Overview of immunotherapy toxicity in oncology: A focus on CAR-T and checkpoint inhibitors

Kevin Michael Ohara PA
Memorial Sloan Kettering Cancer Center
Adjunct Professor, Pace University
New York, New York
oharak@mskcc.org

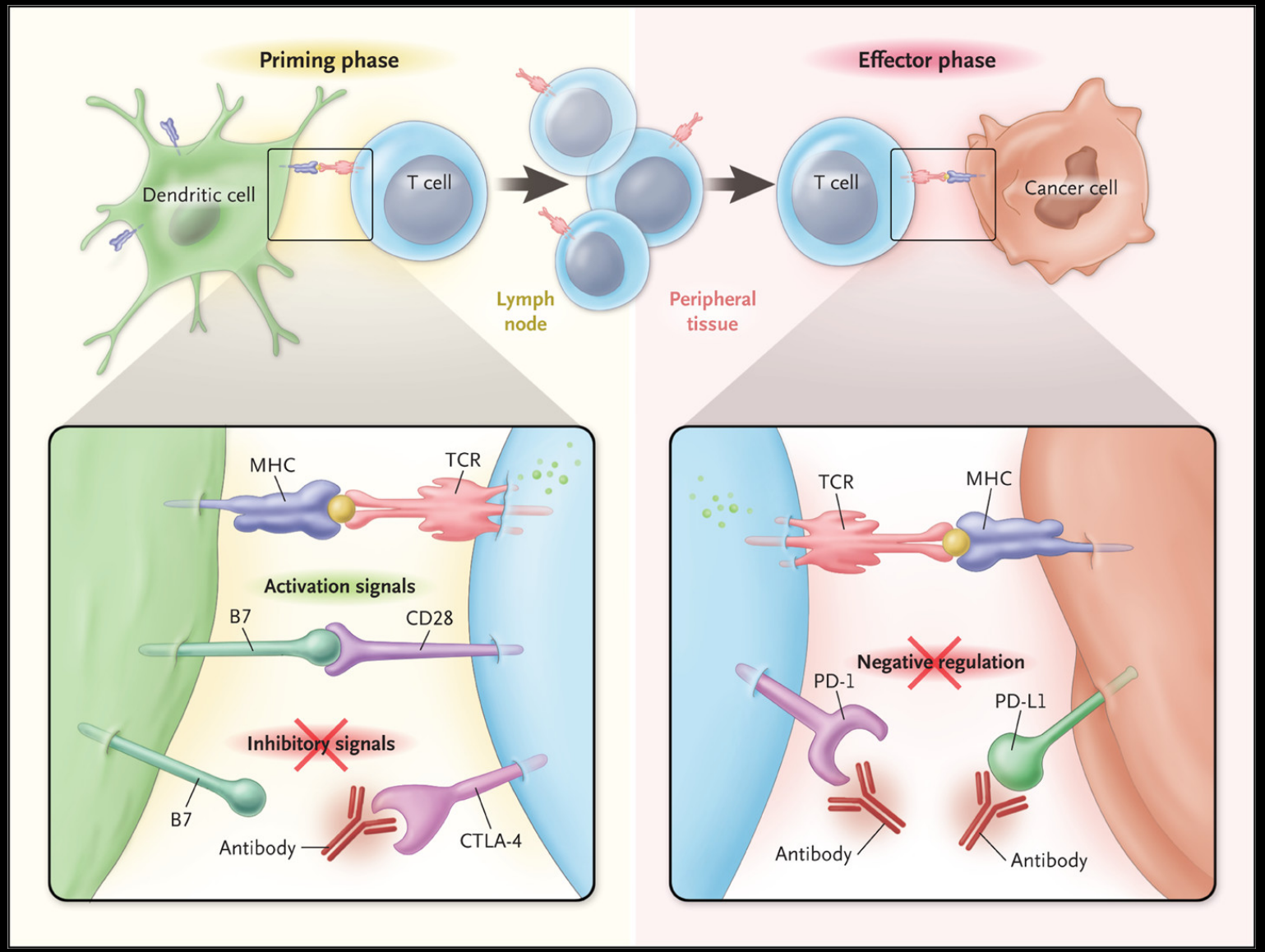
- I have no financial or other bias inducing disclosures

Objectives

- Describe CART and Checkpoint inhibitor MOA
- List common toxicities
- Develop a basic understanding of how to diagnose and treat these toxicities

Checkpoint Inhibitors

Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy



Ribas A. N Engl J Med 2012;366:2517-2519.

The NEW ENGLAND JOURNAL of MEDICINE

COMMON APPROVED CHECKPOINT INHIBITORS

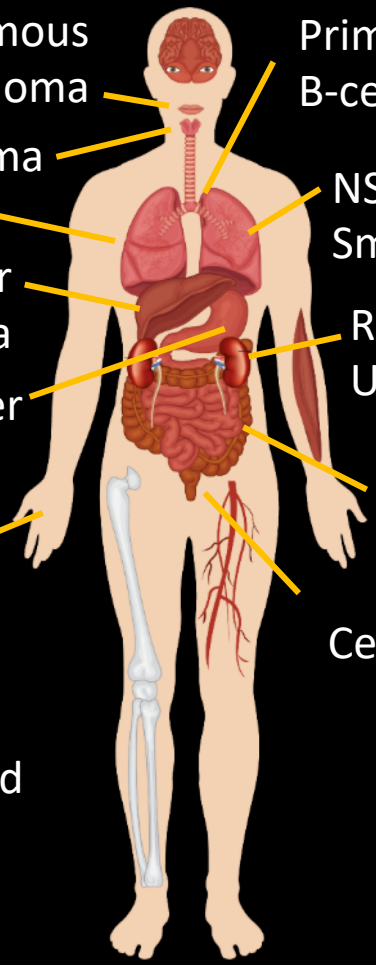
Table 1. Approved immune checkpoint inhibitors and indications

CTLA-4	Ipilimumab (Yervoy)	Melanoma
PD-L1	Pembrolizumab (Keytruda), nivolumab (Optivo)	NSCLC, small-cell lung cancer, head and neck carcinoma, RCC, Hodgkin lymphoma, cervical carcinoma, PMBCL, urothelial carcinoma, hepatocellular carcinoma, gastric cancer, MSI-H or dMMR solid tumor
PD1	Atezolizumab (Tecentriq), durvalumab (Imfinzi), avelumab (Bavencio)	Urothelial cancer, NLCLC, Merckel cell carcinoma
CTLA-4 + PD-L1	Ipilimumab + nivolumab	Metastatic melanoma, RCC, colorectal cancer (MSI-H or dMMR)

CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; NSCLC, nonsmall-cell lung cancer; PD-L-1, programmed cell death-ligand 1; PMBCL, primary mediastinal large B cell lymphoma; RCC, renal-cell carcinoma.

Claire Perrinjaqueta, Nicolas Desbailletsb, and Andreas F. Hottingera. Neurotoxicity associated with cancer immunotherapy: immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy Curr Opin Neurol 2019, 32:500 – 510

Immune Checkpoint Inhibitors FDA Approved in Multiple Cancers (May 2019)

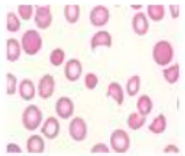


- ICIs include atezolizumab, avelumab, durvalumab, ipilimumab, cemiplimab-rwlc, nivolumab, pembrolizumab
  - Approved as monotherapy, in combination with other ICIs, and in combination with chemotherapy
  - ICIs historically used in later-line metastatic disease, but moving into earlier lines of therapy and earlier stages of disease

Michot. Eur J Cancer. 2016;54:139. Nivolumab PI. Ipilimumab PI. Pembrolizumab PI. Atezolizumab PI. Durvalumab PI. Avelumab PI. Cemiplimab-rwlc PI.

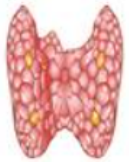
Slide credit: clinicaloption

Toxicities Associated with Checkpoint Inhibitors



BLOOD
Haemolytic anaemia
Thrombocytopaenia
Neutropenia
Haemophilia

CARDIOVASCULAR
Myocarditis
Pericarditis
Vasculitis

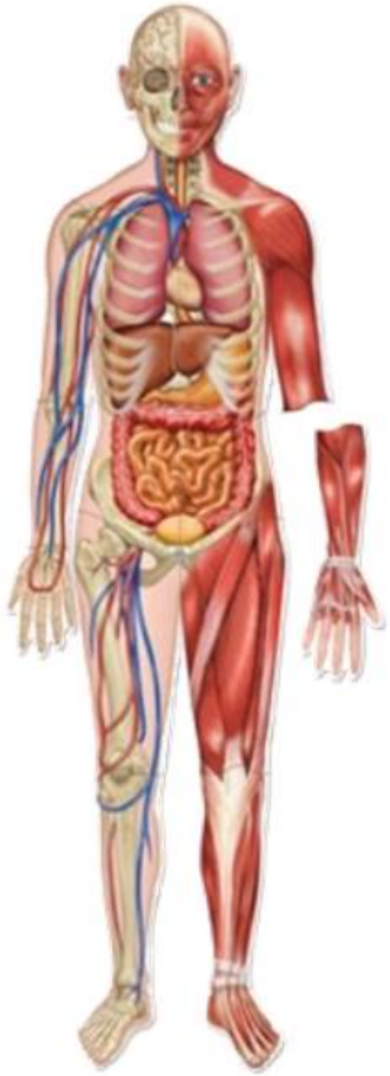


ENDOCRINE
Hyper or hypothyroidism
Hypophysitis
Hypoadrenalism
Type 1 diabetes

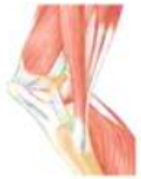
EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis

GASTROINTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis

LIVER
Hepatitis

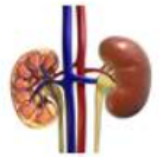


MUSCULOSKELETAL
Dermatomyositis
Arthritis



NEUROLOGICAL
Neuropathy
Guillain Barre
Meningitis
Encephalitis
Myasthenia

RENAL
Nephritis



RESPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like
granulomatosis

SKIN
Rash
Pruritis
Psoriasis
Vitiligo
DRESS
Stevens Johnson

https://cancerforum.org.au/forum/2018/april/cancer-immunotherapy-at-a-new-immune-frontier/

Checkpoint Inhibitor Toxicities

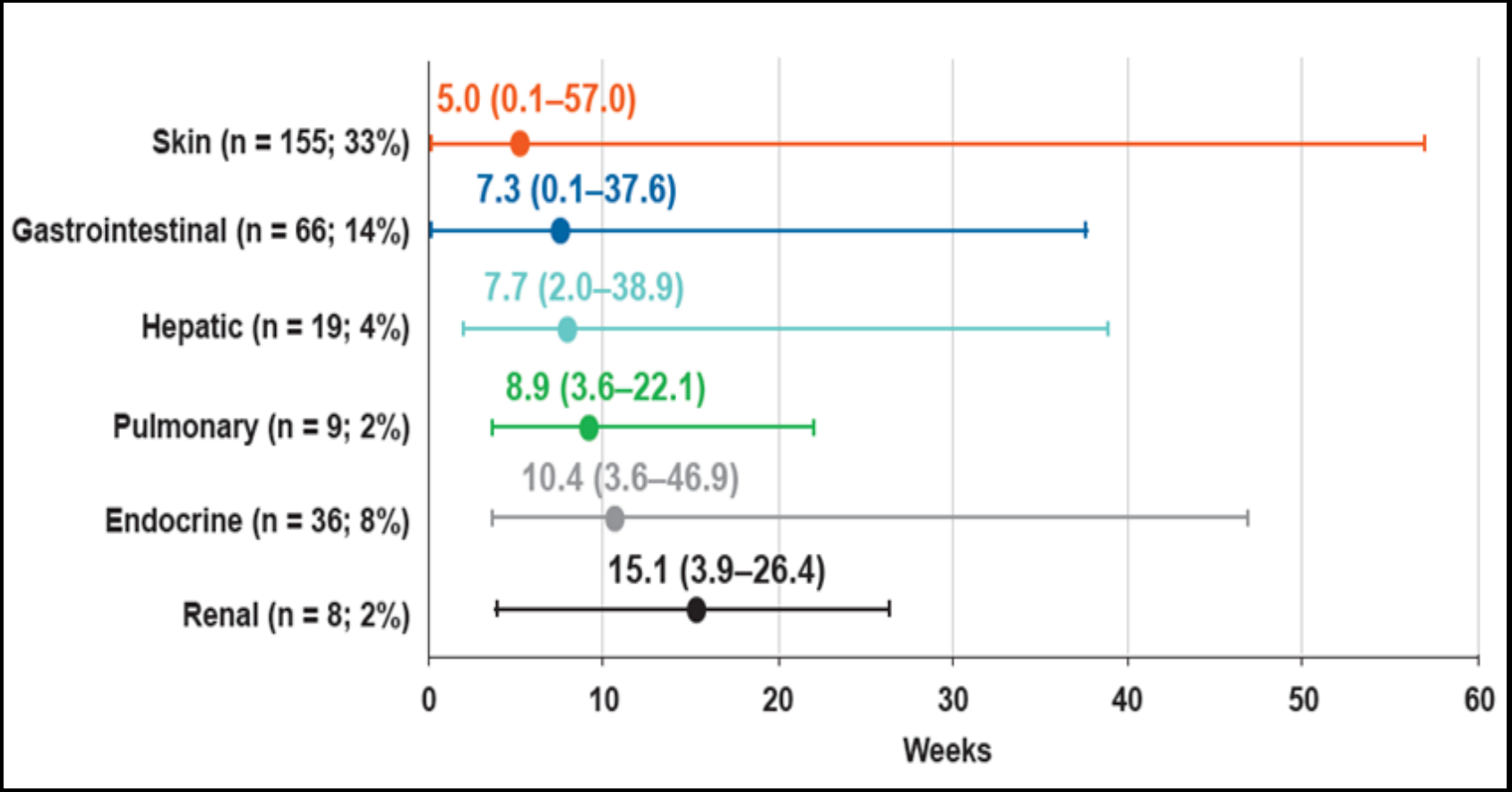
Most Common

- Dermatologic
  - Vitiligo
  - Pruritis
  - Rash/Dermatitis
- Gastrointestinal
  - Colitis
  - Hepatitis
- Endocrine

Less Common, Serious

- Pulmonary
  - Pneumonitis
- Cardiac
  - Myocarditis
- Neurologic
  - Aseptic meningitis/encephalitis
  - Myasthenia gravis
  - Guillain-Barre
  - Auto-immune neuropathies

When do irAEs occur?



Nivolumab

Any grade, n = 474

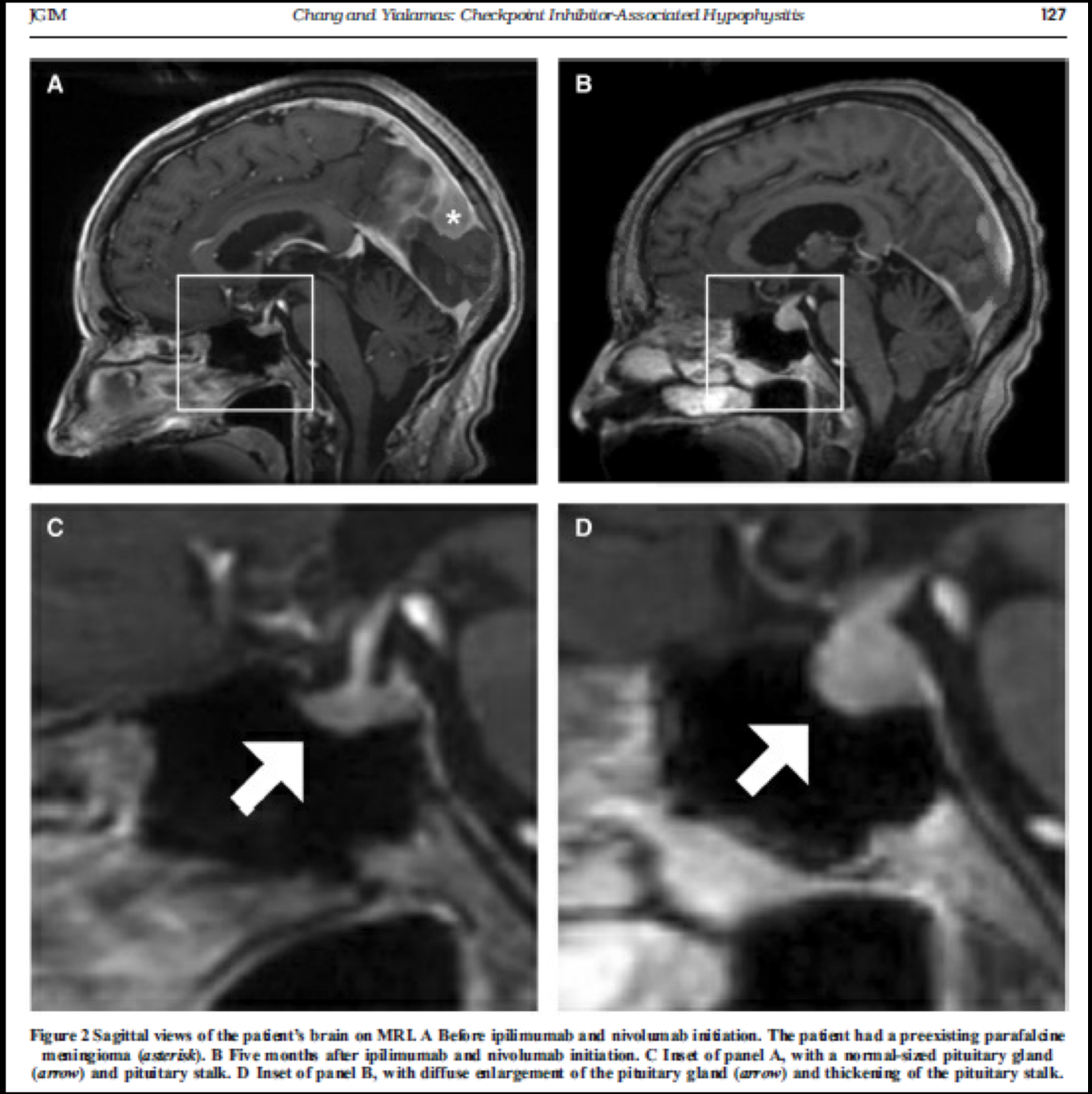
Weber et al. Journal of Clin Oncol 2016

Endocrine Related Adverse Events

- The thyroid, adrenal, and pituitary glands are the organs primarily impacted
- TSH/T4 monitoring
- More common w/ ipilimumab

Hypophysitis

Chang, Checkpoint inhibitor Associated Hypophysitis. JGIM 2018 Jun 10;36



Neurologic toxicities

- Polyneuropathy
- Guillen barre syndrome
- Myasthenia Gravis
- Myositis
- Encephalitis
- Meningitis
- Transverse Myelitis

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ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino,

Toxicities - Management

- Evaluation and Management
  - Site specific
  - Steroids initial Tx for most toxicities
  - If unresponsive, Tx may include
    - MMF
    - Azathioprine
    - Cyclosporine
    - Infliximib
    - IVIG/Plasmapheresis

Case study 1

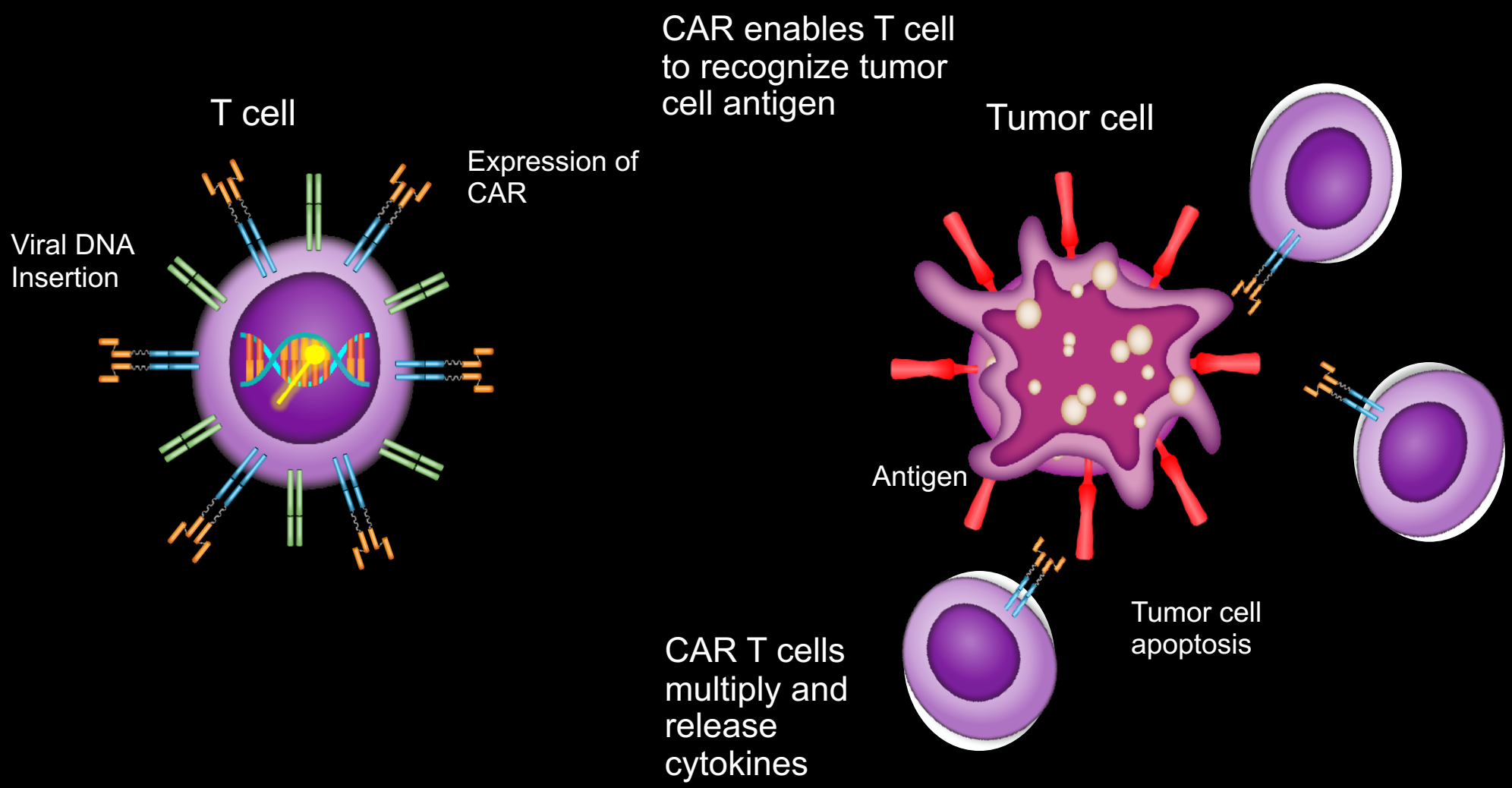
- A 56-year-old woman with metastatic NSCLC comes to ED with non bloody diarrhea approximately 2 liters per day x 4 days. Generalized abdominal cramping rated 3/10.
- PMHx: HTN, NSCLC
- MEDS: Amlodipine, Cycle 3 (pembrolizumab, pemetrexed and carboplatin)
- 98/68 mmhg, 110 hr, 20 RR, 37.8 temp
- CT A/P w, w/o consistent with colitis

- CBC shows mild stable anemia and treatment related neutropenia
- CMP shows hypokalemia at 2.6, no hepatitis
- ESR, CRP elevated.
- GI Pathogen and C Difficile PCR studies negative
- GI consult favors irAE from pembro, also consider infectious, not recommending endoscopy given neutropenia

- Start methylprednisolone 1.5mg/kg
- Anti motility agents
- Potassium repletion IV
- Fluid resuscitation
- CMV PCR blood?
- Consider cycle 4

Chimeric Antigen Receptor (CAR) T cell

CAR T Cells: Mechanism of Action



FDA-Approved CAR T-Cell Therapies

Therapy	Target	Indications
Tisagenlecleucel	CD19	▪ **Patients aged up to 25 yrs with B-cell precursor ALL that is refractory or in second or later relapse** ▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy**, including: ○ DLBCL NOS ○ DLBCL arising from follicular lymphoma ○ High-grade B-cell lymphoma
Axicabtagene ciloleucel	CD19	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including**: ○ DLBCL NOS ○ DLBCL arising from follicular lymphoma ○ Primary mediastinal large B-cell lymphoma ○ High-grade B-cell lymphoma

Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloption

Acute CAR-T Toxicity

- Cytokine release syndrome
- Neurotoxicity (immune effector cell-associated neurologic syndrome)
- Hypersensitivity reaction
- Tumor lysis syndrome

Frequency of CRS and Neurotoxicity With FDA-Approved CAR T-Cell Therapies

Parameter	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2,3]	
Setting	DLBCL	DLBCL	B-ALL
Trial	ZUMA-1	JULIET	ELIANA
Toxicity grading criteria	Lee 2014	Penn Grading Scale	Penn Grading Scale
Any-grade CRS, %	93	58	77
Grade ≥ 3 CRS, %	13	22	47
Any-grade neurotoxicity, %	64	21	40
Grade ≥ 3 neurotoxicity, %	28	12	13
Tocilizumab use, %	43	14	48

1. Neelapu. NEJM. 2017;377:2531. 2. Schuster. NEJM. 2019;380:45. 3. Maude. NEJM. 2018;378:439.

Time Course of Toxicities Associated With FDA-Approved CAR T-Cell Therapies

Number of Days (Range)	CRS		Neurologic AEs	
	Median Time to Onset	Median Duration	Median Time to Onset	Median Duration*
Axicabtagene ciloleucel[1]	2 (1-12)	7 (2-58)	4 (1-43)	17
Tisagenlecleucel[2]	3 (1-51)	8 (1-36)	6 (1-359)	ALL: 6 DLBCL: 14

- CRS: characterized by fever at the onset; symptoms can be progressive and, in addition to fever, may include capillary leak/hypoxia, end organ dysfunction, and hypotension
- ICANS: toxic encephalopathy with symptoms of mild headaches, confusion, and delirium; expressive aphasia; occasional seizures; and rarely, cerebral edema; can occur in the presence or absence of systemic CRS

1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI. Lee. Blood. 2014;124:188.

Slide credit: clinicaloption

Managing Long-term Toxicities

- Consult institutional guidelines for management of the following toxicities and contact CAR T-cell treatment center for special management questions
- **B-cell aplasia/hypogammaglobulinemia**
  - Occurred in ~ 15% of adults with R/R large B-cell lymphoma treated with axicabtagene ciloleucel or tisagenlecleucel and in 43% of pediatric/young adult R/R B-cell ALL treated with tisagenlecleucel in pivotal trials; immunoglobulin levels should be monitored following therapy
- **Cytopenias**
  - Grade ≥ 3 cytopenias unresolved by Day 30 post treatment occur in a significant proportion of patients; blood counts should be monitored following therapy
- **Infections**
  - Occurred in 38% to 55% of patients treated with axicabtagene ciloleucel or tisagenlecleucel in pivotal trials

Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloption

CRS Toxicities by Organ System

Neurologic

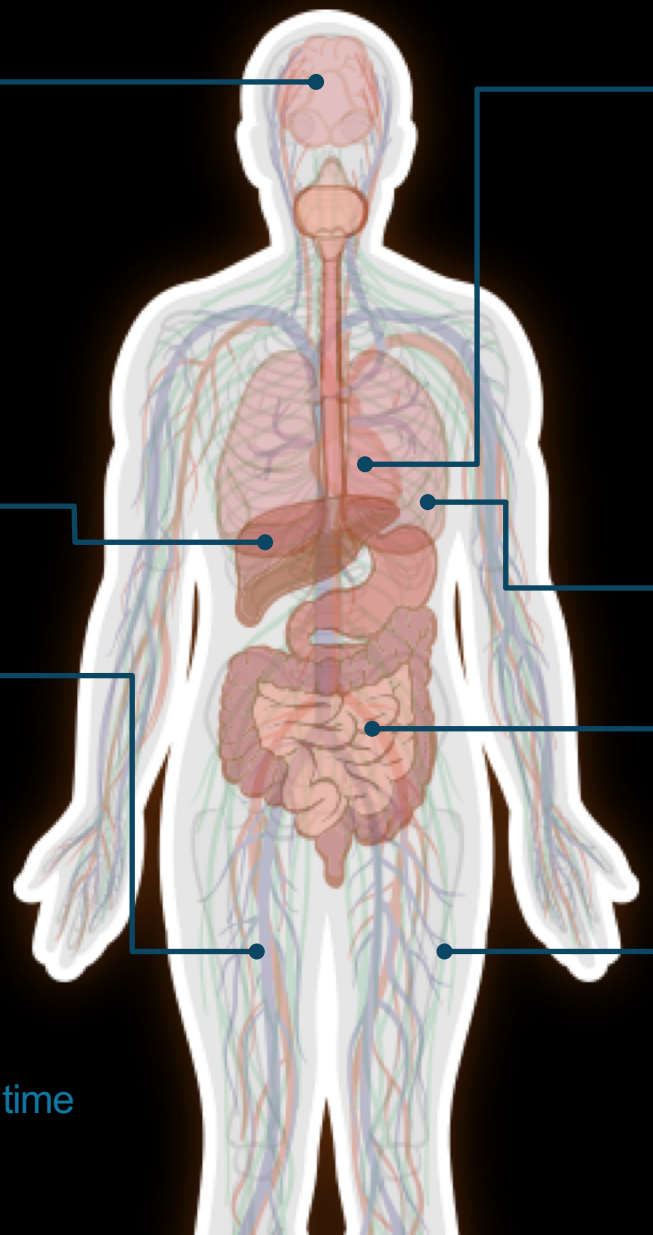
- Headaches
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial Nerve palsy
- Seizures

Hepatic

- Transaminitis
- Hyperbilirubinemia

Hematologic

- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile Neutropenia
- Lymphooenia
- B-Cell Aplasia
- Elevated D-Dimer
- Hypofibrinogenemia
- Dissembled Intravascular Coagulation
- Hemophagocytic Lymphohisticyclosis
- Prolonged Prothrombin time
- Prolonged Activated Partial Thromboplastic time



Cardiovascular

- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fracture
- Troponinemia
- QY prolongation

Pulmonary

- Tachypnea
- Hypoxia

Gastrointestinal

- Nausea
- Diarrhea
- Emesis

Musculoskeletal

- Myalgias
- Weakness
- Elevated creatine kinase

Constitutional

- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Aethralgais

Renal

- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

ASTCT Guidelines for Grading of Cytokine Release Syndrome

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

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Slide credit: clinicaloption

General Considerations for CRS Management

- Management of CRS is based on clinical parameters, not laboratory values
  - Ferritin, CRP, serum cytokines should only be used to support the diagnosis
- CRS is managed with high level of clinical surveillance, fluids, and vasopressors
  - CRS requires continuous monitoring
- The IL-6 receptor antibody tocilizumab is indicated for 1L treatment of CRS
  - Not currently recommended for prophylactic use as impact on T-cell expansion and persistence is not known. This is currently being investigated
- 2L treatment for CRS varies by protocol and / or institutional guidelines
  - Steroids are effective for treating CRS; however, they are lymphotoxic
  - Other cytokine-modulating agents are currently being investigated. Examples include siltuximab, anakinra, etc

Principles of Toxicity Management

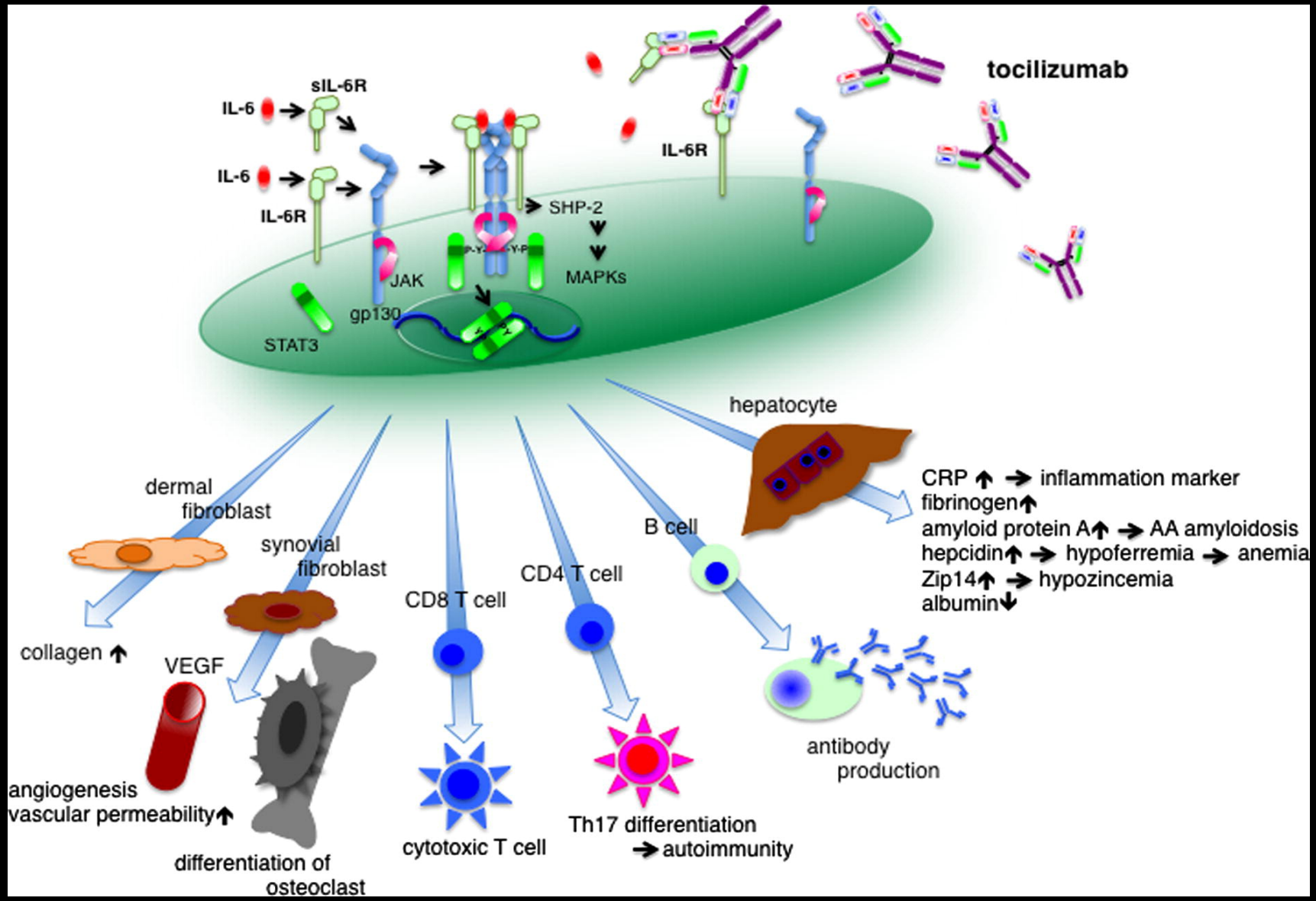
- Appropriate screening per institutional standards
- Baseline labs
  - CRP, ferritin
  - CBC, CMP, coagulopathy
  - Tumor lysis syndrome labs
- Consider antiepileptic drugs
- Consider bacterial/fungal/viral prophylaxis per institutional standards

- Preinfusion/LD chemo
- Monitor baseline labs
- Daily assessments for 7-10 days
  - Fevers? Hypotension? Hypoxia?
  - Mental status
- Key acute toxicities: cytokine-release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS)

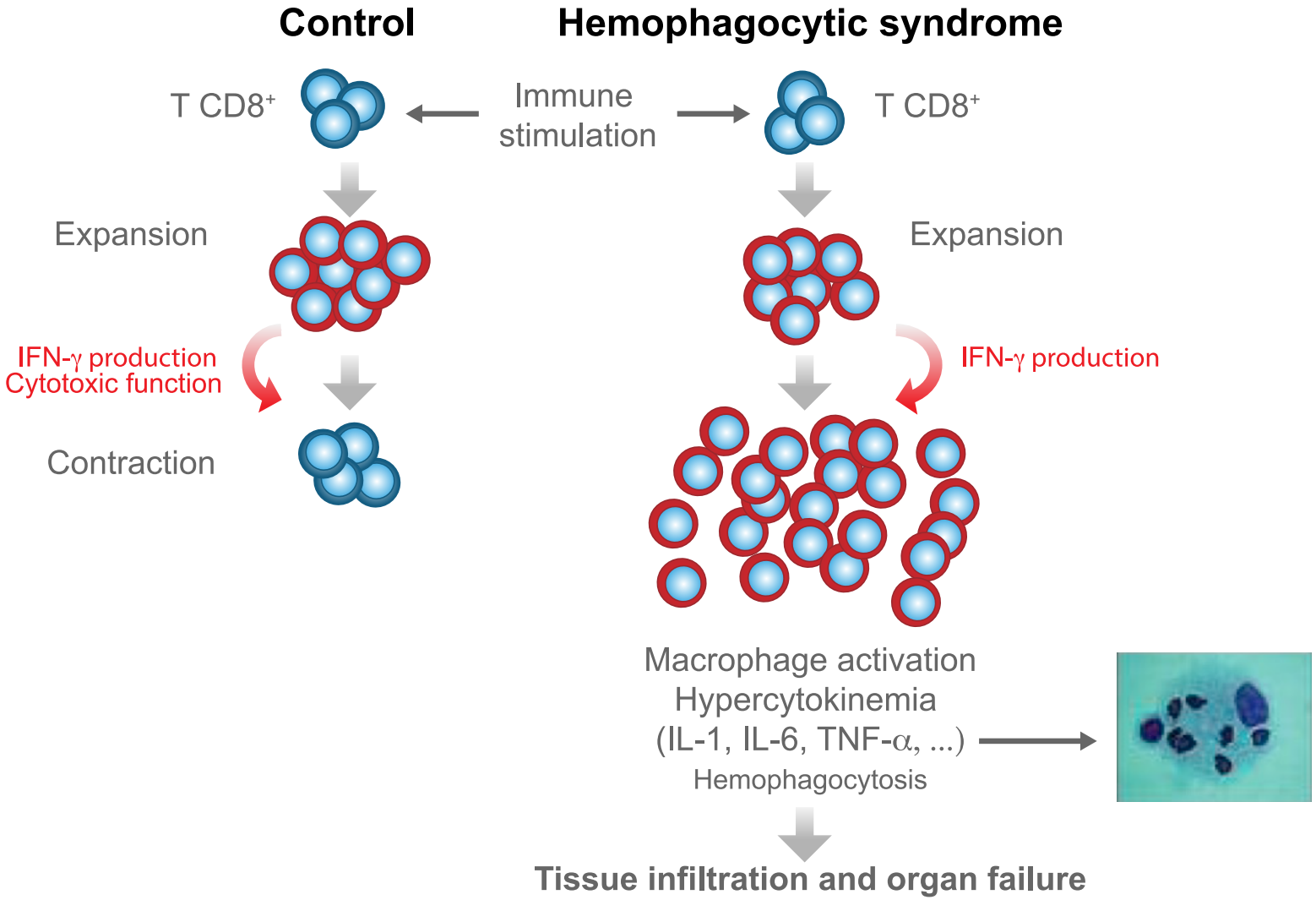
MD Anderson. CAR cell therapy toxicity assessment and management. 2017.
Neelapu. Nat Rev Clin Oncol. 2018;15:47. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloption[illegible]

Tocilizimuab MOA



HLH Pathogenesis



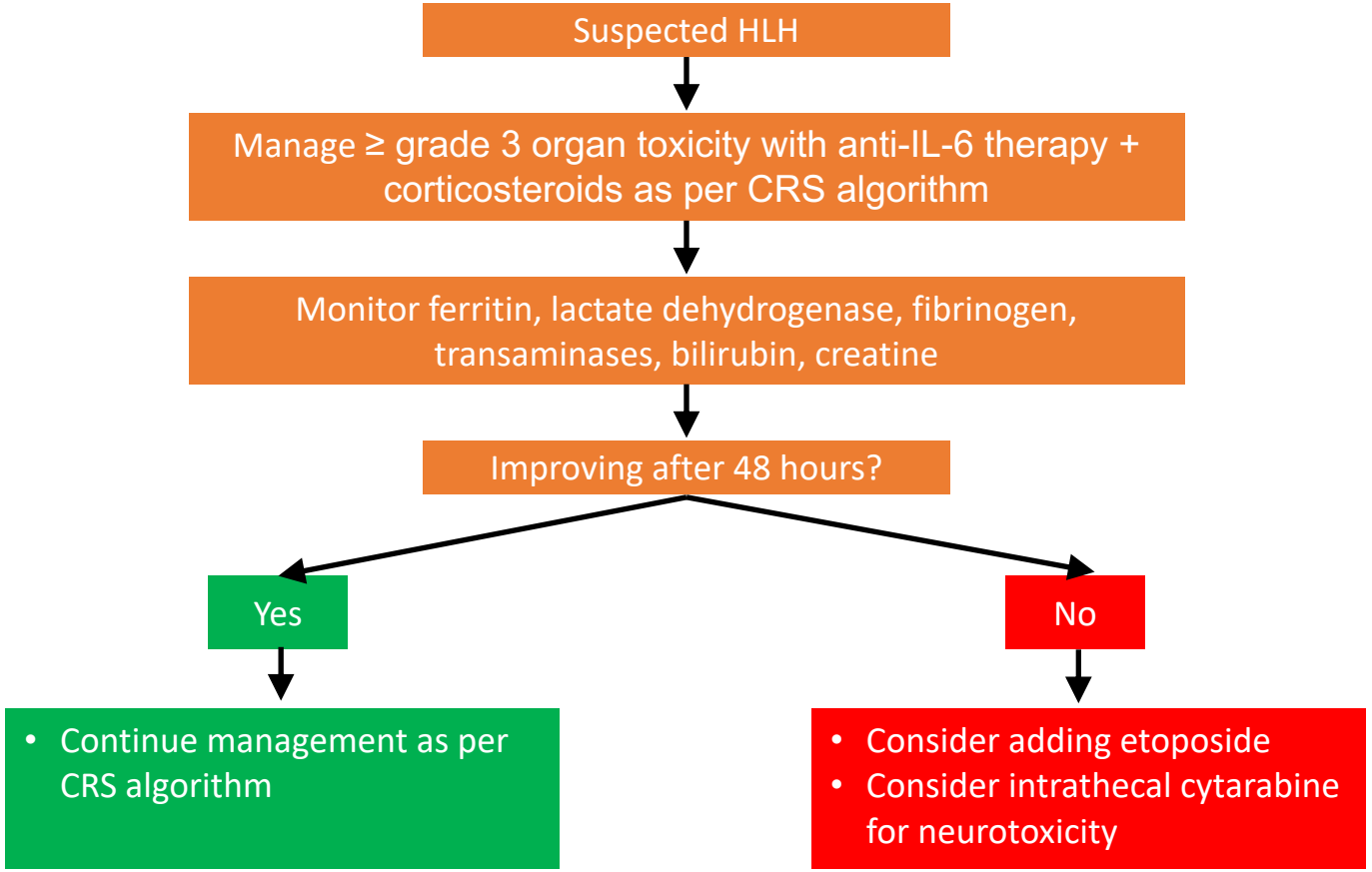
HLH, hemophagocytic lymphohistiocytosis.

CAR T WORKING GROUP

HLH Laboratory Abnormalities

- Elevated ferritin
  - Likely secreted by activated macrophages
- Elevated triglycerides
  - Increased levels of TNF-α suppress activity of lipoprotein lipase
- Elevated LDH
- Depressed fibrinogen
  - Increased levels of plasminogen activator secreted by activated macrophages
- Impaired NK-cell activity
- Elevated soluble IL-2 receptor (sCD25)
- Transaminitis

Recommendations for Management of CAR-Related HLH or MAS per CARTOX Working Group



Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

CAR T WORKING GROUP

Differential Diagnosis for ICANS

- Electrolyte abnormalities
- Infection/sepsis
- Cytotoxic drugs
- Anti seizure drugs
- Hepatic failure
- Delirium
- Progression of disease

Encephalopathy Assessment Tools for Grading of ICANS

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

Historical Grading Systems of Neurologic Toxicity

- CTCAE grading may not adequately quantify the acute neurologic deficits unique to CAR T therapies
- CARTOX Working Group has proposed the following grading scale for CAR-related encephalopathy syndrome (CRES):

Symptom / Sign	Grade 1	Grade 2	Grade 3	Grade 4
Neurological assessment score (see below)	Mild (7 - 9)	Moderate (3 - 6)	Severe (0 - 2)	Critical / obtunded
Raised intracranial pressure			Stage 1 or 2 papilledema[a]; or CSF opening pressure < 20 mm Hg	Stage 3, 4, or 5 papilledema; CSF opening pressure ≥ 20 mm Hg; or cerebral edema
Seizures or motor weakness			Partial seizure; non-convulsive seizures on EEG responding to benzodiazepine	Generalized seizures; convulsive or non-convulsive status epilepticus; new motor weakness
CARTOX 10-point neurological assessment (Assign 1 point for each task performed correctly; score of 10 = normal) • Orientation to year, month, city, hospital, president of the United States: 5 points • Name 3 objects (point to clock, pen, button): 3 points • Ability to write a standard sentence (eg, *Our national bird is the bald eagle*): 1 point • Count backwards from 100 by 10: 1 point				

Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care	Supportive care	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring
- Steroid dosing for neurotoxicity may vary between products
- Patients on steroids should receive appropriate fungal prophylaxis

MD Anderson. CAR cell therapy toxicity assessment and management. 2017. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

Slide credit: clinicaloption

Treatment CRS, ICANS

- Tocilizumab
- Steroids
- Anakinra
- Siltuximab
- Therapeutic LP

Tocilizumab/Steroid Use Did Not Impact Responses But Was Associated With Higher CAR T Cell Levels

	Tocilizumab			Steroids		
	Without n = 58	With n = 43	*P* Value	Without n = 74	With n = 27	*P* Value
ORR, n (%)	47 (81.0)	36 (83.7)	.8	62 (83.8)	21 (77.8)	.56
CR, n (%)	33 (56.9)	22 (51.2)	.69	40 (54.1)	15 (55.6)	1
Ongoing, n (%)	28 (48.3)	16 (37.2)	.31	33 (44.6)	11 (40.7)	.82
Median peak CAR levels, cells/µL (range)	26.52 (1.25-1226.36)	61.06 (0.84-1513.69)	.0011	32.2 (1.25-1226.36)	49.69 (0.84-1513.69)	.0618
Median CAR AUC, cells/µL days (range)	289.49 (16.82-14329.29)	743.85 (5.09-11506.59)	.0022	407.53 (16.82-14329.29)	724.98 (5.09-11506.59)	.0967

- Greater CAR T cell levels were observed in patients requiring AE management with tocilizumab and/or steroids
- This is consistent with reports showing CAR T cell expansion associated with grade ≥3 NE[1]

1. Locke FL, Neelapu S, et al. Blood. 2016;128:LBA-6.

Lugano 2017, slides courtesy of S. Neelapu

Question One

- 56 y/o F receiving pembrolizumab for metastatic non-small cell lung cancer presents with 1 week of lower abdominal pain and approximately 3 liters of diarrhea a day. The work up suggests an immune-related adverse events (irAEs) of colitis. Which of the following medications would be indicated at this time?

A. Methylprednisolone
B. Tocilizumab
C. Rituximab
D. Mesalamine

Question Two

- Which of the following should be suspected in a patient receiving Ipilimumab who presents with headache, profound systemic weakness, and polyuria?

A. Myasthenia Gravis
B. Nephrogenic diabetes insipidus
C. Pituitary Inflammation or Hypophysitis
D. Multiple sclerosis

Question Three

- A 55-year-old M with DLBCL s/p Axicabtagene ciloleucel 6 days ago. Today, he is aphasic, agitated, and delusional. His CARTOX-10 score = 2 (hospital, city). Unable to name objects or write a sentence. He received tocilizumab on day 2 for Grade 2 CRS (hypotension, Grade 3 transaminitis, high fevers), which is now resolved. Vitals: BP 125/73, HR 80, temp 99.1◦F. Which of the following is the best treatment for his neurologic toxicity?

A. 2nd dose Tocilizumab
B. Anakinra
C. Siltuximab
D. Dexamethasone

Citations

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- Kevin Michael Ohara PA
- Memorial Sloan Kettering Cancer Center
- Adjunct Professor, Pace University
- New York, New York
- oharak@mskcc.org