NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma

1 Recommendations

1.1 Brentuximab vedotin is recommended as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, only if:

- they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and
- the company provides brentuximab vedotin according to the commercial access agreement with NHS England.

1.2 When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

1.3 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.

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Why the committee made these recommendations

Brentuximab vedotin has a marketing authorisation for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults, but it is most likely to be used in the NHS as first-line salvage therapy. At this point in the treatment pathway, the appropriate comparator is chemotherapy.

Evidence from the main clinical trial for brentuximab vedotin shows that brentuximab vedotin is effective based on response rates. However, the trial is not comparative, and therefore there is uncertainty about the full extent of the survival benefit from treatment with brentuximab vedotin.

The best available evidence comes from an unadjusted indirect comparison of brentuximab vedotin and chemotherapy, although there is still uncertainty about the robustness of the results because of the differences in age, stage of disease, and performance status in the groups compared.

The plausible estimates of cost effectiveness are below £30,000 per quality-adjusted life year gained, and this was considered to be an acceptable use of NHS resources. However, because the clinical and cost-effectiveness data are based on people with an ECOG performance status of 0 or 1, brentuximab vedotin is only recommended for this group.

2 The technology

Brentuximab vedotin (Adcetris, Takeda UK)

Marketing authorisation	Brentuximab vedotin is indicated for 'the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma'. Brentuximab vedotin has been available to patients in England through the Cancer Drugs Fund since April 2013 for relapsed or refractory systemic anaplastic large cell lymphoma.
Recommended dose and schedule	The recommended dose is 1.8 mg/kg administered by intravenous infusion over 30 minutes every 3 weeks.
Price	The price of brentuximab vedotin is £2,500 for a 50 mg vial (excluding VAT; British national formulary edition 69). Takeda has agreed a commercial access agreement with NHS England in which a discount is applied at the point of purchase or invoice for brentuximab vedotin. The financial terms of the agreement are commercial in confidence.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Takeda UK and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Patient experience

Brentuximab vedotin is well tolerated and could significantly improve quality of life

3.1 The patient expert explained that a diagnosis of systemic anaplastic large cell lymphoma can have a big effect on a person's physical and psychological wellbeing. The clinical and patient experts highlighted that brentuximab vedotin is generally better tolerated than existing treatments because it has more manageable and fewer side effects, and that it can significantly improve patients' quality of life. The committee concluded that

access to effective treatments and improving quality of life are significant benefits to patients.

Clinical management

There is an unmet clinical need for people with relapsed or refractory systemic anaplastic large cell lymphoma

3.2 There is no NICE technology appraisal guidance for systemic anaplastic large cell lymphoma. The committee understood that CHOP chemotherapy (cyclophosphamide, hydroxydaunomycin, vincristine and prednisolone) is a commonly used first-line regimen for people with systemic anaplastic large cell lymphoma. Some people may also have additional first-line treatment with high-dose chemotherapy (most commonly BEAM [carmustine or lomustine, etoposide, cytarabine, and melphalan]) and autologous stem cell transplant. The clinical expert explained that most people with systemic anaplastic large cell lymphoma have relapsed or refractory disease. The committee heard that this group represents a major area of unmet clinical need. People typically have short overall survival after relapse and there is a lack of clear agreement or a strong evidence base to recommend second-line therapies. Salvage therapies are used, followed by either autologous or allogeneic stem cell transplant. The choice of treatment depends on clinician and patient preference, which can be influenced by a number of factors (for example, patient fitness, type of therapy and response to prior therapy, donor availability and clinical trial options). The committee agreed that people with relapsed or refractory systemic anaplastic large cell lymphoma have an unmet clinical need.

Brentuximab vedotin is likely to be mostly used as a first-line salvage therapy

3.3 The committee was aware that brentuximab vedotin is used as an alternative salvage therapy to standard chemotherapy regimens (for example, GDP [gemcitabine, dexamethasone and cisplatin] and ICE [ifosfamide, carboplatin and etoposide]). The committee noted that neither the marketing authorisation for brentuximab vedotin nor its indication in the Cancer Drugs Fund (available in England since April 2013 for relapsed or refractory systemic anaplastic large cell lymphoma) specified a certain number of previous treatments before using brentuximab vedotin. It could therefore potentially be used as second-, third- or fourth-line therapy in the treatment pathway for relapsed or refractory systemic anaplastic large cell lymphoma depending on previous salvage treatments and response to those treatments. It noted that the inclusion criteria for SG035-0004 (section 3.5, the pivotal trial on which the marketing authorisation is based) specified 'after treatment failure of at least 1 therapy with curative intent'. The clinical expert explained that brentuximab vedotin is usually used with 2 strategies in mind: as a first-line salvage therapy before either autologous or allogeneic stem cell transplant, and as a first salvage therapy without future stem cell transplant. The committee was also aware from the Cancer Drugs Fund's clinical lead that brentuximab vedotin is used in the Cancer Drugs Fund as a second-line therapy. The committee noted that both the clinical expert and the Cancer Drugs Fund clinical lead agreed that brentuximab vedotin would be used as a first-line salvage therapy (that is as second-line therapy after first-line chemotherapy [for example, CHOP]) instead of salvage chemotherapy. The committee noted that in response to consultation comments were received that stated brentuximab vedotin would be used for some people later in the pathway, e.g as second-line salvage therapy.

People have fewer cycles of brentuximab vedotin in Cancer Drugs Fund clinical practice than in both SG035-0004 and the summary of product characteristics

3.4 The committee asked if rules for stopping treatment are used in clinical practice. It noted that the summary of product characteristics for brentuximab vedotin states that it should be used for a minimum of 8 cycles up to a maximum of 16 cycles in patients whose disease is stable. The committee noted that the mean number of cycles of brentuximab vedotin received by the intention-to-treat population in SG035-0004 was 8.2 cycles. The clinical expert highlighted that real-world evidence from the Cancer Drugs Fund suggests that the median number of cycles for brentuximab vedotin is 5 to 6, and that this estimate includes people who go on to have stem cell transplant, people who do not, and people who stop taking brentuximab vedotin because of a lack of a clinical response or unmanageable side effects. The committee was aware that there are clinical criteria to identify people for whom stem cell transplant is not appropriate before starting first-line salvage therapy, for example people with comorbidities that would compromise fitness for a stem cell transplant, but it may not always be possible to decide whether stem cell transplant is appropriate before starting brentuximab vedotin. The committee heard that when brentuximab vedotin is used as a first-line salvage therapy before either autologous or allogeneic stem cell transplant, assessing the response with PET-CT imaging would typically be done after 3 to 4 cycles of brentuximab vedotin and treatment stopped after 4 to 6 cycles. The committee was aware that for the small minority of people for whom brentuximab vedotin is used as first-line salvage therapy without future stem cell transplant, the median number of cycles of brentuximab vedotin is 6 to 8, but up to 16 cycles of brentuximab can be used if there is evidence of ongoing response and tolerability. The

committee accepted that most people in clinical practice would have fewer cycles than specified in the summary of product characteristics and the SG035-0004 trial, and agreed this should be considered in its decision-making.

Clinical evidence

The main evidence for brentuximab vedotin comes from 1 single-arm, phase II study

3.5 The company's main evidence was based on a multicentre, phase II, single-arm study (SG035-0004) in 58 patients with relapsed or refractory systemic anaplastic large cell lymphoma after treatment failure of at least 1 therapy with curative intent and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The primary outcome of the trial was objective response rate, with secondary outcomes including duration of response, complete remission, progression-free survival and overall survival. These outcomes were assessed by an independent review at a median follow-up time of 16.8 months. The company also presented data for up to 5-years follow-up (median observation time of 71.8 months) based on investigator assessment.

Table 1 Clinical data from SG035-0004 at median follow-up of 16.8 months (independent review)

Best clinical response (N=58)	**N (%)**	**95% confidence interval**
Objective response rate	50 (86)	74.6 to 93.9
Complete remission	34 (59)	44.9 to 71.4
Partial remission	16 (28)	NA
Disease control rate	52 (90)	78.8 to 96.1
Duration of response	**Median**	**95% confidence interval**
Objective response rate*	13.2	5.7 to NE
Complete remission	NR	13.0 to NE
Overall survival	**Median**	**95% confidence interval**
Median	NR**	21.3 to NE
* The duration of response was 0.1+ months to 21.7+ months and the median follow-up time from first dose for patients who achieved objective response per independent review was 11.8 months. ** The estimated 36-month overall survival was 63% (the median observation time [time to death or last contact]) from first dose was 33.4 months. Abbreviations: NA, not applicable; NE, not estimable; NR, not reached.		

Table 2 Clinical data from SG035-0004 at median follow-up of 5 years (investigator assessment)

Overall population	
Estimated 5-year overall survival rate	60% (95% CI: 47% to 73%)
Median overall survival	Not estimable (95% CI: 21.3 to NR; range 0.8 to 82.4+ months)
Median progression-free survival	20.0 months (95% CI: 9.4 to NR)
Of 58 enrolled patients, 42 (72%) had ALK-negative disease:	
Estimated 5-year overall survival	61% (95% CI: 47% to 76%)
Median progression-free survival	20.0 months (95% CI 6.7 to NR)
Median overall survival	NR
Of 58 enrolled patients, 16 (28%) had ALK-positive disease:	
Estimated 5-year overall survival	56% (95% CI: 32% to 81%)
Median progression-free survival	25.5 months (95% CI 8.0 to NR)
Median overall survival	NR
Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; NR, not reached.	

SG035-0004 is the most appropriate source of clinical data for brentuximab vedotin

3.6 Two retrospective case series (Gopal et al. 2014 and Chihara et al. 2015) and 3 named patient programmes (Gibb et al. 2013 based in the UK) provided further non-randomised supplementary evidence. Gopal et al. (2014) evaluated brentuximab vedotin as a treatment for older people with systemic anaplastic large cell lymphoma and reported a median progression-free survival of 15.6 months (95% CI: 4.2, not reached; range 0.0+ to 22.4+ months). Data from the UK named patient programme demonstrated that in people with CD30+ lymphoma who had several previous treatments, brentuximab vedotin had an objective response rate of 67% and median progression-free survival of 5.1 months. The committee concluded that the results from the SG035-0004 trial were the most appropriate for its decision-making, noting that although the Gopal and Gibb studies only included a few patients with systemic anaplastic large cell lymphoma, the results largely supported those from SG035-0004.

It is appropriate to reflect the performance status of the SG035-0004 trial population in decision-making

3.7 The committee noted that patients in SG035-0004 had an ECOG performance status of 0 or 1, corresponding to a population whose activities are relatively unrestricted by their disease. This is in contrast to the population specified in brentuximab vedotin's marketing authorisation, in which performance status is not a criterion. The committee considered the disparity between the populations in SG035-0004 and the marketing authorisation, and noted that people with a worse performance status than 1 may benefit less from brentuximab vedotin. It also considered this group could require more cycles of treatment. The committee concluded that

because it is unclear how effective brentuximab vedotin is in people with a performance status of more than 1, its decision-making should reflect the available trial evidence.

Trial data suggest that brentuximab vedotin is effective but there is uncertainty

3.8 The committee was concerned that the single-arm design of the trial meant that the results were potentially biased, but appreciated that it would be difficult to do a randomised controlled trial for brentuximab vedotin because of the rarity of systemic anaplastic large cell lymphoma. It accepted that the results from the data cut-off at a median follow-up of 16.8 months and a median observation time of 71.8 months showed that brentuximab vedotin was clinically effective based on response rates, but there was uncertainty in the clinical evidence about the full extent of progression-free survival and overall survival. The committee concluded that there was a large degree of uncertainty in the clinical evidence, but noted that both comments from clinical and patient experts and the response rates from the trials suggested that brentuximab vedotin was an effective treatment for people with an ECOG performance status of 0 or 1.

Indirect treatment comparison

The company indirectly compared overall survival of brentuximab vedotin and chemotherapy, only in people with no stem cell transplant

3.9 The committee was aware that there were no data directly comparing overall survival for brentuximab vedotin and chemotherapy. It noted that the company had done an indirect comparison of brentuximab vedotin and chemotherapy. It compared the outcomes from a subgroup of patients from SG035-0004 who did not go on to have stem cell transplant (n=41, the 'self-control cohort') with those from a subgroup of patients from Mak et al. (2013). Mak et al. reported progression-free survival and overall

survival data for a historical cohort of 153 patients on the British Columbia Cancer Agency Lymphoid Cancer database who had peripheral T-cell lymphoma with relapsed or progressive disease. The committee noted that the company focused its analyses on a subset of people reported in Mak et al. who had already had systemic chemotherapy (n=89) but not stem cell transplant. The company considered 2 subgroups from this subset: a subgroup of patients with anaplastic large cell lymphoma (n=17) and a broader subgroup including patients with peripheral T-cell lymphoma and a performance status of less than 2 (n=47).

The unadjusted indirect comparison is appropriate but the results should be treated with caution

3.10 The committee noted the heterogeneity between the self-control cohort from SG035-0004 (n=41) and the subgroup of patients in Mak et al. who had already had systemic chemotherapy (n=89), particularly for age, stage of disease and performance status. The committee was aware that these issues could to lead to bias in favour of brentuximab vedotin. The committee was also aware that it was not possible for the company to compare the baseline characteristics of the self-control cohort from SG035-0004 with those from the subset of patients from Mak et al. with anaplastic large cell lymphoma (n=17) and peripheral T-cell lymphoma and a performance status less than 2 (n=47) because the baseline characteristics were not reported. The committee acknowledged the company had considered doing a matched adjusted indirect comparison using data from the self-control cohort from SG035-0004 and from the subgroup of patients in Mak et al. who had already had systemic chemotherapy (n=89), but had concluded that it was inappropriate to do this because the effective sample size would be 4.8 after adjusting for available variables. The committee agreed with this. The committee

concluded that the company's unadjusted indirect comparison of overall survival was the best available evidence for its decision-making, although there was still uncertainty about the robustness of the results because of the potential bias in favour of brentuximab vedotin, resulting from the heterogeneity in age, stage of disease, and performance status.

The company's economic model

The company's model is appropriate and represents the treatment pathway

3.11 The committee noted that the company had modelled 6 population cohorts: brentuximab vedotin or chemotherapy with no stem cell transplant, brentuximab vedotin or chemotherapy with autologous stem cell transplant, and brentuximab vedotin or chemotherapy with allogeneic stem cell transplant. These reflect the clinical pathway of care for systemic anaplastic large cell lymphoma. Overall, the committee accepted the structure of the model as representing the treatment pathway for patients with relapsed or refractory systemic anaplastic large cell lymphoma. It noted that the company had modelled brentuximab vedotin consistent with its use in clinical practice (section 3.3). The committee considered the model appropriate for its decision-making. It noted that the company's cost-effectiveness analyses included a confidential commercial access agreement between the company and NHS England.

The company updated its model after consultation to incorporate the committee's preferred assumptions

3.12 In response to consultation, the company updated its economic model to include the committee's preferred assumptions and a number of scenario analyses that explored the use of Mak et al. data to model both progression-free survival and overall survival for chemotherapy, parametric models of progression-free and overall survival for both

brentuximab vedotin and chemotherapy, and the use of higher excess mortality rates than in the original model.

Stem cell transplant rates

The company's model uses appropriate stem cell transplant rates

3.13 The committee noted that the modelling of treatment effectiveness and extrapolation of progression-free survival and overall survival was based on a combination of clinical response rates, stem cell transplant by response categories and survival outcomes by transplant status (that is, no stem cell transplant, autologous or allogeneic stem cell transplant). The committee also noted that the company had assumed that for a proportion of patients, brentuximab vedotin or chemotherapy acts as a bridge to stem cell transplant, which is a potentially curative therapy. Data for clinical response rates for brentuximab vedotin were based on the intention-to treat population in SG035-0004 in the base-case analysis. Response rates for chemotherapy in the base-case analysis were based on responses with the most recent cancer-related therapy before brentuximab vedotin for the subgroup of 39 patients in S035-0004 whose most recent therapy was for relapsed or refractory disease. The committee heard from the clinical expert that the response rates used in the model to obtain the proportions of patients having stem cell transplant reflected those seen in clinical practice. The committee was aware that the National Comprehensive Cancer Network practice guidelines do not indicate how to identify which patients should have allogeneic or autologous stem cell transplant. The committee noted that the company's preferred assumption was to use the ratio of autologous stem cell transplant to allogeneic stem cell transplant from SG035-0004 (47% for autologous stem cell transplant and 53% for allogeneic stem cell

transplant). The committee heard from the clinical expert that the rate of allogeneic stem cell transplant is higher than the rate of autologous stem cell transplant in England, which is consistent with the company's modelling approach.The committee agreed that the company's approach for modelling the rate of stem cell transplant was appropriate for decision-making.

The modelling of progression-free and overall survival for people having stem cell transplant is appropriate

3.14 The committee noted that for people who had a stem cell transplant, progression-free survival and overall survival were modelled on data from Smith et al. 2013 (autologous stem cell transplant, n=115; allogeneic stem cell transplant, n=126) and were assumed to be equivalent irrespective of treatment arm. The committee was aware from the clinical expert that survival after stem cell transplant does not depend on the treatment used as the bridge to stem cell transplant but on the type of stem cell transplant received and the time from transplant. The mortality rate is higher with allogeneic transplant and in the first 100 days after transplant. The committee agreed that the company's approach for modelling progression-free survival and overall survival was appropriate for decision-making.

Survival data

Basing brentuximab vedotin progression-free and overall survival on investigator assessment is appropriate

3.15 The committee was aware that the data source for progression-free survival and overall survival was SG035-0004 (n=41) and that the outcomes were based on investigator assessment at a median observation time of 71.8 months (section 3.5). The committee discussed

the appropriateness of using investigator-assessed data instead of independent review, given that the primary analysis for the trial was independent review, with investigator assessment as a secondary analysis. The committee was aware that the company had used investigator assessment because it provided longer follow-up data (median observation at 71.4 months) and was more reflective of the assessments used in the self-control cohort. The committee was also aware that the ERG had concerns about using the investigator-assessed data. The ERG considered the independent review to have a lower risk of bias and to be more objective, although it acknowledged that the investigator-assessed data were the best available long-term data. The committee examined the investigator-assessed and independent review Kaplan–Meier curves for progression-free survival from SG035-0004 and the ERG's comparison of the company's extrapolation of progression-free survival (using a log-logistic model) for both investigator-assessed and independent review data. The committee noted that in both cases, there was a substantial additional progression-free survival gain using the investigator-assessed data compared with the independent review data. The committee heard from the company that agreement between the 2 assessments for best clinical response (but not progression-free survival) had been investigated as an exploratory analysis in SG035-0004 and that best clinical response was in agreement in 46 of 58 patients. This suggested that investigator assessment of response supported efficacy analyses by independent review. The committee heard from clinical experts and the Cancer Drug's Fund's clinical lead that the investigator-assessed data are more clinically relevant. This is because assessment of response is not based only on CT or PET-CT scans but also includes assessment of symptoms and the findings from clinical examination where the tumours are clinically obvious and there is little scope for bias. Only

the assessment of scans is subject to independent review. The clinical expert also highlighted that the data in Mak et al. were based on investigator assessment and therefore it was appropriate to use investigator-assessed data from SG035-0004 in any comparison of data. The committee concluded that data for progression-free survival and overall survival based on investigator assessment were appropriate for decision-making.

Parametric models are preferable to mixture cure models for extrapolating brentuximab vedotin progression-free and overall survival

3.16 The committee noted that the company's preferred method was to use a log-logistic mixture cure model to extrapolate both progression-free and overall survival. The committee was aware that the company used this model because it assumed that the long plateau in the Kaplan–Meier curves for the investigator-assessed data indicated cure. For progression-free survival, a plateau in the Kaplan–Meier curves based on investigator assessment was seen after about 3 years of follow-up, reflecting a mortality rate equal to that expected in the general population. The company highlighted that this trend was not seen for progression-free survival based on independent review and this was likely to be a result of insufficient follow-up. For overall survival, the company also highlighted a plateau was seen in the Kaplan–Meier curve after about 1.3 years, reflecting a mortality rate equal to that expected in the general population. The committee noted a statement from a clinical expert that the clear tail and plateauing on the progression-free and overall survival curves for brentuximab vedotin were noteworthy, and happened at much higher survival levels than those seen for chemotherapy in Mak et al. The committee considered the company's method for deriving the mixture cure models. The company estimated a mixture cure model in which a

proportion of patients (the cure fraction) was assumed to no longer be at risk of progression or death (function tending towards general population mortality) and the remainder (the uncured fraction) had a survival function tending towards zero. The committee had concerns about how the company estimated the mixture cure models because it was not clear how the proportion of patients in the 'better prognosis' group (which is effectively defined on model entry) can be different between progression-free survival and overall survival for the same patients. The company stated that this was an automated part of the fitting algorithm, but the committee considered it implausible because it would be impossible to interpret in a meaningful way, especially because progression-free survival included pre-progression death events. The committee noted that there was clinical justification for assuming that a proportion of people who have brentuximab vedotin have a similar mortality risk as the general population. The committee concluded that because of concerns about estimating the mixture cure models, it was more appropriate that parametric models be used to extrapolate progression-free and overall survival for brentuximab vedotin.

Both gamma and log-normal curves are plausible for extrapolating brentuximab vedotin progression-free and overall survival when using a parametric model

3.17 In response to consultation the company provided analyses in which it used a parametric model rather than a mixture cure model to extrapolate progression-free and overall survival. The company's preferred parametric model extrapolated progression-free and overall survival using a gamma curve, which the committee noted was the most optimistic assumption. The committee also noted that there was a wide variation in long-term survival using the different curves, but that both the gamma and the more

conservative log-normal curve appeared to fit the data. The committee concluded that the most appropriate curve to extrapolate the brentuximab vedotin data was uncertain, and therefore agreed that it was appropriate to consider both the gamma and log-normal curves in its decision-making.

Mak et al. is the most appropriate source of data for chemotherapy progression-free and overall survival in the model

3.18 The committee noted that the company's original economic model used different sources of data for progression-free survival and for overall survival. Data for progression-free survival came from the self-control cohort in SG035-0004 (n=39), data for overall survival came from Mak et al. (subset with peripheral T-cell lymphoma and performance status of less than 2 [n=47] for the base-case analysis, subset with anaplastic large cell lymphoma [n=17] in sensitivity analyses; section 3.10). The committee noted the ERG's concerns about the self-control cohort because patients whose disease was in long-term remission will not have been captured (which is likely to create a bias in favour of brentuximab vedotin). Also there were no deaths in the self-control cohort so it could not equate with progression-free survival or time to progression (which would censor patients at time of death). It was also not possible to determine if previous treatments used to estimate response for the self-control cohort were representative of the chemotherapy comparators applied in the model. The committee noted that chemotherapy regimens used in practice are not expected to differ significantly. The clinical expert considered Mak et al. to be a more appropriate source of data than the self-control cohort in SG035-0004. The committee agreed that Mak et al. was the most appropriate source of data for modelling progression-free survival and overall survival.

The company's use of a log-normal curve to extrapolate chemotherapy progression-free and overall survival was appropriate

3.19 In response to consultation, the company used a log-normal curve to extrapolate both the progression-free and overall survival data from Mak et al. The committee noted that this curve was the best statistical fit for the data, and that there was very little difference visually when fitting other parametric models to the data. It concluded that a log-normal parametric curve was appropriate to extrapolate the chemotherapy data from Mak et al.

The model estimates that brentuximab vedotin substantially improves progression-free and overall survival

3.20 The committee noted the model estimates brentuximab vedotin results in a mean increase of 4.6 or 2.9 years of progression-free and 8.3 or 6.8 years of overall survival, depending on whether brentuximab vedotin is extrapolated using a gamma or log-normal curve respectively (section 3.17). The committee recalled that there was uncertainty in the clinical evidence used in the model (section 3.8), but concluded that the estimates indicate that treatment with brentuximab vedotin would substantially increase both progression-free and overall survival compared with chemotherapy.

Costs

The number of brentuximab vedotin cycles used has a significant effect on its cost effectiveness

3.21 The committee noted that the in both the company's original and revised models, the acquisition cost for brentuximab vedotin was calculated from the mean number of cycles administered in SG035-0004. These were

calculated separately for each population cohort (8.8 for the stem cell transplant cohorts and 8.0 for the no stem cell transplant cohorts) to enable differences in time-on-treatment to be captured when modelling proportions of patients having stem cell transplant different to those in SG035-0004. The ERG explored a scenario in which it varied the lower and upper boundaries of brentuximab vedotin cycles, to 5 cycles (the median number used in Cancer Drugs Fund clinical practice [see section 3.3]) and 16 cycles (as indicated in the summary of product characteristics) respectively. This scenario showed that the cost-effectiveness results were sensitive to the number of brentuximab vedotin cycles. The committee concluded that the number of cycles used had a substantial effect on brentuximab vedotin's cost effectiveness.

Post-progression therapies

Clinical expert distribution of therapies after progression reflects clinical practice

3.22 The committee noted that in the company's original model, all patients were assumed to have a further line of treatment after progression, with 80% of people whose disease has progressed after chemotherapy modelled to have brentuximab vedotin. The ERG considered this inappropriate and not in line with NICE's final scope, which included established clinical management without brentuximab vedotin as the comparator. In response to clarification, the company provided a revised economic model incorporating 2 alternative distributions of post-progression therapy. The trial-based distribution was the ERG's preferred approach but the company preferred the 'clinical expert-based distribution' which it used in its base-case analysis. The committee heard from the clinical expert that this distribution reflected clinical practice in England

because it included best supportive care (that is, palliative treatments) for people for whom multi-agent chemotherapy regimens are contraindicated or not tolerated. The committee concluded that the clinical expert distribution of therapy after progression was the most appropriate for decision-making.

Excess mortality rates

Higher excess mortality rates sourced from published literature are appropriate for decision-making

3.23 The committee noted that the company had applied general population mortality (based on UK life tables) to the parametric survival models (mixture cure or standard) to extrapolate progression-free survival and overall survival to ensure that the long-term extrapolations were clinically plausible. The committee also noted that the company had applied the general population mortality because there is uncertainty about how the mortality rate for people who are long-term survivors after treatment for relapsed or refractory anaplastic large cell lymphoma compares with that of the general population. The committee was aware that the company understood that long-term survivors would still be at risk of secondary malignancies as a result of the effects of stem cell transplant or pre-stem cell transplant therapy and therefore faced an excess mortality risk compared with the general population. The committee agreed that it was appropriate to apply an excess mortality risk, but was concerned that the values used in the company's original economic model were based on the advice of 1 clinical expert (excess mortality rates used were: 5% for brentuximab vedotin [no stem cell transplant], 10% for brentuximab vedotin [with stem cell transplant], 7% for chemotherapy [no stem cell transplant] and 10% for chemotherapy [with stem cell transplant]). In

response to consultation, the company did a targeted literature search to obtain higher excess mortality rates (excess mortality rates used were: 100% for brentuximab vedotin and chemotherapy [no stem cell transplant], 200% for brentuximab vedotin and chemotherapy [with autologous stem cell transplantation], and 300% for brentuximab vedotin and chemotherapy [with allogeneic stem cell transplantation]. The committee considered the new evidence and concluded that it was appropriate to use the higher rates sourced from published literature in its decision-making.

Cost-effectiveness analyses

The committee only considered 1 ICER for people with systemic anaplastic large cell lymphoma

3.24 The committee was aware that neither the company nor the ERG had presented separate incremental cost-effectiveness ratios (ICERs) for the population who had stem cell transplants and the population who had not had stem cell transplant. Both the company and the ERG presented a single ICER which compared all 3 brentuximab vedotin cohorts with all 3 chemotherapy cohorts (section 3.11). However, the committee acknowledged that a small number of people for whom brentuximab vedotin is used as first-line salvage therapy without future stem cell transplant (that is, no stem cell transplant cohorts) may have up to 16 cycles, with the median number of cycles ranging from 6 to 8. The committee understood that in this population, because of the higher number of cycles and poorer prognosis, brentuximab vedotin was likely to be associated with a higher ICER than in the population who had brentuximab vedotin as a 'bridge' to stem cell transplant. However, it noted the small size of this population (that is, people for whom

brentuximab vedotin is used as first-line salvage therapy without future stem cell transplant) and was persuaded that merging the no stem cell and stem cell cohorts would not cause significant health loss. The committee therefore concluded that it was appropriate to consider cost-effectiveness analyses based on 1 ICER for people with systemic anaplastic large cell lymphoma in its decision-making.

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

3.25 The committee considered the company's deterministic and probabilistic ICERs in its updated model, provided in response to consultation. For brentuximab vedotin compared with chemotherapy, the deterministic ICER was £18,324 per quality-adjusted life year (QALY) gained and the probabilistic ICER was £20,399 per QALY gained. Both of these ICERs included the confidential commercial access agreement between the company and NHS England. The committee acknowledged that the company's updated analyses after consultation included all its preferred assumptions. However, it recalled that uncertainty remained in terms of the most appropriate parametric curve to use for extrapolating long-term survival with brentuximab vedotin data (section 3.17), and that the number of cycles of brentuximab vedotin in the model had a large effect on the cost effectiveness of brentuximab vedotin (section 3.21).

All plausible extrapolation curves result in ICERs below £30,000 per QALY gained

3.26 The committee considered how the company's choice of parametric curve affected the deterministic ICER for brentuximab vedotin. The committee noted that the ICERs ranged from £18,324 per QALY gained using a gamma curve to £32,801 per QALY gained using an exponential curve.

The committee also noted that for the gamma and log-normal parametric curves (the committee's preferred choice of curves; section 3.17), the ICERs were £18,324 per QALY gained and £24,064 per QALY gained respectively. The committee was reassured that only the implausible exponential curve produced an ICER above the range usually considered to be a cost-effective use of NHS resources.

The number of cycles of brentuximab vedotin from the SG35-0004 trial is most appropriate for decision-making

3.27 The committee recalled that the number of cycles of brentuximab vedotin had a substantial effect on the ICER (section 3.21). It noted that the ERG's sensitivity analyses produced ICERs from £11,048 per QALY gained with 5 cycles of brentuximab vedotin to £35,848 per QALY gained with the maximum 16 cycles. The committee noted that, assuming the benefit of treatment remained the same, the ICER for brentuximab vedotin in people having 16 cycles was above the range usually considered to be a cost-effective use of NHS resources. It recalled that in practice, people would have fewer cycles than specified in the summary of product characteristics and the SG035-0004 trial (section 3.4). It concluded that the number of cycles used in SG35-0004 and the company's model was the most appropriate for decision-making, but was reassured that the ICER may plausibly be lower.

Brentuximab vedotin is a cost-effective use of NHS resources

3.28 The committee considered that the most plausible ICER was between £18,324 and £24,064 per QALY gained, depending on whether a gamma or a log-normal curve respectively was used and based on the number of cycles in the SG35-0004 trial. The committee noted that it is plausible that the number of cycles of brentuximab vedotin in clinical practice is fewer

than modelled for some people, which would reduce the ICER. The committee concluded that all plausible ICERs were within the range of those usually considered a cost-effective use of NHS resources.

End of life

Brentuximab vedotin only meets 1 of NICE's end-of-life criteria

3.29 Having concluded that all plausible ICERs were within the range for brentuximab vedotin to be considered a cost-effective use of NHS resources, the committee discussed the additional evidence provided by the company in response to consultation to support the case for brentuximab vedotin as an end-of-life therapy. It considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. It agreed that it could not make reliable conclusions about life expectancy and survival benefit using the results from the self-control cohort from SG035-0004, because it had concerns about using this as a source of data for overall survival for chemotherapy (section 3.18). The committee heard from the company that Mak et al. reported a median overall survival of 13.7 months for people with peripheral T-cell lymphoma and a performance status of 0 or 1 (the subgroup used in the company's model), but noted that median overall survival for people with systemic anaplastic large cell lymphoma was 3.0 months. Because the committee's preference is for mean values for overall survival, it instead considered estimates from the economic model. The committee discussed the criterion of short life expectancy with current treatment, which is normally less than 24 months, and noted that the modelled overall survival with chemotherapy in the company's updated model was 3.98 years. In response to consultation, the company provided supplementary evidence

from the UK-based Haematological Malignancy Research Network (HMRN), the results of which are academic in confidence and cannot be reported here. In discussing this evidence, the committee noted that the population in the HMRN dataset was broader than the population in the SG035-00045 trial (that is, it included people of any performance status). It noted that mean overall survival for the population in the HMRN dataset was therefore likely to be lower than that for people in whom brentuximab vedotin would be an option in NHS practice. The committee therefore concluded that brentuximab vedotin did not meet the criterion of short life expectancy. The committee then discussed whether brentuximab vedotin could meet the criterion for extension to life, normally of at least an additional 3 months. Using the its preferred assumptions and a gamma curve to extrapolate progression-free and overall survival, the committee noted that mean overall survival with brentuximab vedotin was 12.28 years, representing an extension of 8.3 years. The committee considered that, based on the modelled overall survival benefit, brentuximab vedotin would meet the criterion for extension to life. However, it recalled that brentuximab vedotin did not meet the first end-of-life criterion, and concluded that brentuximab vedotin cannot be considered an end-of-life therapy.

Equality

Healthcare professionals should consider ECOG performance status when implementing the recommendations

3.30 The committee considered whether its recommendations were associated with any potential issues related to equality. It concluded that healthcare professionals should take into account any physical, sensory or learning

disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

Other Factors

The committee did not identify any other factors that would affect its recommendations

3.31 The committee discussed the company's comments about the innovative nature of brentuximab vedotin. It heard from a clinical and patient expert that treatment with brentuximab vedotin produces high complete remission rates and that results are seen quickly, allowing treatment to be stopped early for most people. They considered the benefits of brentuximab vedotin to be a major change in the management of relapsed and refractory systemic anaplastic large cell lymphoma, providing patients with a valuable treatment option instead of toxic current treatment. The committee concluded that brentuximab vedotin was an innovative and promising treatment, but that it had not been presented with any evidence of additional benefits that were not captured in the QALY measure.

Conclusion

Brentuximab vedotin is only recommended within its marketing authorisation for people with a performance status of 0 or 1

3.32 The committee considered that the most plausible ICERs for brentuximab vedotin (£18,324 to £24,064 per QALY gained) meant that it could be considered a cost-effective use of NHS resources. However, the committee acknowledged that there was limited representation of people with an ECOG performance status of more than 1 in SG035-0004, the trial on which the cost-effective analyses were based. It therefore considered that its recommendations should closely reflect the population in the

SG035-00045 trial, because it was unclear if the cost-effectiveness results would be reflected in people with an ECOG performance status of more than 1. The committee concluded that it could recommend brentuximab vedotin as an option for treating relapsed or refractory systemic anaplastic clear cell lymphoma in adults, only if they have an ECOG performance status of 0 or 1 and the company provides brentuximab vedotin at the price agreed with NHS England in the commercial access agreement.

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 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.

4.3 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 relapsed or refractory systemic anaplastic large cell lymphoma and the doctor responsible for their care thinks that brentuximab vedotin is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 The company has agreed that brentuximab vedotin will be available to the NHS under commercial terms agreed with NHS England. The nature of these terms are commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the commercial terms should be directed to [NICE to add details at time of publication]

5 Review of guidance

5.1 The guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Selby
Chair, appraisal committee
August 2017

6 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.

Sana Khan and Thomas Strong
Technical Leads

Nicola Hay
Technical Adviser

Stephanie Yates
Project Manager

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