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

Kenneth C. Anderson, M.D.

Director, Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute;Kraft Family Professor
of Medicine Harvard Medical School

Consultant: Celgene, Bristol Myers Squibb, Millennium-Takeda, Sanofi-Aventis, Janssen, Gilead, Precision Biosciences, Tolero
Scientific Founder: Oncopep, C4 Therapeutics

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

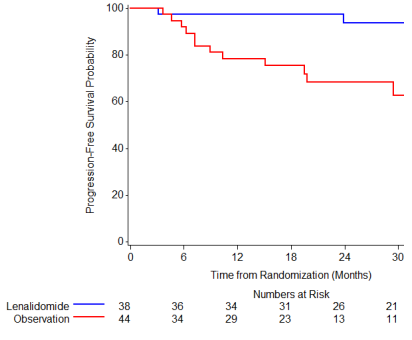
High Risk Smoldering MM (SMM)

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

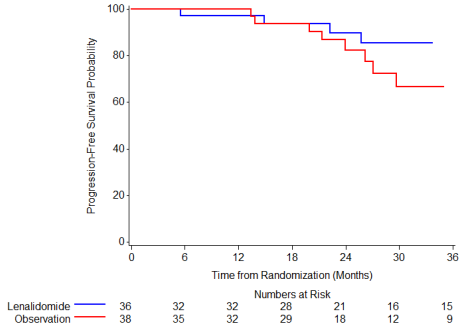
Protocols of novel agents/immune therapies to delay or prevent progression of high risk SMM to active MM.

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

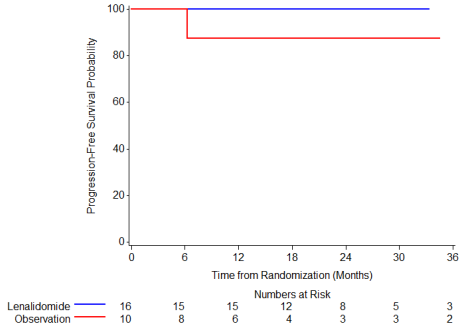
Continuous Lenalidomide (25 mg d1-21 of 28 d) vs Observation in SMM using Mayo 2018 Risk Criteria (>20% plasma cells. M protein> 2gm/dL, serum free lite chain ratio >20)



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

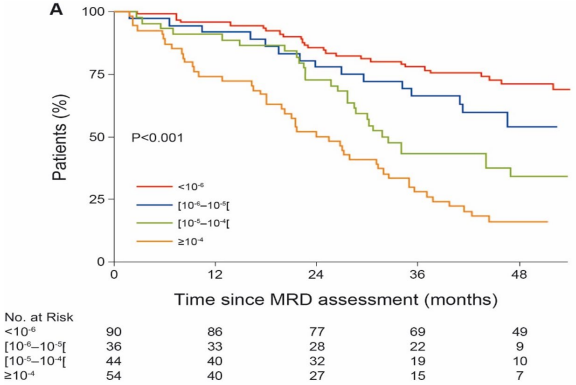
Maintenance

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

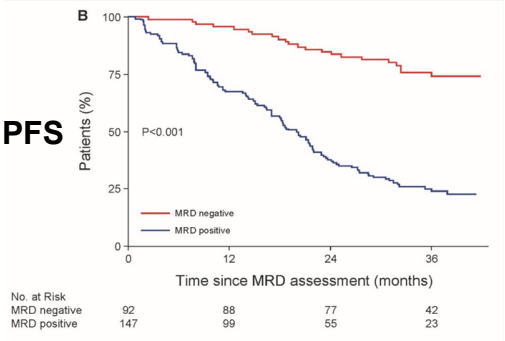
	RVD arm N=350	Transplant arm N=350	p-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

Attal et al NEJM 2017; 376: 1311-20

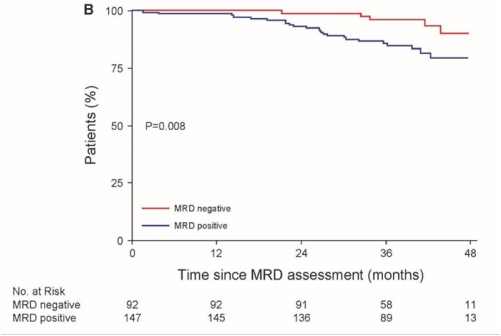


Defined the Sensitivity of the Test

PFS



OS



Validated Clinical Impact of MRD Negativity

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

Carfilzomib, Lenalidomide, and Dexamethasone (KRd) versus Bortezomib, Lenalidomide, and Dexamethasone (VRd) for Non Transplant NDMM (ENDURANCE)

In patients with standard or intermediate risk NDMM not intended for early ASCT, **KRd does not improve PFS compared with VRd**

KRd is associated with a higher VGPR rate

Higher rate of peripheral neuropathy with VRD, rate of cardio-pulmonary and renal toxicity higher with carfilzomib

No difference in overall survival

VRd should remain the standard of care for initial therapy of multiple myeloma

Kumar et al, ASCO 2020

Isatuximab, Carfilzomib, Lenalidomide, Dexamethasone (Isa KRD)Induction Therapy for High Risk MM

HR: del17p, t(4:14), +1q21, ISS2/3

Isa-KRD 100% ORR, 90% ≥VGPR, 46% CR/sCR

20 of 33 MRD- (Arm A, ASCT)

Stem cell collection feasible-after cycle 3 induction

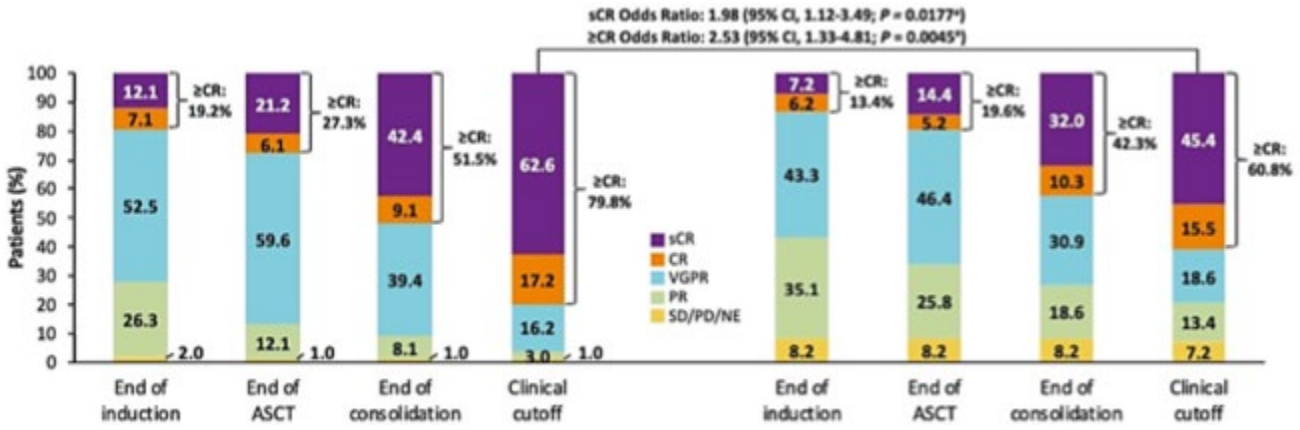
Well tolerated in transplant eligible and ineligible NDMM

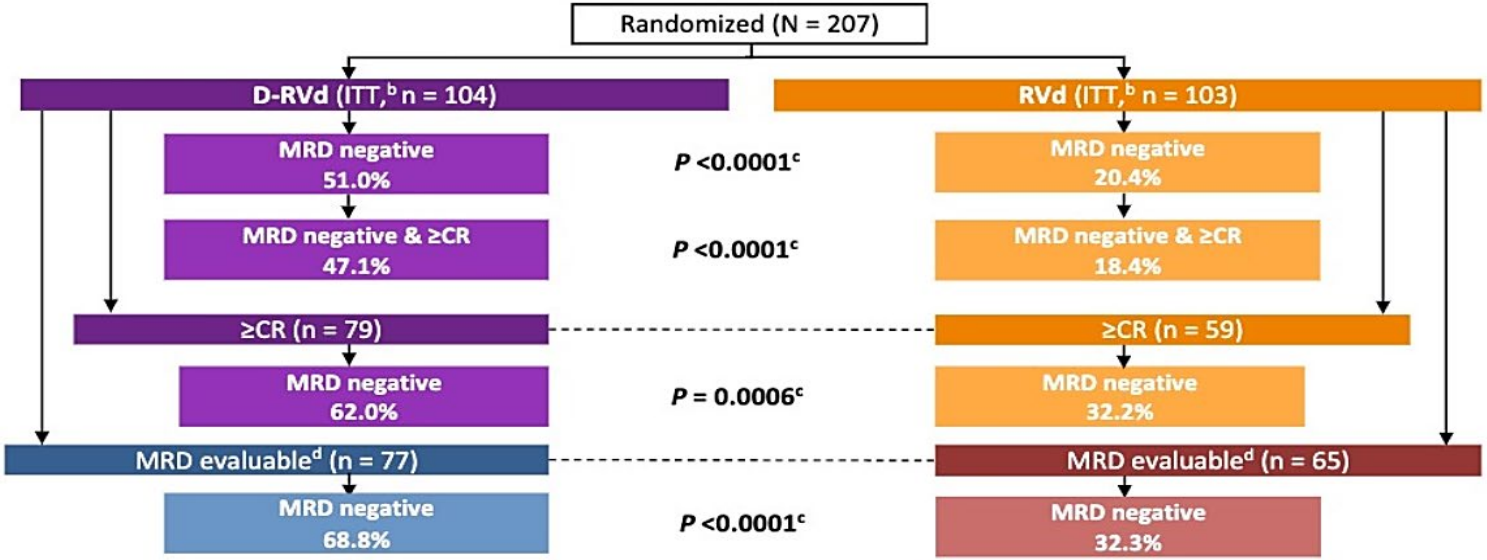
Conclusion: Quadruplet Isa-KRD is an effective induction therapy in high risk myeloma

Weisel et al ASCO 2020

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

	D-RVD	RVD
sCR	62.6%	45.4%
MRD-	51%	20.4%
2yr PFS	95.8%.	89.8%





Voorhees et al
ASH 2019 Abst 691;
Blood 2020 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

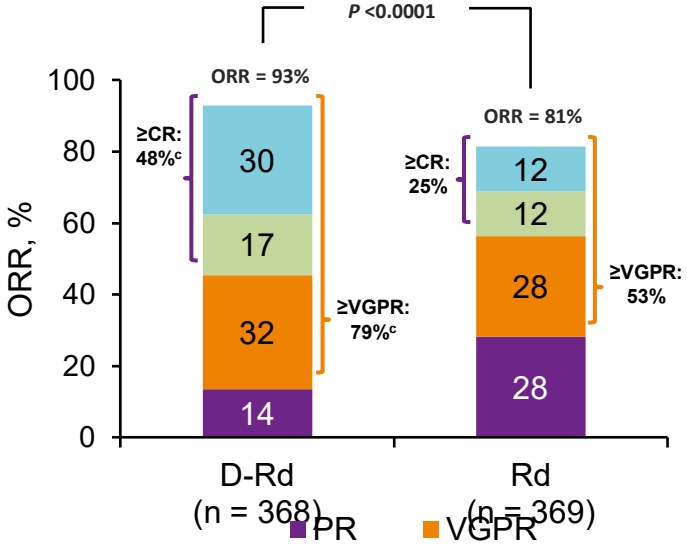
Maintenance

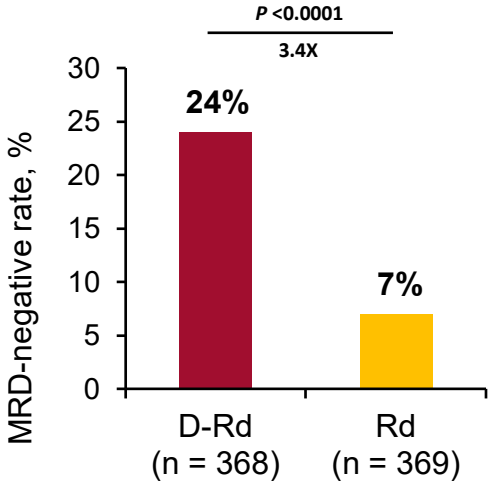
Len in standard risk, Bort or Len Bort in high risk, MoAbs under evaluation

Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Rd in Newly Diagnosed Multiple Myeloma Ineligible for Transplant (MAIA)

FDA approved June 2019

Facon et al, NEJM 2019; 380: 2104-15.

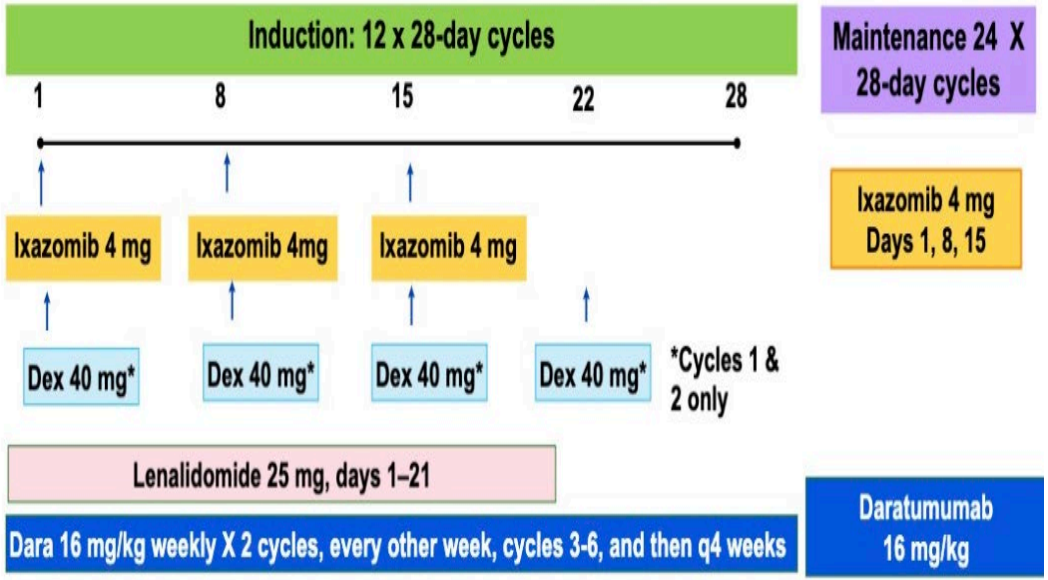


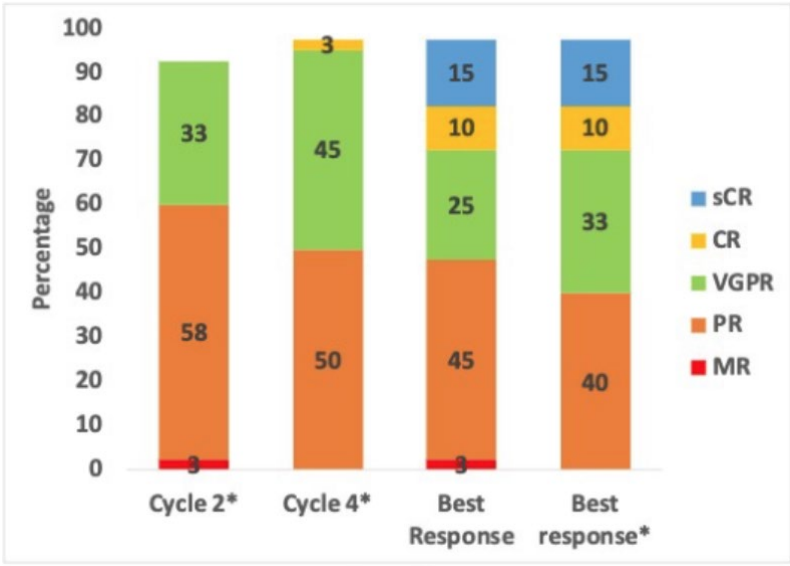


Significantly higher ORR, ≥CR rate, ≥VGPR rate, and >3-fold higher MRD-negative rate with D-Rd

- **Lower risk of progression or death with MRD negativity**

Dara Ixazomib Len Dex in NDMM





Daratumumab in combination with ixazomib, lenalidomide and modified dose dexamethasone is an effective frontline regimen

Rapid responses observed; deepening of responses over time

The regimen is well tolerated, with low rate of dose reductions

Kapoor et al
ASH 2019 Abstr 864

ND High Risk MM: Bortezomib,Lenalidomide, Dexamethasone (RVd) with or without Elotuzumab Induction, Reduced RVd Maintenance

High risk: HR GEP, t(14;16), t(14;20), del (17p), amp 1q21, PCL, LDH

Median PFS RVd Elo 31 mo vs RVd 34 mo, HR0.98, p=0.449

OS RVd Elo 68 mo vs RVd NR, HR 1.279, p=0.478

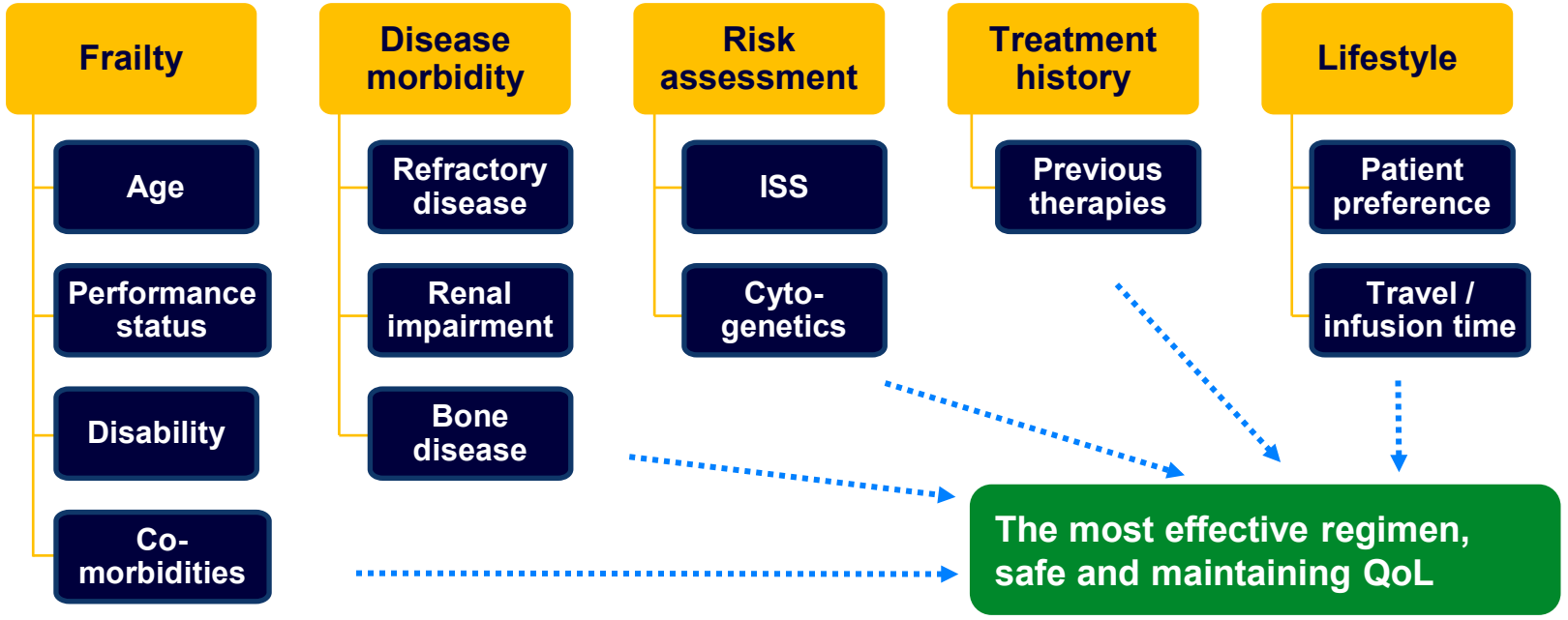
Grade >3 infections RVd Elo 16% vs RVd 8%

Conclusions: No difference in PFS or OS with addition of Elo

Supports RVd maintenance in HR MM

Usmani et al ASCO 2020

Disease and Patient Factors Influence Treatment Choices in RRMM



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) Isatuximab pom dex (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

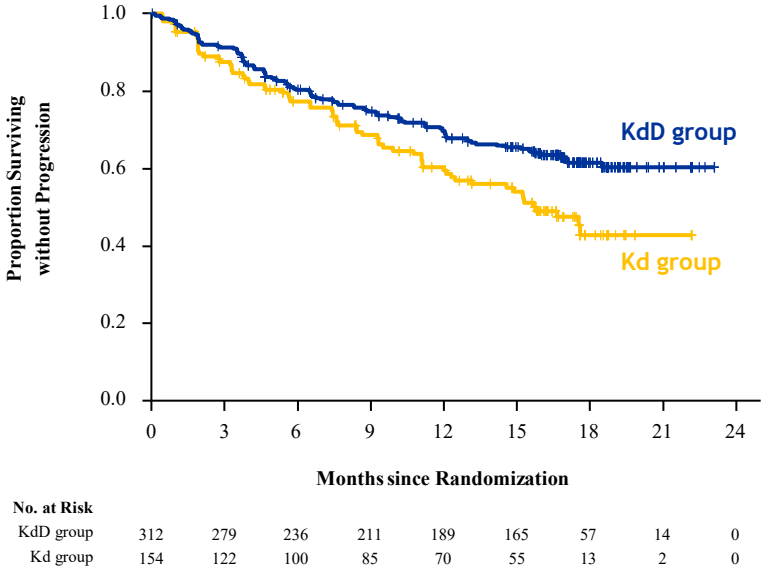
Pom Bort Dex, Dara Bort Dex (MRD- responses)(FDA approved)

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

Selinexor (side effects)(FDA approved) Belantomab mafodotin (FDA approved)

Kyprolis Dex+Daratumumab (KdD) versus Kd (n=466)

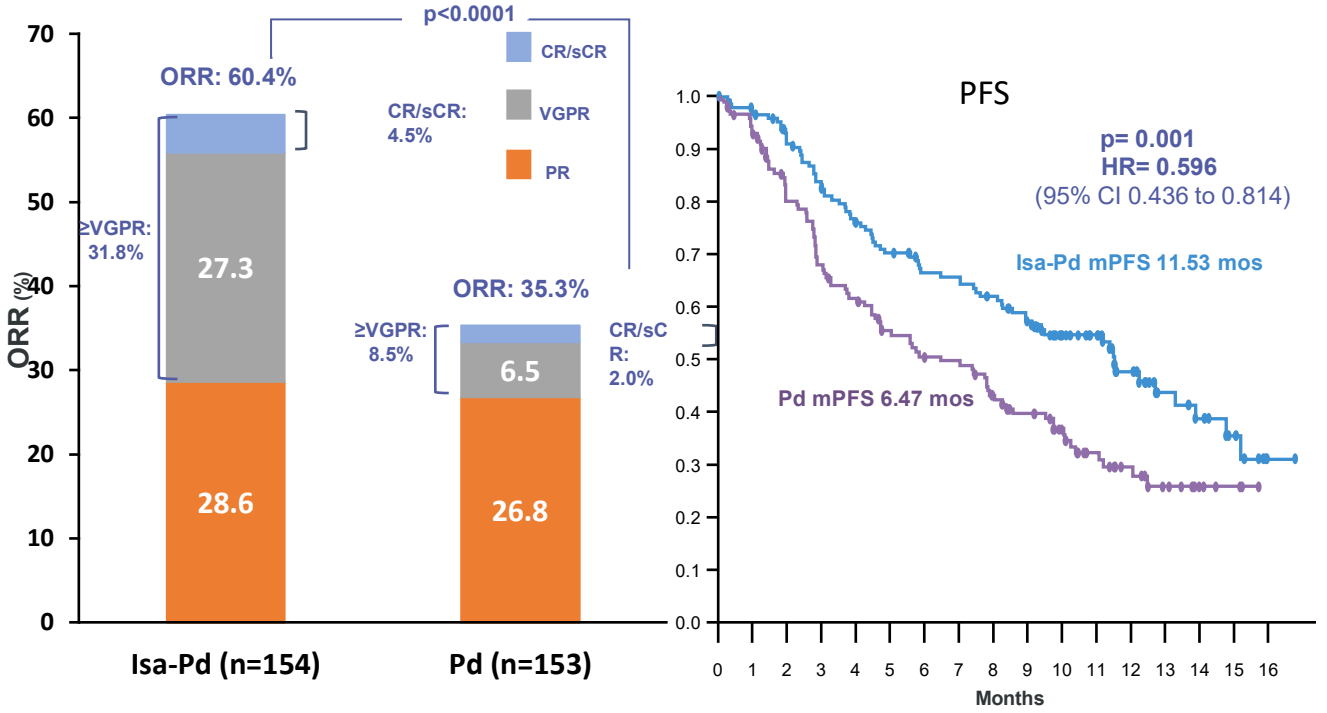
	KdD (n=312)	Kd (n=154)
ORR, %	84.3	74.4
CR, %	28.5	10.4
MRD Negative, %	12.5	1.3
Median follow-up time, months	16.9	16.3
Median PFS, months	**NE**	**15.8**
HR (KdD/Kd) (95% CI)	**0.63 (0.46–0.85)**	
p-value (1-sided)	0.0014	



Usmani S et al.ASH2019: LBA-6.

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.

IKEMA Study: Isatuximab Kyprolis Dex (Ikd) versus Kd (n=302 pts)

	IsaKd (n=179)	Kd (n=123)
ORR, %	86.6	82.9
CR, %	39.7	27.6
MRD negative, %	29.6	13
Median follow-up time, months	20.7	
Median PFS, months	**NE**	**19.15**
HR (IsaKd/Kd) (95% CI)	**0.53 (0.318-0.889)**	
p-value (1-sided)	0.0007	

- Efficacy across the different subgroups
- Toxicity profile seems to be aceptable
  - **AEs leading to discontinuation were more frequent in Kd than Isa-Kd (8.4% Isa-Kd vs 13.8% Kd).**
  - Treatment-emergent SAEs and fatal TEAEs were similar in Isa-Kd and Kd.
  - Infusion reactions were reported in 45.8% (0.6% grade 3-4) Isa-Kd and 3.3% (0% grade 3-4) Kd.
  - Grade ≥3 respiratory infections (grouping) in 32.2% Isa-Kd vs 23.8% Kd. Grade ≥3 cardiac failure in 4.0% Isa-Kd vs 4.1% Kd.

Moreau P et al. LBA EHA 2020

Selinexor in RRMM

- Inhibits XPO1
  - XPO1 is the major nuclear export protein
  - XPO1 is overexpressed in MM
- STORM Study
  - N = 122; median 7 prior treatments
  - 86% refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
  - Selinexor/Dex
  - 19.7% PR, 4.9% VGPR, 1.6% sCR
  - mDOR = 4.4 months
  - Associated with hematologic and GI toxicity
    - Aggressive supportive care needed

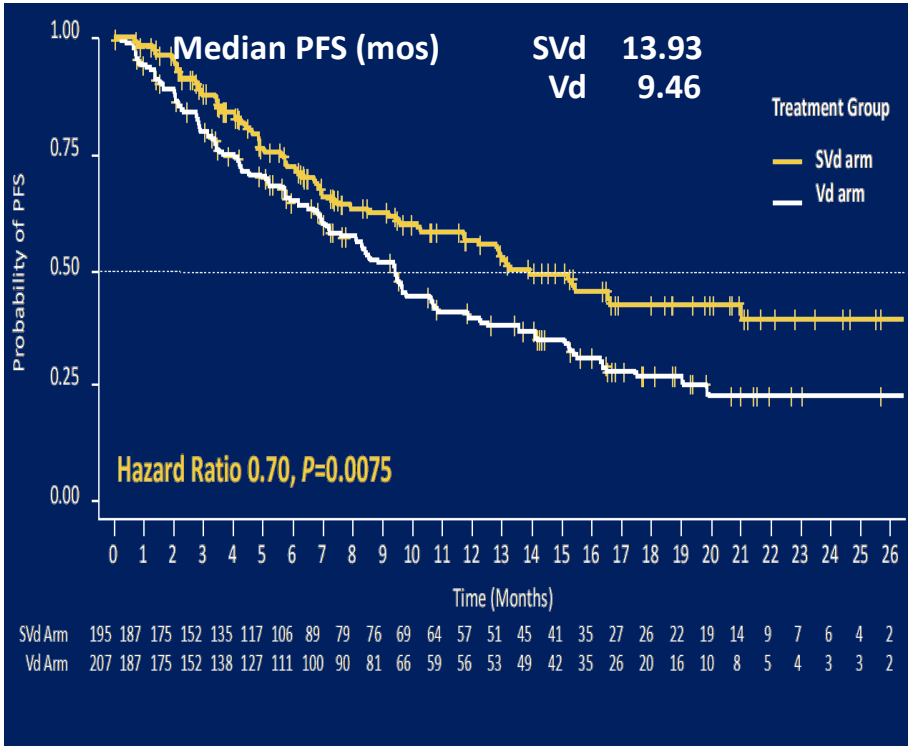
STOMP Study

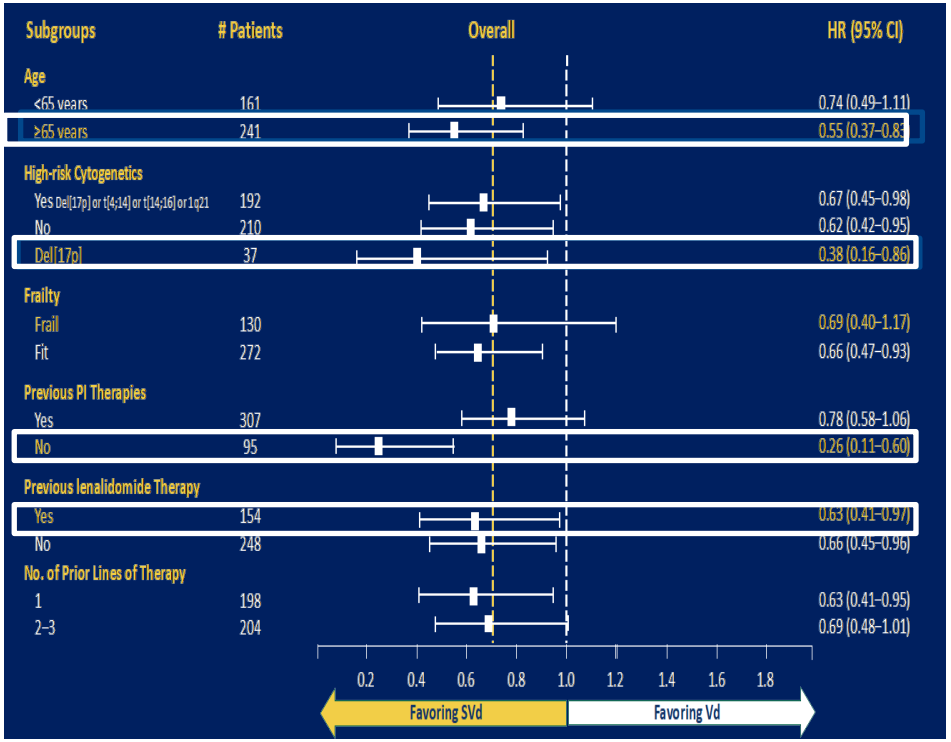
Pom dex selinexor

56% response in pom naïve RRMM (PFS 10.4mo, n=32)
36% response in pom exposed RRMM (n=14)
Associated with hematologic, GI, and constitutional toxicity

Chari NEJM 2019
Chen Ash 2019 abstr 19

BOSTON Trial: Selinexor-Vd vs Vd in Patients with Multiple Myeloma who Had Received 1-3 Prior Therapies





Dimopoulos MA et al ASCO 2020

Selinexor, Daratumumab, and Dexamethasone in Patients with Relapsed/Refractory MM

≥3 lines of prior therapy PI, IMiD or IMiD PI refractory

R2PD: 100mg (31 pts) selinexor with Dara 16mg/kg per label and Dex 40mg weekly

ORR 73% in daratumumab naïve patients

Median PFS 12.5 months in pts with median 3 prior therapies

Common treatment related SAEs: thrombocytopenia, anemia, neutropenia, nausea, dysgeusia, anorexia and fatigue

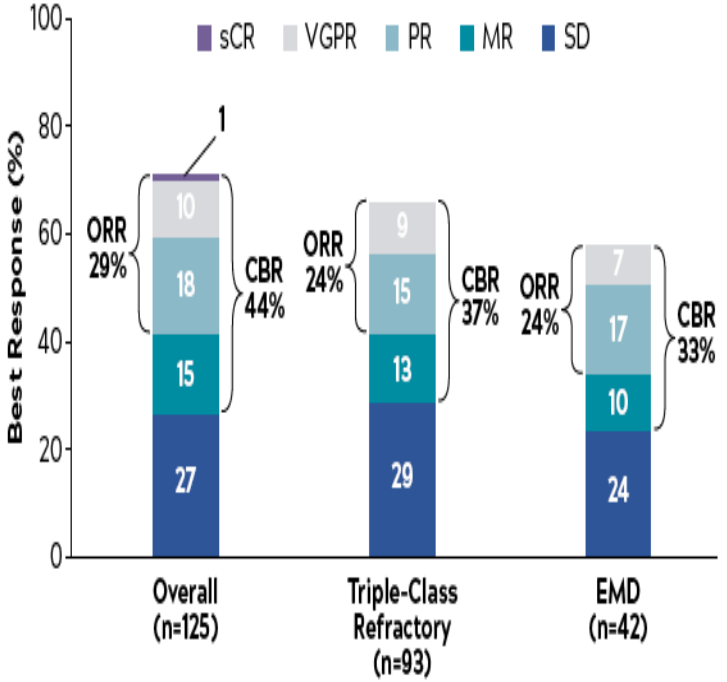
Conclusion: Selinexor weekly with Dara/Dex is active in RRMM.

Gasparetto et al, ASCO 2020

Horizon: Melflufen/Dex in RRMM (pomalidomide, anti-CD38, or both)

Melflufen: Lipophilic peptide-conjugated alkylating agent targets the malignant cell
Peptidases are expressed in MM which cleave Melflufen, entrapping hydrophilic alkylators in MM cell

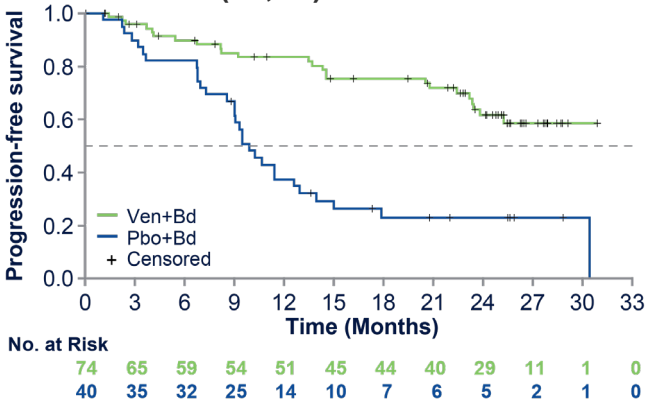
HORIZON ORR 29%
ORR in triple-class refractory disease: 24%
7.5 mo DOR, 4.0 mo mPFS, 11.3 mo mOS
ORR in EMD: 24%; 3.0 mo mPFS; 5.1 mo mDOR
Grade 3/4 hematologic AEs high



Mateos et al ASH 2019 Abstract 1883,
Richardson et al Lancet Hematol, in press

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}

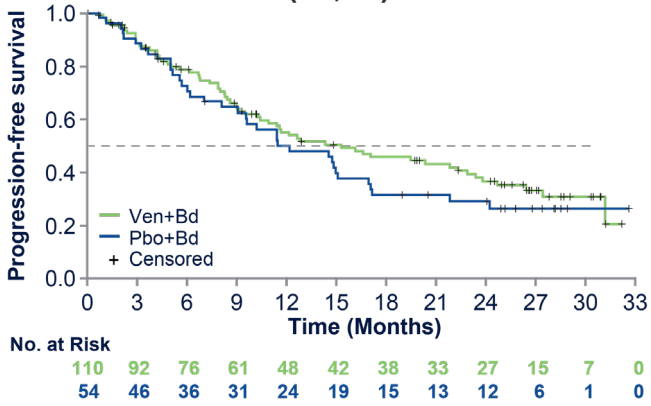


No. at Risk

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

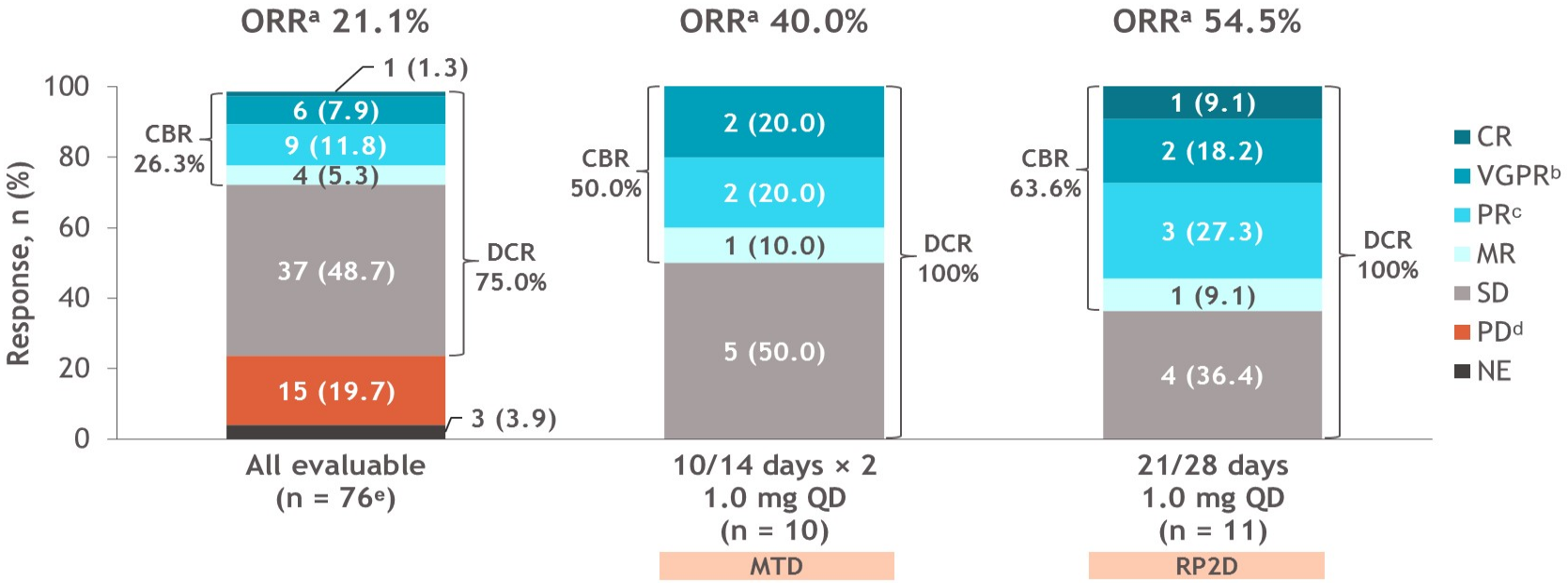
PFS	Ven+Bd	Pbo+Bd
Median, months	15.3	11.5
HR (95% CI)	0.85 (0.56, 1.30)	
P value	0.451	

High *BCL2* gene expression was determined by qPCR.

Harrison et al ASH 2019

CELMod CC-92480 and Dexamethasone in RRMM

Best response

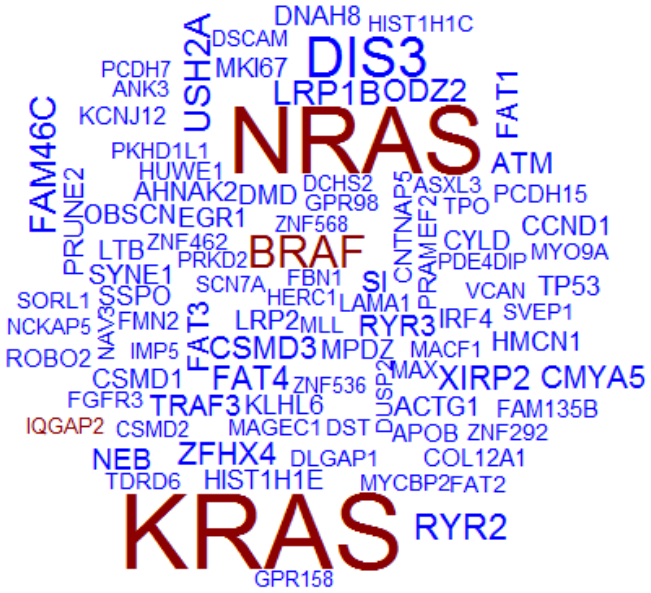


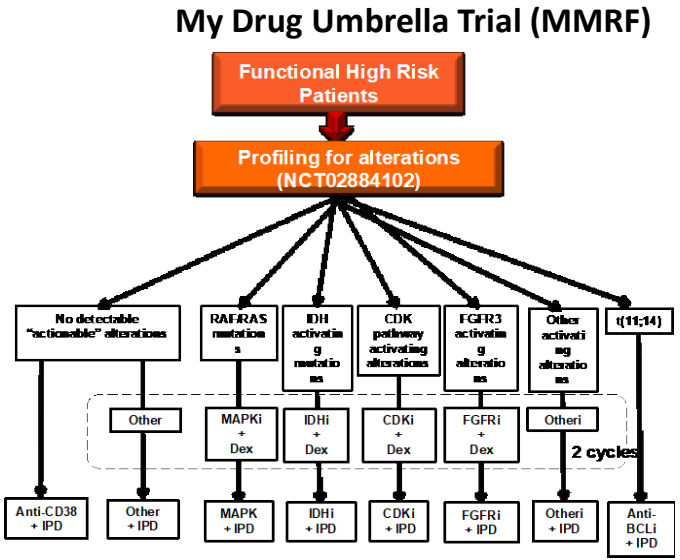
- At the RP2D 1.0 mg QD 21/28 days, 7 out of 11 patients were triple-class-refractory[f]
  - 1 patient had CR, 1 VGPR, 2 PR, and 1 MR

[a]PR or better; [b]1 patient in the 21/28-day 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date; [c]2 patients in the 21/28-day 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date; [d]1 patient in the 21/28-day 0.8 mg QD cohort had an unconfirmed PD as of the data cutoff date; [e]1 patient had a pending response assessment at data cutoff date; [f]Defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.

CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; MR, minimal response; MTD, maximum tolerated dose; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RP2D, recommended phase 2 dose; SD, stable disease; VGPR, very good partial response.

Targeting Mutations in Multiple Myeloma



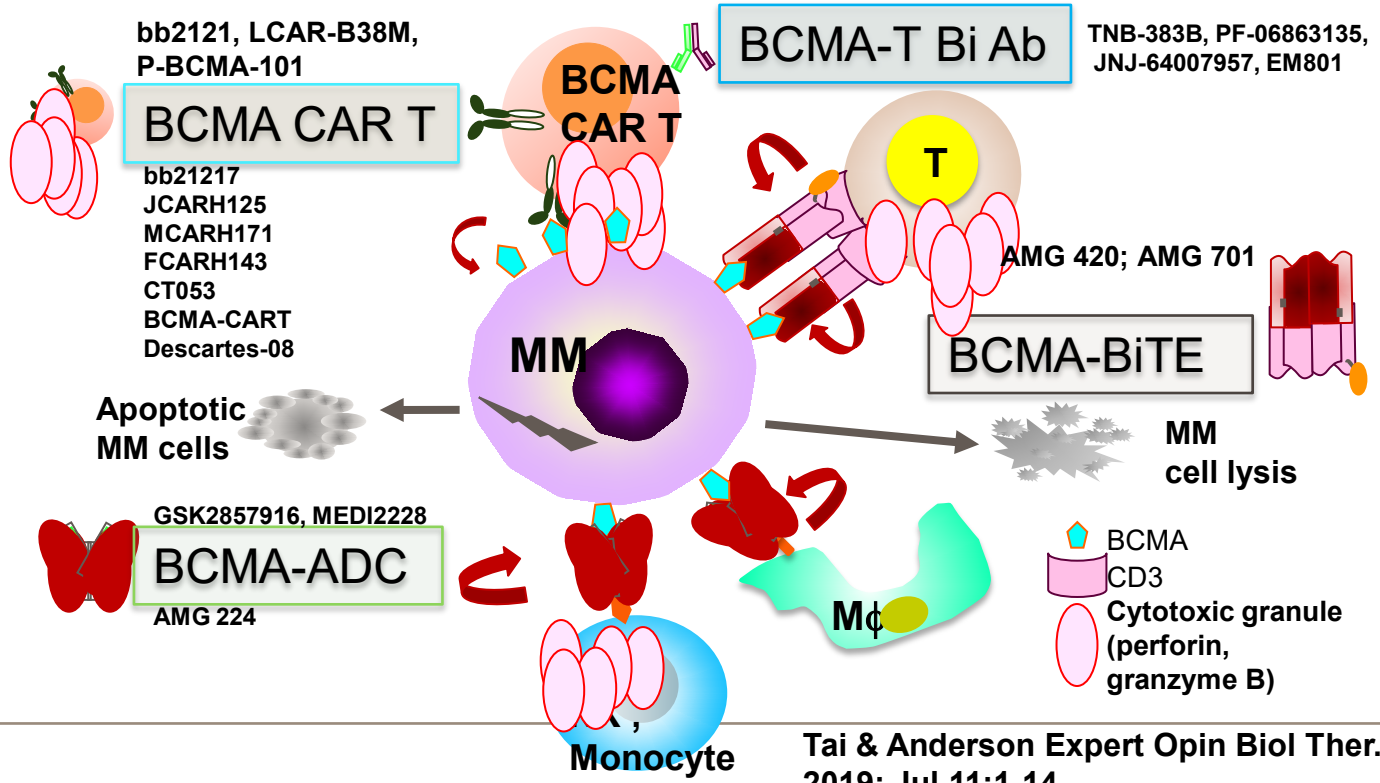


1. Targeting Ras Raf MAPK pathway achieves transient responses; combination clinical trials ongoing

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

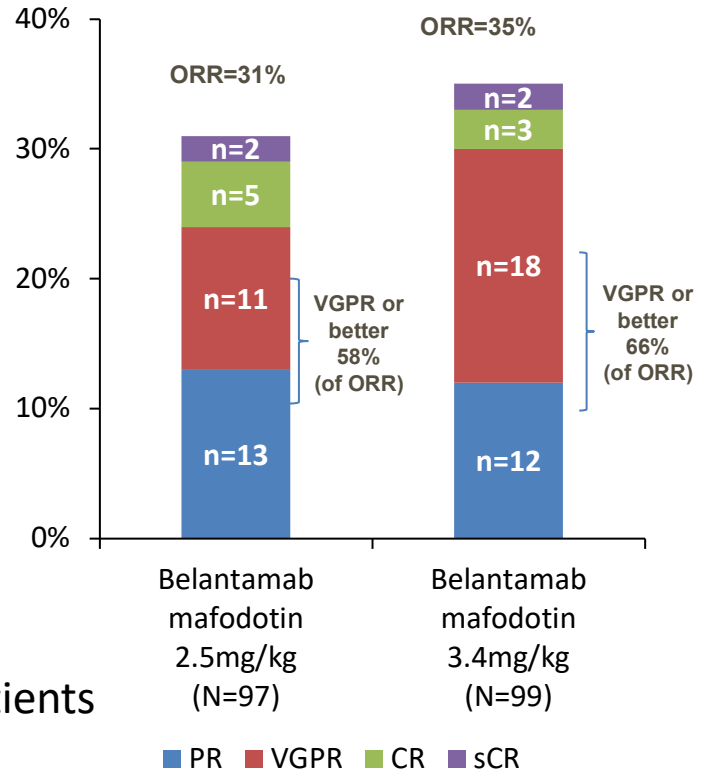
BCMA-Targeted Immunotherapy in MM



Tai & Anderson Expert Opin Biol Ther. 2019; Jul 11:1-14.

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

	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)

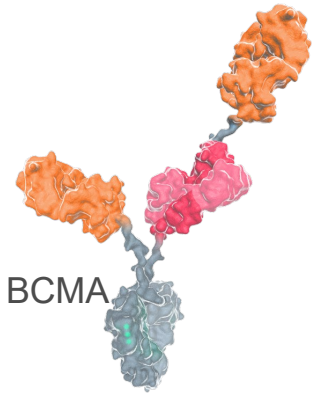


Keratopathy 27% (2.5mg/kg) and 21% (3.4mg/kg) patients

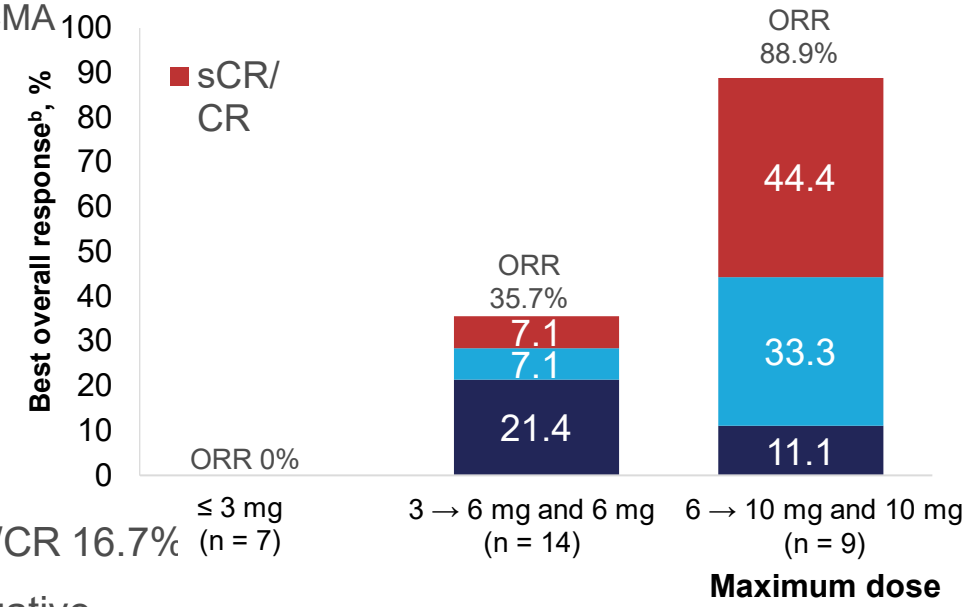
2.5mg/kg chosen for further studies

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

Characteristics Summary

	KarMMa: idecabtagene vicleucel (n=128)	EVOLVE: orvacabtagene autoleucel (n=62)	CARTITUDE-1: JNJ-4528 (n = 29)
Age	61 (33-78)	61 (33-77)	60 (50-75)
High Risk Cytogenetics, %	35	41*	27
Tumor Burden in BM, %	>50% PC = 51	—	≥60% PC = 24
Extramedullary PCs, %	39	23	10
Median prior lines of therapy	6 (3-16)	6 (3-18)	5 (3-18)
Triple refractory, %	84	94	86
Bridging therapy, %	88	63	79
Unique properties	Human BCMA, 4-1BB, CD3z	Modified spacer, CD4:CD8 enriched for CM	Median cell dose **$0.72x10^6$** cells/kg 2 BCMA single chain antibodies

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

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

Future BCMA Cellular Therapies

- **Expansion with PI3K inhibitor to enhance T memory cells (bb21217): early evidence of memory cells and persistence of CAR T cells (83% OR, 10/10 MRD-, 2 pts 15, 18 mo)**

  Shah et al ASH 2018, Berdeja ASH 2019

- **Combination of fixed ratio T4 and T8 cells: enriches for central memory T4 and T8 cells**

  Malinkody et al ASH 2018

- **"Universal" normal donor CAR T cells**

- **RNA CARs**

  Tai et al 2019

- **Peptide stimulated T-cells with vaccine**

  Bae et al Leukemia, in press

- **Combinations ie, vaccination, IMiDs, checkpoint inhibitors to prevent T cell exhaustion and prolong response**

;

Summary and Conclusions

Myeloma defining events even in the absence of CRAB include: BM plasma cells ≥ 60%; FLC ratio ≥ 100 (involved kappa) or <0.01 (involved lambda); focal bone marrow lesions on PET-CT and/or MRI

Immunologic therapies under evaluation to delay progression of high risk SMM (≥ 2 factors: M protein >2gm/dL, BM plasma cells > 20%, FLC ratio >20) to MM

Triplets standard, doublets in frail pts, four drugs under evaluation to treat all newly diagnosed MM.

ASCT with novel agents achieves MRD negativity, increased PFS/OS, remains standard of care

Summary and Conclusions

Choice of therapy for relapsed MM dependent on clinical features and prior therapy

Triplets achieve increased extent and frequency of response, PFS, and OS in relapsed MM

Novel protocol therapies include: melflufen, venetoclax, CELMoDs, and MyDrug

Novel immune approaches include BCMA directed immunotoxin, bispecific T cell engagers, and CAR T cells.

Future Directions

Combination targeted and immune therapies defined in preclinical studies will be used to treat subsets of patients, defined by profiling and informed by biomarkers, N.B. no need for large phase II/III trials to show small improvements.

Long term disease free survival and potential cure of MM will require both minimal residual disease negativity, and restoration of host anti-MM immunity. These patients will then be free of disease and off all therapy.