Innovation Observatory

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Brentuximab vedotin in addition to cyclophosphamide, doxorubicin, and prednisolone (CHP) for CD30+ mature T-cell lymphoma

NIHRIO ID	8929	**NICE ID**	8742
Developer/Company	Takeda UK Ltd	**UKPS ID**	641313

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Brentuximab vedotin in addition to cyclophosphamide, doxorubicin, prednisolone (CHP) as intravenous infusion is in development for the treatment of CD30+ mature T-cell lymphoma also known as peripheral T cell lymphoma (PTCL), a subtype of non-Hodgkins lymphoma. PTCL is a group of aggressive and fast growing lymphomas that develop from mature white blood cells called T-cells and natural killer (NK) cells. If the lymphoma cells express a protein called CD30, it is described as CD30+. In most cases, it is not known what causes T-cell lymphoma. Symptoms vary depending the type of T-cell lymphoma and where it develops. Often, the first symptom of lymphoma is a painless swelling of a lymph node or a group of lymph nodes. Clinical outcomes out of the current standard of care for PTCL are insufficient and there are still unmet needs for a new therapy.

Brentuximab vedotin is a monoclonal antibody cancer treatment medicine that lead to cell death selectively in CD30-expressing tumour cells. Brentuximab vedotin in addition to CHP will offer an additional treatment option for patients with CD30+ mature T-cell lymphoma.

PROPOSED INDICATION

Treatment-naïve CD30+ mature T-cell lymphoma.[a]

TECHNOLOGY

DESCRIPTION

Brentuximab vedotin (ADCETRIS) is an antibody drug conjugate composed of a CD30-directed monoclonal antibody that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE) and delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Nonclinical data suggest that the biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.[1]

Brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisolone (CHP) is in clinical development for patients with CD30-positive mature T-cell lymphomas. In the phase III clinical trial (NCT01777152; ECHELON-2) brentuximab vedotin is given at a dose of 1.8 mg/kg every 3 weeks by IV infusion for 6-8 cycles in newly diagnosed patients.[2]

INNOVATION AND/OR ADVANTAGES

Despite recent progress, there are hurdles to overcome in managing patients with mature T-cell lymphoma, such as the poorly understood role of certain molecular features. Given the insufficient clinical outcomes out of the current standard of care (i.e. cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)), there are still unmet needs for the novel therapy.[3]

Brentuximab vedotin is antibody-drug conjugate composed of a CD30-directed monoclonal antibody that lead to cell death selectively in CD30-expressing tumour cells. It is licensed in the UK for the treatment of certain types of lymphoma such as CD30+ HL and CD30+ CTCL.[1] Data from phase III trial (ECHELON-2) in patient with CD30+ mature T-cell Lymphomas revealed that brentuximab vedotin in combination with CHP demonstrated a significant improvement in the primary endpoint of progression-free survival and all key secondary endpoints, including overall survival, along with a manageable safety profile. Therefore, brentuximab vedotin is a potential treatment option for patients with CD30+ mature T-cell lymphoma.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Brentuximab vedotin in addition to CHP does not currently have Marketing Authorisation in the EU/UK for any indication.

Brentuximab vedotin is licensed in the UK for:[1]

[a] Information provided by Takeda UK Ltd on UK PharmaScan

- the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
- the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT
- the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).
- the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy

Very common adverse effect (>10%) associated with brentuximab vedotin are upper respiratory tract infection, neutropenia, peripheral sensory neuropathy, peripheral motor neuropathy, cough, dyspnoea, nausea, diarrhoea, vomiting, constipation, abdominal pain, rash, pruritus, arthralgia, myalgia, fatigue, pyrexia, infusion-related reactions, and decreased weight.[1]

Brentuximab vedotin is in phase II/III clinical development for different types of lymphomas.[5]

Brentuximab vedotin is a designated orphan drug in the USA for treatment of patients with peripheral T-cell lymphoma, not otherwise specified in April 2013.[6]

Brentuximab vedotin was designated a Breakthrough Therapy by the FDA in November 2018 for previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with CHP.[7]

PATIENT GROUP

DISEASE BACKGROUND

Lymphomas can be grouped as Hodgkin or non-Hodgkin lymphomas (NHL), depending on the types of cell they contain. Non-Hodgkin lymphomas can develop from abnormal T-cells or B cells. All T-cell lymphomas are a type of non-Hodgkin lymphoma. T-cells are made in the bone marrow as immature (unspecialised) T-cells. They then mature into specific types of T-cell in the thymus gland, before moving to the lymph nodes, where they stay. T-cell lymphomas can develop from immature T-cells or mature T-cells.[8]

Mature T-cell lymphoma, also known as peripheral T-cell lymphoma hereby PTCL,[9] is defined as a diverse group of aggressive lymphomas that develop from mature-stage T-cells and natural killer (NK) cells and that for the most part carry a poor prognosis.[10,11] The most common subtype of PCTL is called PTCL-not-otherwise specified (PTCL-NOS) and is most frequently diagnosed in individuals living in North America and Europe. Other subtypes include, anaplastic large cell lymphoma (ALCL), common in North America and Europe; angioimmunoblastic T-cell lymphoma (AITL), the second most common subtype found more often in Europe; and other types known as NK-/ T-cell lymphoma (NKTCL) and adult T-cell leukemia (ATLL), most common in Asia.

Most PTCL subtypes are fast-growing including PTCL-NOS, AITL, ALCL, enteropathy-type T-cell lymphoma, and extranodal natural killer (NK) cell/T-cell lymphoma.[10] When tumour cells express a protein called CD30 on their surface, they are regarded as CD30+.[12] Overall, patients with PTCL have poorer outcomes compared with patients with aggressive B-cell lymphomas. Furthermore, a study has reported that CD30 expression is an adverse prognostic factor in PTCL-NOS.

In most cases, it is not known what causes T-cell lymphoma. In a few types of T-cell lymphoma, research has shown that certain viral infections or medical conditions can increase the risk of

developing lymphoma. For example; the human T-lymphotropic virus 1 (HTLV1) is linked with ATLL; and past infection with Epstein-Barr virus (EBV) is linked to the development of many types of lymphoma, including AITL.[8]

The most common symptoms vary depending on the type of T-cell lymphoma and where it develops. Often, the first symptom of lymphoma is a painless swelling of a lymph node or a group of lymph nodes. T-cell lymphomas often cause people to feel unwell and have night sweats, fevers and unexplained weight loss.[8]

CLINICAL NEED AND BURDEN OF DISEASE

PTCLs represent 10%–15% of all NHLs. In PTCLs, the male/female ratio is 2:1 and the median age at diagnosis is between the sixth and seventh decades of life, but both sex and age patterns vary according to different subtypes.[13] In the UK a study by the Haematological Malignancy Research Network that reported cases registered between 2004 and 2012, the European age standardised incidence rate per 100,000 persons for T-cell lymphoma was 0.92 (95% CI 0.88-0.97) and for Peripheral – common, unspecified was 0.27 (05% CI 0.24-0.29).[14]

In England in 2016 there were 542 (328 males and 214 females) newly diagnosed cases of peripheral T-cell lymphomas (ICD10: C84.4). Age standardised incidence rate was 2.2/100,000 in males and 1.2/100,000 in females.[15]

In 2017-2018 there were 2,528 hospital admissions in England with 2,815 finished consultant episodes and 1,960 day cases for people who primary diagnosis was peripheral T-cell lymphoma, not elsewhere classified (ICD10: C84.4).[16] A prospective, international study revealed that out of 490 PTCL cases that were tested for CD30 expression, 349 (71%) reported as CD30+.[17]

In England in 2016, there were 266 registered death cases (159 males, 107 females) of peripheral and cutaneous T-cell lymphomas (ICD10: C84) with an age standardised death rate of 0.7/100,000 in males and 0.4/100,000 in females.[15]

Five year overall survival and relative survival rates in the UK for peripheral—common, unspecified cases diagnosed 2004 – 2012 and followed through to 2014 were 17.6 (95% CI 10.3–26.5) and 19.7 (95% CI 11.5–29.5) respectively.[14]

The population likely to be eligible to receive brentuximab vedotin in addition to CHP could not be estimated from available published sources.

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

In a few cases, if the initial cancer is very small and can be removed during a biopsy, no further treatment may be needed. The recommended treatment plan will depend on the patient's general health and age, as many of the treatments can put a tremendous strain on the body. A multidisciplinary team will discuss the treatment plan and recommend the best treatment options for the patient.[18]

CURRENT TREATMENT OPTIONS

NICE recommends cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy as first-line treatment for people with peripheral T-cell lymphoma.[19]

PLACE OF TECHNOLOGY

If licensed, brentuximab vedotin in addition to CHP will offer an additional treatment option for patients with CD30+ Mature T-cell lymphoma.

CLINICAL TRIAL INFORMATION

Trial	**ECHELON-2, NCT01777152, SGN35-014; brentuximab vedotin in addition to CHP vs CHOP; phase III**
Sponsor	Seattle Genetics, Inc.
Status	Ongoing
Source of Information	Trial registry;[2] Press release[4]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, active-controlled, parallel assignment
Participants	n=452; aged 18 years and older; CD30-positive mature T-cell lymphomas; newly diagnosed; fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by CT; Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.
Schedule	Randomised to one of the following arms: • Experimental arm: brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion for 6-8 cycles; doxorubicin 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles; prednisone 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles; cyclophosphamide 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles. • Active comparator arm: doxorubicin 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles; prednisone 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles; vincristine 1.4 mg/m2 (maximum 2 mg) every 3 weeks by IV infusion for 6-8 cycles; cyclophosphamide 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles
Follow-up	Active treatment period is for 6 – 8 cycles. Duration of the cycle is not reported. Overall follow-up period is not reported.
Primary Outcomes	Progression-free survival per independent review facility (IRF) [Time Frame: Until disease progression, subsequent anticancer chemotherapy, death, or study closure, up to 5 years post-treatment]
Secondary Outcomes	• Progression-free survival per IRF in patients with systemic anaplastic large cell lymphoma (sALCL) [Time Frame: until disease progression, subsequent anticancer chemotherapy, death, or study closure, up to 5 years post-treatment] • Complete remission rate per IRF at end of treatment [Time Frame: through 1 month following last dose] • Overall survival [Time Frame: until death or study closure, up to 7 years post-treatment]

	• Objective response rate per IRF at end of treatment [Time Frame: through 1 month following last dose] • Type, incidence, severity, seriousness, and relatedness of adverse events [Time Frame: through 1 month following last dose] • Incidence of laboratory abnormalities [Time Frame: through 1 month following last dose]
Key Results	Results from the trial demonstrated that combination treatment with brentuximab vedotin plus CHP was superior to the control arm for PFS as assessed by an IRF; hazard ratio=0.71; p-value=0.0110. The brentuximab vedotin plus CHP arm also demonstrated superior overall survival (OS), a key secondary endpoint, compared to CHOP (hazard ratio=0.66; p-value=0.0244). All other key secondary endpoints, including PFS in patients with systemic anaplastic large cell lymphoma (sALCL), complete remission rate and objective response rate were statistically significant in favour of the brentuximab vedotin plus CHP arm. The safety profile of brentuximab vedotin plus CHP in the ECHELON-2 trial was comparable to CHOP and consistent with the established safety profile of brentuximab vedotin in combination with chemotherapy.
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as December 2019.

ESTIMATED COST

Brentuximab vedotin is already marketed in the UK; a 50mg powder for concentrate for solution for infusion vial costs £2,500.00.[20]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. T-cell lymphoma (peripheral, relapsed or refractory) - romidepsin (ID504). Expected publication date to be confirmed.
- NICE technology appraisal in development. Lymphoma (non-Hodgkin's, peripheral T-cell) - pralatrexate (ID368). Expected publication date to be confirmed.
- Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma (ID1190). Expected publication date: May 2019
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- European Society for Medical Oncology (ESMO). Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[13]
- British Committee of Standards in Haematology. Guideline for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell Lymphoma). Updated August 2013.[21]

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