Health Technology Briefing
February 2024

Brentuximab vedotin with cyclophosphamide, prednisone and doxorubicin for treating peripheral T-cell lymphoma

Company/Developer	Takeda UK Ltd

☐ **New Active Substance** ☒ **Significant Licence Extension (SLE)**

NIHRIO ID: 38151	**NICE ID:** Not available	**UKPS ID:** 673409

Licensing and Market Availability Plans

Currently in phase II and phase III clinical development

Summary

Brentuximab vedotin in combination with cyclophosphamide, prednisone and doxorubicin is in clinical development for the treatment of peripheral T-cell lymphoma (PTCL). Peripheral T-cell lymphomas (PTCLs) are a group of rare blood cancers. They develop in T-cells and affect the lymphatic system. PTCLs happen when the T-cells mutate and become cancerous cells that multiply uncontrollably. PTCL is a long-term debilitating and life-threatening condition, because in most cases the disease does not respond well to therapy, usually comes back within one year, and is associated with early death.

Brentuximab vedotin is delivered via intravenous infusion and is intended to target cancer cells that have a protein called CD30 on their surface. It is a monoclonal antibody (a type of protein) that binds to CD30, linked to monomethyl auristatin E (MMAE), a cytotoxic (cell-killing) molecule. The monoclonal antibody delivers MMAE to the CD30-positive cancer cells. The cytotoxic molecule then enters the cancer cells and stops them from dividing, and the cancer cells eventually die. If given a licence extension, combining brentuximab vedotin with cyclophosphamide and prednisone and doxorubicin may offer a novel treatment approach for adult patients with PTCL.

Proposed Indication

Treatment of adult patients with cluster of differentiation 30 (CD30)+ peripheral T-cell lymphoma (PTCL).[1]

Technology

Description

Brentuximab vedotin (Adcetris, SGN-35) is composed of three parts: a chimeric human-murine IgG1 that selectively targets CD30, monomethyl auristatin E (MMAE), which is a microtubule-disrupting agent, and a protease-susceptible linker that links the antibody and MMAE. The IgG1 antibody enables brentuximab vedotin to target tumour cells expressing CD30 on their surface. Following this, brentuximab vedotin enters the cell. Once inside, the linker is cleaved releasing MMAE which binds to and disrupts the microtubule network within the cell, inducing cell cycle arrest and resulting in apoptotic death of the CD30-expressing tumour cell.[2,3]

Brentuximab vedotin in combination with cyclophosphamide, prednisone and doxorubicin is currently in clinical development for the treatment of adults with CD30+ PTCL. In a phase III clinical trial (NCT01777152) brentuximab vedotin 1.8 mg/kg, was administered every 3 weeks by intravenous (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 and cyclophosphamide 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles.[4]

Key Innovation

PTCL represent a rare heterogeneous group of non-Hodgkin lymphomas that generally have worse outcomes with standard chemotherapy treatment than other similar lymphomas.[5] The management of PTCL patients continues to be a challenge for physicians, and its treatment is still an unmet medical need. For decades cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has remained the most commonly used frontline regimen for previously untreated patients with PTCL.[6]

CD30 is a transmembrane glycoprotein (receptor) that is highly expressed on lymphoma cells and has minimal cross-reactivity with normal tissue, making this molecule an ideal drug target.[7]. Because of the CD30-targeted mechanism of action of brentuximab vedotin, it is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy, irrespective of prior transplant status.[2] The linkage system in brentuximab vedotin is highly stable in plasma, resulting in cytotoxic specificity for CD30-positive cells.[8] CD30 expression at any level is detected by immunohistochemistry (IHC) in ~60% of PTCL-NOS cases.[9]

If given a significant licence extension, brentuximab vedotin in combination with cyclophosphamide, prednisone, and doxorubicin (CHP) will offer novel first line treatment approach for adult patients with CD30 positive PTCL.

Regulatory & Development Status

Brentuximab vedotin as a monotherapy, or as part of a combination treatment, has marketing authorisation in the United Kingdom for the following:[2]

- adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma in combination with doxorubicin, vinblastine and dacarbazine
- adult patients with CD30+ Hodgkin Lymphoma at increased risk of relapse or progression following autologous stem cell transplant (ASCT)

- adult patients with relapsed or refractory CD30+ Hodgkin lymphoma: following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
- as a combination with CHP in adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)
- adult patients with relapsed or refractory sALCL.
- adult patients with CD30+ cutaneous T-cell lymphoma after at least 1 prior systemic therapy.

Brentuximab vedotin has the following designation/awards:

- an orphan drug in the EU in January 2009 for PTCL[10]
- an orphan drug in from US FDA in October 2008 for PTCL, and other lymphomas[11]

Brentuximab vedotin is in phase II clinical development for:

- aggressive Systemic Mastocytosis or Mast Cell Leukaemia.[12]
- extranodal Natural Killer/T-cell Lymphoma.[13]

Patient Group

Disease Area and Clinical Need

PTCLs are uncommon and heterogeneous malignant lymphoproliferative disorders that originate from (post-thymic) peripheral T-cells or mature natural killer cells. They represent 10%–15% of all non-Hodgkin's lymphomas.[14] People with PTCL usually develop lumps, which may grow quite rapidly. Although these lumps most often form in the lymph nodes (nodal PTCL), they can occur in other body sites (extranodal PTCL), including the stomach, skin, and small intestine. By the time the condition is diagnosed, most people have widespread disease, and experience fever, fatigue, weight loss and night sweats, and will require aggressive treatment to manage their condition.[15] A family history of haematological disorders, genetic background, viral infections, occupational and environmental exposures and dietary intake have all been associated with PTCL.[16] Treatment challenges persist for patients with PTCL, as many are refractory to initial therapy and experience poor progression-free survival, even when initially responsive to therapy. Often patients present with advanced stage disease, and frequently have co-occurring comorbidities, resulting in a large clinical and economic burden.[17]

The estimated five-year survival rate for people with aggressive PTCL after first-line therapy is 30%. It generally affects people over 60 years of age and incidence is slightly higher in men than in women.[15]In England, (2022-23), there were 2,447 finished consultant episodes (FCE) and 2,158 admissions for PTCL-NOS (ICD-10 code C84.4) which resulted in 1,812-day cases and 5,183 FCE bed days.[18]

Recommended Treatment Options

Currently the only treatment recommended by the National Institute for Health and Care Excellence (NICE) for the management of PTCL is to consider CHOP chemotherapy as first-line treatment for people with PTCL.[19]

Clinical Trial Information

Trial	**ECHELON-2** NCT01777152 , 2012-002751-42 **:** A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in the Frontline Treatment of Patients With CD30-positive Mature T-cell Lymphomas. **Phase: III –** Completed

	Location(s): 9 EU countries, UK, USA, Australia, and others **Primary completion date:** August 2018
Trial Design	Randomised, parallel assignment, double blinded
Population	N=452 (actual) adult participants with CD30-positive mature T-cell lymphomas, aged 18 years and older
Intervention(s)	Brentuximab vedotin IV Cyclophosphamide IV Doxorubicin IV Prednisone oral
Comparator(s)	Cyclophosphamide IV, Doxorubicin IV, Vincristine IV, Prednisone oral
Outcome(s)	Primary outcome measure: • Progression-free Survival Per Independent Review Facility (IRF) [Time Frame: Up to 60 months] See trial record for full list of other outcomes
Results (efficacy)	A total of 452 subjects were enrolled between January 24, 2013, and November 07, 2016, and 226 subjects were randomly assigned to each arm. The hazard ratios of both the PFS (0·71 [95% CI: 0·54, 0·93], p=0·0110) and overall survival (OS) (0·66 [95% confidence interval: 0·46, 0·95], p=0·0244) favoured A+CHP over CHOP. The median PFS was 48·2 months (95% CI: 35·2, not evaluable) versus 20·8 months (95% CI: 12·7, 47·6), for A+CHP and CHOP, respectively. The median was not met for OS.[6]
Results (safety)	Adverse events (AEs), including incidence and severity of febrile neutropenia (in 41 subjects (18%) in A+CHP arm and 33 (15%) in CHOP) and peripheral neuropathy (in 117 subjects (52%) in A+CHP arm and 124 (55%) in CHOP), were similar between arms. Fatal AEs occurred in 7 subjects (3%) in the A+CHP arm and 9 subjects (4%) in the CHOP arm.[6]

Clinical Trial Information	
Trial	NCT05673785; A Phase 2, Single-Arm, Open-Label, Multicentre Study of Brentuximab Vedotin in Combination with Cyclophosphamide, Doxorubicin (Hydroxydaunorubicin), Prednisone (CHP) in the Frontline Treatment of Chinese Patients with CD30-Positive (CD30+) Peripheral T-Cell Lymphomas (PTCL) **Phase: II –** Recruiting **Location(s):** China **Primary completion date:** July 2025
Trial Design	Single group assignment, open label

Population	N=52 (estimated), adults newly diagnosed with CD30 -positive (CD30+) PTCL; aged 18 years and older
Intervention(s)	Brentuximab vedotin IV Cyclophosphamide IV Doxorubicin IV Prednisone oral
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Overall Response Rate (ORR) by Independent Review Facility (IRF) Assessment per Revised Response Criteria for Malignant Lymphoma [Time Frame: Up to approximately 7 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Brentuximab vedotin is already marketed in the UK: the National Health Service indicative price for one 50mg powder for concentrate for solution for infusion vial is £2,500.[20]

Relevant Guidance

NICE Guidance

- NICE clinical 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/

Other Guidance

- T-Cell Lymphomas, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology.[21]
- ESMO Guidelines Committee. (2015). Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[14]
- British Society for Haematology. Guidelines for the Management of mature T- and natural killer-cell lymphomas (excluding cutaneous T-cell lymphoma). Updated November 2021.[22]

Additional Information

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