Highly Specialised Technologies (HST) criteria checklist

**Tabelecleucel for treating post-transplant lymphoproliferative disorder caused by the Epstein-Barr virus (ID1203)**

**Introduction:** The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable.

### Key – does the technology meet the criteria? Please use the colour key to advise if the technology meets the criteria

|  |  |
| --- | --- |
| Met  | There is clear and strong evidence that this criterion is met |
| Unclear | There is some evidence, or the evidence available is unclear. |
| Not met | There is no evidence or limited evidence that the criterion is met.  |

### MA wording: for the treatment of patients with Epstein-Barr Virus positive post-transplant lymphoproliferative disease (EBV+ve PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate.

| **Number** | **Criterion** | **Description of how the technology meets the criteria**  | **Does the technology meet the criteria?** |
| --- | --- | --- | --- |
|  | The condition is very rare defined by 1:50,000 in England  | **The prevalence of the condition is unclear.**No published estimates are available for the number of people with EBV+ve PTLD in England. The annual incidence is likely to be below 1:50,000 for both the condition as stated in the anticipated marketing authorisation (EBV+ve PTLD) and the population who will be eligible for treatment with tabelecleucel (previously treated EBV+ve PTLD). **Estimates of incidence using annual transplant rates**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Post-HSCT** | **Post-SOT** | **Total** |
| **PTLD** | 35 | 81-811 | 116-846 |
| **EBV+ve PTLD** | 35 | 41-406 | 75-440 |
| **Previously treated EBV+ve PTLD** | 18 | 13-133 | 31-151 |

Clinical experts at the scoping workshop suggested that incidence rates towards the lower end of post-SOT estimated range were most plausible, however noted that there was uncertainty regarding the incidence estimates.The prevalence of EBV+ve PTLD and previously treated EBV+ve PTLD is not clear. Although PTLD occurs most frequently in the first-year post-transplantation ([Shah et al. 2021](https://onlinelibrary.wiley.com/doi/pdf/10.1111/bjh.17421)), it may occur after. It is expected that the prevalence will be higher than the estimated incidence. For this reason, it is unclear whether this criterion is met.**References**Population in England: 56,550,000 ([ONS](https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020#population-change-for-uk-countries))Number of allogeneic HSCTs per year in England: 1,455 ([2019 data, BSBMTCT data for UK, scaled down to England](https://bsbmtct.org/activity/2019/))Number of SOTs per year in England: 4,055 ([2019/20 data, NHS Blood and Transplant; Organ Donation and Activity Data: England](https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/26354/nhsbt-england-summary-report-mar-22.pdf))Percentage of people who develop PTLD post-allogeneic HSCT: 2% ([Gupta et al. 2020](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229077/))Percentage of people who develop PTLD post-SOT: 2-20% ([Gupta et al. 2020](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229077/), [Dierickx and Habermann, 2018](https://www.nejm.org/doi/full/10.1056/NEJMra1702693)) – incidence of PTLD post-SOT varies dependent on type of transplant. The majority (~70%) of SOTs in England are kidney transplants. The incidence PTLD post-kidney transplant is approximately 2% (scoping workshop and [Dierickx and Habermann, 2018](https://www.nejm.org/doi/full/10.1056/NEJMra1702693) (range: 0.8% to 2.5%), and is the lowest among organ transplants. The highest rates of PTLD are following intestinal transplants (~20%), however these only make up 0.05% of all transplants conducted in England ([NHS Blood and Transplant, Organ Donation and Transplantation Activity Data: England](https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/26354/nhsbt-england-summary-report-mar-22.pdf)).Percentage of PTLD that is EBV+ve post-HSCT: ~100% ([Dierickx and Habermann, 2018](https://www.nejm.org/doi/full/10.1056/NEJMra1702693))Percentage of PTLD that is EBV+ve post-SOT: 50% ([Dharnidharka et al. 2021](https://www.sciencedirect.com/science/article/pii/S000649712104475X))Percentage of EBV+ve PTLD post-HSCT that is R/R to rituximab: 51% ([Garcia-Cadenas et al. 2019](https://onlinelibrary.wiley.com/doi/abs/10.1111/ejh.13226))Percentage of EBV+ve PTLD post-SOT that is R/R to rituximab ± chemotherapy: 33% (Pierre Fabre data on file and scoping workshop)**Company comments:*** PTLD is a very rare but life-threatening complication of both SOT and HSCT. Most common PTLDs are EBV+ve 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+ve PTLD following SOT or HSCT, and those eligible for treatment with tab-cel, is likely to be lower.
 | Unclear |
|  | Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications  | **The number of people eligible for tabelecleucel is unclear because the prevalence of EBV+ve PTLD is unclear**Based on the calculation above, 31-151 people are eligible per year for tabelecleucel in line with its MA for the treatment of patients with Epstein-Barr Virus positive post-transplant lymphoproliferative disease (EBV+ve PTLD) who have received at least one prior therapy. It is further noted that the lower end of the incidence estimates were considered most plausible by scoping workshop attendees. The total number of people who would be eligible for tabelecleucel is unclear because there are no available prevalence data for EBV+ve PTLD. For this reason, it is unclear whether this criterion is met.It is also noted that there are no licensed indications for tabelecleucel.There are completed and ongoing trials assessing tabelecleucel in other EBV-associated diseases, such as EBV-associated nasopharyngeal carcinoma, and in EBV-positive patient populations with immunodeficiency-associated lymphoproliferative diseases. However, because tabelecleucel is not yet licensed for these indications, only the number of people who would be eligible for tabelecleucel under the currently proposed indication for previously treated EBV+ve PTLD has been taken into account when assessing this criterion.**Company comments:**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: * EBV+ve autoimmune disease (AID)-lymphoproliferative disorders (LPD)
* EBV+ve primary immunodeficiency (PID)-LPD
* EBV+ve PTLD where standard first line therapy (rituximab or chemotherapy) is not appropriate (1L inappropriate PTLD), including CD20-negative disease
* EBV+ve central nervous system (CNS) PTLD
* EBV+ve 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. | Unclear |
|  | The very rare condition significantly shortens life or severely impairs its quality  | **There are initial treatments for EBV+ve PTLD which can lead to sustained remission in a proportion of people (around 70% of people with EBV+ve PTLD after a SOT and around 50% of people with EBV+ve PTLD after a HSCT). Prognosis is poor in people with EBV+ve PTLD which does not respond to or relapses with rituximab ± chemotherapy. For this criterion, the condition was considered to be EBV+ve PTLD and therefore the criterion was not met****Estimates of prognosis**

|  |  |  |
| --- | --- | --- |
|  | **Post-HSCT** | **Post-SOT** |
| **EBV+ve PTLD** | 50% response rate (sustained remission) to rituximab ([Garcia-Cadenas et al. 2019](https://onlinelibrary.wiley.com/doi/abs/10.1111/ejh.13226)) | 70% response rate (sustained remission) to rituximab and rituximab + CHOP (Pierre Fabre data on file and scoping workshop) |
| **Previously treated EBV+ve PTLD** | Median OS of 0.7 months (95% CI 0.3 to 1) from rituximab failure date and a median OS of 1.7 months (95% CI 1.1 to 2.3) from PTLD diagnosis ([Sanz et al. 2021](https://ashpublications.org/blood/article/138/Supplement%201/1454/480552/Clinical-Outcomes-of-Patients-with-Epstein-Barr?searchresult=1)) | Median OS of 4.1 months (95% CI 1.9 to 8.5) from rituximab plus chemotherapy failure date and a median OS of 15.5 months (95% CI 8.3 to 22.9) from PTLD diagnosis ([Dharnidharka et al. 2021](https://ashpublications.org/blood/article/138/Supplement%201/2528/482470/Clinical-Outcomes-of-Solid-Organ-Transplant?searchresult=1)) |

**Company comments:*** EBV+ve PTLD can have life-threatening consequences and overall mortality [from this condition] is approximately 50%.7
* EBV+ve PTLD patients following SOT who fail rituximab and chemotherapy have a median survival of 4.1 months.8 EBV+ve PTLD patients who fail rituximab following HSCT have a median survival of <0.7 months.9
 | Not met |
|  | There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options. | **There is insufficient evidence that this criterion is met:*** **There may be satisfactory treatment options for people with EBV +ve PTLD.**
* **The magnitude and duration of benefit of tabelecleucel is uncertain because of insufficient available data, and therefore it cannot be demonstrated that tabelecleucel is likely to provide the benefits needed to meet this criterion**

There are no established treatment options for people with EBV-positive PTLD after a SOT for whom rituximab alone or in combination with chemotherapy was not effective, or for people with EBV-positive PTLD after allogeneic HSCT for whom rituximab alone was not effective. In this group the availability of tabelecleucel could address an unmet need. There are however initial treatment options in established clinical practice for people with EBV+ve PTLD. These are clinically effective for a proportion of people. The panel agreed that these initial treatments, rituximab ± chemotherapy, may not be suitable for all people but overall, for EBV+ve PTLD there are treatment options available, and this criterion was not met.Early data from ALLELE suggests a proportion of the trial population had a clinical response to tabelecleucel. However, there is insufficient available evidence to demonstrate that tabelecleucel will provide the magnitude of clinical benefit needed to meet this criterion. **Company comments:*** There are no licensed treatments for EBV+ve 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+ve 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+ve PTLD in SOT and HSCT after failure of standard of care), based on Independent Oncologic and Radiograph Assessment, showed an overall response rate (ORR) of 50% in EBV+ve 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
 | Not met |

Highly specialised technologies vision and routing criteria

The Highly Specialised Technologies Programme is designed to be used in exceptional circumstances. Its purpose is to evaluate technologies for very rare diseases that have:

* small numbers of patients
* limited or no treatment options
* challenges for research and difficulties with collecting evidence, because of the uniqueness of the disease.

The Highly Specialised Technologies Programme aims to:

* encourage research on, and innovation for, very rare conditions when there are challenges in generating an evidence base that is robust enough to bring the product to market
* secure fairer and more equitable treatment access for very small populations with very rare diseases
* recognise that an approach that maximises health gain for the NHS may not always be acceptable: it could deliver results that are not equitable.

The Highly Specialised Technologies Programme acknowledges that:

* It is important for NICE to apply appropriate limits on the very rare populations that can potentially be routed to the programme. This is because the Highly Specialised Technologies Programme is a deliberate departure from the standard technology appraisal process (valuing the benefits from these technologies more highly by having a much higher [incremental cost-effectiveness ratio [ICER]](https://www.nice.org.uk/Glossary/incremental-cost-effectiveness-ratio) threshold) for the reasons outlined above.
* Each time NICE routes a topic to the Highly Specialised Technologies Programme it is deciding that, if the technology is recommended, the NHS must commit to allocate resources that would have otherwise been used on activities that would be expected to generate greater health benefits.
* NICE has sought to strike a balance between the desirability of supporting access to treatments for very rare diseases against the inevitable reduction in overall health gain across the NHS that this will cause. Both considerations are valid and important, and neither can be given absolute priority over the other. Therefore, the Highly Specialised Technologies Programme criteria and their anticipated application intentionally do not seek to capture every case when there are challenges in generating an evidence base or when there is a small population with a rare disease.
* This approach ensures that technologies routed to the Highly Specialised Technologies Programme fulfil the vision of the programme and manages the displacement in the wider NHS.

However, it can be difficult to identify the exceptional circumstances when the highly specialised technologies methods and processes should be used because of the difficulty in getting the information needed. Proxy information is often relied on and used to make subjective judgements. The routing criteria identify which technologies should be routed for highly specialised technologies guidance. These criteria help make subjective judgements as informed, justifiable, consistent and predictable as possible. NICE’s capacity to develop highly specialised technologies guidance can react to need and there is no limit on the number of technologies that can be routed.

The final routing criteria for the Highly Specialised Technologies Programme are:

* The disease is very rare – defined as 1:50,000 population in England.
* Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications.
* The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life.
* There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.

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