National Institute for Health and Care Excellence

Health Technology Evaluation

Brentuximab vedotin in combination for untreated advanced classical Hodgkin lymphoma [ID6437]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Takeda	Takeda believes this is an appropriate topic for NICE to consider via the single technology appraisal route.	Thank you for your comments. No change to scope required.
	The Royal College of Pathologists	Yes this is appropriate	Thank you for your comment. No change to scope required.
Wording	Takeda	The wording of the draft remit should be revised to reflect the licensed indication: *"To appraise the clinical and cost effectiveness of brentuximab vedotin in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone within its marketing authorisation for treating previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV Hodgkin lymphoma (HL)".*	Thank you for your comment. The remit has been updated to reflect the licenced indication.

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	The Royal College of Pathologists	Yes	Thank you for your comment.
Timing Issues	Takeda	Brentuximab vedotin in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) was associated with a statistically significant (p<0.0001) and clinically meaningful [redacted]% reduced risk (relative risk: [redacted]) in treatment-related morbidity (TRMB; [redacted] out of 747 patients with TRMB) compared with escalated-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escBEACOPP; [redacted] out of 741 patients with TRMB) in the HD21 trial at 60 months follow-up.[1,2] At 5-year follow-up, median progression-free survival (PFS) could not be estimated for either treatment arm.[1,2] The hazard ratio (HR) for PFS was [redacted](95% CI: [redacted]), which correlated with a [redacted]% reduction in risk of a PFS event for the BrECADD arm compared with the escBEACOPP arm.[1,2] The estimated PFS rate was [redacted]% (95% CI: [redacted]) for the BrECADD arm after a median follow-up of [redacted] (95% CI: [redacted]) months versus [redacted]% (95% CI: [redacted]) for the escBEACOPP arm after a median follow-up of [redacted] (95% CI: [redacted]) months.[1] Median overall survival (OS) was not reached after a median follow-up of [redacted] (95% CI: [redacted]) months in the BrECADD arm and [redacted] (95% CI: [redacted]) months in the escBEACOPP arm.[1,2] Estimated 72-month OS rates were [redacted]% (95% CI: [redacted]) in the BrECADD arm and [redacted]% (95% CI: [redacted]) in the escBEACOPP arm.[1] Infertility rates at 1-year post-treatment follow-up (PTFU, defined as the percentage of participants whose FSH values at 1-year follow-up were above the upper limit of the normal range) were lower in the BrECADD treatment	Thank you for your comment. No change to scope required.

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		arm ([redacted]%; [redacted] out of [redacted] patients) versus the escBEACOPP treatment arm ([redacted]%; [redacted] out of [redacted] patients). At 1-year PTFU, FSH values were within the normal range for [redacted]% ([redacted] out of [redacted] patients) in the BrECADD arm and [redacted]% ([redacted] out of [redacted] patients) in the escBEACOPP arm.[1] As of trial closure, there were more pregnancies and births reported in female patients or partners of male patients in the BrECADD arm versus the escBEACOPP arm.[1] Takeda is therefore keen to provide access for patients at the earliest possible opportunity.	
	The Royal College of Pathologists	Reasonably urgent.	Thank you for your comment. No change to scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Takeda	None	Thank you for your comment. No change to scope required.
	The Royal College of Pathologists	No changes required	Thank you for your comment. No change to scope required.
Population	Takeda	None	Thank you for your comment. No change to scope required.
	The Royal College of Pathologists	It should be clearer that this appraisal is for **classic HL only** and NLPHL is treated totally differently.	Thank you for your comment. The scope has been amended to

Section	Consultee/ Commentator	Comments [sic]	Action
			include classical Hodgkin lymphoma.
Subgroups	Takeda	None	Thank you for your comment. No change to scope required.
	The Royal College of Pathologists	It is appropriate that this is for 18-60yr old with Stage IIB and stage III/IV disease only.	Thank you for your comment. No change to scope required.
Comparators	Takeda	Current first-line treatment for previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL is combination chemotherapy. Feedback elicited from key opinion leaders (KOLs) is that single-agent chemotherapy is not used to treat this patient population. Therefore, Takeda recommends deleting "*single*" and revising the wording to *"Combination chemotherapy including but not limited to…"*. For patients with previously untreated Stage IIB with risk factors (i.e. large mediastinal mass and/or extranodal lesions[3,4]), Stage III or IV HL, the British Society for Haematology (BSH) guidelines recommend initiating treatment with either doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or escBEACOPP.[5] Due to concerns over gonadal and haematopoietic stem cell toxicity from procarbazine, the BSH guidelines also state that in patients who are considered for treatment with escBEACOPP, clinicians should consider substituting the procarbazine in escBEACOP**P** with dacarbazine (escBEACOP**Dac**).[5,6] Takeda anticipates that BrECADD will predominantly be used in patients who would otherwise be offered an escBEACOP-based regimen (i.e. either escBEACOPP or escBEACOPDac); therefore, an escBEACOP-based regimen is the relevant comparator for the appraisal. Of note, Takeda would	Thank you for your comment. The comparators included in the scope have been amended to include ABVD-based regimens and BEACOP-based regimens.

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		like to highlight that the correct regimen is **esc**BEACOPP or **esc**BEACOPDac, not BEACOPP as stated in the draft scope. As described in Section 3.4 of the final guidance for TA1059, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) is likely to be used in place of ABVD in clinical practice.[7] This is consistent with feedback received from KOLs during the appraisal process. Therefore, based on the expected positioning for BrECADD, Takeda does not believe that ABVD or A+AVD are key comparators for this appraisal.	
	The Royal College of Pathologists	Comparators BRECADD quoted include "BEACOPP" this should read BEACOPDac (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine and dacarbazine) as stated. BEACOPDac is less toxic than BEACOPP but equally efficacious in terms of response rates and OS.	Thank you for your comment. The comparators included in the scope have been amended to include ABVD-based regimens and BEACOP-based regimens.
Outcomes	Takeda	The current outcomes listed are appropriate. Takeda would like to highlight that one of the co-primary endpoints in the Phase III trial is a safety outcome (i.e. treatment-related morbidity). Therefore, Takeda suggests that NICE include treatment-related morbidity as an outcome of interest for the appraisal. Fertility and infertility data were captured in the Phase III trial. These outcomes are important considerations for patients and clinicians in clinical practice as patients receiving an escBEACOP-based regimen are typically younger and may have concerns regarding future fertility.[2] Therefore, Takeda suggests that NICE include fertility as an outcome of interest for the appraisal.	Thank you for your comments. The list of outcomes specified in the scope is not exhaustive and any relevant outcomes will be considered by the committee.

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	The Royal College of Pathologists	Yes	Thank you for your comment. No change to scope required.
Equality	Takeda	No equality issues have been identified.	Thank you for your comment. No change to scope required.
	The Royal College of Pathologists	No obvious changes required.	Thank you for your comment. No change to scope required.
Other considerations	Takeda	None	Thank you for your comment. No change to scope required.
	The Royal College of Pathologists	No	Thank you for your comment. No change to scope required.
Questions for consultation	Takeda	**Where do you consider brentuximab vedotin with etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone will fit into the existing care pathway for advanced Hodgkin lymphoma?** Takeda anticipates that BrECADD will predominantly be used in adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL who would otherwise be offered an escBEACOP-based regimen. **Is current first line treatment the same for people with Stage 2B Hodgkin lymphoma with risk factors and those with stage 3 and 4 Hodgkin lymphoma?**	Thank you for your comment. No change to scope required.

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		Yes, current first line treatment is the same for people with Stage IIB HL with risk factors and those with Stage III and IV HL. The BSH guidelines state that "patients with stage IIB with a large mediastinal mass and/or extranodal disease are also usually managed as advanced-stage disease."[5] Additionally, feedback elicited from KOLs in the UK confirmed that patients with Stage IIB with risk factors HL are treated in alignment with Stage III and IV patients. **Does advanced classical Hodgkin lymphoma include stage 2B with risk factors, as well as stages 3 and 4?** Yes, advanced classical HL includes stage IIB with risk factors, as well as Stages III and IV HL. This is supported by the BSH guidelines, which state that "patients with stage IIB with a large mediastinal mass and/or extranodal disease are also usually managed as advanced-stage disease."[5] Additionally, these guidelines are informed by the German Hodgkin Study Group (GHSG) which classifies stage IIB patients with either large mediastinal adenopathy or extranodal disease as having advanced-stage disease.[5] **Please select from the following, will brentuximab vedotin with etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):**	

Section	Consultee/ Commentator	Comments [sic]	Action
		C - Takeda anticipates that BrECADD will be prescribed in secondary care with routine follow-up in secondary care. This aligns with how brentuximab vedotin is prescribed and managed in other reimbursed indications. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** There is no difference, as all therapies are prescribed and followed-up in secondary care. **Would brentuximab vedotin with etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone be a candidate for managed access?** The preferred funding for BrECADD in adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL is through routine NHS funding via baseline commissioning. If the NICE committee feels unable to make a positive recommendation for routine NHS funding, then Takeda would be open to discussions with NICE and NHS England around potential inclusion in the Cancer Drugs Fund (CDF). However, of note, the appraisal will be informed by the final analysis of the Phase III HD21 trial, a head-to-head randomised controlled trial versus escBEACOPP, with over 5 years of follow-up. **Do you consider that the use of brentuximab vedotin with etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Procarbazine in the escBEACOPP regimen is known to cause gonadal toxicity, and consequently impair fertility.[5] Replacing the procarbazine with dacarbazine in the escBEACOPDac regimen improves fertility outcomes versus escBEACOPP, although residual fertility risk can remain.[8] Gonadal function testing was recommended in the HD21 trial protocol, and BrECADD was associated with significantly improved gonadal function recovery compared with escBEACOPP.[1] The infertility rate at 1 year PTFU was lower among BrECADD patients than escBEACOPP patients. In addition, there were more pregnancies and births reported in female patients or partners of male patients in the BrECADD treatment arm versus the escBEACOPP treatment arm.[1] These findings indicate that BrECADD may improve fertility-related outcomes compared with escBEACOPP and support its use as a preferred first-line therapy, particularly for patients wishing to preserve fertility, an important consideration given the typically young patient population. Current treatment strategies for previously untreated HL are also associated with second malignancies, which are linked to a long-term increased risk of death and can be a significant concern for patients.[9–11] Notably, BrECADD was associated with fewer cases of MDS/CMML/AML (n=[redacted]) compared with escBEACOPP (n=[redacted]).[1] Takeda do not believe it is possible to adequately capture the health-related benefits of fertility preservation, reduced risk of second malignancies, nor the wider societal benefits, within the QALY framework.	

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		Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. Not applicable. To the best of Takeda's knowledge, all regimens are used according to their SmPCs.	
	The Royal College of Pathologists	Where it fits in pathway: Frontline treatment of stage IIB and III/IV Classic Hodgkin. Stage IIB HL is generally treated the same as advanced stage disease. BRECCAD will be prescribed and followed up I secondary care. Comparators at 1st line: ABVD, AAVD and BEACOPDAC – with similar prescribing set up and routine follow up. It could be a candidate for managed access. Outside of QALY calculation – The HD 21 trial showed in comparison to BEACOPP BrECCAD had a marginally higher PFS which would imply there would be a reduced rate of autologous stem cell transplantation with BrECCAD – reducing chance of toxicity associated with the associated high	Thank you for your comment. No change to scope required.

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		intensity (BEAM/LEAM) chemotherapy. There were less non-elective inpatient days with BrECCAD use and less haematological toxicity and less blood product use. It is likely the substituon of procarbazine to dacarbazine in the BrECCAD would reduce the potential for infertility in those treated Vs BEACOPP. Hoveve BEACOPDac is used in preference to BEACOPP in the UK and appears non inferior in terms of OS/PFS (and less toxic) to BEACOPP. It could therefore be theorised that BrECCAD could be potentially more efficacious than, the routinely used, BEACOPDac, in the UK. Without a head-to-head trial it is difficult to be sure that BrECCAD would be less toxic the BEACOPDAC even though it did cause less co-morbidity than - BEACOPP in the HD 21 trial. The omission of bleomycin in BrECCAD may confer better tolerability in older, anthracycline fit, patients.	
Additional comments on the draft scope	Takeda	None	Thank you for your comment. No change to scope required.
	The Royal College of Pathologists	None	Thank you for your comment. No change to scope required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Lymphoma Action

References from company comments:

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3. Borchmann P, Ferdinandus J, Schneider G, Moccia A, Greil R, Hertzberg M, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024 Jul 27;404(10450):341–52. doi:10.1016/S0140-6736(24)01315-1 PubMed PMID: 38971175.
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