San Giuseppe Moscati - Avellino
Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione

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1ST SYMPOSIUM ON INNOVATIVE THERAPIES IN HEMATOLOGY

ADC, CAR-T vs Ab bispecifici nel MM

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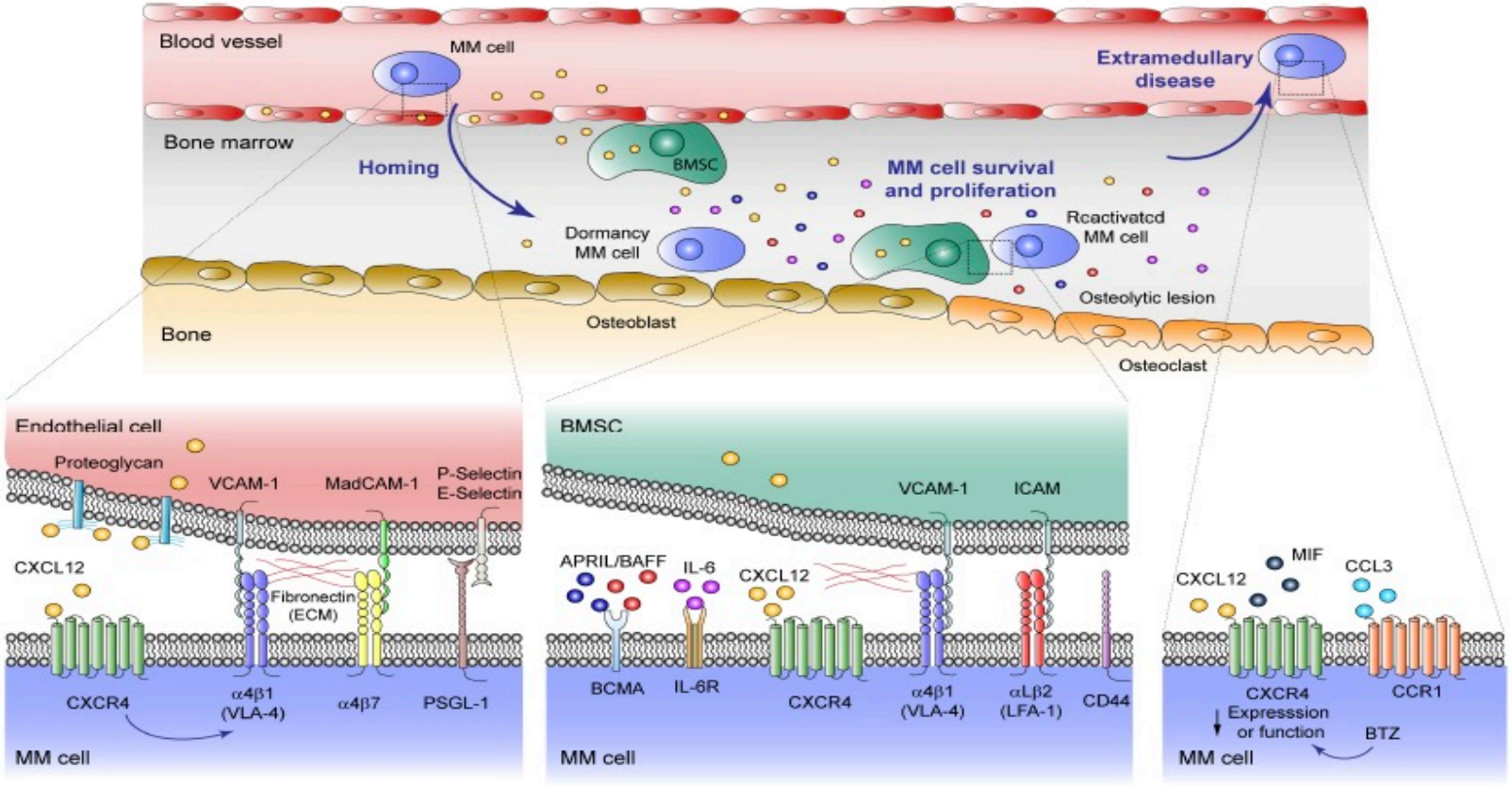
Disclosures of Marco Rossi

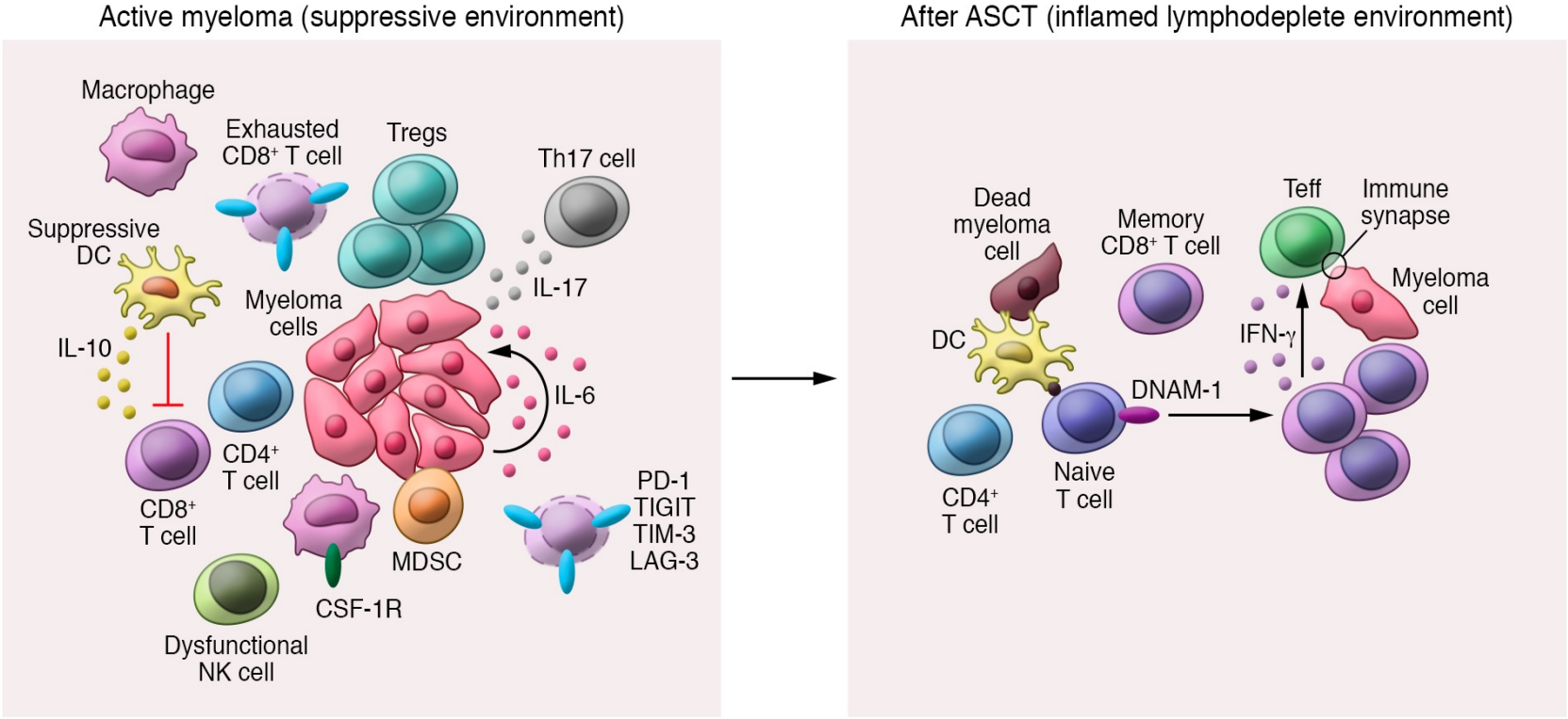
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Jansenn					X	X	
Roche					X		
Sanofi					X		
Amgen					X		

Multiple Myeloma Microenvironment



Garcia –Ortiz A et al., Cancers 2021

Multiple Myeloma Immune Microenvironment



Minnie SA and Hill GR, JCI 2020

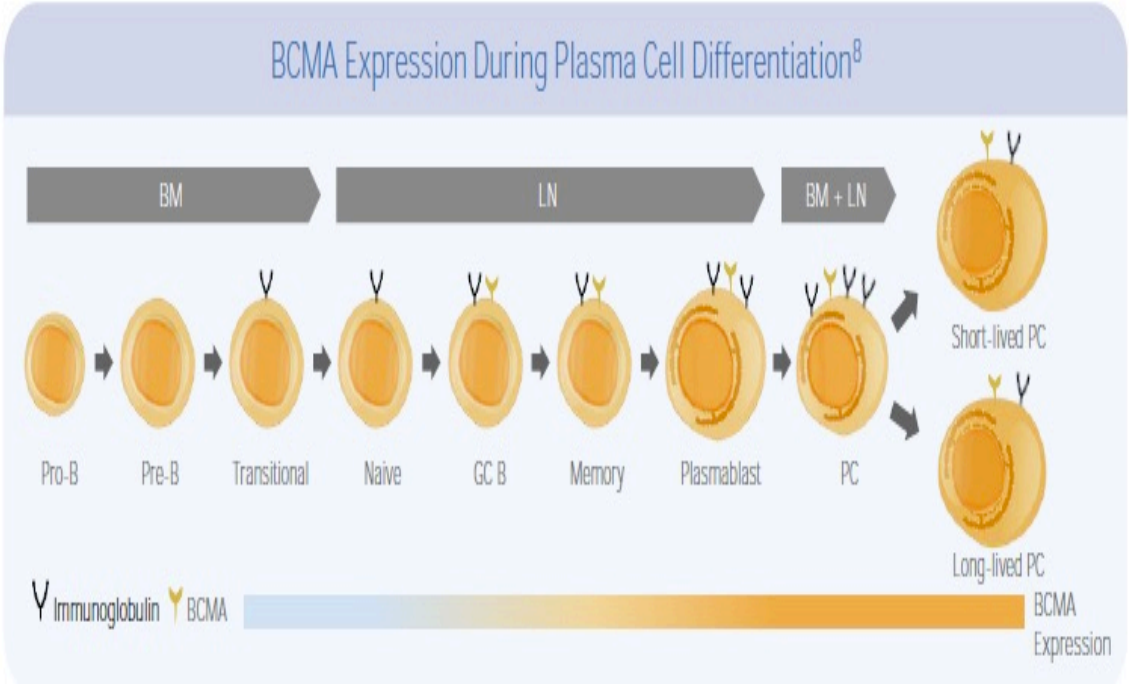
Immune based Targeting Strategies of Malignant PCs

- Effective targeting within tolerogenic ME
- Same efficacy across genetic risk categories («risk agnostic»)
- Selection of appropriate time point along therapy
- Sustained anti-myeloma activity along time (Immune Effectors recruitment)

Immune based Targeting Strategies of Malignant PCs

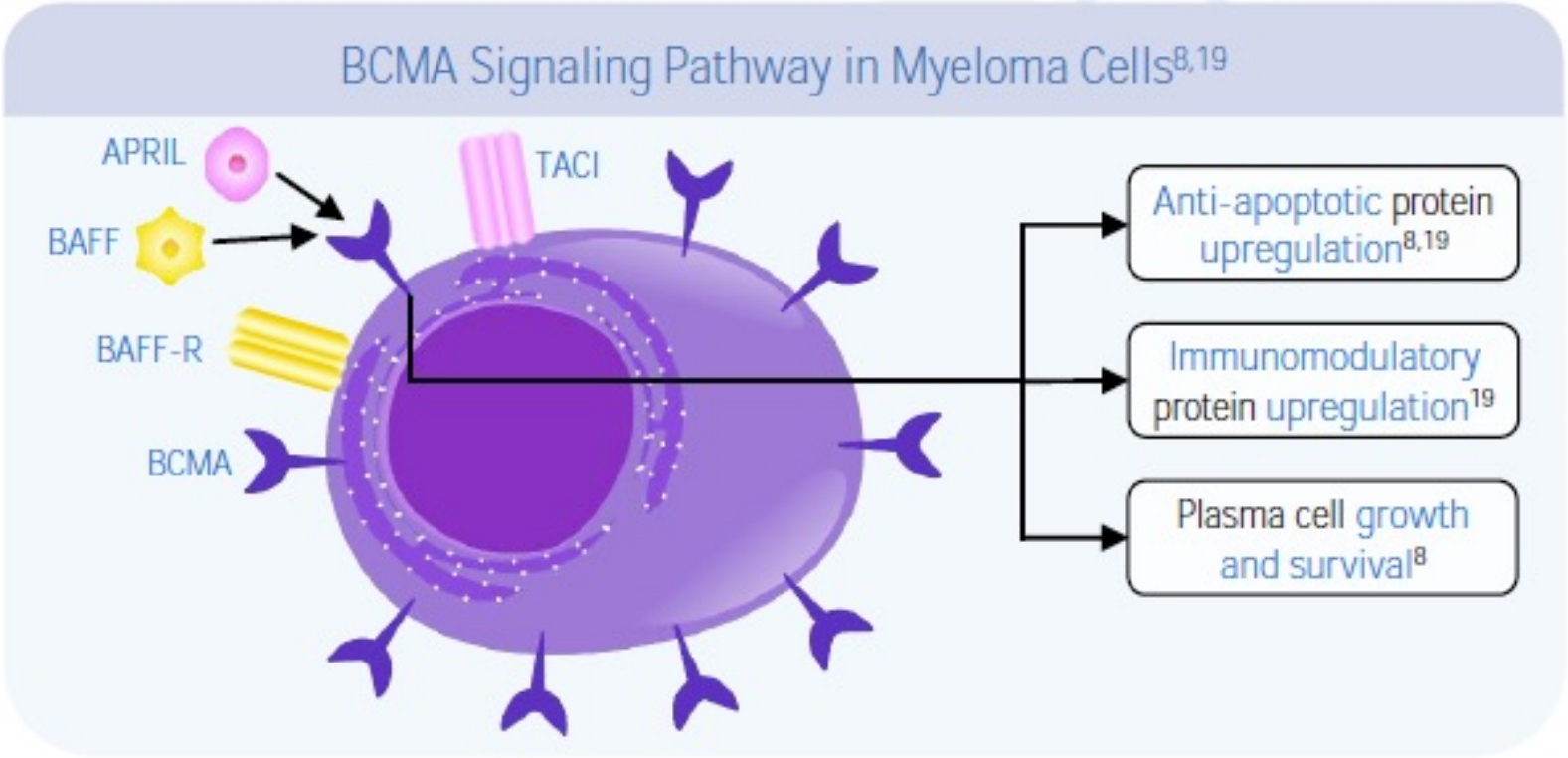
- Antibody Drug Conjugates-ADC
- Chimeric Antigen Receptor (CAR)-T cells
- Bi/Trispecific Abs/T cell Engagers

BCMA as main target of immunebased strategies



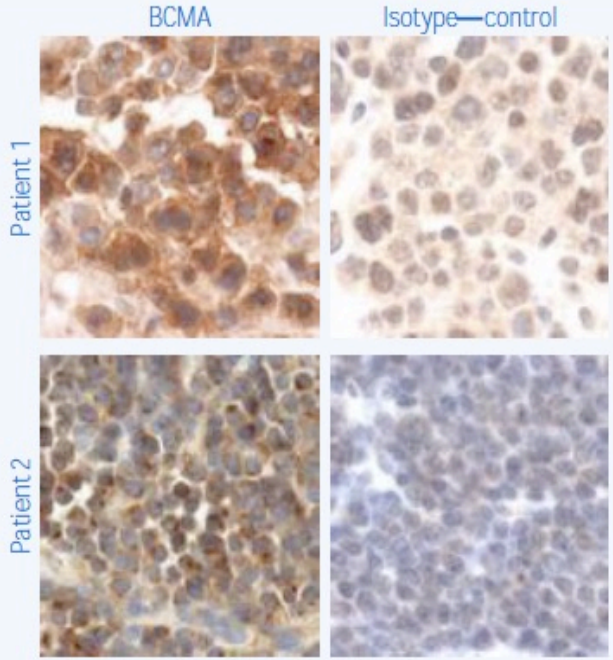
- BCMA is a transmembrane glycoprotein of the TNFR superfamily[9]
- BCMA is exclusively expressed on the cell membrane of late-stage B cells and plasma cells and regulates differentiation and survival of plasma cells[8,10,11]
  - BCMA is minimally expressed in hematopoietic stem cells and non-hematopoietic tissue[12,13]

BCMA as main target of immunebased strategies

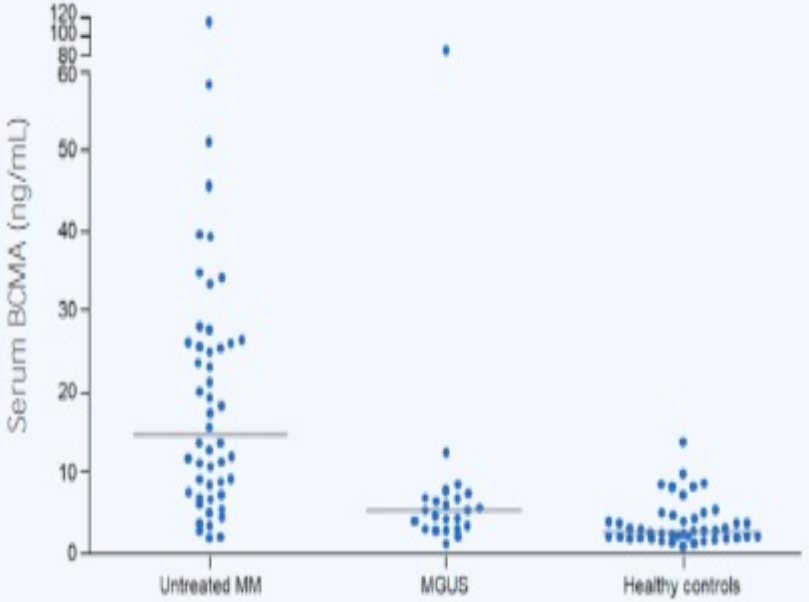


BCMA as main target of immunebased strategies

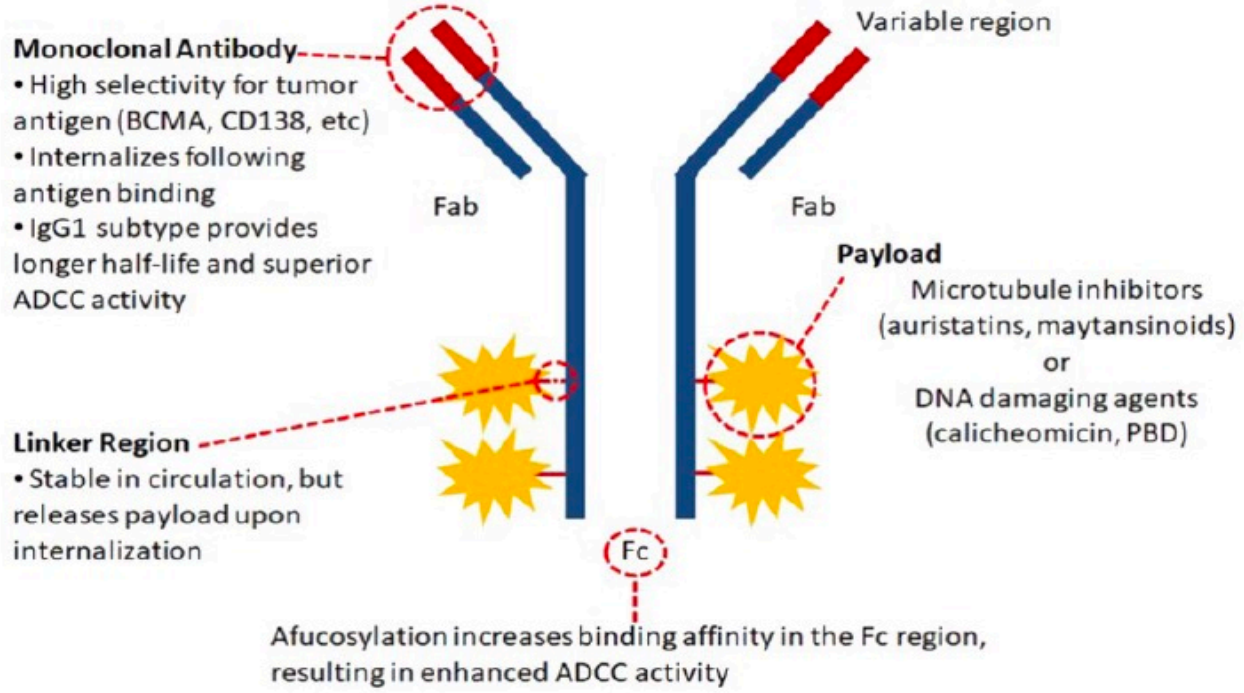
BCMA Expression on Neoplastic Plasma Cells From Patients With MM[13]



Overexpression of sBCMA in Patient Populations With MM[14]

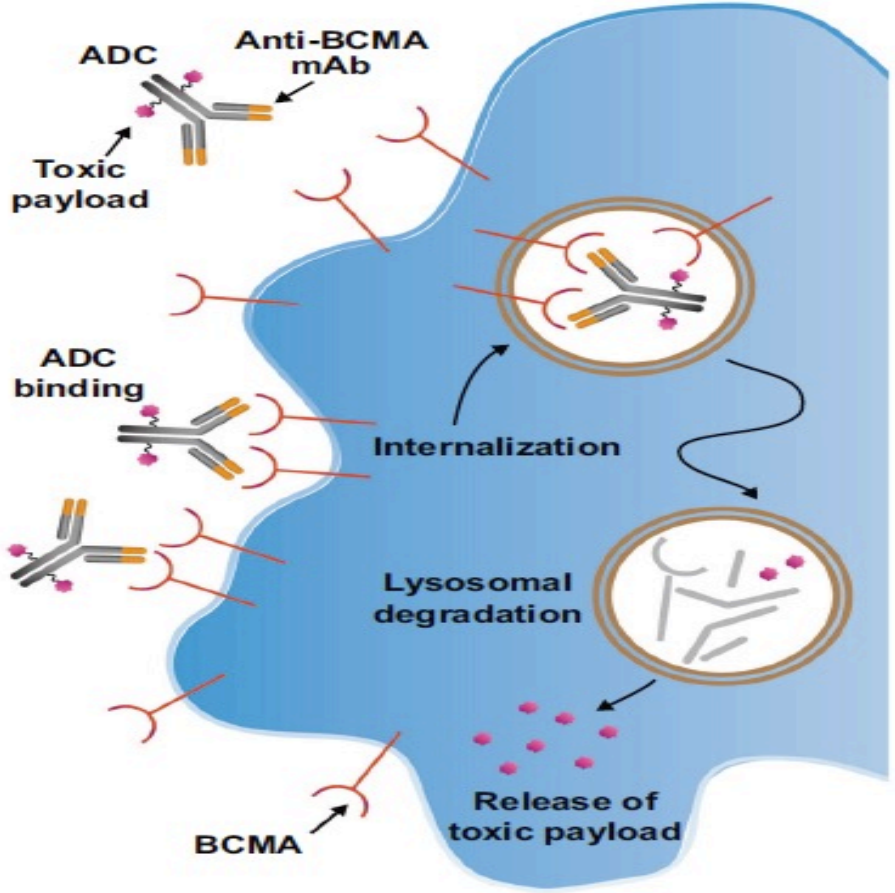


Antibody drug conjugates-ADCs



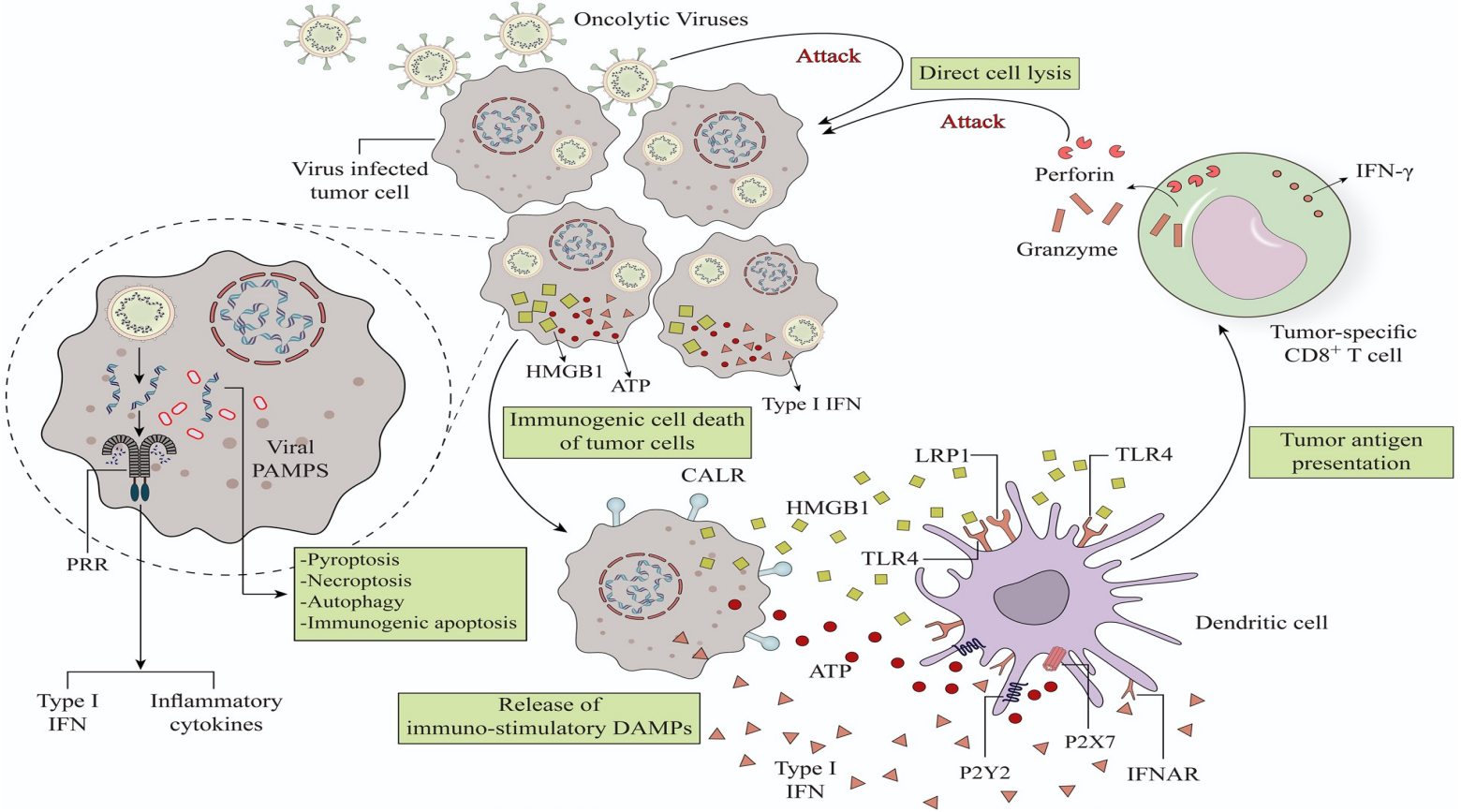
Cipkar et al, ASH 2022

Cell Death by BCMA-ADCs



- Direct Killing by toxic payload release
- ADCC
- ICD

Immunogenic Cell Death



Mardi A et al, cancer cell Intern 2022

DREAMM-2 study design

A phase 2, open-label, randomised, 2-dose study of belamaf in patients with RRMM refractory to immunomodulatory agents and PIs and refractory/intolerant to an anti-CD38 mAb (NCT03525678 and EudraCT: 2017-004810-25)

Eligibility Criteria

- Measurable disease*
- Refractory to immunomodulatory agents and PIs, and refractory/intolerant to an anti-CD38 mAb
- European Cooperative Oncology Group Performance Status of 0–2
- Not exposed to a prior BCMA-targeted therapy
- ≥3 prior lines of therapy
- Prior autologous-stem cell transplant allow… allogeneic-stem cell transplant excluded

A separate cohort of patients were enrolled who received the lyophilized presentation of the 3.4 mg/kg every 3 week dose. *Measurable disease defined as serum myeloma protein (M-protein) ≥0.5 g/dL; urine M-protein ≥200 mg/24h; serum free-light chain (FLC) assay: involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65). 3L+, third and later lines; BCMA, B-cell maturation antigen; DREAMM, Driving Excellence in Approaches to Multiple Myeloma; IMWG, International Myeloma Working Group; IV, intravenous; mAb, monoclonal antibody; PI, proteasome inhibitor; RRMM, relapsed or refractory multiple myeloma.

1. Lonial S et al. Lancet Oncology 2020;21:207. 2. Kumar S et al. Lancet Oncol 2016; 17: e328.

Antibody drug conjugates-ADCs

	Belantamab mafodotin 2·5 mg/kg group (n=97)	Belantamab mafodotin 3·4 mg/kg group (n=99)
Age, median (IQR), years	65 (60–70)	67 (61–72)
18 to <65 years	45 (46%)	36 (36%)
65 to <75 years	39 (40%)	46 (46%)
≥75 years	13 (13%)	17 (17%)
Sex		
Male	51 (53%)	56 (57%)
Female	46 (47%)	43 (43%)
Race		
White or White European	72 (74%)	83 (84%)
Black or African-American	16 (16%)	11 (11%)
Renal impairment per eGFR (ml/min per 1·73m²)		
Normal (≥90)	19 (20%)	17 (17%)
Mild (≥60 to <90)	48 (49%)	52 (52%)
Moderate (≥30 to <60)	24 (25%)	22 (22%)
Severe (≥15 to <30)	2 (2%)	5 (5%)
Time from initial diagnosis, median (IQR), years*	5·49 (4·01–7·02)	5·08 (4·16–7·48)
ISS disease stage at screening		
Stage I	21 (22%)	18 (18%)
Stage II	33 (34%)	51 (52%)
Stage III	42 (43%)	30 (30%)
Unknown	1 (1%)	0
Cytogenetic abnormalities		
t(11;14)	16 (16%)	9 (9%)
t(14;20)	3 (3%)	0
Del 13	18 (19%)	17 (17%)
Hyperdiploidy	7 (7%)	4 (4%)
Other	28 (29%)	23 (23%)
High-risk cytogenetics	41 (42%)	47 (47%)
17p13del	16 (16%)	22 (22%)
t(4;14)	11 (11%)	11 (11%)
t(14;16)	7 (7%)	2 (2%)
1q21+	25 (26%)	30 (30%)
Type of myeloma		
IgG	65 (67%)	73 (74%)
Non-IgG or unknown	32 (33%)	26 (26%)
Extramedullary disease	22 (23%)	18 (18%)
Previous lines of therapy†		
Median (range)	7 (3–21)	6 (3–21)
≤4 lines	16 (16%)	17 (17%)
>4 lines	81 (84%)	82 (83%)

(Table 1 continues in next column)

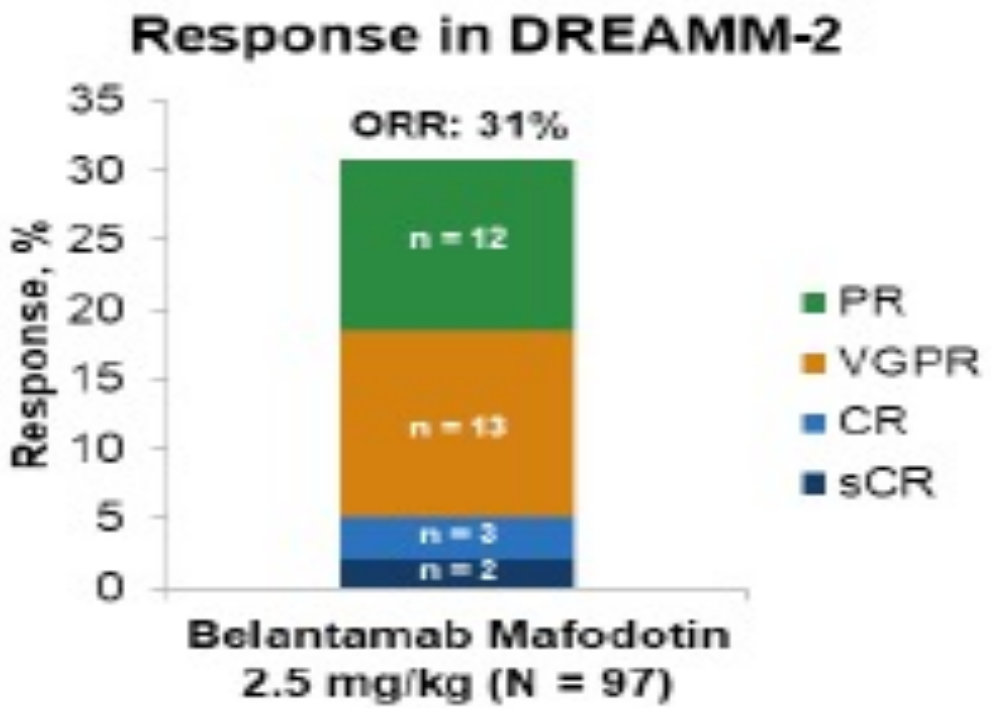
	Belantamab mafodotin 2·5 mg/kg group (n=97)	Belantamab mafodotin 3·4 mg/kg group (n=99)
(Continued from previous column)		
Previous therapies received		
Proteasome inhibitor		
Bortezomib	95 (98%)	97 (98%)
Carfilzomib	74 (76%)	64 (65%)
Immunomodulatory drug		
Lenalidomide	97 (100%)	99 (100%)
Pomalidomide	89 (92%)	84 (85%)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100%)	96 (97%)
Refractory to previous therapies‡		
Proteasome inhibitor		
Bortezomib	74 (76%)	74 (75%)
Carfilzomib	63 (65%)	57 (58%)
Immunomodulatory drug		
Lenalidomide	87 (90%)	88 (89%)
Pomalidomide	84 (87%)	77 (78%)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100%)	91 (92%)
Isatuximab	3 (3%)	1 (1%)

Data are n (%) unless otherwise specified. eGFR=estimated glomerular filtration rate. ISS=International Staging System. *Data available for 47 patients in the 2·5 mg/kg cohort and 36 patients in the 3·4-mg/kg cohort. †The number of previous lines of therapy is derived as the number of previous anticancer regimens received by a patient as reported on the electronic case report form. Combination therapy containing multiple components was counted as one regimen. ‡Based on data available at the time of database lock; however, all patients were refractory to a proteasome inhibitor, immunomodulatory drug, and an anti-CD38 monoclonal antibody as per eligibility criteria.

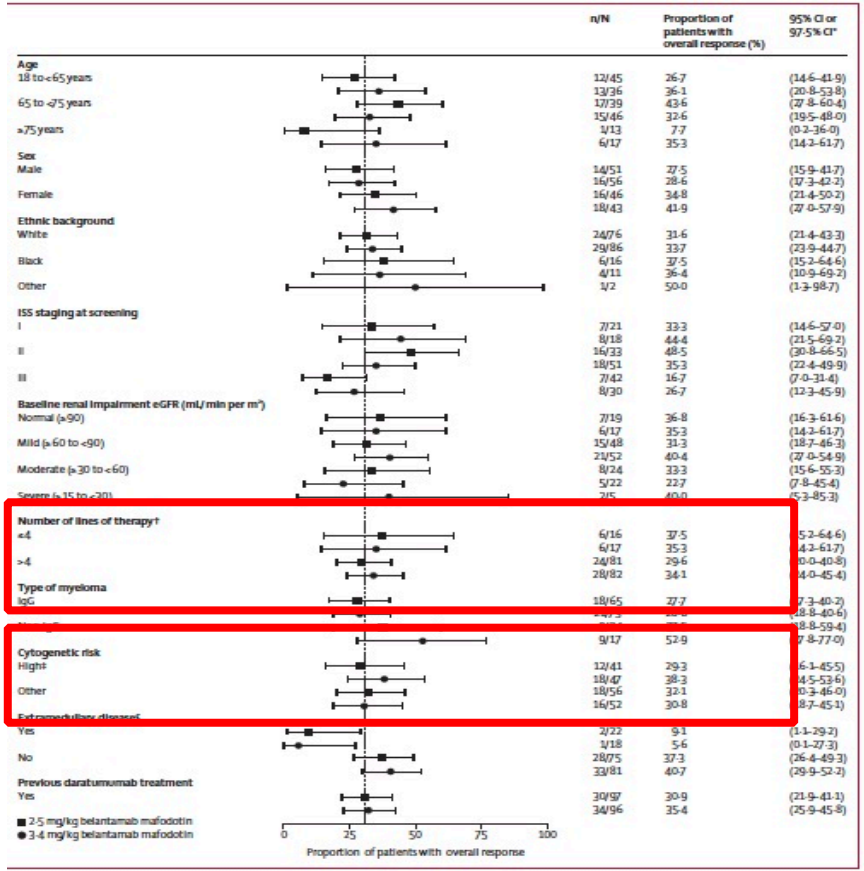
Table 1: Demographics and baseline disease and clinical characteristics in the intention-to-treat population

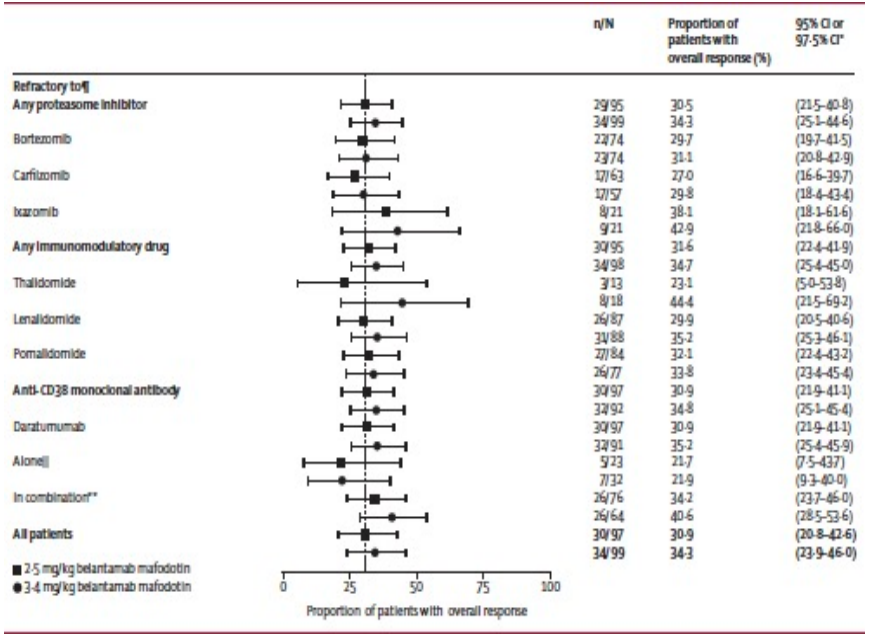
Lonial S et al, Lancet 2019

DREAMM-2 trial



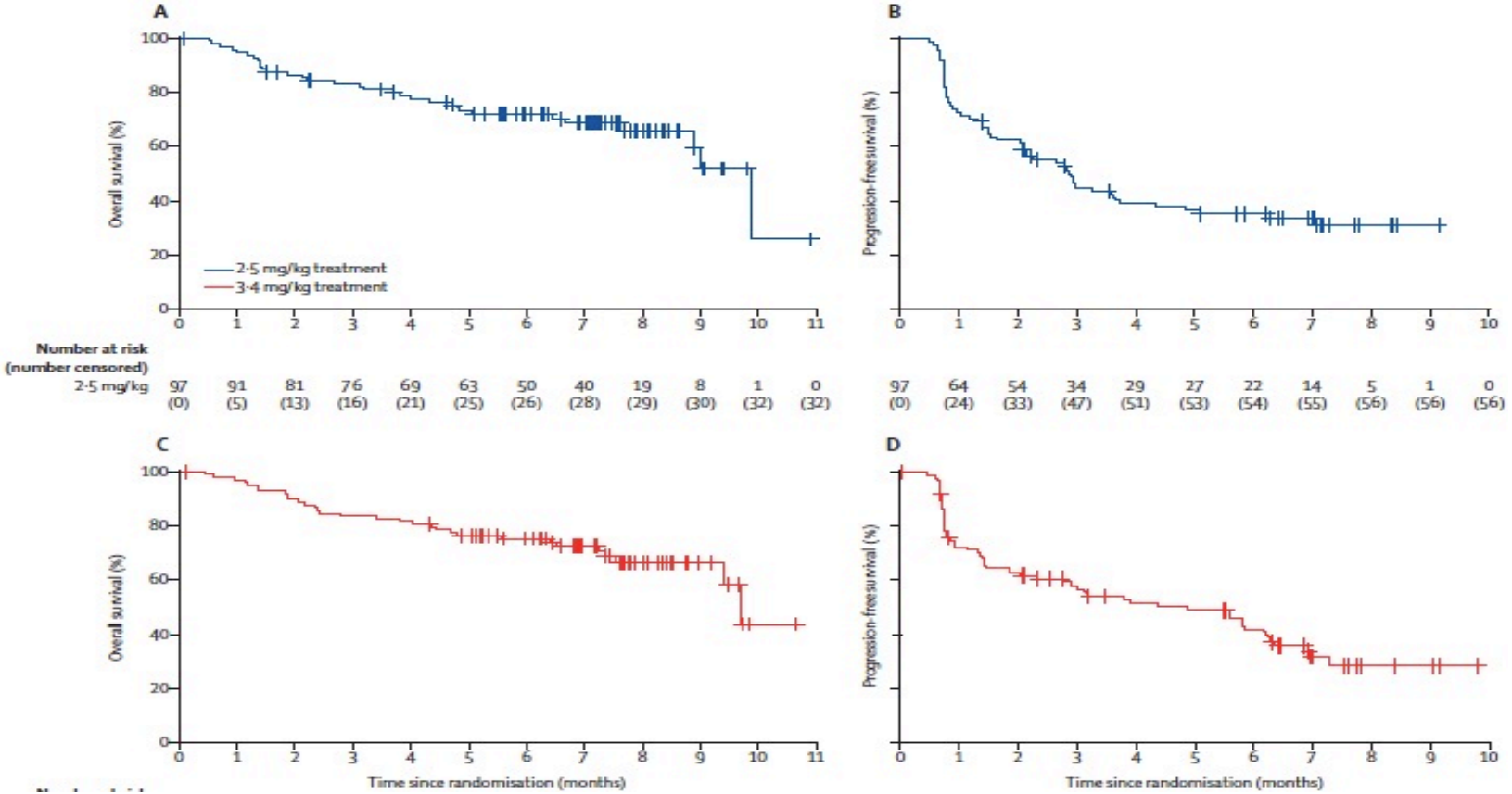
Responses by risk category





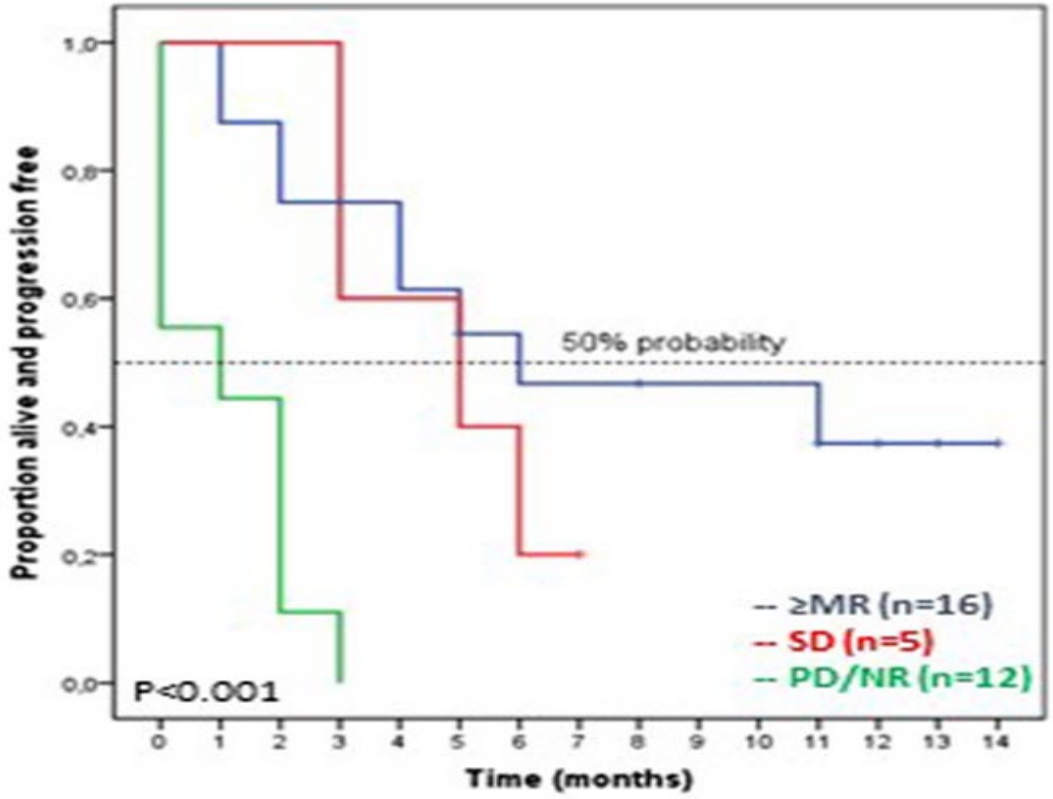
Lonial S et al, Lancet 2019

DREAMM-2 outcome



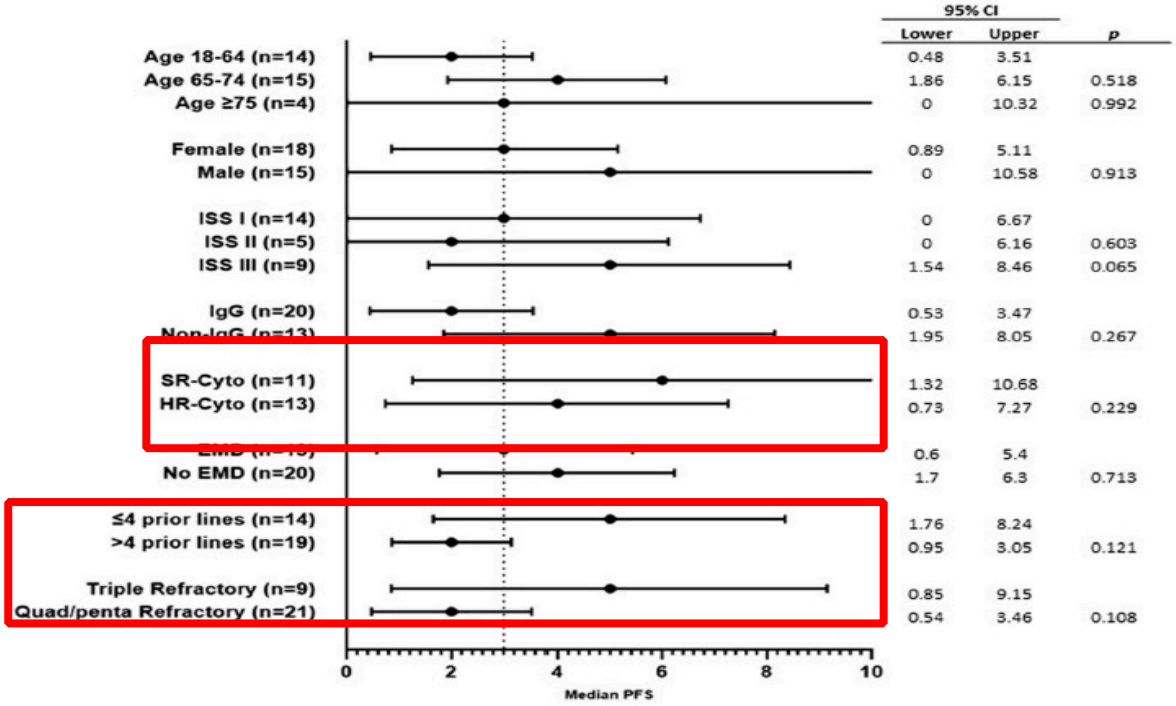
Lonial S et al, Lancet 2019

Belantamab-real world data outcome



Alegre A et al, Oncol Ther 2023

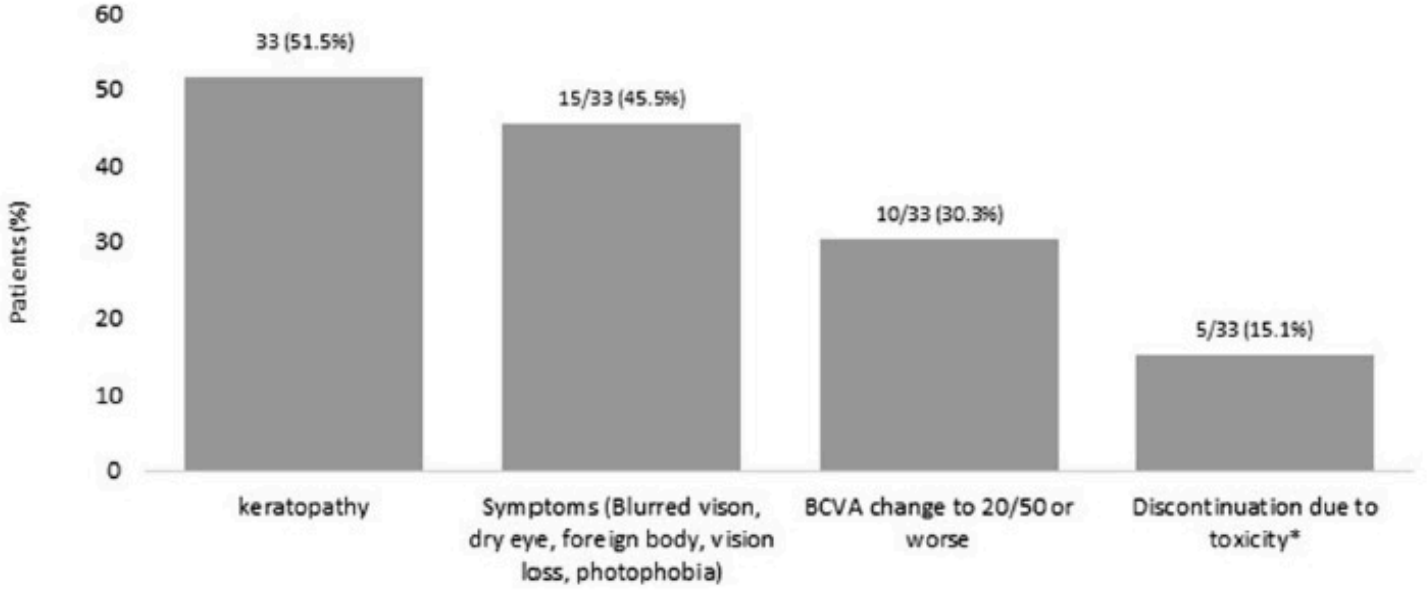
Belantamab-real world data
Response by risk category



Cyto: cytogenetic **EMD:** extramedular disease; **HR:** high risk; **ISS:** International Staging System; **MM:** multiple myeloma; **SR:** standard risk

Alegre A et al, Oncol Ther 2023

Belantamab-real world data



* only ocular toxicity, n=2; 6%; non-ocular toxicity, n=1; 3%: non-ocular + ocular toxicity, n=1, 3%

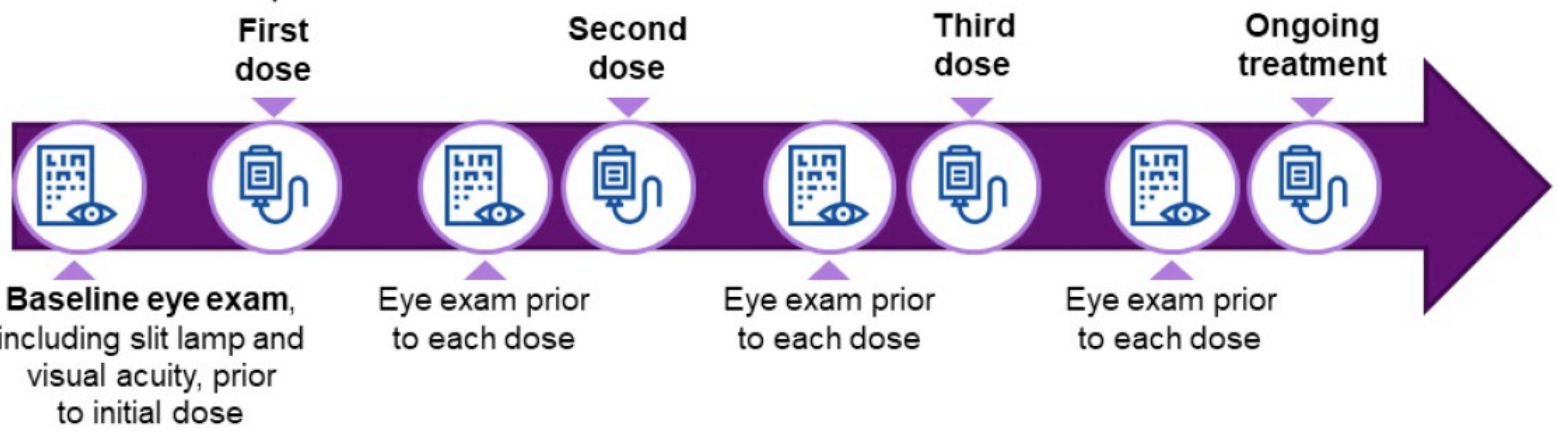
Alegre A et al, Oncol Ther 2023

Management of ocular toxicity

Pharmacy can coordinate *ophthalmic examinations (visual acuity and slit lamp); baseline examinations* ***within 3 weeks prior to the first dose***

Follow-up examination ***at least 1 week after the previous dose and within 2 weeks prior to the next dose***

Use preservative-free lubricant eye drops at least 4x daily starting with the first infusion until the end of treatment ***(no benefit with steroid drops)***

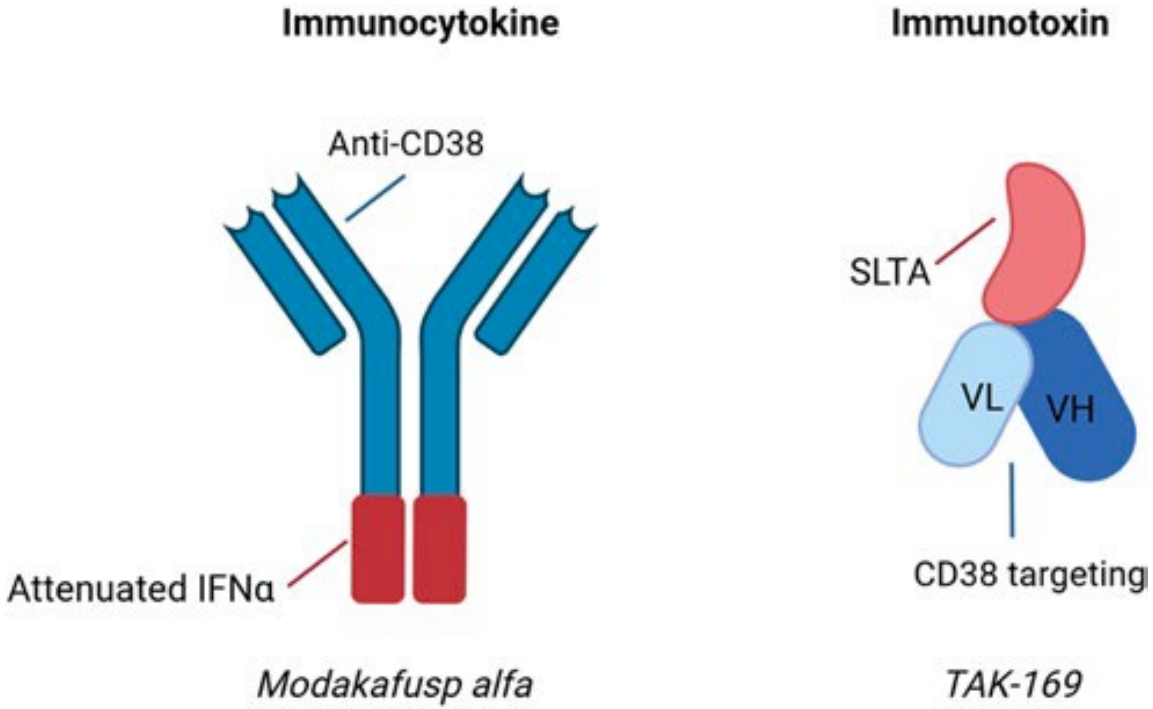


Summary of ADCs trials as single or combo agents

Name	Target	Payload	Combination	Trial phase: number of patients (n)	Response/ activity	Current status (ClinicalTrials.gov)
Belantamab mafodotin (belamaf)	BCMA	MMAF	Monotherapy[28]	Phase 1: n=35	ORR 60%	DREAMM-1 (completed) NCT02064387
				Phase 2: n=196	ORR 31%	DREAMM-2 (completed) NCT03525678
			B (Q3W) vs Pd	Phase 3: n=380 (E)	N/A	DREAMM-3 (recruiting) NCT04162210
			B (Q3W) + Pemb[30]	Phase 1/2: n=41	ORR 47%	DREAMM-4 (active, not recruiting) NCT03848845
			B + novel agent[31]	Phase 1/2: n=464 (E)	ORR 53% with feladilimab	DREAMM-5 (recruiting) NCT04126200
			B-Vd OR Rd[32]	Phase 1/2: n=152 (E)	ORR 78% in BVd arm	DREAMM-6 (active, not recruiting) NCT03544281
			B-Pd[34]	Phase 1/2: n=96 (E)	ORR 88.9%	ALGONQUIN (recruiting) NCT03715478
			B-Rd (transplant-ineligible NDMM)	Phase 1/2: n=66 (E)	N/A	NCT04808037 (recruiting)
			B-Vd vs D-Vd	Phase 3: n=575 (E)	N/A	DREAMM-7 (active, not recruiting) NCT04246047
			B-Pd vs V-Pd	Phase 3: n=450 (E)	N/A	DREAMM-8 (recruiting) NCT04484623
			B-VRd (transplant-ineligible NDMM[33]	Phase 1: n=144 (E)	ORR 100% (n=12)	DREAMM-9 (recruiting) NCT04091126
			Monotherapy in renal impairment	Phase 1: n=36 (E)	N/A	DREAMM-12 (recruiting) NCT04398745
			Monotherapy in liver impairment	Phase 1: n=28 (E)	N/A	DREAMM-13 (recruiting) NCT04398680
			Monotherapy (varying doses and schedules)	Phase 2: n=180 (E)	N/A	DREAMM-14 (recruiting) NCT05064358
AMG 224	BCMA	Mertansine	Monotherapy[36]	Phase 1: n=42 (E)	ORR 27% (3 mg/kg)	NCT02561962 (active, not recruiting)
CC 99712	BCMA	Maytansinoid-like	Monotherapy	Phase 1: n=160 (E)	N/A	NCT04036461 (recruiting)
MEDI2228	BCMA	PBD	Monotherapy[37]	Phase 1: n=82	ORR 66% at 0.14 mg/kg	NCT03489525 (completed)
Indatuximab ravtansine	CD138	Maytansinoid DM4	In combination with R or P	Phase 1/2: n=64	ORR 71.7% with R and 70.6% with P	NCT01001442 (completed)
Lorvotuzumab mertansine	CD56	Mertansine	Monotherapy	Phase 1: n=37	ORR 5.7%	NCT00346255 (completed)
Milatuzumab	CD74	Doxorubicin	Monotherapy	Phase 1: n=25	26% SD	NCT00421525 (completed)
STRO-001	CD74	MMAF	Monotherapy	Phase 1: n=N/A	N/A	NCT03424603 (recruiting)
DFRF4539A	FcRH5	MMAE	Monotherapy	Phase 1: n=39	ORR 5%; 49% SD	NCT01432353 (completed)
SGN-CD48A	CD48	MMAE	Monotherapy	Phase 1: n=14	N/A	NCT03379584 (terminated)
ABBV-838	SLAMF7	MMAE	Monotherapy	Phase 1/1b: n=75	ORR 10.7%	NCT02462525 (terminated)

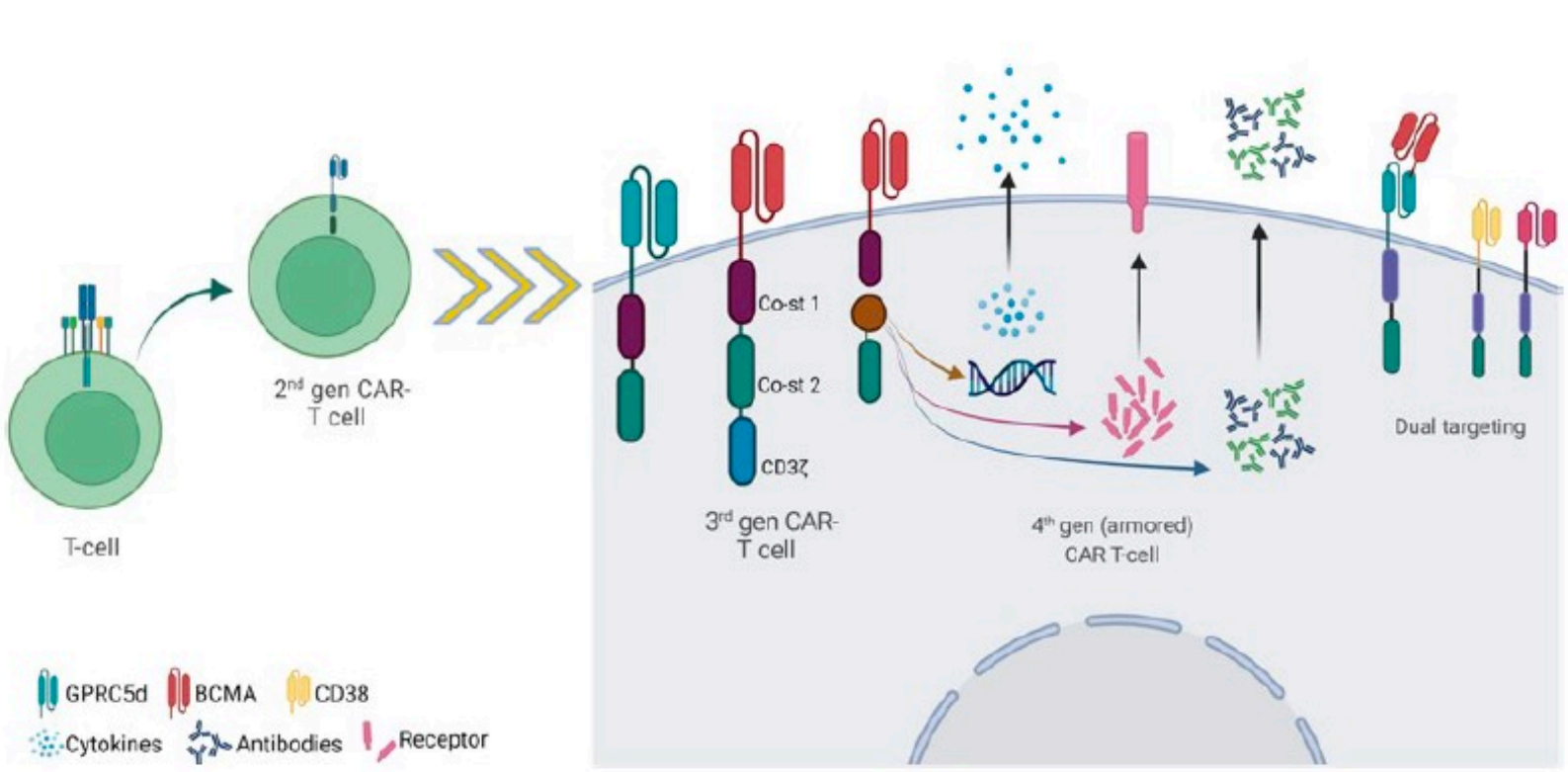
Cipkar et al, ASH 2022

Beyond ADCs: immunocytokines/toxins in MM



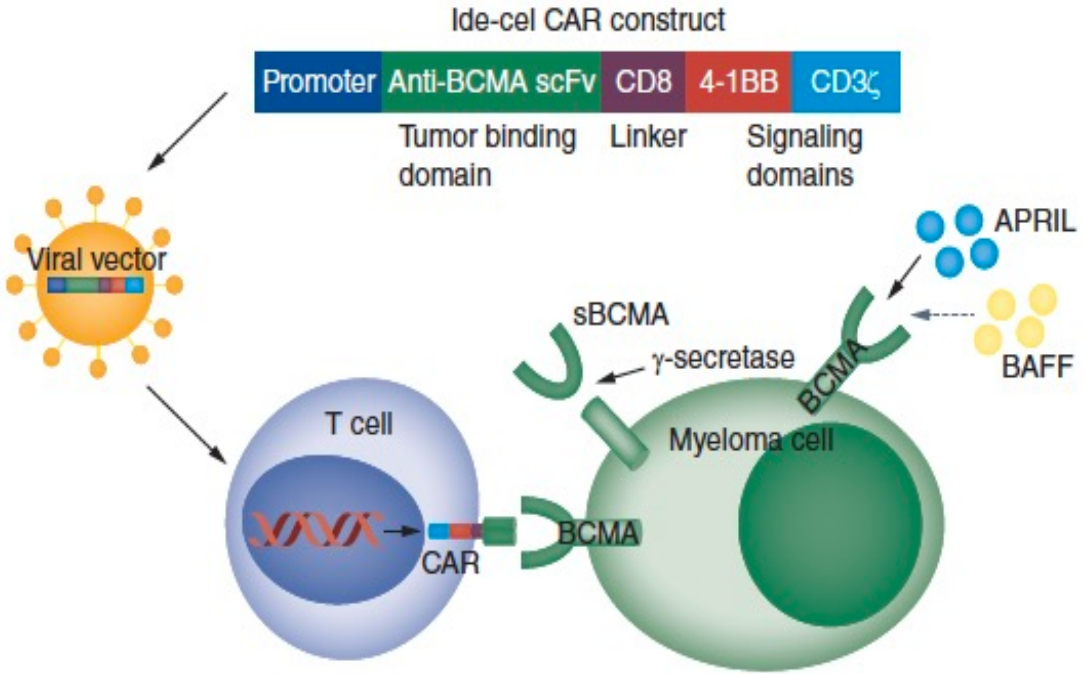
Holstein S, ASH 2022

CAR-T constructs



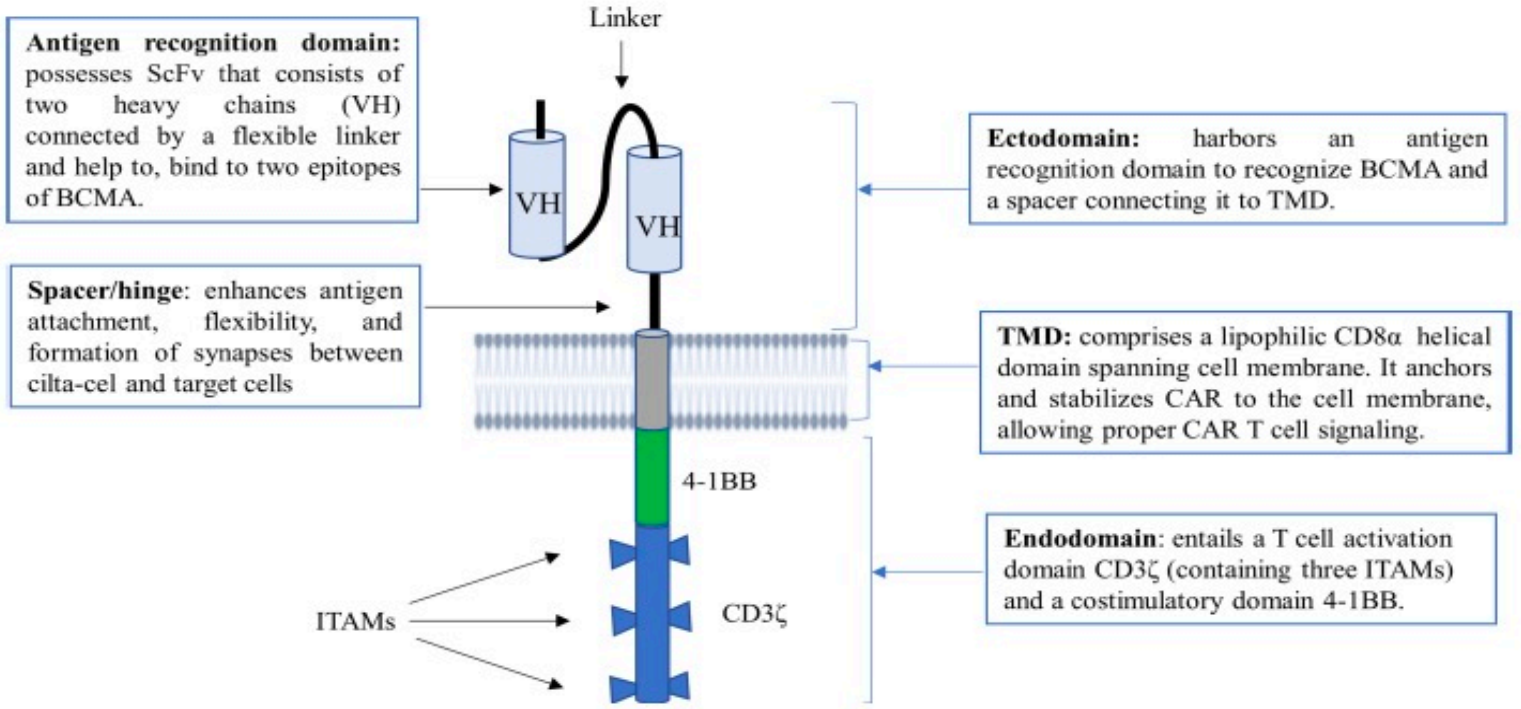
Roriguez-Otero and San Miguel, ASH 2022

Anti BCMA CAR-T constructs: Ide-Cel



Anderson L, Fut Oncol 2022

Anti BCMA CAR-T constructs: Cilta-Cel



Antigen recognition domain: possesses ScFv that consists of two heavy chains (VH) connected by a flexible linker and help to, bind to two epitopes of BCMA.

Spacer/hinge: enhances antigen attachment, flexibility, and formation of synapses between cilta-cel and target cells

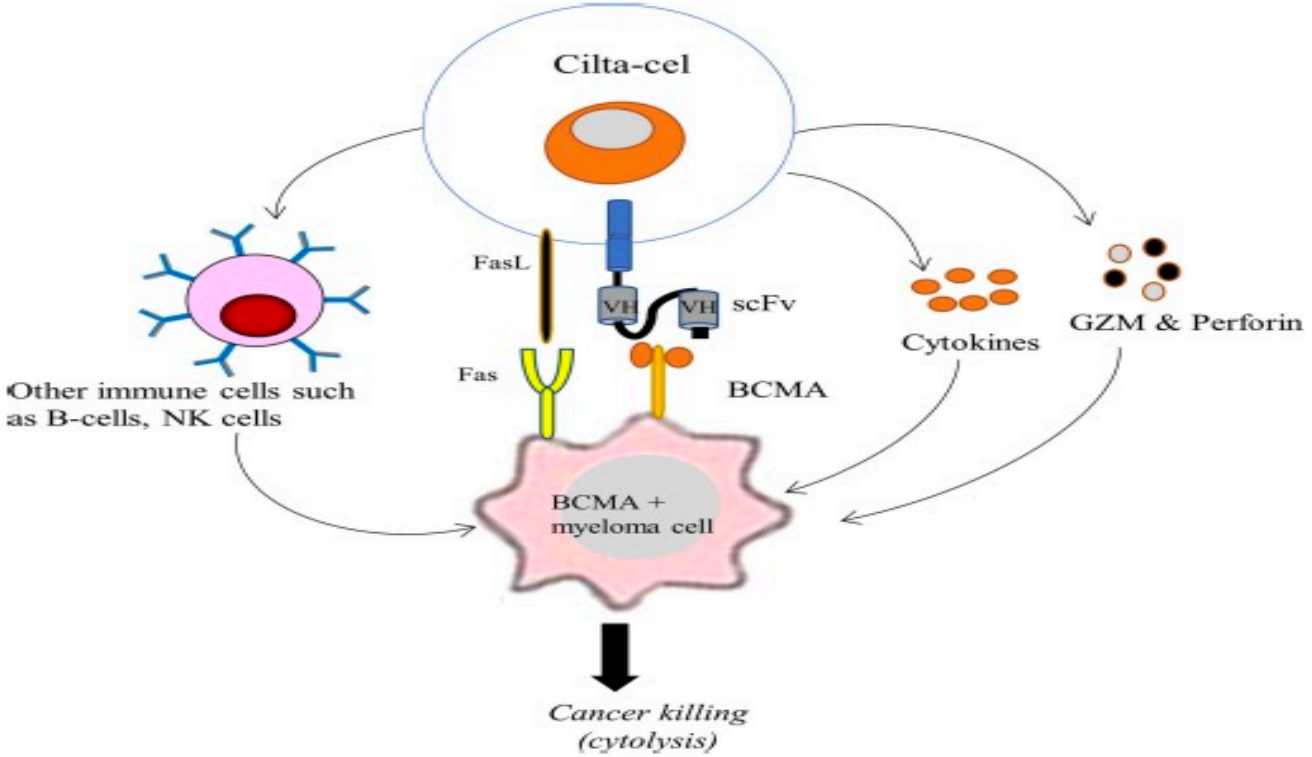
Ectodomain: harbors an antigen recognition domain to recognize BCMA and a spacer connecting it to TMD.

TMD: comprises a lipophilic CD8α helical domain spanning cell membrane. It anchors and stabilizes CAR to the cell membrane, allowing proper CAR T cell signaling.

Endodomain: entails a T cell activation domain CD3ζ (containing three ITAMs) and a costimulatory domain 4-1BB.

Abebe EC et al, Front Immunol 2022

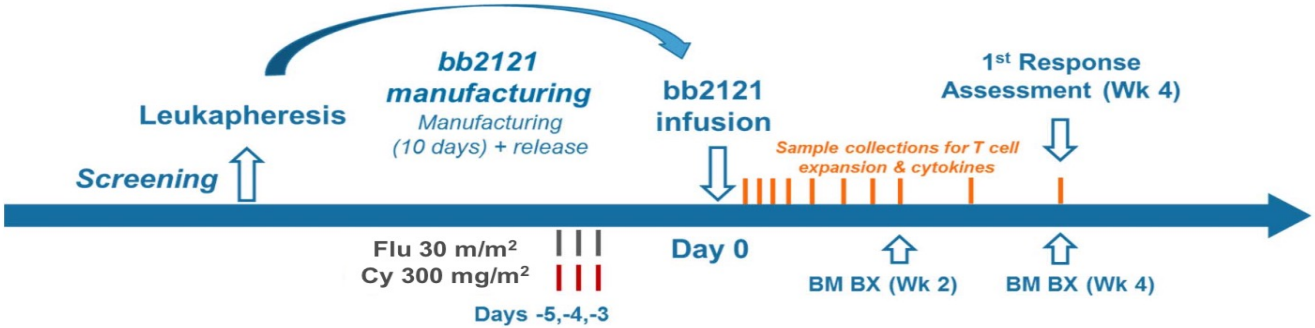
Anti BCMA CAR-T activity in MM



Abebe EC et al, Front Immunol 2022

CAR-T study design in MM

CRB-401 PHASE 1 STUDY DESIGN



Dose Escalation (N=21)

≥50% BCMA expression

50 × 10^6 → 150 × 10^6 → 450 × 10^6 → 800 × 10^6

Dose Expansion (N=22)

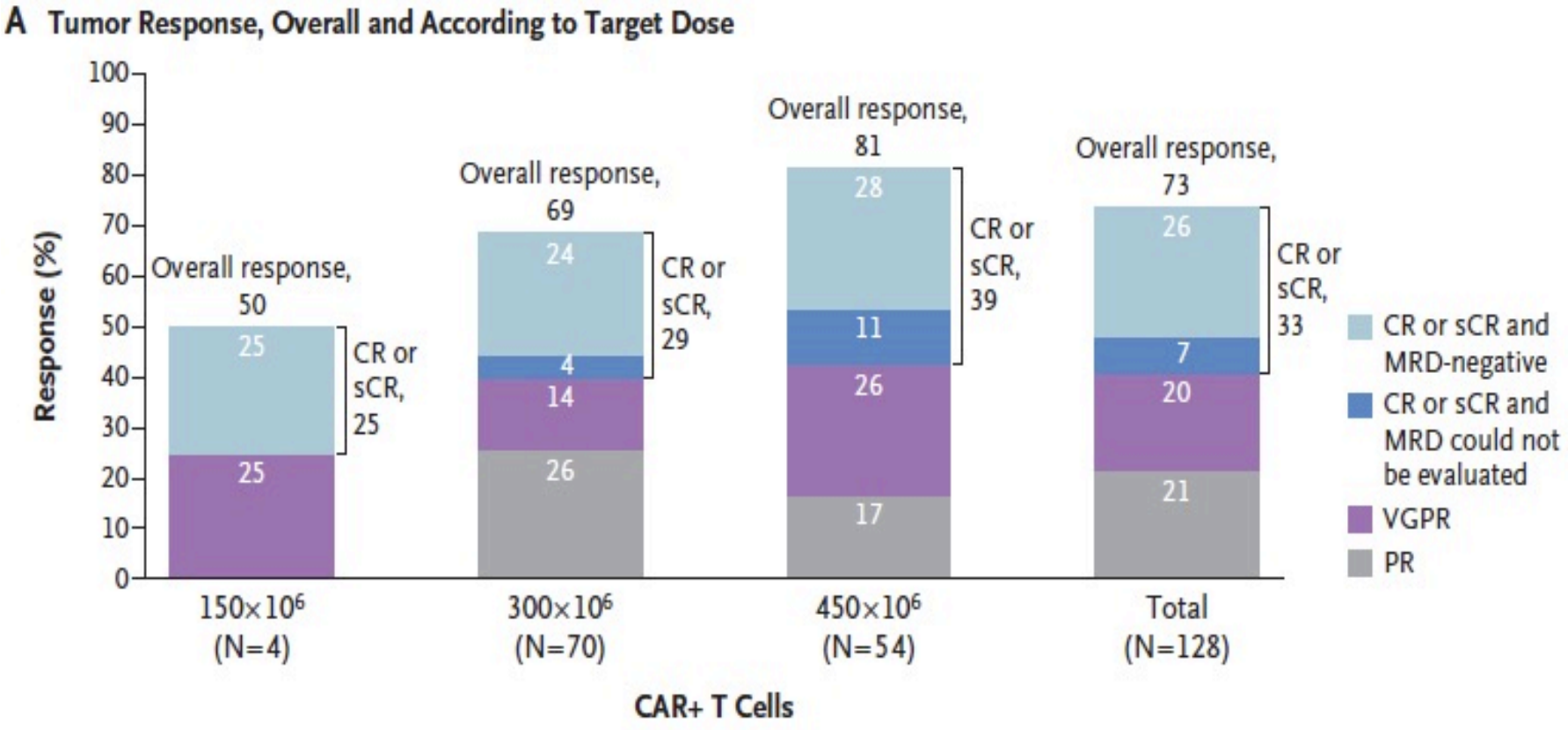
<50% BCMA expression (n=10)

≥50% BCMA expression (n=12)

Dose range: 150–450 × 10^6 CAR+ cells

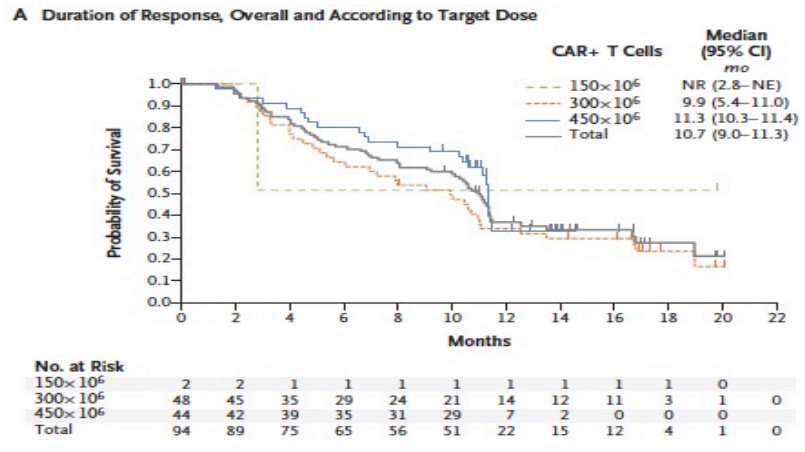
Manufacturing success rate of 100%

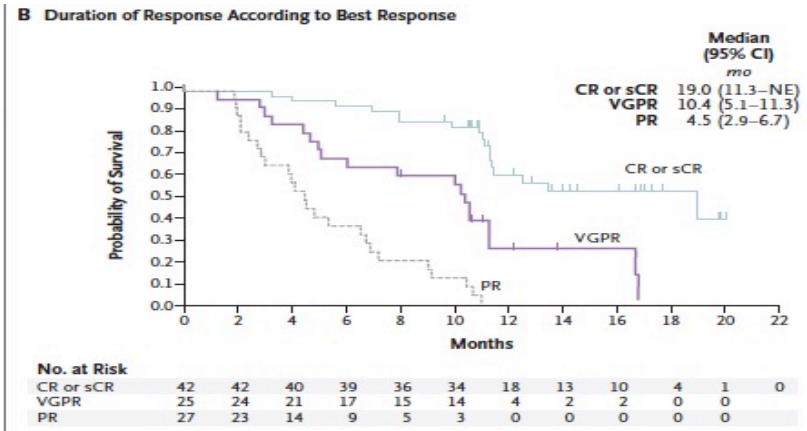
Ide-cel in RRMM

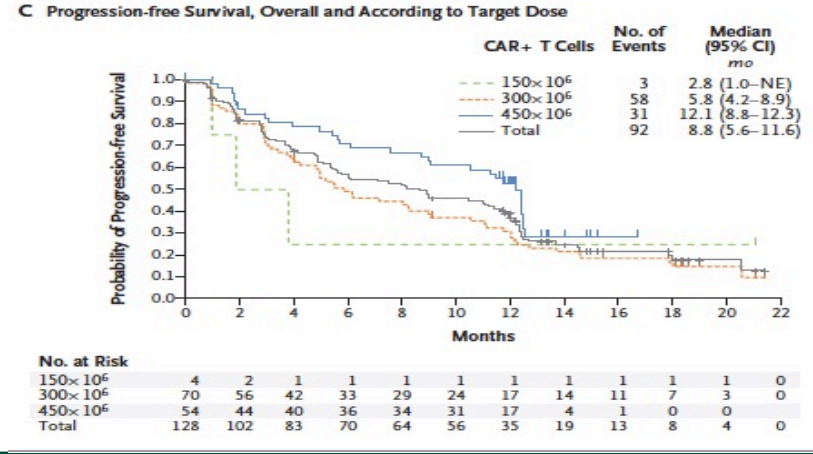


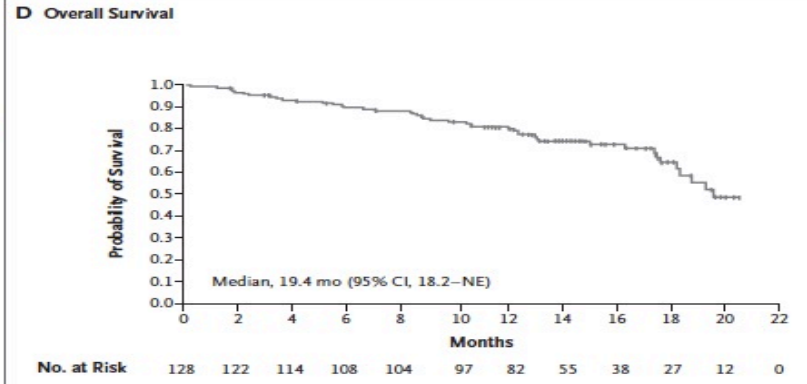
Munshi N et al, NEJM 2021

Ide-cel in RRMM









Munshi N et al, NEJM 2021

Ide-cel in RRMM

Characteristic	Ide-cel (N=254)	Standard Regimen (N=132)
Age		
Median (range) — yr	63 (30–81)	63 (42–83)
Distribution — no. (%)		
<65 yr	150 (59)	78 (59)
≥65 yr	104 (41)	54 (41)
≥75 yr	12 (5)	9 (7)
Male sex — no. (%)	156 (61)	79 (60)
Race — no. (%)†		
Asian	7 (3)	5 (4)
Black	18 (7)	18 (14)
White	172 (68)	78 (59)
Other	3 (1)	4 (3)
Not available or not reported	54 (21)	27 (20)
Median time from initial diagnosis to screening (range) — yr	4.1 (0.6–21.8)‡	4.0 (0.7–17.7)
Median time to progression during last previous antimyeloma therapy (range) — mo	7.1 (0.7–67.7)	6.9 (0.4–66.0)
Extramedullary disease — no. (%)§	61 (24)	32 (24)
High tumor burden — no. (%)¶	71 (28)	34 (26)
ECOG performance-status score — no. (%)‖		
0	120 (47)	66 (50)
1	133 (52)	62 (47)
≥2	1 (<1)	4 (3)
R-ISS disease stage — no. (%)**		
I	50 (20)	26 (20)
II	150 (59)	82 (62)
III	31 (12)	14 (11)
Unknown	23 (9)	10 (8)
Cytogenetic abnormalities — no. (%)		
High-risk abnormality††	107 (42)	61 (46)
del(17p)	66 (26)	42 (32)
t(4;14)	43 (17)	18 (14)
t(14;16)	8 (3)	4 (3)
Other cytogenetic abnormalities		
1q gain or amplification	125 (49)	51 (39)
13q14 deletion	85 (33)	40 (30)
1p deletion	17 (7)	8 (6)
13q34 monosomy	51 (20)	27 (20)
t(14;20)	2 (1)	3 (2)
Median no. of previous regimens (range)	3 (2–4)	3 (2–4)
Previous autologous HSCT — no. (%)	214 (84)	114 (86)
1 Transplantation	167 (66)	87 (66)
>1 Transplantation	47 (19)	27 (20)

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Ide-cel in RRMM

Table 1. (Continued.)

Characteristic	Ide-cel (N=254)	Standard Regimen (N=132)
Previous radiation therapy — no. (%)	90 (35)	46 (35)
Refractory status — no. (%)		
Immunomodulatory agent	224 (88)	124 (94)
Lenalidomide	186 (73)	104 (79)
Pomalidomide	127 (50)	70 (53)
Thalidomide	10 (4)	2 (2)
Proteasome inhibitor	189 (74)	95 (72)
Bortezomib	112 (44)	60 (45)
Carfilzomib	104 (41)	43 (33)
Ixazomib or ixazomib citrate	35 (14)	23 (17)
Anti-CD38 monoclonal antibody	242 (95)	124 (94)
Daratumumab	242 (95)	123 (93)
Isatuximab	1 (<1)	1 (1)
Double-class–refractory disease‡‡	169 (67)	91 (69)
Triple-class–refractory disease§§	164 (65)	89 (67)
Penta-refractory disease¶¶	15 (6)	5 (4)

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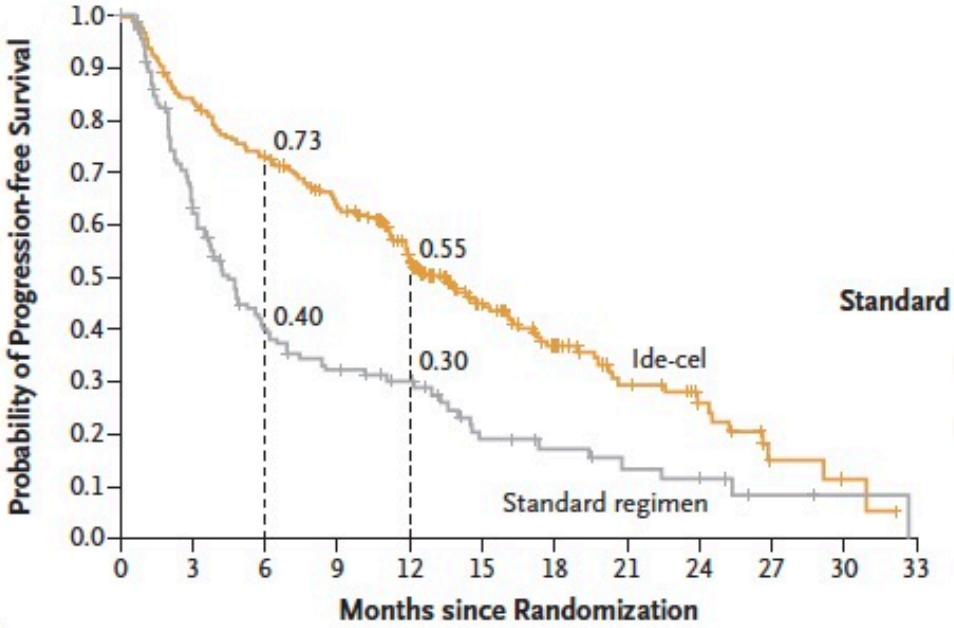
Ide-cel in RRMM



No. at Risk

Ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard regimen	132	75	42	32	25	13	10	7	6	2	1	0

	Median Progression-free Survival (95% CI)
	mo
Ide-cel	13.3 (11.8–16.1)
Standard Regimen	4.4 (3.4–5.9)

Hazard ratio for disease progression or death, 0.49 (95% CI, 0.38–0.65)
P<0.001

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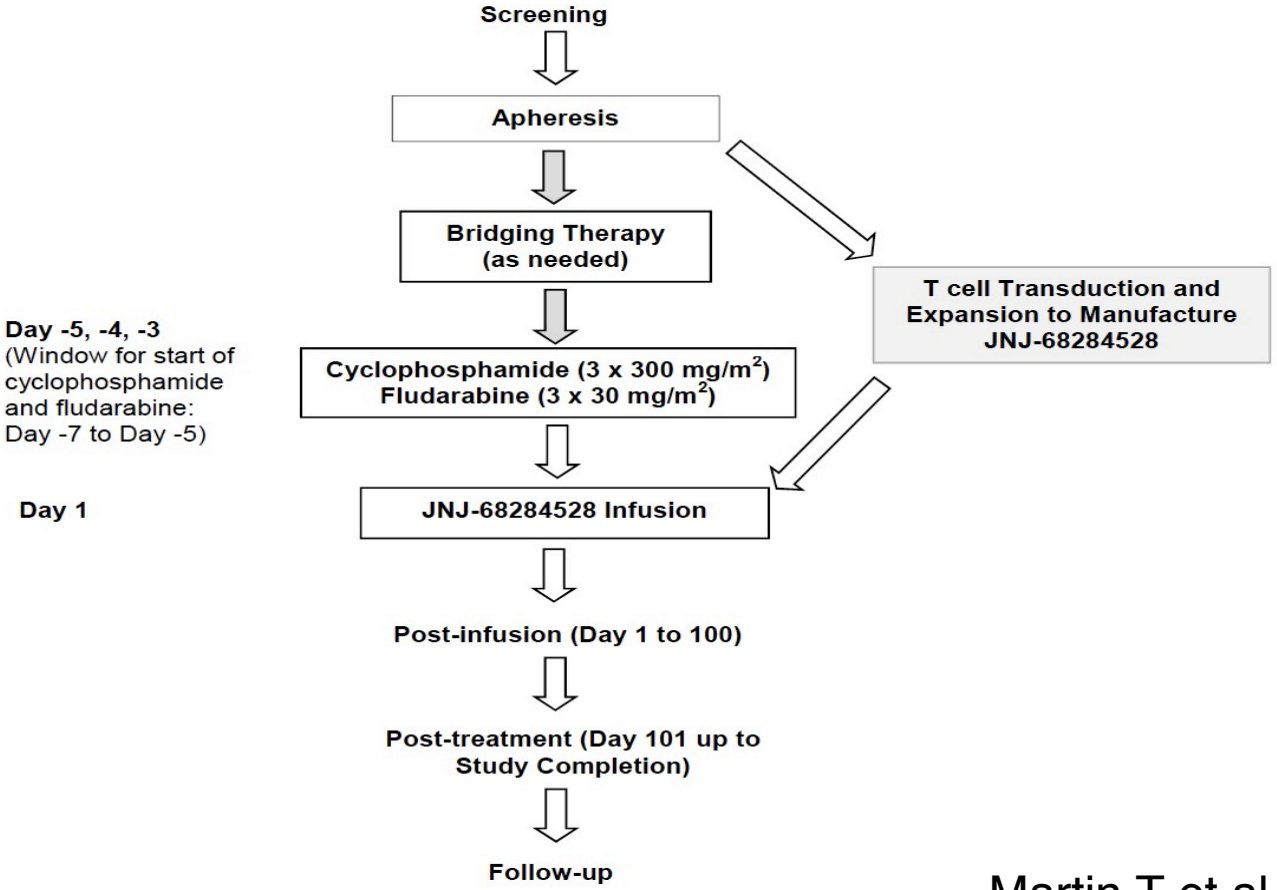
Cartitude study design



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Cilta-cel in RRMM

Overall response	
Patients with a response, No.[b]	95
Rate, % (95% CI)	97.9 (92.7 to 99.7)
Best overall response rate, % (95% CI)	
sCR	82.5 (73.4 to 89.4)
MRD-negative sCR[c]	44.3 (34.2 to 54.8)
CR	0 (NE to NE)
VGPR	12.4 (6.6 to 20.6)
PR	3.1 (0.6 to 8.8)
Minimal response	0 (NE to NE)
SD	0 (NE to NE)
PD	1.0 (0 to 5.6)
Not evaluable	1.0 (0 to 5.6)
Median duration of response, months (95% CI)	NE (23.3 to NE)
Median time to first response, months (range)	1.0 (0.9 to 10.7)
Median time to best response, months (range)	2.6 (0.9 to 17.8)
Median time to CR or better, months (range)	2.9 (0.9 to 17.8)
MRD negativity, No. (%)	
No. of patients evaluable for MRD at 10^{-5}	61
Rate, No. (%)	56 (91.8)
No. of patients evaluable for MRD at 10^{-6}	52
Rate, No. (%)	39 (75.0)

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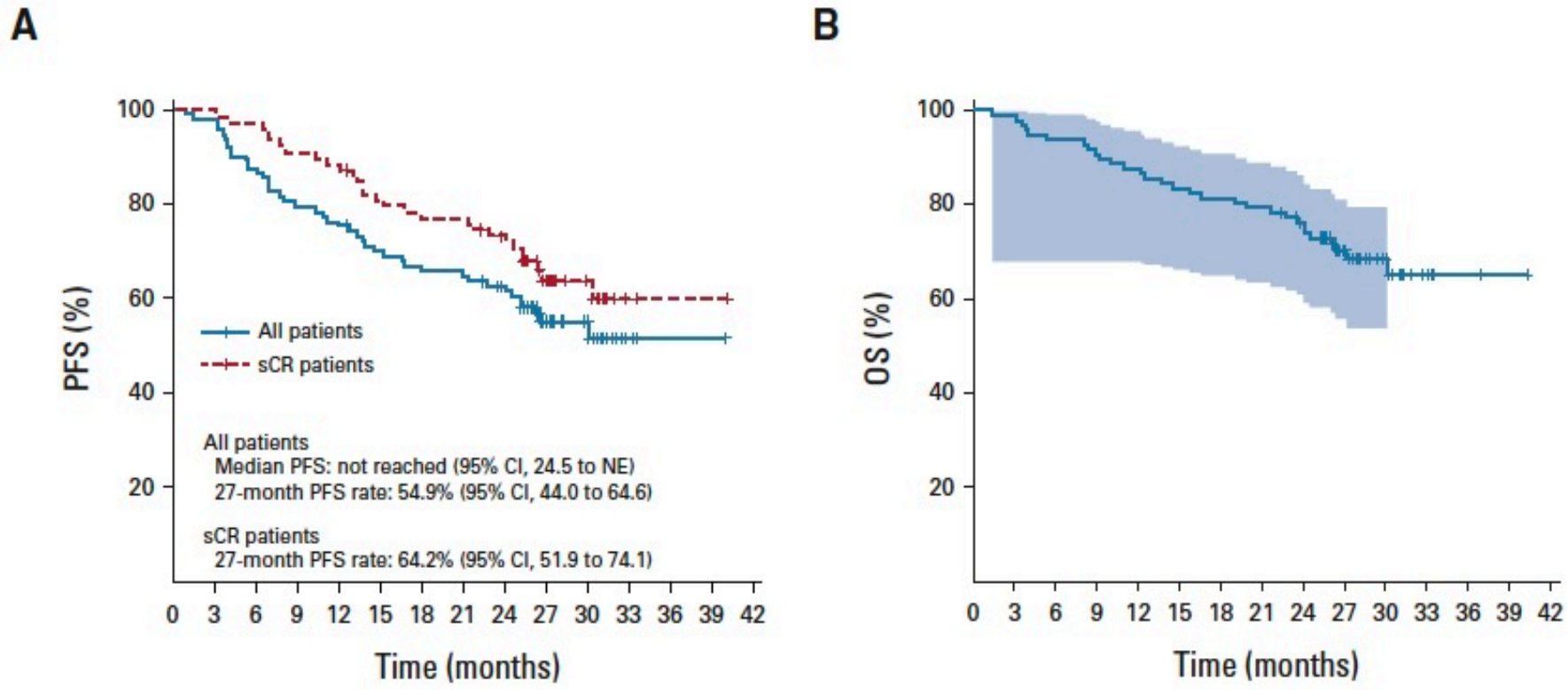
Cilta-cel in RRMM



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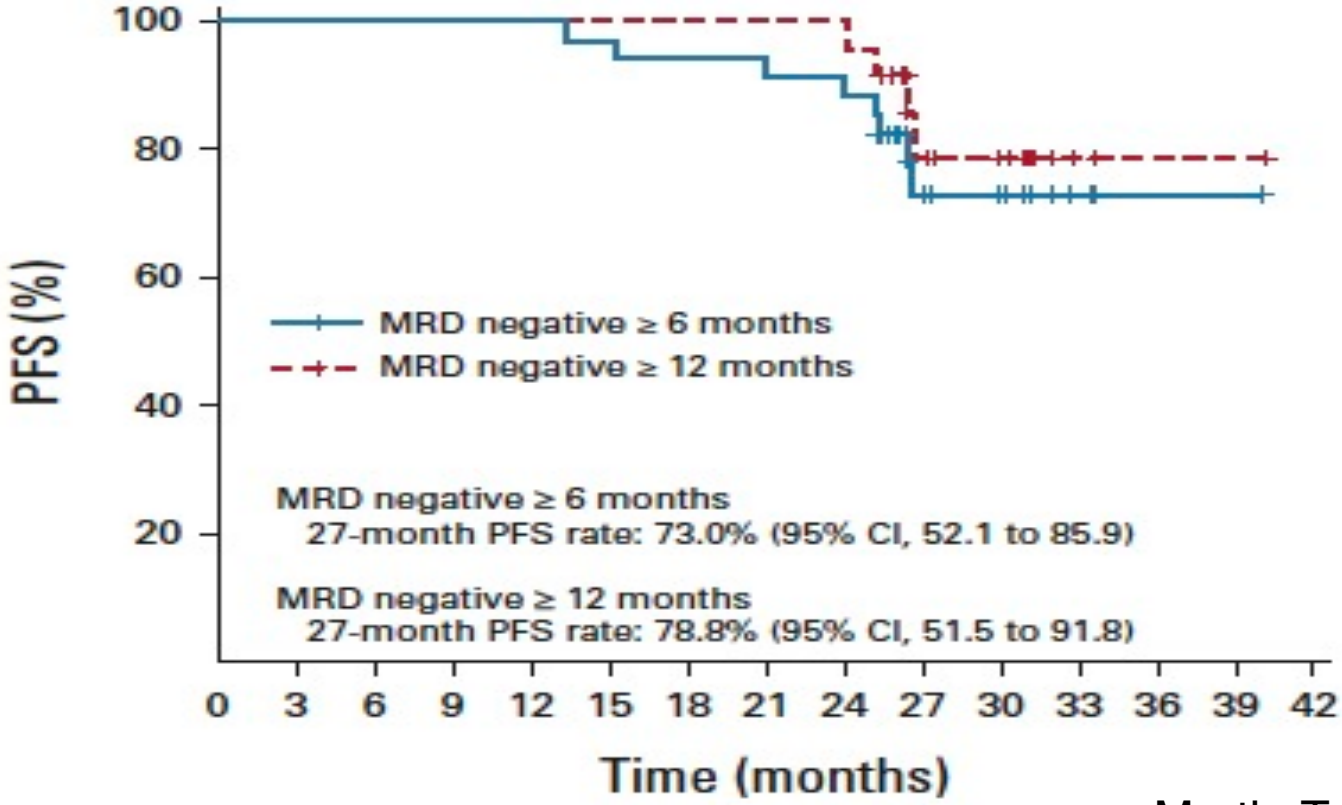
Cilta-cel in RRMM



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Cilta-cel in RRMM

Variable	Patient 1	Patient 2	Patient 3
Best response			
Initial treatment	sCR	sCR	VGPR
After retreatment	PD	SD	SD
CAR-T cell expansion after retreatment	None	None	None
Antidrug antibody status			
Before retreatment	Positive	Negative	Negative
After retreatment	Data not available[a]	Negative	Negative

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Ide vs Cilta cel in RRMM

	Idecabtagene vicleucel KarMMa trial[1-3]	Ciltacabtagene autoleucel CARTITUDE 1 trial
Number of patients infused, n	128 (140 apheresed)	97 (120 apheresed)
Phase	2	1b/2
Target/costimulation	BCMA/4-1BB	BCMA/4-1BB *2 BCMA-targeting heavy-chain antibody
scFv	Chimeric mouse	Chimeric llama
Specificity	Autologous	Autologous
Follow-up, median (range)	13.3 mo (0.2-21.2)	21.7 mo (not reported)
Prior lines, median (range)	6 (3 to 16)	6 (3-18)
Triple-class refractory, n (%)	108 (84)	85 (87.6)
Penta-exposed, n (%)	77 (60)	81 (83.5)
Bridging therapy, n (%)	112 (88)	73 (75)
Response to bridging therapy, n (%)	5/112 (4)	33/73 (45)
EMD, n (%)	50 (39)	13 (13)
CAR T-cell dose	150, 300, 450×10^6 CAR+T	0.75×10^6 CAR T+/kg
LD chemotherapy	Fludarabine 30mg/m^2×3 d Cyclo 300mg/m^2×3 d	Fludarabine 30mg/m^2×3 d Cyclo 300mg/m^2×3 d
ORR, n (%)	94 (73) At 450×10^6 (n=54): 44 (81%)	95 (97.9)
CR or sCR, n (%)	42 (33) At 450×10^6 (n=54): 21 (39)	82.5% (sCR)
Time to first response, median (range)	1.0 mo (0.5-8.8)	1.0 mo (IQR 0.9-1.0)
MRD in CR, n (%)	33/42 MRD neg (10^{-5})	61 evaluable 92% MRD negative (10^{-5})
DOR, median (95% CI)	10.7 mo (9.0-11.3)	Not reported
PFS, median (95% CI)	8.8 mo (5.6-11.6) At 450×10^6: 12.1 mo (8.8-12.3)	NR (16.8-NE) 2-y PFS: 60.5% (48.5-70.4)
PFS in high-risk, median (95% CI)		PFS at 2y, % (95% CI)
ISS 3/R-ISS 3	4.9 mo (1.8-8.2)[a]	NE (NE-NE)
High-risk CA	8.2 mo (4.8-11.9)	48.4% (25.1-68.4)
Plasmacytomas	7.9 mo (5.1-10.9)	47.4% (24.4-67.3)
OS, median (95% CI)	24.8 mo (19.9-31.2)	NR (27.2-NE)
CRS, n (%)		
Overall	107 (84)	92 (95)
Grade 3–4	7 (5)	4 (4)
Time to CRS onset, median (range)	1 d (1-12)	7 d (5-8)
Duration of CRS, median (range)	5 d (1-63)	4 d (3-6)

	Idecabtagene vicleucel KarMMa trial[1-3]	Ciltacabtagene autoleucel CARTITUDE 1 trial
Neurotoxicity, n (%)		
Overall	23 (18)	20 (21)[b]
Grade 3-4	4 (3)	9 (9)
Time to neurotoxicity onset, median (range)	2 d (1-10)	8 d (6-8) for ICANs Other: CAR-T cell neurotoxicites: 26.5 d (11-108)[b]
Grade 3-4 neutropenia, n (%)	114 (89)	92 (95)
Time to recovery, median (range)	1.9 mo (1.2-5.6)	Not reported
Grade 3-4 thrombocytopenia, n (%)	67 (52)	58 (60)
Time to recovery, median (range)	2.1 mo (1.2-13.8)	Not reported
Infections, n (%)	88 (69)	56 (58)
Grade 3-4 infections, n (%)	28 (22)	19 (20)
Death, n (%)	44 (34)	14
Reference	(1) Munshi et al[9] (2) Anderson et al.[34] (3) Oriol et al.[33]	(4) Berdeja et al[8] (5) Martin et al.[36] (6) Jakubowiak et al[11]

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Additional Ide/Cilta CAR-T studies

Trial	Study population	Study design	CAR name	ScFv origin	Phase	n	Antigen	Cell source	End point	Dose	Status
FUMANBA-2 (NCT05181501)	NDMM high-risk	VRD/PAD/PCD×3-ASCT (if eligible) >> CT103A	CT103A	Human	1	20	BCMA	Autologous	MRD negativity 2-year PFS	1×10^6/kg	Not yet enrolling
NCT04287660	NDMM	BiRD + BCMA CAR T cell	NA	NA	3	20	BCMA	Autologous	ORR at 4 weeks	$2–3\times10^7$/kg	Recruiting
CARTITUDE-5 NCT04923893	NDMM not intended for ASCT	A: VRD×8 + Rd B: VRD (6+2) + cilta-cel	Cilta-cel	Llama	3 randomized	650	BCMA	Autologous	PFS	0.75×10^6/kg	Recruiting
NCT04935580	NDMM-TE high-risk	2 cycles induction + CAR T + Len maintenance	GC012F	Human	1/2	20	BCMA-CD19	Autologous	Safety ORR, PFS, MRD	3×10^6/kg	Recruiting
CARTITUDE-6 NCT05257083	NDMM TE	A: DVRD×4 + ASCT +2×DVRD + Len B: DVRD×6 + cilta-cel + Len (2y)	Cilta-cel	Llama	3 randomized	750	BCMA	Autologous	PFS	0.75×10^6/kg	Not yet enrolling
KarMMa-4 NCT04196491	NDMM high-risk (R-ISS 3)	Standard induction×3 cycles + Ide-cel	Ide-cel	Murine	1	13	BCMA	Autologous	Safety	450×10^6	Active Not recruiting
CARTITUDE-2 NCT04133636	Multicohort	Cohort A: 1–3 prior lines Len-ref Cohort B: early relapse after frontline treatment Cohort C: relapse after BCMA Cohort F: NDMM after front-line Cohort E: NDMM-Tx not planned (high-risk)	Cilta-cel	Llama	2	157	BCMA	Autologous	MRD negativity at 1 year	0.75×10^6/kg	Recruiting
KarMMa-2 NCT03601078	Multicohort	2a + b: R-ISS 3 + early relapse 2c: suboptimal response to ASCT	Ide-cel	Murine	2	181	BCMA	Autologous	ORR	$150–450\times10^6$	Recruiting
KarMMa-7 NCT04855136	1–3 PL + Len R ≥3 PL RRMM	(A): Ide-cel + iberdomide maintenance (B): Ide-cel + gamma secretase inhibitor	Ide-cel	Murine	2	181	BCMA	Autologous	ORR	$150–450\times10^6$	Recruiting
KarMMa-3 NCT03651128	2–4 prior lines Len-ref & anti-CD38 exposed	A: DVd/DPd/ EloPd/Ixa-Rd/Kd B: Ide-cel	Ide-cel	Murine	3 Randomized	381	BCMA	Autologous	PFS	450×10^6	Recruiting
CARTITUDE-4 NCT04181827	1–3 prior lines Len refractory	A: PVd or DPd B: cilta-cel	Cilta-cel	Llama	3 randomized	419	BCMA	Autologous	PFS	0.75×10^6/kg	Active Not recruiting
BMTCTN1902 NCT05032820	NDMM post-ASCT	Ide-cel + Len maintenance	Ide-cel	Murine	2	40	BCMA	Autologous	ORR	450×10^6	Recruiting

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Additional Anti BCMA CAR-T studies

	BB21217 CRB-402 (n=72)	Orva-cel EVOLVE (n=62)	CT053 LUMMICAR (n=18)	CT103A FUMANBA-1 (n=79)	C-CAR088 (n=23)	P-BCMA-101 PRIME (n=53)	ALLO-715 UNIVERSAL (n=43)	ARI-002h (n=30)
Phase	1	1	1b/2	1/2	1	1/2	1	1
Follow-up, median (range)	23 (9-46)	9.5 mo	6 mo (2-11)	25.3 mo (4.1-36.7)	6.2 mo (0.7-16.1)	NA	4 mo	13 mo (7-13)
Target/costimulation	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB
scFv	Mouse	Mouse	Human	Human	Human	Mouse	Human	Human
Specificity	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Allogeneic	Autologous
CAR T-cell dose	150-450M	300-600M	1.5-3.0×10⁸ cells	1.0×10⁶/kg	1.0-6.0×10⁶/kg	51-1178×10⁶	40-480×10⁶	3×10⁶/kg
Population								
Age, median (range)	62 (33-76)	61 (33-77)	62 (36-78)	56 (39-70)	60 (45-74)	60 (42-74)	64 (46-77)	61 (36-74)
Prior lines, median (range)	6 (3-17)	6 (3-18)	5 (3-11)	5 (3-13)	4 (2-12)	8 (2-18)	5 (3-11)	4 (2-10)
Triple-class refractory, n (%)	50 (69)	58 (94)	85%	13 (16.5)	NR	60%	NR	61%
Penta-refractory, n (%)	NR	30 (48)	50%	NR	NR	NR	42%	NR
Efficacy							At 320×10⁶	
ORR, n (%)	69%	92%	94%	75 (94.9)	22 (95.7)	50%-75%	71%	100%
CR, n (%)	36%	36%	27.8%	58.2%	43.5%	NR	25%	60%
PFS (mo), median (95% CI)	12.8 mo (7.3-18.6)	9.3 mo (300M)	NR	25.3 mo (3.0-NE)	6 mo PFS: 65.1%	NR	NR	15.8 mo (12.9-NE)
CRS								
All grade, n (%)	54 (75)	55 (89)	15/18 (83.3)	72 (92.4)	21 (91.3)	17%	24 (56)	87%
Grade 3-4, n (%)	3 (2 grade 5)	2 (3)	0 (0)	2 (2.5)	1 (4.3)	0%	1 (2)	0 (0)
Onset (d), median (range)	2 d (1-20)	2 (1-4)	2 (DL0) & 1 (DL1)	6 (1-12)	6 (1-11)	NR	NR	NR
Duration (d), median (range)	4 d	4 (1-10)	4 (DL0) & 3 (DL1)	5 (1-30)	5 (2-9)	NR	NR	4 (1-12)
Tocilizumab/steroids %/%	53/17	76/52	≈30/20	20/34.7	26/9	7/6	23/14	76/12
ICANS								
All grade, n (%)	11 (15)	8 (13)	2 (DL0) & 1 (DL1)	1 (1.3)	1 (4.3)	4%	6 (14)	0
Grade 3-4, n (%)	3 (4)	2 (3)	1 patient	0	0 (0)	4%	0 (0)	0
Onset (d), median (range)	7 d (2-24)	4 (1-6)	NR	10	8	NR	NR	—
Duration (d), median (range)	2 d	4 (1-10)	NR	1	1	NR	NR	—
Status	Not further developed	Not further developed	Ongoing	Ongoing	Ongoing	Not further developed	Ongoing	Ongoing
Reference	Raje et al[37]	Mailankody et al.[37]	Chen et al.[38]	Chunrui et al.[39]	Gan An, et al.[40]	Costello et al.[41]	Mailankody et al.[42]	de Larrea et al[24]
Identification	NCT03274219	NCT03430011	NCT03915184	NCT05066646	NCT05066646	NCT03288493	NCT04093596	NCT04309981

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Other than BCMA CAR-T studies

Trial	Sponsor	CAR name	ScFv origin	Phase	n	Antigen	Costimulatory domain	Cell source	Transfer method	Dose	Efficacy
NCT04499339	European Union & CARAMBA	CARAMBA	Murine	1	38	SLAMF7	NR	Autologous	Sleeping beauty	NA	NR
NCT02135406	University of Pennsylvania	CTL019	Murine	1	10	CD19	4-1BB	Autologous	Lentiviral	$1.1\text{-}6\times10^{8}$	VGPR: 6; PR: 2; PD: 2
NCT01886976	Chinese PLA General Hospital	CART-138	Murine	1/2	5	CD138	4-1BB	Autologous	Retroviral	$0.44\text{–}1.51\times10^{7}$	SD: 4; PD: 1
NCT00881920	Baylor College of Medicine	κ.CARTs	Murine	1	7	κ light chain	CD28	Autologous	Retroviral	2.0×10^{8}	4 SD
NCT03958656	National Cancer Institute	NA	NA	1	42	SLAMF7	CD28 or 4-1BB/ CD3z + inducible caspase 9 (IC9) cell suicide	Autologous	NA	$0.3\text{–}12.0\times10^{6}$	NA
NCT04142619	Cellectis S.A.	UCARTCS1	NA	1	18	SLAMF7 (TALEN-targeted gene editing TCR and SLAMF7)	4-1BB	Allogeneic	NA	NA	NA
NCT02203825	Celyad	NKG2D-CAR	Human	1	12	NKG2D ligands	DAP10	Autologous	Retroviral	$1\text{-}3\times10^{7}$	NA
NCT03464916	Sorrento Therapeutics	CAR2 anti-CD38 A2	NA	1	72	CD38	NA	Autologous	NA	NA	NA
EU-CART	EU Horizon 2020 Program	NA	NA	1	NA	CD44v6 (+HSV-TK suicide gene)	CD28	Autologous	Retroviral	NA	NA
NCT01716364	Peter MacCallum Cancer Centre, Australia	LeY	NA	1	6	Lewis Y	CD28	Autologous	Retroviral	NA	NA
NCT05016778	Zhejiang University	GPR5D-CAR T	NA	1	15	GPRC5d	NA	Autologous	NA	1.0, 3.0, or 6.0×10^{6}/kg	NA
NCT05219721	Tongji Hospital	CAR-GPR5D	Human	1	18	GPRC5d	4-1BB	Autologous	NA	0.5, 1.0, and 2.0×10^{6}/kg	NA
NCT04555551	Memorial Sloan Kettering Cancer Center	MCARH109	Human	1	17	GPRC5d	4-1BB	Autologous	Lentiviral	25, 50, 150, 450×10^{6}	ORR 69% CR 25%

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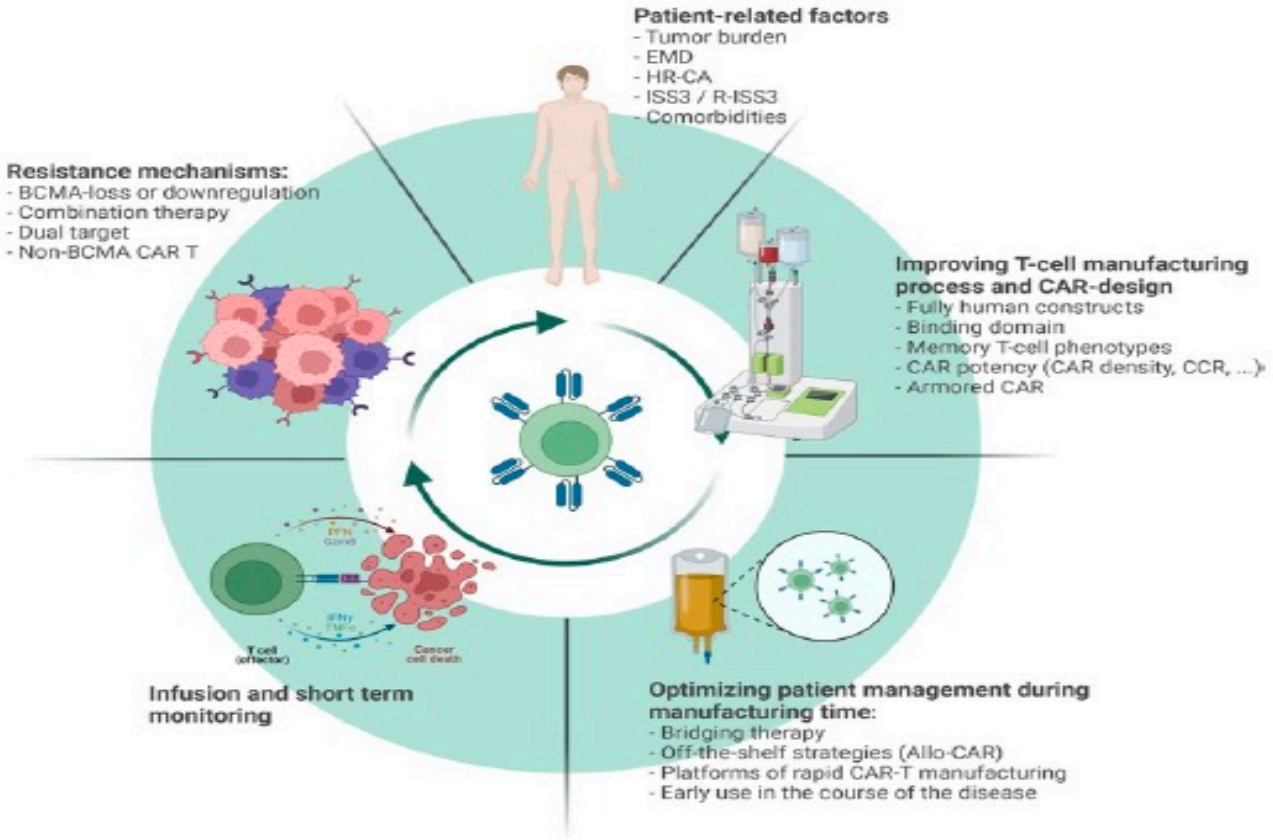
Strategies to improve CAR-T efficiency



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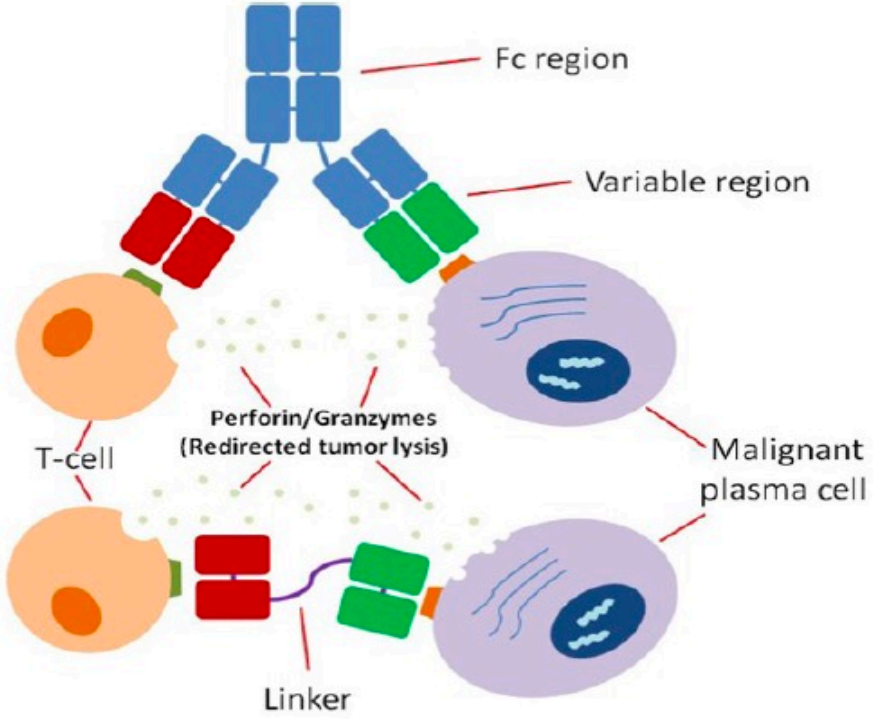
Bispecific T cell Engagers

IgG-like BiAb

- Elranatamab
- REGN-5458
- Teclistamab
- CC-93269
- TNB-383B
- Cevostamab
- Talquetamab

Non-IgG-like BiAb

- AMG 420
- AMG 701 (Extended half-life)



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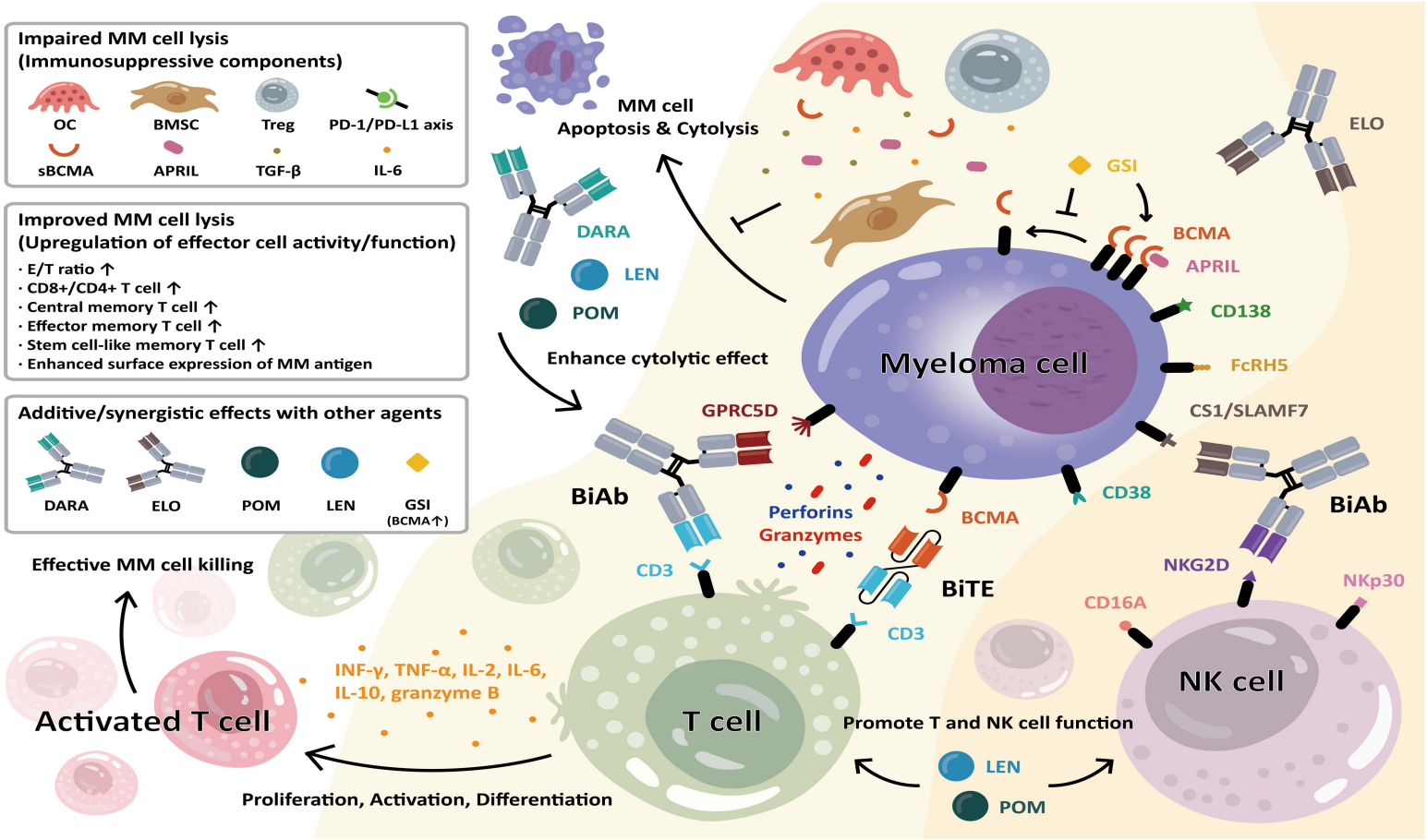
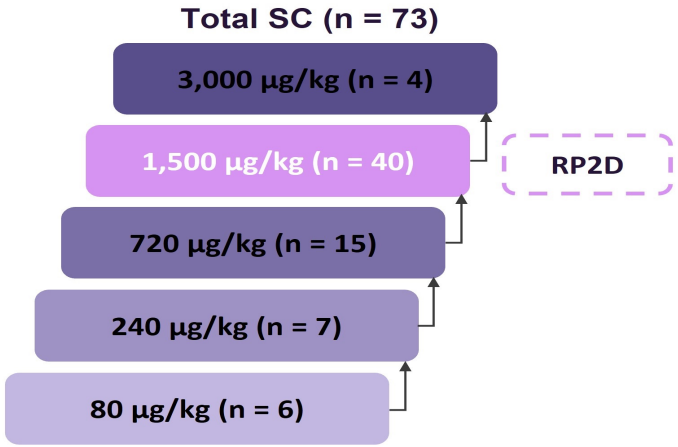
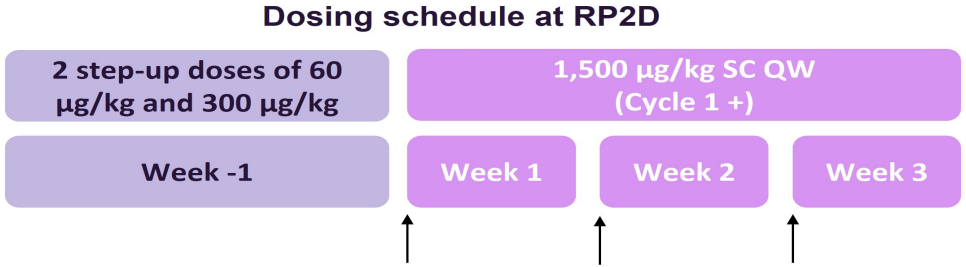

Impaired MM cell lysis
(Immunosuppressive components)
OC
BMSC
Treg
PD-1/PD-L1 axis
sBCMA
APRIL
TGF-β
IL-6
Improved MM cell lysis
(Upregulation of effector cell activity/function)
· E/T ratio ↑
· CD8+/CD4+ T cell ↑
· Central memory T cell ↑
· Effector memory T cell ↑
· Stem cell-like memory T cell ↑
· Enhanced surface expression of MM antigen
Additive/synergistic effects with other agents
DARA
ELO
POM
LEN
GSI
(BCMA↑)
MM cell
Apoptosis & Cytolysis
DARA
LEN
POM
Enhance cytolytic effect
ELO
GSI
BCMA
APRIL
CD138
FcRH5
CS1/SLAMF7
Myeloma cell
GPRC5D
BiAb
CD38
BCMA
Perforins
Granzymes
BiAb
CD3
BiTE
CD3
NKG2D
NKp30
CD16A
NK cell
Effective MM cell killing
INF-γ, TNF-α, IL-2, IL-6,
IL-10, granzyme B
Activated T cell
T cell
Promote T and NK cell function
LEN
POM
Proliferation, Activation, Differentiation

MajesTEC-1 study design

Part 1. Dose escalation



Part 2. Dose expansion†



MajesTEC-1 study

Characteristic	Phase 1 (N=40)	Phase 2 (N=125)	Total (N=165)
Age			
Median (range) — yr	62.5 (39.0–84.0)	64.0 (33.0–83.0)	64.0 (33.0–84.0)
≥75 yr — no. (%)	5 (12.5)	19 (15.2)	24 (14.5)
Sex — no. (%)			
Male	26 (65.0)	70 (56.0)	96 (58.2)
Female	14 (35.0)	55 (44.0)	69 (41.8)
Race — no. (%)*			
White	34 (85.0)	100 (80.0)	134 (81.2)
Black	1 (2.5)	20 (16.0)	21 (12.7)
Asian	0	3 (2.4)	3 (1.8)
Other	5 (12.5)	2 (1.6)	7 (4.2)
Median time since diagnosis (range) — yr	5.6 (0.8–17.4)	6.2 (0.9–22.7)	6.0 (0.8–22.7)
≥1 Extramedullary plasmacytoma — no. (%)†	8 (20.0)	20 (16.0)	28 (17.0)
≥60% Plasma cells in bone marrow — no./total no. (%)	3/38 (7.9)	15/122 (12.3)	18/160 (11.2)
ECOG performance-status score — no. (%)‡			
0	17 (42.5)	38 (30.4)	55 (33.3)
≥1	23 (57.5)	87 (69.6)	110 (66.7)

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MajesTEC-1 study

Characteristic	Phase 1 (N=40)	Phase 2 (N=125)	Total (N=165)
International Staging System class — no./total no. (%)			
I	24/39 (61.5)	61/123 (49.6)	85/162 (52.5)
II	11/39 (28.2)	46/123 (37.4)	57/162 (35.2)
III	4/39 (10.3)	16/123 (13.0)	20/162 (12.3)
High-risk cytogenetic profile — no./total no. (%)	12/37 (32.4)	26/111 (23.4)	38/148 (25.7)
del(17p)	9/37 (24.3)	14/111 (12.6)	23/148 (15.5)
t(4:14)	4/37 (10.8)	12/111 (10.8)	16/148 (10.8)
t(14;16)	1/37 (2.7)	3/111 (2.7)	4/148 (2.7)
Median no. of lines of previous therapy (range)	5 (2–11)	5 (2–14)	5 (2–14)
Previous stem-cell transplantation — no. (%)	34 (85.0)	101 (80.8)	135 (81.8)
Previous therapy exposure — no. (%)			
Triple-class§	40 (100.0)	125 (100.0)	165 (100.0)
Penta-drug¶	26 (65.0)	90 (72.0)	116 (70.3)
Refractory status — no. (%)			
Immunomodulatory agent‖	38 (95.0)	114 (91.2)	152 (92.1)
Proteasome inhibitor**	34 (85.0)	108 (86.4)	142 (86.1)
Anti-CD38 monoclonal antibody††	39 (97.5)	109 (87.2)	148 (89.7)
Triple-class§	32 (80.0)	96 (76.8)	128 (77.6)
Penta-drug¶	16 (40.0)	34 (27.2)	50 (30.3)
Refractory to last line of therapy	33 (82.5)	115 (92.0)	148 (89.7)

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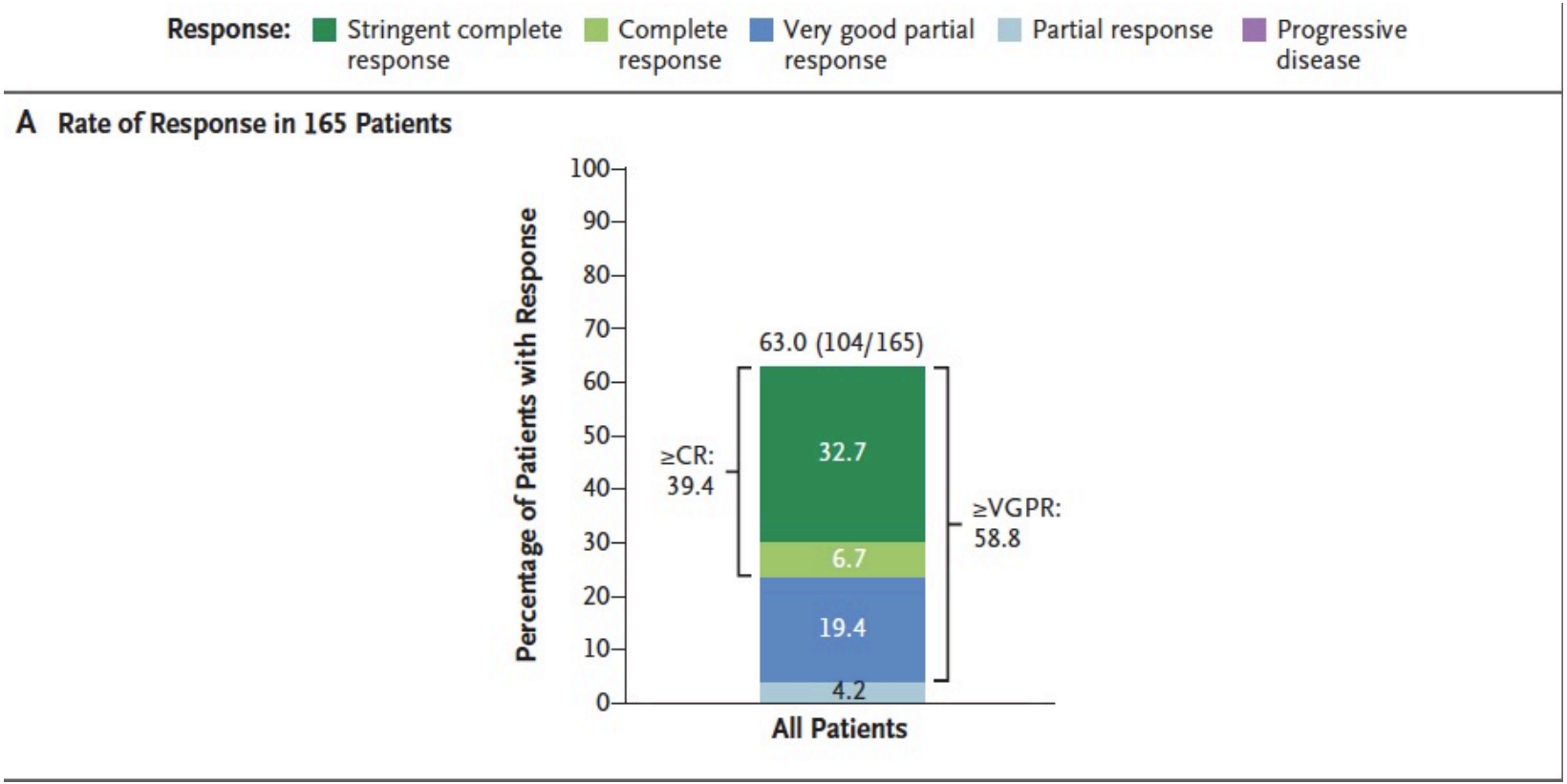
MajesTEC-1 study



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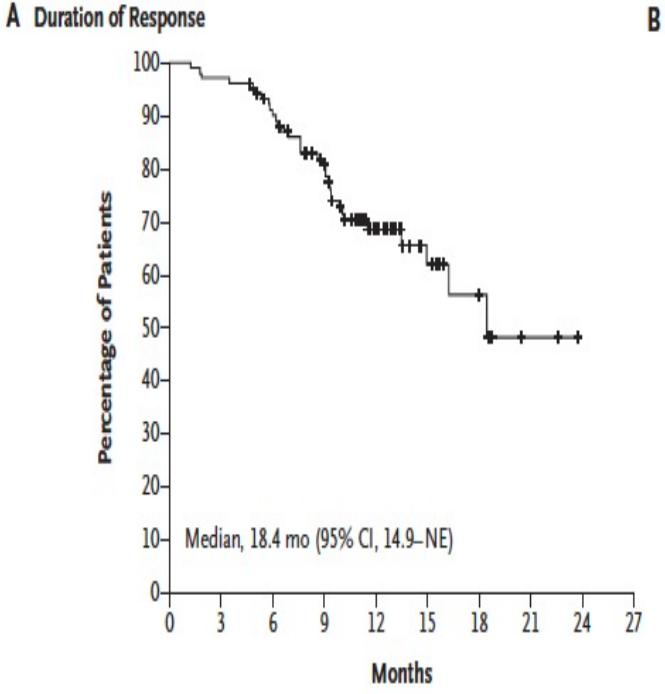
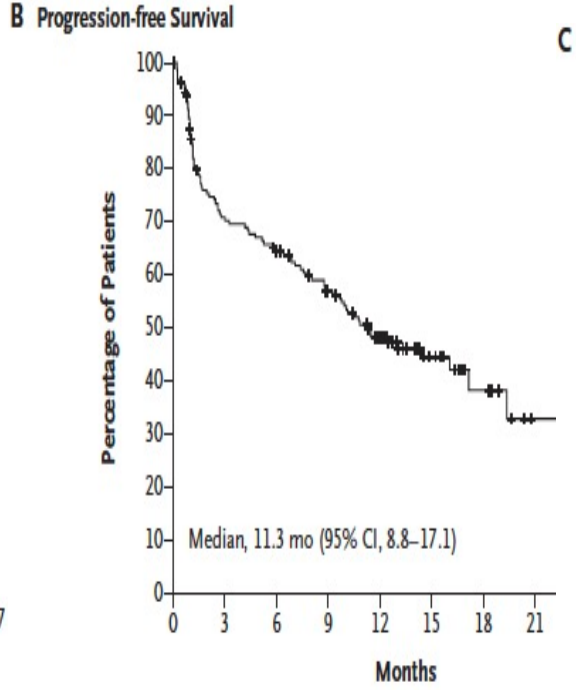
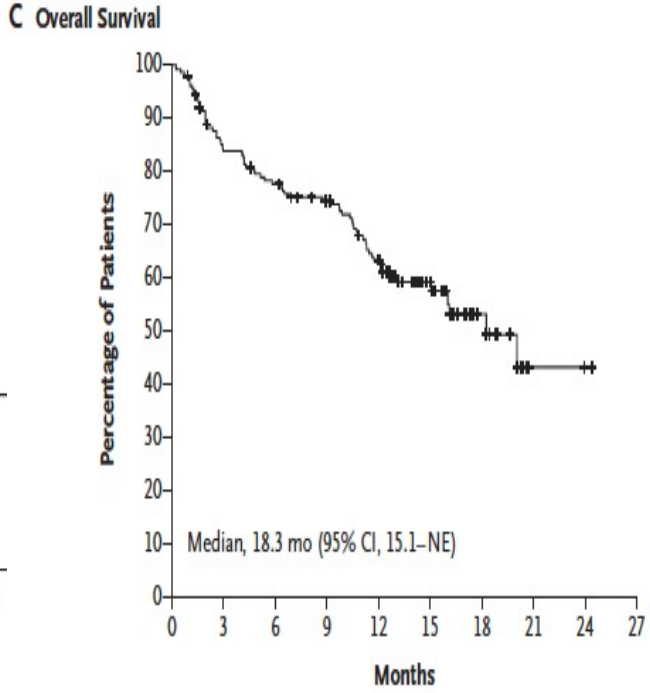
MajesTEC-1 study







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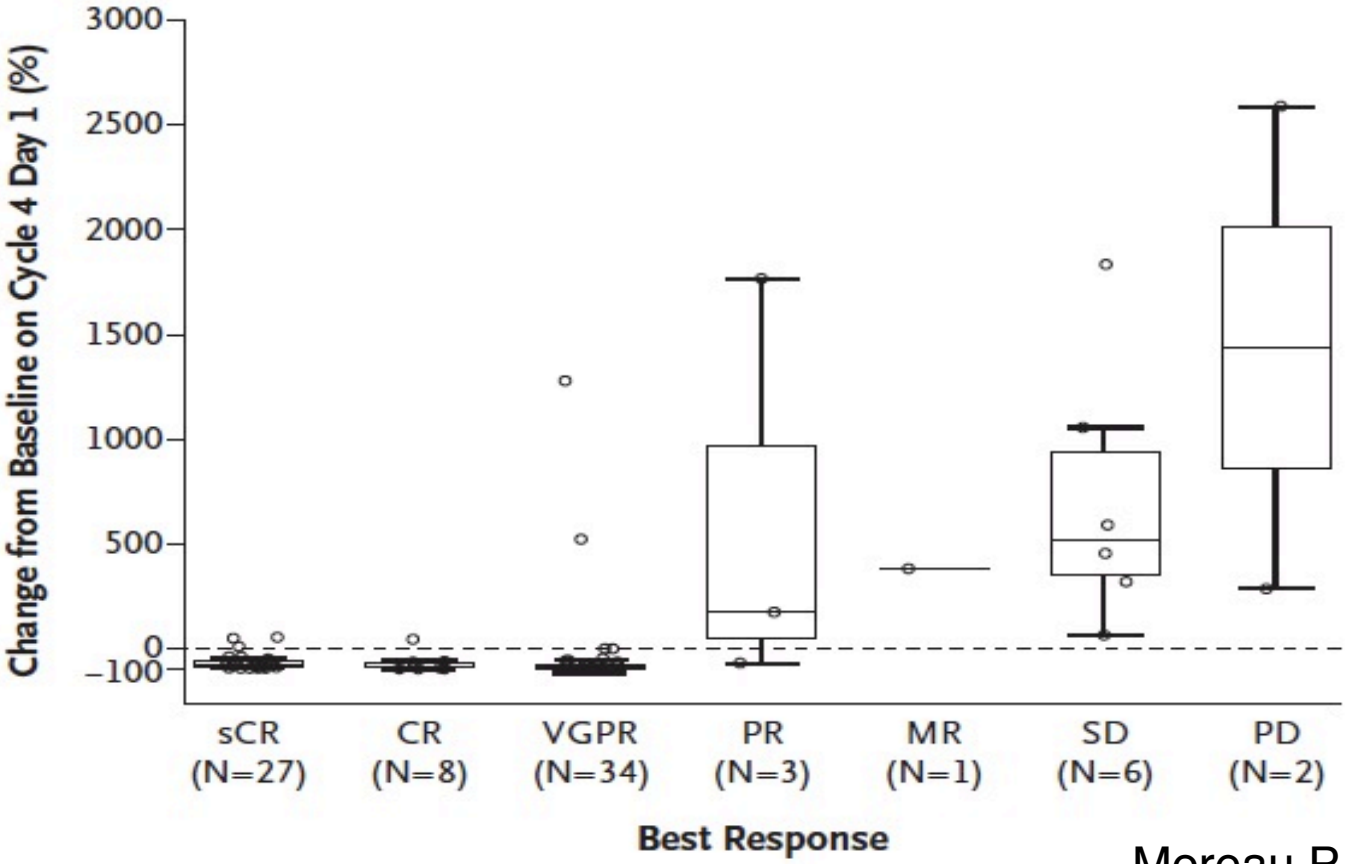
MajesTEC-1 study



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MajesTEC-1 study

Table 2. Adverse Events in 165 Patients (Safety Population).*

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

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Summary of Bispecific Abs trials as single agents

Name	Target	Antibody construct	Triple-class refractory (median LoT)	Trial phase	Schedule	Preliminary response/ activity	Safety	Current status (ClinicalTrials .gov)
AMG 420[38]	BCMA-CD3	BiTE®	N/A (29% prior anti-CD38, median 5 LoT)	Phase 1	Continuous infusion for 4 wk (out of 6)	ORR=31% ORR MTD=70%	38% CRS (6.25% ≥ gr 3) 5% ≥ gr 3 polyneuropathy 24% ≥ gr 3 infection	Active, not recruiting NCT03836053
AMG 701[39]	BCMA-CD3	HLE-BiTE®	68% (median 6 LoT)	Phase 1/2	Weekly IV	ORR=36% ORR=83% at 9 mg	75% CRS (10.5% ≥ gr 3) 8% neurotoxicity (gr 1–2) 13% ≥ gr 3 infection	Recruiting NCT03287908
Elranatamab[41]	BCMA-CD3	Humanized IgG2a Fc	91% (median 6 LoT; 22% prior anti-BCMA)	Phase 1	Weekly or every 2 wk Sc	ORR=64% for doses ≥215 µg/kg	67% CRS (gr 1–2)	MagnetisMM-1 Recruiting NCT03269136
REGN5458[42]	BCMA-CD3	Fc Fab arms	97.1% (median 5 LoT)	Phase 1/2	Weekly IV	ORR=73.3% at 96–200-mg doses	38.2% CRS (gr 1–2) 4% neurotoxicity (gr 1–2) 23% pneumonia (11% ≥ gr 3)	Recruiting NCT03761108
Teclistamab[40]	BCMA-CD3	Humanized IgG4 Fc	77.8% (median 5 LoT; prior anti-BCMA not permitted)	Phase 1/2	Weekly Sc	ORR=63%	72.1% CRS (gr 3, 0.6%; no gr 4) 14.5% neurotoxicity (1 gr 4 event) 44.8% ≥ gr 3 infection	MajestTEC-1 Recruiting NCT03145181
CC-93269[44]	BCMA-CD3	Asymmetric 2-arm IgG	66.7% (median 6 LoT)	Phase 1	Weekly IV	ORR=83.3% in 10 pts with doses ≥6 mg	89.5% CRS (1 gr 5 event) 26.3% infection	Recruiting NCT03486067
TNB-383B[44]	BCMA-CD3	IgG4 Fc CD3 activating T effector cells	62% (median 5 LoT)	Phase 1	Q21d IV	ORR=79% at doses ≥40 mg	52% CRS (3% ≥ gr 3 at RP2D) 28% infection	Recruiting NCT03933735
Cevostamab[45]	FcRH5-CD3	Humanized IgG1 Fc	85% (median 6 LoT; 33.5% prior anti-BCMA)	Phase 1	Q21d IV	ORR=54.5% at 160-mg-dose level	80.7% CRS (1.3% ≥ gr 3) 18.8% ≥ gr 3 infection 14.3% neurotoxicity (0.3% ≥ gr 3)	Recruiting NCT03275103
Talquetamab[46]	GPRC5D-CD3	Humanized IgG4 Fc	Weekly: 77% (median 6 LoT; 30% prior anti-BCMA) Biweekly: 65% (median 5 LoT; 17% prior anti-BCMA)	Phase 1/2	Weekly or biweekly Sc	Weekly: ORR=70% Biweekly: ORR=71%	Weekly: 73% CRS (1 gr 3) Biweekly: 78% CRS (gr 1–2)	MonumenTal-1 Recruiting NCT03399799

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Summary of Bispecific Abs trials as combo agents

Name	Patient population	Trial phase	Combination drugs	Current status (ClinicalTrials.gov)
Elranatamab	RRMM	Phase 1b/2	Arm 1: elranatamab + nirogacestat (GSI)	MagnetisMM-4 (recruiting) NCT05090566
			Arm 2: elranatamab + lenalidomide + dexamethasone	
		Phase 3	Arm 1: elranatamab	MagnetisMM-5 (recruiting) NCT05020236
			Arm 2: elranatamab + daratumumab	
			Arm 3: earatumumab + pomalidomide + dexamethasone	
Teclistamab + talquetamab	RRMM	Phase 3	Arm 1: teclistamab + daratumumab	MajestTEC-3 (recruiting) NCT05083169
			Arm 2: daratumumab + pomalidomide + dexamethasone	
			Arm 3: daratumumab + bortezomib + dexamethasone	
		Phase 1	Arm 1: teclistamab + talquetamab	NCT04586426 (recruiting)
			Arm 2: teclistamab + talquetamab + daratumumab	
		Phase 1b	Arm 1: daratumumab + teclistamab	TRIMM-2 (recruiting) NCT04108195
			Arm 2: daratumumab + talquetamab	
			Arm 3: daratumumab + talquetamab + pomalidomide	
			Arm 4: daratumumab + teclistamab + pomalidomide	
Cevostamab	RRMM	Phase 1	Arm 1: cevostamab	Recruiting NCT04910568
			Arm 2: cevostamab + pomalidomide + dexamethasone	
			Arm 3: cevostamab + daratumumab + dexamethasone	

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ADCs vs Bispecific T cell engagers

	Antibody drug conjugates	Bispecific T-cell engagers	CAR T-cell therapy
Advantages	Off-the-shelf therapy	Off-the-shelf therapy	-
	Immune and nonimmune mechanisms of action	-	-
	Infrequent dosing (every 3 wk-12 wk)	-	One-time therapy
	Encouraging response rates	Deep responses	Deep responses
	No CRS/ICANS	Mostly grade 1–2 CRS/ICANS	-
	Outpatient administration	Only initial dosing as inpatient	Vacation from continuous therapy
Disadvantages	Continuous therapy until progression	Continuous therapy until progression	-
	Frequent dose interruptions	Weekly or biweekly dosing	Administration delays due to manufacturing time
	Ocular toxicity	Significant immunosuppression	Potential for severe CRS/ICANS; prolonged cytopenias
	Ophthalmic exams prior to dosing	Specialized centers required	Complex infrastructure required
	Cost ($$)	Cost ($$)	Cost ($$$)

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Take Home Messages

- Promising data of new generation Immune based therapies
- Right sequencing to sustain immunological reset
- Moving towards a «chronic MM disease»?