TAKING CARE OF THE CAR-T PATIENT

Madiha Iqbal, MD
Senior Associate Consultant
Division of Hematology/Oncology
Assistant Professor of Medicine
Mayo Clinic Florida, Jacksonville, FL, USA

Date: May 17th, 2024

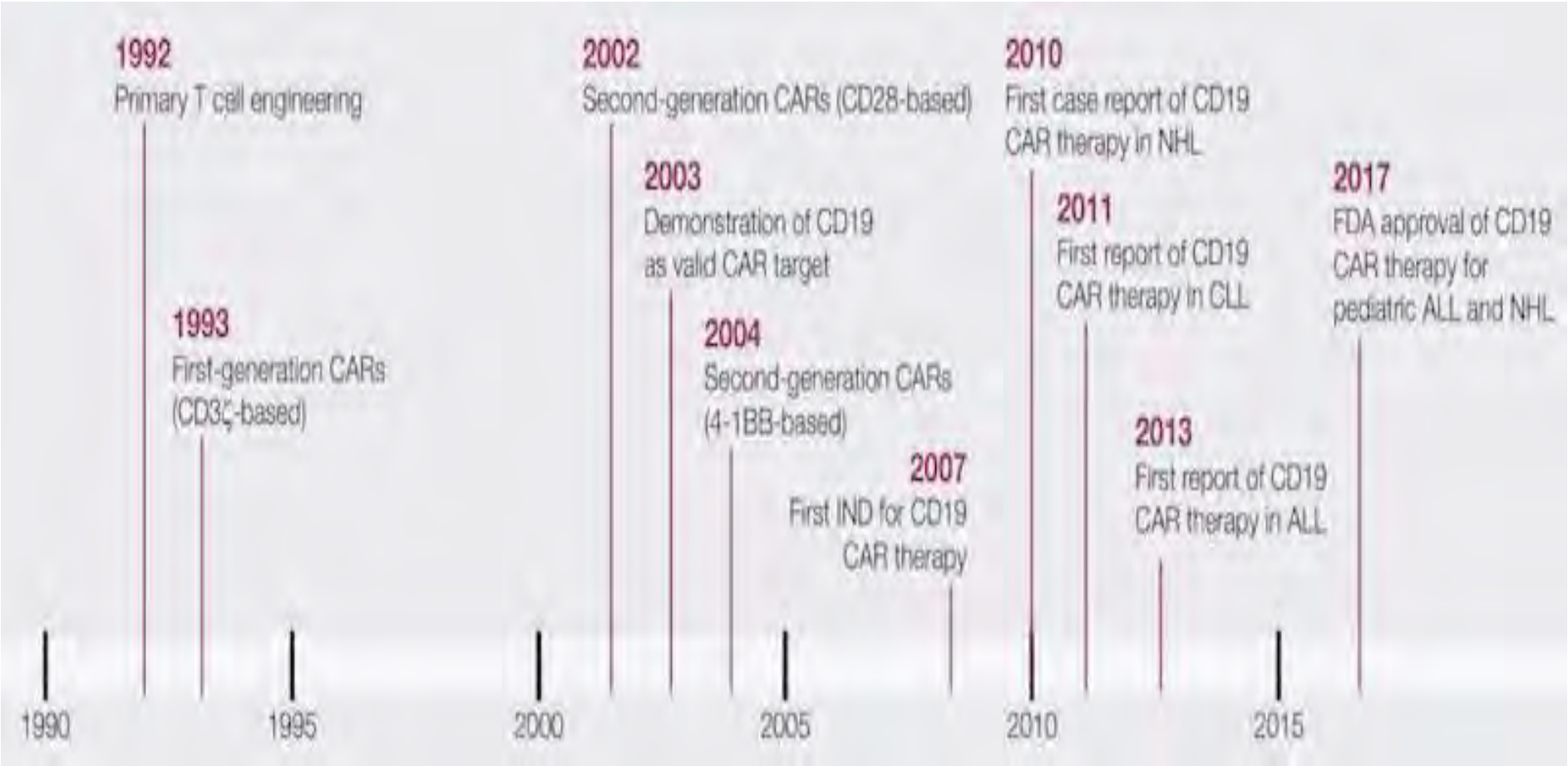
Katelyn Keller, PA-C
Lead APP in outpatient Hematology/Cellular therapy
Division of Hematology/Oncology
Mayo Clinic Florida, Jacksonville, FL, USA

OUTLINE

- Current indications for CAR-T
- Challenges with CAR-T
- Survivorship in the CAR-T patient

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY (CAR-T)

- CAR is an artificial antigen receptor that mediates antibody-targeted recognition
- Binding between CAR and its antigen on tumor cells triggers a signal transduction cascade through signaling domains
- Activates T-cells to kill the target directly or through other components of the immune system
- Effectively creating a graft-vs.-tumor (GVT) effect without graft-vs.-host disease (GVHD)


1992
Primary T cell engineering
1993
First-generation CARs
(CD3ζ-based)
2002
Second-generation CARs (CD28-based)
2003
Demonstration of CD19
as valid CAR target
2004
Second-generation CARs
(4-1BB-based)
2007
First IND for CD19
CAR therapy
2010
First case report of CD19
CAR therapy in NHL
2011
First report of CD19
CAR therapy in CLL
2013
First report of CD19
CAR therapy in ALL
2017
FDA approval of CD19
CAR therapy for
pediatric ALL and NHL
1990
1995
2000
2005
2010
2015

FDA APPROVED INDICTIONS FOR CAR-T

- FDA approved indications in lymphoma
  - Relapsed/refractory large B-cell lymphoma in second (Axi-cel and Liso-cel) and third line (Axi-cel, Tisa-cel and Liso-cel)
  - Relapsed/refractory Low grade follicular lymphoma (Axi-cel)
  - Relapsed/refractory Mantle Cell Lymphoma (Brexu-cel)
- FDA approved indications in Multiple Myeloma
  - Relapsed or refractory multiple myeloma after four or more prior lines of therapy (Ide-cel, Cilta-cel)
- FDA approved indications in B-cell ALL
  - For young adult patients up to age 25 with relapsed or refractory acute lymphoblastic leukemia (ALL) (Tisa-cel)
  - For adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), 18 years and above

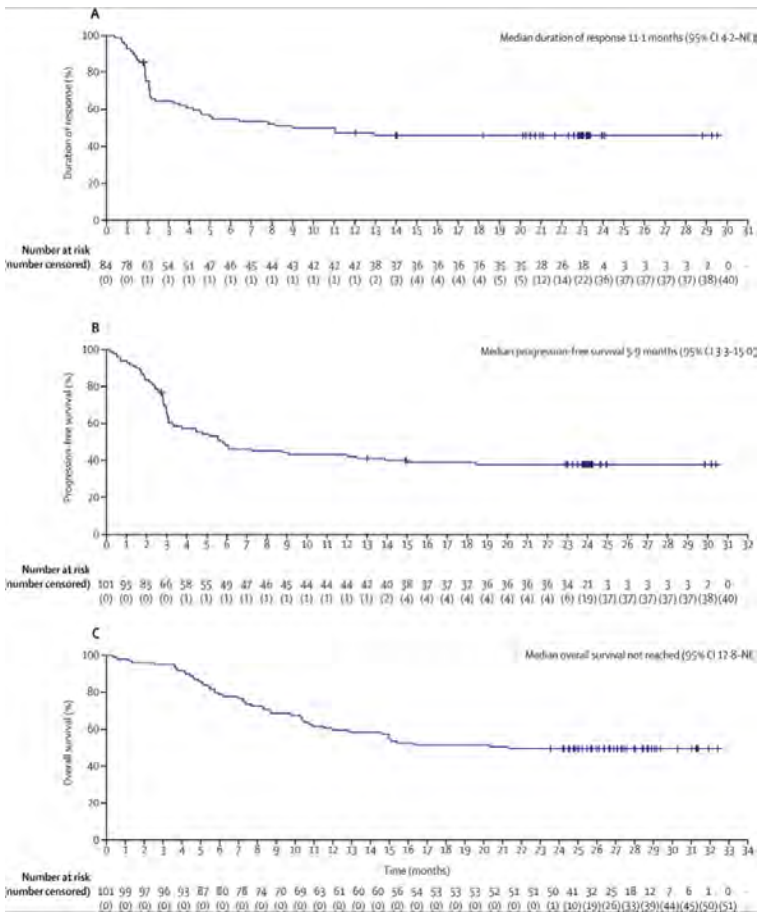
Munshi PN et al. Bone Marrow Transplant. 2021 Dec;56(12):2911-2921.

CART VS AUTO-HCT IN SECOND LINE LBCL

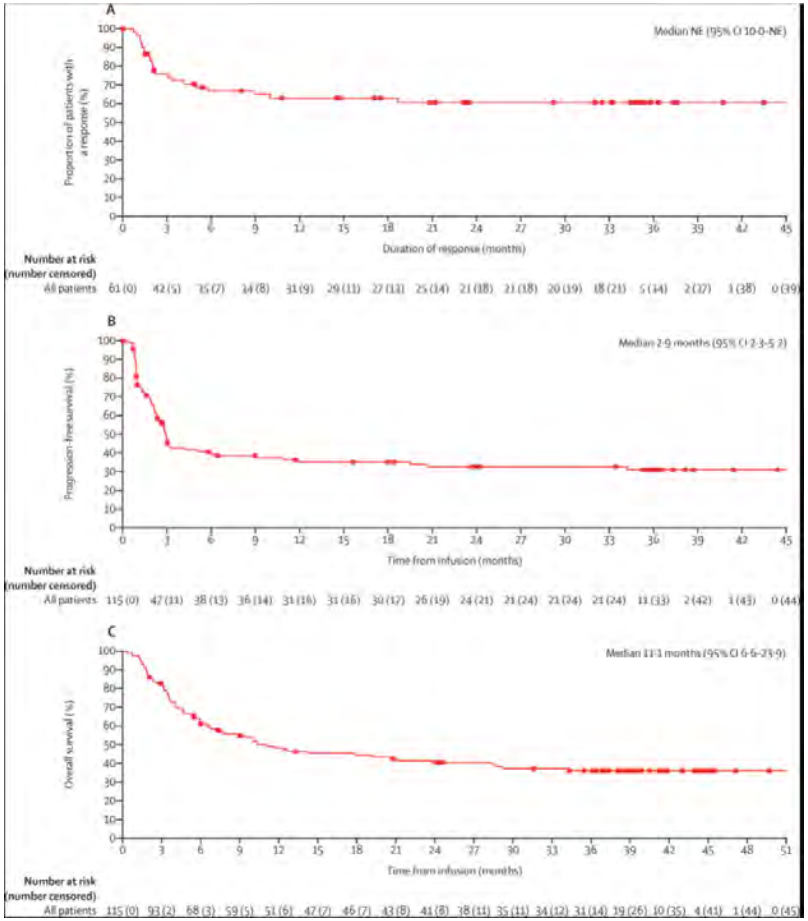
	ZUMA-7		BELINDA		TRANSFORM	
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
Received intended ASCT (%)	—	36	—	32.5	—	45.6
Crossover pn protocol (%)	—	—	—	51	—	51
Received cellular therapy off protocol (%)	—	56	—	—		—
Follow up, median in months	24.9		10		6.2	
ORR/CR rate (%)	83/65	50/32	46/28	43 /28	86/66	48/39
EFS, median in months	8.3	2	3	3	10.1	2.3
EFS, % (timepoint in months)	41 (24 mo)	16 (24 mo)	NR	NR	63 (6 mo)	33 (6 mo)
EFS HR (95% CI)	0.4 (0.31-0.51)		1.07 (0.82-1.4)		0.35 (0.23-0.53)	
PFS, median in months	14.7	3.7	NR	NR	14.8	5.7
PFS HR (95% CI)	0.49 (0.37-0.65)		NR		0.406 (0.21-0.66)	
OS, median in months	NE	25.7	16.9	15.3	NE	16.4
OS HR (95% CI)	0.708 (0.515-0.972)‡		NR		0.51 (0.26-1.004)	

Westin and Sehn. Blood 2022 139: 2737-2746

LONG TERM FOLLOW UP FROM PIVOTAL CLINICAL TRIALS



ZUMA-1 Axi-cel

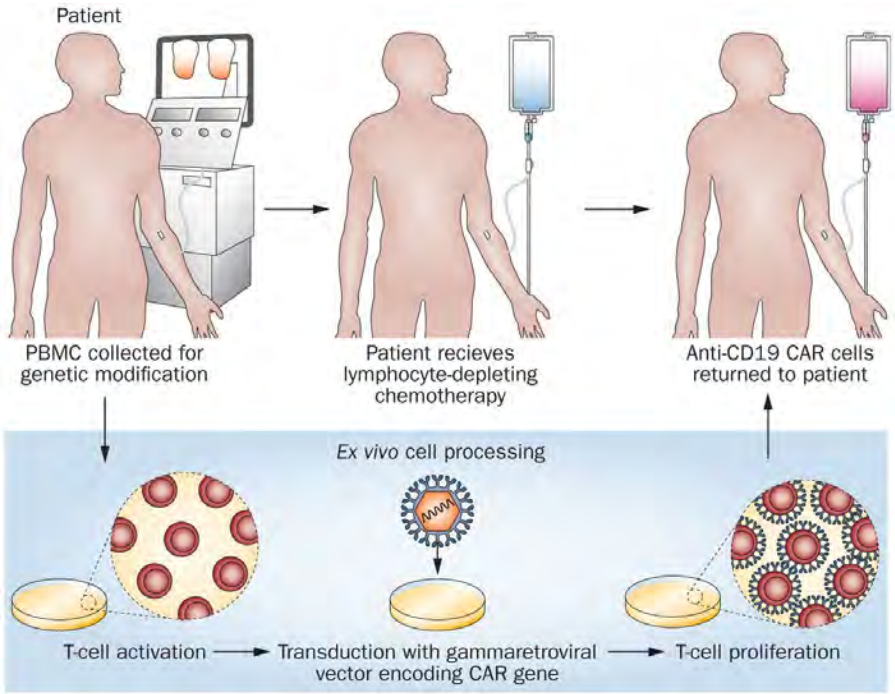


JULIET Tisa-cel

Locke FL et al. Lancet Oncol. 2019 Jan;20(1):31-42
Schuster SJ et al. Lancet Oncol. 2021 Oct;22(10):1403-1415

LIMITATIONS OF CAR-T

- Logistical challenges and unique toxicities
- Requirement of leukophoresis and waiting for several weeks
- Patients with rapidly progressing disease may require temporizing treatment, commonly referred to as bridging therapy
- Cytokine release syndrome
- Neurotoxicity
- Cytopenias
- Financial Toxicity



CYTOKINE RELEASE SYNDROME

- Most common observed toxicity with CAR-T therapy
- Symptoms range from low grade constitutional symptoms to life threatening multiorgan dysfunction and rarely fulminant HLH
- Onset of CRS toxicity usually occurs within the first week after CAR-T-cell therapy, and typically peaks within 1–2 weeks of cell administration
- Approved treatment for CRS
  - Tocilizumab: IL6 Receptor antagonist
  - Corticosteroids

GRADING OF CRS AND NEUROTOXICITY

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or		
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

TREATMENT OF CRS

Grade 1-

- supportive measure;
- Anti-pyretics (consideration for toci in cases of refractory fevers)

Grade 2-

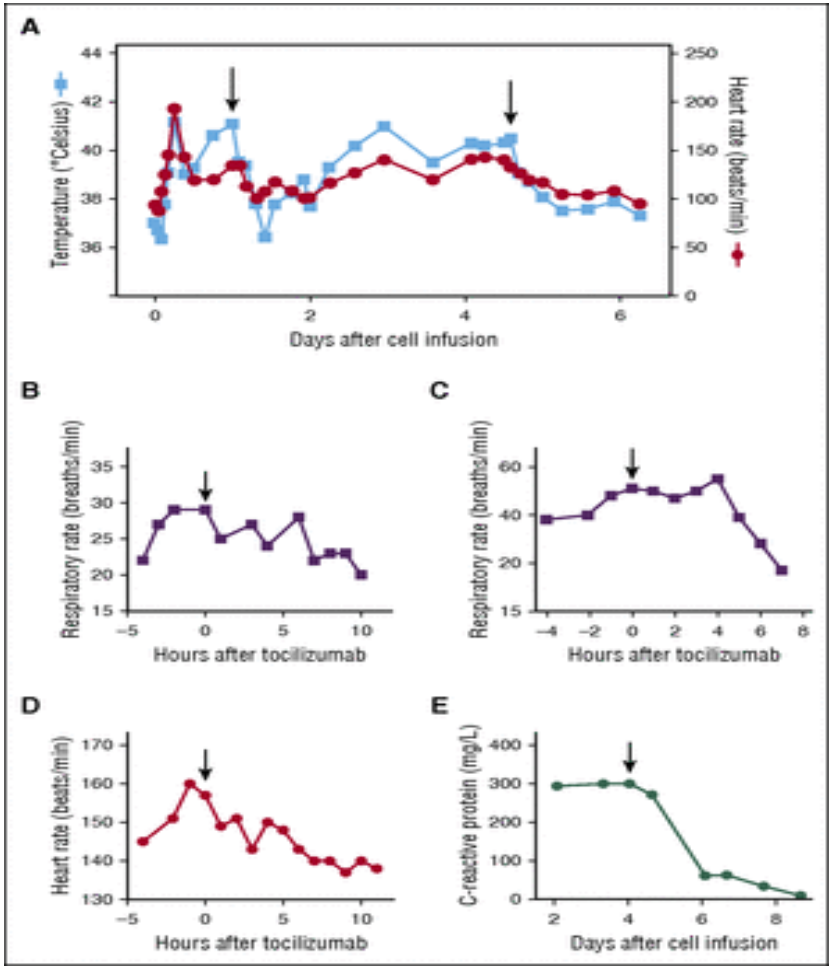
- IV fluids for hypotension, O2 for pulmonary CRS, tocilizumab 8mg/kg
- MICU for impending ventilator support or fluid refractory hypotension requiring vasopressor support

Grade 3, 4-

- tocilizumab, corticosteroids(methylpred 1-2 mg/kg q12hr) and MICU management

Refractory CRS

- Siltuximab
- Anakinra – IL-1 inhibitor
- Jak inhibition



ICANS/NEUROTOXICITY

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Second most common adverse event

- Can occur independent or concurrent with CRS
- Symptoms range from confusion and disorientation to seizures, obtundation, cerebral edema
- Biphasic: first phase within 5 days of cellular infusion; second phase beyond 5 days
- Delayed neurotoxicity during 3rd or 4th week in 10%

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

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

TREATMENT OF ICANS

Grade 1

- Consider levetiracetam seizure prophylaxis (750 mg BD)
- Avoid medications that cause central nervous system depression
- Seek neurology specialist consultation
- Fundoscopic examination to assess for papilledema
- Brain MRI with contrast (brain CT if brain MRI is not feasible)
- Consider diagnostic lumbar puncture with measurement of opening pressure where possible, sending samples for culture and sensitivity, cytology, biochemistry, and virology as a minimum
- Consider spine MRI if the patient has focal peripheral neurological deficits
- Consider electroencephalogram (EEG)
- Consider tocilizumab 8 mg/kg but only if concurrent CRS
- Twice daily neurocognitive assessment using the ICE score and ICANS grading

Grade 2

- Investigations and supportive care as per grade 1
- Consider dexamethasone at a high dose with rapid weaning
- Consider transferring the patient to the intensive care unit (ICU)

Rees JH. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) 2022 Feb 7. In: Kröger N, Gribben J, Chabannon C, et al., editors. The EBMT/EHA CAR-T Cell Handbook [Internet]. Cham (CH): Springer; 2022. Chapter 27.

Grade 3

- Administer dexamethasone 10–20 mg IV every 6 h or methylprednisolone equivalent until improvement to grade 1 and then taper
- Management of seizures with lorazepam 0.5 mg IV or other benzodiazepines as needed, followed by loading with levetiracetam or other anticonvulsants as required
- If fundoscopy reveals stage 1 or 2 papilloedema with cerebrospinal fluid (CSF) opening pressure > 20 mmHg, seek urgent advice from neurologist
- Consider repeat neuroimaging (CT or MRI) every 2–3 days if the patient has persistent grade ≥ 3 ICANS

Grade 4

- Transfer patient to intensive care unit (ICU); consider mechanical ventilation for airway protection
- Seizure management
- For convulsive status epilepticus, seek urgent advice from neurologist Administer methylprednisolone 1000 mg/day for 3 days, then taper at 250 mg every 12 hrs for 2 days, then 125 mg every 12 hrs for 2 days, then 60 mg every 12 hrs for 2 days
- For management of raised intracranial pressure, consider acetazolamide 1000 mg IV, followed by 250–1000 mg IV every 12 h; elevating the head of the bed; hyperventilation; and hyperosmolar therapy with mannitol

HLH/MAS

Typically occurs within 5 days of infusion (RARE)

CRS with:

- Ferritin >10k and 2 of the following
  - Gr 3,4 LFTs
  - GR 3,4 oliguria/ elevated Cr
  - BM or organ hemophagocytosis presence and/or CD68+

Treatment

- Initially treat as GR 3,4 CRS
- If no improvement in 48 hrs- add etoposide and/or IT AraC for neurotoxicity

FOLLOW-UP POST-CART

1

Post Hospital Discharge:

- Follow-up in outpatient Cellular Therapy clinic 2x/week x 30 days post CART
- Follow Labs
- Resolution of toxicities
- Transfusions prn

2

Transfer back to referring provider

- Provide clinical summary, recommended follow-up, treatment of cytopenias, prophylactic meds)

3

Return to CART center for Restaging

Day 30 to 90 days post-CART

Every 3 months for the first 2 years

- Duration of cytopenias post CAR T-cell therapy is variable, ranging from 14 to 180 days and sometimes longer
- Most patients recover blood counts by 30 days, but a notable percentage of patients experience persistent cytopenias lasting beyond 30 days

→ **Infections**

→ **Transfusions**

→ **Prolonged hospitalization**

→ **Increased medical costs**

Zhu F et al. Cell Transplant. 2020 Jan-Dec;29:963689720919434
Yassine F et al. Hematol Oncol Stem Cell Ther. 2022 Nov 25;15(3):122-130

CYTOPENIAS

<30 days

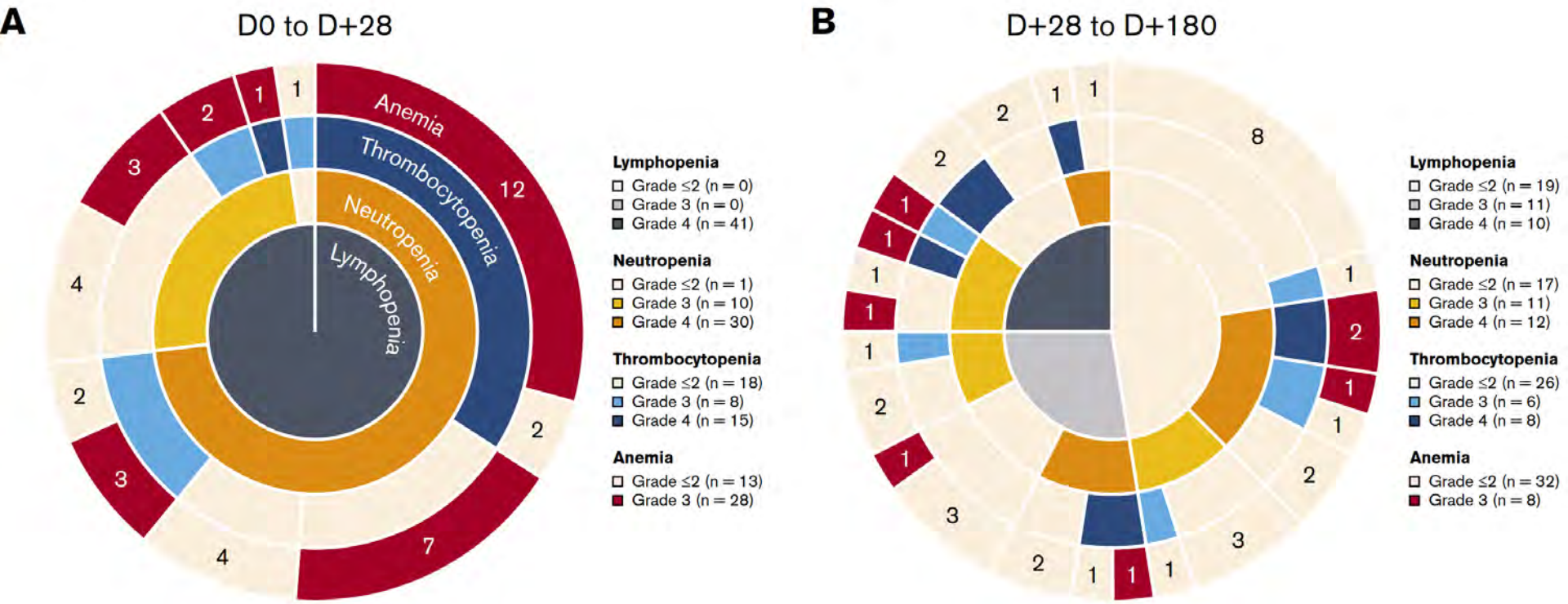
- Chemotherapy prior to CART
  - worse if >/= 4 lines of therapy) independent of CRS
- Median age (older)
- Poor bone-marrow reserve with baseline cytopenias
- Severity of CRS/inflammatory cytokines
- High baseline LDH levels correlating with tumor burden
- Infection

>30 days

- CART cell activity
- Higher grade CRS is associated with prolonged cytopenias

- Monitor CBC weekly through D+60 post CART or as indicated post recovery
- Provide transfusion and/or Growth Factors as needed

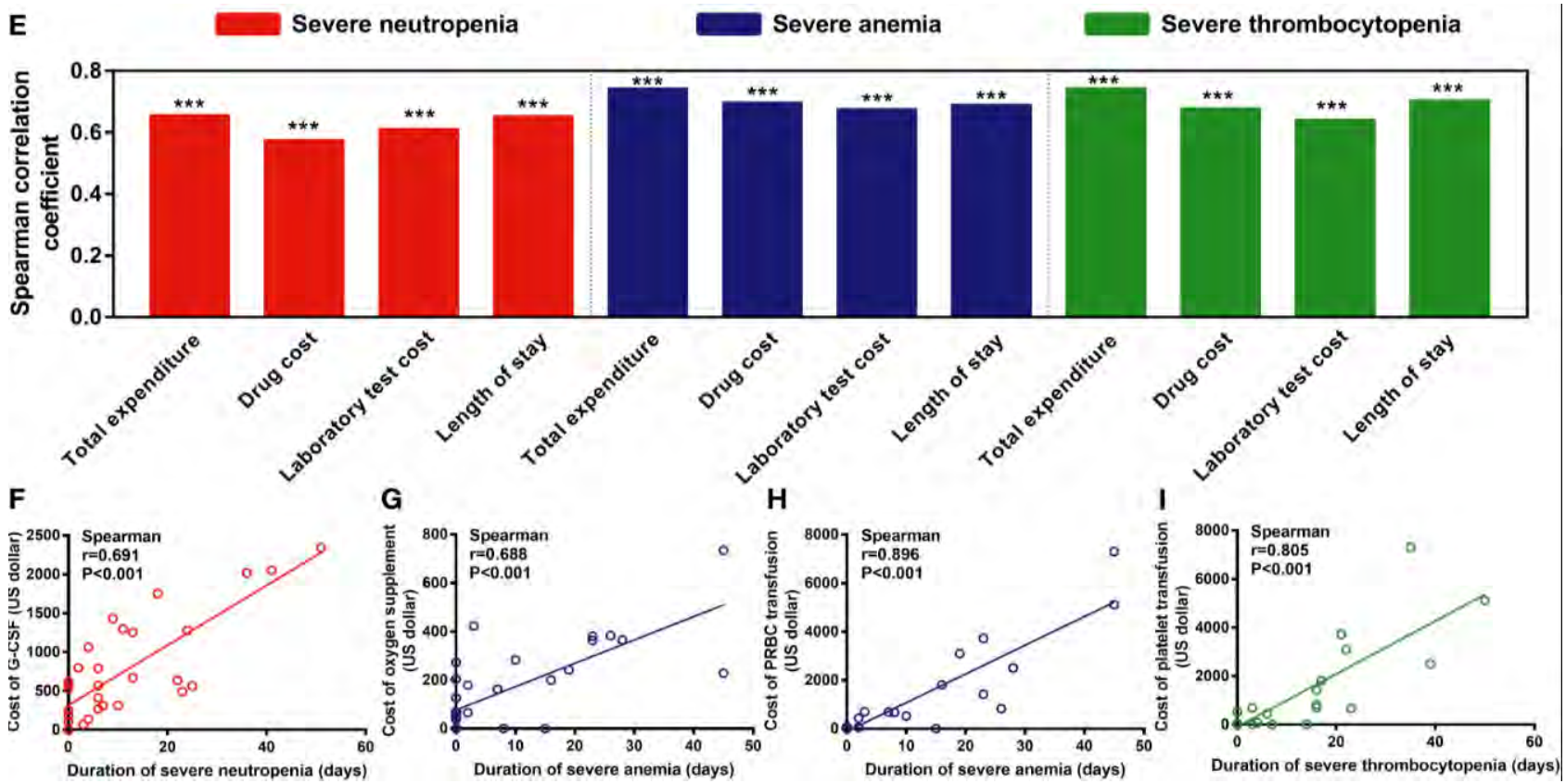
SHARMA, CANCERS 2022.



54% (n=22) required G-CSF after 28 days
17% (n=7) required platelets after 21 days
22% (n=9) required RBC after 21 days

BLAIRD, J. ET AL. BLOOD ADVANCES 2021.

IMPACT OF CYTOPENIA ON HEALTH CARE COSTS



Wang L et al. Front Oncol. 2021 Jun 30;11:702644

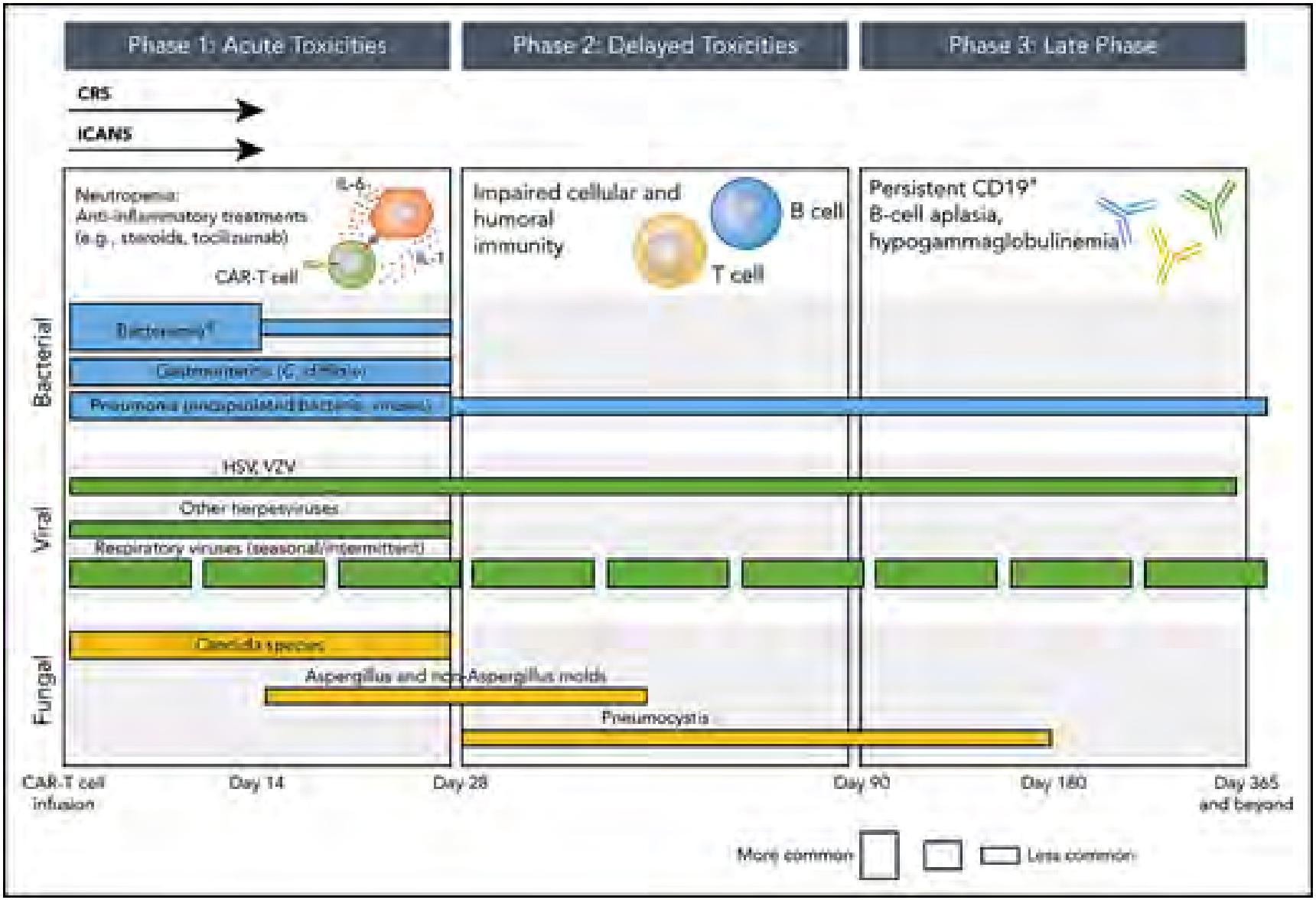
MANAGEMENT OF CYTOPENIAS

Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE)

G-CSF does not worsen toxicities and efficacy of CAR-T cells in refractory/relapsed B-cell lymphoma

Eugenio Galli, Vincent Allain, Roberta Di Blasi, Sophie Bernard, Laetitia Vercellino, Florence Morin, Hannah Moatti, Sophie Caillat-Zucman, Sylvie Chevret & Catherine Thieblemont

- Largely relies on supportive care
- G-CSF is used for the management of neutropenia
- The European Society of Blood and Marrow Transplantation practice guidelines recommend waiting at least 14 days post CAR T-cell infusion prior to considering G-CSF for the management of neutropenia



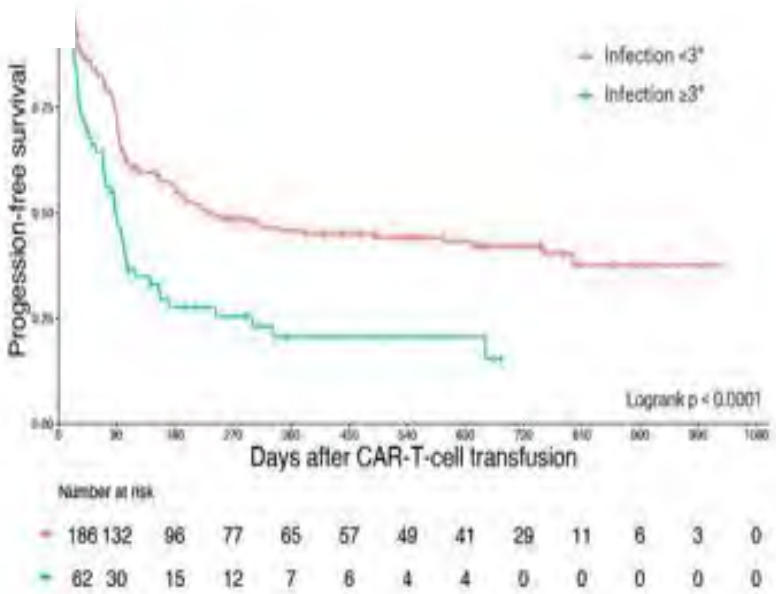
HILL, BLOOD 2020

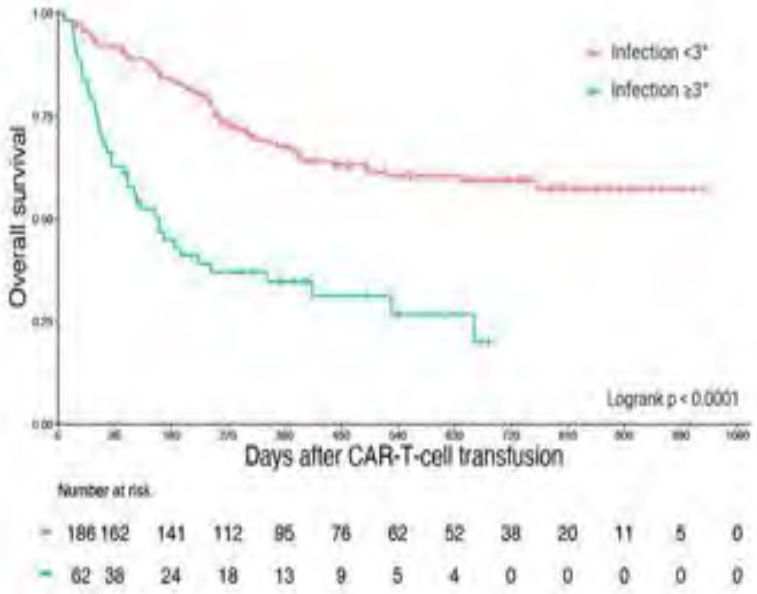
INFECTIONS

- **Approximately 25% of patients will develop infection in the first 30 days**
- **Factors**
  - Type of malignancy
  - >/= 4 lines of prior therapy
  - Higher CART cell dose
  - Higher grade of CRS
- **Risk for Long-term (>day 30) infection**
  - Cytopenias
  - Hypogammaglobulinemia
  - Loss of Vaccination titer

HILL, BLOOD 2018.

INFECTIONS CONTRIBUTE TO RISK OF DYING AFTER CAR-T





Rejeski K et al. J Immunother Cancer. 2022 May;10(5):e004475

PROPHYLAXIS AND HYPOGAMMAGLOBULINEMIA

Routine anti-bacterial and anti-fungal prophylaxis is not recommended

Anti-viral and anti-pneumocystis pneumonia prophylaxis is recommended to be initiated from the start of lymphodepletion to 1 year post CAR T-cell infusion or until CD4 count is >200

Immunoglobulin replacement is recommended to be considered in adults who have had infections with encapsulated organisms

In clinical practice and in trials, IVIG replacement if often considered and targeted to trough IgG levels above 400 mg/dL

Check IgG level monthly

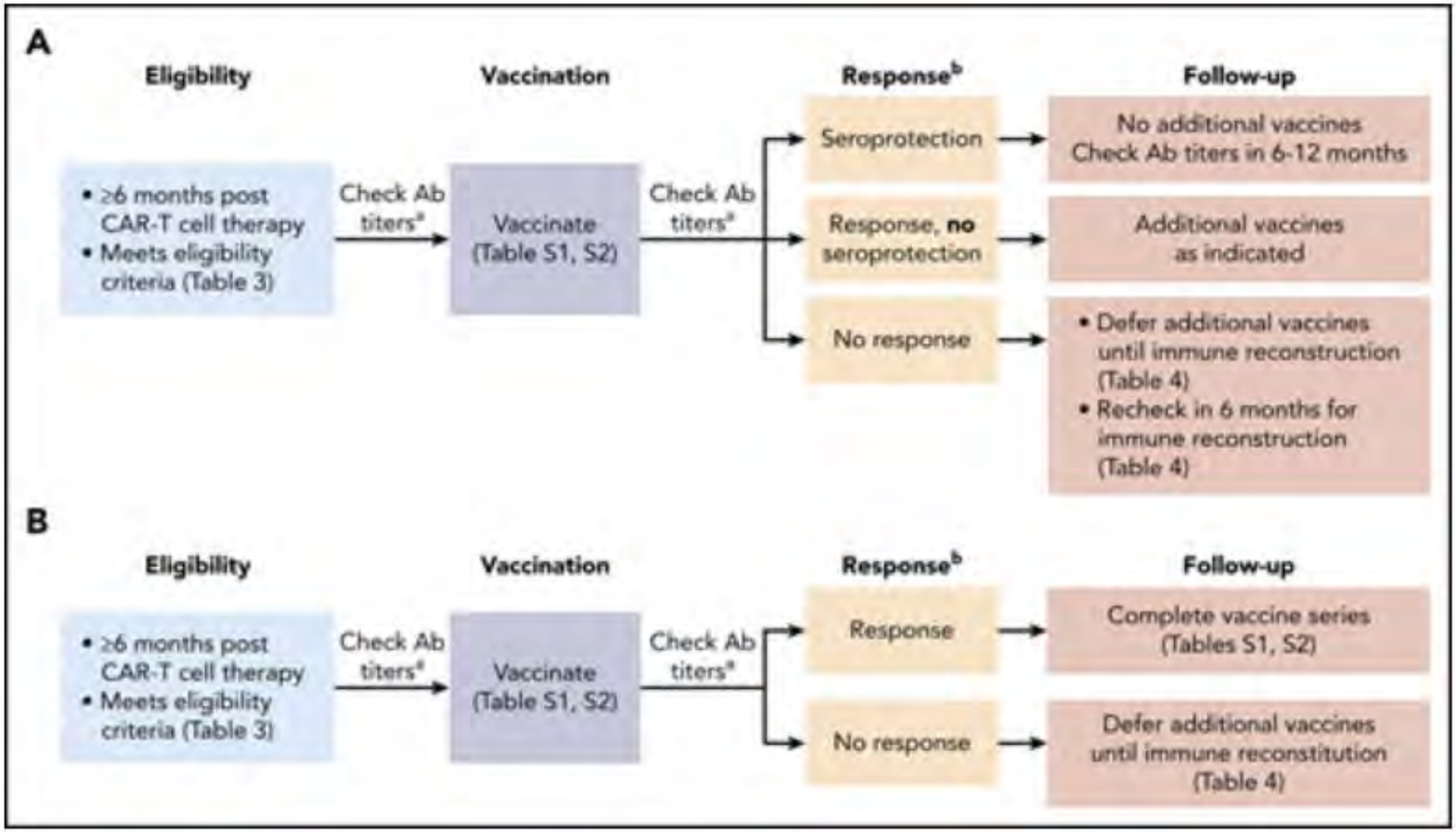
VACCINATIONS

Criteria for vaccinations
Indications*
Killed/inactivated vaccines†
▪ ≥6 mo post CD19-targeted CAR–T-cell therapy
▪ ≥2 mo since last immunoglobulin treatment; a trial off of supplemental immunoglobulins can be considered in patients without chronic or serious bacterial infections in the preceding 6 mo
Live and nonlive adjuvant vaccines
▪ ≥1 y post CD19-targeted CAR–T-cell therapy

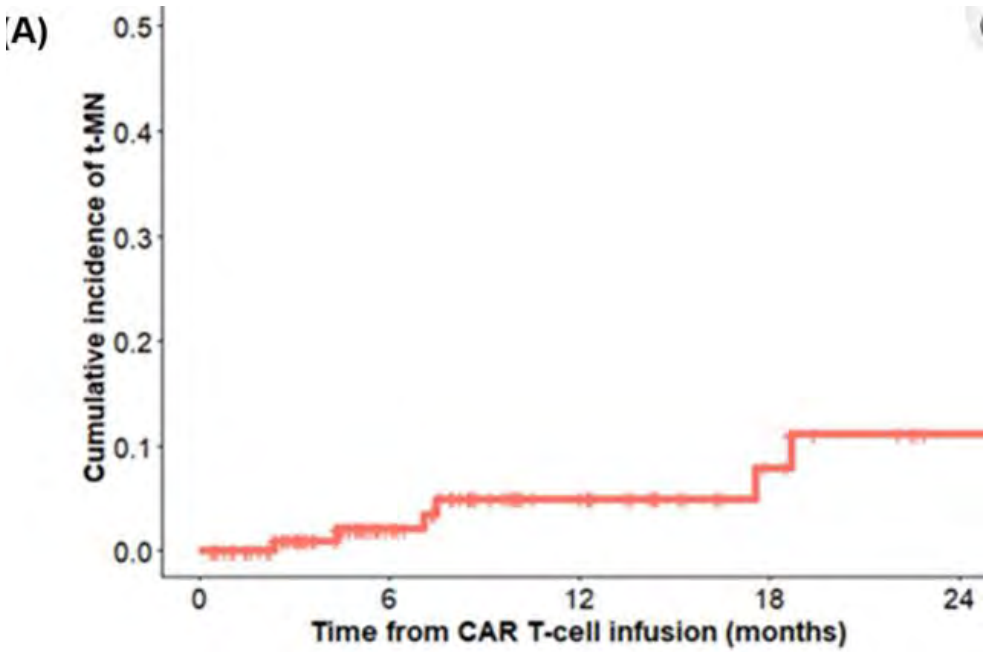
NON-RESPONDERS

Criteria
Detectable serum IgA* (>6 mg/dL) **AND**
$CD19^+$ or $CD20^+$ B-cell count >20 cells/mm^3 **AND**
$CD4^+$ T-cell count >200 cells/mm^3

HILL, BLOOD 2020.


A
Eligibility
Vaccination
Response[b]
Follow-up
• ≥6 months post CAR-T cell therapy
• Meets eligibility criteria (Table 3)
Check Ab titers[a]
Vaccinate (Table S1, S2)
Check Ab titers[a]
Seroprotection
No additional vaccines
Check Ab titers in 6-12 months
Response, no seroprotection
Additional vaccines as indicated
No response
• Defer additional vaccines until immune reconstruction (Table 4)
• Recheck in 6 months for immune reconstruction (Table 4)
B
Eligibility
Vaccination
Response[b]
Follow-up
• ≥6 months post CAR-T cell therapy
• Meets eligibility criteria (Table 3)
Check Ab titers[a]
Vaccinate (Table S1, S2)
Check Ab titers[a]
Response
Complete vaccine series (Tables S1, S2)
No response
Defer additional vaccines until immune reconstitution (Table 4)

THERAPY-RELATED MYELOID NEOPLASMS FOLLOWING CAR T-CELL THERAPY



- 189 patients received commercially available CAR-T for R/R NHL
- Of these, 10 (5.3%) developed t-MN
- 50% had received prior auto-HCT
- Median interval from CAR-T day 0 to t-MN diagnosis was 9.1 months with 60% patients developing t-MN within 1 year from CAR-T
- Cumulative incidences (CI) of t-MN at 1 and 2 years were 5% and 11%, respectively
- NGS at t-MN diagnosis was available in 9 (90%) patients with TP53 being the most mutated gene at 44.4%

Alkhateeb HB et al.Blood Cancer J. 2022 Jul 26;12(7):113

LATE NEUROLOGIC TOXICITIES

Can arise several weeks after infusion

- Seizures, Weakness, Confusion, Aphasia, Coordination problems
- Small cohort @5.25 years: 10% of patients had neurologic even post 90 days CART
  - Stroke, Dementia, Peripheral Neuropathy

Recommendations

- No driving for 8 weeks post-infusion
- Seizure ppx with Levetiracetam
- Steroid ppx in elderly with underlying vascular changes on pre-CART MRI*
  - Zuma-1 Cohort 6 – Dexamethasone 10 mg daily D0→D+2
- Neurology follow-up

1. BUITRAGO, *CLIN J ONC NURS*. 2019. CORDEIRO, *BIOL BLOOD MARROW TRANSPLANT*. 2020

PSYCHOSOCIAL STRESSORS

1. Heightened anxiety

2. Changes in physical function that impact QoL

2. Compromised Coping due to Mental stressors

- Caregiver support
- Financial concerns

4. Avenues of Support

- Social workers
- Clinical psychologist
- Online forums/support groups
- Chaplain