SOP: COORDINATING ADOPTIVE CELLULAR THERAPY

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STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

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TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

Contents

STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

1 INDICATIONS OF PRACTICE

This document reflects the international consensus recommendations from EBMT, JACIE and ASTCT, and complies with the NHS England CAR-T service specification for allogeneic transplant centres commissioned as CAR-T therapy centres with attending transplant physicians.

Adoptive cell therapy, also known as cellular immunotherapy, is a form of treatment that uses infused cells of the immune system to eliminate cancer and builds on the experiences from allogeneic transplants. Examples include; chimeric antigen receptor (CAR) T or NK cell therapy, natural killer (NK) cell therapy, engineered T cell receptor (TCR-T) therapy, gamma delta T and tumour-infiltrating lymphocyte (TIL) therapy. Cell can be of autologous/patient derived or allogeneic.

Autologous donor chimeric antigen receptor T-Cell (CAR-T) therapy is a complex patient derived and specific targeted cellular immunotherapy, with patient apheresis as the first step in the process.

Further updated information on licenced commercial CAR-T products can be found on the NICE website. There are also clinical trials in relation to cellular immunotherapy.

2 AUTHORISED PERSONNEL/TRAINING REQUIRED

2.1 Cellular/CAR-T Therapy Coordinator

is responsible for requesting and co-ordinating collection and scheduling the return of the product, ensuring that the patient is appropriately prepared for cell infusion (as per transplant co-ordination SOP (DOC236) and liaises with the apheresis team for assessment and Eligibility of patients undergoing apheresis SOP (INFO/APH/INPA).. Co-ordination of cellular therapy clinical trial patients should be in conjunction with the responsible trial teams.

2.2 Cellular/CAR-T Therapies Clinical Lead

is responsible for ensuring that the patient is an appropriate candidate for CAR-T therapy, ensuring cases have been presented at the National CAR-T clinical Panel (NCCP) followed by liaison with referral centre for bridging therapy and consent of the patient prior to infusion. They are also responsible for the management of out of specification products (see section below)

2.3 Referring Consultant

will maintain shared responsibility for monitoring the patient and delivering the recommended bridging therapy whist a cell product is being manufactured in conjunction with the Cellular Therapies Team.

2.4 Stem Cell Lab/HTA Designated Individual (DI)

responsible for the management of the cells within The Christie and ensuring relevant procedures are followed for the receipt, verification, packaging, labelling and handling/transfer of the product.

2.5 Clinical Apheresis Unit Lead

and staff are responsible for undertaking the collection of the apheresis product and the safety of the patient during collection as per APH 40 and any specific trial or guidelines specific to that product.

2.6 Haematology Pharmacist

is responsible for confirmation of the specifications surrounding product request, submission of CDF forms in the first instance (Blueteq part a) and ensuring that once the product is available for infusion that all prescriptions are correct and in administered in line with SMPC recommendations. Pharmacy maintain oversight of ordering, storage and release processes of cellular therapy that is designated a medicinal product as per regulatory requirements and service specification.

3 PROCEDURE for CAR-T

3.1 Prior to clinic /presentation

Following referral a minimal data set will be requested form the referring centre and panel request is required prior to clinic review

3.2 Commercial Products

All Patients referred for Cellular/CAR-T treatment at The Christie must meet the NHS England eligibility criteria and be approved by the relevant disease related National CAR T Clinical Panel (NCCP). Patients will be referred to the Cellular Therapies Clinic and will be presented by the Cellular/CAR-T Therapies Lead at the disease related NCCP (leukaemia, lymphoma, myeloma) and the Cellular Therapy MDT and planning meeting.

The CAR-T coordinator will communicate the outcome of the NCCP and CAR-T MDT discussions with the patient, the Referring Consultant and pharmacy

BlueTeq form (A) to secure funding for leukapheresis and manufacturing is completed by pharmacy once approved and before entering onto portal

STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

3.3 Prior to Apheresis

Patients will be discussed at a relevant disease specific MDT (haematology, lymphoma, other solid tumour) on referral and may require further discussion prior to infusion of cells to determine disease burden and status in response to the recommended bridging therapy.

The availability of apheresis and treatment slots along with laboratory capacity will be discussed at the transplant planning meeting, and scheduling sheets updated . The CAR-T coordinator will communicate dates with the patient and relevant consultants.

The consultant or deputy will undertake a patient medical assessment at Clinic.

Medical Assessment should cover:

- Confirmation of cellular therapy eligibility and medical suitability for apheresis in compliance with HTA (INFO/APH/INPA and APH-65). Potential risks and benefits of treatment.
- Product specific GDPR consent form completed (specific to product – needed prior to adding to portal
- Patient information produced by The Christie (available on Hive), supported by other material as appropriate (Q-Pulse DOC911, DOC926).
- Irradiated blood components (7 days pre harvest then lifelong post reinfusion)

Once NCCP eligibility for CAR-T is confirmed a product order will be made using the relevant commercial product ordering system by the CAR-T coordinator. This will require a purchase order form. These are pre requested via the clinical service management team of the cellular therapy department (see appendix 5.1). Purchase order forms should be requested and generated well in advance of need so as not to incur delay in proceeding with collection. – pharmacy need to approve invoices so need to know PO numbers, ensure that the information is shared once added to commercial platform.

The CAR-T coordinator will organize all of the necessary pre procedural investigations.

Post medical assessment clinic review letter (APH-66) will be sent to the Referring Consultant, GP and patient briefly detailing CAR-T eligibility and pre apheresis washout requirements.

Liaison/referral to the CAR-T AHCP team as appropriate to ensure their awareness of the patient and upcoming therapy (patient will be contacted independently and reviewed in a designated clinic accordingly), see appendix 5.4 for pathway.

STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

3.4 Research Products/Allogeneic Donors

All patients/donors involved in clinical cellular therapy trials will be required to follow the pathway above (section 3.1.1).

Product request will be as per trial specifications and undertaken by the relevant trial team with timings for apheresis communication by the CAR-T coordinators.

For co-ordinating Tabcel® please refer to CLN-15

3.5 Commercial Product Ordering

3.5.1 Novartis – Kymriah - Tisagenlecleucel

Product manufacturing requests require the use of an online ordering platform after the Blueteq A form approved to 'Cell Chain' (https://cellchain.force.com/dashboard/login). Training and access are provided by Novartis.The system will generate specific emails to prompt users when action is required. – pharmacy need to confirm approval

Close liaison with the manufacturer is recommended, this can be done by contacting the Novartis Cell and Gene Therapy Network Manager.

3.5.2 Kite Gilead – Yescarta - Axicabtagene ciloleucel and Tecartus - Brexucabtagene Autoleucel

Product manufacturing requests are made via Kite's online ordering platform after the BlueTeq form A is approved 'Kite Konnect' (https://kitekonnect.force.com/s/). Training and access will be provided by Kite.

Close liaison with Kite throughout is recommended, this can be done by contacting the Kite Gilead Cell Therapy Account Manager. – coordination calls will be organized with labs and CART coordinator

3.6 Clinical Trials

Apheresis and processing dates for all patients undergoing cellular therapy trials will be allocated as per the standard process above (assessment and eligibility of patients undergoing apheresis or for immune effector cell therapy SOP (INFO/APH/INPA)).

Product return dates will require close liaison within the Cellular Therapies Lead and the wider Cellular Therapy MDT and Coordinators to ensure appropriate dates for pre admission consent in the Cellular Therapies Clinic and commencement of lymphodepleting chemotherapy/radiotherapy.

The appropriate research team will be responsible for the product specific ordering system and monitoring of the patient pre cellular therapy infusion.

STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

3.7 Specific Product Criteria

3.7.1 Novartis – Kymriah - Tisagenlecleucel

Full collection and processing requirements can be found on Q-Pulse in the Novartis CAR-T Leukapheresis manual (APH-60).

Collection dose:

Optimal collect range of 1.5 - 4 x10/9 CD3 cells but ideally greater than 2 and absolute minimum for acceptance of 1

greater than or equal to 2 x10/9 TNC

at least 3% of TNC being CD3+ cells

3.7.2 Kite Gilead – Yescarta - Axicabtagene ciloleucel and Tecartus - Brexucabtagene autoleucel

Full details on the Kite collection and processing process can be found in DOC914 on Q-Pulse (Yescarta/Tecartus verification, collection and packaging SOP).

3.8 Pre Apheresis Washout Criteria for Novartis, Kite Gilead

A full medication history should be obtained and reference should be made to the SPS (link to add) see appendix 2 and manufacturers guidance

For further information please see the Specialist Pharmacy Service Medication Restrictions for Patients Having CAR-T Cell Therapy guide:

Medication-Restriction
s-for-Patients-having-(

3.9 Post Apheresis Bridging Therapy

Post apheresis patient management and bridging therapy will be discussed with the Referring Consultant by the The Christie Team.

Bridging therapy should ideally commence within 3 days of apheresis. Radiotherapy planning will usually be organised prior to apheresis by the Referring Consultant.

For patients requiring admission to hospital post apheresis during the bridging phase, this will usually be under the care of the Referring Consultant either locally or at The Christie.

CD19-targeted bridging therapies should be avoided.

STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

For high grade lymphoma frequently used bridging therapies include radiotherapy to bulky disease and Polatuzumab with Rituximab and Bendamustine.

Mantle cell lymphoma frequently used bridging therapies include a BTK inhibitor with radiotherapy to reduce bulk as needed.

Acute leukaemia frequently used bridging therapies include Inotuzumab or a TKI.

3.10 Pre Admission

Once confirmation of product manufacture and quality assurance has been received admission dates can be confirmed.

Product delivery is co-ordinated when confirmed admission date has been given and patient suitable to proceed

The patient will be required to attend a consent clinic at The Christie CAR-T Clinic:

- Medical suitability to ensure clinical appropriateness to proceed to cell infusion and confirmed assessment of performance status
- Review of pre treatment investigations including disease reassessment and organ function
- Discuss potential risks and benefits.
- To obtain consents (DOH/Christie consent, EBMT consent and MR scan/and trials if indicated
- Consent for MR scanning in emergency situations
- Ensure the patient has received the Christie hotline card for any issues throughout the CAR-T cell process.
- Within CWP, ensure it is flagged that the patient has received CAR-T cell therapy, via patient letters and medical reviews.
- Reiterate that driving is prohibited within 2 months of cell infusion, and the DVLA must be contacted by the patient if a seizure occurs.
-
- Ensure appropriate teams including OCCU, physio, OT and dietetics are aware of all potential admissions and dates of therapy at this point and have appropriate capacity.

Ensure all pre admission investigations are available including:

- Blood tests and organ function, ECHO and PFTs if clinically indicated.
- ECG and chest x-ray within the past two weeks
- Re-staging, PET scan (DLBCL, MCL, ALL), bone marrow if low counts including MRD (ALL, MCL, transformed lymphoma), chimerism (if post allogeneic stem cell transplant)

On the day of consent blood tests recommended by EBMT:

- Renal function, CRP, ferritin, HLA antibodies
- Transplant assessment including HIV viral load PCR
- Flow cytometry, CD3, 4, 8, 16/56, and 19, FMC63/immune monitoring
- PCR: CMV, EBV, Parvo-virus, HHV6, 7, 8, JC and BK virus
- Cardiac monitoring (including NT-pro-BNP, TROP I and CK), to be followed up if any positive results
- G6PD (if positive the patient is ineligible for rasburicase), further details outlined in the guideline for rasburicase in G6PD deficiency
- If the patient has had previous history of CNS involvement or previous seizures then prophylaxis with Levetiracetam 500mg bd to start from the beginning of lymphodepletion.
- Full blood count, Christie Profile, Coagulation
- B12, folate and vitamin D, ferritin
- Immunoglobulins/B2M and electropheresis, serum free light chains
- Quality of life questionnaire (EBMT)
- Bluteq B form completed pre infusion by coordinators
- Tissue typing on all ALL patients and eligible lymphoma patients as directed by the CAR-T Lead

All patients will require central venous access. The preference is a tunnelled internal jugular line (Hickman). In exceptional circumstance alternatives including a PICC line may be acceptable, as per cellular infusion policy (WRD-5) which specifies a separate cannula without a filter for the CAR-T infusion. Booking is as per standard practice (integrated procedures unit).

3.11 Pre Reinfusion Washout Criteria/Dose Adjustments

For further information please see the Specialist Pharmacy Service Medication Restrictions for Patients Having CAR-T Cell Therapy guide:

https://www.sps.nhs.uk/articles/medication-restrictions-for-patients-having-car-t-cell-therapy/

For trial patients the protocol will mandate the appropriate drug washout period.

Dose modifications for fludarabine lymphodepletion (Kymriah/Yescarta/Tecartus) in patients with decreased renal function – as per pharmacist guidance

STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

Suggested doses as per Vanderbilt University Medical Centre recommendations (*Biol Blood Marrow Transplant 2014;20:908-19*):

Creatinine Clearance ml/min	IV Fludarabine mg/m^2
46-60	(80% dose)
31-45	(75% dose)
*21-30	(65% dose)
*<20 or haemodialysis	(50% dose)

*Typically patients with CrCL <30 will usually not receive CAR-T infusion

3.12 Out of specification (OOS) and non-conforming products

Due to the unique nature of these cell/tissue-based medicines there are occasions (often but not always due to inherent biological variation of starting materials) when the manufactured medicines are not in full compliance with their release specification.

Depending on the nature and degree of non-compliance it may be that the administration of an out-of-specification (OOS) ATMP remains in the best interest of the patient and that administration is the correct course of action.

The below guidance published by the Specialist Pharmacy Service provides further information and guidance

https://www.sps.nhs.uk/wp-content/uploads/2020/02/Out-of-Specification-Advanced-Therapy-Medicinal-Products-V1.2-March-2020.pdf

For commercial products the cellular therapy director will be notified by the manufactures of the nature of the out of specification and forwarded on a full risk evaluation which may require additional completion by the clinician with pharmacy in copy. This risk assessment is then returned to the manufactures and presented to the NCCP for review and acceptance. The OOS product must be approved by the NCCP to secure funding. Medicine governance approval for product use will be obtained via discussion at the weekly cellular therapies MDT

The final decision to treat with the product in this case lies with the lead CAR-T/cellular therapy consultant who will assess the overall risk benefit to the patient and review the safety efficacy.

Where an OOS product is defined as suitable for use the patient should be advised and consented appropriately.

All deviations must be recorded in the Datix system

3.13 CAR-T Discharge Arrangement

Discharge and follow up details can be found within the CAR-T cell therapy patients follow up SOP (DOC944).

3.14 Cancelling/Deferring CAR-T and Damaged Products

If this is required then direct contact with the manufacturing company representatives should be made to ensure the correct process is followed.

For cellular therapy research trial products refer to the protocol as to how to defer, cancel or report a damaged product.

4 REFERENCES AND FURTHER INFORMATION

- Service specification for the delivery of Chimeric Antigen Receptor T Cell (CAR-T) Therapy (all indications, all ages)
- Kymriah SMPC - https://www.medicines.org.uk/emc/product/9456/smpc
- Yescarta SMPC - https://www.medicines.org.uk/emc/product/9439/smpc
- Tecartus SMPC - https://www.medicines.org.uk/emc/product/11987/smpc#gref
- Novartis contact details: my.CART@Novartis.com or phone 00800 100 10 100.
- Kite contact details: 0189 552 7072 or 0800 018 3302.
- DOC645 Inpatient Management of Patients Receiving Immune Effector Cells (including CAR-T Cells)
- AMB-21 Kymriah CAR-T - DLBCL Nursing Protocol for Haematology & TYA Ambulatory Care Unit
- AMB-22 Yescarta CAR-T - DLBCL Nursing Protocol for Haematology & TYA Ambulatory Care Unit
- AMB-23 Kymriah CAR-T - ALL Nursing Protocol for Haematology & TYA Ambulatory Care Unit
- DOC236 Coordinating a Transplant
- INFO/APH/INPA Assessment and eligibility of patients undergoing HPC collection
- APH-40 Optia MNC Apheresis Procedure for HPC and T-Cell Collection
- DOC988 CAR-T follow up
- Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events | Journal for ImmunoTherapy of Cancer (bmj.com)
- CLN-15 Process flow for co-ordinating and ordering Tabelecleucel

STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

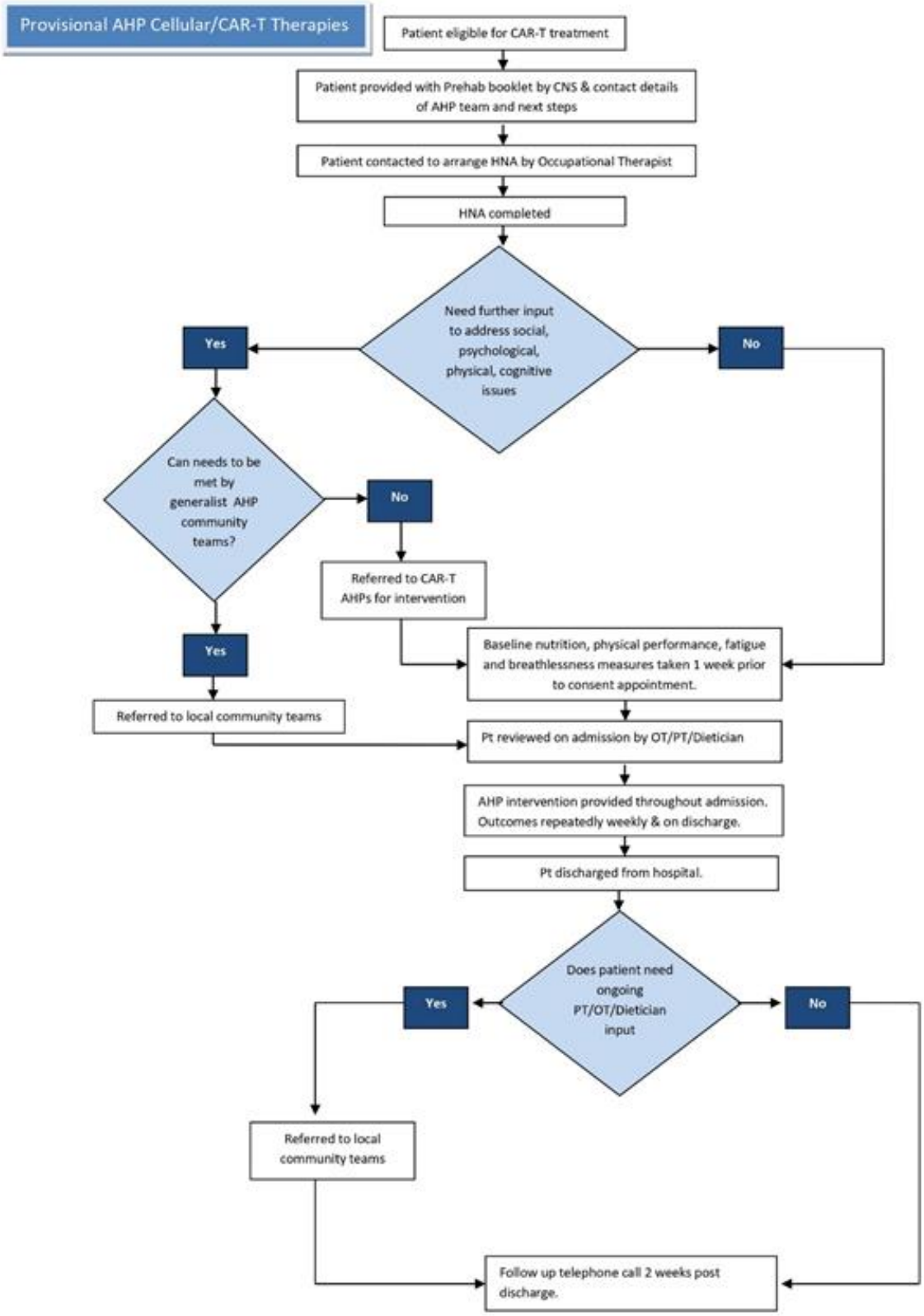
5 APPENDIX 1 – Purchase Order Process

<table>
<tr><td colspan="2">Patient referred as appropriate for CAR-T through national panel and local MDT</td></tr>
<tr><td colspan="2">Drugs request made to Christie commissioning team</td></tr>
<tr><td>English Patient – Christie commissioning team takes request to the NHSE Central funding panel via Blueteq Cancer Drug Form (CDF) completed by Haematology pharmacist. Generated number added to spreadsheet</td><td>Welsh Patient – Pharmacy inform the Christie contracts team of the patient and confirmed treatment dates, the contracts team then take the request to Welsh Health Specialist Services Committee (WHSSC)</td></tr>
<tr><td colspan="2">Approval received from Christie contracts team.
Purchase orders raised in advance by Haematology Operational Manager and printed off.
Kept in a file in the transplant office so they can be linked to patient/product</td></tr>
<tr><td colspan="2">Order placed with either Novartis or Kite once PO available</td></tr>
<tr><td colspan="2">Purchase order number added to patient’s record on the CART spreadsheet and individual patient check list</td></tr>
</table>

STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

6 APPENDIX 2 – AHCP pathway for CAR-T



STANDARD OPERATING PROCEDURE (SOP)

TITLE: COORDINATING ADOPTIVE CELLULAR THERAPY

7 APPENDIX 3 – Commercial Product Washouts

Type of Therapy	Washout	PRODUCT
Bendamustine + Rituximab +/- polatuzumab	14 days pre LD chemotherapy commencement	Axicel/Tecartus
High-dose methylprednisolone + Rituximab	7 days pre commencement of LD chemotherapy	Axicel/Tecartus
Corticosteroid Therapy	5 days prior to reinfusion	Axicel/Tisagen/Tecartus
Any antiproliferative/Lymphodepleting chemotherapy	2 weeks prior to reinfusion	Tisagen
Short acting chemotherapy treatments and TKIs	3 days prior to reinfusion	Tisagen
Immunomodulatory drugs including checkpoint inhibitors	2 weeks prior to reinfusion	Tisagen
Antibody therapies EXCLUDING Rituximab	4 weeks prior to reinfusion	Tisagen
CNS therapies/prophylaxis	1 week prior to reinfusion	Tisagen