

CAR – T Cell Therapy in Myeloma

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Targets for CAR T cells in Myeloma

B Cell Maturation Antigen (BCMA)

- Expressed predominantly on plasma cells – hence best molecule so far – least ‘on target, off tumour’ activity
- TNF superfamily, omnipresent on plasma cells
- Binding and stimulation of ligands, B-cell Activating Factor (BAFF) and A Proliferation-Inducing Ligand (APRIL), to BCMA promotes growth and proliferation of plasma cells in the bone marrow

CD38

- Not highly expressed on myeloma cells
- Expression can be down-regulated in advanced disease- resistance to the anti-CD38-CAR-T may be expected.
- On-target/off-tumor toxicity

CD 138

- Highly expressed on malignant plasma cells but is present in other normal tissues such as epithelial, endothelial, and vascular smooth muscle cells
- Serious mucosal and skin toxicity

CD 19

- Although typically absent on mature plasma cells, minor subsets of myeloma cells with unique propagating properties express low CD19, associated with drug resistance and relapse-promoting properties, making it a plausible therapeutic target.
- A proof-of-concept pilot study was conducted with anti-CD19 CAR T cells, Kymriah. Out of 12 patients treated, 6 achieved VGPR, 2 achieved PR, and 2 other experienced progressive disease
- Cocktail CAR T product of anti-CD19/anti-BCMA produced an impressive 100% ORR

Preparing the Patient for CAR T

Assess Risk of Toxicity and Relapse Risk

- Calculate the CAR-HEMATOTOX score
- MyCARE (Myeloma CAR-T Relapse) model -presence of EMD, PCL, len-refractory disease and elevated ferritin at the time of lymphodepletion: 5 month progression 7% (none), 53% (all)

Rejeski et al. The CAR-HEMATOTOX score as a prognostic model of toxicity and response in patients receiving BCMA-directed CAR-T for relapsed/refractory multiple myeloma. *J Hematol Oncol.* 2023;16:88.

Gagelmann N, et al. Development and validation of a prediction model of outcome after B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in relapsed/refractory multiple myeloma. *J Clin Oncol.* 2024;42:1665–75

Important Do's & Don't before CAR

- When CAR T therapy planned, avoid severe lymphocytotoxic drugs – Fludarabine, Cladribine, Bendamustine
- Avoid intensive cytoreductive bridge therapy (eg. alkylators) after autologous harvest – steroids alone if insignificant disease
- Bispecifics – excellent bridge
- Radiation - EMD

Zafar A, et al. Intensity of cyclophosphamide-based bridging therapy before chimeric antigen receptor T cell therapy in myeloma. *Transplant Cell Ther.* 2023;29:504.e1–e7.

Fandrei D, et al. Sequential administration of bispecific antibodies and anti-BCMA CAR-T cell therapy in relapsed/refractory multiple myeloma is associated with expansion of CD8 effector clones and high response rates. Abstract S194. Presented at the EHA 2024 Congress. 2024.

Manjunath S, et al. The safety of bridging radiation with anti-BCMA CAR T-cell therapy for multiple myeloma. *Clin Cancer Res.* 2021;27:6580–90

Commonest conditioning regime

- Fludarabine 30 mg/m²/day for 3 days
- Cyclophosphamide 300 mg/m²/day for 3 days
- Other regime: Bendamustine single agent

FDA APPROVED CAR T DRUGS - DATA

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 Rajeev, 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.](#)

Article **Figures/Media** **Metrics**

19 References **208** Citing Articles Letters

Abstract

BACKGROUND

Idecabtagene vicleucel (ide-cel, also called bb2121), a B-cell maturation antigen–directed chimeric antigen receptor (CAR) T-cell therapy, has shown clinical activity with expected CAR T-cell toxic effects in patients with relapsed and refractory multiple myeloma.

METHODS

In this phase 2 study, we sought to confirm the efficacy and safety of ide-cel in patients with relapsed and refractory myeloma. Patients with disease after at least three previous regimens

February 25, 2021

N Engl J Med 2021; 384:705-716

DOI: 10.1056/NEJMoa2024850

Chinese Translation [中文翻译](#)

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CORRESPONDENCE JUN 17, 2021

Idecabtagene Vicleucel in Relapsed Myeloma

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PHYSICIAN JOBS

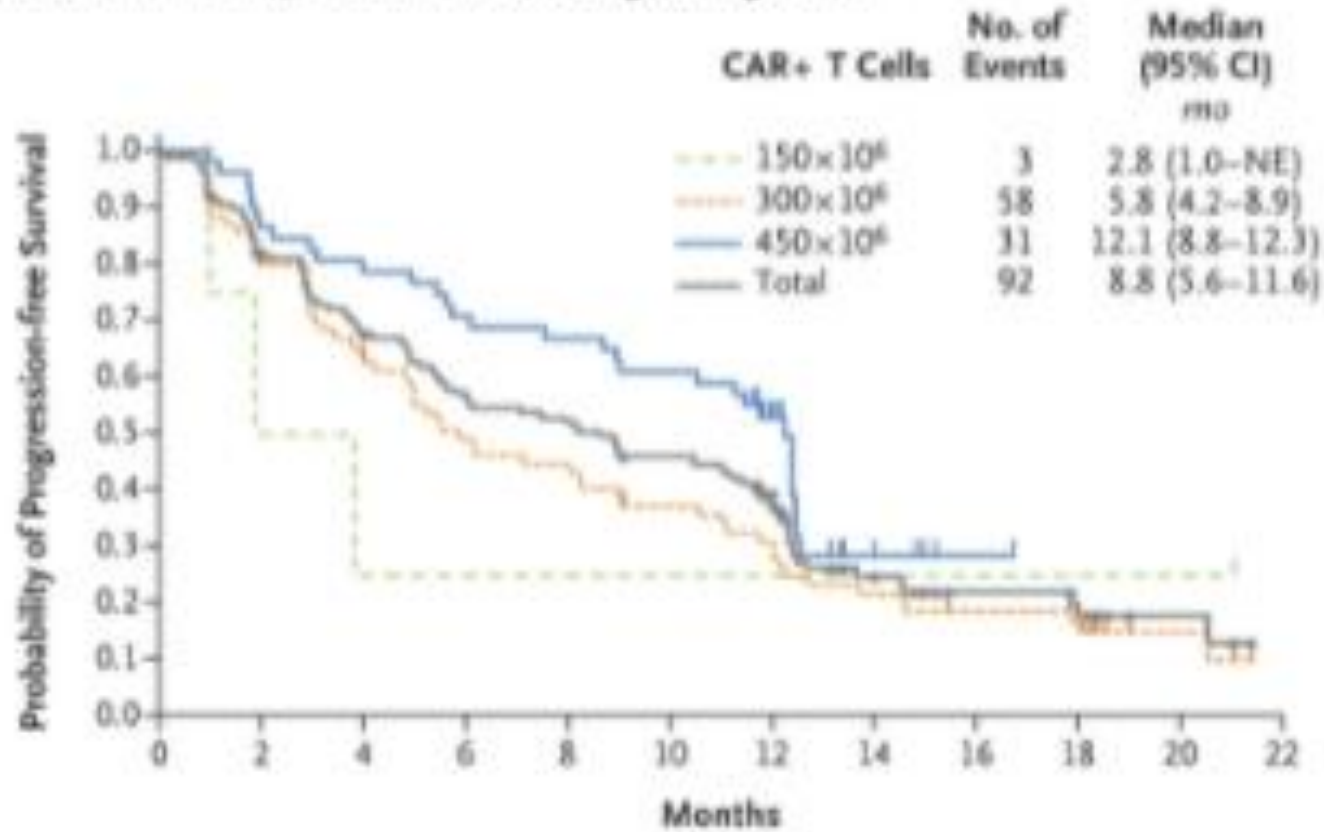
Kar-MMA trial

- Phase 2 study
- R/R myeloma, 3 prior lines
- Target doses of 150×10^6 to 450×10^6 CAR-positive (CAR+) T cells
- Conditioning: Flu - Cy for 3 days, infusion done 2 days later
- 128 pts received the drug
- Median age: 61 (oldest 78 yr)
- 80% triple refractory
- Median F/U: 13.3 months
- ORR: 73%
- CR: 33%
- MRD negative ie $< 10(5)$ plasma cells : 26%

Adverse effects

- Neutropenia: 91%, anemia in 70%, thrombocytopenia in 63% - related to lympho-depleting chemotherapy
- Cytokine release syndrome : 84%, (5% grade 3 or higher) – severity of CRS much lower than in ALL/lymphoma
- Neurotoxic effects: 18% (3% grade 3); no neurotoxic effects higher than grade 3

C Progression-free Survival, Overall and According to Target Dose



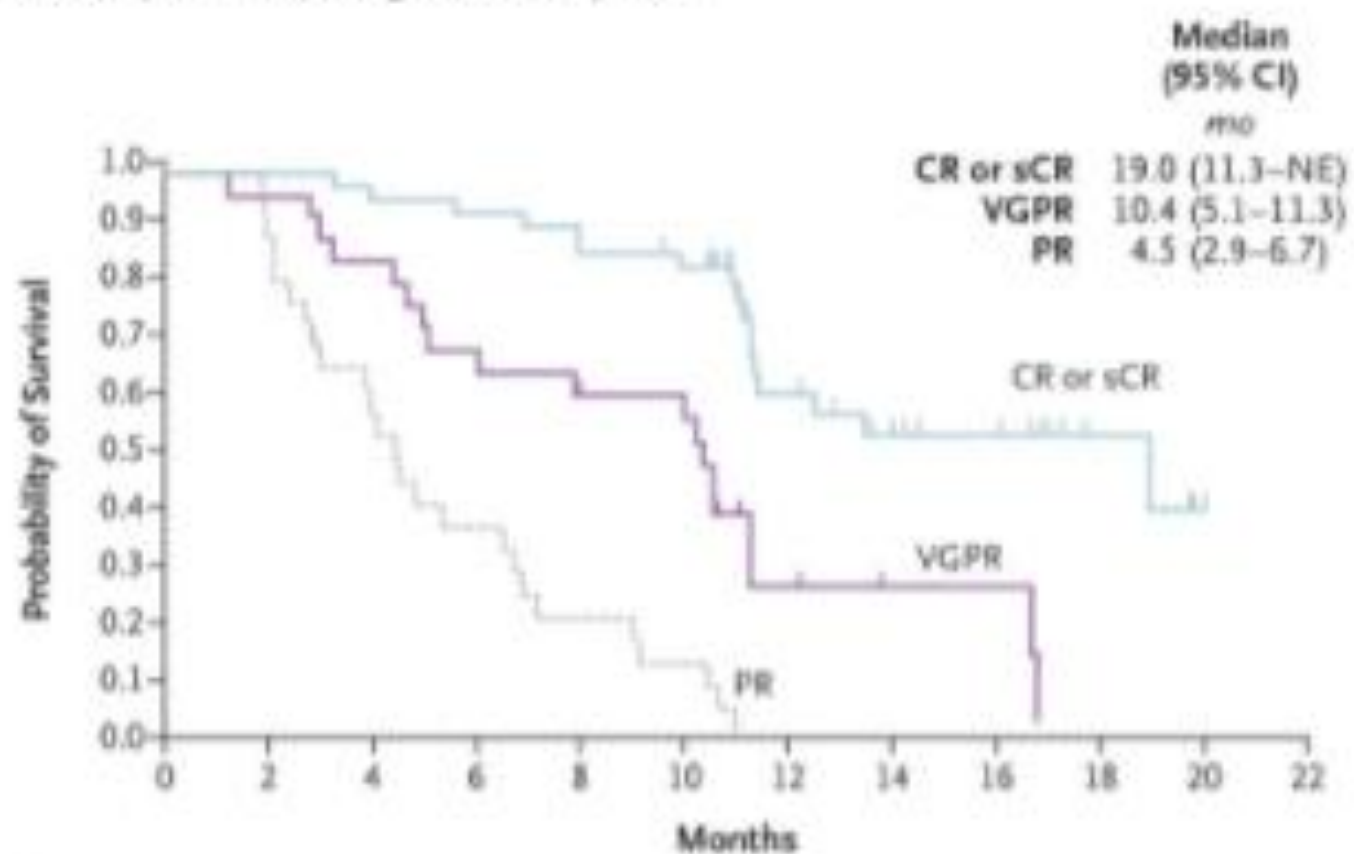
PFS: 8.8 m overall
12.1 m for 450 mill dose

No. at Risk

150x10 ⁶	4	2	1	1	1	1	1	1	1	1	1	0
300x10 ⁶	70	56	42	33	29	24	17	14	11	7	3	0
450x10 ⁶	54	44	40	36	34	31	17	4	1	0	0	0
Total	128	102	83	70	64	56	35	19	13	8	4	0

- High incidence of response – also seen in high risk subgroups – extramedullary disease, high-risk cytogenetics, triple- or penta-refractory disease, a high tumor burden
- Median time to response – 1 month, CR – 2.8 month,

B Duration of Response According to Best Response

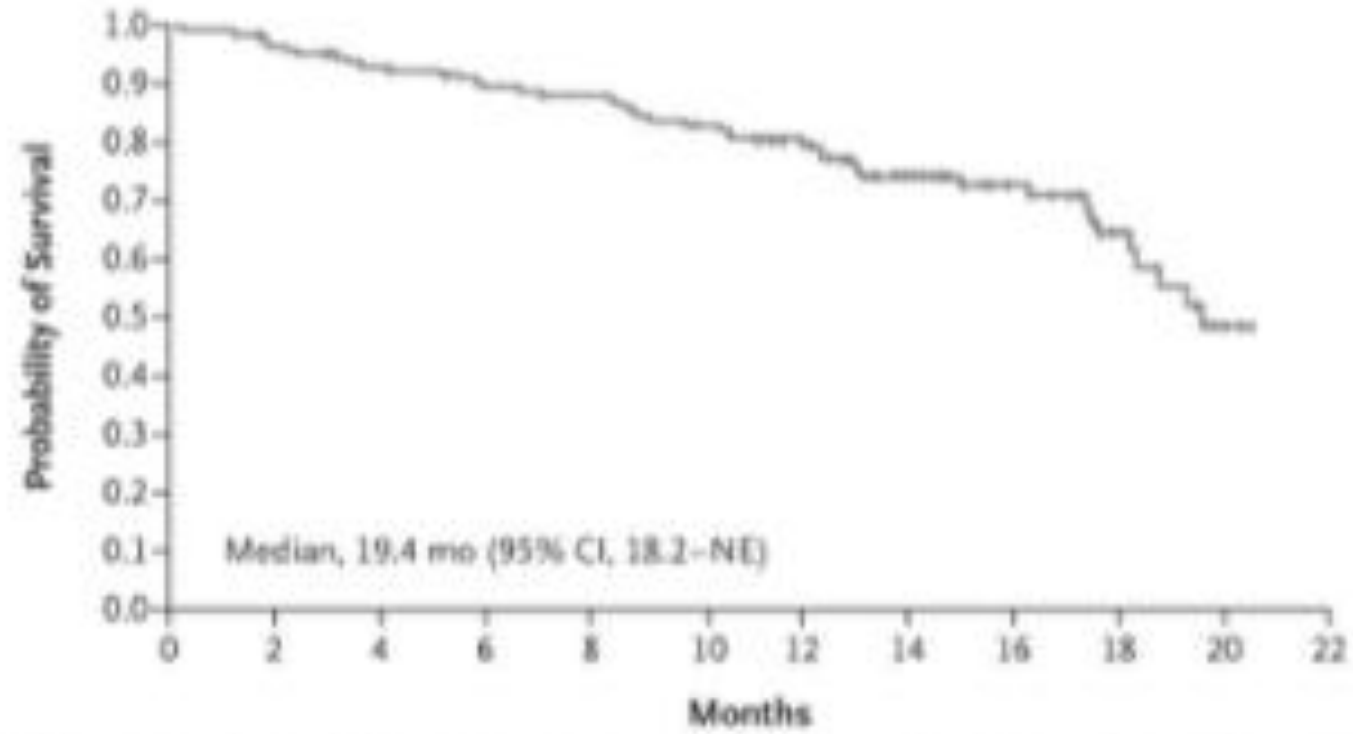


No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22
CR or sCR	42	42	40	39	36	34	18	11	10	4	1	0
VGPR	25	24	21	17	15	14	4	2	2	0	0	0
PR	27	23	14	9	5	3	0	0	0	0	0	0

D Overall Survival

Median OS: 19.4 months
12 month OS: 78%



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22
	128	122	114	108	104	97	82	55	38	27	12	0

Soluble BCMA as biomarker

- S- BCMA levels were high before treatment, decreased at response
- Levels >40 ng per millilitre correlated with relapse

JNJ CAR T: Ciltacabtagene ciloleucel

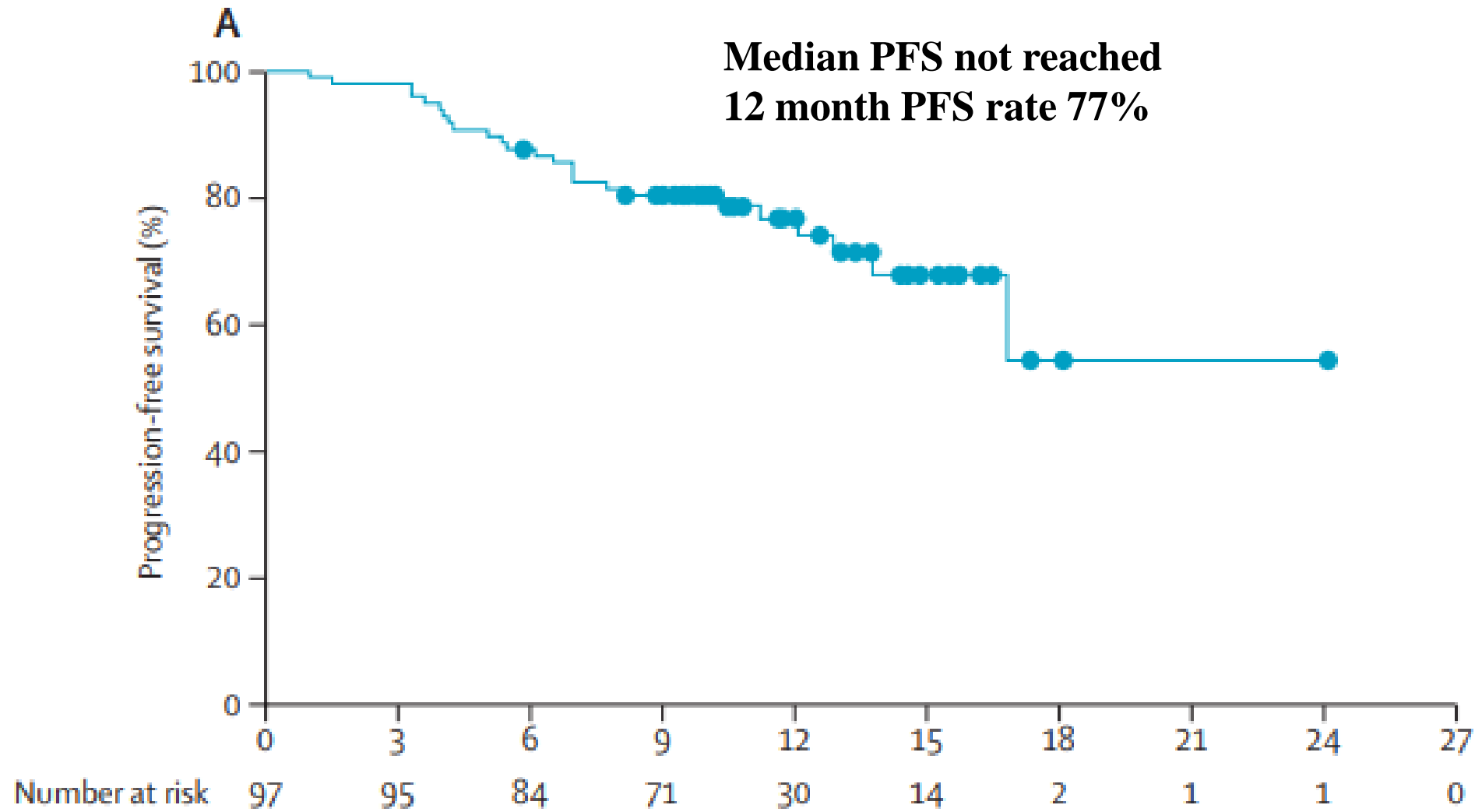
THE CARTITUDE TRIALS

- Vector manufactured by Legend biotech (China)
- Cilta-cel, also known as LCAR-B38M, now JNJ-68284528, is a bioengineered T-cell receptor construct with a CD3 ζ signaling domain, a 4-1BB costimulatory domain, and **two** BCMA binding domains
- CARTITUDE 1: Single arm - multiply pre treated patients
- CARTITUDE 2: Single arm - early relapse following IMiD and PI
- CARTITUDE 4: RCT between JNJ CART vs Pom Bor Dex or Dara Pom Dex in R/R myeloma
- CARTITUDE 5: Newly diagnosed transplant ineligible MM – VRD followed by CAR T vs VRD followed by Len Dex

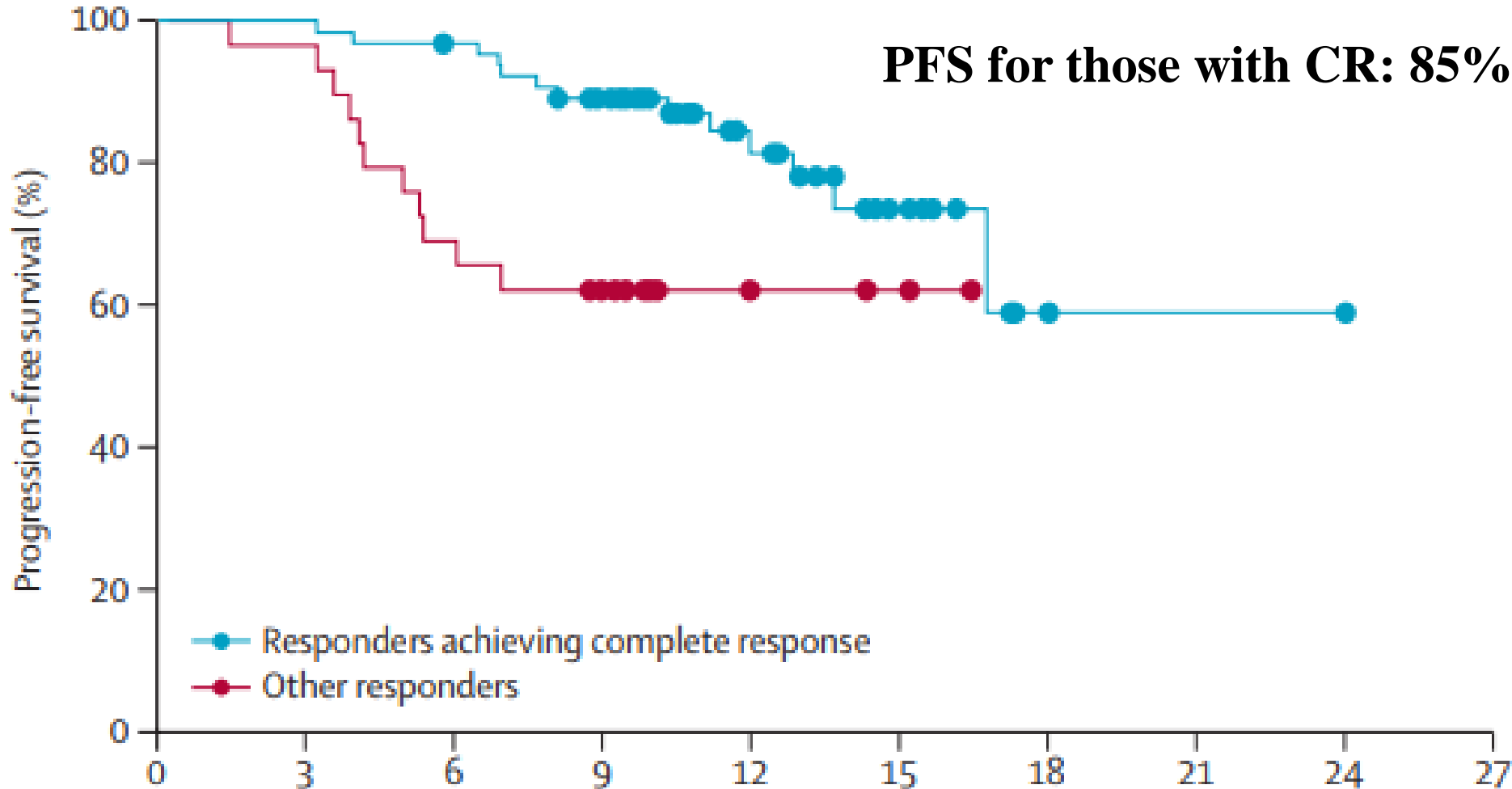
CARTITUDE 1

- At least 3 prior lines of therapy including one PI and IMiD and anti CD 38 mAb
- 97 pts received the infusion
- Median age: 61 (upto 78 yr)
- 26 pts had extramedullary plasmacytomas
- 87% triple refractory, 42% penta refractory
- Single infusion of ciltacabtagene autologous T cells (cilta-cel) at a target dose of 0.75×10^6 cells/kg (range = $0.5-1.0 \times 10^6$ cells/kg)
- Conditioning regime: Flu – Cy, CAR T infusion 5-6 days later

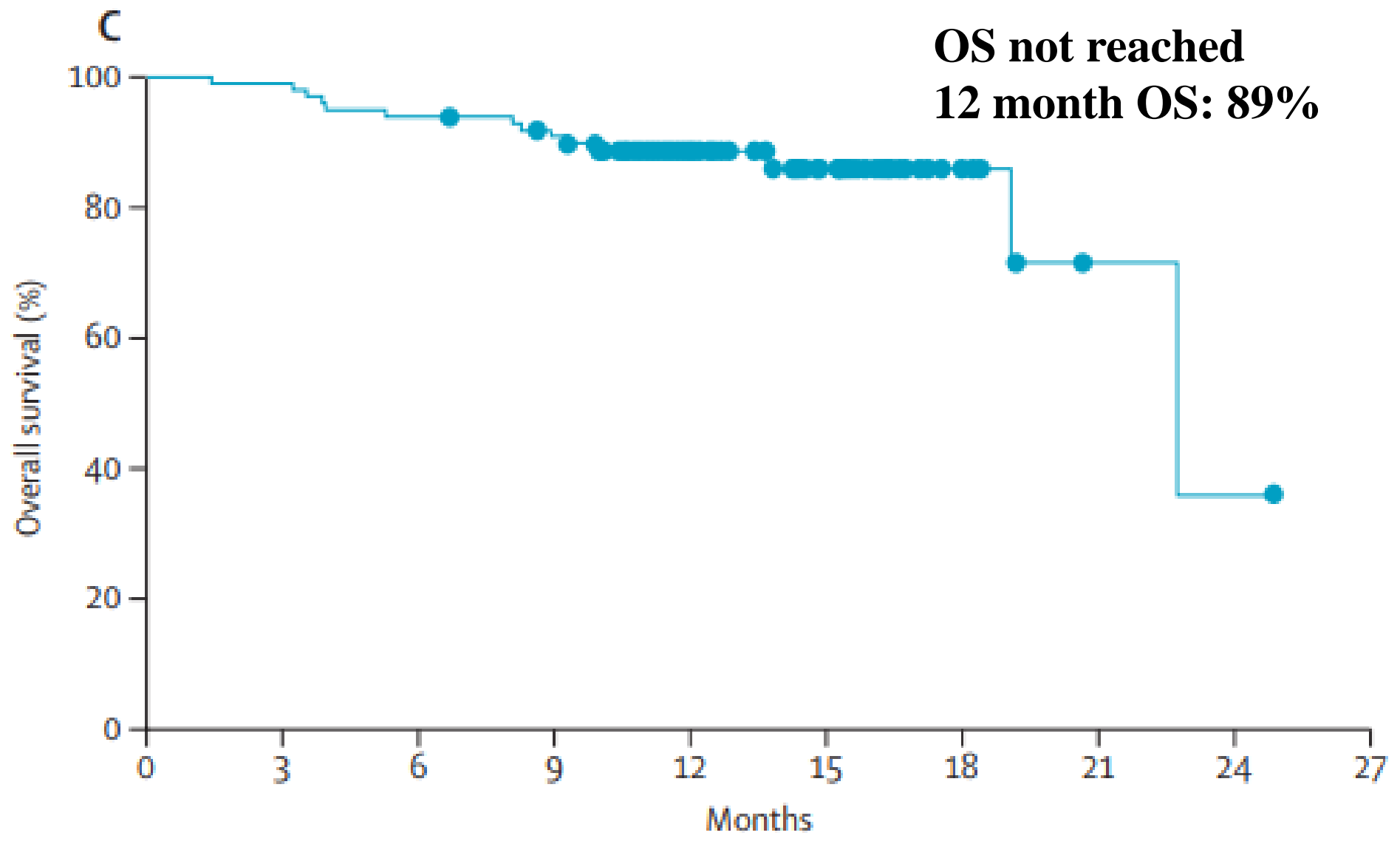
	Patients (n=97)
Overall response	
Number of patients with a response†	94
Proportion of patients with a response, % (95% CI)	96.9% (91.2–99.4)
Best overall response	
Stringent complete response	65 (67%)
MRD-negative complete response or stringent complete response	33 (34%)‡
Complete response	0
Very good partial response	25 (26%)
Partial response	4 (4%)
Minimal response	0
Stable disease	0
Progressive disease	1 (1%)
Not evaluable	2 (2%)
Median time to first response, months	1.0 (0.9–1.0)
Median time to best response, months	2.6 (1.0–6.1)
Median time to complete response or better, months	1.9 (1.0–6.5)
Median duration of response, months (95% CI)	NE (15.9–NE)



PFS for those with CR: 85%



Number at risk		0	3	6	9	12	15	18	21	24	27
Responders achieving complete response		65	65	62	53	27	12	2	1	1	0
Other responders		29	28	20	16	3	2	0	0	0	0



Number at risk 97 96 91 85 45 25 9 2 1 0

	Any grade	Grade 3-4
Any adverse event	97 (100%)	91 (94%)
Haematological*	97 (100%)	96 (99%)
Neutropenia	93 (96%)	92 (95%)
Anaemia	79 (81%)	66 (68%)
Thrombocytopenia	77 (79%)	58 (60%)
Leukopenia	60 (62%)	59 (61%)
Lymphopenia	51 (53%)	48 (50%)
Metabolism and nutrition disorders*	67 (69%)	16 (16%)
Hypocalcaemia	31 (32%)	3 (3%)
Hypophosphataemia	30 (31%)	7 (7%)
Decreased appetite	28 (29%)	1 (1%)
Hypoalbuminaemia	27 (28%)	1 (1%)
Hyponatraemia	22 (23%)	4 (4%)
Hypokalaemia	20 (21%)	2 (2%)
Gastrointestinal*	62 (64%)	4 (4%)
Diarrhoea	29 (30%)	1 (1%)
Nausea	27 (28%)	1 (1%)
Constipation	21 (22%)	0
Other*		
Fatigue	36 (37%)	5 (5%)
Cough	34 (35%)	0
Aspartate aminotransferase increased	28 (29%)	5 (5%)
Alanine aminotransferase increased	24 (25%)	3 (3%)
Chills	20 (21%)	0
Pyrexia	20 (21%)	0
Cytokine release syndrome*	92 (95%)	4 (4%)
Neurotoxicities*†	20 (21%)	9 (9%)

Table 2. Ide-cel and Cilta-cel: CAR-T and clinical characteristics

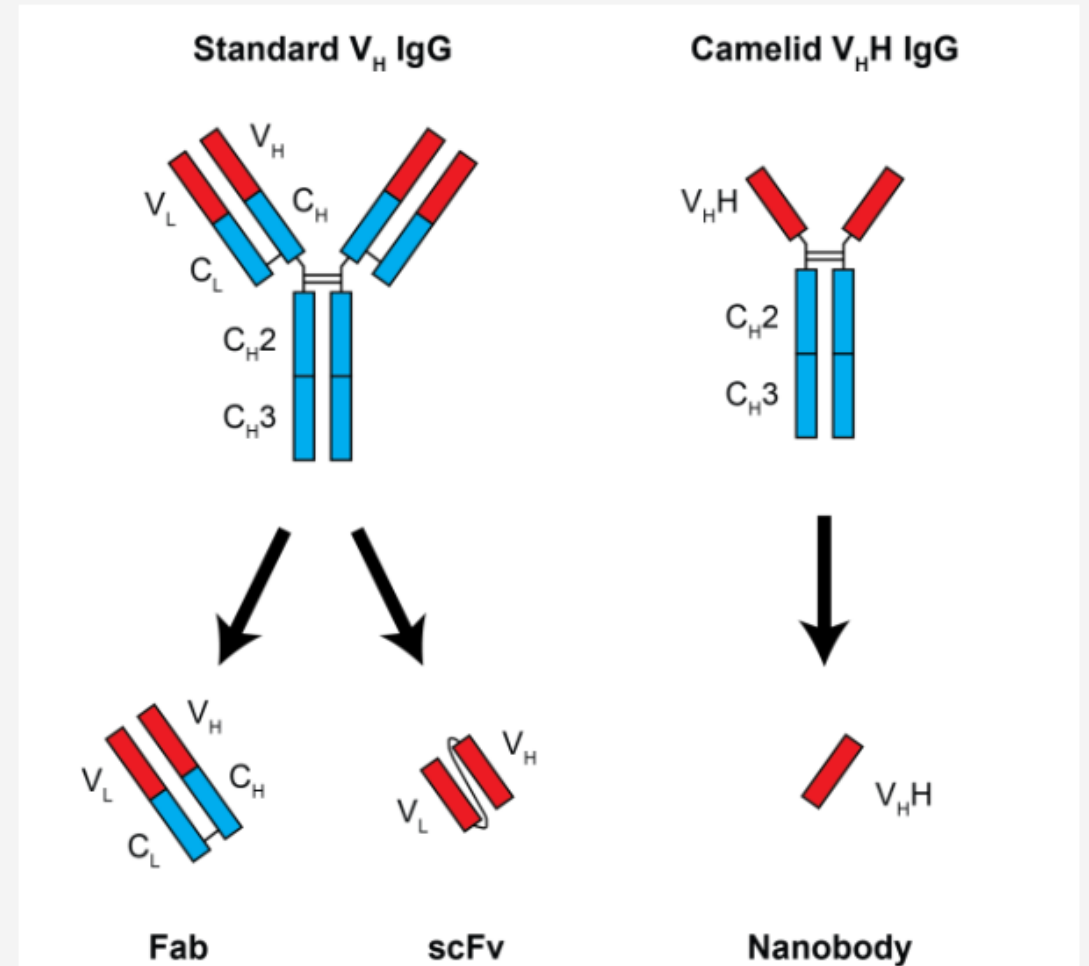
	Ide-cel (bb2121) / KarMMa (phase II)	Cilta-cel (JNJ-4528) / CARTITUDE-1 (phase IB/ II)
Antigen-binding domain	scFv (murine)	Bispecific variable fragments of llama heavy-chain antibodies; two distinct BCMA epitopes are targeted
Signaling domains	CD3 ζ /4-1BB	CD3 ζ /4-1BB
Vector	Lentiviral	Lentiviral
Other features	Bb21217 uses the same CAR construct as used for ide-cel. During <i>ex vivo</i> culture a PI3K inhibitor is added to enrich for CAR-T with memory-like phenotype	Bi-epitope BCMA binding confers high avidity binding
Lymphodepletion	Flu/Cy	Flu/Cy
CAR-T dose	150-450x10 ⁶	Median dose: 0.71x10 ⁶ /kg
Number of patients	128 (140 patients underwent leukapheresis)	Data presented for first 97 (113 patients were enrolled/apheresed)
Bridging therapy (%)	88	65
Number of prior therapies (median)	6	6
Triple-class refractory (%)	84	88
High-risk cytogenetics (del(17p), t(4;14), or t(14;16) (%)		35 24
Extramedullary disease (%)	39	13
≥PR	150-450x10 ⁶ : 73% 150x10 ⁶ : 50% 300x10 ⁶ : 69% 450x10 ⁶ : 82%	97%
≥CR	150-450x10 ⁶ : 33% 150x10 ⁶ : 25% 300x10 ⁶ : 29% 450x10 ⁶ : 39%	67%
Median PFS	150-450x10 ⁶ : 8.8 months 150x10 ⁶ : 2.8 months 300x10 ⁶ : 5.8 months 450x10 ⁶ : 12.1 months	Median PFS: Not reached; 12-month PFS rate: 77%
CRS (all grades) (%)	84	95
CRS (grade ≥3) (%)	5	4
Median time to CRS onset (any grade) (days)	1	7
Median duration of CRS		

Cost: Abecma: 419,000\$
vs Carvykti: 465,000

Nanobodies

Nanobodies are a unique kind of monoclonal antibody derived from a camelid IgG variant, consisting of a single heavy-chain variable domain that can bind its antigen as strongly as a standard antibody. As nanobodies lack a light chain, they are both significantly smaller than standard antibodies, and have unique flexibility at their antigen-binding interface. This combination allows nanobodies to bind in different modes than typical antibodies, covering more chemical space and allowing binding to epitopes otherwise inaccessible to antibodies. Nanobodies are also significantly smaller (~15 kDa) and more stable than standard antibodies, and can be easily genetically engineered for additional functionality. With these advantages in mind, we and many others are actively pursuing nanobodies as improved reagents for multiple applications: antibody therapy and diagnostics, affinity isolations, imaging, and more.

“ nanobodies lack a light chain, they are



IgG variants and their derivatives. Standard IgG structures contain both heavy and light chains. Variable regions from both chains must be combined for use as an Fab fragment or for recombinant expression as a linked scFv. The camelid V_H IgG



Meeting Abstract: 2021 ASCO Annual Meeting I

FREE ACCESS | Hematologic Malignancies—Plasma Cell Dyscrasia | May 28, 2021



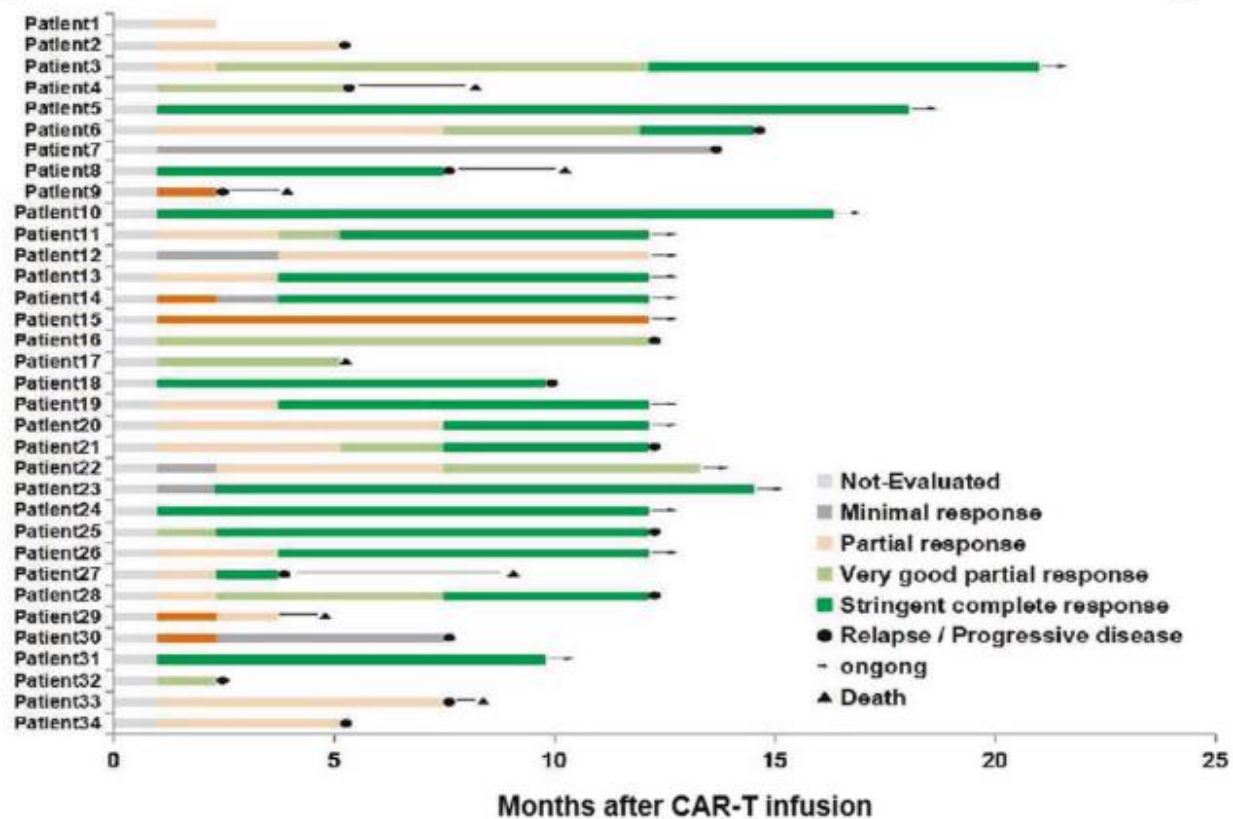
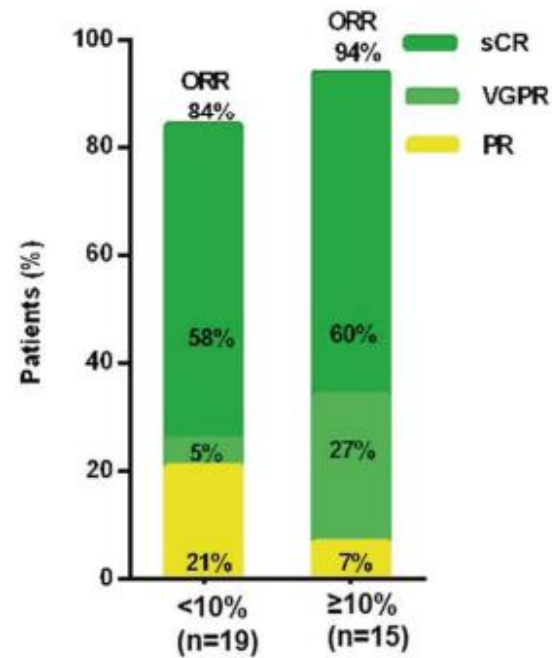
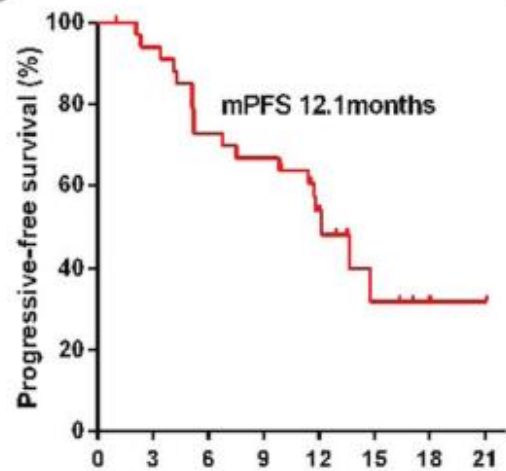
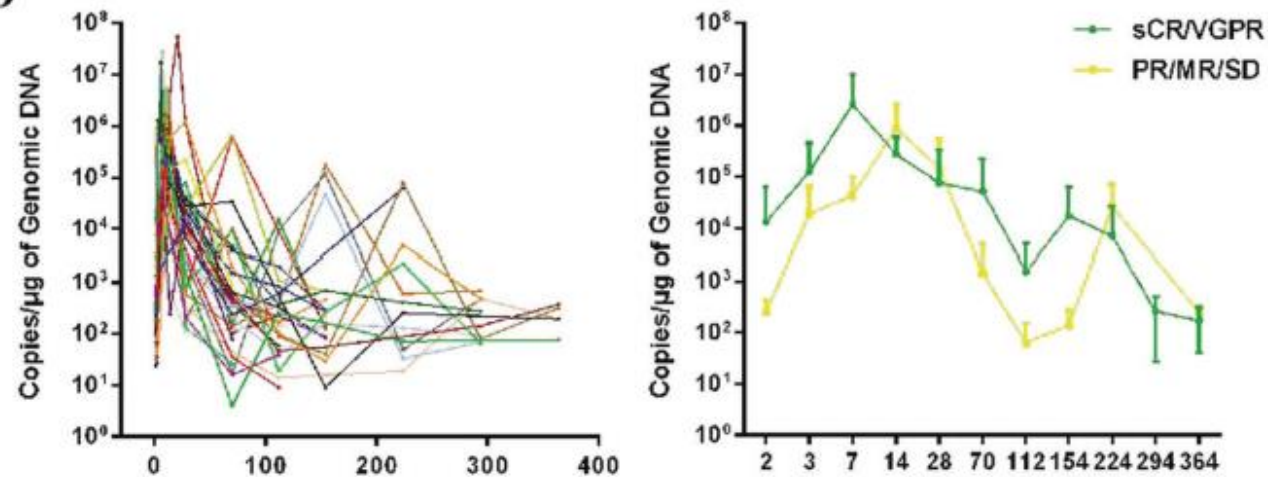
The clinical study of anti-BCMA CAR-T with single-domain antibody as antigen binding domain.

Authors: [Lu Han](#), [Quanli Gao](#), [Keshu Zhou](#), [Jian Zhou](#), [Qing-Song Yin](#), [Baijun Fang](#), [Xing-Hu Zhu](#), [Jishuai Zhang](#), [Chaolemeng Bao](#), and [Yongping](#)

[Song](#) | [AUTHORS INFO & AFFILIATIONS](#)

Publication: Journal of Clinical Oncology • [Volume 39, Number 15_suppl](#) • https://doi.org/10.1200/JCO.2021.39.15_suppl.8025



A**B****C****D**

ABECMA (Idecabtagene)	CARVYKTI (Ciltacabtagene)	PRG 1801
ORR: 73% sCR: 33%	ORR: 97% sCR: 67%	ORR: 94% sCR: 60%
	Nanobody antigen binding site	Nanobody antigen binding site

CAR T in India

Aurigene

- Currently enrolling patients for the phase 2 trial
- Uses vector from Pregene, is a camelid vector – nanobody
- Transduction done in semi – automated system
- Efficacy likely to be high
- Cost likely to be higher for the above reasons

ImmunoAct

- DCGI approval for phase 1/2 trial
- Indigenous vector
- Transduction done manually
- Cost in future likely to be attractive

- T-cell reactivity against the murine BCMA-binding scFv used in Ide-cel, interest in producing fully human BCMA CAR-Ts - to reduce anti-CAR-T immune responses and improve persistence
- Zevorcabtagene-autoleucel, Zevor-cel, which has a human BCMA-directed scFv
- Orvacabtagene-autoleucel, Orva-cel; no longer under development
- Equecabtagene autoleucel

<p>NCT03975907</p> <p>Phase 1</p> <p>Lummicar Study 1</p>	<p>CT053 (Zevor-cel)</p> <p>Human scFv (25C2)</p> <p>4-1BB co-stimulatory domain</p> <p>Lentiviral vector</p> <p>(Equecabtagene)</p>	<p>Fludarabine 30 mg/m², cyclophosphamide 300 mg/m² days -5 to -3</p> <p>1 × 10⁸ CAR-T (<i>n</i> = 3), 1.5 × 10⁸ CAR-T (<i>n</i> = 11)</p>	<p><i>N</i> = 14</p> <p>≥ 3 Prior lines of therapy, including PI/IMiD</p> <p>Median 6 prior lines</p>	<p>ORR 100%, sCR 79% (100% of patients in sCR were MRD negative to 10⁻⁵)</p> <p>12 month PFS 86%</p> <p>CRS 93% (all Grade 1/2)</p>
<p>ChiCTR1800018137</p> <p>Phase 1/2</p> <p>FUMANBA-1 study</p>	<p>CT103A</p> <p>Human scFv</p> <p>4-1BB co-stimulatory domain</p> <p>Lentiviral vector</p>	<p>Fludarabine 25 mg/m², cyclophosphamide 20 mg/kg for 3 days</p> <p>1-6 × 10⁶ CAR-T</p>	<p><i>N</i> = 103</p> <p>≥ 3 Prior lines of therapy including PI/IMiD, refractory to last line, median 4 prior lines, 18.3% prior CAR-T</p>	<p>ORR 96%, ≥CR 74%</p> <p>12-month PFS 79%</p> <p>95% (<i>n</i> = 101 evaluable) MRD negative to 10⁻⁵</p> <p>95% CRS (≥ Grade 3 3%), ICANS in 2 patients (both grade 2)</p>

After a median follow-up of 14 months, ORR was 96%, ≥CR 74%, and 12-month PFS was 79% - has orphan drug approval

Why do CAR T cells fail?

- Intrinsic to the CAR T construct: lack of persistence
- Related to the malignant plasma cells: antigen downregulation by tumour cells, CAR T cell mediated trogocytosis (extraction of surface antigens)
- BCMA loss
- Immunosuppressive role of micro environment in myeloma

Despite an exceptional response rate observed across several BCMA-targeted CAR T cells, response durability has remained an ongoing clinical dilemma, a significant proportion of patients eventually relapse.

Targeting new antigens – dual CAR T 'CAR POOL' approach

- G-protein–coupled receptor class C group 5 member D (GPRC5D)
- Transmembrane activator and calcium-modulator and cyclophilin ligand
- Signalling lymphocytic activation molecule family 7 (SLAM F7)
- Natural killer group 2 member D (NKG2D) ligands
- CD229
- Integrin $\beta 7$
- Gamma secretase inhibitor – inhibits cleavage of BCMA

Most of these non-BCMA–targeted CAR T cells are in early-stage clinical trials or preclinical phase studies

Preclinical Evaluation of Allogeneic CAR T Cells Targeting BCMA for the Treatment of Multiple Myeloma

Cesar Sommer,^{1,5} Bijan Boldajipour,^{2,5} Tracy C. Kuo,² Trevor Bentley,¹ Janette Sutton,¹ Amy Chen,² Tao Geng,² Holly Dong,² Roman Galetto,³ Julien Valton,⁴ Thomas Pertel,¹ Alexandre Juillerat,⁴ Annabelle Gariboldi,³ Edward Pascua,² Colleen Brown,² Sherman M. Chin,² Tao Sai,² Yajin Ni,¹ Philippe Duchateau,³ Julianne Smith,⁴ Arvind Rajpal,² Thomas Van Blarcom,¹ Javier Chaparro-Riggers,² and Barbra J. Sasu¹

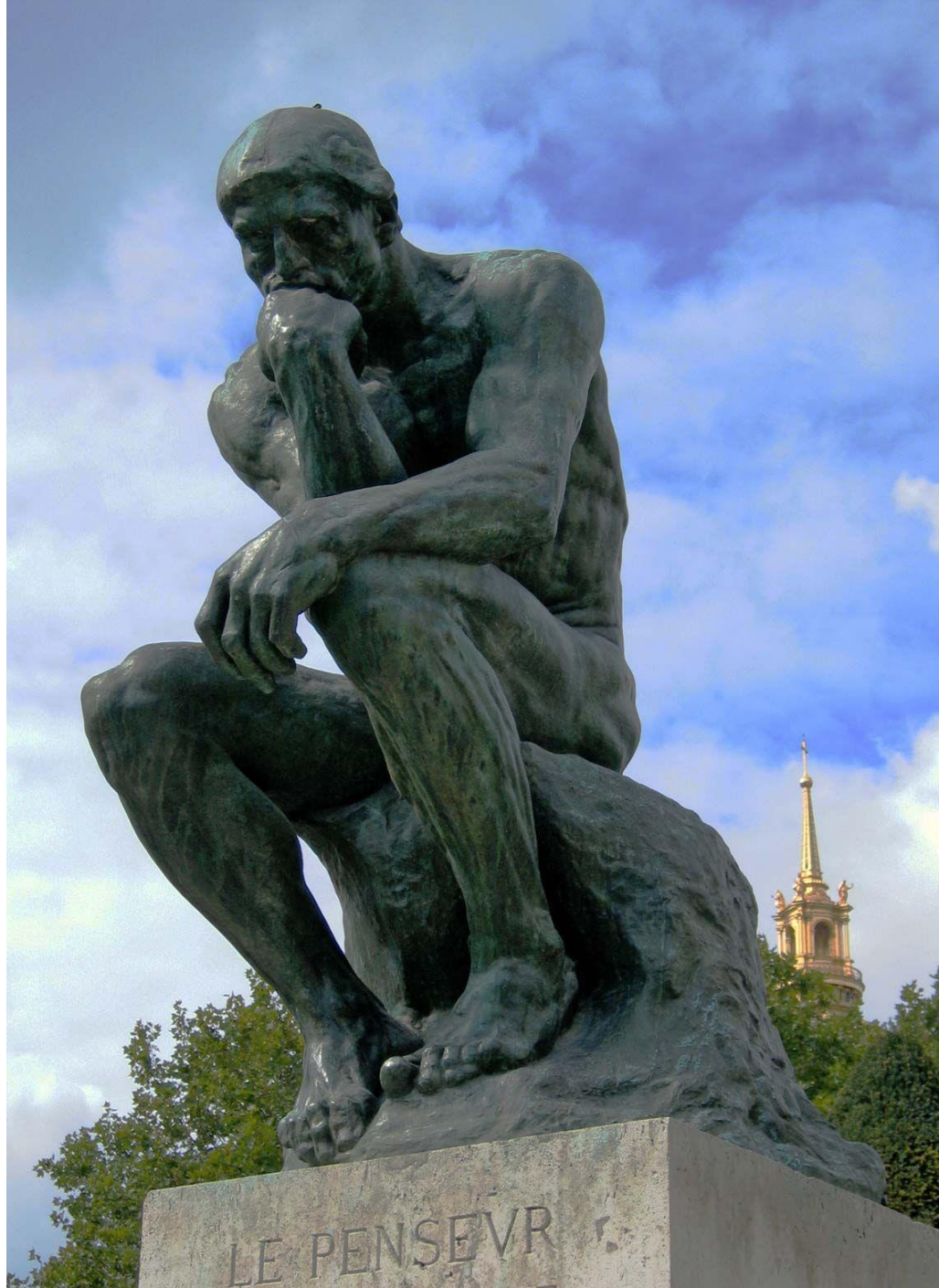
¹Allogene Therapeutics, Inc., 210 E. Grand Avenue, South San Francisco, CA 94080, USA; ²Pfizer Cancer Immunology Discovery, Pfizer Worldwide Research and Development, 230 E. Grand Avenue, South San Francisco, CA 94080, USA; ³Collectis SA, 8 rue de la Croix Jarry, 75013 Paris, France; ⁴Collectis, Inc., 430 East 29th Street, New York, NY 10016, USA

Available allogeneic CAR-expressed immune effector cells in MM

Product	Trial	ClinicalTrials.gov identifier	Phase	Type	Target	Vector	Gene editing event	Inclusion	n (estimated)	Status
UCARTCS1	MELANI-01	NCT04142619	1	CAR T	CS1	Lentivirus	TALEN	RRMM	18	Recruiting
ALLO-715	UNIVERSAL	NCT04093596	1	CAR T	BCMA	Lentivirus	TALEN	RRMM	90	Recruiting
PBCAR269A	PBCAR269A-01	NCT04171843	1/2a	CAR T	BCMA	Adenovirus	ARCUS endonuclease	RRMM	48	Recruiting
CTX120	Unnamed	NCT04244656	1	CAR T	BCMA	CRISPR/Cas9	CRISPR/Cas9	RRMM	80	Recruiting
BCMA-UCART	Unnamed	NCT03752541	1	CAR T	BCMA	Unknown	Unknown	RRMM	20	Recruiting

In – vivo CAR T

- MMyCAR study, a phase 1 study evaluating an in vivo anti-BCMA CAR T-cell therapy for patients with RRMM
- Kelonia therapeutics
- Presented as late breaking abstract at ASH 2025
- Does not require lymphodepleting chemotherapy or apheresis, no manufacturing facility
- 3 pt data, all achieved MRD neg state with minimal toxicity



Where is the future headed?

Will bispecifics+
Dara/JNJ trispecific or
CAR T move into 1st
line care?

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALY AVAILABLE THERAPIES | NOVEMBER 15, 2022

DVRd Followed By Ciltacabtagene Autoleucel Versus DVRd Followed By ASCT in Patients with Newly Diagnosed Multiple Myeloma Who Are Transplant Eligible: A Randomized Phase 3 Study (*EMagine/CARTITUDE-6*)

Mario Boccadoro, Jesús San-Miguel, Kenshi Suzuki, Niels W.C.J. Van De Donk, Gordon Cook, Andrzej Jakubowiak, Deepu Madduri, Salma Afifi, An-Sofie Stevens, Jordan M. Schechter, William Deraedt, Steven Kuppens, Pankaj Mistry, Lida Pacaud, Erika Florendo, Annemiek Broijl, Francesca Gay, Roberto Mina, Leo Rasche, Philippe Moreau, María-Victoria Mateos, Hermann Einsele, Pieter Sonneveld



Blood (2022) 140 (Supplement 1): 4630–4632.

<https://doi.org/10.1182/blood-2022-157021>



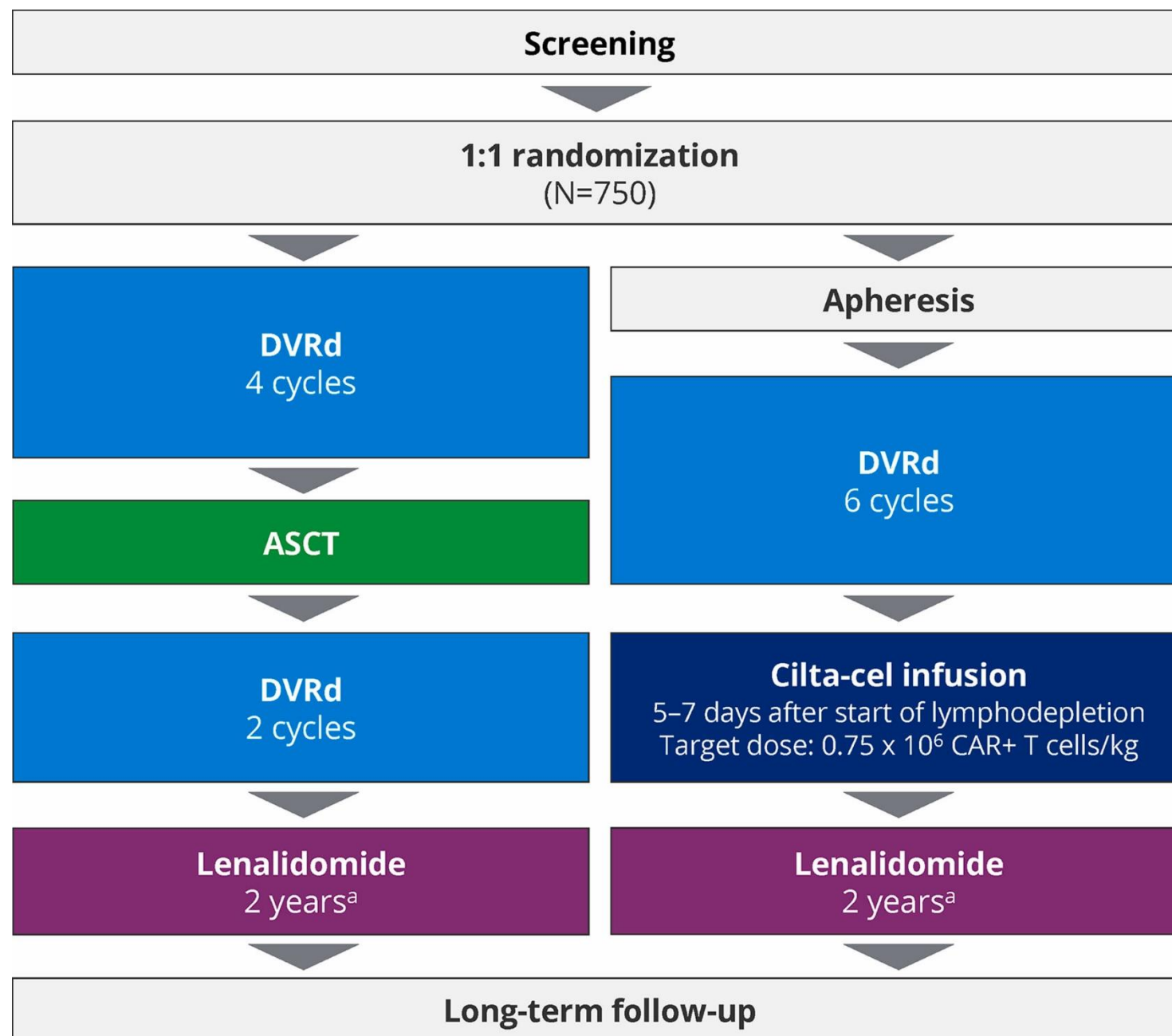
Split-Screen



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^aPatients benefiting from therapy have the option to continue lenalidomide therapy until progressive disease per investigator's discretion after benefit-risk assessment and review by the medical monitor.

Conclusions

- CAR T therapy offers unprecedented response rates which are superior to other anti BCMA therapies currently available
- Adverse effects are manageable in majority
- Studies underway in earlier line of treatment
- CAR T and bispecific combos may provide functional cure in future

THANK YOU



CARS OF THE FUTURE

Questions

Which of the following statements is correct

- 1. Tec – Dara combination in frontline therapy is the best treatment for myeloma
- 2. CAR T in frontline therapy has the best results so far
- 3. In vivo CAR T is the most promising therapy currently available in myeloma
- 4. Cilta-cel has proven to be the best CAR T

You would do a test for BCMA levels or screen for mutations in BCMA genes in the following situation

- 1. A patient is planned for therapy with BCMA bispecific
- 2. A patient is planned for therapy with BCMA CAR T
- 3. A patient has relapsed after BCMA bispecific
- 4. A patient has been planned for CAR T and he/she was treated with Teclistamab earlier