Treating Multiple Myeloma: The Cure is in Reach
Goals of Current Therapy

Kenneth Anderson, MD
Director, Jerome Lipper Multiple Myeloma Center
and LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
Kraft Family Professor of Medicine
Harvard Medical School

Disclosures

Advisory Role: Pfizer, Amgen, Astrazeneca, Janssen, Precision Biosciences

Board Membership: C4 Therapeutics, Dynamic Cell Therapies, Window, Mana

Ownership Interests: C4 Therapeutics, Oncopep, NextRNA, Dynamic Cell Therapies

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; Immunotoxin: belantomab mafodotin; CAR T cell: idecel, ciltacel

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

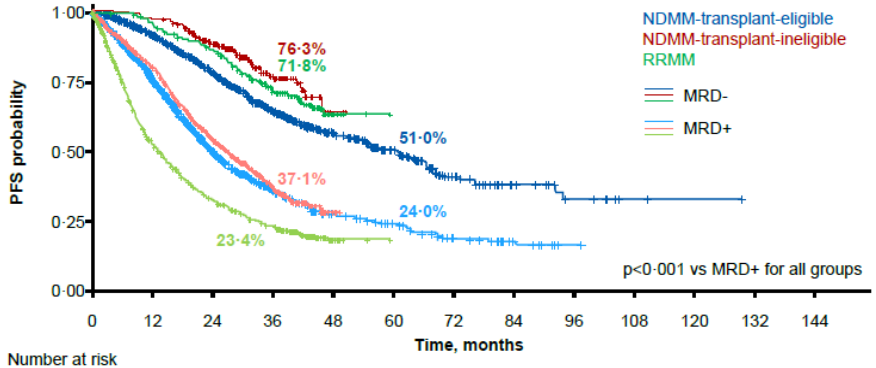
Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

30 FDA approvals (15 agents) 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.

N.B. Four FDA Approvals During the COVID 19 Pandemic

Minimal Residual Disease Negativity in Newly Diagnosed and Relapsed Refractory MM: Prolonged PFS and OS

PFS

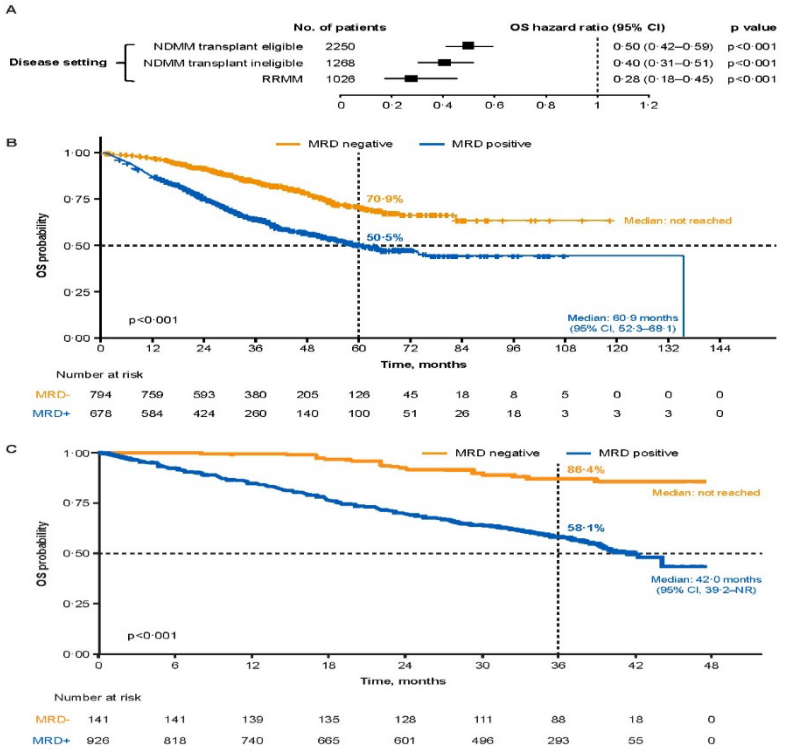


Number at risk

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							

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

OS



NDMM Transplant -eligible

RRMM

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

Treat as MM

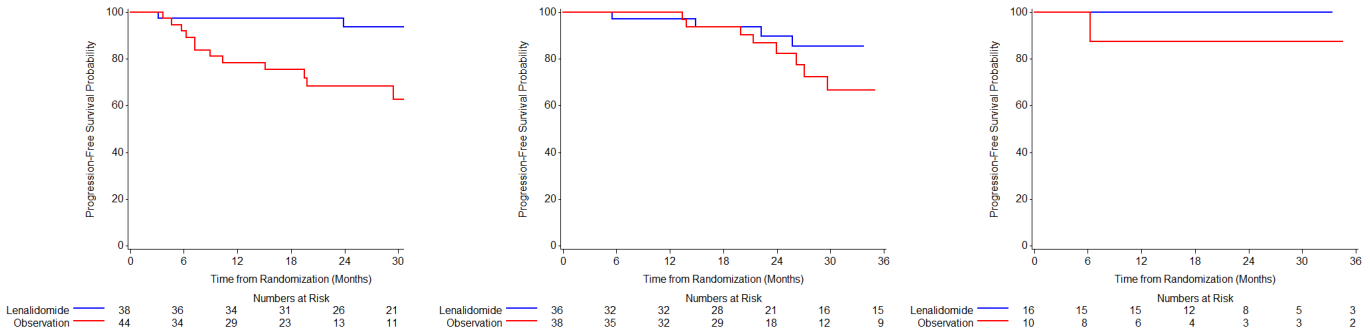
High Risk Smoldering MM (SMM)

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

Novel agents (lenalidomide with or without dex) and immune therapy protocols 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; 8: 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 especially of high risk SMM to to MM
No OS difference; 11.4% vs 3.4% secondary malignancies;
51% discontinuation rate

High risk SMM candidates for clinical trials

Lonial et al, ASCO 2019, JCO 2020; 38: 1126-37.

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

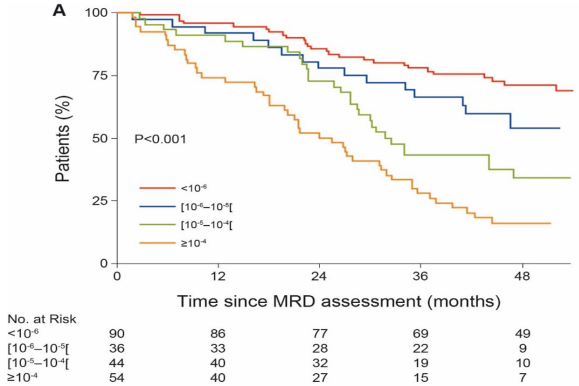
VTD-Daratumumab (Cassiopeia, MRD- responses, FDA approved)
RVD-Dara (Griffin, MRD- responses),
KRD-Dara (Forte, MRD- including high risk)
Elotuzumab RVD equivalent to RVD in high risk
Isatuximab KRD active in high risk
Ixazomib RD Dara under evaluation

Maintenance

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

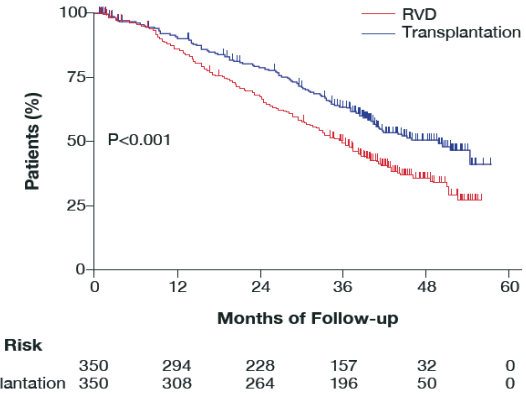
IFM/DFCI 2009 in Newly Diagnosed Transplant Candidates

	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

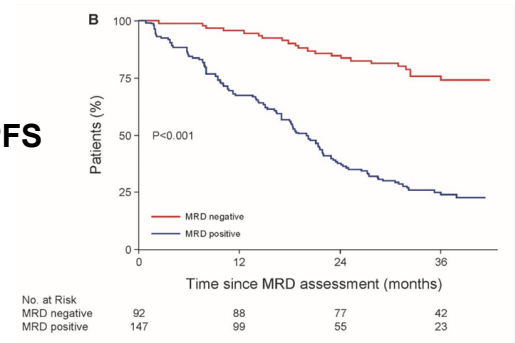


Proportionality of MRD Effect on PFS

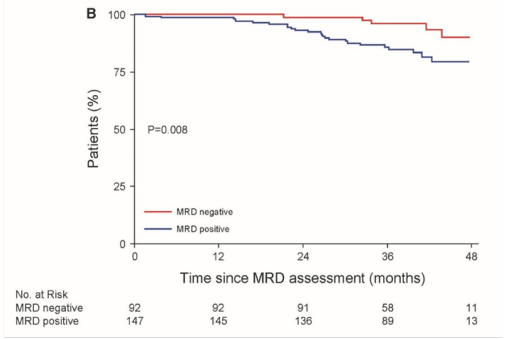
PFS



PFS



OS



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

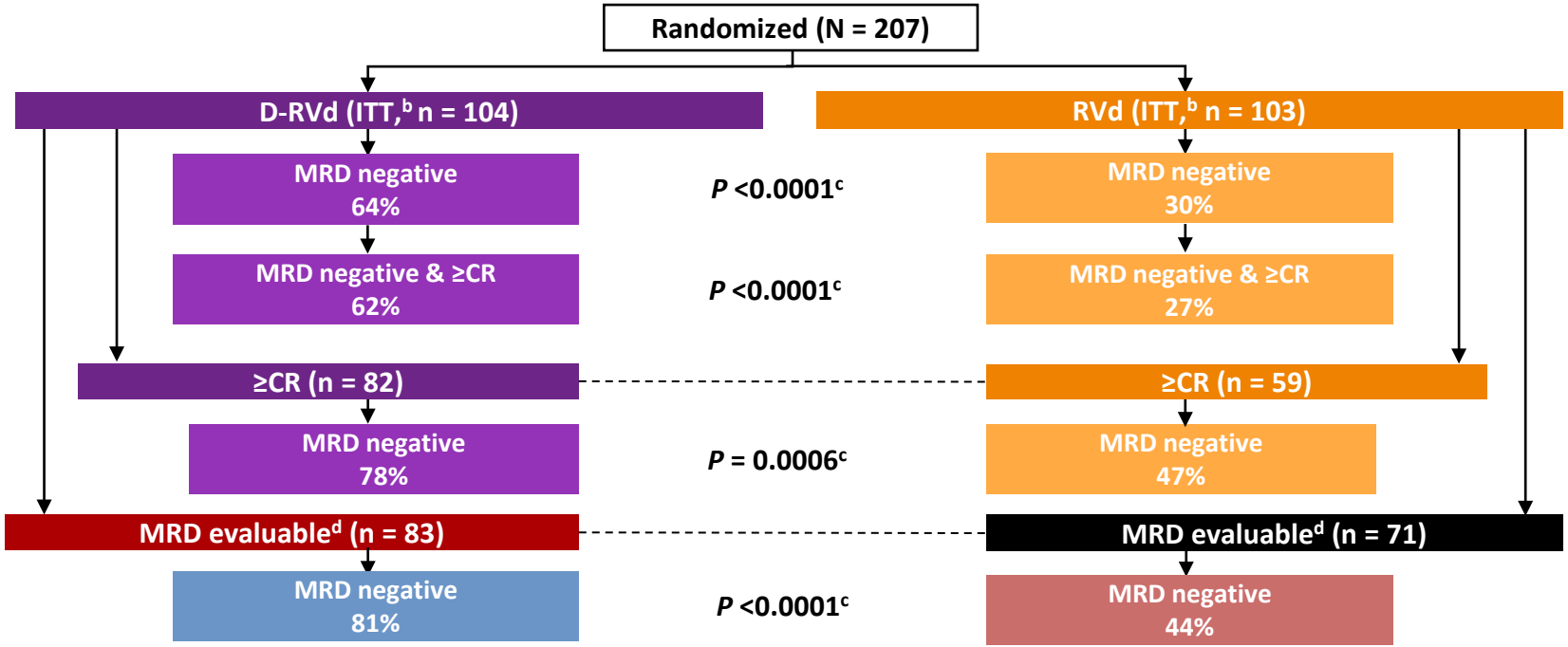
RVd ± ASCT and Continuous Lenalidomide Maintenance to Progression for NDMM

- RVd + ASCT offers significantly superior PFS vs RVd-alone: 67.5 vs 46.2 months
  - Compared to median PFS 47.3 vs 35.0 months with 1 year of maintenance (IFM 2009)
- No OS benefit after median follow-up of more than 6 years: 5-year OS 80.7% vs 79.2%
  - Associated with low rate (28.1%) of ASCT in RVd-alone arm (delayed ASCT) and impact of other novel therapies at first relapse
- Similar ORR (97.5% vs 95.0%) and rates of ≥VGPR (82.7% vs 79.6%) and ≥CR (46.9% vs 42.0%)
- Higher rate of MRD-negative responses with RVd + ASCT: 54.4% vs 39.8%
  - MRD-negative response associated with better outcome vs MRD-positive response in both arms

    5-year PFS in MRD-negative patients similar with RVd + ASCT vs RVd-alone: 53.5% vs 59.2%

Richardson et al ASCO 2022, NEJM in press

GRIFFIN: RVD VERSUS RVD-DARA AS INDUCTION, ASCT, AS CONSOLIDATION, THEN DARA-LEN VERSUS LEN MAINTENANCE: MRD (10^{-5}) NEGATIVITY

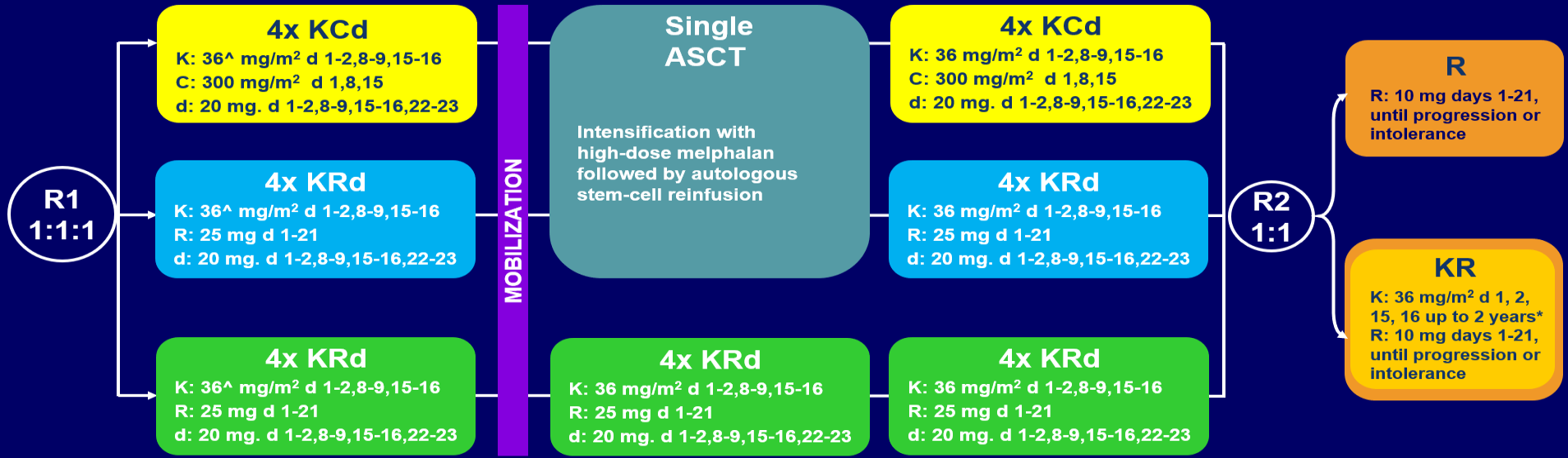


Sustained MRD- ≥ 6 months 48% D-RVd vs 15% RVd, p<0.0001
Sustained MRD- ≥ 12 months 44%D-RVd vs 13% RVd, p<0.0001

Voorhees et al Blood 2020; 136:936-45; Kaufman et al ASH 2020; Laubach et al ASH 2021

Forte Clinical Trial
Trial design

474 NDMM patients, transplant-eligible and younger than 65 years



^20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards. NDMM, newly diagnosed multiple myeloma, R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.

Gay et al, ASH 2020, Lancet 2021; 22:1715-20.

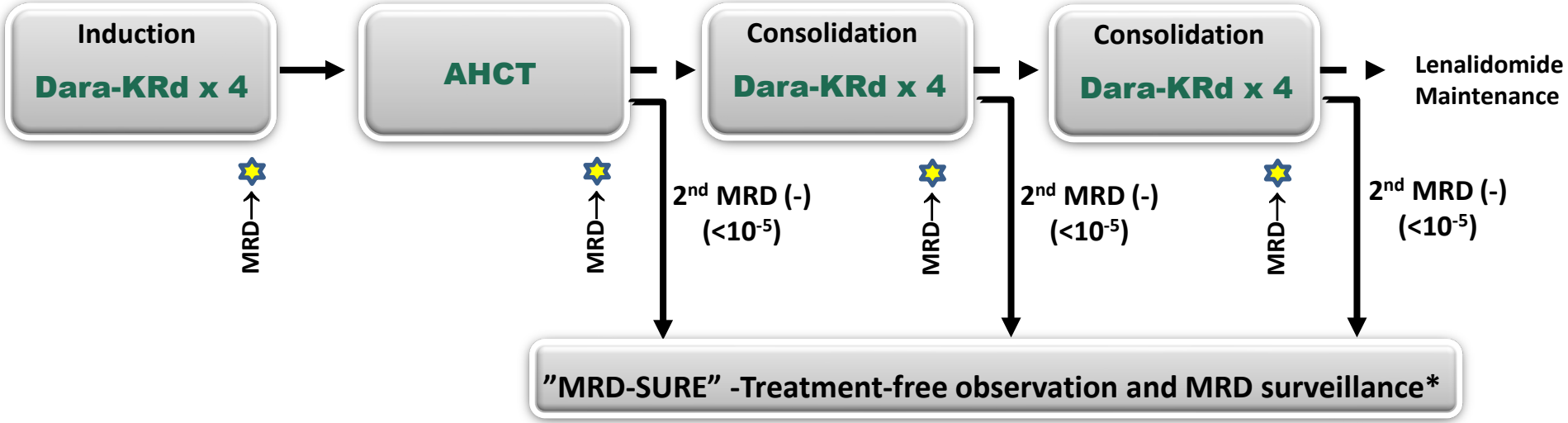
Forte Clinical Trial
Conclusions

- **KRd_ASCT significantly prolonged PFS vs. Krd12 and vs. KCd_ASCT**
  - **3-year PFS → 78%**
- **The benefit of KRd_ASCT was observed in all subgroups of patients:**
  - **KRd_ASCT in ISS I, FISH standard risk, LDH ≤ULN: 3-year PFS 80-84%**
  - **KRd_ASCT in ISS II/III, FISH high-risk, LDH >ULN: 3-year PFS 69-72%**
- **KR significantly prolonged PFS vs. R**
  - **30 months PFS → 81%**
- **The benefit of KR was observed in all subgroups of patients:**
  - **KR in ISS I, FISH standard risk, LDH ≤ULN: 30-months PFS 83-85%**
  - **KR in ISS II/III, FISH high-risk, LDH >ULN: 30-months PFS 60-78%**
- **Maintenance with KR was manageable with no increase in treatment discontinuation due to toxicity**

PFS, progression-free survival; ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; ISS, International Staging System stage; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal, KR carfilzomib-lenalidomide maintenance; R, lenalidomide maintenance.

Gay et al, ASH 2020, Lancet 2021; 22:1715-20

Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), ASCT, MRD Response-Adapted Consolidation and Treatment Cessation-MASTER Trial



- 72% patients MRD-SURE.
- Standard and high-risk NDMM have similar depth of response and low risk of progression
- Quadruplet therapy achieves confirmed MRD (-) responses enables, enabling exploration of treatment cessation and "MRD-SURE" as alternative to continuous therapy

MRD assessment by NGS

Costa LJ et al. J Clin Oncol. 2021;JCO2101935.

UK HD MASTER trial

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

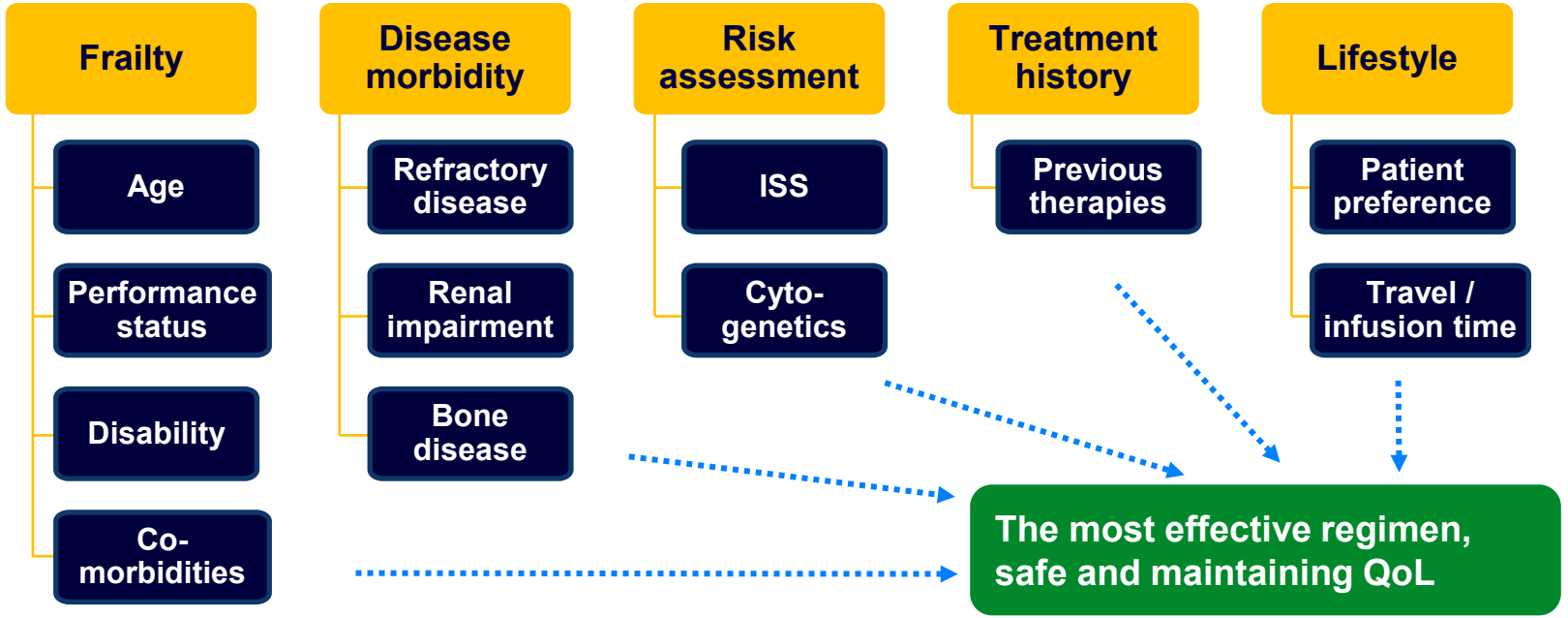
Len in standard risk, Bort or Len Bort in high risk, MoAbs under evaluation

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: 519-527
O'Donnell. Br J Haematol. 2018;182:222
Mateos MV, et al. NEJM. 2018;378:518-528
Mateos MV, et al Lancet 2020:395:132-141
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.

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, Isa Carfilzomib 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)

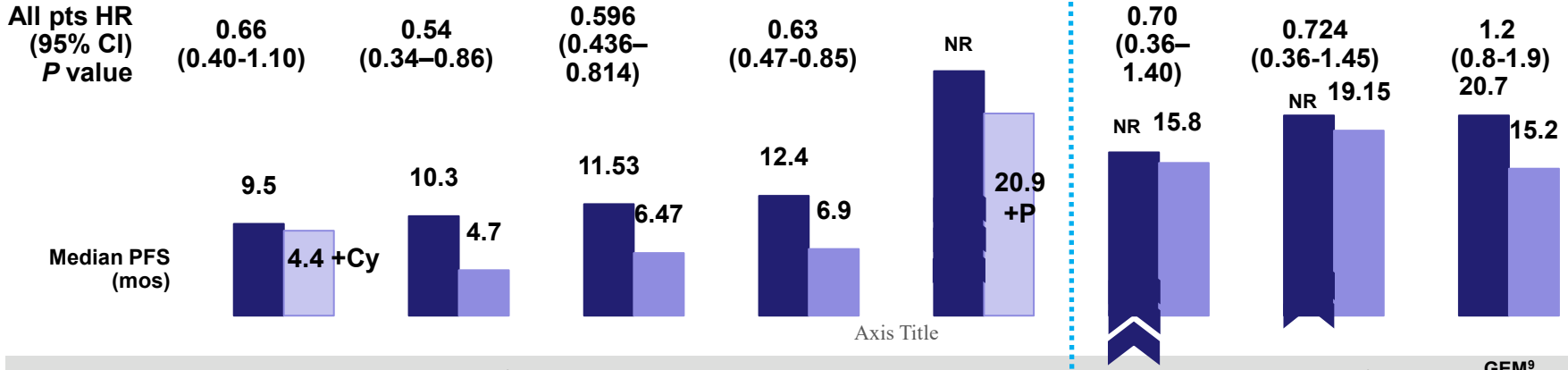
Active in Len refractory MM

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

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

Selinexor (GI side effects), Belantamab mafodotin (keratopathy), Idecel, Ciltacel CAR T cells (all FDA approved)

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.

Belantamab Mafodotin Monotherapy Achieved Clinical Responses in Triple-Class RRMM Patients in DREAMM-2[1]

Data cutoff*[1]:
January 31, 2020

Belantamab mafodotin — **DREAMM-2** (2.5mg/kg cohort) phase II[1]

Patient characteristics[1,2]

Overall population	N=97
Median age, years (range)	65 (60-70)
ECOG PS 2, n (%)	16 (17)
High-risk cytogenetics, n (%)	41 (42)
Median prior lines of therapy, n (range)	7 (3-21)
Triple refractory, n (%)	97 (100)

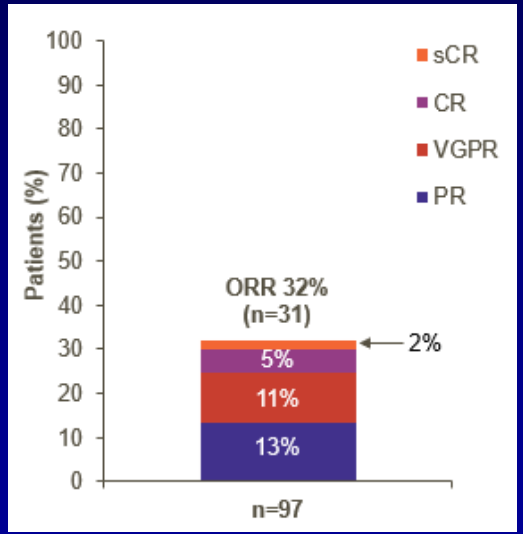
Efficacy outcomes[1,3]

ORR, n (%)	31 (32)
≥VGPR, n (%)	18 (19)
Median time to first response, months	1.4
mDOR, months	11
mPFS, months	2.8
mPFS of responders (≥VGPR), months	14
mOS, months	13.7

Safety data for overall population[1]

AE†	Any grade, n (%)	Grade ≥3, n (%)
Keratopathy‡	68 (72)	44 (46)§
Change in BCVA	51 (54)	29 (31)
Thrombocytopenia‖	36 (38)	21 (22)
Anemia	26 (27)	20 (21)

Overall response rate[1]

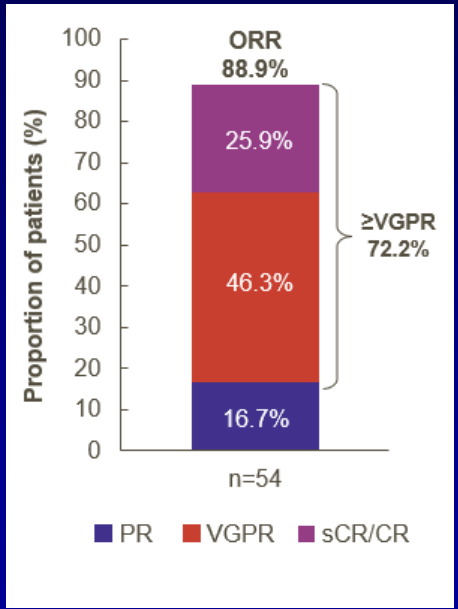


1. Lonial S et al. *Cancer.* 2021;127(22):4198-4212. 2. Prawitz T et al. *Adv Ther.* 2021;38(11):5501-5518. 3. BLENREP. Prescribing Information. GlaxoSmithKline; 2022.
4. Lonial S et al. *Blood Cancer J.* 2021;11(5):103. doi:10.1038/s41408-021-00494-4 5. Lonial S et al. Poster presented at: Society of Hematologic Oncology Annual Meeting; September 9-12, 2020. Poster MM-219.

ALGONQUIN part 1: Belantamab Mafodotin in Combination With Pd Shows High Efficacy in All Cohorts in 2L+ RRMM[1]

Patient characteristics[1]	N=56	
Median age, years (range)	64 (36-81)	
Median prior lines of therapy (range)	2.5 (1-5)	
Anti-CD38 (dara) refractory, n (%)	31 (55.4)	
Double refractory, n (%)	42 (75)*	
Triple refractory, n (%)	27 (48.2)†	
Efficacy outcomes[1]	**n=54**	
ORR, n (%)	48 (88.9)	
mPFS, months (95% CI)	17 (14.5-NR)	
Median follow-up, months (range)	11 (0.5-30.9)	
Safety outcomes,‡ n (%)[2]	**N=56**	
	Any grade	**Grade ≥3**
Keratopathy	56 (100)	41 (73.21)
Blurred vision	47 (83.92)	26 (46.42)
Thrombocytopenia	29 (51.87)	20 (35.71)
Neutropenia	28 (50)	22 (39.28)

Overall response rate[1]



No cases of secondary infections, CRS, or neurotoxicity were reported and no new safety signals were observed[1]

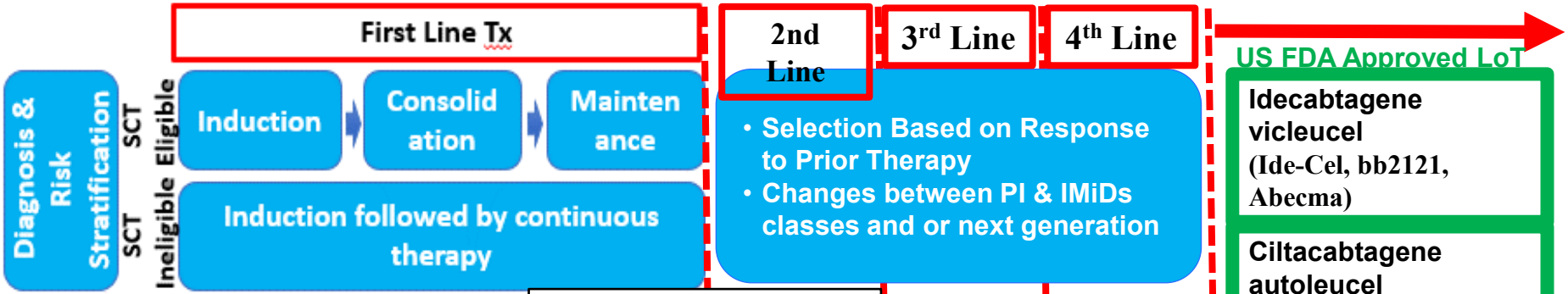
1. Trudel S et al. Poster presented at: American Society of Hematology Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA. Poster 1653.

CAR T-Cell Therapy in Multiple Myeloma

	Ide-cel FDA Approved Ph1 N=128	Cilta-cel FDA Approved Ph1b/2 N=97	Orva-cel Ph1b/2 N=62	bb21217 Ph1 N=72	CT053 Ph1b/2 N=20	P-BCMA-101 Ph1/2 N=55	GC012F Ph1 N=16	GPRC5D Ph1 N=18	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%	92% 5%	52% 3%
NT, % All grade Grade ≥3	18% 3%	21% 0.5%	13% 3%	16% 4%	15% / 17%[a] 8% / 0%	4% 4%	0 0	0 0	3% 0
ORR CR	73% ≥CR 33% (450: OR 81%, CR 39%)	97.9% ≥sCR 82.5%	92% CR 36%)	75% (≥CR 28%)	94% (≥CR 28%)	44% - 75%[b]	94% (≥CR 56%)	83%	61% in DL3 or DL 4 (n=26)
Median follow-up	13.3 mo	24.0 mo		5.8 mo	6 mo	120-508 days[b]	7.3 mo	13 wks	7.4 mo
Median DOR	10.7 mo (450: 11.3 mo)	21.8-NE mo	Not reported	17.0 mo	Not reported	Not reported	Not reached	Not reached	8.3 mo
Median PFS	8.6 mo 12.2 mo 20.2 CR/sCR	All : NR sCR: NR, 70% at 2 yrs	Not reported	Not reported	Not reported	Not reported	Not reported		Not reported
Median OS	24.8 mo	74% at 2 yrs Median NR	Not reported	Not reported	Not reported	Not reported	Not reported		Not reported

Munshi et al NEJM 2021; 705-16; Berjeda et al Lancet 2021; 398:314-24.; Lin et al; Alsina et al; Kumar et al; Costello et al; Jiang et al; Mailankody et al; Anderson et al; Usmani et al ASH/ASCO 2020,2021, 2022; Martin et al; Raje et al; Mailankody et al, ASH 2021

CAR-T Protocols in Earlier Lines of Therapy



KarMMa-2: Ide-cel in high-risk MM, early relapse after 1L/ASCT. (NCT03601078)

KarMMa-3: Randomized, controlled study for Ide-cel vs SOC triplet regimens. (NCT03651128)

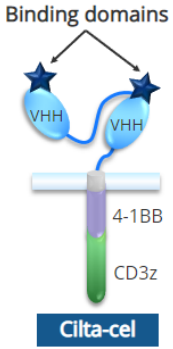
KarMMa-4: Ide-cel in high risk newly diagnosed MM (NCT04196491)

KarMMa-7: Ide-cel with CC-220, BMS-986405 (JSMD194), or other standard triplet regimens.

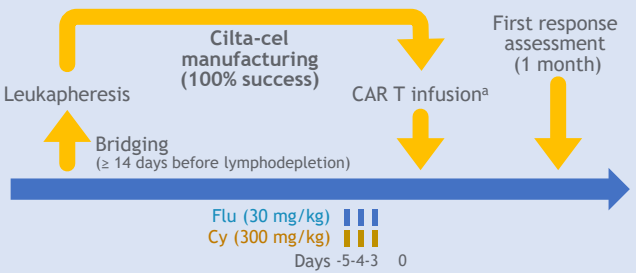
janssen Oncology

Courtesy of Yi Lin, M.D.Ph.D.

Phase 1b/2 CARTITUDE-1: Cilta-cel in RRMM



- RRMM
- ≥ 3 prior regimens
- Previously exposed to:
  - IMiD® agent
  - Proteasome inhibitor
  - Anti-CD38 Ab
  - Measurable disease
- Progressive MM per IMWG criteria



18 month F/U

Screened N = 113

Leukapheresed N = 113

Bridging N = 73

Cilta-cel infusion N = 97

Median administered dose: 0.71×10^6 ($0.51–0.95 \times 10^6$) CAR+ viable T cells/kg

Endpoints

- Phase 1b: Characterize cilta-cel safety and confirm the recommended phase 2 dose
- Phase 2: Evaluate cilta-cel efficacy

Patient characteristics[2]		
Years since diagnosis, median (range)		5.9 (1.6-18.2)
No. of prior antimyeloma regimens, median (range)		6 (3–18)
Prior autologous SCT, %	1	89.7
	> 1	8.2
Any bridging therapies for MM, %		75%
Refractory status, %	Anti-CD38 Ab refractory	99
	Triple refractory	87.6

Berdeja et al Lancet 2021; 398: 314-24; Martin et al ASH 2021

Cartitude 1 Ciltacel 22 mo median FU

ORR 97%, VGPR 95%, 83% sCR
Two year PFS 60.5%, median PFS and OS not reached
Of 61 evaluable pts, 92% MRD negative
Two year PFS if MRD negative at 6 and 12 months was 91% and 100%
No new safety signals

Usmani et al ASCO 2022

Cartitude 2: Ciltacel in Early Relapse (within one year of ASCT, or within one year in those without ASCT)

n=19 pts
ORR 100%, 90% CR, 95% VGPR
12 mo PFS 90%
84% CRS, ICANs grade 4 1 pt

van de Donk ASCO 2022

Cartitude 2 : Ciltacel for Relapse after 1-3 prior therapies

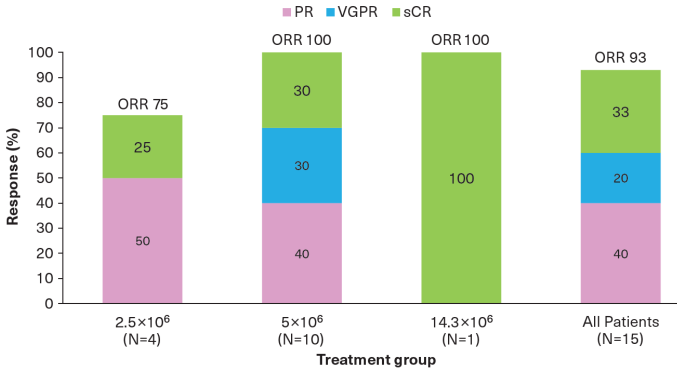
n=20 pts
ORR 95%, 75% CR/sCR, 85% VGPR
Median DOR not reached
CRS 85%, 10% grade ¾
3 pts ICANS grades 1-2

Agha et al ASCO 2022

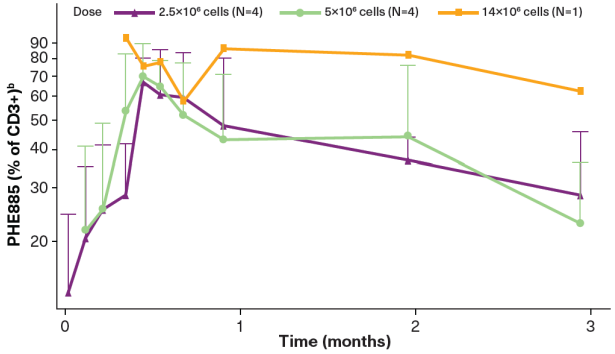
Phase I Study of PHE885, a Fully Human BCMA-Directed CAR-T Cell Therapy for Relapsed/Refractory Multiple Myeloma Manufactured in <2 Days Using the T-Charge™ Platform

- **Anti-BCMA CAR-T cells PHE885 is manufactured using the T-Charge™ platform, which reduces ex vivo culture time to about 24 hours and takes <2 days to manufacture the final product, thereby relying entirely on in vivo expansion after**

Figure 2. Summary of Tumor Response by ORR[a]

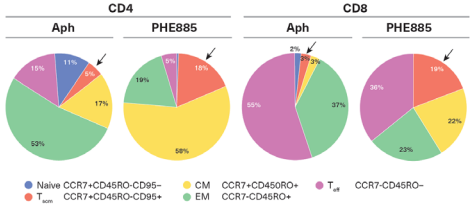


Cellular Kinetics of PHE885 by Flow Cytometry



T-Charge™ Process Preserves T-Cell Stemness in Final Product

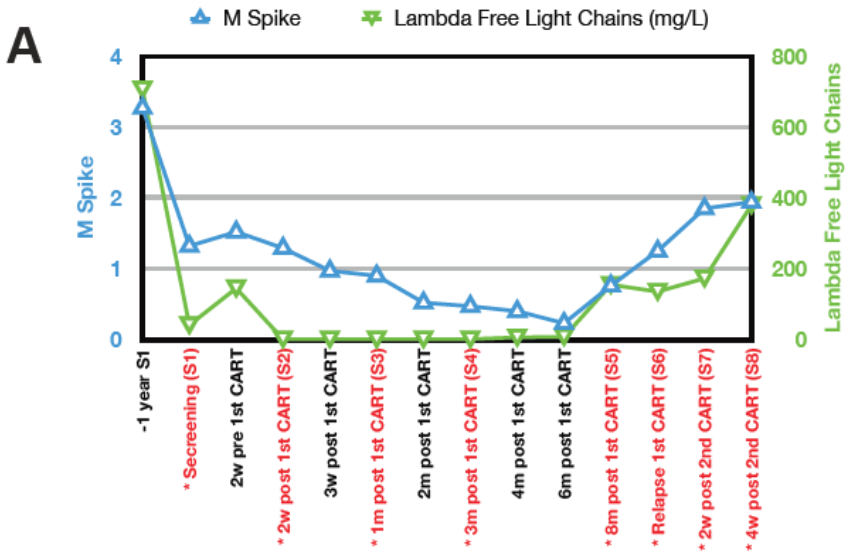
Figure 6. PHE885 Product Stemness

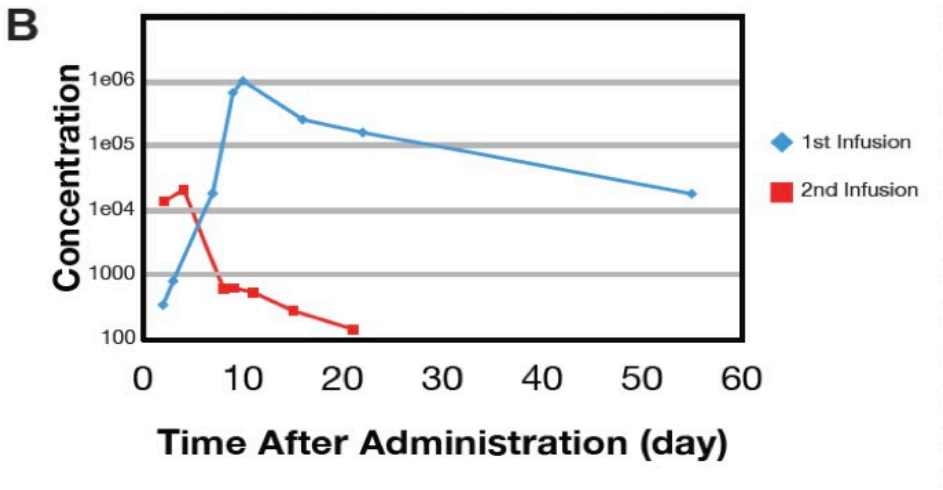


- **A Shift Toward Naive/Tscm Phenotype Is Observed in Patients Following PHE885 Treatment**
- **A shift to Tscm/Tnaive population in both CD4 and CD8 T cells in the >VGPR group but not PD group**

Sperling et al ASH 2021, EHA 2022.

Biallelic BCMA Loss Confers Resistance to BCMA CAR T Cells



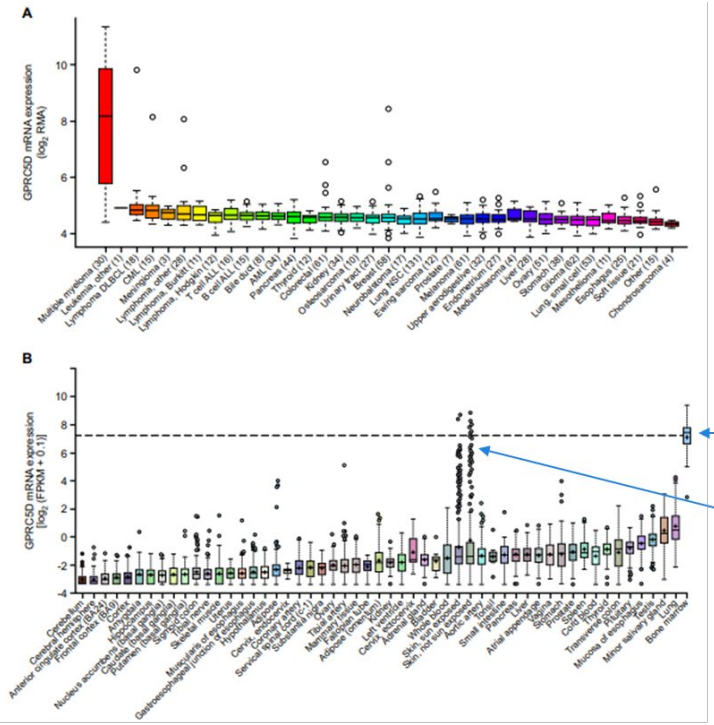


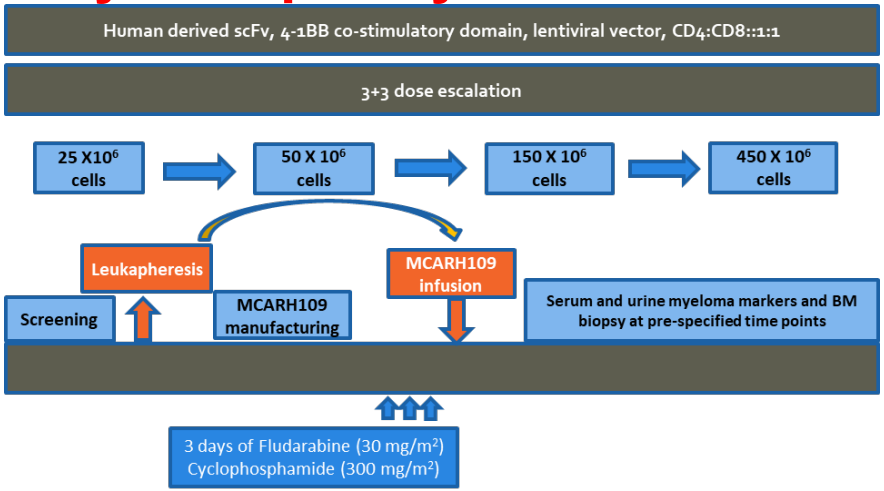
BCMA on 16p: should we be screening patients before BCMA therapy?

Dual targeting to avoid resistance: GPRC5D, CD19, FcHR5, CD38, CD138, SLAMF-7

Samur et al Nat Comm 2021; 12: 868

Phase I First-in-Class Trial of MCARH109, a G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) Targeted CAR T Cell Therapy in Relapsed or Refractory Multiple Myeloma





Response	Prior BCMA (n=10)	Prior CAR (n=8)
≥ PR, n (%)	8 (80)	6 (75)
≥ CR	3 (30)	3 (38)
BM MRD-	5 (50)	2 (25)

Mailankody et al ASH 2021

Smith EL. et al. Science Translational Medicine 2019

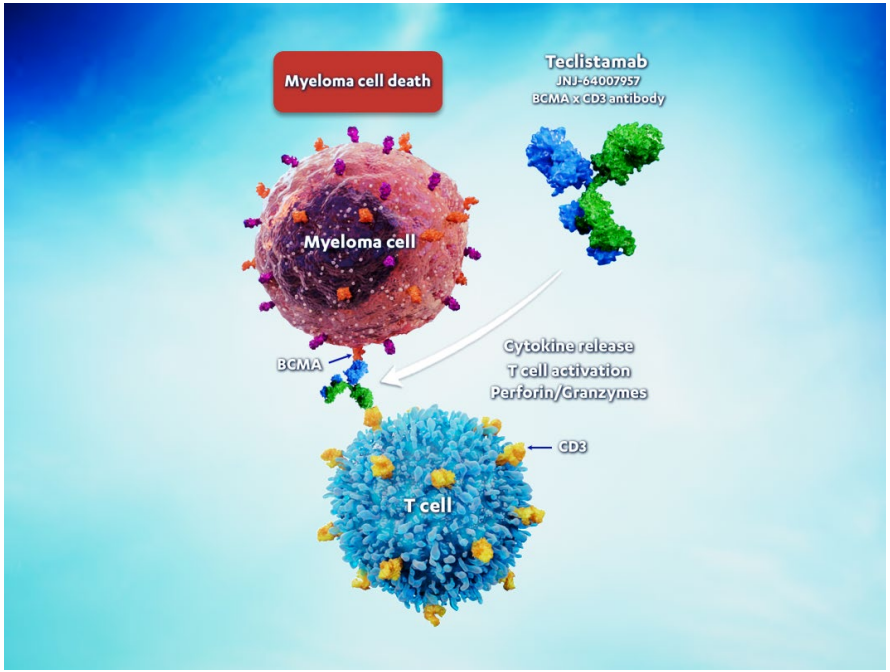
Bispecific T Cell Engagers (Bites) in Multiple Myeloma

	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 2020;
Moreau et al ASH 2021, NEJM 2022; Usmani et al. Lancet 2021; 398: 665-74

Teclistamab: A Novel BCMA × CD3 T-Cell Bispecific Antibody

- Teclistamab (JNJ-64007957) is an off-the-shelf, T-cell redirecting, bispecific antibody binds to CD3 on T cells and BCMA on plasma cells to mediate T-cell lysis of BCMA-expressing MM cells
- RP2D teclistamab monotherapy: 1.5 mg/kg subcutaneous (SC) QW with step-up doses of 0.06 and 0.3 mg/kg[3]
- **ASH 2021: pivotal phase 1/2 data from the 1.5 mg/kg dose of MajesTEC-1 shows 62% ORR with deepening responses over time**



Moreau et al ASH 2021, NEJM 2022; Usmani et al. Lancet 2021; 398: 665-74.

Teclistamab (9 month followup)

ORR 64%, > CR 30%
Median DOR not reached , 12 mo DOR 66%
Infections 63%, 35% grade ¾
CRS 72% 0.6% grade 3 grade ½ ICANS

Nooka et al ASCO 2022

Prior Exposure to BCMA (9.9 month followup)

38 pts, 25 evaluable for efficacy
Prior ADC 64%, prior CAR T 44%, both 2%
ORR 38% in ADC exposed and 45% in CAR T exposed pts
Infections 42%, 26% grade ¾
CRS 63%, 1 pt ICANS
Safety similar to BCMA non exposed pts

Touzeau et al ASCO 2022

Teclistamab with Daratumumab

Pts treated with CD38 Ab within 90 d were excluded

n=46 patients

ORR 78%, VGPR 73%, median DOR not reached
CRS 61% Infections 63%, grade 3/4 28%

Upregulation of CD38+/CD8+ T cells and proinflammatory cytokines support synergy of combination.

Otero et al ASCO 2022

Talquetamab GPRC5D Bispecific T cell Engager

405ug/kg and 800ug/kg cohorts

ORR 70% and 64%; VGPR 57% and 52%

Infections: 47% and 34%, grade ¾ 7% and 9%

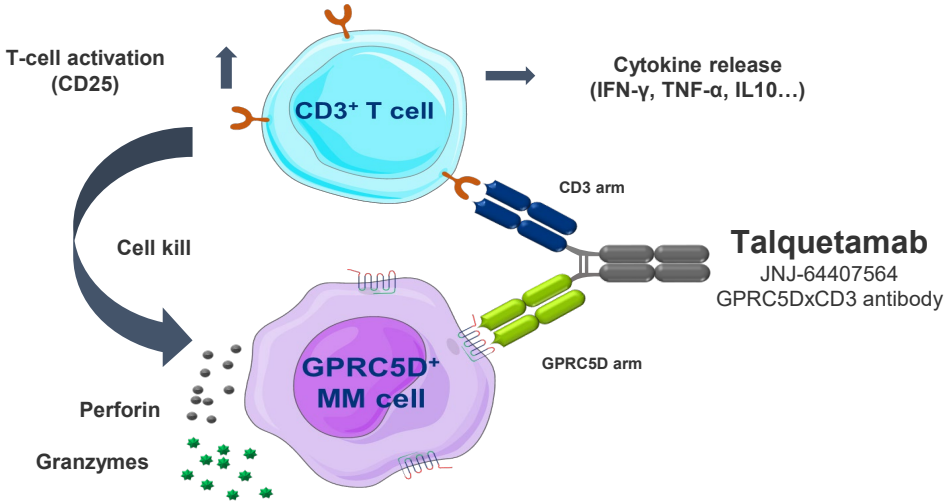
CRS 77% and 80%, grade 3: 3% and 0%

Skin and nails: 83% and 75%

Dysgeusia 63% and 57%

Minnema et al ASCO 2022

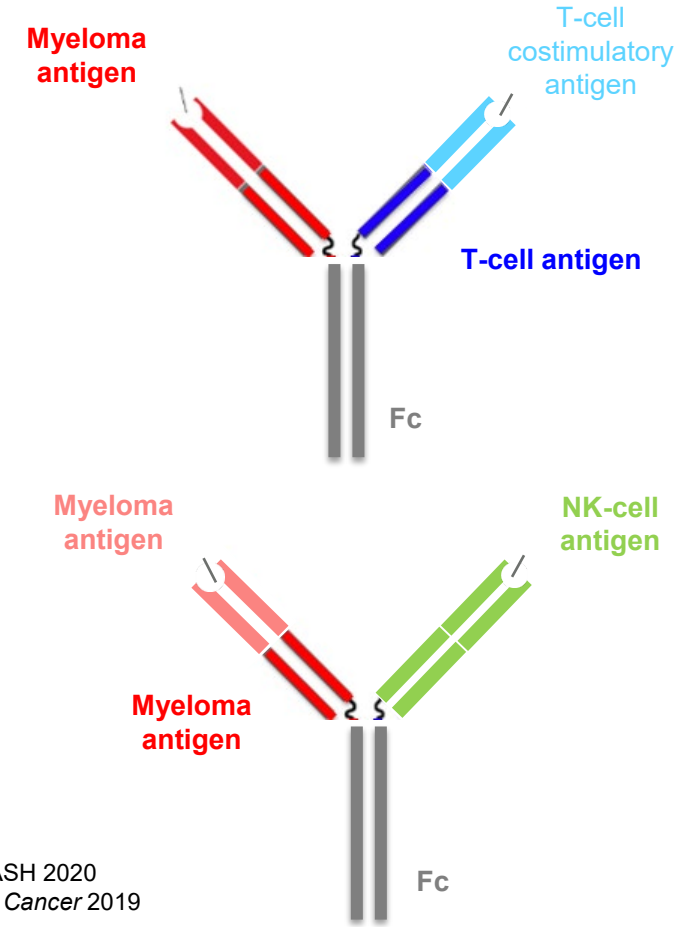
Talquetamab GPRC5D BiTE and Daratumumab



- **Talquetamab, binds to GPRC5D and CD3, well tolerated in heavily pretreated patients with RRMM, with at efficacy and safety 800 µg/kg SC Q2W or 405 µg/kg SC QW dosing**
- **QW or Q2W doses of talquetamab: 60-70% ORR in triple-class and penta-refractory patients (30% prior BCMA therapy) Responses were durable and deepened over time**
- **The combination of talquetamab + daratumumab appears tolerable, with ORR (77–85%) in these heavily pretreated patients/ Responses were observed in both CD38–exposed and –refractory patients**

Krishnan et al, Chari et al ASH 2021

Trispecific Antibodies



- Still in pre-clinical stages of development
- **With bispecifics, absence of T cell co-stimulation may increase likelihood of anergy and suboptimal anti-tumor response**
- A **trispecific T cell engager** targeting CD38, CD3, and CD28 (co-stimulatory protein on T-cells)
  - very potent killing of CD38+ MM cell lines, 3- to 4-log higher than daratumumab
  - suppressed MM growth in mice and promoted proliferation of memory and effector T-cells and downregulation of regulatory T-cells in primates
- **Trispecific NK cell engagers** also being developed targeting CD16A on NK cell as well as BCMA and CD200 on MM cells

Lancman, et al. ASH 2020
Wu, et al. *Nature Cancer* 2019

Conclusion and Future Directions

BCMA immunotoxin, CAR T cells, and BiTEs achieve high rates of MRD negative responses in triple/penta refractory MM and have favorable safety profiles.

Ongoing trials are evaluating BCMA immunotoxin, CAR T and/or BiTEs to treat MM earlier in the disease course.

Current autologous CAR T have logistical challenges versus off the shelf BiTEs/immunotoxin. However, novel CART targets (GPRC5D) and constructs (PHE 885,) and BiTEs (trispecifics) may improve outcome and availability of these therapies.

Future Directions: Combination PI, IMiD, Dex, CD38MoAb, ie Dara RVD now achieves high rates MRD negativity in NDMM, including high risk MM; CARs and/or BiTEs are being compared with ASCT to induce long term MRD negative complete responses with memory anti-MM immunity. These patients will then be free of disease and off all therapy.