ATA129 is a new treatment for Epstein-Barr virus-associated post-transplant lymphoproliferative disorder (EBV-PTLD). EBV-PTLD is a common complication of both organ and stem cell ('bone marrow') transplant. After a transplant, the body's immune system is weakened so that it is unable to respond effectively to infections, leaving the patient very vulnerable to developing PTLD. Some studies have suggested that ATA129 can cells infected by Epstein-Barr virus and kill them. ATA129 is given directly into the bloodstream via intravenous infusion.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Epstein-Barr virus-associated post-transplant lymphoproliferative disorder (EBV-PTLD) – second line in rituximab refractory patients following hematopoietic stem cell transplantation.

TECHNOLOGY

DESCRIPTION

ATA129 (EBV-CTLs; Epstein-Barr virus T-cell therapy) is an EBV-virus specific T-cell therapy that targets EBV proteins. Volunteer donor-derived T-cells are stimulated with EBV antigen presenting cells, resulting in expansion of T-cells active against EBV-infected targets. The allogeneic product is characterised and stored for potential therapeutic use in an appropriate partially human leukocyte antigen (HLA)-matched patient. ATA129 is designed to recognise and target EBV-infected cells in immunocompromised individuals. In clinical trials, ATA129 was administered via intravenous (IV) infusion in a 5 week cycle consisting of 3 weekly infusions of $2 \times 10^6$ T-cells/kg. Patients may receive more than one cycle of therapy as required to achieve the maximal response.

ATA129 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, ATA129 will offer the only licensed treatment option for patients with rituximab refractory EBV-PTLD.

DEVELOPER

Atara Biotherapeutics, Inc. and Atara Biotherapeutics Ireland Limited.

AVAILABILITY, LAUNCH OR MARKETING

ATA129 was awarded PRIME status for EBV-PTLD by the EMA in October 2016 and is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

EBV is a human gamma herpesvirus, which asymptptomatically infects over 95% of adults by the age of 30. Initial infection with EBV typically occurs in childhood, and can be clinically silent or difficult to distinguish from other mild viral infections. Following primary infection, EBV establishes a latent infection with memory B-cells at low levels that the immune system cannot clear.

Allogeneic hematopoietic cell transplantation (alloHCT) is used to treat selected patients with a range of malignant and non-malignant haematological disorders and other specific disorders of the immune system. It involves high-dose chemo- and/or radiotherapy to destroy the patient's immune system followed by replacement of bone marrow stem cells.
with stem cells from a tissue-type matched or unmatched donor\textsuperscript{3}. In the period following transplantation, the immune system is compromised allowing opportunistic pathogens to thrive and the reactivation of latent infections such as EBV. EBV reactivation can cause significant morbidity and mortality in immunocompromised patients, including induction of lymphoproliferation and EBV-positive B-cell tumours\textsuperscript{4,5,6}.

PTLD presents as general or discrete lymphadenopathy. Symptoms are often non-specific and include pyrexia, sweats and weight loss, and extra-nodal involvement is common, including the gastrointestinal tract, lungs, skin, bone marrow and central nervous system\textsuperscript{7}. Its presentation can mimic fulminant sepsis syndrome\textsuperscript{6}.

### CLINICAL NEED and BURDEN OF DISEASE

The incidence of EBV-PTLD is low and it occurs in diverse patient groups\textsuperscript{8}. Following alloHCT, EBV-PTLD incidence ranges from <1\% to 11\%, depending on the type of transplant and degree of immune suppression\textsuperscript{8}. Incidence also varies between transplant centres and whether donors are matched, mismatched, family or unrelated\textsuperscript{10}. The risk of developing EBV-PTLD is elevated during the first year following alloHCT, with the highest occurrence during the first six months\textsuperscript{8}. In 2012, there were 3,616 alloHCTs in England, an increase of 7.7\% on the previous year\textsuperscript{3}. EBV-PTLD significantly impacts survival; a 3-year survival rate of 20\% in patients with PTLD has been reported, as opposed to 62\% among patients without PTLD\textsuperscript{4}. For patients who have either not responded to, or relapsed following first line therapy with rituximab, studies suggest a median overall survival of 16-56 days\textsuperscript{4,11,12}. EBV-PTLD causes high mortality, from both refractory disease and complications of treatment. In addition, as it often occurs in the context of otherwise successful transplants, it may cause donated organs to be wasted\textsuperscript{13}.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

#### NICE Guidance


#### NHS England Policies and Guidance

**CURRENT TREATMENT OPTIONS**

Due to the heterogeneity of EBV-PTLD and patients, there is no one treatment approach. The aim of treatment is to cure the condition whilst preserving the transplant\(^7\). Off-label monotherapy with rituximab is the first line treatment of choice with a positive outcome reported in almost 70% of patients\(^10\). However, around 60-70% of patients treated with rituximab either fail to respond or relapse\(^15,16,17\).

Second line options for EBV-PTLD include\(^9,10,18\):
- Chemotherapy – most commonly CHOP (cyclophosphamide, doxorubicin, oncovin, prednisone) with or without rituximab.
- Cellular therapy – donor lymphocyte infusion (DLI) or EBV-specific cytotoxic T lymphocytes (CTLs).
- Surgery or radiotherapy may be used for select, localised cases of EBV-PTLD.

In the alloHCT setting, chemotherapy has limitations as a therapeutic option as it is frequently associated with high rates of adverse events, including toxic deaths\(^19\). Similarly, although DLI has been shown to produce responses in patients with EBV-PTLD, it is associated with a significant risk for induction of graft versus host disease (GvHD)\(^20\).

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01498484, 11-130; ATA129; phase II.</th>
<th>NCT00002663, 95-024, P30CA008748, MSKCC-95024, NCI-V95-0685; ATA129; phase I/II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Atara Biotherapeutics, Inc.</td>
<td>Atara Biotherapeutics, Inc.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^1), manufacturer.</td>
<td>Trial registry(^21), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
<td>Non-randomised, uncontrolled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=112 (planned); children and adults, any age; EBV-PTLD, lymphoma or other EBV-associated malignancy.</td>
<td>n=84 (planned); children and adults, any age; EBV-PTLD, lymphoma or other EBV-associated malignancy.</td>
</tr>
<tr>
<td>Schedule</td>
<td>All participants receive ATA129, IV, at 2x10(^6) cells/kg on days 1, 8, and 15 of a 5 week cycle. Participants may receive more than one cycle of therapy as required.</td>
<td>All participants receive ATA129, IV, at 1 or 2x10(^6) cells/kg on days 1, 8, and 15 of a 4-6 week cycle. Participants may receive more than one cycle of therapy as required.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Follow-up per protocol is 12 months, however additional follow-up data is available.</td>
<td>Follow-up per protocol is 6 months. Participants achieving complete remission are evaluated at 6 month intervals for one year, or more frequently as clinically required.</td>
</tr>
</tbody>
</table>
In 2017, Atara Biotherapeutics expect to initiate two phase III trials for the treatment of patients with rituximab refractory EBV-PTLD.

### ESTIMATED COST and IMPACT

#### COST

The cost of ATA129 is not yet known.

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**
- ✔ Reduced mortality/increased length of survival
- ☐ Other:
- ☐ Reduced symptoms or disability
- ☐ No impact identified

**Impact on Health and Social Care Services**
- ✔ Increased use of existing services: *long term, due to increased survival.*
- ☐ Re-organisation of existing services
- ☐ Other:
- ☐ Decreased use of existing services: *short term.*
- ☐ Need for new services
- ☐ None identified

**Impact on Costs and Other Resource Use**
- ☐ Increased drug treatment costs
- ✔ Other increase in costs: *additional treatment option.*
- ☐ Reduced drug treatment costs
- ☐ Other reduction in costs: *reduction in costs due to avoidance of toxicity associated with use of alternative treatments such as chemotherapy or radiation therapy.*

**Other Issues**
- ✔ Clinical uncertainty or other research question identified
- ☐ None identified

### REFERENCES

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11 Ocheni S, Kroeger N Zabelina T et al. EBV reactivation and post transplant lymphoproliferative disorders following allogeneic SCT. Bone Marrow Transplantation 2008;42(3):181-186.


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ClinicalTrials.gov. Biological therapy in treating patients at high-risk or with lymphoma, lymphoproliferative disease, or malignancies. https://clinicaltrials.gov/ct2/show/NCT00002663