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Clinical Meeting & Exhibition

Unique Toxicity Profiles of BiTE and Experimental T-cell Therapies: Clinical Presentation and Management

Ali McBride, Pharm.D., M.S., BCPS, BCOP, FAzPA
Clinical Coordinator
The University of Arizona Cancer Center
Tucson, AZ

Brandon R. Shank, Pharm.D., M.P.H., BCOP, CPH
Clinical Pharmacy Specialist
University of Texas MD Anderson Cancer Center
Houston, TX

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Disclosure

Ali McBride

Pfizer: Advisory Board; Sandoz: Advisory Board

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Question #1

Which of the following biomarkers are associated with T cells?

A. CD20
B. CD3
C. CD147
D. CD19

Review of Immunology

Adaptive Immune Mechanisms

Humoral immune responses

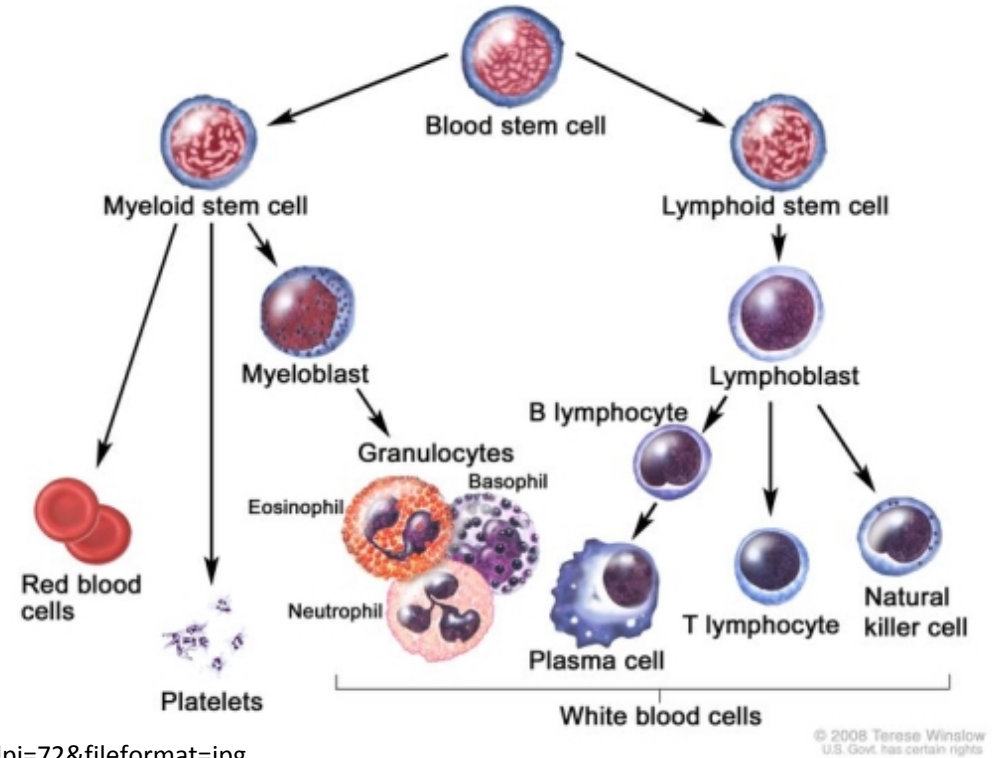
- B cells and antibodies

Cell mediated immune responses

- Cytotoxic T cell (Tc)
- Helper T cells (Th)

Origin of Cells of the Immune System

- Derived from common progenitor cell in bone marrow
  - Pluripotent hematopoietic s cell
- Progenitor stem cells
  - Erythroid lineage
  - Myeloid lineage
  - Lymphoid lineage



Available at: https://visualsonline.cancer.gov/retrieve.cfm?imageid=7177&dpi=72&fileformat=jpg

Cells of Innate and Adaptive Immunity

Innate Immunity

- "Large Lymphocytes"
  - Nonspecific
  - Natural Killer cells (CD16, CD56)

Adaptive Immunity

- "Small Lymphocytes"
  - Specific
  - B cells (CD19)
  - T cells (CD3, CD4 or CD8)

The Cluster of Differentiation (CD)

- Protocol for identification and investigation of cell surface molecules
- "CD number" assigned on basis of **1** cell surface molecule recognized by **2** specific monoclonal antibodies
- CD nomenclature established in 1982
  - 1st International Workshop and Conference on Human Leukocyte Differentiation Antigens (HLDA)

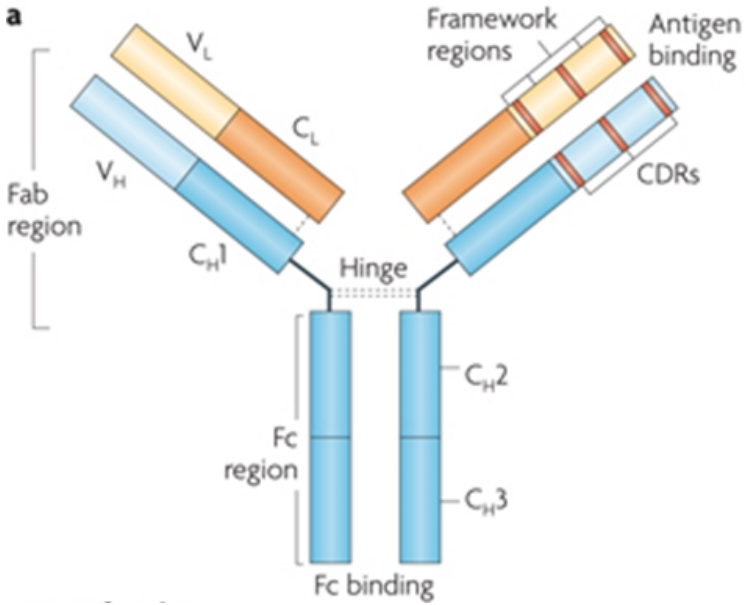
Bernard A, et al. *Human Immunology*. 1984;11:1-10.

The Cluster of Differentiation (CD)

Cell Type	CD Markers
Granulocyte	CD45+, CD15+
Monocyte	CD45+, CD14+
T lymphocyte	CD45+, CD3+
T cytotoxic lymphocyte	CD45+, CD3+, CD8+
B lymphocyte	CD45+, CD19+
Natural killer cell	CD45+, CD16+, CD56+, CD3-

Clark G, et al. *Clin Transl Immunology*. 2016;5:e57.

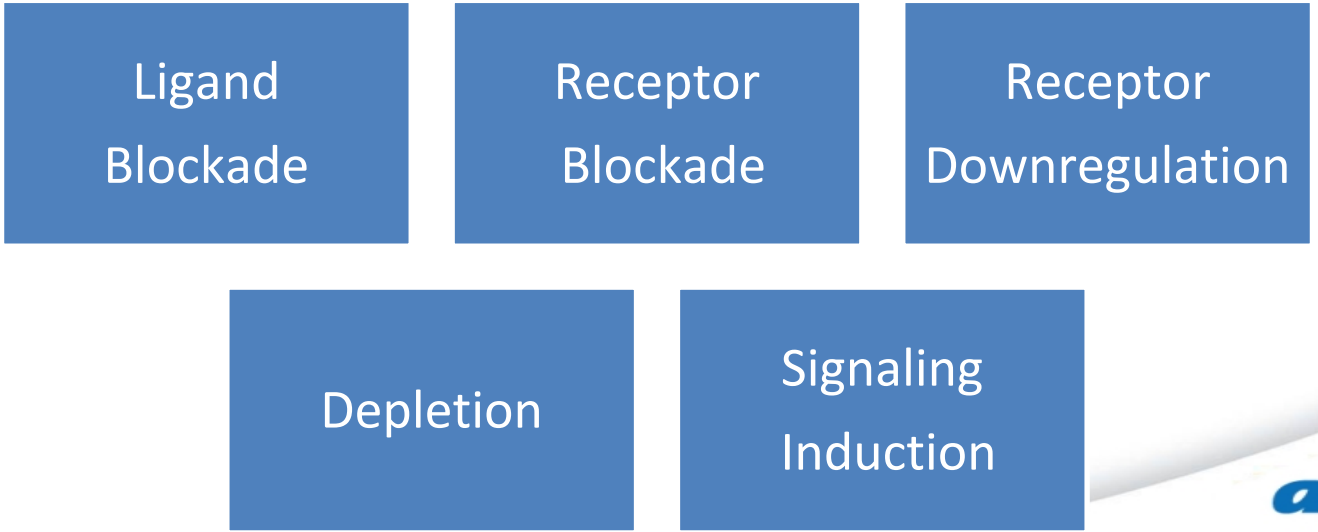
Structure of Antibody Molecules



Types of Monoclonal Antibodies (mAbs)		
Murine	Entirely murine amino acids	'o' = mouse e.g. muromonab
Chimeric	Human constant (C) + murine variable (V) regions	'xi' = chimeric e.g. rituximab
Humanized	Murine complimentary determining regions (CDRs)	'zu' = humanized e.g. alemtuzumab
Human	Entirely human amino acids	'u' = human e.g. adalimumab

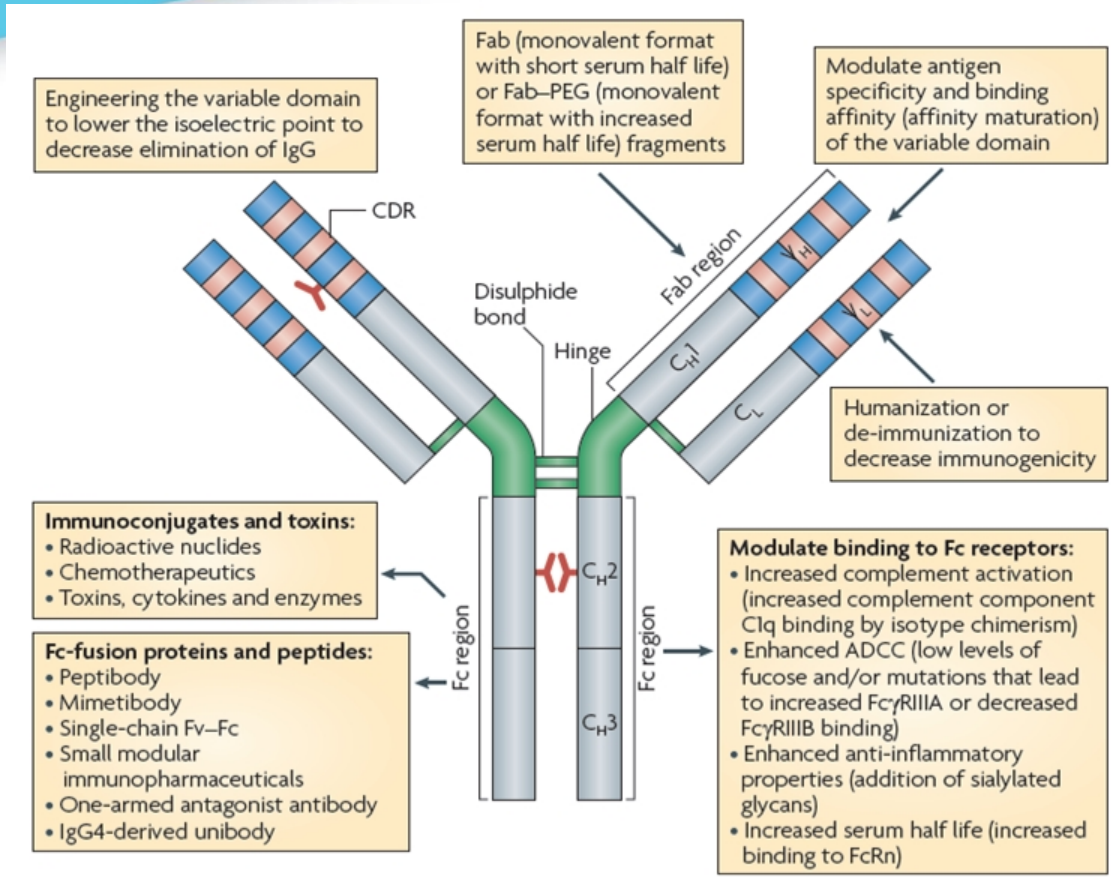
Hansel T, et al. Nat Rev Drug Discovery. 2010; 325-38.

Structure-Function Relationship of Antibody Molecules



Chan A, et al. *Nat Rev Immunology*. 2010;10:301-16.

Modification of Protein Structure to Enhance Function



Beck A, et al. *Nat Rev Immunology*. 2010;10:345-52.

Immuno-oncology in Practice

- Bring T cells and cancer cell targets into physical proximity
- Increase numbers of T cells capable of recognizing a tumor antigen
- Modulate T-cell activity once tumor-associated antigen is encountered
- Make tumors more attractive or accessible targets for cytotoxic T cells
- Disable the "brakes" or inhibitory signals limiting magnitude or duration of activity against neoplastic cells following T-cell activation

Speiser DE, et al. *Nat Rev Immunology*. 2016;16:599-611.

Cytotoxic T Cells

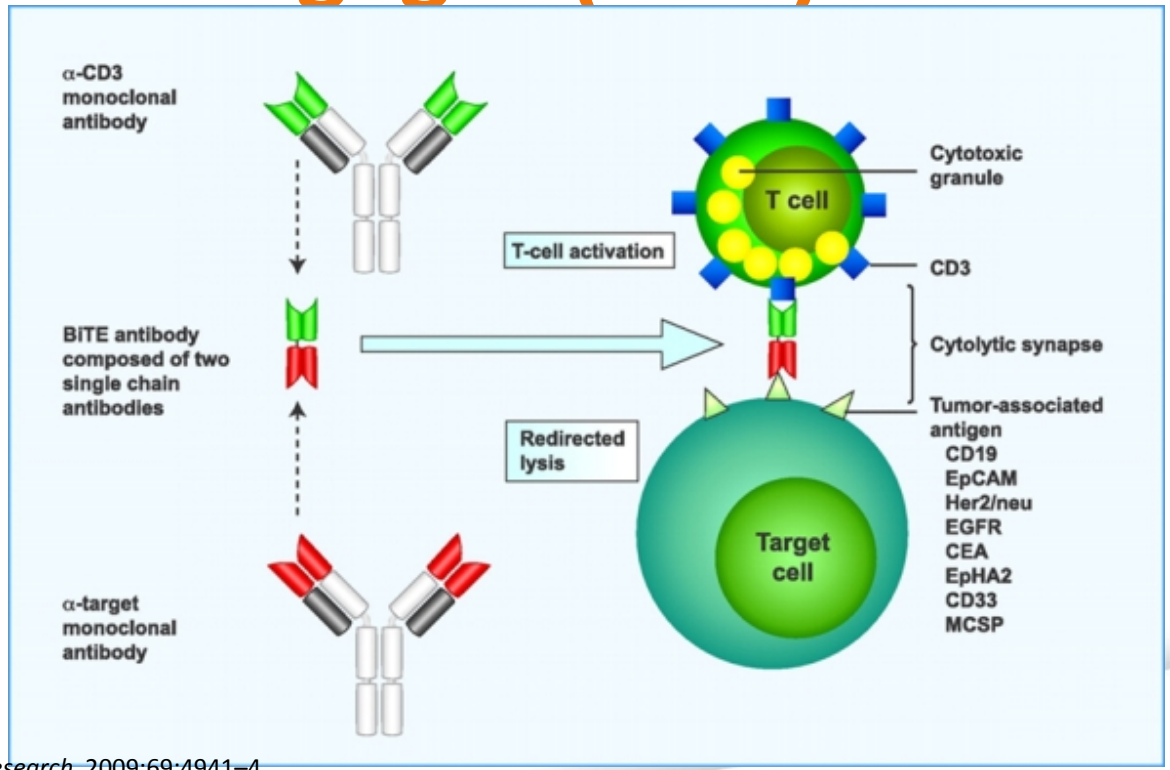
- T cells are a type of lymphocyte that play an active role in the immune response
- T cells recognize and eliminate foreign or abnormal cells, including cancer cells
- Cancer cells have mechanisms to evade T cell recognition

Martinez-Lostao L, et al. *Clin Cancer Res*. 2015;21:5047–56.

Bispecific T cell Engager (BiTE) Antibodies

- BiTE antibodies form a link between T cells and tumor cells
- Causes T cells to exert cytotoxic activity on tumor cells, independently of the presence of MHC I or co-stimulatory molecules, initiating apoptosis
- Mimics physiological processes observed during T cell attacks against tumor cells

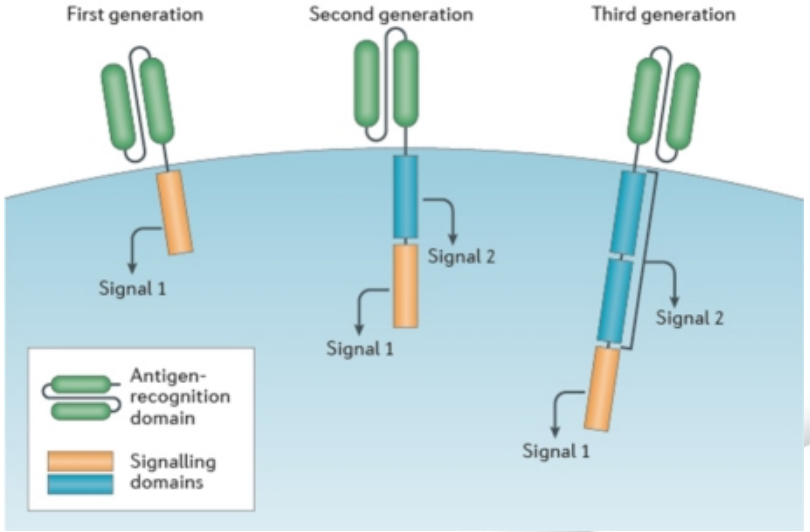
Bispecific T cell Engager (BiTE) Antibodies



Baeuerle PA, et al. *Cancer Research*. 2009;69:4941–4.

CAR-T Cell Therapies

- Engineered expression of chimeric antigen receptors (CARs) on the surface of T cells
- Enables the redirection of T cell specificity



Brentjens R, et al. *Nat Rev Clin Oncol*. 2016;13:370–83.

CAR-T Cell Therapies

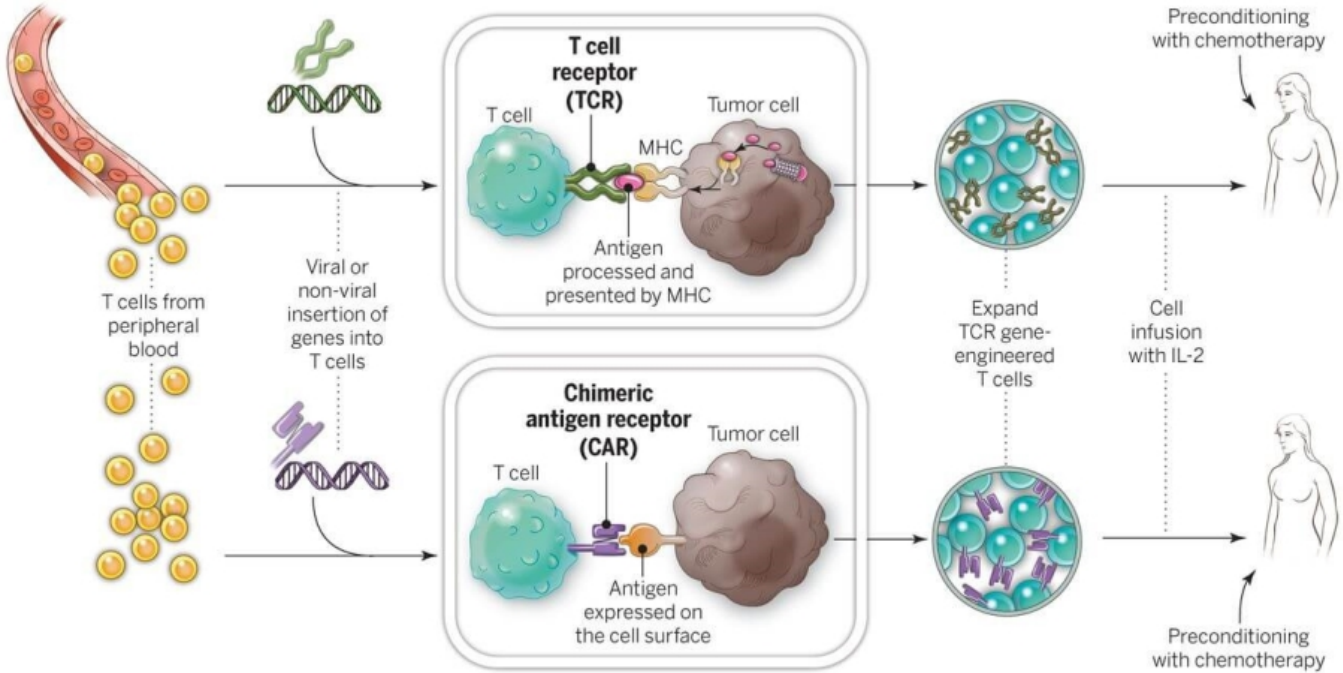


Image available at: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells[Accessed 8/23/17]

Safety and Efficacy of BiTE Antibodies for Hematologic Malignancies

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Question #2

Which of the following adverse effects are not associated with blinatumomab?

A. Cytokine Release Syndrome
B. Hepatotoxicity
C. Seizures
D. Alopecia

Review:
Acute Lymphoblastic Leukemia (ALL)

- ALL can arise from both T cell and B cell precursors
- B cell ALL is more common (~88% of all cases)
- 95% of B precursor leukemic blasts express the surface antigen CD19
- CD19 is a promising target for immunotherapy

SEER Cancer Stat Facts: Acute Lymphocytic Leukemia. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/alyl.html

Blinatumomab

- Bispecific T cell engager (BiTE) antibody with dual specificity for CD19 and CD3
- CD19 is a highly specific B-cell marker expressed throughout B-cell development and in >90% of B cell lineage cancers
- <u>FDA Approvals:</u>
  - 2017: Treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children
  - 2014: Treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL

Dinner S, et al. Leuk Lymphoma. 2011;52;1098-1107. Information available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm566708.htm

Blinatumomab Mechanism of Action

- Simultaneously binds CD3 positive cytotoxic T cells and CD19 positive B cells, resulting in T cell mediated lysis of normal and malignant B cells
- Engages patients' endogenous T cells to attack and eradicates B precursor leukemic blasts

Blinatumomab for Relapsed/Refractoy B Cell Precursor, Ph-Negative ALL

Patients

N = 189

18 years or older, refractory after induction, or relapsed within 12 months of CR1 or HCT or r/r after salvage therapy

Study Design

Multi-center, single arm, open label, phase II

Primary endpoint:

CR and CRh within the first 2 cycles

Intervention

Blinatumomab via continuous intravenous infusion

9 µg/day for 1 week, then

28 µg/day to 4 weeks,

then 2 weeks off; up to 5 cycles

ALL, acute lymphoblastic leukemia;; CR, complete remission; CR1, first CR; CRh, CR with partial hematologic recovery of peripheral blood counts; HCT, hematopoietic stem cell transplantation; Ph, Philadelphia chromosome

Topp MS, et al. Lancet Oncol. 2015;16:57-66

Blinatumomab in R/R ALL: Efficacy

Outcome	All Patients (N = 189)
CR or CRh in first 2 cycles, %	43
CR in first 2 cycles, %	33
MRD negativity in first 2 cycles, %*	82
Median OS, mos ▪ All patients ▪ MRD-negative CR ▪ MRD-positive CR	 6.1 11.5 6.7
Median RFS, mos ▪ CR + CRh ▪ CR ▪ CRh	 5.9 6.9 5.0
Allogeneic HCT, %* ▪ After CR ▪ After CRh	40 44 22
100-day mortality after allogeneic HCT, %	11

ALL, acute lymphoblastic leukemia; CR, complete remission; CRh, CR with partial hematologic recovery of peripheral blood counts; HCT, hematopoietic cell transplant; MRD, minimal residual disease; OS, overall survival; RFS, relapse-free survival.

Topp MS, et al. *Lancet Oncol*. 2015;16:57-66.

Blinatumomab: Safety

Adverse Reaction	Topp et al [1]	Topp et al [2,3]
Leukopenia	2 (9.5%)	15 (7.9%)
Neutropenia	1 (4.8%)	30 (15.8%)
Thrombopenia	1 (4.8%)	16 (8.4%)
Bacterial sepsis	1 (4.8%)	15 (7.9%)
Bronchopneumonia	1 (4.8%)	17 (8.9%)
Syncope/convulsion	1 (4.8%)	2 (1%)
Encephalopathy	ND	6 (3.1%)
Somnolence	1 (4.8%)	1 (<1%)
Hypokalemia	1 (4.8%)	13 (6.8%)
Hypophosphatemia	ND	10 (5.2%)

1. Topp et al. *J Clin Oncol*. 2011;29:2493-98; 2. Topp et al. *J Clin Oncol*. 2014;32:4134-40; 3. Topp et al. *Lancet Oncol*. 2015;16:57–66

Blinatumomab: Adverse Effects

- Cytokine release syndrome
- Infections
- Neurological toxicities
- Tumor lysis syndrome
- Neutropenia
- Elevated liver enzymes

Cytokine Release Syndrome (CRS)

- Potentially serious complication of non-physiological T cell activation
- Produced by T cell engaging therapies such as bispecific T cell engaging antibodies and chimeric antigen receptor-engineered T cells
- May be caused by abnormal activation of macrophages

Cytokine Release Syndrome

- Occurs during the first cycle of treatment with blinatumomab
- Toxicities: CRS, disseminated intravascular coagulation, and central nervous system events (seizure or encephalopathy)
- Lowering the initial dose of blinatumomab to 5µg/m^2/day and the addition of dexamethasone has been shown to reduce the toxicity of the agent

Klinger M, et al. *Blood*. 2012;119:6226-33.
Topp MS, et al. *J Clin Oncol*. 2011;29:2493-98.

Cytokine Release Syndrome Biomarkers

C-Reactive Protein (CRP)

- Acute phase reactant that is synthesized by the liver in response to elevated IL-6
- CRP level of ≥ 200mg/L is linked to CRS with good sensitivity and specificity

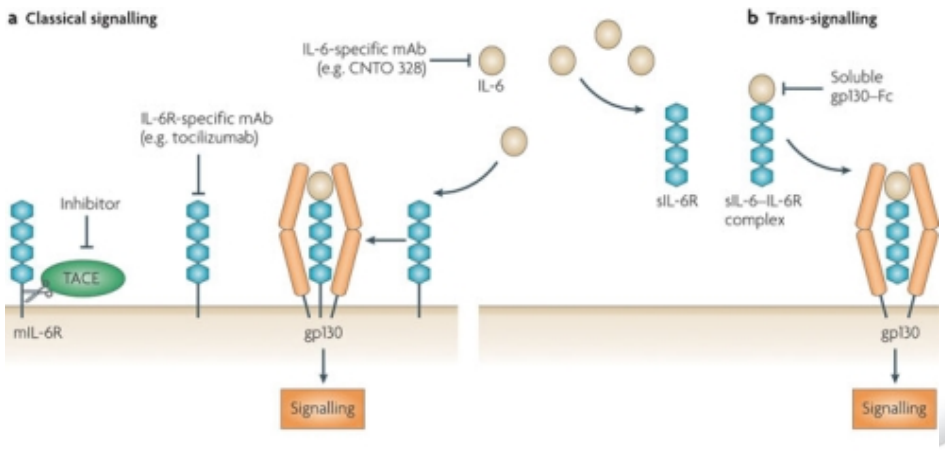
Interleukin-6 (IL-6)

- Rising level of IL-6 is a strong predictor of CRS
- Changes in IL-6 level precede elevation of CRP

Klinger M, et al. *Blood*. 2012;119:6226-33.
Topp MS, et al. *J Clin Oncol*. 2011;29:2493-98.

Tocilizumab

- Humanized monoclonal antibody against IL-6 receptors
- IL-6 blockade with tocilizumab demonstrated rapid reversal of life-threatening symptoms
- First choice therapy for CRS



Kopf M, et al. *Nat Rev Drug Discovery*. 2010;9:703-18.

Blinatumomab: Toxicity Management

Toxicity	Grade	Action
CRS	3	Withhold until resolved, then restart at 9 mcg/day. Escalate to 28 mcg/day after 7 days if toxicity does not reoccur.
	4	Discontinue permanently
Neurologic Toxicity	3	Withhold until resolved to less than Grade 1 for 3 days, then restart at 9 mcg/day. Escalate to 28 mcg/day after 7 days if toxicity does not reoccur. If longer than 14 days to resolve, discontinue permanently.
	4	Discontinue permanently
	Seizure	If more than one seizure, discontinue permanently.
Others	3	Withhold until resolved to less than Grade 1 for 3 days, then restart at 9 mcg/day. Escalate to 28 mcg/day after 7 days if toxicity does not reoccur. If longer than 14 days to resolve, discontinue permanently.
	4	Consider discontinuing permanently

Klinger M, et al. *Blood.* 2012;119:6226-33.
Topp MS, et al. *J Clin Oncol*. 2011;29:2493-98.

Key Takeaways

- Immuno-Oncology is changing the current landscape of cancer therapies
- Toxicity of emerging immunotherapy agents is manageable and usually reversible, but can be severe
- Numerous considerations and precautions for monitoring of cytokine release syndrome should be implemented

Safety and Efficacy of CAR-T cells for Hematologic Malignancies

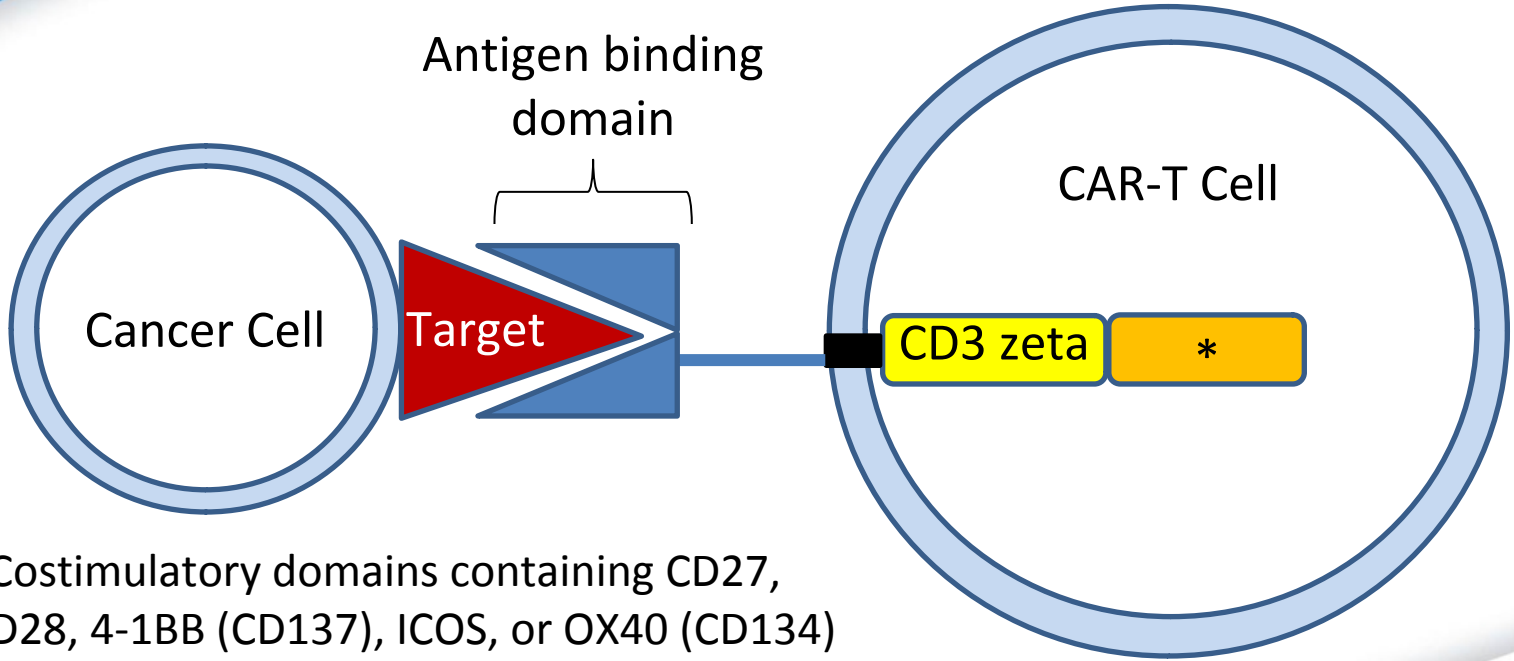
Chimeric Antigen Receptor (CAR)-T Cells

- Genetically programed to bind to transmembrane glycoproteins
- Major histocompatibility complex independent action
- Targets
  - Limited off target effects
  - Specific to certain types of cancer
- Tisagenlecleucel- 1st FDA approved product

Targets Under Development
CD19
CD20
CD33
B-cell maturation antigen (BCMA)

FDA. New Drug Approvals. Available at www.fda.gov. Accessed 9/29/17.
Kebriaei, et al. *Hum Gene Ther*. 2012;5:444-50.

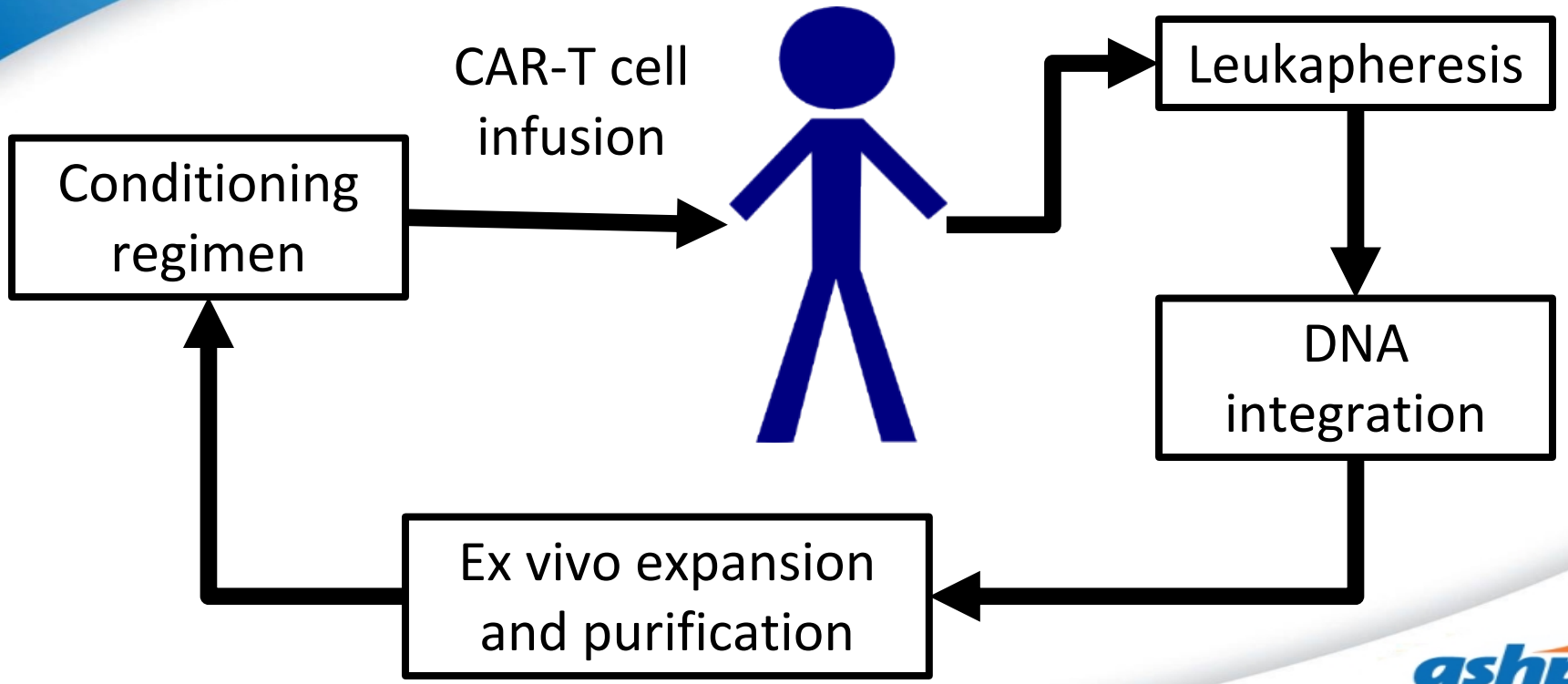
CAR-T Cell Structure



*Costimulatory domains containing CD27, CD28, 4-1BB (CD137), ICOS, or OX40 (CD134)

Jackson, et al. *Nat Rev Clin Oncol.* 2016;13:370-83.

CAR-T Cell Production



Barrett, et al. *Annu Rev Med*. 2014;65:333-47.

Conditioning Regimen

- Depletion of leukocytes that may interfere with adoptive T cell activity
- Decrease in regulatory T-cells
  - Increased levels of interleukin (IL)-15 and IL-17
- Tumor debulking- less disease leads to greater persistence of CAR- T cells
- Anti-programmed cell death protein (PD-1) immune checkpoint inhibitor use after CAR-T cell infusion
  - Enhances CAR-T cell expansion, function, and persistence
- Medications
  - Cyclophosphamide
  - Fludarabine

Brentjens, et al. *Blood.* 2011;118:4817-28.
Maude, et al. *J Clin Oncol.* 2017;35:103.

Role of Fludarabine

- Greater CAR-T cell expansion and persistence with fludarabine
  - Fludarabine- reduces reaction to murine single-chain variable fragment on an antibody
  - B-cell acute lymphoblastic leukemia (ALL)- improved disease-free survival
  - Non-hodgkin's lymphoma- improved progression-free and overall survival
- Juno's ROCKET phase 2 trial (JCAR015)
  - CAR-T-cell-related encephalopathy syndrome (CRES)- 3 deaths from cerebral edema

Turtle, et al. *J Clin Oncol.* 2016;34:102.
Shank, et al. *Pharmacotherapy*. 2017;37:334-45.

Efficacy and Safety: B Cell ALL

CAR-T Cells (Institution)	Product	No.	Efficacy	Safety
CTL019 (CHOP)	Anti-CD19 CD3 zeta, 4-1BB	63 Children	CR 83%	Cytokine release syndrome (CRS) Grade ≥3 47%
19-28Z CAR (MSKCC)	Anti-CD19 CD3 zeta, CD28	51 Adults	CR 84%	Not reported
$CD4^+$:$CD8^+$ (FHCRC)	Anti-CD19 CD3-zeta, CD137, and EGFRt	36 Adults	CR 94%	Reported in aggregate with other B-cell malignancies

Buechner, et al. *Clin Lymphoma Myeloma Leuk*. 2017;17:S263-64.
Park, et al. *J Clin Oncol.* 2017;35:7008.
Turtle, et al. *J Clin Oncol.* 2016;34:102.

Efficacy and Safety: B Cell Lymphoma (BCL)

Study (Manufacture)	Product	No.	Efficacy	Safety
Axicabtagene ciloleucel (ZUMA1, KITE)	Anti-CD19 CD3 zeta, CD28	101	CR 54%	CRS Grade ≥3 13% Febrile neutropenia 31% 3 deaths
CTL019 (JULIET, Novartis)	Anti-CD19 CD3 zeta, 4-1BB	85	CR 43%	CRS 57% 3 deaths*
JCAR017 (TRANSCEND, Juno)	Anti-CD19 CD3 zeta, 4-1BB	28	CR 60%	CRS Grade 1-2 36% 4 deaths*

*Disease progression not attributed to therapy

Neelapu, et al. *Hematol Oncol.* 2017;35:28.
Schuster, et al. *Hematol Oncol.* 2017;35:27.
Abramson, et al. *Hematol Oncol.* 2017;35:138.

Patient Case

- JW is a 40 year old male with past medical history of stage IV refractory B cell lymphoma, hypertension, and seasonal allergies with no known drug allergies.
- Past treatment:
  - R-CHOP x 6 cycles
  - R-ICE x 3 cycles
  - Autologous stem cell transplantation

Home medications	Labs
Loratadine 10 mg PO daily	WBC 3,000/mm3
Lisinopril 20 mg PO daily	ANC 1,500/mm3
Multivitamin 1 tablet PO daily	Hgb 10.1 g/dL
Hydrochlorothiazide 12.5 mg PO daily	Platelets 150,000/mm3

Question #3

The treatment team wants to initiate anti-CD19 CAR-T cell treatment for JW. What would you inform him about CAR-T cell therapy?

A. Complete response rates are similar to conventional chemotherapy
B. Conditioning chemotherapy enhances CAR-T cell expansion and persistence
C. Cytokine release syndrome is a rare complication of CAR-T cell therapy
D. Deaths from toxicities was greater than disease progression in clinical trials

Efficacy and Safety: Chronic Lymphocytic Leukemia (CLL)

Study (Institution)	Product	No.	Efficacy	Safety
CTL019 (UPenn)	Anti-CD19 CD3 zeta, 4-1BB	35	CR 23%	CRS any Grade 54%, Grade ≥3 20%
$CD4^+$:$CD8^+$ (FHCRC)	Anti-CD19 CD3-zeta, CD137, and EGFRt	13	CR 50%	Reported in aggregate with other B-cell malignancies

Porter, et al. *J Clin Oncol.* 2016;34:3009.
Turtle, et al. *J Clin Oncol.* 2016;34:102.

Efficacy and Safety: Multiple Myeloma

Study (Manufacture/ Institution)	Product	No.	Efficacy	Safety
Bb2121 (CRB-401, Bluebird Bio)	Anti-BCMA CD3 zeta, 4-1BB	11	CR 50%*	CRS Grade 1-2 73%
CTL019	Anti-CD19 CD3-zeta and 4-1B	10	PFS 60%	CRS Grade 1 10%
LCAR-B38M (Nanjing Legend Biotech)	Anti-BCMA Domains not reported	35	CR 94%	CRS Grade 1-4 85% Grade ≥3 6%

* Of evaluable pts

Berdeja, et al. *J Clin Oncol.* 2017;35:3010.
Garfall, et al. *NEJM*. 2015;373:1040-7.
Fan, et al. *J Clin Oncol.* 2017;35:LBA3001.

Key Takeaways

- Studies are showing promising results in heavily pretreated patients
- More studies are needed to determine the optimal:
  - CAR-T cell dose
  - Target
  - Co-stimulatory domain
  - Conditioning regimen

Presentation and Management of CAR-T cell Toxicities

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Immunotherapy Toxicity

- Cytokine-associated toxicity
  - CRS and CRES
  - Non-antigen specific
  - High-level of immune activation
- Autoimmune toxicity
  - Antigen-specific attack of host tissue
  - On target, off-tumor toxicity
  - Antigen expression on non-malignant tissue

Lee, et al. *Blood.* 2014;124:188-95.

CAR-T Cell Toxicities

- Rates vary across studies
  - Different products
  - Cell dose
  - Disease state
  - Patient population
- Onset varies with product

Toxicity (Grade ≥3)	Rate
Neutropenia	66%
Leukopenia	44%
Anemia	43%
Febrile neutropenia	31%
Neurologic	28%
Encephalopathy	21%
CRS	13%

Neelapu, et al. *Hematol Oncol.* 2017;35:28.

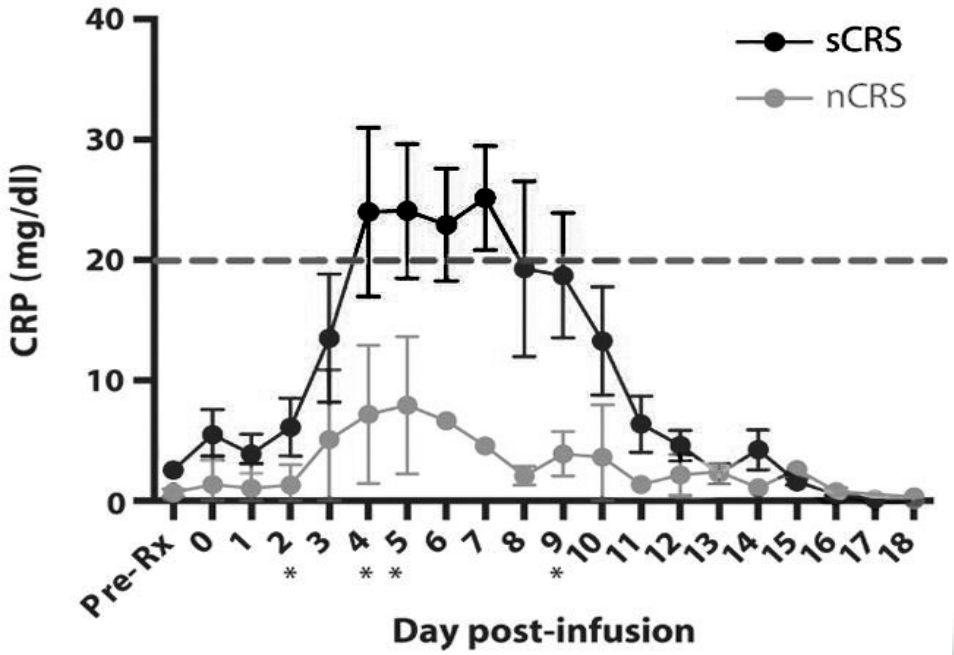
Pathophysiology of CRS/CRES

- Excretion of endogenous cytokines
- Cell dose: response relationship and onset dependent on specific product
- Risk factors
  - Large tumor burden
  - Early onset CRS
  - Multiple co-morbidities
  - Older age
  - Elevated C reactive protein (CRP) prior to CAR-T cell infusion

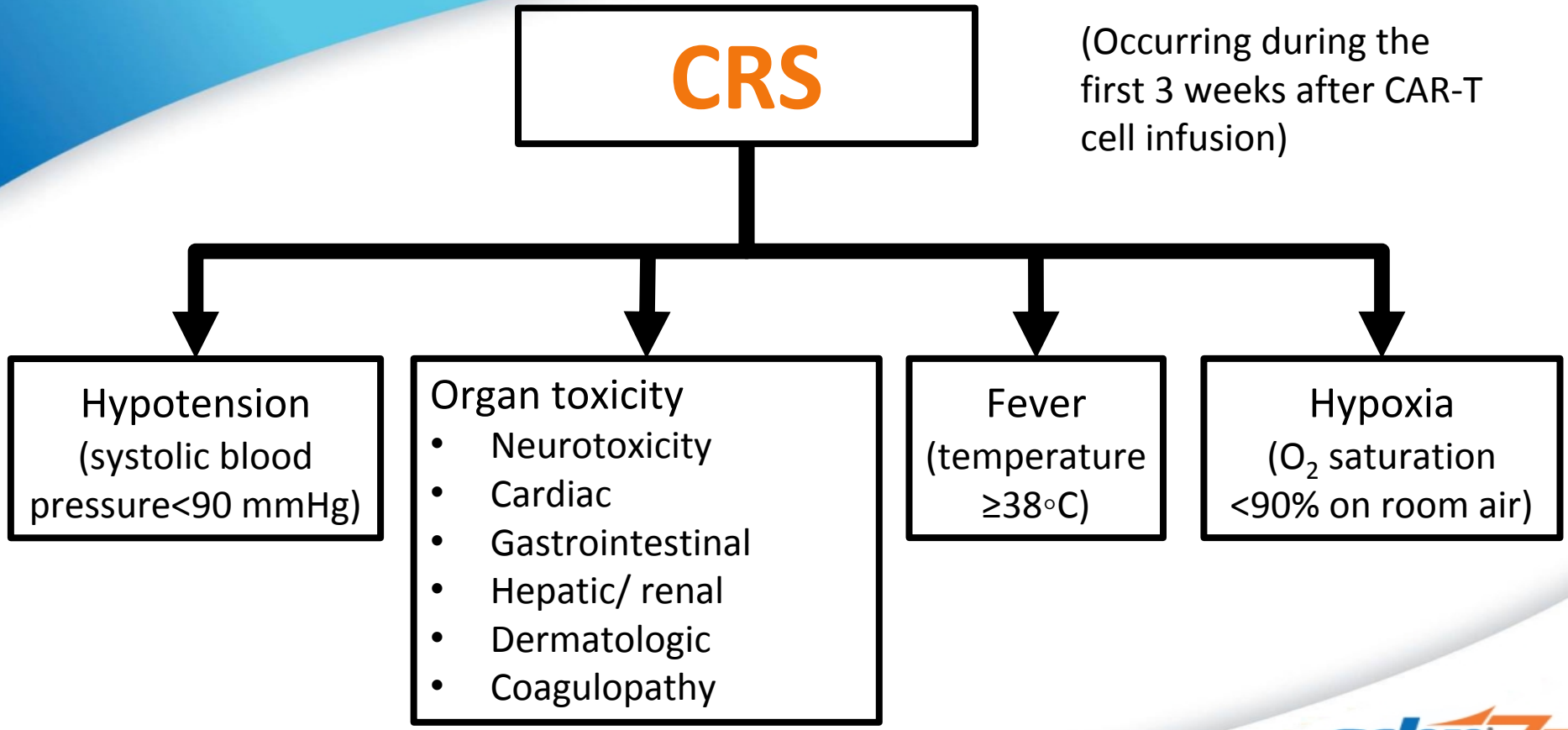
Cytokine Elevations	
TNF alpha	IL-6
IFN gamma	IL-8
IL-1 beta	IL-10
IL-2	IL-15

Lee, et al. *Blood.* 2014;124:188-95.

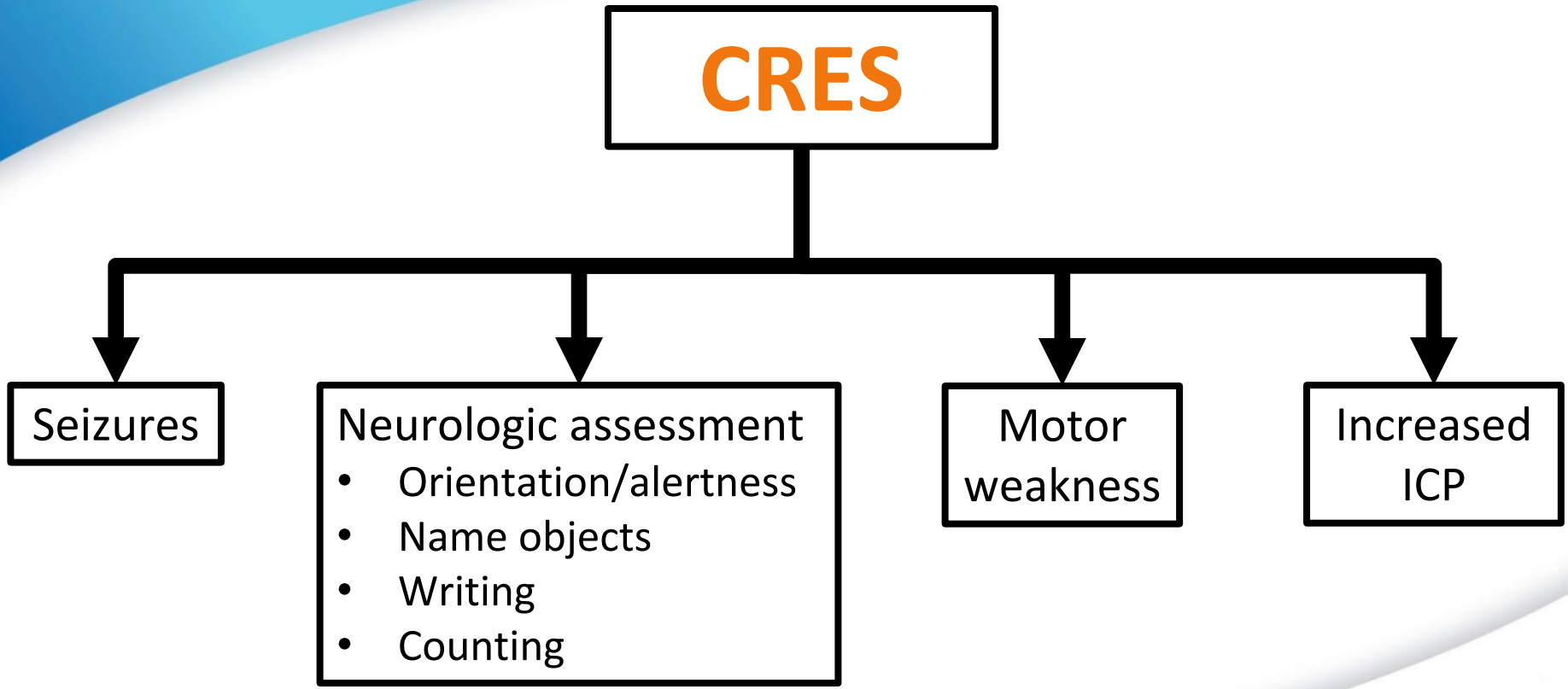
CRS and CRP



From Davila, et al. *Sci Transl Med.* 2014;224:224ra25.
Reprinted with permission from AAAS.



Lee, et al. *Blood.* 2014;124:188-95.



Neelapu, et al. *Nat Rev Clin Oncol*. Forthcoming 2017.

Grading of CRS/CRES

CRS/CRES Grade	Criteria	Management
1	Non-life threatening symptoms requiring symptomatic treatment • Constitutional symptoms	• Fever- supportive care acetaminophen +/- hypothermia blanket • Assess and treat infection(s)/seizures • Consider tocilizumab or siltuximab for refractory fevers

Neelapu, et al. *Nat Rev Clin Oncol*. Forthcoming 2017.

Grading of CRS/CRES

CRS/CRES Grade	Criteria	Management
2	Symptoms require and respond to moderate intervention • Oxygen requirement < 40% • Hypotension responsive to fluids or low dose vasopressor • Grade 2 organ toxicity	• Manage similar to grade 1 • Monitor for cardiac and other organ dysfunction • Fluid bolus, may repeat if SBP less than 90 mmHg • +/- *tocilizumab/ siltuximab, *dexamethasone • Supplemental oxygen

*High-risk patients/CRES

Neelapu, et al. *Nat Rev Clin Oncol*. Forthcoming 2017.

Grading of CRS/CRES

CRS/CRES Grade	Criteria	Management
3	Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40% • Hypotension requiring high-dose or multiple vasopressors • Grade 3 organ toxicity or Grade 4 elevation in AST/ALT	• Manage similar to grade 2 • ICU transfer • Supplemental oxygen, non-invasive positive pressure ventilation • Consider tocilizumab/ siltuximab +/- dexamethasone
4	Life-threatening symptoms – • Ventilator support • Grade 4 organ toxicity (excluding elevation in AST/ALT)	• Manage similar to grade 3 • High-dose corticosteroids

Neelapu, et al. *Nat Rev Clin Oncol*. Forthcoming 2017.

Treatment of CRS/CRES

Drug Class	Dose
IL-6 receptor antagonist	Tocilizumab 8 mg/kg (maximum 800 mg/dose) IV - Dose may be repeated Siltuximab 11 mg/kg IV x 1 dose
Corticosteroids	Dexamethasone 10-20 mg IV every 6 hours Methylprednisolone 1 g/day IV followed by a rapid taper (severe grade 4 toxicity)

Shank, et al. *Pharmacotherapy.* 2017;37:334-45.
Lee, et al. *Blood.* 2014;124:188-95.

Patient Case

- JW is a 40 year old male with past medical history of stage IV refractory B cell lymphoma, hypertension, and seasonal allergies with no known drug allergies.
- He is day +4 of anti-CD19 CAR- T cells he developed:
  - Fever (temp 39°C)
  - Headache
  - Hypotension (SBP 84 mmHg).
- The team ordered blood cultures, x-ray, and 500 mL IV NS bolus. SBP improved to 88 mmHg, temp 38.8 °C, and A&O x 3.

Current Scheduled Medications	Labs
Keppra 750 mg PO every 12 hours	WBC 700/mm3
Filgrastim 480 mcg SubQ daily	ANC 300/mm3
Cefepime 2 g IV every 8 hours	Hgb 7.9 g/dL
Vancomycin 1.5 g IV every 12 hours	Platelets 25,000/mm3

Question #4

What interventions are appropriate for JW at this time?

A. Repeat fluid bolus, acetaminophen, and neurology consult
B. Repeat fluid bolus, cooling blanket, and acetaminophen
C. Tocilizumab 8 mg/kg, repeat fluid bolus, and acetaminophen
D. Dexamethasone 10 mg IV q6h and acetaminophen

Other CRS Related Organ Toxicity

- Cardiac - tachycardia, arrhythmias, heart block, heart failure
- Respiratory - tachypnea, pulmonary edema, pleural effusions
- Gastrointestinal - nausea, vomiting, diarrhea
- Hepatic - increase in AST/ALT or bilirubin
- Renal - decreased urine output, increased serum creatinine
- Coagulopathy - disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis
- Dermatologic - rash

Lee, et al. *Blood.* 2014;124:188-95.

Short-term Adverse Effects

- Infusion reactions - pre-medicate
- Tumor lysis syndrome - allopurinol
- Hematologic
  - Neutropenia - neupogen
  - Thrombocytopenia - platelet transfusions
  - Anemia - red blood cell transfusions
- Fever - cultures and antibiotics
- Headache
- Nausea and vomiting

Shank, et al. *Pharmacotherapy.* 2017;37:334-45.
Lee, et al. *Blood.* 2014;124:188-95.

Intermediate to Long-term Adverse Effects

- Monitor for infections
- Hypogammaglobulinemia
  - Monitor IgG levels and give IVIG for low IgG levels
- Hematologic toxicities

Shank, et al. *Pharmacotherapy.* 2017;37:334-45.
Lee, et al. *Blood.* 2014;124:188-95.

Interventions

- Avoid medications causing central nervous system depression
- Assess for drug interactions or excluded medications
  - Avoid corticosteroids as pre-medications for transfusions
  - Avoid non-steroidal anti-inflammatory medications NAIDS
- Prophylaxis
  - Varicella-zoster virus- continue acyclovir or valacyclovir for 1 year
  - Seizure
  - Pneumocystis pneumonia
  - Stress ulcer

Shank, et al. *Pharmacotherapy.* 2017;37:334-45.

Key Takeaways

- CAR-T cell toxicities have a unique presentation compared to traditional chemotherapy
- Training on the recognition, treatment, and monitoring of CRS/CRES is essential to decrease treatment related morbidity and mortality
- Interdisciplinary teams are necessary to optimally care for patients undergoing CAR-T cell therapy