CNO SIG Oncology Pharmacy Talk, Wellington 2025

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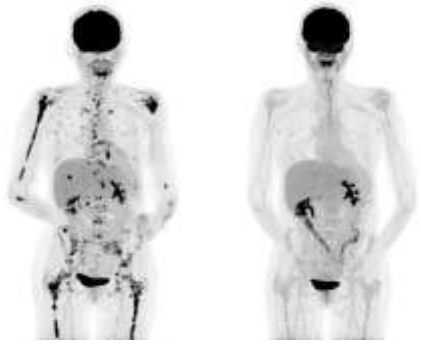
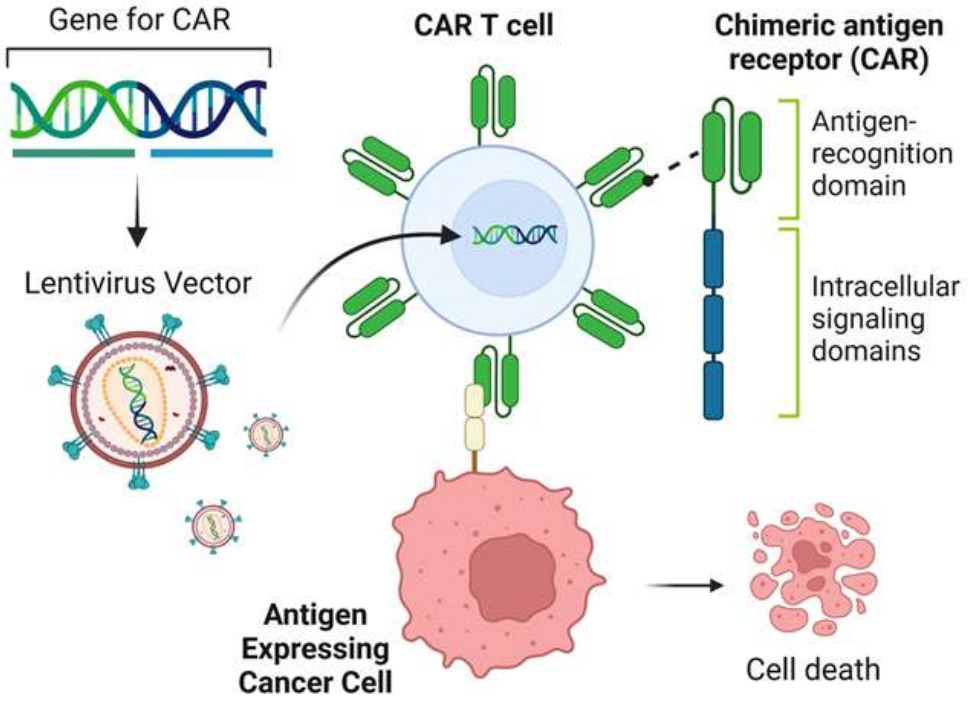
Te Whatu Ora
Health New Zealand

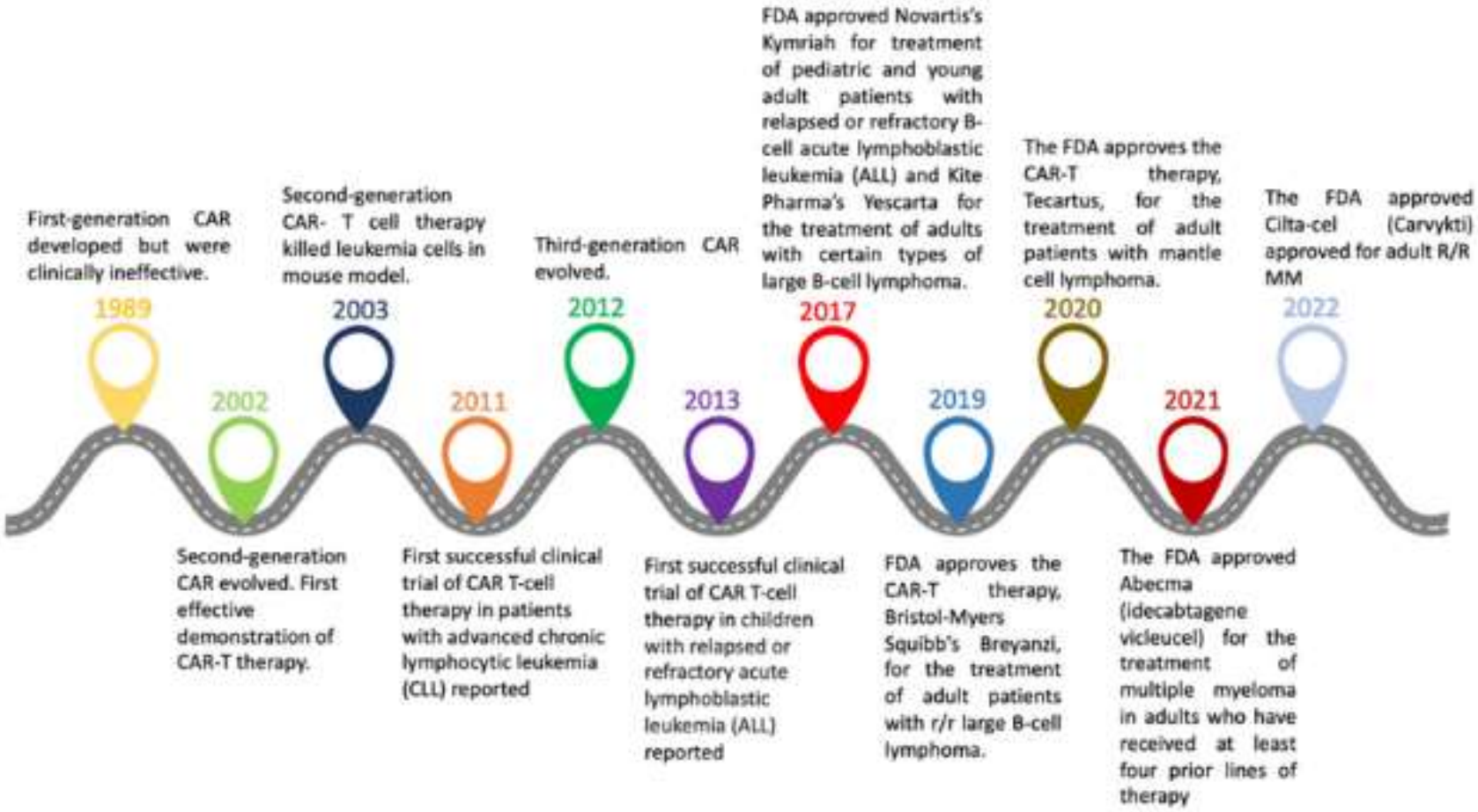


What is CAR T-cell therapy?

- An immunotherapy treatment in which a patients own T cells are utilized to attack cancer cells.
- T cells are harvested from the patient using leukapheresis.
- The T cells are then cultured in the laboratory and transduced with a lentiviral vector.
- This viral vector induces T cells to express a Chimeric Antigen Receptor (CAR) and become CAR T-cells.

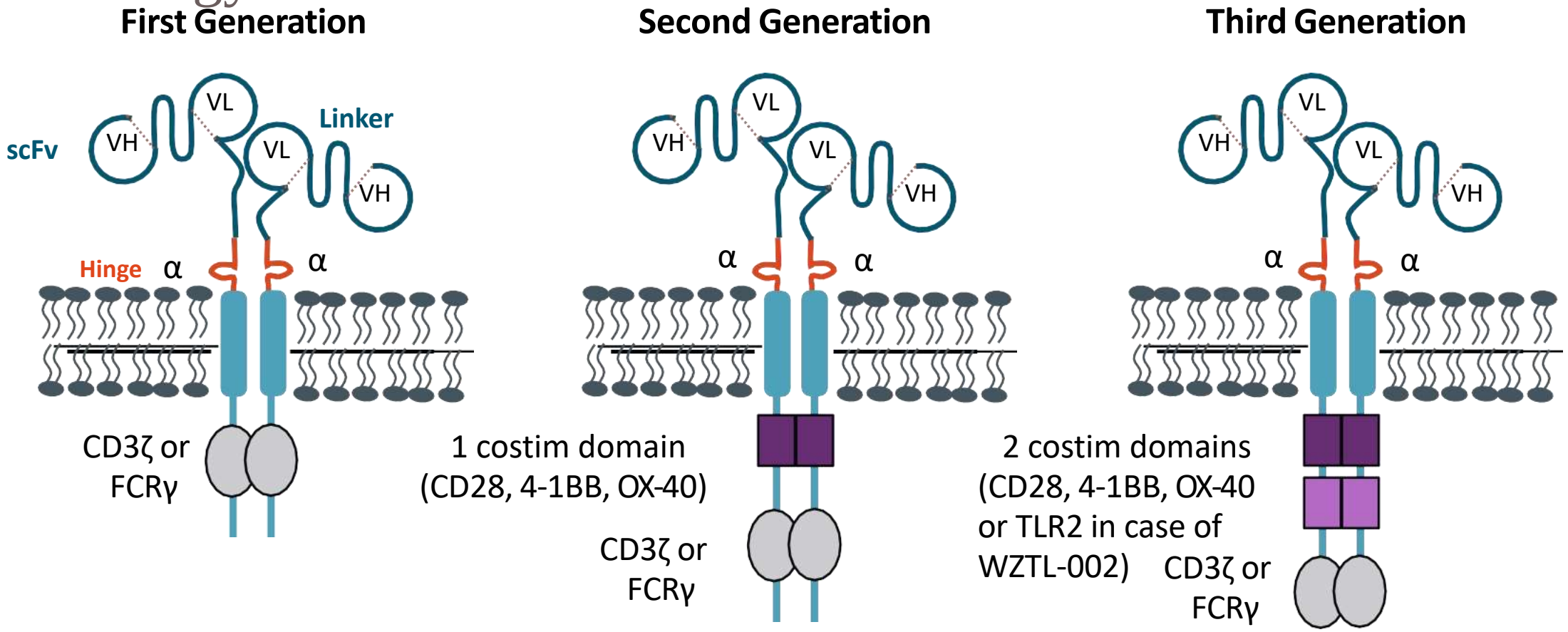


History



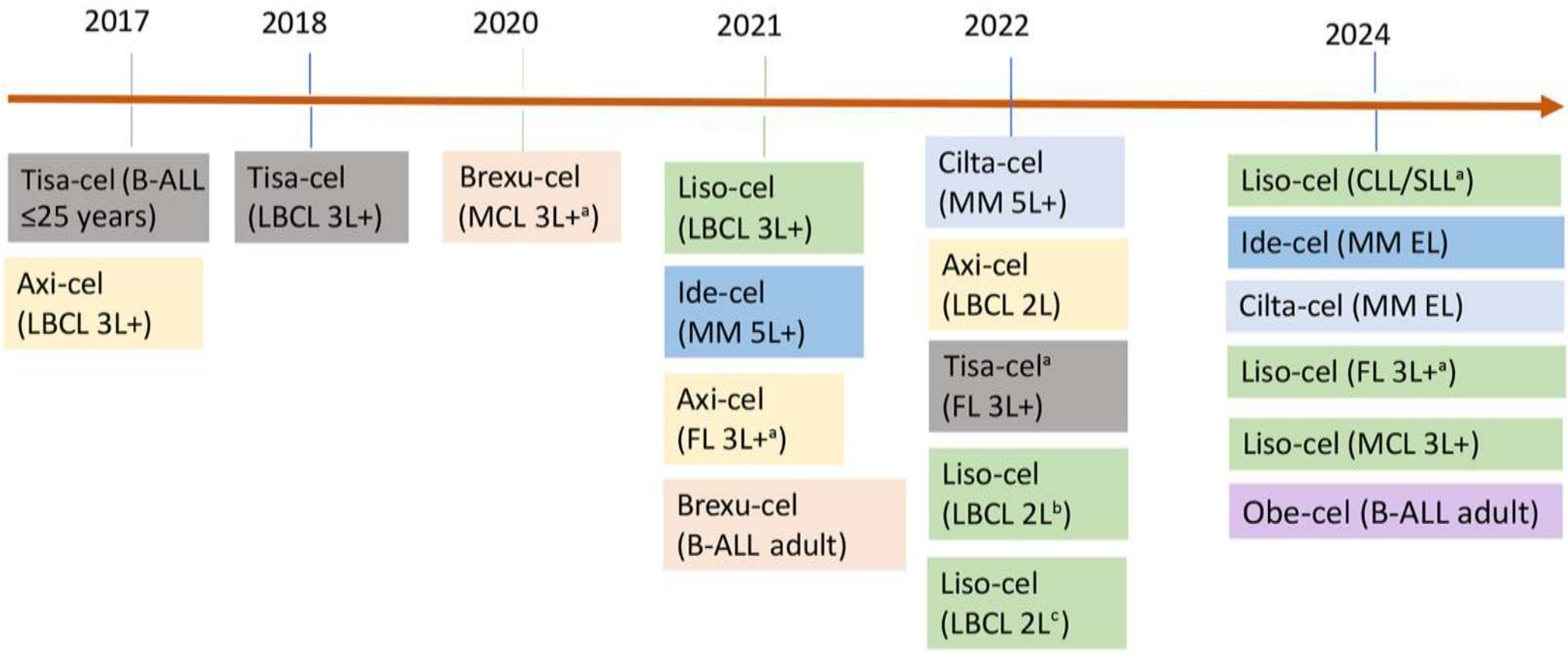
Dabas, Preeti & Danda, Adithi. (2023). Revolutionizing cancer treatment: a comprehensive review of CAR-T cell therapy. Medical Oncology. 40. 10.1007/s12032-023-02146-y.

Multiple Generations of CAR T-Cell Technology-



Park. JCO. 2015;33:651.

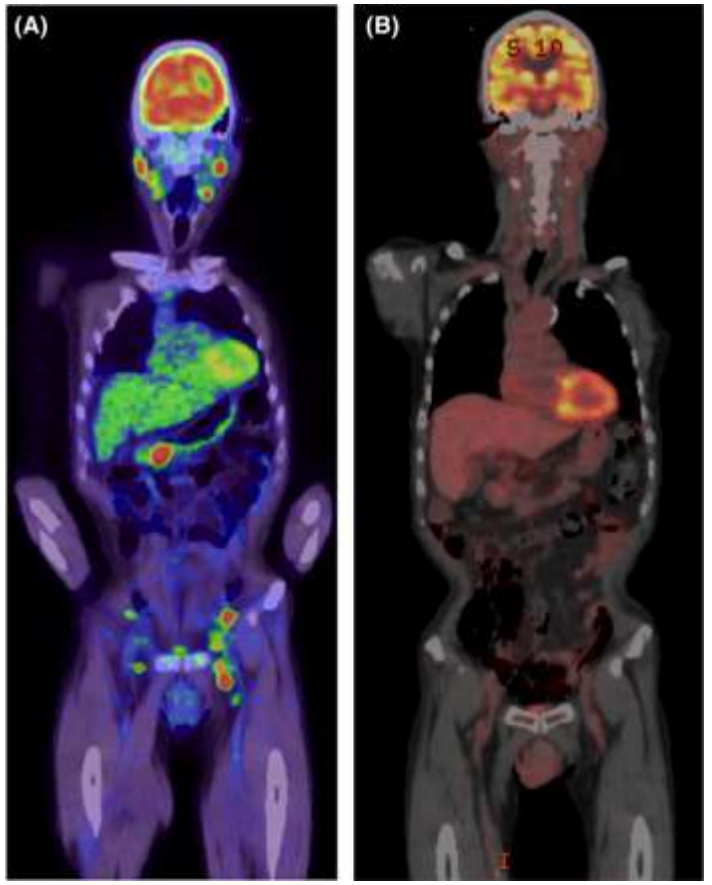
CAR T-Cell Therapy for Haem Malignancies



Reinhorn, D. *et al.* (2025) 'Autologous T-cell therapies in solid tumor malignancies: Current landscape and future opportunities', *American Society of Clinical Oncology Educational Book*, 45(3). doi:10.1200/edbk-25-473440.

Indications for anti-CD19 CAR T-Cell Therapy in Wellington

- CAR T-cell therapy is currently not a funded therapy in NZ
- It's use in NZ has been as part of the ENABLE CAR T-cell clinical trial, sponsored by the Malaghan Institute and run at Wellington Regional Hospital
- Currently indications are adult patients with relapsed and refractory large B-cell Lymphoma and its variants
- Internationally (*but not in Wellington currently*), CAR T-cells are used to treat:
  - Relapsed or Refractory B-Acute Lymphoblastic Leukaemia
  - Multiple Myeloma
  - Indolent B-cell lymphomas



ENABLE Trial

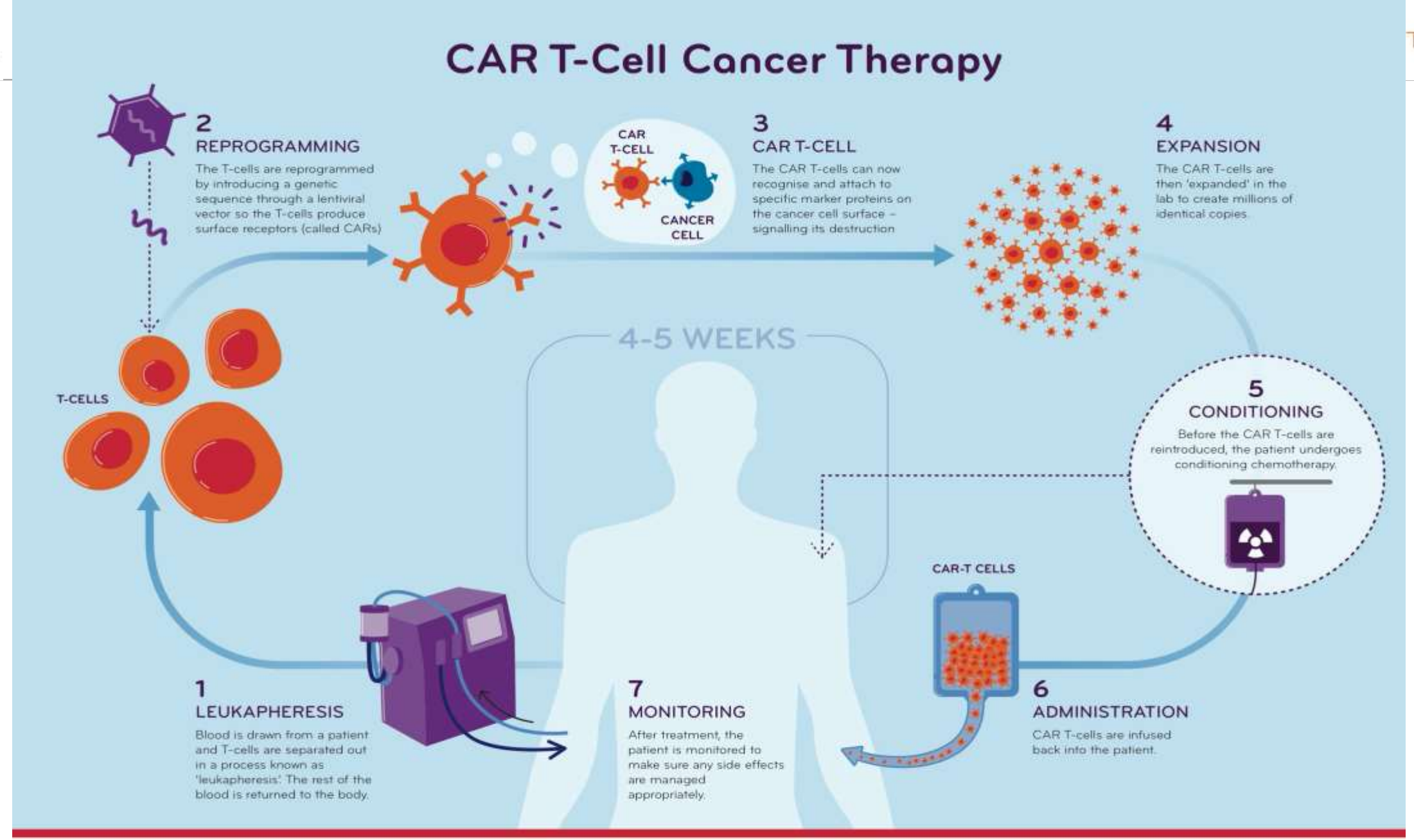
- ENABLE-1 was Phase 1 safety Trial
  - Lower CRS and ICANS rates compared to funded International CAR T products (CRS rate 57%, no severe CRS and ICANS rate 3%)
  - Comparable efficacy to funded International CAR T products (53% Complete Response at Month 3)
- Outpatient management
  - D0-D14 outpatient monitoring, D14-28 self temperature and ICANS monitoring with D28 and M3 PET scanning for disease response assessment
- Multi-site with Auckland and Christchurch planned as study sites

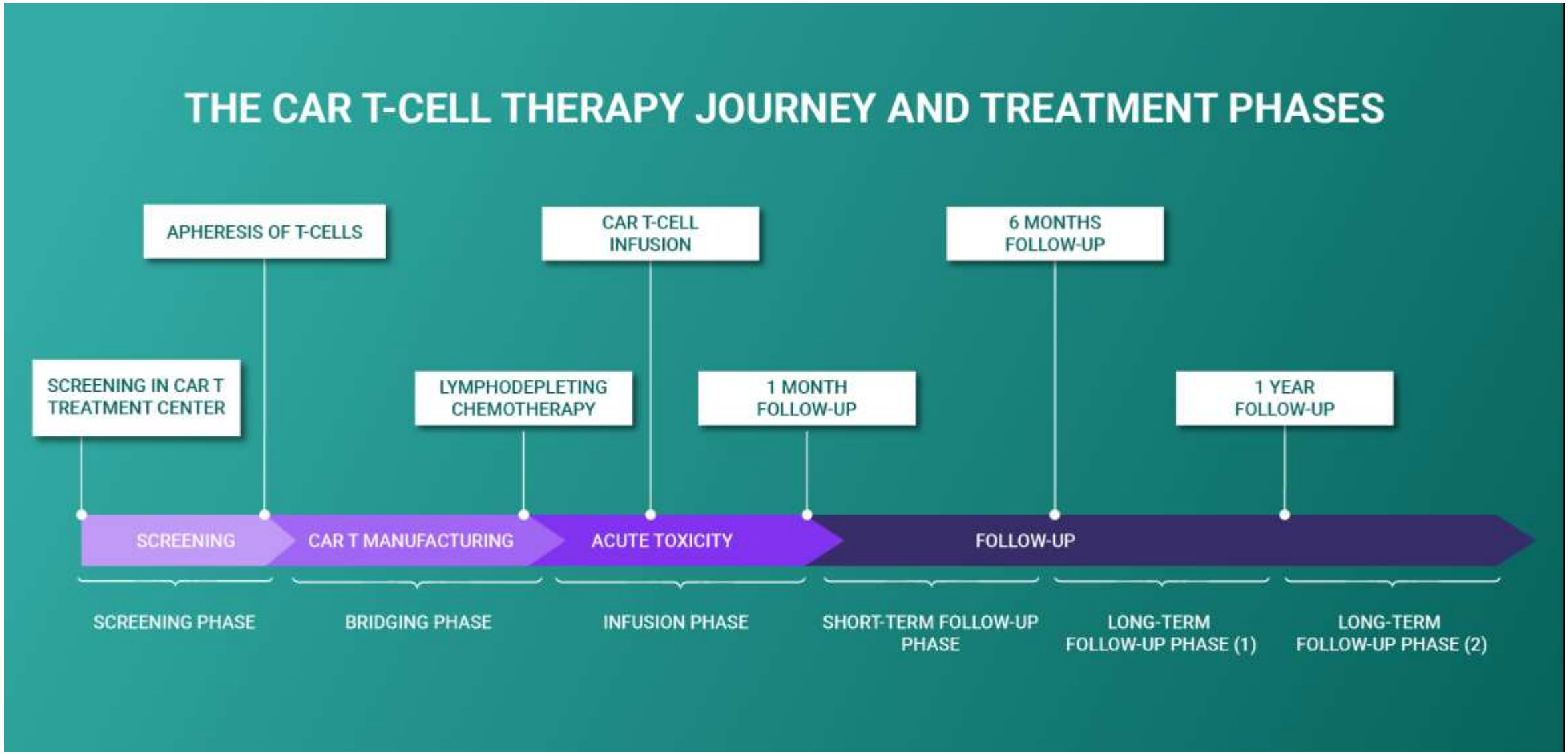
ENABLE-2 Trial Update

- ENABLE-2 Trial Started 12/07/2024
- Key Difference ENABLE-2 vs. ENABLE
- Phase II trial
  - Treating patients with relapsed or refractory DLBCL as 2nd line or 3rd line therapy
  - Early relapse within 12 months of front-line therapy, fail to respond to platinum-containing salvage chemotherapy or relapse post autologous stem cell transplant
  - Histology: High-grade B-cell lymphoma de novo or transformed from low-grade

Notable Exclusion Criteria:

- Active CNS involvement
- Richter's Transformation of CLL
- Requirement for urgent therapy
- Prior Allogeneic stem cell transplant


CAR T-Cell Cancer Therapy
2
REPROGRAMMING
The T-cells are reprogrammed by introducing a genetic sequence through a lentiviral vector so the T-cells produce surface receptors (called CARs)
CAR T-CELL
CANCER CELL
3
CAR T-CELL
The CAR T-cells can now recognise and attach to specific marker proteins on the cancer cell surface – signalling its destruction
4
EXPANSION
The CAR T-cells are then 'expanded' in the lab to create millions of identical copies
T-CELLS
4-5 WEEKS
5
CONDITIONING
Before the CAR T-cells are reintroduced, the patient undergoes conditioning chemotherapy.
CAR-T CELLS
1
LEUKAPHERESIS
Blood is drawn from a patient and T-cells are separated out in a process known as 'leukapheresis'. The rest of the blood is returned to the body.
7
MONITORING
After treatment, the patient is monitored to make sure any side effects are managed appropriately.
6
ADMINISTRATION
CAR T-cells are infused back into the patient.

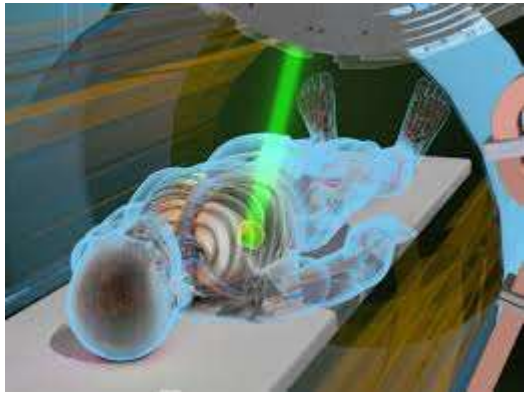

THE CAR T-CELL THERAPY JOURNEY AND TREATMENT PHASES
APHERESIS OF T-CELLS
CAR T-CELL INFUSION
6 MONTHS FOLLOW-UP
SCREENING IN CAR T TREATMENT CENTER
LYMPHODEPLETING CHEMOTHERAPY
1 MONTH FOLLOW-UP
1 YEAR FOLLOW-UP
SCREENING
CAR T MANUFACTURING
ACUTE TOXICITY
FOLLOW-UP
SCREENING PHASE
BRIDGING PHASE
INFUSION PHASE
SHORT-TERM FOLLOW-UP PHASE
LONG-TERM FOLLOW-UP PHASE (1)
LONG-TERM FOLLOW-UP PHASE (2)

Prior Treatment...

- Patients will have received at least one or more prior lines of chemotherapy for their lymphoma prior to enrolment in the study e.g. R- CHOP or R-DA-EPOCH, salvage lines of chemo including R-CVP, R-GDP or R-GemOx
- Prior chemotherapy can affect blood cell counts and cause toxicities e.g. cardiac, neurological **which** can be detected at the screening phase
- Immunotherapy such as rituximab can deplete B cells that can cause immune compromise and put patients undergoing CAR- T therapy at a higher risk of infection
- Patients may receive bridging therapy to control their lymphoma and reduce disease bulk prior to CAR-T often with a combination of steroids, chemo or radiotherapy

Role of bridging therapy

- Aims to stabilize disease and reduce disease burden during manufacture, usually with either radiation, chemotherapy or chemoimmunotherapy
- Reduce tumour burden to improve CAR T-cell efficacy [1]
- High tumour burden increases risks of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS). Reduced burden lowers severe toxicity rates [2]



[1] Lyu C, Cui R, Wang J, Mou N, Jiang Y, Li W, Deng Q. Intensive Debulking Chemotherapy Improves the Short-Term and Long-Term Efficacy of Anti-CD19-CAR-T in Refractory/Relapsed DLBCL With High Tumor Bulk. Front Oncol. 2021 Jul 30;11:706087. doi: 10.3389/fonc.2021.706087.

Lymphodepletion Chemotherapy

- Patients will receive lymphodepletion on days -5 to -3 with fludarabine and cyclophosphamide on WBCC.
- Lymphodepletion chemotherapy can improve the efficacy of CAR T-cells by reducing existing T cell numbers
- But, it can lead to cytopenias and increase the risk of infection!

CAPITAL, COAST AND HUTT VALLEY (WELLINGTON BLOOD AND CANCER CENTRE)

LYMPHODEPLETION CHEMOTHERAPY CHART

Te Whatu Ora Health New Zealand Capital, Coast and Hutt Valley

CAR T-cell conditioning regimen ***Fludarabine/Cyclophosphamidelymphodepletion***	**Date of CAR T-cell infusion (Day 0)** ____-____-____ (dd-mm-yyyy)	**Deliver to: WBCC** ***(circle)***
(Affix Patient Label Here)	**Dose Modified: Yes / No** ***(if yes, state reason)*** ***Note: If eCrCl < 70 mL/Min or platelets < 75 x10e9/L or neutrophils < 1.0 x10e9/L, review ENABLE-2 Protocol Section 11.3.2 for dose adjustments.***	**Allergies/ADRs:** **Weight (kg) at Leukapheresis:** / **Height (cm):** / **BSA (m2):** **Weight (kg) at Day -5 [If ≥ 10% change in body weight from leukapheresis, please re-calculate dosage]:**
Treatment Outline: Fludarabine 30 mg/m2/day for 3 days (D-5 to D-3 inclusive) Cyclophosphamide 500 mg/m2/day for 3 days (D-5 to D-3 inclusive)	**Emetogenic Potential:** ☐☐ Moderate – refer to appropriate guideline (must not give dexamethasone)	**Pharmacist Check:**

DATE	MEDICATION	DOSE	ROUTE	INSTRUCTIONS/NOTES	DOCTORS SIGNATURE & PAGER #	Checked by	Given by	Time
DAY -5								
	Fludarabine 30 mg/m2		IV	Infuse in 100mL sodium chloride 0.9% over 30 minutes				
	Cyclophosphamide 500 mg/m2		IV	Infuse in 500 mL sodium chloride 0.9% over 1 hour				
	Sodium chloride 0.9%	500 mL	IV	Post-hydration – infuse over 30 minutes	Date:			

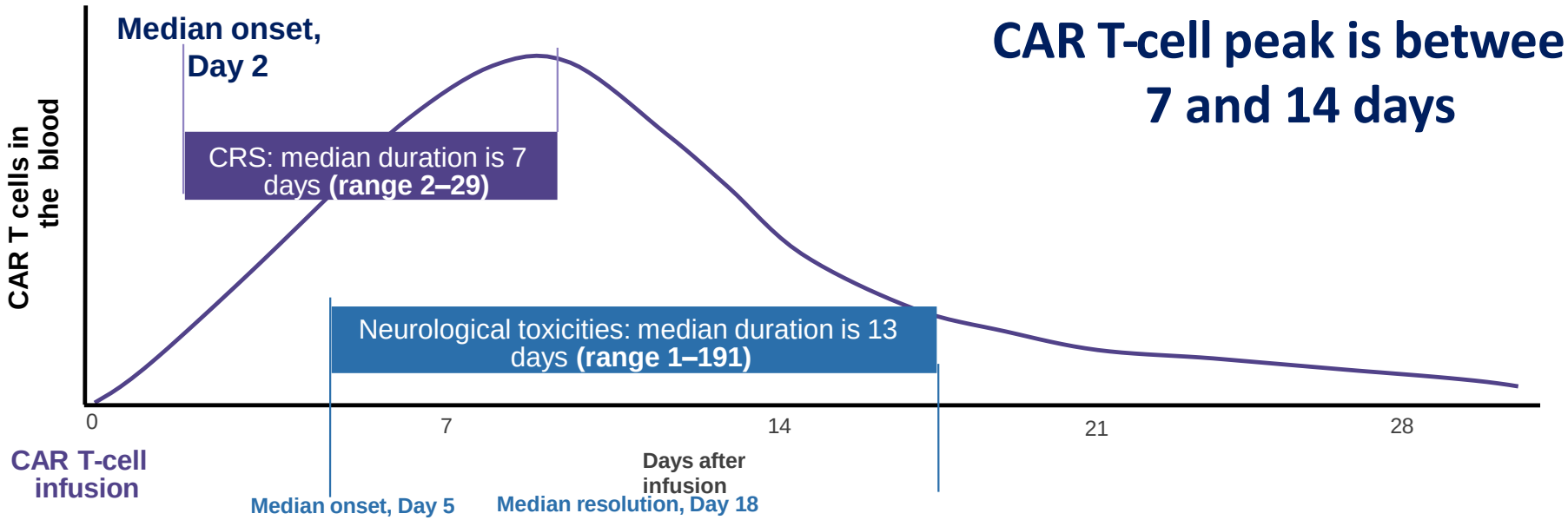
Notes: Pre-lymphodepletion CAR T-cell checklist must be completed before starting chemotherapy

CAR T-cell Therapy Toxicities

- Cytokine Release Syndrome [CRS]
- Immune Effector-Cell Associated Neurotoxicity Syndrome [ICANS]
- Immune Effector-Cell Associated Haematological Toxicity [ICAHT]
- Immune Effector-Cell Associated HLH
- B-cell aplasia
- Hypogammaglobulinemia
- Infection Risk
- Secondary Malignancies

Clinical trials have established the timing and duration of acute adverse events

CRS coincides with maximal T-cell expansion[1]
CRS may occur within minutes but more typically within days[1,2]



CAR T-cell peak is between 7 and 14 days

ICANS uncommon to begin before D14

Cytopenias are common and can be long-lasting.

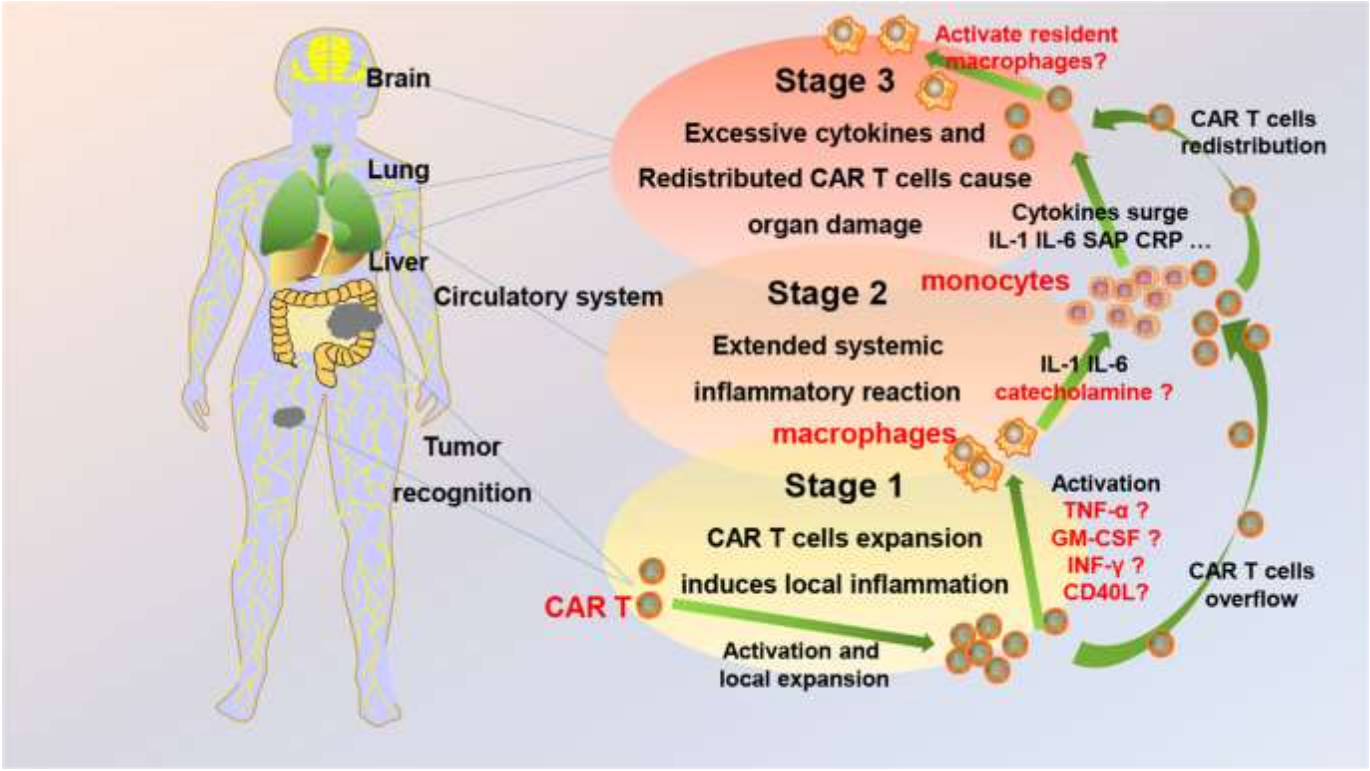
AE: adverse event; CAR: chimeric antigen receptor; CRS: cytokine release syndrome; SmPC: Summary of Product Characteristics; NE: neurological event; RMM: risk minimisation measure 1. Lee DW, *et al. Blood* 2014; 124:188–195. 2. Yescarta SmPC (May 2019; available at www.ema.europa.eu).

CRS and Neurotoxicity of Major Clinical Trials

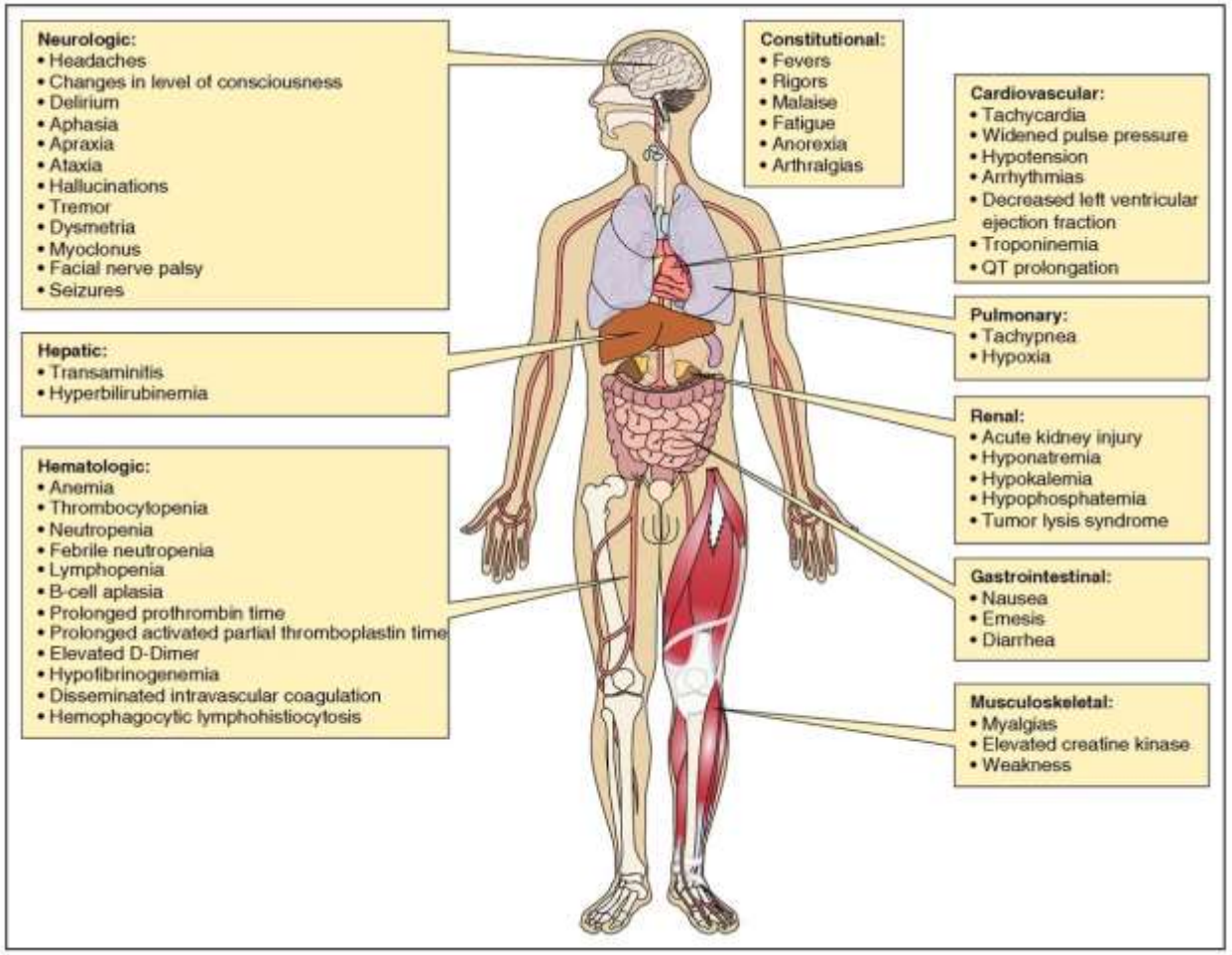
	JULIET	ZUMA-1	TRANSCEND	ENABLE
CAR T-cell Agent	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel	WZTL-002
Construct	Anti–CD19-41BB-CD3z (2nd gen)	Anti–CD19- CD28-CD3z (2nd gen)	Anti–CD19-41BB-CD3z (2nd gen)	Anti-CD19-CD28-TLR2 (3rd gen)
No. Treated	111	101	269	30
CRS, %	58%	93%	42%	57%
Grade ≥ 3 CRS, %	22%	13%	2%	0%
ICANS %	21%	64%	30%	3%
Grade ≥ 3 ICANS %	12%	28%	10%	0%

Cytokine Release Syndrome [CRS]

- CAR T-cells are thought to be a “living drug”.
- Recognise the CD19 antigen on malignant B cells and cause cell death
- As part of their duties T cells release cytokines that help signal to other immune cells
- Macrophages can produce IL-1 and IL-6 triggering a systemic inflammatory response triggering fever and hypotension



Cytokine Release Syndrome (CRS)



Brudno and Kochenderfer, *Blood* 2016; 127:3321-3330

- CRS is a systemic inflammatory response caused by cytokines released by CAR T-cells and other immune cells and results in reversible organ dysfunction.
- Axi-cel patients- Patients experiencing grade 1 to 2 CRS had superior CR rate and PFS, as compared to those without CRS or with grade 3 to 5 CRS. Grade 3 to 5 CRS was associated with a worse OS. [1]

- [1] Jacobs, M.T. *et al.* (2022) 'Severity of cytokine release syndrome influences outcome after Axicabtagene Ciloleucel for large B cell lymphoma: Results from the US lymphoma car-T consortium', *Clinical Lymphoma Myeloma and Leukemia*, 22(10), pp. 753–759.

Risk Factors for CRS

- High- disease burden [1]
- Second generation CAR T products
- Younger age
- Higher dose of infused CAR T-cells
- High inflammatory markers
- Axi-cel and Brexu-cel carry higher risk than Tisa-cel

- **mEASIX** score is a way of predicting severe CRS and ICANS
- (lactic dehydrogenase [LDH; U/L] × CRP [mg/dL]/platelets [PLTs; 10^9 cells/L] [2]
- Higher the number → Higher the risk of CRS and ICANS

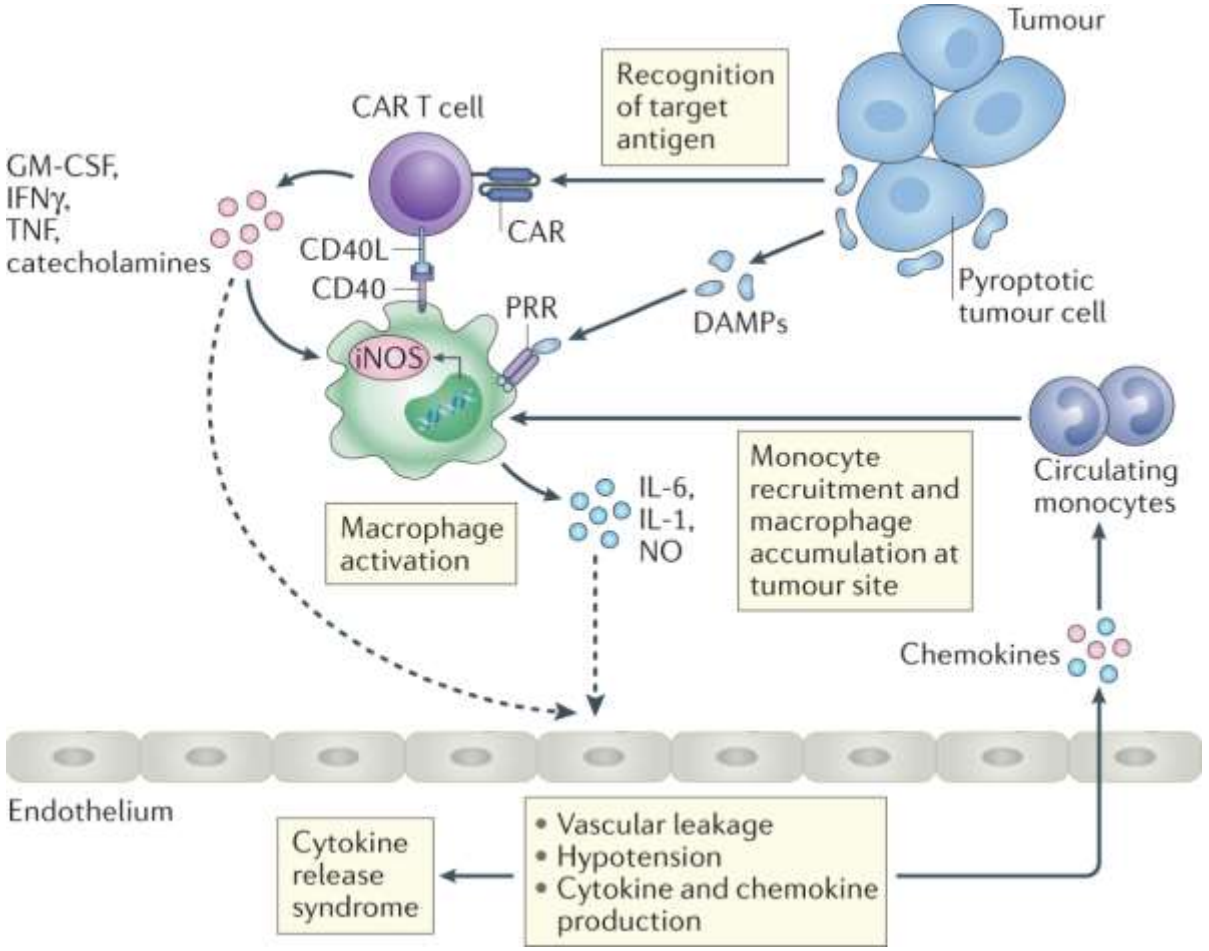
[1] Shimabukuro-Vornhagen, A.; Gödel, P.; Subklewe, M.; Stemmler, H.J.; Schlößer, H.A.; Schlaak, M.; Kochanek, M.; Böll, B.; Bergwelt-Baildon, M.S. von Cytokine Release Syndrome. *J. Immunother. Cancer* **2018**, *6*, 56.

[2] Pennisi, M. *et al.* (2021) 'Modified EASIX predicts severe cytokine release syndrome and neurotoxicity after chimeric antigen receptor T cells', *Blood Advances*, 5(17), pp. 3397–3406. doi:10.1182/bloodadvances.2020003885

Tocilizumab for CRS

- Tocilizumab is an IL-6 receptor inhibitor and the first-line therapy for moderate to severe CRS triggered by CAR T-cell therapy.

- Dosing: up to 8 mg/kg IV, max 3 doses as per Pharmac.



Pharmac Criteria

- **Initial application — cytokine release syndrome**
- Applications from any relevant practitioner. Approvals valid without further renewal unless notified.
- **Prerequisites**(tick boxes where appropriate)

☐ The patient has developed grade 3 or 4 cytokine release syndrome associated with the administration of blinatumomab for the treatment of acute lymphoblastic leukaemia

and

☐ Tocilizumab is to be administered at doses no greater than 8 mg/kg IV for a maximum of 3 doses (if less than 30kg, maximum of 12 mg/kg)

or

☐ The patient is enrolled in the Malaghan Institute of Medical Research ENABLE trial programme

and

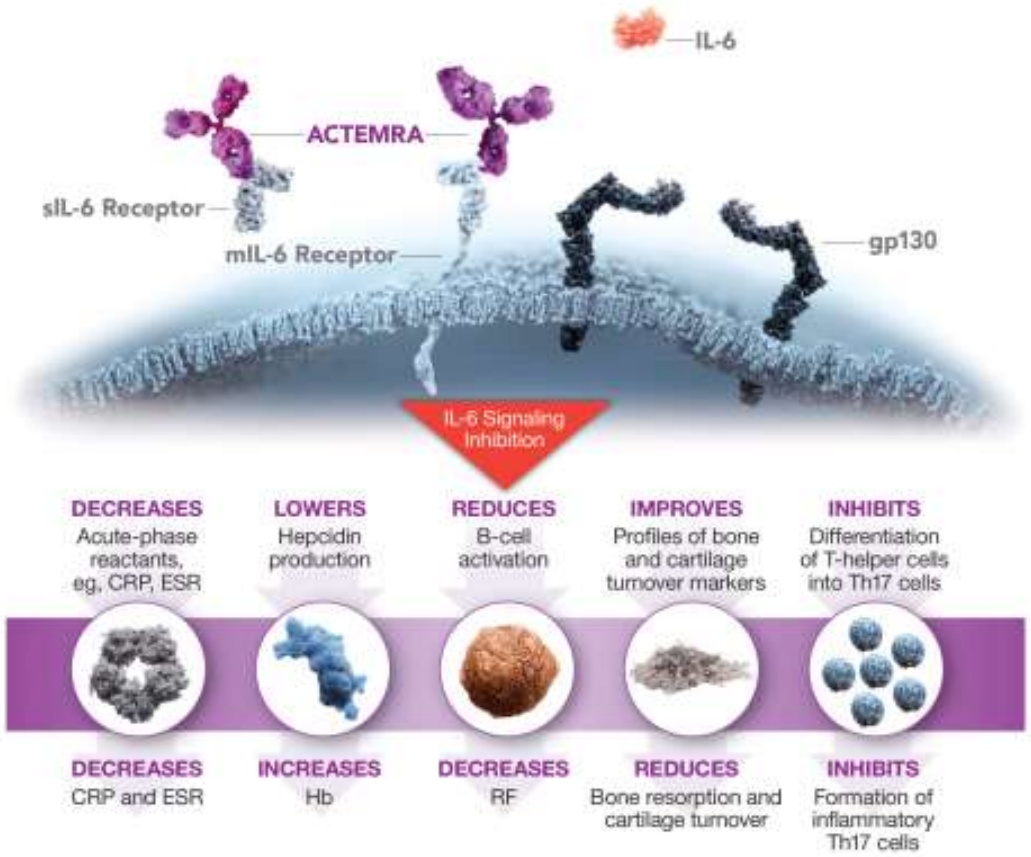
☐ The patient has developed CRS or Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) following CAR T-cell

and

☐ Tocilizumab is to be administered according to the consensus guidelines for CRS or ICANS for CAR T-cell therapy at doses no greater than 8 mg/kg IV for a maximum of 3 doses

Risks of Tocilizumab?

- Hypofibrinogenemia
- Elevated cholesterol levels
- Strongyloides reactivation
- CRP- no longer our diagnostic friend
- GI perforation



ENABLE Trial Quick Sheet: Adult CRS Management

APPLIES ONLY TO MANAGEMENT AFTER CAR T-CELL THERAPY; NOT TO OTHERIMMUNOTHERAPIES SUCH AS BiTE THERAPY

If your patient is experiencing **any** of the following after CAR T-cell therapy:

- Fever (temperature ≥ 38°C)
- Hypotension (systolic BP ≤ 90mm Hg)
- Hypoxia (SpO_2 ≤ 92%)

→ **Consider Cytokine Release Syndrome Management – see PML**

Key contacts

Haematology SMO on-call 24 hour contact:	Via CCDHB switchboard
PAR Team:	#6785
CAR T - Principal Investigator:	(Dr Philip George)
CAR T - Clinical fellow:	(Dr Aine Hurley) 021 992422
CAR T - Research Nurse:	(Tess Ostapowicz) 021 055 0639
	(LJ Geniston) 027 269 0628

Grade	Description	Management
1	**Fever ≥ 38°C** No hypotension No hypoxia	**Broad spectrum antibiotics** if neutropenic, or if any suspicion of sepsis (see Febrile Neutropenia policy) **Alert key contacts** (must inform Haem SMO on call) **Monitor vital signs** for hypotension, hypoxia, **increase frequency of observations** while febrile and as clinically indicated. **Daily blood tests** If persistent or refractory fevers lasting ≥ 3 days **Consider Tocilizumab + corticosteroids (Consult with Haematology SMO)**
2	**Hypotension** (SBP < 90mm Hg; no vasopressors), **and/or** **Hypoxia** (O_2 via nasal prongs up to 4L/min)	**As for grade 1 CRS, plus** **Initiate PAR team review** for hypotension +/- up to 1.5L IV fluids in up to 2 fluid boluses (avoid repeat fluid boluses) **Contact ICU** to consider early vasopressor use Administer O_2 via nasal prongs if hypoxic **Consider Tocilizumab + corticosteroids (Consult with Haematology SMO)**
3	**Hypotension** (SBP < 90mm Hg; 1 vasopressor), **and/or** **Hypoxia** needing high-flow O_2 via nasal prongs (>4L/min), facemask, non rebreather or venturi mask	**As for grade 2 CRS, plus** **MET call** and ICU admission Vasopressor and high-flow O_2 as needed **Consider Tocilizumab + corticosteroids (Consult with Haematology SMO)**
4	**Hypotension** (SBP < 90mm Hg; 2+ vasopressors), **and/or** positive pressure O_2 (intubation or mechanical ventilation)	**As for grade 3 CRS, plus** **Consider high dose methylprednisone (consult with Haematology SMO on call)**

Tocilizumab administration - see Protocol

Tocilizumab is a monoclonal antibody, an IL6 inhibitor

Dose:	8mg/kg (max 800mg) single use vial 400mg in 20ml
Frequency:	Once only; consider further dose after 8-12 hours if no improvement
Administration:	Intravenous add to 100ml 0.9% normal saline bag, infuse over 1 hour – first 15 mins 10ml/hr then 130ml/hour rest of infusion, 20-40mls n/saline flush post infusion. **Compatibility** 0.9% normal saline
Monday-Friday:	0800-1630hrs- contact clinical area pharmacist Consult CAR T Fellow/nurse and Haem SMO
After Hours:	Contact A/H SMO and the on-call pharmacist if Tocilizumab required via CCDHB switchboard

- 1 dose kept in fridge on Ward 5 North, 2 doses kept in pharmacy. Maximum timeframe from call to administration = 2 hours
- Tocilizumab has a **24 hour expiry** once made

Corticosteroid dosing

Dexamethasone:	IV 10mg 12-hourly, if no improvement within 8-24 hrs, consider increasing to 6 hrly
Methylprednisone:	IV 500mg BD for 3 days, then IV 250mg BD for 2 days, then IV 125mg BD for 2 days, then IV 60mg BD for until CRS resolved

Reference: Lee, D.W. et al., ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant, 2019

Case Study No.1

On Review

- Mr Jon Doe, a 61 year-old man D+5 post CAR T-cell therapy for relapsed Diffuse Large B cell lymphoma.
- Feeling “hot” but otherwise well. Denies pain or focal infective symptoms. His vitals are noted in CRS assessment
- Today’s blood results are pending as you have just accessed his PICC but you note yesterday’s CBC results below.
- He has no known drug allergies. His weight is 100kg.

Haemoglobin 117 g/L L (130 - 175)
Haematocrit 0.36 L (0.40 - 0.52)
MCV 94 fL (80 - 99)
MCH 31 pg (27 - 33)
Platelets 76 x 10^9/L L (150 - 400)
WBC 1.7 x 10^9/L L (4.0 - 11.0)
Neutrophils 0.3 x 10^9/L L (1.9 - 7.5)
Lymphocytes 0.5 x 10^9/L L (1.0 - 4.0)

CRS Clinical Assessment

Time of Assessment	08:50	**08:55**	09:00
Has a temperature >38°C been recorded?	No	No	Yes
Temperature (°C)	**36.5**	**36.6**	**38.7**
Has the systolic Blood Pressure dropped <90mmHg?	No	No	Yes
Blood Pressure (mmHg)	**117/85**	**130/8-**	**89/60**
Has the patient required supplementary oxygen?	N	N	N
O_2 saturations (%)	**99%**	**99%**	**99%**
Has patient required oxygen to maintain O_2 saturations >90%?	No	No	No
If patient has required supplementary O_2, state concentration (in L/min) and mode of delivery (e.g. high flow, intranasal, other)	**No**	**No**	**No**
Has a pulse rate >100bpm been recorded?	No	No	Yes
Pulse Rate (bpm)	**90**	**95**	**101**
Respirations (per minute)	**18**	**19**	**22**

Case Study No. 1

What are the next most appropriate steps?

a. Consult the quick sheet for CRS and ICANS
b. Prepare a dose of intravenous broad spectrum antibiotics as per the Neutropenic Sepsis Pathway
c. Administer a 500mls bolus of intravenous fluids
d. Alert the Haematology SMO on call, CAR-T clinical fellow, CAR-T research nurse and PAR team
e. Confirm there is a dose of tocilizumab available on the ward
f. All of the above

1	**Fever ≥ 38°C** No hypotension No hypoxia	**Broad spectrum antibiotics** if neutropenic, or if any suspicion of sepsis (see Febrile Neutropenia policy) **Alert key contacts** (must inform Haem SMO on call) **Monitor vital signs** for hypotension, hypoxia, **increase frequency of observations** while febrile and as clinically indicated. **Daily blood tests** If persistent or refractory fevers lasting ≥ 3 days **Consider Tocilizumab + corticosteroids (Consult with Haematology SMO)**
2	**Hypotension** (SBP < 90mm Hg; no vasopressors), **and/or** **Hypoxia** (O_2 via nasal prongs up to 4L/min)	**As for grade 1 CRS, plus** **Initiate PAR team review** for hypotension +/- up to 1.5L IV fluids in up to 2 fluid boluses (avoid repeat fluid boluses) **Contact ICU** to consider early vasopressor use Administer O_2 via nasal prongs if hypoxic **Consider Tocilizumab + corticosteroids (Consult with Haematology SMO)**
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4	**Hypotension** (SBP < 90mm Hg; 2+ vasopressors), **and/or** positive pressure O_2 (intubation or mechanical ventilation)	**As for grade 3 CRS, plus** **Consider high dose methylprednisone (consult with Haematology SMO on call)**

Case Study No. 1- Outcome

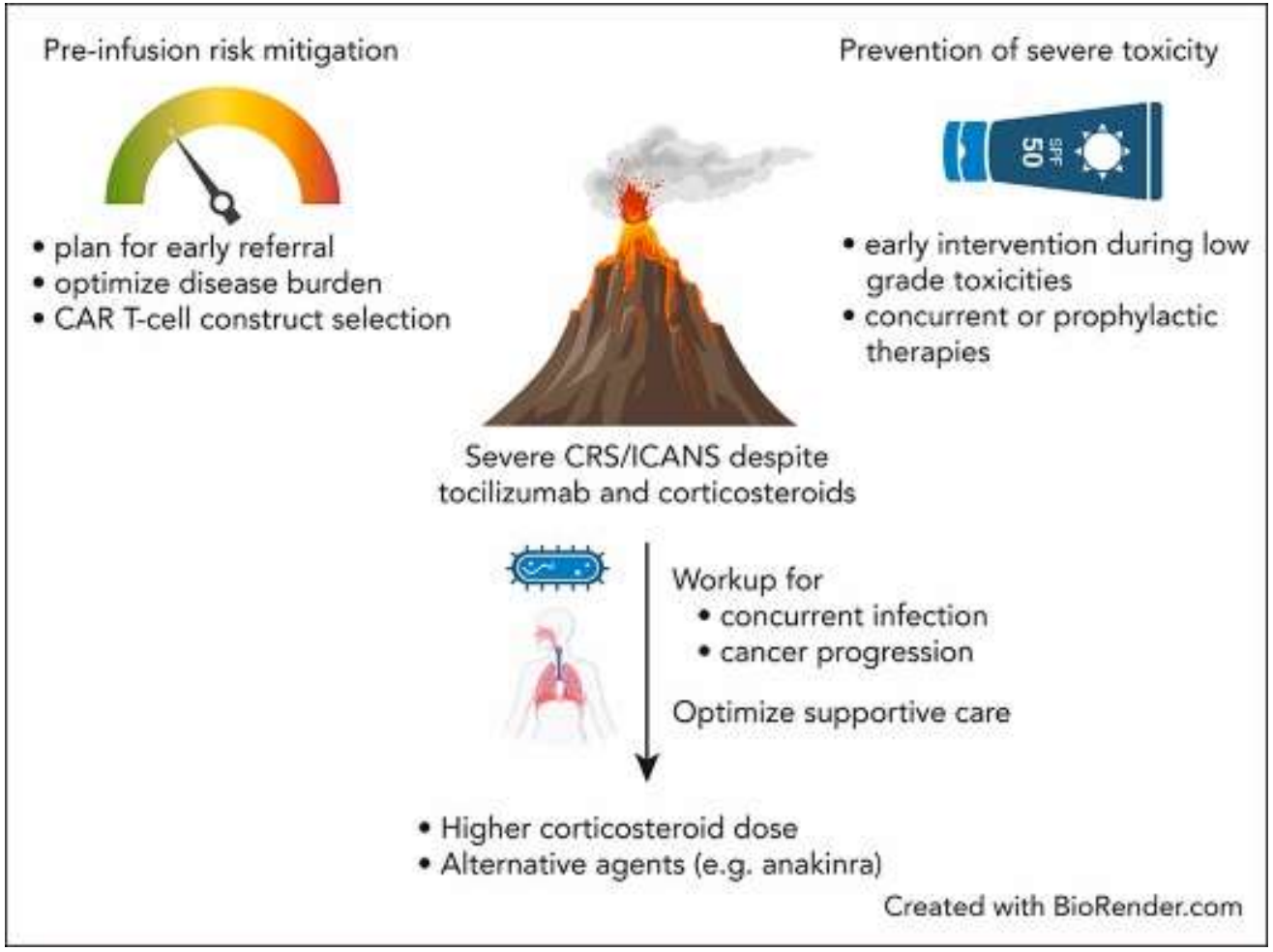
- Commenced on IV cefepime as empiric cover for neutropenic sepsis.
- Cytokine Release Syndrome Grade 2 due to hypotension and fever. He was treated with a bolus of 500ml 0.9% NaCl but he remained hypotensive at 89/60. He was given tocilizumab 800mg IV (8mg/kg).
- After 12 hours his blood pressure improved to 112/80 and his temp improved to 36.5 ◦C, so dexamethasone was not required.
- The PAR nurse discharged him from their f/u but advised ICU were happy to be contacted.
- Remained an inpatient for 48 hours for monitoring - IV cefepime was stopped as blood and urine cultures were negative and chest x-ray was normal.
- DC back to his local accommodation and outpatient WBCC monitoring resumed. He received a dose of G-CSF to support his neutropenia.

Key Learning Points

- *Always consider neutropenic sepsis as well as CRS- patients may need treatment for both!*
- *Refer to the Institutional Guidelines for CRS and escalate to medical staff promptly*
- *Check tociluzumab stock with Pharmacy*

Updates for Cytokine Release Syndrome

- How I Treat Series for Refractory CRS and ICANS 2023
  - Early intervention with tocilizumab and/or corticosteroids at lower grades of CRS and ICANS
  - Anakinra, an IL-1 receptor antagonist, as a potential treatment for CRS that is refractory to high-dose corticosteroids. –
  - Perform a thorough workup to rule out other potential causes of clinical deterioration, including infections and disease progression.



Jain, M.D., Smith, M. and Shah, N.N. (2023) 'How I treat refractory CRS and ICANS following car T-cell therapy', *Blood* [Preprint]. doi:10.1182/blood.2022017414.

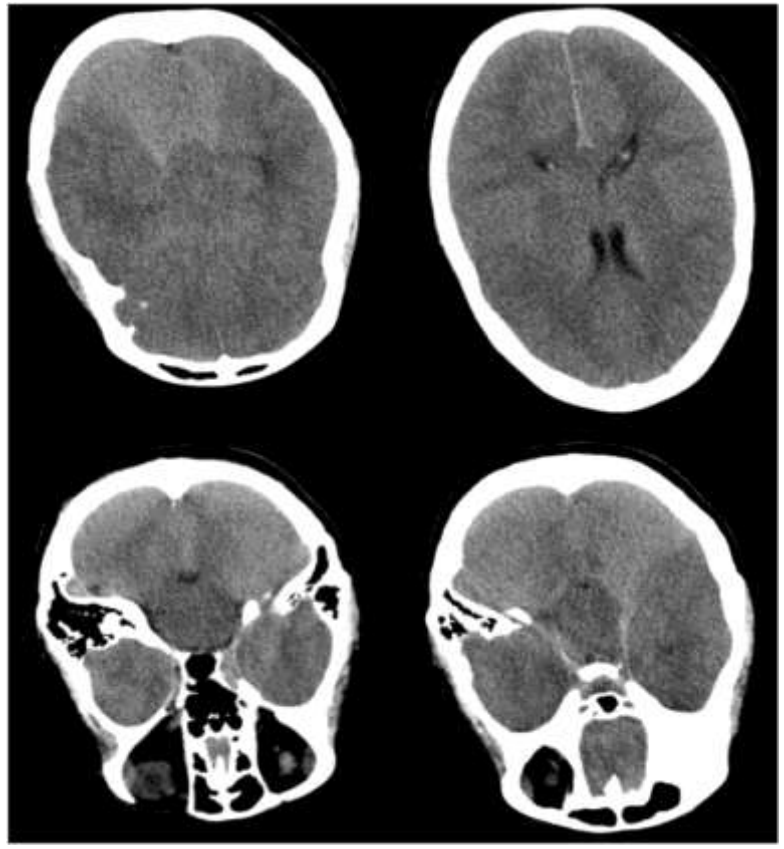
?Steroids for Cytokine Release Syndrome

- Single –centre retrospective comparative analysis of two cohorts, one early steroids + toci, other no steroids for low-grade CRS → NO high-grade CRS in steroid group and no impact on ICANS rates, CR, PFS and OS suggesting benefit to giving steroids early with toci. [Lakomy et al, 2023] [1]

[1] Lakomy, T. *et al.* (2023) 'Early use of corticosteroids following car T-cell therapy correlates with reduced risk of high-grade CRS without negative impact on neurotoxicity or treatment outcome', *Biomolecules*, 13(2), p. 382. doi:10.3390/biom13020382.

Immune Effector Cell Associated Neurotoxicity [ICANS]

- Mechanisms not fully understood
- May occur concurrently with CRS or independently
- Systemic inflammation and high levels of cytokines may disrupt the blood brain barrier
- You can think of ICANS as CRS within the brain, as Tocilizumab does not cross the blood/brain barrier steroids are the mainstay of treatment used for ICANS
- This can lead to altered neurological function and cerebral oedema in severe cases



A non-contrast CT head of a patient post CAR-T with ICANS showing signs of cerebral oedema, a potentially fatal complication.

Pensato, U. et al (2022). Fulminant cerebral edema following CAR T-cell therapy: case report and pathophysiological insights from literature review. *Journal of Neurology*, [online] 269(8), pp.4560–4563.

Pathophysiology of ICANS

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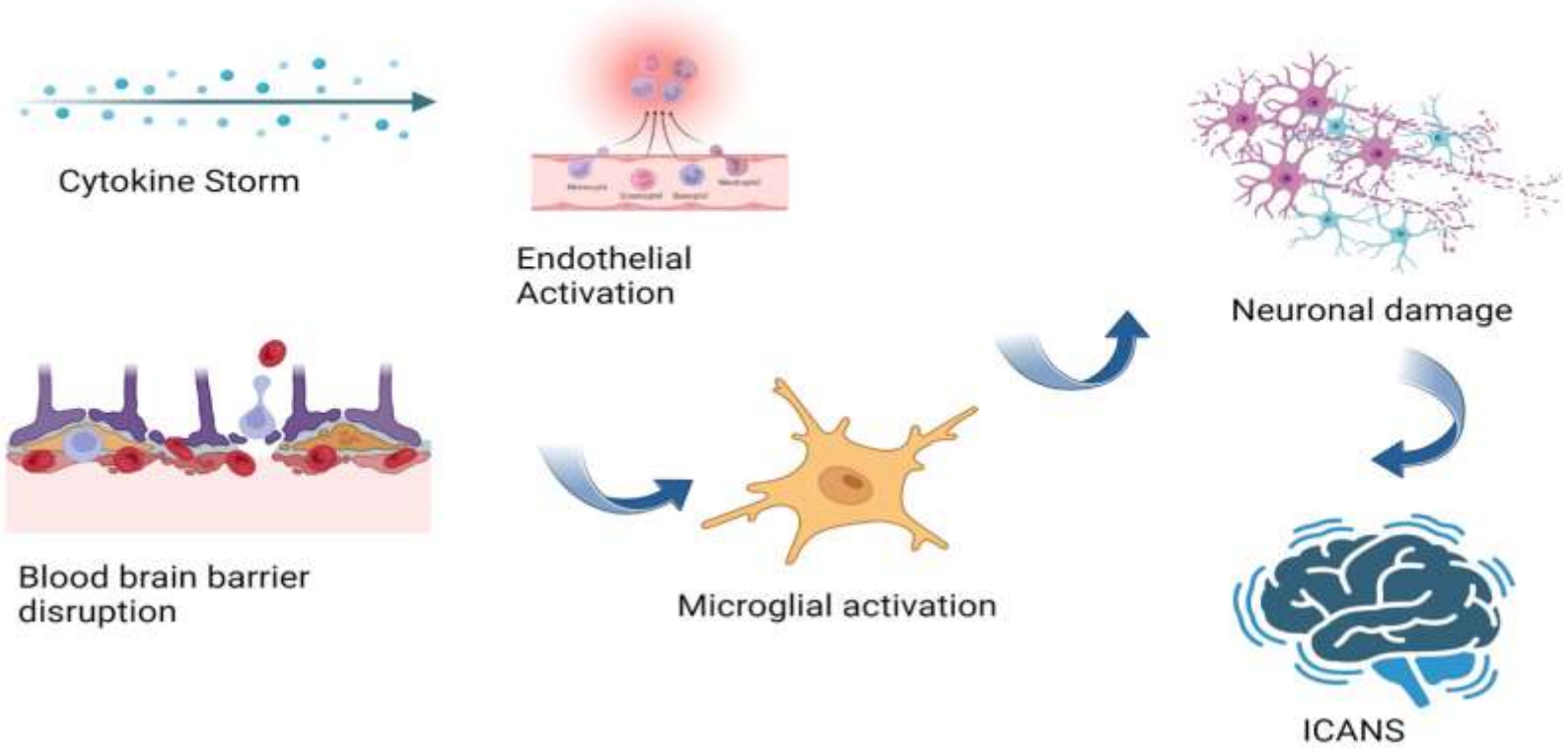


ENABLE Trial Quick Sheet: Adult ICANS Management

APPLIES ONLY TO MANAGEMENT AFTER CAR T-CELL THERAPY; NOT TO OTHER IMMUNOTHERAPIES SUCH AS BiTE THERAPY

If your patient is experiencing any of the following after CAR T-cell therapy:

- Reduced ICE score, Language disturbance, reduced attention
- Disorientation, Seizure, Motor weakness
- Raised Intracranial pressure

→ **Initiate Immune effector cell-associated Neurotoxicity Syndrome (ICANS) management – see PML**

Key contacts

Haematology SMO on-call 24 hour contact:	Via CCDHB switchboard
PAR Team:	#6785
CAR T - Principal Investigator:	(Dr Philip George)
CAR T - Clinical fellow:	(Dr Aine Hurley) 021 992422
CAR T - Research Nurse:	(Tess Ostapowicz) 021 055 0639
	(LJ Geniston) 027 269 0628

Grade	Description	Management
1	ICE score 7-9, **and** Awakens spontaneously	**NBM** until medical review and swallow assessment **Increase frequency of ICE assessments** **Switch to IV** meds and hydration (max 3L/day) Review medications for risk of CNS depression **Alert** CAR T-Trial 24 hour contact or Haematology SMO on call Consult with neurology per PML guideline and PAR team Consider MRI or CT Brain scan Consider Tocilizumab and corticosteroids if concurrent with CRS (see CRS quicksheet for dosing)
2	ICE score 3-6, **or** Awakens only to voice	As for grade 1 ICANS, plus PAR team referral Alert ICU and consider ICU admission If there is concurrent CRS give corticosteroids and Tocilizumab, if no CRS consider giving corticosteroids
3	ICE score 0-2, **or** Awakens only to touch, **or** Non-convulsive seizures **or** Focal or generalized seizures that resolves rapidly **or** Focal/local cerebral oedema on imaging	As for grade 2 ICANS, plus ICU admission for airway protection & monitoring Consider repeat neuroimaging every 2-3 days; monitor intracranial pressure (ICP); exclude non-convulsive status (see status epilepticus guidance) Administer Tocilizumab if there is concurrent CRS (see CRS sheet for dosing) Administer corticosteroids
4	Unrousable, **or** Life threatening prolonged seizure > 5 mins **or** Repetitive seizures without returning to baseline **or** diffuse cerebral oedema, **or** Decerebrate posture **or**	As for grade 3 ICANS, plus Consider invasive measures to relieve raised ICP (neurosurgical consult) Administer Tocilizumab if there is concurrent CRS (see CRS sheet for dosing) High-dose corticosteroids Convulsive status epilepticus management if needed

Immune effector Cell-associated Encephalopathy (ICE) assessment Tool

Orientation (4 points)	Orientation to year, month, city, hospital (1 point each)
Naming (3 points)	Name 3 objects: (eg point to clock, pen, button) (1 point each)
Following commands (1 point)	Ability to follow simple commands (eg "Show me 2 fingers", or "Close your eyes and stick out your tongue")
Writing (1 point)	Ability to write a standard sentence Ask patient to write 'my name is…..'
Attention 1 point)	Count backwards from 100 by 10s

Corticosteroid dosing

Grade 1-2 ICANS: Dexamethasone IV 10mg 12-hourly, if no improvement within 8-24 hrs, Increase to 20mg 12hrly

Grade 3 ICANS: Dexamethasone IV 20mg 12 hrly

If seizures present: Dexamethasone IV 20mg 6 hrly

Grade 4 ICANS or evidence of cerebral oedema: Methylprednisone IV 500mg BD for 3 days, then taper as per CRS quicksheet pathway

ICE Score **/10**

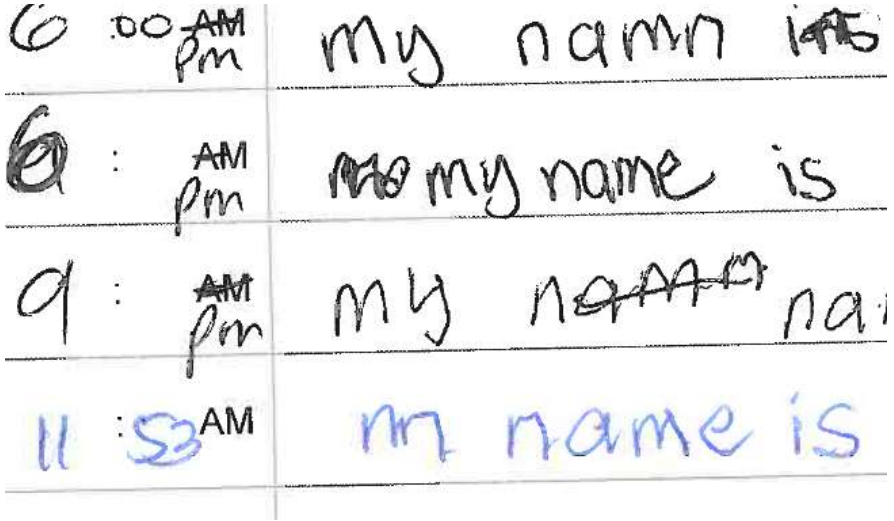
10:	No impairment
7 – 9:	Grade 1 ICANS
3 – 6:	Grade 2 ICANS
0 – 2:	Grade 3 ICANS
0:	Grade 4 ICANS – Unrousable & unable to perform ICE assessment

Reference: Lee, D. W., et al., ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector cells. Biol

Case Study No. 2

- **On Review**
- Mr. Joe Bloggs is a 58 year-old man presenting for outpatient assessment at WBCC on D+7 post CAR T-cell therapy for Transformed follicular lymphoma.
- He is complaining of feeling tired. He has noticed difficulty doing the crossword. His support person also reports him to be less alert than usual.
- Your ICE score is noted here. A sample of his handwriting is shown here.

ICE SCORE		
Time of Assessment	08:45	09:00
Write score		
Can patient say what year it is? ***1 pt***	1	1
Can patient say what month it is? ***1 pt***	**1**	**0**
Does patient know what city they are in? ***1 pt***	**1**	**1**
Does patient know what hospital they are in? ***1 pt***	**1**	**1**
Ask patient to show 2 fingers or close their eyes and stick out their tongue ***1 pt***	**1**	**1**
Can patient name three objects? i.e. pen, clock (point to 3 objects) ***3 pts***	**1**	**1**
Can patient write 'my name is…'? on back page ***1 pt***	**1**	**0**
Can patient count backwards from 100 in 10s? ***1 pt***	**1**	**1**
Score	**10/10**	**8/10**



Case Study No. 2

- What are the next most appropriate steps?

- a. Review the ICANS Quicksheet
- B. Increase frequency of ICE monitoring
- C. Arrange admission to 5 North for inpatient monitoring, swallow assessment and consider imaging of brain
- D. Alert Haematology SMO, CAR T fellow and research nurse
- E. Alert the PAR team, and neurology services
- F. All of the above

Immune effector Cell-associated Encephalopathy (ICE) assessment Tool

Orientation (4 points)	Orientation to year, month, city, hospital (1 point each)
Naming (3 points)	Name 3 objects: (eg point to clock, pen, button) (1 point each)
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0:	Grade 4 ICANS – Unrousable & unable to perform ICE assessment

Case Study No. 2- Outcome

- Mr. Joe Bloggs was admitted to 5 North for inpatient monitoring of Grade 1 ICANS (ICE score 8/10). Vital signs were normal with no CRS evident. Twelve hours after admission he became more drowsy with a deterioration in ICE score to 6/10 due to difficult naming objects and disorientation.
- He was treated with IV dexamethasone. Neurology was consulted and prophylactic levetiracetam was commenced IV to prevent seizures. EEG did not show seizure activity. SLT were consulted and swallow assessment was normal. CT head was unremarkable.
- ICU were consulted but as GCS 14/15 they recommended ongoing ward-based care.
- Overnight ICE score improved to 9/10 with subsequent resolution of ICANS the next day. He was discharged back to outpatient WBCC monitoring .

Key Learning Points

- *Signs of early ICANS can be subtle-pay particular attention to handwriting and speech*
- *Refer to ICANS Quicksheet and escalate promptly.*
- *Involve neurology team in ICANS management*

ICANS Key Management Points

- Early recognition and grading
- Seizure Prevention
  - Anti-epileptic drugs
  - Monitoring e.g. EEG
- Exclude other pathologies e.g. CNS disease/infection
- Steroids
  - Tocilizumab if concurrent CRS, but doesn't penetrate CSF!
- Swallow- keep patients NBM, switch medications PO to IV
- and early SLT referral

ICE SCORE		
Time of Assessment	08:45	09:00
Write score		
Can patient say what year it is? ***1 pt***	1	1
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Grant, S.J. *et al.* (2022) 'Clinical Presentation, Risk Factors, and Outcomes of Immune Effector Cell-Associated Neurotoxicity Syndrome Following Chimeric Antigen Receptor T Cell Therapy: A Systematic Review', *Transplantation and Cellular Therapy*

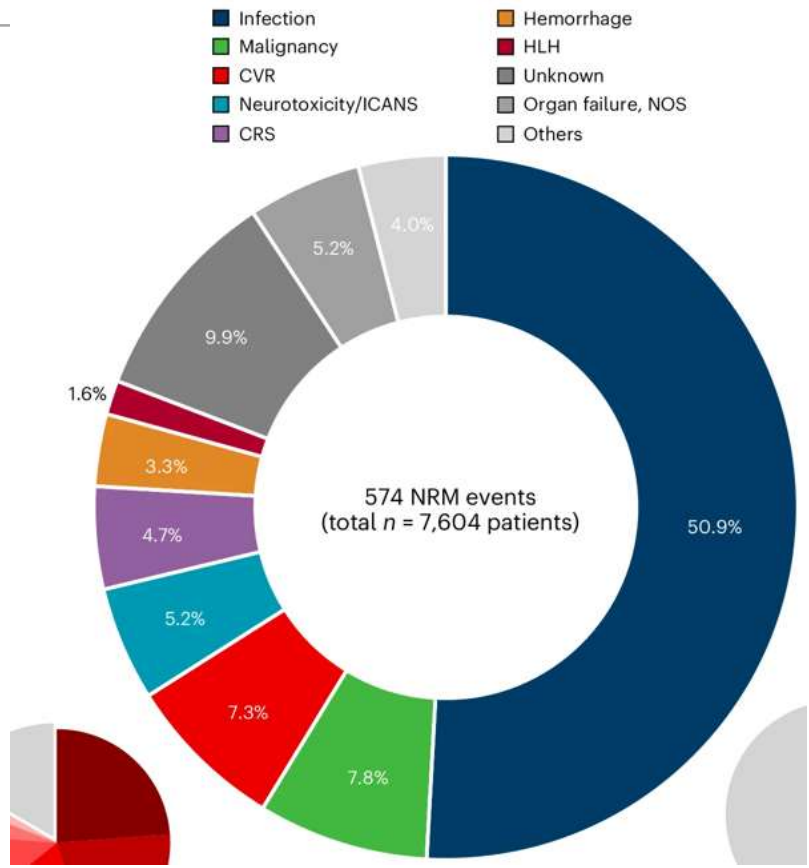
Updates ICANS Management 2023/2024

- Single- arm phase II trial of prophylactic Anakinra found it reduced rates of CRS and ICANS without impact on CR- all grade and ≥ grade 3 ICANS rates of 22% and 9% vs. reported 56% all grade and 38% ≥ grade 3 ICANS rates in 168 patients receiving axi-cel. [1]
- Given low rates of ICANS from ENABLE-1 unlikely to need to consider prophylaxis.
- Continuous video EEG monitoring in patients with ICANS captured 75% incidence of non-convulsive seizures [2]

1. Park, J.H., Nath, K., Devlin, S.M. *et al.* CD19 CAR T-cell therapy and prophylactic anakinra in relapsed or refractory lymphoma: phase 2 trial interim results. *Nat Med* **29**, 1710–1717 (2023)2. Satyanarayan S, Spiegel J, Hovsepian D, et al. Continuous EEG monitoring detects nonconvulsive seizure and Ictal-Interictal Continuum abnormalities in moderate to severe ICANS following systemic CAR-T therapy. *The Neurohospitalist*. 2023;13(1):53-60

Infection Prophylaxis

- Infection leading cause of non-relapse mortality after CAR T-cell
- therapy (56%,29% with non–COVID-19 and 27% with COVID-19) [*]
- Bacterial infections predominate early (<d30), respiratory viral infections predominate later.
- Australasian Consensus Guidelines for Prevention of Infection post anti CD19 CAR T-cell therapy- under progress.



Lemoine J, et al.. Nonrelapse mortality after CAR T-cell therapy for large B-cell lymphoma: a LYSA study from the DESCAR-T registry. Blood Adv. 2023 Nov 14;7(21):6589-6598. doi: 10.1182/bloodadvances.2023010624. PMID: 37672383; PMCID: PMC10641092.

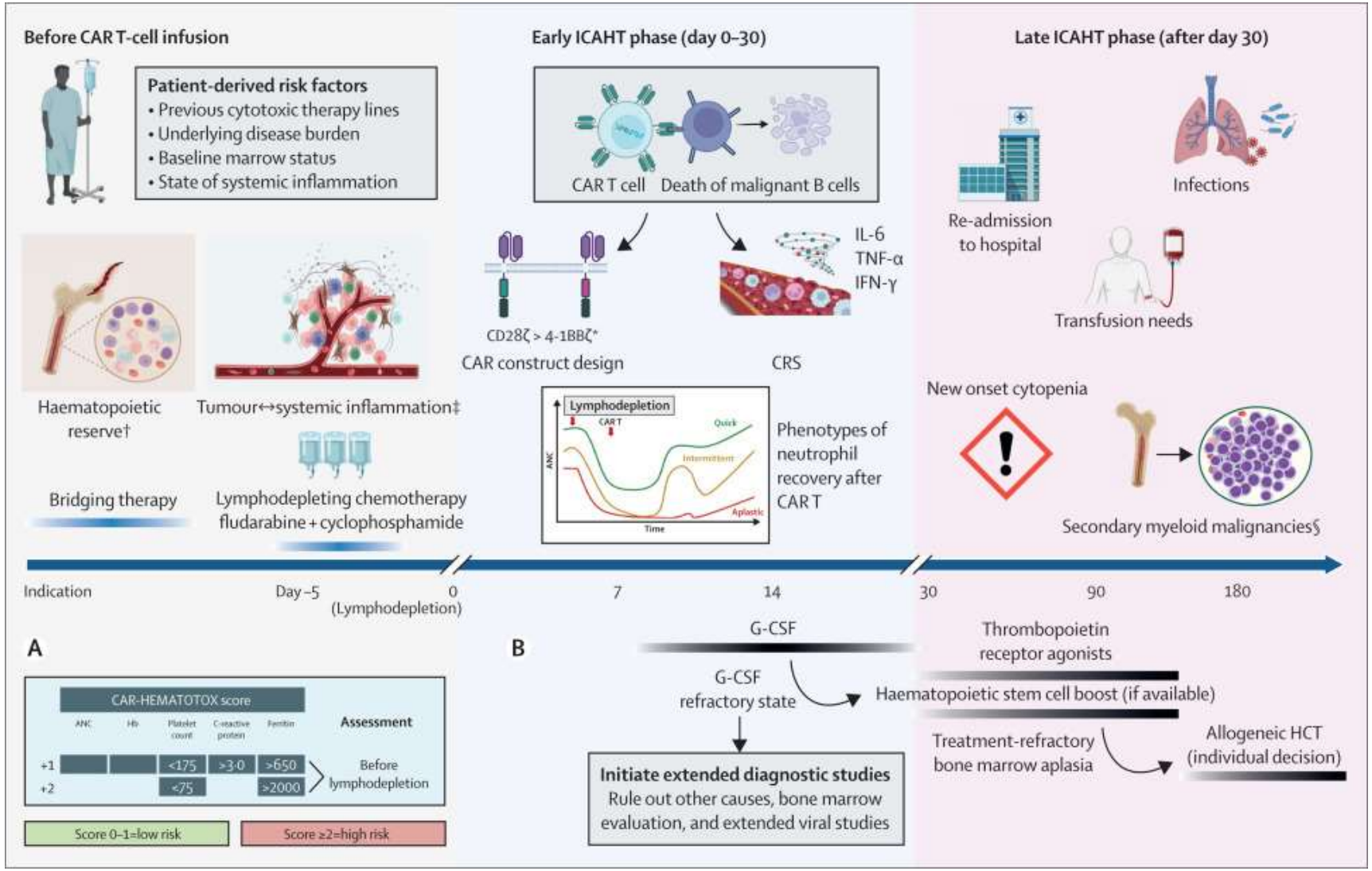
Infection Prophylaxis

- Antimicrobials
  - Valacylcovir for at least 1 year
  - Cotrimoxazole or alternative PJP prophylaxis for at least 1 year
  - Fluconazole for 1 month or longer if prolonged neutropenia or high-dose steroids
  - Entecavir for at least 18 months in hep B core ab +ve patients
- Vaccination
  - COVID-19 and flu from 6/12 post CAR T
  - HiB, Hep B, Shingrix, HPV (18-45y), 4CMenB, MenACWY, Prevenar13, Pneumovax, polio, Tdap from 1 year
  - MMR, Varicella if negative serology post Shingrix

Infection Prophylaxis

- IV IG
  - Commence monthly IVIG if IgG <4.0 g/dL
  - Consider if IgG 4.0 to 6.0 with recurrent or serious infections
  - Can consider trial off IGRT if IgG levels maintained at >6.0g/dL for three consecutive months without bacterial infections

ICAHT- *Immune Effector-Cell Associated Haematological Toxicity*



ENABLE-1 Preliminary Results

- CAR- Haematatox score can be used to predict risk.
- ENABLE-1 50% 15/30 had HIGH CAR HAEMATOTOX score
- Late ICAHT occurred in 10 patients (33%) and was grade 3–4 in 4 (13%).

Risk Factors for ICAHT

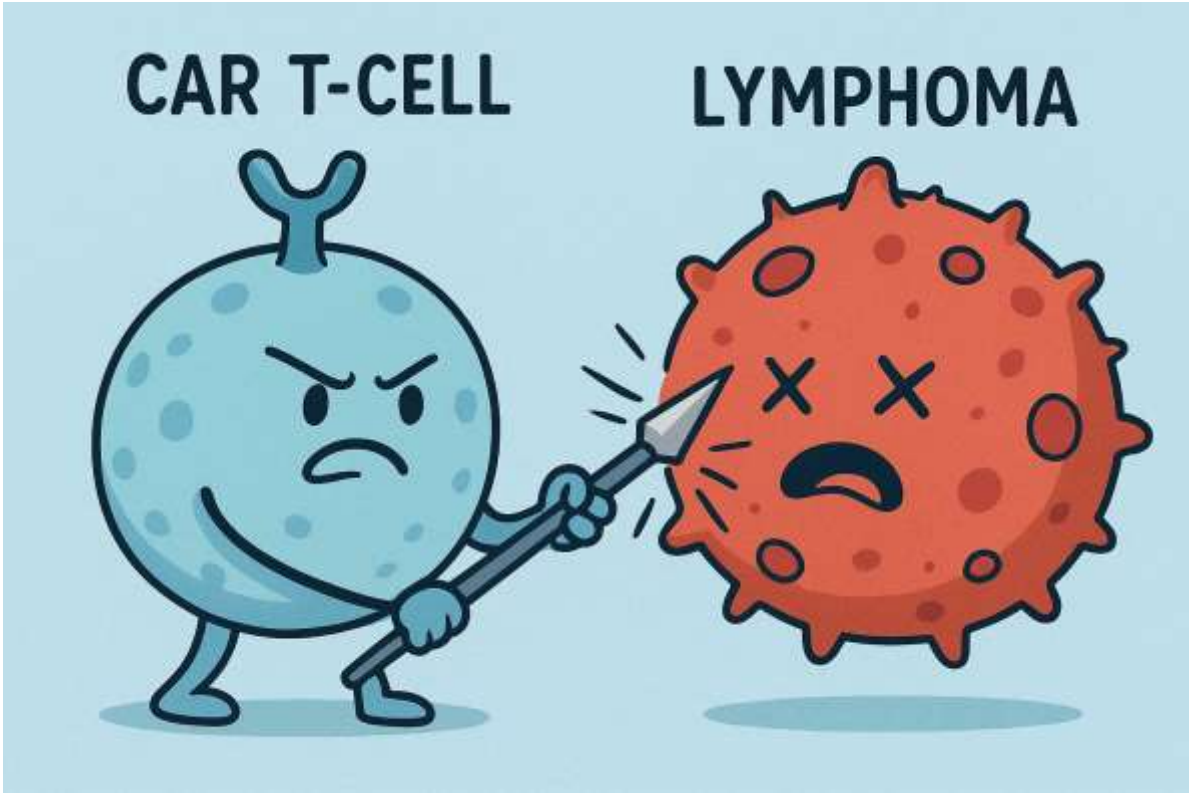
- Prior Therapy
- Baseline marrow disease
- Disease features
- Baseline inflammatory state
- CAR T product
- Severe CRS

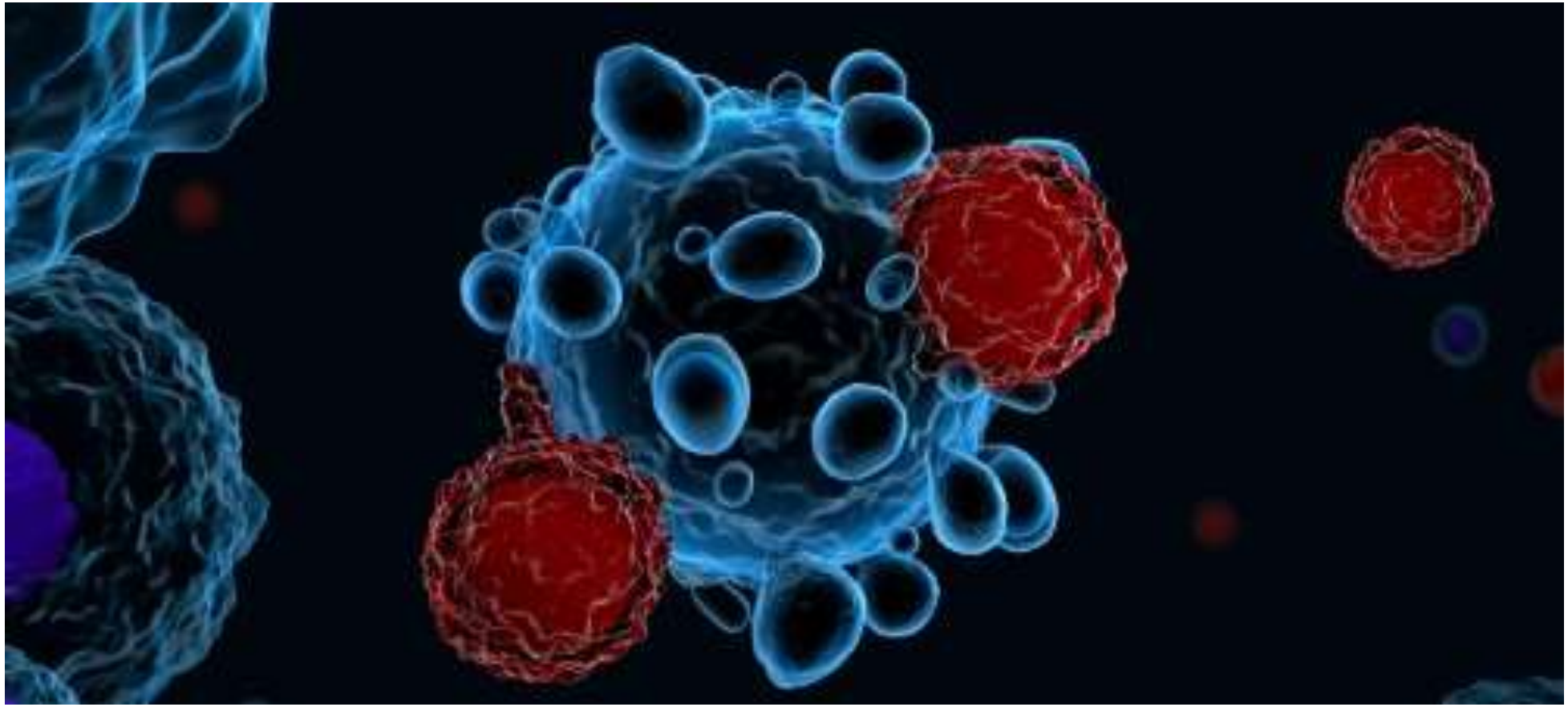
Work-Up of ICAHT

	Categories	Putative causes	Test	Time points	Comments
TIER 1	Lower threshold to perform – minimal workup				
	Poor bone marrow reserve	Prior treatments including allo-HCT, fludarabine, marrow infiltration	Complete blood count (CBC), reticulocyte production index (RPI), peripheral blood smear	Routinely	Recommended
	Medication – drug side effects	Check for concomitant myelosuppressive medications		Routinely	
	Vitamin deficiencies	Vitamin B12, folic acid	Serum levels	Routinely	Recommended
	Rule out infections	Bacterial/viral/fungal infections	Blood cultures, CMV PCR, procalcitonin, $CD4^+$ T-cell, IgG, B-cell levels	Routinely	Recommended
	Rule out macrophage-activation syndrome*	CRS/MAS or IEC-HS	Serum ferritin, triglycerides	Routinely	Recommended
TIER 2	Subsequent work-up – In case of G-CSF refractory state, if tier 1 results are negative and/or risk factors are present				
	Viral PCR considering the clinical presentation	Parvovirus	Parvovirus B19 PCR	In case of prolonged anemia	Recommended
		HHV6, JCV	HHV6, JCV PCR blood/CSF	In case of neurologic symptoms	Recommended
		EBV, adenovirus, HSV	PCR	In case of HLH	Recommended
	Bone marrow disease	(MDS/AML/myelofibrosis) or relapse	BM aspirate, biopsy, flow cytometry, immunohistochemistry, cytogenetics, NGS	In case of prolonged cytopenia	Recommended
		Relapse of leukemia/lymphoma	Flow cytometry peripheral blood / bone marrow, including B-cell panel	Routinely	Recommended
	Other causes	Other rare hematologic diseases, myeloid diseases, PNH, autoimmune processes	Myeloid panel, GPI-linked structures, direct antiglobulin test (DAT)	In case of suspected MPN/ PNH/autoimmune processes	Recommended

Summary

- CAR T-cell therapy is international standard of care for refractory and relapsed B-cell lymphoma
- ENABLE-2 Trial Recruitment ongoing
- CRS and ICANS are immune-effector cell toxicities that carry morbidity and mortality as well as implications for disease outcomes- early intervention is key
- More to follow on infection with Australasian Consensus Guidelines for Prevention of Infection in Adults after treatment with CAR T-cell





THANK YOU!