Supplementary File 2

Tisagenlecleucel OBMEA Eligibility Criteria

England, Wales - NICE CDF

ALL

Application is made by leukapheresis and initiated by a consultant haematologist 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 acute lymphoblastic leukaemia **and** a member of the treating Trust's acute lymphoblastic leukaemia and CAR T cell multidisciplinary teams.

- Once the date of CAR T cell infusion is known, the patient must be reassessed to ensure they continue to meet key patient eligibility criteria

Has relapsed or refractory acute lymphoblastic leukaemia, defined by one of the following criteria:

- 2nd or more bone marrow relapse following conventional doses of chemotherapy/monoclonal antibody therapy, or
- Any bone marrow relapse after allogeneic stem cell transplantation (SCT) and if so, a period of 4 months must have passed since time of transplant to planned time of tisagenlecleucel infusion, or
- primary refractory disease i.e. not achieving a complete remission after 2 cycles of 1st line standard chemotherapy, or
- secondary refractory disease i.e. not achieving a complete remission after 1 cycle of standard chemotherapy for relapsed disease, or
- if Philadelphia positive acute lymphoblastic leukaemia, has disease that has failed standard therapy including 2 TKIs or patient is intolerant of TKIs or if TKIs are contraindicated, or
- Relapsed disease and ineligible for allogeneic SCT due to comorbid disease (but still fit enough for CAR T cell therapy with tisagenlecleucel) or contraindicated to allogeneic SCT conditioning or lack of a suitable donor or prior SCT.

Bone marrow with **both** flow cytometry detectable ALL **and** CD19 ALL positivity in the bone marrow.

- Molecularly detectable minimal residual disease is not sufficient to comply with access to tisagenlecleucel

Karnofsky (age ≥16 years) or a Lansky (<16 years) performance status of 50% or more sufficient end organ function to tolerate treatment with tisagenlecleucel

does **not** have an isolated extramedullary acute lymphoblastic leukaemia relapse, i.e. if the patient has extramedullary disease, then the patient must also have bone marrow disease

Does not have active central nervous system involvement by acute lymphoblastic leukaemia

No previous therapy with any genetically modified autologous T cell immunotherapy

Prior to infusion a minimum of 4 doses of tocilizumab are available for use for this patient in the event of cytokine release syndrome

Use of tisagenlecleucel has been formally given by the National acute lymphoblastic leukaemia CAR T cell Clinical Panel

- following national approval, 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

Tisagenlecleucel will otherwise be used as set out in its Summary of Product Characteristics (SPC)

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

DLBCL

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 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:

- 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

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.

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.

Spain

Spain JE Nat Clin Ass
- IPT - Kymriah 26022

Italy - AIFA

Exclusion criteria

Acute lymphoblastic leukaemia (ALL)

- Age (years) ≥26
  - For B-cell LLA in post-transplant relapse, those with allogenic SCT in <4 months
  - No persistent expression of CD-19 after previous treatment with anti-CD19
  - HIV/HBV/HCV- positive infection or Not evaluated
  - <5% bone marrow blasts
  - Performance status <50 (Karnofsky patients ≥16 years, Lansky age <16 years)
  - Active CNS involvement defined as CNS-3 according to the NCCN Guidelines

Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

  - Age (years) >70 AND <18
  - ECOG >1
  - Life expectancy <12 weeks
  - Only 1 systemic therapy line administered
  - Pat eligible for ASCT
- Previous Allogenic SCT
  - No persistent C-19 expression in case of previous anti-CD-19 therapy
- HIV/HBV/HCV-positive infection or Not evaluated
- Only 1 line of previously systemic treatment (including rituximab and anthracycline)
  - Active CNS involvement or inflammatory or autoimmune neurological disorders or other CNS disorders
  - History of autoimmune disorders with terminal organ damage or requiring certain treatments in past 2 years
  - Impaired renal, hepatic, lung functions and medullary reserve (defined explicitly)
  - Ejection fraction <50%
  - DVT or PE in past 6 months

Other clinical data

- Presence of high-risk genetic characteristics (only for ALL)
- Number of systemic treatments (if B-cell ALL in second or further relapse)
- Stage (Lugano mod Ann Arbor criteria) (only for DLBCL)
- IPI score (only for DLBCL)
- Regimen of lymphodepleting chemotherapy
- Was it necessary to administer 'bridge' therapy before the Kymriah infusion
- Any reasons that have delayed or not allowed for Kymriah administration
- Mandatory FUP at time 0 (infusion), 6 months (+180 days), 12 months (+365 days) and 18 months (+545) from the infusion (both the indications)
- Status of the disease (from FUP2 onwards): Complete remission (CR), Complete remission with incomplete recovery of peripheral blood counts (CRh), Refractory disease, Relapse after CR/CRh
- Presence of MRD (assessed with a sensitivity of at least 1 x 10-4)
- Following post-infusion complications: [Cytokine release syndrome (CRS), if yes was it necessary to administer tocilizumab], Neurological events, Infections, Prolonged cytopenia, Febrile neutropenia, Hypo/ agammaglobulinemia, Tumor lysis syndrome (TLS)

Registry construct


AIFA IT Kymriah ALL.pdf


AIFA IT Kymriah DLBCL.pdf