# Updates in CAR T-Cell Therapy

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# Learning Objectives

- Discuss the current role of CAR (chimeric antigen receptor) T-cell therapies in the management of hematologic malignancies
- Review the evidence supporting the latest FDA approved CAR T-cell therapies in multiple myeloma
- Understand the management of toxicities associated with CAR T-cell therapies

# FDA Approved CAR T-Cell Therapies:

## *B-cell Lymphomas and Acute Lymphoblastic Leukemia*

| CAR T-cell Therapy | Abbreviation | Mechanism of Action | Indications |
|---|---|---|---|
| Axicabtagene ciloleucel (Yescarta) | Axi-cel | CD-19 targeted | Large B-cell lymphoma, relapsed or refractory<br><br>Follicular lymphoma, relapsed or refractory |
| Brexucabtagene autoleucel (Tecartus) | Brexu-cel | CD-19 targeted | B-cell acute lymphoblastic leukemia, relapsed or refractory<br><br>Mantle cell lymphoma, relapsed or refractory |
| Lisocabtagene maraleucel (Breyanzi) | Liso-cel | CD-19 targeted | Large B-cell lymphoma, relapsed or refractory |
| Tisagenlecleucel (Kymriah) | Tisa-cel | CD-19 targeted | Large B-cell lymphoma, relapsed or refractory<br><br>Follicular lymphoma, relapsed or refractory<br><br>B-cell acute lymphoblastic leukemia, relapsed or refractory (patients up to 25 years of age) |

# FDA Approved CAR T-Cell Therapies:
## *Multiple Myeloma*

| CAR T-cell Therapy | Abbreviation | Mechanism of Action | Indications |
|---|---|---|---|
| Idecabtagene vicleucel (Abecma) | Ide-cel | BCMA targeted | Multiple myeloma, relapsed or refractory after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody |
| Ciltacabtagene autoleucel (Carvykti) | Cilta-cel | BCMA targeted | |

BCMA=B cell maturation antigen

# BCMA as a Target in Multiple Myeloma

- BCMA is an antigen expressed predominantly on differentiated B cells
- Higher expression on myeloma cells than normal plasma cells
- Key role in B-cell maturation and differentiation
- Promotes myeloma cell growth, chemotherapy resistance, immunosuppression in bone marrow microenvironment
- Expression of BCMA increases with progression from MGUS to advanced myeloma

Cho et al. 2018. Front. Immunol. 9:1821

# Pivotal Anti-BCMA CAR T-Cell Trials

| | KarMMa | CARTITUDE-1 |
|---|---|---|
| CAR T-cell agent | Idecabtagene vicleucel | Ciltacabtagene autoleucel |
| Study phase | II | Ib/II |
| Patient population | Adults with R/R Multiple Myeloma | Adults with R/R Multiple Myeloma |
| Number of patients treated (n) | 128 | 97 |
| Number of cells infused | 150-450 M | 0.75 M/kg |
| Population | | |
| • Age, median (range) years | 61 (33-78) | 61 (43-78) |
| • Number of prior lines of therapy, median (range) | 6 (3-16) | 6 (3-18) |
| • Triple-refractory | 84% | 86% |
| • Penta-refractory | 26% | 28% |

Munshi NC, et al. N Engl J Med 2021;384:705–16.
Berdeja JG, et al. Lancet. 2021;398(10297):314-324

# Pivotal Anti-BCMA CAR T-Cell Trials

| | KarMMa (n=128) | CARTITUDE-1 (n=97) |
|---|---|---|
| CAR T-cell agent | Idecabtagene vicleucel | Ciltacabtagene autoleucel |
| Overall response rate (ORR), % | 73 | 98 |
| Complete remission (CR), % | 33% | 80% |
| Progression free survival, median months | 12.1 | 66% at 18 months |

Munshi NC, et al. N Engl J Med 2021;384:705–16.
Berdeja JG, et al. Lancet. 2021;398(10297):314-324

# KarMMa Safety (idecabtagene vicleucel)

| Adverse effects, n (%) | N=128 | |
|---|---|---|
| | Any Grade | Grade 3/4 |
| Hematologic (>25%) | | |
| ▪ Neutropenia | 117 (91) | 114 (89) |
| ▪ Anemia | 90 (70) | 78 (61) |
| ▪ Thrombocytopenia | 82 (64) | 67 (52) |
| ▪ Leukopenia | 54 (42) | 50 (39) |
| ▪ Lymphopenia | 36 (28) | 35 (27) |
| Gastrointestinal | | |
| ▪ Diarrhea | 45 (35) | 2 (2) |
| ▪ Nausea | 37 (29) | 0 |

| CRS | N=128 |
|---|---|
| Any grade, n (%) | 107 (84) |
| Grade ≥3, n (%) | 7 (5) |
| Median onset, days | 1 |
| Tocilizumab use, % | 52 |
| Steroid use, % | 15 |
| **Neurotoxicity** | **N=128** |
| Any grade, n (%) | 23 (18) |
| Grade 3, n (%) | 5 (4) |
| Median onset, days | 2 |
| Median duration, days | 3 |

Munshi NC, et al. N Engl J Med 2021;384:705–16.

# CARTITUDE-1 Safety (ciltacabtagene autoleucel)

| Adverse effects, n (%) | N= 97 | |
|---|---|---|
| | Any Grade | Grade 3/4 |
| Hematologic (>20%) | | |
| ▪ Neutropenia | 93 (96) | 92 (95) |
| ▪ Anemia | 79 (81) | 66 (68) |
| ▪ Thrombocytopenia | 77 (79) | 58 (60) |
| ▪ Leukopenia | 60 (62) | 59 (61) |
| ▪ Lymphopenia | 52 (54) | 49 (51) |
| Gastrointestinal | | |
| ▪ Diarrhea | 29 (30) | 1 (1) |
| ▪ Nausea | 27 (28) | 1 (1) |
| Other | | |
| ▪ AST increase | 28 (29) | 5 (5) |
| ▪ ALT increase | 24 (25) | 3 (3) |

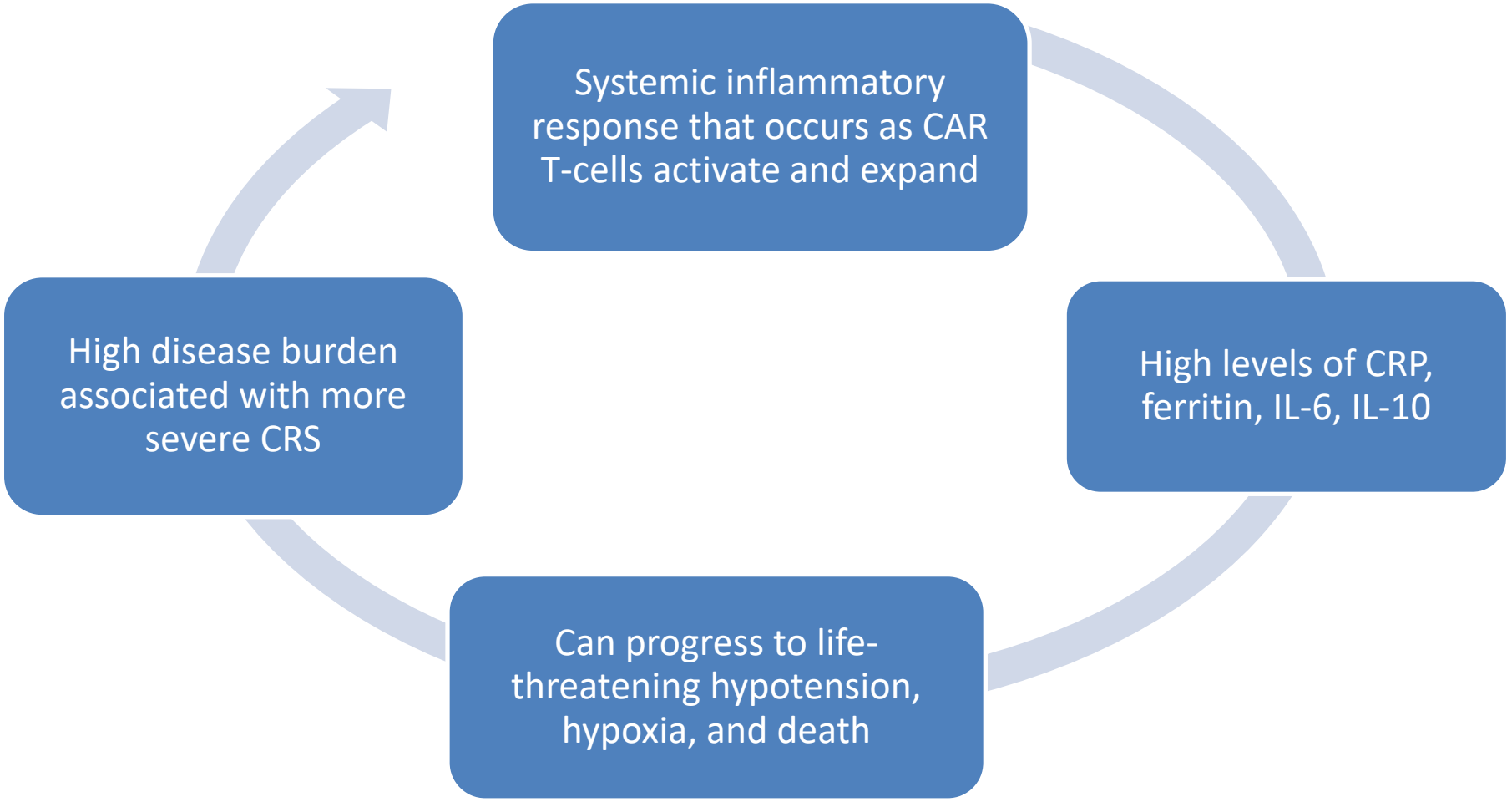
| CRS | N=97 |
|---|---|
| Any grade, n (%) | 92 (95) |
| Grade ≥3, n (%) | 5 (5) |
| Median onset, days (IQR) | 7 (5-8) |
| **Neurotoxicity** | **N=97** |
| Any grade, n (%) | 20 (21) |
| Grade 3, n (%) | 9 (9) |
| ICANS (any grade), n (%)<br>• Median time to onset, days (range) | 16 (17)<br>8 (6-8) |
| Other neurotoxicity (any grade), n (%)<br>• Median time to onset, days (range) | 12 (12)<br>27 (16-73) |

Berdeja JG, et al. Lancet. 2021;398(10297):314-324

# Acute Toxicities of CAR T-cell therapy

| |
|---|
| Cytokine Release Syndrome (CRS) |
| Neurotoxicity |
| Tumor lysis syndrome (varies based on disease and disease burden) |
| Infection |
| Hemophagocytic lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS) |

# Cytokine Release Syndrome (CRS)




## Symptoms

- Fever
- Rash
- Tachycardia
- Hypoxia
- Hypotension
- Respiratory failure
- Coagulopathy
- Multiorgan system failure

Lee et al. Blood. 2014; 124 (2): 188–195.
NCCN Guidelines Version 1.2022. Management of Immunotherapy-Related Toxicities.

# CRS Management Principles

- Evaluate for and treat other causes of fever, hypoxia, and hypotension.
  - Assess for infection with blood and urine cultures and chest radiography
  - Empiric broad-spectrum antimicrobials should be considered as well as C-GSF if neutropenic
- CRS treatment modalities include the use of tocilizumab with or without corticosteroids
- Patients who experience Grade 2 or higher CRS should be monitored with continuous cardiac telemetry and pulse oximetry.
- For patients experiencing severe CRS:
  - Consider performing an echocardiogram to assess cardiac function
  - Consider intensive-care supportive therapy
- Monitor patients for signs or symptoms of CRS for 4 weeks after infusion

NCCN Guidelines Version 1.2022. Management of Immunotherapy-Related Toxicities.

# CRS Management: Tocilizumab

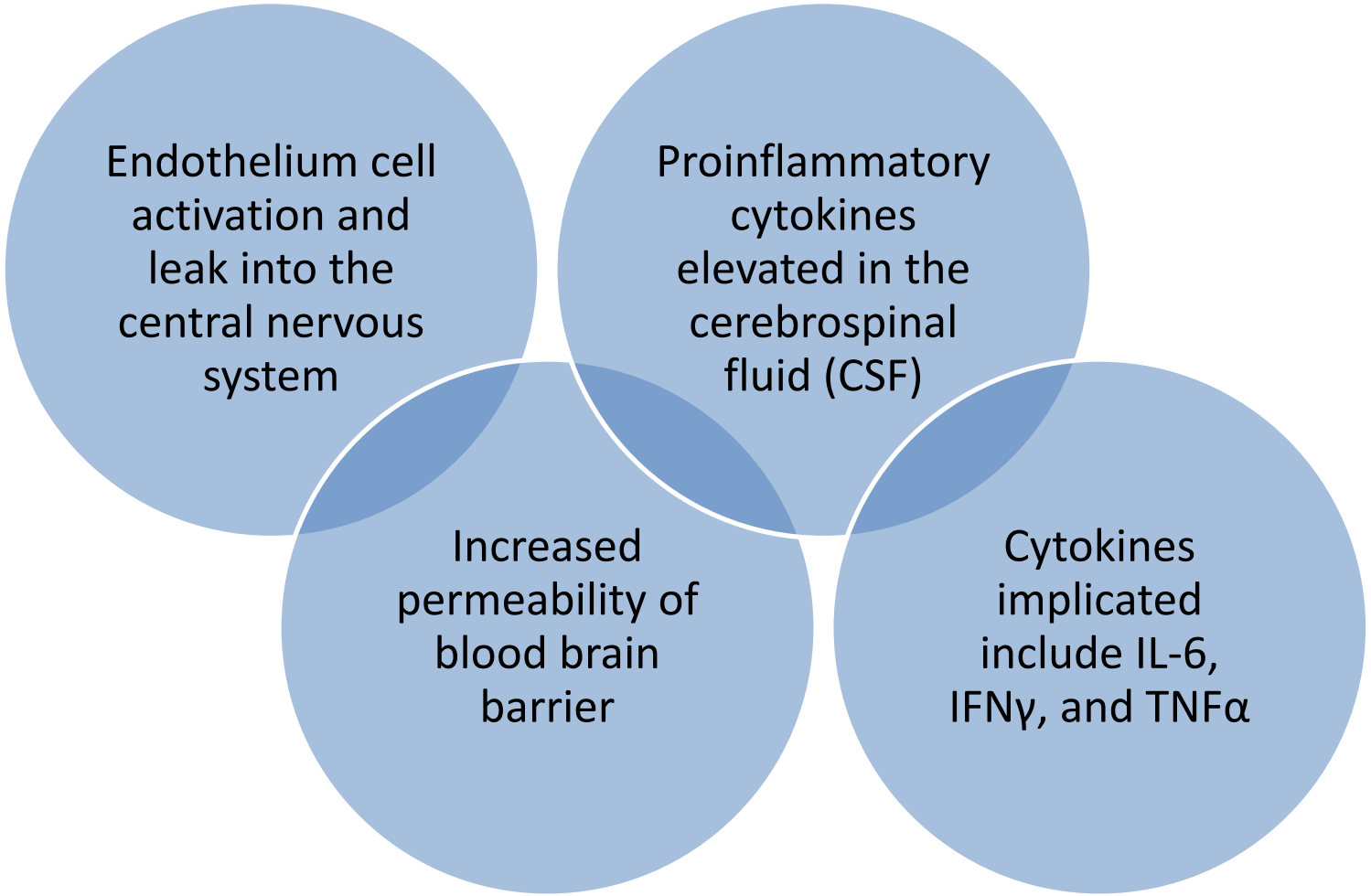
| | |
|---|---|
| Mechanism | IL-6 receptor antagonist |
| Dosing | **≥30 kg:** 8 mg/kg<br>**<30 kg:** 12 mg/kg<br>*Maximum 800 mg/dose |
| Administration | Give tocilizumab IV over 60 minutes +/- corticosteroids<br>*DO NOT give subcutaneously for CRS |
| Frequency | Administer subsequent doses at least **8 hours apart** as needed for CRS for maximum of 3 doses per 24 hours or 4 doses total |

To remain compliant with FDA Risk Evaluation and Mitigation Strategy (REMS):

- ✓ 2 doses of tocilizumab must always be readily available
- ✓ Tocilizumab must be given within 2 hours of CRS symptom onset

Santomasso BD, et al. J Clin Oncol. 2021;39(35):3978-3992.

# Immune Effector Cell–Associated Neurotoxicity




## Symptoms

- Encephalopathy
- Delirium
- Aphasia
- Headache
- Tremor
- Motor dysfunction
- Ataxia
- Psychosis
- Seizures
- Cerebral edema

Gust J, et al. Cancer Discov. 2017 Dec;7(12):1404-1419
NCCN Guidelines Version 1.2022. Management of Immunotherapy-Related Toxicities.

# Neurotoxicity Management Principles

- Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness
- Consider levetiracetam for seizure prophylaxis
- Rule out other causes of neurologic symptoms
- For Grade 2 or higher neurologic toxicities:
  - MRI of the brain with and without contrast (or brain CT if MRI is not feasible)
  - Conduct electroencephalogram (EEG) for seizure activity
  - Consider treatment with steroids
- For severe or life-threatening neurologic toxicities, provide intensive-care supportive therapy
- Monitor patients for signs and symptoms of neurologic toxicity/immune effector cell-associated neurotoxicity syndrome (ICANS) for 4 weeks after infusion

NCCN Guidelines Version 1.2022. Management of Immunotherapy-Related Toxicities.

# Additional CAR T-Cell Therapy Toxicities

- Prolonged cytopenias
  - Transfusions as indicated
  - G-CSF support as needed
- B-cell aplasia and hypogammaglobulinemia
  - Monitor IgG levels
  - Replete with IVIG for levels < 400 ug/L
- Infections
  - Provide antimicrobial prophylaxis per institutional protocols (HSV, PJP)
- Residual effects of acute toxicity
- Long-term effects
  - Secondary malignancies
  - Quality of life impairment: fatigue, memory issues

NCCN Guidelines Version 1.2022. Management of Immunotherapy-Related Toxicities.

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