Health Technology Briefing
January 2024

Brentuximab vedotin with chemotherapy (BrECADD) for previously untreated advanced classical Hodgkin lymphoma

Company/Developer	Takeda UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33922	NICE ID: Not Applicable	UKPS ID: 671745

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Hodgkin lymphoma (HL) is an uncommon cancer that develops in the lymphatic system, which is a network of vessels and glands spread throughout the body. About 95% of all HL cases are classical HL. Lymphomas are cancers that occur if white blood cells of the immune system start to multiply uncontrollably. Symptoms of classical HL include swelling of lymph nodes in the neck, armpit or groin, recurring fever, night sweats, weight loss, cough, breathlessness, abdominal pain and itching. There is an unmet need for treatment strategies which improve survival outcomes that are not offset by more serious treatment side-effects.

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 licensed, brentuximab vedotin with combination chemotherapy (referred to as BrECADD) will offer a treatment option for adults with a diagnosis of advanced stage classical Hodgkin lymphoma who have few treatment options available.

Proposed Indication

The first-line treatment of advanced stage Hodgkin lymphoma (HL).[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 allowing brentuximab vedotin to enter 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 the combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone (BrECADD) is being evaluated for the first line treatment of advanced classical HL. In the phase III clinical trial (NCT02661503), brentuximab vedotin is administered via intravenous infusion as part of the BrECADD combination chemotherapy protocol.[1]

Key Innovation

Brentuximab vedotin is designed to be stable in the bloodstream, but to release MMAE upon internalisation into CD30-expressing tumour cells, resulting in a targeted cell-killing effect.[4] Improved progression free survival without elevated morbidity is an unmet need in the treatment of HL, necessitating detailed assessment of patients' individual risk profiles and preference.[5] The most common treatments currently are called ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone); eBEACOPP is more effective, but has such high rates of significant toxicity such that it cannot, for example, be offered to over-60s.[5,6] The brentuximab vedotin combination BrECADD is designed and selected to be as effective as eBEACOPP, but with lower (more acceptable) morbidity.

If licenced, brentuximab vedotin in the BrECADD combination chemotherapy regimen will provide a new option for patients with previously untreated advanced HL who currently have few well-tolerated effective therapies available.

Regulatory & Development Status

Brentuximab vedotin currently has Marketing Authorisation in the EU/UK for the following indications:[3]

- Adult patients with previously untreated CD30+ Stage IV HL in combination with doxorubicin, vinblastine and dacarbazine
- Adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT)
- Adult patients with relapsed or refractory CD30+ HL following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option
- As a combination therapy with cyclophosphamide, doxorubicin and prednisone in adult patients with previously untreated systemic anaplastic large cell lymphoma
- Adult patients with relapsed or refractory systemic anaplastic large cell lymphoma
- Adult patients with CD30+ cutaneous T-cell lymphoma after at least 1 prior systemic therapy

Brentuximab vedotin has the following regulatory designation/awards:

- Breakthrough therapy for frontline treatment of classical HL from the US FDA in October 2017.[7]
- An orphan drug in the EU in 2009 for the treatment of HL.[8]
- Fast track designation for the treatment of HL from the US FDA in March 2009.[4]

Brentuximab vedotin with chemotherapy in the BrECADD combination is not currently in clinical development for any other conditions.[9]

Brentuximab vedotin, alone or in combination, is in phase II and III clinical development for the treatment of a number of conditions including:[9]

- Sezary syndrome
- Mycosis fungoides
- Lymphoma (T-cell lymphomas, HL (various indications), cutaneous lymphomas, follicular lymphoma, diffuse large B-cell lymphoma)
- Other cancers (melanoma, non-small cell lung cancer, squamous cell carcinoma, T-cell leukemia, malignant mesothelioma)
- Diffuse cutaneous systemic sclerosis

Patient Group

Disease Area and Clinical Need

HL is a type of blood cancer that develops when white blood cells called lymphocytes grow out of control. Lymphocytes are part of the immune system, and travel around the lymphatic system, helping fight infections.[10] The causes of HL are not fully understood but a person's risk of developing the condition increases if they are genetically pre-disposed, have a pre-existing medical condition which has compromised the immune system, take immunosuppressant medication(s), or have previously been infected with the Epstein-Barr virus.[11] Symptoms commonly include painless enlargement or swelling of lymph nodes in the neck, armpit, or groin, other symptoms can include; itching, fever, cough, shortness of breath, abdominal pain and weight loss.[12]

HL is an uncommon cancer, accounting for less than 1% of new cancer cases between 2016-2018 in the UK.[13] About 95% of all HL is classical HL.[14] The age standardised incidence rate of HL in England is 2.7 and 3.9 per 100,000 amongst females and males respectively.[13] In England (2021-22) there were 23,010 finished consultant episodes (FCEs) and 22,258 admissions for HL (ICD-10 code C81), which resulted in 20,273 day cases and 15,073 FCE bed days.[15] In England (2017) there were 1,802 patients diagnosed with HL and 275 deaths registered where HL was the underlying cause.[16] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 90.6% and 82.2% respectively.[17]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatments for previously untreated, advanced classical HL.[18]

Stage IIB HL with a large mediastinal mass and/or extranodal disease, as well as stage III/IV, are usually managed as advanced disease.[5] Standard treatment for advanced HL is combination chemotherapy; the most common regimens are called ABVD and escalated BEACOPP (eBEACOPP); a PET scan is used to determine the ongoing treatment.[5]

Clinical Trial Information	
Trial	NCT02661503; EudraCT 2014-005130-55; HD21 for Advanced Stages Treatment Optimization Trial in the First-line Treatment of Advanced Stage Hodgkin Lymphoma; Comparison of 6 Cycles of Escalated BEACOPP With 6 Cycles of BrECADD **Phase III** – Recruiting **Location**: One EU country **Primary completion date**: December 2022
Trial Design	Randomised, parallel assignment, open-label
Population	N= 1500 (planned); adults 18-60 years of age with previously untreated classical HL classed as intention-to-treat (ITT) after recruitment; Stage IIB with large mediastinal mass and/or extranodal lesions; Stage III or IV
Intervention(s)	BrECADD treatment: 4 or 6 cycles of BRECADD (21-day cycles): Brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone
Comparator(s)	BEACOPP treatment: 4 or 6 cycles of BEACOPP (21-day cycles): Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
Outcome(s)	Primary outcome measures: • Progression Free Survival [Time frame: 5 years] • Treatment Related Morbidity (TRMB) [Time frame: during 6 cycles of chemotherapy (21-day cycles)]
Results (efficacy)	59% of patients received 4 and 41% received 6 cycles of therapy. Median follow-up was 40 months. 3-year PFS was 92.3% for eBEACOPP and 94.9% for BrECADD, the corresponding point estimate for the HR was 0.63 (99% CI 0.37–1.07) and thus below the pre-specified bound. Progression or early relapse of HL ≤1 year was documented for 37 patients in the eBEACOPP arm (5%) and 16 patients in the BrECADD arm (2.2%). 3-year overall survival was 98.5% in both groups.[19]
Results (safety)	Treatment-related morbidity (TRMB) was analysed in the ITT cohort comprising 732 patients in the eBEACOPP and 738 patients in the BrECADD group. Overall, TRMB was documented in 59% and 42 % of patients in the eBEACOPP and BrECADD groups, respectively (relative risk for eBEACOPP 1.41; 95% CI, 1.27 - 1.56, p<0.001, relative risk for BrECADD 0.72; 95% Confidence interval [CI], 0.65 - 0.79, p<0.001). The relative risk estimates remained stable among the stratification factors (sex, age, IPS, location). In the eBEACOPP group 52% of patients had hematological TRMB events compared to 31% in the BrECADD group (p<0.001). The significant difference for haematological TRMB was reflected in the reduction in red cell and platelet transfusions. At least one red cell transfusion was given in 22% of patients in the eBEACOPP group and in 8% of the BrECADD group, and at least one platelet transfusion in 13% and 6%, respectively. Leukopenia grade 4 was observed in 94% and 87%, respectively. TRMB organ toxicity was documented in 17% of patients in the eBEACOPP group and 19% in the BrECADD group (p = 0.455). Peripheral sensory neuropathy all grades was documented in 49% and 38% in the eBEACOPP and BrECADD group,

	respectively, which was mainly grade 1 (33% and 31%), whereas grade 2 occurred in 14% and 6%, and grade 3 in 2% and 1%, respectively. Peripheral motor neuropathy all grades was documented in 4% in both treatment groups, which was grade 1 in 3%, and grade 2 in 1% in each group, respectively.[20]

Estimated Cost

The NHS indicative cost of one vial of brentuximab vedotin (50mg) is £2,500.00.[21]

Relevant Guidance

NICE Guidance

- NICE quality standard: Haematological cancers (QS150) June 2017

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult), B15/S/a.

Other Guidance

- George A. et al., British Society for Haematology. Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. 2022.[5]
- Eichenauer DA. et al., on behalf of the ESMO Guidelines Committee. Hodgkin Lymphoma: ESMO Clinical Practice Guidelines. 2018.[22]

Additional Information

References

1 ClinicalTrials.gov. *HD21 for Advanced Stages Treatment Optimization Trial in the First-line Treatment of Advanced Stage Hodgkin Lymphoma; Comparison of 6 Cycles of Escalated BEACOPP With 6 Cycles of BrECADD*. *Trial ID: NCT02661503*. 2016. Status: Recruiting. Available from: https://clinicaltrials.gov/study/NCT02661503?tab=table#recruitment-information [Accessed 28 November 2023].

2 Drugbank. *Brentuximab vedotin*. 2022. Available from: https://go.drugbank.com/drugs/DB08870 [Accessed 9 January 2024].

3 Electronic Medicines Compendium (EMC). *Adcetris 50 mg powder for concentrate for solution for infusion*. 2022. Available from: https://www.medicines.org.uk/emc/product/2859/smpc [Accessed 9 January 2024].

4 Seattle Genetics. *Seattle Genetics Receives FDA Fast Track Designation for SGN-35 for the Treatment of Hodgkin Lymphoma*. Press release 30/3/2009. Available from: https://investor.seagen.com/press-releases/news-details/2009/Seattle-Genetics-Receives-FDA-Fast-Track-Designation-for-SGN-35-for-the-Treatment-of-Hodgkin-Lymphoma/default.aspx [Accessed 29 November 2023].

5 Follows GA, Barrington SF, Bhuller KS, Culligan DJ, Cutter DJ, Gallop-Evans E, et al. Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for

Haematology guideline. *British Journal of Haematology*. 2022;197(5):558-72. Available from: https://doi.org/10.1111/bjh.18083.

6 Hanel W, Herrera AF, Epperla N. Management of classical Hodgkin lymphoma: a look at up to date evidence and current treatment approaches. *Experimental Hematology & Oncology*. 2022;11(1):108. Available from: https://doi.org/10.1186/s40164-022-00360-4.

7 Seattle Genetics. *Seattle Genetics Receives FDA Breakthrough Therapy Designation for ADCETRIS® (Brentuximab Vedotin) in Frontline Advanced Hodgkin Lymphoma*. Press release 2/10/2017. Available from: https://investor.seagen.com/press-releases/news-details/2017/Seattle-Genetics-Receives-FDA-Breakthrough-Therapy-Designation-for-ADCETRIS-Brentuximab-Vedotin-in-Frontline-Advanced-Hodgkin-Lymphoma/default.aspx [Accessed 29 November 2023].

8 European Medicines Agency (EMA). *EU/3/08/596: Orphan designation for the treatment of Hodgkin's lymphoma*. 2009. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu308596 [Accessed 28 November 2023].

9 ClinicalTrials.gov. *Search of ClinicalTrials.gov, ongoing phase 2 and 3 clinical trials of brentuximab vedotin*. Available from: https://clinicaltrials.gov/search?intr=brentuximab%20vedotin&aggFilters=phase:2%203,status:not%20rec%20act [Accessed 29 November 2023].

10 National Health Service. *Hodgkin lymphoma: Overview*. 2021. Available from: https://www.nhs.uk/conditions/hodgkin-lymphoma/ [Accessed 12 December 2023].

11 National Health Service (NHS). *Hodgkin lymphoma - Causes*. 2021. Available from: https://www.nhs.uk/conditions/hodgkin-lymphoma/causes/ [Accessed 28 November 2023].

12 Cancer Research UK. *Hodgkin Lymphoma: Symptoms*. 2020. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/symptoms [Accessed 28 November 2023].

13 Cancer Research UK. *Hodgkin lymphoma incidence statistics*. 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/incidence#heading-Zero [Accessed 28 November 2023].

14 Lymphoma Action. *Classical Hodgkin Lymphoma*. 2022. Available from: https://lymphoma-action.org.uk/types-lymphoma-hodgkin-lymphoma/classical-hodgkin-lymphoma [Accessed 29 November 2023].

15 NHS Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 24 October 2023].

16 Office for National Statisics (ONS). *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 28 November 2023].

17 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed.

18 National Insititute for Health and Care Excellence. *Search of: previously untreated, advanced hodgkin lymphoma*. 2023. Available from: https://www.nice.org.uk/search?q=previously%20untreated,%20advanced%20hodgkin%20lymphoma [Accessed 12 December 2023].

19 Borchmann P, Moccia A, Greil R, Schneider G, Hertzberg M, Schaub V, et al. BRECADD is non-inferior to eBEACOPP in patients with advanced stage classical Hodgkin lymphoma: Efficacy

resutls of the GHSG PHASE III HD21 trial. *Hematological Oncology*. 2023;41:881-2. Available from: https://doi.org/doi:10.1002/hon.3196_LBA5.

20 Borchmann P, Moccia A, Greil R, Hertzberg M, Schaub V, Hüttmann A, et al. Treatment Related Morbidity in Patients with Classical Hodgkin Lymphoma: Results of the Ongoing, Randomized Phase III HD21 Trial By the German Hodgkin Study Group. *Blood*. 2022;140(Supplement 1):771-3. Available from: https://doi.org/10.1182/blood-2022-165917.

21 National Institute for Health and Care Excellence (NICE). *Brentuximab vedotin: Medicinal forms*. 2023. Available from: https://bnf.nice.org.uk/drugs/brentuximab-vedotin-specialist-drug/medicinal-forms/ [Accessed 28 November 2023].

22 Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv19-iv29. Available from: https://doi.org/10.1093/annonc/mdy080.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.