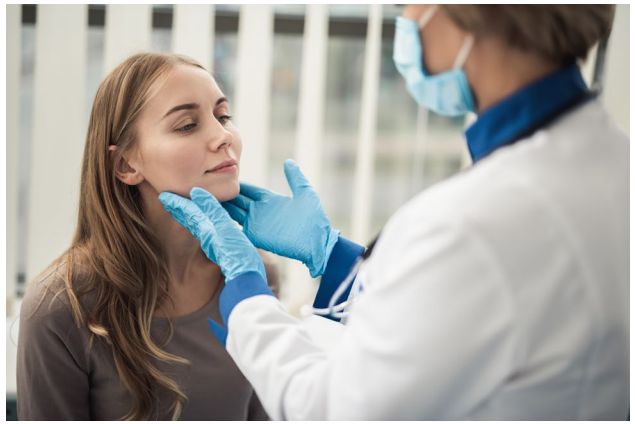
BMTinfonet.org
30 YEARS
EMPOWERING PATIENTS
BLOOD & MARROW TRANSPLANT INFORMATION NETWORK

CAR T-cells in Non-Hodgkin Lymphoma,

A Hopeful Option

Presented by Blood & Marrow Transplant Information Network
BMTInfoNet.org

Thursday, January 13, 2022



Many thanks to Kite, a Gilead Company, for its support of this webinar.

BMTinfonet.org
30 YEARS
EMPOWERING PATIENTS
BLOOD & MARROW TRANSPLANT INFORMATION NETWORK

Meet The Speaker

Gary Simmons, DO

Dr. Gary Simmons is a hematologist-oncologist specializing in stem cell transplantation and cellular immunotherapies for the treatment of blood cancers, including various forms of leukemia, myeloma and lymphoma.

He serves as Medical Director of the Ambulatory Clinics and leads the Disease Working Group in Cellular Immunotherapies and Transplantation at Virginia Commonweath University in Richmond, VA.

CAR T-cells in Non-Hodgkin Lymphoma, A Hopeful Option

Gary L. Simmons, DO

Assistant Professor

Medical Director, Ambulatory Clinics Cellular Immunotherapy and Transplantation

Leader of Disease Working group in Cellular Immunotherapy and Transplantation

Virginia Commonwealth University, Richmond Virginia

MASSEY CANCER CENTER VCU

Disclosures

Speaker's bureau Kite/Gilead

ASH Advisory Board Kite

Consultant for Jazz Pharmaceuticals

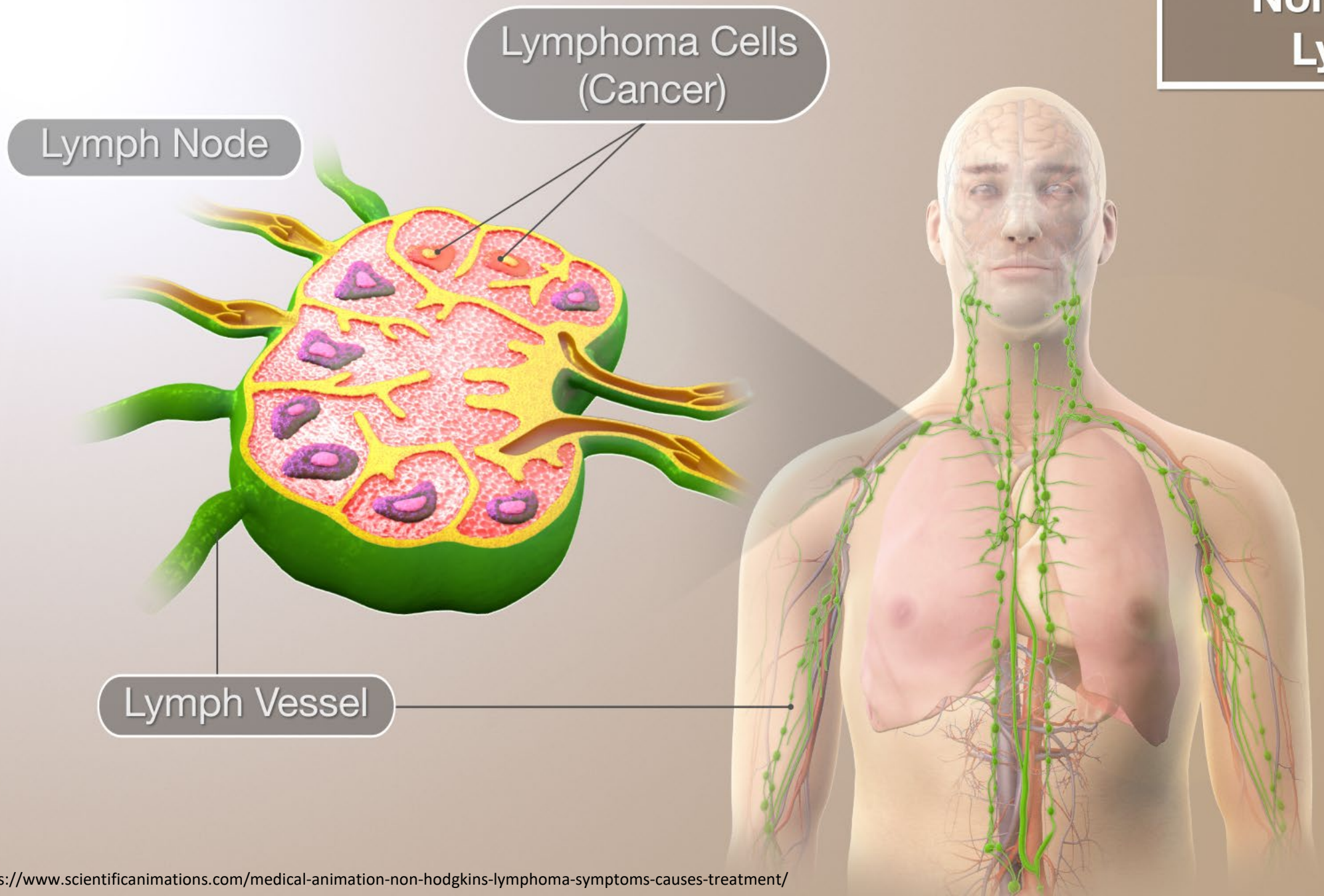
MASSEY CANCER CENTER VCU

Learning Objectives

Review	Non-Hodgkin Lymphoma
Explain	The History of Immuno-oncology and the need for CAR T
Review	FDA indications in Non-Hodgkin lymphoma
Describe	Differences between stem cell transplant and CAR T cells
Review	Review the treatment of CAR T: Both the success and toxicities here at VCU
Look	Look at the future in immunotherapy

MASSEY CANCER CENTER VCU

Non-Hodgkin's Lymphoma



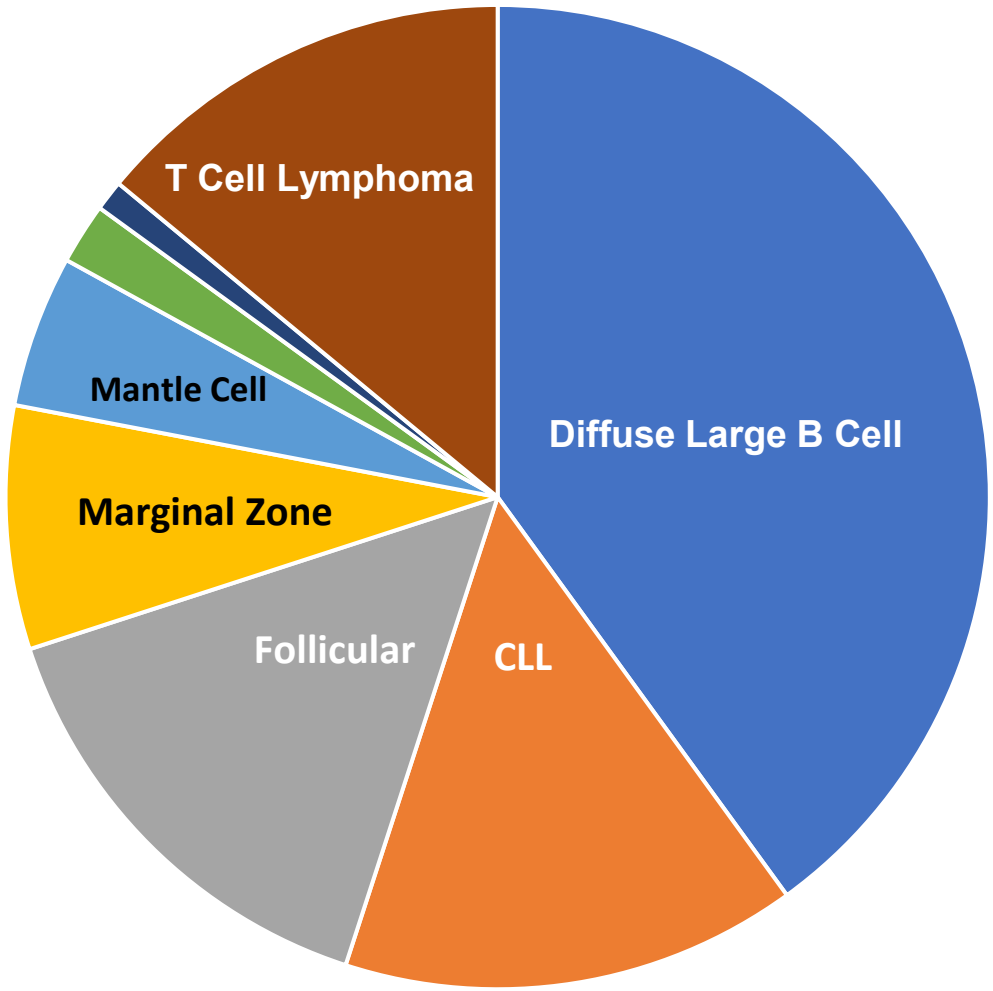
https://www.scientificanimations.com/medical-animation-non-hodgkins-lymphoma-symptoms-causes-treatment/

MASSEY CANCER CENTER VCU

Epidemiology

- NHL is most common hematologic malignancy in US[1]
  - 77,240 case per year
  - 19,940 deaths in 2020

- Diffuse large B Cell lymphoma is most common subset of NHL[2]



1. SEER database. http://seer.cancer.gov
2. Hamadani AM et al. Am J Hematol. 2015

MASSEY CANCER CENTER VCU

Front Line Treatments in NHL

Diffuse Large B Cell

- Chemo First Line

Follicular

- Watch and Wait
- Chemo-Immunotherapy
- Radiation

Mantle Cell

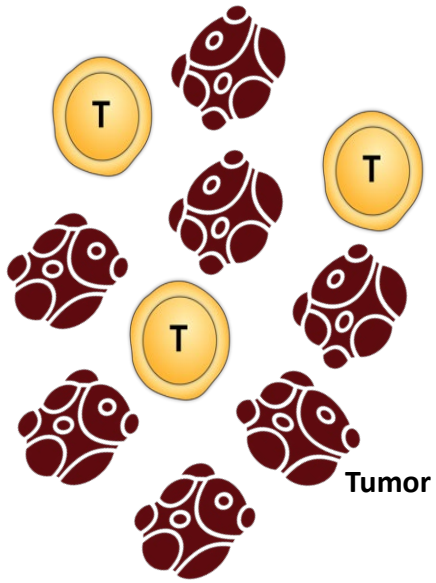
- Chemotherapy
- Autologous Stem Cell Transplant
- Maintenance

MASSEY CANCER CENTER VCU

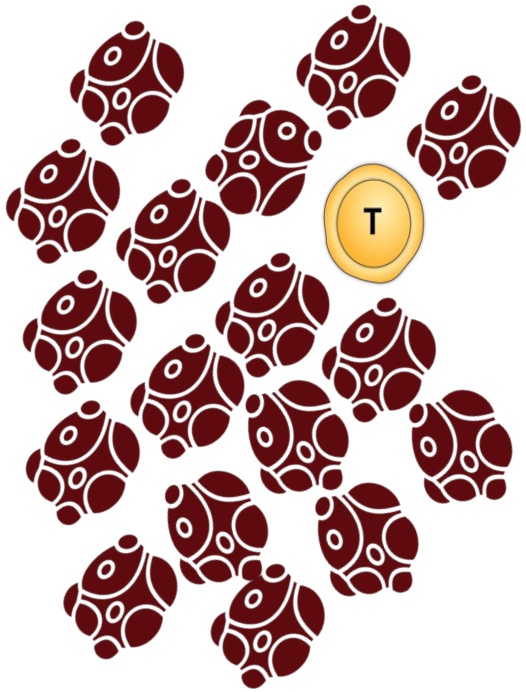
Relapse & Mechanisms of Tumor Evasion

The immune system is unable to eradicate or control cancer cells when:

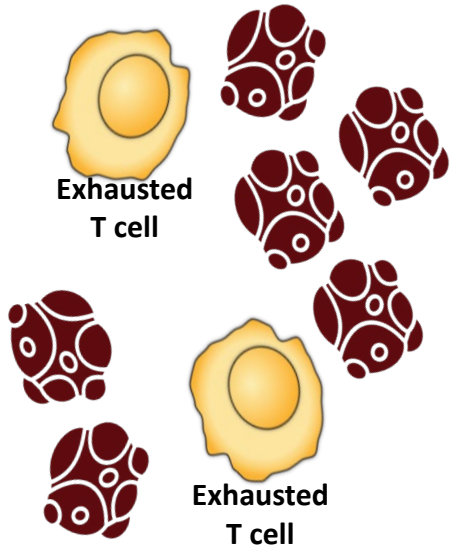
T cells are unable to recognize tumor cells as foreign



Tumor-specific T cells are deficient in number



T cells are unable to function properly

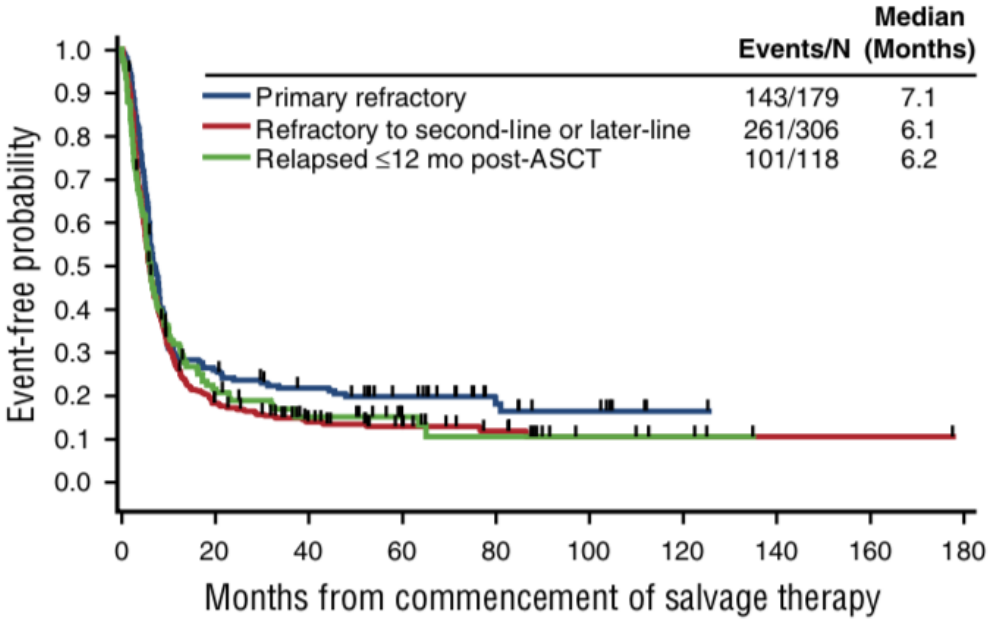


Sharpe M, Mount N. *Dis Model Mech*. 2015;8:337-350.

MASSEY CANCER CENTER VCU

Outcomes for Patients with Relapsed/ Refractory NHL

Relapsed – Lymphoma Returns
Refractory – Lymphoma does not go away



- Retrospective, 636 patients
- Relapsed/Refractory DLBCL
- Complete Response 7%
- Median Survival 6.3 months

Crump M, Neelapu SS et al. Outcomes in refractory diffuse large B cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017; 130 (16): 1800-1808

MASSEY CANCER CENTER VCU

Relapsed/Refractory B Cell Malignancies

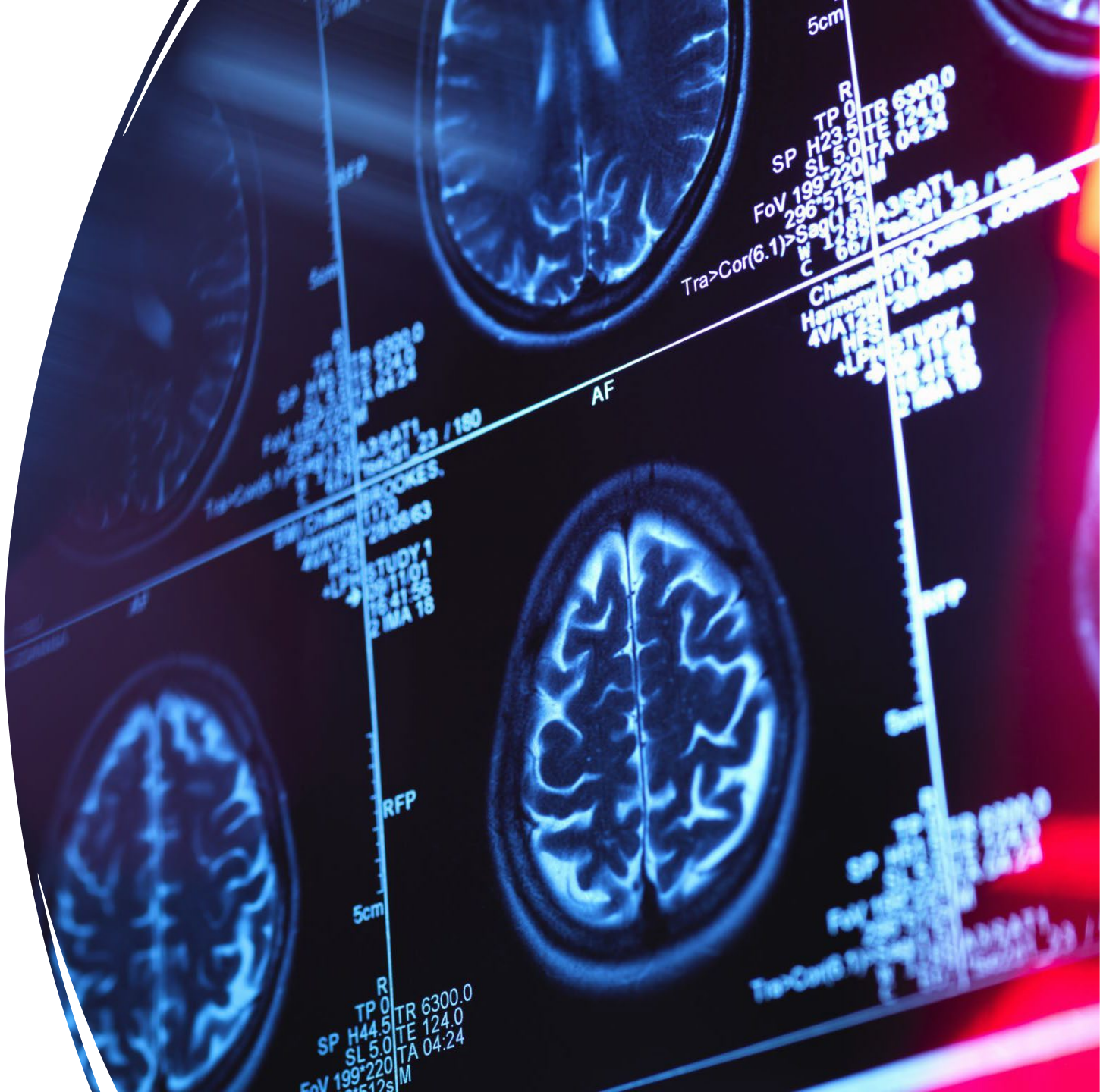
- Mantle Cell Lymphoma[1]
  - Disease progression after (Ibrutinib) have poor prognosisis[2]
    - Overall response rate 25-42%
    - Overall Survival 5.8 months

- Follicular Lymphoma
  - After ≥ 2 lines of therapy, The Complete Response rates were ≤ 14%,
  - Median Duration of Remissions were ≤ 13 months

1 Peter Martin, Blood March 2016.

2. Alfredo Rivas-Delgado et al. British Journal of Haematology, 2019.

Immune Therapy



Paradigm Shift in Oncology Treatment

Chemotherapy

- Cell cycle
- Not specific
- Autologous Stem Cell Transplant

Targeting Therapies

- CD 20 monoclonal antibodies (Lymphoma)
- HER 2 monoclonal antibodies (Breast Cancer)

Immunotherapies

- Allogeneic Stem Cell Transplant
- IL 2
- Checkpoint Inhibitors
- CAR T

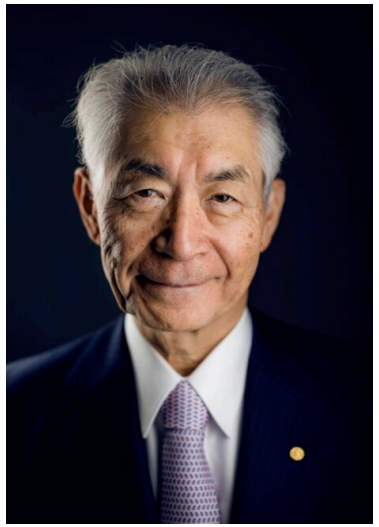
MASSEY CANCER CENTER VCU

Metastatic renal cell cancer cured with high-dose bolus IL-2 in January 1994

Stephen Rosenberg, MD PhD

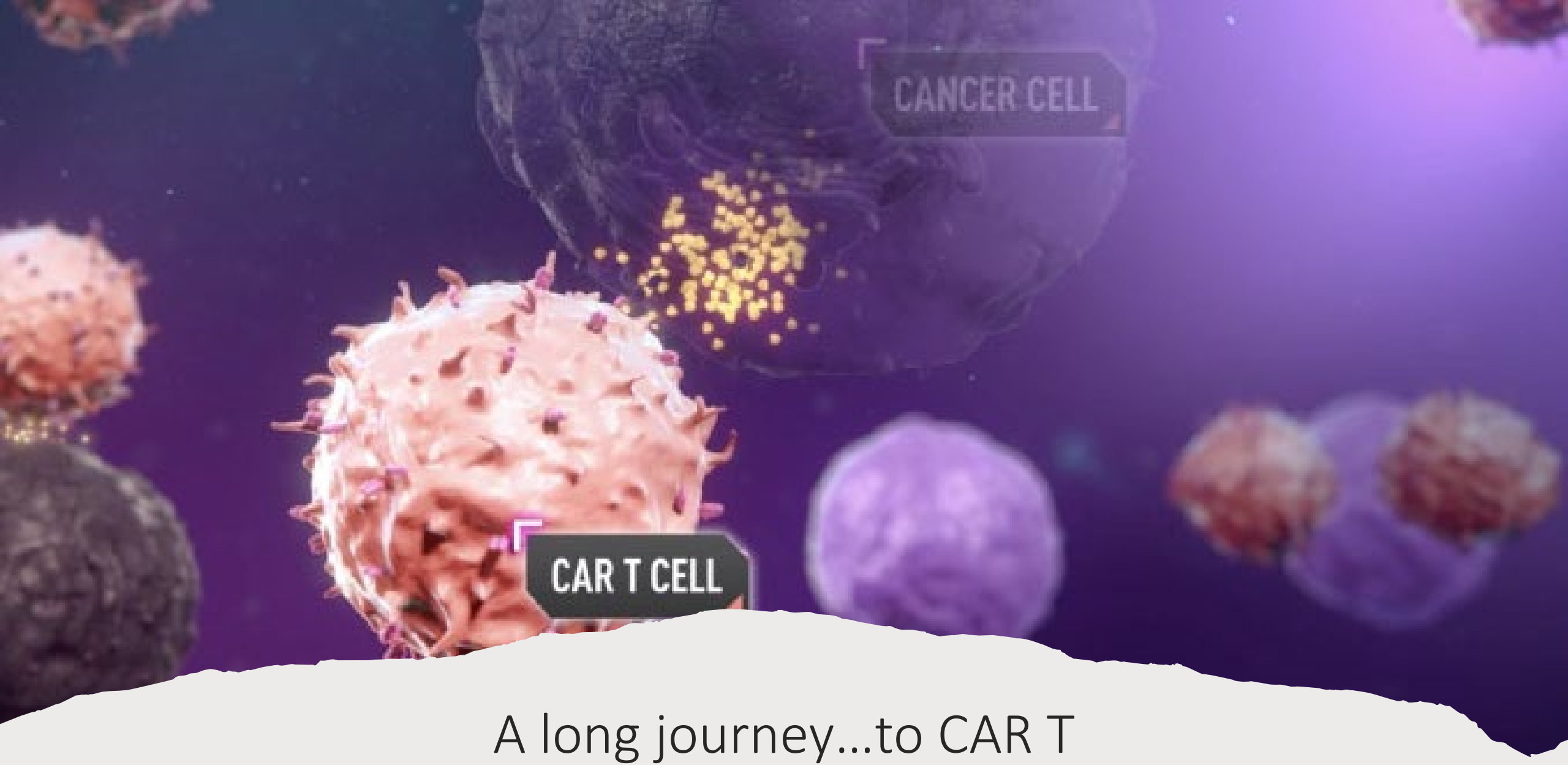
Nobel Prize in Physiology or Medicine 2018
Checkpoint inhibitors for Metastatic Melanoma

James P. Allison



Tasuku Honjo

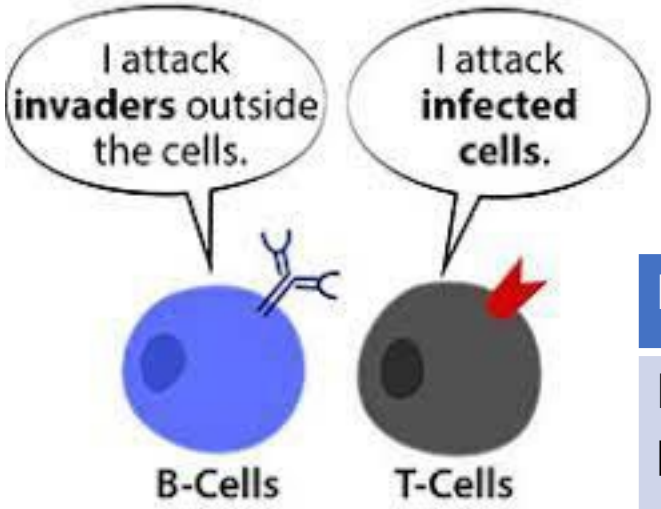
Carl June, MD



A long journey…to CAR T

MASSEY CANCER CENTER VCU

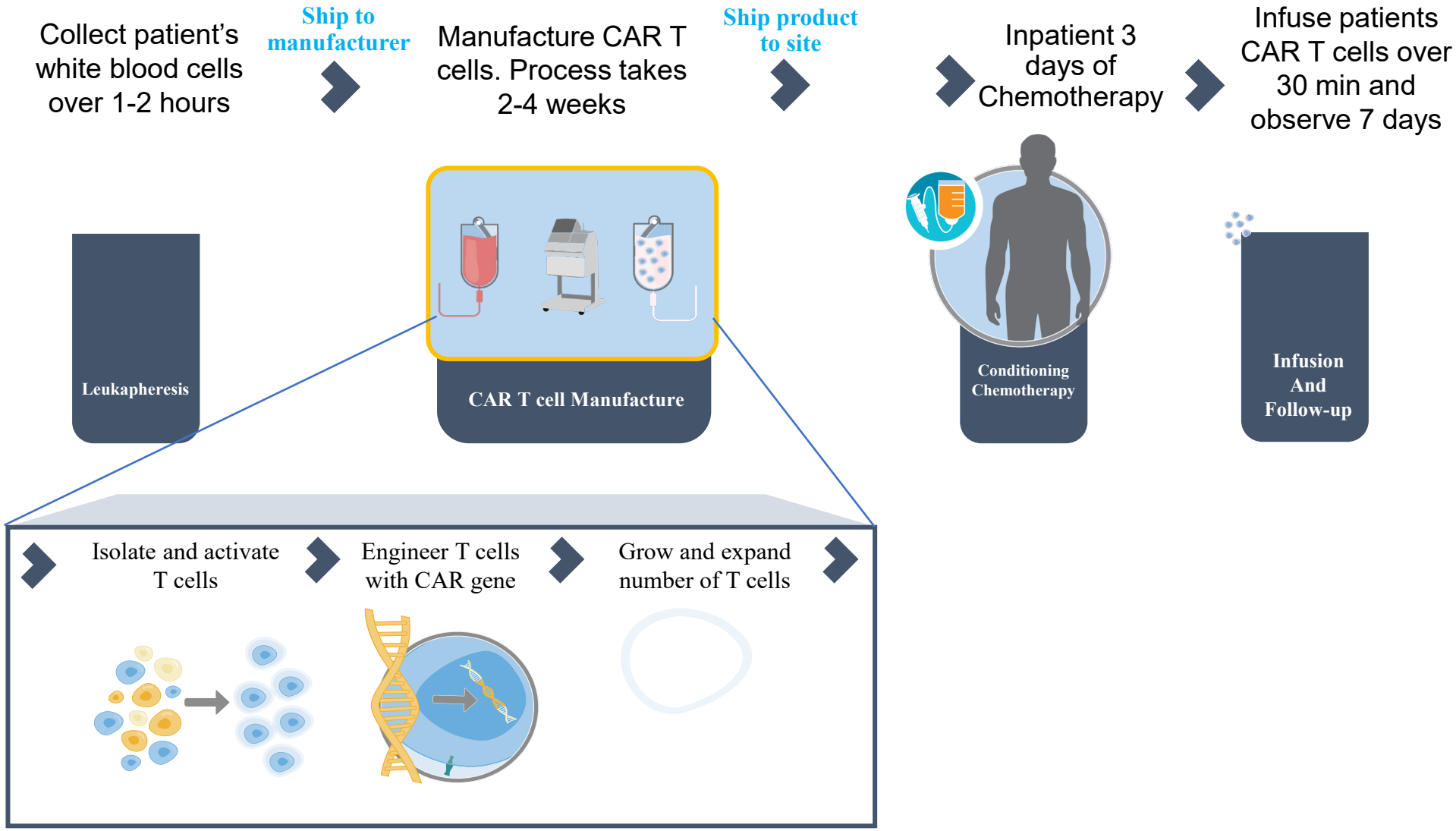
Immune System - B cells and T cells



B Cells	T cells
Have receptors that are specific for a protein and excellent binding to it	Have receptors that require specific receptors (Matched)
Present the protein to T cells	T cells need a lot of signals to get them excited
Not great at killing infected cells	Excellent at killing tumor cells when activated

Janeway 8th Edition Immunology
Abbas A, et al (ed). *Basic Immunology (fourth edition)*. 2014. Elsevier Saunders 2. Schwartz RH. *Ann Rev Immunol*. 2003;21:305-334.

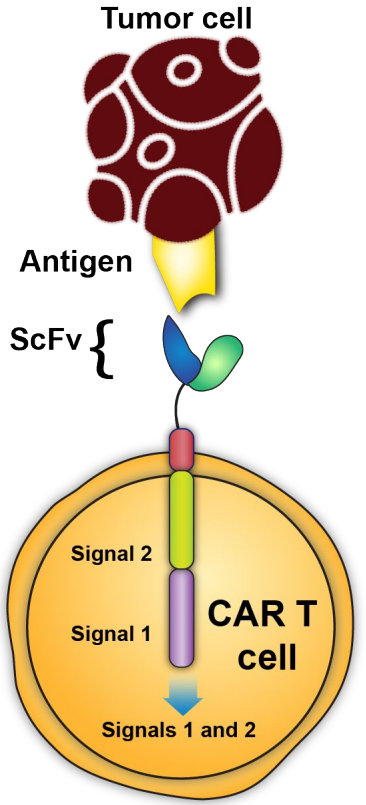
Patient Flow and Therapy Timeline



Chimeric Antigen Receptor (CAR) T cell Therapy

Novel immunotherapy approach that involves engineering patient's own immune cells

- Reprograms patients' own T cells to recognize tumor cells as foreign
- Expands patients' own T cells
- Reactivates patients' own T cells to kill target cells



https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

Lee DW, et al. *Clin Cancer Res*. 2012;18:2780-2790.

MASSEY CANCER CENTER VCU

MASSEY CANCER CENTER VCU

FDA Indications for CAR T-cells in Relapsed/Refractory NHL

Diffuse Large B Cell Lymphoma

Follicular Lymphoma and Marginal Zone

Mantle Cell Lymphoma

Primary Mediastinal B Cell Lymphoma

MASSEY CANCER CENTER VCU

	Axicabtagene Ciloleucel[1]	Axicabtagene Ciloleucel[2]	Tisagenlecleucel[3]	Brexucabtagene Autoleucel[4]
Indications	DLBCL, Primary Mediastinal B Cell Lymphoma, Transformed FL to DLBCL (ZUMA 1)	Relapsed Refractory Follicular Lymphoma (ZUMA 5)	DLBCL, TFL,	Relapsed Mantle Cell Lymphoma (ZUMA 2)
# prior Rx	Majority >3	2	2-7	Median 3
Median Age	58 (range 25-76)	62 (range 34-79)	56 (22-76)	65 (range 38-79)
Prior allo allowed	No	No	No	No
Overall Response Rate	74%	91%	54%	85%
Complete Response	55%	60%	40%	59%

For Comparison in Scholar -1 with chemotherapy ONLY 7% Respond

1. Neelapu SS et al. 2 year Follow Up and High Risk Subset Analysis of ZUMA1 in patients with Refractory Large B Cell Lymphoma. 2018 American Society of Hematology Dec 1-4 San Diego
2. A phase 2 multicenter study of axicabtagene ciloleucel in subjects with relapsed/refractory non-Hodgkin lymphoma (ZUMA-5). Caron Jacobsen, ASH 2020
3. Schuster S et al. Long term Follow up of Tisagenlecleucel in Adult patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Bbmt.2018.12.089
4. Wang M et al. KTE-X19 CAR T-Cell Therapy in Relapsed or RefractoryMantle-Cell Lymphoma. NEJM April 22, 2020, 382;14.

MASSEY CANCER CENTER VCU

TECARTUS®
(brexucabtagene autoleucel) Suspension for IV infusion

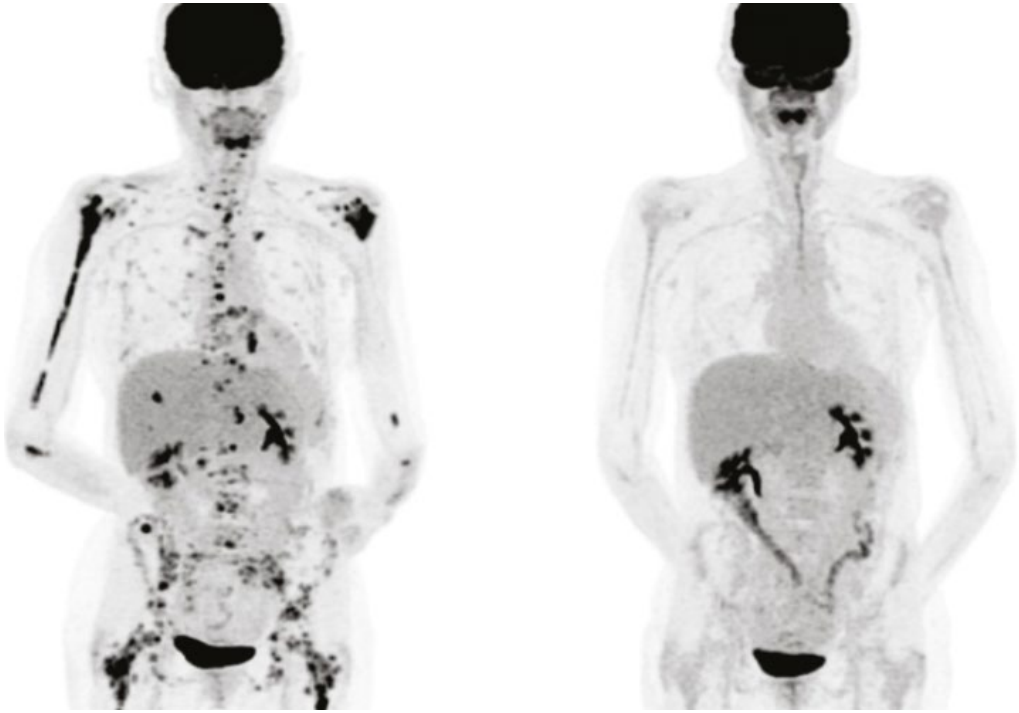
FDA Approved

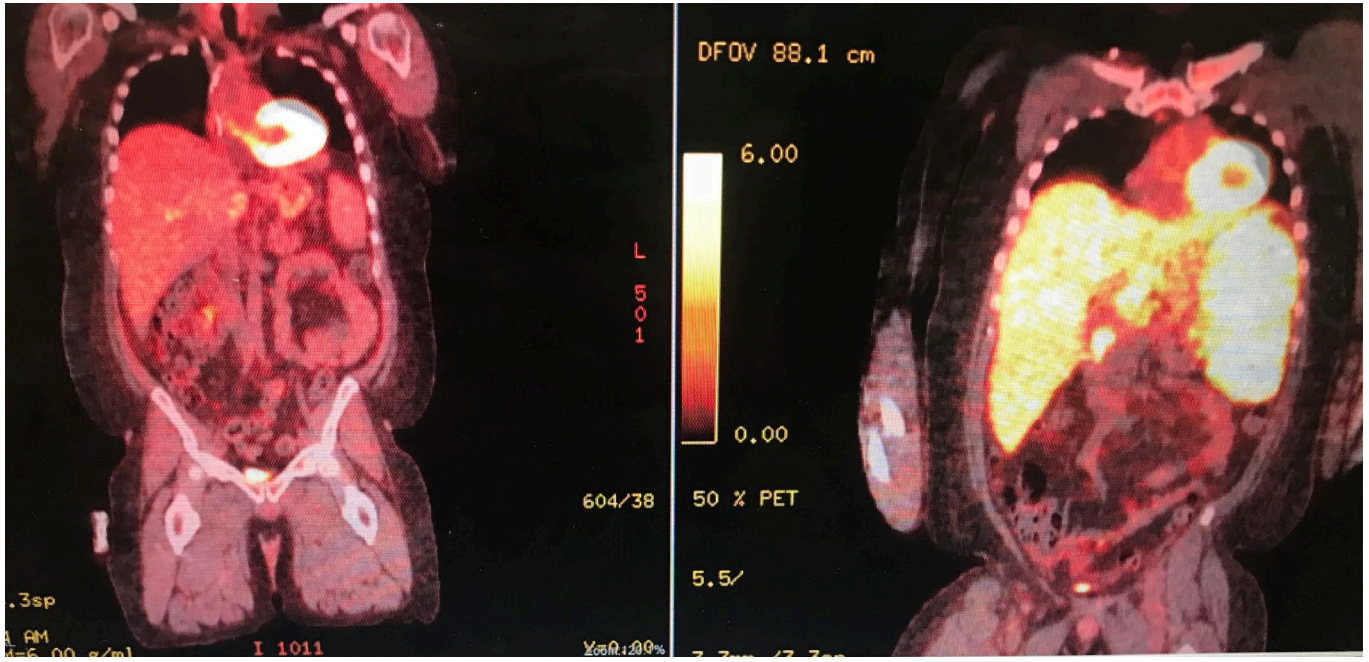
LISOCABTAGENE
(BREYANZI)
FDA APPROVED

KYMRIAH®
(tisagenlecleucel) Suspension for IV infusion

NOW APPROVED
YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion

CAR T-Cells…!





Syed Abbas Ali. T cells expressing anti BCMA CAR T-cells in Myeloma. Blood 2016

MASSEY CANCER CENTER VCU

CAR T-Cells: From Referral to Treatment

MASSEY CANCER CENTER VCU

Questions to ask your physician

- Should we get a biopsy to prove it has come back?
- Should I be referred to transplant / CAR t-cell center?
- Do we need to start treatment now or can I wait until I meet with transplant/car t-cell team?
- Patients can go online and search for authorized treatment centers for CAR T at www.bmtinfonet.org/car-t-medical-centers

MASSEY CANCER CENTER VCU

Differences between Stem Cell Transplant and CAR T cells

Autologous Transplant

- Principle: Uses high dose chemotherapy to kill cancer
- Best results if in remission
- Toxicity from chemo
- Collect stem cells over 1 week
- In hospital 3 weeks
- Short recovery (1 month)
- Risk of death from procedure < 1%

Allogeneic Transplant

- Principle: use new donor immune cells – B, T, NK T cells
- Best if in remission
- Toxicity from GVHD, infection
- Donor gives cells
- In hospital 4-6 weeks
- Long recovery outpatient (months)
- Risk of death fromeedure 10-15%

Car T –cells

- Principle: use engineered T Cells to kill cancer
- Patients are not in remission
- Collect T cells 2-4 hours
- In hospital 2 weeks
- Toxicity of T cells expanding
- Short recovery ~ 30 days
- Risk of death from procedure <2%

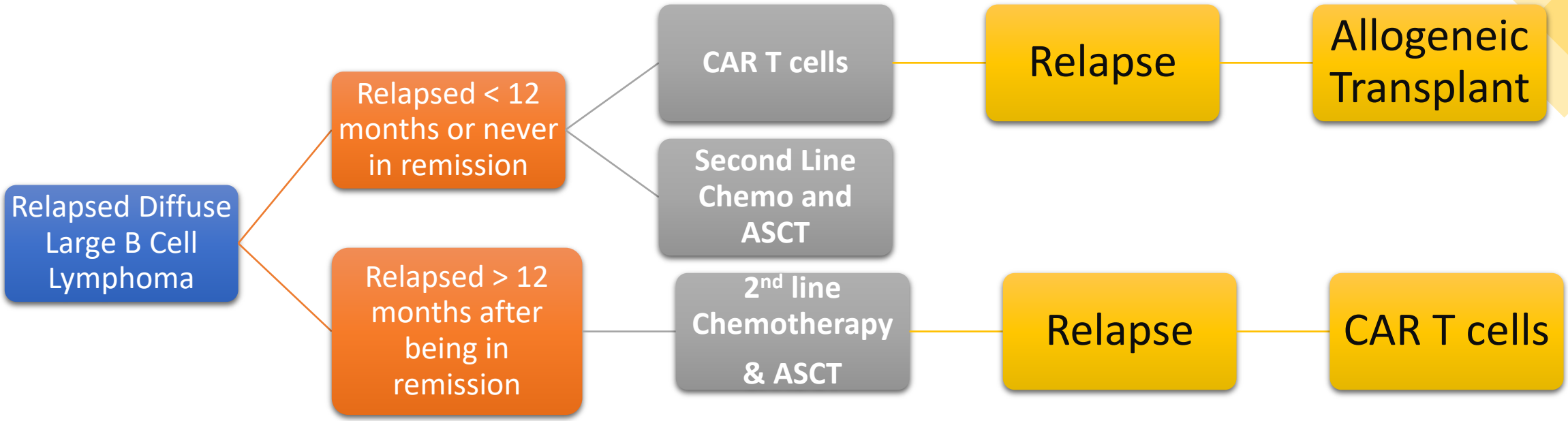
MASSEY CANCER CENTER VCU

Disease Determines the Treatment

Autologous	Allogeneic	CAR T cells
Myeloma	Leukemia – AML, ALL, CML	NHL
Amyloidosis	MDS	Myeloma
Relapsed NHL	Myelofibrosis	
Relapsed Hodgkin Lymphoma	Aplastic Anemia	

MASSEY CANCER CENTER VCU

VCU Algorithm



ASCT: Autologous Stem Cell Transplant (transplant using your own stem cells
Allogeneic Stem Cell Transplant (Donor stem cells)

MASSEY CANCER CENTER VCU

General Processes

Referred from your doctor to transplant/car t cell center

The team reviews options for the disease based on current literature and clinical trials

Organ testing is performed to determine candidacy

Consents are signed and collection begins

1-day for CAR

~1- week for Stem Cells

Toxicities of CAR T

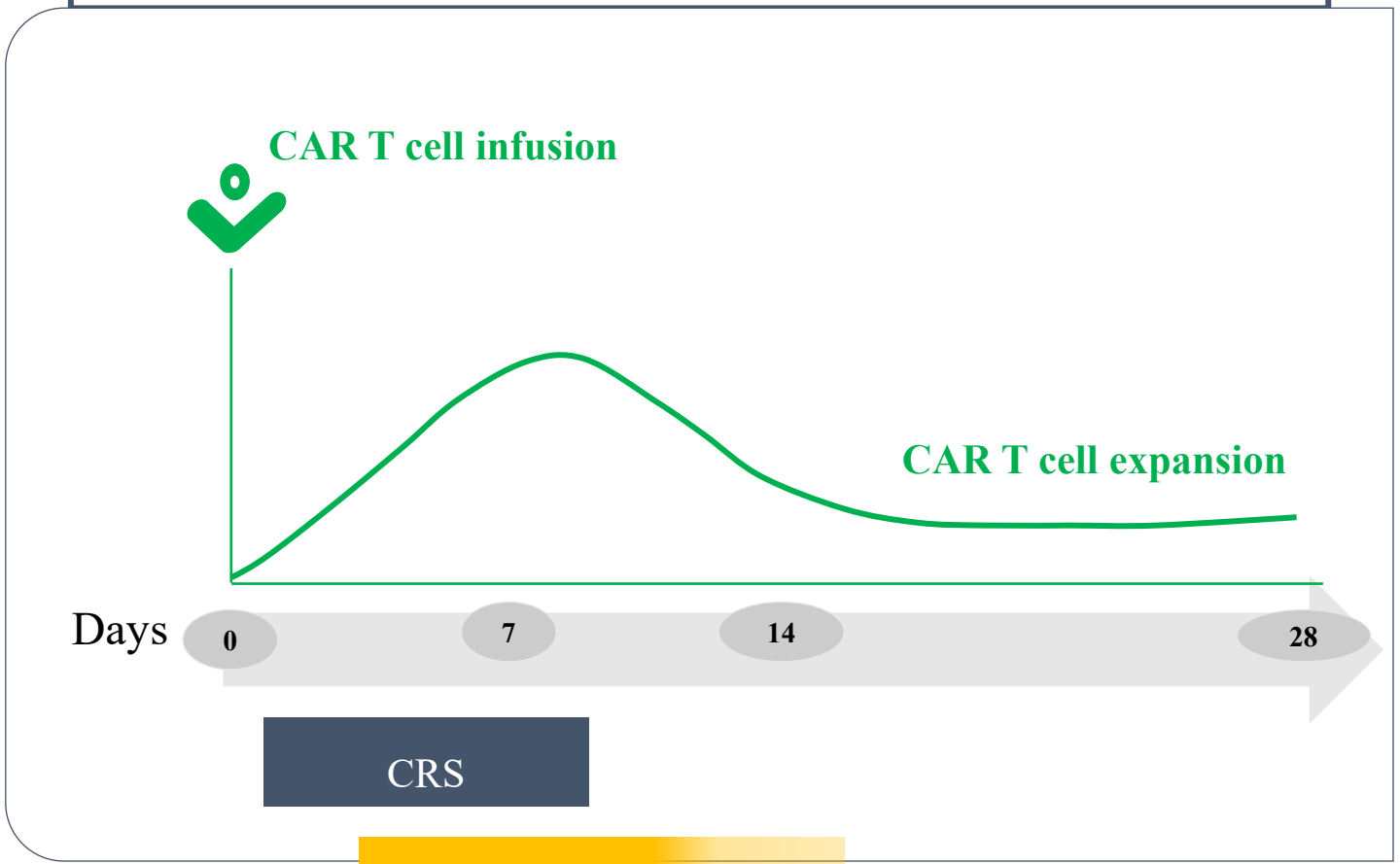
Cytokine Release Syndrome (CRS)

Immune Cell Associated Neurotoxicity Syndrome (ICANS)

MASSEY CANCER CENTER VCU

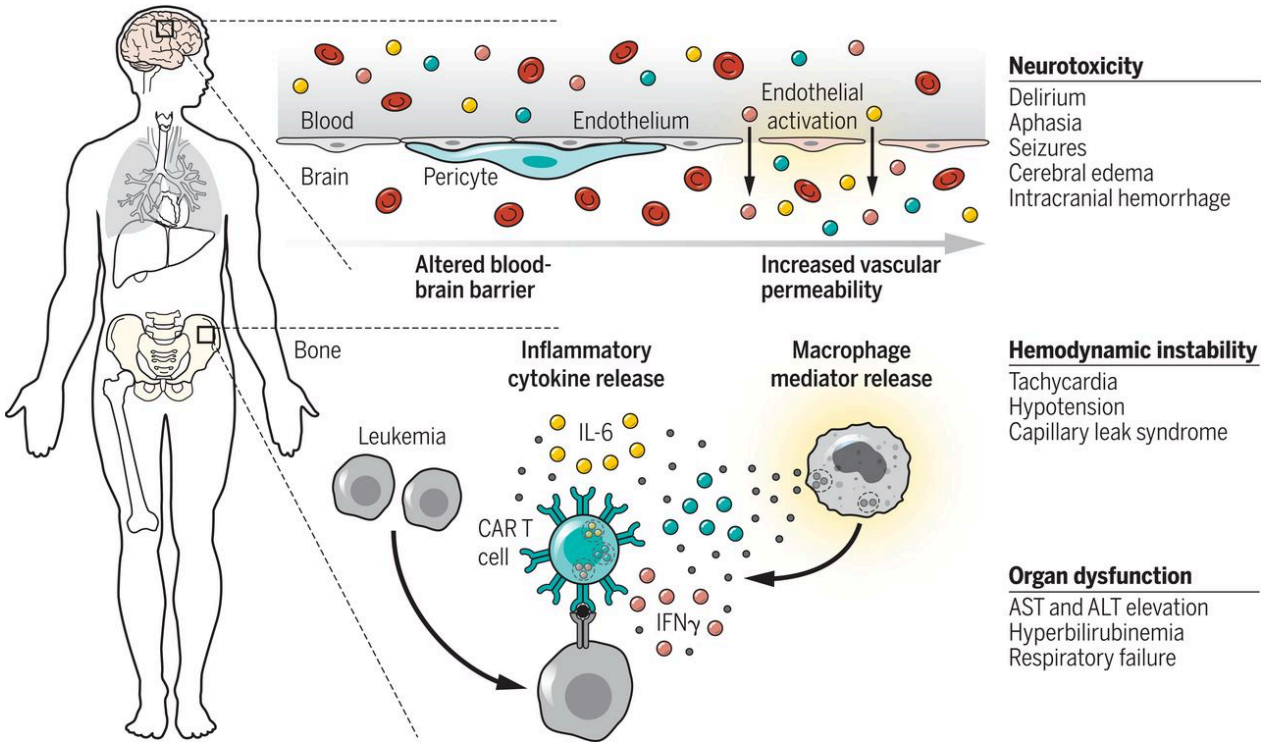
Cytokine release syndrome (CRS)

- Mediated by high levels of inflammatory cytokines, such as IL-6[1]



1. Lee DW, et al. *Blood*. 2014;124(2):188-195.
2. Neelapu SS, et al. *Blood.* 2016;128:LBA-6.
3. Kochenderfer JN, et al. *J Clin Oncol.* 2017; Mar 14:JCO2016713024. doi: 10.1200/JCO.2016

Cytokine Release Syndrome (CRS)



Symptoms

- Fevers
- High heart rates
- Low blood pressure
- Kidney and liver Injury
- Clotting
- Heart damage
- Trouble breathing

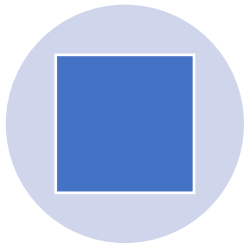
Carl June et al. March 2018; Science

CRS Grading and Treatment

ASBMT 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)

Management of CRS is based on clinical parameters



CRS can be fairly well managed with high level of clinical surveillance, fluids, and vasopressors

The IL-6 receptor antibody tocilizumab is the consensus first line treatment for CRS grade 2 +

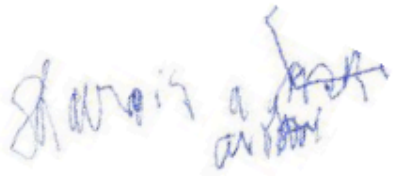
Second line treatment for CRS varies by protocol and/or institutional guidelines

D.W.Lee et al. BBMT 2018

MASSEY CANCER CENTER VCU

Immune Effector Cell Neurotoxicity Syndrome (ICANs)

Impaired handwriting

Day 4 9 am	I love Shawnee, KS.	MMSE score 29/30
Day 5 01:30 PM Toci 8 mg/kg		27/30
Day 5 03:30 PM		27/30
Day 6 9 am	I miss my kids.	29/30

https://www.mascc.org/assets/2019_Meeting_Files/2019_Plenary/02-plenary_Muffly.pdf

MASSEY CANCER CENTER VCU

Immune Effector Cell Associated Neurotoxicity (ICANs)

- Confusion
- Tremor
- Seizure
- Aphasia (trouble speaking)
- Headache
- Hallucinations

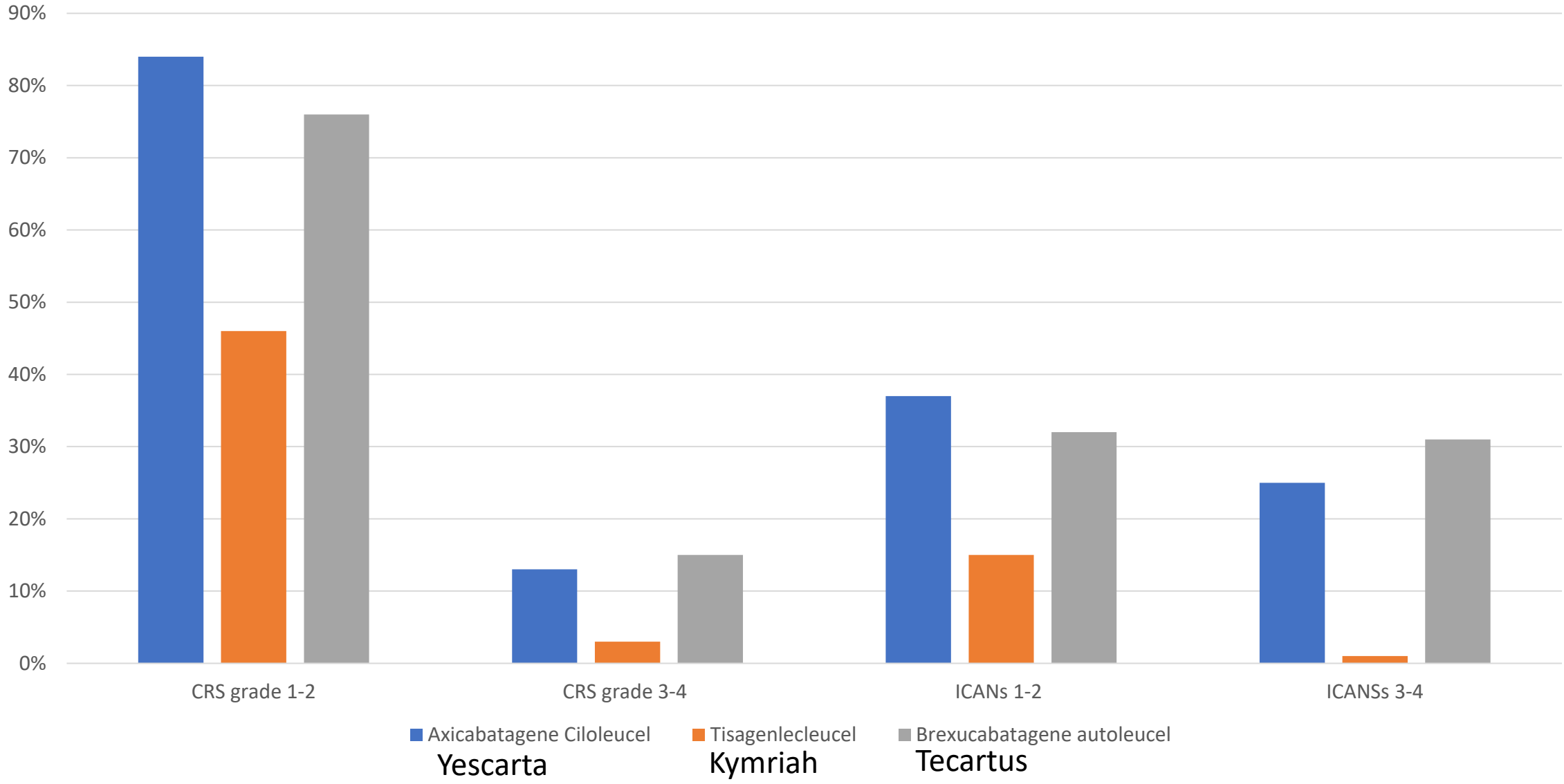
D.W.Lee et al. BBMT 2018

Neurotoxicity Management at VCU

- ICU Level Care
- Continuous electroencephalogram (EEG)
- Examination of the cerebrospinal fluid (CSF)
- Keppra
- Steroids – Dexamethasone required

MASSEY CANCER CENTER VCU

How Common Is Toxicity - Common



1. Neelapu SS et al. 2 year Follow Up and High Risk Subset Analysis of ZUMA1 in patients with Refractory Large B Cell Lymphoma. 2018 American Society of Hematology Dec 1-4 San Diego
2. A phase 2 multicenter study of axicabtagene ciloleucel in subjects with relapsed/refractory non-Hodgkin lymphoma (ZUMA-5). C. Jacobson ASH 2020.
3. Schuster S et al. Long term Follow up of Tisagenlecleucel in Adult patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Bbmt.2018.12.089
4. Wang M et al. KTE-X19 CAR T-Cell Therapy in Relapsed or RefractoryMantle-Cell Lymphoma. NEJM April 22, 2020, 382;14.

MASSEY CANCER CENTER VCU

Post Hospitalization

What we watch for after CAR T cell therapy

FDA mandates the patients remain <2hr from center received CART-cells for 30 days

- At VCU we require < 30 minutes to the center

Monitor Low Blood Counts

- May need transfusions for several months

Low IgG – this is expected post CAR

- May need IVIG if having recurrent infections

Fevers and Infections

- Higher risk of infections
- Use ppx acyclovir, levofloxacin and fluconazole

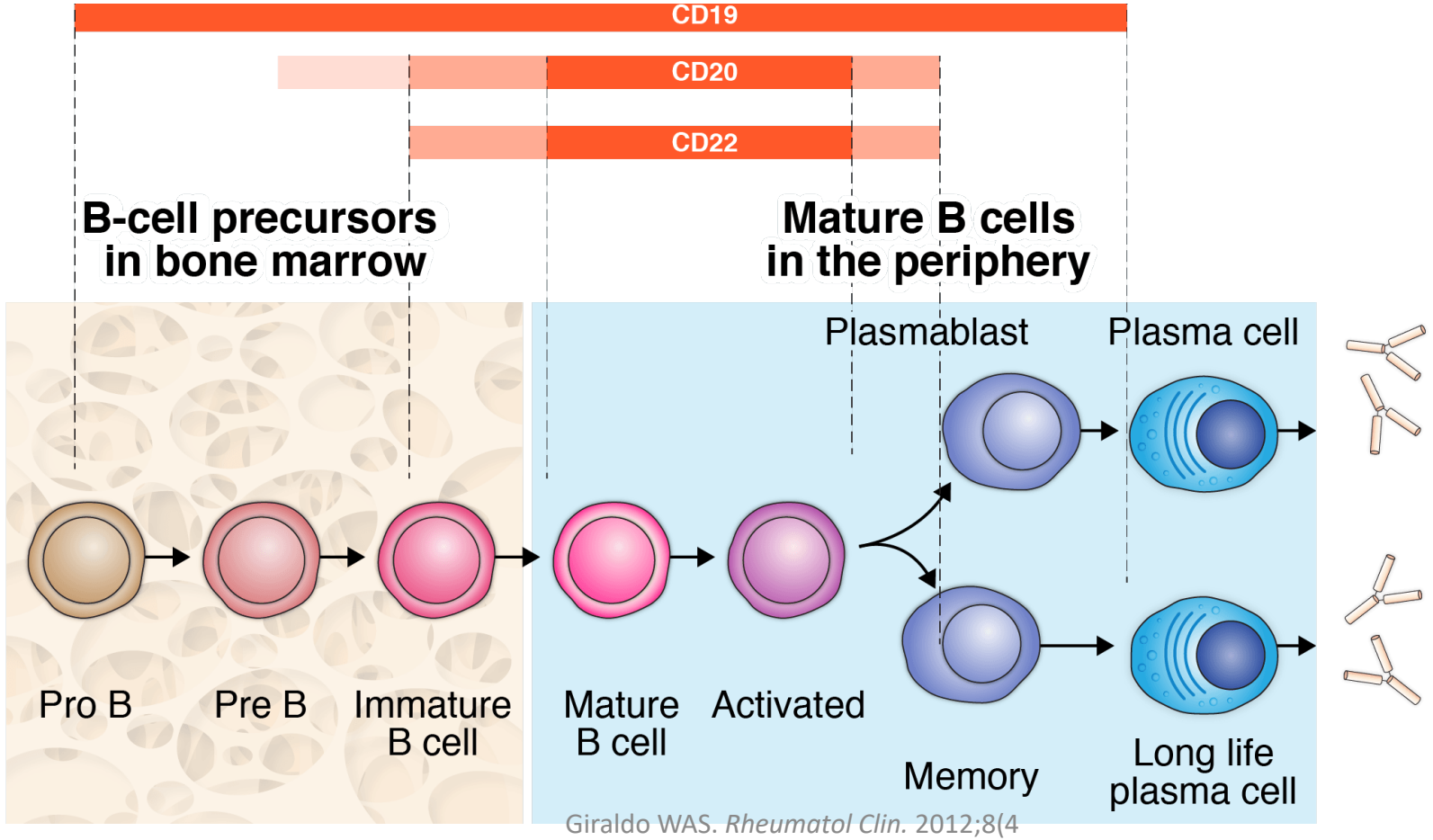
Delayed Neurotoxicity , Rare but has occurred

- FDA – patients cannot drive or operate heavy machinery for 8 weeks after CAR T cells due to risk of neurotoxicity

MASSEY CANCER CENTER VCU

Limitations to CAR – CD 19

1. Proteins need to be expressed on outside of cell
2. Must be able to live without the cell being attacked



Giraldo WAS. *Rheumatol Clin.* 2012;8(4

The Future of Immunotherapies in Cancer

MASSEY CANCER CENTER VCU

VCU – Cellular Immunotherapy Program

- FDA Approved CAR T cells in RELAPSED SETTING
  - Myeloma
  - Mantle Cell Lymphoma
  - Diffuse Large B Cell Lymphoma
  - Follicular Lymphoma
  - B Cell Acute Lymphoblastic Leukemia
- Clinical trials using T-Cell Receptor therapies for metastatic sarcoma
- Coming is Gene Therapy to treat sickle cell disease and thalassemia
- Coming are Tumor Infiltrating Lymphocytes (TIL) therapies for lung cancer and solid tumors

MASSEY CANCER CENTER VCU

Summary

- The paradigm shift of immunotherapy has reached lymphoma and myeloma with CAR T Cells
- CAR T cell therapy is a novel therapy that has shown to show great responses in patients highly treated hematologic B cell malignancies with Curative Intent
- Immune therapy is a powerful therapy with toxicities requiring complex monitoring and care of patients
- Ongoing trials will challenge stem cell transplant vs CAR T cells

Acknowledgements to the CIT Working Group

CIT

Gary L. Simmons, DO

John McCarty MD

Amir Toor, MD

William Clark, MD

Harold Chung, MD

May Aziz Pharm D

Melissa Hunt – ANP, Lead

CIT – Advanced Practioners

Nursing

Jessican Gray RN

Kristen Oliver RN

Billing/Coding/Payor
Penny Trentham
Tessa Proto
Denna Chabner
Suzanne Britt
Kyra McDaniel
Debra Hunt
Carrie Cybulski

Pharmacy Administration
Rodney Stillman
Craig Kirkwood
Denise Lowe

Informatics/IT Office
Victoria Brock
Reuben Southall

MRICU
Kristin Miller MD
Audrey Roberson RN

Apheresis

Susan Roseff, MD

Elizabeth Godbey, MD

Cellular Therapeutics Laboratory

Christina McLaughlin

Margaret Schwerdtferger

QAPI

Ashley Brizendine

CIBMTR

Marilyn Burns

BMT Research

Kathryn Candler

Charles Hall

MASSEY CANCER CENTER VCU

In Closing

We at VCU are grateful to all patients and families for their trust and support!

I am happy to answer any questions – Thank You!

MASSEY CANCER CENTER VCU

Questions?

Gary Simmons, DO

Many thanks to Kite, a Gilead Company for its support of this webinar..

BMT infonet.org
30 YEARS
EMPOWERING PATIENTS
BLOOD & MARROW TRANSPLANT INFORMATION NETWORK

Let Us Know How BMT InfoNet Can Help YOU!

Visit our website: bmtinfonet.org

Email us: help@bmtinfonet.org

Give us call: 888-597-7674

We're here to help every step of the way!