

# T-cells and cancer

Nuria Martinez-Cibrian  
Consultant Haematologist  
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# Overview

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Introduction

CAR structure

Toxicities

Management

Outcomes

Relapses

Conclusions

# Introduction

## First child given pioneering CAR-T cancer therapy



Fergus Walsh  
Medical correspondent  
@BBCFergusWalsh

31 January 2019



## 'Living drug' offers hope to terminal blood cancer patients

By James Gallagher  
Health and science correspondent, BBC News

21 June 2019



# Introduction

## Immunotherapy

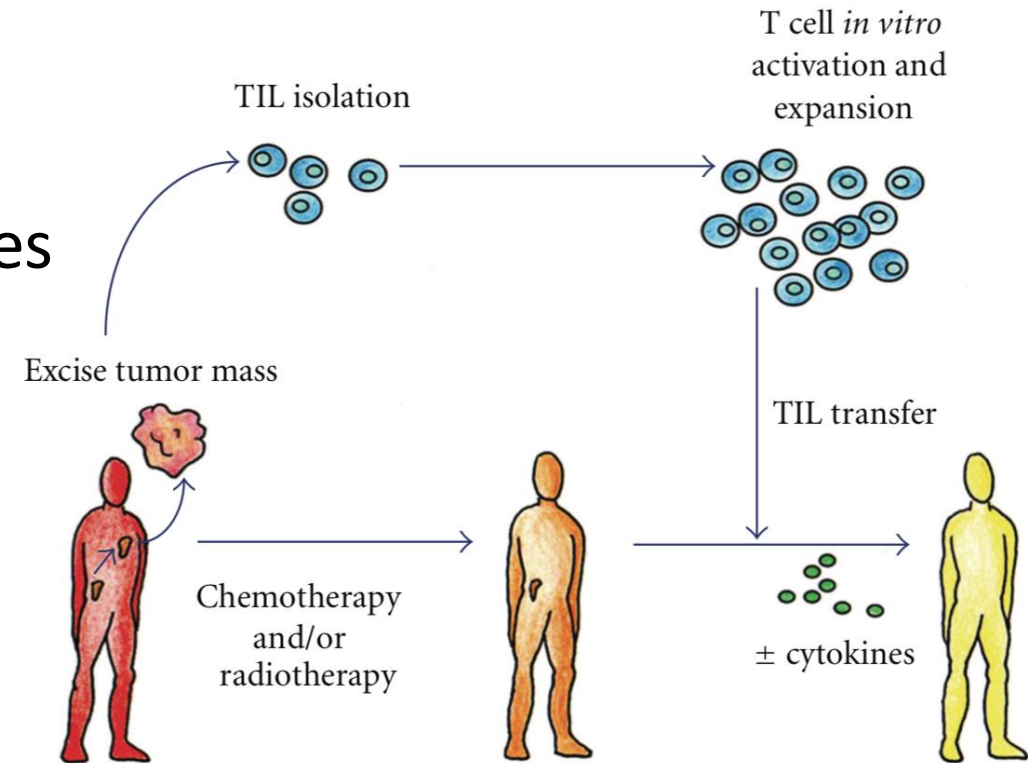
### Adoptive T cell therapy

Tumour infiltrating lymphocytes

TCR engineer T cells

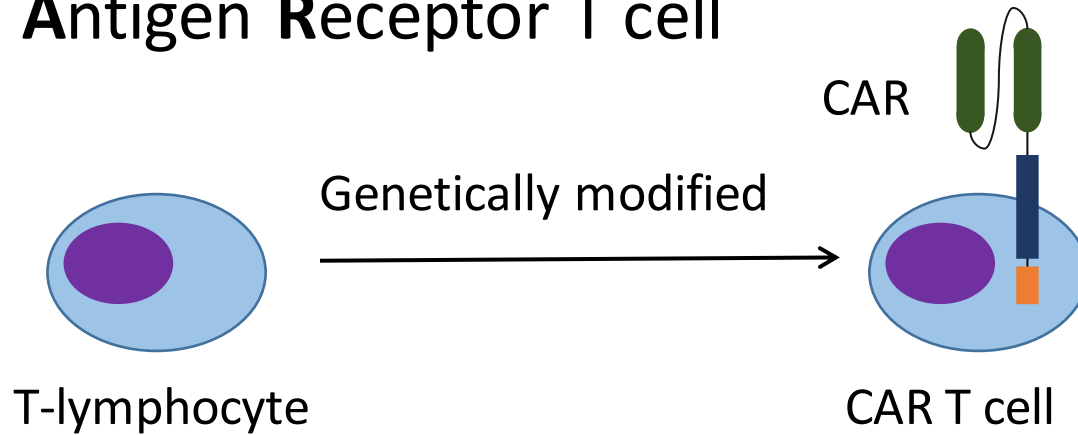
CAR T cells

Tumour mediated immunosuppression



# Introduction

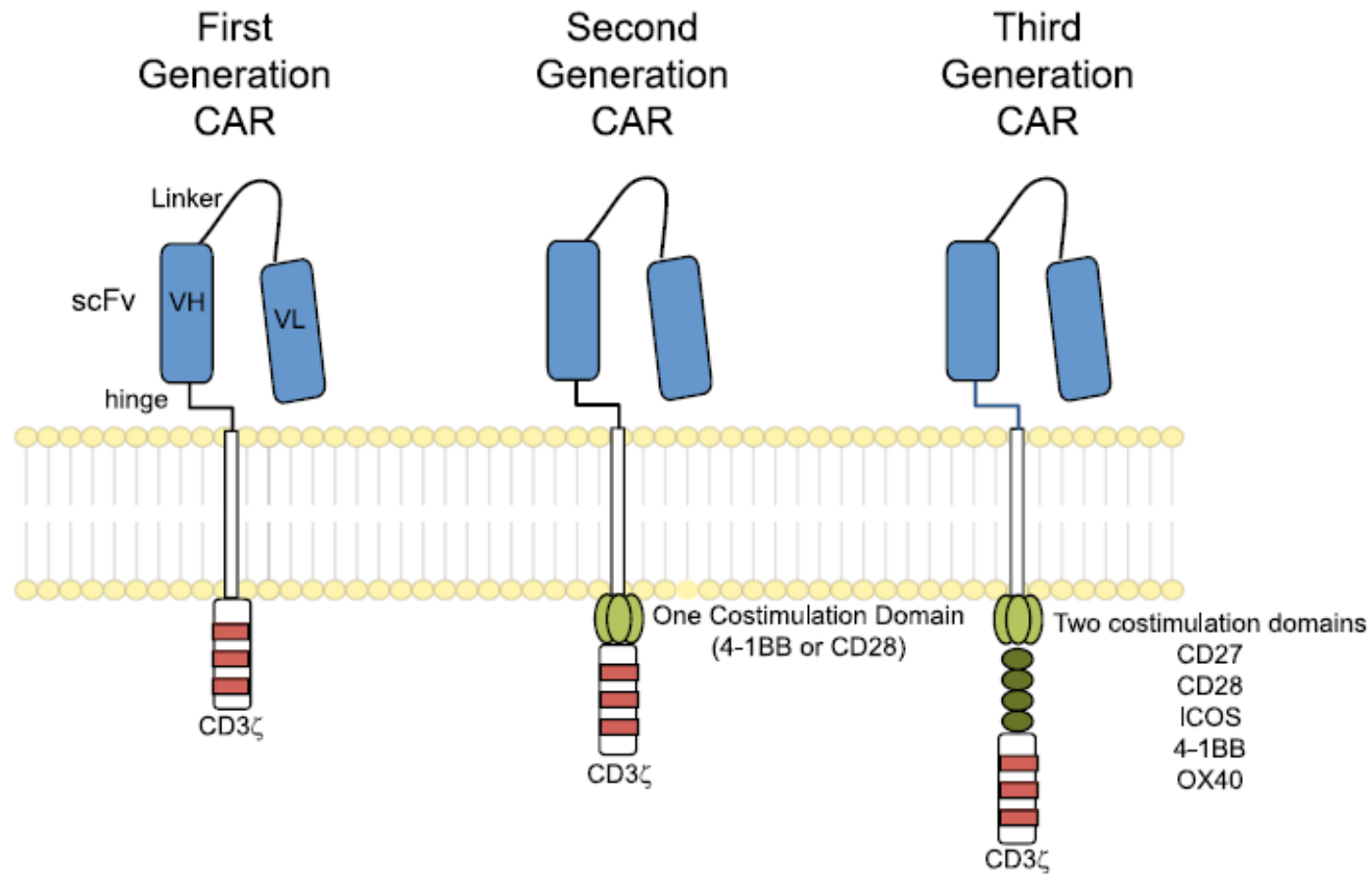
## Chimeric Antigen Receptor T cell



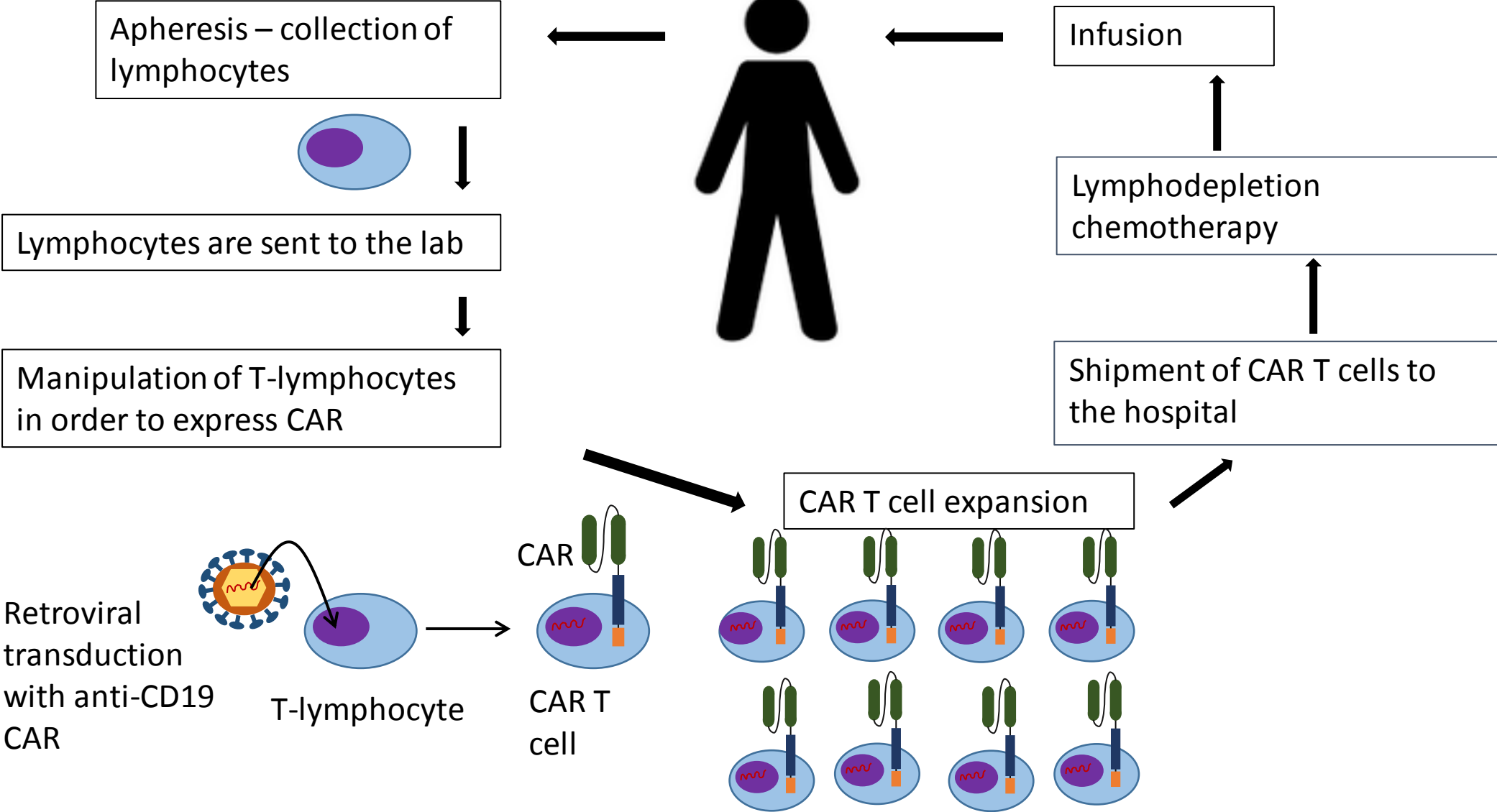
CAR will be targeting a specific antigen on the cancer cell



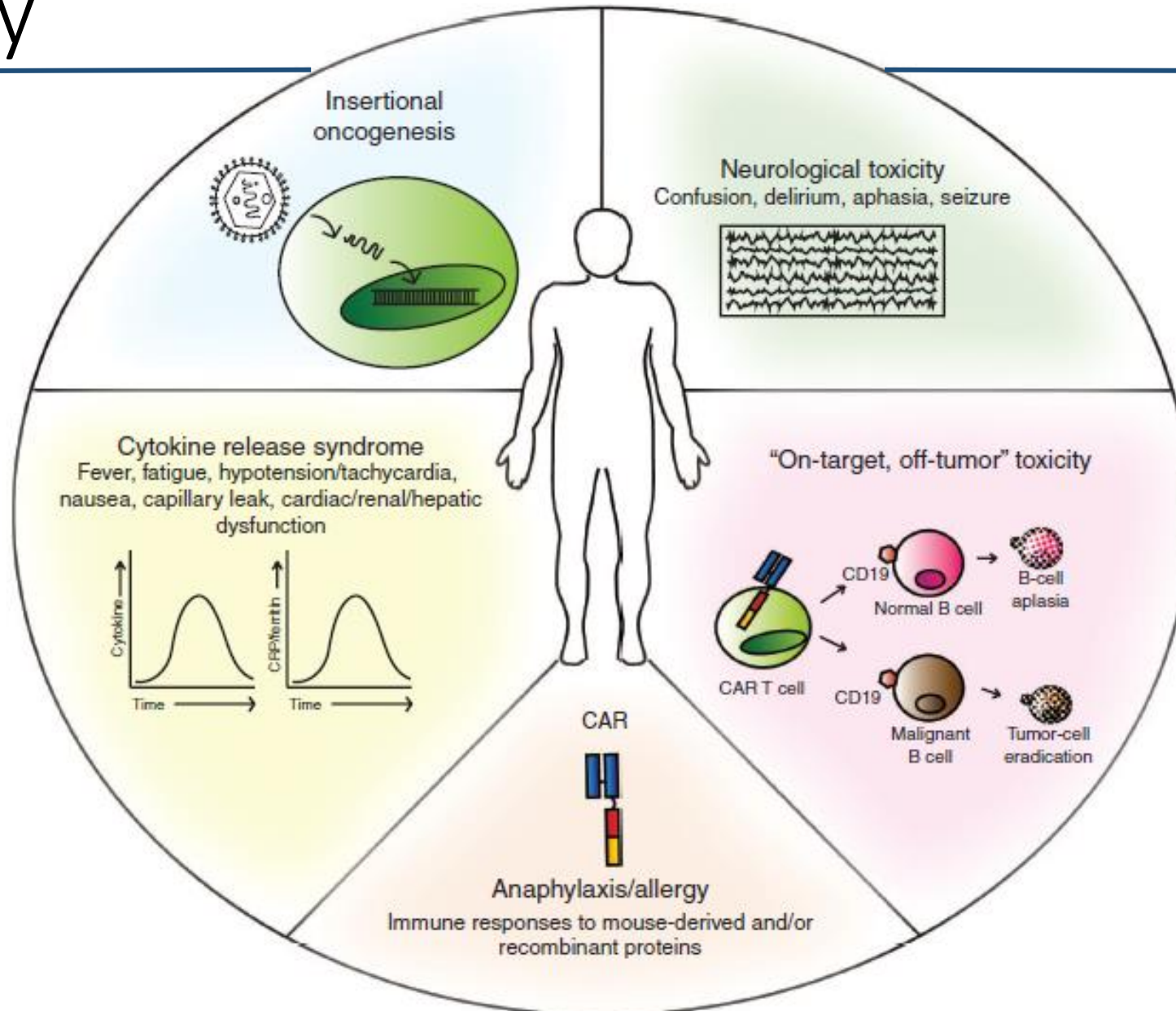
# CAR structure



# Manufacturing CARs



# Toxicity





# Cytokine release syndrome (CRS)

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Incidence 60-100%

severe in 30%

ICU admissions 30-50% (median stay 7 days)

Onset 1-3 days after infusion

Median duration 7-8 days

# CRS - pathophysiology

Systemic inflammatory response caused by elevated levels of cytokines released by:

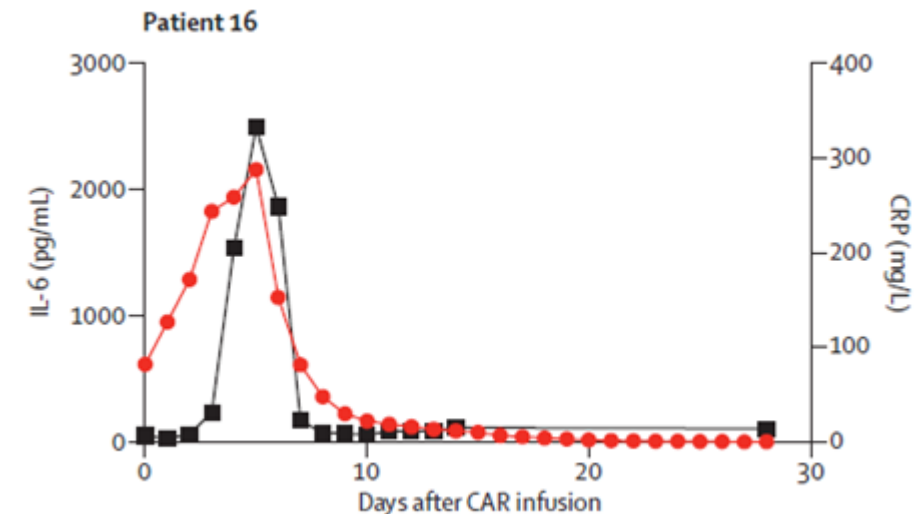
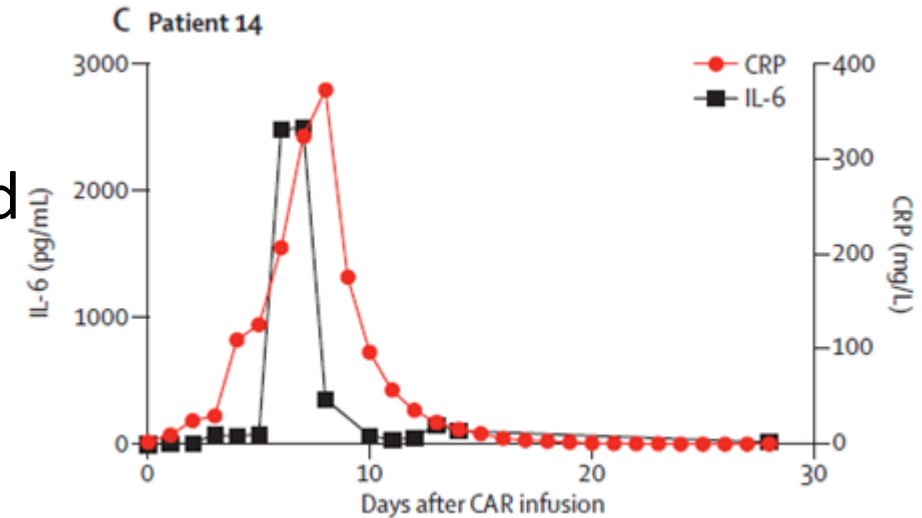
infused CAR T cells

other cells (macrophages, monocytes, dendritic cells, NK cells) in response to cytokines produced by CAR T cells

IL6 (major role),  $\text{INF}\gamma$ ,  $\text{TNF}\alpha$ , IL2, IL2R $\alpha$ , IL1

GM-CSF

Correlates with T-cell activation and expansion

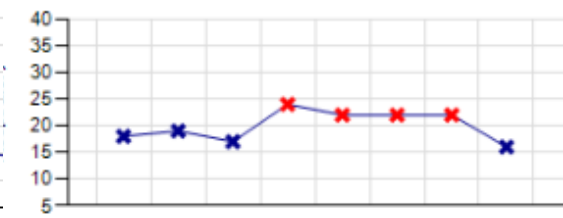
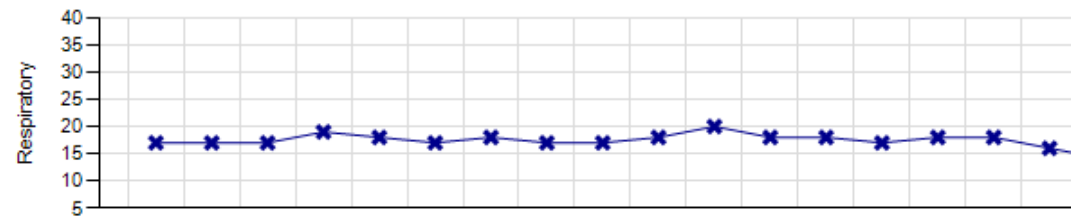
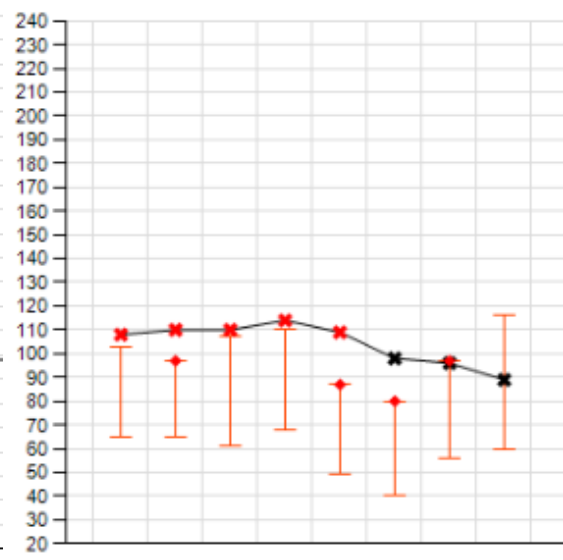
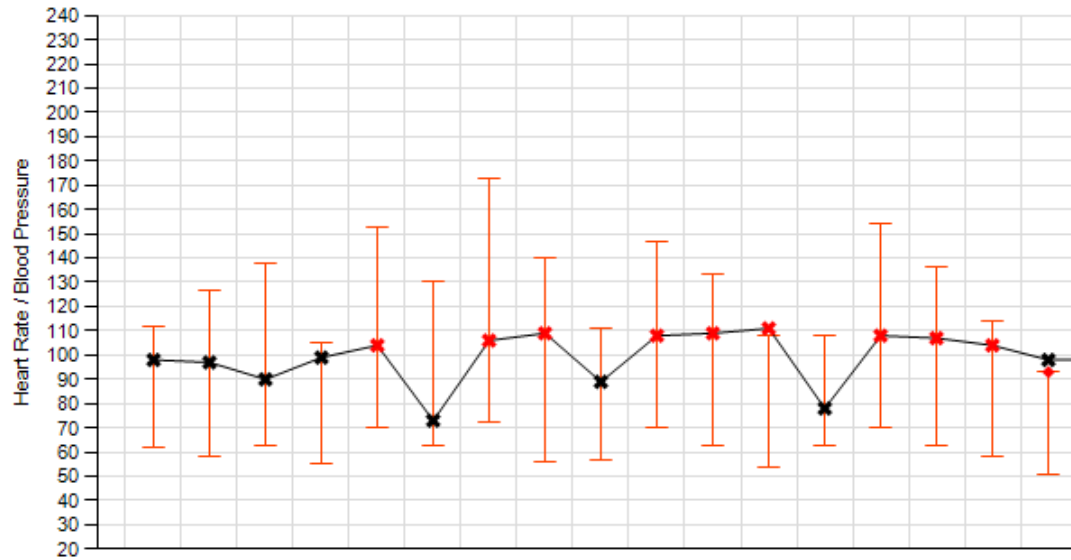
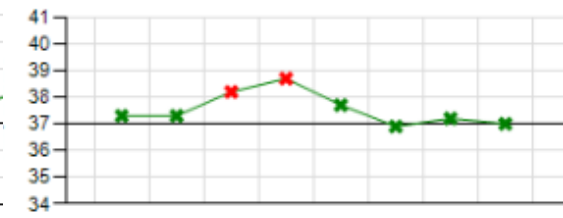
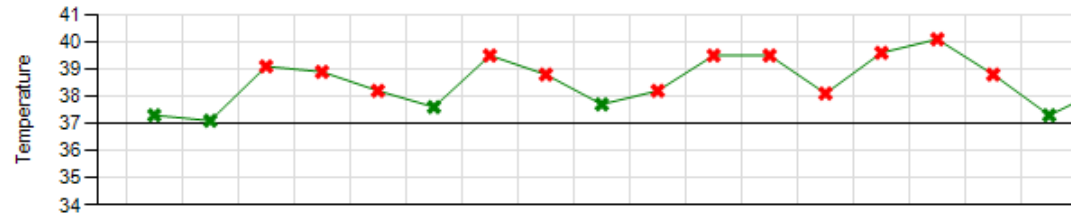


# CRS – clinical manifestations

Temperature

↓BP

↓oxygen



# Immune effector cell-associated neurotoxicity syndrome (ICANS)

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Prevalence 40-65%

Median onset time 4 days (1-43) following infusion

biphasic      early onset (with CRS)

late onset (when CRS subsided), 10% in 3<sup>rd</sup> or 4<sup>th</sup>  
week

Duration 2-4 days

Resolves spontaneously (deaths reported due to brain oedema)

Neelapu et al, N Eng J Med 2017;377:2531-44

Schuster et al, N Eng J Med 2017; 377:2545-54

Maude et al, N Eng j Med 2018; 378:493-48

Park et al, N Eng J Med 2018; 378:449-59

# ICANS - pathophysiology

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## Unknown

- passive diffusion of cytokines into the brain
- trafficking of T cells

## ↑ incidence

- High disease burden
- Higher T cell expansion

# ICANS – clinical manifestations

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## Encephalopathy

early features: reduced attention, language disturbance and impaired handwriting

late features: somnolence, confusion, disorientation, aphasia, tremor

Seizures, ataxia, apraxia, facial nerve palsy, hallucinations

Increased intracranial pressure

Few reports of brain oedema

# ICE score

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## 10-point neurological assessment

- Orientation to year, month, city, hospital: 4 points
- Name 3 objects (e.g. point to clock, pen, button): 3 points
- Following commands: close your eyes and stick out your tongue: 1 point
- Ability to write a standard sentence (e.g. our national animal is a lion): 1 point
- Count backwards from 100 by ten: 1 point

# ICE score

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Our national animal is a lion

Baseline

our national animal is a lion

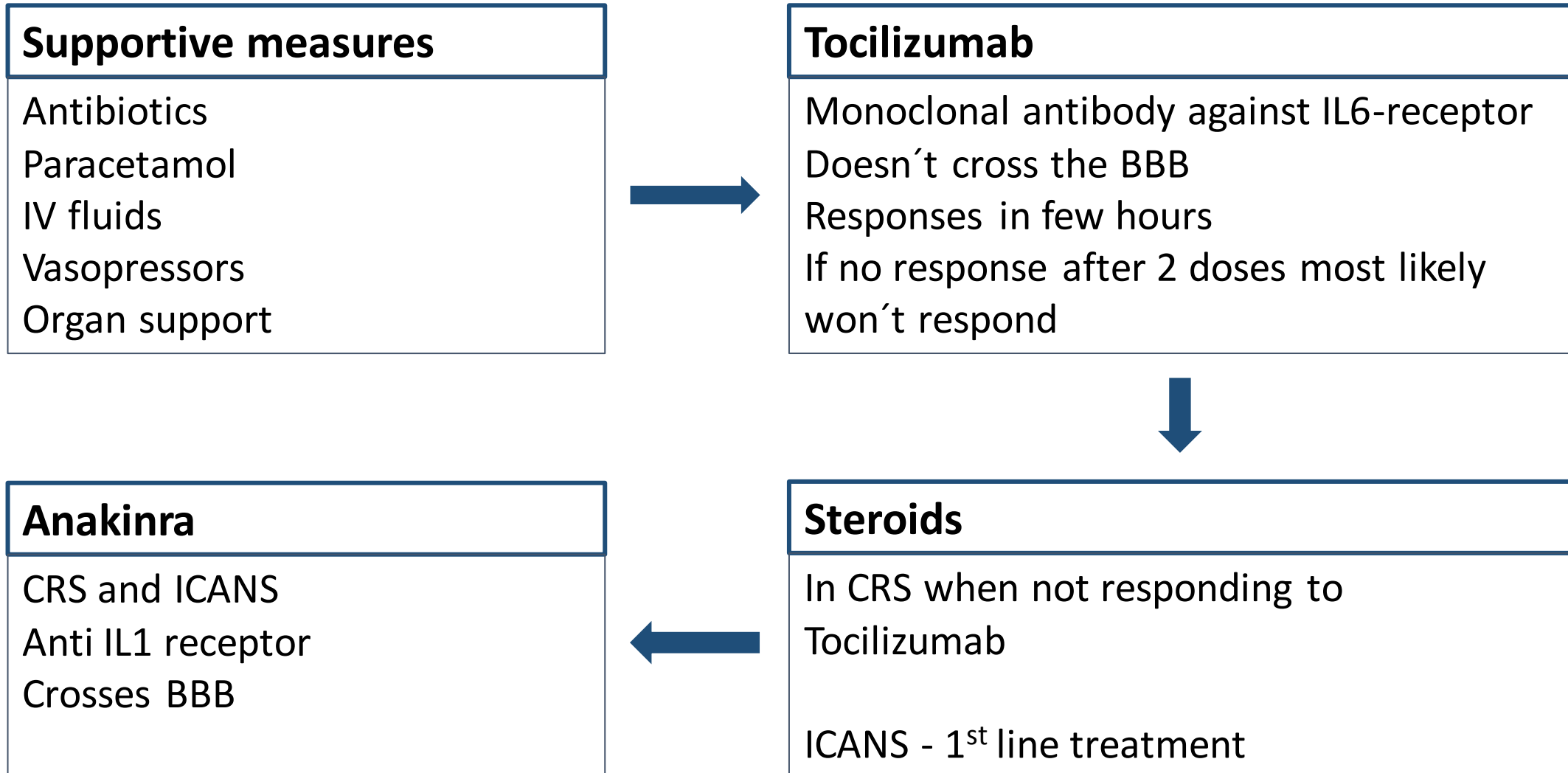
Day +10 - morning

Our national animal is a lion

Day +10 - evening

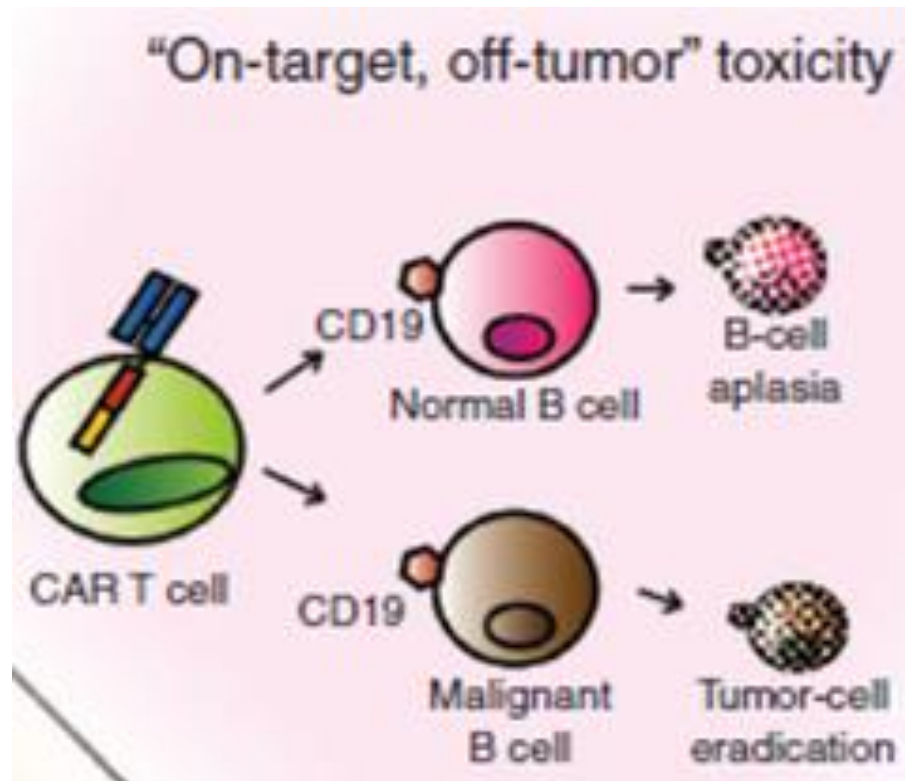


# Management of CRS and ICANS



# On target off tumour

B cell aplasia – immunoglobulin replacement



# Outcomes

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Relapsed and refractory BALL

Responses with standard chemo 18-40% (overall survival 3-9 months)

Overall responses with CAR T cells 81-90% (long remissions, > 4 years)

Relapsed and refractory NHL

Responses with standard chemo 26% (overall survival <6 months)

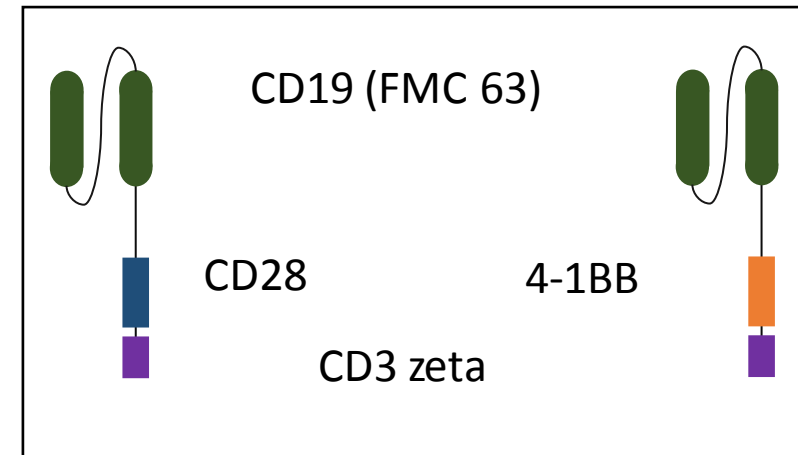
Overall responses with CAR T cells 64-82%

# CAR T cells products

## NHS products

- Paediatric and young adults b-acute lymphoblastic leukaemia
- Adults non Hodgkin lymphoma

Clinical trials (> 560 studies)



# Relapses

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Loss of CAR T cells

humanised CAR T cells

No expression or low expression of CD19

dual CAR T cells

# Take home messages

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CAR T cell therapy is emerging as a promising new treatment for haematological and non-haematological malignancies

It is associated with specific acute toxicities which can be severe

Intensive monitoring and prompt management is essential to minimise morbidity and mortality

Multidisciplinary team is needed to manage these patients

Thank you!

# Generating super-soldiers

## the production of CAR-T cells

