

Brentuximab vedotin in combination for untreated systemic anaplastic large cell lymphoma

Technology appraisal guidance
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Your responsibility

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

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

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

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

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1 Recommendations

- 1.1 Brentuximab vedotin with cyclophosphamide, doxorubicin and prednisone (CHP) is recommended, within its marketing authorisation, as an option for untreated systemic anaplastic large cell lymphoma in adults. It is only recommended if the company provides brentuximab vedotin according to the [commercial arrangement](#).

Why the committee made these recommendations

Standard care for untreated systemic anaplastic large cell lymphoma is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

Clinical evidence shows that people with systemic anaplastic large cell lymphoma who have brentuximab vedotin with CHP live longer and have longer before their disease progresses than people who have CHOP.

There is uncertainty about the modelling, but the most likely cost-effectiveness estimate is within what NICE considers an acceptable use of NHS resources. Therefore, brentuximab vedotin with CHP is recommended.

2 Information about brentuximab vedotin

Marketing authorisation indication

- 2.1 Brentuximab vedotin (Adcetris, Takeda) with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated 'for adult patients with previously untreated systemic anaplastic large cell lymphoma (SALCL)'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The NHS list price of brentuximab vedotin is £2,500 per 50-mg vial (excluding VAT; BNF online, accessed June 2020). Based on a mean of 6 cycles, the cost for an average patient is estimated at about £47,619, at list price. The company has a [commercial arrangement](#). This makes brentuximab vedotin available to the NHS with a discount. The size of the discount is confidential. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Takeda, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- the mean age of the systemic anaplastic large cell lymphoma (sALCL) population seen in the ECHELON-2 trial (52 years) was appropriate for the economic model
- the time-to-death utility model approach was preferable to the health-state utility method for this appraisal
- it was appropriate to cap the patient utility values in the model so that they cannot exceed the age-adjusted utility values for the general population
- the mean number of cycles of brentuximab vedotin monotherapy was 6 when used second line for relapsed or refractory sALCL
- the joint modelling approach was acceptable for this appraisal
- excluding costs for grades 3 and 4 peripheral neuropathy was appropriate.

The committee recognised that there were areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed the choice of model used to estimate progression-free survival and overall survival (see technical report, pages 13 to 17), which was outstanding after the technical engagement stage.

Clinical need

People would welcome a new first-line treatment option

- 3.1 The patient and clinical experts explained that there is a considerable unmet need for people with sALCL. Current treatments are often difficult to tolerate, cause significant side effects and are often given as inpatient

treatment. The patient experts described their experiences of disease relapse after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and other previous treatments and the lack of alternatives. They noted that after treatment with brentuximab vedotin plus cyclophosphamide, doxorubicin and prednisone (CHP) they experienced an improvement in their symptoms and had fewer side effects. Brentuximab vedotin with CHP is given in an outpatient setting, reducing the time in hospital. The committee concluded that brentuximab vedotin with CHP would be welcomed as a new treatment option for people with sALCL.

Clinical management

Brentuximab vedotin with CHP will replace CHOP for untreated sALCL

- 3.2 The clinical experts noted that standard care for untreated sALCL is CHOP, but few patients have disease that is in complete remission. Of those that do, many have disease that relapses in the first year. The clinical lead for the Cancer Drugs Fund advised that a more effective first-line treatment is needed and that, if recommended, brentuximab vedotin with CHP would replace current treatment for sALCL in the NHS. The clinical experts agreed that brentuximab vedotin with CHP would be a useful first-line treatment since it may give a durable response. They explained that for people whose disease relapses, brentuximab vedotin monotherapy would still be an option at a later stage in the treatment pathway. The only exception would be people whose sALCL did not respond to previous treatment with brentuximab vedotin. The clinical experts agreed that brentuximab vedotin with CHP could quickly replace CHOP for people with untreated sALCL because of its clinical advantages. Based on comments from the clinical experts and the clinical lead for the Cancer Drugs Fund, the committee concluded that brentuximab vedotin with CHP would replace CHOP for sALCL in the NHS.

Clinical evidence

Brentuximab vedotin with CHP improves progression-free survival and overall survival compared with CHOP

3.3 The clinical evidence for brentuximab vedotin with CHP came from ECHELON-2. This was a randomised controlled trial of 452 people with CD30-positive peripheral T-cell lymphoma, comparing brentuximab vedotin and CHP with CHOP. The median follow up for the progression-free survival analysis was 36.2 months (95% confidence interval [CI] 35.9 to 41.8), and for the overall survival analysis was 42.1 months (95% CI 40.4 to 43.8). The committee noted that 70% of the patients in ECHELON-2 had a diagnosis of sALCL, which is higher than would be expected in clinical practice in the NHS. The company clarified that this was because of a regulatory requirement of the European Medicines Agency. The company presented analyses from the subgroup of patients with sALCL. This subgroup's objective response rate, measured by independent review facility assessment, was 88% (95% CI 81.6 to 92.3) for people in the brentuximab vedotin with CHP arm compared with 71% (95% CI 62.9 to 77.8) for people in the CHOP arm ($p=0.0001$). Brentuximab vedotin with CHP statistically significantly reduced the risk of a progression event compared with CHOP (stratified hazard ratio [HR] 0.59 [95% CI 0.42 to 0.84]; $p=0.0031$). Overall survival was also statistically significantly improved for brentuximab vedotin with CHP compared with CHOP (HR 0.54 [95% CI 0.337 to 0.867], $p=0.0096$). There were 70% of patients in the CHOP arm who had second-line brentuximab vedotin after progression. This meant the treatment effect was likely to be underestimated for the brentuximab vedotin with CHP arm. The committee concluded that brentuximab vedotin with CHP improves progression-free survival and overall survival compared with current standard care, CHOP.

Survival extrapolation

There are uncertainties about the company model for progression-free survival and overall survival

3.4 The company applied standard parametric functions to the available data from ECHELON-2 to estimate progression-free survival and overall survival. It selected the generalised gamma curve for both progression-free survival and overall survival in the sALCL population. This was based on statistical fit and advice from clinical experts. The company submission noted that the shape of the generalised gamma hazard function matched what would be seen clinically in people with sALCL. People were at an increased risk of dying or having their disease progress during the first 18 to 24 months, but after that the risk declined quickly. This characteristic prognosis for sALCL was confirmed by the clinical experts. The committee noted that a similarly shaped hazard function could also be associated with the log-normal extrapolation, and to a lesser extent the log-logistic extrapolation. The clinical experts agreed that people in the CHOP arm of ECHELON-2 appeared to do better than was expected in clinical practice. They suggested that this could be because of the inclusion and exclusion criteria of the trial. The clinical experts informed the committee that the number of people with sALCL seen in clinical practice is relatively small. This makes it difficult to select an overall survival extrapolation for the CHOP arm. The clinical experts agreed that real-world experience suggests that people would have less optimistic outcomes than suggested by the generalised gamma curve, and that it could be closer to the log-normal extrapolation. The committee concluded that there were considerable uncertainties about how the company modelled progression-free survival and overall survival.

The committee would have preferred to see alternative survival models explored but accepts the available analyses

3.5 The standard parametric curves that were fitted to the data varied considerably. This was partly because of the high degree of censoring in the progression-free survival and overall survival data (the event of

interest was not seen at the end of trial follow up). Also, most of the long-term projections of progression-free survival and overall survival were highly influenced by general population mortality constraints (adjusted for excess risk of mortality in long-term survivors). These were informed by the general population mortality for England and Wales. The company submission assumed that people whose disease is in long-term remission had a small reduction in life expectancy compared with the general population. This reflected slightly increased rates of cardiac toxicity and other malignancies. The company submission further noted that UK clinical expert opinion predicted a reduced survival of between 3% and 10%, relative to the general population. To reflect this in its analysis, the company applied a mortality multiplier of 1.19 in its base case, reflecting a 5% increased mortality risk. The ERG considered that 1.28 was more appropriate for its base case, representing a 6.5% increased mortality risk. This was the midpoint of the clinical expert estimates referenced in the company submission. In the company's model, the time points at which the background mortality risk took over from the parametric model risk differed depending on the progression-free survival and overall survival model selected. When the generalised gamma model was selected, the general population mortality took over from 12 years in the brentuximab vedotin with CHP arm, and 13 years in the CHOP arm. The committee noted that it was unusual for background mortality to take effect at such an early stage in an economic model with a 45-year time horizon, and that it is applied to more than half of the patients in each treatment group. This means the model assumed that there is a cure, or 'near cure', for anyone still alive after these time points. The clinical experts noted that a person presenting 5 years after first-line treatment with brentuximab vedotin and CHP would be considered to have equally low risk of relapsing as someone who had CHOP. The assumed cure point varied a lot between the different parametric models. So, the committee agreed that the standard parametric extrapolations were uncertain and that alternative models, such as spline or mixture cure rate models, should have been more fully explored by the company. However, the incremental cost-effectiveness ratios (ICERs) for brentuximab vedotin with CHP were within what NICE considers cost effective even under pessimistic assumptions. Therefore the committee concluded that it would consider the available analyses.

Cost-effectiveness analysis

The company's base-case ICER for brentuximab vedotin with CHP is less than £30,000 per QALY gained

3.6 [NICE's guide to the methods of technology appraisal](#) notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Therefore, because of the uncertainty in the survival extrapolations (see [sections 3.4 and 3.5](#)), the committee agreed that an acceptable ICER would be around the lower end of the £20,000 to £30,000 per QALY gained range. The company's base-case ICER for brentuximab vedotin plus CHP compared with CHOP was £21,192 per QALY gained (including the simple discount patient access scheme).

The ERG's base-case ICER for brentuximab vedotin is less than £30,000 per QALY gained

3.7 The ERG agreed with the company base case on all points. It only had minor changes to the model to correct the implementation of the time-to-death approach, and adjust the mortality multiplier (see [section 3.5](#)). The selection of the generalised gamma model for both progression-free survival and overall survival represented the most conservative effect on the cost-effectiveness results, with all other parametric extrapolations generating lower ICERs. The committee was reassured that the cost-effectiveness results for brentuximab vedotin with CHP represented the most conservative scenario, but had concerns about the uncertainty of these parametric extrapolations. It agreed that it was important to explore different assumptions about duration of treatment effect. In the company base case, the treatment effect duration was 13 years (the time point when the hazard switches to that of the general population in both groups). The ERG also produced a scenario analysis. This showed the effect on the ICER of varying the time point at which the relative treatment effect in the brentuximab vedotin with CHP arm was assumed

to be equal to that in the CHOP arm. If the relative treatment benefit of brentuximab vedotin with CHP was removed at 5 years (approximately corresponding to the point when the trial data end), the ICER remained broadly consistent with that in both the ERG and company base cases. The committee considered the standard parametric extrapolations to be uncertain. It concluded that the assumption that brentuximab vedotin with CHP had no additional relative clinical benefit over CHOP after 5 years was preferable for decision making. The corresponding ICER for brentuximab vedotin plus CHP compared with CHOP was £23,446 per QALY gained (including the simple discount patient access scheme). The committee concluded that brentuximab vedotin with CHP could be considered a cost-effective use of NHS resources.

Innovation

The model adequately captures the benefits of brentuximab vedotin with CHP

3.8 The company considered brentuximab vedotin with CHP to be innovative because it is a targeted treatment that has shown novel efficacy in the first-line treatment of sALCL. The clinical experts noted that it is expected to replace CHOP, which has been the standard treatment for about 30 years. The committee recognised the additional benefits to people with sALCL related to how the treatment is given and the associated improvements to quality of life. However, it concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of the QALYs and the resulting cost-effectiveness estimates.

Other factors

3.9 No equality or social value judgement issues were identified. The company did not make a case for brentuximab vedotin with CHP satisfying the end-of-life criteria. This was because people with sALCL are expected to live for more than 24 months.

Conclusion

Brentuximab vedotin with CHP is recommended for routine commissioning

- 3.10 The committee acknowledged the need for a better treatment option for adults with untreated sALCL. The most plausible ICER for brentuximab vedotin plus CHP compared with CHOP was £23,446 per QALY gained (including the simple discount patient access scheme). The committee concluded that brentuximab vedotin with CHP could be considered a cost-effective use of NHS resources. Therefore, it was recommended as an option for untreated sALCL.

4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated systemic anaplastic large cell lymphoma and the doctor responsible for their care thinks that brentuximab vedotin with CHP is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

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

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

NICE project team

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

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