# CAR-T CELLS AND BMT LEARNING HOW TO DEAL WITH COMPLICATIONS

**ADALBERTO TORRES-HERNÁNDEZ,** *MSN, BA,CERN, CWCMS, CON*

9TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM MARCH 6 – 8, 2020 IN SAN JUAN, PUERTO RICO

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**NO RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.**

**THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.**

“ What most surprises me about the Western man is

that he loses his health to make money,

then lose money to regain their health.

And for thinking anxiously about the future

don't enjoy the present,

so he lives neither the present nor the future,

and they live, like they never have to die,

and die, as if they had never lived.”



Dalai Lama

CONGRATULATIONS ON

# INTERNATIONAL WOMEN'S DAY

*CLARA ZETKIN*

1857 / 1911 / 1975

*MARCH 08*

# CONTENTS

# WHAT IS CAR-T THERAPY

## T CELLS

*IMMUNE* SYSTEM *CELLS* THAT PLAY SEVERAL KEY ROLES IN THE BODY'S *FIGHT AGAINST THE DISEASE*. THEY HELP THE IMMUNE SYSTEM RESPOND TO A DISEASE AND DIRECTLY KILL DISEASED CELLS.

## "CAR"

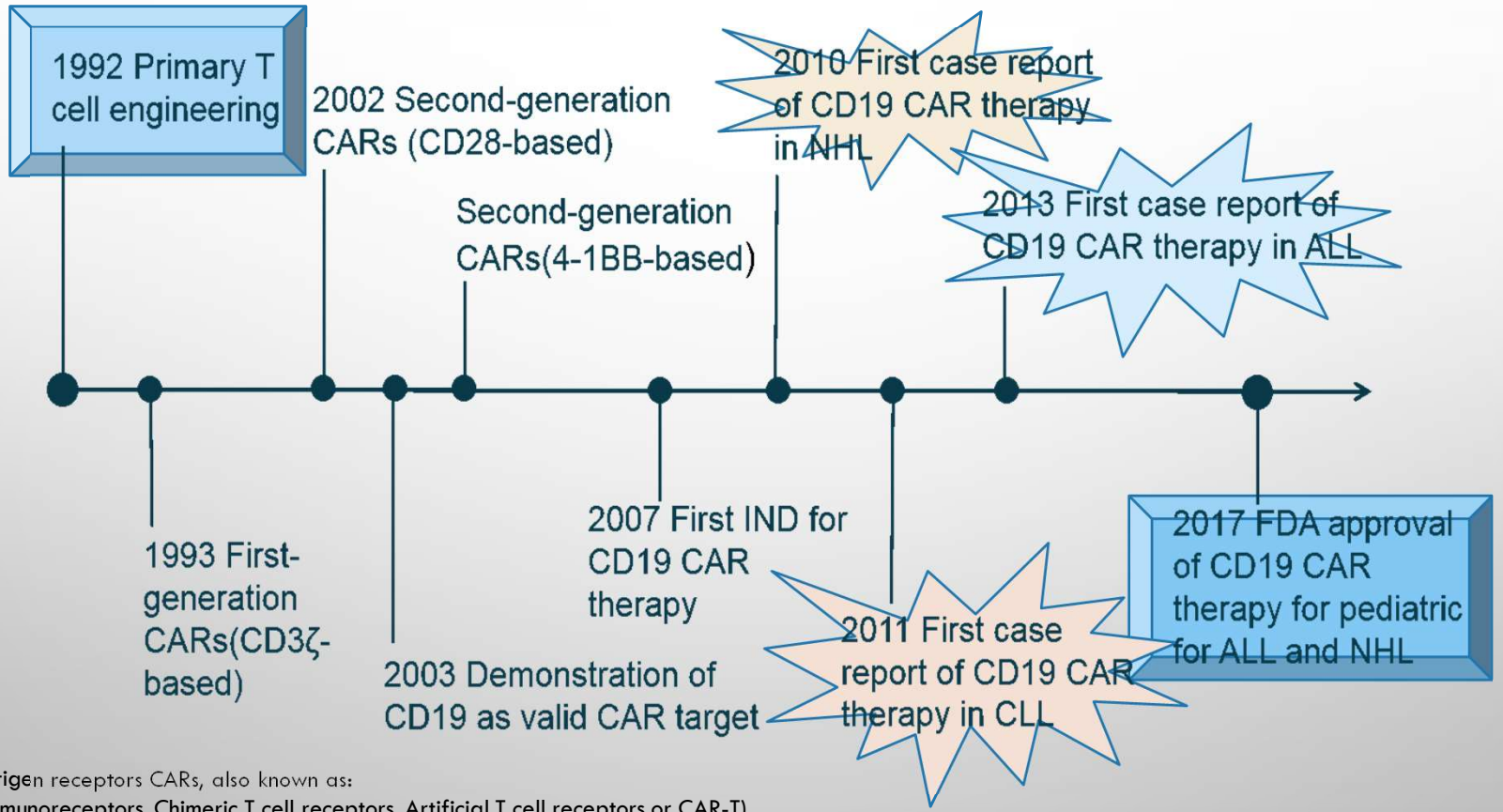
CHIMERIC ANTIGEN RECEPTORS ( **CAR** )ARE *ENGINEERED RECEPTORS* WHICH GRAFT AN ARBITRARY SPECIFICITY ONTO T CELL, THESE RECEPTORS ARE *USED TO GRAFT THE SPECIFICITY OF A MONOCLONAL ANTIBODY* ONTO A T CELL, WITH *TRANSFER OF THEIR CODING SEQUENCE FACILITATED BY RETROVIRAL VECTORS*.

THE RECEPTORS ARE CALLED CHIMERIC BECAUSE THEY ARE COMPOSED OF PARTS FROM DIFFERENT SOURCES.

## CAR T-CELL THERAPY

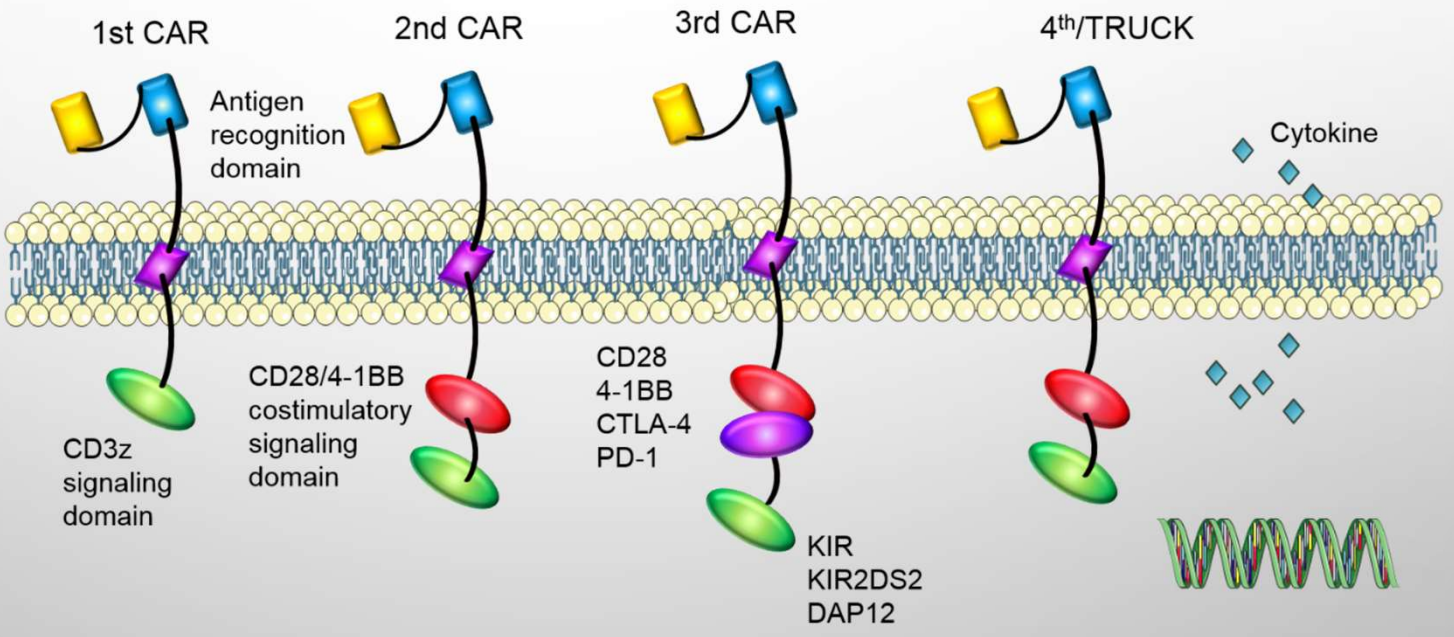
*TYPE OF IMMUNOTHERAPY* THAT CHANGES A PATIENT'S OWN T CELLS SO THEY ARE *ABLE TO RECOGNIZE AND ATTACK CANCER*. T CELLS ARE TAKEN FROM A PATIENT'S BLOOD. THEN THE GENE FOR A SPECIAL RECEPTOR THAT BINDS TO A CERTAIN PROTEIN ON THE PATIENT'S CANCER CELLS IS ADDED IN THE LABORATORY.

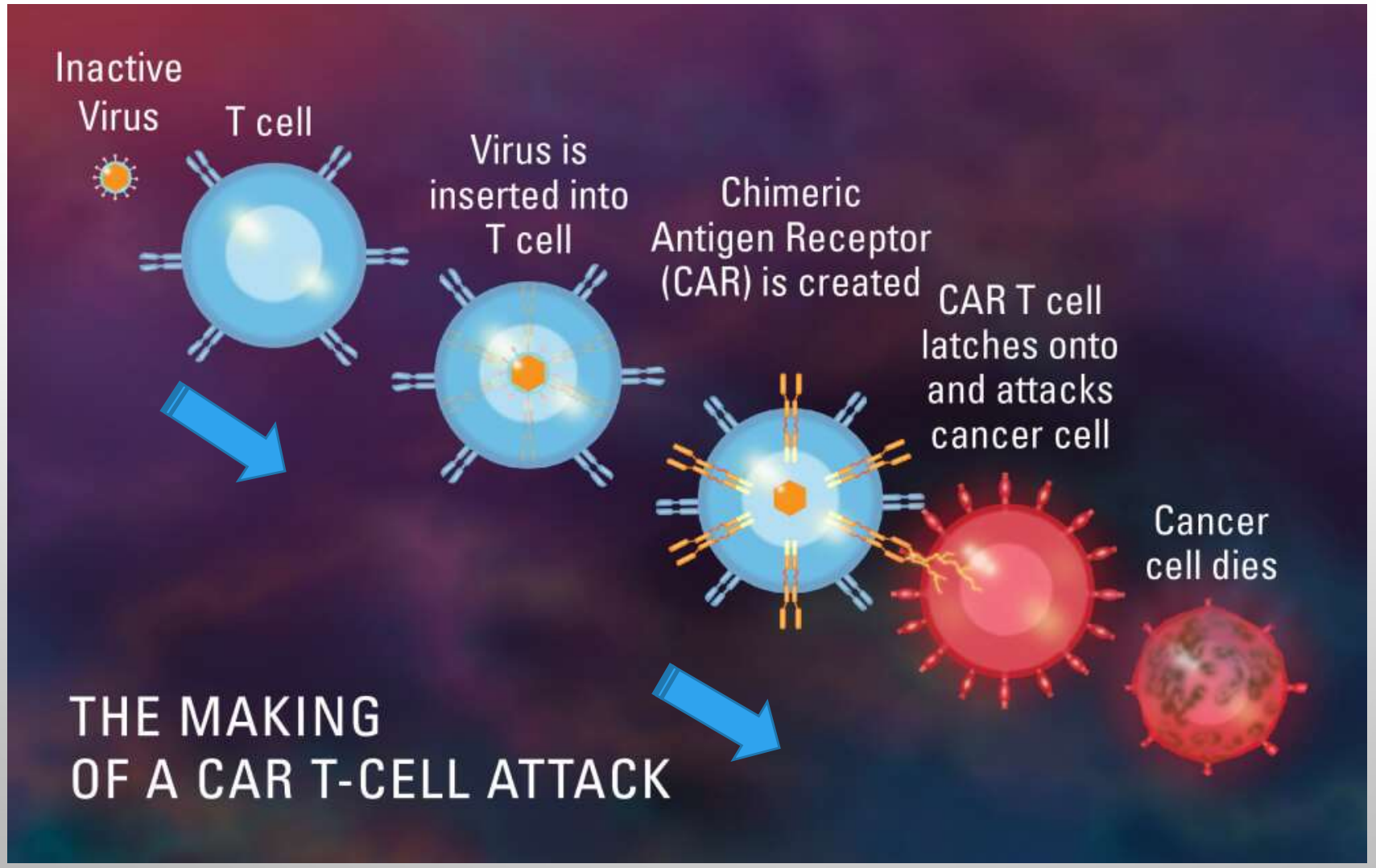
# CHRONOLOGICAL EVOLUTION OF CAR-T CELL




Chimeric antigen receptors CARs, also known as:
Chimeric immunoreceptors, Chimeric T cell receptors, Artificial T cell receptors or CAR-T)

# STRUCTURE AND GENERATIONS OF CAR-T CELL




Inactive Virus
T cell
Virus is inserted into T cell
Chimeric Antigen Receptor (CAR) is created
CAR T cell latches onto and attacks cancer cell
Cancer cell dies
THE MAKING OF A CAR T-CELL ATTACK

# CAR-T-CELL TARGETS FOR THE TREATMENT OF HEMATOLOGICAL TUMORS

| Target | CAR structure | Malignancy |
|---|---|---|
| BCMA | CD3ζ and 41BB | MM |
| CD19 | CD3ζ and CD28;<br>CD3ζ and 41BB<br>KIR2DS2 and DAP12- | Lymphoma;<br>Leukemia |
| CD22 | CD3ζ and CD28 | FL; NHL; DLBCL; ALL |
| CD20 | CD3ζ; CD3ζ and 41BB- | CD20positive malignancies |
| CD138 | CD3ζ and 41BB | MM |
| CD33 | CD3ζ and 41BB | AML |
| CD123 | CD3ζ and CD28 | AML |

# CAR-T-CELL TARGETS FOR THE TREATMENT OF HEMATOLOGICAL TUMORS

| Target | CAR structure | Malignancy |
|---|---|---|
| CD19<br>CD20 | CD3ζ and 41BB | Leukemia; Lymphoma |
| CD19<br>PSMA | CD3ζ and CD28<br>PD-1 or CTLA4 | Leukemias |
| FITC-CD19 Ab | CD3ζ and CD28 | CD19 positive cancers |
| Igκ | CD3ζ and CD28 | CLL |
| LeY | CD3ζ and CD28 | AML |
| ROR1 | CD3ζ and 41BB | CLL; SLL |

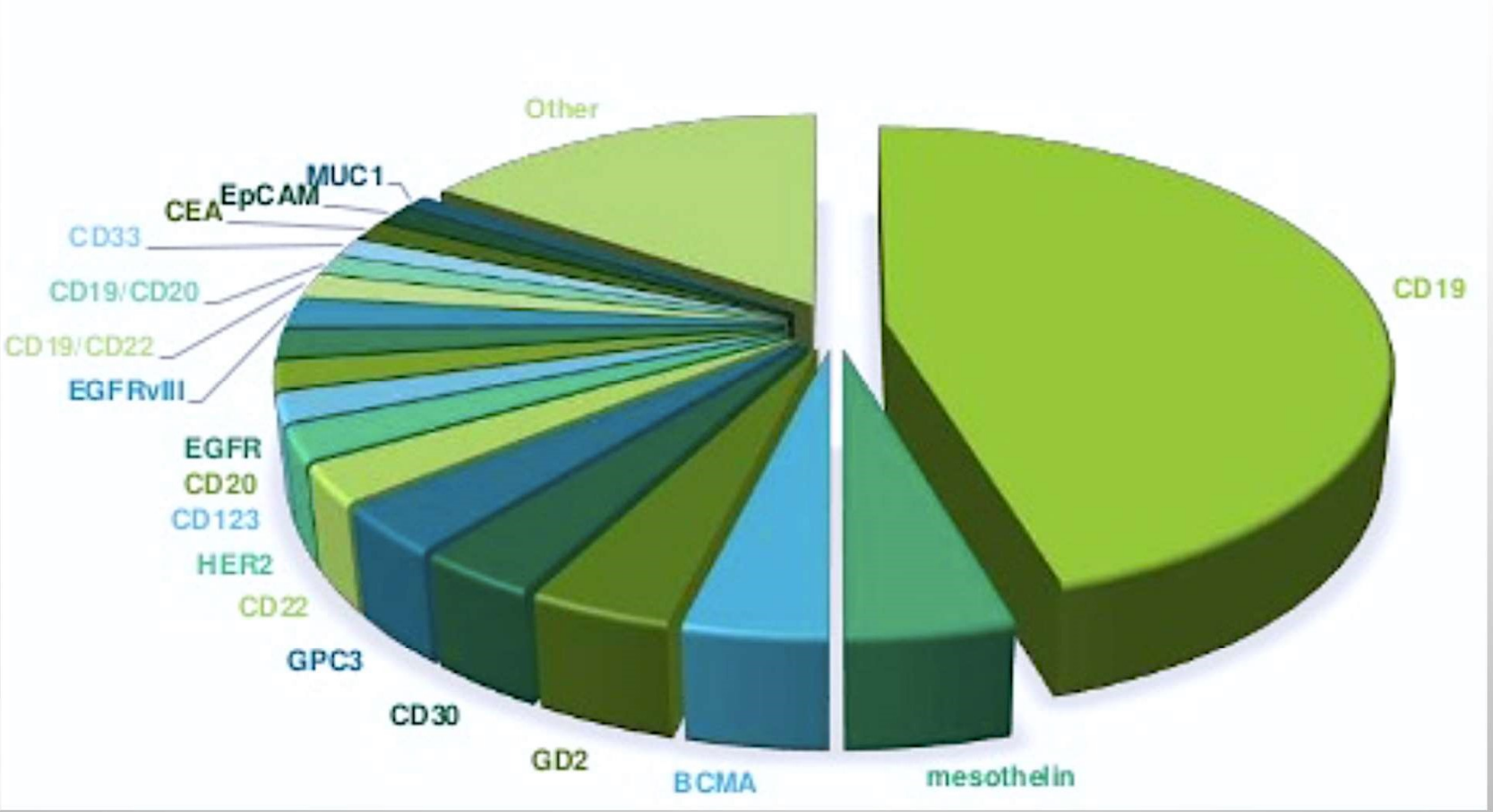
# CAR-T-CELL TARGETS FOR THE TREATMENT OF SOLID TUMORS

| Target | CAR structure | Malignancy |
|---|---|---|
| Biotin | CD3ζ, CD28 and 41BB | EGFRvIII positive cancer |
| CD171 | CD3ζ and 4-1BB;<br>CD3ζ, CD28 and 4-1BB | Neuroblastoma |
| EGFRvIII | CD3ζ and 41BB<br>CD3ζ and ICOS- | Glioma |
| FAP | CD3ζ and CD28<br>KIR2DS2 and DAP12- | Mesothelioma;<br>Lung cancer |
| FR | CD3ζ and CD27 | Ovarian cancer;<br>Breast cancer |

# CAR-T-CELL TARGETS FOR THE TREATMENT OF SOLID TUMORS

| Target | CAR structure | Malignancy |
|---|---|---|
| Glypican-3 | CD3ζ, CD28 and 41BB | Hepatocellular carcinoma |
| HER2 | CD3ζ and CD28 | HER2 positive cancer; Sarcoma |
| HER2<br>MUC1 | CD3ζ and CD28 | Breast cancer |
| HER2<br>IL13Rα2 | CD3ζ and CD28 | Glioblastoma |

# CAR-T-CELL TARGETS




Contents https://www.creativebiomart.net

# CANCERS TREATED WITH CAR-T CELL THERAPY

CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY HAS THE POTENTIAL TO REVOLUTIONIZE THE MANAGEMENT OF B-CELL LYMPHOMAS AND POSSIBLY OTHER CANCERS.

TWO ANTI-CD19 CAR T-CELL PRODUCTS, *AXICABTAGENE CILOLEUCEL* ***( AXI-CEL )*** AND *TISAGENLECLEUCEL* ***( TISA-CEL )**** HAVE BEEN APPROVED FOR THE MANAGEMENT OF RELAPSED / REFRACTORY LARGE B-CELL LYMPHOMA AFTER TWO LINES OF SYSTEMIC THERAPY. (NEELAPU 2019)

# CANCERS TREATED WITH CAR-T CELL THERAPY

- THE NATIONAL CANCER INSTITUTE ESTIMATES THAT IN 2019, AN ESTIMATED **5,930** PEOPLE IN THE U.S. WILL HAVE **ALL, A CANCER OF THE BLOOD AND BONE MARROW.**

- EACH YEAR, APPROXIMATELY **3,100** NEW PATIENTS AGED 20 OR YOUNGER ARE DIAGNOSED WITH ALL

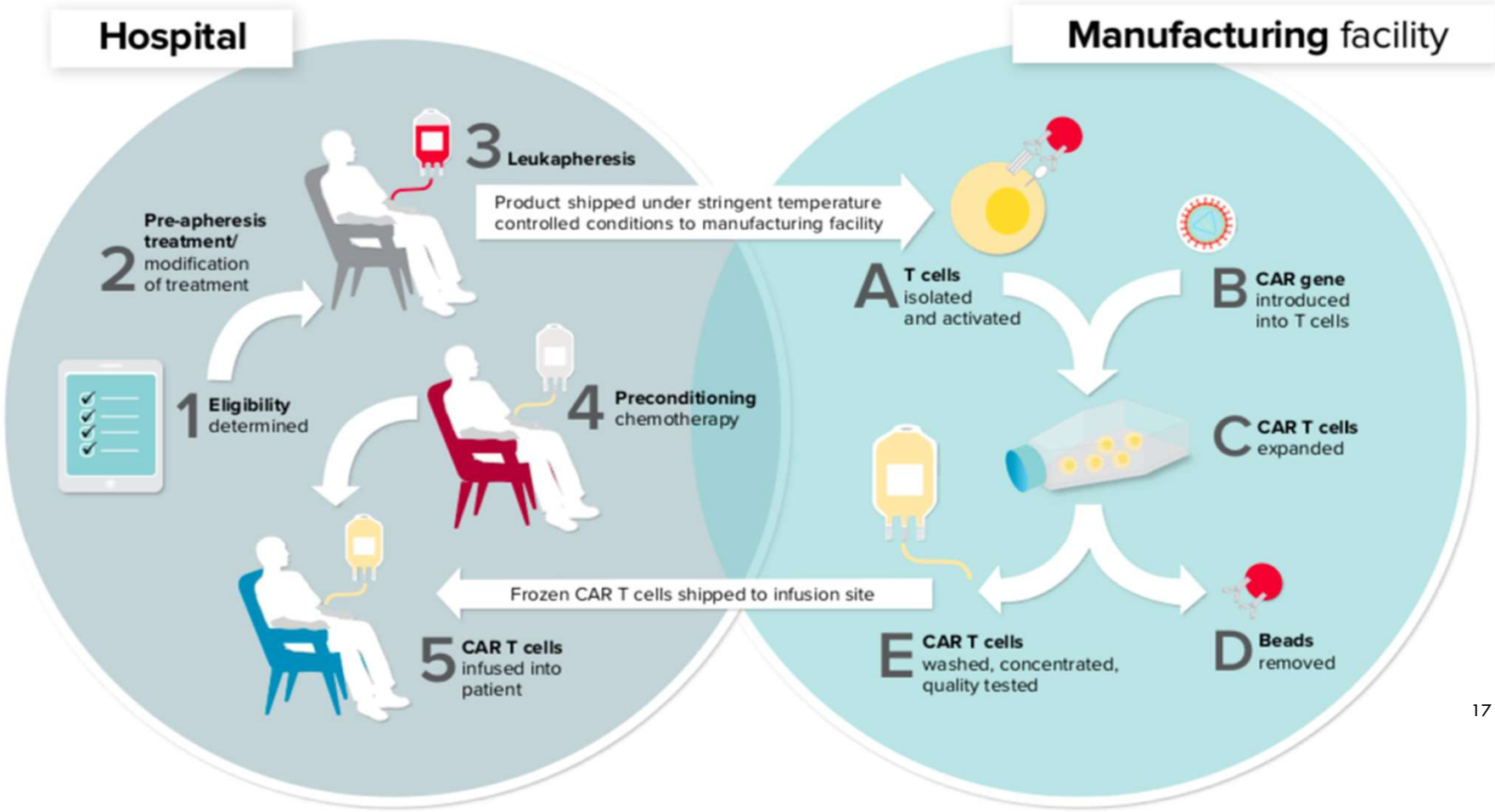
- JULY 2018 TWO COMMERCIAL GENE THERAPY PRODUCTS, ***TISAGENLECLEUCEL*** *(TISA-CEL)* AND ***AXICABTAGENE CILOLEUCEL*** *(AXI-CEL)*, HAVE BEEN APPROVED BY THE US FOOD AND DRUG ADMINISTRATION (FDA)

- FDA-APPROVED CAR T-CELL THERAPY, TISAGENLECLEUCEL, SHOWED A RELAPSE FREE SURVIVAL OF 65% AT 12 MONTHS

# THE PROCESS OF CAR-T CELL THERAPY

1. T CELLS ARE COLLECTED FROM A PATIENT.
2. T CELLS ARE REENGINEERED IN A LABORATORY.
3. AFTER THIS REENGINEERING, THE T CELLS ARE KNOWN AS "CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS."
4. THE REENGINEERED CAR T CELLS ARE THEN MULTIPLIED.
5. WHILE THE CAR T-CELLS ARE MULTIPLYING IN THE LABORATORY, THE PATIENT MAY REMAIN OUT OF THE HOSPITAL AND MAY RECEIVE A BRIEF COURSE OF OUTPATIENT CHEMOTHERAPY
6. AT THE HOSPITAL OR TREATMENT CENTER, THE CAR T CELLS ARE THAWED AND THEN INFUSED INTO THE PATIENT.
7. THE CAR T CELLS MAY HELP GUARD AGAINST RECURRENCE

# THE PROCESS OF CAR-T CELL THERAPY



# FDA APPROVED TREATMENTS

- **TISAGENLECLEUCEL**
  - APPROVED FOR THE TREATMENT OF PATIENTS UP TO 25 YEARS OF AGE WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
- **AXICABTAGENE CILOLEUCEL**
  - APPROVED FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA AFTER TWO OR MORE LINES OF SYSTEMIC THERAPY
  - *MEDIAN TIME TO CRS ONSET OF 2 DAYS (RANGE: 1–12 DAYS), MEDIAN DURATION OF 7 DAYS (RANGE: 2–58 DAYS). MEDIAN TIME TO NEUROTOXICITY ONSET OF 4 DAYS (RANGE: 1–43 DAYS), MEDIAN DURATION OF 17 DAYS.*
- **TOCILIZUMAB**
  - APPROVED FOR THE TREATMENT OF ADULTS AND PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER WITH **CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL-INDUCED SEVERE OR LIFE-THREATENING CYTOKINE RELEASE SYNDROME (CRS).**
  - **HUMANIZED MONOCLONAL ANTIBODY THAT BLOCKS BINDING TO IL-6 RECEPTORS** AND IS APPROVED BY THE FDA FOR THE TREATMENT OF CRS (GENENTECH, 2018)
  - MEDIAN TIME TO CRS ONSET OF 3 DAYS (RANGE: 1–51 DAYS), MEDIAN DURATION OF 8 DAYS (RANGE: 1–36 DAYS). MEDIAN TIME TO NEUROTOXICITY ONSET OF 6 DAYS (RANGE: 1–359 DAYS); MEDIAN DURATION OF 14 DAYS.

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES

## Before and During CAR T-Cell Infusion

- Perform central venous access, preferably with double or triple lumen catheter, for intravenous IV fluid and other infusions in case of toxicities.
- Perform cardiac monitoring at least at the onset of grade 2 cytokine release syndrome (CRS) until resolution to ≤ grade 1, and additionally as clinically indicated.
- Tumor lysis precautions are recommended for patients with large tumor burden and aggressive histologies, as per standard institutional guidelines.
- 
- Start seizure prophylaxis on the day of infusion for CAR T-cell therapies known to cause CAR T-cell-related neurotoxicity (eg, levetiracetam 500–750 mg orally every 12 h for 30 days).
- Consider baseline brain MRI.

# CAR T-CELL THERAPY-RELATED TOXICITIES

*MEDIAN TIME TO CRS ONSET OF 2 DAYS (RANGE: 1–12 DAYS), MEDIAN DURATION OF 7 DAYS (RANGE: 2–58 DAYS)*

| | **Axicabtagene ciloleucela and tisagenlecleucelb** | **Axicabtagene ciloleucela and tisagenlecleucelb** |
|---|---|---|
| **CYTOKINE RELEASE SYNDROME (CRS)** also known as a **cytokine storm** | **Typical time to onset: 2–3 days**<br><br>**Typical duration: 7–8 days**<br><br>CRS may be associated with *cardiac, hepatic, and/or renal dysfunction.* | **Manifestation** may include fever, hypotension, tachycardia, hypoxia, and chills.<br><br>Serious events may include:<br>*Atrial fibrillation and Ventricular tachycardia Cardiac arrest*<br>*Cardiac failure*<br>*Renal insufficiency*<br>*Capillary leak syndrome*<br>*Hypotension*<br>*Hypoxia*<br>*Hemophagocytic Lymphohistiocytosis /macrophage activation syndrome (HLH/MAS).* |

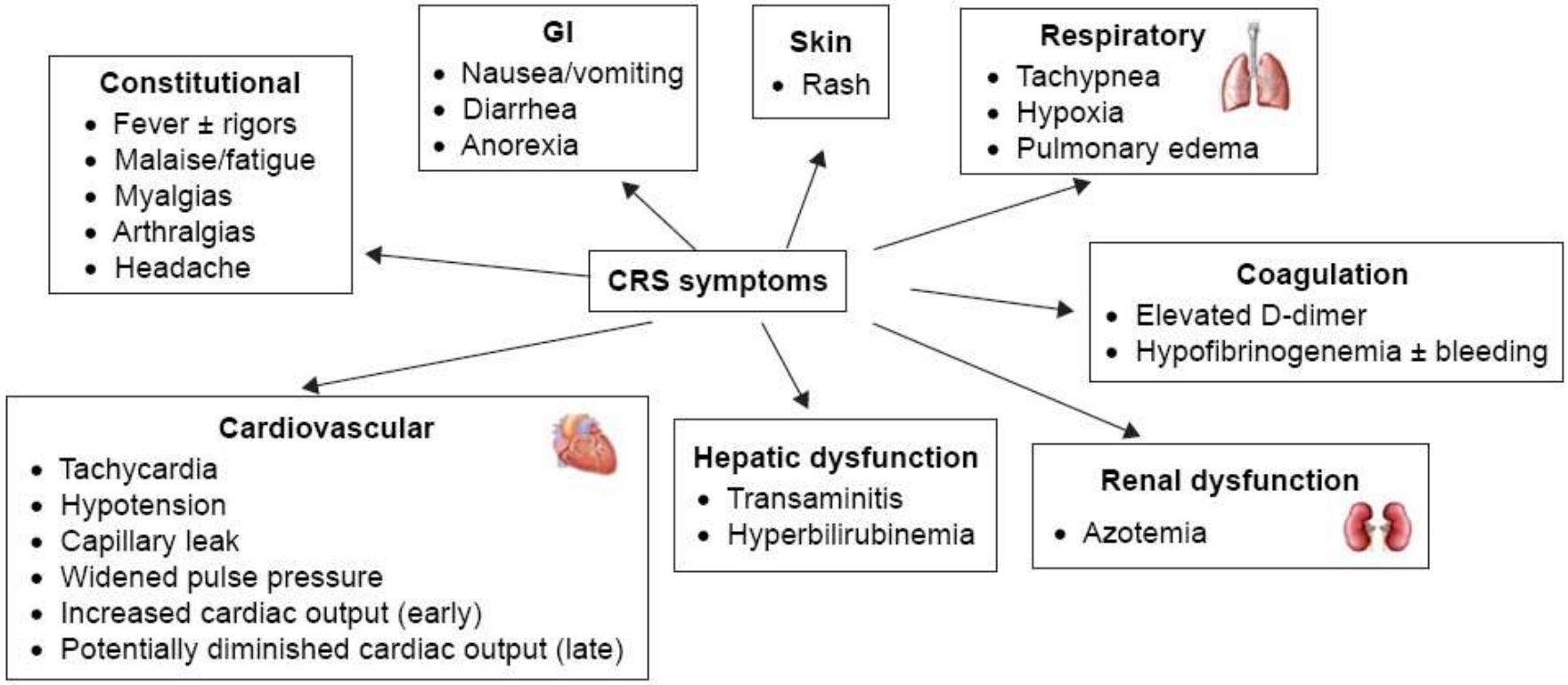



**Figure 1** Symptoms of CRS.

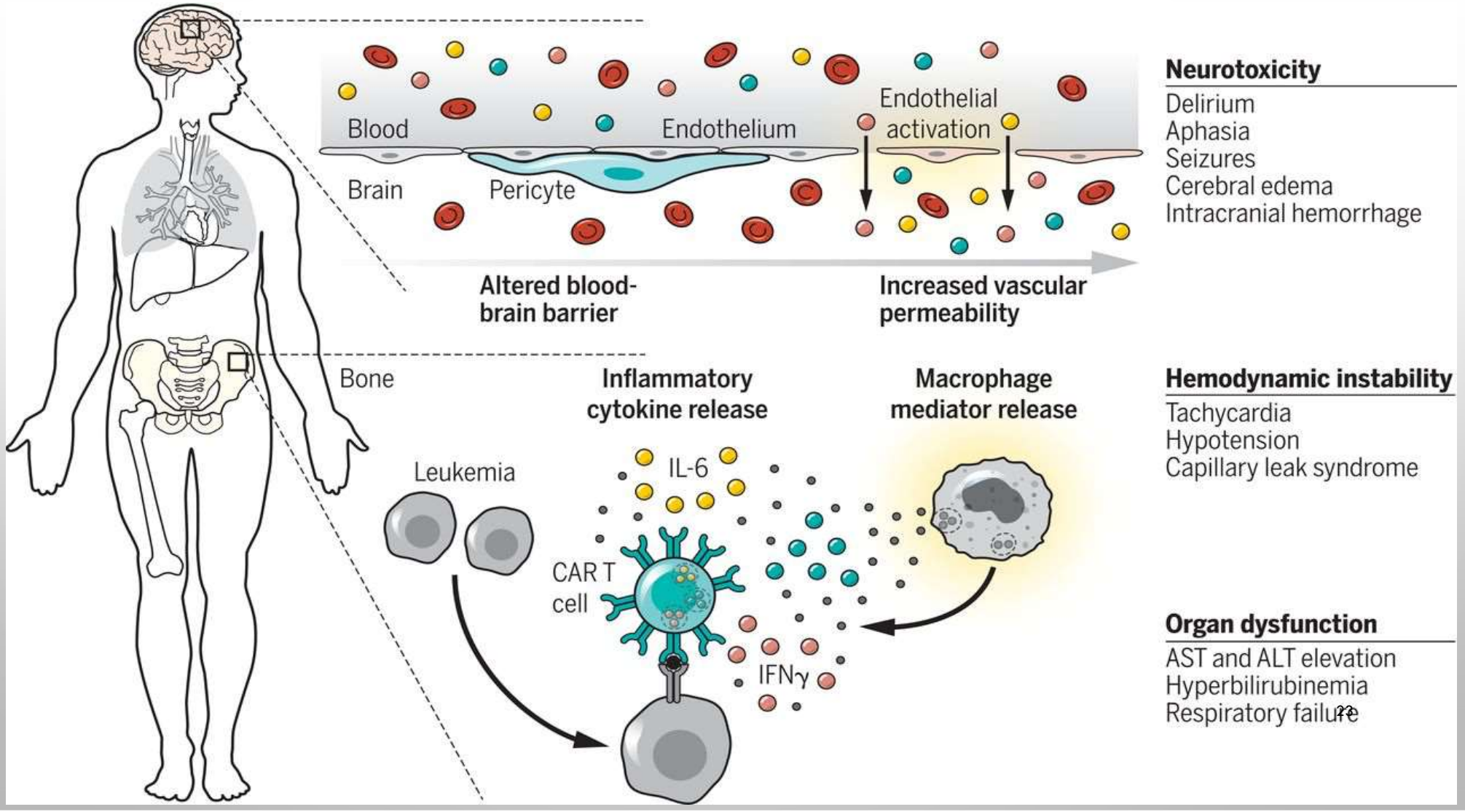
**Notes:** CRS affects a number of organ systems. It requires fever at a minimum but is frequently associated with any of the symptoms shown. Additional manifestations may also rarely occur.

**Abbreviations:** GI, gastrointestinal; CRS, cytokine release syndrome.

# CAR T-CELL THERAPY-RELATED TOXICITIES

*Median time to neurotoxicity onset of 4 days (range: 1–43 days), median duration of 17 days*

| | **Axicabtagene ciloleucela and tisagenlecleucelb** | **Axicabtagene ciloleucela and tisagenlecleucelb** |
|---|---|---|
| **Neurologic Toxicity** | Typical time to onset: 4–6 days<br><br>Typical duration: 14–17 days<br><br>Serious events including **seizures,** as well as fatal and serious cases of **cerebral edema,** have occurred. | **The most common neurologic toxicities include:**<br>*Encephalopathy*<br>*Headache*<br>*Tremor*<br>*Dizziness*<br>*Aphasia*<br>*Delirium*<br>*Insomnia*<br>*Anxiety*<br>*Autonomic neuropathy*<br>*Agitation*<br>*Hyperactivity*<br>*Signs of psychosis can also occur* |


Blood
Endothelium
Endothelial activation
Brain
Pericyte
Altered blood-brain barrier
Increased vascular permeability
Bone
Inflammatory cytokine release
Macrophage mediator release
Leukemia
IL-6
CAR T cell
IFNγ
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage
Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome
Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES (CYTOKINE-RELEASE SYNDROME (CRS))

- PROMPT AND URGENT INTERVENTION TO PREVENT PROGRESSION OF CRS IS REQUIRED
- HOWEVER, OTHER CAUSES OF SYSTEMIC INFLAMMATORY RESPONSE SHOULD BE RULED OUT, INCLUDING INFECTION AND MALIGNANCY PROGRESSION. EMPIRIC TREATMENT FOR INFECTION IS WARRANTED IN THE NEUTROPENIC PATIENT.

| CRS Grade | Anti-IL-6 Therapy | Corticosteroids | Additional Supportive Care |
|---|---|---|---|
| **Grade 1**<br><br>Fever with or without constitutional symptoms | For prolonged CRS (>3 days) in patients with **significant symptoms and/or comorbidities, consider tocilizumab** as per Grade 2 | **N/A** | ○ Empiric broad-spectrum antibiotics<br>○ Consider granulocyte colony-stimulating factor (G-CSF) if neutropenic<br>○ Maintenance IV fluids for hydration<br>○ Symptomatic management of organ toxicities |



Antipyretics and IV hydration / Diagnostic work-up to rule out infection / Consider growth factors and antibiotics if neutropenic

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES (CYTOKINE-RELEASE SYNDROME (CRS))

| CRS Grade | Anti-IL-6 Therapy | Corticosteroids | Additional Supportive Care |
|---|---|---|---|
| **Grade 2**<br><br>Hypotension responding to fluids; hypoxia responding to <40% O2 | **Tocilizumab** 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose) (After each dose, assess need for subsequent dosing) . Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total | For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy:<br>**Dexamethasone** 10 mg IV every 6 hours (or equivalent) | ○ **IV fluid** bolus as needed For persistent refractory hypotension, after two fluid boluses and anti-IL-6 therapy:<br>○ Start **vasopressors consider transfer to intensive care unit (ICU)**<br>○ Consider echocardiogram, and initiate other methods of hemodynamic monitoring<br>○ Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy<br>○ Symptomatic management of organ toxicities |

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES (CYTOKINE-RELEASE SYNDROME (CRS))

| CRS Grade | Anti-IL-6 Therapy | Corticosteroids | Additional Supportive Care |
|---|---|---|---|
| **Grade 3**<br><br>Hypotension managed with one vasopressor; hypoxia requiring ≥40% O2 | **Anti-IL-6 therapy** as per Grade 2 (After each dose, assess need for subsequent dosing) if maximum dose not reached within 24-hour period | **Dexamethasone** 10 mg IV every 6 hours (or equivalent) If refractory, manage as grade 4 | ○ Transfer to ICU<br>○ Obtain echocardiogram<br>○ Perform hemodynamic monitoring<br>○ Supplemental oxygen including high-flow oxygen delivery and noninvasive positive pressure ventilation<br>○ IV fluid bolus and vasopressors as needed<br>○ Symptomatic management of organ toxicities |

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES (CYTOKINE-RELEASE SYNDROME (CRS))

| CRS Grade | Anti-IL-6 Therapy | Corticosteroids | Additional Supportive Care |
|---|---|---|---|
| **Grade 4** Life-threatening consequences; requiring ventilator support or vasopressor-refractory shock | **Anti-IL-6 therapy as per Grade 2** (After each dose, assess need for subsequent dosing) if maximum dose not reached within 24-hour period | **Dexamethasone** 10 mg IV every 6 hours (or equivalent)<br><br>If refractory, consider **methylprednisolone** 1000 mg/day IV | ○ ICU care and hemodynamic monitoring<br>○ Mechanical ventilation as needed (eg, CPAP, BiPAP, intubation and mechanical ventilation)<br>○ IV fluid bolus and vasopressors as needed<br>○ Symptomatic management of organ toxicities |

_ For HLH/MAS during CRS, treat as per CRS with addition of steroids.
_ If symptoms do not improve within 48 hours, consider *etoposide* and intrathecal *cytarabine* for neurotoxicity.
_ Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

All recommendations are category 2A unless otherwise indicated.

# CAR T-CELL THERAPY-RELATED TOXICITIES

## NEUROLOGIC TOXICITY RELATED

- NEUROLOGIC TOXICITY RELATED TO CAR T CELLS, ALSO CALLED *CAR T-CELL–RELATED ENCEPHALOPATHY SYNDROME* AND *IMMUNE EFFECTOR CELL–ASSOCIATED NEUROLOGIC TOXICITY SYNDROME*, IS A COMMON SIDE EFFECT NOTED WITH CD19-DIRECTED CAR T-CELL TREATMENT (LEE ET AL., 2018; NEELAPU ET AL., 2018)

- NEUROLOGIC TOXICITIES OCCURRED IN **87%** OF PATIENTS TREATED WITH (AXI CEL) AXICABTAGENE CILOLEUCEL AND **58%–72%** OF PATIENTS TREATED WITH (TISA-CEL) TISAGENLECLEUCEL (KITE PHARMA, 2017; NOVARTIS PHARMACEUTICALS, 2018)

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES (CAR T-CELL-RELATED NEUROTOXICITY )

| Treatment by Grade | No Concurrent CRS | Additional Therapy if Concurrent CRS |
|---|---|---|
| **Grade 1**<br>Mild impact on ADLs | **Supportive care** | **Dexamethasone** 10 mg IV every 6 hours (or equivalent) If refractory, manage as grade 4 |

| Treatment by Grade | No Concurrent CRS | Additional Therapy if Concurrent CRS |
|---|---|---|
| **Grade 2**<br>Moderate impact on ADLs | **Supportive care**<br><br>**Dexamethasone** 10 mg IV x 1<br>Can repeat every 6 hours<br><br>**Methylprednisolone** 1 mg/kg IV every 12 h if symptoms worsen | **Anti-IL-6** therapy as per Grade 1<br><br>Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS<br>(Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses) |

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES (CAR T-CELL-RELATED NEUROTOXICITY )

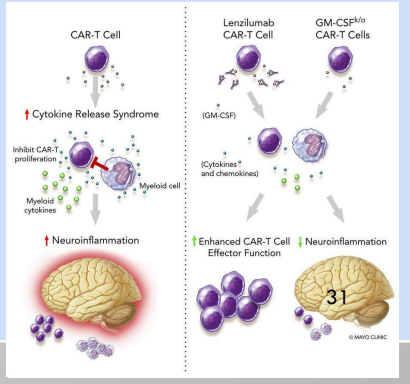
| Treatment by Grade | No Concurrent CRS | Additional Therapy if Concurrent CRS |
|---|---|---|
| **Grade 3**<br><br>**Severe impact** on **ADLs**<br>Seizure<br>Signs of elevated intracranial pressure<br>(eg, papilledema, Cushing's triad, hypertension, bradycardia)<br>  | ICU care is recommended<br><br>Dexamethasone, 10 mg IV every 6 h or methylprednisolone, 1 mg/ kg IV every 12<br><br>Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. | Anti-IL-6 therapy as per Grade 1<br>(Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses) |



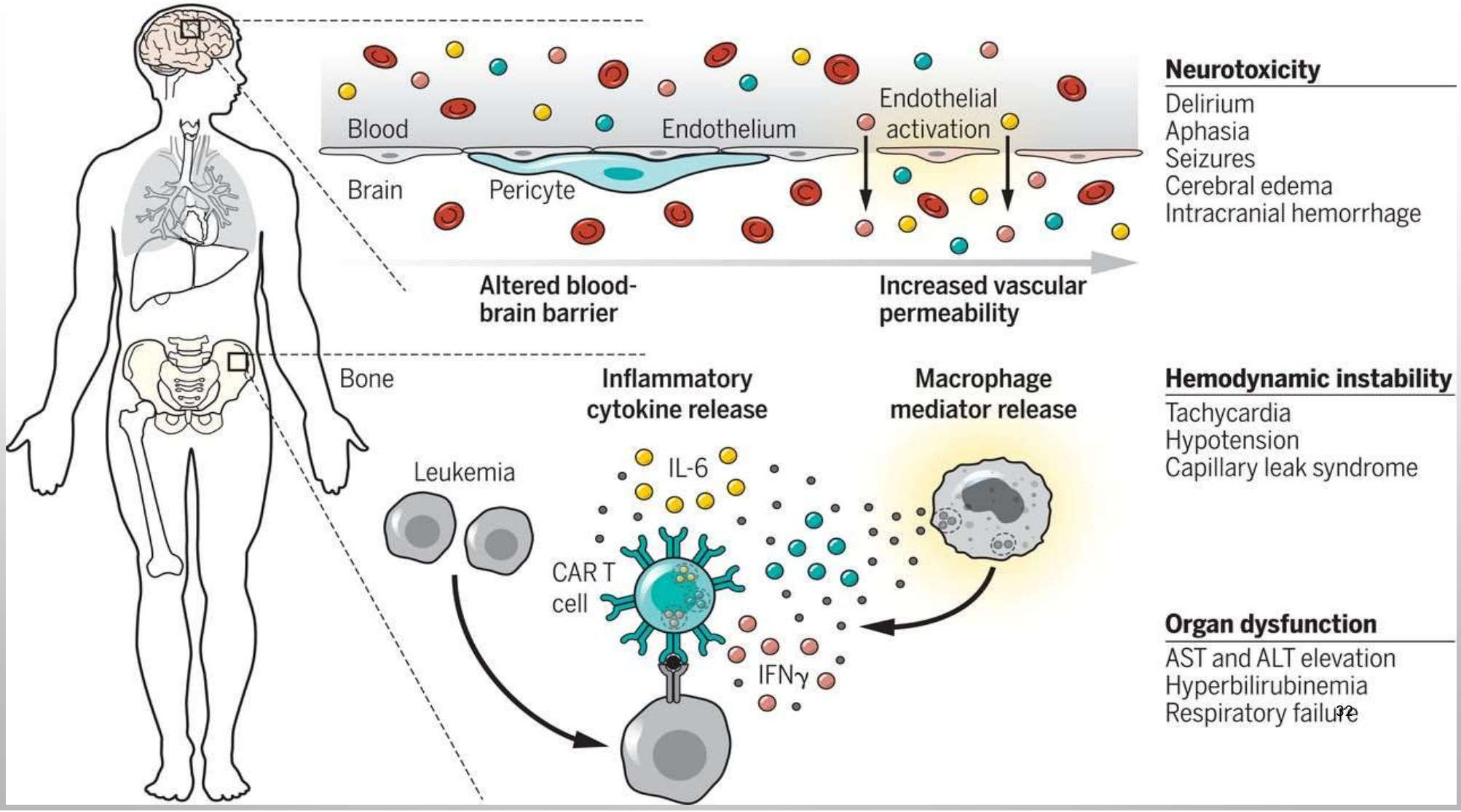
Diagnostic lumbar puncture for grade 3-4 neurotoxicity; consider for grade 2.

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES (CAR T-CELL-RELATED NEUROTOXICITY )

| Treatment by Grade | No Concurrent CRS | Additional Therapy if Concurrent CRS |
|---|---|---|
| **Grade 4**<br><br>Patient in critical condition and/ or obtunded and cannot perform assessment of tasks; repetitive seizures without return to baseline or life-threatening seizures (non- convulsive or convulsive) | ICU care<br><br>Consider mechanical ventilation for airway protection<br><br>High-dose corticosteroids<br><br>Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity<br><br>Treat convulsive status epilepticus per institutional guidelines. | Anti-IL-6 therapy as per Grade 1<br>(Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses) |

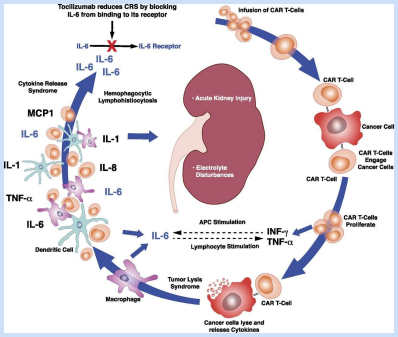



Diagnostic lumbar puncture for grade 3-4 neurotoxicity; consider for grade 2.


Blood
Endothelium
Endothelial activation
Brain
Pericyte
Altered blood-brain barrier
Increased vascular permeability
Bone
Inflammatory cytokine release
Macrophage mediator release
Leukemia
IL-6
CAR T cell
IFNγ
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage
Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome
Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

# MACROPHAGE- ACTIVATION SYNDROME

MACROPHAGE- ACTIVATION SYNDROME

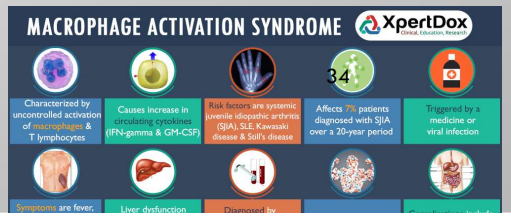
| | Axicabtagene ciloleucela and tisagenlecleucelb<br>Criteria for considering HLH/MAS: | Axicabtagene ciloleucela and tisagenlecleucelb<br>Criteria for considering HLH/MAS: |
|---|---|---|
| Hemophagocytic Lymphohistiocytosis/ Macrophage-Activation Syndrome (HLH/MAS) During CRS | Rapidly rising and high **ferritin (>5,000 ng/mL)** with **cytopenias** in the context of CRS, **especially if accompanied by *any of the following*:**<br>○ Grade ≥ 3 increase in serum bilirubin, AST, ALT<br>○ Grade ≥ 3 oliguria or increase in serum creatinine<br>○ Grade ≥ 3 pulmonary edema |  <br>Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 IHC. |

# POSSIBLE SIDE EFFECTS OF CAR T-CELL THERAPY

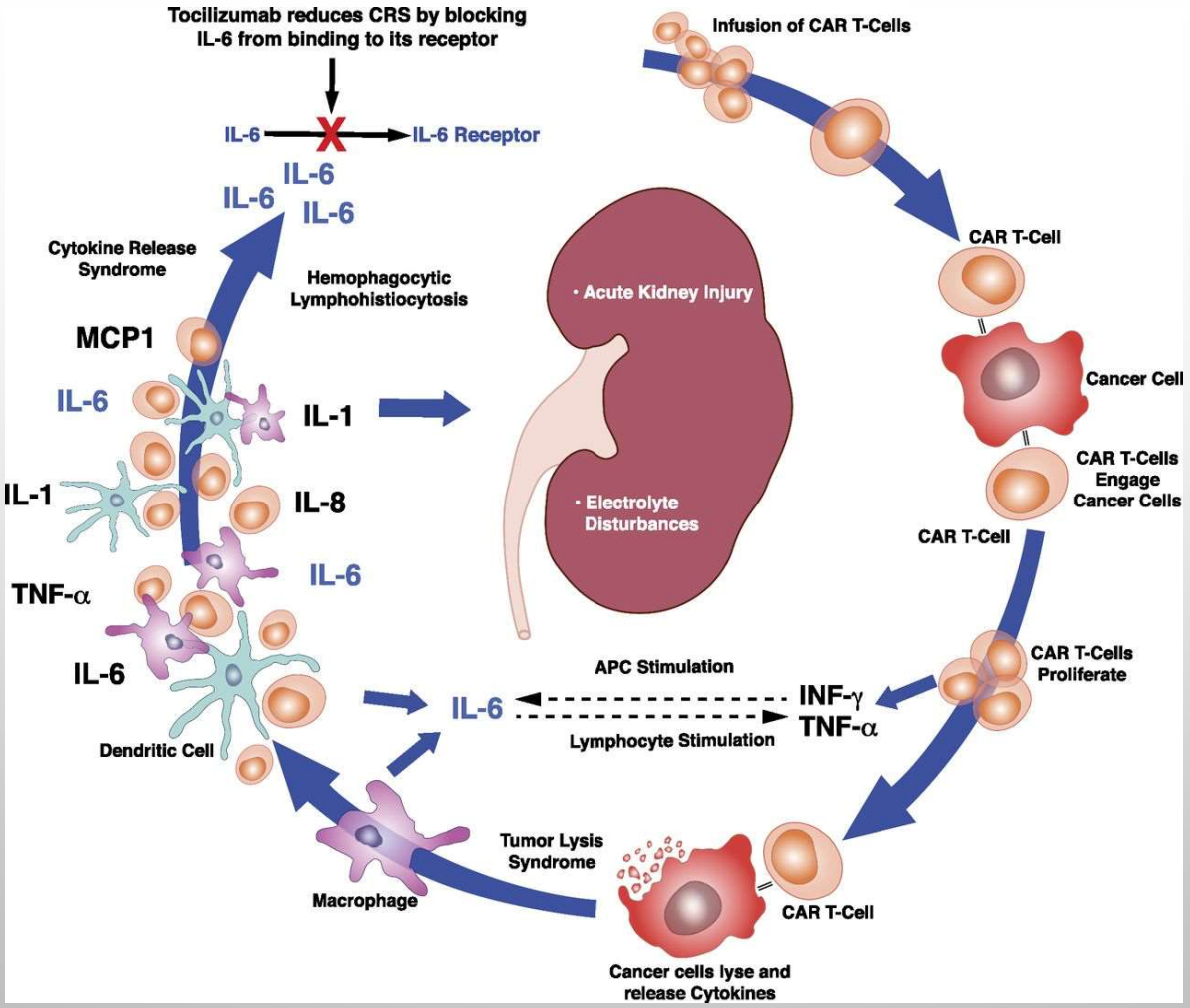
## MACROPHAGE ACTIVATION SYNDROME (MAS)

*CLOSELY ASSOCIATED WITH SEVERE CRS*

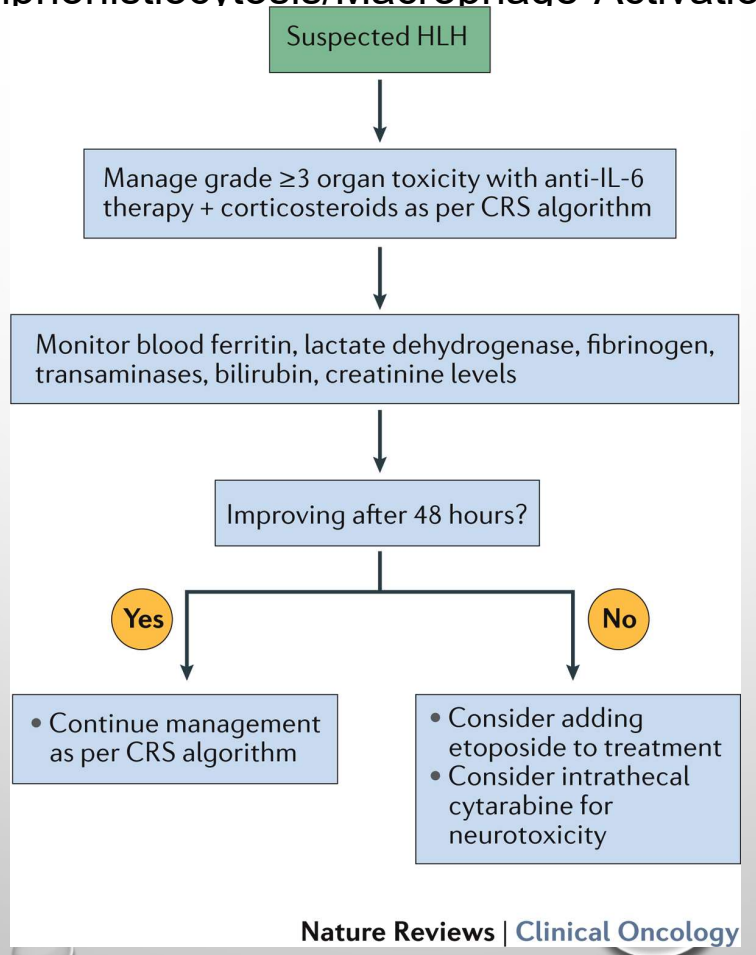
- SEEN IN PATIENTS WITH CHRONIC AUTOIMMUNE AND RHEUMATIC DISEASES
  - CAN BE MITIGATED BY THE INFUSION OF THE ***MONOCLONAL ANTIBODY TOCILIZUMAB***
  - ***CORTICOSTEROIDS***
  - ***ANTICYTOKINE THERAPY*** CAN BE CONSIDERED AS TREATMENT OPTIONS IF MAS IS SEVERE AND THE SYMPTOMS PERSIST OR ARE GETTING WORSE.



# MACROPHAGE ACTIVATION SYNDROME (MAS)



# Recommendations for the management of Chimeric antigen receptor(CAR)-T-cell-related Haemophagocytic Lymphohistiocytosis/Macrophage-Activation Syndrome (**HLH/MAS**)






Neelapu, S. S. *et al.* (2017) Chimeric antigen receptor T-cell therapy — assessment and management of toxicities *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2017.148

## OTHER CAR T-CELL–RELATED TOXICITIES

## CYTOPENIAS

- PROLONGED CYTOPENIAS, *INCLUDING NEUTROPENIA, ANEMIA, AND THROMBOCYTOPENIA,* MAY OCCUR FOR SEVERAL ***WEEKS AFTER LYMPHODEPLETING CHEMOTHERAPY AND CAR T-CELL INFUSION*** (KITE PHARMA, 2017; NOVARTIS PHARMACEUTICALS, 2018)

TO TREAT *CYTOPENIAS*, PROVIDERS PRESCRIBE:

- RED BLOOD CELLS
- PLATELET TRANSFUSIONS
- GROWTH FACTORS, AS NEEDED, ACCORDING TO INSTITUTION GUIDELINES

# OTHER CAR T-CELL–RELATED TOXICITIES
# **INFECTIONS**

- PATIENTS RECEIVING CAR T CELLS CAN DEVELOP BACTERIAL, FUNGAL, AND VIRAL INFECTIONS (HILL ET AL., 2018; KITE PHARMA, 2017; PARK ET AL., 2018)

- DECREASED ANTIBODY PRODUCTION BECAUSE OF HYPOGAMMAGLOBULINEMIA MAY INCREASE SUSCEPTIBILITY TO INFECTION (DOAN & PULSIPHER, 2018).

- PATIENTS SHOULD BE MONITORED FOR LOW IMMUNOGLOBULIN LEVELS AFTER CAR T-CELL TREATMENT (KITE PHARMA, 2017).
  - THE TREATMENT IS IMMUNOGLOBULIN THERAPY,
  - ***PATIENTS WITH ACTIVE, SYSTEMIC INFECTIONS SHOULD NOT BE TREATED WITH CAR T CELLS UNTIL SYMPTOMS ARE RESOLVED (KITE PHARMA, 2017)**

# OTHER CAR T-CELL–RELATED TOXICITIES

## HYPOGAMMAGLOBULINEMIA

- THE DESTRUCTION OF NORMAL B CELLS BY CAR T CELLS TARGETING CD19 RESULTS IN B-CELL APLASIA AND HYPOGAMMAGLOBULINEMIA (BRUDNO & KOCHENDERFER, 2016).
- DECREASED ANTIBODY PRODUCTION BECAUSE OF HYPOGAMMAGLOBULINEMIA MAY INCREASE SUSCEPTIBILITY TO INFECTION (DOAN & PULSIPHER, 2018).
- PATIENTS SHOULD BE MONITORED FOR LOW IMMUNOGLOBULIN LEVELS AFTER CAR T-CELL TREATMENT (KITE PHARMA, 2017).
- TREATMENTS FOR HYPOGAMMAGLOBULINEMIA INCLUDE IV IMMUNOGLOBULIN AND ANTIBIOTIC PROPHYLAXIS FOR INFECTION, AS NEEDED (KITE PHARMA, 2017; NEELAPU ET AL., 2018).

# POSSIBLE SIDE EFFECTS OF CAR T-CELL THERAPY

- **TUMOR LYSIS SYNDROME (TLS)**
  - CAN BE DELAYED AND MAY OCCUR ONE MONTH OR MORE AFTER CAR T-CELL THE
    - THE COMPLICATION HAS BEEN MANAGED BY STANDARD SUPPORTIVE THERAPY

- **ANAPHYLAXIS (LIFE-THREATENING ALLERGIC REACTION)**
  - OVERWHELMING IMMUNE RESPONSE AGAINST THE CAR ITSELF,
    - HIVES,
    - FACIAL SWELLING,
    - LOW BLOOD PRESSURE
    - RESPIRATORY DISTRESS
  - THOROUGH MONITORING AND IMMEDIATE TREATMENT OF THIS LIFE-THREATENING SIDE EFFECT ARE CRITICAL FOR PATIENTS RECEIVING CAR T-CELL THERAPY



Patients usually stay in the hospital for at least a week after CAR T-cell infusion, or until the side effects subside (generally around two weeks).

# POSSIBLE SIDE EFFECTS OF CAR T-CELL THERAPY

- **ON-TARGET, OFF-TUMOR TOXICITY**
  - MANY TUMOR ANTIGENS ARE ALSO EXPRESSED ON HEALTHY CELLS IN TISSUES
    - MAY POSE LIFE-THREATENING RISKS, ESPECIALLY WHEN CELLS IN ESSENTIAL TISSUES
      - HEART
      - LUNG
      - LIVER
- **B-CELL APLASIA**
  - IS AN EXPECTED RESULT OF SUCCESSFUL CD19-SPECIFIC CAR T-CELL TREATMENT AND HAS SERVED AS A USEFUL INDICATOR OF ONGOING CAR T-CELL ACTIVITY.
    - INTRAVENOUS OR SUBCUTANEOUS IMMUNOGLOBULIN REPLACEMENT THERAPY MAY BE GIVEN WITH THE AIM OF PREVENTING INFECTION



Patients usually stay in the hospital for at least a week after CAR T-cell infusion, or until the side effects subside (generally around two weeks).

# NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES

## Post-CAR T-Cell Infusion

- Hospitalization or extremely close outpatient monitoring at centers with transplant or prior outpatient CAR T-cell transplant experience.
- Close monitoring in the hospital is preferable with current products used for adults; however, extremely close outpatient monitoring may be possible at centers with outpatient transplant experience.
- Hospitalization for patients with CRS is warranted.

## NCCN GUIDELINES VERSION 1.2019 MANAGEMENT OF CAR T-CELL-RELATED TOXICITIES

**Post-CAR T-Cell Infusion**

- Monitor **CBC, complete metabolic panel** (including *magnesium and phosphorus*), and **coagulation profile.**
- Baseline CRP and ferritin; **recheck at least 3 times per week for 2 weeks post-infusion.** Consider daily checks during CRS. CRP can normalize prior to the onset of neurotoxicity.
- Assessment for CRS should be done at least twice daily, or when the patient's status changes, during the peak window of CRS risk.
- Neurotoxicity assessment should be done at least twice daily or when the patient's status changes, during the peak window of neurotoxicity risk.
- If neurologic concern develops, assess at a minimum of every 8 hours to include cognitive assessment and motor weakness.

# REMS PROGRAMS (RISK AND MITIGATION STRATEGY )

- AS STATED PREVIOUSLY, REMS PROGRAMS FOR CAR T-CELL AGENTS REQUIRE AUTHORIZED CENTERS TO COMPLY WITH SPECIFIC GUIDELINES TO MITIGATE THE RISKS OF THE TREATMENT.

- ALL HEALTHCARE FACILITIES THAT DISPENSE AND ADMINISTER FDA-APPROVED CAR T-CELL THERAPY MUST HAVE TOCILIZUMAB AVAILABLE WITHIN TWO HOURS FOR EACH PATIENT IF NEEDED FOR CRS.

- IN ADDITION, AS A REQUIREMENT OF REMS PROGRAMS, ALL HEALTHCARE FACILITIES MUST ENSURE THAT PROVIDERS WHO PRESCRIBE, DISPENSE, AND ADMINISTER CAR T CELLS ARE TRAINED TO MANAGE CRS AND NEUROLOGIC TOXICITIES (KITE PHARMA, 2018; NOVARTIS PHARMACEUTICALS, 2018).

- NURSES, PHARMACISTS, AND ADVANCED PRACTICE PROVIDERS CARING FOR PATIENTS RECEIVING CAR T CELLS SHOULD ALSO BE TRAINED TO THE REMS PROGRAMS AND INSTITUTIONAL WORKFLOWS (PERICA, CURRAN, BRENTJENS, & GIRALT, 2018).

# RESULTS, LIMITATIONS, AND THE FUTURE OF CAR T-CELL THERAPY

- STUDIES OF CAR T-CELL THERAPY IN OTHER BLOOD CANCERS, INCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), AS WELL AS MULTIPLE MYELOMA, ALSO SHOW POTENTIAL. RESEARCH IS ALSO UNDER WAY, EXPLORING THE APPLICATION OF CAR T-CELL THERAPY IN THE TREATMENT OF SOLID TUMORS.

- IT IS IMPORTANT FOR MORE PEDIATRIC AND ADULT PATIENTS TO BE ENROLLED IN CLINICAL TRIALS. LARGER STUDY SAMPLES, EVALUATED OVER MORE EXTENDED PERIODS, WILL HELP RESEARCHERS FURTHER UNDERSTAND THE IMPACT OF THIS TYPE OF THERAPY, WAYS TO REDUCE ITS TOXICITY AND IMPROVE THE MANAGEMENT OF ADVERSE SIDE EFFECTS.

# BOTTOM LINE

- ALL SITES THAT PROVIDE CAR T-CELL THERAPY MUST HAVE A SPECIAL CERTIFICATION, WHICH INCLUDES TRAINING TO RECOGNIZE AND MANAGE ISSUES THAT COME UP.

- CLINICAL TRIALS: NCCN BELIEVES THAT THE BEST MANAGEMENT OF ANY PATIENT WITH CANCER IS IN A CLINICAL TRIAL. PARTICIPATION IN CLINICAL TRIALS IS ESPECIALLY ENCOURAGED.

- AS ORGANIZATIONAL AND INSTITUTIONAL GUIDELINES EMERGE, NURSES MUST BE AWARE OF ANTICIPATED TOXICITIES AND INTERVENTIONS USED IN CLINICAL PRACTICE TO PROVIDE TIMELY AND EFFECTIVE CARE.

WITH APPROPRIATE SUPPORT, MANY PATIENTS WITH ACUTE TOXICITIES WILL EXPERIENCE RESOLUTION OF SYMPTOMS WITHIN WEEKS OF CAR T-CELL TREATMENT.

EVIDENCE-BASED STANDARDIZED APPROACHES TO CAR T-CELL TOXICITY MANAGEMENT CONTINUE TO BE REFINED AS DATA AND EXPERIENCE INCREASE, AND

**NURSES PLAY AN IMPORTANT ROLE IN IDENTIFYING PATIENT STATUS CHANGES TO EXPAND THIS KNOWLEDGE BASE.**

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