

BMT and immunotherapies for pediatric leukemia: Current and novel treatments and financial implications

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Jointly planned by the National Marrow Donor
Program® /Be The Match® and The Aplastic
Anemia & MDS International Foundation



Learning objectives

- Define current BMT and immunotherapy agent outcomes with mechanisms of action used to treat pediatric leukemia
- List the common side effects associated with immunotherapy and the supportive care needs for monitoring and educating patients and families
- Examine financial burdens associated with BMT and immunotherapy
- Identify educational resources available to assist in addressing a family's information and financial needs

Continuing Education

- **Social Workers:** National Marrow Donor Program, #1386, is approved as a provider for social work continuing education by the Association of Social Work Boards (ASWB) www.aswb.org, through the Approved Continuing Education (ACE) program. National Marrow Donor Program maintains responsibility for the program. ASWB Approval Period: 08/10/2016 - 08/10/2019. Social workers should contact their regulatory board to determine course approval for continuing education credits.
- Social workers participating in this course will receive 1.0 clinical continuing education clock hours.
- **Nurses:** The National Marrow Donor Program is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation (COA).
- Up to 1.0 contact hours may be claimed for this educational activity.

Continuing Education cont.

- **Insurance case managers:** This program has been pre-approved by The Commission for Case Manager Certification to provide continuing education credit to CCM® board certified case managers. The course is approved for 1.0 CE contact hour(s).
- Activity code: I00036831 Approval Number: 190001352
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- Up to 1.0 contact hours may be claimed for program #115-006-19.

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Disclosures

The planners and speakers have the following financial disclosures.

Name	Role	Disclosure
Debbie Jacobson, OPN-CG	Moderator	None
Vicki Szenes, MS, RN, CPNP	Speaker	MSKCC research support – Atara, Novartis, Jazz
Meghan Wellenbrink, BSN, RN, CPHON	Speaker	Consulting fee – Novartis
Jackie Foster, MPH, RN, OCN	Planner	Stock ownership – Pfizer
Ellyce Hayes	Planner	None
Nicole Heino	Planner	None
Alice Houk	Planner	None
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Lauren Marks	Planner	None
Katie Schoeppner, MSW, LICSW	Planner	None

Questions

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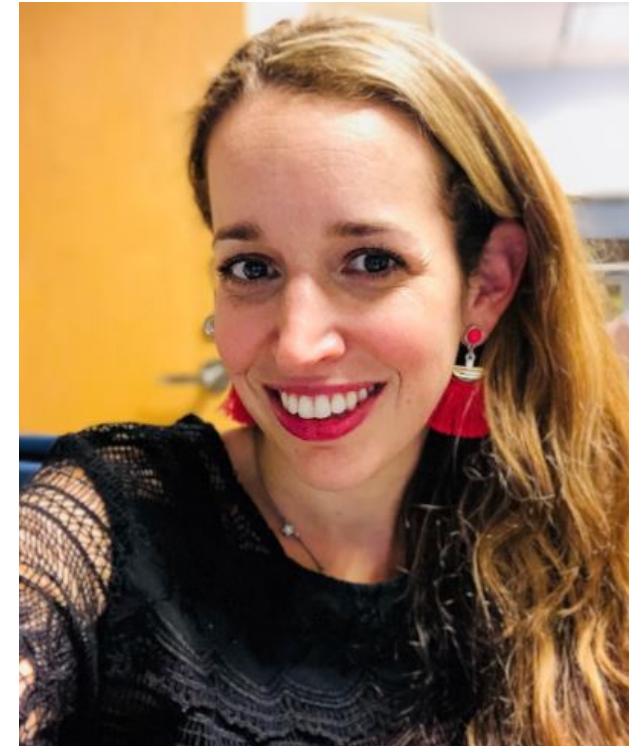
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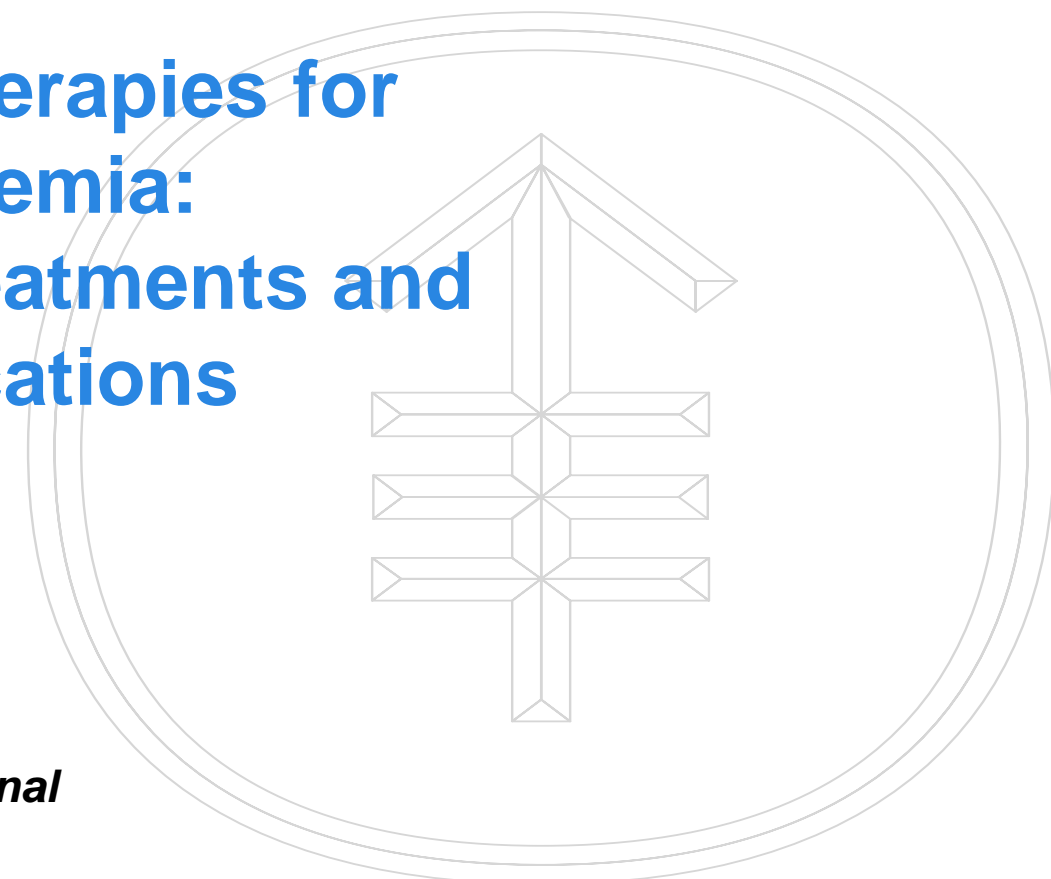
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Memorial Sloan Kettering
Cancer Center

BMT and Immunotherapies for Pediatric Leukemia: Current and Novel Treatments and Financial Implications



We will discuss the following off label use and/or investigational use in this presentation: CD19-specific CAR T cells

Overview

- Bone Marrow Transplant (BMT)
- Cancer Immunotherapy – “The 3 E’s”
- Chimeric Antigen Receptors (CARs)
 - Overview
 - Screening/Collection Process
 - Infusion
 - Toxicity and Management
- CAR T cells - Future Directions
- Case study presentation



Pediatric Acute Lymphoblastic Leukemia

- Most common form of cancer in children – 30%

Treatment

- **Chemotherapy** - high success rate
- **Five-year event-free survival rates**
 - Low- or standard-risk B-precursor ALL > 90%
 - High-risk features/responsive to induction chemo - >80%
 - Adverse prognostic factors (hypodiploidy, slow response to induction, relapsed ALL) - poor outcomes
- Approximately 75-80% of children with newly diagnosed ALL participate in clinical trials



Blood and Marrow Transplant for pediatric ALL

- **Blood and Marrow Transplant (BMT)** – curative therapy option
- **BMT indications for consultation associated with high-risk disease:**
 - Infant at diagnosis
 - Primary induction failure
 - Presence of minimal residual disease after initial therapy } Response to Tx
 - High/very high-risk at first complete remission including:
 - Philadelphia chromosome positive slow-TKI responders or with *IKZF1* deletions
 - Philadelphia-like
 - iAMP21
 - 11q23 rearrangement
 - First relapse
 - Second complete remission and beyond, if not previously evaluated



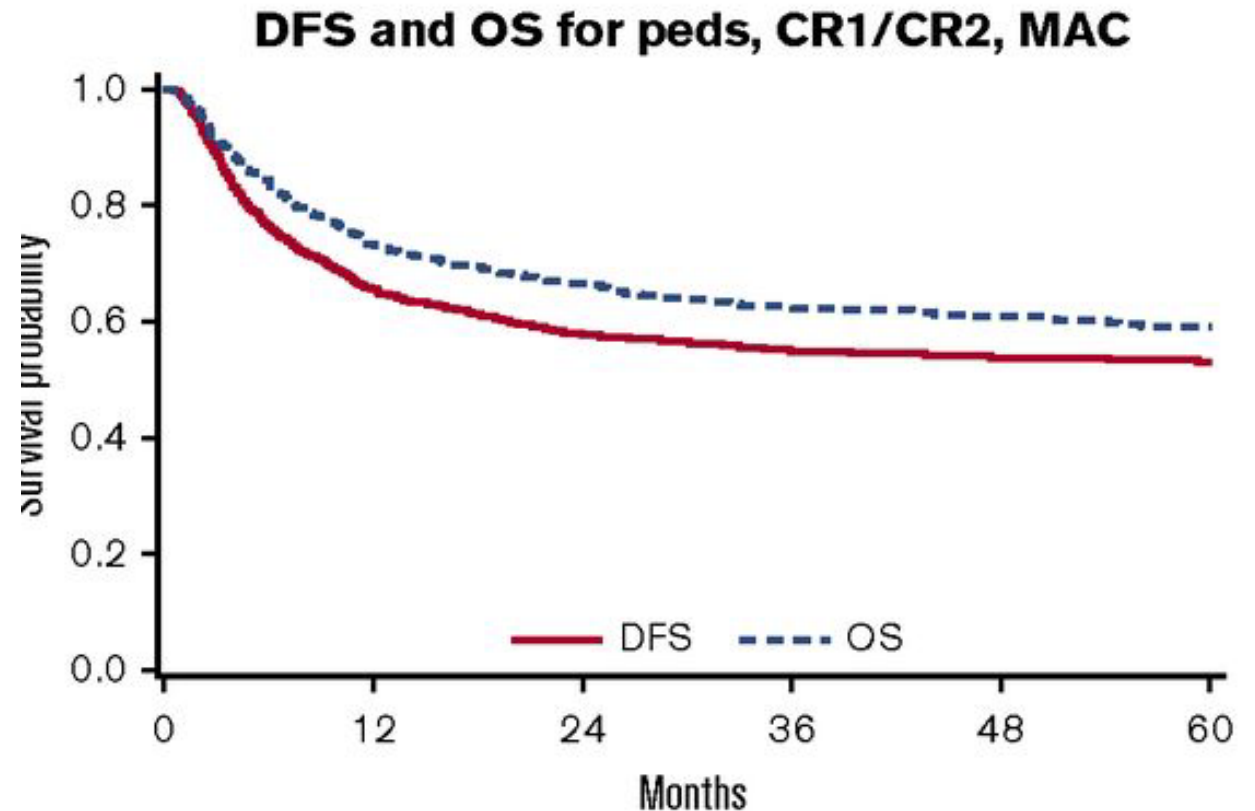
Post BMT care

- **Late effects**
 - central nervous system
 - growth impairment
 - cardiotoxicity
 - infertility
 - cataracts
 - secondary cancers
- Ongoing monitoring and screening recommended



Overall survival with BMT for Pediatric ALL

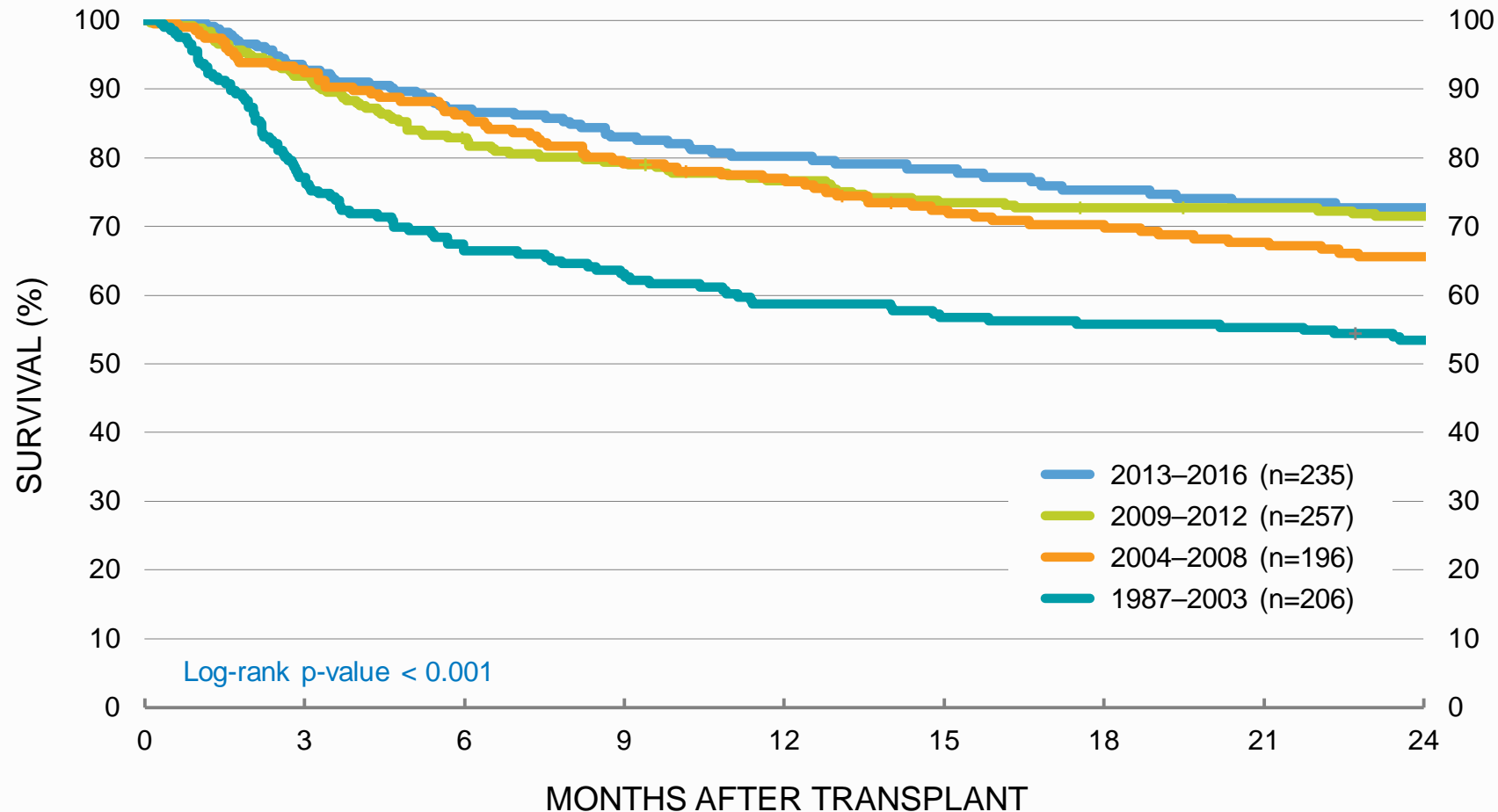
- Pediatric patients with ALL (n=1619)
 - 40% in CR1
 - 60% in CR2
- Median follow up: 72 months
- Overall survival
 - 1 year – 73%
 - 5 year – 59%



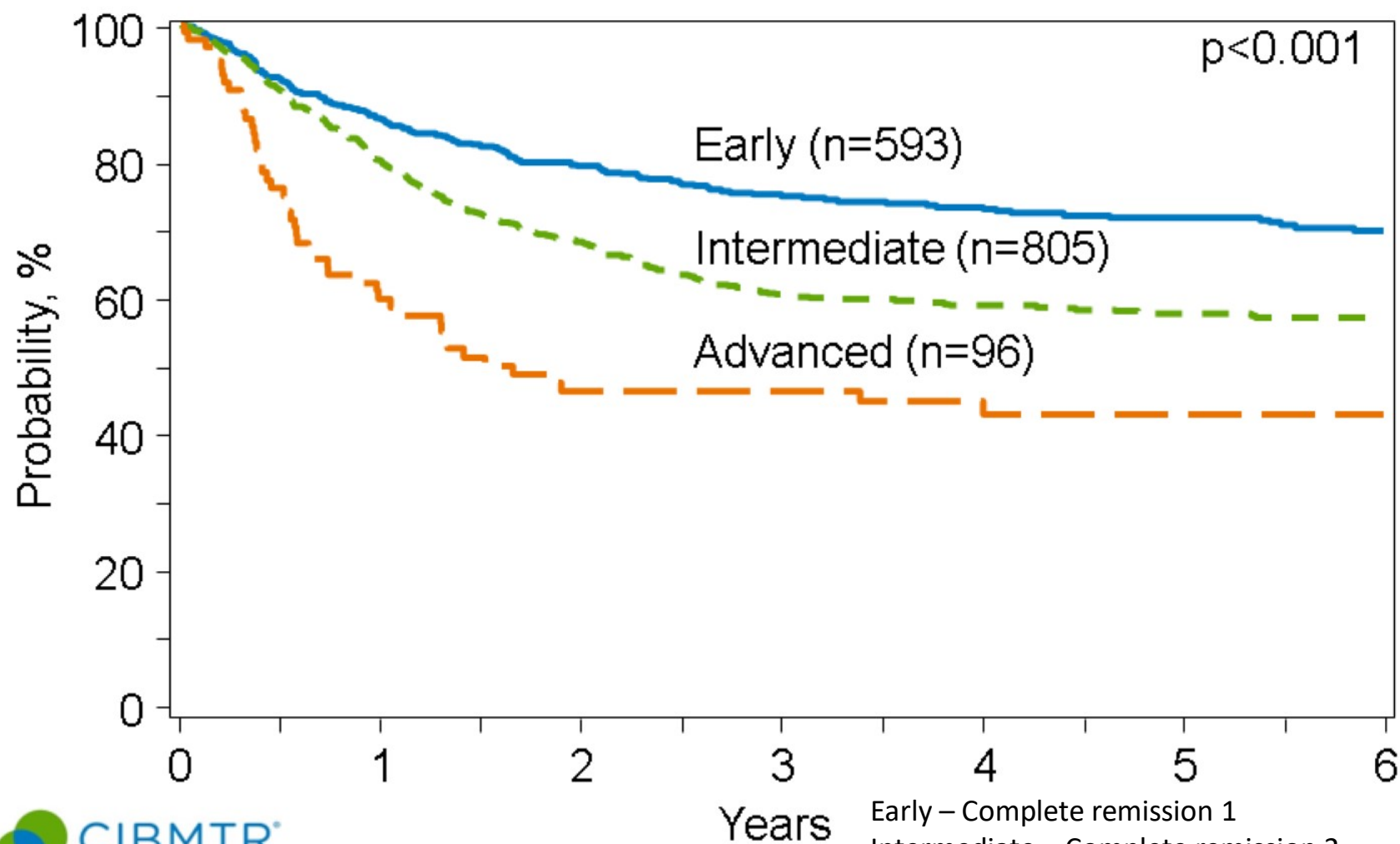
Acute Lymphoblastic Leukemia Overall Survival

Pediatric Patient Transplantation in First Complete Remission by Year of Transplant
Unrelated Transplants Facilitated by NMDP/Be The Match

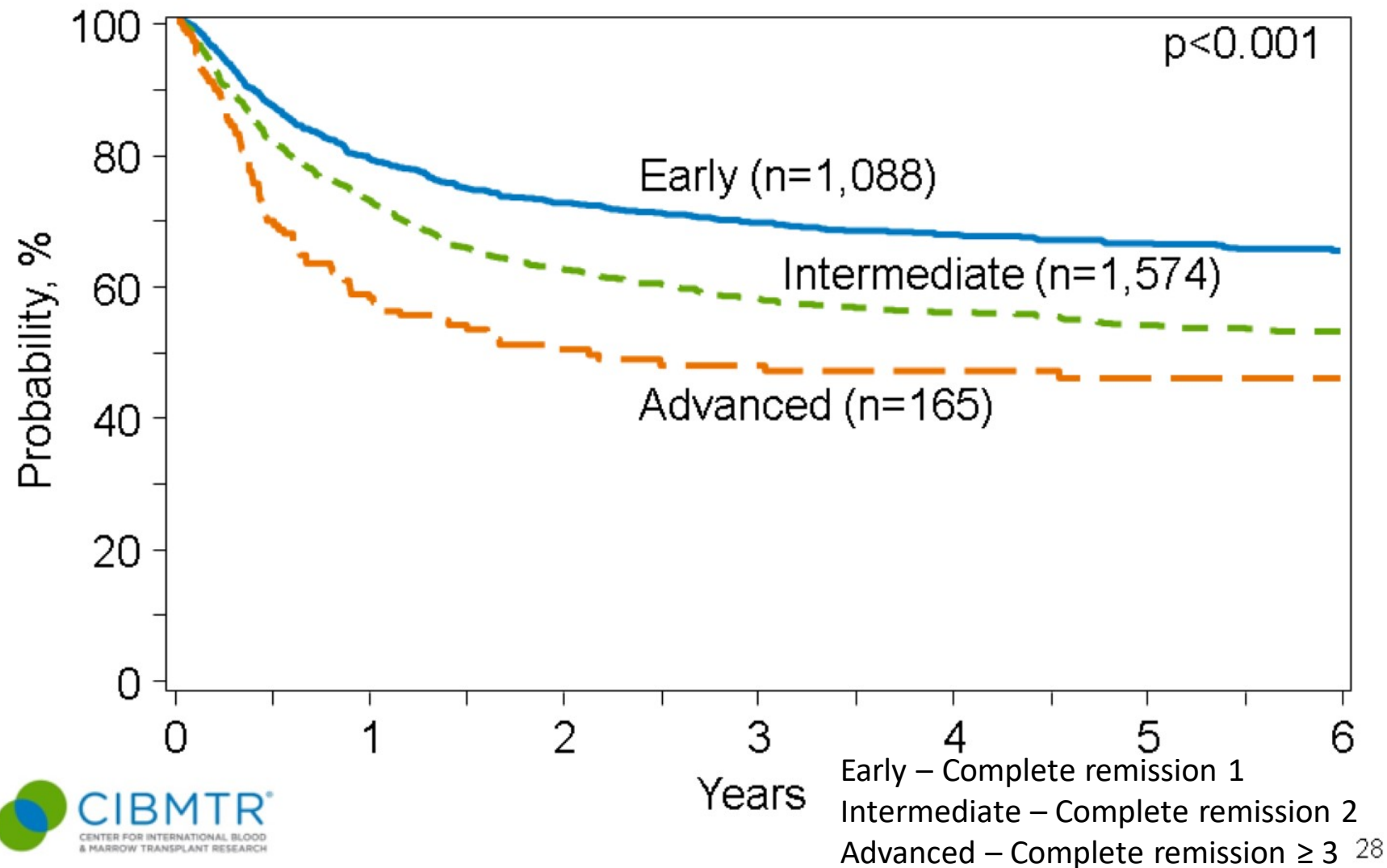
(1987–2016)



Survival after HLA-Matched Sibling Donor HCT for ALL, Age <18 Years, 2006-2016



Survival after Unrelated Donor HCT for ALL, Age <18 years, 2006-2016



BMT Outcomes for patients under age 3

- Retrospective, international, multicenter study - 717 patients who received myeloablative BMT between 1987–2012, who survived relapse-free for ≥ 1 year.
- 87% - estimated 10-year OS
- 30% reported at least one late effect
 - Growth disturbance, cataracts, and hypothyroidism
- TBI and chronic graft-versus-host-disease- associated with adverse outcomes

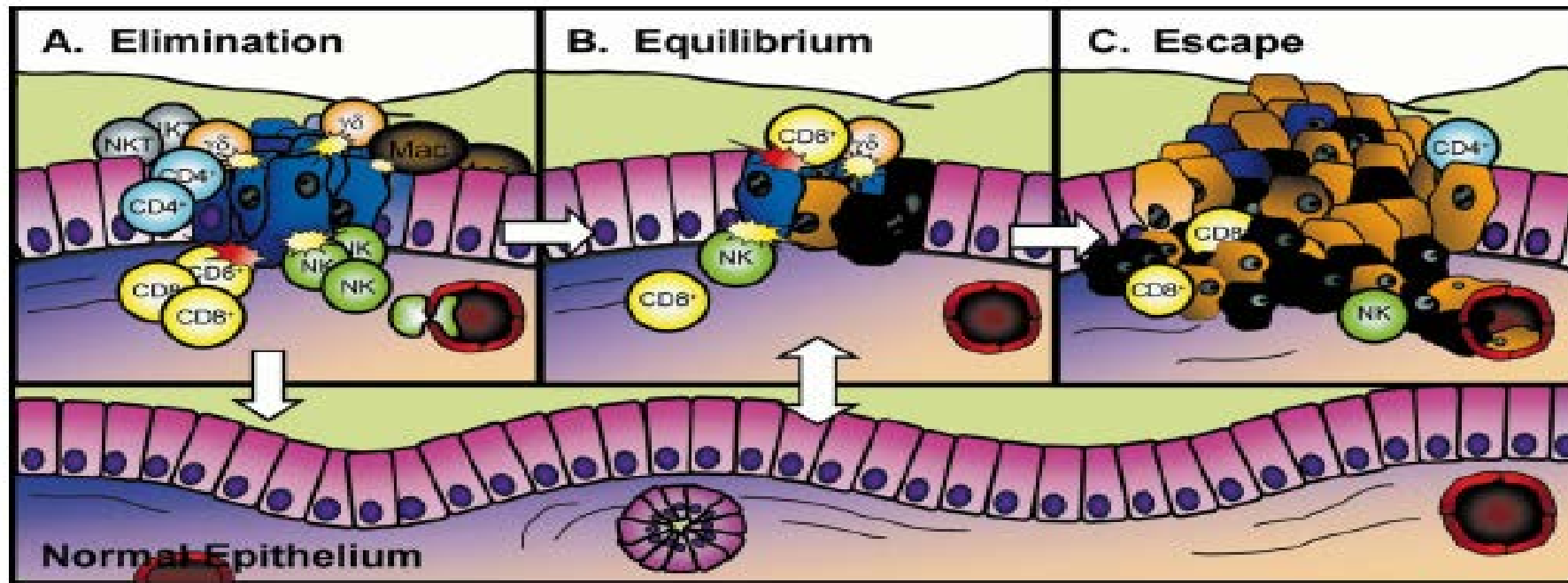


What is Immunotherapy?

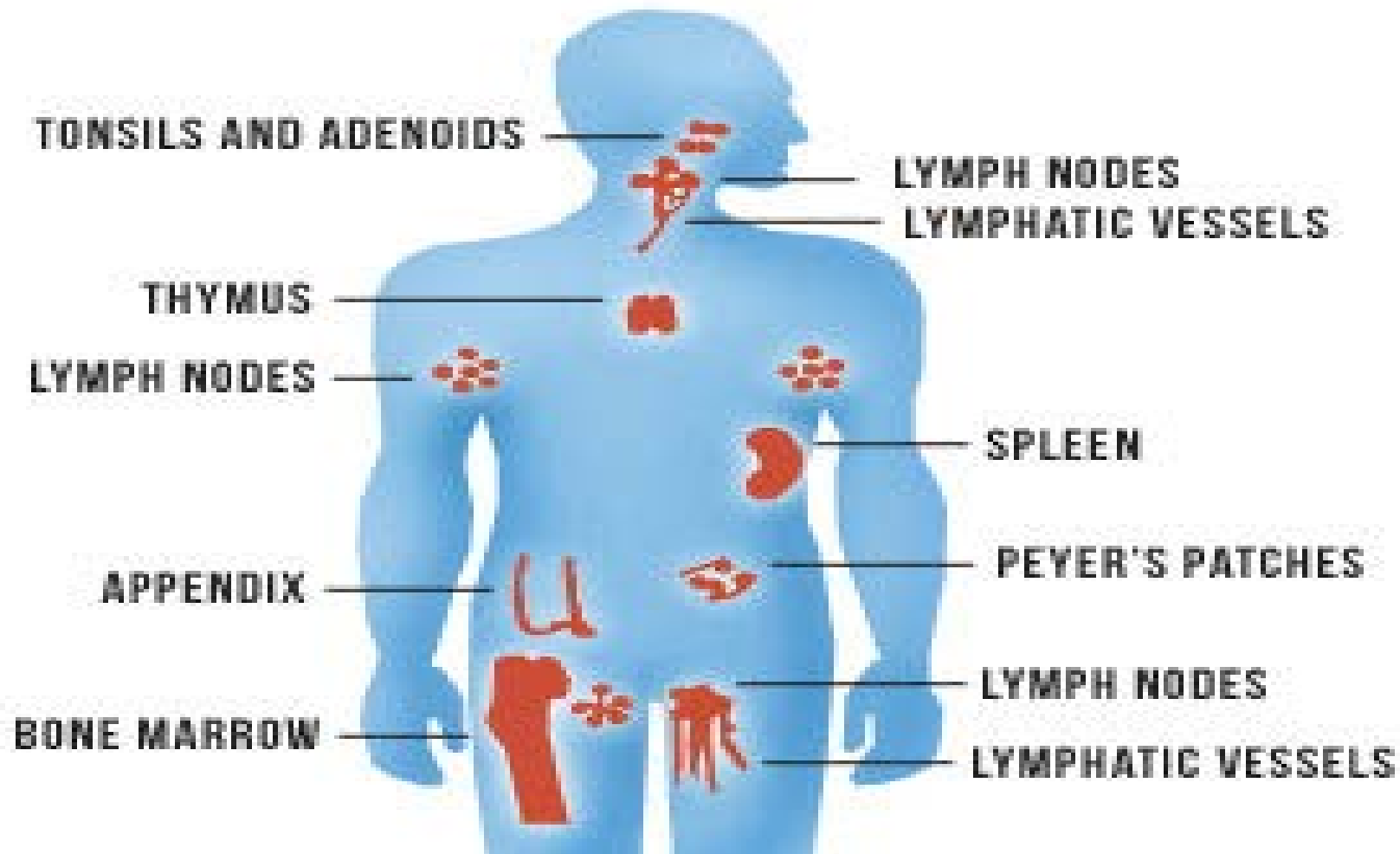
“Immunotherapy, also called biologic therapy, is a type of cancer treatment that boosts the body's natural defenses to fight the cancer. It uses substances made by the body or in a laboratory to improve or restore immune system function.”



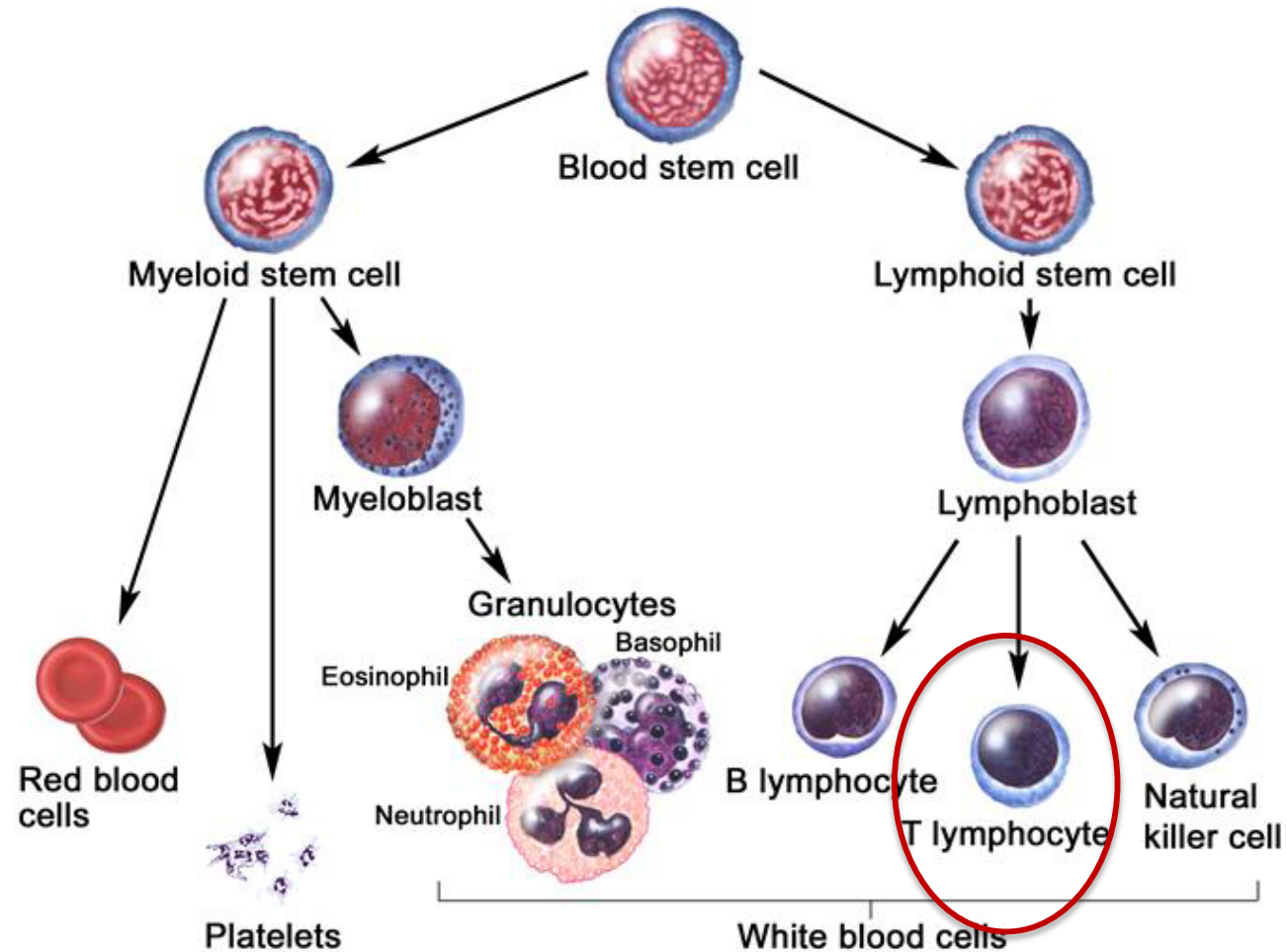
Cancer and Immune Escape – “The 3 E’s”



ORGANS OF THE IMMUNE SYSTEM



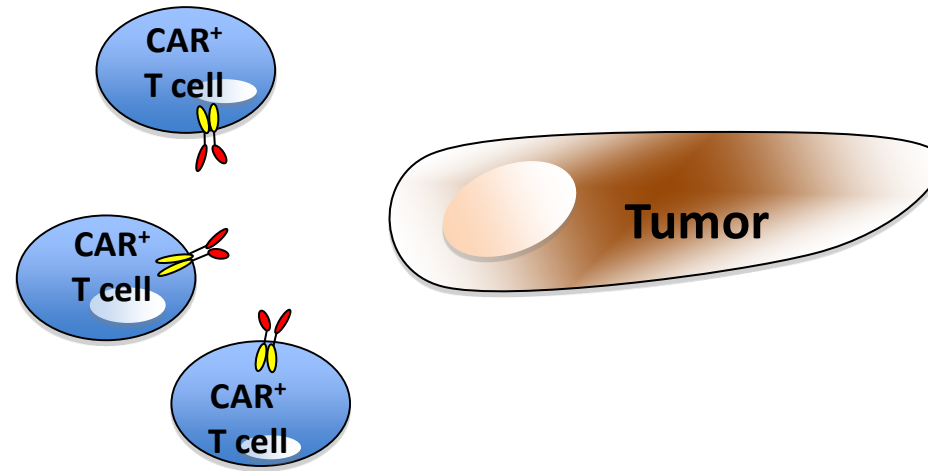
Blood Cells of the Immune System



Chimeric Antigen Receptor (CAR) T cells

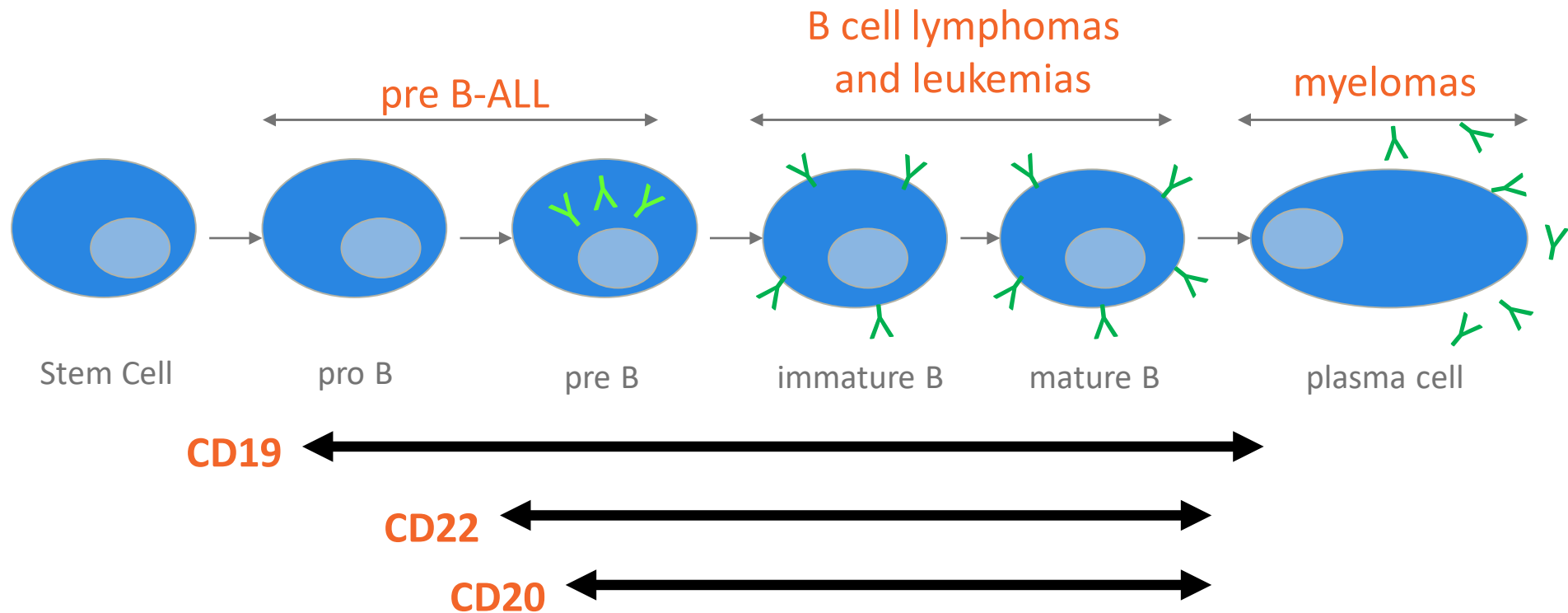


Targeting Expansion Tumor Lysis

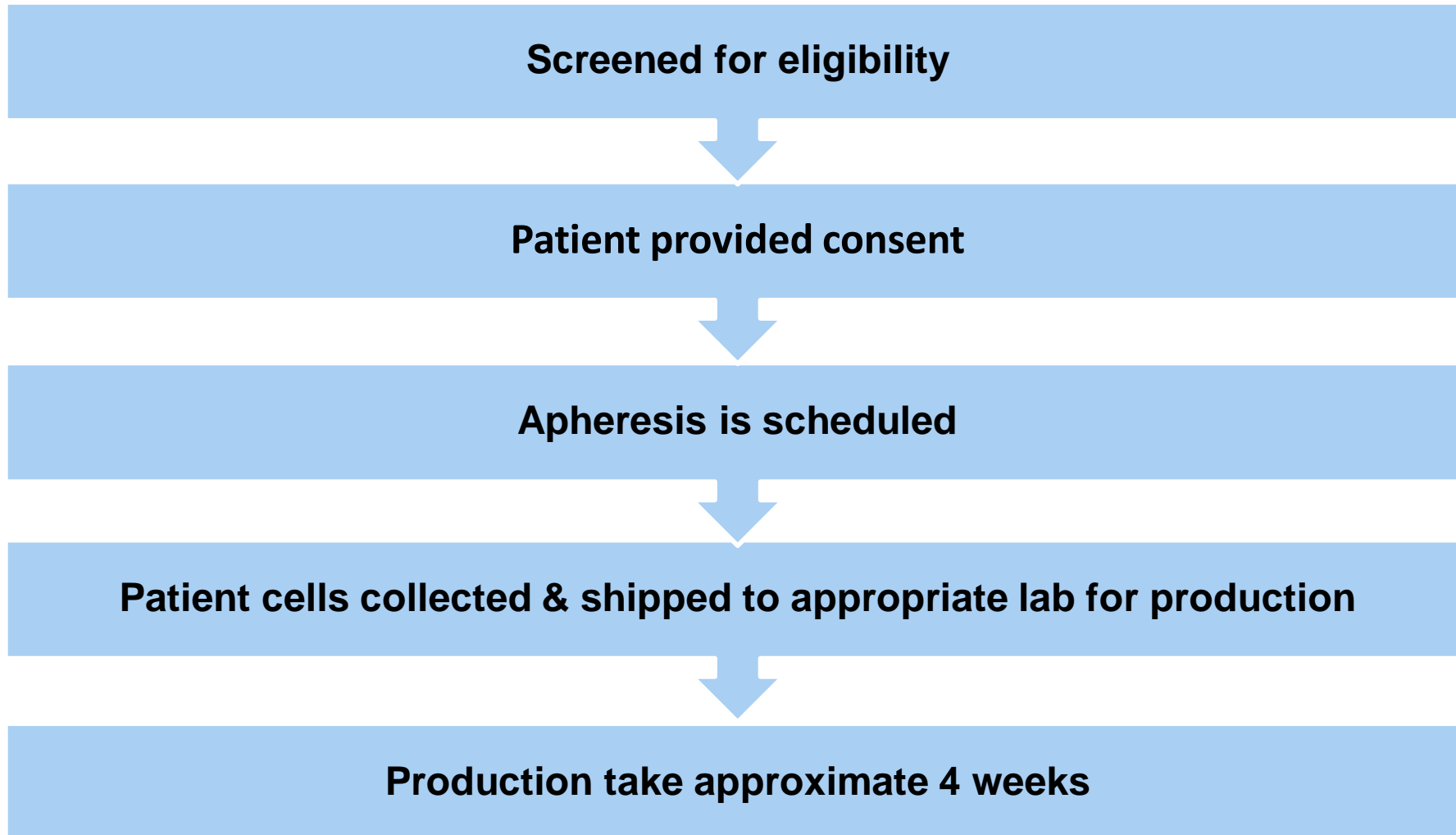


Why Target CD19?

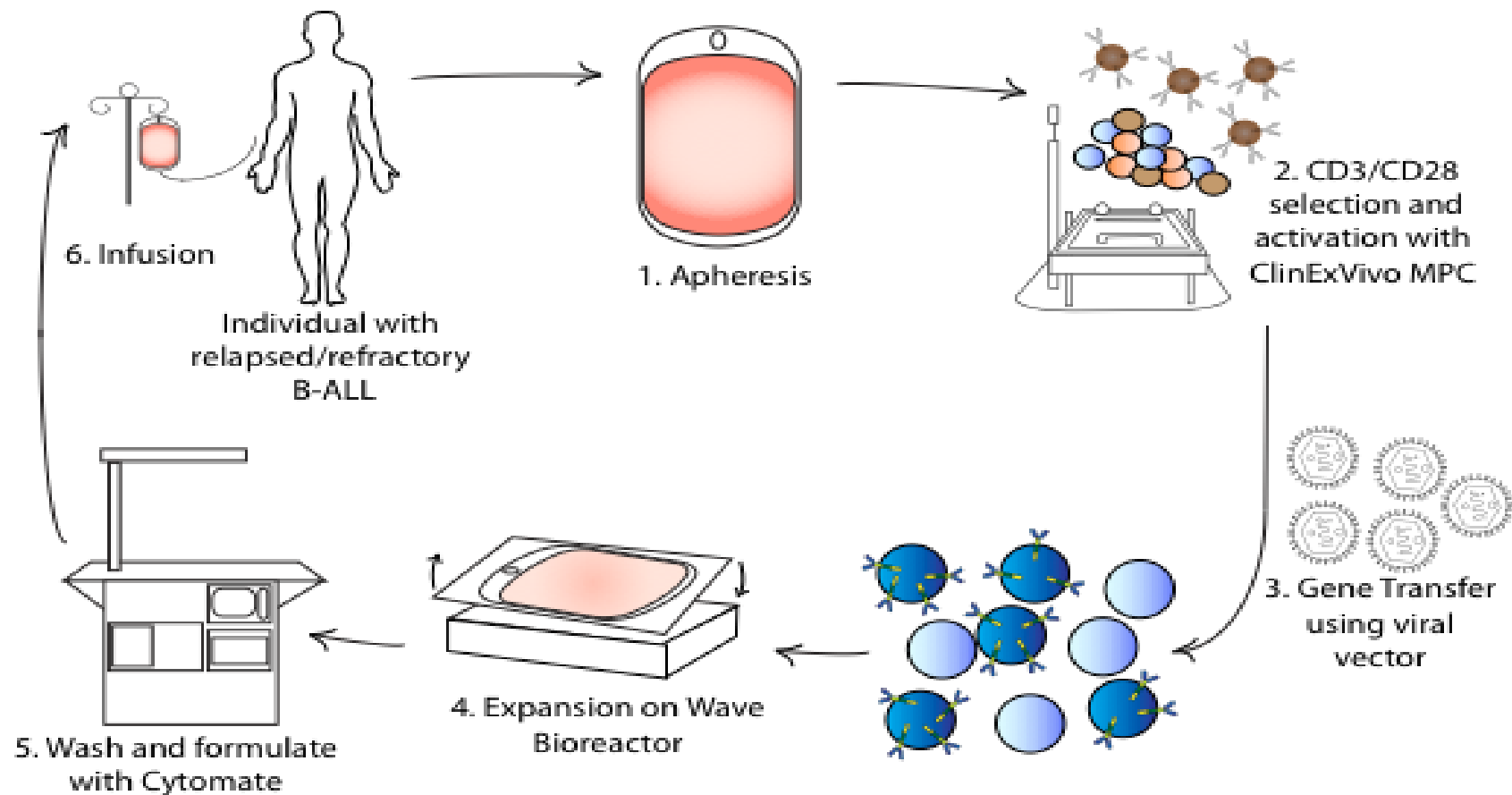
(Near Universal Expression on B-cell Malignancies)



Patient Flow: Pre Infusion



Clinical Application: An Overview



Screening for Collection CD19-specific CAR T cells

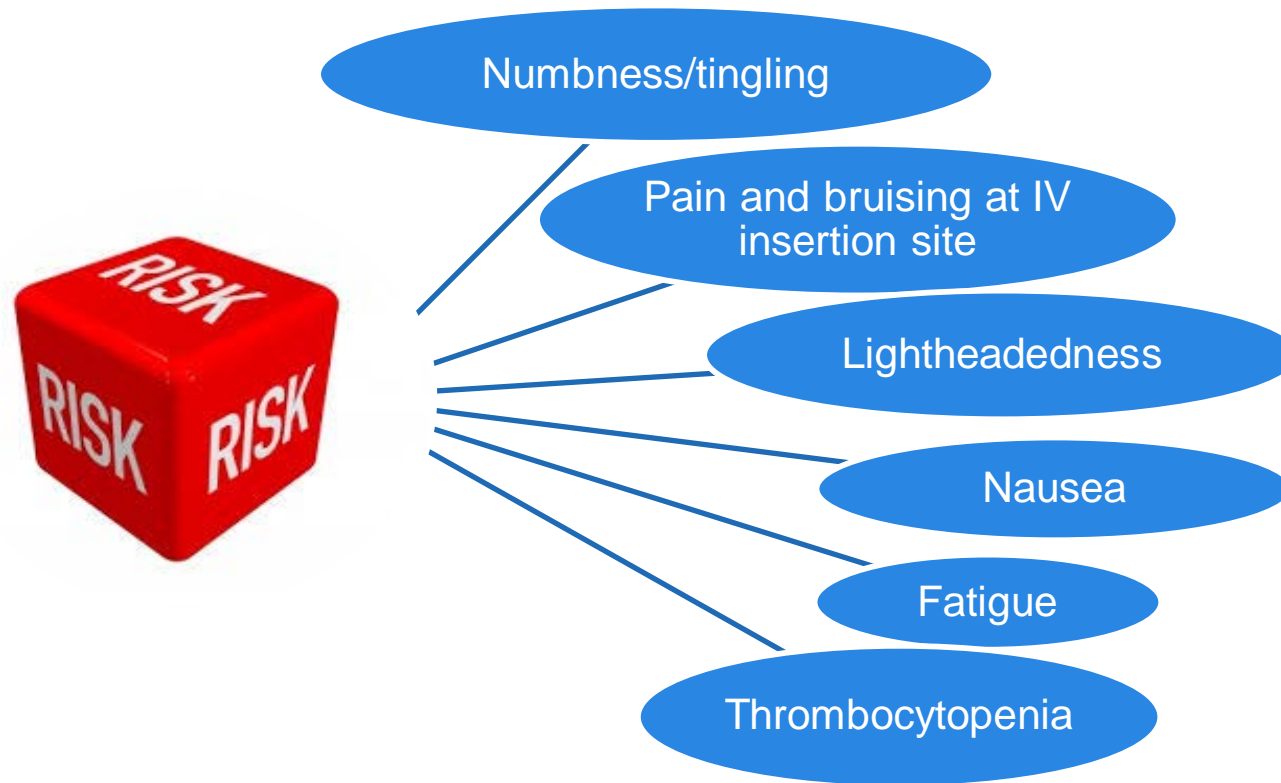


- **CD19 + disease**
- Relapse/Refractory disease
- Performance status
- No active infectious diseases
- Negative for HIV, Hepatitis B or C
- Not pregnant
- Adequate Lymphocytes (**ALC >0.5**)
- 6 months from allo-BMT
- Off any immune suppressive therapy
- No active GVHD

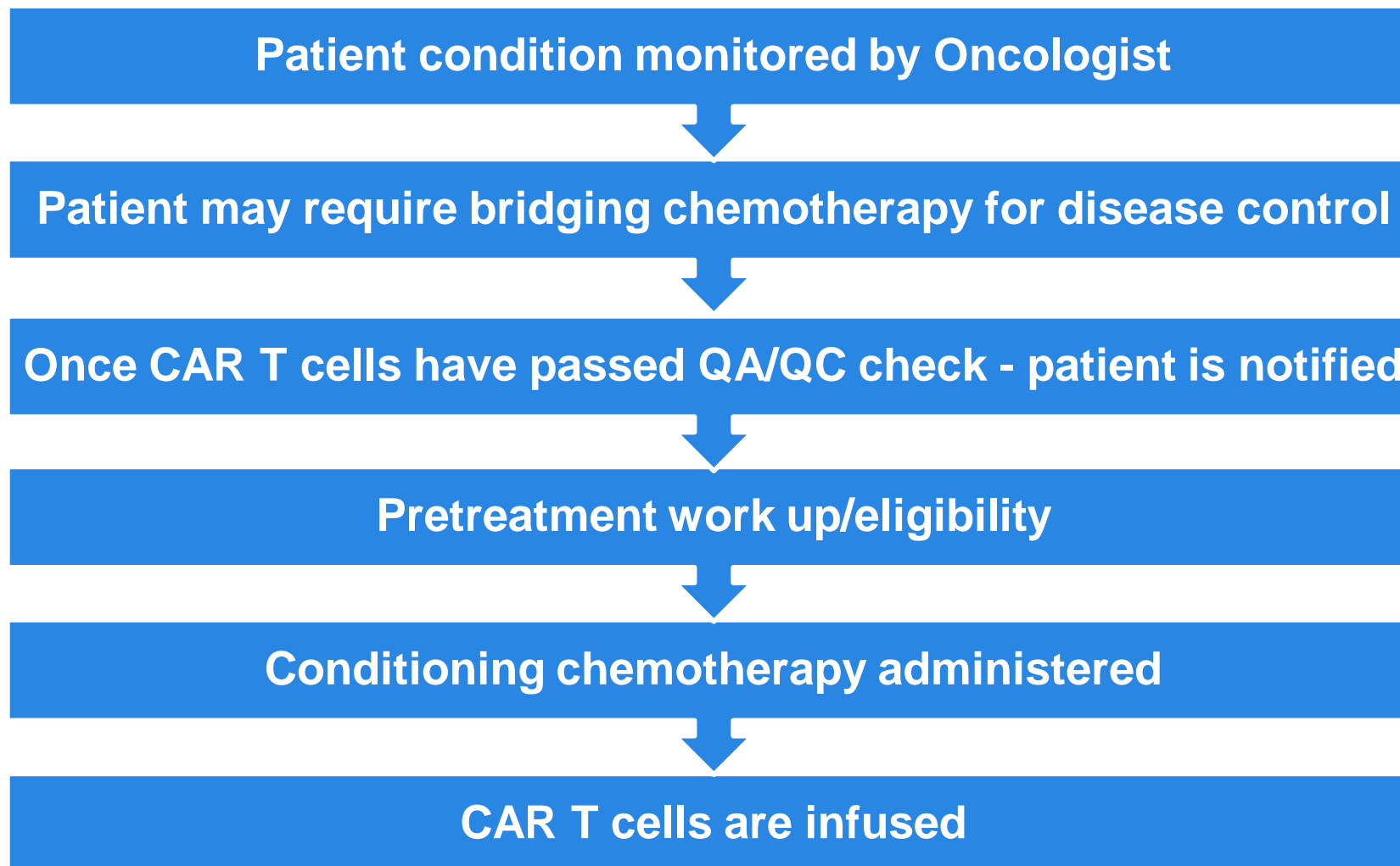


Collection Process

- Peripheral/Central access for collection
 - Peripheral IV if large veins
 - Leukophereses catheter placement



Patient Flow: Production to Infusion



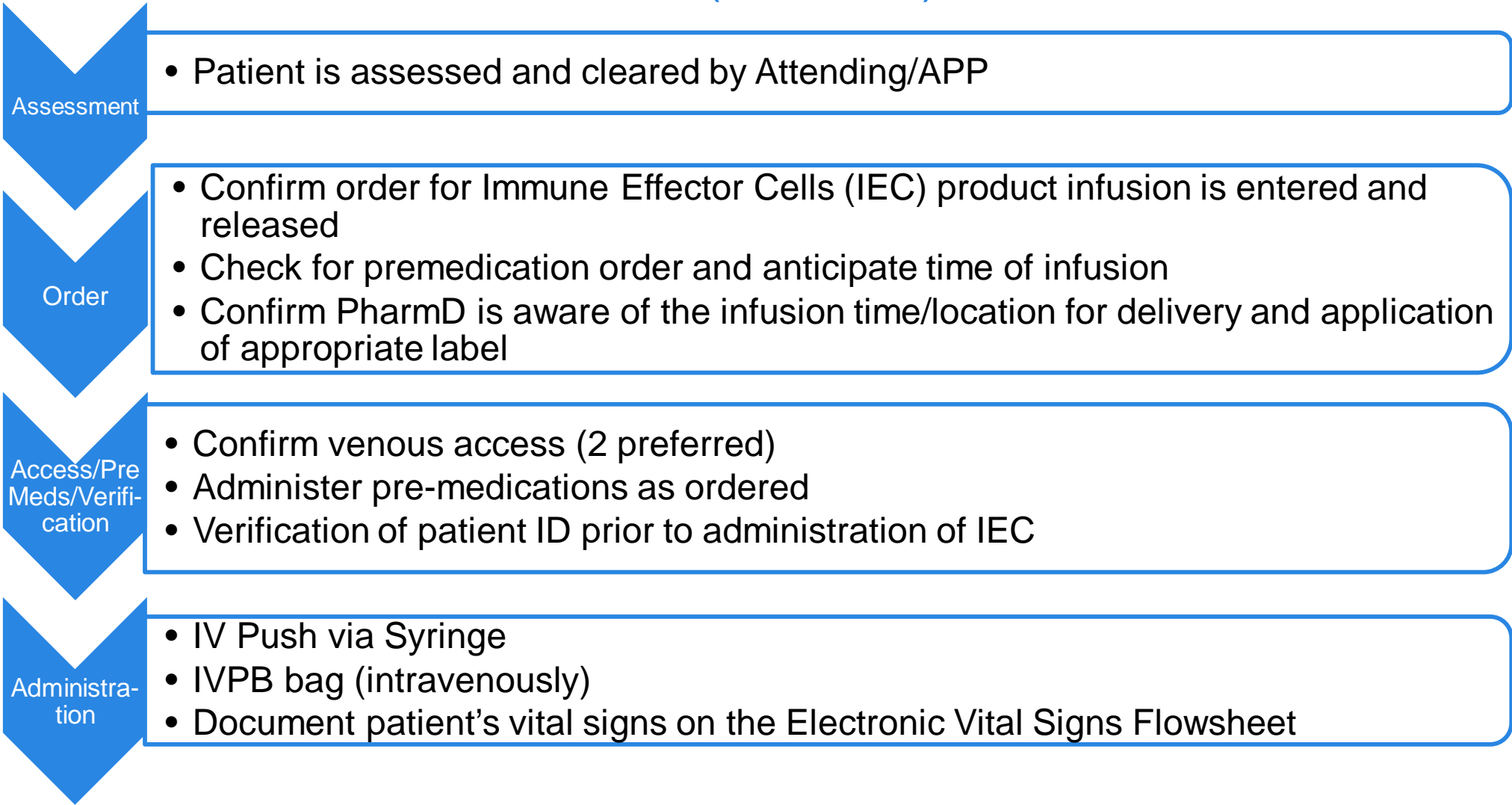
CAR T-cell Infusion: Conditioning

- Conditioning regimen:
 - Depletes T cells
 - Creates “favorable” environment for CAR T-cell expansion
 - Eradicate suppressor cells in the microenvironment
 - Debulks tumor/malignancy
- Conditioning regimen can vary depending on:
 - Product and different indications
 - Diagnoses for the same product
- **NO steroids** for antiemetic pre- or post-CAR T Cell Infusion



CAR-Modified T-cells: Day of Infusion (Day 0)

(NUR NPM-8001)



Verification Process

Verification	When?	Who?	Verifying what?
First Verification	When cell product arrives in the unit	<ul style="list-style-type: none"> Laboratory staff member Clinical Staff member receiving the cell product (Attending/APP) 	<ul style="list-style-type: none"> The cell product against the laboratory form (electronic or paper) Inspect for condition of the cell product.
Second Verification *label is placed by pharmacy once the product is thawed	Prior to infusion	<ul style="list-style-type: none"> 2 clinicians <ul style="list-style-type: none"> Attending and APP or RN 	<ul style="list-style-type: none"> Verification of the product information, labeling and patient information will be done by an Attending MD and an APP against <u>order</u> and the <u>Cell Distribution Report</u>. <u>Patient verification</u> is also performed immediately prior to administration (MD/APP or RN)
Third verification	Prior to infusion	<ul style="list-style-type: none"> 2 RNs 	<ul style="list-style-type: none"> Verify the following against the product <ul style="list-style-type: none"> Patient identification Product against order Document in medical record

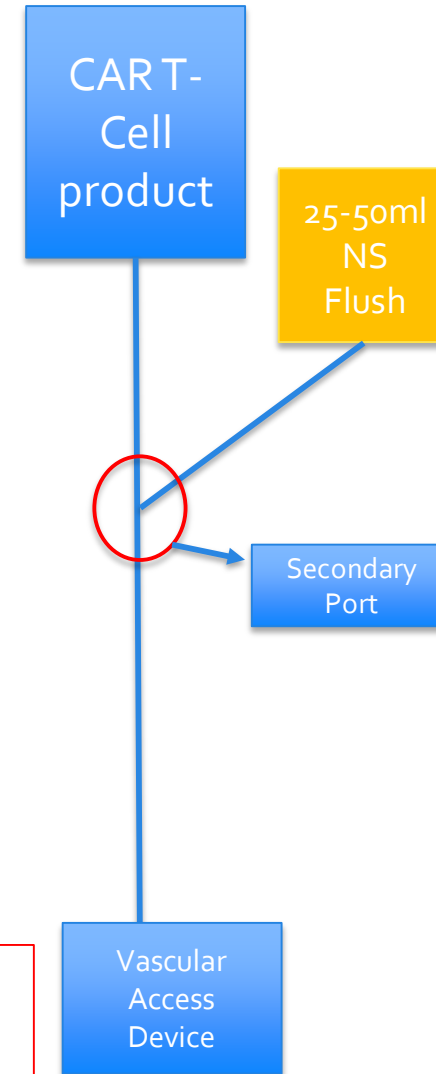


CAR T-Cell Administration (NUR NPM-8001)

- Cells Infused via IV Bag
 - ☐ Administered by RN
 - ☐ Macro IV Tubing for Cells (No Filters /No Pumps)
 - ☐ Normal Saline 25-50 ml IV bag with a secondary line to flush cells
 - ☐ Ensure you have NS liter bag, suction set up, non-rebreather, hypersensitivity kit and code card available
 - ☐ Check for blood return prior to infusion
 - ☐ Vital signs pre infusion, q 15min during infusion, and q 1hour x 2 post infusion
 - ☐ Physician/APP determines infusion rate
 - ☐ Primary RN establishes/monitors rate

$$\text{gtts/min} = \frac{\text{TOTAL VOLUME X 15 (MACRO DRIP TUBING)}}{\text{TIME TO BE INFUSED}}$$

<http://www.manuelsweb.com/gttPerMin.htm>



CAR T-Cell Administration

- Cells Infused via IV Push
 - Administered by Physician or APP
 - Between 5-20 minutes as per MSKCC Policy
 - 10 cc NS Flush
 - RN documents vital signs
 - RN monitors for adverse reactions during the infusion

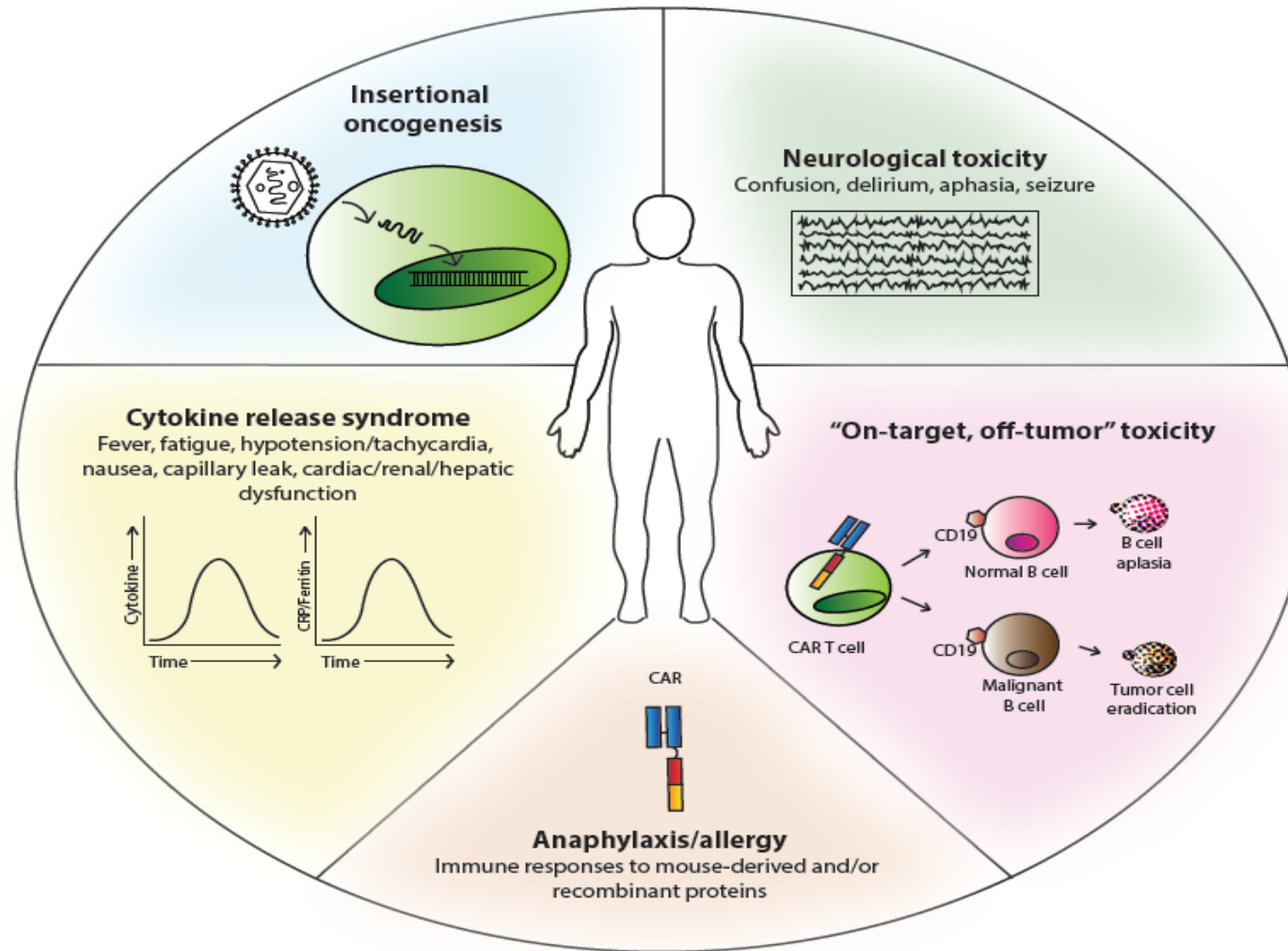


Clinical Consideration

- RN should not leave the room during the first 15 minutes of the infusion
- APP must be physically present on the patients unit during this time to immediately address life-threatening reactions
- APP's name and beeper number should readily be available



CAR T Cell Toxicity



Boxed Warning

KYMRIA[™] (tisagenlecleucel) suspension for intravenous infusion
Initial U.S. Approval: YYYY

**WARNING: CYTOKINE RELEASE SYNDROME AND
NEUROLOGICAL TOXICITIES**

See full prescribing information for complete boxed warning.

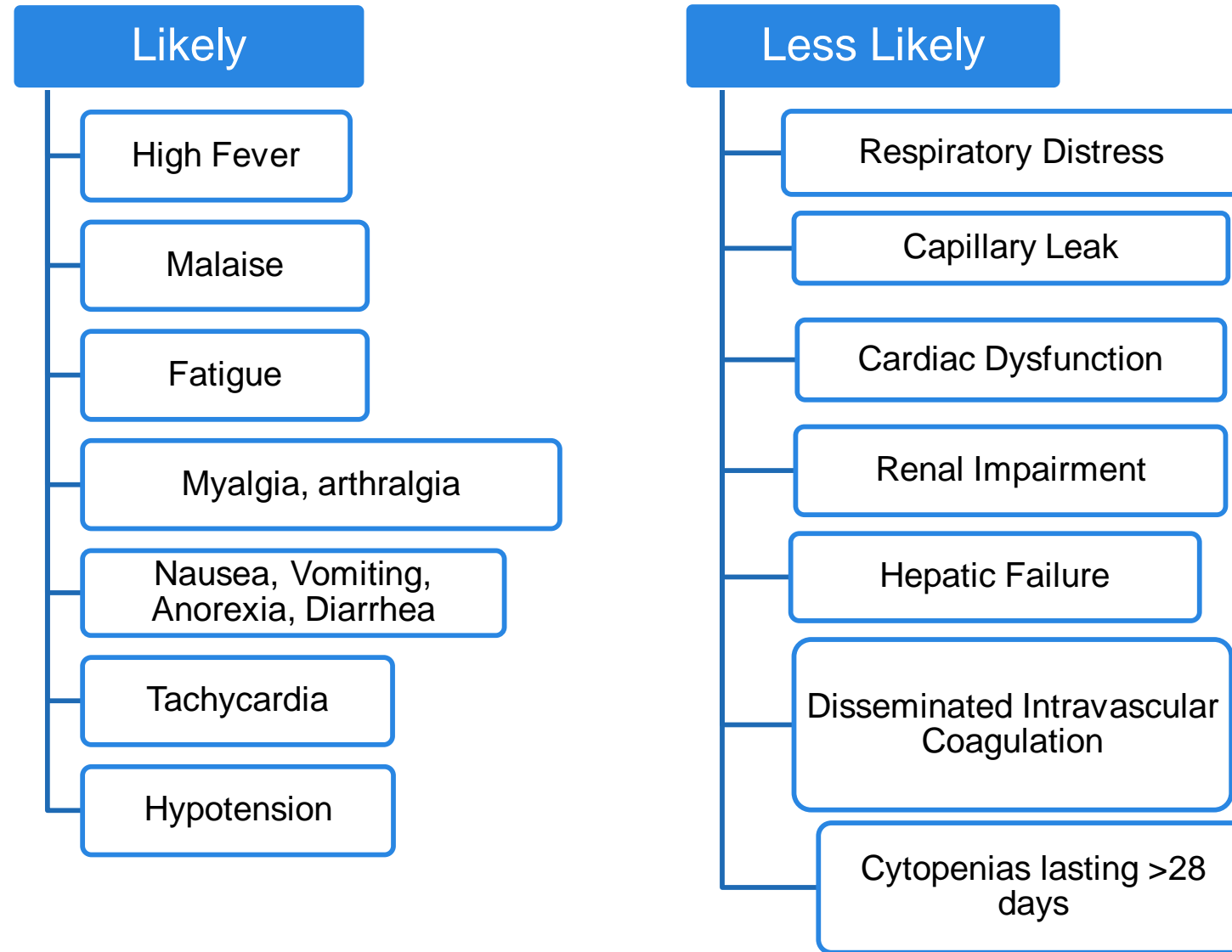
YESCARTA[™] (axicabtagene ciloleucel) suspension for intravenous infusion
Initial U.S. Approval: 2017

**WARNING: CYTOKINE RELEASE SYNDROME AND
NEUROLOGIC TOXICITIES**

See full prescribing information for complete boxed warning.



Cytokine Release Syndrome (CRS)



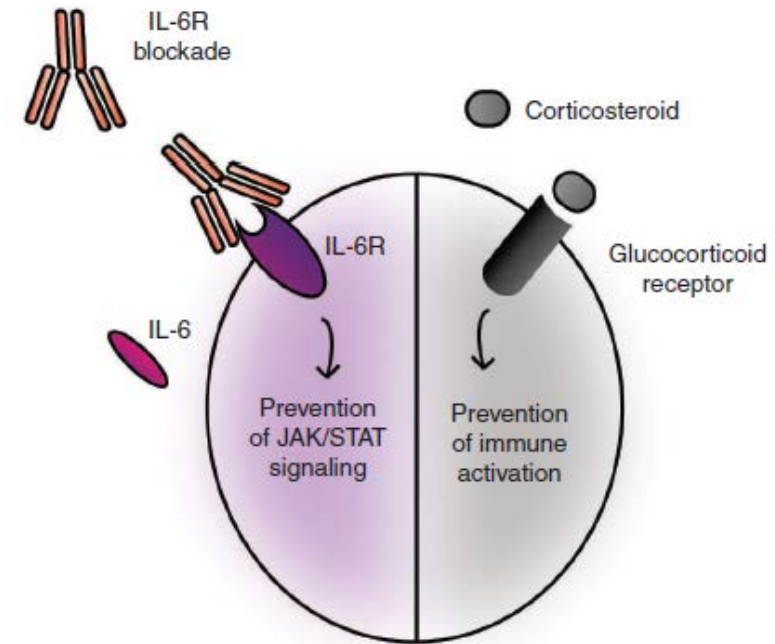
Management of CRS

- Fever
 - T_{max} of 108.5 F (42.5 C)
 - Median time to onset: 3 days
 - Acetaminophen
- Hypotension
 - NS/LR bolus
 - Vasopressor
- Hypoxia
 - Oxygen
 - Ventilator support



Management of CRS

- Tocilizumab
 - *Monoclonal antibody - IL-6 receptor antibody*
 - Fever and hypotension often resolve within a few hours
 - Prevailing theory is no impact on CAR T outcome or function
- Corticosteroids
 - Thought to be more efficacious for neurotoxicity
 - Prolonged use of high dose steroids may result in ablation of CAR T cell population



ASTCT Consensus Grading in CRS

	Grade 1	Grade 2	Grade 3	Grade 4
Fever[†]	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one 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, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

*Organ toxicities should be graded using CTCAE but do not inform CRS grading



Neurological Toxicities and Management



Symptoms

Headache
Tremor
Anxiety
Confusion
Delirium
Expressive aphasia
Myoclonus
Seizure- like activity
Obtundation
Encephalopathy

Management

Typically reversible
Levetiracetam prophylaxis
Dexamethasone
Neuro evaluations
MRI/EEG/LP as needed



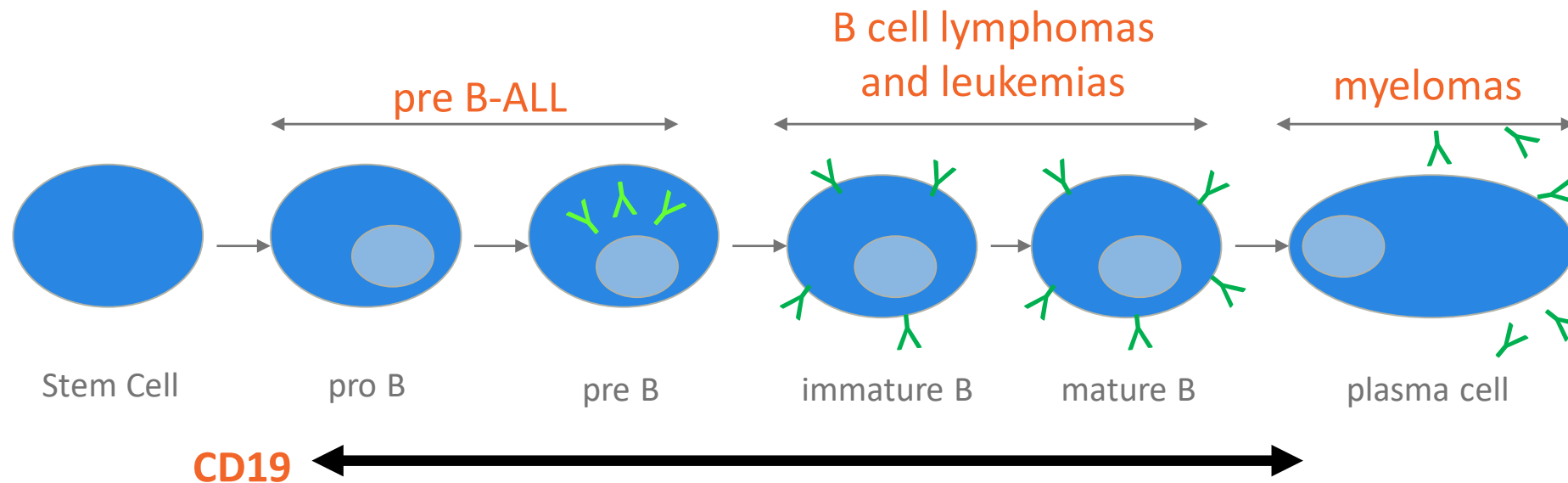
ASTCT Consensus Grading for Neurotoxicity

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Immune Effector Cell-Associated Encephalopathy (ICE) Score for children ≥ 12 years[^]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
CAPD score for children age < 12 years	1-8	1-8	≥ 9	Unable to perform CAPD
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	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 Non-convulsive 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 weakness	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging.	Decerebrate or decorticate posturing; cranial nerve VI palsy; papilledema; Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

Long Term toxicity

B Cell Aplasia

- CD19 therapy also targets normal B cells
- Hypogammaglobulinemia may limit the patient's ability to produce antibodies
- Serum IGG levels: baseline, 1, 3, and 6 months
- IVIG if IGG <500 or clinical indicated



Management of CAR T cells Side Effects

- Patient condition/status will dictate management
- **Each patient is unique and management is not always straightforward**
- Management guidelines can aid in the initial recognition and management of toxicity
- Post Infusion Toxicity – need to manage all:
 - Chemotherapy Side Effect
 - Cytokine Release Syndrome (CRS)
 - Infection/Sepsis



Preventing Toxicity

- Tumor de-bulking
 - Re-induction and conditioning chemotherapy
- Levetiracetam Prophylaxis
 - Unclear benefit
- Prophylactic Tocilizumab
 - Increased Neurotoxicity (Axi-cel Prophylaxis study)
- Suicide or Elimination Gene



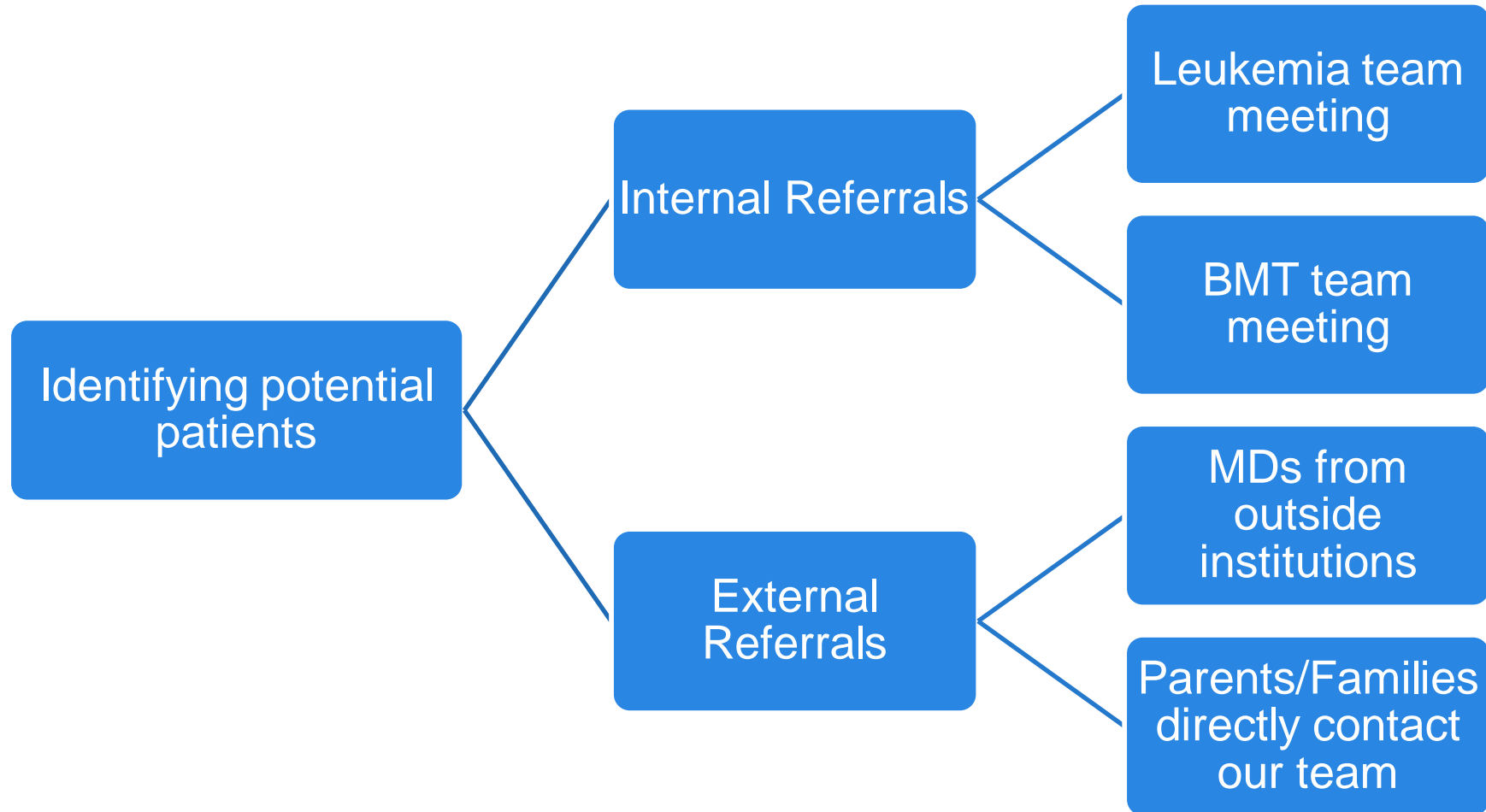
ELIANA Trial Results

- N= 79
- Overall response rate - 82% (65/79)
 - Complete Remission (CR) - 62%
 - CR –incomplete blood count recovery - 20% (16/79)
- Relapse free survival for 12 and 18 months - 66%
- Overall survival for 12 months is 76% and for 18 months is 70%.

Toxicity	% Patients
CRS	77% (Grade 3 or 4 48%)
Neurological events within 8 Weeks	40%
Grade 3 or 4 Thrombocytopenia	43%
Grade 3 or 4 Neutropenia	54%
Neutropenic Fever	62%



Patient Identification



Clinical/Financial Authorization

Clinical team obtains “clinical approval”



Patient Financial Services (PFS) starts the financial approval process



Letter of Medical Necessity, CPT codes, pertinent information
sent to insurance company

- Current commercial CAR T products have up to a \$500,000 price tag
- We have a dedicated team for CAR-related financial services
- Our institution achieves Single Case Agreements (SCA) for each patient
- Our institution has seen a 1-13 day range for obtaining the SCA



Bridging Therapy

Patients may need additional treatment prior to collection if there are delays in treatment (approval and/or production)



- Potential delayed count recovery**
- Side effects and unexpected complications from this treatment**



Resources for our patients

- The FDA requires patients stay within two hours of the institution for 30 days following CAR T.
 - Due to Manhattan traffic our institution has mandated that they stay within 1 hour.
 - Many of our patients require housing following their infusions.
- Ronald McDonald Housing (RMH)
- Social Work plays a huge role in ensuring patients have the resources they need.
 - In contact with the original institution right off the bat to evaluate/anticipate patient needs
 - Prepare family for coping with side effects of treatment
 - Preparing for the possibility of the PICU and what that entails.



Data Management

- Foundation for the Accreditation of Cellular Therapy (FACT)
 - National Accrediting agency for BMT and Immune Effector Cell (IEC) Therapy
 - Mandated requirements for capturing all adverse events
- Manufacturers reporting requirements
- FDA mandated to track patients for up to 15 years.



Future Directions

- Hematologic Malignancies
 - BIANCA Trial
 - Pediatric R/R NHL – CAR T cells
 - Comparison trials NHL (adult)
 - Auto-HSCT vs CAR T cells
- Solid Tumors
 - Successfully target/eradicate solid tumors
 - Armored CAR T cells – recruit the immune system or counter act the suppressive microenvironment.
 - Combination with check-point blockade

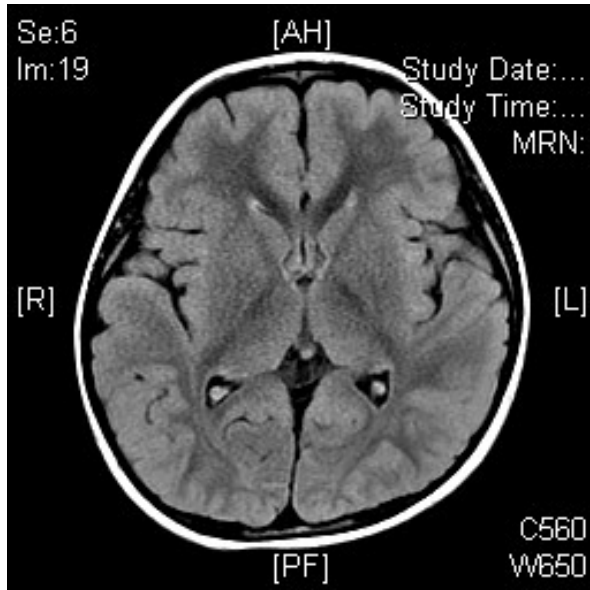


Case Presentation

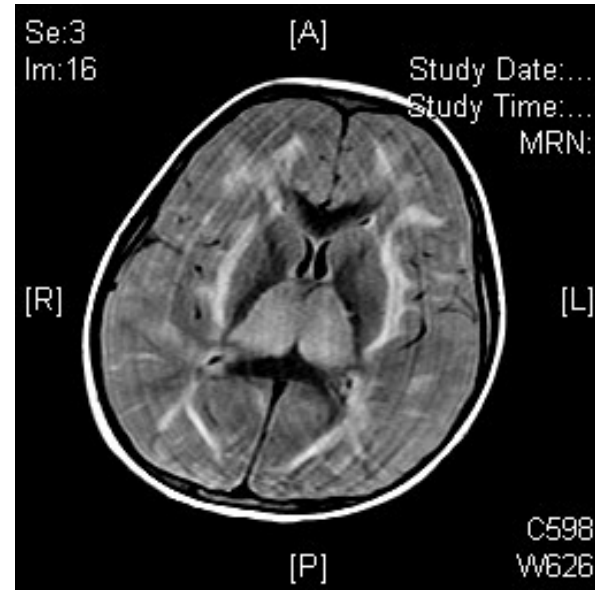
- M.W. - 4 y/o male with refractory pre-B cell ALL
 - MRD Cohort: (Bone Marrow Aspirate: 0.41%)
 - Conditioning Chemotherapy + 19-28z CAR T cells (MSK CAR T cell)
 - Cyclophosphamide (1500mg/m²/dose daily x 2 days)
 - Fludarabine (25mg/m²/dose given daily x 3 days)
- **Day +3** – Fever
- **Day +4** – Compensated shock → IVF only (PICU transfer)
- **Day+5** – Dizziness; Right sided weakness + **Seizure/post-ictal**
 - Lorazepam, increased levetiracetam
 - Tocilizumab
 - CT negative
 - VEEG – diffuse cerebral dysfunction (no focal epileptiform activity)
 - Seizure #2 in the afternoon – Dexamethasone + Valproate
- **Day +6** – MRI + *Diffuse supratentorial white matter vasogenic edema*
 - Improving Neuro Sx - +Left hemiparesis



Vasogenic Edema (FLAIR)



Baseline



Day +6

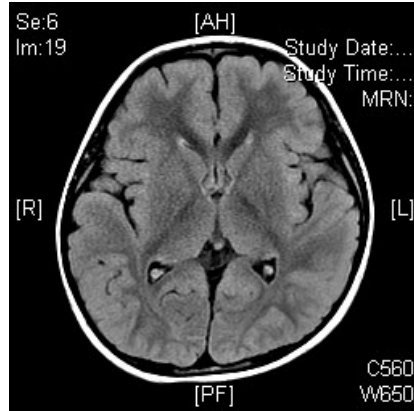


Case Study

- **Day +7** – Improving neurologic symptoms but left hemiparesis still present; speaking
- **Day +9** – Transfer to Floor (5 day steroid pulse completed)
- **Day +14** – Discharged from hospital
 - MRI: *improvement in diffuse supratentorial white matter signal abnormality and diffuse cerebral edema*
 - BMA - MRD negative CR
- **Day +47** – *Received a 9/10 matched unrelated donor T cell depleted BMT*



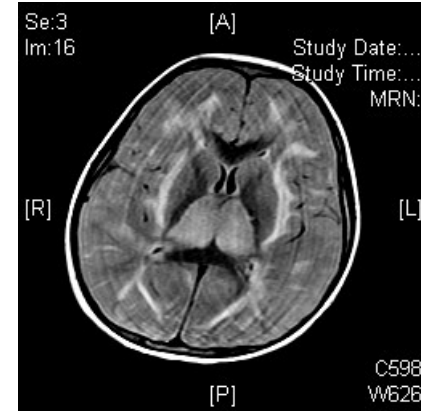
Vasogenic Edema (FLAIR)



Baseline



Day +14



Day +6



Day + 32



Conclusions (1)

- Immunology and CAR T cells
 - B & T cells play an integral role in our immune system
 - Autologous cells are sent to the lab for genetic modification
 - Autologous CAR T cells can identify and destroy the CD19 protein on B cells
- Collection
 - Rapid coordination
 - Multidisciplinary approach
 - Organized with referring institution, donor room, lab and patient's family



Conclusions (2)

- Infusion
 - Timing of infusion involves multiple staff members
 - Close monitoring is imperative
- Treatment/Toxicity Management
 - Patient's require complex nursing care
 - Nursing plays an important role in monitoring and recognizing immunotherapy related toxicities and BMT late effects
 - Prompt response to neurological and vital sign changes



AAMDSIF Mission

To support patients, families and caregivers coping with aplastic anemia, myelodysplastic syndromes (MDS), paroxysmal nocturnal hemoglobinuria (PNH) and related bone marrow failure diseases.



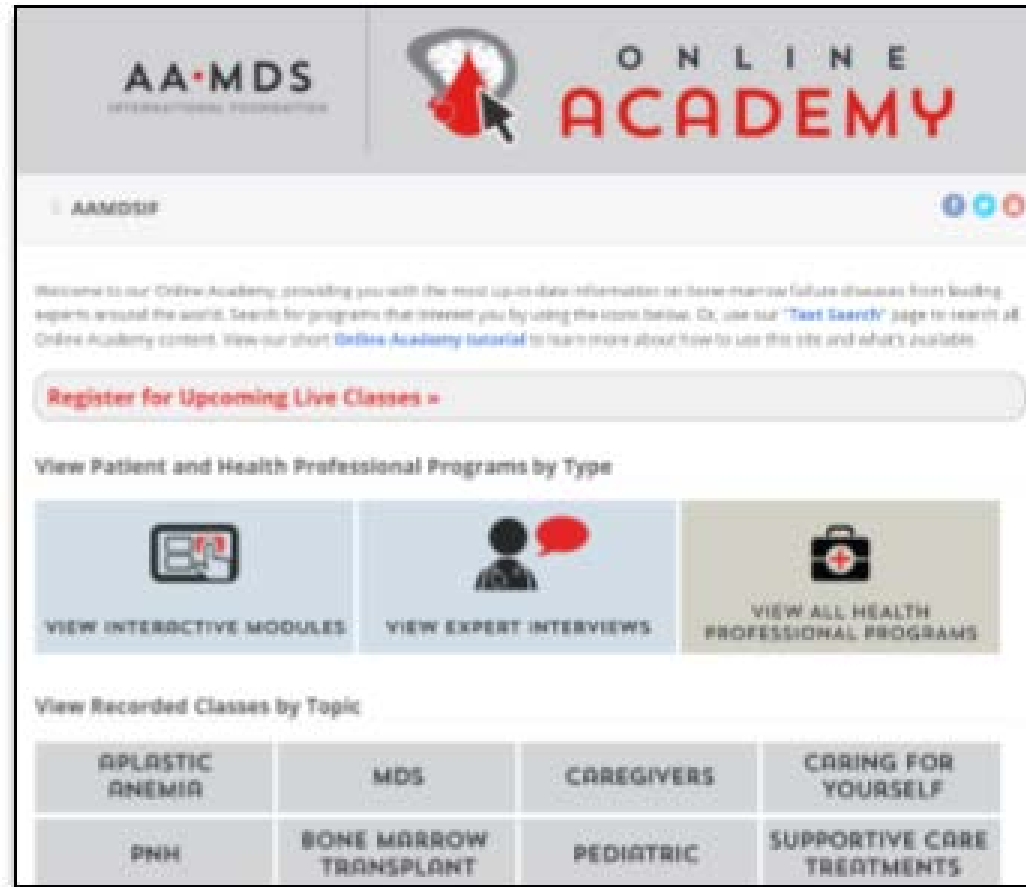
AAMDSIF Health Professional Education

- Biennial Scientific Symposium
- Satellite Symposium at ASH Annual Meeting
- Satellite Symposium at ONS Congress
- Regional Bone Marrow Failure Disease Symposia
- “MDS Rounds” CE program for community hospitals



Online Academy for Professionals and Patients

www.aamds.org/learn



AAMDSIF Patient Support and Education

- Free patient education materials
- Print and electronic newsletters
- Patient information specialist
- Peer support network
- Community Connection support groups

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Rockville, Maryland

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Online: <https://www.aamds.org/conferences>

Call: (800) 747-2820 x2

Email: conferences@aamds.org

Cost: Conference registration is **FREE**



Programs and resources for you and your patients



Debbie Jacobson, OPN-CG
Manager, Patient Support Center
Patient Advocacy and Navigation
National Marrow Donor Program /Be The Match

Be The Match *Patient Support Center*

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Learn more: [BeTheMatch.org/one-on-one](https://www.BeTheMatch.org/one-on-one)



Bilan, MSW
BMT Patient Navigator

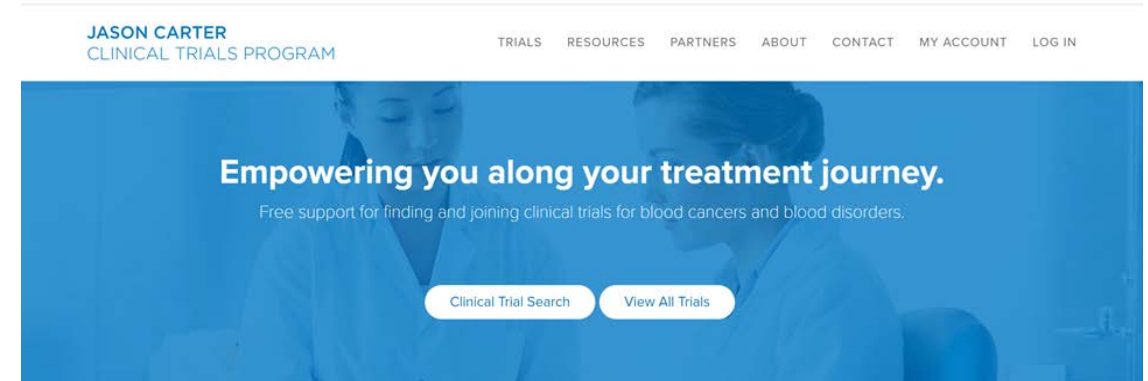
Phone: 1 (888) 999-6743

Email: patientinfo@nmdp.org

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- **Easy-to-understand resources** to learn about cancer treatments and clinical trials

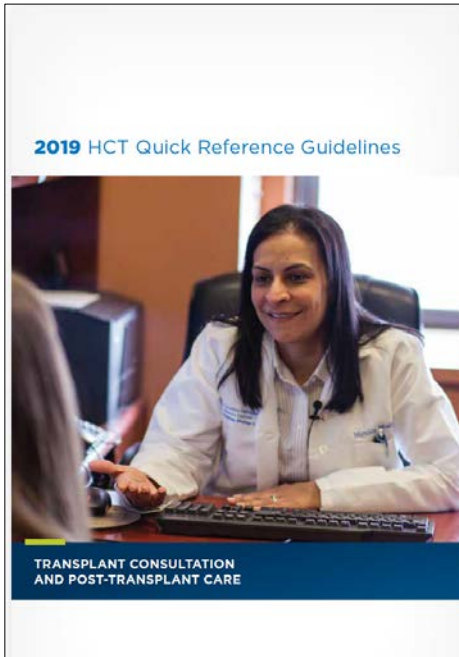


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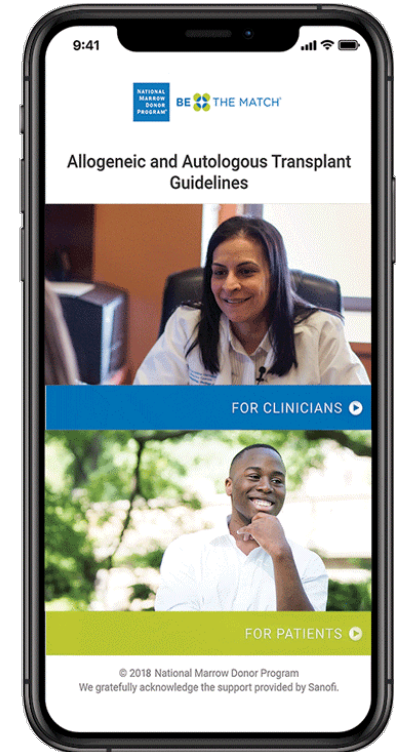
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Quick Reference Guidelines for Transplant Consultation and Post-Transplant Care



- Referral Guidelines – 2019 update
 - NMDP/Be The Match & ASBMT:
Recommended Timing for Transplant Consultation
 - Up-to-date referral for HCT consultation timing for more than 20 diseases
- Long-Term Survival Guidelines
 - Part I: Long-term screening
 - Part II: Vaccinations
 - Part III: Screening for chronic GVHD



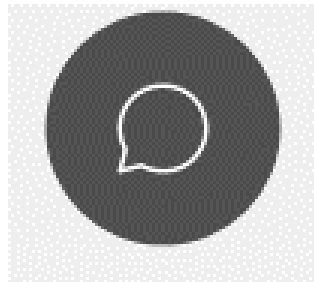
Available in mobile app, print and online:

BeTheMatchClinical.org/guidelines

Questions

Vicki Szenes, MS, RN, CPNP
Meghan Wellenbrink, BSN, RN, CPHON

To ask a question, use
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Thank you for participating!

Webinar Evaluation

- Attendees will receive an email following the webinar with a link to the evaluation.
- All attendees completing the online program evaluation will receive a certificate of attendance or a continuing education certificate.

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