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Health Technology Briefing
June 2023

Brentuximab vedotin with doxorubicin, dacarbazine and vinblastine for previously untreated late-stage classical Hodgkin lymphoma

Company/Developer	Takeda UK Ltd in collaboration with Seagen Inc (SGEN).

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 35942	NICE TSID: Not available	UKPS ID: 665218

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Lymphoma is a blood cancer which occurs if white blood cells of the immune system, grow and multiply uncontrollably. Twenty percent of all lymphoma patients are diagnosed with Hodgkin lymphoma. The disease usually occurs in individuals either aged between 20 to 25 or over 75 years. Symptoms 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 novel strategies to improve survival rates.

The proposed therapy is delivered via intravenous infusion and is intended to target malignant CD30 positive cells. The active substance, brentuximab vedotin, is a monoclonal antibody (a type of protein) that binds to CD30, linked to monomethyl auristatin E, a cytotoxic (cell-killing) molecule. The monoclonal antibody delivers monomethyl auristatin E 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, in combination with chemotherapies (doxorubicin, vinblastine and dacarbazine) will offer a treatment option for adults with a diagnosis of advanced stage classical Hodgkin lymphoma who have few treatment options available.

This briefing reflects the evidence available at the time of writing 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. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

Brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine in treatment naïve adults with advanced classical Hodgkin lymphoma.[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 combination with doxorubicin, vinblastine and dacarbazine is being evaluated for the first line treatment for advanced classical Hodgkin lymphoma. In the pivotal, randomised, open label, phase III clinical trial ECHELON-1, brentuximab vedotin is administered via intravenous infusion at 1.2 milligram per kilogram (mg/kg) along with 25 mg/m^2 of doxorubicin, 6 mg/m^2 vinblastine, and 375 mg/m^2 dacarbazine on days 1 and 15 of a maximum of six 28-day cycles.[4]

Key Innovation

Standard, first-line treatment for advanced-stage classic Hodgkin lymphoma is a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), however, a substantial proportion of patients with stage III or IV disease relapse or are refractory to ABVD treatment.[5] Data from a six year follow up of patients with advanced Hodgkin lymphoma who received combination treatment with brentuximab vedotin demonstrates improved survival compared to active comparator.[5] If licenced brentuximab vedotin will offer and additional treatment option for patients with advanced classical Hodgkin lymphoma.

Regulatory & Development Status

Brentuximab vedotin currently has Marketing Authorisation in the EU/UK for the following indications:[6]

- 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 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 is in phase II and III clinical development for a number of conditions, including the treatment of:[7]

- Sclerosis
- Mycosis fungoides
- Cancer (T-cell lymphoma, Non-small cell lung cancer)

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Brentuximab vedotin has the following regulatory designation/award:[8]

- An orphan drug in the EU in 2009 for the treatment of Hodgkin lymphoma.

Patient Group

Disease Area and Clinical Need

Classical Hodgkin lymphoma is a B-cell lymphoma that develops in the lymphatic system and is typically characterised histologically by the presence of large mononuclear Hodgkin cells and multinucleated Reed-Sternberg cells.[9] The aetiology of Hodgkin lymphoma is not yet 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.[10] Onset most commonly occurs in young adults aged between 20 and 25, followed by adults over the age of 75 but can be difficult to detect because many patients are asymptomatic in the early stages. Symptoms commonly include painless enlargement or swelling of lymph nodes that are located in the neck, armpit, or groin, other symptoms can include; itchy skin, fatigue, fever, cough, breathlessness, abdominal pain and decreased appetite/weight loss.[11]

Hodgkin lymphoma is an uncommon cancer, accounting for less than 1% of new cancer cases between 2016-2018 in the UK.[12] The age standardised incidence rate of Hodgkin lymphoma in England is 2.7 and 3.9 per 100,000 amongst females and males retrospectively.[13] In England (2021-22) there were 21,293 finished consultant episodes (FCEs) and 20,523 admissions for Classical Hodgkin lymphoma (C81.1, C81.2, C81.3, C81.4, C81.7 C81.9 (NOS)), which resulted in 18,550 day cases and 16,127 FCE bed days.[14] In England (2017) there were 1,802 patients diagnosed with Hodgkin lymphoma and 275 deaths registered where Hodgkin disease was the underlying cause.[15] Data from 2016-18 by Cancer Research UK report 2,124 new cases of Hodgkin lymphoma each year between 2016-18.[12] Additionally, 311 deaths per year between 2017-19 were reported between 2017-19 in the UK.[16]

Recommended Treatment Options

There are currently no NICE recommended treatments for untreated, late-stage classical Hodgkin lymphoma.

Treatments for late-stage Hodgkin lymphoma may include chemotherapy (regimes include ABVD; doxorubicin, bleomycin, vinblastine and dacarbazine and eBEACOPP; bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone), and steroid medicines.[17,18] For ABVD and eBEACOPP, the treatment after cycle 2 is determined by results of a Positron Emission Tomography (PET) scan.

Clinical Trial Information

Trial	**ECHELON-1,** NCT01712490, EudraCT 2011-005450-60; A Randomised, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma **Phase III –** Active, not recruiting **Location(s):** Nine EU countries, UK, USA, Canada, and other countries **Actual study primary completion date:** April 2017
Trial Design	Randomised, open-label, parallel assignment

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Population	N = 1,334 (actual); Treatment naïve with advanced (stage III or IV) classical Hodgkin lymphoma; aged over 18 years.
Intervention(s)	Brentuximab vedotin 1.2mg/kg plus doxorubicin 25mg/m^2, vinblastine 6mg/m^2 and dacarbazine 375mg/m^2 (A+AVD) administered by IV infusion on days 1 and 15 of each 28-day cycle.
Comparator(s)	Doxorubicin 25mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 (ABVD) administered by IV infusion on days 1 and 15 of each 28-day cycle.
Outcome(s)	The primary outcome measure is modified progression-free survival [Time Frame: Baseline until progressive disease or death or receipt of any subsequent anticancer therapy for Hodgkin lymphoma after completion of frontline therapy (approximately up to 4 years)] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The NHS indicative cost of one vial of brentuximab vedotin (50mg) is £2,500.00.[19]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (TA524). June 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult), B15/S/a.
- NHS England. 2013/14 Standard Contract for Cancer: Radiotherapy (All Ages). B01/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.[20]
- Eichenauer DA. et al., on behalf of the ESMO Guidelines Committee. Hodgkin Lymphoma: ESMO Clinical Practice Guidelines. 2018.[21]

Additional Information

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