

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

**Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma [ID1062]**

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:**
  - Merck, Sharpe and Dohme
  - NCRI-ACP-RCP

***DHSC submitted a "no comments" response***

***There were no comments received from patient or clinical experts***

- 3. Comments on the Appraisal Consultation Document received through the NICE website**
- 4. ERG critique of the company's ACD responses and updated information**

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

## Pembrolizumab for treating relapsed or refractory classical Hodgkin 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 determination (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	Public	Patient 1	<p>1.1 and 1.3: If Pembrolizumab is not agreed as an option for either of these groups then I would urge the committee to consider how limited any further treatment options are for these adults. I am an adult who has had 5 different times of chemotherapy and Brentuximab. I have not had a stem cell transplant as I have not reached a suitable remission to do so. Without the option of Nivolumab or Pembro on the NHS I am left with only the hope of possibly finding a clinical trial to enter.</p> <p>1.2: The committee has recommended a cost comparison of Pembrolizumab with Nivolumab. Currently the only Hodgkin Lymphoma patients who can access Nivolumab on the NHS are those who have had Brentuximab and a failed autologous stem cell transplant. This leaves patients, like me, in an extremely difficult and unfair position. Costs cannot be compared for patients like me, who have not had a transplant, on the NHS because we are not able to access Nivolumab this way. However, I would urge the committee to request data on patients, like me, who are on Nivolumab and are self-funding. I cannot access Nivolumab, at present, or Pembrolizumab, via the NHS. However, my friends and family raised the funds for me to access 8 lots of Nivolumab, of which I have so far had 4 treatments. My quality of life has improved significantly since being on Nivolumab, which I started in January 2018. I am aware of other patients in a similar position to myself. My fear is that when my funds run out I will no longer be able to access this pioneering immunotherapy and may not be ready then for an allogenic stem cell transplant, which is the aim. My hope is that NICE will approve Pembrolizumab for patients like me so that I can reach a suitable remission and have a transplant. Pembrolizumab works in the same way as Nivolumab and therefore I would hope to go onto it if approved by NICE. I cannot fund Nivolumab endlessly but it is improving all my stats, my mood and my ability to look after my children, who are 1 and 3 years old. Without access to these immunotherapy drugs I, and others like me, may not ever reach the point of a curative allogenic stem cell transplant. I would urge the committee to consider the ethics in denying me and others like access to something that could cure us and enable us to live good quality lives. I think the social impact of me not surviving and bringing up my two little children should be taken into consideration too. I am almost 34 years old and desperately want to see my children grow up.</p>	<p>Comment noted. At the third appraisal committee meeting, the committee further discussed the unmet treatment need for people with relapsed or refractory Hodgkin lymphoma who have been unable to have a stem cell transplant and who have had brentuximab vedotin (population 2). Section 3.1 of the FAD has been updated to reflect this.</p> <p>Following consultation comments and additional analyses received from the company, recommendation 1.2 in the FAD (previously recommendation 1.3 in the ACD) has been amended to recommend pembrolizumab for use within the Cancer Drugs Fund as an option for treating relapsed or refractory Hodgkin lymphoma who have been unable to have a stem cell transplant and who have had brentuximab vedotin.</p>
2	Public	Patient 1	<p>Section 3.3.1 - Consideration has been given to patients like me, population 2, who have not had an autologous stem cell transplant, but have been treated with a number of therapies including Brentuximab. I have not, as considered in the document, relapsed after Brentuximab, as it was not effective at all in treating my Hodgkin Lymphoma. When first diagnosed I was pregnant and my medical team believe this effected the lymphoma I have. Brentuximab did not put me in remission and therefore I did not replase after it.</p> <p>I feel the committee should consider the group I am in very carefully as we are running out of options if immunotherapy is not made available to us on the NHS. If I were to be put forward for an autologous stem cell transplant at present it would, most likely, fail. However, it would make</p>	<p>Comment noted. Pembrolizumab was appraised within its Marketing Authorisation, that is for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin, or who are</p>

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
			<p>me eligible for Nivolumab on the NHS. This would, however, I feel, be a misuse of resources and I would question the ethics too. Unless I have a failed auto transplant or I win the lottery and am able to fund Nivolumab or Pembrolizumab for my treatment I am going to die from this disease.</p> <p>Section 3.2.1 - The paper states, 'The committee noted that because nivolumab is not licenced for use in population 2 (that is, people who have had brentuximab vedotin and who cannot have allogeneic stem cell transplant), a cost-comparison approach could not be used for this population' - then this does not reflect patients, like me and others I know, who are being treated with Nivolumab, who have not had an auto transplant, and for whom Brentuximab has not worked. Although Nivolumab is not yet available to patients like me on the NHS it does not mean we do not exist. I am on Nivolumab, the quality of my life now compared to when I was first diagnosed (October 2016) and when on chemotherapy is vastly greater. I was in intensive care 3 times in 2017. I actually wondered if I was dying on 2 of those occasions. At one point a doctor told me I was 'one of the most ill people in the hospital'. Now I am on Nivolumab I can drive, go shopping, care for my children and live my life relatively normally. To state that it is not possible to compare the cost effectiveness simply reflects that a need for the data concerning self funding patients like me exists.</p>	<p>transplant-ineligible and have failed brentuximab vedotin.</p> <p>At the third appraisal committee meeting, the committee further discussed the unmet treatment need for people with relapsed or refractory Hodgkin lymphoma who have been unable to have a stem cell transplant and who have had brentuximab vedotin (population 2). Section 3.1 of the FAD has been updated to reflect this.</p> <p>Recommendation 1.2 in the FAD (previously recommendation 1.3 in the ACD) has been amended to recommend pembrolizumab for use within the Cancer Drugs Fund as an option for treating relapsed or refractory Hodgkin lymphoma for people who have been unable to have a stem cell transplant and who have had brentuximab vedotin.</p>
3	Public	Patient 1	<p>I would also urge the committee to consider the position that clinicians find themselves in when faced with patients like me. On a weekly basis I have conversations with my nurses and consultants about what the next steps should be should I no longer be able to fund Nivolumab in order to get me ready for an allogenic stem cell transplant. I feel it is unethical and difficult to put clinicians in the position where they cannot prescribe treatment, on the NHS, to patients when they are confident and data exists to show it is effective. I feel very sorry for my consultants who believe immunotherapy is the way forward who cannot let me be treated on the NHS with it.</p> <p>In considering cost effectiveness I would urge the committee to consider the cost of failed treatments for Hodgkin Lymphoma patients like me. If Pembrolizumab or Nivolumab were to be approved for patients like me, who have not had a transplant and for whom Brentuximab has not worked, then this would, I suggest, longer term be much more cost effective than putting patients through numerous costly chemotherapy regimen. I appreciate there are patients for whom chemotherapy is effective, but there is also the cost of the drugs that go with the chemo and the cost to the NHS of treating the side effects patients endure. For example, Escalated BEACOPP resulted in bleeds on both my eyes in February 2017. The NHS then were funding my treatment along with associated drugs, e.g. anti sickness, pain relief, also my staff in</p>	<p>Comment noted. The costs of standard care (where Pembrolizumab is not used) are considered in the economic model. The model also considers any adverse reactions to treatment (if pembrolizumab is used or not) and the impact that this can have on patients.</p> <p>Following consultation comments and additional analyses received from the company, recommendation 1.2 in the FAD (previously recommendation 1.3 in the ACD) has been amended to recommend pembrolizumab for use</p>

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
			<p>intensive care and then my consultations and treatment in the eye clinic too.</p> <p>I would urge the committee to consider the side effects of Pembrolizumab and Nivolumab. Whilst of course they exist they are not as brutal as chemotherapy. There were times, on GDP chemotherapy, when I could barely walk because I felt so spaced out and nauseous. I could not drive and relied on my family to look after me. I certainly could not look after my children. Immunotherapy is a much kinder treatment. Not only is it making me feel so much better, it is also improving my heart rate and oxygen levels. Also, rather than taking 8+ hours, which some treatments I have been on do, it takes 1 hour with a flush of saline before and after. 2 hours of my life every 2-3 weeks instead of days at a time (ICE treatment requires a stay in hospital when administered - again there are cost implications).</p> <p>I have had ABVD, Escalated BEACOPP, ICE, Brentuximab and GDP. None of these have made me as well as I am now and I am desperate for Pembrolizumab, which works like Nivolumab, to be available to me and others like me. I am a young adult with a lot to give. I work with mentally unwell adults and I am mother to two little children. I don't want to die in my 30's.</p>	<p>within the Cancer Drugs Fund as an option for treating relapsed or refractory Hodgkin lymphoma for people who have been unable to have a stem cell transplant and who have had brentuximab vedotin.</p>
4	Public	Patient 2	<p>I am writing in response to the recent appraisal meeting on the consultation on Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma. My understanding from the Appraisal Consultation Document of 9th March 2018 is that the committee is not inclined to make Pembrolizumab available for patients who have had unsuccessful treatment with Brentuximab Vedotin and are ineligible for autologous stem cell transplant. This is due to lack of evidence showing the benefits of Pembrolizumab for this population and the impossibility of conducting a cost comparison on Pembrolizumab versus Nivolumab for this population, as Nivolumab is not funded for this patient group.</p> <p>I would like to provide a patient's perspective on this consultation which I hope you will consider in your decision.</p> <p>I was diagnosed with Hodgkin lymphoma in March 2016, shortly after finding out I was pregnant with my second child. I had ABVD throughout my pregnancy, completing my sixth round four days after my healthy baby daughter was born. Four weeks later I had my first PET scan and we learned ABVD hadn't worked at all, the lymphoma had progressed.</p> <p>The plan was then to have high dose chemotherapy followed by an autologous stem cell transplant. I had two rounds of ESHAP, during which the lymphoma progressed, then a round of IVE, during which it continued to progress. The infusion of these drugs required several days of hospitalisation and care from a dedicated nurse for the duration. They caused me horrendous side effects including sickness, diarrhoea, weight loss, tinnitus, mood changes and severe fatigue. Sadly the hospital stays, side effects and the fact that they didn't work made the first few months of life with my daughter extremely traumatic for me and my family. I had to start antidepressants, sleeping tablets and appointments with a clinical psychologist.</p> <p>At this point it was decided my disease was too stubborn for an autologous transplant to be successful and the aim would now be to get me into remission for an allogeneic stem cell</p>	<p>Comment noted. At the third appraisal committee meeting, the committee further discussed the unmet treatment need for people with relapsed or refractory Hodgkin lymphoma who have been unable to have a stem cell transplant and who have had brentuximab vedotin (population 2). Section 3.1 of the FAD has been updated to reflect this.</p> <p>Following consultation comments and additional analyses received from the company, recommendation 1.2 in the FAD (previously recommendation 1.3 in the ACD) has been amended to recommend pembrolizumab for use within the Cancer Drugs Fund as an option for treating relapsed or refractory Hodgkin lymphoma for people who have been unable to have a stem cell transplant and who have had brentuximab vedotin.</p>

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
			<p>transplant. I went on to have two rounds of CHIVPP, to which I had a mixed response, then four rounds of Brentuximab Vedotin, which initially showed promising results, but the lymphoma eventually progressed. These drugs were more tolerable but still caused significant fatigue.</p> <p>Radiotherapy finally got me into remission in September 2017. However, this also caused very troublesome side effects including complete voice loss for four weeks, severe pain and difficulty swallowing, burns to my skin and fatigue. Not to mention the stress and fatigue caused by having to do an 80 mile round trip to Southampton every week day for almost four weeks, while organising childcare for my two young children.</p> <p>Unfortunately after achieving remission and being ready for my transplant, my immune system had been so weakened by the all the harsh treatments that I was struck down by pneumonia and a series of viruses which took a long time to shake, and prevented it from going ahead. In December 2017 it was confirmed that while I had been overcoming these infections and viruses the lymphoma returned, this time to my abdomen, spine and pelvis.</p> <p>It was at this point I was given the option of trying another traditional chemotherapy available on the NHS, or self-funding Nivolumab, with the ultimate goal still being to go for allogeneic stem cell transplant. It was not an easy decision but my consultant felt Nivolumab was more likely to be effective. As a family we have had to pull together to cover the cost of a few rounds. Not everybody in this position would be so fortunate as to be able to manage this, and indeed for myself it is certainly not an arrangement that can last indefinitely, though I understand that immunotherapy drugs vary in terms of how long they may take to work fully. (Cont...)</p> <p>(...cont) Before I started Nivolumab I had become very unwell. I was in and out of hospital for 1-2 week stays throughout November and December 2017 with unbearable back, stomach and hip pain, sickness, diarrhoea, anaemia and fatigue. I couldn't get out of bed until I'd had my daily dose of 50mg Prednisolone. I was separated from my children for six weeks because I was so vulnerable to viruses, which caused a lot of distress on both sides.</p> <p>I started Nivolumab on 29th December. After an initial inflammatory reaction, which did put me in hospital, I began to feel much better. Within a week of my first dose I was off the steroids completely. I have continued to feel better and better and have just had my sixth dose. I have very few side effects and no symptoms of lymphoma. I have energy to do things with my family, my pain is greatly reduced, I have a good appetite and have gained weight and my blood results are now all within or very close to normal ranges. Although I suffered a nasty virus two weeks ago, for the first time in a year I was able to recover without being admitted to hospital, which would indicate that my immune system seems to be improving. Mentally I feel much more robust, positive and excited about life. My quality of life is immeasurably better than it has been at any time in the two years since I was diagnosed.</p> <p>I had a PET scan after four rounds which showed great improvement of all the disease present in the previous scan. Two new areas lit up but my consultant is hopeful these represents inflammatory processes which may well resolve with more treatment.</p>	

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
			<p>The other huge benefit to me is that Nivolumab is administered very quickly and I am usually in and out of the hospital within two hours - far less time than any other treatments I've had. It seems far less labour intensive to the NHS than the other treatments I've had.</p> <p>Currently the only way for me to be eligible for Nivolumab on the NHS would be to go through an autologous transplant, which would almost certainly fail, putting me at risk and wasting NHS resources. As a 36 year old woman with two young children I feel in complete despair that neither Nivolumab nor Pembrolizumab are available on the NHS to patients in my 'population'. I have always been in good health otherwise, I have a 10/10 matched unrelated donor lined up and am told that I stand a decent chance of a cure if the Nivolumab gets me into remission and I go on to have the transplant.</p> <p>I believe if Nivolumab or Pembrolizumab (which I am told work very similarly) had been offered to me sooner I could have avoided many months of illness caused by side effects of traditional treatments, the infections and viruses caused by the damage these have done to my immune system and the lymphoma which ultimately progressed through every other treatment. I believe with all the hospital admissions and treatment I've required to manage this ill health I have cost the NHS significantly more than if immunotherapy had been offered to me earlier. I believe I would have had my transplant and be on the road to recovery, with less risk of suffering the longer term consequences of multiple chemotherapies and radiotherapy which are likely to be a drain on NHS resources later in my life.</p> <p>As far as being unable to conduct a cost comparison between Pembrolizumab and Nivolumab as Nivolumab is not currently available on the NHS is concerned, this seems somewhat a 'Catch 22' situation. Would it be possible to compare costs using examples of patients such as myself who have self-funded?</p> <p>Thank you in advance for considering my opinions. Please do feel free to contact me if you have any questions or would like to discuss this further.</p>	
5	Consultee	NCRI-ACP-RCP	<p>The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation, We have liaised with our experts and would like to make the following comments.</p>	Comment noted.
6	Consultee	NCRI-ACP-RCP	<p>Our experts are concerned to see that NICE are recommending to not fund pembrolizumab in the group of patients who are not able to receive a stem cell transplant (SCT).</p> <p>Our experts believe that it does not matter to patients and clinicians if pembrolizumab is funded post- (ASCT) and post-BV, as nivolumab is already funded for this indication.</p> <p>However the group who can't make it to an SCT are in desperate need of access to a PD1 inhibitor. These drugs are the go-to drugs the world over (apart from the UK) for this group of mainly young and still potentially curative patients.</p> <p>Our experts believe it would be tragic to deny pembrolizumab to this group as will lead to the needless death of some patients. Clearly it's a small group, but when you have an active drug</p>	<p>Comment noted. At the third appraisal committee meeting, the committee further discussed the unmet treatment need for people with relapsed or refractory Hodgkin lymphoma who have been unable to have a stem cell transplant and who have had brentuximab vedotin (population 2). Section 3.1 of the FAD has been updated to reflect this.</p>

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
			<p>like pembrolizumab which can bridge to curative therapy, really it should be available as a matter of urgency.</p> <p>There is also an equity issue here. Currently people in that group either die, or they crowd fund for the drug, or they fund for it privately. Not everyone can do this so a negative decision will inevitably lead to a disparity based on wealth and ability to mount a social media campaign.</p> <p>Our experts are hopeful that NICE can re-consider its position.</p>	<p>Following consultation comments and additional analyses received from the company. Recommendation 1.2 in the FAD (previously recommendation 1.3 in the ACD) has been amended to recommend pembrolizumab for use within the Cancer Drugs Fund as an option for treating relapsed or refractory Hodgkin lymphoma for people who have been unable to have a stem cell transplant and who have had brentuximab vedotin.</p> <p>The committee noted the equity issue highlighted by the consultee, however it did not consider this to be an equality issue that could be addressed in its decision making. Considerations of the ability of people to pay for treatments privately does not override the committee's duty to take into account the relative costs and benefits of the interventions when deciding whether it should be recommended or not.</p>
7	Company	Merck Sharp & Dohme	<p>MSD recognise the challenges associated with single arm clinical trial evidence and the uncertainty of immature outcome data. We would note however, a lack of consistency for Committee decision making in this instance (population one of ID1062 compared with a recent NICE recommendation (TA462)), where the data from KEYNOTE-087 versus Checkmate-205 are numerically higher. In light of clinical uncertainties about comparable efficacy and the unknown net price for nivolumab, MSD would be reluctant to gamble on responding to the Committee's request for a cost comparison. To do so and subsequently not be recommended would mean that MSD had closed down the ability to fully use the NICE process to achieve a positive recommendation.</p> <p>In relation to population two, we believe there has been insufficient consideration of access opportunities given the significant unmet need. MSD believes population two would benefit from additional data collection within the CDF, which would also provide patients and clinicians with a treatment option where none currently exist.</p>	<p>Comment noted.</p> <p>In the third appraisal committee meeting, the committee were aware that in TA462 the committee concluded that the most plausible ICER was likely to be around £30,000 per QALY gained, which was considerably lower than ICERs generated for population 1 for the current appraisal. The committee also heard from the ERG that in TA462 the committee's and ERG's preferred analyses used the same</p>

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
			<p>We are aware that the SMC has been confident to recommend both nivolumab<sup>1</sup> for population one, and pembrolizumab<sup>2</sup> for populations one and two, although we recognise that the process is different in Scotland.</p> <p>Based on the content of the ACD, the key drivers underpinning the draft negative recommendation(s) are the uncertainty/scepticism around the following points:</p> <p>Model structure</p> <ul style="list-style-type: none"> <li>• Stem cell transplant timing – 12 or 24 week model</li> <li>• Lack of face validity for comparator OS vs. the literature</li> </ul> <p>Comments specific to population 1 and 2</p> <ul style="list-style-type: none"> <li>• Relevance of Cheah et al. 2016 for population 2</li> <li>• Justification that end-of-life criteria are met (short life expectancy)</li> </ul> <p>MSD has responded to the Committee's concerns using the data available. Should you have any questions about the content, or suggestions on how MSD can move this forward to a successful conclusion for patients, please do contact me.</p>	<p>cost of allogenic stem cell transplant as used in the current appraisal. The committee's consideration of this issue is described in section 3.15 of the FAD. The committee considered that, in the absence of a cost comparison with nivolumab, the cost effectiveness models submitted by the company should be used for decision making. Given the considerably higher ICER for population 1 in this appraisal, the committee considered that it was justified in reaching a different conclusion to that reached by the committee for TA462.</p> <p>At the third appraisal committee meeting, the committee considered if pembrolizumab could be recommended for treating population 2 in the Cancer Drugs Fund (see sections 3.21 to 3.25 in the FAD). Recommendation 1.2 in the FAD (previously recommendation 1.3 in the ACD) has been amended to recommend pembrolizumab for use within the Cancer Drugs Fund as an option for treating relapsed or refractory Hodgkin lymphoma for people who have been unable to have a stem cell transplant and who have had brentuximab vedotin.</p>
8	Company	Merck Sharp & Dohme	<p><u>Key points supportive of the MSD approach and assumptions as stated within the released ACD:</u></p> <ul style="list-style-type: none"> <li>• Cheah et al. 2016 is the best available evidence source for population one; and is aligned with the Committee conclusion of TA462</li> <li>• The Committee concluded that pembrolizumab is potentially an important treatment option for population two as the clinical expert explained there is considerable need for this</li> </ul>	Comment noted.

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
			<p>population who have relapsed following treatment with brentuximab vedotin.</p> <ul style="list-style-type: none"> <li>• The Committee heard from the ERG “that on balance the naïve comparison is more appropriate because it provides a more conservative estimate” in terms of comparative clinical effectiveness presented by MSD.</li> <li>• The Committee concluded that incorporating a 2-year stopping rule in its decision-making “was appropriate”.</li> <li>• The Committee agree with the addition of the progressed disease health state post alloSCT and how this has been incorporated into the new 12 and 24 week models.</li> <li>• The agreement that it is appropriate to assume patients with progressed disease would not have an alloSCT.</li> </ul>	
9	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li>• <u>Requested cost comparison of pembrolizumab versus nivolumab for population one of the company’s submission</u><sup>3</sup>.</li> </ul> <p>MSD demonstrated with the initial submission that pembrolizumab is a cost effective treatment option. In response to the Committee discussion (19th December 2017) MSD additionally provided an economic model aligned with the timing used in the economic model by nivolumab (24 weeks); note both the initial and subsequent models produced ICERs below the £50,000 threshold<sup>4 5</sup>.</p> <p>The clinical and economic case has been demonstrated versus the historical control described by Cheah et al. 2016<sup>6</sup> using a conservative estimate derived from a naïve indirect- (base-case) and matched adjusted indirect- (scenario) comparison. This is the same approach considered for the historical mixed standard of care used in the TA462 appraisal for nivolumab<sup>7</sup>.</p> <p>As discussed at the ACM on the 13th February 2018, the Clinical lead of the Cancer Drug Fund (CDF) commented that the true timing of a transplant in England would fall at variable time-points between 12 and 24 weeks. Given that the economic models presented by MSD have demonstrated cost effectiveness at the extremes, a transplant within this time-window would also be cost effective.</p> <p>The ACD reports that clinical experts have informed the Committee “that the clinical effectiveness of pembrolizumab and nivolumab are likely to be similar for population one”<sup>3</sup>. MSD cannot rule out that this is the case; however, when considering the independent data reported from both the nivolumab and pembrolizumab single arm trials, result are more favourable for pembrolizumab in population one. Given the nature of the single arm evidence and the lack of a common comparator the only potential link would be through the use of Cheah et al. 2016, which as noted by the committee is a observational non-controlled historical trial. Taking into consideration the points described above it is unclear what additional certainty the requested analysis would provide. Pembrolizumab is expected to displace a level of current standard of care use, and would occupy the same point of the treatment pathway as TA462.</p> <p>At the time of the company submission (September 2017) TA462 was still within the 90 day implementation period, and NICE confirmed in communication with the ERG “it would be inappropriate to include nivolumab as a new comparator given it is still within the 90-day</p>	<p>Comment noted. At the first appraisal committee meeting, the committee considered the initial company submission for this appraisal. It noted that a fixed time point of 12 weeks was used in the company’s economic model for time to allogeneic stem cell transplant which the committee considered was inappropriate (see section 3.5 of the FAD). In addition, the committee concluded that the omission of a progressed-disease state after allogeneic transplant in the company’s original model was not clinically plausible (see section 3.6 of the FAD).</p> <p>At the second appraisal committee meeting, the committee noted that the company had provided a further model that assumes all allogeneic stem cell transplants occur at 24 weeks and included a progressed-disease state after allogeneic stem cell transplant. However, the committee concluded that, because of considerable concerns about the models provided by the company and uncertainties that had not been fully addressed, the committee could not</p>

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
			implementation period and hence is not considered established practice”8.	<p>accurately estimate a plausible ICER for population 1 or 2 (see sections 3.14, 3.15, 3.20 and 3.21 in the ACD). The committee considered that a cost-comparison with nivolumab for population 1 should be used to address these uncertainties for population 1 (see section 3.14 and 1.2 in the ACD).</p> <p>At the third appraisal committee meeting, the committee noted that a cost comparison with nivolumab had not been provided by the company. It noted both the company’s response to the consultation which highlights that single arm trials are more favourable for pembrolizumab and their statement in the meeting that the two drugs differ in structure (section 3.15 of the FAD). The committee noted that the company had not provided evidence to demonstrate different clinical efficacy between nivolumab and pembrolizumab or provided a convincing explanation as to why the treatment effects would be likely to differ (see section 3.15 of the FAD). The committee therefore considered that ICERs from the company’s submitted models should be used for decision-making because a cost comparison had not been made available.</p>
10	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li data-bbox="631 1329 1655 1433">• <u>Consideration of the best available evidence source for population one and population 2.</u> The Committee concluded that Cheah et al. 2016 was the best available evidence for standard of care for population one, but may not fully reflect UK clinical practice3. This was also</li> </ul>	Comment noted. At the third appraisal committee meeting the committee noted the company’s

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
			<p>discussed and accepted by the Committee for TA4627. MSD has previously acknowledged the limitations of Cheah et al. and has provided a conservative estimate of comparative efficacy by utilising survival estimates based on the whole population at 25.2 months by means of a naïve indirect comparison<sup>5</sup>. This overall estimate is skewed by the inclusion of investigation agents that reported an OS of 47.7 months<sup>6</sup>, but was supported by the ERG and follows the approach used in TA4627. Unfortunately, the use of this overall OS estimate negatively impacts the consideration of short life expectancy (EoL criteria) as discussed below.</p> <p>This ACD states that a recent study by Eyre et al. 2017<sup>9</sup> is now available and might be a useful source of additional comparator data; namely for population two as confirmed by the ERG<sup>3</sup>. In response, MSD carefully reviewed the publically available information and confirmed that due to the aggregate reporting these data would not provide any further certainty around the comparative effect estimates already presented in the company submission versus Cheah et al. 2016. As per earlier dialogue with NICE and the ERG, MSD does not have access to IPLD data for either Cheah et al. 2016 or Eyre et al. 2017<sup>4</sup>. However, in an attempt to aid the Committee in their decision making, MSD has contacted the primary author (Eyre) on the 13th March 2018, and is awaiting a response.</p> <p>We outlined in the MSD response dated 25th January 2018<sup>4</sup>. Key differences relate to the treatment intent of patients included in Eyre et al. compared with KEYNOTE-087; for example, patients in Eyre et al.<sup>9</sup> were enrolled with the intent of subsequent stem cell transplant, which was not considered for patients within KEYNOTE-087<sup>10</sup>. Patients within KEYNOTE-087 are more heavily pre-treated versus Eyre et al. with 96.3%<sup>10</sup> 11 of patients treated with ≥3 lines of therapy versus 71%<sup>9</sup> treated with 2 lines of therapy, respectively. This attests to a potentially “less fit” population in KEYNOTE-087 and would suggest that based on treatment experience, although neither data source are ideal, Cheah et al. 2016 represents the nearest comparable population<sup>6</sup>.</p> <p>In an attempt to explore the impact of Eyre et al. as a relevant patient population for population two of KEYNOTE-087, MSD has conducted a naïve indirect comparison using the publically available data presented within Kaplan-Meier curves in Figure 2C and 2D. The evidence considered represents only those patients (n=38)<sup>9</sup> who did not go on to receive a stem cell transplant at any time. It is possible that additional patients from Eyre et al. could be relevant if IPLD were available. These data should be interpreted with caution as estimates have been digitised from published figures, and comparability of the baseline characteristics is unknown.</p> <p>The results of the naïve indirect comparison are presented Figure 1 and Figure 2 below. Due to the underlying differences observed between the included population and the digitised data from the publication, these analyses are indicative of a direction of treatment effect only. The comparative effectiveness results for pembrolizumab versus Cheah et al. and Eyre et al. are summarised in Table 1. These results show that the HR implemented in the economic model of 13.13 (equivalent to HR 0.08) for population 1 and 2 combined vs. Cheah et al. is comparable to the HR █████ as observed for the comparison between pembrolizumab and the Eyre et al. publication. As per the Committee’s comments in Section 3.4, the results of the naïve indirect</p>	<p>concerns about the Eyre et al. study and discussed the analysis of data from this study which they had provided. Section 3.3 of the FAD has been amended to reflect that the company had provided some exploratory analyses using available data from Eyre et al, which produced similar results to those produced when Cheah et al. is used as the data source for standard of care.</p>

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
			<p>comparison demonstrate that MSD has underestimated the effect of pembrolizumab using the overall Cheah et al. evidence, and therefore represents a more conservative comparative effect estimate; but again these results are only indicative. [Figures 1 and 2 provided but not reproduced here] [Table 1 provided but not reproduced here]</p>	
11	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li>• <u>MSD implementation of Eyre et al. 2017 naïve indirect comparison using 12 and 24 week model</u> As described above, a naïve indirect comparison of population two of KN-087 versus the publically available data reported for Eyre et al. 2017 (n=38)9 has been included in the SA below:</li> <li>• PFS pre 24/12 weeks - The PFS HR derived was [redacted] and inverted [redacted]. When this is applied in the first 24 weeks it slightly over predicts (18%) the observed data from Eyre (13% at 6 months); hence as for the Cheah data MSD has calculated a HR to predict the reported PFS which is HR=4.21 (24 week model) and HR=6.57 (12 week model).</li> <li>• OS pre 24/12 weeks – The OS HR derived was [redacted] and inverted to [redacted]=[redacted] estimated which slightly under predicts the survival of Eyre of 78% at 76%. Hence as for the Cheah data MSD has calculated a HR to predict the reported OS which is HR=10.08 (24 week model) and HR=6.77 (12 week model).</li> <li>• Response data – There is no reported response data from Eyre. Thus the RR from Cheah et al. 2016 has been used, which given the high rate of progression in the first 6 months the response rates will have a minimal impact on the results.</li> <li>• PF post 24/12 weeks – HR [redacted] (for the 24 week model) and HR=[redacted] (for the 12 week model) in line with methodology vs. Cheah et al. 2016</li> <li>• PPS – Calculated as it was for Cheah using a mOS of 12.2 months from Eyre [Calculations provided but not reproduced here] [Table 2 provided but not reproduced here]</li> </ul>	Comment noted.
12	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li>• <u>The difference in overall survival between pembrolizumab and standard care is overestimated at week 24</u> In response to the ACD Section 3.7, the Committee was noted to disagree with the HR used for OS 0-24 weeks. The ACD states that the using this HR, the model predicts an underestimation of SoC patients alive at week 24 of 78% and 72% (population 1 and 2) alive versus the Cheah 2016 paper – 88% across both populations3. This is correct using the original week 12 parametric curve (log normal). Using the 24 week model base case 0-24 week OS parametric curve of exponential, this is 81% and 72% (population 1 and 2). MSD note that the company submission showed the extreme conservative value of HR=1 for 0-24 week OS in scenario analysis which over predicted survival to 98% in the SoC arm and that the base case HR was the only evidence based estimate available11. In order to resolve these issues, MSD presents a new analysis for population 1 and 2 below with alternative HR for week 0-24 OS. Using Goal Seek in Microsoft excel to return the exact HR which produces SoC OS at week 24 of that reported in Cheah et al. 2016. It should be noted, that this approach is not evidence based. Given that the Committee already had the upper and lower bounds of this HR, we are unclear what additional certainty this could provide.</li> </ul>	Comment noted. At the third appraisal committee meeting the committee considered the new analysis and alternative hazard ratios provided by the company. It heard from the ERG that they had concerns about the use of a methodology that matched overall survival estimates to those at a single point, because this did not follow conventional curve fitting methodology and may result in the curve being a poor fit to the data at other time points. However, because data were not provided to

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
			<p>A scenario analysis is shown below (Table 3) including the 24 week model base case using base case settings from the company submission, other than those explained in the analysis report 25th January, to update for 24 week time point with an additional analysis using this base case with the following HR which force the model to predict 88% OS for SoC based on Cheah at week 24 for both population 1 (HR=8.01 exponential distribution) and 2 (HR=5.18 exponential distribution). Please note the PFS pre 24 weeks in the table below is as per the company submission (gen gamma population 2 and log logistic population 1). [Table 3 provided but not reproduced here]</p>	<p>validate the use of the 13.13 hazard ratio and a hazard ratio of 1.0 lacked face validity, the ERG had a slight preference for using the alternative hazard ratios in the week 24 economic model. The committee further concluded that the difference in overall survival at week 24 is subject to uncertainty, but is likely to have been overestimated in the model using a naïve indirect comparison between Cheah and KEYNOTE-087. Section 3.7 of the FAD has been amended to reflect this.</p>
13	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li><u>The choice of parametric overall and progression-free survival curves used to model the pre-allogeneic transplant period introduces additional uncertainty</u> In the ACD Section 3.8, the Committee was noted to disagree with the parametric model used for week 0-24 OS in the base case analysis. As stated in the company submission, the exponential distribution was chosen as it estimated the closest proportions of patients alive versus the KN-087 data at week 24. However, it was not the best statistical fit based on AIC/BIC. MSD have fitted a 0-24 week HR in response to Section 3.7 above which results in the exact SoC OS at week 24 reported in the literature. However, the Committee mention the use of KM data for weeks 0-24 from KN-087 for the pembrolizumab arm. In order to use this, MSD would also need to digitise the KM from the Cheah et al. study for the SoC arm since the IPLD for Cheah is not available. MSD notes that the use of the comparative HR in the SA above would produce almost identical results.</li> </ul>	<p>Comment noted. The committee considered that the use of observed survival data in the pre-allogeneic stem cell transplant period would have been preferable (section 3.8 of the FAD).</p>
14	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li><u>The uptake rate of allogeneic stem cell transplant is uncertain</u> Section 3.9 of the ACD states that the Committee remain uncertain about the validity and reliability of clinical predictions from the clinician survey presented in the company submission to estimate the rate of alloSCT uptake. MSD responded during clarification questions that KEYNOTE-087 was not designed as a bridge to transplant study, and therefore data were not reflective of transplant use, or specific UK clinical practice<sup>5</sup>. This uncertainty was also a discussed by the committee for nivolumab for a group of patients equivalent to population one<sup>12</sup>.  MSD recognise that there are limitations associated with the use of qualitative research methods. However, we are mindful that this approach was accepted by the Committee for TA4627. MSD believes that the same consideration should be applied to both population one and two of this submission, to ensure consistency with TA462.  Population two was not considered in TA462. MSD believes that should the Committee decide</li> </ul>	<p>Comment noted. The committee noted that to estimate the uptake of allogeneic stem cell transplant, the company combined results from 2 surveys of clinicians, and that the same clinicians could have been included in both surveys, potentially resulting in double-counting in the combined results. The committee concluded that in addition to uncertainty in rates of allogeneic stem cell transplant because of concerns about the validity and</p>

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
			that, given no precedent, it cannot make a positive recommendation for this group, consideration should be given to what additional real world data could be collected that would reduce uncertainty whilst patients gained access via the CDF.	reliability of clinical predictions, there were further concerns because of potential duplication of clinicians in the combined survey (see section 3.9 in the FAD).  At the third appraisal committee meeting the committee considered recommending population 2 in the Cancer Drugs Fund. Sections 3.21 to 3.24 have been added to the FAD to reflect this.
15	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li>There is considerable uncertainty about the utility value for progressed disease<sup>3</sup> MSD notes the agreement that the utility value for progressed disease (PD), which the ERG had used is considered to be too high and that the true value lays between the company submission and ERG base case PD utility value. In order to address some of this uncertainty, MSD have presented a SA below using the 0-24 OS HR detailed above (cohort 1 HR=8.01 and cohort 2 HR=5.176) and a PD utility of [REDACTED] which is the average of the company base case PD utility and the ERG preferred mixed model PD utility. Using this PD utility produced ICERs for cohort 1 and 2 both below £50,000/QALY for week 24 and 12 (Table 4). [Table 4 provided but not reproduced here]</li> </ul>	Comment noted.
16	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li><u>The time to allogeneic stem cell transplant is a key driver of cost-effectiveness estimates and there is considerable uncertainty about the true value</u> Within the original company submission MSD based the time to allogeneic stem cell transplant (alloSCT) (12 weeks) on the availability of data and the feedback of clinical experts. In response to the request for additional modelling analyses by NICE (January 2018)<sup>4</sup>, MSD provided an economic model incorporating a 24 week time point. This is aligned to the time-point accepted by the Committee for TA4627. Subsequent discussion at the second committee meeting (13th February 2018) has reflected that alloSCT within English clinical practice is likely to occur somewhere between weeks 12 and 24 and not at a fixed time point for all patients, nor for all patients at once<sup>5</sup>. This was supported by the comments from clinical experts and the Clinical lead of the CDF at the same meeting. The committee has been presented ICERs using both a 12 and 24 week time-point model; this provides the extreme ICER range and the logic that a clinical practice ICER exists between these bounds.</li> </ul>	Comment noted. Section 3.13 of the FAD notes the committee's conclusion that most plausible ICER is therefore likely to fall between the values predicted by models using a fixed time of transplant of 12 and 24 weeks. The committee considered the full range of ICERs produced from updated models provided for the third appraisal committee meeting. However, because of the considerable uncertainty associated with model results there is insufficient justification for recommending pembrolizumab as a cost-effective use of NHS resources.
17			<ul style="list-style-type: none"> <li><u>The cost effectiveness of pembrolizumab in population 1 is highly uncertain and a plausible ICER cannot be accurately estimated using the company's 12 or 24 week model. An alternative cost comparison approach is recommended AND</u></li> </ul>	Comment noted.

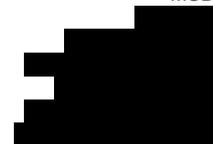
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			<p>• <u>The cost effectiveness of pembrolizumab in population 2 is highly uncertain, and a plausible ICER cannot be accurately estimated using the company's 12 or 24 week models</u><sup>3</sup> As per the comments above, MSD questions the validity of a cost comparison vs. nivolumab, and reflect the prior Committee decision that nivolumab is a cost effective treatment option (TA462) for patients that are comparable with population one of this submission. The ACD states that the ERG model preferences were not fully implemented in the updated 12 or 24 week models. As per the results of Table 5 below, MSD has conducted an analysis taking into account all of the ERG preferences (as per ERG report, page 98)<sup>8</sup>, with the exception of alloSCT transplants in PD patients, as the Committee agreed this is not plausible.</p> <p>Preferred ERG assumptions<sup>8</sup>: [List of model amendments provided but not reproduced here]</p> <p>The ICERs taking into account the ERG preferences in the week 24 model, other than PD alloSCT, produce ICERs below £50,000/QALY for both cohorts 1 and 2 (Table 5). Therefore, MSD disagree that the ERG base case ICER would be about £14,000/QALY more than the new 24 week model base case presented for cohort 1 and above £50,000 in cohort 2. Whilst the 12 week model ICERs are above £50,000/QALY using the ERG base case assumptions, MSD reflect that the Committee were able to reach a conclusion considering only a single time point of 24 weeks in the nivolumab submission and that the true ICER value is likely to lie somewhere between the two estimates.</p> <p>Section 3.14 of the ACD also states that the costs generated by modelling SoC in the original model were double that of the nivolumab submission in the same population. MSD propose that the rationale for this is that the nivolumab submission utilised a much lower alloSCT cost (£21,672), the higher alloSCT cost used in the MSD model (£110,374) accounts for around 50% of the costs in the model. The submitting company for the nivolumab submission was subsequently asked to include higher cost for alloSCT which the MSD model included from the beginning in order to be conservative.</p> <p>To contextualise the impact using lower costs associated with alloSCT (£21,672) and monitoring (£91.69/month), comparable to those used in the nivolumab base case from their original company submission, MSD has provided a SA applying these costs (Table 6). It can be seen that this has a significant impact on reducing the ICER across both populations but also that the SoC total costs are much more in line with those reported in the original nivolumab company submission alloSCT scenario analysis (Table 76)<sup>12</sup> of between £22,866 and £24,880 at the same time point for alloSCT of 24 weeks. It should also be noted that the nivolumab submission ICER, on which a decision was made, included a higher proportions of alloSCT (██████████) and when these values are tested in the MSD model the ICER is reduced further to the mid £20,000's/QALY versus the same time point for alloSCT used in the nivolumab model of 24 weeks.</p> <p>[Tables 5 and 6 provided but not reproduced here]</p>	<p>At the third appraisal committee meeting, the committee considered the results of the updated models, including analysis provided by the company that implemented the ERG's preferences in its base case. It further noted the ERG's analysis implementing its preferred assumptions in the company's updated models and the ERG's comment that the ICERs produced were very close to those produced by the company.</p> <p>The committee noted an ERG comment that the committee's preferred analysis in TA462 used the higher costs for allogenic stem cell transplant from Radford et al. (2017); which had been used in the base case model analyses in this appraisal. The committee further noted that the committee in TA462 concluded that the most plausible ICER for nivolumab is likely to be around £30,000 per QALY gained.</p> <p>Despite considerable uncertainty in the results of the model provided by the company for this appraisal, the model results had to be used for decision making because a requested cost comparison with nivolumab for this population was not</p>

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
				<p>provided. The committee noted that the estimated ICERs in the current appraisal are substantially higher than the most plausible ICER in TA462. The committee took into account the case for pembrolizumab meeting the end-of-life criteria (see sections 3.19 and 3.20). However, because of the considerable uncertainty associated with model results there is insufficient justification for recommending pembrolizumab for routine commissioning as a cost-effective use of NHS resources.</p>
18	Company	Merck Sharp & Dohme	<ul style="list-style-type: none"> <li>• <u>Consideration of end of life criteria, a lack of face validity between modelled survival estimates and the clinical evidence AND</u></li> <li>• <u>The total life years predicted by the company's models exceeds 24 months<sup>3</sup></u></li> </ul> <p>The criteria for End of Life (EoL) were accepted for TA4627, with the committee acknowledging uncertainty based on the nivolumab model outputs. For consistency MSD believes, given the same uncertainty applied, that EoL criteria should apply.</p> <p>As previously confirmed by the company, and as per the case of TA462<sup>7</sup>, the modelled OS is overestimated by the economic models for standard care. MSD that the nivolumab FAD states that: 'The Committee noted that the company's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. However, the Committee also considered the data from the Haematological Malignancy Research Network provided by the company in response to consultation, which showed shorter survival and suggested that the Cheah study may have been optimistic. The Committee acknowledged that nivolumab did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply. It therefore agreed that on balance, nivolumab met the criterion for short life expectancy, and that it would take this into account in its decision-making'<sup>7</sup>.</p> <p>Regarding the LYs predicted by the company model versus the nivolumab model, the SoC data could not be separated in terms of those who had alloSCT (around 20% in Cheah), which would increase the OS for SoC patients even with the company model set to zero alloSCT. The nivolumab ACD response from the Committee papers dated May 2017 stated that when alloSCT was not included in the nivolumab submission the ERG base case total LYs generated was 2.93312. For comparison if alloSCT is excluded from the MSD model a total LYs of 2.946 are generated for SoC and therefore the models are predicting almost identical survival with the exclusion of alloSCT. This is aligned with the mean of 39.4 months predicted by extrapolated overall survival data from Cheah in the nivolumab submission (see Figure 5 extrapolation from</p>	<p>Comment noted. At the third appraisal committee meeting, the committee noted the company's explanation for the higher number of life years produced by the models (see section 3.17 of the FAD) and noted the conclusion of the NICE technology appraisal committee for nivolumab, in which models using Cheah data for standard care also predicted overall survival of more than 24 months for the comparator treatment arm. The committee concluded that while pembrolizumab did not unequivocally meet the criterion for short life expectancy, it was plausible that the criterion could apply, and therefore the committee agreed that on balance, pembrolizumab met the criterion for short life expectancy. Section 3.19 of the FAD has been amended to reflect this.</p>

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
			<p>the submission documents below)<sup>12</sup>. The marked difference in the median and the mean is due to the skew in the overall survival data.</p> <p>[Figure 5 provided but not reproduced here]</p> <p>The issue around life expectancy of SoC patients relates to the external validity of the model due to the relevance of the Cheah data to the target population in this submission. For cohort 1 the consensus from the Committee in the nivolumab submission was that despite the model predicting in excess of 24 months survival there was external evidence that the Cheah data overestimated survival. However, none of the additional clinical evidence is suitable for use within an economic model; therefore, Cheah represents the best available data. Given this is the case; the current model is conservative as the ICER is generated from a superior SoC that results in lower incremental gain than expected in UK clinical practice.</p> <p>Similarly, given the mean overall survival from Lafferty is &gt;10 years, if ~20% received alloSCT in SoC (estimation from the model) the mean overall survival cannot be less than 2 years after the first 24 weeks and this is assuming that the remaining 80% die immediately, therefore MSD cannot produce a model which underestimates life expectancy given the use of the agreed best available data but note the difference in opinion of the clinical community in both this and the nivolumab submission that the life expectancy of SoC patients is less than 24 months.</p> <p>MSD recognise the opinion of clinical experts that confirm the short life expectancy of both population as evident by the available literature "...expect overall survival, particularly for population two, to be close to that reported in the literature (median OS between 17.1 and 19 months)" (Section 3.16). MSD has reviewed the findings of Eyre et al. 2017 and believe that these results further support the short life expectancy of population two, with a reported median OS of 12.2 months (95% CI 8.1-18.3 months) for patients who did not receive a stem cell transplant.</p>	<p>The committee took into account the case for pembrolizumab meeting the end-of-life criteria (see sections 3.19 and 3.20). However, because of the considerable uncertainty associated with model results there is insufficient justification for recommending pembrolizumab for routine commissioning as a cost-effective use of NHS resources.</p>
19	Company	Merck Sharp & Dohme	<p><u>MSD request consideration of population two for use within Cancer Drugs Fund</u> Given all the above MSD believe that there is no reason that the Committee cannot give a positive recommendation for population one.</p> <p>Population two was not considered within TA462 and there is unmet need for this population. As per section 3.15 of the ACD, the Committee noted that the cost effectiveness of pembrolizumab is highly uncertain and cannot be accurately estimated using the company's 12 or 24 week model. As communicated within the company submission there are no further data planned to support this submission.</p> <p>MSD would suggest that this underlying uncertainty expressed by the Committee should be addressed by recommending pembrolizumab for population two within the CDF. This would allow additional data to be collected to help reduce uncertainty; furthermore, it would also provide access to an innovative and clinically effective treatment option for a population who currently have no alternative treatment choice following relapse with brentuximab vedotin</p>	<p>Comment noted. At the third appraisal committee meeting, the committee considered that there is considerable uncertainty about the most plausible ICER for pembrolizumab in this population (see section 3.16 of the FAD), and therefore it cannot be recommended for use in routine commissioning. However the committee considered that it is plausible that pembrolizumab could be cost effective in this population and that</p>

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
			<p>(Section 3.13). MSD believe that pembrolizumab has the potential to be cost effective within population two and that the company has presented a number of ICERs that are below the £50,000 threshold.</p> <p>The following data points are feasible for collection within the CDF:</p> <ul style="list-style-type: none"> <li>o Timing of stem-cell transplant</li> <li>o Duration of treatment with pembrolizumab before stem cell transplant</li> <li>o The proportion of patients treated with pembrolizumab who go to receive subsequent stem cell transplant (currently based on expert clinical opinion)</li> <li>o The long term follow-up of patients treated with pembrolizumab, with or without subsequent SCT post pembrolizumab.</li> </ul> <p>[Reference list provided but not reproduced here]</p>	<p>further data collection facilitated by inclusion in the Cancer Drugs Fund would provide data to give a more accurate estimate of the cost effectiveness of pembrolizumab in this population. Sections 3.21 to 3.25 have been added to the FAD to reflect this.</p>

No comment received from Department of Health and Social Care.



Donna Barnes  
Technology Appraisals Project Manager - Committee A  
National Institute for Health and Care Excellence

23<sup>rd</sup> March 2018

**Pembrolizumab for treating relapsed or refractory classical Hodgkin's Lymphoma [ID1062] – Response to Appraisal Consultation Document (ACD)**

Dear Donna,

MSD recognise the challenges associated with single arm clinical trial evidence and the uncertainty of immature outcome data. We would note however, a lack of consistency for Committee decision making in this instance (population one of ID1062 compared with a recent NICE recommendation (TA462)), where the data from KEYNOTE-087 versus Checkmate-205 are numerically higher. In light of clinical uncertainties about comparable efficacy and the unknown net price for nivolumab, MSD would be reluctant to gamble on responding to the Committee's request for a cost comparison. To do so and subsequently not be recommended would mean that MSD had closed down the ability to fully use the NICE process to achieve a positive recommendation.

In relation to population two, we believe there has been insufficient consideration of access opportunities given the significant unmet need. MSD believes population two would benefit from additional data collection within the CDF, which would also provide patients and clinicians with a treatment option where none currently exist.

We are aware that the SMC has been confident to recommend both nivolumab<sup>1</sup> for population one, and pembrolizumab<sup>2</sup> for populations one and two, although we recognise that the process is different in Scotland.

Based on the content of the ACD, the key drivers underpinning the draft negative recommendation(s) are the uncertainty/scepticism around the following points:

Model structure

- Stem cell transplant timing – 12 or 24 week model
- Lack of face validity for comparator OS vs. the literature

Comments specific to population 1 and 2

- Relevance of Cheah et al. 2016 for population 2
- Justification that end-of-life criteria are met (short life expectancy)

MSD has responded to the Committee's concerns using the data available. Should you have any questions about the content, or suggestions on how MSD can move this forward to a successful conclusion for patients, please do contact me.

Kind regards,

[Redacted signature]

[Redacted contact information]

**Key points supportive of the MSD approach and assumptions as stated within the released ACD<sup>3</sup>:**

- Cheah et al. 2016 is the best available evidence source for population one; and is aligned with the Committee conclusion of TA462
- The Committee concluded that pembrolizumab is potentially an important treatment option for population two as the clinical expert explained there is considerable need for this population who have relapsed following treatment with brentuximab vedotin.
- The Committee heard from the ERG “that on balance the naïve comparison is more appropriate because it provides a more conservative estimate” in terms of comparative clinical effectiveness presented by MSD.
- The Committee concluded that incorporating a 2-year stopping rule in its decision-making “was appropriate”.
- The Committee agree with the addition of the progressed disease health state post alloSCT and how this has been incorporated into the new 12 and 24 week models.
- The agreement that it is appropriate to assume patients with progressed disease would not have an alloSCT.

## **MSD UK response to key drivers underpinning the preliminary negative recommendation in the ACD:**

- Requested cost comparison of pembrolizumab versus nivolumab for population one of the company's submission<sup>3</sup>.

MSD demonstrated with the initial submission that pembrolizumab is a cost effective treatment option. In response to the Committee discussion (19<sup>th</sup> December 2017) MSD additionally provided an economic model aligned with the timing used in the economic model by nivolumab (24 weeks); note both the initial and subsequent models produced ICERs below the £50,000 threshold<sup>4 5</sup>.

The clinical and economic case has been demonstrated versus the historical control described by Cheah et al. 2016<sup>6</sup> using a conservative estimate derived from a naïve indirect- (base-case) and matched adjusted indirect- (scenario) comparison. This is the same approach considered for the historical mixed standard of care used in the TA462 appraisal for nivolumab<sup>7</sup>.

As discussed at the ACM on the 13<sup>th</sup> February 2018, the Clinical lead of the Cancer Drug Fund (CDF) commented that the true timing of a transplant in England would fall at variable time-points between 12 and 24 weeks. Given that the economic models presented by MSD have demonstrated cost effectiveness at the extremes, a transplant within this time-window would also be cost effective.

The ACD reports that clinical experts have informed the Committee “that the clinical effectiveness of pembrolizumab and nivolumab are likely to be similar for population one”<sup>3</sup>. MSD cannot rule out that this is the case; however, when considering the independent data reported from both the nivolumab and pembrolizumab single arm trials, result are more favourable for pembrolizumab in population one. Given the nature of the single arm evidence and the lack of a common comparator the only potential link would be through the use of Cheah et al. 2016, which as noted by the committee is a observational non-controlled historical trial. Taking into consideration the points described above it is unclear what additional certainty the requested analysis would provide. Pembrolizumab is expected to displace a level of current standard of care use, and would occupy the same point of the treatment pathway as TA462.

At the time of the company submission (September 2017) TA462 was still within the 90 day implementation period, and NICE confirmed in communication with the ERG “it would be inappropriate to include nivolumab as a new comparator given it is still within the 90-day implementation period and hence is not considered established practice”<sup>8</sup>.

- Consideration of the best available evidence source for population one and population 2<sup>3</sup>.

The Committee concluded that Cheah et al. 2016 was the best available evidence for standard of care for population one, but may not fully reflect UK clinical practice<sup>3</sup>. This was also discussed and accepted by the Committee for TA462<sup>7</sup>. MSD has previously acknowledged the limitations of Cheah et al. and has provided a conservative estimate of comparative efficacy by utilising survival estimates based on the whole population at 25.2 months by means of a naïve indirect comparison<sup>5</sup>. This overall estimate is skewed by the inclusion of investigation agents that reported an OS of 47.7 months<sup>6</sup>, but was supported by the ERG and follows the approach used in TA462<sup>7</sup>. Unfortunately, the use of this overall OS estimate negatively impacts the consideration of short life expectancy (EoL criteria) as discussed below.

This ACD states that a recent study by Eyre et al. 2017<sup>9</sup> is now available and might be a useful source of additional comparator data; namely for population two as confirmed by the ERG<sup>3</sup>. In response, MSD carefully reviewed the publically available information and confirmed that due to the aggregate reporting these data would not provide any further certainty around the comparative effect estimates already presented in the company submission versus Cheah et al. 2016. As per earlier dialogue with NICE and the ERG, MSD does not have access to IPLD data for either Cheah et al. 2016 or Eyre et al. 2017<sup>4</sup>. However, in an attempt to aid the Committee in their decision making, MSD has contacted the primary author (Eyre) on the 13<sup>th</sup> March 2018, and is awaiting a response.

We outlined in the MSD response dated 25<sup>th</sup> January 2018<sup>4</sup>. Key differences relate to the treatment intent of patients included in Eyre et al. compared with KEYNOTE-087; for example, patients in Eyre et al.<sup>9</sup> were enrolled with the intent of subsequent stem cell transplant, which was not considered for patients within KEYNOTE-087<sup>10</sup>. Patients within KEYNOTE-087 are more heavily pre-treated versus Eyre et al. with 96.3%<sup>10 11</sup> of patients treated with  $\geq 3$  lines of therapy versus 71%<sup>9</sup> treated with 2 lines of therapy, respectively. This attests to a potentially “less fit” population in KEYNOTE-087 and would suggest that based on treatment experience, although neither data source are ideal, Cheah et al. 2016 represents the nearest comparable population<sup>6</sup>.

In an attempt to explore the impact of Eyre et al. as a relevant patient population for population two of KEYNOTE-087, MSD has conducted a naïve indirect comparison using the publically available data presented within Kaplan-Meier curves in Figure 2C and 2D. The evidence considered represents only those patients (n=38)<sup>9</sup> who did not go on to receive a stem cell transplant at any time. It is possible that additional patients from Eyre et al. could be relevant if IPLD were available. These data should be interpreted with caution as estimates have been digitised from published figures, and comparability of the baseline characteristics is unknown.

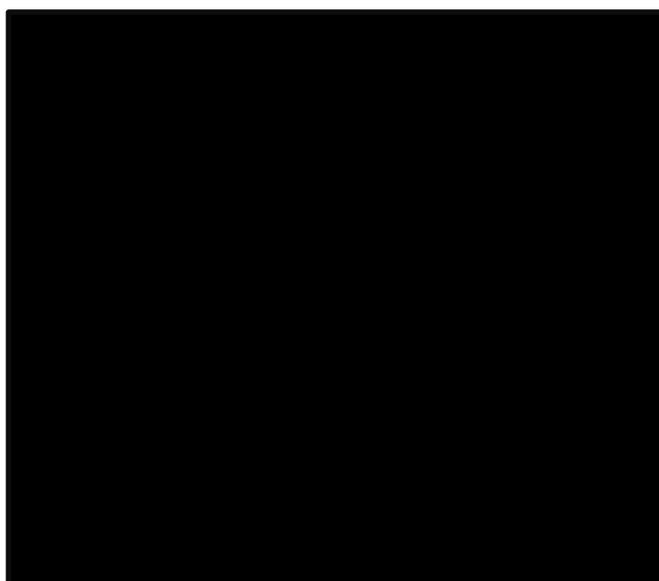
The results of the naïve indirect comparison are presented Figure 1 and Figure 2 below. Due to the underlying differences observed between the included population and the digitised data from the publication, these analyses are indicative of a direction of treatment effect only. The comparative effectiveness results for pembrolizumab versus Cheah et al. and Eyre et al. are summarised in Table 1. These results show that the HR implemented in the

economic model of 13.13 (equivalent to HR 0.08) for population 1 and 2 combined vs. Cheah et al. is comparable to the HR [REDACTED] as observed for the comparison between pembrolizumab and the Eyre et al. publication. As per the Committee's comments in Section 3.4, the results of the naïve indirect comparison demonstrate that MSD has underestimated the effect of pembrolizumab using the overall Cheah et al. evidence, and therefore represents a more conservative comparative effect estimate; but again these results are only indicative.

**Figure 1. Overall survival naïve indirect comparison (KEYNOTE-087 population 2, versus Eyre et al. 2017)**



**Figure 2. Progression free survival naïve indirect comparison (KEYNOTE-087 population 2, versus Eyre et al. 2017)**



**Table 1. Results of Naïve indirect comparison**

	KN-087* (C2) vs. Eyre et al. 2017	KN-087* (C1&C2) vs. Cheah et al. 2016	KN-087 <sup>†</sup> (C1 & C2) vs. Cheah et al. 2016
<b>OS</b>	██████████	██████████	0.08 (0.02, 0.33)
<b>PFS</b>	██████████	██████████	0.18 (0.12, 0.27)

\*These data are derived using a March 2017 data cut for KEYNOTE-087

<sup>†</sup>These data were provided in response to updated model request (24 weeks) and were based on a KEYNOTE-087 data cut of June 2016<sup>4</sup>

- MSD implementation of Eyre et al. 2017 naïve indirect comparison using 12 and 24 week model

As described above, a naïve indirect comparison of population two of KN-087 versus the publically available data reported for Eyre et al. 2017 (n=38)<sup>9</sup> has been included in the SA below:

- **PFS pre 24/12 weeks** - The PFS HR derived was ██████████ and inverted ██████████ = ██████████. When this is applied in the first 24 weeks it slightly over predicts (18%) the observed data from Eyre (13% at 6 months); hence as for the Cheah data MSD has calculated a HR to predict the reported PFS which is HR=4.21 (24 week model) and HR=6.57 (12 week model).
- **OS pre 24/12 weeks** – The OS HR derived was ██████████ and inverted to ██████████ = ██████████ estimated which slightly under predicts the survival of Eyre of 78% at 76%. Hence as for the Cheah data MSD has calculated a HR to predict the reported OS which is HR=10.08 (24 week model) and HR=6.77 (12 week model).
- **Response data** – There is no reported response data from Eyre. Thus the RR from Cheah et al. 2016 has been used, which given the high rate of progression in the first 6 months the response rates will have a minimal impact on the results.
- **PF post 24/12 weeks** – HR ██████████ (for the 24 week model) and HR=██████████ (for the 12 week model) in line with methodology vs. Cheah et al. 2016
- **PPS** – Calculated as it was for Cheah using a mOS of 12.2 months from Eyre

$$\begin{aligned}
 \bullet \quad E[\text{median}] &= \frac{\ln(2)}{\lambda} \\
 \lambda_{\text{month}} &= \frac{\ln(2)}{12.2} \\
 \lambda_{\text{week}} &= \lambda_{\text{month}} / \left( \left( \frac{365.25}{7} \right) / 12 \right) \\
 1 - \lambda_{\text{week}} &= 98.69\%
 \end{aligned}$$

**Table 2. Cohort 2 naïve indirect comparison with Eyre data scenario analysis**

Scenario	Cohort	Pembrolizumab			UK SOC			Pembrolizumab vs UK SOC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base case 24 week model	Cohort 2	84,651	5.302	3.069	29,827	2.998	1.585	54,823	1.484	36,950
Base case 12 week model	Cohort 2	90,953	5.775	3.392	51,425	4.832	2.681	39,527	0.711	55,628
Base case new 24 week model with updated Eyre HR	Cohort 2	81,533	4.433	2.692	25,141	2.075	1.147	56,392.	1.546	36,483
Base case new 12 week model with updated Eyre HR	Cohort 2	88,147	4.993	3.054	42,824	3.442	1.994	45,322	1.061	42,724

- The difference in overall survival between pembrolizumab and standard care is overestimated at week 24<sup>3</sup>

In response to the ACD Section 3.7, the Committee was noted to disagree with the HR used for OS 0-24 weeks. The ACD states that the using this HR, the model predicts an underestimation of SoC patients alive at week 24 of 78% and 72% (population 1 and 2) alive versus the Cheah 2016 paper – 88% across both populations<sup>3</sup>. This is correct using the original week 12 parametric curve (log normal). Using the 24 week model base case 0-24 week OS parametric curve of exponential, this is 81% and 72% (population 1 and 2). MSD note that the company submission showed the extreme conservative value of HR=1 for 0-24 week OS in scenario analysis which over predicted survival to 98% in the SoC arm and that the base case HR was the only evidence based estimate available<sup>11</sup>.

In order to resolve these issues, MSD presents a new analysis for population 1 and 2 below with alternative HR for week 0-24 OS. Using Goal Seek in Microsoft excel to return the exact HR which produces SoC OS at week 24 of that reported in Cheah et al. 2016. It should be noted, that this approach is not evidence based. Given that the Committee already had the upper and lower bounds of this HR, we are unclear what additional certainty this could provide.

A scenario analysis is shown below (Table 3) including the 24 week model base case using base case settings from the company submission, other than those explained in the analysis report 25<sup>th</sup> January, to update for 24 week time point with an additional analysis using this base case with the following HR which force the model to predict 88% OS for SoC based on Cheah at week 24 for both population 1 (HR=8.01 exponential distribution) and 2 (HR=5.18 exponential distribution). Please note the PFS pre 24 weeks in the table below is as per the company submission (gen gamma population 2 and log logistic population 1).

**Table 3. Scenario analysis using new Goal Seek function to derive HR's**

Scenario	Cohort	Pembrolizumab			UK SOC			Pembrolizumab vs UK SOC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base case 24 week model	Cohort 1	107,185	6.177	3.730	41,475	3.925	2.170	65,710	1.560	42,123
	Cohort 2	84,651	5.302	3.069	29,827	2.998	1.585	54,823	1.484	36,950
Base case new 24 week model with updated HR	Cohort 1	107,185	6.177	3.730	42,545	4.132	2.263	64,640	1.467	44,057
	Cohort 2	84,651	5.302	3.069	32,318	3.468	1.799	52,332	1.270	41,208

- The choice of parametric overall and progression-free survival curves used to model the pre-allogeneic transplant period introduces additional uncertainty<sup>3</sup>

In the ACD Section 3.8, the Committee was noted to disagree with the parametric model used for week 0-24 OS in the base case analysis. As stated in the company submission, the exponential distribution was chosen as it estimated the closest proportions of patients alive versus the KN-087 data at week 24<sup>11</sup>. However, it was not the best statistical fit based on AIC/BIC. MSD have fitted a 0-24 week HR in response to Section 3.7 above which results in the exact SoC OS at week 24 reported in the literature. However, the Committee mention the use of KM data for weeks 0-24 from KN-087 for the pembrolizumab arm. In order to use this, MSD would also need to digitise the KM from the Cheah et al. study for the SoC arm since the IPLD for Cheah is not available. MSD notes that the use of the comparative HR in the SA above would produce almost identical results.

- The uptake rate of allogeneic stem cell transplant is uncertain<sup>3</sup>

Section 3.9 of the ACD states that the Committee remain uncertain about the validity and reliability of clinical predictions from the clinician survey presented in the company submission to estimate the rate of alloSCT uptake. MSD responded during clarification questions that KEYNOTE-087 was not designed as a bridge to transplant study, and therefore data were not reflective of transplant use, or specific UK clinical practice<sup>5</sup>. This uncertainty was also a discussed by the committee for nivolumab for a group of patients equivalent to population one<sup>12</sup>.

MSD recognise that there are limitations associated with the use of qualitative research methods. However, we are mindful that this approach was accepted by the Committee for TA462<sup>7</sup>. MSD believes that the same consideration should be applied to both population one and two of this submission, to ensure consistency with TA462.

Population two was not considered in TA462. MSD believes that should the Committee decide that, given no precedent, it cannot make a positive recommendation for this group, consideration should be given to what additional real world data could be collected that would reduce uncertainty whilst patients gained access via the CDF.

- There is considerable uncertainty about the utility value for progressed disease<sup>3</sup>

MSD notes the agreement that the utility value for progressed disease (PD), which the ERG had used is considered to be too high and that the true value lays between the company submission and ERG base case PD utility value. In order to address some of this uncertainty, MSD have presented a SA below using the 0-24 OS HR detailed above (cohort 1 HR=8.01 and cohort 2 HR=5.176) and a PD utility of [REDACTED] which is the average of the company base case PD utility and the ERG preferred mixed model PD utility. Using this PD utility produced ICERs for cohort 1 and 2 both below £50,000/QALY for week 24 and 12 (Table 4).

**Table 4 Different progressed disease utility value scenario analysis**

Scenario	Cohort	Pembrolizumab			UK SOC			Pembrolizumab vs UK SOC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base case 24 week model	Cohort 1	107,185	6.177	3.730	41,475	3.925	2.170	65,710	1.560	42,123
	Cohort 2	84,651	5.302	3.069	29,827	2.998	1.585	54,823	1.484	36,950
Base case 12 week model	Cohort 1	103,961	6.252	3.754	52,018	4.864	2.695	51,943	1.059	49,058
	Cohort 2	90,953	5.775	3.392	51,425	4.832	2.681	39,527	0.711	55,628
Base case new 24 week model with updated HR and average PD utility	Cohort 1	107,185	6.177	4.221	42,545	4.132	2.691	64,640	1.530	42,254
	Cohort 2	84,651	5.302	3.550	32,318	3.468	2.208	52,332	1.342	38,998
Base case new 12 week model with average PD utility	Cohort 1	103,961	6.252	4.253	52,018	4.864	3.179	51,943	1.074	48,382
	Cohort 2	90,953	5.775	3.886	51,426	4.832	3.161	39,528	0.725	54,516

- The time to allogeneic stem cell transplant is a key driver of cost-effectiveness estimates and there is considerable uncertainty about the true value<sup>3</sup>

Within the original company submission MSD based the time to allogeneic stem cell transplant (alloSCT) (12 weeks) on the availability of data and the feedback of clinical experts. In response to the request for additional modelling analyses by NICE (January 2018)<sup>4</sup>, MSD provided an economic model incorporating a 24 week time point. This is aligned to the time-point accepted by the Committee for TA462<sup>7</sup>. Subsequent discussion at the second committee meeting (13<sup>th</sup> February 2018) has reflected that alloSCT within English clinical practice is likely to occur somewhere between weeks 12 and 24 and not at a fixed time point for all patients, nor for all patients at once<sup>5</sup>. This was supported by the comments from clinical experts and the Clinical lead of the CDF at the same meeting. The committee has been presented ICERs using both a 12 and 24 week time-point model; this provides the extreme ICER range and the logic that a clinical practice ICER exists between these bounds.

- The cost effectiveness of pembrolizumab in population 1 is highly uncertain and a plausible ICER cannot be accurately estimated using the company's 12 or 24 week model. An alternative cost comparison approach is recommended **AND**
- The cost effectiveness of pembrolizumab in population 2 is highly uncertain, and a plausible ICER cannot be accurately estimated using the company's 12 or 24 week models<sup>3</sup>

As per the comments above, MSD questions the validity of a cost comparison vs. nivolumab, and reflect the prior Committee decision that nivolumab is a cost effective treatment option (TA462) for patients that are comparable with population one of this submission.

The ACD states that the ERG model preferences were not fully implemented in the updated 12 or 24 week models. As per the results of Table 5 below, MSD has conducted an analysis taking into account all of the ERG preferences (as per ERG report, page 98)<sup>8</sup>, with the exception of alloSCT transplants in PD patients, as the Committee agreed this is not plausible.

Preferred ERG assumptions<sup>8</sup>:

1. Inclusion of results of mixed modelling of utilities by response status in KEYNOTE-087
  - Week 12 model: PF: [REDACTED] cohort 1 and 2 pembrolizumab and [REDACTED] SoC, Post alloSCT 0.708 pre 14 weeks and 0.800 post 14 weeks and PD: [REDACTED] (non-rounded figures used).
  - Week 24 model: PF: [REDACTED] cohort 1 and 2 pembrolizumab and [REDACTED] SoC, Post alloSCT 0.708 pre 14 weeks and 0.800 post 14 weeks and PD [REDACTED] (non-rounded figures used).
2. Inclusion of long term monitoring costs post alloSCT using the same assumptions applied in TA462; a monthly cost of £91.69.
3. Use of MSD survey means for alloSCT only (CR: 56.79%, PR: 43.93%, SD: 18.36%)
4. Time horizon of 50 years.
5. Distributions for pre-12 weeks OS to reflect ERG
  - Cohort 1: exponential (5a)

- Cohort 2: lognormal (5b)
- Please note, that instead of assumption 5 for the week 24 model since it does not apply, we have used the HR detailed above (cohort 1=8.01 and cohort 2=5.176 using exponential distribution) to provide the published SoC alive at 24 weeks of 88% in the model.

The ICERs taking into account the ERG preferences in the week 24 model, other than PD alloSCT, produce ICERs below £50,000/QALY for both cohorts 1 and 2 (Table 5). Therefore, MSD disagree that the ERG base case ICER would be about £14,000/QALY more than the new 24 week model base case presented for cohort 1 and above £50,000 in cohort 2. Whilst the 12 week model ICERs are above £50,000/QALY using the ERG base case assumptions, MSD reflect that the Committee were able to reach a conclusion considering only a single time point of 24 weeks in the nivolumab submission and that the true ICER value is likely to lie somewhere between the two estimates.

Section 3.14 of the ACD also states that the costs generated by modelling SoC in the original model were double that of the nivolumab submission in the same population. MSD propose that the rationale for this is that the nivolumab submission utilised a much lower alloSCT cost (£21,672), the higher alloSCT cost used in the MSD model (£110,374) accounts for around 50% of the costs in the model. The submitting company for the nivolumab submission was subsequently asked to include higher cost for alloSCT which the MSD model included from the beginning in order to be conservative.

To contextualise the impact using lower costs associated with alloSCT (£21,672) and monitoring (£91.69/month), comparable to those used in the nivolumab base case from their original company submission, MSD has provided a SA applying these costs (Table 6). It can be seen that this has a significant impact on reducing the ICER across both populations but also that the SoC total costs are much more in line with those reported in the original nivolumab company submission alloSCT scenario analysis (Table 76)<sup>12</sup> of between £22,866 and £24,880 at the same time point for alloSCT of 24 weeks. It should also be noted that the nivolumab submission ICER, on which a decision was made, included a higher proportions of alloSCT ( [REDACTED] ) and when these values are tested in the MSD model the ICER is reduced further to the mid £20,000's/QALY versus the same time point for alloSCT used in the nivolumab model of 24 weeks.

**Table 5. ERG preferences scenario analysis (using updated HR for week 24 model)**

Scenario	Cohort	Pembrolizumab			UK SOC			Pembrolizumab vs UK SOC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base case 24 week model	Cohort 1	107,185	6.177	3.730	41,475	3.925	2.170	65,710	1.560	42,123
	Cohort 2	84,651	5.302	3.069	29,827	2.998	1.585	54,823	1.484	36,950
Base case 12 week model	Cohort 1	103,961	6.252	3.754	52,018	4.864	2.695	51,943	1.059	49,058
	Cohort 2	90,953	5.775	3.392	51,425	4.832	2.681	39,527	0.711	55,628
Base case new 24 week model with ERG preferences and updated HR	Cohort 1	107,395	5.895	4.373	40,493	3.955	2.923	66,902	1.451	46,122
	Cohort 2	83,908	5.054	3.745	31,356	3.384	2.522	52,551	1.224	42,950
Base case new 12 week model with ERG preferences and HR 0-12=1 (as in base case)	Cohort 1	104,572	5.936	4.387	48,305	4.562	3.354	56,267	1.034	54,431
	Cohort 2	89,933	5.455	4.030	47,958	4.566	3.358	41,974	0.672	62,503

**Table 6. Cost of alloSCT scenario analysis.**

Scenario	Cohort	Pembrolizumab			UK SOC			Pembrolizumab vs UK SOC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base case 24 week model	Cohort 1	107,185	6.177	3.730	41,475	3.925	2.170	65,710	1.560	42,123
	Cohort 2	84,651	5.302	3.069	29,827	2.998	1.585	54,823	1.484	36,950
Base case 12 week model	Cohort 1	103,961	6.252	3.754	52,018	4.864	2.695	51,943	1.059	49,058
	Cohort 2	90,953	5.775	3.392	51,425	4.832	2.681	39,527	0.711	55,628
Base case new 24 week model with updated HR and alloSCT costs	Cohort 1	74,679	6.177	3.730	25,520.	4.132	2.263	49,158	1.467	33,505
	Cohort 2	58,607	5.302	3.069	24,135	3.468	1.799	34,471	1.270	27,144
Base case new 12 week model with updated alloSCT costs and HR 0-12=1 (as in base case)	Cohort 1	69,254	6.252	3.754	27,723	4.864	2.695	41,531	1.059	39,224
	Cohort 2	59,231	5.775	3.392	27,537	4.832	2.681	31,693	0.711	44,603

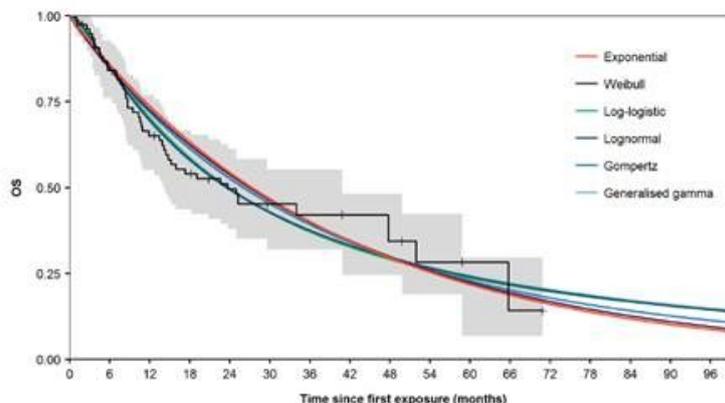
- Consideration of end of life criteria, a lack of face validity between modelled survival estimates and the clinical evidence AND
- The total life years predicted by the company's models exceeds 24 months<sup>3</sup>

The criteria for End of Life (EoL) were accepted for TA462<sup>7</sup>, with the committee acknowledging uncertainty based on the nivolumab model outputs. For consistency MSD believes, given the same uncertainty applied, that EoL criteria should apply.

As previously confirmed by the company, and as per the case of TA462<sup>7</sup>, the modelled OS is overestimated by the economic models for standard care. MSD that the nivolumab FAD states that: 'The Committee noted that the company's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. However, the Committee also considered the data from the Haematological Malignancy Research Network provided by the company in response to consultation, which showed shorter survival and suggested that the Cheah study may have been optimistic. The Committee acknowledged that nivolumab did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply. It therefore agreed that on balance, nivolumab met the criterion for short life expectancy, and that it would take this into account in its decision-making'<sup>7</sup>.

Regarding the LYs predicted by the company model versus the nivolumab model, the SoC data could not be separated in terms of those who had alloSCT (around 20% in Cheah), which would increase the OS for SoC patients even with the company model set to zero alloSCT. The nivolumab ACD response from the Committee papers dated May 2017 stated that when alloSCT was not included in the nivolumab submission the ERG base case total LYs generated was 2.933<sup>12</sup>. For comparison if alloSCT is excluded from the MSD model a total LYs of 2.946 are generated for SoC and therefore the models are predicting almost identical survival with the exclusion of alloSCT. This is aligned with the mean of 39.4 months predicted by extrapolated overall survival data from Cheah in the nivolumab submission (see Figure 5 extrapolation from the submission documents below)<sup>12</sup>. The marked difference in the median and the mean is due to the skew in the overall survival data.

Figure 5. Parameterisation of overall survival: Cheah 2016 overall population (including investigational agents)



Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exponential	506.82	509.16	lambda: 0.02537	27.3	39.4
Weibull	508.68	513.36	shape: 0.9591; scale: 39.4382	26.9	40.2
Log-logistic	507.21	511.89	shape: 1.264; scale: 23.768	23.8	96.7
Lognormal	504.87	509.56	mu: 3.164; sigma: 1.324	23.7	56.8
Gompertz	508.41	513.10	shape: -0.004893; rate: 0.028328	26.1	44.2
Generalised gamma	506.85	513.88	mu: 3.12157; sigma: 1.33678; Q: -0.07549	23.5	60.3

The issue around life expectancy of SoC patients relates to the external validity of the model due to the relevance of the Cheah data to the target population in this submission. For cohort 1 the consensus from the Committee in the nivolumab submission was that despite the model predicting in excess of 24 months survival there was external evidence that the Cheah data overestimated survival. However, none of the additional clinical evidence is suitable for use within an economic model; therefore, Cheah represents the best available data. Given this is the case; the current model is conservative as the ICER is generated from a superior SoC that results in lower incremental gain than expected in UK clinical practice.

Similarly, given the mean overall survival from Lafferty is >10 years, if ~20% received alloSCT in SoC (estimation from the model) the mean overall survival cannot be less than 2 years after the first 24 weeks and this is assuming that the remaining 80% die immediately, therefore MSD cannot produce a model which underestimates life expectancy given the use of the agreed best available data but note the difference in opinion of the clinical community in both this and the nivolumab submission that the life expectancy of SoC patients is less than 24 months.

MSD recognise the opinion of clinical experts that confirm the short life expectancy of both population as evident by the available literature "...expect overall survival, particularly for population two, to be close to that reported in the literature (median OS between 17.1 and 19 months)" (Section 3.16). MSD has reviewed the findings of Eyre et al. 2017 and believe that these results further support the short life expectancy of population two, with a reported median OS of 12.2 months (95% CI 8.1-18.3 months) for patients who did not receive a stem cell transplant.

#### MSD request consideration of population two for use within Cancer Drugs Fund

Given all the above MSD believe that there is no reason that the Committee cannot give a positive recommendation for population one.

Population two was not considered within TA462 and there is unmet need for this population. As per section 3.15 of the ACD, the Committee noted that the cost effectiveness of pembrolizumab is highly uncertain and cannot be accurately estimated using the company's 12 or 24 week model. As communicated within the company submission there are no further data planned to support this submission.

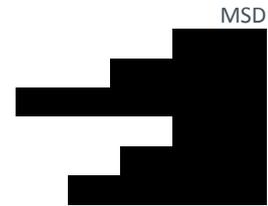
MSD would suggest that this underlying uncertainty expressed by the Committee should be addressed by recommending pembrolizumab for population two within the CDF. This would allow additional data to be collected to help reduce uncertainty; furthermore, it would also provide access to an innovative and clinically effective treatment option for a population who currently have no alternative treatment choice following relapse with brentuximab vedotin (Section 3.1<sup>3</sup>). MSD believe that pembrolizumab has the potential to be cost effective within population two and that the company has presented a number of ICERs that are below the £50,000 threshold.

The following data points are feasible for collection within the CDF:

- Timing of stem-cell transplant
- Duration of treatment with pembrolizumab before stem cell transplant
- The proportion of patients treated with pembrolizumab who go to receive subsequent stem cell transplant (currently based on expert clinical opinion)
- The long term follow-up of patients treated with pembrolizumab, with or without subsequent SCT post pembrolizumab.

## **References**

1. SMC. Nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®) SMC No (1240/17) detailed advice document, 2017.
2. SMC. Pembrolizumab (Keytruda®) 50mg powder for concentrate for solution for infusion and 25mg/mL concentrate for solution for infusion SMC No 1296/18. 2018.
3. NICE. Appraisal consultation document: Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma, 2018.
4. MSD UK L. Data on File, Pembrolizumab for treating relapsed or refractory classical Hodgkin's lymphoma [ID1062]: New Evidence Request January 2018, 2018.
5. NICE MUL. D1062 pembrolizumab NICE Clarification letter v0.6 TW [REDACTED] Final\_20171019. 2017.
6. Cheah CY, Chihara D, Horowitz S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. *Ann Oncol* 2016;27(7):1317-23.
7. NICE. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [TA462]. 2017.
8. NICE KSR. ID1062 Pembrolizumab for CHL - ERG report [redacted] 20Nov\_ TW 7 Dec watermarked, 2017.
9. Eyre TA, Phillips EH, Linton KM, et al. Results of a multicentre UK-wide retrospective study evaluating the efficacy of brentuximab vedotin in relapsed, refractory classical Hodgkin lymphoma in the transplant naive setting. *Br J Haematol* 2017;179(3):471-79.
10. Chen R ZP, Fanale M, et al. . Pembrolizumab For Relapsed/Refractory Classical Hodgkin Lymphoma (R/R CHL): Phase 2 KEYNOTE-087 Study. *J Clin Oncol* 2016;34:(suppl; abstr 7555).
11. MSD. MSD Submission - Pembrolizumab (ID1062) [Redacted]\_12122017, 2017.
12. NICE. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972] Committee Papers. <https://www.nice.org.uk/guidance/ta462/documents/committee-papers>, 2017.



Donna Barnes  
Technology Appraisals Project Manager - Committee A  
National Institute for Health and Care Excellence



6<sup>th</sup> April 2018

**Pembrolizumab for treating relapsed or refractory classical Hodgkin's Lymphoma [ID1062] – Response to Appraisal Consultation Document (ACD)**

Dear Donna,

In response to the email received on the 4<sup>th</sup> April 2018, MSD has responded to the Committee's clarification questions. As requested we have also uploaded four excel model files; this includes two base case models (12 and 24 weeks), and two ERG preferred assumption models (12 and 24 weeks).

As noted in your covering email, we await communication from the CDF team regarding the consideration of pembrolizumab for use in population two within the CDF. If population two was to be recommended for use within the CDF the level of discount described below would be amended to reflect an appropriate level of rebate. However, until we have confirmation of a plausible ICER range we are unable to comment on the expected CAA value for population two.

Should you have any questions about the content, or suggestions on how MSD can move this forward to a successful conclusion for patients, please do contact me.

Kind regards,

[Redacted signature]

[Redacted contact information]

1. Please confirm which CAA discount has been used in the analysis. We note that an updated CAA has been offered for a different technology appraisal for pembrolizumab; please confirm if this CAA is now offered for this appraisal.

At the time of the company submission MSD included a [REDACTED] discount, this is no longer correct and a discount of [REDACTED] is relevant. In the analyses presented on the 23<sup>rd</sup> March 2018 a discount of [REDACTED] was applied. As per your clarification question, this discount is aligned with the ongoing technology appraisal for pembrolizumab. For the avoidance of doubt the discount of [REDACTED] does not represent the full CAA which in addition includes a rebate value; however, this rebate value is not applicable to this (ID1062) appraisal.

2. Please provide clear details of how the 12 week model previously submitted (on 25<sup>th</sup> January) has been amended to produce the 'base case 12 week model' ICERs for both cohorts reported in tables 2, 4, 5 and 6 of the consultation response (23<sup>rd</sup> March). These figures have not been previously presented, and appear to be higher than previous base case ICER values presented for this 12 week model (totals costs and LYs appear as per the previous model, but QALYs generated look to be different).

The base case 12/24 week model ICERs for both cohorts detailed in the document dated 23<sup>rd</sup> March are correct. The 12/24 week model files previously submitted do not contain any technical errors.

The discount for pembrolizumab can be updated to [REDACTED] from [REDACTED] and has in the base case ICERs generated in the March 23<sup>rd</sup> document. (Cost\_treatment! Worksheet, cell F11).

As detailed on page 8 of the document submitted 23<sup>rd</sup> March, the base case settings from the company submission were used to re-generate and check the base case 12/24 week ICERs for the 23<sup>rd</sup> March document. On re-producing these ICERs for the March 23<sup>rd</sup> document, MSD realised that the pre 12/24 week survival parametric distributions may have been altered when running SA and so base case ICERs for both models were re-produced. The various parametric distributions to generate the base case 12/24 week models are detailed in the company submission and below which can be input into the week 12/24 model files submitted on 25<sup>th</sup> January:

For ease, we have uploaded two new base case models with these settings saved.

**Table 1: Parametric distribution summary**

Survival	12 week		24 week	
	Cohort 1	Cohort 2	Cohort 1	Cohort 2
PFS 0-12/24	Log logistic	Generalised gamma	Log logistic	Generalised gamma
OS 0-12/24	Log normal	Exponential	Exponential	Exponential
PFS 12/24+	Exponential	Exponential	Exponential	Exponential
Post alloSCT PFS	Weibul	Weibul	Weibul	Weibul
Post alloSCT OS	Weibul	Weibul	Weibul	Weibul
ToT	Exponential	Exponential	Exponential	Exponential

3. Please provide clear details of how the 24 week model previously submitted (on 25<sup>th</sup> January) has been amended to produce the 'base case 24 week model' ICERs reported in tables 2, 3, 4, 5 and 6 of the consultation response (23<sup>rd</sup> March). We believe that the following changes have been made, please confirm this:

**Discount for pembrolizumab changed (Cost\_treatment! Worksheet, cell F11)**

- Correct, as detailed above the discount has been changed to [REDACTED]

**Progression-free survival from Week 0 to 24 set to log-logistic for cohort 1 and generalised gamma for cohort 2 (Survival! Worksheet, cell I15)**

- Correct, as detailed above and on page 8 of the document submitted 23<sup>rd</sup> March.

**Overall survival from Week 0 to 24 set to exponential for both cohorts (Survival! Worksheet, cell I32; cohort 1 had previously used log-normal)**

- Correct, explanation detailed above. OS for week 0-24 should be set to exponential for both cohorts as detailed in the January 25<sup>th</sup> response when the 24 week model was first introduced.

**In addition:**

**Please provide the model files used to produce the analyses presented in the consultation response (dated March 23<sup>rd</sup>):**

**The base case analyses for 12 and 24 week models**

- As detailed above, we have uploaded.

**The additional analyses presented (in particular, the implementation of the preferred ERG assumptions)**

- We have uploaded the ERG assumptions model.

**If possible, it would be helpful if you could provide a description of what changes to the base case model excel files have been made to carry out the additional analyses presented in the consultation response.**

As detailed in the document 23<sup>rd</sup> March, the parameters changed in each analysis are detailed below with some additional information where applicable.

Parametric distributions not mentioned in Table 2 are as base case and as per Table 1 above.

**Table 2: Details of Scenario Analysis**

Analysis	Detail of alterations
Base case new 24 week model with updated Eyre HR Cohort 2	<p><b>PFS pre 24 weeks</b> - The PFS HR=4.21.</p> <p><b>OS pre 24 weeks</b> – The OS HR=10.08.</p> <p><b>PF post 24 weeks</b> – HR= [REDACTED] in line with methodology vs. Cheah et al. 2016</p> <p><b>PPS</b> – Calculated as it was for Cheah using a mOS of 12.2 months from Eyre of 98.69%</p>
Base case new 12 week model with updated Eyre HR Cohort 2	<p><b>PFS pre 12 weeks</b> - The PFS HR=6.57.</p> <p><b>OS pre 12 weeks</b> – The OS HR=6.77.</p> <p><b>PF post 12 weeks</b> – HR= [REDACTED] in line with methodology vs. Cheah et al. 2016</p> <p><b>PPS</b> – Calculated as it was for Cheah using a mOS of 12.2 months from Eyre of 98.69%</p>
Base case new 24 week model with updated HR	<p>Cohort 1 HR=8.01 exponential distribution</p> <p>Cohort 2 HR=5.18 exponential distribution</p>
Base case new 24 week model with updated HR and average PD utility	<p>Cohort 1 HR=8.01 exponential distribution</p> <p>Cohort 2 HR=5.18 exponential distribution</p> <p>PD utility of [REDACTED].</p>
Base case new 12 week model with average PD utility	<p>PD utility of [REDACTED].</p>
Base case new 24 week model with ERG preferences and updated HR	<p>Inclusion of results of mixed modelling of utilities by response status in KEYNOTE-087</p> <ul style="list-style-type: none"> <li>Week 24 model: PF: [REDACTED] cohort 1 and 2 pembrolizumab and [REDACTED] SoC, Post alloSCT 0.708 pre 14 weeks and 0.800 post 14 weeks and PD [REDACTED] (non-rounded figures used).</li> </ul> <p>Inclusion of long term monitoring costs post alloSCT using the same assumptions applied in TA462; a monthly cost of £91.69. Cell E34 “cost of disease management” sheet input 91.69*12/52. Cell S8 on “cost calcs” input 91.69*12/52.</p> <p>Use of MSD survey means for alloSCT only (CR: 56.79%, PR: 43.93%, SD: 18.36%)</p> <p>Time horizon of 50 years.</p> <p>Distributions for pre-12 weeks OS to reflect ERG</p> <p>Please note, that instead of assumption 5 for the week 24 model since it does not apply, we have used the HR detailed above.</p> <p>Cohort 1 HR=8.01 exponential distribution</p> <p>Cohort 2 HR=5.18 exponential distribution</p>
Base case new 12 week model with ERG preferences and HR 0-12=1 (as in base case)	<p>Inclusion of results of mixed modelling of utilities by response status in KEYNOTE-087</p> <ul style="list-style-type: none"> <li>Week 12 model: PF: [REDACTED] cohort 1 and 2 pembrolizumab and [REDACTED] SoC, Post alloSCT 0.708 pre 14 weeks and 0.800 post 14 weeks and PD: [REDACTED] (non-rounded figures used).</li> </ul>

Analysis	Detail of alterations
	<p>Inclusion of long term monitoring costs post alloSCT using the same assumptions applied in TA462; a monthly cost of £91.69. Cell E34 "cost of disease management" sheet input <math>91.69 * 12 / 52</math>. Cell S8 on "cost calcs" input <math>91.69 * 12 / 52</math>.</p> <p>Use of MSD survey means for alloSCT only (CR: 56.79%, PR: 43.93%, SD: 18.36%)</p> <p>Time horizon of 50 years.</p> <p>Distributions for pre-12 weeks OS to reflect ERG</p> <ul style="list-style-type: none"> <li>a. Cohort 1: exponential (5a)</li> <li>b. Cohort 2: lognormal (5b)</li> </ul>
<p>Base case new 24 week model with updated HR and alloSCT costs</p>	<p>Cohort 1 HR=8.01 exponential distribution</p> <p>Cohort 2 HR=5.18 exponential distribution</p> <p>Lower costs associated with alloSCT (£21,672) applied in cell F105 on "cost_treatment" sheet.</p> <p>Inclusion of long term monitoring costs post alloSCT using the same assumptions applied in TA462; a monthly cost of £91.69. Cell E34 "cost of disease management" sheet input <math>91.69 * 12 / 52</math>. Cell S8 on "cost calcs" input <math>91.69 * 12 / 52</math>.</p>
<p>Base case new 12 week model with updated alloSCT costs</p>	<p>Lower costs associated with alloSCT (£21,672) applied in cell F105 on "cost_treatment" sheet.</p> <p>Inclusion of long term monitoring costs post alloSCT using the same assumptions applied in TA462; a monthly cost of £91.69. Cell E34 "cost of disease management" sheet input <math>91.69 * 12 / 52</math>. Cell S8 on "cost calcs" input <math>91.69 * 12 / 52</math>.</p>

# Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma [ID1062]

**NICE** National Institute for Health and Care Excellence

**Consultation on the appraisal consultation document – deadline for comments 5pm on 29 March 2018 email: [TACommA@nice.org.uk](mailto:TACommA@nice.org.uk)/NICE DOCS**

	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> <li>• has all of the relevant evidence been taken into account?</li> <li>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</li> <li>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?</li> </ul> <p>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:</p> <ul style="list-style-type: none"> <li>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;</li> <li>• could have any adverse impact on people with a particular disability or disabilities.</li> </ul> <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p><b>Organisation name – Stakeholder or respondent</b> (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>NCRI-ACP-RCP</p>
<p><b>Disclosure</b> Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>None</p>
<p><b>Name of commentator person completing form:</b></p>	<p>██████████</p>

Please return to: [diagnostics@nice.org.uk](mailto:diagnostics@nice.org.uk) / NICE DOCS

# Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma [ID1062]

**NICE** National Institute for Health and Care Excellence

**Consultation on the appraisal consultation document – deadline for comments 5pm on 29 March 2018 email: [TACommA@nice.org.uk](mailto:TACommA@nice.org.uk)/NICE DOCS**

Comment number	Comments
General	<p style="text-align: center;">Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.</p> <p>The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation, We have liaised with our experts and would like to make the following comments.</p>
1	<p>Our experts are concerned to see that NICE are recommending to not fund pembrolizumab in the group of patients who are not able to receive a stem cell transplant (SCT).</p> <p>Our experts believe that it does not matter to patients and clinicians if pembrolizumab is funded post-(ASCT) and post-BV, as nivolumab is already funded for this indication.</p> <p>However the group who can't make it to an SCT are in desperate need of access to a PD1 inhibitor. These drugs are the go-to drugs the world over (apart from the UK) for this group of mainly young and still potentially curative patients.</p> <p>Our experts believe it would be tragic to deny pembrolizumab to this group as will lead to the needless death of some patients. Clearly it's a small group, but when you have an active drug like pembrolizumab which can bridge to curative therapy, really it should be available as a matter of urgency.</p> <p>There is also an equity issue here. Currently people in that group either die, or they crowd fund for the drug, or they fund for it privately. Not everyone can do this so a negative decision will inevitably lead to a disparity based on wealth and ability to mount a social media campaign.</p> <p>Our experts are hopeful that NICE can re-consider its position.</p>

Insert extra rows as needed

## Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 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 2<sup>nd</sup> 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

Please return to: [diagnostics@nice.org.uk](mailto:diagnostics@nice.org.uk) / NICE DOCS

## **Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma [ID1062]**

**NICE** National Institute for  
Health and Care Excellence

**Consultation on the appraisal consultation document – deadline for comments 5pm on 29 March 2018 email: [TACommA@nice.org.uk](mailto:TACommA@nice.org.uk)/NICE DOCS**

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.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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

<b>Name</b>	
<b>Role</b>	Patient
<b>Other role</b>	
<b>Organisation</b>	
<b>Location</b>	England
<b>Conflict</b>	None
<b>Notes</b>	
<b>Comments on individual sections of the ACD:</b>	
<b>Section 1</b> (Appraisal Committee's preliminary recommendations)	<p>1.1 and 1.3: If Pembrolizumab is not agreed as an option for either of these groups then I would urge the committee to consider how limited any further treatment options are for these adults. I am an adult who has had 5 different times of chemotherapy and Brentuximab. I have not had a stem cell transplant as I have not reached a suitable remission to do so. Without the option of Nivolumab or Pembro on the NHS I am left with only the hope of possibly finding a clinical trial to enter.</p> <p>1.2: The committee has recommended a cost comparison of Pembrolizumab with Nivolumab. Currently the only Hodgkin Lymphoma patients who can access Nivolumab on the NHS are those who have had Brentuximab and a failed autologous stem cell transplant. This leaves patients, like me, in an extremely difficult and unfair position. Costs cannot be compared for patients like me, who have not had a transplant, on the NHS because we are not able to access Nivolumab this way. However, I would urge the committee to request data on patients, like me, who are on Nivolumab and are self-funding. I cannot access Nivolumab, at present, or Pembrolizumab, via the NHS. However, my friends and family raised the funds for me to access 8 lots of Nivolumab, of which I have so far had 4 treatments. My quality of life has improved significantly since being on Nivolumab, which I started in January 2018. I am aware of other patients in a similar position to myself. My fear is that when my funds run out I will no longer be able to access this pioneering immunotherapy and may not be ready then for an allogenic stem cell transplant, which is the aim. My hope is that NICE will approve Pembrolizumab for patients like me so that I can reach a suitable remission and have a transplant. Pembrolizumab works in the same way as Nivolumab and therefore I would hope to go onto it if approved by NICE. I cannot fund Nivolumab endlessly but it is improving all my stats, my mood and my ability to look after my children, who are 1 and 3 years old. Without access to these immunotherapy drugs I, and others like me, may not ever reach the point of a curative allogenic stem cell transplant. I would urge the committee to consider the ethics in denying me and others like access to something that could cure us and enable us to live good quality lives. I think the social impact of me not surviving and bringing up my two little children should be taken into consideration too. I am almost 34 years old and desperately want to see my children grow up.</p>
<b>Section 3</b> (The manufacturer's submission)	<p>Section 3.3.1 - Consideration has been given to patients like me, population 2, who have not had an autologous stem cell transplant, but have been treated with a number of therapies including Brentuximab. I have not, as considered in the document, relapsed after Brentuximab, as it was not effective at all in treating my Hodgkin Lymphoma. When first diagnosed I was pregnant and my medical team believe this effected the lymphoma I have. Brentuximab did not put me in remission and therefore I did not rephase after it.</p>

	<p>I feel the committee should consider the group I am in very carefully as we are running out of options if immunotherapy is not made available to us on the NHS. If I were to be put forward for an autologous stem cell transplant at present it would, most likely, fail. However, it would make me eligible for Nivolumab on the NHS. This would, however, I feel, be a misuse of resources and I would question the ethics too. Unless I have a failed auto transplant or I win the lottery and am able to fund Nivolumab or Pembrolizumab for my treatment I am going to die from this disease.</p> <p>Section 3.2.1 - The paper states, 'The committee noted that because nivolumab is not licenced for use in population 2 (that is, people who have had brentuximab vedotin and who cannot have allogeneic stem cell transplant), a cost-comparison approach could not be used for this population' - then this does not reflect patients, like me and others I know, who are being treated with Nivolumab, who have not had an auto transplant, and for whom Brentuximab has not worked. Although Nivolumab is not yet available to patients like me on the NHS it does not mean we do not exist. I am on Nivolumab, the quality of my life now compared to when I was first diagnosed (October 2016) and when on chemotherapy is vastly greater. I was in intensive care 3 times in 2017. I actually wondered if I was dying on 2 of those occasions. At one point a doctor told me I was 'one of the most ill people in the hospital'. Now I am on Nivolumab I can drive, go shopping, care for my children and live my life relatively normally. To state that it is not possible to compare the cost effectiveness simply reflects that a need for the data concerning self funding patients like me exists.</p>
<p><b>General</b></p>	<p>I would also urge the committee to consider the position that clinicians find themselves in when faced with patients like me. On a weekly basis I have conversations with my nurses and consultants about what the next steps should be should I no longer be able to fund Nivolumab in order to get me ready for an allogenic stem cell transplant. I feel it is unethical and difficult to put clinicians in the position where they cannot prescribe treatment, on the NHS, to patients when they are confident and data exists to show it is effective. I feel very sorry for my consultants who believe immunotherapy is the way forward who cannot let me be treated on the NHS with it.</p> <p>In considering cost effectiveness I would urge the committee to consider the cost of failed treatments for Hodgkin Lymphoma patients like me. If Pembrolizumab or Nivolumab were to be approved for patients like me, who have not had a transplant and for whom Brentuximab has not worked, then this would, I suggest, longer term be much more cost effective than putting patients through numerous costly chemotherapy regimen. I appreciate there are patients for whom chemotherapy is effective, but there is also the cost of the drugs that go with the chemo and the cost to the NHS of treating the side effects patients endure. For example, Escalated BEACOPP resulted in bleeds on both my eyes in February 2017. The NHS then were funding my treatment along with associated drugs, e.g. anti sickness, pain relief, also my staff in intensive care and then my consultations and treatment in the eye clinic too.</p> <p>I would urge the committee to consider the side effects of Pembrolizumab and Nivolumab. Whilst of course they exist they are not as brutal as chemotherapy. There were times, on GDP</p>

	<p>chemotherapy, when I could barely walk because I felt so spaced out and nauseous. I could not drive and relied on my family to look after me. I certainly could not look after my children. Immunotherapy is a much kinder treatment. Not only is it making me feel so much better, it is also improving my heart rate and oxygen levels. Also, rather than taking 8+ hours, which some treatments I have been on do, it takes 1 hour with a flush of saline before and after. 2 hours of my life every 2-3 weeks instead of days at a time (ICE treatment requires a stay in hospital when administered - again there are cost implications).</p> <p>I have had ABVD, Escalated BEACOPP, ICE, Brentuximab and GDP. None of these have made me as well as I am now and I am desperate for Pembrolizumab, which works like Nivolumab, to be available to me and others like me. I am a young adult with a lot to give. I work with mentally unwell adults and I am mother to two little children. I don't want to die in my 30's.</p>
--	---

<b>Name</b>	██████████
<b>Role</b>	Patient
<b>Other role</b>	
<b>Organisation</b>	
<b>Location</b>	England
<b>Conflict</b>	No
<b>Notes</b>	

**Comments on individual sections of the ACD:**

<b>General</b>	<p>I am writing in response to the recent appraisal meeting on the consultation on Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma. My understanding from the Appraisal Consultation Document of 9th March 2018 is that the committee is not inclined to make Pembrolizumab available for patients who have had unsuccessful treatment with Brentuximab Vedotin and are ineligible for autologous stem cell transplant. This is due to lack of evidence showing the benefits of Pembrolizumab for this population and the impossibility of conducting a cost comparison on Pembrolizumab versus Nivolumab for this population, as Nivolumab is not funded for this patient group.</p> <p>I would like to provide a patient's perspective on this consultation which I hope you will consider in your decision.</p> <p>I was diagnosed with Hodgkin lymphoma in March 2016, shortly after finding out I was pregnant with my second child. I had ABVD throughout my pregnancy, completing my sixth round four days after my healthy baby daughter was born. Four weeks later I had my first PET scan and we learned ABVD hadn't worked at all, the lymphoma had progressed.</p> <p>The plan was then to have high dose chemotherapy followed by an autologous stem cell transplant. I had two rounds of ESHAP, during which the lymphoma progressed, then a round of IVE, during which it continued to progress. The infusion of these drugs required several days of hospitalisation and care from a dedicated nurse for the duration. They caused me horrendous side effects including sickness, diarrhoea, weight loss, tinnitus, mood changes and severe fatigue. Sadly the hospital stays, side effects and the fact that they didn't work made the first few months of life with my daughter extremely traumatic for me and my family. I had to start antidepressants, sleeping tablets and appointments with a clinical</p>
----------------	--

psychologist.

At this point it was decided my disease was too stubborn for an autologous transplant to be successful and the aim would now be to get me into remission for an allogeneic stem cell transplant. I went on to have two rounds of CHlvPP, to which I had a mixed response, then four rounds of Brentuximab Vedotin, which initially showed promising results, but the lymphoma eventually progressed. These drugs were more tolerable but still caused significant fatigue.

Radiotherapy finally got me into remission in September 2017. However, this also caused very troublesome side effects including complete voice loss for four weeks, severe pain and difficulty swallowing, burns to my skin and fatigue. Not to mention the stress and fatigue caused by having to do an 80 mile round trip to Southampton every week day for almost four weeks, while organising childcare for my two young children.

Unfortunately after achieving remission and being ready for my transplant, my immune system had been so weakened by the all the harsh treatments that I was struck down by pneumonia and a series of viruses which took a long time to shake, and prevented it from going ahead. In December 2017 it was confirmed that while I had been overcoming these infections and viruses the lymphoma returned, this time to my abdomen, spine and pelvis.

It was at this point I was given the option of trying another traditional chemotherapy available on the NHS, or self-funding Nivolumab, with the ultimate goal still being to go for allogeneic stem cell transplant. It was not an easy decision but my consultant felt Nivolumab was more likely to be effective. As a family we have had to pull together to cover the cost of a few rounds. Not everybody in this position would be so fortunate as to be able to manage this, and indeed for myself it is certainly not an arrangement that can last indefinitely, though I understand that immunotherapy drugs vary in terms of how long they may take to work fully. (Cont...)

(...cont) Before I started Nivolumab I had become very unwell. I was in and out of hospital for 1-2 week stays throughout November and December 2017 with unbearable back, stomach and hip pain, sickness, diarrhoea, anaemia and fatigue. I couldn't get out of bed until I'd had my daily dose of 50mg Prednisolone. I was separated from my children for six weeks because I was so vulnerable to viruses, which caused a lot of distress on both sides.

I started Nivolumab on 29th December. After an initial inflammatory reaction, which did put me in hospital, I began to feel much better. Within a week of my first dose I was off the steroids completely. I have continued to feel better and better and have just had my sixth dose. I have very few side effects and no symptoms of lymphoma. I have energy to do things with my family, my pain is greatly reduced, I have a good appetite and have gained weight and my blood results are now all within or very close to normal ranges. Although I suffered a nasty virus two weeks ago, for the first time in a year I was able to recover without being admitted to hospital, which would indicate that my immune system seems to be improving. Mentally I feel much more robust, positive and excited about life. My quality of life is immeasurably better than it has been at any time in the two years since I was diagnosed.

I had a PET scan after four rounds which showed great improvement of all the disease present in the previous scan. Two new areas lit up but my consultant is hopeful these represents inflammatory processes which may well resolve with more treatment.

The other huge benefit to me is that Nivolumab is administered very quickly and I am usually in and out of the hospital within two hours - far less time than any other treatments I've had. It seems far less labour intensive to the NHS than the other treatments I've had.

Currently the only way for me to be eligible for Nivolumab on the NHS would be to go through an autologous transplant, which would almost certainly fail, putting me at risk and wasting NHS resources. As a 36 year old woman with two young children I feel in complete despair that neither Nivolumab nor Pembrolizumab are available on the NHS to patients in my 'population'. I have always been in good health otherwise, I have a 10/10 matched unrelated donor lined up and am told that I stand a decent chance of a cure if the Nivolumab gets me into remission and I go on to have the transplant.

I believe if Nivolumab or Pembrolizumab (which I am told work very similarly) had been offered to me sooner I could have avoided many months of illness caused by side effects of traditional treatments, the infections and viruses caused by the damage these have done to my immune system and the lymphoma which ultimately progressed through every other treatment. I believe with all the hospital admissions and treatment I've required to manage this ill health I have cost the NHS significantly more than if immunotherapy had been offered to me earlier. I believe I would have had my transplant and be on the road to recovery, with less risk of suffering the longer term consequences of multiple chemotherapies and radiotherapy which are likely to be a drain on NHS resources later in my life.

As far as being unable to conduct a cost comparison between Pembrolizumab and Nivolumab as Nivolumab is not currently available on the NHS is concerned, this seems somewhat a 'Catch 22' situation. Would it be possible to compare costs using examples of patients such as myself who have self-funded?

Thank you in advance for considering my opinions. Please do feel free to contact me if you have any questions or would like to discuss this further.



in collaboration with:



---

## **Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma - Addendum**

<b>Produced by</b>	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
<b>Authors</b>	Debra Fayter, Systematic Reviewer, KSR Ltd, UK Sabine Grimm, Health Economist, Maastricht UMC Bram Ramaekers, Health Economist, Maastricht UMC Svenja Petersohn, Health Economist, Maastricht UMC Rob Riemsma, Reviews Manager, KSR Ltd, UK Nigel Armstrong, Health Economist, KSR Ltd, UK Xavier Pouwels, Health Economist, Maastricht UMC Willem Witlox, Health Economist, Maastricht UMC Caro Noake, Information Specialist, KSR Ltd, UK Gill Worthy, Statistician, KSR Ltd, UK Manuela Joore, Health Economist, Maastricht UMC Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University
<b>Correspondence to</b>	Rob Riemsma, Kleijnen Systematic Reviews [REDACTED] [REDACTED] [REDACTED] [REDACTED]
<b>Date completed</b>	30/04/2018

The company provided additional evidence following the second appraisal committee meeting. The ERG was asked to validate the additional work and comment on the impact of the amendments to the model.

### **ACD recommendations**

In the ACD, it was stated that, based on expert opinion, the effectiveness of pembrolizumab was thought to be similar to that of nivolumab in population 1 (i.e. people who have had autologous stem cell transplant and brentuximab vedotin), but that there remained substantial uncertainty around its relative effectiveness compared with standard of care (SoC) in this population. The committee requested that the company provide a cost comparison with nivolumab for treating relapsed or refractory classical Hodgkin lymphoma in population 1. The committee furthermore concluded that the uncertainty was too great for it to recommend pembrolizumab as cost effective treatment for use in population 2 (i.e. adults who have had brentuximab vedotin but did not have autologous stem cell transplant).

### **Updated price scheme**

In their recent submission in response to the ACD,<sup>1</sup> the company offers a discount of [REDACTED] on the list price of pembrolizumab. The company's new ICERs are produced with this new price scheme taken into account.

### **Company's updated models**

The company has provided updated model files, which present ICERs with the updated price scheme and the original company base-case settings. Compared to the model versions submitted in the previous submission,<sup>2</sup> the company corrected the use of distributions for estimating OS and PFS in the pre-12 and pre-24 week periods. Furthermore, the company provided updated model files, in which the company claimed to have incorporated the ERG preferences. It is, however, noteworthy, that the majority of ICERs presented in the company's ACD response document<sup>1</sup> (with the exception of the ERG scenarios) are based on the company's base-case, not on the ERG base-case. Furthermore, the ERG would like to reiterate the substantial uncertainty about the 24-week model ICERs, in particular due to the use of a hazard ratio (HR) of 13.13 for estimating overall survival (OS), which could not be validated by the ERG, was not reflected in the probabilistic sensitivity analysis, and which was believed by the committee<sup>3</sup> to over-estimate the difference between pembrolizumab and SoC at 24 weeks. The 24-week model results should therefore be interpreted with caution and considering that these ICERs may over-estimate cost effectiveness of pembrolizumab versus SoC in both populations.

The ERG successfully reproduced the company's ICERs. The ERG also attempted to reproduce the company's ICERs (with ERG preferences) using the ERG's previous amended model versions. The ICERs could not be exactly reproduced but came very close. The ERG notes minor deviations in the way the company implemented the ERG's preferences regarding utilities and post-alloSCT monitoring costs. The ERG therefore implemented their preferences in the company's new model files and notes that the resulting ICERs are very close to the company's (using their implementation of the ERG preferences). The ERG produced its own ERG base-case and scenarios (Table 1).

### **Population 1 – Cost comparison with nivolumab**

The company did not provide a cost comparison of nivolumab and pembrolizumab as treatment options for population 1. The company claimed that this comparison would not reflect any potential superiority in treatment effectiveness of pembrolizumab over nivolumab. The company considered that based on the independent data from both the nivolumab and pembrolizumab single arm trials, results are more favourable for pembrolizumab in population 1. The ERG wishes to highlight that naïve comparisons are subject to substantial uncertainty. Without any more detailed justification given by the company for their claim, it is furthermore unclear to the ERG based on what particular endpoints and at which time points the company compared results from KEYNOTE-087 and CHECKMATE-205.

If the company wished to substantiate this claim, it could attempt a matched adjusted indirect comparison using the Cheah et al<sup>4</sup> study as a common link. In the absence of any further analyses, the ERG wishes to caution against drawing any conclusions from this comparison. Furthermore, an attempt to compare the effectiveness of nivolumab and pembrolizumab should also be accompanied by the requested cost comparison, and be done within the framework of a cost effectiveness model.

### **Population 2 – Proposal for Cancer Drugs Fund**

The company proposed that pembrolizumab be considered for reimbursement and additional data collection within the Cancer Drugs Fund (CDF) for population 2, and highlighted the significant unmet need in this population. The company provided an attempt at utilising a new study in this population (Eyre et al 2017)<sup>5</sup> to inform relative effectiveness of pembrolizumab over standard of care. A naïve indirect comparison using the publicly available Kaplan-Meier data was performed. The company highlighted the small sample size of patients who have not had an autologous stem cell transplant (autoSCT) (n=38) in Eyre et al and warned that this analysis should be interpreted with caution as estimates have been digitised from published figures and comparability of the baseline characteristics is unknown. The resulting HR for overall survival (OS) was [REDACTED], which the company highlighted was similar to the HR of 13.13 (equivalent to HR 0.076) submitted in the previous submission.<sup>2</sup> The company concluded that their previous model may have underestimated relative effectiveness of pembrolizumab versus SoC in population 2.

The ERG agrees with the company's assessment of both, the potential under-estimation of relative effectiveness in population 2 (which the ERG had already highlighted in its original ERG report),<sup>6</sup> and the substantial uncertainty associated with the HR of [REDACTED], which is induced by small sample size, uncertainty in comparability between populations and the digitisation of Kaplan-Meier curves. In addition, the ERG wishes to highlight that it is unclear how this study was selected and potential selection bias cannot be excluded. Furthermore, the scenario using HRs obtained from Eyre et al uses HRs that are calibrated to match the observed Eyre et al data, which is not considered by the ERG to be an evidence-based approach that allows for application of appropriate statistical methods. Lastly, the ERG wishes to caution from using this analysis for the purpose of validating the company's HR in both populations of 13.13 (or 0.076 if inverted). This is because this HR of 0.076 was derived using a comparison in both populations, which should result in numerically higher values than [REDACTED] (derived from the population 2 only comparison), if it is accepted that pembrolizumab is likely to be relatively more effective in population 2 than in population 1.

In the ERG's analyses, the use of the Eyre et al HR calibrated to the Eyre et al observations reduces the ICERs substantially (Table 1). However, due to the highlighted uncertainty and the fact that the company's hazard ratios were calibrated to match the observed Eyre et al data, the ERG wishes to note that these results should be interpreted with caution.

### **Both populations – Concerns about the week 24 model**

The ERG had reservations about the implementation of the model, in which patients would receive alloSCT 24 weeks into their treatment. The reservations mostly related to the HR implemented for the time from week 0 to week 24 for OS when treated with pembrolizumab with OS when treated with SoC, which could not be validated due to the necessary evidence not having been provided by the company. The company acknowledged the committee's (as per the ACD<sup>3</sup>) and the ERG's reservations regarding this HR of 13.13 and, to address this, attempted to calibrate the HR to match the SoC observed data. The resulting HRs (matching the SoC data at 24 weeks) significantly decreased to 8.01 and 5.18 for populations 1 and 2 respectively. The ERG was able to validate that these hazard ratios produce model estimates approximately in line with observed data from Cheah et al at 24 weeks. The company correctly pointed out that this is not an evidence-based approach. Further caveats include that the resulting HR would only hold for the time of interest and that this method does not allow for application of statistical methods and the estimation of uncertainty.

The ERG wishes to reiterate that it was unable to validate the company estimated HR of 13.13 (95% CI (3.07-56.04)) and that the company still did not provide the data necessary for validating it. As the company pointed out, the comparison of model predictions for 24 weeks OS for patients treated with SoC are not in line with what is observed in Cheah et al, even when the exponential distribution is used. The ERG would have preferred to be able to validate the company's presented HR over the new attempt at calibrating the HR towards single point in time observed OS estimates. Given that the necessary data were not presented, and given that the previously assumed HR of 1 may be considered to lack face validity in the context of 24 week waiting times until alloSCT, the ERG has a slight preference for using the estimates from the company's calibration exercise, which appear to be superior in terms of external validity. The ICERs reduce substantially in both populations when the 24-week scenarios are selected. However, the ERG wishes to highlight that the 24-week model results should therefore be interpreted with caution, and only be considered as scenario analysis.

### **Both populations – Uncertainty about the progressed disease utility health state**

The company's approach of taking the mid-point between the ERG's and company's original estimate of the progressed disease (PD) utility value is considered arbitrary by the ERG, as this is not evidence-based. Results of this analysis should purely be used for illustration of the potential direction into which the ICERs change, and interpreted with extreme caution. In this context, it is noteworthy that the ICERs increase with the decrease in the PD utility value. This is likely due to the fact that the proportion of patients treated with pembrolizumab in the two PD health states (the recently introduced post-alloSCT and without alloSCT PD health states) is larger than the proportion of patients treated with SoC in these.

### **Both populations – Costs of alloSCT**

The company explored alternative costs for alloSCT and claimed that it had taken the costs from the nivolumab appraisal TA462 base-case in the same indication. However, in TA462,<sup>7</sup> alloSCT was only included in scenario analysis, and two alloSCT cost scenarios were considered. The committee's and ERG's preferred analysis was the one using alloSCT costs by Radford et al (2017),<sup>8</sup> which was also used in this TA for the pembrolizumab model. The committee furthermore explicitly discounted any alternative cost scenarios. The ERG therefore considers that alternative costs should not be considered for decision-making.

## **ERG results**

Deterministic ERG results for each cohort and for the respective 12-week and 24-week assumptions are presented in Table 1. The ERG base-case is equivalent to the company's base-case with ERG preferences, but numerically different because of slight changes made to the company's implementation of ERG preferences regarding utilities and monitoring costs associated with alloSCT. For the 24-week models, the ERG's base-case uses the newly calibrated HR. Scenarios are based on the new ERG base-case.

## **Conclusion**

The company has provided new analyses with a new price scheme in place and has explored some of the uncertainties that were previously identified. Despite the company's efforts, relative effectiveness and model predictions of OS and PFS continue to be associated with substantial uncertainty. This issue is especially pronounced in population 2, and the 24-week alloSCT models in both populations. The ICER produced by the ERG in its base-case for population 2 (week 12) is associated with uncertainty in both directions: alternative assumptions around model extrapolations, and OS post-alloSCT may increase the ICER further, and the use of a mixed population to inform SoC OS and PFS may mean that the ICER is over-estimated. The latter is explored in the Eyre et al scenario, the former was explored in previous ERG reports. A cost comparison with nivolumab was not provided and there remains uncertainty about whether pembrolizumab is similar to nivolumab in terms of its effectiveness.

**Table 1. ERG deterministic base-case and scenarios**

	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Pembrolizumab ICER (£/QALY)
<b>Cohort 1</b>						
<b>ERG base-case week 12</b>	Pembrolizumab	£103,503	4.383			
	SoC	£47,558	3.353	£55,944	1.03	£54,325
<b>ERG week 12 scenario - Lower PD utility</b>	Pembrolizumab	£103,503	3.894			
	SoC	£47,558	2.875	£55,944	1.02	£54,877
<b>ERG week 24*</b>	Pembrolizumab	£106,396	4.37			
	SoC	£39,956	2.92	£66,440	1.45	£45,829
<b>ERG week 24* scenario – Lower PD utility</b>	Pembrolizumab	£106,396	3.89			
	SoC	£39,956	2.50	£66,440	1.39	£47,673
<b>Cohort 2</b>						
<b>ERG base-case week 12</b>	Pembrolizumab	£88,965	4.03			
	SoC	£47,224	3.36	£41,741	0.67	£62,527
<b>ERG week 12 scenario - Lower PD utility</b>	Pembrolizumab	£88,965	3.54			
	SoC	£47,224	2.88	£41,741	0.66	£63,549
<b>ERG week 12 scenario – Eyre et al</b>	Pembrolizumab	£88,965	4.03			
	SoC	£43,813	3.19	£45,152	0.84	£54,085
<b>ERG week 24*</b>	Pembrolizumab	£83,099	3.75			
	SoC	£31,098	2.52	£52,001	1.22	£42,501
<b>ERG week 24* scenario - Lower PD utility</b>	Pembrolizumab	£83,099	3.27			
	SoC	£31,098	2.11	£52,001	1.16	£44,969
<b>ERG week 24* scenario - Eyre et al</b>	Pembrolizumab	£83,099	3.75			
	SoC	£27,624	2.21	£55,475	1.53	£36,177

ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; PD = progressed disease; QALY = quality-adjusted life year

\*The 24 week estimates should be interpreted with caution, due to substantial uncertainty about the hazard ratios for OS.

## REFERENCES:

- [1] Merck Sharp & Dohme. *Pembrolizumab for treating relapsed or refractory classical Hodgkin's Lymphoma [ID: 1062]: response to Appraisal Consultation Document (ACD) [Word document provided by the company]*, 23 March 2018 [accessed 26.4.18]. 17p.
- [2] Merck Sharp & Dohme. *Pembrolizumab for treating relapsed or refractory classical Hodgkin's Lymphoma [ID: 1062]: additional analyses [Word document provided by the company]*, 9 Feb 2018 [accessed 26.4.18]. 8p.
- [3] National Institute for Health and Care Excellence. *Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma: Appraisal consultation document [Internet]*. London: NICE, March 2018 [accessed 26.4.18]. 21p. Available from: <https://www.nice.org.uk/guidance/gid-ta10130/documents/appraisal-consultation-document>
- [4] Cheah CY, Chihara D, Horowitz S, Sevin A, Oki Y, Zhou S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. *Ann Oncol* 2016;27(7):1317-23.
- [5] Eyre TA, Phillips EH, Linton KM, Kassam S, Gibb A, Allibone S, et al. Results of a multicentre UK-wide retrospective study evaluating the efficacy of brentuximab vedotin in relapsed, refractory classical Hodgkin lymphoma in the transplant naive setting. *Br J Haematol* 2017;179(3):471-479.
- [6] Fayter D, Grimm S, Ramaekers B, Petersohn S, Riemsma R, Armstrong N, et al. *Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma; A Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd, 2017
- [7] National Institute for Health and Care Excellence. *Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma: NICE technology appraisal guidance TA462 [Internet]*. London: NICE, 2017 [accessed 18.9.17] Available from: <https://www.nice.org.uk/guidance/ta462/resources/nivolumab-for-treating-relapsed-or-refractory-classical-hodgkin-lymphoma-pdf-82604902197445>
- [8] Radford J, McKay P, Malladi R, Johnson R, Bloor A, Percival F, et al. Treatment pathways and resource use associated with recurrent Hodgkin lymphoma after autologous stem cell transplantation. *Bone Marrow Transplant* 2017;52(3):452-4.