



Australian Government

Department of Health

MSAC Application 1723

Brexucabtagene autoleucel for adult relapsed or refractory B-precursor acute lymphoblastic leukaemia

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 to determine whether a proposed medical service is suitable.

Please use this template, along with the associated [Application Form Instructions](#) 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. The separate [MSAC Guidelines](#) should be used to guide health technology assessment (HTA) content of the Application Form

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

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: Gilead Sciences Pty Ltd

ABN: REDACTED

Business trading name: Gilead Sciences Pty Ltd

Primary contact name: REDACTED

Primary contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

2. (a) Are you a consultant acting on behalf on an applicant?

Yes

No

(b) If yes what is the Applicant(s) name that you are acting on behalf of?

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

(c) Have you engaged a consultant on your behalf?

Yes

No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

Brexucabtagene autoleucl for the treatment of adult patients (≥ 18 years of age) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (B-ALL). Relapsed or refractory disease is defined as one of the following:

- Primary refractory
- First relapse if remission was 12 months or less
- Relapsed or refractory after two or more lines of systemic therapy
- Relapsed or refractory after allogeneic stem-cell transplant

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)

Acute lymphoblastic leukaemia (ALL) is a haematologic malignancy propagated by impaired differentiation, proliferation, and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites (Paul et al., 2016¹). In Australia, approximately 446 people (children and adults) diagnosed with, and 109 deaths from, ALL are expected in 2021 (AIHW 2021²). ALL occurs with a bimodal age distribution and is mainly considered a paediatric leukaemia with 80% of cases occurring in children and 20% occurring in adults (≥ 18 years of age; Paul et al., 2016¹). While 5-year overall survival (OS) is approximately 90% in children, the treatment success of paediatric ALL has not been achieved in adult ALL, with 5-year survival rates from 20% to 40% in adults and elderly patients (NCCN 2021³; Paul et al., 2016¹). Therefore, prognosis and survival are particularly poor among adults (Katz 2015) and represents a devastating disease when it occurs in adults (Terwiliger et. al., 2017⁴) compared to children.

Precursor B-cell ALL (B-ALL) is the most common type in adults (Bassan et. al., 2019⁵) representing 75%-80% of adult cases, and the accumulation of lymphoblasts can spread to the bloodstream, affecting various organs (Terwiliger et. al., 2017⁴; Leukaemia Foundation 2020⁶). The mainstay treatment for adult ALL patients with B-ALL is induction chemotherapy, followed by consolidation, and long-term maintenance therapy (Paul et al., 2016¹). Allogeneic stem-cell transplant (allo-SCT) is recommended following consolidation in selected high-risk groups (Bassan et. al., 2019⁵). After initial treatment, 40–50% of adults with B-ALL relapse and have poor prognosis (Paul et al., 2016¹). The 1-year overall survival rate is low and has been reported as 26% after first salvage therapy, decreasing with subsequent relapses (Gokbuget et. al., 2016⁷; Paul et al., 2016¹).

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)

Brexucabtagene autoleucl (TECARTUS®) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell product.

CAR T-cell therapy is a type of immunotherapy in which a patient's T-cells (immune cells with anticancer activity) are collected and genetically modified in a laboratory process to recognise cancer cells that express CD19 on their surface linked to CD3 ζ and CD28 T-cell activation and signalling domains that result in elimination of CD19-expressing cells. The modified T-cells are expanded to several million and these modified cells are then infused back into the patient, where they target and kill cancer cells.

Following CAR engagement with CD19+ target cells, the CD3 ζ 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 costimulatory signal that works in concert with the primary CD3 ζ signal to augment T-cell function, including interleukin (IL)-2 production. Together, these signals stimulate proliferation of the CAR T cells and direct killing of target cells. In addition, activated T cells secrete cytokines, chemokines, and other molecules that can recruit and activate additional antitumor immune cells.

An application ([MSAC Application 1647](#)) requesting joint public funding by the Commonwealth and the States and Territories under the National Health Reform Agreement (NHRA) of brexucabtagene autoleucl (TECARTUS®) for the treatment of patients with relapsed or refractory mantle cell lymphoma (R/R MCL) was reviewed by MSAC at the 82nd MSAC Meeting, 29-30 July 2021, and the committee supported public funding (see redacted [Public Summary Document](#)¹).

Gilead would like to request the application to bypass the PASC, considering:

- previous application for brexucabtagene autoleucl (TECARTUS) in refractory/replaced mantle cell lymphoma (R/R MCL) was recently expedited bypassing PASC and
- the ratified PICO for tisagenlecleucel (Kymriah) for treatment of confirmed for R/R ALL up to age 25 is available.

Error! Reference source not found., in Section 8 of this application, summarises the proposed key components of the PICO criteria to be addressed in a submission. The application is requested to be expedited (bypassing the PASC) as the proposed PICO is based on [Application 1519](#) (and accompanying Ratified PICO) for tisagenlecleucel (Kymriah) which MSAC recommended for funding to treat relapsed/refractory CD19-positive ALL in children and young adults up to 25 years old; a very similar and overlapping indication for this application.

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

- Yes
 No

Brexucabtagene autoleucl is not eligible for funding through the MBS or PBS.

(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?

N/A

(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/technology:

N/A

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

Not applicable

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

- A new item which also seeks to allow access to the MBS for a specific health practitioner group
 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)
 A new item for a specific single consultation item
 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:

The Commonwealth and the States currently jointly fund various CAR T-cell therapies as Highly Specialised Therapies under the Addendum to the National Health Reform Agreement 2020-2025 (NHRA). This application proposes that the same funding mechanism be used to fund brexucabtagene autoleucl when used in adult patients (≥ 18 years of age) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (B-ALL).

¹ MSAC Application 1647 Redacted Public Summary Document - [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/A10E3D10B9DBC1F2CA258614002163DC/\\$File/1647%20Final%20PSD%20-%20July%202021_redacted.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/A10E3D10B9DBC1F2CA258614002163DC/$File/1647%20Final%20PSD%20-%20July%202021_redacted.pdf)

8. What is the type of medical service/technology?

- 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):

- To be used as a screening tool in asymptomatic populations
- Assists in establishing a diagnosis in symptomatic patients
- Provides information about prognosis
- Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- 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
- No

Bridging therapy

Prespecified bridging chemotherapy to stabilise the patient's condition during brexucabtagene autoleucl manufacturing is allowed at the physician's discretion.

In the pivotal ZUMA-3 study, bridging therapy was administered after leukapheresis and prior to lymphodepleting chemotherapy. Bridging chemotherapy was recommended for all subjects, particularly those subjects with high disease burden at baseline (M3 marrow [$> 25\%$ leukemic blasts] or $\geq 1,000$ blasts/ mm^3 in the peripheral circulation). If prescribed, bridging chemotherapy was administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever was shorter, prior to initiating lymphodepleting chemotherapy. The most commonly administered bridging therapy administered in the pivotal study was dexamethasone, which is listed on the PBS as an unrestricted benefit.

Lymphodepleting chemotherapy

Conditioning chemotherapy is required to be administered prior to infusion of brexucabtagene autoleucl. The lymphodepleting chemotherapy regimen administered in the pivotal ZUMA-3 study consisted of: fludarabine 25 mg/m^2 intravenous (IV) administered on the fourth, third and second day prior to infusion of brexucabtagene autoleucl and cyclophosphamide 900 mg/m^2 IV administered on the second day prior to infusion of brexucabtagene autoleucl. Both of these therapies are available as unrestricted benefits on the PBS.

Cerebrospinal fluid (CSF) prophylaxis

All subjects in the ZUMA-3 study received CSF prophylaxis, consisting of an intrathecal regimen (e.g. methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose). CSF prophylaxis was supplied by the investigative site and administered any time during screening (e.g. at the time of the screening lumbar puncture) through 7 days prior to CAR-T infusion. Both cytosine arabinoside (i.e. cytarabine) and dexamethasone are listed on the PBS as unrestricted benefits.

Concomitant therapies

As with the other CAR T-cell therapies, corticosteroids and tocilizumab may be administered to patients requiring management of cytokine release syndrome (CRS). Although tocilizumab is PBS-listed, it is not reimbursed for the management of CRS.

As with the other CAR T-cell therapies, immunoglobulin was administered to some patients in the ZUMA-3 study. Immunoglobulin is funded via the National Blood Authority.

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

Dexamethasone: 1292B, 2507Y, 1291Y, 2509C, 3472R
Fludarabine: 4393F
Cyclophosphamide: 4327R
Methotrexate: 4502Y, 4512L, 7250N, 7251P
Cytarabine: 4357H, 7227J
Tocilizumab: not reimbursed for the CRS indication
Immunoglobulin: funded through the National Blood Authority (see <https://www.blood.gov.au/national-product-list> [Last accessed: 24 Oct 2021])

(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

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

Trade name: Not applicable
Generic name: Not applicable

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

N/A

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

N/A

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

N/A

(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?

N/A

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

N/A

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

There are a number of stages in the process of delivering brexucabtagene autoleucel that require the use of consumables e.g. collection of leucocytes from the patient by leukapheresis; administration of bridging therapy, administration of intrathecal CSF prophylaxis, administration of conditioning chemotherapy and infusion of brexucabtagene autoleucel.

Consumables that are likely to be required include: gloves, masks, sterile alcohol wipes, sterile field procedural mats, spill kits, labels, syringes, needles, gauze, plasma collection sets, collection containers, adhesive tapes, IV administration sets, filters, IV fluids (e.g. standard saline).

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer, or any other type of therapeutic good, please provide 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) Has it been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? If the therapeutic good has been listed on the ARTG, please state the ARTG identification numbers, TGA-approved indication(s), and TGA-approved purpose(s).

Brexucabtagene autoleucl was listed on the ARTG on 21st July 2021. Details of the registration are provided below:

ARTG ID: 371431

TGA approved indication(s), if applicable:

TECARTUS is a genetically modified autologous immunocellular therapy for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL), who have received two or more lines of therapy, including a BTK inhibitor, unless ineligible or intolerant to treatment with a BTK inhibitor.

Proposed new indication (R/R ALL) details provided in Q15.

TGA approved purpose(s), if applicable: Not applicable

- (c) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

- Class III
 AIMD
 N/A

- (d) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

No

15. (a) If not listed on the ARTG, 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 the therapeutic good is not ARTG listed, is the therapeutic good in the process of being considered by TGA?

- Yes (if yes, please provide details below)
 No

REDACTED

TGA approved indication(s), if applicable: *TECARTUS is a genetically modified autologous immunocellular therapy for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL), who have received two or more lines of therapy, including a BTK inhibitor, unless ineligible or intolerant to treatment with a BTK inhibitor.*

REDACTED

TECARTUS is already approved for R/R MCL ([ARTG ID 371431](#))

TECARTUS is a genetically modified autologous immunocellular therapy for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL), who have received two or more lines of therapy, including a BTK inhibitor (unless ineligible or intolerant to treatment with a BTK inhibitor).

(c) If the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?

Yes (please provide details below)

No

PART 4 – SUMMARY OF EVIDENCE

16. Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At ‘Application Form lodgement’, please do not attach full text articles; just provide a summary.

Note: There is a single Phase 1/2 trial (ZUMA-3) with separate publications for Phase 1, Phase 2 or combined Phase 1/2. The trial can be identified on Clintrials.gov by study number NCT02614066, A Study Evaluating Brexucabtagene Autoleucel (KTE-X19) in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ZUMA-3) (ZUMA-3) <https://clinicaltrials.gov/ct2/show/NCT02614066>

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	A phase 2 single-arm, open-label ZUMA-3 study at 25 sites in the USA, Canada and Europe (NCT02614066) Manuscript	KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study	KTE-X19 showed a high rate of complete remission or complete remission with incomplete haematological recovery in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia, with the median overall survival not reached in responding patients, and a manageable safety profile. These findings indicate that KTE-X19 has the potential to confer long-term clinical benefit to these patients.	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01222-8/fulltext (Shah et. al., 2021 ⁸)	2021
2.	A Phase 1 of ZUMA-3 conducted at 19 sites in the United States. Manuscript (NCT02614066)	KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results	Adults with R/R B-ALL achieved high rates of CR and undetectable bone marrow minimal residual disease with a tolerable safety profile after treatment with KTE-X19.	https://ashpublications.org/blood/article/138/1/11/475697/KTE-X19-anti-CD19-CAR-T-cell-therapy-in-adult (Shah et. al., 2021 ⁹)	2021

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	A phase 1/2 single-arm, open-label ZUMA-3 multicentre study Abstract (NCT02614066)	Phase 2 results of the ZUMA-3 study evaluating KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in adult patients (pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL)	After a median follow-up of 16.4 months, KTE-X19 demonstrated compelling clinical benefit in heavily pre-treated adults with R/R B-ALL, with the median OS not yet reached for responding patients and a manageable safety profile.	https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7002	2021
4.	A Phase 1 of ZUMA-3 Abstract (NCT02614066)	Updated Phase 1 Results of Zuma-3: Kte-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia	High remission rates were achieved by adult pts with R/R ALL, with approximately 3/4 of patients achieving CR or CRi with undetectable MRD after a single dose of KTE-X19 in ZUMA-3. The safety profile was generally manageable, and most cases of high-grade CRS and neurologic events resolved. These results demonstrate that KTE-X19 offers clinical benefit for patients with otherwise limited treatment options.	https://www.astctjournal.org/action/showPdf?pii=S1083-8791%2818%2931153-4	2019

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
5.	A retrospective cohort study	The Comparison of Kte-X19 to Current Standards of Care: A Pre-Specified Synthetic Control Study Utilizing Individual Patient Level Data from Historic Clinical Trials (SCHOLAR-3).	<p>Analysis of the synthetic control arm (SCA)-1 cohort shows an objective complete response rate at week 24 (OCR24) of 85% (95% CI 62.1%, 96.8%) in the Zuma-3 patients and 35.0% (95% CI 15.4, 59.2) among propensity matched controls. This corresponds to an odds ratio of 10.5 (95% CI 2.3, 48.7; p-value 0.0031). No OCR24 data was available for SCA-2.</p> <p>The comparison of overall survival (OS) between all matched ZUMA-3 and all SCA patients demonstrated a significantly higher median OS of 18.20 months (95% CI: 12.22, NE months) for patients in ZUMA-3 versus 5.49 months (95% CI: 3.32, 9.23 months) in SCA-3. A cox regression model showed that ZUMA-3 patients had a 64% lower risk of death with a hazard ratio 0.36 (95% CI 0.20, 0.66) p-value 0.0005.</p> <p>This comparative analysis of ZUMA-3 versus historical controls demonstrated a clinically relevant improvement of OCR24 and OS following KTE-X19 vs available therapies and provides strong evidence for its use in adult patients with R/R B-ALL</p>	<p>https://ashpublications.org/blood/article-split/138/Supplement%201/3844/481068/The-Comparison-of-Kte-X19-to-Current-Standards-of</p> <p>ABSTRACT: Shah et. al., 2021¹⁰</p> <p>POSTER: Shah et. al., 2021¹¹</p>	2021

17. Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 18. List all appropriate professional bodies/organisations representing the health professionals who provide the service. For MBS-related applications ONLY, please attach a brief ‘Statement of Clinical Relevance’ from the most relevant college/society.**

Haematology Society of Australia and New Zealand (HSANZ)

Australasian Leukaemia & Lymphoma Group (ALLG)

The Australian and New Zealand Transplant and Cellular Therapies (ANZTCT)

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

The same groups as above

- 20. List the consumer organisations relevant to the proposed medical service (noting there is NO NEED to attach a support letter at the ‘Application Lodgement’ stage of the MSAC process):**

The Leukaemia Foundation (TLF)

Rare Cancers Australia (RCA)

Snowdome Foundation

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

Novartis Pharmaceuticals Australia Pty Ltd is the sponsor for tisagenlecleucel (Kymriah) for treatment of confirmed relapsed/refractory CD19-positive ALL in children and young adults up to 25 years old

- 22. Nominate two experts that can be contacted about the proposed medical service, and current clinical management of the condition:**

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**

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

23. 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):

Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is a haematologic malignancy propagated by impaired differentiation, proliferation, and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites (Paul et al., 2016¹).

In Australia, approximately 446 diagnoses (in both children and adults) with and 109 deaths from ALL are expected in 2021 (AIHW 2021)². ALL is mainly considered a paediatric leukaemia with 80% of cases occurring in children and 20% occurring in adults (Paul et al., 2016¹). The median age at diagnosis for ALL is 17 years old. The disease occurs with a bimodal age distribution, with 53.5% of patients diagnosed at younger than 20 years old and of the remainder: 29.6% of cases diagnosed in adult patients \geq 45 years old and 13.7% of patients diagnosed at \geq 65 years (NCCN 2021³). Survival is particularly poor among adults (Katz et. al., 2015¹²) and represents a devastating disease when it occurs in adults with high mortality (Terwiliger et. al., 2017⁴).

The 5- year overall survival (OS) is approximately 90% in children but only 20% to 40% in adults and elderly patients (NCCN 2021³; Paul et al., 2016¹).

Unfortunately, the treatment success of paediatric ALL has not been achieved in adult ALL. Therefore, there remains a high unmet clinical need for adult patients with relapsed or refractory ALL, compared to the paediatric population with a similar condition in whom tisagenlecleucel (Kymriah[®]) is currently funded in public hospitals in Australia.

ALL can develop from different types of lymphocytes, including B-cells or T-cells. Precursor B-cell ALL (B-ALL) is the most common type in adults (Bassan et. al., 2019⁵) representing 75%-80% of cases, and the accumulation of lymphoblasts can spread to the bloodstream, affecting various organs (Terwiliger et. al., 2017⁴; Leukaemia Foundation 2020)³.

Risk factors, early symptoms and diagnosis

The exact causes of ALL remain largely unknown but it is thought to result from mutations in one or more of the genes that normally control blood cell development. This mutation will result in abnormal growth (Leukaemia Foundation 2020)⁴. The main symptoms of ALL are caused by a lack of normal circulating blood cells. ALL develops quickly, so people are usually only unwell for only a short period (it could be days, or weeks) before diagnosis. Possible signs of adult ALL include fever, feeling tired and increased or unexplained bleeding or bruising due to a low platelet count. ALL is diagnosed by examining samples of patient's blood and bone marrow in a variety of tests (Rare Cancers Australia 2021)⁵. The diagnosis of ALL generally requires demonstration of \geq 20% bone marrow lymphoblasts, upon hematopathology review of bone marrow aspirate and biopsy materials (NCCN 2021³).

² AIHW 2021 - <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation>

³ Leukaemia Foundation - <https://www.leukaemia.org.au/blood-cancer-information/types-of-blood-cancer/leukaemia/acute-lymphoblastic-leukaemia/>

⁴ Leukaemia Foundation - <https://www.leukaemia.org.au/blood-cancer-information/types-of-blood-cancer/leukaemia/acute-lymphoblastic-leukaemia/>

⁵ Rare Cancers Australia - <http://knowledge.rarecancers.org.au/knowledgebase/cancer-types/132/acute-lymphoblastic-leukaemia-all>

Prognosis and treatment

Accurate assessment of prognosis is central to the management of ALL. Risk stratification allows the physician to determine the most appropriate initial treatment regimen as well as when to consider allo-SCT. A comprehensive diagnostic approach requires the study of cell morphology, immunophenotype, genetics/cytogenetics and genomics, as detailed in the 2008 World Health Organisation (WHO) classification which was recently updated (Hoelzer et. al., 2016¹³; Figure 1).

Figure 1 Diagnostic work-up in adult ALL (ESMO)

Diagnostic step	Results/ALL subsets	Recommendations
Morphology		
– Bone marrow and peripheral blood	– Lymphoid/undifferentiated blasts (≥20% bone marrow involvement)	Mandatory
– Cerebro-spinal fluid	– FAB L3 morphology in Burkitt leukaemia	Recommended
	– CNS involvement	Mandatory
Immunophenotype		
– MPO (differential diagnosis versus AML)	– MPO negative; B/T markers >20% (CD3, CD79a >10%)	Mandatory
– B-lineage markers: CD19, CD79a, cCD22 (at least 2); others: TdT, CD10, CD20, CD24, cIgM, sIg (kappa or lambda)	– B-lineage ALL:	Mandatory
– T-lineage markers: cCD3; others: TdT, CD1a, CD2, CD5, CD7 CD4, CD8, TCR α/β or γ/δ	Pro-B/B-I (CD19/CD79a/cCD22+)	
– Stem/myeloid cell markers (variable): CD34, CD13, CD33, CD117	Common/B-II (CD10+/cIgM–)	
	Pre-B/B-III (cIgM+/sIg–)	
	Mature-B/B-IV (sIg+)	
	– T-lineage ALL:	Mandatory
	Pro-T/T-I (cCD3/CD7+)	
	Pre-T/T-II (CD2/CD5)	
	Cortical-T/T-III (CD1a+)	
	Mature-T/T-IV (CD3+/CD1a–)	
Cytogenetics/genetics		
– Cytogenetics/FISH/RT-PCR	– ALL with adverse clinico-biological features: Ph+ ALL (rapid detection, to TKI therapy) t(4;11)+ ALL t(1;19)+ ALL other high-risk cytogenetics	Mandatory
– CGH/SNP/GEP/NGS	– ALL with adverse clinico-biological features: Ph-like ALL ETP ALL NOTCH1/FBW7-unmutated/RAS/ PTEN-altered T-ALL IKZF1, CLRF2, MLL, TP53, CREBBP, RAS alterations	Recommended for new clinical trials
MRD study		
– MRD marker(s): LAIP (immunophenotype)/molecular probe (PCR)	– MRD-based risk classification	Mandatory
Storage of diagnostic material		
– Cell banking/storage of DNA/RNA/protein lysates	– Additional/future studies	Highly recommended
HLA typing		
– Patient/siblings	– Early application of SCT if required	Recommended
<p>ALL, acute lymphoblastic leukaemia; CNS, central nervous system; MPO, myeloperoxidase; AML, acute myelogenous leukaemia; c, cytoplasmic; IgM, immunoglobulin M; s, surface; Ig, immunoglobulin; FISH, fluorescence <i>in situ</i> hybridisation; RT-PCR, reverse transcriptase polymerase chain reaction; Ph+, Philadelphia-positive; TKI, tyrosine kinase inhibitor; CGH, comparative genomic hybridisation; SNP, single nucleotide polymorphism; GEP, gene expression profiling; NGS, next-generation sequencing; Ph, Philadelphia; ETP, early T-cell precursor; T-ALL, T-cell ALL; MRD, minimal residual disease; LAIP, leukaemia-associated immunophenotype; PCR, polymerase chain reaction; HLA, human leucocyte antigen; SCT, stem-cell transplantation.</p>		

Source: (Hoelzer et. al., 2016¹³)

The mainstay treatment for adult ALL patients with B-ALL is induction chemotherapy, followed by consolidation, and long-term maintenance therapy along with central nervous system (CNS) prophylaxis interwoven during the first year of treatment. The purpose of this multi-drug treatment approach is to eradicate the disease and restore normal haematopoiesis, provide prophylaxis to “sanctuary sites,” and prevent an upsurge of resistant clones that may lead to relapse (Paul et al., 2016¹). Allo-SCT is recommended following consolidation in selected high-risk groups (Bassan et. al., 2019⁵).

Although adults with B-ALL respond to initial treatment, 40–50% of patients relapse with poor prognosis (Paul et al., 2016¹). The 1-year overall survival rate is 26% after first salvage therapy and decreases with subsequent relapses (Gokbuget et. al., 2016⁷; Paul et al., 2016¹). Although the novel agents blinatumomab and inotuzumab ozogamicin lead to a proportion of patients with complete remission or complete remission with incomplete haematological recovery of 35.1% (blinatumomab) and 80.7% (inotuzumab ozogamicin), median overall survival remains at less than 8 months and is largely contingent on allo-SCT consolidation (Shah et. al., 2021⁹; Shah et. al., 2021⁸).

24. Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):

The population for whom reimbursement of brexucabtagene autoleucl is proposed is intended to be consistent with the proposed indication for brexucabtagene autoleucl and the eligibility criteria that were applied in recruiting patients to the ZUMA-3 pivotal study investigating the efficacy and safety of brexucabtagene autoleucl. The population of patients for whom it is proposed that brexucabtagene autoleucl be made available can be summarised as follows:

REDACTED

Depending on clinical circumstances, patients could have received previous blinatumomab, inotuzumab ozogamicin or tyrosine kinase inhibitors (if Ph-positive).

On the basis of what is known about prognostic factors in adult ALL, the National Comprehensive Cancer Network (NCCN) has developed recommendations to approach risk stratification. The National Cancer Institute defines adolescent and young adults (AYA) to be those aged 15-39 years. Both age groups are then stratified into high-risk Ph-positive and standard-risk Ph-negative subgroups. The Ph-negative subgroup can further be categorised as high-risk based on the presence of MRD, elevated WBC ($\geq 30 \times 10^9/L$ for B lineage or $\geq 100 \times 10^9/L$ for T lineage) or unfavourable cytogenetics (Table 1).

Table 1 Cytogenetic risk groups for B-ALL (NCCN)

Risk Groups	Cytogenetics
Good risk	<ul style="list-style-type: none"> • Hyperdiploidy (51-65 chromosomes) <ul style="list-style-type: none"> - Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favourable outcome • t(12; 21)(p13;q22): <i>ETV6-RUNX1</i>
Poor risk	<ul style="list-style-type: none"> • Hyperdiploidy (<44 chromosomes) • <i>KMT2A</i> rearranged (t[4;11] or others) • t(v;14q32)/IgH • t(9;22)(q34;q11.2): <i>BCR-ABL1</i> (defined as high risk in the pre-TKI era) • Complex karyotype (5 or more chromosome abnormalities) • <i>BCR-ABL1</i>-Like (Ph-like) ALL <ul style="list-style-type: none"> - JAK-STAT (<i>CRLF2r</i>, <i>EPORr</i>, <i>JAK1/2/2r</i>, <i>TYK2r</i>, mutations of <i>SH2B3</i>, <i>IL7R</i>, <i>JAK1/2/3</i>) - ABL class (rearrangements of <i>ABL1</i>, <i>ABL2</i>, <i>PDGFRA</i>, <i>PDGFRB</i>, <i>FGFR</i>) - Other (<i>NTRKr</i>, <i>FLT3r</i>, <i>LYNr</i>, <i>PTL2Br</i>) • Intrachromosomal amplification of chromosome 21 (iAMP21) • t(17;19): <i>TCF3-HLF</i> fusion • Alteration of <i>IKZF1</i>

PART 6b – INFORMATION ABOUT THE INTERVENTION

25. Describe the key components and clinical steps involved in delivering the proposed medical service/technology:

Brexucabtagene autoleucl is a CAR T-cell product that is unique to each patient. Each individual patient's T-cells (immune cells with anticancer activity) are collected and genetically modified in the laboratory to recognise cancer cells that express CD19 on their surface. The modified T-cells are then expanded to several million and the modified cells are then infused back into the patient. The steps involved in developing and eventually delivering the product are described in greater detail below:

1. **Leukapheresis and harvesting of peripheral blood mononuclear cells:** A sufficient amount of blood is drawn from patients to obtain enough peripheral blood mononuclear cells to support the manufacture of engineered T-cells. The remaining blood products are transfused back into the patient. The collected peripheral blood mononuclear cells are then transported immediately to the brexucabtagene autoleucl manufacturing facility.
2. **Isolation of T-cells:** In the laboratory, T-cells are purified from the peripheral blood cells that were collected from patients. The manufacturing process for brexucabtagene autoleucl includes a CD4+ and CD8+ T-cell enrichment step (to separate circulating tumour cells from T-cells) to address the potential negative impact of high levels of cellular impurities on the activation and expansion of T-cells in the laboratory.
3. **Modification of T-cells:** The T-cells are then genetically modified by retroviral transfection to encode receptors that recognise cancer-specific antigen and activate T-cells.
4. **Expansion of CAR T-cells:** Following modification, the T-cells are then cultured in the laboratory. Cytokines are used to stimulate the expansion of CAR T-cells.
5. **Testing and shipping of CAR T-cells:** The final product is washed, formulated into a suspension, cryopreserved and tested for identity, potency, and sterility. After establishing that the final product meets all quality control requirements, the product is transported back to the patient's qualified delivery centre using a validated cryo-shipper.
6. **Bridging therapy (if necessary):** Patients are monitored while the production of CAR T-cells is in progress. If necessary, patients may receive bridging therapy to ensure the patient remains viable for infusion of brexucabtagene autoleucl.
7. **Cerebrospinal fluid (CSF) prophylaxis:** Patients to receive CSF prophylaxis, consisting of an intrathecal regimen according to institutional or national guidelines (e.g. methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose).
8. **Conditioning chemotherapy:** Prior to infusion of brexucabtagene autoleucl, 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 25 mg/m² intravenous (IV) administered on the fourth, third and second day prior to infusion of brexucabtagene autoleucl and cyclophosphamide 900 mg/m² IV administered on the second day prior to infusion of brexucabtagene autoleucl on Day 0).
9. **Infusion of brexucabtagene autoleucl:** Brexucabtagene autoleucl is a single infusion product. Each bag for IV infusion contains a suspension of anti-CD19 CAR T-cells. The contents of the bag containing brexucabtagene autoleucl is infused within 30 minutes. Successful infusion is the successful delivery into the patient the prescribed dose per kg. Patients receiving treatment with brexucabtagene autoleucl are required to be hospitalised. Patients will require daily monitoring for at least 7 days at the qualified healthcare/clinical facility following infusion for signs and symptoms of CRS or neurologic toxicities. Patients are then instructed to remain within proximity of the qualified healthcare/clinical facility for at least 4 weeks following infusion.

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

Brexucabtagene autoleucl is already registered by TGA for MCL and branded TECARTUS.

A separate TGA application is being submitted for brexucabtagene autoleucl for ALL and once registered by the TGA, brexucabtagene autoleucl will be supplied as a trademarked (TECARTUS) class 4 biological product.

27. 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?

N/A

28. 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)?

Brexucabtagene autoleucl will be administered at selected tertiary public hospitals that have successfully completed Gilead's rigorous site qualification process to ensure all quality and safety requirements are satisfied.

Patients will require daily monitoring for at least 7 days at the qualified healthcare/clinical facility following infusion for signs and symptoms of CRS or neurologic toxicities.

Patients are then instructed to remain within proximity of the qualified healthcare/clinical facility for at least 4 weeks following infusion.

29. 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:

Bridging therapy may be administered to some patients in the period between the collection of cells and the infusion of brexucabtagene autoleucl. Bridging therapy may be required in patients who have a high disease burden to ensure that the patient remains viable to have the brexucabtagene autoleucl product infused.

Patients to receive CSF prophylaxis, consisting of an intrathecal regimen according to institutional or national guidelines (e.g. methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose). Conditioning chemotherapy is required to be administered in the days prior to infusion of brexucabtagene autoleucl.

Paracetamol 650 mg and diphenhydramine 12.5 mg were administered one hour prior to infusion in the key ZUMA-3 trial.

Brexucabtagene autoleucl is administered by IV infusion in an inpatient hospital setting. Administration of brexucabtagene autoleucl is performed under the supervision of a haematologist or haematologist-oncologist.

Some patients may require administration of treatments following infusion of brexucabtagene autoleucl as supportive care and for management of adverse events (e.g. blood products, antiemetics, tocilizumab).

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

Haematologists and haematologist-oncologists.

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

Not applicable

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

CAR T-cell therapies funded under the NHRA for delivery in public hospitals, it is proposed that brexucabtagene autoleucl will only be able to be administered in accredited treatment centres.

33. 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:

Brexucabtagene autoleucl will be prescribed by physicians who are experienced in the treatment of patients with haematological malignancies. **REDACTED**

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

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms - GP
- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- 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:

Patient’s T-cells will generally be collected at an outpatient clinic (leukapheresis). The materials collected by apheresis are then couriered to an offsite manufacturing facility in **REDACTED** and returned to the accredited healthcare/clinical facility in Australia.

Lymphodepleting chemotherapy with fludarabine and cyclophosphamide, which is to be administered before brexucabtagene autoleucl infusion will typically be performed at an outpatient clinic.

CSF prophylaxis, consisting of an intrathecal regimen according to institutional or national guidelines (e.g. methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose. Brexucabtagene autoleucl will be administered at the accredited healthcare/clinical facility. Patients will be monitored daily for adverse events such as CRS for at least 7 days.

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

- Yes
- No – please specify below

Brexucabtagene autoleucl will be infused at an accredited facility in Australia, however the manufacture of brexucabtagene autoleucl is anticipated to be undertaken off-shore in **REDACTED**.

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

36. 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**). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service):

The target population is patients aged 18 years or older, has Eastern Cooperative Oncology Group performance status of 0-1, and has relapsed or refractory B-precursor acute lymphoblastic leukaemia with morphological disease in the bone marrow (>5% blasts). Relapsed or refractory disease is defined as one of the following:

- Primary refractory disease
- First relapse if remission was 12 months or less
- Relapsed or refractory after two or more lines of systemic therapy
- Relapsed or refractory after allo-SCT.

The proposed comparators to be investigated are:

- 1- Salvage therapy in second and third line with the most relevant specific salvage therapies being blinatumomab or inotuzumab with the intention to proceed to allo-SCT; and the alternative comparator is conventional salvage chemotherapy with the intention to proceed to allo-SCT.
- 2- Dasatinib in second and third line, in patients with Ph1-positive ALL and *BCR-ABL* mutations. Tisagenlecleucel in second and third line in eligible adult patients from aged 18 years up to 25 years of age.

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

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

38. (a) Will the proposed medical service/technology be used in addition to, or instead of, the nominated comparator(s)?

- In addition to (i.e. it is an add-on service)
 Instead of (i.e. it is a replacement or alternative)

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

The likely comparator will be second and third line therapy for R/R ALL.

PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)

39. Define and summarise the CURRENT clinical management pathway (algorithm) that patients follow when they receive the COMPARATOR service (i.e. the landscape before the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current clinical management pathway, but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g. pharmaceuticals, diagnostics and investigative services, etc.).

The treatment approach to acute lymphoblastic leukaemia (ALL) represents one of the most complex and intensive programs in cancer therapy. As discussed above, diagnostic work-up is crucial to determine the appropriate initial treatment regimen as well as when to consider allo-SCT. Although the specific treatment regimens and selection of drugs, dose schedules, and treatment durations differ between adolescent and young adults (AYA) patients (defined by the National Cancer Institute as individuals aged 15-39 years old) amongst different subtypes of ALL, the basic treatment principles are similar.

Front-line treatment

Pre-phase: When the diagnosis is established, treatment should start immediately. A pre-phase therapy with corticosteroids (usually prednisone 20-60 mg/day or dexamethasone 6-16 mg/day, both i.v. or p.o.) alone, or in combination with another drug (e.g. vincristine, cyclophosphamide), is often given together with allopurinol and hydration for ~5–7 days. The pre-phase therapy allows a safe tumour reduction, avoiding in most cases a tumour lysis syndrome (TLS).

Induction, consolidation and maintenance: This consist of induction chemotherapy, followed by consolidation, and long-term maintenance therapy along with central nervous system (CNS) prophylaxis interwoven during the first year of treatment. The purpose of this multi-drug treatment approach is to eradicate the disease and restore normal haematopoiesis, provide prophylaxis to “sanctuary sites,” and prevent an upsurge of resistant clones that may lead to relapse.

Targeted agents: Tyrosine Kinase inhibitors (TKIs) are used in the treatment of Ph-positive disorders. Other targeted agents include an anti-CD20 monoclonal antibody (e.g. rituximab) for CD-20 expressing B-ALL.

Allogeneic stem-cell transplant: Allo-SCT in first complete remission significantly improves overall survival (OS) and event free survival (EFS) in high-risk patients/MRD+ patients and is the best post-remission option for Ph+ ALL and MLL-rearranged ALL. Conditioning regimens are age-adapted with full allo versus reduced-intensity conditioning (RIC) for elderly patients or patients unfit for full conditioning

Relapsed/refractory treatment (second or later line)

Full diagnostic work-up necessary to exclude/reveal clonal aberrations, and to provide bases for targeted therapies. Relapsed ALL in adults is still a major clinical challenge as, there is no universally accepted treatment protocol. In addition, treatment options are extremely limited for patients who experience relapse after receiving consolidation with allo-SCT.

Reinduction chemotherapy followed by Allo-SCT: Patients with ALL who experience a relapse following chemotherapy and maintenance therapy are unlikely to be cured by further chemotherapy alone. These patients should be considered for reinduction chemotherapy followed by alloSCT.

Blinatumomab (BLINCYTO) followed by Allo-SCT: Blinatumomab is a bispecific antibody targeting CD19 and CD3 for use in patients with relapsed or refractory B-cell ALL. In patients with minimal residual disease of B-ALL, (ie Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1), who have achieved complete remission following intensive combination chemotherapy for initial treatment of acute lymphoblastic leukaemia (ALL) or for subsequent salvage therapy, minimal residual disease (MRD) defined as polymerase chain reaction (PCR) or flow cytometry 0.01% blasts (ie $<1 \times 10^{-4}$) based on measurement in bone marrow, documented after an interval of at least 2 weeks from the last course of systemic chemotherapy given as intensive combination chemotherapy treatment of ALL or as subsequent salvage therapy, whichever was the later. The treatment must not be more than 2 treatment cycles under this restriction in a lifetime.

PBS Items: 11850Q, 11867N

Blinatumomab (BLINCYTO) followed by Allo-SCT: Blinatumomab is a bispecific antibody targeting CD19 and CD3 for use in patients with relapsed or refractory B-ALL. On the PBS, in patient with relapsed/refractory B-ALL, with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less and disease must not be present in the central nervous system or testis, and patient must have previously received a tyrosine kinase inhibitor (TKI) if the condition is Philadelphia chromosome positive, and patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy, and patient must not have received more than 1 line of salvage therapy, and must not have received blinatumomab previously for the treatment of minimal residual disease; or must have had a relapse-free period of at least six months following completion of treatment with blinatumomab for minimal residual disease, and must have more than 5% blasts in bone marrow, and treatment must not be more than 2 treatment cycles under this restriction in a lifetime.

PBS Items: 11115B, 11116C, 11117D, 11118E, 11119F, 11120G

Inotuzumab ozogamicin (BESPONSA) followed by Allo-SCT: Inotuzumab ozogamicin is an antibody-drug conjugate targeting CD22, which contains a conjugated toxin, calicheamicin. Inotuzumab ozogamicin is approved by for use in patients with relapsed or refractory B-ALL with CD22 expression. On the PBS patient must be relapsed/refractory B-ALL, with ECOG performance status of 2 or less, and must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy and must not have received more than 1 line of salvage therapy, and must have previously received a tyrosine kinase inhibitor (TKI) if the condition is Philadelphia chromosome positive, and must be CD22-positive and must have more than 5% blasts in bone marrow and treatment must not be more than 3 treatment cycles under this restriction in a lifetime.

PBS Items: 11668D, 11673J, 11680R, 11696N

Dasatinib (SPRYCEL): Patients with Ph1-positive ALL will often be taking imatinib at the time of relapse and thus will have imatinib-resistant disease. Dasatinib, a novel tyrosine kinase inhibitor with efficacy against several different imatinib-resistant *BCR-ABL* mutations, for use in Ph1-positive ALL patients who are resistant to or intolerant of imatinib. On the PBS, patient must be expressing the Philadelphia chromosome or must have the transcript *BCR-ABL* and must have failed treatment with chemotherapy and must have failed treatment with imatinib and must have failed an allogeneic haemopoietic stem cell transplantation if applicable.

PBS Items: 9343R

Ponatinib (ICLUSIG): Patient must be expressing the T315I mutation, and must have failed treatment with chemotherapy, with or without another tyrosine kinase inhibitor, and must have failed allogeneic haemopoietic stem cell transplantation (where appropriate).

PBS Items: 10523W, 10524X

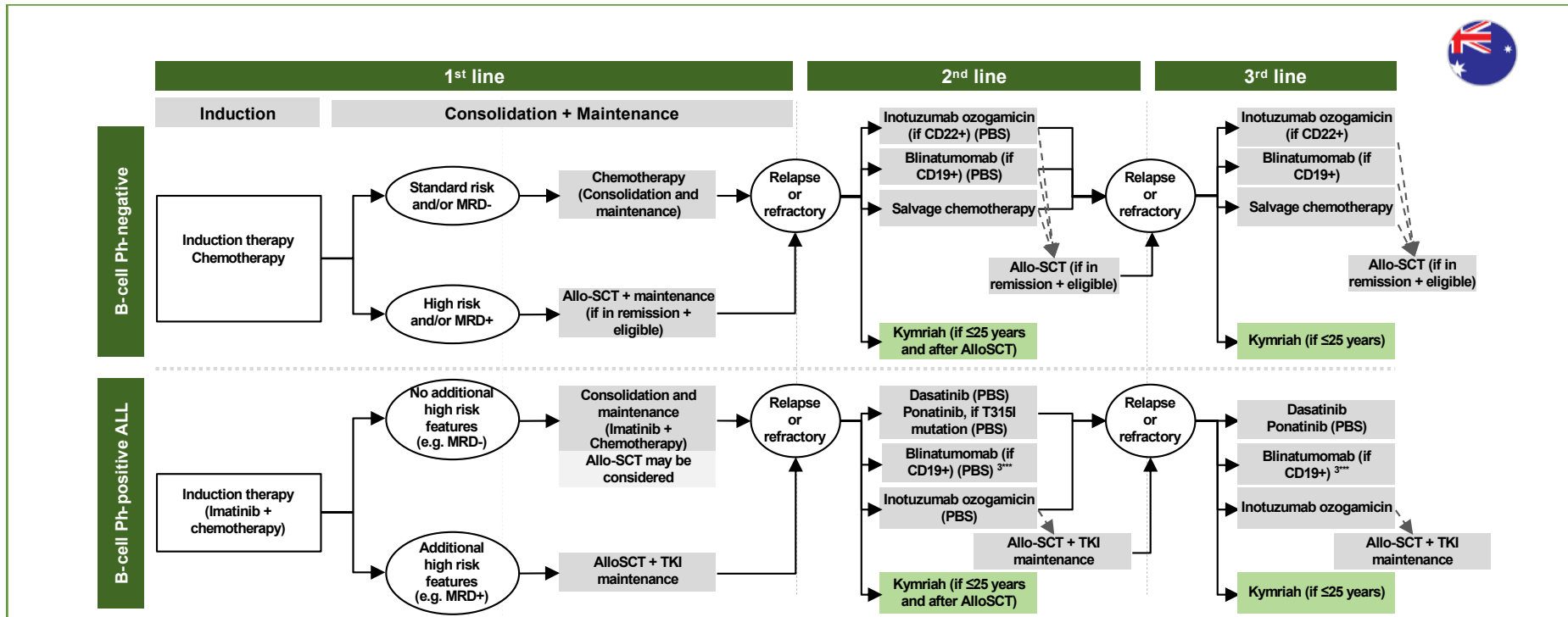
Ponatinib (ICLUSIG): Patient must be expressing the Philadelphia chromosome; OR must have the transcript BCR-ABL, and patient must have failed prior treatment with PBS-subsidised dasatinib for this condition; or patient must have developed intolerance to PBS-subsidised dasatinib of a severity requiring treatment withdrawal.

PBS Items: 11453T, 11454W

Tisagenlecleucel CAR T-cell: Tisagenlecleucel is a treatment option in patients aged 18 years up to 25 years of age with confirmed relapsed/refractory B-ALL disease.

Based on the treatment strategies above for adults with relapsed/refractory B-ALL which vary according to Ph status and prior treatment, the aim of treatment is to achieve CR/CRi and durable response with MRD negativity, which are generally associated with improved survival. Figure 2 shows the current treatment pathway.

Figure 2: Current treatment algorithm for relapsed/refractory B-ALL



Source: Treatment options have been based on literature review, guidelines PBS listings and National Health Reform Arrangements (NHRA) funding status for Kymriah, ***If the patient has not responded to prior treatments with at least two TKIs, and there are no alternative treatment options available

Abbreviations: ALL: Acute lymphoblastic leukaemia; allo-SCT: Allogeneic stem cell transplant; MRD+/-: Minimal residual disease positive/negative; Ph: Philadelphia chromosome; TKI: Tyrosine kinase inhibitor

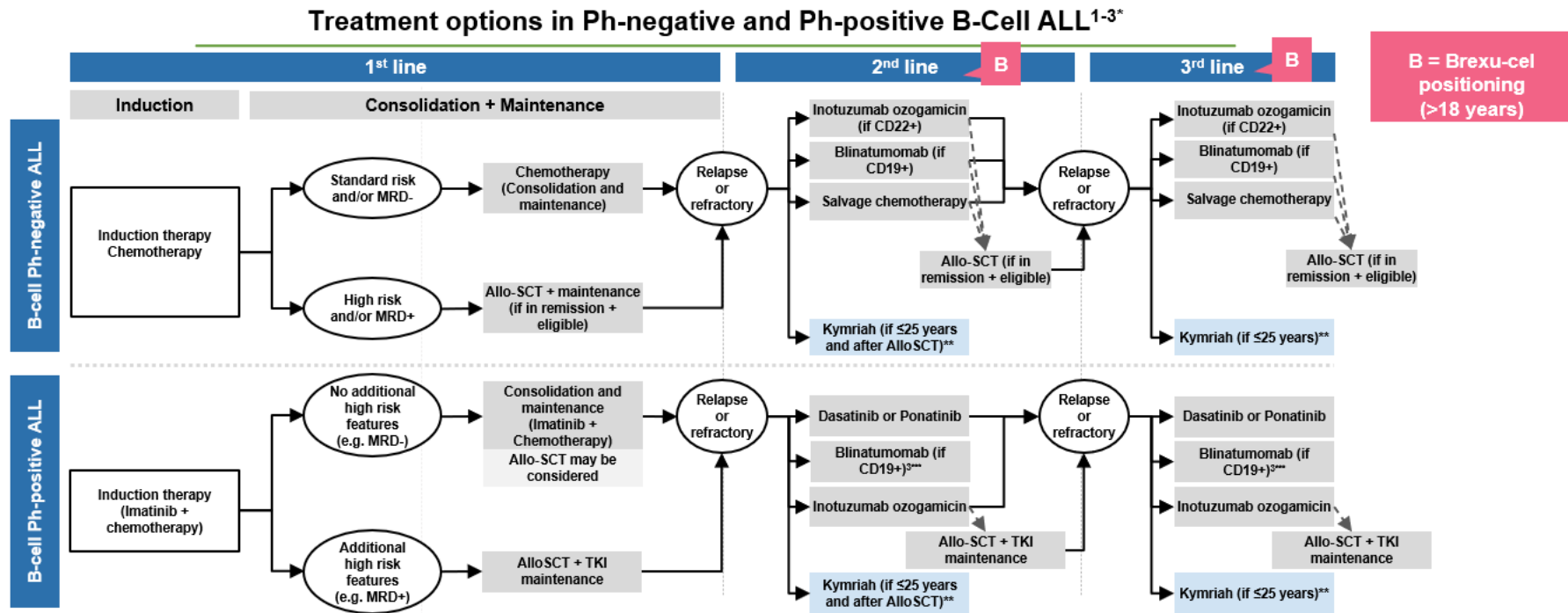
40. Define and summarise the PROPOSED clinical management pathway (algorithm) that patients would follow after the proposed service/technology is introduced, including variation in health care resources.

CAR-T cells: Brexucabtagene autoleucl will be available for adult patients (≥ 18 years of age) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (B-ALL). Relapsed or refractory disease is defined as one of the following:

- Primary refractory disease
- First relapse if remission was 12 months or less
- Relapsed or refractory after two or more lines of systemic therapy
- Relapsed or refractory after allogeneic stem-cell transplant

Brexucabtagene autoleucl for patients with relapsed or refractory B-ALL will represent a new treatment option, substituting salvage therapy or tisagenlecleucl (in patients 18 to ≤ 25 years) in the relapsed/refractory setting (second and third line) (Figure 3).

Figure 3: Proposed treatment algorithm for relapsed/refractory B-ALL



PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES

41. 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):

Brexucabtagene autoleucl is superior in terms of effectiveness in adult patients (≥ 18 years of age) with relapsed or refractory disease B-precursor acute lymphoblastic leukaemia (B-ALL).

In the pivotal ZUMA-3 study, the primary efficacy endpoint was met: the overall complete remission or complete remission with incomplete haematological recovery (CR+CRi) rate of 70.9% in the Phase 2 modified ITT (mITT) analysis set was significantly greater ($p < 0.0001$) than the prespecified historical control rate of 40% at a 1-sided alpha level of 0.025. The complete remission (CR) rate in the mITT analysis set was 56.4%. The overall MRD⁻ rate in the mITT analysis set was 76%, which was significantly greater ($p < 0.0001$) than the prespecified control rate of 30%; thus, the secondary efficacy endpoint was also met. Among subjects who achieved a CR or CRi, the MRD negative rate was 97%.

KM estimates of overall survival (OS) at 12 and 18 months were 71.4% (95% CI: 57.0%, 81.7%) and 58.6% (95% CI: 41.8%, 72.1%), respectively. The KM median OS was 18.2 months (95% CI: 15.9 months, NE). The KM median OS was not reached (95% CI: 16.2 months, NE) for subjects with CR or CRi and for subjects who were MRD⁻.

The safety profile was manageable. The most common adverse events of grade 3 or higher were anaemia (27 [49%] patients) and pyrexia (20 [36%] patients). A total of 14 (25%) patients had infections of grade 3 or higher. Two grade 5 brexucabtagene-related events occurred (brain herniation and septic shock). Cytokine release syndrome of grade 3 or higher occurred in 13 (24%) patients and neurological events of grade 3 or higher occurred in 14 (25%) patients.

42. Please state what the overall clinical claim is:

Brexucabtagene autoleucl is clinically superior to current standard of care in the treatment of adult patients with B-ALL in the second- and third- line settings with comparable safety profile.

43. List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator): - see also Error! Reference source not found. – Summary of Proposed PICO Criteria

Clinical Effectiveness Outcomes:

- Overall complete remission or complete remission with incomplete haematological recovery (CR+CRi) per central assessment
- Centralised minimal residual disease negativity (MRD⁻) rate
- Investigator-assessed rate of overall complete remission or complete remission with incomplete haematological recovery (CR+CRi)
- Duration of remission (DOR)
- Relapse-free survival with patients undergoing new anticancer therapies (including allo-SCT) censored
- Overall survival; and
- Allo-SCT rate

Safety Outcomes:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of AEs of special interest (cytopenia, cytokine release syndrome, neurotoxicity and infections)
- Incidence of anti-brexucabtagene autoleucl antibodies

Other outcomes:

- Patient-reported outcomes measured by EQ-5D-5L and visual analogue scale (VAS) scores

Exploratory outcomes:

- Levels of CAR-T cells in blood and cytokines in serum

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

44. Estimate the prevalence and/or incidence of the condition in the proposed population:

The age-standardised incidence of acute lymphoblastic leukaemia (ALL) in 2021 in Australia is expected to be 1.7 per 100,000 accounting for approximately 446 people expected to be diagnosed with ALL. The median age at diagnosis for ALL is 17 years old. The disease occurs with a bimodal age distribution, with 53.5% of patients diagnosed at younger than 20 years old and 29.6% of cases diagnosed in adult patients ≥ 45 years old and 13.7% of patients diagnosed at ≥ 65 years (NCCN 2021³). Precursor B-cell ALL (B-ALL) is the most common type in adults (Bassan et. al., 2019⁵) affecting 75%-80% of cases (Terwiliger et. al., 2017⁴; Leukaemia Foundation 2020⁶).

Age specific rates from the Australian Institute of Health and Welfare (AIHW)⁶ were used to estimate the incidence number of adult ALL patients (≥ 18 years of age). Linear regression was used to estimate the annual increase from Year 1 to Year 6. Estimating the number of patients eligible for each year is summarised below in the following steps:

1- Annual incidence of adult ALL (≥ 18 years of age) using incidence age specific rates of ALL

The AIHW reported incidence age-specific rates of ALL is applied to the projected Australian population for each year (2023-2027) (Table 2).

Table 2 Estimated total incidence of ALL patients

Data	Year 1 2023	Year 2 2024	Year 3 2025	Year 4 2026	Year 5 2027	Year 6 2028
Projected Australian population 18-19	645,805	664,569	690,252	707,559	713,570	721,487
ASR per 100,000 (15-19)	1.9	1.9	1.9	1.9	1.9	1.9
Cases	12	13	13	14	14	14
Projected Australian population 20-39	7,829,309	7,915,046	7,996,335	8,078,263	8,166,968	8,251,781
ASR rate per 100,000 (20-39)	0.7	0.7	0.7	0.7	0.7	0.7
Cases	55	56	57	58	59	60
Projected Australian population 40-59	6,575,634	6,654,924	6,750,810	6,854,290	6,959,407	7,064,759
ASR per 100,000 (40-59)	0.9	0.9	0.9	0.9	0.9	0.9
Cases	60	61	62	63	64	65
Projected Australian population 60-79	4,890,621	4,990,806	5,071,925	5,145,231	5,187,162	5,242,734
ASR per 100,000 (60-79)	1.4	1.4	1.4	1.4	1.4	1.4
Cases	69	70	72	73	74	75
Projected Australian population 80+	1,141,102	1,186,507	1,235,180	1,287,877	1,365,994	1,433,417
ASR per 100,000 (80+)	2.4	2.4	2.4	2.4	2.4	2.4
Cases	27	29	30	31	33	35
Total estimated adult ALL	224	229	234	239	244	249

Source: AIHW 2021

Abbreviations: ALL = acute lymphoblastic leukaemia; ASR = age specific rate

45. Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:

The proposed therapy involves the administration of a single infusion.

⁶ AIHW 2021 - <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-incidence-by-age-visualisation>

46. How many years would the proposed medical service/technology be required for the patient?

The proposed therapy involves the administration of a single infusion in a patient's lifetime.

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

The projected number of patients who will utilise Tecartus for relapsed/refractory B-ALL in the first year will be fully calculated in the application.

48. Estimate the anticipated uptake of the proposed medical service/technology 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.

The likely rate of uptake of brexucabtagene autoleucel in the population of patients with relapsed or refractory B-ALL after first-line treatment is currently unknown; however, Gilead plans to conduct market research to ascertain the likely uptake in this setting. A detailed analysis of likely extent of use of brexucabtagene autoleucel will be presented in the applicant-developed assessment report (ADAR) that will be lodged with MSAC.

The risk of use beyond the proposed population is low given that it is highly unlikely the product would be used in patients other than those for whom reimbursement is sought due to the strict eligibility criteria for funding CAR-T therapies.

PART 8 – COST INFORMATION

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

The cost of providing brexucabtagene autoleucl has not been determined at this point in time. Information regarding costs will be provided in the submission.

50. Specify how long the proposed medical service/technology typically takes to perform:

REDACTED

51. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and usage characteristics that defines eligibility for the medical service/technology.

N/A

52. If public funding is sought through an alternative (non-MBS) funding arrangement, please draft a service description to define the population and usage characteristics that defines eligibility for the service/technology.

N/A

PROPOSED PICO CRITERIA

Error! Reference source not found.3 summarises the proposed key components of the PICO criteria to be addressed in a submission that seeks to provide an answer to the fundamental research question of the use of:

Brexucabtagene autoleucl for the treatment of adult patients (≥ 18 years of age) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (B-ALL). Relapsed or refractory disease is defined as one of the following:

- Primary refractory
- First relapse if remission was 12 months or less
- Relapsed or refractory after two or more lines of systemic therapy
- Relapsed or refractory after allogeneic stem-cell transplant

Table 3: Summary of proposed PICO criteria

Component	Description
Population	Brexucabtagene autoleucl for the treatment of adult patients (≥ 18 years of age) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (B-ALL). Relapsed or refractory disease is defined as one of the following: <ul style="list-style-type: none"> • Primary refractory • First relapse if remission was 12 months or less • Relapsed or refractory after two or more lines of systemic therapy • Relapsed or refractory after allogeneic stem-cell transplant
Intervention	Brexucabtagene autoleucl
Comparator	The proposed comparators to be investigated are: <ol style="list-style-type: none"> 1- Salvage therapy in second and third line with the most relevant specific salvage therapies being blinatumomab or inotuzumab with the intention to proceed to allo-SCT); and the alternative comparator is conventional salvage chemotherapy with the intention to proceed to allo-SCT. 2- Dasatinib in second and third line, in patients with Ph1-positive ALL and <i>BCR-ABL</i> mutations. 3- Tisagenlecleucel in second and third line in eligible patients up to 25 years of age.
Outcomes	<p><u>Clinical Effectiveness:</u></p> <ul style="list-style-type: none"> • Objective response rate (ORR) and Complete response rate (CRR) • Duration of response • Health-related quality of life (HRQoL) in patients achieving and those not achieving response • Survival in responders and non-responders • Quality of life in responders and non-responders • Progression-free survival (PFS) • HRQoL in patients who are progression-free and those with progression • Overall survival • Quality adjusted survival <p><u>Clinical efficacy:</u></p> <ul style="list-style-type: none"> • Percentage of patients having brexucabtagene autoleucl infused of those who underwent leukapheresis • Time from collection (leukapheresis) to infusion of brexucabtagene autoleucl <p><u>Safety Outcomes:</u></p> <ul style="list-style-type: none"> • Incidence of adverse events (AEs) and serious adverse events (SAEs) • Incidence of events of special interest (e.g., cytokine release syndrome) <p><u>Cost-effectiveness:</u></p> <ul style="list-style-type: none"> • Healthcare resource use and associated costs (including pre- and post-infusion), presented in disaggregated and aggregated format • Incremental cost per life year gained (LYG) • Incremental cost per quality adjusted life year (QALY) <p><u>Financial implications:</u></p> <ul style="list-style-type: none"> • Number of patients suitable for treatment • Number of patients who receive treatment and associated financial implications

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