Cancer Drugs Fund

Managed Access Agreement

Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]

Company name: Novartis Pharmaceuticals Ltd

Primary source of data collection: Ongoing clinical trials: JULIET and Schuster

Secondary source of data collection: Public Health England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

NICE Agreement Manager	Linda Landells (Associate Director)
Public Health England Agreement Manager	Rebecca Smittenaar
NHS England Agreement Manager	Peter Clark (CDF Clinical Lead)
Novartis Pharmaceuticals Ltd Agreement Manager	Deb Lancaster

1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166] (to be updated with TA number after final guidance has been published). A positive recommendation within the context of a managed access agreement has been decided by the appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on publication of the managed access agreement. The data collection period is anticipated to conclude February 2023 when it is expect that the JULIET clinical trial is due to end (Clinical study report due: August 2023). If Novartis are able to provide an earlier data cut from JULIET trial prior to February 2023 that address the uncertainty, the parties to this arrangement can agree to end the

data collection period early . Once the data collection period has ended the process for exiting the Cancer Drugs Fund will begin and the review of the NICE guidance will start.

2.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies.

2.3 If during the data collection period there is a change in the treatment landscape for relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies, a pragmatic decision will need to be made as to whether the current NICE scope would still be applicable.

3 Patient eligibility

3.1 Tisagenlecleucel has been recommended for use within the Cancer Drugs Fund (CDF) as an option for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies, only if the conditions in the managed access agreement are followed.

3.2 Key patient eligibility criteria for the use of tisagenlecleucel in the Cancer Drugs Fund comprise:

- Application is made by leukapheresis for and treatment with tisagenlecleucel will be initiated by a consultant haematologist or medical oncologist specifically trained and accredited in the use of systemic anti-cancer therapy and working in an accredited CAR-T cell treatment centre and who is
    - a member of the National CAR-T Clinical Panel for diffuse large B-cell lymphoma, and transformed follicular lymphoma; and
    - a member of the treating Trust's diffuse large B-cell lymphoma, and transformed follicular lymphoma and CAR-T cell multidisciplinary teams
- Patient has a confirmed histological diagnosis of diffuse large B-cell lymphoma or transformed follicular lymphoma and the diagnosis has been either made by or reviewed and confirmed by a designated lymphoma stem cell transplant centre.
- Prior to consideration of CAR-T cell therapy the patient's disease has been re-biopsied, unless a biopsy was unsafe, in which case the patient must have progressive disease at previously known sites of active disease. In such situations the original diagnostic biopsy review is acceptable. All patients with transformed follicular lymphoma who fulfil criteria 5 below must have a re-biopsy and confirmation of transformed follicular lymphoma histology prior to consideration of CAR-T cell therapy
    - re-biopsy has confirmed diffuse large B-cell lymphoma or
    - re-biopsy has confirmed transformed follicular lymphoma to diffuse large B-cell lymphoma or

- re-biopsy is unsafe, there is progressive disease at previously documented sites of active disease and previous histology was diffuse large B-cell lymphoma or

- Patient fulfils one of the following clinical scenarios relating to the definition of relapsed or refractory lymphoma[1]:

  Note: Refractory disease is defined as progressive disease or stable disease (lasting <6 months) as best response to last line of therapy, or disease progression within 12 months of stem cell transplantation. Radiotherapy cannot be counted as a line of therapy.

  - Patient has diffuse large B-cell lymphoma and received 2 or more lines of systemic therapy and relapsed after the last line of systemic therapy OR

  - Patient has diffuse large B-cell lymphoma and received 2 or more lines of systemic therapy and was refractory to the last line of systemic therapy OR

  - Patient has transformed follicular lymphoma to diffuse large B-cell lymphoma and received 2 or more lines of systemic therapy since diagnosis of transformation and relapsed after the last line of systemic therapy OR

  - Patient has transformed follicular lymphoma to diffuse large B-cell lymphoma and received 2 or more lines of systemic therapy since diagnosis of transformation and was refractory to the last line of systemic therapy OR

  - Patient has transformed follicular lymphoma to diffuse large B-cell lymphoma, received an anthracycline-containing regimen before transformation and then received 1 or more lines of systemic therapy and was refractory to the last line of systemic therapy

[1] Please note that the criteria were updated February 2019 to correct a minor inaccuracy. The full Blueteq criteria can be found on the Cancer Drugs Fund list on the NHS England website: https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/

- Patient has been previously treated with a full dose of anthracycline-containing regimen for the lymphoma
- Patient has been previously treated with at least one anti-CD20 monoclonal antibody unless there is clear documentation of the determination of CD20 negative disease
- Confirm whether the patient has not had stem cell transplantation or has had stem cell transplantation
- Patient does not have primary CNS lymphoma
- Patient does not have known active CNS involvement by the lymphoma
- Patient is aged 18 years or older on the date of approval for tisagenlecleucel by the National CAR-T Clinical Panel
- Patient has an ECOG performance score of 0 or 1
- Patient has sufficient end organ function to tolerate treatment with tisagenlecleucel
- Patient has either had no previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy or the patient has been treated with doses of genetically modified autologous or allogeneic T cell immunotherapy within an abandoned dosing cohort in a first in human dose-escalation phase I clinical trial.
- Prior to infusion a minimum of 4 doses of tocilizumab are available for use in this patient in the event of the development of cytokine release syndrome
- Tisagenlecleucel -modified CAR-T cell therapy will otherwise be used as set out in its Summary of Product Characteristics

- Approval for the use of tisagenlecleucel has been formally given by the National DLBCL/PMBCL/TFL CAR-T cell Clinical Panel

- Following national approval for use of tisagenlecleucel there has been local CAR-T cell multidisciplinary team agreement, that this patient continues to have the necessary fitness for treatment and fulfils all of the treatment criteria listed here.

3.3 There are no additional patients from compassionate access schemes that would form part of the data collection for the CDF, other than those starting treatment following the initiation of this agreement.

3.4 NHS England consider a phased implementation to the NHS will be necessary to deliver this treatment in a safe and equitable manner and to maximise clinical benefits for patients. Working collaboratively, NHS England and Novartis aim to mitigate risks associated with the introduction of this innovative and disruptive treatment by adopting cautious approach to treatment planning, particularly concerning the management of adverse events.

3.5 A cautious approach is needed because the technology is associated with serious side effects such as cytokine release syndrome and acute neurological deterioration. These are rare conditions in existing care pathways and consequently experience in treating them is not extensive. For further information see 'Special warnings and precautions for use' of the summary of product characteristics.

3.6 Providers require JACIE accreditation for Immune Effector Cell therapy, quality assurance from Novartis in line with their marketing authorisation and demonstrate that they meet the requirements of the NHS England service specification. A list of treatment centres that have successfully completed these assessments to be commissioned by NHS England to deliver tisagenlecleucel is available at: https://www.england.nhs.uk/cancer/cdf/car-t-therapy/.

3.7 It is estimated that there will be up to 200 new patients per year who will be eligible to have tisagenlecleucel. The number of patients who are expected to have treatment during the phased implementation cannot presently be estimated because this is highly dependent on the number of providers that receive JACIE accreditation, meet Novartis' quality assurance and NHS England's service specification standards. NHS England and Novartis anticipate being able to deliver services and treatment for the full eligible population by April 2020, and if it is able to deliver full capacity sooner, they will do so.

3.8 Given the phased implementation, NHS England has established a National CAR T Clinical Panel (NCCP) to prioritise patients for treatment as providers and manufacturers ramp up capacity across the country. This will include the scheduling of patients by taking into consideration patient need, available capacity and geographical access to ensure equity of access across the country. The NCCP is comprised of clinical experts, clinical leads from commissioned CAR T providers' and patient representation. For further details please refer to the documentation available at: https://www.england.nhs.uk/cancer/cdf/car-t-therapy/.

3.9 The first meeting of the NCCP took place in early December 2018 when the first patients were prioritised for treatment.

4 Area(s) of clinical uncertainty

4.1 Based on the NICE committee deliberations, the areas of most clinical uncertainty that are proposed to be addressed during the CDF data collection process are:

- Immaturity of data to support the curative nature of tisangenlecleucel. Specifically the committee considered that the overall survival data were immature and this lead to uncertainty in the cure point of tisangenlecleucel.
- The proportion of people who would need treatment for B-cell aplasia with intravenous immunoglobulin, and the duration of this treatment.

5 Source(s) of data collection

Clinical trial

5.1 The primary source of data collection will be derived from the ongoing, international, multicenter, phase II, single-arm, open-label study – JULIET trial (C2201). A final data cut and clinical study report is expected to be available in approximately August 2023 (data cut-off date: February 2023). Further overall survival data will also be available from the Schuster case-series study to support the NICE re-appraisal

Other data

5.2 NHS England's Blueteq database captures the CDF population. NHS England shares Blueteq data with Public Health England for the CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

5.3 Public Health England identifies, collects, collates, quality-assures and analyses large population-level datasets for specific diseases and conditions, including cancer. These datasets include the Systemic Anti-cancer Therapy (SACT) dataset, which is a mandated dataset as part of the Health and Social Care Information Standards. Public Health England will use the routinely-captured data collected during the period of the data collection arrangement to collect data

5.4 Medical Data Solutions and Services (MDSAS) manage clinical information systems, registries, patient management systems, clinical trial systems and product surveillance systems. They are Information Governance Statement of Compliance (IGSOC) registered, which enables them to host clinical systems on the secure NHS network. NHS England are exploring the potential for MDSAS to collect intravenous immunoglobulin use in the NHS.

6 Outcome data

Clinical trial

6.1 The following data will continue to be collected in the JULIET trial. The data from this trial will help resolve the clinical uncertainty surrounding overall

survival of patients treated with tisagenlecleucel and the number of people who would need treatment for B-cell aplasia with intravenous immunoglobulin, and the duration of this treatment.

Key outcomes for data collection	• Overall survival
Secondary outcomes	• Progression free survival • Intravenous immunoglobulin use

Other data

6.2 Data will be collected via Public Health England's routine population-wide datasets, including the SACT dataset. This collection will support data collected in the clinical trial. During the managed access agreement period, Public Health England will collect data to provide information on overall survival. These data will be collected alongside the primary source of data collection.

6.3 NHS England will explore the possibility for MDSAS to collect and collate intravenous immunoglobulin use in the NHS. The percentage of patients receiving tisagenlecleucel that require intravenous immunoglobulin as a consequence of their treatment will be quantified via NHS England's Blueteq database which will capture the CDF population.

7 Data analysis plan

Clinical trials

7.1 The analysis will follow that of the existing JULIET analysis plan and its associated trial protocol. The final analysis will follow the analysis plan outlined in the trial protocol. The following data analysis has been planned for overall survival:

- Overall survival (OS) is the time from date of first tisangenlecleucel infusion to the date of death due to any reason.

In case a patient is alive at the date of last contact on or before data cutoff, overall survival is censored at the date of last contact. No censoring will be

done in case of SCT. Thus, patients should be followed-up for survival also in case of SCT.

7.2 Overall survival will be assessed in all patients in the Interim efficacy analysis set and the full analysis set. The distribution function of overall survival will be estimated using the Kaplan Meier method. The median overall survival along with 95% confidence intervals will be presented if appropriate. Analysis for the further clinical trials, JULIET and Schuster, will follow the analysis plan outlined in the trial protocol. No interim analyses from the JULIET study are currently scheduled.

Other data

7.3 At the end of the data collection period Public Health England will provide a final report for NHS England based on routinely collected population-wide data, including that collected via SACT. The report will present depersonalised summary data, including the total number of patients starting treatment and overall survival from the date of infusion. The date of infusion will be provided to PHE by NHSE from part B of the Blueteq form. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with Novartis in advance of the planned review of guidance.

7.4 Completeness of SACT dataset reporting will be shared with NHS England and Novartis on a regular basis. Public Health England will provide summary results survival to NHS England and Novartis on a regular basis, to check the continuing validity of the period of the data collection arrangement.

7.5 It is anticipated that at the end of the data collection period MDSAS will provide a report on the Intravenous immunoglobulin use of patient identified as receiving tisagenlecleucel under this data collection agreement.

7.6 At a minimum, an annual report will be provided by any other organisation collecting the data, and should be submitted to NHS England to check whether the data collection is on track, and to establish whether any additional action is needed

8 Ownership of the data

8.1 For all clinical trial data listed above, Novartis will be the owner

8.2 Governance arrangements are not needed for the ongoing Novartis clinical trials.

8.3 The data analysed by Public Health England is derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to the data was facilitated by the Public Health England Office for Data Release. Novartis will not have access to the Public Health England patient data, but will receive de-personalised summary data, with appropriate controls in place to cover this. Public Health England will provide a report to NHS England and Novartis at the end of the managed access period.

8.4 The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. All necessary governance arrangements through SACT, and other datasets brought together by Public Health England, have been established with NHS Trusts and NHS England.

8.5 Blueteq's CDF system data is owned by NHS England. NHS England is responsible for implementing Blueteq data collection and generally for analysis of these data.

9 Publication

9.1 The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results.

9.2 Publication of the analysis results of data collected by Public Health England, including through SACT and the data from Blueteq's CDF system, will be planned and implemented by Public Health England.

10 Data protection

10.1 The terms of clause 7 (data protection) of the managed access agreement, as apply between NHS England and Novartis, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement

11 Equality considerations

11.1 Do you think there are any equality issues raised in data collection?

☐ Yes ☒ No

Commercial Access Agreement

Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies

The contents of this document have been redacted as they are confidential

- A glossary of terms relating to managed access agreements in the Cancer Drugs Fund is available here.