Cancer Drugs Fund

Managed Access Agreement

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

Company name: Gilead Sciences Ltd (the legal entity in the UK for Kite, a Gilead company) and referred to as Kite in this Agreement

Primary source of data collection: Ongoing clinical trial (ZUMA-1;NCT02348216)

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

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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 axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]. A positive recommendation for use of axicabtagene ciloleucel within the Cancer Drugs Fund (CDF) and in the context of a managed access agreement has been made by the NICE appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on the publication of the agreed managed access agreement. The data collection period is anticipated to conclude February 2022, when it is expected that sufficient data will have been collected to provide additional evidence to help resolve

the clinical uncertainty highlighted in Section 4.1. Specifically, 5 year-follow-up data from the ZUMA-1 clinical trial and additional evidence on intravenous immunoglobulin (IVIG) use. If Kite is able to provide 3 year follow-up data from the ZUMA-1 clinical trial, together with the further evidence on IVIG use, the signatories can unanimously agree to conclude the data collection period ahead of the anticipated date. When the data collection period finishes, the process for exiting the CDF will begin and the review of NICE's guidance for axicabtagene ciloleucel will start.

2.2 As part of the managed access agreement, axicabtagene ciloleucel will continue to be available through the CDF 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.

3 Patient eligibility

3.1 Axicabtagene ciloleucel is recommended for use within the CDF for treating adult patients with relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies, if the condition of the managed access agreement are followed.

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

- Application is made by leucapheresis for and treatment with axicabtagene ciloleucel 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, primary mediastinal B-cell lymphoma and transformed follicular lymphoma; and
    - a member of the treating Trust's diffuse large B-cell lymphoma, primary mediastinal 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 primary mediastinal 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 primary mediastinal 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
  - re-biopsy is unsafe, there is progressive disease at previously documented sites of active disease and previous histology was primary mediastinal B-cell lymphoma

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

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

- 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 axicabtagene ciloleucel 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 axicabtagene ciloleucel
- Patient has had no previous therapy with any genetically modified autologous T cell immunotherapy[1]
- 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
- Axicabtagene ciloleucel-modified CAR-T cell therapy will otherwise be used as set out in its Summary of Product Characteristics
- Approval for the use of axicabtagene ciloleucel has been formally given by the National DLBCL/PMBCL/TFL CAR-T cell Clinical Panel
- Following national approval for use of axicabtagene ciloleucel 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 Kite is currently working with a number of centres on the accreditation and validation process to ensure they meet the necessary requirements for the delivery of axicabtagene ciloleucel. Given the complexities of the accreditation and validation process it is unlikely that all proposed treatment centres will be operational at the same time.

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 Kite aim to mitigate risks associated with the introduction of this

[1] This criteria has been expanded by NHS England to include patients that have 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. This change has been incorporated into NHS England's Blueteq criteria.

innovative and disruptive treatment by adopting a 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 and validation from Kite 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 axicabtagene ciloleucel is available at: https://www.england.nhs.uk/cancer/cdf/car-t-therapy/.

3.7 It is estimated that there may be around 200 new patients per year who will be eligible to have axicabtagene ciloleucel. 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 Kite's quality assurance and validation requirements and NHS England's service specification standards. NHS England and Kite anticipate being able to deliver services and treatment for the full eligible population by March 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) for lymphoma 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 comprises 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 is scheduled for mid-December 2018, when the first patients will be prioritised for treatment, and as providers and manufactures begin to ramp up capacity across the country.

4 Area(s) of clinical uncertainty

4.1 The areas of uncertainty outlined in the NICE appraisal committee's discussions included:

- Overall survival estimates for axicabtagene ciloleucel
    - As median overall survival had not been reached in ZUMA-1, at the date of NICE appraisal, long-term overall survival had to be extrapolated over the time horizon of the cost-effectiveness model. Further data provision will come from the ZUMA-1 clinical trial with available two-year follow-up data presented at the American Society for Hematology (ASH) 2018 annual meeting in December and three-year follow-up data potentially available in Q1 2020. Further data provision will come from the available five-year follow-up data set which is anticipated to be available in Q1 2022 (see Section 5.1).
- Convergence of progression-free survival and overall survival curves
    - Available two-year follow-up and available three-year follow-up data from ZUMA-1 is anticipated to help inform the timeline over which that the curves for progression-free survival and overall survival may converge. Further data provision will come from the available five-year follow-up data set anticipated to be available in Q1 2022 (see Section 5.1).

- Intravenous immunoglobulin (IVIG) use
    - Data from ZUMA-1 demonstrated that IVIG was rarely used and not expected to be required over a prolonged period of time - a total of 8.3% patients received IVIG. However, the NICE appraisal committee believes the need for IVIG in a real-world setting remains uncertain and that this can be resolved through further data collection and analysis. The focus of the data collection will be the proportion of patients who require IVIG treatment in the ZUMA 1 clinical trial and who access axicabtagene ciloleucel through the CDF and the duration of treatment required by these patients.

5 Source(s) of data collection

ZUMA-1 clinical trial data

5.1 The primary source of data collection during the managed access period will be the ZUMA-1 clinical trial. Two-year data is due to be presented at ASH 2018 annual meeting in December and a five-year outcome data set is expected to be available in Q1 2022, which may then be analysed and reported confidentiality to NICE. In addition, outcome data at a three-year time point may also be available. Kite will deliver the available two-year dataset at the three year time point together with the three-year outcome data (if available). Should three-year outcome data be available, NICE may request Kite to have an earlier review with NICE in around Q1 2020.

5.2 The proportion of patients who require IVIG treatment in the ZUMA 1 clinical trial may be analysed with the two-year dataset referred to in 5.1 above. Additionally, the proportion of patients who access axicabtagene ciloleucel through the CDF who require IVIG treatment can also be analysed.

Other data

5.3 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.

5.4 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 provide analyses as defined in sections 6.3 and 7.3

5.5 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. They are able to collect intravenous immunoglobulin use in the NHS.

6 Outcome data

Clinical trial

6.1 The key outcomes of interest are overall survival and progression-free survival. It is anticipated that these outcomes will resolve some of the clinical uncertainty associated with earlier analyses of the ZUMA-1 trial data. For example, the available two-year overall survival and progression-free survival data results may:

- Validate the company's choice of overall survival extrapolation and as a result give more certainty to the ICER estimates in the cost-effectiveness analyses.

- Inform an appropriate convergence assumption between the overall survival and progression free survival curves for axicabtagene ciloleucel as part of our NICE appraisal modelling

Other data, including SACT

6.2 Data on IVIG use in real-world UK population from patients who access axicabtagene ciloleucel through the CDF. Data on patient selection particulars for CAR-T therapy – e.g. previous lines of therapy, performance status.

6.3 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 and patient characteristics.

6.4 MDSAS will collect and collate intravenous immunoglobulin use in the NHS. The percentage of patients receiving axicabtagene ciloleucel 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 It is anticipated that the two-year data set from ZUMA-1 provided in accordance with 5.1 above may provide more mature data on the key outcomes of interest – progression-free survival and overall survival.

7.2 The two-year follow-up data and five-year follow-up from ZUMA-1 will be analysed in line with the trial protocol. If it is possible, three-year follow-up data from ZUMA-1 will be provided. There is no planned analysis; however, if available, the data will be analysed in line with the trial protocol.

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 data. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with Kite in advance of the planned review of guidance.

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

7.5 At the end of the data collection period MDSAS will provide a report on the IVIG use of patient identified as receiving axicabtagene ciloleucel 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, Kite will be the owner.

8.2 The SACT 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. Kite will not have access to the Public Health England patient data, but will receive depersonalised summary data, with appropriate controls in place to cover this. Public Health England will provide a report to NHS England and Kite at the end of the managed access period.

8.3 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.

8.4 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. NHS England, however, shares Blueteq data with Public Health England for CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

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

The terms of clause 7 (data protection) of the managed access agreement, as apply between NHS England and Kite, 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

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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.