

SCHEDULE 2 – THE SERVICES

A. Service Specifications

Service Specification No:	170100S (draft interim)
Service	Interim specification for the delivery of Tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) Therapy for <ul style="list-style-type: none"> - B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-stem cell transplant or in second or later relapse in patients up to 25 years of age - Diffuse large B-cell lymphoma (DLBCL) that is relapsed or refractory (r/r) after two or more lines of systemic therapy in adults.
Commissioner Lead	<i>For local completion</i>
Provider Lead	<i>For local completion</i>

1. Scope
<p>Prescribed Specialised Service</p> <p>CAR T is a new medicine manufactured from the patient's own cells and reinfused to treat certain types of cancer. Close post-infusion management is required to manage toxicities.</p> <p>Clinicians experienced in allogeneic stem cell transplant, immunotherapy and in treating these cancers are best placed to deliver the service and this new service is being developed by building on the requirements for allogeneic Blood and Marrow Transplantation (BMT).</p> <p>Clinical practice in CAR T has developed in haematology and Stem Cell Transplant Units with Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) (hereafter JACIE) accreditation for cellular therapy, building on the services for transplant / immunotherapy and clinical trial and academic research activity.</p> <p>CAR T therapy is another innovative anti-cancer treatment. The NHS has experience of developing and / or introducing novel and toxic anti-cancer treatments (e.g. complex immunotherapy) and the need to concentrate and develop expertise is key.</p> <p>CAR T cell therapies are amongst the first of a pipeline of cell therapies</p>

transitioning from 'bench to bedside' for both malignant and non-malignant diseases. They are considered to be highly innovative personalised treatments offering potentially effective therapy with severe but manageable adverse events (AEs) which require specialised monitoring and management. Indications for Advanced Cell Therapies are expected to expand beyond current indications, which are largely haematological malignancies. This will have implications for the teams involved and also where the treatment is administered. Therefore this and other interim specifications will remain under regular review.

The specification relates to commissioned clinical care, not research or trial activity.

Description

The following is a description of CAR T in general:

"Chimeric antigen receptor (CAR) T cell therapy is a promising approach for the treatment of refractory malignancies, but is associated with unique acute toxicities that need specialised monitoring and management. Cytokine-release syndrome (CRS) and CAR T cell-related encephalopathy syndrome (CRES) are the most common toxicities observed after CAR T-cell therapy and, rarely, CRS can evolve into fulminant haemophagocytic lymphohistiocytosis (HLH). Intensive monitoring, accurate grading, and prompt management of toxicities with aggressive supportive care, anti-IL-6 therapy, and/or corticosteroids for severe cases are required to reduce the morbidity and mortality associated with CAR T cell therapy" (Neelapu SS et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol.* 2018 Jan;15(1):47-62. doi: 10.1038/nrclinonc.2017.148. Epub 2017 Sep 19).

Tisagenlecleucel (CTL019) is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signalling domains for 4-1BB (CD137) and CD3 zeta. CD19 is expressed on B cells from early development until differentiation into plasma cells but is not present on pluripotent blood stem cells and most normal tissues other than B cells.

Tisagenlecleucel is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure, cryopreserved in liquid nitrogen and shipped to the Novartis manufacturing facility. The mononuclear cells are enriched for T cells, transduced with the lentiviral vector containing the anti-CD19 CAR transgene, and activated with anti-CD3/CD28 antibody coated beads. The transduced T cells are expanded in cell culture, washed, and formulated into a suspension, which then is cryopreserved and returned to the treating centre. The frozen suspension is shipped in patient-specific infusion bag(s) which is thawed prior to administration.

According to the EPAR for Tisagenlecleucel, in ALL the most common non haematological adverse reactions were cytokine release syndrome (77%), infections (65%), hypogammaglobulinaemia (47%), pyrexia (40%) and decreased appetite (39%). In DLBCL, the most common non-haematological adverse reactions

were cytokine release syndrome (58%), infections (54%), pyrexia (35%), diarrhoea (32%), nausea (29%), hypotension (26%) and fatigue (26%). Hypogammaglobulinaemia may require immunoglobulin replacement therapy.

The European licence for the product was granted in August 2018
<https://www.medicines.org.uk/emc/product/9456/smhc>

There is also a service specification for Axicabtagene Ciloleucelel for relapsed refractory DLBCL (diffuse large B cell lymphoma) in adult patients.

Adult patients with DLBCL

The relevant issues in determining the potential number of adult patients eligible to receive tisagenlecleucel are:

- 5130 new patients diagnosed with DLBCL in the UK each year (data from Haematological Malignancy Research Network [HMRN]) of which **4361** are in England. The median age of patients with DLBCL at diagnosis is 70 years.
- In the updated analysis of the JULIET trial of tisagenlecleucel treatment in DLBCL, the median age of the 111 patients treated was 56 years with an age range of 22-76 years and 23% were 65 years old or older. This bias towards selecting younger patients for CAR T cell therapies in this study reflects the need for patients to be very fit for a treatment with potentially severe and acute AEs which are manageable by skilled trained staff.
- 20% of patients with DLBCL do not receive any active treatment. This figure comes from the HMRN for 2007 and is incorporated in a health economic model developed by the HMRN in conjunction with York University (Eur J Health Economics 2017; 18: 255-267). This 20% figure remains valid in view of the opposing trends that are evident: increasing diagnoses of DLBCL made since 2007, particularly so in older people (who due to assessment of fitness are less likely to receive active treatment) and the ability of greater numbers of patients to undergo chemotherapy in 2018 that is better tolerated/supported than in 2007.
- 5% of the total patients diagnosed will receive radiotherapy only.
- 75% of the total patients diagnosed with DLBCL will receive chemotherapy, this equating to 3270 patients.
- Not all of these 3270 patients will receive optimal 1st line chemotherapy but 2nd line chemotherapy is only likely to proceed in relapsed patients treated with optimal 1st line chemotherapy.
- The HMRN/York economic model indicated that in 2007, **11.2%** of all DLBCL patients proceeded to have 2nd line chemotherapy, **3.2%** with subsequent Haematopoietic Stem Cell Therapy (HSCT) and **8%** without SCT. Most but not all of this **8%** in 2007 will have had aggressive 2nd line chemotherapy. Changes in practice since 2007 mean that more patients remain disease-free with 1st line chemotherapy and 2nd line salvage therapy is better tolerated and supported. Thus it is reasonable to assume similar percentages in 2018 to those in 2007 i.e. **3.2%** of all DLBCL patients still have 2nd line chemotherapy plus HSCT (**142 patients**) and **8%** of all patients have 2nd line chemotherapy without HSCT (**349 patients**)
- Of the 142 patients that have 2nd line chemotherapy and HSCT, approximately one quarter will remain disease-free. This therefore means

that about 100 patients will relapse, often with very aggressive disease. Nevertheless, as these patients started 2nd line treatment as a fit group of patients, it is reasonable to assume that about 30-40 patients will subsequently be eligible for Tisagenlecleucel

- Of the 349 patients that have and nearly all fail 2nd line chemotherapy, a large proportion will be unfit for CAR T therapy either as a consequence of disease progression or because they lack the fitness required for CAR T therapy (see the trial selection criteria). It is important to note that DLBCL that has progressed after 2 lines of therapy is often rapidly growing and thus can cause a steep and rapid decline in a patient's performance status and therefore contra-indicate CAR T therapy. This therefore makes the likely eligible number of fit patients with relapsed DLBCL who have not had HSCT to be about a third of those that had such 2nd line chemotherapy – **110-120** patients
- In one study, 21% of patients had previously had HSCT. Thus the proportional estimate of patients eligible for CAR T therapy post HSCT in England (about 30-40 of such patients) is in broad accordance with the 110-120 patients estimated to have not had HSCT
- In total, NHS England estimates that approximately **135-150** patients with relapsed/refractory DLBCL will be eligible for tisagenlecleucel.
- The numbers of children and teenagers with relapsed/refractory DLBCL will almost all be post HSCT and the number estimated to be potentially eligible in the event that off label CAR T cell therapy in future is permitted is 5-10.

Children and Young people with ALL

Expert clinical opinion of the numbers of patients aged 1-24 years with B ALL who would fit the eligibility criteria for this product was sought. Based on data from current and previous national ALL trials for patients aged 1-24 years (UKALL2003, UKALL2011) and activity of the national paediatric leukaemia MDT at which relapsed/refractory ALL patients are discussed, together with wider clinical opinion, it is estimated that there will be between **15 -30** patients per year.

In total, NHS England estimates that there will be about **150-180 patients per year** eligible for treatment with tisagenlecleucel within its licensed indication. There would be 5-10 children or teenagers who have diseases with similar biology to adults and who could also benefit from CAR T therapy in the event that off label use is available in future. At present, there is no data to support this use and it is not licenced for such use.

1.3 The principles underpinning the specification are:

- As NICE is evaluating the product and its place in the pathway, the final specification will be amended once the final appraisal is published and the first wave centres have started to deliver treatment.
- CAR T therapy is novel with remaining uncertainties about outcomes and complications. Therefore in the first instance there will be a phased approach to commissioning focused on beginning access at a small number of geographically spread JACIE accredited providers of allogeneic haematopoietic stem cell transplantation (HSCT) who gain accreditation for

Immune Effector Cell (IEC) therapy. The number of providers will increase as demand and capacity requires but is unlikely to be comparable with the number of commissioned allogeneic transplant centres due to the need to concentrate expertise in management at least in the early years of access.

- Commissioned providers will need to
 - evidence accreditation to JACIE standards for IEC therapy
 - evidence previous experience of CAR T and other IEC therapy
 - evidence effective implementation of standard operating procedures and risk management arrangements for successfully providing CAR T therapy and treating all complications including those that are severe and life-threatening.
 - evidence experience of managing serious toxicities associated with therapies such as CAR T therapy e.g. complex immunotherapy and allogeneic transplantation
- All necessary regulatory approvals and company accreditation are also pre-requisites for consideration for commissioning. This will include evidence of MHRA Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP).
- This specification will be reviewed annually or at earlier intervals as service experience and patient need requires.
- The primary clinicians for the delivery of this CAR T therapy (a cell infusion procedure) will be undertaken by consultants (haematologists / haemato-oncologists) and their teams with appropriate training and competency in DLBCL or ALL, immunotherapy and allogeneic HSCT according to quality managed policies and procedures. Support from medical oncology (immunotherapy / lymphoma) will be essential. In future and in relation to other CAR T therapies in other indications, the role of other clinicians in the delivery of treatment may evolve. The core CAR T Team which will also include immunotherapy / ITU / nursing / psychology / pharmacy / laboratory. The extended team would include neuro-physiology and neuromedicine +/- neurosurgery, cardiology, renal, etc as required.
- Training, competencies, policies and procedures are defined in the current FACT-JACIE standards (the 6.01 and 7th editions include IEC therapy standards). Commissioned providers must maintain full active JACIE accreditation and certification. JACIE reaccreditation occurs every four years. The JACIE website provides two lists of providers and their accreditation status, updated monthly. List one includes those with valid accreditation (not yet expired). The second list includes those who have formally requested reaccreditation (applied, awaiting inspection, inspected awaiting report or in corrections phase). As the second makes no assessment of the centres' compliance with Standards, commissioners will seek evidence from both the Trust and JACIE to establish the circumstances of those awaiting reaccreditation.

- The selected providers will need to demonstrate age appropriate disease specific expertise and immunotherapy experience, a level of training and competency in treating patients with the toxicities associated with the treatment (e.g. multi-organ failure managed in ITU and immediate access to neurological diagnostic and management interventions which are matched to the neurological toxicity profile associated with CAR T therapy).
- The aim is to develop over time a number of commissioned CAR T therapy centres. In order to develop that expertise, providers will be commissioned on the expectation that they will deliver all relevant CAR T therapy products which are licenced and approved. For example, where CAR T therapy products cover a similar patient group, providers will be expected to be able to deliver all products available. This will include training and accreditation by each individual company providing the relevant CAR T therapy.
- All children and young people receiving CAR T cell therapy must be treated within designated CYP providers with full access to age-appropriate care as defined in the NHS England Paediatric Cancer Networks and Teenage and Young Adult Cancer Networks service specifications. Commissioned providers for individual CAR T cell products will ensure that CYP will have access to CAR T cell products for which they are eligible.
- Although the initial wave of CAR T therapies will be directed at haematological cancers, the indications are expected to expand and are likely to include solid tumours. The nature of the CAR T technology means that it is expected that such future indications will also be commissioned to be delivered by those with JACIE accreditation for allogeneic HSCT and for all standards relating to IEC therapy. Such centres will also be responsible for the necessary aftercare of patients following CAR T therapy, including rapid admission pathways and treatment of complications. Over time, it is expected that developments in CAR T and associated therapies will require further consideration of the future workforce requirements for such treatments. This is out of scope of this interim specification.

1.4 How the service is differentiated from services falling within the responsibilities of other commissioners

ATMPs are listed as a general exclusion to national tariff although individual drugs are not listed in the 2017/18 list of exclusions. Managed entry agreements may be developed with regard to the cost of the medicinal product.

Approaches to reimbursement for service delivery are in development. It is anticipated that the pricing for allogeneic transplant will form the basis of the service reimbursement, with some uplifts to account for the additional MDT arrangements and treatment complexity in the initial implementation phase. Provider costing information will be required to be collected and submitted to commissioners to improve the approach to reimbursement for service costs as experience with CAR T improves. Bespoke activity reporting will be used.

The specification will remain under review as the CAR T therapy product pipeline develops.

Specialised allogeneic haematopoietic stem cell transplantation (HSCT) services are commissioned 30 days prior to and 100 days after transplant, after which commissioning responsibility returns to CCGs. It is expected that in the first instance the same approach will be applied.

2. Care Pathway and Clinical Dependencies

2.1 Current Care Pathway

Current care pathway relapsed refractory DLBCL (diffuse large B cell lymphoma)

Chemo-immunotherapy remains the cornerstone of treatment for patients with DLBCL. If patients are to receive optimal therapy, they have to be medically fit to receive combination chemotherapy (cyclophosphamide, vincristine, doxorubicin and prednisolone) given in conjunction with rituximab. Such patients have a 70-80% chance of remaining free of disease progression.

Patients who relapse do so within the first 2 years after completing treatment and if fit for optimal (but toxic) chemo-immunotherapy have a low chance of remaining free of disease progression if just treated with conventional doses of chemotherapy. Patients who respond to 2nd line chemotherapy and who are sufficiently medically fit will usually be offered high dose chemotherapy and HSCT. Such consolidation of a response to 2nd line chemotherapy with HSCT is considered to be part of 2nd line chemotherapy. If not salvaged by 2nd line chemotherapy with or without HSCT, life expectancy is short and usually measured in terms of single numbers of months.

Salvage chemotherapy in DLBCL with new agents (e.g. B cell pathway inhibitors, checkpoint inhibitors, inotuzumab) have been disappointing and hence for relapsed/refractory DLBCL after 2 lines of chemotherapy, CAR T therapy is a novel and potentially efficacious treatment to improve outcomes in DLBCL.

Small numbers of children and teenagers are also diagnosed with DLBCL and a few of these will have relapsed/refractory disease after 2nd line therapy. These patients could benefit from CAR T therapy in the event that off label use is permitted in future.

Current pathway B-cell acute lymphoblastic leukaemia (ALL) including refractory, in relapse post-stem cell transplant or in second or later relapse

According to the Children's Cancer and Leukaemia Group (CCLG) there are about 300 new cases of ALL each year. The aim of treatment is to destroy leukaemia cells and restore normal bone marrow function.

Chemotherapy is the main treatment for ALL. Induction therapy starts within days of diagnosis and continues for 4-6 weeks. Remission and prevention of spread into the brain and spinal cord is achieved usually through methotrexate lumbar puncture. If required, further drug and chemotherapy treatment is provided as indicated by the

individual response to treatment. All patients have maintenance treatment involving 2-3 years of daily oral treatment and in some cases monthly injections of chemotherapy, oral pulses of steroids and three monthly intrathecal treatment. Treatment is provided on an outpatient basis.

HSCT is only needed in a small minority of patients who experience relapse.

Relapsed ALL although only occurring in the minority of ALL patients, remains a leading cause of cancer death in children. Within children that relapse, it is possible to identify those with high risk features whose long term survival is dismal i.e. 20-30% even with standard intensive therapy including allogeneic stem cell transplantation (allo-SCT). Children with relapsed ALL often reach the ceiling of acceptable toxicity with standard chemo and radiotherapy. Allo-SCT comes with a potential burden of long term toxicity in the form of chronic graft versus host disease and absolute treatment related mortality (TRM) of 5-20% depending on procedural and factors relating to the donor/recipient. For those who relapse post allo-SCT, outcomes are even poorer, especially for those who relapse early (<1year) post-transplant.

In some cases, boys may require testicular radiotherapy and both boys and girls may require additional intrathecal administration of methotrexate chemotherapy if leukaemia cells are detected in the CNS at diagnosis.

2.2 Decision to Treat

If approved, clinicians currently treating patients in the indicated populations will consider their patient's eligibility for the treatment. At this stage they will

- Identify eligible patients who might benefit from CAR T therapy
- Confirm patient eligibility in line with the manufacturer's licence with regard to age, fitness, disease and treatment stage
- Confirm that patients have been informed and understand the potential benefits, risks and complications of treatment as part of shared decision-making
- Refer such patients in line with agreed pathways (to be provided separately) to the CAR T provider specialist Multi-Disciplinary Teams (MDT) and then to the disease specific National CAR T Multi-Disciplinary Teams (NCMDT).

The NCMDT will meet weekly and ensure that patients referred do meet the eligibility criteria, taking an overview of capacity planning and scheduling, and undertaking audit to ensure equity of access as well as outcomes.

Clinical decision making about individual patient treatment (assessment prior to treatment preparation, initiation and complications management) will be made by specialist MDTs operating at CAR T providers (and in the initial phase, with support from the disease specific National CAR T Multi-Disciplinary Teams (NCMDT) – see below. MDTs must operate in line with NICE IOG recommendations for MDTs:

<https://www.nice.org.uk/guidance/ng47>

The primary clinicians overseeing the planned CAR T pathway will include transplant physicians / immunotherapy leads. Other named specialists for

pharmacy, critical care, neurology support and nursing will be part of the MDT available 24/7 to manage the planned and unplanned needs of CAR T patients. Psychology input into the MDT will also be required given the nature of the treatment, the need for high levels of patient awareness of symptoms and the side effects profile.

The role of the centre MDTs will be to:

- identify eligible patients from their own and neighbouring NHS trusts who may benefit for CAR T therapy in accordance with the agreed criteria implemented by the NCMDT. Referral to the NCMDT would occur at this point. Once approved, the centre MDT would also do the following:
- confirm that patients (and / or their carers) have been informed and understand the potential benefits, risks and complications of treatment as part of shared decision-making and psychological support is available.
- assess individual patients prior to treatment preparation and initiation
- manage the treatment, post treatment management and follow up in line with the approved and accredited SOP
- undertake reporting, data analysis and audit – this may include engagement with manufacturers as required.
- review cases 3 months after treatment from a learning perspective and feed results into audit/service evaluation and national learning processes.
- ensuring appropriate patient monitoring post treatment

CAR T provider MDTs will demonstrate governance arrangements which meet the requirements for robust and effective quality management systems from a company accreditation, JACIE IEC therapy accreditation and NICE IOG perspective.

Requirements for a disease specific National CAR T Multi-Disciplinary Teams (NCMDT) for patient selection

At the beginning of the phased implementation of the treatment, it will be necessary to have structures in place – such as a NCMDT - to ensure selection of patients is not restricted to those patient treated at selected CAR T providers, but that equity of access is applied in considering all eligible, fit patients who are most able to benefit. Scheduling of patients will be required given that medicine manufacture can take about 1 month and clinically services will likely start by treating 1 patient per month expanding potentially to 1 per week over a period of time, based on the US experience. It is possible that depending on the number of providers deemed ready to provide CAR T that such arrangements may be in place for a limited period.

At the national level, this will mean establishing a newly adopted infrastructure.

The role of the disease specific NCMDT will be to:

- implement agreed criteria for patient selection for each indication and prioritisation for this and other licenced and approved CAR T products and processes for receiving and prioritising referrals.
- confirm patient eligibility in line with the manufacturers licence and the trials on which the licence is based with regard to age, fitness, disease and treatment stage, including direct review of tissue and radiological

diagnostics and staging and fitness for treatment.

- prioritise patients for treatment based on assessment of information regarding patient fitness, patient disease severity and available capacity.
- provide expert advice for the management of complex cases.
- work closely with UK JACIE to ensure compliance with relevant standards and the EBMT/BSBMT registries to support data submission for long term outcomes analysis in NHS England centres.
- provide a forum for learning, sharing experience, audit/service evaluation and research, which will support the expansion of CAR T centres over time.

The core members of disease specific NCMDT will also be in line with NICE IOG guidance. Named representation covering adults and paediatrics and including deputising arrangements would be required. Membership will support delivery of the functions and will therefore include:

- Independent clinical member (not a CAR T provider)
- Named clinical lead and deputy from each commissioned CAR T provider (Haematologist or other specialist meeting FACT-JACIE standards for BMT clinical programme director and/or physicians with tertiary level experience in the disease / age group)

Depending on experience over time, volume and geographical considerations, the structures for patient selection, scheduling and audit may change. These structures would need to remain under review. Further information about the operation of the NCMDT and MDTs and referral pathways will be produced.

2.3 Initial Admission

Before administration of CAR T cells, patients are likely to require chemotherapy (which should complete 2-14 days before infusion) and require an inpatient admission. Following infusion, patients are likely to remain as an inpatient for c10 days and if the patient is stable, they can be discharged thereafter. If patients have low disease burden, patients may be discharged earlier on an individual basis. Following discharge from inpatient care, patients should then remain within c.1 hour drive time of the administering unit for c4 weeks post infusion (note company requirements are 2 hours). Adhering to these arrangements for safe clinical management can represent a significant burden for patients and their families. CAR T providers must ensure that patients and families are supported to secure the most appropriate arrangements to meet this. This may include signposting to forms of support including charities and benefits. For this period, principles of ambulatory care can be applied, as per the recommendations for ambulatory care for high intensity chemotherapy NICE Improving Outcomes Guidance for Haematological Cancer

<https://www.nice.org.uk/guidance/NG47/chapter/Recommendations#ambulatory-care>

A supportive care protocol for CAR T treatment in the US has been produced and published by Neelapu SS et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018 Jan;15(1):47-62. doi: 10.1038/nrclinonc.2017.148. Epub 2017 Sep 19. Whilst this is pertinent to

treatment in the US, in the absence of any other protocol, the clinical consensus is that this provides important contextual information on clinical presentations to help establish management of CAR T therapy patients in England. However, it is not the case that all the investigations listed are recommended, mandated or commissioned in England. In some cases, the treatments listed are not routinely commissioned e.g. baseline brain MRI or siltuximab. Providers must note that this specification and the associated published NICE guidance sets out the commissioned position for England. Treatments and interventions not included in these documents will not be supported or funded.

Where it relates to the regulatory requirements of the procurement, manufacture, storage and delivery of the product, the company requirements must be followed. In some cases, clinical consensus regarding the clinical management of the patient prior, during and after treatment and in relation to the management of toxicities may differ from the companies perspective and may be more stringent than those required by the company. These must be followed.

2.4 Product Preparation / Manufacture

Please see commercially confidential Appendix D to be included in the contract of commissioned providers only.

2.5 Product Delivery (to patient)

Receipt of the CAR T product will be by Pharmacy (Chief Pharmacist) or Pharmacy approved location and recorded in line with regulatory requirements.

The commissioned provider will follow the instructions for preparation of the product for infusion in accordance with manufacturer quality assurance (see below and Appendix D). Care provided will be in accordance with the SOP and JACIE 6.01 edition standards for IEC therapy delivery.

All staff involved in handling the Novartis CAR-T product will be trained in the following areas and confirmation will be required

- Apheresis
- Cell Collection/Processing
- Handling and Storage
- Process
- Product, Administration and Safety

Tisagenlecleucel can only be administered in a certified clinical setting. A trained, named individual will receive the product at the hospital and sign for the receipt of the product. The individual will document the temperature of the product upon receipt. The product may be stored at the hospital in the vapour phase of liquid nitrogen until the patient is ready to receive the infusion. The hospital needs to confirm the patient identity and match the correct product at the time of treatment. If the patient is ready and has been conditioned as required, then the product is then transferred to the preparation area and is thawed according to manufacturer instructions. The member of staff has to be able to trace the product throughout the process. The product is infused into the patient as per package instructions and by

a trained member of staff. CAR-T therapy should be initiated under the direction of and supervised by physicians experienced in the treatment of haematological malignancies. In summary, the product must be prepared and delivered and patients monitored in line with the Summary of Product Characteristics (SMPC) and the company specific requirements about which all authorised providers must complete training and follow specific instructions provided.

The company requirements are that the patient must be monitored for at least 10 days at a certified clinical facility following infusion for signs and symptoms of cytokine release syndrome (CRS) and neurologic toxicities (NT). The licence requires that patients should be instructed to remain within 2 hours travelling distance of a certified clinical facility for at least 4 weeks following infusion. Patients should be issued with relevant patient information to alert them to side effects and guide their action to seek medical attention.

In the initial phase, a more cautious approach to treatment will be undertaken with clinical opinion recommending patients remain within c 1 hour of the CAR T cell therapy centre and it is recommended this remains under review in the initial implementation phase. Providers must support patients and their families during this phase and ensure accurate and complete contact information is provided.

Clinical consensus of the specification writing group is that at the introduction of CAR T cell therapy, treating centres will need to follow the grading systems set out in Appendix B and C to inform decision making with regard to ITU admission (grade 2 and above).

2.6 Management of Cytokine Release Syndrome (CRS)

Frequent daily monitoring is required at commissioned CAR T providers during the inpatient stay for at least 10 days for signs of CRS and for signs and symptoms of CRS for 4 weeks after infusion. The company will provide a Risk Management Programme with training and materials to be provided. Patients and their carers should be counselled to seek immediate attention should the signs or symptoms occur. CRS grading and action is set out in Appendix B and also further information from the company in Appendix D.

Cytokine Release Syndrome is a form of Systemic Inflammatory Response Syndrome and is characterised by elevated circulating levels of several cytokines, including interleukin (IL) 6. This side effect is present in all CAR T products.

The product licence requires a grading system be used for assessment/description of CRS. Risk Management Plan materials are provided.

The purpose of using a grading system is to guide critical care management, which largely consists of supportive measures to reduce likelihood of further organ dysfunction/failure whilst recovery occurs and to determine timing of rescue therapy. There are 2 systems for grading CRS, National Cancer Institute Consensus criteria (Lee et al) and the University of Pennsylvania (UPENN/CHOP), with the main difference being in grades 2 and 3 categories. Whilst the licence refers to the use of UPENN, the Lee system permits greater descriptors for grades

2 and 3 which are relevant for critical care management of adults and paediatric patients and therefore use of the Lee system is recommended by commissioned CAR T therapy providers (see Appendix B).

CAR T cell toxicities are familiar to those experienced in the delivery of allogeneic stem cell transplantation and immunotherapy although on a much smaller scale. These specialists, together with critical care and neurology specialists, are experienced in identifying immunologically-mediated toxicities early, to intervene in a timely manner and thus increasing the likelihood of managing side effects effectively.

Supportive drugs

Access to supportive treatments as set out in the SPC will require pharmacy facilities, expertise and capacity. Provision of immunoglobulin will be required for the management of CAR T complications. This is categorised as a blue indication and will need to be assessed through the Immunoglobulin Assessment Panel.

At least 4 doses of tocilizumab per patient must be available prior to infusion. The regulatory requirements for access to tocilizumab as part of CAR T therapy will be specified by the manufacturer. Further information will be included in the British National Formulary (BNF).

2.7 Management of Neurologic Sequelae

Frequent daily monitoring is required at commissioned CAR T providers during the inpatient stay for at least 10 days for signs of CRS and for signs and symptoms neurologic toxicities for 4 weeks after infusion. Patients and their carers should be counselled to seek immediate attention should the signs or symptoms occur. CRES grading and action is set out in Appendix C and also further information from the company in Appendix D.

Neurotoxicity has been defined as CAR T cell related encephalopathy syndrome (CRES). Prevalence of encephalopathy varies and it is not possible to directly compare, for example, prevalence in Diffuse Large B-Cell Lymphoma with B-cell acute lymphoblastic leukaemia (34% in DLBCL as per Neelapu, 11% in ALL as per Maude et al). It can occur concurrently with or after CRS. Its pathophysiology remains incompletely understood, with possible roles for passive diffusion of cytokines into the brain and trafficking of T cells into the CNS. CSF protein levels are often increased compared with baseline measurements, suggesting disruption of the blood-brain barrier (BBB). Liver and kidney dysfunction as well as hypoxemia and infection can also contribute to the encephalopathy.

A CAR T cell therapy associated Toxicity (CARTOX) Working Group in the US has provided recommendations for monitoring, grading, and managing acute toxicities that can occur in patients treated with CAR T therapy (Neelapu et al., 2018; Nat Rev Clin Oncol 15:47-62).

CRES typically manifests as a toxic encephalopathy, with the earliest signs typically including diminished attention, language disturbance, and impaired handwriting.

Other symptoms and signs include confusion, disorientation, agitation, aphasia, somnolence, and tremor.

A grading system of CRES severity must be used. One example is the CARTOX 10-point neurologic assessment (CARTOX-10) tool (validated in adults, not validated in children) in which one point is assigned for each of the following tasks that is performed correctly: orientation to year, month, city, hospital, and President / Prime Minister of country of residence (total of 5 points); naming three objects (maximum of 3 points); writing a standard sentence (1 point); counting backwards from 100 in tens (1 point). Normal cognitive function is defined by an overall score of 10. The score can be used to define Grade 1 (CARTOX-10 score 7-9, mild impairment), Grade 2 (score 3-6, moderate impairment), Grade 3 (score 0-2, severe impairment), and Grade 4 CRES (patient in critical condition, and/or obtunded and cannot perform assessment tasks). From an equalities perspective, it is important to note that patients may not have English as a first language or may have cognition issues related to age or disability which need to be taken into account when using such tools.

Other parameters of CRES severity include raised intracranial pressure (stage 1-2 papilloedema or CSF opening pressure up to 27 cm H₂O in CRES Grade 3, stage 3-5 papilloedema or CSF opening pressure >27 cm H₂O or brain oedema in CRES grade 4), and seizures or motor weakness (partial seizure, or non-convulsive seizures on EEG with response to benzodiazepine in CRES Grade 3, generalised seizures, or convulsive or non-convulsive status epilepticus, or new motor weakness in CRES Grade 4).

Median onset time to CRES is 5 days (although this ranges 1-17 days), dependent on disease indication. It has been observed that clinical manifestation is often biphasic, with a first phase occurring concurrently with high fever and other CRS symptoms, typically within the first 5 days after cell infusion, whereas a second phase occurs after the fever and other CRS symptoms subside, often beyond 5 days after infusion. However, delayed neurotoxicity has been observed in up to 10% of patients, with seizures or confusion occurring during the third or fourth week after CAR T therapy. Anti-IL6 / IL-6R therapy has been reported to reverse CRES during the first, whereas corticosteroids are the preferred treatment for the second phase, possibly due to higher BBB permeability during the first phase enabling better diffusion of the therapeutic monoclonal into the CNS.

For Tisagenlecleucel, the majority of neurological events occurred within 8 weeks following infusion and were transient. The median time to onset of neurological events was 7 days in ALL and DLBCL. The median time to resolution was 7 days for ALL and 12 days for DLBCL.

Other causes of neurologic symptoms should always be considered. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with EEG. Unhindered access to Critical Care should be available for severe or life threatening neurologic toxicities.

The typical duration of CRES can vary between a few hours to weeks. Rapid fluctuations in severity are possible and require close patient monitoring.

In patients with CRES, secondary cortical irritation is indicated by EEG findings of epileptiform discharges or non-convulsive electrographic seizures. The most common EEG findings are diffuse generalised slowing in keeping with encephalopathy, with or without triphasic waves at 1-2 Hz.

Treatment (anti-epileptics) should be administered as per British National Formulary (BNF).

2.8 Interdependence with other Services

All commissioned CAR T providers must be able to demonstrate they have the required protocols, clinical facilities, staffing, medical supervision and care, training and education, accreditation and governance to address the following:

Regulatory

Compliance with Human Tissue Authority (HTA) (for product procurement), JACIE-FACT HSCT standards and Medicines and Healthcare Regulatory Agency (MHRA) standards.

Approval as a Tissue Establishment (TE) site that is authorised under the EU Tissue and Cells Directive (EUTCD) to perform procurement, testing, processing, storage, distribution, and import/export of human and tissue cells relevant to CAR T. The Human Tissue Authority (HTA) in the UK and HPRA in Ireland are the Competent Authorities responsible for regulating TE registration.

Accredited Quality Management System, SOPs and Protocols and Risk Evaluation and Mitigation Strategy capable of demonstrating a high quality, safe treatment pathway capable of effectively managing all side effects including those that are life threatening.

JACIE accreditation

JACIE accreditation as a collection, storage and clinical centre for allogeneic transplantation. JACIE accreditation should be age appropriate i.e. cover paediatrics. As patients may be unstable and/or recovering from chemotherapy during harvest, accredited collection facilities (leukapheresis and/or bone marrow harvest procedures) should be on-site or via a JACIE compliant 3rd party sub contracted arrangement.

Pharmacy

CAR-T therapy is a medicine and therefore its governance (via medicines management / clinical effectiveness committees) and operational management ie receipt, storage, preparation, prescription and issue are the responsibility of pharmacy. Pharmacy will need to collaborate with local experts e.g. stem cell laboratory colleagues, or third party colleagues e.g. NHSBT to ensure that optimal arrangements are in place for the implementation site.

A facility (e.g. pharmacy/cell therapy laboratory) capable of receipt of the products

with regard to suitable vapour phase liquid nitrogen Dewars with adequate space for storage. Prolonged storage will require facilities capable of <-150 degrees centigrade temperature monitoring and 24 hour alarm system. This means having the required capacity, technology and expertise for handling, storage and non-manufacturing preparation steps of advanced therapy medicinal products (ATMPs) in line with MHRA GMP and GCP requirement. (Manufacturer QA process is set out in commercially confidential Appendix D).

Where the facility maybe part of a different organisation or hospital department, the local site Pharmacy are responsible for ensuring appropriate supplier approval assurances and technical agreements detailing the roles of both parties and ongoing monitoring are in place.

Specialist MDT for clinical management by CAR T providers

An MDT led by the haematologist or equivalent specialist who meets JACIE standards for training and competency in allogeneic BMT and IEC therapy (including the ability to deal with safety issues such as CRS, TLS, GVHD and neurotoxicity), immunotherapy, disease specialist, critical care staff, nursing and a clinical pharmacist with ATMP knowledge. This MDT must have named members and clear agreements in place and operate in accordance with criteria implemented by the NCMDT for the appropriate selection of patients and management of complications.

The clinical team to include a role similar to a HSCT coordinator with sufficient seniority to negotiate and manage the significant logistical issues and interfaces involved in effective scheduling of cell procurement; product manufacture, storage and preparation; treatment delivery and clinical patient management.

Procedures for the appropriate clinical monitoring of patients immediately following CAR T therapy using Early Warning Scores (EWS) and minimum of 4-hourly observations. Patients who develop grade 1 symptoms and signs should have monitoring escalated according to their EWS and admission to Critical Care should follow as indicated (Grade 2 and above).

Immediate access to specialised diagnostic services for assessment of potential complications is required. Electroencephalogram (EEG) must be available, with interpretation available during the working day of the working week. For grade 1 CRES, management will involve daily 30min EEG until toxicity symptoms resolve. For higher grades (i.e. worse encephalopathy) patients should be on ITU with neurological assessment including use of regular standard EEGs (up to daily) or other treatment as indicated. Co-location with neurosurgery is preferred but not a mandatory requirement. An evidenced referral pathway for neurosurgical input required.

Infrastructure for ambulatory care and rapid re-admission supported by Standard Operating Procedures (SOPs) must be in place as per NICE guidance <https://www.nice.org.uk/guidance/NG47/chapter/Recommendations#ambulatory-care> to safeguard patients in the 3-4 weeks following discharge from in-patient care. As patients may not recognise the onset of encephalopathy on their own, 24-hour availability of a carer is mandatory. Provision of appropriate patient and carer information is required

Management of toxicities and critical care

Requirements:

- On-site critical care
- Age appropriate critical care which meets the NHS England service specifications
- Capability to deliver the critical care needs of all CAR T patients at all times including those with the most serious side effects (e.g. level 3)

Risk management plans and documented evidence of experience in managing the types of toxicities associated with CAR T will be required e.g. sustained and frequent experience in the management of multi-organ failure. CAR T cell centres will need immediate and 24/7 access to a wide range of support specialists in intensive, renal, respiratory, cardiovascular and neurological medicine.

For cardiac support, echocardiography should be immediately available along with either cardiac monitoring by telemetry, or continuous ECG monitoring and pulse oximetry monitoring if patients develop CRS symptoms of grade 2 or above. This should be continued until cytokine-release syndrome (CRS) resolves, in order to detect arrhythmias.

There should be clear pathways, policies and SOPs in place for the diagnosis and management of complications and treatments.

The ICU facilities should be age-appropriate and should comply with either or both the draft service specification for adult critical care or Paediatric Critical Care service specification (5th edition PICS standards 2015 <http://picsociety.uk/news/new-pics-standards-2016-now-available/>).

The ICU should have sufficient capacity to receive recipients of CAR T therapy and be able to demonstrate how that capacity is maintained throughout the year including at times of winter pressures.

Training

Completed all training for all staff as required by the regulators, the company and JACIE.

Patient / data registry

A written agreement is required to submit to or provide access for NHS England the long term follow-up data required by safety registries and a clear outline for how they will ensure the accuracy and sustainability of this data collection.

The Committee for Medicinal Products for Human Use (CHMP) issued a draft opinion in July 2018 stating it considers that the cellular therapy module of the EBMT registry may be used as a data source for regulatory purposes in the context of CAR-T cell therapies authorised for haematological malignancies. The draft opinion goes on to stipulate in detail the scope of the studies that may be performed based on the registry

<http://newsletters.ebmt.org/view.php?J=ZcaC2Q0sbcK763xTElBndiSQ&C=GCDza>

[HNVNS9uPBdyjkgVMA](#)

EBMT already have forms and data collection covering cell therapy including CAR-T (Cell Therapy – MED-A). England already subscribes data to EBMT via BSBMT. Utilising an established and credible existing registry will ensure good quality data and access. There may be additional requirements to be added to Cell Therapy MED-A depending on regulatory requirements.

3. Population Covered and Population Needs

3.1 Population Covered By This Specification

This specification covers all ages, in line with the licence for the product.

3.2 Population Needs

See section 1. This is an innovative technology which will require phased implementation over the first 3 years. During the period that capacity is built, eligible patients may need to be prioritised (survival of the eligible patient population with current treatments estimated to be median OS around 6 months). Once full capacity is achieved, it is expected annual eligible patients will be treated.

3.3 Expected Significant Future Demographic Changes

None as the specification has considered geographic distribution of centres administering CAR T therapy.

3.4 Evidence Base

NICE guidance <https://www.nice.org.uk/guidance/ng47>

JACIE website www.JACIE.org

EBMT website <https://www.ebmt.org/Contents/Pages/Default.aspx>

BSBMT website <http://www.bsbmt.org/>

4. Outcomes and Applicable Quality Standards

4.1 Quality Statement – Aim of Service

The aim is to commission providers who will oversee the clinical delivery of Tisagenlecleucel CAR T Therapy to eligible patients.

The specification will ensure:

- Patient access is secured at a national level.
- Best practice for the safe and effective delivery of CAR T therapy.
- Clinical dependencies are addressed and secured.
- Traceability and tracking and best practice for patient follow-up and data

capture is secured.

The main aim of this service specification is to support the interim introduction and delivery of this CAR T once it is recommended as a clinically and cost effective 3rd line treatment for the conditions set out in its licence.

As novel treatment, commissioned centres will support research activity and where appropriate be willing to support future phased adoption across the NHS in England working closely with designated Advanced Therapies Treatment Centres supported by Innovate UK and Cell and Gene Therapy Catapult. There is a need for shared learning between teams regarding these new technologies and their toxicities. This will also need to include how teams involved in cell therapies for non-malignant and malignant conditions collaborate and share resource, expertise and learning.

NHS Outcomes Framework Domains

Domain 1	Preventing people from dying prematurely	✓
Domain 2	Enhancing quality of life for people with long-term conditions	✓
Domain 3	Helping people to recover from episodes of ill-health or following injury	✓
Domain 4	Ensuring people have a positive experience of care	✓
Domain 5	Treating and caring for people in safe environment and protecting them from avoidable harm	✓

4.2 **Indicators Include** the following, Novartis will also have indicator requirements as part of their regulatory arrangements and all efforts will be taken to harmonise these to ensure key data are collected without duplication. Complete and timely data collection, reporting and submission will be a mandatory requirement for commissioned providers as will agreements for data sharing. Data to be collected and reported separately for each indication. The indicators will be subject to further amendment based on the regulatory requirements / EMBT.

Number	Indicator	Data Source	Outcome Framework Domain	CQC Key question
Clinical Outcomes				
101	Proportion of patients transferred to ITU from a ward within 60 minutes	Provider / SSQD	1, 2, 3, 4	Effective, caring
102	Proportion of patients who complete treatment and are alive 28 days after infusion.	Provider / SSQD	1, 2, 3	Effective
103	Proportion of patients who complete treatment and are alive one year after first infusion.	Provider / SSQD	1, 2, 3	Effective
104	Proportion of patients who complete treatment and are alive two years after first infusion.	Provider / SSQD	1, 2, 3	Effective
105	Total number of Incidences of CRS at grade 2 and above requiring level 3 critical care or PICU.	Provider / SSQD	1, 2, 3, 4	Effective
106	Total number of Incidences of CRES at grade 2 and above requiring level 3 critical care or PICU.	Provider / SSQD	1, 2, 3, 4	Effective
107	Median duration of a admission for patients where an incidence of CRS at grade 2 and above has occurred.	Provider / SSQD	1, 2, 3, 4	Effective
108	Median duration of a admission for patients where an incidence of CRES at grade 2 and above has occurred.	Provider / SSQD	1, 2, 3, 4	Effective
109	3 month mortality rate	Provider / SSQD	1, 2, 3	Effective
110	Average length of stay of patients following treatment	Provider / SSQD	1, 2, 3, 4	Effective, caring
Patient Experience				
201	The provider has a process in place that ensures that patients receive the manufacturers patient information regarding side effects.	Self-declaration	4	Effective, responsive
202	A patient feedback exercise is undertaken three months post discharge.	Self-declaration	4	Effective, responsive
203	A patient feedback exercise is undertaken one year post discharge.	Self-declaration	4	Effective, responsive
204	A patient feedback exercise is undertaken at least annually.	Self-declaration	4	Effective, responsive
205	An assessment has been undertaken by the provider to assess the patient's experience prior to treatment.	Self-declaration	4	Effective, caring
206	An assessment of the patient experience is undertaken by the provider at three months post discharge.	Self-declaration	4	Effective, caring
207	An assessment of the patient experience is undertaken by the provider at least annually.	Self-declaration	4	Effective, caring
Structure and Process				
301	There is a MDT as per the service specification.	Self declaration	1, 3, 4	Safe, effective, caring, responsive

302	All relevant patients applicable for CAR-T are discussed at the local haematological cancer MDT	Self declaration	1, 3, 4	Safe, effective, responsive
303	All members of the MDT undertake training as per the service specification.	Self declaration	4, 5	Safe, effective
304	There is an infrastructure to support being a specialist provider of this service as detailed within the service specification.	Self declaration	1, 3, 4	Safe, effective, caring, responsive
305	Where cellular therapy products are received via a third party there is a written agreement in place.	Self declaration	5	Safe, effective
306	There are agreed clinical guidelines as per the service specification.	Self declaration	1, 2, 3, 4, 5	Safe, effective, caring, responsive
307	There are commissioner agreed patient pathways.	Self declaration	1, 2, 3, 4, 5	Safe, effective, caring, responsive
308	The service participates in local and national audits as required including patient selection in line with indication.	Self declaration	1, 2	Safe, well-led
309	The service submits EBMT / other registry information for Cell Therapy (via MED-A forms) to the NHS England commissioned database/registry.	Self declaration	1, 2	Safe, well-led

Detailed definitions of indicators, setting out how they will be measured is included in schedule 6.

- 4.3 Commissioned providers are required to participate in annual quality assurance and collect and submit data to support the assessment of compliance with the service specification as set out in Schedule 4A-C
- 4.4 Applicable CQUIN goals are set out in Schedule 4D. It is not currently proposed to develop a CQUIN for CAR T therapy for 2019/20.

5. Applicable Service Standards

5.1 Applicable Obligatory National Standards

All commissioned providers must meet the standards and be JACIE accredited for age appropriate delivery of allogeneic HSCT, including standards covering immune effector cell (IEC) therapy as set out in the 6.01 edition of the FACT-JACIE International Standards for Haematopoietic Cellular Therapy Product Collection, Processing, and Administration. Over the next 4 years, all cellular therapy providers are expected to complete reaccreditation against the 7th edition of the standards published in 2018.

Commissioned providers for adult patients must meet the mandatory requirements set out in NHS England's draft service specifications for Adult Critical Care and

Haematopoietic Stem Cell Transplantation (Adult). Commissioned providers for paediatric patients must meet the mandatory requirements set out in NHS England's draft service specifications for paediatric intensive care and Haematopoietic Stem Cell Transplantation (children).

All providers must hold HTA licenses as well as the current version of the FACT-JACIE International Standards for Haematopoietic Cellular Therapy Product Collection, Processing, and Administration.

5.2 Other Applicable National Standards to be met by Commissioned Providers

CCLG ALL guidelines

https://www.cclg.org.uk/write/MediaUploads/Publications/Parents%20Guide%20Factsheets%20-%20PDFs/PGFactsheet_-_ALL2014_WEB.pdf

5.3 Other Applicable Local Standards

Not applicable

6. Designated Providers (if applicable)

Interim phase 1 - commissioned providers for ALL and DLBCL to be confirmed from Q3 2018. **Note, based on JACIE and manufacturer accreditation and age appropriate facilities, providers may be commissioned only for ALL, only for DLBCL or for both.**

Interim phase 2 process for commissioned providers to be confirmed following phase 1.

7. Abbreviation and Acronyms Explained

The following abbreviations and acronyms have been used in this document:

AE	Adverse Event
ALL	B-cell acute lymphoblastic leukaemia
BMT	Blood and marrow transplantation, which is used interchangeably with HSCT (see below)
CAR T	<i>Chimeric antigen receptor T-cell</i> : Artificial receptor that combines an antigen specificity domain coupled with an intracellular signaling domain typically expressed by an immune effector cell (e.g., T cell or natural killer cell)
CCLG	Children's Cancer and Leukaemia Group
DLBCL	Diffuse Large B-Cell Lymphoma
EEG	Electroencephalogram
EPAR	European Public Assessment Report
FACT	Foundation for the Accreditation of Cellular Therapy (North American Counterpart of JACIE, who collaborate to

	produce the FACT-JACIE standards).
HSCT	Haematopoietic stem cell transplantation
ICU	Intensive Care Unit – critical care level 3
IEC Therapy	Immune effector cell therapy - A cell that has differentiated into a form capable of modulating or effecting a specific immune response
JACIE	The <u>J</u> oint <u>A</u> ccreditation <u>C</u> ommittee of the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT)
LN2	Liquid nitrogen
MED-A/B	Minimal Essential Data-A/B (EBMT data collection forms). MED-A are short and generic and MED-B are more detailed and disease specific
MDT	Multi-disciplinary team
NCMDT	National CAR T Multi-disciplinary team
OS	Overall survival
PICU	Paediatric Intensive Care Unit
PMBCL	Primary Mediastinal B-cell Lymphoma
SOP	Standard operating procedure

Date published: 07 December 2018

Appendix A – CAR T Toxicities and management (AS REPORTED BY MANUFACTURERS)

CRS reported in EPAR (all grades and in accordance with UPENN)

DLCBL: 58% all grades (22% Grade 3 or 4) EPAR page 137

ALL: 77% all grades (47% Grade 3 or 4) EPAR page 137

Encephalopathy reported in EPAR (all grades)

DLBCL: 6% all grades (1% Grade 3, 3% Grade 4)
Ref: Table 63 (page 145) and Table 67 (page 153) EPAR

ALL: 29% all grades (6% Grade 3, 1% Grade 4)
Ref: Table 52 (page 132) EPAR

Renal support; FiO2 >40%; mechanical ventilation; prevalence of Pa/fiO2 ratios <=26, <=13;hypotension requiring vasopressor therapy

DLBCL:

- Renal support - 4.5% (5 of 111 infused) received dialysis
- FiO2 >40% - not published
- Mechanical ventilation - 7% (8 out of 111 infused) were intubated
- Hypotension requiring vasopressors – intervention among patients with CRS was reported for 49.1% of patients; use of high dose vasopressors was reported in 10.5%. (EPAR p138)

ALL:

- Renal support - In Study B2202, 7 patients (out of 75) underwent renal dialysis for fluid overload and/or renal failure. (EPAR p146)
- FiO2 – not published
- Mechanical ventilation (not published)
- Hypotension requiring vasopressors - 58.3% patients had hypotension that required intervention. High-dose vasopressors were required for 33.3% patients. (EPAR p138)

Outcome: median length of stay in Critical care; measure of the use of EEG; need for IL6 antagonist; need for intervention for encephalopathy; mortality; median stay in hospital

DLBCL:

- ICU median length of stay 5.5 days
- Use of EEG – (not published)
- IL6 antagonist use - anti-cytokine therapy was received by 28% of patients with CRS. 19% of patients with CRS received corticosteroids. (EPAR page139)
- Intervention for encephalopathy – as per CRS above
- Mortality – no deaths attributable to CTL019
- Median length of hospitalisation 19.5 days

ALL:

- ICU median length of stay 7 days (EPAR page 148)
- Use of EEG - (not published)
- IL6 antagonist use - anti-cytokine therapy was received by 42% of patients with CRS. 23% of patients with CRS received corticosteroids in addition. (EPAR page138)
- Intervention for encephalopathy – as per CRS above
- Mortality – no deaths attributable to CTL019
- Median length of hospitalisation 29.0 days. (EPAR page 148)

INTERIM

Appendix B – Grading System for CRS*

LEE SYSTEM:

Recommended by the writing group based on greater descriptors for grades 2 and 3 which are relevant for critical care management of adults and paediatric patients. The Lee system is recommended by commissioned CAR T therapy providers to guide clinical management

Grade	Assessment	Additional critical care treatment
Grade 1	Symptoms not life threatening and require symptomatic treatment only	Vigilant supportive care, assess for infection. Critical care outreach /critical care to be notified of patient. NEWS with escalation process in place to detect deterioration and respond. 4 hourly observations.
Grade 2	Symptoms require and respond to moderate intervention e.g. Hypotension: responds to fluids or one low dose vasopressor required Hypoxia: Requires < 40% oxygen	Admitted to critical care (level 3) with enhanced monitoring.
Grade 3	Symptoms require and respond to aggressive intervention e.g. Hypotension: requires multiple vasopressors or high dose single agent vasopressor Hypoxia: Requires ≥40% oxygen Other organ toxicity: renal/hepatic/neurological	Echocardiography (Transthoracic) immediately available with ability to deliver optimal advanced cardiovascular and basic respiratory support
Grade 4	Life threatening symptoms Requirement for advanced respiratory support (intubation) and other organ support. (excludes transaminitis)	Advanced respiratory support immediately available and experience in management of ARDS patients. Renal support available on site (CVVHF and haemodialysis). EEG available on site.
Grade 5	Death	

* - Note: In some cases, the treatments listed are not routinely commissioned e.g. baseline brain MRI or siltuximab. Providers must note that this specification and the associated published NICE guidance sets out the commissioned position for England. Treatments and interventions not included in these documents will not be supported or funded.

UPENN SYSTEM:
Referred to in licence:

Penn/CHOP CRS Grading Scale
Porter DL, et al. *Sci Transl Med.* 2015;7(303):303ra139

CRS Toxicity Grade			
Grade 1	Grade 2	Grade 3	Grade 4
Mild reaction: treated with supportive care such as antipyretics and antiemetics.	Moderate reaction: requiring intravenous therapies or parenteral nutrition; some signs of organ dysfunction (i.e. Grade 2 creatinine or Grade 3 liver function tests [LFTs]) related to CRS and not attributable to any other condition. Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including Grade 4 LFTs or Grade 3 creatinine increase related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids ^a or low dose vasopressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have Grade 2 CRS.	Life-threatening complications such as hypotension requiring high dose vasopressors or hypoxia requiring mechanical ventilation.
<p>Marked elevations in IL-6, interferon gamma and less intensely tumor necrosis factor (TNF). Symptoms occur 1 to 14 days after cell infusion in acute lymphoblastic leukemia (ALL). Symptoms may include: high fevers, rigors, myalgia, arthralgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea and hypoxia. The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (i.e. sepsis). The stop date of CRS is defined as the date when the patient has been afebrile for 24 hours and off vasopressors for 24 hours.</p>			
<p>^a Defined as: multiple fluid boluses for blood pressure support.</p>			

Appendix C – CRES grading system*

Grading Assessment of CRES	No concurrent CRS	Concurrent CRS
Grade 1	<ul style="list-style-type: none"> • Neurology consultation • Vigilant supportive care; aspiration precautions; intravenous (IV) hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam or haloperidol (in accordance with BNF) can be used, with careful monitoring, for agitated patients • Fundoscopic exam to assess for papilloedema • MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if the patient has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible • Daily 30 min electroencephalogram (EEG) until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam (in accordance with BNF) • If EEG shows non-convulsive status epilepticus, treat as per institutional algorithm ** 	<ul style="list-style-type: none"> • Consider anti-IL-6 therapy with tocilizumab / siltuximab (in accordance with BNF)
Grade 2	<ul style="list-style-type: none"> • Supportive care and neurological work-up as described for grade 1 CRES • Dexamethasone or methylprednisolone (in accordance with BNF) • Consider transferring patient to intensive-care unit (ICU) if CRES associated with grade ≥ 2 CRS 	<ul style="list-style-type: none"> • Tocilizumab / siltuximab (in accordance with BNF) • Dexamethasone or methylprednisolone (in accordance with BNF) if refractory to anti-IL-6 therapy
Levetiracetam in accordance with BNF		
Grade 3	<ul style="list-style-type: none"> • Supportive care and neurological work-up as indicated for grade 1 CRES • ICU transfer <i>required</i> 	<ul style="list-style-type: none"> • Anti-IL-6 therapy, as described for grade 2 CRES and if not administered

	<ul style="list-style-type: none"> • Corticosteroids as outlined for grade 2 CRES; continue corticosteroids until improvement to grade 1 CRES and then taper • Stage 1 or 2 papilloedema with cerebrospinal fluid (CSF) opening pressure <20 mmHg should be treated as per algorithm presented in BOX 4 • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥ 3 CRES 	<p>previously</p> <ul style="list-style-type: none"> • Corticosteroids as outlined for grade 2 CRES if symptoms worsen despite anti-IL-6 therapy; continue corticosteroids until improvement to grade 1 CRES and then taper
Levetiracetam in accordance with BNF		
Grade 4	<ul style="list-style-type: none"> • Supportive care and neurological work-up as outlined for grade 1 CRES • consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for grade 3 CRES • High-dose corticosteroids continued until improvement to grade 1 CRES and then taper; for example, methylprednisolone IV (in accordance with BNF), followed by rapid taper • For convulsive status epilepticus, treat as per algorithm in BOX 3 • Stage ≥ 3 papilloedema, with a CSF opening pressure ≥ 27 cm H₂O cerebral oedema, should be treated as per institutional algorithm ** 	<ul style="list-style-type: none"> • Anti-IL-6 therapy, as described for grade 2 CRES and if not administered previously • Corticosteroids as outlined for grade 2 CRES if symptoms worsen despite anti-IL-6 therapy; continue corticosteroids until improvement to grade 1 CRES and then taper
Levetiracetam in accordance with BNF		

* - Note: In some cases, the treatments listed are not routinely commissioned e.g. baseline brain MRI or siltuximab. Providers must note that this specification and the associated published NICE guidance sets out the commissioned position for England. Treatments and interventions not included in these documents will not be supported or funded.

** Detailed protocols available in Neelapu et al., 2018; *Nat Rev Clin Oncol* 15:47-62

For CRES grading see page 11 - <https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf>

Clinical opinion to NHS England is for critical care admission for Grade 2 CRS and CRES