NCCN Virtual Nursing Program:
Advancing Oncology Nursing™

Wednesday, March 17, 2021
12:35 PM – 1:20 PM EDT

Evolution of CAR T-Cell Therapy

Lauren M. Sullivan, MSN, RN, AGCNS-BC, OCN, BMTCN
Dana-Farber Cancer Institute

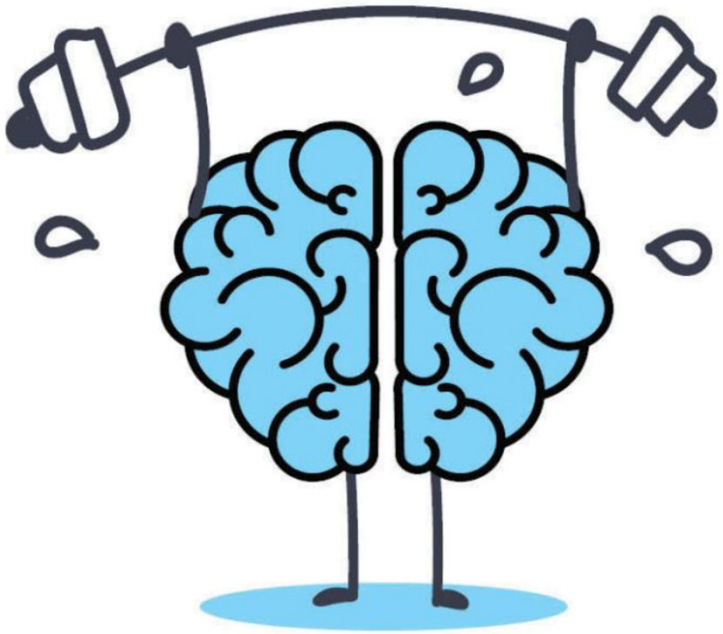
Learning Outcomes

By the end of this presentation participants can:

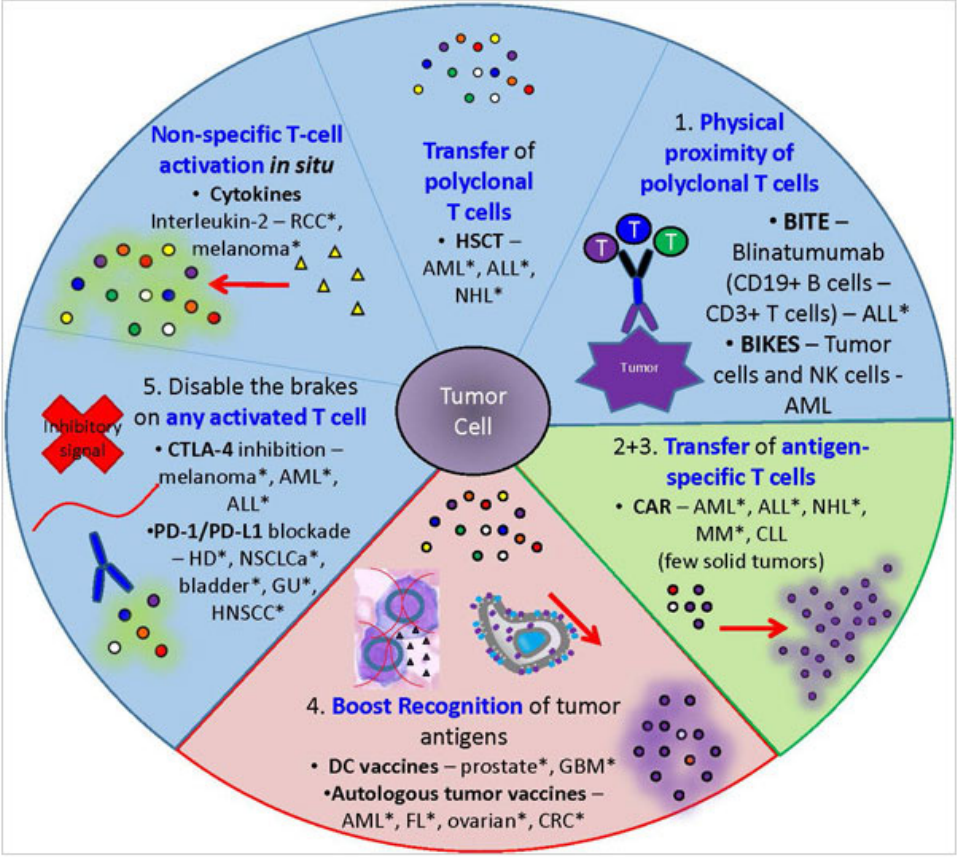
- Outline the indications for existing CAR T-cell therapies.
- Discuss supportive care and logistics needed during CAR T-cell therapy administration.
- Identify key components of educational materials needed for a successful CAR T-cell therapy program.

Outline

- Immunotherapy and CAR-T Cell Therapy
- Indications of CAR-T Cell Therapy
  - Standard of Care
  - Research
- Symptom Management
  - Assessment
  - Treatment
- Logistics and Education

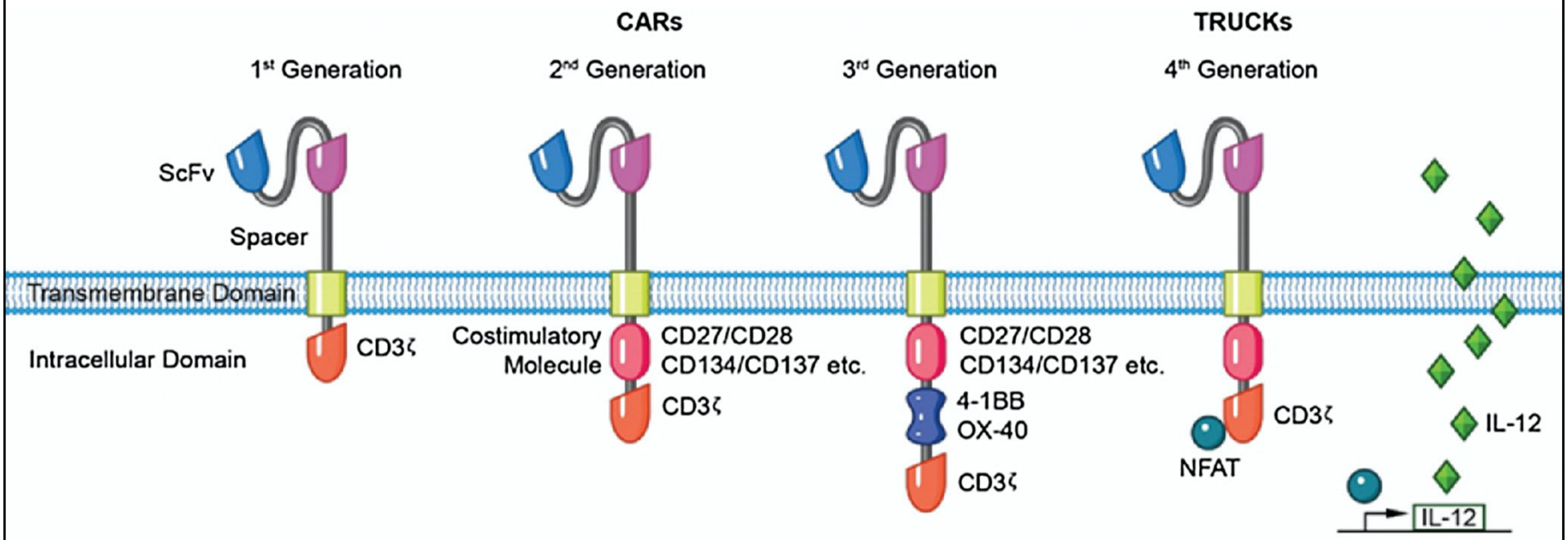


Overview of Immunotherapy



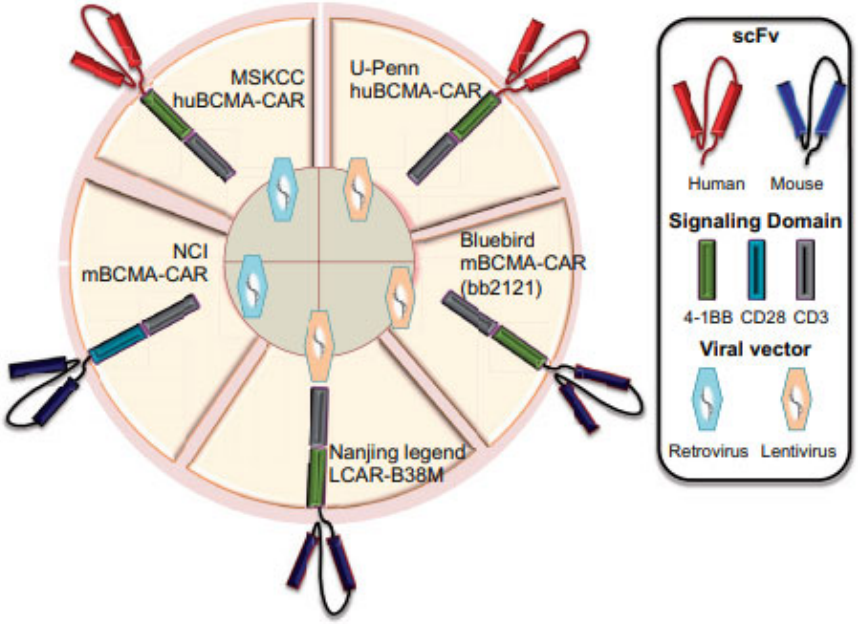
Nikiforow, 2016

CAR-T Generations



Smith, et, Al., 2016
Gagelmann, et, Al., 2020

What is CAR-T?



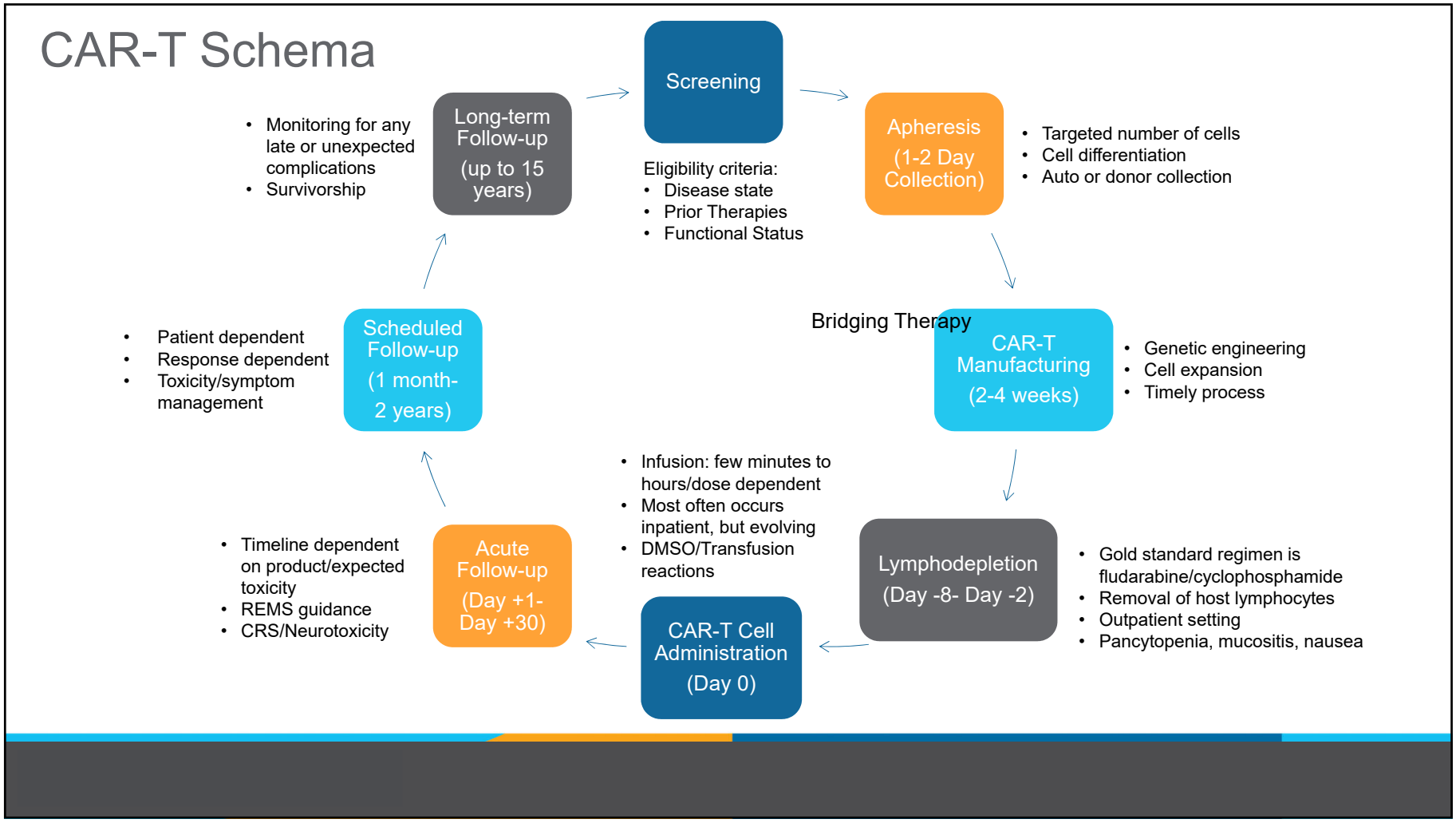
Nikiforow, 2020
Ghosh, et al, 2018
Maus, et al, 2014
Sadelain, JCI, 2015

- T-Cell Mechanism of Action:
  - Recognized antigen
  - Trigger of co-stimulatory molecule
  - Primary Activation Signal (CD3-Zeta)

Chimeric Antigen Receptor (CAR; 2nd Generation)

- Synthetic fusion protein genetically engineered to bind to a specific cell surface antigen
  - CD19, CD20, CD22, BCMA
- Single-chain variable fragment
  - Antibody, ligand, etc.
  - Murine or Human
- Intracellular signaling domain
  - CD28 or 4-1BB
- Vector
  - Stores genetic material inside
  - Retrovirus or lentivirus
  - Gene editing

CAR-T Schema



FDA Approved Products

- Tisagenlecleucel (Approved 8/2017)
  - R/R B-Cell Acute Lymphoblastic Leukemia (Under 25)
  - R/R Large B-Cell Lymphoma (Adult)
    - DLBCL primary and arising from Follicular Lymphoma
    - High-grade B-Cell Lymphoma arising from Follicular Lymphoma
- Axicabtagene ciloleucel (Approved 10/2017)
  - R/R Large B-Cell Lymphoma (Adult)
    - DLBCL primary and arising from Follicular Lymphoma
    - Primary Mediastinal Large B-Cell Lymphoma
    - High-grade B-Cell Lymphoma arising from Follicular Lymphoma
- Brexucabtagene autoleucel (Approved 7/2020)
  - R/R Mantle Cell Lymphoma (Adult)
- Lisocabtagene maraleucel (Approved 2/2021)
  - R/R Large B-Cell Lymphoma (Adult)
    - DLBCL primary and arising from Indolent Lymphoma
    - Primary Mediastinal Large B Cell Lymphoma
    - Follicular Lymphoma Grade 3B
- Idecabtagene vicleucel (Pending Approval 3/2021)
  - R/R Multiple Myeloma (Adult)
    - 3 prior therapies: IMiD, PI, & anti-CD38 antibody)

Lymphoma

NHL:

- 72% 5 Year Survival
- R/R population- poor prognosis
- DLBCL
  - Most common form of NHL
  - 20-30% R/R to 1st line therapy
  - 40-50% (R/R population) ineligible for ASCT
  - 40-50% (of ASCT recipients) relapse & have ORR 26% OS 6.3 months

	Jacobsen, et al	Nastoupil, et al	Axi-cel CIMBTR	Tisa-cel CIMBTR
Product	Axi-cel	Axi-cel	Axi-cel	Tisa-cel
Patients treated	122	275	533	80
ORR/CR	70/50	82/64	74/54	58/40
6M CR	41	NR	NR	NR
CRS (%)	93	91	83	49
Gr 3+ CRS (%)	16	7	9	3
Neurotox (%)	70	69	53	16
Gr 3+ Neurotox (%)	35	31	17	5

National Cancer Institute, 2020
Kallam & Vose, 2019

Non-Trial vs Trial Setting: Axi-cel

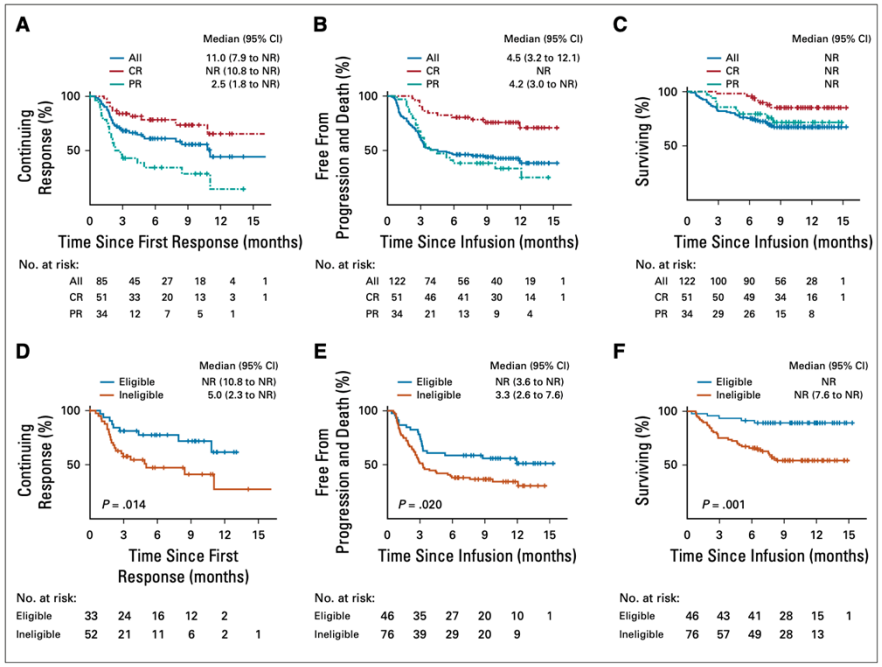


FIG 1. Efficacy outcomes of axicabtagene ciloleucel (axi-cel) overall and by ZUMA-1 eligibility. (A) Duration of response (DOR) curves for patients with overall response at first restage after chimeric antigen receptor (CAR) T-cell therapy. (B) Progression-free survival (PFS) curves for all patients. (C) Overall survival (OS) curves for all patients who underwent infusion of axi-cel. (D) DOR curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). (E) PFS curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). (F) OS curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). All, all patients who underwent infusion of axi-cel; CR, complete response at first restage; NR, not reached; PR, partial response at first restage.

Jacobson, et Al, 2020

Non-Trial vs Trial Setting: Axi-cel

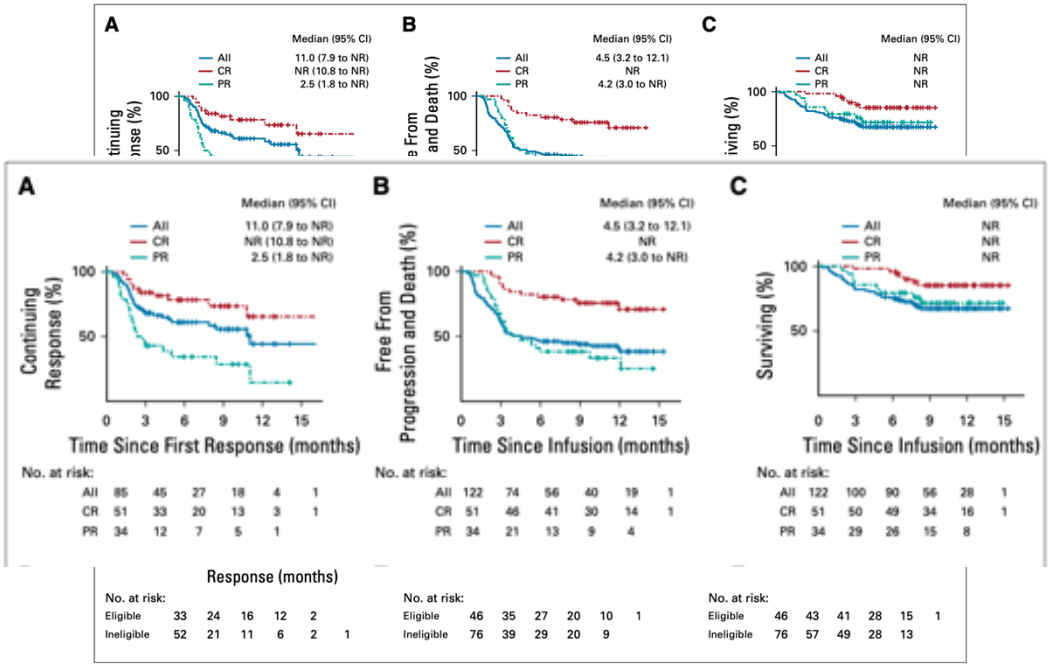


FIG 1. Efficacy outcomes of axicabtagene ciloleucel (axi-cel) overall and by ZUMA-1 eligibility. (A) Duration of response (DOR) curves for patients with overall response at first restage after chimeric antigen receptor (CAR) T-cell therapy. (B) Progression-free survival (PFS) curves for all patients. (C) Overall survival (OS) curves for all patients who underwent infusion of axi-cel. (D) DOR curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). (E) PFS curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). (F) OS curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). All, all patients who underwent infusion of axi-cel; CR, complete response at first restage; NR, not reached; PR, partial response at first restage.

Jacobson, et Al, 2020

Non-Trial vs Trial Setting: Axi-cel

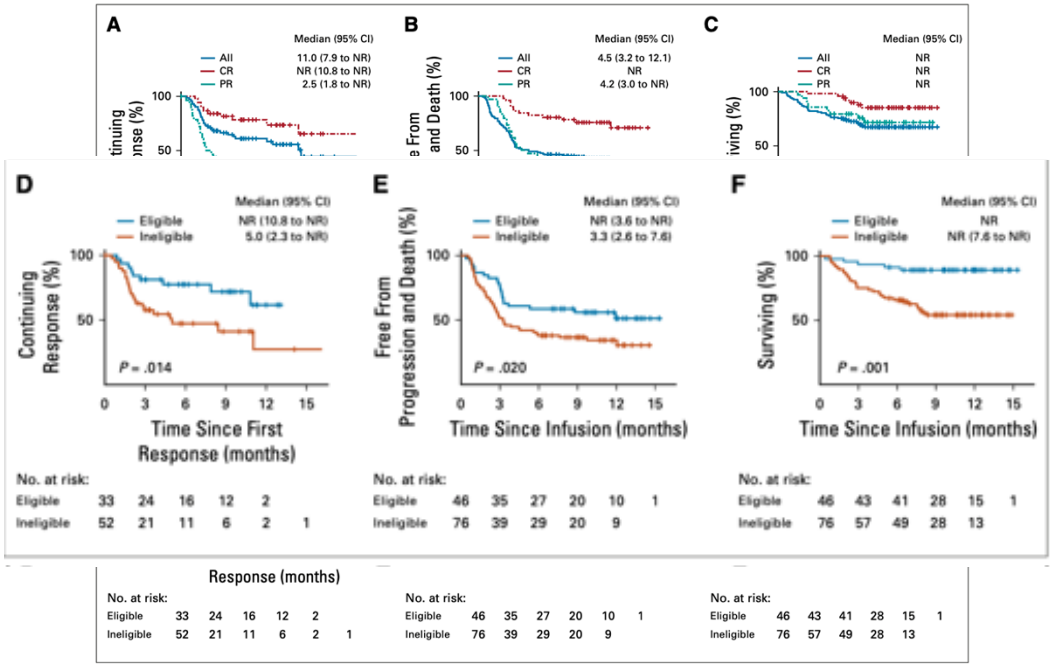


FIG 1. Efficacy outcomes of axicabtagene ciloleucel (axi-cel) overall and by ZUMA-1 eligibility. (A) Duration of response (DOR) curves for patients with overall response at first restage after chimeric antigen receptor (CAR) T-cell therapy. (B) Progression-free survival (PFS) curves for all patients. (C) Overall survival (OS) curves for all patients who underwent infusion of axi-cel. (D) DOR curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). (E) PFS curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). (F) OS curves for patients who would have been eligible for ZUMA-1 (blue) and those who were ineligible for ZUMA-1 (orange). All, all patients who underwent infusion of axi-cel; CR, complete response at first restage; NR, not reached; PR, partial response at first restage.

Jacobson, et Al, 2020

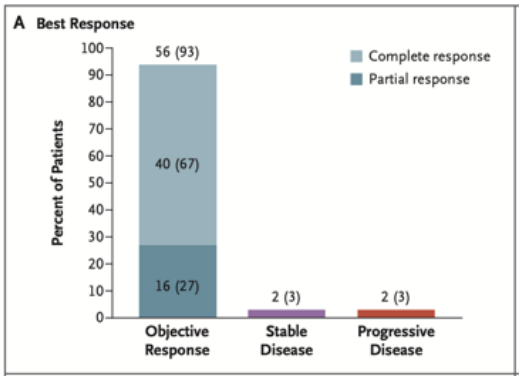
Mantle Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan



- Bruton's tyrosine kinase (BTK) inhibitors have improved outcomes for patients with R/R Mantle Cell Lymphoma (MCL)
- R/R MCL (after BTK inhibitor therapy)
  - OR: 25-42%
  - OS 6-10 months (w/ salvage therapies)
  - Allo SCT Non-relapse mortality 10-24%

- CAR-T
  - 12 months
    - PFS: 61%
    - OS: 83%

Multiple Myeloma

- 65 clinical research trials
  - 44 Single target CAR-T
  - 6 Allogeneic CAR-T
  - 9 Multi-target CAR-T
  - 6 Other

Table 2 Data synthesis from 20 single-target anti-BCMA studies.

Endpoint	Pooled proportion (95% CI)
Response	
ORR	84% (78–89%)
CR	43% (32–53%)
MRD-negativity	83% (67–92%)
Relapse	45% (27–64%)
Overall survival	84% (60–95%)
Safety	
CRS grades ≥3	15% (9–23%)
Neurotoxicity	17% (10–27%)

ORR overall response rate, *CR* complete response, *MRD* minimal residual disease, *CRS* cytokine release syndrome, *CI* confidence interval.

Table 3 Comparison of single-target anti-BCMA trials published as manuscript.

	Brudno et al. 2018 (NCI) [41]	Raje et al. 2019 [43]	Cohen et al. 2019 (UPenn) [44]	Xu et al. 2019 [42]	Zhao et al. 2018 [45]
Patients	24	33	25	17	57
Vector/ costimulatory domain/ scFv	RVV/CD28/murine	LVV/4-1BB/murine (bb2121)	LVV/ 4-1BB/human	LVV/ 4-1BB/ 2 Llama VHH (LCAR-B38M)	LVV/ 4-1BB/ 2 Llama VHH (LCAR-B38M)
Dose (CAR + T cells/kg)	0.3-9 $\times 10^6$ [a]	50–800 $\times 10^6$	Cohort 1 + 3: 1-5 $\times 10^8$ Cohort 2: 1-5 $\times 10^7$	0.21-1.52 $\times 10^6$	0.07–2.10 $\times 10^6$ [b]
Lymphodepletion	Flu/Cy	Flu/Cy	No or Cy	Flu/Cy or Cy	Cy
Prior treatment lines	10 (3–19)	7 (3–14)	7 (3–13)	4 (3–11)	3 (1–19)
ASCT before CAR-T	85%	97%	92%	47%	18%
BCMA + required	>50%	≥50% in dose escalation	No	NR	NR
ORR	81%	85%	64% (highest dose)	88%	88%
ORR in high-risk cytogenetics	55%	73%	42%	85%	NR
ORR in extramedullary disease	NR	89%	57%	100%	NR
PFS/EFS, months	7	12	8	12	15

ORR overall response rate, *ASCT* autologous stem cell transplantation, *BCMA* B cell maturation antigen, *Flu* fludarabine, *Cy* cyclophosphamide, *LVV* lentiviral vector, *RVV* retroviral vector, *scFv* single-chain variable fragment, *NCI* National Cancer Institute, *UPenn* University of Pennsylvania, *VHH* variable domain of heavy chain antibody, *PFS* progression-free survival, *EFS* event-free survival, *NR* not reported.

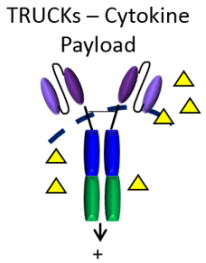
[a]Two patients received treatment twice, at lowest (0.3×10^6) and highest dose (9×10^6).

[b]Split into 3 infusions over 7 days.

Gagelmann, et, Al., 2020

Solid Tumor Challenges

- Target Selection
- Migration of T-Cells to Specific Sites
- CAR-T Expansion and Longevity
- Metabolism Associated Immune Suppression



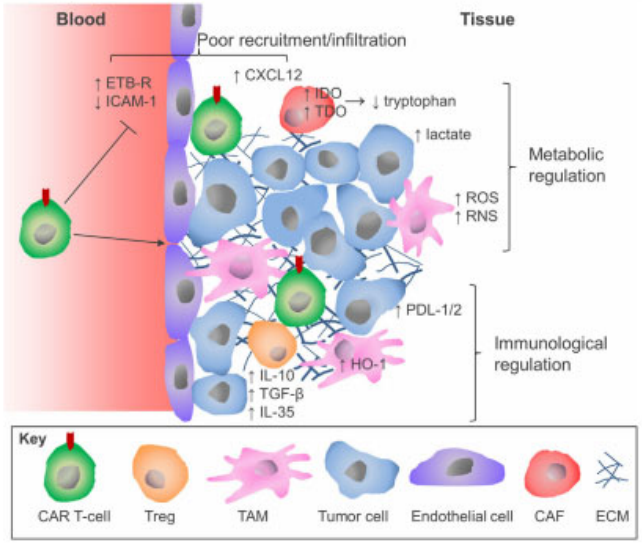


FIGURE 2 | Overview of the barriers to CAR T-cells in solid tumors.

Kosti, et al, 2018
Nikiforow, 2020

Research Agenda

Treatment

- Earlier treatment initiation
- Identification of new targets for CAR-T
  - Diseases
  - Specific Targets
- CAR-T Structure
  - Durability
- CAR-T Manufacturing Processes
  - Allo: “Off the shelf”
  - Auto: More efficient processing

Symptom Management

- New Drug Therapies
- Timing of Therapy
  - Prophylactic
  - Earlier treatment initiation
- Identification of Predictors of Toxicity
  - Cytokine Panels
- CAR-T Structure
  - Toxicity reduction

Lee, D.W & Shah, N.N, 2020
Brundo & Kochenderfer, 2019

Symptom Management & The Patient Experience

Cytokine Release Syndrome (CRS)

Production of inflammatory cytokines
-IFN-γ

Recruitment of other immune mediators
-Macrophages & monocytes

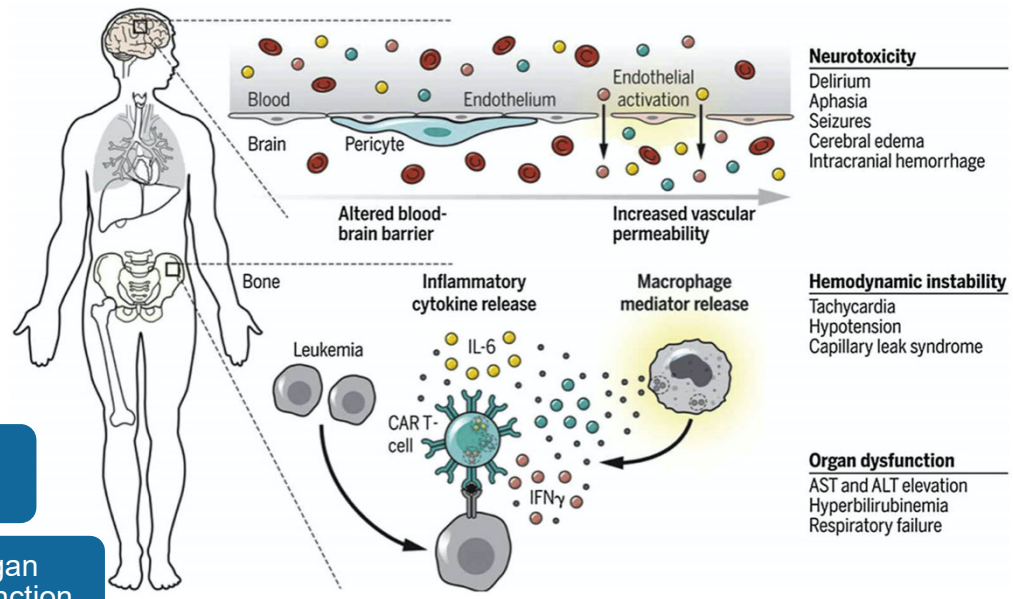
Release of IL-6 and other inflammatory cells

Hemodynamic instability

Compromised perfusion

Organ dysfunction

Endothelium activation



Lee, D.W & Shah, N.N, 2020

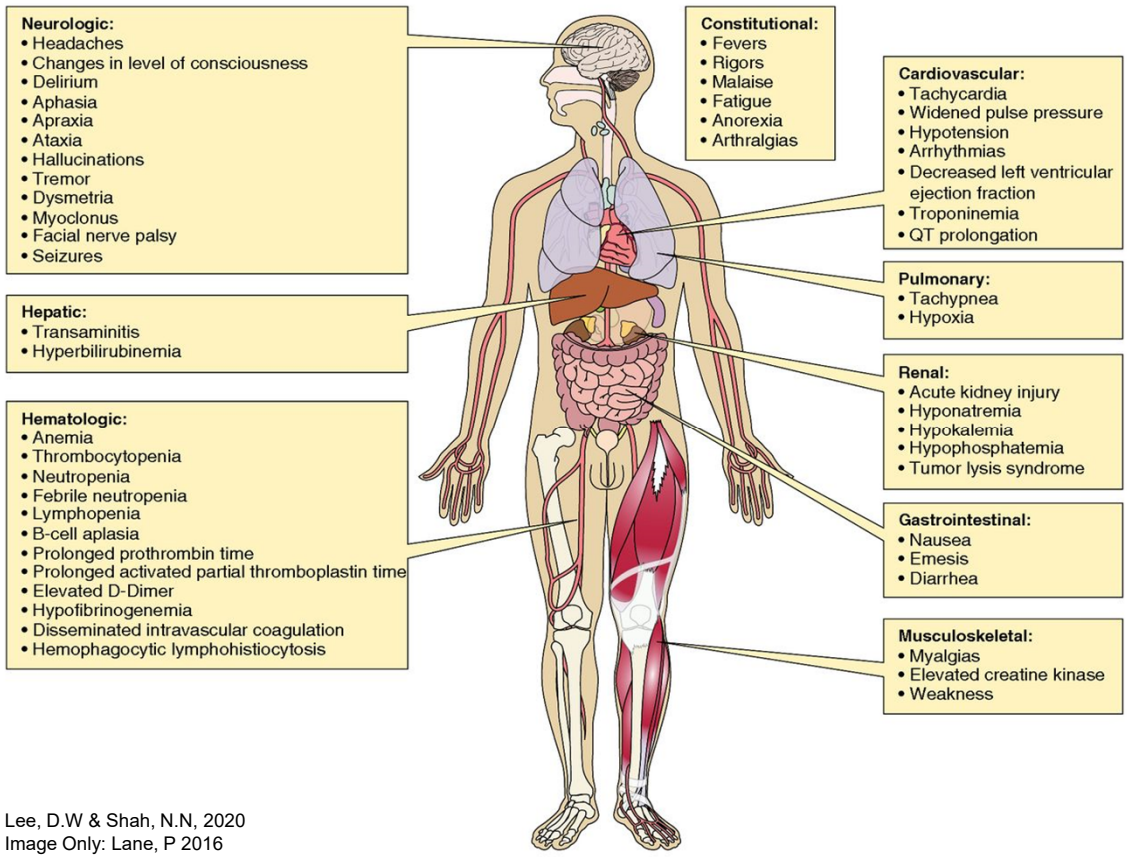
CRS Risk Factors

Clinical Risk Factors	Proposed Interventions
Increased CAR T-cell expansion	• Improve selection of ideal T-cell subset for CAR T-cell therapy • Continue dose finding studies to find ideal CAR T-cell dose to infuse
High disease burden in bone marrow	• Consider earlier treatment with CAR T-cell therapy (i.e.: prior to relapse) • Investigate strategies to reduce disease burden prior to CAR T-cell therapy
Thrombocytopenia	• Consider earlier treatment with CAR T-cell therapy (i.e.: prior to relapse)
Bulk CD8+ T-cells	• Improve selection of ideal T-cell subset for CAR T-cell therapy
Higher CAR T-cell dose infused	• Individualize dosing based on mathematical modeling (yet to be developed) balancing probability of toxicity and response
Lymphodepleting chemotherapy including fludarabine	• Evaluate other lymphodepleting regimens without fludarabine for efficacy

Lee, D.W & Shah, N.N, 2020

CRS Presentation

- Sepsis without bacteremia
  - Important to r/o sepsis while monitoring CRS
- Onset & Duration: Variable
  - Diagnosis
  - Disease Burden
  - Costimulatory domain
- Focal Points
  - Fever
    - within 3 weeks of CAR-T infusion
    - Duration variable (3-8 days)
  - Hypotension
    - Typically occurs after fever
  - Hypoxia
    - Typically occurs after fever



Lee, D.W & Shah, N.N, 2020
Image Only: Lane, P 2016

CRS Grading Variation

- Challenging to compare CAR-T products
- Difficult to develop standard management guidelines
- Subjective assessment
- Time-based criteria not ideal for real-time grading & intervention

D.W. Lee et al. / Biol Blood Marrow Transplant 25 (2019) 625-638

Table 1
Published CRS Grading Systems

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE version 4.03 [11]	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrate)	Life-threatening consequences; pressor or ventilatory support indicated
CTCAE version 5.0 [13]	Fever, with or without constitutional symptoms	Hypotension responding to fluids. Hypoxia responding to <40% FiO_2	Hypotension managed with one pressor. Hypoxia requiring ≥40% FiO_2	Life-threatening consequences; urgent intervention needed
Lee criteria [14]	Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: • Oxygen requirement <40% FiO_2 OR • Hypotension responsive to i.v. fluids or low dose of one vasopressor OR • Grade 2 organ toxicity*	Symptoms require and respond to aggressive intervention: • Oxygen requirement ≥40% FiO_2 OR • Hypotension requiring high-dose or multiple vasopressors OR • Grade 3 organ toxicity* or grade 4 transaminitis	Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity* (excluding transaminitis)
Penn criteria [17]	Mild reaction: Treated with supportive care, such as antipyretics, antiemetics	Moderate reaction: Some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for i.v. therapies (not including fluid resuscitation for hypotension)	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition Hypotension treated with multiple fluid boluses or low-dose vasopressors Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	Life-threatening complications such as hypotension requiring high-dose vasopressors Hypoxia requiring mechanical ventilation
MSKCC criteria [16]	Mild symptoms requiring observation or supportive care only (eg, antipyretics, antiemetics, pain medication)	Hypotension requiring any vasopressors <24 h Hypoxia or dyspnea requiring supplemental oxygen <40%	Hypotension requiring any vasopressors ≥24 h Hypoxia or dyspnea requiring supplemental oxygen ≥40%	Life-threatening symptoms Hypotension refractory to high dose vasopressors Hypoxia or dyspnea requiring mechanical ventilation
CARTOX criteria [12]	Temperature ≥38°C Grade 1 organ toxicity†	Hypotension responds to i.v. fluids or low-dose vasopressor Hypoxia requiring FiO_2 <40% Grade 2 organ toxicity†	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FiO_2 ≥40% Grade 3 organ toxicity† or grade 4 transaminitis	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity† except grade 4 transaminitis

NSAIDs indicates nonsteroidal anti-inflammatory drugs; LFTs, liver function tests; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure.
* As per CTCAE version 4.03.
† Cardiac (tachycardia, arrhythmias, heart block, low ejection fraction), respiratory (tachypnea, pleural effusion, pulmonary edema), gastrointestinal (nausea, vomiting, diarrhea), hepatic (increased serum alanine aminotransferase, aspartate aminotransferase, bilirubin level), renal (acute kidney injury, increased serum creatinine, decreased urine output), dermatologic (rash), or coagulopathy (disseminated intravascular coagulation).

ASTCT CRS Consensus Grading

ASTCT CRS Consensus Grading

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 CTCAE 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.

D.W. Lee et al. / Biol Blood Marrow Transplant 25 (2019) 625-638

CRS Management

- No clinical consensus…yet
- Fever alone does not indicate treatment with anti-cytokine therapy and/or steroids
- Symptom management/Vigilant assessment
- Fever
  - Antipyretics
  - F(+N) work-up & Treatment
- Hypotension
  - Fluid bolus (Limited)
  - Vasopressors (Early initiation)
- Hypoxia
  - O_2 Support
  - Correction of Hypoventilation

Drug	Dose	Route	Action	Comments
Tocilizumab	8mg/kg/dose (max 800mg/dose) over 60 minutes	IV	Binds to soluble & membrane-bound IL-6 receptors (inhibits IL-6 signaling)	Premedicate with acetaminophen & diphenhydramine May repeat q6-8^0 Administer steroids with 2nd dose Decreased efficacy with > 3 doses
Dexamethasone	Max 10mg/dose	IV	Lymphocytotoxic Inhibits monocytes and macrophages, reducing further immune activation	Preferred if concurrent ICANS Improved CNS penetration over methylprednisolone Dose q6-24^0 based on clinical response/presentation Wean once CRS ≤ Grade 1
Methylprednisolone	1mg/kg/dose q4-6^0	IV	Lymphocytotoxic Inhibits monocytes and macrophages, reducing further immune activation	Consider dexamethasone due to improved CNS penetration Use lower doses for stable-appearing patients Wean once CRS ≤ Grade 1
Siltuximab	11mg/kg/dose	IV	Binds to IL-6	3rd line agent Premedicate with acetaminophen & diphenhydramine
Anakinra	2-4mg/kg/day (may increase to 8mg/kg/day)	SQ	153 amino acid antagonist to IL-1 receptor inhibiting the binding of IL-1 to the IL-1 receptor	3rd line agent
Cyclophosphamide	Variable	IV	Destroys reactive T-cells	3rd line agent Unclear of the impact on CAR-T cells

Lee, D.W & Shah, N.N, 2020

Neurotoxicity Grading Variation

Grading System	Adverse Event Term/Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE v5.0 [13],*	Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
	Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New-onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences
	Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly	
	Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	
	Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	
	Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
	Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated
	Cerebral edema			New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated

D.W. Lee et al. / Biol Blood Marrow Transplant 25 (2019) 625-638

Neurotoxicity Grading Variation

Grading System	Adverse Event Term/Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE v5.0 [13],*	Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
	Seizure	Brief partial seizure and no loss of	Brief generalized seizure	New-onset seizures (partial or general-	Life-threatening consequences
CARTOX criteria [12]	Neurologic Assessment Score (CARTOX-10)	7-9 (mild impairment)	3-6 (moderate impairment)	0-2 (severe impairment)	Patient in critical condition, and/or obtunded and cannot perform assessment of tasks
	Elevated ICP	N/A	N/A	Stage 1-2 papilledema† or CSF opening pressure <20 mmHg	Stage 3-5 papilledema†, or CSF opening pressure ≥20 mmHg, or cerebral edema
	Seizures or motor weakness	N/A	N/A	Partial seizure or nonconvulsive seizures on EEG with response to benzodiazepine	Generalized seizures or convulsive or nonconvulsive status epilepticus, or new motor weakness

ADL indicates activities of daily living; CSF, cerebrospinal fluid; EEG: electroencephalography.

* CTCAE: Under CRS listing: "Also consider neurologic toxicities such as psychiatric disorders: hallucinations or confusion; nervous system disorders: seizure, dysphasia, tremor, headache."

† Papilledema grading is performed according to the Modified Frisén scale [35].

D.W. Lee et al. / Biol Blood Marrow Transplant 25 (2019) 625-638

ASTCT ICANS Consensus Grading: Adults

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
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's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

D.W. Lee et al. / Biol Blood Marrow Transplant 25 (2019) 625-638

ICE Score

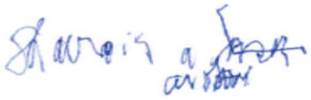
ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point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

Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

Day 4, MMSE 29/30

I love Shawnee, KS.

Day 5, MMSE 27/30



Day 6, MMSE 29/30

I miss my kids.

D.W. Lee et al. / Biol Blood Marrow Transplant 25 (2019) 625-638

ICANS Management

- Vigilant Assessment
  - Neuro Assessment Q8º minimum
  - Neurologist Consult
  - Role of transcranial doppler assessment
- Seizure Prophylaxis
  - Levetiracetam
- Early Neuro ICU Transfer
  - In setting of neuro deterioration
  - EEG monitoring
- Optimization of Cerebral Perfusion
  - Antipyretics
  - Maintaining normotension

Drug	Dose	Route	Action	Comments
Tocilizumab	8mg/kg/dose (max 800mg/dose) over 60 minutes	IV	Binds to soluble & membrane-bound IL-6 receptors (inhibits IL-6 signaling)	Premedicate with acetaminophen & diphenhydramine May repeat q6-8º Administer steroids with 2nd dose Decreased efficacy with > 3 doses
Dexamethasone	Max 10mg/dose	IV	Lymphocytotoxic Inhibits monocytes and macrophages, reducing further immune activation	Preferred if concurrent ICANS Improved CNS penetration over methylprednisolone Dose q6-24º based on clinical response/presentation Wean once CRS ≤ Grade 1
Methylprednisolone	1mg/kg/dose q4-6º	IV	Lymphocytotoxic Inhibits monocytes and macrophages, reducing further immune activation	Consider dexamethasone due to improved CNS penetration Use lower doses for stable-appearing patients Wean once CRS ≤ Grade 1
Siltuximab	11mg/kg/dose	IV	Binds to IL-6	3rd line agent Premedicate with acetaminophen & diphenhydramine
Anakinra	2-4mg/kg/day (may increase to 8mg/kg/day)	SQ	153 amino acid antagonist to IL-1 receptor inhibiting the binding of IL-1 to the IL-1 receptor	3rd line agent
Cyclophosphamide	Variable	IV	Destroys reactive T-cells	3rd line agent Unclear of the impact on CAR-T cells

CNS Case Study

- 60M 2/19 Dx DLBCL
  - R-CHOP x 3 cycles
- 6/20 DLBCL in CNS only
  - R-MTX
  - Etoposide/Cytarabine
- 1/11/21 Axi-cel
  - Grade 1 CRS (Toci + Dex x 1 on Day +3)
    - Fevers Day +1 through Day + 5
  - Grade 3 Neurotoxicity (Dex + increase in antiseizure ppx)
    - Somnolence; ICE 8/10 (Day +6)
    - Within 8 hours ICE 2-3/10 more somnolence w/ periods of agitation
    - Tx to Neuro ICU
    - Dex 10mg IV q6 x 9 doses Day +6- Day + 8
- d/c Day +12
  - Slight residual LLE weakness
- 1 month f/u: significant reduction in enhancements on Brain MRI (4+ areas)

	D0	Day +1	Day +2	Day +3	Day +4	Day +5	Day +6	Day +7
Ferritin	348	414	605	712	1096	1000	1082	1069
CRP	8.3	9.9	108.4	142.6	159	74.5	56.9	48.5
IL-6	12.4	108.2	192.2	136.1	461.6	870.4	192.5	80.1
Pro-Cal	0.22	n/a	0.52	0.51	0.57	0.45	0.22	0.13

Lessons Learned

Toci + Dex for CRS may lessen neurotoxicity
Screening: MRI, Head CT, EEG, TCD
Early transfer to Neuro ICU

Electrolyte Imbalances

CAR-T Expansion

- Need for profound metabolic support
- ATP Production
    - Hypokalemia
    - Hypophosphatemia
    - Hypomagnesemia
- Electrolyte Repletion

Tumor Lysis Syndrome (TLS)

- Presentation
    - Hyperkalemia
    - Hyperphosphatemia
    - Hyperuricemia
- Prophylaxis
    - Allopurinol
- Treatment
    - Rasburicase
    - Hydration*
    - Sevelamer
    - Dialysis

Lee, D.W & Shah, N.N, 2020

Case Study

58F MM

- Heavy disease burden
- RVD, VCD, DCEP, Auto SCT, Dara/Pom, Carfilz/Dex/Cy
- CAR-T: Compassionate Use Approval
- CRS/ICANS Grade 1: Toci/Dex x 1
- TLS Day +12: Rasburicase
- Renal tubular acidosis

	D0	Day +8	Day +9	Day +10	Day +11	Day +12	Day +13	Day +14
ANC	339	145	346.5	0	0	132	304.2	338.4
HCT	23.6	22.6	21.6	20.7	22	21.4	21.7	20.8
PLT	10	13	10	14	11	5	8	13
Uric Acid	4	3.4	4.3	5.6	5.5	13.4	4.7	<0.4
Cre	089	1.13	1.18	1.30	1.13	1.37	1.28	1.25
Phos	4.1	4.8	5.4	4.8	4.6	7.5	5.9	3.6
K	4.3	3.9	3.4	3.6	4.1	3.1	3.3	4.2

Sevelamer

Rasburicase
Sevelamer dose increased
Bicarb

	11/23/2020 1609	1/13/2021 0855	1/14/2021 1726	2/5/2021 1655	2/12/2021 0422	2/25/2021 0935
IMMUNOGLOBULIN						
Kappa FLC (mg/L)	1,217.0 * ▲	2,907.9 * ▲	2,758.8 * ▲	2,092.5 ▲	15.9 *	7.1 *

Cytopenias

Etiology

- Suboptimal marrow function
  - Disease
  - Prior treatment
- CAR-T Cells
  - Myelosuppression 2/2 cytokine meditated mechanism

Treatment

- G-CSF
- Blood Transfusions
- Prophylactic Antibiotics

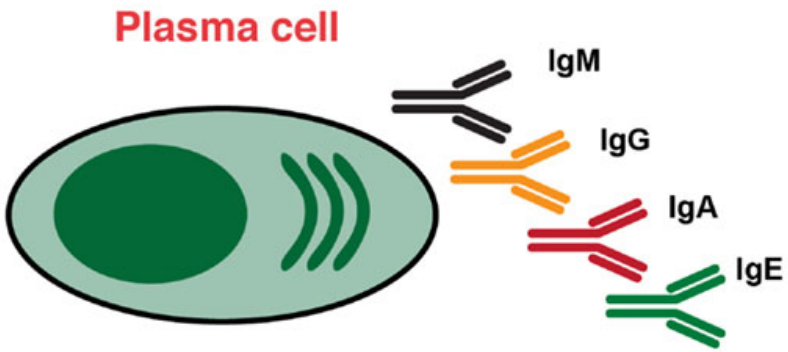
Resolution (Tiso-cel study)

- Neutropenia
  - 53% of patients grade 3 or 4 at Day +28
  - 66% had resolution to grade 2 by month 3
- Thrombocytopenia
  - 41% grade 3 or 4 at Day +28
  - 73% had resolution to grade 2 by month 3

Lee, D.W & Shah, N.N, 2020

B-Cell Aplasia

- CAR-T resilience
- Hypogammaglobulinemia
  - 2 months – 2 years for recovery
  - Baseline low levels of IGG
    - Require IVIG replacement 2/2 disease/treatment
  - Typically longer when 4-1BB is costimulatory domain
    - Compared to CD28
- Treatment
  - IVIG replacement
  - Antibiotics

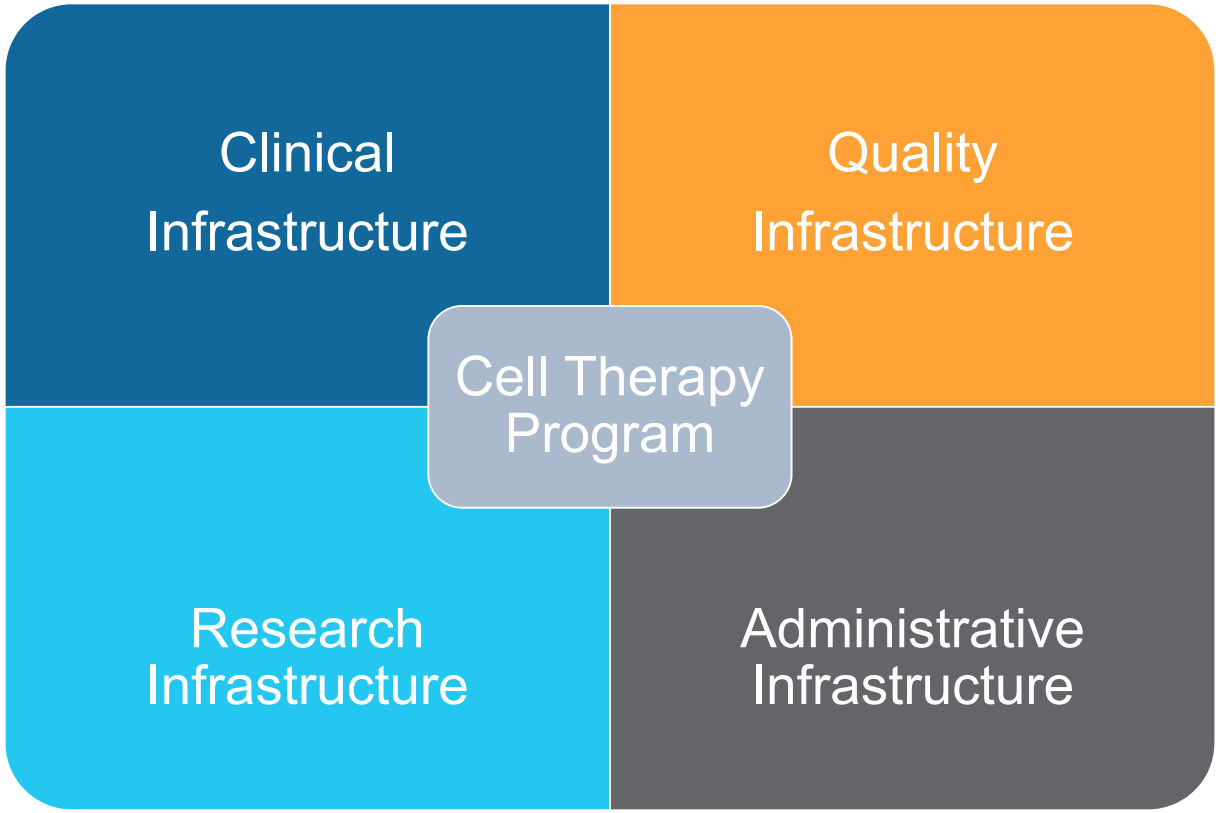


Moens & Tangye, 2014

Lee, D.W & Shah, N.N, 2020

CAR-T Logistical Operations & Education

Program Infrastructure



Education

Clinical Staff

- Required Education
  - Risk Evaluation and Mitigation Strategy (REMS) Programs
  - Clinical Trial Orientation
  - Standard Operating Procedures
- Enhanced Education
  - Knowing the why behind the treatment
  - Understanding the patient in relation to the treatment

Patient/Caregiver(s)

- Preparation
- Acute Phase
- Follow-up
- Survivorship

Communication

- Nurse-nurse
- Patient/Caregiver-team
- Interdisciplinary communication
  - HM
  - Cell therapies
  - Nursing
  - Neurology
- Inpatient-outpatient
- Logistical communication

Standardization

- Utilization of EMR
  - Flowsheets
  - Templated notes
- Objective Assessments
  - ASTCT Consensus Grading CRS/ICANS
- Management of Toxicities
  - Future steps

Neurological	
Level of Consciousness	
Cognition	
Speech	
R Pupil Size (mm)	
R Pupil Shape	
R Pupil Reaction	
L Pupil Size (mm)	
L Pupil Shape	
L Pupil Reaction	
RUE Motor Strength	
LUE Motor Strength	
RLE Motor Strength	
LLE Motor Strength	
Orientation	
Year	
Month	
City	
Hospital	
Naming	
Object #1	
Object #2	
Object #3	
Follows Commands	
Follows simple commands	
Writing	
Writes a standard sentence	
Attention	
Ability to count backwards from 100 by 10	
ICE Score	
ICE Score	

Alencar, et Al, 2019

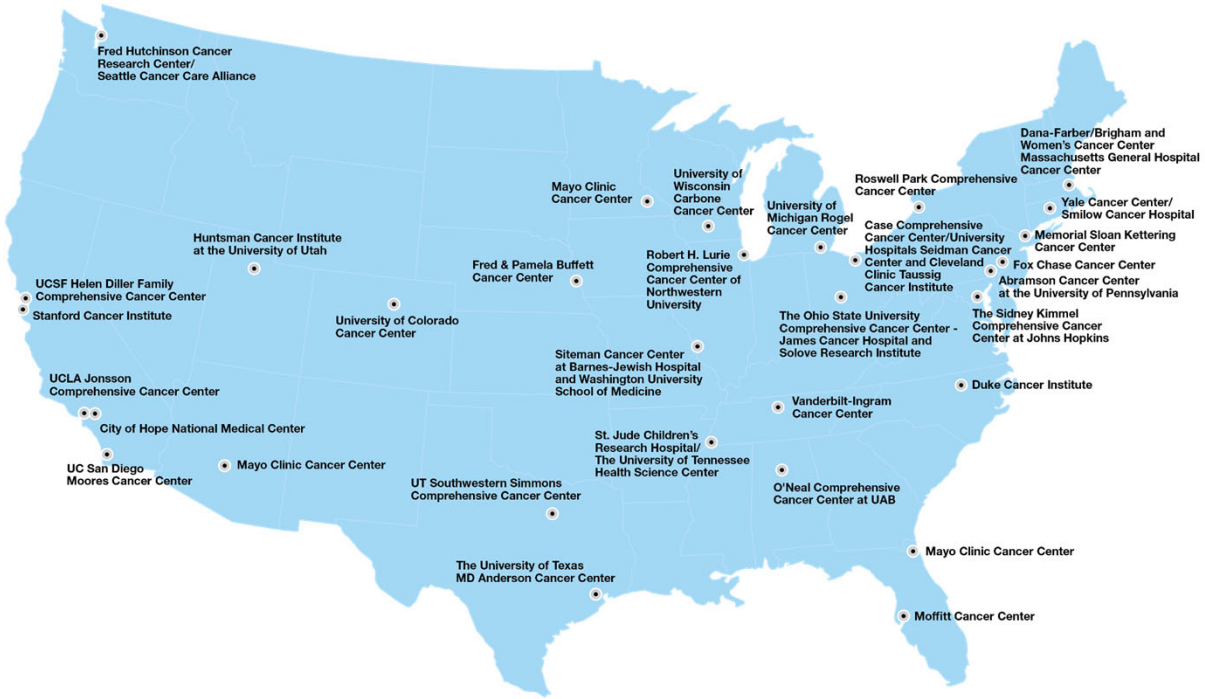
Conclusion

- CAR-T Therapy has proven to a be successful treatment opportunity for R/R hematologic malignancies
- Further research is needed to identify CAR-T's niche in SOC treatment options
- CAR-T has opened the door to infinite cellular therapy possibilities
- CAR-T toxicity is significant, but management strategies have improved significantly
- Further research is needed to mitigate toxicity and improve efficacy
- Up-to-date education is vitally important
    - The CAR T-Cell Therapy Landscape is changing rapidly and requires vigilance
- Coordination of care is crucial
    - It takes [a skilled] village

National Comprehensive Cancer Network®

NCCN Member Institutions

- **Who We Are**
  An alliance of leading cancer centers devoted to patient care, research, and education
- **Our Mission**
  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives
- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally



NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients