NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

Contents:

The following documents are made available to consultees and commentators:

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 after stem cell transplant or at least 2 previous therapies [ID1557]

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Lymphoma Action	**We are concerned that this recommendation excludes people with the highest unmet need despite clear clinical benefits.** People with relapsed or refractory Hodgkin lymphoma who are not eligible for stem cell transplant have a poor prognosis. Treatment options at this point in the pathway are limited and typically include multi-agent chemotherapy or brentuximab vedotin. However, most people who are ineligible for stem cell transplant are also unable to tolerate multi-agent chemotherapy. Median progression-free survival after brentuximab vedotin in this population is less than 6 months and is also associated with significant adverse effects (in particular, peripheral neuropathy). Pembrolizumab offers significant benefits for these people (see below) and providing access to it earlier in the treatment pathway would provide better remissions early in the disease course, with immeasurable benefits to patients' lives. At many points in their pathway, patients tell us that the options available on the NHS are very limited and they feel that more effective, better tolerated treatment options should be available earlier.	Thank you for your comment. Following a second appraisal committee meeting, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
2	Consultee	Lymphoma Action	**We feel the recommendation dismisses robust evidence of the efficacy of pembrolizumab in people with relapsed or refractory Hodgkin lymphoma who have not had brentuximab vedotin and are ineligible for stem cell transplant.** The KEYNOTE-204 trial has clearly demonstrated the benefits of pembrolizumab over brentuximab vedotin in this population, with median progression-free survival of 12.5 months compared to just 5.7 months. The committee itself concluded that "for people who had had at least 2 previous treatments with or without previous stem cell transplant, pembrolizumab improves progression-free survival." It is therefore inexplicable that those without a previous stem cell transplant have not been included in the recommendation. With such clearly demonstrated clinical	Thank you for your comment. The recommendations made by the appraisal committee are based both on evidence of clinical and cost effectiveness. Following a second appraisal committee meeting

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			effectiveness in people with relapsed or refractory Hodgkin lymphoma ineligible for stem cell transplant, to exclude this population from NHS funding is an unreasonable interpretation of the evidence and is not a sound and suitable basis for guidance to the NHS.	where further cost effectiveness evidence was considered, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
3	Consultee	Lymphoma Action	**We are concerned that this recommendation will disproportionately impact older people, who are less likely to be eligible for stem cell transplantation.** It may also lead to inequity of access between UK nations, pending the SMC's appraisal of pembrolizumab for a broader indication.	Thank you for your comment. Following a second appraisal committee meeting, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.

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4	Consultee	Lymphoma Action	**We are dismayed and disillusioned that this recommendation ignores the patient view and gives no consideration to the 'intangible benefits' that patient organisations such as ours are asked to provide.** The most important factor patients with lymphoma rate in a treatment is effectiveness. There is clear evidence that pembrolizumab is more effective than brentuximab vedotin in people who are ineligible for a stem cell transplant. Patients feel that the progression-free survival benefit with pembrolizumab, combined with its generally favourable tolerability profile, offer an advantage over brentuximab vedotin that would have a significant impact on their quality of life. They also feel that, as an outpatient treatment with minimal pre-meds required, it is more convenient and less time consuming than many other options (for example, multi-agent chemotherapy), which again has the potential to improve quality of life.	Thank you for your comment. The recommendations made by the appraisal committee are based both on evidence of clinical and cost effectiveness. The committee recognised the benefits of pembrolizumab for this population. Following a second appraisal committee meeting where further cost effectiveness evidence was considered, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
5	Consultee	Lymphoma Action	**We would like to reiterate that given the ongoing coronavirus pandemic, it is more important than ever to consider the potential benefits of effective, well tolerated treatments that can be safely administered in the outpatient setting without the need for frequent hospital attendance.** Pembrolizumab has the	Thank you for your comment. The benefits of outpatient administration were

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			advantage of being able to be administered as a 6-weekly regimen, necessitating fewer hospital visits for patients and therefore a lower risk of hospital-acquired infection.	considered by the committee. Following a second appraisal committee meeting, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
6	Clinical expert	N/A	Many thanks to the committee for their dedication and hard work in appraising the evidence for pembrolizumab use in this indication and producing the ACD. However, I am rather confused by the ACD as it excludes the group of patients most likely to benefit from the technology being appraised with no evidence to suggest they should be excluded. The Keynote 204 study compared brentuximab with pembrolizumab in patients relapsing after stem cell transplant, or ineligible for stem cell transplant. 63% (almost 2/3) of patients in the study were ineligible for stem cell transplantation. This was mainly due to refractory disease but also included older and / or co-morbid patients who would never be eligible for a stem cell transplant irrespective of future remission status. Subgroup analysis showed no subgroup heterogeneity so there is no subgroup that can be said to be not benefiting from pembrolizumab compared with brentuximab. I therefore find it very hard to understand why the ACD excludes patients who have not received a stem cell transplant. If this is the final conclusion it would have the	Thank you for your comment. The recommendations made by the appraisal committee are based both on evidence of clinical and cost effectiveness. Following a second appraisal committee meeting where further cost effectiveness evidence was considered, pembrolizumab is recommended for people in whom a stem cell transplant is not an

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			following very unfortunate consequences:	option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
7	Clinical expert	N/A	Older, less fit patients would be forced to have less effective treatment prior to receiving a more effective treatment. This would be a bizarre clinical pathway. It is a general principle of cancer medicine to use more effective treatment first so the maximum benefit can be obtained for most patients (assuming toxicity is not an issue). Whilst I appreciate the number of elderly patients in Keynote 204 was fairly low, there is no trial evidence, or biological rationale, to suspect older patients will not benefit. I appreciate the committee do not in any way intend to discriminate based on age, but this decision could be interpreted by some in this way.	Thank you for your comment. The committee considered the implication that the draft recommendations may have had regarding inequity of access for older patients. It also considered the treatment pathway for this condition when making its recommendations and noted that pembrolizumab is included in the Cancer Drugs Fund (CDF) for fourth line treatment for people who have not had a previous stem cell transplant but noted that treatments available in the CDF are not considered standard practice. Following a

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				second appraisal committee meeting, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
8	Clinical expert	N/A	Fitter patients who are aiming for stem cell transplantation will again be made to receive less effective treatment (brentuximab) before receiving more effective treatment (pembrolizumab). Whilst there maybe reasons for offering brentuximab prior to pembrolizumab on a case by case basis, generally speaking the efficacy of the treatment dictates the preferential order of use assuming toxicity is roughly equal and there were no concerning toxicity signals of pembrolizumab seen in Keynote 204.	Thank you for your comment. The committee considered the treatment pathway for this condition when making its recommendations and noted that pembrolizumab is included in the Cancer Drugs Fund (CDF) for fourth line treatment for people who have not had a previous stem cell transplant but noted that treatments available in the CDF are not considered standard practice. Following a

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				second appraisal committee meeting, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
9	Clinical expert	N/A	Denying access to pembrolizumab higher in the treatment pathway to those in most need of active, non-chemotherapy agents. Refractory patients have the highest risk of poor outcomes and also have the poorest responses to subsequent chemotherapy or brentuximab (which is chemotherapy). Early PD1 inhibition is of proven benefit compared with brentuximab in this setting.	Thank you for your comment. Following a second appraisal committee meeting, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
10	Clinical	N/A	I am also concerned that my comments and the comments of the other clinical expert	Thank you for your

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	expert		may have been mis-represented. On page 9 and 10 of the ACD it says this: > The clinical experts also highlighted the possibility that pembrolizumab treatment increases toxicity to allogenic stem cell transplant and may reduce the effectiveness of autologous stem cell transplant but evidence on this is still emerging. Whilst pembrolizumab may increase toxicity to allogeneic stem cell transplantation, there is NO evidence that it may reduce the effectiveness of an autologous stem cell transplant. In fact the opposite may be true – there is some evidence PD1 inhibition may sensitise patients to subsequent chemotherapy making a subsequent autologous stem cell transplant more effective. Data is emerging but there is no data to suggest it makes it less effective. In conclusion I would ask the committee to reconsider the decision to only include patients relapsing after a stem cell transplant. Many thanks for taking the time to read this response and considering its contents.	comment. The wording in section 3.6 of the final appraisal document has been amended in line with this response and the clinical expert views heard at the second appraisal committee meeting.
11	Clinical expert	N/A	I am concerned that excessive weight has been placed on transplant status in these recommendations. Keynote-204 is the largest and only randomised trial to compare 3L treatment in Hodgkin lymphoma, to my knowledge, and therefore represents the best available evidence in this setting. To make recommendations based on post-hoc subgroup analyses that exclude the majority of patients recruited to Keynote-204, without clear evidence demonstrating that the PFS significantly differs according to transplant status, seems spurious. PD-1 inhibitors are a major breakthrough in the treatment of Hodgkin lymphoma and are internationally recognised as a pivotal part of management pathways for relapsed and refractory disease. Response rates with these agents in Hodgkin lymphoma are higher than in any other malignancy. There is no clinical or biological rationale to support the premise that PD-1 inhibitors are only effective in patients who have had prior autologous stem cell transplant. However, these recommendations will remove this treatment option entirely for transplant-naïve patients if access is no longer available via the CDF, even though it may be curative for a subset of	Thank you for your comment. The recommendations made by the appraisal committee are based both on evidence of clinical and cost effectiveness. Following a second appraisal committee meeting where further cost effectiveness evidence was considered, pembrolizumab is recommended for people in whom a stem

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			chemorefractory, patients when combined with subsequent transplantation.	cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
12	Clinical expert	N/A	I do not entirely agree that *'the prognosis for people with a previous stem cell transplant may be expected to be better than for people without a previous stem cell transplant and that the subsequent treatment options for these subgroups also differ'* significantly. The PFS benefit with pembrolizumab over brentuximab vedotin in Keynote-204 was marginally greater in the transplant-naïve population than for patients who had received prior transplant. There was no definite evidence of a difference in median PFS following pembrolizumab according to prior transplant status (12.5m versus 14.7m for patients without/with prior transplant; Kuruvilla *et al*, Lancet Oncology 2021). Whether a patient is considered 'transplant fit' has a much greater influence on both treatment pathways and prognosis. This group includes patients who have relapsed after autologous transplant and are eligible for subsequent allogeneic transplant, as well as transplant-naïve patients. For transplant-fit patients (presumed to represent the majority of patients in Keynote-204), it is unclear whether the prognosis is any better for those who have received a previous autologous stem cell transplant. Transplant-naïve patients are likely to be more chemorefractory, but potentially have more consolidation treatment options available, i.e. both autologous and allogeneic transplantation. Patients that are unfit for transplant, due to age and/or co-morbidities, form a minority of Hodgkin lymphoma patients and are usually treated with palliative intent. These	Thank you for your comment. The wording in section 3.9 of the final appraisal document has been amended in line with this response and the clinical expert views heard at the second appraisal committee meeting.

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			patients certainly do have worse outcomes, partly due to reduced fitness and performance status, but also have the greatest clinical need. They usually experience greater toxicity with standard treatments, such as neuropathy with brentuximab vedotin, but not PD-1 inhibitors, and are ineligible for combination chemotherapy. Despite worse outcomes, there is a strong argument for early use of pembrolizumab in this population (as early as 2L, as in Keynote-204) given the lack of tolerable and effective alternative treatment options.	
13	Clinical expert	N/A	The ERG assumed that '*time on treatment should be largely similar to progression-free survival, because progression often triggers a change in treatment*.' This is often incorrect for transplant-fit patients. If fit for autologous or allogeneic transplant, responding patients will usually stop treatment before progression to receive transplant consolidation; the majority of these patients will not subsequently relapse. Transplant-fit patients may also stop pembrolizumab before overt progression if clearly not responding to pursue alternative potentially curative treatment options, rather than continue with pembrolizumab for 24 months. In Keynote-204, out of 110 patients who discontinued pembrolizumab, only 59 had experienced disease progression (Kuruvilla *et al*, Lancet Oncology 2021).	Thank you for your comment. Reference to time on treatment being similar to progression-free survival has been removed from the final appraisal document.
14	Clinical expert	N/A	'*The clinical experts explained that pembrolizumab may not have the same relative benefit compared with brentuximab vedotin for people with and without previous transplant. This is because, in some people, the lymphoma will not have responded well enough to chemotherapy to allow a stem cell transplant and these people's condition may have a poorer response to further chemotherapy, including brentuximab vedotin. Pembrolizumab is an immunotherapy and is not expected to be affected by previous response to chemotherapy.'* By this rationale, one might expect pembrolizumab to have a greater benefit compared with brentuximab in the transplant-naïve population than in patients who have received prior transplant. Furthermore, this is the population with the greatest unmet clinical need, and where the only access to PD-1 inhibition is with pembrolizumab via the CDF.	Thank you for your comment. The recommendations made by the appraisal committee are based both on evidence of clinical and cost effectiveness. The committee recognised the benefits of pembrolizumab for this population. Following a second appraisal committee meeting where further cost effectiveness evidence

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				was considered, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
15	Clinical expert	N/A	*'The clinical experts also highlighted the possibility that pembrolizumab treatment increases toxicity to allogeneic stem cell transplant and may reduce the effectiveness of autologous stem cell transplant but evidence on this is still emerging.'* There is no current evidence to suggest that the effectiveness of autologous stem cell transplant after pembrolizumab is reduced. Indeed, a number of recent publications have demonstrated that autologous transplant is highly effective in patients who have respond to immunotherapy with PD-1 inhibition: 1) Merryman *et al*, Blood Advances 2021;5(6):1648-1659, and 2) Herrera *et al,* Blood 2019;134(S1):239. It is therefore very attractive to use pembrolizumab as a bridge to autologous stem cell transplant for transplant-naïve patients. In such circumstances, the cost of pembrolizumab treatment will be lower (typically only 4-8 cycles of pembrolizumab are given prior to transplant) and the likelihood of cure will be much higher, therefore presumably the cost-effectiveness ratio will be more favourable.	Thank you for your comment. The wording in section 3.6 of the final appraisal document has been amended in line with this response and the clinical expert views heard at the second appraisal committee meeting.
16	Consultee (company)	MSD	Summary of response MSD thanks NICE, the ERG and the committee for their hard work on this appraisal and for the opportunity to comment. We agree with the committee that pembrolizumab is a cost-effective option for	Thank you for your comment. Following a second appraisal committee meeting where further cost effectiveness evidence

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			patients who are at third line plus and have had an SCT (the "SCT+3L+" subpopulation). We support the committee's recommendations and have no further comments on the ACD's considerations of the evidence for this group. MSD is very disappointed that the ACD' positive recommendations exclude those patients who are currently ineligible for a potentially curative SCT (the "SCT-3L+" subpopulation), numbering approximately 30 per year in the UK. We note that the clinical effectiveness of pembrolizumab is just as strong in this group and that the difference in apparent cost-effectiveness between the two subgroups is due to which subsequent treatment costs NICE's rules permit the economic model to include. MSD has responded to the ACD by submitting additional evidence that better reflects the anticipated consequences of being able to offer pembrolizumab to this population by including an overall survival benefit in the economic model. The base case ICER for consideration is [redacted] with a range of ~£8,000/QALY - £19,000/QALY in more than 40 scenario analyses examining the effect of key drivers on the model. It should be noted the risk of decision error is extremely low; a positive recommendation would lead to pembrolizumab displacing itself in the treatment pathway one step earlier, not adding an additional step. This displacement, coupled with the small patient population mean that the budget impact of a positive recommendation would be extremely small.	was considered, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
17	Consultee (company)	MSD	MSD considers that the decision for this patient group is fundamentally about whether patients should be offered pembrolizumab then BV or BV then pembrolizumab. The major barrier to a positive recommendation so far has been that the costs of pembrolizumab in the fourth line setting are not allowed to be included in the model as it is funded via the CDF. Therefore, instead of the model reflecting a reality where pembrolizumab just displaces itself in the pathway, the model is forced to consider pembrolizumab as an additional treatment step in the pathway. We understand NICE's rules in this regard but consider that the committee should bear in mind that the treatment is displacing itself when deliberating the effect of their recommendations on NHS resource use. This can be done with negligible risk of decision error; the committee has already concluded pembrolizumab is more	Thank you for your comment. The committee considered the treatment pathway for this condition when making its recommendations and noted that pembrolizumab is included in the Cancer Drugs Fund (CDF) for fourth line treatment for

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			effective than BV and because it would displace itself in the pathway there will be no additional treatment costs, at least until TA540 (pembrolizumab 4L) is considered for exit from the CDF.	people who have not had a previous stem cell transplant but noted that treatments available in the CDF are not considered standard practice. Following a second appraisal committee meeting, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
18	Consultee (company)	MSD	Given the negligible risk of decision error in recommending pembrolizumab for this small group of patients, we hope that the committee will take an open-minded rather than a conservative approach to handling uncertainty when considering their recommendations. Attaining certain data on cost-effectiveness in small sub-populations is always a challenge and we are concerned that the SCT-3L+ subgroup may be disadvantaged simply because they are relatively small in number and therefore harder to research.	Thank you for your comment. The appraisal committee considered the small population size for this condition and noted that this can introduce additional uncertainty. Following a second appraisal committee meeting, pembrolizumab is recommended for

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				people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
19	Consultee (company)	MSD	MSD's response to the ACD is detailed in a separate technical report. Our principal response has been to revise our economic modelling and include plausible differences in overall survival between the pathways. We consider this better reflects the value of this treatment in this indication, given the PFS HR for the SCT-3L+ sub-group was [redacted] This is a profound improvement in a cHL patient subgroup that routinely has poor outcomes due to ineligibility for stem cell transplant.	Thank you for your comment. The appraisal committee considered the additional analysis provided in the separate technical report.
20	Consultee (company)	MSD	<u>Modelling overall survival (OS) benefit in the SCT-3L+ subgroup</u> In MSD's original submission, we did not include any overall survival benefit for pembrolizumab over BV in the economic model. This was because our model produced a "dominant" result for the combined 3L+ population. No OS data are yet available from KEYNOTE-204 and no other comparative study has ever been conducted in this space. The most relevant NICE technology appraisals (TA524 for BV and TA540 for pembrolizumab 4L) have concluded substantial OS benefits are plausible in the absence of any comparative data on OS. This is a reflection of the small subpopulation under consideration and the relatively long natural history of the disease making obtaining the relevant data difficult. MSD agrees with the committee that assuming equal effectiveness between pembrolizumab and BV is conservative and with the testimony of clinical experts that pembrolizumab may lead to an overall survival benefit (ACD 3.11). Accordingly, we have sought the best available evidence to model differential overall survival outcomes in the BV and pembrolizumab arms of the economic model.	Thank you for your comment. The appraisal committee considered the additional analysis provided on overall survival, as described in sections 3.12 and 3.13 of the final appraisal document.

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			We examined the Systematic Literature Reviews from this submission, from TA540 and conducted an additional search to try to identify papers that reported long term OS data for BV and pembrolizumab in the SCT-3L+ population. Our preferred approach is to use the data considered most relevant by the NICE committee in TA524 to model OS for BV along with the data from TA540 on the SCT-4L+ population to model OS for pembrolizumab. Our base case is a naïve comparison but we have also included an adjusted analysis and another data source for each intervention in sensitivity analyses. Figure 1 below contains an updated schematic of the model.	

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			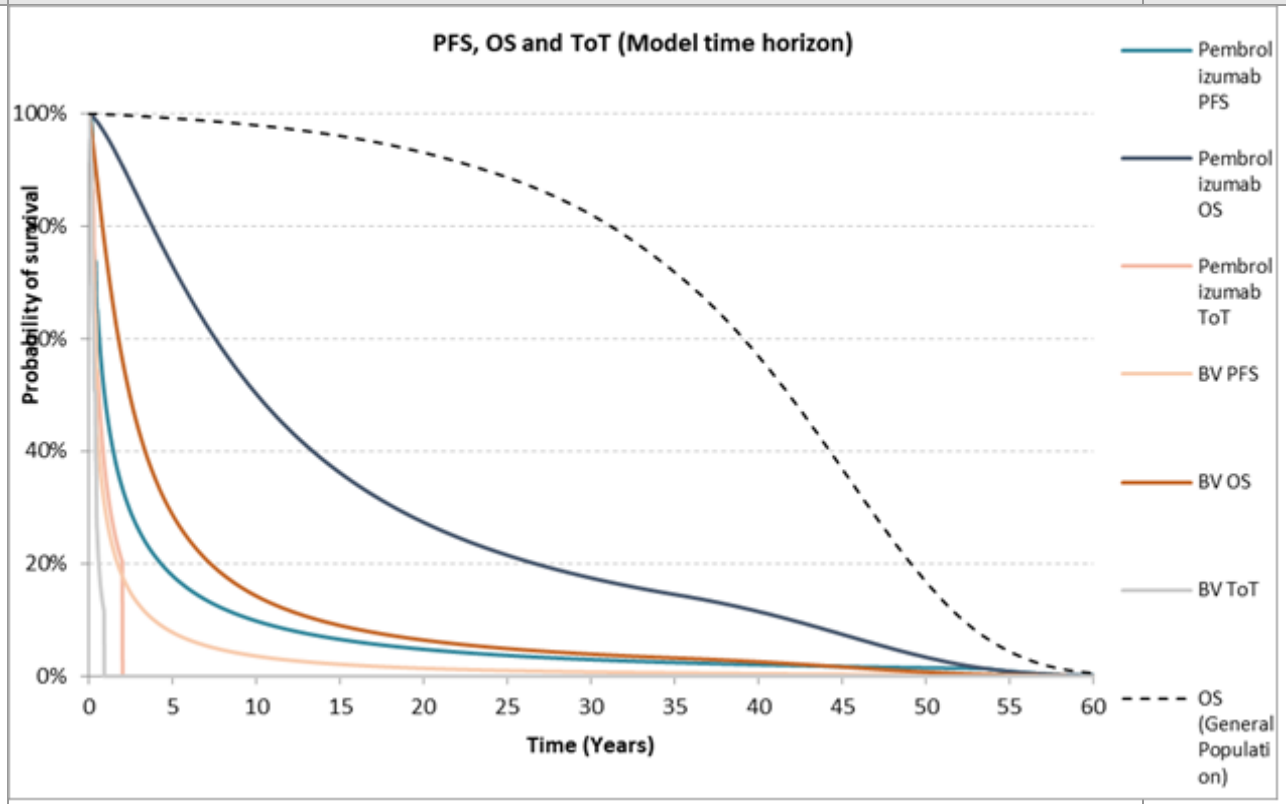 The median age of enrolment of SCT-3L+ patients into KEYNOTE-204 was [redacted] years. cHL is a disease with a long natural history and the potential for patients to receive curative SCT interventions. MSD has received clinical advice that the model's long term extrapolations are plausible. Indirect comparisons are inherently uncertain but the benefit of pembrolizumab over BV may be underestimated rather than overestimated as the surrogate data for BV matched the population of interest well whereas the surrogate data for pembrolizumab was taken from a trial of older fourth line patients. An assessment of the PFS curves shows good agreement in average PFS time for the majority of	

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			patients between the surrogate trials and the two arms of KEYNOTE-204.	
21	Consultee (company)	MSD	Validation of OS extrapolations It was not possible to validate the long term extrapolations in the model from external data; BV and pembrolizumab have not been available for long and the natural history of the disease is too long for the 10 year+ data that would be necessary to have become available. MSD has received clinical advice about which curves are considered plausible and implausible. The epidemiology of the disease and potential for SCT- patients to become eligible for curative interventions mean that survival extrapolations with a decreasing hazard are more likely. No models should be considered where OS drops to zero over 20 years. Exponential models are implausible due to the monotonic nature of their hazards. We have provided some epidemiological sources in our technical report which illustrate these points. It was not possible to validate the survival extrapolations using a linked evidence approach, for example linking the probability of SCT to the probability of success of SCT to long term time-dependent transition probabilities for the originally SCT-3L+ population. Long term data of this additional level of granularity do not exist.	Thank you for your comment. The appraisal committee considered the overall survival analysis presented and concluded that the size of benefit for people without previous stem cell transplant is highly uncertain (section 3.13 of the final appraisal document).
22	Consultee (company)	MSD	Pembrolizumab as a bridge to SCT MSD agrees with the committee that it is possible that, given the significant PFS benefit and favourable side effect profile, it is plausible that more patients would receive a curative SCT with pembrolizumab than BV. The data from KEYNOTE-204 are unfortunately not able to be used to draw inferences; bridging to SCT was not allowed by the trial protocol and many patients in the BV arm had access to immunotherapy after progressing on BV. The data may therefore be unrepresentative of the comparative ability of pembrolizumab and BV to bridge patients to SCT. The estimated mean time to SCT was far longer than the average treatment duration in the BV arm of the trial. It may be that the similar proportions seen in the trial reflect the availability of immunotherapy to patients failing on BV, for example.	Thank you for your comment. The appraisal committee considered the potential benefits of pembrolizumab treatment in increasing the number of people who might be able to have a stem cell transplant and concluded that pembrolizumab may increase the number of people who are able to have an autologous

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				stem cell transplant compared with brentuximab vedotin, although data is limited (section 3.6 of the final appraisal document).
23			Alternate sources of OS data for pembrolizumab KEYNOTE-087 has reported OS data. While this is a later line of treatment, it is possible to identify patients with similar baseline characteristics in the SCT- cohort of KEYNOTE-087 and KEYNOTE-204. Therefore, MSD has conducted a match adjusting exercise. This has produced an OS curve for pembrolizumab treatment patients in KEYNOTE-087, based on the characteristics of the KEYNOTE-204 patients, which may be a better surrogate for OS that would be observed in KEYNOTE-204 than the unadjusted data would. The estimates are shown in Figure 2 and should be treated with caution as the Effective Sample Size is small. We also have real world data from a much older and less fit cohort that produces very conservative estimates. 	Thank you for your comment. The appraisal committee considered the additional analysis provided on overall survival, as described in sections 3.12 and 3.13 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
24	Consultee (company)	MSD	Subsequent treatments approach MSD has provided an alternate approach to accruing subsequent treatment costs based on exits from the PFS state rather than entries to the PD state. Both approaches are examined in sensitivity analysis. The ICERs using the approach based on PD entry are about £2,000/QALY lower than the PFS exit approach. The company considers the PFS exit approach to better reflect the data in the clinical trial.	Thank you for your comment. The appraisal committee considered the alternative approach to accruing subsequent treatment costs, as described in section 3.15 of the final appraisal consultation document.
25	Consultee (company)	MSD	Alternate value for PD utility In the ACD the clinical experts felt it was plausible that PD utility would be higher in the pembrolizumab arm due to fewer enduring side effects. The measured difference in utility in the PD state was large between the arms. It is reasonable to expect that had the subsequent treatment of choice in the trial been multi-agent chemotherapy rather than immunotherapy, this difference might have been even larger. We have sourced an alternate value for PD utility in the pembrolizumab arm that is more conservative than the benefit recorded in KEYNOTE-204 but more realistic than assuming PD utility is equal between the arms.	Thank you for your comment. The appraisal committee considered the alternative values for progressed disease utility, as described in section 3.14 of the final appraisal document.
26	Consultee (company)	MSD	Results of the economic model The base case analysis shows that pembrolizumab is comfortably within the range usually considered cost-effective by NICE with a base case ICER of [redacted] These conclusions are robust to a great number of plausible scenario analyses. The plausible scenario analyses produced ICERs that ranged between £8,000/QALY and £19,000/QALY gained.	Thank you for your comment. At a second appraisal committee meeting, the committee agreed that it was likely that pembrolizumab was a cost-effective use of NHS resources. The

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Although OS data were immature, the model's conclusions were not sensitive to different parametric extrapolations, provided these were confined to clinically plausible curves. The model was not sensitive to probabilistic sensitivity analysis, with mean results being similar to the deterministic base case and the 95% CI lying wholly below £20,000/QALY gained. The model was most sensitive to the choice of studies used to model overall survival, the choice of assumptions about the proportion of patients receiving subsequent treatment, the long term costs in the PD state and assumptions about treatment waning. Only in the most pessimistic combinatorial scenario analysis did the ICER marginally exceed [redacted]	committee recommended pembrolizumab for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
27	Consultee (company)	MSD	<u>Closing remarks</u> The SCT-3L+ subpopulation is a small and under-researched group. KEYNOTE-204 provides the only comparative trial data in this space. All other research has been confined to single arm studies and it is only possible to make naïve comparisons of overall survival between pembrolizumab and BV or to attempt to model the differences by even less certain linked-evidence modelling. cHL is a disease with a long natural history, a potential for patients to receive curative interventions and non-linear hazards of death over time. This makes obtaining the relevant data for robust modelling difficult. When taking into account plausible estimates of overall survival, the company's revised model finds that pembrolizumab>BV is cost-effective compared to BV>chemotherapy. These estimates are robust to sensitivity analyses. While the data informing the model is imperfect, the decision risk is low and it is highly likely this is a good use of NHS resources.	Thank you for your comment. Following a second appraisal committee meeting, pembrolizumab is recommended for people in whom a stem cell transplant is not an option following 2 lines of previous therapy, which has not included brentuximab vedotin and for people who have had an autologous stem cell transplant that has not worked and have not have brentuximab vedotin.
28	Commentator	Takeda	**Wording in Section 3.3, Page 7**	Thank you for your comment. Section 3.3 of

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
			"The committee noted that the comparator treatment in KEYNOTE-204 is brentuximab vedotin and NICE recommends brentuximab vedotin for people who have had 2 or more previous treatments. It concluded that the trial results for this subgroup are generalisable to NHS practice." In the KEYNOTE-204 trial, patients were permitted to receive up to 35 cycles of brentuximab vedotin, which is not generalisable to NHS practice or within its marketing authorisation. The EMA marketing authorisation for brentuximab vedotin in the treatment of relapsed or refractory Hodgkin lymphoma indicates patients should receive a maximum of 16 cycles of brentuximab vedotin.[1] Brentuximab vedotin is not approved for use beyond 16 cycles in any indication; the NHS Treatment Criteria, which outline the funding requirements in England, state that "*no more than 16 cycles of brentuximab may be administered per patient*".[2] However, 18 (12%) patients treated with brentuximab vedotin in the KEYNOTE-204 received greater than 16 cycles of brentuximab vedotin.[3] We request that the wording around generalisability of the KEYNOTE-204 trial should be updated to reflect the off-licence use of brentuximab vedotin that occurred in this trial.	the final appraisal document has been updated to include reference to the off-label use of brentuximab vedotin in KEYNOTE-204.
29	Commentator	Takeda	**Wording in Section 3.4, Page 8** *"The clinical experts explained that pembrolizumab may not have the same relative benefit compared with brentuximab vedotin for people with and without previous transplant. This is because, in some people, the lymphoma will not have responded well enough to chemotherapy to allow a stem cell transplant and these people's condition may have a poorer response to further chemotherapy, including brentuximab vedotin. Pembrolizumab is an immunotherapy and is not expected to be affected by previous response to chemotherapy."* The current wording suggests that brentuximab vedotin should be considered in the same treatment group, in terms of outcomes and chemosensitivity, as standard chemotherapy. However, brentuximab vedotin is an anti-CD30 monoclonal antibody-drug conjugate, and is therefore considered a targeted chemotherapy. Clinical trial and real-world evidence is available to demonstrate the benefit of treatment with brentuximab vedotin in patients with poor responses to prior chemotherapy: • In the pivotal Phase 2 study of brentuximab vedotin for patients with relapsed or refractory classical Hodgkin lymphoma, 71% (72/102) of patients had	Thank you for your comment. Section 3.4 of the final consultation document has been updated in line with the views heard from clinical experts at the second appraisal committee meeting. The final appraisal document specifies that brentuximab vedotin is a targeted chemotherapy.

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
			primary refractory disease and the median number of prior chemotherapy regimens was 3.5. These patients therefore represented a heavily pre-treated population with a poor prognosis. Nevertheless, tumour reductions were observed in almost all patients (96/102, 94%) and the objective response rate was 75% (76/102 patients); therefore supporting the efficacy of brentuximab vedotin in patients with poor response to prior chemotherapy.[4] • A UK-wide retrospective study evaluating the efficacy of brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma in the transplant-naïve setting demonstrated an overall response rate of 56% following brentuximab vedotin treatment, with 61% of patients reaching stem cell transplant (SCT). This real-world study concluded that brentuximab vedotin is efficacious in this difficult-to-treat population, and confirmed its role in the treatment pathway as an effective bridge to SCT.[5] We request that the wording is updated to acknowledge that patients could achieve a response with brentuximab vedotin treatment, despite poor response to prior chemotherapy.	
30	Commentator	Takeda	**Wording in Section 3.6, Page 9–10** *"The committee concluded that in practice, pembrolizumab may increase the number of people who are able to have a stem cell transplant compared with brentuximab vedotin, but data are limited."* We agree that the data are limited on the number of patients in the KEYNOTE-204 who reach SCT following treatment with pembrolizumab or brentuximab vedotin. Initial results presented at American Society of Clinical Oncology (ASCO) in 2020 indicate that 30 (20.3%) patients treated with pembrolizumab and 34 (22.4%) patients treated with brentuximab vedotin received subsequent autologous SCT.[6] A minimal difference was similarly observed for patients reaching subsequent allogenic SCT: 14 (9.5%) patients treated with pembrolizumab and 13 (8.6%) patients treated with brentuximab vedotin.[6] A complete response tends to be considered by clinicians to offer the best chances of a successful SCT, compared to partial or no response. Given complete response by blinded independent central review in the KEYNOTE-204 trial was similar between treatment arms (37 [24.5%] patients treated with pembrolizumab and 37 [24.2%] patients treated with brentuximab vedotin),[3] we	Thank you for your comment. Section 3.6 of the final consultation document has been updated in line with the views heard from clinical experts at the second appraisal committee meeting. It concludes that pembrolizumab may increase the number of people who are able to have an autologous stem cell transplant compared with brentuximab vedotin, but data is limited.

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
			believe the statement in Section 3.6 that "*the proportions of people having a stem cell transplant after pembrolizumab will be greater than after brentuximab vedotin*" lacks supporting evidence. We request the wording to be updated to accurately reflect currently available evidence from the KEYNOTE-204 trial, of similar rates of complete response and subsequent transplant in both arms.	
31	Commentator	Takeda	**Wording in Section 3.12, Page 14–15** *"This is because brentuximab vedotin is associated with higher rates of side effects, including neuropathy, which can be debilitating and persist for several months. The committee agreed that some side effects of brentuximab vedotin may persist after stopping treatment…"* We believe this statement around the side effects of brentuximab vedotin does not provide a true representation of the side effects of both medicines. Five (3%) patients in the brentuximab vedotin arm and one (1%) patient in the pembrolizumab arm experienced peripheral neuropathy at Grade 3–5 in the KEYNOTE-204 trial.[3] Although peripheral neuropathy can persist in some patients following treatment with brentuximab vedotin, the clinical experts noted during the Committee meeting that side effects of brentuximab vedotin can also improve with time in some patients. Clinical experts also raised that the immune-related adverse events associated with pembrolizumab cause significant morbidity for a minority of patients, and should therefore be considered. We request the wording of Section 3.12 to be updated to highlight the safety profiles of both pembrolizumab and brentuximab vedotin, to ensure the wording is balanced.	Thank you for your comment. Section 3.14 of the final consultation document has been updated in line with the views heard from clinical experts at the second appraisal committee meeting.

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Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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: • 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; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Merck, Sharp and Dohme Ltd.**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** 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.

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Example 1	We are concerned that this recommendation may imply that ……..
1	Summary of response MSD thanks NICE, the ERG and the committee for their hard work on this appraisal and for the opportunity to comment. We agree with the committee that pembrolizumab is a cost-effective option for patients who are at third line plus and have had an SCT (the "SCT+3L+" subpopulation). We support the committee's recommendations and have no further comments on the ACD's considerations of the evidence for this group. MSD is very disappointed that the ACD' positive recommendations exclude those patients who are currently ineligible for a potentially curative SCT (the "SCT-3L+" subpopulation), numbering approximately 30 per year in the UK. We note that the clinical effectiveness of pembrolizumab is just as strong in this group and that the difference in apparent cost-effectiveness between the two subgroups is due to which subsequent treatment costs NICE's rules permit the economic model to include. MSD has responded to the ACD by submitting additional evidence that better reflects the anticipated consequences of being able to offer pembrolizumab to this population by including an overall survival benefit in the economic model. The base case ICER for consideration is ~£10,000/QALY with a range of ~£8,000/QALY - £19,000/QALY in more than 40 scenario analyses examining the effect of key drivers on the model. It should be noted the risk of decision error is extremely low; a positive recommendation would lead to pembrolizumab displacing itself in the treatment pathway one step earlier, not adding an additional step. This displacement, coupled with the small patient population mean that the budget impact of a positive recommendation would be extremely small.
2	MSD considers that the decision for this patient group is fundamentally about whether patients should be offered pembrolizumab then BV or BV then pembrolizumab. The major barrier to a positive recommendation so far has been that the costs of pembrolizumab in the fourth line setting are not allowed to be included in the model as it is funded via the CDF. Therefore, instead of the model reflecting a reality where pembrolizumab just displaces itself in the pathway, the model is forced to consider pembrolizumab as an additional treatment step in the pathway. We understand NICE's rules in this regard but consider that the committee should bear in mind that the treatment is displacing itself when deliberating the effect of their recommendations on NHS resource use. This can be done with negligible risk of decision error; the committee has already concluded pembrolizumab is more effective than BV and because it would displace itself in the pathway there will be no additional treatment costs, at least until TA540 (pembrolizumab 4L) is considered for exit from the CDF.
3	Given the negligible risk of decision error in recommending pembrolizumab for this small group of patients, we hope that the committee will take an open-minded rather than a conservative approach to

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	handling uncertainty when considering their recommendations. Attaining certain data on cost-effectiveness in small sub-populations is always a challenge and we are concerned that the SCT-3L+ subgroup may be disadvantaged simply because they are relatively small in number and therefore harder to research.
	MSD's response to the ACD is detailed in a separate technical report. Our principal response has been to revise our economic modelling and include plausible differences in overall survival between the pathways. We consider this better reflects the value of this treatment in this indication, given the PFS HR for the SCT-3L+ sub-group was [redacted] This is a profound improvement in a cHL patient subgroup that routinely has poor outcomes due to ineligibility for stem cell transplant.
	<u>Modelling overall survival (OS) benefit in the SCT-3L+ subgroup</u> In MSD's original submission, we did not include any overall survival benefit for pembrolizumab over BV in the economic model. This was because our model produced a "dominant" result for the combined 3L+ population. No OS data are yet available from KEYNOTE-204 and no other comparative study has ever been conducted in this space. The most relevant NICE technology appraisals (TA524 for BV and TA540 for pembrolizumab 4L) have concluded substantial OS benefits are plausible in the absence of any comparative data on OS. This is a reflection of the small subpopulation under consideration and the relatively long natural history of the disease making obtaining the relevant data difficult. MSD agrees with the committee that assuming equal effectiveness between pembrolizumab and BV is conservative and with the testimony of clinical experts that pembrolizumab may lead to an overall survival benefit (ACD 3.11). Accordingly, we have sought the best available evidence to model differential overall survival outcomes in the BV and pembrolizumab arms of the economic model. We examined the Systematic Literature Reviews from this submission, from TA540 and conducted an additional search to try to identify papers that reported long term OS data for BV and pembrolizumab in the SCT-3L+ population. Our preferred approach is to use the data considered most relevant by the NICE committee in TA524 to model OS for BV along with the data from TA540 on the SCT-4L+ population to model OS for pembrolizumab. Our base case is a naïve comparison but we have also included an adjusted analysis and another data source for each intervention in sensitivity analyses. Figure 1 below contains an updated schematic of the model.

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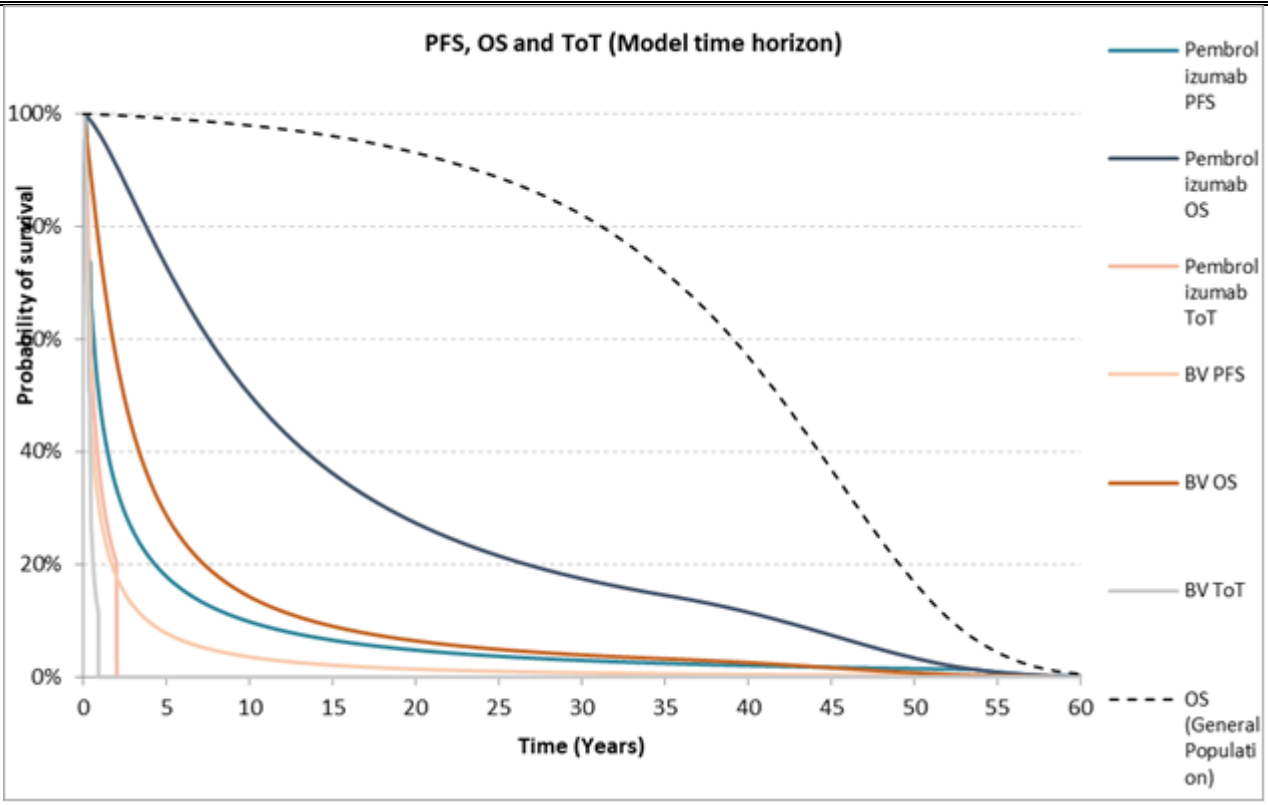
Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 12 October 2021. Please submit via NICE Docs.



The median age of enrolment of SCT-3L+ patients into KEYNOTE-204 was [redacted] years. cHL is a disease with a long natural history and the potential for patients to receive curative SCT interventions. MSD has received clinical advice that the model's long term extrapolations are plausible.

Indirect comparisons are inherently uncertain but the benefit of pembrolizumab over BV may be underestimated rather than overestimated as the surrogate data for BV matched the population of interest well whereas the surrogate data for pembrolizumab was taken from a trial of older fourth line patients. An assessment of the PFS curves shows good agreement in average PFS time for the majority of patients between the surrogate trials and the two arms of KEYNOTE-204.

<u>Validation of OS extrapolations</u>

It was not possible to validate the long term extrapolations in the model from external data; BV and pembrolizumab have not been available for long and the natural history of the disease is too long for the 10 year+ data that would be necessary to have become available.

MSD has received clinical advice about which curves are considered plausible and implausible. The epidemiology of the disease and potential for SCT- patients to become eligible for curative interventions mean that survival extrapolations with a decreasing hazard are more likely. No models should be considered where OS drops to zero over 20 years. Exponential models are implausible due to the monotonic nature of their hazards. We have provided some epidemiological sources in our technical report which illustrate these points.

It was not possible to validate the survival extrapolations using a linked evidence approach, for example linking the probability of SCT to the probability of success of SCT to long term time-dependent transition probabilities for the originally SCT-3L+ population. Long term data of this additional level of granularity do not exist.

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Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 12 October 2021. Please submit via NICE Docs.

	Pembrolizumab as a bridge to SCT MSD agrees with the committee that it is possible that, given the significant PFS benefit and favourable side effect profile, it is plausible that more patients would receive a curative SCT with pembrolizumab than BV. The data from KEYNOTE-204 are unfortunately not able to be used to draw inferences; bridging to SCT was not allowed by the trial protocol and many patients in the BV arm had access to immunotherapy after progressing on BV. The data may therefore be unrepresentative of the comparative ability of pembrolizumab and BV to bridge patients to SCT. The estimated mean time to SCT was far longer than the average treatment duration in the BV arm of the trial. It may be that the similar proportions seen in the trial reflect the availability of immunotherapy to patients failing on BV, for example.
	Alternate sources of OS data for pembrolizumab KEYNOTE-087 has reported OS data. While this is a later line of treatment, it is possible to identify patients with similar baseline characteristics in the SCT- cohort of KEYNOTE-087 and KEYNOTE-204. Therefore, MSD has conducted a match adjusting exercise. This has produced an OS curve for pembrolizumab treatment patients in KEYNOTE-087, based on the characteristics of the KEYNOTE-204 patients, which may be a better surrogate for OS that would be observed in KEYNOTE-204 than the unadjusted data would. The estimates are shown in Figure 2 and should be treated with caution as the Effective Sample Size is small. [redacted] [redacted] We also have real world data from a much older and less fit cohort that produces very conservative estimates.
	Subsequent treatments approach MSD has provided an alternate approach to accruing subsequent treatment costs based on exits from the PFS state rather than entries to the PD state. Both approaches are examined in sensitivity analysis. The ICERs using the approach based on PD entry are about £2,000/QALY lower than the PFS exit approach. The company considers the PFS exit approach to better reflect the data in the clinical trial.
	Alternate value for PD utility In the ACD the clinical experts felt it was plausible that PD utility would be higher in the pembrolizumab arm due to fewer enduring side effects. The measured difference in utility in the PD state was large between the arms. It is

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Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 12 October 2021. Please submit via NICE Docs.

	reasonable to expect that had the subsequent treatment of choice in the trial been multi-agent chemotherapy rather than immunotherapy, this difference might have been even larger. We have sourced an alternate value for PD utility in the pembrolizumab arm that is more conservative than the benefit recorded in KEYNOTE-204 but more realistic than assuming PD utility is equal between the arms.
	Results of the economic model The base case analysis shows that pembrolizumab is comfortably within the range usually considered cost-effective by NICE with a base case ICER of ~£10,000/QALY gained. These conclusions are robust to a great number of plausible scenario analyses. The plausible scenario analyses produced ICERs that ranged between £8,000/QALY and £19,000/QALY gained. Although OS data were immature, the model's conclusions were not sensitive to different parametric extrapolations, provided these were confined to clinically plausible curves. The model was not sensitive to probabilistic sensitivity analysis, with mean results being similar to the deterministic base case and the 95% CI lying wholly below £20,000/QALY gained. The model was most sensitive to the choice of studies used to model overall survival, the choice of assumptions about the proportion of patients receiving subsequent treatment, the long term costs in the PD state and assumptions about treatment waning. Only in the most pessimistic combinatorial scenario analysis did the ICER marginally exceed £30,000/QALY.
	Closing remarks The SCT-3L+ subpopulation is a small and under-researched group. KEYNOTE-204 provides the only comparative trial data in this space. All other research has been confined to single arm studies and it is only possible to make naïve comparisons of overall survival between pembrolizumab and BV or to attempt to model the differences by even less certain linked-evidence modelling. cHL is a disease with a long natural history, a potential for patients to receive curative interventions and non-linear hazards of death over time. This makes obtaining the relevant data for robust modelling difficult. When taking into account plausible estimates of overall survival, the company's revised model finds that pembrolizumab>BV is cost-effective compared to BV>chemotherapy. These estimates are robust to sensitivity analyses. While the data informing the model is imperfect, the decision risk is low and it is highly likely this is a good use of NHS resources.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 12 October 2021. Please submit via NICE Docs.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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MSD Response to ACD for ID1557 – Updated Economic Analysis Technical Report

Oct 12th 2021

Note: this report does not include any new data from KEYNOTE-204 for the SCT+3L+[1] subpopulation, it is concerned largely with our attempts to characterise the OS benefit that may be associated with pembrolizumab compared with Brentuximab Vedotin (BV) in the SCT-3L+ subpopulation and the effect of incorporating these estimates into the economic model. Other less substantial model updates and sensitivity analyses are also included.

Executive summary

On the basis of a revised economic model that includes clinically plausible incremental overall survival benefit for pembrolizumab (pembro) compared with brentuximab vedotin (BV) for the SCT-3L+ cohort, the estimated ICER is ~£10,000/QALY gained, with a range of £8,000 - £19,000/QALY in plausible scenario analyses. This is a robust ICER estimate for a small population of ~30 patients per year. MSD believes the evidence submitted in this ACD response supports a positive decision for these rrcHL patients.

The focus of this response is the inclusion of plausible OS estimates, sourced from the best available evidence for the BV and pembrolizumab cohorts in the economic model.

Note, in scenarios in which the cost of pembrolizumab 4L is included to reflect the current CDF pathway, the ICER is extremely low (~£5,000/QALY) or dominant.

On this basis, while acknowledging some uncertainty, the decision risk is low, pertaining to approximately 30 patients per year, all of whom can access pembrolizumab in later line, the clinical plausibility is high and the ICER estimates should reassure committee that a positive recommendation would be appropriate for this subgroup.

Navigating this document

We discuss how we identified and appraised the evidence on overall survival in sections 2.1 and 2.2. We discuss statistical adjustments to the OS data in section 2.3 and the detailed technical information on match adjusting is available in Appendix section 5.3.

Survival analysis on the new data and a discussion of the plausibility of different extrapolations is within section 2.5.

[1] Notation from the appraisal; the “SCT+” group are patients who have had a Stem Cell Transplant. The “SCT-“ group are those who are ineligible. 3L+ means that at least two lines of prior therapy have failed.

Amendments to the cost-utility model are discussed in section 3 including a comparison of two methods to costing subsequent treatments and a new value for PD utility. A detailed model change log, which points the user at cells that have changed since MSD's original submission is in Appendix section 5.4.

The results of the updated model, suite of scenario analyses and discussion are available in section 4.

1. Summary of changes

1.1 Inclusion of overall survival (OS) benefit

MSD's initial submission, modelled OS as equal between the pembrolizumab (pembro) and brentuximab vedotin (BV) strategies. This decision was taken because no OS data are available from the KEYNOTE-204 (KN204) trial and because our original base case analysis predicted pembro would be the dominant intervention when the two subgroups (based on prior stem cell transplant (SCT) experience) were combined (1).

It is highly likely, given the substantial PFS benefit [redacted] observed in KEYNOTE 204 (KN204) (see Appendix 5.1.7) and the testimony of clinical experts referenced by the committee in the Appraisal Consultation Document (ACD) that pembro is associated with an overall survival benefit. In light of the committee's decision not to recommend pembro in the SCT-3L+ we are submitting additional analyses, which incorporate the best available evidence on overall survival for each intervention in this population into the economic model.

The approach we have employed is a naïve comparison of the OS evidence for pembro and BV in the SCT-3L+ population with a match-adjusted comparison used a sensitivity analysis. We note that both previous appraisals for medicines in this small population have relied on single arm trials and indirect/naïve comparisons such as this (TA524 and TA540) (2, 3). Both TA524 and TA540 resulted in positive CDF recommendations based on the modelled data from these naïve comparisons forecasting substantial OS gains. It was acknowledged in these appraisals that the small patient population and relatively long overall survival time contributed to difficulty in companies being able to collect mature comparative overall survival data.

Modelling subsequent treatments

MSD's original approach to accruing subsequent treatment costs was based on net increases in occupancy of the Progressed Disease health state in the economic model. We have submitted a new approach that is based on PFS exits that we believe is more representative of what would be seen in clinical practice. After discussion with the ERG, we have included scenario analyses using both approaches.

Proposed changes to utility values

The committee recognized that the ERG's preferred assumption of post-progression utility being equal is conservative. The clinical experts highlighted that they would expect it to be higher in the pembrolizumab arm because side effects are more common in BV and can be debilitating for prolonged periods of time. We have sourced an alternate estimate for PFS utility for pembrolizumab, which is higher than the empirical data for BV but not as high as the empirical data collected in KN204. Various scenario analyses are presented.

Minor technical corrections to model

We have made some minor programming fixes to the model. The first is that the proportion of patients in different health states were not referencing the correct weekly cycle and the second was an update to the statistical analysis of Time on Treatment. Both these changes are documented in full in section 3.6 and have a very minor effect on the ICER.

1.1. A note on the risk of decision error

We feel it is important to highlight that if the committee choose to recommend pembrolizumab for the SCT-3L+ population, there is little risk of decision error regardless of the uncertainty in the magnitude of OS benefit. Throughout this appraisal, it has always been the case that a pathway of pembrolizumab followed by BV (the proposed pathway) either dominates a pathway of BV followed by pembrolizumab (the current CDF pathway) or produces an extremely low ICER, depending on the scenario selected. The reason the ICERs have not reflected this reality is we cannot include the cost of 4L pembrolizumab in the model.

The practical effect of recommending pembrolizumab 3L is not to introduce new cost into the system but simply to switch the order of pembrolizumab and BV so that patients will be able to access the better treatment sooner.

2. Modelling Overall Survival

It is highly likely, given the substantial PFS benefit observed in KN204 and the testimony of the clinical experts that the committee heard at ACM1 that pembro is associated with an overall survival benefit. Indeed, the large PFS benefit observed in KN204 may even be underestimated compared to the reality the model is trying to represent as patients who could not tolerate BV and discontinued treatment prior to progression in the trial would have been able to access immunotherapy. The BV arm of the model needs to reflect outcomes where the treatment pathway is BV>chemotherapy but the BV arm of KN204 followed the CDF pathway where the subsequent treatment of choice was pembrolizumab.

Identification of evidence

In the original submission, the company's preferred source of overall survival data for the combined 3L+ population was Gopal et al 2015 (4). The ERG's preferred source for the SCT-3L+ population was

Balzarotti et al. 2016 on the basis that it reported outcomes for cHL patients that had not received prior SCT. Neither of these studies should be considered appropriate to model OS in the SCT-3L+ population treated with BV or pembrolizumab. MSD apologies for any confusion due to including these sources in the original submission.

The study population in Balzarotti (2016) is not representative of patients who have had 2 lines of therapy without stem cell transplant (SCT-3L+ subgroup) treated with BV for several reasons, being essentially a study of 2L chemotherapy used specifically as a bridge to SCT (5). Patients from the Balzarotti study were treated after only 1 line of therapy. The population from Balzarotti were specifically selected on their suitability for consolidation with auto-SCT after multi-agent chemotherapy at second line. This is further supported on the grounds that majority of patients (approx. 90%) in the Balzarotti paper receive SCT after second-line treatment, which is much higher than would be expected for 3L no prior SCT patients. As expected, visual comparison of the survival curves with Gopal (2015) show much better OS with Balzarotti. This doesn't have face validity on the basis that the no prior SCT patients were acknowledged in committee to have a worse prognosis.

The committee and ERG highlight concerns about the applicability of Gopal 2015 to the subgroup of patients with SCT-3L+. Gopal is a study of BV specifically in patients who have failed or progressed after an auto-SCT and is unlikely to be reflective of those patients who are currently SCT ineligible. It had been used in the original submission as a surrogate for the combined 3L+ population.

MSD has explored alternative data sources that are more suitable for modelling overall survival.

To begin with, further assessment of the ten studies identified from the SLR that report outcomes on BV treatment (Table 1) was undertaken. This table is taken directly from Table 6 in the appendices of MSD's original submission.

Table 1: List of BV studies considered for inclusion

Trial ID	NCT code	Intervention 1	Intervention 2	Primary publication	Subsequent publications	Reasons for exclusion/inclusion	Included?
AETHERA	NCT01100502	Brentuximab vedotin	placebo	Moskowitz 2015a (6)	Moskowitz 2018 Gautam 2018 Nademanee 2018 Anonymous 2016 Ramsey 2016 Sureda 2015 Moskowitz 2018 Gautam 2016 Sweetenham 2016 Moskowitz 2015b Moskowitz 2015c Walewski 2015	• Post autologous stem cell transplant patients • Treatment not representative of UK clinical practice – BV used as consolidation therapy post-transplant	Excluded
Bartlett 2014	NCT00947856	Brentuximab vedotin	--	Bartlett 2014 (7)	NCT00947856	• Study population is	• Excluded

						patients retreated with BV.	
Chen 2015	NCT01393717	Brentuximab vedotin	--	Chen 2015 (8)	Herrera 2016 Anonymous 2016 NCT01393717	• Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma	• Excluded
FIL ONLUS	NCT02227433	Brentuximab vedotin	--	Stefoni 2020 (9)	Tonialini 2018	• Second-Line Therapy – treatment of elderly Hodgkin lymphoma patients at first relapse or with primary refractory disease	• Excluded
Goranova-Marinova 2019	--	Brentuximab vedotin	--	Goranova-Marinova 2019 (10)	--	• Limited information – only abstract published.	• Excluded
KEYNOTE-204	NCT02684292	Pembrolizumab	Brentuximab vedotin	Kuruvilla 2020 (1)	Merck 2020	• No OS data available.	• Excluded
NCT02939014	NCT02939014	Brentuximab vedotin	--	NCT02939014 (11)	--	• Majority of participants (67%) received BV after at least 3 prior systematic therapies and 17% after one line of therapy.	• Excluded
Ogura 2014	JapicCTI-111650	Brentuximab vedotin	--	Ogura 2014 (12)	--	• No OS data available.	• Excluded
Walewski 2018	NCT01990534	Brentuximab vedotin	--	Walewski 2018 (13)	NCT01990534		Included
Younes 2012b	NCT00848926	Brentuximab vedotin	--	Younes 2012 (14)	Chen 2016 Gopal 2015 Anonymous 2016	• Patient with prior treatment with autologous	• Excluded

						stem cell transplant. • OS data considered highly uncertain by committee at ACM1.	

As the review from MSD's original submission excluded observational studies, an additional search was conducted in PubMed using the following terms:-

((relaps*[Title/Abstract] OR refract*[Title/Abstract] OR recurrence[Title/Abstract]) AND (classical hodgkin lymphoma[Title/Abstract] OR hodgkin*[Title/Abstract]) AND (ineligib*[Title/Abstract] OR unfit[Title/Abstract] OR unsuitable[Title/Abstract])

This search identified two potentially relevant observational studies with data from UK patients: Eyre et al., 2017 and Brockelmann et al., 2017 (15, 16). A Systematic Literature Review for observational studies was included as part of the submission for KEYNOTE-087 (TA540) which was cross referenced with the results of the PubMed search to ensure no potentially relevant studies were missed (3). KEYNOTE-087 (KN087) was a single arm study of pembrolizumab in the 4L setting. It included a subgroup ("cohort"), who were ineligible for SCT. Pembro was recommended for the CDF for this subgroup as part of TA540.

We excluded the Brockelmann study from our considerations. The median age at enrollment was 70, which was far older than in KN204 and Eyre (2017), the populations most relevant to UK clinical practice. The study included a high proportion of German patients who appeared to have a greater prevalence of ASCT inhibiting comorbidities than the UK patients. The second-line chemo and radiotherapeutic options were also highly unrepresentative of the UK and may be correlated with a lower probability of receiving ASCT, which influences outcomes.

The study by Eyre et al (2017) was also highlighted in NICE's "Technical engagement questions for clinical experts" section of the Committee Papers page 527 (citation) where it was considered a reasonable source of OS data for patients not suitable for SCT (3, 16).

MSD identified the Eyre (2017) and Walewski (2018) studies as containing data most applicable to the population relevant to the subgroup of interest (SCT-3L+) (13, 16). Both studies were considered as sources for clinical effectiveness during the brentuximab vedotin (BV) technology appraisals (TA446 & TA524) (2).

- Eyre et al., 2017
    - In the submission for BV (TA524), the NICE committee concluded that this real-world UK dataset provides the most relevant evidence, but any comparisons are likely to be uncertain:
        - *"The committee also agreed that the real-world UK dataset provided more relevant clinical data to estimate the clinical effectiveness of brentuximab vedotin from a NHS perspective."*
- Walewski et al., 2018

- In the submission for BV (TA524), the appraisal committee had concerns that the findings of this study may not be generalizable to UK clinical practice
    - *"The first concern was the generalisability of the C25007 data to the UK population. A proportion of patients (18%) in the study only had 1 previous treatment, so did not mirror the marketing authorisation for brentuximab vedotin. Also, 88% of patients in C25007 came from outside the UK, and clinical experts stated that routine clinical practice would be quite different to that of the UK. The ERG highlighted that these differences were seen in the study outcomes of mean treatment cycles and relative rates of allogeneic and autologous stem cell transplant."*

The Eyre (2017) study is the most applicable because it is UK data using the intervention of interest in the population of interest. It was considered the most applicable source of OS data by the NICE committee for TA524. The only other plausible candidate is Walewski (2018), which we have included as a sensitivity analysis.

We have therefore used the OS data from Eyre (2017) as a stand-in for OS in the BV arm of the economic model.

MSD is certain that no data on the long term OS of SCT-3L+ patients treated with pembrolizumab exist. The only relevant data are for patients who are SCT-4L+, which is likely an older and sicker cohort. Two data sources are available to the company; individual patient data from KN087 cohort 2 (discussed above) and real world evidence from the Systemic Anti-Cancer Therapy (SACT) database (discussed in section 2.2.2) (17). We have used the KN087 cohort 2 data to model OS for pembrolizumab in the 3L+ setting as our base case and the SACT data as a sensitivity analysis.

2.1. Assessment of applicability

2.2.1 Patient level characteristics

The primary reasons for inclusion/exclusion of the studies as being able to provide OS data representative of the SCT-3L+ population receiving BV are detailed in Table 1.

Table 2 provides a comparison of baseline characteristics from the various included studies for BV and Table 3 provides the same for pembrolizumab.

It can be seen that the patient level characteristics on age, sex, ECOG and bulky disease are similar between Eyre (2017) and KN204. Presence of B symptoms and prior radiation treatment are somewhat different. One noteworthy difference is that many more patients eventually had an SCT in Eyre (2017) than the BV arm of KN204. It may be that there are unmeasured differences in comorbidities that contribute to this difference in outcome. This suggests that Eyre (2017) may overestimate OS compared with what would be observed on the BV arm of KN204. The Eyre (2017) study was set entirely in the UK NHS.

Walewski had a somewhat older population than the other studies, fewer ECOG 0 patients, more refractory patients, more patients who had had prior radiation therapy and a similar proportion of patient had B symptoms as in the BV arm of KN204. The most noteworthy difference is that a significant proportion of patients had only had one prior line of therapy, which suggests they could be expected to have a better prognosis. The proportion eventually achieving SCT was lower than in Eyre (2017) but higher than KN204. This was a multi-national study with no UK patients.

To our knowledge there are no additional published data on the baseline characteristics of SCT-3L+ rrcHL patients who are candidates for BV in the UK.

Table 2: Relevant patients characteristics for KEYNOTE-204, Walewski et al. 2018 and Eyre et al. 2017

Variable	Variable as measured in studies		KEYNOTE 204 SCT-3L+; BV arm (n=[redacted])	BV; Walewski et al., 2017 (n=60)	BV; Eyre et al., 2017 (n=99)
Age	Age, n/N (%)	≥ 65 years	[redacted]	5 (8)	--
		< 65 years	[redacted]	55 (92)	--
		≥ 60 years	[redacted]	--	--
		< 60 years	[redacted]	--	--
	Age, median (range)		[redacted]	40 (20-76)	32 (13-70)
Sex	Male, n (%)	Yes	[redacted]	36 (60)	45/99 (45)
Disease status	Disease status, n/N (%)	Refractory	[redacted]	44 (75)	--
		Relapsed	[redacted]	15 (25)	--
				--	
Number of prior lines of therapy	Number of prior lines, n/N (%)	2	[redacted]	--	70/99 (71)
		3	[redacted]	--	24/99 (24)
		4+	[redacted]	--	5/99 (5)
	Number of prior lines, median (range)		[redacted]	2 (1-7)	2 (2-4)
Prior auto-SCT	Prior auto-SCT, n (%)	Yes	[redacted]	0 (0)	0 (0)
Prior treatment	Radiation therapy, n (%)	Yes	[redacted]	25 (42)	(7-14)
Presence of B symptoms	Presence of B symptoms, n (%)	Yes	[redacted]	22 (37)	33/88 (38)
Performance status	ECOG, n/N (%)	0	[redacted]	27 (45)	45/99 (52)
		1	[redacted]	33 (55)	36/99 (42)
Presence of bulky disease	Bulky disease, n (%)	Bulky disease	[redacted]	--	20/95 (21)
Subsequent SCT			[redacted]	47%	61%

Table 3 compares the patient level characteristics from KN087 and KN204. The most obvious difference is that KN087 takes place in the setting where third line treatment had already been unsuccessful. *A priori,* this population represents a sicker cohort with more advanced disease. It can be seen that the patients are older on average in KN087 and that most other characteristics are well balanced between the cohort with the exception of prior radiotherapy and bulky disease where the KN087 cohort had lower percentages.

Table 3: Relevant patients characteristics for KEYNOTE-204 SCT-3L+ subgroup and KEYNOTE-87 cohort 2 (SCT ineligible)

Variable	Variable as measured in studies		KEYNOTE-87 cohort 2 (n=81)	KEYNOTE-204; SCT-3L+ pembrolizumab arm (n=[redacted])
Age	Age, n/N (%)	≥ 65 years	15 (18.5)	[redacted]
		< 65 years	66 (81.5)	[redacted]
		≥ 60 years		
		< 60 years		
	Age, median (range)		40 (20-76)	[redacted]
Sex	Male, n (%)	Yes	43 (53.1)	[redacted]
Disease status	Disease status, n/N (%)	Refractory	--	[redacted]
		Relapsed < 12 months	--	[redacted]
		Relapsed ≥ 12 months	--	[redacted]
Number of prior lines of therapy	Number of prior lines, n/N (%)	2	<3: 3 (3.7)	[redacted]
		3	≥3: 78 (96.3)	[redacted]
		4		[redacted]
	Number of prior lines, median (range)		4 (1-11)	
Prior auto-SCT	Prior auto-SCT, n (%)	Yes	0 (0)	[redacted]
Prior treatment	Radiation therapy, n (%)	Yes	21 (25.9)	[redacted]
Presence of B symptoms	Presence of B symptoms, n (%)	Yes	26 (32.1)	[redacted]
Performance status	ECOG, n/N (%)	0	44 (54.3)	[redacted]
		1	37 (45.7)	[redacted]
Presence of bulky disease	Bulky disease, n (%)	Bulky disease	11 (13.6)[e]	[redacted]
Subsequent SCT			[redacted]	[redacted]

2.2.2 SACT Data from TA540

The company has received the 2-year SACT report produced by Public Health England as part of the ongoing Cancer Drugs Fund agreement for TA540 (KN087 cohort 2) (17). Overall Survival has been collected for 105 patients in this report but there are limited additional data on patient variables (see Table 4) and no PFS data.

The overall survival data (Figure 1) from this report is relatively poor compared to those observed in KN087. We believe these data are likely to underestimate the OS that would be seen in the pembrolizumab arm of KN204. Firstly, the SACT patient cohort is much older, with a median age of 50 vs. 34.5 in KN204. Secondly, they have poorer ECOG performance status and thirdly, these patients are all in the fourth line plus setting and may have been for some; the average time from third line treatment failure is not known.

We consider the data from KN087 represents a better surrogate estimate for the OS that would be seen in the pembrolizumab arm of KN204 but we have included the SACT data in sensitivity analysis.

*******Figure 1: KM data from TA540 SACT Report (N=105)**

*******Table 4: TA540 SACT data patient characteristics**

[redacted] [redacted] [redacted]

[redacted] [redacted] [redacted]

*****Table 5: Number at risk table from OS analysis in SACT report for TA540

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.2.3 Visual comparison of PFS curves from pembrolizumab and BV studies

The following graphs were produced using the real individual patient level data (IPD) from KN204 and KN087 and digitized IPD from Eyre (2017). They are simple Kaplan-Meier outputs from the *ggsurvplot* command in R (18). Digitised KM curves and numbers at risk tables were converted into synthetic IPD using a validated algorithm commonly used in NICE HTAs (19). We present the PFS curves for the BV arms then the PFS curves for the pembro arms.

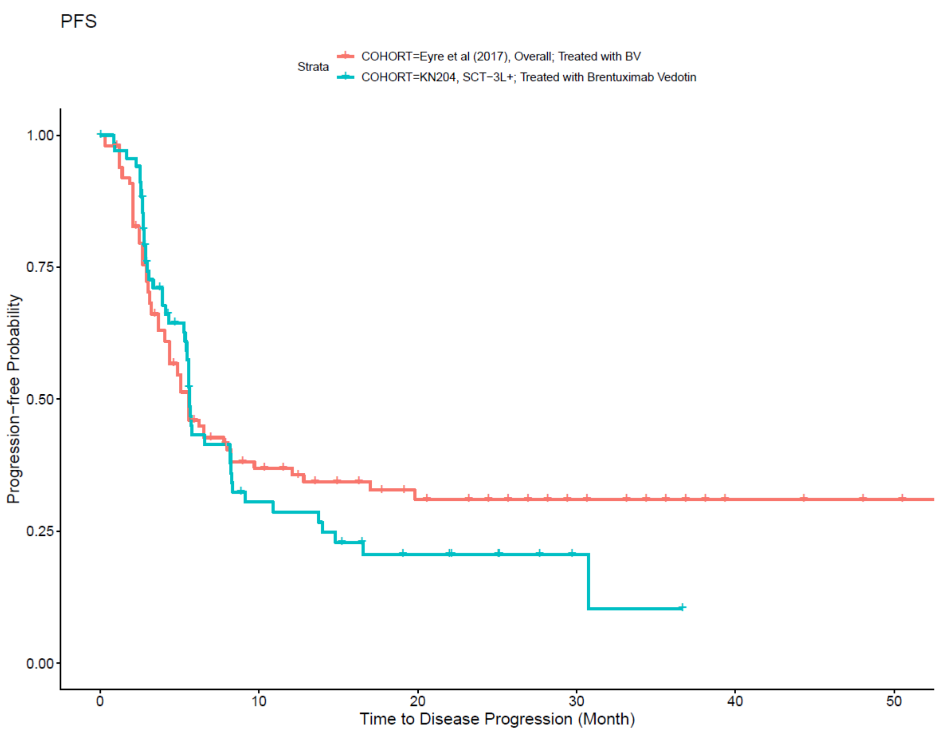


Figure 2: Comparison of PFS curves between BV study arms

The data in Figure 2 show that PFS time is similar for around 70% of the patients in both Eyre (2017) and KN204. After around 10 months it appears that the patients in Eyre had better and more durable PFS

than patients in KN204. This is a possible indication that OS data from Eyre (2017) may overestimate what would have been seen in KN204.

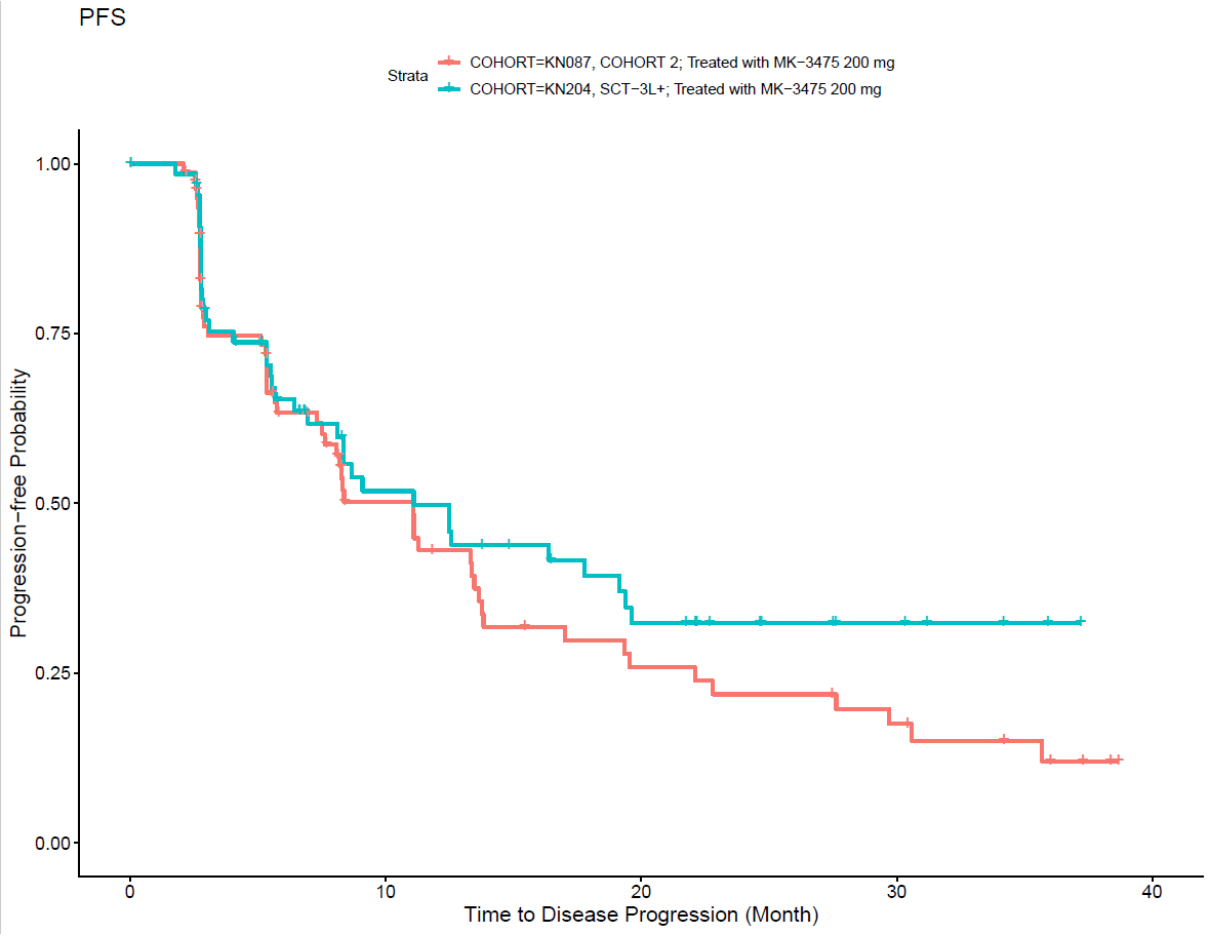


Figure 3: Comparison of PFS for the pembro arms of KN087 cohort 2 and KN204

Figure 3 shows that PFS was fairly similar for about 60% of KN087 cohort 2 patients receiving pembrolizumab and KN204 patients receiving pembrolizumab. Thereafter their curves diverge and better PFS is seen in KN204, which is what we might expect as the patient cohort is younger and less progressed in their disease. These curves give an indication that the OS data observed in KN087 might underestimate what would be seen in KN204.

Overall the PFS data was fairly similar between the surrogate trials and KN204. There is some indication that the difference in OS that would be seen in KN204 might be underestimated rather than overestimated by the naïve comparison of KN087 cohort 2 and Eyre (2017).

2.3 Consideration of use of statistical techniques to improve upon naïve comparison

2.3.1 Regression analysis

Individual patient data from KN204 (PFS only) and KN087 (both PFS and OS) for pembrolizumab are available to the company. We considered whether it would be possible to explore the relationship between PFS and OS in KN087 and, if we were able to define a predictive equation, use this to predict OS for the patients in KN204. Such a method was not considered feasible, however; the sample size for cohort 2 in KN087 is only 81 patients, only [redacted] patients had had an OS event at the 3 year data cut, several more are censored and we do not have any individual patient OS data on BV to plausibly estimate a similar equation for the comparator arm. Overall, we did not feel that any attempts at using the data we have in KN204 to predict OS would be robust enough to inform decision-making.

2.3.2 Match adjustments

2.3.2.1 Match adjusting is not possible for any BV data

Individual patient data from KN204 (PFS only) and KN087 (both PFS and OS) for pembrolizumab are available to the company. We do not have any individual patient OS data for BV so weighting OS via any sort of matching technique is not possible for the BV arm.

2.3.2.2 Match adjusting was not possible for CDF data on pembrolizumab but would likely have increased OS were it possible

We do not have patient level data available from the SACT report on 4L pembrolizumab so it is not possible to use matching techniques to adjust this data. It can be seen from the prognostic variables that are available that the SACT population is much older and less fit than the population in theKN204. It is therefore reasonable to expect that younger and fitter patients would have had their OS outcomes upweighted and older and sicker patients their OS outcomes down-weighted, which would likely have led to better OS. It is worth noting that it would have been very difficult to match based on a key predictive variable; line of therapy, since the KN204 population were 3L+ and the SACT population were all 4L+.

We have provided options in the model to arbitrarily increase OS if the CDF data are selected as the source of evidence for pembrolizumab 3L+ to examine how changing the curve affects the ICER.

2.3.2.3 Match adjusting has been undertaken for KN087

We considered whether we would be able to use the patient level variables in KN204 to re-weight the OS data from KN087. Such an analysis is technically feasible and we were asked to provide this data by the ERG.

Based on clinical advice and key stratification factors from KN204, we selected variables of interest that were expected to be prognostic of overall survival. We then re-weighted the patient level data in KN087 to match that in KN204 and re-analysed overall survival.

Table 6: Table of prognostic factors ranked by importance

Variable	Rank-importance as prognostic factor	Variable as measured in studies		Availability in KN204		Availability in KN204 – ASCT-ineligible 2L cohort	
				Pembro	BV	Pembro	BV
Disease status	1	Disease status, n/N(%)	Refractory	[redacted]	[redacted]	[redacted]	[redacted]
			Relapsed < 12 months	[redacted]	[redacted]	[redacted]	[redacted]
			Relapsed >= 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Age	2	Age, n/N(%)	>= 65 years	[redacted]	[redacted]	[redacted]	[redacted]
			< 65 years	[redacted]	[redacted]	[redacted]	[redacted]
		Age, median (range)		[redacted]	[redacted]	[redacted]	[redacted]
Performance status	3	ECOG PS, n/N (%)	0	[redacted]	[redacted]	[redacted]	[redacted]
			1	[redacted]	[redacted]	[redacted]	[redacted]
Presence of bulky disease	4	Bulky disease, n(%)	Bulky disease	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment	5	Radiation therapy, n (%)	Prior RT	[redacted]	[redacted]	[redacted]	[redacted]
Sex	6	Males, n (%)	Male	[redacted]	[redacted]	[redacted]	[redacted]
Presence of B symptoms	7	B symptoms, n(%)	B symptoms	[redacted]	[redacted]	[redacted]	[redacted]

We considered two separate scenarios; one which adjusted for all the important prognostic factors (scenario 1) we were able to adjust for and another than adjusted for only a subset (Scenario 2; omitting sex and B symptoms, see Appendix 5.3 for details). After examining the results we selected Scenario 1 to bring forward into the economic model because it adjusted for the most variables, appeared to contain information that led to changes in the OS curve and appeared to be the most conservative and therefore the most likely to be of interest to decision-makers.

Scenario 1 results in a small drop in the KM curve relative to the unadjusted KM data. We have re-fitted parametric models to this new data for use in sensitivity analysis in the economic model. The generalized gamma function did not converge properly so was omitted from the economic model.

Looking at the differences between Scenarios 1 and 2 it appears that the small drop in OS is related to the proportion of patients who have received prior radiation in each of the trials.

We would caution that there were only [redacted] OS events in KN087 and that, post-matching, the Effective Sample Size is small. The OS curve could have been influenced by over-weighting of patients who died particularly early in the trial period. The estimates from this analysis should be treated with caution. A full technical report is available in Appendix section 5.3.

Table 7: Table of weighted patient characteristics before and after matching in "Scenario 1" (KN087 and KN204)

[redacted]	[redacted]	[redacted]	
		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

Figure 4: OS KM and match-adjusted KM for KN087 based on "Scenario 1"

2.4 Data extraction

Individual patient data were available for studies of pembrolizumab (KN087 and KN204) so OS and PFS curves were fitted directly to these data.

The only BV individual patient data we had was from KN204 and did not include OS. Synthetic individual patient data were extracted from Eyre (2017), Walewski (2018) and the SACT report using a standard IPD extraction algorithm and digitization software (19, 20).

2.5 Survival analysis

Full details on the survival analysis including curve extrapolations and model fit statistics for all the identified data sources can be found in Appendix section 5.1. All models are one-piece fits; piecewise models were not considered appropriate due to the immaturity of the OS data. Median OS was only just reached in one of the studies under consideration (Eyre 2017).

2.5.1 MSD's base case choice of curves

As noted in section 2.1, our preferred sources of OS data are Eyre (2017) for BV and KN087 for pembrolizumab.

Below are graphical projections and model fit statistics for the two studies' datasets. Additional survival analysis data are available in Appendix section 5.1.

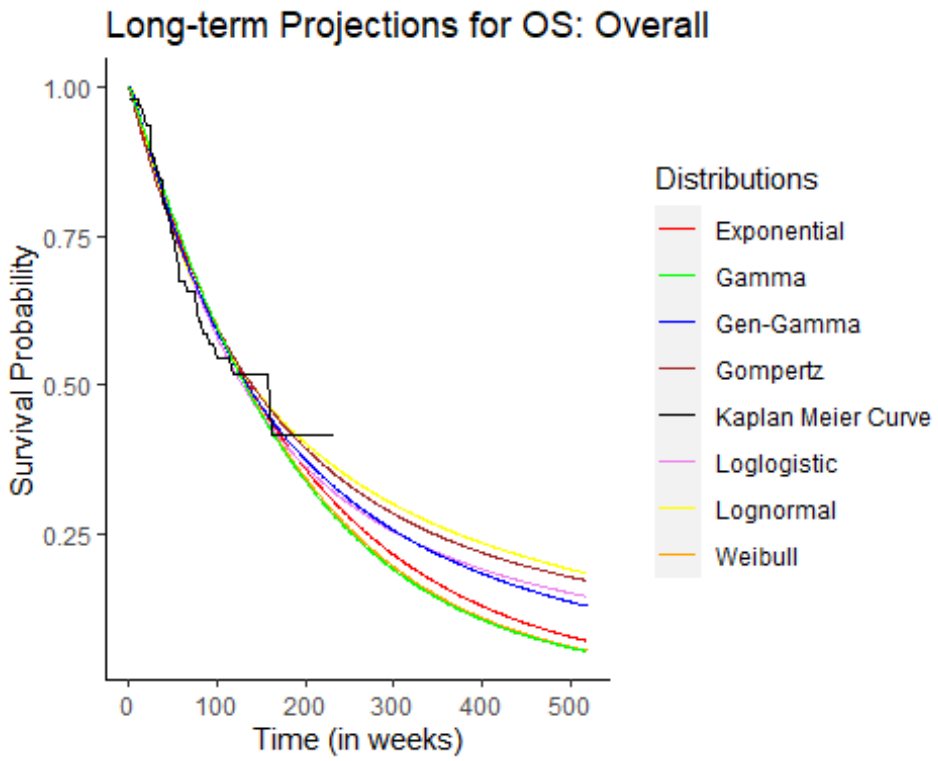


Figure 5: Long term OS projections for BV in Eyre (2017)

Table 8: AIC/BIC statistics for BV OS in Eyre (2017)

Distributions	AIC	BIC	Avg AIC BIC
Exponential	466.1	468.7	467.4
Weibull	468.0	473.1	470.5
LogNormal	467.0	472.2	469.6
Loglogistic	465.8	470.9	468.3
Gompertz	467.7	472.9	470.3
Generalized Gamma	468.4	476.2	472.3
Gamma	467.8	473.0	470.4

Based on a combination of model fit statistics and clinical plausibility the log-logistic curve has been chosen by MSD in the base case. Based on clinical advice, we have discounted any curve that results in extremely low OS at 20 years e.g. Exponential (please see the section below for further discussion). Of the clinically plausible curves, the log-logistic model has the lowest AIC/BIC.

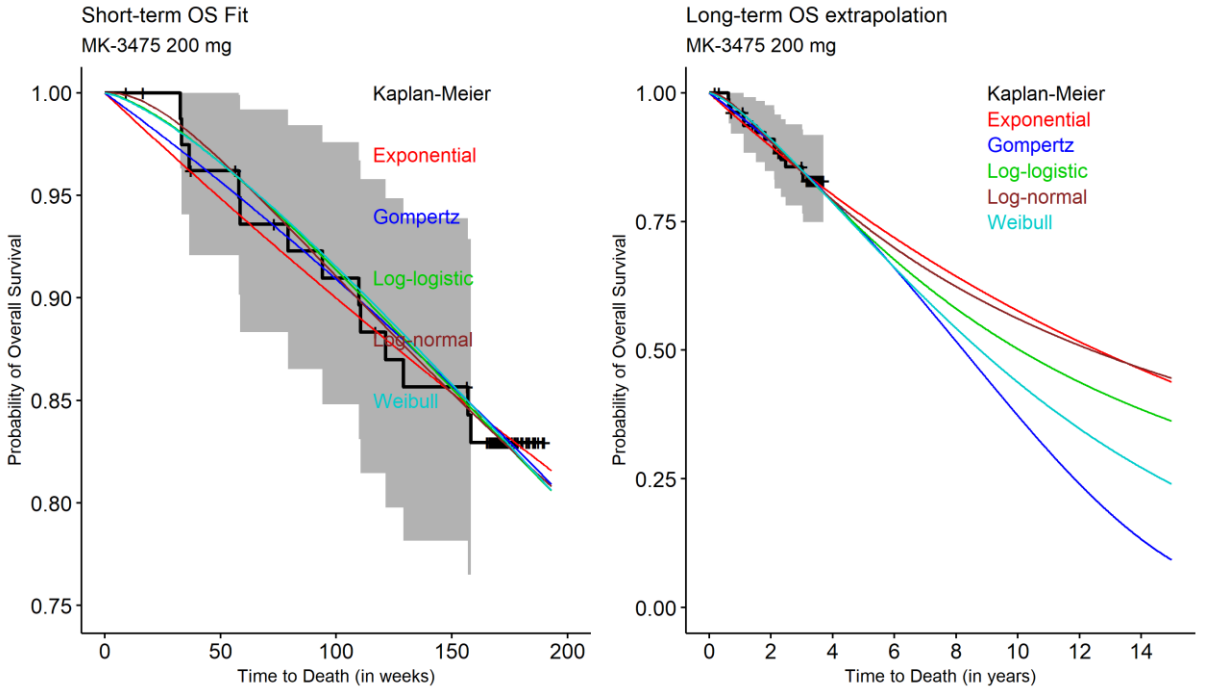


Figure 6: Long term OS extrapolations for pembrolizumab in KN087

Table 9: AIC/BIC statistics for KN087 OS

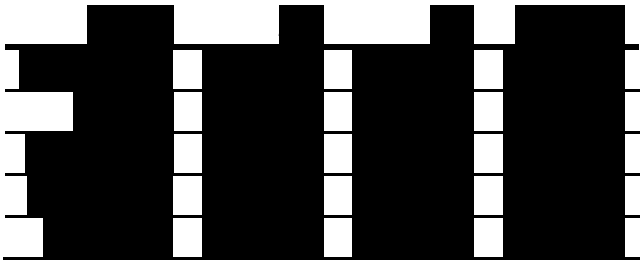


Figure 6 shows the parametric extrapolations from the OS data in KN087.

The generalized gamma curve failed to converge so no estimates are available for this model. NICE TSD14 advises selecting the same type of parametric model between the arms. Because the log-logistic curve appeared to be most plausible for the comparator study, which has much more data available, we also selected the log-logistic model for KN087. We note that there is little difference in model fit statistics between the different models but that the gompertz model appears to produce implausibly low OS at 20 years.

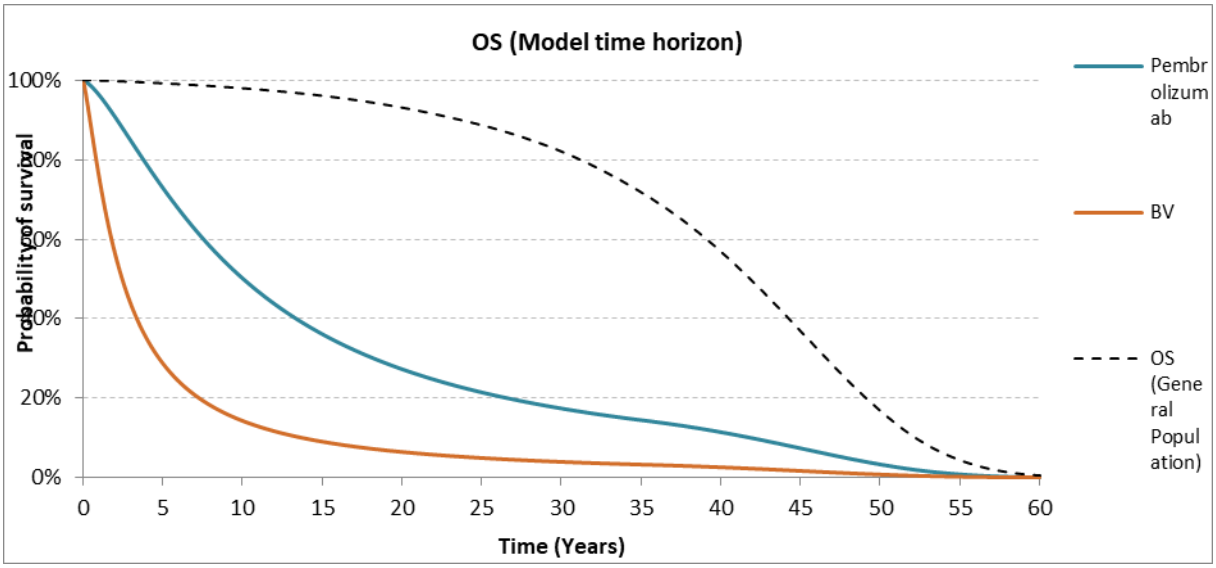


Figure 7: Comparison of OS; KN-087 and Eyre - preferred extrapolations

As a sensitivity analysis, we also present data comparing OS in Eyre (2017) to OS for the older, less fit patients receiving pembrolizumab via the CDF (data from the SACT report). Again, the log-logistic model is chosen based on the same criteria.

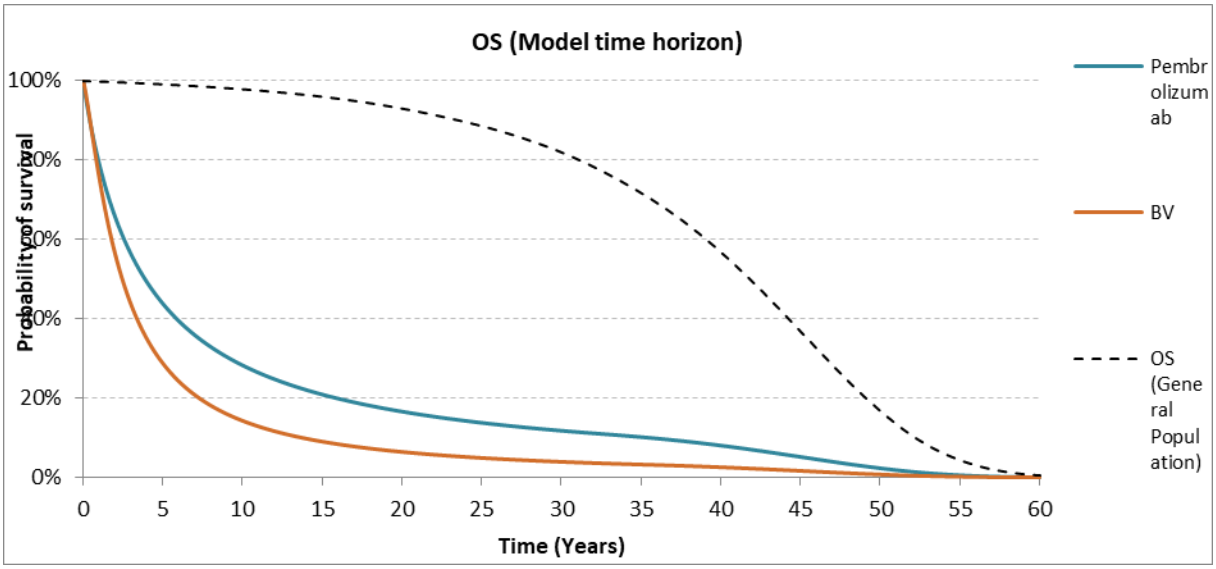


Figure 8: Comparison of OS; SACT data and Eyre preferred extrapolations

MSD has received advice that the log-logistic models for BV and pembrolizumab appear clinically plausible although it is difficult to select between the various non-exponential models for reasons discussed in section 2.5.3 below. Please see the sections below that detail other ways in which the

company has considered whether it is possible to validate/select between different parametric models. We have provided a sensitivity analysis where the modeler is able to set the OS curve for pembrolizumab to equal a weighted average between the OS curves derived from the KN087 trial and the CDF data, assigning an arbitrary weight to each of these sources.

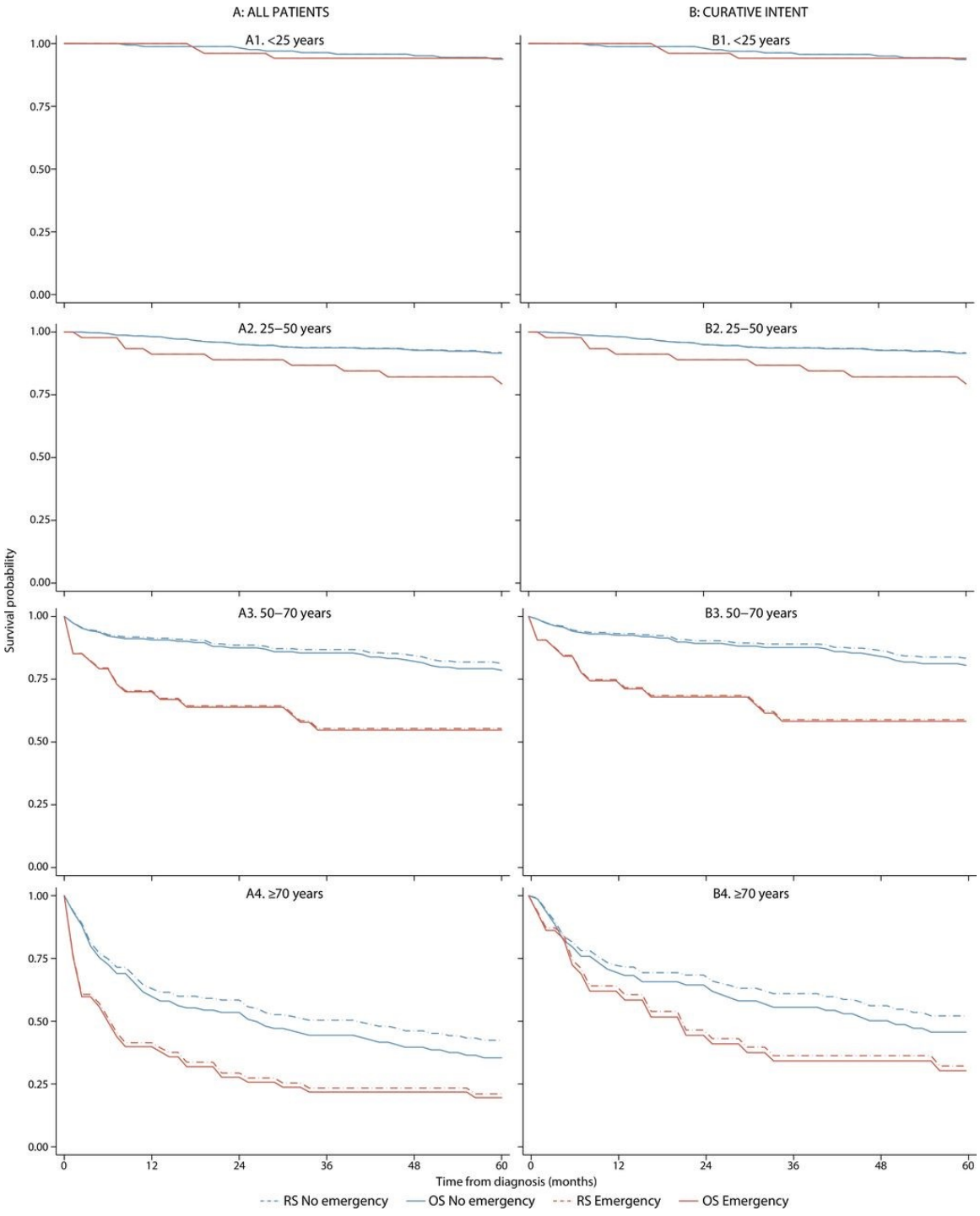
2.5.2 The exponential model is implausible, other models that produce ~zero OS within 20 years are implausible

The exponential parametric survival model is characterized by having a monotonic hazard of death across time i.e. the patient cohort who have survived for 10 years has exactly the same instantaneous (cycle-specific in the model) hazard of death as the patient cohort who have survived for one year after treatment initiation. The result of this is that the exponential models predict that ~99% of patients will be dead at ~17 years when using the Eyre (2017) data to represent BV OS and ~20 years when using the CDF 4L data to represent pembro 3L OS. MSD has received clinical advice that this prediction is highly implausible and that many patients would be expected to still be alive 20 years after a diagnosis of relapsed cHL, even before the era of BV and pembrolizumab.

It is important to note that patients in the SCT-3L+ cohort of the KN204 trial had a median age of 33 in the BV arm or 34.5 in the pembrolizumab arm. Patients in the Eyre (2017) study had a median age of 32. cHL is a disease with a long natural history and the potential for a significant proportion of patients to receive curative SCT interventions, even if beginning in a state of ineligibility for SCT. The data sources included in this review report between 25%-60% of patients received an SCT following treatment. While there are no data on the proportion of SCTs in each dataset that led to long term remission and no external data on the long-term success of SCT in this population, particularly following pembrolizumab or BV, it is certain that some level of long-term remission would be expected in each model arm.

MSD considers that if some patients would achieve long term remission and some wouldn't, a model that assumes a constant hazard of death across time is epidemiologically implausible. Another consideration is the very wide age range for patients included in the trials. 50% of patients were in their early 30s or younger but the range in Eyre was 13-70 years. It is reasonable to expect older patients to die sooner and for the average cohort hazard to drop over time. For a patient cohort that begins modelled time in their early 30s, some of which would achieve long-term remission, we conclude that it is implausible for OS to be only 1% by their early 50s. For reference, OS in the general population would be ~97% at this timepoint in the model. The exponential model should not therefore be considered a realistic base case for decision making, nor should any other extrapolation that produces similarly low OS at 20 years.

The following is an OS graph taken from an epidemiological study of UK patients diagnosed with cHL between 2004-2015 and followed until 2018 (21). It is clear that there is a relationship between survival and age, that OS is high at 5 years and that hazards are higher in the short than medium and long term for the older age groups. The purpose of including this graph is not to validate the curves for the subpopulation under consideration but to further illustrate the general pattern of OS in cHL.



An excerpt from a Canadian epidemiological study (Hapgood et al 2016) is also provided below, which clearly shows the lengthy survival and flattening of hazard and cumulative risk over time for patients with cHL (22). This provided not to validate specific survival predictions for the SCT-3L+ cohort but to further illustrate the natural history of the disease, which is informative when selection which survival extrapolations will be plausible or not.

Table 1. Summary of Characteristics of 1,402 Patients With cHL at Diagnosis and Causes of Death

Characteristic	No. of Patients (%)
Male sex	749 (53)
Age, years	
Median	32
Range	16-70
16-24	360 (26)
25-44	684 (49)
45-60	246 (17)
61-70	112 (8)
Treatment approach	
Limited	453 (32)
Advanced	949 (68)
Radiotherapy treatment era	
EF, May 1989 to December 1996	370 (26)
IF, January 1997 to January 2001	238 (17)
IN, February 2001 to December 2014	794 (57)
Radiotherapy received*	
EF	125 (9)
IF	390 (28)
IN	57 (4)
None	830 (59)
Chemotherapy for primary therapy	
VECABOP	72 (5)
MOPP/ABVD or CVPP/ABO	232 (16)
ABVD	1,084 (78)
Miscellaneous	15 (1)
Limited-stage treatment	
Combined modality	271 (60)
Chemotherapy only	182 (40)
Stage	
I	132 (9)
II	729 (52)
III	319 (23)
IV	222 (16)
Bulky disease ≥ 10cm†	387 (29)
B symptoms	617 (44)
Performance status‡	
0-1	1,146 (83)
≥ 2	231 (17)
IPS§	
Low, 0-3	719 (84)
High, ≥ 4	141 (16)
Histology	
Nodular sclerosis	1,074 (76)
Mixed cellularity	139 (10)
Lymphocyte rich	39 (3)
Lymphocyte deplete	12 (< 1)
cHL NOS	137 (10)
Cause of death (n = 205)	
Hodgkin lymphoma	86 (42)
Acute treatment toxicity	23 (11)
Second cancer	33 (16)
Cardiac	15 (7)
Other	32 (16)
Unknown	16 (8)

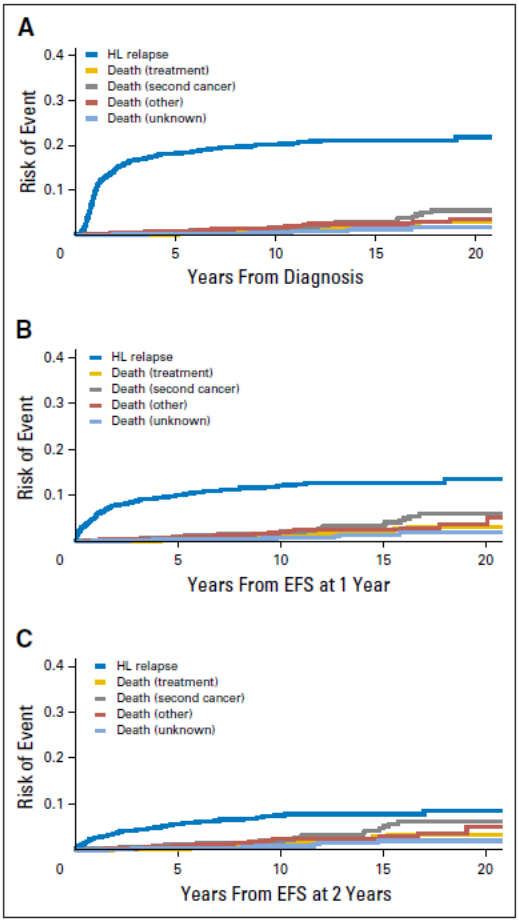


Fig 1. The risk of relapse compared with the risk of death from all causes for all patients with classical Hodgkin lymphoma (HL) at (A) diagnosis (n = 1,402), (B) event-free survival (EFS) at 1 year (n = 1,257), and (C) EFS at 2 years (n = 1,156).

11.7%; Fig 1B); event free at 2 years, 5.6% (95% CI, 4.3% to 7.1%; Fig 1C); event free at 3 years, 3.5% (95% CI, 2.4% to 4.9%); and event free at 5 years, 2.5% (95% CI, 1.5% to 3.9%; Table 2). The

2.5.3 Validation/selection of the long-term survival extrapolations by data or clinical experience is not possible

MSD discussed the possibility of validating long term OS extrapolations in this patient group with the ERG but have concluded that detailed validation based on external observational data is not possible and detailed validation by clinical experience/expectation, beyond identifying a range of curves that are plausible, would be difficult.

The company is certain that no longer-term data on pembrolizumab in the SCT- rrcHL population exist, other than those that have been made available for this report. There is limited clinical experience using pembrolizumab in this population at this point in time. NICE only published TA540 in 2018 and, as can be seen from the relevant CDF data, no information exists on the tail of the OS curve. Given the long

natural history of the disease, broad age range in trials and possibility for patients to become eligible for curative SCT, clinicians cannot be realistically expected to validate the specific survival percentages at different years of the projections with confidence.

Given the time available, we were unable to conduct an epidemiological systematic literature review to attempt to validate the long term parametric projections of overall survival following BV. We strongly suspect, however, that such an exercise would not have yielded helpful results and note that our targeted literature review and a review of the SLR for TA540, which included observational studies identified no additional papers for inclusion. It is unlikely that longer term data than those that have been used to fit the OS curves for the model (principally Eyre 2017), that are specific to the SCT-3L+ population receiving BV would be available. NICE only published the original TA446, which recommended BV for use on the CDF in 2017 so it is unlikely that 10 and 20 year follow up data exist on BV, particularly in the understudied SCT-3L+ subpopulation. MSD understands that BV has been available on compassionate grounds in the UK prior to the TA and therefore there may be a maximum of 10 years of relevant clinical experience.

2.5.4 Validation/selection of the long-term survival extrapolations by linked-evidence modelling based on SCT or other events is not possible

NICE TSD14 suggests that companies can seek to validate the long term extrapolations from survival analysis models using linked evidence model structures; for example by combining short and long term probabilities of events and health state transitions occurring in a Markov model framework. Such an approach is, of course, theoretically possible but demands the sourcing of additional parameters that are highly unlikely to exist in this case. In particular, long term survival probabilities would still be needed but would need to be even more granular if relating to more criteria than just treatment arm and SCT-3L+ criteria. Were it possible to use such an approach, key events of interest could include level of response to initial treatment, probability of auto-SCT, probability of allo-SCT, probability of success of SCT by treatment arm, progression and second progression. Time dependent transition probabilities that reflect the natural history of the disease and relate to health states reflecting (even simple) combinations of these probabilities would be extremely difficult to estimate with any confidence.

It is not possible to use the KN204 trial data to estimate event-conditional survival probabilities to populate, for example, a mixture-cure model. As noted in MSD's original submission, the KN204 study protocol did not permit the trialists to use BV or pembrolizumab as a bridge to SCT. SCT was therefore largely confined to use after completion of a full course of treatment if appropriate. While the proportions were slightly higher in the pembrolizumab arm [redacted] these data cannot be taken as indicative of clinical practice in the UK. Firstly, in KN204 the estimated mean time to SCT in the pembrolizumab arm was [redacted], whereas the CDF data show that [redacted] of 4L patients received SCT and the median time to SCT was just [redacted] which is a clear indication that it was being used as a bridge to SCT in some patients in the UK. A full course of pembrolizumab is over 2 years for this population. Secondly and more critically, these data cannot be used to infer that the probability of SCT is similar between the arms of the economic model because the 2nd line treatment of choice in the BV arm of KN204 was pembrolizumab and many SCTs took place after 2nd line treatment. A full course of BV is only

one year, most patients progressed before this and became eligible for 2nd line pembrolizumab in KN204, which may then have been used as a bridge to SCT. Because of the CDF rule that precludes us from including pembrolizumab 4L in the BV arm, these probabilities are unlikely to reflect the reality the model is trying to represent (that there is no access to pembrolizumab after BV).

As a matter of theory, we could have attempted to re-estimate the differential probability of SCT by adjusting the data in the trial. Such an approach would have produced uncertain, potentially biased estimates that would still have needed to be coupled to unavailable long term transition probabilities.

SCT probabilities cannot be reliably taken from the other data sources either. This is because the type of comorbidities that make patients ineligible for SCT, and therefore the relative ability of the treatments to modify a patient's probability of becoming eligible are unknown. On this basis there is no reason to change the committee's conclusions that the current model approach is sufficient for decision making. We do not believe any other model structure would be more suitable given the nature of the data that is available.

MSD concludes that the data to reliably estimate 10-20+ year survival probabilities in this population is unlikely to exist and the choice of OS model should instead be selected based on model fit statistics and what is known about the likely shape of such a survival curve i.e. that the cohort level OS hazards are lower in the medium and long term than they are in the short term and that some patients in each arm will receive a curative intervention leading to long term remission. MSD has received clinical advice that our base case log-logistic extrapolations produce long term OS curves that appear plausible.

3. Amendments to Cost-Utility Model

3.1 Overall survival curves

The various overall survival curves discussed in the survival analysis have been added to the economic model, along with the functionality for the user to select independent curves for each of the model arms. Locations of data and formulae are available in the Change Log, which has been supplied to NICE along with the updated economic model.

3.2 Subsequent treatments costs

When a patient accrues a subsequent treatment cost in the model, this is estimated from UK unit costs and either the mean number of cycles among patients who received that subsequent treatment in KN204 or, where chemotherapy regimens are UK specific, this is taken from average kilogram weight-based dosing and mean cycles are taken from similar regimens in KN204.

It is important to note that these mean durations only apply to patients who receive treatment and consideration of patients who do not receive treatment is estimated by separate weights, which can be set to 0% if the model user wishes to conduct a sensitivity analysis where every progressing patient receives a subsequent treatment.

MSD considers that there are three types of patients that must be accounted for, either implicitly or explicitly, when estimating subsequent treatment costs; patients who die in the PFS state and do not receive subsequent treatment, patients who progress and receive subsequent treatment and patients who progress and do not receive subsequent treatment.

3.2.1 Subsequent treatment accrual – there are two approaches

The model includes two approaches to accruing subsequent treatments. An original approach based on change in the PD health state and an updated approach based on exits from the PFS health state. Partitioned survival analyses include no explicit transition probabilities so costs that would normally be assigned on transition must be estimated via the changes in the health state membership over time. The ERG has indicated to MSD that they would like to see analyses based on both approaches.

3.2.2 MSD's original approach to subsequent treatments (Approach 1)

The economic model in our original submission for this topic accrued subsequent treatment costs cycle by cycle based on the net change in the Progressed Disease health state, if this net change was positive. This had the disadvantage that at a certain point later on in the model, the net change ceased to be positive and there would be some underestimation of subsequent treatment costs. This approach does have the advantage that it already implicitly accounts for patients who die in the PFS health state so this does not need to be estimated separately. Below is a table of weights that can be used with this approach. All weights are derived from the patient numbers in the table. The probabilities are derived by dividing the number of patients receiving subsequent treatment by the number of PFS events that are not deaths.

Table 10: Subsequent treatment weights for use with Approach 1 (Source: KN204)

	KEYNOTE-204 SCT-3L+ cohort	**Pembrolizumab**	**BV**
	Total Patients	[redacted]	[redacted]
	PFS events	[redacted]	[redacted]
	PFS event is a death	[redacted]	[redacted]
	Patients that received subsequent treatment	[redacted]	[redacted]
ERG's preferred weight	Probability receive subs trt in the PD state	[redacted]	[redacted]
MSD base case	Probability receive subs trt in the PD state	[redacted]	[redacted]
MSD Scenario Analysis 1	Probability receive subs trt in the PD state	[redacted]	[redacted]
MSD Scenario Analysis 2	Probability receive subs trt in the PD state	[redacted]	[redacted]

3.3.3 MSD's updated approach to subsequent treatments (Approach 2)

We have updated the model with a second approach that accrues subsequent treatment costs based on net exits from the Progression Free health state. This has the disadvantage that some of these exits will

be due to death within the Progression Free state, a parameter which must be estimated separately. MSD believes that some patients who exit to Progressed Disease will not receive subsequent systemic therapy because they are either not fit enough or decline it. Table 11 below is similar to Table 10 above. The only difference is that an additional weight has been included to take account of the patients who die in the PFS state. This weight is not needed with Approach 1 as these patients are accounted for implicitly. All weights in the table are derived from the patient data in the table. For example, MSD's preferred weight is based on the probability that a PFS event is not a death (i.e. is a progression) multiplied by the probability of a progressed patient receiving treatment.

Table 11: Subsequent treatment weights for use with Approach 2 (Source: KN204)

	KEYNOTE-204 SCT-3L+ cohort	[redacted]	[redacted]
	Total Patients	[redacted]	[redacted]
	PFS events	[redacted]	[redacted]
	PFS event is a death	[redacted]	[redacted]
	Patients that received subsequent treatment	[redacted]	[redacted]
ERG's preferred weight	= PFS events that are Progressions	[redacted]	[redacted]
	Probability subsequent treatment if progressed	[redacted]	[redacted]
MSD base case	Probability of receiving subs trt on a PFS event	[redacted]	[redacted]
MSD Scenario Analysis 1	Probability of receiving subs trt on a PFS event	[redacted]	[redacted]
MSD Scenario Analysis 2	Probability of receiving subs trt on a PFS event	[redacted]	[redacted]

MSD understands that the ERG's preference is for the model to accrue subsequent treatment costs to 100% of patients whose PFS event is a progression. This approach ignores any probability for patients not to be fit enough or to decline subsequent treatment upon progression. It also ignores the observed data from the trial in which [redacted] of alive-and-progressed patients in the pembrolizumab arm and [redacted] of alive-and-progressed patients in the BV arm did not receive subsequent systemic anti-cancer therapy.

MSD has included a base case where this probability is set equal to the observed data from the trial and two scenario analyses where it is set equal between the arms anchored to either the observed probability in the BV arm or the pembrolizumab arm.

3.3.4 Subsequent treatment unit costs

In line with the committee's preferences in the ACD, we have costed multi-agent chemotherapy rather than bendamustine as the subsequent treatment after BV.

Based on the distribution of chemotherapy from the Eyre et al (2017), the proportion of patient treated where redistributed after clinical elicitation to reflect treatment pattern after progressing with BV (see

Table 12). The weighted average cost is of multi-agent chemotherapy is used for the cost of treatment post progression

Table 12. Proportion of multi-agent chemotherapy used in the post-progression population

Second Line Therapy	Redistributed proportion treated
ESHAP	24.10%
DHAP	14.80%
IGEV	6.90%
ICE	6.20%
IVE	4.00%
GDP	40.00%
ChlVPP-based	4.00%
RT	-
Other	-
G-CSF	100%

Table 13: Mean cycles for multi-agent chemo regimens

Multi-agent chemo regimen	Mean cycles	Source
ESHAP	[redacted]	KN204
DHAP	[redacted]	KN204
IGEV	[redacted]	Assumed similar to Gemcitabine + ifosfamide + vinorelbine tartrate in KN204
ICE	[redacted]	Assumed similar to Carboplatin + etoposide + ifosfamide in KN204
IVE	[redacted]	Assumed similar to Epirubicin hydrochloride + etoposide + ifosfamide in KN204
GDP	[redacted]	KN204
cHLVPP	[redacted]	KN204

Administration costs for chemotherapy regimens were unchanged from MSD's original submission.

Unit costs were sourced from the BNF (Accessed Oct 2021) and were multiplied by the average number of cycles among patients who received that subsequent regimen in the trial and by body surface area estimates where appropriate. Wastage was assumed where partial vials were used. The average drug and administration costs for an average course of each of the regimens are included below.

In addition, we have added G-CSF prophylaxis costs based on clinical advice that this is used alongside multi-agent chemotherapy in this population for 7 days per cycle. In the absence of data, we assumed that 50% of patients would get the high dose of G-CSF prophylaxis and 50% would get the low dose. We do not expect this assumption to affect decision-making because the costs are relatively small.

The total costs of a course of treatment are the administration costs plus the drug unit costs and G-CSF prophylaxis costs multiplied by the average number of cycles. A weighted average based on the weights in Table 12 is then used for the subsequent treatment cost in the model.

3.4 Utility values

EQ-5D scores were collected for both the PFS and PD health states in the trial. The committee's preference was to include the relevant data for PFS but ignore the EQ-5D data on pembrolizumab in the PD health state and assign utility equal between the arms. A key reason for this was that the committee were unsure about the extent that pembrolizumab would continue to influence quality of life after first progression, although it accepted that assuming utility is equal is a conservative assumption.

The Scottish Medicines Consortium appraisal of nivolumab in cHL yields another estimate for PD utility on immunotherapy, which the committee may prefer. This estimate is slightly higher than the PD utility for BV collected in the KN204 trial but not as high as the PD collected for pembrolizumab in KN204. MSD would prefer to use the data collected from patients receiving pembrolizumab but given the committee and clinical experts' considerations in the ACD, using the nivolumab estimate appears more credible than assuming equal utility in the PD state. It is worth noting that the PD utility in the SMC's appraisal of nivolumab vs. standard care was highly differential, 0.715 vs. 0.39. This is a different comparison and line of treatment and MSD does not consider the magnitude of this difference plausible for pembrolizumab vs. BV, but at least provides some additional evidence of the clinical plausibility of differential utilities in post-progression utility in cHL.

When examining the PFS2 data from the trial (see Appendix 5.1.7), however, it appears as though pembrolizumab provides a durable benefit despite patients in the BV arm having had access to immunotherapy. The hazard ratio for time to second progression is [redacted] is even greater than the hazard ratio for first progression. It is reasonable to expect that, if multi-agent chemo were the subsequent treatment of choice in KN204, this difference in second progression would be even larger. The three-state partitioned survival model cannot account for this benefit explicitly but we suggest that a differential utility value be considered to reflect this durable benefit.

Table 14: Utility values (EQ-5D-3L)

Parameter	Notes	Value	s.e.	Source
Pembrolizumab PF utiltiy 3L (KN204)		[redacted]	[redacted]	KN204
BV PF utility 3L (KN204)		[redacted]	[redacted]	KN204
Pembrolizumab PD utility (KN204)		[redacted]	[redacted]	KN204
Pembrolizumab PD utility (nivolumab surrogate)	MSD updated base case	0.715	assumed 0.024	SMC Appraisal of Nivolumab in cHL (2017)
Pembrolizumab PD utility (assumed equal to BV)	ERG assumption	[redacted]	[redacted]	Assumption
BV PD utility (KN204)		[redacted]	[redacted]	KN204

3.5 Treatment Waning

There was little discussion of treatment waning in the ACD and the ERG's and committee's preferred assumptions did not include it. MSD considers that treatment waning is not appropriate in this cohort due to the significant proportion of patients that can enter long term remission with or without curative SCT. We consider that there is no data to validate any assumptions on time point or extent of any waning.

We did, however, provide a sensitivity analysis in our initial submission which included waning of OS so that the cycle specific hazard for the pembro curve can be set equal to the BV curve at a certain time point (arbitrarily set at 5 years). We have updated this approach to gradually wane the cycle-specific hazard between years 5 and 7 (again, the time points are arbitrary but have been used in sensitivity analysis in previous pembrolizumab appraisals in other indications) as it was felt that if treatment waning does exist, it would be more likely to wane gradually rather than instantly.

The committee's preferred assumptions also do not include the ERG's sensitivity analysis on PFS waning over time. We support this conclusion, firstly because a large proportion of patients in both arms are able to enter long term remission or access curative SCT and secondly because there are no data to substantiate such an analysis.

Modified cells references are available in Change Log supplied to NICE along with the updated model.

3.6 Technical fixes

The locations of cells that have been the subject of programming fixes have been noted in the Change Log supplied to NICE along with the updated model.

3.6.1 KM formula correction

The formulas in the 'KMdata' sheet for cell range B7:G207 have been updated with a new formula to accurately adjust the KM curve from the raw KM data to the weekly KM data. The previous formula recorded the first PFS event in the pembrolizumab arm at week 1 rather than after week 7. The updated formula demands that the week first occur before the event can be recorded.

<u>Example: cell B8</u>

Previous formula –
=IF(ISNUMBER(MATCH(A8,$H$7:$H$95,0)),INDEX($I$7:$I$95,MATCH(A8,$H$7:$H$95,0)),INDEX($I$7:$I$95,MATCH(TRUE,$H$7:$H$95>A8,0)))

Updated formula –
=IF(AGGREGATE(4,6,$H$7:$H$95)>$A8,INDEX($I$7:$I$95,MATCH($A8,$H$7:$H$95,1)),NA())

The effect of this change on the model's results is small.

3.6.2 Time on Treatment data

Upon recent review, the MSD's statisticians advised us that there had been a minor technical error in database coding when analysing Time on Treatment. Patients who had completed an entire course of treatment had been classified as censored rather than events. In practice, this makes almost no difference to the economic model as it relates to very few patients at the very end of the ToT curve. The differences between the new and old data can be seen in Figure 9 and Figure 10. Note that mean ToT is almost the same.

The relevant parametric extrapolations have been fitted in the model and the effect on the ICER is negligible. This is understandable given the KM data is almost complete for both treatments and both treatments have a hard stopping rule so long term extrapolation is not relevant.

[redacted]**Figure 9: Original ToT data from KN204 SCT-3L+ population**

[redacted]

Figure 10: Updated data on ToT from KEYNOTE-204 (SCT-3L+ population)

4. Results

4.1 MSD's base case assumptions

Table 15 contains a list of MSD's base case modelling assumptions. The choices for which have either been justified through this report or are taken from the committee's preferred assumptions following ACM1.

All scenarios include pembrolizumab at the prevailing Patient Access Scheme price. The discount associated with BV is unknown to the company so is set to 0% in the base case and varied in sensitivity analyses.

Table 15: List of MSD's base case assumptions for the cost-utility model

Assumption Number	Assumption relates to	Choice of Data
1	Pembrolizumab OS data source	KN-087 cohort 2 (unadjusted)
2	Pembrolizumab OS parametric distribution	Log-logistic
3	BV OS data source	Eyre (2017)
4	BV OS parametric distribution	Log-logistic
5	Subsequent treatment accrual	PFS exits
6	Subsequent treatment proportion	KN-204 Trial data
7	Utility in the pembro PD health state	0.715
8	PFS break point	26 weeks
9	ToT break point	80 weeks
10	Time horizon	50 years
11	BV discount	0%
12	Subsequent treatments in BV arm	Weighted average of multi-agent chemo

4.2 List of scenarios in the model

We examined a wide range of scenarios in the model. Each potential parametric extrapolation for the various OS curves was examined along with varying the other base case assumptions to examine the effect of uncertainty on the model's results. Various combinations of these scenario analyses are also examined.

We have included results for survival curves that result in implausibly low overall survival estimates for completeness only. These curves are not suitable for decision-making even if their fit to the immature OS data is similar to more plausible extrapolations. For each dataset the curves that appear to produce implausibly low (and in one case [the KN-087 adjusted-gompertz model] implausibly high) OS data are:-

Eyre 2017	**Exponential**	**Weibull**		
Walewski 2018	**Exponential**	**Weibull**	**Gompertz**	**Gen-gamma**
SACT data	**Exponential**	**Gompertz**	**Gen-gamma**	
KN-087 cohort 2	**Exponential**	**Gompertz**		

Table 16: OS data sources and list of implausible extrapolations

Eyre 2017	Exponential	Weibull		
Walewski 2018	Exponential	Weibull	Gompertz	Gen-gamma
SACT data	Exponential	Gompertz	Gen-gamma	
KN-087 cohort 2	Exponential	Gompertz		
KN-087 Adjusted	Exponential	Gompertz	Gen-gamma	

4.3 Base case results

Table 17: Deterministic Results

Treatment	Total LYs	Total QALYs	Total cost (£)	Incr. LYs (pembro vs. BV)	Incr. QALYs (pembro vs.BV)	Incr. cost (pembro vs. BV)	Cost (£) per LY (pembro vs. BV)	Cost (£) per QALY (pembro vs. BV)
Pembrolizumab	10.39	[redacted]	[redacted]	--	--	--	--	--
BV	4.36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,133

Table 18: Deterministic disaggregated results costs

Treatment	PF costs (£)	PD costs (£)	Terminal costs (£)	Acq. costs (£)	Admin. costs (£)	Sub. treat cost (£)	AE costs (£)	SCT costs (£)	Societal costs (£)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 19: Deterministic disaggregated QALYs

Treatment	PF	PD	Age related decrement	AEs
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
BV	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: Probabilistic Sensitivity Analysis (Mean of 1,000 iterations) Absolute Results

Treatment	Total LYs	95% CI for total LYs	Total QALYs	95% CI for total QALYs	Total cost (£)	95% CI for total Cost
Pembro	10.39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BV	4.36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 21: Probabilistic Sensitivity Analysis (mean of 1,000 iterations) Incremental Results

Incr. LYs (pembro vs.)	Incr. QALYs (pembro vs.)	Incr. cost (pembro vs.)	Cost (£) per QALY (pembro vs.)
5.87 (0.92 - 10.22)	[redacted]	[redacted]	£10,065 (£6,156 - £18,768)

4.4 Results of scenario analyses

Table 22 lists the results of scenario analyses presented in costs, QALYs and Incremental Net Health Benefits (INHB) where QALYs are valued at £30,000 each. Individual scenarios are varied against the base case assumptions unless otherwise noted. Some deliberately conservative combinatorial analyses appear towards the bottom of the table.

Table 22: Results of scenario analyses

Scenario	Pembro Total Costs	BV Total Costs	Pembro Total QALYs	BV Total QALYs	ICER	INHB (£30k/Q)
Basecase	[redacted]	[redacted]	[redacted]	[redacted]	£10,133	[redacted]
PFS modelling method - Pembrolizumab: Piecewise (52 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	£8,577	[redacted]
PFS modelling method - UK comparator: Piecewise (52 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	£10,332	[redacted]

PFS distribution (Both Pembrolizumab and BV): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£11,286	[redacted]
PFS distribution (Both Pembrolizumab and BV): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£11,013	[redacted]
PFS distribution (Both Pembrolizumab and BV): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£6,675	[redacted]
PFS distribution (Both Pembrolizumab and BV): Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£10,248	[redacted]
PFS distribution (Both Pembrolizumab and BV): Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£9,188	[redacted]
Apply treatment waning years 5-7	[redacted]	[redacted]	[redacted]	[redacted]	£10,282	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 cohort 2): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£9,932	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 cohort 2): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£10,187	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 cohort 2): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£11,626	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 cohort 2): Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	£10,057	[redacted]
OS modelling method - Pembrolizumab: KN087 Full cohort	[redacted]	[redacted]	[redacted]	[redacted]	£10,108	[redacted]
OS modelling method - Pembrolizumab: KN087 CDF Data	[redacted]	[redacted]	[redacted]	[redacted]	£9,499	[redacted]
OS modelling method - UK comparator: Walewski OS data	[redacted]	[redacted]	[redacted]	[redacted]	£10,262	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 CDF): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£10,271	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 CDF): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£9,624	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 CDF): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£8,094	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 CDF): Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	£9,417	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 CDF): Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£9,499	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 CDF): Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£5,672	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£9,158	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£9,136	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£9,307	[redacted]
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	£10,114	[redacted]

OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£9,233	[redacted]
ToT modelling approach - Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£9,856	[redacted]
ToT modelling approach - BV	[redacted]	[redacted]	[redacted]	[redacted]	£10,032	[redacted]
ToT distribution (Both Pembrolizumab and BV): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£10,014	[redacted]
ToT distribution (Both Pembrolizumab and BV): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£10,157	[redacted]
ToT distribution (Both Pembrolizumab and BV): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£9,971	[redacted]
ToT distribution (Both Pembrolizumab and BV): Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£10,085	[redacted]
ToT distribution (Both Pembrolizumab and BV): Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£10,132	[redacted]
Mean health state utility value for PD state (Pembrolizumab): Assume same as BV	[redacted]	[redacted]	[redacted]	[redacted]	£10,515	[redacted]
Age related disutility: FALSE	[redacted]	[redacted]	[redacted]	[redacted]	£9,622	[redacted]
Prop receive 2nd line therapy (KEYNOTE-204 SCT-3L+ cohort): PFS events that are Progressions	[redacted]	[redacted]	[redacted]	[redacted]	£13,119	[redacted]
Prop receive 2nd line therapy (KEYNOTE-204 SCT-3L+ cohort):Probability of receiving subs trt on a PFS event (MSD Scenario Analysis 1)	[redacted]	[redacted]	[redacted]	[redacted]	£10,311	[redacted]
Prop receive 2nd line therapy (KEYNOTE-204 SCT-3L+ cohort):Probability of receiving subs trt on a PFS event (MSD Scenario Analysis 2)	[redacted]	[redacted]	[redacted]	[redacted]	£12,425	[redacted]
% of receiving Pembro as subsequent treatment in BV arm as 100%	[redacted]	[redacted]	[redacted]	[redacted]	£5,595	[redacted]
Prop receive 2nd line therapy_Based on PD entry: MSD Base case	[redacted]	[redacted]	[redacted]	[redacted]	£8,547	[redacted]
Prop receive 2nd line therapy_Based on PD entry: all patients	[redacted]	[redacted]	[redacted]	[redacted]	£10,787	[redacted]
Prop receive 2nd line therapy_Based on PD entry: MSD Scenario Analysis 1	[redacted]	[redacted]	[redacted]	[redacted]	£8,661	[redacted]
Prop receive 2nd line therapy_Based on PD entry: MSD Scenario Analysis 2	[redacted]	[redacted]	[redacted]	[redacted]	£10,236	[redacted]

BV discount arbitrary 50%	[redacted]	[redacted]	[redacted]	[redacted]	£12,663	[redacted]
BV discount arbitrary 50%, PD health state costs discounted by 20%	[redacted]	[redacted]	[redacted]	[redacted]	£11,388	[redacted]
BV discount arbitrary 50%, PD health state costs discounted by 50%	[redacted]	[redacted]	[redacted]	[redacted]	£9,476	[redacted]
BV disc. 50%, PD entry	[redacted]	[redacted]	[redacted]	[redacted]	£12,024	[redacted]
BV disc. 50%, PD entry, all patients get subs trt,	[redacted]	[redacted]	[redacted]	[redacted]	£13,152	[redacted]
BV disc. 50%, PD entry, all patients get subs trt, pembro OS from CDF (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£14,490	[redacted]
BV disc. 50%, PFS exit, subs trt from trial, pembro OS from CDF (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£16,208	[redacted]
BV disc. 50%, PFS exit, all patients get subs trt, pembro OS from CDF (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£19,117	[redacted]
BV disc. 50%, PFS exit, all patients get subs trt, pembro OS from CDF (log-log), treatment waning OS	[redacted]	[redacted]	[redacted]	[redacted]	£22,349	[redacted]
BV disc. 50%, PFS exit, all patients get subs trt, pembro OS from CDF (log-log), treatment waning OS, equal PD utility	[redacted]	[redacted]	[redacted]	[redacted]	£23,394	[redacted]
BV disc. 50%, PFS exit, all patients get subs trt, pembro OS from CDF (log-log), treatment waning OS, equal PD utility, BV OS from Walewski (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£32,107	[redacted]
BV disc. 50%, PD entry, all patients get subs trt, pembro OS from CDF (log-log), treatment waning OS, equal PD utility, BV OS from Walewski (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£21,336	[redacted]
Weighted average pembro OS – KN-087 and CDF data	[redacted]	[redacted]	[redacted]	[redacted]	£9,272	[redacted]
Pembro 2nd line in BV arm, No OS benefit (OS = Eyre for both arms)	[redacted]	[redacted]	[redacted]	[redacted]	Dom - inant	[redacted]

4.5 Discussion

The base case analysis finds that pembrolizumab is comfortably cost-effective vs. BV with a base case ICER of ~£10,000/QALY gained. Substantial costs incurred in the Progressed Disease health state as well as substantial subsequent treatment costs are offset by large gains in overall survival.

The results were robust to probabilistic sensitivity analysis with the central estimates being very similar and with the central 95% of iterations all being below £20,000/QALY gained.

Pembrolizumab remains cost effective in all scenario analyses where the overall survival comparison is modelled via KN087 cohort 2 and Eyre (2017). Despite differences in absolute numbers of QALYs, the choice of parametric distributions appears to have a relatively minor effect on the ICER. As has been noted in the discussion of the evidence, the relatively older and sicker population in KEYNOTE-087 is more likely to underestimate OS vs. BV than overestimate it. Similarly, the Eyre (2017) study may be more likely to overestimate it. MSD therefore considers that its base case analysis is more likely to be conservative than optimistic.

When considering the comparison of the SACT data and Eyre (2017), there are two extrapolations that produce cost-ineffective results but these are from implausible OS curves and should be discounted from decision-making.

When using OS data from the match-adjusted pembrolizumab curve, the ICERs remained consistent with the base case analysis. This suggests that despite a lower OS in the short term, the tail of the parametric models produced a similar amount of Net Health Benefit in the long run.

The model was completely insensitive to different approaches to modelling Time on Treatment. This is not a surprised as the real KM data were almost complete.

Treatment waning assumptions had a moderate effect on the ICERs. MSD considers that there is no data to substantiate treatment waning (either inclusion or appropriate time period) and considers any such assumption uncertain, particularly in the context of potentially differential levels of curative SCT interventions between the arms.

Assumptions about what proportion of progressing patients receive subsequent treatments had some influence on the ICER. This is principally because the subsequent treatment after pembrolizumab in the model is BV, which has a high cost and the subsequent treatment after BV is multi-agent chemotherapy, which is relatively cheap. Whether subsequent treatment accrual is based on PFS exit or PD entry also has some influence on the ICER. We note that pembrolizumab remains costs effective in all combinations of scenarios regarding subsequent treatment with ICER ranges of ~£8,000 - ~£13,000/QALY gained.

We do not know the discount that is available for BV on the NHS so have used an arbitrary 50% to examine its effect on the ICER. We note a moderate effect, increasing the base case from £10,000/QALY to £12,000/QALY.

It is possible that the cost of the PD health state is overestimated in the model if some people will achieve long lasting remission. We varied this cost arbitrarily and found that it had a moderate effect on the ICER.

We have included some deliberately conservative combinatorial scenario analyses towards the end of the table. We note that only if the most conservative assumptions about subsequent treatments, treatment waning, utility, BV discount and overall survival are applied is the ICER just above the threshold of £30,000/QALY. We do not believe the comparison of Walewski and the SACT data is the most plausible, however. Walewski included many second line patients and likely overestimates OS on

BV whereas the SACT data includes much older, sicker, fourth line plus patients and likely underestimates OS on pembrolizumab.

Overall we conclude that, even though there is some uncertainty inherent in indirect comparisons of overall survival, such comparisons are necessary in this small subpopulation and the economic model's findings that pembrolizumab>BV is cost-effective compared to BV>chemotherapy is robust to all plausible scenario and sensitivity analyses.

It should be noted that, if the comparison between pembrolizumab>BV and BV>pembrolizumab is made, the ICER is extremely low. It is only not dominant because of the long term PD costs, which may be overestimated.

4.6 Conclusions

The rrcHL population who are SCT-3L+ is a small and under-studied subgroup. The natural history of their disease is long and highly variable as many patients will receive a potential curative SCT. Clinical experts and epidemiological data suggest that a significant proportion of patients will be alive 20 years after the start time of the economic model. The data from the only comparative RCT in the area (KN204) find a profound PFS benefit for pembrolizumab over BV. This suggests that it is plausible there is an OS benefit.

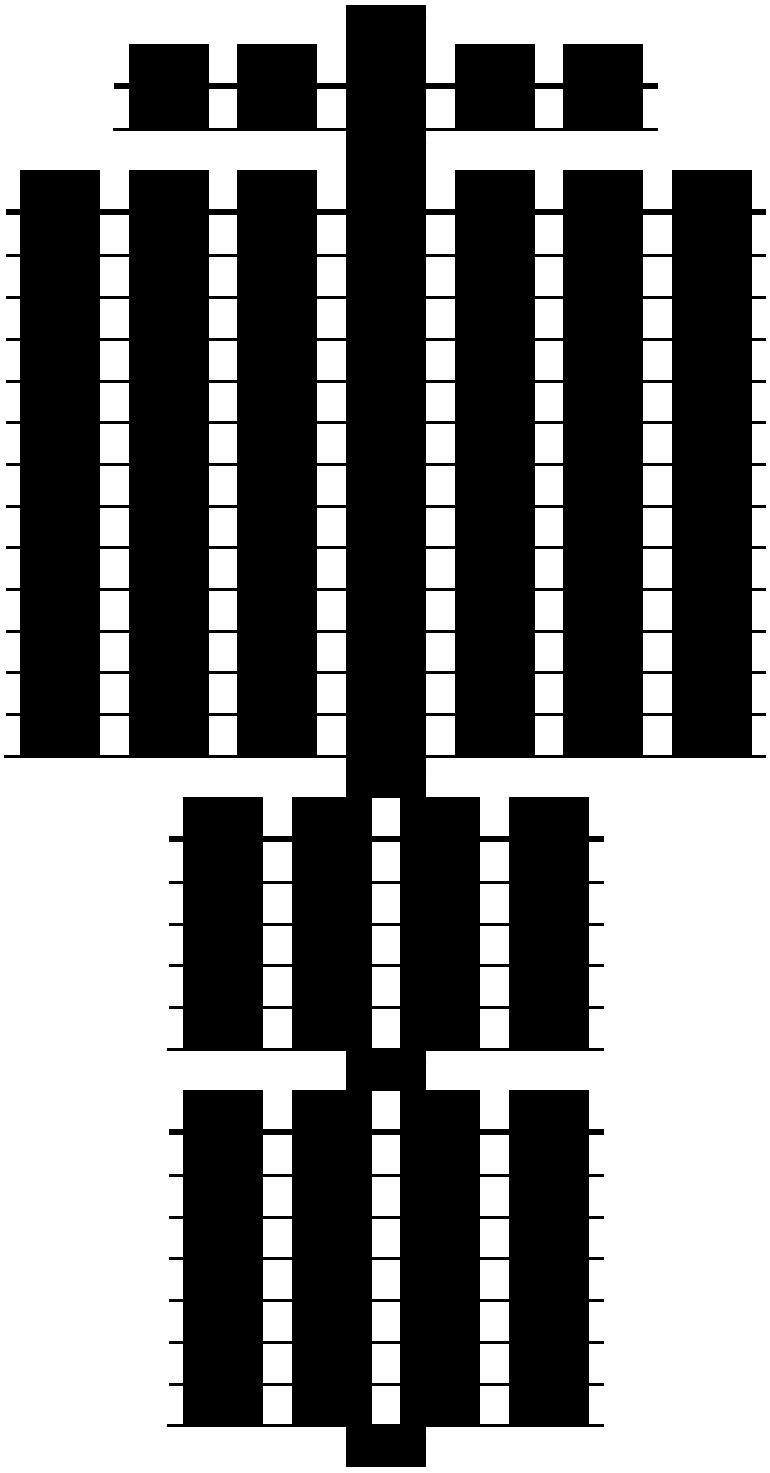
No comparative overall survival data is available to inform long-term time-dependent transition probabilities following treatment with BV or pembrolizumab or following SCT. The best available evidence therefore comes from naïve comparisons of single arm studies and suggests that the significant PFS benefit observed in KN204 may be followed by a significant OS benefit. The magnitude of this benefit is uncertain but the most plausible data suggest that pembrolizumab>BV is cost-effective compared to BV>chemotherapy. The results were robust to a range of plausible sensitivity and scenario analyses.

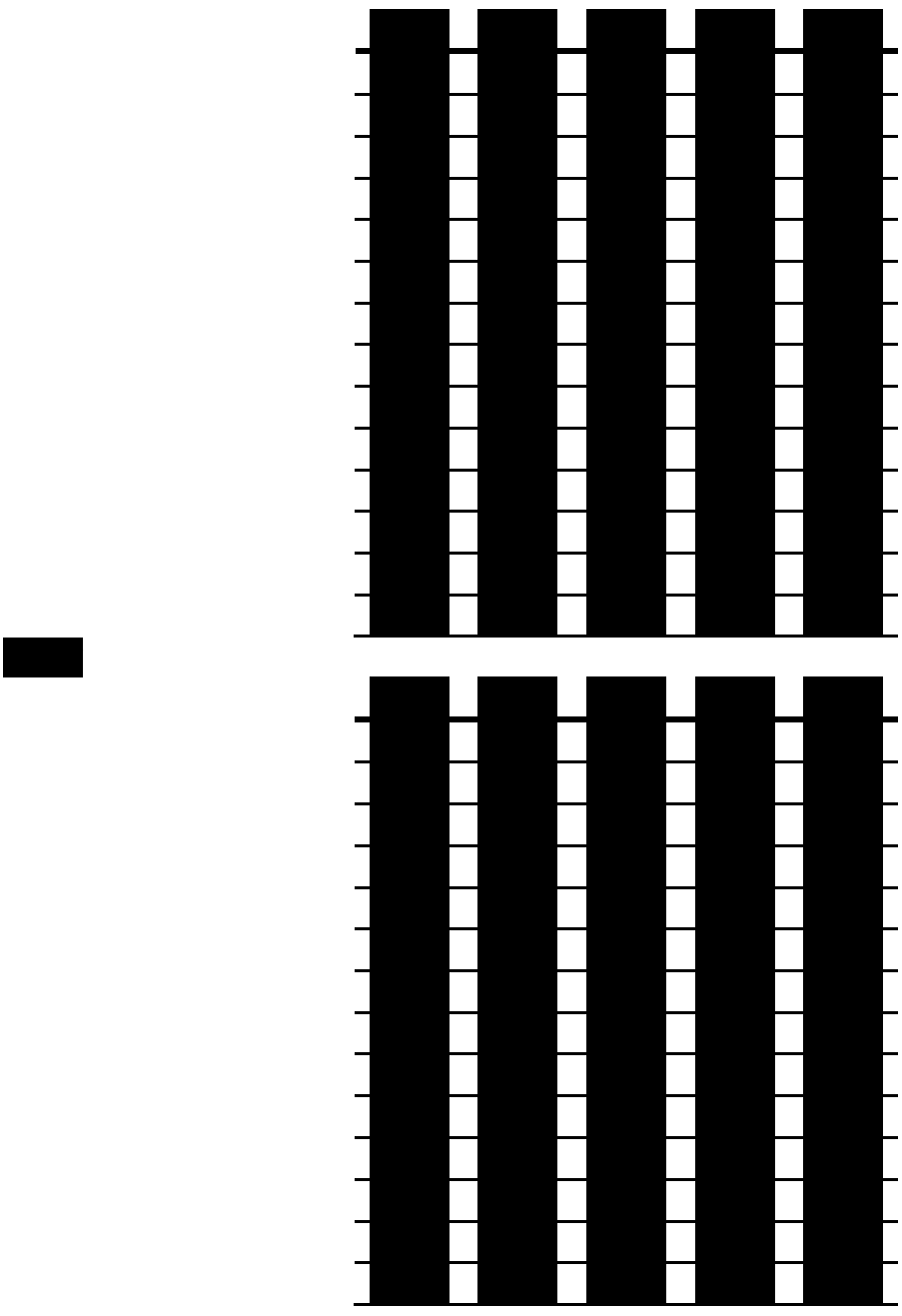
While there is inherent uncertainty in naïve comparisons, MSD considers that this uncertainty should not be a cause of caution in decision-making as the risk of decision error is negligible. Overall, these data support a recommendation in favour of patients being able to access pembrolizumab one step earlier in the treatment pathway.

5. Appendix

5.1 Survival Analysis Data

5.1.1 Overall Survival Analysis for KEYNOTE-087 cohort 2





5.1.2 Overall Survival Analysis for KEYNOTE-087 – All cohorts combined

KM data and model fit statistics redacted

5.1.3 Overall Survival Analysis for SACT data on Pembrolizumab 4L+

[redacted]

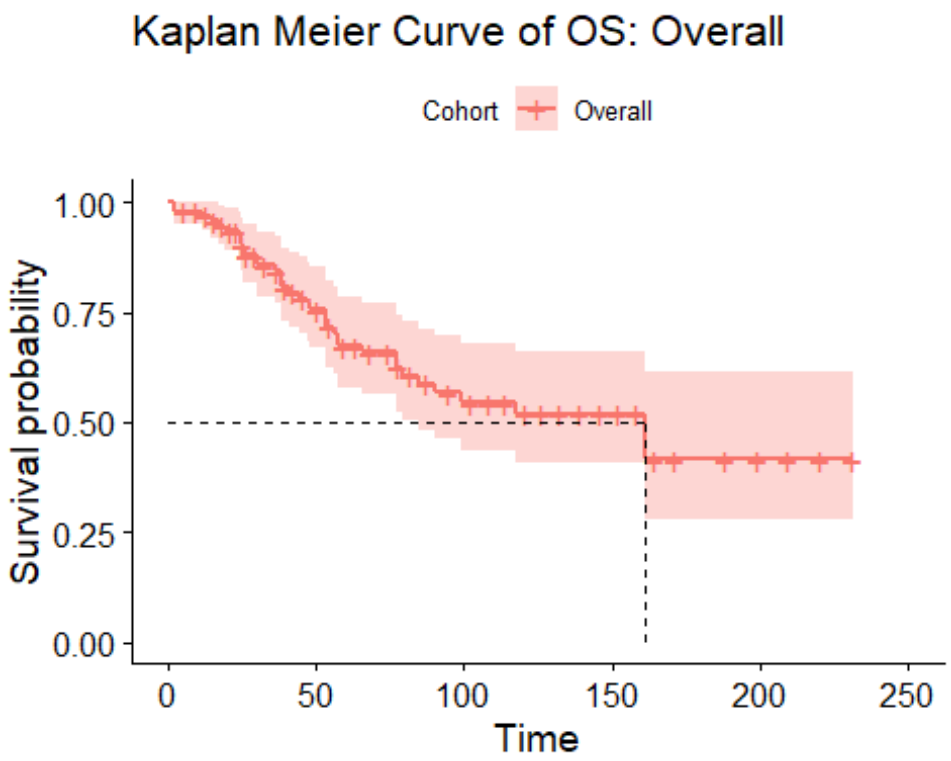
[redacted]

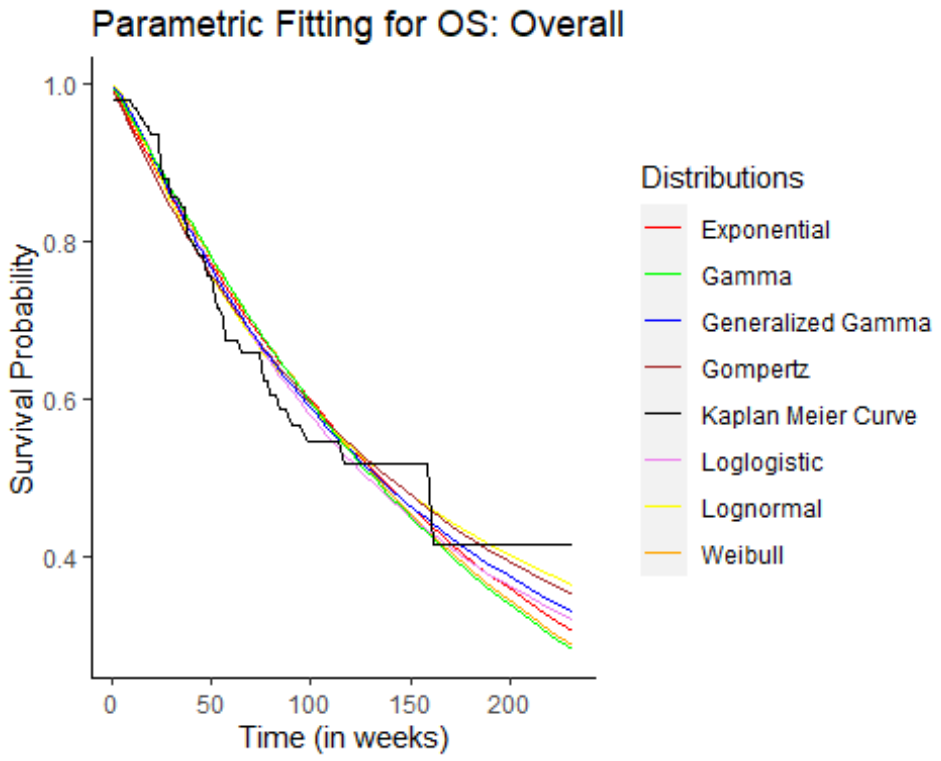
[redacted]

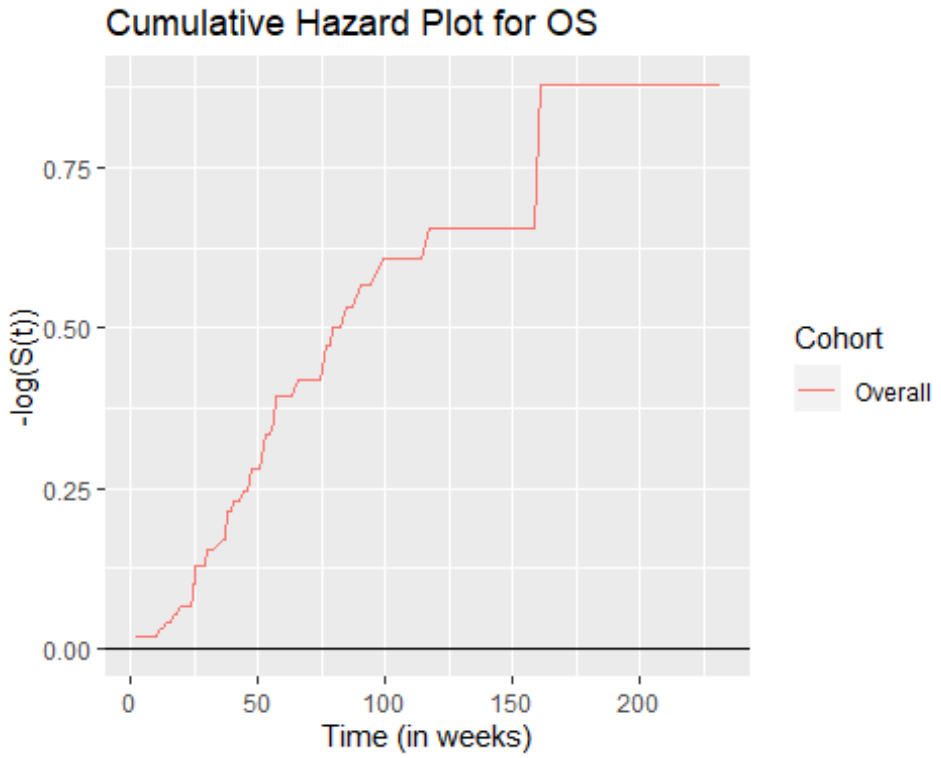
[redacted]

[redacted]

5.1.4 Overall Survival Analysis for Eyre (2017)




Parametric Fitting for OS: Overall
Survival Probability
1.0
0.8
0.6
0.4
0
50
100
150
200
Time (in weeks)
Distributions
Exponential
Gamma
Generalized Gamma
Gompertz
Kaplan Meier Curve
Loglogistic
Lognormal
Weibull


Cumulative Hazard Plot for OS
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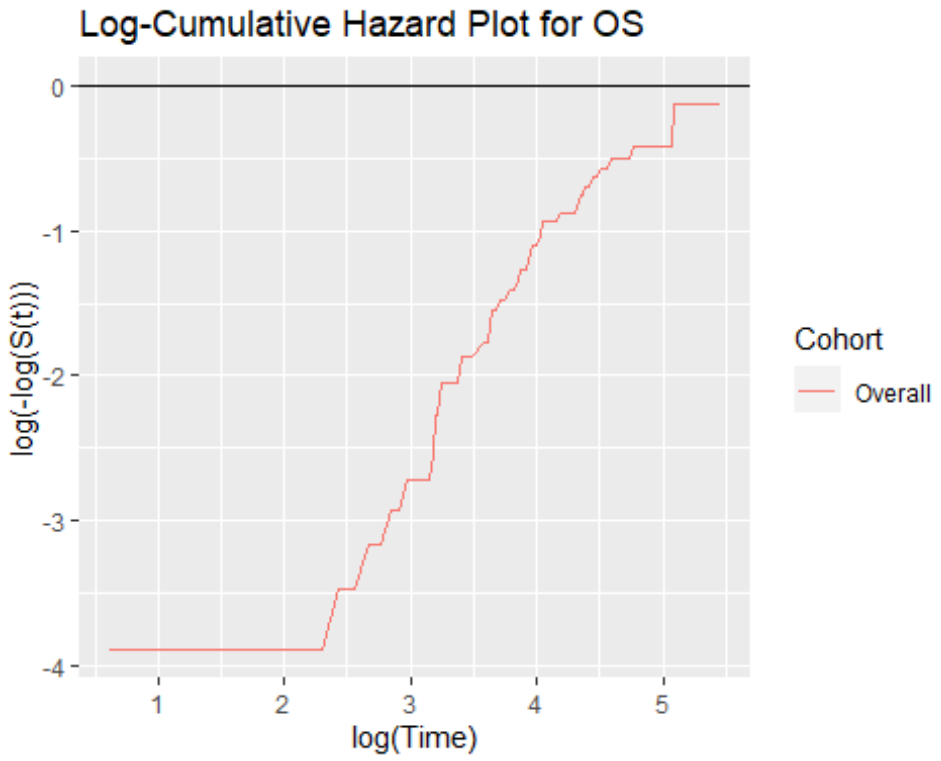
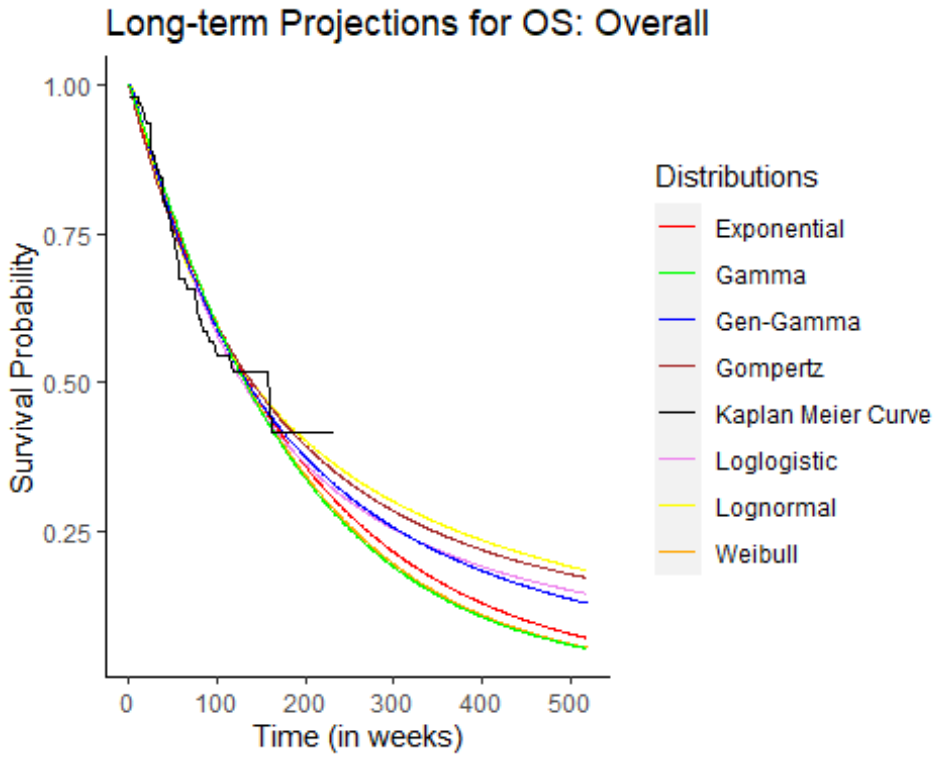
0.25
0.00
0
50
100
150
200
Time (in weeks)
Cohort
Overall






```
## AIC-BIC table for OS: Overall
```

Distributions	AIC	BIC	Avg AIC BIC

Exponential	466.1	468.7	467.4
Weibull	468.0	473.1	470.5
LogNormal	467.0	472.2	469.6
Loglogistic	465.8	470.9	468.3
Gompertz	467.7	472.9	470.3
Generalized Gamma	468.4	476.2	472.3
Gamma	467.8	473.0	470.4

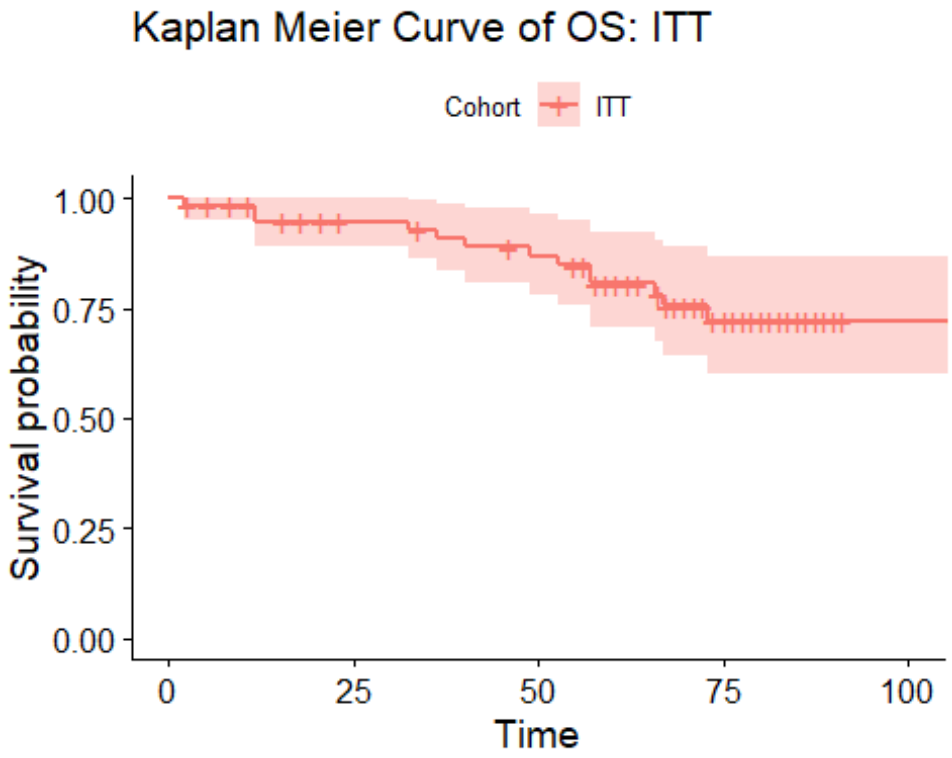
	Estimates	Lower(95%)	Upper(95%)	Standard Error
Exp_rate	-5.2717	-5.5939	-4.9495	0.1644
Weib_shape	0.0541	-0.2132	0.3213	0.1364
Weib_scale	5.2349	4.8833	5.5864	0.1794
LogNorm_meanlog	4.9352	4.5183	5.3522	0.2127
LogNorm_sdlog	0.3769	0.1335	0.6203	0.1242
LogLogis_shape	0.2439	-0.0255	0.5133	0.1375
LogLogis_scale	4.8554	4.4944	5.2164	0.1842
Gomp_shape	-0.0023	-0.0095	0.0049	0.0037
Gomp_rate	-5.1473	-5.6426	-4.6521	0.2527
Gamma_shape	0.1076	-0.2480	0.4632	0.1814
Gamma_rate	-5.0968	-5.7382	-4.4554	0.3272
GenGamma_mu	5.0556	4.5755	5.5358	0.2450
GenGamma_sigma	0.2277	-0.2363	0.6916	0.2367
GenGamma_Q	0.3765	-0.5471	1.3002	0.4713

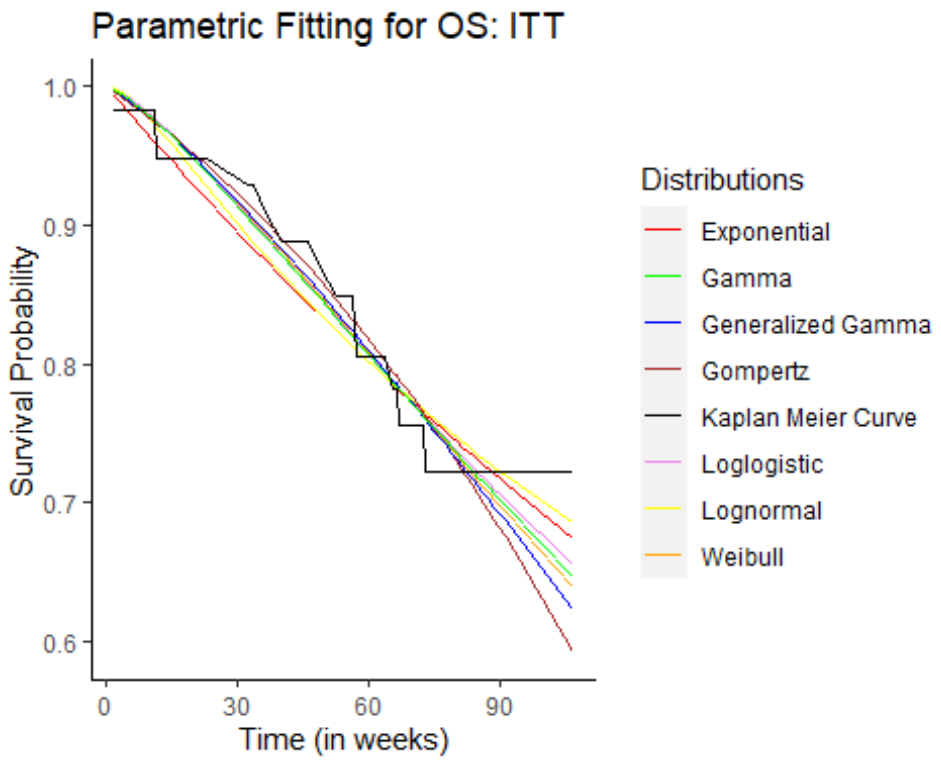
```
##
##  Variance Covariance matrix for OS: Overall
```

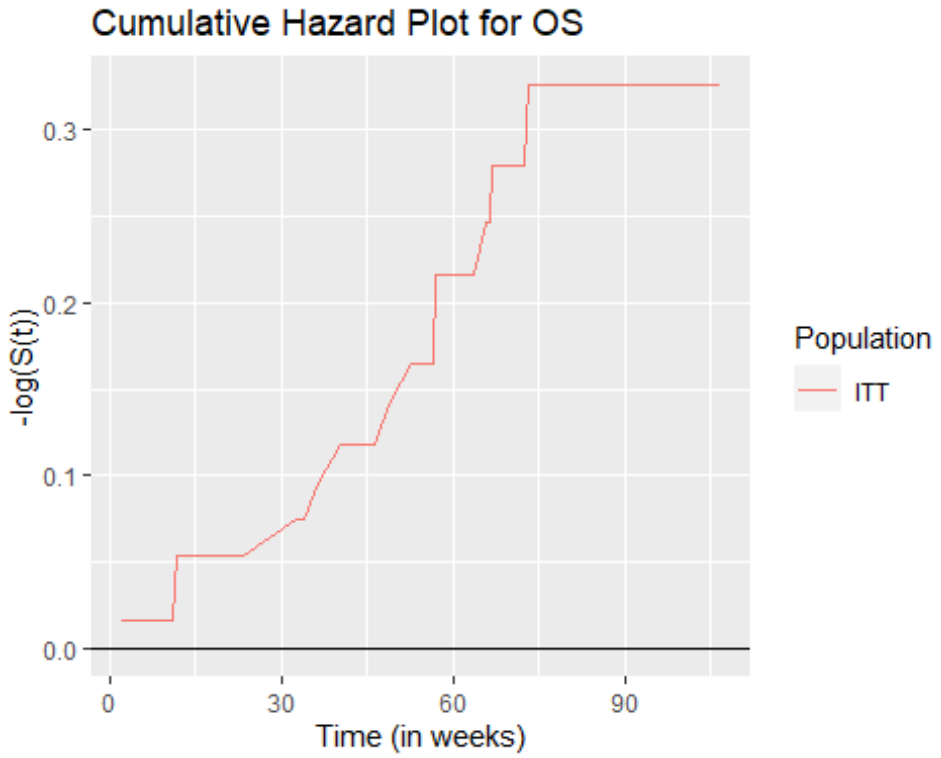
	V1	V2	V3
Exp_rate	0.0270	NA	NA
Weib_shape	0.0186	-0.0121	NA
Weib_scale	-0.0121	0.0322	NA
LogNorm_meanlog	0.0453	0.0145	NA
LogNorm_sdlog	0.0145	0.0154	NA
LogLogis_shape	0.0189	-0.0115	NA
LogLogis_scale	-0.0115	0.0339	NA
Gomp_shape	0.0000	-0.0007	NA

Gomp_rate	-0.0007	0.0639	NA
Gamma_shape	0.0329	0.0525	NA
Gamma_rate	0.0525	0.1071	NA
GenGamma_mu	0.0600	-0.0146	0.0675
GenGamma_sigma	-0.0146	0.0560	-0.0933
GenGamma_Q	0.0675	-0.0933	0.2221

5.1.5 Overall Survival Analysis for Walewski (2018)




Parametric Fitting for OS: ITT
Survival Probability
1.0
0.9
0.8
0.7
0.6
0
30
60
90
Time (in weeks)
Distributions
Exponential
Gamma
Generalized Gamma
Gompertz
Kaplan Meier Curve
Loglogistic
Lognormal
Weibull


Cumulative Hazard Plot for OS
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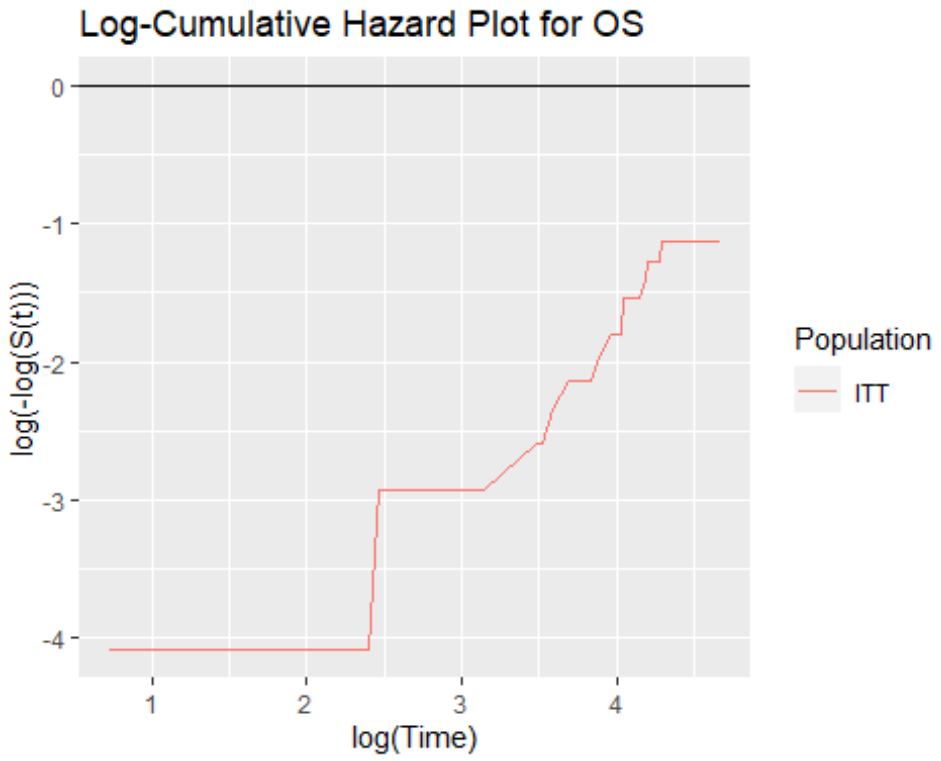
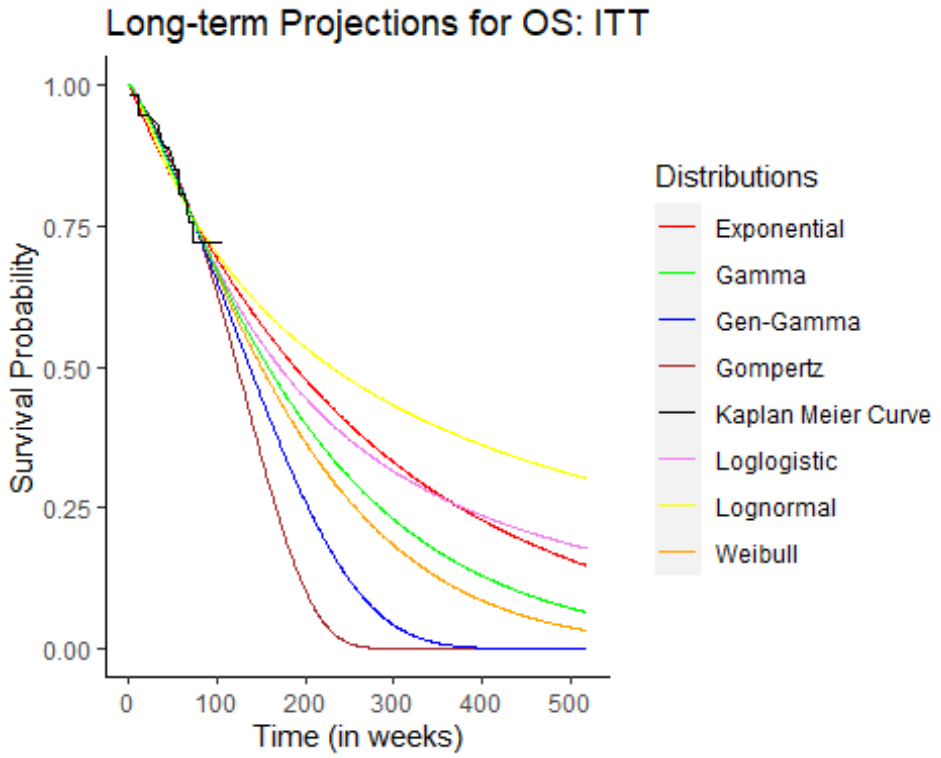
0.1
0.0
0
30
60
90
Time (in weeks)
Population
ITT






```
## AIC-BIC table for OS: ITT
```

Distributions	AIC	BIC	Avg AIC BIC

Exponential	173.7	175.8	174.7
Weibull	174.8	179.0	176.9
LogNormal	176.5	180.7	178.6
Loglogistic	175.0	179.2	177.1
Gompertz	174.3	178.5	176.4
Generalized Gamma	176.6	182.9	179.7
Gamma	174.9	179.1	177.0

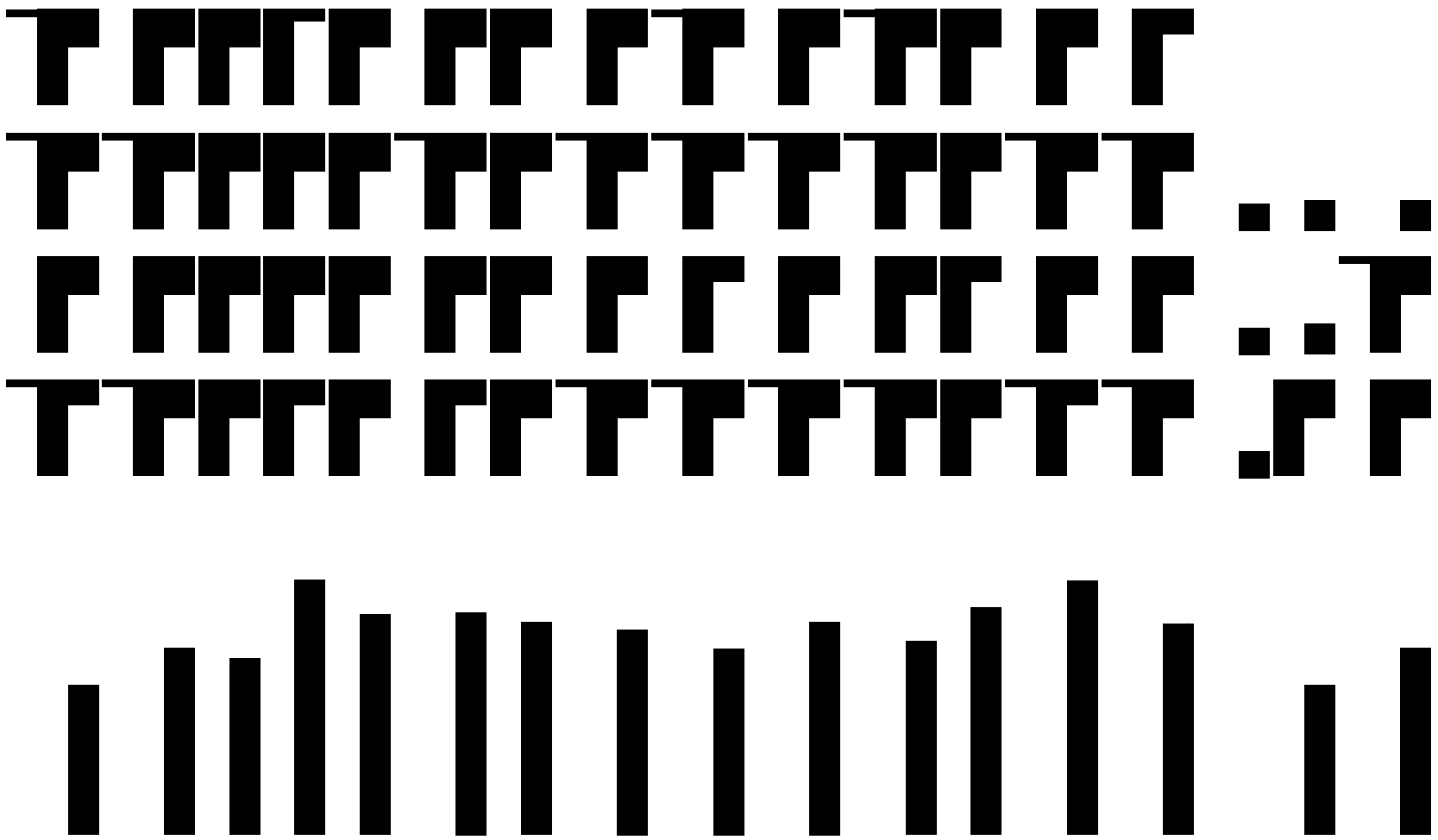
	Estimates	Lower(95%)	Upper(95%)	Standard Error
Exp_rate	-5.6022	-6.1458	-5.0586	0.2774
Weib_shape	0.2531	-0.2480	0.7543	0.2557
Weib_scale	5.2940	4.6184	5.9696	0.3447
LogNorm_meanlog	5.4327	4.5765	6.2889	0.4368
LogNorm_sdlog	0.4558	0.0285	0.8830	0.2180
LogLogis_shape	0.3170	-0.1780	0.8119	0.2525
LogLogis_scale	5.1369	4.4793	5.7946	0.3356
Gomp_shape	0.0137	-0.0094	0.0367	0.0118
Gomp_rate	-6.1351	-7.2605	-5.0097	0.5742
Gamma_shape	0.2757	-0.3225	0.8740	0.3052
Gamma_rate	-5.0558	-6.2538	-3.8578	0.6112
GenGamma_mu	5.2634	4.6206	5.9062	0.3279
GenGamma_sigma	-0.7267	-4.8722	3.4189	2.1151
GenGamma_Q	1.7195	-5.5822	9.0212	3.7254

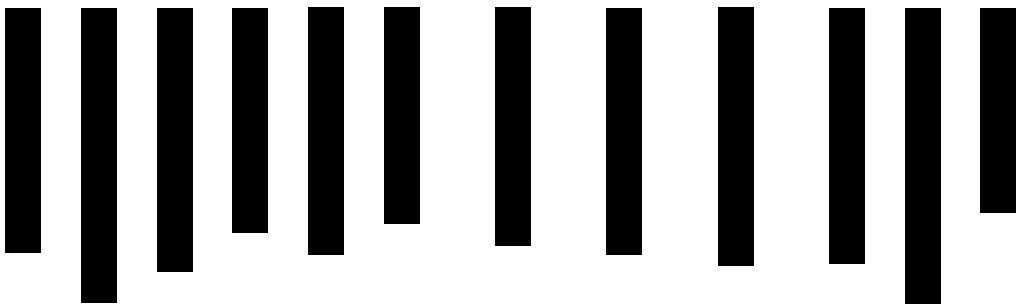
```
##
##  Variance Covariance matrix for OS: ITT
```

	V1	V2	V3
Exp_rate	0.0769	NA	NA
Weib_shape	0.0654	-0.0688	NA
Weib_scale	-0.0688	0.1188	NA
LogNorm_meanlog	0.1908	0.0730	NA
LogNorm_sdlog	0.0730	0.0475	NA
LogLogis_shape	0.0638	-0.0618	NA
LogLogis_scale	-0.0618	0.1126	NA
Gomp_shape	0.0001	-0.0059	NA

Gomp_rate	-0.0059	0.3297	NA
Gamma_shape	0.0932	0.1734	NA
Gamma_rate	0.1734	0.3736	NA
GenGamma_mu	0.1075	-0.0888	0.2725
GenGamma_sigma	-0.0888	4.4738	-7.8199
GenGamma_Q	0.2725	-7.8199	13.8788

5.1.6 Overall Survival Analysis for KN087 Match-Adjusted Data





5.1.7 Progression Free Survival Analysis in KEYNOTE-204 SCT-3L+ subpopulation

KM data and model fit statistics redacted

5.1.8 Second Progression Free Survival (KEYNOTE-204)

[redacted]

KM data and model fit statistics redacted

5.2 Table of unit costs

Regimen		Dosage (mg)	Dosage unit	# per cycle	Cycle length (days)	Vial size (1), mg	Vial (1) price, £/vial	Vials (1) used*		Packs per admin	Packs per cycle	Cost per cycle	Source (Drug Prices)	Source (UK Dosing Schedule)
		Default	Default	Default	Default	Default	Default	User	Default	Calculated	Calculated	Calculated		
ESHAP	Etoposide	40	mg/m²	4	28	100	£ 11.50		1.00	1.00	4.00	£ 46.00	BNF (Oct 2021)	Thames Valley Strategic Clinical Network (Accessed 2021)
	Methyl-prednisolone	500	mg	1	28	500	£ 9.60		13.00	1.00	1.00	£ 9.60	BNF (Oct 2021)	
	Cytrabine	2,000	mg/m²	1	28	2,000	£ 73.63		38.00	2.00	2.00	£ 147.26	BNF (Oct 2021)	
	Cisplatin	25	mg/m²	4	28	10	£ 5.36		5.00	5.00	20.00	£ 107.20	BNF (Oct 2021)	
Bendamustine	Bendamustine	120	mg/m²	2	21	25	£ 5.55		10.00	10.00	20.00	£ 111.00	BNF (Oct 2021)	Not recommended as an option
DHAP	Dexamethasone	40	mg	4	21	4	£ 1.67		80.00	10.00	40.00	£ 66.68	BNF (Oct 2021)	Cheshire and Merseyside Strategic Clinical Network (Accessed 2021)
	Cytrabine	2,000	mg/m²	1	21	2,000	£ 73.63		38.00	2.00	2.00	£ 147.26	BNF (Oct 2021)	
	Cisplatin	100	mg/m²	1	21	10	£ 5.36		19.00	19.00	19.00	£ 101.84	BNF (Oct 2021)	
IGEV	Ifosfamide	2,000	mg/m²	4	21	1,000	£ 115.79		4.00	4.00	16.00	£ 1,852.64	BNF (Oct 2021)	Cheshire and Merseyside Strategic Clinical
	Mesna	2,800	mg/m²	4	21	400	£ 13.41		13.00	14.00	56.00	£ 750.96	BNF (Oct 2021)	

	Gemcitabine	800	mg/m²	2	21	200	£ 32.00		8.00	8.00	16.00	£ 512.00	BNF (Oct 2021)	Network (Accessed 2021)
	Vinorelbine	20	mg/m²	1	21	10	£ 29.00		4.00	4.00	4.00	£ 116.00	BNF (Oct 2021)	
	Prednisolone	100	mg	4	21	10	£ 0.35		100.00	10.00	40.00	£ 13.80	BNF (Oct 2021)	
ICE	Ifosfamide	5,000	mg/m²	1	21	1,000	£ 115.79		10.00	10.00	10.00	£ 1,157.90	BNF (Oct 2021)	Cheshire and Merseyside Strategic Clinical Network (Accessed 2021)
	Mesna	8,000	mg/m²	1	21	400	£ 13.41		24.00	38.00	38.00	£ 509.58	BNF (Oct 2021)	
	Carboplatin	800	mg	1	21	50	£ 20.20		16.00	16.00	16.00	£ 323.20	BNF (Oct 2021)	
	Etoposide	100	mg/m²	3	21	100	£ 11.50		2.00	2.00	6.00	£ 69.00	BNF (Oct 2021)	
IVE	Ifosfamide	3,000	mg/m²	3	21	1,000	£ 115.79		6.00	6.00	18.00	£ 2,084.22	BNF (Oct 2021)	Cheshire and Merseyside Strategic Clinical Network (Accessed 2021)
	Mesna	10,200	mg/m²	1	21	400	£ 13.41		15.00	49.00	49.00	£ 657.09	BNF (Oct 2021)	
	Epirubicin	50	mg/m²	1	21	10	£ 20.00		10.00	10.00	10.00	£ 200.00	BNF (Oct 2021)	
	Etoposide	200	mg/m²	3	21	100	£ 11.50		4.00	4.00	12.00	£ 138.00	BNF (Oct 2021)	
GDP	Gemcitabine	1,000	mg/m²	2	21	200	£ 32.00		10.00	10.00	20.00	£ 640.00	BNF (Oct 2021)	University Hospital Southampton (Accessed 2021)
	Dexamethasone	40	mg	4	21	4	£ 1.67		80.00	10.00	40.00	£ 66.68	BNF (Oct 2021)	
	Cisplatin	75	mg/m²	1	21	10	£ 5.36		15.00	15.00	15.00	£ 80.40	BNF (Oct 2021)	
cHLVPP	Chlorambucil (oral)	6	mg/m²	14	28	2	£ 11.15		6.00	6.00	84.00	£ 936.60	BNF (Oct 2021)	University Hospital Southampton (Accessed 2021)
	Vinblastine (IV)	6	mg/m²	2	28	10	£ 17.00		2.00	2.00	4.00	£ 68.00	BNF (Oct 2021)	
	Procarbazine (oral)	100	mg/m²	14	28	50	£ 8.23		4.00	4.00	56.00	£ 460.71	BNF (Oct 2021)	
	Prednisolone (oral)	40	mg	14	28	10	£ 0.35		4.00	4.00	56.00	£ 19.32	BNF (Oct 2021)	
G-CSF (filgrastim)		30	MU	1	21	30	£53		1	-	-	£53*50%*7	BNF (Oct 2021)	Assumption
G-CSF (filgrastim)		48	MU	1	21	48	£84		1	-	-	£84*50%*7	BNF (Oct 2021)	

5.3 Match adjusted KEYNOTE-087 survival analysis

Keytruda (MK-3475) HL

KN087

Database Cutoff 21-Mar-2019

NICE Query Report

[redacted]

5.3.1 OBJECTIVES

The objective of this report is to provide Kaplan-Meier estimates of Cohort 2 Overall Survival for KN087 in subjects with relapsed or refractory classical Hodgkin Lymphoma (rrcHL) after re-weighting the KN087 Cohort 2 subjects to match the baseline characteristics of patients included in KN204 for the population of interest who are randomized to pembrolizumab.

The analysis is conducted in response to a question raised by NICE and is of interest in the absence of Overall Survival data of KN204. The baseline characteristics of the patients from KN204 who are randomized to pembrolizumab, are at least third line and had no prior stem cell transplant will be used for matching.

5.3.2 STATISTICAL ANALYSIS

5.3.2.1 Endpoints

5.3.2.1.1 Overall Survival

Overall survival (OS) is defined as time from first dose intake to death due to any cause, expressed in days. Subjects without documented death are considered right censored at the day of last contact. Subjects who had a survival update after the data cutoff date of the 21st March, 2019 are censored at the cutoff date. OS is expressed in weeks.

5.3.2.1.2 Analysis Populations

The All Subjects as Treated (ASaT) population is used for the analyses of OS in KN087 which includes all participants who received at least 1 dose of pembrolizumab. This approach is consistent with CSR approach.

The population of interest for this report is Cohort 2, which includes subjects who were SCT-ineligible and relapsed after treatment with or failed to respond to BV, as defined in the protocol (details in section 0).

For KN204, used for the matching, the Intention-to-Treat (ITT) population is used. All subjects randomized to pembrolizumab that are at least third line without SCT are considered.

5.3.2.2 Data Used in the Analysis

5.3.2.2.1 KN087

This report covers the statistical analysis based on IPD data of KN087 in rrcHL indication. Database cutoff information is provided in Table 23.

Table 23 List of Protocols and DBLs Used in the Submission

MK Number	Protocol number	Database cutoff date
MK-3475	P087	21st March, 2019

5.3.2.2.2 KN204

The baseline characteristics used for the weighting, as descrived in section 0, are based on protocol 204 in the Hodgkin Lymphoma (HL) indication. Subjects from the pembrolizumab arm that are at least third line without SCT are considered. Database cutoff date information is provided in Table 24.

Table 24

List of Protocols and DBLs Used in the Submission

MK Number	Protocol number	Database Cutoff date
MK-3475	P204	16th Jan, 2020

5.3.2.3 Treatment arm and Design

5.3.2.3.1 KN087

Protocol 087 is multicentre, single arm, multi-cohort, nonrandomised Phase 2 trial of Pembrolizumab in subjects with refractory or relapsed classical Hodgkin lymphoma (rrcHL). Subjects meeting eligibility criteria were allocated to receive pembrolizumab 200 mg every 3 weeks (Q3W) within one of three cohorts, depending on their prior disease history and therapy:

- Cohort 1: subjects who failed to respond or progressed after auto-SCT therapy and relapsed or failed to respond after treatment with BV post auto-SCT.
- Cohort 2: subjects who were SCT-ineligible and relapsed after treatment with or failed to respond to BV.
- Cohort 3: subjects who did not respond or progressed after auto-SCT and had not received BV treatment post auto-SCT. These subjects could have received BV as part of primary treatment or salvage therapy.

5.3.2.3.2 KN204

Protocol 204 is a worldwide, open-label, multi-national, clinical trial of pembrolizumab as compared with brentuximab vedotin (BV) in subjects with relapsed or refractory classical Hodgkin lymphoma (cHL). Subjects were randomised in a 1:1 ratio to either receive pembrolizumab 200 mg, or 1.8 mg/kg BV.

The population of interest for KN204 are the subjects who are randomized to pembrolizumab and are at least third line with no prior stem cell transplant.

5.3.2.4 Statistical Methods

5.3.2.4.1 Re-weighting of patients

Data from KN087 (pembrolizumab, cohort 2) patients were re-weighted to match the average baseline characteristics of patients included in the KN204 study for the population of interest (subjects who are at least third line with no prior SCT).

Patients of KN087 with a similar baseline characteristic profile as KN204 will be up-weighted to compensate for their under-representation in the KN087 sample; patients with a different baseline characteristic profile as KN204 will be down-weighted to compensate for their over-representation in the KN087 sample.

We first need to estimate the weight w_i for each of the patients with available IPD from KN087 to match the observed aggregate data of KN204. The individual weights can be estimated using a logistic model as shown below – similarly as in matching methods using propensity score.[1]

$$w_i = exp(\alpha + x_i'\beta) \qquad (1)$$

To apply the method of moments to estimate the parameters of the propensity score model as shown in equation (1) we re-weight the IPD of KN087 patients to exactly match their mean baseline characteristics to the aggregate data available from KN204. $\hat{\beta}$ is estimated solving the following equation:

$$0 = \frac{\sum_{i:t_i=0} x_i \exp(x_i'\hat{\beta})}{\sum_{i:t_i=0} \exp(x_i'\hat{\beta})} - \overline{x_1}$$

X_i's contain the baseline characteristics, identified as prognostic factors

By applying these weights, the patient characteristics of KN087 match perfectly the aggregate data of KN204.

To assess the impact of re-weighting on the available statistical information in the IPD, an effective sample size (ESS) can be computed as the square of the summed weights divided by the sum of the squared weights. The maximum ESS occurs when all patients have equal weight. The occurrence of a small ESS might indicate that some patients receive extreme weights.

5.3.2.4.2 Variable selection

The objective of the weighting is to obtain patient populations that are as homogenous as possible across both studies. The objective is to include as many variables as possible, regardless of the level of imbalance across the compared studies. Nevertheless, a balance needs to be found as too many variables reduce the ESS. In the current analyses, the selection of prognostic factors were determined based on the baseline characteristics reported in both trials and clinical expertise. In addition, the feasibility assessment document as prepared in the context of MAIC KN204 for UK[below] was used as a tool to identify the prognostic factors of interest.

The following baseline characteristics were identified and selected as potential prognostic factors.

1. Disease status (refractory, relapsed)
2. Line of Therapy
3. Age (<65, ≥ 65)
4. ECOG (0 vs 1)
5. Prior radiation therapy
6. Sex

7. Presence of B symptoms
8. Region (US, ex-US)

The use of prior BV is an additional factor identified as an important prognostic factor. As all KN087 subjects of cohort 2 and none of KN204 (pembrolizumab arm, subjects who are at least third line with no prior SCT) had a use of prior BV it is not possible to weight for this factor for the analysis as presented in this report. In addition, after investigation the adjustment for the prognostic factor of bulky disease was not retained as the decrease to ESS (ESS N=17.43 after matching, see 5.3.6 Appendix 1) was considered too large compared to the clinical relevance of this parameter.

Analyses for two scenarios were retained and presented in this report:

Scenario 1:

- Disease status (refractory, relapsed), Line of Therapy (≤3, >3), Age (<65, ≥ 65 years), ECOG status (0 vs 1), Prior radiation therapy (Yes/No), Sex, Presence of B symptoms (Yes/No), Region (US, ex-US)

Scenario 2:

- Disease status (refractory, relapsed), Line of Therapy (≤3, >3), age (<65, ≥ 65 years), ECOG status (0 vs. 1)

To evaluate the impact of the different prognostic factors towards the ESS, an additional analysis adjusting for prior radiation therapy in addition towards factors considered in scenario 2 has been included (see 5.3.7 Appendix 2). As the ESS was close to Scenario 1, it was not retained as main analysis for consideration.

5.3.2.4.3 Baseline Characteristics

Descriptive summaries are provided for the prognostic factors used for the re-weighting process. Summaries are displayed for patients before and after weighting. The effective sample size (ESS; measure to assess the impact of re-weighting) is also displayed for KN087.

5.3.2.4.4 Overall Survial

The Overall Survival curve is estimated using the Kaplan-Meier method on the re-weighted patients of KN087, results are presented graphically.

5.3.3 RESULTS

The process of re-weighting to match the average baseline characteristics of patients included in the KN204 study might lead to a low effective sample size (ESS) considering the sample size of pembrolizumab in KN087 Cohort 2 (N=81). The analyses as part of this report should be interpreted with great caution.

5.3.3.1 Scenario 1

5.3.3.1.1 Baseline Characteristics

The baseline characteristics for the prognostic factors used for the weighting of patients enrolled in KN087 Cohort 2 for Scenario 1, before and after matching, are presented in Table 25 along with the baseline characteristics for the selected subset from KN204 KN204 (pembrolizumab arm, subjects who are at least third line with no prior SCT). It is expected that this scenario leads to biased results as not all prognostic factors were adjusted for.

5.3.3.1.2 Overall Survival

Unadjusted and adjusted (towards KN204) overall survival Kaplan-Meier curves are presented in **Error! Reference source not found.**.

5.3.3.2 Scenario 2

5.3.3.2.1 Baseline Characteristics

The baseline characteristics for the prognostic factors used for the weighting of patients enrolled in KN087 Cohort 2 for Scenario 2, before and after matching, are presented in **Error! Reference source not found.** along with the baseline characteristics for the selected subset from KN204 KN204 (pembrolizumab arm, subjects who are at least third line with no prior SCT). It is expected that this scenario is likely to be more biased as compared to Scenario 1.

5.3.3.2.2 Overall Survival

Unadjusted and adjusted (towards KN204) overall survival Kaplan-Meier curves are presented in **Error! Reference source not found.**.

The observed difference of the adjusted Kaplan Meier curve compared to Scenario 1 most likely indicates that some important prognostic factors are missing in Scenario 2.

5.3.4 TABLES AND FIGURES

5.3.4.1 Scenario 1

5.3.4.1.1 Baseline Characteristics

Table 25

Redacted

[redacted]*5.3.4.1.2 Overall Survival Curve*

Figure Redacted

[redacted]

5.3.4.2 Scenario 2

5.3.4.2.1 Baseline Characteristics

Table Redacted

[redacted]*5.3.4.2.2 Overall Survival Curve*

Figure Redacted

[redacted]

5.3.5 REFERENCES FOR MATCHING EXERCISE

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2 Feasibility Assessment – UK - Comparative efficacy of pembrolizumab and competing interventions for relapsed or refractory cHL – PRECISION HEOR - September 2020

5.3.6 Appendix 1

5.3.6.1 Baseline Characteristics

[redacted]

Tables Redacted

[redacted]5.3.7 Appendix 2

5.3.7.1 Baseline Characteristics

Table Redacted

5.3.7.2 Overall Survival Curve

Figure Redacted

References

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NICE National Institute for Health and Care Excellence

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 12 October 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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: • 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; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lymphoma Action
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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NICE National Institute for Health and Care Excellence

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

Consultation on the appraisal consultation document – deadline for comments 5pm on Tuesday 12 October 2021. Please submit via NICE Docs.

	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.
Example 1	We are concerned that this recommendation may imply that ……..
1	**We are concerned that this recommendation excludes people with the highest unmet need despite clear clinical benefits.** People with relapsed or refractory Hodgkin lymphoma who are not eligible for stem cell transplant have a poor prognosis. Treatment options at this point in the pathway are limited and typically include multi-agent chemotherapy or brentuximab vedotin. However, most people who are ineligible for stem cell transplant are also unable to tolerate multi-agent chemotherapy. Median progression-free survival after brentuximab vedotin in this population is less than 6 months and is also associated with significant adverse effects (in particular, peripheral neuropathy). Pembrolizumab offers significant benefits for these people (see below) and providing access to it earlier in the treatment pathway would provide better remissions early in the disease course, with immeasurable benefits to patients' lives. At many points in their pathway, patients tell us that the options available on the NHS are very limited and they feel that more effective, better tolerated treatment options should be available earlier.
2	**We feel the recommendation dismisses robust evidence of the efficacy of pembrolizumab in people with relapsed or refractory Hodgkin lymphoma who have not had brentuximab vedotin and are ineligible for stem cell transplant.** The KEYNOTE-204 trial has clearly demonstrated the benefits of pembrolizumab over brentuximab vedotin in this population, with median progression-free survival of 12.5 months compared to just 5.7 months. The committee itself concluded that "for people who had had at least 2 previous treatments with or without previous stem cell transplant, pembrolizumab improves progression-free survival." It is therefore inexplicable that those without a previous stem cell transplant have not been included in the recommendation. With such clearly demonstrated clinical effectiveness in people with relapsed or refractory Hodgkin lymphoma ineligible for stem cell transplant, to exclude this population from NHS funding is an unreasonable interpretation of the evidence and is not a sound and suitable basis for guidance to the NHS.
3	**We are concerned that this recommendation will disproportionately impact older people, who are less likely to be eligible for stem cell transplantation.** It may also lead to inequity of access between UK nations, pending the SMC's appraisal of pembrolizumab for a broader indication.
4	**We are dismayed and disillusioned that this recommendation ignores the patient view and gives no consideration to the 'intangible benefits' that patient organisations such as ours are asked to provide.** The most important factor patients with lymphoma rate in a treatment is effectiveness. There is clear evidence that pembrolizumab is more effective than brentuximab vedotin in people who are ineligible for a stem cell transplant. Patients feel that the progression-free survival benefit with pembrolizumab, combined with its generally favourable tolerability profile, offer an advantage over brentuximab vedotin that would have a significant impact on their quality of life. They also feel that, as an outpatient treatment with minimal pre-meds required, it is more convenient and less time consuming than many other options (for example, multi-agent chemotherapy), which again has the

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

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	potential to improve quality of life.
5	**We would like to reiterate that given the ongoing coronavirus pandemic, it is more important than ever to consider the potential benefits of effective, well tolerated treatments that can be safely administered in the outpatient setting without the need for frequent hospital attendance.** Pembrolizumab has the advantage of being able to be administered as a 6-weekly regimen, necessitating fewer hospital visits for patients and therefore a lower risk of hospital-acquired infection.
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies [ID1557]

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Comment number	Comments 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.
1	**Wording in Section 3.3, Page 7** *"The committee noted that the comparator treatment in KEYNOTE-204 is brentuximab vedotin and NICE recommends brentuximab vedotin for people who have had 2 or more previous treatments. It concluded that the trial results for this subgroup are generalisable to NHS practice."* In the KEYNOTE-204 trial, patients were permitted to receive up to 35 cycles of brentuximab vedotin, which is not generalisable to NHS practice or within its marketing authorisation. The EMA marketing authorisation for brentuximab vedotin in the treatment of relapsed or refractory Hodgkin lymphoma indicates patients should receive a maximum of 16 cycles of brentuximab vedotin.[1] Brentuximab vedotin is not approved for use beyond 16 cycles in any indication; the NHS Treatment Criteria, which outline the funding requirements in England, state that "*no more than 16 cycles of brentuximab may be administered per patient*".[2] However, 18 (12%) patients treated with brentuximab vedotin in the KEYNOTE-204 received greater than 16 cycles of brentuximab vedotin.[3] We request that the wording around generalisability of the KEYNOTE-204 trial should be updated to reflect the off-licence use of brentuximab vedotin that occurred in this trial.
2	**Wording in Section 3.4, Page 8** *"The clinical experts explained that pembrolizumab may not have the same relative benefit compared with brentuximab vedotin for people with and without previous transplant. This is because, in some people, the lymphoma will not have responded well enough to chemotherapy to allow a stem cell transplant and these people's condition may have a poorer response to further chemotherapy, including brentuximab vedotin. Pembrolizumab is an immunotherapy and is not expected to be affected by previous response to chemotherapy."* The current wording suggests that brentuximab vedotin should be considered in the same treatment group, in terms of outcomes and chemosensitivity, as standard chemotherapy. However, brentuximab vedotin is an anti-CD30 monoclonal antibody-drug conjugate, and is therefore considered a targeted chemotherapy. Clinical trial and real-world evidence is available to demonstrate the benefit of treatment with brentuximab vedotin in patients with poor responses to prior chemotherapy: • In the pivotal Phase 2 study of brentuximab vedotin for patients with relapsed or refractory classical Hodgkin lymphoma, 71% (72/102) of patients had primary refractory disease and the median number of prior chemotherapy regimens was 3.5. These patients therefore represented a heavily pre-treated population with a poor prognosis. Nevertheless, tumour reductions were observed in almost all patients (96/102, 94%) and the objective response rate was 75% (76/102 patients); therefore supporting the efficacy of brentuximab vedotin in patients with poor response to prior chemotherapy.[4] • A UK-wide retrospective study evaluating the efficacy of brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma in the transplant-naïve setting demonstrated an overall response rate of 56% following brentuximab vedotin treatment, with 61% of patients reaching stem cell transplant (SCT). This real-world study concluded that brentuximab vedotin is efficacious in this difficult-to-treat population, and confirmed its role in the treatment pathway as an effective bridge to SCT.[5] We request that the wording is updated to acknowledge that patients could achieve a response with brentuximab vedotin treatment, despite poor response to prior chemotherapy.

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3	**Wording in Section 3.6, Page 9–10** *"The committee concluded that in practice, pembrolizumab may increase the number of people who are able to have a stem cell transplant compared with brentuximab vedotin, but data are limited."* We agree that the data are limited on the number of patients in the KEYNOTE-204 who reach SCT following treatment with pembrolizumab or brentuximab vedotin. Initial results presented at American Society of Clinical Oncology (ASCO) in 2020 indicate that 30 (20.3%) patients treated with pembrolizumab and 34 (22.4%) patients treated with brentuximab vedotin received subsequent autologous SCT.[6] A minimal difference was similarly observed for patients reaching subsequent allogenic SCT: 14 (9.5%) patients treated with pembrolizumab and 13 (8.6%) patients treated with brentuximab vedotin.[6] A complete response tends to be considered by clinicians to offer the best chances of a successful SCT, compared to partial or no response. Given complete response by blinded independent central review in the KEYNOTE-204 trial was similar between treatment arms (37 [24.5%] patients treated with pembrolizumab and 37 [24.2%] patients treated with brentuximab vedotin),[3] we believe the statement in Section 3.6 that "*the proportions of people having a stem cell transplant after pembrolizumab will be greater than after brentuximab vedotin*" lacks supporting evidence. We request the wording to be updated to accurately reflect currently available evidence from the KEYNOTE-204 trial, of similar rates of complete response and subsequent transplant in both arms.
4	**Wording in Section 3.12, Page 14–15** *"This is because brentuximab vedotin is associated with higher rates of side effects, including neuropathy, which can be debilitating and persist for several months. The committee agreed that some side effects of brentuximab vedotin may persist after stopping treatment…"* We believe this statement around the side effects of brentuximab vedotin does not provide a true representation of the side effects of both medicines. Five (3%) patients in the brentuximab vedotin arm and one (1%) patient in the pembrolizumab arm experienced peripheral neuropathy at Grade 3–5 in the KEYNOTE-204 trial.[3] Although peripheral neuropathy can persist in some patients following treatment with brentuximab vedotin, the clinical experts noted during the Committee meeting that side effects of brentuximab vedotin can also improve with time in some patients. Clinical experts also raised that the immune-related adverse events associated with pembrolizumab cause significant morbidity for a minority of patients, and should therefore be considered. We request the wording of Section 3.12 to be updated to highlight the safety profiles of both pembrolizumab and brentuximab vedotin, to ensure the wording is balanced.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Dr Elizabeth Phillips, Clinical Expert; Consultant Haematologist at The Christie Hospital Manchester**]
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Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that excessive weight has been placed on transplant status in these recommendations. Keynote-204 is the largest and only randomised trial to compare 3L treatment in Hodgkin lymphoma, to my knowledge, and therefore represents the best available evidence in this setting. To make recommendations based on post-hoc subgroup analyses that exclude the majority of patients recruited to Keynote-204, without clear evidence demonstrating that the PFS significantly differs according to transplant status, seems spurious. PD-1 inhibitors are a major breakthrough in the treatment of Hodgkin lymphoma and are internationally recognised as a pivotal part of management pathways for relapsed and refractory disease. Response rates with these agents in Hodgkin lymphoma are higher than in any other malignancy. There is no clinical or biological rationale to support the premise that PD-1 inhibitors are only effective in patients who have had prior autologous stem cell transplant. However, these recommendations will remove this treatment option entirely for transplant-naïve patients if access is no longer available via the CDF, even though it may be curative for a subset of chemorefractory, patients when combined with subsequent transplantation.
2	I do not entirely agree that *'the prognosis for people with a previous stem cell transplant may be expected to be better than for people without a previous stem cell transplant and that the subsequent treatment options for these subgroups also differ'* significantly. The PFS benefit with pembrolizumab over brentuximab vedotin in Keynote-204 was marginally greater in the transplant-naïve population than for patients who had received prior transplant. There was no definite evidence of a difference in median PFS following pembrolizumab according to prior transplant status (12.5m versus 14.7m for patients without/with prior transplant; Kuruvilla *et al*, Lancet Oncology 2021). Whether a patient is considered 'transplant fit' has a much greater influence on both treatment pathways and prognosis. This group includes patients who have relapsed after autologous transplant and are eligible for subsequent allogeneic transplant, as well as transplant-naïve patients. For transplant-fit patients (presumed to represent the majority of patients in Keynote-204), it is unclear whether the prognosis is any better for those who have received a previous autologous stem cell transplant. Transplant-naïve patients are likely to be more chemorefractory, but potentially have more consolidation treatment options available, i.e. both autologous and allogeneic transplantation. Patients that are unfit for transplant, due to age and/or co-morbidities, form a minority of Hodgkin lymphoma patients and are usually treated with palliative intent. These patients certainly do have worse outcomes, partly due to reduced fitness and performance status, but also have the greatest clinical need. They usually experience greater toxicity with standard treatments, such as neuropathy with brentuximab vedotin, but not PD-1 inhibitors, and are ineligible for combination chemotherapy. Despite worse outcomes, there is a strong argument for early use of pembrolizumab in this population (as early as 2L, as in Keynote-204) given the lack of tolerable and effective alternative treatment options.
3	The ERG assumed that '*time on treatment should be largely similar to progression-free survival, because progression often triggers a change in treatment*.' This is often incorrect for transplant-fit patients. If fit for autologous or allogeneic transplant, responding patients will usually stop treatment before progression to receive transplant consolidation;

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	the majority of these patients will not subsequently relapse. Transplant-fit patients may also stop pembrolizumab before overt progression if clearly not responding to pursue alternative potentially curative treatment options, rather than continue with pembrolizumab for 24 months. In Keynote-204, out of 110 patients who discontinued pembrolizumab, only 59 had experienced disease progression (Kuruvilla *et al*, Lancet Oncology 2021).
4	'*The clinical experts explained that pembrolizumab may not have the same relative benefit compared with brentuximab vedotin for people with and without previous transplant. This is because, in some people, the lymphoma will not have responded well enough to chemotherapy to allow a stem cell transplant and these people's condition may have a poorer response to further chemotherapy, including brentuximab vedotin. Pembrolizumab is an immunotherapy and is not expected to be affected by previous response to chemotherapy.'* By this rationale, one might expect pembrolizumab to have a greater benefit compared with brentuximab in the transplant-naïve population than in patients who have received prior transplant. Furthermore, this is the population with the greatest unmet clinical need, and where the only access to PD-1 inhibition is with pembrolizumab via the CDF.
5	*'The clinical experts also highlighted the possibility that pembrolizumab treatment increases toxicity to allogeneic stem cell transplant and may reduce the effectiveness of autologous stem cell transplant but evidence on this is still emerging.'* There is no current evidence to suggest that the effectiveness of autologous stem cell transplant after pembrolizumab is reduced. Indeed, a number of recent publications have demonstrated that autologous transplant is highly effective in patients who have respond to immunotherapy with PD-1 inhibition: 1) Merryman *et al*, Blood Advances 2021;5(6):1648-1659, and 2) Herrera *et al,* Blood 2019;134(S1):239. It is therefore very attractive to use pembrolizumab as a bridge to autologous stem cell transplant for transplant-naïve patients. In such circumstances, the cost of pembrolizumab treatment will be lower (typically only 4-8 cycles of pembrolizumab are given prior to transplant) and the likelihood of cure will be much higher, therefore presumably the cost-effectiveness ratio will be more favourable.
6	It is not valid to use the data from Balzarotti et al 2016, which solely apply to 2L combination chemotherapy, to make any assumptions about overall survival after 3L chemotherapy as standard of care.

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Response to the ACD on Pembrolizumab for treating relapsed or refractory classical Hodgkin Lymphoma after stem cell transplant or at least 2 previous therapies.

Author: Dr Graham Collins
Clinical Expert on NICE STA committee
Representing: NCRI Hodgkin Lymphoma Study group (chair)
Oxford University Hospitals NHS Foundation Trust

Date of writing: 29/09/2021

Many thanks to the committee for their dedication and hard work in appraising the evidence for pembrolizumab use in this indication and producing the ACD. However, I am rather confused by the ACD as it excludes the group of patients most likely to benefit from the technology being appraised with no evidence to suggest they should be excluded.

The Keynote 204 study compared brentuximab with pembrolizumab in patients relapsing after stem cell transplant, or ineligible for stem cell transplant. 63% (almost 2/3) of patients in the study were ineligible for stem cell transplantation. This was mainly due to refractory disease but also included older and / or co-morbid patients who would never be eligible for a stem cell transplant irrespective of future remission status. Subgroup analysis showed no subgroup heterogeneity so there is no subgroup that can be said to be not benefiting from pembrolizumab compared with brentuximab.

I therefore find it very hard to understand why the ACD excludes patients who have not received a stem cell transplant. If this is the final conclusion it would have the following very unfortunate consequences:

1. Older, less fit patients would be forced to have less effective treatment prior to receiving a more effective treatment. This would be a bizarre clinical pathway. It is a general principle of cancer medicine to use more effective treatment first so the maximum benefit can be obtained for most patients (assuming toxicity is not an issue). Whilst I appreciate the number of elderly patients in Keynote 204 was fairly low, there is no trial evidence, or biological rationale, to suspect older patients will not benefit. I appreciate the committee do not in any way intend to discriminate based on age, but this decision could be interpreted by some in this way.

2. Fitter patients who are aiming for stem cell transplantation will again be made to receive less effective treatment (brentuximab) before receiving more effective treatment (pembrolizumab). Whilst there maybe reasons for offering brentuximab prior to pembrolizumab on a case by case basis, generally speaking the efficacy of the treatment dictates the preferential order of use assuming toxicity is roughly equal and there were no concerning toxicity signals of pembrolizumab seen in Keynote 204.

3. Denying access to pembrolizumab higher in the treatment pathway to those in most need of active, non-chemotherapy agents. Refractory patients have the highest risk of poor outcomes and also have the poorest responses to subsequent chemotherapy or

> brentuximab (which is chemotherapy). Early PD1 inhibition is of proven benefit compared with brentuximab in this setting.

I am also concerned that my comments and the comments of the other clinical expert may have been mis-represented. On page 9 and 10 of the ACD it says this:

> The clinical experts also highlighted the possibility that pembrolizumab treatment increases toxicity to allogenic stem cell transplant and may reduce the effectiveness of autologous stem cell transplant but evidence on this is still emerging.

Whilst pembrolizumab may increase toxicity to allogeneic stem cell transplantation, there is NO evidence that it may reduce the effectiveness of an autologous stem cell transplant. In fact the opposite may be true – there is some evidence PD1 inhibition may sensitise patients to subsequent chemotherapy making a subsequent autologous stem cell transplant more effective. Data is emerging but there is no data to suggest it makes it less effective.

In conclusion I would ask the committee to reconsider the decision to only include patients relapsing after a stem cell transplant.

Many thanks for taking the time to read this response and considering its contents.

Pembrolizumab for treating relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens [ID1557]

A Single Technology Appraisal

ERG Review of additional data submitted by the company

October 2021

Produced by

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This addendum is linked to ERG report Barnish MS, O'Toole B, Packman D, Muthukumar M, Matthews J, Shaw N, Rudin CE, Crathorne L, Melendez-Torres GJ.Pembrolizumab for treating relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens [ID1557]. Peninsula Technology Assessment Group (PenTAG), 2020.

1. INTRODUCTION

Pembrolizumab (ID1557) was recommended as a treatment option for treating relapsed or refractory classical Hodgkin lymphoma in people aged three years-plus, who are at least 3rd line with prior stem cell transplant (SCT+3L+). However, pembrolizumab was not recommended for use in patients who are at least 3rd line and have not had an autologous stem cell transplant (SCT-3L+).

Post ACD, the company has provided additional OS data for the SCT-3L+ population in an attempt to characterise the OS benefit that may be associated with pembrolizumab compared to brentuximab vedotin (BV; see Section 2). The company has also made several changes to the economic model as part of the revised analysis (a full list of model changes are outlined in Section 3, Table 1).

The ERG would like to highlight that the additional information provided by the company was extensive and that there was limited time to provide a full in-depth critique of every change made to the model. Therefore, following discussion with the NICE Technical Team, the ERG took a pragmatic approach by outlining and commenting on the key changes to the model and identifying the primary drivers of cost effectiveness, which may be of interest to the committee. Should further exploratory analysis be required to test any outstanding uncertainties, the ERG will complete following the second appraisal committee meeting as agreed.

2. ADDITIONAL CLINICAL EFFECTIVENESS DATA

The company provided additional clinical effectiveness data to address the SCT-3L+ population, for which pembrolizumab was not recommended by the Committee.

The company has fundamentally changed its approach to overall survival (OS). In the original company submission, the company did not provide OS data from the pivotal KEYNOTE-204 trial,[1,2] since the data were immature. This meant that no directly observed data comparing OS on pembrolizumab and BV that could be used to inform the economic model. The company made a conservative assumption of OS equivalence between pembrolizumab and BV. This was additionally motivated by the company's expectation of dominance.

However, as of this ACD response, this approach is no longer used. The company contends in the ACD response that it is 'highly likely' that pembrolizumab is associated with an OS benefit. This rationale is based on clinical expert opinion from the Committee meeting and the observation of a 'substantial' PFS benefit in the KEYNOTE-204 trial [redacted]. The ERG considered the claim of an OS benefit to be plausible. However, the claim that such an effect was 'highly likely' to be observed was considered an overstatement in the absence of directly observed data from the KEYNOTE-204 SCT-3L+ population, and not probative as to the magnitude of effect.

In order to identify suitable sources of evidence for OS in the SCT-3L+ population, the company instead reconsidered studies from the SLR presented in the original company submission. The company considered the Gopal et al. (2015)[3] and Balzarotti et al. (2016)[4] studies to not be suitable for the SCT-3L+ population in light of mismatches in the population. The ERG broadly agreed with this assessment.

The company profiled ten studies from this SLR considered for potential inclusion (ACD technical response, Table 1, pp.4-5). Additionally, since the company's search had excluded observational studies, the company conducted an additional search (ACD technical response, p.5) focused on such studies. The ERG thought that this search was adequate, but could have been more extensive, was limited by being conducted in only one database (PubMed) and did not include any relevant MeSH terms, as it was conducted on a free text only basis on titles and abstracts. However, the ERG noted that this search was cross-referenced against the search for TA540,[5] which the ERG considered would mitigate the risk of studies being missed, although

not in cases where the studies were more recent than the TA540 search. This observational studies search yielded two additional studies for consideration.[6,7]

The ERG conducted additional searches of Ovid MEDLINE and EMBASE to look for any further relevant observational studies, due to the limitations of the company's searches. Five references were identified that merited consideration. The ERG identified two further publications on KEYNOTE-087, for pembrolizumab. Chen et al. (2017)[8] represented an earlier analysis than the reference used by the company,[9] so the ERG was satisfied that it had nothing further to add. Zinzani et al. (2019)[10] is more recent, but is limited as it is only a conference abstract. In this study, median OS was not yet reached either in the overall population or the cohorts. The ERG would be interested in the company's rationale as to why this was not also a relevant source to consider for KEYNOTE-087. The ERG identified three references from two other studies[11-13] for BV. The Gillatt et al. (2020)[13] study was only presented as a conference abstract and this does not specify the number of lines of chemotherapy. Therefore, it does not appear to be a relevant source, based on the available information. However, the study by Viviani et al.[11,12] appears potentially relevant, as it considered patients who had failed on at least two prior therapies and where ASCT was not considered a treatment option. The company did not evaluate these references in its assessment of potential sources for pembrolizumab or for BV (the latter in Table 1 of the company's ACD technical response, pp.4-5).

The company selected KEYNOTE-087 (cohort 2) as the primary source of OS data for pembrolizumab (with the Systemic Anti-Cancer Therapy (SACT) database as a scenario analysis) and selected OS data from Eyre et al. (2017)[7] for BV. The ERG considered the data sources not to be ideal. However, the ERG did consider that the company's selection of these particular data sources was likely reasonable from among the sources considered by the company (noting the caveats above about potentially relevant sources not considered). The ERG noted and accepted the company's observation that patients in KEYNOTE-087 – who are SCT-4L+ – are likely to be older and sicker than the target population. The ERG considered this to be a conservative assumption with regard to the relative effectiveness of pembrolizumab and BV in terms of OS. The ERG agreed that the SACT database would not likely be considered preferable as a data source.

The company's primary means of comparing OS data for pembrolizumab and BV – given that the estimates came from different data sources – was a naïve comparison. Additionally, as a sensitivity analysis, the company conducted a matched-adjusted indirect comparison (MAIC).

The company was only in a position to perform matching and adjusting on the KEYNOTE-087 dataset, due to the availability of individual patient data. It is therefore important to take into consideration in the interpretation of the MAIC results that the relative OS effectiveness estimates produced on the matched-adjusted population are directly applicable only in the population of the Eyre et al. (2017)[7] trial, since the patient characteristics of KEYNOTE-087 are adjusted to match those of the Eyre et al. (2017)[7] trial. This is a key limitation of MAIC analysis. The ERG noted that the company selected variables of interest based on clinical advice and key stratification factors from the KEYNOTE-204 trial. The selected variables were considered to be prognostic of overall survival by the company. These are outlined in Table 6 of the company's ACD technical response. The ERG considered that the factors considered by the company appeared to be reasonable, but additionally noted that the company did not systematically address all the requirements for a MAIC analysis as outlined in NICE DSU TSD 18.[14]

Methodologically, based on NICE DSU TSD 18,[14] the ERG considered MAIC to be superior to a naïve unadjusted comparison, noting that both were associated with substantial limitations. However, in terms of applying these results in an economic model, the ERG noted with concern that the MAIC results provided estimates for OS in the population of Eyre et al. (2017),[7] while the PFS results were directly observed. This entails a population mismatch between OS and PFS. However, a mismatch would also occur using the naïve data from KEYNOTE-087, although this may not be as substantial as using data from outside the KEYNOTE trial series. The ERG noted that the Kaplan-Meier curves for adjusted and unadjusted data were parallel in Scenario 1 (which informs the company's modelling scenario that uses the MAIC data instead of the naïve unadjusted data) but that the unadjusted data offered a higher OS estimate than the unadjusted data (Company ACD technical response, Fig 12, p.83). Therefore, the ERG considered on balance that the OS estimate produced by the MAIC analysis is likely to be preferable to the naïve unadjusted comparison.

OS results for KEYNOTE-087 were presented graphically rather than as numerical estimates of central tendency and variation. Figure 12 in the company's ACD technical response (p.83) provided KM curves for OS in KEYNOTE-087 using both the naïve approach (the company base case) and data adjusted using MAIC analysis (the company's scenario 1, using the full set of prognostic factors). The unadjusted data provided a more optimistic picture of OS on pembrolizumab than the MAIC adjusted data. Consulting the published literature, median OS was not reached in the available data for KEYNOTE-087, although this was limited to 2-year follow up.[9] The Eyre et al. (2017)[7] study was able to report median OS – although this

information was not provided in the company's ACD technical response. The median OS in Eyre et al. (2017)[7] was 37.2 months. The absence of comparable summary statistics or a statistical test comparing the OS values on pembrolizumab using KEYNOTE-087 and on BV using Eyre et al. (2017)[7] problematized gaining a succinct picture of the relative effectiveness of the treatments. The clearest picture available of this came from the KM curves available in the economic model, although this is of course subject to the assumptions of the extrapolation used.

With regard to equity, the ERG noted the company's point that the treatment sequences able to be considered in this appraisal are not reflective of clinical practice, and that this may be disadvantageous to the SCT-3L+ subgroup. This situation arises since the costs of pembrolizumab in the fourth line setting cannot be included as this treatment is provided via the CDF rather than routine commissioning. In terms of the company's suggestion that it should be taken into account as a special consideration that pembrolizumab is displacing itself at a later point in the treatment pathway – i.e. the matter at hand is about the relative ordering of pembrolizumab and BV in the treatment pathway – the ERG understood the company's viewpoint, but considered that it was a matter for the Committee to determine whether and how to take into account this matter. Within the options provided, the ERG did not consider that subsequent treatment options were likely to be a major determinant of cost-effectiveness.

The most substantial concern that the ERG had was the absence of OS data from KEYNOTE-204, since OS is the primary measure used to assess the clinical effectiveness of cancer trials. The ERG was less concerned about the absence of KEYNOTE-204 OS data when the company took the conservative assumption of OS equivalence between pembrolizumab and BV. However, this has become more important now that the company asserts and models a quite substantial OS benefit for pembrolizumab. Based on the company's revised modelling approach, the modelled median OS for pembrolizumab was estimated to be [redacted], compared to [redacted] for BV (see Section 4.2). This makes it especially important to be confident that the magnitude of clinical benefit presented is realistic. The older and sicker population of KEYNOTE-087 Cohort 2 may lead to a conservative OS estimate. However, the limitations of naïve comparisons (the company's preferred approach) and MAIC analysis (the company's sensitivity analysis) mean that there is considerable uncertainty about the comparison between pembrolizumab and BV, and indeed whether the modelled estimate is indeed conservative.

The ERG's preference would be for SCT-3L+ OS data from KEYNOTE-204. In the original company submission, the key rationale presented for not using OS data from KEYNOTE-204 was that the OS data were immature and that median OS was not reached. However, the OS data presented from KEYNOTE-087 are also immature (OS exceeds [redacted] at the tail of the KM curve) and median OS was not reached. Noting that data from the pivotal trial would be more directly applicable to decision-making that data from alternative less relevant sources, the ERG considered that OS data from KEYNOTE-204 should have been used, either as the base case, a scenario or for validation purposes, or a stronger rationale provided as to why this was not possible, and why the alternative data sources provide a sufficiently robust basis for decision making. The ERG accepts that a fully mature analysis of OS data from KEYNOTE-204 is not yet available. It is unclear how the number of OS events in KEYNOTE-087 and KEYNOTE-204 compares – there are only [redacted] OS events to data in KEYNOTE-087, which is a very limited number of events upon which to base the primary analysis. The latest number of OS events for KEYNOTE-204 is not stated in the company's ACD technical response. This information would allow informed evaluation of the relative merits of immature OS data from KEYNOTE-087 and immature OS data from KEYNOTE-204 in informing decision making, and allow an assessment of how close the number of OS events is to the first pre-specified OS analysis point, and therefore when this may be reached. Nevertheless, an interim analysis of OS based on the data collected to date – even if the data are immature, may not be fully reliable in isolation, and thus would not constitute a primary analysis – would serve a useful purpose, at least to provide a useful validation exercise to assess the suitability of the KEYNOTE-087 data provided.

3. COMPANY REVISED MODEL INPUTS

The company made a number of changes to key model inputs (See Table 1 below)**.** The ERG noted that most of the changes to the model were not undertaken as a result of NICE committee preferences, but rather to support the cost effectiveness of pembrolizumab in the SCT-3L+ subgroup.

Table 1: Summary of model revisions

Assumption number	Assumption relates to	Input used in the company's original submission	Revised inputs for SCT-3L+	Was the revision based on NICE committee preferences?
1	Pembrolizumab OS data source	Gopal et al	KN-087 cohort 2 (unadjusted)	No. NICE did not state a preference for KN087 as the primary OS data source for pembrolizumab
2	Pembrolizumab OS parametric distribution	Log-normal	Log-logistic	No
3	BV OS data source	Gopal et al	Eyre (2017)	No
4	BV OS parametric distribution	Log-normal	Log-logistic	No
5	Subsequent treatment accrual	PD entry	PFS exits	No. NICE did not state a preference for the most appropriate approach to estimating subsequent treatment costs
6	Subsequent treatment proportion	ITT KN204 trial proportions: [redacted]% for pembrolizumab, [redacted]% for BV SCT-3L+ Clinical pathway: 100% for both arms	KN204 trial data	Unclear

7	Utility in the pembro PD health state	[redacted]	0.715	No. NICE preferred the ERG's assumption of equivalent utility values in the PD state, though acknowledged that this assumption may be conservative
8	PFS break point	52 weeks	26 weeks	No, but reflects ERG preference
9	ToT break point	80 weeks	26 weeks	No, but reflects ERG preference
10	Time horizon	40 years	50 years	No. However, a 50-year time horizon had been used previously in TA540.
11	BV discount	0%	0%	BV includes a cPAS. The ERG have therefore re-run the company's base case analysis (and select scenario analyses) using the appropriate discount rate for BV in a confidential appendix.
12	Subsequent treatments in BV arm	List of subsequent treatments and proportions based on KN204 data	Weighted average of multi-agent chemo (based on Eyre et al)	Yes, NICE stated a preference for multi-agent chemotherapy post BV. However, the ERG noted that there may be some uncertainty surrounding the list of treatments and proportions used by the company in this revised analysis

Abbreviations: BV, brentuximab vedotin; c PAS, comparator patient access scheme; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PFS, progression free survival; TA, technology appraisal; ToT, time on treatment

4. ERG COMMENTARY ON KEY MODEL REVISIONS

The ERG comments in brief on several key model revisions below: overall survival data, extrapolation of OS estimates, utility values, and subsequent treatment distributions and costs.

4.1. Overall survival data

The company explored alternative data sources to ascertain OS estimates for both pembrolizumab and BV. Balzarotti et al. (2016)[4] was not considered to be appropriate for use by the company, as patients were not considered to be representative of the current patient population under review (SCT-3L+). The company stated that '*the study was 'essentially a study of 2L chemotherapy used specifically as a bridge to SCT*.'

For BV, the company identified Eyre et al. (2017)[7] and Walewski et al. (2018)[15] as the most relevant sources, stating that both sources were used during the BV technology appraisals TA446[16] and TA524.[17] The company selected Eyre for use in the revised base case on the basis that it UK data based on the population of interest. Walewksi et al. (2018)[15] was used by the company in scenario analyses.

For pembrolizumab, the company opted to use OS data from KN087 (cohort 2).[9] The company identified a potential further data source for pembrolizumab OS data i.e. 2 year SACT data which was collected as part of the ongoing CDF agreement for TA540. However, these data were only considered in scenario analyses as the company noted that these patients were SCT-4L+ and were therefore older and sicker than the relevant patient population under consideration (SCT-3L+) i.e. patients had a higher median age and lower ECOG performance status than patients in KN204. The company stated that it was not possible to match adjust the SACT data on pembrolizumab given that the KN204 population were 3L+ and the SACT population were all 4L+.

The ERG has several concerns surrounding the company's revised approach to modelling OS (see Section 4.2 below).

4.2. Extrapolation and validity of modelled OS estimates

OS for pembrolizumab was derived from KN087 Cohort 2 (unadjusted) and OS for BV was based on Eyre et al. The company provided scenario analysis results whereby KN087 data were adjusted to match patient characteristics in KN204, however results were relatively insensitive to using these adjusted data (see Section 5.3). Due to the lack of long-term OS data,

the company extrapolated OS using parametric curves. The ERG noted that median survival was reached for BV in Eyre et al (37.2 months), however median OS was not reached in KN087, therefore data were considered immature.

As part of their survival analysis, the company generated one-piece models, which were fitted on top of KM curves. Graphical representations of these fits were provided alongside AIC/BIC statistics. The company selected the Log-logistic distribution for use in both BV and pembrolizumab arms (see **Error! Reference source not found.** and **Error! Reference source not found.** below for AIC/BIC statistics, and Figure 1 for modelled curves). The company justified this curve selection for use in both arms on the basis that the Log-logistic appeared to be the most plausible fit for BV, which had more data available.

Table 2: AIC/BIC statistics for KN087 OS

Model	AIC	BIC	Average
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 3: AIC/BIC statistics for BV OS in Eyre (2017)

Model	AIC	BIC	Average
Exponential	466.1	468.7	467.4
Weibull	468.0	473.1	470.5
Log-normal	467.0	472.2	469.6
Log-logistic	465.8	470.9	468.3
Gompertz	467.7	472.9	470.3
Generalized Gamma	468.4	476.2	472.3
Gamma	467.8	473.0	470.4

Key: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; BV, brentuximab vedotin; OS, overall survival

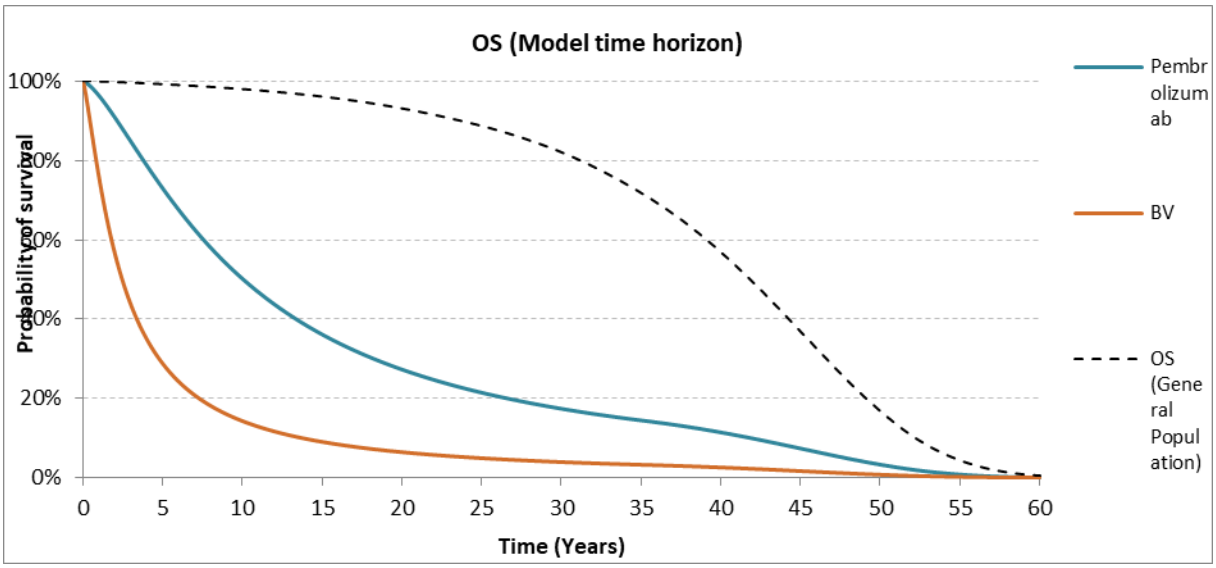
The ERG noted that there was minimal difference in AIC/BIC scores between the different parametric functions, and that the exponential function provided the lowest average AIC/BIC scores in both KN087 (Cohort 2) and Eyre et al. The company, however, did not consider the exponential function to be relevant for consideration on the basis that the exponential curve is

associated with a monotonic hazard of death across time. The ERG noted that the company did provide sensitivity analysis using alternative parametric functions to model OS in both treatment arms, including the exponential function. However, results were not sensitive to these analyses.

Based on the company's revised modelling approach, the modelled median OS for pembrolizumab was estimated to be [redacted], compared to [redacted] for BV. The ERG considered that modelled pembrolizumab OS estimates are subject to uncertainty (given that estimates are based on immature data). The ERG acknowledged that Cohort 2 patients in KN087 were 4th line, older and generally in poorer health than those in KN204, which may suggest that modelled OS estimates for pembrolizumab could be underestimated. However, the ERG would advise against accepting this as a settled point, as OS data from KN204 are required to support this.

For completeness, the ERG sought clinical opinion to comment on the plausibility of the company's modelled OS estimates. Based on feedback to the ERG, modelled pembrolizumab median OS lacks plausibility, as patients are expected to remain on pembrolizumab for a relatively short duration (<1 year), and are unlikely to achieve complete response. Thus, the committee should interpret these results with caution. The company presented a scenario analysis whereby SACT data were used to estimate OS for pembrolizumab. The ERG noted that results were not sensitive to this analysis. To explore uncertainty surrounding OS, the ERG conducted scenario analyses whereby pembrolizumab not associated with an OS gain compared to BV (see Table 8 and Table 9).

Figure 1: Modelled OS for pembrolizumab and BV



4.3. Pembrolizumab utility value for PD health state

As part of this revised analysis, the company opted to derive the PD utility value for pembrolizumab from Nivolumab (SMD ID1240/17), which reported a PD utility value of 0.715. The company stated that using the PD value from Nivolumab may be a more credible approach than assuming equivalent PD values and noted that (SMD ID1240/17) provides some evidence to support the use of differential utility values for use in the post progression health state.

It should be noted that NICE preferred the ERG's assumption of equivalent utility values in the PD state, though acknowledged that this assumption may be conservative. Thus, the ERG maintained that the using equivalent utility values within the PD state for both pembrolizumab and BV remains the appropriate base case approach, though the committee may wish to consider using the nivolumab PD utility value in the pembrolizumab PD health state, as part of a scenario analysis.

Based on the scenario analyses results provided by the company, the ERG noted that assuming equivalent PD utility values in both arms did not have a large impact on results. To explore uncertainty, the ERG conducted a combined scenario analysis, which used equivalent PD utility values in both arms and alternative OS sources. Results were not very sensitive to this (see Table 8 and Table 9).

4.4. Approach to subsequent treatments

The company provided updated results using two alternative approaches to modelling subsequent treatment (estimating subsequent treatment costs). For Approach 1, the probability of patients receiving subsequent treatment in both treatment arms was based on the proportion of patients entering the PD health state per cycle. This approach is referred to as the PD entry approach and aligns with the company's original base case approach to estimating subsequent treatment costs.

Approach 2 differs slightly in that the probability of patients receiving subsequent treatment in both treatment arms is based on the proportion of patients exiting the PFS state per cycle. This approach is referred to as the PFS exit approach and aligns with the company's revised base case approach to estimating subsequent treatment costs. The ERG noted that the model was not sensitive to the use of either approach i.e. estimating the proportion of patients receiving subsequent treatments using the PD entry or PFS exit approach, does not have a major impact on the ICER.

It should be noted that for each approach, the company provided two scenario analyses whereby the probability of receiving subsequent treatments was set to be equal between arms and anchored to the observed probability in the pembrolizumab arm (MSD approach 1) or in the BV arm (MSD approach 2). Based on exploratory analyses conducted by the ERG, it was noted that results were sensitive when MSD approach 2 was combined with a removal of OS benefit for pembrolizumab (see Table 8 and Table 9).

The ERG sought clinical opinion to determine the proportion of patients likely to receive subsequent treatment in practice. Based on the response received it was noted that approximately 30% of patients would receive subsequent treatment in both treatment arms. The ERG noted that this proportion is considerably lower than the proportion estimated by the company and the ERG, and is likely to represent the variation seen within local practice. As an exploratory analysis, the ERG conducted a scenario analysis, which assumed 30% of patients would receive subsequent treatments in both arms (see Table 10).

4.5. Subsequent treatment costs in the BV arm

Overall, the ERG considered that the list of subsequent treatments and associated proportions used in the BV arm is not a key cost effectiveness driver in the current revised model. This is because there are fewer patients in the PD health state in the BV arm compared to the

pembrolizumab PD health state i.e. the modelled median OS for patients in the BV arm was substantially lower than modelled median OS for patients in the pembrolizumab arm ([redacted] vs [redacted] respectively). Changing the list of subsequent treatments and proportions post BV therefore does not have a material impact on results.

Given that OS may be a key determinant of subsequent treatment cost, the ERG has undertaken scenario analyses using alternative OS sources i.e. OS from either Eyre et al. (2017)[7] or Gopal et al. (2015)[3] is applied to both treatment arms (see Table 8 and Table 9).

4.5.1. Company's approach to estimating subsequent treatments

The list of subsequent treatments and proportions used in the model for patients that progress after BV has changed (see Table 12 in the company response document). The company stated that treatments have now been updated to reflect the distribution of chemotherapy used in the post-progression population within Eyre et al. (2017),[7] on the basis that the NICE committee preferred a multi-agent chemotherapy approach rationale (as opposed to using bendamustine only). The ERG agreed with the company's decision to use multi-agent chemotherapy in this revised analysis, as this reflects NICE committee preferences. However, the ERG noted several minor points surrounding the company's revised approach, which warrant further comment.

First, the list of treatments used by the company are reflective of patients receiving 2nd line therapy (as outlined in Table 11, p.474 in Eyre et al[7]). The ERG therefore considered that these treatments may not be reflective of patients who are SCT-3L+. The company also appear to have altered the proportions based on clinical input, as proportions did not match those in Table 11. Furthermore, the ERG identified that Table 11 presented a list of treatments used by patients post BV and pre SCT which included bendamustine only, gemcitabine-based, carmustine, etoposide, cytarabine, melphalan (Mini BEAM), dexamethasone, etoposide, chlorambucil, lomustine (DECC), radio therapy and others. It was unclear why these treatments were not used in the model to estimate subsequent treatment costs post BV.

The ERG sought clinical expert opinion to elicit the most relevant treatments subsequent treatments used in practice (see Table 4 below for a list of treatments and estimated proportions). The ERG did not conduct a scenario analysis using these estimates, given that this would require the ERG to make further assumptions, for instance with respect to cycle length for each subsequent treatment, thereby increasing uncertainty. Furthermore, as

discussed previously, modelling these subsequent treatments is unlikely to have a material impact on results.

Table 4: Subsequent treatments post BV (based on expert opinion to the ERG)

Subsequent treatments post BV	%
Bendamustine alone	20
Bendamustine with gemcitabine and vinorelbine	15
Gemcitabine with cisplatin or carboplatin and dexamethasone	20
ChlVPP	15
VEEP	15
BEAM/LEAM + autograft	15

Key: BEAM, B – carmustine (BiCNU ®) + E – etoposide + A – cytarabine (Ara-C ®) + M – melphalan; BV, brentuximab vedotin; ChlVPP, Chlorambucil with Vinblastin, Procarbazine and Prednisolone; ERG, Evidence Review Group; LEAM, L – lomustine + E – etoposide + A – cytarabine (Ara-C ®) + M – melphalan; VEEP, vincristine, epirubicin, etoposide, and prednisolone

5. COMPANY REVISED BASE CASE RESULTS AND SENSITIVITY ANALYSES RESULTS

5.1. Base case results

In the company's revised analysis, pembrolizumab resulted in an ICER of £10,133 compared to BV, based on an incremental QALY gain of [redacted] and an incremental cost of [redacted] (see Table 5). See Table 1 for a list of the revisions made to the company's base case in order to produce these results.

Table 5: Revised base case results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	--	--	--	--
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

5.2. Probabilistic sensitivity analysis results

The ERG has conducted a probabilistic sensitivity analysis (PSA) to explore the impact of parameter uncertainty on the company's revised base case results, reported in Table 6 with scatterplot in Figure 2 and cost-effectiveness acceptability curve in Figure 3. The PSA was run for 1,000 iterations.

Table 6: Revised PSA results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (probabilistic)							
Pembrolizumab	[redacted]			--	--	--	--
BV	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

Figure 2: PSA scatterplot (pembrolizumab vs BV)

Key: QALY, quality adjusted life year.

Figure 3: Cost-effectiveness acceptability curve

Key: QALY, quality adjusted life year.

5.3. Scenario analyses results

The company conducted a large number of scenario analyses; see Table 7 below. However, the ERG noted that these could be categorised as follows;

- Alternative PFS modelling method for both arms (Piecewise 52 weeks)
- Alternative PFS distributions for both arms (Weibull, Exponential, Gompertz, Generalised Gamma)
- Incorporate treatment waning (cycle specific hazard for pembro OS curve set to be equal to the BV curve, waning from Year 5 and equal to BV by Year 7)
- Alternative OS distributions for both arms (Exponential, Weibull, Gompertz, Lognormal)
- Alternative OS data for pembrolizumab (OS data from KN087 full cohort, OS data from KN087 CDF)
- Alternative OS modelling method for BV (OS data from Walewski et al)
- Alternative OS data source for pembrolizumab (KN087 CDF) and alternative OS distribution for pembrolizumab (Exponential, Weibull, Gompertz, Lognormal, Log logistic and Generalised Gamma)
- OS data from KN087 match adjusted to reflect KN204 and alternative OS distributions (Exponential, Weibull, Gompertz, Lognormal, Log logistic)
- Alternative ToT modelling approach for both pembro and BV, using a piecewise approach with break-points at week 52 or 80, rather than at Week 26
- Alternative ToT distributions (Exponential, Weibull, Gompertz, Log logistic and Generalised Gamma)
- Mean health state utility for pembrolizumab PD set to be the same as BV
- Exclude age related disutility
- Proportion of patients receiving subsequent treatments based on PFS exits (all patients, MSD Scenario 1 and 2)

- Proportion of patients receiving subsequent treatments based on PD entry (all patients, MSD Scenario 1 and 2)
- Reduction in BV acquisition cost by 50%
- Combination scenarios

The ERG considered the scenario analyses presented by the company to be extensive (perhaps overly so given the short time frame for review and the need for clear concise presentation). Results were mostly insensitive to scenario analyses, with ICERs remaining relatively robust/static. Based on the analyses below, pembrolizumab was no longer cost effective at a cost effectiveness threshold of £30k for a combined scenario analysis which assumed that the drug acquisition cost for BV was reduced by 50%, 100% of patients received subsequent treatment, pembrolizumab OS based on CDF data, equal utility in the PD health state for both pembro and BV, subsequent treatment approach based on PD entry, treatment waning for OS and an alternative source for BV OS (Walewski et al[15]). The ERG considered this scenario to include several conservative assumptions and therefore may be overly pessimistic.

Table 7: Company scenario analyses results

Scenario	Pembro Total Costs	BV Total Costs	Pembro Total QALYs	BV Total QALYs	ICER
Basecase	[redacted]	[redacted]	[redacted]	[redacted]	£10,133
PFS modelling method - Pembrolizumab: Piecewise (52 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	£8,577
PFS modelling method – BV: Piecewise (52 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	£10,332
PFS distribution (Both Pembrolizumab and BV): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£11,286
PFS distribution (Both Pembrolizumab and BV): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£11,013
PFS distribution (Both Pembrolizumab and BV): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£6,675
PFS distribution (Both Pembrolizumab and BV): Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£10,248

PFS distribution (Both Pembrolizumab and BV): Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£9,188
Apply treatment waning years 5-7	[redacted]	[redacted]	[redacted]	[redacted]	£10,282
OS distribution (BV-Eyre, Pembro-KN087 cohort 2): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£9,932
OS distribution (BV-Eyre, Pembro-KN087 cohort 2): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£10,187
OS distribution (BV-Eyre, Pembro-KN087 cohort 2): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£11,626
OS distribution (BV-Eyre, Pembro-KN087 cohort 2): Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	£10,057
OS modelling method - Pembrolizumab: KN087 Full cohort	[redacted]	[redacted]	[redacted]	[redacted]	£10,108
OS modelling method - Pembrolizumab: KN087 CDF Data	[redacted]	[redacted]	[redacted]	[redacted]	£9,499
OS modelling method - UK comparator: Walewski OS data	[redacted]	[redacted]	[redacted]	[redacted]	£10,262
OS distribution (BV-Eyre, Pembro-KN087 CDF): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£10,271
OS distribution (BV-Eyre, Pembro-KN087 CDF): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£9,624
OS distribution (BV-Eyre, Pembro-KN087 CDF): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£8,094
OS distribution (BV-Eyre, Pembro-KN087 CDF): Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	£9,417
OS distribution (BV-Eyre, Pembro-KN087 CDF): Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£9,499
OS distribution (BV-Eyre, Pembro-KN087 CDF): Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£5,672
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£9,158
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£9,136
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£9,307
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	£10,114
OS distribution (BV-Eyre, Pembro-KN087 Adjusted): Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£9,233
ToT modelling approach - Piecewise (52 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	£9,856

ToT modelling approach - Piecewise (80 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	£10,032
ToT distribution (Both Pembrolizumab and BV): Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£10,014
ToT distribution (Both Pembrolizumab and BV): Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£10,157
ToT distribution (Both Pembrolizumab and BV): Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£9,971
ToT distribution (Both Pembrolizumab and BV): Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£10,085
ToT distribution (Both Pembrolizumab and BV): Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£10,132
Mean health state utility value for PD state (Pembrolizumab): Assume same as BV	[redacted]	[redacted]	[redacted]	[redacted]	£10,515
Age related disutility: FALSE	[redacted]	[redacted]	[redacted]	[redacted]	£9,622
Prop receive 2nd line therapy (KEYNOTE-204 SCT-3L+ cohort): PFS events that are Progressions	[redacted]	[redacted]	[redacted]	[redacted]	£13,119
Prop receive 2nd line therapy (KEYNOTE-204 SCT-3L+ cohort):Probability of receiving subs trt on a PFS event (MSD Scenario Analysis 1)	[redacted]	[redacted]	[redacted]	[redacted]	£10,311
Prop receive 2nd line therapy (KEYNOTE-204 SCT-3L+ cohort):Probability of receiving subs trt on a PFS event (MSD Scenario Analysis 2)	[redacted]	[redacted]	[redacted]	[redacted]	£12,425
% of receiving Pembro as subsequent treatment in BV arm as 100%	[redacted]	[redacted]	[redacted]	[redacted]	£5,595
Prop receive 2nd line therapy_Based on PD entry: MSD Base case	[redacted]	[redacted]	[redacted]	[redacted]	£8,547
Prop receive 2nd line therapy_Based on PD entry: all patients	[redacted]	[redacted]	[redacted]	[redacted]	£10,787
Prop receive 2nd line therapy_Based on PD entry: MSD Scenario Analysis 1	[redacted]	[redacted]	[redacted]	[redacted]	£8,661

Prop receive 2nd line therapy_Based on PD entry: MSD Scenario Analysis 2	[redacted]	[redacted]	[redacted]	[redacted]	£10,236
BV discount arbitrary 50%	[redacted]	[redacted]	[redacted]	[redacted]	£12,663
BV discount arbitrary 50%, PD health state costs discounted by 20%	[redacted]	[redacted]	[redacted]	[redacted]	£11,388
BV discount arbitrary 50%, PD health state costs discounted by 50%	[redacted]	[redacted]	[redacted]	[redacted]	£9,476
BV disc. 50%, PD entry	[redacted]	[redacted]	[redacted]	[redacted]	£12,024
BV disc. 50%, PD entry, all patients get subs trt,	[redacted]	[redacted]	[redacted]	[redacted]	£13,152
BV disc. 50%, PD entry, all patients get subs trt, pembro OS from CDF (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£14,490
BV disc. 50%, PFS exit, subs trt from trial, pembro OS from CDF (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£16,208
BV disc. 50%, PFS exit, all patients get subs trt, pembro OS from CDF (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£19,117
BV disc. 50%, PFS exit, all patients get subs trt, pembro OS from CDF (log-log), treatment waning OS	[redacted]	[redacted]	[redacted]	[redacted]	£22,349
BV disc. 50%, PFS exit, all patients get subs trt, pembro OS from CDF (log-log), treatment waning OS, equal PD utility	[redacted]	[redacted]	[redacted]	[redacted]	£23,394
BV disc. 50%, PFS exit, all patients get subs trt, pembro OS from CDF (log-log), treatment waning OS, equal PD utility, BV OS from Walewski (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£32,107
BV disc. 50%, PD entry, all patients get subs trt, pembro OS from CDF (log-log), treatment waning OS, equal PD utility, BV OS from Walewski (log-log)	[redacted]	[redacted]	[redacted]	[redacted]	£21,336
Weighted average pembro OS – KN-087 and CDF data	[redacted]	[redacted]	[redacted]	[redacted]	£9,272
Pembro 2nd line in BV arm, No OS benefit (OS = Eyre for both arms)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Key: BV, brentuximab vedotin; CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; ToT, time on treatment

6. MODEL VALIDATION

The ERG checked the implementation of the changes outlined in the company's updated economic analysis technical report: the addition of new OS data options, the changes related to subsequent treatment usage, the addition of PD health state utility options, the update of the approach for the treatment waning scenario for OS and the addition of the granulocyte colony-stimulating factor (G-SCF) costs. The ERG did not identify errors in the implementation of these changes that were consequential to the base-case cost-effectiveness results.

The ERG noted, however, that in the OS treatment waning scenario, the post-waning adjusted survival rate (Trace Pembro sheet, Column BN) was found to be higher than that without waning (Trace Pembro sheet, Column BE), which was somewhat counterintuitive. Nevertheless, as the results for the OS treatment waning scenario do not differ greater from those of the base case, this potential discrepancy is unlikely to have a significant impact.

The committee should be aware that extensive validation of the company's revised model was not possible given the time constraints.

7. ERG ADDITIONAL ANALYSES

The company conducted a large number of scenario analyses in order to ascertain the impact of different assumptions on the cost-effectiveness results. The ERG noted that a single scenario was explored with the assumption of equal OS in both arms, which also involved pembrolizumab as the subsequent treatment in the BV arm. In all analyses prior to the ACD, no OS benefit was assumed, with exception of a scenario in which a predictive equation was used to link OS with PFS. Gopal et al. (2015)[3] was used as the source of OS for both arms in the company's previous base case analysis, while Eyre et al. (2017)[7] was used as the source of OS in the BV arm in the company's revised analysis. The ERG has therefore explored two sets of additional scenarios with the assumption of equal OS in the two arms: one set using Eyre et al.[7] (Table 8Table 8) and another using Gopal et al.[3] (Table 9).

Following advice from a clinical expert, the ERG have also explored a scenario with 30% of patients receiving subsequent treatment in both treatment arm (Table 10). In this scenario, subsequent treatments costs were accrued based on PFS exits, with OS from the KEYNOTE-87 Cohort 2[9] data for pembrolizumab and from Eyre et al. (2017)[7] for BV, as in the company's revised base case analysis.

ICERs in all analyses were generally static, with the exception of those analyses combining subsequent treatment assumptions from MSD Scenario 2 and equal OS. When both of these assumptions were included, layering on equal PD state utility values did not generate a substantial impact on the ICER.

Table 8: ERG scenario results with OS from Eyre et al.

Scenario	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
OS from Eyre et al. for both arms	Pembrolizumab	[redacted]	4.36	[redacted]	[redacted]	--	[redacted]	[redacted]
	BV	[redacted]	4.36	[redacted]	[redacted]	0.00	[redacted]	[redacted]
	Pembrolizumab	[redacted]	4.36	[redacted]	[redacted]	--	[redacted]	[redacted]

Scenario	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Equal mean HSUV for PD state ([redacted]) for both arms, with OS from Eyre et al. for both arms	BV	[redacted]	4.36	[redacted]	[redacted]	0.00	[redacted]	[redacted]
MSD subsequent treatment scenario 1, with OS from Eyre et al. for both arms	Pembrolizumab	[redacted]	4.36	[redacted]	[redacted]	--	[redacted]	[redacted]
	BV	[redacted]	4.36	[redacted]	[redacted]	0.00	[redacted]	[redacted]
MSD subsequent treatment scenario 2, with OS from Eyre et al. for both arms	Pembrolizumab	[redacted]	4.36	[redacted]	[redacted]	--	[redacted]	[redacted]
	BV	[redacted]	4.36	[redacted]	[redacted]	0.00	[redacted]	[redacted]
MSD subsequent treatment scenario 2, with equal mean HSUV for PD state ([redacted]) & OS from Eyre et al. for both arms	Pembrolizumab	[redacted]	4.36	[redacted]	[redacted]	--	[redacted]	[redacted]
	BV	[redacted]	4.36	[redacted]	[redacted]	0.00	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

Table 9: ERG scenario results with OS from Gopal et al.

Scenario	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	Lys	QALYs	Costs (£)	LYs	QALYs	
OS from Gopal et al. for both arms	Pembrolizumab	[redacted]	4.93	[redacted]	[redacted]	--	[redacted]	[redacted]
	BV	[redacted]	4.93	[redacted]	[redacted]	0.00	[redacted]	[redacted]
Equal mean HSUV for PD state ([redacted]) for both arms, with OS from Gopal et al. for both arms	Pembrolizumab	[redacted]	4.93	[redacted]	[redacted]	--	[redacted]	[redacted]
	BV	[redacted]	4.93	[redacted]	[redacted]	0.00	[redacted]	[redacted]
MSD subsequent treatment scenario 1, with OS from Gopal et al. for both arms	Pembrolizumab	[redacted]	4.93	[redacted]	[redacted]	--	[redacted]	[redacted]
	BV	[redacted]	4.93	[redacted]	[redacted]	0.00	[redacted]	[redacted]
	Pembrolizumab	[redacted]	4.93	[redacted]	[redacted]	--	[redacted]	[redacted]

Scenario	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	Lys	QALYs	Costs (£)	LYs	QALYs	
MSD subsequent treatment scenario 2, with OS from Gopal et al. for both arms	BV	[redacted]	4.93	[redacted]	[redacted]	0.00	[redacted]	[redacted]
MSD subsequent treatment scenario 2, with equal mean HSUV for PD state ([redacted]) & OS from Gopal et al. for both arms	Pembrolizumab	[redacted]	4.93	[redacted]	[redacted]	--	[redacted]	[redacted]
	BV	[redacted]	4.93	[redacted]	[redacted]	0.00	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

Table 10: ERG scenario results with 30% subsequent treatment in both arms

Scenario	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	Lys	QALYs	Costs (£)	LYs	QALYs	
Subsequent treatment proportion of 30% for both arms	Pembrolizumab	[redacted]	10.39	[redacted]	[redacted]	--	--	[redacted]
	BV	[redacted]	4.36	[redacted]	[redacted]	6.03	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

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Pembrolizumab for treating relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens [ID1557]

A Single Technology Appraisal

ERG additional analysis post-ACM2

Appendix

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Produced by

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1. INTRODUCTION

The purpose of this addendum is to provide additional scenario results for the SCT-3L+ population, requested by NICE post ACD 2. The ERG has provided the following threshold analyses:

- Option 1: OS from Eyre et al. with a HR applied to the pembrolizumab arm, and equal mean HSUV for the PD state ([redacted]) for both arms (Table 1)
- Option 2: OS from KN-087 cohort-2 with a HR applied to the BV arm, and equal mean HSUV for the PD state ([redacted]) for both arms (Table 2)

As per correspondence with NICE, the ERG consider option 1 to be more appropriate for decision making.

2. ERG ADDITIONAL ANALYSES

As noted previously, the ERG has provided two threshold analyses for NICE's consideration:

- Option 1: OS from Eyre et al. with a HR applied to the pembrolizumab arm, and equal mean HSUV for the PD state ([redacted]) for both arms (Table 1).
- Option 2: OS from KN-087 cohort-2 with a HR applied to the BV arm, and equal mean HSUV for the PD state ([redacted]) for both arms (Table 2).

Fitting exponential distributions to the OS data from KN-087 cohort-2 and from Eyre et al. for the pembrolizumab and BV arms respectively resulted in a hazard ratio of [redacted]. We note as well that to construct the relevant curves, we applied a hazard ratio to a parametric distribution that is not from the proportional hazards family. While this is not strictly appropriate from a mathematical perspective, we regard that this is the most relevant option for this exploratory analysis.

Table 1: ERG scenario results for Option 1

OS Hazard Ratio Pembrolizumab vs BV	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
HR = 1.00	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.95	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.90	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS Hazard Ratio Pembrolizumab vs BV	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
HR = 0.85	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.80	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.75	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.70	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.65	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.60	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.55	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 0.50	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BV, brentuximab vedotin; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life year; OS, overall survival; QALY, quality adjusted life year; vs, versus

Table 2: ERG scenario results for Option 2

OS Hazard Ratio BV vs Pembrolizumab	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
HR = 1.00	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.05	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.10	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.15	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.20	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.25	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.30	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.35	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.40	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.45	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS Hazard Ratio BV vs Pembrolizumab	Arm	Total			Incremental			ICER (£/QALY)
		Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR = 1.50	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BV, brentuximab vedotin; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life year; OS, overall survival; QALY, quality adjusted life year; vs, versus

3. REFERENCES

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