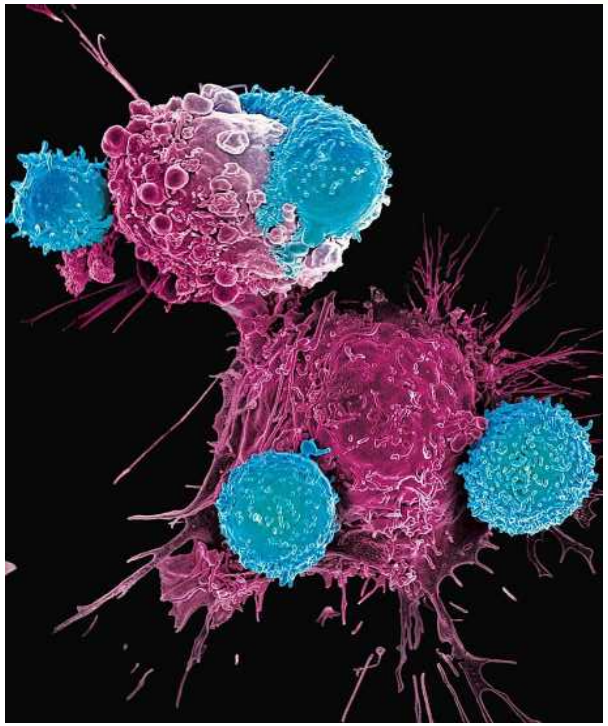

Priniciples of Cell Therapy and Toxicities

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Outline

The Fundamentals: Introduction to cell therapy
- Rationale for Immunotherapy and IEC therapy
- Historical Roots

The Evolution of Cell Therapy
- Landmark developments
- The Challenge of Solid Tumours

Cell Therapy Modalities and Future Developments
- CAR-T vs other IECs
- Emerging Concepts

Patient Care
- Planning the Patient Journey
- Toxicities

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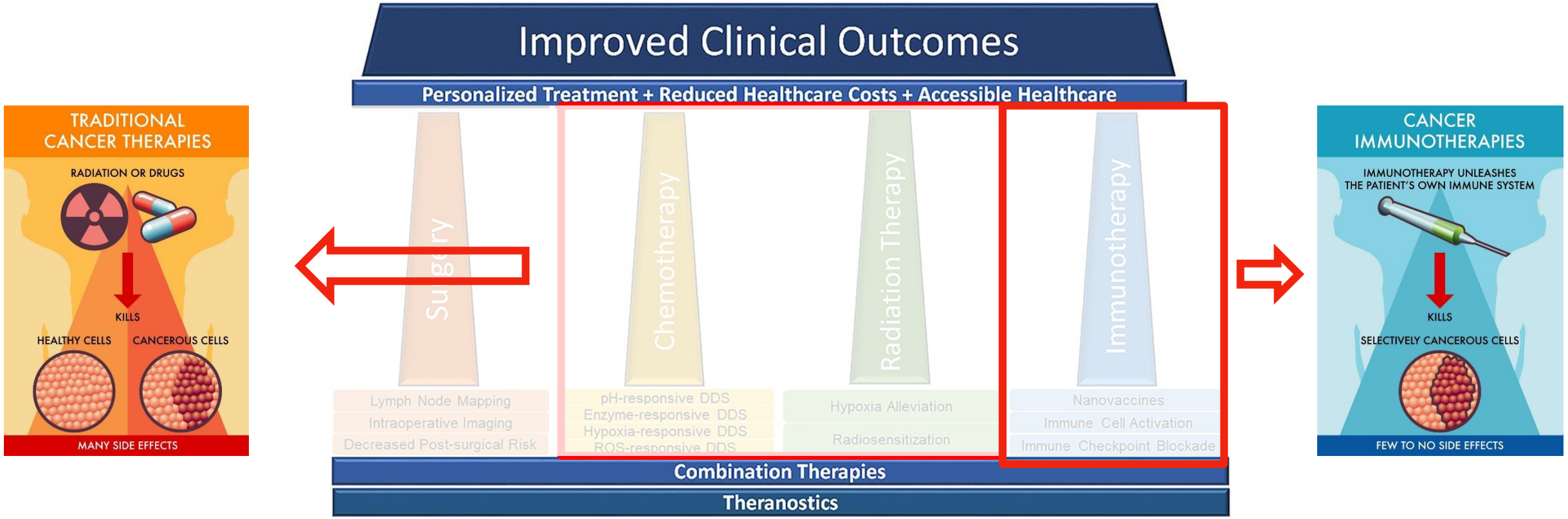
Premise



Paradigm shift in cancer care: Cytotoxics >> Immunotherapy

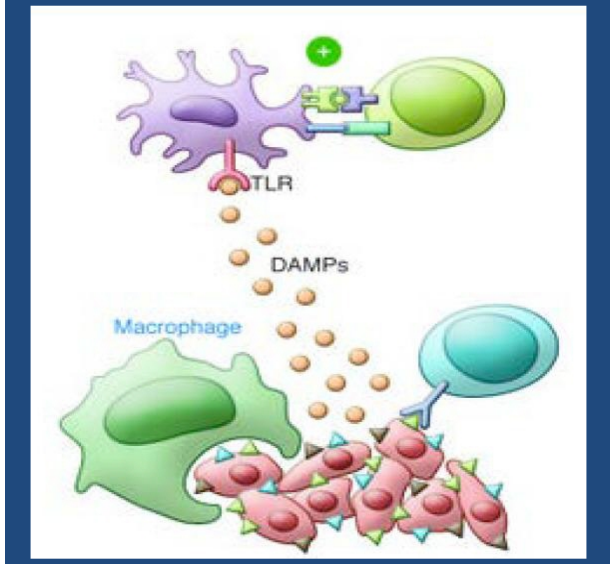
Restricted, Sensitive (Normal)

Siamof et al. *Front chem.* (2020)

Basis for immunotherapy

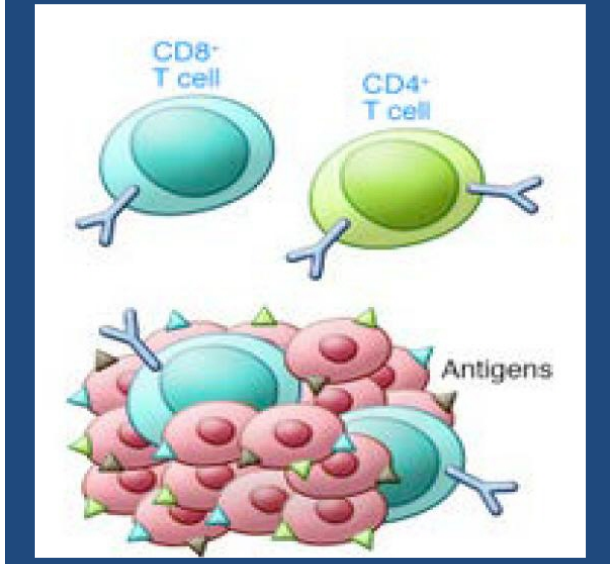
Basis for immunotherapy in cancer

ELIMINATION



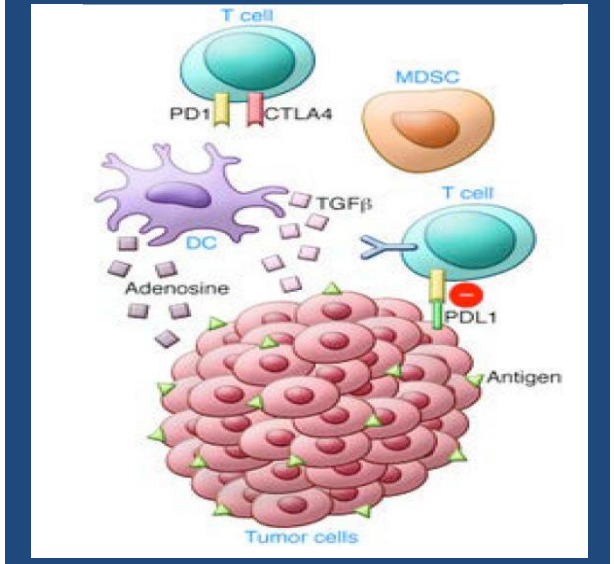
The immune system has the ability to eliminate cancer cells. Highly antigenic cancer cells are recognized and eliminated by the immune system.

EQUILIBRIUM



Cancer cells that escape the elimination phase enter the equilibrium phase. These transformed cells are poorly immunogenic and have the ability to coexist with immune cells

ESCAPE



Cancer cells have acquired resistance by:

- Poor antigenic expression
- Immunosuppressive cytokines
- MDSCs
- Expression of PD-L1

Kalbasi A et al. *J Clin Invest.* 2013:123(7):2756-2763

Basis for immunotherapy

Tumors go to great lengths to evade the immune response

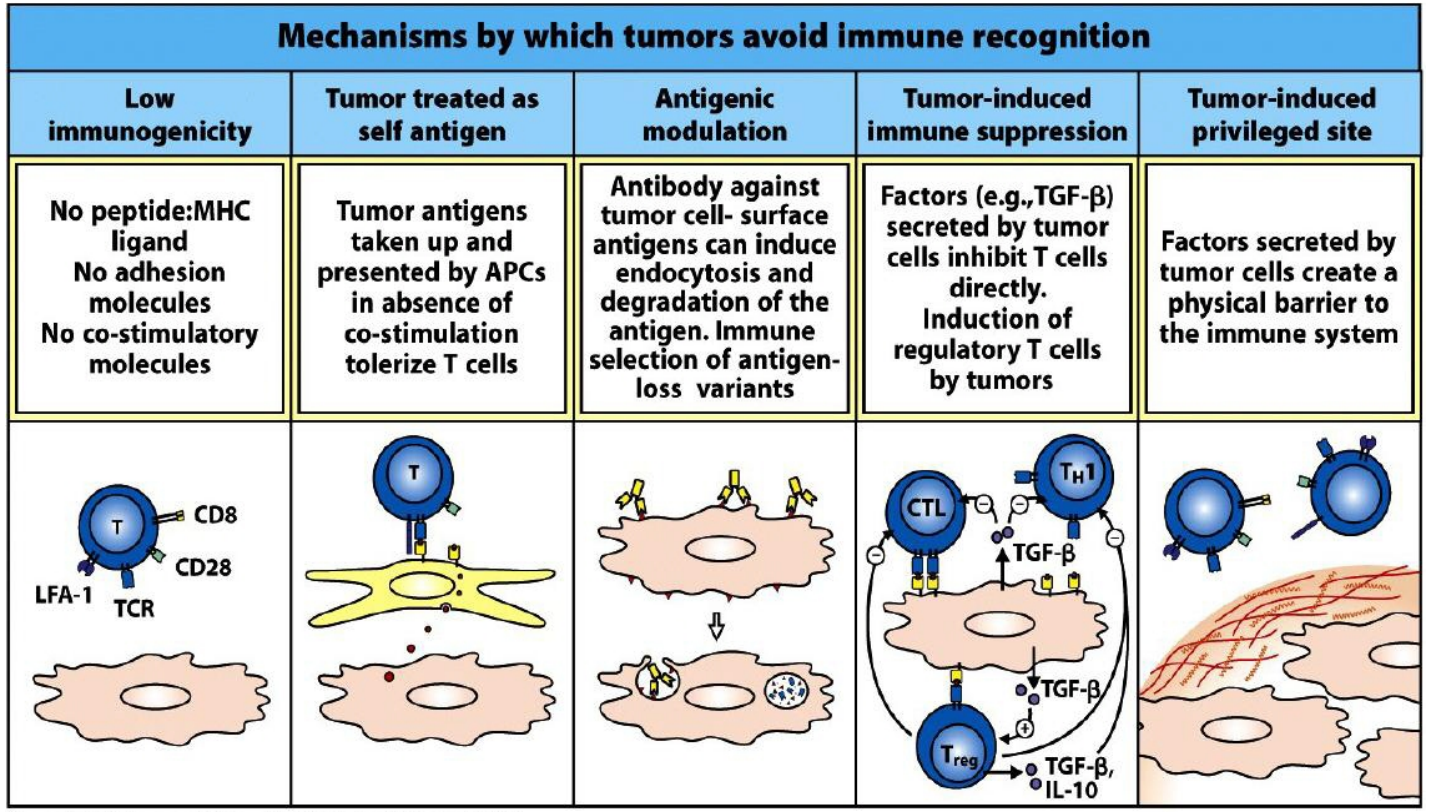
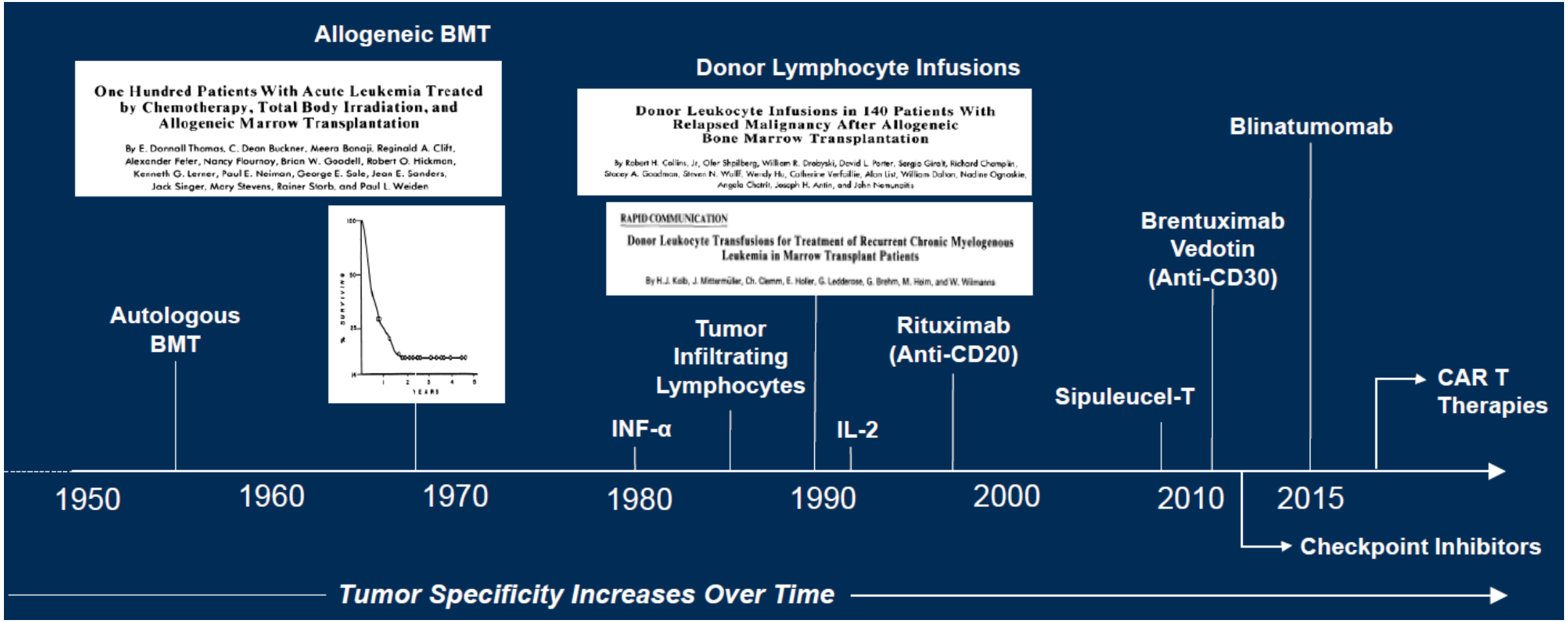


Figure 15-14 Immunobiology, 7ed. (© Garland Science 2008)

Weiner LM. N Engl J Med. 2008;358:2664-2665.

Advances in immune cell therapy



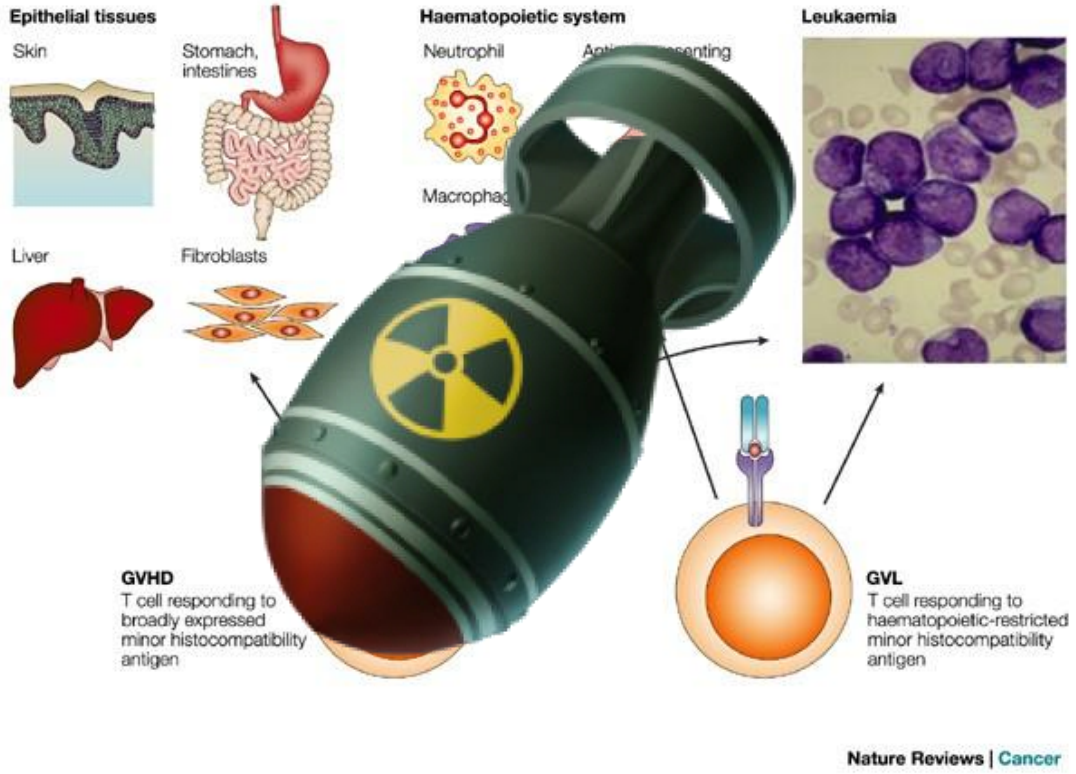
Haematopoietic stem cell transplant

1. High dose chemotherapy with stem cell rescue (Autologous Transplantation)
   - Benefit relies on chemo-sensitivity of cancer

2. Allogeneic HSCT
   - Combines chemotherapy and immunotherapy
   - Can cure patients with chemo-refractory disease
   - Graft-v-tumor (GVT) → Prevents Relapse
   - Graft-v-host disease (GVHD) → Toxicity

Allogeneic stem cell transplant

“Bystander”



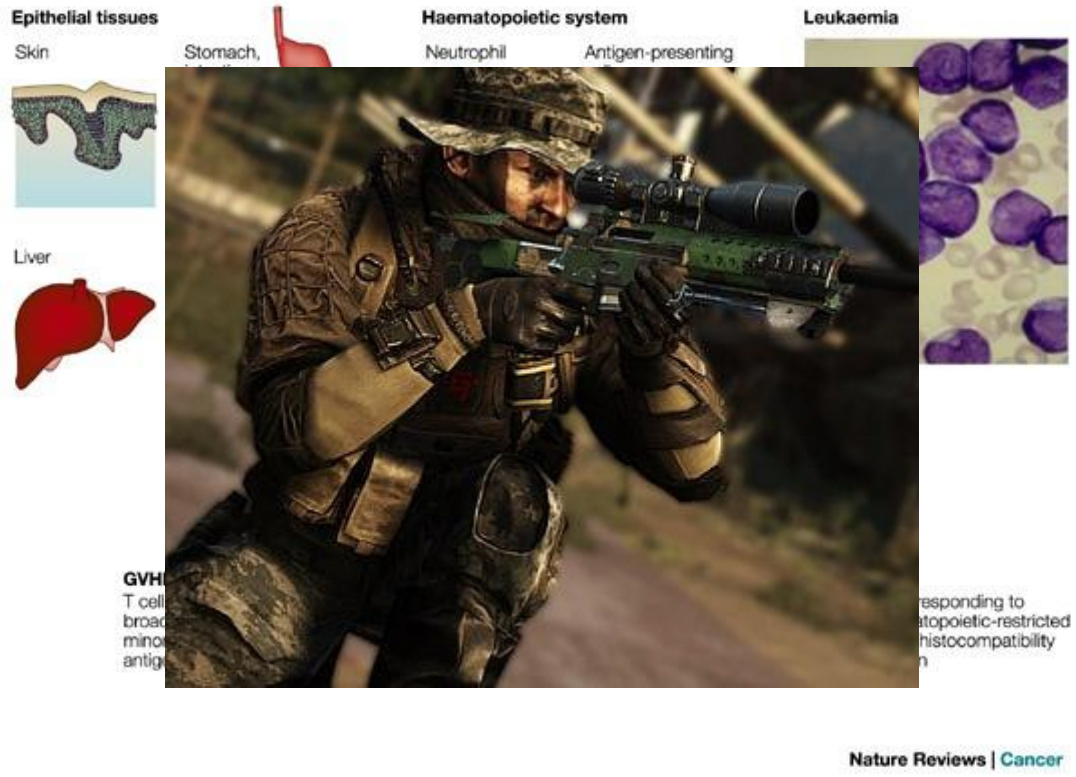
“Enemy”

Bleakley et al; Nat Rev Ca (2004)

Advances in immune cell therapy

Can we do this?

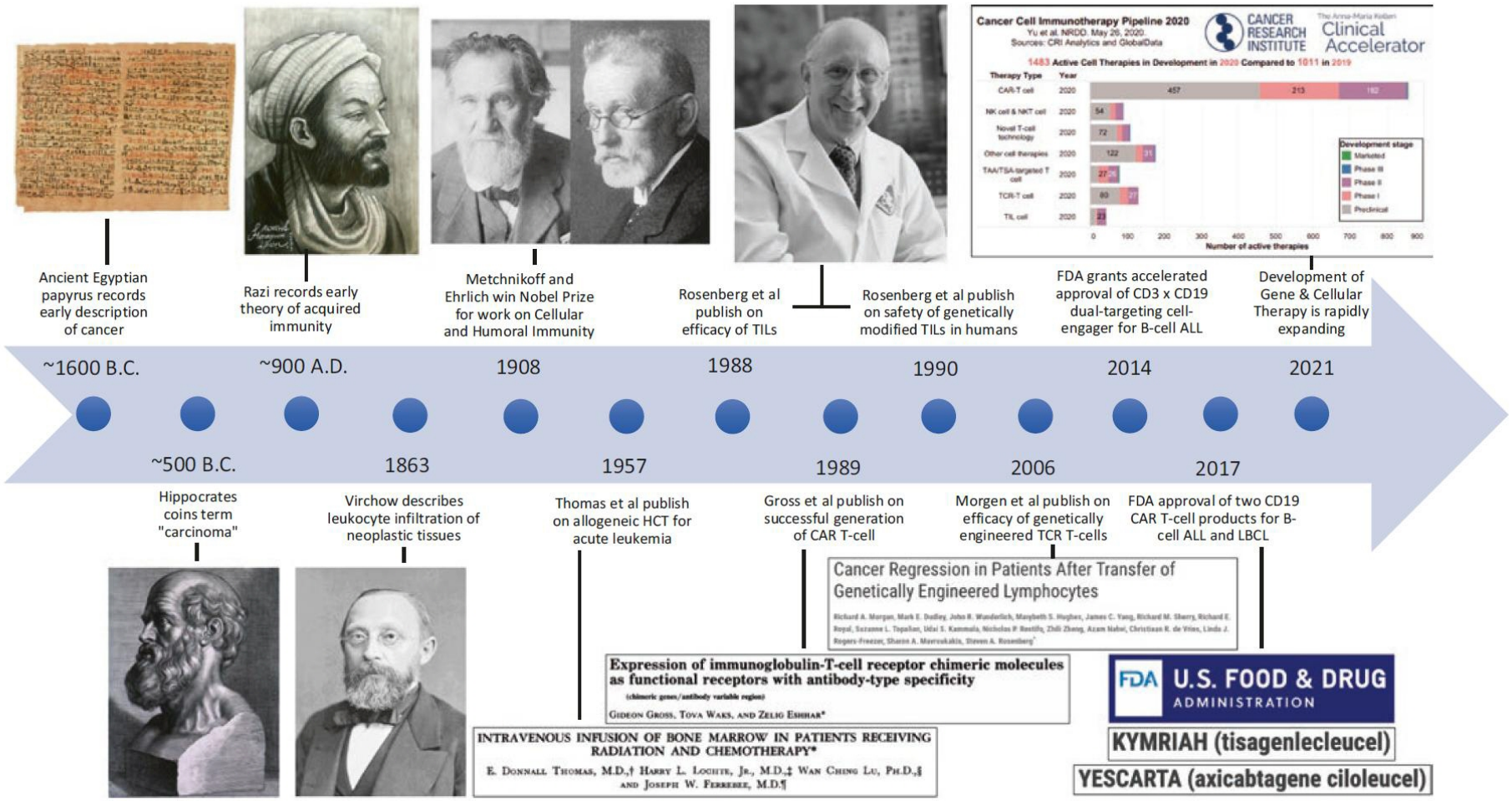
“Bystander”



“Enemy”

Bleakley et al; Nat Rev Ca (2004)

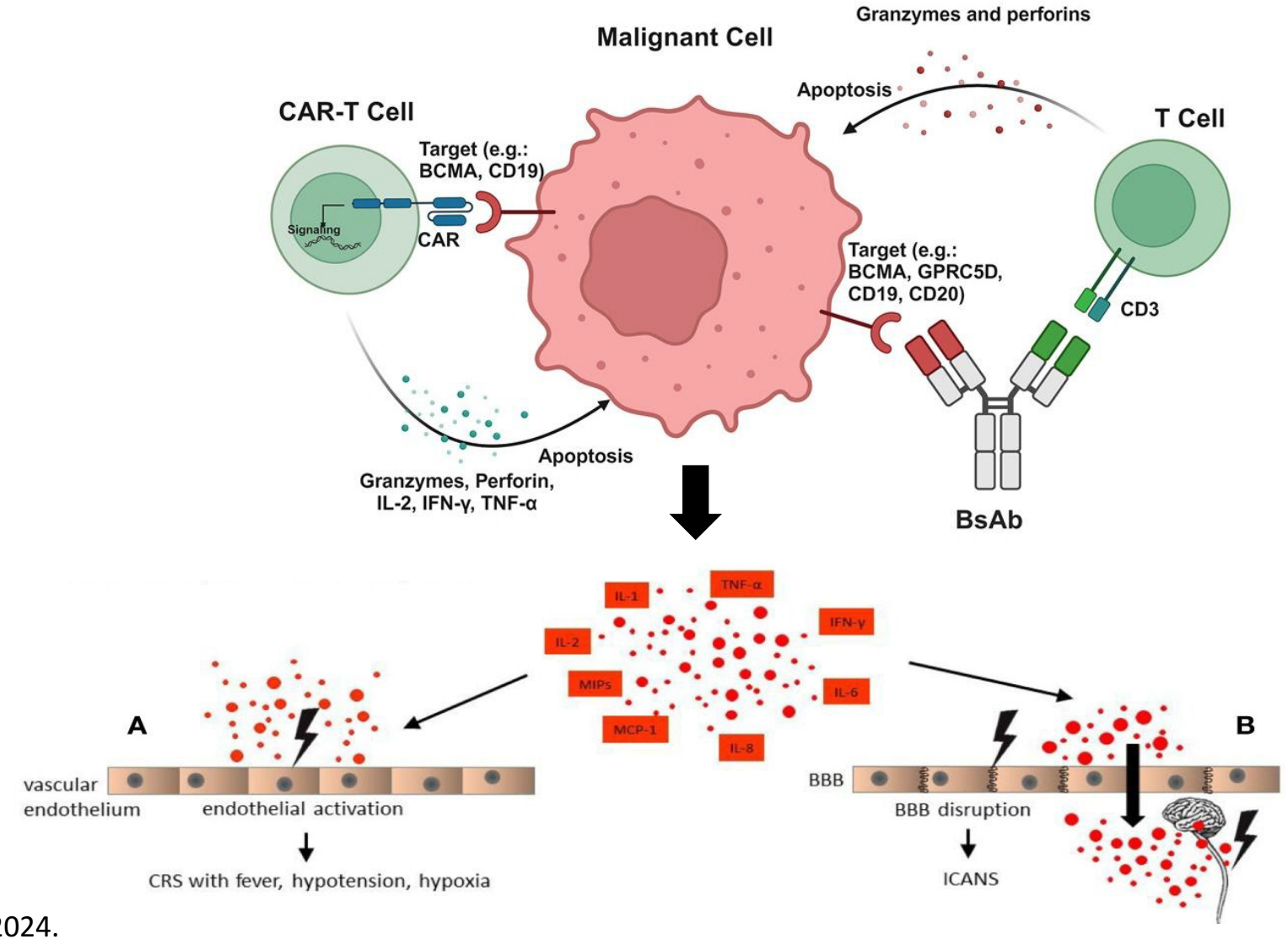
Landmark developments in CAR T-cell therapy



Razi's portrait courtesy of master artist Homayoun Alvand

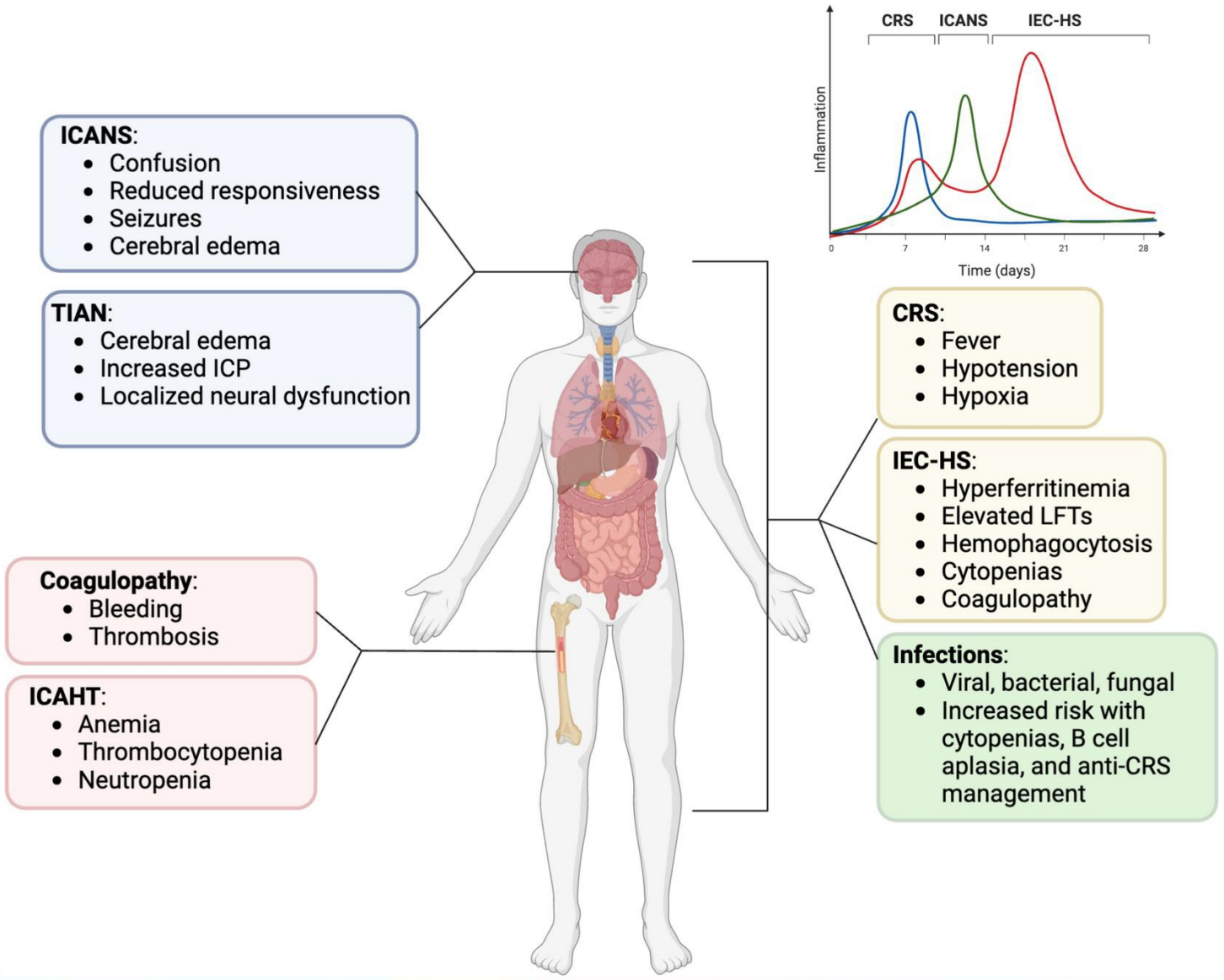
Fig. 2 Milestones in cellular therapy development

Toxicities of CAR T-cell Therapy and T-cell Engagers



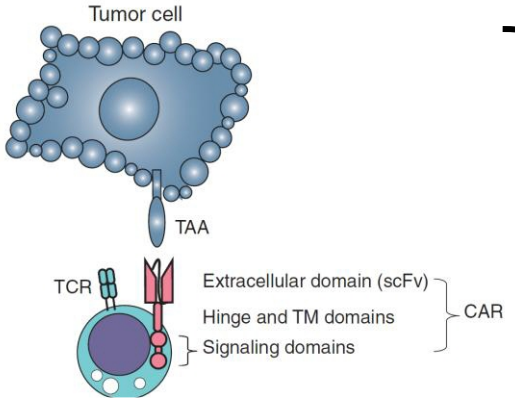
Hadidi et al, Mol Ther 2024.
Zhou et al, Front Immunol 2020.

Toxicities of CAR T-cell Therapy and T-cell Engagers

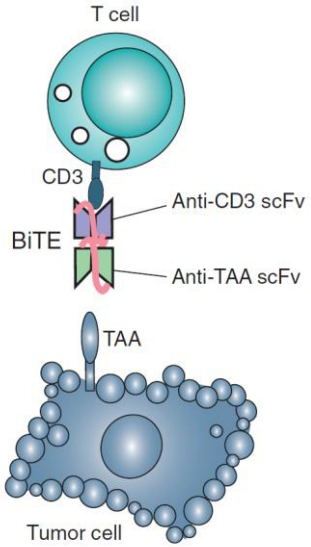


Toxicities related to Adoptive T-cell Therapy

CAR T-cell



Bispecific T-cell engager

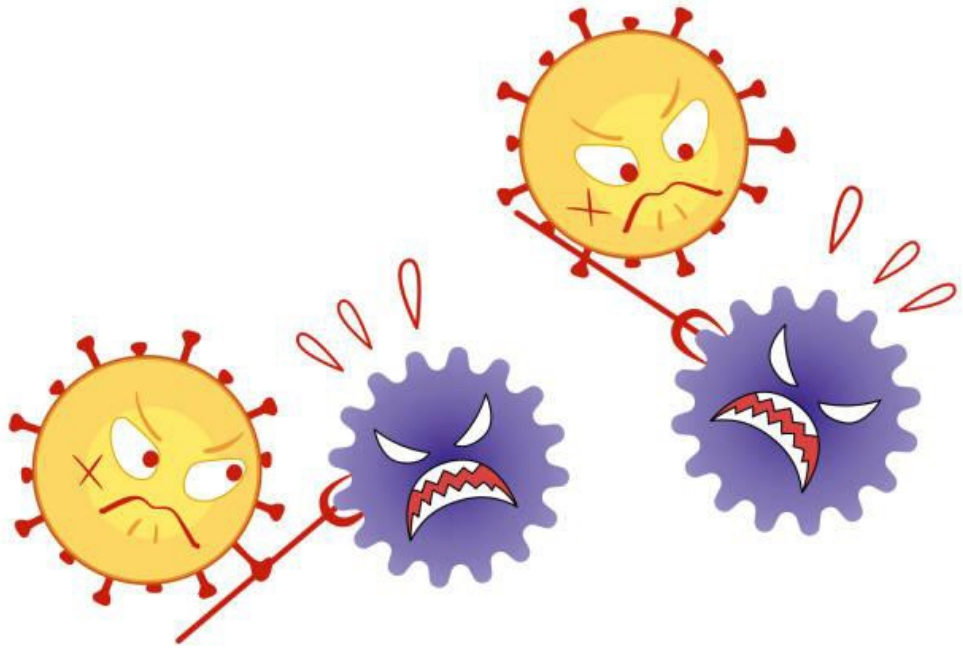


Acute Phase (D0-D30)	Late Phase (D30+)
▪ Cytokine-release syndrome ▪ Immune effector cell–associated neurotoxicity syndrome ▪ Cytopenias – MAS/HLH is a very rare and severe form – DIC ▪ B-cell aplasia and hypogammaglobulinemia ▪ Tumor lysis is rare and likely varies by disease and disease burden	▪ Persistent cytopenias ▪ B-cell aplasia and hypogammaglobulinemia ▪ T-cell deficiency ▪ Infections ▪ Residual effects of acute toxicity ▪ Delayed CRS and neurotoxicity is rare but can occur ▪ Long-term effects – Secondary malignancies – Impairment to QoL: fatigue, memory issues, not yet well described

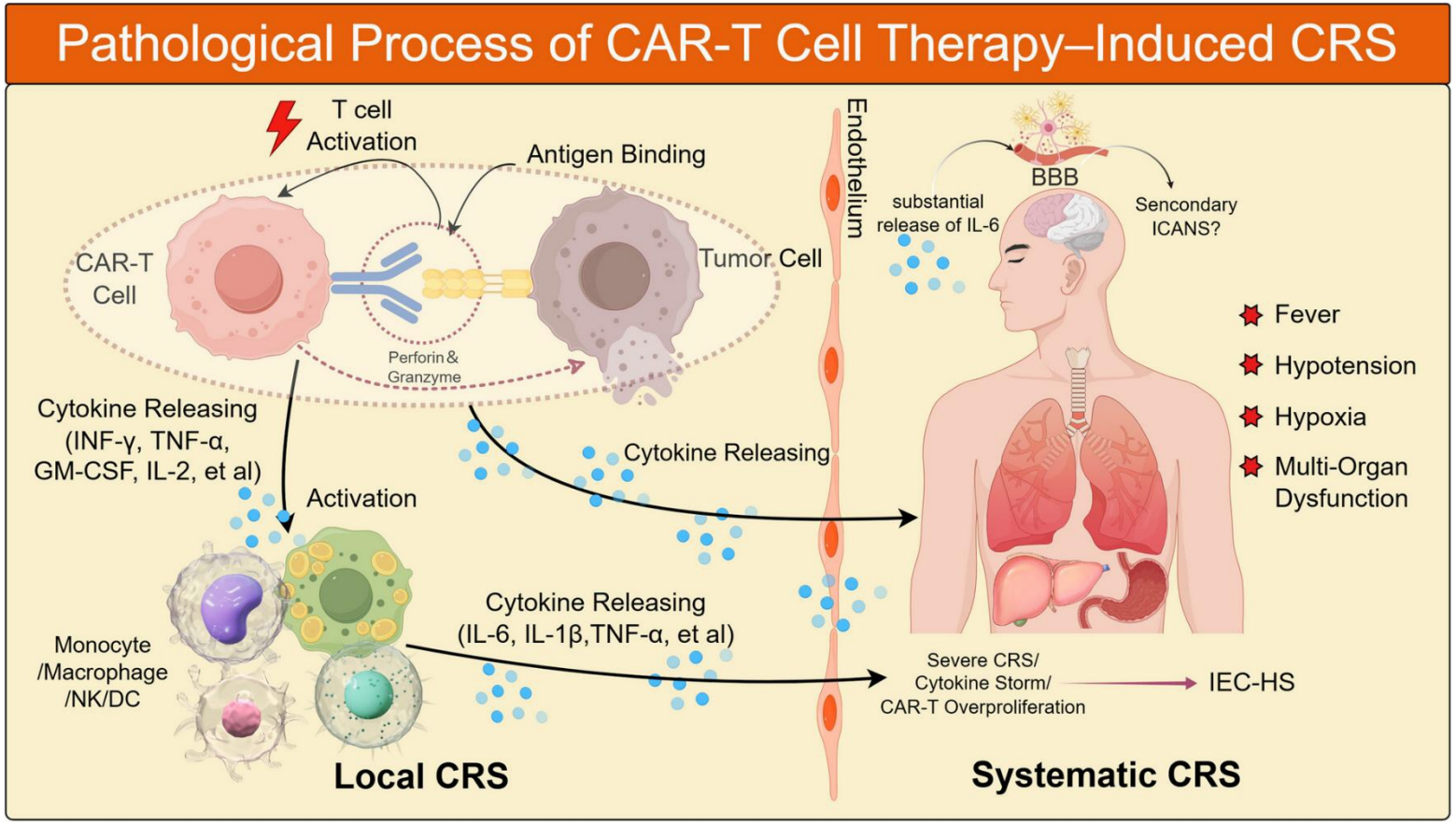
Although toxicity profile overlaps, there are differences in presentation / management

https://www.amunix.com/technology/

Standardized Grading Systems



CRS – Cytokine Release Syndrome



- An acute systemic inflammatory syndrome
- Clinical severity can range from a mild febrile flu-like illness to a severe potentially fatal syndrome of capillary leak, hypoxic respiratory failure, and vasodilatory shock with multiorgan toxicities.

Zhang et al, Clinical Cancer Bulletin 2025.

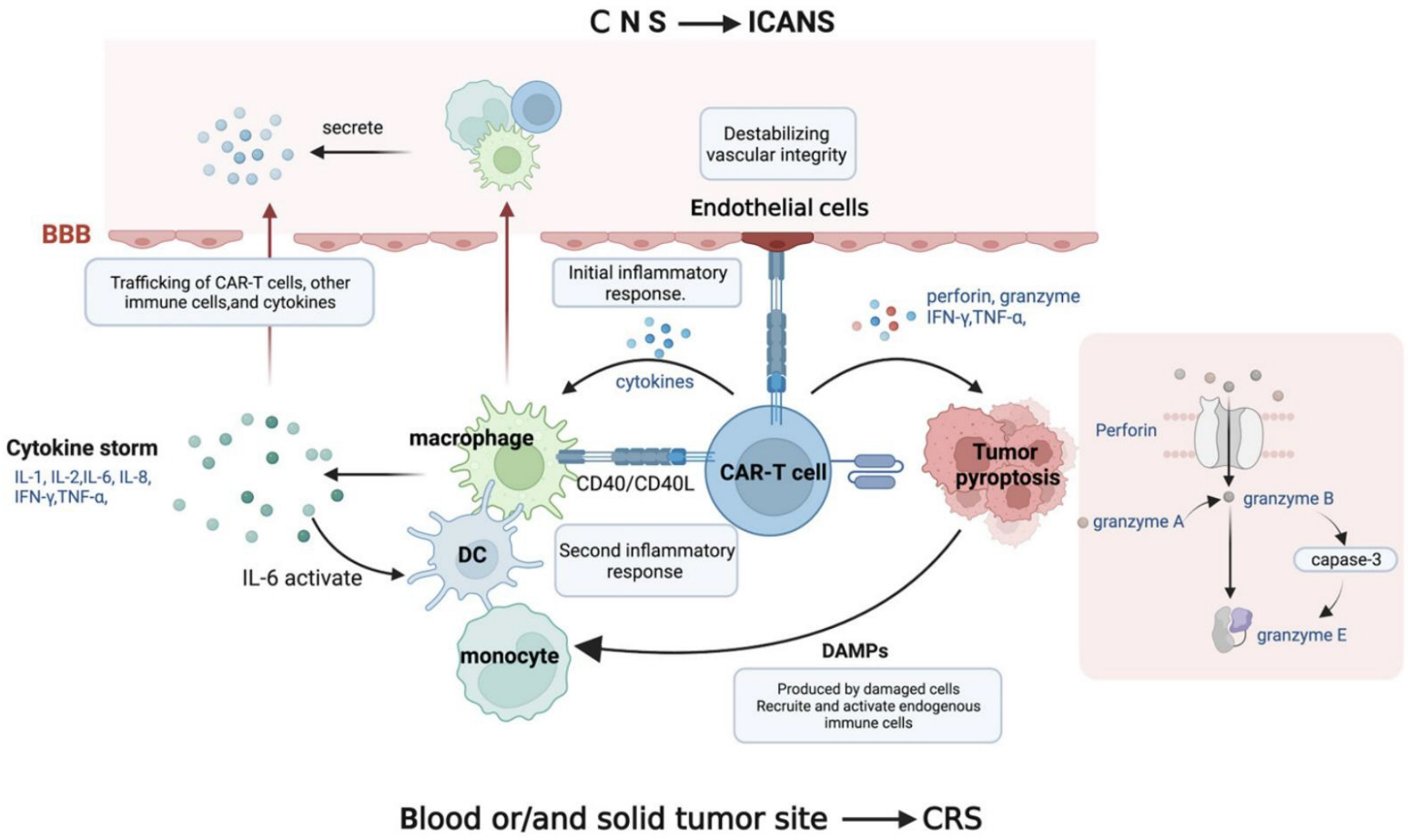
CRS Grading

ASTCT harmonized definitions and grading criteria for CRS

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	≥38.0°C	≥38.0°C	≥38.0°C	≥38.0°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or [b]				
Hypoxia	None	Requiring low-flow [c] nasal cannula or blow-by	Requiring high-flow [c] nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg. CPAP, BiPAP, intubation and mechanical ventilation)

Lee et al, BBMT 2019.

ICANS - IEC-associated neurotoxicity syndrome



- Early manifestations of ICANS include expressive aphasia, tremor, dysgraphia, and lethargy.
- Can progress to global aphasia, seizures, obtundation and coma.
- Reversible but severe ICANS can lead to fatal intracerebral hemorrhage and malignant cerebral edema.

Zhang et al, J Clin Med 2023.

ICANS Grading

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 [a]	Awakes 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 om EEG that resolve with intervention	Life-threatening prolonged seizure (> 5min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings [b]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or parapersis
Elevated IOP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging [c]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Lee et al, BBMT 2019.

ICANS Grading

Table 4. Immune Effector Cell Encephalopathy (ICE) Scoring

	Task	Points
Orientation	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects (e.g., pen, mouse, keyboard)	3
Follow commands	Ability to follow simple commands (e.g., point to the computer)	1
Language/writing	Ability to write a simple sentence	1
Attention	Ability to count backwards from 100 by 10	1

Note. Adapted from Rees et al. (2022).

Other Toxicities

Immune effector cell–associated hematotoxicity: EHA/EBMT

Grading	1	2	3	4
Early ICAHT (day 0-30)				
ANC ≤500/μL	<7 d	7-13 d	≥14 d	Never above 500/μL
ANC ≤100/μL	—	—	≥7 d	≥14 d
Late ICAHT (after day +30)*				
ANC	≤1500/μL	≤1000/μL	≤500/μL	≤100/μL

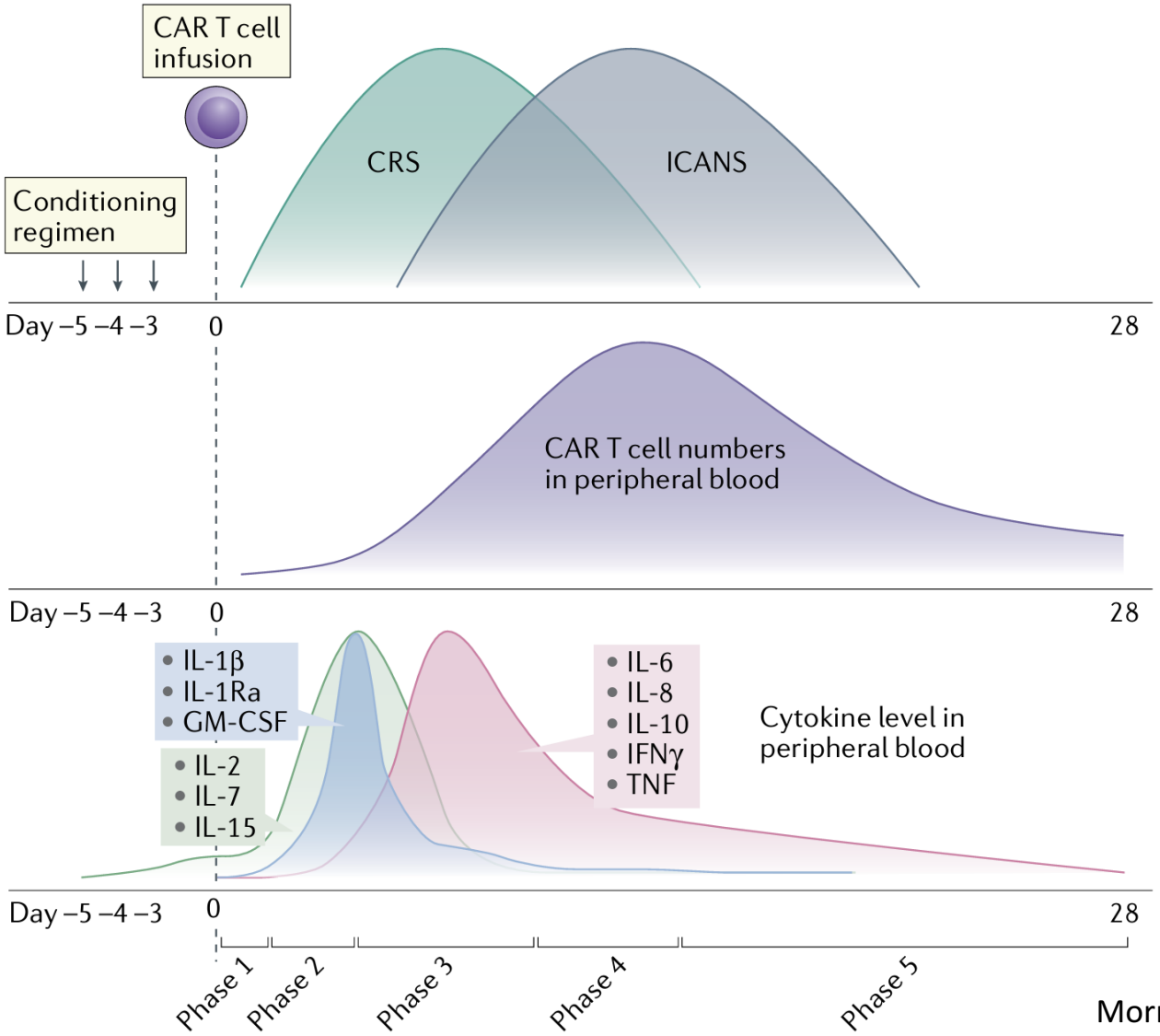
Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS)

Adverse Event	Grade				
	1	2	3	4	5
IEC-HS*	Asymptomatic or mild symptoms; requires observation and/or clinical and diagnostic evaluation. Intervention not indicated.	Mild to moderate symptoms, with intervention indicated (eg, immunosuppressive agents directed at IEC-HS, transfusions for asymptomatic hypofibrinogenemia)	Severe or medically significant but not immediately life- threatening (eg, coagulopathy with bleeding requiring transfusion support, or hospitalization required for new-onset acute kidney injury, hypotension, or respiratory distress)	Life-threatening consequences: urgent intervention indicated (eg, life-threatening bleeding or hypotension, respiratory distress requiring intubation, dialysis indicated for acute kidney injury)	Death

Rejeski et al, Blood 2023
Hines et al, Tx Cell Ther 2023

Anticipate clinical trajectory

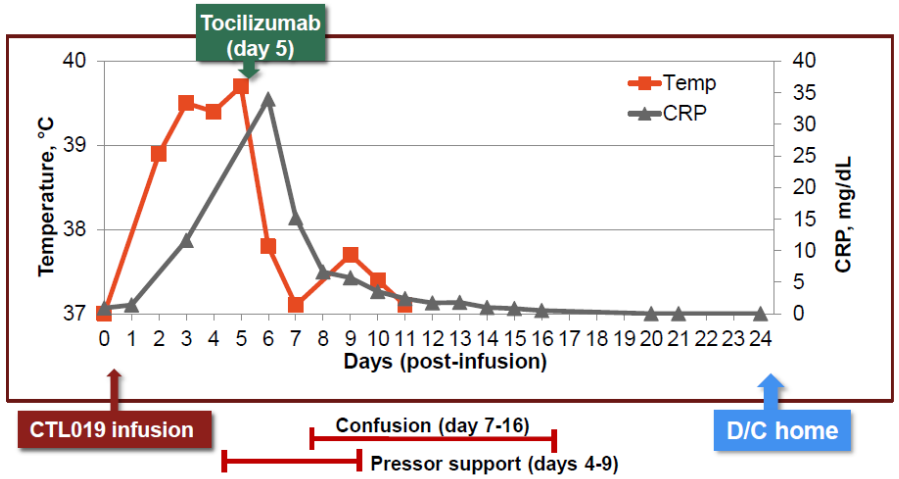
Typical Clinical Trajectory in CAR-T



Morris et al, Nat Rev 2022.

CRS / ICANS with Tisa-cel

Clinical trajectory for Tisa-cel

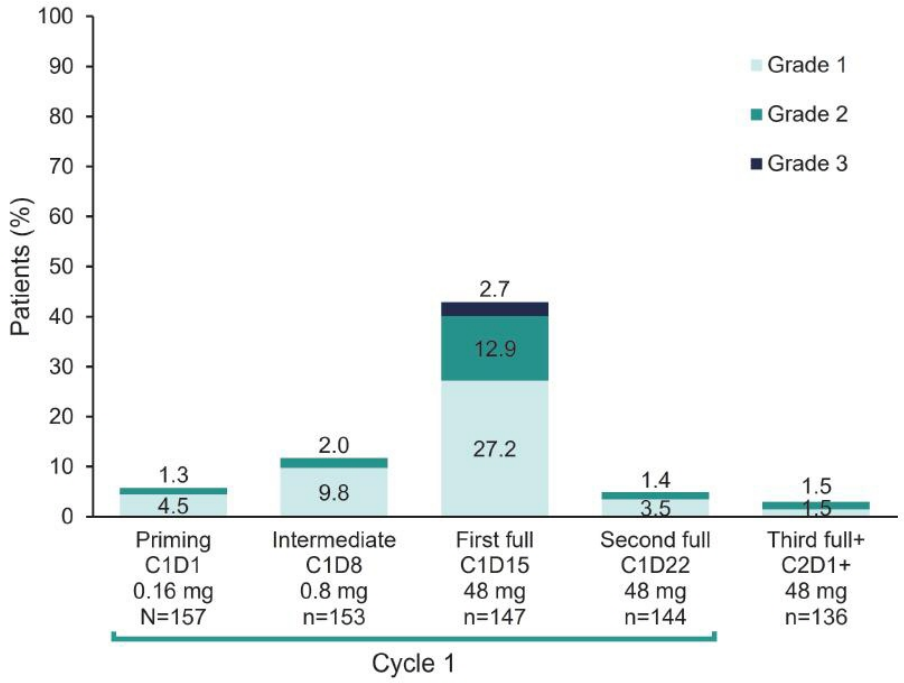


Typical clinical trajectory

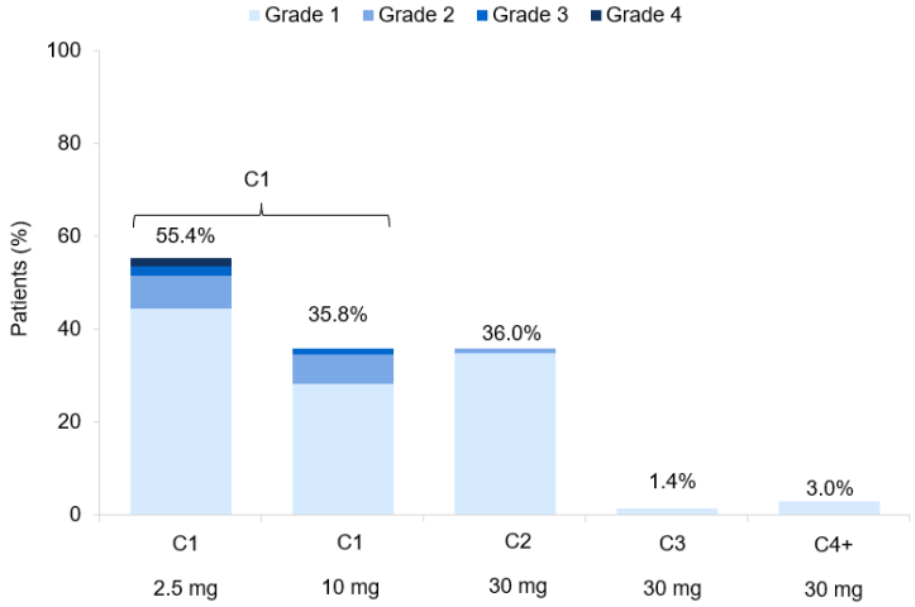
- Median time to onset of CRS: 3 days
- Median time to resolution of CRS: 10 days
- Median time to onset of NT: 5 days
- Median duration of NT: 17 days

CRS in TCE

CRS in Epcoritamab



CRS in a Glofitamab (pre-treatment with obinutuzumab)



ICANS: All grade – 8%; ≥G3- 3%

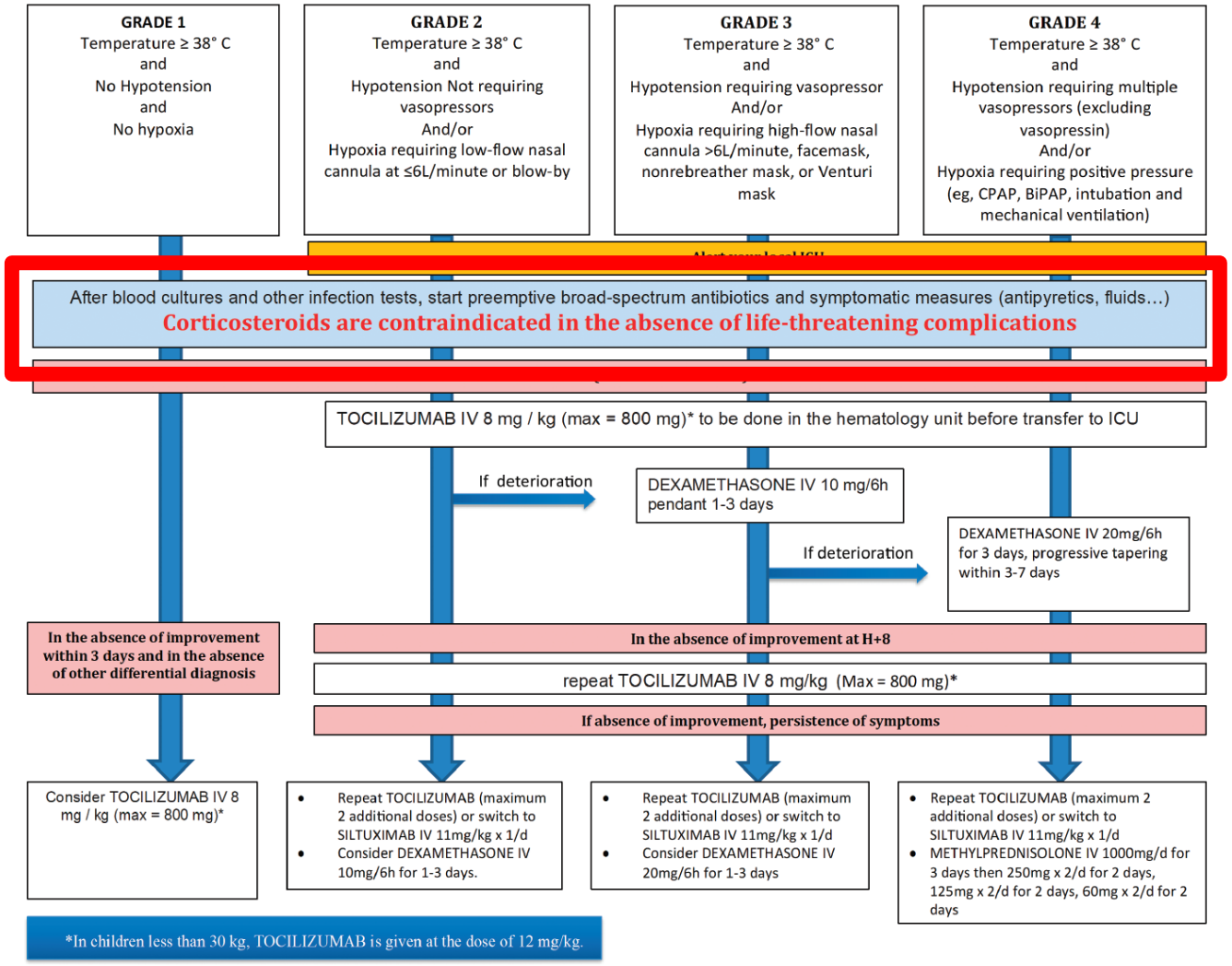
Thieblemont et al. JCO 2022.
Dickinson et al. NEJM 2022.

Drug	Mosunetuzumab[3]					Epcoritamab[4]					Glofitamab[5]					Odronextamab[6,7]				
Structure	Fully humanized IgG1 CD3×CD20 BsAb with 1:1 CD3:CD20 ratio of Fab arms					IgG-like anti-CD3×CD20 BsAb. Proprietary format, with point mutations in the Fab portion of the Fc of the antibody and heterodimerization.					Humanized mouse-derived BsAb with 1:2 CD3:CD20 ratio of Fab arms					Fully humanized IgG4 anti-CD3×CD20 BsAb developed using an Fc domain with a mutation in the protein A of the Fc portion				
Route of administration	IV					SC					IV					IV				
Dosing schedule	C1: days 1, 8, 15; C2+: day 1, every 21 d, for up to 8 cycles in CR or up to 17 cycles for PR or SD					C1-3: days 1, 8 ,15, and 22; C4-9: days 1 and 15; C10+: day 1, every 28 d until progression					C1: obin, day 1; glofit, days 8 and 15; C2-12: day 1, every 21 d					C1: days 1, 2, 8, 9, 15, 16 of a 21-d cycle; C2-4: days 1, 8, 15 of a 21-d cycle; C5+: day 1, every 14 d; If CR for at least 9 mo: day 1, every 28 d				
CRS mitigation																				
Step-up dosing	C1D1: 1 mg C1D8: 2 mg C1D15: 60 mg C2D1: 60 mg C3+D1: 30 mg					C1D1: 0.16 mg C1D8: 0.8 mg C1D15: 48 mg C1D22: 48 mg C2D1+: 48mg					C1D1: obin 1000 mg C1D8: 2.5 mg C1D15: 10 mg C2D1+: 30 mg					C1D1: 0.2 mg C1D2: 0.5 mg C1D8: 2 mg C1D9: 2 mg C1D15: 10 mg C1D16: 10 mg C2-C4: 80 mg (FL) or 160 mg (DLBCL) C5+: 160 mg (FL) or 320 mg (DLBCL)				
Premedications	(1) A/P 500-1000 mg, 30 min prior, for C1 and C2 (2) Diphenhydramine 50-100 mg, 30 min prior, for C1 and C2 (3) Dexamethasone 20 mg or methylprednisolone 80 mg, 1 h prior, for C1 and C2. Continue all premedications if CRS with prior dose.					(1) A/P 650-1000 mg, 30-120 min before C1 treatments (2) Diphenhydramine 50 mg, 30-120 min before C1 treatments (3) Dexamethasone 15 mg, 30-120 min before C1 treatments and for 3 consecutive days after. Continue dexamethasone thereafter if G2 or G3 CRS with prior dose.					(1) A/P 500-1000 mg, 30 min before all treatments (2) Diphenhydramine 50 mg, 30 min before all infusions (3) Dexamethasone 20 mg, 1 h before treatment on C1D8, C1D15, C2D1, and C3D1. Continue if CRS with prior dose.					(1) A/P 650 mg, 30-60 min prior, during step-up dosing, continue if IRR or CRS with prior dose (2) Diphenhydramine 25 mg, 30-60 min prior during step-up dosing, continue if IRR or CRS with prior dose (3) Dexamethasone 10 mg orally, 12-24 h before split dose, 20 mg IV on day of dosing, 10 mg orally on the day after step-up dosing. Following first full dose, dexamethasone 10 mg before dosing; continue if CRS with prior dose.				
Hospitalization	Optional					C1D15: 24-h admission					C1D8: 24-h admission					Performed during step-up dosing				
CRS occurrence	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
	26%	17%	1%	1%	0%	34%	15%	3%	0%	0%	47%	12%	3%	1%	0%	35%-39%	13% (DLBCL)	0%	0%	0%
	Time course for CRS onset C1D1: 23.3% C1D8: 5.6% C1D15: 36.4% C2D1: 10.3% C3+D1: 2.4%			Median time (h) to CRS onset C1D1: 5 C1D8: 20 C1D15: 27 C2D1: 38		Time course for CRS onset C1D1: 5.8% C1D8: 11.8% C1D15: 42.8% C1D22: 4.9% C3+ 3%			Median time (h) to CRS onset All doses: 24 C1D15: 20		Time course for CRS onset C1D8: 42.8% C1D15: 25.2% C2: 26% C3+: 0.9%			Median time (h) to CRS onset C1D8: 13.5 (range: 6-52)		Time course for CRS onset C1D1/2: 22%-24% C1D8/9: 27%-32% C1D15/16: 21%-35% C2D1: 14%-17% C2D8+: 9%-14%			Median time (h) to CRS onset All doses: 18-20	
Median duration of CRS	3 d (1-29 d)					2 d (range: 1-27 d)					30.5 h (range, 0.5-317 h)					8-10 h (range, 0.1-190 h)				
Neurotoxicity	G 1-2		G3	G4	G5	G1	G2	G3	G4	G5	G 1-2		G 3-4		G5	G 1-2		G 3-4		G5
	3%		0%	0%	0%	4.5%	1.3%	0%	0%	0.6%	5%		3%		0%	4% (DLBCL)		0%		0%

Crombie et al. Blood 2024.

Management of immune toxicities (CAR-T vs TCE)

CAR-T CRS Management



Yakoub-Agha et al, Haematologica 2019

TCE CRS Management

CRS Grade	Actions	Supportive Care	Anti-cytokine Therapy	Corticosteroids
Grade 1	Withhold drug Ensure CRS symptoms are resolved prior to next dose of drug	Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Supportive care per institutional standard of care (antipyretics and IV hydration). Closely monitor neurologic status. In patients with persistent (3 days) or refractory fever, consider managing as per Grade 2.	Consider first dose tocilizumab in certain cases e.g. advanced age, high tumour burden, circulating tumour cells, fever refractory to antipyretics Note: In case of concurrent ICANS choose alternative to tocilizumab if possible (eg, siltuximab, anakinra)	Dexamethasone 10-20mg per day (or equivalent) may be initiated. Note: In case of concurrent ICANS, initiation of corticosteroids are highly recommended
Grade 2	Withhold drug Ensure CRS symptoms are resolved prior to next dose of drug Administer premedication prior to next dose For the next dose, monitor more frequently and consider hospitalization.	Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Antipyretics, oxygen, intravenous fluids as needed. Symptomatic management of constitutional symptoms and organ toxicities as per standard/ local guidelines. If refractory, manage as per Grade 3.	Anticytokine therapy recommended. If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. Note: In case of concurrent ICANS choose alternative to tocilizumab if possible (eg, siltuximab, anakinra)	Consider dexamethasone 10-20mg per day (or equivalent). Note: In case of concurrent ICANS, initiation of corticosteroids are highly recommended

TCE CRS Management

CRS Grade	Actions	Supportive Care	Anti-cytokine Therapy	Corticosteroids
Grade 3	Hold drug Ensure CRS symptoms are resolved prior to the next dose Administer premedication prior to next dose Hospitalize for the next dose If recurrent G3 CRS - ppermanently discontinue drug	High-flow oxygen Intravenous fluids and vasopressor with or without vasopressin Symptomatic management of constitutional symptoms and organ toxicities as per standard/ local guidelines Admit patients to high dependency/ICU If ECHO was not already performed, obtain ECHO to assess cardiac function and conduct haemodynamic monitoring If refractory, manage as per Grade 4	Tocilizumab as per Grade 2 If not improvement after tocilizumab and steroids, consider other anti-cytokine therapies • Anakinra 200mg every 8 hours • Siltuximab 11mg/kg if symptoms persist with concurrent neurotoxicity	Dexamethasone 10-20 mg IV every 6 hours If no response, initiate methylprednisolone 1000mg/day Once CRS improves to Grade 1, taper and/or stop corticosteroids depending on clinical situation
Grade 4	Permanently discontinue drug	Mechanical ventilation and/or renal replacement therapy may be required. Manage in ICU. IV fluids and vasopressors as indicated. Treat other organ toxicities as per local guidelines Consider and assess for development of MAS/HLH, including monitoring of fibrinogen and triglyceride levels	Tocilizumab as per Grade 2 Consider other anticytokine (as above) and anti- T-cell therapies • Cyclophosphamide 1,500mg/m2 IV for one dose • Anti-thymocyte globulin 1-2mg/kg IV daily for 3 days	Dexamethasone 10-20 mg IV every 6 hours If no response, initiate methylprednisolone 1000mg/day followed by rapid taper as per clinical situation

TCE ICANS Management

ICANS Grade	Actions	Supportive Care	Anti-cytokine Therapy	Corticosteroids
Grade 1	Withhold drug until resolution of ICANS.	Vigilant supportive care; aspiration precautions; IV hydration. MRI brain; diagnostic LP with opening pressure; MRI spine if the patient has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible. Early EEG ideally within 24 hours of occurrence of Grade 1 ICANS. Repeat EEG if condition deteriorates and previous EEG did not detect seizures. Consider levetiracetam 750 mg every 12 hours (oral or IV) for a month. If EEG shows non-convulsive status epilepticus, follow algorithm for status epilepticus Consider neurology consult. Worsening: treat as Grade 2	No concurrent CRS: Anticytokine therapy not indicated Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible.	Dexamethasone, 10 mg IV every 12 hours
Grade 2	Withhold drug until resolution of ICANS.	Monitor closely. Supportive care and neurological work-up as indicated for Grade 1. Continuous cardiac telemetry and pulse oximetry as indicated Closely monitor neurologic status with serial neurologic exams to include fundoscopy. Neurology consult.	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated. Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. • Consider anakinra SC 100mg OD or BD • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone at 10-20 mg IV every 12 hours

(Repriming / pre-meds for dose delays vary across products – to check accordingly)

TCE ICANS Management

CRS Grade	Actions	Supportive Care	Anti-cytokine Therapy	Corticosteroids
Grade 3	Permanently discontinue drug. Management in monitored care or intensive care unit.	Supportive care and neurological work-up as indicated for lower grades.	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated. Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. • Consider anakinra SC 100mg OD or BD • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day.
Grade 4	Permanently discontinue drug. Management in monitored care or intensive care unit.	Supportive care and neurological work-up as indicated for lower grades. Consider mechanical ventilation for airway protection.	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated. Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. • Consider anakinra SC 100mg OD or BD • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day.

(Repriming / pre-meds for dose delays vary across products – to check accordingly)

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Special Report

Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy

Jennifer L. Crombie,[1,*] Tara Graff,[2,*] Lorenzo Falchi,[3,*] Yasmin H. Karimi,[4,*] Rajat Bannerji,[5] Loretta Nastoupil,[6] Catherine Thieblemont,[7] Renata Ursu,[8] Nancy Bartlett,[9] Victoria Nachar,[4] Jonathan Weiss,[4] Jane Osterson,[2] Krish Patel,[10] Joshua Brody,[11] Jeremy S. Abramson,[12] Matthew Lunning,[13] Nirav N. Shah,[14] Ayed Ayed,[15] Manali Kamdar,[16] Benjamin Parsons,[17] Paolo Caimi,[18] Ian Flinn,[19] Alex Herrera,[20] Jeffrey Sharman,[21] Marshall McKenna,[5] Philippe Armand,[1] Brad Kahl,[9] Sonali Smith,[5,22] Andrew Zelenetz,[3] Lihua Elizabeth Budde,[20,†] Martin Hutchings,[23,†] Tycel Phillips,[4,†] and Michael Dickinson[24,†]

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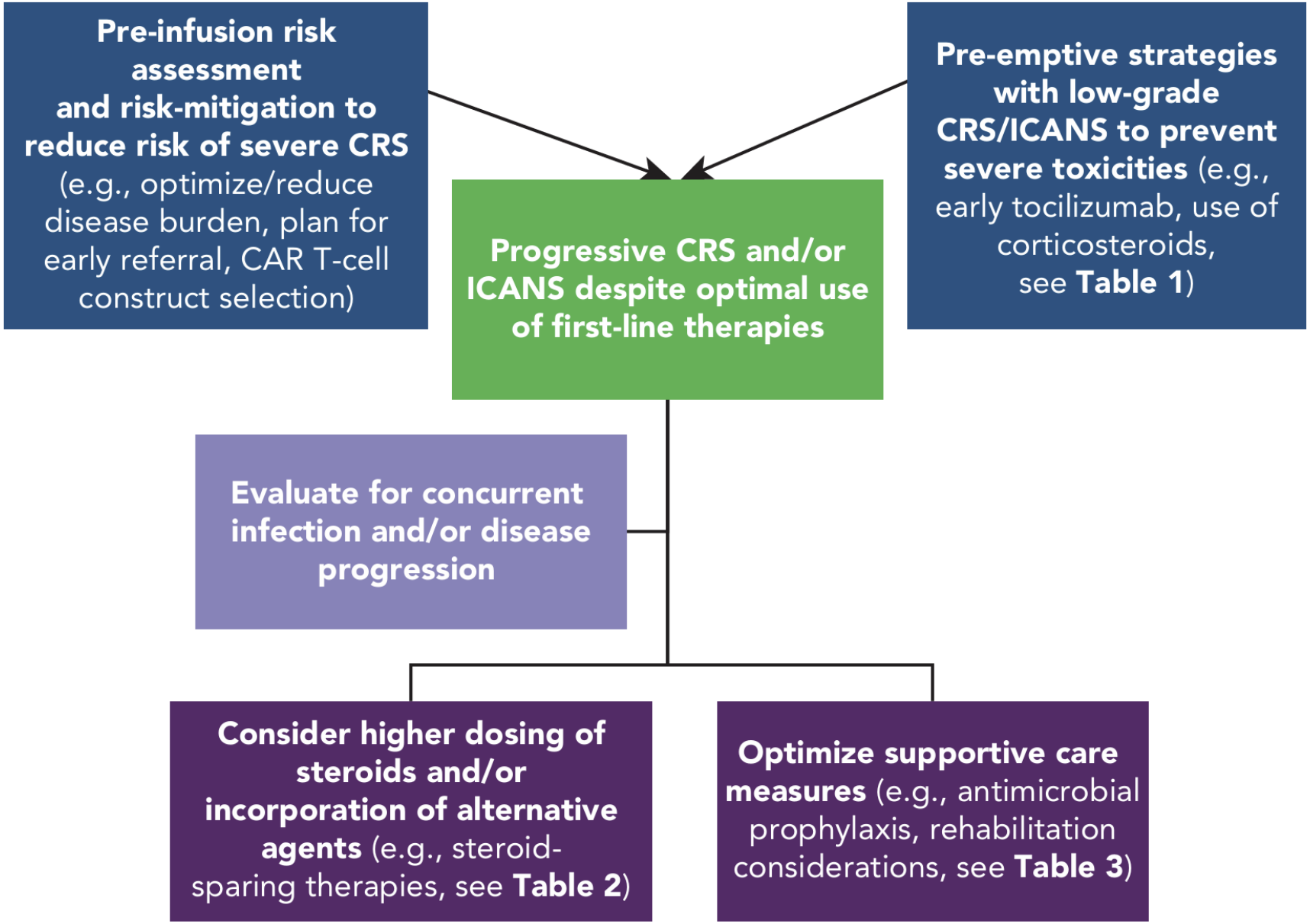
How I Treat Series

EMERGENT CAR T-CELL TOXICITIES

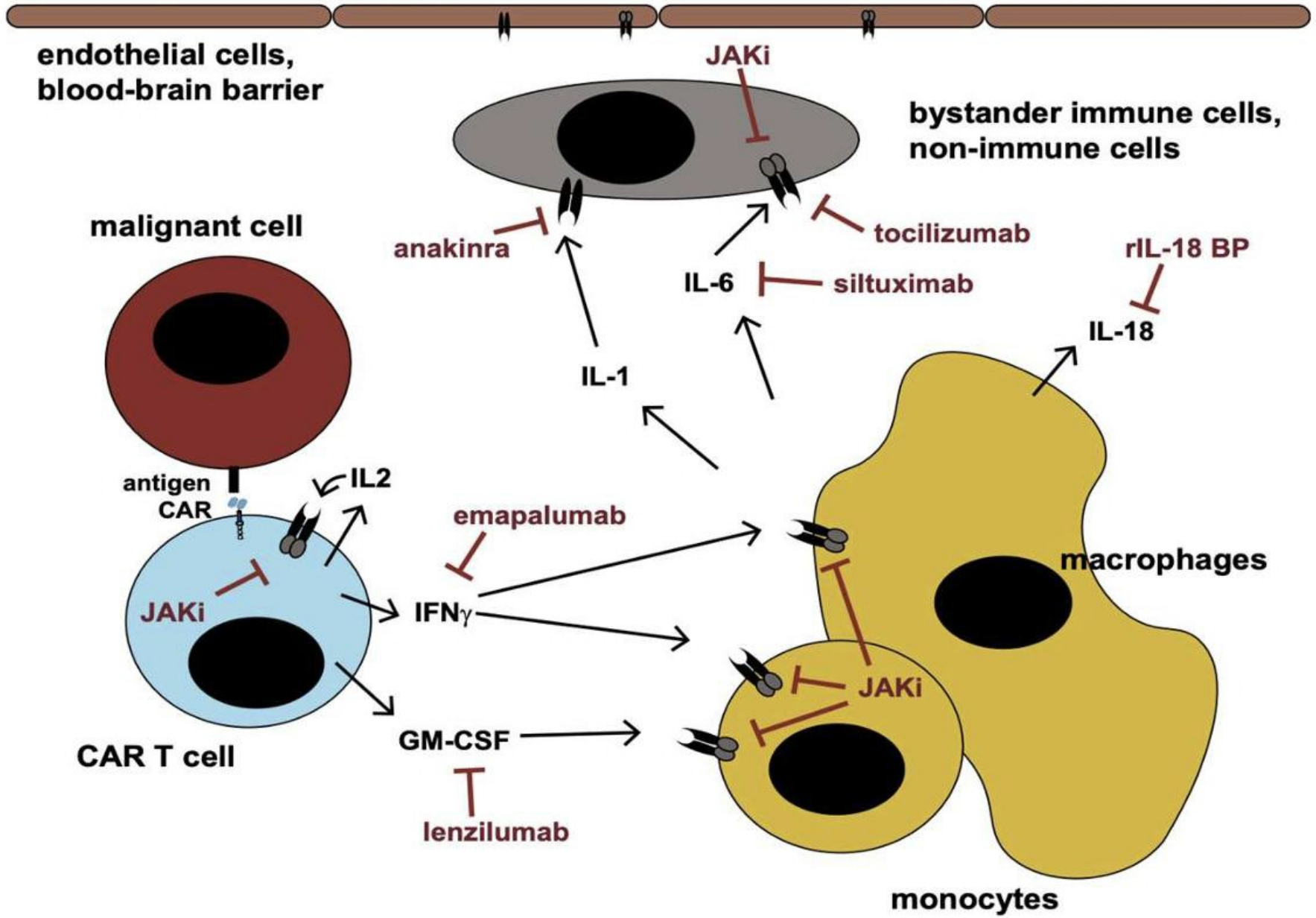
How I treat refractory CRS and ICANS after CAR T-cell therapy

Michael D. Jain,[1,*] Melody Smith,[2,*] and Nirali N. Shah[3]

[1]Department of Blood and Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL; [2]Division of Blood and Marrow Transplantation and Cellular Therapy, Department of Medicine, Stanford University School of Medicine, Stanford, CA; and [3]Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD



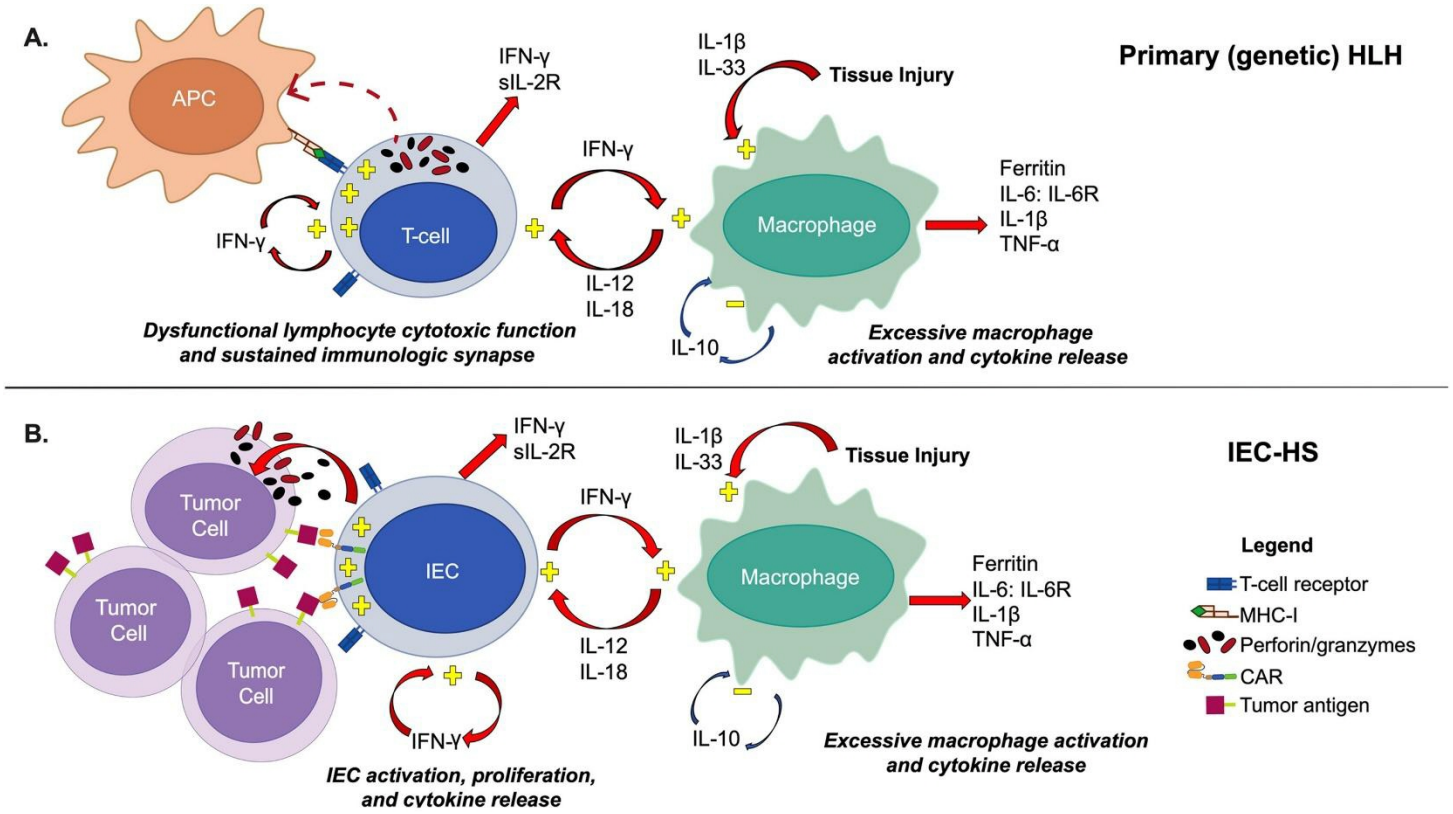
Jain et al, Blood 2023



Walton ZE et al. Expert OpinPharmacother. 2024 Feb;25(3):263-279.

IEC-HS (IEC-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome)

- HLH is a documented AE following treatment with CAR-T products
- In 2023, a novel definition was introduced to better capture the distinct features of HLH post CAR-T treatment (Hines et al, 2023)

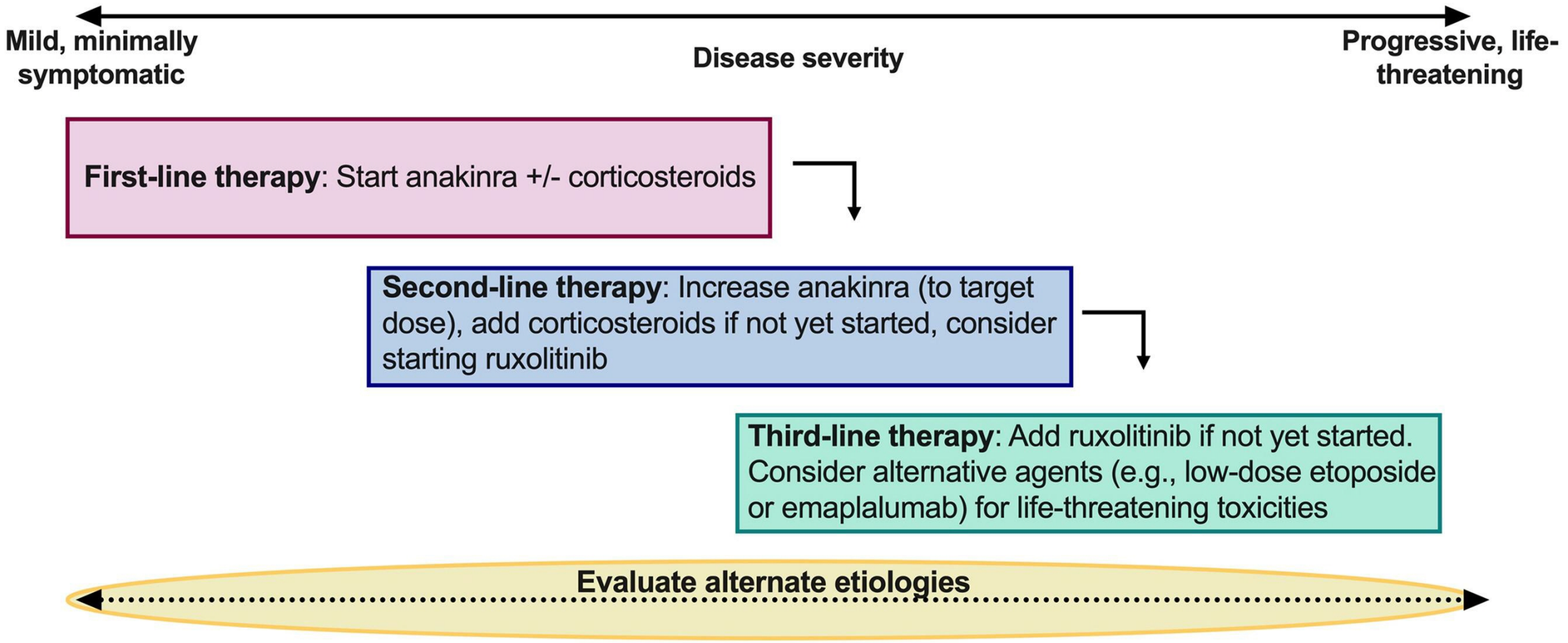


IEC-HS is a pathological and biochemical hyperinflammatory syndrome distinct from CRS and ICANS that:

i. Manifests with features of MAS/HLH
ii. Attributable to IEC therapy
iii. A/w progression of new onset of cytopenia, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis

Hines et al, Tx and Cell Rx 2023

IEC-HS (IEC-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome)



Hines et al, Tx and Cell Rx 2023

Conclusion

- Exciting era with novel immune- / cell- therapies but there is still much to be learnt.
- Every product is different. Immune responses may vary across patients.
- Clear SOPs in place for managing immune toxicities but it is imperative to maintain vigilance for unexpected immune related toxicities
- Important to build up and manage patient in a multi-disciplinary team