

BCMA-Targeting Agents in Relapsed/ Refractory Multiple Myeloma

Current Approved Indications and General Management of Toxicities



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Currently Approved BCMA-Targeting Agents for Relapsed/Refractory Multiple Myeloma

- Indication: after ≥ 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody¹⁻³

Agent	Delivery Mechanism	Approval Date	Dosing and Administration*
Idecabtagene vicleucel	CAR T-cell therapy	March 2021	Single infusion of $300-460 \times 10^6$ CAR-positive T-cells
Ciltacabtagene autoleucel	CAR T-cell therapy	February 2022	Single infusion of $0.5-1.0 \times 10^6$ CAR-positive viable T-cells per kg
Teclistamab	Bispecific antibody	October 2022	Subcutaneous: Day 1, 0.06 mg/kg Day 4, 0.3 mg/kg Day 7, 1.5 mg/kg 1.5 mg/kg/wk thereafter

*Following agent-specific premedication recommendations.

BCMA-Targeted Agents in Multiple Myeloma: Clinical Trial Findings

Parameter	Idecabtagene Vicleucel		Ciltacabtagene Autoleucel		Teclistamab
	KarMMa ⁴ (N = 128)	KarMMa-3 ⁵ (N = 254)	CARTITUDE-1 ^{6,7} (N = 97)	CARTITUDE-4 ^{8,9} (N = 208)	MajesTEC-1 ^{10,11} (N = 165)
Trial phase	II	III	Ib/II	III	I/II
ORR, %	73	71	98	85	63
Median PFS, mo	8.8	13.3	35.0	NR	11.0
Median OS, mo	24.8	NR	NR	NR	22.0
CRS, any (grade ≥ 3), %	84 (5)	88 (4)	95 (5)	76 (1)	72 (<1)
NT, any (grade ≥ 3), %	18 (3)	15 (3)	22 (9)	21 (3)	15 (<1)
Infection, any (grade ≥ 3), %	—	58 (28)	—	62 (27)	80 (55)

CRS, cytokine-release syndrome; NR, not reached; NT, neurotoxicity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Cytokine-Release Syndrome: ASTCT Grading System and Presentation^{12,13}

- CRS may manifest with constitutional symptoms (fever, flulike symptoms) and can progress to hypotension, hypoxia, and multiorgan failure

ASTCT Parameter for CRS	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp $\geq 38^\circ\text{C}$	Temp $\geq 38^\circ\text{C}$	Temp $\geq 38^\circ\text{C}$	Temp $\geq 38^\circ\text{C}$
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, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

ASTCT Guidelines for Grading of ICANS¹²

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 min) 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 triad

ICE

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

EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; N/A, not applicable.

Management of CRS With BCMA-Targeted Therapies

- Rule out other etiologies: infection, heart failure, pulmonary edema, possibly treat for infection

Grade	CAR T-Cell Therapy ^{1,2,13}	Teclistamab ³
	Supportive Care + Intervention	Supportive Care + Intervention
1	± Tocilizumab*	Withhold until CRS resolution and administer pretreatment medications prior to next dose
2	Tocilizumab ± corticosteroid	Grade 1 interventions + 48-hr hospitalization following next dose
3	Tocilizumab + corticosteroid	First grade 3 occurrence with duration ≤48 hr: Grade 2 interventions + ICU/critical care as needed Recurrent grade 3 or grade 3 with duration ≥48 hr: grade 4 interventions
4	Tocilizumab + high-dose corticosteroid ICU/critical care	Permanently discontinue; provide ICU/critical care as needed

*High-burden, high-risk products; older; comorbidities, etc.

Management of Neurologic Toxicity and ICANS With BCMA-Targeted Therapies

Grade	CAR T-Cell Therapy ^{1,2}		Teclistamab ³	
	Neurotoxicity	CRS + Neurotoxicity	Neurologic Toxicity Excluding ICANS	ICANS
1	Supportive care (± steroids)	Supportive care (± tocilizumab)*	Withhold until symptoms resolve or stabilize	Withhold until resolution
2	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)	Withhold until symptoms improve to grade ≤1	Withhold until resolution + steroids + 48-hr hospitalization with next dose
3	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)	<i>First occurrence:</i> grade 2 actions + supportive therapy <i>Recurrence:</i> grade 4 actions	<i>First occurrence:</i> grade 2 actions + supportive therapy + steroids <i>Recurrence:</i> grade 4 actions + steroids
4	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care	Permanently discontinue + steroids (dexamethasone or methylprednisolone) ICU/critical care	

*High-burden, high-risk products; older; comorbidities, etc.

Add anticonvulsants (levetiracetam, benzodiazepines)
Low threshold for inpatient management
(if outpatient at time of onset)
Multidisciplinary team approach

Infection Prophylaxis and Vaccinations^{1-3,10,14-16}

Toxicity, %	Ide-cel	Cilta-cel	Teclistamab
Infections (bacterial, viral, fungal)	69	58	80
Hypogammaglobulinemia	21	12	21
Grade ≥3 neutropenia	89	95	64

- Complete outstanding vaccinations at least 2 wk prior to starting CAR T-cell therapy or bispecific antibodies (eg, influenza, pneumococcal, COVID-19)
- Delay postinfusion vaccinations for at least 3-6 mo (1 yr for live)
- Consider checking antibody titers

Antibacterial Prophylaxis	Antiviral Prophylaxis	Antifungal Prophylaxis
Consider for patients with high risk of infection	HSV/VZV prophylaxis in all patients	Consider for patients with previous history of fungal infection, prolonged neutropenia, steroid therapy

Cilta-cel, ciltacabtagene autoleucel; HSV, herpes simplex virus; Ide-cel, idecabtagene vicleucel; VZV; varicella virus

Other BCMA-Targeted Therapy Safety Considerations¹⁻³

- Tumor lysis syndrome prophylaxis (CAR T-cell therapies)
 - Fluids with cyclophosphamide lymphodepletion, allopurinol if high risk (institutional specific)
- Infections
 - Patient-specific vaccinations prior to treatment and antimicrobial prophylaxis
- Neutropenia (avoid during CRS)
 - Consider G-CSF use for prolonged, severe neutropenia with CAR T-cell therapies
- Hypogammaglobulinemia
 - Administer IVIG for IgG <400 mg/dL and/or persistent respiratory illnesses
 - Utility of prophylactic infusions is unknown

Recommended Monitoring:

- Monitor blood counts and immunoglobulin levels after CAR T-cell infusion or treatment with teclistamab
- Can support neutropenia with growth factor and/or transfusion support for other cytopenias; manage per institutional policies

REMS for BCMA-Targeted Therapies¹⁷

CAR T-Cell Therapies^{1,2}

- Each patient must have a dedicated caregiver present from the start of lymphodepleting chemotherapy through at least 30 days after infusion
- Driving for the first 8 wk after therapy is restricted
- Provide patients/caregivers with the Patient Wallet Card and instruct patient to remain within 2 hr of the certified administering hospital/associated clinics for at least 4 wk following infusion
- All relevant staff involved in the prescribing, dispensing, or administering of CAR T-cell therapy must have FDA-mandated training in management of CRS and neurologic toxicities
- Ensure that the hospital/associated clinics have ≥2 doses of tocilizumab available on-site for each patient and are ready for immediate administration (within 2 hr)

Teclistamab³

- All relevant staff involved in the prescribing or dispensing must be specially certified and trained in the management of CRS and neurologic toxicity, including ICANS
- Provide patients/caregivers with the Patient Wallet Card before starting teclistamab and instruct patients to remain at a healthcare setting for CRS monitoring for 48 hr after administration of the first dose and step-up doses
- Wholesalers/distributors only can provide teclistamab to certified pharmacies and healthcare settings

Refer to FDA or manufacturer websites for more specific REMS guidance

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