CAR T-Cell Therapy for Patients with Multiple Myeloma

Hosted by Blood & Marrow Transplant Information Network

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Multiple Myeloma - CAR T CELL AND T-CELL ENGAGER THERAPY

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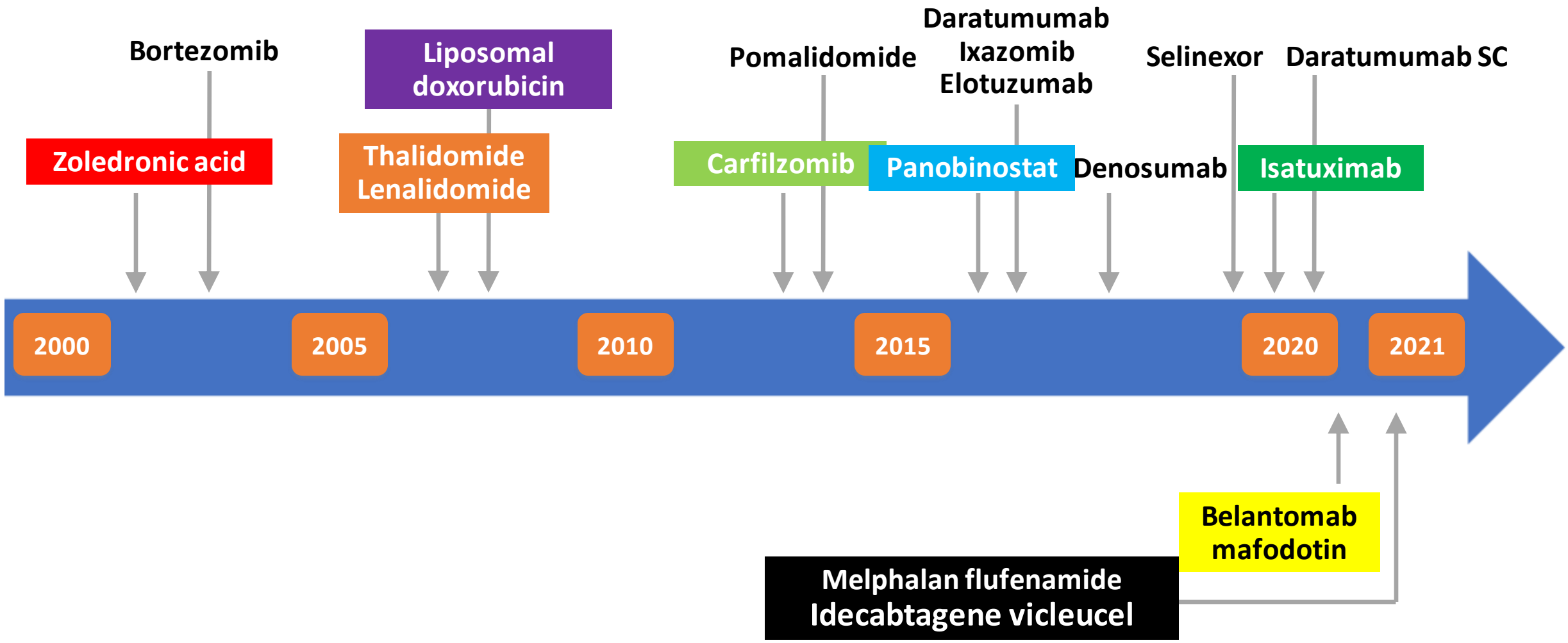
Providing Extraordinary Care

Myeloma Drugs Approved Since 2000

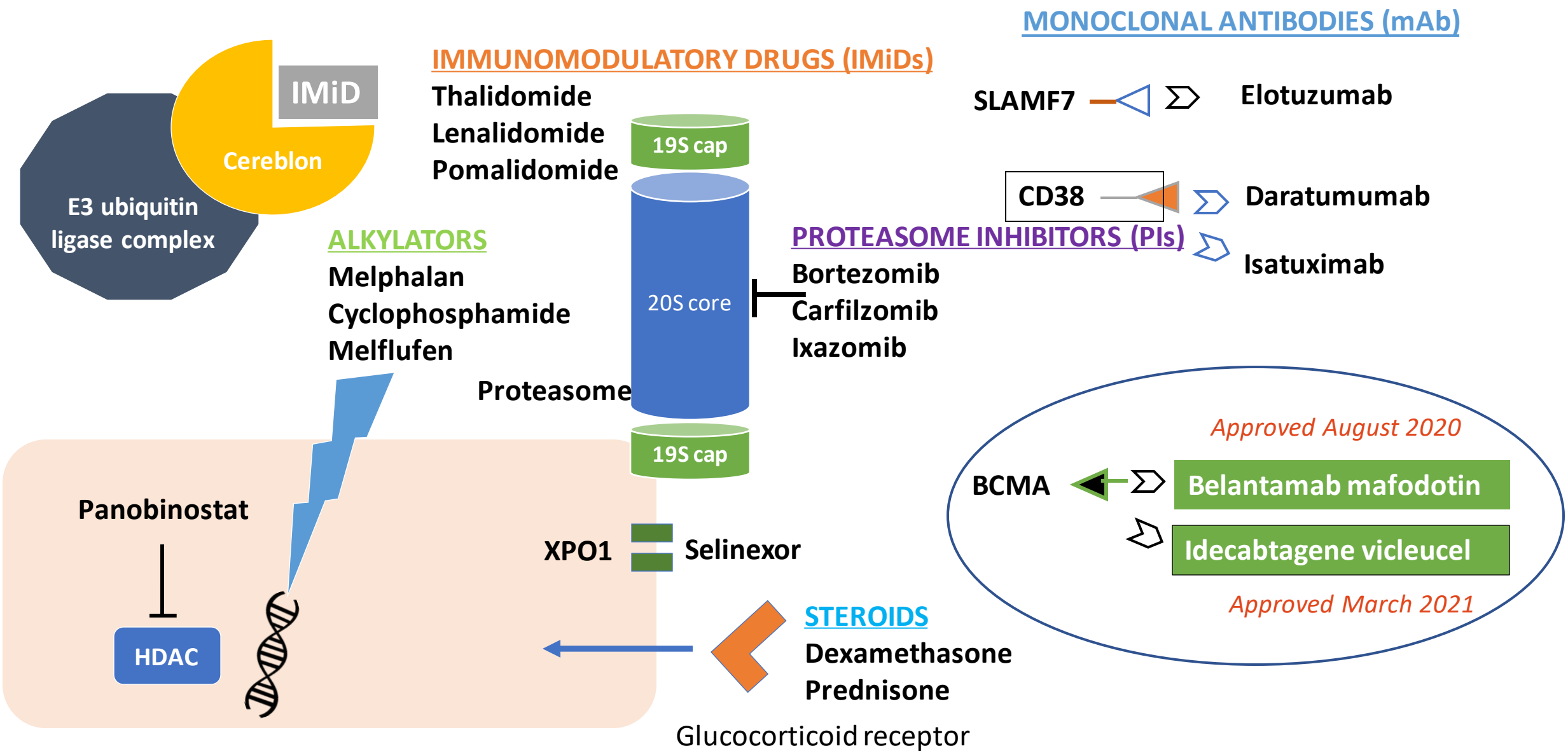


Choosing Therapy for Patients With Relapsed/Refractory Multiple Myeloma

Chosen 1st-line Therapy	Options for 2nd-line Therapy	Subsequent Therapy
Induction Therapy ± Consolidation → Len Maintenance Until PD	Daratumumab or Isatuximab + Pomalidomide/Dex	Carfilzomib/ Cyclophosphamide/Dex
	Daratumumab or Isatuximab + Carfilzomib/Dex	Pomalidomide/ Cyclophosphamide/Dex
	Carfilzomib/Pomalidomide/Dex	Selinexor/ Bortezomib/Dex
	Elotuzumab/Pomalidomide/Dex	Belantamab Mafodotin
	Ixazomib/Pomalidomide/Dex	Idecabtagene Vicleucel
	Pomalidomide/Cyclophosphamide/Dex	Melphalan Flufenamide
	Carfilzomib/Cyclophosphamide/Dex	

Clinical trial should be considered for all eligible patients

Treatment Options for Multiple Myeloma



Suboptimal Outcomes in Patients With Multiple Myeloma Refractory to CD38 Antibody

- MAMMOTH: Retrospective analysis of 275 patients from 14 academic centers

Characteristic	Median Overall Survival	Description
Not triple refractory	11.2 mos	Refractory to 1 CD38 mAb, but not to both PI and mAb
Triple and quad refractory	9.2 mos	Refractory to 1 CD38 mAb + 1 PI + 1 or 2 IMiDs
Penta refractory	5.6 mos	Refractory to 1 CD38 mAb + 2 PIs + 2 IMiDs
Overall cohort	8.6 mos	

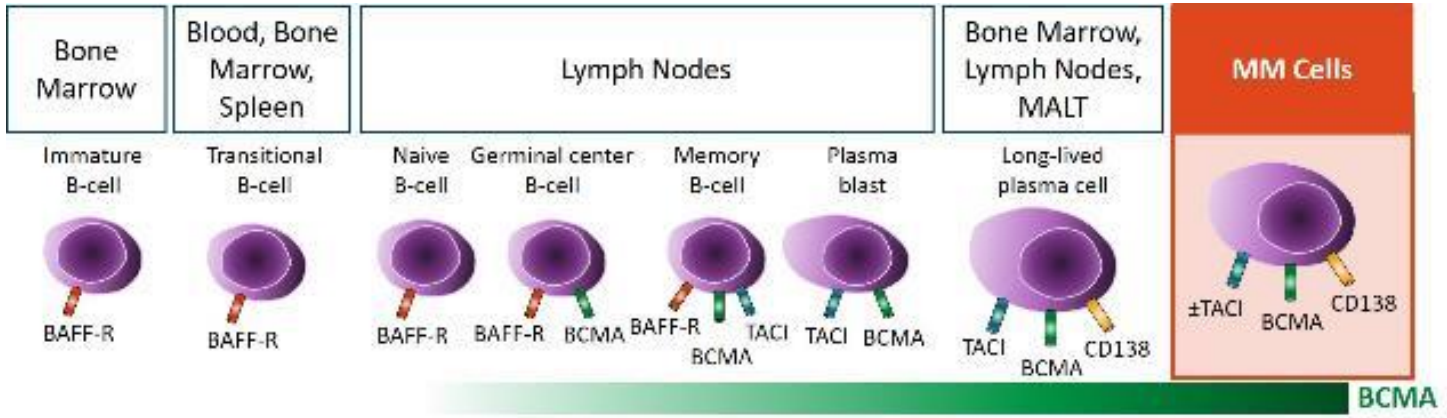
- 249 patients received further treatment
  - Overall response rate: 31%; Progression-free survival: 3.4 mo; Overall survival: 9.3 mo

Patient population for BCMA-targeted therapy has challenging disease to treat

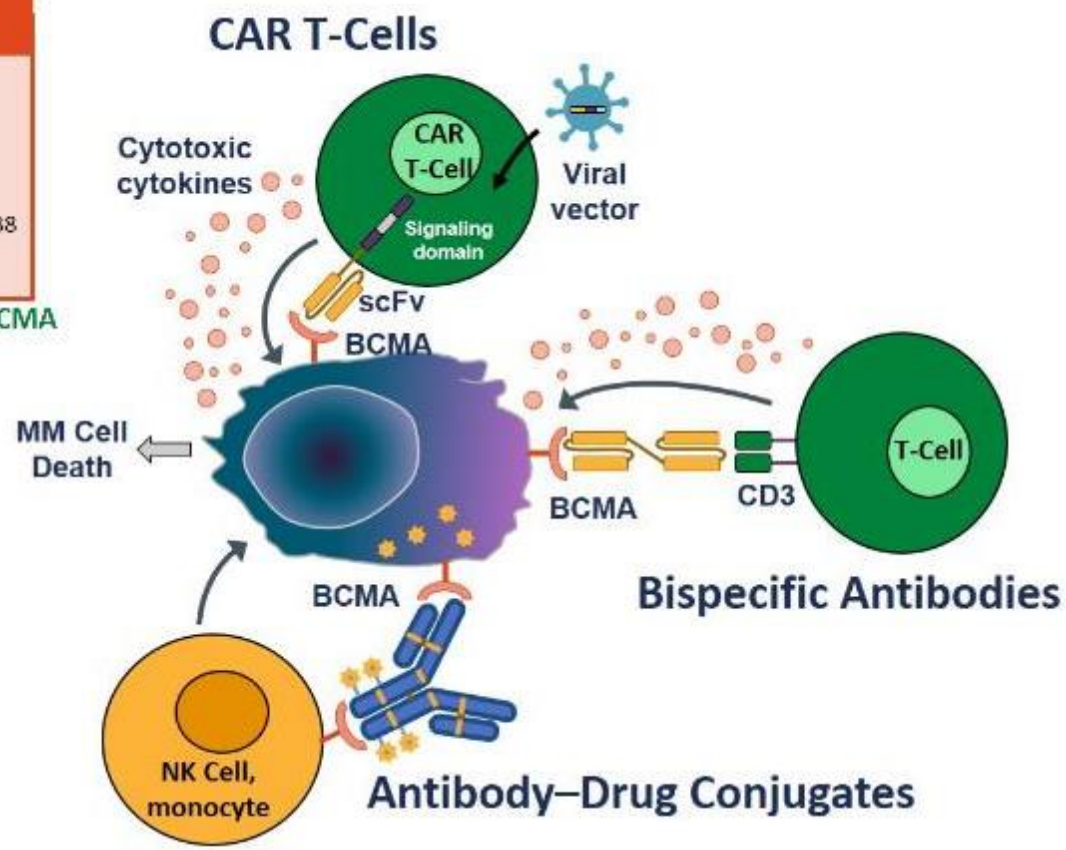
Gandhi. Leukemia. 2019;33:2266.

mAb: monoclonal antibody; IMiD, immunomodulatory imide drug; PI, proteasome inhibitor

B-Cell Maturation Antigen (BCMA) in Multiple Myeloma

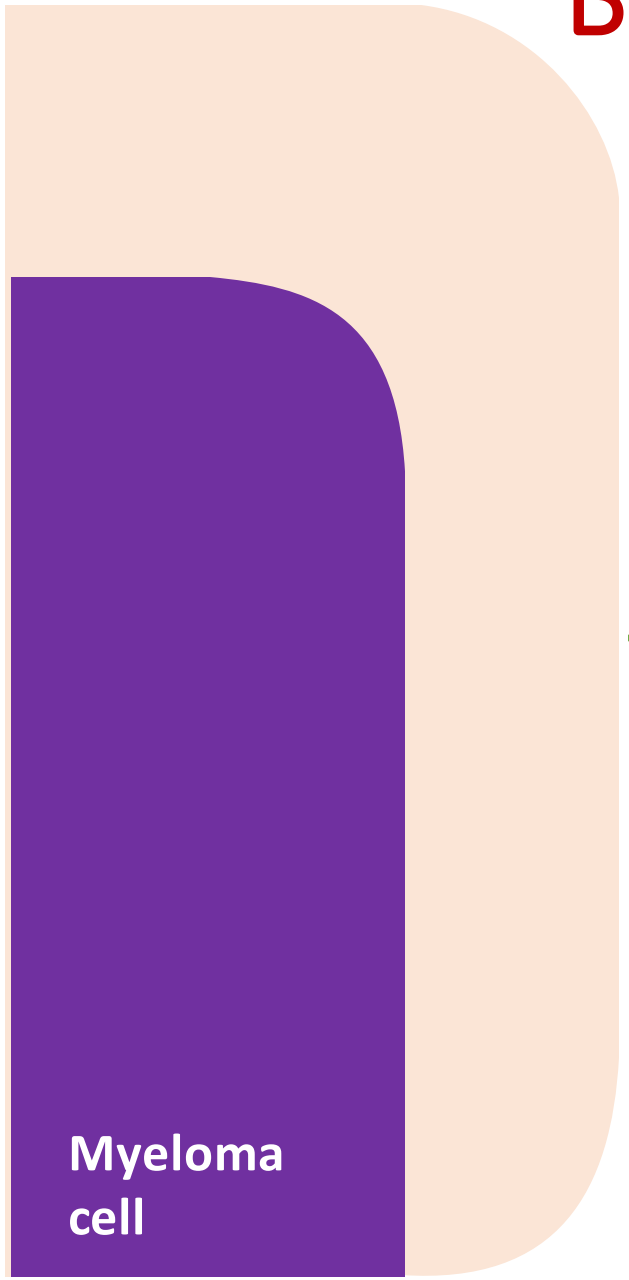


- Expressed on late memory B-cells committed to plasma cell differentiation
- BCMA plays a role in survival of long-lived plasma cells



Cho. Front Immunol. 2018;10:1821.

BCMA-Targeted Therapies



Antibody–Drug Conjugates
Belantamab mafodotin
MEDI2228
CC-99712

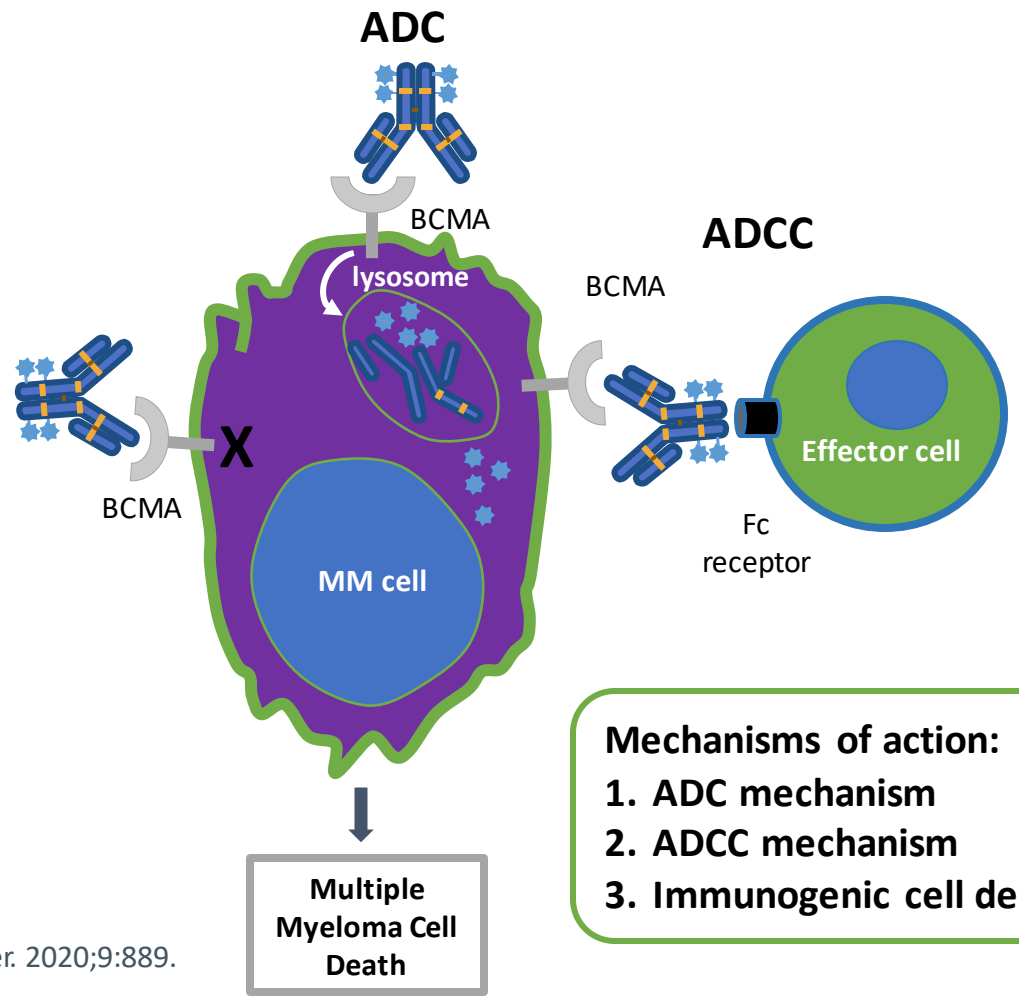
Bispecific T-Cell Engagers
AMG 420
AMG 701
CC-93269
REGN5458
JNJ-64007957
PF-06863135

CAR T-Cell Therapies
Idecabtagene vicleucel
Ciltacabtagene autoleucel
Orvacabtagene autoleucel
P-BCMA-101
bb21217
ALLO-715

Belantamab Mafodotin (Blenrep®): A BCMA-Targeted Antibody Drug Conjugate

Belantamab mafodotin

- Humanized anti-BCMA antibody
- Conjugated to a chemotherapy disrupting agent MMAF



Fc region of the Ab	– Target specific – Enhanced ADCC
Linker	– Stable in circulation
Drug	– MMAF (non-cell permeable, highly potent auristatin)

Mechanisms of action:

1. **ADC mechanism**
2. **ADCC mechanism**
3. **Immunogenic cell death**

Tai. Blood. 2014;123:3128. Farooq. Ophthalmol Ther. 2020;9:889.

Belantamab Mafodotin for Relapsed/Refractory Multiple Myeloma

- DREAMM-2: Open-label, randomized phase II trial in patients with Relapsed/Refractory Myeloma after ≥3 prior lines of therapy; refractory or intolerant to IMiDs, PIs, and CD38 mAbs (N = 196)y

Outcome	2.5 mg/kg (n = 97)
Median lines of therapy, n (range)	7 (3–21)
Overall Relapse Rate	31%
Median Progression-free survival	2.9 mos
Median Overall Survival	Not reached

Key Adverse Events	2.5 mg/kg (n = 95)
Grade 1/2	
▪ Keratopathy (eye damage)	41 (43%)
Grade 3/4	
▪ Keratopathy	26 (27%)
▪ Thrombocytopenia	19 (20%)
▪ Anemia	19 (20%)
Parameter, n (%)	**2.5 mg/kg**
Dose delay	51 (54%)
Dose reduction	28 (29%)

- Approved for patients with relapsed/refractor myeloma who have received ≥4 previous therapies including an anti–CD-38 mAb, a PI, and an IMiD

Lonial. Lancet Oncol. 2020;21:207.

IMiD: immunomodulatory drug; mAb: monoclonal antibody; PI, protease inhibitor

Belantamab Mafodotin + Pomalidomide/Dexamethasone

Outcome	Patients (n = 34)
Overall Response Rate	88%
▪ Complete Remission	14.7%
▪ Very Good Partial Remission	52.9%
▪ Partial Remission	20.6%
Median Progression-Free Survival (95% CI)	NR (10.8-NR)

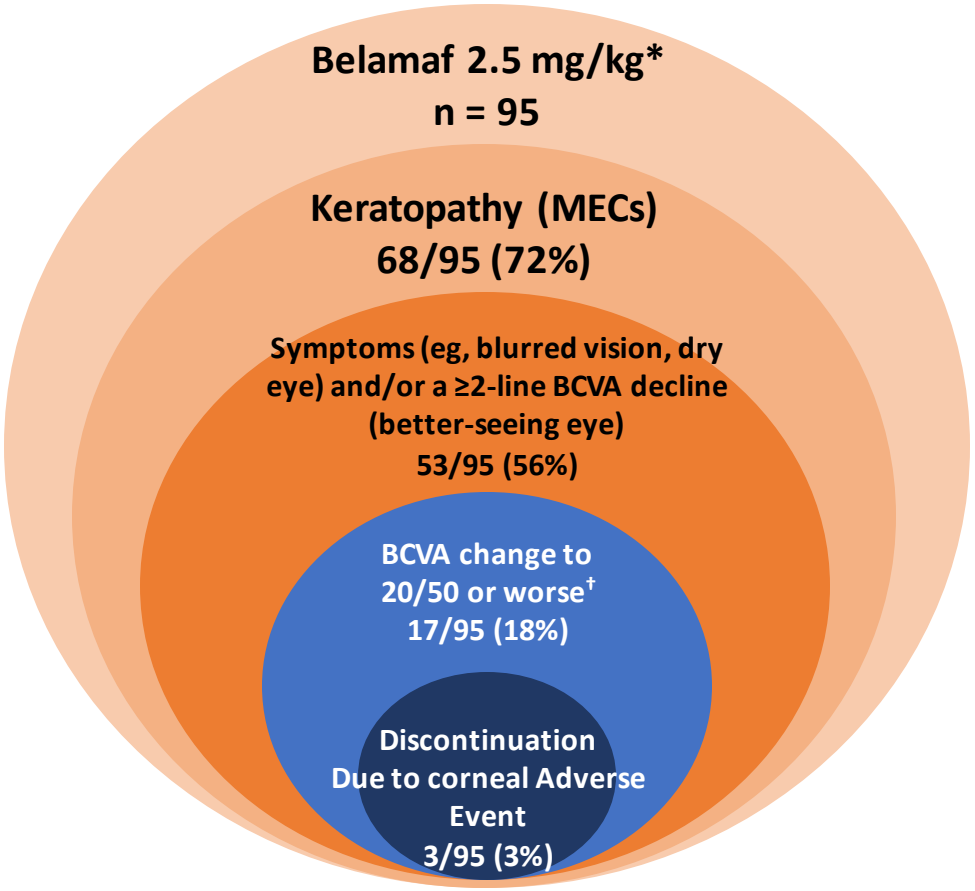
- 9 patients discontinued treatment for Pom/Dex (n = 7), patient withdrawal (n = 1); grade 4 decreased visual acuity (n = 1)
- Most frequent adverse events of any grade: corneal surface layer changes (75.7%), low white counts (56.8%), low platelets counts (48.6%), decreased visual acuity (45.9%), and fatigue (40.5%)

Trudel. ASH 2020. Abstr 725.

Ocular Adverse Events - Belantamab Mafodotin

- BCMA not expressed in the cornea; ocular toxicity an off-target effect of belantamab mafodotin leading death of surface layer of corneal cells
- With dose holds, majority of patients recover from keratopathy and visual changes
- Dose holds may not affect response; 88% of patients maintained or deepened response with dose holds >63 days
- Risk Evaluation and Mitigation Strategy (REMS) program, with ophthalmology evaluation prior to each dose of belantamab mafodotin

DREAMM-2: Outcomes due to Ocular Adverse Events

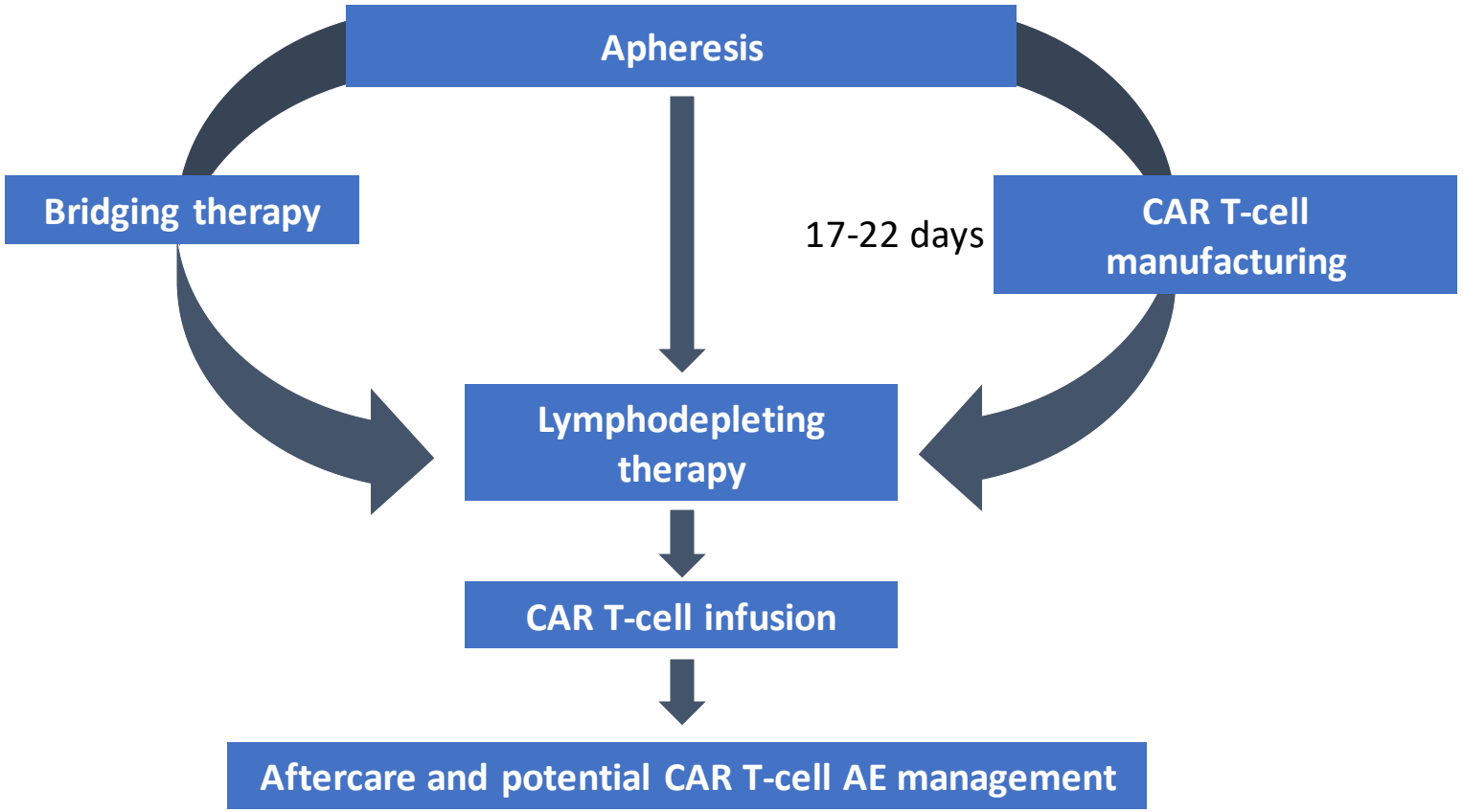


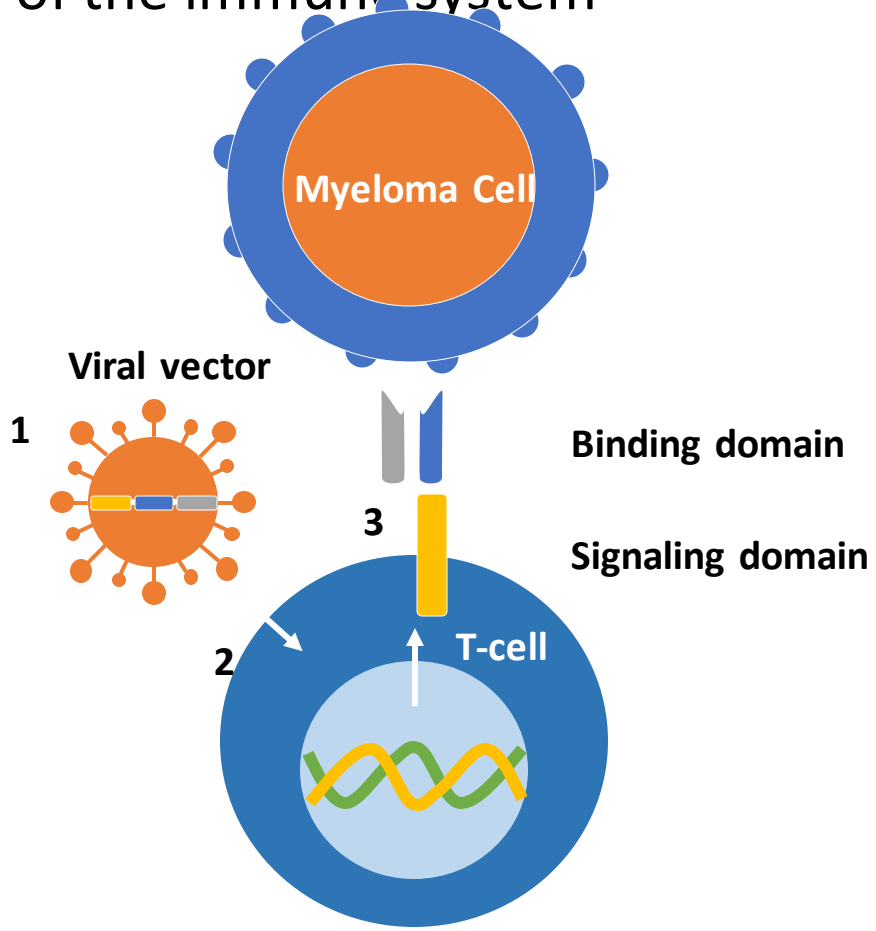
Lonial. ASH 2020. Abstr 3224. Lonial. Lancet Oncol. 2020;21:207.
Farooq. Ophthalmol Ther. 2020;9:889. Belantamab mafodotin PI. Cohen. SOHO 2020.

BCVA: best corrected visual acuity; KVA: keratopathy and visual acuity; MEC: microcyst-like epithelial changes epithelial changes

What Is CAR T-Cell Therapy?

- A treatment strategy that engineers a patient's T-cells to target and attack malignant cells;
  T-cells are a type of white blood cell, which are part of the immune system



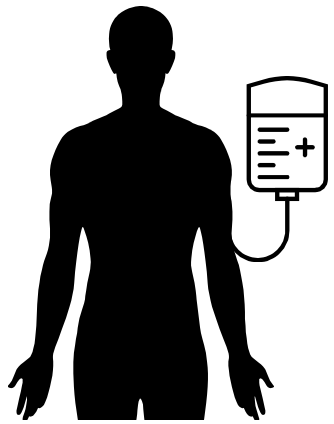


Feins. Am J Hematol. 2019;94:S3.

Autologous CAR T-Cell Therapy: Underlying Principles

Leukapheresis

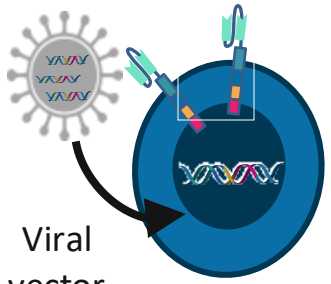
Collect patient's white blood cells

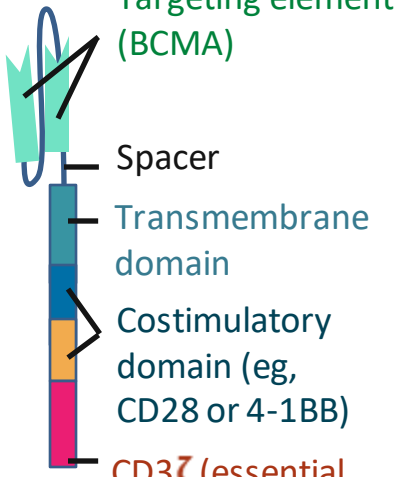


Manufacturing

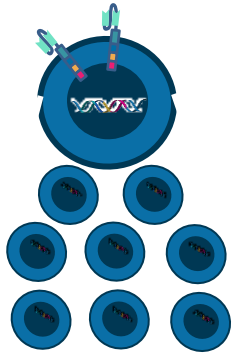
Isolate and activate T-cells

Engineer T-cells with CAR gene





Expand CAR T-cells

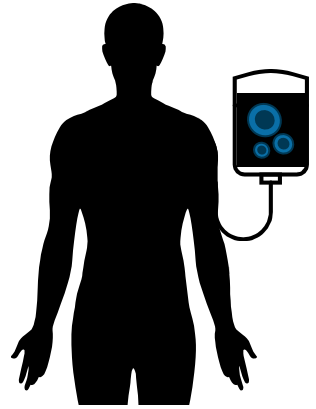


Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

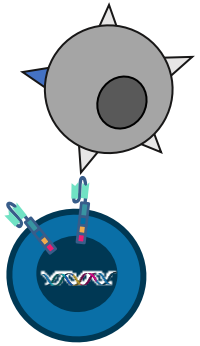
Infusion

Infuse same patient with CAR T-cells



Activity

BCMA



Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Multidisciplinary Team Roles in Delivering CAR T-Cell Therapies

Essential Steps and Required Personnel

INTAKE
- Non-CAR MDs
- Administrative staff
- Financial coordinator

COLLECTION
- Cell therapy/donor room
- Laboratory medicine
- Nurse coordinator
- Manufacturers, FACT

INFUSION
- CAR MDs
- Cell therapy
- Nursing
- Pharmacy
- FACT

LATE CARE
- CAR MDs
- Non-CAR MDs

CONSULTATION
- CAR-certified MDs
- Nurse coordinator
- Social worker
- Apheresis staff

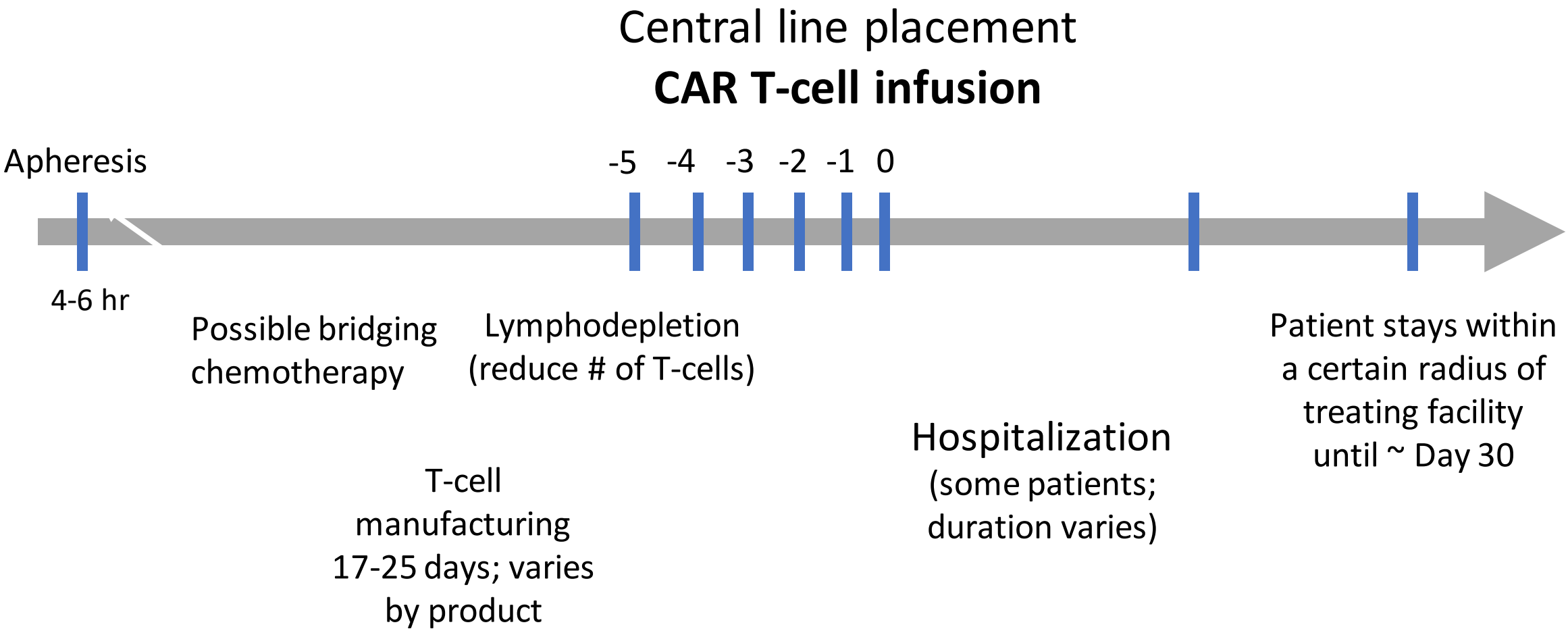
BRIDGING
- Non-CAR MDs
- CAR MDs
- Nursing

EARLY CARE
- CAR MDs
- ICU, neurology
- Nursing
- Pharmacy
- FDA

REGULATION
- Financial services
- Billing
- Data management
- FACT, CIBMTR, FDA

Perica. Biol Blood Marrow Transplant. 2018;24:1135. Axicabtagene ciloleucel PI. Brexucabtagene autoleucel PI. Idecabtagene vicleucel PI. Lisocabtagene maraleucel PI. Tisagenlecleucel PI.

CAR T-Cell Treatment Schema

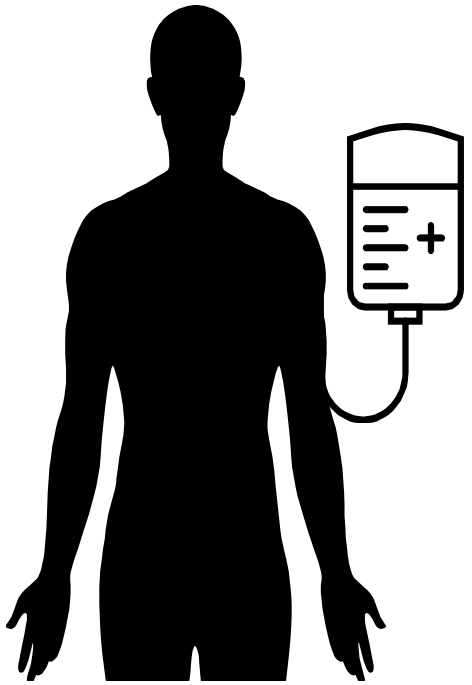


Beaupierre. J Adv Pract Oncol. 2019;10(suppl 3):29. Perica. Biol Blood Marrow Transplant. 2018;24:1135.

Leukapheresis

- Blood is collected from patient, after which T-cells are separated and removed and remaining blood is returned to the patient

- Apheresis takes ~4-6 hr, after which T-cells are labeled, packaged, and shipped to the manufacturing facility



Beaupierre. J Adv Pract Oncol. 2019;10(suppl 3):29.

Bridging Therapy

- Several weeks may pass between leukapheresis and the administration of CAR T-cells; bridging therapy may be given to patients to:
  - Palliate symptoms
  - Debulk the primary tumor
  - Preserve functional status to safely administer CAR T-cells
- May consist of chemotherapy, steroids, radiation therapy

Beaupierre. J Adv Pract Oncol. 2019;10(suppl 3):29.

CAR T-Cell Treatment

- Treatment can be given inpatient or outpatient[1]
  - Institution policies
  - Patient risk factors
- Approved fludarabine and cyclophosphamide for adults given on Days -5, -4, -3 prior to CAR T-cell infusion[3-7]
- Supportive care during chemotherapy includes IV fluids, anti-emetics, prophylactic medication for infection[8-11]
- CAR T-cells are infused on Day 0[2]
- Patients receive wallet card required by the FDA prior to infusion[2]

1. Brudno. Blood. 2016;127:3321. 2. Beaupierre. J Adv Pract Oncol. 2019;10(suppl 3):29. 3. Axicabtagene ciloleucel PI.
4. Brexucabtagene autoleucel PI. 5. Idecabtagene vicleucel PI. 6. Lisocabtagene maraleucel PI. 7. Tisagenlecleucel PI.
8. Neuss. J Oncol Pract. 2013;9(2 suppl):5s. 9. Alakel. Onco Targets Ther. 2017;10:597. 10. Rao. Am Health Drug Benefits. 2012;5:232.
11. MDACC. IEC therapy toxicity assessment and management (also known as CARTOX) – adult. Approved September 15, 2020.

Cytokine Release Syndrome

- Systemic inflammatory response that can occur as CAR T-cells activate and expand[1]
- Median time to onset: 1-5 days[2-6]
- Signs/symptoms[7]
  - Fever
  - Constitutional symptoms (flulike symptoms)
  - Hypotension (low blood pressure)
  - Hypoxia (low oxygen in tissues)
  - End organ dysfunction
- Infectious workup[7]
- Treatment[7]:
  - supportive care
  - Tocilizumab
  - steroids
- Tocilizumab: humanized monoclonal antibody against IL-6R[7]
  - Rapid reversal of life-threatening CRS symptoms

1. Adkins. J Adv Pract Oncol. 2019;10(suppl 3):21. 2. Axicabtagene ciloleucel PI. 3. Brexucabtagene autoleucel PI.
4. Idecabtagene vicleucel PI. 5. Lisocabtagene maraleucel PI. 6. Tisagenlecleucel PI. 7. Lee. Blood. 2014;124:188.

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Median onset 2-8 days, can occur in the absence of CRS or concurrently[1-6]
- Signs/symptoms[7]
  - Aphasia (difficulty speaking)
  - Altered or loss of consciousness
  - Cognitive impairment
  - Motor weakness
  - Seizures
  - Cerebral edema (fluid around the brain)
- Evaluation[8,9]
  - CT scan head/brain MRI
  - Lumbar puncture
  - Infectious workup
  - EEG
  - Consider Neurology consultation
- Treatment: supportive care, steroids, seizure prophylaxis and precautions[9]

1. Adkins. J Adv Pract Oncol. 2019;10(suppl 3):21. 2. Axicabtagene ciloleucel PI. 3. Brexucabtagene autoleucel PI.
4. Idecabtagene vicleucel PI. 5. Lisocabtagene maraleucel PI. 6. Tisagenlecleucel PI. 7. Gust. Cancer Discov. 2017;7:1404.
8. Lee. Biol Blood Marrow Transplant. 2019;25:625. 9. MDACC. IEC therapy toxicity assessment and management. 2020.

Idecabtagene vicleucel (Ide-cel, Abecma®)

- KarMMa: Multicenter, single-arm phase II CAR T-cell trial (updated study design)

Patients with Relapsed/Refractory Multiple Myeloma and ≥3 prior regimens each with ≥2 consecutive cycles, prior IMiD, PI, and anti-CD38 mAb, and refractory to last therapy by IMWG criteria
(N = 140)

Leukapheresis

Lymphodepletion

Cyclophosphamide 300 mg/m^2 +
Fludarabine 30 mg/m^2
on Days -5, -4, -3
(n = 140)

Bridging therapy ≥14 days before lymphodepletion as needed

CAR T-Cell Infusion (Day 0)

Idecabtagene vicleucel
150 x 10^6 CAR T-cells
(n = 4)
300 x 10^6 CAR T-cells
(n = 70)
450 x 10^6 CAR T-cells
(n = 54)

Idecabtagene vicleucel manufacturing (99% success rate)

IMiD: immunomodulatory drug; IMWG: International Myeloma Working Group; mAb: monoclonal antibody; PI:, proteasome inhibitor

Anderson. ASCO 2021. Abstr 8016. Munshi. NEJM. 2021;384:705.

Idecabtagene vicleucel (Ide-cel, Abecma®)

KarMMa Trial: Baseline Characteristics

Characteristic	Ide-cel Treated (n = 128)
Median age,	61 Yrs (33-78 yrs)
Male	59%
Stage:	
I	11%
II	70%
III	16%
High-risk cytogenetics (del[17p], t[4;14], t[14;16])	35%

Characteristic	Ide-cel Treated (n = 128)
Median time since initial diagnosis (range)	6 yr (1-18 yrs)
Median no. of prior anti-multiple myeloma regimens (range)	6 (3-16)
Prior autologous stem cell transplant	
▪ 1	94%
▪ >1	34%
Any bridging therapies for multiple myeloma	88%
Refractory status	
▪ Anti-CD38 mAb refractory	94%
▪ Triple refractory	84%

88% of patients received bridging therapy; only 4% responded

Munshi. NEJM. 2021;384:705.

mAb: monoclonal antibody

Efficacy of Idecabtagene vicleucel
(Ide-cel, Abecma®)

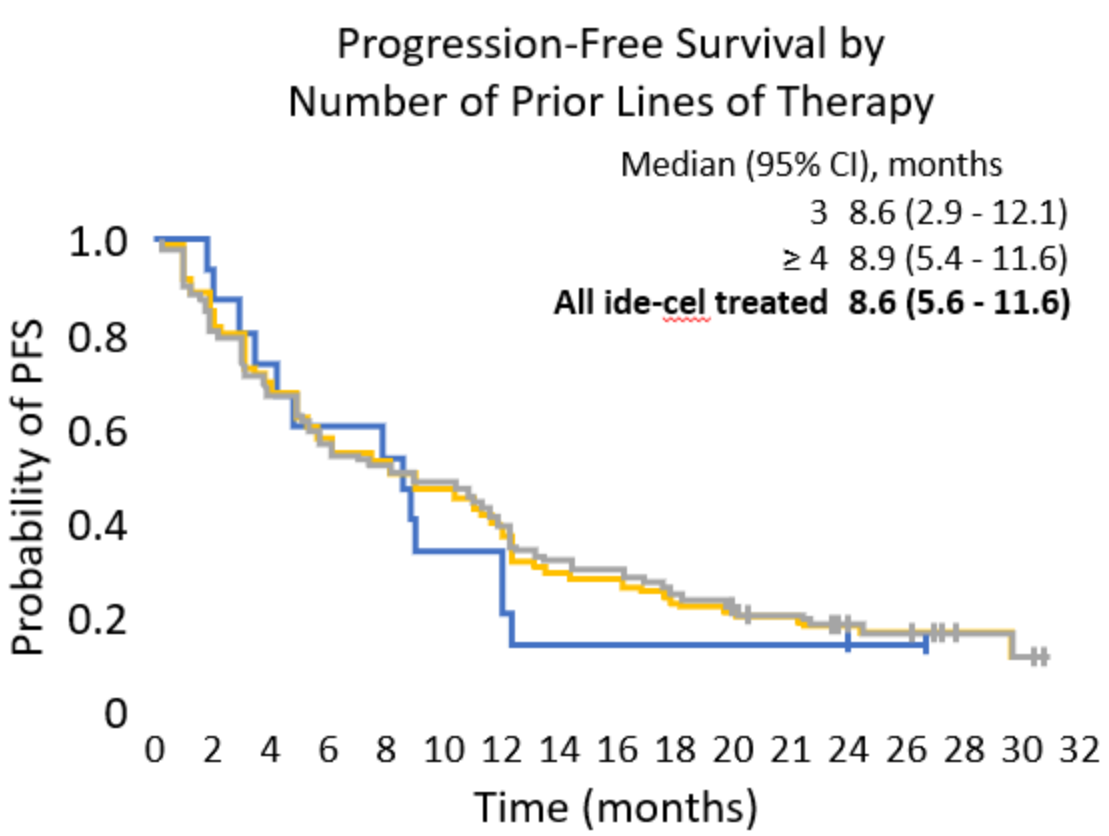
Outcome – KarMMa Trial	Patients (N = 128)
Overall Response Rate	73%
▪ Stringent Complete Response + Compete Response	33%
▪ Very Good Partial Response	20%
▪ Partial Response	21%
Median Duration of Response	10.7 mos
Median Progression-Free Survival	8.8 mos
Median Overall Survival	19.4 mos

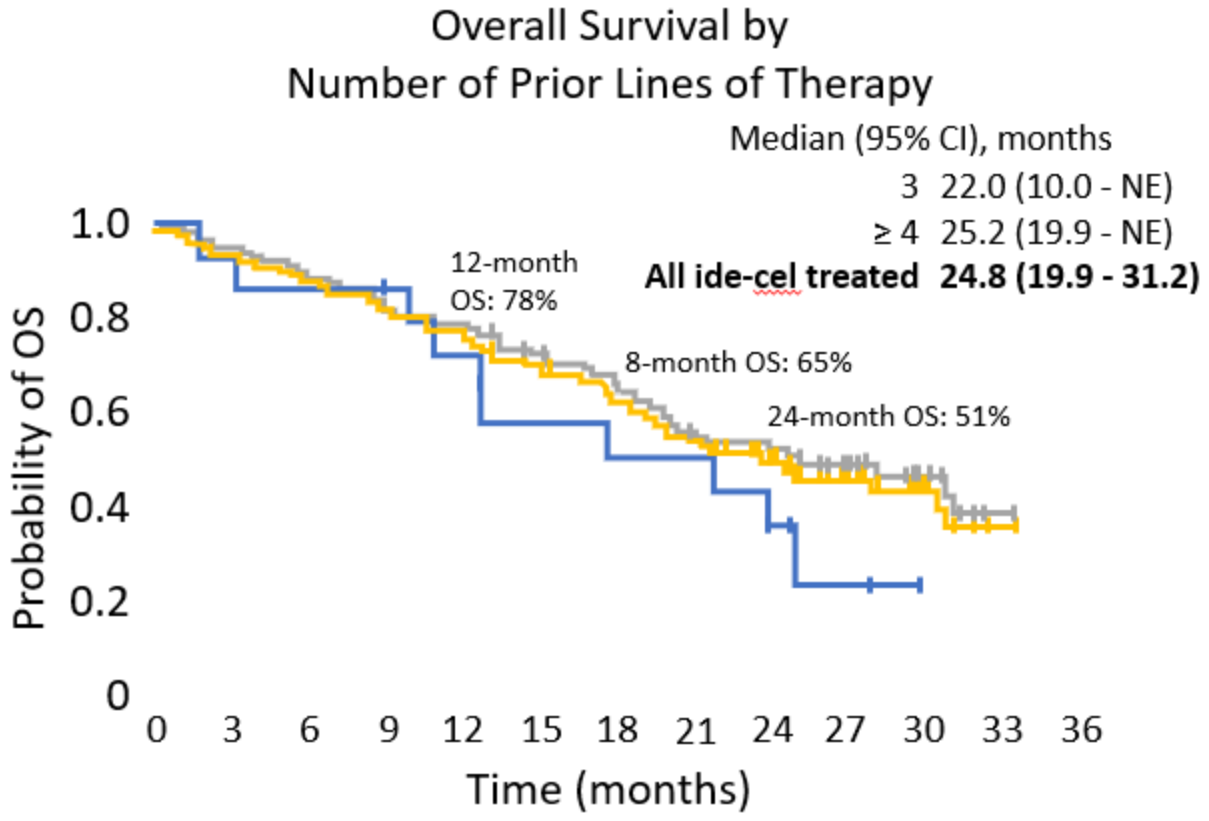
Munshi. NEJM. 2021;384:705.

Progression-Free Survival and Overall Survival

Idecabtagene vicleucel (Ide-cel, Abecma®)

(Updated KarMMa Trial)





Anderson. ASCO 2021. Abstr 8016.

Cytokine Release Syndrome
Idecabtagene vicleucel (Ide-cel, Abecma®)

Incidence of Cytokine Release Syndrome KarMMa Update	All Patients (N = 128)
≥ 1 event	107 (84%)
Maximum grade	
1 or 2	100 (78%)
3	5 (4%)
4	1 (<1%)
5	1 <1%)
Median onset (range)	1 day (1-12 days)
Median duration (range)	5 days (1-63 days)
Tocilizumab	67 (52%)
Corticosteroids	19 (15%)

Cytokine Release Syndrome events mostly low grade; ≤6% grade ≥3, including 1 grade 5 event

1. Munshi. NEJM. 2021;384:705. 2. Manier. ASCO 2021. Abstr 8036.

Neurotoxicity
Idecabtagene vicleucel (Ide-cel, Abecma®)

Characteristics of Neurotoxicity KarMMa Update	Grade 1 (n = 11)	Grade 2 (n = 7)	Grade 3 (n = 5)
Median time to first onset, (range)	2 days (1-10 days)	2 days (1-4 days)	2 days (1-4 days)
Median duration of neurotoxicity per event (range)	2.5 days (1-9 days)	5.5 days (1-26 days)	8.5 days (2-22 days)
Events by duration			
▪ 1-5 days	75%	43%	50%
▪ 6-10 days	25%	29%	0%
▪ >10 days	0%	14%	50%
▪ Ongoing	0%	14%	0%
Tocilizumab	9%	0%	40%
Steroids	18%	57%	80%
Anakinra	0%	0%	20%

Neurotoxicity in 18% patients (23/128) treated, all events occurred in ≤1 week of CRS event[1,2]

1. Munshi. NEJM. 2021;384:705. 2. Manier. ASCO 2021. Abstr 8036.

Adverse Events of Interest
Idecabtagene vicleucel (Ide-cel, Abecma®)

Adverse Events of Interest KarMMa Update	All Ide-cel Patients (N = 128)	
	Any Grade	Grade 3/4
Hematologic		
▪ Neutropenia	117 (91%)	114 (89%)
▪ Anemia	90 (70%)	78 (61%)
▪ Thrombocytopenia	82 (64%)	67 (52%)
▪ Leukopenia	54 (42%)	50 (39%)
▪ Lymphopenia	36 (28%)	35 (27%)
Nonhematologic		
Infections	90 (70%)	34 (27%)
SPM*	9 (7%)	3 (2%)
HLH/MAS	4 (3%)	2 (2%)

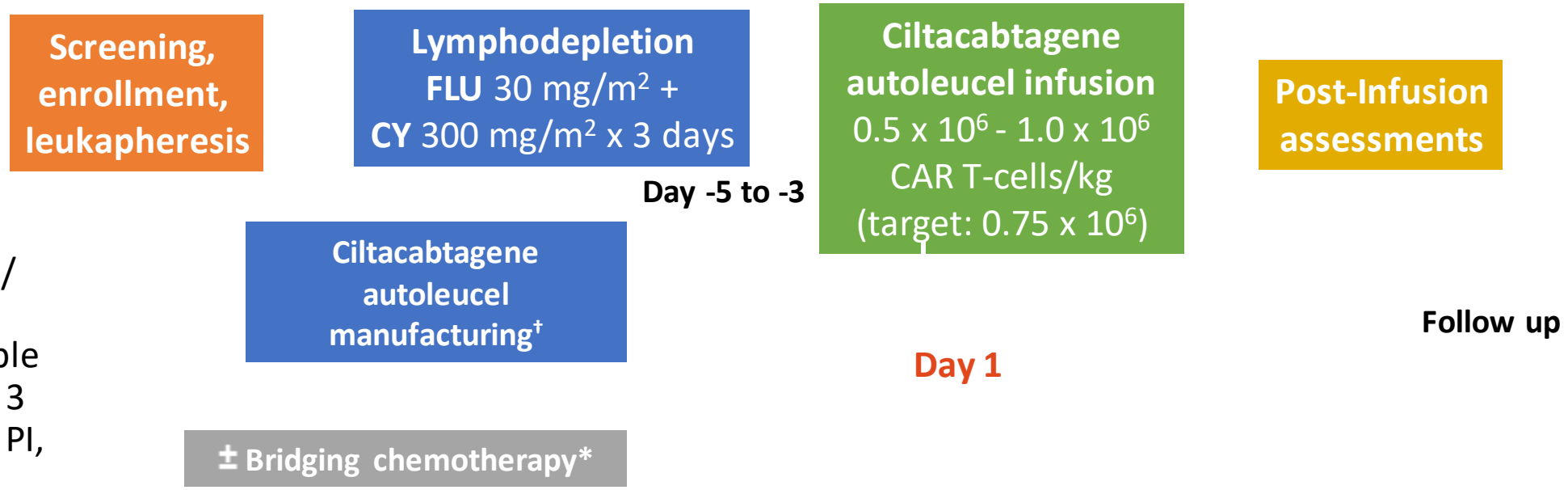
- Low blood counts were common; not dose related
- Median time to recovery
  - Grade ≥ 3 white count: 1.9 mo
  - Grade ≥ 3 platelet counts: 2.1 mo
- Infections (including bacterial, viral, fungal) were common (70%); not dose related

*SPM events include basal cell carcinoma (n = 5), anal cancer (n = 1), lung adenocarcinoma (n = 1), myelodysplastic syndrome (n = 1), and squamous cell carcinoma (n = 1). Basal cell carcinoma and lung adenocarcinoma events were new and observed since the January 14, 2020, cutoff date.

1. Anderson. ASCO 2021. Abstr 8016. 2. Munshi. NEJM. 2021;384:705.

Ciltacabtagene autoleucel (cilta-cel)

- CARTITUDE-1: Phase Ib/II CAR T-cell therapy trial conducted in the United States



Patients with Relapsed/ Refractory Multiple Myeloma with measurable disease, ECOG PS ≤ 1; ≥ 3 prior therapies including PI, IMiD, and anti-CD38 therapy, or double refractory to PI and IMiD (N = 113)

*73 patients received bridging therapy with previously used agents to maintain at least SD. 0 patients discontinued due to manufacturing failure.

Madduri. ASH 2019. Abstr 577. Madduri. ASH 2020. Abstr 177.

Ciltacabtagene autoleucel (cilta-cel)

CARTITUDE-1 TRIAL: Baseline Characteristics

Characteristic	All Patients (N = 97)
Median age (range)	61 yrs (43-78 yrs)
Male	57 (58.8%)
Median time from diagnosis, (range)	5.9 yrs (1.6-18.2 yrs)
Any high-risk cytogenetics	23 (23.7%)
▪ del(17p)	19 (19.6%)
▪ t(14;16)	2 (2.1%)
▪ t(4;14)	3 (3.1%)
Median number prior lines of therapy (range)	6 (3-18)

Characteristic	All Patients (N = 97)
Previous Stem Cell Transplant	
▪ Autologous	87 (89.7%)
Penta refractory[§]	41 (42.3%)
Refractory to	
▪ Carfilzomib	63 (64.9%)
▪ Pomalidomide	81 (83.5%)
▪ Anti-CD38 Ab	96 (99.0%)
Refractory to last line of therapy	96 (99.0%)

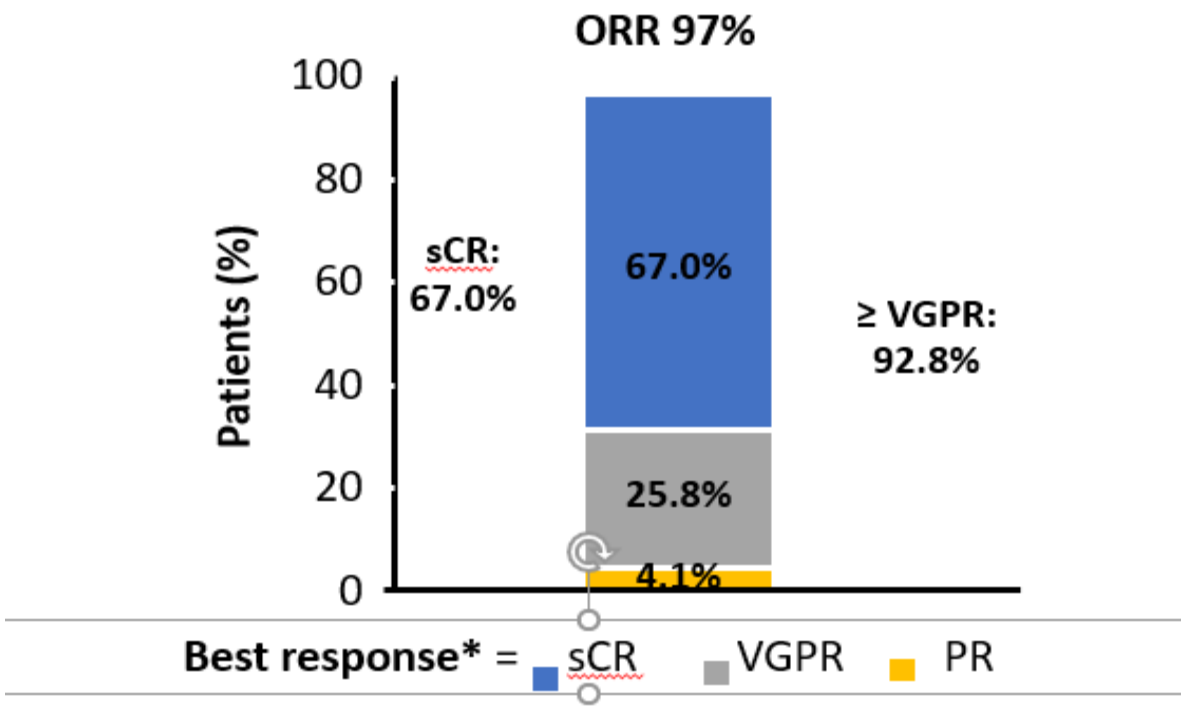
*Additional 6 patients had soft-tissue part of bone-based plasmacytoma (total plasmacytomas, 19.6)

[‡]At least 1 PI, at least 1 IMiD, and 1 anti-CD38 antibody.

[§]At least 2 PIs, at least 2 IMiDs, and 1 anti-CD38 antibody

Madduri. ASH 2020. Abstr 177.

Overall Response Rate and Minimal Residual Disease
Ciltacabtagene autoleucel (cilta-cel)



Minimal Residual Disease Status Cartitude -1 Trial	Number	Evaluable Patients* (n = 57)	All treated Patients (%) (N = 97)
Overall MRD neg	53	93.0%	54.6
MRD neg and sCR	33	57.9%	34.0
MRD neg and ≥ VGPR	49	86.0%	50.5

- Median time to first response: 1 mo (range: 0.9-8.5 mos)
- Minimal Residual Disease 10^{-5} negativity achieved by 93.0% of evaluable patients

*MRD assessed in evaluable samples at 10^{-5} threshold NGS in all treated patients at Day 28, and at Month 6, 12, 18, and 24 regardless of disease status measured in blood or urine

CAR: chimeric antigen receptor; MRD: measurable residual disease; PB: peripheral blood; sCR: stringent complete remission.

Madduri. ASH 2020. Abstr 177.

Hematologic Adverse Events and Infections

Ciltacabtagene autoleucel (cilta-cel)

Adverse Events (≥ 20% All Grade) CARTITUDE-1 trial	All Patients (N = 97)	
	All Grade	≥ Grade 3/4
Any hematologic adverse event	97 (100%)	96 (99.0%)
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%)
Any infection	57.7	19.6
Pneumonia	--	8.2
Sepsis	--	4.1

Time to Recovery, Wks

- > 1 month recovery from onset of grade 3/4 low blood counts: low white count, 10.3%; low platelet count, 2.58

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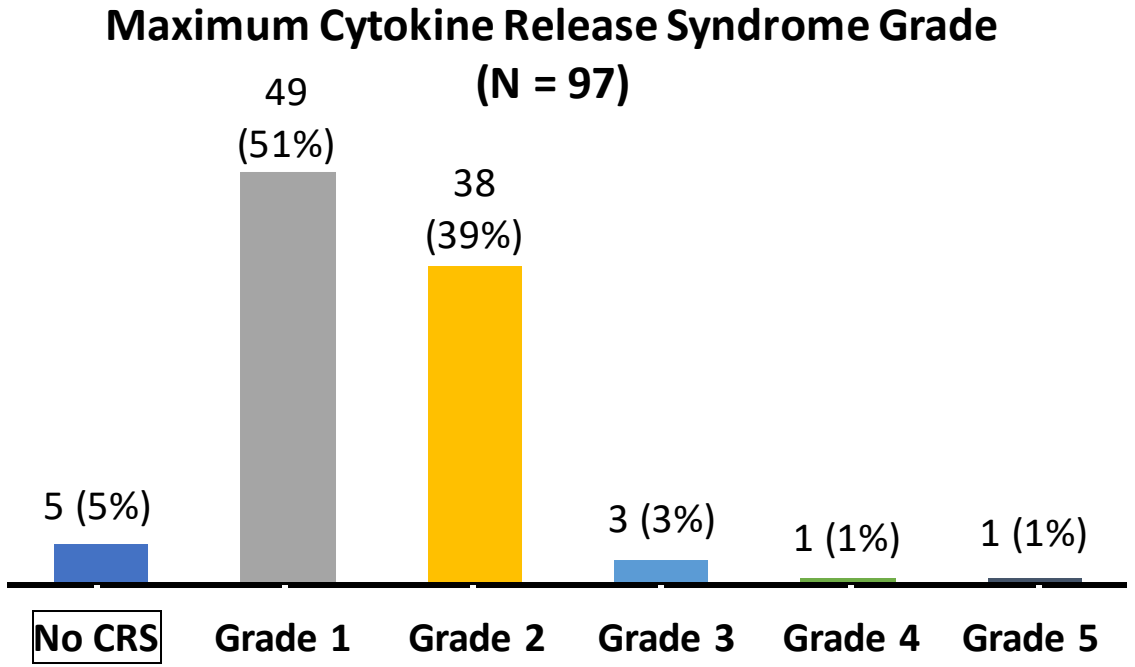
Cytokine Release Syndrome
Ciltacabtagene autoleucel (cilta-cel)

Cytokine Release Syndrome CARTITDE-1 trial	All Patients (N = 97)
Patients with Cytokine Release Syndrome	92 (94.8%)
Median time of onset (range)	7 days (1-12 days)
Median duration (range)	4 days (1-97 days)



- Among 92 patients with CRS, 94.6% were grade 1/2
- Cytokine release syndrome: onset:
  - Day 4 or later: 89.1% (n = 82)
  - Day 6 or later: 73.9% (n = 68)
- Cytokine release syndrome resolved in 91 patients (98.9%) ≤ 14 days of onset

Madduri. ASH 2020. Abstr 177. Reproduced with permission.

Neurotoxicity (NT)
Ciltacabtagene autoleucel (cilta-cel)

Neurotoxicities CARTITUDE-1 trial	All Patients (N = 97)	
	All Grade	Grade ≥ 3
Total CAR T-cell NT AEs	20 (20.6%)	10 (10.3%)
ICANS	16 (16.5%)	2 (2.1%)
Other NTs*	12 (12.4%)	9 (9.3%)

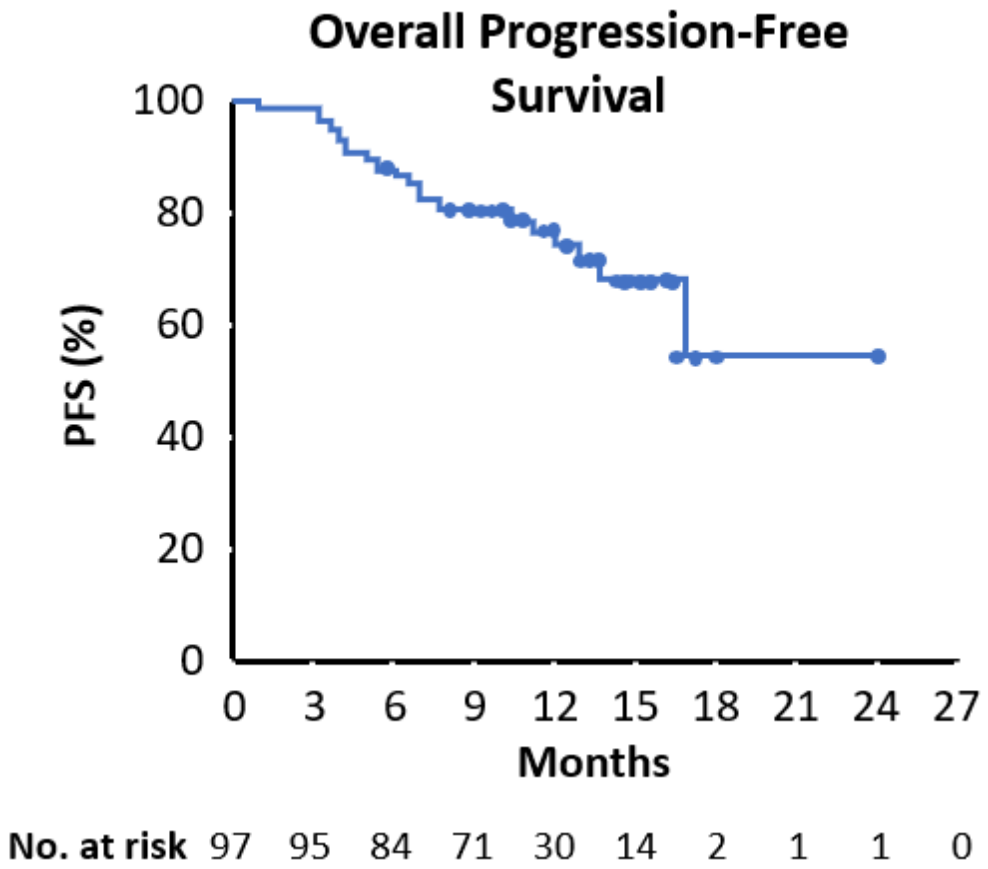
Characteristic	ICANS	Other NT*
Median time to onset, (range)	8 days (3-12 days)	27 days (11-108 days)
Median time to recovery, (range)	4 days (1-12 days)	75 days (2-160 days)

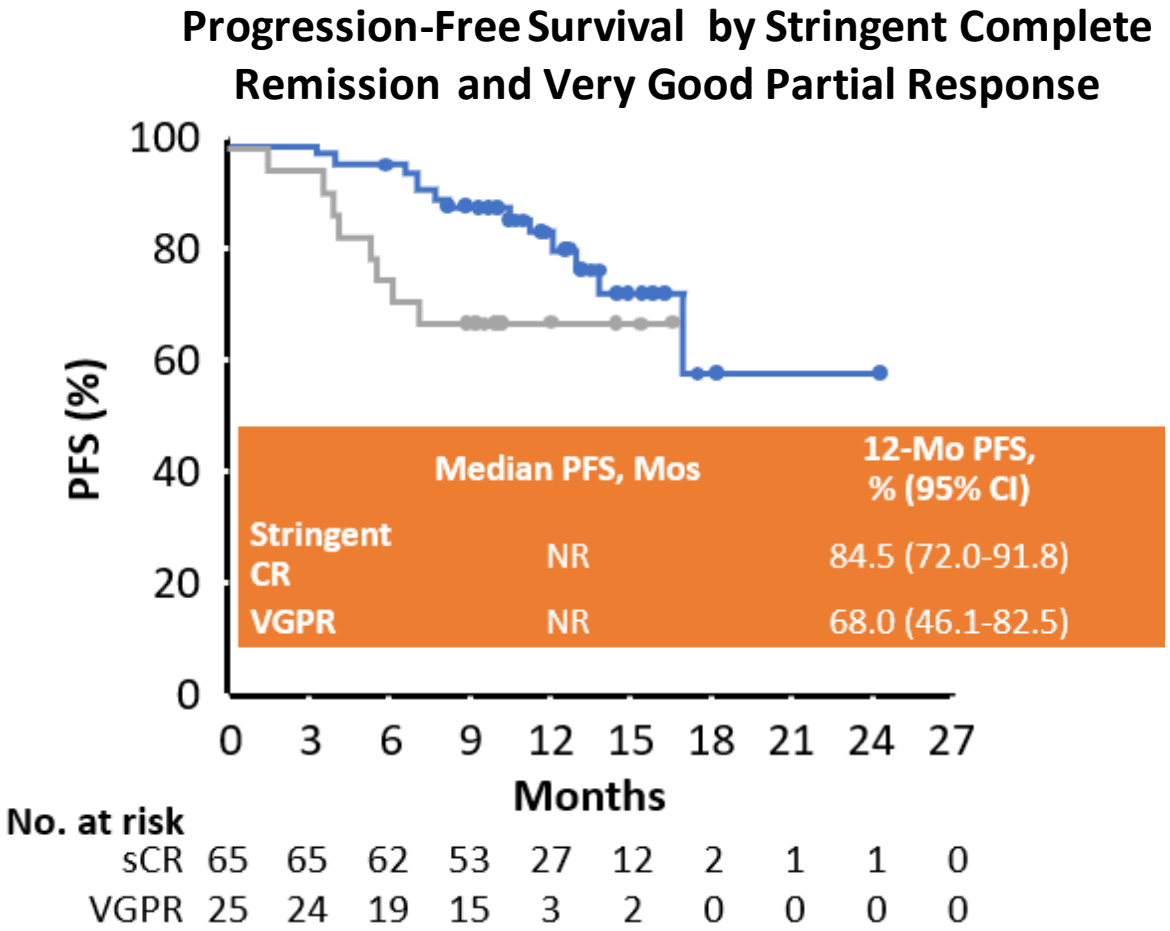
- All patients with ICANS recovered
- Other NTs resolved in 6 patients, and did not resolve in 6 patients:
  - 1 patient has ongoing NT
  - 1 patient died from NT complications
  - 4 patients died of other causes
- No other movement and neurocognitive adverse evebts observed in the CARTITUDE development program

Other neurotoxicities occurred after cytokine release syndrome and/or ICANS resolved included 5 patients with movement and/or neurocognitive changes, 7 patients with nerve palsy, peripheral motor neuropathy.

Madduri. ASH 2020. Abstr 177.

Progression-Free Survival
Ciltacabtagene autoleucel (cilta-cel) – CARTITUDE-1





- Median duration of follow-up: 12.4 mos (range: 1.5-24.9); median Progression-free survival: NR
- 12-mo progression-free survival rate: 76.6% (95% CI: 66.0-84.3); 12-mo Overall survival rate: 88.5% (95% CI: 80.2-93.5)

Madduri. ASH 2020. Abstr 177. Reproduced with permission.

Efficacy and Safety Across BCMA CAR T Trials in Relapsed/Refractory Multiple Myeloma

Parameter	Cilta-cel[1,2] (n = 97) CARTITUDE-1	Ide-cel[3,4] (n = 54) KarMMa
Dose	0.75 x 10^6 cells/kg	450 x 10^6 cells
Median prior lines of tx, (range)	6 (3-18)	6 (3-16)
Triple-class refractory	88%	81%
Overall Response Rate	97.9%	81%
Minimal Residual Disease	57.7%	48%
≥Complete Response	43%	39%
Progression-Free Survival	66% at 18 mo	Median: 12.1 mo

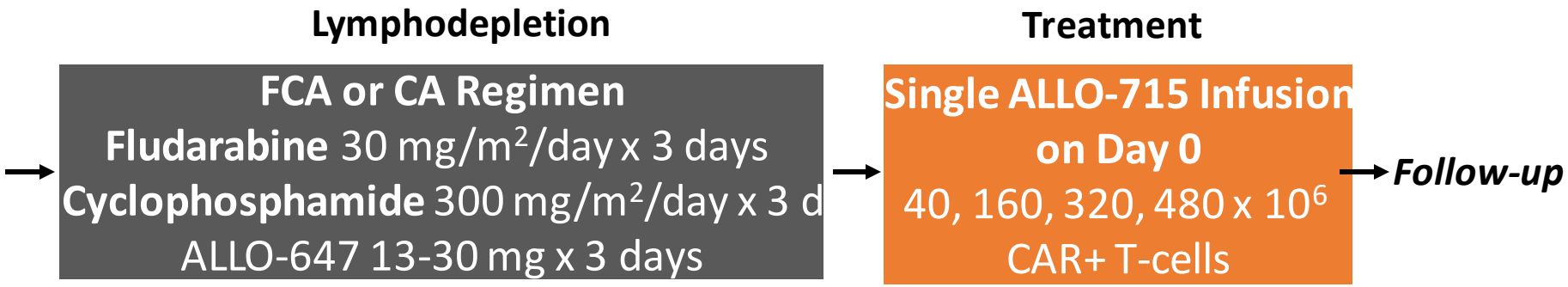
1. Madduri. ASH 2020. Abstr 177. 2. Usmani. ASCO 2021. Abstr 8005. 3. Anderson. ASCO 2021. Abstr 8016.
4. Munshi. NEJM. 2021;384:705.

Allogeneic (donor) CAR T-Cell Therapy

First-in-Human Phase I Trial (UNIVERSAL)

- Multicenter, open-label, dose-escalation phase I study

Adults with Relapsed/ Refractory Myeloma; ≥ 3 previous therapies (including IMiD, PI, anti-CD38); refractory to last therapy; ECOG PS 0/1; no donor specific antibodies; no bridging therapy permitted (N = 35)*



Two Lymphodepletion regimens tested

FCA= fludarabine/cyclophosphamide/ALLO-647

CA = cyclophosphamide/ALLO-647

Abs: antibodies; CA: cyclophosphamide; FCA: fludarabine/cyclophosphamide/ALLO-647; IMiD: immunomodulatory drug; PI: proteosome inhibitor;

Mailankody. ASH 2020. Abstr 129.

Allogeneic (donor) CAR T-Cell Therapy: Safety

- Manageable safety profile observed with allogeneic BCMA CAR T-cell therapy
  - No graft-versus-host disease OR neurotoxicity
  - 45% experienced grade 1/2 cytokine release syndrome; low use of tocilizumab (19%) and steroids (10%)
  - 23% experienced grade 1/2 infusion reaction to ALLO-647
- Serious adverse events (grade ≥3) in 19%
  - 5 (16%) grade ≥ 3 infection
  - 1 grade 5 event related to progressive myeloma in CA cohort

Adverse Events of Interest	Safety Population (N = 31)
Cytokine Release Syndrome	14 (45%)
▪ Grade 1	5 (16%)
▪ Grade 2	9 (29%)
▪ Grade ≥ 3	0
Infection (bacterial, fungal, viral)	13 (42%)
▪ Grade 1	2 (7%)
▪ Grade 2	6 (19%)
▪ Grade 3	4 (13%)
▪ Grade 5	1 (3%)
Infusion reaction to ALLO-647	7 (23%)
▪ Grade 1	4 (13%)
▪ Grade 2	3 (10%)

Mailankody. ASH 2020. Abstr 129.

Allogeneic (donor) CAR T-Cell Therapy: Response Rate

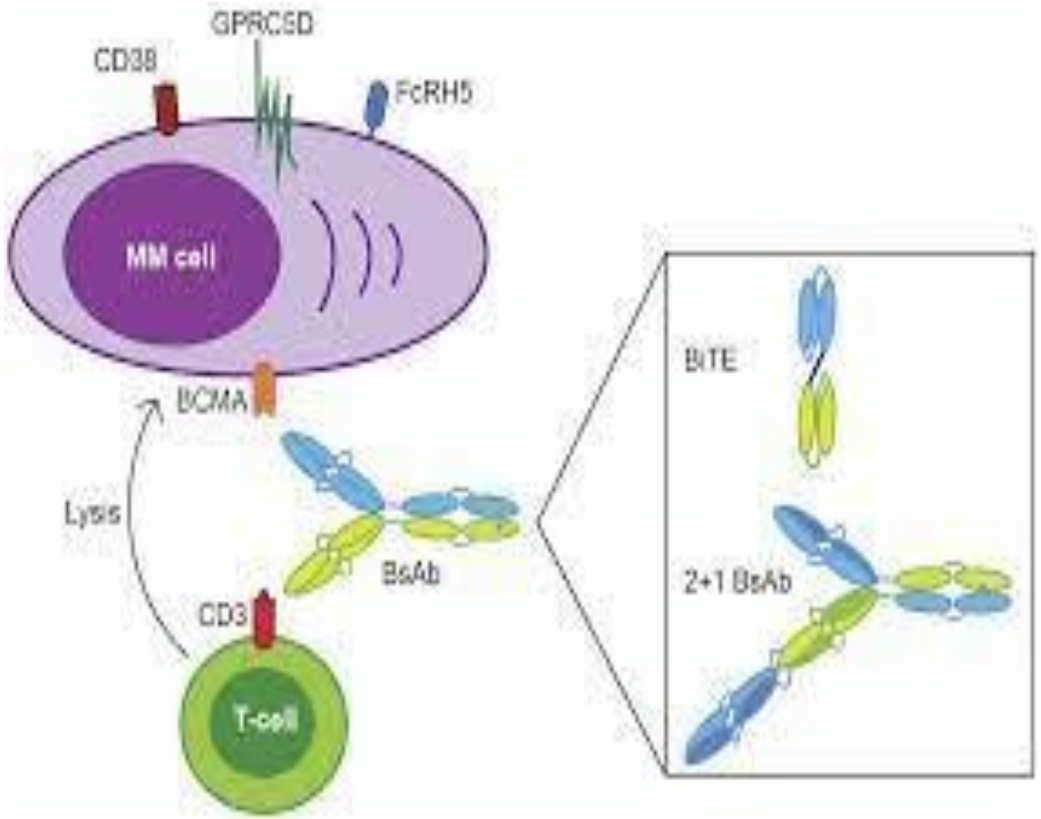
- 60% of patients in FCA plus 320 x 10^6 dose of ALLO-715 cohort responded to treatment; 40% achieved ≥ Very Good Partial Response[1]
- 5/6 patients assessed with ≥ Very Good Partial Response had negative Minimal Residual Disease status[1]

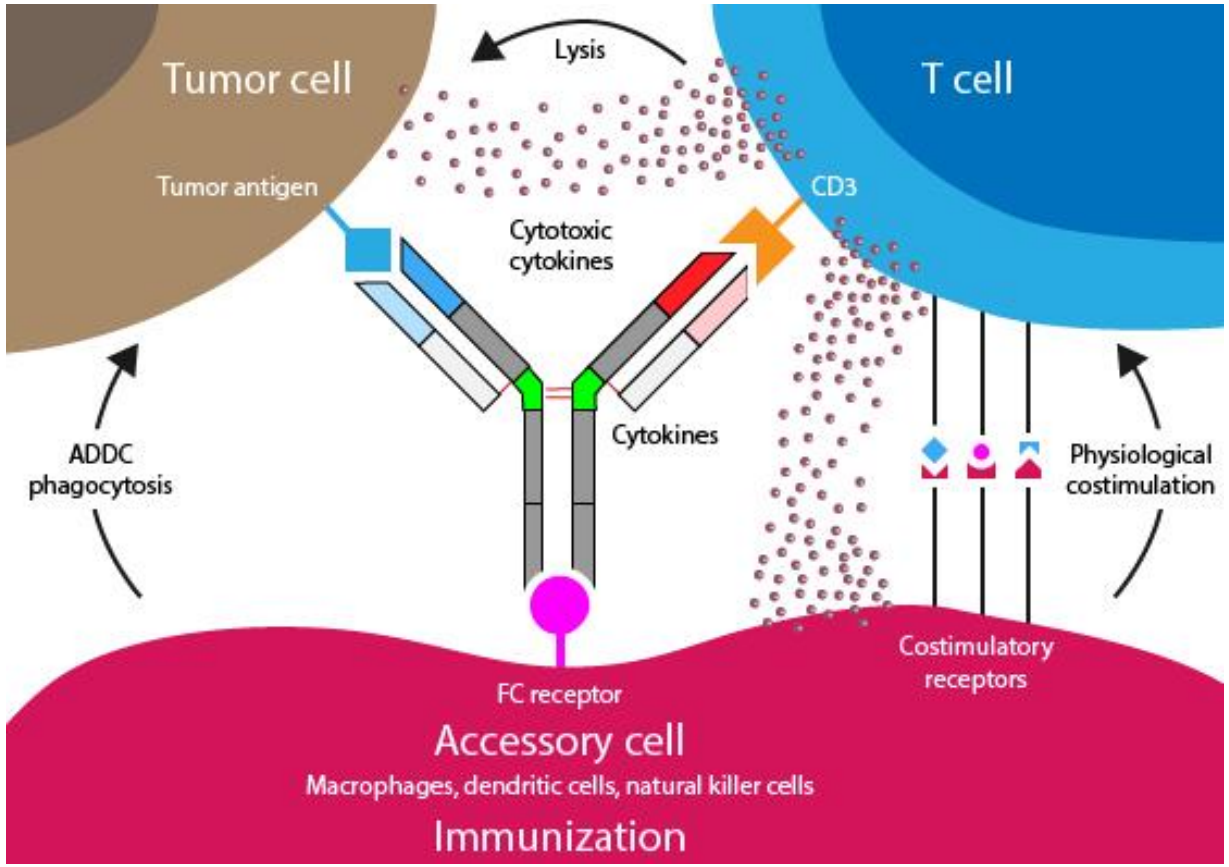
Cell Dose and Lymphodepleting Regimen	Fludarabine/Cyclophosphamide Cohort (FCA)						Cyclophosphamide Cohort (CA)	
ALLO-715	40	160	320	320	320	480	160	320
ALLO-647	Low (n = 3)	Low (n = 4)	Low (n = 6)	High (n = 4)	All (n = 10)	Low (n = 3)	Low (n = 3)	Low (n = 3)
Overall Response Rate	--	2 (50%)	3 (50%)	3 (75%)	6 (60%)	1 (33%)	--	2 (67%)
≥ Very good Partial Remission	--	1 (25%)	3 (50%)	1 (25%)	4 (40%)	--	--	1 (33%)

Clinical response evaluation based on International Myeloma Working Group response criteria.[2] ≥ Very Good Partial Remission defined as stringent Complete Remission, Complete Remission or Very Good Partial Remission.

1. Mailankody. ASH 2020. Abstr 129. 2. Kumar. Lancet Oncol. 2016;17:e328.

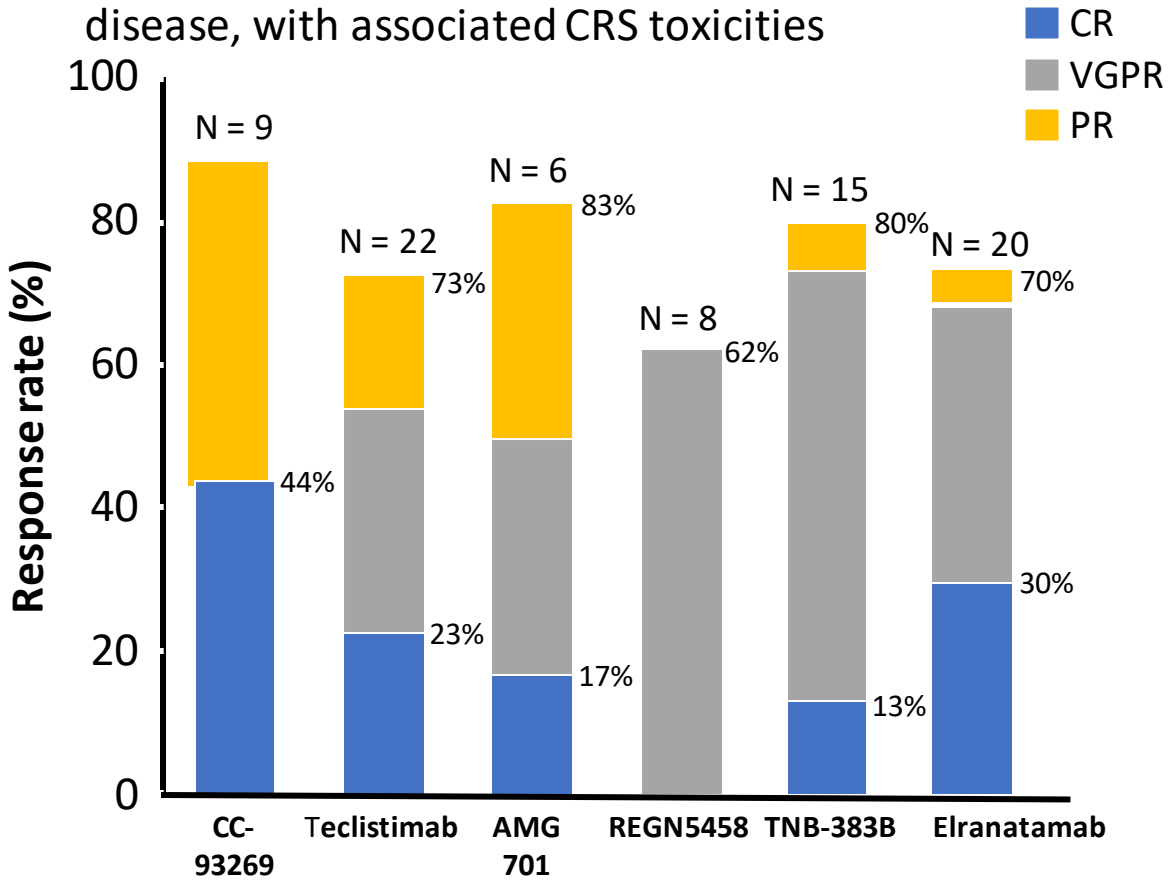
Bispecific and Trispecific Antibodies

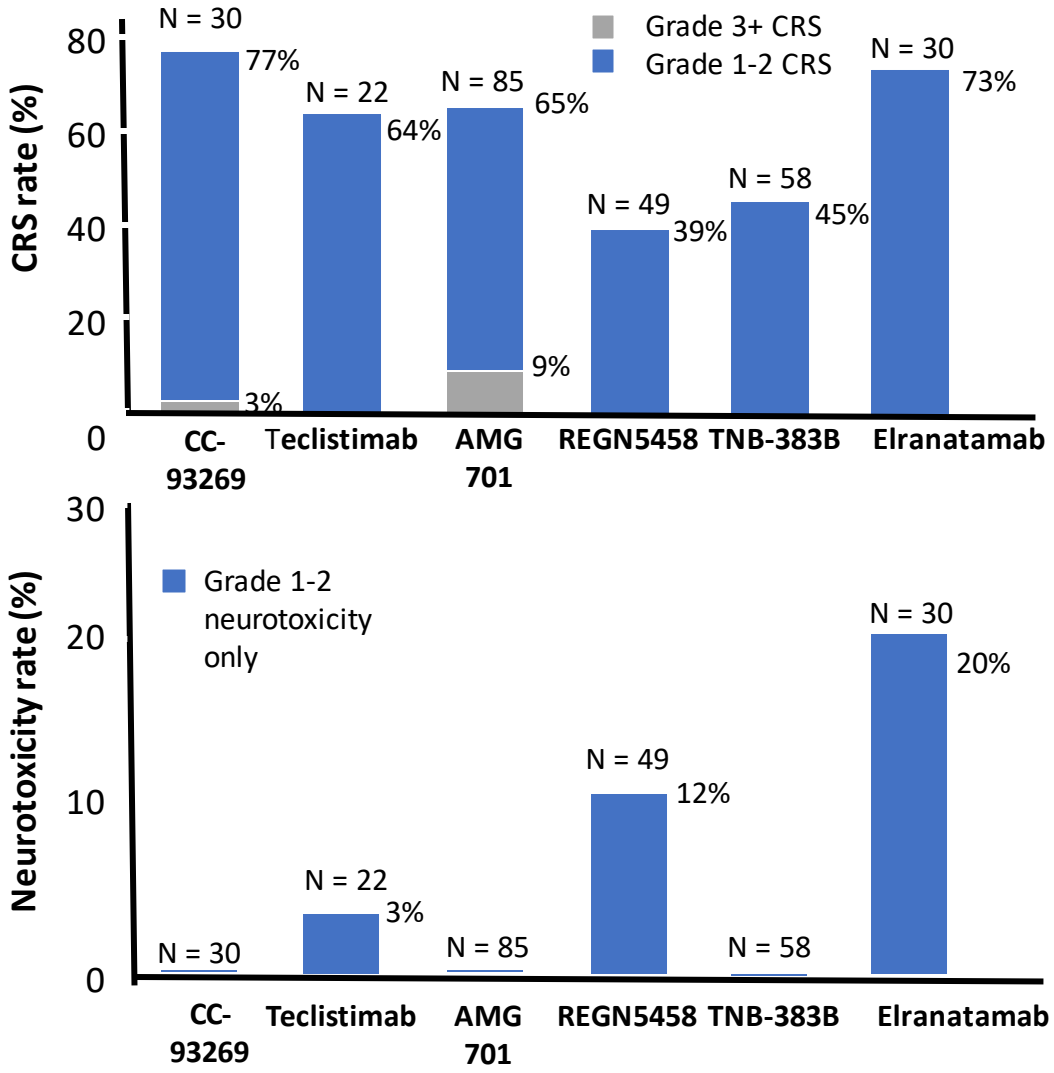




Data With Anti-BCMA Bispecific Antibodies

- Promising responses in patients with "triple-class exposed" disease, with associated CRS toxicities

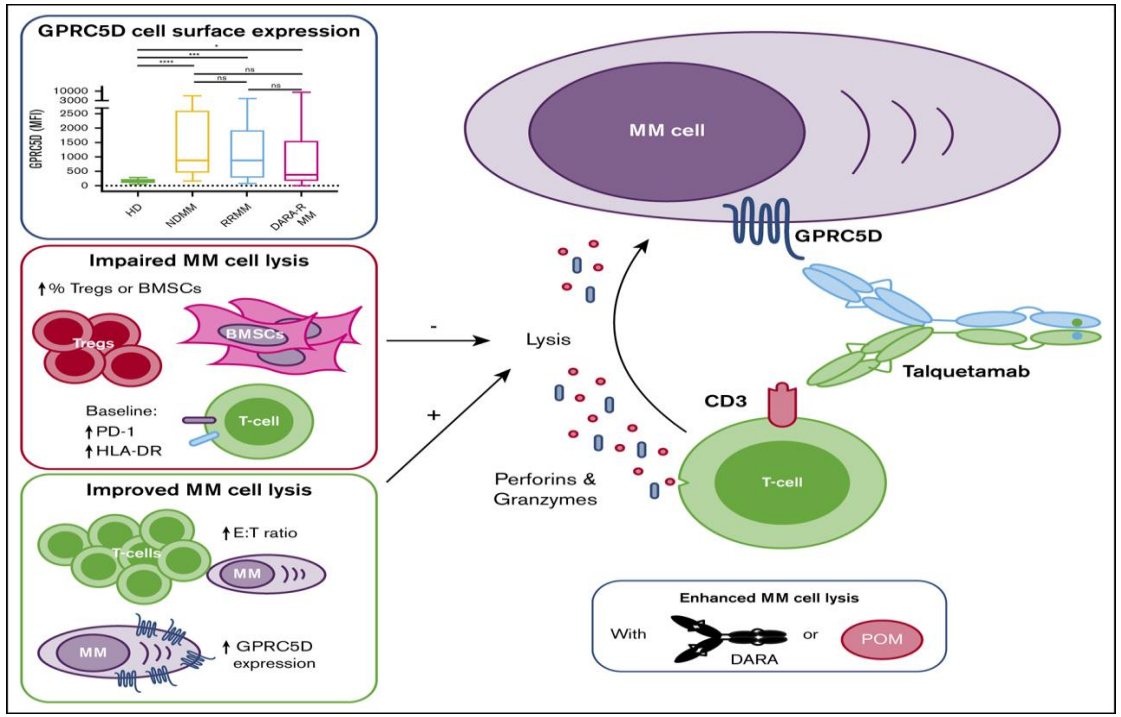




Nearly all patients had prior anti-CD38 antibody across trials.

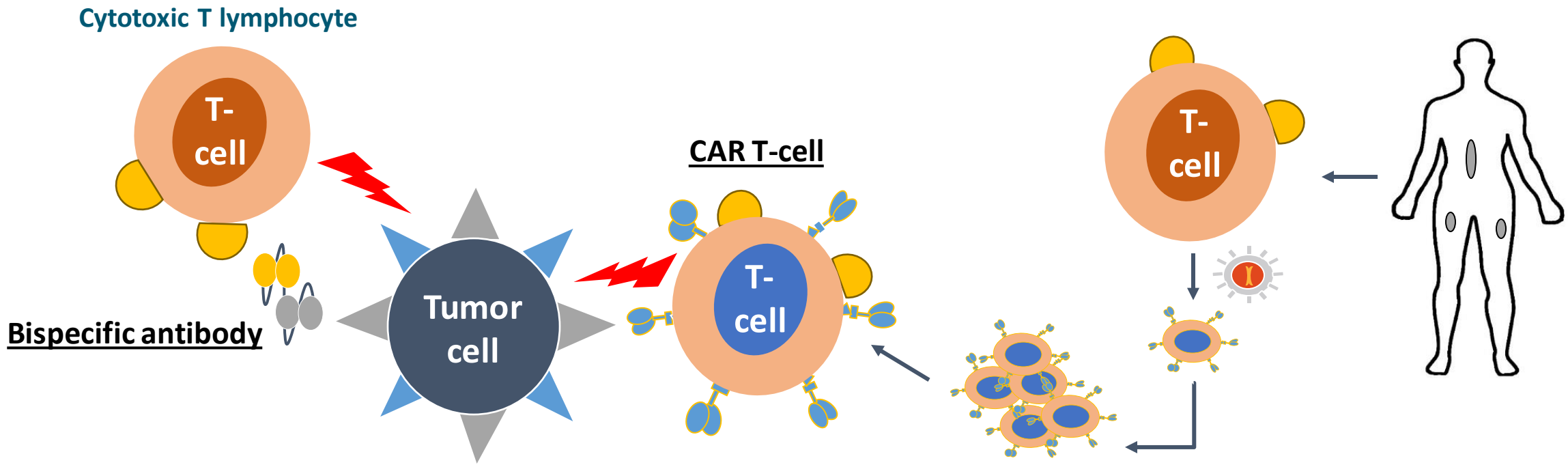
1. Costa. EHA 2020. Abstr S205. 2. Garfall. ASH 2020. Abstr 180. 3. Harrison. ASH 2020. Abstr 181.
4. Madduri. ASH 2020. Abstr 291. 5. Rodriguez. ASH 2020. Abstr 293. 6. Bahlis. ASCO 2021. Abstr 8006.

Talquetamab: GPRC5DxCD3 Bispecific Antibody



Response, n (%)	5-45 μg/kg SC (n = 14)	135 μg/kg SC (n = 8)	405 μg/kg SC (RP2D) (n = 13)	800 μg/kg SC (n = 11)
ORR	2 (14)	4 (50)	9 (69)	8 (73)
▪ sCR/CR	0	0	2 (15)	0
▪ VGPR	0	1 (13)	3 (23)	5 (45)
▪ PR	2 (14)	3 (38)	4 (31)	3 (27)

Bispecific Antibodies vs CAR T-Cell Therapy



Characteristic	Bispecific Antibodies	CAR T-Cell Therapy
Preparation	"Off the shelf"	In vitro manufacturing (3-4 wk)
Dosing	Repetitive	Single (following lymphodepleting CT)
Cytokine Release Syndrome incidence	Less	Greater

Slaney. Cancer Discov. 2018;8:924. Blinatumomab PI. Tisagenlecleucel PI.

Select Studies of CAR T-Cell Therapies for Relapsed/Refractory Multiple Myeloma:

136 Trials of CAR T Cells in Clinicaltrials.gov

Study	CAR T-Cell Therapy	Phase	Key Findings
KarMMa-3 (NCT03651128)	Idecabtagene vicleucel	III	▪ Ongoing; **RCT vs standard triplet therapy**
KarMMa-2 (NCT03601078)	Idecabtagene vicleucel	II	▪ Ongoing
CARTITUDE-4 (NCT04181827)	Ciltacabtagene autoleucel	III	▪ Ongoing; **RCT vs standard triplet therapy**
CARTITUDE-2 (NCT04133636)	Ciltacabtagene autoleucel	II	▪ Ongoing; ORR 95% (N = 20)[1]
CARTIFAN-1 (NCT03758417)	Ciltacabtagene autoleucel	I/II	▪ Ongoing
NCT03288493	P-BCMA-101	I/II	▪ Ongoing
CRB-402 (NCT03274219)	bb21217	I	▪ Ongoing; ORR 83% (n = 18)[2]

- Additional targets in MM: CD44v6, CD70, CD56, CD38, CD138, CD19, SLAMF7[6]

1. Agha. ASCO 2021. Abstr 8013. 2. Berdeja. ASH 2019. Abstr 927. 3. Friedman. Hum Gen Ther. 2018;29:585.
4. Fraietta. Nat Med. 2018;24:563. 5. Gregory. ASH 2018. Abstr 1012. 6. Mikkilineni. Blood. 2017;130:2594.

Abbreviations Used in Presentation

AE	Adverse event
BCMA	B-cell maturation antigen
BM	Bone marrow
CA	Cyclophosphamide
CAR	Chimeric Antigen Receptor
CR	Complete response
CRR	Complete remission rate
Dex	Dexamethasone
DoR	Duration of response
ECOG PS	Eastern Cooperative Oncology Grooup Performance Status
FCA	Fludarabine/cyclophosphamide
HEOR	Health economics and outcomes research
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
LD	Lymphodepletion
mAb	Monoclonal antibody
MM	Multiple Myeloma
mOS	Median overall survival
mPFS	Median progression-free survival
MR	Minimal response
MRD	Measurable residual disease
NE	Not estimable
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Proteasome inhibitor
PK	Pharmokinetics
Pom	Pomalidomide
PR	Partial response
QoL	Quality of Life
R/R	Relapsed/refractory
SAE	Severe adverse event
sCR	Stringent complete response
Tx	Therapy
VGPR	Very good partial response