NICE National Institute for Health and Care Excellence

NICE guidance

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Brentuximab vedotin is recommended as an option for treating CD30-positive cutaneous T-cell lymphoma (CTCL) after at least 1 systemic therapy in adults, only if:

- they have mycosis fungoides stage 2B or over, primary cutaneous anaplastic large cell lymphoma or Sézary syndrome and
- the company provides brentuximab vedotin according to the commercial arrangement.

1.2 These recommendations are not intended to affect treatment with brentuximab vedotin that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Brentuximab vedotin is licensed to treat CD30-positive CTCL after at least 1 systemic therapy. It is most likely to be used in the NHS as an alternative to systemic treatments to treat advanced disease. At this point in the pathway, current treatment options include methotrexate, bexarotene and interferon alfa.

Clinical trial evidence shows that brentuximab vedotin is better than methotrexate or bexarotene in terms of response rates and extending how long people live without their disease getting worse. For some people with CTCL, brentuximab vedotin will be used as a bridge to a stem cell transplant.

The most plausible cost-effectiveness estimates for brentuximab vedotin compared with current treatments are less than £30,000 per quality-adjusted life year gained, which is within the range considered to be a cost-effective use of NHS resources. However, these estimates are based on data from people with specific subtypes of advanced disease (mycosis fungoides stage 2B or over, primary cutaneous anaplastic large cell lymphoma and Sézary syndrome), so brentuximab vedotin is only recommended for these subtypes.

2 Information about brentuximab vedotin

Marketing authorisation indication

2.1 Brentuximab vedotin is indicated for the treatment of 'adult patients with CD30-positive cutaneous T-cell lymphoma after at least 1 prior systemic therapy'.

Dosage in the marketing authorisation

2.2 The recommended dose is 1.8 mg/kg given as an intravenous infusion over 30 minutes every 3 weeks. People with CTCL should have up to 16 cycles.

Price

2.3 The price of brentuximab vedotin is £2,500 for a 50 mg vial (excluding VAT; BNF edition 76). The company has a commercial arrangement. This makes brentuximab vedotin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Takeda and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Potential new treatment option

Cutaneous T-cell lymphoma significantly affects quality of life

3.1 Cutaneous T-cell lymphoma (CTCL) is a form of non-Hodgkin lymphoma that affects the skin. It may start as flat red patches or plaques on the surface of the skin, which progress to skin tumours. People may also have systemic symptoms, such as chronic pain and itching, that can severely limit daily activities. The clinical experts explained that CTCL is a rare disease and people usually live with their condition for many years. The patient experts explained that being diagnosed with CTCL can severely affect a person's physical and psychological wellbeing. It may take several years before CTCL is accurately diagnosed, and symptoms flare up unpredictably. The clinical and patient experts also explained that there is no uniform response to treatment; people with CTCL may be very self-conscious about how their skin looks and uncertain about how the disease will respond to treatment, which has a negative psychological effect. Consultation responses from NHS professionals highlighted the emotional and financial effects on patients and their families and carers. The committee concluded that CTCL significantly reduces patients' quality of life.

There is an unmet need for more effective treatment options

3.2 There is no NICE guidance on treating CTCL. The disease can be divided into a number of subtypes, only some of which express the tumour marker CD30. CD30 is expressed in both primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis, which together form the group of primary cutaneous CD30-positive lymphoproliferative disorders. Mycosis fungoides and Sézary

syndrome can also express CD30. CTCL is treated based on the subtype and stage of the disease. Treatments either target the skin (skin-directed) or the entire body (systemic), but there is no standard therapy. The clinical experts highlighted that treatment options are diverse; they aim to relieve symptoms, control local disease and improve quality of life. The committee understood that compared with earlier stages of CTCL, advanced disease is associated with poorer prognosis, lower survival and lower quality of life. Although current treatments are palliative, the clinical experts noted that allogeneic stem cell transplants may consolidate treatment response to achieve durable remission, or possibly cure, and should be considered for certain patients with advanced CTCL. Without a transplant the disease has a cycle of remission and relapse. Because there are limited treatment options available, people with advanced CTCL may live for several years without treatment while having painful, itchy and uncomfortable symptoms on a daily basis. The committee agreed that there is an unmet need for effective treatments that extend the amount of time the disease is in remission and improve quality of life. The committee concluded that both patients and healthcare professionals would welcome potential new treatments.

Treatment pathway and comparators

Brentuximab vedotin will be used as an alternative to systemic therapies for specific subtypes of advanced cutaneous T-cell lymphoma

3.3 The marketing authorisation does not specify whether brentuximab vedotin may be used for early-stage CTCL or advanced CTCL. The committee noted that the inclusion criteria for ALCANZA (the pivotal trial on which the marketing authorisation was based) included patients with early-stage disease. The committee was also aware that the company's submission focused on a narrower population than the marketing authorisation, including only patients with advanced disease (specifically mycosis fungoides stage 2B or over, primary cutaneous anaplastic large cell lymphoma and Sézary syndrome). The clinical experts explained that skin-directed therapies are often effective for managing early-stage CTCL, but systemic agents (like brentuximab vedotin) are more commonly used for advanced disease. They also highlighted that lymphomatoid

papulosis, another subtype of CTCL, is usually treated with skin-directed therapies (because it is less aggressive), so brentuximab vedotin would not be used for this subtype of CTCL. The committee concluded that brentuximab vedotin is most likely to be used in the NHS as an alternative to systemic treatments to treat specific subtypes of advanced CTCL (mycosis fungoides stage 2B or over, primary cutaneous anaplastic large cell lymphoma and Sézary syndrome).

Methotrexate, bexarotene and interferon alfa are the most appropriate comparators

3.4 The committee recalled that systemic agents are most commonly used to treat advanced subtypes of CTCL. The clinical experts explained that patients are first offered retinoids (bexarotene), interferon alpha or single-agent chemotherapy (methotrexate). They highlighted that low-dose methotrexate is not licensed for CTCL but that it has been used in UK clinical practice for over 40 years. Multi-agent chemotherapy regimens are generally not used as standard care and are only considered when first-line systemic therapy options have been exhausted. This is because of their lack of efficacy and associated toxicities, which are especially problematic in people with CTCL who are susceptible to infection. The clinical experts agreed with the company's positioning of brentuximab vedotin as an alternative to bexarotene, interferon alpha and methotrexate, and stated that it would be used after first-line therapy. The committee noted that its marketing authorisation restricted the use of brentuximab vedotin to after at least 1 systemic therapy, and so concluded that it would be used after at least 1 systemic therapy for patients with advanced disease and that, based on current clinical practice, methotrexate, bexarotene and interferon alfa were the most appropriate comparators.

Current treatment options are considered equally effective

3.5 The committee considered the currently available treatment options for people with advanced CTCL. The clinical experts explained that the choice of treatment often depends on the associated adverse events and the patient's needs because all initial therapies are considered equally effective. The committee was

aware that evidence for the efficacy of bexarotene monotherapy, low-dose methotrexate monotherapy and interferon alfa for advanced CTCL was from outdated and low-quality studies. The committee concluded that although there was limited evidence, for the purposes of this appraisal it was appropriate to assume that all first-line systemic treatments are equally effective.

Stem cell transplant is part of the treatment pathway

3.6 The clinical experts explained that brentuximab vedotin would be used in 2 ways: either as a bridge to transplant or as a treatment without a future transplant. The committee recalled that allogeneic stem cell transplant may be a potentially curative therapy for certain patients with advanced CTCL (see section 3.2). The clinical experts advised that transplants should only be considered for patients whose disease adequately responds to systemic therapy. This normally means at least a partial response, although they commented that current treatment options produce only short-term responses that are not adequate to allow for a bridge to transplant. The clinical experts explained that everyone who is newly referred to a specialist centre with a diagnosis of advanced CTCL would be assessed for eligibility for a transplant. Consultation responses from NHS professionals supported the view that stem cell transplant gives people with advanced CTCL the best chance of a cure. The clinical experts advised that it is not always possible to identify people for whom transplant is appropriate before starting brentuximab vedotin. However,there are clinical criteria to identify people for whom transplants are not appropriate (for example, people with comorbidities that would compromise their fitness for a transplant). The committee concluded that it would consider the use of brentuximab vedotin as both a treatment without a future transplant and a bridge to transplant for advanced CTCL.

Clinical evidence

The clinical-effectiveness evidence is relevant to NHS clinical practice

3.7 The main evidence for brentuximab vedotin was from ALCANZA, an international,

multicentre, open-label, randomised controlled trial. It included 128 adults (median age 60 years) with CTCL (mycosis fungoides or primary cutaneous anaplastic large cell lymphoma) who had 1 previous systemic therapy and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 and under; 95 patients had advanced CTCL. The trial compared brentuximab vedotin with physician's choice of treatment (either methotrexate or bexarotene). The committee noted that ALCANZA did not assess the comparative effectiveness of brentuximab vedotin and interferon alfa. It noted the company's comment that there was insufficient evidence for an indirect comparison. Having concluded that all first-line systemic treatments are equally effective (see section 3.5), the committee agreed that the lack of a comparison between brentuximab vedotin and interferon alfa was not a major limitation in the evidence. The committee noted that the trial was both international and multicentre, but only 4 centres were in the UK (24 patients). The clinical experts confirmed that patients in the trial were representative of UK patients who would be eligible for brentuximab vedotin. The committee concluded that the clinical-effectiveness evidence from ALCANZA was relevant to clinical practice in the NHS in England.

Brentuximab vedotin improves progression-free survival and had longer responses compared with current treatment options

3.8 The company presented results for all patients in the ALCANZA study and separate results for the advanced disease subgroup. The primary outcome was the rate of objective response that lasted at least 4 months. Secondary outcomes included response rates, length of response, progression-free survival and health-related quality of life. Overall survival was not a prespecified end point, but the company included these data in its submission. The clinical experts stated that the results (see table 1) were clinically meaningful and important to people with advanced CTCL, because current treatments provide only short-term responses. They reiterated that the response rates with brentuximab vedotin meant that more patients could be offered stem cell transplants. The committee concluded that brentuximab vedotin improved progression-free survival and had longer clinical responses compared with methotrexate or bexarotene and accepted that this would also be the case when compared with interferon alfa (see section 3.5).

Table 1 Results from the ALCANZA advanced subgroup

End point	Brentuximab vedotin (n=49)	Methotrexate or bexarotene (physician's choice; n=46)	P value
Objective response rate lasting for at least 4 months, n (%)	29 (59.2)	4 (8.7)	<0.001
Overall response rate, n (%)	34 (69.4)	8 (17.4)	<0.001
Complete response, n (%)	10 (20.4)	1 (2.2)	0.005
Partial response, n (%)	24 (49.0)	7 (15.2)	Not reported
Progression-free survival, months (95% confidence interval)	16.5 (15.5 to 27.5)	3.5 (2.4 to 4.9)	Not reported

The exact proportion of patients who have a stem cell transplant after having brentuximab vedotin is uncertain

3.9 The company presented results from a post-hoc analysis of allogeneic stem cell transplants in ALCANZA, which included 7 patients who had a transplant: 5 in the brentuximab vedotin group and 2 in the comparator group. Only 2 of the 5 patients in the brentuximab vedotin treatment group had a transplant directly after treatment; the other 3 had additional systemic therapies before their transplant. Both patients in the comparator group had switched to receive brentuximab vedotin before their transplant. The clinical experts explained that the trial was done in 2013 and although transplants were allowed in ALCANZA, their use was not a prespecified end point. They emphasised that UK clinical practice has evolved since 2013 and transplants are now more common. A clinical expert who had used brentuximab vedotin on the compassionate use programme suggested that around 25% of patients bridged to transplant. The committee understood that the compassionate use programme is highly selective and therefore may not reflect clinical practice in the NHS. In response to consultation, the company presented data on transplant rates from the compassionate use programme (26.3%) and from the UK patients in the ALCANZA trial (16.7%); these were both lower than the transplant rate in the company's base case (27.5%). The committee recalled that not all patients who had a transplant in ALCANZA did so directly after having brentuximab vedotin. The committee concluded that

brentuximab vedotin could be used as a bridge to transplant for some patients whose disease adequately responds to treatment, but that there was uncertainty about the exact proportion in clinical practice.

For patients who cannot have a transplant, it is unclear whether brentuximab vedotin improves overall survival compared with current treatment

3.10 The company provided evidence on overall survival from ALCANZA for the advanced disease subgroup. Median overall survival was 43.6 months in the brentuximab vedotin group and 41.6 months in the comparator group. Based on these results, the company considered that it was not possible to assume a difference in overall survival between the 2 groups in patients who were not able to bridge to transplant. They highlighted that the data were immature, based on a relatively small sample size with few events, and may be confounded by treatment switching. Almost half (46%) of patients switched from the comparator group and subsequently had brentuximab vedotin. The company attempted to adjust for this treatment switching, but considered the results to be clinically implausible. The committee acknowledged the company's concerns, such as the limited number of events in each arm, but considered that the adjustment may have been conducted incorrectly. The clinical experts explained that from the available evidence, they had not seen a proven association between progression-free and overall survival in patients with CTCL who were not able to bridge to transplant. However, in the second committee meeting, the clinical lead for the Cancer Drugs Fund explained that it was likely that a substantial gain in progression-free survival (as seen in the ALCANZA trial) would lead to a gain in overall survival. The committee concluded that there was uncertainty about whether brentuximab vedotin increased overall survival compared with current treatments for patients who were not able to bridge to transplant.

Data from ALCANZA can be generalised to other subgroups of cutaneous T-cell lymphoma

3.11 The committee recalled that the ALCANZA trial included patients with mycosis

fungoides or primary cutaneous anaplastic large cell lymphoma, but did not include other subgroups of CTCL. Two phase 2 trials provided further non-randomised supporting evidence for Sézary syndrome and lymphomatoid papulosis, other subtypes of CTCL which are included in brentuximab vedotin's marketing authorisation. The committee noted that the studies included only a small number of patients with subtypes of CTCL other than mycosis fungoides, but it recalled that CTCL is a rare disease. The clinical experts explained that treatment would be similar for most subtypes of CTCL, but that they would not use brentuximab vedotin for lymphomatoid papulosis (see section 3.3). Having reviewed the supporting data, the committee noted that the findings for response rates and median progression-free survival were generally consistent across the studies and subgroups, and that the European Public Assessment Report for brentuximab vedotin stated that 'the available data appears in support for the extrapolation of efficacy from mycosis fungoides and primary cutaneous anaplastic large cell lymphoma to other subtypes'. The committee concluded that the clinical-effectiveness data from ALCANZA could be generalised to other subtypes of CTCL, such as Sézary syndrome.

People may have fewer cycles of brentuximab vedotin in clinical practice than in both ALCANZA and the summary of product characteristics

3.12 The committee noted that the summary of product characteristics for brentuximab vedotin states that it should be used for up to 16 cycles. The clinical experts explained that the number of cycles used depended on whether brentuximab vedotin was being used to bridge to allogeneic stem cell transplant. They explained that when brentuximab vedotin is used without the intention of bridging to transplant, 16 cycles is common and in some cases patients have retreatment with brentuximab vedotin (that is, they have brentuximab vedotin for a second time after a break from treatment with it). The committee noted that it had not seen evidence of retreatment with brentuximab vedotin and that no evidence on treatment breaks was available from the ALCANZA trial data. The committee was also aware that the summary of product characteristics makes no explicit reference to retreatment. It heard from NHS England's clinical lead for the Cancer Drugs Fund that retreatment with brentuximab vedotin would not be done in clinical practice in the NHS. The clinical experts also advised that, in their

experience, treatment with brentuximab vedotin may be stopped after only 2 or 3 cycles if the response is sufficient to allow for a transplant. The committee noted that this was much lower than the maximum number of cycles specified in the summary of product characteristics. It concluded that the number of cycles of brentuximab vedotin used in clinical practice varied, and that this should be factored into its considerations of the cost-effectiveness evidence.

The size of brentuximab vedotin's effect on health-related quality of life is unclear and the full benefit may not be captured in the trial data

3.13 The company provided health-related quality of life and symptom relief data for the advanced disease subgroup using the Skindex-29 and EQ-5D-3L tools. The data showed that patients who had brentuximab vedotin had better symptom relief compared with those who had the comparators. However, the committee noted that there was no statistically significant difference in overall Skindex-29 score or EQ-5D-3L values between the brentuximab vedotin and comparator groups. The clinical experts explained that neither tool fully captures all skin-related and physiological symptoms of CTCL. They further explained that a health-related quality-of-life tool specific to CTCL was being developed but was not yet available. In response to consultation, NHS professionals emphasised the importance of symptom improvement with brentuximab vedotin. The committee acknowledged the limitations of the EQ-5D-3L as an assessment tool for advanced CTCL because it may not be sensitive to skin-related diseases, but noted that it should capture depression and pain described by patients in consultation responses. The company explained that the EQ-5D-3L data from ALCANZA had a low completion rate in the comparator arm, which also had a high rate of treatment switching, and that it failed to capture nocturnal pruritus, which affects people with advanced CTCL. The committee agreed that further research is needed in this area. It concluded that brentuximab vedotin appears to improve health-related quality of life, but that the size of this effect is unclear. It agreed that this was at least partly because of the health-related quality of life tools available, such that the benefit of brentuximab vedotin may not be fully captured in the trial data. It concluded that this should be factored into its considerations of the cost-effectiveness evidence.

Adverse effects

Brentuximab vedotin is generally well tolerated

3.14 The committee noted that the adverse effects reported in the ALCANZA study were broadly comparable between the brentuximab vedotin and comparator groups. It noted that there was 1 treatment-related death caused by tumour lysis, but that this was not unique to brentuximab vedotin. A patient expert commented that they had found brentuximab vedotin to be more tolerable than other treatments, but they noted that each patient was likely to react differently. The committee concluded that brentuximab vedotin was generally well tolerated.

Cost effectiveness

The company's model structure is appropriate for decision making

3.15 The company presented cost-effectiveness analyses comparing brentuximab vedotin with 'physician's choice' of treatment (in clinical practice, either methotrexate or bexarotene) using a partitioned survival model with 5 mutually exclusive health states. The model comprised 2 pathways, 1 that included allogeneic stem cell transplant and 1 that did not. All patients start in the pre-progression health state. Eligibility for a transplant is based on response to treatment in this state. All eligible patients move to the allogeneic stem cell transplant health state at 18 weeks. Patients on either pathway can relapse and move into a post-progression or death state. The clinical experts confirmed that the model reflected the clinical pathway for CTCL. The model was informed by data from the advanced disease subgroup of ALCANZA. This included only patients with the mycosis fungoides and primary cutaneous anaplastic large cell lymphoma subgroups of CTCL, but the committee recalled that the data could be generalised to other subgroups (see section 3.11). The committee concluded that the model's structure was appropriate for decision making.

Pathway including stem cell transplants

Rates of stem cell transplant from UK patients in the ALCANZA trial should be used in the cost-effectiveness modelling

3.16 The company's base case assumed that 40% of patients whose disease showed at least a partial response to treatment (based on objective response rates) would be eligible for a stem cell transplant. This was based on clinical advice, which accounted for the eligibility of patients for a transplant based on age, comorbidities and likelihood of a matching donor, as well as patient choice. The committee noted that, using the company's base-case assumptions, 27.5% of people who had brentuximab vedotin and 7.1% who had the comparator would go on to have a transplant. The clinical experts confirmed that the assumptions used to inform the 40% proportion of responders reflected clinical practice, but only a small number of patients have had brentuximab vedotin in England. The committee recalled that the company had submitted alternative data from 2 sources in response to consultation, which suggested lower rates of transplant after brentuximab vedotin (16.7% and 26.3%; see section 3.9). The company highlighted that responses to consultation indicated transplant rates after brentuximab vedotin may be as high as 33%. It also presented analyses using a 5% transplant rate in the comparator arm (rather than 7.1% as in the company's base case), reflecting information from the clinical expert submission to NICE. The clinical lead for the Cancer Drugs Fund emphasised that all data sources included small numbers of patients and explained that clinical advice to NHS England suggested that a 20% transplant rate after brentuximab vedotin was high, and that the figure in England is likely to be significantly lower. The committee concluded that the exact transplant rate in each group was uncertain, but that the company's lower rate of 16.7% after brentuximab vedotin and original rate of 7.1% for the comparator arm were acceptable for decision making.

The company's approach to modelling outcomes after transplant is appropriate for decision making

3.17 The committee noted that for people who had a stem cell transplant and moved to the model's transplant pathway, progression-free and overall survival were

modelled on real-world evidence presented at the 2018 European Organisation for Research and Treatment of Cancer conference. The company digitised the Kaplan–Meier progression-free survival data and fitted a Gompertz single parametric curve for extrapolation. Overall survival was extrapolated using a log-normal parametric curve. The results are considered academic in confidence and cannot be reported here. The company's model assumed outcomes after disease progression to be substantially worse after a transplant, compared with in people who did not have a transplant. The company explained that people whose disease relapses after transplant are likely to have exhausted all systemic options and have aggressive disease. It also explained that after transplant, many patients remain progression-free for a long time such that many die before their disease progresses. The ERG advised that the short time spent in the post-progression state meant that patients were not entering the resource-intensive 'end-stage care', which may underestimate costs in the brentuximab vedotin arm. The ERG also explained that there was insufficient evidence to support the rate and timing of cure after transplant implied by the progression-free survival curve in the company's model. Responses to consultation from the clinical experts advised that patients whose disease does not relapse within 15 months after transplant are expected to have sustained remission thereafter. The committee noted that there were limited data on transplants in patients who have had brentuximab vedotin. The clinical experts explained that although there had been few stem cell transplants after brentuximab vedotin in clinical practice, there was no reason to expect any differences in outcomes after a transplant in patients after having brentuximab vedotin compared with those after having methotrexate or bexarotene. The committee acknowledged there were limitations in the evidence, including its small sample size and relevance to clinical practice because few patients had a transplant directly after having brentuximab vedotin. However, it was aware that there are limited data on transplants for people with advanced CTCL, and that disease that had not relapsed within 15 months of treatment was likely to remain in long-term remission. The committee concluded that the company's approach to modelling outcomes after transplant was appropriate for decision making.

Pathway not including stem cell transplants

The extrapolation of progression-free survival for people not

having stem cell transplants is appropriate for decision making

3.18 The company explored various parametric survival curves for extrapolating the progression-free survival data. It considered the Weibull models to have the best statistical and visual fit for both the brentuximab vedotin and comparator groups. The committee concluded that the company's approach and its rationale for selecting the Weibull models for its base-case analysis were appropriately justified.

Assumptions about overall survival with brentuximab vedotin affect the post-progression pathway

3.19 The committee recalled that the overall survival data from ALCANZA were immature and confounded by treatment switching (see section 3.10). The company had therefore assumed that the unadjusted survival data for patients in the comparator group could be used to represent overall survival for all patients who did not have a transplant. The committee noted that the company's assumption of equal overall survival for brentuximab vedotin and the comparators alongside a progression-free survival gain for people who had brentuximab vedotin meant that, after disease progression, patients who had brentuximab vedotin died more quickly than patients who had the comparators. The company assumed that patients in both groups spent equal time on subsequent active therapies after disease progression, based on data from the PROCLIPI study. Patients in the brentuximab vedotin group whose disease progressed after subsequent active therapies therefore had a higher risk of death and spent less time in the resource-intensive end-stage care state compared with patients in the comparator group. The committee noted that spending less time in the resource-intensive end-stage care state would reduce overall costs, so this may lead to an overestimation of brentuximab vedotin's cost effectiveness. The committee concluded that assumptions around overall survival in the brentuximab vedotin arm affected the post-progression pathway, and that it should consider this in its decision making.

The modelling of overall survival for people not having stem cell transplants is uncertain

3.20 The company fitted a parametric curve to each treatment group of the trial. It considered the log-logistic parametric model for overall survival in the comparator group to have the best fit, and therefore used it in its base-case analysis to model overall survival for both brentuximab vedotin and the comparators. The company's choice was based on clinical plausibility and on how closely the parametric curves aligned with historical data collected from UK patients with CTCL. The committee recalled that a substantial gain in progression-free survival (as seen in the ALCANZA trial) would also result in a gain in overall survival. It discussed an ERG scenario analysis which examined a potential survival gain with brentuximab vedotin for people who did not have a transplant. The ERG's scenario analysis adjusted the company's base-case overall survival curve for the comparators to generate a 9.5-month mean gain in overall survival for brentuximab vedotin (equal to the mean gain in progression-free survival for people who don't have a transplant when transplant is included in the treatment pathway). The committee noted that the cost-effectiveness estimates for brentuximab vedotin were much higher in this scenario than in the company's base case. In response to consultation, the company presented scenarios exploring the effect of 2, 4, and 9.5 months' survival benefit after brentuximab vedotin for patients who did not have a transplant. The committee was aware that there was no evidence to show which overall survival gain was most likely to be seen in clinical practice, but recalled that assumptions around overall survival affected the post-progression pathway. It concluded that it should consider this in its decision making.

An overall survival gain of 9.5 months in the model better reflects the post-progression treatment pathway after brentuximab vedotin in clinical practice

3.21 The committee recalled that the company's assumption of equal overall survival with brentuximab vedotin and the comparators alongside a progression-free survival gain with brentuximab vedotin meant that patients having brentuximab vedotin spend less time in the post-progression state than patients having the comparators. The clinical experts explained that the post-progression treatment

pathway would be the same for people whose disease relapsed after having brentuximab vedotin (who did not have a transplant) and after having methotrexate or bexarotene. The clinical experts also noted that people having brentuximab vedotin were not expected to have worse outcomes after progression than those having the comparators. The committee therefore agreed that the company's post-progression pathway did not reflect clinical practice. It considered an exploratory analysis by the ERG that assumed equal overall survival and equal time spent in end-stage care for the brentuximab vedotin and comparator arms. The committee understood that this scenario may not accurately represent the current pathway but noted that it was intended to show the model's sensitivity to assumptions about time spent in end-stage care. The committee agreed that both the company's and the ERG's models of the post-progression pathway had limitations, but noted that the scenario analysis assuming a 9.5-month gain in overall survival after brentuximab vedotin (equal to the gain in progression-free survival) made the time spent in end-stage care after brentuximab vedotin similar to the time spent in end-stage care in the comparator arm for patients who did not have a transplant. The committee concluded that although the clinical evidence did not demonstrate a gain in overall survival, based on its effect on the post-progression pathway, a gain in overall survival of 9.5 months with brentuximab vedotin was more likely to reflect clinical practice and should be considered in its decision making.

Utility values

The ERG's approach to calculating utility values is more appropriate

3.22 To calculate the utility values for the progression-free state in the model, the company used EQ-5D-3L data from the ALCANZA trial but fitted a regression model including Skindex-29 scores as a covariate. The committee noted that the cost-effectiveness estimates calculated using Skindex-29 scores would differ to those based on an approach that excluded the scores. It also noted that the utility values in ALCANZA were higher for brentuximab vedotin than for the comparators because of differences at baseline, and that the ERG considered it more appropriate to assume that the utility values for the progression-free state

were equal for brentuximab vedotin and the comparators. The ERG's preferred utility value was calculated using an average of the EQ-5D-3L values from the brentuximab vedotin and comparator groups (0.689). The ERG also preferred not to include treatment-related disutilities based on descriptions of side effects in the model: the EQ-5D-3L data from ALCANZA should capture changes in health-related quality of life as a result of adverse events, so further utility decrements would be unnecessary. The committee concluded that the ERG's approach to modelling utility values was more appropriate and suitable for decision making.

Costs in the model

The ERG's resource use scenario should be used in the cost-effectiveness modelling

3.23 The company's original base case included costs for administering oral chemotherapy. The ERG considered this to be double-counting of costs for the comparator group and the committee agreed that extra costs for oral chemotherapy should not be included. In response to consultation, the company removed extra oral chemotherapy costs from its updated base case but the committee noted that this change had little effect on the cost-effectiveness results. The committee recalled that if there are no treatment options remaining, the only option for patients with advanced CTCL is high-resource care (see section 3.21). End-stage care in the company's model included several outpatient appointments and regular visits from both palliative care and Macmillan nurse teams. The company noted that the resource use data were obtained from semi-structured interviews with clinical experts, with mean values used in its base-case model. The clinical experts reiterated that CTCL is a rare disease; any guidelines would likely recommend that patients have regular hospital admissions and visits from district nurses, but in practice it is likely that some patient care will be managed by families and carers. The committee considered the ERG's scenario analysis which reduced the frequency of outpatient appointments, district and Macmillan nurse visits and palliative support based on its clinical expert advice. In response to consultation the company submitted a scenario analysis using the lower range of resource use from the clinical experts. The clinical lead for the Cancer Drugs Fund explained that the company's estimates

for resource use in end-stage care may most closely reflect that for patients with very severe advanced disease, with expert advice to NHS England indicating that such intense care and support would apply to around 25% of patients. The committee concluded that the ERG's scenario analysis may better reflect end-stage care for most patients with advanced CTCL.

Cost-effectiveness estimates are not sensitive to the length of treatment with brentuximab vedotin before stem cell transplant

3.24 Both the company's and ERG's analyses estimated the cost of brentuximab vedotin based on the time-on-treatment data from the ALCANZA study. The company assumed that all patients having a stem cell transplant have the transplant at 18 weeks, after 6 cycles of brentuximab vedotin. The committee recalled the clinical experts' suggestion that if a patient's disease had an adequate response to allow for a transplant, brentuximab vedotin may be stopped after only a few cycles. In response to consultation the company presented scenario analyses in which transplant was done between 12 and 30 weeks of having brentuximab vedotin. The committee concluded that the length of treatment with brentuximab vedotin before transplant has a limited effect on the cost-effectiveness estimates.

Cost-effectiveness results

The company's updated analyses include the committee's preferred assumptions but some uncertainty remains

3.25 In response to consultation, the company updated its base-case analysis to include the committee's preferred assumptions, using equal utility values for both brentuximab vedotin and the comparators, and excluding extra oral chemotherapy costs. The company also presented a number of scenario analyses that explored uncertainties, including:

- the length of treatment before a transplant

- the transplant rate in both the brentuximab vedotin and comparator arms
- overall survival in the brentuximab vedotin arm
- lower resource use than in the original model.

In all updated analyses, brentuximab vedotin was dominant compared with methotrexate or bexarotene (that is, it was more effective and less costly). The committee acknowledged that the company's updated analyses after consultation included all its preferred assumptions, but it recalled that uncertainty remained in terms of the overall survival benefit, resource use and transplant rate.

The ERG's cost-effectiveness estimates are higher than the company's estimates

3.26 The ERG presented exploratory analyses to illustrate the sensitivity of the model to different assumptions, including:

- assuming an overall survival gain of 9.5 months with brentuximab vedotin (see section 3.20)
- using an alternative progression-free survival curve (changing the proportion and timing of cure) after transplant (see section 3.17)
- using lower resource use for end-stage care (see section 3.23)
- using the transplant rate from UK patients in the ALCANZA trial (16.7%; see section 3.16).

Results from the ERG's sensitivity analyses ranged from an incremental cost-effectiveness ratio (ICER) for brentuximab vedotin compared with methotrexate or bexarotene of £58,516 per quality-adjusted life year (QALY) gained, to brentuximab vedotin being dominant (that is, it was both less costly and more effective). The committee noted the wide range of cost-effectiveness estimates in the ERG's scenario analyses and recognised that this was a result of the model's sensitivity to uncertainties in the evidence

base.

Brentuximab vedotin is a cost-effective use of NHS resources for advanced CD30-positive cutaneous T-cell lymphoma after 1 systemic therapy

3.27 The committee recalled that the assumptions which best reflected clinical practice were: a lower transplant rate after brentuximab vedotin (16.7%), overall survival of 9.5 months with brentuximab vedotin, and applying the ERG's lower resource use. Using these assumptions, the ICER for brentuximab vedotin compared with methotrexate or bexarotene was £29,613 per QALY gained. The committee noted that this scenario also included a transplant rate of 7.1% in the comparator arm; it agreed that this rate may be higher than in clinical practice, and so the cost-effectiveness estimate for brentuximab vedotin would be lower (see section 3.16). The committee also recalled that the evidence may not have fully captured the health-related quality of life benefit of brentuximab vedotin, and that doing so would reduce the cost-effectiveness estimate (see section 3.13). It concluded that the most plausible ICER for brentuximab vedotin compared with methotrexate or bexarotene was less than £30,000 per QALY gained, which is within the range normally considered an acceptable use of NHS resources. However, because the clinical and cost-effectiveness data were based on people with specific subtypes of advanced disease (mycosis fungoides stage 2B or over, primary cutaneous anaplastic large cell lymphoma and Sézary syndrome), the committee concluded that brentuximab vedotin was recommended only for these subtypes.

Other factors

Brentuximab vedotin is innovative and health-related quality of life benefits not captured in the analyses should be considered

3.28 The company considered that brentuximab vedotin was an innovative treatment because it represents a step-change in managing a disease for which there is

significant unmet need. Brentuximab vedotin may allow more patients to proceed to a potentially curative transplant. The company also highlighted that brentuximab vedotin is given every 3 weeks in an outpatient setting, which means patients need to spend less time in hospital. The clinical experts agreed that brentuximab vedotin was innovative and that clinical trial results showed longer clinical responses which are rarely achieved with current treatments. The committee agreed that brentuximab vedotin would be beneficial for patients, but that it had not been presented with robust health-related quality of life evidence to show any additional benefits. It agreed that this was at least partly because of the health-related quality of life tools available (see section 3.13). It concluded that this should be factored into its considerations of the cost-effectiveness evidence.

There are no relevant equality issues

3.29 There were no relevant equality issues raised in the company submission or ERG report, or in patient and professional statements. During scoping, stakeholders highlighted that excluding CTCL with less than 5% CD30 expression from the recommendations may deny some patients access to the treatment because of evidence that 1 in 6 cases of CTCL with less than 5% CD30 expression may respond to treatment. However, the marketing authorisation for brentuximab vedotin does not specify a percentage of CD30 expression so this was not considered to be a relevant equality issue.

Brentuximab vedotin does not meet the end-of-life criteria

3.30 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It noted that the company had not provided any evidence to make a case for brentuximab vedotin meeting the criteria to be considered a life-extending treatment at the end of life. It was aware that the clinical experts considered that brentuximab vedotin did not fulfil either criteria for end of life because people with CTCL may survive for several years after treatment (see section 3.2). Based on advice from the clinical experts and data presented by the company and ERG, the committee accepted that brentuximab vedotin did not

meet the end-of-life criteria.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has CD30-positive cutaneous T-cell lymphoma and the healthcare professional responsible for their care thinks that brentuximab vedotin is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Lorna Dunning
Technical lead

Nicola Hay and Jamie Elvidge
Technical advisers

Stephanie Callaghan and James Maskrey
Project managers

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