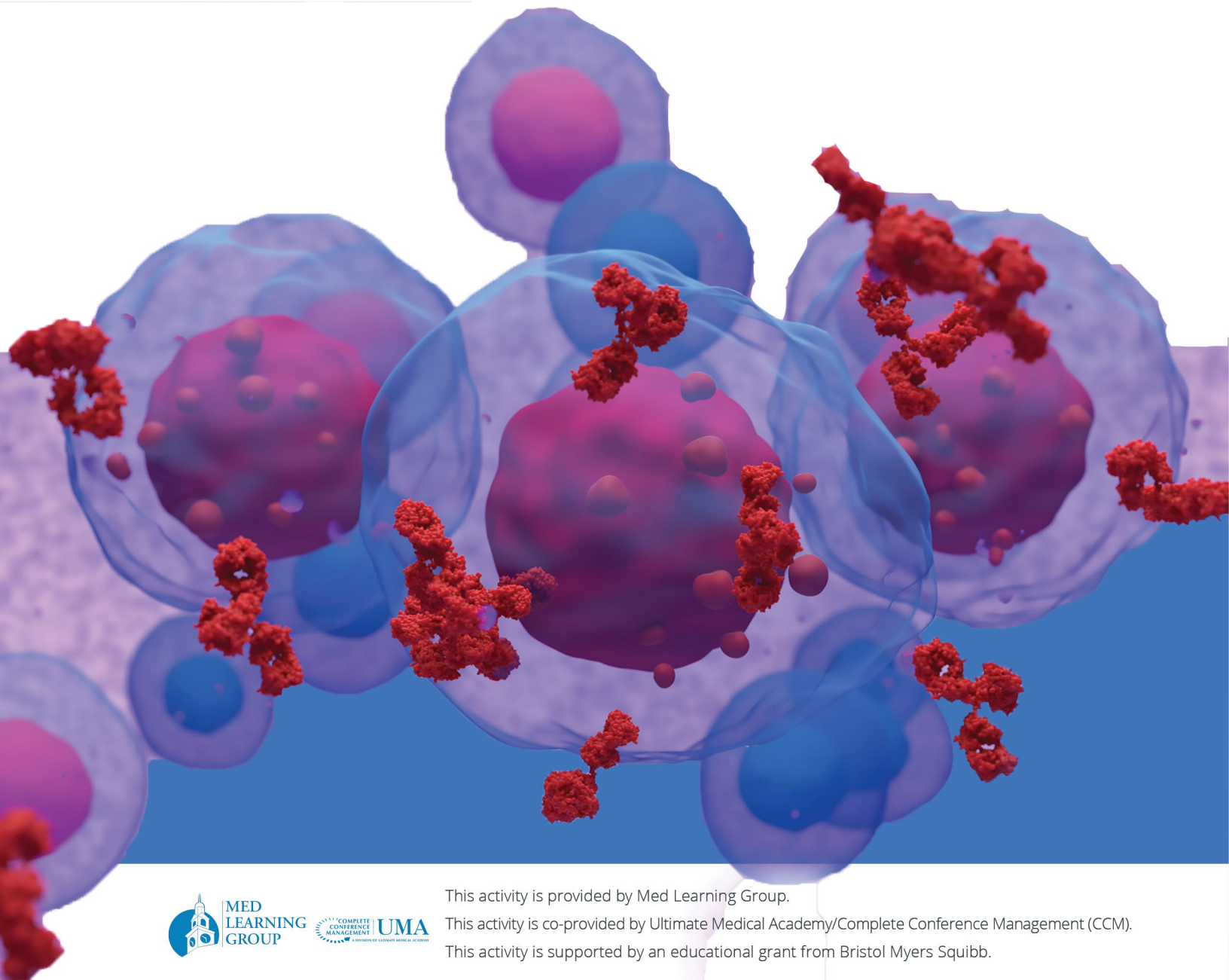
Community Practice Considerations for Integrating CAR-T Therapy for Relapsed/Refractory

MULTIPLE MYELOMA:

The Role of Multidisciplinary Care

PRE-READ MATERIAL



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Community Practice Considerations for Integration of CAR-T Therapy for Relapsed/Refractory Multiple Myeloma: The Role of Multidisciplinary Care

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Disclosures

- Dr Young has received research support from High-Throughput Genomics and EUSA Pharma. He serves on the scientific advisory board for Precision Genomic Testing.
- During this lecture, Dr Young may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications.

This activity is supported by an educational grant from Bristol Myers Squibb.

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Learning Objectives

- Summarize concerns regarding therapeutic resistance in patients with multiple myeloma (MM) with relapsed/refractory disease treated in the community setting
- Evaluate current efficacy and safety data with CAR T-cell (CAR-T) therapy in relapsing/refractory MM
- Generate plans to appropriately sequence CAR-T therapy for patients and manage adverse events associated with CAR-T therapy

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Multiple Myeloma Overview

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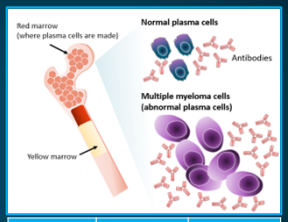
Multiple Myeloma Overview

- Malignant neoplasm of clonal plasma cells
  - Abnormal plasma cells accumulate in bone marrow (BM)
- Results in organ/immune dysfunction
- US prevalence in 2022 (SEER)
  - Estimated 34,470 new diagnoses and 12,640 deaths
  - Lifetime risk: 1 in 128 (0.8%)
- Median age at diagnosis: ~69 years
- 5-year overall survival (OS): 58%



	2017	AGR 2017-2027
USA	141,697	5.33%
Eastern	126,020	10.60%
Western	353,890	4.60%

SEER = Surveillance, Epidemiology, and End Results Program; AGR=average growth rate.

van de Donk N, et al. *Lancet*. 2021;397(10272):410-427. Rajkumar SV. *Am J Hematol*. 2020;95:548-567. Siegel RL, et al. *CA Cancer J Clin*. 2022;72:7-33. National Cancer Institute (NCI). *Cancer stat facts: myeloma*. (seer.cancer.gov/statfacts/html/mulmy.html). Accessed 8.22.2022. Manier S, et al. *Nat Rev Clin Oncol*. 2017;14(2):100-113.

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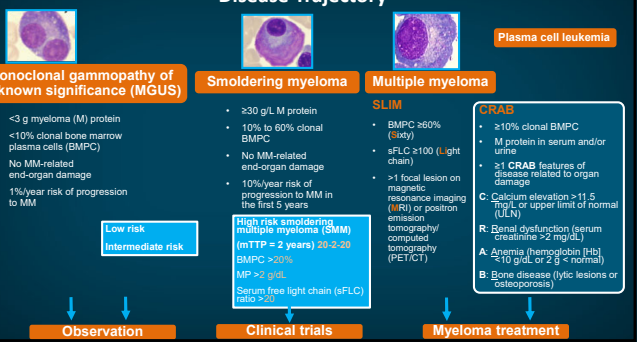
Disease Trajectory



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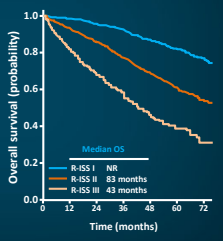
Multiple Myeloma Is a Heterogeneous Disease

- MM is highly complex at diagnosis and relapse due to genomic events and clonal evolution so 1 size or therapy does not fit all
  - Different treatment regimen and plan per risk score
  - Different treatment regimen per stage
  - Different treatment regimen per location
  - Different treatment regimen per age
  - Different treatment regimen per specific biomarkers
- Host response factors – tumor microenvironment (TME): cellular, matrix, vascular
- Pathologic and molecular factors
  - Standard vs high risk
  - Genetic alterations for translocations and *TP53*
  - Primary resistant



R-ISS = revised International Staging System; NR = not reached.

Morgan GJ, et al. *Nat Rev Cancer*. 12(5):335-348. Manier S, et al. *Nat Rev Clin Oncol*. 2017;14(2):100-113. Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2869.

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Staging and Cytogenetic Risk-Assessment

Stage[1]	R-ISS[1]
I	Serum albumin ≥3.5 g/dL[1] Serum β2M <3.5 mg/L[1] No high-risk cytogenetics Normal LDH level
II	Not stage I or III
III	Serum β2M >5.5 mg/L[1] High-risk cytogenetics: t(4;14), t(4;16), or del(17p) or elevated LDH
Stage[1]	**International Staging System (ISS)**
I	Serum β2 microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
II	Not ISS stage I or III
III	Serum β2 microglobulin ≥5.5 mg/L

Risk[2]	mSMART[2]
Standard	Trisomies t(11;14) t(6;14)
	t(4;14)
	t(14;16)
	t(14;20)
High	Del(17p) *p53* mutation
	Gain 1q
	High plasma cell S-phase
	GEP high-risk signatures

LDH = lactate dehydrogenase; GEP = gene expression profiling.

1. Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2869. 2. mSMART website. *mSMART 2.0: classification of active MM*. 2022. (https://static1.squarespace.com/static/5b44f08ac258b493a25098a3/t/624485944572cf719ccab933/1648657812271/RiskStrat+3.0_Mar2022_FINAL_REV.pdf).

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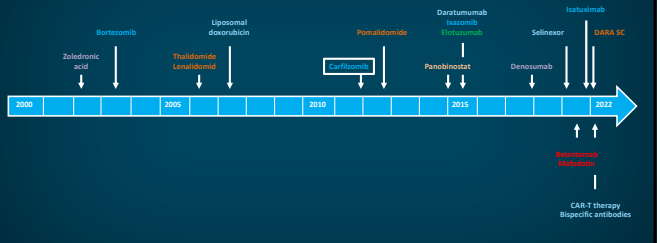
Myeloma Drugs Approved Since 2000



www.FDA.gov. Durie BGM. *Multiple myeloma: concise review of the disease and treatment options*. 2018. (https://imf-d8-prod.s3.us-west-1.wasabisys.com/resource/ConciseReview.pdf). Accessed 8.22.2022.

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R/R Multiple Myeloma

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Relapsed/Refractory Multiple Myeloma (R/R MM)

Criteria for R/R MM[2-5]

- Meets IMWG criteria for progressive disease (PD)[1]
- R/R MM: PD on treatment after at least minimal response (MR) or PD ≤60 days on most recent treatment
- Primary refractory MM: Not achieving at least MR on a given treatment
- Relapsed MM: Meets IMWG criteria for PD but not R/R MM or primary refractory MM

International Myeloma Working Group (IMWG) criteria for PD[1]

- ≥25% increase from nadir in ≥1 of the following
  - Serum/urine M-protein (absolute increase ≥0.5 g/dL* and ≥200 mg/24 hours, respectively)
  - Difference between involved and uninvolved FLC levels† (absolute increase >100 mg/L)
  - BM plasma cells‡ (absolute increase ≥10%)
  - New lesions (≥50% increase in SPD of >1 lesion or longest diameter of previous lesion >1 cm in short axis)
  - Circulating plasma cells (≥50% increase [minimum 200 cells/μL] if only measure of disease)

*If lowest M component ≥5 g/dL, increase must be ≥1 g/dL. †In patients without measurable serum/urine M-protein. ‡In patients without measurable serum/urine M-protein or involved FLC. SPD = sum of the products of the maximal perpendicular diameters of measured lesions.

1. Kumar S, et al. *Lancet Oncol*. 2016;17:e328-e346. 2. Nooka AK, et al. *Blood*. 2015;125:3085-3099. 3. Rajkumar SV, et al. *Blood*. 2011;117:4691-4695. 4. Richardson PG, et al. *N Engl J Med*. 2003;348:2609-2617. 5. Richardson PG, et al. *Cancer*. 2006;106:1316-1319.

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Treatment Indication in R/R MM

Type of relapse	Indications
Clinical relapse	Development of new soft-tissue plasmacytomas or bone lesions • Definite increase (≥50%) in size of existing plasmacytomas or bone lesions • Hypercalcemia (≥11.5 mg/dL; 2.875 mmol/L) • Decrease in hemoglobin of ≥2 g/dL (1.25 mmol/L), or of <10 g/dL because of myeloma • Rise in serum creatinine by ≥2 mg/dL or more (≥177 mmol/L), due to myeloma • Hyperviscosity requiring therapeutic intervention
Significant biochemical relapse in patients without clinical relapse	Doubling of the M-component in 2 consecutive measurements separated by 2 months with the reference value of 5 g/L, or • In 2 consecutive measurements, any of the following increases – The absolute levels of serum M-protein by ≥10 g/L, or – An increase of urine M-protein by ≥500 mg per 24 h, or – An increase of involved FLC level by ≥20 mg/dL (plus an abnormal FLC ratio) or 25% increase (whichever is greater)

Questions

- **Does the patient need immediate treatment?**
- **Does the patient have high-risk factors?**
- **What is the patient's general condition and tolerability**
- **What is the condition of the patient's bone marrow**
- **What is the treatment goal?**

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Navigating the MM Treatment Options

Proteasome inhibitors	Immunomodulatory agents	Monoclonal antibodies	BCMA-specific targets	Small-molecule inhibitors	Corticosteroids
Bortezomib (V)	Lenalidomide (R)	Daratumumab (D)	Belantamab mafodotin-blmf (Bel)	Selinexor (X)	Dexamethasone (d)
Carfilzomib (K)	Pomalidomide (P)	Isatuximab-irfc (Isa)	Idecabtagene vicleucel (Ide-cel)	Venetoclax (if t[11;14]) (Ven)	Prednisone (p)
Ixazomib (I)	Thalidomide (T)	Elotuzumab (E)	Ciltacabtagene autoleucel (Cilta-cel)	Panobinostat (Pano)	

Rajkumar SV. *Am J Hematol*. 2020;95:548-567. Su CT, Ye JC. *J Hematol Oncol*. 2021;14:115.

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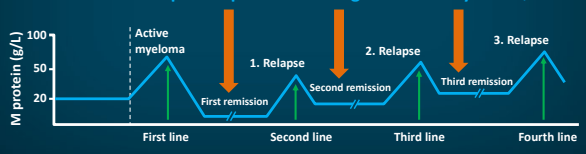
Treatment Goals and Aims in R/R MM

Short term: Maximal response

Throughout:
- Limited toxicity
- Maintained QoL

Long term: Prolonged PFS and OS

Maintain and deepen response with long-term efficacy and QoL.



Sonneveld P, et al. *Crit Rev Oncol Hematol*. 2017;112:153-170. Sonneveld P, Broijl A. *Haematologica*. 2016;101(4):396-406. Gugliemelli T, Palumbo A. *Expert Rev Hematol*. 2015; 8(3):253-256. Borrello I. *Leuk Res*. 2012;36:53-512.

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Selecting Treatment for R/R MM: PDTR Principles

Patient	Disease	Treatment	Regimen
• Age/frailty • Performance status • Lifestyle • Patient preference • Caregiver support • Comorbidities – Renal status – Neuropathy – Cardiac – Diabetes – Cytopenias	• Disease burden: ISS – Rate of progression – Marrow burden – CRAB symptoms – Extramedullary disease • Biology – LDH – Cytogenetics • t(4;14) • del(17p) • +(14;16) • amp(1q)	• Toxicity – Myelosuppression – Infections – Neuropathy – Secondary cancers – Ocular toxicity • Cost • Administration route • Relapsed vs refractory • Depth/duration of response to prior treatment	• Triplet* (eg, KRD) is preferred over doublet • Include ≥1 agent from a new or nonrefractory class • Previously used agents may be effective in different combinations • Treat to maximum response • Maintain on 21 agent until progression or intolerability

*2 active classes plus dexamethasone.

Laubach J, et al. *Leukemia*. 2016;30:1005-1007. NCCN. *Multiple myeloma guidelines* v5.2022. (https://www.nccn.org/professionals/physician_gls/pdf/myeloma. pdf). Sanchez L, et al. *Expert Rev Hematol*. 2020;13:943. Sonneveld P, Broijl A. *Haematologica*. 2016;101:396-406.

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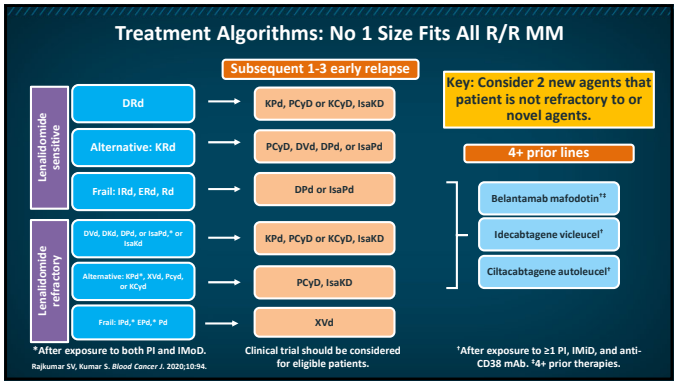

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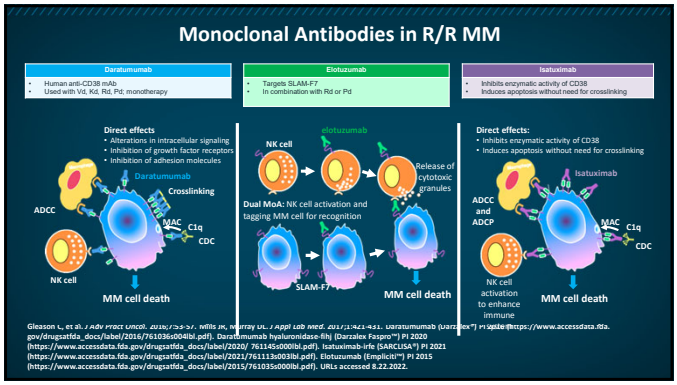

Gleason L, et al. J Adv Pract Oncol. 2016;7:54-57. Wills JK, Murray DL. J Appl Lab Med. 2017;1:421-431. Daratumumab (Darzalex™) PI Update (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761036s004lbl.pdf). Daratumumab hyaluronidase-fihj (Darzalex Faspro™) PI 2020 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/ 761145s000lbl.pdf). Isatuximab-irfc (SARCLISA®) PI 2021 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761113s003lbl.pdf). Elotuzumab (Empliciti™) PI 2015 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s008lbl.pdf). URLs accessed 8.22.2022.

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Practice Points for the First Relapse

- Consider re-treatment with the original schedule in patients with relapse after previous good and lasting response of at least 18 months or treatment-free interval of 6 to 9 months
  - A switch to an alternative regimen is more practical because possibly resistant clones are more likely to respond
- Consider ASCT for transplant-eligible patients, especially if they have not received it in first line; however, it should be reserved for young and fit patients with high-risk disease
- Consider escalating to at least 1 agent not previously used in patients with suboptimal response to relapse retreatment
- Treat patients with high-risk relapse with a 3- or 4-drug regimen, preferably including a PI, an IMiD and dexamethasone, or both, plus 1 of the recently approved novel agents
- Carfilzomib and pomalidomide can be used in patients who were primary refractory to bortezomib and lenalidomide, respectively
- Continuous treatment should be considered
- Offer all eligible patients participation in a clinical trial

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Practice Points for Second or Third Relapse

- Patients should be treated with a regimen containing at least 1, preferably more, agents to which they were not previously exposed
- Consider treatment with agents used in first line to which patient has responded
- Daratumumab monotherapy is a valuable option that can be combined with Rd or Vd; alternatives include elotuzumab plus Rd, carfilzomib plus Rd, and ixazomib plus Rd
- Patients should receive ongoing therapy until next relapse/progression, when a switch to an alternative regimen is recommended
- Eligible patients should be considered for trial participation with new drugs or CAR-T

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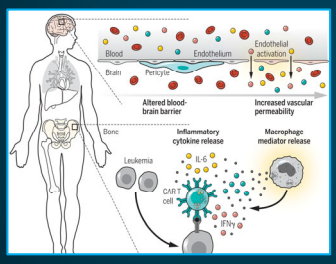
Mechanisms of CAR-T Therapy Related AEs



Neurotoxicity
- Delirium
- Aphasia
- Seizures
- Cerebral edema
- Intracranial hemorrhage

Hemodynamic instability
- Tachycardia
- Hypotension
- Capillary leak syndrome

Organ dysfunction
- AST and ALT elevation
- Hyperbilirubinemia
- Respiratory failure

- CAR T-cells traffic to tumor cells
- Target cell recognition, CAR T-cell proliferation, target cell kill, CAR T-cell and bystander cell cytokine production (CRS)
- CAR T-cells expand, cytokines increase, inflammatory response, endothelial damage
- Transmigration through BBB, CAR-T, T-cells and monocytes into CSF (ICANS)
- Death of activated T-cells, less cytokines, reduced inflammation, CRS diminished

Shimabukuro-Vornhagen A, et al. *J Immunother Cancer.* 2018;6(1):56. Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62. Lee DW, et al. *Blood.* 2014;124:188-195. June CH, et al. *Science.* 2018;359(6382):1361-1365.

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CAR-T

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CAR-T Cell Structure and Technology

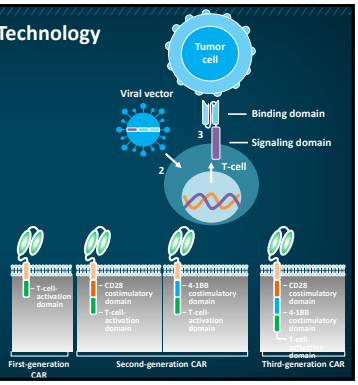
Tumor antigen–binding domain

Fusion protein

- T-cell costimulatory receptor signaling domain
- T-cell receptor (TCR)ζ activation domain

BCMA-directed CAR-T

- Comprising a BCMA antigen–binding domain, a costimulatory domain (generally CD28 or 4-1BB), and CD3-ζ signaling domain



Maus MV, Levine BL. *The Oncologist*. 2016;21:608-617. Li H, Zhao Y. *Protein Cell*. 2017; 8(8):573-589. Bruno B, et al. *Haematologica*. 2021;106:2054-2065. Morgan RA, Boyerinas B. *Biomedicines*. 2016;4:9. Chang ZL, Chen YY. *Trends Mol Med*. 2017;23(5): 430-450. Brudno JN, Kochenderfer N. *Nat Rev Clin Oncol*. 2018;15:31-46.

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Principles of Toxicity Management

- Appropriate screening per institutional standards
- Baseline labs
  - C-reative protein (CRP), ferritin
  - Complete blood count (CBC), comprehensive metabolic panel (CMP), coagulopathy
  - Tumor lysis syndrome labs
- Initiation of antiepileptic drugs
- Appropriate bacterial/fungal/viral prophylaxis per institutional standards
- Pre-infusion/low dose chemotherapy
- Monitor CBC, CMP, and coagulopathy
- Monitor for tumor lysis syndrome
- Monitor CRP and ferritin
- Daily assessments for at least 7 days
  - FDA requirement for axicabtagene ciloleucel
  - Fevers, hypotension, hypoxia?
  - Mental status?

REMS program shows management of CRS and neurologic toxicities are associated with CAR-T therapies.

Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47-62. Axicabtagene ciloleucel (Yescarta®) PI 2022 (https://www.fda.gov/files/vaccines%2C%20blood%20&%20biologics/published/Package-Insert-YESCARTA.pdf). Tisagenlecleucel (Kymriah®) PI 2022 (https://www.fda.gov/media/107296/download). URLs accessed 8.22.2022.

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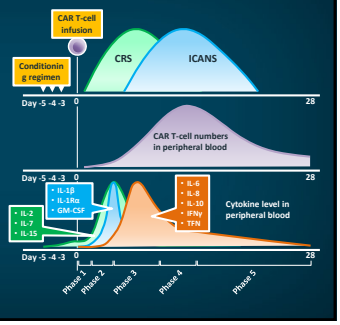
Onset and Duration of CRS and ICANS

- The onset and peak of cytokine release syndrome (CRS) generally precede those of immune effector cell-associated neurotoxicity syndrome (ICANS)
- CAR T-cell numbers peak in the peripheral blood 1 to 2 weeks after infusion
- Levels of homeostatic cytokines, such as IL-2, IL-7, and IL-15, may increase after conditioning therapy due to lymphodepletion and the elimination of cytokine sinks, with a further increase in cytokine levels observed after CAR T-cell infusion
- Cytokines promote the survival and proliferation of CAR T-cells



Morris EC, et al. *Nat Rev Immunol*. 2022;22(2):85-96.

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ASTCT Guidelines for Grading ICANS: ICE Score

Parameter	Score (Points)
Orientation: Year, month, city, hospital	4
Naming: Ability to name 3 objects (eg, point to clock, pen, button)	3
Following commands: Ability to follow simple commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue")	1
Writing: Ability to write a standard sentence (eg, "our national bird is the bald eagle")	1
Attention: Ability to count backwards from 100 by 10	1

Scoring:
10, no impairment
7-9, grade 1 ICANS
3-6, grade 2 ICANS
0-2, grade 3 ICANS
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

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Principles of Toxicity Management

Grade	CRS	Neurotoxicity	CRS + neurotoxicity
1	Supportive care	Supportive care	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids intensive care unit (ICU)/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive antiepileptic drugs (AEDs) and appropriate CNS imaging, electroencephalogram (EEG) monitoring
- Steroid dosing for neurotoxicity may vary between products
- Patients on steroids should receive appropriate fungal prophylaxis

MD Anderson Cancer Center. *Immune effector cells (IEC) therapy toxicity assessment and management*. 2020. (https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf). Accessed 8.22.2022. Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47-62.

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BCMA CAR-T Therapies: Moving Closer to the Front Line*

Fourth line | Third line | Second line | First line

- KarMMa-2: Ide-cel in TCE high-risk, early-relapse after first line or aHCT
- KarMMa-4: Ide-cel in high-risk ND MM
- KarMMa-3: RCT of Ide-cel vs SOC triplet
- CARTITUDE 4: RCT of Cilta-cel vs SOC triplet
- CARTITUDE 5: Cilta-cel in HCT-ineligible ND MM
- CARTITUDE 2: Cilta-cel in multiple exploratory cohorts

Ide-cel and cilta-cel are only FDA-approved for use in patients with R/R disease after 4 lines of treatment.

ClinicalTrials.gov: NCT03601078, NCT03651128, NCT04196491, NCT04133636, NCT04181827, NCT04923893.

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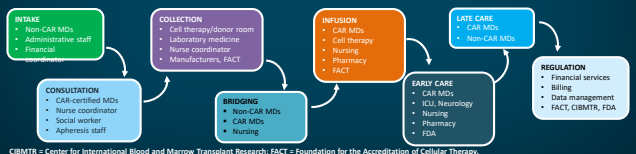
Multidisciplinary Team Efforts in R/R MM

- All physicians, pharmacists, nurses, and other medical providers interacting with patients receiving CAR-T therapy must have FDA-mandated training in the management of therapy-related AEs
- Medical professionals serve vital roles in patient and caregiver education and in prevention, identification, and management of CAR-T therapy associated toxicities

Essential steps for the CAR-T therapy program



CIBMTR = Center for International Blood and Marrow Transplant Research; FACT = Foundation for the Accreditation of Cellular Therapy.

Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135. Tisagenlecleucel PI. Axicabtagene ciloleucel PI.

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