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

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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

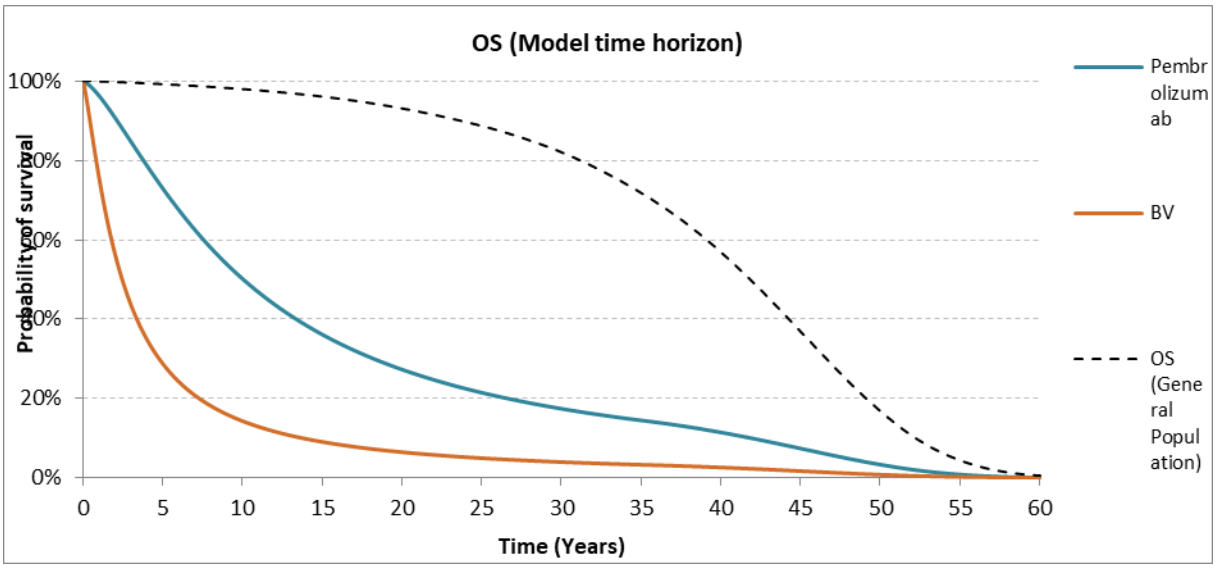
The ERG noted that there was minimal difference in AIC/BIC scores between the different parametric functions, and that the exponential function provided the lowest average AIC/BIC scores in both KN087 (Cohort 2) and Eyre et al. The company, however, did not consider the exponential function to be relevant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

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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