NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using brentuximab vedotin in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: June 2017

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using brentuximab vedotin in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 5 July 2017

Second appraisal committee meeting: 12 July 2017

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 The committee is minded not to recommend brentuximab vedotin, within its marketing authorisation, for treating relapsed or refractory systemic anaplastic large cell lymphoma in adults.

1.2 The committee recommends that NICE requests a revised probabilistic cost-effectiveness analysis from the company, which should be made available for the second appraisal committee meeting and should:

- Use data from Mak et al. (2013) for extrapolating both progression-free and overall survival for chemotherapy.
- Explore a number of parametric models for extrapolating progression-free and overall survival for brentuximab vedotin and chemotherapy, including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate.
- Include a range of excess mortality rates higher than those used in the company's base-case analyses. The range should come from published literature identified through a systematic literature review rather than clinical expert opinion.

Why the committee asked for more evidence

Brentuximab vedotin has a marketing authorisation for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma. However, it is likely to be used in the NHS as first-line salvage therapy. The appropriate comparator at this point in the pathway is standard chemotherapy.

Results of a single arm study (SG035-0004) in 58 patients suggest brentuximab vedotin is clinically effective based on response rates and there was uncertainty regarding the extent of progression-free survival and overall survival because median progression-free survival and overall survival were not reached.

As there were no data directly comparing brentuximab vedotin with current treatment (chemotherapy), an unadjusted indirect comparison was carried out. This was considered to be the best available evidence although there was uncertainty because of differences in age, stage of disease, and performance status in the groups compared.

Neither the company's nor the ERG's base case analyses included all of the committee's preferred assumptions. To account for the uncertainties in the data, more evidence for brentuximab vedotin is requested, in particular the use of Mak et al. to model both progression-free survival and overall survival for chemotherapy, a full exploration of the parametric models for progression-free and overall survival for both brentuximab vedotin and chemotherapy and the use of higher excess mortality rates than the company used in its base-case analysis. Until these analyses are presented, brentuximab vedotin could not be recommended.

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). The pricing arrangement was one in which the company (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 vedotion. The financial terms of the agreement are commercial in confidence.

3 Committee discussion

The appraisal committee (section 5) 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 well tolerated because it has more

manageable and fewer side effects than existing treatments, 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 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 (see section 2) 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 line, third line 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 (see section 3.7, 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 the use of brentuximab vedotin in the Cancer Drugs Fund is as a second-line therapy. The committee noted that both the clinical expert and the Cancer Drugs Fund clinical lead were in agreement 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.

People have fewer cycles of brentuximab vedotin in Cancer Drugs Fund clinical practice than in the clinical trial and 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 and those who do not. 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. For example, if a person's performance status is impaired because of their disease, they may have an improved performance status after brentuximab vedotin, allowing stem cell transplant to become a viable treatment option later. 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.

Clinical evidence

The main evidence 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. 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)	**Independent review 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 per independent review**	**95% confidence interval**
Objective response rate*	13.2	5.7 to NE
Complete remission	Not reached	13.0 to NE
Overall survival	**Median**	**95% confidence interval**
Median	Not reached**	21.3 to NE
Abbreviations: NE: not estimable; NA: not applicable * 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.		

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 -; range 0.8 to 82.4+ months)
Median progression-free survival	20.0 months (95% CI: 9.4 to -)
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 -)
Median overall survival	Not reached
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 -)
Median overall survival	Not reached
Abbreviations: CI, confidence interval; ALK, anaplastic lymphoma kinase; -,not reached	

3.6 Further non-randomised supplementary evidence was provided by two retrospective case series (Gopal et al. 2014 and Chihara et al. 2015) and three named patient programmes (Gibb et al. 2013 based in the UK). Gopal et al. 2014 reported progression free survival in people with systemic anaplastic large cell lymphoma had a median duration of 15.6 months (95% CI: 4.2, not reached; range 0.0+ to 22.4+ months) and a median duration of 9.0 months (95% CI: 1.9, not reached, range 1.9 to 23.3+ months). Data from the UK named patient programme demonstrated that brentuximab vedotin was effective with an objective response rate of 67% and a median progression-free survival of 5.1 months in a population of heavily pre-treated patients with CD30+ lymphoma managed in a non-trial setting at a single UK centre. The committee noted that while the Gopal and Gibb studies only included a small number of people with systemic anaplastic large cell lymphoma, the results largely supported those from SG035-0004.

Trial data suggest brentuximab vedotin is effective but there is uncertainty

3.7 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 time of 16.8 months and at a median observation time of 71.8 months showed that brentuximab vedotin was clinically effective based on response rates and there was uncertainty in the clinical evidence about the extent of progression-free survival and overall survival. Overall the committee concluded there was a large degree of uncertainty in the clinical evidence, but noted comments from clinical and patient experts and the response

rates from the trials suggested that brentuximab vedotin was an effective treatment.

Indirect treatment comparison with chemotherapy (no stem cell transplant population)

Overall survival

3.8 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 of brentuximab vedotin with chemotherapy is appropriate and should be treated with caution

3.9 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 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

3.10 The committee discussed the company's economic model and modelling assumptions. It 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 as a first-line salvage therapy, which was consistent with its use in clinical practice (see 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.

Stem cell transplant rates in the economic model

The stem cell transplant rates used in the company's model are appropriate

3.11 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 used the ratio of autologous stem cell transplant to allogeneic stem cell transplant from SG035-0004 in its base-case analysis (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 approach of progression-free survival and overall survival for people having stem cell transplant is appropriate

3.12 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.

Brentuximab vedotin survival data in the economic model

Progression-free survival and overall survival based on investigator assessment is appropriate

3.13 The committee was aware that the data source for progression-free survival and overall survival came from SG035-0004 (n=41) and that the outcomes were based on investigator assessment at a median observation time of 71.8 months (see 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 the 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 rather than mixture cure models are preferred for extrapolating progression-free survival and overall survival

3.14 The committee noted that the company had used a mixture cure model to extrapolate both progression-free survival and overall survival. The

committee was aware that this model was used because the company had 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, 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 the statement from a clinical expert that the clear tail and plateauing on the progression-free survival 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 therefore agreed that there was a clinical justification for considering the company's use of mixture cure models further. 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 since progression-

free survival included pre-progression death events. The committee therefore considered the ERG's sensitivity analyses in which it used a parametric gamma model rather than a mixture cure model to extrapolate progression-free survival and overall survival and noted that the use of a parametric model did not have a large effect on the incremental cost-effectiveness ratio (ICER). However, the committee was aware that the ERG could not explore other parametric models because of the lack of functionality in the company's model. The committee concluded that it would have liked to have seen cost-effectiveness analyses based on a number of parametric models including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate.

Chemotherapy survival data in the economic model

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

3.15 The committee noted that the company 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, see section 3.9). 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 and concluded that it would have liked to have seen cost-effectiveness analyses using data from Mak et al. for chemotherapy.

Additional parametric modelling is needed for progression-free survival and overall survival

3.16 The committee noted that the company had used parametric modelling for both progression-free survival and overall survival. It also noted that the company had selected the log-normal model in its base-case analysis for both progression-free survival (based on the self-control cohort from SG035-0004) and overall survival (based on Mak et al.). The committee was aware that the ERG considered the company's method for selecting these models was appropriate but because of the lack of functionality in the company's model, the ERG was unable to replicate all of the progression-free survival and overall survival parametric models considered in the company's submission. The committee concluded that it would have liked to have seen cost-effectiveness analyses based on a number of parametric models including those already considered in the company's submission (which were all accelerated failure time models) and others (proportional hazards models) if considered appropriate.

Costs

Number of cycles of brentuximab vedotin is a key driver of cost effectiveness

3.17 The committee noted that the in the company's base case analysis, 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 (mean number of cycles 8.8 for the stem cell transplant cohorts and 8.0 cycles for the no stem cell transplant cohorts) to enable differences in time-on-treatment to be captured when modelling alternative proportions of patients receiving stem cell transplant compared with that in SG035-0004. The company also explored in sensitivity analyses a stopping rule after 4 cycles of brentuximab vedotin to reflect the Cancer Drugs Fund clinical practice (see section 3.4) and found it had little impact on the cost-effectiveness results. The ERG explored a scenario to reflect the upper boundary of brentuximab vedotin costs with 16 cycles, reflecting the summary of product characteristics, which showed that the cost effectiveness results were sensitive to the number of brentixumab vedotin cycles. The committee concluded that the number of cycles of brentuximab vedotin in the model was a key driver of cost effectiveness.

Post-progression therapies

Clinical expert distribution of therapies after progression reflects clinical practice

3.18 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 should be used and sourced from published literature

3.19 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 was also aware that although the ERG considered it appropriate to apply an excess mortality risk, it was concerned that the values used 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]).The committee heard from the clinical expert that the values used in the company model were appropriate for treatment-related excess mortality but not applicable for general mortality rates. The committee was aware that excess mortality rates considered in appraisals for haematological cancers (such as acute lymphoblastic leukaemia) were much higher (up to 4 times greater). The committee agreed that the excess mortality rates used in the company's model were too low. The committee concluded that it would have liked to have seen cost-effectiveness analyses based on a range of excess mortality rates higher than those used in the company's base-case analyses and that the range should be sourced from published literature identified through a systematic literature review rather than based on clinical expert opinion.

Results of cost-effectiveness analyses

It is appropriate to consider cost-effectiveness analyses based on one ICER for people with systemic anaplastic large cell lymphoma.

3.20 The committee was aware that neither the company nor the ERG had presented separate ICERs for the population who had received stem cell transplants and for the population who had not received a stem cell transplant. Both the company and the ERG presented a single ICER

which compared all 3 brentuximab vedotin cohorts (see section 3.10) with all 3 chemotherapy cohorts (see section 3.10). However, the committee acknowledged that a small minority of people for whom brentuximab vedotin is used as first-line salvage therapy without future stem cell transplant (no stem cell transplant cohorts) can receive up to 16 cycles of brentuximab vedotin with a median number of cycles ranging from 6-8. The committee understood that the higher number of cycles received by this population and their poorer prognosis was likely to lead to an ICER higher than that for people who received brentuximab vedotin with the intention to bridge to stem cell transplant. It noted the small size of the population for whom brentuximab vedotin is used as first-line salvage therapy without future stem cell transplant and was persuaded that the merging of the 2 cohorts (that is the no stem cell cohorts and the stem cell cohorts) would not cause significant health loss. The committee therefore concluded it was appropriate to consider cost-effectiveness analyses based on one ICER for people with systemic anaplastic large cell lymphoma in its decision making.

The cost effectiveness of brentuximab vedotin compared with chemotherapy is uncertain

3.21 The committee noted that the company's deterministic base-case ICER using the 'clinical expert based distribution' for post-progression therapy was £12,873 per quality-adjusted life year (QALY) gained for brentuximab vedotin compared with chemotherapy. The committee noted that the company only provided deterministic analyses and the ERG's deterministic base-case ICER was £21,267 per QALY gained (probabilistic ICER £20,667 per QALY gained), when using:

- the 'trial-based' distribution for post-progression costs

- the chemotherapy comparator with the costs of brentuximab vedotin removed
- data from Mak et al. for both progression-free survival and overall survival and
- corrected values from the company's model (corrected errors in discounting of post-progression therapy costs and probabilistic sensitivity analysis).

It noted that neither the company's nor the ERG's base-case analyses included all of the committee's preferred assumptions, in particular using data from Mak et al. for both progression-free survival and overall survival for chemotherapy, a full exploration of the parametric models for progression-free survival and overall survival for both brentuximab vedotin and chemotherapy, and much higher excess mortality rates. Until it considers these analyses, the committee concluded that it was minded not to recommend brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma.

End of life

Brentuximab vedotin does not meet NICE's end-of-life criteria

3.22 The committee 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 was aware that the company had not presented data to support the consideration of brentuximab vedotin as an end-of-life therapy because the ICERs in its original submission were below £10,000 per QALY gained. 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 the appropriateness of using this as a source of data for overall survival for chemotherapy (see section 3.15). 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 less than 2 (the subgroup used in the company's base-case analysis) but noted that the 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, the committee 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 original submission was 4.6 years and for the 'trial-based' post-progression therapy distribution analysis it was 3.35 years (discounted life-years). The committee therefore concluded that brentuximab vedotin does not meet the criterion of short life expectancy. Although brentuximab vedotin did not meet the first end-of-life criterion, the committee discussed whether it has the potential to meet the criterion for extension to life, which is normally at least an additional 3 months. The committee considered the modelled overall survival benefit with brentuximab vedotin and noted that in the company's original submission the mean overall survival was 16.31 years (representing an extension in mean overall survival of 11.7 years) and for the 'trial-based' post-progression therapy distribution this was 9.53 years (discounted life-years, representing an extension of 6.18 years). The committee considered that the modelled overall survival benefit with brentuximab vedotin suggests that it has the potential to meet the criterion for extension to life, but agreed that these results were uncertain because of the mixture cure models used for extrapolating overall survival with brentuximab vedotin (see section 3.14) and the low excess mortality rates

used in the model (see section 3.18). The committee concluded that, based on the currently available data, brentuximab vedotin cannot be considered as an end-of-life therapy.

Other factors

3.23 No equality or social value judgement issues were identified.

3.24 The committee discussed the company's comments about the innovative nature of brentuximab vedotin. It heard from the 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

3.25 The committee is minded not to recommend brentuximab vedotin, within its marketing authorisation, as an option for treating relapsed or refractory systemic anaplastic clear cell lymphoma. It requested further analyses from the company.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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

June 2017

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.

Sana Khan

Technical Lead

Nicola Hay

Technical Adviser

Stephanie Yates

Project Manager

ISBN: [to be added at publication]