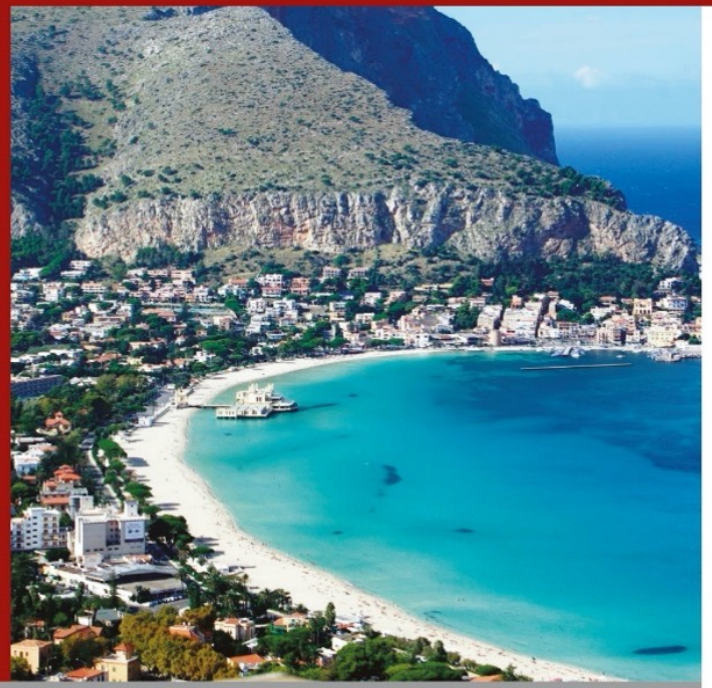
International Palermo Workshop on: Innovative Therapies for Lymphoid Malignancies



Palermo March 18, 2023
Hotel Federico II Central Palace

CAR T in Multiple Myeloma

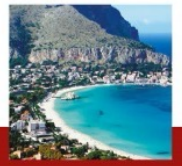
Benedetto BRUNO

Division of Hematology

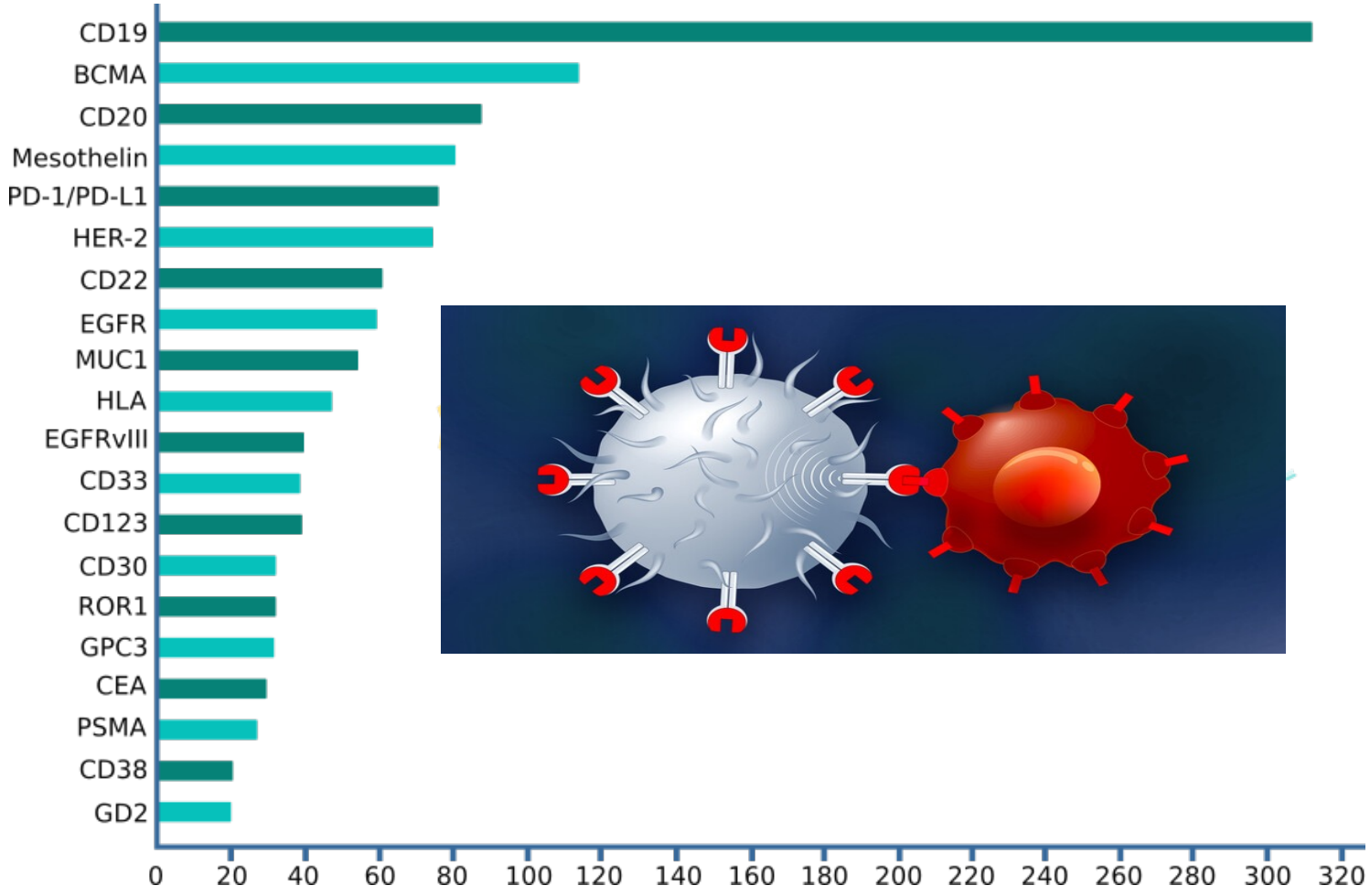
University of Torino – Torino - Italy

Disclosures of Benedetto BRUNO

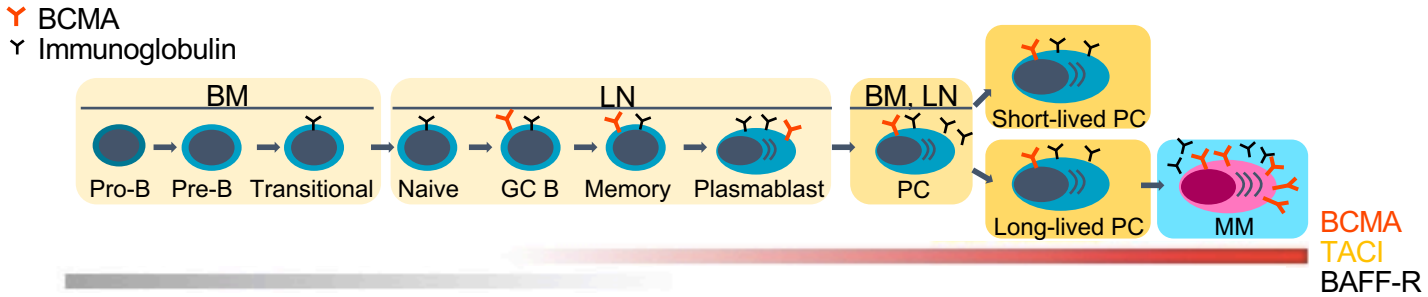
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GENENTA							X
JAZZPHARMA					X		
JANSSEN	X						X
NOVARTIS							X
BD SCIENCES					X		

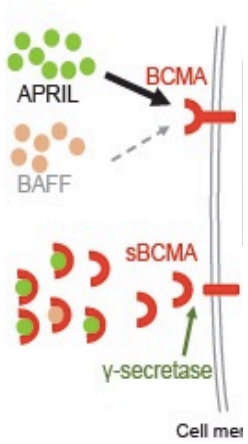


CAR-T Immunotherapy: The most popular CAR-T Targets



B-Cell Maturation Antigen (BCMA): A Promising Target





- BCMA is an antigen expressed specifically on PCs and myeloma cells
  - Member of TNFR superfamily. Binds 2 ligands (BAFF e APRIL)
  - higher expression in myeloma cells than normal PCs
  - key role in B-cell maturation and differentiation
  - promotes myeloma cell growth, chemoresistance, and immunosuppression in the BM microenvironment
- Expression of BCMA increases as the disease progresses from MGUS to advanced myeloma

APRIL, a proliferation-inducing ligand; BAFF-R, B-cell activating factor receptor; GC, germinal centre; LN, lymph node; MGUS, monoclonal gammopathy of unknown significance; sBCMA, soluble BCMA; TACI, transmembrane activator and CAML interactor.

Cho SF, et al. Front Immunol. 2018;9:1821. Moreaux J, et al. Blood. 2004;103:3148-57. Sanchez E, et al. Br J Haematol. 2012;158:727-38.

Treatment landscape in multiple myeloma: before BCMA

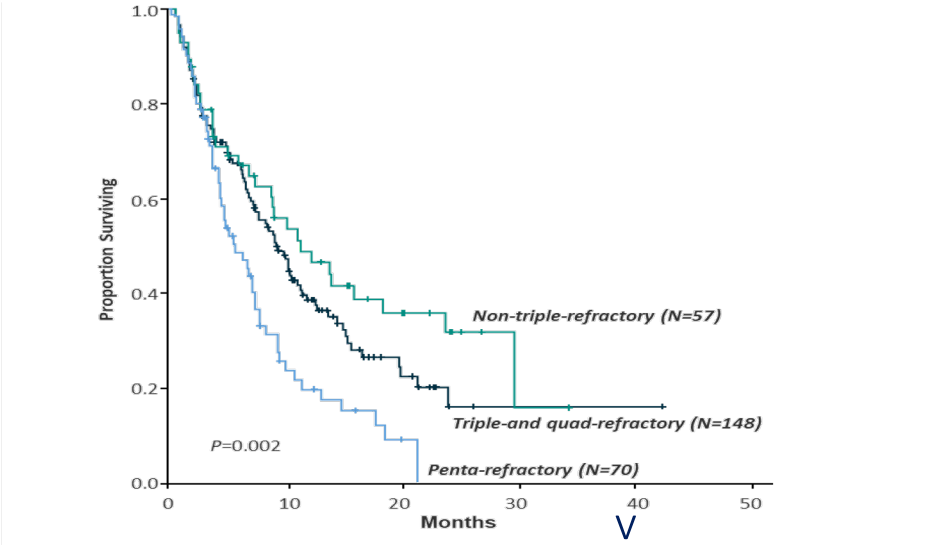
1° line	2° line	3° line	4° line and beyond
Anti-CD38 MoAbs			
Bortezomib and lenalidomide			
	Carfilzomib/ixazomib, pomalidomide, elotuzumab		

BCMA, B-cell maturation antigen; MoAb, monoclonal antibody;

Treatment landscape in multiple myeloma: before BCMA

1° line	2° line	3° line	4° line and beyond
Anti-CD38 MoAbs			
Bortezomib and lenalidomide			
	Carfilzomib/ixazomib, pomalidomide, elotuzumab		

MAMMOTH STUDY[1]	ORR	Median PFS	Median OS
Triple class refractory (1 PI, 1 IMiD, anti CD-38)	30%	3.4 months	9.2 months
Penta refractory (2 PIs, 2 IMiDs, anti CD-38)	<30%	NR	5.6 months



BCMA, B-cell maturation antigen; MoAb, monoclonal antibody; IMiD, immunomodulatory drug; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor

1. Gandhi UH et al. Leukemia 2019; 33(9):2266-2275;

Potential therapeutic targets in multiple myeloma

BCMA

- BCMA is a member of the TNF receptor superfamily
- APRIL and BAFF are known ligands, leading to activation of the NF-κB pathway
- BCMA promotes plasma cell survival, growth, resistance to apoptosis, adhesion, and angiogenesis
- γ-secretase cleaving causes shedding of soluble BCMA
- BCMA is expressed on malignant PCs, at low levels on normal PCs and is absent in non-hematological tissues

GPRC5D

- GPRC5D is a member of the G protein-coupled receptor family with an unknown function
- It is highly expressed on malignant PCs, as well as hard keratinized structures (hair shaft, nail, and central region of the tongue)

FcHR5

- FcRH5 is a surface protein in the Ig superfamily
- It is expressed only in B cells, with increasing expression in mature B cells and plasma cells
- FcRH5 is involved in proliferation and isotype expression

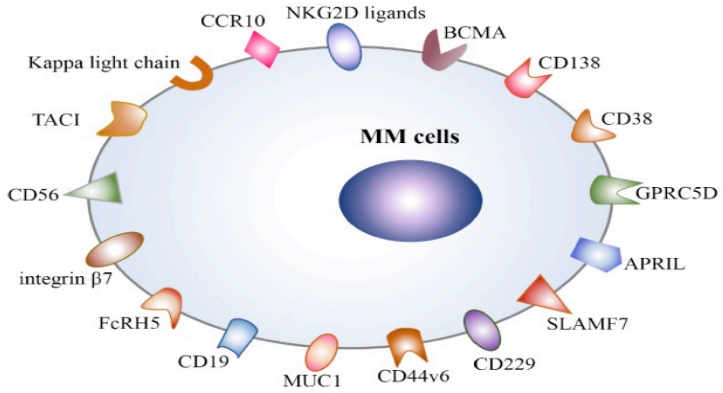
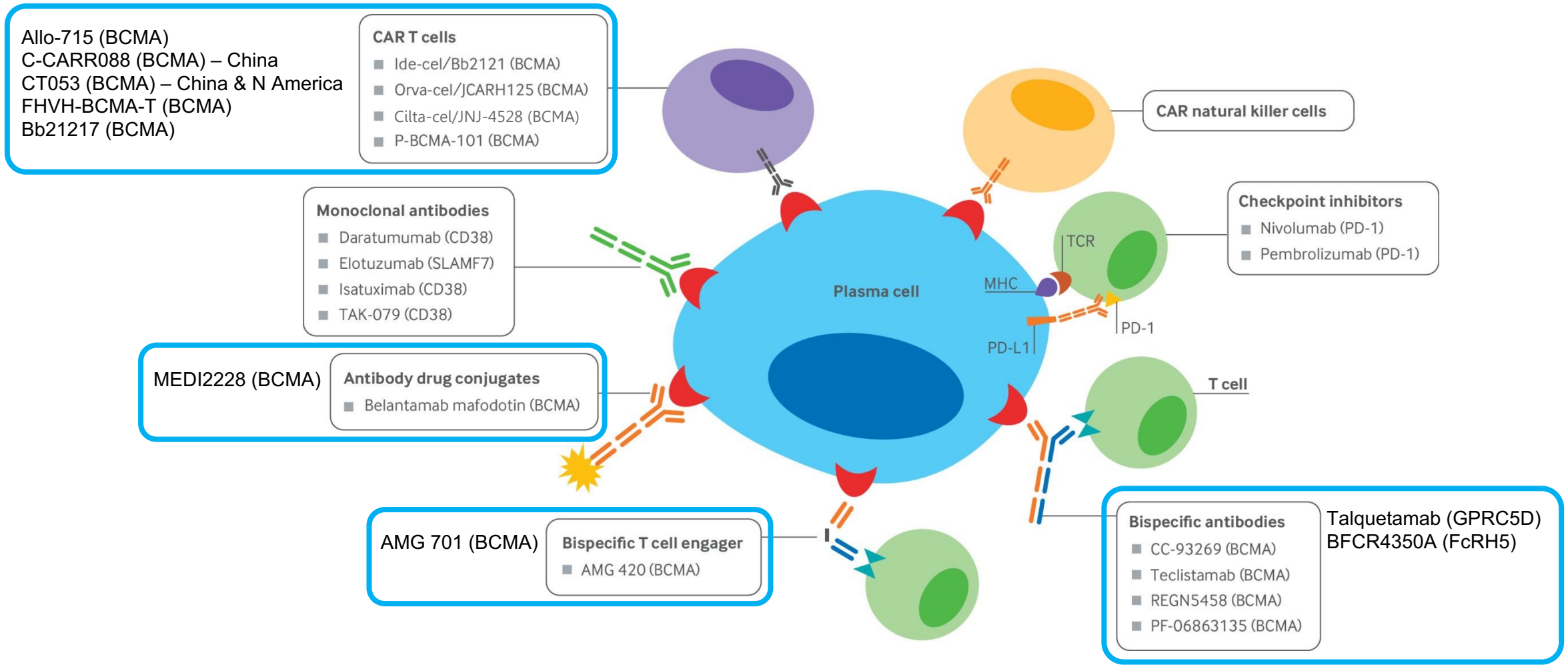


Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.

APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CD, cluster of differentiation; FcRH5, Fc receptor-like 5; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; MM, multiple myeloma; NF-κB, nuclear factor Bs; PC, plasma cell; SLAMF7, signaling lymphocytic activation molecule family member 7; TNF, tumor necrosis factor.

1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538-49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij CPM, et al. Blood Adv. 2020;5;2196-215. 5. Smith EL, et al. Sci Transl Med. 2019;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-95. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155. 8. Lancman G, et al. Blood Cancer Discov. 2021;2:423-33.

Recent Immunotherapeutic Approaches in Multiple Myeloma



BCMA, B-cell maturation antigen; PD-1, programmed cell death protein 1.

Ongoing CAR T cell therapy studies

CAR T cell therapy

BCMA

Ide-cel
Cilta-cel
CART-ddBCMA
PHE885
ARI0002h
GC012F

GPRC5D

MCARH109
OriCAR-017

Region Name	Number of Studies
World	**125**
East Asia	62
Japan	6
Europe	15
Middle East	7
North America	55
Canada	5
United States	55
Pacifica	6
South America	1
Southeast Asia	1

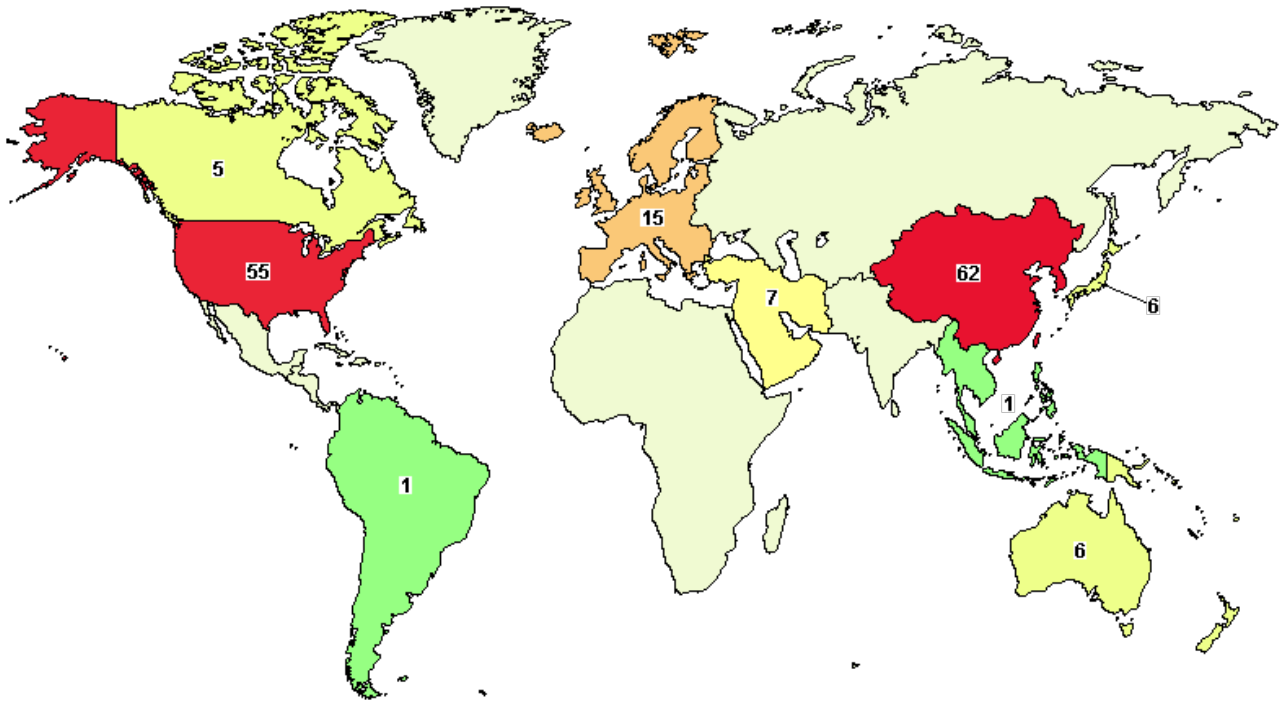
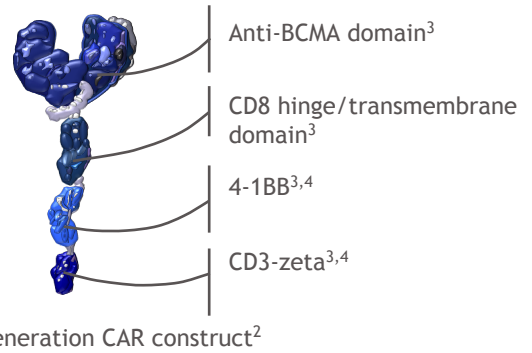
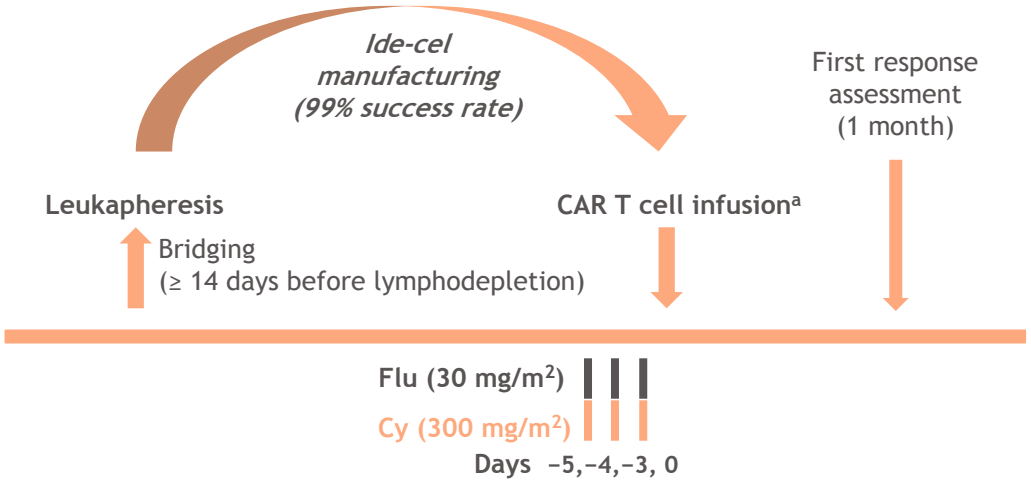


Image adapted from ClinicalTrial.gov (for: CAR T | Multiple Myeloma); available from: https://clinicaltrials.gov/ct2/results/map?term=CAR+T&recrs=abdf&cond=Multiple+Myeloma&map=, accessed September 2022

Ide-cel: KarMMa phase 2 trial[1]
Anti-BCMA CAR-T cell therapy



2nd generation CAR construct[2]



RRMM

- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to an IMiD® agent, PI, and anti-CD38 mAb
- Refractory to last prior therapy per IMWG criteria

Characteristics	All ide-cel treated (n = 128)
Age, median (range), years	61 (33-78)
High-risk cytogenetics, %	35
High tumor burden, %	51
Extramedullary disease, %	39
Any bridging therapies for MM, %	88
Refractory status, %	
Double refractory	89
Triple refractory	84
Penta refractory	26

Ide-cel is approved for patients with RRMM after ≥4 (FDA) or ≥3 (EMA) prior therapies including an IMiD®, a PI, and an anti-CD38 MoAb.

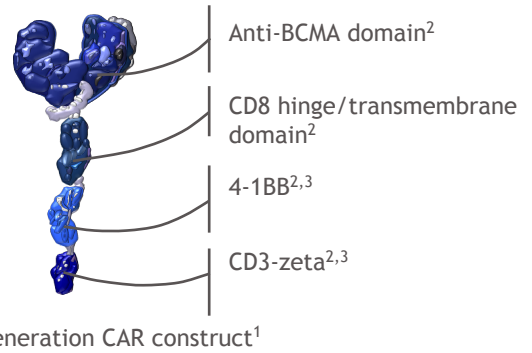
Data cutoff date: January 14, 2020. Values may not add up due to rounding. Data cutoff date: December 2020. Values may not add up due to rounding.

[a]MRD negative defined as <10−5 nucleated cells by next-generation sequencing; only MRD values within 3 months of achieving CR/sCR until PD/death (exclusive) were considered; [b]Defined as ≥PR.

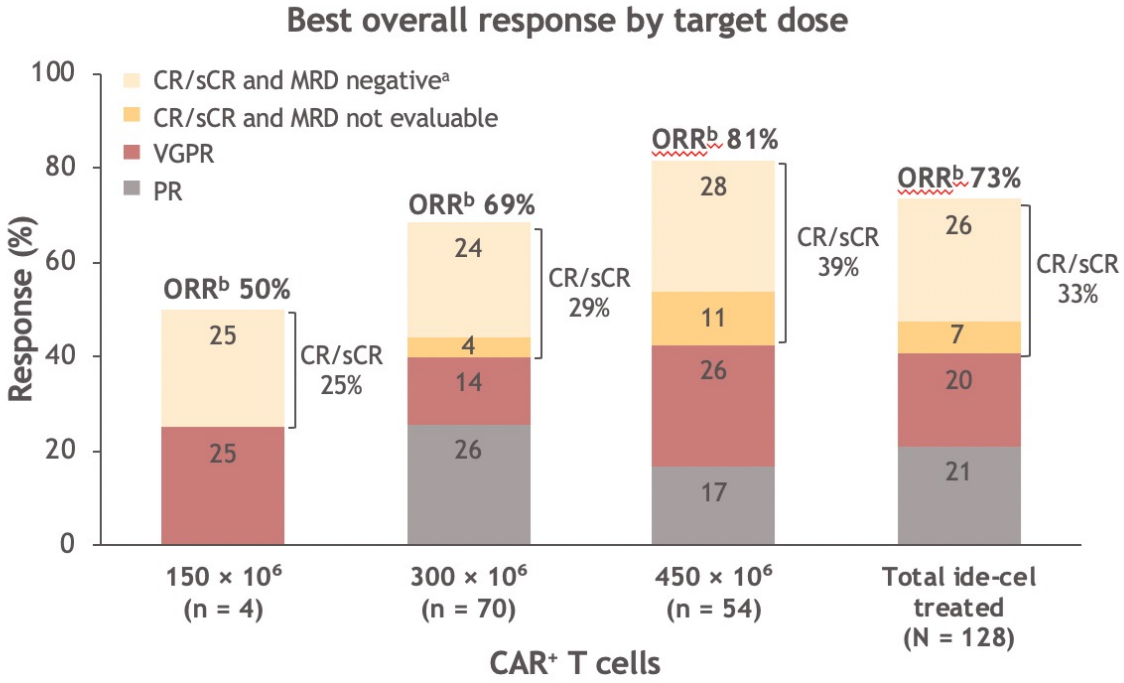
CI, confidence interval; CR, complete response; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory imide drug; MoAb, monoclonal antibody; MRD, minimal residual disease; NE, not estimable; ORR, objective response rate; PD, progressive disease; PI, proteasome inhibitor; PFS, progression-free survival; PR, partial response; RRMM, relapsed/refractory MM; sCR, stringent complete response; VGPR, very good partial response.

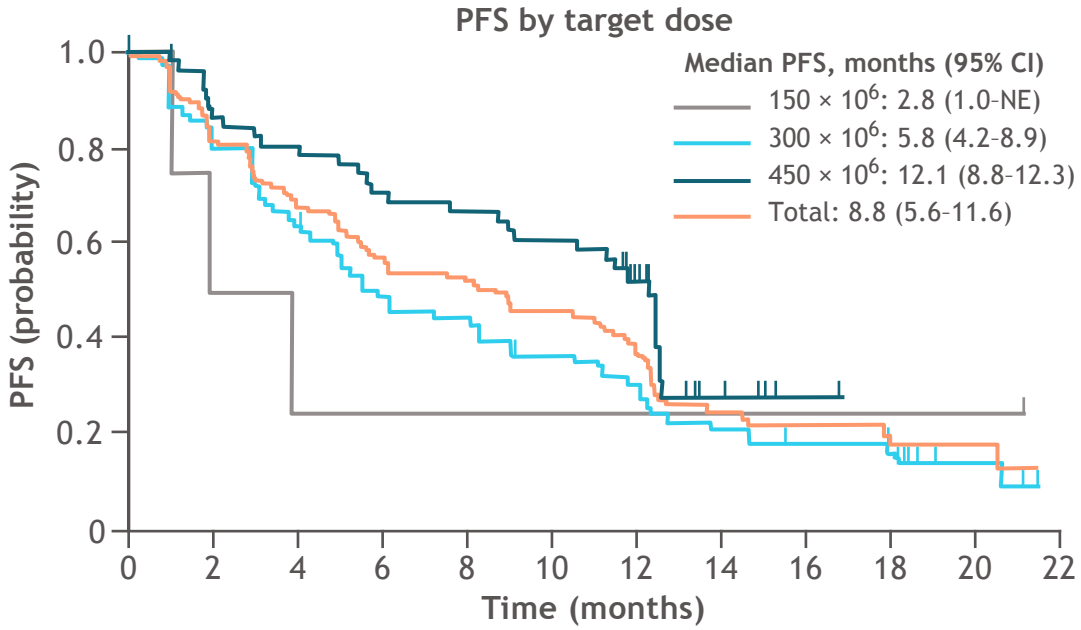
1. NCT03601078. Available at https://clinicaltrials.gov/ct2/show/NCT03601078, accessed September 2022. 2. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 3. van de Donk NWCJ, et al. Lancet Haematol. 2021;8:e446-61. 4. Manier S, et al. Blood Reviews. 2022;54. Munshi NC, et al. N Eng J Med. 2021;384:705-16. Anderson LD, et al. Poster presented at ASCO 2021; abstract 8016.

Ide-cel: KarMMa phase 2 trial[1]
Efficacy results



2nd generation CAR construct[1]





Ide-cel is approved for RRMM patients after ≥4 (FDA) or ≥3 (EMA) prior therapies including an IMiD, a PI, and an anti-CD38 MoAb.

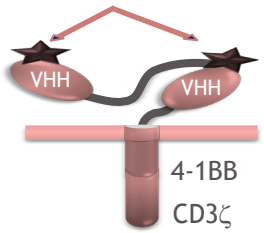
Data cut-off date: 14 January 2020. Values may not add up due to rounding. Data cut-off date: December 2020. Values may not add up due to rounding.

[a]MRD negative defined as <10−5 nucleated cells by next-generation sequencing; only MRD values within 3 months of achieving CR/sCR until PD/death (exclusive) were considered. [b]Defined as ≥ PR.

CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

1. NCT03601078. Available at https://clinicaltrials.gov/ct2/show/NCT03601078, accessed September 2022. 2. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 3. van de Donk NWCJ, et al. Lancet Haematol. 2021;8:e446-61. 4. Manier S, et al. Blood Reviews. 2022;54. Munshi NC, et al. N Eng J Med. 2021;384:705-16. Anderson LD, et al. Poster presented at ASCO 2021; abstract 8016.

Cilta-cel: CARTITUDE-1 phase1b/2[1]

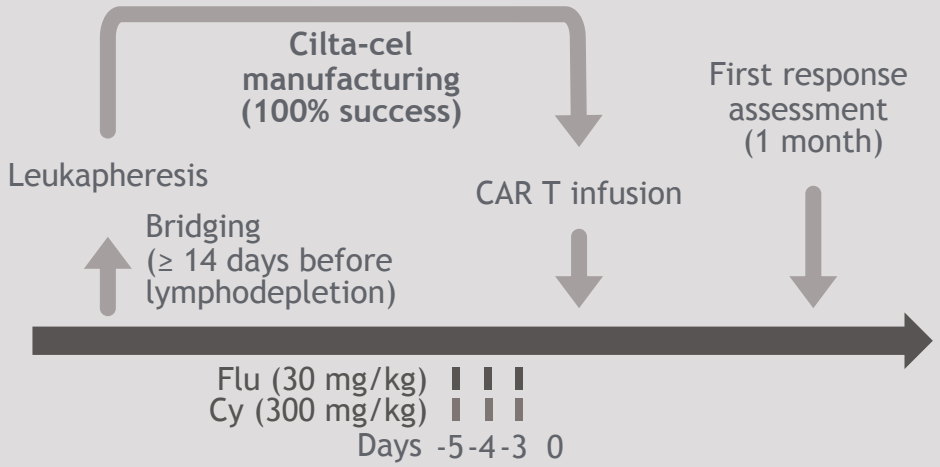


Cilta-cel

Endpoints

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

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



Patient characteristics

Median time since diagnosis, years (range)		5.9 (1.6-18.2)
Median prior antimyeloma regimens, n (range)		6 (3–18)
Extramedullary plasmocytomas, %		13.4
High-risk cytogenetics, %		23.7
Prior autologous SCT, %	1 > 1	89.7 8.2
Any bridging therapies for MM, %		75%
Refractory status, %	Anti-CD38 Ab refractory Triple refractory	99 87.6

18-month F/U

Screened N = 113

Leukapheresed N = 113

Bridging N = 73

Cilta-cel infusion N = 97

Median administered dose: 0.71x10⁶ (0.51-0.95x10⁶) CAR+ viable T cells/kg

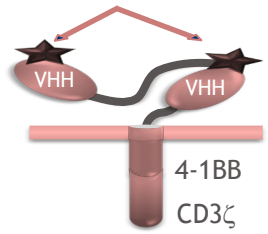
Cilta-cel is approved for RRMM patients after ≥4 (FDA) or ≥3 (EMA) prior therapies including an IMiD, a PI, and an anti-CD38 MoAb.

Cilta-cel, ciltacabtagene autoleucel; F/U, follow-up; PI, proteasome inhibitor. Berdeja JG, et al. Lancet. 2021;398:314-24. Martin T, et al. Oral presentation at ASH 2021; abstract 549. Ciltacabtagene autoleucel. Prescribing information. Date of revision February 2022. (Janssen Biotech and Legend Biotech Corporation). Available from: https://www.fda.gov/media/156560/download. Accessed June 2022. European Medicines Agency. CARVYKTI (Ciltacabtagene Autoleucel) Summary of Product Characteristics. Conditional marketing authorisation. The European Medicines Agency. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation. Accessed June 2022.

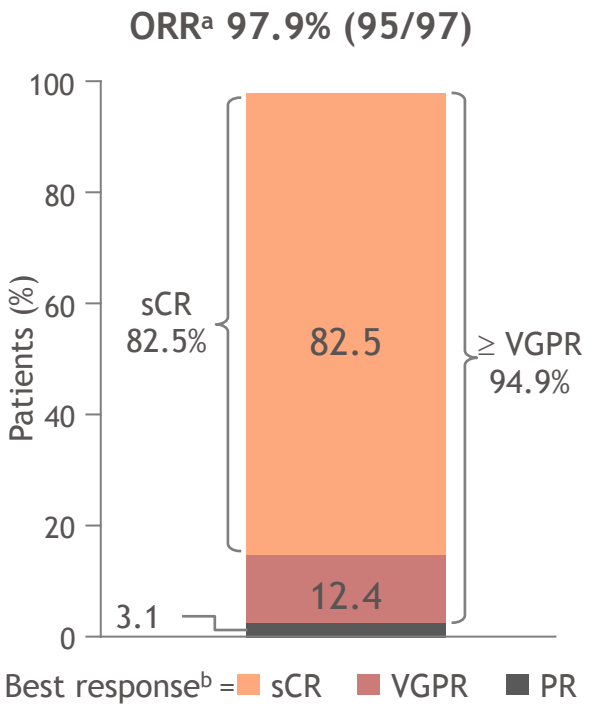
1. NCT03548207. Available at https://clinicaltrials.gov/ct2/show/NCT03548207. Accessed September 2022.

Cilta-cel: CARTITUDE-1 phase1b/2[1]

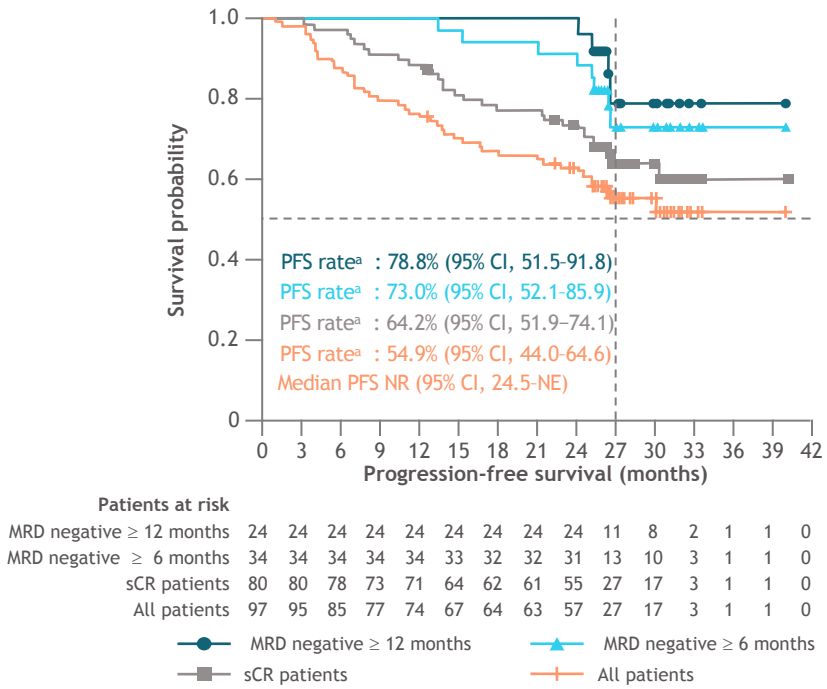
deep responses in RRMM patients treated with cilta-cel

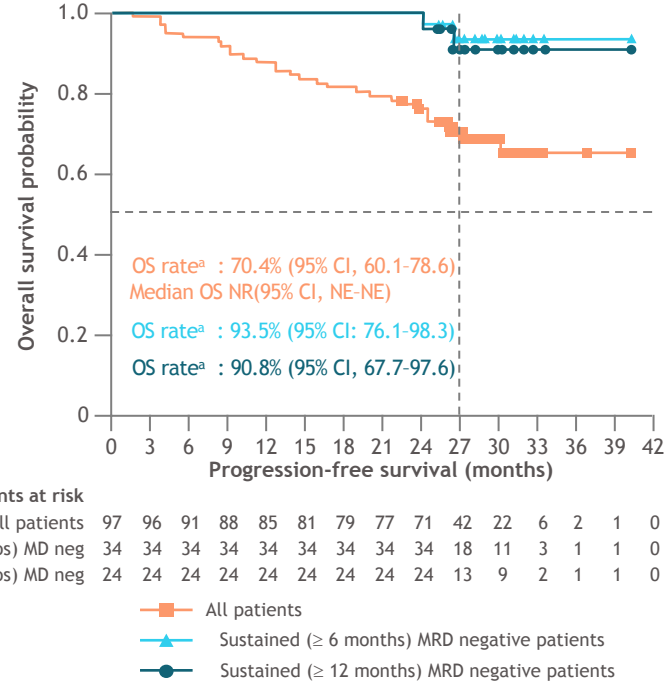


Cilta-cel



Median follow-up: 21.7 months





ASCO 2022 UPDATE	
27-month PFS	54.9% (95% CI, 44.0-64.6)
Median PFS	NR (95% CI, 24.5-NE)

ASCO 2022 UPDATE	
27-month OS	70.4% (95% CI: 60.1-78.6)
Median OS	NR (95% CI, NE-NE)

Cilta-cel is approved for patients with RRMM after after ≥4 (FDA) or ≥3 (EMA) prior therapies including an IMiD, a PI, and an anti-CD38 MoAb.

[a]ORR assessed by independent review committee; [b]No patient had CR or stable disease as best response.

cilta-cel, ciltacabtagene autoleucel; F/U, follow-up; NR, not reached; OS overall survival.

1. NCT03548207. Available at https://clinicaltrials.gov/ct2/show/NCT03548207. Accessed September 2022. 2. Martin T, et al. Oral presentation at ASH 2021. Blood. 2021;138:abstract 549. 3. Berdeja JG, et al. Lancet. 2021;398:314-24. 4. Usmani SZ, et al. Poster presentation at ASCO 2022. J Clin Oncol. 2022;40:abstract 8054.

Safety results from KarMMa and CARTITUDE-1 trials

	Ide-cel treated (N = 128)[1]	Cilta-cel treated (N = 97)[2,3]
CRS		
CRS event, %	84	95
Grade 1 or 2, %[a]	78	90
Grade ≥ 3, %	5.4	5
Median onset (range), days	1 (1–12)	7 (IQR 5–8)
Median duration (range), days	5 (1–63)	4 (IQR 3–6)
NT		
≥ 1 NT event, %	18	21
≥ 3 NT event, %	3	9
Median onset (range), days	2 (1–10)	27 (IQR 16-73)[b] 8 (IQR 6-8)[c]
Median duration (range), days	3 (1–26)	4 (IQR 3–7)[c]
Delayed NT		
All	0	12
Grade 3-4		9
Hematologic AEs, Grade 3/4		
Grade 3–4 neutropenia > 1 month, %	41	95
Grade 3–4 thrombocytopenia > 1 month, %	48	60
Infection		
Infections, any, %	69	58
Infections, Grade 3–4, %	22	20

Long term cytopenias: Ide-cel: > 1 month post-CAR-T cell therapy[1]; Cilta-cel: >1 month from onset of cytopenias[2].

Inter-trial comparisons should not be made because of differences in study design, patient populations, treatment interventions, and duration of follow-up, among others. We cannot make direct comparisons or draw conclusions from one trial to another. For descriptive purposes, safety results for each of the studies mentioned are listed.

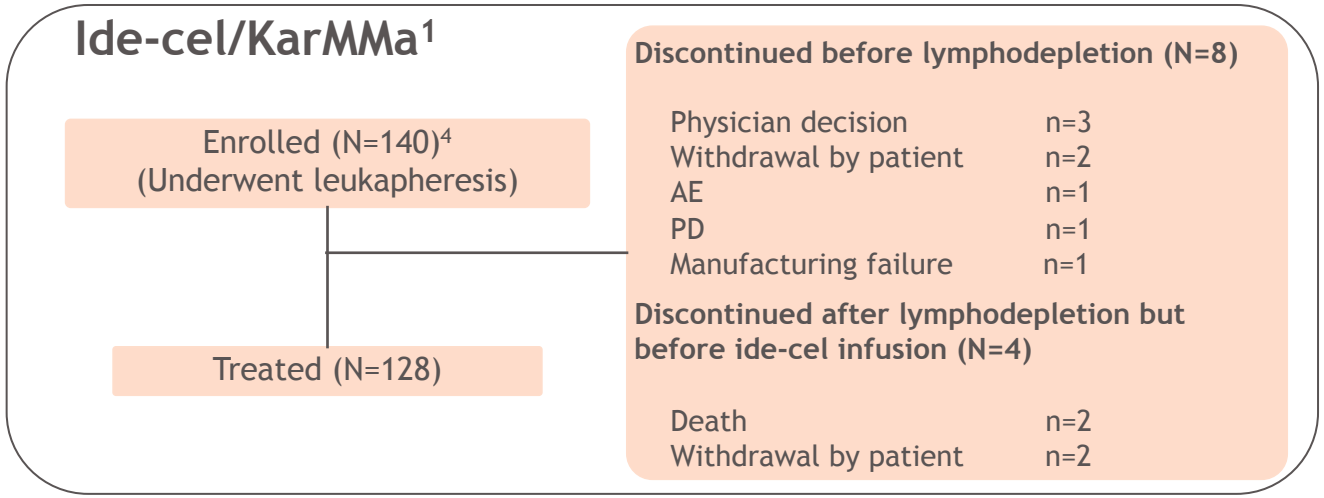
[a]Cytokine release syndrome was graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03; [b]Other NT; cICANS.

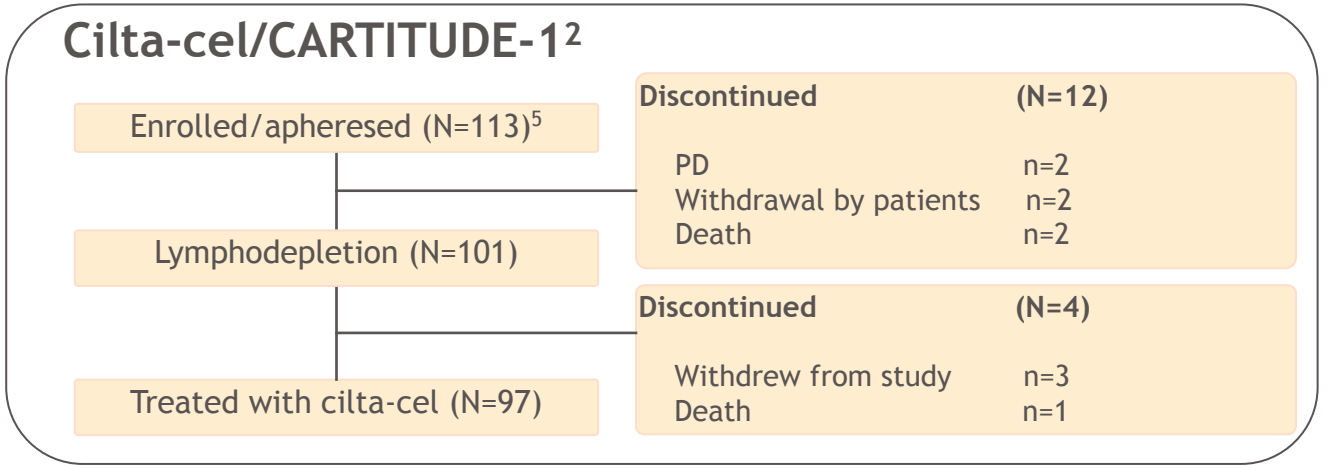
AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NT, neurotoxicity.

1. Munshi NC, et al. N Engl J Med. 2021;384:705-16. 2. Berdeja JG, et al. Lancet. 2021;398:314-24. 3. Martin T, et al. J Clin Oncol. 2022;JCO2200842. 4. U.S. Food and Drug Administration. ABECMA (idecabtagene vicleucel). https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel. Published April 21, 2021. Accessed September 2022.

CAR-T cell therapy: … and challenges

- **Timing:** Around 10% of apheresed patients were not able to receive CAR-T cell therapy, mostly due to death or PD[3]
- **Accessibility:** In the real world, 44% of patients, after 4 prior treatment lines, would be eligible to receive CAR-T cell therapy based on KarMMa study[3]
- **Improved efficacy:** better understanding of resistance disease related (antigen loss, myeloma stem cell), immune-micro-environment (synergistic treatments) and CAR-T cell therapy related (persistence) mechanisms[4,5]
- **Improved safety:** better patient selection, less heavily pretreated patients and reduced tumor burden → less CRS/ICANS[5]





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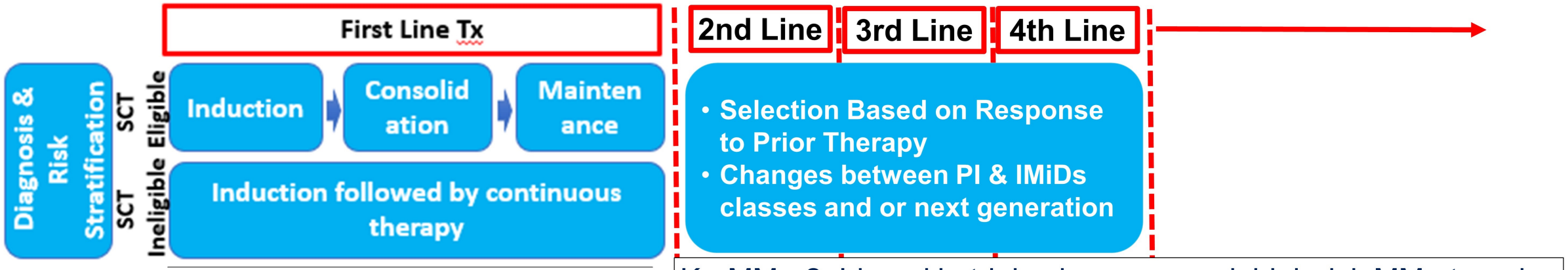
Ongoing Trials



KarMMa-2: Ide-cel in triple class exposed, high risk MM pt, early relapse after 1L or ASCT.

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

CARTITUDE-5: Cilta-cel in newly diagnosed, transplant ineligible

CARTITUDE-4: Cilta-cel vs SOC triplet regimens in randomized, controlled study

CARTITUDE-2: Cilta-cel in multiple exploratory cohorts

CARTITUDE-6: Randomised, controlled study for Cilta-cel vs autologous transplant

KarMMa-7: Ide-cel in RRMM in combination with other therapies

GPRC5D-Targeted CAR T Cells for Myeloma

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	25×10^6 CAR T cells (N=3)	50×10^6 CAR T cells (N=3)	150×10^6 CAR T cells (N=6)	450×10^6 CAR T cells (N=5)	Total (N=17)
Median age (range) — yr	60 (38–76)	50 (39–56)	59 (40–74)	65 (63–73)	60 (38–76)
Male sex — no. (%)	2 (67)	3 (100)	4 (67)	4 (80)	13 (76)
High-risk cytogenetic feature — no. (%)†	3 (100)	2 (67)	3 (50)	5 (100)	13 (76)
Extramedullary plasmacytoma — no. (%)	3 (100)	1 (33)	4 (67)	0	8 (47)
Nonsecretory myeloma — no. (%)	2 (67)	0	1 (17)	0	3 (18)
Previous lines of therapy — median (range)	6 (6–8)	5 (4–8)	7 (5–14)	6 (5–12)	6 (4–14)
Disease refractory to last line of therapy — no. (%)	3 (100)	3 (100)	5 (83)	3 (60)	14 (82)
Penta-exposed — no. (%)‡	3 (100)	3 (100)	6 (100)	5 (100)	17 (100)
Triple-refractory disease — no. (%)§	3 (100)	3 (100)	6 (100)	4 (80)	16 (94)
Previous autologous transplantation — no. (%)	3 (100)	3 (100)	6 (100)	5 (100)	17 (100)
Previous allogeneic transplantation — no. (%)	0	2 (67)	1 (17)	0	3 (18)
Previous BCMA therapy — no. (%)¶	1 (33)	1 (33)	4 (67)	4 (80)	10 (59)
Previous CAR T-cell therapy — no. (%)	0	1 (33)	3 (50)	4 (80)	8 (47)
Bridging therapy — no. (%)	3 (100)	3 (100)	6 (100)	4 (80)	16 (94)
Disease refractory to bridging therapy — no./total no. (%)	3/3 (100)	3/3 (100)	5/6 (83)	4/5 (80)	15/16 (94)

* BCMA denotes B-cell maturation antigen, and CAR chimeric antigen receptor.
† High-risk cytogenetic features included del(17p), t(4;14), t(14;16), and 1q gain.
‡ Penta-exposed patients were those who had received previous treatment with two proteasome inhibitors, two immunomodulatory drugs, and one anti-CD38 antibody.
§ Triple-refractory disease was defined as refractory to a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody.
¶ Included are BCMA-targeted antibody–drug conjugates, bispecific antibodies, and CAR T-cell therapies.

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Clinical Responses in All Patients and in Patients with or without Previous BCMA-Directed Therapies.

Table 3. Clinical Responses in All Patients and in Patients with or without Previous BCMA-Directed Therapies.

Response	All Patients		Previous BCMA Therapies		No Previous BCMA Therapies	
	All Dose Levels (N=17)	25×10^6–150×10^6 CAR T Cells (N=12)	All Dose Levels (N=10)	25×10^6–150×10^6 CAR T Cells (N=6)	All Dose Levels (N=7)	25×10^6–150×10^6 CAR T Cells (N=6)
	number (percent)					
Partial response or better	12 (71)	7 (58)	7 (70)	3 (50)	5 (71)	4 (67)
Very good partial response or better	10 (59)	5 (42)	6 (60)	2 (33)	4 (57)	3 (50)
Complete response or better	6 (35)	3 (25)	4 (40)	2 (33)	2 (29)	1 (17)
Negativity for MRD in bone marrow*	8 (47)	6 (50)	3 (30)	2 (33)	5 (71)	4 (67)

* Negativity for minimal residual disease (MRD) in bone marrow was assessed by means of 10-color flow cytometry with a sensitivity of 1 in 10^5 at 4 weeks after CAR T-cell therapy, at the occurrence of a complete response, and as clinically indicated.

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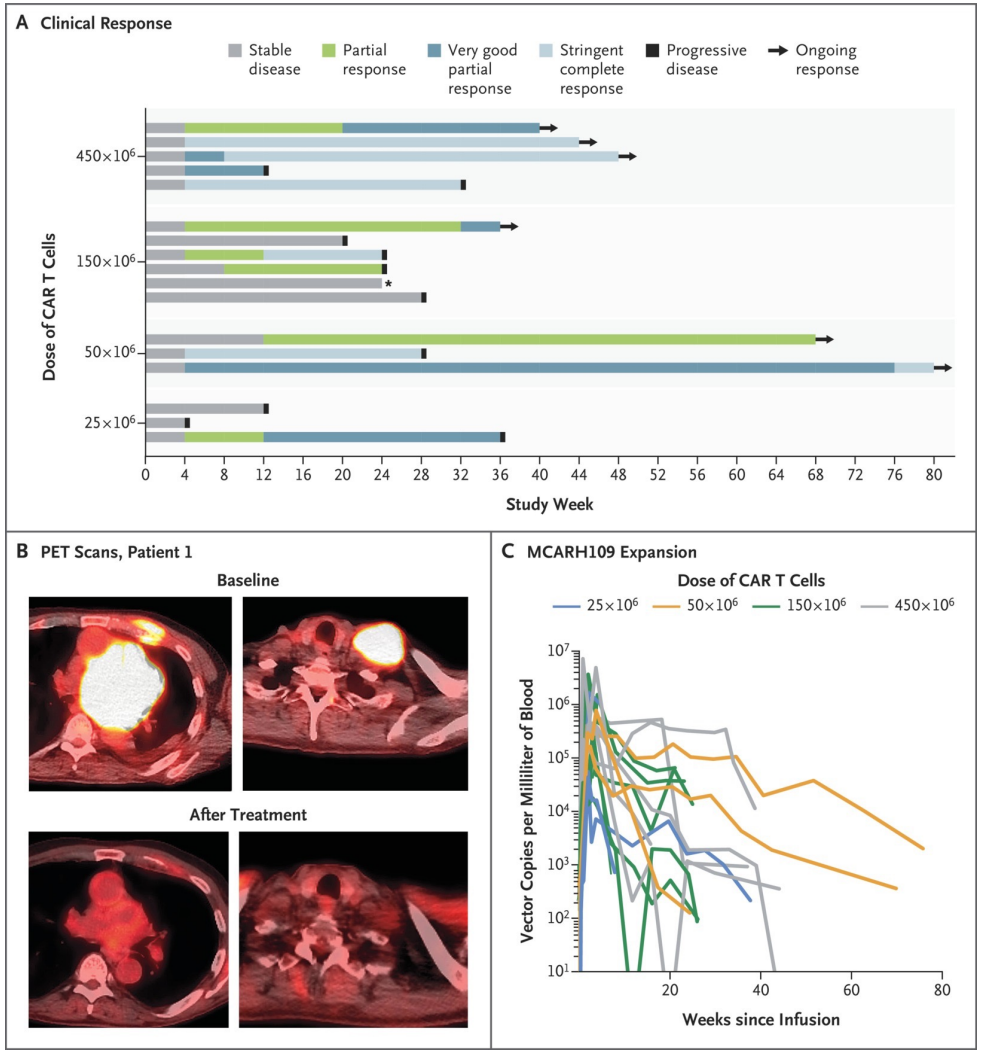
Clinical Responses to GPRC5D-Targeted Chimeric Antigen Receptor (CAR) T-Cell Therapy.



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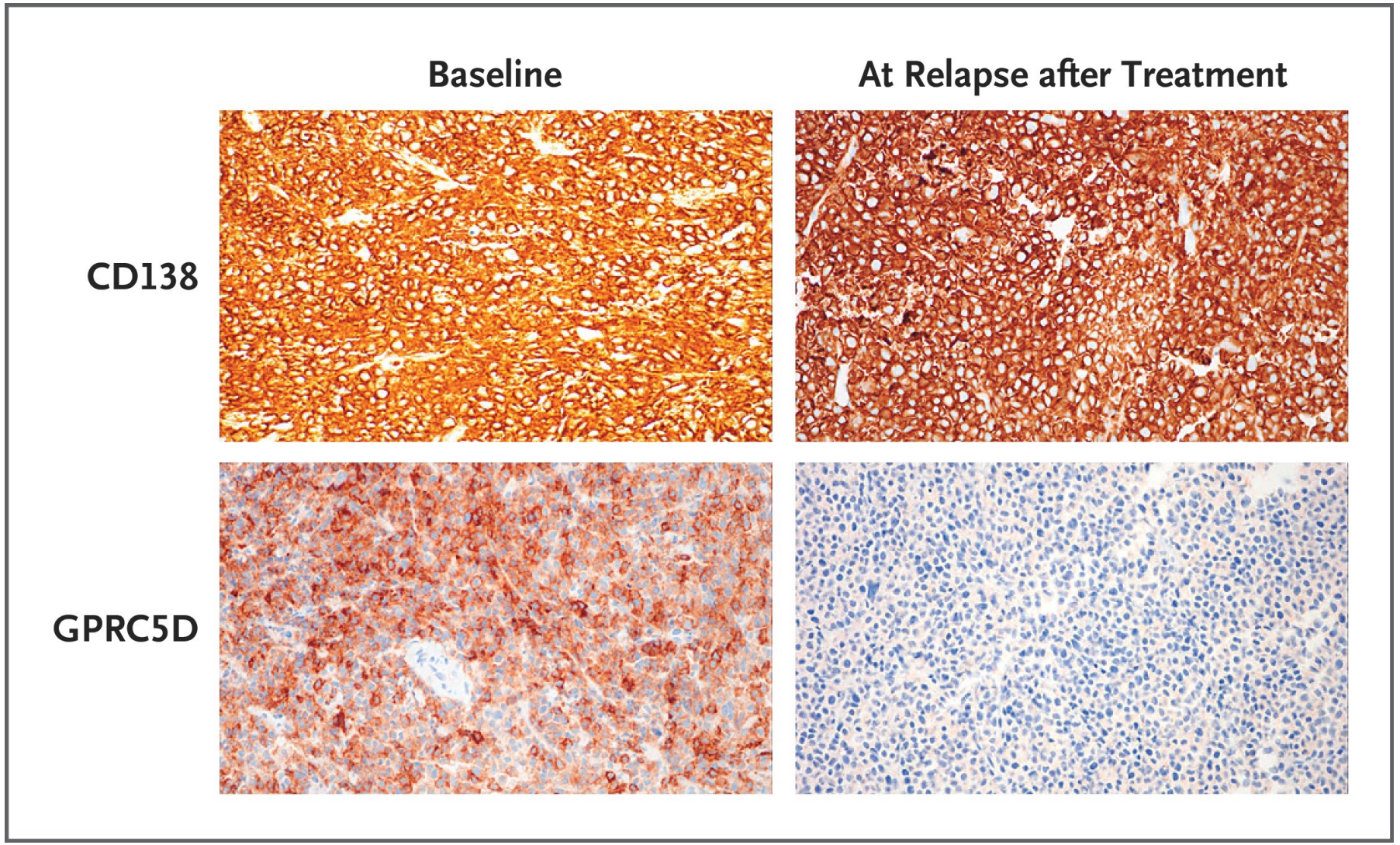
Loss of GPRC5D on Immunohistochemical Analysis at Relapse after MCARH109 Infusion.



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Adverse Events.

Table 2. Adverse Events.*

Adverse Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
			number (percent)		
Cytokine release syndrome	15 (88)	7 (41)	7 (41)	0	1 (6)
Nail changes	11 (65)	11 (65)	0	0	0
Fatigue	7 (41)	6 (35)	1 (6)	0	0
Nausea	4 (24)	4 (24)	0	0	0
Infections	3 (18)	0	1 (6)	2 (12)	0
Rash	3 (18)	3 (18)	0	0	0
Cerebellar disorder	2 (12)	0	0	2 (12)	0
Dysgeusia	2 (12)	2 (12)	0	0	0
Immune effector cell–associated neurologic syndrome	1 (6)	0	0	0	1 (6)
Macrophage activation syndrome	1 (6)	0	0	0	1 (6)
Pruritus	1 (6)	0	1 (6)	0	0
Pain	1 (6)	0	1 (6)	0	0
Bleeding	1 (6)	0	1 (6)	0	0
Dry mouth	1 (6)	1 (6)	0	0	0
Dizziness	1 (6)	1 (6)	0	0	0
Allergic reaction	1 (6)	1 (6)	0	0	0
Lymphocyte count decreased	17 (100)	0	0	0	17 (100)
Neutropenia	17 (100)	0	0	5 (29)	12 (71)
White-cell count decreased	17 (100)	0	0	5 (29)	12 (71)
Thrombocytopenia	15 (88)	3 (18)	1 (6)	7 (41)	4 (24)
Hypocalcemia	15 (88)	1 (6)	10 (59)	3 (18)	1 (6)
Anemia	15 (88)	1 (6)	7 (41)	7 (41)	0
Hypoalbuminemia	14 (82)	6 (35)	8 (47)	0	0
Elevated AST level	11 (65)	8 (47)	0	2 (12)	1 (6)
Elevated partial-thromboplastin time	10 (59)	9 (53)	1 (6)	0	0
Elevated ALT level	7 (41)	3 (18)	3 (18)	1 (6)	0
Hypokalemia	6 (35)	6 (35)	0	0	0
Decreased fibrinogen	6 (35)	2 (12)	3 (18)	1 (6)	0
INR increased	5 (29)	3 (18)	2 (12)	0	0
Hypomagnesemia	3 (18)	3 (18)	0	0	0
Elevated creatinine level	3 (18)	2 (12)	0	1 (6)	0
Hypernatremia	3 (18)	3 (18)	0	0	0
Elevated alkaline phosphatase level	2 (12)	2 (12)	0	0	0
Hyperkalemia	1 (6)	0	0	0	0

* Shown are events that were considered by the investigator to be possibly, probably, or definitely related to lymphodepleting chemotherapy or MCARH109. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and INR international normalized ratio.

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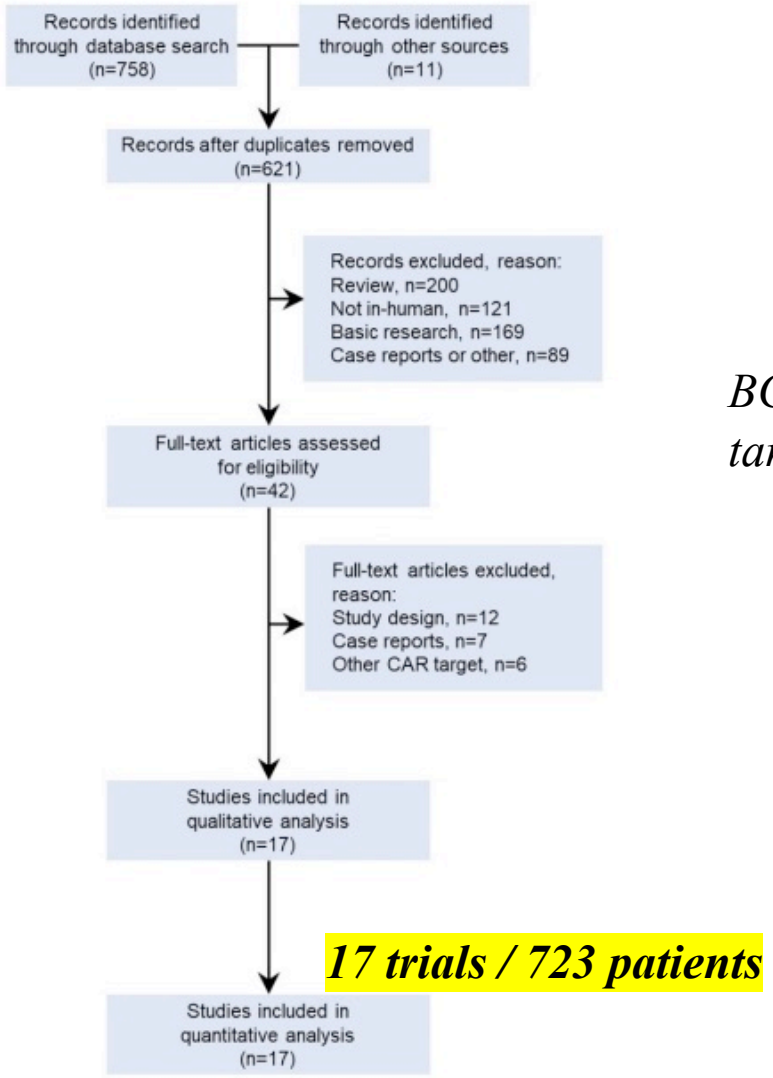
Comparison of anti-GPRC5D CAR T-cell studies

	OriCAR-017	MCARH109
Characteristics		
Enrolled patients	12	17
Origin	China	USA
CAR T design	• V_HH1 and V_HH2 DNA • lentiviral plasmid pCore-Ori • human EF-1α promoter • signal peptide • CD8 hinge • CD8 transmembrane domain • 4-1BB costimulatory domain • CD3ζ signaling domains • Ori transmembrane signaling domain	• second-generation human B-cell–derived GPRC5D single-chain variable fragment • 4-1BB costimulatory domain • CD3ζ signaling domain • Lentiviral vector • CD4+/8+ ratio 1:1
Median lines of pretreatment	6	6
Pior autograft	20%	100%
Prior CAR T-cell therapy	50%	47%
High-risk cytogenetics	60%	76%
Safety		
Any CRS	100%	88%
Grade 3-4 CRS	0%	6%
Any ICANS	0%	6%
Grade 3-4 ICANS	0%	6%
Cerebellar disorder	0%	12%
Nail changes	30%	65%
Efficacy		
Overall response	100%	71%
MRD-negative	100%	47%
Median follow-up	8 months	10 months

Gagelmann N, Brudno J
Lancet Haematol 2023

Impact of high-risk disease on efficacy of CAR-T cell therapy for multiple myeloma: a meta-analysis



17 trials / 723 patients

BCMA most frequent single target / Four trials used tandem CARs (BCMA + CD38 and BCMA and CD19)

Gagelmann N et al. Haematologica 2023 Feb 231

Impact of high-risk disease on efficacy of CAR-T cell therapy for multiple myeloma: a meta-analysis

Definitions:

cytogenetic high-risk: presence of at least either **del(17p), t(14;16) or t(4;14)**

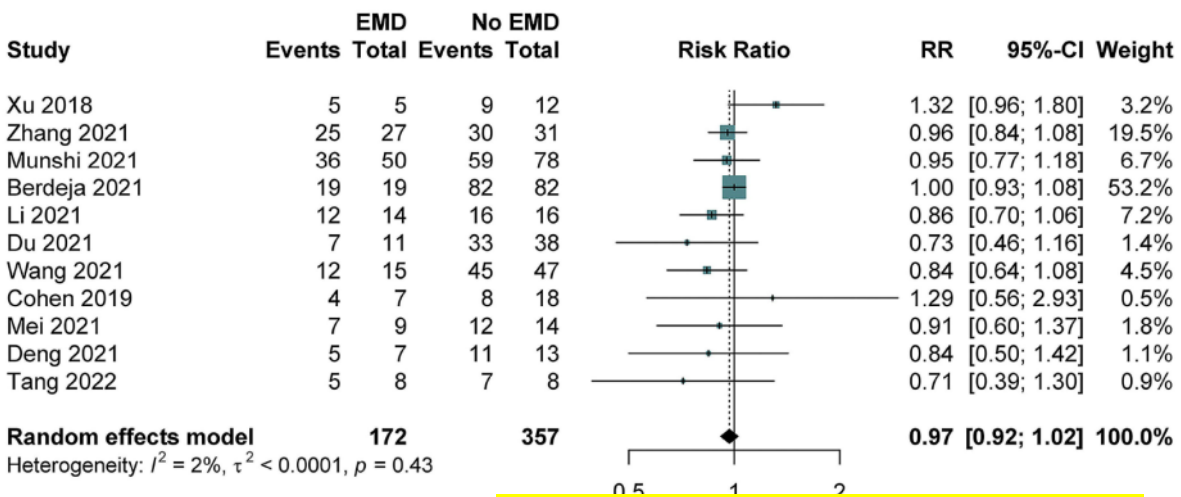
disease risk: presence of extramedullary disease (**EMD**) or a revised International Staging System (**R-ISS) stage III**

Gagelmann N et al. Haematologica 2023 Feb 231

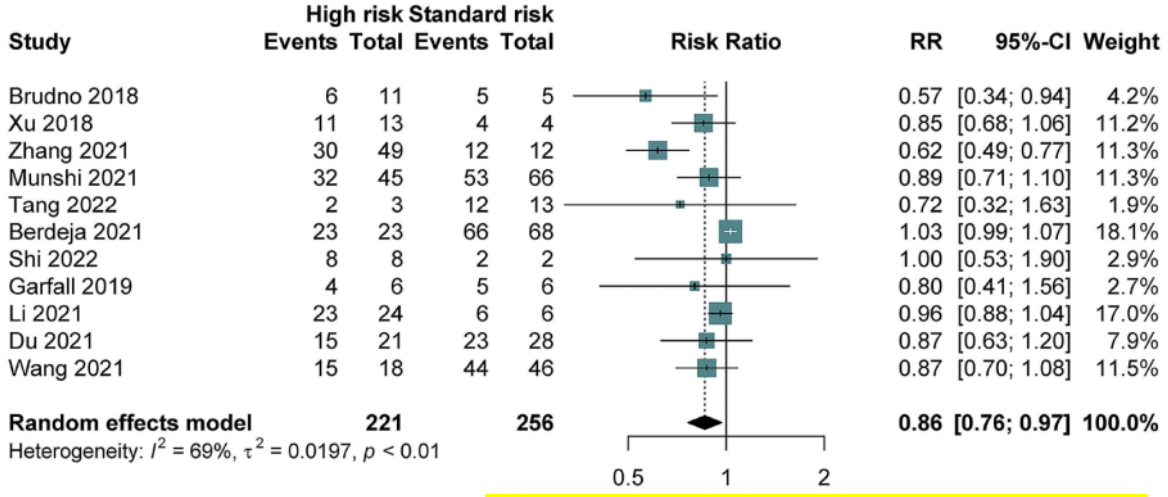
Impact of high-risk disease on efficacy of CAR-T cell therapy for multiple myeloma: a meta-analysis

Results for overall response rate

A



0.97 (95% CI, 0.92-1.02; P=0.26)



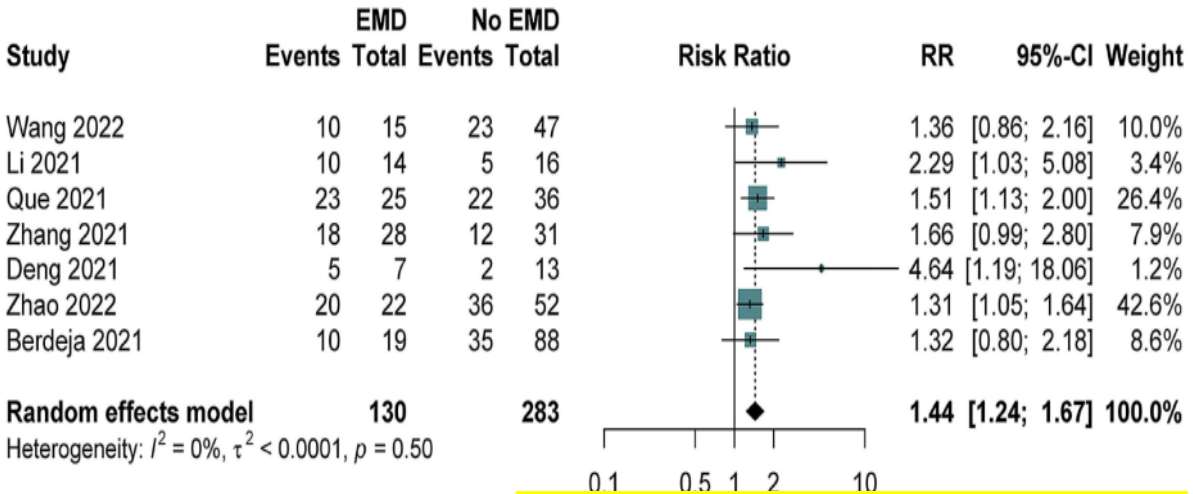
0.86 (95% CI, 0.76-0.97); P=0.01)

RR, risk ratio; CI, confidence interval.

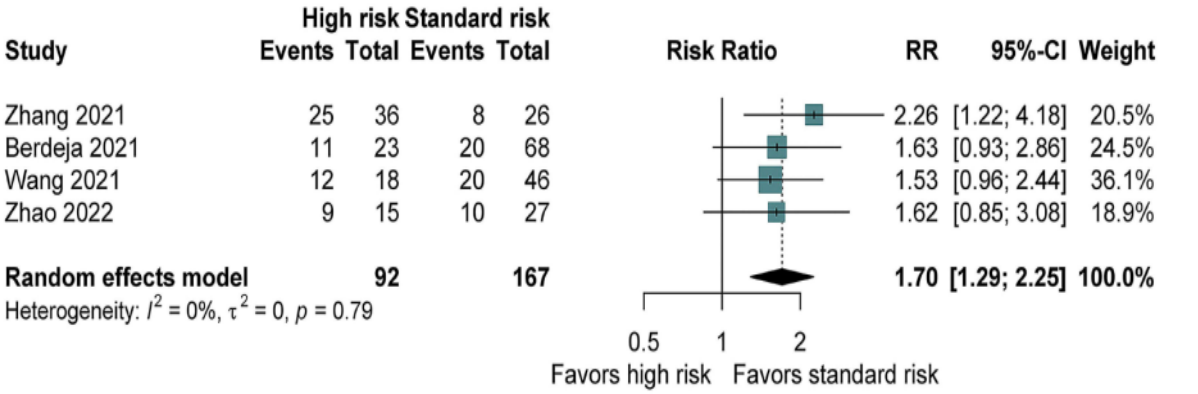
Gagelmann N et al. Haematologica 2023 Feb 231

Impact of high-risk disease on efficacy of CAR-T cell therapy for multiple myeloma: a meta-analysis

Results for progression-free survival



1.44 (95% CI, 1.24-1.67; P<0.001)



1.70 (95% CI, 1.29-2.25; P<0.001)

RR, risk ratio; CI, confidence interval.

Gagelmann N et al. Haematologica 2023 Feb 231

How to improve overall clinical outcomes?

- **Optimize CAR T product?**
  - Dual epitope or dual antigen binding
  - Novel costimulatory domains
  - Transposon-based
  - Suicide genes/safety switches
  - Gene editing (e.g. PD-1 knockdown, allogeneic CARTs)
- **Optimize manufacturing**
  - Defined CD4:CD8 ratios? PI3K inhibitors?
- **Optimize target expression**
  - Gamma-secretase inhibitors for BCMA
- **Rational combinations**
  - Immune checkpoint inhibitors? IMiDs? Other CAR T cells?
- **Optimize infusion schedule**
  - Serial infusions? Retreatment at progression?
- **Patient selection**
  - Only high expressors? Earlier lines of therapy? High-risk?

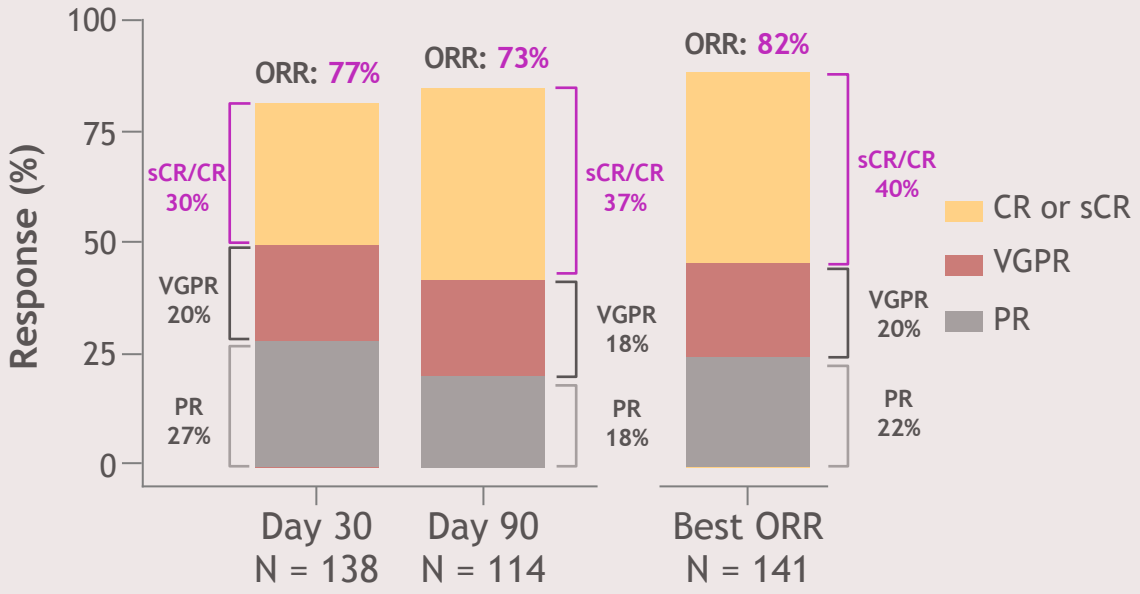
Dual-targeted CAR-T cell therapy	Dose of CAR-T cells	No. of patients	Median follow-up	Response	Toxicities	Reference
BCMA/CD38 bispecific CAR-T cells	4.0×10^6/kg	23 R/R MM patients (39% of them with EMD)	9 months	ORR 87%, sCR 52% PR 33%	CRS (87%), CRES (0%), cytopenia (96%), infections (22%)	Mei H et al. (30)
BCMA/CD38 bispecific CAR-T cells	median dose: 2.1×10^6/kg (range: $0.5\text{-}10.0 \times 10^6$/kg)	16 R/R MM patients (50% of them with EMD)	11.5 months	ORR 88%, CR 81%, PR 6%	CRS (75%), cytopenia (100%), HLH (6%), infections (38%)	Tang Y et al. (31)
BCMA/CS1 bispecific CAR-T cells	0.75×10^6/kg, 1.5×10^6/kg, 3.0×10^6/kg	16 R/R MM patients(19% of them with EMD)	290 days	ORR 100%, sCR 31% PR 13%	CRS (38%) CRES (0%)	Li C et al. (34)
Combined infusion of anti-BCMA and anti-CD38 CAR-T cells	2×10^6/kg, 2×10^6/kg, respectively	22 R/R MM patients (14% of them with EMD)	24 months	ORR 91%, CR 55%,	CRS (100%), CRES (14%), cytopenia (100%) infections (17%)	Zhang H et al. (25)
Combined infusion of anti-BCMA and anti-CD19 CAR-T cells	1×10^6/kg, 1×10^6/kg, respectively	21 R/R MM patients	268 days	ORR 95%, CR 14%, PR 14% sCR 43%	CRS (90%), cytopenia (95%), B cell aplasia (100%), lung infections (5%)	Yan Z et al. (26)

Dual-targeted CAR-T cell therapy	Dose of CAR-T cells	No. of patients	Median follow-up	Response	Toxicities	Reference
Combined infusion of anti-BCMA and anti-CD19 CAR-T cells	1×10^6/kg, 1×10^6/kg, respectively	62 R/R MM patients (24% of them with EMD)	21.3 months	ORR 92%, CR 60%, PR 21%	CRS (95%), CRES (11%), cytopenia (98%), B cell aplasia (30%), infections (45%)	Wang Y et al. (27)
Combined infusion of anti-BCMA and anti-CD19 CAR-T cells after auto-HSCT	5×10^7/kg, 1×10^7/kg, respectively	10 high-risk NDMM patients	42 months	ORR 100%, CR 10% sCR 90%	CRS (100%), CRES (0%), cytopenia (100%), infections (100%)	Shi X et al. (35)
Combined infusion of anti-BCMA and anti-CD19 CAR-T cells	5×10^8 cells, 5×10^8 cells, respectively	10 MM patients with relapse (Phase A) and 20 high-risk MM patients (Phase B, as a randomized controlled trial)	follow-up ranging from 248 to 966 days in Phase B	ORR 23%, CR 6% PR 6%	CRS (90%), CRES (3%),	Garfall AL et al. (32)
Combined infusion of anti-BCMA and anti-CD19 FasTCAR-T Cells	1×10^5/kg, 2×10^5/kg, 3×10^5/kg	13 high-risk NDMM patients	5.3 months	ORR 95% sCR 69%	CRS (23%) CRES (0%)	Du J et al. (33)

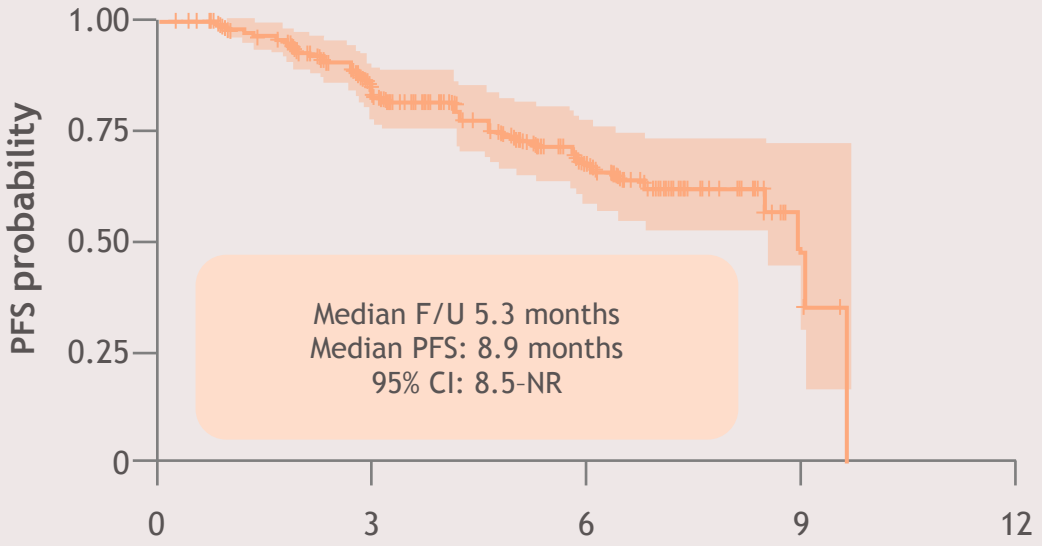
CAR T cell therapy: hopes…

Real-world outcomes of patients treated with ide-cel

Day 30, 90, and best overall tumor responses



Real world PFS



Real world data with Ide-cel mirrors data from clinical trial[1]

1. Hansen DK, et al. Poster presented at IMS 2022:abstract OAB-004. J Clin Oncol 2023

RESEARCH SUMMARY

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Rodriguez-Otero P et al. DOI: 10.1056/NEJMoa2213614

CLINICAL PROBLEM

Idecabtagene vicleucel (ide-cel) — a chimeric antigen receptor (CAR) T-cell therapy that targets B-cell maturation antigen expressed on myeloma cells — is approved in the United States for the treatment of relapsed or refractory multiple myeloma after the receipt of at least four previous lines of therapy. Its efficacy in less heavily pretreated disease is unclear.

CLINICAL TRIAL

Design: An international, phase 3, open-label, randomized trial assessed the efficacy and safety of ide-cel, as compared with standard regimens, in adults with triple-class–exposed relapsed and refractory multiple myeloma who had received two to four lines of therapy previously and who had disease refractory to the most recent regimen.

Intervention: 386 patients whose previous lines of therapy included daratumumab, immunomodulatory agents, and proteasome inhibitors and who had progressive disease within 60 days after completing the last therapy were assigned in a 2:1 ratio to receive a single infusion of ide-cel or to one of five standard regimens. The primary end point was progression-free survival. Key secondary end points were overall response (partial response or better) and overall survival.

RESULTS

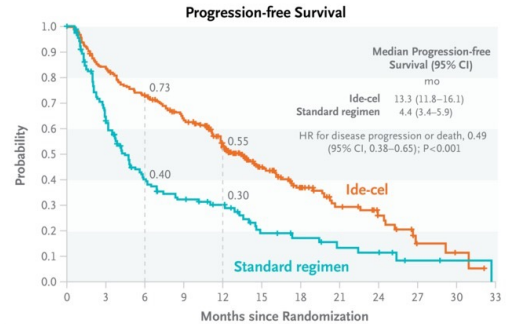
Efficacy: At a median follow-up of 18.6 months, progression-free survival was significantly longer in the ide-cel group than in the standard-regimen group.

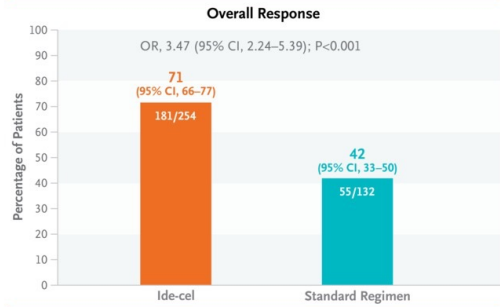
Safety: Grade 3 or 4 adverse events occurred more often with ide-cel than with standard regimens. Most ide-cel recipients had cytokine release syndrome, which usually was low-grade. Neurotoxic effects also occurred in the ide-cel group.

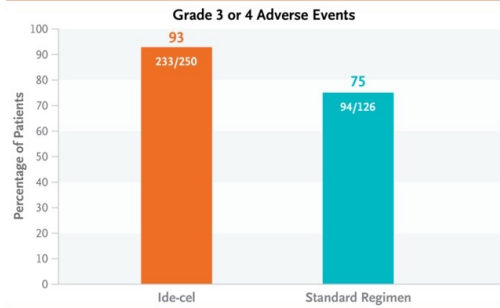
LIMITATIONS AND REMAINING QUESTIONS

- The proportion of Black patients was not balanced between the groups.
- The investigators' choice of standard regimens may have introduced treatment heterogeneity in that group.
- Mechanisms underlying ide-cel resistance remain unknown.

Links: Full Article | NEJM Quick Take





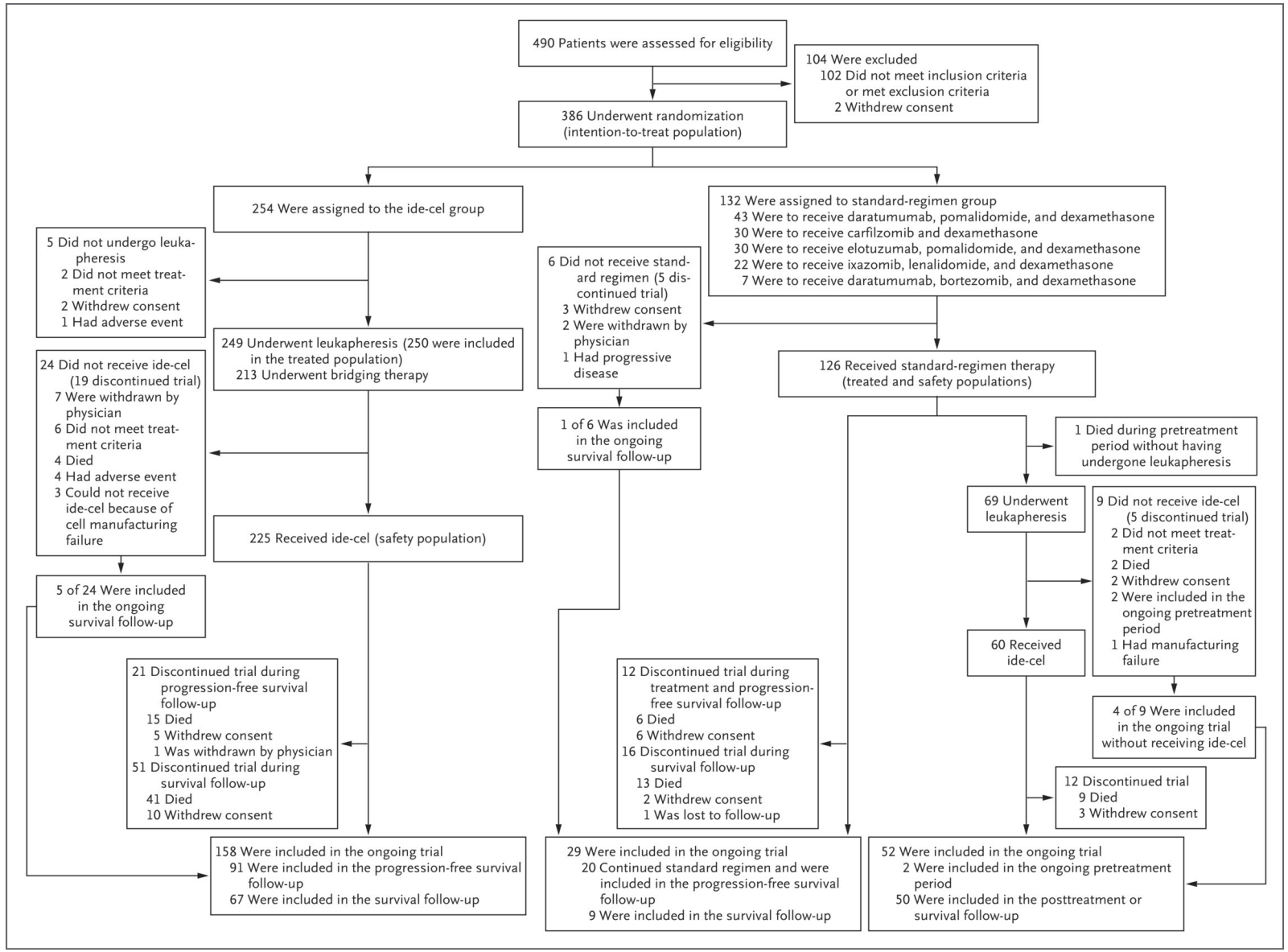


CONCLUSIONS

Among adults with heavily pretreated relapsed and refractory multiple myeloma who had received two to four lines of therapy previously, the CAR T-cell therapy ide-cel led to significantly longer progression-free survival than standard regimens.

P Rodriguez-Otero et al. N Engl J Med 2023

Randomization, Treatment, and Follow-up of the Patients.



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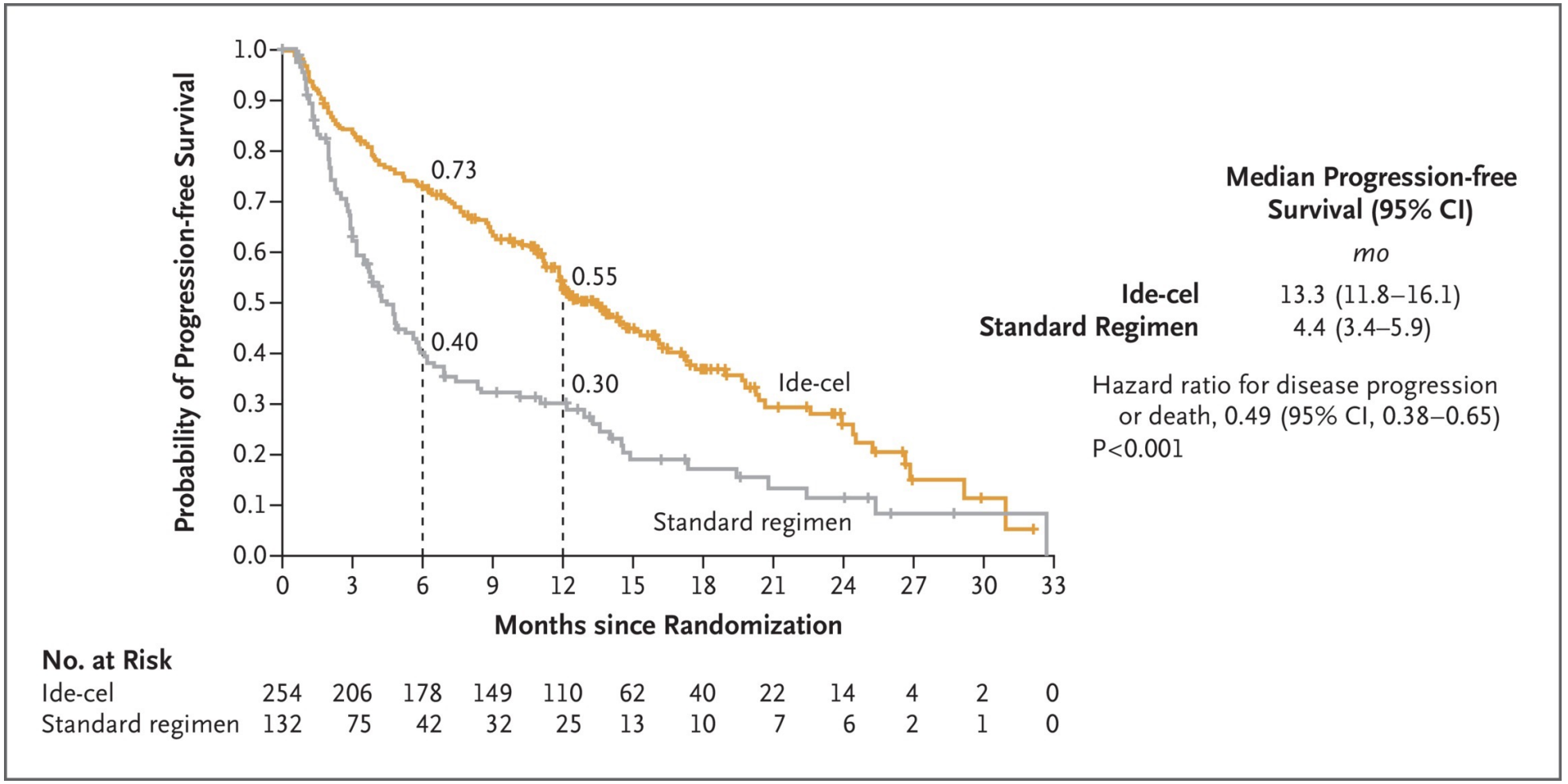
Progression-free Survival (Intention-to-Treat Population)



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Disease	CAR T therapy Approved	Date of Approval	Target	Costimulatory Domain	Pivotal Trial
Large B cell Lymphoma	**Axicabtagene ciloleucel (Axi-cel)** **Tisagenlecleucel (Tisa-cel)** **Lisocabtagene maraleucel (Liso-cel)**	Oct 2017 May 2018 Feb 2021	CD19 CD19 CD19	CD28-CD3zeta 41BB-CD3zeta 41BB-CD3zeta	ZUMA-1[1,2] JULIET[3] TRANSCEND[4]
Mantle Cell Lymphoma	**Brexucabtagene autoleucel (Brexu-cel)**	July 2020	CD19	CD28-CD3zeta	ZUMA-2[5]
Follicular Lymphoma	**Axicabtagene ciloleucel (Axi-cel)** **Tisagenlecleucel (Tisa-cel)**	Mar 2021 May 2022	CD19 CD19	CD28-CD3zeta 41BB-CD3zeta	ZUMA-5[6] ELARA[11]
Multiple Myeloma	**Idecabtagene vicleucel (Ide-cel)** **Ciltacabtagene autoleucel (Cilta-cel)**	Mar 2021 Feb 2022	BCMA BCMA	41BB-CD3zeta 41BB-CD3zeta	KarMMa[7] CARTITUDE-1[10]
Pediatric ALL	**Tisagenlecleucel (Tisa-cel)**	Aug 2017	CD19	41BB-CD3zeta	ELIANA[8]
Adult ALL	**Brexucabtagene autoleucel (Brexu-cel)**	Oct 2021	CD19	CD28-CD3zeta	ZUMA-3[9]

[1] Neelapu et al. NEJM 2017 [2]Locke et al. Lancet Oncol 2019 [3] Schuster et al. NEJM 2019 [4] Abramson et al. Lancet 2020 [5] Wang et al. NEJM 2020
[6] Jacobson et al. ASH 2020 [7] Munshi et al NEJM 2021 [8] Maude et al NEJM 2018
[9] Shah et al Lancet 2021 [10] Berdeja et al Lancet 2021 [11] Fowler et al Nat Med 2022

Patient Assessment for CAR T Therapy: Factors Considered in Initial Studies

- Each institution can develop their own specific guidelines based on experience within framework of FDA label

Factors to consider when selecting patients for CAR T therapy:

1. Age
2. Organ function
3. ECOG PS
4. Underlying neurological disorders, including seizures
5. Active infections
6. CNS disease
7. Concomitant medications/comorbidities, prior allo-HSCT

CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status.

Practice Changes Based on Post-Marketing Data

Post-marketing data has shown a shift toward a more inclusive approach in the following areas:

1. Biologic age/frailty/ECOG PS rather than chronologic age
2. More latitude in organ function, especially in GFR
3. Patients with aggressive disease requiring bridging therapy are now considered eligible
4. Patients with active CNS disease have been treated in case reports
5. Prior and currently controlled hepatitis and HIV are no longer absolute contraindications
6. Patients post-allogeneic stem cell transplant, without active GvHD, have been treated with CARs
7. Availability of previously collected autologous cells should be explored for pts with poor marrow function

CAR, chimeric antigen receptor; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; GvHD, graft versus host disease; HIV, human immunodeficiency virus.

Efficacy in real-world studies (22000)

	LBCL	ALL	MM
ORR	55%-82%	NA	32%-83%
CR	32%-64%	86% (95% CI 80.6-89.7)	34%-35%
12-month PFS	32%-45%	NA	NA
12-month OS	54%-64%	NA	56%

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

They surveyed 1 CAR-T expert (director of MM and/or CAR-T program) each from 20 centers (selected for adequate geographic representation of the highest-volume MM CAR-T therapy centers across the US

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

The first section assessed current use and prioritization of ethical principles for slot allocation, and the second section addressed organization and the process of patient selection.

The median year of the earliest CAR-T infusion (SOC/trial) was 2017 (range, 2010 to 2019).

In 2021, 13/17 centers treated more than 50 patients with MM (SOC/trial) (All centers reported no major decrease in CAR-T practice volume in the previous year despite the COVID-19 pandemic)

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

A median of **1 ide-cel slot was allocated per month** per center,

and 15 centers were allocated 2 slots per month (range, 0 to 4/month/center).

However, the median number of patients per center on the waitlist since ide-cel approval was 20 per month (range, 5 to 100).

patients remained on the waitlist for a median of 6 months prior to leukapheresis (range, 2 to 8).

results reported across 14 centers showed that **approximately 25% of patients received a leukapheresis slot for commercial CAR-T therapy, 25% enrolled on another non-CAR-T clinical trial, 25% enrolled on a CAR-T clinical trials, and approximately 25% died or enrolled in hospice**

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

Criterium	Numbers of Centers
availability of alternative therapy options	14
patients more likely to successfully undergo leukapheresis	13
receive CAR-T therapy after leukaphe-resis	13
time spent on the waitlist among their prioritization criteria	12
high disease burden	11

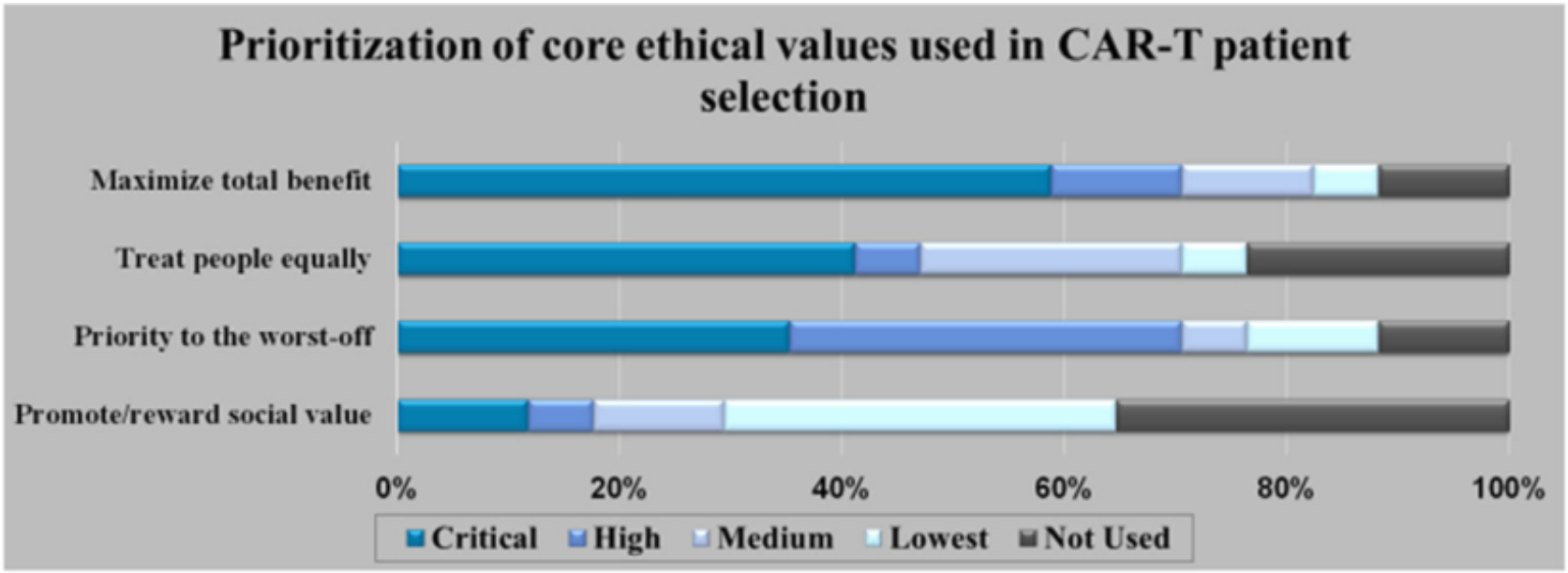
Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

Criterion	Numbers of Centers
more likely to achieve clinical response	5
higher HCT-CI	5
social value (young patient with family)	3
using a lottery system	1
selecting 1 patient per CAR-T clinician on a rotating basis	1

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience



The simple ethical principles of CAR-T slot allocation that embody the core values. The bar graph shows prioritization of the core ethical values used in patient selection for CAR-T therapy from highest to lowest as a percentage of total survey respondents.

Kourelis et al. / TCT 00 (2023) 1-4, in press

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

Core Ethical Value	Numbers of Centers
Maximizing the total benefit	10
treating people equally	7
giving priority to the worst off	6
promoting social value	2

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Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience

cilta-cel was approved shortly after completion of the initial survey

in October 2022 centers were asked how many slots per month they had received for cilta-cel and how patients were selected for ciltacel over ide-cel.

(15/17 responded) The median number of **monthly cilta-cel slots was 2 (range, 1 to 4).**

All centers identified physician and patient preference as the most common factor influencing the decision to prescribe one product over the other.

Five centers reported that longer manufacturing times for cilta-cel also influenced their decision regarding which product to prescribe according to the clinical scenario, but no center reported the use of formal criteria for patient allocation to each product.

Kourelis et al. / TCT 00 (2023) 1-4, in press

Patient selection for CAR T or BiTE therapy in multiple myeloma: Which treatment for each patient?

T-cell-redirecting BiAb/BiTE vs CAR-T cell therapy in MM

	BiAb/BiTE	CARs
Structure	BiAb: Engineered artificial antibodies to recognize two epitopes of an antigen or two antigens. BiTE: A recombinant protein composed of two linked scFvs, with one targeting CD3 and the other one targeting MM antigen.	A synthetic receptor composed of a target antigen-binding domain (scFv), a hinge region, a transmembrane domain, and intracellular signaling domains.
Immune synapse	Typical	Atypical
Effector cells	CD4 and CD8 cells	CD4 and CD8 cells
Availability	Off the shelf	1. Maybe > 2 weeks for manufacture. 2. Rapid manufacturing process is under development.
Manufacturing failure	Not applicable	Around 10%

Adapted from Zhang X et al Front. Immunol. 2023

T-cell-redirecting BiAb/BiTE vs CAR-T cell therapy in MM

	BiAb/BiTE	CARs
Administration	1. No conditioning treatment. 2. Pretreatment: steroid. 3. Repeat dosing.	1. Conditioning treatment (+). 2. Pretreatment: anti-histamine, acetaminophen. 3. One-time infusion.
The treatment response rate in RRMM	1. Generally lower. 2. It may be similar to CAR-T therapy in patients treated with top doses or at the RP2D.	Generally higher
Target antigen loss	Lower risk	Higher risk
CRS risk (≥ Gr 3)	1. Generally lower. 2. Increase with a higher dose.	Generally higher.
Neurotoxicity (≥ Gr 3)	Lower	Higher
Financial burden	Expensive	Expensive
FDA approval	Talquetamab (2022).	Idecabtagene vicleucel (2021) Ciltacabtagene autoleucel (2022).
EMA approval	Teclistamab (2022).	Idecabtagene vicleucel (2021).

Adapted from Zhang X et al Front. Immunol. 2023

Conclusions

- New targets on PCs (BCMA, GPRC5D, FcHR5) and the development of new immuno-therapeutics tools (ADC, TCE and CAR T cell therapy) pave the way for new treatment strategies

- TCE and CAR T represents a highly effective treatment option for heavily pretreated patients in later lines;

- CAR T cell therapy will be compared head-to-head to ASCT while TCEs will be incorporated in upfront treatment regimens for transplant-ineligible patients challenging current triplets and quadruplet regimens.

- Despite the high efficacy observed with immunotherapies, relapse still occurs. Actions needed:
  - To improve understanding of the mechanism of action (MoA),
  - To improve understanding of the mechanism of resistance,
  - To make sequential/alternating strategies with different drugs and targets more feasible,
  - Optimize patient selection for each treatment strategy.

ASCT, autologous stem cell transplantation.

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Thank you for your attention!!