



**ICT 2023**

28th International  
Congress on Thrombosis

# Thrombotic and bleeding risk in CAR-T cell therapy

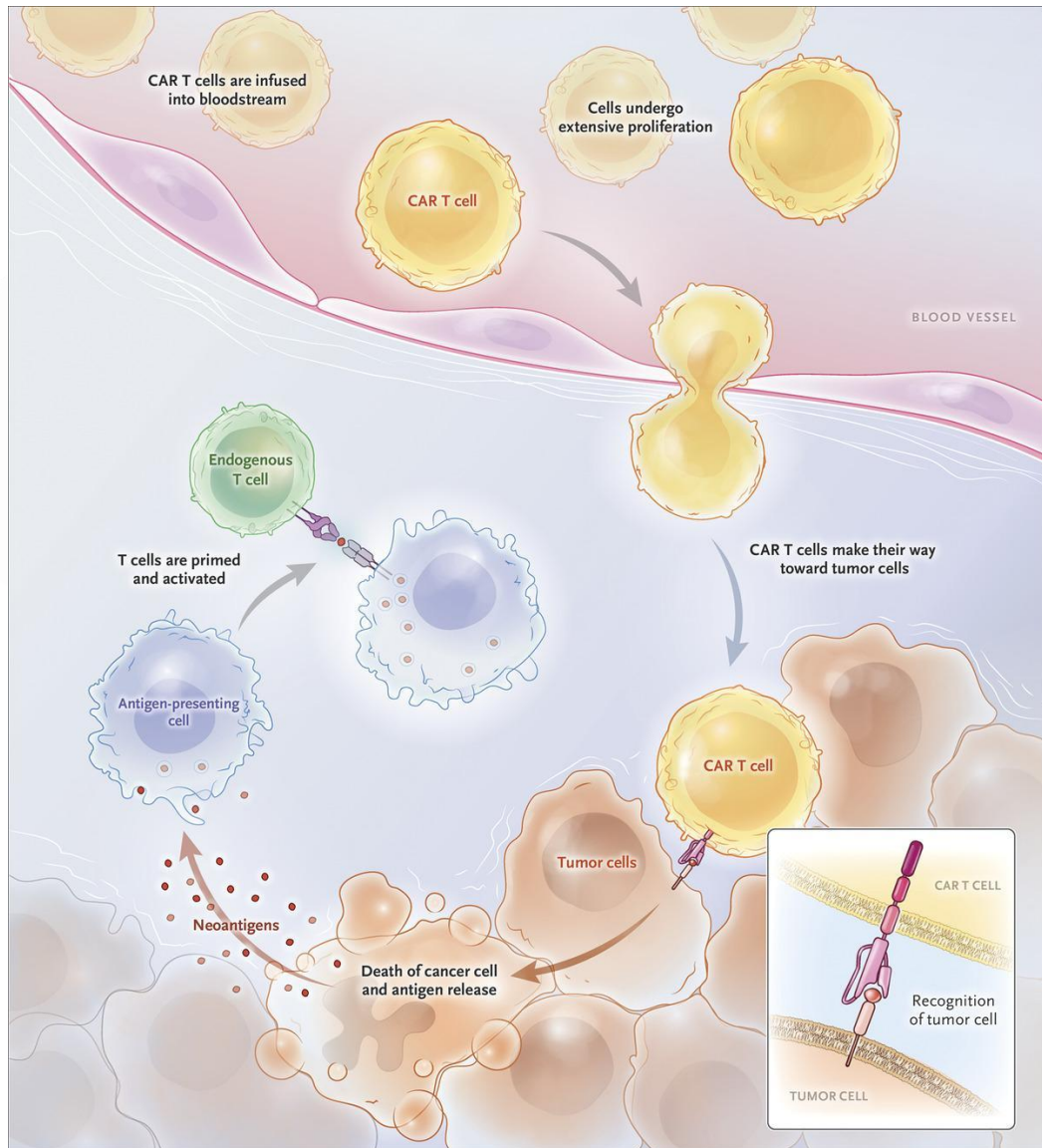
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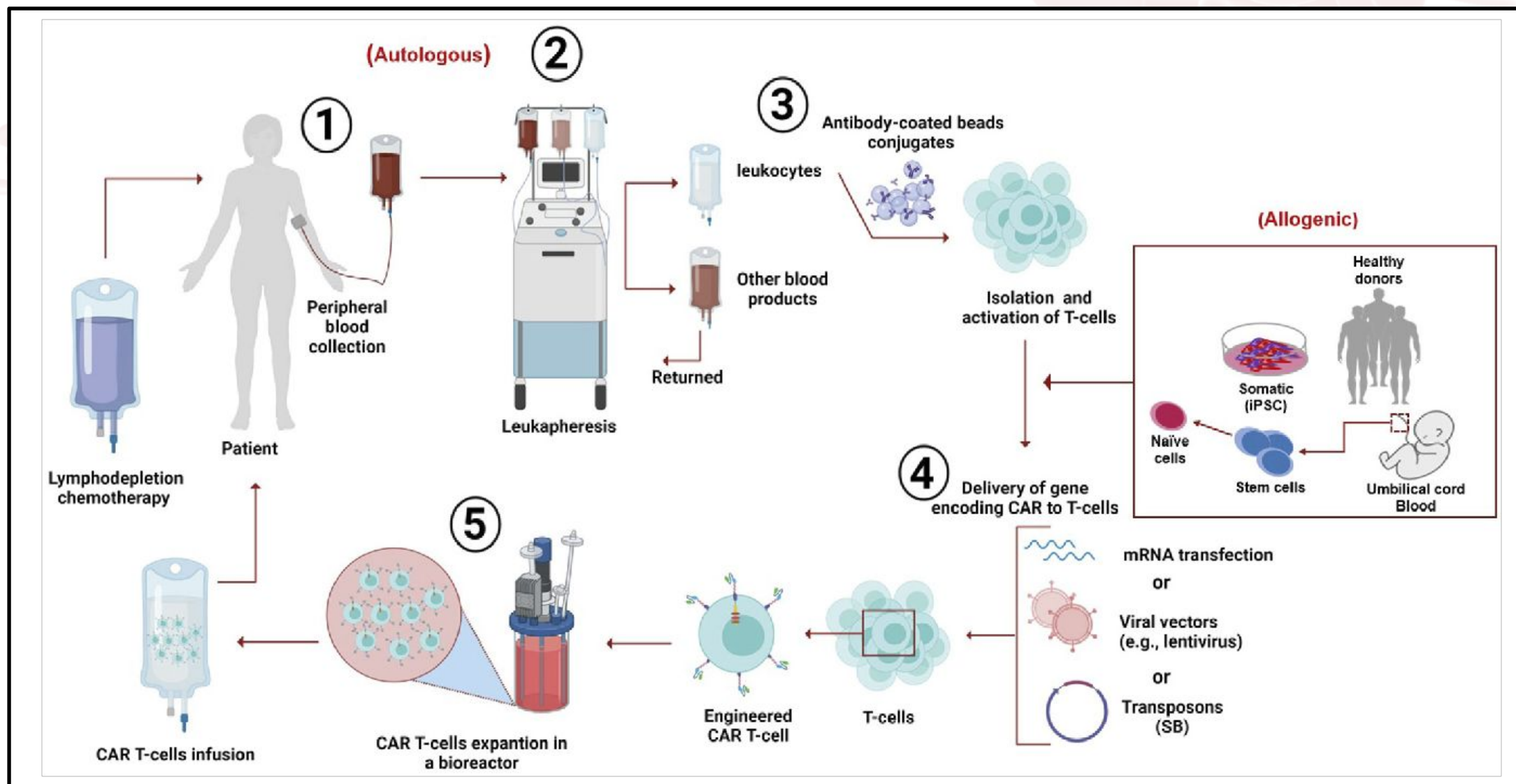
## Declaration of Conflict Of Interest

**I have no potential conflict of interest to report**

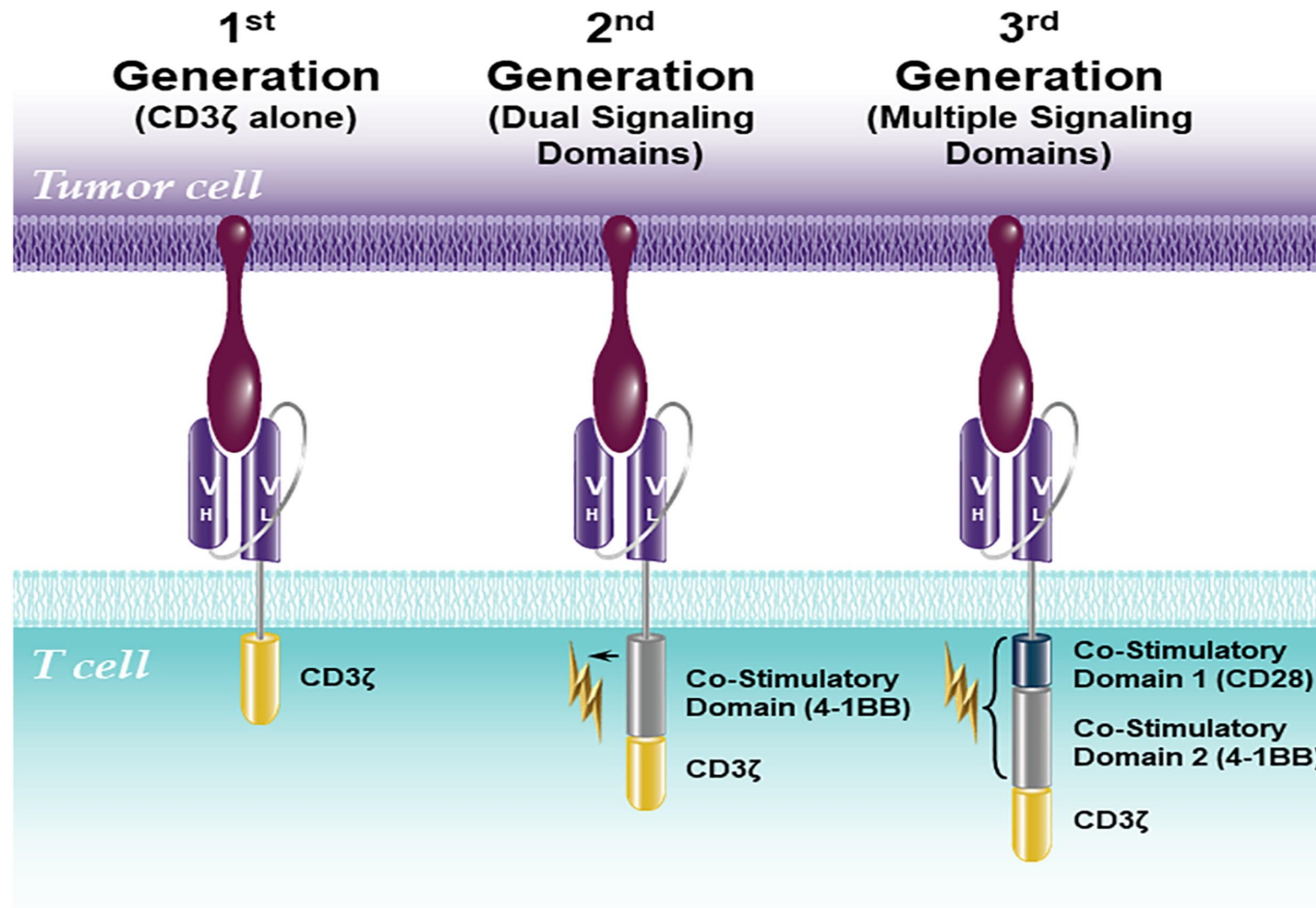
# Introduction to CAR-T cell therapy



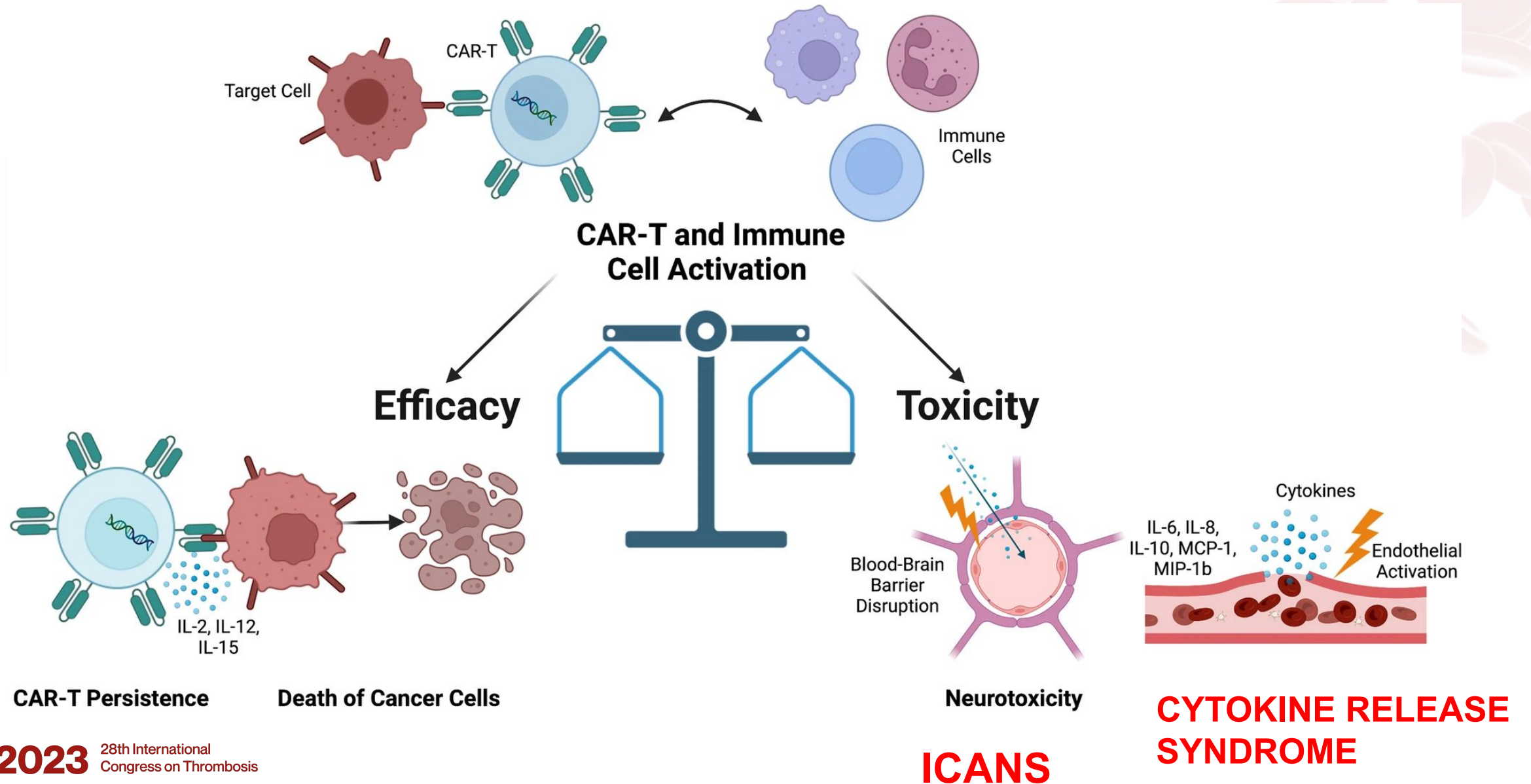
# Introduction to CAR-T cell therapy



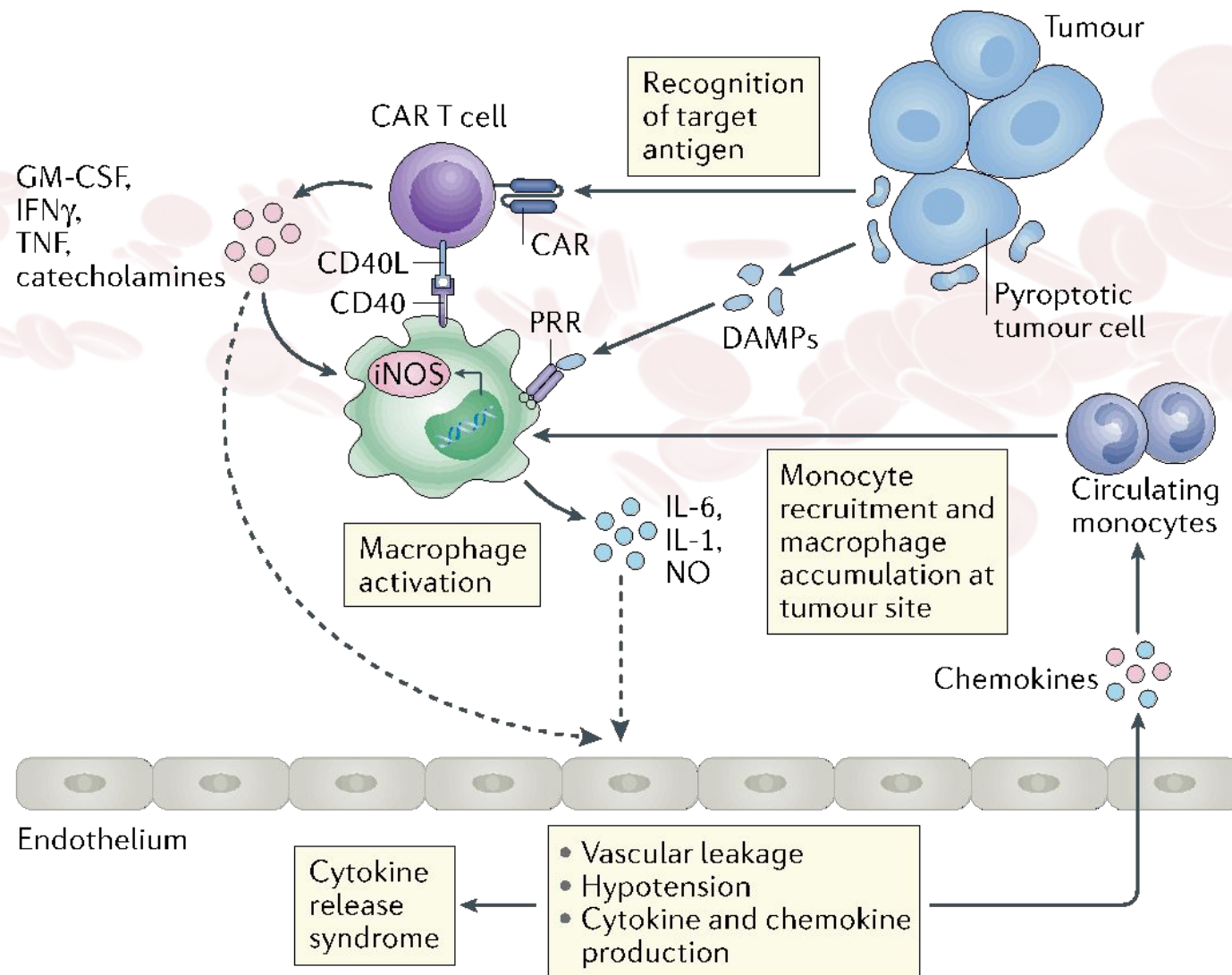
# An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer



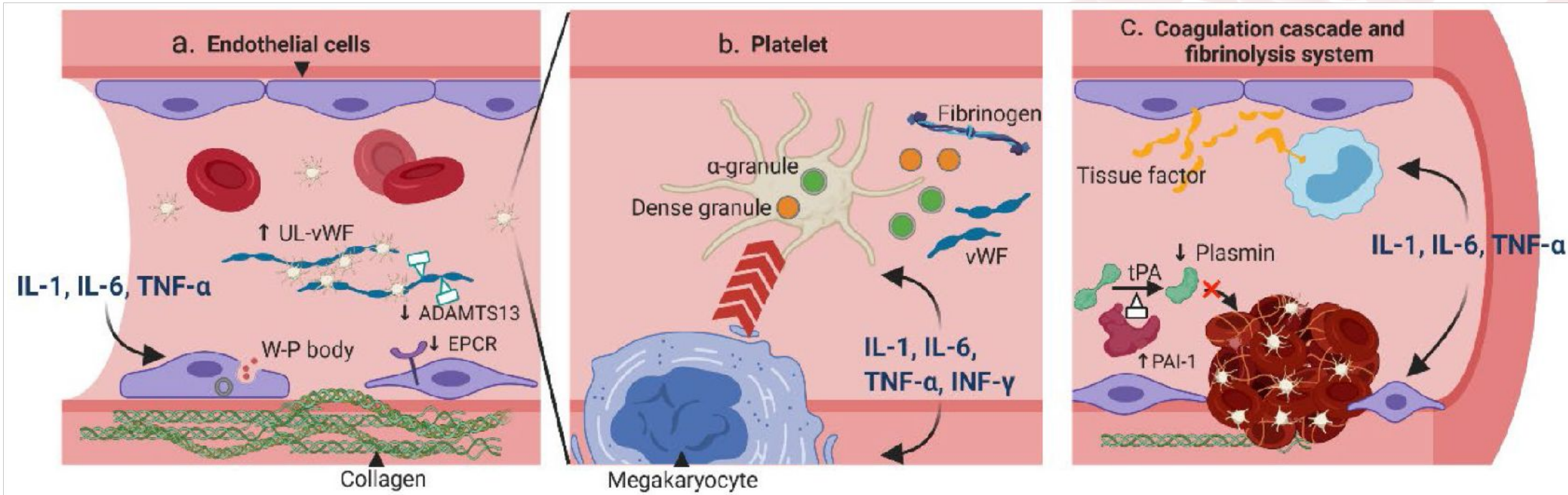
# CAR-T cell therapy: the Efficacy and Toxicity Balance



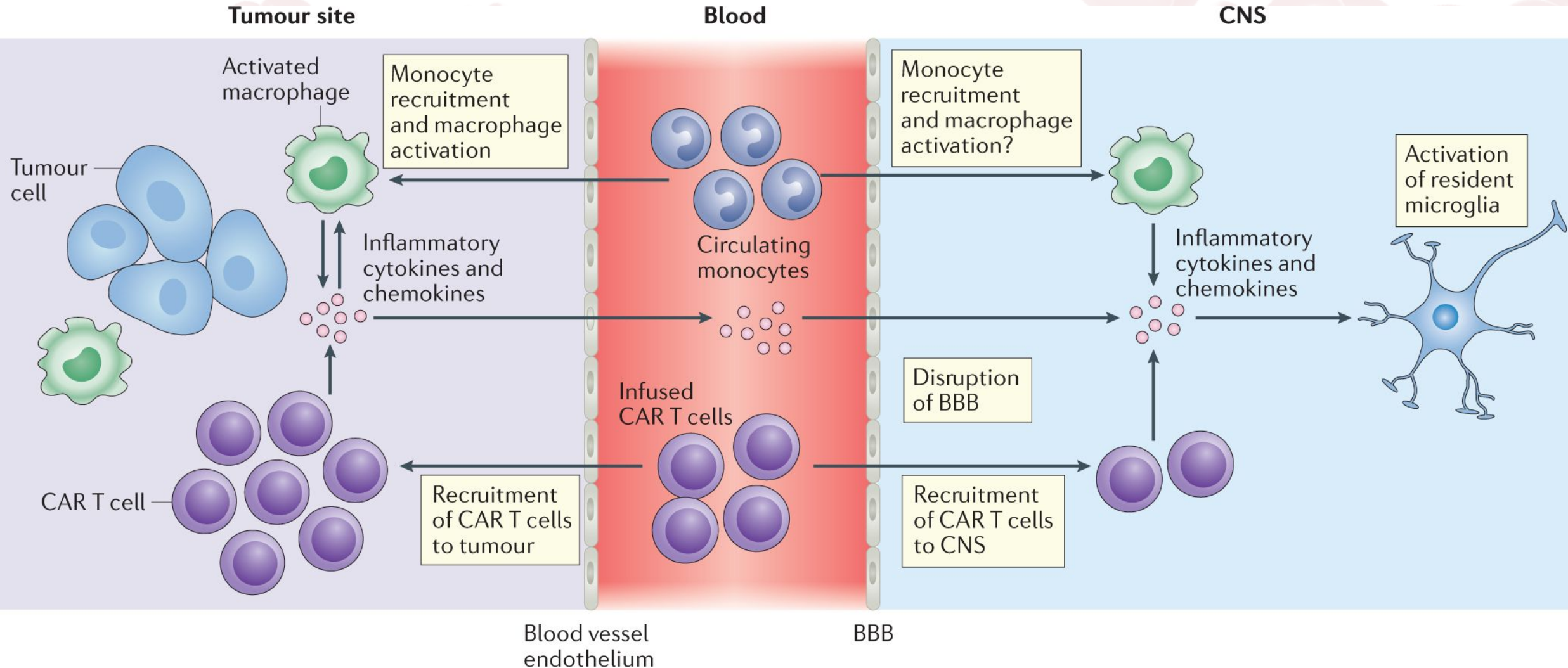
# Cytokine release syndrome



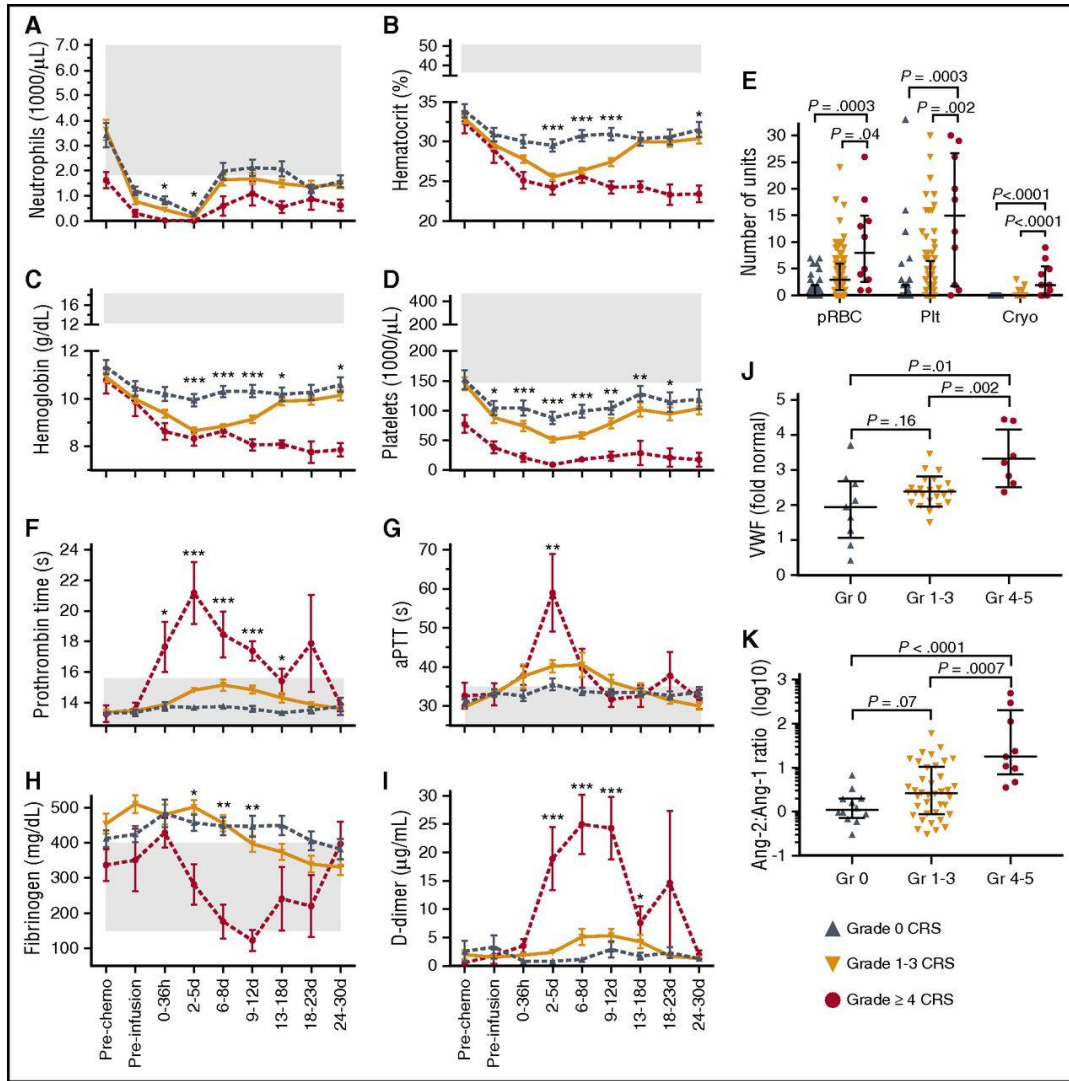
# Cytokine release syndrome coagulopathy



# Immune effector cell-associated neurotoxicity syndrome (ICANS)

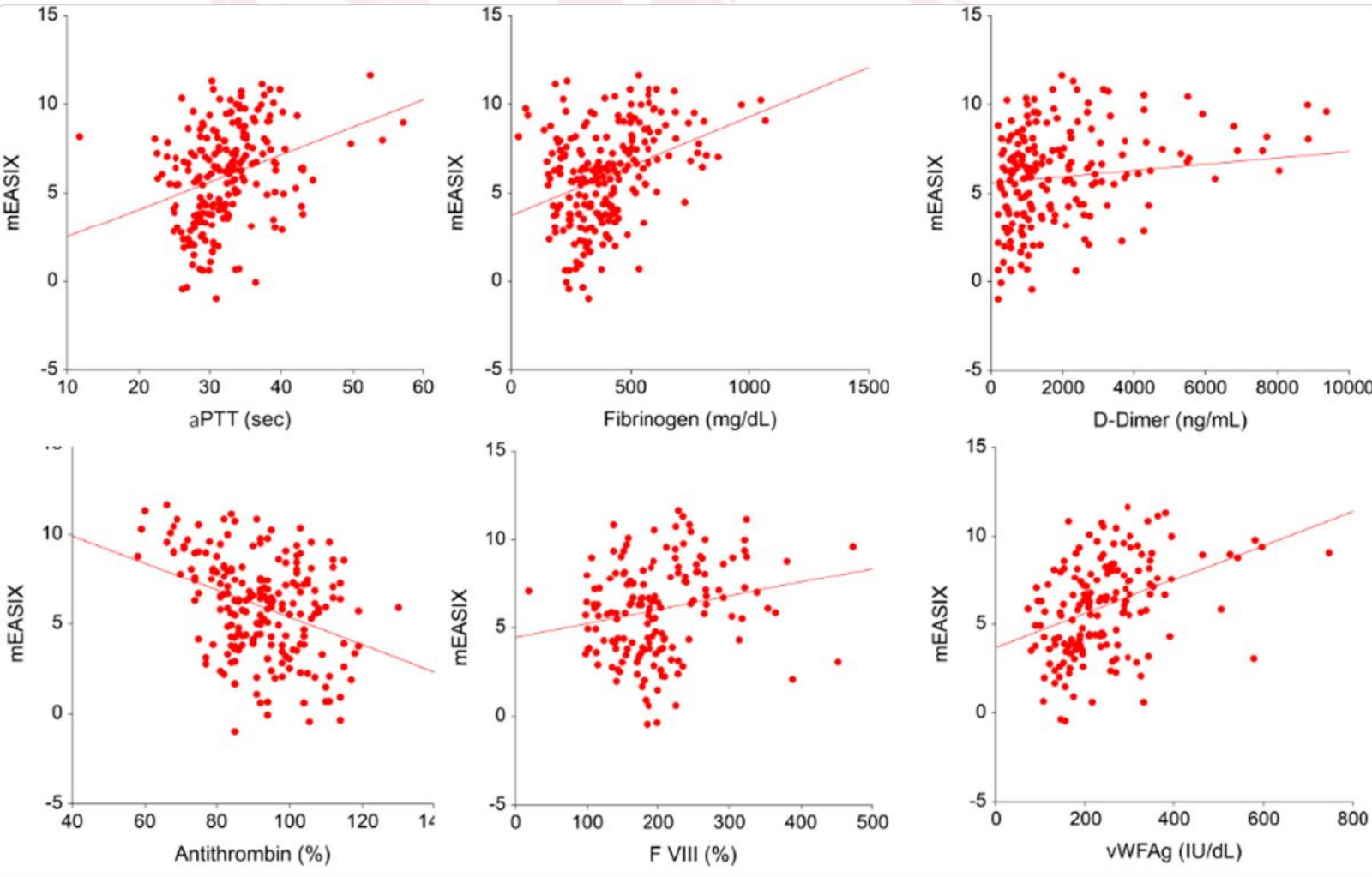


# Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor–modified T-cell therapy



Kevin A. Hay, et al. Blood 2017

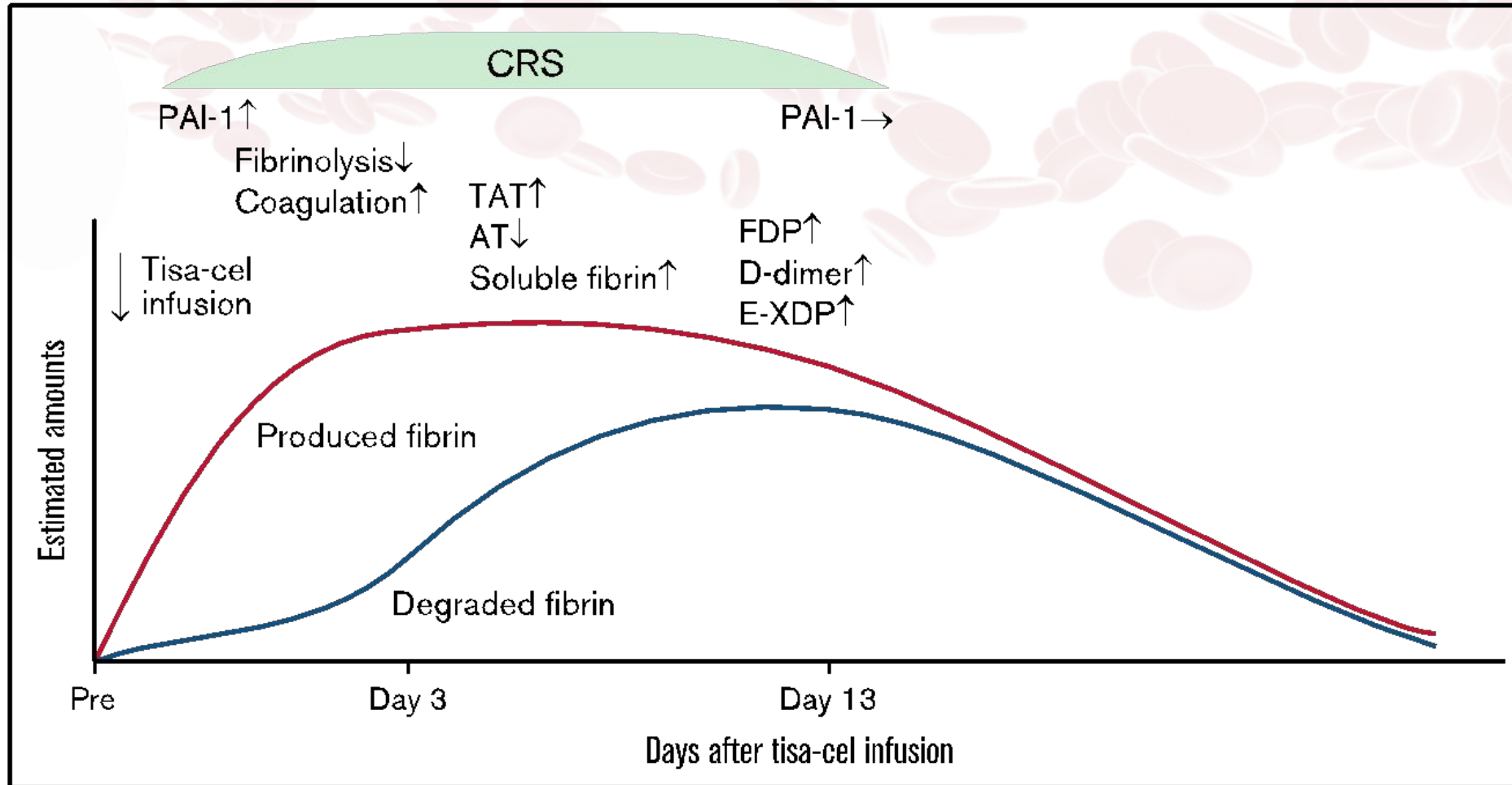
# Endothelial activation predicts disseminated intravascular coagulopathy, cytokine release syndrome and prognosis in patients treated with anti-CD19 CAR-T cells



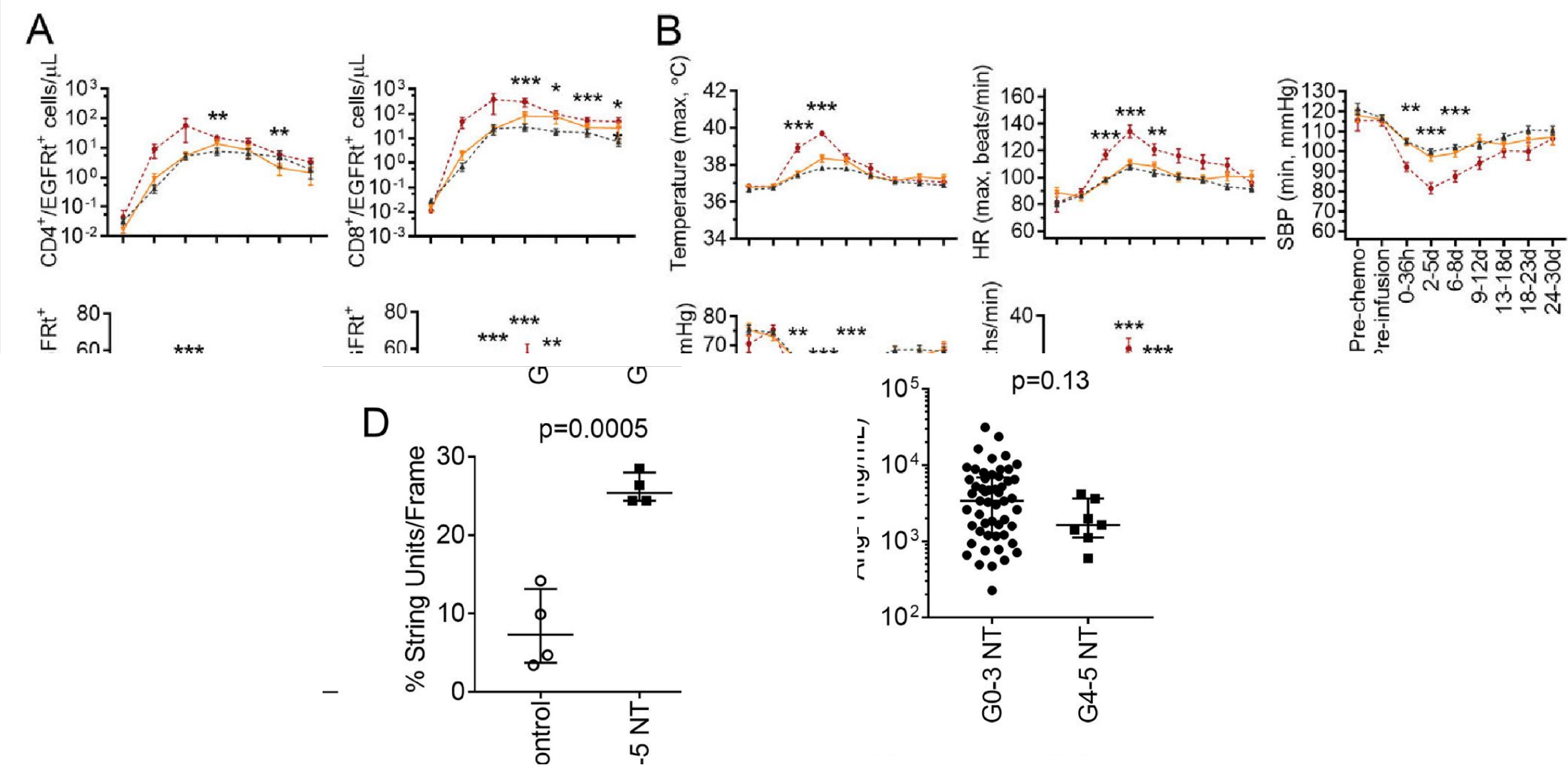
Higher mEASIX was associated with

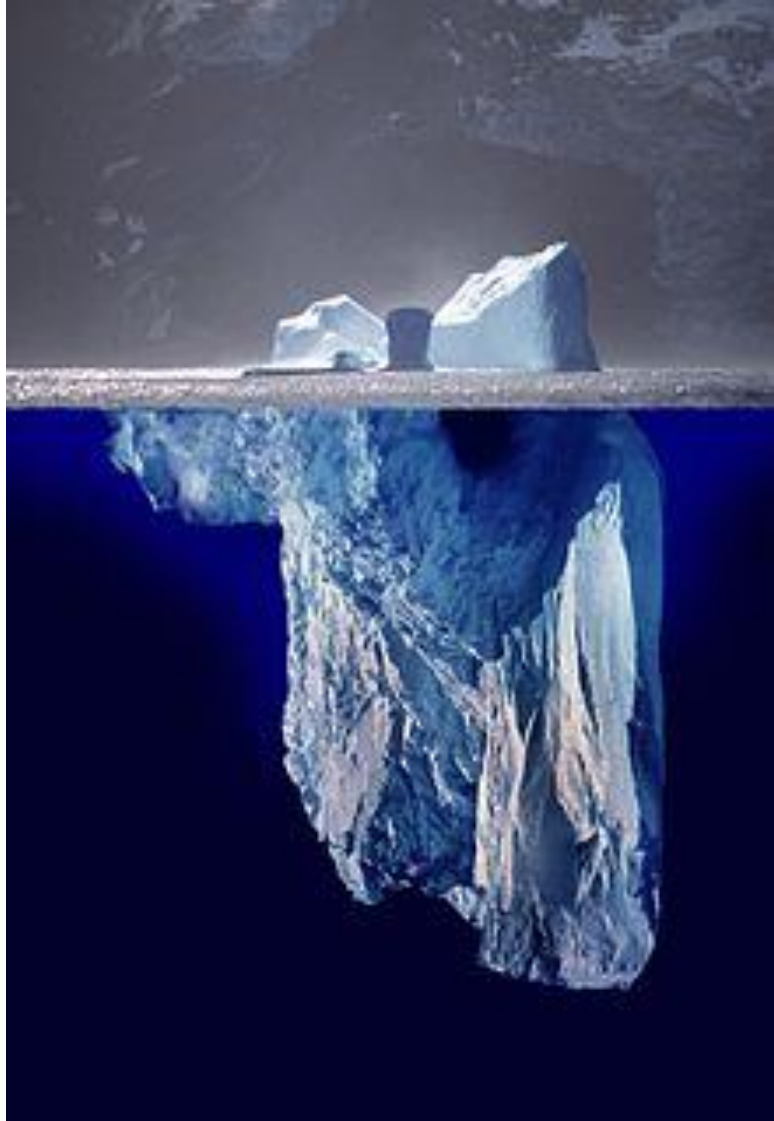
- Coagulopathy parameters
- Higher CRS severity
- Worse prognosis

# Relative hypercoagulation induced by suppressed fibrinolysis after tisagenlecleucel infusion in malignant lymphoma



# Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells





## CAR-T CELL INDUCED COAGULOPATHY

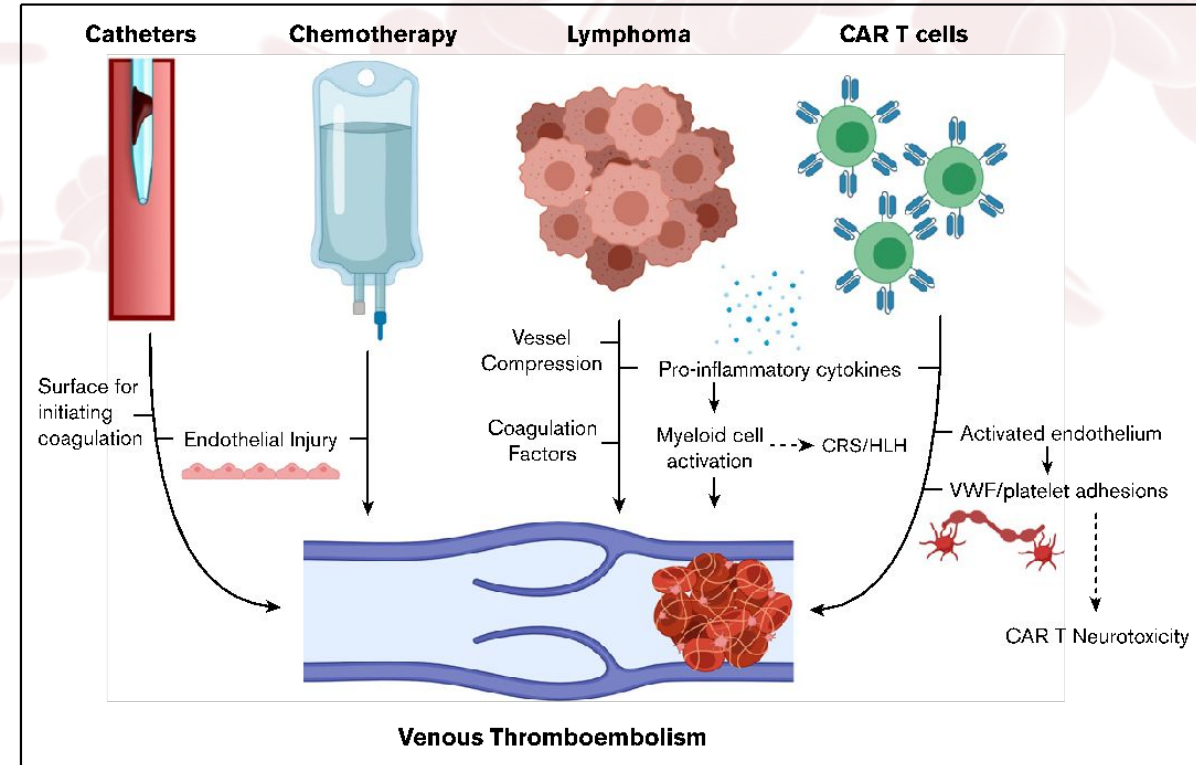
- In more than 50% of the patients
- Correlated with CRS and ICANS
- Primary and secondary hemostasis
- Key role for endothelium

# Venous thromboembolism associated with CD19-directed CAR T-cell therapy in large B-cell lymphoma

VTE 11%

- Bulky disease
- Use of bridging therapy
- Poor PS
- Severe CRS
- Severe neurotoxicity

No relation with coagulopathy  
No bleeding despite anticoagulation



**Figure 1. Mechanisms of VTE in patients with lymphoma receiving CAR T-cell therapy.** HLH, hemophagocytic lymphohistiocytosis. Created with BioRender.com, adapted from elsewhere.<sup>11-13</sup>

N=127. DLBCL/ALL

- 89: Axi-cel
- 38: Anti-CD19/CD22

Bleeding: 12/127 = 9.4%

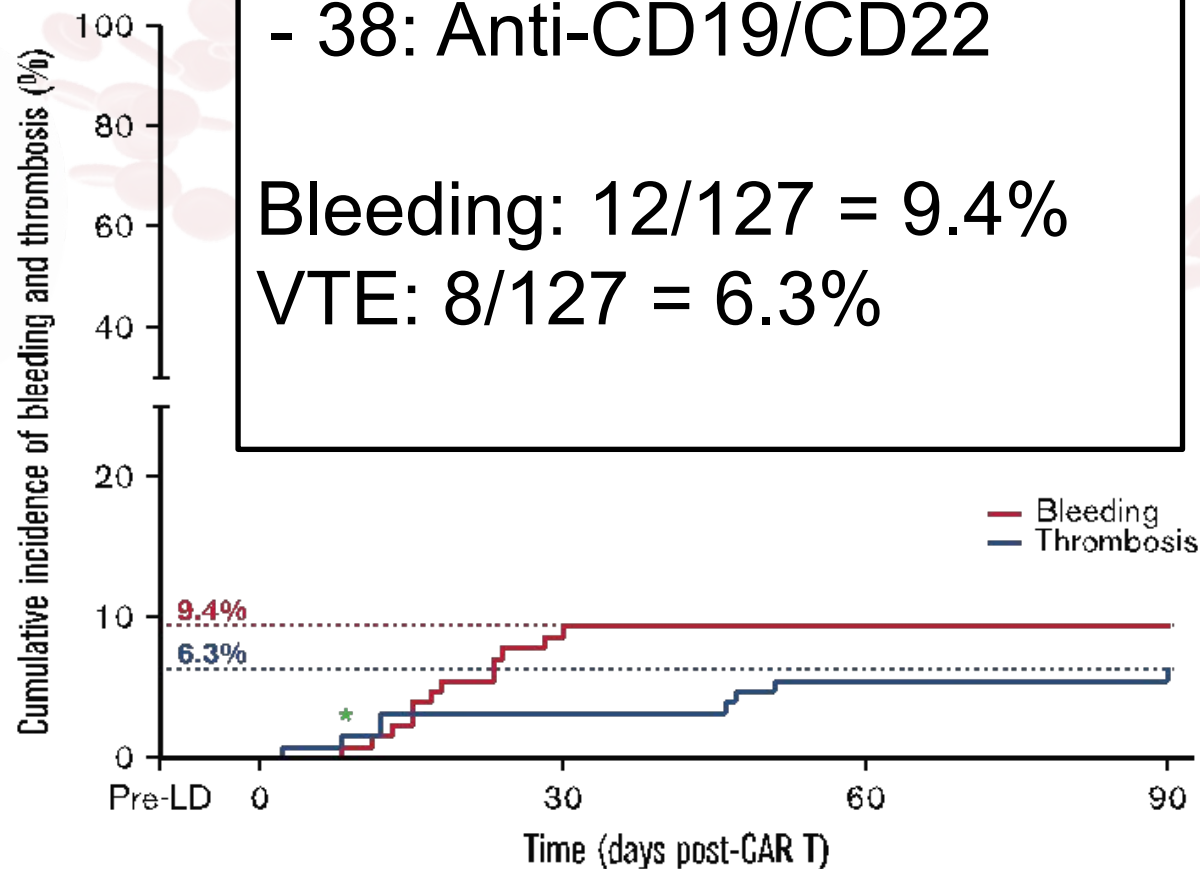
VTE: 8/127 = 6.3%

**B**

Causes of bleeding	No. of cases (%)	WHO grade
Gross hematuria	6(50)	2-3
Subdural hematoma	2(16.6)	3
Skin/Soft tissue, Musculoskeletal	2(16.6)	2-3
Gastrointestinal bleed	1(8.3)	4
Hemoptysis	1(8.3)	3

Causes of thrombosis	No. of cases (%)	CTCAE Grade
Deep venous thrombosis (DVT)	3(37.5)	2
Line-associated DVT	2(25)	2
Thrombotic stroke	1(12.5)	3
Portal vein thrombosis	1(12.5)	2
Splenic vein thrombosis	1(12.5)	2

**A**



No. at risk	127	116	116	115
No. at risk	127	125	121	120

# Laboratory abnormalities associated with bleeding and thrombosis

## Risk factors for bleeding:

- PT prolongation
- TTP prolongation
- Lower fibrinogen nadir
- **Lower platelet nadir**
- Lower monocyte count
- Higher ferritin peak

**History of bleeding (25% vs 5%)**

**Anticoagulation did not increase the risk of bleeding**

## Risk factors for thrombosis:

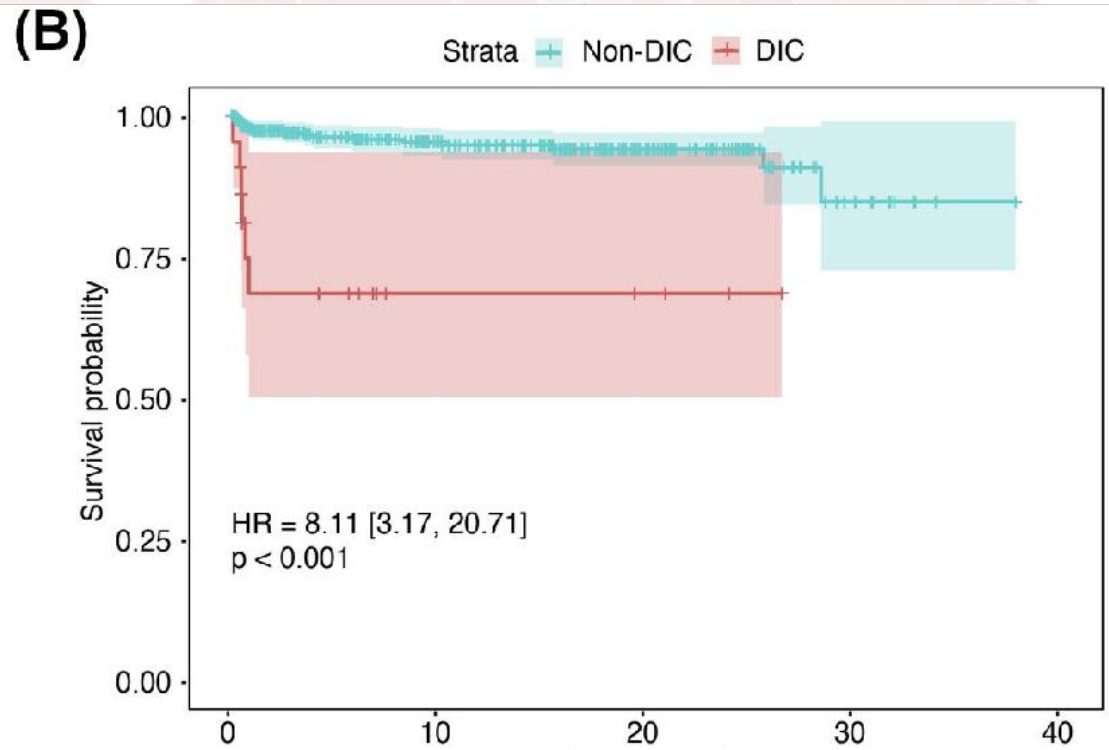
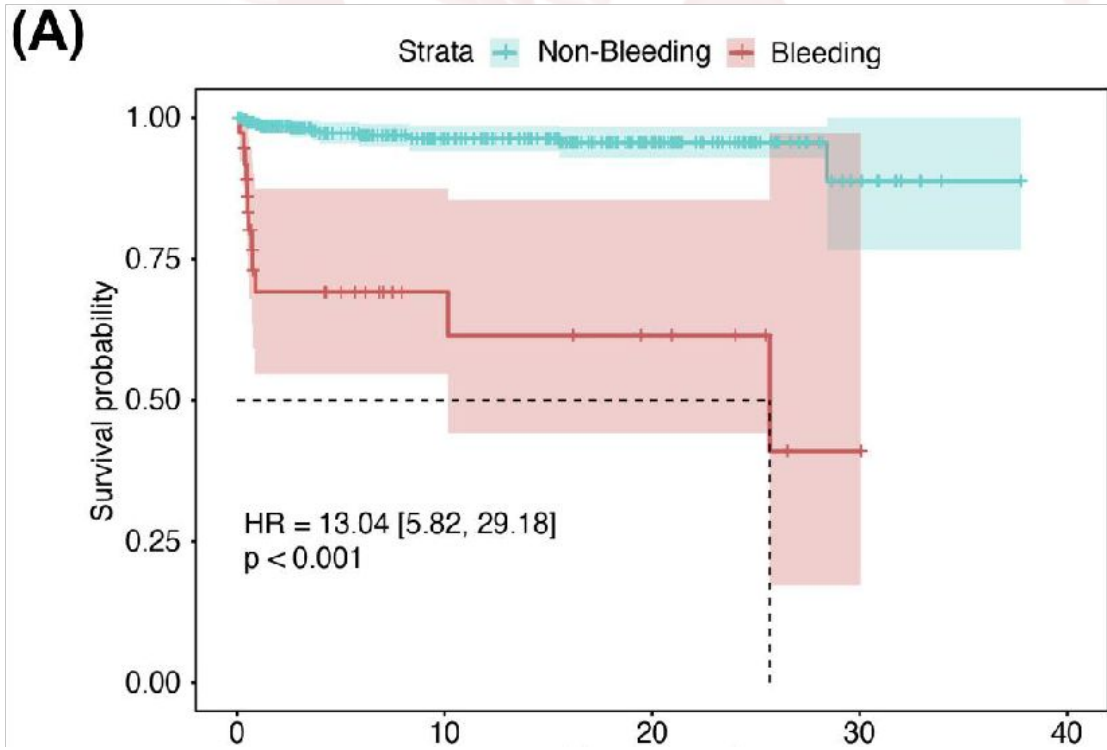
- No differences in laboratory values

**History of thrombosis (12% vs 5%)**

**Table 3. Association of CRS and ICANS with incidence of adverse bleeding and thrombosis events**

	Total (N = 127)	Bleeding		P	Thrombosis		P
		Yes (n = 12)	No (n = 115)		Yes (n = 8)	No (n = 119)	
<b>CRS maximum grade n, (%)</b>				.26			.18
Grade 0-2	124 (97.6)	11 (91.7)	113 (98.3)	–	7 (87.5)	117 (98.3)	–
Grade 3-4	3 (2.4)	1 (8.3)	2 (1.7)	–	1 (12.5)	2 (1.7)	–
<b>ICANS maximum grade n, (%)</b>				.01			.04
Grade 0-2	104 (81.9)	6 (50)	98 (85.2)	–	4 (50)	100 (84)	–
Grade 3-4	23 (18.1)	6 (50)	17 (14.8)	–	4 (50)	19 (16)	–

# TNF- $\alpha$ increases the risk of bleeding in patients after CAR T-cell therapy: A bleeding model based on a real-world study of Chinese CAR T Working Party



**TABLE 1** Multivariate analysis on risk factors for bleeding in patients undergoing CAR T-cell therapy

Variation	HR (95% CI)	p value
CRS stage, high risk vs low risk	6.07 [2.35, 16.76]	<0.001
Transfusion, Yes vs. No	3.85 [0.88, 21.57]	0.092
Blast (%), >20% vs. ≤20%	0.42 [0.14, 1.24]	0.113
Diagnosis_AL, Yes vs. No	0.67 [0.26, 1.73]	0.409
CR, Yes vs. No	0.67 [0.25, 1.73]	0.405
Hemoglobin, < 100g/L vs. ≥ 100g/L (BF-Car-T)	1.44 [0.53, 4.05]	0.481
Platelet, < 30X10 <sup>9</sup> vs. ≥ 30X10 <sup>9</sup> (BF-Car-T)	1.05 [0.32, 3.34]	0.933
APTT(s), ≥31.4 vs. < 31.4 (BF-Car-T)	1.64 [0.51, 5.46]	0.41
PT(s), ≥12.2 vs. < 12.2 (BF-Car-T)	3.10 [0.95, 10.88]	0.066
Platelet, < 30X10 <sup>9</sup> vs. ≥ 30X10 <sup>9</sup> (AF-Car-T)	1.94 [0.71, 5.32]	0.192
CRP(mg/L), ≥23.325 vs. < 23.325 (AF-Car-T)	0.61 [0.17, 2.10]	0.435
APTT(s), ≥38.42 vs. < 38.42 (AF-Car-T)	1.52 [0.45, 5.40]	0.503
PT(s), ≥13.24 vs. < 13.24 (AF-Car-T)	1.03 [0.31, 3.52]	0.966
IL-2(pg/mL), ≥4.875 vs. < 4.875	0.58 [0.17, 2.03]	0.398
IL-6(pg/mL), ≥15.09 vs. < 15.09	3.15 [0.71, 15.66]	0.141
IL-10(pg/mL), ≥5.91 vs. < 5.91	0.64 [0.19, 2.22]	0.483
TNF-α(pg/mL), ≥2.12 vs. < 2.12	4.00 [1.53, 11.35]	0.006
IFN-γ(pg/mL), ≥9.41 vs. < 9.41	1.75 [0.56, 5.84]	0.344



# How can we manage CAR-T cell associated coagulopathy?

- Prevention and early treatment of CRS / ICANS
- Monitorization of coagulation parameters

Fibrinogen replacement.  $> 1,5$  g/L

Platelet transfusion

- Pharmacologic thromboprophylaxis ??

1

Evaluated global multicenter experience with cytokine release syndrome (CRS)-associated coagulopathy following tisagenlecleucel therapy; 137 patients with relapsed or refractory B-cell acute lymphoblastic leukemia from the ELIANA and ENSIGN trials

2

Hypofibrinogenemia requiring replacement was observed only in patients with severe CRS

2.1

Patients With Grade 3 or 4 CRS: Fibrinogen Level Status

Use of fibrinogen concentrate vs cryoprecipitate is based on local availability and physician judgment

✓ KNOWN

Fibrinogen concentrate dose is based on serum fibrinogen level; should be targeted to  $\geq 1.5$  g/L and maintained until CRS grade  $< 3$

? UNKNOWN

If very-low fibrinogen is suspected and...

Minor bleeding event

30 mg/kg initial dose of fibrinogen concentrate

Major bleeding event (rare)

60 mg/kg initial dose of fibrinogen concentrate

3

Fibrinogen levels should be monitored 30 minutes after infusion in the setting of very-low fibrinogen and/or severe bleeding and, once CRS has resolved, daily for 3 days until maintained above the target

4

CRS-associated coagulopathy with hypofibrinogenemia is manageable according to empiric guidelines of fibrinogen replacement for chimeric antigen receptor (CAR)-T trials

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Melody et al. Leuk Lymph 2022 □ 55/97 patients received anticoagulation (mostly prophylactic), without bleeding events and with a very low incidence of thrombosis.

# Conclusions

## HIGH INCIDENCE OF COAGULOPATHY AFTER CAR-T CELL INFUSION

- Correlation with CRS and ICANS severity
- Hypofibrinogenemia is the most clinically significant anomaly
- Need for fibrinogen level monitorization and replacement of high grade CRS and/or ICANS develop

## BLEEDING EVENTS OCCUR IN 10% OF THE CASES

- Identification and early treatment of CRS and/or ICANS is essential
- “Agressive” fibrinogen replacement as needed

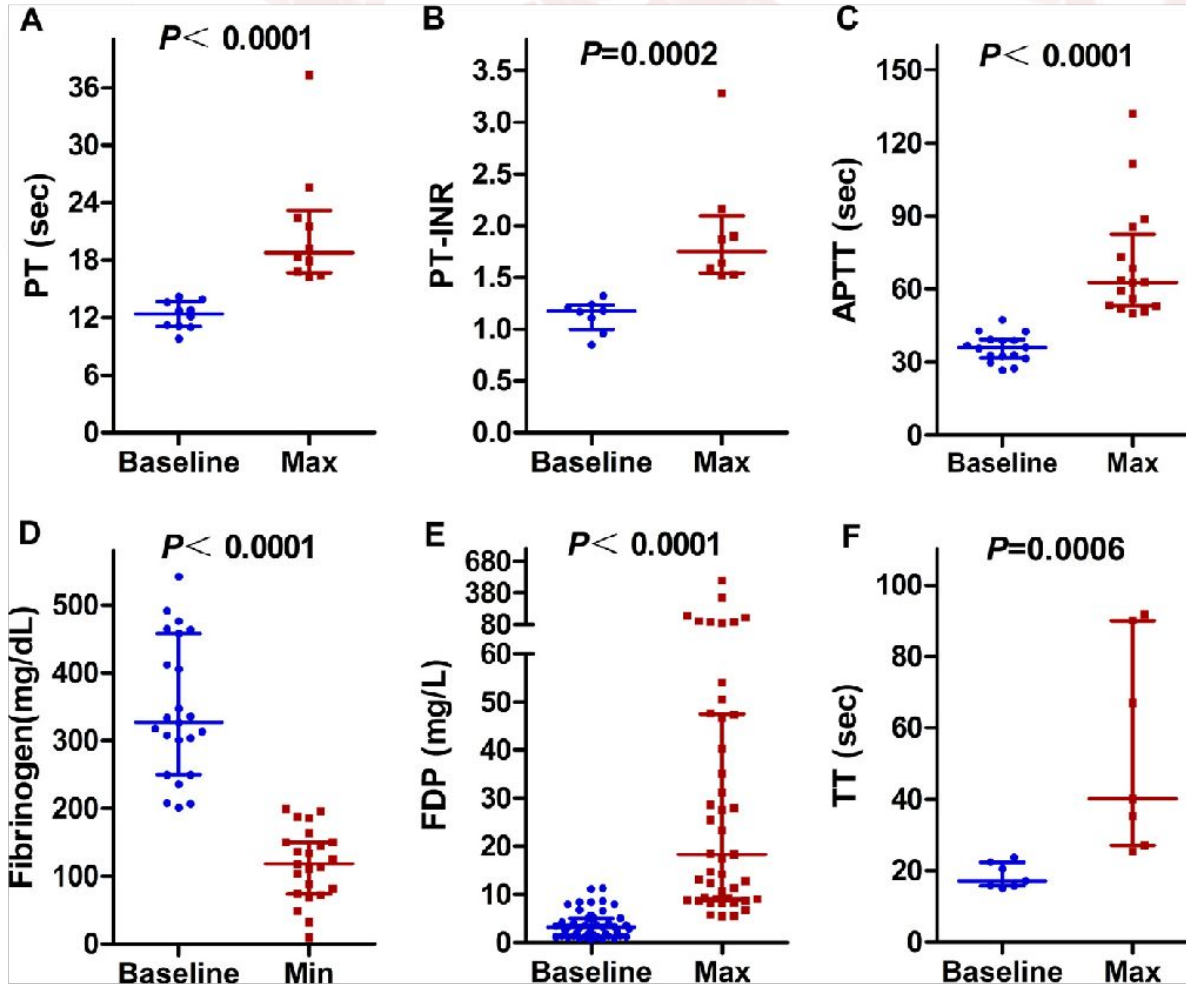
## THROMBOTIC EVENTS OCCUR IN 6% OF THE CASES

- Related with high grade CRS and/or ICANS
- Anticoagulation seems safe



Moltes gràcies  
Muito obrigada  
Thank you  
[mnomdedeu@clinic.cat](mailto:mnomdedeu@clinic.cat)

# Coagulation Disorders after Chimeric Antigen Receptor T Cell Therapy: Analysis of 100 Patients with Relapsed and Refractory Hematologic Malignancies



Day 6-20 after infusion

Coagulopathy is associated with:

- High tumour burden (ALL)
- More lines of previous therapy
- Lower baseline platelets
- Cytokine release syndrome

DIC in 7 patients with grade 3 CRS