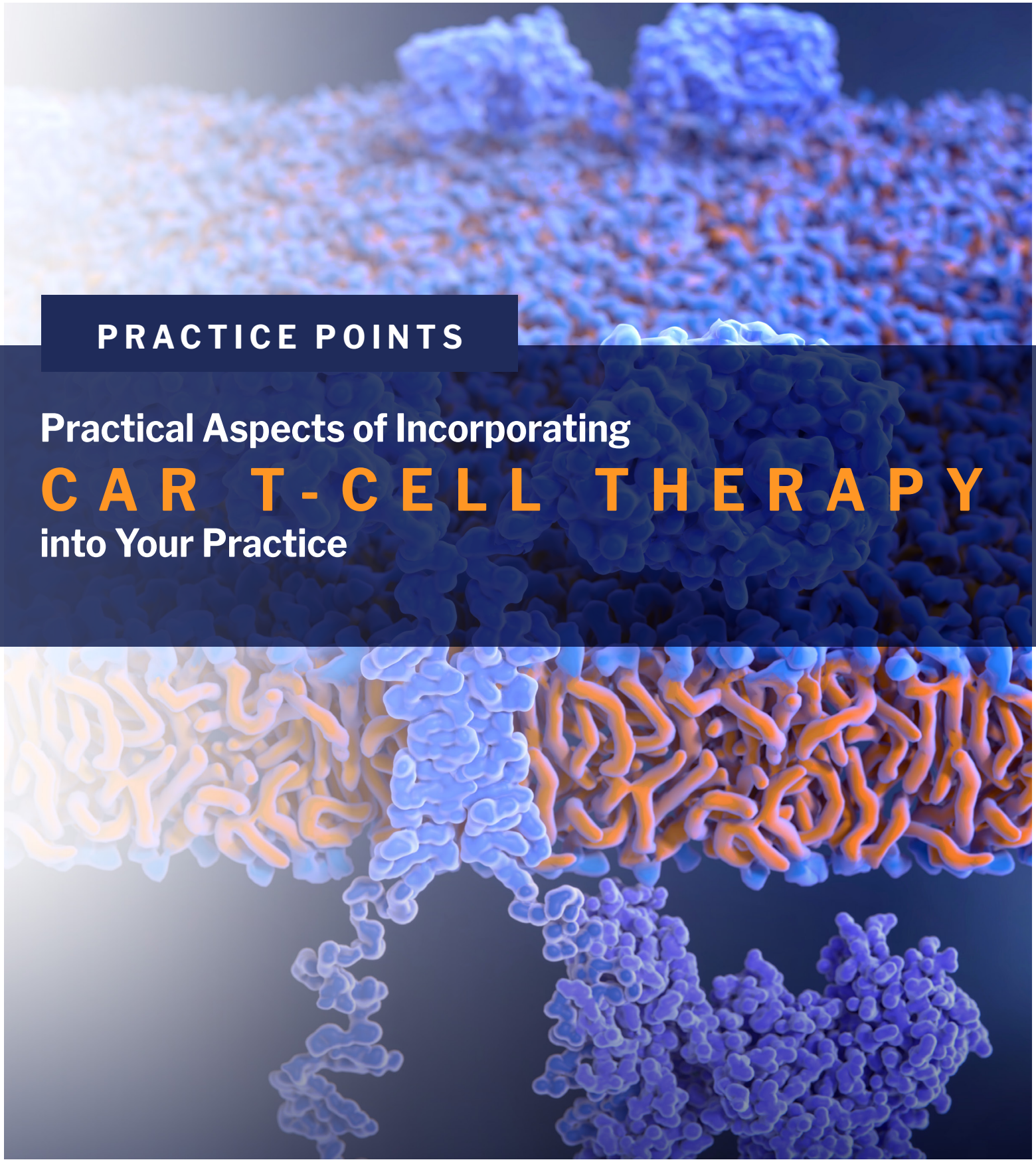

PRACTICE POINTS

Practical Aspects of Incorporating CAR T-CELL THERAPY into Your Practice

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

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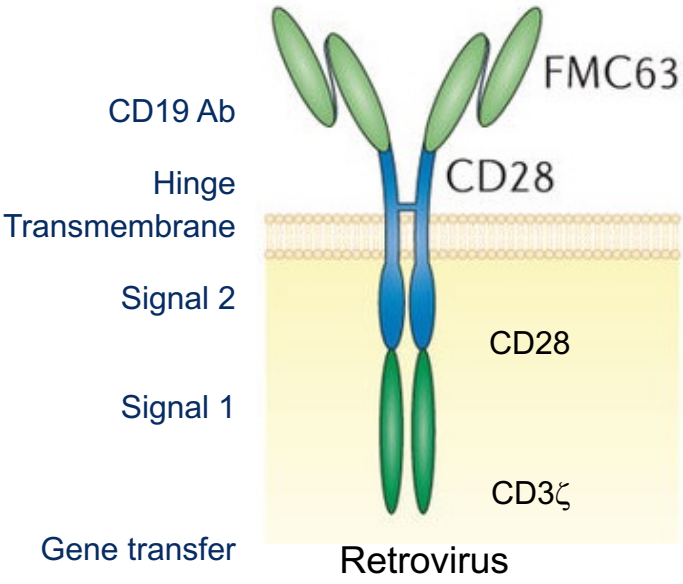
PRACTICE POINTS

Practical Aspects of incorporating CAR T-Cell Therapy into Your Practice

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

Axicabtagene ciloleucel



Study	ZUMA 1
CAR T dose	2×10^6 / kg
Conditioning therapy	Cyclophosphamide/fludarabine
Lymphoma subtypes	Diffuse large B-cell lymphoma / primary mediastinal large B-cell lymphoma / transformed follicular lymphoma
Treated / Enrolled	101 / 111 (91%)
Relapsed/Refractory	Refractory
Relapse post-ASCT	21%
Bridging therapy	None
Manufacturing success	99%
ORR / CR (%)	82 / 54

Safety

Cytokine release syndrome All Grades	Cytokine release syndrome Grade ≥3	Neurotoxicity All Grades	Neurotoxicity Grade ≥3
93%	**13%**	**64%**	**28%**

FDA Approved

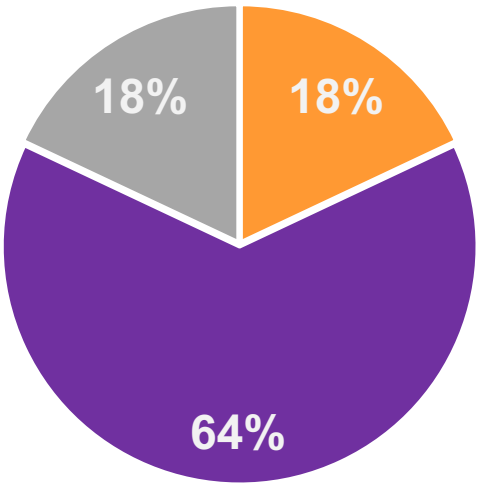
- R/R large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise speci ied, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
- R/R follicular lymphoma (FL) after two or more lines of systemic therapy
- Not indicated for the treatment of patients with primary central nervous system lymphoma

YESCARTA (axicabtagene ciloleucel)[Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc.; 2021. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med*. 2017;377(26):2531-2544. doi:10.1056/NEJMOA170744. van der Stegen S, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. *Nat Rev Drug Discov*. 2015;14(7):499-509.

Axi-Cel in Clinical Practice

Response to Standard of Care Axi-Cel Treatment

82% ORR Partial Response Complete Response Stable Disease / Progressive Disease



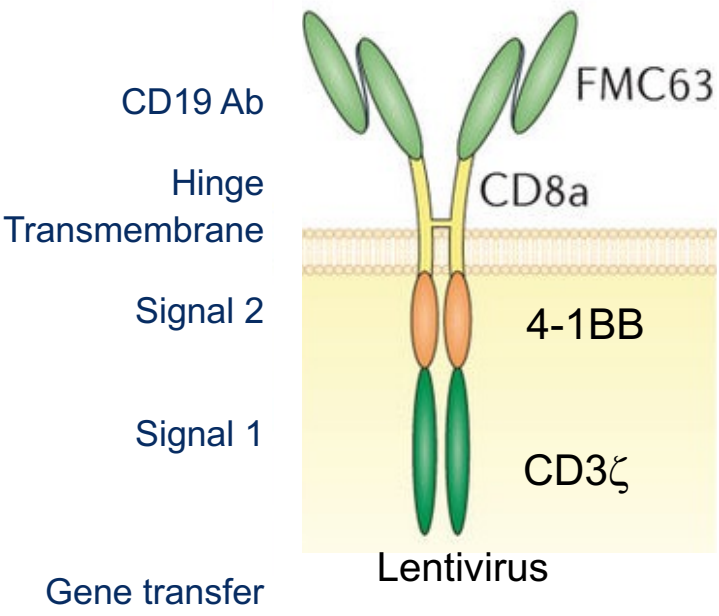
- **Median time to response was 30 days,** and no patients achieved a first response beyond day 90.
- **The majority of patients who achieved a CR** (n = 121) **at day 30 remained in CR at day 90** (78%).
- **Among the 93 patients with a partial response** (PR) **at day 30, 32% improved to a CR at day 90,** and even 1 (7%) of 14 patients with stable disease at day 30 improved to a CR at day 90.

Safety

	SOC axi-cel N=255	ZUMA 1 N=108
All grade CRS	251 (91%)	100 (93%)
Grade ≥ 3	19 (7%)	14 (13%)
Median time to onset	3 days	2 days
All grade neurotoxicity	189 (69%)	70 (65%)
Grade ≥ 3	85 (31%)	33 (31%)
Median time to onset	6 days	5 days
Median hospital stay	14	NA
ICU stay	91 (33%)	NA
Tocilizumab use	170 (62%)	45%
Corticosteroid use	149 (54%)	29%

Nastoupil L, Jain M, Feng L, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. *J Clin Oncol.* 2020;38(27):3119-3128.

Tisagenlecleucel



Study	JULIET
CAR T dose	0.6-6 x 10^8
Conditioning therapy	Cy / Flu or bendamustine
Lymphoma subtypes	DLBCL / TFL
Treated / enrolled	111 / 165 (67%)
Relapsed / refractory	Relapsed or refractory
Relapse post-ASCT	49%
Bridging therapy	Allowed
Manufacturing success	93%
ORR / CR (%)	52 / 40

Safety

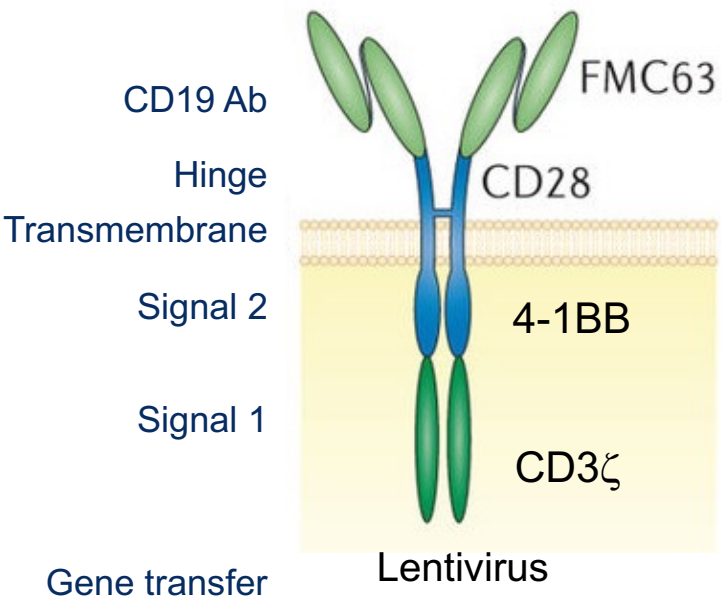
N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
111	**58%**	**22%**	**21%**	**12%**

FDA Approved

- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- R/R large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma
- Not indicated for treatment of patients with primary central nervous system lymphoma

KYMRIAH (tisagenlecleucel). [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2018;380(1):45-56. van der Stegen S, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. *Nat Rev Drug Disc.* 2015;14(7):499-509.

Lisocabtagene maraleucel



Study	TRANSCEND
CAR T dose	0.5-1.5 x 10^6
Conditioning therapy	Cy / Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL / FL Grade 3B
Treated / Enrolled	269 / 344 (78%)
Relapsed / Refractory	Relapsed or refractory
Relapse post-ASCT	33%
Bridging therapy	Allowed
Manufacturing success	99%
ORR / CR (%)	73 / 53

Safety

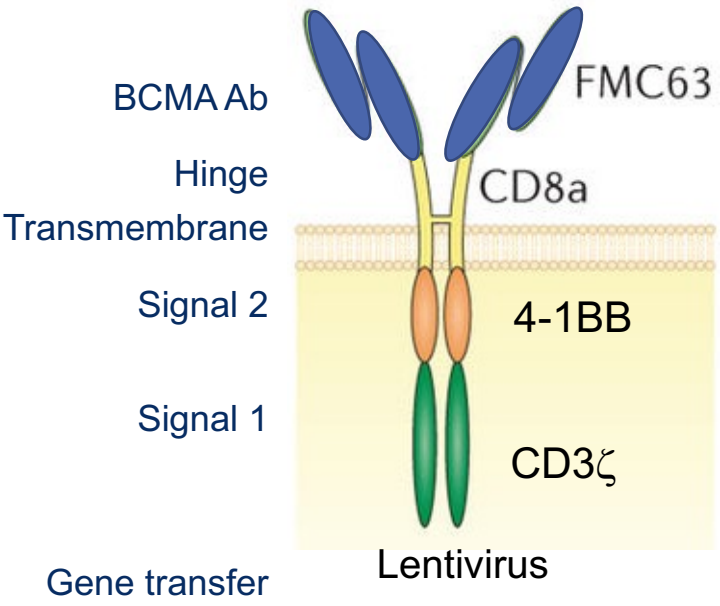
N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
268	**42%**	**2%**	**30%**	**10%**

FDA Approved

- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B
- Not indicated for the treatment of patients with primary central nervous system lymphoma

BREYANZI (lisocabtagene maraleucel). [Prescribing Information]. Bothell, WA: Juno Therapeutics Inc.; 2021. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *The Lancet.* 2020;396(10254):839-852. van der Stegen S, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. *Nat Rev Drug Disc. 2015;14(7):499-509.*

Idecabtagene vicleucel



Study	KarMMA
CAR T dose	150-450 x 10^6
Treated / enrolled	128
Relapsed / refractory	Relapsed or refractory
Manufacturing success	99%
ORR / CR (%)	73 / 33

Safety

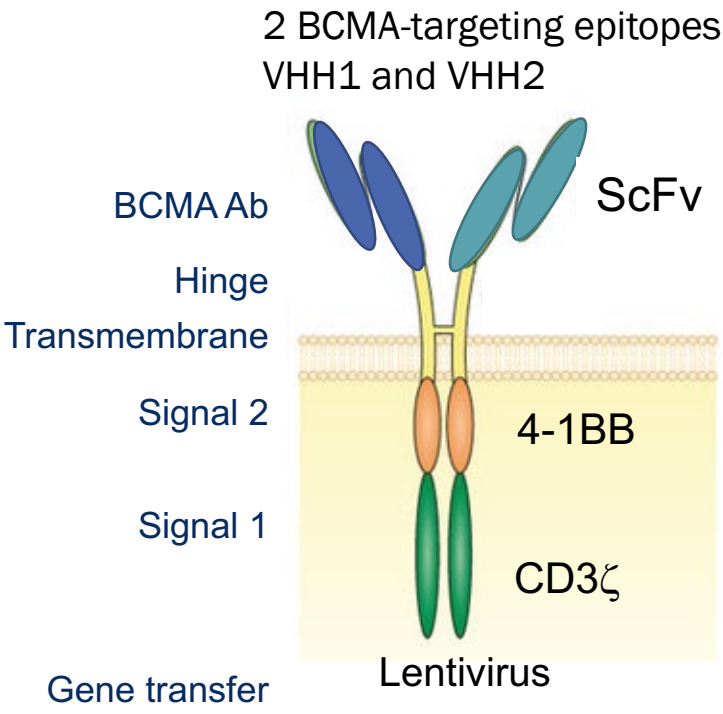
N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
128	**84%**	**5%**	**18%**	**3%**

FDA Approved

- Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

Munshi NC, Larry D. Anderson Jr, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med.* 2021;384(8):705-716. doi:10.1056/NEJMOA2024850. ABECMA (idecabtagene vicleucel) [Prescribing Information]. Summit, NJ: Celgene Corporation; 2021.

Ciltacabtagene autoleucel



Study	CARTITUDE
CAR T dose	0.75×10^6
Treated / enrolled	97
Relapsed / refractory	Relapsed or refractory
Bridging therapy	Permitted
ORR / sCR (%)	95 / 67

Safety

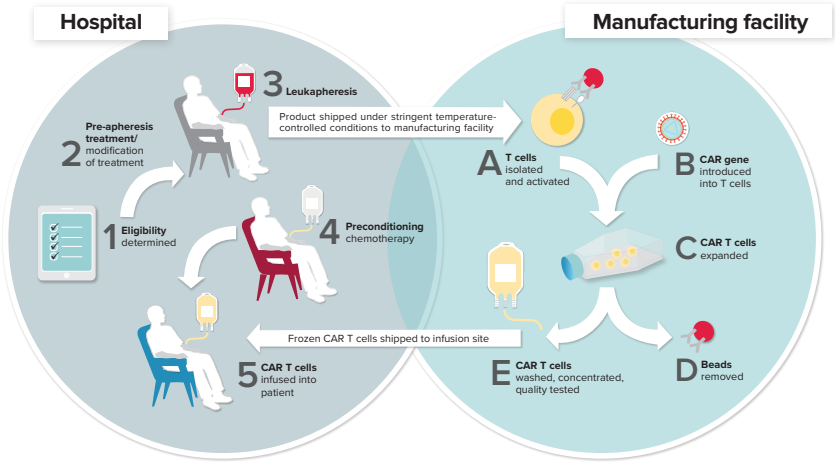
N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3
97	**95%**	**4%**	**21%**	**10**

Not yet FDA Approved

Usmani, S. Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (R/R MM): Updated results from CARTITUDE-1. *Abstract #8005* [Oral]. Presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting.

PRACTICE POINTS

How Are CAR T Cells Manufactured/Engineered?



- On average, the production of CAR T cells takes approximately 10 to 14 days
- The time from endogenous T-cell collection to CAR T-cell infusion varies, but typically ranges from 1 to 4 weeks

Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. https://www.lls.org/sites/default/files/2021-05/FSHP1_CART_Factsheet_Sept2020_Rev.pdf Accessed October 21, 2021.

CRS: Revised American Society for Transplantation and Cellular Therapy Grading System

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥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)

Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events v5.0 but they do not influence CRS grading.

- *Fever is defined as temperature 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
- CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
- Low-flow nasal cannula is defined as oxygen delivered at 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

CRS management				
Supportive care	**Tocilizumab**	**Steroids (dexamethasone)**	**More steroids (methylprednisolone)**	**Cyclophosphamide or other**

Lee D, Santomasso B, Locke F, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

PRACTICE POINTS

CAR T-related neurotoxicity, aka ICANS: Immune effector cell-associated neurotoxicity syndrome

- Delirium
- Encephalopathy
- Aphasia
- Lethargy
- Difficulty concentrating
- Agitation
- Tremor
- Seizures
- Cerebral edema
- Headache
- Fever

ICANS Management				
Seizure prophylaxis	Steroids (dexamethasone)	Increase steroids	Change steroids (methylprednisolone)	Consider cyclophosphamide or other

Lee D, Santomasso B, Locke F, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

Practical Aspects of CAR T-Cell Therapy Summary

- Extending the durability of remission following CAR T-cell therapy is the primary goal
  - The study of late effects and development of optimal guidelines for supportive care is imperative
- CAR T-cell recipients are at high risk of infection owing to a host of factors
  - Monitoring immune reconstitution after treatment will help identify those at risk and inform vaccination strategies
- Comprehensive care models that include the patient, their caregivers, and referring primary teams should be embedded in all CAR T-cell therapy programs
  - Open communication is critical to successful transitioning of patients to and from treating centers