Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2351

autologous anti-CD19-transduced CD3+ cells (KTE-X19) 0.4 to 2 × 10^8 cells dispersion for infusion (Tecartus®)*

Kite, a Gilead company

09 July 2021

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 assessed under the orphan and end of life process

autologous anti-CD19-transduced CD3+ cells (KTE-X19) (Tecartus®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

In a single-arm, open-label, phase II study in patients with relapsed or refractory MCL, autologous anti-CD19-transduced CD3+ cells (KTE-X19) (Tecartus®) improved overall response rate compared with historical controls.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ 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 adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.[1]

Dosing Information

Tecartus® is intended for intravenous autologous use only. A single dose of Tecartus® contains 2×10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), or maximum of 2×10^8 CAR-positive viable T cells for patients 100kg and above in approximately 68mL dispersion in an infusion bag. Tecartus® should be infused 3 to 14 days after completion of the lymphodepleting chemotherapy. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen. Details of the lymphodepleting regimen and pre-medication are provided in the summary of product characteristics (SPC).

Tecartus® must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus®. At least one dose of tocilizumab for use in the event of cytokine release syndrome and emergency equipment must be available prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of cytokine release syndrome and/or neurologic events. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus®.[1]

Product availability date

December 2020
Tecartus® meets SMC end of life and orphan criteria in this indication.
Tecartus® has conditional marketing authorisation from the European Medicines Agency (EMA).

Summary of evidence on comparative efficacy

Tecartus® is an advanced therapy medicinal product (ATMP) that comprises autologous T-cells genetically modified with an anti-CD19 chimeric antigen receptor (CAR). After the anti-CD19 CAR T-cells bind to CD19 on cancer cells and normal B cells, the CD28 and CD3-zeta domains activate

signalling cascades that lead to T-cell activation and proliferation. This results in death of CD19-expressing cells.[1] To manufacture Tecartus® a patient undergoes leukapheresis to provide T-cells that are genetically engineered to express an anti-CD19 CAR before being returned to the patient.

An ongoing, open-label, single-arm, phase II study (ZUMA-2) has recruited 74 adults with MCL characterised by cyclin D1 overexpression or translocation of t(11;14) whose disease was relapsed or refractory after up to five previous regimens including an anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody and a BTK inhibitor. All patients had leukapheresis to obtain T cells to manufacture Tecartus®. After conditioning chemotherapy (fludarabine 30mg/m^2 plus cyclophosphamide 500mg/m^2 intravenous (IV) on Day -5, -4 and -3), 68 eligible patients received Tecartus® 2x10^6 CAR-T cells/kg as a single IV infusion on Day 0.

The primary outcome was objective response rate (ORR), defined as a complete response (CR) or partial response (PR) according to Lugano classification assessed by an independent radiological review committee (IRRC). The primary analysis was conducted after the first 60 recipients of Tecartus® had been evaluated for response 6 months after their week 4 disease assessment (inferential analysis set [IAS]). This was supported by analyses in all patients who underwent leukapheresis (full analysis set [FAS]; n=74), with the European Medicines Agency (EMA) review focusing on analyses in the FAS. The primary analysis compared ORR in the IAS to a historical control rate of 25%.[2,3]

The results at the data cut-off for the primary analysis (24 July 2019), after median follow-up of 12.3 months, and an updated analysis (data cut-off 31 December 2019) are detailed in Table 1.[2,3]

Table 1: Best objective response in ZUMA-2 study.[2,3]

	Inferential Analysis Set (N=60) Cut-off 24 July 2019		**Full Analysis Set (N=74) Cut-off 31 December 2019**	
	Events	**% (95% CI)**	**Events**	**% (95% CI)**
Overall response	56	93% (84% to 98%)	62	84% (73% to 91%)
Complete response	40	67% (53% to 78%)	44	59% (47% to 71%)
Partial response	16	27% (16% to 40%)	18	24% (15% to 36%)
Stable disease	2	3.3% (0.4 to 12%)	3	4.0% (0.8% to 11%)
Progressive disease	2	3.3% (0.4 to 12%)	2	2.7% (0.3% to 9.4%)
Not evaluable			1	1.4% (0.0% to 7.3%)
Not done			6	8.1% (3.0% to 17%)

Overall response rate (ORR) = complete response or partial response. Response assessed centrally using Lugano classification. CI = confidence interval.

Secondary outcomes included duration of response in patients with CR or PR; progression-free survival (PFS) defined as the time to disease progression or death from any cause; with overall survival defined as the time to death from any cause. The latter two outcomes were measured from the time of Tecartus® infusion in the IAS and from the time of leukapheresis in the FAS. At the latest data cut-off (31 December 2019), median results had not been reached for any of these outcomes, except PFS in the FAS, as detailed in Table 2 below.[2-5]

Table 2: Secondary Outcomes in ZUMA-2 study at data cut-off December 2019.[2-5]

	Inferential Analysis set (N=60)	Full Analysis Set (N=74)
Duration of Response (central assessment Lugano classification)		
Median duration of follow-up (months)	14.1	13.8
Patients with response	55	62
DOR events	21	24
Median DOR (95% CI)*, months	NR (13.6; NE)	NR (10.4, NE)
Event-free at 18 months*	59%	56%
Progression Free Survival (central assessment Lugano classification)		
PFS events	24	33
Median PFS (95% CI)*, months	NR (9.6; NE)	16.2 (9.9; NE)
PFS at 24 months*	55%	49%
Overall survival		
Deaths	16	23
Median overall survival (95% CI)*, months	NR (NE; NE)	NR (24.6; NE)
Overall survival at 24 months*	69%	66%

DOR = duration of response; DOR events = death or disease progression; PFS = progression free survival; CI = confidence intervals; NR = not reached; NE = not evaluable; * based on Kaplan-Meier estimate.

Health-related quality of life was assessed using the European Quality of Life 5-dimension questionnaire (EQ-5D-5L), which was completed at screening and every post-treatment visit. Results indicate that there were a number of patients who had reductions in quality of life measures, including mobility, self-care, usual activity, pain/discomfort, anxiety/depression and overall health, which was assessed on a 100-point visual analogue scale (VAS). The number of patients with deterioration in quality of life decreased with time. For example, for EQ-5D VAS, a deterioration from baseline of at least 10 points was noted for 50% (26/52), 29% (16/55) and 12% (5/42) of patients at week 4, month 3 and month 6, respectively.[3]

Supportive evidence is provided by a second cohort of the ZUMA-2 study, which comprised 14 patients who received an unlicensed dose of Tecartus® $0.5x10^6$ CAR-T cells/kg IV infusion. There were 13 patients who achieved an ORR, 93% (95% CI: 66% to 99.8%), with 9 patients having a CR, 64% (95% CI: 35% to 87%). After a median follow-up of 11.3 months, median duration of response was not reached and 8 patients had an ongoing response. After median potential follow-up of 16 months, median PFS and overall survival were not reached and the 12-month estimate of PFS was 78% and of overall survival was 79%.[2]

To support the economic analysis, there was a naïve indirect comparison of Tecartus® versus 'standard of care' in patients with relapsed or refractory MCL previously treated with a BTK inhibitor using the outcomes of overall survival and PFS. It included data from patients in the FAS of ZUMA-2 who received Tecartus® (the modified intention to treat [mITT] population; n=68) and results of a meta-analysis of four single-arm, retrospective studies of treatments used as standard of care: Martin 2016 (mixed treatments),[6] Jain 2018 (mixed treatments),[7] Eyre 2019 (venetoclax)[8] and McCulloch 2020 (rituximab, bendamustine and cytarabine; R-BAC)[9]. Results were applied to the economic analysis.

Summary of evidence on comparative safety

The EMA review concluded that Tecartus® is associated with a high incidence of adverse events and a clinically relevant proportion are of at least grade 3 severity and/or serious.

In the ZUMA-2 study all 68 patients in the FAS who received Tecartus® at the licensed dose had an adverse event, which were of at least grade 3 severity in 99% (67/68) and serious in 71% (48/68) of patients. These were treatment-related for 97%, 79% and 54%, respectively.[2,3] All 14 patients in the cohort that received the unlicensed dose (0.5×10^6 CAR-T cells) had an adverse event, which were of at least grade 3 severity in 93% (13/14) and serious in 57% (8/14). These were treatment-related for 100%, 71% and 50%, respectively.[2]

In patients who received the licensed dose of Tecartus® (n=68) common adverse events included neutropenia (87%; grade ≥3 in 85%), thrombocytopenia (74%; grade ≥3 in 51%) and anaemia (68%; grade ≥3 in 50%). Cytokine release syndrome was reported by 91% of patients, but the severity grade was ≥3 in 15% of patients. The most common symptoms of cytokine release syndrome were pyrexia (91%), hypotension (51%), hypoxemia (34%), chills (31%), tachycardia (24%) and headache (22%). Neurologic adverse events occurred in 63% (43/68) of patients and were at least grade 3 severity in 31% of patients. These included tremor (35%), encephalopathy (31%), confusional state (21%) and aphasia (15%). Infections developed in 56% (38/68) of patients, with 32% at least grade 3 severity. The most common were upper respiratory tract infections (13%) and pneumonia (10%). Hypogammaglobulinaemia was reported by 19% of patients.[3] A similar profile of adverse events was observed in the 14 patients who received the unlicensed dose of Tecartus®. The EMA noted that there are no significant dose dependent differences with respect to adverse events in the two cohorts.[2] Two patients had grade 5 (fatal) adverse events: one had organising pneumonia related to conditioning chemotherapy and one had staphylococcal bacteraemia related to conditioning chemotherapy and Tecartus®.[3]

Summary of clinical effectiveness issues

Mantle cell lymphoma is a rare, aggressive and generally incurable subtype of B-cell non-Hodgkin lymphoma that is often characterised by the chromosomal translocation t(11;14)(q13;q32), which results in overexpression of the cell cycle regulator cyclin D1. Most cases of MCL are usually sensitive to initial chemotherapy, but relapsed disease can become increasingly resistant to chemotherapy.[2] The 2018 British Society for Haematology (BSH) guideline for the management of MCL notes that there is no standard therapeutic approach at relapse. An individualised approach should be adopted based on age, co-morbidities, performance status, and response and toxicity with prior therapy. For patients with second or higher relapse, it recommends immuno-chemotherapy, which differs from that given previously, a BTK inhibitor or other targeted therapy.[10] For patients who have relapsed after a BTK inhibitor, there are limited treatment options and there is an unmet need for more effective therapies.[2]

Key strengths

- Tecartus® is the first CAR T-cell therapy licensed for the treatment of relapsed or refractory MCL after failure of a BTK inhibitor.
- At the latest follow-up in the ZUMA-2 study within the IAS and FAS (licensed dose) populations the ORR were 92% and 84%, respectively, with 67% and 59% of patients achieving a CR. These were greater than a historical control rate of 25% and clinically meaningful.
- Median PFS in the FAS was 16.2 months. Data on secondary outcomes, duration of response and overall survival are supportive, but are immature.[2,3]

Key uncertainties

- ZUMA-2 is a single arm study with no control arm, making assessment of relative efficacy highly uncertain.
- The relevant comparator in patients with relapsed or refractory MCL after BTK inhibitor is not well defined.
- The EMA had concerns that there was heterogeneity amongst the studies used to support the ORR of 25% for historical controls and that the populations may not be representative of the ZUMA-2 study patients, who may be fitter than historical controls and contain a higher proportion who could be eligible for allogeneic stem cell transplant. This uncertainty supported the decision to issue a conditional marketing authorisation with a requirement to generate further clinical data.[2]
- In the naïve indirect comparison of Tecartus® versus 'standard of care', there were similar uncertainties around the comparator in relation to Scottish practice. Also, there were differences across the studies in design, baseline characteristics, maturity of data, measurement of outcomes and sample size, with some of the studies having limited number of patients.[2,3,6-9] The indirect comparison did not include safety or health related quality of life outcomes and ORR results were not applied to the economic analysis.
- The ZUMA-2 study was open-label and uncontrolled which limits the assessment of subjective outcomes such as quality of life and safety. The number of evaluated patients was low and there were limited data in some subgroups such as female, elderly and more severely diseased patients. Also, long-term data were not available to evaluate sustained responses.[2]
- In the ZUMA-2 study, 62% of treated patients were refractory to BTK inhibitor.[2,3] In practice, fewer patients who receive Tecartus® may be refractory to BTK inhibitor. In the ZUMA-2 study, 81% of treated patients had received at least three prior lines of therapy.[2,3] In practice, if Tecartus® was used after BTK inhibitor at second-line then patients may be less heavily pre-treated.
- The study population may be younger and fitter than the 'average' patient with MCL in NHSScotland. However, it is expected that in practice, Tecartus® would be used in slightly younger patients, specifically those free of significant co-morbidities and end-organ dysfunction.

The introduction of Tecartus® may be associated with service implications as it is administered in a Bone Marrow Transplant Unit and is associated with a prolonged period of monitoring. Patients

should be monitored daily for the first 10 days post-infusion for signs and symptoms of potential cytokine release syndrome, neurologic events and other toxicities. Physicians should consider hospitalisation for this period or at the first signs of cytokine release syndrome and/or neurologic events. Subsequently the patient should be monitored at the physician's discretion, but should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.[1]

Tecartus® has an EMA conditional marketing authorisation. To confirm the long-term efficacy and safety and the benefit/risk balance in female, elderly and severely diseased patients, the marketing authorisation holder is required to submit results of a prospective study based on data from a registry according to an agreed protocol to the EMA (Due: 30 September 2025).[2]

To confirm the long-term efficacy and safety of Tecartus® the marketing authorisation holder is required to submit 24-month follow-up data from all patients in cohort 1 of the ZUMA-2 study to the EMA (Due: 31 March 2022).[2]

The additional data provided through the EMA specific obligations may address some of current uncertainties in the clinical evidence, such as age at initiation of Tecartus® treatment, PFS, overall survival and quality of life.

SMC will consider an updated submission from the company after specific obligations and conditions of the licence have been removed. In the interim, Tecartus® is accepted for use in NHSScotland subject to ongoing evaluation and future reassessment.

Clinical experts consulted by SMC advised that Tecartus® in the treatment of relapsed or refractory MCL is a therapeutic advance due to its efficacy and potential for sustained complete responses ('cure'). They consider that it would be used in accordance with the product licence, that is in patients who have failed treatment with a BTK inhibitor. They note that it may be associated with service implications as patients are treated within specialist Bone Marrow Transplant Units with limited capacity.

*Other data were also assessed but remain confidential.***

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of autologous anti-CD19-transduced CD3+ cells (Tecartus), as an end of life and orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Relapsed mantle cell lymphoma is generally an incurable disease, with several disabling symptoms. Treatment options are limited, often poorly tolerated and at best produce short remissions for the majority of patients.

- Tecartus has a novel (non-chemotherapy) mechanism of action and it has induced remission in a high proportion of patients (including those refractory to all previous treatment lines). At 12 months the number of patients progression-free and alive after Tecartus is increased compared with immuno-chemotherapies. The magnitude of benefit represents a significant advance in the treatment of this patient group. Long-term data are awaited, but the data available suggest that Tecartus may provide durable remissions and for some patients it might be curative.
- Tecartus is given as a single infusion with total treatment period of about 4 to 6 weeks, which is shorter than immuno-chemotherapy regimens and allogeneic stem cell transplant.
- Patients see Tecartus as a beneficial and a potentially life-saving therapy. Having access would provide hope and reassurance that they are receiving the optimum treatment for their condition.
- Tecartus is administered in accredited units. Within Scotland there is established clinical experience of using CAR-T cell therapies.
- Patients receiving Tecartus are required to stay close to the treatment centre for the first month after treatment. Patients are generally happy to live in accommodation nearer the treatment centre to achieve the potential benefits from Tecartus.

Additional Patient and Carer Involvement
We received a patient group submission from Lymphoma Action, which is a registered charity. Lymphoma Action has received 12.7% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of Tecartus® compared to standard of care for the treatment of relapsed or refractory MCL after two or more lines of systemic therapy including a BTK inhibitor. Standard of care (SoC) post ibrutinib was assumed to be a limited mixture of chemotherapy options consisting of rituximab, bendamustine and cytarabine (R-BAC) (65% of patients), R-bendamustine (30% of patients), and rituximab, cyclophosphamide, doxorubicin, vincristine plus prednisolone (R-CHOP) (5% of patients), based on clinical expert opinion in England received as part of the National Institute for Health and Care Excellence (NICE) appraisal and stated to have been verified by NHS Scotland clinicians. SMC clinical experts have indicated that SoC is not clearly defined, but is likely to include the therapies in the SoC comparator.

The economic analysis used a partitioned survival model with three health states (pre-progression, post-progression and death). The model had a one month cycle and a lifetime horizon of 50 years, with a mean starting age of patients of 63 years. The clinical data for Tecartus® were from the single arm ZUMA-2 clinical study in 68 patients in the modified intention to treat (mITT) population.[2,3] These data were used to estimate PFS and overall survival outcomes, which were extrapolated over the lifetime horizon using a mixture cure survival model in the base case, with a log-normal parametric function fitted to the observed Kaplan-Meier data. In this model, a

proportion of Tecartus® patients were estimated to be long term survivors for both the PFS and overall survival curves, with a separate cure fraction estimated using logistic regression for the proportion of patients surviving in the pre-progression state (for PFS) or surviving overall (for OS). PFS and overall survival was extrapolated for non-long term survivors applying parametric functions to the observed ZUMA-2 data. Long term survivors were assumed to achieve age and gender-matched general population mortality adjusted by a standardised mortality rate (SMR) of 1.09, based on a study of excess mortality in newly diagnosed diffuse large B-cell lymphoma (DLBCL) patients who were responders to chemotherapy and event free at 24 months.[13] The relative effectiveness of Tecartus® was based on a naïve indirect treatment comparison with PFS and overall survival of SoC based on a meta-analysis of four published studies, two for PFS and all four for overall survival[6-9] and extrapolated fitting a log-normal function in the base case.

Utility values were applied by health state and assumed the same across both treatment arms. Utility values for PFS were based on analysis of EQ-5D-5L data captured in the ZUMA-2 study, which was the main evidence base for Tecartus®, with the EQ-5D-3L utilities mapped to the EQ-5D-3L using the van Hout et al. (2012)[14] crosswalk algorithm. The pre-progression utility for SoC was assumed the same as Tecartus®. A separate age-matched general population utility value was assumed for long term survivors (0.797). Post progression utility was based on published estimates used in a prior NICE technology appraisal for ibrutinib in relapsed or refractory MCL (TA502)[15] with the pre and post progression ratio applied to the ZUMA-2 pre-progression utility estimate to derive a post progression utility in the model. Adverse event data for the Tecartus® arm were derived from ZUMA-2 to capture costs and disutilities associated with cytokine release syndrome, grade 3/4 hypogammaglobulinanaemia and other grade 3/4 adverse events, and B-cell aplasia in particular. A disutility was applied for R-chemo toxicity for the SoC arm. A utility decrement was applied to the SoC comparator arm based on a previous NICE technology appraisal of ibrutinib in RR MCL (TA502).[15]

Tecartus® is a one-time administration hence acquisition costs are assumed to be fully incurred in cycle one of the economic model. Treatment related costs for Tecartus® included leukapheresis, post leukapheresis bridging therapy, conditioning chemotherapy, and Tecartus® infusion and hospital inpatient monitoring. The medicine acquisition and administration costs for the SoC mix of chemotherapies was estimated assuming administration on an outpatient basis and assuming 6 cycles of treatment, with costs allowing for the different cycle lengths of the medicines included. The lowest MIMS cost was used for each therapy.

In addition, pre- and post-progression healthcare resource use costs were based on a survey of clinicians performed as part of NICE technology appraisal TA502[15] of ibrutinib in relapsed or refractory MCL, supplemented with NHS Scotland clinical opinion. Long term survivors were assumed to only incur the cost of a regular GP visit, based on clinical expert opinion from Scotland and England. AE costs were applied in cycle one of the model, with an additional assumption based on ZUMA-2 data and expert clinical opinion that 67% of Tecartus® patients would require prophylactic intravenous immunoglobulin (IVIG) therapy over a 1 year period for the management of hypogammaglobulinanaemia. Further, costs of intensive care unit hospitalisations and use of a cytokine inhibitor (tocilizumab) by a proportion of patients based on ZUMA-2 data, were included in the economic analysis. Unit costs were sourced from publicly available sources, aligned with

SMC guidance. Subsequent allogenic stem cell transplant (allo-SCT) was assumed to have been received by a proportion of Tecartus® patients based on ZUMA-2, and 20% of SoC patients based on feedback from clinicians from England, assumed to apply to Scottish clinical practice. Unit costs of allo-SCT were based on 2018-19 NHS reference costs. Terminal care costs were included based on a published source.

A complex Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of Tecartus®.

In the base case for Tecartus® versus SoC, the incremental cost-effectiveness ratio (ICER) is estimated at £49,711/quality-adjusted life-year (QALY) (at PAS price) (Table 3). These results were based on higher life years and QALYs and incremental costs for Tecartus®.

Table 3: Base case results (with PAS)

Analysis	ICER (cost/ QALY)
Tecartus® versus SoC	£49,711

SoC = standard of care, ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years. * Not discounted

Results of key sensitivity analyses are shown below (Table 4). The ICER was sensitive to a number of parameters including the time horizon, age, and the proportion, utility, and SMR of long-term survivors. However, the ICER had lower sensitivity to a range of other scenarios including: alternative overall survival extrapolation approaches and fitting of different parametric functions to the data; alternative data sources for overall survival estimation for SoC; shorter time point for long term survival assumed; proportion and duration of IVIG received; proportion of SoC patients receiving subsequent allo-SCT; and alternative utility estimates for pre-progression (Table 4).

Table 4: Key scenario analysis results Tecartus versus SoC (with PAS)

Scenarios presented within submission:		ICER with PAS
1.	Time horizon 20 years	£54,540
2.	Fitting parametric functions to the ZUMA-2 PFS and OS data generalised gamma (i.e. not applying mixture cure model)	£52,966
3.	Proportion of patients receiving subsequent allo-SCT with SoC range [30% - 15%] [Base case = 20%)	£48,679 - £50,226
4.	Utility for long term survivors – multiplier of 0.92 applied	£52,433
5.	Mean start treatment age of patients: 68, 73 years (base case = 63 years]	£59,769 - £75,805
6.	Lower proportion of long term survivors assumed	£53,058 - £63,494
7.	Long term survivor timepoint, OS: 8 years (base case = 5 years)	£51,663
8.	SMR of long-term survivors	£55,951
Combined scenarios requested by SMC:		
9.	Combined SMR of 1.58 and 0.92 age adjusted general population utility multiplier applied to long term survivors	£58,936
10.	SMR 1.58 and utility multiplier 0.92 + higher baseline age: 68 years	£72,392
11.	SMR 1.58 and utility multiplier 0.92 + higher allo-SCT cost of £100,000	£56,567
12.	SMR 1.58 and utility multiplier 0.92 + prop. allo-SCT, SoC, 15%	£59,552
13.	SMR 1.58 and utility multiplier 0.92 + retreatment with Tecartus for proportion observed in ZUMA-2*	£59,011 - £60,998

14.	Scenarios 9 to 13 combined*	£71,171 - £73,640
15.	Scenario 14 with 20-year time horizon*	£72,777 - £75,306

allo-SCT, allogeneic stem cell transplant; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival; QALY, quality-adjusted life year; SMR, standardised mortality ratio; SoC, standard of care; *range presented includes a confidential assumption regarding retreatment patterns.

The economic analysis was associated with a number of limitations and uncertainties:

- The patients in ZUMA-2 could be younger than those with relapsed or refractory MCL in Scotland as described in the clinical effectiveness issues section above. The mean age of 63 has been used in the economic model based on ZUMA-2, but scenario analysis was requested applying a higher mean age of 68 and 73 years which increased the ICER (see Table 4, Scenario 5).
- The time horizon of 50 years reflects the potential "cure" element associated with CAR-T therapy for some patients. However, with a starting age of 63 in the economic analysis (which could be higher in practice) a 50 year horizon is too long. The scenario with a 20 year time horizon increases the ICER to £54,540/QALY (Table 4, Scenario 1); the relevance of this analysis is dependent on the starting age of patients within NHSScotland.
- The long-term outcomes associated with Tecartus® are uncertain, including the proportion of patients estimated to be long term survivors, the timepoint for long term survival, the SMR for long term survivors and the utility assumed for these patients. It is likely that the SMR based on newly diagnosed DLBCL is too low to reflect the excess mortality for long term survivors with relapsed or refractory MCL – a higher SMR of 1.58 increased the ICER to £55,951/QALY with PAS (Table 4, Scenario 8). Due to a lack and immaturity of clinical data there is high uncertainty over the durability of benefit for Tecartus®. Scenario analysis has been provided by the company to explore the impact of less optimistic long-term survivor assumptions with regards to long term treatment benefit, mortality and HRQoL impact (Table 4, Scenarios 4, 6 - 8).
- The approach to estimating cure fractions relies upon separate long-term survivor fractions for the PFS and overall survival analyses, with a higher proportion of patients assumed to be long-term survivors (and therefore cured) in the latter. In terms of modelling overall survival, this creates a face validity issue where a proportion of patients whose disease had progressed are still assumed to be long-term survivors and no longer at risk of death due to MCL. The use of lower proportions of long-term survivors results in a significant increase in the ICER (Table 4, Scenario 6).
- The age adjusted general population utility estimate associated with long term survivors is likely to be too high for relapsed or refractory MCL. A multiplier of 0.92 applied to this utility increased the ICER to £52,433/QALY (Table 4, Scenario 4), which may be a more realistic estimate of HRQoL impact. A requested scenario analysis combining a higher SMR of 1.58 and utility multiplier of 0.92 to general population utility for long term survivors increased the ICER to £58,936/QALY (Table 4, Scenario 9).
- No retreatment with Tecartus® is assumed despite a proportion of patients in ZUMA-2 receiving a second treatment. The impact of incorporating potential re-treatment for a proportion of patients was explored in requested scenario analysis from the company,

although this did not individually have a large impact on the ICER (not shown). However, this analysis was sensitive to a confidential assumption that may otherwise result in greater increases in the ICER, and was included in combined analyses (Table 4, Scenarios 13 – 15).

- The company assumed that subsequent allo-SCT after Tecartus would be required in a proportion of patients, based on the same proportion receiving this in the ZUMA-2 mITT population compared to 20% assumed for SoC patients. However, allo-SCT is associated with a high cost and this may be underestimated in the economic analysis based on the NHS reference costs used. The company was requested to vary the percentage of Tecartus patients who may get subsequent allo-SCT, and use a higher estimate for the cost of allo-SCT. Alternative estimates of the cost of allo-SCT, and proportion of patients requiring allo-SCT, were included in a number of combined analyses (Table 4, Scenarios 11, 14, 15).

Overall, the limitations highlight a number of uncertainties in the evidence that, when the use of a plausible combination of alternative estimates are used, results in a significant increase in the ICER. The majority of these uncertainties relate to evidence gaps that could be addressed through further data collection. The Committee also considered the benefits of Tecartus® in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was demonstrated. In addition, as Tecartus® 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 Tecartus® for use in NHS Scotland, subject to ongoing evaluation and future reassessment.

Additional information: guidelines and protocols

In 2018 the British Society for Haematology (BSH) published a 'Guideline for the management of mantle cell lymphoma'. This notes that there is no standard therapeutic approach at relapse. An individualised approach should be adopted based on age, co-morbidities, performance status, and response and toxicity with prior therapy. For patients with second or higher relapse, the guideline recommends an immuno-chemotherapy, which differs from that given previously, a BTK inhibitor or other targeted therapy.[10]

In 2017 the European Society for Medical Oncology (ESMO) published 'Newly diagnosed and relapsed mantle cell lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up'. This notes that a repeated biopsy is recommended to identify important prognostic features of MCL. Selection of salvage treatment depends on efficacy of prior regimens. For patients with second of higher relapse, the guideline recommends targeted therapies such as ibrutinib, lenalidomide, temsirolimus and bortezomib (preferably in combination with chemotherapy) or alternatively, repeat previous therapy for those with long remissions.[16]

Additional information: comparators

In practice, Tecartus® may be used in place of other therapies currently used for patients with relapsed or refractory MCL post-BTK inhibitor, such as immuno-chemotherapies.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Tecartus®	2 x 10^6 CAR-T cells intravenous infusion	£316,118

Costs from new product assessment form (NPAF). Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 8 patients eligible for treatment with Tecartus® in each year. Confidential estimates of treatment uptake were applied to these figures.

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.

*Other data were also assessed but remain confidential.***

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This assessment is based on data submitted by the applicant company up to and including 14 May 2021.

** Kite, a Gilead company, advised on 6 July 2021 that the International Nonproprietary Name for autologous anti-CD19-transduced CD3+ cells (KTE-X19) 0.4 to 2 × 10^8 cells dispersion for infusion (Tecartus®) has not yet been approved for use in Europe.*

***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.