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CAR-T CELL THERAPY

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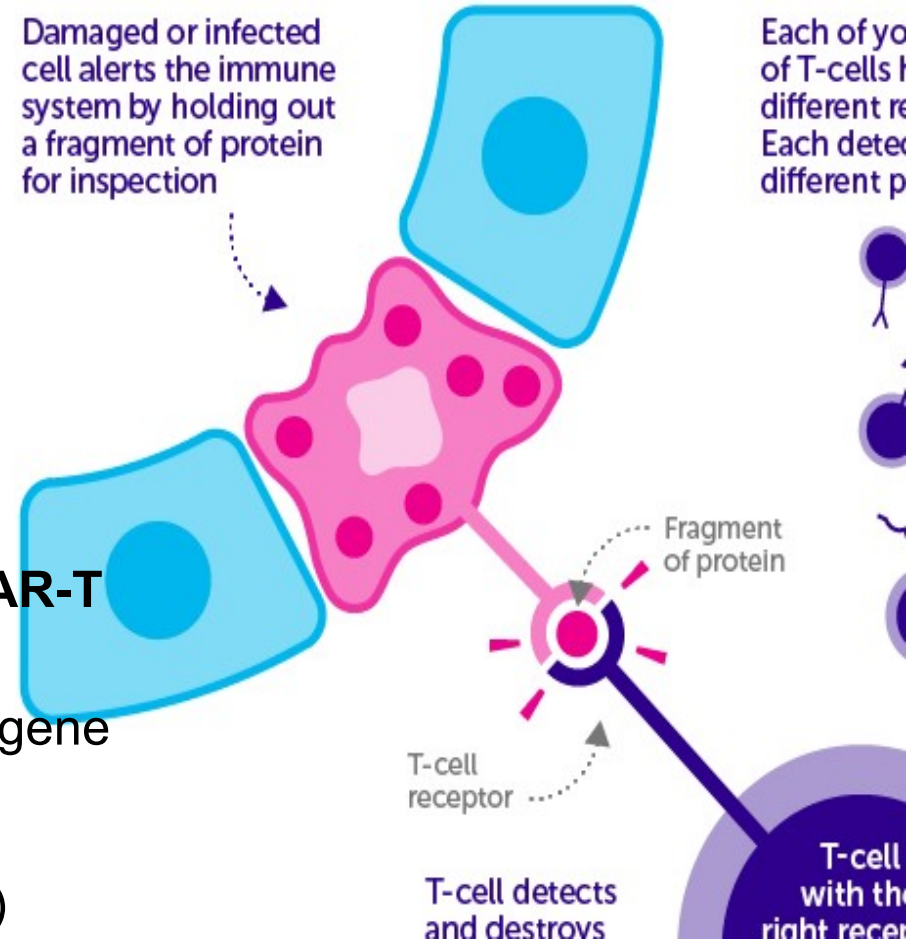
STRUCTURE

- 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?

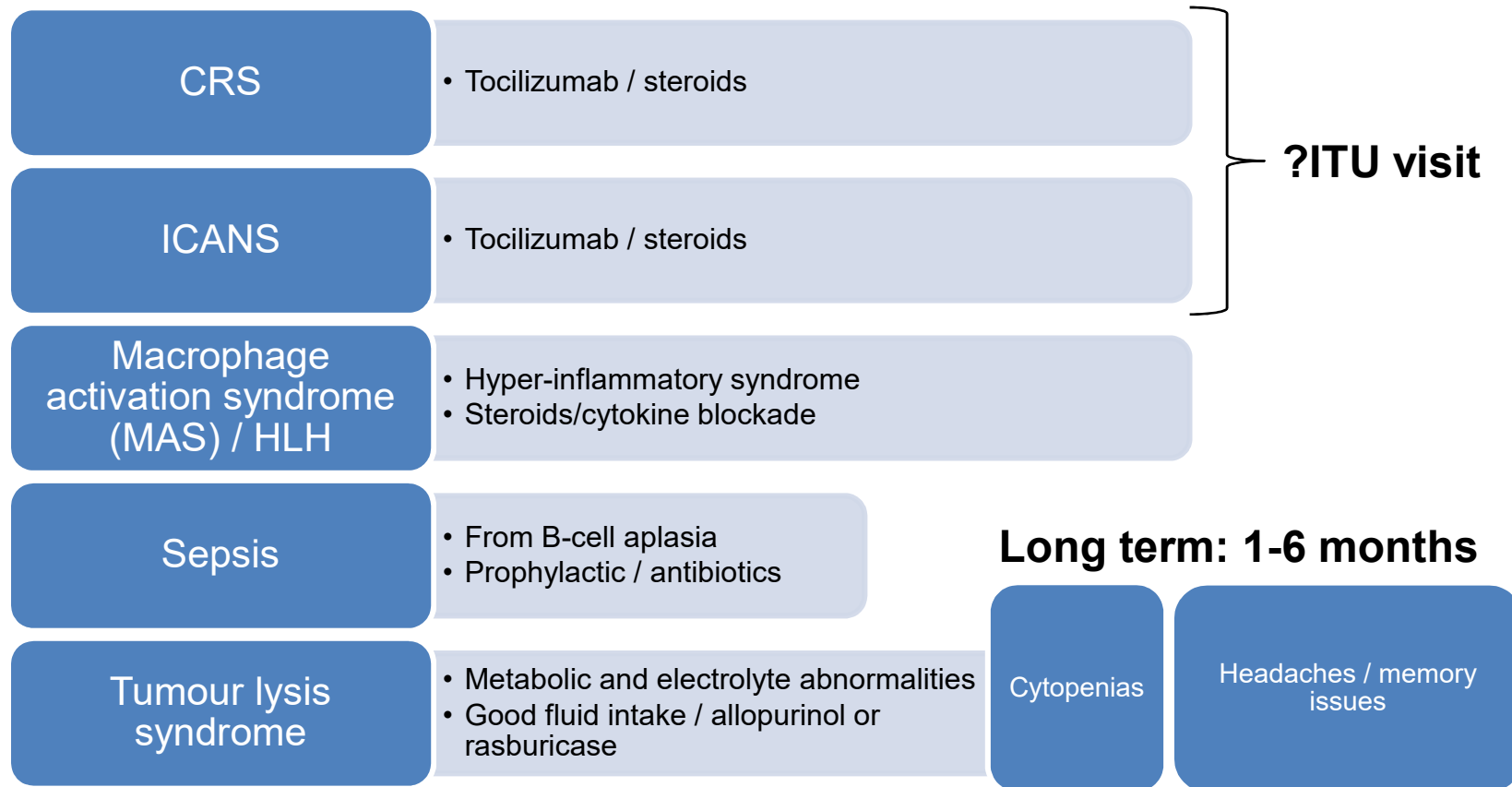
- A new, promising approach
- How does it work?
- Two companies that make the CAR-T cells commercially in the UK:
 - KITE Gilead makes “Axicabtagene Ciloleucel” (“Axi-cel”)
 - NOVARTIS makes “Tisagenlecleucel” (“Tisagen”)

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



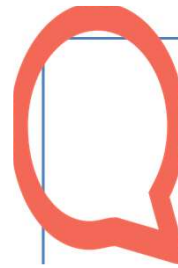
Prolonged
cytopenias



Longer-term side
effects unclear



Psychological
support

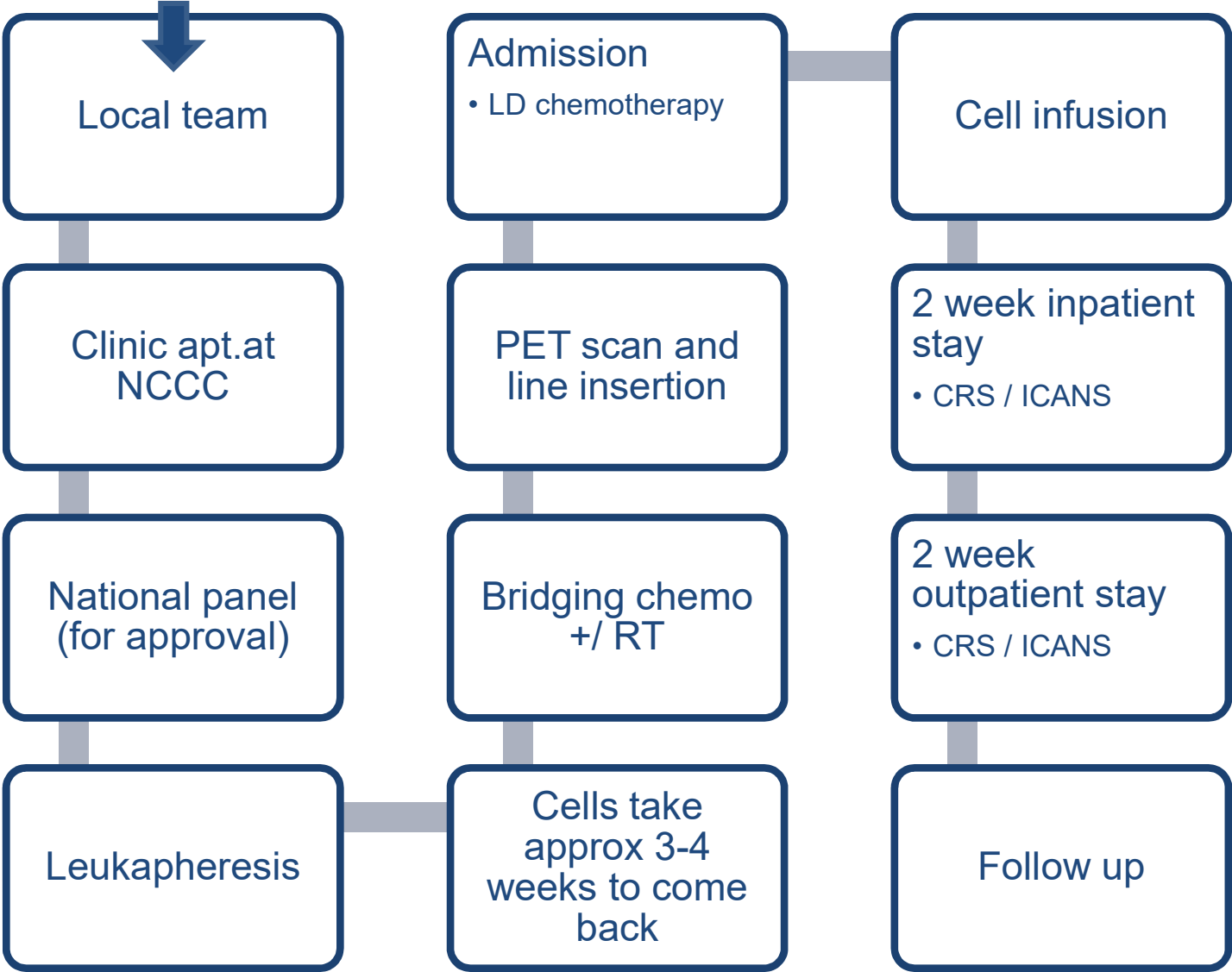


Clinical picture can
change very quickly

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

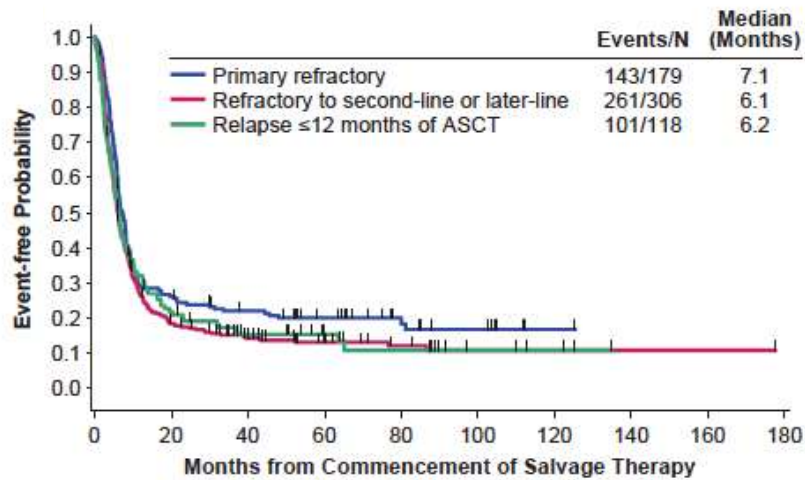


MORBIDITY AND MORTALITY

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

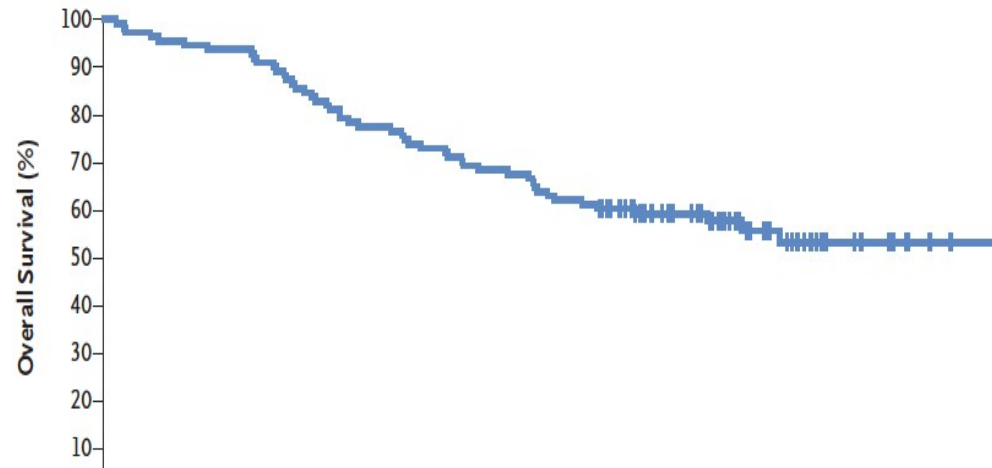
TRIAL OUTCOMES

Overall survival: SCHOLAR-1¹



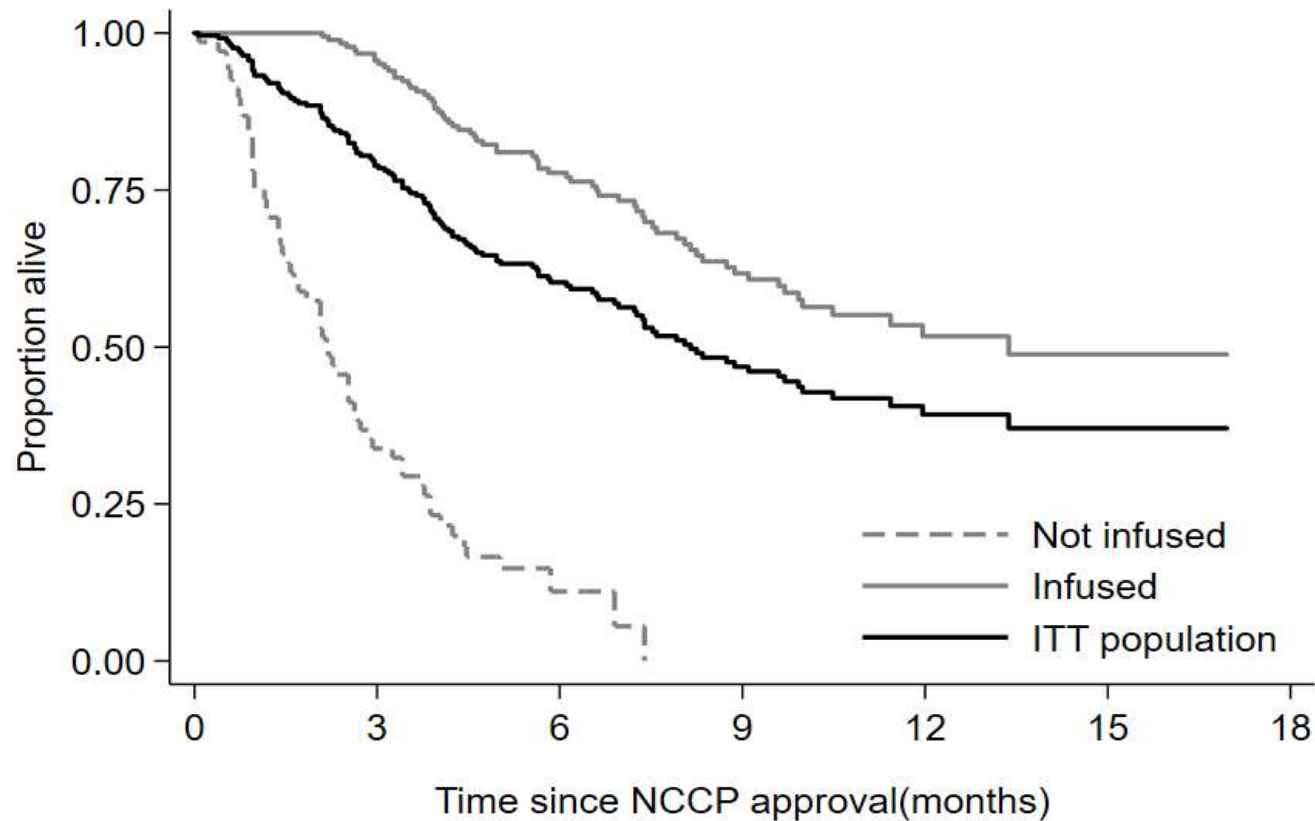
- N = 636
- ORR: 26%; CR rate: 7%
- Median OS: 6.3 months

Overall survival: ZUMA-1²



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

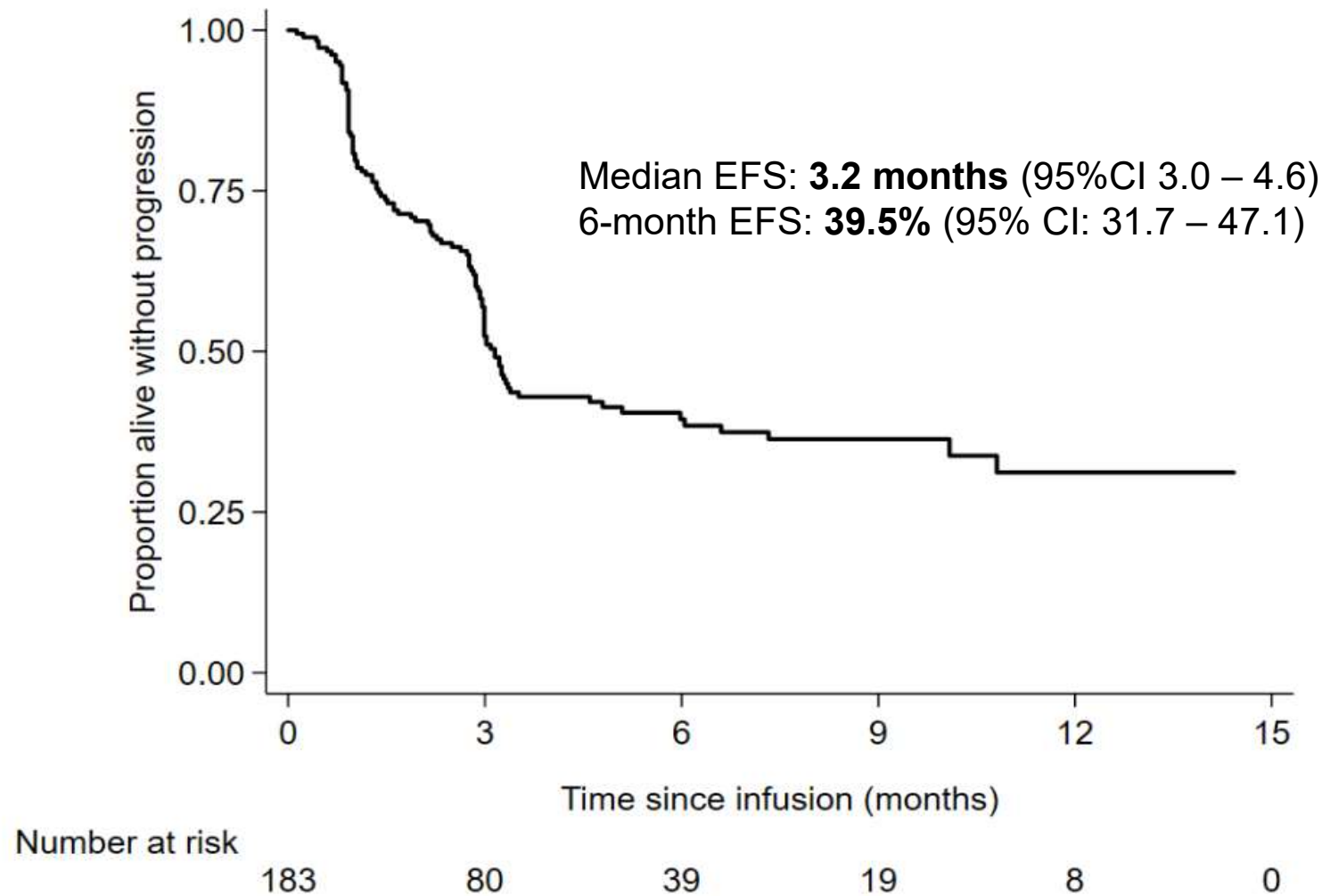
UK OVERALL SURVIVAL OF PATIENTS APPROVED FOR CAR-T



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

EVENT-FREE SURVIVAL OF INFUSED PATIENTS

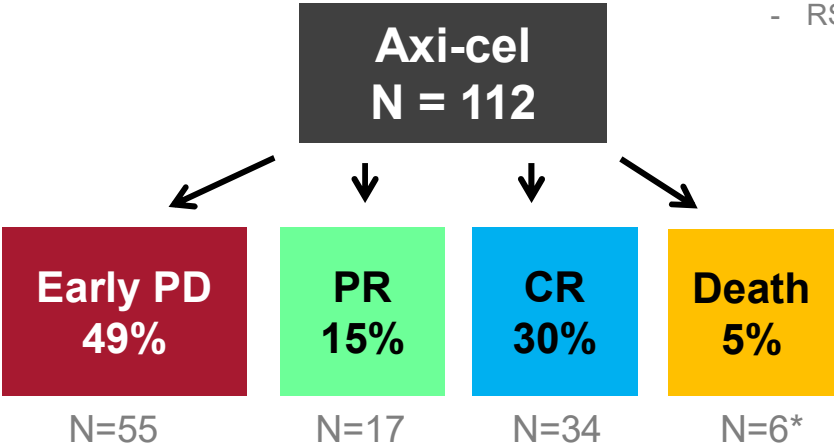
- “Events“:
- Radiological progression
 - Clinical progression
 - Start of new treatment



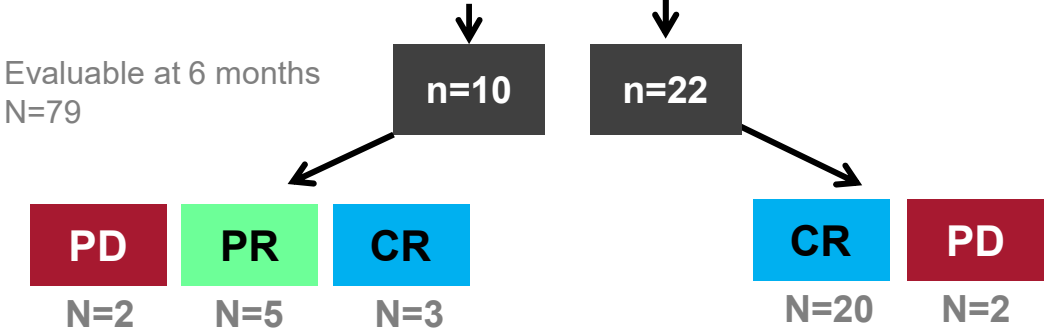
EHA DATA: TREATMENT RESPONSE

- *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)

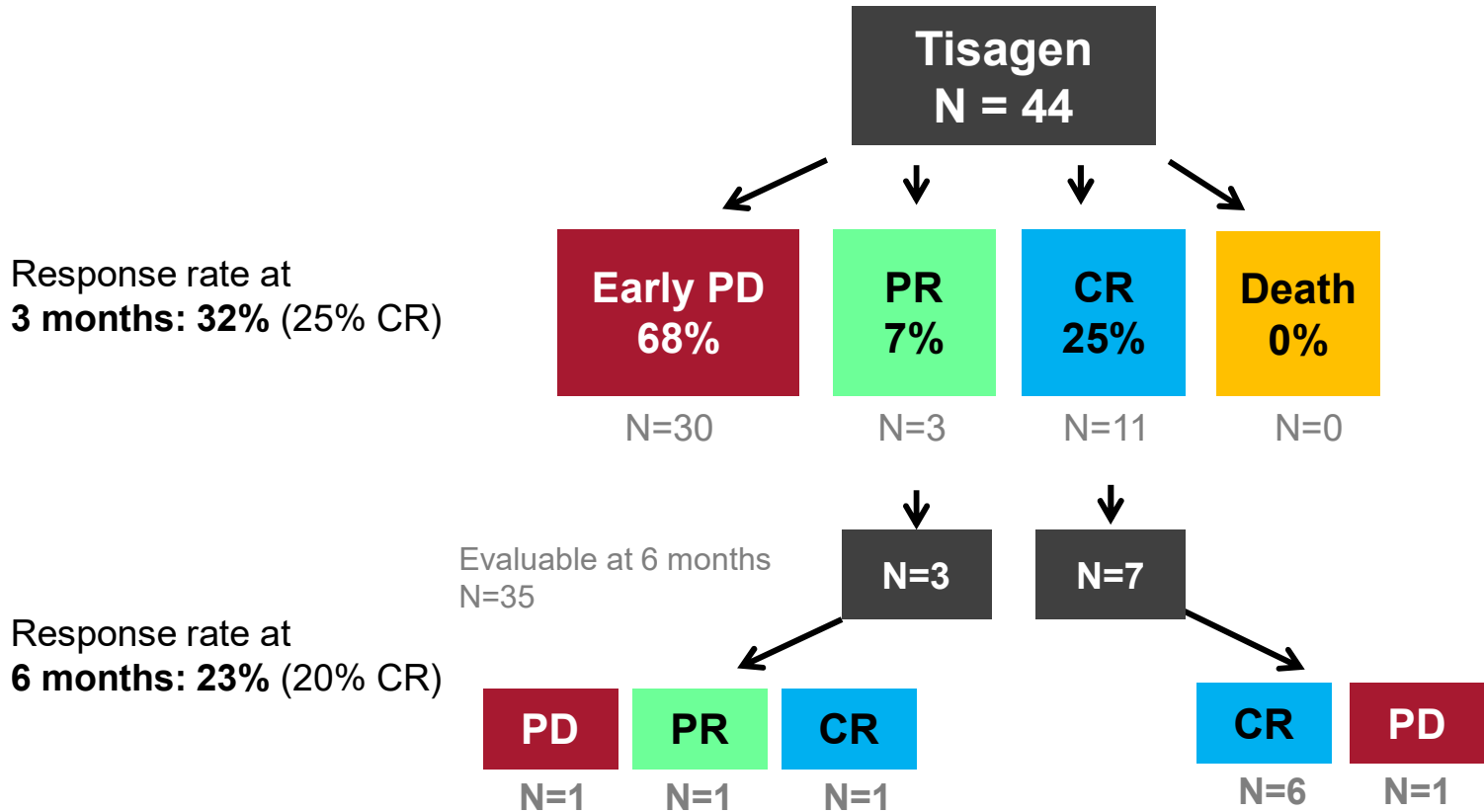
Response rate at 3 months: 45% (30% CR)



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>