Chemotherapy Protocol

CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY
LISOCEL – CYCLOPHOSPHAMIDE (300) – FLUDARABINE (30)

This regimen will only be available to prescribe at the Wessex Blood and Marrow Transplant Unit

Regimen

- Lisocabtagene maraleucel – Cyclophosphamide (300) – Fludarabine (30)

Indication

- CAR-T therapy with Lisocel (lisocabtagene maraleucel) for the treatment of adult patients with:
  - Diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who have relapsed, within 12 months from completion of, or are refractory to first-line chemoimmunotherapy.
  - Relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy.
- Lymphodepleting chemotherapy must be administered prior to Lisocel. This protocol includes both lymphodepletion and CAR-T administration.
- For autologous use only.

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Chemical haemorrhagic cystitis, leucopenia, nausea and vomiting, hepatic toxicity, altered carbohydrate metabolism, pancreatitis, hyper and hypoglycaemia, inappropriate secretion of antidiuretic hormone, interstitial pulmonary fibrosis.
Fludarabine	Transfusion related GVHD, fever, malaise, neurotoxicity, opportunistic infections, GI disturbances -nausea, vomiting, diarrhoea.
Lisocel (lisocabtagene maraleucel)	Cytokine release syndrome (CRS), hepatic dysfunction, renal dysfunction, cardiac dysfunction, neurologic adverse reactions -immune effector cell-associated neurotoxicity syndrome (ICANS), opportunistic infections, febrile neutropenia, HBV reactivation, HHV-6 reactivation, prolonged cytopenias, hypogammaglobulinaemia, tumour lysis syndrome (TLS), hypersensitivity reactions, hypophosphataemia, delirium, anxiety, encephalopathy, aphasia, peripheral neuropathy, hypotension, hypertension, thrombosis, cough, dyspnoea, vomiting, diarrhoea, acute kidney injury, fatigue, pyrexia, oedema.

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

Patients treated with fludarabine carry a lifelong risk of transfusion associated graft versus host disease (TA-GVHD). Where blood products are required, these patients must receive only irradiated blood products for life. Local blood transfusion departments must be notified as soon as the decision to treat is made and the patient must be issued with an alert card to carry with them at all times.

Symptoms of CRS or ICANS can occur weeks after infusion and therefore the patient must be issued with an alert card to carry with them at all times.

Any suspected adverse reaction to a CAR-T cell infusion should be reported. Reporting forms and information can be found at – www.mhra.gov.uk/yellowcard. Consideration should also be given to reporting adverse events to the relevant manufacturer via their usual channels.

Monitoring

Regimen

- FBC, U&Es, renal, liver and bone, CRP, coagulation screen, ferritin and LDH prior to initiating treatment and daily thereafter.
- Screening for HBV, HCV and HIV must be performed before collection of cells for Lisocel manufacture.
- Echocardiogram and baseline measure of lung function must be taken prior to initiating lymphodepleting chemotherapy.

Lisocel

Nearly all patients treated with Lisocel experience some degree of CRS, including life-threatening and fatal reactions. -See WBMT Policy P-G-1 and SOP P-P-78 and P-P-79 for monitoring requirements.

CRS:

- Symptoms: pyrexia, tiredness, cardiac failure, tachycardia, cardiac arrythmias, dyspnoea, hypoxia, capillary leak syndrome, chills, renal impairment, headache, malaise, transaminitis, nausea, diarrhoea, hypotension.
- Temperature, blood pressure and oxygen saturation monitored 4-hourly after Lisocel. administration on Day 0 and then twice daily as directed in accordance with local procedures.
- This must be documented, and CRS graded on the WBMT CRS Assessment Form in the patient's notes.

ICANS:

- Symptoms: seizures, somnolence, headaches, confusion, agitation, speech disorders, tremor, encephalopathy, ataxia, memory impairment, mental status changes, hallucinations, depressed level of consciousness, delirium, dysmetria.

- ICE score of the patient must be assessed twice daily and documented on the WBMT ICE Assessment Form in the patient's notes.

Dose Modifications

As a cell-based therapy and based on the mechanism of action, renal and hepatic impairment is not expected to impact lisocel expansion and cellular kinetics; hence no formal renal and hepatic impairment studies have been performed.

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Confirm with consultant before proceeding if there are signs of possible disease relapse.

Hepatic Impairment

No dose modification is recommended for hepatic dysfunction in those receiving fludarabine.

Severe hepatic impairment may be associated with a decreased activation of cyclophosphamide. This may alter the effectiveness of the cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected.

Renal Impairment

Drug	**Creatinine Clearance (ml/min)**	**Dose (% of original dose)**
Cyclophosphamide	Greater than 50	100%
	30-50	75%
	Less than 30	As directed by cell therapy consultant.
Fludarabine	Greater than 70	100%
	50-69	Reduce dose by 20%
	30-49	Reduce dose by 40%
	Less than 30	As directed by cell therapy consultant.

Other

Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of the cellular therapy and therefore, they should not be administered as part of the pre-medication. However, corticosteroids may be used in the treatment of CRS or ICANS under consultant advice.

Due to the risks associated with Lisocel treatment, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse events (especially pulmonary events, cardiac events or hypotension) including those after preceding chemotherapies.
- Active infections or inflammatory disorders.
- Active graft-versus-host disease (GVHD).
    - NOTE: It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GVHD receive treatment because of the potential risk of Lisocel worsening GVHD.

Regimen

Drug	Dose	Days	Route
Cyclophosphamide	300 mg/m^2	-5, -4, -3	Intravenous bolus over 10 minutes
Fludarabine	30mg/m^2	-5, -4, -3	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
Lisocel (lisocabtagene maraleucel)	Target dose: 100 x10^6 CAR+ viable cells consisting of: CD8+ cell component and CD4+ cell component	0	Intravenous infusion from 2 or more syringes -see below

Dose Information

- Lymphodepleting regimen must only be started after availability of Lisocel is confirmed.

- Cyclophosphamide will be dose banded in accordance with national dose banding table (20mg/ml).

- Fludarabine will be dose banded according to the national dose band (25mg/ml).

- A minimum period of time must elapse between last dose of lymphodepleting chemotherapy and CAR-T infusion, and a longer period may be required for patients with renal insufficiency. This information can be found on the patient's CAR-T cell schedule.

- CAR-T administration should not occur out of core hours or over the weekend.

- Lisocel has a total target dose of 100 $x10^6$ cells. However, there is a dosing range of 44 to 120 x 10^6 CAR-positive viable T cells. The dose will vary between patients.
  - This dose consists of a target 1:1 ratio of CD4+ and CD8+ cell components.

Administration Information

Lisocel

- Lisocel contains genetically modified human blood cells. Exposure to Lisocel must be avoided. Procedures for handling, personal protective equipment, accidental spills and waste disposal must be adhered to.

- Lisocel is supplied as two components: CD8+ and CD4+
  - These will be supplied as vials. Each vial will be a "single dose" vial which requires draw up into a separate syringe (supplied with Lisocel).

- Lisocel cells are cryopreserved in vial(s) and require thawing at room temperature prior to administration.
  - Both component vials must be thawed at the same time at room temperature.

- One individual treatment dose comprises a minimum of 2 vials and a maximum of 8 vials (up to 4 vials of CD8+ and 4 vials of CD4+ components). More than one vial of each of the CD8+ component and /or CD4+ component may be needed.

- Each vial contains an extractable volume of 4.6ml however a variable volume may be drawn up from each vial and each component for the required dose. The total volume may differ between components.
  - Refer to Release for Infusion Certificate for each component which will be provided with the Lisocel.

- Following thaw, one Luer-lock syringe per vial is required for Lisocel extraction. The CD8+ component syringe(s) should be prepared for infusion prior to CD4+ syringe(s).

- Once both component syringe(s) are prepared, the CD8+ component must be administered first, and CD4+ administration following immediately after CD8+ infusion is complete with flush of line.
  - If more than one syringe is required per component, these must be administered consecutively.

- The cells must **not** be administered via a volumetric pump, as there is no data to assure cell integrity is maintained via a pump.

- Administer via a giving set with a non-leukodepleting in-line filter primed with sodium chloride 0.9% at approximately 0.5ml/minute.

- Administration may be via central or peripheral line.

- The infusion must be administered within 2 hours from start of thaw (i.e. removal from frozen storage). The start and stop time of infusion must be documented.

- Once the full volume of Lisocel has been administered, rinse the tubing at the same rate with 0.9% sodium chloride solution to ensure all Lisocel is delivered. Once completed, the infusion bag and giving set must be disposed of in clinical waste, in accordance with Trust policy.

- If the intended dose is not fully administered, this must be documented and the consultant & pharmacist notified. The manufacturer must be informed and the remaining Lisocel should be discarded in clinical waste, with their approval.

- A GM spill-kit must be transported with Lisocel and available on the ward of administration. Local procedures must be followed in the event of a spill.

- Local guidelines on handling of waste of human-derived-materials must be followed in case of accidental exposure. Work surfaces and materials which have potentially been in contact with Lisocel must be decontaminated with approved disinfectants.

- See WBMT SOP P-P-78, P-P-79 and Policy P-G-1 for further administration direction. BMS SOP

Extravasation

- Cyclophosphamide – non-vesicant
- Fludarabine – non-vesicant

Additional Therapy

- Antiemetics
  - metoclopramide 10mg three times a day oral or intravenous
  - ondansetron 8mg twice a day oral or intravenous

- Anti-infective prophylaxis as follows:
  - Aciclovir 400mg oral twice a day
  - Pentamidine 300mg nebuliser during lymphodepletion. To be continued every 28 days until count recovery sufficient for co-trimoxazole use at consultant advice.
  - Fluconazole 100mg once a day
  - Posaconazole 300mg once daily if prolonged neutropenia or previous invasive fungal infection

- Gastric protection with a proton pump inhibitor or a H2 antagonist to commence on first day on lymphodepletion until platelet count >50 $x10^9$/L

- Mouthwashes according to local or national policy on the treatment of mucositis. May include:
  - Nystatin 1ml four times a day
  - Sodium chloride 0.9% 10ml four times a day

- Prior to the administration of the Lisocel
  - Chlorphenamine 10mg intravenous
  - Paracetamol 1000mg oral

  Pethidine 25mg intravenous can be administered under the supervision of a doctor for the treatment of rigors.

- Seizure prophylaxis may be considered due to the risk of neurotoxicity associated with Lisocel or if the patient has a history of seizures.

- Levetiracetam 500mg twice daily orally commencing on day 0 until day +28.
- For weaning, this may then be reduced to 250mg orally twice daily for two weeks, and then stopped.

- Tocilizumab must be prescribed as when required in advance of CAR-T infusion, in the event of CRS.
  - Tocilizumab 8mg/kg (maximum 800mg) intravenously 8-hourly if required. Maximum of four doses.
  - Four doses of tocilizumab must be available on the ward prior to infusion of Lisocel. Follow local procedures for administration.

- Tumour lysis syndrome (TLS) prophylaxis should be prescribed according to the individual patient TLS risk and at consultant review. This must start on the day of lymphodepleting chemotherapy and be re-reviewed on the day of Lisocel infusion. TLS prophylaxis may include:
  - Allopurinol 300mg oral once a day
  - Rasburicase 3mg intravenous injection once a day

References

1. Dosage Adjustments for Cytotoxics in Hepatic Impairment January 2009 University College London Hospitals
2. P-P-78 Wessex Blood and Marrow Transplant – CAR-T and IEC infusion procedure Version 1.3
3. P-P-79 Wessex Blood and Marrow Transplant – Immune effector cells including CAR-T cells policy Version 2.1
4. P-G-1 Wessex Blood and Marrow Transplant -Patient monitoring after CAR-T cell infusion Version 1.1
5. Pan UK Pharmacy Working Group for ATMPs -Supportive medications recommended for adults receiving licensed chimeric antigen receptor -T (CAR-T) cell therapy Version 1 May 2022
6. Pan UK Pharmacy Working Group for ATMPs -Medication restrictions for patients having CAR-T cell therapy Version 4 July 2022
7. European Medicines Agency Summary of product characteristics & Summary of risk management plan for Breyanzi 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi
8. Medicines & Healthcare products Regulatory Agency: Lisocabtagene Maraleucel. Available from: https://products.mhra.gov.uk (accessed 29/01/2025)
9. Summary of Product Characteristics for Fludarabine (Sanofi) -Last updated 18 March 2019
10. Summary of Product Characteristics for Cyclophosphamide (Sandoz Limited) -Last updated 6 April 2021

REGIMEN SUMMARY

LISOCEL – CYCLOPHOSPHAMIDE (500) – FLUDARABINE (30)

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describe the agents that must be prescribed on the in-patient chart or general electronic prescribing system.

Day – 5

1. Warning – Check supportive medication prescribed
   Administration instructions
   Please refer to the individual CAR-T schedule for full details of the required supportive medicines.
   1. Antibacterials in accordance with the individual CAR-T schedule
   2. Antifungals in accordance with the individual CAR-T schedule
   3. Antivirals in accordance with the individual CAR-T schedule
   4. Tocilizumab 8mg/kg (maximum 800mg) intravenous 8-hourly when required in the event of CRS. Maximum four doses.
   5. Metoclopramide 10mg three times a day oral or intravenous
   6. Ondansetron 8mg twice a day oral or intravenous
   7. Nystatin mouthwash 1ml four times a day
   8. Sodium chloride 0.9% mouthwash 10ml four times a day
   9. Chlorphenamine 10mg intravenous when required as a premedication
   10. Paracetamol 1000mg when required as a premedication oral
   11. Furosemide 20mg four times a day when required for the treatment of fluid overload oral or intravenous
   12. Gastric protection
   13. Levetiracetam 500mg twice daily oral
   14. Heparin line lock in accordance with Trust central venous access device management procedure
   15. Reminders for chemotherapy administration and Lisocel.

   Ensure patient has been issued with Lisocel treatment alert card.

2. Warning – Check blood transfusion status
   Administration instructions
   Patients treated with fludarabine carry a lifelong risk of transfusion associated graft versus host disease. Where blood products are required these patients must receive ONLY IRRADIATED BLOOD PRODUCTS for life. Ensure transfusion departments are notified and the patient has been issued with an alert card to carry with them at all times.
   Ensure patient has been issued with Lisocel treatment alert card.

3. Cyclophosphamide 300mg/m^2 intravenous bolus over 10 minutes

4. Fludarabine 30mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Day – 4

5. Cyclophosphamide 300mg/m^2 intravenous bolus over 10 minutes

6. Fludarabine 30mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Day – 3

7. Cyclophosphamide 300mg/m^2 intravenous bolus over 10 minutes

8. Fludarabine 30mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Day 0

9. Chlorphenamine 10mg intravenous
   Administration Instructions
   Administer 30 minutes prior to Lisocel. Check on the in-patient system if the patient has already received a dose

10. Paracetamol 1000mg oral
    Administration Instructions
    Administer 30 minutes prior to Lisocel. Check to ensure the patient has not already been administered paracetamol. The maximum dose is 4000mg/24 hours.

11. LisocabtageneCD8+ cell component 1 dose intravenous infusion
    Administration Instructions
    Prescribed CD8+ dose for this patient: ……
    Prescribed Total CAR+ viable cell dose for this patient: ……
    This is also known as LISOCEL
    Administer at approximately 0.5ml/minute via a giving set with a non-leukodepleting in-line filter primed with sodium chloride 0.9%. The cells must not be administered via a volumetric pump.
    Lisocel is supplied as two components: CD8+ and CD4+.
    CD8+ component must be administered first, and CD4+ administration following immediately after CD8+ infusion is complete with flush of line.
    Lisocel infusion should be infused within 2 hours of thaw start time.

12. Lisocabtagene maraleucel CD4+ cell component 1 dose intravenous infusion
    Administration Instructions
    Prescribed CD4+ dose for this patient: ……
    Prescribed Total CAR+ viable cell dose for this patient: ……
    This is also known as LISOCEL
    Administer at approximately 0.5ml/minute via a giving set with a non-leukodepleting in-line filter primed with sodium chloride 0.9%. The cells must not be administered via a volumetric pump.
    Lisocel is supplied as two components: CD8+ and CD4+.
    CD8+ component must be administered first, and CD4+ administration following immediately after CD8+ infusion is complete with flush of line.
    Lisocel infusion should be infused within 2 hours of thaw start time.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	February 2025	None	Madeleine Norbury Pharmacist	Dr Rob Lown Consultant

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

University Hospital Southampton NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.