### Summary

Due to the rarity of the condition and the licensing of brentuximab vedotin, randomised control trials are now unlikely to be conducted for brentuximab vedotin in this indication.

The best available data at this time come from a multinational Phase II study (n=102) that found brentuximab vedotin to be associated with an objective response rate of 75%, with a complete remission seen in 34%. At the time of the analysis, the median duration of response for those in complete remission was 20.5 months and the estimated 12-month survival was 89%. The US and UK licence for brentuximab vedotin for Hodgkin’s lymphoma was based on the results of this phase II trial.

The phase II clinical trial included patients who had received prior ASCT. The licensed indication also states that brentuximab vedotin is indicated for relapsed or refractory HL following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. These patients may not have necessarily had a prior ASCT. The European Medicines Agency EPAR report states that the manufacturer submitted data for 56 patients with relapsed or refractory HL who had received at least 2 prior chemotherapy regimens and no ASCT, 40 of whom received the licensed dose of brentuximab vedotin. The overall response rate for these patients was approximately 54%, with 22% CR.

In the phase II study, grade 3 adverse events occurring in ≥5% of pts were neutropenia, peripheral sensory neuropathy, thrombocytopenia, and anaemia. No cases of febrile neutropenia were observed. A total of 20 patients had adverse effects that led to treatment discontinuation – most commonly peripheral sensory neuropathy and peripheral motor neuropathy.

The US FDA issued an alert in January 2012 notifying healthcare professionals of two newly reported cases of progressive multifocal leukoencephalopathy (PML) associated with the use of brentuximab vedotin. The FDA has advised the manufacturer to include a boxed warning highlighting this risk, in addition to a contra-indication to the use of the drug in combination with bleomycin due to the increased risk of pulmonary toxicity. The UK SPC for brentuximab vedotin also carries this contra-indication and a warning regarding PML.
Background

Hodgkin lymphoma (HL) is a neoplasm arising from germinal or post germinal B cells. HL is characterised histologically by malignant Hodgkin and Reed Sternberg cells that are surrounded by non-malignant inflammatory cells. HL is divided into two major subtypes, based on immunohistological features and microscopic appearance of the malignant cells. The nodular lymphocyte predominant subtype (NLPHL) makes up 5% of all HL and has a generally more indolent course than classical Hodgkin lymphoma (cHL). Most but not all NLPHL are CD30 negative, whereas CD30 expression is a standard feature of Reed Sternberg cells in cHL. NLPHL expresses CD45 and CD20, whereas cHL is typically CD45 negative and CD20 negative in 60–80% of cases (1).

Classical Hodgkin lymphoma has four subtypes. The most common subtype is the nodular sclerosis subtype: 40–70%. The mixed cellularity subtype makes up 30–50% of cHL and possibly has a less favourable clinical course. The lymphocyte depletion subtype is rare and can be associated with AIDS. The lymphocyte rich subtype has been distinguished from NLPHL since 1999. It differs from NLPHL in that it is CD30+, CD20- and it has a higher relapse rate (1).

HL is highly curable, with 80% of patients reaching complete remission. Prognosis is worse in patients who present with advanced disease, with 30–40% relapse after initial treatment or immediate treatment failure. Staging is according to the Ann Arbor criteria, which are based on localisation, the extent of nodal and extranodal involvement, and the presence of the classical B symptoms (1).

Standard first line treatment for limited stage disease consists of the ABVD combination chemotherapy regimen, followed by involved field radiotherapy. There is no consensus on the optimum treatment for advanced stage disease, with different approaches in the U.S. and Europe. Different combination chemotherapy regimens such as ABVD, BEACOPP and Stanford V have been compared. The role of radiotherapy and intermediate staging by FDG-PET are also being currently evaluated (1).

There is no standard treatment of relapsed or primary refractory disease. Salvage chemotherapy regimens such as DHAP/VIM/DHAP or repeated ICE are usually followed by high dose chemotherapy and autologous stem cell transplantation. Patients, who are not cured with front-line or second-line therapy, including stem cell transplantation, have an estimated median survival of less than 3 years. Gains are limited to disease free survival, but usually no overall survival gains are achieved (1).

Brentuximab vedotin

Brentuximab vedotin (Adcetris® — also known as SGN-35), is a CD30-directed antibody-drug conjugate (ADC) composed of the monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). It is produced via the chemical conjugation of cAC10 to the small molecule SGD-1006 intermediate (SGD-1006), which contains both the linker and the MMAE. Brentuximab vedotin consists of on average four molecules of monomethyl auristatin E (MMAE) conjugated to the cAC10 monoclonal antibody. Binding of SGN-35 to CD30 on the cell surface initiates internalisation of the SGN-35-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, MMAE is released from the monoclonal antibody via proteolytic cleavage and degradation of the drug linker. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces mitotic cell cycle arrest, and results in apoptotic death of the CD30-expressing tumour cell (1).

Brentuximab vedotin is licensed in the UK for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin Lymphoma:

• Following autologous stem cell transplant (ASCT) or
• Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option (2).

Brentuximab vedotin is also licensed for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) (2).

Epidemiology

Data supplied by the manufacturer of brentuximab vedotin, Takeda, state that there are 0.12/100,000 population eligible for brentuximab vedotin following an autologous stem cell transplant, and 0.1/100,000 population eligible for brentuximab vedotin following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. They base these estimates on the following:

Following autologous stem cell transplant (ASCT): 74 patients.

The number of eligible patients for brentuximab vedotin within this indication in the UK is calculated as the number of Autologous Stem Cell Transplant (ASCT) procedures per year multiplied by the probability of eventual relapse from ASCT (assuming 100% of these relapse patients were offered brentuximab vedotin treatment.)
Brentuximab vedotin for Hodgkin’s lymphoma

The number of ASCT procedures for Hodgkin Lymphoma in the UK and Ireland in 2011 was 164 (3). The UK estimate is derived as the number of ASCT procedures conducted in the UK and Ireland adjusted downwards by 6% to reflect the proportion conducted in Ireland. The proportion of patients who ultimately relapse is calculated from Sirohi 2008 (4). This study followed up 195 patients who received ASCT in the UK in the period 1985–2005. Patients were followed up for a median of 10.3 years. The study observed progressive disease in 87 of the 195 patients (45%) during long term follow-up. We therefore use a figure of 45% to estimate the proportion of incident cases who eventually relapse. This results in an estimate of 74 incident cases per year in UK eligible for treatment with brentuximab vedotin. The UK population is estimated at 63 million (5). Therefore, 74 patients per 63 million would be eligible for brentuximab vedotin using this assumption (or 0.12/100,000 population).

Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option: 62 patients.

Based on data from the Adcetris® CHMP oral presentation held on May 22nd 2012, 30% of relapsed/refractory HL patients receiving first-line treatment progress or relapse, and 30% of patients who receive second-line therapy do not achieve complete/partial remission. Based on this data, the number of patients who do not respond to two lines of salvage therapy and thus become ASCT ineligible is 62 for one year (assuming 100% of these patients were offered brentuximab vedotin treatment). This would mean that 62 patients per 63 million would be eligible for brentuximab vedotin (which equates to 0.1/100,000 population).

Published data

NICE have stated that due to the small patient population in the UK, they will not be appraising brentuximab vedotin for relapsed or refractory CD30+ HL (personal communication with manufacturer).

The US and UK approval of brentuximab for the treatment of HL was based on the results of a multinational Phase II study, published in the Journal of Clinical Oncology (6). This open-label study enrolled 102 patients with relapsed or refractory HL following high-dose chemotherapy and ASCT. They received treatment with BV at a dose of 1.8 mg/kg every three weeks as an outpatient IV infusion for up to 16 cycles. The median age of participants was 31 yrs (range 15–77 yrs) and 53% were female. The majority (71%) had primary refractory disease (defined as failure to obtain a complete remission with front-line therapy or relapse within 3 months of front-line therapy) and 42% had disease that was refractory to the most recent prior therapy. 41% had an ECOG performance status of 0 and 59% had performance status of 1. They had received a median of 3.5 (range 1–13) prior cancer-related systemic therapies excluding ASCT; all patients had received ASCT. The median time to relapse following ASCT was 6.7 months (range 0–131 months) (6).

The primary endpoint, objective response rate according to the independent review facility, was 75% (95% CI 64.9% to 82.6%), with a complete response seen in 34% (25.2% to 44.4%). At the time of the analysis, the median time to response was 5.7 weeks (range 5.1 to 56 weeks). For those who responded to treatment, the median duration of response was 6.7 months (95% CI 3.6 to 14.8 months); this was longer in those who had a complete response (20.5 months; 95% CI 10.8 to not estimable). The estimated median progression-free survival (PFS) for all patients was 5.6 months (95% CI 5.0–9.0 months) and the estimated 12-month survival was 89% (95% CI 83–95%). Follow-up of patients within this study is ongoing. Subgroup analyses did not identify any particular subgroup of patients for whom brentuximab vedotin treatment did not result in any clinically meaningful tumour activity.

At the time of the analysis, eight patients (5 with a complete response and 3 with a partial response) had received an allogeneic SCT. Only details of those who had a CR are discussed – these had a median PFS of 21.1 months, compared to 21.7 months in the 30 patients who achieved a complete response but did not receive an allogeneic SCT.

Retrospective analysis

Rothe A. et al conducted a retrospective analysis of 45 patients with primary refractory or relapsed HL (7). Patient data was collected from heavily pretreated HL patients treated in Germany, Switzerland, and Austria. Patients had an ECOG performance status of ≤2, and normal organ function including peripheral blood counts within the normal range. Brentuximab vedotin 1.8mg/kg was given every 3 weeks until disease progression.

The median age of the patients was 35 years and all patients had classical HL with nodular sclerosis as the most frequent histological subtype. 73% of patients had stage III/IV disease. The median number of prior therapy regimens was 4 (range 2–12), including high-dose chemotherapy and ASCT or allogeneic stem cell transplantation in 39 patients. In total, 64% of patients were refractory to their last treatment and the median time between the last systemic therapy and initiation of brentuximab vedotin was only 2 months (range 0–24).
The median number of brentuximab vedotin cycles administered was 7 (range 1–12). The ORR was 60%, with 22% (10 patients) achieving a CR. The PFS at 12 months was 43% (95% CI 28–58%) and the median PFS was 8 months. Overall survival at 12 months was 83% (95% CI 72–95%).

European Medicines Agency Assessment report for brentuximab

The EMEA assessment report for brentuximab vedotin, July 2012, states that the manufacturer submitted data from 59 patients who had not received prior ASCT and who had received one or more doses of brentuximab vedotin (1). Of these 59 patients, 41 received 1.8 mg/kg brentuximab vedotin every 3 weeks. The patients were part of phase I/II studies, a Japanese only study (TB-BC010088), and named patient programmes. Three patients had received just one prior therapy before brentuximab vedotin and 56 patients had received 2 or more prior therapies before brentuximab vedotin, of which 40 patients were treated with brentuximab vedotin 1.8mg/kg every 3 weeks.

The median age of the 59 patients was 35 years (range 12–88) and 45 patients (76.3%) had an ECOG performance status of 0 or 1. Patients’ most common first line of prior therapy was doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Of the 56 no-prior-ASCT patients, 64% of the patients received the same first line of therapy, i.e. ABVD. The next most common frontline treatment was a BEACOPP-based regimen (6 patients, 11%). The most common second-line therapy among no-prior-ASCT patients was etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP) as received by 11 of the 56 patients (20%); 10 of 56 patients (18%) received radiotherapy as second-line therapy; and 8 of 56 patients (14%) received ICE.

Response data, among the 41 patients who received 1.8mg/kg every 3 weeks, are summarised below:

<table>
<thead>
<tr>
<th>Response Data</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>22 (54%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>9 (22%)</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>Patients going on to SCT after brentuximab</td>
<td>8 (19%)</td>
</tr>
</tbody>
</table>

Safety

Phase II study

The median number of cycles of brentuximab vedotin received was 9 (range 1–16) and the median relative dose intensity was 96%. The most common (≥10%) treatment-related adverse events of any grade were peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), neutropenia (19%), diarrhoea (18%), pyrexia (14%), vomiting (13%), arthralgia (12%), pruritis (12%), myalgia (11%), peripheral motor neuropathy (11%) and alopecia (10%). Grade 3 adverse events occurring in ≥5% of pts were neutropenia, peripheral sensory neuropathy, thrombocytopenia, and anaemia. No cases of febrile neutropenia were observed. A total of 20 patients had adverse effects that led to treatment discontinuation – most commonly peripheral sensory neuropathy and peripheral motor neuropathy (6).

Retrospective analysis

Dose reduction due to grade 3 toxicity was necessary in 4 patients. No patient had to discontinue treatment because of toxicity. Peripheral sensory neuropathy grade 1/2 was documented in 14 patients and no case of grade 3/4 neuropathy was reported. The most common grade 3/4 adverse events were neutropenia (n=6), thrombocytopenia (n=3), fatigue (n=3), and infections (n=3) (7).

The US FDA issued an alert in January 2012 notifying healthcare professionals of two newly reported cases of progressive multifocal leukoencephalopathy (PML) associated with the use of brentuximab vedotin. The FDA has advised the manufacturer to include a boxed warning highlighting this risk, in addition to a contra-indication to the use of the drug in combination with bleomycin due to the increased risk of pulmonary toxicity (8). The UK SPC for brentuximab vedotin also carries this contra-indication and a warning regarding PML (2).

Cost

The brentuximab vedotin dose used in the phase II trial was 1.8mg/kg. Using an average body weight of 70kg, this would give a dose of 126mg every 3 weeks. The vial sizes are 50mg and so this would mean 3 vials are reconstituted every 3 weeks. The cost per vial is £2500 (excluding VAT). The cost per cycle per patient would be £9000 (including VAT). The median number of cycles in the phase II study was 9. The average cost per patient using a median of 9 cycles would be £81,000 (including VAT).

Assuming epidemiology of 0.12/100,000 for the number of patients eligible for brentuximab vedotin following autologous stem cell transplant, the cost per 100,000 population would be £9,700 (including VAT).
Assuming epidemiology of 0.1/100,000 for the number of patients eligible for brentuximab vedotin following at least 2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, the cost per 100,000 population would be £8,100 (including VAT).

Service implications
Brentuximab vedotin is administered as a 30 minute outpatient infusion every three weeks for an average of 9 cycles. Therefore, there will be an impact on outpatient day units in terms of capacity if this medicine is approved for funding.

Summary
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for this treatment)</th>
<th>Average duration of treatment (taken from trial data)</th>
<th>Cost per month/cycle (incl VAT)</th>
<th>Cost per 100,000 population per month/cycle</th>
<th>Cost per 100,000 for average treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin</td>
<td>Relapsed or refractory HL following autologous SCT</td>
<td>0.12/100,000</td>
<td>9 cycles</td>
<td>£9,000 per cycle</td>
<td>£1,080 per cycle</td>
<td>£9,700</td>
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<td>£900 per cycle</td>
<td>£8,100</td>
</tr>
</tbody>
</table>

**Reference**

Brentuximab vedotin for Hodgkin’s lymphoma

Details of search strategy:

1. EMBASE; BRENTUXIMAB VEDOTIN/ OR BRENTUXIMAB/; 254 results.
2. EMBASE; HODGKIN DISEASE/; 38426 results.
3. EMBASE; 1 AND 2; 163 results.
4. MEDLINE; brentuximab.ti,ab; 54 results.
5. MEDLINE; HODGKIN DISEASE/; 29876 results.
6. MEDLINE; 4 AND 5; 19 results.
7. MEDLINE; SGN.ti,ab; 284 results.
8. MEDLINE; 4 OR 7; 322 results.
9. MEDLINE; 5 AND 8; 27 results.
10. EMBASE, MEDLINE; Duplicate filtered: [1 AND 2], [5 AND 8]; 190 results.

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