The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE:** following a full submission considered under the ultra-orphan and end of life process

tisagenlecleucel (Kymriah®) is accepted for use within NHSScotland.

**Indication under review:** treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

Tisagenlecleucel was associated with an overall remission rate of 81% within three months of treatment in a single-arm, open-label, phase II study in paediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL.

SMC advice takes account of the benefit of Patient Access Schemes (PAS) that improve the cost effectiveness of tisagenlecleucel and is contingent upon the continuing availability of this PAS in NHSScotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium
**Indication**

The treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.¹

**Dosing Information**

Tisagenlecleucel is intended for autologous use only. Tisagenlecleucel is to be administered via intravenous infusion.

A single dose of tisagenlecleucel contains:

- for patients 50kg and below: 0.2 to 5 x 10⁶ CAR [chimeric antigen receptor] positive viable T cells/kg body weight.
- for patients above 50kg: 0.1 to 2.5 x 10⁸ CAR positive viable T cells (non-weight based).

Lymphodepleting chemotherapy is recommended to be administered before tisagenlecleucel infusion unless the white blood cell count within one week prior to infusion is ≤1,000 cells/microlitre. The recommended lymphodepleting chemotherapy regimen is fludarabine (30mg/m² intravenously for four days) and cyclophosphamide (500mg/m² intravenously for two days starting with the first dose of fludarabine). It is recommended that tisagenlecleucel is infused two to 14 days after completion of the lymphodepleting chemotherapy. The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting regimen.

To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol and diphenhydramine (or another H1 antihistamine) approximately 30 to 60 minutes before tisagenlecleucel infusion.

Tisagenlecleucel must be administered in a qualified treatment centre, and should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with tisagenlecleucel. A minimum of four doses of tocilizumab for use in the event of cytokine release syndrome and emergency equipment must be available prior to infusion.

Please refer to the summary of product characteristics (SPC) for further information.¹
Product availability date
December 2018

Tisagenlecleucel was designated an orphan medicinal product for the treatment of B-lymphoblastic leukaemia/lymphoma on 29 April 2014 (EU/3/14/1266). It also meets SMC ultra-orphan and end of life criteria for this indication.

Background

Tisagenlecleucel is an advanced therapy medicinal product (ATMP). It is a chimeric antigen receptor (CAR-T) therapy, manufactured by taking patient’s own T-cells which are genetically engineered ex vivo to express a receptor targeting CD19. Cells are then re-infused as a single intravenous infusion back into the patient, where they can recognise and eliminate CD19 expressing target cells.\(^1,2\)

Tisagenlecleucel for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

B-cell ALL is a rare, chronically debilitating and life-threatening type of blood cancer with around 60% of cases occurring in patients under 20 years old.\(^2\) Cure rates are related to the age of the patient and can be 80% to 90% in children.\(^3\) For patients who have relapsed or refractory B-cell ALL, there is no standard treatment approach and outcomes are poor.\(^1,2\) Treatment options are limited for these patients and include: salvage chemotherapy (potentially with fludarabine- and anthracycline-containing regimens or clofarabine-based regimens); subsequent allogeneic stem cell transplant (SCT) if appropriate; targeted treatment with small molecule pathway inhibitors (blinatumomab has recently been licensed for use in children with relapsed/refractory ALL); enrolment in clinical trials; or palliative care.\(^2,3\) Median overall survival has previously been reported as 7.5 months in paediatric patients with relapsed or refractory ALL.\(^4\) Tisagenlecleucel was the first CAR-T therapy to be approved by the European Medicines Agency (EMA) for the treatment of relapsed or refractory B-cell ALL in children and young adults and is considered by the EMA to be a major therapeutic innovation.\(^2\) Tisagenlecleucel meets SMC ultra-orphan and end of life criteria.

Clinical experts consulted by SMC considered that tisagenlecleucel may fill an unmet need in this therapeutic area, as outcomes are poor and treatment options are very limited in children and young adults with relapsed or refractory ALL.
A patient and clinician engagement (PACE) meeting was held to consider the added value of tisagenlecleucel in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the extremely poor prognosis and the very limited treatment options for patients with refractory or relapsed ALL. A diagnosis of ALL can have a huge emotional, physical and financial impact on both the patient and their families. Symptoms may include fatigue, chest pain, infections, weight loss, pain and sleeping problems. These can affect patients’ mobility and ability to care for themselves and cause significant disruptions to education or work and social life. Significant time is required for caring for the patient which can also have financial implications. For children, young adults and their families, refractory or relapsed ALL can be a very difficult diagnosis to come to terms with. Feelings of fear, isolation, anxiety and depression may occur.

**Impact of new technology**

**Summary of evidence on comparative efficacy**

Key evidence for the use of tisagenlecleucel for this indication comes from the pivotal ELIANA study. This is an open-label, single-arm, multicentre, phase II study that recruited paediatric and young adult patients (aged three years at the time of screening to ≤21 years at initial diagnosis) with CD19+ relapsed or refractory B-cell ALL. Study patients had refractory disease, either primary refractory or chemorefractory; or second or greater bone marrow relapse; or any bone marrow relapse after allogeneic stem cell transplantation (SCT). Patients with Philadelphia chromosome positive (Ph+) ALL were eligible if intolerant to or failed two lines of tyrosine kinase inhibitor therapy (TKI), or if TKI therapy is contraindicated. Patients who were ineligible for allogeneic SCT could also be included in the study. For relapsed patients, CD19 expression was to be demonstrated in bone marrow or peripheral blood within three months of study entry. Eligible patients had a, Karnofsky or Lansky performance status of at least 50, and bone marrow with at least 5% lymphoblasts by morphologic assessment at screening.\(^5\)

Patient’s white blood cells were collected by leukapheresis, cryopreserved and transported to the manufacturing facility where tisagenlecleucel was manufactured through a process that involved enriching for and activating the T-cells, transduction with a retroviral vector containing the CAR gene construct and expanding ex vivo for approximately 10 days. The product was concentrated and then cryopreserved before undergoing final testing and was then transferred back to the clinical area. The investigator decided if patients were also to receive bridging chemotherapy. Lymphodepleting chemotherapy was administered 2 to 14 days prior to tisagenlecleucel infusion, unless their white blood cell count was \(\leq 1,000\) cells/microlitre within the previous week. The lymphodepleting regimen comprised fludarabine (30mg/m\(^2\) intravenously daily for four doses) and cyclophosphamide (500mg/m\(^2\) intravenously daily for two doses starting with the first dose of fludarabine). A single
intravenous infusion of tisagenlecleucel was given at the maximum dose within the range that could be manufactured: target dose range of 2.0 to 5.0×10⁶ tisagenlecleucel cells per kg body weight for patients ≤50 kg and of 1.0 to 2.5×10⁸ tisagenlecleucel cells per kg for patients >50 kg. Patients were given premedication with paracetamol and diphenhydramine or an H1 antihistamine every six hours as needed. Of the 92 patients enrolled, 75 received tisagenlecleucel. The reasons for not receiving tisagenlecleucel were: tisagenlecleucel product-related issues in seven patients; seven patients died; and three patients had adverse events.

The primary outcome was overall remission rate defined as complete remission or complete remission with incomplete haematologic recovery within 3 months post-infusion and maintained for at least 28 days. This was assessed by independent review committee in the full analysis set which included all patients who received tisagenlecleucel. At a median duration of follow up of 13.1 months (cut-off date 25 April 2017), the overall remission rate was 81% (61/75) (95% confidence interval [CI]: 71 to 89). Forty-five patients (60%) had complete remission and 16 patients (21%) had complete remission with incomplete haematologic recovery. No relationship between dose and expansion was observed and clinical responses were observed across the entire dose range. All patients who had a best response of complete remission or complete remission with incomplete haematologic recovery had undetectable minimal residual disease (<0.01%), as assessed by central multiparameter flow cytometry.

Duration of remission was defined as the time from the date of achievement of overall remission to the date of relapse or death due to underlying cancer. At the 25 April 2017 cut off, 28% (17/61) of the patients in overall remission had relapsed prior to receiving additional anticancer therapy; the median duration of remission was not reached.

Event-free survival was defined as the time from infusion to an event including no response, relapse before response maintained for ≥28 days or relapse after response. At the 25 April 2017 cut off, 36% (27/75) of patients had had an event; the median event-free survival had not been reached. The probability of event-free survival was 73% at 6 months and 50% at 12 months. Eight patients had an allogeneic SCT while they were in remission. At the same data cut off, 25% (19/75) of patients had died. The probability of overall survival was 90% at 6 months and 76% at 12 months.

Patient reported outcomes were assessed using the paediatric quality of life inventory (PedsQL) instrument and EQ-5D questionnaire in patients aged ≥8 years (n=58). In the patients who responded, a clinically meaningful improvement from baseline was shown at each time point post-tisagenlecleucel infusion.

Supportive data come from two studies, ENSIGN and B2101J.
ENSIGN is an open-label, single-arm, multicentre, phase II study of tisagenlecleucel in paediatric and young adult patients with relapsed or refractory B-cell ALL. Patient eligibility criteria were broadly similar to the ELIANA study, however patients with active CNS leukaemia (defined as CNS3) were permitted in ENSIGN. Following lymphodepletion with fludarabine and cyclophosphamide, a single dose of tisagenlecleucel was administered. The primary endpoint, overall remission rate within six months, was 69% (29/42). Complete remission was achieved by 64% of patients and complete remission with incomplete haematologic recovery was achieved by 4.8% of patients; 64% had minimal residual disease-negative bone marrow. The median duration of remission was not reached. Estimated relapse-free survival at 12 months was 61%. Median overall survival was 23.8 months.

B2101J is an ongoing open-label, single-arm, single-centre, phase I/II study of tisagenlecleucel in 56 paediatric and young adult patients with CD19+ B-cell malignancies with no available curative treatment options (such as autologous or allogeneic SCT) who had limited prognosis (several months to less than two years survival) with currently available therapies. Tisagenlecleucel was given according to a dose escalation protocol of up to three infusions with a wider target dose range the ELIANA and ENSIGN studies. The primary endpoint was safety but overall remission rate at day 28 after tisagenlecleucel infusion was included as a secondary endpoint. At the latest data cut off (30 January 2017), the overall remission rate was 95% (53/56). Response with minimal residual disease-negative bone marrow was achieved by 86%. Estimated median duration of response was 33.4 months, median event-free survival was 28.8 months and median overall survival was 37.9 months.

Other data were also assessed but remain confidential.*

Summary of evidence on comparative safety
Safety data are published for the 75 patients who had received tisagenlecleucel by the 25 April 2017 data cut off in the single arm ELIANA study. No comparative safety data are available.

The majority of adverse events occurred within eight weeks of infusion. All patients had at least one adverse event and 95% (71/75) of patients had an adverse event that was suspected to be related to tisagenlecleucel. Adverse events of grade 3 or 4 in severity were experienced by 88% of patients, of which the adverse event was suspected to be related to tisagenlecleucel in 73%.

Adverse events of special interest included cytokine release syndrome (77%), infections (43%), neurologic events (40%), cytopenias not resolved by day 28 (37%), febrile neutropaenia (35%) and tumour lysis syndrome (4.0%). During the study, 37% (28/75) of patients received tociluzumab for the management of cytokine release syndrome.
Summary of clinical effectiveness issues
The primary outcome of the pivotal ELIANA study identified an overall remission rate of 81% within 3 months of tisagenlecleucel treatment which was considerably higher than the historical control rate of 20%. The company suggest that tisagenlecleucel is a potentially curative treatment.

The studies were all of single-arm design therefore no comparative data are available. The EMA notes that the response rate observed in the ELIANA study ‘considerably exceeds the response rates observed with clofarabine, blinatumomab or a combination therapy of clofarabine, cyclophosphamide and etoposide in a similar patient population’. No phase III studies are available. The studies were all open-label and survival data are immature for the pivotal study. During the pivotal study, 87% of patients received bridging chemotherapy but the EMA did not expect this to have significantly affected the results.

Cytokine release syndrome was reported by the majority of patients in the included studies. Neurological events were also common. The SPC specifies that at least four doses of tocilizumab and emergency equipment must be available on-site for each patient for the management of cytokine release syndrome. Longer term safety data are also awaited.

The submitting company presented the results of a matching adjusted indirect comparison (MAIC) of pooled data from the ELIANA, ENSIGN and B2101J studies for tisagenlecleucel with either blinatumomab or clofarabine (considered a proxy for salvage chemotherapy) in patients up to 25 years old with relapsed or refractory ALL. For the outcomes included, overall survival and overall remission rate, hazard ratios suggest that tisagenlecleucel may be superior to the comparators. The MAIC was associated with a number of limitations and was not used for the economic base case, but was included as part of a scenario analysis. There were some differences in the included studies that could not be matched, length of follow-up was different and no safety or patient reported quality of life outcomes were reported.

Clinical experts consulted by SMC considered that tisagenlecleucel is a therapeutic advancement due to it being a novel treatment option for the population of paediatric and young adult patients with relapsed or refractory B-cell ALL for whom outcomes are poor and unmet need is high.

At the PACE meeting, it was noted that tisagenlecleucel could potentially be a life-extending treatment option for some patients. There are significant toxicities associated with tisagenlecleucel but in patients that respond this treatment may offer disease remission and associated patient wellbeing. This could reduce the emotional burden and improve overall quality of life. The potential to achieve durable response or longer term cure would be
extremely valuable for patients. As this is a young group of patients, for each individual that has a long term remission there could be many potential years of life gained.

**Patient and clinician engagement**

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of tisagenlecleucel as an ultra-orphan and end of life medicine in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. A diagnosis of ALL can have a huge emotional, physical and financial impact on both the patient and their families. Refractory or relapsed ALL is a devastating disease with significant symptoms and an extremely poor prognosis. Five-year survival has been estimated at 10%.

- There is very high unmet need in these patients as there are limited treatment options and no standard treatment. Alternative treatments include intensive chemotherapy, blinatumumab or inotuzumab ozogamicin and potentially stem cell transplant for appropriate patients. These are associated with significant adverse events and are time intensive for patients. However, despite these treatments, the outlook remains poor.

- Tisagenlecleucel offers a new treatment approach. In patients who respond, this treatment may be life-extending. Although long-term outcomes are not yet known, as this is a young group of patients, long term remission could potentially lead to many years of life gained.

- Patients who respond may be able to resume work, education, self-care and social activities. For patients and their families, the emotional and financial burden associated with this life-threatening illness could be reduced.

- Tisagenlecleucel would need to be delivered by appropriately trained medical and nursing teams in a unit with access to intensive care. There is a requirement for an inpatient hospital stay and a high risk of potentially serious adverse events. However, patients may be willing to accept these for the chance of a potential cure for their blood cancer.

**Additional Patient and Carer Involvement**

We received patient group submissions from Leukaemia CARE and Bloodwise, both organisations are registered charities. Leukaemia CARE has received 12.6% pharmaceutical company funding in the past two years, including from the submitting company. Bloodwise has received 0.9% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Leukaemia CARE participated in the PACE
meeting. The key points of the submissions from both organisations have been included in the full PACE statement considered by SMC.

**Value for money**

The company submitted a cost-utility analysis which compared tisagenlecleucel against salvage chemotherapy and blinatumomab in the licenced indication. Salvage chemotherapy was assumed to reflect fludarabine, cytarabine and idarubicin (FLA-IDA). SMC expert responses suggested salvage chemotherapy may be the primary comparator in the analysis with some potential displacement of blinatumomab.

A cohort-based partitioned survival model was used to assess the cost-effectiveness of tisagenlecleucel versus the comparators. In terms of model structure, the model consisted of three health states event-free survival (EFS), relapsed/progressed disease (PD) and death. Patients were redistributed across the three health states throughout the analysis at each model cycle according to whether patients remain in a given health state or progress to a worse health. The economic analysis also included a decision tree which was applied before entry to the partitioned survival model in the tisagenlecleucel arm only. The decision tree included three outcomes which reflected different events which may occur in the early stages of treatment. The three outcomes were: successfully receive infusion with tisagenlecleucel (and proceed to the partitioned survival model for tisagenlecleucel), do not receive tisagenlecleucel due to manufacturing failure or adverse event (therefore discontinue treatment and revert to comparator therapies), and death before tisagenlecleucel infusion. For patients who withdrew from tisagenlecleucel and switched to comparator therapies in the decision tree, the model assumed a 50/50 split of blinatumomab and salvage chemotherapy and assigned the costs and QALYs associated with each treatment to these patients. The time horizon used in the analysis was 88 years.

Clinical data used in the economic model included a pooled analysis of the ELIANA, ENSIGN and B2101J studies which informed estimates of EFS and OS for tisagenlecleucel. Published studies were used to estimate OS for blinatumomab and salvage therapy, thus meaning that a naïve indirect comparison was used as the basis of the estimation of clinical outcomes in the economic model. In order to extrapolate the available data for tisagenlecleucel over the duration of the time horizon the economic analysis applied mixture cure modelling to the observed data. Mixture cure models take into account a proportion of the population treated with the intervention that can be considered “cured” (also referred to as the “cured” fraction). The cured fraction also reflected the proportion of patients who were assumed to follow mortality of the general population. For tisagenlecleucel the analysis used a generalised gamma mixture cure model for EFS and an exponential mixture cure model for OS. Mixture cure modelling was also employed in the blinatumomab arm for OS with the lognormal mixture cure model used to extrapolate OS outcomes. When modelling OS for salvage chemotherapy, a different approach was used whereby the company applied a standard generalised gamma function up to 5 years with an assumption that for patients who survived beyond 5 years, the risk of death switched to general population estimates. An adjustment to the general population mortality estimates (a standardised mortality ratio;
SMR) based on the published literature to reflect an increased risk of death for long term survivors was also applied.

EFS for blinatumomab and salvage therapy was modelled by using a published study of mitoxantrone in children with ALL to estimate a relationship between OS and EFS and apply this ratio to the OS estimates for each treatment. This method was used in the model for the first 5 years after which the EFS curve was assumed to flatten and the risk of events assumed to be similar to that used in the modelling of OS.

It is also worth noting the EFS and OS data described above for tisagenlecleucel and the comparators were unadjusted and taken directly from the studies. The company provided a MAIC which was not used in the base case economic model however has been used in sensitivity analysis. Outcomes for salvage chemotherapy were also based on a study of clofarabine monotherapy which was used as a proxy within the analysis.

Utility values were taken from a published study and estimates for the EFS and PD health states were 0.91 and 0.75 respectively. The model assumed patients still alive at 5 years were effectively cured and therefore these patients would be assigned the EFS utility value irrespective of health state or treatment. A range of other utilities were also considered in the analysis such as a disutilities associated with adverse events, grade 3 or 4 CRS (ICU stay), ICU stays not associated with CRS and age related utility decrements (to take into account the patient population becoming older over time). The economic model also allowed patients to receive allogeneic-SCT as a subsequent treatment and a disutility associated with allogeneic-SCT was included in the analysis.

Costs included pre-treatment costs for tisagenlecleucel (leukapheresis, bridging chemotherapy and lymphodepleting chemotherapy), medicine acquisition costs for all comparators, and associated administration costs. Associated hospitalisation and ICU costs, adverse event, subsequent allogeneic-SCT, follow-up and monitoring and terminal care costs were also included in the economic model. CRS costs were applied to tisagenlecleucel and blinatumomab only while a cost related to B-cell aplasia was also included in the tisagenlecleucel arm of the analysis. Specifically, the CRS cost included an ICU admission and treatment with tocilizumab. The cost of B-cell aplasia reflected treatment with intravenous immunoglobulin (IVIG) applied to a proportion of paediatric patients for a duration 11.4 months. For patients aged 18-25, the IVIG cost was applied to 20% of patients with hypoammaglobulinaemia for a duration of 9 months.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. A PAS is in place for the comparator blinatumomab and this was included in the results used for decision-making by the SMC by using an estimate of the PAS price of blinatumomab.

The base case results and selected sensitivity analysis versus salvage chemotherapy are presented in the table below
Table 1: base case results and selected sensitivity analysis versus salvage chemotherapy (with PAS for tisagenlecleucel)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Salvage chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>£25,238</td>
</tr>
<tr>
<td>10 year time horizon</td>
<td>£70,045</td>
</tr>
<tr>
<td>20 year time horizon</td>
<td>£42,652</td>
</tr>
<tr>
<td>Generalised gamma mixture cure model OS for tisagenlecleucel</td>
<td>£43,678</td>
</tr>
<tr>
<td>Use standard parametric functions for all treatments with cure assumption 5 years</td>
<td>£30,664</td>
</tr>
<tr>
<td>Use standard parametric functions for all treatments with cure assumption 5 years – exponential function for OS</td>
<td>£42,183</td>
</tr>
<tr>
<td>SMR from a different published source</td>
<td>£33,171</td>
</tr>
<tr>
<td>SMR adjustment applied to cured patients in mixture cure modelling</td>
<td>£29,806</td>
</tr>
<tr>
<td>Use the MAIC: standard parametric functions for all treatments with cure assumption 5 years</td>
<td>£28,188</td>
</tr>
<tr>
<td>Patients alive at 5 years assigned 90% of the EFS health state utility, combined with using Weibull mixture cure model for tisagenlecleucel EFS</td>
<td>£27,474</td>
</tr>
<tr>
<td>100% tisagenlecleucel patients are attributed the tisagenlecleucel EFS</td>
<td>£30,340</td>
</tr>
<tr>
<td>EFS and PD monitoring and follow-up costs doubled for tisagenlecleucel</td>
<td>£25,971</td>
</tr>
</tbody>
</table>

For the comparison versus blinatumomab, SMC would wish to present the results which take account of the PAS for blinatumomab and the PAS for tisagenlecleucel as these results informed the SMC decision. Alternatively, SMC would wish to present results using the list price for tisagenlecleucel and blinatumomab. However owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish either set of results.

The main weaknesses were

- The economic analysis reflected a naïve indirect comparison. The company provided a MAIC which was used in sensitivity analysis; however the MAIC has a number of weaknesses. Both the base case analysis and the MAIC used proxy data to model the efficacy of salvage chemotherapy.
- In terms of estimating EFS and OS, there is a degree of variation in outcomes depending on the mixture cure model selected and a number of curves may be a similar fit to the observed data. The company’s justification for selecting the appropriate mixture cure model is based on assumption and may be considered speculative at times. An alternative approach to mixture cure modelling would be to use standard parametric functions (potentially supplemented with a 5 year cure
point) and the standard curves report a wide range of EFS and OS outcomes depending on the function estimated. The company has subsequently provided a sensitivity analysis which used a generalised gamma mixture cure model for tisagenlecleucel OS, and a separate analysis which used a standard exponential function for tisagenlecleucel OS up to five years, with a switch to general population mortality estimates (plus the SMR adjustment). The results are available in Table 1 above.

- An excess mortality estimate was applied in the salvage chemotherapy arm to the general population mortality estimates for cured patients. It did not appear the same adjustment was included for tisagenlecleucel. However the company provided a sensitivity analysis which included an excess mortality adjustment in the tisagenlecleucel arm of the analysis (i.e. applied the SMR) and the results are available in Table 1 above.
- The model assumed patients still alive at 5 years were effectively cured and these patients would be assigned the relatively high EFS utility value of 0.91 irrespective of health state or treatment. However the company subsequently provided a sensitivity analysis where patients alive at 5 years were assigned 90% of the EFS health state utility, combined with using a Weibull mixture cure model for tisagenlecleucel EFS (see Table 1 for results).

*Other data were also assessed but remain confidential.*

**Impact beyond direct health benefits and on specialist services**

Tisagenlecleucel is administered as a single infusion but daily monitoring is necessary, possibly in hospital, for 10 days following infusion. Thereafter, monitoring is at the physician’s discretion but patients should remain close to a qualified clinical facility for four weeks after the infusion. At PACE, it was reported that a single infusion, versus several rounds of treatment involved in chemotherapy, may be preferable to patients. Additionally patients and their families may be willing to accept the inconvenience of an inpatient hospital stay and the need to remain close to the hospital for a period after the infusion, if there was an opportunity of recovery from ALL.

Clinical experts considered that the introduction of this medicine would impact on the service due to specialist requirements for manufacture, administration and monitoring, however patient numbers are expected to be low. Specialist services and suitably trained staff would be required for collection, storage and transport of patients’ lymphocytes. Tisagenlecleucel would be manufactured in a specialist laboratory. Administration must be carried out in a hospital with appropriate facilities and specialist staff who have clinical expertise in this area including critical care bed capacity for managing potential adverse
events. The introduction of tisagenlecleucel would require additional consultant and medical support, specialist nursing, pharmacy and laboratory staffing.

The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

Patients with ongoing disease remission may be able to resume work, education, self-care and social activities as they should be free of leukaemia-associated symptoms. This could reduce their emotional and financial burden. Improvements in a patient’s condition and prognosis will also have a wider impact on the lives of their family and friends. If a patient responded to treatment there would likely be reduced emotional strain, less caring responsibilities for family members and also reduced financial burden as they may be able to return to work.

Costs to NHS and Personal Social Services

The submitting company estimated the population eligible for treatment to be 3 patients in all years. Based on an estimated uptake of 40% in year 1 and 80% in year 5 this resulted in 1 patient estimated as treated in year 1 rising to 2 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

The submitting company did not estimate any costs outside the NHS.

*Other data were also assessed but remain confidential.*

Conclusion

The Committee considered the benefits of tisagenlecleucel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as tisagenlecleucel is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted tisagenlecleucel for use in NHS Scotland.
There is no guidance specific to paediatric and young adult patients with acute B-cell ALL. Guidance was published in 2016 on behalf of the European Society for Medical Oncology: Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. It notes that there is no universally accepted treatment protocol for relapsed/refractory ALL and that the overall clinical situation should be considered. Treatment with a curative aim involves achievement of complete remission with chemotherapy followed by allogeneic SCT. The guideline notes that the most commonly used chemotherapy regimens in Europe are fludarabine- and anthracycline-containing regimens, for example, FLAG-IDA (fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor and idarubicin) or clofarabine-based regimens, the latter based mostly on data in childhood ALL. Novel agents may be considered including blinatumomab and inotuzumab or a clinical trial involving immunotherapy with CD19 CAR T-cell therapy. The guideline predates the approval of tisagenlecleucel.

Salvage chemotherapy (potentially followed by allogeneic SCT), blinatumomab or palliative therapies.

**Cost of relevant comparators**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tisagenlecleucel</td>
<td>Single dose intravenous infusion. Patients ≤50kg: 0.2 to 5 x 10⁶ CAR positive viable T cells/kg body weight. Patients &gt;50kg: 0.1 to 2.5 x 10⁸ CAR positive viable T cells (non-weight based).</td>
<td><strong>282,000</strong></td>
</tr>
<tr>
<td>blinatumomab</td>
<td>Continuous IV infusion Patients ≥45kg: Cycle 1</td>
<td>Cycle 1: 48,408</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subsequent cycles: 56,476</td>
</tr>
</tbody>
</table>
Days 1 to 7: 9 micrograms/day  
Days 8 to 28: 28 micrograms/day  
Subsequent cycles (Day 1 to 28): 28 micrograms/day

| clofarabine | 52 mg/m$^2$ of body surface area administered by intravenous infusion daily for 5 consecutive days, repeated every 2 to 6 weeks | 8,819 to 30,237 |

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from submitting company for tisagenlecleucel, BNF online for clofarabine and blinatumomab on 31 October 2018. Blinatumomab has not been assessed by SMC for use in children. Costs for blinatumomab are based on dosing for patients ≥45kg, costs may be lower for children <45kg. Costs for clofarabine are based on one treatment cycle and body surface area range 0.49 to 1.8. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.*
References

This assessment is based on data submitted by the applicant company up to and including 15 November 2018.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence
of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.