Promise of Bispecifics and CAR-T in Multiple Myeloma

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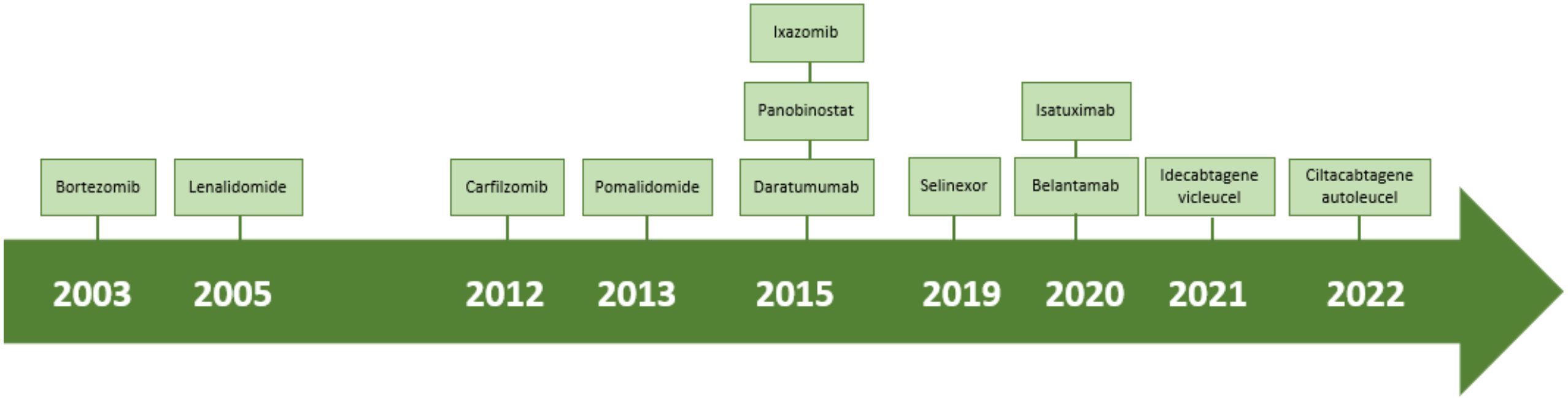
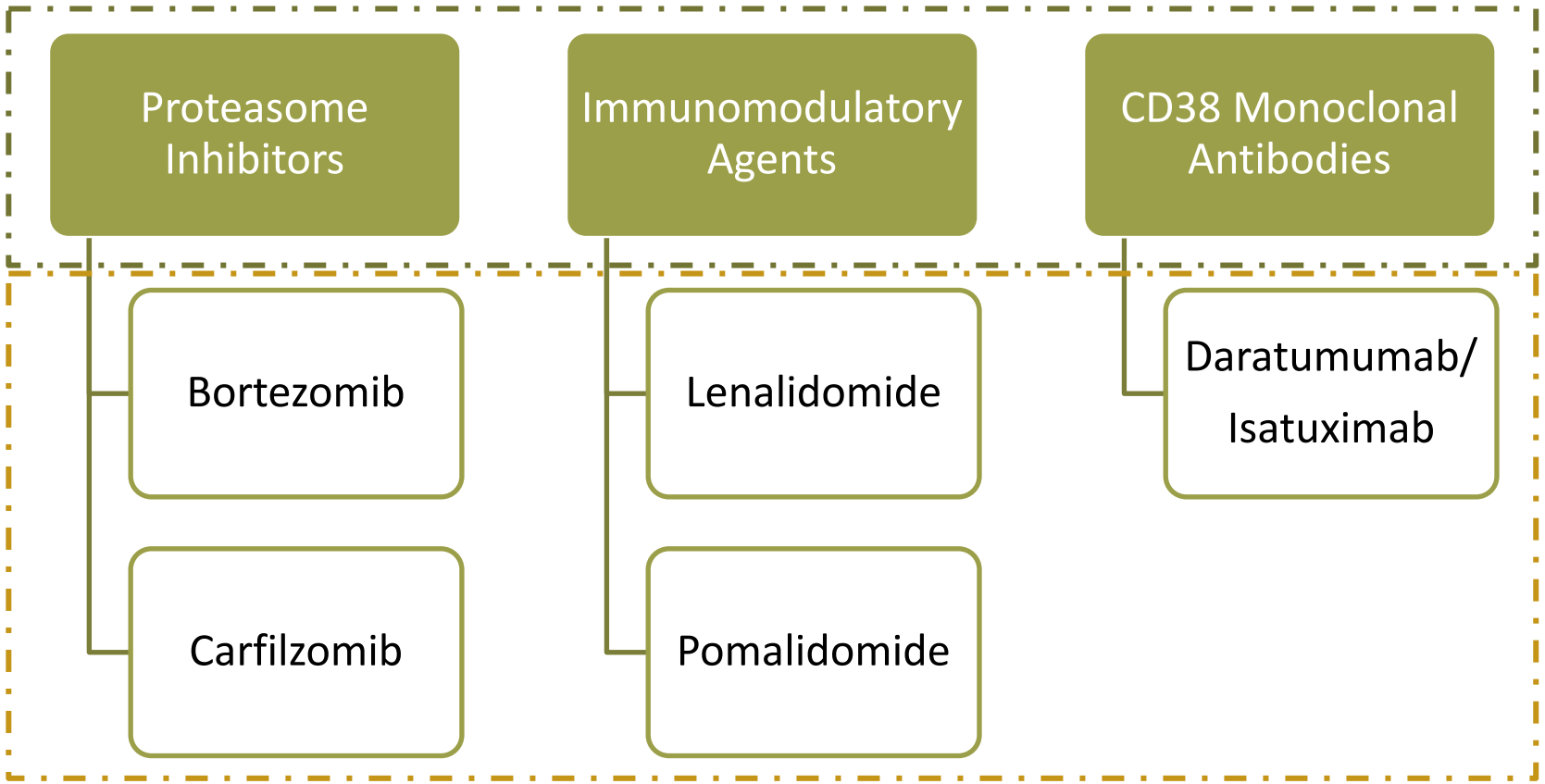
Development of Therapeutics in MM



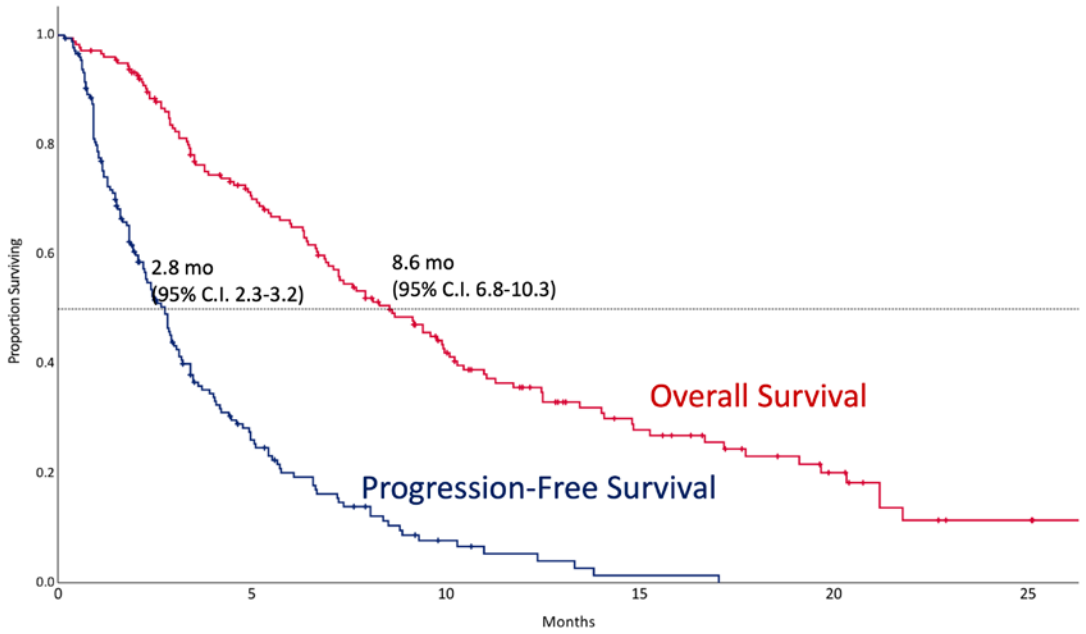
Definitions

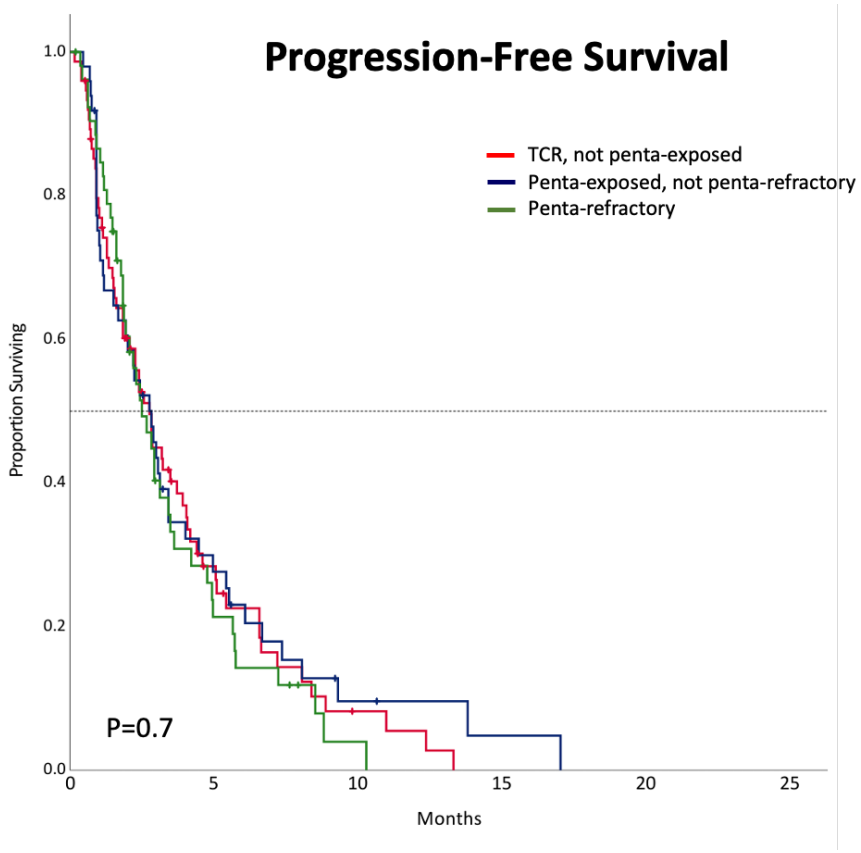


Triple Class Refractory

Penta-Refractory

Treatment beyond TCR MM – MAMMOTH study





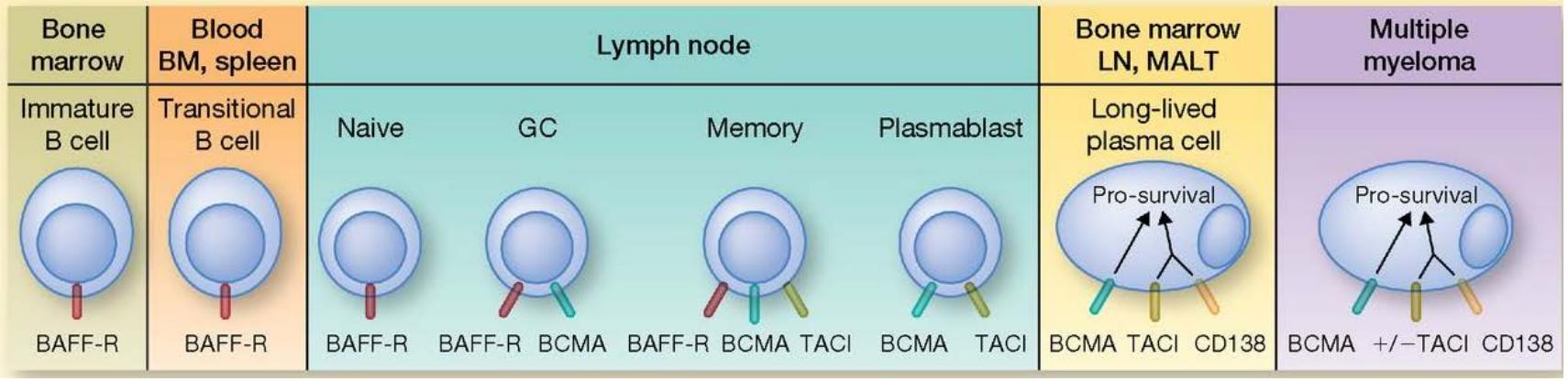
Bal S et al. Leukemia 2021 (Epub ahed of print)

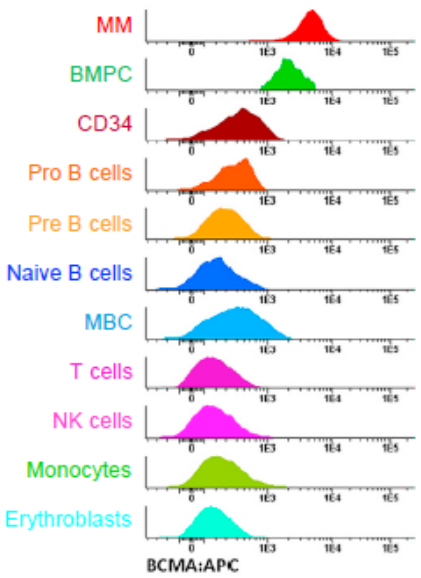
Treatment beyond TCR MM – MAMMOTH study

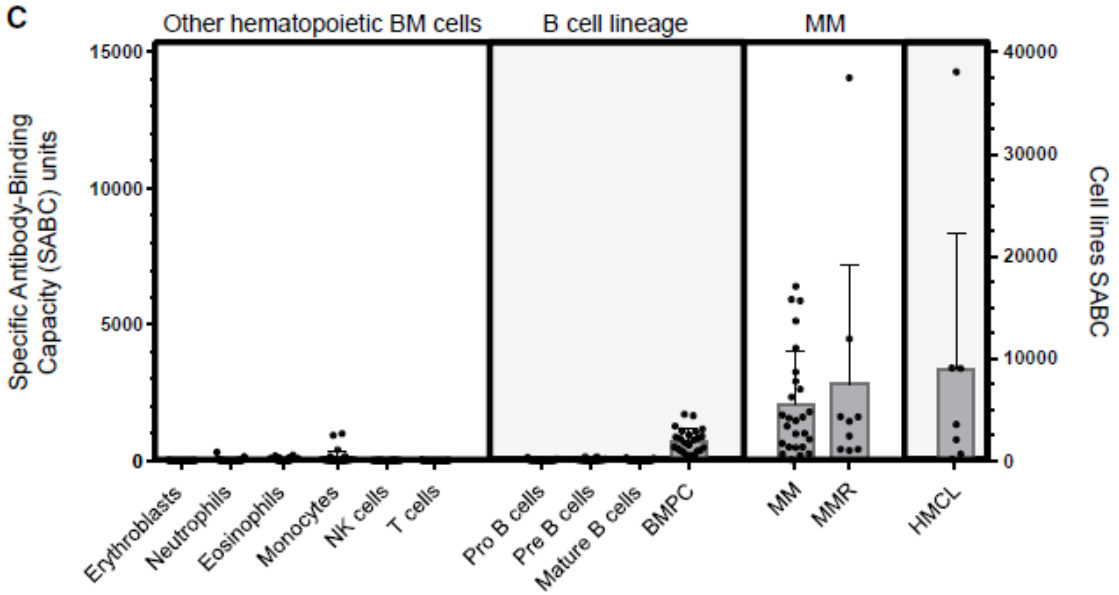
	Next Regimen after MM becomes TCR				
Characteristic	All patients	Cytotoxic chemotherarpy	CD38 MoAb-containing	Carfilzomib-containing	Pomalidomide-containing
N	177	80	45	42	60
Cytogenetic high-risk	29%	33%	29%	24%	18%
ISS3	28%	26%	27%	33%	32%
Median time diagnosis-TCR (y)	4.8	4.3	5.3	3.8	4.4
N prior lines (range)	5 (3-17)	5.5 (3-12)	5 (3-17)	5 (3-9)	5 (3-10)
Penta-exposed	58%	68%	47%	41%	58%
Penta-refractory	30%	33%	22%	14%	22%
ORR	**30%**	**44%**	**20%**	**31%**	**28%**
Median PFS in mo. (95% C.I)	2.8 (2.3-3.2)	2.4 (1.9-3.0)	3.1 (2.6-3.5)	4.0 (1.0-7.0)	3.4 (2.3-4.5)
Median OS in mo. (95% C.I)	8.6 (6.8-10.3)	7.6 (5.4-9.8)	11.0 (8.5-13.5)	9.2 (5.4-13.0)	9.4 (7.1-11.7)

Bal S et al. Leukemia 2021 (Epub ahed of print)

B-Cell Maturation Antigen (BCMA)

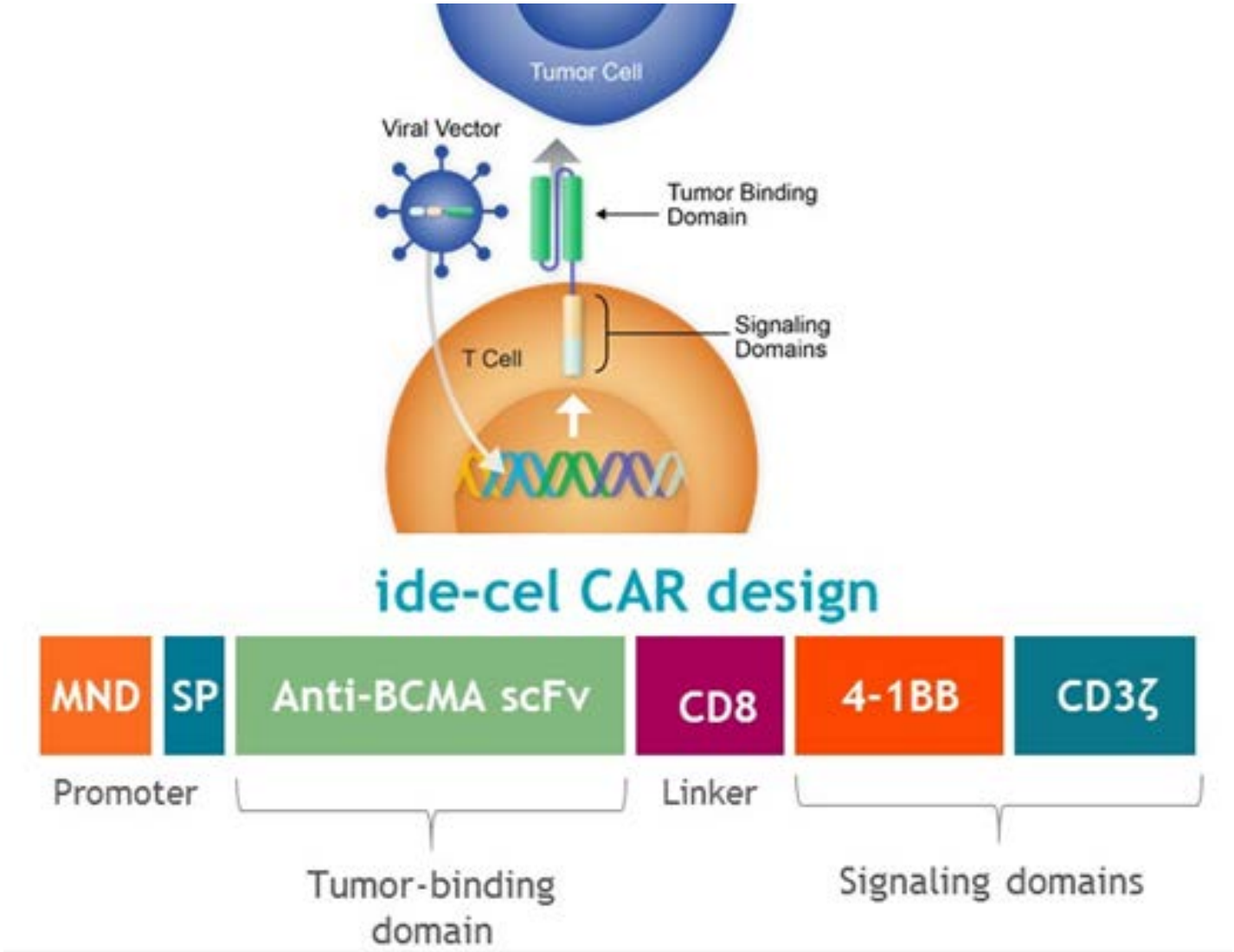






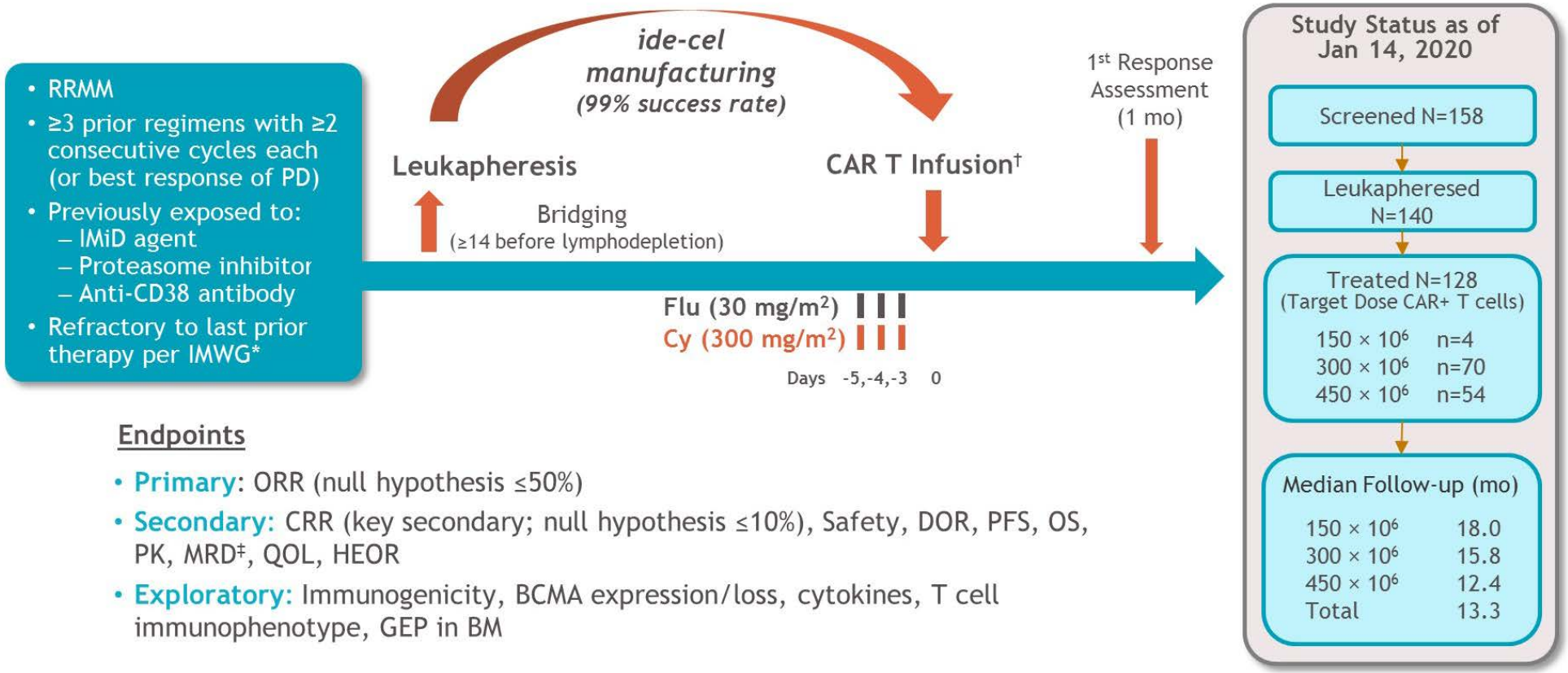
Seckinger A. Cancer Cell 31:1, 2017

IDE-CEL



Munshi et al. ASCO 2020

KARMMA STUDY



Endpoints

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

Munshi et al. N Engl J Med 384 ;705, 2021

KARMMA STUDY

Characteristics		Ide-cel Treated (N=128)
Age, median (range), y		61 (33–78)
Male, %		59
ECOG PS, %	0 1 2	45 53 2
R-ISS Stage,* %	I II III	11 70 16
High-risk cytogenetics [del(17p), t(4;14), t(14;16)],† %		35
High tumor burden (≥50% BMPCs), %		51
Tumor BCMA expression (≥50% BCMA+),‡ %		85
Extramedullary disease, %		39
Time since initial diagnosis, median (range), y		6 (1–18)
No. of prior anti-myeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1 >1	94 34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab-refractory Triple-refractory	94 84

Munshi et al. N Engl J Med 384 ;705, 2021

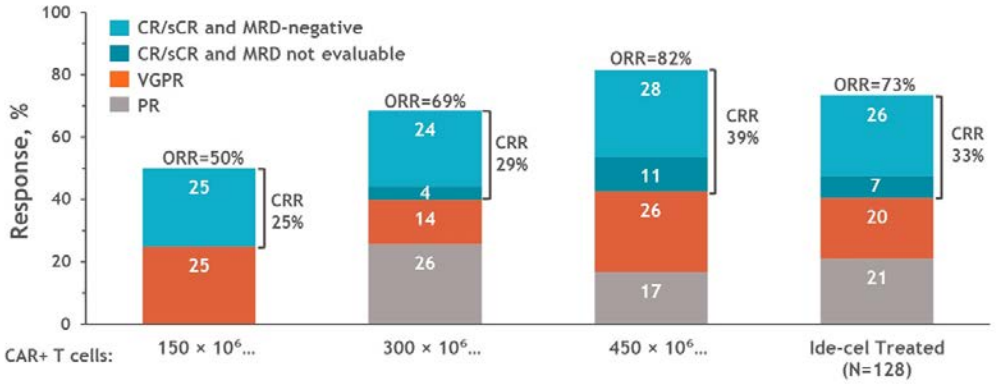
KARMMA STUDY

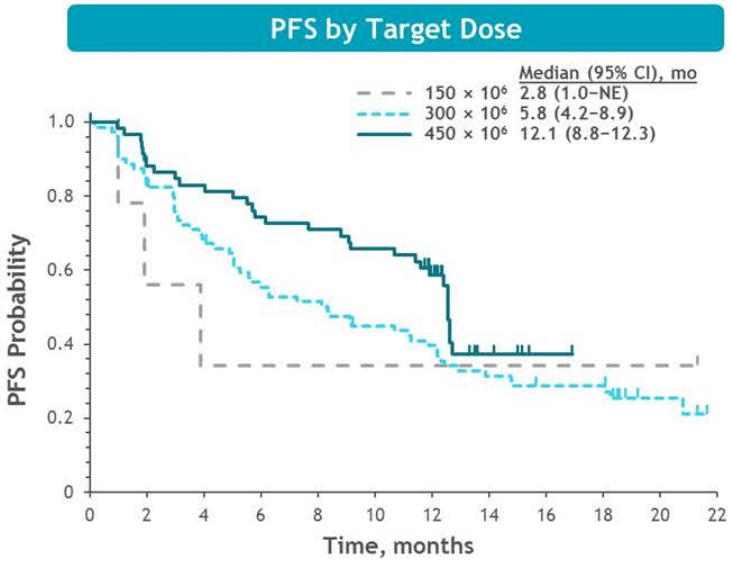
Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 CRS event, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Max. grade (Lee Criteria)*				
1/2	2 (50)	49 (70)	49 (91)	100 (78)
3	0	2 (3)	3 (6)	5 (4)
4	0	1 (1)	0	1 (<1)
5	0	1 (1)	0	1 (<1)
Median onset, d (range)	7 (2–12)	2 (1–12)	1 (1–10)	1 (1–12)
Median duration, d (range)	5 (3–7)	4 (2–28)	7 (1–63)	5 (1–63)
Tocilizumab, n (%)	1 (25)	30 (43)	36 (67)	67 (52)
Corticosteroids, n (%)	0	7 (10)	12 (22)	19 (15)

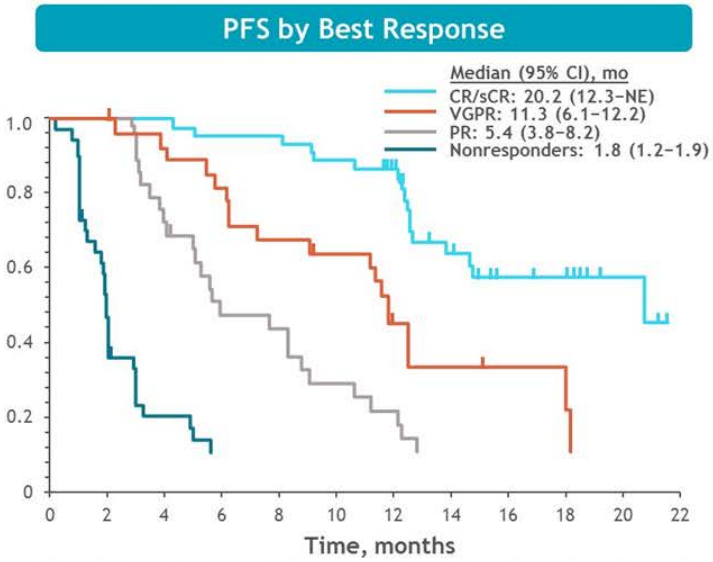
- 3% grade 3 neurotoxicity
- Cytopenias were common, median 2 months for improvement

Munshi et al. N Engl J Med 384 ;705, 2021

KARMMA STUDY

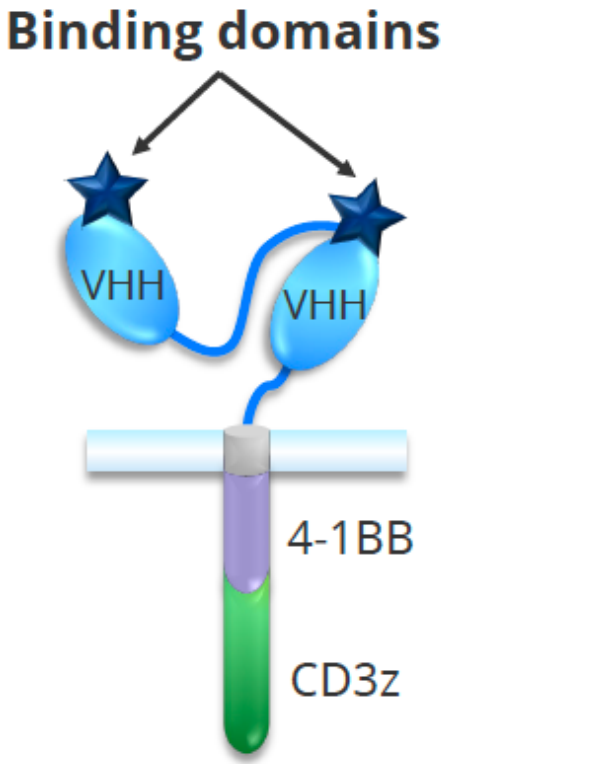






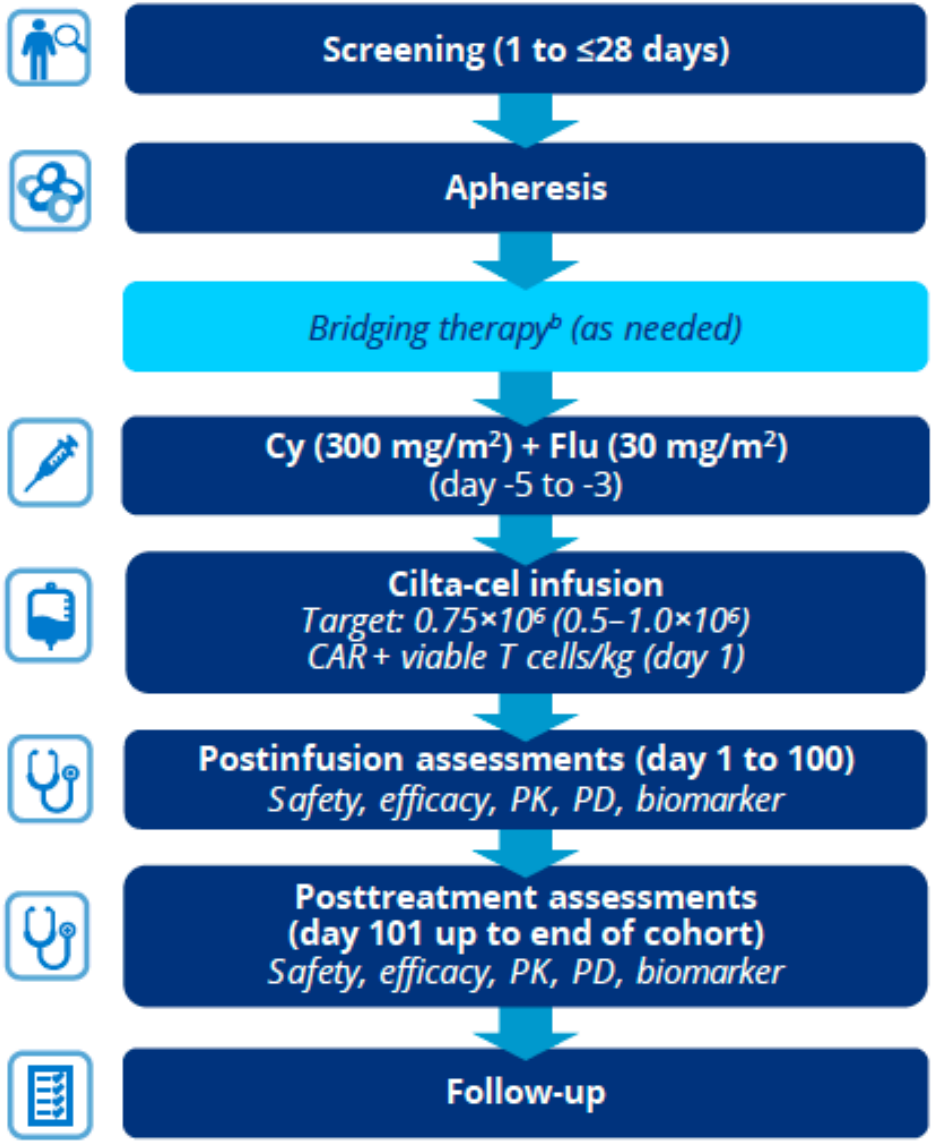
Munshi et al. N Engl J Med 384 ;705, 2021

CILTA-CEL, CARTITUDE-1



Cilta-cel

2 BCMA-targeting single-domain antibodies designed to confer avidity



Martin et al ASH 2021

CILTA-CEL, CARTITUDE-1

Characteristic	
Age, median (range) years	61.0 (43–78)
Male, n (%)	57 (58.8)
Black/African American, n (%)	17 (17.5)
All plasmacytomas,[a] n (%)	19 (19.6)
Extramedullary plasmacytomas, n (%)	13 (13.4)
Bone-based plasmacytomas, n (%)	6 (6.2)
Bone-marrow plasma cells ≥60%, n (%)	21 (21.9)
Years since diagnosis, median (range)	5.9 (1.6–18.2)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)[b]

Characteristic	
Prior lines of therapy, median (range)	6.0 (3–18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
≥5	64 (66.0)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-drug exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-drug refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)

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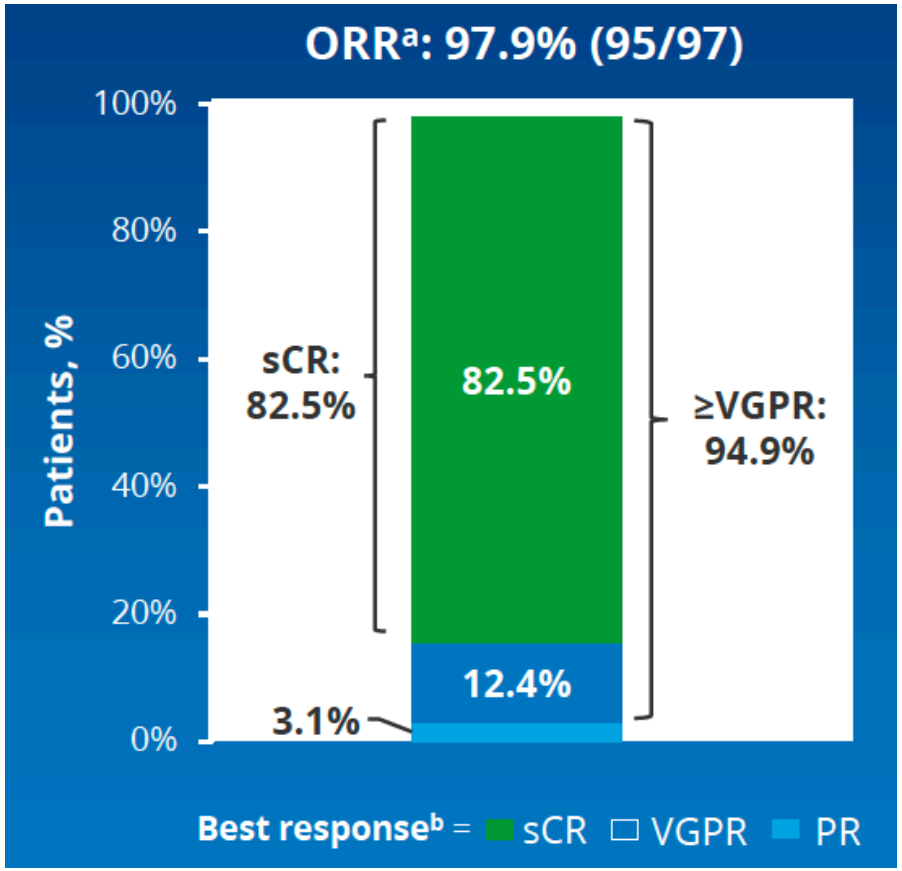
CILTA-CEL, CARTITUDE-1



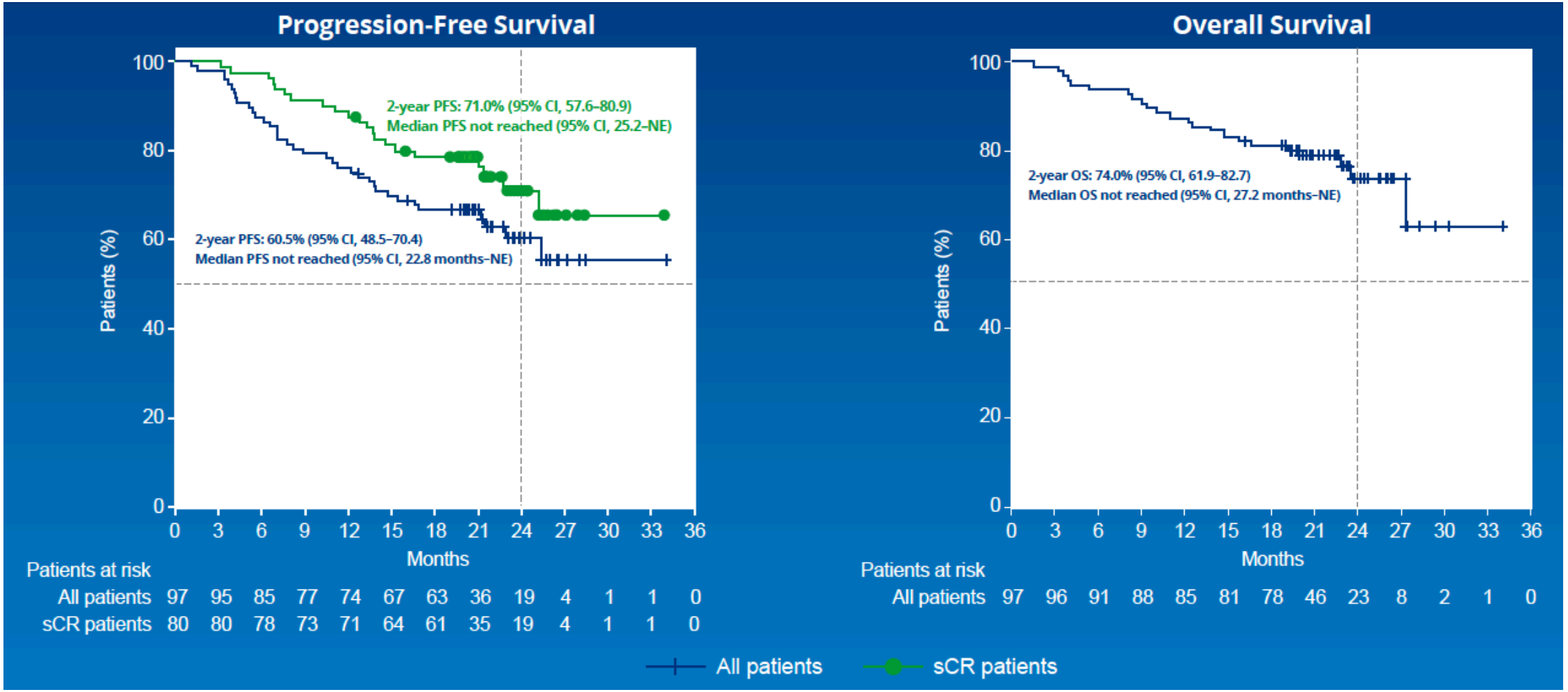
Responses deepened over time from the 1-year follow-up

Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

- Median time to first response was 1 month (range, 0.9–10.7)
- Median time to best response was 2.6 months (range, 0.9–17.8)
- Median time to CR or better was 2.9 months (range, 0.9–17.8)
- Median duration of response was not estimable (21.8 months–NE)
- 60.5% of patients are still progression-free at 2 years

Martin et al ASH 2021

CILTA-CEL, CARTITUDE-1



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CILTA-CEL, CARTITUDE-1

	N=97	
	Any grade	Grade 3/4
Hematologic AEs ≥25%, n (%)		
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)
Nonhematologic AEs ≥25%, n (%)		
Metabolism and nutrition disorders		
Hypocalcemia	31 (32.0)	3 (3.1)
Hypophosphatemia	30 (30.9)	7 (7.2)
Decreased appetite	28 (28.9)	1 (1.0)
Hypoalbuminemia	27 (27.8)	1 (1.0)
Gastrointestinal		
Diarrhea	29 (29.9)	1 (1.0)
Nausea	27 (27.8)	1 (1.0)
Other		
Fatigue	36 (37.1)	5 (5.2)
Cough	34 (35.1)	0
AST increased	28 (28.9)	5 (5.2)
ALT increased	24 (24.7)	3 (3.1)

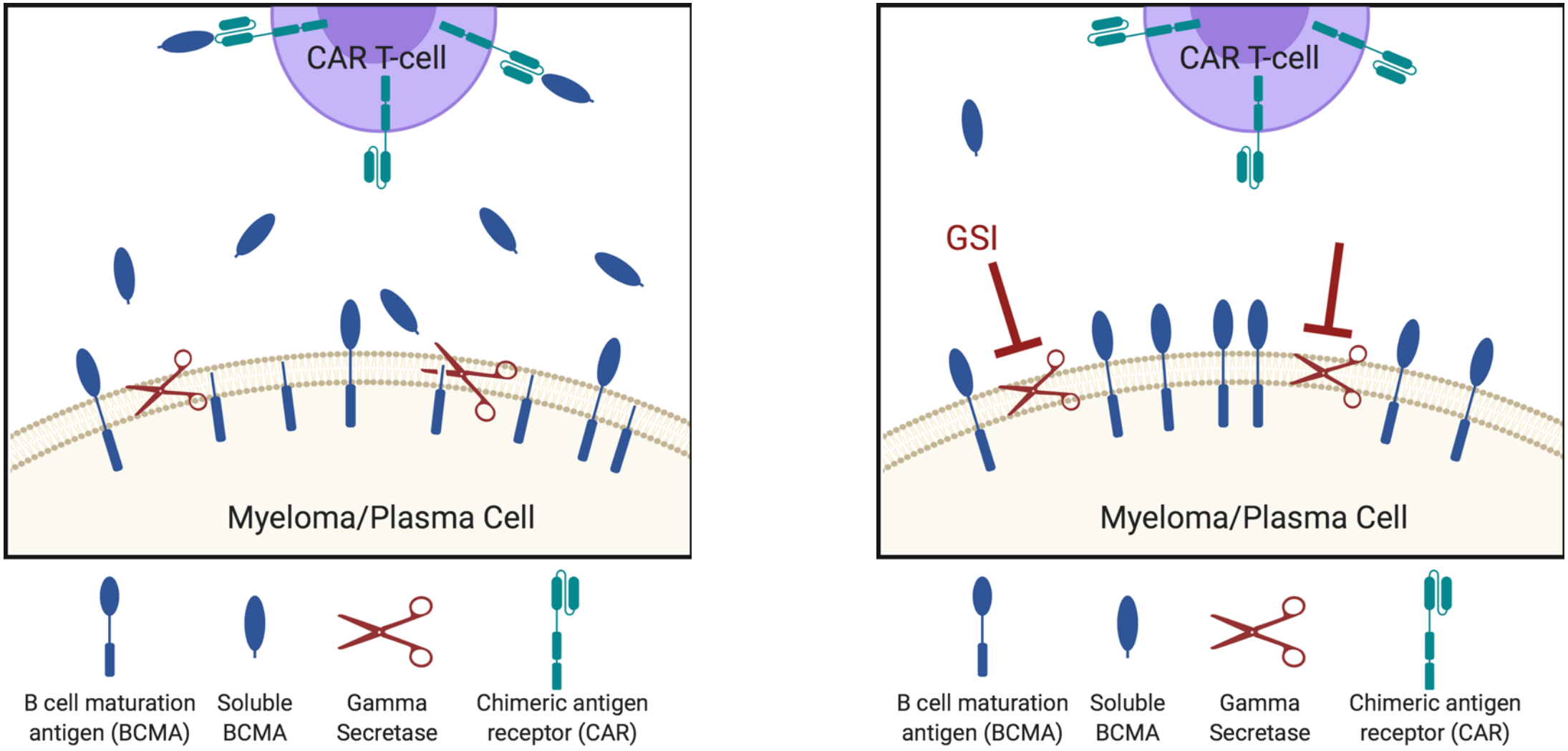
CRS	**N=97**
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]

Of 92 patients with CRS, majority (94.6%) were grades 1/2
CRS resolved in 91 (98.9%) patients within 14 days of onset

	N=97
Total CAR T-cell neurotoxicities, n (%)	
Any Grade	20 (20.6)
Grade ≥3	10 (10.3)
ICANS, n (%)	
Any Grade	16 (16.5)
Grade ≥3	2 (2.1)
Other neurotoxicities,[c] n (%)	
Any Grade	12 (12.4)
Grade ≥3	9 (9.3)

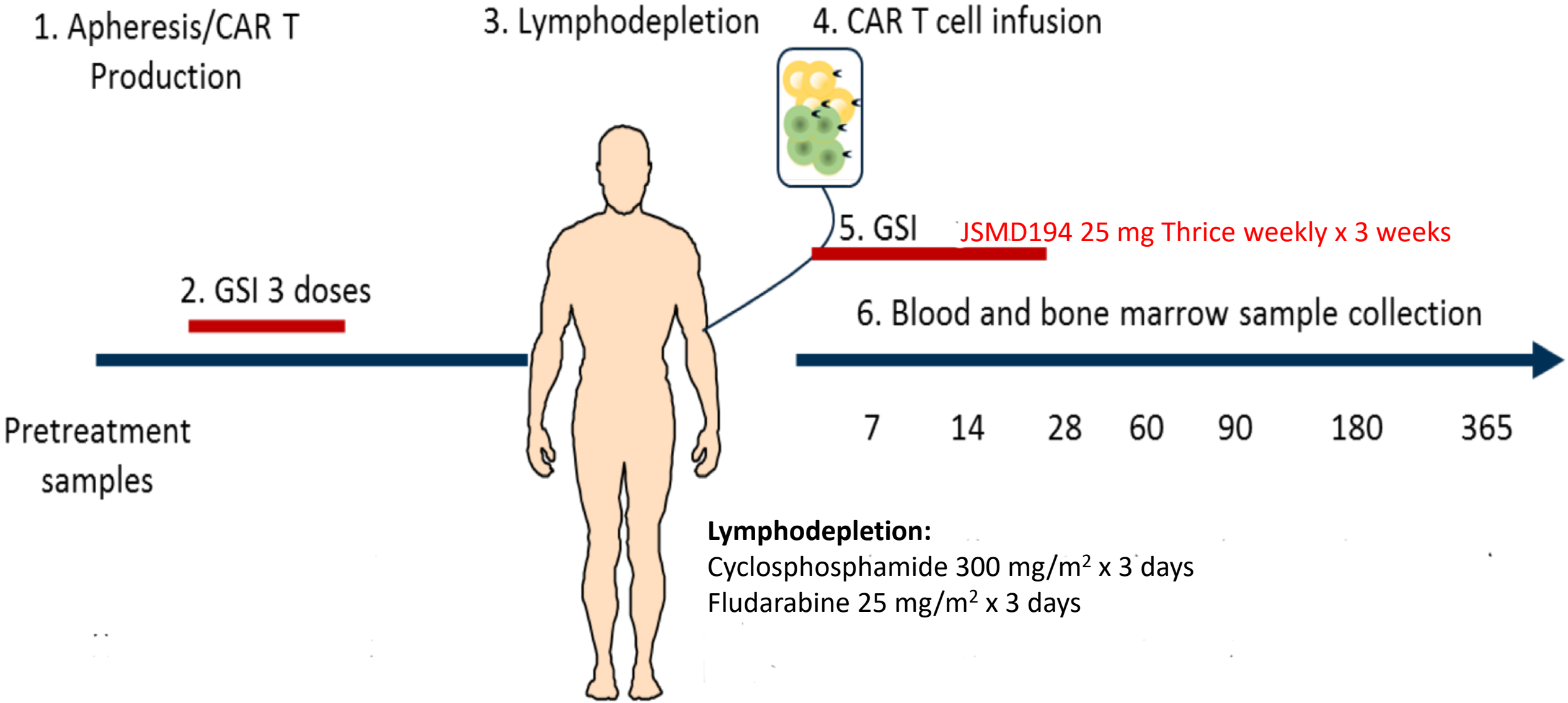
Martin et al ASH 2021

Gamma Secretase Cleaves BCMA from Plasma Cells



Pont MJ et al. Blood. 2019 Nov 7; 134(19):1585-1597

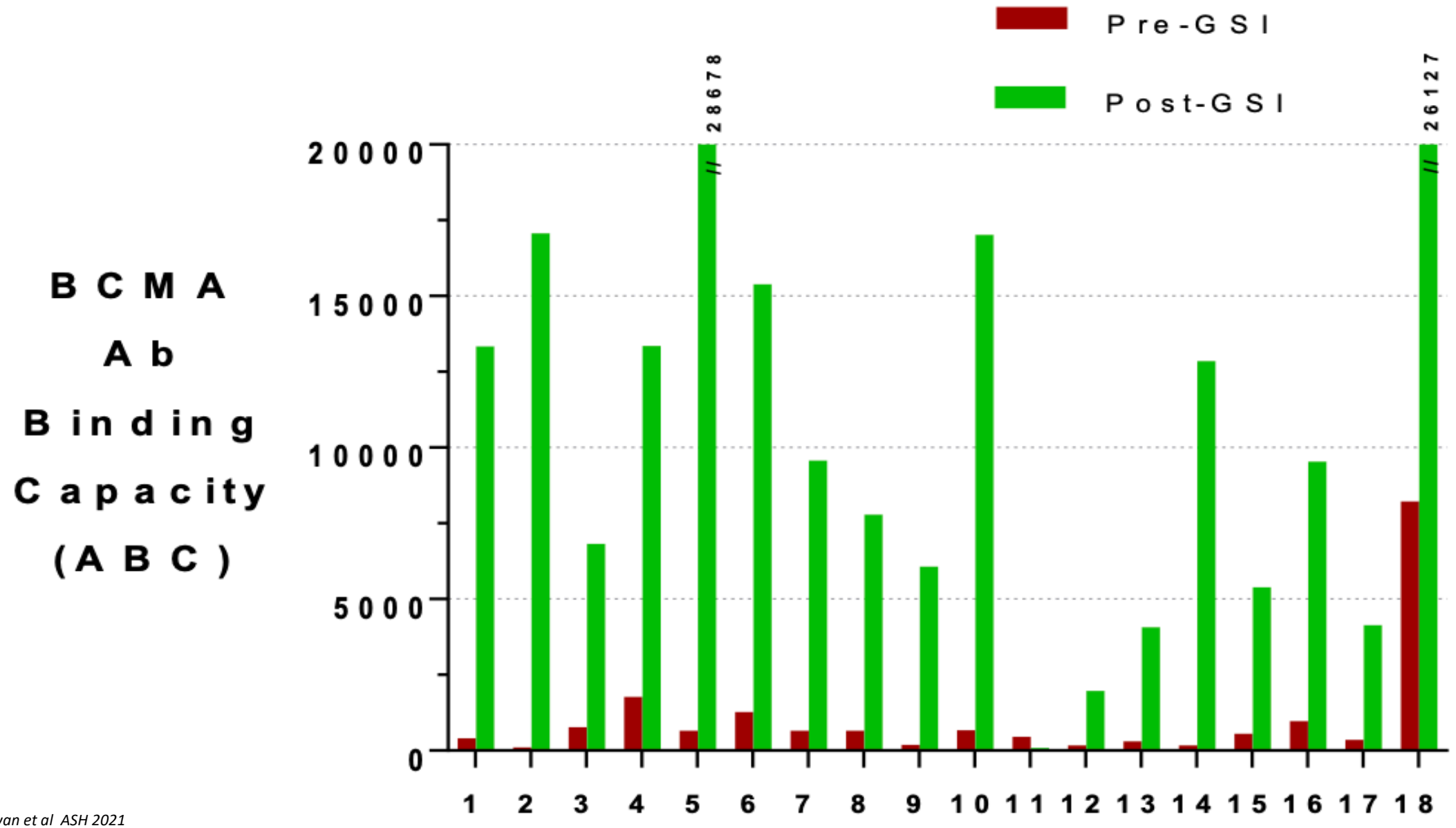
Study Design



Lymphodepletion:
Cyclosphosphamide 300 mg/m^2 x 3 days
Fludarabine 25 mg/m^2 x 3 days

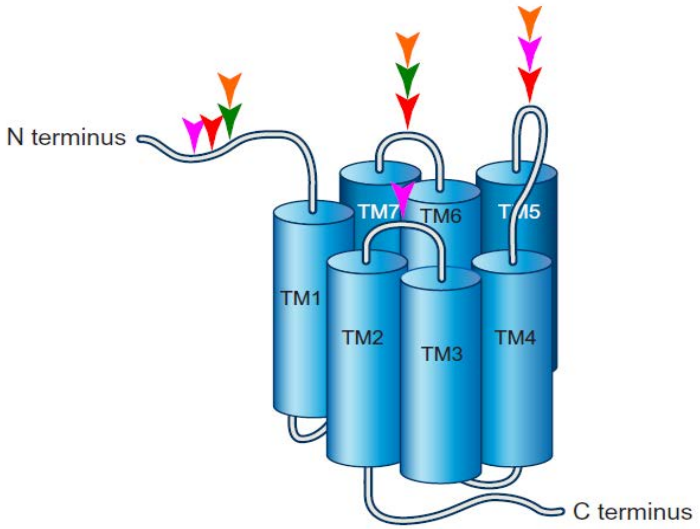
Cowan et al ASH 2021

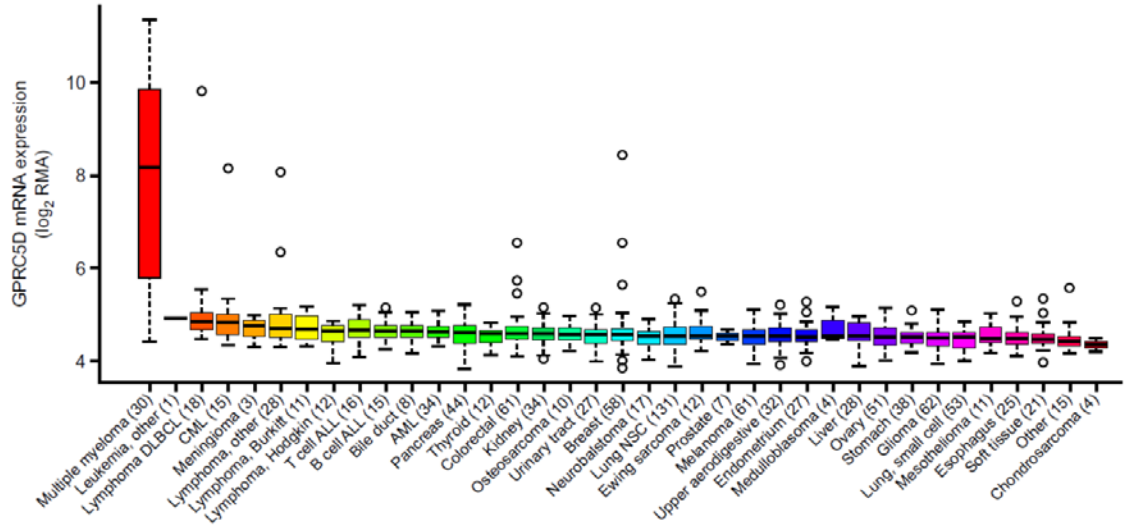
Gamma Secretase Inhibition Increases BCMA Surface Density

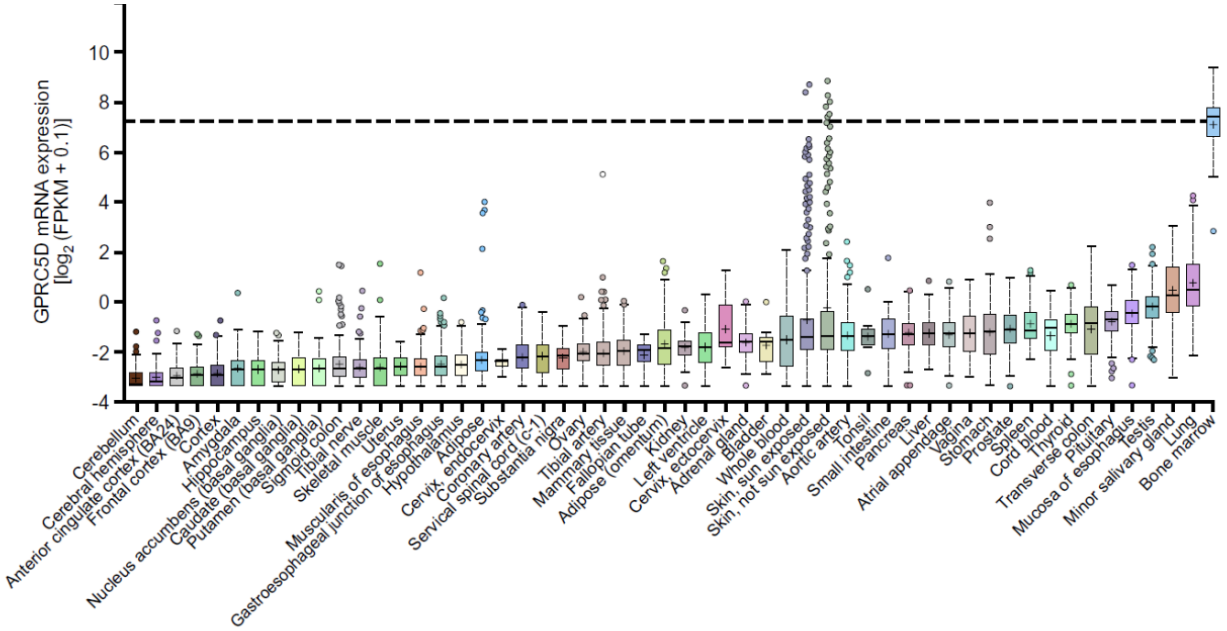


Cowan et al ASH 2021

GPRC5D



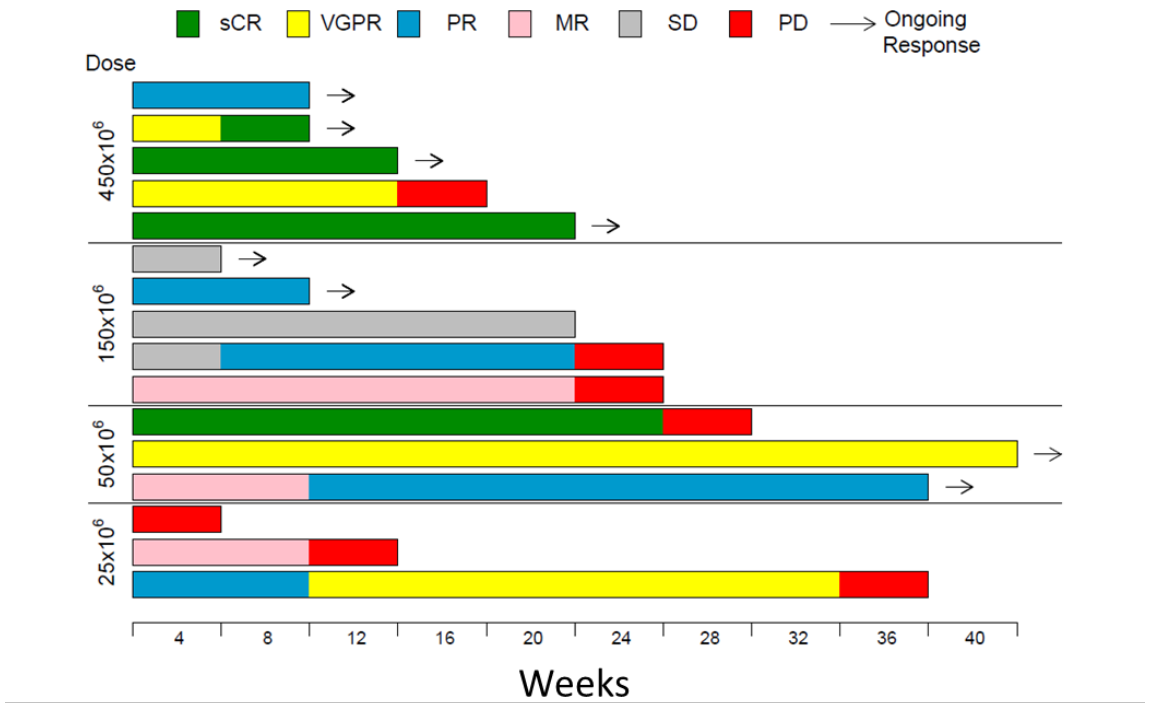




Smith E.L. Transl. Med 11:7746, 2019

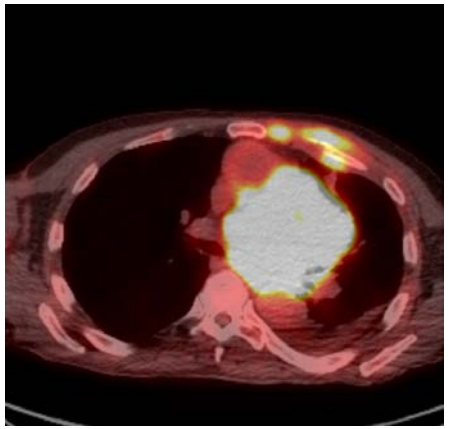
GPRC5D CAR-T

- MCARH109, FIH study
- 3+3 design
- Median 8 prior lines of therapy
- 25, 50, 150, 450 x 10^6 viable CAR-T cells
- 18 patients treated, 16 with response assessment
- 93% had CRS, grade 3 in 1/12
- 69% ORR

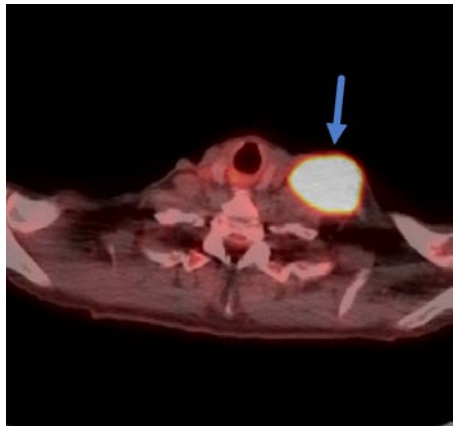


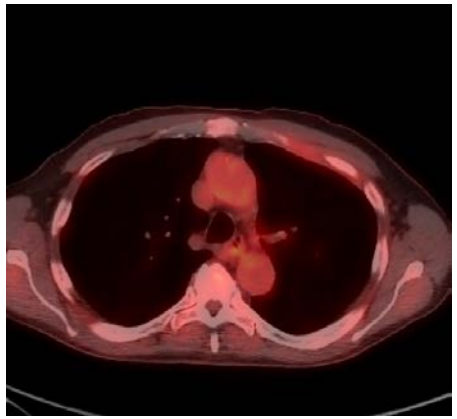
Mailankody et al ASH 2021

GPRC5D CAR-T

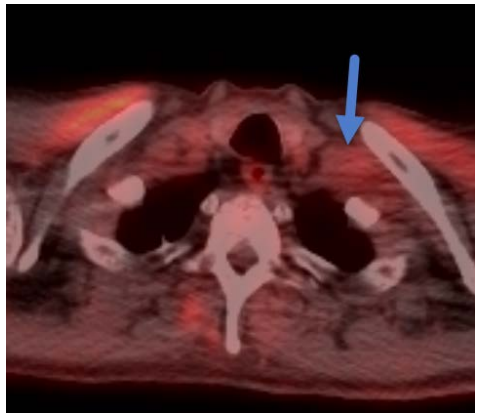


Pre-treatment



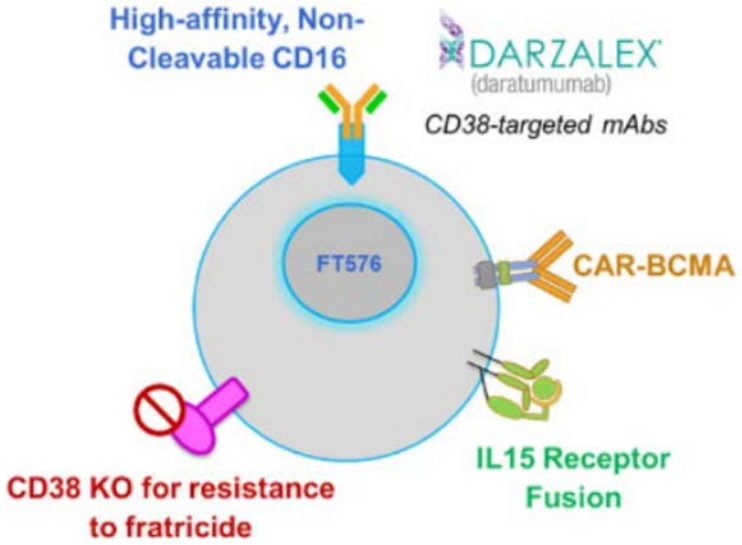


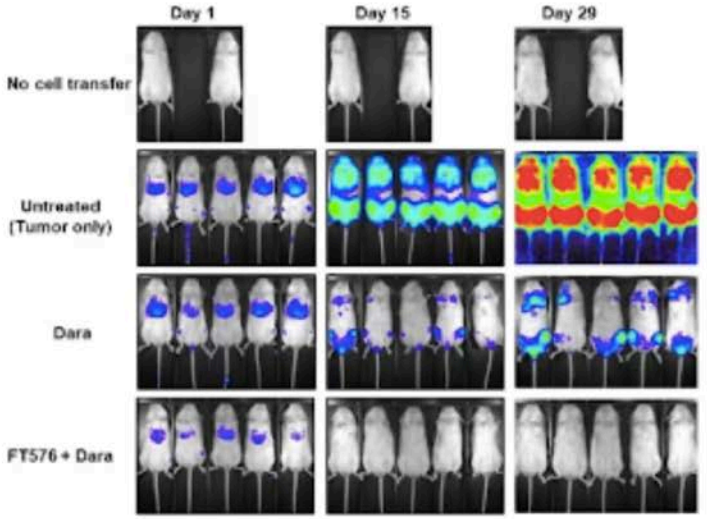
4 week follow-up

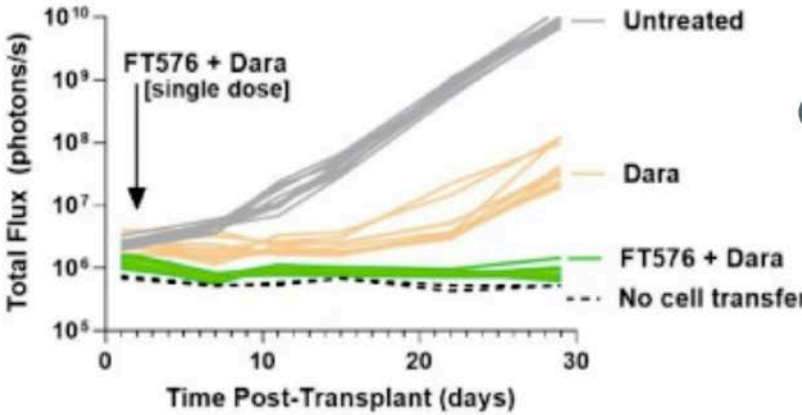


Mailankody et al ASH 2021

Redirecting NK Cells







- Allogeneic product
- No delayed manufacturing/bridging
- No need for HLA compatibility

- No/Less CRS
- No ICANS
- Potentially more durable

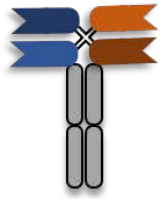
Bjordahl R et al, ASH 2019

FUTURE OF CELL THERAPY IN MM

- Better manufacturing, enrichment for memory CAR-T cells (BB21217, NEX-T platform)
- Mitigation of CRS
- Increase BCMA expression-γ secretase inhibitors
- CAR-T in earlier lines of therapy (KARMMA 3, CARTITUDE 4)
- Upfront use in high risk NDMM (CARTITUDE 2, KARMMA-4)
- Post-AHCT in high-risk patients (BMT-CTN)
- CAR-T followed by maintenance therapy (KARMMA-7)
- Non-BCMA target
  - GPRC5D (CC95266)
  - CD38/CD138

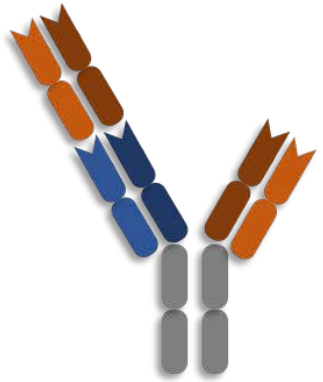
BCMA TCE IN MM

AMG-420
(BiTE®)

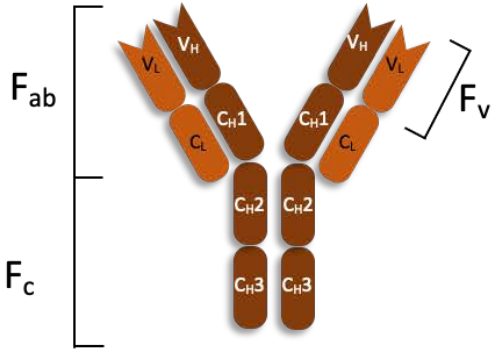


AMG-701
(BiTE® with HLE)

Teclistamab
(Duobody®)



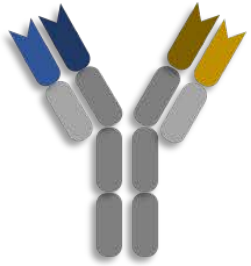
CC-93269
(2+1 TCE)



REGN5458

Elranatamab

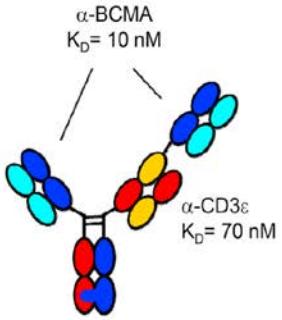
ABBV-383

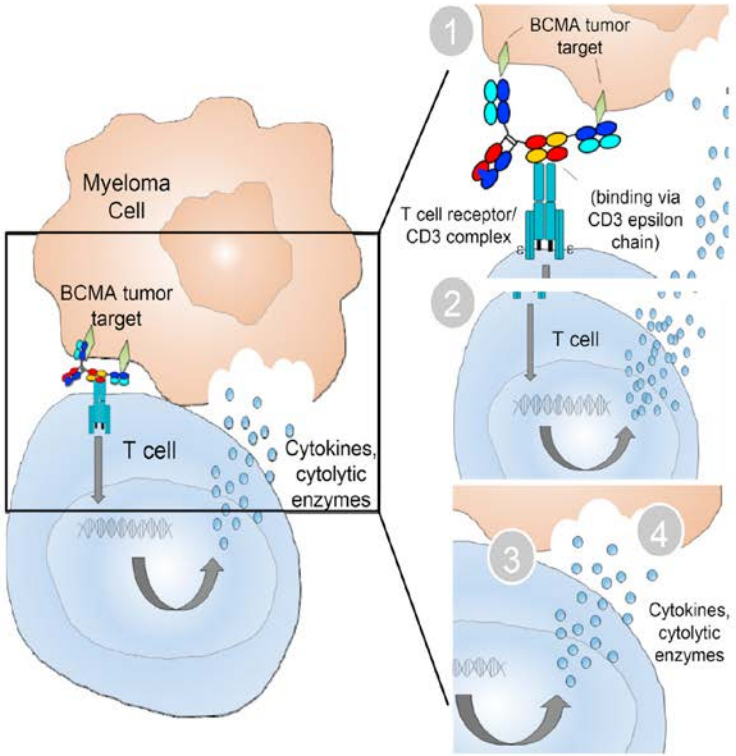


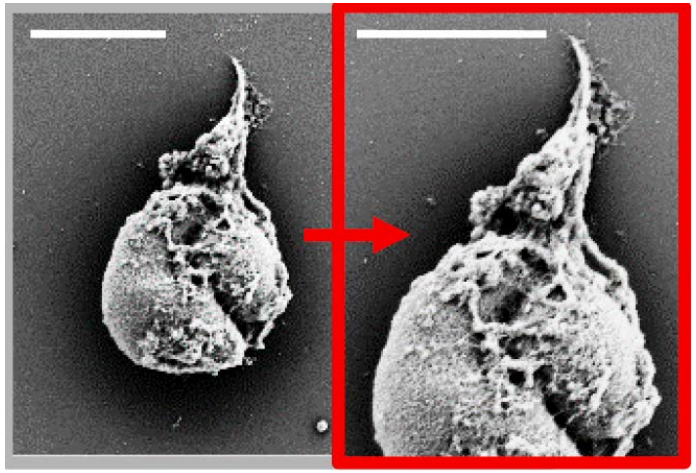
Cevostamab

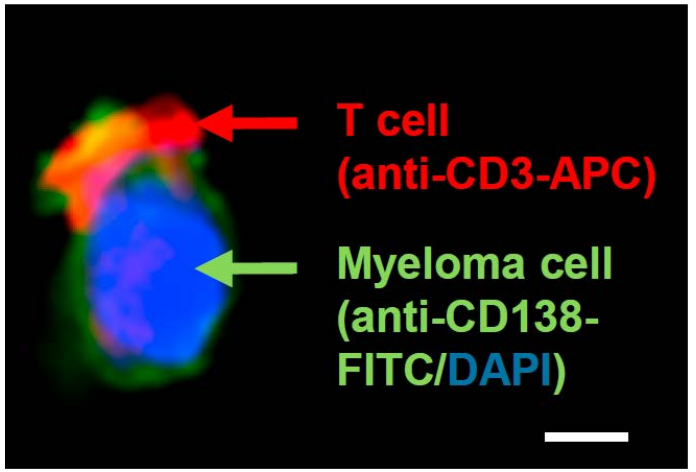
Talquetamab
(Duobody®)

BCMA TCE IN MM



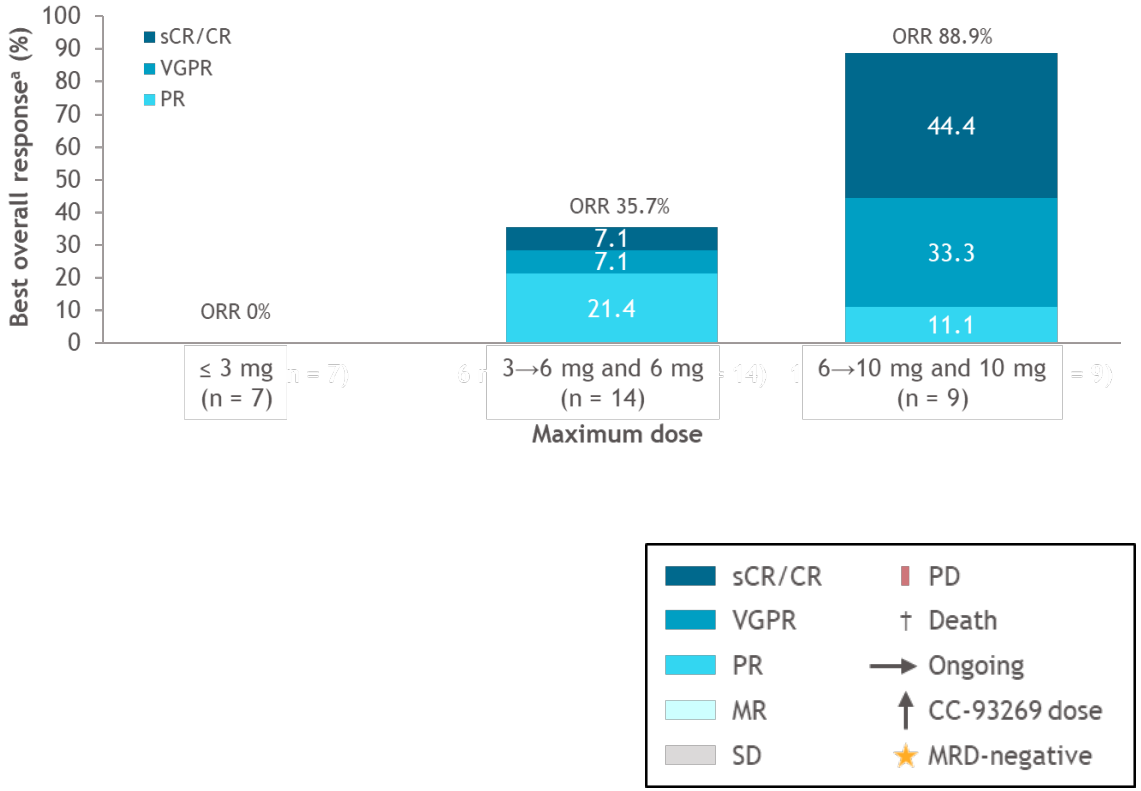


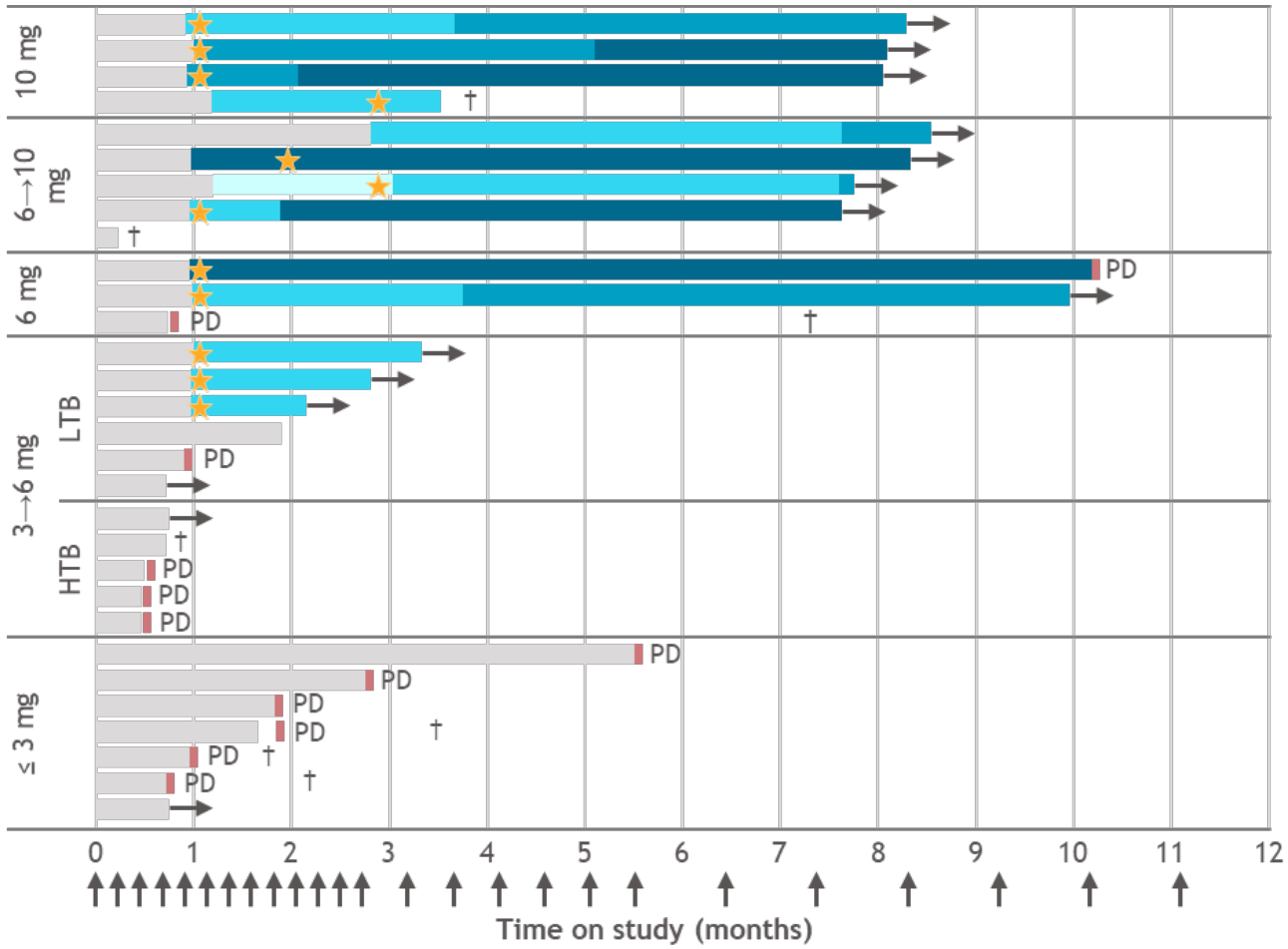




Seckinger A, et al. *Cancer Cell.* 2017;31:396-410.

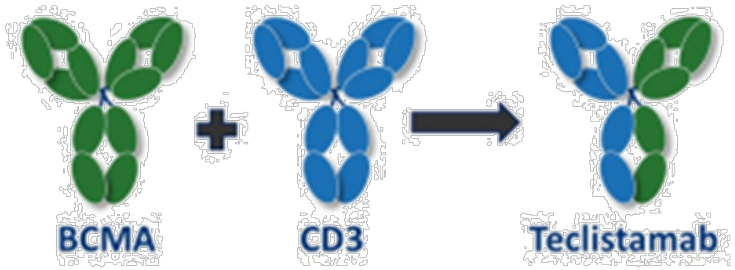
CC-93269

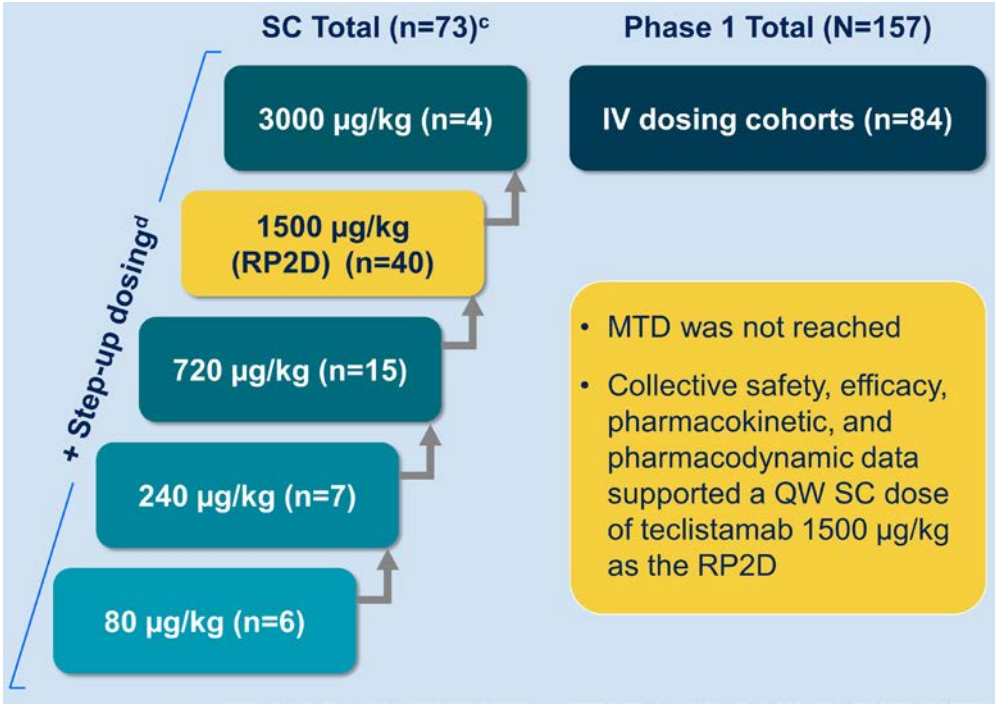


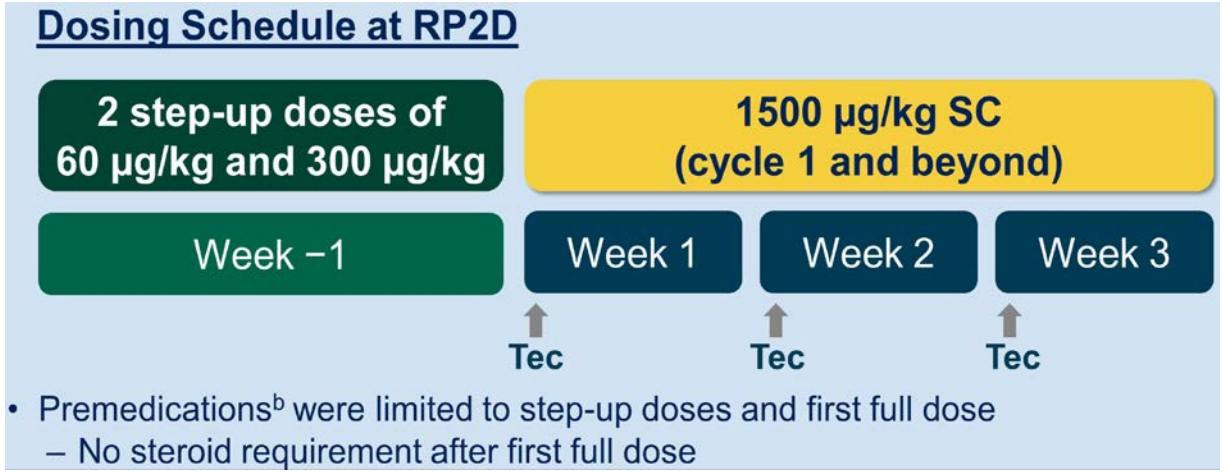


Costa LJ, et al. EHA 2020 Annual Meeting. #S205.

TECLISTAMAB



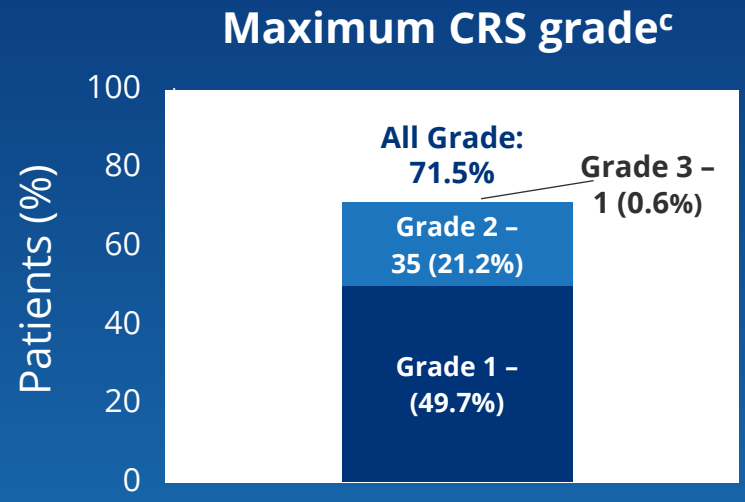




Krishnan et al. ASCO 2021; Moreau et al. ASH 2021 Annual Meeting.

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[a], n (%)	109 (66.1)
Tocilizumab	60 (36.4)
Low-flow oxygen by nasal cannula[b]	21 (12.7)
Steroids	13 (7.9)
Single vasopressor	1 (0.6)



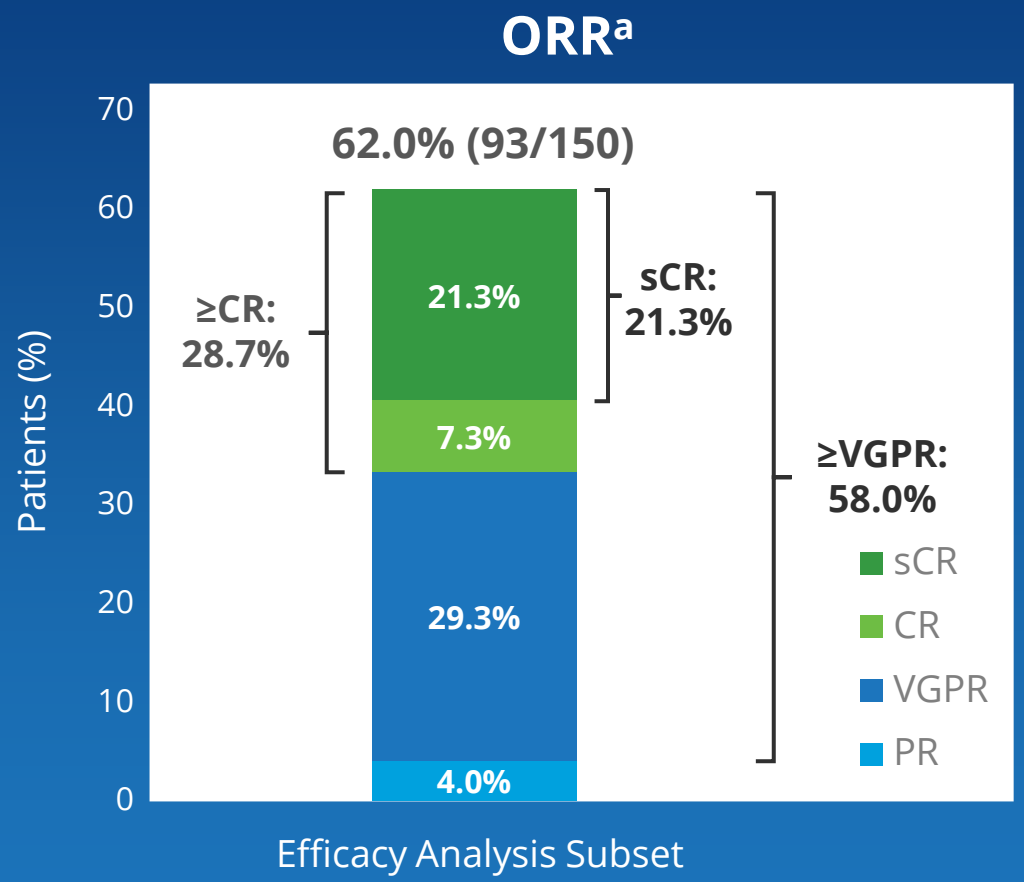
- All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that fully resolved, and 97% of events were confined to step-up and cycle 1
- All CRS events resolved, with no treatment discontinuations due to CRS
- Over the course of their treatment, 2.4% of patients received >1 dose of tocilizumab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

[a]A patient could receive >1 supportive therapy; [b]≤6 L/min; [c]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; CRS, cytokine release syndrome

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

MajesTEC-1: Overall Response Rate for Teclistamab Monotherapy



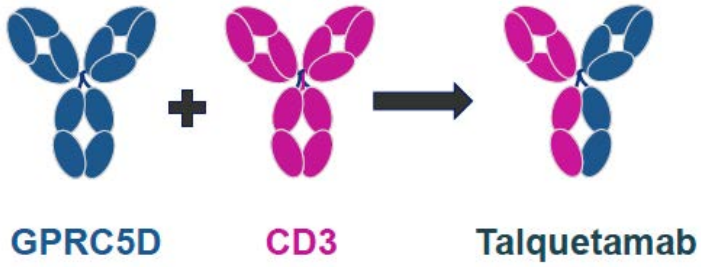
- At a median follow-up of 7.8 months (range: 0.5+–18):
  - ORR of 62.0% (95% CI: 53.7–69.8) represents a substantial benefit for patients with triple-class exposed disease
- Median time to first response: 1.2 months (range: 0.2–5.5)
- MRD negativity rate[b]
  - 24.7% (37/150; 95% CI: 18.0–32.4) at a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

[a]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); [b] Baseline clones were obtained for all patients All MRD assessments were done by next-generation sequencing; [c]Patients who were not negative at the 10^{-6} threshold were indeterminate.

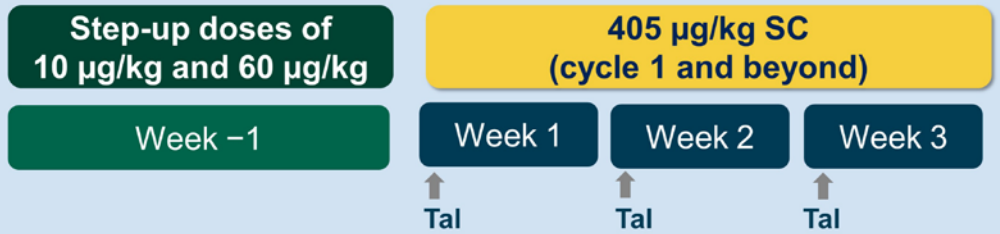
CR, complete response; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

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

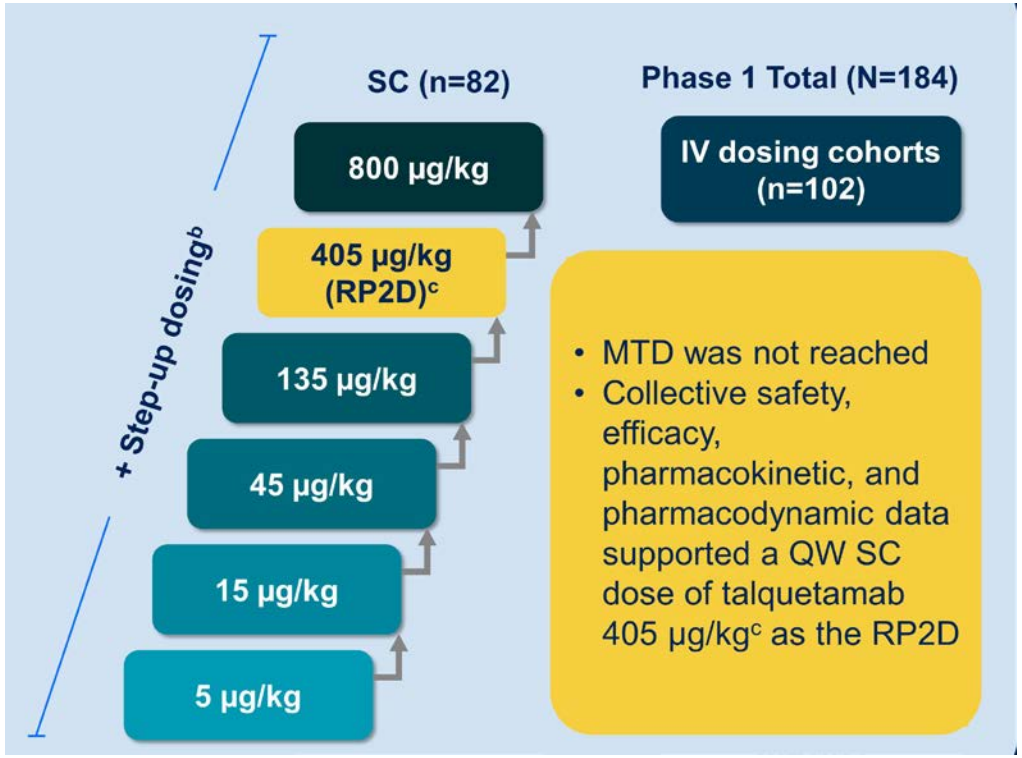
Talquetamab – MonumenTAL-1



Dosing Schedule at RP2D



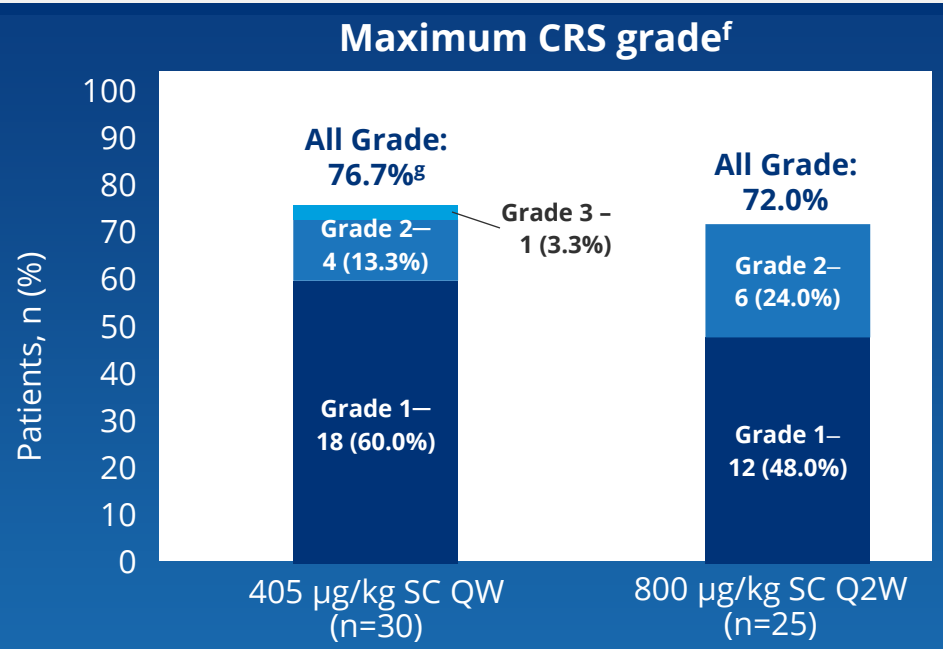
- Premedications[a] were limited to step-up doses and first full dose
  - No steroid requirement after first full dose



Berdeja et al ASCO, 2021

MonumenTAL-1: Cytokine Release Syndrome

Parameter	405 µg/kg SC QW[a] n=30	800 µg/kg SC Q2W[a] n=25
Patients with CRS, n (%)	23 (76.7)	18 (72.0)
Time to onset (days),[b] median (range)	2 (1–22)	2 (1–4)
Duration (days), median (range)	2 (1–3)	2 (1–5)
Patients who received supportive measures,[c] n (%)	23 (76.7)	18 (72.0)
Tocilizumab[d]	19 (63.3)	15 (60.0)
Steroids	1 (3.3)	1 (4.0)
Low-flow oxygen by nasal cannula	0 (0)	1 (4.0)
High-flow oxygen by face mask[e]	1 (3.3)	0 (0)
Single vasopressor[e]	1 (3.3)	0 (0)

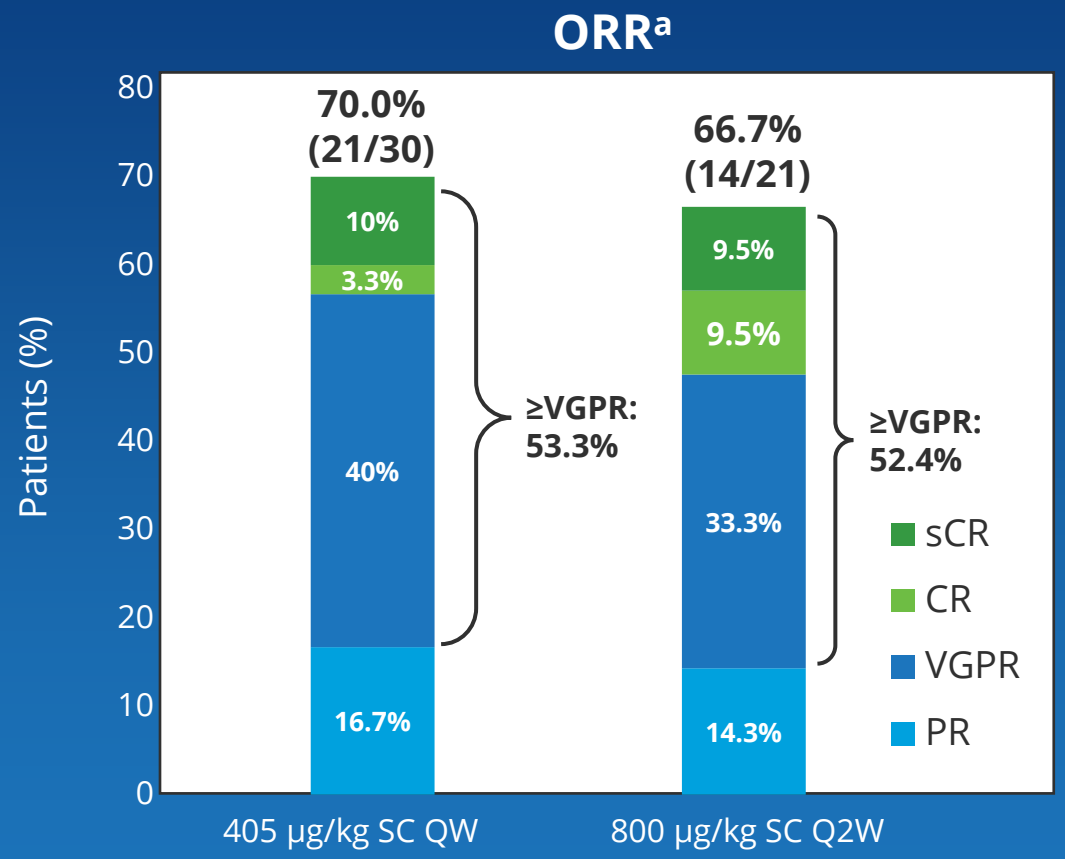


- **CRS was mostly grade 1/2 and limited to step-up dosing and Cycle 1 Day 1 dose**
  - Only 1 patient with grade 3 CRS
  - CRS events after Cycle 1 Day 1 were limited to grade 1
  - 2 (3.6%) patients received >1 dose of tocilizumab for a single CRS event[h]

[a]With 2–3 step-up doses; [b]Relative to the most recent dose; [c]A patient could receive >1 supportive therapy; [d]Tocilizumab was allowed for all CRS events; [e]1 patient in the 405µg/kg SC QW cohort received a single vasopressor and high-flow oxygen by face mask as supportive measures for CRS; [f]Graded according to Lee, et al. *Blood* 2014; 124:188; [g]Due to rounding; [h]Both patients received the 405 µg/kg SC QW dose level.
CRS, cytokine release syndrome; Q2W, every other week; QW, weekly; SC, subcutaneous

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

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

[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

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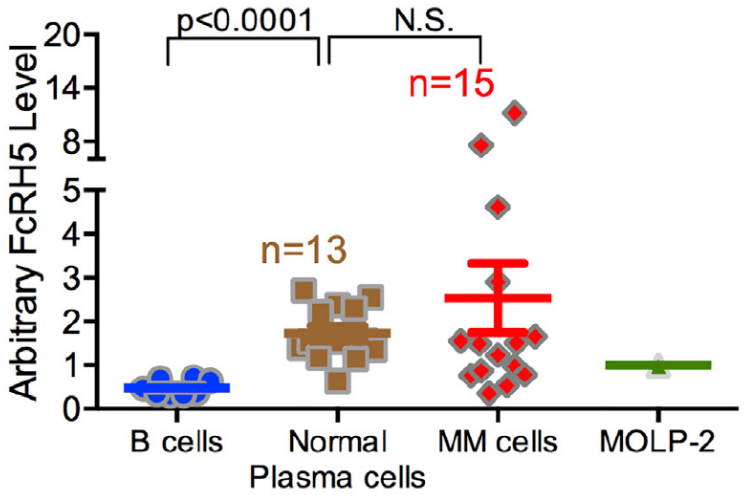
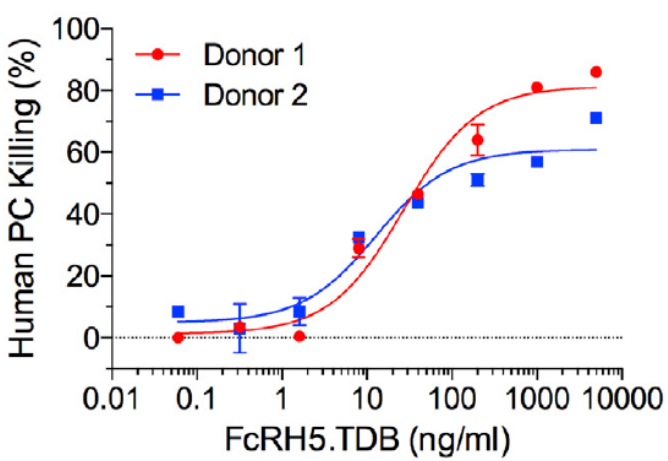
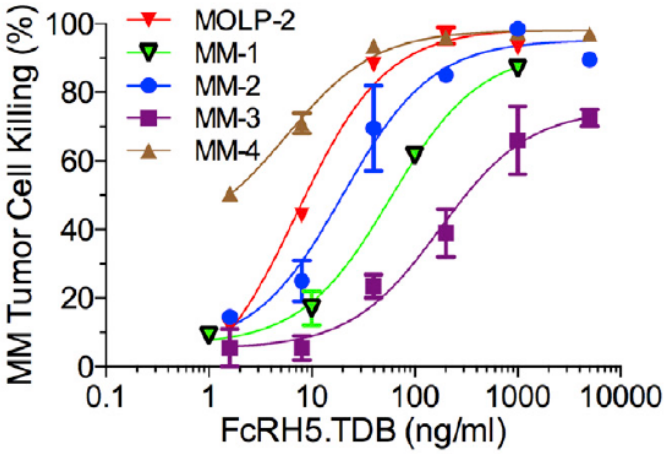
BFCR4350A - Cevostamab – CD3/FcRH5





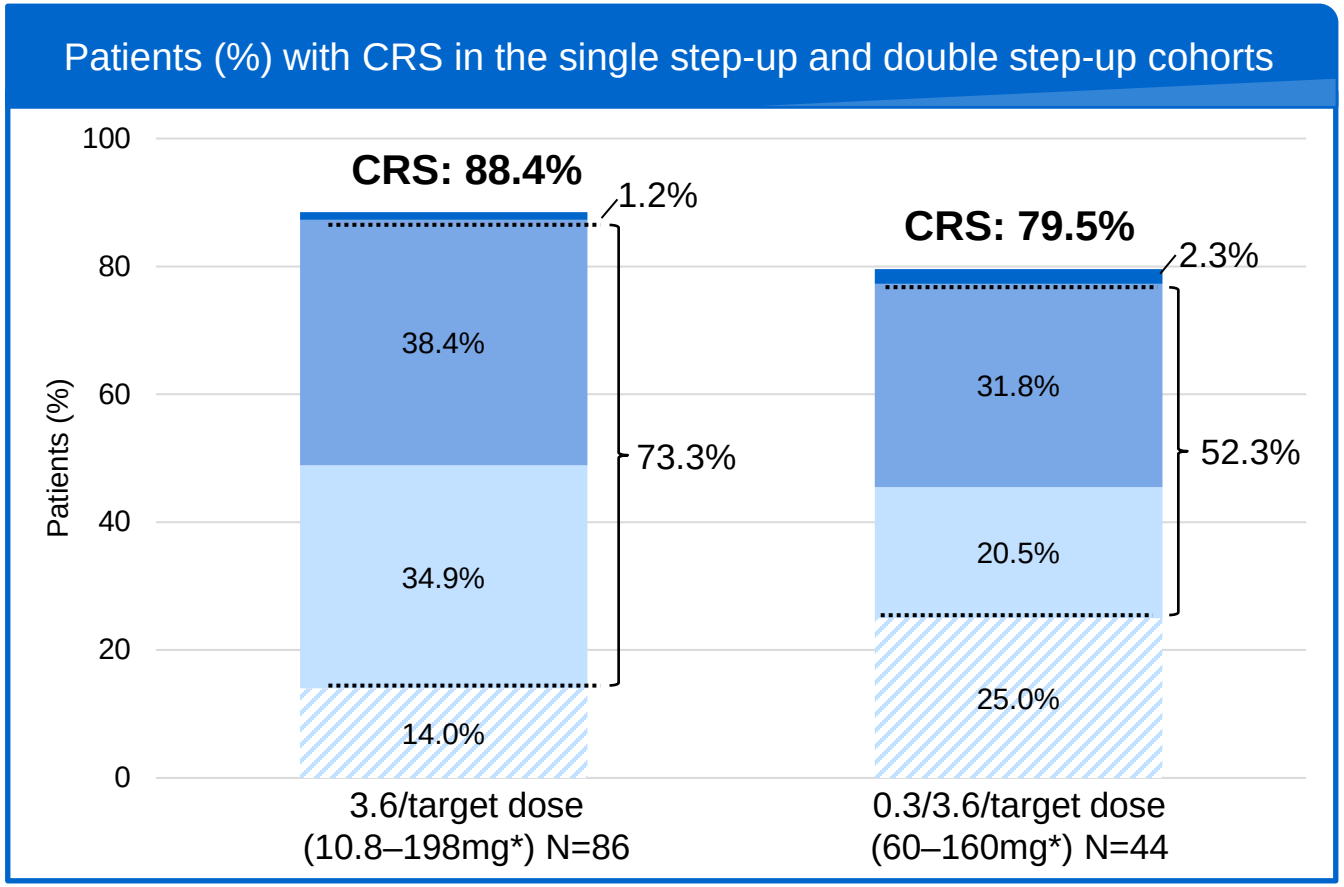


- Fc Receptor Homologue 5
- Gene in Ch 1q
- Expressed in B cells, including PC

Ongoing Phase 1 dose/schedule finding

Li J. Cancer Cell 31:7746, 2017

CRS profile with C1 single step-up dosing and C1 double step-up dosing



- CRS profile in the 3.6mg and 0.3/3.6mg cohorts
  - no target-dose dependent increase in CRS observed in C1
  - lower rate of Grade 1 CRS with symptoms in addition to fever AND Grade 2 CRS observed with 0.3/3.6mg than with 3.6mg

- C1 double step-up dosing has an improved CRS profile compared with C1 single step-up dosing

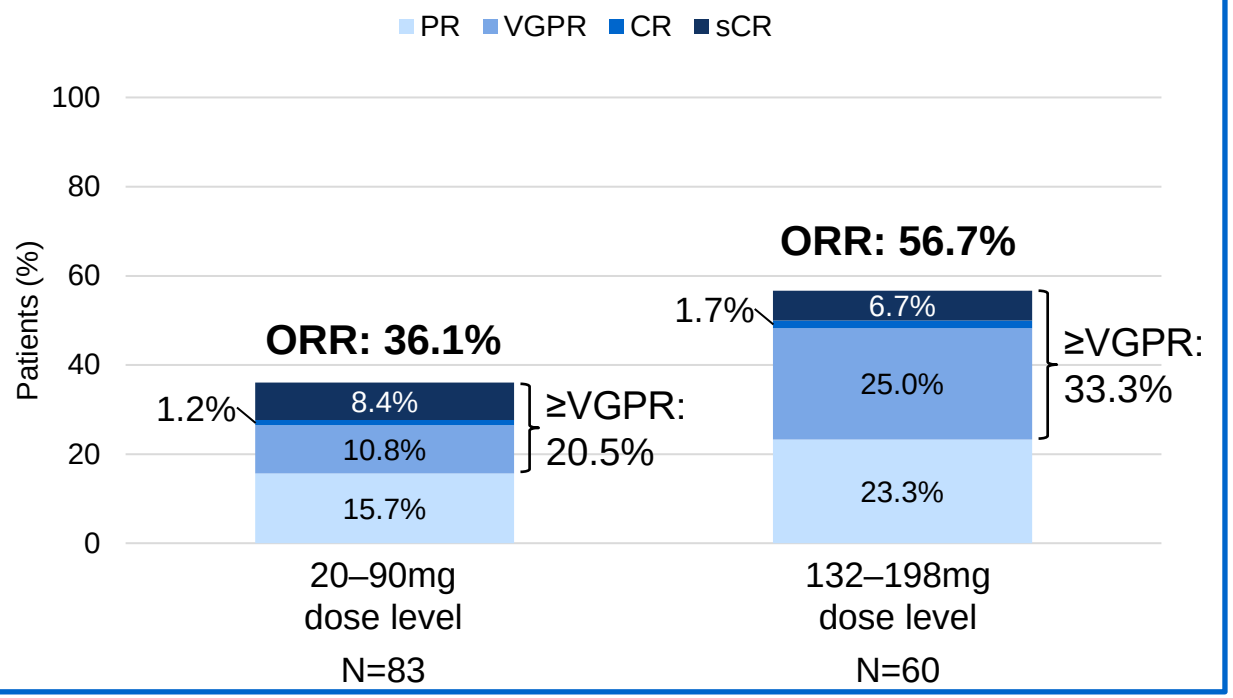
*dose ranges represent all target dose levels evaluated in combination with the 3.6mg or 0.3/3.6mg step-up doses

Trudel S , et al. ASH 2021 Annual Meeting.

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

Trudel S , et al. ASH 2021 Annual Meeting.

Preliminary Efficacy of TCE in MM

Study	N	Prior lines of therapy*	%TCR	Schedule/Route	ORR	Comments
BCMA-directed T-cell engagers						
Teclistamab	165	5 (2-14)	77%	W, SQ	**62%**	Nine-month PFS 59%. Use of step up dosing
REGN5458	73	5 (2-17)	89%	W, IV	**75%** (at higher doses)	Use of step up dosing
Elranatamab	55	6 (2-15)	91%	W, SQ	**65%** (patients receiving 215-1000 mcg/kg)	Use of step up dosing, responses seen in patients with prior BCMA-targeting therapy.
ABBV-383	75	5 (1-12)	63%	Q3W, IV	**60%** (53% in TCR)	
AMG 701	75	6 (1-25)	68%	W, IV	**36%** (patients receiving 3-12 mg)	
CC-93269	30	5 (3-13)	67%	W, IV	**89%** (higher doses)	Use of step up dosing.
Non-BCMA-directed T-cell engagers						
Talquetamab	55	6 (2-17)	77%	W or q2W, SQ	**69%**	Use of step up dosing.
Cevostamab	161	6 (2-18)	85%	Q3W, IV	**57%** (higher doses)	Use of step up dosing.

TCR= Triple-class refractory; ORR= overall response rate; PFS= progression-free survival; OS= overall survival; MoAb = monoclonal antibody; mo.= months; AHCT= autologous hematopoietic cell transplantation; CRS= cytokine release syndrome; TTP= time to progresssion; *=Median(range)

Costa et al. *Br J Haematol*. 2022;00:1–13.

Preliminary Toxicity of TCE in MM

Study	N	CRS		Neurotoxicity		Neutropenia ≥ Gr 3 N(%)	Thrombocytopenia ≥ Gr 3 N(%)	Comments
		Any N (%)	≥ Gr 3 N(%)	Any N (%)	≥ Gr 3 N(%)			
BCMA-directed T-cell engagers								
Teclistamab	165	118 (72%)	1 (1%)%	21 (13%)	0 (0%)	94 (57%)	35 (21%)	
REGN5458	73	28 (38%)	0 (0%)	3 (4%)	0 (0%)	16 (22%)	10 (13%)	
Elranatamab	55	48 (87%)	0 (0%)	0 (0%)	0 (0%)	37 (67%)	15 (27%)	
ABBV-383	75	52 (69%)	3 (4%)	8 (11%)	0 (0%)	18 (24%)	7 (9%)	Most episodes of neurologic toxicity were headaches
AMG 701	75	45 (60%)	5 (7%)	6 (8%)	0 (0%)	n/a	n/a	
CC-93269	30	23 (77%)	1 (3%)%	0 (0%)	0 (0%)	13 (43%)	5 (17%)	
Non-BCMA-directed T-cell engagers								
Talquetamab	55	41 (75%)	1 (2%)	2 (4%)	0 (0%)	27 (49%)	9 (16%)	Skin and nail-related disorders, dysgeusia
Cevostamab	161	130 (81%)	2 (1%)	23 (14%)	1 (1%)	56 (35%)	29 (18%)	Most common neurologic toxicity was confusion

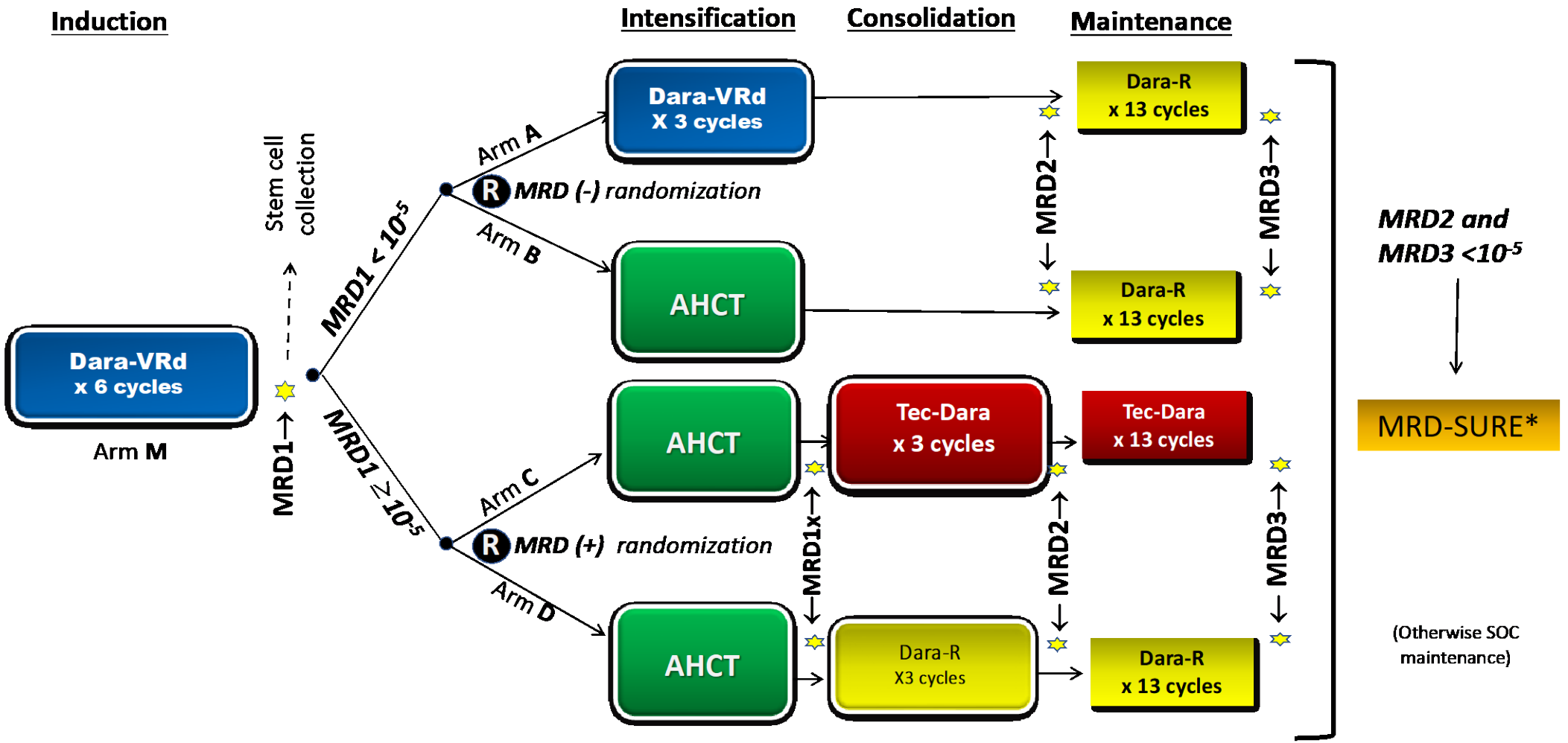
TCR= Triple-class refractory; ORR= overall response rate; PFS= progression-free survival; OS= overall survival; MoAb = monoclonal antibody; mo.= months; AHCT= autologous hematopoietic cell transplantation; CRS= cytokine release syndrome; TTP= time to progresssion; *=Median(range)

Costa et al. *Br J Haematol*. 2022;00:1–13.

FUTURE OF TCE IN MM

- Likely multiple approvals/multiple targets in RRMM setting
- Greater scalability than CAR-T
- Combination with anti-CD38 MoAB, IMiDs, Pis
- Combination of 2 TCEs with different targets (TEC-TAL)
- Earlier lines of therapy (MajesTEC-3, MagnetisMM-5)
- Upfront use (MajesTEC-2)
- Post-AHCT as maintenance/consolidation (MagnetisMM-7; MASTER-2)

MASTER-2 Design



MRD assessment by ClonoSEQ®

*MRD-SURE – Treatment-free observation and MRD surveillance

Thank you!

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