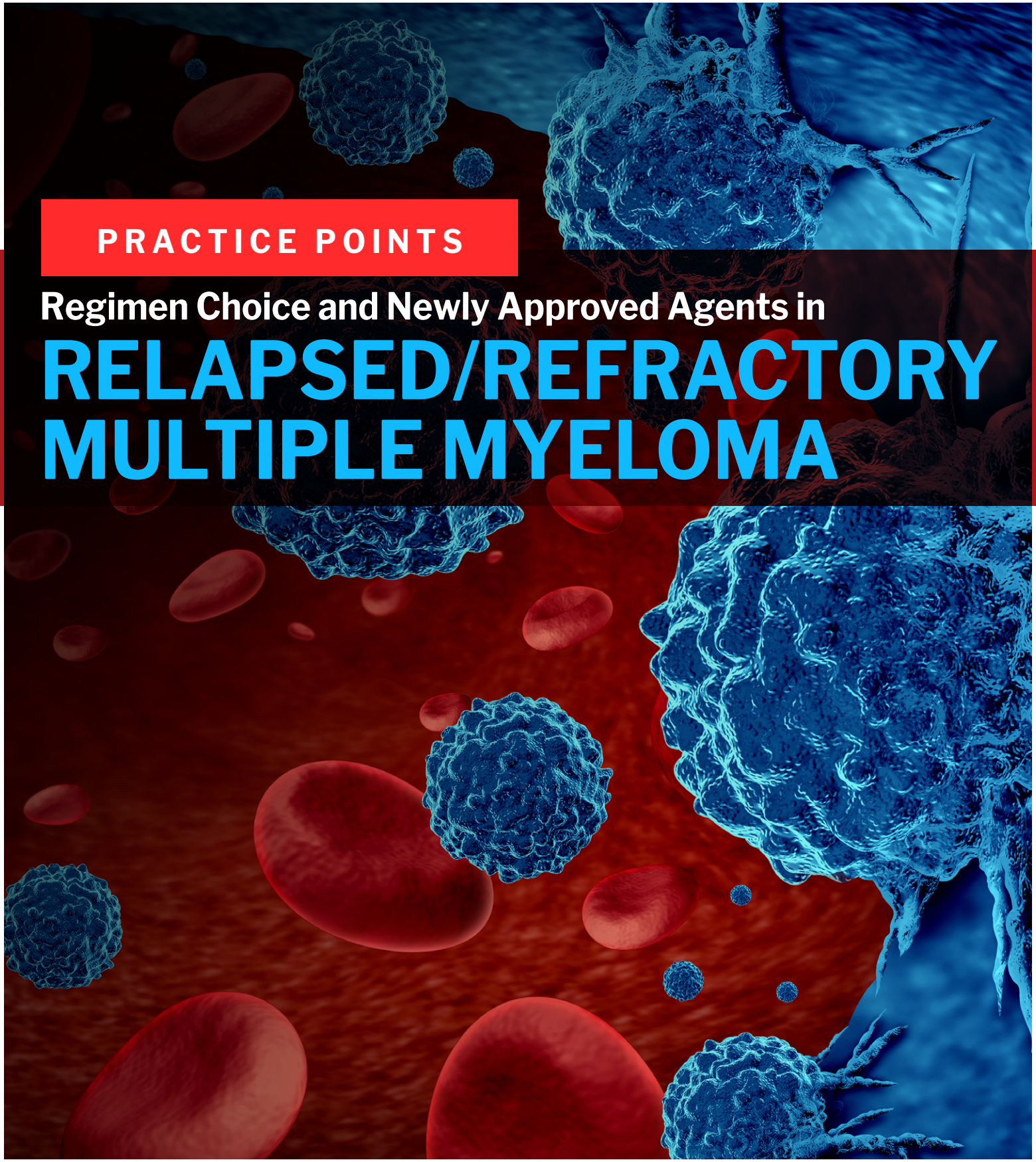

PRACTICE POINTS

Regimen Choice and Newly Approved Agents in

RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Recently Approved Agents/Regimens for Relapsed/Refractory MM*

July 9, 2021
Daratumumab and hyaluronidase-fihj + pomalidomide and dexamethasone for relapsed/refractory (R/R) MM after at least 1 prior line of therapy including lenalidomide and a PI

March 31, 2021
Isatuximab + carfilzomib and dexamethasone for R/R MM who have received 1 to 3 prior lines of therapy

March 26, 2021
Idecabtagene vicleucel for R/R MM after 4 or more lines of therapy

February 26, 2021
Melphalan flufenamide + dexamethasone for R/R MM who have received at least 4 prior lines of therapy and are refractory to at least one PI, IMiD, and CD38-directed mAb

December 18, 2020
Selinexor + bortezomib and dexamethasone for R/R MM who have received at least 1 prior therapy

August 5, 2020
Belantamab mafodotin for R/R MM who have received at least 4 prior therapies, including an anti-CD38 mAb, a PI, and an IMiD

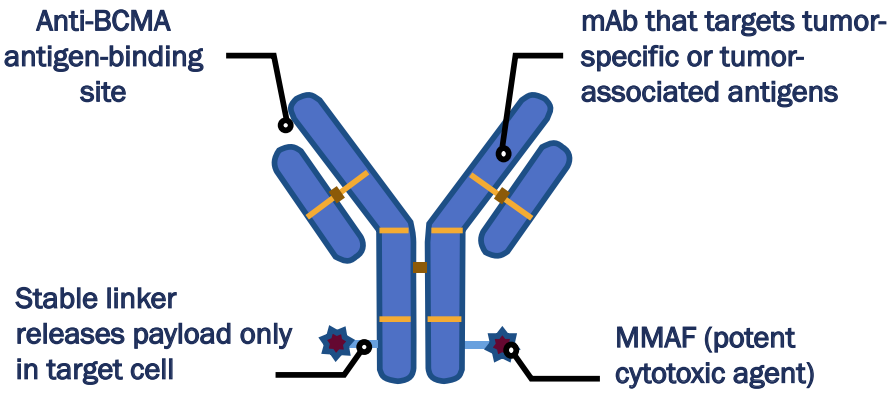
March 2, 2020
Isatuximab + pomalidomide and dexamethasone for R/R MM who have received at least 2 prior therapies including lenalidomide and a PI

IMiD, immunomodulatory agent; mAb, monoclonal antibody; PI, proteasome inhibitor.
*As of October 14, 2021.
Oncology (Cancer)/Hematologic Malignancies Approval Notifications. U.S. Food and Drug Administration. Accessed July 1, 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications?t=493234

Practical Aspects to Using BCMA-Targeted Agents: Belantamab Mafodotin

Belantamab Mafodotin Summary

- Belantamab mafodotin: humanized, afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA



Cytotoxic agent	–MMAF (highly potent auristatin)
Afucosylation	–Enhanced ADCC
Linker	–Stable in circulation

FDA approved

- For patients with R/R MM after ≥4 previous therapies including an anti–CD38 mAb, a PI, and an IMiD

Dosing	2.5 mg/kg IV once every 3 wk as infusion over 30 min

Systemic steroids not required prior to initial infusion or in combination with belantamab, but patients should be monitored for infusion-related reactions

Belantamab is only available through REMS program due to potential for ocular toxicity

Counsel patients on what to expect when receiving belantamab, including about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose

ADC, antibody-drug conjugate; ADCC, antibody-depented cellular cytotoxicity.

Tai YT, et al. *Blood*. 2014;123:3128-3138. Trudel S, et al. *Lancet Oncol*. 2018;19:1641-1653. Trudel S, et al. *Blood Cancer J*. 2019;9:37. doi: 10.1038/s41408-019-0196-6.
BLENREP [package insert]. Research Triangle Park: GlaxoSmithKline; 2020.

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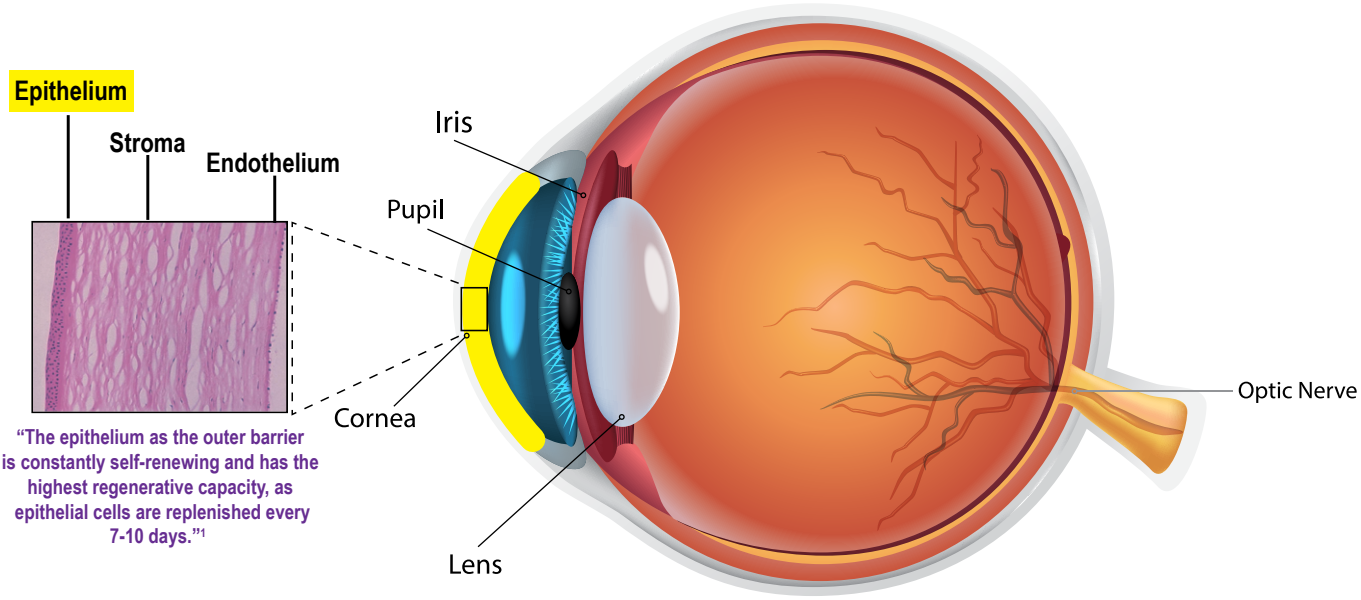
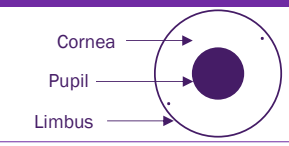
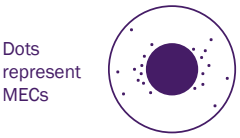
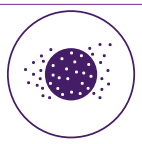
Anatomy of the Eye and Reporting of Corneal Adverse Reactions



"The epithelium as the outer barrier is constantly self-renewing and has the highest regenerative capacity, as epithelial cells are replenished every 7-10 days."[1]

Keratopathy was reported during DREAMM-2 and is defined as changes to the corneal epithelium observed by ophthalmic examination, with or without symptom[2]

Grading Corneal Adverse Events per the Keratopathy and Visual Acuity (KVA) Scale

Corneal Adverse Reaction			Presentation of microcyst-like epithelial changes (MECs)[b]	
	Change in Best Corrected Visual Acuity (BCVA) **due to treatment-related corneal findings**	**Corneal examination finding(s)**	**Evaluate based on density and location**	**Example schematics by severity**
Grade 1	Decline from baseline of 1 line on Snellen Visual Acuity	**Mild superficial keratopathy**[a] (documented worsening from baseline), with or without symptoms	**Mild** **Density:** Non-confluent **Location:** Predominantly (≥80%) peripheral *Few, if any, microcysts observed*	
Grade 2	Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200	**Moderate superficial keratopathy**[a] with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity	**Moderate** **Density:** Semi-confluent **Location:** Predominantly (≥80%) paracentral	
Grade 3	Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200	**Severe superficial keratopathy**[a] with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity	**Severe** **Density:** Confluent **Location:** Predominantly (≥80%) central	
Grade 4	Snellen Visual Acuity worse than 20/200	**Corneal epithelial defect** such as corneal ulcers	***The worst severity for microcyst-like epithelial change density or location should be used in grading. Grading is based on the worst finding in the worst affected eye.***	

1. Bukowiecki A, et al. *Int J Mol Sci.* 2017;18:1257. 2. Lonial S, et al. *Lancet Oncol.* 2020;21:207-221.

[a] Patients may have superficial punctate keratopathy, microcyst-like epithelial changes, or both. Keratopathy refers to superficial punctate keratopathy (revealed by fluorescein staining) or microcyst-like epithelial changes (not stained by fluorescein). Fluorescein staining should be part of each eye exam, including baseline examination. The worst grade for the keratopathy and the change in BCVA should be used to determine the grade of the corneal adverse event.

[b] These evaluations and examples do not apply to, or include, superficial punctate keratopathy.

Lonial S, et al. *Blood Cancer Journal.* 2021;11:103.

PRACTICE POINTS

Regimen Choice and Newly Approved Agents in Relapsed/Refractory Multiple Myeloma

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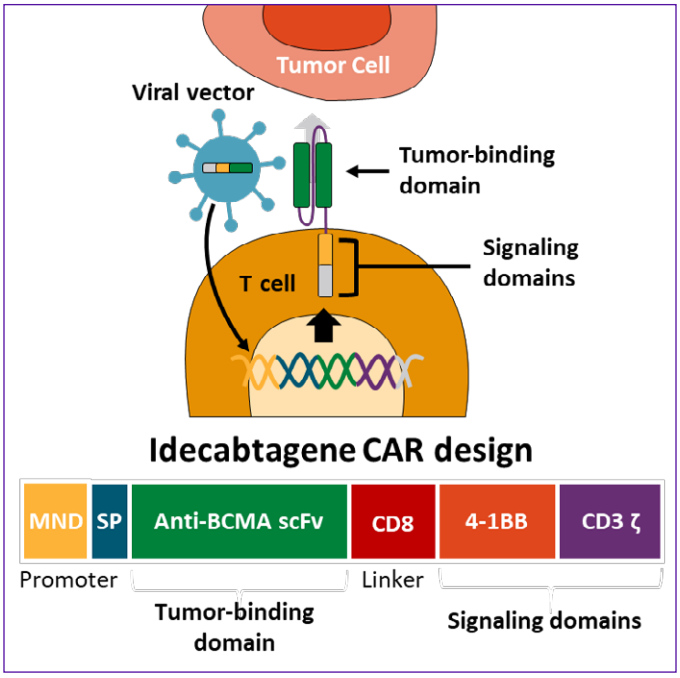
Practical Aspects to Using BCMA-Targeted Agents: Idecabtagene Vicleucel

Idecabtagene Vicleucel Summary

- Idecabtagene vicleucel: BCMA-directed genetically modified autologous CAR T-cell therapy



FDA approved

- For patients with R/R MM after ≥4 previous lines of therapy including a PI, an IMiD, and an anti-CD38 mAb

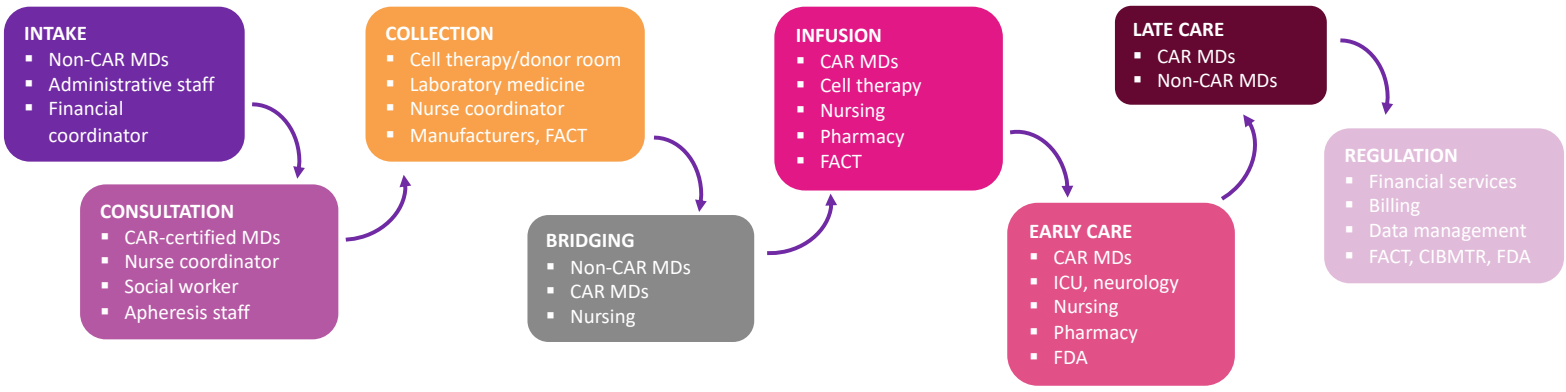
Dosing	Recommended dose range: 300 to 460×10^6 CAR-positive T cells
Must be administered at certified healthcare facility under REMS; Lymphodepleting chemotherapy regimen (cyclophosphamide and fludarabine) must be administered before infusion	
Premedicate with acetaminophen and H^1-antihistamine, but avoid prophylactic use of systemic corticosteroids (eg, dexamethasone)	
Counsel patients on what to expect when receiving idecabtagene vicleucel, including the risk of CRS and neurotoxicity	

ABECMA. Package insert. Celgene Corporation, a Bristol-Myers Squibb Company; 2021.

Multidisciplinary Team Roles in Delivering CAR T-Cell Therapies

- All physicians, pharmacists, nurses, and other advanced practice providers interacting with patients receiving CAR T-cell therapy must have FDA-mandated training in management of CRS and neurologic toxicities
- Pharmacists and nurses have vital roles in patient and caregiver education and in prevention, identification, and management of CAR T-cell–associated toxicities

Essential Steps and Required Personnel



Common CAR T-Cell Toxicities: CRS and ICANS

Cytokine-Release Syndrome (CRS)

- Onset typically 2 to 3 days, duration 7 to 8 days
- Symptoms: fever, hypotension, tachycardia, hypoxia, chills
- Can range in severity from low-grade to high-grade symptoms with life-threatening multiorgan system failure

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Onset typically 4 to 10 days, duration 14 to 17 days
- Toxic encephalopathy with symptoms of headaches, confusion, and delirium; expressive aphasia; occasional seizures; and rarely, cerebral edema
- Can occur in the presence or absence of systemic CRS
- Severe neurotoxicity associated with endothelial activation (eg, disseminated intravascular coagulation, capillary leak, increased blood–brain barrier permeability)

ASTCT, American Society for Transplantation and Cellular Therapy; 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;24:1135-1141. Jacobson CA, et al. *Oncologist.* 2020;25:e138-e146. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, v3.2021. Gust J, et al. *Cancer Discov.* 2017;7:1404-1419.

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ASTCT Guidelines for Grading of CRS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥38 °C	Temp ≥38 °C	Temp ≥38 °C	Temp ≥38 °C
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

ASTCT Guidelines for Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 mins) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

BiPAP, Bilevel positive airway pressure; CPAP, Continuous positive airway pressure; ICE, Immune Effector Cell-Associated Encephalopathy; ICP, intracranial pressure.

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

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Management of CRS and ICANS

CRS

- Supportive care (antipyretics, hydration)
- Tocilizumab (IL-6)
- Must have 2 doses readily available to administer due to REMS requirements
- Corticosteroids
- Secondary agents: anakinra (IL-1), siltuximab (IL-6)
- Vasopressors

ICANS

- Supportive care
- Corticosteroids
- Seizure prophylaxis

No universal guideline for toxicity management; protocols vary by institution

Rates of CRS and neurotoxicity vary among products, disease states, and patient characteristics

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

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