National Institute for Health and Care Excellence

Health Technology Evaluation

Tabelecleucel for treating post-transplant lymphoproliferative disorder caused by the Epstein-Barr virus [ID1203]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Anthony Nolan	Tabelecleucel is an off-the-shelf, allogeneic T-cell immunotherapy for the treatment of EBV+ malignancies and diseases. Epstein–Barr virus (EBV) related Post-transplant lymphoproliferative disease (PTLD) is a relatively rare but well-known complication for some allogeneic stem cell transplant patients. Front-line management of PTLD in HSCT patients following diagnosis and classification, typically begins with Reduction in Immunosuppression (RIS), followed by sequential treatment with rituximab and subsequently by CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy in adult B-cell PTLD[1]. HSCT patients present the highest risk to developing EBV-related PTLD in the first 3 months following Day 0 infusion of an unrelated donor graft.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.

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		EBV-PTLD develops in fewer than 1% of recipients without risk factors, but in more than 10% of those with several risk factors. PTLD after allo-HSCT is almost exclusively EBV positive, although rare cases of EBV-negative PTLD are reported[2]. For patients who fail to respond to rituximab, this population can range around 20%[3]. Following a poor response to rituximab, Tabelecleucel could offer an alternative therapy to the current standard of care such as multiple cycles of CHOP. Whilst the affected population is limited and the current protocols largely effective, any treatments which demonstrate improved clinical outcomes or improved quality of life with treatment tolerance should be evaluated. **References** 1. Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol. 2012;13(2):196–206. 2. Liu L, Liu Q, Feng S. Management of Epstein-Barr virus-related post-transplant lymphoproliferative disorder after allogeneic hematopoietic stem cell transplantation. Ther Adv Hematol. 2020 Apr 28;11:2040620720910964. 3. Zhu CY, Zhao SS, Wang XK, Wang L, Wang FY, Fang S, Liu ZX, Guan LX, Liu YC, Ding Y, Dou LP, Wang LL, Gao CJ. Outcome of Rituximab-Based Treatment for Post-Transplant Lymphoproliferative Disorder After Allogeneic Hematopoietic Stem Cell Transplantation: A Single-Center Experience. Ann Transplant. 2019 Apr 3;24:175-184.	
	Pierre Fabre	Whilst Pierre Fabre Limited agrees that it is appropriate to refer [redacted](tabelecleucel, abbreviated to tab-cel) to NICE for appraisal we strongly	Thank you for your comments. The routing

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		believe tab-cel fulfils all the entry criteria for consideration via the Highly Specialised Technology (HST) programme. In summary: • Epstein-Barr virus positive post-transplant lymphoproliferative disorder (EBV+ PTLD) is a rare type of lymphoma that may occur after a solid organ transplant (SOT) or haematopoietic stem cell transplantation (HSCT) in patients who are severely immunocompromised. • EBV+ PTLD is classed as an **ultra-rare** disorder affecting an estimated 12-20 SOT patients and 9-14 HSCT patients per year in the UK.[1-4] • Across all six potential future indications the total population eligible for treatment in the UK would likely be no greater than 250 to 300 patients.[5] In England, the number of patients is likely to be lower. • EBV+ PTLD can have life-threatening consequences and overall mortality is approximately 50%.[6] • There are currently no licensed treatments indicated for EBV+ PTLD. Current treatment includes rituximab either as a single agent (monotherapy) or as part of a drug regimen (immunochemotherapy) however, not all patients respond to treatment. • In clinical studies tab-cel has demonstrated significant improvements in overall survival (OS) in EBV+ PTLD patients after SOT (after failure of rituximab or rituximab with chemotherapy), and for EBV+ PTLD patients after HSCT (after failure of rituximab).[7] Further information for all the HST criteria is provided in the Section 'Questions for consultation'. **References**	of this topic was discussed by the topic selection oversight panel and the decision was to assess this topic as a single technology appraisal (STA).

Section	Stakeholder	Comments [sic]	Action
		1. Dierickx D, Longo DL, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. N Eng J Med. 2018;378(6):549-562. 2. Opelz G, Döhler B. Impact of HLA mismatching on incidence of posttransplant non-Hodgkin lymphoma after kidney transplantation. Transplantation. 2010;89(5):567-572. 3. Lowery EM, Adams W, Grim SA, Clark NM, Edwards L, Layden JE. Increased risk of PTLD in lung transplant recipients with cystic fibrosis. J Cyst Fibros. 2017;16(6):727-734. 4. Pierre Fabre Limited, MA001 data on file. June 2022. 5. Pierre Fabre Limited, MA002 data on file. June 2022. 6. NIHR Evidence Briefing. Tabelecleucel for Epstein-Barr Virus-associated lymphoproliferative disease following solid organ transplant. January 2019. 7. Pierre Fabre Limited, MA003 data on file. October 2021.	
Wording	Anthony Nolan	The wording of the remit does reflect the issue in question.	No action required
	Pierre Fabre	No comments.	No action required
Timing issues	Anthony Nolan	The incidence rate of EBV-PTLD is low, however, aggressive cases have been known to be fatal. Given its rare occurrence, rarer subtypes and in the relapsed/refractory setting, treatment decisions are informed by small case series and case reports. Limited surveillance data and a need for protocol harmonisation in this area would be benefitted from this evaluation.	Thank you for your comment. NICE has scheduled this topic into its work programme.
	Pierre Fabre	There is an urgent need for the NICE appraisal of tab-cel as there are no licensed treatment options for EBV+ PTLD, and patient prognosis is incredibly poor for those who have failed treatment with rituximab monotherapy/rituximab with chemotherapy. Current treatment includes rituximab (off-label) either as a single agent (monotherapy) or as part of a drug regimen (immunochemotherapy).	Thank you for your comment. NICE has scheduled this topic into its work programme.

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		However, not all patients are eligible and of those who are, not all respond to treatment. In HSCT, the European Conference on Infections in Leukemia (ECIL) guidelines recommend rituximab as a prophylactic treatment approach for EBV+ PTLD. In this group it is reported 51% (n=87) of patients fail initial treatment with rituximab when not given pre-emptively.[1,2] In SOT, it is reported that approximately 33% of patients relapse or become refractory to initial treatment with rituximab or rituximab plus chemotherapy.[3] In SOT patients who relapse or become refractory to initial treatment with rituximab, no further licensed treatments are available, while in HSCT patients, donor lymphocyte infusion may be considered as an option.[1] Prognosis for EBV+ PTLD patients who fail initial rituximab-based therapy is very poor; for SOT patients who fail rituximab and chemotherapy a median survival of 4.1 months has been reported,[4] while for HSCT patients who fail rituximab ± chemotherapy, have a median survival <0.7 months.[5] The poor survival reported in patients with EBV+ PTLD who have failed rituximab ± chemotherapy, combined with no licensed treatment options, demonstrates an urgent and high unmet need for patients and clinicians. **References** 1. Styczynski et al. Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell	

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		transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. Haematologica 2016:101(7): 803-811. 2. Garcia-Cadenas I et al. Frequency, characteristics, and outcome of PTLD after allo-SCT: A multicenter study from the Spanish group of blood and marrow transplantation (GETH). Eur J Haematol 2019:102(6): 465-471. 3. Pierre Fabre Limited, MA002 data on file. June 2022. 4. Dharnidharka V et al Clinical outcomes of solid organ transplant patients with Epstein-Barr Virus-Driven (EBV+) post-transplant lymphoproliferative disorder (PTLD) who fail rituximab plus chemotherapy: A multinational, retrospective chart review study. 63rd ASH Meeting December 2021. Abstract 2528. 5. Sanz et al. Clinical outcomes of patients with Epstein-Barr Virus-Driven (EBV+) post-transplant lymphoproliferative disorder (PTLD) who fail rituximab: A multinational, retrospective chart review study. 63rd ASH Meeting December 2021. Abstract 1454.	
Additional comments on the draft remit	Anthony Nolan	It is important that the remit includes in its review the comprehensive range of PTLD categories, and the any final guidance highlights specific regimen according to type. This will reduce any ongoing off-label use, for lack of official guidance.	Thank you for your comment. This remit is inclusive of all categories of PTLD, covered by the anticipated marketing authorisation and the recommendations will be for the use of tabelecleucel within its marketing authorisation therefore, no action is required.
	Pierre Fabre	No comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Anthony Nolan	The substantive points currently included appear to be correct. A few additional points of context would be helpful: - Incidence rates should also have best-available case figures, even if this is set against a longitudinal dataset. - An explanation of antiviral agent use, and clinical research into prophylaxis strategies would develop a fuller picture around disease progression and management. - With regards to HSCT patients, risk factors should be cited such as particular T-cell depleting strategies, use of HLA mismatched donor, use of Antithymocyte globulin (ATG), acute GvHD condition, CMV status.[1] - Within HSCT, it should be noted the incidence range evidenced dependent on donor type. Umbilical-cord transplantation (4%-5%); Transplant from unrelated donors (4%-10%); and Transplant from matched, related donors (1%-3%).[2] - To clarify that almost all cases of HSCT (100%) are EBV positive.	Thank you for these comments. - We have been unable to identify further documented case figures for this population. - We have included a description of EBV monitoring post-HSCT and the use of pre-emptive rituximab if there is evidence of EBV reactivation. It is anticipated that further information regarding disease progression and management would be considered in the appraisal - We have updated the background section and to add that incidence of PTLD post-HSCT is dependent on donor type. This section is intended to provide a brief description of the background to the disease. It is anticipated that any factors relevant to PTLD outcomes will be considered during the appraisal, therefore we have not included further information regarding risk factors at this stage - We have updated the background section of the scope to clarify that

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		- A description of Late onset PTLD, and the high incidence of late onset Hodgkin's lymphoma after allogeneic HSCT and their relation to EBV negative tumours. Helpful in narrowing down the population for Tabelecleucel. **References** 1. Hou, Hsin-An & Yao, M & Tang, Jih-Luh & Chen, Y-K & Ko, Bor-Sheng & Huang, Shuan-Yu & Tien, H-F & Chang, Hsiu-Hao & Lu, Min Yu & Lin, T-T & Lin, Kai-Hsin & Hsiao, C-H & Lin, C-W & Chen, Y-C. (2008). Poor outcome in post transplant lymphoproliferative disorder with pulmonary involvement after allogeneic hematopoietic SCT: 13 years' experience in a single institute. Bone marrow transplantation. 43. 315-21. 10.1038/bmt.2008.325. 2. Abbas F, El Kossi M, Shaheen IS, Sharma A, Halawa A. Post-transplantation lymphoproliferative disorders: Current concepts and future therapeutic approaches. World J Transplant. 2020 Feb 28;10(2):29-46.	almost all cases of PTLD post-HSCT are EBV+ - The population in the remit for this scope is people with EBV-positive PTLD, and therefore the scope focuses on this population.
	Pierre Fabre	Background information appropriate.	Thank you for your comment. No action required
Population	Anthony Nolan	The defined population appears to be appropriate.	Thank you for your comment. No action required. Please note population has been updated to specify that there are 2 groups of people with PTLD, people who have PTLD post-SOT and post-HSCT.

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	Pierre Fabre	The patient population would be better defined by highlighting the two distinct EBV+ PTLD patient cohorts i.e. those who have undergone: • solid organ transplant (SOT) *or* • haematopoietic stem cell transplantation (HSCT) The following text is suggested: People with previously treated EBV-positive post-transplant lymphoproliferative disorder (EBV+ PTLD) who have undergone either a solid organ transplant (SOT), or a haematopoietic stem cell transplantation (HSCT).	Thank you for your comment. We have updated the population to highlight these two cohorts (post-SOT and post-HSCT). Following the scoping workshop, we have updated the language to clarify that PTLD develops following the transplant.
Subgroups	Anthony Nolan	With respect to 'people who have had more than one previous treatment' – it should be clarified whether Reduction in Immunosuppression (RIS) is considered a therapeutic intervention. It appears to be so in some guidance, whereas rituximab can also referred to as a first-line therapy. It should be determined what a previous treatment includes.	Thank you for your comment. We have updated the subgroups section to remove the group, 'people who have had more than one previous treatment' and have specified the relevant previous treatments. Please note that the subgroups have been further updated following the updates to the description of the population.
	Pierre Fabre	We recommend that subgroups align with the pivotal phase III (ALLELE) study: • people who have EBV+ PTLD following SOT: - treated with rituximab monotherapy - treated with rituximab with chemotherapy i.e. cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP)	Thank you for your comment. We have updated the subgroups to people who have EBV+ PTLD: • following HSCT • following SOT • following SOT

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		• people who have EBV+ PTLD following HSCT, treated with rituximab monotherapy 'People who have had more than one previous treatment', is not a standalone subgroup and is encompassed in the above subgroups.	○ previously treated with rituximab monotherapy ○ previously treated with rituximab with chemotherapy
Comparators	Anthony Nolan	For people who have EBV-positive PTLD after allogeneic HSCT who have had rituximab monotherapy: Should chemotherapy regimens such as CHOP be explicitly listed here as the preferred regimen for B-cell PTLD.	We have now removed chemotherapy as a comparator for tab-cel, following a comment from the company that this would be included within prior therapy and this would be specified in the marketing authorisation Therefore, no action required.
	Pierre Fabre	We would recommend that 'best supportive care' be considered as the only treatment comparator for tab-cel for the following reasons: • **Rituximab with chemotherapy/ chemotherapy** Tab-cel is anticipated to be indicated for the treatment of patients with EBV+ PTLD who have received at least one prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate. Patients eligible for tab-cel will have already been treated with rituximab monotherapy/rituximab with chemotherapy in a first line setting, and therefore tab-cel would be used in a later line of therapy. • **Radiotherapy** Based on an internal literature search and clinician consultation, it is recommended	Thank you for your comments. We have removed rituximab with chemotherapy and chemotherapy as comparators. At the scoping workshop, clinicians agreed that radiotherapy has a very limited role in routine clinical practice. Therefore, we have also removed radiotherapy from the list of comparators.

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		radiotherapy be removed as a treatment comparator for EBV+ PTLD following SOT. While radiotherapy may have a role in the treatment of lymphoproliferative disorders, local clinical advice suggests that it does not form routine treatment in the EBV+ PTLD SOT patient population.	
Outcomes	Anthony Nolan	The principle measures should be overall survival (OS) and response rate, both of which are included. Progression-free survival is covered by duration of response.	We have updated the outcome measures to include progression-free survival.
	Pierre Fabre	**Additional outcome** Progression-free survival (PFS) was recorded as an exploratory endpoint within the ALLELE study and should be included in addition to those listed. **Allograft loss or transplant rejection** 'Table 36' (below), from the ALLELE study interim Clinical Study Report, provides detail on the only patient who experienced graft versus host disease. As shown, there are minimal data available in relation to allograft loss or transplant rejection (n=1) and due to this lack of data, we recommend the outcome be removed. Table containing confidential information from the Clinical Study Report not shown.	We have updated the outcome measures to include progression-free survival. The inclusion of 'rate of allograft loss or transplant rejection' was discussed at the scoping workshop, and clinicians agreed that it would be important to monitor allograft loss or transplant rejection, even if there is limited data available from the trial. Therefore, we have retained this outcome measure in the scope.

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Equality	Anthony Nolan	As previously stated, particular donor characteristics and patient profiles can affect the likelihood of a HSCT patient developing EBV-reactivation. Patients with HLA mix-matched donors or those needing t-cell depletion protocols using ATG, are at higher known risk of EBV-reactivation Also, EBV+ patients receiving EBV- donor grafts will no longer have immunity to residual cells within patient, from before the donor cell infusion. For aggressive diseases, age and frailty remain a concern in tolerating RIS and the toxicity profiles of other therapy lines.	Thank you for your comment. We have added that age and frailty impact eligibility for previous treatments to the equality impact assessment form. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.
	Pierre Fabre	None	No action required.
Other considerations	Anthony Nolan	No comments	No action required.
	Pierre Fabre	**<u>Appraisal via the HST programme</u>** It would be inappropriate to appraise tab-cel via a Single Technology Appraisal, given the ultra-rare nature of the condition and the absence of licensed treatments. Tab-cel has been granted Breakthrough Therapy Designation for EBV+ PTLD by the U.S. Food and Drug Administration and PRIME designation by the EMA for the same indication. Tab-cel also has orphan drug designation in the U.S. and E.U.	Thank you for your comments. The routing of this topic was discussed by the topic selection oversight panel and the decision was to assess this topic as a single technology appraisal (STA).

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		In addition, tab-cel fulfils **all** the entry criteria for consideration via the HST programme and should be appraised via this route. Details for each criterion are as follows: **Routing criterion 1: The disease is very rare** • PTLD is a very rare but life-threatening complication of both SOT and HSCT. Most common PTLDs are EBV+ and result from loss of immune surveillance over EBV. • In the UK, the number of patients is estimated at 12-20 SOT patients and 9-14 HSCT patients per year.[1-4] In total approximately 8-14 patients will be relapsed/refractory and therefore eligible for tab-cel.[5,6] • In England, the number of patients with EBV+ PTLD following SOT or HSCT, and those eligible for treatment with tab-cel, is likely to be lower. **Routing criterion 2: Normally, no more than 300 people in England are eligible for the technology it's licensed indication and no more than 500 across all its indications** A maximum of six potential future indications are possible. A phase II multi-cohort 205 study (NCT04554914) is ongoing and recruiting the following patient populations:	

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		• EBV+ autoimmune disease (AID)-lymphoproliferative disorders (LPD) • EBV+ primary immunodeficiency (PID)-LPD • EBV+ PTLD where standard first line therapy (rituximab or chemotherapy) is not appropriate (1L inappropriate PTLD), including CD20-negative disease • EBV+ central nervous system (CNS) PTLD • EBV+ sarcomas including leiomyosarcoma (LMS) • Chronic active Epstein-Barr virus (CAEBV) *or* EBV viremia with haemophagocytic lymphohistiocytosis (HLH) Across all six potential future indications the total population eligible for treatment in the UK would likely be no greater than 250 to 300 patients.[6] In England, the number of patients is likely to be lower. **Routing criterion 3: The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life** EBV+ PTLD can have life-threatening consequences and overall mortality is approximately 50%.[7] EBV+ PTLD patients following SOT who fail rituximab and chemotherapy have a median survival of 4.1 months.[8] EBV+ PTLD patients who fail rituximab following HSCT have a median survival of <0.7 months.[9]	

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		Routing criterion 4: There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options There are no licensed treatments for EBV+ PTLD. Current treatment includes rituximab either as a single agent (monotherapy) or as part of a drug regimen (immunochemotherapy). However, not all patients are eligible and of those who are, not all respond to treatment. In HSCT approximately 51% fail initial treatment with rituximab,[5] while 33% of SOT patients relapse or become refractory to initial treatment with rituximab or rituximab plus chemotherapy.[6] In patients who fail initial treatment with rituximab, relapse or become refractory to initial treatment with rituximab or rituximab with chemotherapy, no further treatments are available. There is therefore a high unmet need for a new licensed treatment option which is both effective and well tolerated. Tab-cel is anticipated to be indicated for the treatment of patients with EBV+ PTLD who have received at least one prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate. Interim analysis conducted in May 2021 of the ALLELE study (to assess efficacy and safety for the treatment of EBV+ PTLD in SOT and HSCT after failure of standard of	

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		care), based on Independent Oncologic and Radiograph Assessment, showed an overall response rate (ORR) of 50% in EBV+ PTLD patients following HSCT or SOT with a best overall response of Complete Response (26.3%, n=10) or Partial Response (23.7%, n=9).[9] Estimated median OS was 18.4 months (95% CI; 6.9, NE) among all patients.[10] **References** 1. Dierickx D, Longo DL, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. N Eng J Med. 2018;378(6):549-562. 2. Opelz G, Döhler B. Impact of HLA mismatching on incidence of posttransplant non-Hodgkin lymphoma after kidney transplantation. Transplantation. 2010;89(5):567-572. 3. Lowery EM, Adams W, Grim SA, Clark NM, Edwards L, Layden JE. Increased risk of PTLD in lung transplant recipients with cystic fibrosis. J Cyst Fibros. 2017;16(6):727-734. 4. Pierre Fabre Limited, MA001 data on file. June 2022. 5. Garcia-Cadenas I et al. Frequency, characteristics, and outcome of PTLD after allo-SCT: A multicenter study from the Spanish group of blood and marrow transplantation (GETH). Eur J Haematol 2019:102(6): 465-471. 6. Pierre Fabre Limited. MA002 data on file. June 2022. 7. NIHR Evidence Briefing. Tabelecleucel for Epstein-Barr Virus-associated lymphoproliferative disease following solid organ transplant. January 2019. 8. Dharnidharka V et al Clinical outcomes of solid organ transplant patients with Epstein-Barr Virus-Driven (EBV+) post-transplant lymphoproliferative disorder (PTLD) who fail	

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		rituximab plus chemotherapy: A multinational, retrospective chart review study. 63rd ASH Meeting December 2021. Abstract 2528. 9. Sanz et al. Clinical outcomes of patients with Epstein-Barr Virus-Driven (EBV+) post-transplant lymphoproliferative disorder (PTLD) who fail rituximab: A multinational, retrospective chart review study. 63rd ASH Meeting December 2021. Abstract 1454. 10. Prockop S et al. Multicenter, Open-Label, Phase 3 Study of Tabelecleucel for Allogeneic Hematopoietic Cell or Solid Organ Transplant Recipients with Epstein–Barr Virus-Driven Post Transplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE). Pub00280, oral presentation. 63rd ASH Meeting December 2021.	
Questions for consultation	Anthony Nolan	No comments	No action required.
	Pierre Fabre	**Is EBV routinely tested for in people who have PTLD in the NHS?** PTLD is a rare, but well-known complication of SOT and HSCT, and in most instances is associated with EBV. In PTLD following SOT, around 50% of all cases are EBV-related,[1,8] while the majority (~100%) of PTLD cases following HSCT are EBV-related.[11] Consequently, EBV is routinely tested for. Patients who have undergone HSCT are at the highest risk of EBV+ PTLD in the first 6 months post-transplant.[12] Whilst SOT patients are at highest risk of PTLD in the first year following transplant,[7] the presentation may be	Thank you for your comments. We have updated the description of the treatment pathway as noted in the responses to these questions.

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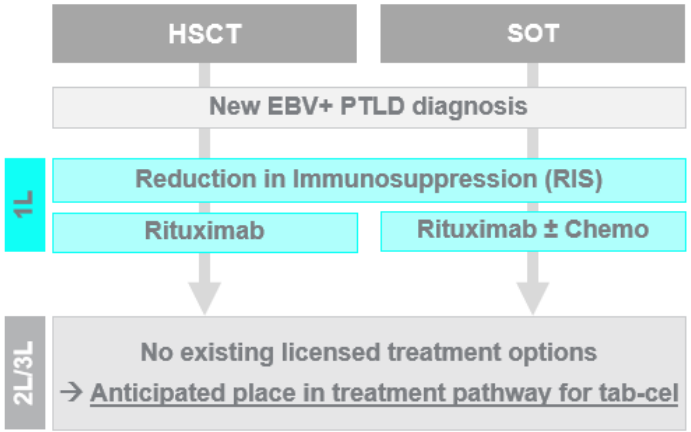
		much later. If EBV+ PTLD arises at a longer interval post-SOT, the patients may no longer be in routine follow up and so may represent with new symptoms of EBV+ PTLD. **Where do you consider tabelecleucel will fit into the existing care pathway for PTLD caused by EBV?** The diagram below shows where tab-cel will likely fit into the existing care pathway for EBV+ PTLD. Tab-cel will provide a treatment option for: • SOT patients who are relapsed/refractory following first line treatment with reduction in immunosuppression (RIS) and rituximab ± chemotherapy. • HSCT patients who are relapsed/refractory following first line treatment with RIS and rituximab.  	

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		What proportion of people have CD20-positive PTLD? What is the treatment pathway for people who are not eligible for rituximab? Despite their heterogeneity, about 85% of the PTLD cases are classified as CD20-positive diffuse large B-cell lymphomas.[13] • For CD20-negative PTLD, CHOP-based chemotherapy is the primary treatment option available.[14] • For CD20-positive PTLD, rituximab monotherapy is recommended for patients who are refractory following RIS as an initial therapy.[15] **Would tabelecleucel be a candidate for managed access?** With the pivotal phase III ALLELE study ongoing, it is anticipated that tab-cel will be a potential candidate for a Managed Access Agreement within the Cancer Drugs Fund. **Do you consider tabelecleucel to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Tab-cel is a first-in-class off-the-shelf, allogeneic T-cell immunotherapy in development for EBV+ PTLD, and a	

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		step-change in the management of the condition. In previously treated EBV+ PTLD patients tab-cel shows unprecedented efficacy improving objective response rates and overall survival and has a favourable safety profile. Tab-cel is currently being investigated in the phase III ALLELE study (NCT03394365) to assess efficacy and safety for the treatment of EBV+ PTLD in SOT and HSCT (n=14) or SOT (n=24) with best overall response of CR (26.3%, n=10) or PR (23.7%, n=9).[9] Estimated median overall survival (OS) was 18.4 months among all patients, and patients responding to tab-cel had a longer survival compared with non-responders (OS at 1 year: 89.2% vs. 32.4%).[10] Tab-cel provides a potentially curative treatment option for EBV+ PTLD patients following SOT/HSCT where currently, there are no licensed treatments. **Do you consider that the use of tabelecleucel can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Outside of the QALY, no additional substantial health-related benefits are anticipated. **References** 1. Dierickx D, Longo DL, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. N Eng J Med. 2018;378(6):549-562.	

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		2. Opelz G, Döhler B. Impact of HLA mismatching on incidence of posttransplant non-Hodgkin lymphoma after kidney transplantation. Transplantation. 2010;89(5):567-572. 3. Lowery EM, Adams W, Grim SA, Clark NM, Edwards L, Layden JE. Increased risk of PTLD in lung transplant recipients with cystic fibrosis. J Cyst Fibros. 2017;16(6):727-734. 4. Pierre Fabre Limited, MA001 data on file. June 2022. 5. Garcia-Cadenas I et al. Frequency, characteristics, and outcome of PTLD after allo-SCT: A multicenter study from the Spanish group of blood and marrow transplantation (GETH). Eur J Haematol 2019:102(6): 465-471. 6. Pierre Fabre Limited. MA002 data on file. June 2022. 7. NIHR Evidence Briefing. Tabelecleucel for Epstein-Barr Virus-associated lymphoproliferative disease following solid organ transplant. January 2019. 8. Dharnidharka V et al Clinical outcomes of solid organ transplant patients with Epstein-Barr Virus-Driven (EBV+) post-transplant lymphoproliferative disorder (PTLD) who fail rituximab plus chemotherapy: A multinational, retrospective chart review study. 63rd ASH Meeting December 2021. Abstract 2528. 9. Sanz et al. Clinical outcomes of patients with Epstein-Barr Virus-Driven (EBV+) post-transplant lymphoproliferative disorder (PTLD) who fail rituximab: A multinational, retrospective chart review study. 63rd ASH Meeting December 2021. Abstract 1454. 10. Prockop S et al. Multicenter, Open-Label, Phase 3 Study of Tabelecleucel for Allogeneic Hematopoietic Cell or Solid Organ Transplant Recipients with Epstein–Barr Virus-Driven Post Transplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy	

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		(ALLELE). Pub00280, oral presentation. 63rd ASH Meeting December 2021. 11. National Organization for Rare Disorders, Post-Transplant Lymphoproliferative Disease. Available from: https://rarediseases.org/rare-diseases/posttransplantlymphoproliferative-disorders/. Accessed 5 May 2022. 12. Lymphoma Action, Post-Transplant Lymphoproliferative Disorder information sheet, May 2022. Available from: https://lymphoma-action.org.uk/sites/default/files/media/documents/2022-05/LYMweb0186PTLD2022v3.pdf. Accessed June 2022. 13. Dierickx D, Vergote V. Management of Post-transplant Lymphoproliferative Disorders. HemaSphere, 2019. 14. Zimmermann H, Trappe RU. Therapeutic options in post-transplant lymphoproliferative disorders. Ther Adv Hematol. 2011 Dec;2(6):393-407. 15. Shah N et al. Front-line management of post-transplantation lymphoproliferative disorder in adult solid organ recipient patients – A British Society for Haematology Guideline. Br J Haem, 2021:193:727-740.	
Additional comments on the draft scope	Anthony Nolan	No comments	No action required
	Pierre Fabre	No comments	No action required

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Lymphoma Action