Emerging Treatment Paradigms in Multiple Myeloma: Targeting the Neighborhood and Beyond

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Therapeutic Advances in Multiple Myeloma

Proteasome inhibitors: bortezomib, carfilzomib, ixazomib;
immunomodulatory drugs: thalidomide, lenalidomide, pomalidomide;
HDAC inhibitor: panobinostat; **monoclonal antibodies:** elotuzumab daratumumab, and isatuximab; **nuclear transport inhibitor:** selinexor

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

27 FDA approvals and median patient survival prolonged 3-4 fold, from 3 to at least 8-10 years, and MM is a chronic illness In many patients.

In 2019: 32,110 new cases: 18,130 men, 13,980 women
12,960 deaths: 6990 men, 5970 women

Even without CRAB (Calcium, Renal, Anemia, Bone) Myeloma Defining Events (IMWG) Include:

Bone marrow plasma cells ≥ 60%

Abnormal FLC ratio ≥ 100 (involved kappa) or <0.01 (involved lambda)

Focal bone marrow lesions on PET-CT and/or MRI

Treat as MM

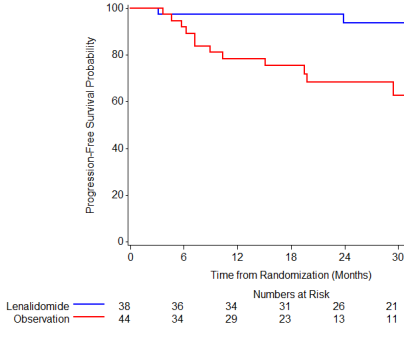
High Risk Smoldering MM (SMM)

≥ 2 factors: M protein >2gm/dL, BM plasma cells > 20%, FLC ratio >20)

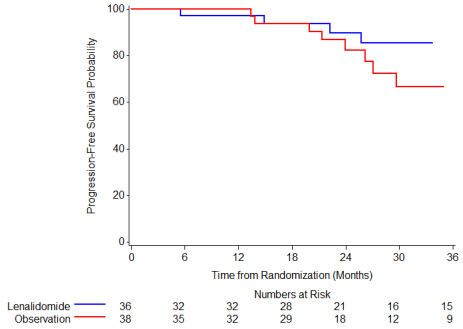
Protocols of novel agents/immune therapies to delay or prevent progression of high risk SMM to active MM.

Rajkumar et al. *Lancet Oncol* 2015; 12:e538-e548
Kumar et al Blood Cancer J 2018; 59

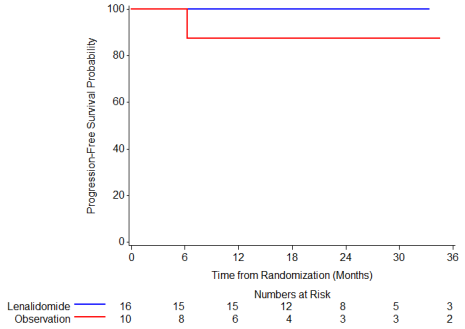
Continuous Lenalidomide (25 mg d1-21 of 28 d) vs Observation in SMM using Mayo 2018 Risk Criteria (>20% plasma cells. M protein> 2gm/dL, serum free lite chain ratio >20)



High Risk



Intermediate Risk



Low Risk

Decreased progression of high risk SMM to to MM

11.4% vs 3.4% secondary malignancies

51% discontinuation rate

No OS difference

Lonial et al J Clin Oncol 2020;38:1126-37.

Therapy for Newly Diagnosed MM Transplant Candidates

Triplets preferred

Lenalidomide (Len)/ Bortezomib (Bort)/ Dexamethasone (Dex) RVD

Cyclophosphamide (Cy)/Bort/Dex CyBorD

Carfilzomib RD if neuropathy KRD

Ixazomib RD all oral IRD

VRD equivalent to KRD in non high risk

Doublets

rarely used, ie Bort/Dex to improve renal dysfunction, then add Len

Quadruplets

VTD-Dara (Cassiopeia, FDA approved)

RVD-Dara (Griffin) deep responses , KRD, Ixa RD with or without Dara under evaluation

Elo RVD equivalent to RVD in high risk, Isa KRD active in high risk

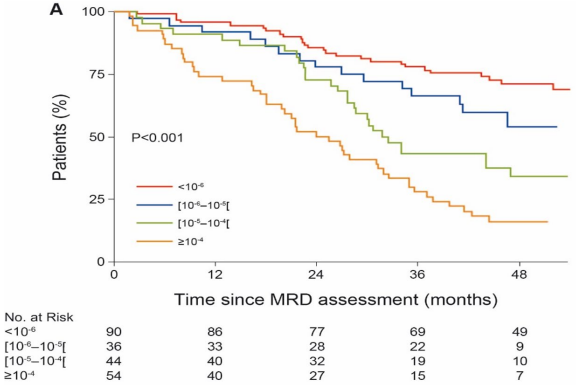
Maintenance

Len in standard risk, Bort or Len Bort high risk, MoAbs under evaluation

Role of Transplant and Minimal Residual Disease (MRD) as a Clinical Endpoint in Multiple Myeloma

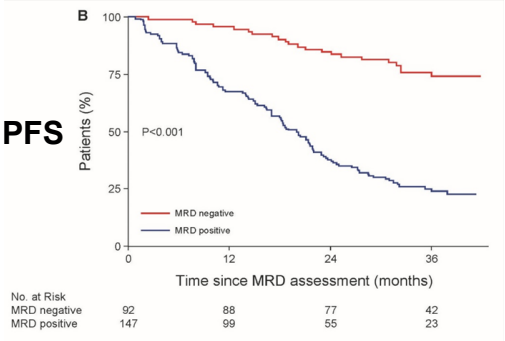
	RVD arm N=350	Transplant arm N=350	p-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

Attal et al NEJM 2017; 376: 1311-20

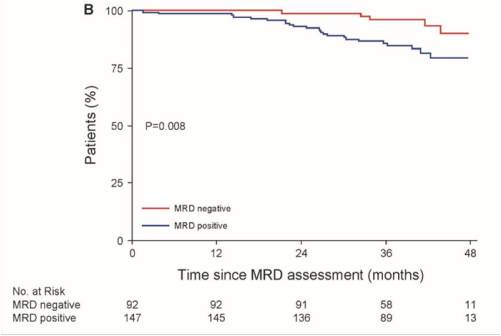


Defined the Sensitivity of the Test

PFS



OS

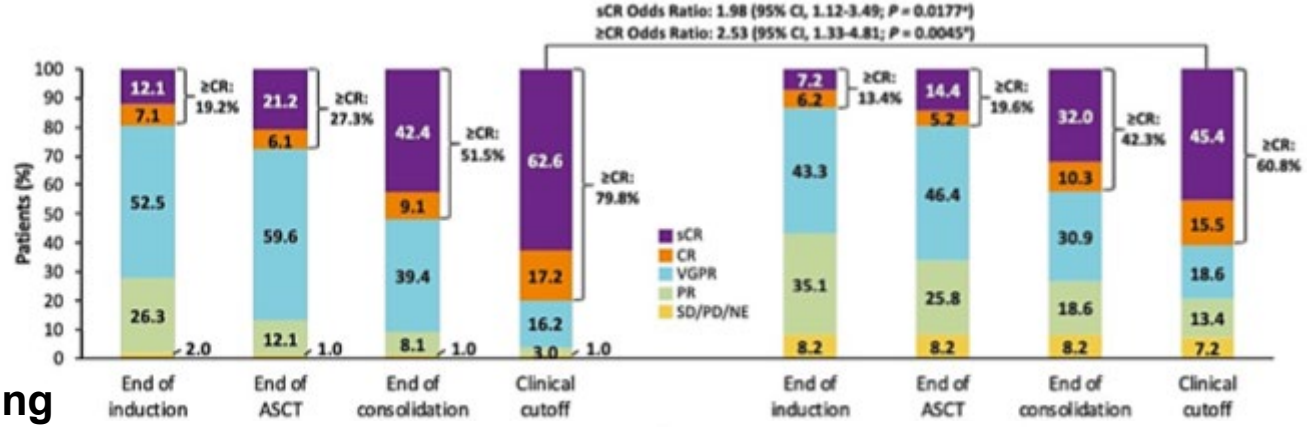


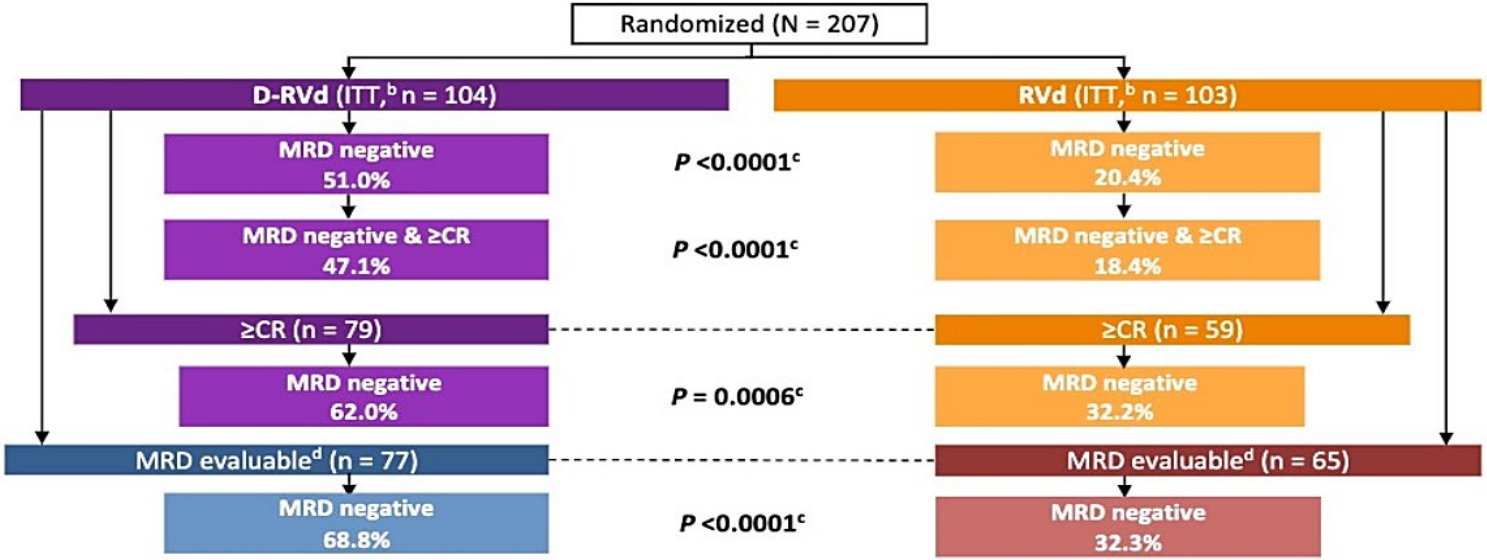
Validated Clinical Impact of MRD Negativity

Perrot A et al Blood 2018; 132:2456-64

Griffin: Dara/Len/Bor/Dex vs Len/Bor/Dex, ASCT, Consolidation, Maintenance

Response depth, including MRD, was greater for D-RVD





Voorhees et al
ASH 2019 Abst 691
Blood in press

Therapy for Newly Diagnosed MM Transplant Ineligible

Triplets preferred at attenuated dose/schedule:

Lenalidomide (Len)/ Bortezomib (Bort)/ Dexamethasone (Dex) RVD Lite

Cyclophosphamide (Cy)/Bort/Dex CyBorD

Carfilzomib RD if neuropathy KRD

Ixazomib RD all oral regimen IRD

Daratumumab RD DRD (Maia, FDA approved)

Doublets

Frail patients, ie Bort/Dex or Len/Dex at reduced doses

Quadruplet

Daratumumab MPV (FDA approved); RVD lite

R ixazomib D with or without MoAbs under evaluation

Maintenance

Len in standard risk, Bort or Len Bort in high risk, MoAbs under evaluation

Therapy for Relapsed MM:Triplets Preferred With Second Generation IMiDs, PIs, MoAbs

Active In Len and Bort refractory MM

Carfilzomib Pom Dex (no neuropathy)

Dara Pom Dex(FDA approved), Dara Carfilzomib Dex (deep responses)

Elo Pom Dex (well tolerated, FDA approved)

Active in Bort refractory MM

Elotuzumab Len/Dex (indolent relapse), Ixazomib Len

Dex (all oral), Carfilzomib Len Dex (no neuropathy), Dara Len dex (MRD- responses) (all FDA approved)

Active in Len refractory MM

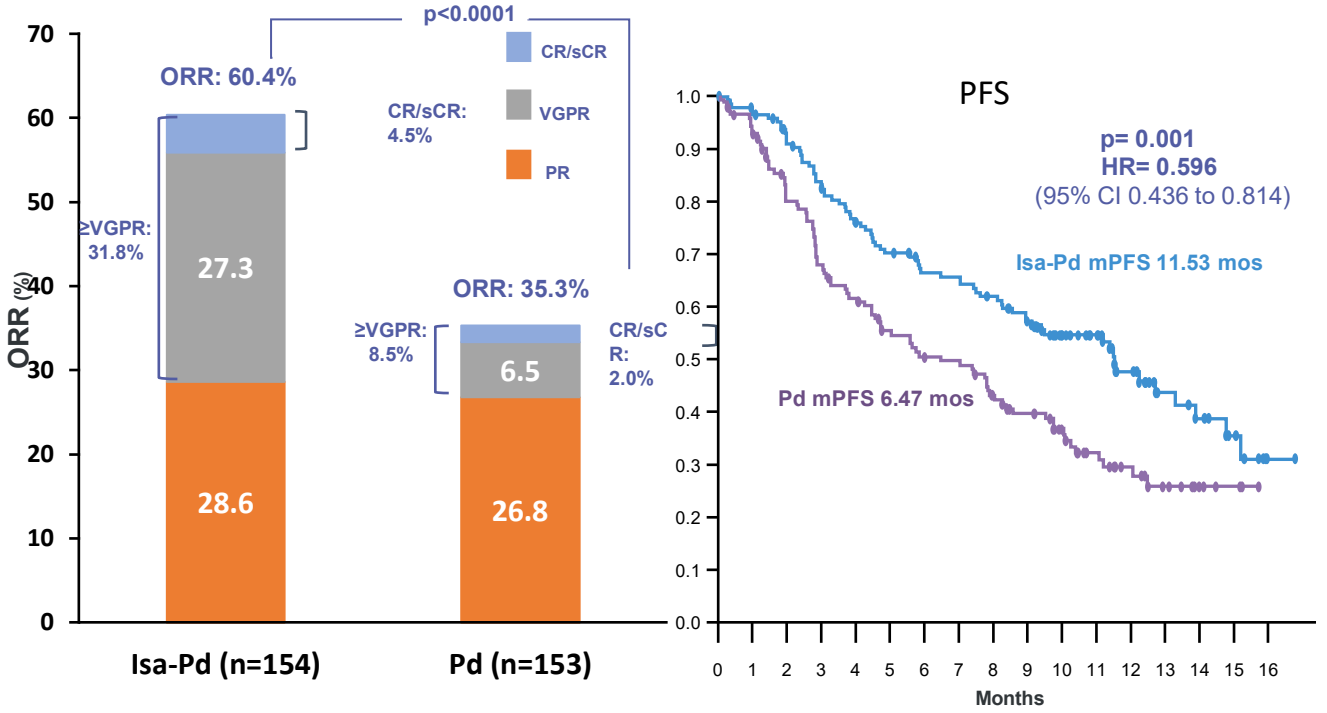
Pom Bort Dex, Dara Bort Dex (MRD- responses)(FDA approved)

Active in Len, Pom, Bort, Carfil, Dara refractory MM

Selinexor (side effects)(FDA approved)

Isatuximab (CD38 Ab with Distinct Mechanism from Daratumumab)
Pomalidomide, dexamethasone (Ipd) versus Pd in RRMM

FDA Approved

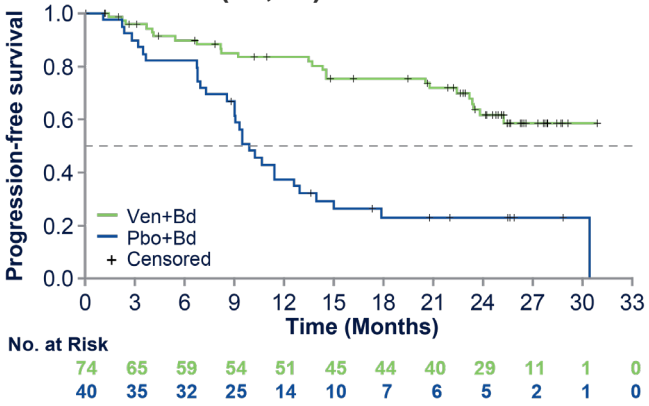


Isatuximab increases response rate and extent, prolongs PFS

Attal et al Lancet 2019; 394: 2072.

PFS is Significantly Prolonged with Venetoclax in Patients With t(11;14) or *BCL2*^{high}, but not in Patients With Non-t(11;14), *BCL2*^{low} MM

t(11;14) or *BCL2*^{high}

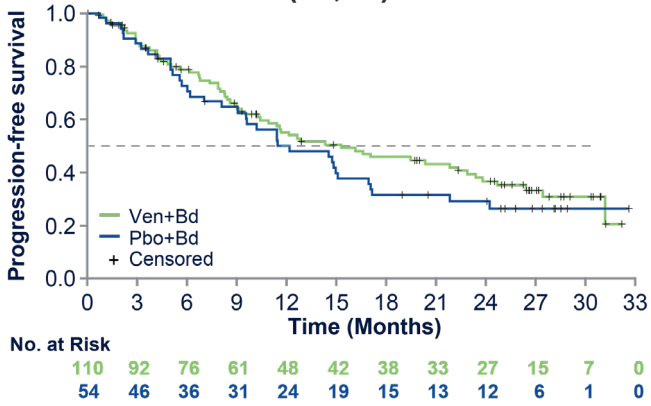


No. at Risk

Ven+Bd	74	65	59	54	51	45	44	40	29	11	1	0
Pbo+Bd	40	35	32	25	14	10	7	6	5	2	1	0

PFS	Ven+Bd	Pbo+Bd
Median, months	Not reached	9.9
HR (95% CI)	0.30 (0.17, 0.53)	
P value	<0.001	

Non-t(11;14) *BCL2*^{low}



No. at Risk

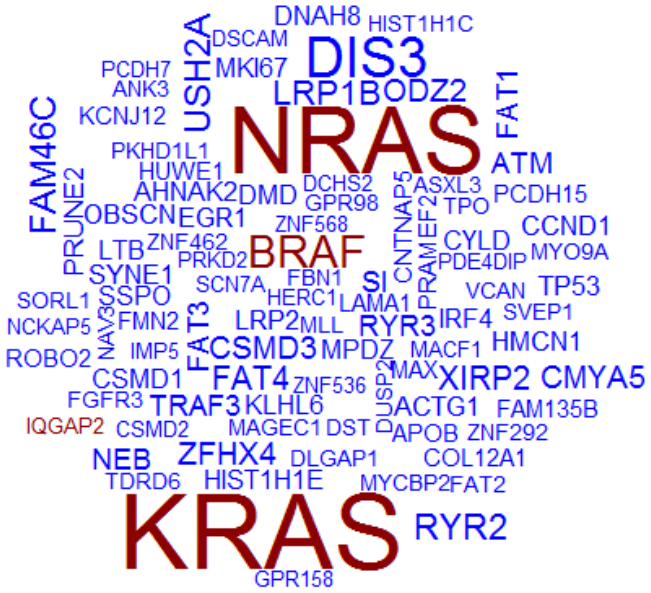
Ven+Bd	110	92	76	61	48	42	38	33	27	15	7	0
Pbo+Bd	54	46	36	31	24	19	15	13	12	6	1	0

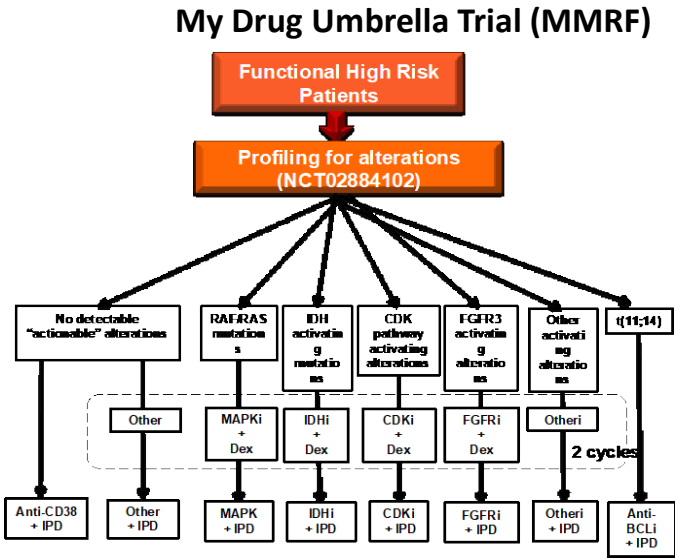
PFS	Ven+Bd	Pbo+Bd
Median, months	15.3	11.5
HR (95% CI)	0.85 (0.56, 1.30)	
P value	0.451	

High *BCL2* gene expression was determined by qPCR.

Harrison et al ASH 2019

Targeting Mutations in Multiple Myeloma





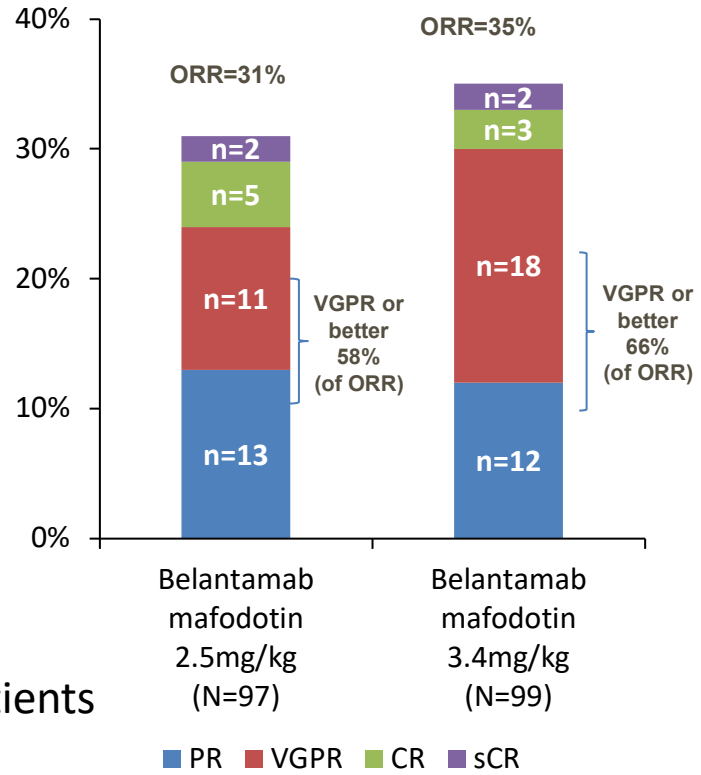
1. Targeting Ras Raf MAPK pathway achieves transient responses; combination clinical trials ongoing

2. AMG 510 targeting KRASG12C: 50% response in colorectal and lung (Fakih et al ASCO 2019)

Morgan GJ, Walker BA and Davies FE. Nature Reviews Cancer. 2012 Chapman *et al* Nature Genetics 2011, Walker et al 2012 Blood, Lohr et al Cancer Cell 2014, Bolli et al Nat Comm 2014, Walker BA et al Nat Comms 2015

BCMA Immunoxin: Belantamab Mafodotin 3.4mg/kg vs 2.5-mg/kg in RRMM (13 month followup)

	belantamab mafodotin 2.5mg/kg (n=97)	belantamab mafodotin 3.4mg/kg (n=99)
mOS	14.9 months (95% CI: 9.9-NR)	14.0 months (95% CI: 10-NR)
mDOR	**11.0 months (95% CI: 4.2-NR)**	6.2 months (95% CI: 4.8-NR)
mPFS	2.8 months (95% CI: 1.6-3.6)	3.9 months (95% CI: 2.0-5.8)
ORR*	31% (97.5% CI: 21.7-43.6)	35% (97.5% CI: 24.8-47.0)

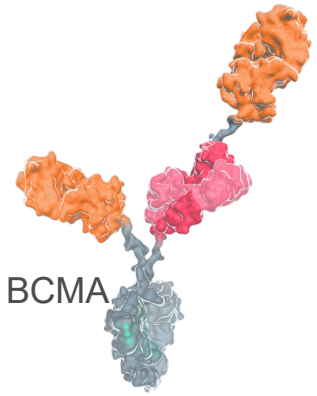


Keratopathy 27% (2.5mg/kg) and 21% (3.4mg/kg) patients

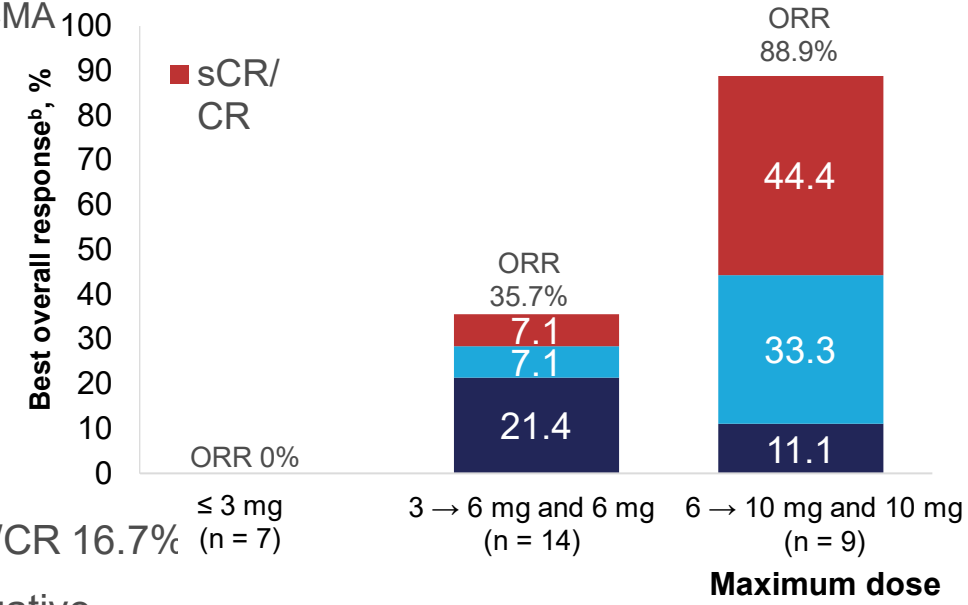
2.5mg/kg chosen for further studies

Lonial et al Lancet Oncol 2020; 21: 207-21.; ASCO 2020

CC-93269 Bivalent Bispecific T Cell Engager in Relapsed/Refractory Multiple Myeloma (RRMM)



Bivalent Bite



- ORR 43.3% (n = 30), sCR/CR 16.7%
- 40% (n = 12) pts MRD-negative
- 92.3% responders MRD negative
- CRS (%): 23 (76.7) first dose; 23 (76.7) second dose; 2 (7.4) third dose

Costa et al ASH 2019

BCMA CAR T CELLS ASCO 2020

Safety

	KarMMa	EVOLVE	CARTITUDE-1
ANC ≥G3, %	89	90	100
plts ≥G3, %	52	47	69
CRS: all, ≥G3,%	84, 6	89, 3	93, 7
Med. time to CRS, duration, days	1 (1-12) 5 (1-63)	2 (1-4) 4 (1-10)	7 (2-12) 4 (2-64)
ICANS: all, ≥G3,%	17, 3	13, 3	10, 3
HLH/MAS, %	--	5	? 7 (lfts)
Infections: all, ≥G3 %	69, --	40, 13	--, 19
Toci/steroid/ anakinra use, %	52/15/0	76/52/23	79/21/21

? This was not listed at MAS/HLH, I am just speculating → could this have been early MAS

Efficacy

	KarMMa (n = 128)	EVOLVE (n = 62)	CARTITUDE-1 (n = 29)
ORR, %	73 (66-81)	92	100
sCR/CR, %	33	36	86
MRD neg ≥10^{-5}, % (of evaluable)	94	84	81
PFS/DoR, months	8.8/10.7	NR*	NR**
Screened Apheresed Treated	150 140 128	--	35 35 29

* 300 x10^6 cell dose cohort (lowest) = PFS 9.3 months, other med F/U = 8.8 and 2.3 month
** 9 mo PFS = 86%

Munshi et al, Mailankody et al, Berjada et al
Discussant Krina Patel

Summary and Conclusions

- Novel agent trials to delay or prevent progression of SMM.
- Triplets standard, doublets in frail, four drugs promising in both transplant and non transplant NDMM
- ASCT with novel agents achieves MRD-, increased PFS
- Triplets achieve increased extent and frequency of response, PFS, and OS in relapsed MM
- GenomicTargets: Venetoclax, MyDrug
- Novel immune therapies: Isotuximab CD38 Ab, BCMA immunotoxin, Bites, and CAR T cells
- Combination targeted and immune therapies will achieve

MRD and restore patient anti-MM immunity, potential cure.