Tisagenlecleucel (Kymriah®) (CAR-T) B-ALL

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.	C91	00686a	ODMS 01/07/2021

* This is for post 2012 indications only.

TREATMENT:

Tisagenlecleucel (Kymriah®) must be administered in an NCCP designated CAR-T centre

Tisagenlecleucel (Kymriah®) is intended for autologous use only.

Facilities to treat anaphylaxis MUST be present when lymphodepleting therapy and CAR-T cells are administered.

Pre-treatment conditioning:

- Lymphodepleting chemotherapy is recommended to be administered before Tisagenlecleucel infusion unless the white blood cell (WBC) count within one week prior to infusion is ≤1x10^9/L)
- At the discretion of the prescribing consultant, lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is ≤1 x10^9/L within 1 week prior to tisagenlecleucel infusion
- Please refer to the relevant lymphodepletion regimen as decided by the treating clinician at the designated CAR-T centre

Tisagenlecleucel Administration:

- Please refer to the local CAR-T policy for tisagenlecleucel (Kymriah®) administration information
- Tisagenlecleucel is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy
- If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the tisagenlecleucel (Kymriah®) infusion and the WBC count is >1x10^9/L, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving tisagenlecleucel

- Tocilizumab for use in the event of cytokine release syndrome and emergency equipment must be available for each patient prior to infusion. The treatment centre must have access to additional doses of tocilizumab within 8 hours
- The total dose is contained in 1 or more infusion bags

Table 1: Tisagenlecleucel Administration

Day	Treatment	Dose	Route
Infuse 2 to 14 days **after** completion of the lymphodepleting chemotherapy	**Tisagenlecleucel (Kymriah®)**	- For patients 50kg and below: 0.2 to 5 x 10^6 CAR-positive viable T cells/kg body weight - For patients above 50kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based)	IV infusion[1, 2, 3]
[1]Through latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow. All contents of the infusion bag(s) should be infused. NaCl 0.9% solution for injection should be used to prime the tubing prior to infusion and to rinse it after infusion. When the full volume of tisagenlecleucel has been infused, the infusion bag should be rinsed with 10-30mL NaCl 0.9% solution for injection by back priming to ensure as many cells as possible are infused into the patient.			
[2] Refer to local policy for alternative administration procedures where appropriate			
[3]The product should be administered immediately after thawing. After thawing, the product should be kept at room temperature (20°C-25°C) and infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.			

ELIGIBILITY:

- Indications as above
- Medical assessment as per local CAR-T assessment form

EXCLUSIONS:

- Known or suspected hypersensitivity to tisagenlecleucel or the excipients
- Known or suspected hypersensitivity to fludarabine or cycloPHOSphamide or the excipients
- Contraindications of the lymphodepleting chemotherapy must be considered
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Pregnancy or lactation

CAUTION IN USE:

- Due to the risks associated with tisagenlecleucel treatment, infusion should be delayed if a patient has any of the following conditions:
  - Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies.
  - Active uncontrolled infection
  - Active graft-versus-host disease (GVHD)
  - Significant clinical worsening of leukaemia burden or lymphoma following lymphodepleting chemotherapy

PRESCRIPTIVE AUTHORITY:

- Haematology consultant working in the area of haematological malignancies who is trained in the administration and management of patients treated with tisagenlecleucel within a designated CAR-T treatment centre.

TESTS:

- Baseline and regular tests carried out in accordance with the hospital's CAR-T Workup Protocol

Disease monitoring:

- Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant
- No steroids should be administered without approval of the treating Haematology Consultant

DOSE MODIFICATIONS:

- No dose modifications are recommended for tisagenlecleucel
- Any dose modification consideration should be discussed with a Haematology Consultant

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Please refer to appropriate NCCP/local lymphodepletion regimen for further information on anti-emetic regimen

PREMEDICATIONS:

Please refer to hospital's CAR-T policy

- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 1g PO once only 60 minutes prior to tisagenlecleucel infusion and chlorphenamine 10mg IV Injection once only 60 minutes prior to tisagenlecleucel infusion
- No steroids should be administered without approval of the treating Haematology Consultant

OTHER SUPPORTIVE CARE:

- All patients should receive irradiated blood products (**Refer to local policy)**

Table 2: Suggested supportive care[a] (refer to local policy as appropriate to patient's age and hospital site)

HSV prophylaxis	All patients should receive the following until CD4 count >200/microlitre: • Valaciclovir 500mg once daily PO or • Aciclovir 250mg TDS IV (if oral route not available or ANC < $0.5X10^9$/L) Patients with an active herpes infection should receive the following: • Valaciclovir 1g TDS PO or • Aciclovir 10mg/kg TDS IV (if oral route not available)
Antifungal prophylaxis	Anti-fungal prophylaxis is commenced on the first day of lymphodepleting chemotherapy and continued until neutrophil count ≥$1x10^9$/L and complete remission. • Posaconazole PO 300mg twice daily on first day, then 300mg once daily thereafter.
PJP prophylaxis	**All patients should receive the following for three months post-CAR-T infusion or until CD4 count >200/microlitre:** **PJP prophylaxis is started on the first day of lymphodepleting chemotherapy regimen.** **1st line therapy** • Co-trimoxazole 960mg BD Mon/Wed/Fri PO **2nd line therapy (if allergic to co-trimoxazole or contraindicated):** • Pentamidine 300mg nebule and salbutamol 2.5mg nebule pre-pentamidine, every 4 weeks
Mouthcare	Mucositis WHO grade < 2: • Sodium chloride 0.9% 10ml QDS mouthwash • Nystatin 1ml QDS PO (use 15 minutes after sodium chloride 0.9% mouthwash) Mucositis WHO grade ≥ 2: • Chlorhexidine digluconate 0.12% (Kin®) 10mls QDS PO • Nystatin 1ml QDS PO (use 15 minutes after Kin® mouthwash)
Gastro protection	• Lansoprazole 30mg / omeprazole 40mg once daily PO Or • Esomeprazole 40mg once daily IV (if oral route not available)
Prevention of vaginal bleeding	If required for menstruating female patients until platelets > 50 $x10^9$/L • Norethisterone 5mg TDS PO if >55Kg • Norethisterone 5mg BD PO if <55kg

Tumour Lysis syndrome	Consider allopurinol in active disease pre CAR-T infusion • Allopurinol 300mg once daily PO for 5-7 days and review
Hepatitis B prophylaxis/treatment	A virology screen is completed as part of CAR-T workup. Hepatitis B prophylaxis or treatment may be initiated in consultation with a Virology Consultant or Hepatology Consultant if required. Options may include: • Lamivudine 100mg once daily PO Or • Entecavir 750microgram once daily PO
Prevention of constipation	Consider laxatives if appropriate e.g. • Senna two tablets (15mg) nocte PO while on ondansetron
Antibiotic standing order	Antibiotic standing order should be prescribed for neutropenic sepsis/neutropenic fever based on previous microbiology and renal function • Piptazobactam 4.5g QDS IV Plus • Amikacin* 15mg/kg once daily IV *Ciprofloxacin 400mg BD IV may be considered instead of amikacin in cases of renal impairment Refer to local hospital antimicrobial guidelines for antibiotic choice where a patient is allergic to any of the above
Magnesium and potassium standing order	Magnesium and potassium standing orders should be prescribed for all CAR-T patients in accordance with stem cell unit practice
VTE prophylaxis	Consider VTE prophylaxis in accordance with local policy
Bone Health	Consider calcium and vitamin D supplementation prior to discharge for patients who are on high dose steroids. Other medications for maintenance of bone health may need to be considered as appropriate. • Calcium carbonate and colecalciferol (Caltrate® 600mg/400units) 1 tablet BD

[a]Based on local practice in St James Hospital when V1 of regimen developed

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Tisagenlecleucel is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

- Please refer to the relevant Summary of Product Characteristics and local Stem Cell Transplant Programme PPGs for full details.

DRUG INTERACTIONS:

- The relevant Summary of Product Characteristics and current drug interaction databases should be consulted.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP.

https://www.hcp.novartis.com/products/kymriah/acute-lymphoblastic-leukemia-children/hcp-resources/

REFERENCES:

1. Tisagenlecleucel (Kymriah®) Summary of product characteristics EMA. Last updated: 03/05/2023. Accessed Nov 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf
2. ELIANA study: Maude SL et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018; 378:439-448

Version	Date	Amendment	Approved By
1	02/11/2021		Dr Larry Bacon
2	16/05/2022	Amendment to include paediatric patients and CHI as the treatment centre.	Dr Pamela Evans
3	14/05/2024	Reviewed. Updated pre-treatment conditioning section, treatment table footnotes, title of table 2	Dr Larry Bacon, Dr Pamela Evans
3a	19/07/2024	Typographical errors removed	NCCP
3b	01/04/2025	Amended wording of indication 686a (in line with SPC) to clarify age limit	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.