NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Takeda
   - Leukaemia Care
   - Lymphoma Action
   - Royal College of Pathologists
   - NHS England

3. **Comments on the Appraisal Consultation Document from experts:**
   - Julia Scarisbrick – clinical expert, nominated by The Royal College of Pathologists-British Society of Haematology
   - Sean Whittaker - clinical expert, nominated by Takeda Ltd

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Appendix of new evidence –** submitted by Takeda Ltd

6. **Evidence Review Group critique of company response** – prepared by Liverpool Reviews & Implementation Group

7. **NICE follow up questions to clinical experts from technical lead**
   - Response from Professor Sean Whittaker – clinical expert, nominated by Takeda Ltd and Dr Julia Scarisbrick, Consultant Dermatologist – clinical expert, nominated by Royal College of Pathologists-British Society of Haematology

8. **NICE follow up questions to clinical experts from technical advisor**
   - Response from Professor Sean Whittaker – clinical expert, nominated by Takeda Ltd

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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 number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Lymphoma Action	We are concerned that this recommendation does not give enough consideration to the impact of CTCL on patients' lives. Psychological and social wellbeing are significantly affected, particularly at more advanced stages. Patients can suffer severe discomfort, itching, pain and fatigue with subsequent effects on employment, leisure activities, relationships and day-to-day living. In addition, the psychological impact of the condition is significant: patients report feelings of uncertainty, frustration, embarrassment, helplessness, confusion, worry, anxiety and depression. Current treatment options also have an impact on quality of life: skin care regimes and wound dressing in later stages are time-consuming for both the patient and their family or carer. There is a clear need for an effective, durable treatment that reduces symptoms.	Thank you for your comment. The committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness. Please see sections 3.1 and 3.2 of the final appraisal document.
2	Consultee	Lymphoma Action	We are concerned that this recommendation understates the effectiveness of brentuximab vedotin. The report acknowledges that there is an unmet need for effective treatment that extends time in disease remission. However, the superior clinical efficacy of brentuximab vedotin to comparators, evidenced by a significantly higher response rate and significantly longer progression-free survival, does not seem to have been given sufficient importance. Existing treatments do not, in general, produce durable responses and patients are keen for treatment options that give them longer disease control.	Thank you for your comment. The committee agreed that brentuximab vedotin was clinically effective and produced durable clinical responses compared with current treatments. Please see sections 3.2, 3.5 and 3.7 of the final appraisal document.
3	Consultee	Lymphoma Action	We are concerned that this recommendation does not give sufficient consideration to symptom control. The ALCANZA trial showed that patients treated with brentuximab vedotin had significantly greater improvements in symptoms than those treated with comparators. Although this did not reach statistical significance in the subset of patients with advanced disease, improvements in symptom scores	Thank you for your comment. The committee agreed that brentuximab vedotin appears to improve health-related quality of life, but that the benefit of

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			were nevertheless clinically meaningful and were consistently greater than those in patients treated with comparator agents. Symptoms have a considerable impact on the day-to-day lives of patients and even small improvements can be beneficial.	brentuximab vedotin may not be fully captured in the trial data. It agreed that this should be factored into its considerations of the cost-effectiveness evidence. Please see sections 3.12 and 3.25 of the final appraisal document.
4	Consultee	Lymphoma Action	We are concerned that too much emphasis is placed on overall survival data. The recommendation acknowledges that current treatment pathways are palliative and that treatment aims to relieve symptoms, control local disease and improve quality of life. In this context, overall survival is of little relevance to patients, who are more concerned with durable symptom control. In addition, overall survival was not a prespecified endpoint of the ALCANZA trial and it is therefore not surprising that the data is limited. Nevertheless, brentuximab vedotin did result in clinically meaningful improvements in overall survival.	Thank you for your comment. The recommendations are based on evidence of both clinical and cost effectiveness. The committee considered all the evidence for overall survival in its decision-making. Please see sections 3.9, 3.18, 3.19 and 3.25 of the final appraisal document.
5	Consultee	Lymphoma Action	We are concerned that the potential for brentuximab vedotin to act as a bridge to allogeneic stem cell transplant has been underestimated. Given that the rate-limiting step for allogeneic stem cell transplant is usually poor response rate to current bridging agents, it would seem reasonable to assume that the significantly higher response rates to brentuximab vedotin versus comparators would also result in higher rates of allogeneic stem cell transplant, despite the limited data available at present. Allogeneic stem cell transplant is often the only hope of a ‘cure’ for patients and it is vital to keep this option available whenever possible.	Thank you for your comment. The committee agreed that allogeneic stem cell transplant should be considered as part of the treatment pathway for a proportion of patients with advanced CTCL. Please see sections 1, 3.5, 3.8 and 3.15 of the final appraisal document.
6	Consultee	Lymphoma Action	We feel this recommendation does not fully consider all the financial implications of current treatment pathways for CTCL, including the sometimes considerable cost of dressings and the cost of outpatient	Thank you for your comment. The NICE reference case stipulates

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			vs inpatient administration as well as the financial implications of time off work (both for symptoms and medical appointments), cost of dressings, the cost to the patient of additional laundry. This can have a significant impact on the patient and family or carers as well as NHS budgets.	that the perspective on costs should be that of the NHS and Personal Social Services. Please see sections 5.1.7 to 5.1.10 of the Guide to the methods of technology appraisal (2013).
7	Consultee	Royal College of Pathologists	I would agree with the summaries regarding the improvement in symptoms for those patients taking BV as opposed to PC (physicians' choice, as measured by the Skindex tool) albeit not statistically significant.	Thank you for your comment.
8	Consultee	Royal College of Pathologists	The data regarding OS is confounded by the short time of follow-up/ cross-over from PC to brentuximab. There is an improvement in PFS (16.7 months to 3.5 months)	Thank you for your comment. The committee agreed that brentuximab vedotin improves response rates and progression-free survival, but it was unclear whether it improves overall survival compared with current treatment. Please see sections 3.9, 3.18 and 3.19 in the final appraisal document, which sets out the committee's conclusions about clinical effectiveness and overall survival.
9	Consultee	Royal College of Pathologists	I would agree that the introduction of brentuximab could lead to more patients becoming eligible for allogeneic transplant, due to the improved response rates compared to current standard therapies.	Thank you for your comment.

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10	Consultee	Royal College of Pathologists	Brentuximab is able to reduce the tumour burden on the skin in nearly all patients (46/48 in Alcanza) and able to reduce this by >50% for at least 4 months in 56%. This leads to a reduction in number of dressings and allows a better quality of life. The improvement lasts with a median response duration of 15.1 months. There are no equivalent drugs available with this efficacy for CD30 positive CTCL. This response duration allows time for eligible patients to have allogeneic bone marrow transplant which is there only chance of cure. Of the 15 patients I have personally treated with brentuximab 5 have received allogeneic BMT. Brentuximab is listed as second line treatment option for our UK, European (EORTC) and NCCN (US) guidelines.	Thank you for your comment. The final appraisal document has been revised. Please see sections 3.5, 3.8 and 3.15.
11	Consultee	Royal College of Pathologists	I would agree with the committee's interpretation of the clinical effectiveness with brentuximab showing a marked improvement in ORR4, PFS and symptom burden as shown in the ALCANZA trial. In particular, given that the application for NICE approval is for patients with advanced disease, I would highlight the subgroup analysis showing an improvement in RR of 69.4% vs 17.4% in this group of patients, that also translated into a significantly higher ORR4 59.2 vs 8.7, PFS and time-to next treatment.	Thank you for your comment. The committee agreed brentuximab vedotin would be used for people with advanced disease. Please see sections 1 and 3.3 in the final appraisal document.
12	Consultee	Royal College of Pathologists	I agree with the interpretation regarding toxicity/ safety of brentuximab both from the data submitted and also personal experience.	Thank you for your comment.
13	Consultee	Royal College of Pathologists	a lot of uncertainty in terms of modelling the use of brentuximab compared to current therapies, both in terms of costs saved due to patients having responsive disease that lasts longer, the number of patients who will go on to allogeneic transplant and finally whether there is a OS benefit with brentuximab.	Thank you for your comment. The final appraisal document has been revised. Please see sections 1 and 3.25.
14	Consultee	Royal College of Pathologists	I would support the use of brentuximab on the CDF with a view to reviewing the data in the future.	Thank you for your comment. Information on a CDF recommendation was included in the ACD, but has been amended following consultation. The committee recommended brentuximab as an option

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				for treating CTCL after at least 1 systemic therapy in adults with advanced stage disease. Please see sections 1 and 3.25 of the in the final appraisal document.
15	Consultee	Royal College of Pathologists	the cost of brentuximab must be offset by number of work days saved by return to work, less nursing care, less dressings and ultimately a potential cure if the patients gets transpalnted	Thank you for your comment. The committee considered the relative costs from the perspective of the NHS or PPS and all direct health effects, whether for patients or, when relevant, carers from treatment with brentuximab vedotin compared with current treatments. For additional information please see the Guide to the methods of technology appraisal sections 6.2.13 to 6.2.19
16	Consultee	Royal College of Pathologists	In my opinion brentuximab must be made available a second line therapy for this rare subset (CD30+, in only 10-20%) of a rare disease (CTCL incidence 7 per million). Brentuximab is already available in other European countries and US and being used to manage these patients. Brentuximab is part of the UK CTCL guidelines. Denying brentuximab for CD30+CTCL patients would severely restrict our ability to adequately treat these patients and result in an inferior service in these patients compared to other countries.	Thank you for your comment. The final appraisal document (FAD) has been revised. Please see sections 3.1 and 3.25 of the in the FAD.
17	Clinical expert	Julia Scarisbrick	Since having brentuximab available on a compassionate basis from the company I have treated 4 patients, results continue to be far superior to alternatives. Below are some of patients under my cares quotes. [redacted] (COMPASSIONATE USE)	Thank you for your comment. The committee carefully considered the comments received from experts, consultees, commentators and the

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			[redacted] with Stage IV Mycosis fungoides, receiving BV on compassionate basis as 6th line of systemic therapy. Cycle 3 completed. Prior to starting Brentuximab I was having 24 dressings a day (which were being changed by my wife). I was depressed and off my food and struggled with every aspect of daily living. Since starting Brentuximab I am now down to only 4 dressings a day. I have put weight back on, my personality has changed my wife says I am now myself! [redacted] (COMPASSIONATE USE) [redacted] with stage IIB MF also has systemic follicular lymphoma stage IV. Receiving BV as 4th line of therapy for MF. I have had 2 cycles of Brentuximab so far. It's AMAZING! I had about 80 patches on my skin some as big as 5 inches. They wept and made me extremely unhappy. They have all dried up and are healing and fading. I noticed a difference after one cycle. [redacted] (ALCANZA) [redacted] stage IIB Mycosis fungoides received BV 2nd line in Alcanza trial. Had Allo BMT immediately after BV in 2015 and remains in complete response. Works full time and has 6 year old son. I had immediate relief after starting Brentuximab. The itching stopped after the 1st infusion. By the time I had finished all of the cycles my lesions had all disappeared. It gave me back my confidence and life. Prior to starting the treatment, I went to Jamaica on a family holiday; whilst out there, someone asked me if I knew I had ring worm. It was devastating and made me so self-conscious. Brentuximab gave me my life back. I went on the have a transplant and am now living my life to the full	public in response to the draft guidance when formulating its recommendations. This included a number of patient perspectives submitted by NHS professionals and clinical experts. The final appraisal document has been updated to reflect this. Please see sections 3.1 and 3.12.

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			Thank you!	
18	Clinical expert	Sean Whittaker	We would like to submit the following comments on the NICE appraisal of Brentuximab vedotin for CD30+ cutaneous T-cell lymphomas (ID1190) on behalf of the UK Cutaneous Lymphoma Group (UKCLG). We have recently published our updated UK guidelines for the treatment of primary cutaneous lymphomas (Gilson et al Br J Dermatol 2018: DOI 10.1111/bjd.17240). These represent evidence based guidelines and the consensus views of UK specialists treating these rare malignancies from different specialities including clinical oncology, dermatology, haemato-oncology and transplantation in NICE approved supra-regional centres for CTCL. There are only three EMA approved treatment options for CTCL namely Bexarotene, alpha interferon and Brentuximab and, whilst the evidence base is weak for other non-approved treatment options, recent phase II trials and a large randomised phase III study (Prince et al 2017) with appropriate endpoints has provided compelling clinical evidence for the use of Brentuxumab Vedotin in advanced stages of CD30+ CTCL in view of the significant improvement in ORR4 and PFS compared to physicians choice of Methotrexate or Bexarotene. This has led to our conclusion that Brentuximab should be considered as a second line therapy for CD30+ CTCL patients with stage IIB-IV including those patients with Sezary syndrome (level of evidence I+/strength of recommendation B). We also recommend that reduced intensity HSCT should be considered for selected groups of patients with advanced CTCL to consolidate treatment responses based on emerging evidence for long term clinical remission in a majority of patients (strength of recommendation B). Of course the availability of a transplant for patients depends on multiple factors but an excellent treatment response prior to transplantation is critical to eligibility and a major determinant of transplant outcome. We note that the committee has questioned the evidence for an improvement in QoL (3.12 & 3.26) but we would like to draw attention to emerging data (submitted for publication) showing a significant improvement in the symptom domain of Skindex-29 for Brentuximab	Thank you for your comment. The committee agreed that brentuximab vedotin was clinically effective and produced durable clinical responses compared with current treatments which could lead to a proportion of patients being able to bridge to allogeneic stem cell transplant. The final appraisal document (FAD) has been updated to reflect new evidence submissions in response to consultation. Please see sections 3.1 and 3.25 of the in the FAD.

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			compared to physicians choice, whilst we acknowledge that there is no significant difference for the functional and emotional domains of Skindex-29 between the treatment arms. We note that the committee agrees with the clinical evidence but has not recommended Brentuximab for CD30+ CTCL after one systemic therapy based on cost-effectiveness modelling. Advanced stages of CTCL are rare malignancies causing severe morbidity and high mortality rates. Until recently there have been no approved effective treatment options for advanced stages of CTCL but based on recent large phase III randomised studies, we now have the evidence to support the use of Brentuxumab Vedotin for CD30+ CTCL. This is reflected in the significant increase in use of Brentuximab supported by a compassionate use program since completion of the trial and the increased numbers of patients who are becoming eligible for transplantation based on the quality of clinical response to Brentuximab which we have not been able to achieve with other chemotherapy options. We would strongly recommend that the committee re-evaluate their decision and also clarify why, as CTCL is a rare malignancy, the treatment could not be considered eligible for the CDF. On behalf of the UKCLG: [redacted]	
19	Public	NHS Professional: [redacted]	I am a haematologist who looks after patients with CTCL which is resistant to skin directed therapy. When patients are resistant to systemic chemotherapy it is not possible to palliate symptoms. The	Thank you for your comment.

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			pain and discomfort from advanced CTCL is significant and as well as pain it often affects mobility. Unlike systemic lymphoma, which we can palliate with oral chemotherapy or steroids, CTCL is often resistant to this if one line of systemic therapy has failed. It is therefore very difficult to achieve any quality of life for my patients, requiring high doses of analgesia often as an inpatient in hospital. There are currently limited options for patients with CTCL who have failed systemic chemotherapy and again unlike systemic lymphoma where we can give alternative regimens whether of curative or palliative intent this is not true for CTCL. I feel strongly that having brentuximab available, it is of use both in terms of clinical effectiveness as a bridge to allogeneic stem cell transplant or as a palliative measure to obtain good quality of life for patients and keep them out of hospital. Having used brentuximab on compassionate use basis I have allowed 2 patients to have more than a year of good quality of life as an outpatient. Prior to this they were requiring inpatient care with daily skin dressing and high doses of analgesia. I think that the high cost of end of life care for these patients should be taken into account when considering the cost effectiveness.	The committee agreed that there is unmet need for more effective treatment options. They also agreed the improved response rates from brentuximab vedotin could lead to a proportion of patients being able to bridge to allogeneic stem cell transplant. Please see sections 3.2, 3.5 and 3.7 of the final appraisal document.
21	Public	NHS Professional: [redacted]	Many thanks for sending this out for public consultation. I was very disappointed to see the provisional 'no' from NICE however. My main concerns are the following: - Cutaneous T-cell lymphoma, especially when advanced, is a truly horrible disease: it is extremely itchy and disfiguring. Current QoL scoring systems do not capture these aspects well and I feel the trial data has underestimated the QoL benefit from inducing a durable remission. I realise NICE do have patient representation which I applaud but I think their voice should be listened to perhaps more so than for other appraisals - I would wholeheartedly agree with the clinical experts you had, saying that allogeneic stem cell transplantation is now considered for all patients with relapsed disease. Brentuximab acts as a far superior bridge than current options. My understanding is that a significant	Thank you for your comment. The views of clinical and patient representatives were considered by the appraisal committee when formulating its recommendations. The committee also carefully considered the comments received from consultees, commentators and the public in response to the draft guidance. This included a number of

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			number of curative transplants would bring down the cost per QALY of BV and I think it necessary that this is included in the economic modelling. As with other lymphomas, the UK transplants more patients with CTCL than other countries, so it is important to factor this in. I fully appreciate the uncertainties in the literature. As for brentuximab in Hodgkin, I would have thought the way to try to resolve these is to allow BV use via the cancer drugs fund and then coordinate a national data collection exercise to evaluate how many people are actually bridged to a stem cell transplant. CDF and compassionate use patients could be included. This approached worked very well with Hodgkin - with an excellent engagement from UK clinicians supplying data. To simply not fund this drug now would be a huge shame to a very needy patient group who have a lymphoma with a high unmet need. Many thanks for considering this response.	patient perspectives submitted by NHS professionals and clinical experts. The final appraisal document (FAD) has been updated to reflect the new evidence and committee's updated recommendation. Please see sections 1, 3.12, 3.15 and 3.25 for the FAD.
22	Public	NHS Professional: [redacted]	1. The great majority (> 90%) of allogeneic transplants for CTCL are carried out between 2 centres: Hammersmith and Birmingham. We therefore have the most experience of transplantation for this disorder. 2. Although most patients with CTCL do not come to transplant (because they have low-grade disease which is controllable with lesser measures), a proportion of patients progress and have life-threatening disease which is ONLY curable with allogeneic stem cell transplantation (current cure rate is 40-50% following transplantation). 3. In order for patients to reach transplantation they have to have responding disease (otherwise the transplant outcome is severely compromised). The 2 methods of achieving disease response prior to transplant are either intensive chemotherapy or brentuximab. Brentuximab has the definite advantage as a bridge to transplant in that it does not cause intense immunosuppression (unlike chemotherapy) and therefore is much less likely to be associated with antibiotic-resistant bacterial colonisation of skin lesions, which increases the risk of poor outcome with transplant. 4. We strongly support the use of brentuximab as a bridge to	Thank you for your comment. The committee agreed that the improved response rates from brentuximab vedotin could lead to a proportion of patients being able to bridge to allogeneic stem cell transplant. Please see sections 3.5, 3.7 and 3.15 of the final appraisal document.

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			allogeneic transplant in patients with CTCL. This use results in more patients being eligible for transplantation as the only curative option, and also reduces the risk of serious infection complications during the transplant itself (see 3. above).	
23	Public	NHS Professional: [redacted]	1. Quality of Life (QOL) This disease has a huge debilitating effect on the quality of life of its patients. Many are unable to go out of the house due to the mobility issues caused by pain and the need for regular dressing changes. They are unable to regulate their body temperature as the skin is so badly effected - they are always freezing cold. The disease has a massive psychological effect on all patients. Patients can be embarrassed about the appearance of their skin, wounds leak and often smell offensive, leading to them becoming isolated from friends and family and the general public. Sleep deprivation is a massive issue (for the patient and their partners) as constant itching and skin weeping and pain is something that is often over looked and under estimated. Patients complain of not being able to sleep for days, sometimes weeks when their skin is bad. All can effect the quality of their relationships (sleeping in different beds). This disease can also put financial pressure on a patient and their family. The need to constantly wash, change and buy bed linen is costly along with increased heating bills. Many patients will buy their own dressings (which can be very costly) as dressings may need to be changed in between district nurse visits. In my experience, patients on Brentuximab have overcome all of these issues. All have reported that they have gone back to 'being themselves.'	Thank you for your comments. The committee agreed CTCL is a distressing disease which significantly reduces quality of life of patients. It noted that the benefit of brentuximab vedotin may not be fully captured in the trial data and that this should be factored into its considerations of the cost-effectiveness evidence. Please see sections 3.2 and 3.12 of the final appraisal document (FAD). The committee agreed that patients in end-stage care have no treatment options remaining and require high-resource care. The FAD has been updated to reflect the new evidence submissions in response to consultation and committee's updated recommendation. Please see sections 3.21 and 3.25.

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			The need for dressings are reduced dramatically / if not stopped all together. Patients are able to live a 'normal' life - by going back to work, socialising and are able to rebuild relationships. Quality of sleep is much improved and many go back to sleeping in the same bed as their partner. We feel that all of the patients we have treated with Brentuximab have had significant improvement of their health / emotional related quality of life since commencing the drug; contradictory to the interpretation of existing trial data. 2. Resource use in the end- stage care health state. Patients who are at end stage disease often require regular multiple change of expensive dressings (sometimes 10 times a day). District nurse input is required for this, this is not always available and would then lead to hospital / out of hours GP visits or local A&E departments, all of these are already under a lot of pressure. Palliative care referral and treatment would ultimately be required (with consultant oncologist and specialist nurse input.) Admission to hospice and all associated care costs. Hospital admission required for wound infection treatment. Potential for pressure ulcer development due to reduced mobility and skin quality. 3. In my experience, every patient that has received Brentuximab in order to achieve remission has successfully gone on to have alloSCT. Some patient's report that they have felt to have a better quality of life ("I felt better than ever when on Brentuximab.") on the Brentuximab than they did after transplant.	The committee agreed that allogeneic stem cell transplant should be considered as part of the treatment pathway for a proportion of patients with advanced CTCL. Please see sections 1, 3.5, 3.8 and 3.15 of the FAD.

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			Patient experience on Brentuximab has been hugely positive. Overall, the benefit of the treatment outweighed side effects. CTCL symptoms resolved. Patients claimed that it is a life changing treatment. This relatively rare disease has limited treatment options and a lack of patient focused support unlike many other diseases. If this drug was denied for our small group of physically and emotionally vulnerable patients then I feel they would be denied the opportunity to be able to regain a functional quality of life. The alternative would likely be a harrowing painful progression to death. Please see patient personal statement below. This is on the patients medical records. I was diagnosed with T cell lymphoma in 2009 and since that date my skin has gradually worsened although I have attended many trials at QE hospital and been subject to many different treatments including radiotherapy, full body radiation at University Hospital, Coventry and different types of chemotherapy - but still in 2018 I spent a month in my local hospital with very infected skin where I was put in isolation. Then, in September 2018 I received my first dose of brentuximab and immediately my skin began to show significant improvement. I had been administering 24 dressings each day and now after 6 treatments I am down to 2 dressings. It took 2 hours each day to get dressed, I had to sleep on towels each night because the skin oozed, my wife was hoovering 4 times each day because of the skin flaking and the continuous itching made my life very miserable. Not to mention the amount of washing of clothes! I now feel better generally and have put on weight. Others are noticing my improvement and are asking me what miracle has happened? I can only answer Brentuximab and offer many thanks.	

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			[redacted]	
24	Public	NHS Professional: [redacted]	As a health care professional with expertise in delivering intensive chemotherapy, brentuximab and allogeneic stem cell transplants for patients with advanced stage mycosis fungoides, I would like to comment specifically on 3 issues relating to this appraisal. 1. BV vs chemotherapy as a bridge to allograft: I have treated several patients with chemotherapy with a view to bridging them to a transplant as a potential curative treatment. Unfortunately the response rates are rather sub-optimal and only a small minority eventually end up qualifying for a transplant. I have also treated a few patients with BV with a much better success rate in terms of proceeding to a transplant. I note the company's submission assumes a transplant rate of around 25-30% with BV vs <10% with conventional chemotherapy. This is very much in keeping with me personal clinical experience. Most responding patients will show a response by 4 cycles of treatment and will often proceed to transplant between 4-6 cycles of treatment. 2. Impact of BV on QoL: I think the committee significantly underestimates this. I have patients whose QoL has been transformed by BV. Advanced stage MF can have quite an adverse impact on QoL as itching is a prominent symptom which can be debilitating and many patients have ulcerated skin tumours with a smelly discharge leading the patients to become socially withdrawn. BV significantly improves their chances of having a good remission and symptom survival. Many patients would value this immensely even if they did not have an OS benefit. One of my patients was needing 25 dressings every day to cover all ulcerated tumours on his skin. There was no response to intensive chemo using gemcitabine. He ended up needing multiple hospital admissions due to sepsis whilst on chemo adding a huge burden to healthcare provision and nursing care due to the amount of time spent applying dressings on a daily basis. Since starting BV on a compassionate use basis, his lesion have all healed nicely and he is only needing dressing for 1 lesion now which is also in advanced stages of healing. He has received 4 cycles of BV so far. This patient is now being worked up for an allograft.	Thank you for your comments. Please see the response to the comments above from the previous NHS Professional.

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			3. Resource use at the end of life: I think the committee underestimates the amount of resource needed for provision of care for this complex group of patients. I have had patients with extensive skin tumours on a palliative pathway needing extensive nursing input for dressing the wounds on their skin. I have had patients needing to be admitted to hospital for this and in some instances needing ketamine sedation for dressings on a daily basis as the wounds were very painful. Managing this situation in the community is often very difficult due to lack of proper resource and expertise. Also important to remember, patients may be on the "palliative" path for several months which compounds the resource utilisation.	
25	Public	NHS Professional: [redacted]	Dear NICE Re: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma I am a Consultant Clinical Oncologist at Guys hospital with a specialist interest in treating skin lymphoma. I treated patients with Brentuximab in the Alcanza study and have treated patients with Brentuximab via the compassionate use programme. The Skin tumour unit at Guys is the largest centre for cutaneous lymphoma in the UK and we see patients for opinions from all over the UK and internationally. Cutaneous T-cell Lymphoma (CTCL) is very difficult to treat and none of our established systemic therapies have shown an improvement in overall survival. I have treated patients with CTCL at Guys since 2003 and Brentuximab vedotin is the best new drug I have used, and has made the largest impact of any new treatment over the last 15 years. The only treatment that has been shown to induce long term remission and survival in this group of patients is a reduced intensity stem cell allograft RIC-Allo-SCT. To get patients to RIC-Allo-SCT we need to get the patients into a complete or very good partial remission. Brentuximab is proving to be the best systemic therapy option at doing this. In patients where transplant is not an option the rapid response and duration of response to Brentuximab is better than any other current systemic agent and it provides a significant improvement in quality of life for these patients.	Thank you for your comments. The committee agreed that brentuximab vedotin was clinically effective and produced durable clinical responses compared with current treatments. They noted that the improved response rates from brentuximab vedotin could lead to a proportion of patients being able to bridge to allogeneic stem cell transplant. The final appraisal document has been updated to reflect the new evidence submissions and committee's updated recommendation. Please see sections 1, 3.15 and 3.16.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			I presented the outcomes of the RIC-Allo-SCT protocol currently used in the UK at the EORTC meeting in 2018 and I believe this data has been made available to you. Between Aug 2017 and Sep 2018 I secured funding for 21 patients to receive treatment with Brentuximab via the compassionate use programme. 2 patients unfortunately progressed and died while awaiting funding agreement. This is the nature of this condition which can progress rapidly and with wide spread skin involvement the problems with skin infection and declining fitness due to extensive skin erosions and ulcerations makes treatment very difficult. I have treated 19 patients between Aug 2017 and Jan 2019 with Brentuximab. Of these patients 14 were eligible to be considered for a RIC-Allo-SCT. 5 out of 14 patients (36%) have responded and are now fit for a RIC-Allo-SCT, 3 of whom have been transplanted and are alive and well in complete response and 2 patients continue on Brentuximab awaiting a match for a transplant. The 3 patients who have been transplanted received 6, 10 and 11 cycles of Brentuximab each. The 2 patients awaiting transplant are on cycles 5 and 9 of Brentuximab currently with an excellent partial response. The results of treatment for the 19 patients treated on the compassionate use programme are summarised below: 19 patients treated. Started Treatment between Aug 2017 and Sep 2018. Last Follow up 4th January 2019. 14/19 (73%) fit and eligible for transplant RIC-ALLO-SCT Median number of cycles received: 5 (Range 1 to 11) Global Response at 6 weeks pre cycle 3: CR 2/19 (10.5%), PR 14/19 (73.7%), ORR 16/19 (84.2%), PD 2/19 (10.5%) NA 1/19 stopped after cycle 1 (Neutropenic sepsis)	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Global Response at 12 weeks pre cycle 5: CR 2/19 (10.5%), PR 10/19 (52.6%), ORR 12/19 (63.1%), PD 6/19 (31.5%) NA 1/19 stopped after Cycle 1 (Neutropenic Sepsis) Toxicity: Peripheral Neuropathy: Grade 0 = 6, Grade 1 = 9, Grade 2 = 3, Grade 3 = 1 Neutropenic Sepsis: Grade 3 = 1 Survival: At last follow up: 3 patients transplanted and alive in CR 2 patients in PR on Brentuximab awaiting transplant 2 patients in PR on Brentuximab 6 patients receiving palliative care or further systemic treatments 6 patients died due to CTCL. We have learnt to recognise early signs of peripheral neuropathy and with treatment delays and dose reductions all patients who developed peripheral neuropathy have had recovery of function and we have no patients with ongoing peripheral neuropathy greater than grade 1. My experience is that Brentuximab vedotin has made a real and significant impact on the management of patients with advanced CTCL. The response rate is higher than any other systemic therapy and the duration of this response is impressive. Seeing a patient with	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			such a devastating illness respond and come back to clinic without pain, without itch, being able to wear normal clothes without extensive dressings is amazing. Brentuximab in the clinic has made a significant improvement to this patientâ€™s groupâ€™s quality of life. Brentuximab has also helped us get patients to RIC-Allo-SCT who would not otherwise have done so and this will induce a lasting remission and possible cure for some patients. I hope you can approve access for Brentuximab for CTCL patients on the NHS, otherwise it will be a real tragedy. CTCL is a very difficult disease to treat, recruiting to clinical trials is very difficult and the multicentre international Alcanza trial is probably the best randomised controlled trial carried out in this patient group reporting better results than any other current treatment. I will submit a letter from a patient who was a GP with advanced Mycosis Fungoides. He wrote to NHSE to support the application I made to treat him with Brentuximab. This application was turned down and several months later the Compassionate use programme started and I was able to treat him with Brentuximab on the compassionate use programme. Unfortunatley waiting those 3 months caused his skin lymphoma to progress further and despite initial response to Brentuximab his lymphoma was to advanced and he fitness deteriorated and he died. Before he died he gave me his consent to share his experience and the letter he sent to NHSE to help future patients. Kind regards [redacted]	
26	Public	NHS Professional: [redacted]	[redacted] 1 July 2017 Dear Sir or Madam, I am writing regarding the application made by [redacted] for the use of Brentuximab for treatment of my Mycosis Fungoides (cutaneous T cell lymphoma). I would like to provide further	Thank you for your comment. The committee considered patient perspectives alongside the evidence on clinical and cost effectiveness. Please see sections 3.1 and 3.2 of the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			information on my condition and to draw your attention to four issues in support of my application for exceptional funding, which I cover in more detail later in this letter. This includes: 1. Recent research, published in the Lancet in June 2017, which states the significant medical benefits of Brentuximab in treating my illness over any other drug available; 2. The probability of a cure and full recovery if this committee accepts my application for exceptional funding; 3. The long-term cost to the NHS of managing my condition should my application for exceptional funding be rejected; and 4. The exceptional nature of my disease, which necessarily requires the application of an exceptional approach. Background to my condition Until March this year (2017) I was a fit, healthy newly retired 63 year old playing tennis three times a week and golf twice a week, with a skin rash easily controlled by UV light treatment delivered from a privately acquired and managed home unit when required. My only input from the NHS was 6-12 monthly follow -ups by the local dermatologist. It goes without saying that I enjoyed an exceptionally good quality of life. Since March, my condition has deteriorated rapidly and I've spent nearly ten weeks as an in-patient at Guys hospital across two separate admissions under oncology, dermatology, microbiology and palliative care. I received IV antibiotics for sepsis and skin infections, as well as having pain control and daily treatments and dressings taking at least 2 hours. I also received Caelyx Chemotherapy, which failed to work. My skin is so severely affected that my mobility has suffered significantly, having become virtually bed bound and in constant pain within a matter of weeks. There is no prospect of my life improving unless I have this	final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			treatment and, without treatment, I fear my future is one of pain and disability. My skin has broken down and, whereas I had 5% involvement with itchy dry lesions for many years, I now have 80% of my skin involved. This includes widespread lymphoedema and swelling, open weepy skin, itchy flaking dry areas, tumours, ulceration and areas of excoriation. My hands and feet are peeling and weepy and I have painful fissures and tender friable skin, resulting in severe limitation of use. My face is progressively involved with severe involvement of my genital area and perineum which makes toileting extremely difficult and sitting down for any length of time an impossibility. The pain is indescribable. Itch is also a massive problem. I take morphine and gabapentin regularly, and 'top up' with oromorph when I need to do anything difficult. In my condition this includes undergoing dressings or moving around. If I had to describe the pain, it is akin to being wrapped in barbed wire while someone jumps on me or, at times, like having boiling water poured over me. Even the gentlest touch in the wrong place will make me cry out involuntarily. Sleep is induced with hydroxyzine to reduce itch and zopiclone sleeping tablets. My life, as a sufferer of a debilitating, chronic, life-limiting illness with total skin failure, has been completely taken away from me. My wife has become, and has registered, as my carer. I have daily visits from the district nurse for dressings, which would take 3 hours without help from my wife. I can't tolerate 'outdoor' clothes on my skin, and wearing shoes is impossible. I have limited use of my hands. I cannot stay away from home as I require a hospital airbed and I need a stretcher in an ambulance for my weekly trips to Guys hospital outpatients, as I cannot stay seated for long.	
27		NHS Professional: [redacted]	Mycosis fungoides remains a challenging disease to treat. As a rare cancer, it is hard to develop sufficient expertise, and with limited effective treatment options it is important to find the right place for new therapies. It is also important that for younger, fitter patients, we	Thank you for your comments. The committee agreed that

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			continue to look for a role of alloSCT as a potentially curative option. Emerging data shows improving outcomes following accumulating experience with careful patient selection and delivery of the complex conditioning regimens. Having good induction treatment options to achieve remission or even stable disease is very worthwhile, hence the relevance of having brentuximab available for these patients. UK centre experience with alloSCT following brentuximab is growing and this indication remains the most important. In my small practice, brentuximab initiated as a potential bridge to allograft has achieved this in 2/2 young fit patients. For patients not eligible for alloSCT, treatment with brentuximab can still provide significant benefit, predominantly with respect to progression free survival or time to next treatment, as well as symptomatic/quality of life benefit. Being able to continue to treat responding patients for up to a year, and rechallenge if necessary, is clinically valuable. The majority of patients respond well and tolerate brentuximab without significant toxicity. Most palliative treatments are not necessarily expected to increase overall survival, but control of disease and improved progression free survival may translate into improved overall survival, particularly as controlling skin lesions/tumours can reduce the risk of life-threatening sepsis from superinfection of ulcerating skin tumours. Again, in my small practice, patients have reported improved symptoms such as pruritus and pain, and require fewer dressings and skincare needs. There is no specific QOL tool for CTCL patients, though this is in development, so current instruments have limitations and do not necessarily accurately capture changes that are meaningful to CTCL patients. I can only emphasize that brentuximab has been an extremely valuable addition to the very small armamentarium of active treatments for CTCL. For selected patients, it would be my first choice within its licensed indication as responses can be seen rapidly and patients tolerate it well. For young fit patients it provides an unrivalled means of disease control that might allow these patients to proceed to alloSCT. It would be very disappointing not to be able to use an effective treatment for patients who have such a difficult lymphoma to treat, and such difficult and distressing symptoms to manage. Managing these patients requires truly multidisciplinary input and expertise; ideally they can stay at home and not have to	there is unmet need for more effective treatment options. They also agreed the improved response rates from brentuximab vedotin could lead to a proportion of patients being able to bridge to allogeneic stem cell transplant. Please see sections 3.2, 3.5 and 3.7 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			come into hospital, but meeting their needs in the community can be very challenging as primary care teams are not experienced in managing rapidly growing and ulcerating skin tumours and widespread skin involvement. We need as many effective treatment options as possible, and brentuximab definitely has an important place in the treatment of CTCL.	
28		NHS Professional: [redacted]	In my experience as an Oncologist looking after patients with Cutaneous T cell lymphoma (CTCL) for more than 25 years, Brentuximab offers a whole new approach to treating patients with more advanced CTCL who are destined to die from this very distressing and debilitating disease. Up until now, our treatment options have been very limited and in the advanced stage, when patients have to live with painful and embarrassing ulcerating skin disease, conventional chemotherapy has provided only transient respite at the cost of significant and sometimes life threatening toxicity. Sepsis presents a serious problem to these patients with widespread open wounds who are rendered neutropenic by their chemotherapy. We now recognise that the future for the treatment of this condition will involve immunotherapy in a variety of forms and conventional chemotherapy will give way to these more effective and appropriate treatments. Brentuximab is the first of this new generation of immunologically driven agents. The number of patients requiring Brentuximab each year in the UK will be small due to the rarity of CTCL (600 - 700 new patients per year), and the fact that only the minority of these patients will be deemed appropriate to receive Brentuximab. As a result this will not present a significant financial burden upon the NHS budget.	Thank you for your comments. The potential budget impact of the adoption of a new technology does not determine the appraisal committee's decision. Please see section 6.2.14 of the Guide to the methods of technology appraisal.
29		NHS Professional: [redacted]	We recognise that the ALCANZA trial did not show an overall survival advantage for Brentuximab, however this was not adequately powered for this and the follow up is still relatively short. We know that it is responsible for a substantial improvement in PFS and the importance of this should not be underestimated. These patients suffer greatly with active disease and can live for long periods of time with severely symptomatic lymphoma requiring analgesia, regular skin care and dressing and sometimes with unbearable pruritis which is only improved by disease control.	Thank you for your comment. The committee agreed that brentuximab vedotin was clinically effective and produced durable clinical responses compared with current treatments which could lead to a proportion

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			In a disease such as CTCL which is largely incurable, QOL is of paramount importance to the patient and we have clear evidence of the beneficial impact of Brentuximab on QOL. A significant number of these patients are of working age and control of their disease allows them to continue work with the resulting benefit on their QOL, their financial situation and allows them to continue their contribution to society through their work. In recent years, it has become more apparent that some patients with advanced disease may enter a more durable remission following an allogeneic stem cell transplant (ASCT). It is a little early to say whether some of these patients have been cured, but clearly this procedure has dramatically changed the course of the disease and offers the potential for cure - which would be the first time this has been achieved. The secret of proceeding to an ASCT is the achievement of a complete or near complete remission. Any treatment which can bridge a patient to an ASCT plays a pivotal part in achieving the possibility of cure. To date, Brentuximab is the agent which offers this potential above other current therapies.	of patients being able to bridge to allogeneic stem cell transplant. The committee also agreed that brentuximab vedotin appears to improve health-related quality of life, but that the size of the effect was unclear. Please see sections 3.5, 3.8 and 3.12 of the final appraisal document.
30	Consultee	Leukaemia Care	We are disappointed with the decision not to recommend this treatment. CTCL is a rare condition, therefore uncertainties in the data will always be present. As Sir Andrew Dillon, Chief Executive of NICE stated: “NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair.” To address this unfairness, NICE set up the Highly Specialised Technologies (HST) programme. However, this drug has been chosen to be appraised through the STA programme instead, leading to the inevitable uncertainties in the data. If the committee feels there is still too much uncertainty in the data to approve the drug for baseline commissioning, we urge the committee to allow the treatment to be accessed via the CDF, allowing more time for data to be collected.	Thank you for your comment. It was considered that NICE should follow the STA process when appraising this technology. The final appraisal document (FAD) has been updated to reflect the new evidence submissions in response to consultation and committee’s updated recommendation. Please see sections 1 and 3.25 of the FAD.

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31	Consultee	Leukaemia Care	We would like to highlight the data showing that this treatment can extend the disease-free period from 3 to 16 months, giving patients more time to plan for a transplant or simply much more times without the frustrating symptoms patients experience. The ability of a treatment to bring about a remission or response was important to 70% of non-Hodgkin lymphoma patients we surveyed in 2017, second only to life extending treatments.	Thank you for your comment. The committee agreed that the improved response rates from brentuximab vedotin could lead to a proportion of patients being able to bridge to allogeneic stem cell transplant. Please see sections 3.2, 3.5 and 3.7 of the final appraisal document.
32	Consultee	Leukaemia Care	The potential to be a bridge to a stem cell transplant is important for patients. In our 2017 patient survey, 92% of non-Hodgkin lymphoma patients would consider it a positive if a new treatment could bridge to a transplant. It is important to note that patients are also now able to undergo reduced intensity transplants, meaning that even more patients could be potentially cured.	Thank you for your comment. The committee agreed that allogeneic stem cell transplant may consolidate treatment response to achieve durable remission for certain patients with advanced CTCL. Please see sections 3.8, 3.15 and 3.16 of the final appraisal document.
33	Consultee	Leukaemia Care	Whilst we appreciate that EQ5D did not show improvement in quality of life issues, we feel this model of quality of life was not sensitive enough to measure the challenges faced by CTCL patients. We feel there are still significant quality of life issues that could be addressed by this treatment and therefore might not have been captured by the models. For example, Beynon et al. (2015) shows that patients may have to sleep apart from their significant other due to the extreme itchiness they experience. This extended disease-free period that this treatment provides, as mentioned above, would give patients relief from these distressing symptoms.	Thank you for your comment. The committee noted that the EQ-5D-3L data from the ALCANZA trial failed to capture nocturnal pruritus, which severely affects people with advanced CTCL. It agreed that this

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				should be factored into its considerations of the cost-effectiveness evidence Please see section 3.12 of the final appraisal document.
34	Consultee	Leukaemia Care	We would like to highlight that the symptoms of CTCL that patients experience can limit their everyday activities, as recognised at the committee meeting. A diagnosis of any cancer has an impact not only on those diagnosed, but on their friends and family as well; this could be an emotional, practical or financial impact. The ACD document suggests that patient's family are likely to take on caring duties, meaning the savings to the NHS were overestimated. Whilst many families are likely to take on this responsibility, they should not be expected to do so, given the difficult situation they may already be in. The family are often in need of support themselves, perhaps increasing costs to the NHS in other capacities. Beynon et al. (2014) highlights how the needs of patients are not well quantified, and the needs of those providing care is even less so, yet it could be significant given the circumstances.	Thank you for your comment. The committee considered patient perspectives, which highlighted the emotional and financial impact of advanced CTCL on some family members and carers, alongside the evidence on clinical and cost effectiveness. Please see sections 3.1, 3.2 and 3.21 of the final appraisal document.
35	Consultee	Leukaemia Care	We would like to note that once patients have reached this stage in their illness, there a few other treatment options available to them. Therefore, patients are need of any treatment that will reduce the significant symptom burden that would come from being untreated; such as increased infection risk, itchiness and skin lesions.	Thank you for your comment. The committee agreed that there is unmet need for more effective treatment options. Please see section 3.2 of the final appraisal document.

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]: ACD Response

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute for Health and Care Excellence

Submitted 24 January 2019

Table of Contents

List of Figures

List of Tables

List of Abbreviations

ACD	Appraisal consultation document
AlloSCT	Allogeneic stem-cell transplant
BSC	Best supportive care
BV	Brentuximab vedotin
CDF	Cancer Drugs Fund
CTCL	Cutaneous T-cell Lymphoma
DOR	Duration of response
DOT	Duration of therapy
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence review group
EU PROCLIPI	European PROCLIPI (Prospective Cutaneous Lymphoma International Prognostic Index) Study
ICER	Incremental cost-effectiveness ratio
MF	Mycosis fungoides
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PC	Physician's choice
pcALCL	Primary cutaneous anaplastic large cell lymphoma
PFS	Progression free survival

1. Executive Summary

Takeda would like to thank the National Institute for Health and Care Excellence (NICE) and the Appraisal Committee for their consultation on this appraisal. Although Takeda disagrees with the Committee's draft position not to recommend brentuximab vedotin for the treatment of CD30-positive cutaneous T-cell lymphoma (CTCL), we hope that the information included in this response to the Appraisal Committee Document (ACD) (along with other responses received during the consultation period) will help the Committee to reach a positive final recommendation.

Takeda is pleased to note that agreement has been reached with the Committee regarding a number of critical points within this appraisal. These include, but are not limited to, agreement on the following:

- the unmet need in advanced CTCL wherein the disease has a significant, long-term clinical and humanistic burden arising from severe skin symptoms, and the morbidity and mortality associated with a cancer diagnosis
- that there is an unmet need for effective treatments that extend the amount of time the disease is in remission and improve quality of life
- brentuximab vedotin's place in therapy and likely use in clinical practice in patients with advanced disease
- the relevant comparators for the purposes of this appraisal (i.e. methotrexate, bexarotene and interferon alfa)
- that an objective response lasting for at least 4months (ORR4) is a clinically meaningful outcome for patientsthe significant efficacy of brentuximab vedotin in improving ORR4 and PFS compared with physician's choice of therapy
- that data from patients with mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) in the ALCANZA study are representative of, and applicable to, all subtypes of CTCL
- that allogeneic stem-cell transplant (alloSCT) is standard of care in the UK for eligible patients and should be included in the cost-effectiveness model
- the potential of brentuximab vedotin to enable more patients to achieve at least a partial response to treatment and thereby become potentially eligible for an alloSCT

Additionally, Takeda consider that the Committee's preferred assumptions for inclusion in the economic model are reasonable. With the Committee's preferred assumptions brentuximab vedotin remains dominant relative to the comparator with a revised base case reduced net monetary benefit (NMB) of £150,415. By applying the Committee preferred assumptions, the revised base case NMB is slightly lower than Takeda's prior base case NMB of £153,693, as presented in the addendum to the submission dossier in November, however brentuximab vedotin remains dominant relative to physician's choice.

There are issues highlighted in the ACD which we believe warrant further discussion, including: (1) quality of life impact of brentuximab vedotin, (2) rate of alloSCT and duration of treatment prior to alloSCT, (3) overall survival (OS) without alloSCT and (4) the post-progression pathway and associated resource use. We have endeavoured to clarify and

address these issues within this document and where uncertainty remains we have provided scenario analyses varying key parameters between extreme lower and upper bounds. These scenarios demonstrate that brentuximab vedotin remains cost-effective at these upper and lower bounds – brentuximab vedotin is shown to dominate the comparator in all scenarios.

In conclusion, we would ask the Committee to consider carefully the case we have made, the proven ORR4 and progression-free survival (PFS) benefits of brentuximab vedotin, and the step-change that this offers to patients with advanced CTCL by providing improved durable disease control which has a positive impact on their quality of life and, in some cases, by enabling significantly more eligible patients to undergo a potentially curative alloSCT. Takeda is optimistic that the information provided in this response document can now allow the Committee to conclude that the range of plausible incremental cost-effectiveness ratios (ICERs) associated with brentuximab vedotin, across a range of modelled scenarios, fall within NICE's threshold for cost effectiveness, thereby allowing the Committee to issue a positive recommendation for brentuximab vedotin for CD30+ advanced CTCL. This would enable patients with advanced stage CTCL and the NHS to benefit from having access to this very important and potentially transformative therapy.

2. Introduction

2.1 Appraisal committee's preliminary recommendations

On the 18th December 2018, the Appraisal Committee of NICE prepared an ACD summarising the evidence, views and draft recommendations of the Committee regarding the use of brentuximab vedotin for treating CD30-positive CTCL. The ACD sets out the draft recommendations made by the Committee which currently state that:

'Brentuximab vedotin is not recommended, within its marketing authorisation, for treating CD30-positive cutaneous T-cell lymphoma (CTCL) after at least 1 systemic therapy in adults'.

In this response document Takeda have addressed uncertainties raised by the Appraisal Committee and provided a balanced response which includes updated analyses and a revised base case reflecting the Committee's preferred assumptions, as outlined on page 24 of the ACD. Additional scenario analyses requested by the Committee are also presented to assess the impact of variations in key parameters on the cost-effectiveness results. All cost-effectiveness results shown in this document have the current PASLU/DH approved patient access scheme (PAS) applied to the price of brentuximab vedotin (with PAS price of [redacted] per vial after the application of a [redacted] straight discount). The corresponding without PAS results are shown in Appendix 1.

Takeda is optimistic that the information provided in this response document will allow the Committee to conclude that the plausible ICERs associated with brentuximab vedotin fall within NICE's threshold for cost-effectiveness. Takeda hope that the Committee will reconsider their draft negative recommendation and issue a positive final recommendation for brentuximab vedotin, thus enabling patients with advanced stage CD30+ CTCL and the NHS to benefit from having access to this very important and potentially transformative therapy.

3. Response to the appraisal committee's key standard questions

Please find below Takeda's responses to the questions from the Appraisal Committee listed on page 1 of the ACD.

3.1 Has all of the relevant evidence been taken into account?

Takeda have provided all relevant evidence currently available from the brentuximab vedotin clinical trial programme. The main clinical evidence to support the case for the clinical and cost-effectiveness of brentuximab vedotin versus physician's choice of therapy in the sub-group of patients with advanced CTCL who have received 1 prior systemic therapy is from the ALCANZA trial. In the ACD (see Clinical evidence sections 3.6 – 3.10), the Committee concluded that:

> *"The clinical-effectiveness evidence is relevant to NHS clinical practice……..brentuximab vedotin was clinically effective and produced durable clinical responses compared with methotrexate or bexarotene, and accepted that this would also be the case for interferon alfa ……..the lack of a comparison between brentuximab vedotin and interferon alfa was not a major limitation in the evidence……the clinical-effectiveness data from ALCANZA could be extrapolated to other subtypes of CTCL, such as Sézary syndrome.....and the clinical-effectiveness evidence from ALCANZA was relevant to clinical practice in the NHS in England."*

Real-world data from 53 UK patients across six centres who had received the recommended Stanford Protocol conditioning alloSCT was presented within an addendum to the submission dossier (sent to NICE on the 21st of November 2019). These data were reflected in the updated economic model submitted to NICE alongside the addendum. As a reminder, the updated dataset includes both a longer follow-up and also more patients than the original dataset from five additional centres. [redacted], presented by Dr. Ranuka Palanicawandar at the 2017 EORTC conference, [redacted] despite the addition of more patients (including patients from centres other than London). [redacted]. This is encouraging and adds both validity and robustness to the original single-centre results. Takeda is pleased that the Committee has accepted the updated multi-centre data presented in the addendum and that the Committee agreed with the relevance of alloSCT in the treatment pathway for advanced CTCL. Furthermore, we note that the Committee has agreed that Takeda's approach to modelling survival outcomes following alloSCT was appropriate, as stated in Section 3.19 on page 16 of the ACD.

In relation to the question raised by the Evidence Review Group (ERG) on outcomes of alloSCT following brentuximab vedotin compared to current standard of care (cited on page 16 of the ACD), Takeda has consulted with the transplant specialists from the centres included in the updated dataset. There was a consensus among all transplant consultants from the study that there is no reason to believe the outcomes of alloSCT would be different following the use of brentuximab vedotin as a bridging agent. They believe assuming equivalent

outcomes is reasonable (and perhaps conservative) because outcomes after alloSCT may improve due to deeper responses observed with brentuximab vedotin compared to standard of care prior to the transplant.

In response to the issues raised in the ACD, Takeda have sought to confirm the data on the rates of alloSCT following use of brentuximab vedotin from the compassionate use programme at the London supra-centre, as mentioned by a clinical expert during the first Appraisal Committee meeting. Section 3.8 of the ACD notes that a clinical expert suggested around 25% of patients from the compassionate use program have bridged to an alloSCT. We have received, as a personal communication, the following information from Dr Stephen Morris, the oncologist who works at the London supra-regional centre alongside one of the clinical experts who gave evidence at the first committee meeting. [redacted] This real-world data is very similar to the 27.5% of patients assumed to receive an alloSCT in the brentuximab vedotin arm in Takeda's base case health economic model, as discussed in further detail in Section 3.2.2.1.

Based on this real-world data, the median number of cycles of brentuximab vedotin received for all alloSCT eligible patients is five. However, those five patients who have had or are currently undergoing a transplant have received an average of eight cycles. Scenarios exploring the impact of varying the number of cycles of brentuximab vedotin prior to receiving an alloSCT are presented in Section 3.2.2.2.

Takeda can also confirm that the British Association of Dermatologists and UK Cutaneous Lymphoma Group (BAD/UKCLG) guidelines for the management of primary cutaneous lymphomas 2018, referenced in the original submission and marked as Academic in Confidence, have now been published in the British Journal of Dermatology.[1] Importantly, the recommendations regarding the role and positioning of brentuximab vedotin and alloSCT in these published guidelines are consistent with those presented in the original company submission.

3.2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Takeda consider that the Committee's summary of the impact of CTCL on patients and the unmet need reasonably reflect the disease and treatment pathway. Takeda agree with the Committee that there is currently an unmet need for effective treatments that extend the amount of time the disease is in remission and improve quality of life (Section 3.2 of the ACD).

The positioning of brentuximab vedotin and the relevant comparators agreed by the Committee in the ACD are in line with Takeda's original submission dossier (Sections 3.3,

3.4 and 3.5 of the ACD). Additionally, Takeda consider that the Committee's preferred assumptions presented in Section 3.25 of the ACD are reasonable. These include:

- Inclusion of alloSCT in the treatment pathway (as in the company's base case)
- Equal utility values for brentuximab vedotin and physician's choice at baseline
- Removing treatment-related disutilities
- Removing additional oral chemotherapy costs

The Committee's preferred assumptions are included in the revised base case presented in this document. With the Committee's preferred assumptions, brentuximab vedotin remains dominant over the comparator with a NMB of £150,415. Table 1 presents the step change in results from each additional revision. The revised based case results are shown in Table 2.

Please note that all of the ICERs presented in the document include the current PAS; without PAS results are shown in the Appendix. The economic model set up to this revised base case accompanies this document: ""*Brentuximab vedotin for RR CTCL_CE model_ACD response (24JAN2018).xlsb"* ***All scenarios presented within this document are based on this revised base case.***

Table 1: Step change in results from the company's base case to the revised base case reflecting the Committee's preferred assumptions (with PAS)

	Cost per QALY	NMB
Company's base case	BV Dominates	£153,693
Equal utility values for brentuximab vedotin and physician's choice	BV Dominates	£153,061
Equal utility values for brentuximab vedotin and physician's choice + Removing treatment-related disutilities	BV Dominates	£153,401
Committee's preferred assumptions – the revised base case Equal utility values for brentuximab vedotin and physician's choice + Removing treatment-related disutilities + Removing additional oral chemotherapy costs	BV Dominates	£150,415

Abbreviations: BV, brentuximab vedotin; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life year.

Table 2: Revised base case with PAS

	Total			Incremental			Cost per QALY	NMB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Physician's choice	[redacted]	[redacted]	7.36					
Brentuximab vedotin	[redacted]	[redacted]	8.93	[redacted]	[redacted]	1.58	BV Dominates	£150,415

Abbreviations: LY, life year; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life year.

However, there are sections of the ACD which warrant further discussion; we have endeavoured to clarify and address these points within this response document, including the following four key issues:

- Quality of life impact of brentuximab vedotin on patients with CTCL (Section 3.2.1)
- Rates of alloSCT following treatment with brentuximab vedotin and physician's choice, and assumptions relating to duration of treatment with brentuximab vedotin prior to alloSCT (Section3.2.2)
- OS for patients not undergoing an alloSCT (Section 3.2.3)
- Post-progression pathway and associated resource use (Section 3.2.4)

We believe that the clarifications provided in these four areas will assist the Committee in its decision making for this appraisal.

3.2.1 Quality of life in the ALCANZA trial (response to Section 3.11 of the ACD)

Takeda understand the Committee's conclusion in Section 3.11 of the ACD that based on the available evidence *"Brentuximab vedotin's effect on health-related quality of life is unclear from the trial data".* However, we believe that brentuximab vedotin does improve the lives of patients with CTCL based on both patient and clinician feedback. We consider that the full quality of life impact was not able to be captured in the ALCANZA clinical trial because of the insensitivity of the quality of life instruments included and the low completion rates observed.

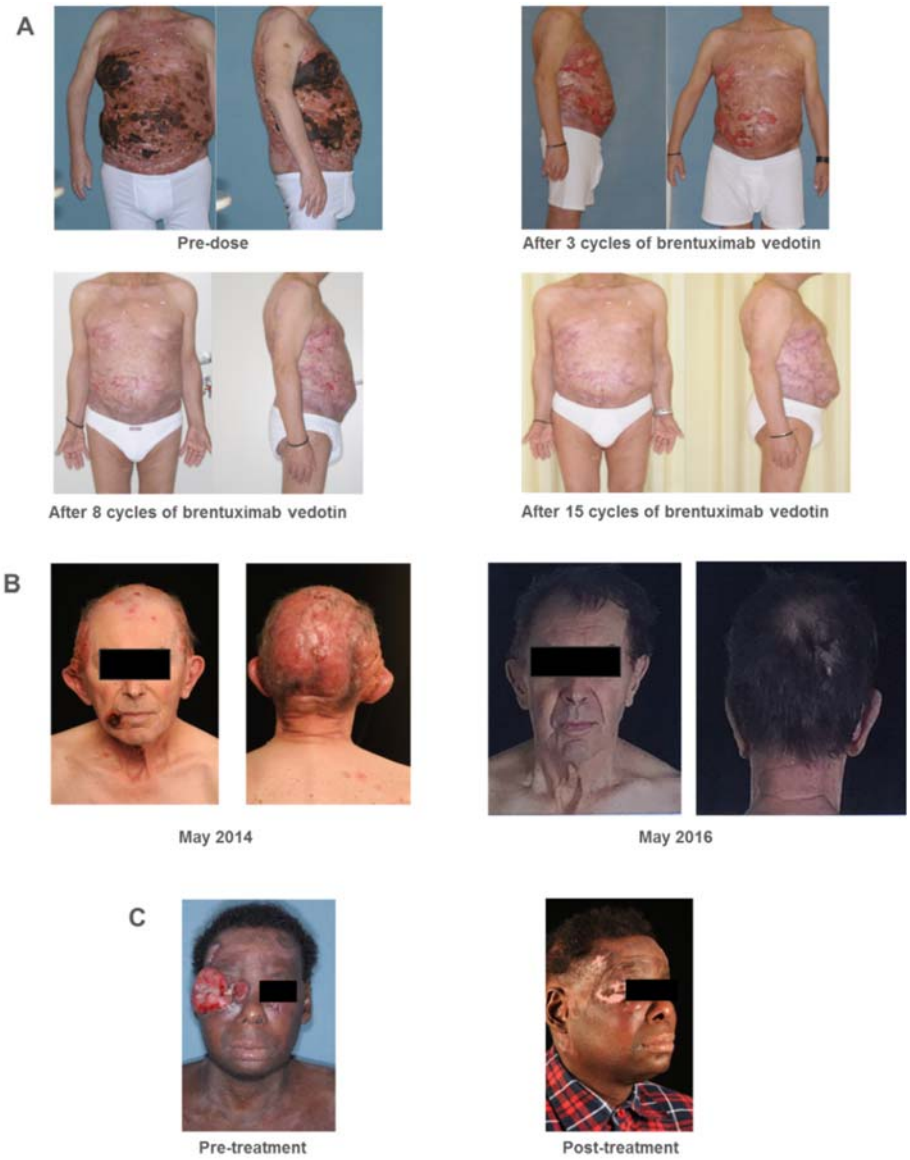
The EQ-5D is the preferred measure of quality of life by NICE; as such the economic analysis utilises the EQ-5D data collected in the ALCANZA trial. However, the EQ-5D is insensitive to particular burdens associated with CTCL and so may not be an accurate reflection of a patient's quality of life as evidenced by the lack of correlation between the skin specific Skindex-29 and EQ-5D scores in ALCANZA. Takeda is pleased to see that the ERG and Committee acknowledge the limitations of the EQ-5D and the data available from ALCANZA in drawing conclusions on the impact of brentuximab vedotin on quality of life.

Skindex-29 is frequently cited in the literature and used in clinical trials as a tool to measure the impact on quality of life for patients with CTCL. This instrument is more sensitive than the EQ-5D and can therefore provide a more accurate reflection of a patient's quality of life with this disease. For this reason, a key secondary endpoint of ALCANZA was the symptom domain of Skindex-29 which showed that patients treated with brentuximab vedotin had significantly greater symptom reduction compared with those treated with physician's choice (maximum reduction from baseline, mean [SD]: -27.96 [26.88] vs. -8.62 [17.01], respectively; $p<0.0001$).[2] The results of the functional and emotional domains of Skindex-29 were also collected and both showed a nearly double-digit improvement with treatment with brentuximab vedotin compared to physician's choice. The mean change from baseline to end of treatment for the emotions domain was –14·43 mean SD [20.90] for the brentuximab vedotin arm and –1·84 [18.55] for the physician's choice arm. The mean change from baseline to end of treatment for the functioning domain was –11·10 [25.31] for the brentuximab vedotin group and –1·22 [22.45] for the physician's choice group.[2] Please note that a reduction in the Skindex-29 score is reflective of a lesser burden on quality of life. As the functional and emotional domains of Skindex-29 were not pre-specified secondary end-

points, no minimally significant difference for improvement was set thus no statistically significant improvement can be claimed.

Takeda does acknowledge that there are also some limitations of the Skindex-29 instrument; as mentioned by clinical experts at the committee meeting there is no tool which is currently able to fully capture the impact on quality of life of patients with CTCL. However, we believe the significant improvement in depth of response (complete response or complete resolution of symptoms of 20.4% versus 2.2% for brentuximab vedotin and physician's choice, respectively), duration of response and 13 month longer PFS seen with brentuximab vedotin in the ALCANZA trial with advanced patients does offer a significant reduction in disease burden and that this almost certainly translates into quality of life benefits for patients. As an illustrative example of this, consider the following "before treatment" and "after treatment" photos of some patients who received brentuximab vedotin in the ALCANZA trial.

Figure 1: Responses observed with brentuximab vedotin treatment in ALCANZA: A) a patient with MF (T3NXM0B0) after 15 cycles, B) an MF folliculotrophic patient after 2 years of treatment achieved durable CR, and C) an ALCANZA patient with MF stage IIB[3,4]



Abbreviations: B, blood; CR, complete response; M, metastases; MF, mycosis fungoides; N, node; T, tumour.

3.2.2 Discussion on pathway which includes alloSCT (response to Sections 3.8, 3.11, 3.15, 3.16 and 3.22 of the ACD)

Takeda agree with the Committee that alloSCT should be considered as part of the treatment pathway, as this reflects current UK clinical practice (Section 3.5 of the ACD).

Takeda appreciate that because of the rarity of the disease and the evolving landscape, availability of data relevant to patients with advanced CTCL undergoing transplant in the UK is limited. However, as presented within the addendum to the original submission dossier, data on 53 patients treated with alloSCT across six UK centres, with a median follow-up of [redacted] is included in the economic model. Therefore, we believe the outcomes included in the model for patients undergoing an alloSCT reflect UK clinical practice.

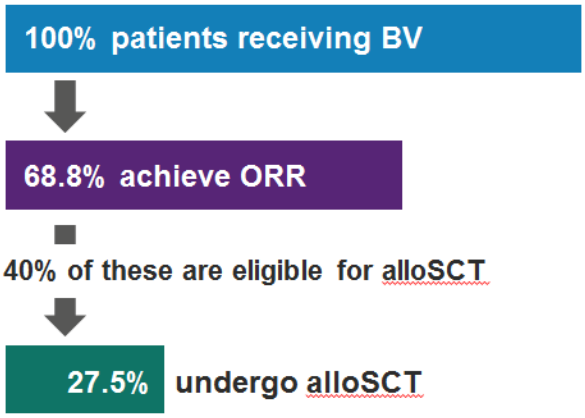
Takeda understand that these data do not inform on the rate of transplant or the time on treatment prior to transplant. Therefore, we have sought transplant-specific data from the compassionate use programme (see Section 3.1 of this response) and clinical expert advice to address these data gaps. Furthermore, we have conducted scenario analyses testing the underlying assumptions within the model between clinically plausible ranges to demonstrate the impact on the cost-effectiveness results. Section 3.2.2.1 discusses the rates of alloSCT after treatment and Section 3.2.2.2 discusses the time on treatment prior to transplant.

3.2.2.1 Rates of alloSCT after treatment with brentuximab vedotin or physician's choice (response to Section 3.8, 3.15 and 3.16 of the ACD)

Takeda would like to clarify that the company's health economic model assumes that 27.5% of patients treated with brentuximab vedotin and 7.1% of patients treated with physician's choice will be bridged to an alloSCT, respectively.

The 27.5% bridging rate applied in the model for brentuximab vedotin is based on applying a value of 40% (the proportion of patients assumed to be eligible for a transplant based on age and underlying comorbidities) to the objective response rate (ORR) seen with brentuximab vedotin in the ALCANZA trial (see Figure 2). Section 3.15 of the ACD states: *"the clinical experts confirmed that the response rates used to inform the assumption of 40% reflected those seen in clinical practice"*. Takeda would like to clarify that the 40% is not based on response to treatment; rather it is based on eligibility for transplant considering age, co-morbidities, likelihood of matching to a donor and patient choice. It is then multiplied by the proportion of responders to brentuximab vedotin in the ALCANZA trial. This has been validated as a reasonable assumption by clinical experts and is supported by the compassionate use data presented in Section 3.1.

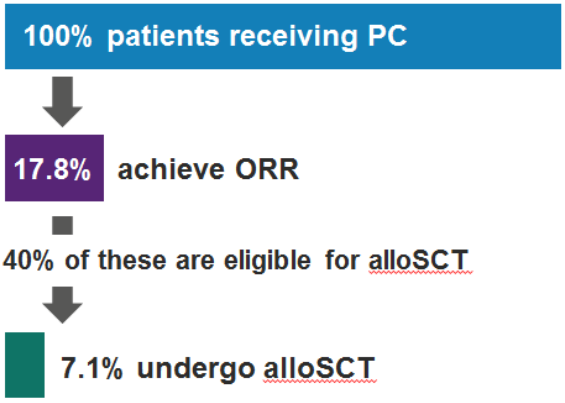
Figure 2: Assumed alloSCT rate after brentuximab vedotin based on the ALCANZA ORR data and transplant eligibility for advanced CTCL patients



Abbreviations: alloSCT, allogeneic stem-cell transplant; BV, brentuximab vedotin; CTCL, cutaneous T cell lymphoma; ORR, objective response rate.

Similarly, the 7.1% bridging rate applied in the model for physician's choice, the comparator, is based on applying the 40% transplant eligibility rate to the ORR seen with physician's choice in the ALCANZA trial (Figure 3).

Figure 3: Assumed alloSCT rate after physician's choice based on the ALCANZA ORR data and transplant eligibility for advanced CTCL patients



Abbreviations: alloSCT, allogeneic stem-cell transplant; CTCL, cutaneous T-cell lymphoma; ORR, objective response rate; PC, physician's choice of therapy.

The proportion of patients receiving an alloSCT after treatment with brentuximab vedotin (27.5%) is consistent with the real-world data from the compassionate use programme (26.3%) and clinical expert opinion.

The real-world data from the compassionate use of brentuximab vedotin in the London supra-centre (see Section 3.1) found that 26.3% of patients who received brentuximab vedotin have either had a transplant or are on the way to having a transplant. This is supported by the clinical expert feedback documented within the ACD (Section 3.8): *"A*

clinical expert who had used brentuximab vedotin on the compassionate use programme suggested that around 25% of patients bridged to transplant." This value was also validated by Takeda prior to submission by discussions with five clinical experts. Takeda consider that, whilst there is some uncertainty regarding the exact proportion of patients who have an alloSCT after brentuximab vedotin, a clinically plausible range can be derived based on the evidence which is many times higher than what is currently achieved with the comparators. We believe that the evidence included in our submission, and discussed in the Appraisal Committee meeting, consistently shows that the rate of alloSCT after brentuximab vedotin lies in a relatively narrow range between 16.7% and 27.5%. This range is derived from three sources. Firstly, as explained above, the economic model assumes an alloSCT bridging rate of 27.5% for patients treated with brentuximab vedotin - based largely on the response rate seen in the ALCANZA trial that had a rigorous and controlled measurement of ORR. Secondly, the real-world data from the compassionate use program (presented in Section 3.1) shows that of the 19 patients who were treated with brentuximab vedotin, five had either already received an alloSCT or were due to receive an alloSCT. This equates to a rate of 26.3% of patients receiving brentuximab vedotin bridging to transplant. Thirdly, we also note that four of the 24 UK patients enrolled in the ALCANZA trial were bridged to alloSCT (a rate of 16.7%); this rate is likely to be an underestimate given that alloSCT practice has evolved and has become more commonly used in the UK since the time when ALCANZA was conducted.

Takeda regards the comment in Section 3.15 of the ACD *"that only 2 of 128 patients in ALCANZA had a transplant after their first treatment"* as an extremely pessimistic and clinically implausible scenario, not least because these 128 patients include patients with early-stage disease rather than the relevant population, advanced-stage patients, which have been accepted by the Committee as the focus for this appraisal. Furthermore, 128 patients includes patients from both arms of the trial and not only patients treated with brentuximab vedotin; although many patients in the physician's choice arm did cross-over to receive brentuximab vedotin following progression, this was not pre-specified in the protocol and was therefore not consistently available to all patients. Finally, the majority of patients in ALCANZA were not from UK centres but were from other countries where the use of alloSCT is less common than it is in the UK.

Nevertheless, despite our continued belief that the alloSCT rate of 27.5% assumed in our model remains a reasonable base case assumption, we have explored the impact of assuming a lower rate of transplant after brentuximab vedotin. These scenarios are presented assuming 7.1% of patients receiving physician's choice are bridged to alloSCT (as in the base case) and assuming a lower range of 5% of patients receiving physician's choice are bridged to alloSCT (as submitted by Dr Julia Scarisbrick in the committee papers, presented on page 184 of the *ID1190 brentuximab company committee papers ACIC.pdf*) . The results arising from these scenarios and including the PAS are shown in Table 3. Without PAS results are shown in the Appendix.

The results demonstrate that brentuximab vedotin is a cost-effective option across the plausible range of rates of alloSCT after brentuximab vedotin.

Table 3: Scenario analyses exploring the rates of alloSCT (with PAS)

Physician's choice arm	Brentuximab arm	ICER	NMB
7.1% bridged to alloSCT	Revised base case (27.5% bridged to alloSCT)	BV Dominates	£150,415
	26.3% bridged to alloSCT	BV Dominates	£144,816
	16.7% bridged to alloSCT	BV Dominates	£99,198
5% bridged to alloSCT	Revised base case (27.5% bridged to alloSCT)	BV Dominates	£162,112
	26.3% bridged to alloSCT	BV Dominates	£156,514
	16.7% bridged to alloSCT	BV Dominates	£110,895

Abbreviations: alloSCT, allogeneic stem-cell transplantation; BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme.

3.2.2.2 Duration of treatment with brentuximab vedotin (i.e. number of cycles) prior to alloSCT (response to Sections 3.11 and 3.22 of the ACD)

Based on the balance of clinical expert opinion, Takeda had assumed in its modelling that patients who are bridged to alloSCT after treatment with brentuximab vedotin would undergo transplant at week 18 (i.e. after 6-cycles of brentuximab vedotin, which is given once every 3-weeks). However, we acknowledge that, as stated in Section 3.11 of the ACD: "*treatment with brentuximab vedotin may be stopped after only 2 or 3 cycles if the response is sufficient to allow for an allogeneic stem cell transplant."* While we do not disagree with this, based on consultations with transplant specialists involved in the EORTC 2019 alloSCT outcomes data, we understand that such early bridging to alloSCT is an exception rather than the norm. The consultations with transplant specialists who have the most experience to date with using brentuximab vedotin as a bridge to alloSCT have supported our initial assumption of bridging after 6-cycles (18-weeks); we believe this remains a valid base case assumption for modelling and decision-making purposes.

To address the request made by the Committee in Section 3.15 of the ACD, we have nevertheless explored scenarios where bridging to alloSCT takes place after 12-weeks (i.e. 4-cycles), 24-weeks (i.e. 8-cycles) and 30-weeks (i.e. 10-cycles) of treatment with brentuximab vedotin. The results with PAS are shown in Table 4; the impact of this on the cost-effectiveness results is minimal. Without PAS results are shown in the Appendix.

Table 4: Scenario analysis exploring duration of treatment with brentuximab vedotin prior to alloSCT (with PAS)

	ICER	NMB
Revised base case (alloSCT after 18-weeks [6-cycles])	BV Dominates	£150,415
alloSCT after 12-weeks (4-cycles)	BV Dominates	£152,970
alloSCT after 24-weeks (8-cycles)	BV Dominates	£147,905
alloSCT after 30-weeks (10-cycles)	BV Dominates	£145,304

Abbreviations: alloSCT, allogeneic stem-cell transplantation; BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme.

3.2.3 Overall survival for patients not undergoing an alloSCT (response to Section 3.9, 3.17 and 3.18 of the ACD)

In Sections 3.9 and 3.18 the Committee discuss the uncertainty regarding whether or not there is an OS benefit for brentuximab vedotin relative to physician's choice in patients not undergoing an alloSCT, and consider that this should be considered in its decision-making.

As explained in our submission, Takeda recognise that the OS data from the ALCANZA trial are immature, based on a small sample size and are confounded by a high rate of crossover (46%). Directionally there appears to be a trend towards longer OS observed in the brentuximab vedotin arm over physician's choice (median OS [95% CI]: 43.6 months [41.0–NA] vs. 41.6 months [21.1–NA], respectively) or a net difference of 2-months, however this analysis is highly uncertain as illustrated by the single figure difference in the number of observed events (16 and 18 deaths for brentuximab vedotin and physician's choice, respectively). It is important to note that these results are highly confounded and not statistically significant and that there is no robust evidence to support an OS benefit.[5]

In the ERG report and at the first Committee meeting, the ERG presented an illustrative scenario (ERG's scenario analysis 2) which assumed that brentuximab vedotin was associated with a 9.5 month mean gain in OS compared with physician's choice. This scenario was not based on evidence and was intended to consider an extreme upper bound based on the mean difference in PFS as predicted by the base case economic model which includes alloSCT (mean PFS in the brentuximab vedotin arm was 16-months and in the physician's choice arm it was 6.5-months). As acknowledged in Section 3.18 of the ACD, the ERG accepted that this scenario is *"illustrative of the sensitivity of the cost-effectiveness results to the assumption of no overall survival, but cautioned that it may not accurately represent what is seen in clinical practice."* The results of this scenario, excluding alloSCT, were presented at the Committee meeting and exceeded the £30,000/QALY cost-effectiveness threshold.

In response to this illustrative scenario, Takeda have two key points. Firstly, Takeda do not consider a 1:1 relationship between PFS and OS benefit as clinically proven in the CTCL population – based on both the ALCANZA data and feedback from clinical experts who have used brentuximab vedotin in a real-world setting. This was echoed by the clinical experts present at the Committee meeting who stated: *"that they had not seen a proven association between progression-free and overall survival in patients with CTCL for patients who were not able to bridge to transplant"* (Section 3.9 of the ACD).

Secondly, the scenario presented by the ERG ***did not*** reflect the Committee's preferred assumption with regards to the inclusion of alloSCT in the treatment pathway, something that has substantial implications for the cost-effectiveness of brentuximab vedotin. Nevertheless, despite not accepting the clinical plausibility of an OS benefit equal to the PFS benefit, Takeda have presented this scenario in Table 5 to highlight that when including alloSCT in the treatment pathway (as per the Committee's preferred assumptions) even with an extreme upper bound of a 9.5-month OS benefit, brentuximab vedotin remains a very cost-effective option with a NMB of £99,672 (including PAS).

To explore the impact of an illustrative OS benefit further, Table 5 presents the revised base case results when considering: (1) no OS benefit (Takeda's revised base case), (2) a 2-month OS benefit (based on the non-significant difference between the median OS in ALCANZA), (3) a 4-month OS benefit (mid-point between the lower and the upper bound to test sensitivity) and (4) a 9.5-month OS benefit (the illustrative upper bound from the ERG). These results demonstrate that brentuximab vedotin remains a cost-effective treatment option even when considering an extreme upper bound for the assumed OS benefit of brentuximab vedotin relative to physician's choice.

Table 5: Scenario analysis exploring an OS benefit for patients who do not have an alloSCT and are treated with brentuximab vedotin (with PAS)

	ICER	NMB
Revised base case (no OS gain for patients without alloSCT)	BV Dominates	£150,415
2-months OS gain for patients without an alloSCT	BV Dominates	£139,451
4-months OS gain for patients without an alloSCT	BV Dominates	£129,181
9.5-months OS gain for patients without an alloSCT	BV Dominates	£99,672

Abbreviations: alloSCT, allogeneic stem-cell transplantation; BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme.

3.2.4 Modelling the post-progression pathway and associated resource use (response to Section 3.19 and 3.21 of the ACD)

3.2.4.1 Modelling the post-progression pathway

In Section 3.19 of the ACD the Committee state that: *"Neither the company's nor the ERG's approaches to modelling treatment after disease progression are appropriate."* This statement largely arises from the implications of the assumption of equal OS across the brentuximab vedotin and physician's choice arms on the post-progression pathway. As there is a much longer pre-progression period (i.e. PFS) in the brentuximab vedotin arm relative to physician's choice, the assumption of equal survival necessitates a shorter post-progression period for brentuximab vedotin relative to physician's choice.

Takeda agree that the ERG's approach to modelling this pathway is inappropriate based on three key validity issues.

Firstly, the ERG assumed that patients would receive different durations of active therapy dependent on their prior therapy (i.e. whether they had received brentuximab vedotin or physician's choice). This was not considered as clinically valid by the clinical experts at the first Committee meeting. Section 3.19 on page 18 of the ACD states: "*the clinical experts explained that the post-progression treatment pathway would likely be the same for people whose disease relapsed following treatment with brentuximab vedotin (who did not have an allogeneic stem cell transplant) and people whose disease relapsed after having methotrexate or bexarotene".* Furthermore, there is no clinical rationale why the duration of

subsequent active therapy would differ between patients progressing on brentuximab vedotin compared with physician's choice.

Secondly, the ERG assumed that patients would receive active therapy for far longer than the estimate derived from the literature and supported by both the number of lines of therapy from the PROCLIPI registry and clinical experience (i.e. 3.6 - 4.8 years compared with 1.9-years). The post-progression assumptions of the lines and duration of subsequent therapies in Takeda's base case are shown in Table 6 below. As explained in the company's submission, there are limited treatment options available for patients who have progressed; patients quickly exhaust all available active therapies and unfortunately there are not enough systemic treatments available to facilitate treatment for neither a further 3.6 nor 4.8 years. Therefore, we believe our estimate of 1.9-years of subsequent active therapy, which is derived from the literature, is reflective of UK clinical practice. Furthermore, this has been validated by discussions with UK clinical experts and was supported by the clinical experts present at the Committee meeting.

Table 6: Active therapy received by stage IIB+ patients in the PROCLIPI study[3]

Treatment	Proportion of patients receiving therapy	Duration & Dosing	Source
[redacted]	[redacted]	DOT: 4 cycles Gemcitabine 1000mg/m2 IV D1, D8, D15 in q28 days	Proportion: EU PROCLIPI Data DOT: Duvic et al 2006[6]
[redacted]	[redacted]	DOT: 6m	Proportion: EU PROCLIPI Data DOT: Dummer et al 2012[7]
[redacted]	[redacted]	DOT: 3 cycles CHOP IV; D1, D8, D15	Proportion: EU PROCLIPI Data DOT: Clinical consultation
[redacted]	[redacted]	DOT: low dose 12Gy, 8 fractions over 2 weeks (cost split across DOR) DOR: 11m	Proportion: Clinical input DOT: Morris et al 2017[8]

*Other monochemotherapy includes doxorubicin (all formulations) and chlorambucil.
Abbreviations: DOT, duration of therapy; DOR, duration of response; EU PROCLIPI, European PROCLIPI (Prospective Cutaneous Lymphoma International Prognostic Index) Study.

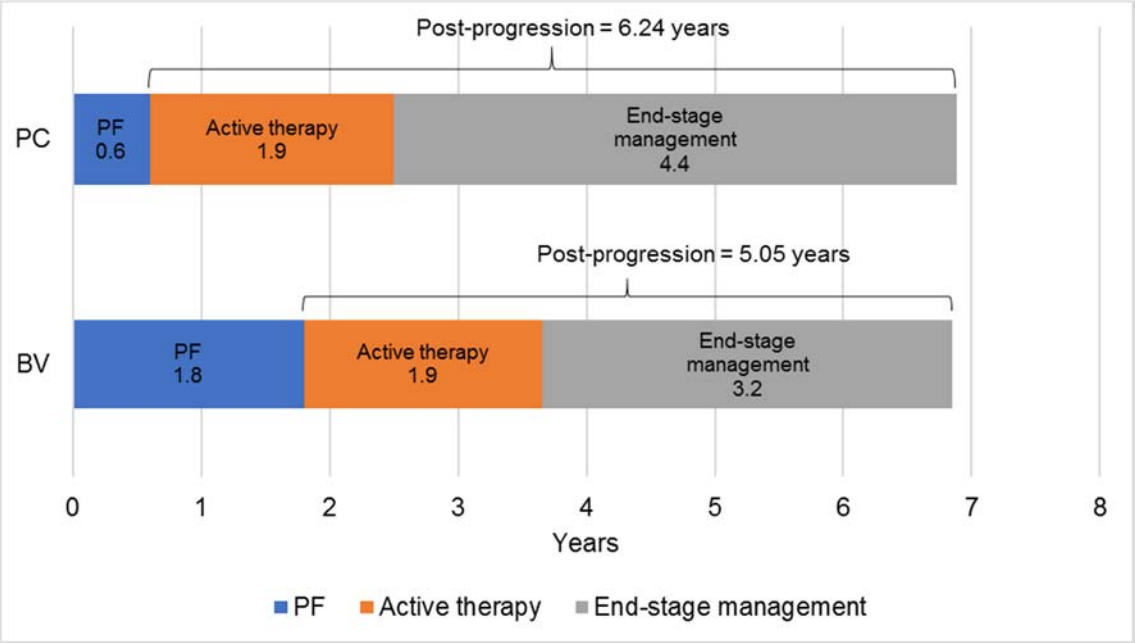
Thirdly, the ERG considered best supportive care (BSC) as a subsequent therapy, a state where patients are not receiving active systemic anti-cancer therapy (i.e. no underlying treatment of their lymphoma) but do not require support for their symptoms and notably wound care; this is not relevant to the post-progression pathway in patients with advanced CTCL as stated by the clinical experts at the first Committee meeting and reflected in the ACD: *"the clinical experts noted that best supportive care does not exist for CTCL because current treatments are unable to sustain a response"*.

One very significant implication of the ERG's assumptions is that patients only received end-stage management for 6-months in both the brentuximab vedotin and physician's choice arm. This is simply not reflective of UK clinical practice and it is not clinically plausible; we

note that the Committee have heard from clinical experts that this resource use intensive state can last for several years.

In Takeda's base case, patients received active therapies in the post-progression health state for 1.9-years followed by end-stage management for 3.2-years in the brentuximab vedotin arm. This is compared with 1.9-years of active therapy followed by 4.4-years of end-stage management in the post-progression health state in the physician's choice arm. The post-progression pathway in the company's base case is presented in Figure 4.

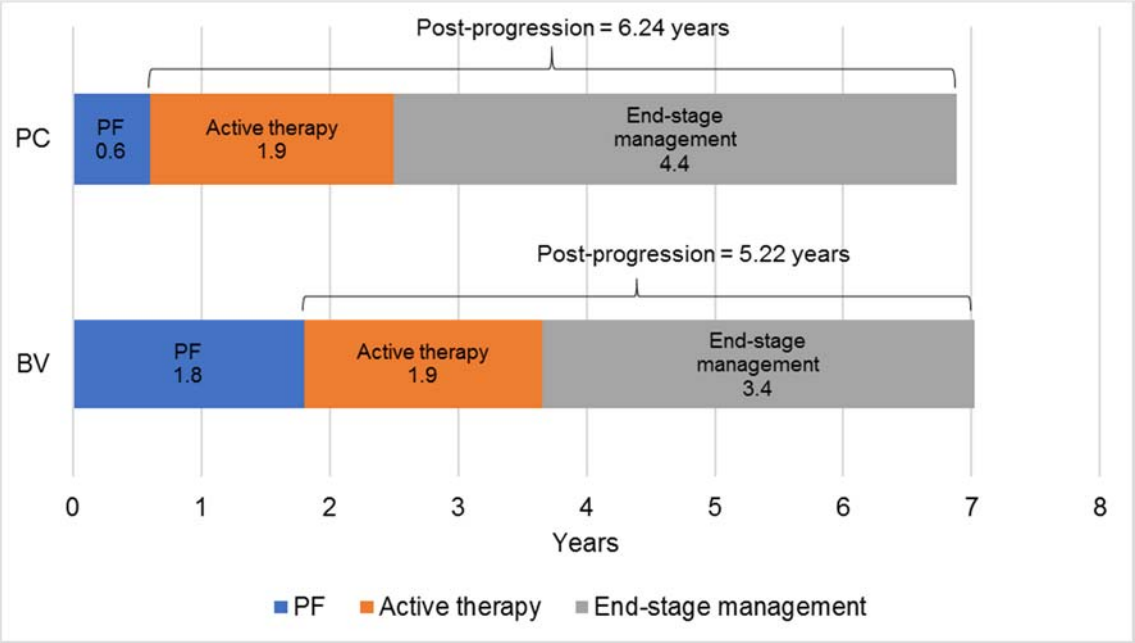
Figure 4: Post-progression pathway - base case (no OS benefit from brentuximab vedotin)



Abbreviations: BV, brentuximab vedotin; PC, physician's choice; PF, progression-free

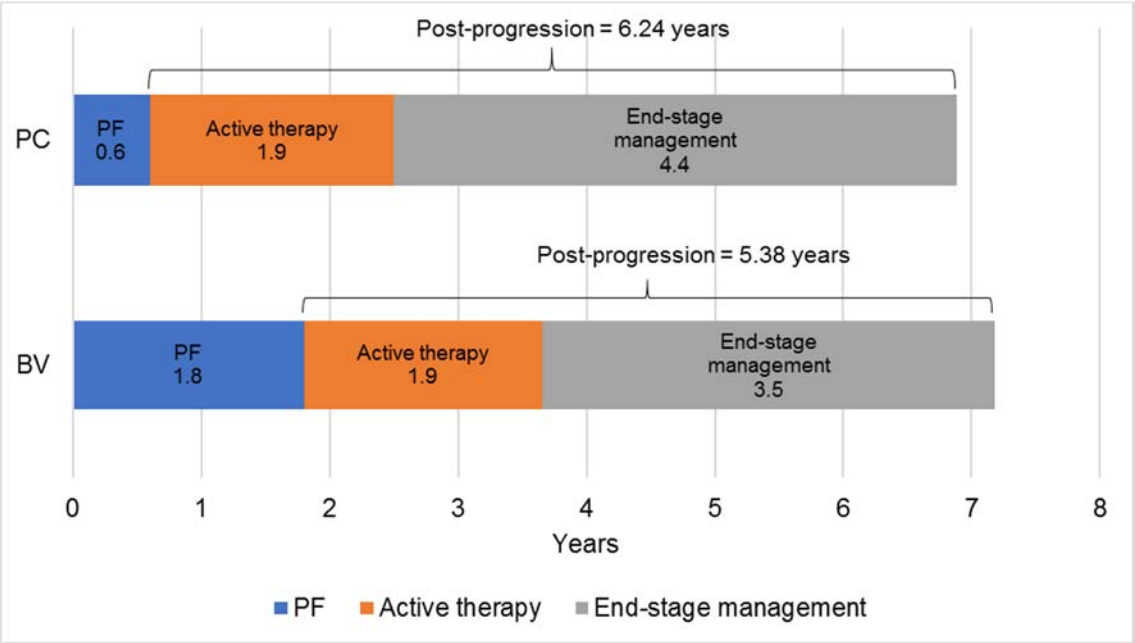
In Section 3.2.3 we present the implications of an illustrative OS benefit on the cost-effectiveness results. Here we present the implications of these scenarios on the post-progression pathway. To recap, three scenarios were considered: a 2-month OS benefit (based on the non-significant difference between the observed median OS in ALCANZA), a 4-month OS benefit (mid-point), and a 9.5-month OS benefit (the upper bound based on ERG's illustrative scenario 2) – see Section 3.2.3 for more details. Figure 5, Figure 6 and Figure 7 present the post-progression pathway associated with each of these scenarios.

Figure 5: Post-progression pathway: Illustrative assumption of 2-month OS benefit for brentuximab vedotin



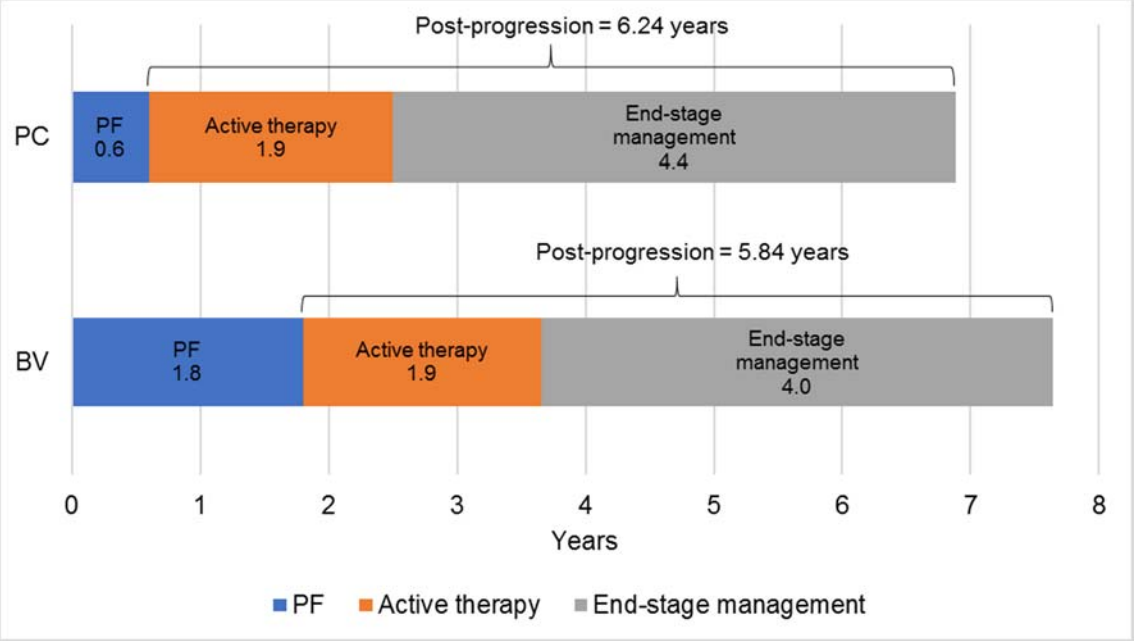
Abbreviations: BV, brentuximab vedotin; PC, physician's choice; PF, progression-free

Figure 6: Post-progression pathway: Illustrative assumption of 4-month OS benefit for brentuximab vedotin



Abbreviations: BV, brentuximab vedotin; PC, physician's choice; PF, progression-free

Figure 7: Post-progression pathway: Illustrative assumption of 9.5-month OS benefit for brentuximab vedotin



Abbreviations: BV, brentuximab vedotin; PC, physician's choice; PF, progression-free

As demonstrated, increasing the OS benefit associated with brentuximab vedotin increases the length of the post-progression pathway and thus the duration of end-stage management in the brentuximab vedotin arm. In Section 3.2.3, it is shown that brentuximab vedotin remains a very cost-effective option across these scenarios – including when applying the extreme upper bound of a 9.5-months OS benefit (ERG's illustrative scenario 2 which assumes an implausible 1:1 ratio between PFS and OS) where the duration of end-stage management is similar between the brentuximab vedotin and physician's choice arms. Therefore, even when the post-progression pathways are similar for brentuximab vedotin and physician's choice, brentuximab vedotin remains a very cost-effective option.

3.2.4.2 Resource use assumptions in the model for end-stage care (response to Section 3.21 of the ACD)

In Section 3.21 of the ACD the Committee states that resource costs of end-stage management and administration costs of oral chemotherapy as presented in Takeda's original submission "*may overestimate resource unit costs."* In the revised base case presented in this response, Takeda has acknowledged the ERG's and the Committee's comments and removed the costs of administering oral chemotherapy from the assumptions – all results presented in this document reflect this.

Due to the scarcity of evidence in the literature associated with resource use relevant to patients with advanced-stage CTCL, particularly for end-stage management, Takeda conducted semi-structured interviews with clinical experts who are involved in end-stage management from all seven supra-regional centres in England and the main centre in Wales. The interview guide was developed based on qualitative literature on care for patients with CTCL from Beynon et al (2013) and Orwloska (2018) and covered the following

main areas of care: pain, anxiety/depression, itch relief, and skin care and wound management.[9, 10]

The data collected from the medical experts were collated and the average for each measurement was taken to inform the economic model. The greatest burden was associated with dressings and wound care, which necessitated frequent and lengthy nurse visits (up to two hours) and constant therapies to control infection, pain and intractable pruritus. Takeda acknowledges that the amount of resource use per patient is a significant strain on the NHS but notes that because advanced CTCL is a rare condition and very few patients require this type of support, the overall burden on the NHS may not be immediately noticed, particularly as care is delivered both at supra-centres and by local support teams. This was supported by the clinical experts during the meeting as presented in the ACD. Furthermore, Takeda agrees with the ACD and clinical expert input that some patients' wounds are managed by themselves or family members; 50% of localised wound management is provided by families or patients themselves in the original Takeda assumptions in our health economic model, supportive of the results from the semi-structured interviews.

While Takeda understands the requirement to scenario test the end-stage resource use assumptions, as done by the ERG, we emphasise that the reduction in resources applied by the ERG was not based on evidence and it is unclear how these inputs were selected. We acknowledge that the assumptions we have presented in our base case are derived from the average of clinician responses. Therefore, we have provided scenarios considering the lower range of resource use from the clinical experts. The assumptions from our base case, the ERG assumptions and the plausible lower-range resource assumptions are presented in Table 7 below; the main differences have been highlighted.

Table 7: Resource use assumptions

	Company base case		ERG scenario 3		Lower-range	
	% Patients	Frequency per week	% Patients	Frequency per week	% Patients	Frequency per week
End-stage care						
Hospital outpatient						
Clinical nurse specialist	100	2.25	100	**0.25**	100	**1.63**
Dermatologist visit	100	0.17	**50**	0.17	**100**	0.17
Psychologist	50	0.25	**5**	0.25	**5**	0.25
Home visit						
District nurse visit	100	2.63	100	**0.25**	100	**2.63**
Macmillan nurse/social services	100	1	100	**0.25**	100	**0.5**
Palliative care support team	100	2	100	**0.25**	100	**0.5**
Dressings						
Meptiel dressings	25	7 (x3)	**12.5**	7 (x3)	**12.5**	7 (x3)
Mepilex large sheet dressings	25	7 (x2)	**12.5**	7 (x2)	**12.5**	7 (x2)
Mepilex heels	25	7 (x2)	**12.5**	7 (x2)	**12.5**	7 (x2)
Elasticated garments	25	1 (x3)	**12.5**	1 (x3)	**12.5**	1 (x3)
Medium Allevyn	75	7	**37.5**	7	**75**	7
Pre-progression / Post -progression						
District nurse visit	100	2.6	100	**0.25**	100	**0.25**
Dressings - localised coverage	60	7 (x7)	**37.5**	7 (x7)	**37.5**	7 (x7)

Abbreviations: ERG, evidence review group.

The following resource categories have been modified in the lower-range resource scenario:

- Proportion and frequency of dressing changes in the pre-progression and post-progression but on active therapy states: As patients are receiving systemic treatments to control the underlying lymphoma, it is plausible that less wound management would be needed. Therefore, the ERG's assumption of 37.5% requiring dressing management and less frequent district nurse visits is applied.

- Frequency and proportion receiving psychology care: Takeda acknowledge that not all patients may have regular access to a psychologist. Therefore, the lower assumption of 5% as suggested by the ERG is applied.

- Proportion of patients requiring hospital outpatient visits for wound management (end-stage): The range of inpatient support from the semi-structured interviews was 10%-30%. However, the most frequently cited figure was 25% which is why it was selected in Takeda's base case. However, the ERG's proportion of 12.5% is within the range of answers provided. Therefore, this is applied in the lower-range resource scenario. Please note: based on clinical feedback, patients receiving hospital outpatient visits will receive all the Mepitel, Mepilex and Elasticised garments dressings.

- Frequency of Clinical Nurse Specialist (CNS) visits (end-stage): The frequency of CNS visits is directly related to the proportion of patients who require in-hospital dressing changes. Therefore, reducing the assumption to 12.5% has also reduced the frequency of CNS appointments per week. The assumption is based on 12.5% patients requiring in-patient wound management every other day (due to heightened infection risk) or 2.63 times/week and the remaining 75% requiring visits in person or via telephone every 2 weeks for a regular check-up. Overall, the lower-range scenario assumes 1.63 CNS visits per week.

- Frequency of Macmillan nurse/ social services and palliative care support team visits: The ERG's assumption of visits once per month is not supported by the results of the semi-structured interviews. We have applied an assumption of fortnightly visits in the lower-range resource assumption scenario based on the lowest reported frequency of visits from these support teams.

The remaining resource categories have not been modified in the lower-range resource scenario as they are not supported by any of the specialists' responses and are not deemed to be reflective of UK clinical practice:

- Proportion of patient visits with a dermatologist (end-stage): During the end-stages of CTCL, patients are predominantly managed by dermatologists and CNS (i.e. oncologists and haematologists are less likely to be involved in care at this stage) and all patients will see a prescribing clinician, mainly a dermatologist, for regular appointments until they succumb to their condition. This is supported by every semi-structured interview and therefore original 100% assumption is maintained.

- Proportion of patients with localised dressings (home based end-stage): The ERG's assumption of halving the proportion of patients who receive dressings at home from

75% to 37.5% is not plausible; this implies that 37.5% of patients with advanced CTCL at the end-stages of their disease do not require any wound care management which is not realistic given the nature of the condition. Every response received by clinical experts affirmed that all patients will require wound management. Therefore, the lower-range resources scenario keeps the original 75% assumption.

- Frequency of district nurse visits (end-stage): The frequency of district nurse visits is directly driven by the proportion of patients requiring localised dressing support. The ERG's assumptions of decreasing the frequency of district nurse visits to 0.25 per week or once per month is implausible as patients who are at high risk for infections, due to open wounds, require very frequent dressing changes (daily or every other day). The assumption of 2.63 visits per week is equivalent to dressing changes every other day, which is arguably on the lower range of what was reported by experts. Notably, the Takeda assumption is based on an hourly visit meanwhile literature and clinical experts cite that these visits can take two hours or longer depending on the extent of the wounds.

The cost-effectiveness results of the lower-range resource assumptions are presented below. Brentuximab vedotin remains dominant relative to physician's choice when the plausible lower-range resource assumptions are applied. However, the NMB decreases to £104,658 from the revised base case NMB of £150,415.

Table 8: Scenario analysis exploring plausible lower-range resource assumptions (with PAS)

	ICER	NMB
Revised base case (resource use assumptions as per the company's original base case)	BV Dominates	£150,415
Resource use assumptions from a combination of the company's base case and the ERG's analyses	BV Dominates	£104,658

Abbreviations: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme.

3.2.5 Discussion on Cancer Drugs Fund: *"Brentuximab vedotin does not meet the criteria to be considered for inclusion in the Cancer Drugs Fund"* (response to Section 3.30 of the ACD)

Takeda note the Committee comment in the ACD that "*the company had not made a case for brentuximab vedotin to be included in the Cancer Drugs Fund*" in the original submission. The Committee also state "*it was unclear if brentuximab vedotin had the plausible potential to be cost-effective*". Takeda believe that the revised base case and scenario analyses presented in this document demonstrate that brentuximab vedotin is cost-effective at NICE's conventional cost-effectiveness threshold and hence should be recommended for routine use on the NHS. However, Takeda would be willing to consider the CDF for brentuximab vedotin for this indication if that is the Committee's recommendation.

3.3 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

In conclusion, Takeda disagrees that the Committee's provisional negative recommendation for brentuximab vedotin is sound and a suitable basis for guidance to the NHS (see Section 1.1 and Section 3.29 of the ACD). However, Takeda appreciate that, prior to receiving this response document, the Committee had not seen the results based on their preferred assumptions. Takeda consider that these preferred assumptions provide a reasonable base case that can be used in the decision-making process. These results are presented in Section 3.2 of this document and result in brentuximab vedotin dominating physician's choice with an NMB of £150,415.

Takeda have acknowledged the uncertainties raised during the first Committee meeting and in the ACD, and we have attempted to clarify and address these fully within this ACD response. Where uncertainty remains, we have provided scenarios varying key parameters between extreme lower and upper bounds– brentuximab vedotin is shown to dominate the comparator in all these scenarios and remains cost-effective even at these extreme assumptions.

Taking all factors into account, Takeda is optimistic that the information provided in this response document can now allow the Committee to conclude that the range of plausible ICERs for brentuximab vedotin fall within NICE's threshold for cost-effectiveness, thereby allowing the Committee to revise their draft negative recommendation and issue a final positive recommendation for the treatment of advanced CD30+ CTCL with brentuximab vedotin. This would enable patients with advanced stage CTCL and the NHS to benefit from having access to this very important and potentially transformative therapy.

Takeda remains committed to reaching a positive outcome for this appraisal and we are hopeful that NICE will continue to work with us to demonstrate that the plausible ICER for brentuximab vedotin represents a cost-effective use of NHS resources.

4. References

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Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are disappointed with the decision not to recommend this treatment. CTCL is a rare condition, therefore uncertainties in the data will always be present. As Sir Andrew Dillon, Chief Executive of NICE stated: "NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair." To address this unfairness, NICE set up the Highly Specialised Technologies (HST) programme. However, this drug has been chosen to be appraised through the STA programme instead, leading to the inevitable uncertainties in the data. If the committee feels there is still too much uncertainty in the data to approve the drug for baseline commissioning, we urge the committee to allow the treatment to be accessed via the CDF, allowing more time for data to be collected.
2	We would like to highlight the data showing that this treatment can extend the disease-free period from 3 to 16 months, giving patients more time to plan for a transplant or simply much more times without the frustrating symptoms patients experience. The ability of a treatment to bring about a remission or response was important to 70% of non-Hodgkin lymphoma patients we surveyed in 2017, second only to life extending treatments.
3	The potential to be a bridge to a stem cell transplant is important for patients. In our 2017 patient survey, 92% of non-Hodgkin lymphoma patients would consider it a positive if a new treatment could bridge to a transplant. It is important to note that patients are also now able to undergo reduced intensity transplants, meaning that even more patients could be potentially cured.
4	Whilst we appreciate that EQ5D did not show improvement in quality of life issues, we feel this model of quality of life was not sensitive enough to measure the challenges faced by CTCL patients. We feel there are still significant quality of life issues that could be addressed by this treatment and therefore might not have been captured by the models. For example, Beynon et al. (2015) shows that patients may have to sleep apart from their significant other due to the extreme itchiness they experience. This extended disease-free period that this treatment provides, as mentioned above, would give patients relief from these distressing symptoms.
5	We would like to highlight that the symptoms of CTCL that patients experience can limit their everyday activities, as recognised at the committee meeting. A diagnosis of any cancer has an impact not only on those diagnosed, but on their friends and family as well; this could be an emotional, practical or financial impact. The ACD document suggests that patient's family are likely to take on caring duties, meaning the savings to the NHS were overestimated. Whilst many families are likely to take on this responsibility, they should not be expected to do so, given the difficult situation they may already be in. The family are often in need of support themselves, perhaps increasing costs to the NHS in other capacities. Beynon et al. (2014) highlights how the needs of patients are not well quantified, and the needs of those providing care is even less so, yet it could be significant given the circumstances.
6	We would like to note that once patients have reached this stage in their illness, there a few other treatment options available to them. Therefore, patients are need of any treatment that will reduce the significant symptom burden that would come from being untreated; such as increased infection risk, itchiness and skin lesions.

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is

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submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lymphoma Action
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation does not give enough consideration to the impact of CTCL on patients' lives. Psychological and social wellbeing are significantly affected, particularly at more advanced stages. Patients can suffer severe discomfort, itching, pain and fatigue with subsequent effects on employment, leisure activities, relationships and day-to-day living. In addition, the psychological impact of the condition is significant: patients report feelings of uncertainty, frustration, embarrassment, helplessness, confusion, worry, anxiety and depression. Current treatment options also have an impact on quality of life: skin care regimes and wound dressing in later stages are time-consuming for both the patient and their family or carer. There is a clear need for an effective, durable treatment that reduces symptoms.
2	We are concerned that this recommendation understates the effectiveness of brentuximab vedotin. The report acknowledges that there is an unmet need for effective treatment that extends time in disease remission. However, the superior clinical efficacy of brentuximab vedotin to comparators, evidenced by a significantly higher response rate and significantly longer progression-free survival, does not seem to have been given sufficient importance. Existing treatments do not, in general, produce durable responses and patients are keen for treatment options that give them longer disease control.
3	We are concerned that this recommendation does not give sufficient consideration to symptom control. The ALCANZA trial showed that patients treated with brentuximab vedotin had significantly greater improvements in symptoms than those treated with comparators. Although this did not reach statistical significance in the subset of patients with advanced disease, improvements in symptom scores were nevertheless clinically meaningful and were consistently greater than those in patients treated with comparator agents. Symptoms have a considerable impact on the day-to-day lives of patients and even small improvements can be beneficial.
4	We are concerned that too much emphasis is placed on overall survival data. The recommendation acknowledges that current treatment pathways are palliative and that treatment aims to relieve symptoms, control local disease and improve quality of life. In this context, overall survival is of little relevance to patients, who are more concerned with durable symptom control. In addition, overall survival was not a prespecified endpoint of the ALCANZA trial and it is therefore not surprising that the data is limited. Nevertheless, brentuximab vedotin did result in clinically meaningful improvements in overall survival.
5	We are concerned that the potential for brentuximab vedotin to act as a bridge to allogeneic stem cell transplant has been underestimated. Given that the rate-limiting step for allogeneic stem cell transplant is usually poor response rate to current bridging agents, it would seem reasonable to assume that the significantly higher response rates to brentuximab vedotin versus comparators would also result in higher rates of allogeneic stem cell transplant, despite the limited data available at present. Allogeneic stem cell transplant is often the only hope of a 'cure' for patients and it is vital to keep this option available whenever possible.
6	We feel this recommendation does not fully consider all the financial implications of current treatment pathways for CTCL, including the sometimes considerable cost of dressings and the cost of outpatient vs inpatient administration as well as the financial implications of time off work (both for symptoms and medical appointments), cost of dressings, the cost to the patient of additional laundry. This can have a significant impact on the patient and family or carers as well as NHS budgets.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Pathologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I would agree with the summaries regarding the improvement in symptoms for those patients taking BV as opposed to PC (physicians' choice, as measured by the Skindex tool) albeit not statistically significant.
2	The data regarding OS is confounded by the short time of follow-up/ cross-over from PC to brentuximab. There is an improvement in PFS (16.7 months to 3.5 months)
3	I would agree that the introduction of brentuximab could lead to more patients becoming eligible for allogeneic transplant, due to the improved response rates compared to current standard therapies.
4	Brentuximab is able to reduce the tumour burden on the skin in nearly all patients (46/48 in Alcanza) and able to reduce this by >50% for at least 4 months in 56%. This leads to a reduction in number of dressings and allows a better quality of life. The improvement lasts with a median response duration of 15.1 months. There are no equivalent drugs available with this efficacy for CD30 positive CTCL. This response duration allows time for eligible patients to have allogeneic bone marrow transplant which is there only chance of cure. Of the 15 patients I have personally treated with brentuximab 5 have received allogeneic BMT. Brentuximab is listed as second line treatment option for our UK, European (EORTC) and NCCN (US) guidelines.
5	I would agree with the committee's interpretation of the clinical effectiveness with brentuximab showing a marked improvement in ORR4, PFS and symptom burden as shown in the ALCANZA trial. In particular, given that the application for NICE approval is for patients with advanced disease, I would highlight the subgroup analysis showing an improvement in RR of 69.4% vs 17.4% in this group of patients, that also translated into a significantly higher ORR4 59.2 vs 8.7, PFS and time-to next treatment.
6	I agree with the interpretation regarding toxicity/ safety of brentuximab both from the data submitted and also personal experience.
7	a lot of uncertainty in terms of modelling the use of brentuximab compared to current therapies, both in terms of costs saved due to patients having responsive disease that lasts longer, the number of patients who will go on to allogeneic transplant and finally whether there is a OS benefit with brentuximab.
8	I would support the use of brentuximab on the CDF with a view to reviewing the data in the future.
9	the cost of brentuximab must be offset by number of work days saved by return to work, less nursing care, less dressings and ultimately a potential cure if the patients gets transpalnted
10	In my opinion brentuximab must be made available a second line therapy for this rare subset (CD30+, in only 10-20%) of a rare disease (CTCL incidence 7 per million). Brentuximab is already available in other European countries and US and being used to

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

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	manage these patients. Brentuximab is part of the UK CTCL guidelines. Denying brentuximab for CD30+CTCL patients would severely restrict our ability to adequately treat these patients and result in an inferior service in these patients compared to other countries.

Insert extra rows as needed

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NHS England submission in February 2019 for the 2nd meeting of the NICE appraisal of brentuximab in advanced CD30+ cutaneous T cell lymphoma after at least 1 prior systemic therapy

1. Clinical advice to NHS England is that though there are 7-10 supra-regional centres for the management of cutaneous T cell lymphomas (CTCLs), there are about 7-10 regional centres which also care for CTCL patients. The regional centres may refer patients to the supra-regional centres for the management of the more complicated patients and for potential inclusion in clinical trials. Patients who are less fit may be largely managed at even more local level than the regional centres. Many patients are therefore managed more locally than just in the supra-regional centres.
2. NHS England notes that the marketing authorisation (MA) for brentuximab vedotin (BV) is as a treatment option for those patients with CD30+ CTCL who have already received at least 1 prior systemic therapy. The MA also specifies a maximum of 16 cycles of therapy with BV per patient. If BV is recommended by NICE, NHS England would commission the use of BV in line with the MA unless recommended to do otherwise by NICE.
3. NHS England notes that the patients in the BV RCT in CTCL had a median age of 60 years and 95% were of ECOG performance status of 0 or 1. Although generally heavily pre-treated (chemotherapy 71%, immunotherapy 43% and bexarotene 38%), the population in the study was a very fit one. The direct translation of the benefits achieved in this study would have to be to an equally fit population.
4. The durable overall response rate was much higher in the BV arm than with standard therapy and this benefit is important for patients given their often distressing cutaneous infiltration with TCL. The difference in median progression free survival (PFS) is noteworthy (16.7 mo vs 3.5 mo).
5. NHS England notes that the median duration of follow-up of 34 months is not very long in a disease in which patients can live for much longer. There is no difference in median durations of survival (about 43 mo in both arms) but this is not surprising given that cross over to BV occurred in 46% of patients in the standard therapy arm, the size of the study was modest and follow up was relatively short.
6. A tiny numbers of patients in the RCT subsequently had an allogeneic stem cell transplant, 5 in the BV arm and 2 in the standard care arm. NHS England notes these very small numbers and observes that 3 of the 5 patients who had an allogeneic transplant after BV required further therapy in between BV and the transplant. Thus only in 2 of the 5 patients treated with BV did patients proceed straight from BV therapy to allogeneic therapy.
7. Clinical advice to NHS England is that only a small number of patients with advanced CTCL currently receive allogeneic transplantation as part of their treatment although these numbers are beginning to increase. This advice also indicates that a 20% rate of allogeneic transplantation after BV is high and the likely figure in England is significantly lower. Allogeneic transplantation is the only curative treatment for advanced CTCL and hence if there is a significant rate of allogeneic transplantation then it would be expected to make a significant difference to the mean overall survival gain achieved with BV therapy.
8. CTCL is a distressing disease which significantly reduces the life expectancy of patients. It would therefore be most unusual in a non-curative setting and in a disease which causes the death of most patients with advanced CTCL for there to be a large difference in PFS (a

median difference of 13.2 months) with BV which does have an impact on survival. NHS England cannot recall an example in which a very substantial gain in PFS has not been modelled into a gain in overall survival. What that gain in survival is likely to be is very difficult to estimate but NHS England would wish scenario analyses to be presented to NICE with various modelled gains in survival from zero gain (ie a pessimistic estimate) up to a gain assuming a 1:1 relationship between PFS and overall survival (ie an optimistic estimate). If Takeda believes there will be a high allogeneic transplantation rate then the subsequent gain in overall survival would be in addition to that modelled on varying relationships between PFS and overall survival.

9. Since NHS England considers that it is highly likely that there will be a gain in mean overall survival, both from the direct effect of BV and from allogeneic transplantation, then a model which assumes no gain in overall survival is wrong. It is counter-intuitive to the clinical advice received by NS England for the economic model to assume a reduced time in end stage care in those patients treated with BV.
10. NHS England notes with surprise that there was no difference in quality of life between the two arms in the RCT given the type of (distressing) disease and the high response rate seen in the BV arm. This may reflect the sensitivity of the tools used for measuring quality of life in a disease such as CTCL.
11. Clinical advice to NHS England was surprised at the amount of care assumed by Takeda in the end stage care state. The number of weekly visits to clinical nurse specialists and from district nurses, Macmillan nurses and palliative care teams for <u>all</u> patients was extremely high. Whilst NHS England acknowledges that some patients have very difficult and distressing cutaneous disease, expert advice to NHS England is that such intense care and support would apply to about 25% of patients. The resource use applied by the ERG is therefore much more realistic. Clinical advice to NHS England observes that whilst a much higher proportion of CTCL patients have psychological morbidity that requires specialist input than seen in other types of lymphoma, this proportion is likely to be 10-20% rather than the 50% figure used by the company.
12. NHS England notes that the only evidence submitted to NICE was for continuous use of BV and that the MA for BV stipulates a maximum of 16 cycles per patient. If BV is recommended by NICE in CTCL in accordance with the MA, then NHS England would commission continuous use up to a maximum of 16 cycles. It would not commission the use of BV with any elective treatment breaks.

Prof Peter Clark

Chair NHS England Chemotherapy Clinical Reference Group and CDF National Clinical Lead for the Cancer Drug Fund

February 2019

We would like to submit the following comments on the NICE appraisal of Brentuximab vedotin for CD30+ cutaneous T-cell lymphomas (ID1190) on behalf of the UK Cutaneous Lymphoma Group (UKCLG). We have recently published our updated UK guidelines for the treatment of primary cutaneous lymphomas (Gilson et al Br J Dermatol 2018: DOI 10.1111/bjd.17240). These represent evidence based guidelines and the consensus views of UK specialists treating these rare malignancies from different specialities including clinical oncology, dermatology, haemato-oncology and transplantation in NICE approved supra-regional centres for CTCL.

There are only three EMA approved treatment options for CTCL namely Bexarotene, alpha interferon and Brentuximab and, whilst the evidence base is weak for other non-approved treatment options, recent phase II trials and a large randomised phase III study (Prince et al 2017) with appropriate endpoints has provided compelling clinical evidence for the use of Brentuxumab Vedotin in advanced stages of CD30+ CTCL in view of the significant improvement in ORR4 and PFS compared to physicians choice of Methotrexate or Bexarotene. This has led to our conclusion that Brentuximab should be considered as a second line therapy for CD30+ CTCL patients with stage IIB-IV including those patients with Sezary syndrome (level of evidence I+/strength of recommendation B).

We also recommend that reduced intensity HSCT should be considered for selected groups of patients with advanced CTCL to consolidate treatment responses based on emerging evidence for long term clinical remission in a majority of patients (strength of recommendation B). Of course the availability of a transplant for patients depends on multiple factors but an excellent treatment response prior to transplantation is critical to eligibility and a major determinant of transplant outcome.

We note that the committee has questioned the evidence for an improvement in QoL (3.12 & 3.26) but we would like to draw attention to emerging data (submitted for publication) showing a significant improvement in the symptom domain of Skindex-29 for Brentuximab compared to physicians choice, whilst we acknowledge that there is no significant difference for the functional and emotional domains of Skindex-29 between the treatment arms.

We note that the committee agrees with the clinical evidence but has not recommended Brentuximab for CD30+ CTCL after one systemic therapy based on cost-effectiveness modelling. Advanced stages of CTCL are rare malignancies causing severe morbidity and high mortality rates. Until recently there have been no approved effective treatment options for advanced stages of CTCL but based on recent large phase III randomised studies, we now have the evidence to support the use of Brentuxumab Vedotin for CD30+ CTCL. This is reflected in the significant increase in use of Brentuximab supported by a compassionate use program since completion of the trial and the increased numbers of patients who are becoming eligible for transplantation based on the quality of clinical response to Brentuximab which we have not been able to achieve with other chemotherapy options.

We would strongly recommend that the committee re-evaluate their decision and also clarify why, as CTCL is a rare malignancy, the treatment could not be considered eligible for the CDF.

On behalf of the UKCLG

[redacted]

[redacted]

Name	Julia Scarisbrick
Role	NHS Professional
Other role	Consultant Dermatologist
Organisation	NHS
Location	England
Conflict	None
Notes	I pride myself in providing an excellent service in Birmingham for CTCL which is internationally renowned. As a consultant managing a large supraregional centre for CTCL I would not be able to provide competitive care for my patients with refractory CD30+ disease if Brentuximab V is denied my patients.

Comments on the ACD: Since having brentuximab available on a compassionate basis from the company I have treated 4 patients, results continue to be far superior to alternatives. Below are some of patients under my cares quotes.

MW (COMPASSIONATE USE)

62 year old Male with Stage IV Mycosis fungoides, receiving BV on compassionate basis as 6th line of systemic therapy. Cycle 3 completed.

Prior to starting Brentuximab I was having 24 dressings a day (which were being changed by my wife). I was depressed and off my food and struggled with every aspect of daily living. Since starting Brentuximab I am now down to only 4 dressings a day. I have put weight back on, my personality has changed my wife says I am now myself!

LS (COMPASSIONATE USE)

51 year old female with stage IIB MF also has systemic follicular lymphoma stage IV. Receiving BV as 4th line of therapy for MF.

I have had 2 cycles of Brentuximab so far. It's AMAZING! I had about 80 patches on my skin some as big as 5 inches. They wept and made me extremely unhappy. They have all dried up and are healing and fading. I noticed a difference after one cycle.

LW (ALCANZA)

30 year old female stage IIB Mycosis fungoides received BV 2nd line in Alcanza trial. Had Allo BMT immediately after BV in 2015 and remains in complete response. Works full time and has 6 year old son.

I had immediate relief after starting Brentuximab. The itching stopped after the 1st infusion. By the time I had finished all of the cycles my lesions had all disappeared.

It gave me back my confidence and life. Prior to starting the treatment, I went to Jamaica on a family holiday; whilst out there, someone asked me if I knew I had ring worm. It was devastating and made me so self-conscious. Brentuximab gave me my life back.

I went on the have a transplant and am now living my life to the full Thank you!

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Haematologist
Organisation	Not provided
Location	England
Conflict	None
Notes	Travel and speaker fees Takeda

Comments on the ACD:

I am a haematologist who looks after patients with CTCL which is resistant to skin directed therapy. When patients are resistant to systemic chemotherapy it is not possible to palliate symptoms. The pain and discomfort from advanced CTCL is significant and as well as pain it often affects mobility. Unlike systemic lymphoma, which we can palliate with oral chemotherapy or steroids, CTCL is often resistant to this if one line of systemic therapy has failed. It is therefore very difficult to achieve any quality of life for my patients, requiring high doses of analgesia often as an inpatient in hospital.

There are currently limited options for patients with CTCL who have failed systemic chemotherapy and again unlike systemic lymphoma where we can give alternative regimens whether of curative or palliative intent this is not true for CTCL. I feel strongly that having brentuximab available, it is of use both in terms of clinical effectiveness as a bridge to allogeneic stem cell transplant or as a palliative measure to obtain good quality of life for patients and keep them out of hospital.

Having used brentuximab on compassionate use basis I have allowed 2 patients to have more than a year of good quality of life as an outpatient. Prior to this they were requiring inpatient care with daily skin dressing and high doses of analgesia. I think that the high cost of end of life care for these patients should be taken into account when considering the cost effectiveness.

Name	[redacted]
Role	NHS Professional
Other role	None
Organisation	T-cell lymphoma working group
Location	England
Conflict	None
Notes	I have received honoraria (speaker fees and advisory work) from Takeda.

Comments on the ACD:

Many thanks for sending this out for public consultation. I was very disappointed to see the provisional 'no' from NICE however. My main concerns are the following:

- Cutaneous T-cell lymphoma, especially when advanced, is a truly horrible disease: it is extremely itchy and disfiguring. Current QoL scoring systems do not capture these aspects well and I feel the trial data has underestimated the QoL benefit from inducing a durable remission. I realise NICE do have patient representation which I

applaud but I think their voice should be listened to perhaps more so than for other appraisals

- I would wholeheartedly agree with the clinical experts you had, saying that allogeneic stem cell transplantation is now considered for all patients with relapsed disease. Brentuximab acts as a far superior bridge than current options. My understanding is that a significant number of curative transplants would bring down the cost per QALY of BV and I think it necessary that this is included in the economic modelling. As with other lymphomas, the UK transplants more patients with CTCL than other countries, so it is important to factor this in.

I fully appreciate the uncertainties in the literature. As for brentuximab in Hodgkin, I would have thought the way to try to resolve these is to allow BV use via the cancer drugs fund and then coordinate a national data collection exercise to evaluate how many people are actually bridged to a stem cell transplant. CDF and compassionate use patients could be included. This approached worked very well with Hodgkin - with an excellent engagement from UK clinicians supplying data. To simply not fund this drug now would be a huge shame to a very needy patient group who have a lymphoma with a high unmet need.

Many thanks for considering this response.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Haematologist, Lead Clinician Lymphoma
Organisation	[redacted]
Location	England
Conflict	None
Notes	None

Comments on the ACD:

1. The great majority (> 90%) of allogeneic transplants for CTCL are carried out between 2 centres: [redacted]. We therefore have the most experience of transplantation for this disorder.

2. Although most patients with CTCL do not come to transplant (because they have low-grade disease which is controllable with lesser measures), a proportion of patients progress and have life-threatening disease which is ONLY curable with allogeneic stem cell transplantation (current cure rate is 40-50% following transplantation).

3. In order for patients to reach transplantation they have to have responding disease (otherwise the transplant outcome is severely compromised). The 2 methods of achieving disease response prior to transplant are either intensive chemotherapy or brentuximab. Brentuximab has the definite advantage as a bridge to transplant in that it does not cause intense immunosuppression (unlike chemotherapy) and therefore is much less likely to be associated with antibiotic-resistant bacterial colonisation of skin lesions, which increases the risk of poor outcome with transplant.

4. We strongly support the use of brentuximab as a bridge to allogeneic transplant in patients with CTCL. This use results in more patients being eligible for transplantation as the only curative option, and also reduces the risk of serious infection complications during the transplant itself (see 3. above).

Name	[redacted]
Role	NHS Professional
Other role	Skin Lymphoma clinical nurse specialist
Organisation	None
Location	England
Conflict	None
Notes	Patient statement included in separate comment box.

Comments on the ACD: 1. Quality of Life (QOL)

This disease has a huge debilitating effect on the quality of life of its patients.

Many are unable to go out of the house due to the mobility issues caused by pain and the need for regular dressing changes.

They are unable to regulate their body temperature as the skin is so badly effected - they are always freezing cold.

The disease has a massive psychological effect on all patients. Patients can be embarrassed about the appearance of their skin, wounds leak and often smell offensive, leading to them becoming isolated from friends and family and the general public.

Sleep deprivation is a massive issue (for the patient and their partners) as constant itching and skin weeping and pain is something that is often over looked and under estimated. Patients complain of not being able to sleep for days, sometimes weeks when their skin is bad. All can effect the quality of their relationships (sleeping in different beds).

This disease can also put financial pressure on a patient and their family. The need to constantly wash, change and buy bed linen is costly along with increased heating bills. Many patients will buy their own dressings (which can be very costly) as dressings may need to be changed in between district nurse visits.

In my experience, patients on Brentuximab have overcome all of these issues.

All have reported that they have gone back to 'being themselves.'

The need for dressings are reduced dramatically / if not stopped all together.

Patients are able to live a 'normal' life - by going back to work, socialising and are able to rebuild relationships.

Quality of sleep is much improved and many go back to sleeping in the same bed as their partner.

We feel that all of the patients we have treated with Brentuximab have had significant improvement of their health / emotional related quality of life since commencing the drug; contradictory to the interpretation of existing trial data.

2. Resource use in the end- stage care health state.

Patients who are at end stage disease often require regular multiple change of expensive dressings (sometimes 10 times a day).

District nurse input is required for this, this is not always available and would then lead to hospital / out of hours GP visits or local A&E departments, all of these are already under a lot of pressure.

Palliative care referral and treatment would ultimately be required (with consultant oncologist and specialist nurse input.)

Admission to hospice and all associated care costs.

Hospital admission required for wound infection treatment.

Potential for pressure ulcer development due to reduced mobility and skin quality.

3. In my experience, every patient that has received Brentuximab in order to achieve remission has successfully gone on to have alloSCT. Some patient's report that they have felt to have a better quality of life ("I felt better than ever when on Brentuximab.") on the Brentuximab than they did after transplant.

Patient experience on Brentuximab has been hugely positive. Overall, the benefit of the treatment outweighed side effects. CTCL symptoms resolved.

Patients claimed that it is a life changing treatment.

This relatively rare disease has limited treatment options and a lack of patient focused support unlike many other diseases.

If this drug was denied for our small group of physically and emotionally vulnerable patients then I feel they would be denied the opportunity to be able to regain a functional quality of life.

The alternative would likely be a harrowing painful progression to death.

Please see patient personal statement below. This is on the patients medical records.

I was diagnosed with T cell lymphoma in 2009 and since that date my skin has gradually worsened although I have attended many trials at [redacted] and been subject to many different treatments including radiotherapy, full body radiation at [redacted] and different types of chemotherapy - but still in 2018 I spent a month in my local hospital with very infected skin where I was put in isolation. Then, in September 2018 I received my first dose of brentuximab and immediately my skin began to show significant improvement. I had been administering 24 dressings each day and now after 6 treatments I am down to 2 dressings. It took 2 hours each day to get dressed, I had to sleep on towels each night because the skin oozed, my wife was hoovering 4 times each day because of the skin flaking and the continuous itching made my life very miserable. Not to mention the amount of washing of clothes! I now feel better generally and have put on weight. Others are noticing my improvement and are asking me what miracle has happened? I can only answer Brentuximab and offer many thanks.

[redacted]

Name	[redacted]
Role	NHS Professional
Other role	Consultant Haematologist
Organisation	None
Location	England
Conflict	None
Notes	I am a Haematologist and transplant physician with expertise and considerable experience in looking after patients with advanced stage mycosis fungoides. I have done consultancy work for Takeda and have received financial support for travel and accommodation for meeting attendance.

Comment on the ACD:

As a health care professional with expertise in delivering intensive chemotherapy, brentuximab and allogeneic stem cell transplants for patients with advanced stage mycosis fungoides, I would like to comment specifically on 3 issues relating to this appraisal.

1. BV vs chemotherapy as a bridge to allograft: I have treated several patients with chemotherapy with a view to bridging them to a transplant as a potential curative treatment. Unfortunately the response rates are rather sub-optimal and only a small minority eventually end up qualifying for a transplant. I have also treated a few patients with BV with a much better success rate in terms of proceeding to a transplant. I note the company's submission assumes a transplant rate of around 25-30% with BV vs <10% with conventional chemotherapy. This is very much in keeping with my personal clinical experience. Most responding patients will show a response by 4 cycles of treatment and will often proceed to transplant between 4-6 cycles of treatment.

2. Impact of BV on QoL: I think the committee significantly underestimates this. I have patients whose QoL has been transformed by BV. Advanced stage MF can have quite an adverse impact on QoL as itching is a prominent symptom which can be debilitating and many patients have ulcerated skin tumours with a smelly discharge leading the patients to become socially withdrawn. BV significantly improves their chances of having a good remission and symptom survival. Many patients would value this immensely even if they did not have an OS benefit. One of my patients was needing 25 dressings every day to cover all ulcerated tumours on his skin. There was no response to intensive chemo using gemcitabine. He ended up needing multiple hospital admissions due to sepsis whilst on chemo adding a huge burden to healthcare provision and nursing care due to the amount of time spent applying dressings on a daily basis. Since starting BV on a compassionate use basis, his lesion have all healed nicely and he is only needing dressing for 1 lesion now which is also in advanced stages of healing. He has received 4 cycles of BV so far. This patient is now being worked up for an allograft.

3. Resource use at the end of life: I think the committee underestimates the amount of resource needed for provision of care for this complex group of patients. I have had patients with extensive skin tumours on a palliative pathway needing extensive nursing input for dressing the wounds on their skin. I have had patients needing to be admitted to hospital for this and in some instances needing ketamine sedation for dressings on a daily basis as the wounds were very painful. Managing this situation in the community is often very difficult due to lack of proper resource and expertise.

Also important to remember, patients may be on the "palliative" path for several months which compounds the resource utilisation.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical Oncologist
Organisation	[redacted]
Location	England
Conflict	None
Notes	None

Comment on ACD:

Dear NICE

Re: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma

I am a Consultant Clinical Oncologist at [redacted] with a specialist interest in treating skin lymphoma. I treated patients with Brentuximab in the Alcanza study and have treated patients with Brentuximab via the compassionate use programme. The Skin tumour unit at [redacted] is the largest centre for cutaneous lymphoma in the UK and we see patients for opinions from all over the UK and internationally.

Cutaneous T-cell Lymphoma (CTCL) is very difficult to treat and none of our established systemic therapies have shown an improvement in overall survival. I have treated patients with CTCL at [redacted] since 2003 and Brentuximab vedotin is the best new drug I have used, and has made the largest impact of any new treatment over the last 15 years. The only treatment that has been shown to induce long term remission and survival in this group of patients is a reduced intensity stem cell allograft RIC-Allo-SCT. To get patients to RIC-Allo-SCT we need to get the patients into a complete or very good partial remission. Brentuximab is proving to be the best systemic therapy option at doing this. In patients where transplant is not an option the rapid response and duration of response to Brentuximab is better than any other current systemic agent and it provides a significant improvement in quality of life for these patients.

I presented the outcomes of the RIC-Allo-SCT protocol currently used in the UK at the EORTC meeting in 2018 and I believe this data has been made available to you.

Between Aug 2017 and Sep 2018 I secured funding for 21 patients to receive treatment with Brentuximab via the compassionate use programme. 2 patients unfortunately progressed and died while awaiting funding agreement. This is the nature of this condition which can progress rapidly and with wide spread skin involvement the problems with skin infection and declining fitness due to extensive skin erosions and ulcerations makes treatment very difficult. I have treated 19 patients between Aug 2017 and Jan 2019 with Brentuximab. Of these patients 14 were eligible to be considered for a RIC-Allo-SCT. 5 out of 14 patients (36%) have responded and are now fit for a RIC-Allo-SCT, 3 of whom have been transplanted and are alive and well in complete response and 2 patients continue on Brentuximab awaiting a match for a transplant. The 3 patients who have been transplanted received 6, 10 and 11 cycles of Brentuximab each. The 2 patients awaiting transplant are on cycles 5 and 9 of Brentuximab currently with an excellent partial response.

The results of treatment for the 19 patients treated on the compassionate use programme are summarised below:

19 patients treated. Started Treatment between Aug 2017 and Sep 2018.

Last Follow up 4th January 2019.

14/19 (73%) fit and eligible for transplant RIC-ALLO-SCT

Median number of cycles received: 5 (Range 1 to 11)

Global Response at 6 weeks pre cycle 3:

CR 2/19 (10.5%), PR 14/19 (73.7%), ORR 16/19 (84.2%), PD 2/19 (10.5%)

NA 1/19 stopped after cycle 1 (Neutropenic sepsis)

Global Response at 12 weeks pre cycle 5:

CR 2/19 (10.5%), PR 10/19 (52.6%), ORR 12/19 (63.1%), PD 6/19 (31.5%)

NA 1/19 stopped after Cycle 1 (Neutropenic Sepsis)

Toxicity:
Peripheral Neuropathy:

Grade 0 = 6, Grade 1 = 9, Grade 2 = 3, Grade 3 = 1

Neutropenic Sepsis:

Grade 3 = 1

Survival:

At last follow up:

3 patients transplanted and alive in CR

2 patients in PR on Brentuximab awaiting transplant

2 patients in PR on Brentuximab

6 patients receiving palliative care or further systemic treatments

6 patients died due to CTCL.

We have learnt to recognise early signs of peripheral neuropathy and with treatment delays and dose reductions all patients who developed peripheral neuropathy have had recovery of function and we have no patients with ongoing peripheral neuropathy greater than grade 1.

My experience is that Brentuximab vedotin has made a real and significant impact on the management of patients with advanced CTCL. The response rate is higher than any other systemic therapy and the duration of this response is impressive. Seeing a patient with such a devastating illness respond and come back to clinic without pain, without itch, being able to wear normal clothes without extensive dressings is amazing. Brentuximab in the clinic has made a significant improvement to this

patients groups quality of life. Brentuximab has also helped us get patients to RIC-Allo-SCT who would not otherwise have done so and this will induce a lasting remission and possible cure for some patients. I hope you can approve access for Brentuximab for CTCL patients on the NHS, otherwise it will be a real tragedy. CTCL is a very difficult disease to treat, recruiting to clinical trials is very difficult and the multicentre international Alcanza trial is probably the best randomised controlled trial carried out in this patient group reporting better results than any other current treatment.

I will submit a letter from a patient who was a GP with advanced Mycosis Fungoides. He wrote to NHSE to support the application I made to treat him with Brentuximab. This application was turned down and several months later the Compassionate use programme started and I was able to treat him with Brentuximab on the compassionate use programme. Unfortunately waiting those 3 months caused his skin lymphoma to progress further and despite initial response to Brentuximab his lymphoma was to advanced and he fitness deteriorated and he died. Before he died he gave me his consent to share his experience and the letter he sent to NHSE to help future patients.

Kind regards

[redacted]

RE: [redacted]; DOB: [redacted]; NHS No. [redacted]; Reference: [redacted]

1 July 2017

Dear Sir or Madam,

I am writing regarding the application made by [redacted] for the use of Brentuximab for treatment of my Mycosis Fungoides (cutaneous T cell lymphoma). I would like to provide further information on my condition and to draw your attention to four issues in support of my application for exceptional funding, which I cover in more detail later in this letter. This includes:

1. Recent research, published in the Lancet in June 2017, which states the significant medical benefits of Brentuximab in treating my illness over any other drug available;

2. The probability of a cure and full recovery if this committee accepts my application for exceptional funding;

3. The long-term cost to the NHS of managing my condition should my application for exceptional funding be rejected; and

4. The exceptional nature of my disease, which necessarily requires the application of an exceptional approach.

Background to my condition

Until March this year (2017) I was a fit, healthy newly retired 63 year old playing tennis three times a week and golf twice a week, with a skin rash easily controlled by UV light treatment delivered from a privately acquired and managed home unit when required. My only input from the NHS was 6-12 monthly follow -ups by the local

dermatologist. It goes without saying that I enjoyed an exceptionally good quality of life.

Since March, my condition has deteriorated rapidly and I've spent nearly ten weeks as an in-patient at [redacted] across two separate admissions under oncology, dermatology, microbiology and palliative care. I received IV antibiotics for sepsis and skin infections, as well as having pain control and daily treatments and dressings taking at least 2 hours.

I also received Caelyx Chemotherapy, which failed to work. My skin is so severely affected that my mobility has suffered significantly, having become virtually bed bound and in constant pain within a matter of weeks. There is no prospect of my life improving unless I have this treatment and, without treatment, I fear my future is one of pain and disability.

My skin has broken down and, whereas I had 5% involvement with itchy dry lesions for many years, I now have 80% of my skin involved. This includes widespread lymphoedema and swelling, open weepy skin, itchy flaking dry areas, tumours, ulceration and areas of excoriation. My hands and feet are peeling and weepy and I have painful fissures and tender friable skin, resulting in severe limitation of use. My face is progressively involved with severe involvement of my genital area and perineum which makes toileting extremely difficult and sitting down for any length of time an impossibility.

The pain is indescribable. Itch is also a massive problem. I take morphine and gabapentin regularly, and 'top up' with oromorph when I need to do anything difficult. In my condition this includes undergoing dressings or moving around. If I had to describe the pain, it is akin to being wrapped in barbed wire while someone jumps on me or, at times, like having boiling water poured over me. Even the gentlest touch in the wrong place will make me cry out involuntarily. Sleep is induced with hydroxyzine to reduce itch and zopiclone sleeping tablets.

My life, as a sufferer of a debilitating, chronic, life-limiting illness with total skin failure, has been completely taken away from me. My wife has become, and has registered, as my carer. I have daily visits from the district nurse for dressings, which would take 3 hours without help from my wife. I can't tolerate 'outdoor' clothes on my skin, and wearing shoes is impossible.

I have limited use of my hands. I cannot stay away from home as I require a hospital airbed and I need a stretcher in an ambulance for my weekly trips to [redacted] outpatients, as I cannot stay seated for long.

Name	[redacted]
Role	NHS Professional
Other role	Clinical Oncologist
Organisation	[redacted]
Location	Wales
Conflict	None
Notes	I have received advisory board honoraria and educational support from Takeda.

Comments on the ACD:

Mycosis fungoides remains a challenging disease to treat. As a rare cancer, it is hard to develop sufficient expertise, and with limited effective treatment options it is important to find the right place for new therapies. It is also important that for younger, fitter patients, we continue to look for a role of alloSCT as a potentially curative option. Emerging data shows improving outcomes following accumulating experience with careful patient selection and delivery of the complex conditioning regimens. Having good induction treatment options to achieve remission or even stable disease is very worthwhile, hence the relevance of having brentuximab available for these patients. UK centre experience with alloSCT following brentuximab is growing and this indication remains the most important. In my small practice, brentuximab initiated as a potential bridge to allograft has achieved this in 2/2 young fit patients. For patients not eligible for alloSCT, treatment with brentuximab can still provide significant benefit, predominantly with respect to progression free survival or time to next treatment, as well as symptomatic/quality of life benefit. Being able to continue to treat responding patients for up to a year, and rechallenge if necessary, is clinically valuable. The majority of patients respond well and tolerate brentuximab without significant toxicity. Most palliative treatments are not necessarily expected to increase overall survival, but control of disease and improved progression free survival may translate into improved overall survival, particularly as controlling skin lesions/tumours can reduce the risk of life-threatening sepsis from superinfection of ulcerating skin tumours. Again, in my small practice, patients have reported improved symptoms such as pruritus and pain, and require fewer dressings and skincare needs. There is no specific QOL tool for CTCL patients, though this is in development, so current instruments have limitations and do not necessarily accurately capture changes that are meaningful to CTCL patients.

I can only emphasize that brentuximab has been an extremely valuable addition to the very small armamentarium of active treatments for CTCL. For selected patients, it would be my first choice within its licensed indication as responses can be seen rapidly and patients tolerate it well. For young fit patients it provides an unrivalled means of disease control that might allow these patients to proceed to alloSCT. It would be very disappointing not to be able to use an effective treatment for patients who have such a difficult lymphoma to treat, and such difficult and distressing symptoms to manage. Managing these patients requires truly multidisciplinary input and expertise; ideally they can stay at home and not have to come into hospital, but meeting their needs in the community can be very challenging as primary care teams are not experienced in managing rapidly growing and ulcerating skin tumours and widespread skin involvement. We need as many effective treatment options as possible, and brentuximab definitely has an important place in the treatment of CTCL.

Name	[redacted]
Role	NHS Professional
Other role	Consultant in Clinical Oncology
Organisation	[redacted]
Location	England
Conflict	None
Notes	None

Comments on the ACD:

In my experience as an Oncologist looking after patients with Cutaneous T cell lymphoma (CTCL) for more than 25 years, Brentuximab offers a whole new

approach to treating patients with more advanced CTCL who are destined to die from this very distressing and debilitating disease.

Up until now, our treatment options have been very limited and in the advanced stage, when patients have to live with painful and embarrassing ulcerating skin disease, conventional chemotherapy has provided only transient respite at the cost of significant and sometimes life threatening toxicity. Sepsis presents a serious problem to these patients with widespread open wounds who are rendered neutropenic by their chemotherapy. We now recognise that the future for the treatment of this condition will involve immunotherapy in a variety of forms and conventional chemotherapy will give way to these more effective and appropriate treatments. Brentuximab is the first of this new generation of immunologically driven agents. The number of patients requiring Brentuximab each year in the UK will be small due to the rarity of CTCL (600 - 700 new patients per year), and the fact that only the minority of these patients will be deemed appropriate to receive Brentuximab. As a result this will not present a significant financial burden upon the NHS budget.

Name	[redacted]
Role	NHS Professional
Other role	Consultant in Clinical Oncology
Organisation	[redacted]
Location	England
Conflict	None
Notes	None

Comments on the ACD:

We recognise that the ALCANZA trial did not show an overall survival advantage for Brentuximab, however this was not adequately powered for this and the follow up is still relatively short. We know that it is responsible for a substantial improvement in PFS and the importance of this should not be underestimated. These patients suffer greatly with active disease and can live for long periods of time with severely symptomatic lymphoma requiring analgesia, regular skin care and dressing and sometimes with unbearable pruritis which is only improved by disease control.

In a disease such as CTCL which is largely incurable, QOL is of paramount importance to the patient and we have clear evidence of the beneficial impact of Brentuximab on QOL.

A significant number of these patients are of working age and control of their disease allows them to continue work with the resulting benefit on their QOL, their financial situation and allows them to continue their contribution to society through their work.

In recent years, it has become more apparent that some patients with advanced disease may enter a more durable remission following an allogeneic stem cell transplant (ASCT). It is a little early to say whether some of these patients have been cured, but clearly this procedure has dramatically changed the course of the disease and offers the potential for cure - which would be the first time this has been achieved.

The secret of proceeding to an ASCT is the achievement of a complete or near complete remission. Any treatment which can bridge a patient to an ASCT plays a pivotal part in achieving the possibility of cure. To date, Brentuximab is the agent which offers this potential above other current therapies.

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]: Appendix 1: Additional Economic Analyses – in response to the ACD (December 2018) for the consideration of the NICE Appraisal Committee

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute of Health and Care Excellence

Submitted 24 January 2019

Table of Contents

1. Without-PAS results

1.1 Overview

This document presents the results for each of the scenarios presented within the main Appraisal Committee Document (ACD) response excluding the confidential patient access scheme (PAS) i.e. results are shown at list price for brentuximab vedotin (£2,500 per 50mg vial). Further information on the rationale and methodology associated with each scenario can be found in the main ACD response document along with the results applying the PAS of [redacted] to the list price of brentuximab vedotin.

1.2 Results: Revised base case (without PAS)

Table 1 presents the step change in results from the company's original base case to the revised base case. The revised base case results are shown in Table 2. Note: these tables present the without-PAS results; Table 1 and Table 2 in the main ACD response document present the with-PAS results.

Table 1: Step change in results from the company's base case to the revised base case reflecting the Committee's preferred assumptions (without PAS)

	Cost per QALY	NMB
Company's base case	[redacted]	[redacted]
Equal utility values for brentuximab vedotin and physician's choice	[redacted]	[redacted]
Equal utility values for brentuximab vedotin and physician's choice + Removing treatment-related disutilities	[redacted]	[redacted]
Committee's preferred assumptions – the revised base case Equal utility values for brentuximab vedotin and physician's choice + Removing treatment-related disutilities + Removing additional oral chemotherapy costs	[redacted]	[redacted]

Abbreviations: BV, brentuximab vedotin; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life year.

Table 2: Revised base case (without PAS)

	Total			Incremental			Cost per QALY	NMB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Physician's choice	[redacted]	[redacted]	7.36					
Brentuximab vedotin	[redacted]	[redacted]	8.93	[redacted]	[redacted]	1.58	[redacted]	[redacted]

Abbreviations: LY, life year; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life year.

1.3 Results: Scenario analyses (without PAS)

1.3.1 Rates of alloSCT after brentuximab vedotin or physician's choice

Table 3 presents the impact of the scenarios exploring the impact of the rate of allogeneic stem cell transplant (alloSCT) on the cost-effectiveness results. Note: this table presents the without-PAS results; Table 3 in the main ACD response document presents the with-PAS results.

Table 3: Scenario analyses exploring the rates of alloSCT (without PAS)

Physician's choice arm	Brentuximab vedotin arm	ICER	NMB
7.1% bridged to alloSCT	Revised base case (27.5% bridged to alloSCT)	[redacted]	[redacted]
	26.3% bridged to alloSCT	[redacted]	[redacted]
	16.7% bridged to alloSCT	[redacted]	[redacted]
5% bridged to alloSCT	Revised base case (27.5% bridged to alloSCT)	[redacted]	[redacted]
	26.3% bridged to alloSCT	[redacted]	[redacted]
	16.7% bridged to alloSCT	[redacted]	[redacted]

Abbreviations: alloSCT, allogeneic stem-cell transplantation; BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme.

1.3.2 Duration of treatment with brentuximab vedotin (i.e. number of cycles) prior to alloSCT

Table 4 presents the impact of the scenarios exploring the impact of the duration of treatment with brentuximab vedotin (i.e. the number of cycles) prior to alloSCT. Note: this table presents the without-PAS results; Table 4 in the main ACD response document presents the with-PAS results.

Table 4: Scenario analysis exploring duration of treatment prior to alloSCT (without PAS)

	ICER	NMB
Revised base case (alloSCT after 18-weeks [6-cycles])	[redacted]	[redacted]
alloSCT after 12-weeks (4-cycles)	[redacted]	[redacted]
alloSCT after 24-weeks (8-cycles)	[redacted]	[redacted]
alloSCT after 30-weeks (10-cycles)	[redacted]	[redacted]

Abbreviations: alloSCT, allogeneic stem-cell transplantation; BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme.

1.3.3 Overall survival for patients not undergoing an alloSCT

Table 5 presents the impact of the scenarios exploring the impact of an overall survival (OS) benefit for patients who do not have an alloSCT and are treated with brentuximab vedotin. Note: this table presents the without-PAS results; Table 5 in the main ACD response document presents the with-PAS results.

Table 5: Scenario analysis exploring a survival benefit for patients who do not have an alloSCT and are treated with brentuximab vedotin (without PAS)

	ICER	NMB
Revised base case (no survival gain for patients without alloSCT)	[redacted]	[redacted]
2-months survival gain for patients without an alloSCT	[redacted]	[redacted]
4-months survival gain for patients without an alloSCT	[redacted]	[redacted]
9.5-months survival gain for patients without an alloSCT	[redacted]	[redacted]

Abbreviations: alloSCT, allogeneic stem-cell transplantation; BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme.

1.3.4 Resource use

Table 6 presents the impact of the scenario exploring the combination of resource use assumptions from the company's base case and from the Evidence Review Group's (ERG's) analyses. Note: this table presents the without-PAS results; Table 8 in the main ACD response document presents the with-PAS results.

Table 6: Scenario analysis exploring a combination of resource use assumptions from the company's base case and the ERG's analyses (without PAS)

	ICER	NMB
Revised base case (resource use assumptions as per the company's original base case)	[redacted]	[redacted]
Resource use assumptions from a combination of the company's base case and the ERG's analyses	[redacted]	[redacted]

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme.

CRITIQUE OF ACD RESPONSE

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Brentuximab vedotin for treating relapsed or refractory CD30-positive cutaneous T-cell lymphoma [ID 1190]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 17/56/12

Completed 01 February 2019

CONTAINS [redacted]
AND [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

BRENTUXIMAB VEDOTIN FOR TREATING RELAPSED OR REFRACTORY CD30-POSITIVE CUTANEOUS T-CELL LYMPHOMA [ID 1190]

ERG critique of company response to the ACD

The Evidence Review Group (ERG) received the company's submitted response to the appraisal consultation document (ACD) for the appraisal of brentuximab vedotin (BV) for treating relapsed or refractory CD30-positive cutaneous T-cell lymphoma (CTCL) on 25 January 2019. The company's response included cost-effectiveness results from a model. The company revised its original base case model using a combination of the Appraisal Committee (AC)'s preferred assumptions as stated in the ACD and updated analyses of outcomes following allogeneic stem cell transplantation (alloSCT) from a real-world dataset. This document presents a critique of the points raised by the company's analyses in its response to the ACD.

1.1 Company revised base case

The company provides revised base case cost-effectiveness estimates based on its interpretation of the AC's preferred assumptions in the ACD (Table 1). These include:

- Inclusion of alloSCT (updated modelling of post-alloSCT outcomes)
- Equal utility values for BV and physician's choice (PC) at baseline
- Remove treatment-related disutilities
- Remove additional oral chemotherapy costs

The ERG has been able to replicate the results presented by the company in its revised base case.

Table 1 Revised company base case with PAS

	Total			Incremental			Cost per QALY	NMB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Brentuximab vedotin	[redacted]	[redacted]	8.93					
Physician's choice	[redacted]	[redacted]	7.36	[redacted]	[redacted]	1.58	BV Dominates	£150,415

LY=life year; NMB=net monetary benefit; PAS=patient access scheme; QALY=quality adjusted life year
Source, Table 2, Company response to ACD

1.2 Updated alloSCT outcomes data

The company's original model included estimates of overall survival (OS) and disease-free survival (DFS) following alloSCT based on outcomes for 40 UK patients in a real-world study presented by Ranuka Palanicawandar at a conference in 2017.[1] The company submitted a revised model shortly before the first AC meeting that included updated estimates of OS and progression-free survival (PFS) following alloSCT, based on outcomes for 53 UK patients in an later cut from an expanded version of the same real-world study, which was presented by Stephen Morris at a conference in 2018.[2] The ERG was unable to provide a critique of the company's updated modelling of post-alloSCT OS and PFS before the first AC meeting due to the late submission of the new evidence.

The ERG's original concerns about the evidence base for post-alloSCT outcomes have not been resolved with the new real-world data submitted by the company. However, the ERG acknowledges that the AC concluded that it was appropriate to assume no difference in outcomes after transplant following treatment with BV compared with transplant following treatment with PC. The ERG notes that there remain uncertainties about the relevance of the population in the real-world study when compared to the population in this appraisal. High-level patient characteristics from the real-world study were reported in the conference abstract,[2] which indicated that patients were younger than those in the advanced-stage population of the ALCANZA trial and had more advanced stage disease (

Table 2).

The ERG acknowledges that younger patients are more likely to be suitable for alloSCT, which may account for the difference in median ages between the studies. However, since the patient starting age in the model is 57.1 years, alloSCT is modelled to take place when patients are 57.4 years of age (18 weeks after beginning treatment), at which point patients would be almost 10 years older than the median age of the patients in the real-world study. The ERG notes that there is uncertainty about whether there may be a difference in outcomes for older patients who receive alloSCT versus younger patients, when both are considered fit enough to undergo transplant.

The ERG also notes the difference in disease stages between the ALCANZA trial and the real world data, with patients in the real world study having more advanced stage disease than patients in the ALCANZA trial. If patients with more advanced disease are more likely to receive alloSCT than patients with less advanced disease, then the eligible patient population in the ALCANZA trial (and in the economic model) may be lower than in the company base case. The company states in its response to the ACD that it considers the transplant rate from

treatment with BV to fall in the range 16.7% to 27.5%. The ERG has included the lower bound of this range in a scenario analysis to capture the possibility that patients with more advanced disease are more likely to go to transplant.

Table 2 Comparison of baseline characteristics: ALCANZA trial and real-world alloSCT study

Characteristic		ALCANZA (advanced-stage population)		Real-world study	
		BV (n=49)	PC (n=46)	Protocol 1 (n=22)	Protocol 2 (n=31)
Median age (range)		62 (31-82)	54 (25-83)	49 (NR)	48 (NR)
MF and SS, n (%)		33 (67.4)	31 (67.4)	22 (100)	31 (100)
MF and SS disease stage, n (%)	IIB	19 (57.6)	19 (61.3)	8 (15.1)	
	IIIA	4 (12.1)	2 (6.5)	4 (7.5)	
	IIIB	0	0	1 (1.9)	
	IVA1	0	1 (3.2)	7 (13.2)	
	IVA2	2 (6.1)	8 (25.8)	25 (47.2)	
	IVB	7 (21.2)	0	8 (15.1)	
	Unknown	1 (3.0)	1 (3.2)	0 (0.0)	
pcALCL, n (%)		16 (32.7)	15 (32.6)	0 (0.0)	

BV=brentuximab vedotin; MF=mycosis fungoides; PC=physician's choice; pcALCL=primary cutaneous anaplastic large cell lymphoma; SS=Sezary syndrome
Source: CS, Table 17; Morris 2018[2]

1.3 Updated modelling of alloSCT outcomes

The company's revised model includes updated modelling of PFS and OS outcomes following alloSCT, based on data from the Morris 2018 study.[2] The ERG highlights several implications of the company's modelling of alloSCT outcomes, which may or may not be plausible. The ERG does not consider the following implications to be supported by evidence:

- patients whose disease progresses (relapses) following alloSCT have substantially worse outcomes than patients whose disease progresses without alloSCT. The longest a patient can live once their disease progresses following alloSCT is 6.2 years, compared with 25 years for patients whose disease progresses and has not received alloSCT. Mean life expectancy in the company base case is 9.4 months after relapse following alloSCT versus more than 5 years (depending on initial treatment) after progression without alloSCT;
- patients who relapse following alloSCT do not receive any end-stage care;
- patients who live [redacted] or more years after alloSCT without relapsing are assumed to be cured, which equates to [redacted] of the alloSCT population.

Outcomes after relapse following alloSCT

The company modelling of relapse following alloSCT implies that outcomes are substantially worse for patients whose disease progresses following alloSCT than for patients whose disease progresses without having received alloSCT.

In the revised model, all patients who relapse following alloSCT have died 6.2 years after transplant. In the original model, all patients who relapsed following alloSCT had died 12.8 years after transplant. The company discussed the original model outcomes with clinical experts. The company states that:

> "[a]lthough [12.8 years] was considered shorter than the non-alloSCT population, where progressed patients could live up to 25-years, it was considered the most plausible out of the presented [options]. Additionally, it was commented that outcomes after relapsing following an alloSCT may be worse than in the non-alloSCT population as these patients have been immunosuppressed. However, there are no data to corroborate this." (CS, p.134)

In the revised model, patients who relapse following alloSCT live on average 9.4 months after relapse. This is a substantially shorter mean lifetime after progression than patients who progress following treatment with BV or PC but have not received alloSCT (5.1 years and 6.2 years respectively).

The ERG questions whether it is plausible that patients who have relapsed following alloSCT will have worse outcomes than patients whose disease progresses without alloSCT, especially considering that the company has already stated that there are no data to support the possibility that outcomes for patients whose disease progresses following alloSCT may be worse than for patients whose disease progresses without alloSCT.

End-stage care after relapse following alloSCT

In the revised model, patients who have relapsed following alloSCT do not receive resource-intensive end-stage care. This is due to a combination of short mean life expectancy folllowing relapse (9.4 months in the revised model) and the model structural requirement for all patients to spend 11.3 months receiving subsequent therapy following relapse in the company base case. This is shorter than the 1.9 years of subsequent therapy given to patients whose disease has progressed but who did not receive alloSCT. The company states that this is because these patients would already have received total skin electron beam (TSEB) radiation as part of the conditioning for alloSCT, which is included as a subsequent therapy for patients who do not receive alloSCT, and would not receive it again.

The ERG does not consider it plausible that patients whose disease progresses following alloSCT would not require any end-stage care. Since end-stage care is a highly resource-intensive state that is associated with low utility values, the costs of alloSCT treatment are likely to be underestimated in the company base case. Given that a far greater proportion of patients are modelled to receive alloSCT after treatment with BV than with PC, and given these patients do not enter end-stage care, the incremental costs are likely to be understimated and the QALYs are likely to be overestimated in the company base case

Proportion of patients cured and time of cure following alloSCT

The company models PFS following alloSCT using a single parametric (Gompertz) curve that incorporates two populations: patients who are cured of the disease and patients who are at risk of relapse. The Gompertz model is based on PFS Kaplan-Meier (K-M) data from the updated datacut from the Morris 2018 study.[2] The Gompertz curve in the company base case flattens after around [redacted], which means that the risk of relapse reaches effectively zero around [redacted] after transplant (Figure 1). Background mortality is added to the flattened part of the Gompertz PFS curve in the model to incorportate general all-cause mortality risk. Since the definition of PFS is the time to progression or death, a PFS curve should not be totally flat even if there is zero risk of progression because people will still be at risk of death from other causes.

The company states in the addendum to its original submission (dated 21 November 2018) that, "the Gompertz curve is the only curve that reflects the decreasing probability of relapse with time reducing over time to a zero probability (a plateau) for the updated Morris 2018 data" (pp.17-18). The ERG considers this to be a misreading of the PFS K-M data, as a plateau in PFS would indicate zero risk of death as well as zero risk of progression. The plateau apparent in the PFS K-M data from the Morris study is due to censoring and should not be taken to indicate zero risk of relapse.

The ERG acknowledges that clinical advice to the company was that patients who had not relapsed in the first few years following transplant were unlikely to susequntly relapse and could be considered to be in long-term remission (or "cured") from the disease. However, the ERG does not consider that the evidence presented by the company supports the assumption that cure should be assumed around [redacted] after transplant. There is therefore uncertainty surrounding the time at which cure can be assumed.

The ERG notes that the company's modelling of PFS following alloSCT implies that around [redacted] of patients will enter long-term remission or be cured of CTCL. The ERG does not consider the K-M data provided by the company from the Morris 2018 study to robustly support the

implication that [redacted] of patients receiving alloSCT will enter long-term remission from advanced CTCL.

Due to the structure of the model, it is not straightforward to investigate the impact on the ICER per QALY gained of varying the time at which cure might be assumed nor the proportion of people likely to be cured following transplant. The ERG would have preferred to see an analysis including a cure fraction model to investigate the impact of assumptions around the proportion of patients who are cured and the time at which they can be considered cured.

The ERG has investigated the effect of increasing the time until zero risk of relapse byt modifying the model within the constraints of the single-curve approach used by the company. In the ERG's exploratory scenario, the overall cure rate is half that assumed in the company base case ([redacted]) and the Gompertz curve reaches a plateau at around [redacted] (Figure 1). The Gompertz curve is fitted to the same underlying K-M data as the company's base case curve but ignores the influence of the censored data in the tail, replacing it with the assumption that 25% of patients will not be at risk of relapse. The ERG emphasises that this is a scenario within the confines of the company model structure and not its preferrred method of modelling cure for a proportion of the population.

Applying the ERG's [redacted] cure-rate scenario reduces net monetary benefit by £76,136 to £74,279. The ERG's [redacted] cure-rate scenario increases mean life expectancy after relapse following alloSCT to 4.2 years. Patients with relapsed disease receive end-stage care for 3.4 years in this scenario.

Figure 1 Cure rate scenarios following alloSCT

Source: Company revised mode; ERG calculations

1.4 Health-related quality of life in the ALCANZA trial

The company argues that the health-related quality of life (HRQoL) data collected in the ALCANZA trial do not fully capture the impact of treatment with BV. The ERG acknowledges that the EQ-5D may not be sensitive to the full impact of skin-related disease. However, the ERG notes that the EQ-5D should theoretically be sensitive to some of the impact of advanced skin involvement in CTCL reported by patients in their responses to the ACD, such as depression and pain. The ERG notes that there was no significant difference in EQ-5D advanced population in the ALCANZA trial reported by the company in the CS for patients treated with BV versus PC and highlights that baseline EQ-5D scores were different for patients treated with BV versus PC. The ERG also notes that the EMA concluded that no firm conclusions can be drawn about the impact of treatment with BV on HRQoL in the Skindex-29 symptom domain.

Given the difference in baseline utilities between treatment with BV and treatment with PC in the ALCANZA trial, and the lack of a statistically significant difference in mean EQ-5D utilities over time in each arm of the trial, the ERG maintains its preference for using equal PFS utility values for treatment with BV and treatment with PC.

1.5 Overall survival without alloSCT

The ERG does not agree with the company that a 9.5 month OS gain for treatment with BV for patients who do not receive alloSCT represents an "extreme upper bound" for OS gain versus treatment with PC. Setting OS gain to 9.5 months (equal to the gain in PFS) for patients who do not receive an alloSCT means that patients treated with BV are modelled to have the same post-progression outcomes as patients treated with PC. In the company base case, where there is no OS gain attributed to treatment with BV, patients treated with BV are modelled to have worse outcomes after progression than patients treated with PC.

1.6 Post-progression pathway

The ERG provided an alternative post-progression pathway in its original report to illustrate the sensitivity of the model to the assumption that all patients whose disease progresses receive a set amount of subsequent therapy, but the time they spend receiving resource-intensive end-stage care varies depending on their initial treatment. This assumption is important because, in the company base case, patients treated with BV have worse outcomes after progression than patients treated with PC: they die more quickly and they spend less time receiving resource-intensive end-stage care. This means that patients treated with BV accrue substantially lower costs after progression than patients treated with PC.

The ERG recognises that it is plausible that patients treated with BV might have worse outcomes after progression than patients treated with PC. However, it considers it important that this implication of the company base case model is recognised when assessing the credibility of the cost-effectiveness results.

1.7 Resource use assumptions

The ERG has retained the resource use scenario from its original report, which was based on clinical advice to the ERG.

1.8 Impact on the ICER per QALY gained of the ERG's amendments

The ERG has investigated the individual and combined impact of several scenarios informed by the ACD and the company response to ACD. The individual scenarios are:

- Scenario 1 [S1]: OS gain for treatment with BV in non-alloSCT population equals PFS gain (9.5 months)
- Scenario 2 [S2]: Proportion of patients cured or in long-term remission following alloSCT is [redacted], cure is assumed after around [redacted]
- Scenario 3 [S3]: Resource-use assumptions as per the ERG's scenario in its original report
- Scenario 4 [S4]: Lower bound of company estimate of transplant rate (16.7%) in company response to the ACD

When each scenario is applied individually, treatment with BV dominates treatment with PC (Table 3). However, each scenario reduces net monetary benefit (NMB) by at least £50,000. Amending the resource use assumption (S3) and assuming the proportion of patients cured following alloSCT is reduced to [redacted] (S2) both generate less than half the NMB than the company base case.

In each combination of scenarios, NMB is reduced compared to the company base case (Table 4). Treatment with BV is no longer dominant in eight of the eleven scenario combinations, with positive ICERs per QALY gained in these scenario combinations of between £3,183 and £58,516. Two of the scenario combinations generate ICERs per QALY gained between £20,000 and £30,000, and two generate ICERs per QALY gained of over £30,000.

The ERG notes that it has not included a scenario to investigate the impact of fixing the time spent receiving end stage care and allowing time spent on treatment following progression to vary. Any scenario that decreases the incremental cost difference of the end-stage care state between treatment with BV and treatment with PC would increase the ICER per QALY gained.

The ERG underlines that these scenarios are exploratory and intended to highlight the sensitivity of the model to different assumptions. The ERG considers there to be insufficient evidence to support some of the major assumptions, and the implications of those assumptions, included in the company revised base. The ERG cautions that the cost-effectiveness results generated by the company model are not only limited by the interpretation of the data used to parametrise the model but also by structural uncertainties related to the modelling of outcomes in both the non-alloSCT and alloSCT populations.

Table 3 Cost-effectiveness results for individual ERG scenarios (PAS price for BV)

Revision	BV			PC			Incremental			ICER per QALY gained	Net monetary benefit
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY		
Company revised base case	[redacted]	[redacted]	8.93	[redacted]	[redacted]	7.36	[redacted]	[redacted]	1.58	BV Dominates	£150,415
[S1]: OS gain for treatment with BV in non-alloSCT population equals PFS gain (9.5 months)	[redacted]	[redacted]	9.51	[redacted]	[redacted]	7.36	[redacted]	[redacted]	2.15	BV Dominates	£99,672
[S2]: Proportion of patients cured or in long-term remission following alloSCT is [redacted], cure is assumed after [redacted]	[redacted]	[redacted]	8.22	[redacted]	[redacted]	7.17	[redacted]	[redacted]	1.05	BV Dominates	£74,279
[S3]: Resource-use assumptions as per the ERG's scenario in its original report	[redacted]	[redacted]	8.93	[redacted]	[redacted]	7.36	[redacted]	[redacted]	1.58	BV Dominates	£56,584
[S4]: Lower bound of company estimate of transplant rate	[redacted]	[redacted]	8.11	[redacted]	[redacted]	7.36	[redacted]	[redacted]	0.75	BV Dominates	£99,356

AE=adverse events; BV=brentuximab vedotin; PC=physician's choice; ICER=incremental cost effectiveness ratio; LY=life years; QALY=quality adjusted life year; PAS=patient access scheme

Table 4 Cost-effectiveness results for combined ERG scenarios (PAS price for BV)

Revision	BV			PC			Incremental			ICER per QALY gained	Net monetary benefit
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY		
Company revised base case	[redacted]	[redacted]	8.93	[redacted]	[redacted]	7.36	[redacted]	[redacted]	1.58	BV Dominates	£150,415
[S1] and [S2]	[redacted]	[redacted]	8.79	[redacted]	[redacted]	7.17	[redacted]	[redacted]	1.62	£3,839	£23,535
[S1] and [S3]	[redacted]	[redacted]	9.51	[redacted]	[redacted]	7.36	[redacted]	[redacted]	2.15	£3,183	£33,894
[S1] and [S4]	[redacted]	[redacted]	8.77	[redacted]	[redacted]	7.36	[redacted]	[redacted]	1.41	BV Dominates	£41,118
[S2] and [S3]	[redacted]	[redacted]	8.22	[redacted]	[redacted]	7.17	[redacted]	[redacted]	1.05	£12,295	£12,885
[S2] and [S4]	[redacted]	[redacted]	7.67	[redacted]	[redacted]	7.17	[redacted]	[redacted]	0.50	BV Dominates	£63,549
[S3] and [S4]	[redacted]	[redacted]	8.11	[redacted]	[redacted]	7.36	[redacted]	[redacted]	0.75	BV Dominates	£26,384
[S1], [S2] and [S3]	[redacted]	[redacted]	8.79	[redacted]	[redacted]	7.17	[redacted]	[redacted]	1.62	£40,899	-£9,805
[S1], [S2] and [S4]	[redacted]	[redacted]	8.33	[redacted]	[redacted]	7.17	[redacted]	[redacted]	1.16	£22,506	£5,311
[S1], [S3] and [S4]	[redacted]	[redacted]	8.77	[redacted]	[redacted]	7.36	[redacted]	[redacted]	1.41	£29,613	£341
[S2], [S3] and [S4]	[redacted]	[redacted]	7.67	[redacted]	[redacted]	7.17	[redacted]	[redacted]	0.50	£18,602	£5,832
[S1], [S2], [S3] and [S4]	[redacted]	[redacted]	8.33	[redacted]	[redacted]	7.17	[redacted]	[redacted]	1.16	£58,516	-£20,211

AE=adverse events; BV=brentuximab vedotin; PC=physician's choice; ICER=incremental cost effectiveness ratio; LY=life years; QALY=quality adjusted life year; PAS=patient access scheme

References

1. Palanicawandar RM, S; Lozano-Cerrada, S; et al. Allogeneic stem cell transplantion for advanced cutaneous T-cell lymphoma with minimal-intensity conditioning. EORTC, 2017.
2. Morris S. Reduced intensity allogeneic stem cell transplantation for advanced stage mycosis fungoides and Sezary syndrome. A series of 53 patients from the UK. Eur J Cancer. 2018; 101:S36.

31 January 2019 – sent via email

Dear Dr Scarisbrick and Dr Whittaker,

I am the NICE technical lead for the brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma appraisal (ID1190).
Thanks very much for your input at the first committee meeting and submitting consultation responses. We are currently preparing for the second committee meeting on Tuesday 5th February. After reviewing the consultation responses we had some clinical questions about the treatment pathway and wondered whether we could get your input to take to committee.

As shown in the first committee meeting the company present the post-progression treatment pathway for people who relapse following treatment with either brentuximab or PC in two stages. First people receive '**active therapies**' such as combination chemotherapy followed by '**end stage care**' when treatments are no longer effective. End stage care is resource intensive and high cost.

In your clinical experience, for people with advanced CTCL whose disease is not able to be treated with active therapies ('end-stage care'):

1. What treatment/management do people on 'end-stage care' receive, and who would this care be administered by?
2. How long are people expected to receive this 'end-stage care'?
3. Is treatment/management of people in 'end-stage care' expected to change over time, for example, as a patient gets closer to end of life?

Any insight you have on these queries would be greatly appreciated. Apologies that it is such late notice.
If you would prefer to discuss these on the phone. I am available anytime tomorrow or Monday.

Many thanks,
Lorna

Lorna Dunning
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10 Spring Gardens | London SW1A 2BU | United Kingdom
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Web: http://nice.org.uk

Dear Lorna,

We have considered your questions and responded below.

1. What treatment/management do people on 'end-stage care' receive, and who would this care be administered by? Patients with advanced stage MF/SS have a poor prognosis and median survival of just 3 years. There are no curative systemic therapies but for patients with a good performance status allogeneic bone marrow transplantation (allo-HSCT) is considered in first remission as the only curative option. The remaining patients will receive chemotherapeutic regimes after failure of immunotherapies and some will receive palliative radiotherapy for skin disease during this period. All patients end their lives with considerable cutaneous disease requiring intensive skin care and supportive measures which can last years.

2. How long are people expected to receive this 'end-stage care'? Patients with advanced stage disease are in palliative care once they have relapsed after systemic therapy and are not considered candidates for allo–HSCT. Median survival in advanced disease is 3 years so such high intensity end of life care is typically around 30 months. Patients require multiple dressings, pain relief, psychological support and may suffer prolonged periods with significant skin infections.

3. Is treatment/management of people in 'end-stage care' expected to change over time, for example, as a patient gets closer to end of life? In advanced disease once the decision is made that a patient cannot be salvaged for allo-HSCT then end-stage care is initiated. This end of life care tends to involve ongoing intensive treatment psychological and skin care support throughout with little change.

We hope this is self-explanatory but please feel free to contact us with any questions.

Julia , Sean

01 February 2019 – sent via email

Dear Dr Scarisbrick and Dr Whittaker,

I am the NICE technical adviser for the brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma appraisal (ID1190).

To follow up on Lorna Dunning's recent email, we have another clinical question for which we'd appreciate your input ahead of the second appraisal committee meeting, next Tuesday.

We understand that in advanced CTCL patients who have an allogeneic stem cell transplant (alloSCT), if they do not relapse in the first few years following SCT then they are unlikely to relapse thereafter – and that we might consider such individuals to have been successfully cured. We'd like to understand the proportion of patients for whom alloSCT is curative in this way.

Therefore, from your clinical experience, could you please advise whether the proportion of alloSCT patients who are cured (i.e. they never go on to relapse) is closer to 25% or 50%?

If you get chance to get back to us about this, in addition to Lorna's query, we'd be very grateful. Again, please accept our apologies for the late notice of this request.

With best wishes,

Jamie Elvidge
HTA Adviser – Technology Appraisals
National Institute for Health and Care Excellence
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Tel: 44 (0)161 219 3827

Received via email

From: Whittaker Sean
Sent: 01 February 2019 18:21
To: Jamie Elvidge
Cc:
Subject: RE: Additional clinical query on NICE appraisal ID1190 - Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma

Dear Jamie

Our data from the UK cohort and indeed emerging data at major centres in EU and US suggest that the figure is closer to 50% long term CR after reduced intensity alloSCT.

Of course this reflects careful selection of patients ie those with a good response to prior therapy and lack of significant co-morbidities. Of course the data is based on relatively small numbers in view of the rarity and variable follow up. Our experience also suggests that if patients do not relapse within 12-15 months after transplant, they have a sustained remission.

Hope this helps.

Sean