Fludarabine & cycloPHOSphamide Lymphodepletion for Tisagenlecleucel (Kymriah®) DLBCL and FL

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Lymphodepletion chemotherapy regimen pre-treatment for CAR-T therapy Tisagenlecleucel (Kymriah®) in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.	C83	00606a	N/A
Lymphodepletion chemotherapy regimen pre-treatment for CAR-T therapy Tisagenlecleucel (Kymriah®) in adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.	C82	00606b	N/A

* This is for post 2012 indications only.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

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

Facilities to treat anaphylaxis MUST be present when the chemotherapy 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

Tisagenlecleucel Administration:

- Please refer to the local CAR-T policy for tisagenlecleucel (Kymriah®) information
- **DLBCL indication:**
  - Tisagenlecleucel is recommended to be infused **2 to 14** days after completion of the lymphodepleting chemotherapy
- **FL indication:**
  - Tisagenlecleucel is recommended to be infused **2 to 6** days after completion of the lymphodepleting chemotherapy

Day	Drug	Dose	Route	Diluent & Rate	Cycle
-5,-4,-3	**Fludarabine**[1]	25mg/m^2	IV	100mL NaCl 0.9% over 30 minutes	1
-5,-4,-3	**Mesna**	100mg/m^2	IV	Slow IV bolus Into the side arm fast flowing NaCl 0.9% infusion immediately prior to cycloPHOSphamide	1
-5,-4,-3	**cycloPHOSphamide**	250mg/m^2	IV	500mL NaCl 0.9% over 60 minutes	1
-5,-4,-3	**Mesna**	100mg/m^2	IV	At 2 and 6 hours after the start of cycloPHOSphamide infusion (6 doses in total)	1
0	**Tisagenlecleucel (Kymriah®)**		IV	Please refer to the hospital's CAR-T policy for Tisagenlecleucel (Kymriah®)	

[1]All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation)
Dose rounding:
Fludarabine doses ≤50mg to the nearest 2.5mg and doses ≥50mg to the nearest 5mg
cycloPHOSphamide to the nearest 20mg
Mesna to the nearest 100mg for IV route

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Notes:

The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting regimen. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion and the WBC count is >1x10^9/L, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving tisagenlecleucel.

ELIGIBILITY:

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

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

EXCLUSIONS:

- Known or suspected hypersensitivity to fludarabine, cycloPHOSphamide or tisagenlecleucel or any of the excipients
- Pregnancy and lactation
- Haemolytic anaemia

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 local 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:

- Any dose modifications of should be discussed with the treating Haematology Consultant.
- **Chemotherapy dosing in obese adult patients**: See local policy

Renal and Hepatic Impairment:

- Discuss with the treating consultant if hepatic impairment or if creatinine clearance is < 70mL/min for advice on fludarabine dosing
- Consult the following resources to inform any renal or hepatic dose modification discussions:
    - Summary of product characteristics (SPC) available at http://www.hpra.ie
    - 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
    - Local hospital policy

MANAGEMENT OF ADVERSE EVENTS:

- Refer to local policy

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

  - Fludarabine: Minimal **(Refer to local policy)**
  - cycloPHOSphamide: Moderate **(Refer to local policy)**

For information:

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists. Information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for Inclusion in NCIS (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for Inclusion in NCIS (Haemato-oncology) - Available on the NCCP website

Table 1: Suggested Regimen Specific Anti-emetics[a]

Prevention of acute emesis			Prevention of delayed emesis			Comments
Drug	**Dose**	**Admin day**	**Drug**	**Dose**	**Admin day**	
Cyclizine	50mg PO TDS	-5 to -3	Cyclizine	50mg PO TDS PRN	-2 to -1	dexAMETHasone not used as part of anti-emetic regimen prior to tisagenlecleucel infusion
Ondansetron	8mg PO/IV TDS PRN	-5 to -1				

[a]Based on local practice in St James Hospital

OTHER SUPPORTIVE CARE:

Table 2: Other Suggested Supportive Medication[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 (D-5) and continued until neutrophil count ≥1x10^9/L and complete remission. • Posaconazole PO 300mg twice daily on D-5, 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 (D-5)** **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 transplant • Allopurinol 300mg once daily PO for 5-7 days and review
Hepatitis B prophylaxis/treatment	A virology screen is completed as part of transplant 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 transplant 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) one 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 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

HCP Information: https://www.hcp.novartis.com/products/kymriah/

REFERENCES:

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2. Schuster SJ, Bishop MR et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma. N Engl J Med 2019; 380:45-56 DOI: 10.1056/NEJMoa1804980.
3. 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.
4. Lymphodepletion protocol for DLBCL v1.0. King's College Hospital London.
5. Kymriah® Summary of Product Characteristics. Accessed Aug 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf
6. 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.
7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
8. NCCP BACKGROUND DOCUMENT EXTRAVASATION CLASSIFICATION OF SYSTEMIC ANTI-CANCER THERAPY V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/classification.pdf

Version	Date	Amendment	Approved By
1	02/11/2021		Dr Larry Bacon
2	03/05/2022	Amended SJH regimen specific anti-emetics (replaced domperidone with cyclizine).	Dr Larry Bacon
3	04/03/2024	Reviewed	Dr Larry Bacon
3a	19/07/2024	Typographical errors removed	NCCP
4	05/12/2024	Amended regimen specific anti-emetics	Dr Larry Bacon, Dr Robert Henderson
5	14/03/2025	Added indication 606b	Dr Larry Bacon

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.