Miracles of modern hematooncology

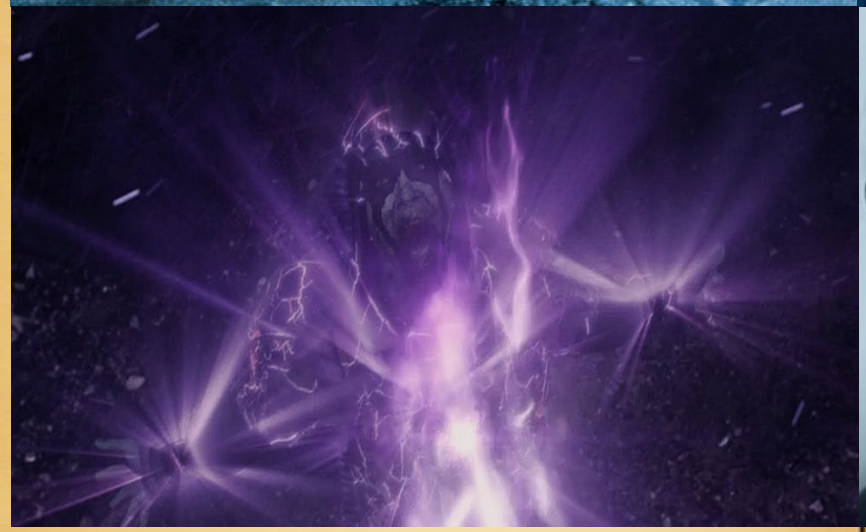
Jakub Radocha

IV. INTERNÍ HEMATOLOGICKÁ KLINIKA
FAKULTNÍ NEMOCNICE HRADEC KRÁLOVÉ

CMG Czech Myeloma Group

25th Colours of Sepsis, Ostrava, 23.-27. 1. 2023

Spellbook of



Spellbook of Hematology

Blenrep

Besponsa

Adcetris

Lunsumio

Tecvayli

Blincyto

Abecma

Carvykti

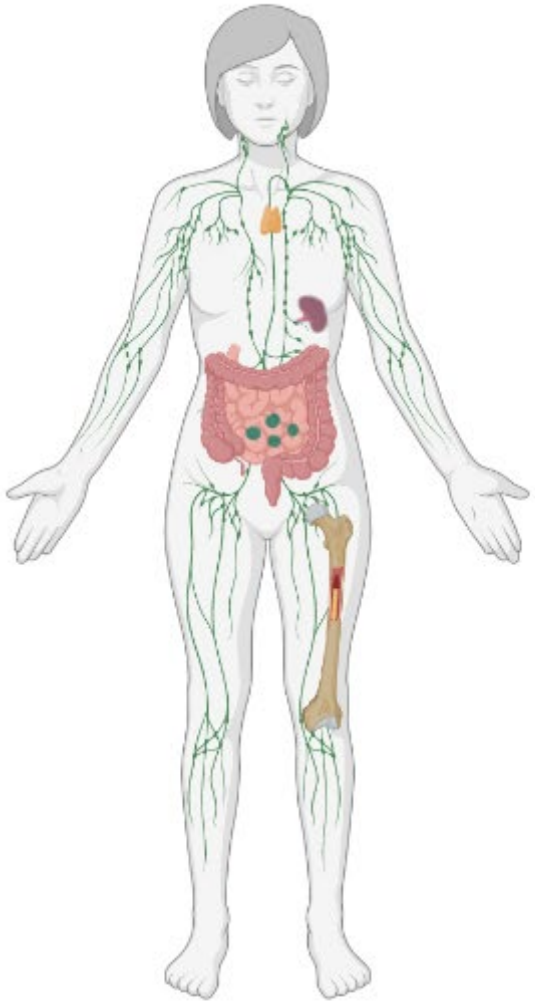
Yescarta

Tecartus

Zynteglo

Hemgenix

Immune system as a drug source



Immune organs

Lymph node

Thymus

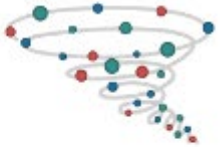
Thymus (cross-section)

Bone marrow

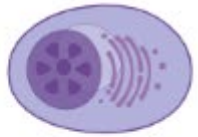
Spleen

Antibody

Bi-specific antibody

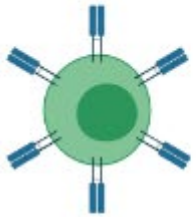


Cytokine storm



Plasma cell

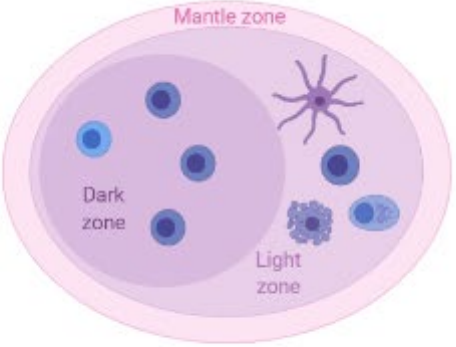
Cell



T cell (with TCR)

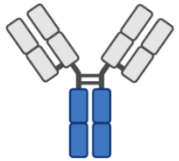
B cell (with antibodies)

Dendritic cell

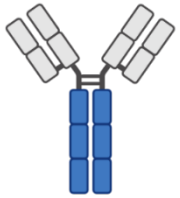


Germinal center

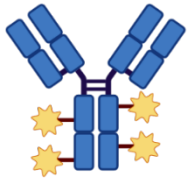
Antibody constructs



4 Fc domains



6 Fc domains



Antibody-drug conjugate

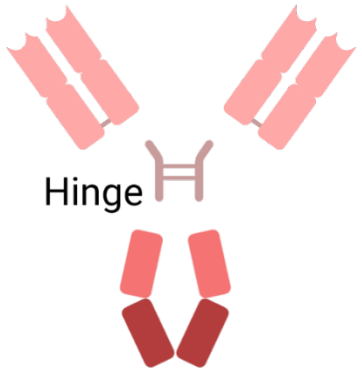
Chimeric

Humanized

Bispecific

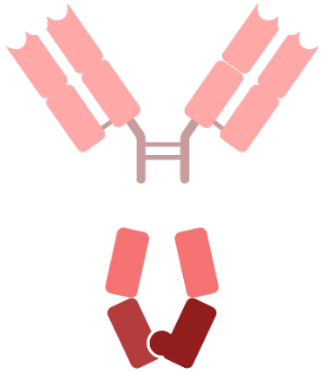
Antibody-drug conjugate

Fab

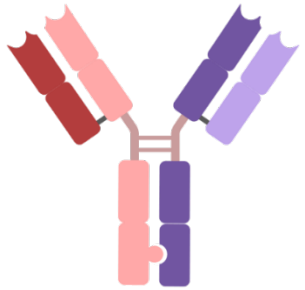


Fc homodimer

Fab('ab')$_2$



Fc heterodimer



Bispecific (custom domains)

BiTE

BiKE

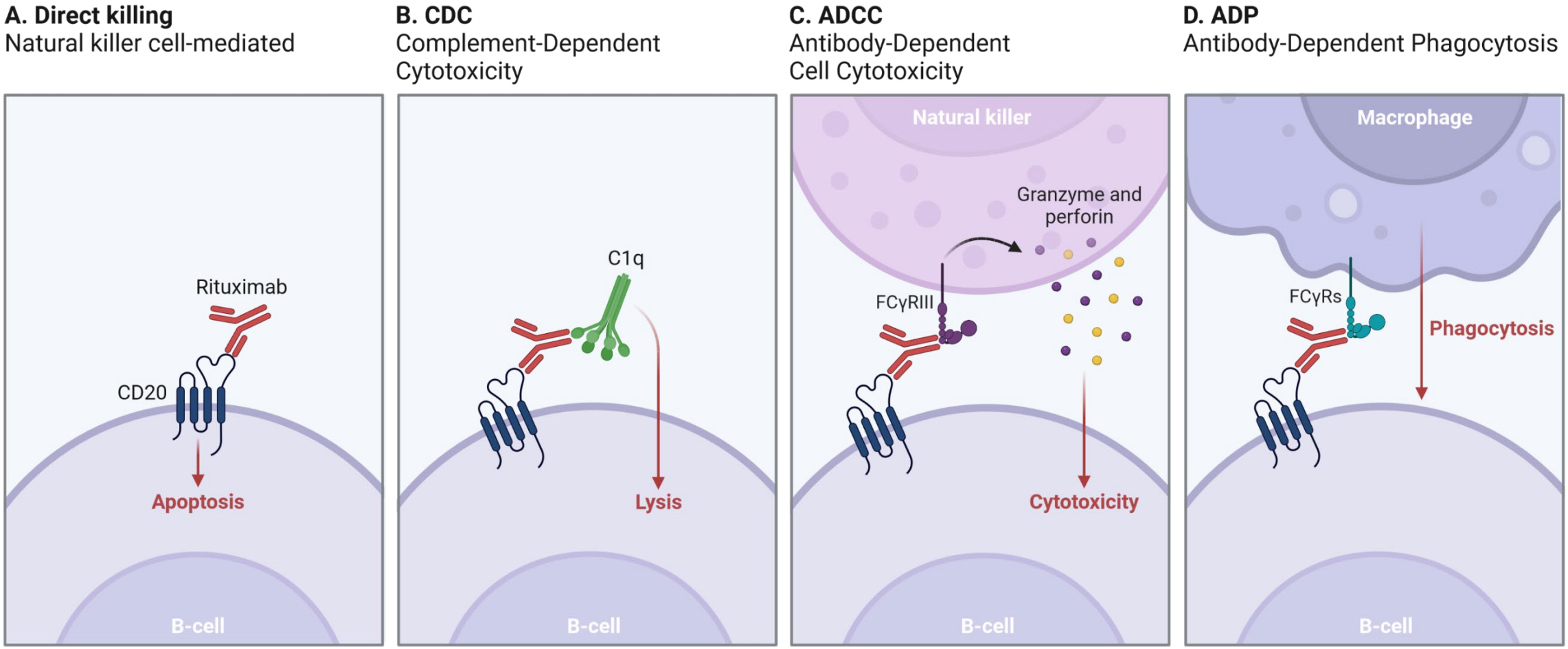
sdAb x 2

Nanobody-scFv

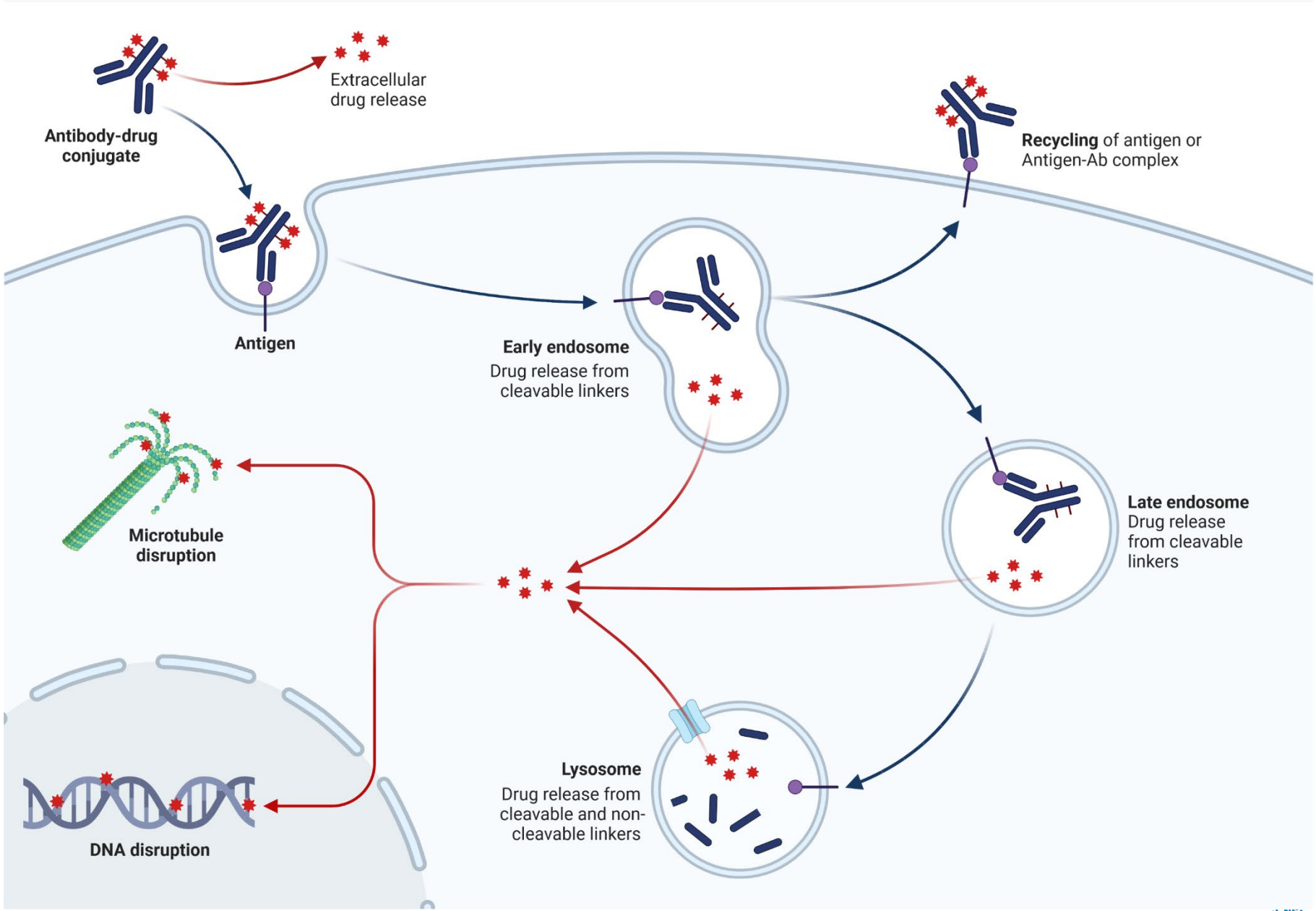
scFv

sdAb x 3

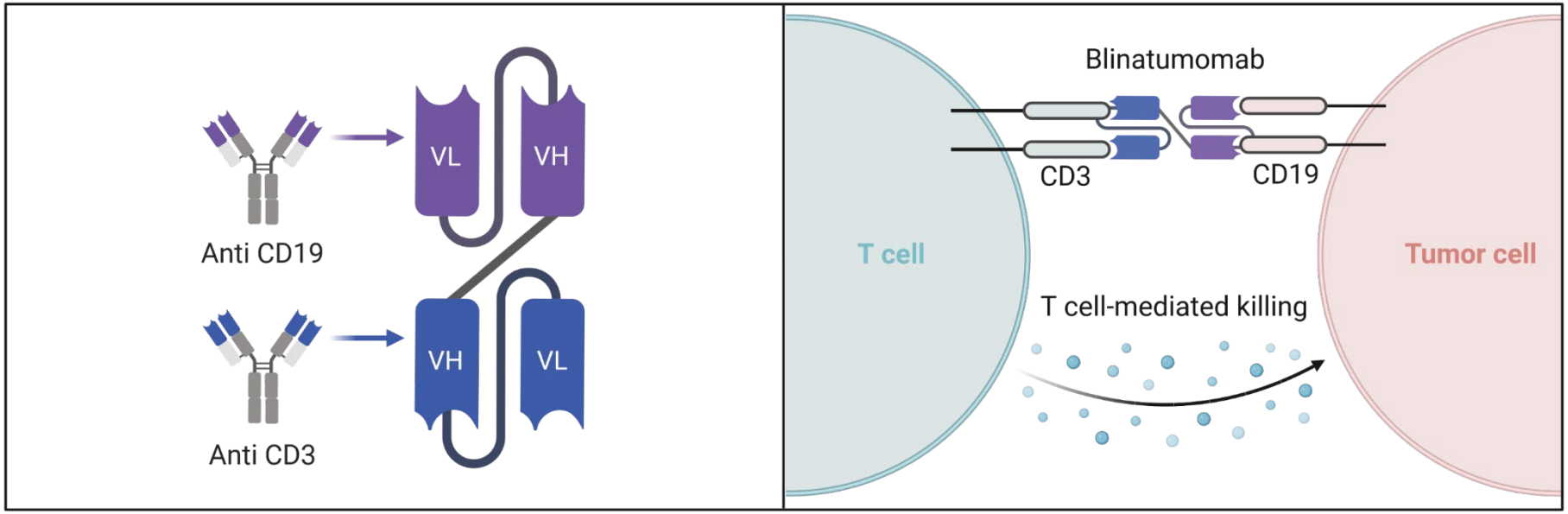
Naked antibodies

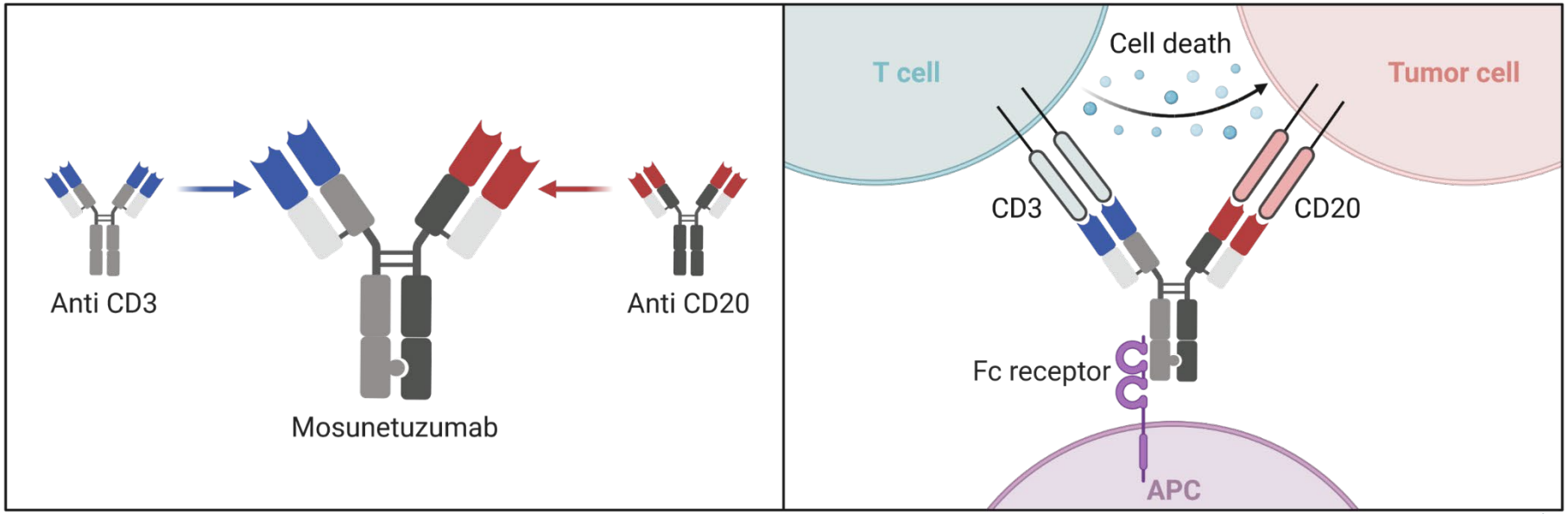


Antiboty drug conjugates

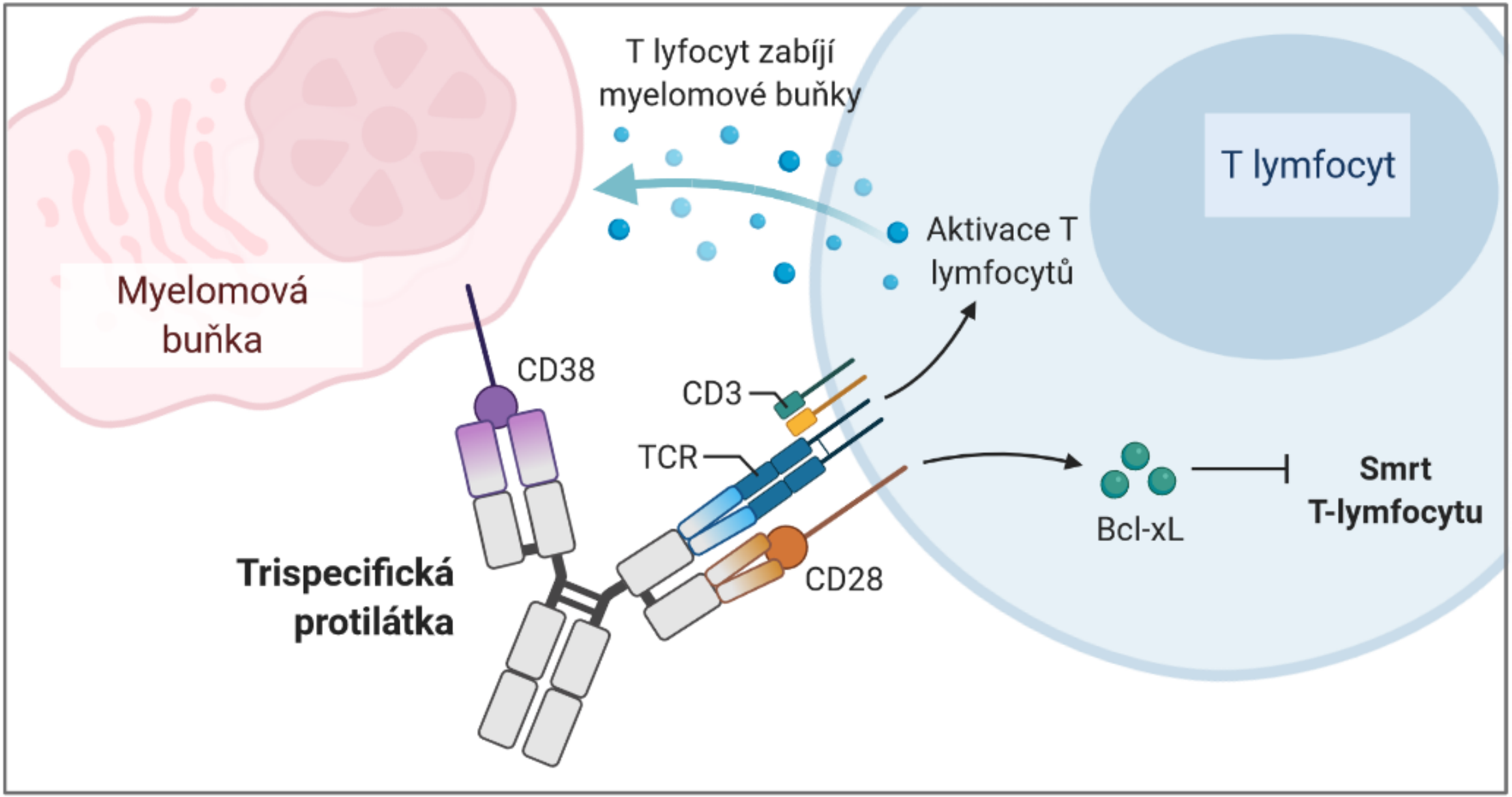


Bispecific antibodies





Trispecific antibodies

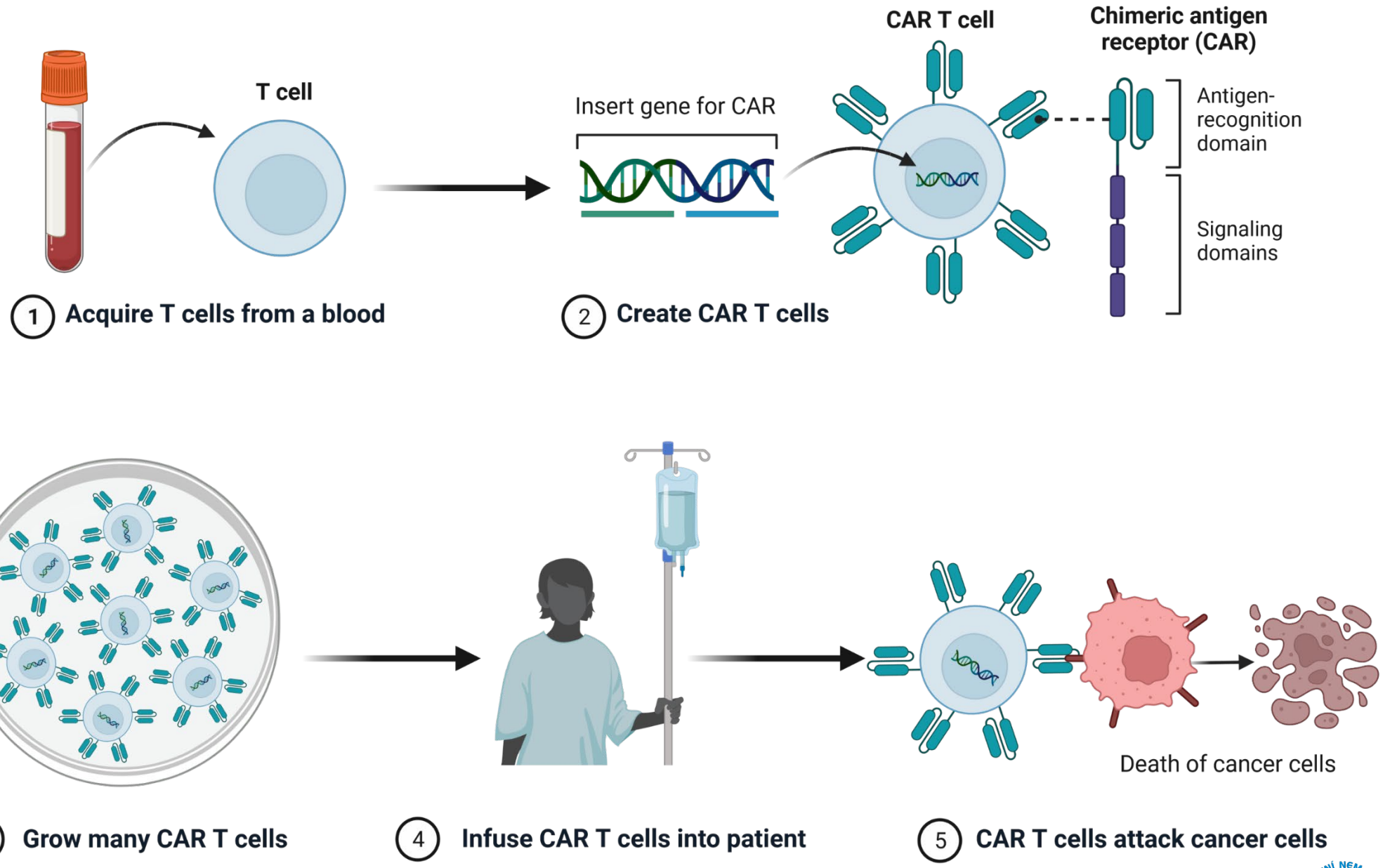


Bispecific antibodies - outcomes

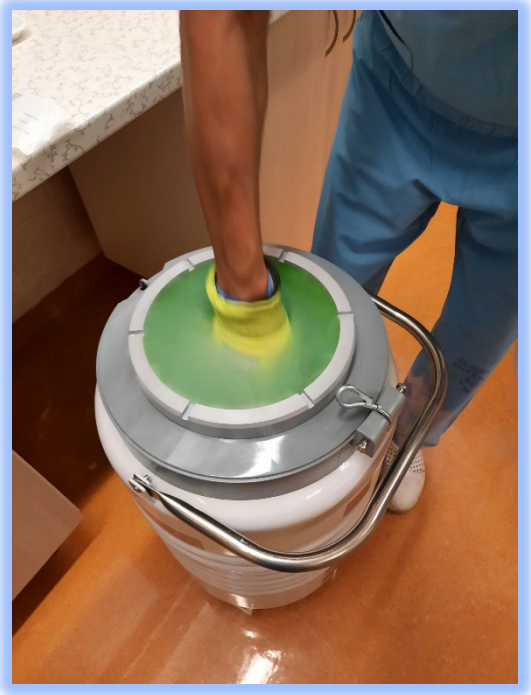
Drug	Target	ORR, %	CRS, %	Neurotoxicity, %
Teclistamab[1] (n = 40 RP2D)	BCMA	65 @RP2D (59.4 @other SC doses)	70 @RP2D (no grade 3)	1 (0 in other SC doses)
TNB-383B[2] (n = 58, 15)	BCMA	80 @higher doses (n = 15)	45 (no grade 3)	0
REGN-5458[3] (n = 49, 8)	BCMA	63 @highest doses (n = 8)	39 (no grade 3)	12
Pavurutamab/ AMG-701[4] (n = 85, 6)	BCMA	83 @highest doses (n = 6)	64 (9% grade 3)	3.8
Elranatamab[5] (n = 30)	BCMA	70 @≥215 µg/kg	73	20
Talquetamab[6] (n = 82 all SC, 30 RP2D)	GPRC5D	53.3% all SC doses (70.0% @ RP2D)	67 all SC (73 @RP2D) (3% grade 3 @RP2D)	4.9% all SC (7% @RP2D)
Cevostamab[7] (n = 53, 34)	FcRH5	53%, higher doses 61%, highest dose (n = 18) 63% in prior BCMA (n = 8)	76% (2% grade 3)	28%

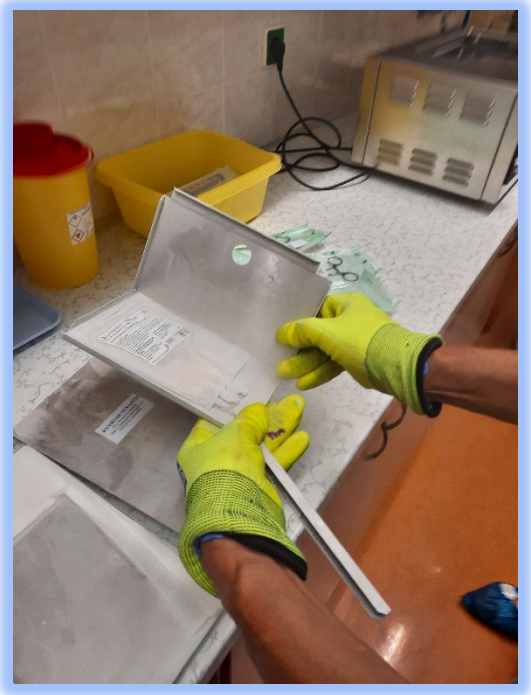
1. Krishnan. ASCO 2021. Abstr 8007. 2. Rodriguez. ASH 2020. Abstr 293. 3. Madduri. ASH 2020. Abstr 291.
4. Harrison. ASH 2020. Abstr 181. 5. Bahlis. ASCO 2021. Abstr 8006. 6. Berdeja. ASCO 2021. Abstr 8008. 7. Cohen. ASH 2020. Abstr 292.

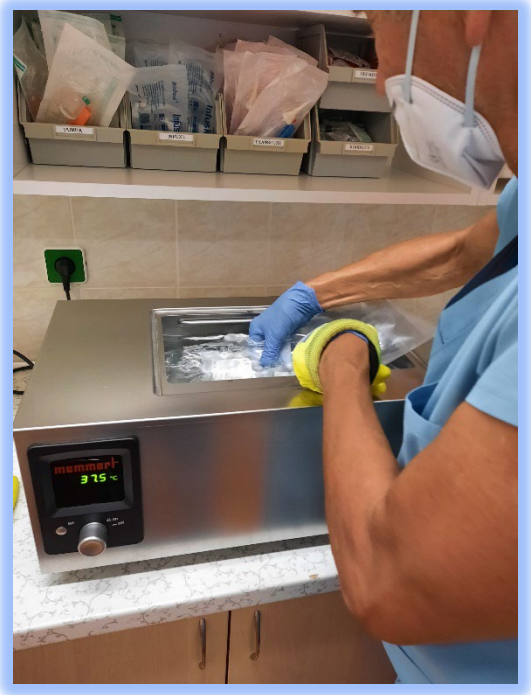
Chimeric antigen receptor T-cells

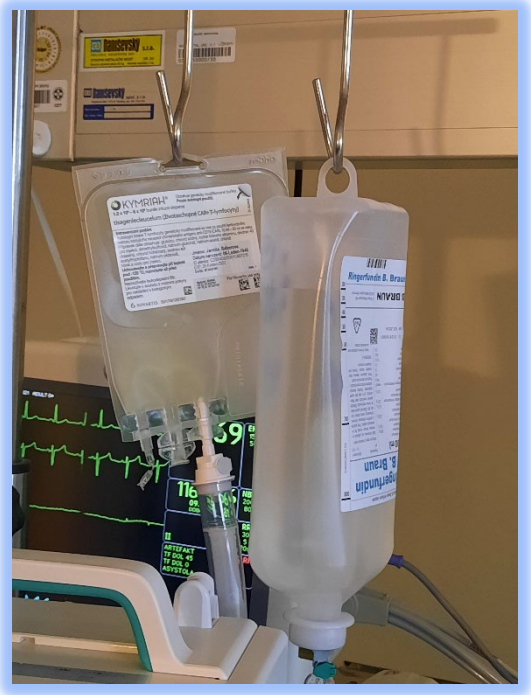


Chimeric antigen receptor T-cells









CAR-T outcomes

	CARTITUDE-1[1] Cilta-cel Phase I	CRB-401[2] Ide-cel Phase I	LUMMICAR-2[3] CT053 Phase Ib	PRIME[4] BCMA-101 Phase I/II	GC012F[5] Dual CAR T-Cell BCMA + CD19
Patients	97	62	20	55	19
Median prior regimens, n	6	6	5	8	5
Triple refractory, %	87.6	69.4	85	60	NR
CAR T-cell therapy dose	0.75×10^6 ($0.5\text{-}1.0 \times 10^6$)	50, 150, 450, 800×10^6	$1.5\text{-}1.8/2.5\text{-}3.0 \times 10^8$	$0.75\text{-}15 \times 10^6$	$1.0\text{-}3.0 \times 10^5$
ORR, %	97.9	75.8	94	67	94.7
CR/sCR, %	80.4	38.7	25	NR	84.2
CRS (all grades), %	94.8	75.8	77/83§	17	95
CRS (grade ≥3), %	5.4	6.5	0/0§	0	11
Neurotoxicity (all grades), %	20.6	35.5	15/17§	3.8	0
Neurotoxicity (grade ≥3), %	10.3	1.6	8/0§	3.8	0

1. Usmani. ASCO 2021. Abstr 8005. 2. Lin. ASH 2020. Abstr 131. 3. Kumar. ASH 2020. Abstr 133.
4. Costello. ASH 2020. Abstr 134. 5. Jiang. ASCO 2021. Abstr 8014.

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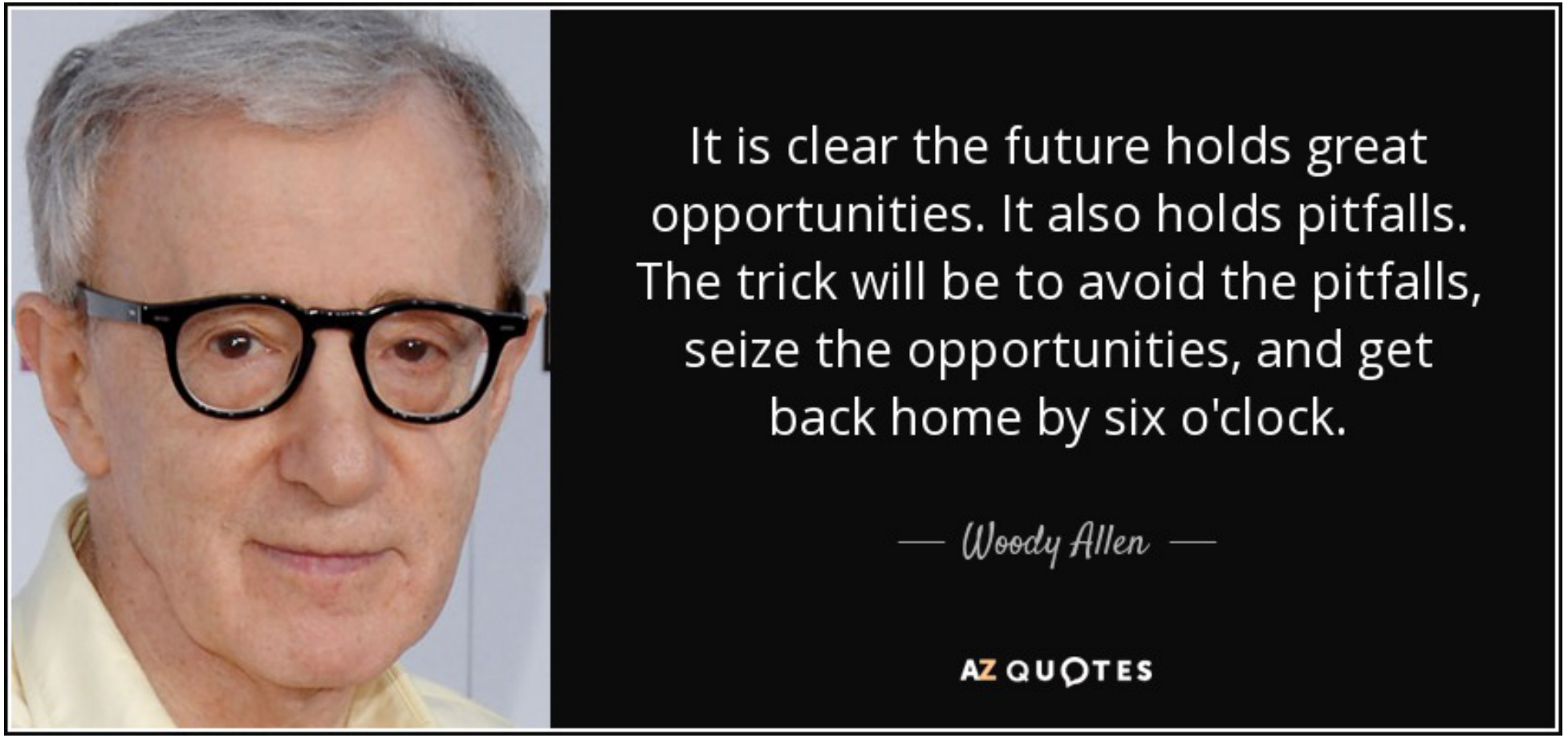
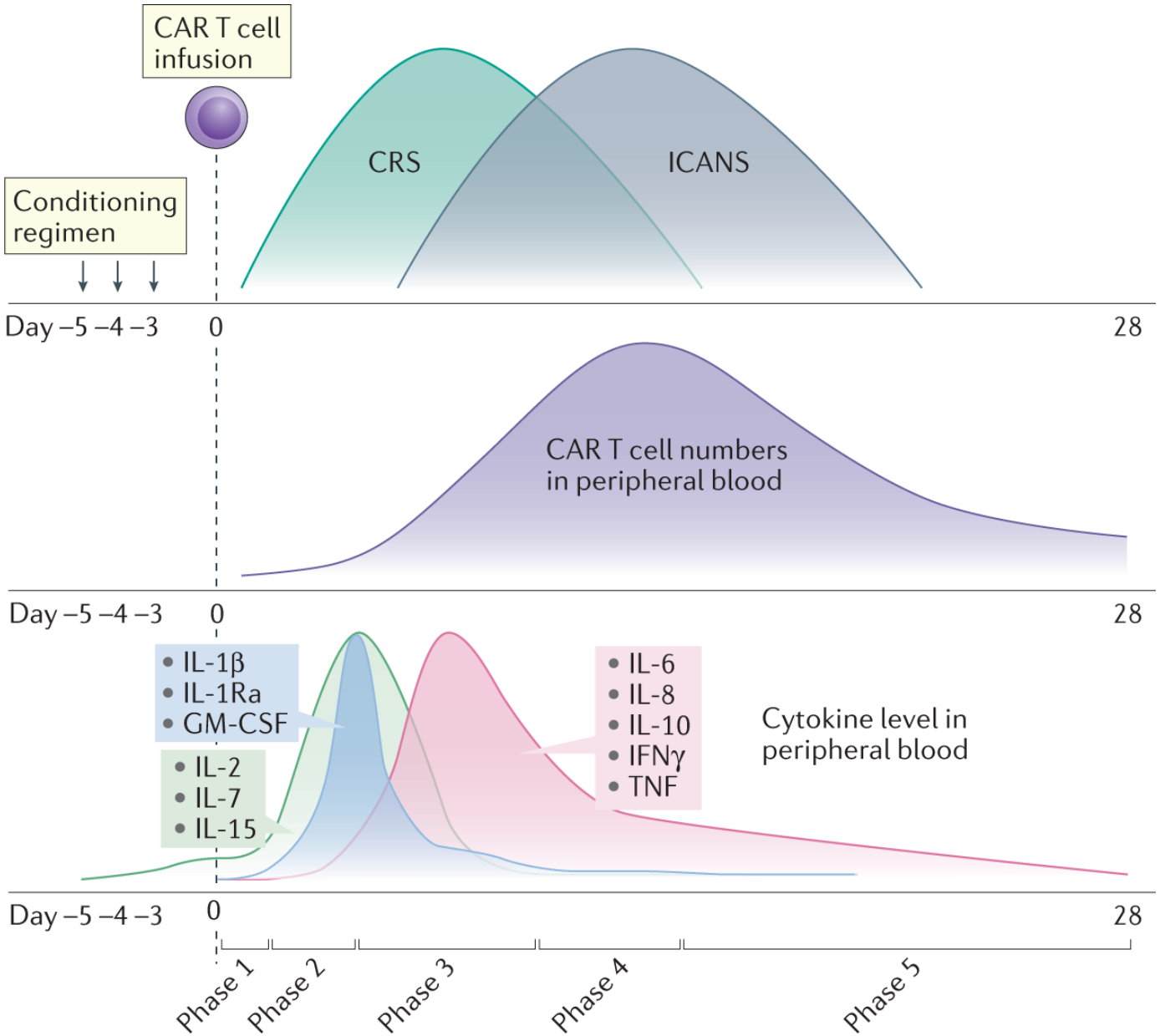
Everything comes at a price



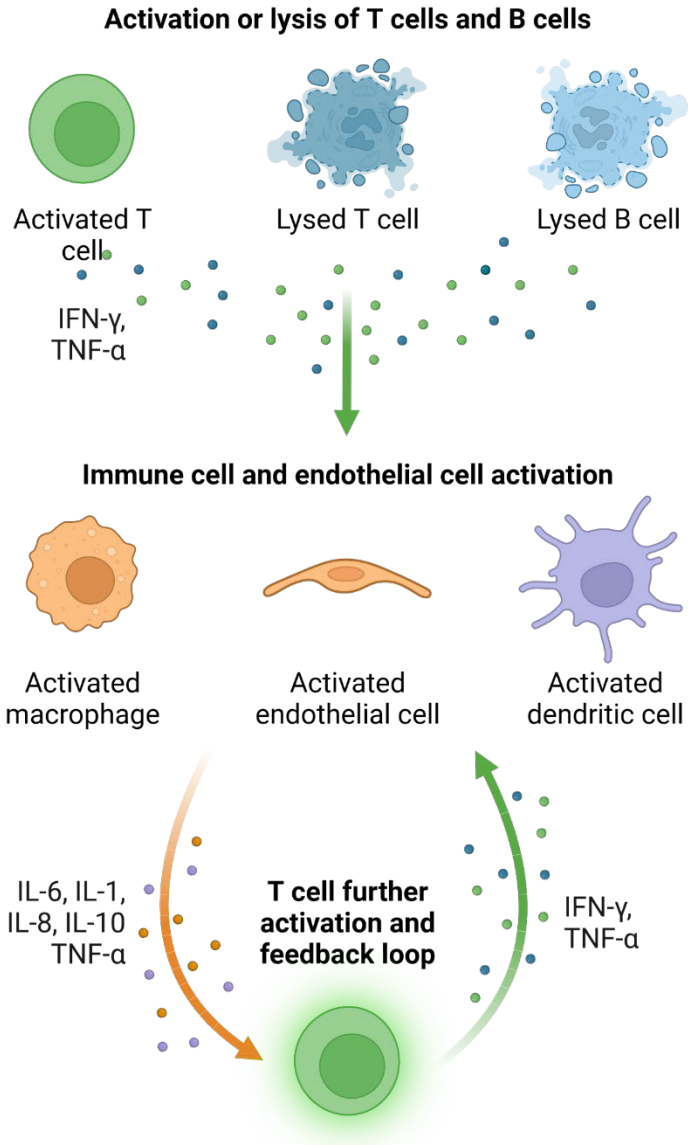
https://www.azquotes.com

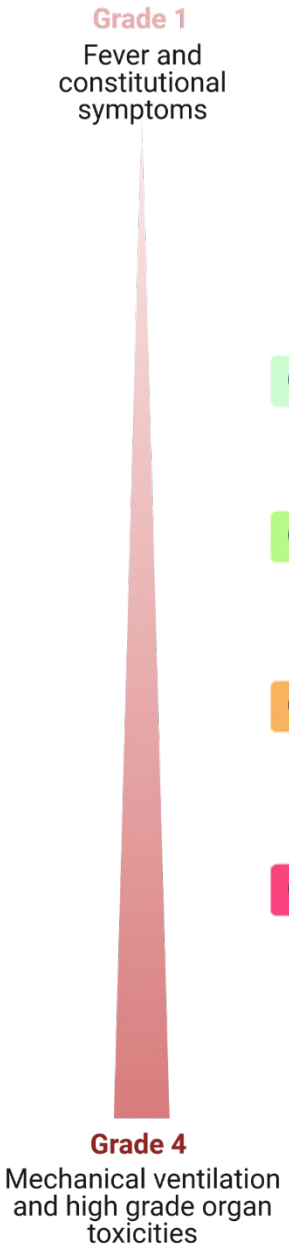
Cytokine release syndrom



Nat Rev Immunol 22, 85–96 (2022).

Cytokine release syndrom





CRS grading and management approaches

CRS grade 1	• temperature >38°C • flu-like symptoms • nausea	• infectious workup • broad spectrum antibiotic • supportive measures (antipyretics)
CRS grade 2	• temperature >38°C • hypotension not requiring vasopressors • hypoxia requirin low- flow nasal cannula or blow-by	• manage fever and symptoms as grade 1 • transfer to IMC/ICU • low dose vasopressor • tocilizumab 8mg/kg i.v.
CRS grade 3	• temperature>38°C • hypotension requiring one vasopressor with or with vasopressin • hypoxia requiring high- flow orfacemask	• manage fever and symptoms as grade 2 • repeat tocilizumab • low dose corticosteroids
CRS grade 4	• temperature >38°C • hypoxia requring positive airway pressure • hypotension requiring multiple vasopressors (excl. vasopressin)	• manage fever and symptoms as grade 2 • high dose corticosteroids • consider further individual treatment

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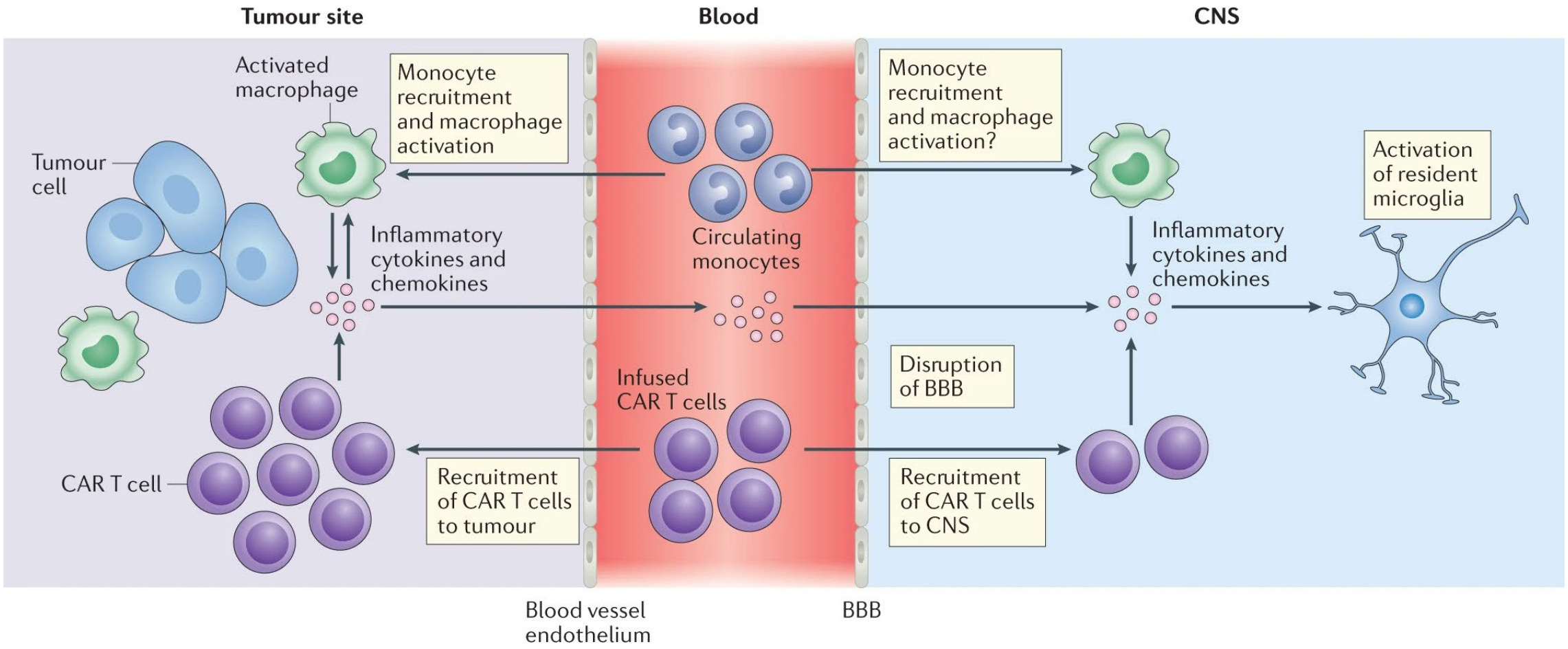
Immune effector cell-associated neurotoxicity syndrome



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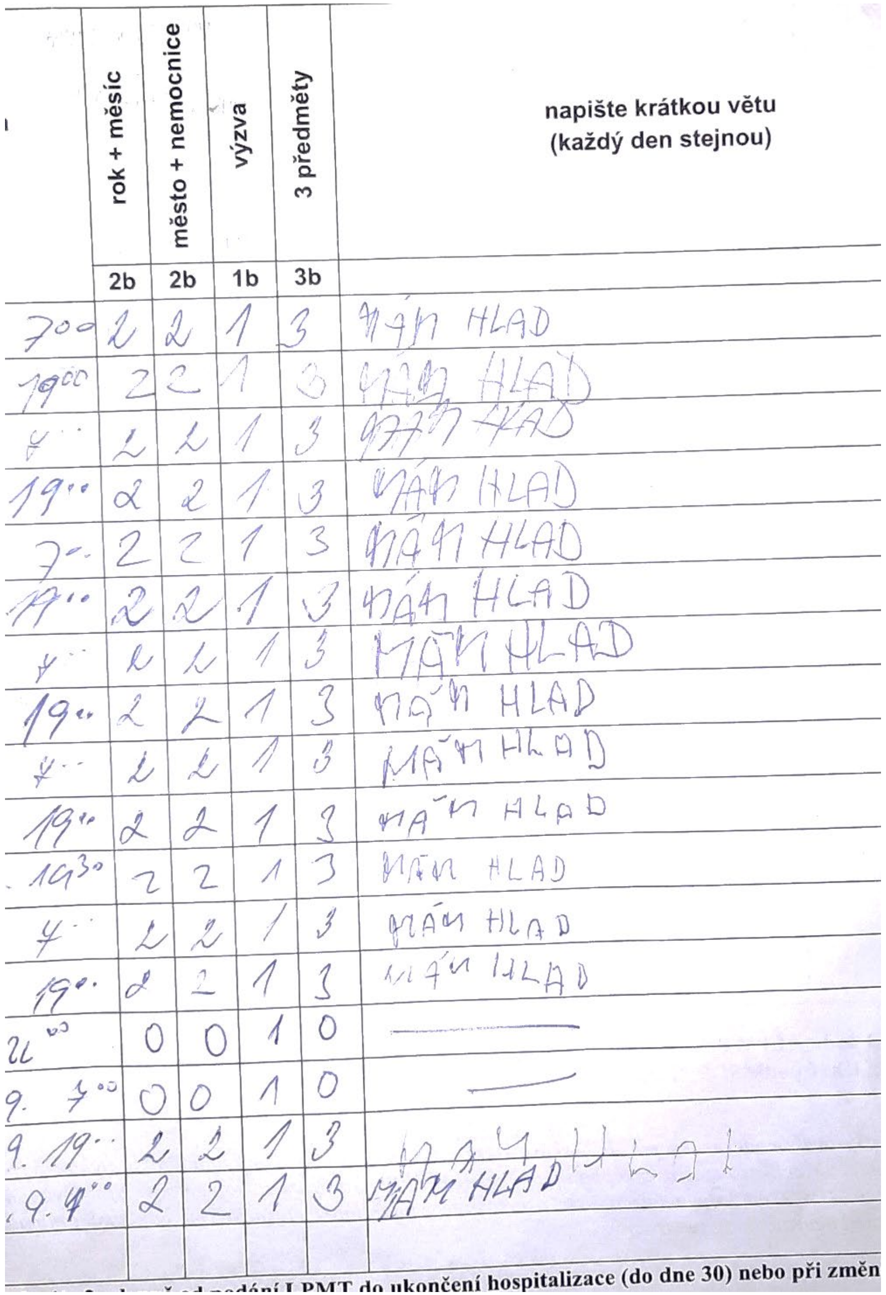
Immune effector cell-associated neurotoxicity syndrome



	rok + měsíc	město + nemocnice	výzva	3 předměty	napište krátkou větu (každý den stejnou)
	2b	2b	1b	3b	
7⁰⁰	2	2	1	3	MÁM HLAD
19⁰⁰	2	2	1	3	MÁM HLAD
7..	2	2	1	3	MÁM HLAD
19..	2	2	1	3	MÁM HLAD
7..	2	2	1	3	MÁM HLAD
19..	2	2	1	3	MÁM HLAD
7..	2	2	1	3	MÁM HLAD
19..	2	2	1	3	MÁM HLAD
7..	2	2	1	3	MÁM HLAD
19..	2	2	1	3	MÁM HLAD
19³⁰	2	2	1	3	MÁM HLAD
7..	2	2	1	3	MÁM HLAD
19..	2	2	1	3	MÁM HLAD
22⁰⁰	0	0	1	0	—
9. 7⁰⁰	0	0	1	0	—
9. 19..	2	2	1	3	MÁM HLAD
9. 7⁰⁰	2	2	1	3	MÁM HLAD

... od podání LPMT do ukončení hospitalizace (do dne 30) nebo při změn

CRS grading and management approaches

Grade	Symptoms	Management
ICANS grade 1	• awakens spontaneously • fatigue • ICE: 7-9 points	• supportive care • IV hydration • neurology consultation • EEG/MRI • consider antiepileptic drug
ICANS grade 2	• awakens to voice • delirius/somnolent • ICE: 3-6 points	• supportive care as grade 1 • consider ICU transfer • consider antiepileptic drug, if not started • low dose corticosteroids (i.e. dexamethasone 10mg)
ICANS grade 3	• awakens to tactile stimulus • ICE: 0-2 points • local edema on imaging • seizure, that resolves with intervention	• Supportive care as grade 2 • ICU transfer • continous corticosteroids (i.e. dexamethasone 10mg every 6 hours) and antiepileptic drugs • repeat MRI
ICANS grade 4	• comatose • ICE:0 • cerebral edema • life-threatening (>5min) seizure • motor weakness	• supportivecareasgrade3 • highdosecorticosteroids specific neurointensive treatment (status epilecticus, brain edema) • consider further individual treatment

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Macrophage activation syndrome

Genetic predisposition Immunodeficiency

Trigger event Infection Malignancy Autoimmunity

Damage to NK/Tc-ly

Macrophage activation and proliferation

↑GM-CSF receptor

Splenomegaly Hepatomegaly

Phagocytosis

Fever (IL-1, TNF-α)

Hyperactivation Cytokines

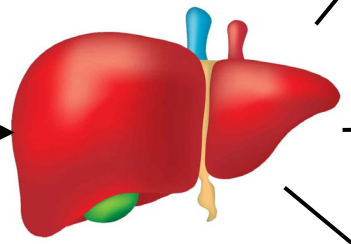
Cytopenias (IL-2, IFN-γ, TNF-α)

DIC, MODS

Fibrinogen hypoproduction Consumption

Inflammation (portal, sinusoidal) hemosiderosis necrosis ↑ALT, AST

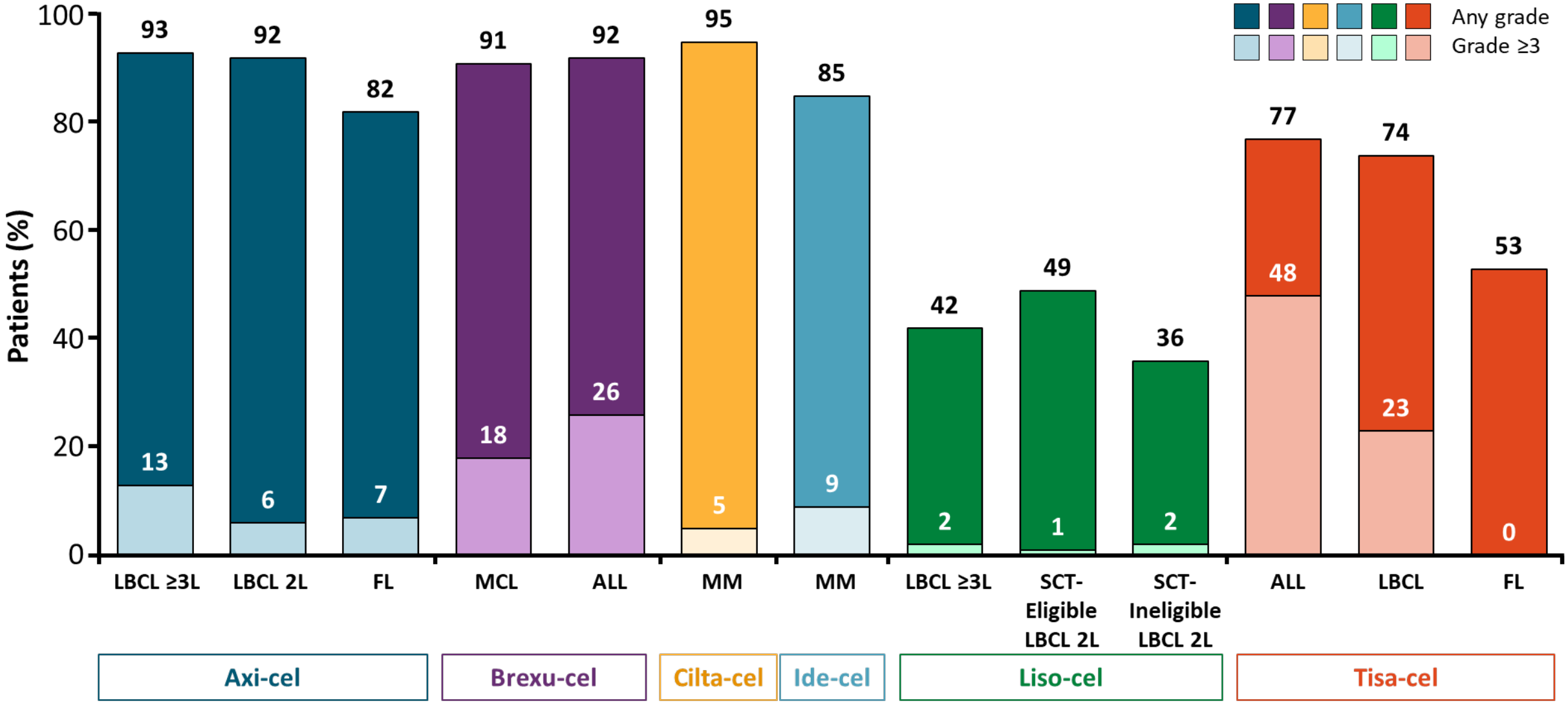
Dilation of sinusoids endothelial activation infiltration by histiocytes haemophagocytosis hemosiderosis



Lymphocyte-induced bile duct damage cholestasis Hypertriglyceridemia (IL-1, TNF-α, IL-6)

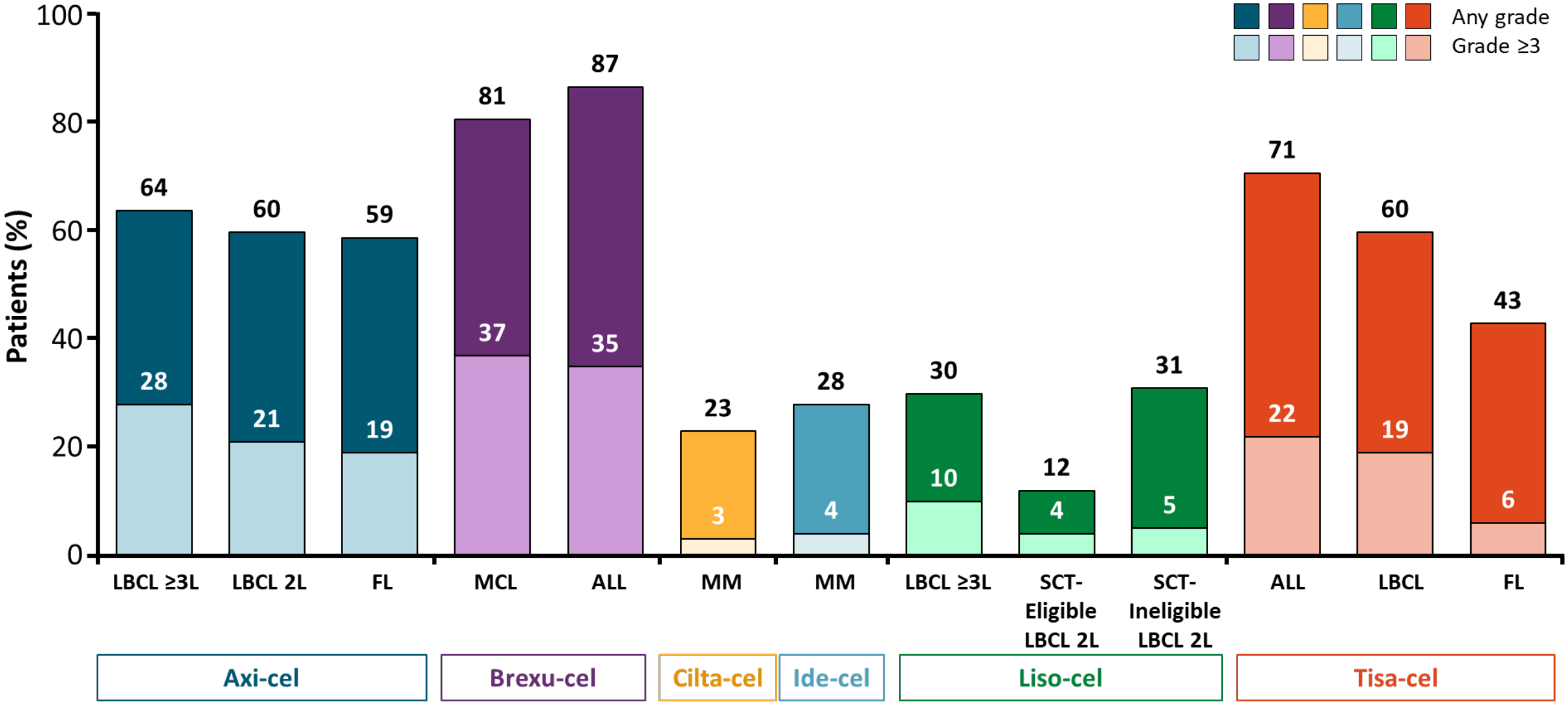
Ferritin acute phase reactant phagocytosis by Kupffer cells and histiocytes

CRS Incidence by CAR T-Cell Product



Brudno. Blood Rev. 2019;34:45. Axicabtagene ciloleucel PI. Neelapu. NEJM. 2017;377:2531. Locke. NEJM. 2022;386:640. Jacobson. Lancet Oncol. 2022;23:91. Brexucabtagene autoleucel PI. Shah. Lancet. 2021;398:491. Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Lisocabtagene maraleucel PI. Abramson. Lancet. 2020;396:839. Kamdar. Lancet. 2022;399:2294. Sehgal. Lancet Oncol. 2022;23:1066. Tisagenlecleucel PI.

ICANS Incidence by CAR T-Cell Product



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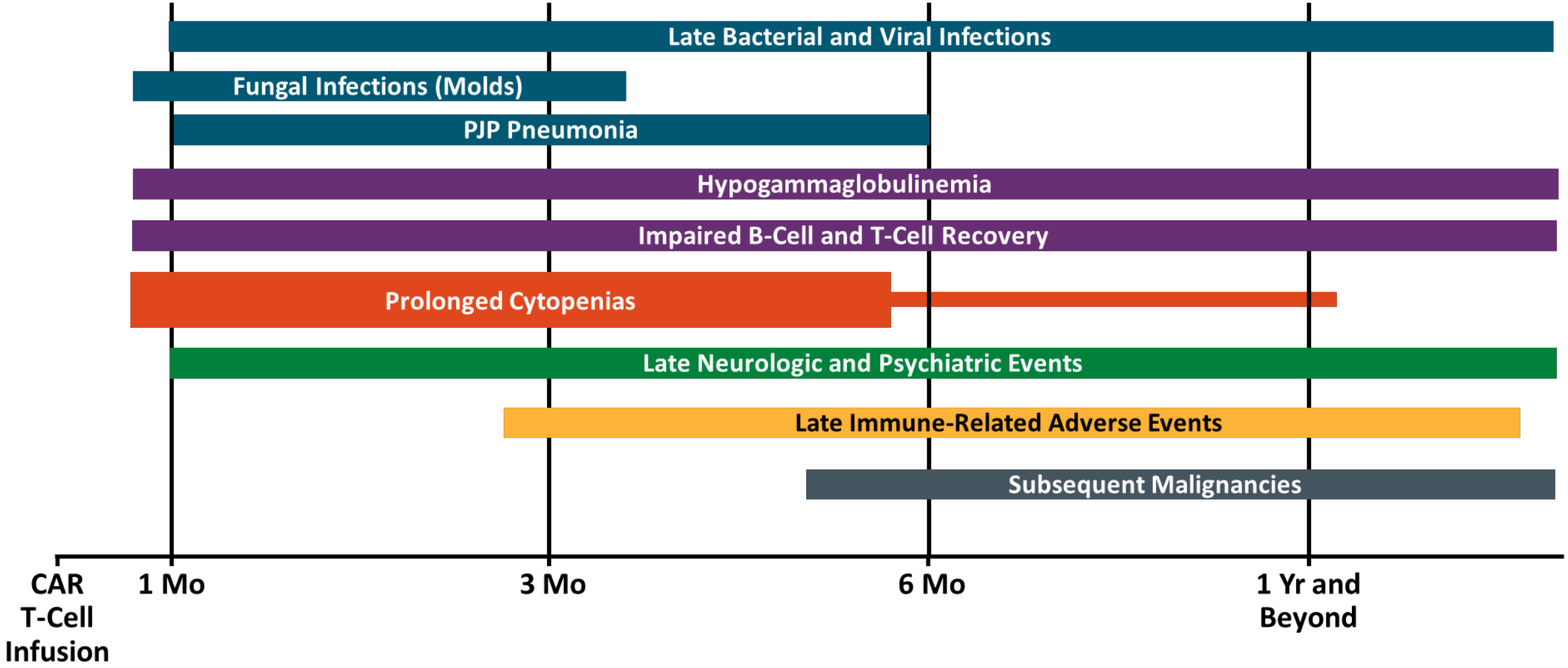
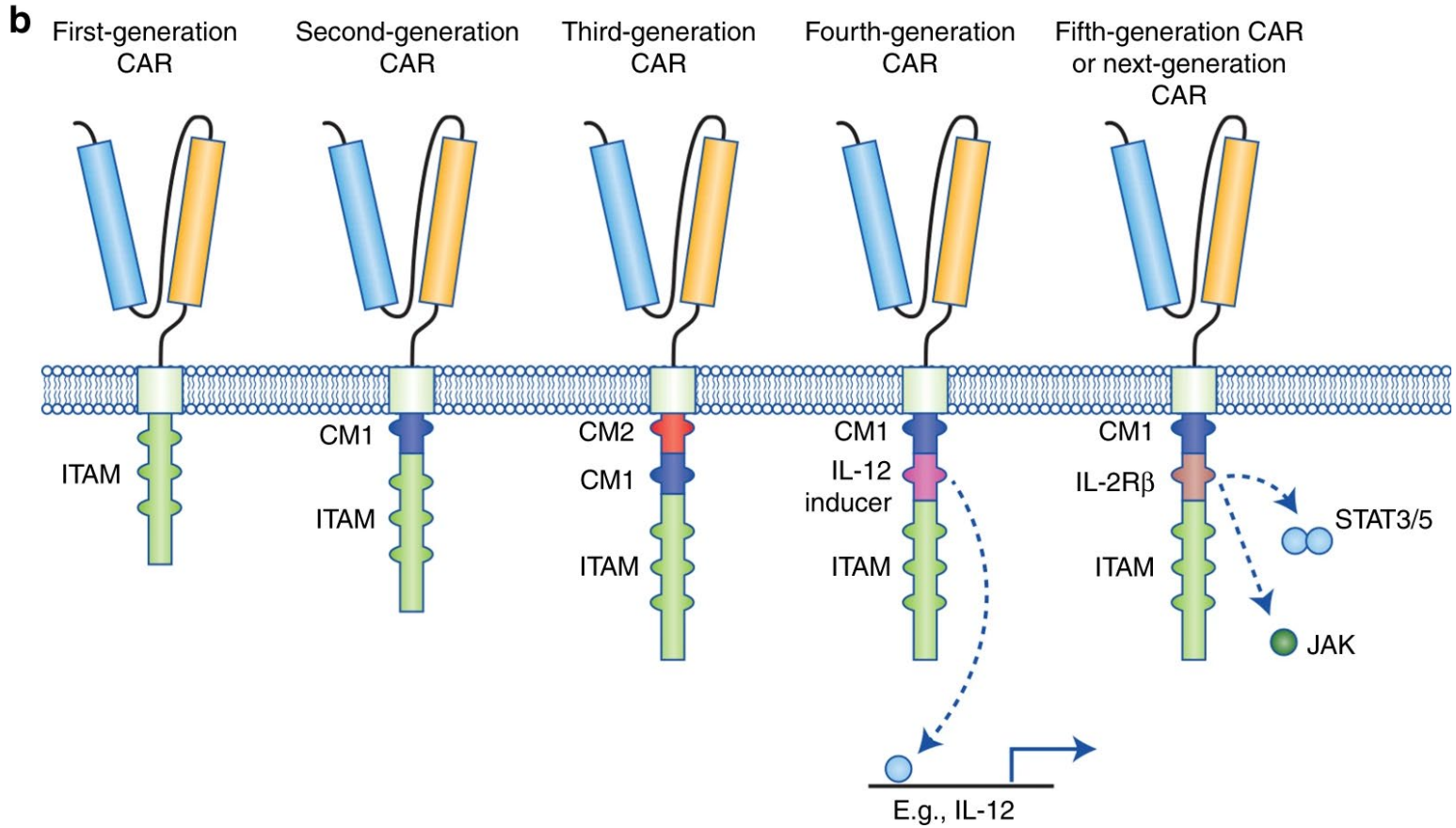
Timeline for Delayed Toxicities



Teaching an old dog new tricks



- **Suicide genes**
- **Dual-antigen receptor**
- **ON-switch**
- **Bispecific molecules as switches**

Hardcore Science and Technology

~~Miracles~~ of modern hemato~~oncology~~logy

Děkuji za pozornost

IV. INTERNÍ HEMATOLOGICKÁ KLINIKA
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