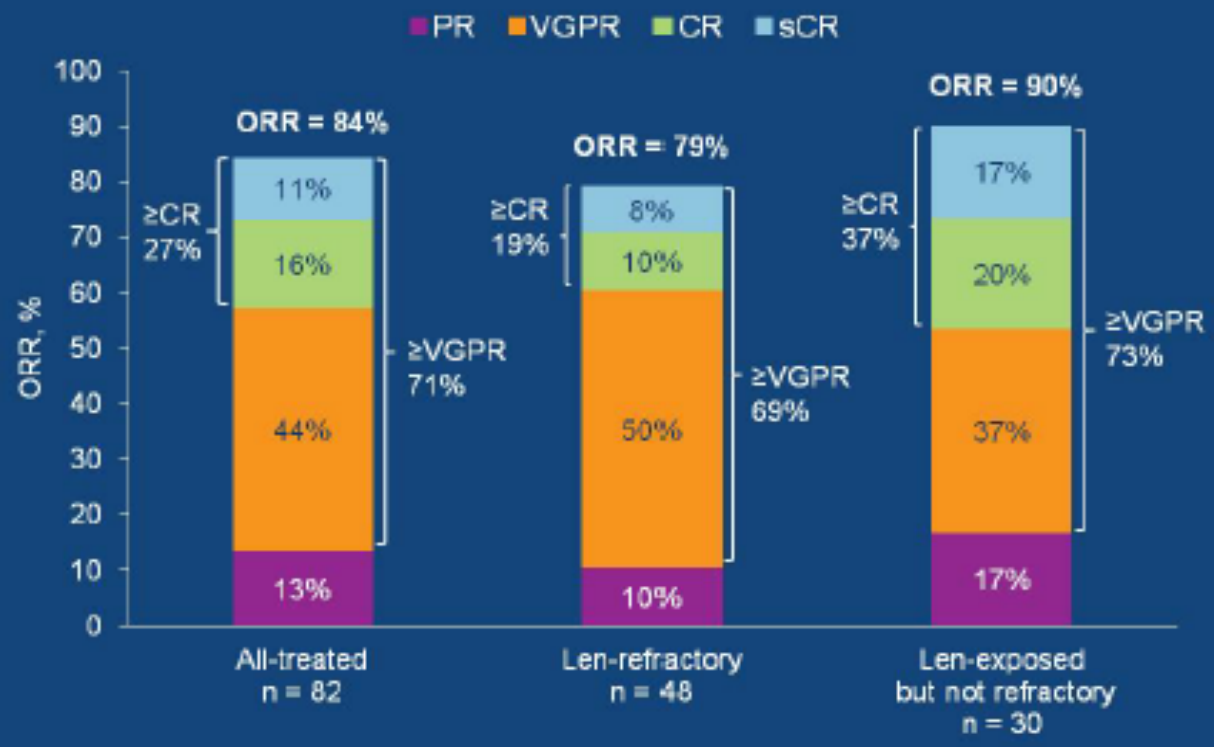
Thrombocytopenia (58%), anemia (44%), neutropenia (21%), Fatigue (25%), hyponatremia (21%), nausea (10%)

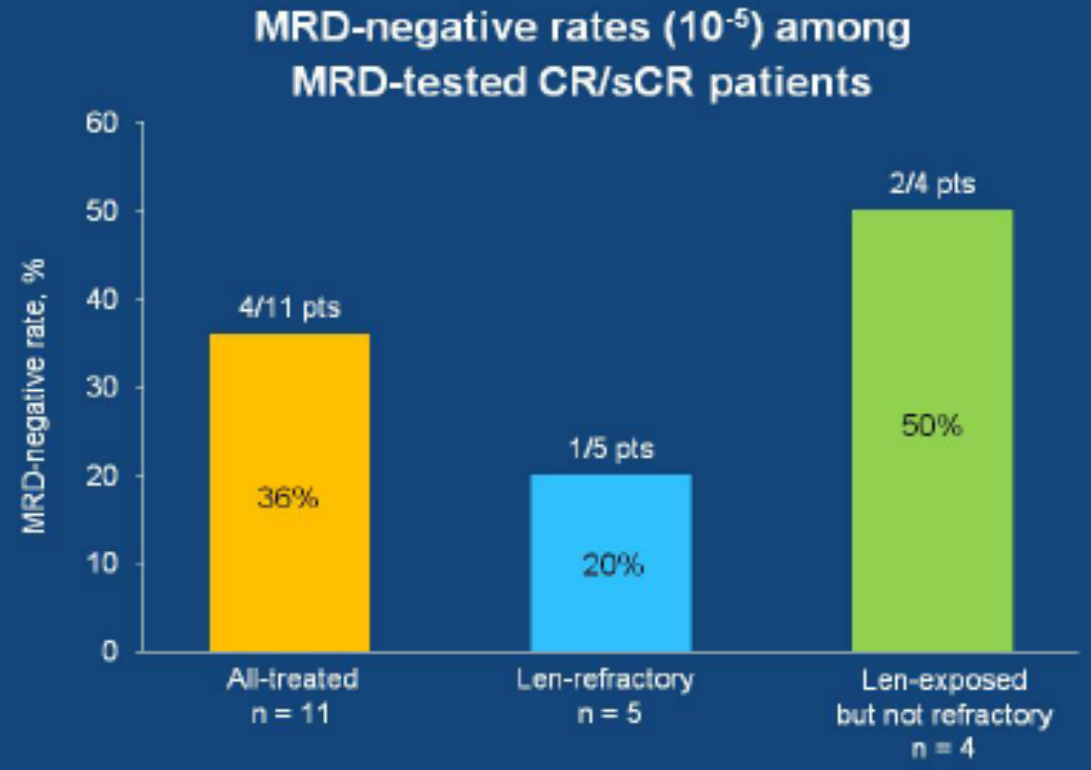
Chari et al.
N Engl J Med 2019

Pending

Overall Response[a] and Confirmed MRD-negative Rates

- Median follow-up: 12.0 months
- Optional MRD testing in 11 patients with CR/sCR; 4 were MRD negative at 10^{-5}





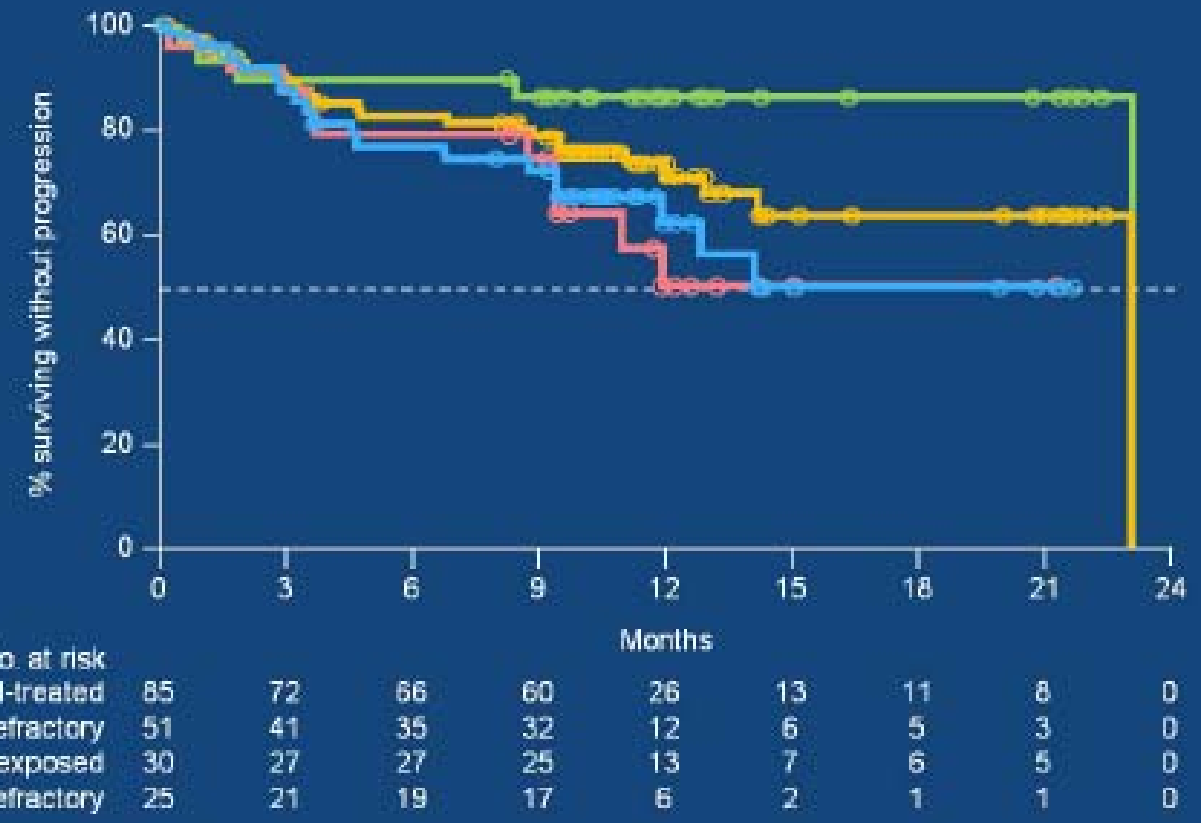
Responses are anticipated to deepen over longer follow-up

Daratumumab + Carfilzomib + Dexamethasone MMY1001 Chari et al. ASCO 2018

Progression-free Survival Across Subgroups

- Median follow-up: 12.0 months

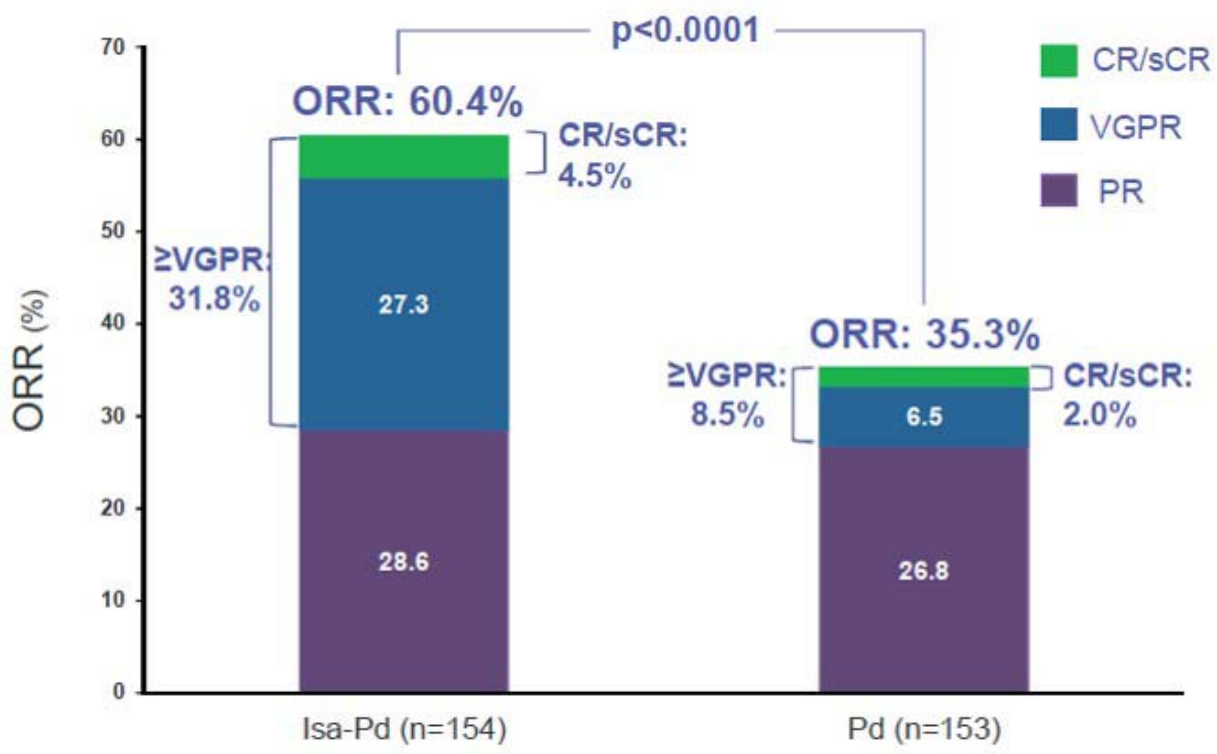
	Median PFS, mo	12-month PFS, %
All-treated	NE	71%
Len-exposed but not refractory	NE	87%
Len-refractory	14.1 (95% CI, 12.0-NE)	62%
PI/IMiD-refractory	NE (95% CI, 9.4-NE)	51%

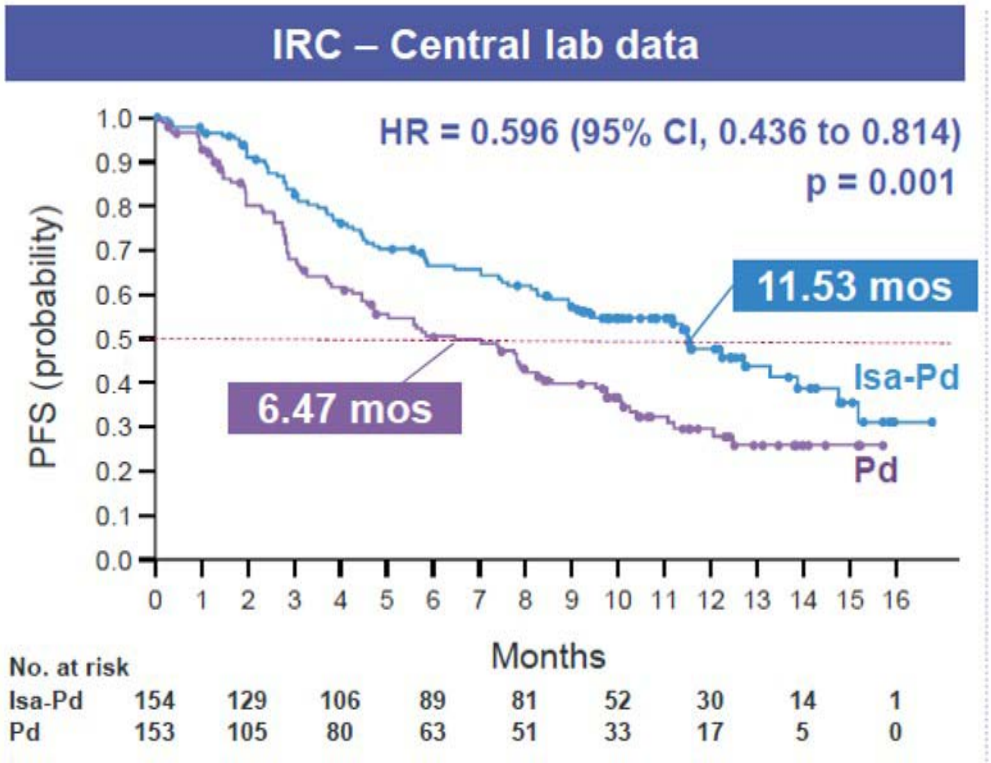


No. at risk									
All-treated	85	72	66	60	26	13	11	8	0
Len-refractory	51	41	35	32	12	6	5	3	0
Len-exposed	30	27	27	25	13	7	6	5	0
PI/IMiD-refractory	25	21	19	17	6	2	1	1	0

Encouraging PFS observed in lenalidomide- and PI/IMiD-refractory patients

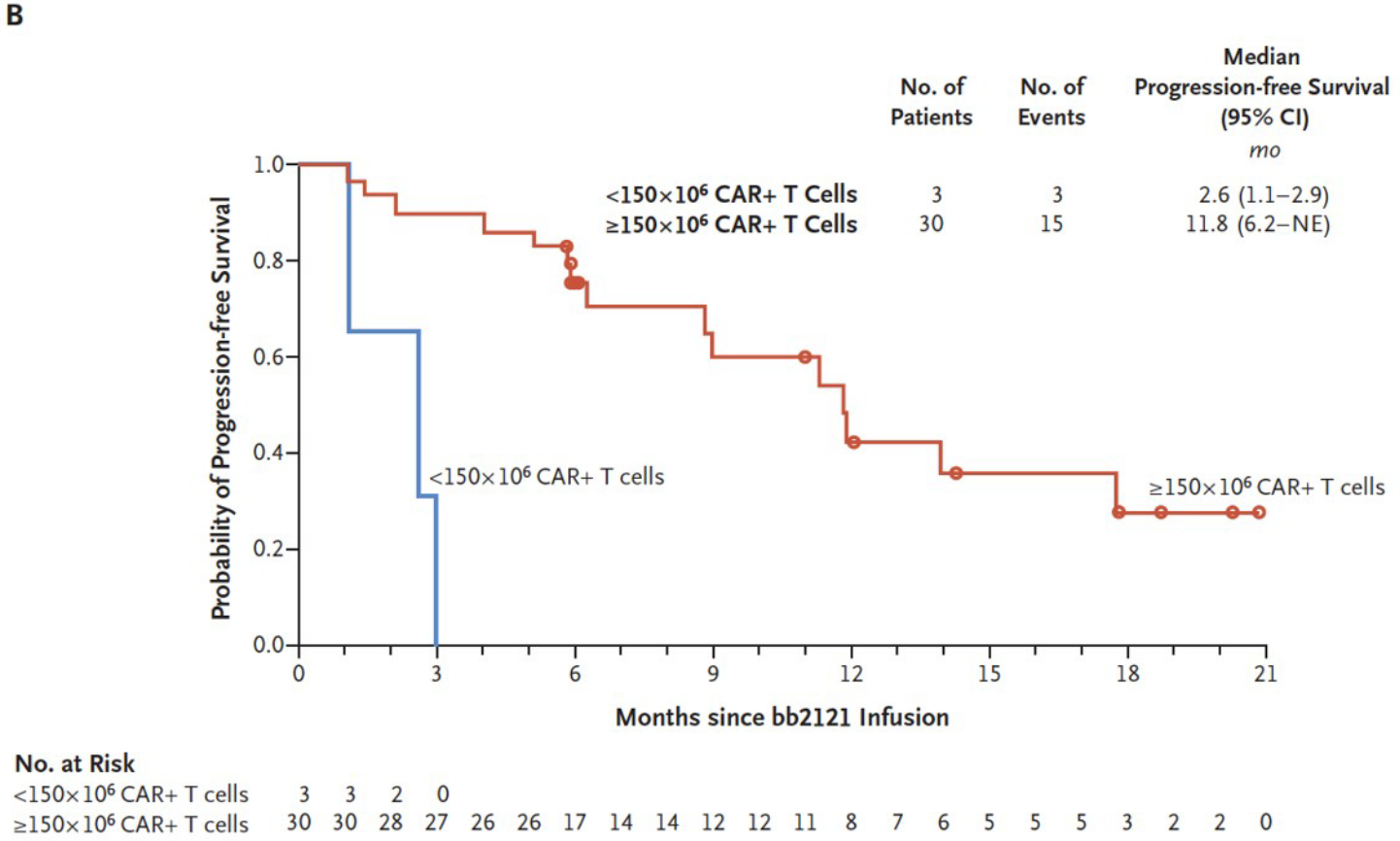
Global Phase III Pivotal Study of Isatuximab with Pd in RRMM





Richardson et al. ASCO 2018

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma



Refractory to:

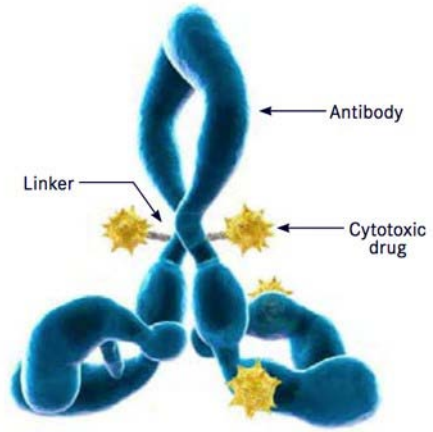
- Bortezomib 61%
- Carfilzomib 58%
- Lenalidomide 73%
- Pomalidomide 79%
- Daratumumab 55%

Grade ≥3 adverse events:

- Neutropenia 85%
- Thrombocytopenia 45%
- Anemia 45%
- Cytokine release sx 6%

Raje et al. N Engl J Med 2019

Targeting B-cell maturation antigen with GSK2857916 antibody–drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial

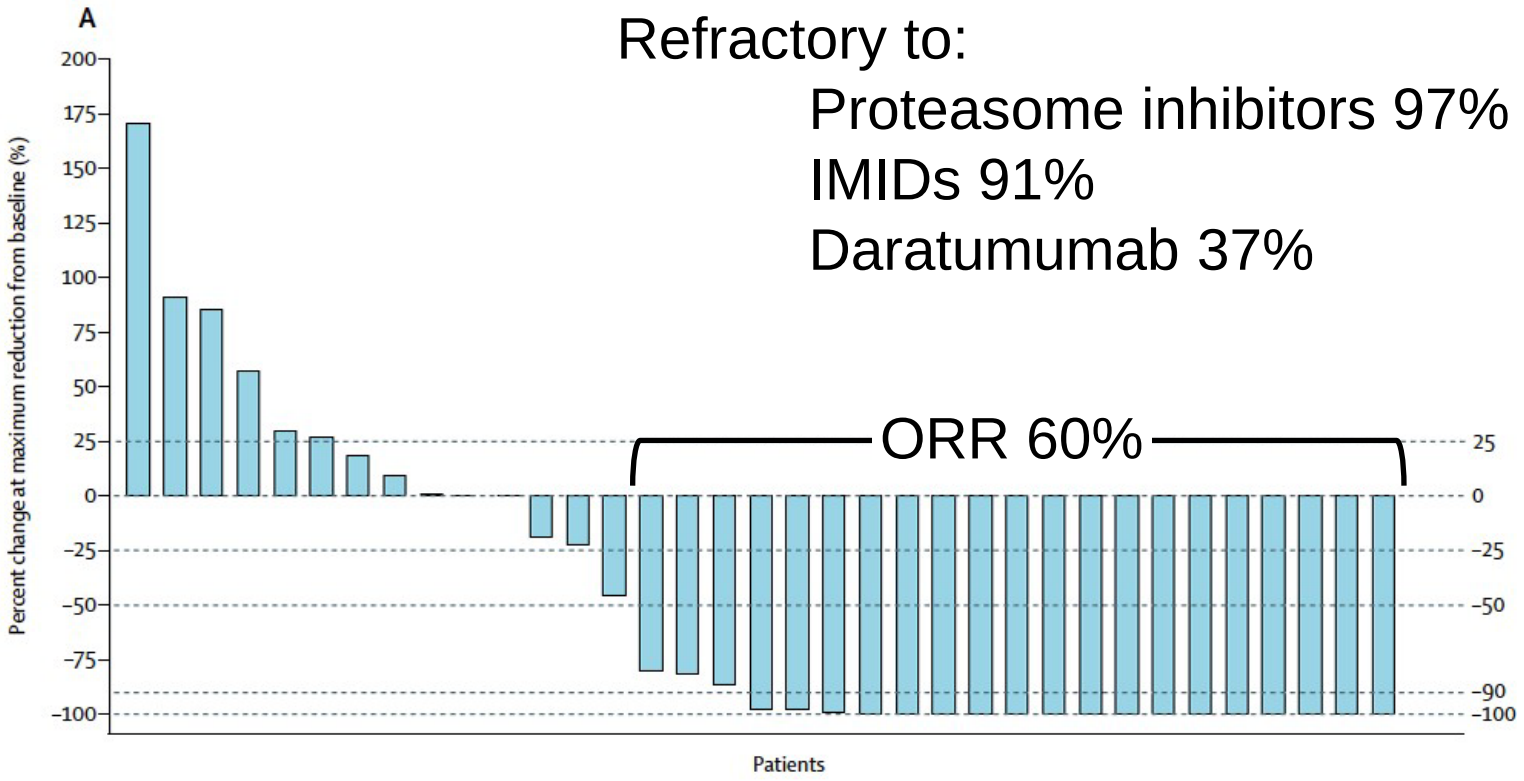


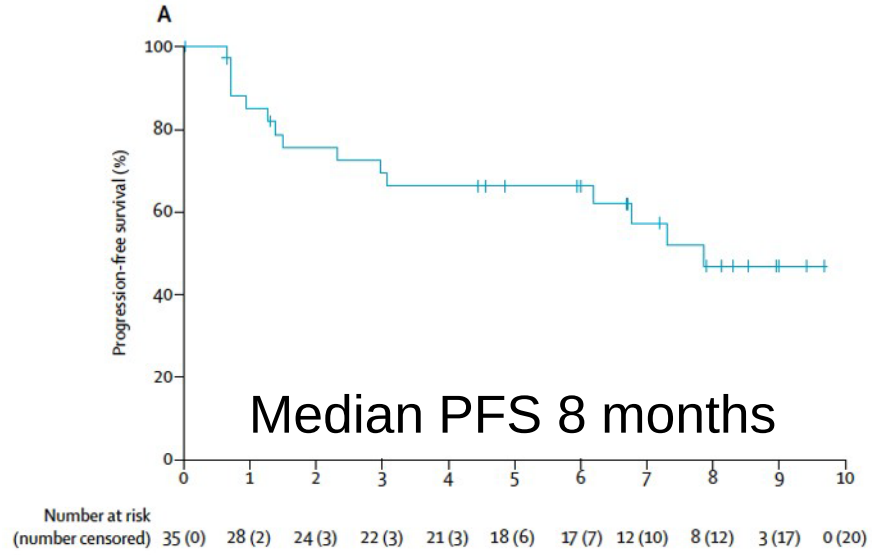
Refractory to:

Proteasome inhibitors 97%

IMIDs 91%

Daratumumab 37%



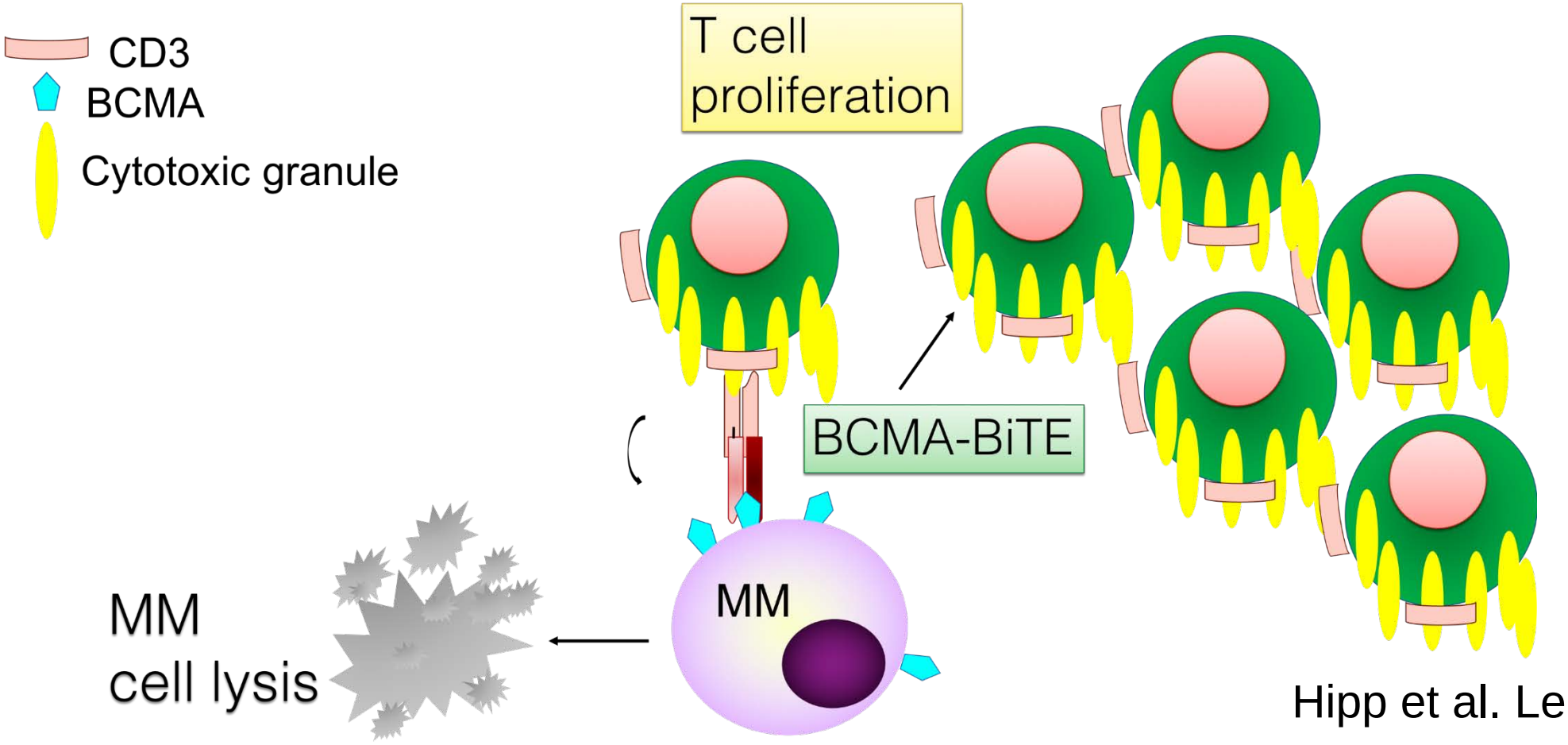


Median PFS 8 months

Trudel et al. Lancet Oncol 2018

BCMA directed therapy

Anti-BCMA Bispecific T-cell engager (BiTE)



Hipp et al. Leukemia 2017

Options for Relapsed/Refractory Multiple Myeloma

IMids	Proteasome Inhibitors	Monoclonal Abs	HDAC-inhibitor	BCL-2 inhibitor	XPO1 inhibitor	Anti-BCMA
Thalidomide	Bortezomib	Daratumumab	Panobinostat	Venetoclax[5]	Selinexor[6]	AMG 420[7] Anti-BCMA BiTE® BCMA-ADC-GSK Bb2121/CARs
Lenalidomide	Carfilzomib	Elotuzumab				
Pomalidomide	Ixazomib	Isatuximab[2]				
	Oprozomib[1]	MOR202[3]				
		Atezolizumab[4] (Anti-PD-L1 Ab)				

1. Hari et al. Abs 803, 2. Dimopoulos et al. Abs 155 3. Raab et al. Abs 153 4. Cho et al. Abs 597 5. Costa et al. Abs 303 6. Chari et al. Abs 598 7. Topp et al. Abs 1010

ASH 2018	Oprozomib Hari # 803	Isatuximab Dimopoulos # 155	MOR202 Raab # 152	Atezolizumab Cho # 597	Venetoclax Costa # 303	Selinexor Chari # 598	AMG 420 Topp # 1010
Mechanism	**PI**	**Anti-CD38 Ab**	**Anti-CD38**	**Anti-PD-L1 Ab**	**BCL-2 Inhibitor**	**XPO-1 inhibitor**	**Anti-BCMA BiTE**
	Oral (IR 200 mg/d) (IR) or (GR) Day 1-2 QW	IV 20 mg/kg QWx1, then Q2W	IV (30 min-2 hours) QW	IV 840 mg Cycle 1 Day 1,2, 16 Cycle2+ Day 1,15	Oral daily	Oral biWeekly	IV Continuous Infusion
Phase/N	1b/N=47	2/N=164	1/N=56	1b/N=40	1-2/N=42	2/N=123	FIH 1/N=35
Combination	O+Dex O+Pom+Dex	Isa or Isa+Dex	-MOR+Dex -MOR+Dex+Len -MOR+Dex+Pom	Atezo+dara Atezo+dara+len Atezo+dara+pom	Ven+Kyprolis+dex	Selinexor+Dex	Single agent
Prior Lines of Treatment	4 (1-17)	4 (2-11)	2-3	4 (1-10)	2 (1-3)	7 (3-18) Penta-refractory	4 (2-13)
ORR	~67%	Isa:26% ≥VGPR 8% IsaD 44% ≥VGPR 18%	-28% -65% -48%	Atezo+dara 26% Atezo+dara+len 57% Atezo+dara+pom70%	79%≥CR 38% +T11;14 100%	26.2% 2 sCR/MRD neg	6 CRs, 2 PR, 1 VGPR 400 mg ORR 83%
PFS	-------	Isa-4.86 months IsaD-9.26 months	-1.5 month -NR -15.9 months	------	-------	3.7 months	-----
Safety	GI NVD (1 GI bleeding), Anemia, Neutropenia, URI, Pneumonia	IR (40%) 4% d/c Back pain, URI, Pancytopenia	Pancytopenia, Hypertension, URI	G3 Rash G3 Elevated LFTs G3pancreatitis	GI, Pancytopenia, Pneumonia, CHF, AKI, TLS	GI, Pancytopenia, Fatigue, Weight loss, Hyponatremia	CRS, Polyneuropathy, Edema, Infections

CONCLUSIONS – Myeloma Therapies in Relapse

- There are a multitude of treatment options for relapsed Myeloma, it is important to think about optimal sequences individualizing management for patients (preference, comorbidities, disease/relapse characteristics)
- Early relapse
  - First line therapy if durable response
  - Monoclonal antibody based
  - Proteasome Inhibitor based – (High risk disease, PI sensitive)
- Later relapses
  - Pomalidomide based regimens
  - Clinical trial (CAR-T, BITE, Antibody drug conjugate)
  - Cytotoxic chemotherapy
- Need trials exploring the sequencing of drug combinations and optimal duration of treatment

THANK YOU!