Penn Medicine

An Update on Novel Immunotherapy Approaches in Multiple Myeloma

Patricia Mangan RN, MSN, APRN-BC

Nurse Lead, Hematologic Malignancies
Abramson Cancer Center
University of Pennsylvania
Philadelphia, PA

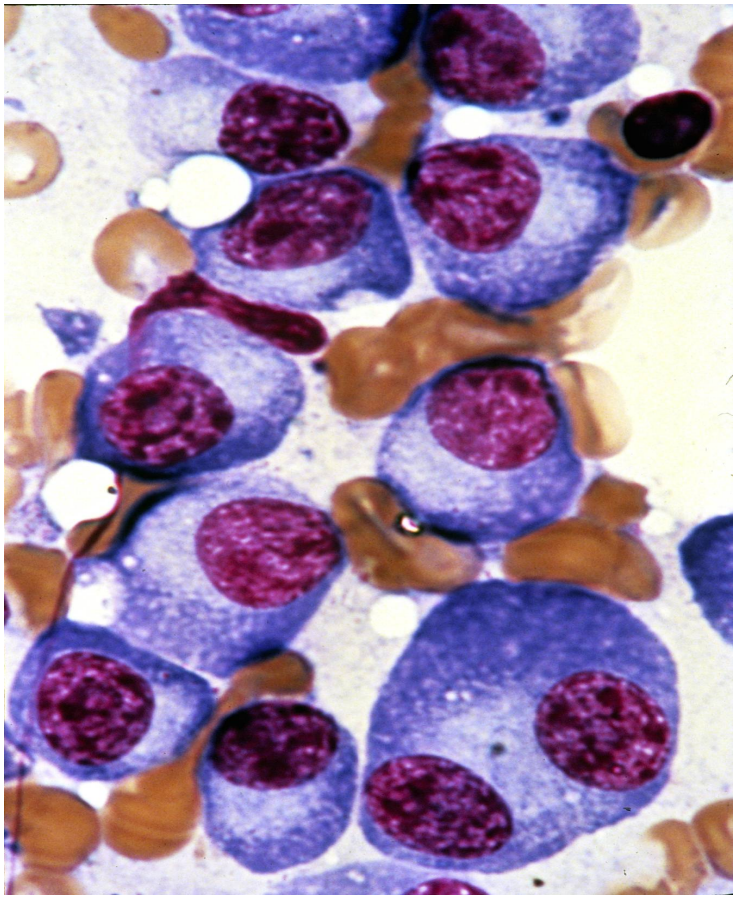
May 6, 2021

the cure is within
ABRAMSON CANCER CENTER

Objectives

- Discuss the rationale of immunotherapies in the treatment of relapsed refractory multiple myeloma.
- Review emerging treatment options that target BCMA and their MOAs
- Describe the CAR-T process, its potential toxicities and interventions in relapsed refractory multiple myeloma.

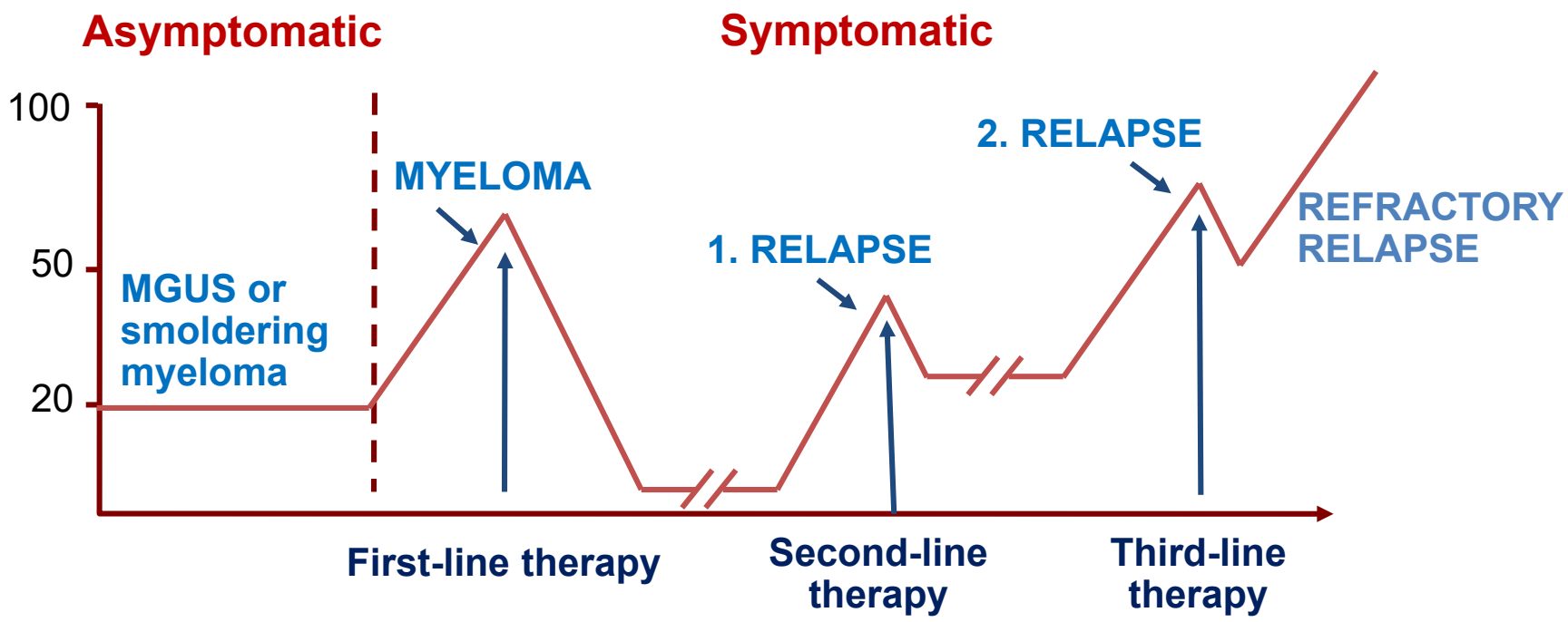
What Is Multiple Myeloma



- **Cancer of the plasma cells in bone marrow**
- **Growth of myeloma cells**
  - Disrupts normal bone marrow function
  - Reduces normal immune function
  - Results in abnormal production and release of monoclonal protein into blood and/or urine
  - Destroys and invades surrounding bone
- **Common Features**
  - Anemia
  - Lytic bone lesions
  - Renal insufficiency or failure
  - Hypercalcemia

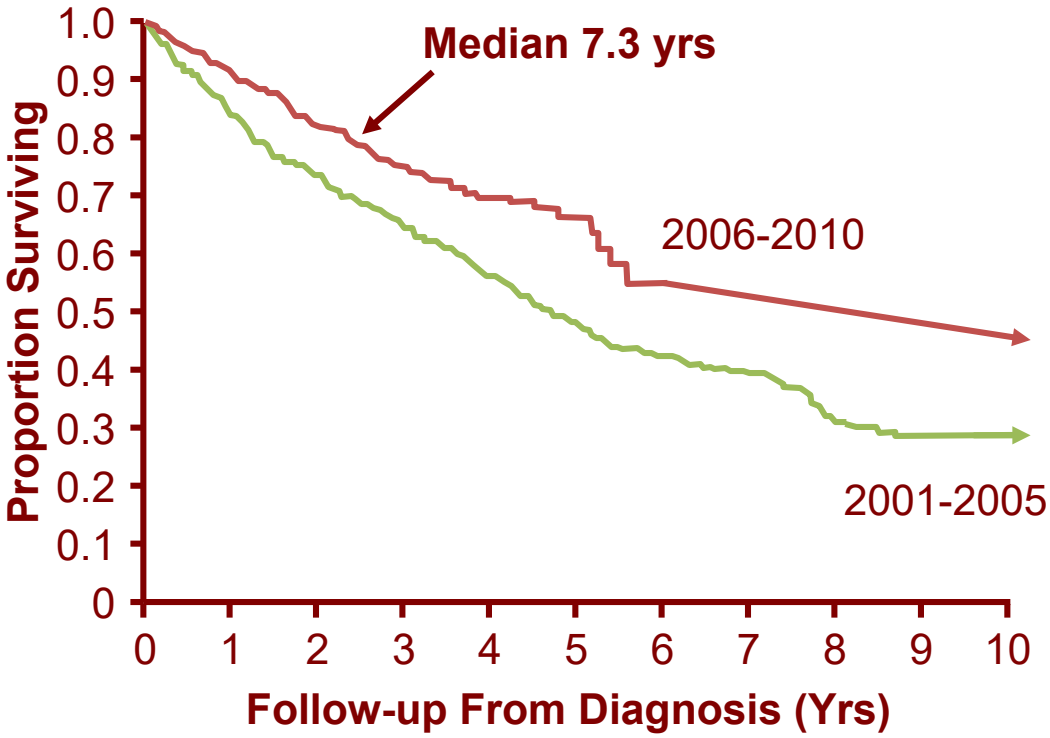
Barlogie et al. In: *Williams Hematology.* 7th ed. 2006:1501.
Durie. International Myeloma Foundation. 2007. www.myeloma.org.

Natural History of Multiple Myeloma



Kuehl WM, et al. Nat Rev Cancer. 2002;2:175-187. Vacca A, et al. Leukemia. 2006;20:193-199. Siegel DS, et al. Community Oncol. 2009;6:12:22-29. Durie BG, et al. Hematol J. 2003;4:379-398; Adapted with permission from Durie B @ www.myeloma.org.

MM Survival is Improving With Novel Agents



5-Yr Survival by Age

	≤ 65 Yrs	> 65 Yrs
2006-2010	73%	56%
2001-2005	63%	31%

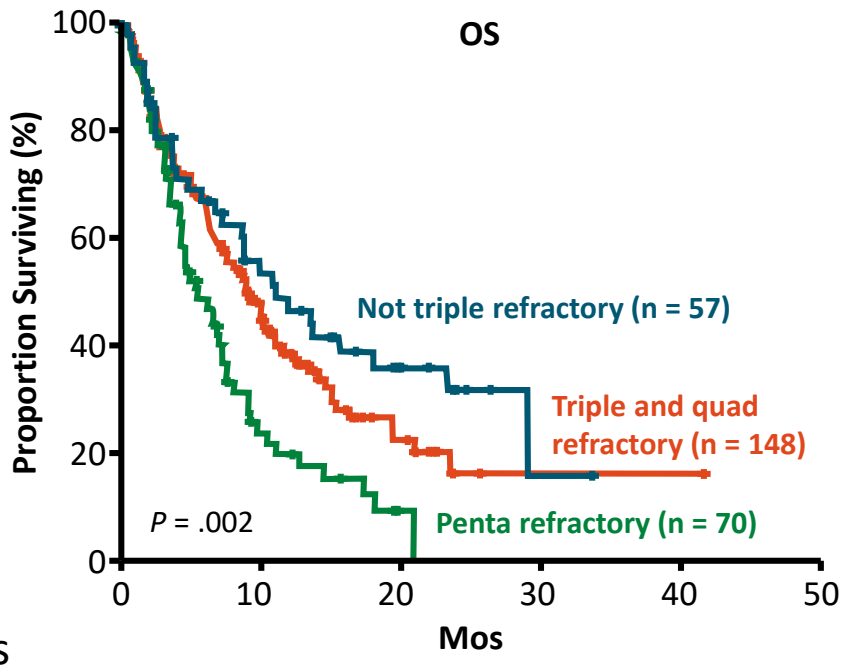
Use of **novel agent inductions** with **melphalan and ASCT** have doubled median survival for nearly all patients

Kumar SK, et al. Poster presentation. American Society of Hematology Annual **M**eeting. Atlanta, GA. 2012. Abstract 3972.

MAMMOTH: Suboptimal Outcomes in Patients With MM Refractory to CD38 Antibody

- Retrospective analysis of 275 patients from 14 academic centers

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



- 249 patients received further treatment
  - ORR: 31%; mPFS: 3.4 mos; mOS: 9.3 mos

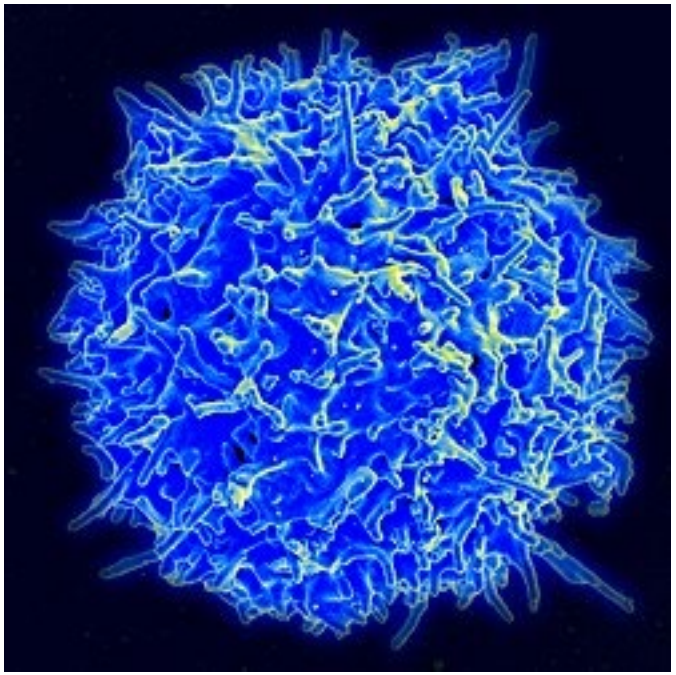
Gandhi. Leukemia. 2019;33:2266.

Slide credit: clinicaloptions.com

Targeted Cellular Therapy: Rationale

T cells are central to immunity, playing an important role in combating cancer

Possess T-cell receptors (TCR) on their surface that circulate and destroy infected or tumor cells by binding to the antigen on surface of abnormal cells

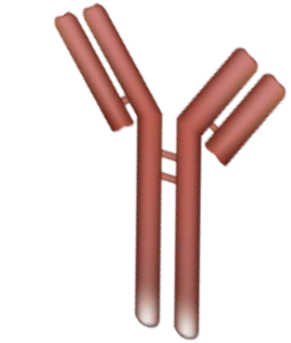


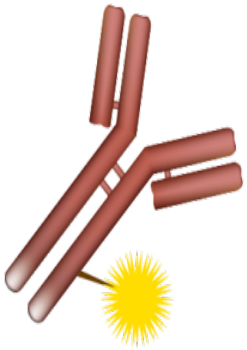
T cells may fail to eliminate cancer:

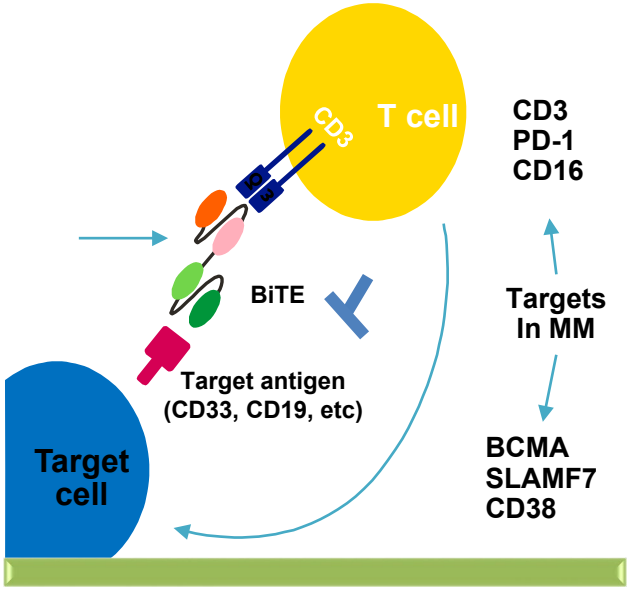
- T cells are unable to recognize tumor cells as foreign
- T-cell activation is suboptimal
- T-cell activity is suppressed

Types of Monoclonal Antibodies

Naked	Drug conjugates	Bispecific







- Nothing is attached
- Target in MM:

CD 38: Dara
Isa
DaraSq

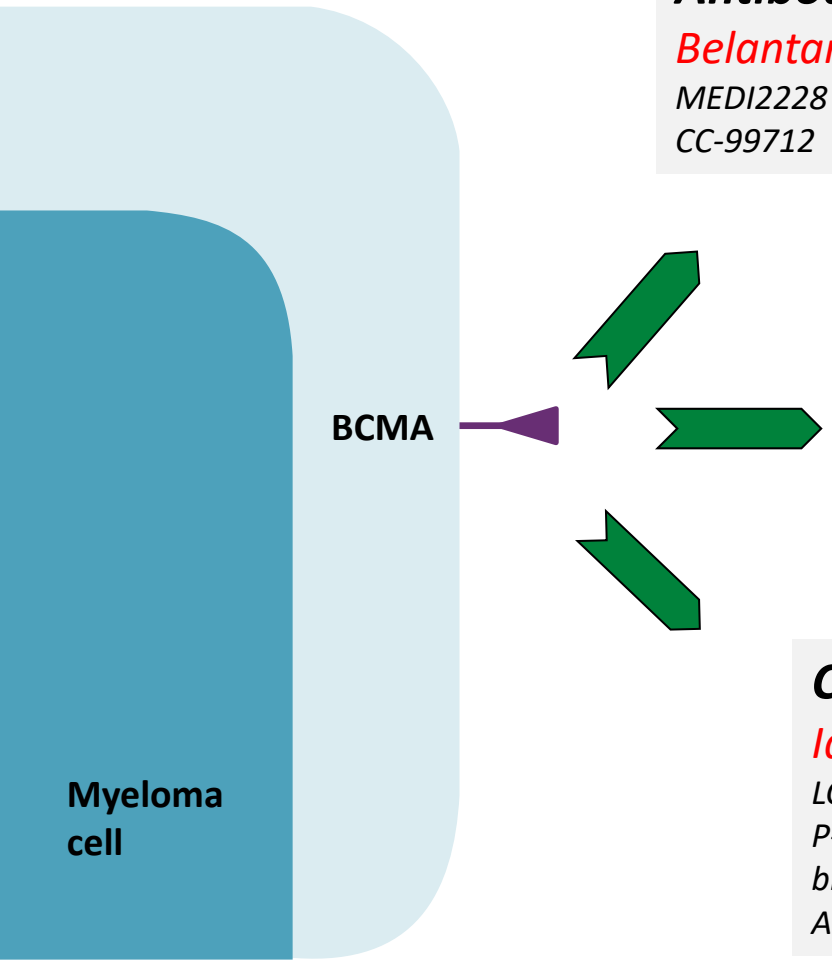
SLAMF7/CS1:
Elo

- A toxin or radioactive isotope is attached

- Simultaneously bind to two different types of antigens

Courtesy of Noa Biran, MD

BCMA-Targeted Therapies



Antibody–Drug Conjugates

Belantamab mafodotin

MEDI2228

CC-99712

Bispecific T-Cell Engagers

AMG 420

AMG 701

CC-93269

REGN5458

JNJ-64007957 teclistamab

PF-06863135

CAR T-Cell Therapies

Idecabtagene vicleucel "ide-cel" (ABECMA)

LCAR-B38M

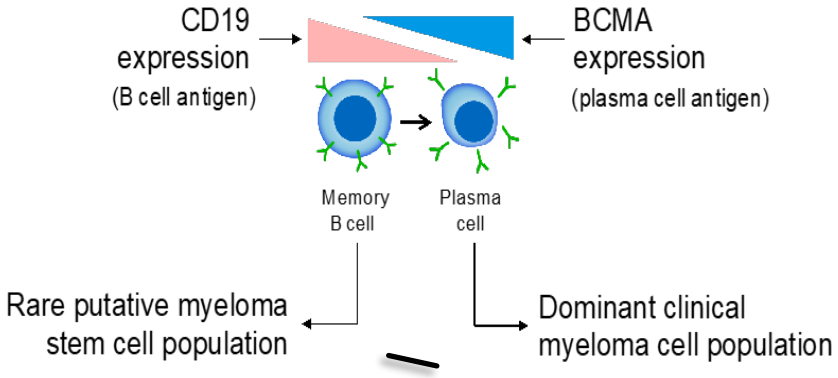
P-BCMA-101

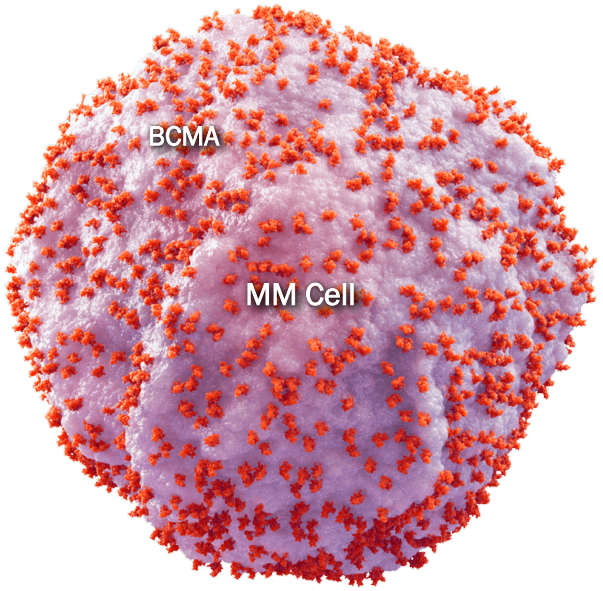
bb21217

ALLO-715

BCMA is an Important Target in MM

- All MM cells express BCMA
  - BCMA expression is elevated in MM cells relative to normal plasma cells[1,2]
- BCMA expression correlates with disease progression[1,2]
- BCMA
  - activates signal transduction pathways
  - upregulates anti-apoptotic proteins to drive MM cell proliferation and survival[1]



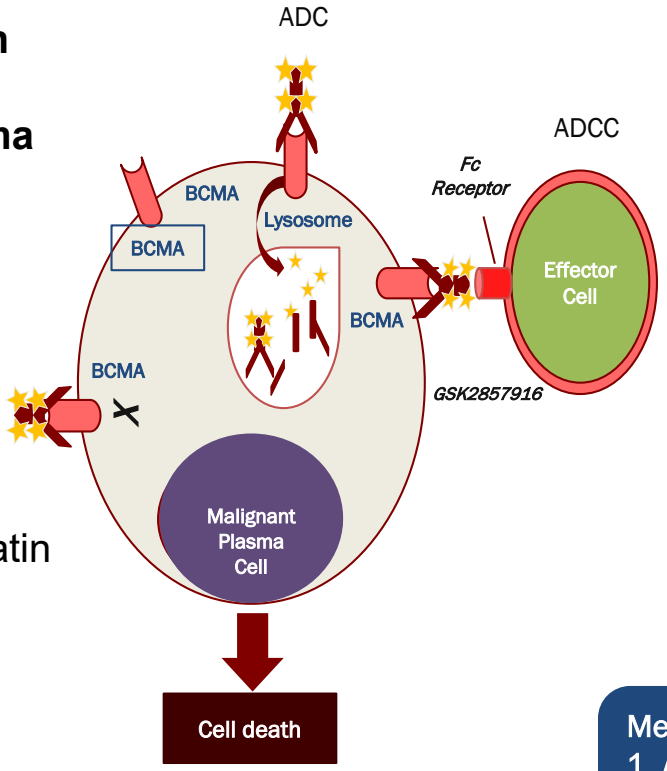


BCMA, B-cell maturation antigen; MM, multiple myeloma.

References: 1. Cho SF, et al. *Front Immunol*. 2018;9:1821. **2.** Sanchez E, et al. *Br J Haematol*. 2012;158:727-738.

Belantamab Mafodotin: A BCMA-Targeted ADC

- **B-cell maturation antigen Expressed on normal plasma cells and myeloma cells**
  - Highly expressed on myeloma cells and promotes MM pathogenesis
- **Belantamab Mafodotin**
  - Anti-BCMA mAb conjugated to auristatin F through a non-cleavable linker



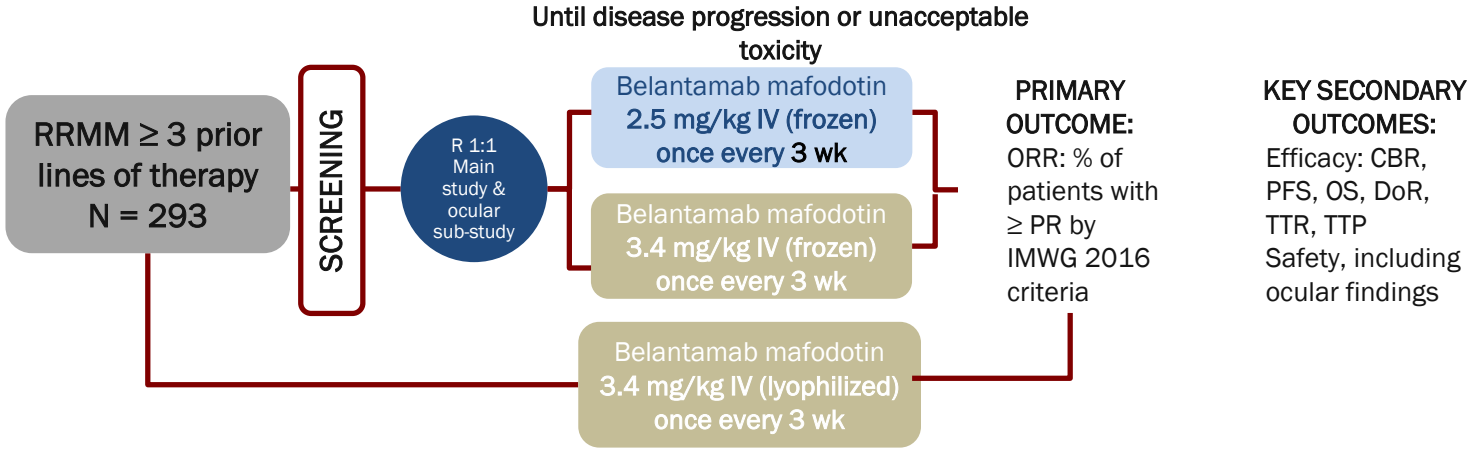
Fc region of the antibody	• Target specific • Enhanced ADCC
Linker	• Stable in circulation
Drug	• MMAF (non-cell-permeable, highly potent auristatin)

Mechanisms of action:
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death

- *Every 3 weeks until disease progression or unacceptable toxicity.
- Tai YT, et al. *Blood*. 2014;123:3128–3138.

DREAMM-2 Trial

Study Design



ORR: 2.5 mg/kg cohort 34%

3.4 mg/kg cohort 31%

Led to FDA accelerated approval of 2.5 mg/kg belantamab mafodotin-blmf for adult patients with RRMM who have received ≥ 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent

- Lonial S, et al. *Lancet Oncol*. 2020;21:207-221.

Potential Toxicities

- **Keratopathy/Ocular toxicity**
  - Deceased visual acuity (53%)
  - Blurred vision (22%)
  - Dry eyes (14%)
  - Corneal ulceration
  - No permanent loss of vision

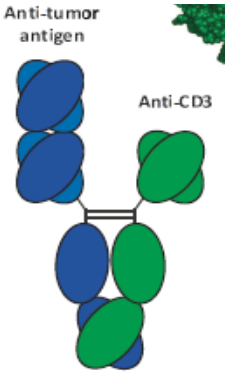
REMS program in place (BLENREP REMS)

- Ophthalmic exam w/ split lamp at baseline and within 14 days prior to each dose
- Use preservative free saline eye drops and avoid use of contact lens
- If occurs, decrease dose or hold dose or both

- **Some hematological toxicity:**
  - Thrombocytopenia (21% Gr 3/4)
- **Nausea (24%)**
- **Pyrexia (22%)**
- **Infusion-related reactions (21%)**
- **Fatigue (20%)**

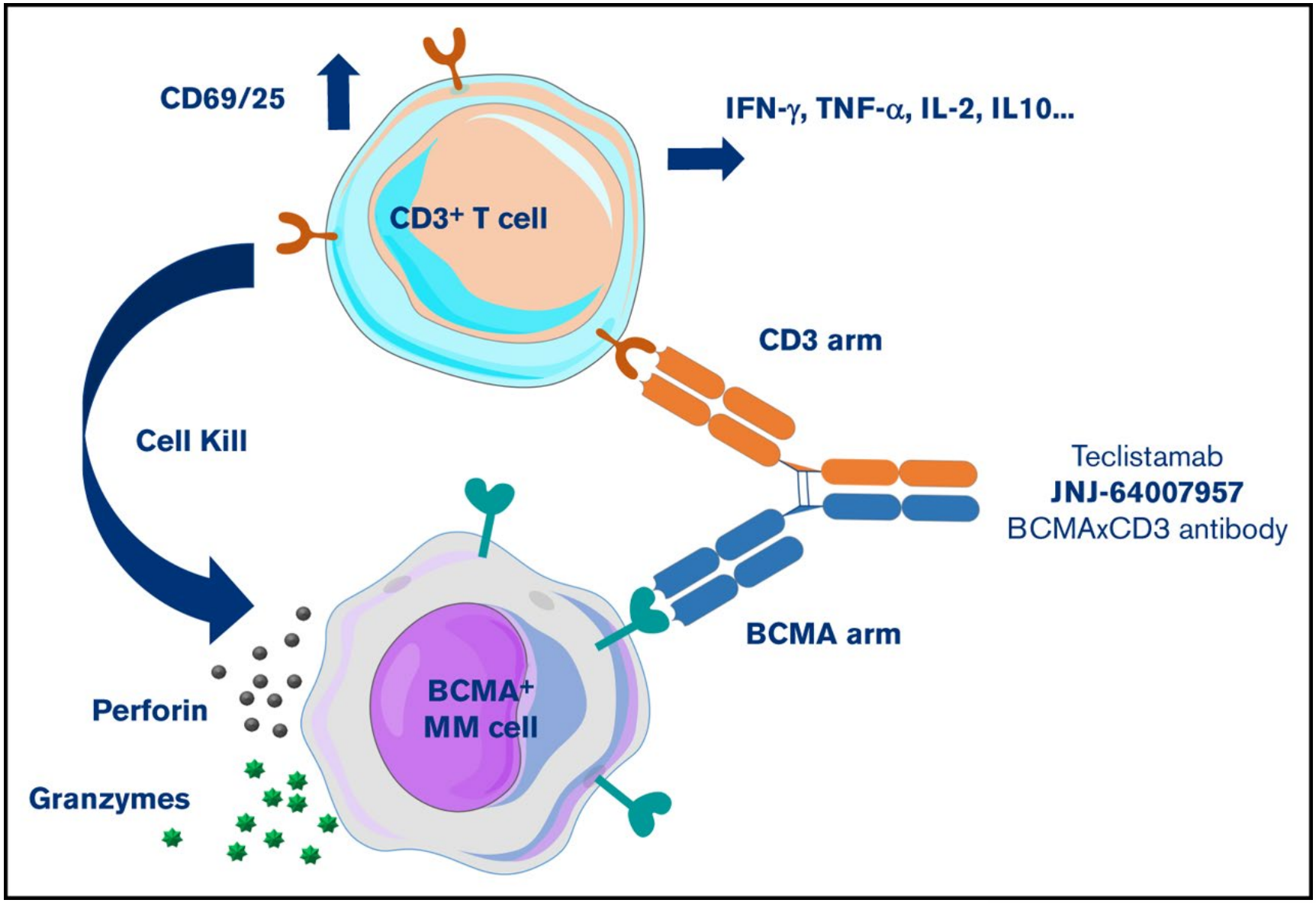
Reference: 1. BLENREP Prescribing Information.

Bispecific Antibodies for MM



	IgG-like molecules	Non-IgG-like molecules
Fc domain	Yes	No
Half-life	Long	Short
	AMG701 (BCMA) PF-06863135 (BCMA) JNJ-64007957 (BCMA) EM801 (BCMA) CC-93269 (BCMA) REGN5458 (BCMA) HPN217 (BCMA) TNB-383B (BCMA) AFM26 (BCMA) BFCR4350A (FcRH5) GBR1342 (CD38) TRIMM-2 JNJ-64407564 (GPRC5D)	AMG420 (BCMA) Blinatumumab (CD19)

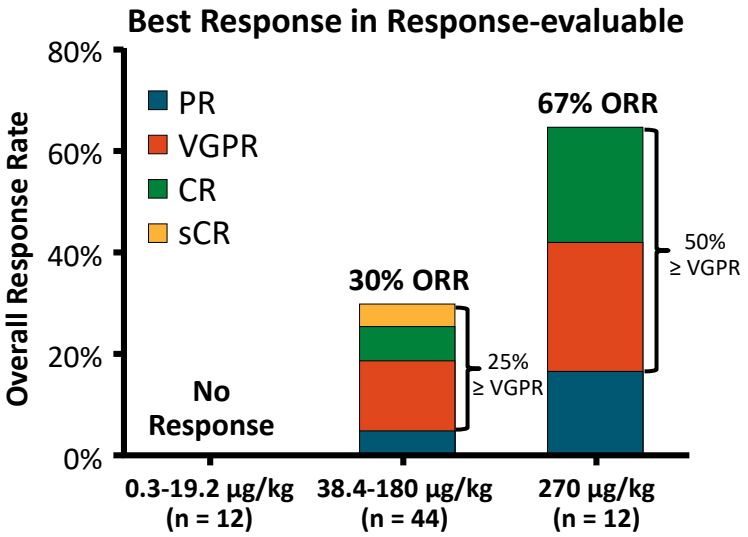
Teclistamab BCMA x CD3 antibody

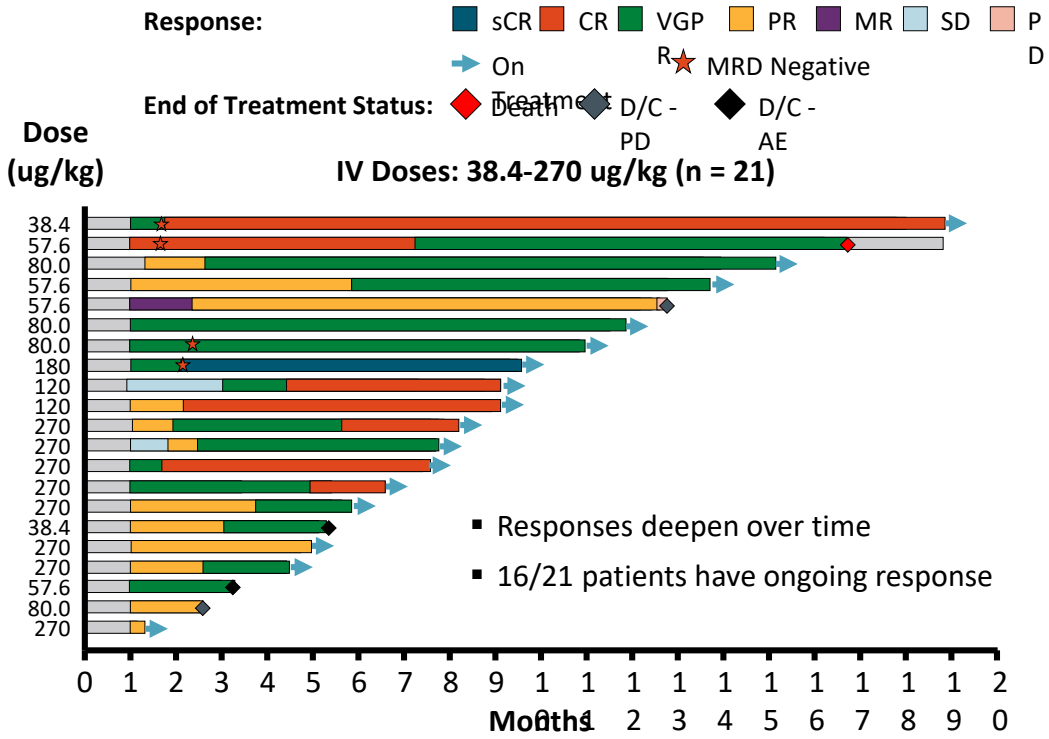


Phase I Dose Escalation of Teclistamab: Efficacy

Teclistamab is a BCMA x CD3 bispecific antibody

- Key eligibility criteria: RR or intolerant to established MM therapies
- Median prior lines: 6 (2 – 14)
- Triple class refractory 86%



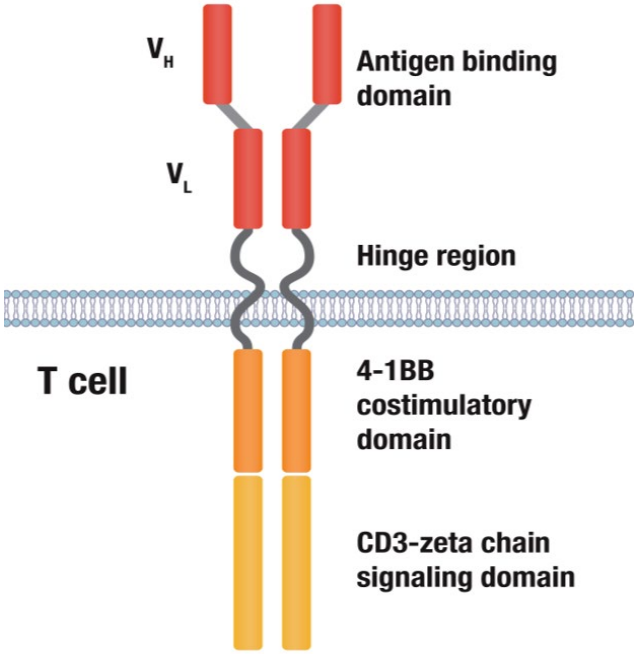


Usmani. ASCO 2020. Abstr 100. Mateos. EHA 2020. Abstr S206.

Slide credit: clinicaloptions.com

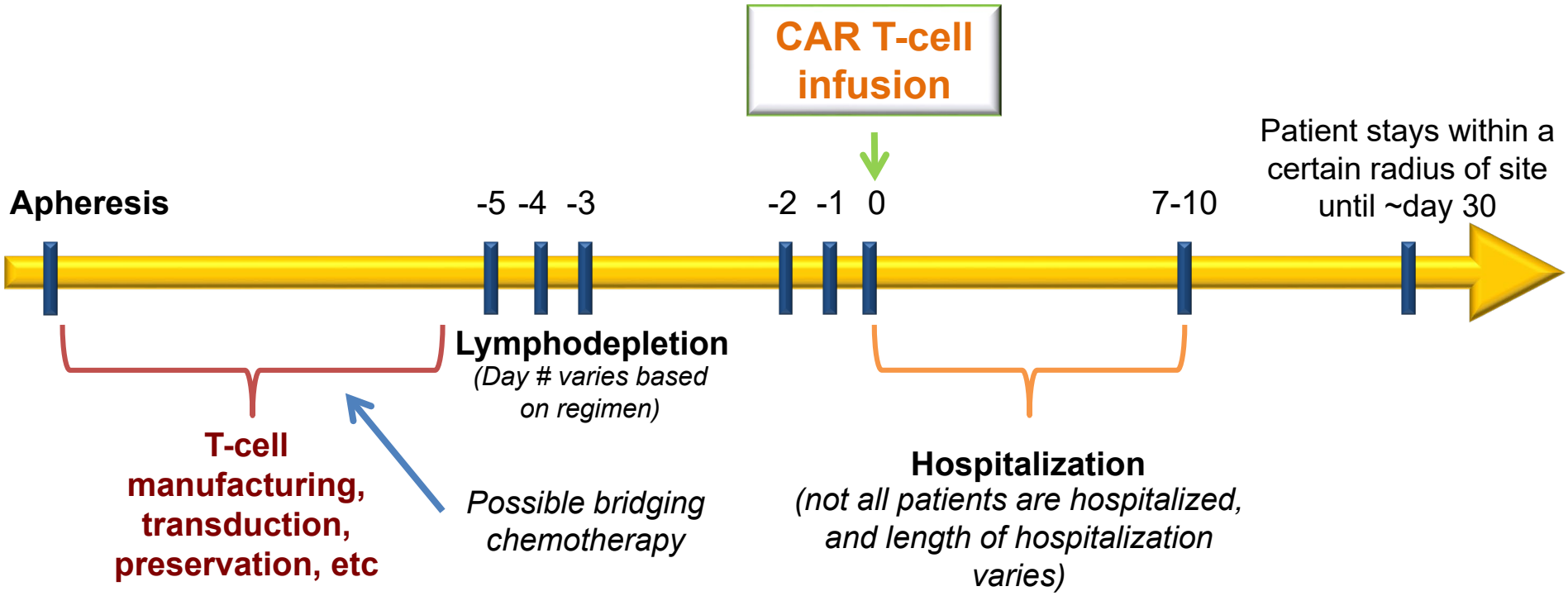
Anatomy of a Chimeric Antigen Receptor

- **Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity**
- **CARs combine antigen recognition domain (Anti-CD19, BCMA, CD38, CS1) with intracellular signaling domain**
- **Intracellular signaling domain:**
  - Same functionality as endogenous T cells
  - Co-stimulatory endodomain mediates potent anti-myeloma effects & promotes persistence



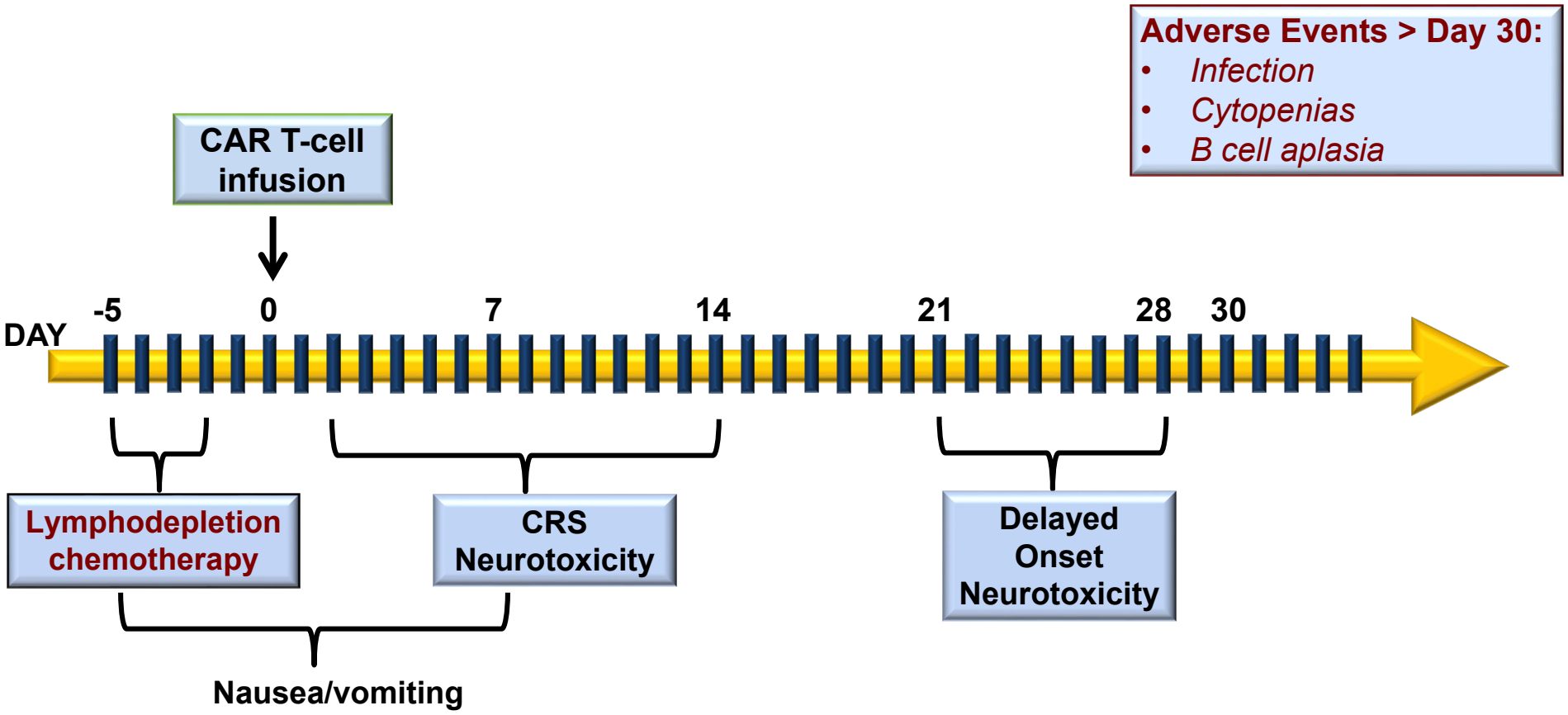
. Milone, et al. Mol Ther 2009. 2. Carpenito, et al. PNAS 2009

The CAR-T Process



Locke FL, et al. J Immunother Cancer. 2017;5:59.

CAR-T Toxicities Timeline



Brudno JN, et al. Blood. 2016;127:3321-30. Neelapu SS, et al. Nat Rev Clin Oncol. 2018; 15:47-62.

CAR T-Cell Toxicity/Treatments

Cytokine Release Syndrome

Cause:
Activation/expansion of CAR T-cells increased levels of cytokines (IL-6, IL-15, INF-γ, GM-CSF, others)

Onset: variable; 1 to 3 days CD28; 3 to 5 days 4-1BB

Duration: 3 to 5 days

Risk: variable up to 30% grade 3

- Disease burden
- Peak CAR T-cell levels
- Pre-treatment and peak cytokine levels

Neurotoxicity

Cause:
Mechanism less understood

- High CSF: blood cytokine levels
- CAR-positive and CAR-negative T-cells in CSF

Onset: 5 to 7 days; later than CRS

Duration: 5 to 10 days

- Fully reversible except in cases of fatal cerebral edema

Risk: variable, up to 40% grade 3

- Disease burden
- Peak CAR T-cell levels
- Early and high-grade CRS
- Pre-treatment and peak cytokine levels
- DIC

- Santomasso B, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:433-444.

Management of CRS

ASTCT CRS Grade	Management
Grade 1	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2	• Supportive care as in grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab +/- dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in grade 1 • Consider monitoring in ICU • Vasopressor support and/or supplemental oxygen • Tocilizumab + dexamethasone 10 mg to 20 mg IV every 6 h or its equivalent of methylprednisolone
Grade 4	• Supportive care as in grade 1 • Monitoring in ICU • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1000 mg/day

- Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15:47-62; Neelapu SS. *Hematol Oncol.* 2019;37:48-52.

Management of ICANS

ASTCT ICANS Grade	Management
Grade 1	• Aspiration precautions and IV hydration • Seizure prophylaxis with levetiracetam • EEG • Imaging of brain • Consider tocilizumab if there is concurrent CRS
Grade 2	• Supportive care as in grade 1 • Consider dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in grade 1 • Dexamethasone 10 mg to 20 mg IV every 6 h or its equivalent of methylprednisolone • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide • High-dose methylprednisolone 1000 mg/day for focal/local edema
Grade 4	• Supportive care as in grade 1 • High-dose methylprednisolone 1000 mg/day • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide • Imaging of spine for focal motor weakness • For diffuse cerebral edema, lower ICP by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt

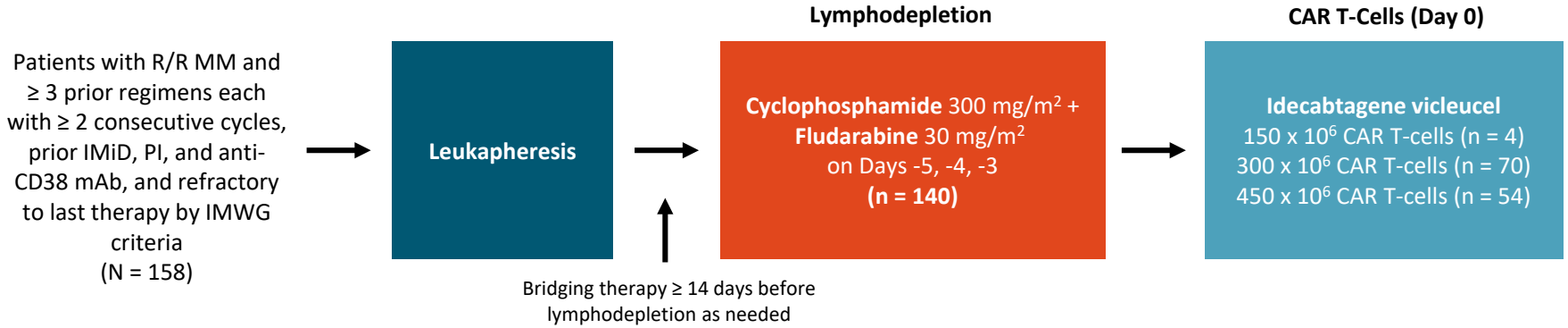
Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15:47-62; Neelapu SS. *Hematol Oncol.* 2019;37:48-52.

FDA Approves Idecabtagene vicleucel (Abecma) on March 26, 2021

- First in Class BCMA-directed personalized immune cell therapy in myeloma (CAR-T therapy)
- Triple-class exposed (patients who have received an IMiD agent, a PI, and an anti-CD38 monoclonal antibody) and have received at least 4 prior lines of therapy
- ABECMA Only available through a restricted program called the ABECMA REMS
- One time infusion at a dose range of 300-460 x 10 6th
- Approval is based on the findings from the pivotal phase 2 KarMMA trial
- ORR was 72%
- Stringent CR (sCR) of 28%

KarMMa: Idecabtagene Vicleucel for R/R Multiple Myeloma

- Multicenter, single-arm phase II trial



	ORR	≥VGPR	sCR	mDoR (≥PR)	mDoR for sCR
300-460 x 10^6 (N=100)	**72%** (95% CI, 62-81) (n=72)	**53%** (95% CI, 43.2-62.8) (n=53)	**28%** (95% CI, 19-38) (n=28)	**11.0 months** (95% CI, 10.3-11.4) (n=72)	**19.0 months** (95% CI, 11.4-NE) (n=28)

Munshi. ASCO 2020. Abstr 8503.

KarMMa: CRS

- **Incidence -> All grades 85%. >/= Gr 3 9%**
- **Median time to onset -> Day 1 (range 1-23)**
- **Median duration -> 7 days (range 1-63)**

54% (68/127) of patients received tocilizumab

- 35% (45/127) received a single dose
- 18% (23/127) received more than 1 dose

Overall, 15% (19/127) of patients received at least 1 dose of corticosteroids for treatment of CRS

- All patients that received corticosteroids for CRS also received tocilizumab

KarMMa: Neurtoxicities

- Incidence -> All grades 28% Gr 3 1% No Gr 4
- Median time to onset -> Day 2 (range 1-42)
- Median duration -> 5 days (range 1-61)

Selected AEs and Prophylaxis for Immunotherapies in Myeloma

Monoclonal Antibodies	ADCs	Bispecific Antibodies	CAR T
• Infusion-related reactions • Herpes zoster prophylaxis	• Monitor for potential corneal events • Thrombocytopenia	• Potential for CRS • Potential of neurotoxicities	• Close monitoring for potential for CRS • Close monitoring for potential for neurotoxicities • Use of IL-6 inhibitors for emerging CRS and neurotoxicities • Monitor for hypo-gammaglobulinemia

Comparison of immunotherapy approaches

	ADCs	CARs	Bispecifics
Off-the-shelf	Yes	No	Yes
Ease of administration	++++	+	+ to ++
Repeated dosing required	Yes	No	Yes
Dependent on patient T cell “fitness”	No	Yes	Yes
Toxicities	IRR, Toxin-dependent	CRS, neuro	CRS, neuro
Toxicity duration	Ongoing	~14-21 days	Ongoing
Durable clinical activity seen	Yes	Yes	Yes
Requires LD Chemo	No	Yes	No

Conclusion

- Significant advances in the treatment of myeloma has improved survival
- Now have 2 FDA approved immunotherapies that target BCMA
- Aggressive management of toxicities is essential
- Clinical trials of newer agents and combination of agents continues to improve survival
- Myeloma patients are now “Survivors”