Brentuximab vedotin (Adcetris) for CD30-positive cutaneous T-cell lymphoma

**SUMMARY**

Brentuximab vedotin is an antibody-drug conjugate (ADC) comprised of an anti-CD30 monoclonal antibody attached by an enzyme-cleavable linker to the antimicrotubule agent, monomethyl auristatin E (MMAE). The ADC employs a novel linker system that is designed to be stable in the bloodstream but to release MMAE upon internalisation into CD30-expressing tumor cells. Brentuximab vedotin is intended for use as a second line treatment for relapsed or refractory CD30-positive cutaneous T-cell lymphoma (CTCL). It is administered intravenously (IV) at 1.8mg/kg over 30 minutes every 21 days for a maximum of 16 cycles.

CTCL is a rare type of non-Hodgkin lymphoma (NHL) that affects the skin. It is caused by the uncontrolled growth of T-lymphocytes. Many types of CTCL start as flat red patches (tumours) on the skin, which may be itchy and sometimes painful. Some people with CTCL experience swelling of the lymph nodes. About half of those diagnosed with CTCL have mycosis fungoides: a very slow growing form of CTCL. Patches may appear anywhere on the body but are commonly found on the chest, abdomen, back and buttocks. These abnormal areas of skin may form scaly raised patches, called plaques. Cutaneous anaplastic large cell lymphoma (c-ALCL) is one of the less common subtypes of T-cell lymphoma and belongs to the group of primary cutaneous CD30-positive lymphoproliferative disorders. ALC can initially appear in the skin, lymph nodes, or in organs throughout the body. The characteristic features of primary c-ALCL include the appearance of solitary or multiple raised red skin lesions that do not go away, have a tendency to ulcerate, and may itch.

The UK incidence of CTCL is around 0.4 per 100,000 population. In 2013-14, there were 206 hospital admissions due to mycosis fungoides in England, equating to 230 finished consultant episodes and 1,075 bed days; there were a further 38 hospital admissions due to primary cutaneous CD30-positive T-cell proliferations (including primary cutaneous anaplastic large-cell lymphoma), equating to 42 finished consultant episodes and 69 bed days. Brentuximab vedotin is currently undergoing two phase II clinical trials and one phase III clinical trial assessing its effect on disease progression. All trials are expected to be complete by June 2016.
TARGET GROUP

- Cutaneous T-cell lymphoma (CTCL): CD30-positive; relapsed or refractory – second and subsequent line in patients with primary cutaneous anaplastic large cell lymphoma who have received prior radiation therapy or at least one prior systemic therapy; or in patients with mycosis fungoides who have received at least one prior systemic therapy.

TECHNOLOGY

DESCRIPTION

Brentuximab vedotin (Adcetris; SGN-35) is an antibody-drug conjugate (ADC) comprised of an anti-CD30 monoclonal antibody attached by an enzyme-cleavable linker to the antimicrotubule agent, monomethyl auristatin E (MMAE). The ADC employs a novel linker system that is designed to be stable in the bloodstream but to release MMAE upon internalisation into CD30-expressing tumor cells. Brentuximab vedotin is intended for use as a second line treatment for relapsed or refractory CD30-positive CTCL. It is administered via intravenous (IV) infusion at 1.8mg/kg over 30 minutes every 21 days for a maximum of 16 cycles.

Brentuximab vedotin is licensed in the EU for the treatment of adult patients with relapsed or refractory CD30-positive 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. Brentuximab vedotin is also indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma.

Very common (>10%) recognised adverse effects of brentuximab vedotin when used for its current licensed indications include: neutropenia, infection, peripheral sensory neuropathy, diarrhoea, nausea, vomiting, alopecia, pruritus, myalgia, fatigue, pyrexia, and infusion-related reactions.

Brentuximab vedotin is also in phase II clinical trials for the following indications:
- CD30-positive malignancies including multiple myeloma, leukaemia and solid tumours.
- Diffuse large B-cell lymphoma.
- Follicular non-Hodgkin's lymphoma (NHL).

INNOVATION and/or ADVANTAGES

If licensed, brentuximab vedotin will offer an additional treatment option for patients with primary cutaneous anaplastic large cell lymphoma who have received prior radiation therapy or at least one prior systemic therapy; or in patients with mycosis fungoides who have received at least one prior systemic therapy, who currently have few effective therapies available.

DEVELOPER

Takeda UK Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Currently in phase III clinical trials.
PATIENT GROUP

BACKGROUND

CTCL is a rare type of non-Hodgkin lymphoma (NHL) that affects the skin. It is caused by the uncontrolled growth of T-lymphocytes\(^2\). Many types of CTCL start as flat red patches (tumours) on the skin, which may be itchy and sometimes painful\(^2\). Some people with CTCL experience swelling of the lymph nodes\(^2,3\). Early stage CTCL is typically indolent; some patients with early-stage CTCL do not progress to later stages at all, while others progress rapidly, with the cancer spreading to lymph nodes and/or internal organs\(^4\).

The two most common subtypes of CTCL are mycosis fungoides and Sézary syndrome\(^2\). About half of those diagnosed with CTCL have mycosis fungoides\(^4\). Starting as an irregular shaped area of dry or scaly skin, mycosis fungoides is a very slow growing (low grade) form of CTCL\(^2\). Patches may appear anywhere on the body but are commonly found on the chest, abdomen, back and buttocks\(^2\). These abnormal areas of skin may form scaly raised patches, called plaques\(^2\). In a small number of people, raised lumps (tumours) can appear. In rare advanced cases of the disease the skin appears red, swollen and sore all over. This is called erythrodermic mycosis fungoides\(^2\). About 5% of patients with CTCL have Sézary syndrome\(^2\). It is closely related to mycosis fungoides but most or all of the skin is covered in a red itchy rash\(^2\). Cancerous T-cells (called Sezary cells) are also found in the blood\(^2\). It is a high grade form of CTCL.

Cutaneous anaplastic large cell lymphoma (c-ALCL) is one of the less common subtypes of T-cell lymphoma and belongs to the group of primary cutaneous CD30-positive lymphoproliferative disorders\(^5\). ALCL can initially appear in the skin, lymph nodes, or in organs throughout the body\(^5\). ALCL that appears in the skin is called primary cutaneous ALCL (pc-ALCL), which has a less aggressive disease course than systemic types\(^5\). The characteristic features of pc-ALCL include the appearance of solitary or multiple raised red skin lesions that do not go away, have a tendency to ulcerate, and may itch\(^5\).

Other less common subtypes of CTCL include\(^6\): panniculitis-like T-cell lymphoma, cutaneous CD8+ expressing aggressive epidermotropic T-cell lymphoma, gamma-delta T-cell lymphoma, and hypopigmented/vitiligenous mycosis fungoides.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:


CLINICAL NEED and BURDEN OF DISEASE

The UK incidence of CTCL is around 0.4 per 100,000 population\(^2\). In 2013-14, there were 206 hospital admissions due to mycosis fungoides (ICD-10 C84.0) in England\(^7\), equating to
230 finished consultant episodes and 1,075 bed days; there were a further 38 hospital admissions due to primary cutaneous CD30-positive T-cell proliferations (including primary cutaneous anaplastic large-cell lymphoma)7 (ICD-10 C86.6), equating to 42 finished consultant episodes and 69 bed days. Most people with CTCL are aged between 40 and 60 years old and it is twice more common in men than women2.

Prognosis in mycosis fungoides (and clinical variants) is related to age at presentation (worse if aged >60 years), to the stage of the disease, and possibly to the presence of a peripheral blood T-cell clone; some clinical variants of mycosis fungoides also have a better prognosis8. The median survival in patients with Sézary syndrome is 32 months from diagnosis. Primary cutaneous CD30+ lymphoproliferative disorders without peripheral nodal disease have an excellent prognosis8; 96-100% of patients are expected to achieve 5-year survival. The prognosis for other types of CTCL is generally poor due to the frequent development of systemic disease8.

Fifteen deaths from mycosis fungoides were registered in England and Wales during 2013 (ICD-84.0)9a. The population likely to be eligible to receive brentuximab vedotin could not be estimated from available published sources.

### PATIENT PATHWAY

#### RELEVANT GUIDANCE

**NICE Guidance**

**Other Guidance**
- European Society for Medical Oncology (ESMO). Primary cutaneous lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 201310.

### CURRENT TREATMENT OPTIONS

Guidelines recommend the use of the following treatments for relapsed or refractory CTCL8,10:

**Mycosis fungoides**
- Systemic chemotherapy — methotrexate, gemcitabine or liposomal doxorubicin.
- Fusion toxin proteins — denileukin diftitox (not yet registered in Europe).
- Systemic retinoids — bexarotene.
- Histone deacetylase (HDAC) inhibitors — such as vorinostat and romidepsin (not yet registered in Europe).
- Multiagent chemotherapy — only indicated in patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumour stage mycosis.

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*Expert opinion suggests this figure is an underestimate.*
fungoides which cannot be controlled with skin-targeted and immunomodulating therapies.

- Local radiotherapy — local palliation of cutaneous as well as extracutaneous lesions may be achieved with doses ≥8 Gy.
- Allogeneic stem cell transplantation — may be considered in relatively young patients with refractory, progressive mycosis fungoides or with Sézary syndrome.

pc-ALCL

- Systemic retinoids — including bexarotene or interferon alpha.
- Multiagent chemotherapy — only indicated in patients presenting with or developing extracutaneous disease and in rare patients with rapidly progressive skin disease.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCANZA, NCT01578499; brentuximab vedotin vs physician’s choice (methotrexate or bexarotene); phase III.</td>
<td>Millenium Pharmaceuticals, Inc.</td>
<td>Ongoing.</td>
<td>Trial registry, manufacturer.</td>
<td>EU (incl UK), USA, and other countries.</td>
<td>Randomised, active-controlled, open label.</td>
<td>n=124 (planned); aged ≥18 years; mycosis fungoides or pc-ALCL; patients with pc-ALCL received prior radiation therapy or at least 1 prior systemic therapy; patients with mycosis fungoides received at least 1 prior systemic therapy; histologically confirmed CD30-positive disease; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; no concurrent diagnosis of systemic ALCL, other NHL (excluding lymphomatoid papulosis), Sézary syndrome or B2 disease; no significant co-morbid conditions; no known active cerebral/meningeal disease; no oral retinoid or corticosteroid therapy for any indication ≥3 weeks;</td>
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<tr>
<td>NCT01352520; brentuximab vedotin; phase II.</td>
<td>M.D. Anderson Cancer Center.</td>
<td>Ongoing.</td>
<td>Abstract, trial registry.</td>
<td>USA only.</td>
<td>Non-randomised, uncontrolled.</td>
<td>n=84 (planned); aged ≥18 years; diagnosis of mycosis fungoides, pc-ALCL, or lymphomatoid papulosis; CD30-positive disease; patients with pc-ALCL that has spread systemically may be included so long as pc-ALCL was the primary diagnosis for ≥6 months before systemic involvement confirmed; mycosis fungoides patients stage IB or greater. Relapsed after treatment with local radiation therapy, phototherapy, topical chemotherapy, or have failed systemic therapy with ≥1 single agent or one multi-agent chemotherapy; pc-ALCL patients are required to have ≥1 cutaneous tumour(s) present for ≥3 months; eligible for systemic therapy; ≥4 weeks since</td>
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<tr>
<td>NCT01396070; brentuximab vedotin; phase II.</td>
<td>Youn Kim.</td>
<td>Ongoing.</td>
<td>Abstract, trial registry.</td>
<td>USA only.</td>
<td>Non-randomised, uncontrolled.</td>
<td>n=32; aged ≥18 years; mycosis fungoides or Sézary syndrome stage IB-IVB; failed one systemic therapy; skin biopsy obtained within 3 months of beginning study medication (to determine CD30 expression level: low, intermediate, high); ≥3 weeks since last local radiation therapy, systemic cytotoxic anticancer therapy, or treatment with other anti-cancer investigational agents (including monoclonal antibody); &gt;3 weeks since last received retinoids, interferons, vorinostat, romidepsin, denileukin diftitox, or phototherapy; &gt;2 weeks since last topical therapy; ECOG performance status of ≤2; no patients with mycosis fungoides with limited</td>
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<td>Schedule</td>
<td>Randomised to brentuximab vedotin 1.8mg/kg IV over 30 minutes once every 21 days in duration sections; or investigator’s choice of methotrexate 5-50mg oral once weekly (dose adjustment guided by patient response and toxicity), or bexarotene 300mg/m² once daily with meals.</td>
<td>Patients receive brentuximab vedotin 1.8mg/kg IV over 30 minutes once every 21 days for up to 16 cycles.</td>
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<td>Follow-up</td>
<td>Active treatment for up to 16 cycles (48 weeks). Follow-up for up to 3 years.</td>
<td>Not reported.</td>
<td>Not reported.</td>
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<td>Primary outcome/s</td>
<td>Objective response rate (ORR) lasting ≥4 months (until disease progression or death) up to 3 years after enrolment of last patient.</td>
<td>Response Rate at 12 months (percentage of participants whose best response during the observation period is a partial response (PR), regression of measurable disease, CR, or complete disappearance of all clinical evidence of disease); objective tumour response (PR, CR, PR+CR) based on Response Evaluation Criteria In Solid Tumours (RECIST) criteria.</td>
<td>Clinical response rate (CRR) at 4 weeks.</td>
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### Secondary outcome/s

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<th>Complete response (CR); progression-free survival (PFS); Skindex-29 questionnaire&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Not reported. No quality of life measurement included in trial outcomes.</th>
<th>Correlation of clinical response with CD30 expression levels; duration of response; safety.</th>
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### Key results

- 46 patients were evaluable at the time of analysis. 31/46 achieved an objective response (19/19 patients with lymphomatoid papulosis and/or pc-ALCL and 12/27 with mycosis fungoides).

- 30 patients were evaluable at the time of analysis. ORR, 21/30 (70%) with 1 CR and 7 near CR (>90% reduction) in skin. Median best mSWAT reduction (response measure in the skin), 73% (range, 100% to -54%). Median time to response, 6.6 weeks (range 3.0 to 27.0 weeks). Survival estimate shows 79% of responses ongoing and 54% progression-free at 12 months. Median CD30 expression levels higher in responders vs non-responders (15% vs 3%, p=0.037); those with CD30 expression <5% had a lower likelihood of clinical response (17% vs 83%, p=0.0046).

### Adverse effects (AEs)

- The most common AEs were peripheral neuropathy (44%), fatigue (30%), skin rash (26%), diarrhoea (22%), nausea (18%) and myalgia (18%). The most common grade 3 AEs were neutropaenia (3 patients), elevated liver function tests (2 patients), and deep vein thrombosis (two patients).

- Related AEs observed were mostly grade 1-2 and limited to AEs previously reported with brentuximab vedotin.

### Expected reporting date

| Study completion date reported as Jun 2015. | Primary completion date reported as Q4 2016. | Study completion date reported as Q4 2015. |

### ESTIMATED COST and IMPACT

#### COST

A 50mg vial of brentuximab vedotin costs £2,500<sup>c</sup>. Therefore, one cycle of treatment with brentuximab vedotin administered IV at 1.8mg/kg would cost £7,500<sup>c</sup>.

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<sup>b</sup> Skindex-29 questionnaire: quality of life questionnaire to assess patients with dermatologic conditions.

<sup>c</sup> Based on average adult bodyweight of 77.9kg. Assumes wastage.
IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other:

Impact on Health and Social Care Services
- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other: expert opinion suggests brentuximab vedotin may offer a critical bridge to transplant.

Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs: more patients eligible for treatment.
- Other reduction in costs:

Other Issues
- Clinical uncertainty or other research question identified:

REFERENCES

d Expert personal communication


