National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults [ID1494]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Gilead	Gilead anticipate that the marketing authorisation will be for the treatment of 'relapsed/refractory B-precursor acute lymphoblastic leukaemia', rather than 'previously treated B-precursor acute lymphoblastic leukaemia', and therefore propose a change to the wording to reflect this.	Thank you for your comments. The wording of the remit has been updated. Autologous anti-CD19-transduced CD3+ cells will be appraised for treating acute lymphoblastic leukaemia (ALL) within its marketing authorisation.
	Leukaemia Care	No comment.	No action required.

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Timing Issues	Gilead	Adult patients with relapsed/refractory ALL have very poor outcomes and survival. It is therefore important that patients have access to autologous anti-CD19-transduced CD3+ cells (henceforth Tecartus) at the earliest possible opportunity as Tecartus would be the first CAR-T therapy available for these patients.	Thank you for your comment. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. No action required.
	Leukaemia Care	We believe that this is an urgent appraisal. There is no CAR-T therapies available in adult populations at present, only paedatric settings. Yet adult ALL is an area of high unmet need, with patients being harder to treat with current treatment options.	Thank you for your comment. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. No action required.

Comment 2: the draft scope

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Background information	Gilead	Gilead agree with the information contained in the background section of the draft scope, with two suggested amendments: • '*In England, 666 people were diagnosed with ALL in 2017..*'. This number includes paediatric patients and therefore does not reflect the	Thank you for your comments. The background section has been updated to include

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		population under review. A clinical expert consulted by Gilead estimated that there are approximately 250 adult ALL cases per year (1). Of these, 17% are T-cell ALL and can be excluded on this basis. • In line with the response to comparators seen in the below 'Comparators' section, Gilead suggests the removal of FLAG-based chemotherapy as a treatment option for relapsed/refractory adult ALL, as well as the removal of imatinib and dasatinib as treatment options for Philadelphia-chromosome-positive relapsed/refractory adult ALL.	the incidence of acute lymphoblastic leukaemia (ALL) specifically in adults. Reference to the use of FLAG-based chemotherapy, imatinib and dasatinib in relapsed or refractory ALL has been retained in the background section, please see response to comment in "comparators" section.
	Leukaemia Care	The wording the TKIs "may also" be used for Philadelphia chromosome positive illness may not reflect the full extent of the use of TKIs in this group. Clinical guidelines, such as the ESMO 2016 guidelines, state that all Ph+ patients should be given a TKI with their chemotherapy upfront. This is important as this would influence the options in the relapsed/refractory setting.	Thank you for your comment. The wording in this section has been strengthened to reflect the use of tyrosine kinase inhibitors in people with Philadelphia-chromosome-positive acute lymphoblastic leukaemia.
The technology/ intervention	Gilead	The technology should be referred to as 'autologous anti-CD19-transduced CD3+ cells' (Tecartus)	Thank you for your comment. The

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			description of the technology and brand name have been updated throughout the scope.
	Leukaemia Care	No comment.	No action required.
Population	Gilead	No comment.	No action required.
	Leukaemia Care	No comment	No action required.
Comparators	Gilead	After consulting with clinical experts, Gilead propose the following changes to the comparator section, with rationale provided: • Removal of FLAG-based chemotherapy as a comparator • Removal of imatinib and dasatinib as a comparator in Philadelphia-chromosome-positive ALL • Removal of people who are unable to take chemotherapy <u>Philadelphia-chromosome-negative ALL:</u> • <u>Fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy</u> • FLAG-based combination chemotherapy is not typically used in the population under review. Clinical trials of both inotuzumab and blinatumomab demonstrated that these two therapies achieve better outcomes compared to FLAG-based chemotherapy, and so FLAG-based chemotherapy has been displaced in clinical practice. A clinical expert consulted by Gilead stated that he has not used FLAG-based	Thank you for your comments. This section has been updated to remove the wording “people who are unable to take chemotherapy”. The scope is intended to be broad, so as not to exclude potentially relevant comparators. Current clinical guidelines suggest that FLAG-based chemotherapy remains a treatment option for some adults with relapsed or refractory

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		chemotherapy in the population under review for at least three years, corresponding to the launch of more targeted therapies. Philadelphia-chromosome-positive ALL: • Imatinib or dasatinib alone or in combination with FLAG-based chemotherapy • FLAG-based chemotherapy has been covered in the above paragraph on Philadelphia-chromosome-negative ALL • Imatinib is used as the first-line tyrosine kinase inhibitor of choice in the UK for treatment of Philadelphia-chromosome-positive ALL. A Clinical expert explained to Gilead that it therefore has no place in the treatment pathway after first-line therapy has failed, as in the relapsed/refractory adult ALL patient population under review. • Dasatinib is not used in clinical practice for ALL in the UK due to lack of approval from NICE [ID1297], as confirmed by a clinical expert. The typical use of tyrosine kinase inhibitors was described as 'I*matinib is always given straight away as front-line treatment, patients who then relapse or are refractory may be offered ponatinib.'.* For people who are unable to take chemotherapy: • best supportive care (including palliative care) • People who are unable to tolerate chemotherapies or targeted treatments would not be eligible for CAR-T, and so this patient population is not in scope.	ALL. Imatinib, dasatinib and ponatinib are also recommended in clinical guidelines for relapsed or refractory Philadelphia-chromosome-positive ALL, with the choice of tyrosine kinase inhibitor depending on a person's previous treatment and T315I gene mutation status. Therefore, FLAG-based chemotherapy, imatinib and dasatinib have been retained as comparators in the scope.
	Leukaemia Care	We believe the comparators are appropriate in light of all current guidelines for adult ALL. Both imatinib and dasatinib are relevant, depending on which may have been used first line, the other then may be an option in relapsed.	Thank you for your comments. No action required.

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		However, it may need to be quantified as to which is more common under which circumstances.	
Outcomes	Gilead	Please note that while relapse-free survival and treatment response rate will be considered as outcomes of interest in the clinical sections of the submission we do not anticipate they will play a prominent role in the CE model. The CE model will primarily be informed by the key clinical efficacy measures of overall survival and event-free survival.	Thank you for your comments. No action required.
	Leukaemia Care	No comment.	No action required.
Economic analysis	Gilead	No comment.	No action required.
	Leukaemia Care	No comment.	No action required.
Equality	Gilead	We do not envisage any equality issues arising from the proposed remit and scope.	Thank you for your comment. No action required.
	Leukaemia Care	We are keen to address the inequity between access to CAR-T therapies by age. We would like to avoid further potential discrimination by restriction on age in this appraisal.	Thank you for your comment. This appraisal will consider the technology for treating acute lymphoblastic leukaemia (ALL) within its marketing authorisation and depending on the

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			evidence presented to the committee.
Other considerations	Gilead	No comment.	No action required.
	Leukaemia Care	No comment.	No action required.
Innovation	Gilead	Tecartus is a personalised medicine in which the patient's own T cells are collected and engineered ex-vivo to express a chimeric antigen receptor (CAR) which programmes them to target and kill the cancer cells when they are returned to the patient in a single infusion. This CD19-directed genetically modified autologous T cell immunotherapy is a breakthrough treatment offering a potentially curative treatment option for patients with an extremely poor life expectancy. We believe Tecartus will be associated with significant-health related benefits and represent a step-change in treatment for this heavily pre-treated patient population. Our submission will be supported by upcoming data from: • The ZUMA-3 trial • RWE on current treatment patterns and outcomes	Thank you for your comments. The appraisal committee will consider the innovative nature of this technology during the appraisal. No action required.
	Leukaemia Care	No comment.	No action required.
Questions for consultation	Gilead	*Q. Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory B-precursor acute lymphoblastic leukaemia? In particular:* *Is clofarabine-based chemotherapy a relevant comparator?* A. A Clinical expert consulted by Gilead explained that clofarabine-based chemotherapy is not used in clinical practice in the UK for the population	Thank you for your comments. No action required.

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		under review, and that it had never been used or approved in the adult relapsed/refractory ALL setting. Established clinical practice for relapsed or refractory B-precursor acute lymphoblastic leukaemia is aligned to the NICE ALL pathway, consisting of: 1. Blinatumomab – in Philadelphia-chromosome negative patients only 2. Inotuzumab 3. Ponatinib – in Philadelphia-chromosome-positive patients only 4. Tisagenlecleucel – in patients ≤25 years of age (currently being assessed under the Cancer Drugs Fund) *Q: Are there any subgroups of people in whom KTE-X19 is expected to be more clinically effective and cost effective or other groups that should be examined separately?* A: No subgroups are proposed at this stage *Q: Where do you consider KTE-X19 will fit into the existing NICE pathway Blood and bone marrow cancers?* A: Gilead consider that Tecartus would fit into the existing NICE pathway as another treatment option for treating relapsed or refractory acute lymphoblastic leukaemia. Q: *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* A: There are CAR-T products currently available to patients in the UK, across several indications. Therefore, it is not anticipated that there will be any barriers to adoption of this technology into practice	

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	Leukaemia Care	No comment.	No action required.