NICE National Institute for Health and Care Excellence

NICE guidance

Brentuximab vedotin in combination for untreated stage 3 or 4 CD30-positive Hodgkin lymphoma

Technology appraisal guidance
Published: 7 May 2025

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Your responsibility

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

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

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

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

Contents

This guidance replaces TA594.

1 Recommendation

1.1 Brentuximab vedotin plus doxorubicin, dacarbazine and vinblastine is recommended, within its marketing authorisation, as an option for untreated stage 3 or 4 CD30-positive Hodgkin lymphoma in adults. It can only be used if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

Untreated stage 3 or 4 CD30-positive Hodgkin lymphoma is usually treated with a chemotherapy regimen. This is usually doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). Bleomycin is sometimes removed because of its toxic effects for some people.

Evidence from a clinical trial shows that brentuximab vedotin plus doxorubicin, dacarbazine and vinblastine (brentuximab combination) could increase how long people have before their cancer gets worse and how long they live compared with ABVD.

The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, brentuximab combination is recommended.

2 Information about brentuximab vedotin

Marketing authorisation indication

2.1 Brentuximab vedotin (Adcetris, Takeda) is indicated for 'adult patients with previously untreated CD30+ stage III or IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for brentuximab vedotin.

Price

2.3 The list price of brentuximab vedotin is £2,500 per 50-mg vial (excluding VAT; BNF online, accessed November 2024).

2.4 The company has a commercial arrangement. This makes brentuximab vedotin available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Takeda and a review of this submission by the external assessment group (EAG). See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Hodgkin lymphoma is a type of cancer that affects cells in the lymphatic system called lymphocytes. The lymphatic system is part of the body's disease-fighting immune system. Lymphoma begins when healthy cells in the lymphatic system change and grow out of control. Because of their expression of cell membrane receptor 30 (CD30), classical Hodgkin lymphoma is also referred to as CD30-positive Hodgkin lymphoma. Advanced (stage 3 and 4) CD30-positive Hodgkin lymphoma is most likely to affect people aged 20 to 24 years, and 75 to 79 years. The patient experts explained that people with Hodgkin lymphoma experience fatigue, fever, sweats, pain, swollen lymph nodes and need frequent medical appointments. Many people with Hodgkin lymphoma often rely on family and friends and are unable to work. The patient experts explained that Hodgkin lymphoma is a debilitating condition that has a major impact on quality of life and mental wellbeing. The committee concluded that living with the condition is physically and emotionally challenging.

Unmet need

3.2 Treatment options for stage 3 and 4 CD30-positive Hodgkin lymphoma depend on several factors such as:

- the stage of the disease
- the risk profile

- balancing toxicity and efficacy of treatment.

The patient and clinical experts explained that the main aim of treatment for stage 3 and 4 Hodgkin lymphoma is to cure the disease or create long-term remission. They explained that people whose disease is not cured by initial treatment, and who are fit enough, have intensive therapy such as a stem cell transplant with the aim of curing the disease. People 60 years or over have a reduced chance of cure, partly because of biological differences in Hodgkin lymphoma, and partly because older people are less likely to be able to tolerate intensive regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and BEACOPDac (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone and dacarbazine). The clinical experts explained that current treatments are associated with toxic effects, such as lung toxicity, and may lead to long-term issues including fertility problems and an increased risk of heart disease. They explained that having different options is particularly important as people often choose treatments based on their side-effect profiles. The committee concluded that there is an unmet need for effective treatments with less toxic effects, and that people with the condition and their families would welcome an additional treatment option.

Clinical management

PET-adapted treatment

3.3 Treatment options for untreated CD30-positive Hodgkin lymphoma are chemotherapy regimens such as ABVD and BEACOPDac. The clinical experts explained that the use of chemotherapy regimens depends on multiple factors such as stage of disease, risk profile, and balance between toxicity, efficacy and patient choice. They explained that people who are fit enough, usually people younger than 60 years, can have BEACOPDac because it has greater efficacy than ABVD, but it is associated with greater toxicity. People who are not fit enough to tolerate BEACOPDac or are older than 60 years may have ABVD or AVD (doxorubicin, vinblastine and dacarbazine). Bleomycin pulmonary toxicity is more frequent in people 60 years or over, so people over 60 years often have

AVD rather than ABVD. The clinical experts explained that the availability of brentuximab vedotin plus doxorubicin, dacarbazine and vinblastine (from here, brentuximab combination) would be particularly beneficial for people who are not able to tolerate bleomycin, because they have fewer effective treatment options. They also explained that UK practice follows a positron emission tomography (PET)-adapted strategy called the response-adapted therapy for advanced Hodgkin lymphoma (RATHL) approach. This includes treatment de-escalation or escalation, depending on PET status. People have 2 cycles of ABVD and then have a PET-CT scan. People with a negative scan have another 4 cycles of AVD (without bleomycin). People with a positive scan have either 4 further cycles of ABVD, or their treatment is escalated to BEACOPDac. The choice of ABVD or BEACOPDac in young, fit people is complex and involves shared decision making as well as centre preference. The clinical experts highlighted that most centres in England and Wales use the RATHL approach, but a few centres do not. The committee concluded that the RATHL approach is the most common method for delivering ABVD treatment.

Positioning

3.4 The population in the NICE scope was 'previously untreated late-stage classical Hodgkin lymphoma'. The company proposed brentuximab combination for a narrower population than the NICE scope: untreated CD30-positive stage 3 or 4 Hodgkin lymphoma in people who would otherwise have been offered ABVD. The EAG's clinical experts thought that the company's decision-problem population was reasonable. The clinical experts at the committee meeting explained that BEACOPDac is also a treatment option (see section 3.3). The committee noted that treatment decisions are complex for untreated CD30-positive stage 3 or 4 Hodgkin lymphoma. There may be some people who would otherwise have had BEACOPDac who would choose brentuximab combination if it was available. There are other people, particularly people aged over 60 years, who would have AVD for whom brentuximab vedotin may be appropriate. But the committee concluded that in general, brentuximab combination would be likely to be used in place of ABVD in clinical practice.

Clinical effectiveness

ECHELON-1

3.5 ECHELON-1 was an open-label, multicentre, randomised, phase 3 clinical trial comparing brentuximab combination with 6 cycles of ABVD. The primary outcome of the trial was modified progression-free survival. Secondary outcomes included overall survival, overall response rate, treatment-emergent adverse events (TEAEs) and quality of life. ECHELON-1 enrolled 1,334 people with previously untreated CD30-positive stage 3 or 4 Hodgkin lymphoma. A total of 664 people had brentuximab combination and 670 people had ABVD. Progression-free survival and overall survival results were reported for the latest data cut-off (March 2023). The results indicated that brentuximab combination was significantly more effective at preventing progression than ABVD (hazard ratio [HR] 0.677; 95% confidence interval [CI] 0.53 to 0.86; p=0.001). The results also indicated that brentuximab combination was significantly more effective at preventing death than ABVD (HR 0.617; 95% CI 0.423 to 0.899; p=0.011). The clinical experts considered that the overall survival rates associated with brentuximab combination were impressive. The committee concluded that the brentuximab combination was an effective treatment for adults with untreated classical Hodgkin lymphoma, delaying disease progression and prolonging survival.

Comparator

3.6 The company used a weighted average of ABVD treatment for 6 cycles (10%) and ABVD treatment using the PET-adapted RATHL approach (90%) as the comparator in its model. The clinical experts broadly agreed that the company's weighted comparator reflected clinical practice, but they highlighted that only a minority of UK centres uses 6 cycles of ABVD (see section 3.3). There was no head-to-head data available comparing brentuximab combination with ABVD using the PET-adapted RATHL approach. So, the company assumed equal efficacy between 6 cycles of ABVD and PET-adapted ABVD, and used the data comparing ABVD and brentuximab combination from ECHELON-1 to inform clinical effectiveness. The company assumed equal efficacy based on the

following:

- De-escalated ABVD and AVD regimens demonstrated non-inferior 3-year progression-free survival compared with 6 cycles of ABVD in the RATHL trial.
- A small proportion of people in ECHELON-1 were PET-positive and treatment escalation was potentially suitable for them.
- The RATHL trial included a minority of people who were PET-positive after 2 initial cycles of ABVD.
- An indirect treatment comparison of ABVD compared with PET-adapted ABVD.
- Clinical expert opinion.

The company explained that the results of the fully adjusted, unanchored matching-adjusted indirect comparison (MAIC) of 6 cycles of ABVD from ECHELON-1 compared with PET-adapted ABVD from RATHL were driven by age. This was because the RATHL population was younger than the ABVD arm of ECHELON-1. The company also did an updated MAIC, adjusting for all available baseline characteristics, excluding age. Relative efficacy in terms of overall survival for 6 cycles of ABVD compared with PET-adapted ABVD had a hazard ratio of 0.88 (95% CI 0.61 to 1.27, p=0.490) when excluding adjustment for age. The fully adjusted MAIC gave a hazard ratio of 0.59 (95% CI 0.40 to 0.85, p=0.005). The EAG explained that the company's justification for removing age from the MAIC was not sufficient and that the results of the fully adjusted MAIC suggested that 6 cycles of ABVD was more effective than PET-adapted ABVD. It thought the company's MAIC lacked face validity and should be interpreted with caution. The EAG explained that clinical equivalence between PET-adapted ABVD and 6-cycle ABVD had not been proven. But, in the absence of head-to-head comparative data for PET-adapted ABVD and brentuximab combination, evidence for 6-cycle ABVD compared with brentuximab combination from ECHELON-1 was the most robust source of evidence. The committee agreed that the MAIC results were not sufficiently robust to prove equivalence between 6 cycles of ABVD and PET-adapted ABVD. The clinical experts explained that in their experience, both treatment approaches have similar efficacy. But PET-adapted ABVD has benefits over 6 cycles of ABVD because toxicity is

reduced by dropping the bleomycin in most people who have PET-negative scans. The committee noted that ABVD and PET-adapted ABVD treatment approaches were likely to have similar efficacy. It concluded that the weighted average comparator assuming mostly PET-adapted ABVD, informed by clinical efficacy data from 6-cycle ABVD in ECHELON-1, was suitable for decision making in this evaluation.

Adverse events

3.7 In ECHELON-1, the incidence of grade 3 or higher drug-related TEAEs including neutropenia, febrile neutropenia, decreased neutrophil count and anaemia was 80% in people who had brentuximab combination and 60% in people who had ABVD. Peripheral neuropathy of grade 3 or higher occurred in 10% of people who had brentuximab combination and 2% of people who had ABVD. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was used in 13% of people in the brentuximab combination arm and 6.5% of people in the ABVD arm to prevent neutropenia or febrile neutropenia. This resulted in lower rates of neutropenia and febrile neutropenia than in people who had not had G-CSF prophylaxis. Pulmonary toxicity events were lower in the brentuximab combination arm than the ABVD arm: 2% compared with 7% respectively. Peripheral neuropathy of grade 3 or higher occurred in 10% of people having brentuximab combination and 2% of people having ABVD. The committee noted that brentuximab combination was associated with more TEAEs and peripheral neuropathy events than ABVD. It concluded that it was important to appropriately capture the balance of the benefits and risks of brentuximab combination in the model.

Economic model

Company's modelling approach

3.8 The company presented a de novo partitioned survival model with a time horizon of 60 years. This comprised 3 mutually exclusive health states: progression-free survival, progressed disease and death. The EAG thought that the company's

model had captured the key health outcomes associated with stage 3 and 4 Hodgkin lymphoma. But it noted that the company's model had used fewer health states than those published in the literature identified by the company, which modelled 5 health states. It explained that the model included people with relapsed and refractory progressive disease modelled within a single health state. The company clarified that models identified through its literature searches were informed using data with much shorter follow up than ECHELON-1, making it appropriate to use more health states. The committee concluded that the company's model structure was appropriate for decision making.

Bimodal age distribution

3.9 The committee was aware that stage 3 or 4 CD30-positive Hodgkin lymphoma affects people bimodally, that is, there are peaks in diagnosis rate for people aged 20 to 24 years and aged 75 to 79 years. The company modelled a mean age of 39.53 years (95% CI 38.68 to 40.39) based on the intention-to-treat (ITT) population from ECHELON-1 to inform its economic model. The EAG explained that the company's approach to modelling age may not have been appropriate because 2 separate populations are mainly affected by the condition. So, it thought that an age-weighted approach may be a more appropriate method to account for the bimodal population. At the clarification stage, the EAG requested an alternative approach based on age subgroups (below 60 years and 60 years or over) to explore the impact of age distribution on the results. In response, the company stated that considering the results by subgroups based on age was inappropriate. It explained that using an age-weighted approach would break randomisation, and would mean a smaller population than the ITT population would inform the subgroup analyses (60 years or more subgroup: brentuximab combination n=84, ABVD n=102 compared with the ITT population: brentuximab combination n=664, ABVD n=670). The company had concerns that modelling the population in age-related subgroups could result in these being considered separately, which could cause equality issues. The company also noted that the EAG's age-weighted approach may not have fully characterised uncertainty, and provided deterministic but not probabilistic results.

The committee questioned the face validity of the EAG's approach and asked if it had explored any different age group scenarios. The age distribution in

ECHELON-1 was skewed because it had included a high proportion of younger people, which did not reflect the bimodal nature of the disease seen in clinical practice. The committee noted that the EAG's age-weighted approach was informed by subgroup data from ECHLEON-1 rather than subgroup data that would accurately reflect clinical practice. It also noted that by using subgroups, the numbers included in each treatment arm were smaller, especially for the 60 years or more subgroup. This introduced more uncertainty into the model. It noted that the EAG did not do any further subgroup analysis reflecting the older population in clinical practice. The committee noted that some people would not have qualified for the trial as they could not tolerate ABVD because of their age or fitness. But this population would be able to have brentuximab combination. The size of this population in clinical practice was uncertain. The committee thought it was uncertain if brentuximab combination would be used as widely in older people as in younger people because treatment choice is complex, especially for older people for whom the toxicity profile is particularly important. So, it was uncertain whether bimodal age distribution should be taken into account in the modelling. It also noted that the age distribution in the trial did not reflect the bimodal age distribution in clinical practice, and so the EAG's approach of using data from the trial did not necessarily improve the generalisability of the model. The committee noted that using an age-weighted approach had a large impact on the results. It concluded that there were methodological uncertainties introduced into the model if an age-weighted approach was used, especially as the EAG's approach did not reflect the bimodal age distribution in practice. There was also uncertainty around whether it was appropriate to account for the bimodal age distribution. So, the committee concluded that it would use the company's mean age approach as a basis for decision making, but it would account for the limitations and uncertainties in its decision making.

Progression-free and overall survival extrapolations

3.10 To estimate progression-free survival beyond the observed ECHELON-1 data, the company used a mixed cure model (MCM) and applied it to the progression-free survival Kaplan–Meier data. Based on the appropriateness of cure fraction from ECHELON-1, literature and clinical expert opinion, the company selected the log-logistic MCM model to extrapolate brentuximab combination and ABVD progression-free survival in its base case. For overall survival, the company noted

that the log-cumulative hazard plot curves crossed, and concluded that the proportional hazards assumption was violated. It explained that the MCMs and 1-knot splines predicted highly similar extrapolations when fitted to the overall data from ECHELON-1. The company clarified that the MCM also provided a good fit to the observed data in deterministic conditions, but under probabilistic conditions provided implausible cure fractions because of a small number of events and wide confidence intervals. It explained that under probabilistic conditions, it would generate a higher estimated cure fraction in ABVD than brentuximab combination, which is not clinically plausible. So, the company chose a 1-knot spline model to extrapolate overall survival data. The EAG noted that the characteristics of the data that made it appropriate to model progression-free survival with an MCM similarly applied to overall survival. It explained that the cure fraction was not being estimated by the 1-knot spline model; instead, the spline was modelled around the cure fraction assumed by the company, which introduced bias and potentially overfitted the model to the Kaplan–Meier data. The EAG preferred to use MCMs to extrapolate overall survival, using a Gompertz MCM for brentuximab combination and an exponential MCM for ABVD. The committee noted that the use of an MCM was supported by mature data and cure fractions observed from ECHELON-1 and literature. It noted that the choice of extrapolation had a limited impact on the results if the bimodal age distribution was not modelled. It concluded that the EAG's approach for extrapolating overall survival was the most appropriate for decision making.

Long-term mortality risk

3.11 The company's model applied a standardised mortality rate of 1.10 to model the mortality risk for people having ABVD. It assumed a lower standardised mortality rate of 1.05 for brentuximab combination. The company stated that a standard mortality rate was applied in addition to general mortality. It explained that ABVD is a bleomycin-containing regimen, which is associated with pulmonary toxicity and increased secondary malignancies, disease progression and subsequent treatment toxicity compared with brentuximab combination. So, it suggested that it was appropriate to apply a greater standardised mortality rate to the cured population in the ABVD arm than the population having brentuximab combination, reflecting the proposed higher risk of death because of treatment with ABVD. The company's clinical experts suggested that the risk of death after the cure time

point was between 5% and 10% higher than that of the general population. The EAG agreed with using a standardised mortality rate to adjust background mortality because of the long-term mortality effects of secondary malignancies, treatment toxicities and long-term adverse events. It noted that the same standardised mortality rates were applied to both intervention and comparator in previous NICE technology appraisals on polatuzumab vedotin, axicabtagene ciloleucel, brentuximab vedotin, brexucabtagene autoleucel and tisagenlecleucel. It explained only 5 people had a grade 3 or more pulmonary toxicity in ECHELON-1 and the number of secondary malignancies was similar in the brentuximab combination and ABVD arms. So, it preferred to apply the same standardised mortality rates to both brentuximab combination and ABVD in its base case. The committee recalled that most centres in England and Wales use PET-adapted ABVD (see section 3.3), in which people with a negative scan after 2 cycles have another 4 cycles of AVD without bleomycin to reduce pulmonary toxicity. The committee noted that the company's approach of using a higher standardised mortality rate for the brentuximab combination arm lacked face validity because longer overall survival was estimated for this arm. The committee concluded that the EAG's approach of using the same standardised mortality rate for the brentuximab combination and ABVD arms was appropriate.

Peripheral neuropathy

3.12 The company's model did not account for people with lifelong peripheral neuropathy. The EAG highlighted that in ECHELON-1, a higher proportion of people who had brentuximab combination had grade 3 or higher peripheral neuropathy than people who had ABVD (see section 3.7). At the clarification stage, the company provided a scenario including peripheral neuropathy in the model. The EAG noted that the company's scenario used an adverse-event duration calculated from people whose peripheral neuropathy had resolved, but that 16 (2.4%) people in the brentuximab combination arm and 4 (0.6%) people in the ABVD arm had unresolved grade 3 or higher peripheral neuropathy at the last follow up. So, the EAG assumed that 2.4% of people having brentuximab combination and 0.6% of people having ABVD would have lifelong peripheral neuropathy. It applied a -0.33 disutility for lifelong peripheral neuropathy from a study by Swinburn et al. (2015) in its base case. The company explained that peripheral neuropathy is resolvable for most people who have treatment with

brentuximab combination or ABVD. It thought that the EAG overestimated the proportion of people with lifelong peripheral neuropathy and that the EAG's approach was not in line with how lifelong peripheral neuropathy was modelled in previous NICE technology appraisals. It clarified that only people who had ongoing grade 3 or higher peripheral neuropathy at the last follow up, who were alive at that time, and had had grade 3 or higher peripheral neuropathy for at least 3 years before the last follow up should be considered to have lifelong peripheral neuropathy. Based on this data, the company assumed a lower proportion of people would have lifelong neuropathy, and in its base case applied a utility decrement for peripheral neuropathy of -0.0836, based on its multivariate utility analysis of ECHELON-1 data. The clinical experts explained that peripheral neuropathy can have a substantial and long-lasting effect on quality of life. But, they agreed with the company that for most people, peripheral neuropathy is resolvable or becomes less severe and manageable within 2 to 3 years. The committee agreed that grade 3 or higher peripheral neuropathy was associated with a reduced quality of life and so a disutility should be applied to account for this. But, it noted that the company's and EAG's disutility estimates both had a very small impact on the results. The committee concluded that the company's estimates for the proportion of people and disutility associated with lifelong peripheral neuropathy were appropriate.

Utilities and disutilities

3.13 In the company's model, health-related quality of life was accounted for by deriving utility values from EQ-5D-3L data collected in ECHELON-1. Utility values were derived using a mixed effects linear regression model fitted to the available EQ-5D-3L data. A regression model was used to inform health state utility values for the progression-free and progressed disease health states. The EAG thought the utilities in the company's base case lacked face validity. It noted that the mean utility value for people in the progression-free health state on treatment was 0.78 at baseline, which was lower than the utility value for people in the progressed disease health state (0.791 at the baseline). It explained that it would expect the opposite, because the progressed disease state included people in later treatment stages with severe disease. The EAG noted that people having brentuximab combination had a lower rate of disease progression than people having ABVD. So, a high value for the progressed disease state would reduce the

calculated incremental quality-adjusted life years (QALYs) for brentuximab combination compared with ABVD, favouring ABVD. The company's model also applied a one-off disutility to cover all adverse events. The EAG believed sourcing disutilities from existing literature (Doyle et al. [2008], Lloyd et al. [2006], Nafees et al. [2008] and Swinburn et al. [2015]) would be more appropriate because it allowed decrements of adverse events to be applied individually to each corresponding disutility, rather than applying a weighted average duration of disutilities. The committee noted that the utility values used had a minimal impact on the cost-effectiveness results. It concluded that the EAG's approach to estimating and applying disutility values was appropriate for decision making.

Subsequent treatments

3.14 The company's model included a single, one-off cost for acquisition and administration of subsequent treatments, stem cell transplants and radiation therapy that was applied to all people upon disease progression. The company's base case assumed that the subsequent treatments used, and the proportion of people expected to have each treatment, aligned with observed subsequent treatments in ECHELON-1. The EAG thought it more appropriate and reflective of clinical practice to base the proportions of people having subsequent treatments on clinical opinion. The EAG's clinical experts suggested that the proportion of people having radiotherapy was around 5% to 10% instead of the 0% suggested by the company's clinical expert. The committee concluded that its preferences on subsequent treatments were aligned with EAG's approach, but noted this had a minimal effect on the cost-effectiveness results.

Severity

3.15 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluation manual. The company estimates were below 0.85 for the proportional QALY shortfall and below 12 for the absolute QALY

shortfall. So, brentuximab combination did not meet the criteria for applying a severity weighting.

Cost-effectiveness estimates

Acceptable ICER

3.16 NICE's manual on health technology evaluations notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per 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. But it will also take into account other aspects including uncaptured health benefits. The committee noted that ECHELON-1 was a randomised controlled trial with long-term follow up, and showed a statistically significant survival benefit. But there was also a high level of uncertainty, specifically around whether bimodal age distribution should be accounted for in the model and how this could be reliably achieved if it was appropriate (see section 3.9). The population in ECHELON-1 may be younger than the population in clinical practice (see section 3.9). So, there was also uncertainty around the generalisability of the trial population to the population who would be likely to have brentuximab combination. Because of the uncertainty in the cost-effectiveness estimates, the committee concluded that an acceptable ICER would be around or below the middle of the range NICE considers a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.17 The cost-effectiveness estimates used by the committee for decision making took into account all of the available confidential discounts, including those for comparators and subsequent treatments. These discounts, and the resulting cost-effectiveness estimates, are confidential and cannot be reported here. The company's base-case results for brentuximab combination compared with ABVD were below the range normally considered a cost-effective use of NHS

resources. The EAG updated the company's model using its preferred assumptions. The EAG's base-case results for brentuximab combination compared with ABVD were towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

The committee's preferred assumptions

3.18 The committee's preferred assumptions were:

- extrapolating overall survival using a Gompertz MCM (brentuximab combination) and an exponential MCM (ABVD), based on the mean age in the model (see sections 3.9 and 3.10)
- using a 1.05 standardised mortality rate for both brentuximab combination and ABVD (see section 3.11)
- using the proportion of people with lifelong peripheral neuropathy, and disutility associated with this, in line with the company's estimates (see section 3.12)
- the EAG's approach for estimating adverse-event disutility and duration sourced from literature (see section 3.13)
- subsequent treatments informed by clinical opinion, with 5% of people with progressed disease having radiation therapy (see section 3.14).

Equality

3.19 No equality issues were raised by the company, EAG or stakeholders. The committee did not identify any equality issues.

Uncaptured benefits

3.20 The committee considered whether there were any uncaptured benefits of brentuximab combination. It did not identify additional benefits not captured in

the economic modelling. So, the committee concluded that all additional benefits of brentuximab combination had already been taken into account.

Conclusion

Recommendation

3.21 The committee took into account its preferred assumptions and its acceptable ICER threshold. Using its preferred assumptions, the ICER was below the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). So, the committee recommended brentuximab vedotin with doxorubicin, dacarbazine and vinblastine within its marketing authorisation for untreated stage 3 or 4 CD30-positive Hodgkin lymphoma in adults.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

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 stage 3 or 4 CD30-positive Hodgkin lymphoma and the healthcare professional responsible for their care thinks that brentuximab vedotin is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Stephen O'Brien
Chair, technology appraisal committee C

NICE project team

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

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