Infection Prevention after CAR-T Cell Therapy for Hematologic Malignancies

Josh Hill, MD
Assistant Professor, VIDD, Fred Hutchinson Cancer Research Center
Assistant Professor, Division of Allergy and Infectious Diseases, UW
Seattle, WA, USA

Course: Essentials of Oncology, Solid Organ and Blood/Marrow Transplant Management for the Health Care Team
May 6th, 2021

jahill3@fredhutch.org
@JoshuaHillMD

FRED HUTCH
CURES START HERE®

UW Medicine
SCHOOL OF MEDICINE

Disclosures

All unrelated to this work:

- Consultant for Gilead Sciences, Amplyx, Allovir, Allogene
- Research support from Takeda (formerly Shire), Allovir, Karius, Gilead

Presentation outline

Part 1: Background

Part 2: Screening prior to CAR-T cell therapy

Part 3: Prophylaxis and monitoring

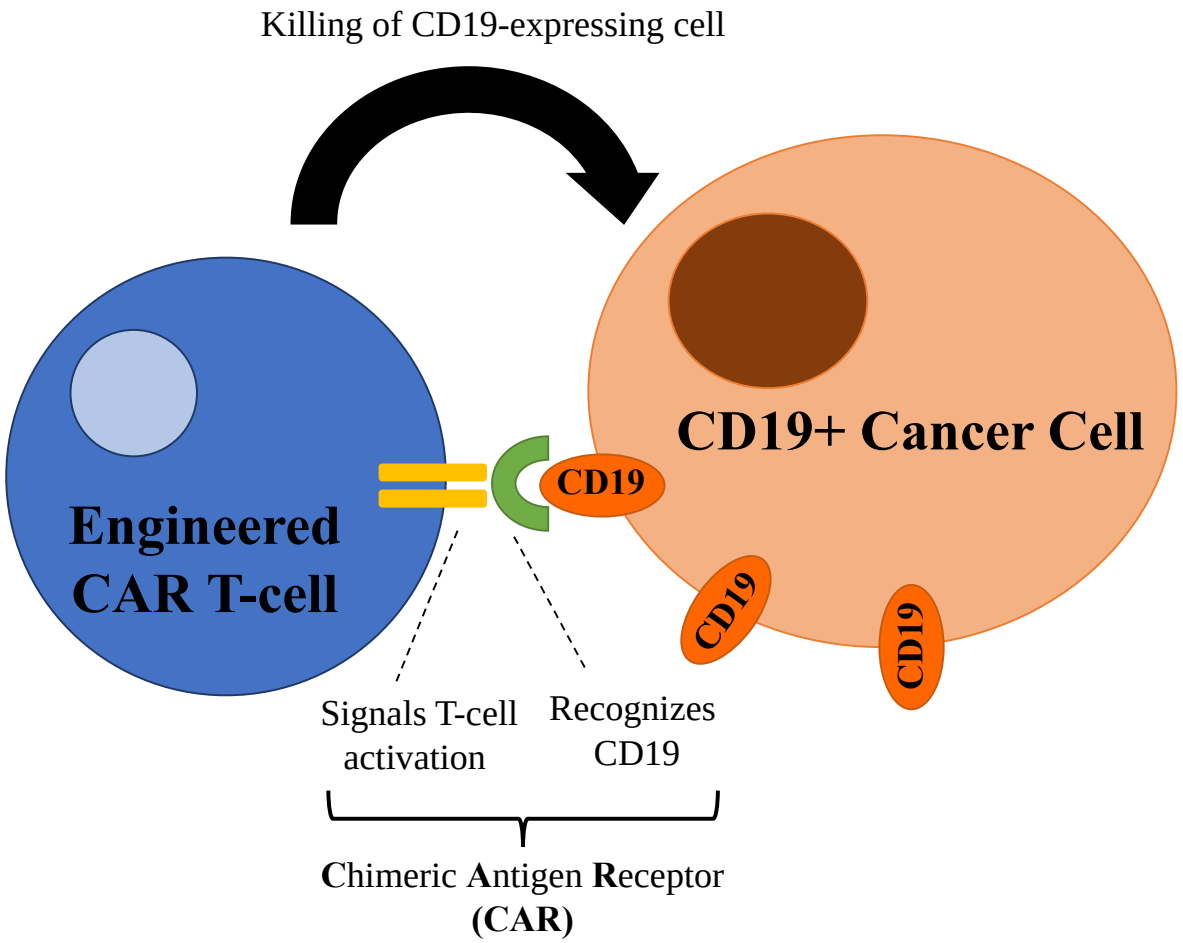
Part 4: Immunoglobulin monitoring, replacement, and vaccination

Part 1

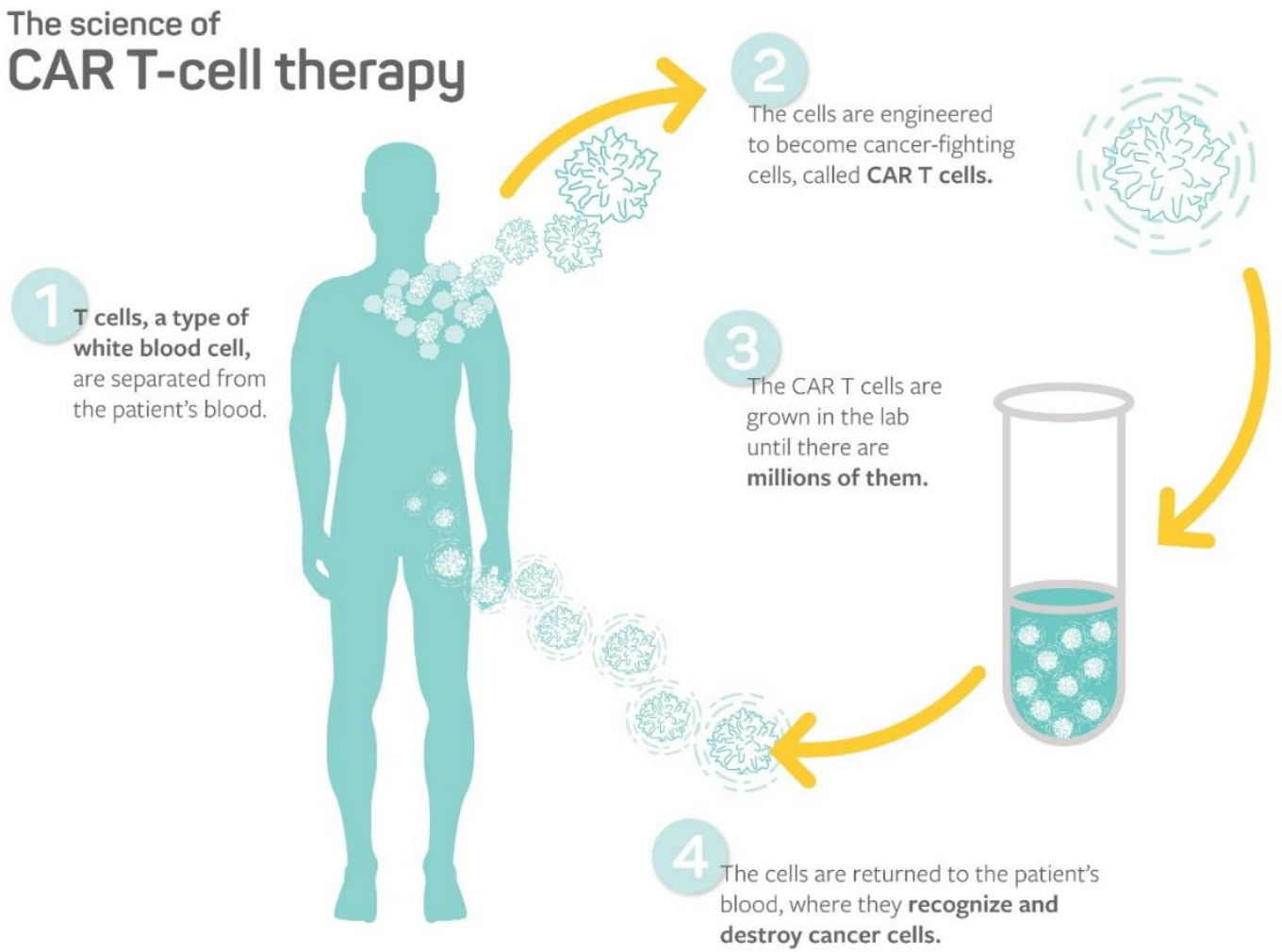
Background

What is a chimeric antigen receptor (CAR)?

- Single chain variable fragment derived from a monoclonal antibody specific to a tumor antigen, linked to an intracellular T-cell signaling sequence



How are CAR-T cells generated and administered?



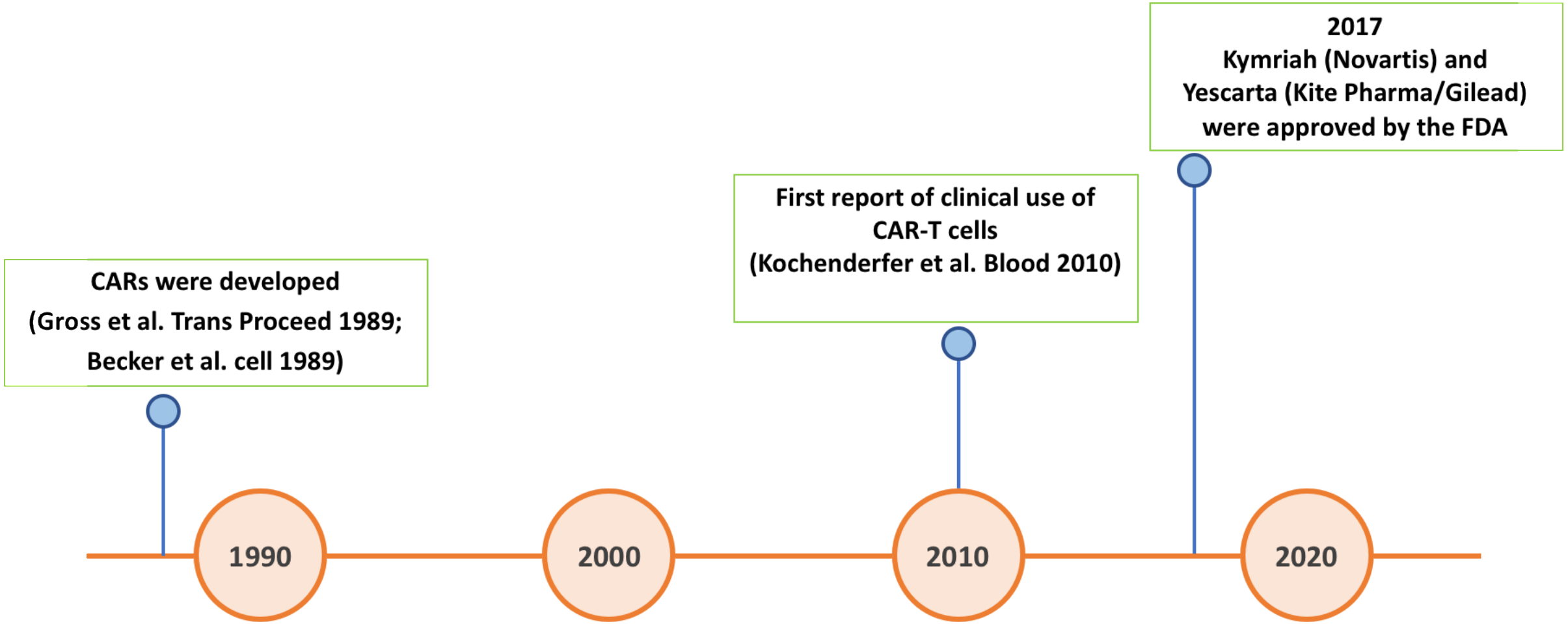
Target hematologic malignancies

- ALL
- NHL
- CLL
- Multiple myeloma

Overall response rates of 70-90%

Turtle et al, Clin Pharm and Therap 2016
Grupp et al, NEJM 2013
Maude et al, NEJM 2014 & 2018
Porter et al, Sci Transl Med 2015
Kochenderfer et al, JCO 2015
Turtle et al, JCI 2016
Turtle et al, Sci Transl Med 2016
Schuster et al, NEJM 2017
Neelapu et al, NEJM 2017
Turtle et al, JCO 2017

Development of CAR-T cell therapy for clinical use



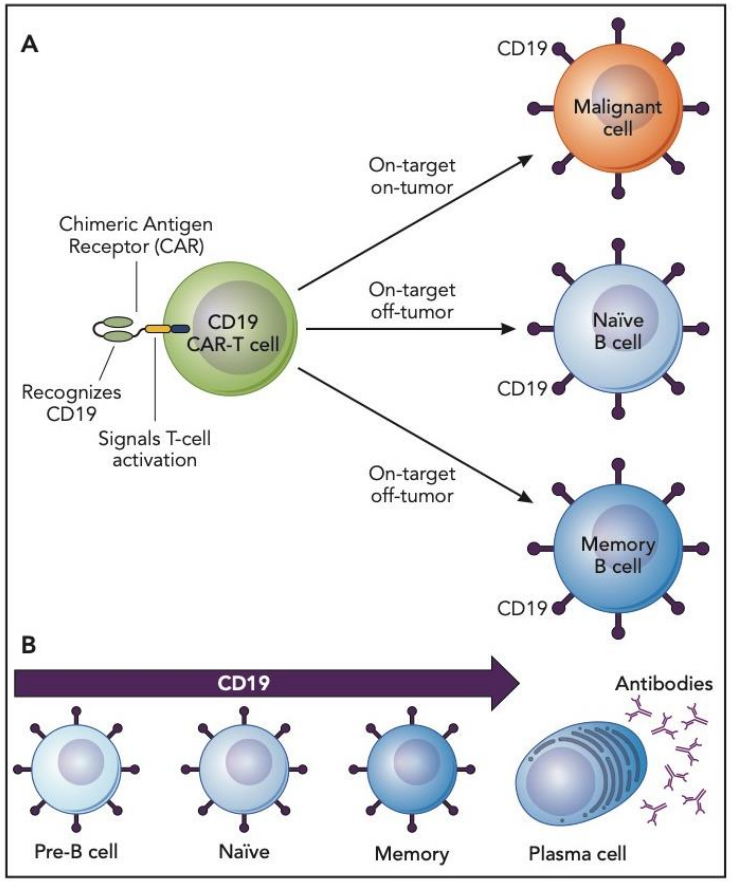
FRED HUTCH

Slide courtesy of Merav Bar, MD

What are the side effects of CAR-T cell therapy for hematologic malignancies?

CAR-T cell recipients have a high net state of immunosuppression:

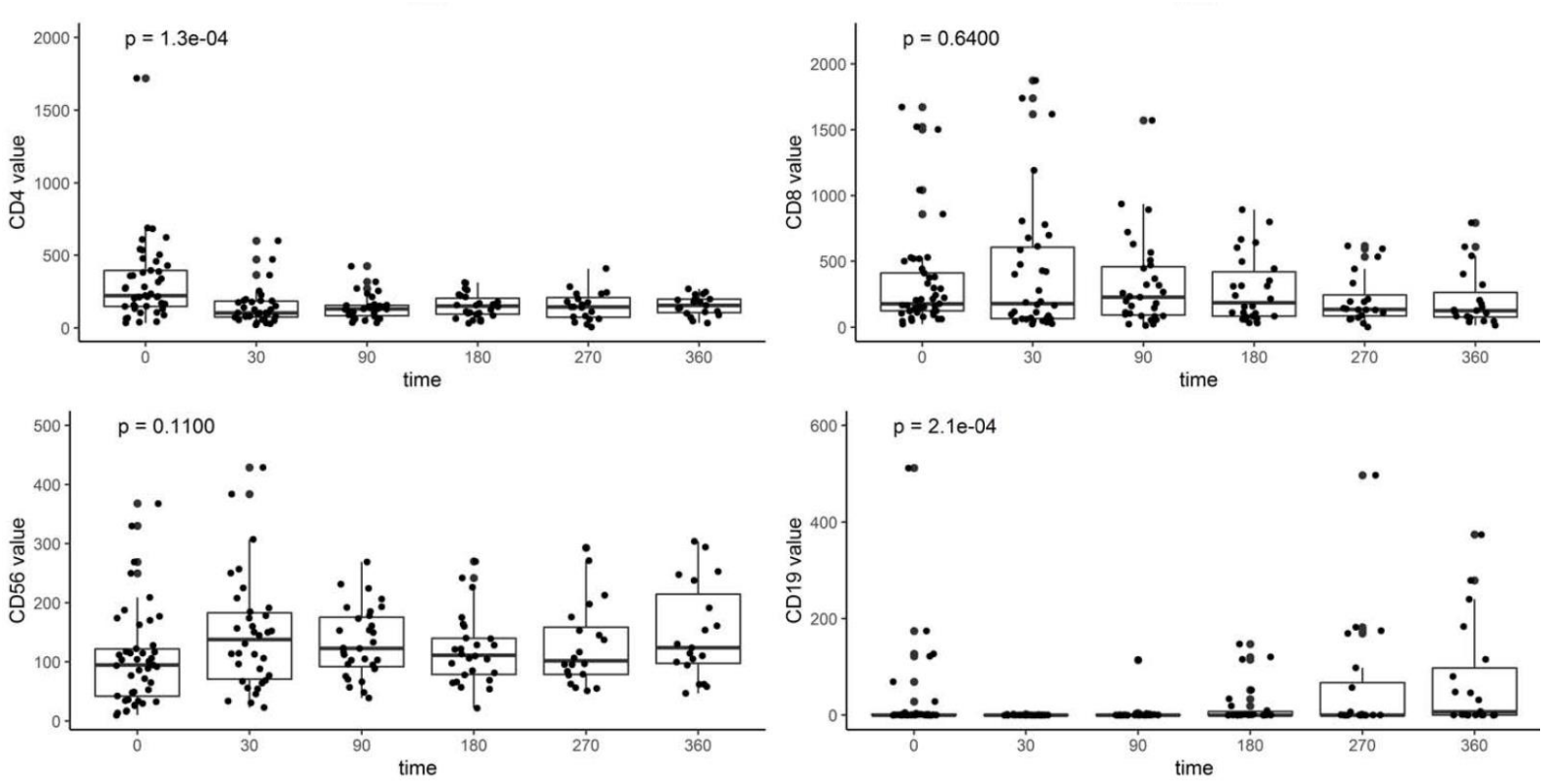
- Highly immunosuppressed patients: extensive past treatment +/- prior transplantation
- Lymphodepletion chemotherapy prior to CAR-T cell infusion
- Cytokine release syndrome and neurotoxicity
- Depletion of malignant AND normal/healthy B cell subsets



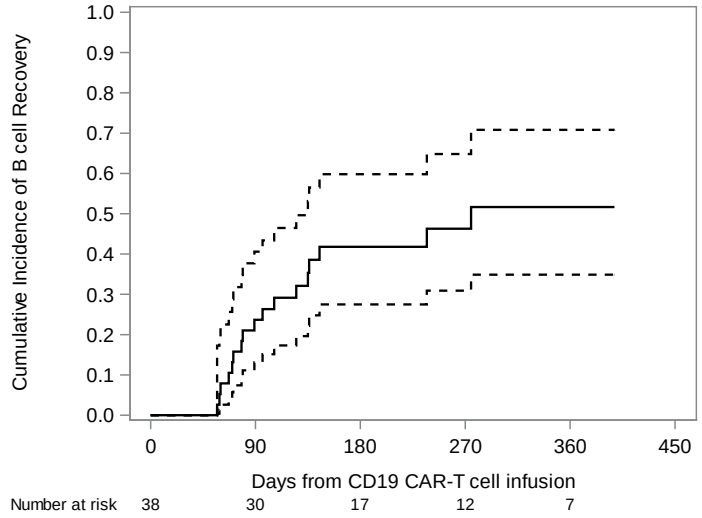
Hill and Seo, Blood 2020

Kochenderfer et al, Blood 2012
Davila et al, Sci Transl Med 2014
Maude et al, NEJM 2014
Lee et al, Lancet 2015
Porter et al, Sci Transl Med 2015

Persistent cytopenias are common but can recover



CD19⁺ B cell detection occurred in 45% of patients in remission within 180 days



Non-B cell cytopenias persist in:

~30% of patients by day +30

~15% of patients beyond day +90

~10% of patients by 1 year after CD19-CAR-T cell therapy

FRED HUTCH

Logue et al, Haematologica 2020
Cordeiro et al, BBMT 2019
Hill et al, Blood Advances 2019

Kymriah (tisagenlecleucel)

Indications:

- R/R B cell ALL (pediatric)
- R/R large B cell lymphomas (adult)

Yescarta (axicabtagene ciloleucel)

Indication:

- R/R large B cell lymphomas (adults)

Maude et al, NEJM 2018
Schuster et al, NEJM 2017
Neelapu et al, NEJM 2017
Raje et al, NEJM 2019

Kymriah (tisagenlecleucel)

Indications:
- R/R B cell ALL (pediatric)
- R/R large B cell lymphomas (adult)

CRS:
- Any in 74%, ≥ Grade 3 in 23%
- Median onset, 3 days

Yescarta (axicabtagene ciloleucel)

Indication:
- R/R large B cell lymphomas (adults)

CRS:
- Any in 94%, ≥ Grade 3 in 13%
- Median onset, 2 days

Maude et al, NEJM 2018
Schuster et al, NEJM 2017
Neelapu et al, NEJM 2017
Raje et al, NEJM 2019

Kymriah (tisagenlecleucel)

Indications:
- R/R B cell ALL (pediatric)
- R/R large B cell lymphomas (adult)

CRS:
- Any in 74%, ≥ Grade 3 in 23%
- Median onset, 3 days

Neurotoxicity:
- Any in 58%, ≥ Grade 3 in 18%
- Median onset, 6 days

Yescarta (axicabtagene ciloleucel)

Indication:
- R/R large B cell lymphomas (adults)

CRS:
- Any in 94%, ≥ Grade 3 in 13%
- Median onset, 2 days

Neurotoxicity:
- Any in 58%, ≥ Grade 3 in 18%
- Median onset, 6 days

Maude et al, NEJM 2018
Schuster et al, NEJM 2017
Neelapu et al, NEJM 2017
Raje et al, NEJM 2019

Kymriah (tisagenlecleucel)

Indications:
- R/R B cell ALL (pediatric)
- R/R large B cell lymphomas (adult)

CRS:
- Any in 74%, ≥ Grade 3 in 23%
- Median onset, 3 days

Neurotoxicity:
- Any in 58%, ≥ Grade 3 in 18%
- Median onset, 6 days

Infectious Complications:
- Febrile neutropenia in 17%
- ≥ Grade 3 infection in 25%

Yescarta (axicabtagene ciloleucel)

Indication:
- R/R large B cell lymphomas (adults)

CRS:
- Any in 94%, ≥ Grade 3 in 13%
- Median onset, 2 days

Neurotoxicity:
- Any in 58%, ≥ Grade 3 in 18%
- Median onset, 6 days

Infectious Complications:
- Febrile neutropenia in 36%
- ≥ Grade 3 infection in 23%

BCMA-targeted CAR-T cell therapy for multiple myeloma is coming!

Maude et al, NEJM 2018
Schuster et al, NEJM 2017
Neelapu et al, NEJM 2017
Raje et al, NEJM 2019

Part 2

Infectious diseases screening prior to CAR-T cell therapy

Clinical case

- 52-year-old woman with relapsed diffuse large B cell lymphoma
- Persistent disease despite 4 prior treatment regimens
- Not a suitable candidate for a hematopoietic cell transplantation
- Referred for treatment with CD19-targeted CAR-T cell therapy using axicabtagene ciloleucel.

FAQ 1: what screening tests should be performed prior to CAR-T cell therapy?

Required

HIV (fourth-generation antigen/antibody combination HIV-1/2 immunoassay[a])
HBV surface antigen and core antibody[a]
HCV IgG[a]

Consider

HSV-1 and HSV-2 IgG
VZV IgG
CMV IgG
HTLV-1 IgG
Toxoplasma gondii IgG
Treponema pallidum (syphilis) treponemal or nontreponemal test
Mycobacterium tuberculosis skin test and/or blood interferon gamma-release assay[b]
Strongyloides stercoralis IgG or empiric treatment[b]

[a]If positive, perform reflexive nucleic acid testing.
[b]In patients with risk factors for exposure.

FAQ 2: can CAR-T cell therapy be administered in patients with ongoing or new infections?

- CAR-T cell therapy should generally be delayed, when feasible, in patients with serious, uncontrolled infections.

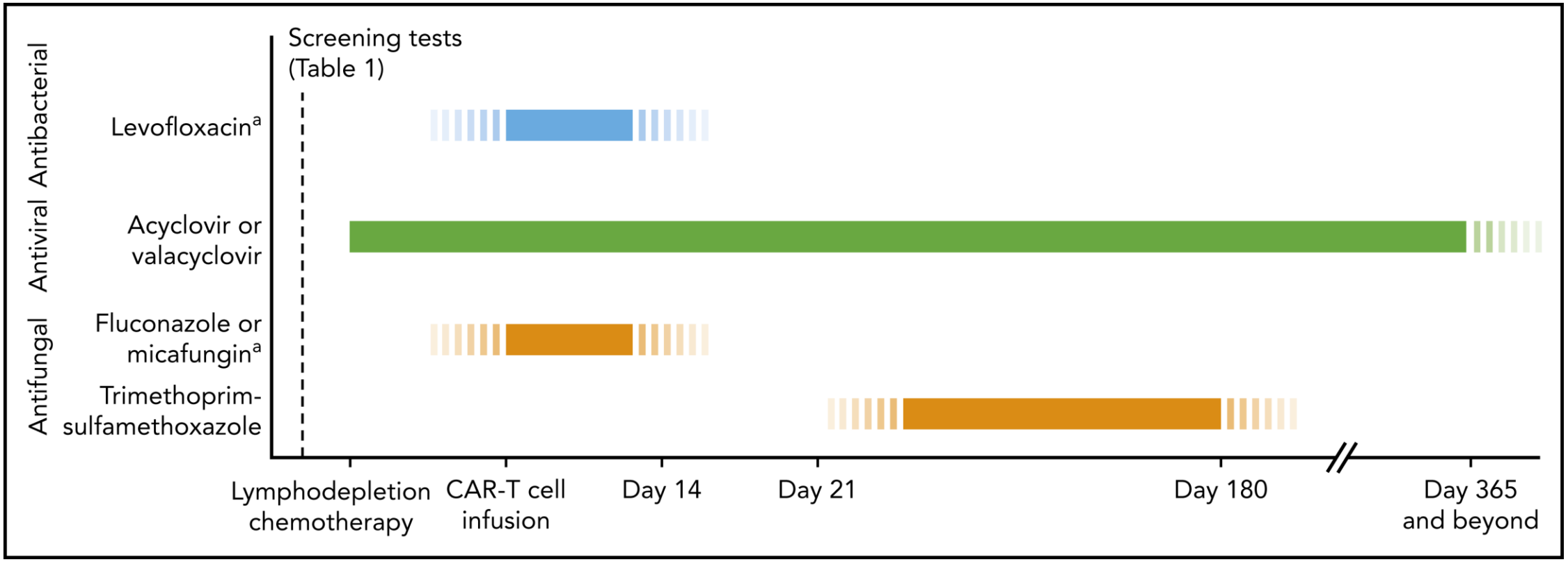
Part 3

Prophylaxis and monitoring

Clinical case continued

- Clinically stable
- Started valacyclovir pre-lymphodepletion chemotherapy; IVIG administered for IgG 320 mg/dL
- Day +1: started levofloxacin and fluconazole for ANC <500 cells/mm^3
- Day +2: tachycardia and fever → ceftazidime 2 grams every 8 hours
- Day +3: hypotension requiring initiation of two vasopressors prompting tocilizumab and dexamethasone 10 mg
- Days +4-6: continued symptoms, dosed with toci x 2 and dex continued
- Day +6: BCx positive for *Streptococcus mitis* and vancomycin added in addition to posaconazole for mold-active prophylaxis.
- Day +7: symptoms improved, steroid taper started
- Day +13: ANC >500 cells/mm^3

FAQ 3: what antimicrobial prophylaxis should be used?



Mold-active azoles may be required in certain circumstances:

- already receiving a mold-active azole for prophylaxis or prior infection
- severe neutropenia for >3 weeks
- requiring substantial immunosuppression for CRS/ICANS

FRED HUTCH

Hill and Seo, Blood 2020

FAQ 4: what antiviral monitoring strategies should be used for herpesviruses?

- We do not recommend routine screening for herpesviruses by PCR

- Targeted testing should be considered in the appropriate clinical context, especially in patients who received a HCT within the prior year or who require substantial immunosuppression for acute management after CD19-targeted CAR-T cell therapy

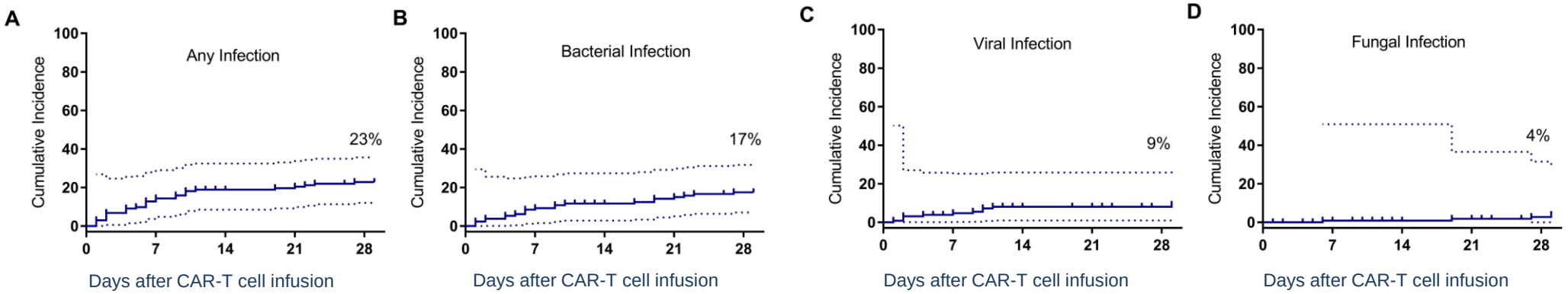
FAQ 5: what antiviral prophylaxis and monitoring strategies should be used for HBV, HCV, and HIV?

- Patients who are HBV surface antigen positive or have detectable HBV DNA in blood should receive treatment with entecavir 0.5 mg orally daily starting pre-CAR-T cell infusion and for at least 6 months
- In patients who are HBV core antibody positive but are negative for HBV surface antigen and HBV DNA, monitoring with serum nucleic acid testing for HBV DNA and alanine aminotransferace (ALT) every 1 to 3 months can be considered as an alternative.
- Patients with chronic HCV should be referred to a specialist to discuss HCV monitoring and timing of anti-HCV therapy
- There are a handful of reports of successful CAR-T cell therapy in patients with HBV, HCV, and HIV.

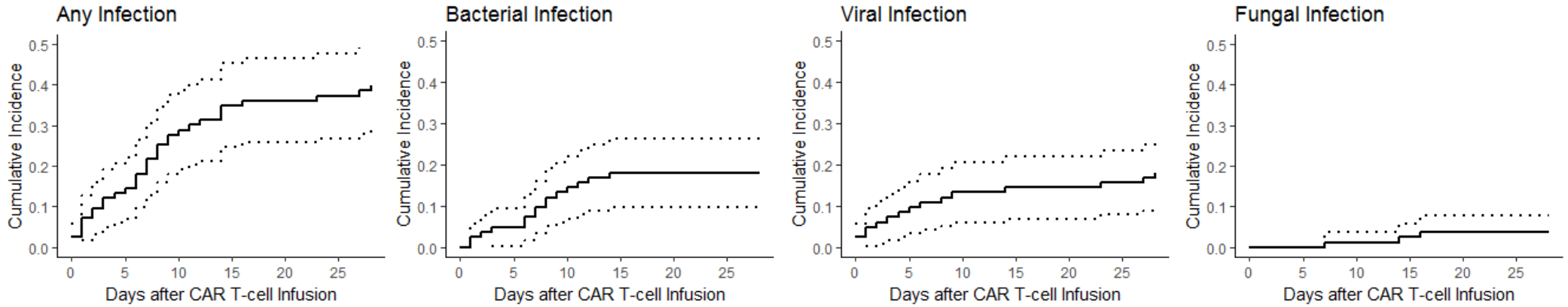
Strati et al, Blood 2019

FAQ 6: what types of infections do patients get after CD19-targeted CAR-T cell therapy?

133 adults with relapsed ALL, CLL, or NHL



83 children and young adults (1-26 yo) with relapsed ALL



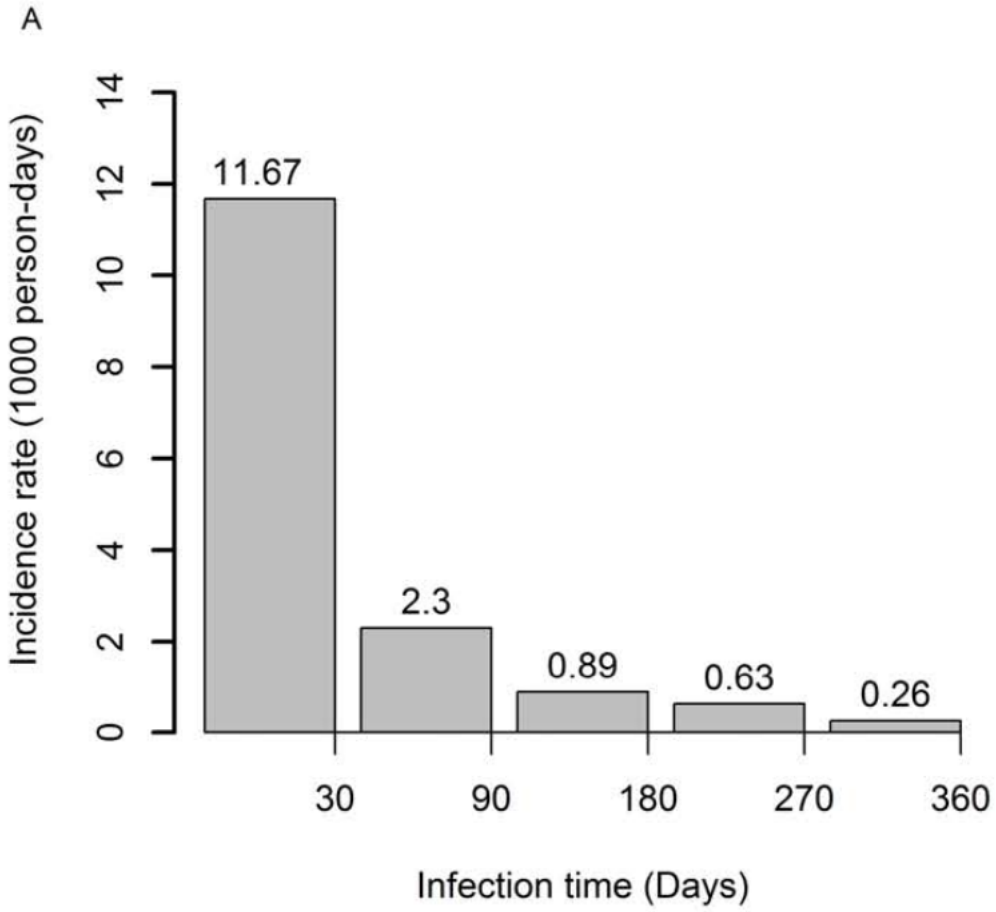
FRED HUTCH

Hill et al, Blood 2018
Vora e al, OFID 2020

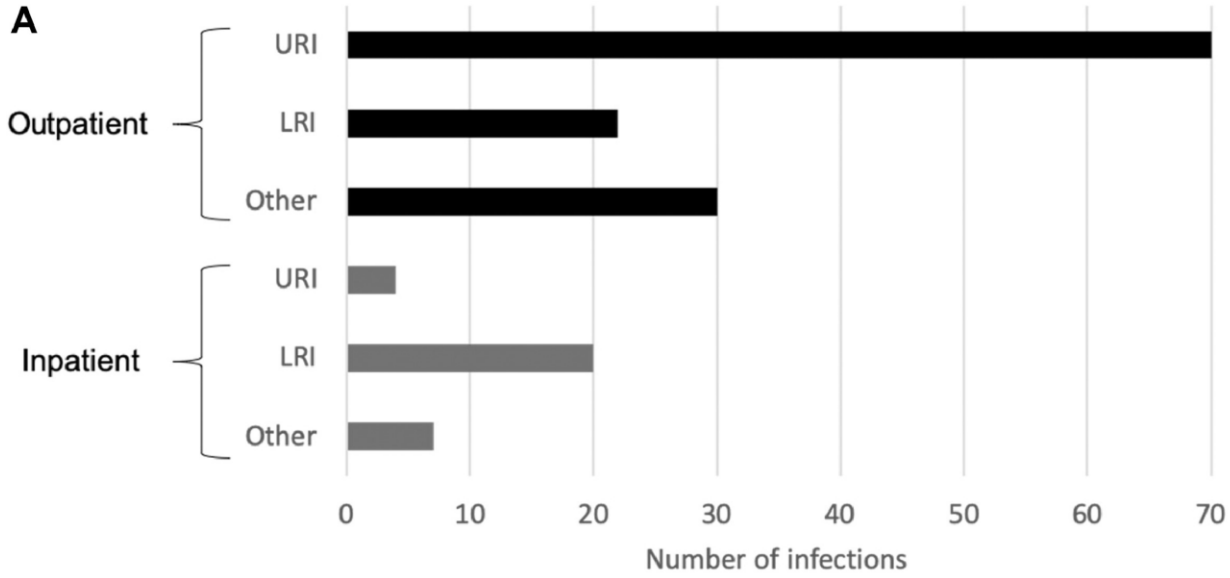
FAQ 6: what types of infections do patients get after CD19-targeted CAR-T cell therapy?

Infection incidence quickly declines but remains relatively frequent:

85 patients treated with Yescarta for LBCL

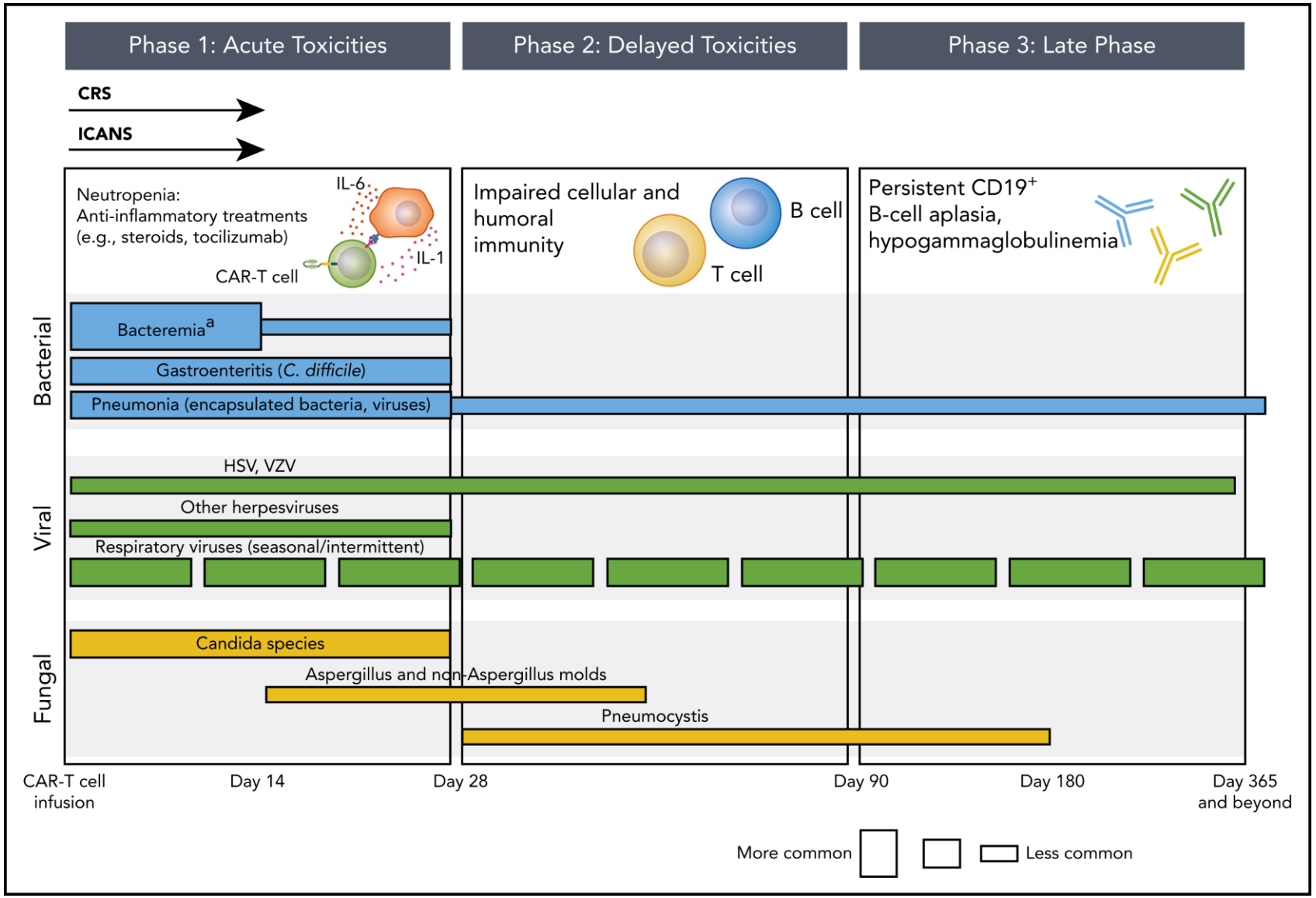


Among 1-year survivors, there was an average of 2 infections per year; 67% received IVIG.



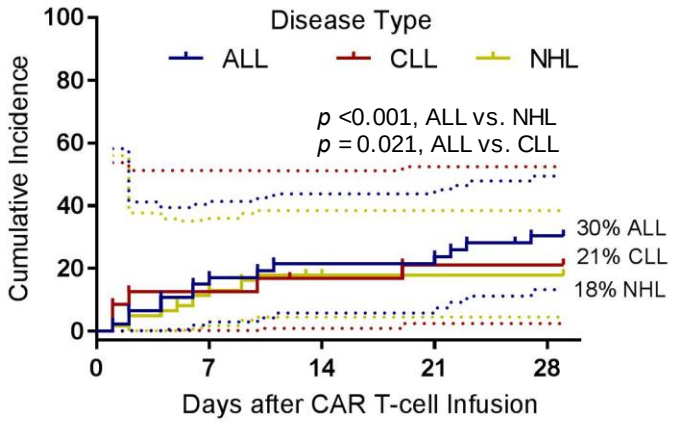
Cordeiro et al, BBMT 2019
Logue et al, Haematologica 2020

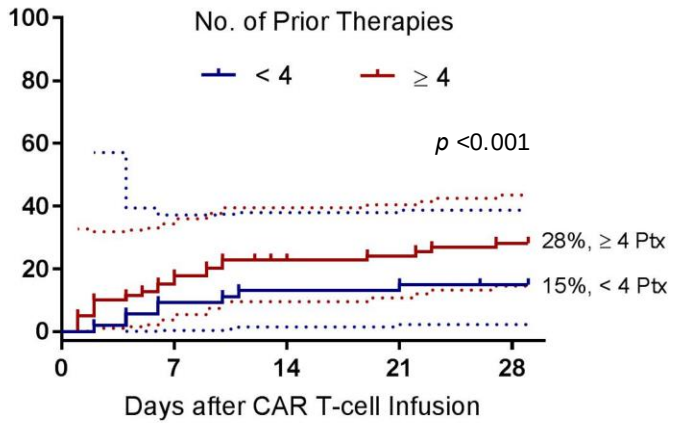
FAQ 6: what types of infections do patients get after CD19-targeted CAR-T cell therapy?

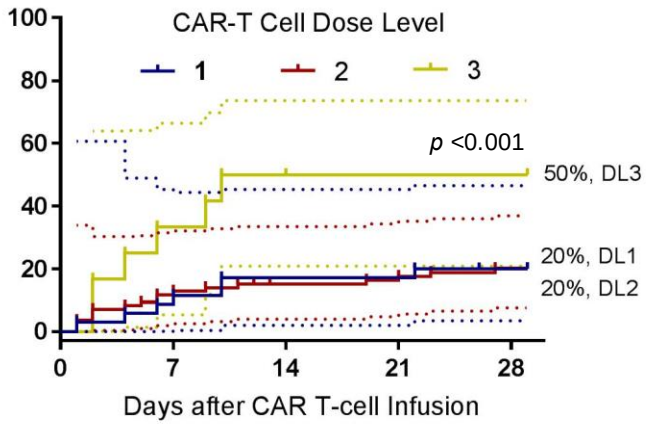


Hill and Seo, Blood 2020

FAQ 7: what are the risk factors for infections?

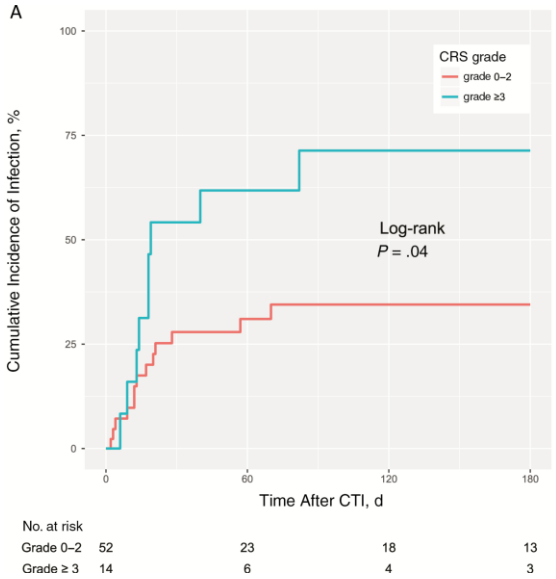




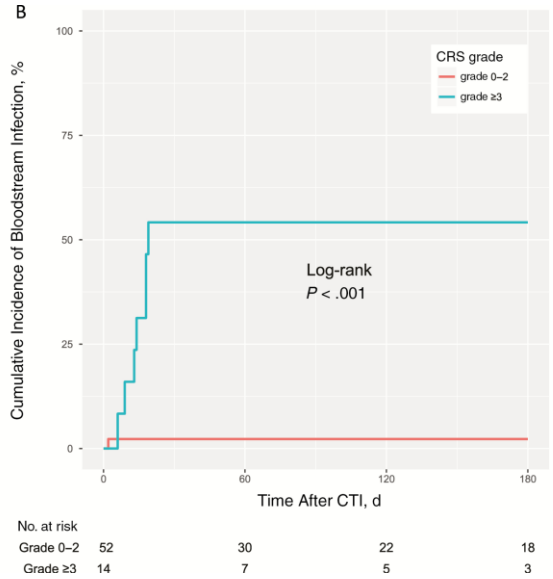


133 adults with relapsed ALL, CLL, or NHL at Fred Hutch

Any Infection



Bacteremia



53 adults with relapsed ALL at MSKCC

Hill et al, Blood 2018
Park et al, CID 2018

What are the risk factors for infections?

	Hazard ratio (95% CI)	*P* value
Fred Hutch (adults; ALL, NHL, CLL)		
CRS grade		
0 versus 1-3 versus 4-5	3.38 (1.99-5.73)	<0.001
MSKCC (adults; ALL)		
CRS grade ≥3		
Any Infection	2.67 (1.00–7.34)	0.05
Bloodstream infection	19.97 (4.3-190.3)	<0.001
SCH (0-26 years old; ALL)		
CRS grade		
0 versus 3-5	1.81 (0.53–6.15)	0.34
Prior HCT and IgG<400	2.15 and 2.41	0.04

Park et al, CID 2018
Hill et al, Blood 2018
Vora et al, OFID 2020

FAQ 8: how should patients with CRS and/or ICANS be managed for possible concurrent or new infections?

- Most patients with CRS and/or ICANS will have neutropenia.
- Symptoms are indistinguishable from infection.
- Treatment for CRS and/or ICANS may mask typical signs/symptoms of infection.
- Initial management needs to account for the possibility of infection.

FAQ 8: how should patients with CRS and/or ICANS be managed for possible concurrent or new infections?

- Empiric broad-spectrum antibiotics according to fever and neutropenia guidelines
- Infectious Diseases consultation to guide escalation and de-escalation of antimicrobial therapy, particularly in **high-risk** patients.
  - **High-risk** patients are those who meet any of the below criteria:
    - Receiving >1 dose of tocilizumab
    - Requiring > 3 days of ≥ 10 mg dexamethasone per day within a 7-day period
    - Receiving 1 or more doses of methylprednisolone ≥1 g per day
    - Receiving second-line agents for management of CRS or ICANS (e.g. anakinra, siltuximab)
- Antibiotic de-escalation should be addressed daily with consideration for the type of immunosuppressive therapies that have been administered.
- Consider weekly CMV monitoring with serum PCR testing in **high-risk** patients who are CMV seropositive.
- Consider using mold-active azole prophylaxis with posaconazole in **high-risk** patients.

Hill and Seo, Blood 2020

Part 4

Immunoglobulin monitoring, replacement, and vaccination

Clinical case continued

- Day +21: discharged from the hospital.

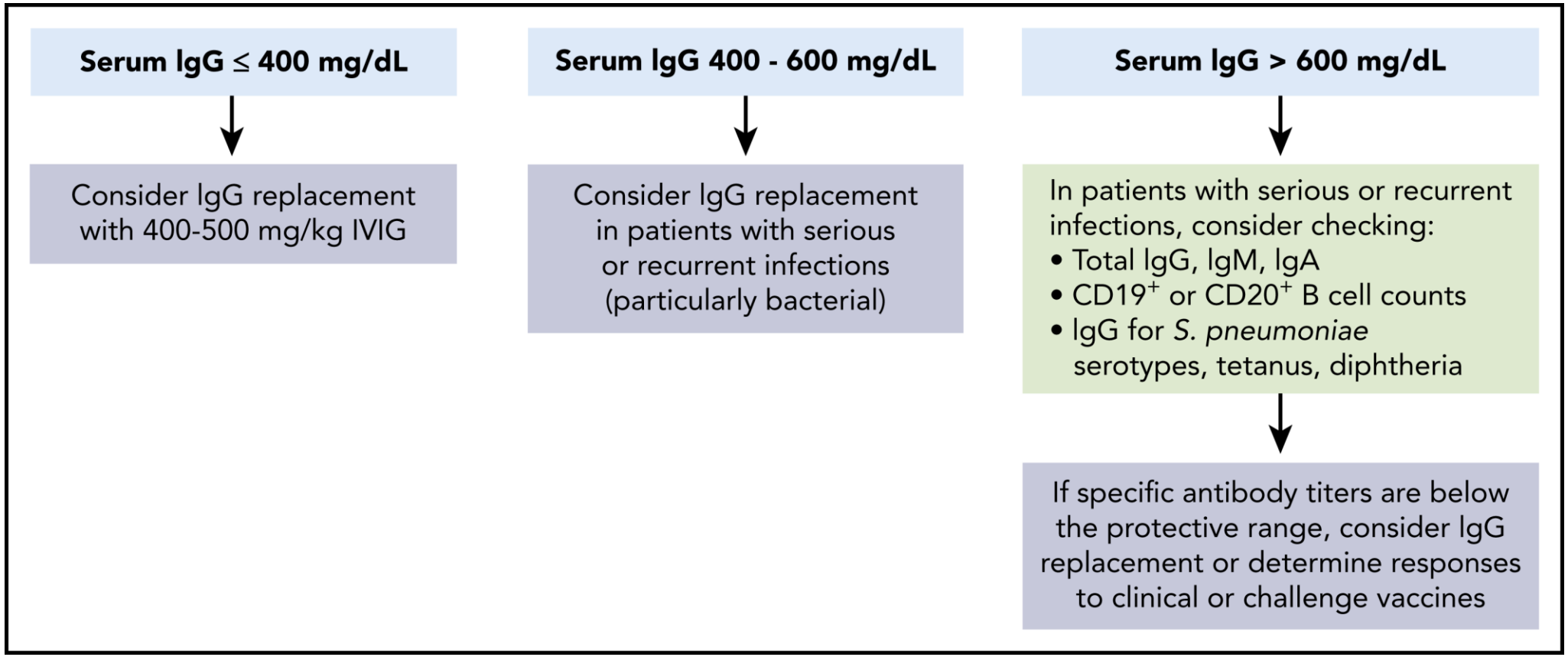
- Day +29: evaluation demonstrated complete remission.
  - Total IgG was 320 mg/dL and she received another dose of IVIG.
  - Discharged home for local management.
  - At the time of discharge, she was taking valacyclovir, trimethoprim-sulfamethoxazole, and posaconazole for antimicrobial prophylaxis.

- Over the next 6 months, she received 4 doses of IVIG for persistent hypogammaglobulinemia and recurrent upper respiratory tract infections.

- Local oncologist called our immunotherapy long-term follow up clinic to inquire about the need for vaccinations.

FAQ 9: how should immunoglobulin levels be monitored and replaced?

Pre-CAR-T cell therapy and monthly for the first 3 months:

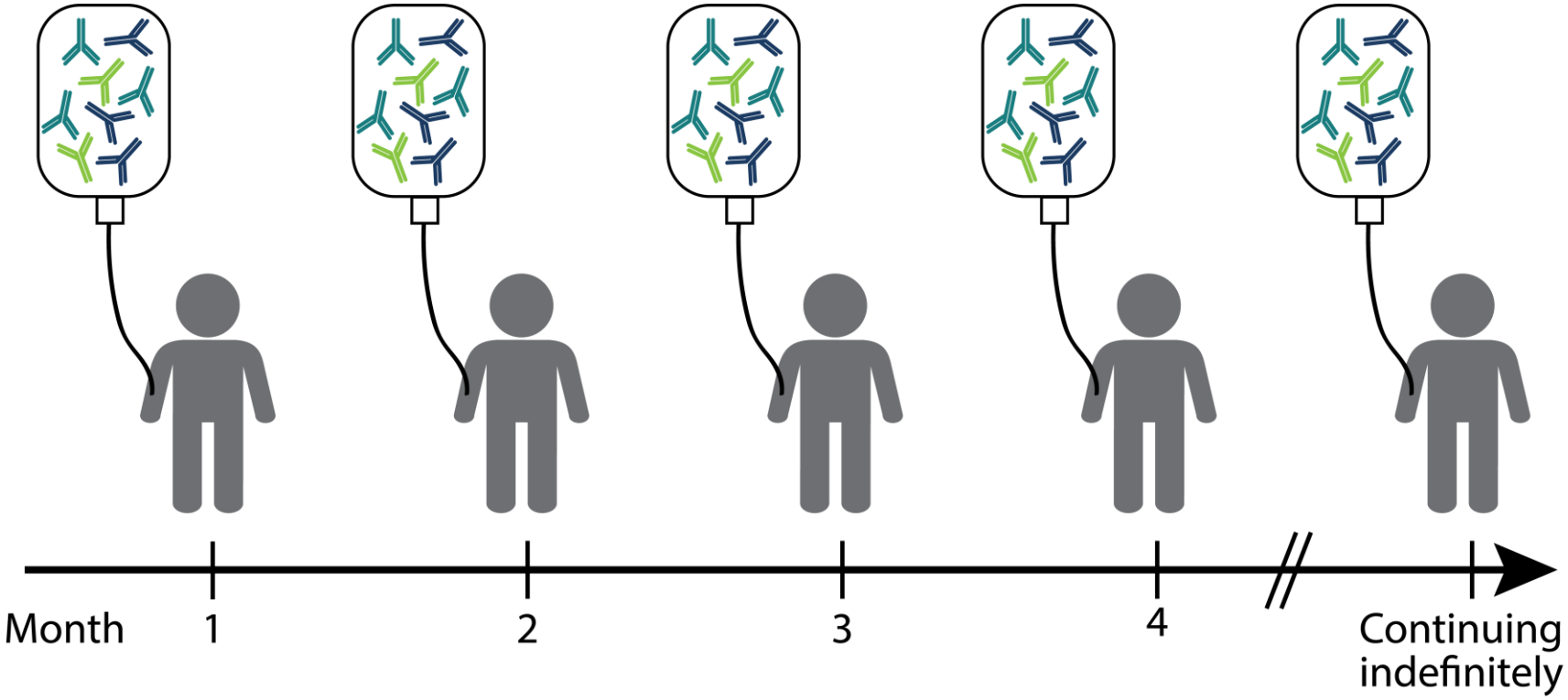


Hill et al, Blood Reviews 2019

FAQ 9: how should immunoglobulin levels be monitored and replaced?

Is there a better approach than chronic immunoglobulin replacement?

Emily Whitehead



???

FAQ 10: should patients who received CAR-T cell therapy be (re)vaccinated?

- Vaccination after CD19-targeted CAR-T cell therapy should be a critical component of a patient's long-term care plan.
- Who, when, and how to vaccinate is unclear at this time.
- Annual influenza vaccination should be given to all patients

FAQ 11: what vaccinations should be administered before CD19-targeted CAR-T cell therapy?

- Vaccination history, including whether they are up-to-date with influenza and pneumococcal vaccinations, should be reviewed as part of the pre-CAR-T cell therapy evaluation.

- During the influenza season, administer the annual influenza vaccine at least 2 weeks prior to lymphodepleting chemotherapy.

- Additional vaccines are not recommended prior to CAR-T cell therapy given the lower immunologic response anticipated in the context of patients with R/R malignancies receiving anti-tumor therapies.

FAQ 12: when should vaccinations be administered after CAR-T cell therapy?

Killed/inactivated vaccines

- In remission
- ≥6 months post-CAR-T cell therapy
- ≥2 months after last IVIG
- Not receiving chemotherapy or other immunosuppressive therapies affecting T or B cell function

Live and non-live adjuvant vaccines

- In remission
- ≥1 year post-CAR-T cell therapy
- ≥2 years post-autologous or allogeneic HCT (and meeting other post-HCT criteria)
- ≥1 year post-systemic immunosuppressive therapies
- ≥8 months after last IVIG
- Absolute CD4 T cell count >200 cells/mm^3

Hill and Seo, Blood 2020

https://www.fredhutch.org/en/research/patient-treatment-support/long-term-follow-up/cellular-immunotherapy-ltfu.html

FAQ 13: what vaccines should be administered after CAR-T cell therapy?

First-priority vaccines include:

- Prevnar for *S. pneumoniae*
- Twinrix for hepatitis A and hepatitis B viruses
- DTaP for *Clostridium tetani*, *Corynebacterium diphtheriae*, and *Bordetella pertussis*

Other considerations:

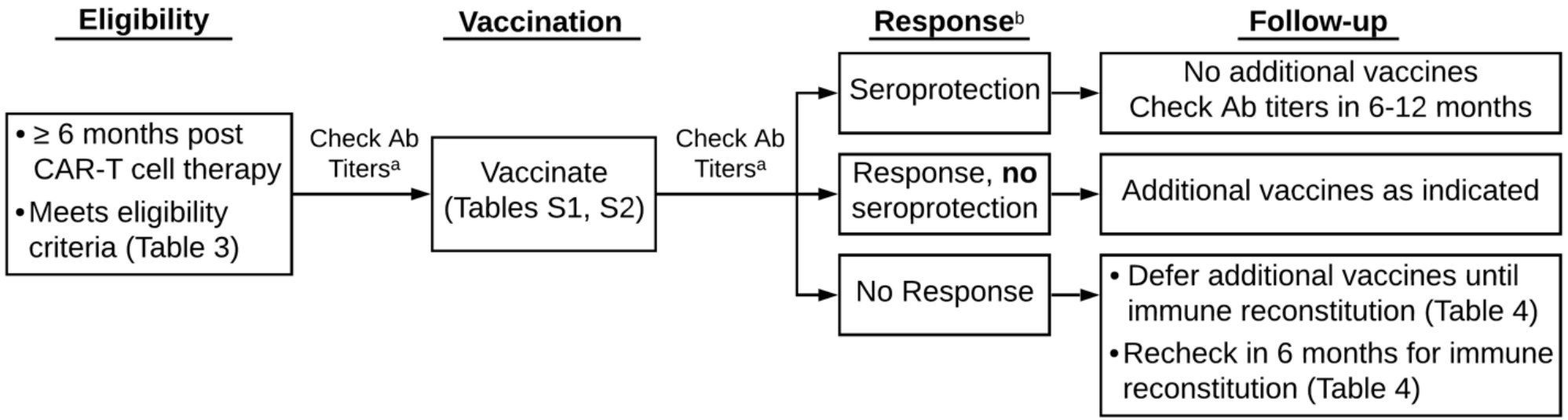
- Shingrix® in adults ≥50 years old can be considered in VZV seropositive patients (or history of chickenpox/shingles)
- Administration of other indicated vaccines should be considered, especially in children and prior HCT recipients
- Conjugated vaccines should be preferentially used when available given higher response rates in immunocompromised patients compared to polysaccharide vaccines

Hill and Seo, Blood 2020

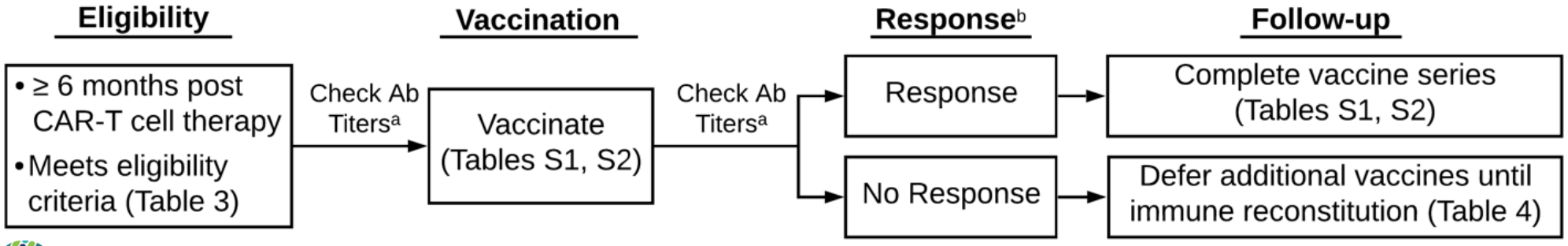
https://www.fredhutch.org/en/research/patient-treatment-support/long-term-follow-up/cellular-immunotherapy-ltfu.html

FAQ 14: how should patients be vaccinated if they received a HCT or did not complete primary vaccines?

No history of prior HCT or completed post-HCT vaccines



Prior HCT and did not complete post-HCT vaccines.



Hill and Seo, Blood 2020

https://www.fredhutch.org/en/research/patient-treatment-support/long-term-follow-up/cellular-immunotherapy-ltfu.html

FAQ 14: how should patients be vaccinated if they received a HCT or did not complete primary vaccines?

Criteria to consider in patients who do not respond to initial vaccination

- 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

Summary

- We need to remain diligent for infectious complications in the context of evolving CAR-T cell therapies, tumor targets, and patient populations.
- Early infections are associated with cytokine release syndrome severity.
- The long-term implications are just starting to be evaluated.
- CD19-CARTx does not affect virus-specific IgG levels, and pre-existing humoral immunity may be preserved in adults.
    - These findings may differ by CAR-T cell target and age.
- Many questions remain about optimal prophylactic strategies such as antimicrobials, IVIG, and vaccination in this patient population.

Acknowledgements

Infectious Diseases Sciences (IDS) Group, VIDD, Fred Hutch

Immunotherapy Integrated Research Center, Fred Hutch

Standard Practice Committee, Fred Hutch

Cellular Immunotherapy SOP and Policy Workgroup, Fred Hutch

Bezos Family Immunotherapy Clinic, Fred Hutch

Funding