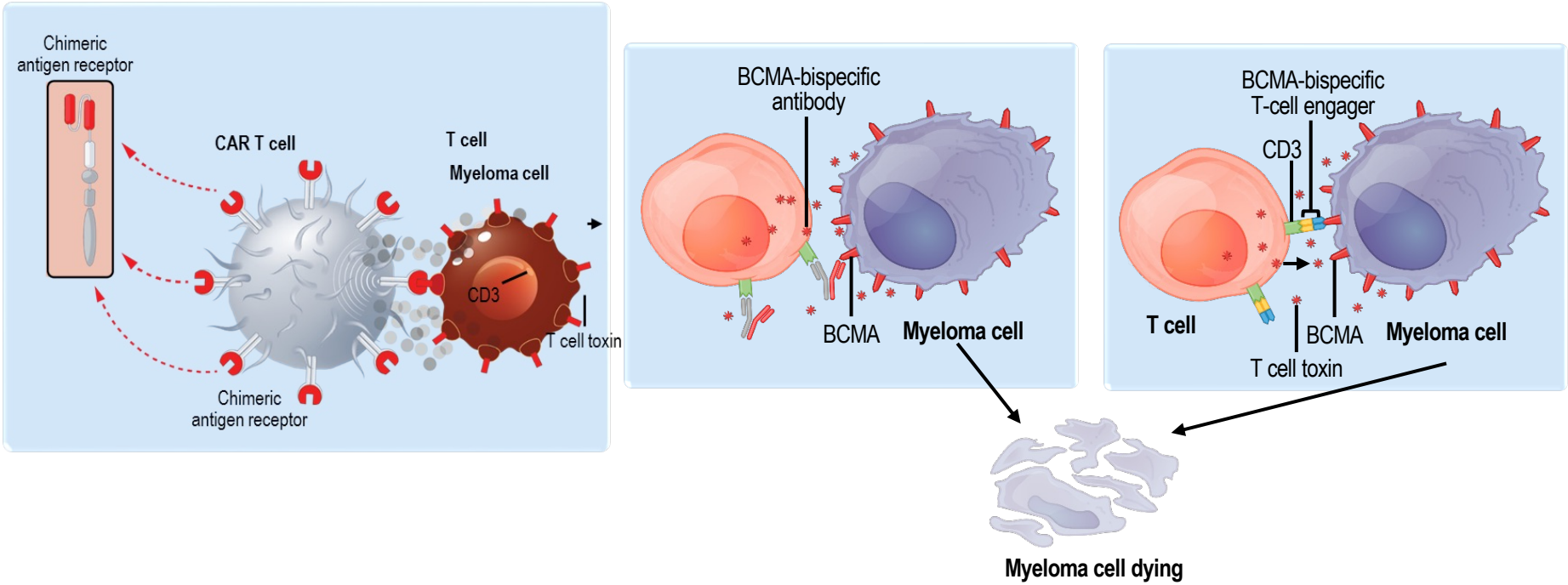
Memorial Sloan Kettering Cancer Center

Role of Immunotherapy in Multiple Myeloma

Saad Z. Usmani, MD MBA FACP
Chief of Myeloma Service

Memorial Sloan Kettering Cancer Center

The Promise of T-cell redirection



CAR, chimeric antigen receptor; MM, multiple myeloma
CAR T-cell therapy is not yet FDA-approved for patients with MM.

Adapted from Cho S-F et al. *Front Immunol*. 2018;9:1821.

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BCMA CARTs: Summary

	CARTITUDE-1[1] Cilta-cel Phase 1/2	CRB-401[2] Ide-cel Phase 1	KarMMa[3] Ide-cel Phase 2	LUMMICAR-2[4] Zivo-Cel Phase 1b	PRIME[5] P-BCMA-101 Phase 1/2	GC012F[6] Dual CAR-T BCMA+CD19
Patients	97	62	128	20	55	19
Median prior regimens	6	6	6	5	8	5
Triple refractory, %	87.6%	69.4%	84.0%	85%	60%	95%
CAR-T dose	0.71×10^6 (range 0.5–0.95×10^6)	50, 150, 450 and 800 x 10^6	150, 300, 450 x10^6	1.5-1.8/2.5-3.0 x10^8	0.75-15 x10^6	1.0-3.0 x10^5
ORR	97.9%	75.8%	50%/69%/82.0%	94.0%	67%[b]	94.7%
CR/sCR	80.4%	38.7%	25%/29%/39%	28%	NR	84.2%
PFS	66%@ 18m	8.8m	12m @450mil			
CRS, all grades	94.8%	75.8%	50%/76%/96%	77%/83%[a]	17%	95%
CRS, grade 3/4	4%	6.5%	0/7%/6%	0%	0%	11%
Neurotoxicity, all grades	20.6%	35.5%	0/17%/20%	15%/17%[a]	3.8%	0%
Neurotoxicity, grade 3/4	10.3%	1.6%	0/1%/6%	8%/0[a]	3.8%	0%

[a]1.5-1.8/2.5-3.0 x10^8 dose, [b]0.75x10^6 dose

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; CRS, cytokine release syndrome; NR, not reported

1. Usmani et al., ASCO 2021: Abstract 8005; 2. Lin et al., ASH 2020: Abstract 131;
3. Anderson et al., ASCO 2021: Abstract 130; 4. Kumar et al., ASH 2020: Abstract 133;
5. Costello et al., ASH 2020: Abstract 134; 6. Jiang et al., ASCO 2021: Abstract 8014

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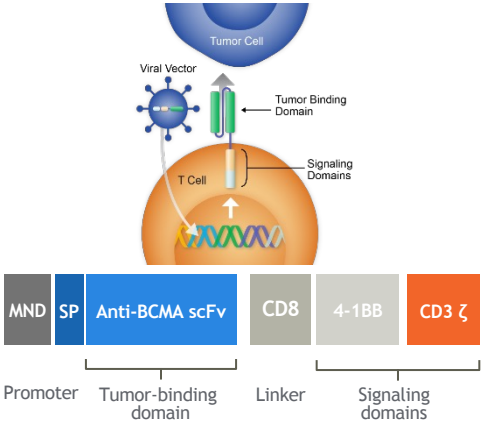
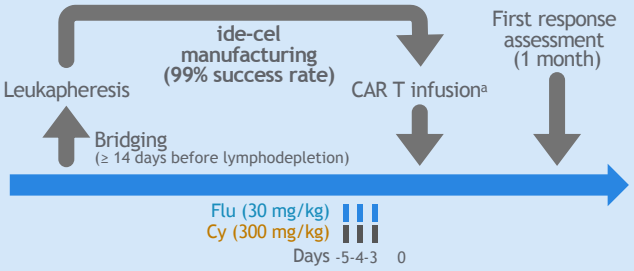
Phase 2 KarMMa Study: Ide-cel in Relapsed Refractory Multiple Myeloma



- RRMM
- ≥ 3 prior regimens
- Previously exposed to:
  - IMiD® agent
  - Proteasome inhibitor
  - Anti-CD38 Ab
- Refractory to last prior therapy per IMWG[b]



Study status as of 14 January 2020

Screened N = 158

↓

Leukapheresed N = 140

↓

Treated N = 128 (Target dose CAR T cells)

150 × 10⁶	n = 4
300 × 10⁶	n = 70
450 × 10⁶	n = 54

↓

Median follow-up (months)

150 × 10⁶	18.0
300 × 10⁶	15.8
450 × 10⁶	12.4
Total	13.3

Endpoints[2,3]

- **Primary:** ORR (null hypothesis ≤ 50%)
- **Secondary:** CRR (key secondary; null hypothesis ≤ 10%), safety, DOR, PFS, OS, PK, MRD[c], QOL, HEOR
- **Exploratory:** Immunogenicity, BCMA expression/loss, cytokines, T-cell immunophenotype, GEP in BM

Patient characteristics[2]		
Time since initial diagnosis, median (range) in yrs		6 (1–18)
No. of prior antimyeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1	94
	> 1	34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab refractory	94
	Triple refractory	84

ORIGINAL ARTICLE FREE PREVIEW

The NEW ENGLAND JOURNAL of MEDICINE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D., Deepu Madduri, M.D., Jesús Berdeja, M.D., Sagar Lonial, M.D., Noopur Raje, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Albert Oriol, M.D., Philippe Moreau, M.D., Ibrahim Yakoub-Agha, M.D., Ph.D., et al.

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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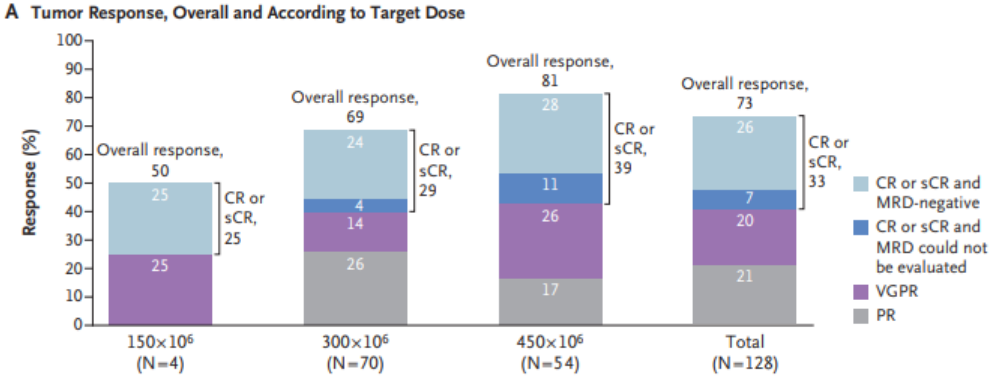
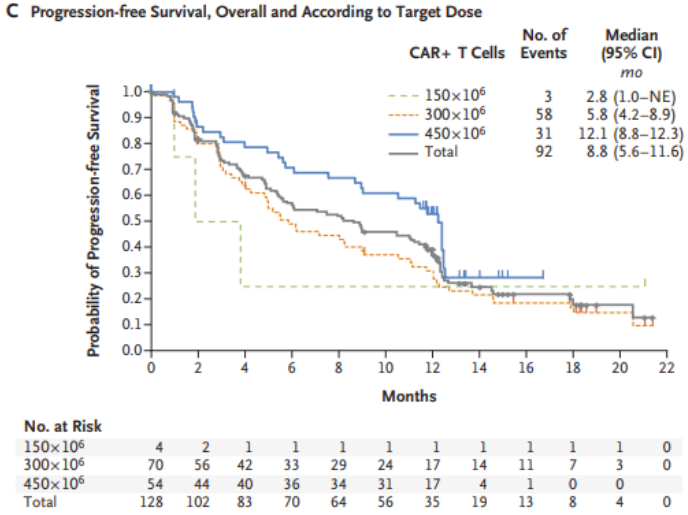
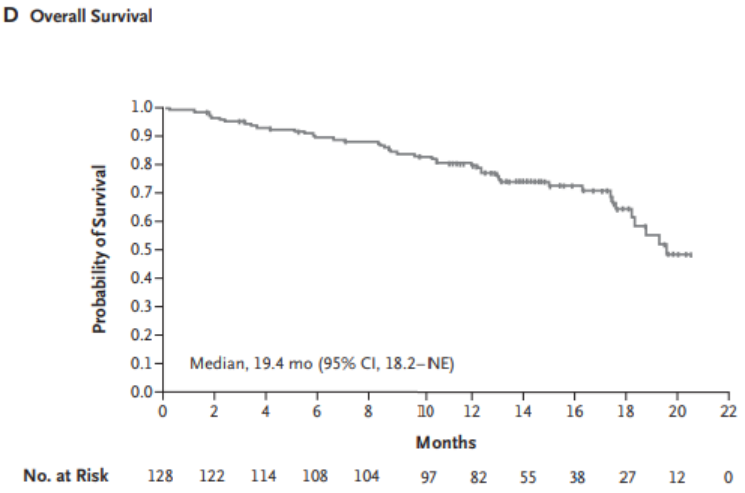
Ide-cel Delivers High Response Rate and PFS in Relapsed and Refractory Multiple Myelom







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Updated Results From the CARTITUDE-1 Phase 1/2 Study of Cilta-cel in Patients With RRMM: Study Design and Patients

Key Eligibility Criteria
- Progressive MM per IMWG criteria
- ECOG PS ≤1
- ≥3 prior lines or double-refractory, prior PI, IMiD, and anti-CD38 mAb

Screening (1 to ≤28 days)

Apheresis

Bridging therapy[a] (as needed)

Cy (300 mg/m^2) + Flu (30 mg/m^2), day -5 to -3

Cilta-cel infusion (Day 1)
Target dose 0.75x10^6 (range, 0.5-1.0x10^6) CAR+ viable T cells/kg

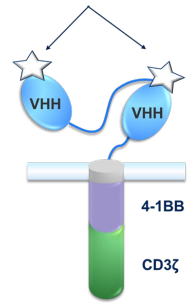
Postinfusion assessments (day 1-100)
Safety, efficacy, PK, PD, biomarker

Posttreatment assessments (day 101 to end of cohort)
Safety, efficacy, PK, PD, biomarker

Follow-up

Primary objectives: Safety and confirm RP2D (phase 1b); efficacy (phase 2)

Binding domains



Patient Characteristics	N=97
Median age (range), years	61 (43-78)
Extramedullary plasmacytomas, n (%)	13 (13.4)
BM plasma cells ≥60%, n (%)	21 (21.9)
High-risk cytogenetics, n (%)	23 (23.7)
del(17p)	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)
Median prior lines of therapy (range), n	6 (3-18)
≥5 prior lines of therapy, n (%)	64 (66)
Prior ASCT, n (%)	87 (89.7)
Triple-class refractory, n (%)	85 (87.6)
Penta-refractory, n (%)	41 (42.3)
Refractory to last line of therapy, n (%)	96 (99)
Median years since diagnosis (range)	5.9 (1.6-18.2)

Martin T, et al. ASH 2021. Abstract 549.

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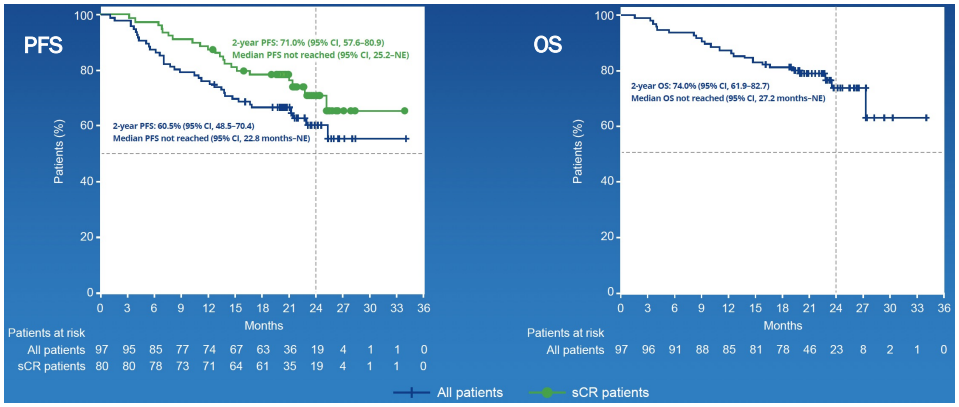
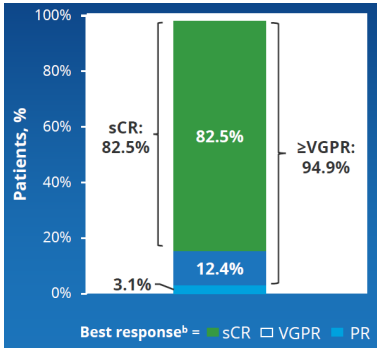
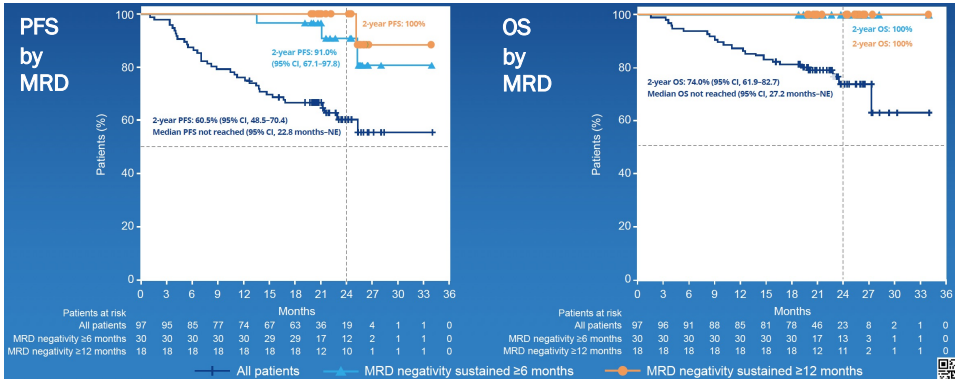
Updated Results From the CARTITUDE-1 Phase 1/2 Study of Cilta-cel in Patients With RRMM: Efficacy



ORR (by IRC): 97.9% (95/97)





Efficacy		(N=97)
Best response of sCR by median follow-up, %	1 year	67
	2 years	83
Median time to __ (range), months	First response	1 (0.9-10.7)
	Best response	2.6 (0.9-17.8)
	≥CR	2.9 (0.9-17.8)
Median DOR (range), months		NE (21.8-NE)
MRD-negative (10^{-5}) [n=61], %		92

Martin T, et al. ASH 2021. Abstract 549.

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CRS/NT Events With BCMA CAR T-Cell Therapies

- CRS and NT events were primarily grade 1/2 and manageable

	KarMMa[1] N = 128	CARTITUDE-1[2] N = 97
≥ 1 CRS event, n (%)	107 (84)	92 (95)
Grade 1/2	100 (78)	87 (95)
≥ Grade 3	7 (5)	5 (5)
Median onset (range), days	1 (1 – 12)	7 (1 – 12)
Median duration (range), days	5 (1 – 63)	4 (1 – 97)
≥ 1 NT event, n (%)	23 (18)	20 (21)
Grade 1/2	18 (12)	10 (10)
≥ Grade 3	5 (4)	10 (10)
ICANS any grade, %	-	17

Munshi et al. NEJM 2021; 384(8):705-716. Berdeja et al. Lancet 2021; 398:314

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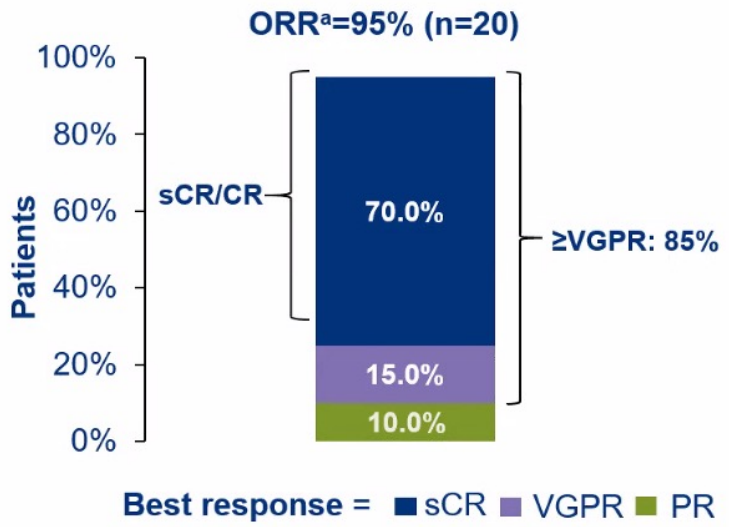
Efficacy and Safety of Cilta-cel in Lenalidomide-Refractory Patients with Progressive Multiple Myeloma after 1–3 Prior Lines of Therapy: CARTITUDE-2

- As of Jan 2021 data cut-off, median follow-up was 5.8 months, median age 60 years; 65% were male
- All patients were exposed to PI, IMiD, and dexamethasone, 95% to alkylating agents, and 65% to daratumumab
- **Efficacy**
  - Median time to first response: 1.0 month
  - Median time to best response: 1.9 months
  - Median duration of response: not reached
  - All patients (n=4) with MRD-evaluable samples at the 10^{-5} threshold were MRD negative at data cut-off
- **Safety**

  No movement and neurocognitive treatment-emergent AEs were observed.



Agha M et al. ASCO 2021

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CARTITUDE-4: Phase 3 Study of Cilta-cel vs PVd or DPd in RRMM (NCT04181827)

Primary objective

- To compare efficacy of cilta-cel to the standard treatments of PVd or DPd

Secondary objectives

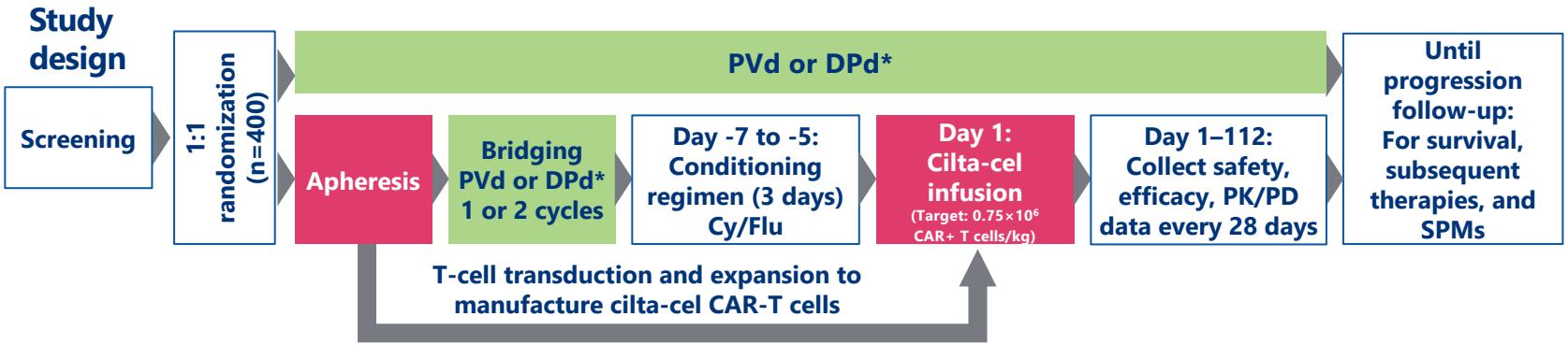
- To further compare efficacy of cilta-cel with PVd or DPd
- To further characterize the safety of cilta-cel to characterize PK/PD and immunogenicity of cilta-cel
- To evaluate the impact of cilta-cel treatment vs PVd or DPd on HRQOL

Key inclusion criteria

- Age ≥18 with diagnosed MM
- Prior 1–3 lines of therapy (must include PI+IMiD), and lenalidomide-refractory

Key exclusion criteria

- Prior CAR-T or BCMA-targeting therapy,
- Diagnosed or treated for malignancy other than MM
- Prior allogenic SCT ≤6 months before apheresis
- Prior ASCT ≤12 weeks before apheresis



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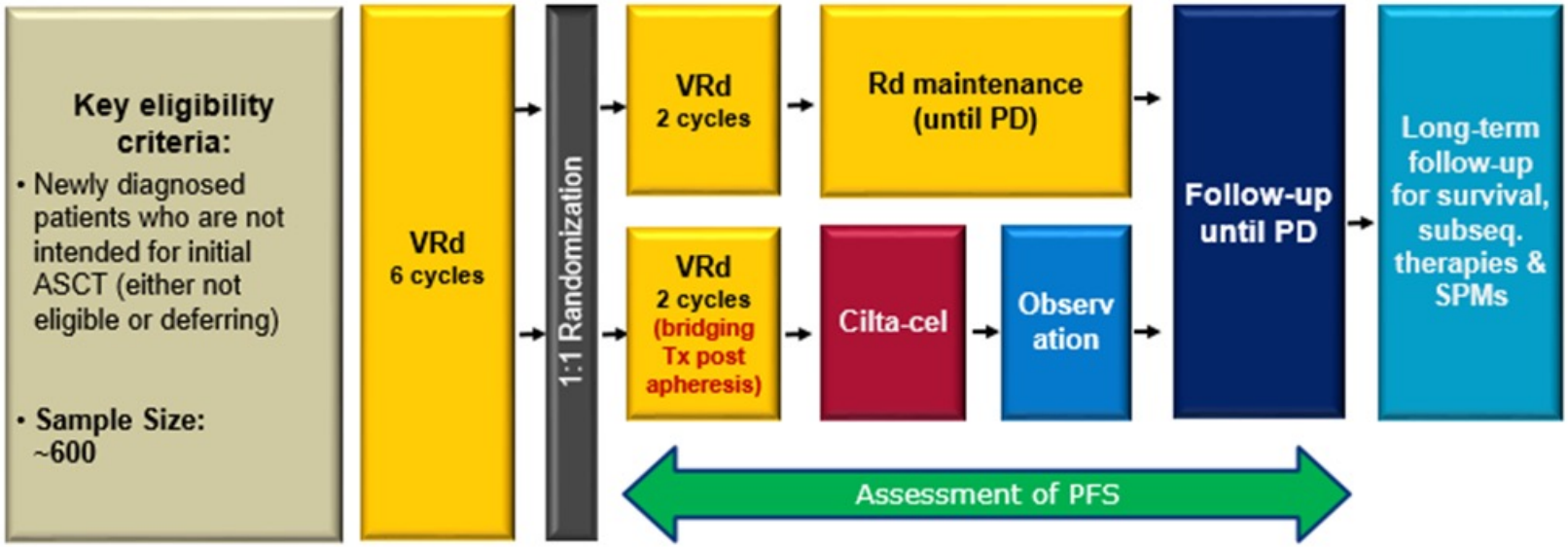
CARTITUDE-5: Randomized, phase 3 in NDMM, not intended for transplant (NCT04923893)



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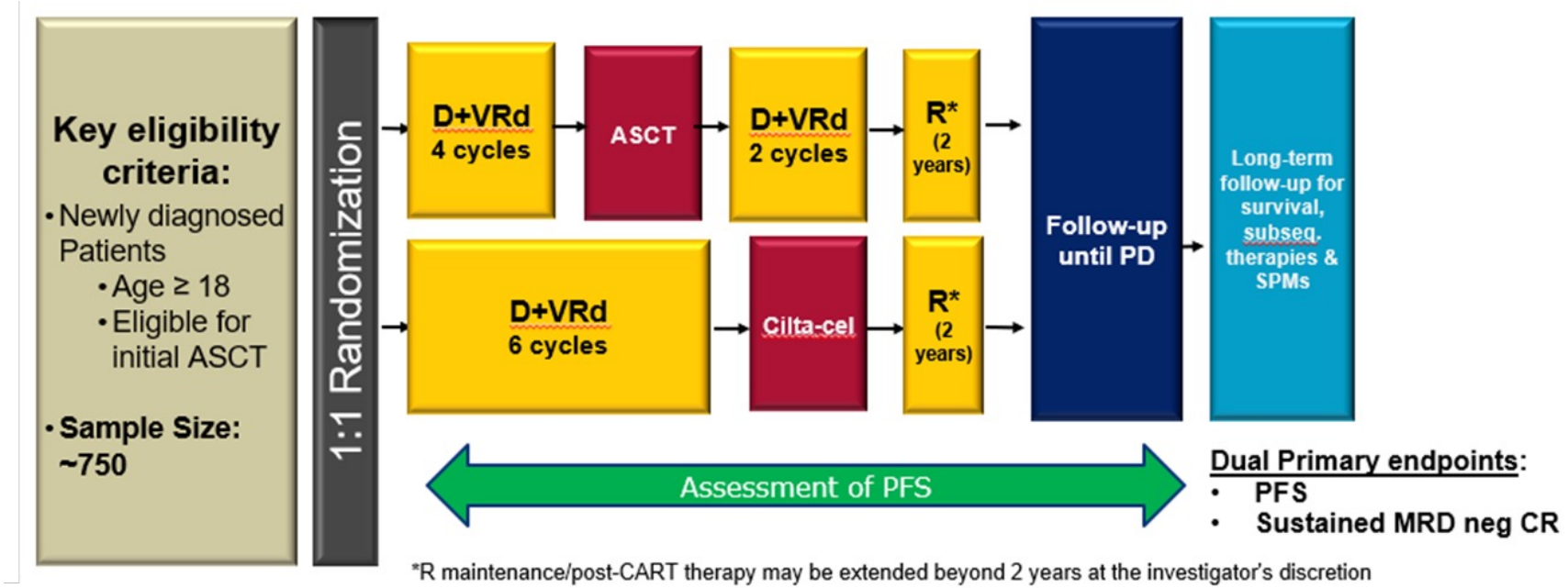
CARTITUDE-6: Randomized, phase 3 in NDMM, transplant eligible (NCT05257083)



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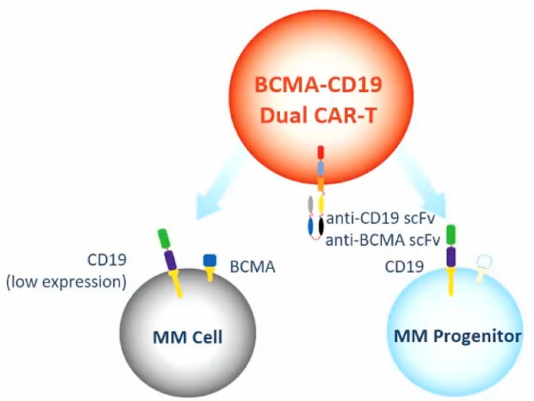
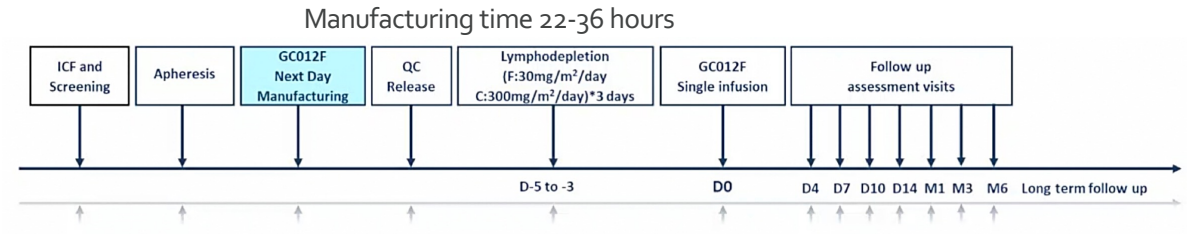
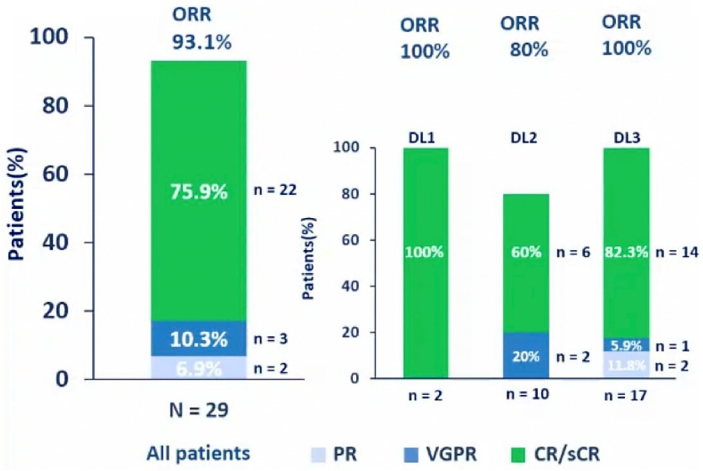
GC012F: Fast, dual-targeting CAR





- Median age, years: 57 (27-76)
- Median PL: 5
- High-risk cytogenetics: 26 (90%)
- Triple-class exposed: 28 (97%)
- MRD negativity (flow cytometry 10^{-4}-10^{-6}): 22/29 (75.9%) in sCR; 25/29 (86.2%) in VGPR
- ICANS: 0
- CRS: all grades 25 (86%); grade ≥3: 2 (7%)



BCMA, B-cell maturation antigen; C, cyclophosphamide; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; D, day; ICANS, immune effector cell-associated neurotoxicity syndrome; F, fludarabine; ORR, overall response rate; PL, prior lines of treatment; PR, partial response; QC, quality control; scFv, single-chain variable fragment; sCR, stringent CR; VGPR, very good partial response

Du J et al. EHA 2022;abstract S186 (oral presentation)

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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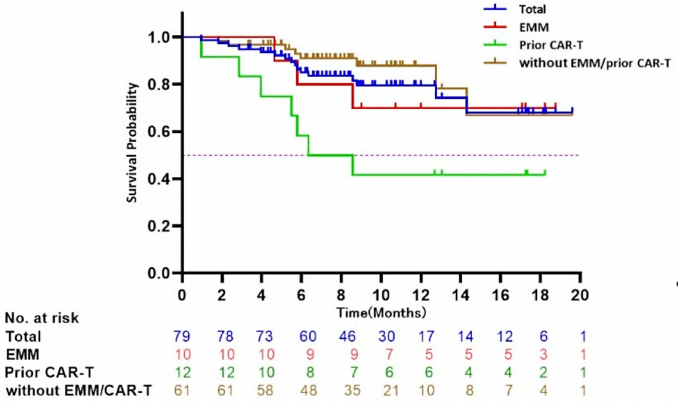
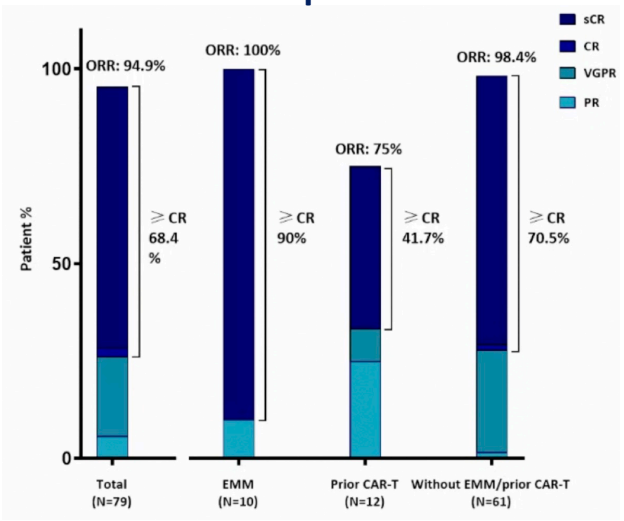
CT103A: Phase I/II trial

- Median age, years: 57 (39-70)
- Median PL: 5
- High-risk cytogenetics: 27 (34.2%)
- Triple-class refractory: 13 (16.5%)

Progression-free survival



Overall response rates



- MRD negativity (NGF 10^{-5}): 92.4%
  - All patients with CR/sCR were MRD negative
- CRS: all grades 75 (94.9%); grade ≥3 O
- ICANS: all grades 2 (2.5%); grade ≥3 0

CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; EMM, extramedullary disease; ICANS, immune effector cell-associated neurotoxicity syndrome; NGF, next-generation flow cytometry; ORR, overall response rate; PL, prior lines of treatment; PR, partial response; sCR, stringent CR; VGPR, very good partial response

Li C et al. EHA 2022;abstract S187(oral presentation)

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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Phase 1 Study of an Allogeneic Anti-BCMA Therapy for Patients With RRMM: Study Design and Patients

Key Eligibility Criteria
- RRMM with ≥3 prior therapies including an IMiD, a PI, and an anti-CD38 mAb
- Refractory to last prior therapy
- ECOG PS 0-1

- *Part A: ALLO-715 dose escalation with 2 lymphodepleting regimens*
- Part B: ALLO-715 + nirogascestat
- Part C: Consolidation dosing with ALLO-715

Part A[a] Enrolled (N=48)[b]: Safety and Efficacy Population (N=43)
Median time from enrollment to start of therapy: 5 days
Overall median follow-up: 4 months

CAR T-Cell Dose, Cells	Lymphodepletion Regimen[c]			
	FCA39	FCA60	FCA90	CA39
40 X 10^6 (DL1)	3	-	-	-
160 X 10^6 (DL2)	4	-	-	3
320 X 10^6 (DL3)	11	10	3	3
480 X 10^6 (DL4)	3	3	-	-

Patient Characteristics		Safety Population (N=43)
Median age (range), years		64 (46, 77)
ECOG PS, %	0	49
	1	51
ISS Stage III, %		19
High-risk cytogenetics,[d] %		37
Extramedullary disease, %		21
High tumor burden at screening, %		33
Median time since diagnosis (range), years		4.9 (0.9, 26.4)
Median prior anti-MM regimens (range), n		5 (3, 11)
Prior ASCT, %		91
Penta exposed/refractory, %		84/42

Primary endpoints: Safety and tolerability
Secondary and exploratory endpoints: ALLO-715 dose and lymphodepletion regimen, ORR, DOR, PFS, MRD, ALLO-715 kinetics, ALLO-647 PK

[a]Part A was single dose of ALLO-715 cell on dose escalation. [b]5 patients became ineligible due to organ failures from PD. [c]FCA conditioning with Flu/Cy/ALLO-647; CA conditioning with Cy/ALLO-647; Flu 30 mg/m²/d x3d; Cy 300 mg/m²/d x3d; ALLO-647 13-20 mg x3d. [d]del(17p), t(4;14), t(14;16), and/or t(14;20),
Mailankody S, et al. ASH 2021. Abstract 651.

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Phase 1 Study of an Allogeneic Anti-BCMA Therapy for Patients With RRMM: Safety, Efficacy, and Summary

TEAEs of Interest (N=43), n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
CRS	13 (30)	10 (23)	1 (2)	0	0	24 (56)
Neurotoxicity	4 (9)	2 (5)	0	0	0	6 (14)
GvHD	0	0	0	0	0	0
Infection	3 (7)	10 (23)	7 (16)	0	3 (7)	23 (54)

Response in DL3[a]	FCA39 (n=11)	FCA60 (n=10)	FCA90 (n=3)	FCA All (n=24)
ORR, n (%)	**7 (64)**	**8 (80)**	**2(67)**	**17 (71)**
VGPR+, n (%)	5 (46)	5 (50)	1 (33)	11 (46)
CR/sCR, n (%)	3 (27)	3 (30)	0	6 (25)
Median DOR, months (95% CI)	8.3 (3.4, 11.3)	NE (5.6, NE)	3.1 (2.4, 3.1)	8.3 (3.4,11.3)
Median follow-up, months (range)	3.3 (0.5, 3.8)	3.8 (3.1, 11.2)	-	3.8 (0.5, 11.2)

Safety

- 20 (47%) patients had a SAE
- 30 (70%) patients experienced grade ≥3 neutropenia
- Grade 5 infections in 3 patients (2 previously reported; 1 additional due to sepsis)
- Use of tocilizumab and steroids: 23% and 14%

Efficacy

- Median time to response was 16 days
- In DL3 FCA expansion, 9 patients with an initial response remain in response with median DOR of 8.3 months
  - Of those with a VGPR+, 92% were MRD neg
  - MRD neg was correlated with durable response and PFS
- sBCMA levels were 10x lower in responders vs nonresponders

Authors' Conclusions

- ALLO-715 with ALLO-647 was well tolerated with low-grade CRS, low-grade reversible neurotoxicity, no GvHD, and manageable safety
- Response rates were comparable to autologous CAR T-cell therapy

[a]3 patients treated with 320M CART-cells and the CA LD regimen are not included. 2 of those responded with 1 patient achieving CR.

Mailankody S, et al. ASH 2021. Abstract 651.

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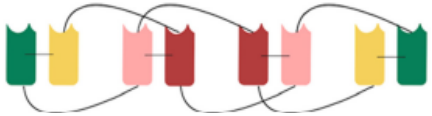
BsAbs – Many Different Platforms

Bispecific T-cell Engager or BiTE

Dual Affinity Re-Targeting or DART

Tandem diabodies or TandAb



BsAb armed activated T-cells or BAT (mostly academic)

T-cell dependent BsAb Xmab

CrossMAb

Duobody

Trifunctional Antibody or TriFAb

Adapted from Lejeune M et al. Front Immunol 2020 11:762.

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Teclistamab: MajesTEC-1 Study Design

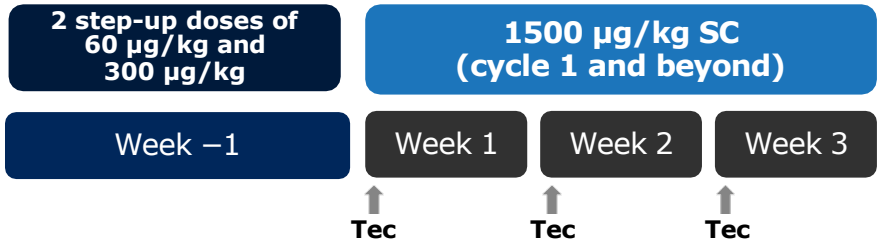
KEY OBJECTIVES

- Part 1: Identify RP2D
- Part 2: Safety and tolerability at RP2D
- Antitumor activity, pharmacokinetics, pharmacodynamics

KEY ELIGIBILITY CRITERIA

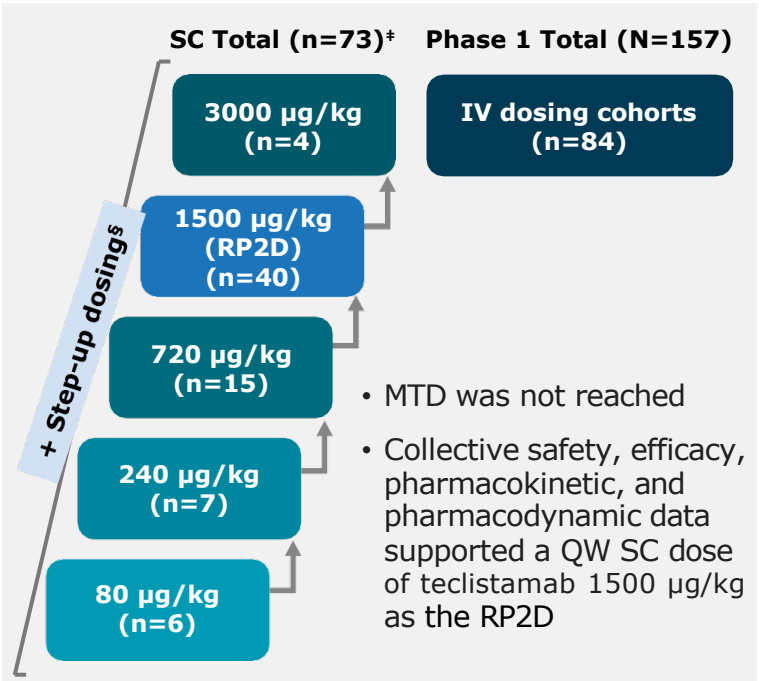
- Adults with measurable MM
- R/R or intolerant to established MM therapies
- Hemoglobin ≥8 g/dL, platelets ≥75 × 10^9/L,* ANC ≥1.0 × 10^9/L
- No prior BCMA-targeted therapy

Dosing Schedule at RP2D



Premedications† were limited to step-up doses and first full dose

- No steroid requirement after first full dose



The data cut-off date for these analyses was March 29, 2021. *≥50 × 10^9/L for patients with ≥50% bone marrow plasma cells. †Glucocorticoid, antihistamine, and antipyretic. ‡1 patient had received step-up doses but not the first full dose as of the data cut-off date. §1-3 step-up doses given within 1 week before a full dose.
ANC = absolute neutrophil count; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose; R/R = relapsed/refractory; QW = once weekly; SC = subcutaneous.

Moreau P et al. Updated results from MajesTEC-1: Phase 1/2 study of teclistamab, a b-cell maturation antigen x CD3 bispecific antibody, in relapsed/refractory multiple myeloma. Presented at: 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021.

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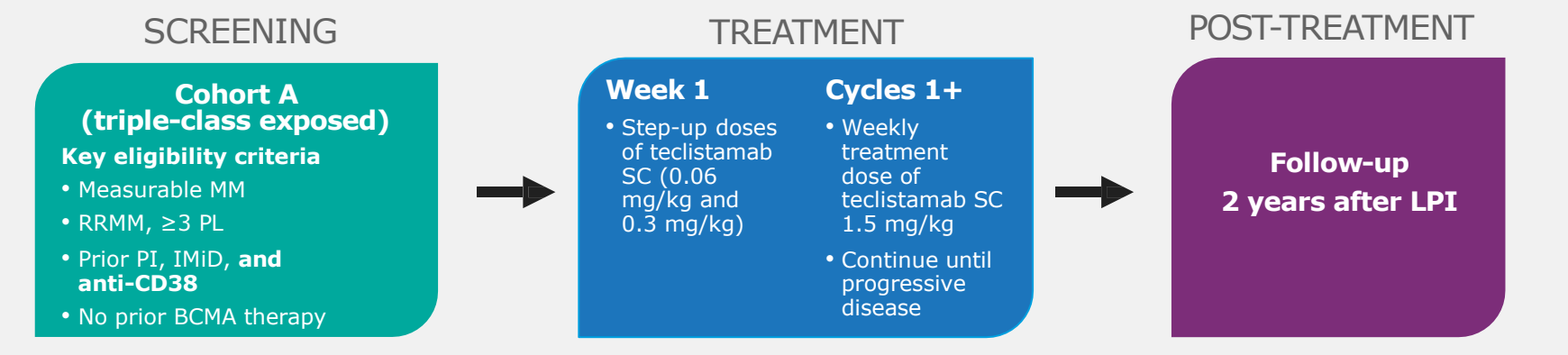
MajesTEC-1: Phase 2 Study Design

- MajesTEC-1 is a first-in-human, phase 1/2, open-label, multicohort, multicenter dose escalation study to evaluate teclistamab in patients with RRMM who previously received ≥3 prior lines of therapy and were triple-class exposed



- **Primary endpoint: ORR**
- **Key secondary endpoints:** DOR, ≥VGPR, ≥CR, sCR, TTR, MRD status, PFS, OS, safety, pharmacokinetics, immunogenicity, PRO

CR = complete response; DOR = duration of response; IMiD = immunomodulatory drug; LPI = last patient in; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI = proteosome inhibitor; PL = prior line; PRO = patient reported outcome; sCR = stringent CR; TTR = time to response; VGPR = very good partial response.

Moreau P et al. Updated results from MajesTEC-1: Phase 1/2 study of teclistamab, a b-cell maturation antigen x CD3 bispecific antibody, in relapsed/refractory multiple myeloma. Presented at: 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021.

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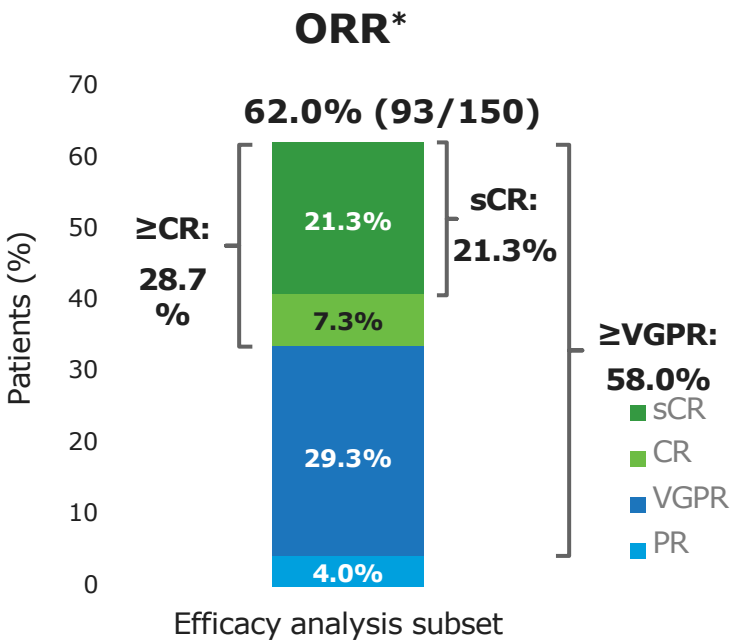
MajesTEC-1: Overall Response Rate for Teclistamab Monotherapy



- At a median follow-up of 7.8 months (range: 0.5–18):
  - **ORR of 62.0%** (95% CI, 53.7–69.8) represents a substantial benefit for patients with triple-class exposed disease
- Median time to first response: 1.2 months (range: 0.2–5.5)
- MRD negativity rate†
  - 24.7% (37/150; 95% CI, 18.0–32.4) at a threshold of 10^{-5}
  - 16.7% (25/150; 95% CI, 11.1–23.6) at a threshold of $10^{-6,‡}$
- In patients who achieved ≥CR, the MRD negativity rate was 41.9%

*PR or better, IRC assessed; ORR was assessed in efficacy analysis population, which includes all patients who received their first dose on or before March 18, 2021 (n=150). †Baseline clones were obtained for all patients. All MRD assessments were done by next-generation sequencing. ‡Patients who were not negative at the 10^{-6} threshold were indeterminate.
CI = confidence interval; IRC = independent review committee; ORR = overall response rate; PR = partial response.

Moreau P et al. Updated results from MajesTEC-1: Phase 1/2 study of teclistamab, a b-cell maturation antigen x CD_3 bispecific antibody, in relapsed/refractory multiple myeloma. Presented at: 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021.

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MajesTEC-1: Overall Safety Profile

Safety Analysis Set N=165		
AEs ≥20%, n (%)	**Any Grade**	**Grade 3/4**
Hematologic		
Neutropenia	108 (65.5)	94 (57.0)
Anemia	82 (49.7)	57 (34.5)
Thrombocytopenia	63 (38.2)	35 (21.2)
Lymphopenia	56 (33.9)	53 (32.1)
Nonhematologic		
CRS	118 (71.5)	1 (0.6)
Injection site erythema	42 (25.5)	0 (0)
Fatigue	41 (24.8)	3 (1.8)
Nausea	40 (24.2)	1 (0.6)
Headache	36 (21.8)	1 (0.6)
Diarrhea	34 (20.6)	4 (2.4)

Teclistamab was well tolerated; no patients required dose reduction

- Only 1 patient discontinued due to an AE (adenoviral pneumonia)
- Serious AEs occurred in 88 patients (53.3%)
  - Teclistamab-related serious AEs* occurred in 33 patients
- Injection-site reactions occurred in 58 patients (35.2%; all grade 1/2)
- Infections occurred in 104 (63%) patients (35.2%; grade 3/4)
  - 9 (5.5%) patients had opportunistic infections†
- 119 patients (72.1%) had evidence of hypogammaglobulinemia‡
  - 41 of these patients received IVIg at any time during the study (at physician discretion)
- There were 9 deaths due to AEs; none were related to teclistamab
  - COVID-19 (n=7)
  - Pneumonia (n=1)
  - Hemoperitoneum (n=1)

*Considered to be related by the investigator. †Included adenovirus infection, adenovirus reactivation, cytomegalovirus viremia, cytomegalovirus reactivation, hepatitis B virus reactivation, BK virus infection, *Pneumocystis jirovecii* pneumonia, and aspergillus. ‡Assessed by AE or lab values (postbaseline IgG level below 500 mg/dL).

AE = adverse event; CRS = cytokine release syndrome; Ig = immunoglobulin; IVIg = intravenous immunoglobulin; TEAE = treatment-emergent adverse event.

Moreau P et al. Updated results from MajesTEC-1: Phase 1/2 study of teclistamab, a b-cell maturation antigen x CD3 bispecific antibody, in relapsed/refractory multiple myeloma. Presented at: 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021.

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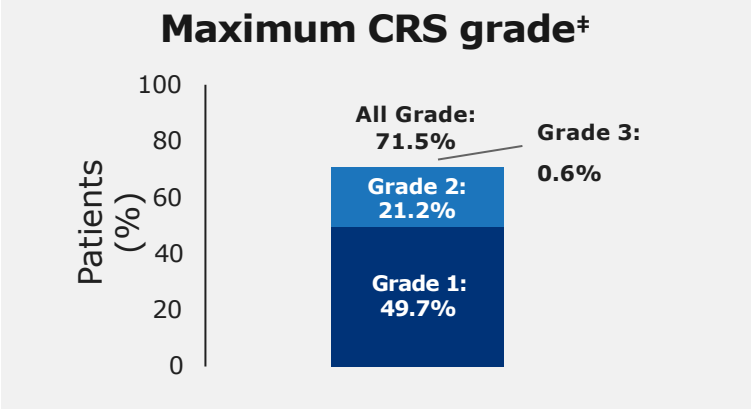
MajesTEC-1: Cytokine Release Syndrome

Parameter	Safety Analysis Set N=165
Patients with CRS, n (%)	118 (71.5)
Patients with ≥2 CRS events	54 (32.7)
Time to onset (days), median (range)	2 (1–6)
Duration (days), median (range)	2 (1–9)
Patients who received supportive measures,* n (%)	109 (66.1)
Tocilizumab	60 (36.4)
Low-flow oxygen by nasal cannula†	21 (12.7)
Steroids	13 (7.9)
Single vasopressor	1 (0.6)



- All CRS events were grade 1/2, except for 1 transient grade 3 CRS event that fully resolved, and 97% of events were confined to step-up and cycle 1
- All CRS events resolved, with no treatment discontinuations due to CRS
- Over the course of their treatment, 2.4% of patients received >1 dose of tocilizumab for a single CRS event

*A patient could receive >1 supportive therapy. †≤6 L/min; CRS was graded using Lee et al, *Blood,* 2014 in the phase 1 portion of the study and ASTCT in phase 2.
‡In this combined analysis, Lee et al, *Blood,* 2014 criteria were mapped to ASTCT criteria for patients in the phase 1 portion.
ASTCT = American Society for Transplantation and Cellular Therapy.
Moreau P et al. Updated results from MajesTEC-1: Phase 1/2 study of teclistamab, a b-cell maturation antigen x CD3 bispecific antibody, in relapsed/refractory

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MajesTEC-1: Neurotoxicity

Parameter	Safety Analysis Set N=165
Patients with neurotoxicity, n (%)	21 (12.7)
Headache	14 (8.5)
ICANS*	5 (3.0)
Enceph alopathy	2 (1.2)
Tremor	2 (1.2)
Patients with grade ≥3 events	0
Time to onset, median (range) days	2.5 (1–7)
Duration, median (range) days	3.0 (1–37)
Patients requiring supportive measures for neurotoxicity, n (%)	12 (7.3)
Tocilizumab	3 (1.8)
Dexamethasone	3 (1.8)
Levetiracetam	1 (0.6)

- The overall incidence of neurotoxicity was low
- The most commonly reported neurotoxicity event was headache (14 patients [8.5%])
- All events were grade 1/2
- There were no treatment discontinuations or dose reductions due to neurotoxicity†
- 12 patients (7.3%) required supportive measures for neurotoxicity
- There were 5 patients with ICANS events at the RP2D
  - All were grade 1/2
  - Most (7/9) ICANS events were concurrent with CRS; all resolved

*1 of the events of confusional state reported in a patient treated at RP2D in phase 1 was considered by the sponsor to be consistent with ICANS and presented as such in summaries of ICANS events. †TEAEs under the "nervous system disorder" or "psychiatric disorder" SOC that were judged by the investigator to be related to study drug; including ICANS events.
ICANS = immune effector cell–associated neurotoxicity syndrome; SOC = system organ class.

Moreau P et al. Updated results from MajesTEC-1: Phase 1/2 study of teclistamab, a b-cell maturation antigen x CD3 bispecific antibody, in relapsed/refractory multiple myeloma. Presented at: 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021.

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MajesTEC Trials

- Majest-TEC-2: A Multi-arm Phase 1b Study of Teclistamab With Other Anticancer Therapies in Participants With Multiple Myeloma

- Majest-TEC-3: Phase III Study of Teclistamab in Combination With Daratumumab Subcutaneously (SC) (Tec-Dara) Versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants With Relapsed or Refractory Multiple Myeloma

- MajesTEC-4: Phase III Study of Teclistamab in Combination With Lenalidomide Versus Lenalidomide Alone in Participants With Newly Diagnosed Multiple Myeloma as Maintenance Therapy Following Autologous Stem Cell Transplantation

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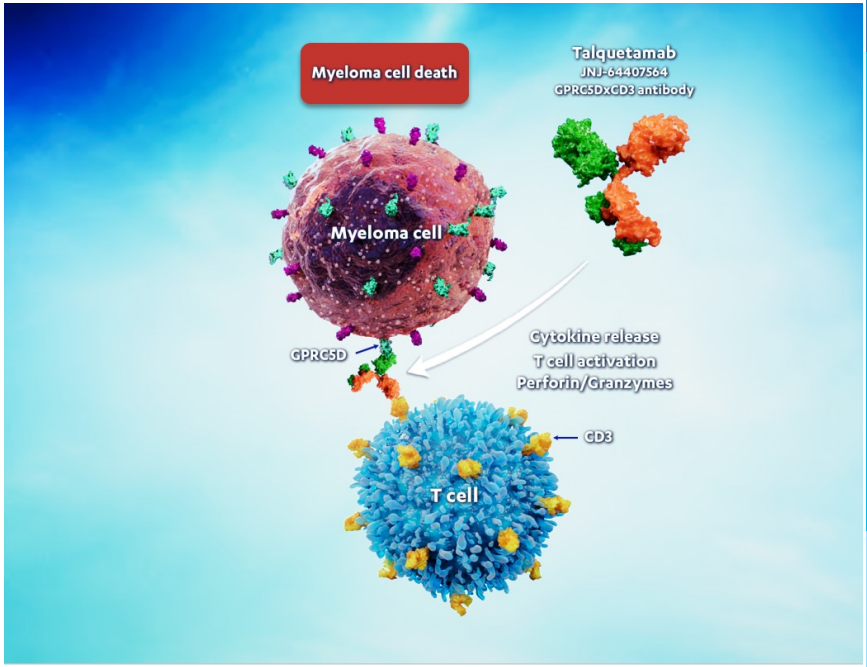
Talquetamab: A GPRC5D × CD3 Bispecific Antibody

- GPRC5D is highly expressed on MM plasma cells, making it a promising target for MM therapy[1-5]
- Talquetamab (JNJ-64407564) is a first-in-class antibody that binds to GPRC5D and CD3 receptors, mediating T cell recruitment, activation and subsequent lysis of GPRC5D+ MM cells[6]
- In the ongoing, phase 1, first-in-human study of talquetamab in patients with RRMM (MonumenTAL-1; NCT03399799), the first RP2D was identified as a weekly SC dose of 405 µg/kg[a,7–8]
- Here we present
  - Updated data from patients treated at the first RP2D[a]
  - Initial results from patients treated at a second RP2D of 800 µg/kg Q2W



[a]In phase 1, 405 µg/kg SC QW was the RP2D; 400 µg/kg SC QW was selected as final dosing concentration in phase 2 for operational convenience.
GPRC5D, G protein-coupled receptor family C group 5 member D; MM, multiple myeloma; RP2D, recommended phase 2 dose; Q2W, every other week; QW, weekly; RRMM, relapsed/refractory MM; SC, subcutaneous
1. Verkleij CPM, et al. *Blood Adv* 2021; 5:2196-215. 2. Smith EL, et al. *Sci Transl Med* 2019; 11:eaau7746. 3. Inoue S, et al. *J Invest Dermatol* 2004; 122:565-73. 4. Brauner-Osborne H, et al. *Biochim Biophys Acta* 2001; 1518:237-48. 5.Goldsmith, R et al. 18th International IMW Workshop 2021. Poster P095. 6. Pillarisetti K, et al. *Blood* 2020; 135:1232-43. 7. Chari A, et al. 62nd ASH Annual Meeting and Exposition 2020. Oral #290.
8. Berdeja J, et al. ASCO Annual Meeting 2021. Oral #8008.

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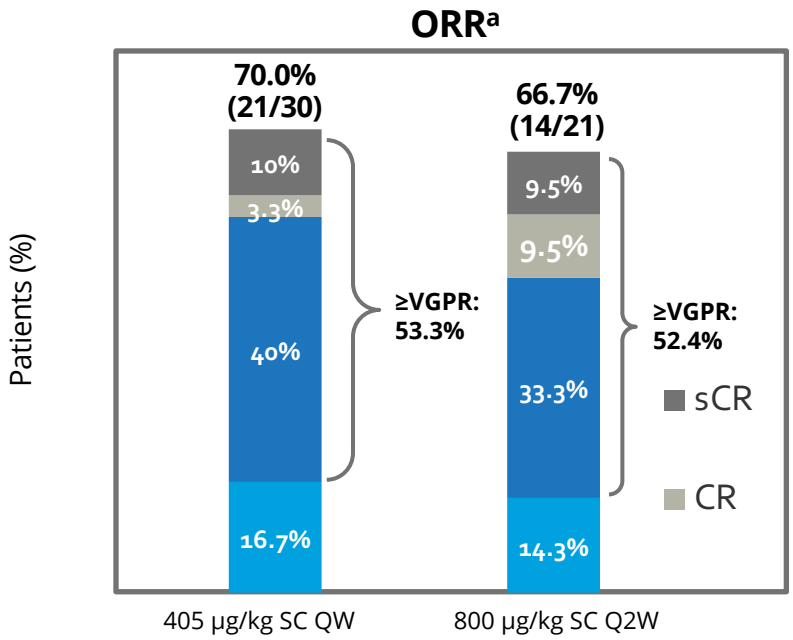
MonumenTAL-1: Overall Response Rate



Response	405 µg/kg SC QW[b] n=30	800 µg/kg SC Q2W[b] n=25
Median follow-up (months), median (range)	9.0 (0.9–17.1)	4.8 (0.4–11.1)
Response-evaluable patients,[c] n	30	21
ORR, n (%)	21 (70.0)	14 (66.7)
ORR in triple-class–refractory patients, n/N (%)	15/23 (65.2)	12/18 (66.7)
ORR in penta-drug–refractory patients, n/N (%)	5/6 (83.3)	5/6 (83.3)
Median time to first confirmed response (months), median (range)	0.9 (0.2–3.8)	1.2 (0.2–6.8)

- ORR appears to be comparable across both RP2Ds

Med prior lines = 5
CRS 77%, 72%

[a]Investigator assessment of evaluable patients per 2011 IMWG response criteria; includes unconfirmed responses; [b]With 2–3 step-up doses; [c]Patients who had ≥1 dose of talquetamab and ≥1 postbaseline disease evaluation. CR, complete response; IMWG, International Myeloma Working Group; ORR, overall response rate; PR, partial response; Q2W, every other week; QW, weekly; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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TRIMM-2: Overall Response Rate

Response Categories	Evaluable patients[a], n (%)		
	Dara 1800 mg SC: Cycle 1-2: QW, Cycles 3-6: Q2W; Cycles 7+: monthly		
	Tal 400 µg/kg SC Q2W (n=5)	Tal 400 µg/kg SC QW (n=7)	Tal 800 µg/kg SC Q2W (n=9)
ORR[b]	**4 (80.0)**	**6 (85.7)**	**7 (77.8)**
sCR/CR	1 (20.0)	2 (28.6)	1 (11.1)
VGPR	2 (40.0)	3 (42.9)	5 (55.6)
PR	1 (20.0)	1 (14.3)	1 (11.1)
MR	0 (0)	0 (0)	0 (0)
SD	0 (0)	1 (14.3)	2 (22.2)
PD	1 (20.0)	0 (0)	0 (0)

- Median follow-up was 4.2 months
- Median time to first confirmed response: 1.0 month (range: 0.9–2.4)
- ORR across all dose levels was improved compared to RP2Ds for tal monotherapy

[a]Patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. Includes unconfirmed responses;
[b]PR or better in response-evaluable patients; includes unconfirmed responses.
CR, complete response; Dara, daratumumab; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; QW, weekly; Q2W, every other week; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; Tal, talquetamab; VGPR, very good partial response

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

Med prior lines = 6
CRS 55%;
Skin/nail events: 65%

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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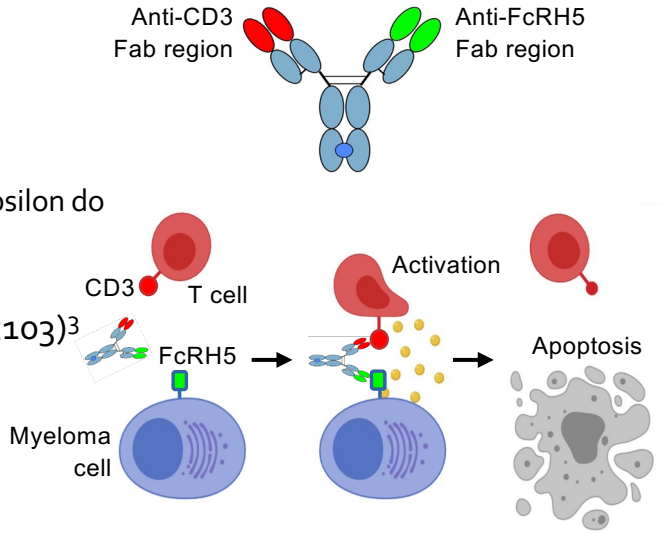
Cevostamab: FcRH5xCD3 Bispecific Antibody

- Fc receptor-homolog 5 (FcRH5)
  - expressed exclusively in B-cell lineage (myeloma cells > normal B cells)[1]
  - near ubiquitous expression on myeloma cells[1,2]
- Cevostamab bispecific antibody
  - targets membrane-proximal domain of FcRH5 on myeloma cells and epsilon do
  - dual binding results in T-cell directed killing of myeloma cells[1]
- Previously reported Phase I dose-finding experience (NCT03275103)[3]
  - promising activity in patients with heavily pre-treated RRMM
  - manageable safety, with C1 single step-up dosing providing effective CRS mitigation



Aims: (1) share updated Phase I dosing-finding results, and
(2) evaluate the impact of C1 single step-up and C1 double step-up dosing on CRS

C, Cycle; CRS, cytokine release syndrome;
Fab, fragment antibody binding; RRMM, relapsed/refractory multiple myeloma

- 1. Li et al. Cancer Cell 2017;31:383–95
  2. Sumiyoshi et al. EHA 2021; 3. Cohen et al. ASH 2020

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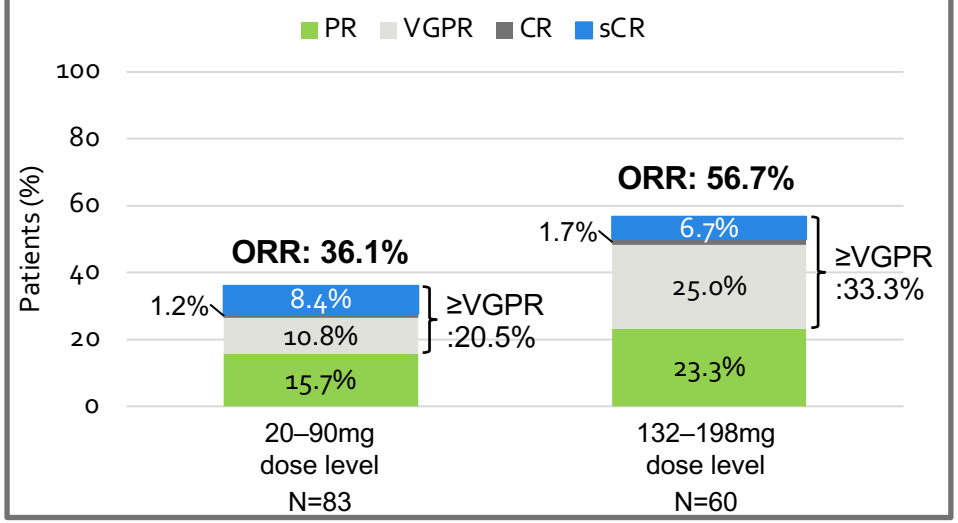
Response

- Response observed at the 20mg target dose level and above (N=143 patients)
- ORR increases with target dose
  - ORR in C1 single step-up expansion (3.6/90mg): 29.0%
  - ORR in C1 double step-up expansion (0.3/3.6/160mg): 54.8%
- Response occurs early
  - median time to first response: 1.0 mo (range: 0.7–5.9)
- Response deepens over time
  - median time to best response: 2.1 mo (range: 0.7–11.4)
- MRD negativity by NGS ($<10^{-5}$) detected in 7/10 evaluable patients with ≥VGPR

Best response rates in efficacy-evaluable patients by dose level



- Cevostamab was efficacious in patients with heavily pre-treated RRMM. ORR increased with target dose.

- CR, complete response; MRD, minimal residual disease; NGS, next generation sequencing; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Dose: IV, q 3 week
Med prior lines = 6
CRS 81%; neurotox 14%

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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The Case for Fixed Duration Treatment with Bispecific Antibodies

75 yo RRMM s/p 16 lines, diagnosed in 2001

Line 1: VAD induction, Mel-ASCT, PR

Line 2: Thal-Dex, PR

Line 3: Bor-Dex, PR

Line 4: Len-Dex, PR

Line 5: Bor-Dex, PR

Line 6: Cyclo-Dex, SD

Line 7: CyBorD, SD

Line 8: RVd, PR

Line 9: RVd-Cy, PR

Line 10: Bendamustine-Bor-Dex, SD

Line 11: Rd, MR

Line 12: Pom-Cy-Dex, SD

Line 13: Dara, MR

Line 14: Dara-Pom-Dex, PR

Line 15: Dara-Pom-Cy-Dex. PR

Line 16: BCMA directed BsAb in summer 2019.

- Off s/p 8 cycles

- Still off therapy, MRD-ve by NGS and flow at 10^{-5}

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The immunotherapy quadrafecta
(BCMA CAR-T, BCMA Bispecific, GPRC5d bispecific, FcRH5 bispecific)

IgA lambda plus lambda MM: Dx: 07/01/11 DS IIIA ISS unknown Cytogenetics 46, XX FISH unknown

Line 1: July 12, 2011: VelDex x 3 → VCD with VGPR followed by SCH. VRD x 3 cycles beginning January 2012
ASCT 06/05/12
Maintenance len-dex Nov 2012 –March 2014

Line 2:	March 2014	VRD
Line 3:	11/24/14	Panobinostat Rd
Line 4:	7/8/15	Dara/Pom/Dex
Line 5:	2/25/16	Carfilzomib/ibrunitinb
Line 6:	12/14/16	Selinexor
Line 7:	6/10/17	VDCEP
Line 8:	7/10/17	BCNU 200 + mel 100 ASCT with pazopanib maintenance
Line 9:	1/11/18	**Talquetamab**
Line 10:	4/23/18	**BCMA CAR T**
Line 11:	8/17/20	**Teclistamab+Dara**
Line 12:	8/31/21	**Cevostamab**

Courtesy Dr. Joshua Richter

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What Will It Take For T-Cell Redirection To Beat ASCT?

	ASCT	CART	Bispecifics Ab
Data			
Cost	$$	$$$$	$$$
Manufacturing concerns	No	Yes	No
Available Globally	Yes		
Non-relapse mortality	Low		
Long-term safety data	Yes	No	No

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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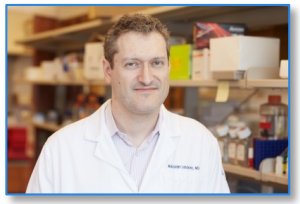
MSKCC Myeloma Service

Saad Z. Usmani (Chief)
High-Risk Disease
Biology/Trials
Bispecific Antibodies
CAR T Cells
Checkpoint Inhibitors
Developmental Therapeutics

Sham Mailankody
MM
Immunotherapy
CAR T Cells

Malin Hultcrantz
MM Precursor Disease
Antibody drug conjugates
Genetics/MRD

Urvi Shah
Early Relapse
MM Precursor Disease
Nutrition & Modifiable Risk Factors



Alex Lesokhin
MM Immunotherapy
Bispecific Antibodies
Checkpoints Inhibitors
Neoantigens
Microbiota

Hani Hassoun
MM Supportive Care
Alliance Liaison
NDMM/RRMM Trials
Elderly and Frail

Neha Korde
NDMM Clinical Trials
MRD Directed therapy
Supportive Care

Carlyn Tan
MM Precursor diseases
Supportive Care
Bone Health

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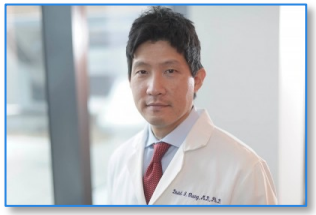
MSKCC Myeloma TCT Program

Sergio Giralt
Allo/Auto HCT for MM
New Regimens
CAR T Cells

David Chung
T Cell exhaustion
Auto HCT + Vaccines
MM Immunotherapies



Gunjan Shah
HCT Toxicities
Precision Drug Dosing
CAR T Cells
Salvage Auto and Allo HCT

Saad Z. Usmani
High-Risk Disease Biology/Trials
CAR T Cells
Auto HCT for MM

Michael Scordo
HCT Toxicities
Precision Drug Dosing
CAR T Cells

Heather Landau
Amyloidosis
HCT Toxicities
Homebound HCT
Precision Drug Dosing
Novel Regimens for Salvage Auto

Oscar Lahoud
Auto HCT and CAR T Cells
Post HCT Therapies