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# CAR-T CELL THERAPY

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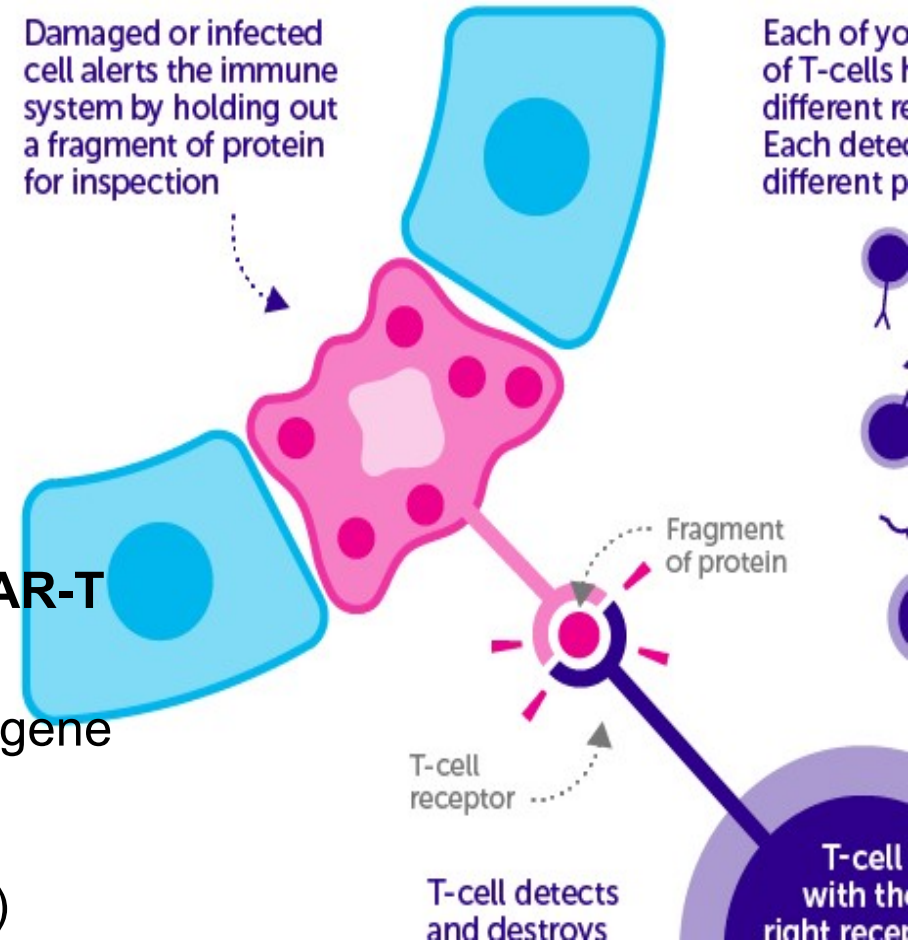
# STRUCTURE

- What is CAR-T cell therapy?
- Side effects
- Who is eligible for it?
- Patient journey
- Mortality and remission
- The future of CAR-T

# WHAT IS CAR-T THERAPY?

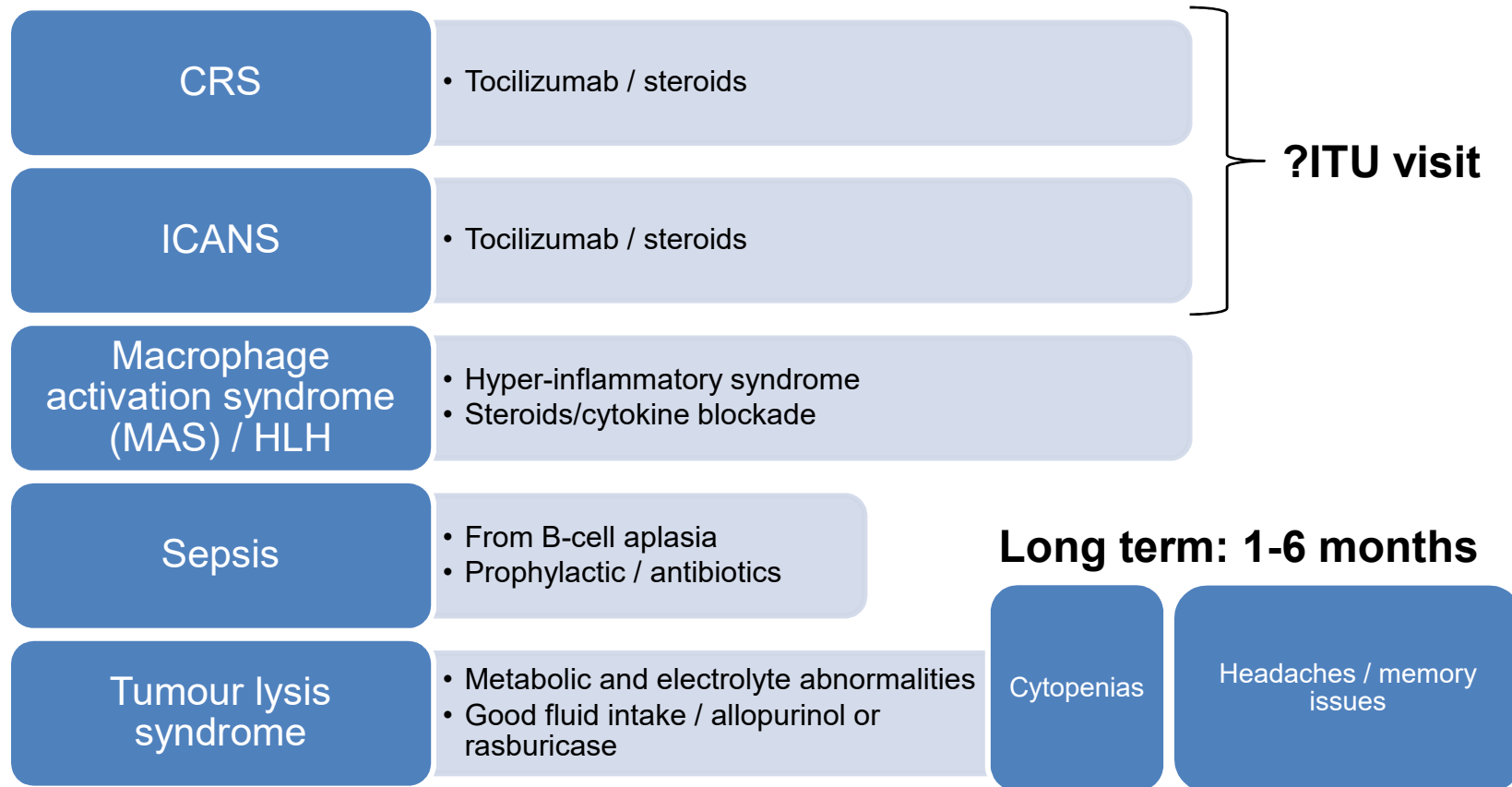
- A new, promising approach
- How does it work?
- Two companies that make the CAR-T cells commercially in the UK:
  - KITE Gilead makes “Axicabtagene Ciloleucel” (“Axi-cel”)
  - NOVARTIS makes “Tisagenlecleucel” (“Tisagen”)

## IDENTIFYING THE ENEMY



# SIDE EFFECTS / RISKS

- **Highly complex and risky procedure**



# CRS

## (CYTOKINE RELEASE SYNDROME)

- **Systemic inflammatory response**
  - Causes **reversible** end organ damage
- **Onset:** usually day 1 – 15
- **Duration:** from 1-10 days
  
- CRS Score → **Grades 1-4**
- When **pyrexial** – blood cults and abx as per protocol,  
**Tocilizumab, Steroids** if further deterioration after tocilizumab,  
**anakinra**

# ICANS

## (IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY SYNDROME)

- Typically manifests as a **toxic encephalopathy**
  - *Word finding difficulty, confusion, disorientation, agitation, dysphasia, aphasia, somnolence, tremors, impaired handwriting, seizures, motor weakness, incontinence, papilloedema, cerebral oedema*
- Generally **reversible** with **no permanent neurological deficits**
- **Onset:** day 1 – 34
- **Duration:** from a few hours to several days
- **Grades 1 – 4**
- **Steroids +/- tocilizumab +/- anakinra** (+EEG, CT head, anti-epileptics)

# Impaired handwriting - neurotoxicity

Day 4  
9 am

I love Shawnee, KS.

MMSE score  
29/30

Day 5  
01:30 PM

Toci 8 mg/kg

Shawnee is a ~~great~~  
city

27/30

Day 5  
03:30 PM

I'm sure ~~about~~  
177.

27/30

Day 6  
9 am

I miss my kids.

29/30

# LONG TERM CONSIDERATIONS



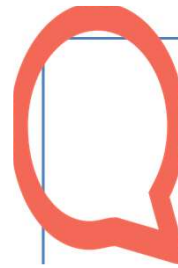
Prolonged  
cytopenias



Longer-term side  
effects unclear



Psychological  
support



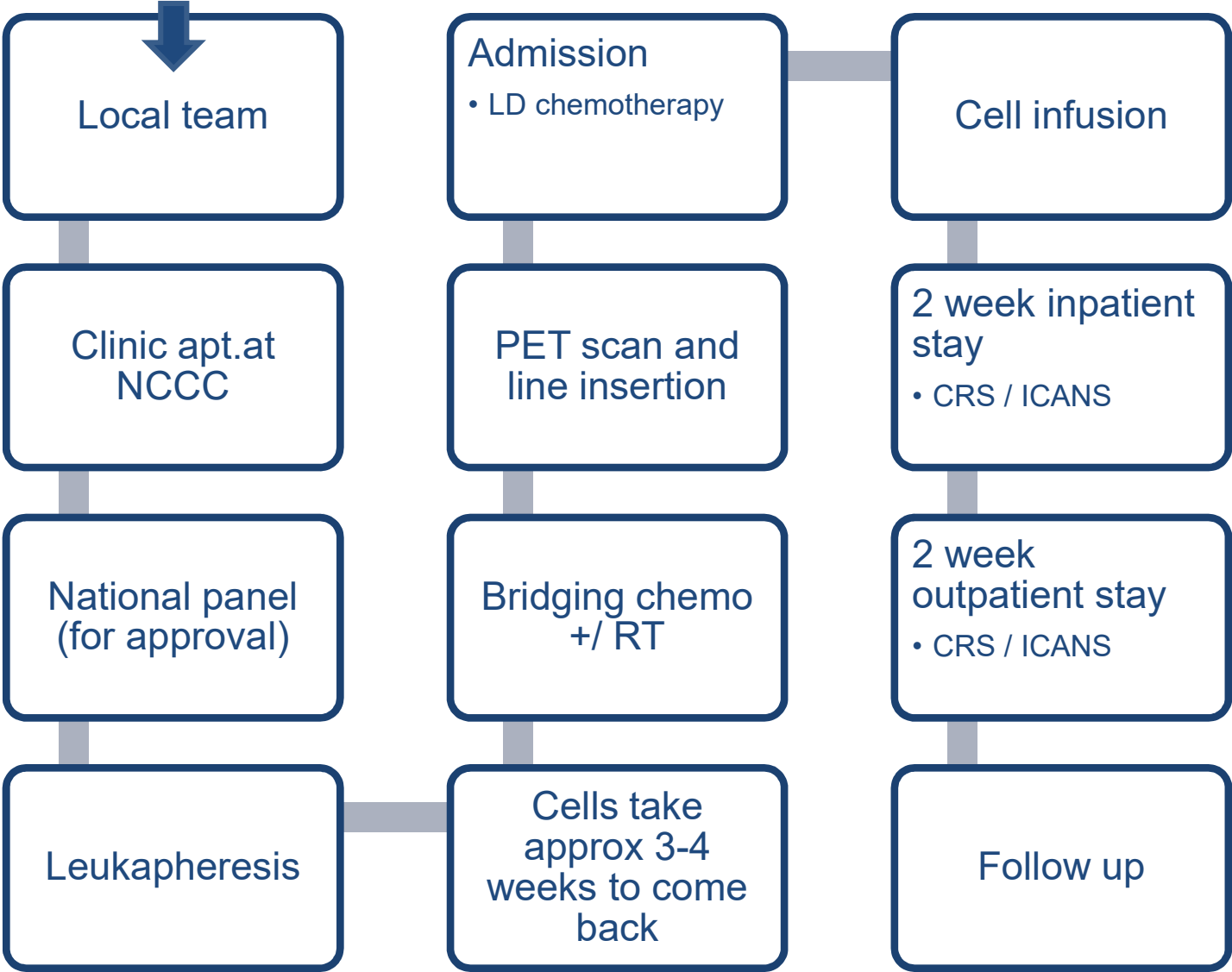
Clinical picture can  
change very quickly



# WHO IS ELIGIBLE?

- **Adults with B cell lymphoma / those under 25 with ALL**
- **Must** have had 2 lines of failed / relapsed systemic treatment
  - this does not include radiotherapy but may include transplant
- **Consider:** fitness, disease and treatment stage.
- **Need to make sure the patient understands the risks and benefits of having the treatment and patient is aware of chances of success.**

# PATIENT JOURNEY

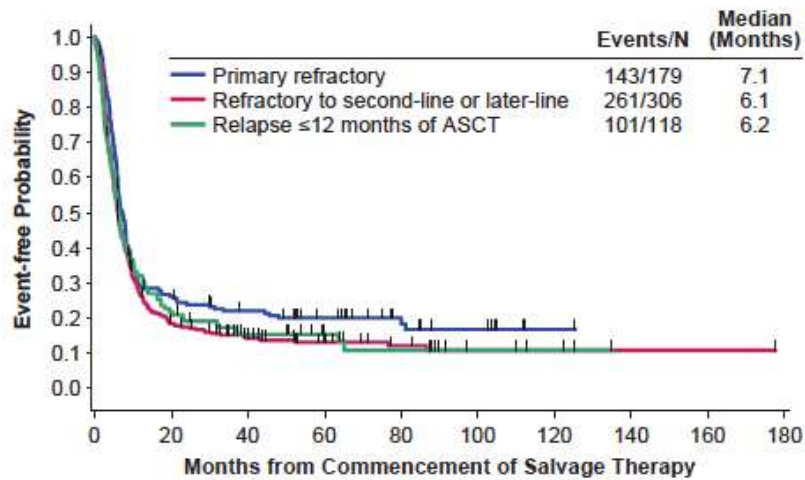


# MORBIDITY AND MORTALITY

- **Baseline:** SCHOLAR-1
- **Trials:** ZUMA and JULIET
- Comparing data from **different countries**

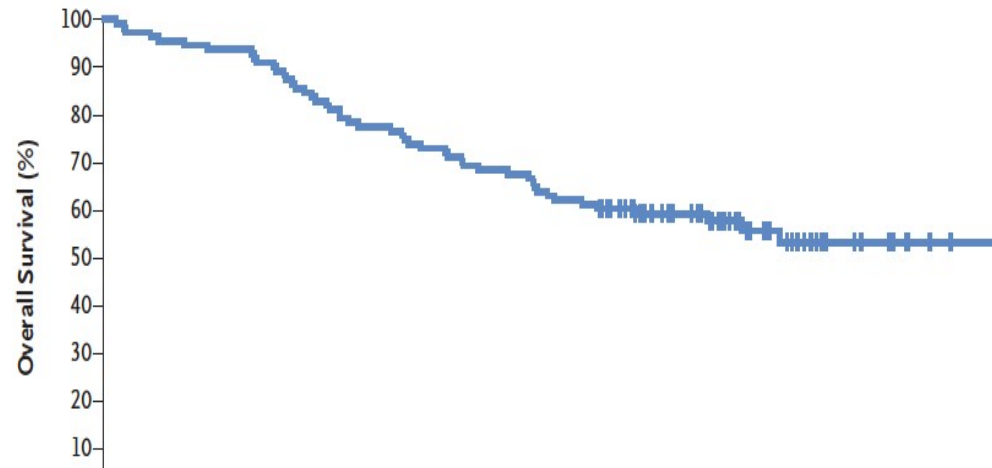
# TRIAL OUTCOMES

Overall survival: SCHOLAR-1<sup>1</sup>



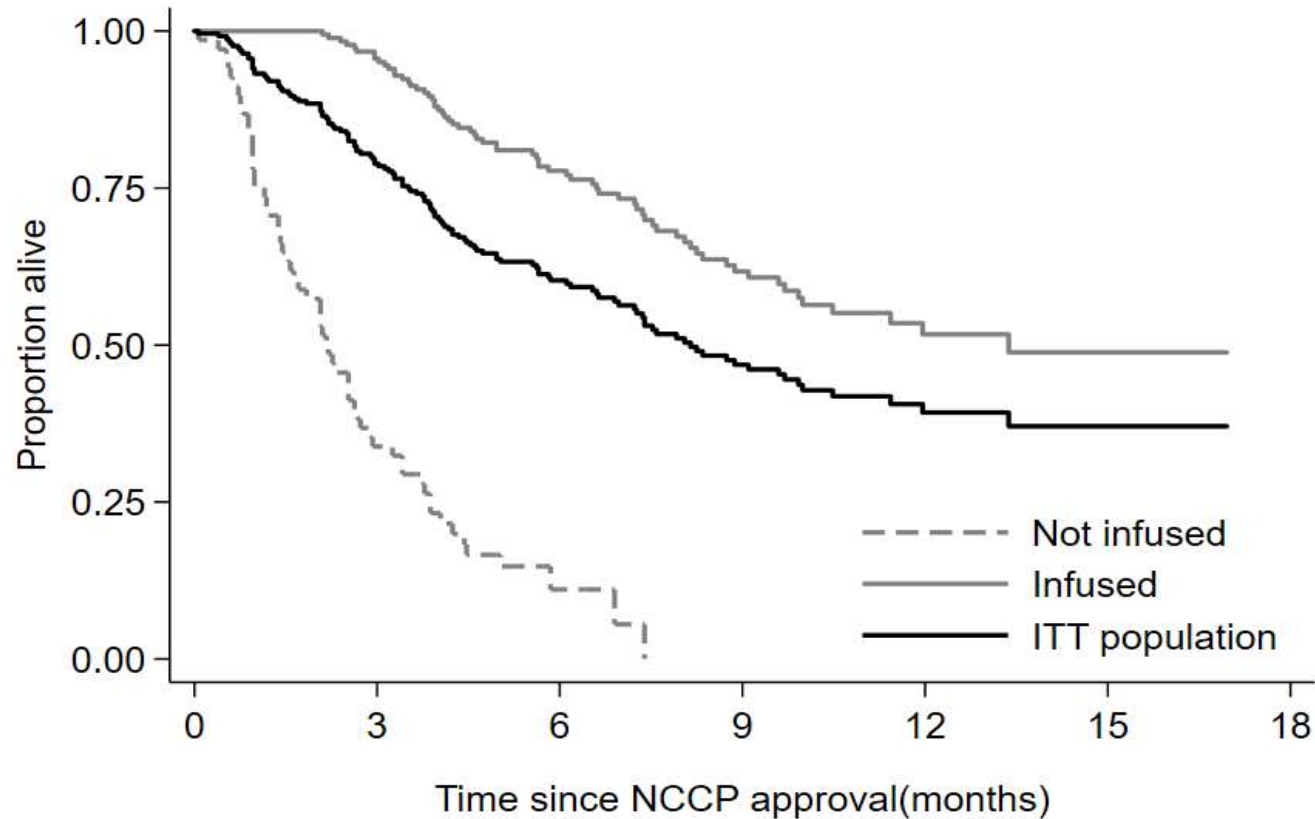
- N = 636
- ORR: 26%; CR rate: 7%
- Median OS: 6.3 months

Overall survival: ZUMA-1<sup>2</sup>



- N = 108
- ORR: 82%; CR rate: 58%
- Median OS: ≥18 months

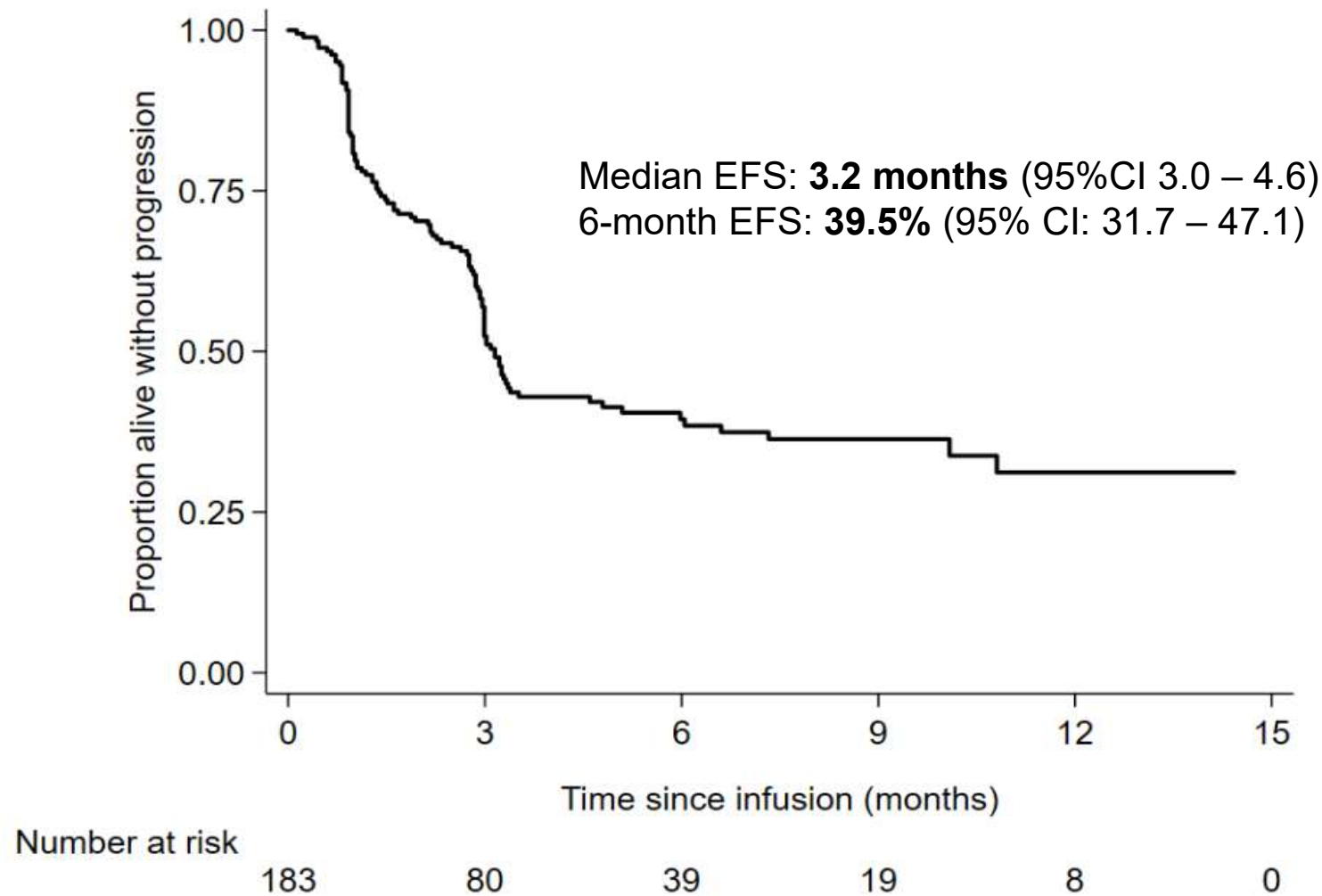
# UK OVERALL SURVIVAL OF PATIENTS APPROVED FOR CAR-T



Number at risk		0	3	6	9	12	15	18
Not infused	70	23	3	0	0	0	0	0
Infused	183	175	112	64	29	6	0	0
ITT population	253	198	115	64	29	6	0	0

# EVENT-FREE SURVIVAL OF INFUSED PATIENTS

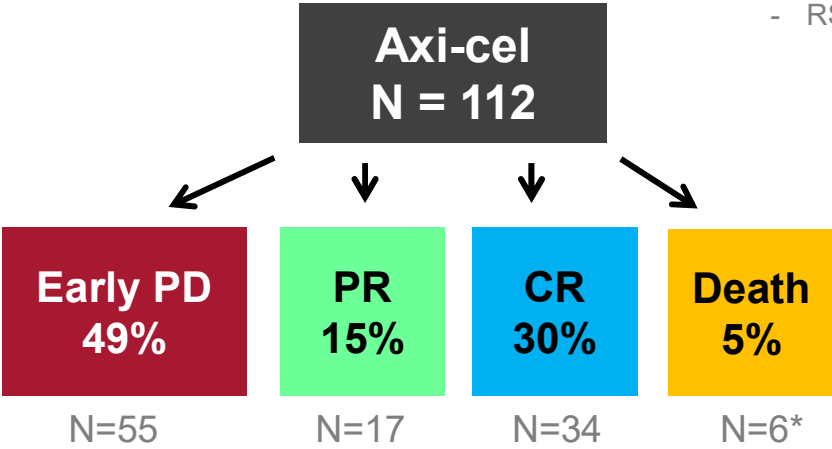
- “Events“:
- Radiological progression
  - Clinical progression
  - Start of new treatment



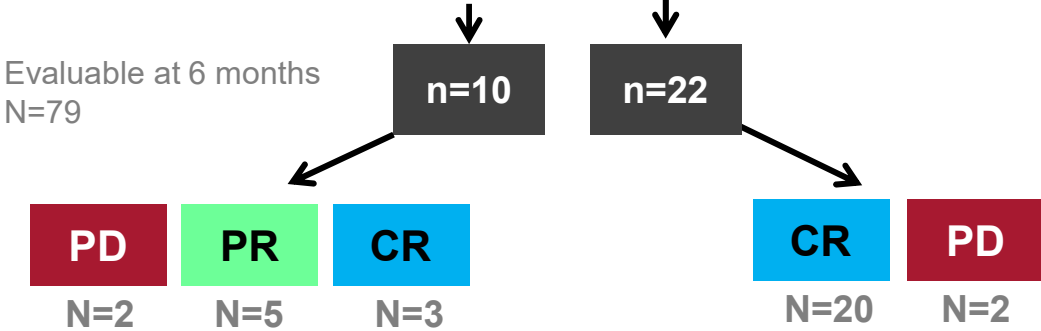
# EHA DATA: TREATMENT RESPONSE

- \*Non-relapse mortality**
- Sepsis (D+18)
  - Heart failure (D+25)
  - Bowel perforation (D+27)
  - Bowel ischaemia (D+41)
  - Sepsis/HLH (D+46)
  - RSV pneumonia (D+76)

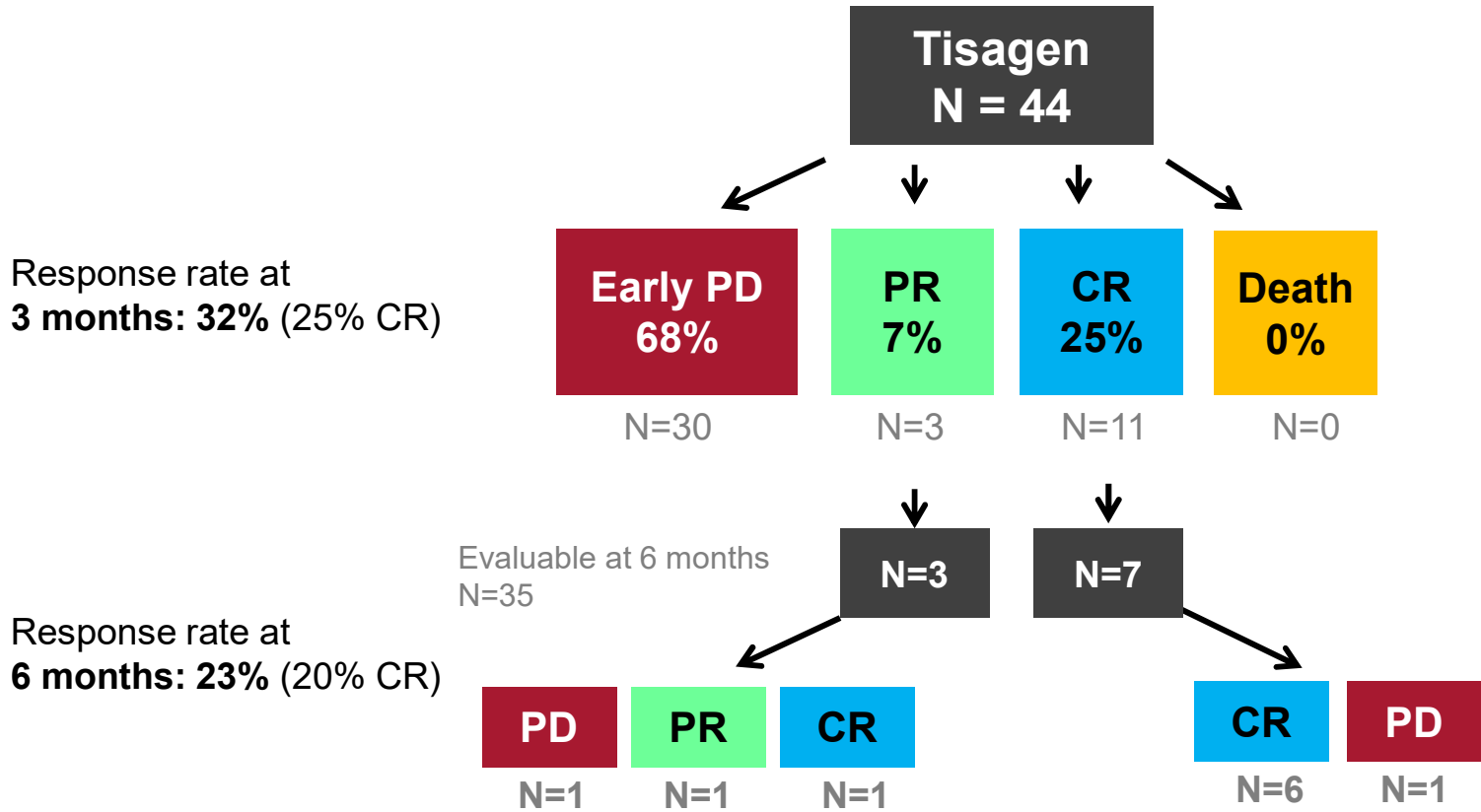
Response rate at 3 months: 45% (30% CR)



Response rate at 6 months: 35% (29% CR)



# EHA DATA: TREATMENT RESPONSE



A.Kuhnl; EHA data courtesy of Dr Menne: not for replication



# UK TREATMENT TOXICITY

	ZUMA-1	JULIET	NHSE
G3+ CRES/ICANS,* %	28	12	13
G3+ CRS,* %	13	22	11
TRM, %	4	0	2
Tocilizumab use, %	43	14	65
Steroids use, %	27	10	29
ICU, %	not known	24	34
G3+ cytopenia, 3 months, %			n=48
Neutropenia	11	0	19
Thrombocytopenia	7	38	19

\*different grading systems; NHSE data based on ASTCT 2019 criteria

# THE FUTURE

## Trials

- Mantle cell lymphoma
- Solid tumours – NAR-T
- Lisocel CAR-T's
- ALLOGENEIC CAR-Ts  
/ 'Off-the-shelf' CAR-Ts
- AUTO 1,3,4

## Services

- More UK centres
- Ambulatory care unit
- Parallel planning & managing expectations
- Better education for staff, patients and families
- Updates from me

## References:

Neelapu SS et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018 Jan;15(1):47-62. doi: 10.1038/nrclinonc.2017.148. Epub 2017 Sep 19.

Ibrahim Yakoub-Agha et al. *Haematologica* 2020;105:297-316  
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MMSE, mini mental status exam; Toci, tocilizumab.  
Neelapu SS et al. *Nat Rev Clin Oncol* 2018; 15:47-62

D.W. Lee et al. / *Biol Blood Marrow Transplant* 25 (2019) 625\_638  
Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

<https://www.bbmt.org/action/showFullTableHTML?isHtml=true&tableId=tbl0004&pii=S1083-8791%2818%2931691-4>