



**Australian Government**

**Department of Health**

# **Application Form**

**(New and Amended**

**Requests for Public Funding)**

**(Version 2.4)**

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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# PART 1 – APPLICANT DETAILS

## 1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: Gilead Sciences Pty Limited

Redacted

ABN: Redacted

Business trading name: Gilead Sciences Pty Ltd

**Primary contact name:** Redacted

Primary contact numbers

Business: Redacted

Mobile: Redacted

Email: Redacted

**2. Alternative contact name:** Redacted

Alternative contact numbers

Business: Redacted

Mobile: Redacted

Email: Redacted

**3. (a) Are you a lobbyist acting on behalf of an Applicant?**

Yes

No

**(b) If yes, are you listed on the Register of Lobbyists?**

Yes

No

## PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

### 4. Application title

YESCARTA™ (axicabtagene ciloleucel [KTE-C19]) for the treatment of refractory or relapsed CD19-positive lymphoma.

### 5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers originating primarily in B lymphocytes (and, to a lesser extent, in T lymphocytes, and natural killer cells). The prognosis depends on the histologic type, stage, and treatment, along with other factors including the patient's age and general health, whether there are certain changes in the genes, the amount of lactate dehydrogenase (LDH) in the blood, and whether the lymphoma has been newly diagnosed or has recurred (NCI, 2017).

Aggressive subtypes of B-cell NHL include diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma (FL) that has transformed histologically to DLBCL (hereafter referred to as transformed follicular lymphoma [TFL]).

Axicabtagene ciloleucel is proposed for the treatment of relapsed or refractory DLBCL, including DLBCL not otherwise specified and high-grade B-cell lymphoma, PMBCL and TFL.

### 6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Axicabtagene ciloleucel is a chimeric antigen receptor T-cell (CAR-T) therapy which can help to address the high unmet need in patients with relapsed or refractory DLBCL, PMBCL or TFL.

Axicabtagene ciloleucel is a CD19-directed genetically modified autologous T-cell immunotherapy. To prepare axicabtagene ciloleucel, patient's own T-cells are harvested via a standard leukapheresis procedure and genetically modified *ex-vivo* by retroviral transduction to express a chimeric antigen receptor (CAR). The anti-CD19 CAR-positive viable T-cells are then expanded and infused back into the patient, where they can recognise and eliminate CD19 expressing target cells.

### 7. (a) Is this a request for MBS funding?

- Yes  
 No

It is Gilead's understanding that neither axicabtagene ciloleucel, nor the broader hybrid health technology, is currently eligible for funding through the MBS. Gilead seeks to work with the Department of Health to consider which, if any, components of the therapy will be funded through current funding mechanisms.

### (b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)  
 New MBS item(s)

### (c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Not applicable.

### (d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

Not applicable.

- i.  An amendment to the way the service is clinically delivered under the existing item(s)  
ii.  An amendment to the patient population under the existing item(s)  
iii.  An amendment to the schedule fee of the existing item(s)

- iv.  An amendment to the time and complexity of an existing item(s)
- v.  Access to an existing item(s) by a different health practitioner group
- vi.  Minor amendments to the item descriptor that does not affect how the service is delivered
- vii.  An amendment to an existing specific single consultation item
- viii.  An amendment to an existing global consultation item(s)
- ix.  Other (please describe below):

Insert description of 'other' amendment here

**(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?**

- i.  A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii.  A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii.  A new item for a specific single consultation item
- iv.  A new item for a global consultation item(s)

**(f) Is the proposed service seeking public funding other than the MBS?**

- Yes
- No

**(g) If yes, please advise:**

At the time of completing this application form, the public funding mechanism for axicabtagene ciloleucel was yet to be determined. Gilead is committed to working with the Department of Health to facilitate public funding for this important therapy.

It is Gilead's understanding that axicabtagene ciloleucel is not currently eligible for funding through the Pharmaceutical Benefits Scheme (PBS). Gilead seeks to work with the Department of Health to consider which, if any, components of the therapy will be funded through current funding mechanisms.

**8. What is the type of service:**

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

**9. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):**

Not applicable.

- i.  To be used as a screening tool in asymptomatic populations
- ii.  Assists in establishing a diagnosis in symptomatic patients
- iii.  Provides information about prognosis
- iv.  Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v.  Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

**10. Does your service rely on another medical product to achieve or to enhance its intended effect?**

- Pharmaceutical / Biological
- Prosthesis or device
- No

**11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?**

Yes

A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m<sup>2</sup> intravenous (IV) and fludarabine 30 mg/m<sup>2</sup> IV is administered on the 5th, 4th, and 3rd day before infusion of axicabtagene ciloleucel.

Tocilizumab may be administered while a patient was admitted for the management of cytokine release syndrome (CRS), a serious adverse event that may occur following treatment with axicabtagene ciloleucel. This medicine would be administered as an inpatient.

Intravenous immunoglobulin may be administered to manage events associated with B-cell aplasia however, intravenous immunoglobulin is funded via the National Blood Authority.

No

**(b) If yes, please list the relevant PBS item code(s):**

It is Gilead's understanding that some patients may be eligible for PBS-funded medicines in a tertiary public hospital setting. The table below lists the medicines that may be required for the delivery of axicabtagene ciloleucel through the PBS. Where PBS-approved indication is not currently available, this has been noted.

Pharmaceutical	Usage	PBS item code/funding
Fludarabine	Chemotherapy for public hospital use, antimetabolite	4393F (unrestricted item)
Cyclophosphamide	Chemotherapy for public hospital use, alkylating agent	4327R (unrestricted item)
Tocilizumab	Treatment of CRS	Funding costs based on PBS codes: 1056G, 1058J, 10060L, 10064Q, 10068X, 10071C, 10072D, 10073E, 10077J, 10078K, 10079L, 10081N  <i>Note: The above PBS item numbers are not indicated for CRS.</i>
Intravenous immunoglobulin	To manage events of B-cell aplasia	(Funded through National Blood Authority for different indications)

Source: Adapted from Kymirah PICO Confirmation

**(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?**

Yes (please provide PBAC submission item number below)

No

Insert PBAC submission item number here

**(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?**

Not applicable.

Trade name: Insert trade name here

Generic name: Insert generic name here

**12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Protheses List?**

- Yes  
 No

**(b) If yes, please provide the following information (where relevant):**

Billing code(s): Insert billing code(s) here

Trade name of prostheses: Insert trade name here

Clinical name of prostheses: Insert clinical name here

Other device components delivered as part of the service: Insert description of device components here

**(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Protheses List Advisory Committee (PLAC)?**

- Yes  
 No

**(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?**

Not applicable.

- Yes  
 No

**(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):**

Insert sponsor and/or manufacturer name(s) here

**13. Please identify any single and / or multi-use consumables delivered as part of the service?**

The diagram provided in the response to Q28 illustrates the different stages involved in the delivery of axicabtagene ciloleucel. The consumables for each stage are stated below.

Leukapheresis: various specialised apheresis systems are available for this process. The apheresis machine is connected to the patient via sterile tubing sets. The patient's blood is pumped into the machine where the blood components are separated using centrifugation and/or filtration. The apheresis machine is a multi-use consumable. Single-use consumables are tubing, sets, bowls, anticoagulant and replacement fluids.

Lymphodepleting chemotherapy: lymphodepleting chemotherapy consists of fludarabine (30 mg/m<sup>2</sup>/day) plus cyclophosphamide (500 mg/m<sup>2</sup>/day) administered IV on the 5th, 4th, and 3rd day before infusion of axicabtagene ciloleucel. Standard single-use consumables for an IV infusion include sterile alcohol wipes, plastic wrap, film dressing, gauze wipes, tubing adhesive tape, spill kit, prep mats, labels, transport bag, and latex gloves.

Axicabtagene ciloleucel infusion: this process includes standard single-use consumables typical to an IV infusion, as listed above.

Management of potential serious adverse events: medicines may be administered via IV infusion for the management of CRS, and standard single-use consumables for an IV infusion will be required, as listed above.

## PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

- 14. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:**

Type of therapeutic good: Class 4 biological product

Manufacturer's name: Kite Pharma, a Gilead Company

Sponsor's name: Gilead Sciences Pty Ltd

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?**

Class III

AIMD

N/A

- 15. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?**

Yes (If yes, please provide supporting documentation as an attachment to this application form)

No

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?**

Yes (if yes, please provide details below)

No

ARTG listing, registration or inclusion number: Insert ARTG number here

TGA approved indication(s), if applicable: Insert approved indication(s) here

TGA approved purpose(s), if applicable: Insert approved purpose(s) here

- 16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?**

Redacted

- 17. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?**

Redacted.

## PART 4 – SUMMARY OF EVIDENCE

18. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	<b>Pivotal Study</b>  Multicentre Phase 2 trial in 101 patients with refractory DLBCL, PMBCL and TFL  (Cohorts 1 and 2)	KTE-C19-101 Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive non-Hodgkin Lymphoma (ZUMA-1) ClinicalTrials.gov Identifier: NCT02348216  Neelapu SS, Locke FL1, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017 December 28; 377(26): 2531–2544. doi:10.1056/NEJMoa1707447.  Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2	Evaluation of axi-cel efficacy in 101 patients with refractory DLBCL (n=77; Cohort 1), PMBCL and TFL (n=24; Cohort 2)  Primary endpoint: ORR; Secondary end points included DOR, PFS, OS, incidence of adverse events, and blood levels of CAR T-cells, anti-axicabtagene ciloleucel antibodies and serum cytokines. (6-month timepoint)  Two year follow up data (median follow up 27.1 months)	<a href="https://www.ncbi.nlm.nih.gov/pubmed/29226797?dopt=Abstract">https://www.ncbi.nlm.nih.gov/pubmed/29226797?dopt=Abstract</a>  <a href="https://www.ncbi.nlm.nih.gov/pubmed/30518502">https://www.ncbi.nlm.nih.gov/pubmed/30518502</a>	2017  2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
		<p>trial. Lancet Oncol. 2019 Jan;20(1):31-42. doi: 10.1016/S1470-2045(18)30864-7. Epub 2018 Dec 2.</p> <p>ClinicalTrials.gov Identifier: NCT02348216</p>			
2.	<p><b>Supportive Study</b> Multicentre, Phase 1 study in 7 refractory DLBCL patients</p>	<p>KTE-C19-101 Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive non-Hodgkin Lymphoma (ZUMA-1) ClinicalTrials.gov Identifier: NCT02348216</p> <p>Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM et al. Phase 1 results of ZUMA-1: a multicenter study of KTEC19 anti-CD19 CAR T-cell therapy in refractory aggressive lymphoma. Mol Ther. 2017; 25:285–95.</p>	<p>Evaluation of safety of axi-cel regimens in refractory DLBCL patients. Primary endpoint: Incidence of dose limiting toxicity; secondary endpoints included ORR, DOR, PFS, OS, incidence of AEs, clinically significant changes in laboratory values, incidences of anti-KTE-C19 antibodies, and levels of anti-CD19 CAR+ T-cells and cytokines in blood and serum</p>	<p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5363293/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5363293/</a></p>	2017

Abbreviations: axi-cel, axicabtagene ciloleucel; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; AE, Adverse event; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma;

\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

\*\*\* If the publication is a follow-up to an initial publication, please advise.

- 19. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only).  
*Please do not attach full text articles, this is just intended to be a summary***

A preliminary literature search, including a search of clinical trial databases, did not identify additional relevant research for inclusion in this application.

## PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

**20. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

- Haematology Society of Australia and New Zealand (HSANZ)
- The Australasian Leukaemia and Lymphoma Group (ALLG)

Statements of clinical relevance from HSANZ and ALLG are provided as attachments to this application.

**21. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

Redacted.

**22. List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

- Rare Cancers Australia
- Lymphoma Australia

A letter of support from Lymphoma Australia is provided as an attachment to this application.

A letter of support from Rare Cancers Australia is to follow.

**23. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

Novartis.

**24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

Name of expert 1: Redacted

Telephone number(s): Redacted

Email address: Redacted

Justification of expertise: Redacted.

Name of expert 2: Redacted

Telephone number(s): Redacted

Email address: Redacted

Justification of expertise: Redacted.

*Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.*

## PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

### **PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION**

#### **25. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:**

DLBCL, PMBCL and TFL are aggressive subtypes of B-cell NHL.

DLBCL, is the most common subtype of B-cell NHL. A family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors of DLBCL (Tilly et al, 2015).

DLBCL comprises a group of lymphoid malignancies composed of large cells with vesicular nuclei, prominent nucleoli, basophilic cytoplasm, and a high proliferation rate (Martelli et al, 2013). DLBCL typically presents as a nodal or extra-nodal mass with fast tumour growth associated with systemic symptoms, such as sweats, fatigue and fever (Freedman et al, 2015). In about 40% of cases, DLBCL presents in areas outside lymph nodes, such as the digestive tract, skin, bone, thyroid, and testes (Freedman et al, 2015). The causes of NHL in general, and DLBCL specifically, are unclear; however identified potential risk factors include: immunosuppression, ultraviolet radiation, pesticides, hair dyes and diet (Ekström-Smedby, 2006). Centробlast- and immunoblast-like cells are the predominant morphology, and these cells typically express the B-cell markers CD19, CD20, CD22, as well as surface immunoglobulin (Martelli et al, 2013).

PMBCL is a rare form of NHL similar to DLBCL. PMBCL represents approximately 6% to 12% of all DLBCL (Falini et al, 1995; Cazals-Hatem et al, 1996; Sehn et al, 1998; Savage, 2006; Dabrowska-Iwanicka and Walewski, 2014; Bhatt et al, 2015). Specific incidences are not available for Australia. Histologically virtually identical to DLBCL, PMBCL is thought to arise from thymic (medullary) B-cells and has distinct clinical, pathological, and molecular characteristics from other subtypes. PMBCL is typically identified in the fourth decade of life and has a female predominance (Savage, 2006; Sehn et al, 1998; Dabrowska-Iwanicka & Walewski, 2014).

PMBCL typically presents as a large, fast-growing mass with invasion. This is usually limited to the anterior-upper mediastinum, but may infiltrate adjacent thoracic structures such as chest wall, pleura, lungs, pericardium and heart, causing pleural/pericardial effusion in approximately 30–50% of cases. Systemic symptoms, mainly weight loss and fever, are relatively rare and they affect less than 20% of patients (Dabrowska-Iwanicka & Walewski, 2014). No risk factors for PMBCL have been identified, although a familial case has been identified in Finland, which may be related to a mutation to the mixed lineage leukaemia (MLL) gene. PMBCL cells typically express the B-cell markers CD19, CD20, CD22; in a majority of cases, CD23, CD45 and myelin and lymphocyte protein (MAL) are also expressed (Dabrowska-Iwanicka & Walewski, 2014).

Follicular lymphoma (FL), the second most common form of NHL in Western countries, accounting for approximately 20% of NHL cases globally (Casulo et al, 2017). Some patients with FL will transform to a high grade DLBCL (known as TFL) which is aggressive and associated with a poor outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% over 15 years. Thus, TFL accounts for approximately 1% of all NHL (Lossos & Gascoyne, 2011; Casulo et al, 2015).

Typically, the treatment algorithm used for the management of patients with DLBCL is also used for patients with PMBCL and TFL.

The current standard of care for first-line treatment is a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in combination with an anti-CD20 monoclonal antibody (mAb) such as rituximab (R-CHOP) (Flowers et al, 2010) (National Comprehensive Cancer Network, 2014; Tilly et al, 2015). Although more effective than chemotherapy alone, first-line R-CHOP only results in long term disease remission in < 40% of subjects.

Relapse is most likely to happen within two years of the end of the first treatment (Lymphoma Association, 2016). Overall, approximately 30% of DLBCL will ultimately relapse. The incidence of relapsed/refractory DLBCL in the European Union (which can be reasonably extrapolated to Australia) is therefore estimated to be around 1/100,000/year (Tilly et al, 2015). Gilead notes that the PICO Confirmation for Kymriah uses an estimated incidence of 2,070 patients for DLBCL in Australia.

Patients with relapsed/refractory aggressive B-cell NHL typically receive salvage therapy with rituximab and platinum-based chemotherapy regimens (Tilly et al, 2015). Treatment regimens for patients with relapsed/refractory DLBCL are also used in the treatment of those with relapsed/refractory PMBCL or TFL.

Studies in relapsed or refractory B-cell NHL indicate that only half of patients who respond to second-line therapy are able to proceed to autologous stem cell transplant (ASCT) (Philip et al, 1995; Moskowitz et al, 1999; Gisselbrecht et al, 2012; Crump et al, 2014).

Clinical observations suggest that patients with refractory DLBCL, defined as no response to last chemotherapy or relapse  $\leq 12$  months post-ASCT, have poor overall survival (OS) rates; however, there is a paucity of published data reporting outcomes in this patient population (Nagle et al, 2013).

In order to address this data shortcoming, the international multi-cohort retrospective non-Hodgkin lymphoma research (SCHOLAR-1) study was conducted to provide a more rigorous assessment of the outcomes of patients with refractory DLBCL whose disease fails to respond to immunochemotherapy or any subsequent salvage regimen and for those whose disease relapses early post-ASCT (Crump et al, 2017).

SCHOLAR-1 was a patient-level, retrospective, pooled analysis of response rates and OS rates in 636 patients with refractory NHL, using data from the databases of three academic centres and from two of the largest randomized, controlled Phase 2 trials of patients with refractory aggressive lymphomas, including DLBCL (87%), PMBCL (2%), and TFL (4%) (Gisselbrecht et al, 2012; Crump et al, 2014; Van Den Neste E et al, 2016). In the pooled patient population overall, 178 (28%) were primary refractory, 318 (50%) were refractory to  $\geq$  second-line therapy, and 140 (22%) were in relapse  $\leq 12$  months post-ASCT (Crump et al, 2017).

Results of SCHOLAR-1 demonstrated the extremely poor outcomes to currently available therapies in this population, with an objective response rate (ORR) of 26% and a complete response (CR) rate of 7% in the overall population of patients (n=523) evaluated for response.

Response rates were also consistently poor when differentiating by refractory subgroup. In primary refractory patients (n=169), ORR was 20% and CR rate was 3%; among patients who were refractory to second-line therapy or later therapy (n=274), ORR was 26% and CR rate was 10%; and for patients who had relapsed  $\leq 12$  months post-ASCT (n=80), ORR was 34% and CR rate was 15% (Crump et al, 2017).

Patient survival was poor in the overall population of refractory patients evaluated for survival (n=603), with median overall survival (OS) of 6.3 months (Crump et al, 2017). Patient survival was also consistently poor when differentiating by refractory subgroup of DLBCL/PMBCL/TFL patients, with median OS of 7.1 months in primary refractory patients (n=179), 6.1 months for patients who were refractory to second-line therapy or later-line therapy (n=306), and 6.2 months among patients who had relapsed  $\leq 12$  months post-ASCT (n=118). Moreover, median OS of refractory DLBCL/PMBCL/TFL patients who were ineligible to receive ASCT (n=423) was 5.1 months (Crump et al, 2017). Poor outcomes are also observed for patients with relapsed/refractory DLBCL who respond to salvage therapy but are ineligible for stem cell transplant (SCT). Reasons for stem cell transplant (SCT) ineligibility include: patient age ( $>65$  years of age is typically ineligible); inadequate response or early relapse after second-line therapy; relapse after second- or later-line of therapy; failure to mobilize stem cells for ASCT; or presence of comorbidities or unresolved toxicities (Colosia et al, 2014).

Survival rates are poor among patients with relapsed/refractory, stem cell transplant-ineligible DLBCL. In a Canadian database review of 326 relapsed/refractory, SCT-ineligible DLBCL patients, median OS was 3.9 months (Kansara et al, 2014). In the international Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, 129 relapsed/refractory DLBCL patients who received third-line therapy but did not undergo SCT had median OS of 3.3 months (Van Den Neste et al, 2016).

AIHW figures show relative 1-year and 5-year survival from DLBCL in Australia was 77.3% (95%CI 75.8-78.8%) and 64.4% (95%CI 62.7-66.1%), respectively (AIHW Australian Cancer database, 2006-2010).

Australian data on the morbidity of NHL (C82-C86; including FL, DLBCL, peripheral and cutaneous T-cell lymphoma and other unspecified types of NHL) indicate that non-Indigenous Australians diagnosed with NHL had a 72% chance, on average, of surviving for five years compared with their counterparts in the non-Indigenous population. In 2007–2014, Indigenous Australians diagnosed with NHL had a 71% chance, on average, of surviving for five years compared with their counterparts in the Indigenous population. (AIHW, 2018)

In summary, prognosis is extremely poor for the proposed patient population. The current standard of care provides refractory DLBCL patients with a median overall survival (OS) of 6.3 months and a complete response (CR) of only 7% (Crump et al, 2017). Moreover, the current standard of care provides ASCT-ineligible, relapsed/refractory DLBCL patients with median OS of 3.3–3.9 months (Van Den Neste et al, 2016; Kansara et al, 2014).

**26. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:**

Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL not otherwise specified and high-grade B-cell lymphoma, PMBCL and TFL after two or more lines of systemic therapy.

This includes patients who have relapsed or refractory disease after at least two lines of chemotherapy, and (1) have relapsed after autologous stem cell transplant, or (2) are ineligible for autologous stem cell transplant.

Patients will be monitored by their haematologists to detect relapsed or refractory disease. A variety of different tests may be undertaken, including blood counts, bone marrow aspiration and biopsy, lumbar puncture, and/or imaging tests.

Patients will be managed by a haematologist or haematological oncologist in a specialist unit within a public tertiary hospital.

**27. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):**

The clinical management pathway is complex, including standard chemotherapy regimens, salvage chemotherapy, radiation therapy, and autologous stem cell transplant. Clinician treatment choices are empirical and individualised approaches to treatment result in a high heterogeneity of the clinical management pathway, particularly in the relapsed setting.

A current and proposed management algorithm is provided as Appendix A to this application and has been adapted from the PICO Confirmation for Kymriah (Application 1519).

**PART 6b – INFORMATION ABOUT THE INTERVENTION**

**28. Describe the key components and clinical steps involved in delivering the proposed medical service:**

Axicabtagene ciloleucel is produced via a process from leukapheresis material obtained from individual patients, and therefore the product is unique to each patient. A replication-incompetent retroviral vector is used to introduce the anti-CD19 CAR gene into patient-derived human T-cells.

The diagram below summarises the manufacture, dosing and treatment protocol.

Step 1: Leukapheresis

Leukocytes (white blood cells) are collected from the patient at their clinical centre. This is done by leukapheresis, whereby whole blood is withdrawn from the patient, leukocytes are extracted and then the remainder of the blood is transfused back into the patient. Redacted.

## Step 2: Procurement of axicabtagene ciloleucel

The manufacturing process is undertaken in an off-shore facility in Santa Monica, California, USA. The manufacturing process involves isolation and activation of T-cells, engineering T-cells with the CAR gene, and growth and expansion of engineered T-cells. The final product is washed, cryopreserved and tested for identity, potency, and adventitious agents. After meeting acceptance criteria, the product is transported back to the patient's clinical centre in Australia using a validated cryo-shipper.

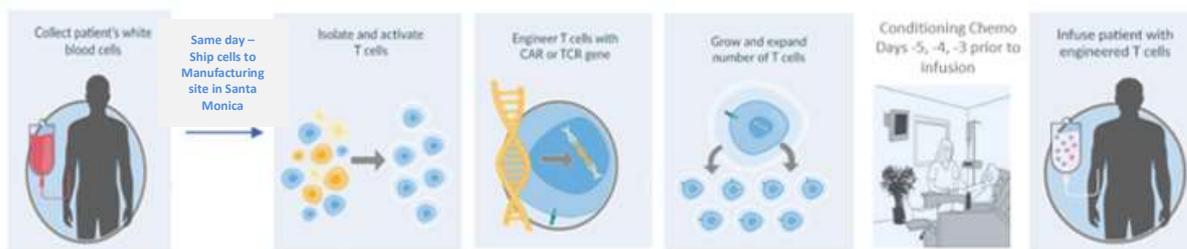
## Step 3: Lymphodepleting chemotherapy

Prior to infusion, patients are treated with low-dose lymphodepleting chemotherapy to eliminate the patient's lymphocytes and allow space for the T-cells to expand. Lymphodepleting chemotherapy consists of fludarabine (30 mg/m<sup>2</sup>/day) plus cyclophosphamide (500 mg/m<sup>2</sup>/day) for three days (on the fifth, fourth, and third day before the infusion of axicabtagene ciloleucel at Day 0).

## Step 4: Treatment infusion

Axicabtagene ciloleucel is a single infusion product. Each bag contains a suspension of anti-CD19 CAR T-cells in approximately 68 mL. Axicabtagene ciloleucel is delivered via an IV infusion.

Axicabtagene ciloleucel binds to CD19, an antigen expressed on the cell surface of the target lymphoma B cells. Following engagement with CD19-expressing target cells, the CD3ζ domain activates the downstream signalling cascade that leads to T-cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity. The intracellular signalling domain of CD28 provides a co-stimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including interleukin-2 (IL-2) production (Finney et al, 1998). Together, these signals act in concert resulting in proliferation of the axicabtagene ciloleucel CAR T-cells and direct killing of target cells. In addition, activated T-cells secrete cytokines and other molecules that can recruit and activate additional anti-tumour immune cells (Restifo et al, 2012).



### 29. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Axicabtagene ciloleucel is not yet TGA registered. However, it is proposed that axicabtagene ciloleucel will be supplied as a trademarked class 4 biological product; YESCARTA®, redacted.

### 30. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Not applicable.

### 31. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Redacted.

### 32. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

Leukapheresis, lymphodepleting chemotherapy and infusion of axicabtagene ciloleucel will require IV administration by a nurse. IV infusion of axicabtagene ciloleucel will also be undertaken under the supervision of a haematologist or haematological oncologist in a hospital setting.

**33. If applicable, advise which health professionals will primarily deliver the proposed service:**

Haematologists and haematological oncologists.

**34. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:**

Not appropriate.

**35. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:**

Axicabtagene ciloleucel will be prescribed and delivered by physicians experienced in the treatment of haematological malignancies.

**36. If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:**

Redacted.

**37. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):**

- Inpatient private hospital
- Inpatient public hospital
- Outpatient clinic
- Emergency Department
- Consulting rooms
- Day surgery centre
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

**(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:**

Redacted.

**38. Is the proposed medical service intended to be entirely rendered in Australia?**

- Yes
- No – please specify below

Redacted.

**PART 6c – INFORMATION ABOUT THE COMPARATOR(S)**

**39. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):**

Axicabtagene ciloleucel is expected to substitute current clinical practice of salvage chemotherapy for relapsed/refractory DLBCL, PMBCL and TFL patients eligible for CAR-T therapy.

Redacted

**40. Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?**

Not applicable.

- Yes (please provide all relevant MBS item numbers below)
- No

- 41. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):**

Following salvage chemotherapy, patients may receive best supportive care (BSC), an allogenic stem cell transplant, further salvage therapy or enrol in a clinical trial.

These are last line treatment options and are considered largely ineffective.

- 42. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?**

- Yes  
 No

- (b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:**

Axicabtagene ciloleucel will substitute salvage chemotherapy in the current treatment algorithm. BSC, allogenic stem cell transplant, salvage chemotherapy or enrolment in a clinical trial will remain last line options.

- 43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):**

If approved for funding as proposed, axicabtagene ciloleucel will provide a more effective treatment option compared to salvage chemotherapy, delaying or eliminating the need for essentially ineffective last line treatment options. There will be no change to earlier lines of therapy.

#### **PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME**

- 44. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):**

Axicabtagene ciloleucel represents a significantly improved treatment option for patients with relapsed/refractory DLBCL, PMBCL and TFL.

Primary analysis of the pivotal ZUMA-1 Phase 2 study was conducted after a median follow-up of 8.7 months after axicabtagene ciloleucel infusion. At the time of the analysis, 44% remained in response, including 39% in CR. The median duration of response (DOR) was 8.2 months, and median DOR had not been reached by patients who were lymphoma-free. Redacted. Median OS had not been reached, with a lower confidence interval of 10.5 months. Redacted, and median progression free survival (PFS) was 5.9 months. The safety profile was manageable, and most CRS and neurological events (NE) were reversible (Kite, 2017A).

Redacted. CT imaging also demonstrated that patients with partial response (PR), stable disease (SD) or progressive disease (PD) following axicabtagene ciloleucel infusion still derived clinical benefit through improvements in symptoms, such as reductions in tumour load and improvements in skin lesions (Neelapu et al, 2017A).

Consistent response rates were observed in both Cohort 1 (DLBCL; n=77) and Cohort 2 (PMBCL or TFL; n=24) and across covariates including disease stage, age, International Prognostic Index scores, CD19 status, and refractory disease subset. Redacted.

An updated analysis was conducted after a median follow-up of 15.4 months after infusion of axicabtagene ciloleucel, when the 108 patients in the Phase 1 and 2 portions of ZUMA-1 had been followed for a minimum of 1 year. At this time, 42% of patients remained in response and 40% were lymphoma-free. The median time that patients had been in response was now 11.1 months, and median DOR had still not been reached by patients who were lymphoma-free. The updated analysis also showed that 52% of patients were still alive at 18 months. Median OS still had not been reached and the lower

confidence interval was now up to 12 months. In addition, 41% of patients had no progression of disease at 15 months, with a median PFS of 5.8 months. The safety profile was again manageable, with no new axicabtagene ciloleucel-related adverse events associated with CRS or NE, and there were no additional deaths from adverse events arising after the primary analysis (Neelapu et al, 2017B).

Furthermore, long term follow up out to 2 years is now available, extending the median follow up from 15.4 months to 27.1 months (Locke et al, 2018). Results indicate that single infusion of axicabtagene ciloleucel achieved durable responses lasting more than 2 years and needed no further consolidation therapy. Additionally, in this population of patients refractory to several lines of treatment, which included a large proportion of patents with activated B-cell-like, double expressor, and high-grade B-cell lymphoma, outcomes were similar across all patient subgroups. Median overall survival was not yet reached at 2 years, with an estimated 24-month survival proportion of 50.5% (95% CI 40.2–59.7) (Locke et al, 2018).

In contrast, the current standard of care in patients with relapsed/refractory DLBCL, PMBCL and TFL who are ineligible for ASCT affords a median OS of 5.1 months (Crump et al, 2017). Axicabtagene ciloleucel therefore provides a significant step change improvement in survival of patients with relapsed/refractory DLBCL, PMBCL and TFL who are ineligible for ASCT, redacted, and a lower confidence interval for OS that is already 5.7 months longer than that provided by the standard of care (Kite, 2017A; Neelapu et al, 2017B).

The safety profile is well understood, with established protocols in place to manage adverse events, to ensure an acceptable risk-benefit ratio for the indicated population of already very ill patients (Kite, 2017A; Neelapu et al, 2017B). Redacted.

The 2 year follow up study with median follow up of 27.1 months showed that axicabtagene ciloleucel had a manageable 2-year safety profile, and late-onset serious adverse events were uncommon. Importantly, despite targeting of CD19 and the expected induction of B-cell aplasia, the frequency of late-onset grade 3 or worse serious infections was low (Locke et al, 2018).

In terms of comparison with historical controls, to provide context to the interpretation of results from ZUMA-1, the results of ZUMA-1 are compared with the results of the aforementioned SCHOLAR-1 study (Crump et al, 2017), a patient-level pooled analysis of a population of refractory DLBCL/PMBCL/TFL patients. This population was chosen to match that of the ZUMA-1 patient population with the comparison conducted after adjusting for imbalances in a broader set of prognostic factors.

In summary, compared with the historical standard of care, treatment with axicabtagene ciloleucel was estimated to have:

- ~5-fold increase in complete response (CR) rate
- 72% reduction in the risk of death
- ~3 fold higher 12-month overall response (OS) rate (Neelapu et al; 2017C)

**45. Please advise if the overall clinical claim is for:**

- Superiority  
 Non-inferiority

**46. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:**

**Clinical Effectiveness Outcomes:** Objective Response Rate (ORR), complete response (CR) rate, Progression Free Survival (PFS), Overall Survival (OS), duration of response (DOR)

**Safety Outcomes:** Rate of adverse events (AEs) and serious adverse events (SAEs), events of special interest, AEs due to medications, neurotoxicity, infections, secondary cancers, blood levels of CAR T-cells and serum cytokines.

## PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

**47. Estimate the prevalence and/or incidence of the proposed population:**

Redacted.

**48. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:**

The proposed therapy is a single infusion per lifetime.

**49. How many years would the proposed medical service(s) be required for the patient?**

The proposed therapy is a single infusion per lifetime.

**50. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:**

Redacted.

**51. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:**

Redacted.

## PART 8 – COST INFORMATION

**52. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:**

The cost of providing the proposed medical service is multi-factorial and not yet fully defined. Further information regarding costs will be provided in the submission.

**53. Specify how long the proposed medical service typically takes to perform:**

Redacted.

**54. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.**

Not applicable.

Category (insert proposed category number here) – (insert proposed category description here)
Proposed item descriptor: insert proposed item descriptor here
Fee: \$(insert proposed fee here)

## PART 9 – FEEDBACK

The Department is interested in your feedback.

*As this form was not intended for this application, Gilead has intentionally left this section blank.*

**55. How long did it take to complete the Application Form?**

Insert approximate duration here

**56. (a) Was the Application Form clear and easy to complete?**

- Yes  
 No

**(b) If no, provide areas of concern:**

Describe areas of concern here

**57. (a) Are the associated Guidelines to the Application Form useful?**

- Yes  
 No

**(b) If no, what areas did you find not to be useful?**

Insert feedback here

**58. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?**

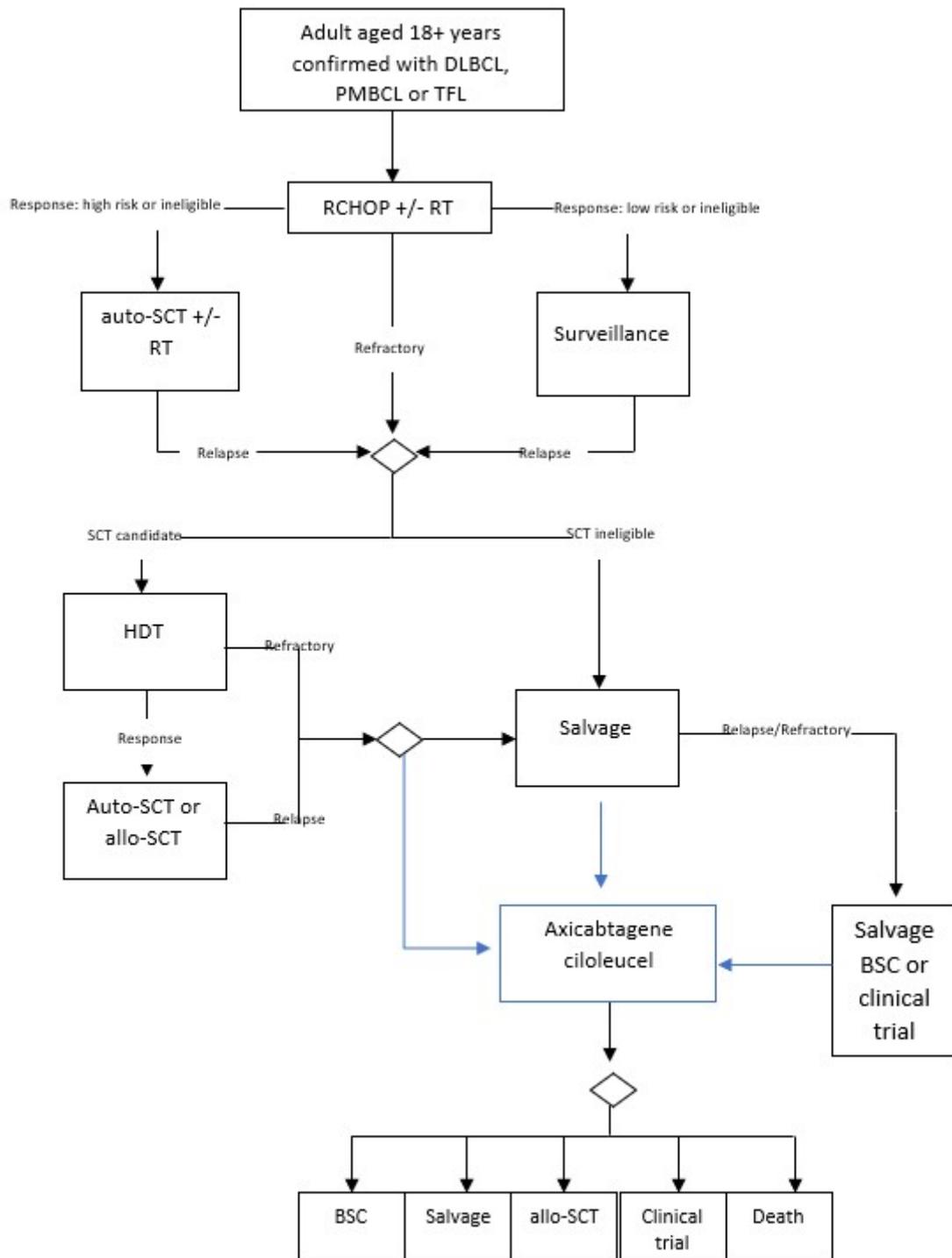
- Yes  
 No

**(b) If yes, please advise:**

Insert feedback here

Appendix A

Figure 1: Current and proposed clinical algorithm of the proposed patient population



Abbreviations: DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma; RCHOP= Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RT= radiotherapy; SCT = Stem Cell Transplant; HDT = high-dose therapy; BSC = best supportive care

The proposed clinical algorithm is depicted by the blue lines in Figure 1. The clinical algorithm was adapted from the PICO Confirmation of Kymriah.

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