

**EVIDENCE BRIEFING  
JANUARY 2019**

**Tabelecleucel for Epstein-Barr Virus-associated  
lymphoproliferative disease following solid organ  
transplant**

<b>NIHRIO ID</b>	24102	<b>NICE ID</b>	10054
<b>Developer/Company</b>	Atara Biotherapeutics Inc	<b>UKPS ID</b>	N/A

<b>Licensing and market availability plans</b>	Currently in phase III clinical trials
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**SUMMARY**

Tabelecleucel is in clinical development for people with Epstein-Barr Virus (EBV)-associated post-transplant lymphoproliferative disease (PTLD) following solid organ transplant, where treatment with rituximab or rituximab and chemotherapy has not been successful. The EBV virus is present in around 90% of people, but people who have had an organ transplant need to take medicine that suppresses their immune system. This means that virus-infected lymphoid cells can grow more easily. The rapid increase in these lymphoid cells can result in lymphoma, a type of cancer. EBV-PTLD can be treated by reducing the immunosuppressive medicines, but may also need treatment with rituximab with or without chemotherapy.

Tabelecleucel is the first product developed to treatment EBV-PTLD in patients who have not been successfully treated with rituximab. Tabelecleucel is made from T-cells which are collected from the blood of healthy donors and exposed to EBV antigens so that they are able to fight EBV. These cells are expanded and stored for future use in appropriately matched patients with EBV-PTLD, who are given the product as an infusion. Tabelecleucel finds the cells expressing EBV and kills them.

## PROPOSED INDICATION

Epstein-Barr virus-associated post-transplant lymphoproliferative disease (EBV-PTLD) following solid organ transplant (SOT), after failure of rituximab or rituximab and chemotherapy<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Tabelecleucel (Tab-cel) utilizes a technology in which T-cells are collected from the blood of third-party donors and then exposed to EBV antigens. The resulting activated T-cells are then expanded, characterized, and stored for future therapeutic use in an appropriate partially human leukocyte antigen (HLA) matched patient, providing an allogeneic, cellular therapeutic option for patients. In the context of EBV infection, tabelecleucel finds the cells expressing EBV and kills them.<sup>2</sup>

Tabelecleucel is in clinical development for patients with EBV-PTLD following SOT, who have failed treatment with rituximab with/without chemotherapy. In the phase III trial (ALLELE; NCT03394365) tabelecleucel is administered intravenously (IV) at  $2 \times 10^6$  cells/kg on Days 1, 8 and 15 of a 35-day cycle. Duration of treatment is not reported.<sup>1</sup>

### INNOVATION AND/OR ADVANTAGES

Tabelecleucel is an advanced therapy medicinal product (ATMP) that could provide an off-the-shelf, allogeneic, cellular therapeutic option for patients with EBV-PTLD who have failed on rituximab or rituximab and chemotherapy. There is currently no treatment available for these patients.<sup>2,3</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tabelecleucel does not currently have Marketing Authorisation in the EU/UK for any indication.

Tabelecleucel is in phase III clinical development for EBV-PTLD following allogeneic hematopoietic cell transplant (HCT) after failure of rituximab.<sup>4</sup>

Tabelecleucel was designated as an orphan drug in the EU in 2016 for EBV-PTLD.<sup>5</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

PTLD is a life-threatening complication of SOT, and is highly associated with EBV. EBV is a gamma herpes virus; over 90% of the human population is infected with the virus, and primary infection usually occurs at an early age.<sup>6</sup> Following primary infection, EBV establishes a latent infection and persists within memory B-cells at low levels, allowing a lifelong infection to be established that the immune system cannot clear.<sup>7</sup>

The EBV-specific cytotoxic T-cell response that is essential in controlling the virus in healthy individuals is suppressed in transplant recipients using immunosuppressive drugs, and the uninhibited growth of virus-infected memory B-cells may lead to the development of PTLD.<sup>6</sup>

PTLD is a proliferation of lymphoid (immune) cells, and represents a spectrum of disease that ranges from early lesions, polymorphic or monomorphic B-cell (including diffuse large B-cell lymphoma and Burkitt lymphoma).<sup>8</sup> PTLD is a relatively common malignant complication after SOT, with differences in incidence rates according to the type of organ transplants, the pre-transplant EBV-serostatus, and the age of the organ recipient. The risk of developing EBV-PTLD is highest in the first year post-transplantation.<sup>6</sup>

The most common symptoms of PTLD is a painless lump, usually in the neck, armpit or groin; this is a swollen lymph node where abnormal lymphocytes collect. Other symptoms are more general, including pyrexia, sweats and weight loss, and can make PTLD difficult to diagnose. A biopsy is required to diagnose the condition.<sup>9</sup>

## CLINICAL NEED AND BURDEN OF DISEASE

Differences in incidence of PTLD by type of organ reflect the different levels of immunosuppression required and the amount of lymphoid tissue in the allograft. The highest incidence is found in small intestine transplant recipients (up to 32%), recipients of pancreas, heart, lung and liver have an intermediate risk (3-12%) and the lowest incidence (<2%) is found in renal transplant recipients. In general, the incidence in paediatric patients is higher than that in adults due to the higher incidence of pre-transplant negative EBV-serostatus among children.<sup>6</sup>

Grouped by these PTLD incidence risk groups, transplant activity figures for the UK for 2017/18 showed that there were 25 high risk, 1,439 intermediate risk and 2,375 low-risk transplants.<sup>10</sup> This would equate to between 43 and 173 intermediate risk cases if PTLD, and less than 47 cases in low risk cases. EBV contributes to the pathogenesis of PTLD in more than 70% of cases<sup>11</sup>, equating to between 30 and 120 intermediate risk and 33 low risk cases per year.

The overall mortality reported in the literature (which may not be representative of current clinical experience) is approximately 50%.<sup>8</sup>

In EBV-PTLD following SOT, patients failing rituximab experience increased chemotherapy-induced treatment-related mortality compared to other lymphoma patients. One- and two-year survival in patients with high-risk EBV-PTLD following SOT is 36% and 0%, respectively.<sup>12</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

Patients with PTLD present a multifaceted clinical challenge. Management of the condition should be planned by a multidisciplinary team of experienced physicians, including transplant physicians, haemato-oncologists, histopathologists and radiologists with particular experience in treating SOT patients.<sup>13</sup>

The first line of treatment for EBV-PTLD is a reduction in immunosuppression (RIS). In some patients this may be adequate therapy to achieve complete remission, whilst facilitating further treatment in others. If the PTLD is localised, surgical resection or radiotherapy may result in long-term disease-free survival.<sup>13</sup>

In patients with life-preserving grafts or those with non-life preserving grafts in whom resection would mean loss of the transplanted organ, and who are deemed suitable, alternative treatment such as rituximab and/or chemotherapy is preferred. Research has shown that rituximab monotherapy following RIS can induce remission in 44-65% of PTLD patients, but significant numbers of patients

progressed on therapy or relapsed after rituximab, and therefore rituximab monotherapy is inadequate for most patients.<sup>13</sup>

Increasing intensity of treatment results in higher response rates but increased toxicity. Anthracycline-based chemotherapy in combination with rituximab (e.g. R-CHOP) has been shown to be effective in achieving long-term disease survival in patients with PTLT, with overall response rates ranging from 65% to 100%, and appears to be effective and well tolerated in selected patients with low risk of transplant organ loss.<sup>13</sup>

Not all patients will be fit for combination chemotherapy. In such patients with poor performance status and aggressive lymphoma, who fail RIS, then alternative less toxic treatment regimens to consider would include rituximab monotherapy, steroids, oral etoposide, alkylating agents, or combination chemotherapy such as R-CVP. Outcome with this therapy is likely to be poor and radiotherapy for symptomatic localised disease may be the best option.<sup>13</sup>

## CURRENT TREATMENT OPTIONS

There are currently limited recommended treatment options for EBD-PTLD patients who have failed on rituximab or rituximab in combination with chemotherapy. Patients may be treated with medicines authorised for non-Hodgkin's lymphoma.<sup>5</sup>

## PLACE OF TECHNOLOGY

If licensed, tabellecleucel will offer an additional treatment option for patients with EBV-PTLD who have failed on rituximab or rituximab and chemotherapy, who currently have no therapies available.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	ALLELE, <a href="#">NCT03394365</a> , ATA129-EBV-302; tabellecleucel; phase III
<b>Sponsor</b>	Atara Biotherapeutics
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial registry <sup>1</sup>
<b>Location</b>	USA and Australia
<b>Design</b>	Single group assignment, open label
<b>Participants</b>	n=66 (planned); any age; EBV-PTLD following prior SOT of kidney, liver, heart, lung, pancreas, small bowel, or any combination of these; failure of rituximab monotherapy or rituximab plus any concurrent or sequentially administered chemotherapy regimen for the treatment of PTLT
<b>Schedule</b>	Tabellecleucel administered in cycles lasting 5 weeks (35 days). During each cycle, subjects receive intravenous (IV) tabellecleucel at a dose of $2 \times 10^6$ cells/kg on Days 1, 8, and 15, followed by observation through Day 35
<b>Follow-up</b>	Active treatment period not stated. Follow-up 2 yrs.
<b>Primary Outcomes</b>	Objective response rate [Time frame: 2 yrs]
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"><li>• Overall survival [Time frame: 5 yrs]</li></ul> Time frame 2 yrs: <ul style="list-style-type: none"><li>• Duration of response</li><li>• Rate of durable response</li><li>• PTLT progression-free survival following best response</li><li>• Time to progression</li></ul>

	<ul style="list-style-type: none"> <li>• Rates of allograft loss or rejection episodes</li> <li>• Patient reported outcome: EQ-5D</li> <li>• Patient reported outcome: Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)</li> <li>• Incidence of related and unrelated adverse events (AE), including AEs of special interest</li> </ul>
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Study completion date reported as Nov 2020

## ESTIMATED COST

The cost of tabelecleucel is not yet known.

## ADDITIONAL INFORMATION

Atara Biotherapeutics Inc did not enter information about this technology onto the *UK PharmaScan* database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. *UK PharmaScan* is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use *UK PharmaScan* so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal in development. ATA129 for treating post-transplant lymphoproliferative disorder caused by the Epstein-Barr virus (ID1203, GID-TA10204). Expected date of publication to be confirmed. NB: ATA129 is the previous name for tabelecleucel. This technology appraisal is for tabelecleucel for the treatment of EBV-PTLD following HCT.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidelines identified.

### OTHER GUIDANCE

- British Society for Haematology. Management of Post-Transplant Lymphoproliferative Disorder in Adult Solid Organ Transplant Recipients. 2010.<sup>13</sup>

## REFERENCES

- <sup>1</sup> ClinicalTrials.gov. *Tabelecleucel for Solid Organ Transplant Subjects With EBV+ PTLD After Failure of Rituximab or Rituximab and Chemotherapy (ALLELE): NCT03394365*. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT03394365> [Accessed 3 January 2019]
- <sup>2</sup> Atara Biotherapeutics. *Atara Bio granted access to Priority Medicines (PRIME) Regulatory Support for Allogeneic Epstein-Barr Virus (EBV)-specific Cytotoxic T Lymphocytes (CTL) for treatment of EBV-associated Post Transplant Lymphoproliferative Disorder (EBV-PTLD)*. [Press release]. 18 Oct 2016. Available from: <http://investors.atarabio.com/news-releases/news-release-details/atarabio-granted-access-priority-medicines-prime-regulatory> [Accessed 4 January 2019]
- <sup>3</sup> Atara Biotherapeutics. *Atara Bio receives EMA Orphan Drug Designation for Allogeneic Epstein-Barr Virus specific cytotoxic T-lymphocytes to treat Epstein-Barr Virus-associated Post-Transplant Lymphoproliferative Disorder*. [Press release]. 23 Mar 2016. Available from: <http://investors.atarabio.com/news-releases/news-release-details/atarabio-receives-ema-orphan-drug-designation-allogeneic> [Accessed 7 January 2019]
- <sup>4</sup> ClinicalTrials.gov. *Tabelecleucel for Allogeneic Hematopoietic Cell Transplant Subjects With EBV+ PTLD After Failure of Rituximab (MATCH): NCT03392142*. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT03392142> [Accessed 3 January 2019]
- <sup>5</sup> European Medicines Agency. *Public summary of opinion on orphan designation: Allogeneic Epstein-Barr virus specific cytotoxic T lymphocytes for the treatment of post-transplant lymphoproliferative disorder*. Available from: [https://www.ema.europa.eu/documents/orphan-designation/eu/3/16/1627-public-summary-opinion-orphan-designation-allogeneic-epstein-barr-virus-specific-cytotoxic-t\\_en.pdf](https://www.ema.europa.eu/documents/orphan-designation/eu/3/16/1627-public-summary-opinion-orphan-designation-allogeneic-epstein-barr-virus-specific-cytotoxic-t_en.pdf) [Accessed 3 January 2019]
- <sup>6</sup> Nijland ML, Kersten MJ, Pals ST, Bemelman FJ, ten Berge IJM. Epstein-Barr Virus–Positive Post-transplant Lymphoproliferative Disease After Solid Organ Transplantation: Pathogenesis, Clinical Manifestations, Diagnosis, and Management. *Transplant Direct*. 2016 Jan;2(1): e48. Available from: <https://doi.org/10.1097/TXD.0000000000000557>
- <sup>7</sup> Houldcroft CJ, Kellam P. Host genetics of Epstein-Barr virus infection, latency and disease. *Rev Med Virol*. 2015 Mar; 25(2): 71-84. Available from: <https://doi.org/10.1002/rmv.1816>
- <sup>8</sup> Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. *Brit Jnl Haem*. Available from: <https://doi.org/10.1111/j.1365-2141.2010.08161.x>
- <sup>9</sup> Lymphoma Action. *Post-transplant lymphoproliferative disorder (PTLD)*. Available from: <https://lymphoma-action.org.uk/types-lymphoma-lymphoma-and-other-conditions/post-transplant-lymphoproliferative-disorder-ptld> [Accessed 8 January 2019]
- <sup>10</sup> NHS Blood and Transplant. *Organ Donation and Transplantation - Activity figures for the UK as at 6 April 2018*. Available from: [https://nhsbt.dbe.blob.core.windows.net/umbraco-assets/1343/annual\\_stats.pdf](https://nhsbt.dbe.blob.core.windows.net/umbraco-assets/1343/annual_stats.pdf) [Accessed 4 January 2019]
- <sup>11</sup> San-Juan R, Comoli P, Caillard S, Moulin B, Hirsch HH, Meylan P. Epstein-Barr virus-related post-transplant lymphoproliferative disorder in solid organ transplant recipients. *Clin Micro and Infect*. 2014 Sep; 20(7): 109-118. Available from: <https://doi.org/10.1111/1469-0691.12534>
- <sup>12</sup> Atara Biotherapeutics. *Atara Biotherapeutics announces initiation of two phase 3 clinical studies to evaluate Tabelecleucel in patients with Rituximab-refractory Epstein-Barr Virus Associated Post-Transplant Lymphoproliferative Disorder (EBV+PTLD)*. [Press release]. 2 Jan 2018. Available from: <http://investors.atarabio.com/news-releases/news-release-details/atarabiotherapeutics-announces-initiation-two-phase-3-clinical> [Accessed 4 January 2019]
- <sup>13</sup> Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients - BCSH and BTS Guidelines. *Brit Jnl Haem*. Available from: <https://doi.org/10.1111/j.1365-2141.2010.08160.x>

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