Tisagenlecleucel (Kymriah®) (CAR-T) DLBCL and FL

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.	C83	00687a	ODMS 01/07/2021
Treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.	C82	00687b	N/A

* 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 $\leq 1 \times 10^9$/L)
- Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is $\leq 1 \times 10^9$/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
- **DLBCL indication:**
  - Tisagenlecleucel is recommended to be infused **2 to 14 days** after completion of the lymphodepleting chemotherapy as per table 1 below.
- **FL indication:**
  - Tisagenlecleucel is recommended to be infused **2 to 6 days** after completion of the lymphodepleting chemotherapy as per table 2 below.
- The total dose is contained in 1 or more infusion bags
- If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the tisagenlecleucel (Kymriah®) infusion and the WBC count is $>1 \times 10^9$/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

Table 1: Tisagenlecleucel Administration in DLBCL

Day	Treatment	Dose	Route
Infuse **2 to 14** days **after** completion of the lymphodepleting chemotherapy	**Tisagenlecleucel (Kymriah®)**	0.6 to 6 x 10^8 CAR-positive viable T cells (non-weight based)	IV infusion[1]
[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.			
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.			

Table 2: Tisagenlecleucel Administration in FL

Day	Treatment	Dose	Route
Infuse **2 to 6** days **after** completion of the lymphodepleting chemotherapy	**Tisagenlecleucel (Kymriah®)**	0.6 to 6 x 10^8 CAR-positive viable T cells (non-weight based)	IV infusion[1]
[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.			
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

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
- 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 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

OTHER SUPPORTIVE CARE:

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

Table 3: Suggested Supportive Care[a]

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	**<u>All patients should receive the following for three months post-CAR-T infusion or until CD4 count >200/microlitre:</u>** **<u>PJP prophylaxis is started on the first day of lymphodepleting chemotherapy regimen.</u>** **<u>1st line therapy</u>** • Co-trimoxazole 960mg BD Mon/Wed/Fri PO **<u>2nd line therapy (if allergic to co-trimoxazole or contraindicated):</u>** • 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

- Please refer to the relevant Summary of Product Characteristics and local CAR-T/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/diffuse-large-b-cell-lymphoma-adults/

REFERENCES:

1. Schuster, SJ et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. NEJM 2019; 380:45-56 DOI:10.1056/NEJMoa1804980 (Including supplementary material)
2. Fowler NH, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med 2022. Feb;28(2):325-332.
3. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229.
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Tisagenlecleucel (Kymriah®) Summary of product characteristics EMA. Last updated: 20/03/2024. Accessed Aug 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	02/11/2021		Dr Larry Bacon
2	04/03/2024	Reviewed.	Dr Larry Bacon
2a	19/07/2024	Typographical errors removed	NCCP
3	14/03/2025	New indication added for follicular lymphoma	Dr Larry Bacon

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.