Management of infective complications in lymphoma patients receiving bispecific antibody / CART

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Disclaimer

For circulation purposes, specific case descriptions have been removed due to confidential patient details.

Barca. *J. Clin. Med. 2023,12, 7376. https://doi.org/10.3390/jcm12237376*

The more lines of treatment…
The more immunosuppressed…
We are not starting at baseline

2nd line

Broadly, infectious cx related to…
1. Lymphoma
2. Chemotherapy
3. Monoclonal antibody (B-cell depletion)
4. SCT (either auto / allo)
5. Then we go to CART / Bispecifics….

? Cumulative effects

≥3rd line

R/R ≤ 1 year

R > 1 year

CAR T-cell

CAR T-cell not eligible

ASCT not eligible

ASCT eligible

Immunochemotherapy
Polatuzumab-R-bendamustine
Tafasitamab-lenalidomide
Clinical trial
Best supportive care

Salvage immunochemotherapy

CR/PR ASCT

No response

R/R

R/R

R/R

CAR T-cell

CAR T-cell not eligible

Immunochemotherapy
Polatuzumab-R-bendamustine
Tafasitamab-lenalidomide
Selinexor*
Bispecific antibodies
Loncastuximab tesirine
Allogeneic SCT
Clinical trial
Best supportive care

Note to self, also for patients who have failed CART

May be used in combination with other Rx e.g. R-GemOx, GemOx RCHOP, PR-CHP, etc)

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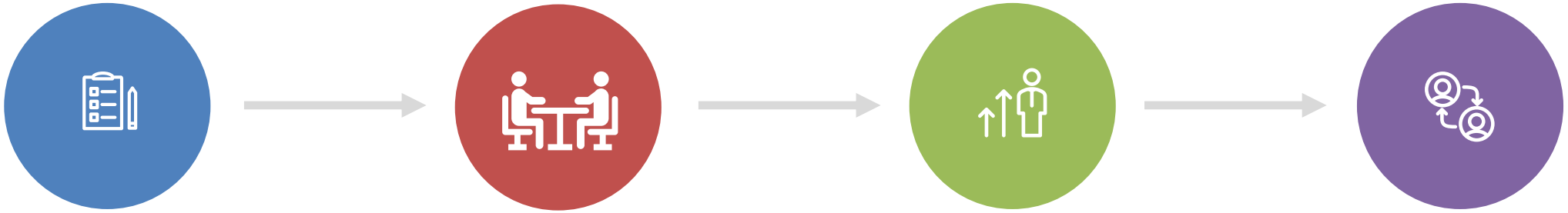
Overview



Case Study (x2)

CART
Bispecific antibody

Discussion points

Review of Literature

Trying to make sense of what we do day to day

Concluding statements

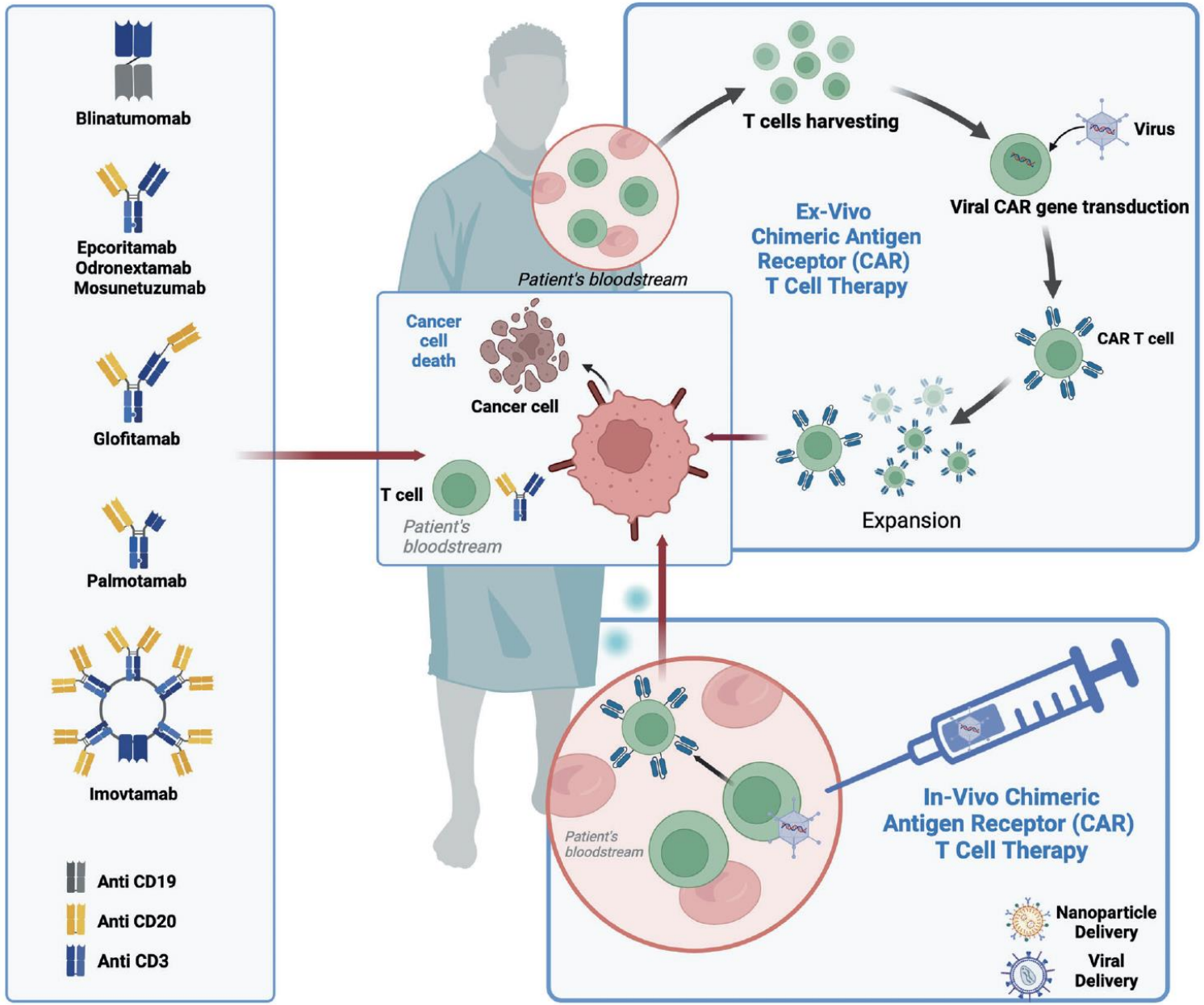


Fig. 1 Landscape of effector cellular therapy for DLBCL therapy. Bispecific T cell engagers (left) include BiTEs like blinatumomab, fused full-length antibodies like the DLBCL-approved products epcoritamab and glofitamab, and multivalent constucts like imovtamab. Approved CAR-19 therapies (top right) are manufactured ex vivo from each patient's T cells, requiring 20–40 days. Viral or nanoparticle delivery of CAR genes (bottom right) in vivo is one of many investigational ways to potentially accelerate targeted cell therapy delivery.

CART

Cell proliferation for ongoing anti-tumoral activity

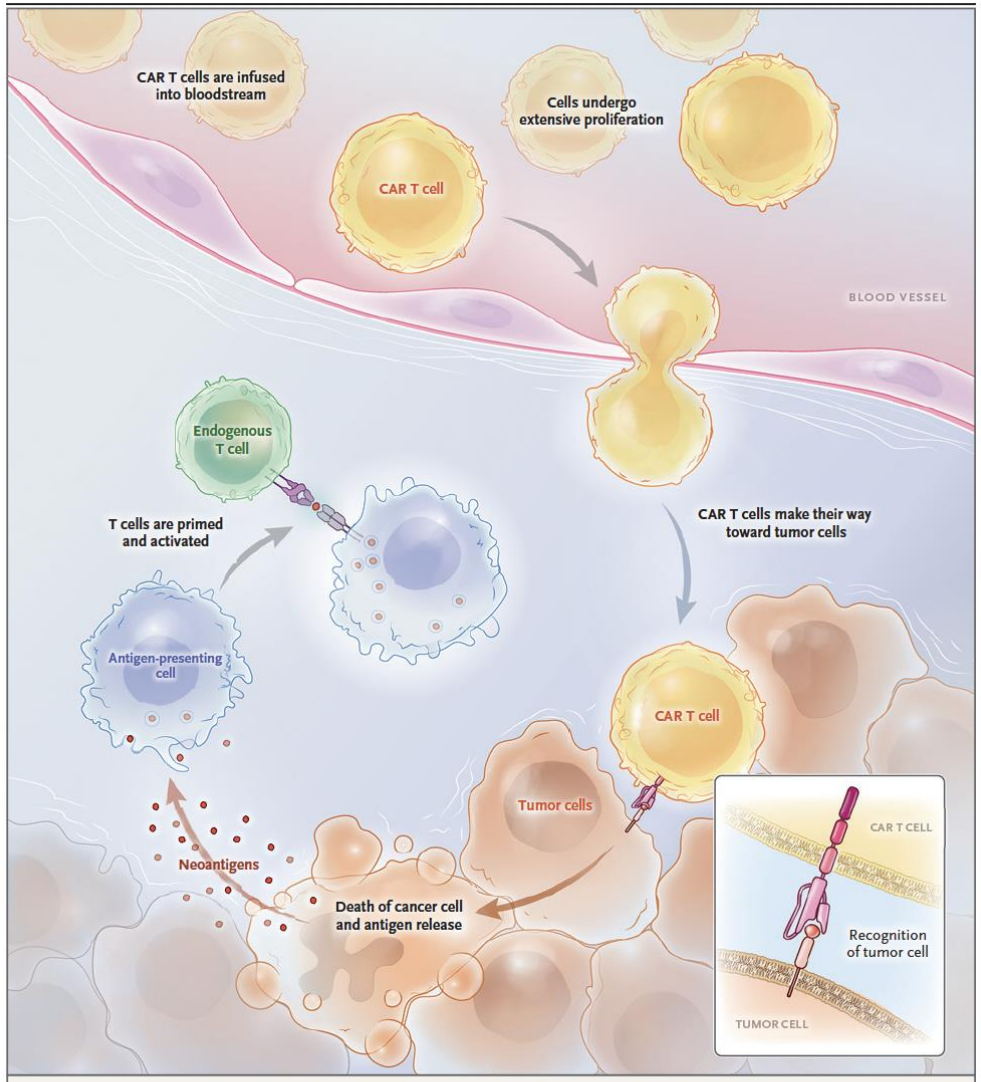
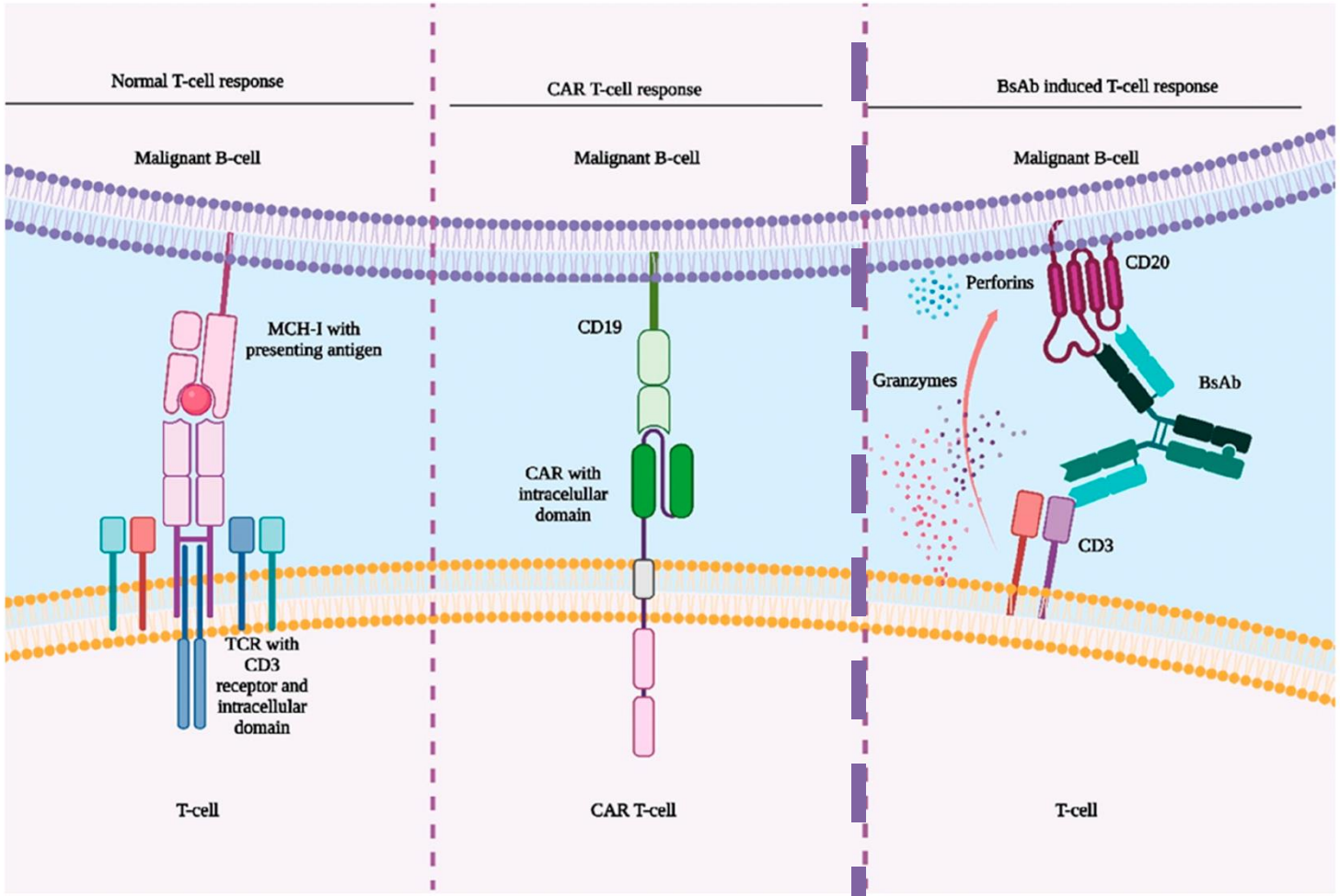


Figure 1. Chimeric Antigen Receptor (CAR) T Cells Engrafting, Trafficking to Tumor, and Proliferating Extensively after Infusion.
After infusion, CAR T cells leave the blood and travel to sites of tumor, where they identify and kill tumor cells. This can trigger extensive proliferation of CAR T cells and the release of tumor antigens, which activates the immune system to recruit non–CAR T cells, thus eliciting further antitumor responses in a process known as cross priming.

CART

BiAbs



Product which requires rpt administration

June et al. N Engl J Med 2018;379:64-73.
Mihaila et al. J. Clin. Med. 2025; 14, 5534.

Cytokine release syndrome (CRS);

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Attributed to the induction of powerful immune effector responses.

Infection vs inflammation?

Treatment diametrically opposed.

In reality, concurrent treatment of both conditions often required while awaiting workup. Review anti-infectives when Ix available.

Systemic inflammatory response

Endothelial injury and vascular leakage in multiple tissues & organs, and their associated effects including hypoxia, hypotension and/or organ damage.

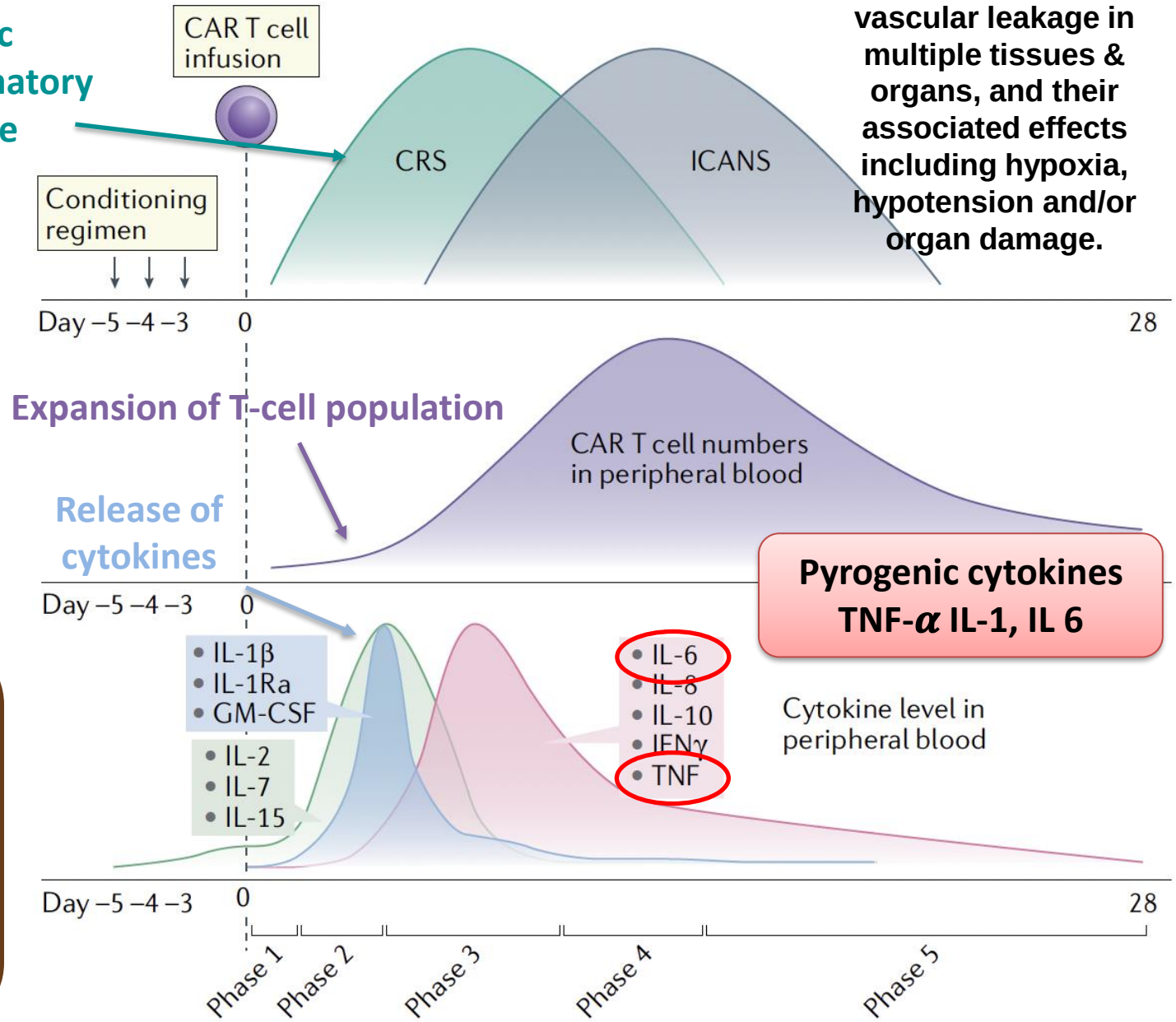


Fig. 1 | **Schematic diagram showing a relative timescale for the onset and duration of CRS and ICANS.** Also shown are the kinetics of chimeric antigen receptor (CAR)

Morris et al. Nat Rev Immunol 22, 85–96 (2022).

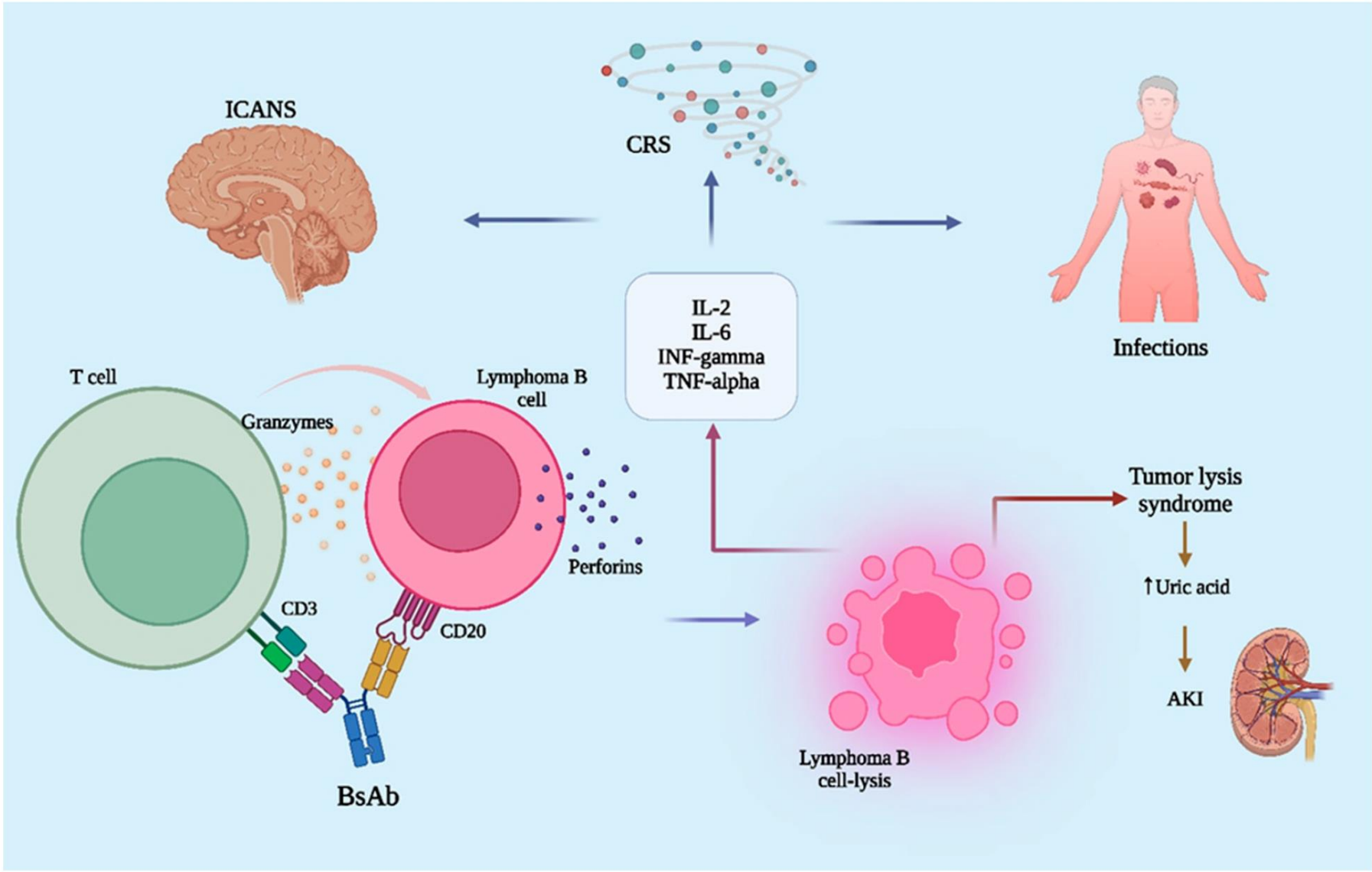


Figure 1. Mechanism of action of bispecific antibodies (BsAbs) in lymphoma and associated adverse effects. BsAbs simultaneously bind to CD3 on T-cells and CD20 on lymphoma cells, facilitating targeted

Mihaila et al. J. Clin. Med. 2025, 14, 5534.

Case 1: ID considerations / Questions

- Pre-CART infectious complications
  - Do infections preclude them from CART?
  - MDRO colonization → risk during treatment

- CART – Managing infections and CRS / ICANS
  - Pre-CART treatment history is important
  - Attention to detail, thorough evaluation
  - **CMV infections post CART in a high risk host**
  - Expect twists and turns

- Long-term complications
  - Ongoing evaluation. Vigilance is key


evaluation
retention
customer
research
sales
customer
plan
management
analysis
planning
implementation
monitor
risk
project
impact
risk
strategy
impact
data
sales
complex
data
assessment
identification
process
risk
sales
impact
opportunity
retention
management
assessment
performance
cost
evaluation
process
management
performance
cost
research
cost
research
evaluation
data
management
treatment
impact
project
plan
strategy
data
research
resources
risk
performance
performance
important
evaluation
data

Evaluation depends on phase of treatment

Pre-CART
Address and Rx infections before

Baseline evaluation
Prophylaxis strategies

CART
Infective complications due to lymphodepleting chemotherapy

After CART (short term)
a/w lympho-depletion / CRS / ICANs / MAS

Being aware of common infections
Treatment for CRS/ICANs modify infection risk
? Role of biomarkers for evaluation
How to work up the patient

After CART (longer term)
A/w hypogamma-globulinemia, T-cell dysfunction, prolonged / delayed cytopenias

Late onset infections
Viral infections common
Prevention strategies including vaccination

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CART

Screening

Baseline serologies
HIV
Hepatitis B
Hepatitis C

R/o respiratory viral infections (Sx)
Strongyloides (if relevant)*
TB^ (if relevant)
? Toxoplasma Ig G
? Endemic mycoses

Review prior hx of CMVi
CMV serology / IGRA^ (?)
MDRO screening per unit protocol

^IGRA – interferon gamma release assays

Chemo-prophylaxis recommended

Bacterial prophylaxis – FQ ppx (some centres may not practice this)

HSV, VZV prophylaxis
HBV prophylaxis if carrier

PCP prophylaxis
Fungal prophylaxis - Fluconazole

Mould prophylaxis

In high risk hosts (prolonged neutropenia, high dose steroids, significant treatment for Tocilizumab)

CMV prevention and management.

Surveillance & pre-emptive Rx in @ risk host (prior infection, or lack of CMV immunity)

Adherence to infection prevention protocols. IVIG replacement may be beneficial in some pts

* Empiric Strongyloides treatment may be offered in at risk patients. ^ We did not assess for latent TB screening. Vigilant for active TB and Rx accordingly.

Shahid et al. Transplantation and Cellular Therapy 30(2024) 955969

Slide courtesy of Dr. Tan BH, SGH, with modifications

Risk of infection after CART

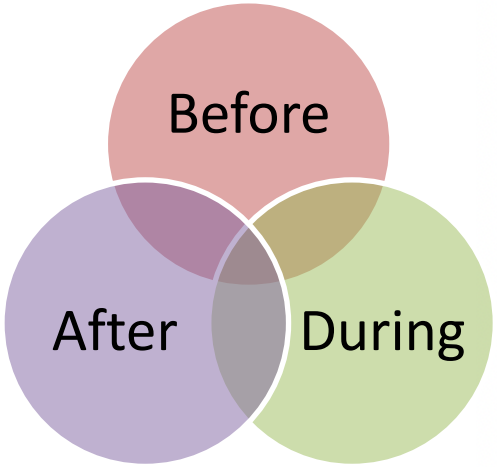

Table 1
Risk Factors Associated with Infections Risk After CAR T Therapy

Host Related Risk Factors	References
Prior lines of pre-CAR T therapy	[10,15,19,48]
Prior history of transplantation	[11,12]
Underlying malignancy, B-ALL and MM	[10,15,107]
CAR-Hematotox Score >2, lymphopenia	[11,70,103,108,109]
Prior history of infection within 100 d	[10,55,48]
Performance status at baseline	[25,55]
Baseline Hypogammaglobulinemia*	[11,55]
Older age†	[14]
CAR T Related Risk Factors	
High CAR T dose and intensity of lymphodepletion	[15,11]
Presence and severity of CRS	[11,15,16]
Immune effector cell-associated hematotoxicity‡ (ICHAT)	[25,105,110]
Corticosteroid use	[10,19,26,55,82,104,111]
Hypogammaglobulinemia post CAR T	[24,25]
IEC-HS§	[18]

* Threshold "low" IgG definition can vary.
† Calculated as adults vs children
‡ Includes thrombocytopenia, anemia, and neutropenia.
§ Immune effector cell- associated hemophagocytic-lymphohistiocytosis-like syndrome

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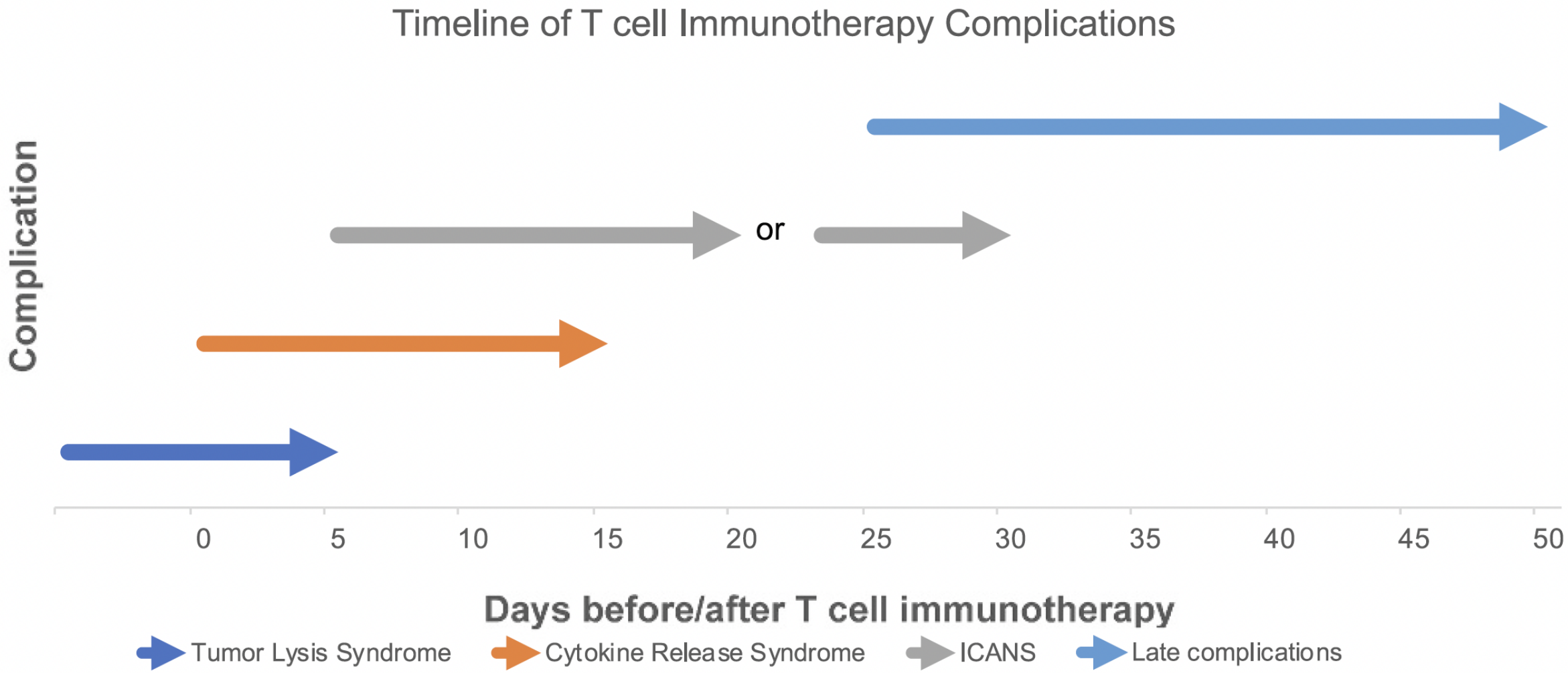


FIGURE 1. Timeline of typical T-cell immunotherapy complications. Tumor lysis syndrome may start with lymphodepleting chemotherapy prior to cell infusion. Patients are generally at risk of CRS within the first 2 weeks of therapy, although this may be delayed for TCR-based therapies. Immune effector cell-associated neurotoxicity syndrome (ICANS) may present during CRS or after CRS has resolved. Late complications of T-cell immunotherapies may persist for years.

Vadarajan et al. Cancer J 2019;25: 223–230

Clinical course of patients receiving CART

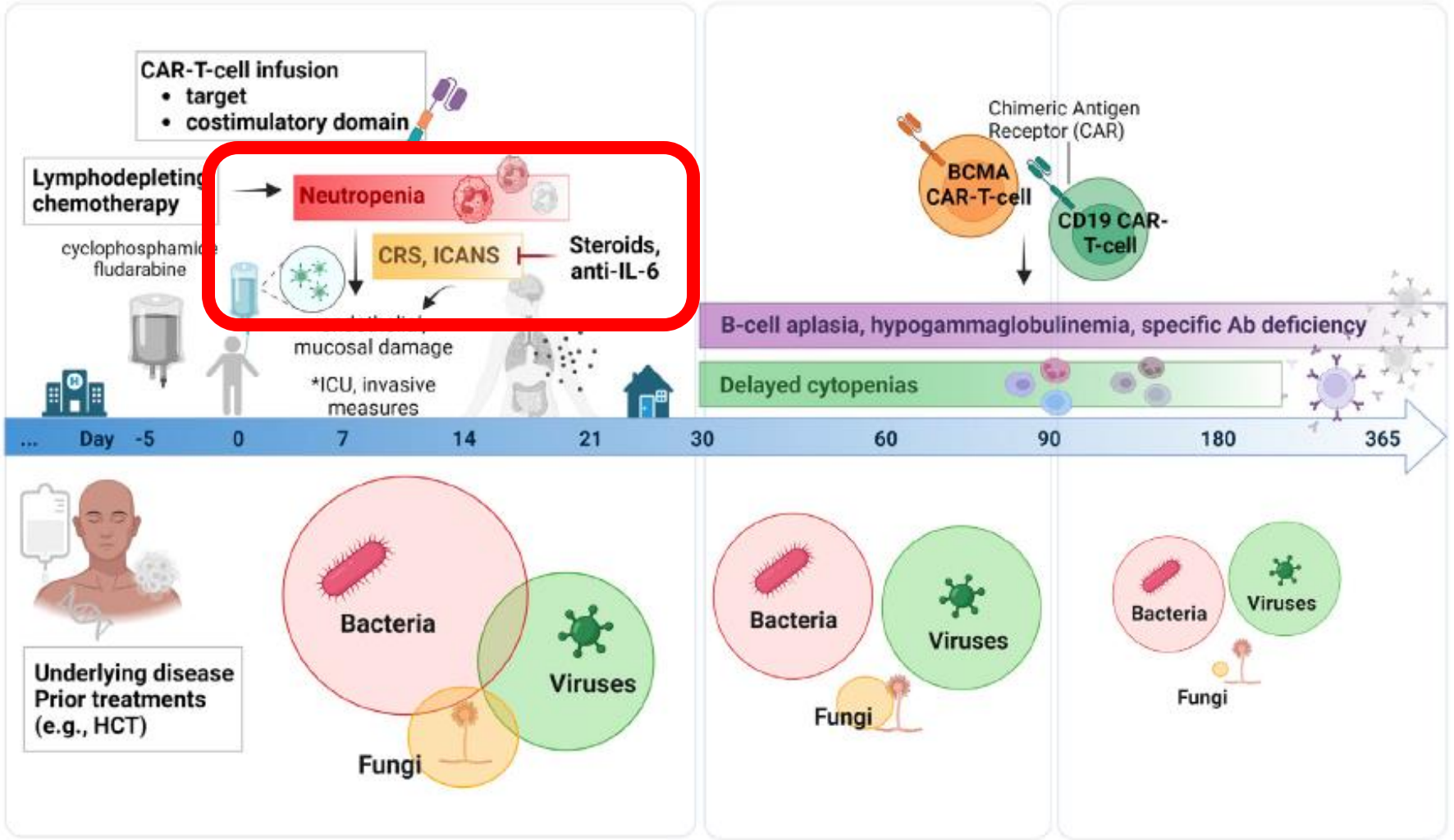
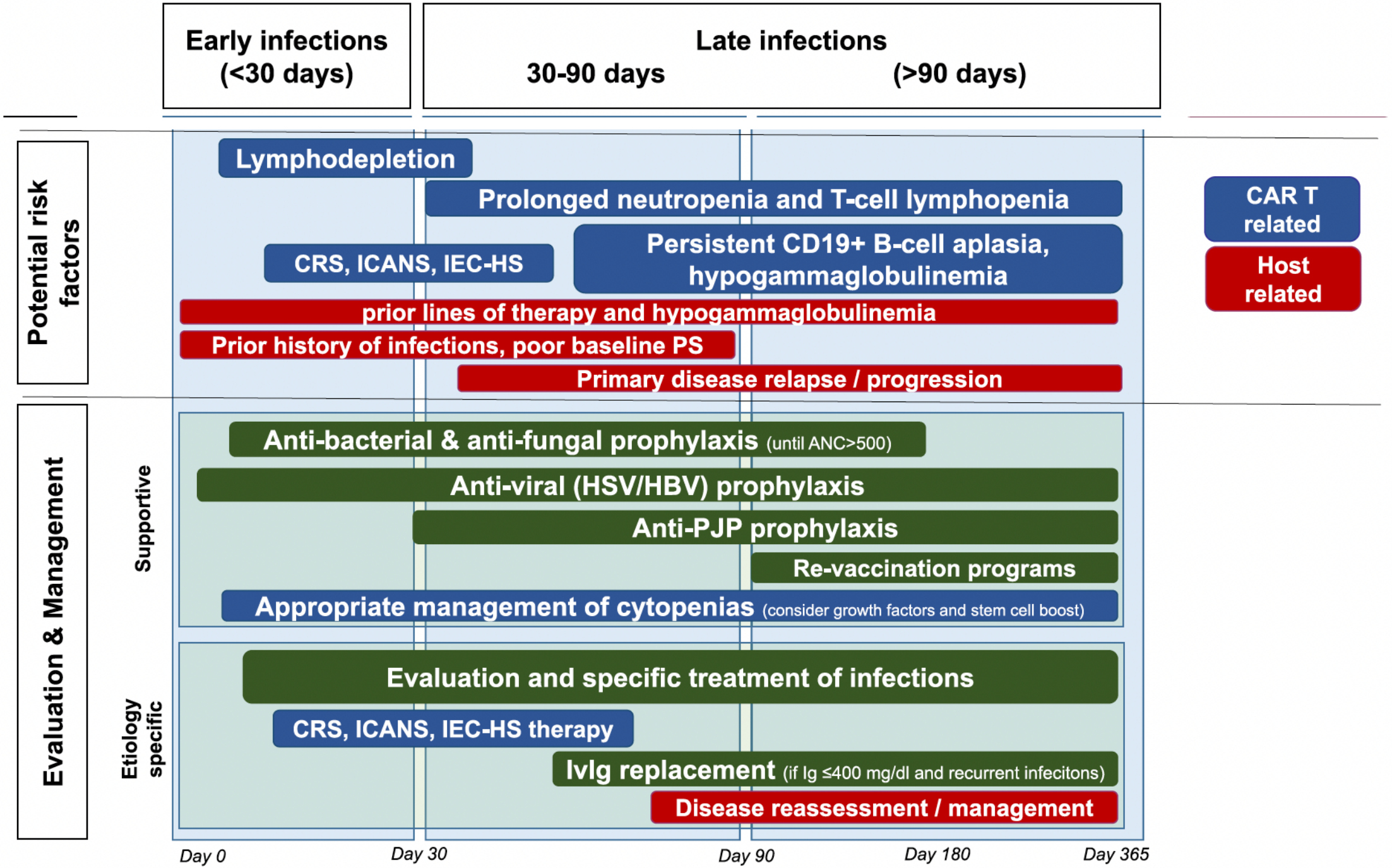


FIGURE 1 Infection risk and epidemiology during different time intervals after chimeric antigen receptor (CAR)-T-cell therapy. The size of the bubble represents the relative approximated frequency for each type of infection (bacterial, viral, and fungal). Neutropenia and delayed cytopenias are now referred to as early and late immune effector cell-associated hematotoxicity (ICAHT). CRS, cytokine release syndrome; HCT, hematopoietic cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; IL-6, interleukin 6. *Source*: Created with BioRender.com.


Early infections (<30 days)
Late infections
30-90 days
(>90 days)
Potential risk factors
Lymphodepletion
Prolonged neutropenia and T-cell lymphopenia
CRS, ICANS, IEC-HS
Persistent CD19+ B-cell aplasia, hypogammaglobulinemia
prior lines of therapy and hypogammaglobulinemia
Prior history of infections, poor baseline PS
Primary disease relapse / progression
CAR T related
Host related
Evaluation & Management
Supportive
Anti-bacterial & anti-fungal prophylaxis (until ANC>500)
Anti-viral (HSV/HBV) prophylaxis
Anti-PJP prophylaxis
Re-vaccination programs
Appropriate management of cytopenias (consider growth factors and stem cell boost)
Etiology specific
Evaluation and specific treatment of infections
CRS, ICANS, IEC-HS therapy
IvIg replacement (if Ig ≤400 mg/dl and recurrent infecitons)
Disease reassessment / management
Day 0
Day 30
Day 90
Day 180
Day 365

How do we differentiate between CRS and infection?

- **CRS and sepsis - considerable overlap;** challenging to distinguish between the two.
- **Detailed medical history, physical exam and lab Ix recommended.**
  - **Procalcitonin may be useful (esp. serial Procal).** CRP is not discriminatory.
- Haematotox score (HT score) has been developed in lymphoma pts receiving CART.
  - By assessing these 5 variables (ANC, Plt, Hb, CRP, ferritin) – HT score pre-lymphodepletion variables — enables risk stratification of hematological toxicity, and it risk stratifies patients for infectious complications.
  - **Assessment of bone marrow reserve and inflammation prior to CART (High HT score → delayed cytopenia)**

Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/µl	75,000 – 175,000/µl	< 75,000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650 – 2000 ng/ml	> 2000 ng/ml
Low: 0-1	High: ≥ 2		

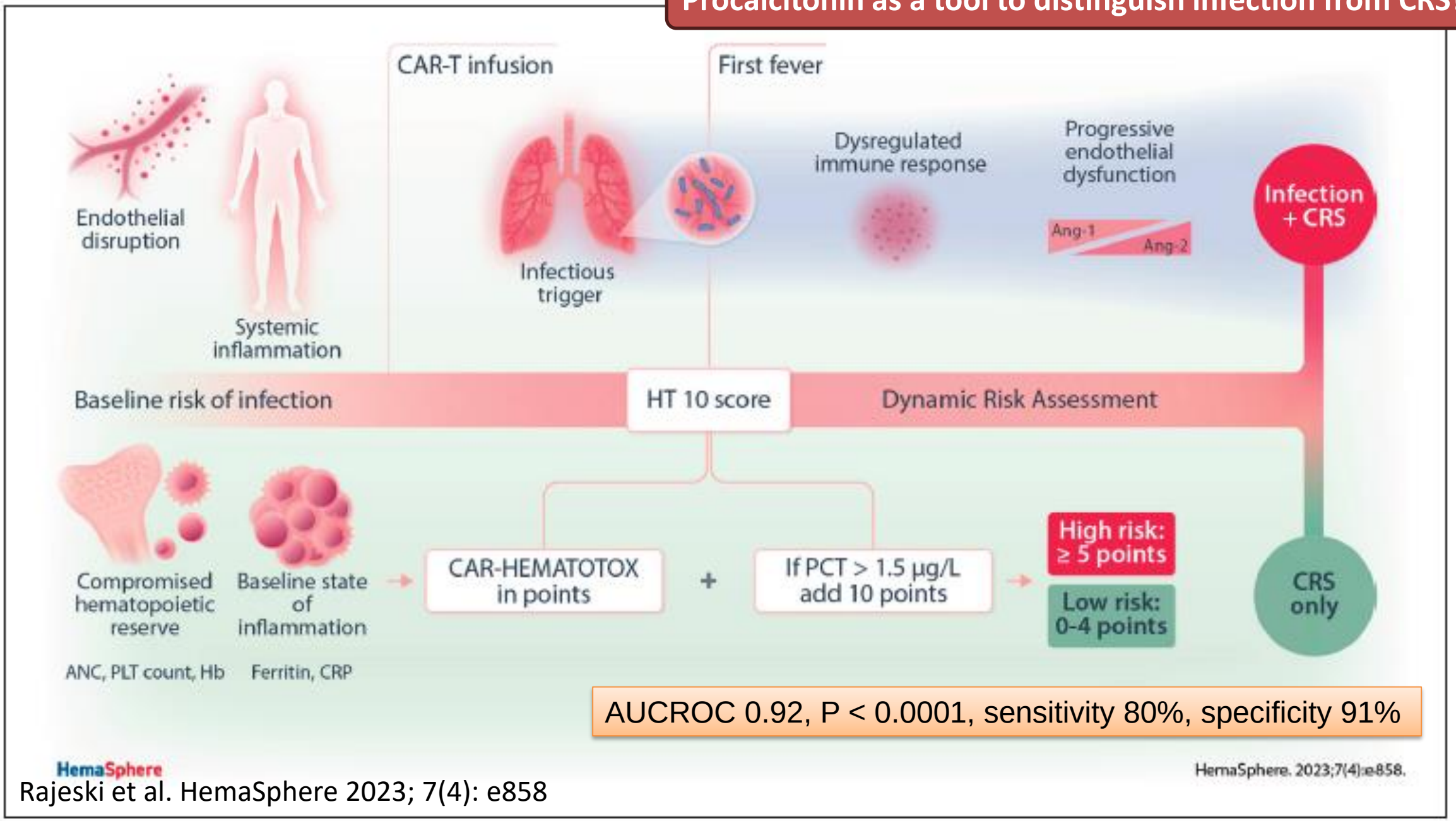
Figure 4. CAR-HEMATOTOX. Determined before lymphodepletion, the score comprises 5 markers of hematotoxicity with additional weighting of the baseline platelet count and ferritin levels. The score discriminates between a high (CAR-HEMATOTOX score ≥2) and low (CAR-HEMATOTOX score 0-1) risk for hematotoxicity.

To accurate distinguish between inflammation vs infection,
- Cytokine profiling
- T-cell profiling
- Use of biomarkers

May provide answers. To date – these are research tools

Athalie et al. Infect Dis Clin North Am 2022; 36(4): 735 – 748
Kampouri et al. Transpl Infect Dis 2023; 25(S1): e14157
Rajeski et al. HemaSphere 2023; 7(4): e858
Rodriguez et al. Lancet Oncol 2024;25:e205-16
Lin et al. Lancet Oncol 2024 https://doi.org/10.1016/S1470-2045(24)00094-9

Procalcitonin as a tool to distinguish infection from CRS?

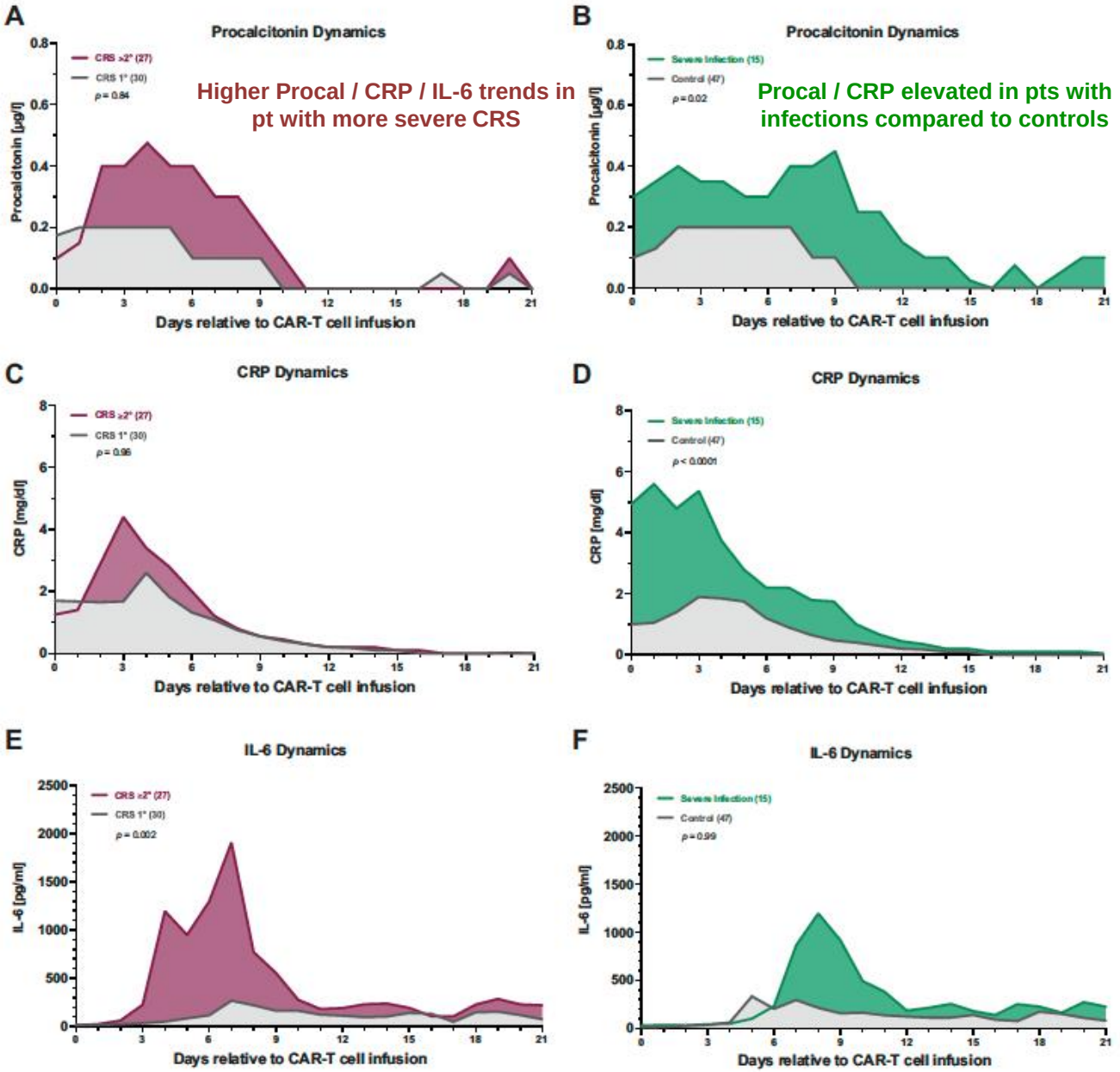


AUCROC 0.92, P < 0.0001, sensitivity 80%, specificity 91%

Rajeski et al. HemaSphere 2023; 7(4): e858

CRS

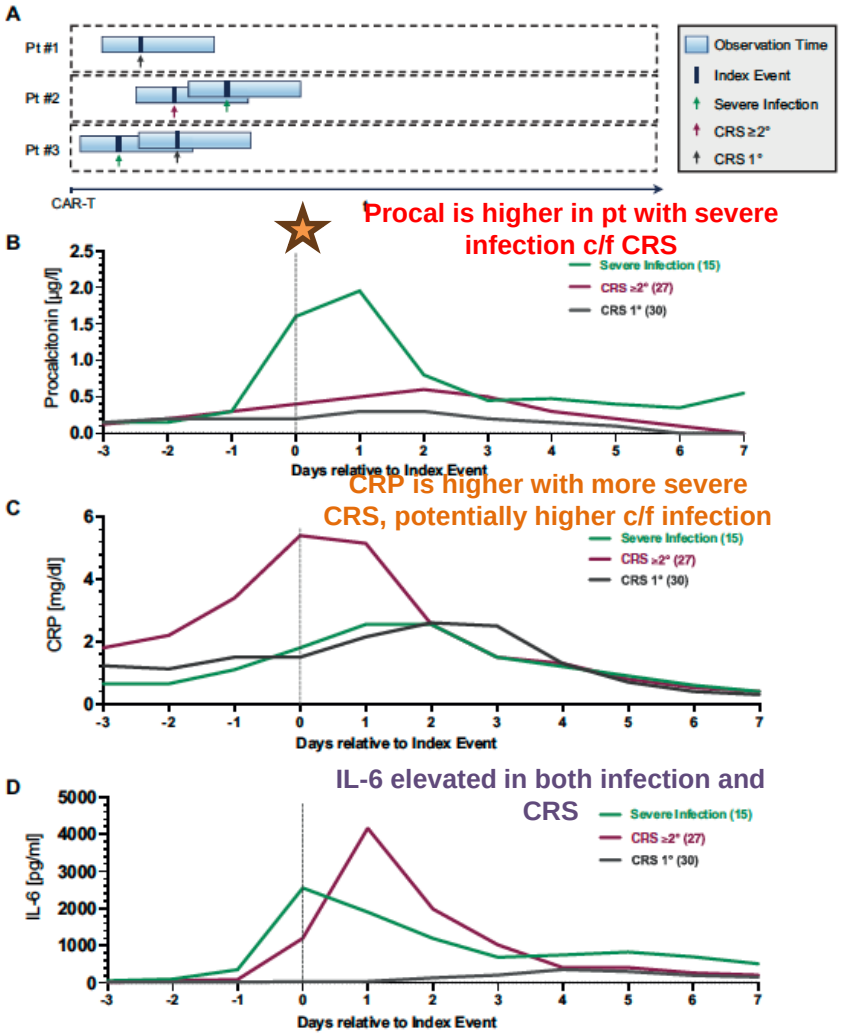
Infection



Higher Procal / CRP / IL-6 trends in pt with more severe CRS

Procal / CRP elevated in pts with infections compared to controls

Figure 2. High-grade CRS is characterized by high interleukin-6 levels, while severe infections are marked by baseline inflammation high pro-calcitonin levels. (A–B) Aggregated median procalcitonin values over time during the first 21 d after CAR-T infusion by CRS grade (A) and presence of severe infection (B). (C–D) Aggregated median CRP values by CRS grade (C) and presence of severe infection (D). (E–F) Aggregated median interleukin-6 values by CRS grade (E) and the presence of severe infection (F). Serum samples were prospectively collected in a laboratory panel that was performed at least daily during the first 2 wk and then as indicated. Significance values were determined with a mixed effects analysis considering both time and effect size. CAR-T = chimeric antigen receptor T-cell therapy; CRS = cytokine release syndrome.



Procal is higher in pt with severe infection c/f CRS

CRP is higher with more severe CRS, potentially higher c/f infection

IL-6 elevated in both infection and CRS

Figure 3. Serum inflammatory dynamics by index event. (A) Graphical representation of index event analysis: hypothetical patient #1 displays early grade 1 CRS and no infections; patient #2 displays grade early 2 CRS followed by a severe infection; patient #3 displays an early severe infection followed by grade 1 CRS. Serum procalcitonin (B), CRP (C), and IL-6 (D) levels were retrospectively assessed relative to the respective index event (severe infection: green; grade 1 CRS: gray; grade ≥2 CRS: magenta). The aggregated median values are depicted. CRP = C-reactive protein; CRS = cytokine release syndrome; IL-6 = interleukin-6.

Rajeski et al. HemaSphere 2023; 7(4): e858

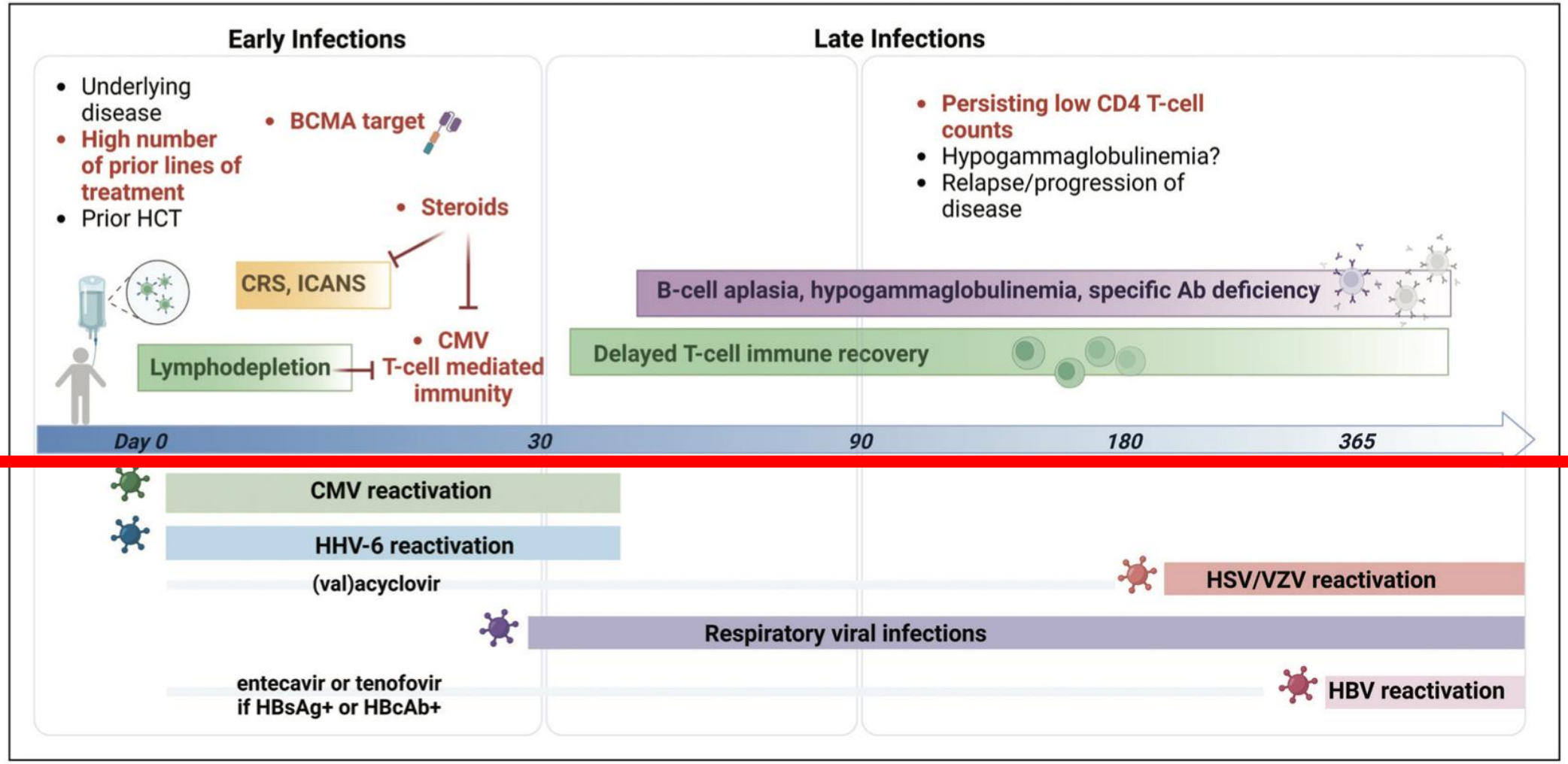


FIGURE 1. Risk factors and epidemiology of viral infection following CAR-T-cell therapy. Risk factors for viral infection are depicted in bullets along with the timeline of different viral infections divided into early (before 30 days) and late (after 30 days from infusion). Risk factors for viral infections identified in clinical studies are in red. CRS, cytokine release syndrome; HCT, hematopoietic cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome. Figure created with BioRender.com.

CART and CMV

- CMV risk is significant
  - Reactivation rates 7.5% - 56%, **csCMVi 3 – 15%, end organ disease - rare**
  - **Pre-infusion CMV viremia not uncommon, ~10% esp in Rx experienced pt**

- Risk Factors
  - Primary refractory disease, severe CRS, high dose steroid administration

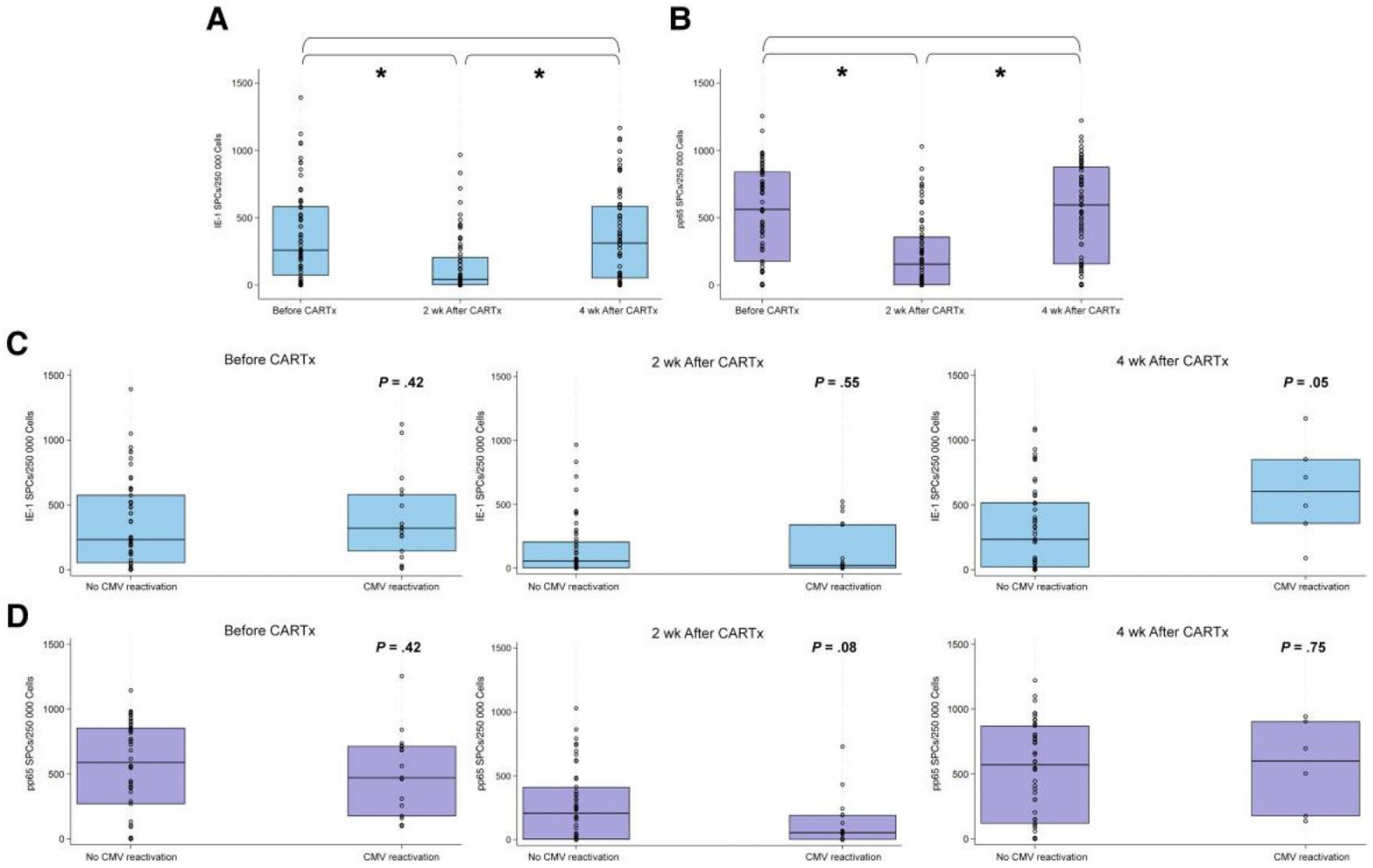
- When do they reactivate?
  - Usually within 1st month, median 13 days.
  - Late reactivation uncommon

- Prevention / Evaluation / Management
  - ? @baseline, or low threshold to test in a symptomatic pt
  - In viremic patients, decision to treat depends on CMV titres / treatment hx

- Associations
  - csCMVi within 1 year post CART a/w higher risk of NRM

Sassine et al. Viruses 2025; E. Marquez-Algaba et al. Transplantation and Cellular Therapy 2022; 28: 851.e1 851.e8, Kampouri et al. CID.2024; 78(4): 1022-32

CMV immunity wanes, then recovers by 4 weeks post CART



Kampouri et al. CID.2024; 78(4): 1022-32

Some patients get by without CMV treatment!

CMV evaluation and management post CART is dynamic

We need to adopt risk stratified approach

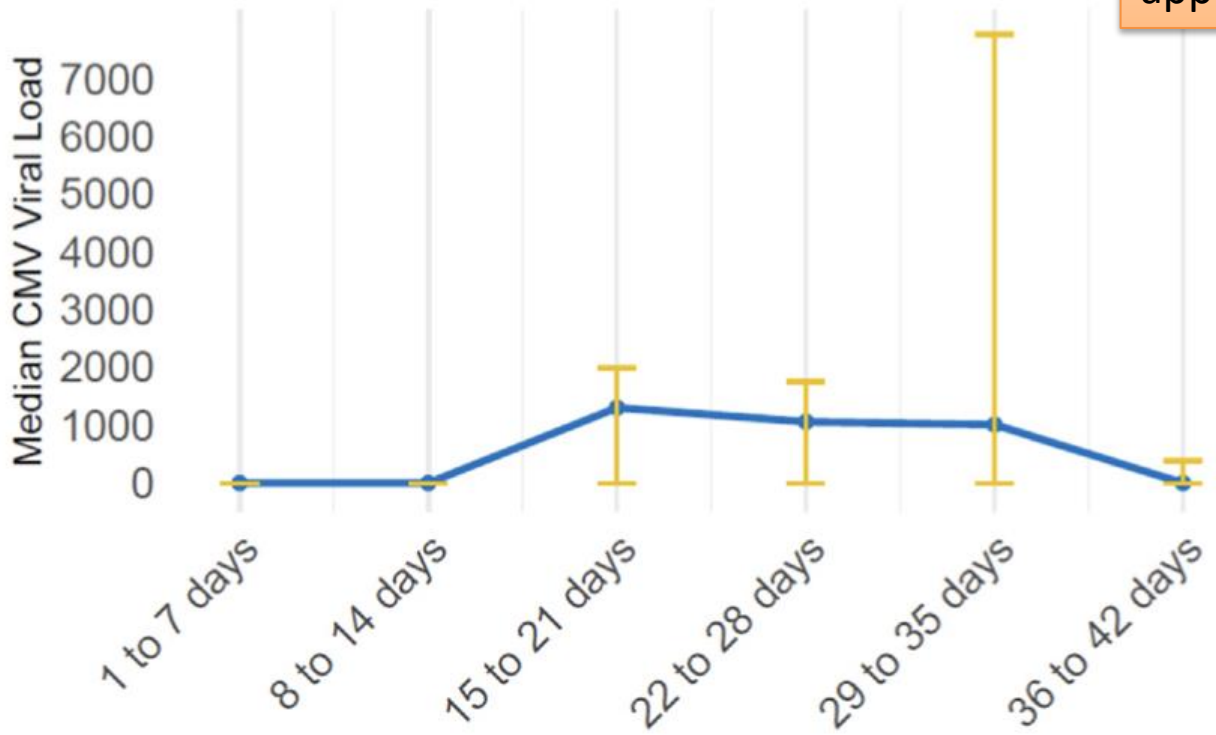


Figure 3. CMV viral load evolution in patients presenting with CMV replication ≥1000 IU/mL who did not receive specific antiviral treatment (n = 18). Shown are median number and IQR of CMV viral load as measured by PCR at specific time points after CAR T cell infusion in patients who did not receive specific antiviral treatment.

E. Marquez-Algaba et al. Transplantation and Cellular Therapy 2022; 28: 851.e1 851.e8

Late complications a/w CART

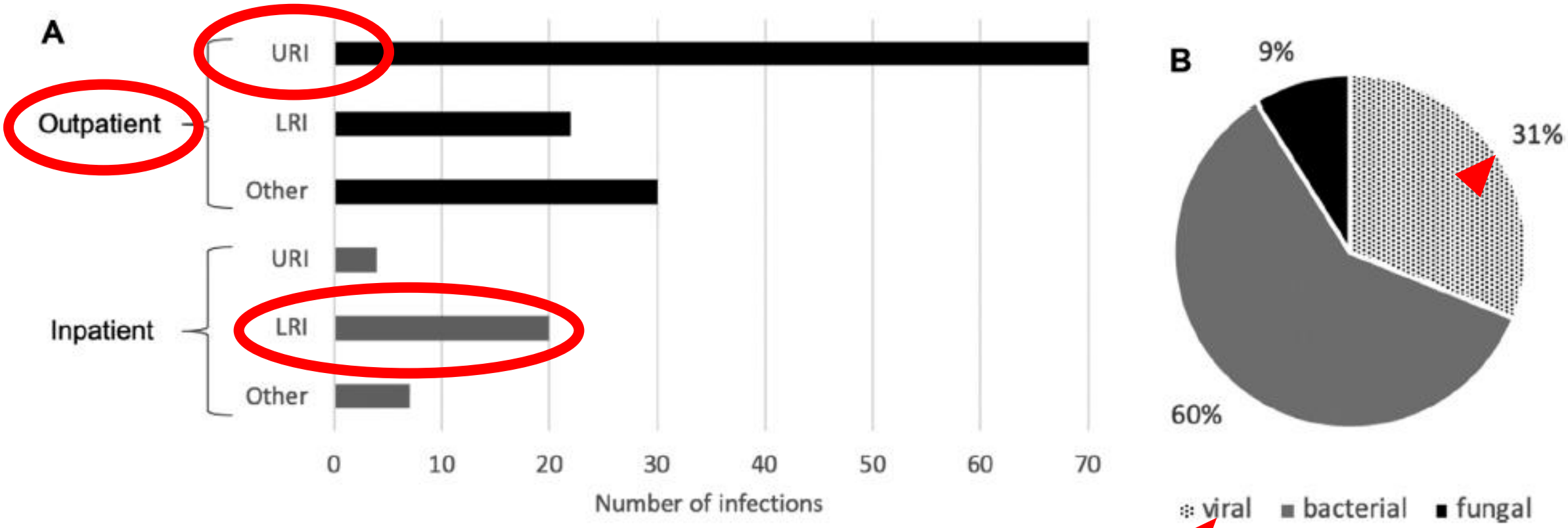


Figure 1. Late infections. (A) Late infections managed in the outpatient (n = 122) or inpatient (n = 31) setting, including infections requiring intensive care (n = 7; all LRI). URI indicates upper respiratory infection; LRI, lower respiratory infection; other, other infections (n = 37): bacteremia (n = 1), febrile neutropenia (n = 1), conjunctivitis (n = 2), oral infections (including herpes simplex virus [HSV] and *Candida*) (n = 4), genitourinary tract infections (n = 4), gastrointestinal infections (n = 5), osteomyelitis (n = 1), and skin infections (including cellulitis, human papillomavirus, HSV, zoster, and tinea) (n = 19). (B) Infections with microbiologic evidence (n = 37).

A. Cordeiro et al. Biol Blood Marrow Transplant (2020) 26: 26 - 33

Vaccinations

Table 4
Vaccination Recommendations for CAR T Recipients

Killed/Inactivated Vaccines*	Pre-CAR	>3m	> 6m	>6m	>8m	>10m	>12	>18	Interval Between Vaccinations
Influenza†	Flu	Flu							Yearly
RSV†		RSV							ACIP guidance
SARS-Cov†	SARS-CoV-2	SARS-CoV-2							ACIP guidance for immuno-compromised patients
Pneumococus‡			PCV20	titers	PCV20	PCV20			1-2 mo
Diphtheria, tetanus, and acellular pertussis (DTap) §,‖			DTap	titers	Td	Td			1-2 mo
Hepatitis A ¶,#			HAV	titers			HAV		6 mo
Hepatitis B #,**			HAB	titers	HBV		HBV		2 mo
Shingrix††							VZV	VZV	

RSV vaccination is shared clinical decision making

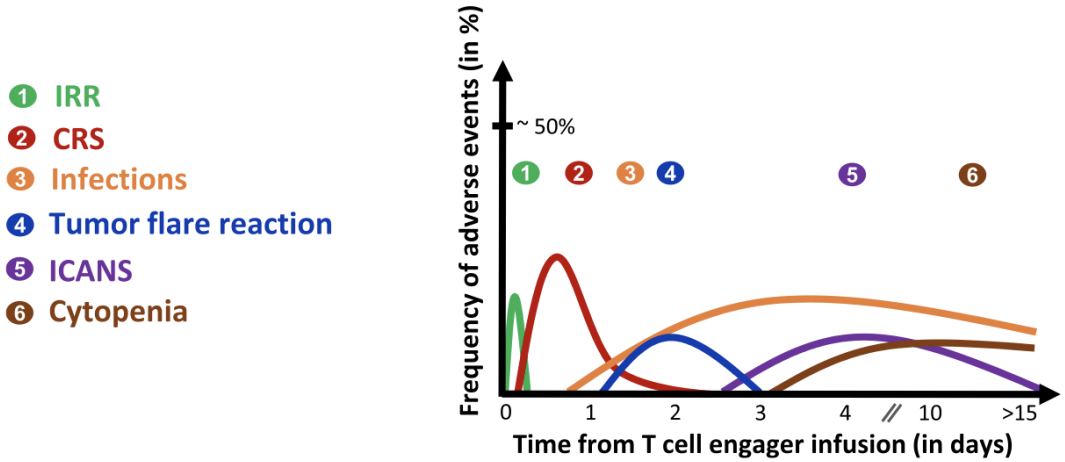
Shahid et al. Transplantation and Cellular Therapy 30(2024) 955969

Case 2: ID Considerations / Observations / Questions

- Infections may run a more protracted course
- A/w T-cell dysfunction / Hypogammaglobulinemia
  - Viral infections are going to be common
  - Prior to Bispecific antibody therapy, may be useful to vaccinate against common respiratory viruses, on treatment consider acyclovir ppx
- Recurrent CMV infections not unexpected
  - When ongoing treatment with bispecific therapy is required, it becomes tricky.
  - Prevention strategies – Close surveillance with pre-emptive treatment. May require secondary prophylaxis
- In other patients, may need to consider prior lines of treatment, and evaluate their infectious diseases risk.

Bispecific antibody: A more accurate framework: Incorporating timing & pathophysiology

Expected timing for reactions and adverse events with T-cell engagers



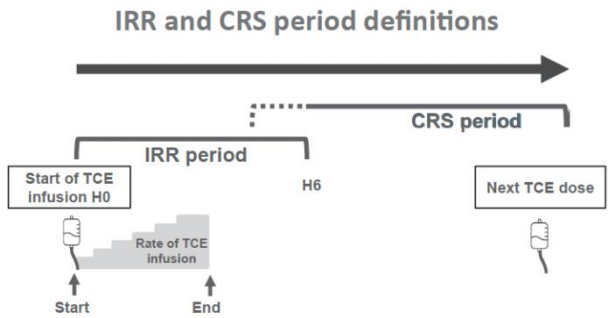


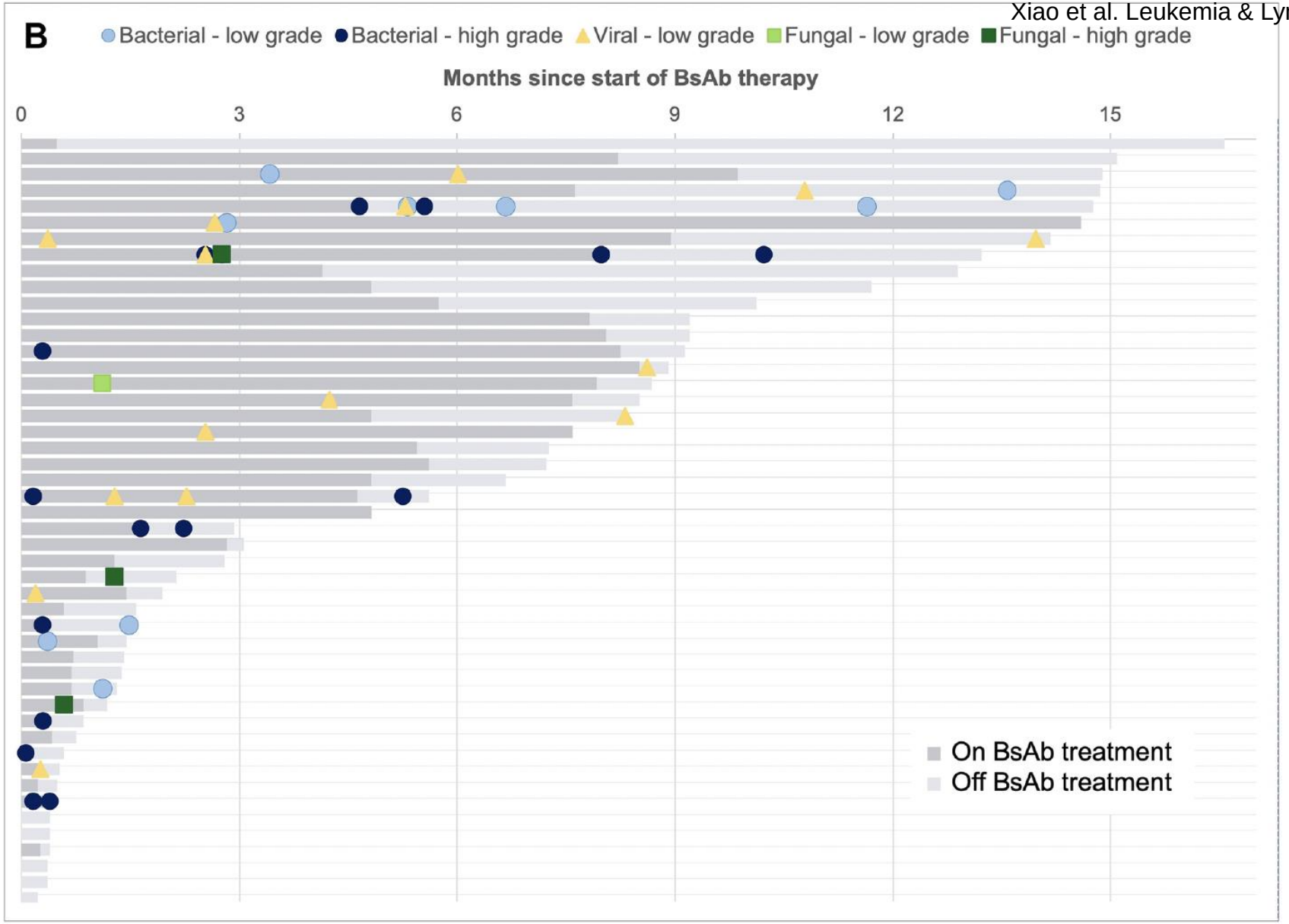
Fig. 2. Diagram proposing definitions of the periods during which infusion related reaction (IRR) and cytokine release syndrome (CRS) are expected after immunotherapy with T cell engagers. CRS: Cytokine release syndrome. IRR: Infusion related reaction TCE: T-cell engager.

Géraudet al Eur J Cancer. 2024 Jul:205:114075.

Key points for the management of reactions and adverse events with T-cell engagers

	IRR *with anaphylaxis*	IRR *without anaphylaxis*	CRS	Infections	Tumor flare reactions	ICANS	Cytopenia
Typical expected time of occurrence	Immediate, in first minutes of treatment, or at second administration	During the 6 first hours after starting infusion	4 – 16 hours after infusion	1-14 days after infusion	1-3 days after infusion	3-9 days after infusion	3-14 days after infusion
Main sign and symptoms	Anaphylaxis, hypotension, laryngeal angioedema, bronchospasm	Chills, flushing, moderate fever, urticaria, nausea, vomiting	Fever, hypotension, hypoxia	Fever, chills, viral or bacterial infections signs	Tumor pain, effusion worsening, tumor compression signs and symptoms.	Speech difficulties, behavior modification, memory trouble, confusion, headache, seizure.	Neutropenia, anemia, thrombocytopenia related symptoms.
Pathophysiology aspects	IgE mediated	Cytokine elevation, none-IgE mediated	Cytokine storm IL-6 mediated	On target effect in immune component	Tumor microenvironement inflammation	Endothelial and blood-brain barrier disturbances	Direct toxicity on hematopoietic precursor (mainly TCE for blood cancer)
Main drugs interventions	Epinephrin IM in life-threatening cases	H1/H2-receptor antagonists,acetaminophen, antileucotriens, corticosteroids, bronchodilators	Anti-IL6 receptor, corticosteroids, vasopressor in severe cases	Anti-infectious agents to treat infection. Prevention and pre-emptive measures are important with prophylaxis, vaccinations, gammaglobulins in severe cases with humoral deficiency	Corticosteroids, analgesic	Corticosteroids (dexamethasone preffered), non sedative anti-convulsant, antagoniste des récepteurs de l'interleukine-1 (IL-1ra) in severe cases	Stimulating factors (GCSF) for neutropenia

Xiao et al. Leukemia & Lymphoma https://doi.org/10.1080/10428194.2025.2540442



igure 1. Infection incidence after BsAb therapy. (A) Cumulative number of any-grade and grade ≥3 infections per person over ime after starting BsAb therapy. (B) Swimmer's plot of time to any-grade and grade ≥3 infections.

Bacterial and viral infections predominate.

40% develop hypogammaglobulinemia

? Cumulative infection risk.

Types of infections and implications for Rx / Followup

Bacterial and viral infections predominate.

Respiratory tract and bloodstream infections common.

Implications *- IVIG replacement / vaccinations may important. Safe living precautions (masking, hand hygiene and other sensible stuff)*

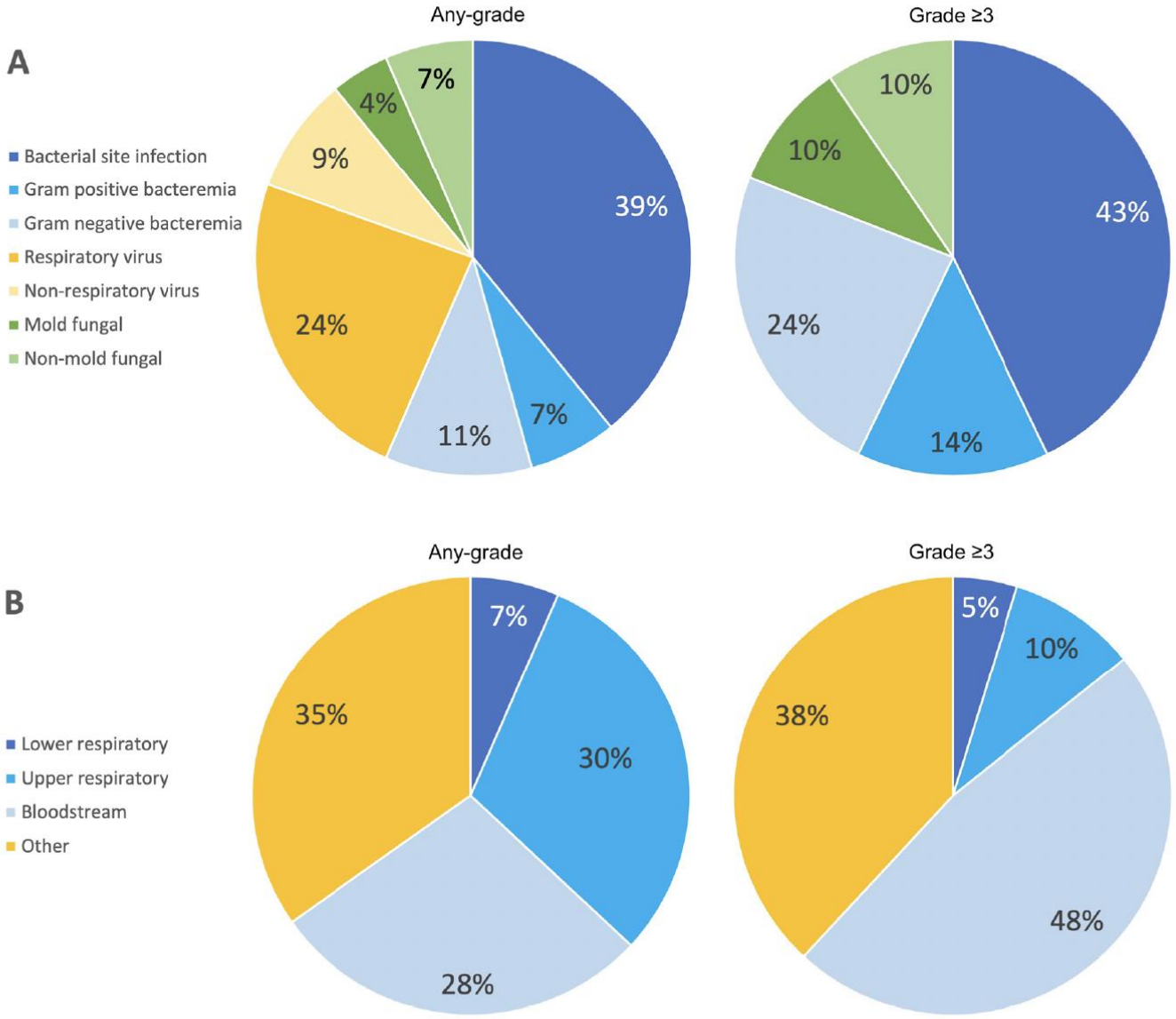


Figure 2. Classification of infections after BsAb therapy. (A) Infections by type and (B) by organ system.

Xiao et al. Leukemia & Lymphoma https://doi.org/10.1080/10428194.2025.2540442

Compare and contrast: CART vs Bispecific antibody

CAR T-cells	Bispecific Antibodies
Excellent efficacy	Excellent efficacy
Manufacturing process (3-4 weeks)	Available off-the-shelf
Usually inpatient, followed by period of time proximal to administering center for monitoring	Usually outpatient, initially with weekly visits that ultimately space out depending on product
"One and done"	Months (fixed duration) or continuous treatment
Requires lymphodepleting chemotherapy +/– bridging	No lymphodepleting chemotherapy or bridging
Higher risk of, and less predictable, CRS and NT	Less risk of, and more predictable, CRS and NT
Infections and cytopenias are common; likely higher rates and more prolonged	Infections and cytopenias are common; potentially lower rates but more follow up needed
Durable responses with years of follow up	Longer follow up needed for response durability

Figure 2. Comparison of CAR T-cell and BsAb characteristics. CAR T cells and BsAbs are associated with unique considerations regarding logistics and toxicity. NT, neurologic toxicity.

More accessible. N larger potentially

Prob dealing with chronic recurrent / refractory infections

? a/w more profound hypogammaglobulinemia

Haydu et al. Blood Advances 2024; 8:17

CART or Bispecific antibody for lymphoma: What does it mean for the ID physician

We may be putting on a different cap when we approach these 2 entities

	CART	Bispecific antibody therapy
Fever	24 – 94 %	FN uncommon < 5%
CRS	**All: 50 – 90%** **≥ Grade 3 CRS: 10 - 28% (some report 1 – 6%)**	All grade: 45 - 65 % ≥ Grade 3 CRS: 2%
ICANs	All grade: 21-65% ≥ Grade 3 ICANS: 2 - 24%	All grade: 44 % ≥ Grade 3 ICANS: 1%
Hypogamma-globulinemia	Baseline hypogammaglobulinemia: 35% Post CART: ~70% (1/3 receive Ig-RT)	Variable, still evolving field
Infections	**Bacterial infections common first 30 days** After D30, resp. viral infxns common Viral infections not uncommon Fungal infections (<6%)	All grade 39 – 39% Grade ≥ 3 infections: 10% - 20% Grade 5: 3% **Severe infections were due to viruses**
T-cell function	Expect recovery beyond the year	T-cell exhaustion from sustained immune activation

Discussion pertains to treatment for lymphoma

Shahid et al. Transplantation and Cellular Therapy 30(2024) 955969; Mihaila et all J Clin Med 2025; Trabolsi et al. Blood Cancer Journal 2024; 14:27
D'Alò et al. Cancers 2024, 16, 2243; Reynolds et al. Blood Advances 2024; 8:13; Falchi L, Vardhana SA, Salles GA. Blood. 2023;141(5):467-480

blood advances

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Jul 2025

Comparative Infection Risk in CAR T vs Bispecific Antibodies in B cell Lymphoma: A Systematic Review and Meta-Analysis

Systematic review for prospective trials assessing commercially approved CAR T vs BsAbs in patients with B-NHL.

N =. 25 studies, 3202 patients

~ CAR T vs BsAbs similar rates of **all grade infections per patient** (0.44 vs 0.54; p = 0.18)
~ CAR T vs BsAbs had similar rates of **grade 3+ infections per patient** (0.16 vs 0.22; p = 0.08)
~ CAR T vs BsAbs products had similar **rates of infection-related mortality**

✗ BsAbs had ↑ rate of infection per patient-month (0.0397 vs 0.0167; p = 0.0012).
✗ BsAbs had a higher rate of grade 3+ infections per patient-month(0.0165 vs 0.0069; p = 0.0003).

Potential ↑ burden of infections over time in patients receiving BsAb therapy, particularly for patients on indefinite therapy.

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BiSpecific Antibody

Screening

Baseline serologies
HIV
Hepatitis B
Hepatitis C
Strongyloides (if relevant)*
TB (if relevant)*

Review prior hx of CMVi
CMV serology / IGRA^ (?)
MDRO screening per unit protocol

^IGRA – interferon gamma release assays

Chemo-prophylaxis recommended

HSV, VZV prophylaxis*#

HBV prophylaxis if carrier*#

PCP prophylaxis # (if steroid dose high or previous HSCT)*

Fungal prophylaxis
Uncommon. Individualise recommendations based on risk profile

CMV prevention and management.
?
Low threshold to test
If detectable, followup is important.

IVIg if hypogammaglbulinemia, central line care, adherence to infection prevention protocols

* from Longhitano AP et al. Blood Rev 2021;49:100810; #Raje N et al. Blood Cancer J 2023;13:113

Slide courtesy of Dr. Tan BH, SGH, with modifications

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Lymphoma and hypogammaglobulinemia

- Hypogammaglobulinemia occurs in pts with lymphoma
- In DLCBL, FL, MZL, HG (IgG < 500 mg/dL to IgG < 700 mg/dL) – 14 – 22%

- Rituximab ↑ the incidence of HG; risk highest in those on maintenance Rx.
  - In one study, 211 patients with B cell lymphoma on Ritxuximab – 15% @baseline had HG, but an 38 % developed HG after Rituximab Rx. 6% required Ig RT
- With CART and bispecific antibody therapy, rates of HG may be higher.

Wonnaparhown et al. Blood Reviews 2025.

CART for lymphoma and hypogammaglobulinemia

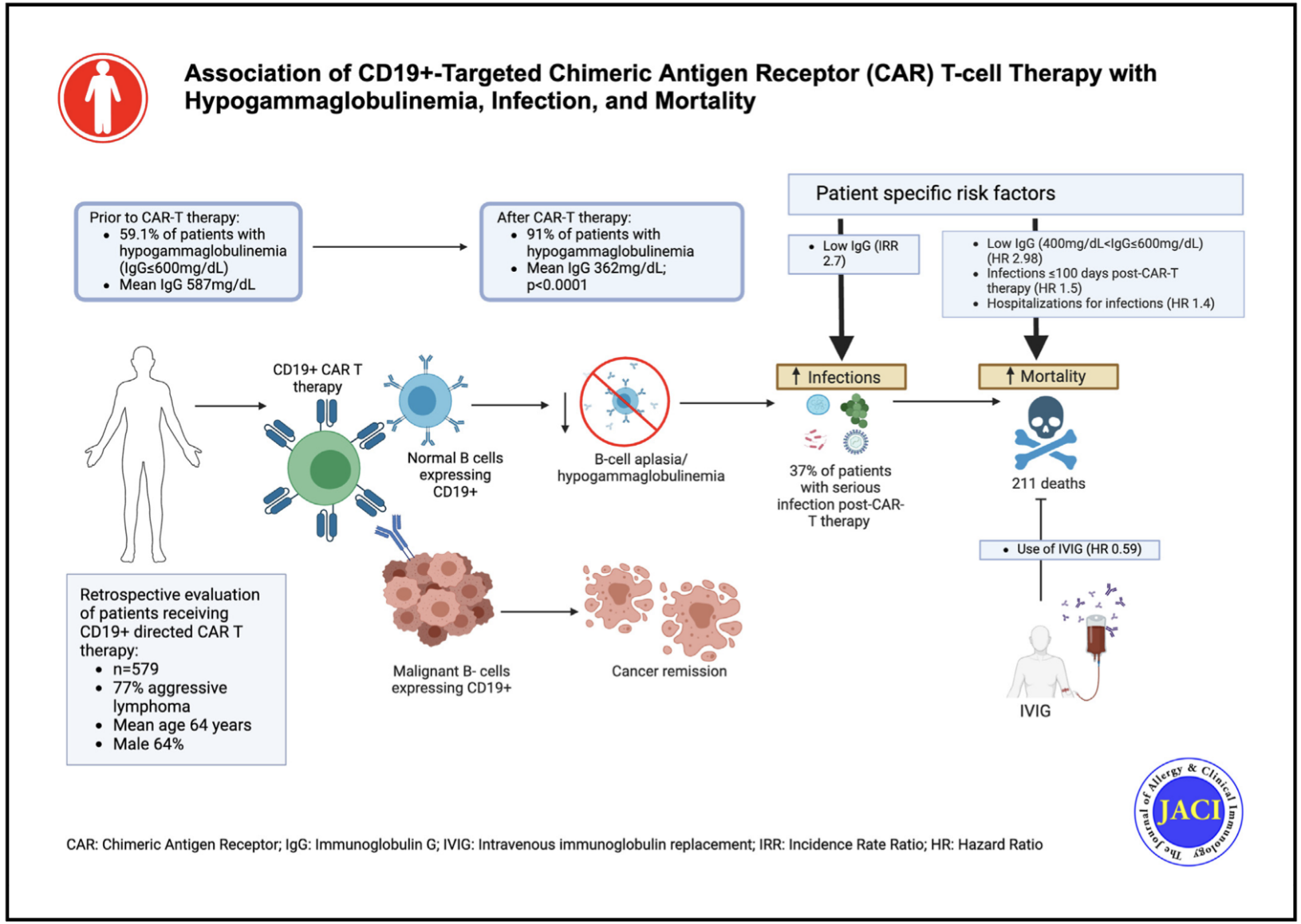
Table 2
Rates of HG and infection post CAR T therapy reported in pivotal trials leading to FDA approval*.

CAR-T construct	Disease and trial name (phase)	Median follow-up	Rate of HG	Rates of infection (grade 3 or higher)
Lisocabtagene maraleucel	CLL, TRANSCEND CLL 004 (Phase 2) [97]	21 months	18/117 (15 %)	20/117 (17 %)
	DLBCL, TRANSFORM (Phase 3) [99]	18 months	10/92 (11 %)	14/92 (15 %)
	FL, TRANSCEND-FL (Phase 2) [103]	19 months	6/130 (5 %)	7/130 (5 %)
Axicabtagene ciloleucel	DLBCL, ZUMA-7 (Phase 3) [100]	25 months	19/170 (11 %)	24/170 (14 %)
	FL, ZUMA-5 (Phase 2) [104]	23 months	25/148 (17 %)	26/148 (18 %)
Tisagenlecleucel	DLBCL, JULIET (Phase 2) [127]	14 months	20/115 (17 %)	47/115 (41 %)
	FL, ELARA (Phase 2) [102]	17 months	9/97 (9 %)	5/97 (5 %)
Brexucabtagene autoleucel	MCL, ZUMA-2 (Phase 2) [101,128]	12 months	13/82 (16 %)	28/82 (34 %)
	B-ALL, ZUMA-3 (Phase 2) [122,128]	16 months	7/78 (9 %)	27/78 (35 %)
Idecabtagene vicleucel	Multiple myeloma, KarMMa (Phase 2) and KarMMa-3 (Phase 3) [129]	13 months (KarMMa), 19 months (KarMMa-3)	158/349 (45 %)	47/222 (21 %)
Ciltacabtagene autoleucel	Multiple myeloma, CARTITUDE-1 (Phase 2) and CARTITUDE-4 (Phase 3) [130]	12 months (CARTITUDE-1), 16 months (CARTITUDE-4)	265/285 (93 %)	69/285 (24 %)

* As reported in specified clinical trials or FDA package insert.

Wonnaparhown et al. Blood Reviews 2025.

GRAPHICAL ABSTRACT



Capsule summary: Hypogammaglobulinemia is present in the majority of patients after CD19-targeted chimeric antigen receptor T-cell therapy. Increased immunologic monitoring is needed to identify those at high risk for serious infections and death, who may benefit from immunoglobulin replacement.

CART for lymphoma and hypogammaglobulinemia

Table 3
Rates of HG and infection with bispecific antibody therapy reported in pivotal trials leading to FDA approval*.

Bispecific Ab	Disease and trial name (phase)	Median follow-up	Rate of HG	Rate of infection (grade 3 of higher)
Epcoritamab	DLBCL, EPCORE NHL-1 (Phase 2) [131]	25 months	NR	40/157 (25.5 %) (2 fatal infections)
	FL, EPCORE NHL-1 (Phase 2) [132]	17 months	NR	24/128 (19 %) COVID-19, 5/128 (4 %) urinary tract infection (8 fatal infections)
Glofitamab	DLBCL, NP30179 (Phase 2) [133]	13 months	NR	15/145 (10 %) (5 % fatal infections)
Mosunetuzumab	FL, GO29781 (Phase 2) [134,135]	18 months	40 %	13/90 (14 %) (1 % fatal infections)
Teclistamab	MM, MajesTEC-1 (Phase 2) [112]	14 months	74.5 % had HG (by report and/or IgG < 500 mg/dL)	44.8 % of the 165 patients had grade 3–4 infections, which included pneumonia (18.2 %), bronchitis (13.3 %), upper respiratory tract infection (10.9 %), and *Pneumocystis jirovecii* pneumonia (PJP) (3.6 %)
Elranatamab	MM, MagnetisMM-3 (Phase 2) [113]	15 months	75.5 % (IgG < 400 mg/dL)	40 % of these patients had grade 3–4 infections, including 6 cases of PJP and fatal infections in 6.5 %
Talquetamab	MM, MonumenTAL-1 (Phase 2) [115]	12 months (405 μg dose) 4 months (800 μg dose)	87 % (IgG < 500 mg/dL) in pts. who received the 405 μg dose and in 71 % of those who received the 800 μg dose	7 % (1.5 % fatal infections)

Wonnaparhown et al. Blood Reviews 2025.

Patient evaluation: infectious diseases point of view

Host / Disease factors

Co-morbidities
Burden of disease
Epidemiological risk factors

Treatment History

Cumulative treatment history
Depth of immunosuppression
“Which arm of the immune system is most affected?”

Prior treatment complications (infectious & non-infectious)

Prophylaxis / Vaccination Hx

Preventable infections
Compliance to ppx
“Breakthrough infections”
Role for IVIG

Infectious disease syndrome

Clarify the diagnosis
Appropriate workup
Site and severity of infection
? Secondary prevention

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Summary:

- Evaluation and treatment of infection in patients with lymphomas on CART / Bispecific antibody –

  Attention to detail is key

- Our strategies:
  - Risk evaluation, consider prevention strategies (ppx, surveillance strategies, vaccination) and prompt recognition of infections

- Fall back on first principles when we are dealing with unknowns.
  - The answer is in the detail

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Thank you.

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