PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Fludarabine & Cyclophosphamide Lympho-depletion prior to CAR-T cell therapy with Brexucabtagene Autoleucel (Tecartus®) Mantle Cell Lymphoma (MCL)

PROTOCOL REF: MPHAMCLTL
(Version No. 1.0)

Approved for use in:

Patients approved for CAR-T cell therapy for adult patients with:

- Relapsed / refractory mantle cell lymphoma:
    - **Refractory** mantle cell lymphoma defined as being either progressive disease as the best response to the last line of systemic therapy or stable disease as the best response after at least 2 cycles of the last line of therapy with stable disease duration lasting no longer than 6 months from the last dose of the last line of systemic therapy.
    - **Relapsed** disease is defined as disease that responded partially or completely to the last line of therapy and has since progressed.
- A confirmed histological diagnosis of MCL with documentation of either cyclin D1 overexpression or the presence of the translocation t(11:14)
- The patient must have been previously treated for MCL with one of the following cytotoxic chemotherapy regimens: an anthracycline-containing regimen or a bendamustine containing regimen or a regimen containing high dose cytarabine with or without cisplatin/carboplatin.
- The patient must have previously received and anti-CD20 monoclonal antibody unless clear documentation of CD20 negative disease.
- The patient has been previously treated for MCL with a Bruton's tyrosine kinase (BTK) inhibitor (such as ibrutinib or acalabrutinib) and that the patient progressed either during treatment or following discontinuation of the BTK inhibitor.
- Either the patient has not previously been treated with an anti-CD19 antibody-drug conjugate or if previously treated with an anti-CD19 antibody-drug conjugate that a biopsy

of the relapsed/refractory disease has been done and has been shown to be CD19 positive.

- The patient must not have known active CNS involvement.
- Each patient must have documented approval for CAR-T treatment from the National CAR-T Clinical Panel for MCL and local MDT.

Blueteq request is required alongside CAR-T therapy. This is completed in 2 parts:

- Part 1 (KTE01a) **MUST** be completed prior to apheresis / manufacturing of CAR-T cell infusion.
- Part 2 (KTE01b) **MUST** be completed once the date of infusion is known and prior to admission for administration of lymphodepletion, to ensure that the Trust is reimbursed.

Note to Pharmacist: Refer to SOP Pharmacist Verification of Prescriptions for Lymphodepletion Chemotherapy associated with CAR-T Therapy

Dosage:

Drug	Dose	Route	Frequency
Fludarabine	**30 mg/m^2**	IV infusion	Once daily on days -5, -4 and -3 (3 days)
Cyclophosphamide	**500 mg/m^2**	IV infusion	Once daily on days -5, -4 and -3 (3 days)
Brexucabtagene autoleucel (Tecartus®) (CAR-T Cells)	**Variable**	IV Infusion	Day 0

Single cycle only

Brexucabtagene autoleucel (Tecartus®) CAR-T cell therapy should be administered 3 to 14 days after lympho-depletion. **Ensure that a minimum of 48 hours elapses between administration of fludarabine and CAR-T cells (Tecartus®).**

Prescribing guidance	Fludarabine	Fludarabine will be dosed (via BSA) using to the recipient's actual body weight unless the actual body weight is ≥2 times their ideal body weight, in which case the SCT Consultant should be contacted for advice.

Administration:

- Lympho-depleting regimen must only be started after availability of brexucabtagene autoleucel (Tecartus®) is confirmed.

- Ensure that the minimum required time has elapsed between the last dose of conditioning chemotherapy and CAR-T infusion (longer is required if renal insufficiency). Contact Haematology Consultant if concerns.
- CAR-T cell administration should not occur out of core working hours or over the weekend. Contact Haematology Consultant if concerns.
- Discuss with a Haematology Consultant and consider delay if the patient has any of the following:
  - Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
  - Active uncontrolled infection.
  - Active graft-versus-host disease (GVHD).
- Lympho-depletion is important for ongoing success of CAR-T therapy, and should only be omitted at haematologist's discretion. Ensure unexplained neutropenia is explored prior to CAR-T therapy.
- Brexucabtagene autoleucel (Tecartus®) has a target dose of 2 x 10^6 CAR-positive viable T cells per kg of body weight (range: 1 x 10^6–2 x 10^6 cells/kg), with a maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above. The dose may vary between patients.
- Brexucabtagene autoleucel (Tecartus®) cells are cryopreserved and require thawing by the Stem Cell Laboratory team prior to administration.
- Brexucabtagene autoleucel (Tecartus®) is for autologous use only. Confirm that the patients' identity matches the product prior to administration.
- Brexucabtagene autoleucel (Tecartus®) cells must be administered gravimetrically and must not be administered via a volumetric pump as there is no data to ensure cell integrity.
- Brexucabtagene autoleucel (Tecartus®) cell infusion must begin within 30 minutes of thaw completion and the cells must be administered over a maximum of 30 minutes (the start and stop time of the infusion must be documented)
- Tocilizumab must be available for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. Additional doses of tocilizumab must be available within 8 hours.

- Ensure that the patient has been provided with adequate verbal and written information and is happy to proceed all pre-procedure checks have been completed.
- Ensure written consent has been obtained.
- Ensure that the patient has suitable intravenous access.
- Ensure that the patient has adequate daily fluid intake - supplement with IV fluids if necessary. Daily weight and urine output is to be maintained at or below baseline with IV furosemide
- Ensure that blood products are irradiated

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Tumour lysis syndrome prophylaxis	Allopurinol 300 mg ONCE daily PO commencing on first day of lymphodepletion until 10 days post CAR-T cell infusion. Reduce dose to 100mg ONCE daily in renal impairment. Consider rasburicase if high risk.
Anti-emetics	Ondansetron 8mg twice daily (oral or IV) Metoclopramide 10mg three times daily (oral or IV) Dexamethasone should **NOT** be used as part of anti-emetic regime in patients receiving CAR-T therapy.
Mouthcare	• Nystatin 1ml QDS, mouthwash • Normal Saline 10ml QDS, mouthwash, as plastic amps • Benzydamine 0.15%, 15ml QDS mouthwash • Ascorbic acid and Zinc tablets, quarter of a tablet QDS, as a mouthwash
Menstruating women only	Norethisterone 5-10 mg (orally) three times a day, if applicable, until platelets > 50 x 10^9/L
Gastric prophylaxis	Oral omeprazole 20 mg once daily from admission. Consider stopping when platelets >50x10^9/L and no upper gastrointestinal symptoms. Consider increasing dose if receiving steroids to manage toxicity.
Antibacterial prophylaxis	Not routinely recommended. Ciprofloxacin 500mg orally twice a day may be considered in case of prolonged neutropenia < 0.5 x 10^9/L.
Anti-PCP prophylaxis	Co-trimoxazole 480mg daily commencing on first day of lymphodepletion until 1 year post CAR-T cell infusion and/ or until CD4+ count >0.2 x10^9/L In case of co-trimoxazole allergy or cytopenias precluding use of co-trimoxazole consider: Pentamidine inhalation 300mg once a month or Atovaquone 750mg orally twice daily Pentamidine:

	• 2.5mg nebulised salbutamol and then 300mg nebulised pentamidine immediately afterwards. The dose should be repeated after 28 days. • Pentamidine should be continued every 28 days if co-trimoxazole is unsuitable
Antifungal prophylaxis	Posaconazole 300mg twice daily for one day (loading dose) then 300mg once daily, commencing on first day of lymphodepletion until day 28 post CAR-T infusion or until neutrophil count is stable and ≥1.0 $x10^9$/L, whichever is later. If using posaconazole consider switching to fluconazole 200mg orally daily beyond day 28 until day 100 if severe lymphopenia, at clinician discretion.
Anti-viral prophylaxis	Aciclovir 400mg BD, from start of conditioning and continued for at least 1 year (or longer in the presence of GvHD and immunosuppressive therapy) until lymphocyte >1 $x10^9$/L and CD4 >0.2 $x10^9$/L on two occasions without infection.
Anti-seizure prophylaxis	Seizure prophylaxis may be considered due to the risk of neurotoxicity associated with CAR-T cells or if the patient has a history of seizures at clinician discretion. • Levetiracetam 500mg twice daily from admission until day +30. This can be reduced to 250mg twice daily for 1 week and then stopped.
CAR-T Pre-medication	• Chlorphenamine 10mg IV 1 hour prior to CAR-T infusion • Paracetamol 1g IV 1 hour prior to CAR-T infusion • Pethidine 12.5mg-25mg IV 8 hourly **(ONLY to be prescribed if needed in the event of rigors)**
Management of CRS	• Tocilizumab must be prescribed in advance of CAR-T infusion in the event of CRS. 8mg/Kg (max. 800mg) IV 8 hourly when required (maximum 4 doses) **Four doses of tocilizumab must be available on the ward prior to CAR-T infusion.**

Extravasation risk:

Cyclophosphamide: non-vesicant

Fludarabine: non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'.

Dosing in renal and hepatic impairment:

Renal	Fludarabine	**Creatinine Clearance (mL/min)**	**Dose adjustment**
		46 - 60	80% dose
		31 - 45	75% dose
		≤30	Contraindicated
	Cyclophosphamide	**Creatinine Clearance (mL/min)**	**Dose adjustment**
		10-20	75% dose
		<10	50% dose

Hepatic	Fludarabine	Fludarabine No information on use of fludarabine in hepatic impairment
	Cyclophosphamide	The dose must be reduced in patients with severe hepatic impairment. **A dose reduction of 25 % is recommended in patients with serum bilirubin concentrations of 53-86micromol/l.** 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.

Interactions:

Please refer to each agent's SPC for further information. See reference section.

Treatment schedule:

Day	Drug	Dose	Route	Diluent + Rate
-5	**Fludarabine**	**30mg/m^2**	**IV**	100ml sodium chloride 0.9% Over 30 minutes
	Cyclophosphamide	**500mg/m^2**	**IV**	500ml sodium chloride 0.9% Over 60 minutes
-4	**Fludarabine**	**30mg/m^2**	**IV**	100ml sodium chloride 0.9% Over 30 minutes
	Cyclophosphamide	**500mg/m^2**	**IV**	500ml sodium chloride 0.9% Over 60 minutes
-3	**Fludarabine**	**30mg/m^2**	**IV**	100ml sodium chloride 0.9% Over 30 minutes
	Cyclophosphamide	**500mg/m^2**	**IV**	500ml sodium chloride 0.9% Over 60 minutes
-2	**REST DAY**			
-1	**REST DAY**			
0	**Sodium Chloride 0.9%**	**1000mL**	**IV**	Over 4 hours (Start 1 hour prior to CAR-T cell infusion)
	Chlorphenamine	**10mg**	IV	1 hour prior to CAR-T infusion
	Paracetamol	**1000mg**	IV	1 hour prior to CAR-T infusion
	Brexucabtagene Autoleucel (Tecartus®)	**Variable**	IV	Refer to CAR-T policy

Main toxicities:

Cyclophosphamide
• Nausea, vomiting (generally mild, more severe with oral formulations), diarrhoea. Anorexia, mucositis, stomatitis, alopecia. • Pancytopenia/myelosuppression: anaemia, leukopenia, thrombocytopenia (bleeding). Thrombosis. • Infections (bacteria, including pneumonia, fungal, viral, protozoal, sepsis. Fever. • Cystitis, micro-haematuria. Haemorrhagic cystitis. Sub urethral haemorrhage, • bladder wall oedema, • fibrosis and sclerosis. • Renal impairment, renal tubular necrosis, rhabdomyolysis, tumour lysis syndrome, disseminated intravascular coagulation, haemolytic uremic syndrome. • Fever, chills, malaise, fatigue, cramps. • Cardiac dysfunction, arrhythmias, myocardial infarction, pericarditis. • Anaphylaxis. Rashes, hyperpigmentation (palms and soles), facial flushing after IV administration. • Seizures, dizziness, dysgeusia, paresthesia, peripheral neuropathy, visual disturbance, conjunctivitis, deafness. • SIADH, dilutional hyponatraemia and water retention (direct injury to distal renal tubules and collecting ducts, resolves within 24 hours of therapy). • Secondary malignancies. • Interstitial pulmonary fibrosis, interstitial pneumonitis, ARDS, bronchospasm. • Infertility. • VOD. Enterocolitis. pancreatitis, LFT elevation, • Treatment related/non-relapse mortality (TRM/NRM).
Fludarabine
• Pancytopenia/myelosuppression. • Infections • Nausea, vomiting (generally mild), diarrhoea. Anorexia, mucositis, stomatitis, alopecia. • Cough, dyspnoea. Pulmonary toxicity (including pulmonary fibrosis, pneumonitis, pulmonary haemorrhage, interstitial pneumonitis). • Fever, chills, malaise, fatigue. • Gastrointestinal haemorrhage, pancreatic enzyme elevation, elevated LFTs, VOD • Autoimmune diseases (including autoimmune haemolytic anaemia, Evan's syndrome, Thrombocytopenic purpura, acquired haemophilia, pemphigus). • Tumour lysis syndrome (if not in remission) (including renal failure, metabolic acidosis, hyperkalaemia, hypocalcaemia, hyperuricaemia, haematuria, urate crystalluria, hyperphosphataemia). Renal and urinary complications including haemorrhagic cystitis. • Post transfusion GvHD. • Secondary malignancies • Neurotoxicity, typically with higher doses (headaches, agitation, somnolence, confusion, paraesthesia, vision changes, rarely coma and seizures). Weakness. Peripheral neuropathy. Visual disturbance. Cerebral haemorrhage, acute toxic leukoencephalopathy. • Stevens-Johnson syndrome. Rash. • Cardiac failure, arrhythmias. Oedema. • EBV reactivation and lympho-proliferative disorder • Treatment related/non-relapse mortality

Investigations:

Instruction	Pre-admit	-5	-4	-3	-2	-1	0	Daily from day +1	Additional Information
Ensure informed and written consent	X								
Clinical Assessment	X	X	X	X	X	X	X	X	Until discharge
SACT Assessment (includes PS and toxicities)	X	X	X	X	X	X	X		
Height	X								
Weight and Fluid Balance	X	X	X	X	X	X	X	X	Report positive fluid balance of > 2L
FBC, U&E & LFTs & Magnesium	X	X	X	X	X	X	X	X	Monitor daily throughout admission
Glucose	X			X					Repeat twice weekly as indicated
Bone Profile (vitamin D level)	X	X		X			X		Monitored on a Mon, Wed and Fri
CRP & ferritin	X	X		X			X		Monitored on a Mon, Wed and Fri
Chest X-Ray, MUGA scan / ECHO / ECG	X								Then as clinically indicated
B12 and folate	X								Then as clinically indicated
Respiratory swabs	X								
Calculated Creatinine Clearance (Wright Formula)	X								Increased if clinically indicated – adjust doses if required
G6PD status	X								Required prior to rasburicase – contraindicated if G6PD deficient
CMV, EBV & Adenovirus PCR monitoring. TB Quantiferon (if applicable)	X								Twice weekly from Day +1 until at least Day 100 or off immune suppression
Specimens for virology and microbiology **(Including Covid-19 swabs)**	X								As clinically indicated
Vital signs (includes TPR, O_2 saturation and BP)	X	X	X	X	X	X	X	X	Monitor signs four times a day and modify if clinically indicated
Neurological Assessment (ICANS)	X					X	X	X	Monitor 4 hourly following CAR-T infusion as per Clinical Guideline
Serum pregnancy test (if applicable)	X								

Dose Modifications and Toxicity Management:

See specific BMT & Cellular Therapies guidelines for toxicity management.

Non- Haematological toxicity:

See section entitled ‘Dosing in Renal and Hepatic Impairment’

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Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
June 2023	1.0	**Jennifer Gibson – Principal Pharmacist**	New protocol