Multiple Myeloma: The Cure Around the Corner

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Disclosures

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Full-time/Part-Time Employee: none

Other: none

Therapeutic Advances in Multiple Myeloma (MM)

Proteasome inhibitors: bortezomib, carfilzomib, ixazomib; immunomodulatory drugs: thalidomide, lenalidomide, pomalidomide; HDAC inhibitor: panobinostat; monoclonal antibodies: elotuzumab daratumumab, and isatuximab; nuclear transport inhibitor: selinexor; immunotoxin: belantomab mafodotin; melflufen, CAR T cell

Target MM in the bone marrow (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

30 FDA approvals (13 agents) and median patient survival prolonged 3-4 fold, from three to at least eight to ten years, and MM is a chronic illness in many patients.

Even without CRAB (Calcium, Renal, Anemia, Bone)
Myeloma Defining Events (International MM Working Group, IMWG)

Bone marrow plasma cells ≥ 60%

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

Focal bone marrow lesions on PET-CT and/or

Treat as MM

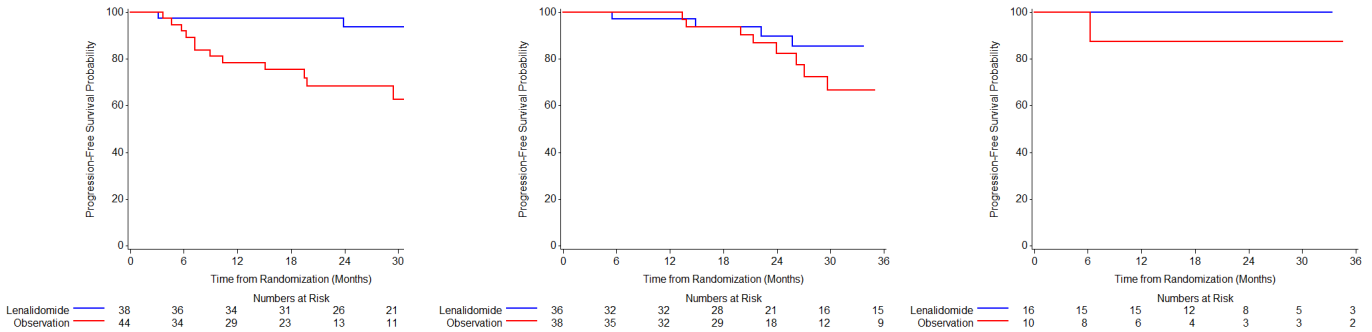
High Risk Smoldering MM (SMM)

≥ 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
Kumar et al Blood Cancer J 2018

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



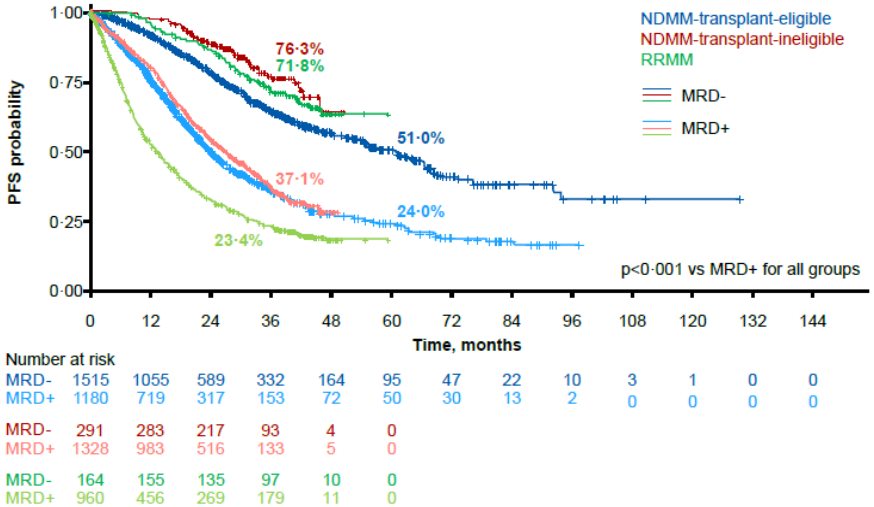
High Risk | Intermediate Risk | Low Risk

Decreased progression of high risk SMM to MM
11.4% vs 3.4% secondary malignancies
51% discontinuation rate
No OS difference

Lonial et al JCO 2020; 38: 1126-37.

Minimal Residual Disease (MRD) as a Goal of Therapy to Prolong PFS and OS

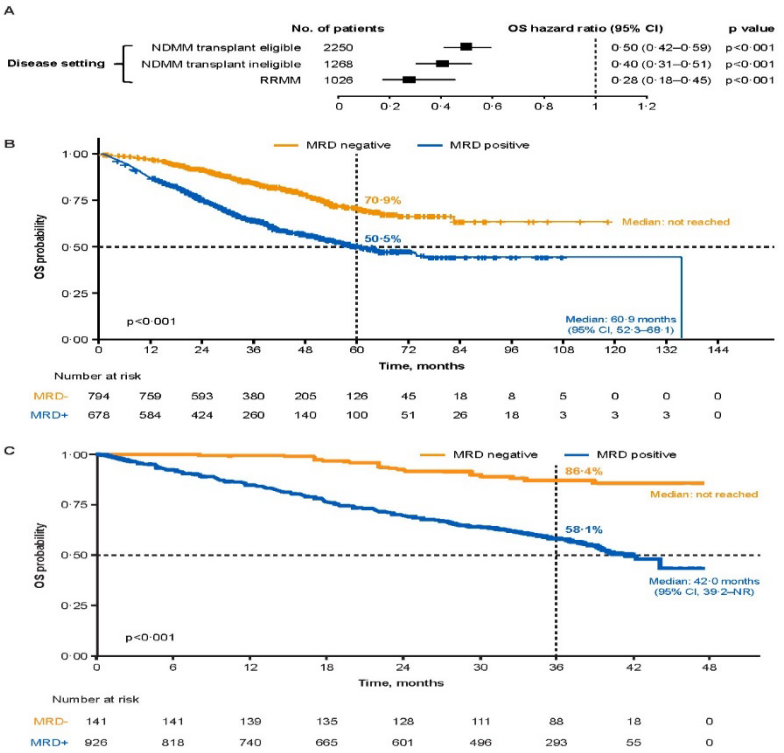
PFS



Number at risk

MRD-	1515	1055	589	332	164	95	47	22	10	3	1	0	0
MRD+	1180	719	317	153	72	50	30	13	2	0	0	0	0
MRD-	291	283	217	93	4	0							
MRD+	1328	983	516	133	5	0							
MRD-	164	155	135	97	10	0							
MRD+	960	456	269	179	11	0							

OS



NDMM Transplant -eligible

RRMM

Munshi et al., Blood Adv 2020; 4: 5988-99.

Therapy for Newly Diagnosed MM Transplant Candidates

Triplets

Lenalidomide (R)/ Bortezomib (V)/ Dexamethasone (Dex) RVD
Cyclophosphamide (Cy)/Bortezomib/Dex CyBorD
Carfilzomib (K) RD if neuropathy KRD
Ixazomib RD all oral IRD
VRD equivalent to KRD in non high risk; KRD in high risk

Quadruplets

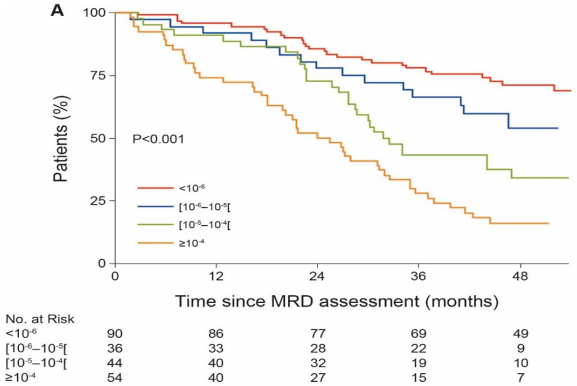
VTD-Daratumumab (Cassiopeia, MRD- responses, FDA approved)
RVD-Dara (Griffin, MRD- responses),
KRD-Dara (Forte, MRD- including high risk)
Elotuzumab RVD equivalent to RVD in high risk
Isatuximab KRD active in high risk
Ixazomib RD Dara under evaluation

Maintenance

R in standard risk; VR Bort, KR, Dara-R in high risk

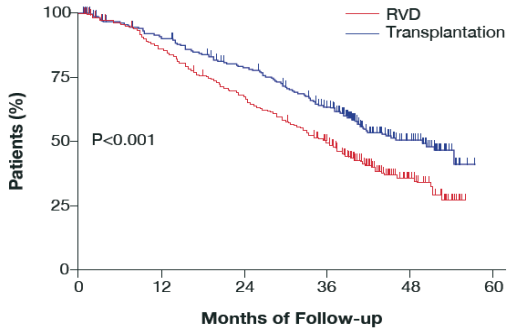
Present: IFM/DFCI 2009 in Newly Diagnosed Transplant Candidates

	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



Proportionality of MRD Effect on PFS

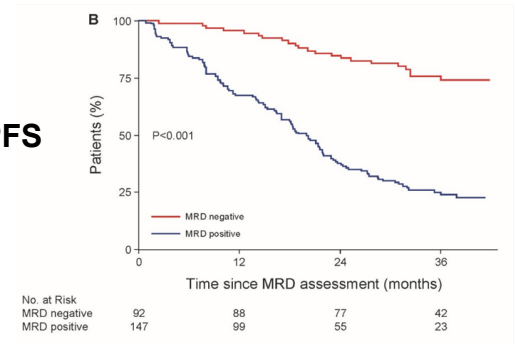
PFS



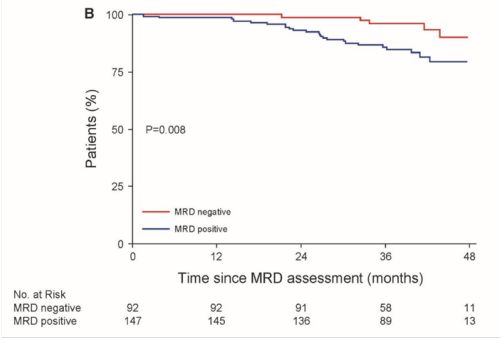
No. at Risk

RVD	350	294	228	157	32	0
Transplantation	350	308	264	196	50	0

PFS

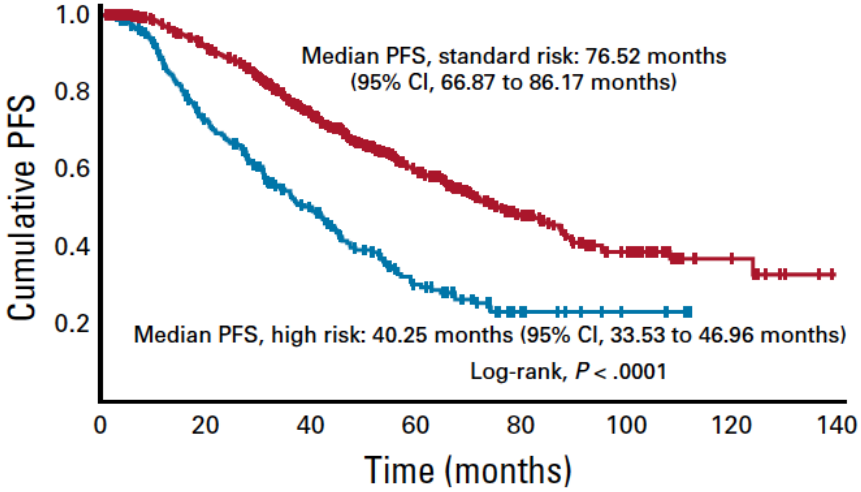


OS

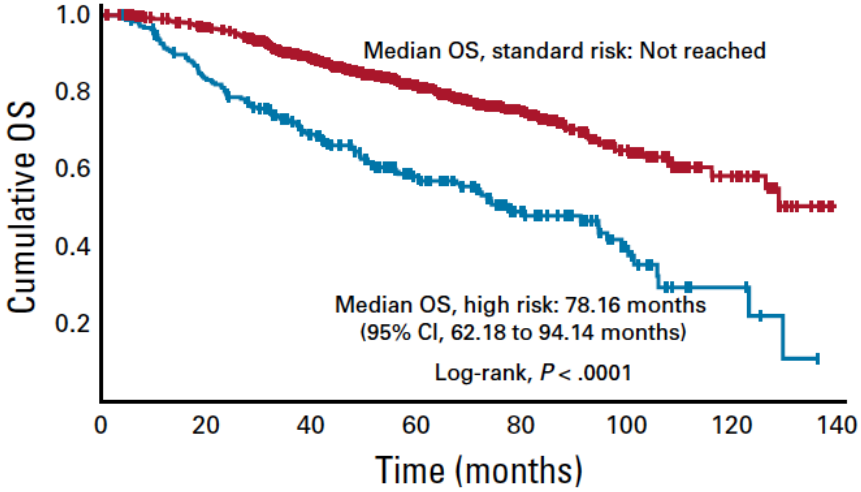


Attal et al NEJM 2017; 376: 1311-20
Perrot A et al Blood 2018; 132:2456-64; ASH 2020

Long Term Followup of Lenalidomide, Bortezomib, and Dexamethasone Induction, ASCT, and Risk Adapted Maintenance



No. at risk:							
Standard risk	503	314	159	75	27	6	1
High risk	154	87	33	9	2	0	0

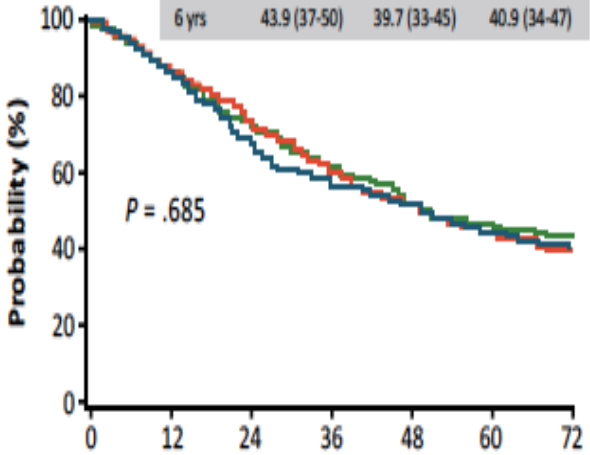


No. at risk:							
Standard risk	550	394	240	133	56	14	1
High risk	193	134	79	37	14	4	0

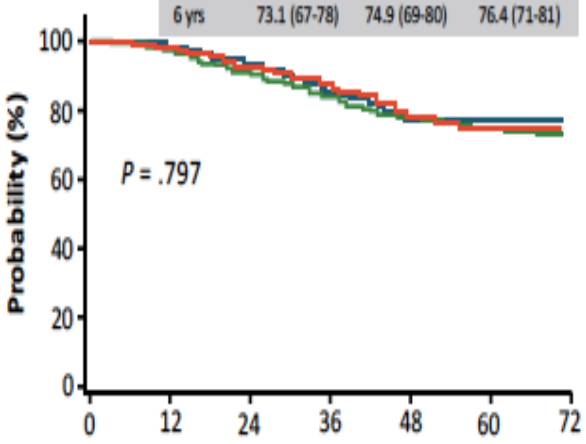
Joseph NS et al. JCO 2020; 38: 1928-37.

After Single ASCT: Len Maintenance (Len) vs RVD Consolidation/Len vs Second ASCT (STAMINA)

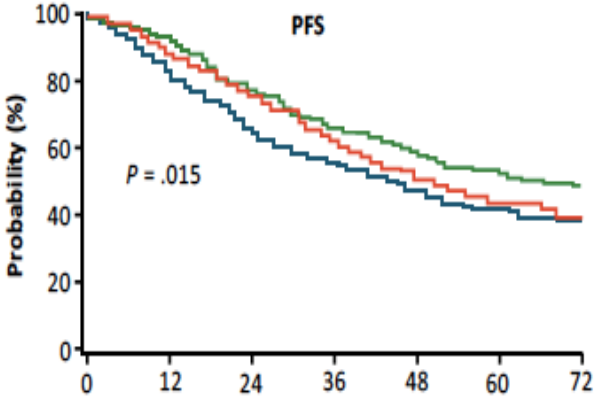
PFS, % (Range)	ASCT/ASCT	ASCT/RVD	ASCT/Maint
5 yrs	47.4 (41-53)	44.1 (38-50)	45 (38-51)
6 yrs	43.9 (37-50)	39.7 (33-45)	40.9 (34-47)



OS, % (Range)	ASCT/ASCT	ASCT/RVD	ASCT/Maint
5 yrs	74.7 (69-80)	75.4 (70-80)	76.4 (71-81)
6 yrs	73.1 (67-78)	74.9 (69-80)	76.4 (71-81)



5-Yr PFS, % (Range)	ASCT/ASCT	ASCT/RVD	ASCT/Maint	P Value
High risk	43.7 (33-58)	37.3 (26-48)	32 (24-40)	.03
Standard risk	58.1 (48-67)	48.2 (40-56)	47.7 (41-54)	.196

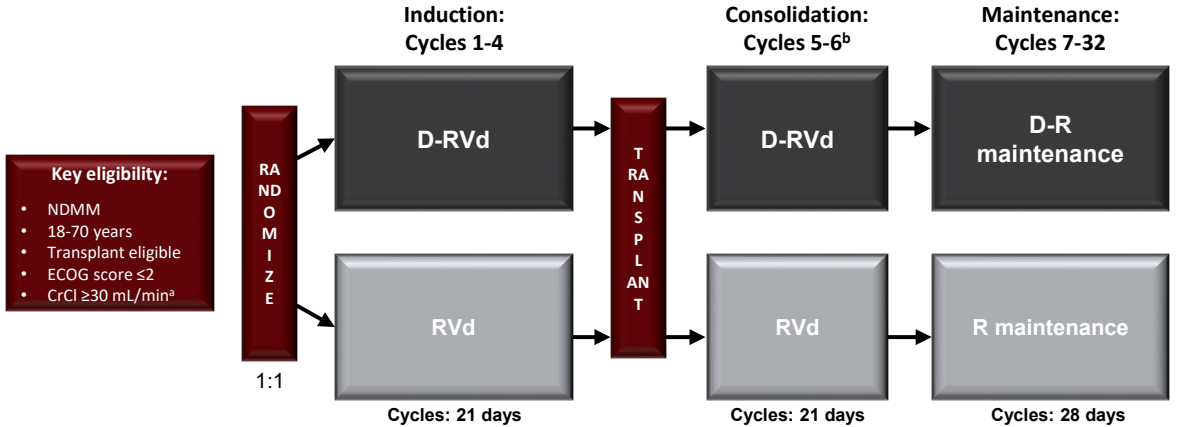


No difference in PFS in standard risk; PFS benefit for second ASCT in high risk

Hari, P et al. ASCO Abstract 8506, 2020.

GRIFFIN Randomized Phase 2 Study Design

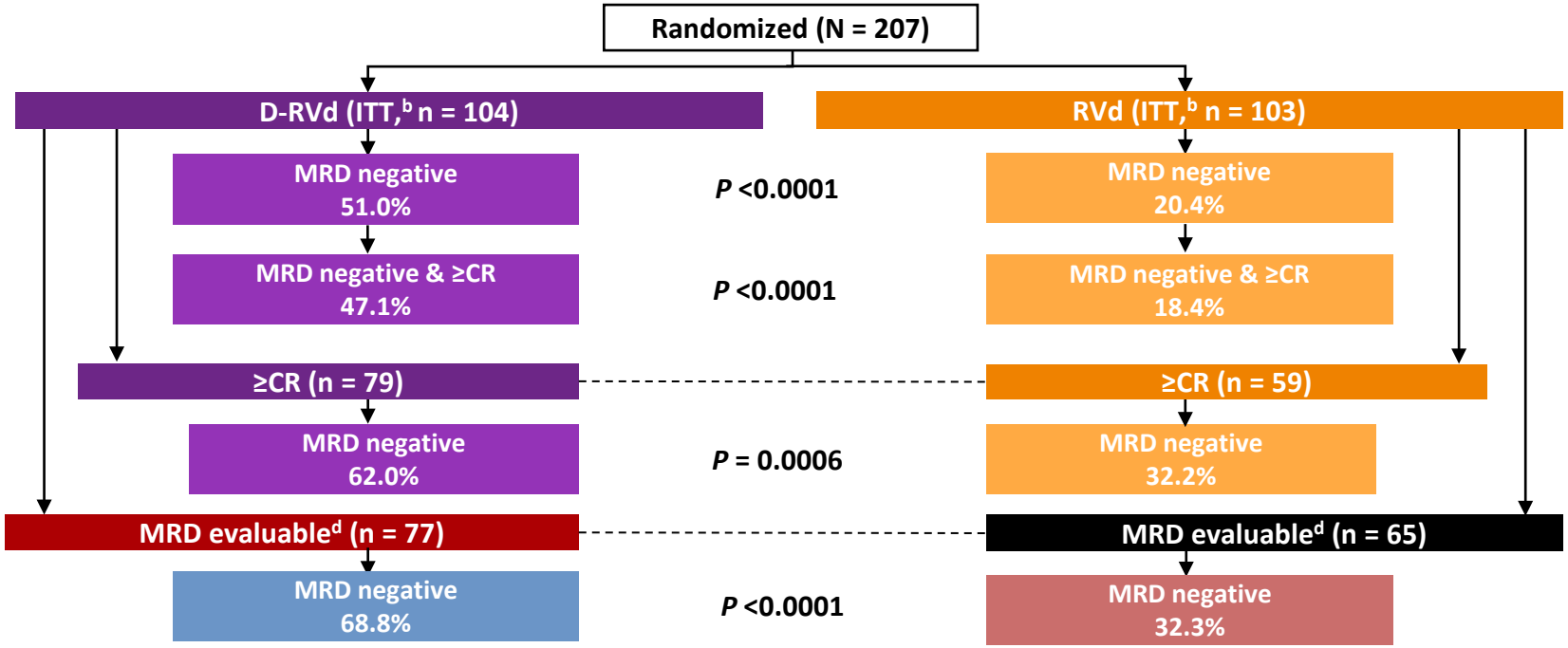
- **Phase 2, randomized, open-label study of D-RVd vs RVd in transplant-eligible NDMM; N = 222**



Primary objective: sCR rate after consolidation

Voorhees et al
Blood 2020; 136:936-45.

Griffin Clinical Trial: MRD (10^{-5}) Negativity[a] at Clinical Cutoff



Sustained MRD- ≥ 6 months 37.5% D-RVd vs 7.8% RVd, p<0.0001
Sustained MRD- ≥ 12 months 28.8%D-RVd vs 2.9% RVd, p<0.0001

Kaufman et al ASH 2020

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 but not used in USA); RVD lite,

R ixazomib D with or without MoAbs under evaluation

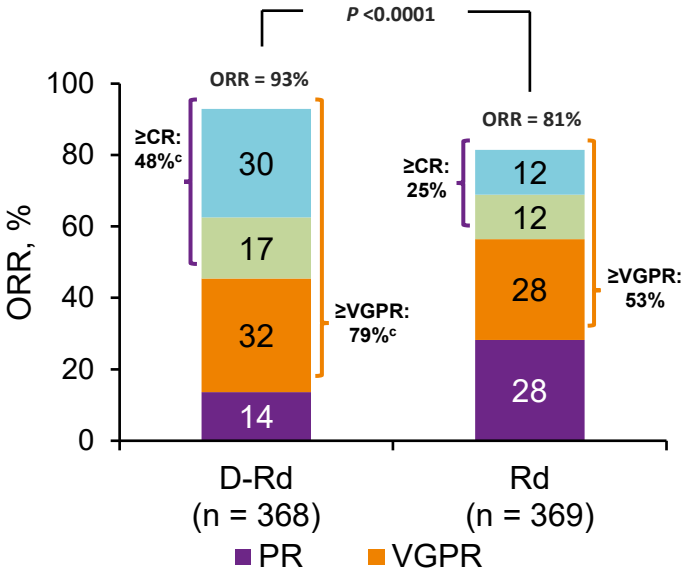
Maintenance

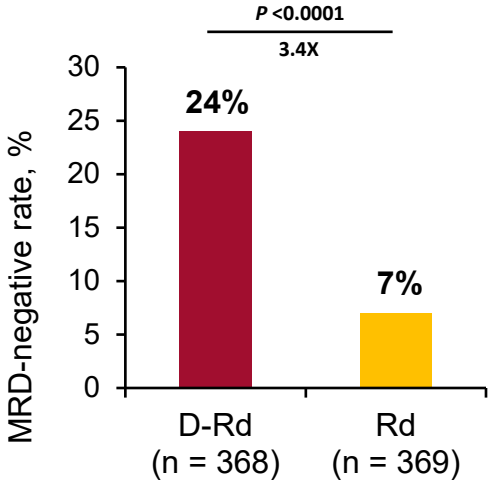
Len in standard risk, Bort or Len Bort in high risk, MoAbs under evaluation

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**

DRd lower risk of progression or death than RVd lite (HR 0.58 or Vd (HR 0.48) Durie et al Am JHematol 2020; 95: 1486.

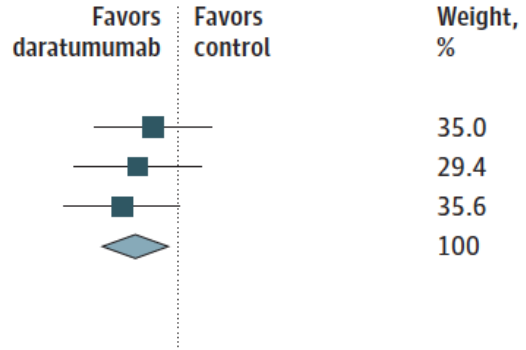
Newly Diagnosed MM Transplant Ineligible

	SWOGG 777 VRd vs Rd	RVd-lite	ALYCYONE Dara VMP vs VMP	MAIA DaraRD vs Rd	TOURMALINE-MM2 Ixazomib-Rd vs Rd
HR (95% CI)	**0.71 (0.56–0.91)**	**N/A**	**0.42 (0.34 - 0.51)**	**0.54 (0.43- 0.67)**	**0.83 (0.68–1.02)**
Median PFS (mos)	43 / 30	35.1	36 / 19	NR / 34	35.3 / 21.8
Total N	242 vs 229	50	350 vs 356	368 vs 369	351 vs 354
Median age	63	73	71	73	73
ORR (%)	82 vs 72	86	91 vs 74	93 vs 82	82 vs 80
CR (%)	16 vs 8.4	44	46 vs 25	51 vs 30	26 vs 14
mFU (months)	55	30	40	48	54
OS HR	0.71 (0.52-0.96)	N/A	0.60 (0.46-0.80)	PFS2 HR 0.65 (0.52-0.83)	0.998 (0.790-1.261)
	V for 6 mos (biw q21 d * 8 cycles)	V for 17 mos (qwk:35d *9, q2wk:28d *6)	V for 12 mos (6 wk cycles, biw *1, qwk * 8)		

Duriet et al. Lancet 2017; 389: 519-27
O'Donnell. Br J Haematol. 2018;182:222
Mateos MV, et al. NEJM. 2018;378:518-28.
Mateos MV, et al Lancet 2020:395:132-41
Dimopolous et al. ASH 2018
Facon et al. NEJM 2019; 380:2104-15
Bahlis et al. ASH 2019 .
Kumar et al. ASH 2020. Abstract 2276.
Facon et al. SOHO 2020.
Facon et al. ASH 2020.

Outcomes Associated With the Addition of Daratumumab to Backbone Multiple Myeloma Regimens for Patients With High-Risk Multiple Myeloma

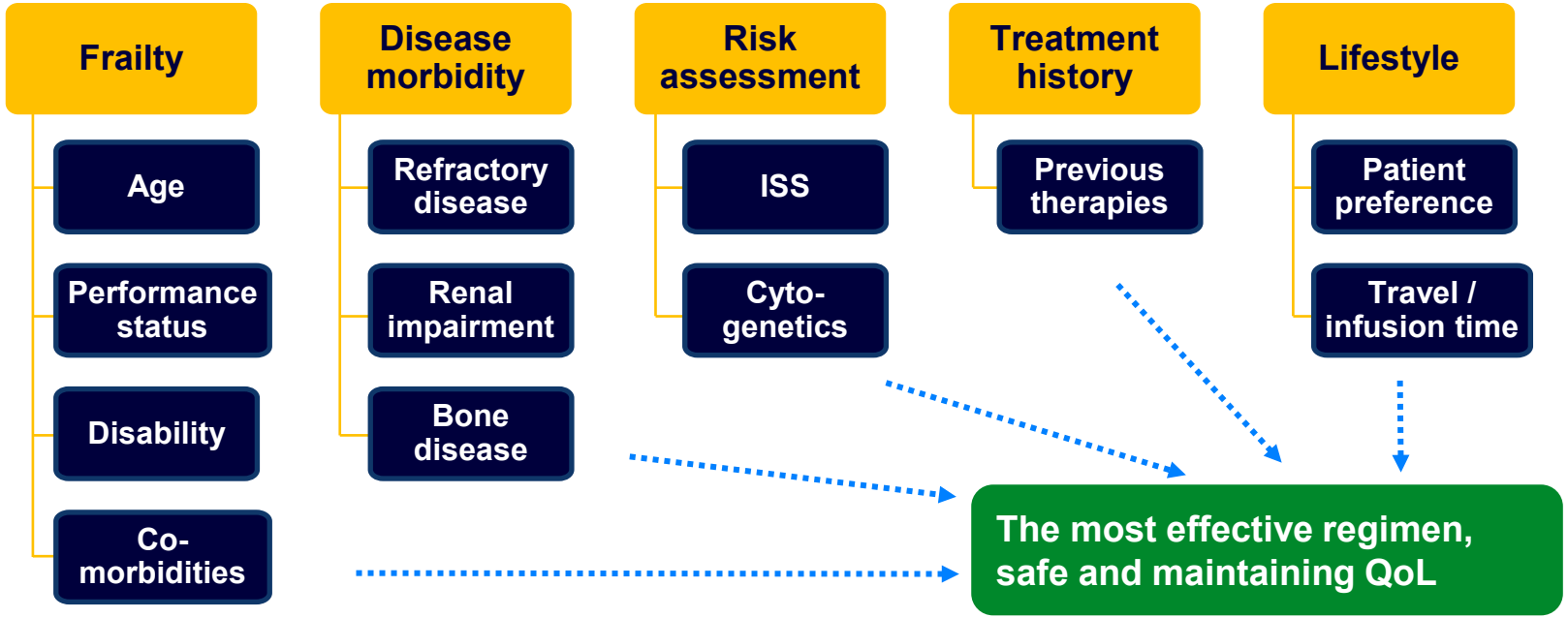
Source	Log (hazard ratio)	SE	Daratumumab total	Control total	Hazard ratio (95% CI) IV, random
Newly diagnosed high-risk multiple myeloma					
ALCYONE,[11] 2018	-0.2485	0.3038	53	45	0.78 (0.43-1.42)
CASSIOPEIA,[12] 2019	-0.4005	0.3313	82	86	0.67 (0.35-1.28)
MAIA,[13] 2019	-0.5621	0.301	48	44	0.57 (0.32-1.03)
Subtotal			183	175	0.67 (0.47-0.95)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.54$; $P = .76$; $I^2 = 0\%$					
Overall effect: $z = 2.25$; $P = .02$					



11 Mateos MV et al N Engl J Med 2018; 378: 518-28.
12 Moreau P et al Lancet 2019; 394: 29-38.
13 Facon T et al N Engl J Med. 2019;380:2104-15

Giri S. JAMA Oncol 2020; 6: 1-8.

Disease and Patient Factors Influence Treatment Choices in Relapsed Refractory MM



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, FDA approved)

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), Belantomab mafodotin (keratopathy), Idecel CAR T cells (all FDA approved)

Randomized Studies With Bortezomib-Dexamethasone Control Arms (Includes lenalidomide refractory MM)

	Pomalidomide		Daratumumab*		Carfilzomib		Selinexor		Venetoclax	
N	PVd vs Vd 559		DVd vs Vd 498		Kd vs Vd 929		SVD vs Vd 195 vs 207		VenVD vs VD 194 vs 97	
Efficacy	**Tx**	**Control**	**Tx**	**Control**	**Tx**	**Control**	**Tx**	**Control**	**Tx**	**Control**
Median follow up, mos	16		26.9		37.5		16.5		18.7	
ORR	82%	50%	85%	63%	76%	63%	76%	62%	82%	68%
CR	16%	4%	30%	10%	13%	6%	17%	11%	13%	1%
Median PFS, mos	11	7	16.7	7.1	18.7	9.4	13.93	9.46	22.4	11.5
PFS HR (95% CI)	0.61 (0.49–0.77)		0.32 (0.25–0.40)		0.53 (0.44–0.65)		0.70		0.63	
Median OS, mos	NR	NR	NR	NR	47.6	40.0	NR	25	NR	25
OS HR (95% CI)	NR		NR		0.79 (0.65-0.96)				**2.03 (1.04-3.95)**	

*Vd 8 *21 day cycles

t(11;14):
PFS HR
0.11
OS HR
0.343

Daratumamab refractory patients excluded in CASTOR trial, not represented in others

Richardson et al. Lancet Oncol 2019; 20: 781–94; Palumbo A et al. *N Engl J Med*. 2016;375:754; Spencer A et al. *Haematologica*. 2018; Sep 20 [epub ahead of print]; Dimopoulos MA et al. *Lancet Oncol*. 2016;17:27; Dimopoulos et al ASCO 2020; Kumar, S EHA 2019

Randomized Studies With Lenalidomide-Dexamethasone Control Arms (FDA approved, includes Bort refractory MM)

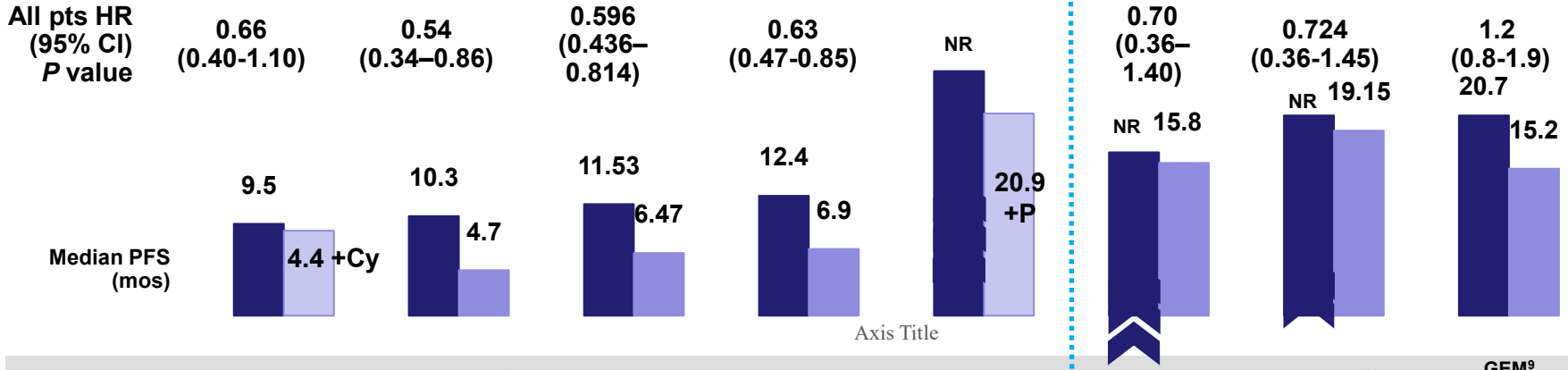
	Ixazomib		Elotuzumab		Carfilzomib*		Daratumumab	
N	IRd vs Rd 722		ERd vs Rd 646		KRd vs Rd 792		DRd vs Rd 569	
Efficacy	**Tx**	**Control**	**Tx**	**Control**	**Tx**	**Control**	**Tx**	**Control**
Median follow up, mos	23		Min 48 mos		67		32.9	
ORR	78.3%	71.5%	79%	66%	87.1%	66.7%	93%	76%
CR	12%	7%	5%	9%	32%	9.3%	55%	23%
Median PFS, mos	21	14.7	19	14.9	26	16.6	NR	17.5
PFS HR (95% CI)	0.74 (0.59–0.94)		0.71 (0.59–0.86)		0.69 (0.57–0.83)		0.44 (0.34–0.55)	
Median OS, mos	NR	NR	48.3	39.6	48.3	40.4	NR	NR
OS HR (95% CI)	NR		0.78 (0.63–0.96)		0.79 (0.67-0.95)		NR	

*PFS HR 0.5 @ 18 mos8

NB Daratumamab refractory patients not included in POLLUX or ELOQUENT trials

Moreau P et al. *N Engl J Med*. 2016;374:1621; Dimopoulos MA et al. *Br J Haematol*. 2017;178:896; Stewart AK et al. *N Engl J Med*. 2015;372:142; Stewart AK et al. *Blood*. 2017;130: Abstract 743.; Dimopoulos M et al. *J Hematol Oncol*. 2018;11:49; Dimopoulos MA et al. N Engl J Med. 2016;375:1319.

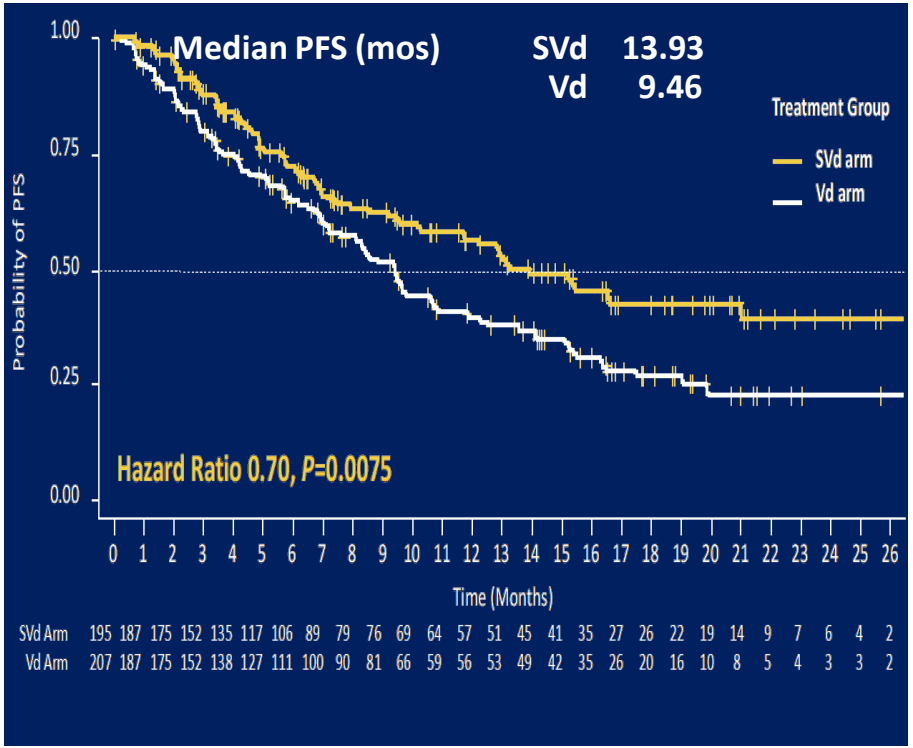
Pomalidomide/Carfilzomib Backbone Randomized Studies

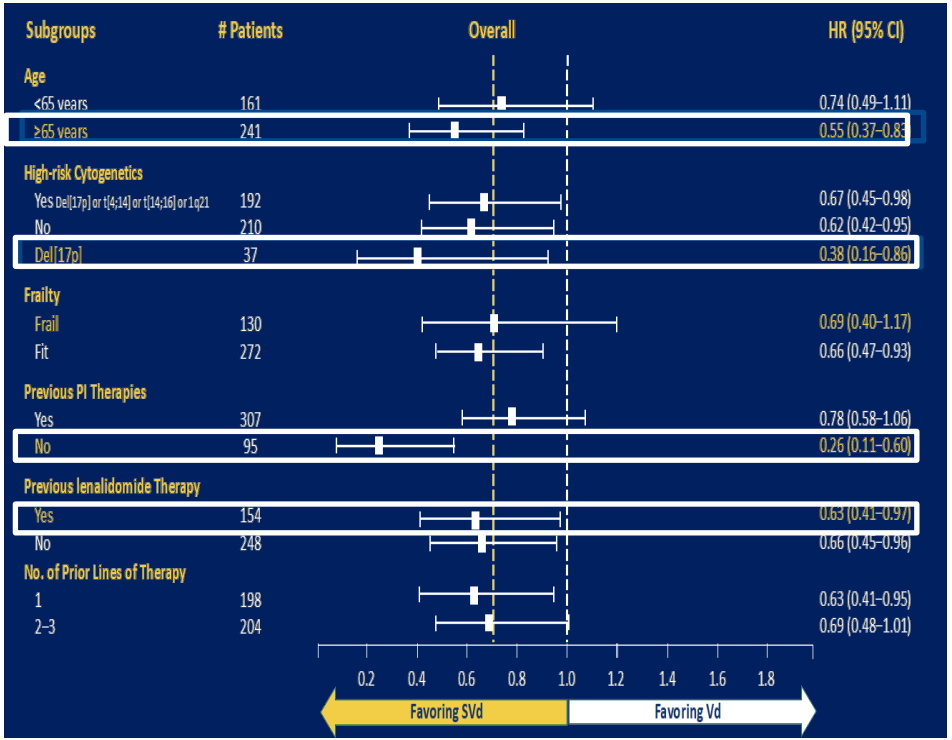


	PomCyDex vs PomDex+Cy[1]	ELOQUENT-3[2] EPd vs Pd	ICARIA-MM[4] Isa-Pd vs Pd	APOLLO[5] D-Pd vs Pd	DCdP vs DCd+P[6]	CANDOR[7] DKd vs Kd	IKEMA[8] IsaKd vs Kd	GEM[9] KyCydex vs Kydex
Total N	34 vs 36	60 vs 57	154 vs 153	151 vs 153	61 vs 59	312 vs 154	179 vs 123	97 vs 101
No. prior lines	4	3	3	2	2	2	2	1
Len refractory (%)	100	90 vs 84	94 vs 92	79.6	97	32 vs 36	31.8 vs 34.1	33 vs 36
PI refractory (%)	78 vs 71	78 vs 82	77 vs 75	48	93			92
mFU (months)		9.1	11.6	16.9	25.3 (8.9 mo after +P in Arm B)	16.9 vs 16.3	20.7	15.6
≥CR (%)	3 vs 3	8 vs 2	5 vs 1	24.5 vs 3.9		29 vs 10	39.7 vs 27.6	18 vs 20
OS HR	0.63 (0.32-1.22)	NR	NR	0.91 (0.61-1.35)	NR			P=0.9
Missing Molecular Data (%)			18 vs 26			51 vs 49	12.8 vs 11.4	24.7 vs 21.7

1. Baz RC et al. Blood (2016) 127 (21): 2561–2568; 2. Dimopoulos MA et al. N Engl J Med. 2018;379:1811; 3. Richardson et al. Lancet Oncol. 2019;20:781-794; 4. Attal M et al. *Lancet.* 2019;394:2096;
5. Dimopoulos MA et al. ASH 2020; 6. Sebag M et al. ASH 2020. 7. Dimopoulos M et al. Lancet. 2020;396:186; 8. Moreau P et al. Presented at the 25th European Hematology Association Annual Meeting; June 2020. Abstract LB2603.
9. Mateos MV et al. ASH 2020.

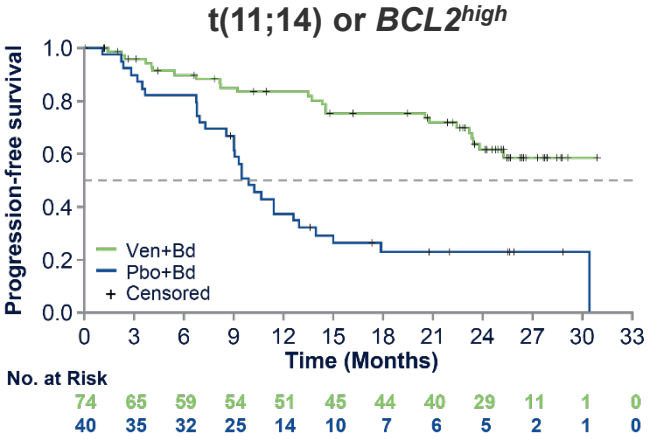
BOSTON Trial: Selinexor-Vd vs Vd in Patients with Multiple Myeloma who Had Received 1-3 Prior Therapies (FDA Approved)



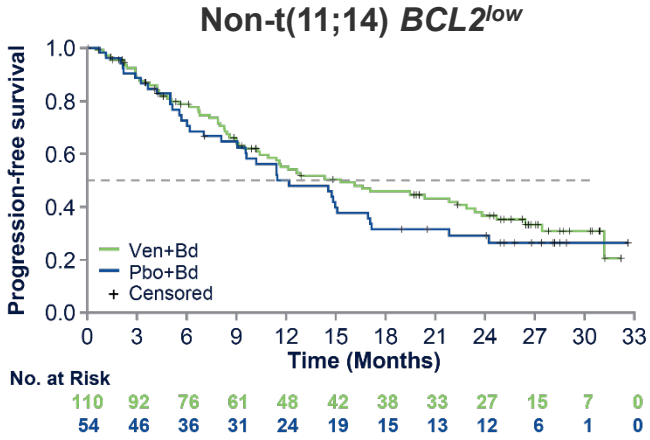


Dimopoulos MA et al Lancet 2020; 396: 1563-73.

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



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



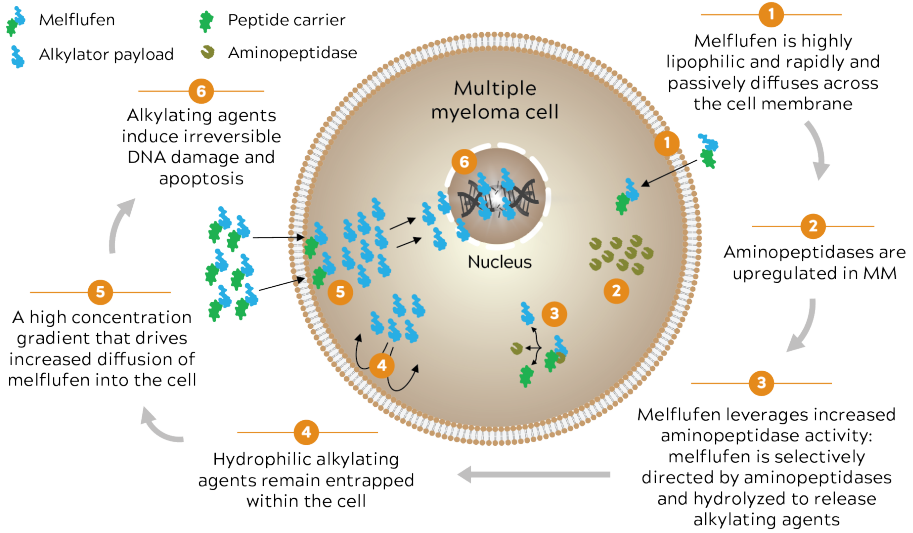
PFS	Ven+Bd	Pbo+Bd
Median, months	15.3	11.5
HR (95% CI)	0.85 (0.56, 1.30)	
P value	0.451	

High *BCL2* gene expression was determined by qPCR.

Kumar et al Lancet Oncol 2020; 21: 1632-42.

Melphalan Flufenamide (Melflufen) Is the First Aminopeptidase-Targeted Peptide-Drug Conjugate (PDC)

(FDA Approved)



- **In the pivotal phase 2 HORIZON study (OP-106) of melflufen plus dexamethasone in MM refractory to pomalidomide and/or anti-CD38 mAb therapy: acceptable safety[6]**
  - **ORR 29%; median PFS 4.2 months, and median OS 11.6 months**
  - **Grade 3/4 hematologic AEs common: 79% neutropenia, 76% thrombocytopenia, and 71% anemia were clinically manageable; nonhematologic AEs were infrequent**

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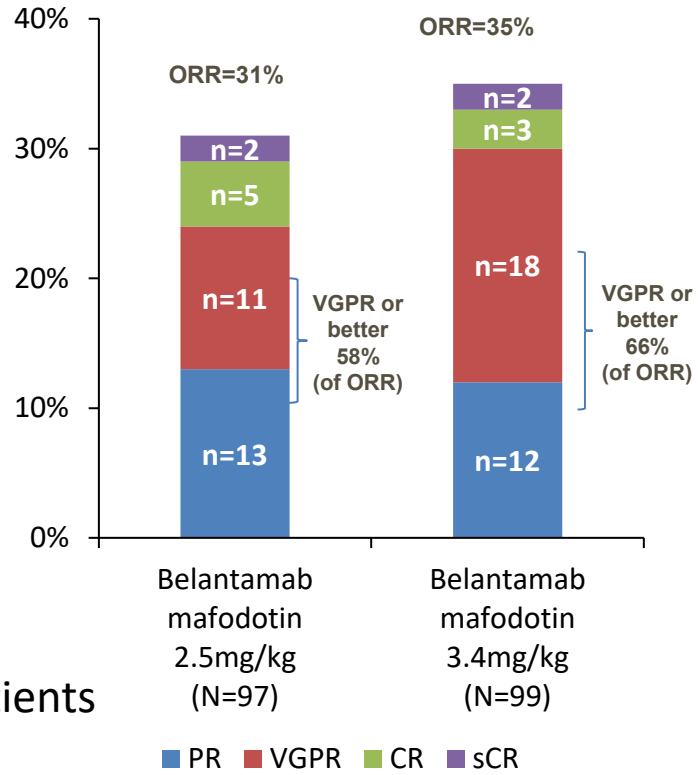
1. Chauhan D, et al. *Clin Cancer Res*. 2013;19:3019-3031. 2. Ray A, et al. *Br J Haematol*. 2016;174:397-409. 3. Wickström M, et al. *Oncotarget*. 2017;8:66641-66655. 4. Wickström M, et al. *Invest New Drugs*. 2008;26:195-204. 5. Strese S, et al. *Biochem Pharmacol*. 2013;86:888-895. 6. Richardson PG, et al. JCO 2021; 39:757-61.

BCMA Immuntoxin: Belantamab Mafodotin 3.4mg/kg vs 2.5-mg/kg in RRMM (13 month followup) (FDA Approved 2020)

	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

CAR T-Cell Therapy in Multiple Myeloma

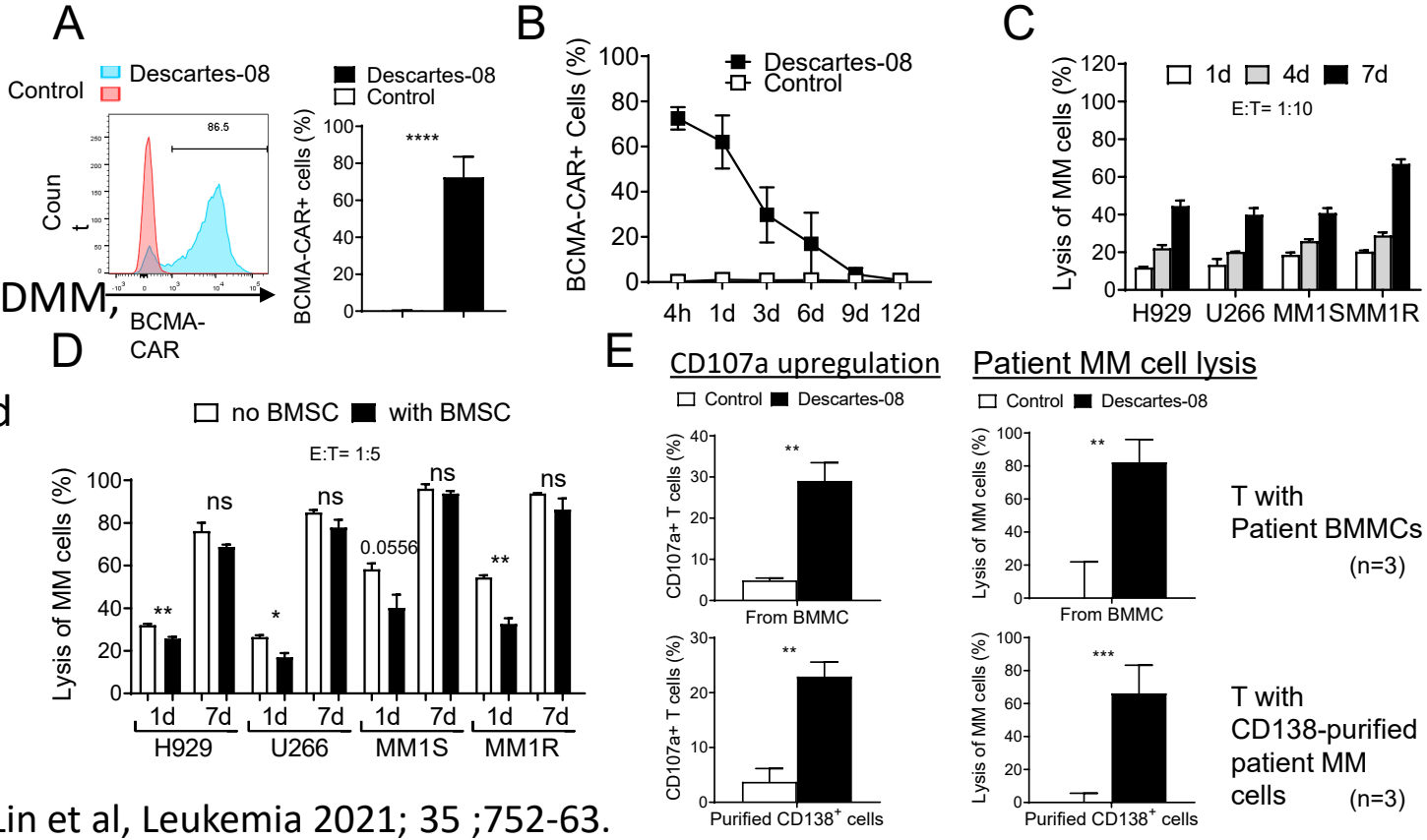
FDA Approved

	Ide-cel Ph1 N=128	Cilta-cel Ph1b/2 N=97	Orva-cel Ph1b/2 N=62	bb21217 Ph1 N=69	CT053 Ph1b/2 N=20	P-BCMA-101 Ph1/2 N=55	GC012F Ph1 N=16	ALLO-715 Ph1 N=31
CRS, % All grades Grade ≥3	84% 5%	9% 4%	89% 3%	70% 4%	77% / 83%[a] 0% / 0%	17% 0%	100% 13%	45% 0%
NT, % All grade Grade ≥3	18% 3%	21% 10%	13% 3%	16% 4%	15% / 17%[a] 8% / 0%	4% 4%	0% 0%	0% 0%
ORR CR	73% ≥CR 33% (450: OR 81%, CR 39%)	97.9% ≥CR 67%	92% CR 36%)	68% (≥CR 29%)	94% (≥CR 28%)	44% - 75%[b]	94% (≥CR 56%)	60% in DL3 (n=10)
Median follow-up	13.3 mo	12.4 mo		5.8 mo	6 mo	120-508 days[b]	7.3 mo	3.2 mo
Median DOR	10.7 mo (450: 11.3 mo)	21.8 mo	Not reported	17.0 mo	Not reported	Not reported	Not reached	Not reported
Median PFS	8.6 mo 12.2 mo 20.2 CR/sCR	22.8 mo sCR: NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Median OS	24.8 mo	18 mo OS: 80.9%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Munshi et al; Madduri et al; Lin et al; Alsina et al; Kumar et al; Costello et al; Jiang et al; Mailankody et al; Anderson et al ASH/ASCO 2020,2021; Usmani et al ASCO 2021

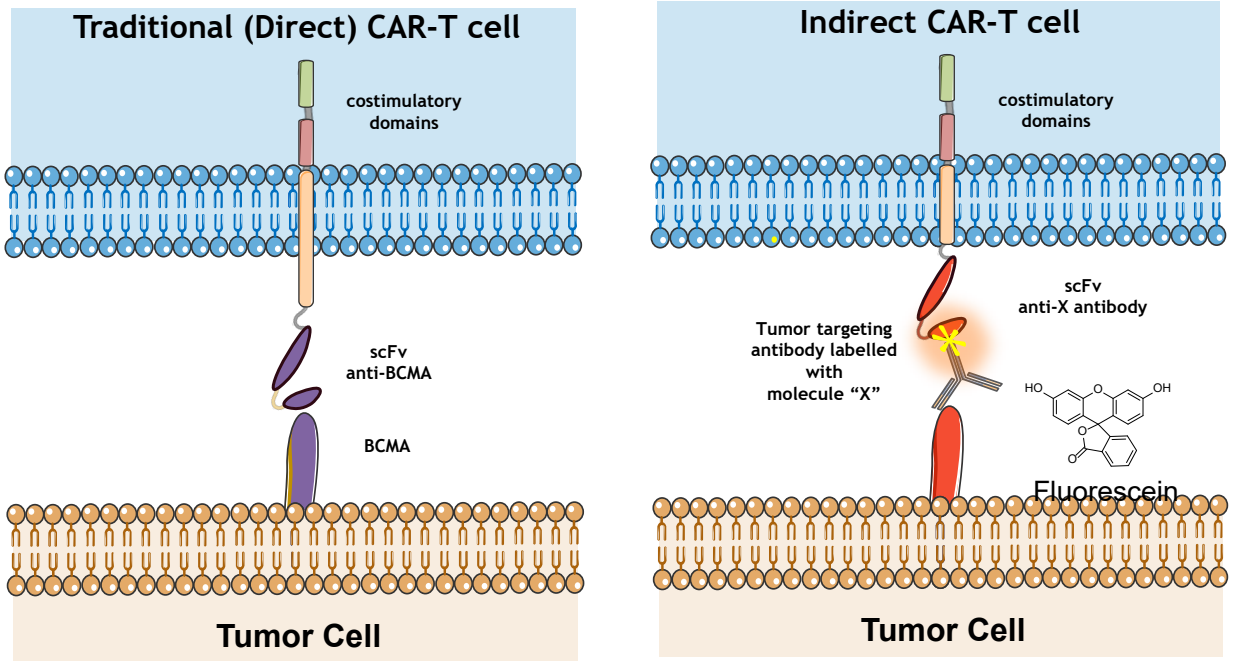
Transiently Active Anti-BCMA mRNA-Electroporated CD8+ CAR T-Cells (Descartes-08) for MM

Trial in NDMM, No CRS, Repeated Doses



Lin et al, Leukemia 2021; 35 ;752-63.

BAT-CAR: Binary Activated T Cell with Chimeric Antigen Receptor



Alberto Nobili, PhD and Carl Novina, MD PhD

Bispecific T Cell Engagers (Bites) in Multiple Myeloma

	Tesclistamab Ph1 N=149	AMG-701 Ph1 N=85	REGN5458 Ph1 N=49	PF-3135 Ph1 N=30	Talquetamab Ph1 N=157	Cevostamab Ph1 N=53
Target	**BCMA-CD3**	**BCMA-CD3**	**BCMA-CD3**	**BCMA-CD3**	**GPRC5D-CD3**	**FcRH5-CD3**
Dosing Schedule	Q2W→QW IV or SC IV: 0.3-19.2 µg/kg SC: 80-3000 µg/kg	QW IV (0.005-18 mg)	QW→Q2W IV (3-96mg)	QW SC (80-1000µg/kg)	QW or Q2W IV: 0.5-180 µg/kg SC: 5-800 µg/kg	Q3W IV (0.05-160mg)
CRS, % **Any grade** **Grade ≥3**	 55% 0	 65% 9%	 39% 0	 73% 0%	 54% 3%	 76% 2%
NT, % **Any grade** **Grade ≥3**	 5% 1%	 Not reported	 12% 0	 Not reported	 6% 2%	 Not reported
ORR	At RP2D (1500 µg/kg SC): 73% (≥CR, 23%)	26% (≥CR, 10%)	39% (≥CR, 16%)	80%	At RP2D (405 µg/kg SC): 69% (≥CR, 15%)	In ≥20 mg cohorts: 53% (≥CR, 18%)
Median follow-up	At RP2D: 3.9 mo	6.5 mo	2.6 mo	Not reported	≥60 µg/kg: 7.4 mo ≥405 µg/kg: 3.7 mo	8.1 mo
Median DOR	Not reached	Not reached	6.0 mo	Not reported	Not reached	8 patients ≥6 mo
Median OS	Not reached	Not reported	Not reported	Not reported	Non reported	Not reported

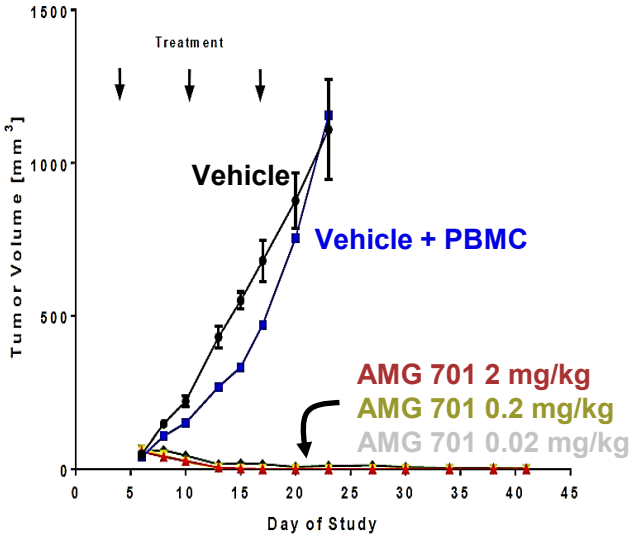
Garfall et al; Harrison et al; Madduri et al Chari et al; Cohen et al ASH, ASCO 2020

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

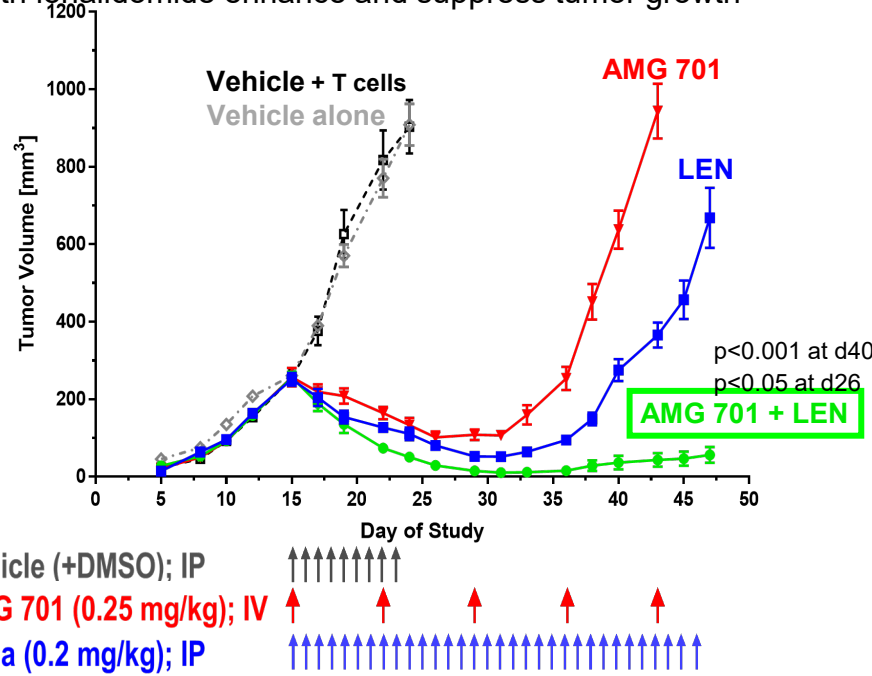
Combination AMG 701 and Lenalidomide Enhanced Anti-tumor Activity in a Mouse Model of Established MM (Clinical Trial Ongoing)

AMG 701 prevents tumor growth in a xenograft model at all doses tested



Monotherapy: 3 separate dosing

Combination of minimally effective doses of AMG 701 with lenalidomide enhance and suppress tumor growth

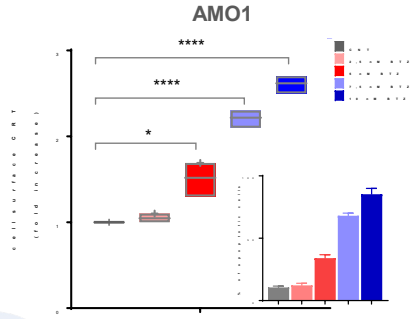


Cho et al Blood Advances 2020; 4: 4195-4207.

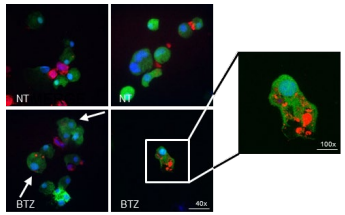
Bortezomib Induces Anti-MM Immune Response Immunogenic Cell Death

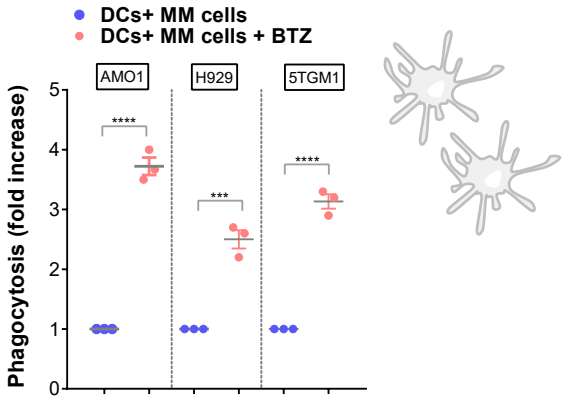
1. MM cells expose CALR on cell surface

BTZ

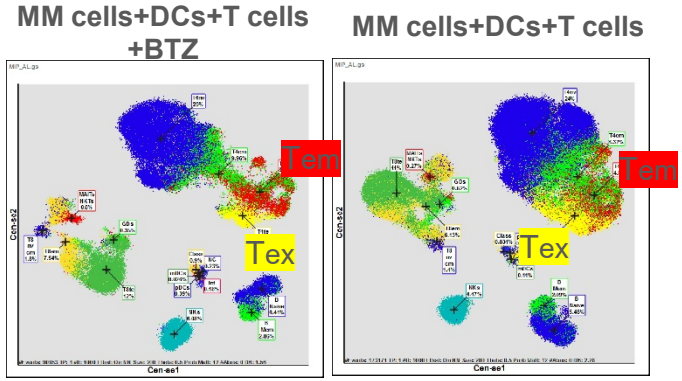


2. Dendritic cells become functionally mature

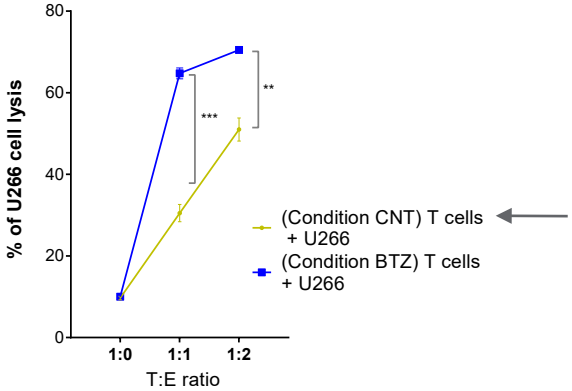




3. T cells are primed against MM



4. MM cell lysis



Gulla et al, Blood Cancer Discovery, in press

Dana-Farber Cancer Institute

Conclusions and Future Directions

Combination PI, IMiD, Dex, CD38MoAb will achieve high rates MRD negativity in NDMM, including high risk MM

BCMA targeted CAR T cells, BiTEs will then be compared with ASCT to induce long term MRD-with memory anti-MM immune response

Combination immunotherapies to enhance response, overcome resistance mechanisms, and improve therapeutic index: BiTEs with IMiDs, BAT CARs

Novel uses of known classes of active agents: proteasome inhibitors to trigger anti-MM immunity

Long term disease-free survival and potential cure of MM will be achieved with combination targeted and immune therapies to both achieve MRD negativity and restore host memory anti-MM immunity. These patients will then be free of disease and off all therapy..