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

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]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from MSD

2. **Clarification questions and company responses**
   a. Appendix

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Lymphoma Action

4. **Evidence Review Group report** prepared by PenTAG

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from** MSD
   a. Additional evidence

7. **Technical engagement response and statements from experts:**
   a. Dr Elizabeth Phillips Senior Clinical Lecturer and Honorary Consultant Haematologist – clinical expert, nominated by the Royal College of Physicians
   b. Dr Graham Collins, Consultant Haematologist - clinical expert, nominated by the MSD and the Royal College of Physicians
   c. Stephen Scowcroft – patient expert, nominated by Lymphoma Action *(*see item 3a)*

8. **Technical engagement responses from consultees and commentators:**
   a. Takeda

9. **Evidence Review Group TE clarification questions and company response.**

10. **Evidence Review Group critique of company response to technical engagement** prepared by PenTAG

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

September 2020

File name	Version	Contains confidential information	Date
MSD submission cHL Pembrolizumab (ID1557) Document B (AICCIC)	**V1.0**	**Yes**	**30/09/2020**

Contents

Tables and figures

FIGURES

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication:

[redacted]

Please see Table 1 below for a summary of the National Institute for Health and Care Excellence (NICE) decision problem.

Table 1. The Decision Problem

	Final scope issues by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with relapsed or refractory classical Hodgkin lymphoma who have received: • autologous stem cell transplant or • at least one prior therapy when autologous stem cell transplant is not a treatment option	As per final scope	Not applicable
Intervention	Pembrolizumab	As per final scope	Not applicable
Comparator(s)	Brentuximab vedotin For people who did not have at least two prior therapies when autologous stem cell transplant is not a treatment option • Chemotherapy regimens	As per final scope	Not applicable
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • proportion receiving subsequent stem cell transplant • adverse effects of treatment • health-related quality of life.	As per final scope	[redacted]

Subgroups to be considered	If the evidence allows the following subgroups may be considered • people who could have a subsequent stem cell transplant (autologous or allogeneic) if they respond to treatment • people for whom stem cell transplant is contraindicated because of comorbidities	Post-hoc efficacy analyses for PFS and ORR are presented for 3 subpopulations; second line subjects with no prior stem cell transplant (“SCT-2L”) subjects who are at least third line with no prior SCT (“SCT-3L+”) subjects who are at least third line with prior stem cell transplant (“SCT+3L+”)	Patients who were considered ineligible for auto SCT included patients who could have a subsequent stem cell transplant if they respond to treatment and patients whom stem cell transplant is contraindicated because of comorbidities and age.

B.1.2 Description of the technology being appraised

The draft of the summary of product characteristics (SmPC) and European Public Assessment Report (EPAR) has been included in Appendix C.

The technology being appraised (Pembrolizumab) us described in Table 2.

Table 2. Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) is a monoclonal antibody (mAb) of the IgG4/kappa isotype designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity[1].
Marketing authorisation/CE mark status	Pembrolizumab currently has a marketing authorisation (MA) covering the following indications: KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection. KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults. KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

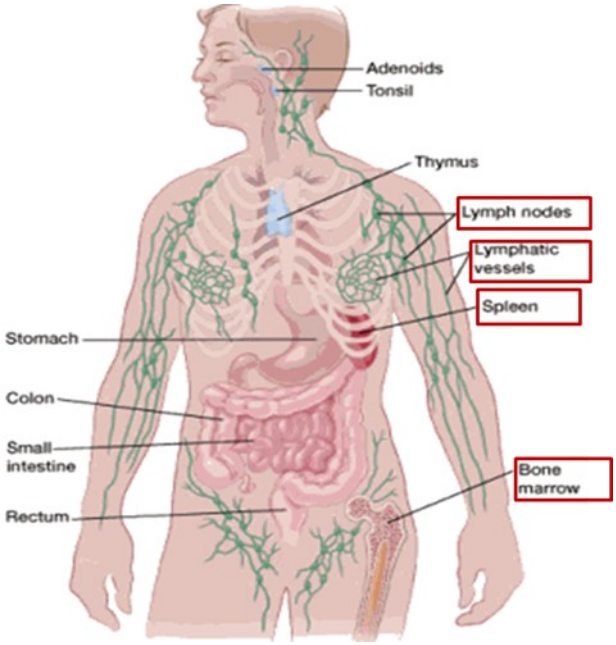
	KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥1[2] KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication for which this submission relates to is: [redacted]
Method of administration and dosage	The recommended dose of KEYTRUDA as monotherapy is either 200 mg every 3 weeks Pembrolizumab 200 mg every three weeks (Q3W); intravenous (IV) infusion (up to a maximum duration of 2 years)[1].
Additional tests or investigations	Not applicable for the proposed indication.
List price and average cost of a course of treatment	The list price for Pembrolizumab is £2,630 per 100mg vial. The mean treatment duration per patient in KEYNOTE-204 was [redacted] Based on 200mg every 3 weeks this equates to an average cost of a course of treatment at list price of £ (no. of cycles[3])x cost per cycle) ([redacted] x (2 x 2630)) = [redacted]
Patient access scheme (if applicable)	[redacted] Therefore, the NHS net discount price for all indications; will be at a [redacted] discount on MSD's list price, plus VAT where applicable. Therefore, the 200mg administration of pembrolizumab will cost [redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

Lymphomas are cancers of the lymphatic system, which forms an important part of the immune system and are classified into two main subtypes: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma. Hodgkin's lymphoma accounts for around 20% of all diagnosed lymphomas[4]. Hodgkin Lymphoma is a rare, localised or disseminated, malignant proliferation of cells of the lymphoreticular system, occurring mostly in lymph node tissues, spleen, liver, and bone marrow[5] (Figure 1). The World Health Organisation (WHO) classifies HL into two distinct groups, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). NLPHL accounts for approximately 5% of all cases of HL and cHL accounts for the remaining 95% of HL cases[6]. In people with cHL the cancer cells are characterized by the presence of an abnormal type of B lymphocyte called Reed-Sternberg cells (RSC). RSC are distinctive large cells and are often multinucleated with a peculiar morphology and an unusual immunophenotype, that does not resemble any normal cell in the body[7]. The remaining tumour microenvironment contains T-cells, non-malignant B cells, granulocytes, eosinophils and stromal cells[8].

Classical Hodgkin lymphoma may be classified by subtype, stage at diagnosis, as well as prognostic group. Patients may also be classified as relapsed/refractory (R/R) if they have progressed (are refractory to initial treatment) or have relapsed following initial response to first-line treatment. There are four cHL subtypes: nodular sclerosis HL (most common), mixed cellularity HL (mostly seen in people with HIV infection), lymphocyte-rich HL and lymphocyte-depleted HL[8] .

Figure 1. Lymphatic system of the human body



Source: Adapted from American Cancer Society[8]
**Red boxes indicate primary cHL sites*

Patients with cHL may present with a variety of symptoms, including swelling of lymph nodes, B symptoms (fever without infection, night sweats and unexplained weight loss), persistent fatigue, loss of appetite, and pruritus[9, 10]. The cause of cHL is unknown, but genetic susceptibility and environmental associations (e.g. radiation therapy, or chemotherapy; infection with Epstein-Barr virus, Mycobacterium tuberculosis) play a role. The risk is slightly increased in individuals with certain types of immunosuppression (post-transplant patients taking immunosuppressants), congenital immunodeficiency disorders and certain autoimmune disease[5].

During 2017, there were 2,145 new cases of HL in the UK; this equates to an age standardized rate of 3.2 (95% CI 3.3-3.5) per 100,000 persons. Surveillance data within the UK (England, Scotland, and Wales), as reported by Cancer Research UK, shows that the incidence of HL follows a bimodal age distribution, with the first peak in young adults (20-24 years) and the second in older males and females (75-79 years). Overall, 41% of HL cases are females and 59% are in males[11]. Based on the observed trends, it is expected that incidence rates may increase by 5% in the UK population overall between 2014 and 2035; this equates to 4 cases per 100,000 persons[11]. It should be noted that age standardized incidence rates in the UK could

also rise by 9% in males between 2014 and 2035 (5 cases per 100,000), whilst decreasing by 1% in females during the same time period (3 cases per 100,000 persons)[11].

Stages of cHL are divided into limited stage (stage I and II), where the cancer is confined to the primary site or the regional lymph nodes, and advanced stage (stage III and stage IV), where the cancer has metastasized[12]. The staging of HL is commonly based on the Lugano Classification System which is a modified version of the Ann Arbor staging system. Patients with early stage cHL are stratified into favorable and unfavorable which can be used to guide treatment[13]. However, data on the staging of HL not routinely available for the UK due to inconsistencies in the collecting and recording of staging data[14].

Survival data for patients diagnosed with HL (England 2013-2017) is 90.6%, 82.2%, and 75% at years 1, 5 and 10, respectively[15]. However, these values should be interpreted with caution and are likely to be substantially different in the context of the later lines of therapy being considered within this submission document. The literature suggests that patients who are described as R/R have poor prognosis compared with their counterparts who respond to therapy. In patients with R/RcHL, time to initial relapse is a key prognostic factor. Patients who relapse within 12 months of treatment show significantly lower survival compared with patients who relapse >12 months after finishing treatment[16]. A single retrospective trial of 81 patients with R/R disease showed that of those who failed ASCT, 96% had relapsed within two years. In addition, the trial reported worse outcomes for those patients who relapsed within 6 months compared with those who relapsed after 6 months with a median OS of 15 month and 36 months, respectively[17].

First-line treatments for cHL is curative chemotherapy with or without radiotherapy. Typically, the chemotherapy regimens are ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and escalated BEACOPP (escalated dose bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) with positron emission tomography-driven strategies used to improve patient outcomes[18]. First line treatment has a high success rate with most patients achieving good outcomes[13]. However, relapses occur in a small proportion of patients with early stage disease (favorable) and are more common in patients with advanced disease[19]. Up to 5-10% patients do not respond (primary refractory) to initial therapy and 10-30% will relapse after achieving initial remission[20].

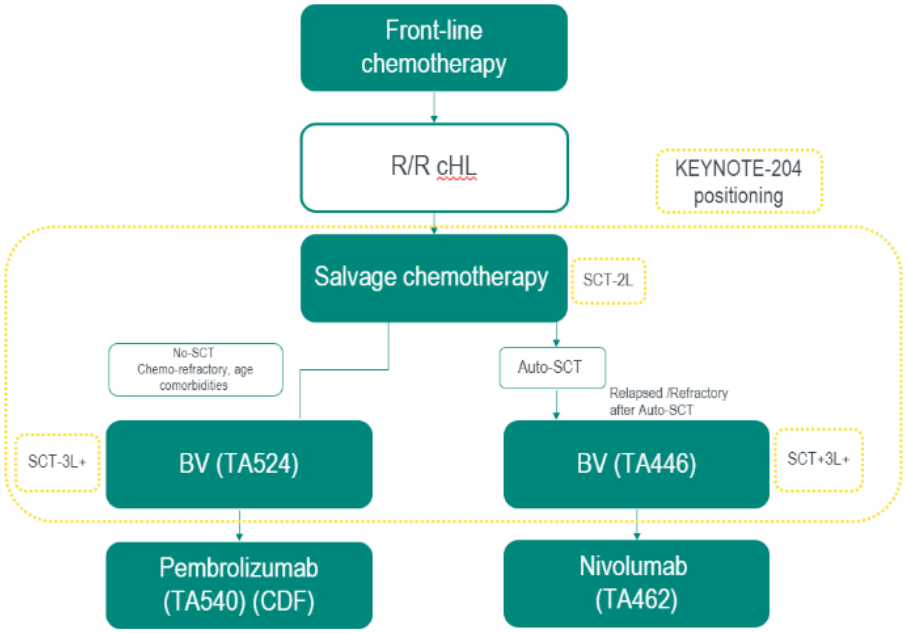
Following failure of front-line chemotherapy, a patient's ASCT eligibility status is determined based on age or presence of comorbidities. In patients who are not fit for ASCT due to advanced age, presence of comorbidities, or poor performance status treatment primarily

involves second-line, non-cross-resistant chemotherapies. In patients who are fit for transplant, treatment primarily consists of salvage regimens with the aim to reduce the tumour burden, assess chemosensitivity, achieve an acceptable remission status, and mobilise stem cells to improve the likelihood of transplant success. Following treatment with second-line chemotherapy, a patient's eligibility status is again reassessed:

- In patients who remain chemo-sensitive to second-line regimens, high dose therapy (HDT)/ASCT is considered to be the standard of care
- Patients who lack chemosensitivity following second-line salvage treatment are deemed ASCT-ineligible
- For patients who fail or are ineligible for ASCT, the goal of treatment is long-term disease control[19, 21].

Figure 2 presents the current treatment algorithm in the UK and where the current indication for KEYNOTE-204 would fit within this pathway.

Figure 2. Treatment Algorithm Summary for Patients with R/RcHL



Prognostic factors in cHL are important in determining likely outcomes of patients and the selection of the appropriate therapy. Optimising treatment for patients with cHL varies according

to number of factors such as clinical staging, age, presence of multiple sites of disease, toxicity and long-term effects[20].

In England, the NICE pathway details that the following therapies are recommended as treatment options for cHL:

- BV is recommended as an option for treating CD30-positive HL in adults with R/R disease[22], only if:
    - they have already had ASCT or
    - they have already had at least 2 previous therapies when ASCT or multi-agent chemotherapy are not suitable and,
    - the company provides BV according to the commercial agreement.
- Nivolumab is recommended, within its marketing authorization, as an option for treating R/RcHL in adults after ASCT and treatment with BV[23]
- Pembrolizumab is recommended, within its marketing authorization, for use within the Cancer Drugs Fund as an option for treating R/RcHL in adults who have had BV and cannot have ASCT[24].

B.1.4 Equality considerations

MSD does not envisage any equality issues with the use of pembrolizumab for the treatment of R/R cHL who have received: ASCT or at least one prior therapy when ASCT is not a treatment option.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

A systematic literature review (SLR) was performed to identify randomized clinical trials (RCTs), non-randomized clinical trials, and single arm studies that evaluated survival, response, safety and patient-reported outcomes for patients with R/RcHL. As the manufacturer of pembrolizumab, MSD is aware of all relevant clinical trials for pembrolizumab in this indication.

The full SLR methodology and results are presented in Appendix D1.1. Overall, 98 publications representing 45 unique clinical trials (38 single-arm trials, 6 randomized controlled trials, and 1 comparative trial) met the PICOS criteria for the UK-specific review. Ten trials reported outcomes for patients that had failed ASCT prior to receiving study treatment. Four trials reported outcomes for patients that were ineligible for ASCT prior to receiving study treatment. 38 studies reported outcomes for patients with a mix of ASCT eligibility status. Safety outcomes and QoL were not consistently reported across the studies.

The clinical effectiveness evidence presented in this submission is focused on the KEYNOTE-204 the pivotal phase III open label RCT assessing the safety and efficacy of pembrolizumab in patients with R/RcHL, see Table 3. Furthermore, the clinical effectiveness evidence in this submission is supplemented by the KEYNOTE-087 and KEYNOTE-051 studies (Table 4 & Table 5). KEYNOTE-087 is a phase II open label, single arm trial. Whilst KEYNOTE-051 is a phase I/II open label, single arm trial assessing the safety and efficacy in pediatric patients. KEYNOTE-204, KEYNOTE-087 and KEYNOTE-051 safety and efficacy data form the basis of the regulatory application to the EMA for marketing authorisation of [redacted]

While the 3 trials listed above are still ongoing. Data from [redacted] data cut-off date [redacted]), [redacted]; data cut-off date [redacted] and [redacted]; data cut-off date [redacted] of KEYNOTE-204, KEYNOTE-087 and

KEYNOTE-051 respectively form the evidence base for this submission as described through Sections B2.2 to B2.6.

The final analysis for PFS of KEYNOTE-204 will occur after [redacted] PFS events are observed, whilst the first protocol-specified analysis for OS is to occur at [redacted] events, which is not yet reached. Hence, this submission will not present OS data from KEYNOTE-204. OS is expected to be reached in [redacted]. The evidence presented for KEYNOTE-087 within this submission is based on an [redacted] analysis, further analysis will only focus on safety. The final analysis of KEYNOTE-051 is not expected to occur before [redacted] and will provide safety and efficacy and safety analyses for participants with melanoma, MSI-H solid tumours, and R/RcHL

In addition, the study data from KEYNOTE-204 form the clinical evidence base included in the cost-effectiveness model and analyses. Considering the lack of OS data from KEYNOTE-204, additional evidence from published literature was also explored Section B.3.3

Table 3. Clinical effectiveness evidence KEYNOTE-204[3]

Study	Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma				
Study design	Multi-national, Randomised, Open-label Study				
Population	Subjects with relapsed or refractory classical HL who have received at least 1 prior multi-agent chemotherapy regimen.				
Intervention(s)	Pembrolizumab 200 mg administered intravenously (IV) on Day 1 of each 3-week cycle for up to 35 cycles.				
Comparator(s)	Brentuximab Vedotin (BV) 1.8 mg/kg (maximum 180 mg per dose) IV on Day 1 of each 3-week cycle for up to 35 cycles.				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	KEYNOTE-204 is one of the pivotal clinical trials in this indication				
Reported outcomes specified in the decision problem	• progression-free survival • response rates • proportion receiving subsequent stem cell transplant • adverse effects of treatment • health-related quality of life.				
All other reported outcomes	• progression-free survival secondary				

Table 4. Clinical effectiveness evidence KEYNOTE-087[25]

Study	A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) (Ref)				
Study design	Multi-centre, single-arm, multi-cohort, non-randomized				
Population	Cohort 1 - participants with rrcHL who failed to achieve a response or progressed after autoSCT and relapsed after treatment with, or failed to respond to treatment with, BV post-auto-SCT Cohort 2 – participants unable to achieve a CR or partial PR to salvage chemotherapy and did not receive autoSCT, but relapsed after treatment with, or failed to respond to treatment with BV Cohort 3 – participants who failed to achieve a response to, or progressed after, auto-SCT, and had not received BV after auto-SCT and did or did not, receive BV as part of primary treatment or salvage treatment.				
Intervention(s)	Pembrolizumab 200 mg administered intravenously (IV) on Day 1 of each 3-week cycle for up to 35 cycles.				
Comparator(s)	N/A this was a single arm trial				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	KEYNOTE-087 is one of the supporting clinical trials in this indication				
Reported outcomes specified in the decision problem	• overall survival • progression-free survival • response rates • proportion receiving subsequent stem cell transplant • adverse effects of treatment				

Table 5. Clinical effectiveness evidence KEYNOTE-051[26]

Study	Phase I/II Study of Pembrolizumab (MK-3475) in Children With Advanced Melanoma or a PD-L1 Positive Advanced, Relapsed or Refractory Solid Tumour or Lymphoma (KEYNOTE-051)				
Study design	Multi-center, single-group assignment, open-label				
Population	Pediatric participants with multiple tumour types enrolled into one of the following tumour cohorts: Advanced melanoma R/RcHL (cohort of interest for this submission) Advanced, R/R MSI-H solid tumour PD-L1-positive advanced, R/R solid tumours or other lymphoma				
Intervention(s)	Pembrolizumab 200 mg administered intravenously (IV) on Day 1 of each 3-week cycle for up to 35 cycles.				
Comparator(s)	N/A this was a single arm trial				
Indicate if trial supports application for marketing authorisation	Yes	*X*	Indicate if trial used in the economic model	Yes	
	No			No	*X*
Rationale for use/non-use in the model	As agreed at the decision problem meeting and detailed in the decision problem form submitted by MSD; MSD do not determine it to be necessary to include this cohort in the cost effectiveness model. Please refer to the explanation below for further information.				
Reported outcomes specified in the decision problem	• overall survival • progression-free survival • response rates • adverse effects of treatment				

KEYNOTE-051 was not used to populate the economic model but is included in sections B 2.2 to B.2.6. The results of this study provide clinical evidence for the use of pembrolizumab in the [redacted]. This study was not included in the economic model in light of the policy set out by NHS England (NHSE), which states; NHSE will fund requests for medicines for children within a specialised service that are approved in adults by a NICE TA when one of the three following criteria are met and all of the conditions listed apply:

1 The medicine has a license for use in children and both the indication for use and the age of the child fall within those specified in the adult license or

2 The medicine is listed in the BNF for Children with a recommended dosage schedule relative to the age of the child or

3 The child is post pubescent[27].

Furthermore, in a previous appraisal of pembrolizumab (TA540) the NHSE submission stated, "The license for pembrolizumab is limited to adults. Relapsed/refractory HL is also seen in patients aged less than 18 years and there is no biological reason why any NICE recommendation as to the clinical and cost effectiveness of pembrolizumab for its indication in HL would not be valid in pediatric and teenager populations. In this situation, NHS England would ensure that the funding of pembrolizumab within baseline commissioning is extended to relevant patients under the age of 18 years." Hence, it is reasonable to assume the same position will be taken for this current situation.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. KEYNOTE-204 trial overview

KEYNOTE-204 is an ongoing, randomized, open-label, phase III study of pembrolizumab compared with BV in subjects with R/RcHL. To be eligible, participants were to have R/R cHL and received at least 1 prior multi-agent chemotherapy regimen. Prior treatment with BV or a BV-containing regimen was allowed, provided the participants had responded (partial or complete response) to the BV or BV-containing regimen.

A total of 300 participants were to be enrolled. As of the data cut-off date for this report, 304 participants were randomized (151 in the pembrolizumab arm and 153 in the BV arm).

After a 28-day screening period, approximately 300 eligible participants were randomly assigned in a 1:1 ratio to receive 1) 200-mg pembrolizumab intravenously on Day 1 every 3 weeks or 2) 1.8 mg/kg BV intravenously on Day 1 every 3 weeks. All trial treatments were administered on an outpatient basis. Treatments will continue for up to 35 cycles per subject or until documented disease progression as described in the International Working Group (IWG) response criteria [Cheson, 2007] [28] by blinded independent central review, unacceptable adverse event(s), (AE)s, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons.

The end of the trial for all currently randomized participants will occur when the OS analysis has been triggered and all participants have had the opportunity to receive at least 35 cycles of treatment (or discontinued for progression or other reason).

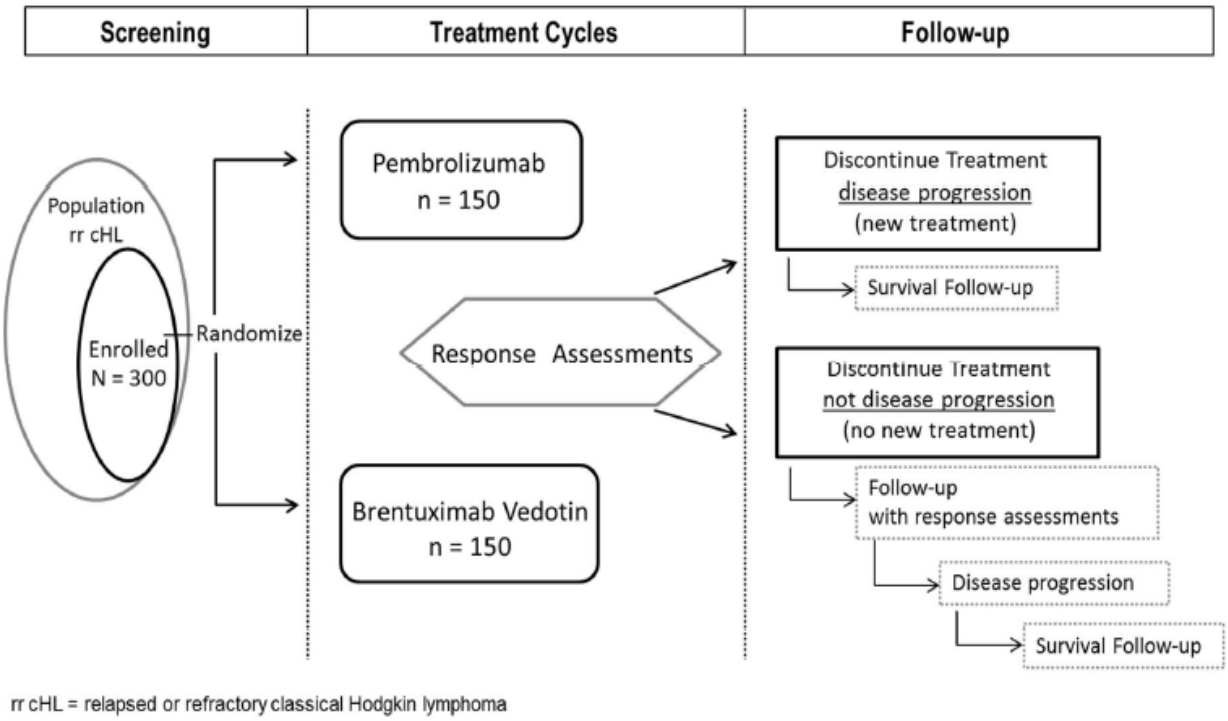
Treatment allocation/randomization was stratified according to the following factors:

1. Prior auto-SCT

At least 100 subjects to be randomized within each level of stratification factor 1; i.e., at least 100 subjects with prior auto-SCT and at least 100 subjects without prior auto-SCT.

2. Hodgkin lymphoma status after frontline therapy: primary refractory disease versus relapsed disease less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy.

Figure 3. KEYNOTE-204 Study Design



rr cHL = relapsed or refractory classical Hodgkin lymphoma

KEYNOTE-204 Key Inclusion Criteria

In order to be eligible, the participant was to have:

1. Been willing and able to provide written informed consent for the trial and adhere to trial procedures. The participant may also provide consent for Future Biomedical Research. However, the participant may participate in the main trial without participating in Future Biomedical Research.

2. Been ≥18 years of age on day of signing informed consent.

3. Relapsed (disease progression after most recent therapy) or refractory (failure to achieve CR or PR to most recent therapy) cHL

4. Responded (achieved a CR or PR) to BV or BV-containing regimens, if previously treated with BV. (Note: Prior treatment with BV or BV-containing regimens was allowed, but not required.).

5. Measurable disease defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral computed tomography (CT) scan or combined CT/positron emission tomography (PET) scan. Minimum measurement was to be >15 mm in the longest diameter or >10 mm in the short axis.

6. Been able to provide an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival (>60 days) or newly obtained (within 60 days) biopsy at Screening (Visit 1).

7. An ECOG PS of 0 or 1.

8. Demonstrated adequate organ function as defined in the study protocol all screening laboratory tests were performed within 7 days of treatment initiation.

KEYNOTE-204 Key Exclusion Criteria

Participants were excluded from the study if they had:

1. A diagnosis of immunosuppression or were receiving systemic steroid therapy (exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

2. A prior monoclonal antibody within 4 weeks prior to first dose of therapy in the study or who had not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.

3. Prior chemotherapy, targeted small molecule therapy, or radiation therapy including investigational agents within 4 weeks prior to study Day 1 or who had not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to a previously administered agent.

4. Undergone prior allo-SCT within the last 5 years.

5. A known additional malignancy that was progressing or required active treatment in the last 3 years.

6. Known active central nervous system metastases and/or carcinomatous meningitis.

7. Participants with previously treated brain metastases could participate provided they were radiologically stable, clinically stable, and did not require steroid treatment for at least 14 days prior to the first dose of trial treatment.

8. Active autoimmune disease that required systemic treatment in the past 2 years.

9. A history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.

10. Eligibility for allogenic or autologous stem cell transplantation per investigator assessment.

KEYNOTE-204 Settings and Locations where data were collected

The study was multinational and was conducted at centers in including USA, UK, Japan, Italy, Sweden, Australia, Poland and Russia. The full list of participating centers is in the study protocol (ref).

Trial drugs and concomitant medication

Table 6. Trial Treatments in KEYNOTE-204[3]

Drugs	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Pembrolizumab	200mg	1 dose on Day 1 of every 3 weeks = 1 cycle	IV infusion	Up to 35 cycles per subject	Investigational
BV	1.8mg/kg (maximum 180mg per dose)	1 dose on Day 1 of every 3 weeks = 1 cycle	IV infusion	Up to 35 cycles per subject	Comparator

Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria were not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and intravenous

medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF. A subject may remain on anticoagulation therapy as long as the PT or PTT is within therapeutic range of the intended use of anticoagulants. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs.

Prohibited Concomitant Medications or Therapy

Subjects are prohibited from receiving the following therapies during the Screening and Treatment portions of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Granulocyte macrophage-colony stimulating factor (GM-CSF); however, granulocyte colony stimulating factor (G-CSF) can be used to treat neutropenia in subjects receiving BV.

-Note: Prophylactic use of growth factors in lieu of dose reduction of BV is not allowed. Therapeutic use of G-CSF in subjects with febrile neutropenia or serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., is at the investigator's discretion, consistent with the American Society of Clinical Oncology (ASCO) guidelines and current prescribing information.

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or BV
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus of Calmette-Guerin (BCG), and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
- Glucocorticoids for any purpose other than to treat toxicities as indicated in the event of contrast infusion reactions, or transfusion reactions.

- Potent/strong CYP3A4 inhibitors and inducers; or P-gp inhibitors in subjects receiving BV
- Potent/strong CYP3A4 inhibitors or inducers, for example: Ketoconazole, a potent CYP3A4 inhibition, Rifampin, a potent CYP3A4 inducer,
- P-glycoprotein (P-gp) inhibitors, for example: Ketoconazole, Clarithromycin, Quinidine, Verapamil.

The investigator should use his/her medical judgment when a subject presents with a medication not on the list or call the Sponsor for clarification.

Subjects who, in the assessment by the investigator and after consultation with the Sponsor, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this trial.

KEYNOTE-204 outcomes used in the economic model or specified in the NICE scope

KEYNOTE-204 Primary Objectives and Hypotheses

Objective (1): To compare PFS as assessed by blinded independent central review, according to the IWG response criteria [Cheson, 2007] [28] between treatment arms, including clinical and imaging data following ASCT or allogeneic stem cell transplantation (allo-SCT).

Hypothesis: Pembrolizumab prolongs PFS as assessed by BICR, using IWG response criteria compared to treatment with BV, including clinical and imaging data following ASCT or allo-SCT.

KEYNOTE-204 Secondary Objectives and Hypotheses

Objective: To compare PFS-secondary (PFS2), as assessed by blinded independent central review (BICR), according to the IWG response criteria [Cheson, 2007] [28] between treatment arms, excluding clinical and imaging data following ASCT or allo-SCT.

Hypothesis: Pembrolizumab prolongs PFS2 as assessed by BICR, using IWG response criteria compared to treatment with BV, excluding clinical and imaging data following ASCT or allo-SCT.

Objective: To compare the objective response rate (ORR) as assessed by BICR according to the IWG response criteria [Cheson, 2007] [28] between treatment arms.

Hypothesis: Pembrolizumab has a higher ORR as assessed by BICR according to the IWG response criteria compared to treatment with BV.

Objective: To evaluate the complete remission rate (CRR) as assessed by BICR according to the IWG response criteria [Cheson, 2007] [28] between treatment arms.

Objective: To evaluate PFS, CRR, and ORR as assessed by the investigator according to the IWG response criteria [Cheson, 2007] [28] by treatment arm.

Objective: To evaluate the safety and tolerability of pembrolizumab.

KEYNOTE-204 Exploratory Objectives

Objective: To determine the duration of response (DOR) as assessed by BICR and investigator assessment according to the IWG response criteria [Cheson, 2007] [28] by treatment arm.

Objective: To compare the changes from baseline between the treatment arms in health-related quality-of-life assessments using the EORTC QLQ-C30 and EuroQol EQ-5D.

Objective: To evaluate PFS2 as assessed by the investigator according to the IWG response criteria [Cheson, 2007] [28] by treatment arm.

Objective: To evaluate PFS as assessed by the investigator, according to the IWG response criteria [Cheson, 2007] by treatment arm, including clinical and imaging data following auto-SCT or allo-SCT.

B.2.3.2. KEYNOTE-204 Participant baseline characteristics

Treatment arms were generally well-balanced for all baseline characteristics. Most participants were white, non-Hispanic, less than 65 years of age, and had disease subtype classical Hodgkin lymphoma nodular sclerosis. Participants had received a median of 2 (range: 1 to 10) or 3 (range: 1 to 11) prior lines of therapy for pembrolizumab and BV, respectively. The percentage of participants with primary refractory disease and prior auto-SCT was consistent in both treatment arms. Most participants did not have a history of prior BV treatment (96.7% and 93.5% for the pembrolizumab and BV arms, respectively). High-risk features such as bulky disease (pembrolizumab 23.2%, BV 16.3%), baseline B symptoms (pembrolizumab 28.5%, BV 23.5%), and baseline bone marrow involvement (pembrolizumab 7.9%, BV 3.3%) were more frequent in the pembrolizumab treatment arm than the BV arm. Participants with ECOG 1 (pembrolizumab were also more frequent in the pembrolizumab arm.

For the c/e model, patient characteristics from the European sites were applied to better reflect the UK population. For more details please see section B.3.2.

Table 7. KEYNOTE-204 Subject Characteristics (ITT Population)[3]

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n (%)		n	(%)	n (%)	
Subjects in population	151		153		304	
Gender						
Male	84	(55.6)	90	(58.8)	174	(57.2)
Female	67	(44.4)	63	(41.2)	130	(42.8)
Age (Years)						
< 65	124	(82.1)	131	(85.6)	255	(83.9)
>= 65	27	(17.9)	22	(14.4)	49	(16.1)
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Median	36.0		35.0		35.0	
Range	18 to 84		18 to 83		[redacted]	
Race						
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian Or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	119	(78.8)	115	(75.2)	234	(77.0)
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race by Ethnicity						
Hispanic Or Latino						
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American						
Multiple						
White						
Not Hispanic Or Latino						
Asian						
Black Or African American						
Multiple						
Native Hawaiian Or Other Pacific Islander						

White	[redacted]					
Not Reported	[redacted]					
Black Or African American	[redacted]					
White	[redacted]					
Missing	[redacted]					
Unknown	[redacted]					
Black Or African American	[redacted]					
White	[redacted]					
Missing	[redacted]					
Missing	[redacted]					
Race Group						
White	119	(78.8)	115	(75.2)	234	(77.0)
All Others	[redacted]					
Missing	[redacted]					
Age Group (Years)						
< 65	124	(82.1)	131	(85.6)	255	(83.9)
>= 65 to < 75	[redacted]					
>= 75 to < 85	[redacted]					
US Region						
US	[redacted]					
Ex-US	[redacted]					
EU Region						
EU	[redacted]					
Ex-EU	[redacted]					
World Region						
North America	[redacted]					
Europe	[redacted]					
Japan	[redacted]					
Rest of the World	[redacted]					
Disease Subtype						
Classical Hodgkin Lymphoma Mixed Cellularity	[redacted]					
Classical Hodgkin Lymphoma Nodular Sclerosis	[redacted]					
Classical Hodgkin Lymphoma Lymphocyte Depleted	[redacted]					
Classical Hodgkin Lymphoma Lymphocyte Rich	[redacted]					
Missing	[redacted]					
ECOG Performance Status						
0	86	(57.0)	100	(65.4)	186	(61.2)
1	[redacted]					
2	[redacted]					
Stratification: Prior Auto-SCT Status						
Yes	56	(37.1)	56	(36.6)	112	(36.8)

No	95	(62.9)	97	(63.4)	192	(63.2)
Stratification: Disease Status After Frontline Therapy						
Primary Refractory	61	(40.4)	62	(40.5)	123	(40.5)
Relapsed < 12 Months	42	(27.8)	42	(27.5)	84	(27.6)
Relapsed >= 12 Months	48	(31.8)	49	(32.0)	97	(31.9)
Refractory or Relapsed After Any Line of Prior Therapy						
Yes	[redacted]					
No	[redacted]					
Response to First Regimen Before Study Treatment						
Refractory	[redacted]					
Relapse	[redacted]					
Other	[redacted]					
Response to Last Regimen Before Study Treatment						
Refractory	[redacted]					
Untreated Relapse	[redacted]					
Other	[redacted]					
Number of Prior Lines of Therapy						
Subjects with data	[redacted]					
Mean SD Median Range	[redacted]					
Number of Prior Regimens						
Subjects with data	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Median	[redacted]					
Range	1 to 10		1 to 11		[redacted]	
PD-L1 Status						
>=1%	[redacted]					
<1%	[redacted]					
Missing	[redacted]					
Prior Use of Brentuximab Vedotin						
Y	5	(3.3)	10	(6.5)	15	(4.9)
N	146	(96.7)	143	(93.5)	289	(95.1)
Prior Radiation						
Yes	58	(38.4)	61	(39.9)	119	(39.1)
No	93	(61.6)	92	(60.1)	185	(60.9)
Bulky Disease						
Yes	35	(23.2)	25	(16.3)	60	(19.7)
No	116	(76.8)	128	(83.7)	244	(80.3)

Baseline B Symptoms						
Yes	43	(28.5)	36	(23.5)	79	(26.0)
No	[redacted]					
Missing	[redacted]					
Baseline Bone Marrow Involvement						
Yes	12	(7.9)	5	(3.3)	17	(5.6)
No	139	(92.1)	148	(96.7)	287	(94.4)
Database Cutoff Date: [redacted]						

B.2.3.3. KEYNOTE-087 trial overview[25]

KEYNOTE-087 (NCT02453594) is a phase II, multicentre, single arm, multi-cohort, non-randomised trial of pembrolizumab in patients with R/RcHL. The three study cohorts included patients with R/RcHL, who have failed to achieve a response or progressed after ASCT and have relapsed after treatment with, or failed to respond to, BV post ASCT (Cohort 1); who were unable to achieve a complete response (CR) or partial response (PR) to salvage chemotherapy and did not receive ASCT but have relapsed after treatment with, or failed to respond to, BV (Cohort 2); and subjects who have failed to respond to, or progressed after, ASCT and have not received BV post ASCT. These patients may or may not have received BV as part of primary or salvage treatment (Cohort 3).

The rationale for selecting a single arm non-comparative trial is largely based on the absence of established clinical practice at this later line setting, and the limited number of eligible patients for treatment. Throughout this report, participants who had no response to, or relapsed after, ASCT or BV will be considered to have 'failed' that therapy.

Approximately 60 participants were planned to be enrolled per cohort. A total of 210 participants were enrolled and treated: 69 in Cohort 1; 81 in Cohort 2, and 60 in Cohort 3; data from all treated participants were analysed.

Participants were treated for up to a maximum of 35 cycles (approximately 24 months) or until documented disease progression, unacceptable AEs, intercurrent illness preventing further administration of treatment, decision by the investigator to withdraw the participant, participant withdrawal of consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements, or administrative reasons leading to discontinuation.

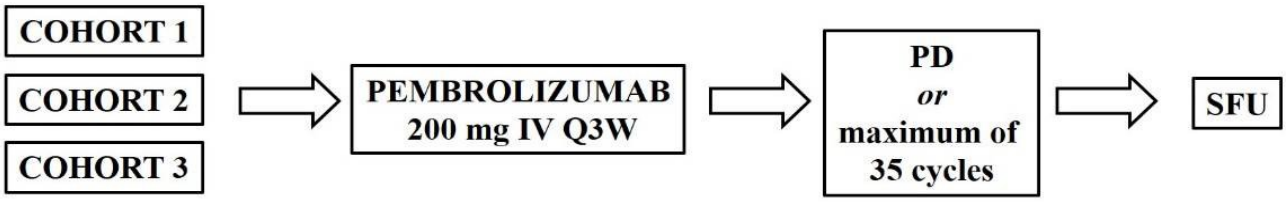
Adverse events were monitored every 3 weeks throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE version 4.0. At the investigator's discretion,

participants who attained an investigator-determined confirmed CR could consider stopping study treatment after receiving at least 24 weeks of therapy. At least 2 doses of study treatment had to be received after CR was documented.

These participants are eligible for retreatment if they experience disease progression as long as no anti-cancer treatment is administered since the last dose of pembrolizumab, they still meet the safety parameters listed in the Inclusion/Exclusion criteria of the study below and the study remains open.

After the end of treatment, each participant was followed for 30 days for AEs (90 days for SAEs and ECIs). Participants who discontinued study treatment for reasons other than disease progression undergo post-treatment follow-up for disease status until disease progression, initiating a non-study anti-cancer therapy, withdrawing consent, or becoming lost to follow-up. All participants are followed by telephone contact for overall survival until death, withdrawal of consent, or the end of the study, whichever comes first.

Figure 4. KEYNOTE-087 Study design



N ≅ 60 participants with R/R cHL / cohort

Cohort 1: Participants who failed to achieve a response or progressed after auto-SCT and relapsed after treatment with, or failed to respond to treatment with, BV post-auto-SCT
Cohort 2: Participants who were unable to achieve a CR or PR to salvage chemotherapy and did not receive auto-SCT, but relapsed after treatment with, or failed to respond to treatment with, BV
Cohort 3: Participants who failed to achieve a response to, or progressed after, auto-SCT, and had not received BV after auto-SCT and did, or did not, receive BV as part of primary treatment or salvage treatment

auto-SCT=autologous stem cell transplant; BV=brentuximab vedotin; cHL=classical Hodgkin lymphoma; CR=complete response or remission; IV=intravenous(ly); PD=progressive disease; PR=partial response or remission; Q3W=once every 3 weeks; R/R=relapsed/refractory; SFU=safety follow-up

As of the date of data cut-off [redacted]), enrolment was closed, and all enrolled participants had either completed or discontinued original protocol treatment. This [redacted] presents

safety and efficacy analyses corresponding to approximately 3 years after the last participant initiated original protocol treatment and does not include data from participants who were retreated with pembrolizumab after experiencing CR and relapsing.

KEYNOTE-087 Eligibility criteria

Male/Female subjects with R/RcHL of at least 18 years of age will be enrolled in this trial.

The key inclusion/ exclusion criteria are provided below.

KEYNOTE-087 Key inclusion criteria:

In order to be eligible for participation in this trial, the subject had to:

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research

2. Be ≥18 years of age on day of signing informed consent.

3. Have relapsed* or refractory* de novo cHL and meet one of the following cohort inclusions:

**Relapsed: disease progression after most recent therapy*

**Refractory: failure to achieve CR or PR to most recent therapy*

Cohort 1: Have failed to achieve a response or progressed after ASCT Patients must have relapsed after treatment with or failed to respond to BV post ASCT.

Cohort 2: Were unable to achieve a CR or a PR to salvage chemotherapy and did not receive ASCT. Patients must have relapsed after treatment with or failed to respond to BV.

Cohort 3: Have failed to achieve a response or progressed after ASCT and have not received BV post ASCT. Note: These patients may or may not have received BV as part of primary treatment, or salvage treatment.

4. Have measurable disease defined as at least one lesion that can be accurately measured in at least two dimensions with spiral computerised tomography (CT) scan. Minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis.

5. Be able to provide an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival or newly obtained biopsy at Screening. In addition, patients may provide additional biopsy at Week 12 and at the time of discontinuation due to progression. If submitting

unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut.

6. Must have a performance status of 0 or 1 on the ECOG Performance Scale

7. Must demonstrate adequate organ function as defined in Table 8; all screening labs should be performed within 7 days of treatment initiation.

Table 8. Lymphoma Adequate Organ Function Laboratory Values

System Laboratory Value	
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets[b]	≥75,000 / mcL
Hemoglobin[b]	≥8 g/dL
Renal	
Creatinine OR Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤ 1.5 X ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended us of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[a] Creatinine clearance should be calculated per institutional standard.

[b]Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support (GCSFor erythropoietin) within 2 weeks prior to treatment initiation.

8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication.

Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.

9. Male subjects should agree to use an adequate method of contraception starting with the

first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.

KEYNOTE-087 Key exclusion criteria

Patients were excluded from participating in the trial if they met any of the following key criteria:

1. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4weeks of the first dose of treatment.

2. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.

3. Has a diagnosis of immunosuppression or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

4. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

-Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

-Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

-Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

-Note: Toxicity that has not recovered to ≤ Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in Table 8.

6. Has undergone prior allogeneic hematopoetic stem cell transplantation within the last 5 years. (Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of GVHD.)

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

8. Has known clinically active CNS involvement.

9. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has evidence of active, non-infectious pneumonitis.

11. Has an active infection requiring intravenous systemic therapy.

12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

13. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

15. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), or Hepatitis C (HCV) infection.

16. Has received a live vaccine within 30 days prior to first dose.

17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

Settings and Location where the data were collected

This was a global study enrolling a total of 210 patients (cohort 1, n=69; cohort 2, n=81; cohort 3, n=60) between the 26th June 2015 and 21st March 2016 across 51 study sites. This included three study sites in the UK, 23 sites across Europe (France, Russia, Italy, Spain, Germany, Greece, Hungary, Sweden, and Norway), eleven in the USA, seven in Japan, four in Israel, two in Australia, and one in Canada.

There were 14 patients ([redacted]) enrolled from three UK study sites.

Trial drugs and concomitant medication

Table 9. KEYNOTE-087 trial treatment

Study Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200mg	Q3W	IV Infusion	Day 1 of each treatment cycle	experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which the subject is allocated/assigned. This was an open label trial; therefore, the sponsor, investigator, and patient knew the treatment administered. All trial treatment was administered in the outpatient setting by qualified site personnel.

All patients received pembrolizumab 200mg via IV infusion as 30-minute infusion every 3 weeks in the outpatient setting. Treatment could be administered up to 3 days before or after the

scheduled Day 1 of each cycle for administrative reasons. Interruptions from the treatment plan for greater than 3 days and up to 3 weeks were allowed, but required consultation between the Investigator and Sponsor, and written documentation of the collaborative decision on subject management. Neither dose escalation nor dose reduction of pembrolizumab was permitted in this trial.

Dose modification due to AE (both non-serious and serious) was permitted as outlined in the KEYNOTE-087 protocol[29] as exposure with pembrolizumab may represent an immunological aetiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

Concomitant Medications/ Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication including all prescription, over-the-counter, herbal supplements, and IV medications and fluids was recorded on the case report form. If changes to medication occurred during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the case report form. Patients were able remain on anti-coagulation therapy if the prothrombin time or activated partial thromboplastin time is within therapeutic range of the intended use of anticoagulants.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment was recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs.

Prohibited Concomitant Medications or Therapy

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Granulocyte macrophage colony-stimulating factor
- Immunotherapy not specified in the protocol
- Chemotherapy not specified in the protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

Note: Any need for radiotherapy was considered indicative of progressive disease and resultant in discontinuation of study therapy.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic aetiology.

KEYNOTE-07 Primary Objectives and Hypotheses

Within each of, and pooled over, the 3 specified cohorts. for subjects with R/RcHL:

Objective: To determine the safety and tolerability of pembrolizumab.

Objective: To evaluate the ORR of pembrolizumab by independent central review according to the International Working Group (IWG) response criteria (Cheson, 2007).

Hypothesis: Intravenous administration of single agent pembrolizumab will result in a ORR of greater than 15% in Cohorts 1 and 3 (5% in Cohort 2) using IWG response criteria (Cheson, 2007) by independent central review.

KEYNOTE-087 Secondary objectives

Objective: Evaluate ORR of pembrolizumab by investigator assessment according to the IWG response criteria; and additionally, by independent central review using the 5-point scale according to the Lugano Classification.

Objective: Evaluate Complete Remission Rate (CRR) of pembrolizumab by independent central review and by investigator assessment according to the IWG response criteria; and additionally, by independent central review using the 5-point scale according to the Lugano Classification.

Objective: Evaluate PFS and Duration of Response (DOR) of pembrolizumab by independent central review and by investigator assessment according to the IWG response criteria.

Objective: Evaluate the OS of pembrolizumab.

B.2.3.4 KEYNOTE-087: Participant baseline characteristics

The majority of participants were white [redacted] the median age was 35.0 years, and just over half of participants (53.8%) were male. Per protocol, all study participants had cHL, participants in Cohorts 1 and 3 were post-ASCT, and participants in Cohort 2 had not received an auto-SCT

Table 10. [redacted] in Cohort 2 were ineligible for ASCT due to reasons other than chemo-refractory disease to salvage therapy: [redacted] were not candidates because of advanced age and comorbidities, and [redacted] refused the procedure. The most common subgroup of cHL was nodular sclerosing HL ([redacted] All participants were heavily pre-treated, with a median of 4.0 prior lines of therapy (range: 1 to 12). A total of 175 participants (83.3%) had

previously failed to respond to or relapsed after treatment with BV. Seventy-seven participants (36.7%) had prior radiation therapy.

Table 10. KEYNOTE-087 Subject Characteristics By Cohort (ASaT Population)

	COHORT 1 n (%)	COHORT 2 n (%)	COHORT 3 n (%)	Total n (%)
Subjects in population	69	81	60	210
Gender				
Male	36 (52.2)	43 (53.1)	34 (56.7)	113 (53.8)
Female	33 (47.8)	38 (46.9)	26 (43.3)	97 (46.2)
Age (Years)				
<65	69 (100.0)	66 (81.5)	57 (95.0)	192 (91.4)
≥65	0 (0.0)	15 (18.5)	3 (5.0)	18 (8.6)
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	34.0	40.0	32.0	35.0
Range	19 to 64	20 to 76	18 to 73	18 to 76
Race				
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Multi-Racial	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Race by Ethnicity				
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Multi-Racial	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]

	COHORT 1 n	(%)	COHORT 2 n	(%)	COHORT 3 n	(%)	Total n	(%)
Race by Ethnicity								
Asian	[redacted]							
Black Or African American								
Missing								
Multi-Racial								
White								
Not Hispanic Or Latino								
American Indian Or Alaska Native								
Black Or African American								
Missing								
White								
Not Reported								
White								
Unknown								
Race Group								
White								
Non-White								
Missing								
US Region								
US								
Ex-US								
Disease Subtype								
Classical Hodgkin Lymphoma- Nodular Sclerosis								
Classical Hodgkin Lymphoma- Mixed Cellularity								
Classical Hodgkin Lymphoma- Lymphocyte Rich								
Classical Hodgkin Lymphoma- Lymphocyte Depleted								
Missing								
ECOG Performance Status								
0	29	(42.0)	44	(54.3)	29	(48.3)	102	(48.6)
1	39	(56.5)	37	(45.7)	31	(51.7)	107	(51.0)
2	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.5)

Prior Lines of Therapy Group								
≥ 3	68	(98.6)	78	(96.3)	36	(60.0)	182	(86.7)
< 3	1	(1.4)	3	(3.7)	24	(40.0)	28	(13.3)
Prior Lines of Therapy								
Subjects with data	69		81		60		210	
Mean	[redacted]		[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]		[redacted]	
Median	4.0		4.0		3.0		4.0	
Range	2.0 to 12.0		1.0 to 11.0		2.0 to 10.0		1.0 to 12.0	
Refractory or Relapsed After 3 or More Lines								
Yes	69	(100.0)	81	(100.0)	60	(100.0)	210	(100.0)
Time of relapse since SCT failure Group								
≥12 months	[redacted]		[redacted]		[redacted]		[redacted]	
<12 months	[redacted]		[redacted]		[redacted]		[redacted]	
Missing	[redacted]		[redacted]		[redacted]		[redacted]	
Time of relapse since SCT failure (Months)								
Subjects with data	[redacted]		[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]		[redacted]	
Brentuximab Use								
Yes	69	(100.0)	81	(100.0)	25	(41.7)	175	(83.3)
No	0	(0.0)	0	(0.0)	35	(58.3)	35	(16.7)
Prior Radiation								
Yes	32	(46.4)	21	(25.9)	24	(40.0)	77	(36.7)
No	37	(53.6)	60	(74.1)	36	(60.0)	133	(63.3)
Bulky Lymphadenopathy								
Yes	2	(2.9)	5	(6.2)	1	(1.7)	8	(3.8)
No	67	(97.1)	76	(93.8)	59	(98.3)	202	(96.2)
Baseline B Symptoms								
Yes	21	(30.4)	27	(33.3)	19	(31.7)	67	(31.9)
No	48	(69.6)	54	(66.7)	41	(68.3)	143	(68.1)

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Baseline Bone Marrow Involvement								
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(Database Cutoff Date: [redacted]								

B.2.3.5. KEYNOTE-051 trial overview[26]

KEYNOTE-051 is a two-part Phase I-II, non-randomized, open-label, single-arm, multi-centre trial to evaluate the pharmacokinetics (PK), pharmacodynamics, toxicity, safety, and anti -tumour activity of Pembrolizumab in pediatric subjects aged 6 months to less than 18 years of age with either;

- Advanced melanoma
- R/RHL
- Advanced, R/R MSI-H solid tumour
- PD-L1-positive advanced, R/R solid tumours or other lymphoma

Enrolment in the PD-L1-negative solid tumours and other lymphoma Cohort could have been initiated only if treatment efficacy was shown in the PD-L1-positive solid tumours and other lymphoma Cohort. Participants with melanoma, R/RcHL, and MSI-H solid tumours were enrolled irrespective of PD-L1 status. Participants with HL were initially enrolled in the Cohort of PD-L1-positive solid tumours and other lymphoma. After implementation of protocol Amendment 7, participants with HL were enrolled in the new, dedicated R/RcHL Cohort.

Part I (Phase I)

Part I of the study (dose finding and dose confirmation) has been completed. It used a modified 3+3 design (dose finding) and dose confirmation design according to a modified Toxicity Probability Interval approach. The initial dose in Part I was pembrolizumab 2 mg/kg Q3W, the equivalent of the clinical adult dose. Based on PK, PD, and safety data, no dose escalation or de-escalation occurred. Therefore, Part I established 2 mg/kg Q3W as the pediatric RP2D for Part II of the study. Part I also evaluated the safety, PK, PD, toxicity, and preliminary efficacy in pediatric participants with advanced melanoma or PD-L1-positive advanced, R/R solid tumours or other lymphoma.

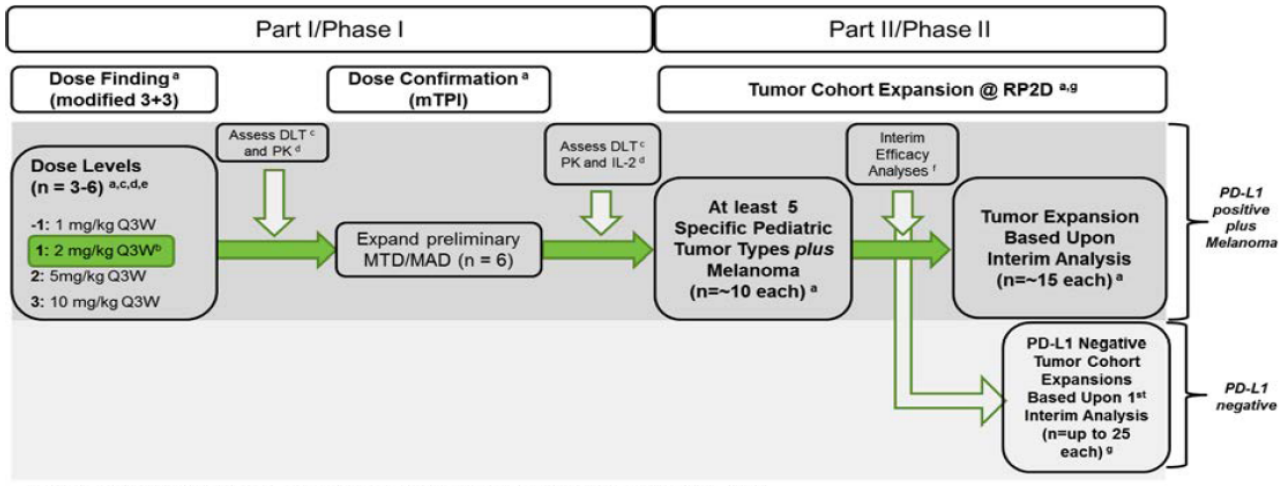
The initial dose in Part I was 2 mg/kg Q3W, the equivalent of the clinical adult dose. The highest dose tested in Part I was no greater than 10 mg/kg Q2W. Based on extensive safety and efficacy experience in adult patient cohorts it is anticipated that the starting dose of 2 mg/kg Q3W in Part I will be the relevant clinical dose in the pediatric population. The Dose

Finding and Dose Confirmation portions of Part I of the trial are described in the KEYNOTE-051 clinical study report (CSR) in Section 2.1.1 (ref).

Part II (Phase II)

The objectives for Part II were to further evaluate safety and efficacy at the pediatric RP2D in children with advanced melanoma or PD-L1 positive advanced R/R solid tumours and lymphoma. safety and efficacy at the established RP2D in pediatric participants in one of the following tumour Cohorts: advanced melanoma; PD-L1-positive advanced, R/R solid tumour or other lymphoma; R/RcHL; or advanced, R/R MSI-H solid tumours. Per the futility rules in of the study protocol, as of Amendment 8 enrolment was stopped for most solid tumours because signals of efficacy were not met in solid tumour target cohorts. However, enrolment was continued for adolescent participants with melanoma (aged 12 to less than 18 years) and pediatric participants with R/RcHL (aged 3 to less than 18 years) or MSI-H solid tumours (aged 6 months to less than 18 years), irrespective of PD-L1 tumour status.

Figure 5. KEYNOTE-051 Trial Design



mTPI = modified Toxicity Probability Interval; MTD = maximum tolerated dose; MAD = maximum administered dose; RP2D = recommended phase 2 dose; Q3W = Once every three weeks; DLT = dose limiting toxicity

a. Pediatric subjects with melanoma or PD-L1 positive advanced relapsed or refractory solid tumor or lymphoma between the ages of 6 months and less than 18 years
b. The starting dose level will be 2 mg/kg Q3W (Dose Level 1)
c. **De-escalation** decisions will be informed by DLT according to modified 3+3 and mTPI approaches (i.e., dose limiting toxicities will result in de-escalation of the dose according to a 3+3/mTPI design); if the starting dose is found to be generally safe and well-tolerated, dose escalation will only occur based on PK and/or PD results
d. **Escalation** decisions will be informed by assessment of PK and/or PD (i.e., dose escalation to a maximum of 10 mg/kg Q2W will occur if PK at the starting dose is <50% of adult value, and/or PD [IL-2 stimulation] is unsatisfactory)
e. Escalation to additional dose levels (e.g. Q2W dosing frequency up to 10 mg/kg Q2W) may occur based upon PK/PD modeling
f. Interim analysis as described in Section 8.1.3
g. PD-L1 negative subjects may be enrolled following the first interim analysis; Enrollment will only remain open for the PD-L1 negative cohort while enrollment to the PD-L1 positive cohort is open; futility rules may be applied as described in Section 8.1.2.3

Table 11 Summary of Tumour Cohorts in KEYNOTE-051

Cohort Name	Indication	Age	PD-L1 Status	Efficacy Criteria
Melanoma[a]	Melanoma	6 months to less than 18 years	Pos or Neg	RECIST 1.1
PD-L1 positive solid tumours and other lymphoma[b]	Any pediatric solid tumour (except brain stem tumours) and lymphoma	6 months to less than 18 years	Pos only	RECIST 1.1
PD-L1 negative[c] solid tumours and Other lymphoma[b]	Any pediatric solid tumour (except brain stem tumours) and lymphoma	6 months to less than 18 years	Neg only	RECIST 1.1
Dedicated rrcHL (post Amendment 7)	Hodgkin lymphoma	3 to less than 18 years	Pos or Neg	IWG
MSI-H[d]	Any pediatric solid tumour (except brain stem tumours)	6 months to less than 18 years	Pos or Neg	RECIST 1.1

[a] As of protocol Amendment 8, melanoma cohort was closed to participants aged 6 months to 11 years.

[b] As of protocol Amendment 7, HL participants will typically be enrolled in the rrcHL Cohort. However, participants with non-Hodgkin lymphoma or who do not meet all the rrcHL Cohort entry criteria may still enroll as “other lymphoma" if they meet entry criteria under the “PD-L1 positive solid tumors and other lymphoma" Cohort.

[c] For solid tumors and other lymphoma, enrollment of PD-L1-negative participants was not initiated because efficacy was not demonstrated in participants with PD-L- positive tumors.

[d] Includes documented biallelic MMR deficiency (constitutional mismatch repair deficiency [CMMRD] or biallelic mismatch repair deficiency [BMMRD]) regardless of MSI-H testing

KEYNOTE-051 Key inclusion criteria:

In order to be eligible for participation in this trial, the subject had to:

1. Be willing and able to provide written informed consent/assent for the trial. The subject could also provide consent/assent for Future Biomedical Research. However, the subject could participate in the main trial without participating in Future Biomedical Research.

2. Be between 6 months and less than 18 years of age on day of signing informed consent/assent. *Note: the first three patients dosed in Part 1 are to be ≥ 6 years of age. As of Amendment 08, for the melanoma Cohort only participants aged 12 to less than 18 years of age at the time of signing the informed consent could have been enrolled.*

3. Have histologically or cytologically-documented, locally-advanced, or metastatic solid malignancy that is incurable and has either (a) failed prior standard therapy, (b) for which no standard therapy exists, or (c) standard therapy is not considered appropriate by the patient and treating physician. There is no limit to the number of prior treatment regimens.

4. Be able to provide tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumour lesion not previously irradiated (tumours progressing in a prior site of radiation are allowed for characterization, other exceptions could be considered after Sponsor consultation). Note: Sponsor consultation is required prior to performing a study-related biopsy procedure for satisfying this screening requirement for any patient with intrinsic brain stem tumours, optic pathway gliomas, or pineal tumours (e.g. if archival specimen is not available).

5. Have either advanced melanoma or a PD-L1 positive advanced, R/R solid tumour or lymphoma as determined by IHC in archival formalin fixed paraffin embedded tumour (FFPET) or newly obtained biopsy to qualify for the PD-L1 positive cohorts in Part I and II of this trial. For this study, tumour specimens with positive stroma or at least 1% of cells expressing PD-L1 by IHC will be defined as PD-L1 positive.

Participants in the MSI-H solid tumour Cohort must have advanced, R/R solid tumour and local MSI positive test results. The selection of the FFPET tissue sample used for MSI testing is at the discretion of the physician treating the participant, and the testing of archived FFPE tumour tissue is permitted. Any pediatric participant with advanced cancer and documented biallelic MMR deficiency (constitutional mismatch repair deficiency [CMMRD] or biallelic mismatch repair deficiency [BMMRD], respectively) syndrome are eligible for study entry into this MSI-H Cohort, regardless of tumour MSI testing results. At least 6 of the 25 participants in the MSI-H Cohort will have CNS tumours (excluding brain stem).

6. Have measurable disease based on RECIST 1.1. Tumour lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Participants with neuroblastoma who do not have measurable disease per RECIST 1.1, but have MIBG-positive evaluable disease, may be enrolled

7. Have a performance status as defined below:
- Lansky Play Scale ≥70 for children up to and including 16 years of age;
- Karnofsky score ≥70 for children > 16 years of age
- Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

8. Demonstrate adequate organ function as defined below:

9. Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those

who have begun menstruating and have not been surgically sterilized. *Note: Abstinence is acceptable if this is the established and preferred contraception for the subject*

11. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.

Inclusion Criteria for the R/R cHL Cohort

1. Be willing and able to provide (and/or their parents or legal guardians) written informed consent/assent for the study.

2. Be 3 to less than 18 years of age on the day the pre-screen informed consent is signed. Patients who do not require pre-screening, must meet the age requirement on the day the main informed consent is signed.

3. Have R/R cHL and are either:

• Refractory to front-line therapy;
High-risk and relapsed from front-line therapy; or

• Relapsed or refractory to second-line therapy.

4. Be able to provide lymph node biopsy tissue from an archival sample or newly obtained biopsy of a tumour lesion not previously irradiated (tumours progressing in a prior site of radiation are allowed for characterization, other exceptions may be considered after Sponsor consultation). Please note, fine needle aspirations are not acceptable for determining PD-L1 status.

5. Have measurable disease based on IWG (i.e., measurement must be >15 mm in longest diameter or >10 mm in short axis).

6. Have a performance status as defined below:

• Lansky Play Scale ≥50 for children 16 years of age and younger;

• Karnofsky score ≥50 for children older than 16 years of age;

• Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

7. Demonstrate adequate organ function.

All R/RcHL Cohort participants must also comply with Inclusion Criteria 9, 10, and 11 above.

KEYNOTE-051 Key exclusion criteria

Subjects were excluded from participating in the trial if the subject:

1. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids (up to 5 mg/m2/day prednisone equivalent) may be approved after consultation with the Sponsor.

2. Has received prior systemic anticancer therapy including investigational agents within 2 weeks before study Day 1 or has not recovered (i.e., ≤Grade 1 or at baseline) from adverse events due to a previously administered agent.

3. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

4. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy.

5. Has known active CNS metastases and/or carcinomatous meningitis.

6. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs).

7. Has undergone solid organ transplant at any time, or prior allogeneic hematopoietic stem cell transplantation within the last 5 years.

Settings and Location where the data were collected for KEYNOTE-051

162 patients were allocated across 31 global study sites including the UK.

Trial drugs and concomitant medication

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered. The study treatments during dose finding and dose confirmation (Part I) are outlined in Table 12. Part I of the study used a modified 3+3 design (dose finding) and dose confirmation design according to an mTPI approach. The initial dose in Part I was pembrolizumab 2 mg/kg Q3W, the equivalent of the clinical adult dose. Based on PK, pharmacodynamic, and safety data, no dose escalation or de-escalation occurred during Part I. Therefore, the established RP2D for Part II of the study is pembrolizumab 2 mg/kg Q3W.

Table 12. Planned Study Treatments During Part 1.

Drug	Dose Level	Dose/Potency	Dose Frequency	Route of Administration
Pembrolizumab	-1[a]	1mg/kg	Q3W	IV
	1[b]	**2mg/kg**	**Q3W**	
	2[c]	5mg/kg	Q3W	
	3[c]	10mg/kg	Q3W	

IV=intravenous; Q3W=every 3 weeks.

[a] De-escalation based on safety observations may have been required to dose at Level -1.

[b] Starting dose level (ie, Dose Level 1). Maximum dose was to be 200 mg.

[c] Escalation to additional dose levels (first to 5 mg/kg and then up to 10 mg/kg) may have occurred based on pharmacokinetic (PK)/pharmacodynamic modeling. It was possible that an every 2 weeks (Q2W) dosing frequency may also have been evaluated based on evaluation of emerging PK/pharmacodynamic data. A Q2W dosing schedule may have been explored at any given dose

Trial treatment was to begin on, or as close as possible to, the day the subject is assigned/allocated to treatment (e.g. when randomization number is assigned). The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

Study drug were administered on Day 1 of each cycle after all procedures/assessments have been completed. Study drug could be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. For subjects enrolled during part I of the trial who are > 16 kg, Cycles 1, 2 and 4, dosing must occur on a Monday or a Tuesday to accommodate IL-2 blood draw and processing.

Pembrolizumab will be administered as 30-minute IV infusion every 3 weeks (treatment cycle intervals may be increased due to toxicity; treatment cycle intervals may be decreased to every 2 weeks based on PK results). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Infusion of pembrolizumab could be performed on an outpatient basis and did not require admission.

During Part II of the trial subjects were assigned to the MTD or MAD dose defined during Part I of the trial.

Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria were not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination could have been required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rested with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication should be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, vaccinations, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Prohibited Concomitant Medications or Therapy

Subjects were prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu -Mist®) are live attenuated vaccines, and are not allowed

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology. Note: The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g. IV contrast dye) is permitted.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase

KEYNOTE-051 Outcomes specified in NICE scope

KEYNOTE-051 Primary Objectives for the R/RcHL Cohort

Part II

1. Objective: To determine the safety and tolerability of pembrolizumab based on AEs and clinical and laboratory measures in children with R/RHL.

2. Objective: To evaluate antitumor activity of pembrolizumab in the R/RcHL Cohort based on the ORR per BICR assessment according to the IWG response criteria, based on assessments every 12 weeks.

Hypothesis: IV administration of pembrolizumab in the R/RcHL Cohort will result in an ORR of greater than 10% using IWG response criteria per BICR assessment.

KEYNOTE-051 Secondary Objectives for the R/RcHL Cohort

Part I and Part II:

1. Objective: To evaluate antitumor activity of pembrolizumab in the rrcHL Cohort according to the IWG response criteria based on assessments every 12 weeks by the following endpoints:

• ORR, DOR and PFS per site assessment

• ORR, DOR and PFS per BICR

• OS

KEYNOTE-051 Exploratory Objectives for the R/RcHL Cohort

1. Objective: To assess ORR of pembrolizumab by BICR assessment using the Lugano Classification.

B.2.3.6 KEYNOTE-051 Participant baseline characteristics

Approximately half of the participants ([redacted]) were 14 to 17 years of age. The [redacted] participants with HL ranged in age from 10 to 17 years. [redacted] participants were 10 to 13 years of age and [redacted] participants were 14 to 17 years of age. The majority of participants were white, not Hispanic or Latino, had received prior treatment for recurrent/metastatic disease, and had Stage IV cancer. Participants were approximately evenly split by sex. Participants were enrolled across approximately 29 tumour types by primary diagnosis. The most common primary diagnoses (in ≥5% of participants) were solid tumor NOS ([redacted]), HL NOS ([redacted]), glioblastoma multiforme ([redacted]), soft tissue neoplasm NOS ([redacted]), neuroblastoma ([redacted]), osteosarcoma ([redacted]), melanoma ([redacted]), and CNS primary tumour NOS ([redacted]). The primary diagnosis of solid tumour NOS ([redacted]) consisted of multiple tumour types by histology. Each tumour type was reported for 4 or fewer participants. The majority of participants had PD-L1-positive tumours, as expected per protocol. [redacted]participants had MSI-H tumour status.

Table 13. KEYNOTE-051 Patient Baseline Characteristics

	All Subjects as Treated n (%)	
Subjects in population	[redacted]	
Gender		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Age (Years)		
6 months - <2 years	[redacted]	[redacted]
2 - 5 years	[redacted]	[redacted]
6 - 9 years	[redacted]	[redacted]

10 - 13 years	[redacted]
14 - 17 years	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
Range	[redacted]
Race	
American Indian Or Alaska Native	[redacted]
Asian	[redacted]
Black Or African American	[redacted]
Multi-Racial	[redacted]
Asian, White	[redacted]
Black, White	[redacted]
Native American, White	[redacted]
White	[redacted]
Missing	[redacted]
Ethnicity	
Hispanic Or Latino	[redacted]
Not Hispanic Or Latino	[redacted]
Not Reported	[redacted]
Unknown	[redacted]
Primary Diagnosis	
Adrenocortical Carcinoma	[redacted]
Alveolar Rhabdomyosarcoma	[redacted]
Alveolar Soft Part Sarcoma	[redacted]
Anaplastic Astrocytoma	[redacted]
Atypical Teratoid Rhabdoid Tumor	[redacted]
CNS Primary Tumor Nos	[redacted]
Diffuse Large B Cell Lymphoma	[redacted]
Embryonal Rhabdomyosarcoma	[redacted]
Ependymoma Nos	[redacted]
Glioblastoma Multiforme	[redacted]
Hepatoblastoma	[redacted]
Hepatocellular Carcinoma	[redacted]
High Grade Astrocytoma Nos	[redacted]
Hodgkin Lymphoma Nos	[redacted]
Low Grade Astrocytoma Nos	[redacted]
Medulloblastoma	[redacted]
Melanoma	[redacted]
Neuroblastoma	[redacted]
Non Rhabdomyosarcoma Soft Tissue Sarcoma Nos	[redacted]
Osteosarcoma	[redacted]
Pilocytic Astrocytoma	[redacted]
Precursor T Lymphoblastic Lymphoma	[redacted]
Relapsed Refractory Classical Hodgkin Lymphoma (Post-Amendment 7)	[redacted]
Renal Cell Carcinoma Nos	[redacted]
Rhabdoid Tumor Of The Kidney	[redacted]
Rhabdomyosarcoma Nos	[redacted]
Soft Tissue Neoplasm Nos	[redacted]
Solid Tumor Nos	[redacted]
Wilms Tumor Nephroblastoma	[redacted]

Lansky / Karnofsky Play Score		
100	[redacted]	[redacted]
90	[redacted]	[redacted]
80	[redacted]	[redacted]
70	[redacted]	[redacted]
60	[redacted]	[redacted]
50	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Overall Staging#	[redacted]	[redacted]
I	[redacted]	[redacted]
IA	[redacted]	[redacted]
IB	[redacted]	[redacted]
II	[redacted]	[redacted]
IIA	[redacted]	[redacted]
IIB	[redacted]	[redacted]
IIE	[redacted]	[redacted]
III	[redacted]	[redacted]
IIIA	[redacted]	[redacted]
IIIB	[redacted]	[redacted]
IV	[redacted]	[redacted]
IVA	[redacted]	[redacted]
IVB	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Brain Metastases Present		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Prior Adjuvant/Neoadjuvant therapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Treatment Naive		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Number of Prior Therapies for recurrent/Metastatic Disease*		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5 or more	[redacted]	[redacted]

Overall Staging not required for diagnoses lacking standard staging systems.
* Those subjects who are naïve, or who received only adjuvant or neoadjuvant prior therapies are categorized as 0. (Data Cutoff Date: [redacted]).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 KEYNOTE-204: Statistical analysis and definition of study groups

This section reports the relevant statistical methodology of KEYNOTE-204[3]

Table 14. KEYNOTE-204 Statistical Analysis Plan

Study Design Overview	This is a randomized, open-label, multi-center, Phase III trial of pembrolizumab versus BV in subjects with R/RcHL
Treatment Assignment	Approximately 300 subjects with R/RcHL will be randomized in a 1:1 ratio between two treatment groups. The two treatment groups are as follows: Treatment Arm A*- Pembrolizumab 200 mg every 3 weeks Treatment Arm B* -BV 1.8 mg/kg every 3 weeks *This is an open label study Stratification factors are 1) prior stem cell transplant (yes vs. no) and 2) disease status following first line therapy (primary refractory vs. relapsed within 12 months vs. relapsed after 12 months)
Analysis Populations	Efficacy: Intention-to-treat (ITT) population. Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1. PFS per IWG 2007 by BICR 2.OS
Key Secondary Endpoints	ORR
Statistical Methods for Key Efficacy Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. No Tier 1 events are defined for this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between- group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment

	confidence intervals will be calculated using the Miettinen and Nurminen method. No formal treatment comparisons with p-values will be carried out.
Interim Analyses	One interim analysis (IA) for PFS and one IA for OS will be performed in this study; results will be reviewed by an external DMC. For PFS, the IA will be conducted 3 months after all subjects have been enrolled and at least [redacted] PFS events have been observed. For OS, the IA will be conducted at the time of the final PFS analysis (if the hypothesis for PFS is not rejected at the IA) or at approximately [redacted] OS events (if the hypothesis for PFS is rejected at the IA);
Multiplicity	The overall Type-I error is strongly controlled at 2.5% (one-sided) with 1.25% initially allocated to the PFS hypothesis and 1.25% initially allocated to the OS hypothesis. The method of Mauer and Bretz will be used to allocate and re-allocate Type I error between hypotheses and group sequential methods will be used to allocate alpha between the interim and final analyses.
Sample Size and Power	The planned sample size is approximately 300 subjects. There are 2 primary endpoints for this study, PFS and OS. The expected median PFS time in the control group is 5.6 months; based on 221 events, the study has 90% power to detect a hazard ratio of 0.622 (pembrolizumab vs. brentuximab vedotin) at alpha = 1.25% (one-sided). The expected median OS in the control group is 22.4 months; based on 146 events, the study has 80% power to detect a hazard ratio of 0.600 at alpha = 1.25% (one-sided).

Discontinuation of Treatment

A subject must be discontinued from the trial for any of the following reasons:

- The subject withdraws consent

A subject must be discontinued from treatment, but may continue to be monitored in the trial, for any of the following reasons:

- The subject withdraws consent for treatment.
- Documented disease progression verified by blinded independent central review
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

KEYNOTE-204 Statistical methods used to compare groups for primary and secondary outcomes and approach to missing data

The statistical methods used to compare groups for primary and secondary efficacy endpoints are summarised in Table 15 below.

Table 15. Analysis strategy for primary and key secondary efficacy endpoints for KEYNOTE-204

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoint			
PFS per IWG 2007 by blinded independent central review	Testing: Stratified Log-rank test. Estimation: Stratified Cox model with Efron's tie handling method	ITT	1. Primary censoring rule 2. Sensitivity analysis 1 3. Sensitivity analysis 2 (details in Table 9)

OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last date known alive
Key Secondary endpoint			
ORR per IWG 2007 by blinded independent central review	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non- responders
† Statistical models are described in further detail in the text. For stratified analyses, Prior SCT (yes vs. no) and disease status following first line therapy (primary refractory vs. relapsed within 12 months vs. months) will be used as the stratification factors in both the stratified log-rank test and the cox model			

The non-parametric Kaplan Meier (KM) method is used to estimate the PFS and OS curves in each treatment group. The treatment differences in PFS and OS is assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will assess the magnitude of the treatment difference (HR) between the treatment groups. The HR and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for the randomisation will be applied to both the stratified log-rank test and the stratified Cox model.

Since PD was assessed periodically, PD could occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD was documented. The true date of disease progression was approximated by the date of the first assessment at which PD was objectively documented per IWG by central review, regardless of discontinuation of study drug. Death was always considered as a confirmed PD event.

Sensitivity analyses was performed for comparison of PFS based on investigator's assessment. In order to evaluate the robustness of the PFS endpoint per IWG by central review, we will perform two sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 16.

Table 16. Censoring rules for Primary and Sensitivity Analyses of PFS for KEYNOTE-204

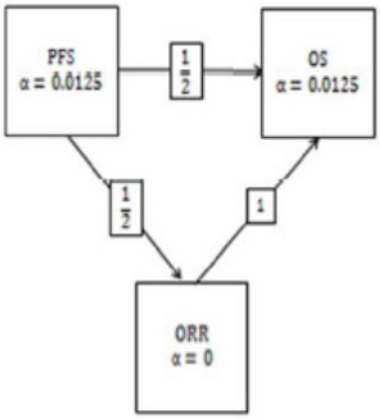
Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No PD and no death; subject receives SCT following response to pembrolizumab	Censored at last disease assessment before SCT	Censored at last disease assessment before SCT	Censored at date of SCT
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessments	Progressed at date of documented PD or death
No PD and no death and lost to follow-up after ≥2 missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to the ≥2 missed disease assessments	Progressed at date of lost to follow-up

The data cutoff for the protocol prespecified [redacted] efficacy analyses was [redacted] and conducted to evaluate [redacted] results and review the totality of the data. There is only one formal test of PFS [redacted] and results of all supportive PFS endpoints are provided.

Multiplicity strategy for PFS, OS and ORR

The multiplicity strategy specified in this section will be applied to the two primary hypotheses (superiority of pembrolizumab on PFS or OS) and the secondary hypothesis of superiority of pembrolizumab in ORR. The overall Type-I error across the testing of the OS, PFS and ORR hypotheses is strongly controlled at 2.5% (one-sided). The multiplicity strategy will follow the graphical approach of Mauer and Bretz, Figure 6 below provides the multiplicity strategy diagram of the study. Group sequential methods will be used to allocate alpha between the interim and final analyses.

Figure 6 Multiplicity Strategy



In this approach, when a particular null hypothesis is rejected, the arrow(s) leading to it are removed, and the Type I error allocated to the null hypothesis that was rejected is re - distributed to the other hypotheses. The arrows on the diagram show how the Type I error allocated to a hypothesis that was successfully tested will be re-distributed for the testing of the other hypotheses. Initially, α=1.25% (one-sided) is allocated to the PFS hypothesis, α=1.25% (one-sided) is allocated to the OS hypothesis, and zero α is allocated to the ORR hypothesis.

The testing of the PFS, OS and ORR hypotheses are as follows:

- Testing will first be performed on PFS (H1) and if H1 is rejected:

  -The corresponding Type I error for PFS is propagated equally, i.e. 0.625% to ORR (H2) and 0.625% to OS (H3)

-Testing will then be performed on ORR (H2) at the 0.625% level. If H2 is rejected, then all of its corresponding Type I error (0.625%) is propagated to OS (H3)

- Testing will then be performed on OS (H3) at either 1) the 1.250% alpha level if H1 is not rejected, 2) the 1.875% alpha level if H1 is rejected and H2 is not rejected, or 3) the 2.500% alpha level if both H1 and H2 are rejected.

KEYNOTE-204 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for PFS, the primary endpoint and OS, the second primary endpoint, will be estimated and plotted within each category of the following classification variables:

- Stratification factor: prior ASCT (yes vs. ≥ no)
- Stratification factor: disease status following first line therapy (refractory vs. relapsed within 12 months vs. relapsed after 12 months)
- Sex (female vs. male)
- Age (<65 years vs. ≥65 years)
- ECOG status (0 vs. 1)
- Geographic region

B.2.4.2 KEYNOTE-087: Statistical analysis and definition of study groups

This section reports the relevant statistical methodology of KEYNOTE-087.

Table 17. KEYNOTE-087 Statistical Analysis Plan

Study Design Overview	This study, "A Phase II clinical trial of MK-3475 (pembrolizumab) in subjects with R/RcHL" is a multicenter, single arm, multi-cohort, nonrandomized trial of pembrolizumab (MK-3475) in subjects with R/RcHL.
Treatment Assignment	Subjects meeting inclusion/exclusion criteria will be allocated to one of three cohorts, depending on their prior disease history and therapy: Cohort 1: failed to achieve a response or progressed after ASCT and have relapsed

	after treatment with or failed to respond to BV post ASCT. Cohort 2: ineligible for an ASCT and have relapsed after treatment with or failed to respond to BV post ASCT Cohort 3: failed to respond to or progressed after ASCT and have not received BV post ASCT. These subjects could have received BV as part of primary treatment or salvage therapy
Analysis Populations	Efficacy: ASaT Safety: ASaT
Primary Endpoint(s)	The primary efficacy endpoint is the ORR, defined as the proportion of subjects in the analysis population who have CR or PR using IWG criteria, Cheson 2007 at any time during the study. Response for the primary analysis will be determined by central review.
Key Secondary Endpoints	1. Complete Remission Rate 2. Progression-Free Survival 3. Duration of Response 4. Overall Survival
Statistical Methods for Key Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	The primary hypothesis will be evaluated, for each Cohort separately, by comparing ORR for MK-3475 to a fixed control rate using a binomial exact test. The point estimate of the ORR will be calculated for each Cohort as well as a 95% 2-sided exact confidence interval.
Statistical Methods for Key Safety Analyses	Within each Cohort, summary statistics (counts, percentage, mean, standard deviation, etc) will be provided for the safety endpoints as appropriate. A pooled analysis over Cohorts may be performed as well to obtain a larger safety database.
Interim Analyses	Depending on the enrolment rate within each Cohort, an interim analysis may be performed by the sponsor in this study for futility alone and the results will be reviewed internally. The interim analysis would be conducted when 50% of the subjects within a cohort have been evaluated for response.

Discontinuation of Treatment

A subject must be discontinued from the trial for any of the following reasons:

The subject or legal representative (such as a parent or legal guardian) withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment

- Documented disease progression
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

KEYNOTE-087 Statistical methods for efficacy outcomes and approach to missing data

Objectives were evaluated within each Cohort. There is one hypothesis, within each Cohort, to be formally tested in this study, i.e. whether the ORR is greater than a fixed control rate using the IWG criteria based on independent central review. Secondary objectives, again within each Cohort, will not involve hypothesis testing, and will assess the efficacy of pembrolizumab on secondary efficacy endpoints (CRR, PFS, DOR, and OS) and will include, where appropriate, assessments based on investigator and Lugano classification

The statistical methods used to compare groups for primary and secondary efficacy endpoints are summarised in the Table 18.

Table 18. Analysis strategy for primary and key secondary efficacy endpoints for KEYNOTE-087

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Overall Response Rate 4. IWG criteria (2007) o Central review	Exact test of binomial parameter; 2-sided 95% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders
Secondary:			
Overall Response Rate 5. IWG criteria (2007) • Study site 6. Lugano criteria (2014) • Central review	Point estimate; 2-sided 95% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders

Complete Remission Rate • IWG criteria (2007) ○ Central review ○ Study site • Lugano criteria (2014) ○ Central review	Point estimate; 2-sided 95% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders
Progression-free survival • IWG criteria (2007) ○ Central review ○ Study site	Summary statistics using Kaplan-Meier method	ASaT/FAS	Censored at last assessment (see Table 12 for sensitivity analyses based on alternative censoring)
Duration of Response • IWG criteria (2007) ○ Central review ○ Study site	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Overall survival	Summary statistics using Kaplan-Meier method	ASaT/FAS	Censored at last assessment

The analysis of ORR will consist of the point estimate and 95% 2-sided exact CI using the Clopper-Pearson method which will have at least 95% coverage of the true rate. An exact binomial test will be conducted for each cohort versus a fixed control rate for each cohort. Secondary analyses for ORR will be performed based on investigator's (i.e. study site) assessment and by central review based on the Lugano Classification (JCO, 2014). Since an investigator may still continue to treat subjects with MK-3475 who have progressed according to central review or by site assessment, exploratory analyses (point estimate and 95% 2-sided exact confidence interval) will be conducted for ORR to consider these subjects who later achieve PR or CR post-progression as responders.

CRR analyses will consist of the point estimate and 95% 2-sided exact CI, separately by Cohort. Additional analyses will be based on site assessment and by central review using the Lugano (2014) criteria.

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve. Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per IWG criteria, regardless of discontinuation of study drug. Death was always considered as a confirmed PD event. A secondary analysis will be performed for PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint, we will perform two sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as

the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 19.

DOR analyses will consist of Kaplan-Meier estimates. Duration of response data will be censored on the date of the last disease assessment documenting absence of PD for subjects who do not have tumour progression and are still on study at the time of an analysis, are given antitumor treatment (including stem cell transplant) other than the study treatment, or are removed from study prior to documentation of tumour progression. Duration of Response will be based upon central review according to the IWG criteria; a secondary analysis of DOR will be conducted using investigator assessment.

Table 19. Censoring rules for Primary and Sensitivity Analyses of PFS for KEYNOTE-087

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

Multiplicity

The false positive rate for testing the primary efficacy endpoint is controlled at 0.025 (1-sided) within each cohort. No additional multiplicity adjustment is required because each cohort will be evaluated independently.

KEYNOTE-087 Subgroup Analyses and Effect of Baseline Factors

To determine whether ORR is consistent across various subgroups, the point estimate of the ORR (with an exact 95% CI) will be provided and plotted within each category of the following classification variables within each Cohort:

- Age category (≤65 vs. >65 years)
- Sex (female vs. male)
- Race (white vs. non-white)
- Region (US, ex-US) and
- Number of prior therapies (< 4 vs ≥4)

For Cohorts 1 and 3 only:

- Time elapsed since transplant failure (<12 months vs. ≥12)

If the observed numbers for a particular subgroup are too small to make a meaningful clinical interpretation, then that subgroup analysis will not be conducted.

B.2.4.3 KEYNOTE-051: Statistical analysis and definition of study groups

This section reports the planned statistical methodology for KENOTE-051. Please note, enrolment was stopped for most solid tumours because signals of efficacy were not met in solid tumour target cohorts. However, enrolment was continued for adolescent participants with melanoma (aged 12 to less than 18 years) and pediatric participants with R/RcHL (aged 3 to less than 18 years) or MSI-H solid tumours (aged 6 months to less than 18 years), irrespective of PD-L1 status.

The FAS population was employed for efficacy analyses. For subjects with advanced melanoma, and PD-L1 positive subjects with a type of solid tumour or lymphoma, the primary hypothesis was evaluated separately in the respective disease indication by evaluating objective response rate by RECIST 1.1. A sequential monitoring approach was used following the time that a minimum of 10 subjects are enrolled in each indication. The

Type-I error rate over the multiple evaluations within an indication will be controlled by the truncated sequential probability ratio test procedure at 0.08 (1-sided). For PD-L1 negative subjects that may be enrolled in one or more solid tumour types or lymphoma, the efficacy endpoints will be summarized by indication and across indications.

Part II

Advanced Melanoma or Solid Tumours with Positive PD-L1 Expression

Within each indication, the study will enrol a minimum of 10 subjects at RP2D, including those who may have already been enrolled in Part I of the study. For solid tumours or lymphoma, the first 10 subjects in an indication need to be PD-L1 positive. Following the time that the first 10 subjects at RP2D have had at least one post-baseline response assessment, if fewer than 25 subjects have been enrolled in a specific indication, a sequential monitoring procedure will be used to evaluate for efficacy and futility simultaneously based on the number of subjects with a confirmed or unconfirmed response in this indication.

Depending on the enrolment rate, it is possible that more than 10 subjects may be enrolled prior to the first evaluation of efficacy or futility. Enrolment is expected to be continuous and will not be suspended within an indication unless the futility bound is crossed.

Once at least 10 subjects are evaluable for confirmed or unconfirmed response, subsequent rules for pausing enrolment and future evaluations will be based on the boundaries identified by the sequential monitoring procedure. A maximum of approximately 25 subjects will be enrolled in each indication. The maximum total sample size is ~150 subjects.

With 25 subjects per indication, this study provides 84% power to demonstrate that the best overall response rate induced by pembrolizumab exceeds 10% at an overall one-sided 8% alpha level, if the true best overall response rate within an indication is 35%. The underlying treatment effect is regarded as clinically important in each of the indications studied. Given the underlying true rate, this may occur when at least 7/25 subjects develop a response.

Solid Tumours with Negative PD-L1 Expression

For solid tumours or lymphoma, enrolment of PD-L1 negative subjects may be initiated if at least 4 confirmed or unconfirmed responses are observed at the first efficacy evaluation for an indication. Enrolment of PD-L1-negative patients may also be initiated if an efficacy

bound is passed during subsequent sequential monitoring for response in PD-L1-positive patients. If at least 10 PD-L1 negative subjects are evaluable for confirmed or unconfirmed responses while the enrolment for PD-L1 negative subjects is still ongoing for an indication, the same futility criteria will be used for the PD-L1 negative subjects.

Table 20. KEYNOTE-051 Decision Rules Based on Futility Bounds

Monitoring Points (# Subjects)	Maximum # Subjects with Response to Declare Futility*
10-14	1
15-19	2
20-24	3
25	4
Design assumes overall Type I error of 8% (1-sided) at true response rate of 10%, and 84% power at true response rate of 35%. *Futility is defined as true response rate of ≤10%.	

Table 21. KEYNOTE-051 Decision Rules Based on Efficacy Bounds

Monitoring Points (# Subjects)	Minimal # Subjects with Response to enrol PD-L1 negative subjects or start future study planning*
10-12	4
13-17	5
18-22	6
23-25	7
Design assumes overall Type I error of 8% (1-sided) at true response rate of 10%, and 84% power at true response rate of 35%. *Enrollment in the same indication may continue in the current study.	

KEYNOTE-051 Interim Analyses

Interim analyses were performed to sequentially monitor the objective response rate of enrolled subjects in Parts I and II (at the RP2D). Based on the futility stop guidance, and the totality of safety and efficacy data across indications, enrolment to one or more indications may be stopped before reaching the maximum of 25 subjects.

Enrolment was stopped for most solid tumours because signals of efficacy were not met in solid tumour target cohorts. However, enrolment was continued for adolescent participants with melanoma (aged 12 to less than 18 years) and pediatric participants with R/RcHL (aged

3 to less than 18 years) or MSI-H solid tumours (aged 6 months to less than 18 years), irrespective of PD-L1 status.

KEYNOTE-051 Planned statistical methods for efficacy outcomes and approach to missing data

For the primary efficacy endpoint investigator assessed RECIST 1.1 best overall response rate, the point estimate, repeated confidence interval, and adjusted p-value for testing the RECIST 1.1 response rate is greater than 10% for each disease indication was be provided using a truncated sequential probability ratio test, which is a specific instance of an exact binomial group sequential design for a single arm trial with a binary outcome. Subjects in the primary analysis population (FAS) without response data were counted as non-responder. Interim decisions were made based on confirmed or unconfirmed response assessments. However, the final analysis (if enrolment in a given indication expands to 25 subjects) will require a confirmation assessment for all subjects who develop a CR or PR.

For PFS endpoint, KM curves and median estimates from the KM curves were provided as appropriate. Subjects without efficacy evaluation data or without survival data were censored at Day 1.

For data collected from subjects with advanced melanoma, and PD-L1 positive subjects with a type of solid tumour or lymphoma, the analysis strategy is summarized in Table 22. Data collected from PD-L1 negative subjects with solid tumour or lymphoma was to be summarized descriptively.

Table 22. KEYNOTE-051 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Part I and II Primary Hypothesis 2 - Within Indication				
Overall RECIST 1.1 response rate by site assessment (each disease indication evaluated separately)	P	Truncated sequential probability test	FAS	Subjects with missing data are considered non-responders
Part I and II Secondary Objectives – Within Indication				
Duration of RECIST 1.1 response (DOR) by site assessment	P	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Duration of irRECIST response (DOR) by site assessment	S	Summary statistics using Kaplan-Meier method	All irRECIST responders	Non-responders are excluded in analysis
PFS using RECIST 1.1 criteria by site assessment	P	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment

PFS using modified RECIST 1.1 criteria by site assessment	S	Summary statistics sing Kaplan-Meier method	FAS	Censored at last assessment
Disease Control Rate by RECIST 1.1 using site assessment	P	Summary Statistics	FAS	Missing observation counted as non-responder
Disease Control Rate by irRECIST using site assessment	S	Summary Statistics	FAS	Missing observation counted as non-responder
OS	P	Kaplan-Meier method	FAS	Censored at last assessment
Overall irRECIST response rate by site assessment (each disease indication evaluated separately)	S	Summary Statistics	FAS	Subjects with missing data are considered non-responders

[1] P=Primary approach; S=Secondary approach.

Multiplicity

The false positive rate for testing the primary efficacy endpoint in each disease indication is controlled at 0.08 (1-sided) for each indication. No additional multiplicity adjustment is required because each disease indication will be evaluated independently.

KEYNOTE-051 Sample Size and Power Calculations

With an approximate maximum of 25 subjects enrolled within each indication, the study provides 84% power to demonstrate that the best overall response rate induced by MK -3475 exceeds 10% at an overall one-sided 8% alpha-level, if the true best overall response rate is 35%. The null hypothesis of 10% is based on the assumption that the population for each indication is expected to consist of subjects with incurable solid tumours that have failed multiple lines of standard therapy. The ORR for the limited treatment options available in these subject populations is generally <10%. The alternative best overall response rate is determined to be a clinically meaningful improvement over other standard treatment options within each studied indication. The power calculation is based on the binomialSPRT function in the gsDesign package and is carried out using R assuming a null ORR of 10%, an alternative ORR of 35%, type I error of 0.08 and type II error of 0.2: (binomialSPRT(p0=0.1,p1=0.35,alpha=0.08,beta=0.2,minn=10,maxn=25)). The minimum criterion for success is that the lower bound of the adjusted CI > 10%. Given the underlying true rate, this may occur when at least 7/25 subjects develop a confirmed PR or CR. Table 23 summarizes the power under various assumptions.

Table 23. KEYNOTE-051 Operating Characteristics of the Sequential Monitoring Approach

True RR	Probability of stopping for Futility	Probability of Positive Trial within an Indication	Average Sample Size
10%	0.94	0.04	13
15%	0.78	0.15	15
20%	0.57	0.32	18
25%	0.37	0.53	20
30%	0.22	0.71	22
35%	0.12	0.84	23
40%	0.06	0.92	24
45%	0.03	0.97	25
50%	0.01	0.99	25

KEYNOTE-051 Subgroup Analyses and Effect of Baseline Factors

No subgroup analysis is planned for KEYNOTE051.

Table 24. Summary of KEYNOTE-204, KEYNOTE-087 and KEYNOTE-051 statistical analyses[3, 25, 26]

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KEYNOTE-204	Primary PFS – per IWG 2007 by blinded independent central review OS Key Secondary ORR	The primary hypotheses for PFS and OS will be evaluated by comparing pembrolizumab vs BV using a stratified log-rank test. Estimation of the HR will be done using a stratified Cox regression model. Event rates over time for PFS and OS will be estimated within each treatment group using the Kaplan-Meier method. The Stratified Miettinen and Nurminen's method, weighted by stratum size, will be used for comparison of the ORR between the treatment groups.	The planned sample size is approximately 300 subjects. There are 2 primary endpoints for this study, PFS and OS. The expected median PFS time in the control group is 5.6 months; based on 221 events, the study has 90% power to detect a hazard ratio of 0.622 (pembrolizumab vs. brentuximab vedotin) at alpha = 1.25% (one-sided). The expected median OS in the control group is 22.4 months; based on 146 events, the study has 80% power to detect a hazard ratio of 0.600 at alpha = 1.25% (one-sided).	Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

KEYNOTE-087	Primary ORR IWG criteria Key secondary CRR PFS DOR OS	The primary hypothesis will be evaluated, for each Cohort separately, by comparing ORR for MK-3475 to a fixed control rate using a binomial exact test. The point estimate of the ORR will be calculated for each Cohort as well as a 95% 2-sided exact confidence interval.	The planned sample size is 60 subjects for each Cohort for the primary analysis. For Cohorts 1 and 3, there is at least 93% power (one-sided 2.5% alpha level) within each Cohort to demonstrate that MK-3475 is superior to a fixed control rate of 15% assuming the underlying MK-3475 ORR is at least 35%. For Cohort 2, there is at least 93% power (one-sided 2.5% alpha level) to 5 is superior to a fixed control rate of 5% assuming the underlying MK-3475 ORR is at least 20%.	Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.
KEYNOTE-051	Primary Part II ORR RECIST 1.1 Key Secondary DOR PFS Disease control rate	A sequential monitoring approach will be used following the time that a minimum of 10 subjects are enrolled in each indication. The Type-I error rate over the multiple evaluations within an indication will be controlled by the truncated sequential probability ratio test procedure at 0.08 (1-sided).	With 25 subjects per indication, this study provides 84% power to demonstrate that the best overall response rate induced by pembrolizumab exceeds 10% at an overall one-sided 8% alpha level, if the true best overall response rate within an indication is 35%. The underlying treatment effect is regarded as clinically important in each of the indications studied. Given the underlying true rate, this may occur when at least 7/25 subjects develop a response.	Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Participant flow in the relevant randomised controlled trials

Details of the participant flow and subject disposition in KEYNOTE-204, KEYNOTE-087 and KEYNOTE-051 are provided in Appendix D (Section D1.3).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment for the clinical trials in Section 2.2 are presented in Appendix D.1.3.

B.2.5.1. Consideration of UK clinical practice

Currently in the UK, there is no innovative immuno-oncology treatment available for the second or third-line treatment of patients with R/RcHL. Data from KEYNOTE-204 show that pembrolizumab is a promising treatment option which has demonstrated clinically meaningful and statistically significant efficacy benefit in the R/RcHL population as well as being well tolerated in this population[3].

KEYNOTE-204 recruited over one third of patients in Europe and baseline demographics suggest these patients were representative of those typically seen in UK clinical practice. The data from KEYNOTE-204 suggest that pembrolizumab could offer a significant step-change in benefit for these patients for R/RcHL patients in the second and third line.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 KEYNOTE-204 Clinical Effectiveness Results[3]

The results for KEYNOTE-204 demonstrate that pembrolizumab provides clinically meaningful and statistically superior PFS, compared with BV, in participants with R/RcHL.

A total of [redacted] participants were screened, of these 304 participants were randomized to pembrolizumab (151 participants) or BV (153 participants). The majority of participants randomized into the study received treatment (148/151 in the pembrolizumab arm and 152/153 in the BV arm). The participant flow and subject disposition from KEYNOTE-204 are provided in Appendix D.

KEYNOTE-204 Primary efficacy endpoint: clinical outcome measures included within the health economic model

As of the data cut-off date for [redacted], the median duration of follow up was [redacted] months (range: [redacted] months) in the pembrolizumab group and [redacted] months (range: [redacted] months) in the BV group (Table 25).

Table 25. Summary of Follow-up Duration (ITT Population)

Follow up duration (months)	MK-3475 200mg (N=151)	BV (N=153)

Median (Range)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Follow-up duration is defined as the time from randomisation to the date of death or the database cutoff date if the subject is still alive		

PFS: ITT analyses

PFS was significantly longer in the pembrolizumab arm compared with the BV arm. The HR for PFS was 0.65 (95% CI: 0.48, 0.88) and the one-sided log-rank test p=0.00271 which crossed the pre-specified boundary for statistical significance at [redacted] of [redacted]. A clinically meaningful improvement in PFS was observed for participants in the pembrolizumab arm, with a median PFS of 13.2 months (95% CI: 10.9, 19.4), compared with 8.3 months (95% CI:5.7, 8.8) for participants in the BV arm (Table 26).

The PFS rates at 12 and 24 months by KM estimation were 53.9% and [redacted] respectively, in the pembrolizumab arm compared with 35.6% and [redacted] in the BV arm (Table 26) The KM curves show clear separation after Month 6, favoring pembrolizumab.

Sensitivity analyses ignoring censoring for events occurring after ≥2 missed visits (Sensitivity analysis 1) and treating discontinuation of treatment as an event (Sensitivity analysis 2) were consistent with the primary PFS result. PFS assessed by the investigator using IWG 2007 criteria showed a more marked PFS benefit than PFS assessed by BICR (Appendix L)

PFS analyses for the subgroups and post-hoc analyses for subpopulations are included in Appendix E and L, respectively.

Table 26. Primary Analysis of PFS Based on Central Review per IWG 2007 (ITT Population)3

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)	PFS Rate at Months 24 in % † (95% CI)
MK-3475 200 mg Brentuximab Vedotin	151 153	[redacted]	[redacted]	[redacted]	13.2 (10.9, 19.4) 8.3 (5.7, 8.8)	53.9 (45.0, 61.9) 35.6 (26.9, 44.4)	[redacted]

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡	p-value§
Primary MK-3475 200 mg vs. Brentuximab Vedotin	0.65 (0.48, 0.88)	0.00271

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

§ One-sided p-value based on log-rank test stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

NR= Not Reached

Database Cutoff Date: [redacted]

Figure 7. Kaplan-Meier Estimates of Progression-Free Survival Based on Central Review per IWG 2007 (Primary Analysis) (ITT Population)3

KEYNOTE-204 Secondary Efficacy Endpoints[3]

PFS-Secondary ITT analyses

PFS-secondary indicated a clinically meaningful improvement in the pembrolizumab arm compared with the BV arm; HR 0.62 (95% CI: 0.46, 0.85), although no alpha was spent for this endpoint. Median PFS was 12.6 months (95% CI: 8.7, 19.2) in the pembrolizumab arm, compared with 8.2 months (95% CI: 5.6, 8.6) for participants in the BV arm. The PFS2 rates at 12 and 24 months by KM estimation were [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]), respectively, in the pembrolizumab arm compared with [redacted]% (95% CI: [redacted] and [redacted]

[redacted] % (95% CI: [redacted] in the BV arm. Results of PFS2 assessed by investigator remained consistent with PFS2 based on BICR and are presented in Appendix L.

*Table **27**. Analysis of Progression-Free Survival Based on Central Review per IWG 2007 (Secondary Analysis) (ITT population)*

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)	PFS Rate at Months 24 in % † (95% CI)
MK-3475 200 mg Brentuximab Vedotin	151 153	[redacted]	[redacted]	[redacted]	12.6 [redacted] 8.2 ([redacted]	[redacted]	[redacted]

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡	p-value§
Primary MK-3475 200 mg vs. Brentuximab Vedotin	0.62 (0.46, 0.85)	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

§ One-sided p-value based on log-rank test stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

NR= Not Reached

Database Cutoff Date: [redacted]

Figure 8 Kaplan-Meier Estimates of Progression-Free Survival Based on Central Review per IWG 2007 (Secondary Analysis) (ITT Population)

ORR ITT Population

The ORR based on BICR was increased in favor of pembrolizumab compared with BV. The ORR was 65.6% (95% CI:) for pembrolizumab and 54.2% (95% CI:) for BV. The (95% CI:) difference in response rates was not statistically significant (stratified Miettinen and Nurminen's method p-value). Subgroup analysis of ORR indicated an improved ORR, relative to BV, in participants without prior ASCT and primary refractory participants (Appendix E).

More than half of participants in the pembrolizumab arm had tumor reductions from baseline Figure 9. Results of ORR assessed by the investigator were consistent with ORR based on BICR and are presented in Appendix L. ORR post-hoc analyses for subpopulations are included in Appendix L

*Table **28**. Analysis of Objective Response Based on Central Review per IWG 2007 (ITT Population)*

Treatment	N	Number of Objective Response	›jective Response Rate (%) (95% CI)	Difference in Percentage MK-3475 200 mg vs. Brentuximab Vedotin	
				Estimate (95% CI)†	p-Value††
MK-3475 200 mg	151	[redacted]	65.6 [redacted]	[redacted]	[redacted]
Brentuximab Vedotin	153	[redacted]	54.2 [redacted]	[redacted]	

† Based on Miettinen & Nurminen method stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Excludes data after autologous SCT or allogeneic SCT.

Database Cutoff Date: [redacted]

Figure 9. Waterfall Plot of Maximum Tumour Change from Baseline Based on Central Review per IWG 2007 (Subjects with Measurable Disease at Baseline and at Least One Post-Baseline Measurement) (ITT Population)

Figure 10. Waterfall Plot of Maximum Tumour Change from Baseline Based on Central Review per IWG 2007(Subjects with Measurable Disease at Baseline and at Least One Post-Baseline Measurement)(ITT Population)BV

Table 29. Summary of Response Outcome in Subjects with Response Based on Central Review per IWG 2007

	MK-3475 200 mg (N=151)	Brentuximab Vedotin (N=153)
Number of Subjects with Response†	[redacted]	[redacted]
Subjects Who Progressed or Died‡ (%)	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]
Censored Subjects (%)	[redacted]	[redacted]
Subjects who missed 2 or more consecutive disease assessments	[redacted]	[redacted]
Subjects who started new anti-cancer treatment	[redacted]	[redacted]
Subjects who were lost to follow-up	[redacted]	[redacted]
Subjects whose last assessment was ≥ 30 weeks prior to data cutoff date	[redacted]	[redacted]
Ongoing response§	[redacted]	[redacted]
≥ 6 months	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]
≥ 18 months	[redacted]	[redacted]
≥ 24 months	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]

† Includes subjects with best overall response as complete response or partial response.

‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.

§ Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <30 weeks prior to data cutoff date.

For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.

'+' indicates there was no progressive disease by the time of last disease assessment.

Database Cutoff Date: [redacted]

The CRR was consistent between the treatment arms. The CRR was [redacted] (95% CI: [redacted] for pembrolizumab and [redacted] (95% CI: [redacted] for BV. CRR assessed by the investigator was consistent with the primary analysis of CRR and is presented in Appendix L.

Table 30. Summary of Best Overall Response Based on Central Review per IWG 2007 (ITT Population)

	MK-3475 200 mg			Brentuximab Vedotin		
	n	(%)	(95% CI)†	n	(%)	(95% CI)†
Number of Subjects in Population	151			153		
Complete Response (CR)	37	(24.5)	[redacted]	37	(24.2)	[redacted]
Partial Response (PR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Objective Response (CR+PR)	**99**	**(65.6)**	[redacted]	**83**	**(54.2)**	[redacted]
Stable Disease (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable (NE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Assessment (NA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Based on binomial exact confidence interval method. Excludes data after autologous SCT or allogeneic SCT.

Database Cutoff Date: [redacted]

KEYNOTE-204 Exploratory Endpoints

DOR and Time to Response

Responses to pembrolizumab were durable. Among all responders, the median time to response by BICR was the same for both treatment arms at [redacted]. The median DOR including clinical and imaging data following ASCT or allo-SCT increased in favor of pembrolizumab compared to BV; 20.7 months (0.0+ - 33.2+ months) and 13.8 months (0.0+-33.9+), respectively (Table 31).

Among the [redacted] pembrolizumab participants with response, a response of at least 12 months was observed in [redacted] by KM method) and of at least 24 months was observed in [redacted] ([redacted] by KM method) Figure 11. For the 83/153 participants who responded to BV, a response of at least 12 months was observed in [redacted] ([redacted] by KM method) and of at least 24 months was observed in [redacted] by KM method). DOR as assessed by the investigator was confirmed with DOR by BICR and is presented in Appendix L.

Table 31. Summary of Time to Response and Duration of Response Based on Central Review per IWG 2007 in Subjects with Response (ITT Population)

	MK-3475 200 mg (N=151)	Brentuximab Vedotin (N=153)
Number of subjects with response†	[redacted]	[redacted]
Time to Response (months)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
Response Duration‡ (months)		
Median (Range)	20.7 (0.0+ - 33.2+)	13.8 (0.0+ - 33.9+)
Number (%‡) of Subjects with Extended Response Duration:		
≥6 months	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]
≥18 months	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]

† Includes subjects with best overall response as complete response or partial response.
‡ From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: [redacted]

Figure 11. Kaplan-Meier Estimates of Duration of Response Based on Central Review per IWG 2007 in Subjects with Response (ITT Population)

Patient Reported Outcomes (PRO)

Longer PFS in the pembrolizumab group was accompanied by an improvement in health related QOL, as compared to BV. The primary analysis approach for the prespecified PRO endpoints was based on a quality of- life-related full analysis set (FAS) population, which consists of all randomized participants who received at least 1 dose of study treatment and had completed at least 1 PRO assessment.

PROs are assessed pre-dose at Cycle 1 (baseline), Cycle 3 (Week 6), Cycle 5 (Week 12), Cycle 7 (Week 18), and Cycle 9 (Week 24) and every 12 weeks thereafter until PD or up to 1 year while the subject is receiving study treatment. Patient-reported outcomes will also be obtained at discontinuation and at the 30-day Safety Follow-up Visit. If discontinuation occurs 30 days from the last dose of study treatment, i.e., at the time of the mandatory 30-day Safety Follow-up Visit, PROs do not need to be repeated.

EORTC QLQ-C30 and EQ-5D Compliance Rate and Completion Rate ITT

In the PRO FAS population, there were [redacted] participants in the pembrolizumab arm and [redacted] participants in the BV arm. Compliance rates for EORTC QLQ-C30 at baseline were similar and [redacted] in both the pembrolizumab and BV arms ([redacted] vs [redacted]) and remained high at Week 24 ([redacted] vs [redacted]). Compliance rates at baseline through Week 24 were similar for EQ-5D. Completion rates decreased at each time point as participants discontinued treatment primarily due to disease progression.

EORTC QLQ-C30 Analysis of Score Change From Baseline at Week 24

At baseline EORTC QLQ-C30 mean scores were similar across treatment arms, but by Week 24 had improved in the pembrolizumab arm and deteriorated in the BV arm. A statistically significant improvement in GHS/QOL mean score from baseline to Week 24 was observed for pembrolizumab compared to BV, where there was a worsening. At Week 24, the GHS/QOL score improved from baseline (least squares [LS] mean = [redacted] , 95% CI: [redacted]) in the pembrolizumab arm, compared to a worsening in the BV arm (LS mean = [redacted] ; 95% CI: [redacted]) Table 32. A statistically significant difference in LS means between pembrolizumab and the BV arm at Week 24 of [redacted] (95% CI: [redacted] ; two-sided p=[redacted] not controlled for multiplicity) was observed.

At Week 24, the EORTC QLC-C30 physical functioning score improved from baseline (LS mean = [redacted], 95% CI: [redacted]) in the pembrolizumab arm, compared to a worsening in the BV arm (LS mean =[redacted]; 95% CI: [redacted]). A statistically significant difference in LS means between pembrolizumab and the BV arm at Week 24 of [redacted](95% CI: [redacted]; two-sided p=[redacted], not controlled for multiplicity) was observed Table 33.

Regardless of disease status, pembrolizumab showed a mean improvement in GHS/QOL from baseline to Week 24 as compared to BV. Among participants with disease progression there was statistically significant improvement in GHS/QOL score from baseline to Week 24 for pembrolizumab arm, approaching clinical significance (LS mean = [redacted] 95% CI: [redacted]) compared to BV, where there was a worsening (LS mean = [redacted]95% CI[redacted]A clinically significant difference of [redacted](95% CI: [redacted]two-sided p=[redacted]not controlled for multiplicity) in LS means between pembrolizumab and the BV arm at Week 24 was observed (Table 34). Among participants without disease progression, there was an improvement in GHS/QOL score from baseline to Week 24 for pembrolizumab arm (LS mean = [redacted], 95% CI: [redacted]) compared to BV, which remained stable (LS mean = [redacted], 95% CI: [redacted]) (Table 35). The difference in LS means between pembrolizumab and

the BV arm at Week 24 was [redacted] (95% CI: [redacted]; two-sided p=[redacted], not controlled for multiplicity).

Based on the mean score change from baseline to Week 24, the EORTC QLQ-C30 GHS/QOL and the 5 functional scales showed an overall improvement in pembrolizumab arm compared to BV arms Figure 12. Pembrolizumab showed an improvement in all functional scale scores from baseline, except cognitive functioning. BV showed a worsening in all functional scale scores from baseline, except for social functioning.

Table 32. Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL at Week 24 (FAS Population)

Treatment	Baseline		Week 24		Change from Baseline at Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
MK-3475 200 mg Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
MK-3475 200 mg vs. Brentuximab Vedotin					[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months, relapsed 12 months or more)) as covariates.
For baseline and Week 24, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: [redacted]

Table 33. Analysis of Change from Baseline in EORTC QLQ-C30 Physical Functioning Scale at Week 24 (FAS Population)

Treatment	Baseline		Week 24		Change from Baseline at Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
MK-3475 200 mg Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
MK-3475 200 mg vs. Brentuximab Vedotin					[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months, relapsed 12 months or more)) as covariates.
For baseline and Week 24, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: [redacted]

Table 34. Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL at Week 24 (Subjects Who Progressed) (FAS Population)

Treatment	Baseline		Week 24		Change from Baseline at Week 24		
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†	
MK-3475 200 mg Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
MK-3475 200 mg vs. Brentuximab Vedotin						[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months, relapsed 12 months or more)) as covariates.

For baseline and Week 24, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Subjects assessed PD by BICR at any time during the study, or before stem cell transplant (SCT) for subjects with post-treatment SCT.

Database Cutoff Date: [redacted]

Table 35. Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL at Week 24 (Subjects Who did not Progress) (FAS Population)

Treatment	Baseline		Week 24		Change from Baseline at Week 24		
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†	
MK-3475 200 mg Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
MK-3475 200 mg vs. Brentuximab Vedotin						[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months, relapsed 12 months or more)) as covariates.

For baseline and Week 24, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Subjects not assessed PD by BICR at any time during the study, or before stem cell transplant (SCT) for subjects with post-treatment SCT.

Database Cutoff Date: [redacted]

Figure 12. Change from Baseline for EORTC QLQ-C30 Functional Scale/Global Health Status/QoL at Week 24* LS Mean Change and 95% CI (FAS Population)

EQ-5D

Results from EQ-5D analyses were consistent with the results of EORTC QLQ-C30 analyses. For EQ-5D utility scores, a statistically significant difference in LS means between pembrolizumab and the BV arm at Week 24 of [redacted](95% CI[redacted]two-sided p=[redacted], not controlled for multiplicity) was observed Table 36. For EQ-5D visual analog scores, a statistically significant difference in LS means between pembrolizumab and the BV arm at Week 24 of [redacted](95% CI: [redacted]; two-sided p=[redacted], not controlled for multiplicity) was observed Table 37.

Table 36. Analysis of Change from Baseline in EQ-5D Utility Score at Week 24 (FAS Population)

Treatment	Baseline		Week 24		Change from Baseline at Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
MK-3475 200 mg Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
MK-3475 200 mg vs. Brentuximab Vedotin	[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months, relapsed 12 months or more)) as covariates.
For baseline and Week 24, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: [redacted]

Table 37. Analysis of Change from Baseline in EQ-5D Visual Analogue Scale (VAS) Score at Week 24 (FAS Population)

Treatment	Baseline		Week 24		Change from Baseline at Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
MK-3475 200 mg Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
MK-3475 200 mg vs. Brentuximab Vedotin	[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months, relapsed 12 months or more)) as covariates.
For baseline and Week 24, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: [redacted]

Analysis of Mean Change Over Time for EORTC QLQ-C30 Scores

A summary of the change from baseline over time for the EORTC QLQ-C30 GHS/QOL scores and functional scales are shown in Figure 13 to Figure 18. Overall, beginning at Week 6, participants in the pembrolizumab arm had a higher GHS/QOL scores compared to the BV arm (ie, 95% CI did not overlap, with the exception [redacted]). For functional scales, overall, beginning at Week 6, participants in the pembrolizumab arm had improvements in mean change scores from baseline and this remained stable over time. For the BV arm, there was a worsening for GHS/QOL and role and physical functioning, and either no change in mean scores from baseline or a slight improvement for the remaining functional scales.

Figure 13. Empirical Mean Change from Baseline in the EORTC QLQ-C30 Cognitive Functioning Scale Score Over Time Mean +/- SE (FAS Population)

Figure 14. Empirical Mean Change from Baseline in the EORTC QLQ-C30 Emotional Functioning Scale Score Over Time Mean +/- SE (FAS Population)

Figure 15. Empirical Mean Change from Baseline in the EORTC QLQ-C30 Physical Functioning Scale Score Over Time Mean +/- SE (FAS Population)

Figure 16. Empirical Mean Change from Baseline in the EORTC QLQ-C30 Global Health Status/QoL Score Over Time Mean +/- SE (FAS Population)

Figure 17 Empirical Mean Change from Baseline in the EORTC QLQ-C30 Role Functioning Scale Score Over Time Mean +/- SE (FAS Population)

Figure 18. Empirical Mean Change from Baseline in the EORTC QLQ-C30 Social Functioning Scale Score Over Time Mean +/- SE (FAS Population)

Time to Deterioration Analysis of EORTC QLQ-C30 Global Health Status/QOL Score and Physical Functioning

Pembrolizumab prolonged the time to true deterioration when compared to BV for the EORTC QLQ-C30 GHS/QOL scores (HR [redacted] 95% CI: [redacted]; two-sided p=[redacted], not controlled for multiplicity) and the physical functioning scores (HR = [redacted]; 95% CI[redacted]; two-sided p=[redacted], not controlled for multiplicity) Table 38 and Table 39. True deterioration was defined as the time to first onset of 10 or more decrease from baseline in the EORTC QLQ-C30 GHS/QOL and physical functioning score.

Table 38. Time to True Deterioration for EORTC QLQ-C30 Global Health Status/QoL (FAS Population)

Treatment	N	Deterioration (Events) %	Brentuximab Vedotin vs. MK-3475 200 mg	
			Hazard Ratio† (95% CI)†	p-Value‡
MK-3475 200 mg Brentuximab Vedotin	[redacted]	[redacted]	--- [redacted]	--- [redacted]

True deterioration is defined as the time to first onset of 10 or more decrease from baseline with confirmation under right-censoring rule (the last observation).

† Based on Cox regression model with treatment as a covariate stratified by prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months, relapse 12 months or more).

‡ Two-sided p-value based on log-rank test.

Database Cutoff Date: [redacted]

Table 39. Time to True Deterioration for EORTC QLQ-C30 Physical Functioning Scale (FAS Population)

Treatment	N	Deterioration (Events) %	Brentuximab Vedotin vs. MK-3475 200 mg	
			Hazard Ratio† (95% CI)†	p-Value‡
MK-3475 200 mg Brentuximab Vedotin	[redacted]	[redacted]	--- [redacted]	--- [redacted]

True deterioration is defined as the time to first onset of 10 or more decrease from baseline with confirmation under right-censoring rule (the last observation).

† Based on Cox regression model with treatment as a covariate stratified by prior auto-SCT (yes, no) and disease status after frontline therapy (primary refractory, relapsed less than 12 months, relapse 12 months or more).

‡ Two-sided p-value based on log-rank test.

Database Cutoff Date [redacted]

A significantly greater proportion of pembrolizumab patients, compared to BV, had a clinically significant improvement (of 10 points or higher) in EORTC QLQ-C30 GHS/QOL (p=[redacted]) and physical functioning scores (p=[redacted]). Improvement was defined as 10 points or more increase from baseline at any time during the trial, with confirmation at the next consecutive visit. Otherwise, a patient was considered to not have improved. A significantly greater proportion of pembrolizumab patients, compared to BV, had a clinically significant improvement or stability (of 10 points or higher) in EORTC QLQ-C30 GHS/QOL (p= [redacted]) and physical functioning scores (p[redacted]). Improvement/stability was defined as a change of more than -10 points from baseline at any time during the trial, with confirmation at the next consecutive visit. Otherwise, a patient was considered to not have been improved/stability.

KEYNOTE-204 Stem Cell Transplant Pre and Post-Study Therapy

Nearly equal percentages of participants in both the pembrolizumab and BV arms underwent ASCT or allo-SCT following study treatment. There were [redacted] participants ([redacted] who underwent ASCT at some point after treatment with pembrolizumab compared with

[redacted]participants ([redacted]in the BV arm (Table 40). A total of [redacted]participants [redacted]underwent allogeneic transplant at some point after treatment with pembrolizumab compared with [redacted]([redacted]in the BV arm. Sensitivity analyses with consideration of SCT indicate that the results are consistent with the primary analysis, regardless of baseline SCT and chemorefractory status or whether participants received SCT post study treatment Table 41.

Table 40. Summary of Subsequent Stem Cell Transplant (ASaT Population)

	MK-3475 200 mg (N=148)	Brentuximab Vedotin (N=152)
Autologous Transplant (%) Allogeneic Transplant (%)	[redacted]	[redacted]
† The following subjects had one autologous transplant and one allogeneic transplant, and is counted in both rows: 204601, 204625, 204631. Database Cutoff Date: [redacted]		

Table 41. Progression-Free Survival Based on Central Review per IWG 2007 (Sensitivity Analyses with consideration of Stem Cell Transplant) (ITT Population)

PFS Analysis	Description	HR† (95% CI)†
1	Baseline SCT and chemorefractory status‡ as a subgroup	
	Received prior SCT	[redacted]
	Chemorefractory and did not receive prior SCT	[redacted]
	Not chemorefractory and did not receive prior SCT	[redacted]
2	Baseline SCT and chemorefractory status‡ as a covariate	[redacted]
3	Post study treatment SCT* as a time-dependent covariate	[redacted]
4	Post study treatment SCT* as a time-dependent covariate with treatment interaction	[redacted]

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

‡ Baseline SCT and chemorefractory status has three levels: received prior SCT versus chemorefractory and did not receive prior SCT versus not chemorefractory and did not receive prior SCT.

*Based on the first autologous or allogeneic stem cell transplant received after study treatment.

B.2.6.2 KEYNOTE-087 Clinical Effectiveness Results[25]

With a median follow-up of over 3 years, results of this study (KEYNOTE-087) demonstrate consistent, highly clinically relevant, and durable anti-tumor activity of pembrolizumab monotherapy (200 mg Q3W) in heavily pre-treated participants with R/R cHL who have exhausted all conventional treatment options.

KEYNOTE -087 Primary efficacy endpoints[25]

With a median follow-up duration of 39.5 months (range, 1.0-44.8), based on IWG response criteria, the ORR by BICR in all treated participants was 71.0% (149/210; 95% CI: 64.3%, 77.0%), with 27.6% CR Table 42.

Table 42. KEYNOTE-087 Summary of Best Overall Response Based on Central Review per IWG (ASaT Population)

Response Evaluation	MK-3475 200 mg (N=210)	
	n (%)	95% CI†
Complete Remission (CR)	58 (27.6)	[redacted]
Partial Remission (PR)	91 (43.3)	[redacted]
Objective Response (CR+PR)	**149 (71.0)**	**(64.3, 77.0)**
Stable Disease (SD)	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]
No Assessment (NA)	[redacted]	[redacted]
† Based on binomial exact confidence interval method. (Database Cutoff Date[redacted]		

KEYNOTE-087 Secondary Efficacy Endpoints[25]

Based on Lugano criteria, the ORR by BICR in all treated participants was [redacted] ([redacted] 95% CI: [redacted] with [redacted]% CR (Table 43). The ORR based on IWG response criteria by site review [redacted] [[redacted]]; was similar to the ORR by BICR. The CRR based on IWG response criteria by site review was [redacted] (Appendix L).

Table 43. KEYNOTE-087 Summary of Best Overall Response Based on Central Review per Lugano Classification (ASaT Population)

Response Evaluation	MK-3475 200 mg (N=210)	
	n (%)	95% CI†
Complete Remission (CR)	[redacted]	[redacted]
Partial Remission (PR)	[redacted]	[redacted]
Objective Response (CR+PR)	[redacted]	[redacted]
Stable Disease (SD)	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]
No Assessment (NA)	[redacted]	[redacted]
† Based on binomial exact confidence interval method. (Database Cutoff Date[redacted]		

Duration of Response

Among all responders (n=149), the median time to response by BICR was [redacted] months (range: [redacted]), and the median DOR was 16.6 months (range: 0.0+ to 39.1+; Table 44). Response durations of ≥12 and ≥24 months were observed in [redacted] ([redacted]% by KM estimation) and [redacted] ([redacted]% by KM estimation) participants, respectively Table 44 and

Figure 19. At the time of the data cutoff, [redacted] responders ([redacted]%) had an ongoing response Table 45. Median time to response and response duration based on site review are presented in Appendix L.

Table 44. KEYNOTE-087 Summary of Time to Response and Response Duration Based on Central Review per IWG in Subjects With Response (ASaT Population)

	MK-3475 200 mg (N=210)
Number of Subjects with Response†	149
Time to Response † (months)	
Mean (SD)	[redacted]
Median (Range)	
Response Duration‡ (months)	
Median (Range)	16.6 (0.0+ - 39.1+)
95% CI	
Number of Subjects with Response ≥ 3 Months (%)‡	[redacted]
Number of Subjects with Response ≥ 6 Months (%)‡	
Number of Subjects with Response ≥ 9 Months (%)‡	
Number of Subjects with Response ≥ 12 Months (%)‡	
Number of Subjects with Response ≥ 24 Months (%)‡	
Number of Subjects with Response ≥ 36 Months (%)‡	

† Analyses on time to response and response duration are based on subjects with a best overall response as complete remission or partial remission only.

‡ From product-limit (Kaplan-Meier) method for censored data.

"+" indicates there is no progressive disease by the time of last disease assessment. (Database Cutoff Date: [redacted]).

Figure 19. KEYNOTE-087 Kaplan-Meier Estimates of Objective Response Duration Based on Central Review per IWG in Subjects With Response (ASaT Population)

Table 45 KEYNOTE-087 Summary of Response Outcomes Based on Central Review per IWG in Subjects With Response (ASaT Population)

	MK-3475 200 mg (N=210)
Number of Subjects with Response†	149
Censored Subjects %)	[redacted]
Subjects who progressed or died after 2 or more missed visits (%)	[redacted]
Subjects started new anti-cancer treatment (%)	[redacted]
Subjects with stem cell transplant (%)	[redacted]
Subjects who were lost to follow-up (%)	[redacted]
Subjects who had no disease assessments in 30 weeks (%)	[redacted]
Ongoing response‡ (%)	[redacted]
Range of DOR (months) Ongoing	[redacted]
response ≥ 3 months Ongoing	[redacted]
response ≥ 6 months Ongoing	[redacted]
response ≥ 9 months Ongoing	[redacted]
response ≥ 12 months Ongoing	[redacted]
response ≥ 24 months	[redacted]
Ongoing response ≥ 36 months	[redacted]

† Response: Analyses are based on subjects with a best overall response as complete remission or partial remission.

‡ Ongoing response: Subjects who are censored, alive, have not progressed, have not started a new anti-cancer therapy, are not lost to follow-up and the last non-"NE" imaging assessment is within 210 days (30 weeks) of the data cutoff date. (Database Cutoff Date: [redacted]).

KEYNOTE-087 Progression-free Survival

In all treated participants, the median PFS by BICR was [redacted] months (95% CI: [redacted];). The PFS rates at 12 and 24 months by BICR were [redacted]% and [redacted]%, respectively, by KM estimation Table 46 and

Figure 20. PFS by site review are presented in Appendix L.

Table 46. KEYNOTE-087 Summary of Progression-Free Survival (PFS) Based on Central Review per IWG (ASaT Population)

	MK-3475 200 mg (N=210)
Number (%) of PFS Events	[redacted]
Person-Months	[redacted]
Event Rate/100 Person-Months (%)	[redacted]
Median PFS (Months)†	13.6
95% CI for Median PFS† PFS	(11.1,16.7)
rate at 3 Months in % † PFS	[redacted]
rate at 6 Months in % † PFS	[redacted]
rate at 9 Months in % † PFS	[redacted]
rate at 12 Months in % † PFS	[redacted]
rate at 24 Months in % †PFS	[redacted]
rate at 30 Months in % †	[redacted]
PFS rate at 36 Months in % †	[redacted]

Progression-free survival is defined as time from first dose to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
(Database Cutoff Date: [redacted]).

Figure 20. Kaplan-Meier Estimates of Progression-Free Survival Based on Central Review per IWG (ASaT Population)

KEYNOTE-087 Overall Survival

In all treated participants, the median OS was not reached (95% CI: not reached, not reached; Table 47. The OS rates at 12 and 24 months were [redacted]%, and [redacted] %, respectively, by KM estimation (Figure 21).

Table 47. Summary of Overall Survival (ASaT Population)

	MK-3475 200 mg (N=210)
Death (%) Median Survival (Months)† 95% CI for Median Survival† OS rate at 6 Months in % † OS rate at 9 Months in % † OS rate at 12 Months in % † OS rate at 15 Months in % † OS rate at 24 Months in % † OS rate at 30 Months in % † OS rate at 36 Months in % †	[redacted] Not reached (Not reached, Not reached) [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] 86.4
OS: Overall survival. † From product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: [redacted]	

Figure 21. Kaplan-Meier Estimates of Overall Survival (ASaT Population)

[redacted]

KEYNOTE-087 SCT Post-study Treatment

Of the 210 participants in the study, [redacted] ([redacted] underwent auto-SCT and [redacted] ([redacted]%) underwent allo-SCT at some point after stopping treatment with pembrolizumab; [redacted] participant underwent both ASCT and allo-SCT post-study treatment.

Table 48. Summary of Subsequent Stem Cell Transplant (ASaT Population)

	MK-3475 200 mg (N=210)
Autologous Transplant (%) Allogenic Transplant (%)	[redacted]
† One subject had one autologous transplant and one allogenic transplant, and is counted in both rows. (Database Cutoff Date: [redacted])	

B.2.6.3 KEYNOTE-051 Clinical Effectiveness Results[26]

Among the [redacted] participants with R/Rtumours other than HL, the 27 different primary diagnoses at baseline consisted of a large number of tumour types by histology. The sample size of each tumour type was small. A small number of confirmed responses to treatment were reported among 6 tumour types. Therefore, hypothesis testing was not performed for any tumour type. To better describe the higher ORR for the [redacted] participants with HL, the results of efficacy analyses were presented separately from the results for the [redacted] participants with all other tumour types. The combined results for all other tumour types were presented as “All R/R Tumours Except HL”.

Among the [redacted] participants with HL, 15 were enrolled in the PD-L1-positive solid tumours and other lymphoma Cohort (Table 13) For these participants, the endpoints ORR, DOR, DCR, and PFS were assessed by investigator review according to RECIST 1.1.

For the remaining [redacted] with HL who were enrolled in the dedicated R/RcHL Cohort (post-Amendment 7), the endpoints ORR, DOR, DCR, and PFS were assessed by investigator review according to IWG 2007 criteria.

For participants with relapsed/refractory tumours other than HL, the endpoints ORR, DOR, DCR, and PFS were assessed by investigator review according to RECIST 1.1/MIBG.

KEYNOTE-051 ORR Based on IWG 2007 Criteria- Relapsed/Refractory Hodgkin Lymphoma

The ORR was [redacted] (per IWG 2007 criteria) for the [redacted] participants in the dedicated rrcHL Cohort and [redacted] (confirmed responses per RECIST 1.1) for 15 participants with HL in the

PD-L1-positive solid tumours and other lymphoma Cohort. All [redacted] participants with HL had at least 1 post-baseline assessment of measurable tumour size in target lesions, and all had a reduction in tumour size post baseline. [redacted] had a maximum reduction in tumour size ⩾ 30%. The ORR was [redacted](confirmed responses per RECIST 1.1) for [redacted] participants with R/R tumours other than HL.

Table 49. KEYNOTE-051 Summary of Best Overall Response Based on IWG 2007 per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (Post-Amendment 7) (All Subjects as Treated Population - Parts II)

Response Evaluation	All Subjects as Treated (N=[redacted])		
	n %		95% CI[T]
Complete Response (CR)	[redacted]	[redacted]	[redacted]
Partial Response (PR)	[redacted]	[redacted]	[redacted]
Best Overall Response (CR+PR)	[redacted]	[redacted]	[redacted]
Stable Disease (SD)	[redacted]	[redacted]	[redacted]
Disease Control Rate (SD+CR+PR)	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]	[redacted]
† Based on binomial exact confidence interval method. (Database Cutoff Date: [redacted]).			

KEYNOTE-051 ORR Based on RECIST 1.1- Relapsed/Refractory Hodgkin Lymphoma

The ORR based on RECIST 1.1 was [redacted] for 15 participants with HL in the PD-L1-positive solid tumours and other lymphoma Cohort[redacted] participant had a CR and [redacted] participants had a PR. All [redacted] responses were confirmed.

Table 50. KEYNOTE-051 Summary of Best Overall Response Based on RECIST 1.1 per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

Response Evaluation	All Subjects as Treated (N=15)		
	n %		95% CI[T]
Complete Response (CR)	[redacted]	[redacted]	[redacted]
Partial Response (PR)	[redacted]	[redacted]	[redacted]
Best Overall Response (CR+PR)	[redacted]	[redacted]	[redacted]
Stable Disease (SD)	[redacted]	[redacted]	[redacted]
Disease Control Rate (SD+CR+PR)	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]	[redacted]
Confirmed responses by RECIST 1.1 are included. † Based on binomial exact confidence interval method. (Database Cutoff Date: [redacted]).			

KEYNOTE-051 Changes from Baseline in Tumour Size – Relapsed/Refractory Hodgkin Lymphoma

All [redacted] participants with HL had at least 1 post-baseline assessment of measurable tumour size in target lesions, and all had a reduction in tumour size post baseline. [redacted] participants had a maximum reduction in tumour size ⩾30% Figure 22.

For the [redacted] participants enrolled in the dedicated rrcHL Cohort, percent change in tumour size was based on the sum of the product of the diameters (SPD) of all target lesions.For the remaining [redacted] participants with HL, percent change was based on the Sum of the longest diameters (SOD) for all target lesions, per RECIST 1.1. A spider plot of the percentage change from baseline in tumour size over time for each participant is provided Figure 23.

Figure 22. KEYNOTE-051 Waterfall Plot of Best Tumor Change from Baseline per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

Figure 23. KEYNOTE-051 Spider Plot of Tumour Change from Baseline per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II) Percentage changes >100% were set to 100%.

KEYNOTE-051 Duration of Response

Duration of Response Based on IWG 2007 Criteria - Relapsed/Refractory Hodgkin Lymphoma

The median time to response based on IWG 2007 criteria was [redacted] months for the 3 responders in the dedicated rrcHL Cohort (post-Amendment 7). The DOR ranged from [redacted] months. [redacted] responder had a DOR of 6 months or longer Table 51.

[redacted] of the [redacted] responses were ongoing at the time of data cutoff for this report Table 52.

Table 51. KEYNOTE-051 Summary of Time to Response and Duration of Response Based on IWG 2007 per Investigator Assessment in Subjects With a Response Relapsed/Refractory Hodgkin Lymphoma (Post-Amendment 7) (All Subjects as Treated Population - Parts II)

	All Subjects as Treated (N=[redacted])
Number of subjects with response†	[redacted]
Time to Response (months)	
Mean (SD)	[redacted]
Median (Range)	[redacted]
Response Duration‡ (months)	
Median (Range)	[redacted]
Number (%‡) of Subjects with Extended Response Duration:	
≥3 months	[redacted]
≥6 months	[redacted]

† Includes subjects with a response.

‡ From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment. NR = Not Reached.
(Data Cutoff Date: [redacted]).

Table 52. KEYNOTE-051 Summary of Response Outcome in Subjects Censored from the DOR Analysis of a Response Based on IWG 2007 per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (Post-Amendment 7(All Subjects as Treated Population - Parts II)

	MK3475 2 mg/kg Q3W (N=[redacted])
Number of Subjects with Response†	[redacted]
Subjects Who Progressed or Died‡ (%)	[redacted]
Range of DOR (months)	[redacted]
Censored Subjects (%)	[redacted]
Subjects who missed 2 or more consecutive disease assessments	[redacted]
Subjects who started new anti-cancer treatment	[redacted]
Subjects who were lost to follow-up	[redacted]
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	[redacted]
Ongoing response§	[redacted]
≥ 5 months	[redacted]
< 5 months	[redacted]
Range of DOR (months)	[redacted]

† Includes subjects with a response.

‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.

§ Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.

For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.

'+' indicates there was no progressive disease by the time of last disease assessment. (Data Cutoff Date: [redacted]).

KEYNOTE-051 Duration of Response Based on RECIST 1.1 - Relapsed/Refractory Hodgkin Lymphoma

The median time to response based on RECIST 1.1 was [redacted] months for the [redacted] confirmed responders with HL in the PD-L1-positive solid tumours and other lymphoma Cohort. The median DOR was [redacted] months by KM estimation [redacted] responders had a DOR of 6 months or longer; [redacted] responders had a DOR of 9 months or longer Table 53.

[redacted] of [redacted] confirmed responses were ongoing at the time of data cutoff for this report Table 54.

Table 53. KEYNOTE-051 Summary of Time to Response and Duration of Response Based on RECIST 1.1 per Investigator Assessment in Subjects With Confirmed Response Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=15)
Number of subjects with response†	[redacted]
Time to Response (months)	
Mean (SD)	[redacted]
Median (Range)	[redacted]
Response Duration‡ (months)	
Median (Range)	[redacted]
Number (%‡) of Subjects with Extended Response Duration:	
≥3 months	[redacted]
≥6 months	[redacted]
≥9 months	[redacted]
† Includes subjects with confirmed response. ‡ From product-limit (Kaplan-Meier) method for censored data. "+" indicates there is no progressive disease by the time of last disease assessment. (Data Cutoff Date: [redacted]	

Table 54. KEYNOTE-051 Summary of Response Outcome in Subjects Censored from the DOR Analysis of Confirmed Response Based on RECIST 1.1 per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	MK3475 2 mg/kg Q3W (N=15)
Number of Subjects with Response†	[redacted]
Subjects Who Progressed or Died‡ (%)	[redacted]
Range of DOR (months)	[redacted]
Censored Subjects (%)	[redacted]
Subjects who missed 2 or more consecutive disease assessments	[redacted]
Subjects who started new anti-cancer treatment	[redacted]
Subjects who were lost to follow-up	[redacted]
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	[redacted]
Ongoing response§	[redacted]
≥ 5 months	[redacted]
< 5 months	[redacted]
Range of DOR (months)	[redacted]

† Includes subjects with a confirmed complete response or partial response.

‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.

§ Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.

For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.

'+' indicates there was no progressive disease by the time of last disease assessment. (Data Cutoff Date: [redacted]).

KEYNOTE-051 Disease Control Rate

Disease Control Rate Based on IWG 2007 Criteria– Relapsed/Refractory Hodgkin Lymphoma

The DCR based on IWG response criteria was [redacted]% for the [redacted] participants in the dedicated rrcHL Cohort Table 49.

Disease Control Rate Based on RECIST 1.1 - Relapsed/Refractory Hodgkin Lymphoma

The DCR based on RECIST 1.1 was [redacted] for 15 participants with HL in the PD-L1-positive solid tumours and other lymphoma Cohort Table 50.

KEYNOTE-051 Progression-free Survival Based on IWG 2007 Criteria - Relapsed/Refractory Hodgkin Lymphoma

The median PFS based on IWG 2007 criteria was [redacted] months by KM estimation for the [redacted] participants in the dedicated rrcHL Cohort. PFS rates at 6 and 12 months were [redacted]% and [redacted]%, respectively Table 55 and Figure 24

Table 55. KEYNOTE-051 Summary of Progression-Free Survival (PFS) by IWG 2007 per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (Post-Amendment 7) (All Subjects as Treated Population - Part II)

	All Subjects as Treated (N=[redacted])
Number (%) of PFS Events	[redacted]
Person-Months	[redacted]
Event Rate/100 Person-Months	[redacted]
(%) Median PFS (Months)§	[redacted]
95% CI for Median PFS§	[redacted]
PFS rate at 6 Months in % §	[redacted]
PFS rate at 12 Months in % §	[redacted]
Progression-free survival is defined as time from first dose to disease progression, death or start of new anti-cancer therapy, whichever occurs first. § From product-limit (Kaplan-Meier) method for censored data. (Data Cutoff Date: [redacted]).	

Figure 24. KEYNOTE-051 Kaplan-Meier Estimates of Progression-Free Survival (PFS) by IWG 2007 per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (Post-Amendment 7) (All Subjects as Treated Population - Part II)

KEYNOTE-051 Progression-free Survival Based on RECIST 1.1 – Relapsed/Refractory Hodgkin Lymphoma

The median PFS based on RECIST 1.1 was [redacted] months by KM estimation for 15 participants with HL in the PD-L1-positive solid tumours and other lymphoma Cohort. PFS rates at 6 and 12 months were [redacted]% and [redacted]%, respectively Table 56 and Figure 24

Table 56 KEYNOTE-051 Summary of Progression-Free Survival (PFS) by RECIST 1.1 per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Part I and II)

	All Subjects as Treated (N=15)
Number (%) of PFS Events Person-Months Event Rate/100 Person-Months (%) Median PFS (Months)§ 95% CI for Median PFS§ PFS rate at 6 Months in % § PFS rate at 12 Months in % §	[redacted]

Progression-free survival is defined as time from first dose to disease progression, death or start of new anti-cancer therapy, whichever occurs first.

§ From product-limit (Kaplan-Meier) method for censored data. (Data Cutoff Date: [redacted]).

Figure 25. KEYNOTE-051 Kaplan-Meier Estimates of Progression-Free Survival (PFS) per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Part I and II)

[redacted]

KEYNOTE-051 Overall Survival – Relapsed/Refractory Hodgkin Lymphoma

For the [redacted] participants with HL, the median OS had [redacted] at the time of data cutoff for this report. The OS rate was [redacted]% at both 6 and 12 months by KM estimation (Table 57 and Figure 26). [redacted] participant died shortly after 12 months.

*Table **57**. KEYNOTE-051 Summary of Overall Survival Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)*

	All Subjects as Treated (N=[redacted])
Death (%)	[redacted]
Median Survival (Months)§	[redacted]
95% CI for Median Survival§	[redacted]
OS rate at 6 Months in % §	[redacted]
OS rate at 12 Months in % §	[redacted]

OS: Overall survival.
§ From product-limit (Kaplan-Meier) method for censored data.
(Database Cutoff Date: [redacted]).

Figure 26. KEYNOTE-051 Kaplan-Meier Estimates of Overall Survival Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Part I and II)

B.2.7 Subgroup analysis

B.2.7.1 KEYNOTE-204 Subgroup analyses

KEYNOTE-204 Prespecified subgroup analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for PFS, the primary endpoint and OS, the second primary endpoint, will be estimated and plotted within each category of the following classification variables:

- Stratification factor: prior ASCT (yes vs. ≥ no)
- Stratification factor: disease status following first line therapy (refractory vs. relapsed within 12 months vs. relapsed after 12 months)

- Sex (female vs. male)
- Age (<65 years vs. ≥65 years)
- ECOG status (0 vs. 1)
- Geographic region
- Prior BV status (Yes vs. No)

PFS by subgroup

PFS for pre-specified subgroups, including participants with and without prior auto-SCT, participants with primary refractory disease, and participants who are BV-naïve, supports the consistency of the overall result. Appendix E

ORR by subgroup

Subgroup analysis of ORR indicated an improved ORR, relative to BV, in participants without prior ASCT and primary refractory participants Appendix E.

KEYNOTE-204 Post Hoc subgroup analyses

The efficacy results for PFS and ORR for the post hoc analyses carried out are presented by prior SCT for the purposes of the current submission to NICE in order to compare the subpopulations within the KEYNOTE-204 trial evaluating pembrolizumab vs BV, is presented in Appendix L as per the population outlined in the scope. Post hoc analyses were carried out for 3 cohorts; second line subjects with no prior stem cell transplant (ASCT-2L), subjects who are at least third line with no prior SCT (SCT-3L+) and subjects who are at least third line with prior stem cell transplant (SCT+3L+). The results for the 3 post-hoc analyses favoured pembrolizumab over BV in support of the results of the ITT population.

B.2.7.2 KEYNOTE-087 Subgroup analyses

To determine whether ORR was consistent across various subgroups, the point estimate of the ORR (with an exact 95% CI) will be provided and plotted within each category of the following classification variables within each Cohort:

- Age category (≤65 vs. >65 years)
- Sex (female vs. male)

- Race (white vs. non-white)
- Region (US, ex-US)
- Number of prior therapies (< 4 vs ≥4)

For Cohorts 1 and 3 only:

- Time elapsed since transplant failure (<12 months vs. ≥12)

If the observed numbers for a particular subgroup are too small to make a meaningful clinical interpretation, then that subgroup analysis will not be conducted. The subgroup analyses were not primary or secondary objectives and were not included in the report for this data cut.

B.2.7.3 KEYNOTE-051 Subgroup Analyses

No subgroup analyses were planned for KEYNOTE-051.

B.2.8 Meta-analysis

There is only one phase III randomised, controlled trial of pembrolizumab compared with the relevant comparator, BV, for the specific population of interest (patients with R/RcHL): KEYNOTE-204. Therefore, it was not possible to conduct a meta-analysis in this overall population.

B.2.9 Indirect and mixed treatment comparisons

Please refer to Appendix D for full details of the methodology used for the match adjusted indirect treatment comparison (MAIC). MAIC statistical analyses of pembrolizumab versus SOC interventions in auto-SCT-naïve cHL patients who are refractory to, or have relapsed after, one line of chemotherapy was carried out in order to supplement the direct evidence for pembrolizumab in KEYNOTE-204.

This MAIC uses the results from a SLR that identified relevant studies.

Summary of the trials included in the MAIC

The population of interest for the indirect comparison is R/R cHL patients who are ineligible for ASCT and have received one line of prior therapy i.e. 2L. ASCT-ineligibility is usually due

to advanced age, refractory disease, or organ dysfunction; however, there are not clear criteria for determining ineligibility for ASCT since some patients may be able to receive ASCT later on in the treatment pathway if they respond to salvage therapy whilst some may never be able to received ASCT. The population that was considered in this feasibility assessment for the MAIC was patients who had not previously received an ASCT and had received one prior line of treatment. The details of the SLR that identified relevant studies for a network meta-analysis are presented in Appendix D.1.2.1. From the set of studies included in the evidence base for the UK-focused SLR described by the PICOS in Appendix D, Table 1, the subset deemed relevant for the feasibility assessment was identified by applying additional criteria listed in Table 2, Appendix D.

It should be noted that KEYNOTE-204 was the only study included to describe pembrolizumab or BV, as this is the most relevant trial to the population of interest. In addition, KEYNOTE-204 is the only RCT comparing these interventions to each other, so any conclusions about the relative treatment effect of pembrolizumab to BV should come from the direct evidence in the trial.

The final list of studies included in the feasibility assessment is given in Table 58.

Table 58. Studies included in the feasibility assessment

Trial ID	NCT code	Intervention(s)	Primary publication	Secondary publications
KEYNOTE-204	NCT02684292	Pembrolizumab, BV	Kuruvilla 2020[30]	Merck CSR [3]
Baetz 2003	--	GDP	Baetz 2003[31]	--
Balzarotti 2016	NCT00636311	IGEV	Balzarotti 2016[32]	Balzarotti 2011[33]
Hu 2018	NCT01169636	ICE, ICE + panobinostat*	Hu 2018[34]	Hu 2016[35]
Josting 2002	--	DHAP	Josting 2002[36]	--
Ramzi 2015	--	GDP, ESHAP	Ramzi 2015[37]	--

Overview of analyses and the base case

As described earlier in this section, the trials in Table 57 were included in the feasibility assessment for the MAIC. 6 MAICs related to the comparison of KEYNOTE-204 (pembrolizumab) versus each of the 6 individual comparative studies, as listed in Table 59, were carried out. The base case analysis, which is also used in the economic comparison, consisted of assessing the comparative effectiveness of pembrolizumab vs. IGEV in second

line subjects without prior stem cell transplant (SCT) based on the KEYNOTE-204 and Balzarotti 2016 studies. This analysis was selected as the base case because the Balzarotti study was the only SOC study that published KM curves for OS or PFS. Only KEYNOTE-204 presented PFS as assessed by independent central review, so this analysis only includes comparisons of PFS (with Balzarotti 2016) as per investigator assessment. The comparator study consisted of patients of 65 years old or younger, therefore the base case analysis is restricted on subjects from KEYNOTE-204 < 65 years old. A sensitivity analysis considering all 2nd line subjects without an SCT of KEYNOTE-204 ([redacted] was performed. These analyses are to be taken with caution as the overlap of populations in KEYNOTE-204 and comparator studies in age is considered a stretch. since age was not specifically an exclusion criterion in the comparator study.

The MAIC results should be interpreted with extreme caution due to the low effective sample size (ESS) obtained for KEYNOTE-204 after matching. Due to this limitation of ESS and further limitations described in section B.2.9.1 the MAICs outlined in the table below, except the comparison with IGEV using the population in Blazarotti 2016, are not presented in this submission because they are not relevant for decision making. Furthermore, pooling of the SoC studies, included in the feasibility assessment, was explored to determine if response rate of pembrolizumab vs chemotherapies could be provided in the absence of PFS and OS. However, for reasons cited in section B.2.9.1 these methodologies were not carried out. Clinical expert opinion elicited by MSD reported that the chemotherapies administered in the 2L are broadly comparable and choice is based on clinician experience.

Table 59. Summary of studies used in MAIC analyses

Data source	Target population	Outcomes (effect measures)
• **Pembrolizumab:** IPD from KEYNOTE-204 (2L ASCT-naïve) • **GDP:** AD from Baetz 2003	Relative treatment effects will be representative of the population in **Baetz 2003**	• ORR, CR, PR
• **Pembrolizumab:** IPD from KEYNOTE-204 (2L ASCT-naïve) • **IGEV:** AD and digitized KM from Balzarotti 2016,	Relative treatment effects will be representative of the population in **Balzarotti 2016**	• PFS • ORR, CR, PR
• **Pembrolizumab:** IPD from KEYNOTE-204 (2L ASCT-naïve)	Relative treatment effects will be representative of the population in **Hu 2018**	• ORR, CR, PR

Data source	Target population	Outcomes (effect measures)
• **ICE:** AD from Hu 2018		
• **Pembrolizumab:** IPD from KEYNOTE-204 (2L ASCT-naïve) • **DHAP + G-CSF:** AD from Josting 2002	Relative treatment effects will be representative of the population in **Josting 2002**	• ORR, CR, PR
• **Pembrolizumab:** IPD from KEYNOTE-204 (2L ASCT-naïve) • **ESHAP:** AD from Ramzi 2015	Relative treatment effects will be representative of the population in **Ramzi 2015**	• ORR, CR, PR
• **Pembrolizumab:** IPD from KEYNOTE-204 (2L ASCT-naïve) • **GDP:** AD from Ramzi 2015	Relative treatment effects will be representative of the population in **Ramzi 2015**	• ORR, CR, PR

MAIC results

Base case analysis

The baseline characteristics of patients enrolled in KEYNOTE-204 and in Balzarotti, before and after matching, are provided in Table 60. The original set of baseline variables used for matching included disease status, age, presence of bulky disease, prior radiotherapy, gender and presence of B symptoms but due to convergence issues the set of baseline variables used for this analysis included age, disease status, presence of Bulky disease, prior radiotherapy and gender. It should be noted that the median age after matching may slightly differ compared with the comparator's study median age as the matching was based on repeated values (integer age values instead of continues values).

Regarding PFS based on the investigator's assessment, the results of pembrolizumab vs IGEV before and after matching are provided in Table 61 and Figure 27. The MAIC results of pembrolizumab vs IGEV for objective response, complete response and partial response based on the investigator's assessment are provided in Table 62, Table 63 and Table 64.

The results for the analysis of PFS based on investigator assessment, after matching, numerically favour pembrolizumab. The results of the analyses of ORR and PRR were statistically significant, after matching, showing patients who received pembrolizumab are

more likely to achieve ORR. Whilst the results for CRR did not favour pembrolizumab, these results were not statistically significant.

The MAIC results should be interpreted with extreme caution due to the low ESS obtained for KEYNOTE-204 after matching.

Table 60. Baseline Characteristics Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Balzarotti[c] (N=38)	Keynote 204[a]	
		Before Matching (N=15)	After Matching (N=10.75[b])
Age [Median]	36.80	[redacted]	[redacted]
Disease Status [Relapsed]	52.60	[redacted]	[redacted]
Presence of bulky disease [Yes]	44.70	[redacted]	[redacted]
Prior radiotherapy [Yes]	23.70	[redacted]	[redacted]
Gender [Male]	55.30	[redacted]	[redacted]

The results are presented in percentages unless indicated otherwise
The median age may slightly differ across studies due to repeated values
a: Database Cutoff Date: [redacted]
b: Effective sample size computed as the square of the summed weights divided by the sum of the squared weights
c: Results from Balzarotti, 2016.

Table 61. Analysis of Progression Free Survival Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Estimated Using pseudo-IPD from Balzarotti Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Pembrolizumab[a]		IGEV[b]		Pembrolizumab[a] vs IGEV[b]	
	N[c]	Patients with Event, n (%)	N[c]	Patients with Event, n (%)	Hazard Ratio[d] [95%-CI]	p-Value[e]
Before Matching	[redacted]	[redacted]	38	22 (57.89)	[redacted]	[redacted]
After Matching	[redacted]	[redacted]	38	22 (57.89)	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
b: IGEV, Balzarotti 2016
c: Number of patients: intention-to-treat, second line subjects with no prior stem cell transplant
d: Based on Cox regression model with treatment as a covariate
e: Two-sided p-value (Wald test)
f: Sample size after matching computed as the sum of the weights
CI: Confidence Interval.

Figure 27 Kaplan Meier estimates of Progression Free Survival Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

Table 62. Analysis of Objective Response Rate Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Pembrolizumab[a]		IGEV[b]		Pembrolizumab[a] vs IGEV[b]			
	N[c]	Patients with Event, n (%)	N[c]	Patients with Event, n (%)	Risk Ratio/ Peto Odds Ratio[d] [95%-CI]	p-Value[e]	Risk Difference [95%-CI]	p-Value[e]
Before Matching	[redacted]	[redacted]	38	25 (65.79)	[redacted]	[redacted]	[redacted]	[redacted]
After Matching	[redacted]	[redacted]	38	25 (65.79)	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
b: IGEV, Balzarotti 2016
c: Number of subjects: intention-to-treat, second line subjects with no prior stem cell transplant
d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <=1% or >=99% in at least one cell
e: Two-sided p-value (Wald test)
f: Sample size after matching computed as the sum of the weights.

Table 63. Analysis of Complete Response Rate Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Pembrolizumab[a]		IGEV[b]		Pembrolizumab[a] vs IGEV[b]			
	N[c]	Patients with Event, n (%)	N[c]	Patients with Event, n (%)	Risk Ratio/ Peto Odds Ratio[d] [95%-CI][f]	p-Value[e]	Risk Difference [95%-CI][f]	p-Value[e]
Before Matching	[redacted]	[redacted]	38	20 (52.63)	[redacted]	[redacted]	[redacted]	[redacted]
After Matching	[redacted]	[redacted]	38	20 (52.63)	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
b: IGEV, Balzarotti 2016
c: Number of subjects: intention-to-treat, second line subjects with no prior stem cell transplant
d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <=1% or >=99% in at least one cell
e: Two-sided p-value (Wald test)
f: Based on a robust sandwich estimator using PROC GENMOD in SAS
g: Sample size after matching computed as the sum of the weights.

Table 64. Analysis of Partial Response Rate Based on Investigator Review per IWG 2007Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Pembrolizumab[a]		IGEV[b]		Pembrolizumab[a] vs IGEV[b]			
	N[c]	Patients with Event, n (%)	N[c]	Patients with Event, n (%)	Risk Ratio/ Peto Odds Ratio[d] [95%-CI][f]	p-Value[e]	Risk Difference [95%-CI][f]	p-Value[e]
Before Matching	[redacted]	[redacted]	38	5 (13.16)	[redacted]	[redacted]	[redacted]	[redacted]
After Matching	[redacted]	[redacted]	38	5 (13.16)	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
b: IGEV, Balzarotti 2016
c: Number of subjects: intention-to-treat, second line subjects with no prior stem cell transplant
d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <=1% or >=99% in at least one cell
e: Two-sided p-value (Wald test)
f: Based on a robust sandwich estimator using PROC GENMOD in SAS
g: Sample size after matching computed as the sum of the weights.

Sensitivity Analysis

The baseline characteristic of patients enrolled in KEYNOTE-204 and in Balzarotti, before and after matching, are provided in Table 65. All subjects in 2L of KEYNOTE-204 were considered for this analysis, since age was not determined as an exclusion criterion in the comparator study. The set of baseline variables used for matching included disease status, age, presence of Bulky disease, prior radiotherapy, gender and presence of B symptoms. It should be noted that the median age after matching may slightly differ compared with the comparator's study median age as the matching was based on repeated values (integer age values instead of continues values).

Regarding PFS based on the investigator's assessment, the results of pembrolizumab vs IGEV before and after matching are provided in Table 66 and Figure 28. The MAIC results of the objective response, complete response and partial response based on the investigator's assessment are provided in Table 67, Table 68 and Table 69.

The results for the scenario analysis of PFS based on investigator assessment, after matching, favour the comparator trial. However, these results are not significant. Additionally, the results of the analyses after matching, of ORR and PRR which favour pembrolizumab, are statistically significant. Whilst the results reported for CRR favored the comparator these were did not show statistical significance.

Table 65. Baseline Characteristics Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Balzarotti[c] (N=38)	Keynote 204[a]	
		Before Matching (N=27)	After Matching (N=14.17[b])
Age [Median]	36.80	[redacted]	[redacted]
Disease Status [Relapsed]	52.60	[redacted]	[redacted]
Presence of bulky disease [Yes]	44.70	[redacted]	[redacted]
Prior radiotherapy [Yes]	23.70	[redacted]	[redacted]
Gender [Male]	55.30	[redacted]	[redacted]
Presence of B symptoms [Yes]	36.80	[redacted]	[redacted]

The results are presented in percentages unless indicated otherwise
The median age may slightly differ across studies due to repeated values
a: Database Cutoff Date: [redacted]
b: Effective sample size computed as the square of the summed weights divided by the sum of the squared weights
c: Results from Balzarotti, 2016.

Table 66. Analysis of Progression Free Survival Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Estimated Using pseudo-IPD from Balzarotti Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Pembrolizumab[a]		IGEV[b]		Pembrolizumab[a] vs IGEV[b]	
	N[c]	Patients with Event, n (%)	N[c]	Patients with Event, n (%)	Hazard Ratio[d] [95%-CI]	p-Value[e]
Before Matching	[redacted]	[redacted]	38	22 (57.89)	[redacted]	[redacted]
After Matching	[redacted]	[redacted]	38	22 (57.89)	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
b: IGEV, Balzarotti 2016
c: Number of patients: intention-to-treat, second line subjects with no prior stem cell transplant
d: Based on Cox regression model with treatment as a covariate
e: Two-sided p-value (Wald test)
f: Sample size after matching computed as the sum of the weights
CI: Confidence Interval.

Figure 28. Kaplan Meier estimates of Progression Free Survival Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

Table 67. Analysis of Objective Response Rate Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Pembrolizumab[a]		IGEV[b]		Pembrolizumab[a] vs IGEV[b]			
	N[c]	Patients with Event, n (%)	N[c]	Patients with Event, n (%)	Risk Ratio/ Peto Odds Ratio[d] [95%-CI][f]	p-Value[e]	Risk Difference [95%-CI][f]	p-Value[e]
Before Matching	[redacted]	[redacted]	38	25 (65.79)	[redacted]	[redacted]	[redacted]	[redacted]
After Matching	[redacted]	[redacted]	38	25 (65.79)	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date[redacted]
b: IGEV, Balzarotti 2016
c: Number of subjects: intention-to-treat, second line subjects with no prior stem cell transplant
d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <=1% or >=99% in at least one cell
e: Two-sided p-value (Wald test)
f: Based on a robust sandwich estimator using PROC GENMOD in SAS
g: Sample size after matching computed as the sum of the weights.

Table 68. Analysis of Complete Response Rate Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Pembrolizumab[a]		IGEV[b]		Pembrolizumab[a] vs IGEV[b]			
	N[c]	Patients with Event, n (%)	N[c]	Patients with Event, n (%)	Risk Ratio/ Peto Odds Ratio[d] [95%-CI][f]	p-Value[e]	Risk Difference [95%-CI][f]	p-Value[e]
Before Matching	[redacted]	[redacted]	38	20 (52.63)	[redacted]	[redacted]	[redacted]	[redacted]
After Matching	[redacted]	[redacted]	38	20 (52.63)	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
b: IGEV, Balzarotti 2016
c: Number of subjects: intention-to-treat, second line subjects with no prior stem cell transplant
d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <=1% or >=99% in at least one cell
e: Two-sided p-value (Wald test)
f: Based on a robust sandwich estimator using PROC GENMOD in SAS
g: Sample size after matching computed as the sum of the weights.

Table 69. Analysis of Partial Response Rate Based on Investigator Review per IWG 2007 Matching-Adjusted Indirect Comparison of Pembrolizumab vs IGEV Second Line Subjects with No Prior Stem Cell Transplant (Intention-to-Treat Population)

	Pembrolizumab[a]		IGEV[b]		Pembrolizumab[a] vs IGEV[b]			
	N[c]	Patients with Event, n (%)	N[c]	Patients with Event, n (%)	Risk Ratio/ Peto Odds Ratio[d] [95%-CI][f]	p-Value[e]	Risk Difference [95%-CI][f]	p-Value[e]
Before Matching	[redacted]	[redacted]	38	5 (13.16)	[redacted]	[redacted]	[redacted]	[redacted]
After Matching	[redacted]	[redacted]	38	5 (13.16)	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
b: IGEV, Balzarotti 2016
c: Number of subjects: intention-to-treat, second line subjects with no prior stem cell transplant
d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <=1% or >=99% in at least one cell
e: Two-sided p-value (Wald test)
f: Based on a robust sandwich estimator using PROC GENMOD in SAS
g: Sample size after matching computed as the sum of the weights.

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

As with any indirect comparison, conclusions from the analyses described above are limited by the extent to which the set of included trials meet the assumptions of the proposed methodology. While some known differences between trials will be explored through subgroup analysis, any unreported or unmeasured differences in patient populations may still introduce bias into the analysis.

In absence of a connected network of evidence, MAIC is used to obtain relative treatment effects. However, an anchored MAIC assumes that all effect modifiers are accounted for while an unanchored MAIC effectively assumes that absolute outcomes can be predicted from the covariates; in other words, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate.

The biggest reported difference in patient population between KEYNOTE-204 and the SOC trials was the distribution of age; none of the SOC trials included any patients over age 65, while [redacted]% ([redacted] out of [redacted]) of ASCT-ineligible patients who received pembrolizumab at 2L therapy in KEYNOTE-204 were 65 or older. Other differences between trials were less

prominent, or insufficient information was included in publications of SOC trials to make a determination as to comparability.

A key limitation of the approach taken for the individual pairwise MAIC's is that treatment effects can only be estimated versus each comparator regimen within a population as defined by the sample from each external trial. This poses a number of challenges. Firstly, the desired comparison versus SOC for the purposes of cost-effectiveness modelling requires a relative treatment effect of pembrolizumab versus the pooled absolute treatment effects from each relevant regimen which is used in clinical practice. Secondly, each treatment effect is estimated for a different target population, which may or may not be reflective of to the target population relevant to the specific decision problem. Finally, most of the SOC studies include smaller populations (less than 50 patients), which when combined with the small number of 2L ASCT-ineligible patients in KEYNOTE-204 means comparisons are likely to be subject to significant uncertainty.

MSD explored a number of approaches to present a comparison of pembrolizumab vs pooled SOC. However, because of the major limitations in the approaches these were not carried out. The possibility of using a two-step approach whereby patient characteristics and outcomes for each study were first pooled before conducting an MAIC was explored. This approach was not pursued further as it would've required strong assumptions regarding the distribution of characteristics in the pooled population (e.g. imputation of missing characteristics among certain studies) and the equivalence in terms of efficacy of the underlying regimens. Clinical expert opinion suggest the latter assumption is likely realistic; however, the former is untestable without access to the IPD from the external studies.

Another approach which was considered in order to pool the various treatment effects from the MAICs in a meta-analytic framework. The advantage of this approach is that it is better able to account for the heterogeneity inherent in the underlying populations (i.e. matching can be performed based on available data on patient characteristics from each study) and estimated treatment effects in each pairwise comparison, while making use of all the available comparator trial data; however, this approach does not solve issues related to potential bias within each MAIC cannot account for the correlation in terms of the pembrolizumab arms in each comparison, which are all drawn from the KEYNOTE-204 study and therefore cannot be assumed to be independent.

Outside of the question of pooling, there is also potential for bias within each pairwise MAIC. In theory, if all relevant prognostic factors and treatment effect modifiers are adjusted for

within an MAIC, then the resulting treatment effects will be unbiased. Although the proposed methods align with existing recommendations, it is important to highlight that adjustments within the MAIC are limited to patient characteristics reported from full-text publications of the SOC studies. The limited reporting of characteristics within the external SOC studies means that specific prognostic factors which are known to influence outcomes cannot be accounted for within the comparisons, leaving them open to potential bias. It is also important to note that there is a known imbalance in terms of the age distribution of the eligible population from KEYNOTE-204 and the SOC studies available in the literature; however, the potential impact of this on the individual MAICs was explored through the sensitivity analysis excluding patients aged over 65 from KEYNOTE-204.

Another limitation is that none of the comparator studies explicitly limited enrollment to ASCT-ineligible patients. Eligibility criteria for undergoing ASCT have not been explicitly mentioned in the latest iterations of the National Comprehensive Cancer Network or European Society for Medical Oncology clinical practice guidelines. A prior response of stable disease or better to chemotherapy, younger age, and absence of organ dysfunction are generally accepted to be the major eligibility criteria for ASCT. Whether the underlying populations in the external studies can truly be considered ASCT-ineligible population, for example comorbidities was not well-described in publications beyond a requirement for “adequate organ function”, is another issue due to the literature base available for this disease regardless of the methodology employed. In the key Balzarotti 2016 study which was only the only study to report PFS, a significant proportion of patients appear to have gone on to receive consolidative stem cell transplantation. Although some patients in KEYNOTE-204 also received stem cell transplantation, the proportion was far lower than Balzarotti 2016, due to the fact that many of the enrolled patients were likely deemed ineligible based on factors unrelated to treatment i.e. age and comorbidities as opposed to prior failure or relapse.

B.2.10 Adverse reactions

B.2.10.1. KEYNOTE-204[3]

The ASaT population was the primary safety analysis population presented in this submission. Participants are counted only once for a specific AE term at the worst severity recorded.

KEYNOTE-204 Extent of exposure

The median duration of exposure was approximately [redacted] in the pembrolizumab arm ([redacted], range: [redacted]) compared with the BV arm ([redacted], range: [redacted]) Table 70. A median of [redacted] and [redacted] doses were administered for pembrolizumab and BV, respectively. Exposure in person-years was higher in the pembrolizumab arm compared with the BV arm. A higher proportion of participants receiving pembrolizumab remained on treatment for at least 12 months (N=[redacted]) and 18 months (N=[redacted]) than participants receiving BV (N=[redacted]) and (N=[redacted]), respectively Table 71.

Table 70. KEYNOTE-204 Summary of Drug Exposure (ASaT Population)

	MK-3475 200 mg (N=148)	Brentuximab Vedotin (N=152)
Number of Days on Therapy (days)		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of Administrations		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Database Cutoff Date: [redacted]		

Table 71. KEYNOTE-204 Exposure by Duration (ASaT Population)

	MK-3475 200 mg (N=148)		Brentuximab Vedotin (N=152)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 6 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 18 m	[redacted]	[redacted]	[redacted]	[redacted]
Each subject is counted once on each applicable duration category row. Duration of exposure is the time from the first dose date to the last dose date. Database Cutoff Date: [redacted]				

KEYNOTE-204 Summary of Adverse Events

Nearly all participants experienced at least 1 AE and the majority in each treatment arm had treatment-related AEs ([redacted] pembrolizumab, [redacted] BV). The incidence of AEs by category

was not appreciably different across treatment arm, generally differing by less than [redacted] percentage points. The biggest difference was noted for SAEs ([redacted] versus [redacted] in the pembrolizumab and BV arms, respectively) Table 73. However, median exposure was approximately [redacted] in the pembrolizumab arm ([redacted]) relative to the BV arm ([redacted]) Table 70.

After adjustment for exposure, the event rate for Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs was higher in the BV arm, while rates for SAEs and treatment-related AEs were similar in each arm Table 74. [redacted] participants ([redacted] in the pembrolizumab arm and [redacted] participants ([redacted]) in the BV arm discontinued due to an AE; [redacted] ([redacted] pembrolizumab participants and [redacted] ([redacted] BV participants discontinued due to a drug-related AE Table 72. Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs were reported for [redacted] ([redacted]) and 29 (19.6%) pembrolizumab participants in comparison to [redacted] ([redacted] and 38 (25.0%) BV participants, respectively Table 73. SAEs and drug related SAEs were reported for [redacted] ([redacted] and [redacted] ([redacted] pembrolizumab participants in comparison to [redacted] ([redacted] and [redacted] BV participants, respectively Table 73.

Deaths due to AEs occurred in [redacted] [redacted] pembrolizumab participants versus [redacted] [redacted] BV participants; for 1 (0.7%) pembrolizumab participant, the death was reported as drug related Table 73.

Table 72. KEYNOTE-204 Disposition of Subject (ITT Population)

	MK-3475 200 mg		Brentuximab Vedotin	
	n (%)		n (%)	
Subjects in population	151		153	
Status for Trial				
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Lost To Follow-Up	[redacted]	[redacted]	[redacted]	[redacted]
Physician Decision	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal By Subject	[redacted]	[redacted]	[redacted]	[redacted]
Trial Ongoing	[redacted]	[redacted]	[redacted]	[redacted]
Status for Study Medication				
Started	148		152	
Completed	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event	[redacted]	[redacted]	[redacted]	[redacted]
Bone Marrow Transplant	[redacted]	[redacted]	[redacted]	[redacted]
Clinical Progression	[redacted]	[redacted]	[redacted]	[redacted]
Complete Response	[redacted]	[redacted]	[redacted]	[redacted]
Excluded Medication	[redacted]	[redacted]	[redacted]	[redacted]
Non-Compliance With Study Drug	[redacted]	[redacted]	[redacted]	[redacted]
Non-Study Anti-Cancer Therapy	[redacted]	[redacted]	[redacted]	[redacted]

Physician Decision	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]
Protocol Deviation	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal By Subject	[redacted]	[redacted]	[redacted]	[redacted]
On Study Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Database Cutoff Date: [redacted]				

Table 73. KEYNOTE-204 Adverse Event Summary (ASaT Population)

	MK-3475 200 mg	Brentuximab Vedotin
	n (%)	n (%)
Subjects in population	148	152
with one or more adverse	[redacted]	[redacted]
events with no adverse event	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]
with toxicity grade 3-5 adverse	[redacted]	[redacted]
events	29 (19.6)	38 (25.0)
with toxicity grade 3-5 drug-related adverse	[redacted]	[redacted]
events with non-serious adverse events	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]
with serious drug-related adverse	[redacted]	[redacted]
events who died	1 (0.7)	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]
discontinued drug due to a drug-related adverse	[redacted]	[redacted]
event discontinued drug due to a serious adverse	[redacted]	[redacted]
event discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: [redacted]

Table 74. KEYNOTE-204 Exposure-Adjusted Adverse Events Summary (Including Multiple Occurrences of Events) (ASaT Population)

	Event Count and Rate (Events/100 person-months)†	
	MK-3475 200 mg	Brentuximab Vedotin
Number of subjects exposed	148	152
Total exposure‡ in person-months	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]

† Event rate per 100 person-months of exposure = event count *100/person-months of exposure.

‡ Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Database Cutoff Date: [redacted]

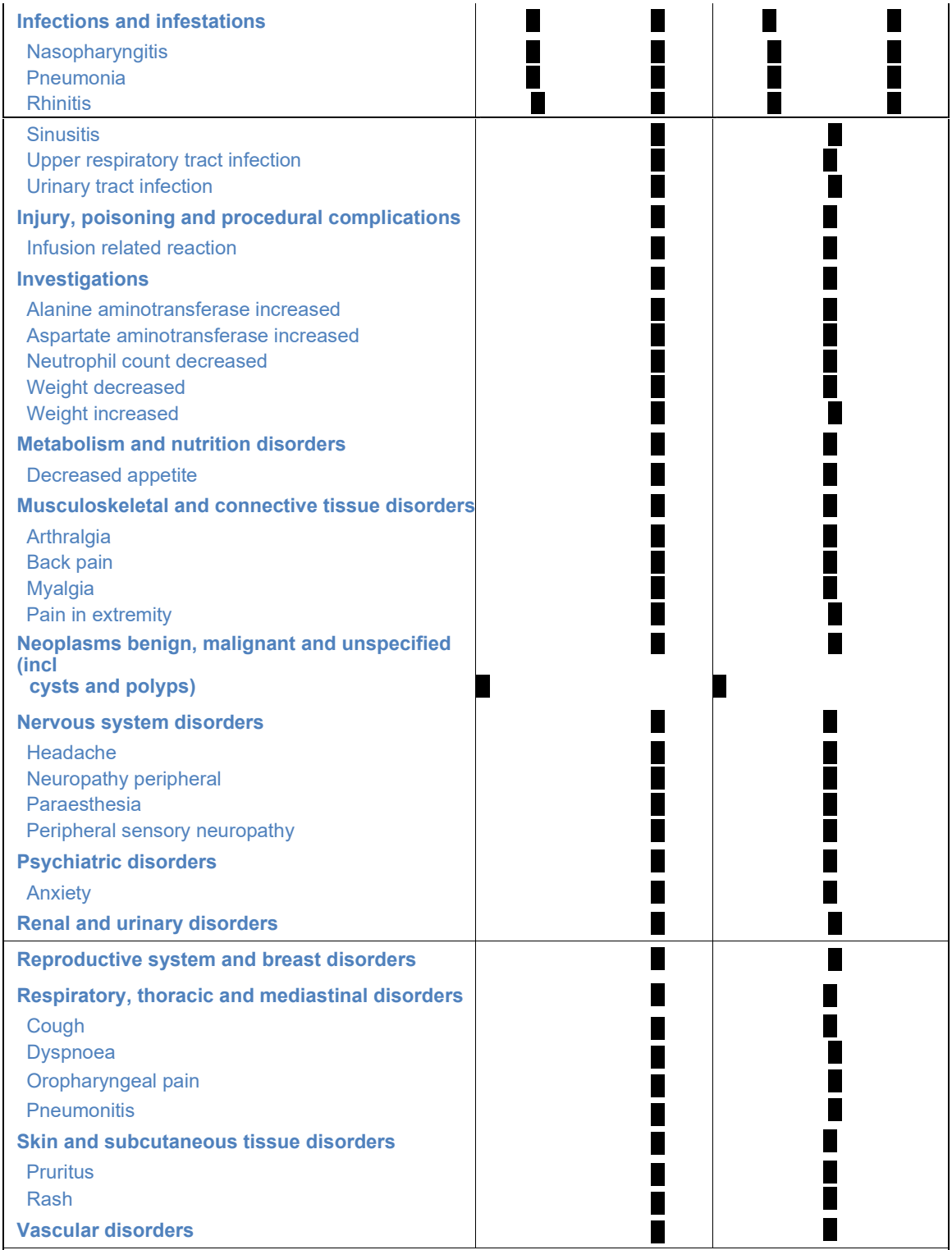
Overall AEs

The overall incidence of AEs was similar in the pembrolizumab (98.0%) and BV (94.1%) Table 75.

The most frequently reported AEs (≥10% of participants) were diarrhea ([redacted]), pyrexia ([redacted]), hypothyroidism ([redacted]), and upper respiratory tract infection ([redacted] in the pembrolizumab arm and nausea ([redacted] vomiting ([redacted]), fatigue ([redacted] and neuropathy peripheral ([redacted] in the BV arm Table 75.

Table 75. KEYNOTE-204 Subjects with Adverse Events (Incidence ≥5% in One or More Treatment Groups) (ASaT Population)

	MK-3475 200 mg		Brentuximab Vedotin	
	n	(%)	n	(%)
Subjects in population	148		152	
with one or more adverse events	[redacted]		[redacted]	
with no adverse events	[redacted]		[redacted]	
Blood and lymphatic system disorders	[redacted]		[redacted]	
Anaemia	[redacted]		[redacted]	
Neutropenia	[redacted]		[redacted]	
Thrombocytopenia	[redacted]		[redacted]	
Cardiac disorders	[redacted]		[redacted]	
Endocrine disorders	[redacted]		[redacted]	
Hyperthyroidism	[redacted]		[redacted]	
Hypothyroidism	[redacted]		[redacted]	
Eye disorders	[redacted]		[redacted]	
Gastrointestinal disorders	[redacted]		[redacted]	
Abdominal pain	[redacted]		[redacted]	
Constipation	[redacted]		[redacted]	
Diarrhoea	[redacted]		[redacted]	
Dyspepsia	[redacted]		[redacted]	
Nausea	[redacted]		[redacted]	
Vomiting	[redacted]		[redacted]	
General disorders and administration site conditions	[redacted]		[redacted]	
Asthenia	[redacted]		[redacted]	
Fatigue	[redacted]		[redacted]	
Pyrexia	[redacted]		[redacted]	
Hepatobiliary disorders	[redacted]		[redacted]	



Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Database Cutoff Date: [redacted]

The rainfall plot shows between-treatment comparisons for AEs occurring at ≥10% incidence in one or more treatment groups. Results show higher incidences of hypothyroidism and urinary tract infection in the pembrolizumab group and higher incidences of nausea and peripheral neuropathy in the BV group (Figure 29).

Figure 29. KEYNOTE-204 Between-treatment Comparisons in Selected Adverse Events (Incidence >=10% in One or More Treatment Groups) and Sorted by Risk Difference (ASaT Population) MK-3475 200 mg (N=148) vs. Brentuximab Vedotin (N=152)

These differences were maintained even after adjustment for exposure Table 76. For AEs occurring at ≥5% incidence in one or more treatment groups, exposure-adjusted event rates tended to be higher in the BV group than the pembrolizumab group, with the exception of pneumonitis.

Table 76. KEYNOTE-204 Exposure-Adjusted Adverse Events (Including Multiple Occurrences of Events) (Incidence ≥10% in One or More Treatment Groups) (ASaT Population)

	Event Count and Rate (Events/100 person-months)[†]	
	MK-3475 200 mg	Brentuximab Vedotin
Number of subjects exposed	148	152
Total exposure[‡] in person-months	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Pruritus		

[†] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.

[‡] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Database Cutoff Date: [redacted]

Drug Related Adverse Events

The most frequently reported drug-related AEs (≥10% of participants) were hypothyroidism ([redacted]), pyrexia ([redacted]), and pruritis ([redacted]) in the pembrolizumab arm and neuropathy peripheral ([redacted]), peripheral sensory neuropathy ([redacted]), and nausea ([redacted]) in the BV arm Table 77.

Notable differences (>10 percentage point difference) in incidence rates of drug-related AEs between the 2 arms were noted for hypothyroidism ([redacted] pembrolizumab, [redacted] BV), neuropathy peripheral ([redacted] pembrolizumab, [redacted] BV), and peripheral sensory neuropathy ([redacted] pembrolizumab, [redacted] BV). Hypothyroidism is a known immune-related event for pembrolizumab. [redacted] of the episodes of urinary tract infection noted for participants in the pembrolizumab arm were considered to be drug-related; in contrast, [redacted] participant in the BV arm had drug-related urinary tract infection.

Table 77. KEYNOTE-204 Subjects With Drug-Related Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) (ASaT Population)

	MK-3475 200 mg	Brentuximab Vedotin
	n (%)	n (%)
Subjects in population	148	152
with one or more drug-related adverse events	[redacted]	[redacted]
with no drug-related adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Rash	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: [redacted]

Grade 3 to 5 Adverse Events

With the exception of neutropenia (pembrolizumab [redacted] BV [redacted]), the incidence of individual Grade 3 to 5 AEs differed by less than [redacted] percentage points between the arms, Table 78. In both treatment arms, the SOC of infections and infestations had the highest proportion of participants reporting a Grade 3 to 5 AE (pembrolizumab [redacted], BV [redacted]).

In the pembrolizumab arm, the most frequently reported Grade 3 to 5 AEs [redacted] of participants) were pneumonia ([redacted]), pneumonitis ([redacted]), and anemia ([redacted]) Table 78; pneumonitis is a known immune-related event for pembrolizumab. In the BV arm, the most frequently reported Grade 3 to 5 AEs ([redacted] of participants) were neutropenia ([redacted]), neutrophil count decreased ([redacted]), and pneumonia ([redacted]).

An examination of exposure-adjusted Grade 3 to 5 AEs showed higher event rates in the BV arm relative to the pembrolizumab arm for most AEs, with pneumonitis being the most notable exception Table 79.

Table 78. KEYNOTE-204 Subjects With Grade 3-5 Adverse Events (Incidence ≥ 1% in One or More Treatment Groups)(ASaT Population)

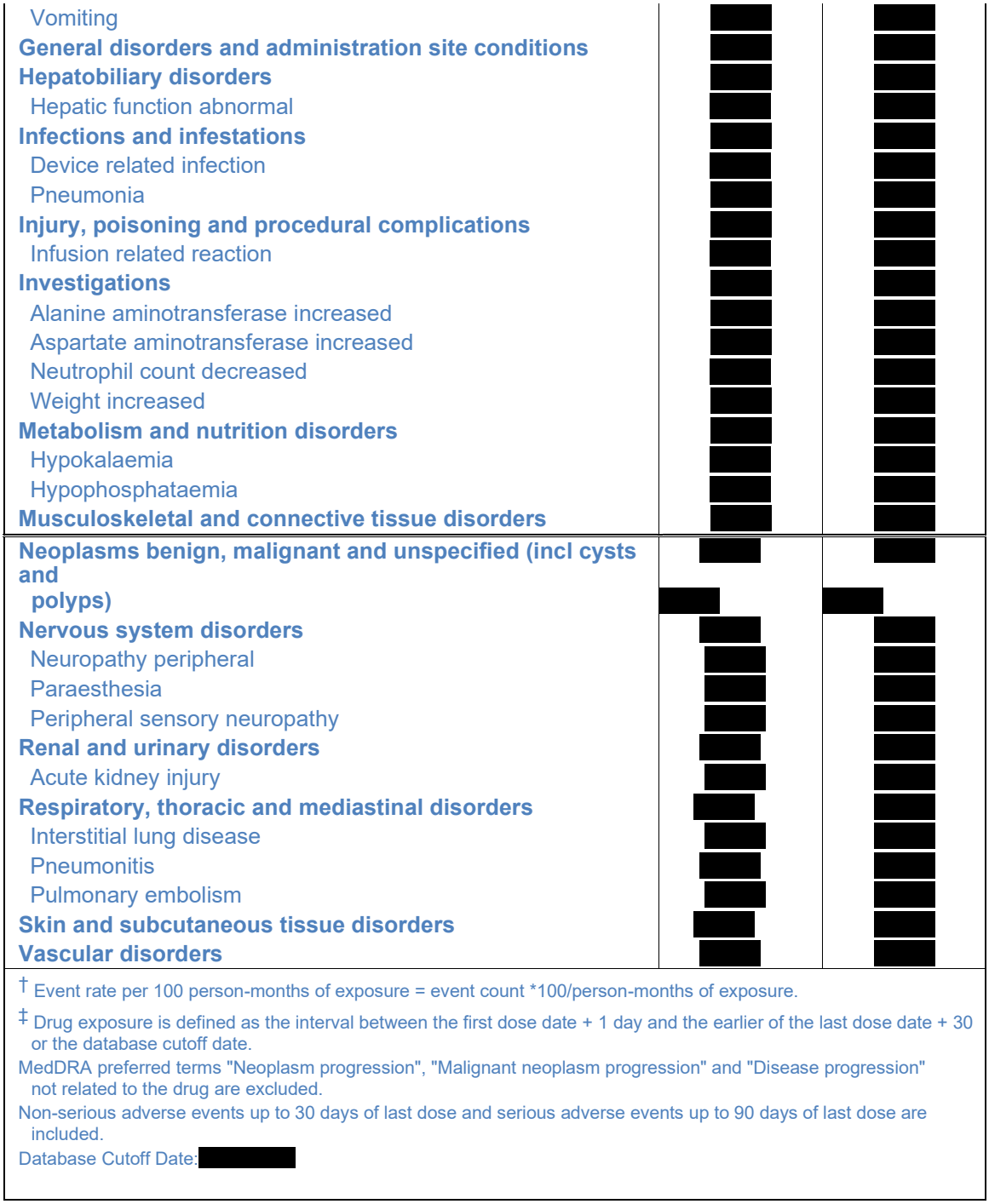
	MK-3475 200 mg	Brentuximab Vedotin
	n (%)	n (%)
Subjects in population	148	152
with one or more Grade 3-5 adverse events	[redacted]	[redacted]
with no Grade 3-5 adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Immune thrombocytopenic purpura	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]

Aspartate aminotransferase increased Neutrophil count decreased Weight increased	[redacted]	[redacted]
Metabolism and nutrition disorders Hypokalaemia Hypophosphataemia **Musculoskeletal and connective tissue disorders** **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** **Nervous system disorders** Neuropathy peripheral Paraesthesia Peripheral sensory neuropathy **Renal and urinary disorders** Acute kidney injury **Respiratory, thoracic and mediastinal disorders** Interstitial lung disease Pneumonitis Pulmonary embolism **Skin and subcutaneous tissue disorders** **Vascular disorders**	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: [redacted]

*Table **79**. Exposure-Adjusted Grade 3-5 Adverse Events (Including Multiple Occurrences of Events) (Incidence ≥1% in One or More Treatment Groups) (ASaT Population)*

	Event Count and Rate (Events/100 person-months)[†]	
	MK-3475 200 mg	Brentuximab Vedotin
Number of subjects exposed	148	152
Total exposure[‡] in person-months	[redacted]	[redacted]
Blood and lymphatic system disorders Anaemia Febrile neutropenia Immune thrombocytopenic purpura Leukopenia Lymphopenia Neutropenia Thrombocytopenia **Cardiac disorders** **Gastrointestinal disorders** Diarrhoea	[redacted]	[redacted]



† Event rate per 100 person-months of exposure = event count *100/person-months of exposure.

‡ Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Database Cutoff Date: [redacted]

Drug Related Grade 3 to 5 Adverse Events

The incidence of individual drug-related Grade 3 to 5 AEs did not differ appreciably between the treatment arms. The biggest difference in incidence rates was noted for pneumonitis ([redacted] pembrolizumab, [redacted] BV). The most frequently reported drug-related Grade 3 to 5 AEs (≥0% of participants) were pneumonitis ([redacted]), pneumonia ([redacted]), and neutropenia ([redacted]) in the pembrolizumab arm and neutropenia ([redacted]), neutrophil count decreased ([redacted]), and neuropathy peripheral ([redacted]) in the BV arm Table 80.

Table 80. KEYNOTE-204 Participants With Drug-Related Grade 3-5 Adverse Events Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	MK-3475 200 mg	Brentuximab Vedotin
	n (%)	n (%)
Subjects in population	148	152
with one or more drug-related grade 3-5 adverse events	29 (19.6)	38 (25.0)
with no drug-related grade 3-5 adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Disseminated intravascular coagulation	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Immune thrombocytopenic purpura	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Deafness	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Bacteraemia	[redacted]	[redacted]
H1N1 influenza	[redacted]	[redacted]
Meningitis	[redacted]	[redacted]
Pharyngotonsillitis	[redacted]	[redacted]
Pneumocystis jirovecii pneumonia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory syncytial virus infection	[redacted]	[redacted]
Respiratory tract infection fungal	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Blood magnesium decreased	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl	[redacted]	[redacted]

cysts and polyps)		
Tumour flare	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Encephalitis autoimmune	[redacted]	[redacted]
Neuromuscular pain	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Peripheral sensorimotor neuropathy	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Tubulointerstitial nephritis	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]
Pleurisy	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Eczema	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Capillary leak syndrome	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Hypovolaemic shock	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: [redacted]

Serious Adverse Events

The most frequently reported SAEs [redacted]) were pneumonia ([redacted]), pneumonitis ([redacted]), and pyrexia ([redacted]) in the pembrolizumab arm and pneumonia ([redacted]), infusion-related reactions ([redacted]), and neuropathy peripheral ([redacted]) in the BV arm. The incidence of SAEs did not differ appreciably between the treatment arms; the biggest difference was noted for pneumonitis ([redacted] pembrolizumab, [redacted]BV).

Drug Related Serious Adverse Events

Drug-related SAEs were reported in [redacted] ([redacted]) participants in the pembrolizumab arm and [redacted] ([redacted]) participants in the BV arm Table 81. The most frequently reported drug-related SAEs [redacted]) were pneumonitis ([redacted]), pneumonia ([redacted]), and interstitial lung disease ([redacted]) in the pembrolizumab arm and infusion-related reaction ([redacted]), pneumonia ([redacted]), and neuropathy peripheral ([redacted]) in the BV arm. The incidence of SAEs did not differ appreciably between the treatment arms, with a notable difference for pneumonitis ([redacted] pembrolizumab, [redacted]BV).

Table 81. KEYNOTE-204 Subjects With Drug-Related Serious Adverse Events up to 90 Days of Last Dose (Incidence > 0% in One or More Treatment Groups)(ASaT Population)

	MK-3475 200 mg	Brentuximab Vedotin
	n (%)	n (%)
Subjects in population	148	152
with one or more drug-related serious adverse events	[redacted]	[redacted]
with no drug-related serious adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Immune thrombocytopenic purpura	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Bacteraemia	[redacted]	[redacted]
H1N1 influenza	[redacted]	[redacted]
Meningitis	[redacted]	[redacted]
Pharyngotonsillitis	[redacted]	[redacted]
Pneumocystis jirovecii pneumonia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory syncytial virus infection	[redacted]	[redacted]
Respiratory tract infection fungal	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]
Tumour flare	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Encephalitis autoimmune	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Peripheral sensorimotor neuropathy	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Tubulointerstitial nephritis	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]
Pleurisy	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]

Eczema	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypovolaemic shock	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: [redacted]

Deaths

Deaths due to AEs occurred in [redacted] ([redacted]) pembrolizumab participants compared to [redacted] ([redacted]) BV participants. Of all the deaths that occurred, 1 in the pembrolizumab arm was attributed to an AE of pneumonia that was considered drug related.

Adverse Events of Special Interest (AEOSI)

Adverse events of special interest were identified in a higher proportion of participants in the pembrolizumab arm ([redacted] participants) compared with the BV arm ([redacted] participants); of these, [redacted] ([redacted]) and [redacted] ([redacted]), respectively, were considered drug-related by the investigator. Once adjusted for exposure, event rates for Grade 3 to 5 AEs, as well as SAEs, were similar in both treatment arms Table 82.

Table 82. KEYNOTE-204 Adverse Event Summary for AEOSI (ASaT Population)

	MK-3475 200 mg	Brentuximab Vedotin
	n (%)	n (%)
Subjects in population	148	152
with one or more adverse	[redacted]	[redacted]
events with no adverse event	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]
with toxicity grade 3-5 adverse	[redacted]	[redacted]
events	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse	[redacted]	[redacted]
events with non-serious adverse events	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]
with serious drug-related adverse	[redacted]	[redacted]
events who died	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]
discontinued drug due to a drug-related adverse	[redacted]	[redacted]
event discontinued drug due to a serious adverse	[redacted]	[redacted]
event discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: [redacted]

KEYNOTE-204 Complications Post-allogeneic SCT

Of the 300 participants in the ASaT population, [redacted] in the pembrolizumab arm and [redacted] in the BV arm underwent allo-SCT at some point after stopping treatment. Of these, [redacted] ([redacted]) in the pembrolizumab arm and [redacted] ([redacted]) in the BV arm experienced an AE post allo-SCT. The most commonly reported AE was acute GVHD ([redacted] participants ([redacted]) in the pembrolizumab arm [[redacted] Grade 1, [redacted] Grade 2, [redacted] Grade 3, [redacted] Grade 4]), and [redacted] participants ([redacted]) in the BV arm [[redacted] Grade 2, [redacted] Grade 3, [redacted] Grade 4]).

B.2.10.2. KEYNOTE-087[25]

The safety analyses were based on the ASaT population up to the data cutoff of [redacted] which corresponds to approximately 3 years after the last participant-initiated study treatment.

KEYNOTE-087 Extent of exposure

Participants were exposed to pembrolizumab for a median of [redacted] (range: [redacted]), resulting in a median of [redacted] administrations (range: [redacted]; Table 73). Overall, the [redacted] of participants (n=[redacted]) remained on pembrolizumab for ≥6 months and approximately [redacted] (n=[redacted]) remained on pembrolizumab for ≥12 months Table 84. The median duration of exposure was longer in Cohort 1 ([redacted]) compared with Cohorts 2 and 3 ([redacted] and [redacted], respectively; Table 83). Likewise, exposure by duration was longer in Cohort 1 ([redacted]person-years for an exposure of ≥6 months) compared Cohorts 2 and 3 ([redacted] person-years and [redacted] person-years, respectively, for an exposure of ≥6 months each; Table 84).

Table 83. KEYNOTE-087Summary of Drug Exposure by Cohort (ASaT Population)

	COHORT 1	COHORT 2	COHORT 3	Total
Subjects in population	69	81	60	210
Number of Days on Therapy (days) n Mea n SD Median Range	69 [redacted]	81 [redacted]	60 [redacted]	210 [redacted]
Number of Administrations				

n Mea n SD Median Range	69 [redacted]	81 [redacted]	60 [redacted]	210 [redacted]
(Database Cutoff Date: [redacted]).				

Table 84 KEYNOTE-087 Clinical Trial Exposure to MK-3475 by Duration (ASaT Population)

Duration of Exposure	Cohort 1 (N=69)		Cohort 2 (N=81)		Cohort 3 (N=60)		Total (N=210)	
	n	Person-years	n	Person-years	n	Person-years	n	Person-years
> 0 months ≥ 1 months ≥ 3 months ≥ 6 months ≥ 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Each subject is counted once on each applicable duration category row.Duration of Exposure is calculated as (last dose date - first dose date +1)/365.25*12 (months). Database Cutoff Date[redacted]								

KEYNOTE-087 Summary of Adverse of Events

The [redacted] of participants ([redacted]) reported at least 1 AE. Of the 210 participants treated in the study overall, 153 (72.9%) experienced ≥1 treatment-related AE. [redacted] participants ([redacted]) experienced ≥1 Grades 3 to 5 AEs, [redacted] of whom experienced ≥1 Grade 3 or 4 AE that was considered related to the study treatment; there were no drug-related Grade 5 AEs. [redacted] participants ([redacted]) experienced at least 1 SAE, [redacted] of whom experienced ≥1 treatment-related SAE Table 86.

Three participants ([redacted]) died due to an AE; none were considered drug-related. Eighteen participants ([redacted]) discontinued study treatment due to an AE, [redacted] of whom discontinued study treatment due to a drug-related AE Table 86.

Pembrolizumab was generally well-tolerated, with a manageable safety profile, as demonstrated by a low rate of drug-related discontinuations ([redacted]). Most participants ([redacted]) experienced AEs that were a maximum toxicity of Grade 1 or 2 severity.

[redacted] of 210 participants ([redacted]) discontinued study treatment due to an AE Table 86. The most commonly reported AEs that resulted in treatment discontinuation by PT were pneumonitis (n=[redacted]) and infusion-related reaction (n=[redacted]). Rates of AEs leading to treatment discontinuation were similar across cohorts.

There were no meaningful differences in AE rates by AE category across cohorts.

Table 85. KEYNOTE-087 Subject Disposition By Cohort (ASaT Population)

	COHORT 1 n (%)	COHORT 2 n (%)	COHORT 3 n (%)	Total n (%)
Subjects in population	69	81	60	210
Status for Study Medication in Trial Segment Treatment				
Started	69	81	60	210
Completed	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event	[redacted]	[redacted]	[redacted]	[redacted]
Bone Marrow Transplant	[redacted]	[redacted]	[redacted]	[redacted]
Clinical Progression	[redacted]	[redacted]	[redacted]	[redacted]
Complete Response	[redacted]	[redacted]	[redacted]	[redacted]
Lost To Follow-Up	[redacted]	[redacted]	[redacted]	[redacted]
Physician Decision	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal By Subject	[redacted]	[redacted]	[redacted]	[redacted]
(Database Cutoff Date: [redacted]).				

Table 86. Adverse Event Summary By Cohort (ASaT Population)

	COHORT 1 n (%)		COHORT 2 n (%)		COHORT 3 n (%)		Total n	(%)
Subjects in population	69		81		60		210	
with one or more adverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
events with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
events with toxicity grade 3-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with non-serious adverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
events with serious adverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
discontinued‡ due to an adverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
event discontinued due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

discontinued due to a serious drug- related adverse event				

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
(Database Cutoff Date: [redacted]).

KEYNOTE-087 Overall AEs

In the total population, the most commonly reported AEs by PT included pyrexia (n=[redacted]; [redacted]), cough (n=[redacted]), fatigue (n=[redacted]), diarrhea and upper respiratory tract infection (n=[redacted] each), nausea and vomiting (n=[redacted]; [redacted] each), nasopharyngitis (n=[redacted]), and hypothyroidism (n=[redacted]; Table 87). AE rates generally differed by <10% across cohorts.

Table 87. KEYNOTE-087Subjects With Adverse Events by Decreasing Incidence (Incidence ≥10% in One or More Treatment Groups) By Cohort (ASaT Population)

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	69		81		60		210	
with one or more adverse events	[redacted]							
with no adverse events								
Pyrexia								
Cough								
Fatigue								
Diarrhoea								
Upper respiratory tract infection								
Nausea								
Vomiting								
Nasopharyngitis								
Hypothyroidism								
Rash								
Pruritus								
Headache								
Arthralgia								
Back pain								
Dyspnoea								
Constipation								
Oropharyngeal pain								
Nasal congestion								
Anaemia								
Sinusitis								
Insomnia								
Bronchitis								
Asthenia								
Rhinorrhoea								
Productive cough								
Muscle spasms								
Alanine aminotransferase increased								
Rhinitis								

Influenza like illness	[redacted]							

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
(Database Cutoff Date: [redacted].

KEYNOTE-087 Drug Related Adverse Events

Of the 210 participants treated in the study overall, 153 (72.9%) experienced ≥1 treatment-related AE Table 88. The most commonly reported drug-related AEs by PT included hypothyroidism (n=30; 14.3%), pyrexia (n=24; 11.4%), and fatigue and rash (n=23; 11.0% each).

Table 88 KEYNOTE-087 Subjects With Drug-Related Adverse Events by Decreasing Incidence (Incidence ≥5% in One or More Treatment Groups) By Cohort (ASaT Population)

	COHORT 1 n (%)		COHORT 2 n (%)		COHORT 3 n (%)		Total n (%)	
Subjects in population	69		81		60		210	
with one or more adverse events	[redacted]		[redacted]		[redacted]		153 (72.9)	
with no adverse events	[redacted]		[redacted]		[redacted]		57 (27.1)	
Hypothyroidism	[redacted]		[redacted]		[redacted]		30 (14.3)	
Pyrexia	[redacted]		[redacted]		[redacted]		24 (11.4)	
Fatigue	[redacted]		[redacted]		[redacted]		23 (11.0)	
Rash	[redacted]		[redacted]		[redacted]		23 (11.0)	
Diarrhoea	[redacted]		[redacted]		[redacted]		[redacted]	
Headache	[redacted]		[redacted]		[redacted]		[redacted]	
Nausea	[redacted]		[redacted]		[redacted]		[redacted]	
Cough	[redacted]		[redacted]		[redacted]		[redacted]	
Pruritus	[redacted]		[redacted]		[redacted]		[redacted]	
Arthralgia	[redacted]		[redacted]		[redacted]		[redacted]	
Infusion related reaction	[redacted]		[redacted]		[redacted]		[redacted]	
Neutropenia	[redacted]		[redacted]		[redacted]		[redacted]	
Pneumonitis	[redacted]		[redacted]		[redacted]		[redacted]	
Vomiting	[redacted]		[redacted]		[redacted]		[redacted]	
Dyspnoea	[redacted]		[redacted]		[redacted]		[redacted]	
Muscle spasms	[redacted]		[redacted]		[redacted]		[redacted]	
Hyperthyroidism	[redacted]		[redacted]		[redacted]		[redacted]	
Upper respiratory tract infection	[redacted]		[redacted]		[redacted]		[redacted]	
Alopecia	[redacted]		[redacted]		[redacted]		[redacted]	
Alanine aminotransferase increased	[redacted]		[redacted]		[redacted]		[redacted]	
Aspartate aminotransferase increased	[redacted]		[redacted]		[redacted]		[redacted]	
Productive cough	[redacted]		[redacted]		[redacted]		[redacted]	
Oropharyngeal pain	[redacted]		[redacted]		[redacted]		[redacted]	

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. (Database Cutoff Date: [redacted]).

KEYNOTE-087 Grade 3 to 5 Adverse Events

Most participants (n=[redacted]; [redacted]) experienced AEs that were a maximum toxicity of Grade 1 or 2 severity; [redacted] of participants experienced Grade 3 AEs, [redacted] of participants experienced Grade 4 AEs, and [redacted] of participants experienced Grade 5 AEs. There were no meaningful differences in rates of Grade 3 or 4 AEs across cohorts.

KEYNOTE-087 Drug Related Grade 3 to 5 Adverse Events

[redacted] participants ([redacted]) experienced ≥1 Grade 3 or 4 AE that was considered related to the study treatment; there were no drug-related Grade 5 AEs. The most commonly reported drug-related Grade 3 or 4 AEs by PT were neutropenia (n=5) and diarrhea and pericarditis (n=2 each); all other Grade 3 or 4 AEs occurred in [redacted] participant each (Table 89).

Table 89. KEYNOTE-087 Subjects With Drug-Related Grade 3-5 Adverse Events (Incidence >0% in One or More Treatment Groups) ASaT Population

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	69		81		60		210	
with one or more adverse	[redacted]							
events with no adverse	[redacted]							
events								
	[redacted]							
Neutropeni	[redacted]							
a	[redacted]							
Diarrhoea	[redacted]							
Pericarditis	[redacted]							
Acute graft versus host disease	[redacted]							
Alanine aminotransferase	[redacted]							
increased Amylase increased	[redacted]							
Arthralgia	[redacted]							
Autoimmune	[redacted]							
hepatitis Bone pain								
Chronic inflammatory	[redacted]							
demyelinating								
polyradiculoneuropat	[redacted]							
hy	[redacted]							
Colitis	[redacted]							
Cytokine release	[redacted]							
syndrome Decreased	[redacted]							
appetite Epilepsy	[redacted]							
Fatigue	[redacted]							
Gastroenteritis	[redacted]							
Gastrointestinal	[redacted]							
pain Herpes	[redacted]							
simplex Herpes	[redacted]							
zoster Lichen	[redacted]							
planus Lipase	[redacted]							
increased	[redacted]							
Lower respiratory tract	[redacted]							
infection Myelitis	[redacted]							
Myocarditis	[redacted]							
Necrotising myositis	[redacted]							
Neuropathy	[redacted]							
peripheral Oedema	[redacted]							
peripheral								
Pneumonitis								

Polyneuropathy Psoriasis Pyrexia										
Rheumatoid arthritis Thrombocytopenia Varicella zoster virus infection Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

(Database Cutoff Date: [redacted]).

KEYNOTE-087 Serious Adverse Events

Overall, [redacted] of 210 participants ([redacted]) experienced an SAE during study treatment through 90 days after the last dose of pembrolizumab. The most commonly reported SAEs by PT included pneumonia (n=[redacted]; [redacted]), pneumonitis and pyrexia (n=[redacted]; [redacted] each), and acute GVHD (n=[redacted]; [redacted]), [redacted] of which was fatal Table 90.

Table 90. KEYNOTE-087 Subjects With Serious Adverse Events Up to 90 Days After Last Dose by Decreasing Incidence (Incidence ≥1% in One or More Treatment Groups) ASaT Population

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	69		81		60		210	
with one or more adverse	[redacted]							
events with no adverse	[redacted]							
events								
	[redacted]							
Pneumonia	[redacted]							
Pneumoniti	[redacted]							
s Pyrexia	[redacted]							
Acute graft versus host	[redacted]							
disease Bronchitis	[redacted]							
Herpes	[redacted]							
zoster	[redacted]							
Pericarditis	[redacted]							
Acute kidney	[redacted]							
injury Acute	[redacted]							
sinusitis Anaemia	[redacted]							
Aortic stenosis	[redacted]							
Autoimmune	[redacted]							
hepatitis Basal cell								
carcinoma	[redacted]							
Blood creatine	[redacted]							
phosphokinase increased	[redacted]							
Bowen's disease								
Bronchopulmonary	[redacted]							
	[redacted]							

aspergillosis Chronic inflammatory demyelinating polyradiculoneuropathy	[redacted]							
Clostridium difficile colitis Cystitis	[redacted]							
Cytokine release syndrome Device related infection	[redacted]							
Diarrhoea	[redacted]							
Diffuse large B-cell lymphoma Epilepsy	[redacted]							
Escherichia bacteraemia								
Gastroenteritis								
Gastroenteritis salmonella Herpes simplex								
Hip fracture								
Hypersensitivity								
Hyperthermia	[redacted]							
Influenza	[redacted]							
Infusion related reaction	[redacted]							
Lower respiratory tract infection	[redacted]							
Lung infection	[redacted]							
Myelitis	[redacted]							
Myelodysplastic syndrome	[redacted]							
Myocardial infarction	[redacted]							
Myocarditis	[redacted]							
Necrotising myositis	[redacted]							
Osteonecrosis	[redacted]							
Pneumothorax	[redacted]							
Polyneuropathy	[redacted]							
Post procedural infection	[redacted]							
Pulmonary embolism	[redacted]							
Respiratory syncytial virus infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory tract infection	[redacted]							
Schizophrenia	[redacted]							
Septic shock	[redacted]							
Small cell lung cancer	[redacted]							
Squamous cell carcinoma	[redacted]							
Stress cardiomyopathy	[redacted]							
Upper respiratory tract infection	[redacted]							
Urosepsis	[redacted]							
Varicella zoster virus infection	[redacted]							

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

(Database Cutoff Date: [redacted]).

KEYNOTE-087 Drug Related Serious Adverse Events

Serious AEs considered drug-related occurred in [redacted] of 210 participants ([redacted]; Table 91). The most commonly reported drug-related SAEs by PT were pneumonitis (n=[redacted]; [redacted]) and pericarditis (n=[redacted]; [redacted]); all other drug-related SAEs occurred in [redacted] participant each Table 91.

Table 91. KEYNOTE-087 Subjects With Drug-Related Serious Adverse Events Up to 90 Days After Last Dose (Incidence > 0% in One or More Treatment Groups) ASaT Population

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	69		81		60		210	
with one or more adverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
events with no adverse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
events								
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumoniti	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
s	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pericarditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute graft versus host	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
disease Autoimmune								
hepatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic inflammatory								
demyelinating	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
polyradiculoneuropat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
syndrome Epilepsy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteriti	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
s Herpes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
simplex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower respiratory tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
infection Myelitis								
Myocarditis								
Necrotising								
myositis								
Polyneuropathy								
Varicella zoster virus infection								

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding
(Database Cutoff Date: [redacted]).

KEYNOTE-087Deaths

Adverse events resulting in death occurred in [redacted] of 210 participants ([redacted]) and included acute GVHD, post-procedural infection, and septic shock (n=[redacted] each); none were considered related to study treatment.

KEYNOTE-087 Adverse Events of Special Interest

Of the 210 participants treated in the study overall, [redacted] ([redacted]) experienced an AEOSI (Table 92): [redacted] participant ([redacted]) experienced Grade 4 myocarditis and Grade 3 necrotizing myositis, [redacted] participants experienced Grade 3 AEOSIs, and the remaining [redacted] participants ([redacted]) experienced AEOSIs that were a maximum toxicity of Grade 1 or 2 severity; there were no Grade 5 AEOSIs.

[redacted]participants ([redacted]) experienced an AEOSI that was considered related to study treatment; [redacted] of whom experienced Grade 3 or 4 treatment-related AEOSIs. [redacted] participants ([redacted]) experienced at least [redacted] serious AEOSI, [redacted] of whom experienced ≥1 treatment related serious AEOSI (Table 92).

[redacted] participants ([redacted]) discontinued study treatment due to an AEOSI, [redacted] of whom discontinued study treatment due to a drug-related AEOSI. No participant died due to an AEOSI Table 92.

Table 92. KEYNOTE-087 Adverse Event Summary for AEOSI By Cohort (ASaT Population)

	COHORT 1 n (%)		COHORT 2 n (%)		COHORT 3 n (%)		Total n	(%)
Subjects in population	69		81		60		210	
with one or more adverse events	[redacted]		[redacted]		[redacted]		[redacted]	
with no adverse event	[redacted]		[redacted]		[redacted]		[redacted]	
with drug-related† adverse events	[redacted]		[redacted]		[redacted]		[redacted]	
with toxicity grade 3-5 adverse events	[redacted]		[redacted]		[redacted]		[redacted]	
with toxicity grade 3-5 drug-related adverse events	[redacted]		[redacted]		[redacted]		[redacted]	
with non-serious adverse events	[redacted]		[redacted]		[redacted]		[redacted]	
with serious adverse events	[redacted]		[redacted]		[redacted]		[redacted]	
with serious drug-related adverse events	[redacted]		[redacted]		[redacted]		[redacted]	
who died	[redacted]		[redacted]		[redacted]		[redacted]	
who died due to a drug-related adverse event	[redacted]		[redacted]		[redacted]		[redacted]	
discontinued‡ due to an adverse event	[redacted]		[redacted]		[redacted]		[redacted]	
discontinued due to a drug-related adverse event	[redacted]		[redacted]		[redacted]		[redacted]	
discontinued due to a serious adverse event	[redacted]		[redacted]		[redacted]		[redacted]	
discontinued due to a serious drug- related adverse event	[redacted]		[redacted]		[redacted]		[redacted]	

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

Grades are based on NCI CTCAE version 4.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

(Database Cutoff Date: [redacted]).

KEYNOTE-087 Complications Post-allogeneic Stem Cell Transplantation in Participants Previously Treated With Pembrolizumab

Of the 210 participants in the ASaT population, [redacted] underwent allo-SCT at some point after stopping treatment with pembrolizumab (Table 48). Twenty-three of these participants

experienced an AE post-allo-SCT. The most commonly reported AE was GVHD (n=[redacted]), either acute (n=[redacted], including [redacted] hyperacute), chronic (n=[redacted]), or both (n=[redacted]). [redacted] participants had more than [redacted] event of GVHD (acute and/or chronic). Among the [redacted] events of GVHD, [redacted] were Grade 5, [redacted] were Grade 3, [redacted] were Grade 2, and [redacted] were Grade 1. No participants experienced hepatic veno-occlusive disease. [redacted] died due to AEs post-allo-SCT: acute GVHD, hyperacute GVHD, pneumonia, and sepsis (n=1 each); none were considered related to study treatment.

B.2.10.3. KEYNOTE-051[26]

Safety analyses were based on the ASaT population.

KEYNOTE-051 Extent of Exposure (Parts I and II)

The median duration of exposure to pembrolizumab was approximately [redacted] for participants with HL ([redacted]) than for participants with relapsed/refractory tumors other than HL ([redacted]) (Table 93 and Table 94).

The median number of pembrolizumab administrations was approximately [redacted] for participants with HL ([redacted] administrations) than for participants with relapsed/refractory tumors other than HL ([redacted] administrations) (Table 93 and Table 94). The percentage of participants who received pembrolizumab for ≥6 months and ≥12 months was 3- to 4-fold higher among those with HL than participants with relapsed/refractory tumors other than HL (72.7% and 40.9% vs 18.0% and 12.9%, respectively) (Table 95 and Table 96).

Table 93. KEYNOTE-051Summary of Drug Exposure Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=[redacted])
Study Days On-Therapy (days)	
Mean	[redacted]
Median	[redacted]
SD	[redacted]
Range	[redacted]
Number of administration	
Mean	[redacted]
Median	[redacted]
SD	[redacted]
Range	[redacted]
(Data Cutoff Date: [redacted]).	

Table 94. KEYNOTE-051 Summary of Drug Exposure All Relapsed/Refractory Tumors Except Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=[redacted])
Study Days On-Therapy (days)	
Mean	[redacted]
Median	[redacted]
SD	[redacted]
Range	[redacted]
Number of administration	
Mean	[redacted]
Median	[redacted]
SD	[redacted]
Range	[redacted]
(Data Cutoff Date: [redacted]).	

Table 95. Exposure by Duration Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=[redacted])	
	n	(%)
Duration of Exposure		
> 0 m	[redacted]	[redacted]
≥ 1 m	[redacted]	[redacted]
≥ 3 m	[redacted]	[redacted]
≥ 6 m	[redacted]	[redacted]
≥ 12 m	[redacted]	[redacted]
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. (Data Cutoff Date: [redacted]).		

Table 96. Exposure by Duration All Relapsed/Refractory Tumours Except Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=[redacted])	
	n	(%)
Duration of Exposure		
> 0 m	[redacted]	[redacted]
≥ 1 m	[redacted]	[redacted]
≥ 3 m	[redacted]	[redacted]
≥ 6 m	[redacted]	[redacted]
≥ 12 m	[redacted]	[redacted]

Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1.
(Data Cutoff Date: [redacted]).

KEYNOTE-051 Summary of Adverse Events

Although the majority of participants ([redacted]) had treatment-related AEs, pembrolizumab was well tolerated as evidenced by the small proportions of participants with Grade 3 to Grade 5 treatment-related AEs ([redacted]), treatment-related SAEs ([redacted]), and treatment-related AEs leading to discontinuation of study treatment ([redacted]) (Table 97). Two ([redacted]) participants died due to a treatment-related AE.

Table 97. Adverse Event Summary (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated n (%)
Subjects in population	[redacted]
with one or more adverse events	[redacted]
with no adverse event	[redacted]
with drug-related† adverse events	[redacted]
with toxicity grade 3-5 adverse events	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]
with serious adverse events	[redacted]
with serious drug-related adverse events	[redacted]
with dose modification‡ due to an adverse event	[redacted]
who died	[redacted]
who died due to a drug-related adverse event	[redacted]
discontinued drug due to an adverse event	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]
discontinued drug due to a serious adverse event	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
Reporting for serious adverse events and serious drug-related adverse events goes through 90 days.
(Database Cutoff Date: [redacted]).

KEYNOTE-051 Overall AEs

The type and incidence of the most frequently reported AEs were consistent with a heavily pre-treated pediatric population with advanced cancers. Most participants ([redacted]) had at least 1 AE. The most frequently reported AEs (in [redacted] of participants) were pyrexia, vomiting, headache, abdominal pain, anaemia, cough, and constipation (Table 98). The majority of these AEs were toxicity Grade 1and Grade 2. Of

note, the most frequently reported medical history conditions included vomiting (15.5%), headache ([redacted]), and anemia ([redacted]).

*Table **98**. KEYNOTE-051 Subjects With Adverse Events By Decreasing Incidence (Incidence ≥ 10%) (All Subjects as Treated Population - Parts I and II)*

	All Subjects as Treated	
	n	(%)
Subjects in population	[redacted]	
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: [redacted]).

KEYNOTE-051 Drug Related Adverse Events

The type and incidence of the most frequently reported treatment-related AEs were consistent with a heavily pretreated pediatric population with advanced cancers and with the established safety profile of pembrolizumab in adults. The majority of participants ([redacted]) had at least 1 treatment-related AE (Table 99).The most frequently reported treatment-related AEs (in >5% of participants) were fatigue, anaemia, pyrexia, aspartate aminotransferase increased, lymphocyte count decreased, diarrhea, alanine aminotransferase increased, and hypothyroidism

(Table 99). The majority of these treatment-related AEs were toxicity Grade 1 and Grade 2.

Table 99. Subjects With Drug-related Adverse Events By Decreasing Incidence (Incidence ≥ 5%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	[redacted]	
with one or more Adverse Events	[redacted]	[redacted]
with no Adverse Events	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: [redacted]).

KEYNOTE-051 Grade 3-5 Adverse Events

Approximately half of participants ([redacted]) had at least 1 Grade 3 to Grade 5 AE

Table 100. The most frequently reported Grade 3 to Grade 5 AEs (in >5% of participants) were anemia and lymphocyte count decreased Table 100.

Table 100. KEYNOTE-051 Subjects With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥ 5%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	[redacted]	
with one or more Adverse Events	[redacted]	[redacted]
with no Adverse Events	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: [redacted]).

KEYNOTE-051 Drug Related Grade 3-5 Adverse Events

Few participants ([redacted]) had at least 1 treatment-related Grade 3 to Grade 5 AE

Table 101. The most frequently reported treatment-related Grade 3 to Grade 5 AEs (in >1% of participants) were lymphocyte count decreased in [redacted] and anemia in [redacted] (Table 101).

Table 101. KEYNOTE-051 Subjects With Drug Related Grade 3-5 Adverse Events (Incidence > 0%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	[redacted]	
with one or more Drug-related Grade 3-5 adverse events	[redacted]	[redacted]
with no Drug-related Grade 3-5 adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Gastric ulcer	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Myelitis	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pulmonary oedema	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Photosensitivity reaction	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
(Database Cutoff Date: [redacted]).

KEYNOTE-051 Serious Adverse Events

Approximately [redacted] of participants ([redacted]) had at least 1 SAE up to 90 days after receiving the last dose of pembrolizumab Table 102. The most frequently reported SAEs (in ≥2% of participants) were pyrexia, pneumonia, pleural effusion, device related infection, seizure, sepsis, and vomiting (Table 102).

Table 102. KEYNOTE-051 Subjects With Serious Adverse Events By Decreasing Incidence Up to 90 Days from Last Dose (Incidence ≥ 1%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	[redacted]	

with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]
Seizure	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: [redacted]).

KEYNOTE-051 Drug Related Serious Adverse Events

Sixteen ([redacted]) participants had at least 1 treatment-related SAE up to 90 days after the last dose of pembrolizumab. The most frequently reported treatment-related SAEs (in >1% of participants) were pyrexia in [redacted] participants, hypertension in [redacted] participants, and pleural effusion in [redacted] participants (Table 103).

Table 103. KEYNOTE-051 Subjects With Drug-related Serious Adverse Events By Decreasing Incidence Up to 90 Days from Last Dose (Incidence > 0%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	[redacted]	
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Diaphragmatic hernia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Enterocolitis infectious	[redacted]	[redacted]
Gastric ulcer	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]
Myelitis	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Photosensitivity reaction	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Pulmonary oedema	[redacted]	[redacted]
Tumour flare	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: [redacted]).

KEYNOTE-051 Deaths

[redacted] participants had 1 or more AEs that resulted in death up to 90 days after receiving the last dose of pembrolizumab (Table 97). [redacted] had fatal AEs reported by the investigator as treatment related: [redacted] participant had pulmonary oedema and [redacted] participant had pneumonitis and pleural effusion. The fatal, treatment-related AE of pulmonary oedema occurred in [redacted] experiencing concomitant sepsis. The fatal, treatment-related AEs of pneumonitis and pleural effusion occurred in [redacted] with extensive right chest involvement of the underlying epithelioid sarcoma.

KEYNOTE-051 Adverse Events of Special Interest

The incidence, severity, and nature of AEOSI observed during the study were, in general, similar to the established safety profile for pembrolizumab monotherapy. No new indication-specific, immune-mediated AEs causally associated with pembrolizumab were identified. The AEOSI were manageable with standard therapeutic strategies or concomitant corticosteroids.

[redacted] participants had at least 1 AEOSI (Table 104). The most frequently reported AEOSI (in ≥2.5% of participants) were hypothyroidism ([redacted]), hyperthyroidism ([redacted]), hypersensitivity ([redacted]), and pneumonitis ([redacted]). [redacted] ([redacted]) participants had a Grade 3 to Grade 5 AEOSI: [redacted] participants with a Grade 3 AEOSI (colitis, myelitis, and pruritus) and [redacted] participant with Grade 5 pneumonitis. [redacted] participants had an AEOSI that led to discontinuation of study treatment: [redacted] with Grade 3 myelitis and [redacted] with Grade 5 pneumonitis.

Use of concomitant corticosteroids to manage AEOSI was reported for the categories of adrenal insufficiency, thyroiditis, colitis, pneumonitis, severe skin reactions, and myelitis. Among the [redacted] participants who had at least 1 AEOSI, [redacted] ([redacted]) participants had resolution of an event by the time of data cutoff for this report. Among the [redacted] ([redacted]) participants with at least 1 AEOSI that had not resolved, [redacted] events were endocrinopathies that require long-term hormone replacement therapy ([redacted] events of hypothyroidism, [redacted] events of hyperthyroidism, [redacted] event of thyroiditis, and [redacted] event of adrenal insufficiency).

Table 104. Adverse Event Summary AEOSIm(All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated n (%)
Subjects in population	[redacted]
with one or more adverse events	[redacted]
with no adverse event	[redacted]
with drug-related† adverse events	[redacted]
with toxicity grade 3-5 adverse events	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]
with serious adverse events	[redacted]
with serious drug-related adverse events	[redacted]
with dose modification‡ due to an adverse event	[redacted]
who died	[redacted]
who died due to a drug-related adverse event	[redacted]
discontinued drug due to an adverse event	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]
discontinued drug due to a serious adverse event	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
Reporting for serious adverse events and serious drug-related adverse events goes through 90 days.
(Database Cutoff Date: [redacted]).

KEYNOTE-051 Complications Post-allogeneic SCT

[redacted] received an allogeneic SCT after discontinuing treatment with pembrolizumab: [redacted] with HL and [redacted] with a primary diagnosis of solid tumour NOS. [redacted] with HL developed a complication post allogeneic SCT: Grade 2 chronic GvHD in [redacted] and Grade 2 acute GvHD in [redacted]. Before receiving an allogeneic SCT, the participants had entered Survival Follow-up and transitioned to alternative systemic anticancer therapy. The participants were diagnosed with GvHD approximately [redacted] post allogeneic SCT. At the time of data cutoff for this report, both participants were alive and the GvHD had not resolved. The investigators considered both the chronic GvHD and acute GvHD not related to pembrolizumab.

B.2.11 Ongoing studies

KEYNOTE-204 study is ongoing, with the first [redacted] expected to be reached in [redacted].

B.2.12 Innovation

Pembrolizumab represents a stepwise change in the management of patients with R/RcHL. Pembrolizumab, a checkpoint inhibitor, is able to interact with a patient's immune system to destroy cancer cells, as described in Section B.1.2. Furthermore, given the limited treatment options available for patients with R/R cHL who have failed or are ineligible for ASCT, it is expected that both clinicians and patients would value an alternative to current standard of care. Thus, there is a substantial level of unmet need within this patient population.

Classical Hodgkin Lymphoma cells demonstrate high levels of PD-L1 due to the expression by RS cells comprising cHL[38]. CHL cell lines exhibit amplification of chromosomes 9p24.1, which correlates with cell surface PD-L1 protein expression in RS cells. In addition, in cHL cells that are EBV-positive, aberrant signalling through EBV-encoded gene products provides further mechanisms to upregulate PD-L1[38]. Pembrolizumab is an effective immunotherapy for the treatment of cHL as a result of the role of PD-L1 expression in the pathophysiology of cHL.

The innovative nature of pembrolizumab was first recognized by the US Food and Drug Administration (FDA) in January 2013 by granting it Breakthrough Therapy Designation (BTD) for advanced melanoma [39]. The FDA's BTD is intended to expedite the development and review of a drug that is planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoint[40]. Pembrolizumab has continued to be recognized for its innovation within numerous tumour types.

Specifically, pembrolizumab received accelerated approval by the FDA on March 14, 2017 for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after three or more prior lines of therapy. Pembrolizumab received EMA approval on May 5, 2017 for the treatment of adult patients with R/RcHL who have failed ASCT and BV or who are transplant-ineligible and have failed BV EMA approval of pembrolizumab in adult patients was based on data from the KEYNOTE-087 and KEYNOTE-013 trials, while FDA approval was based on KEYNOTE-087[2, 41].

In the UK, in March 2015 pembrolizumab became the first medicine to be granted positive scientific opinion under the MHRA's Early Access to Medicines Scheme (EAMS) for the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent

disease on or following treatment with standard of care [42, 43]. Pembrolizumab received Promising Innovative Medicines (PIM) designation (EAMS Step 1) in November 2015, and in March 2016 a positive Scientific Opinion was granted (MHRA EAMS number 00025/0001) for "*the treatment as monotherapy of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation or whose disease has progressed on or after platinum-containing chemotherapy. Patients who have an EGFR sensitising mutation or an ALK translocation should also have had disease progression on approved therapies for these aberrations prior to receiving pembrolizumab*" [2].EAMS aims to give earlier access to promising new unlicensed or 'off label' medicines to UK patients that have a high unmet clinical need. This validates MSD's position that pembrolizumab should be considered innovative in its potential to make a significant and substantial impact on health-related benefits in an area of high unmet need.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The results of KEYNOTE-204 presented in this submission show that in patients with R/RcHL, pembrolizumab therapy provides a clinically meaningful and statistically significant benefit in PFS compared with BV. The ORR and DOR findings presented in this submission support the PFS results which show PFS was significantly longer in the pembrolizumab arm compared with the BV arm.

The incidence of AEs for most AE categories was not appreciably different across treatment arms. After adjustment to account for increased exposure in the pembrolizumab arm, the incidence of SAEs was similar in both arms, with the exception of higher incidences of hypothyroidism, urinary tract infection, and pneumonitis in the pembrolizumab group and higher incidences of nausea and peripheral neuropathy in the BV group. AEOSIs were more common in the pembrolizumab arm than the BV arm with hypothyroidism and pneumonitis being the most common AEOSIs. No new AEOSIs were identified. The frequency and severity of laboratory test toxicity was comparable in the intervention groups. In both arms, most changes in toxicity grade from baseline to worst post-baseline values were to Grades ≤2. Overall, the observed events were largely representative of the relapsed or refractory cHL patient population in which underlying disease plays a contributary role. The safety profile of pembrolizumab within this target population of R/RcHL was consistent with the previously characterized safety profile seen in the prior analysis of data from KEYNOTE-087

and with the established safety profile of pembrolizumab monotherapy. No new immune-mediated events causally associated with pembrolizumab were identified in this study. No new safety risks were identified.

This evidence is further supported by the results of KEYNOTE-087, with a median follow-up of over 3 years, results demonstrate consistent, highly clinically relevant, and durable anti-tumour activity of pembrolizumab monotherapy in heavily pre-treated participants who have exhausted all conventional treatment options. With extended treatment and follow-up, pembrolizumab monotherapy was well tolerated: most AEs were of low-grade toxicity, did not require treatment interruption, and resolved if treatment interruption was necessary; the incidence of treatment discontinuation due to drug-related AEs or SAEs was low.

The evidence from KEYNOTE-051 show that pembrolizumab monotherapy demonstrates a high level of clinically relevant antitumor activity in pediatric patients with R/RcHL. In addition pembrolizumab monotherapy is generally well tolerated in pediatric patients within the indications of advanced melanoma; R/RHL; advanced, R/R MSI-H solid tumours; or PD-L1-positive, advanced R/R solid tumours or other lymphoma, as shown by low rates of treatment discontinuation.KEYNOTE-051 highlighted that in the pediatric patient population, pembrolizumab is associated with a favourable safety profile, characterized by AEs, SAEs, and AEOSI that are generally predictable and manageable with standard therapeutic and supportive care strategies. Importantly, no new immune-mediated AEs causally associated with pembrolizumab are identified in this population.

End-of-life criteria

Table 105. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Current clinical expert opinion does not support the argument that patients in the current SoC have a life expectancy of less than 24 months except potentially from a subset who are very old with comorbidities. According to the economic model base case, 4.98 life years were gained for the overall population.	n/a
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	OS data not available to address this criterion	n/a

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

In line with the NICE Guide to the methods of technology appraisal (2013)[44], a comprehensive single SLR was conducted in March 2020 with the overall objective being to identify and summarize: a) the published cost-effectiveness analyses, b) healthcare costs and resource requirements and c) health-related quality of life associated with the treatment of patients with R/RcHL.

Full details of the SLR search strategy, study selection process and results for the economics studies are presented in Appendix G.

B.3.2 Economic analysis

No cost-effectiveness study relevant to England was identified, indicating that a de novo cost-effectiveness model is required to assess the cost-effectiveness of pembrolizumab compared with the relevant comparator. Therefore, a cost-utility analysis is presented based on a three-state partitioned survival model, an approach consistent with many oncology submissions developed for NICE[45].

B.3.2.1 Patient population

The patient population included in the economic evaluation consisted of [redacted]. This is in line with the anticipated licensed indication and the final scope issued by NICE[46].

The main body of evidence was derived from KEYNOTE-204 and for the base case analysis, the full ITT population from this trial was considered. It should be noted that the [redacted] is not included in the economic analysis.

The baseline characteristics of the patients included in the model are presented in Table 106. Sensitivity analyses will assess the impact of alternative baseline patient parameters.

Table 106. Baseline patient parameters ITT population - European subjects

Characteristic	Mean	Source
Baseline age (years)	41.35	KEYNOTE-204 ITT population[47]
Proportion female	42.77%	
Weight (kg)	77.65	KEYNOTE-204 ITT population, European subjects[47]
Body Surface Area (BSA)(m2)	1.90	

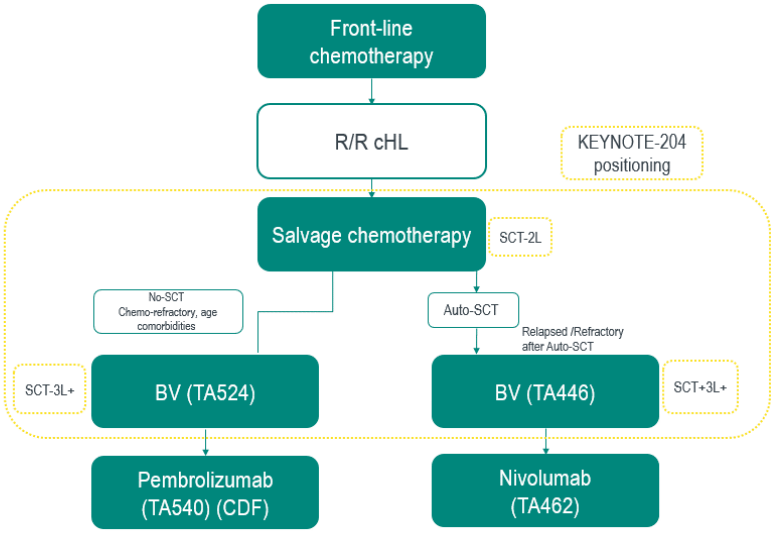
Post hoc analyses of subpopulations

Three subpopulations of the overall ITT population were considered and analysed in section B.3.9

- Patients with R/RcHL who did not have at least two prior therapies when autologous stem cell transplant is not a treatment option (SCT-2L)
- People with R/RcHL who are at least third line with prior autologous stem cell transplant. (SCT+3L+) and
- People with relapsed or R/RcHL who are at least third line when autologous stem cell transplant is not a treatment option (SCT-3L+).

SCT-2L: The final scope takes into consideration the population "who did not have at least two prior therapies when ASCT is not a treatment option". This is a small subgroup of the ITT population and final scope defines the relevant comparator as chemotherapy.

Figure 30. Simplified treatment pathway of R/RcHL



Third line patients were also presented separately as two different subpopulations based on whether they received prior ASCT or not.

Third line subpopulations are also for consistent with previous NICE TAs[22, 48] for BV where cost effectiveness was presented separately for the following two:1) relapsed or refractory Hodgkin's lymphoma after autologous stem cell transplant (ASCT) and 2) after at least 2 previous therapies when ASCT or multi-agent chemotherapy is not a treatment option and evidence supporting each analyses came from different trials.

Table 107 summarises the subgroups and comparators from KEYNOTE-204 for whom an economic analysis is presented in the section B.3.9

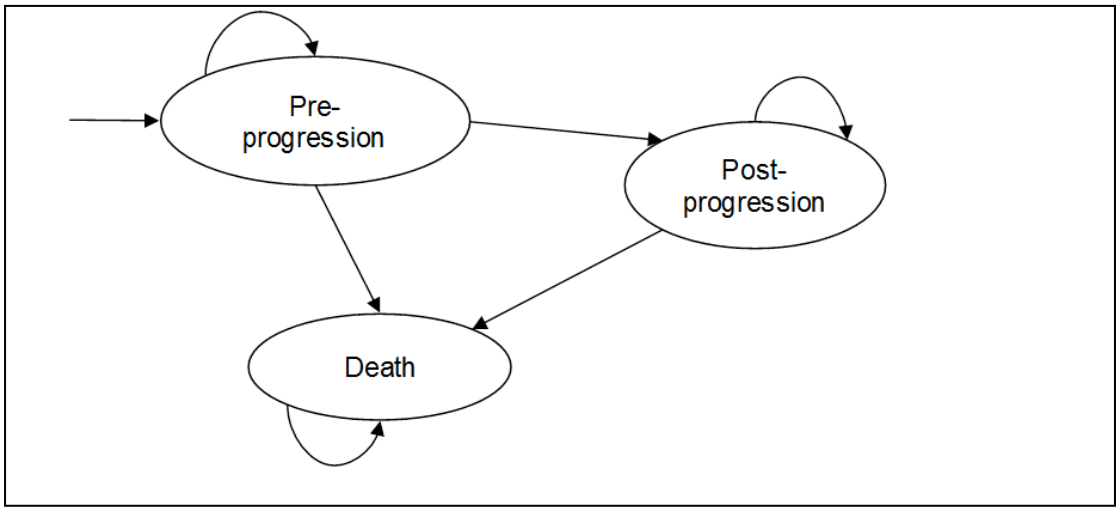
Table 107. Summary of subgroups and comparators assessed for cost -effectiveness

Post-hoc Subpopulation	Comparator
SCT-2L	Salvage chemotherapy
SCT+3L+	BV
SCT-3L+	BV

B.3.2.2 Model structure

The model structure is shown in Figure 31. It comprises three mutually exclusive health states that are designed to reflect the natural course of the disease.

Figure 31. Model structure



It is a partitioned survival model and, in this approach, the treatment-specific OS curve is used to determine the proportion of patients alive at each model cycle. The area under the

OS curve is partitioned into the progression-free (PF) and progressed disease (PD) health states based on the PFS curve, which estimates the proportion of patients experiencing a progression event, defined as tumour progression or death. The proportion of the cohort in the PF health state over time is based on the treatment specific PFS curve, determining how many patients are in the entrance health state over time. As the OS curve associated with the treatment received describes the proportion of patients alive, the remainder represents the proportion in the death state over time. The PD health state membership is estimated as the difference between the OS and PFS curves, since the health states are mutually exclusive, i.e. patients can be in only one state at each time point. The modelled population enters the model in the pre-progression (PF) health state. At the end of each weekly cycle, patients in the PF health state can remain in that health state or experience disease progression and enter the post-progression (PP) health state. Patients in the PP health state can, at the end of each cycle, remain in that health state but they cannot return to the PF health state. Transitions to the death health state can occur from either the PF health state or the PP health state. Death is an absorbing health state from which transitions to other health states are not permitted.

Partitioned survival models allow the proportion of patients in each health state to be defined by the individual survival curves extrapolated from the trial data or hazard ratios. This structure is most commonly used within oncology models and is an established method with straightforward implementation and explanation. It does not require the definition of explicit transitions between health states and automatically incorporates time dependencies in the event rates. Given the lack of OS data from KEYNOTE-204 in this analysis as well as the need to take into account different subpopulations of the KEYNOTE-204 ITT population, the use of a PSM was considered the better approach compared to other structures requiring further complex assumptions and multiple evidence sources to estimate transition probabilities.

In previous R/RcHL submission (TA524), the model structure[49] (Semi-Markov transition matrix model) for patients who had at least two therapies and transplant was not an option, a separate health state of stem cell transplant was modelled. However, in this submission, a health state representing the prognosis of patients undergoing SCT was not considered to avoid complexity but also based on the outcomes and design of the KEYNOTE-204 trial:

1) The number and proportion of patients who received auto or allo- SCT, prior to PD, between the two treatment arms was evenly balanced and low. For pembrolizumab,

[redacted] received SCT prior to PD and similarly [redacted] received auto- or allo-SCT prior to PD for BV (Table 108).

2) The time to ASCT or allo-SCT before disease progression is long and evenly balanced between pembrolizumab ([redacted]) and BV ([redacted]). Upon review, neither treatment was used among this trial population in a systematic way as a bridge-to-transplant. Unlike other models and associated trials which incorporated SCT as a separate health state, the majority of patients in KEYNOTE-204 did not undergo transplant and those who did undergo transplant was [redacted] and not the earlier timepoints used in these alternative model structures.

3) The majority of patients who received ASCT or allo-SCT, received it post progression. Again, this proportion was relatively well balanced, with [redacted] receiving SCT after PD and subsequent therapy for pembrolizumab. This proportion was [redacted] for BV representing [redacted] patients who received SCT (Table 108).

Therefore, the efficacy of the SCT was considered only as part of the true trial efficacy included in the economic model via the PFS data from KN204 and OS data from literature described later in section B.3.3 while costs were assigned based on the proportion that patients receive SCT in KEYNOTE-204.

Table 108: Time to first SCT, Pembrolizumab vs. BV (ITT population)

ITT population	Pembrolizumab			BV		
	N	Number of events (%)	Estimated Mean Time in weeks	N	Number of events (%)	Estimated Mean Time in weeks
Time to first SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first allo-SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first auto-SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first SCT prior to PD and subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first SCT after PD and subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In line with the NICE reference case, cost-effectiveness was assessed in terms of the cost per Quality Adjusted-Life Years (QALY) gained. The total costs and outcomes of treatments are estimated by combining the occupancy of each health state over time with the costs and utilities ascribed to the respective health states. Costs and health outcomes are discounted based on an annual discount rate of 3.5% for both measures, in line with NICE Reference case. Half-cycle correction was also applied to reduce bias when calculating cumulative outcomes in discrete time.

B.3.2.3 Key features of the economic analysis

Table 109. Features of the economic analysis

	Previous appraisals		Current appraisal	
Factor	TA446	TA524	Chosen values	Justification
Time horizon	40 years	70 years	40 years	The disease history of the simulated cohort evaluated for a lifetime time horizon, assumed to be 40 years since most death events are expected to occur within this period based on clinical data. Modelled OS at 40 years predicts 1.4% patients alive on pembrolizumab arm vs 1.1% on BV arm.
Cycle length	Daily	weekly	Weekly	Weekly cycle length was chosen to accommodate the different treatment administration schedules and capture costs accurately. The cycle length is consistent with previous TAs in oncology and in this indication and considered to be sufficiently short to allow an accurate estimation of the event timings while not adding the complexity of the daily cycles
Discount rate for utilities and costs	3.5%	Not reported	3.5%	Consistent with NICE reference case
Perspective	NHS and personal social services	NHS	NHS and Personal Social Services perspective	In line with NICE final scope
Source of utilities?	Utilities for the PFS and post-progression health states were derived from the published vignette based TTO utility elicitation study conducted in a representative sample of 100 UK members of the general public (Swinburn et al. 2015)	Utility data were taken from published sources including BV clinical studies (Swinburn 2015), and a published study of utility post ASCT (van Agthoven 2001)	Utilities were sourced from KEYNOTE-204 trial (based on EQ-5D-3L questionnaires collected during the trial)	Consistent with NICE reference case - measurement of changes in health-related quality of life were reported directly from patients in KEYNOTE-204 and the utility of these changes were based on public preferences using a choice-based method like EQ-5D.
Source of costs	Patients with relapsed or refractory Hodgkin's lymphoma after ASCT • Drug costs were taken from BNF March-September 2015 • Unit costs for all other resources (administration and	• Clinical expert opinion advised the medical and administration costs	Drug costs were sourced from BNF and eMit. Drug administration costs and AE costs from NHS Reference costs 18/19	Consistent with the NICE reference case.

	health-states) were sourced from the NHS Reference Costs 2013-14 • Expert clinical opinion to evaluate resource use requirements Resource use estimates for the adverse events were obtained from interviews with UK clinical experts		Disease management costs and terminal care costs from previous TAs based on PSSRU and NHS reference costs	
Treatment waning effect	Not reported	Not reported	Not applied	Treatment waning is not applicable as the base case assumed a very conservative scenario for the OS benefit for pembrolizumab: in the absence of OS data from KEYNOTE-204, equal OS curves were assumed for pembrolizumab and BV based on published BV curves (Gopal, et al) (see section B.3.3) and therefore treatment waning is implicitly included in the extrapolation in the most conservative way.

B.3.2.4 Intervention technology and comparators

The intervention (i.e. pembrolizumab) was applied in the model as per the anticipated licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks [Q3W]).

The final scope specifies the following treatment regimens as relevant comparators:

- BV
- Chemotherapy regimens - For people who did not have at least two prior therapies when ASCT is not a treatment option (SCT-2L)

BV was the comparator in the KEYNOTE-204 trial and therefore the comparison of BV versus pembrolizumab is presented as the base case for the ITT population. BV was applied in the model as per the trial of 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

The comparison of pembrolizumab versus chemotherapy regimens for the SCT-2L subgroup is presented in section B.3.9.1

Treatment discontinuation

Treatment discontinuation was applied in the model according to the KEYNOTE-204 protocol: treatment with pembrolizumab and BV was continued for up to 35 cycles per participant or until documented disease progression as described in the IWG response criteria by blinded independent central review, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, or administrative reasons[3]. It should be noted that for BV, the SmPC suggests that patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles[50]. A maximum doses of 35 doses was assumed in the base case for BV to reflect its efficacy from KEYNOTE-204, however a scenario analysis is presented in Table 140 (section B.3.8) where maximum dose of BV is set to 16 cycles as per its license.

B.3.3 Clinical parameters and variables

B.3.3.1 Overview of Modelling Effectiveness

The clinical effectiveness parameter of PFS for pembrolizumab and BV was sourced from patient-level data from KEYNOTE-204. Additionally, the duration that patients stay on

treatment, for both arms, was also modelled from Time on Treatment (ToT) KM data from the same trial.

However, OS was not reported in this analysis of KEYNOTE-204 (see Table 1), therefore, different methods needed to be considered in order to model the OS of patients on pembrolizumab and BV. The clinical SLR (Appendix D.1.1.3) identified a publication that reported OS outcomes for BV and was examined further for its appropriateness in the economic modelling: the publication by Gopal et al (2015)[51], reported survival outcomes from a pivotal phase 2 multi centre, single arm, open-label trial of BV in subjects with R/RcHL after failing ASCT (N=102). This trial was also the main body of evidence supporting the NICE TA446 for patients who were R/R after ASCT[52]. The population of Gopal et al, is a subpopulation of the KEYNOTE-204 ITT population and Table 110 compares the main patient characteristics of the two trials and the common subpopulation of KEYNOTE-204. Even though patients in Gopal et al. have a slightly more burdensome profile of prognostic factors, PFS was not too dissimilar across the BV arms and it was deemed that the outcomes of the publication are broadly generalisable to use for modelling OS for KEYNOTE-204.

Table* 110*: Comparison of Gopal 2015 and KEYNOTE-204

	Gopal 2015- overall	**KEYNOTE-204- overall**	**KEYNOTE-204 – SCT+3L+**
Patients	cHL patients who are refractory or have relapsed after auto-SCT	R/R cHL patients who failed ASCT or who were ineligible for ASCT and who had received at least 1 prior multi-agent chemotherapy regimen.	R/R cHL in a subpopulation, who were third line subjects with prior SCT and
Design	Single-arm trial (Phase II, open-label, multi-centre, single-arm trial)	RCT (Phase III, randomised, open-label, multi-centre, two-arm trial)	Post-hoc analysis
Median age, year	31	36	[redacted]
Male	47%	[redacted]	[redacted]
ECOG status 0 / 1	41% / 59%	[redacted]	[redacted]
Baseline B symptoms: YES	34%	[redacted]	[redacted]
Primary refractory	71%*(includes patients that relapsed <3months)	[redacted]	[redacted]
Number of prior regimens (median)	3.5	[redacted]	[redacted]

Prior SCT	100%	[redacted]		[redacted]	
Intervention/comparator	Brentuximab vedotin (comparator N/A as single-arm trial)	Pembrolizumab	Brentuximab vedotin (1.8 mg/kg Q3W, IV)	Pembrolizumab	Brentuximab vedotin (1.8 mg/kg Q3W, IV)
N patients	102	151 (Total = 304)	153 (Total = 304)	[redacted]	[redacted]
Median follow-up	33.3 months	24.7 months	24.7 months	24.7 months	24.7 months
Median PFS	9.3 months	13.2 months	8.3 months	[redacted]	[redacted]

Whilst OS data for pembrolizumab from another trial - single arm KEYNOTE-087- was available, it was more immature (mOS not reached) than the Gopal et al (mOS 40.5months). As there is no external OS data published for the KEYNOTE-204 population, PFS data from KEYNOTE-204 combined with the most mature OS data like the Gopal et al. was considered as the most applicable to use as a proxy. Three alternative methods were considered to model OS (Table 111):

1) The base case assumed no OS benefit for pembrolizumab over BV. The OS data for BV from Gopal were used to model OS for both treatments.

2) A scenario analysis assumed no OS benefit for pembrolizumab over BV. The OS data for pembrolizumab from KEYNOTE-087 were used to model OS for both treatments

3) A scenario analysis was conducted assuming that the relationship observed between PFS and OS observed in Gopal (2015) will translate to KEYNOTE-204.

- Based on this, OS and PFS data from Gopal et al was utilized to estimate a predictive equation between the two endpoints which was then applied to KEYNOTE-204 PFS to generate estimated OS curves for each of the comparators.

Table 111: Summary of the methods explored to estimate OS curves for the model

	Option	Description	Comment
Equal OS for all treatment arms			
Base case	Gopal et al. OS data	Assumption of no OS benefit for pembrolizumab over other treatments; Use of parametric modelling of Gopal et al. 2015	
Alternative scenario 1	KEYNOTE-087 data	Assumption of no OS benefit for pembrolizumab over other treatments; Use of parametric modelling of KEYNOTE-087	
Predictive equation			
Alternative scenario 2	PFS/OS from Gopal	A parametric distribution for Gopal et al. OS is derived using the PFS endpoint and a time varying HR estimated from Gopal et al data. The OS to PFS ratio is then applied to the pembrolizumab PFS curve from KEYNOTE-204.	

Initially, the predictive equation was explored to model OS based on the PFS to OS relationship from Gopal et al paper. This approach has been considered before in other oncology submissions to NICE when OS data were not available or were very immature [39]. The main assumption of this approach is that PFS gain is a good predictor of OS extension and this assumption was previously confirmed by clinical experts– and accepted by the NICE committee- in the R/RcHL setting for cHL patients in high risk of relapsing: "it was reasonable to assume that an extension to progression-free survival would lead to some extension in overall survival." [49] Interviews with independent health economists as well as elicitation of clinical expert opinion suggested that it might be an appropriate approach to model OS. However, in the absence of confirmatory trial data or robust evidence from literature, the face validity of the model would not be clear as OS gains for pembrolizumab may be too optimistic. Therefore, a decision was taken that the base case for the economic model would assume the same OS for both arms as the most conservative argument to derive OS.

Please note that the base case assumption was selected as the most conservative way to model pembrolizumab OS and demonstrate the potential for cost-effectiveness in order to enable access to patients until OS data from KEYNOTE-204 become available. [redacted] As mentioned in the Decision problem form, MSD considers that pembrolizumab for the proposed licensed indication assessed in this submission should be considered a candidate for the CDF on the basis of further data collection in both the pivotal clinical trial (KEYNOTE-204) and via real world data sources which MSD are exploring.

B.3.3.2 Progression-free survival

The follow-up period in KEYNOTE-204 (median follow-up 24.7 months) was shorter than the time horizon of the economic model. Therefore, extrapolation of the PFS was required for the partitioned survival approach.

Survival analyses for PFS were conducted using approaches outlined by the Decision Support Unit (DSU) by NICE[53]: The first step was the assessment of the proportional hazards (PH) assumption judged via the plotting of the log-cumulative hazard function (Figure 32) and associated residual plots (Figure 33): when comparing the PFS outcomes observed in the pembrolizumab and BV, PH may not hold based on the visual assessment of the log-cumulative hazards plot. The curves do not cross but the hazards change over time since the curves appear to start parallel, before merging and separating again. The statistical test supports the PH assumption since the result is not statistically significant (p >0.05), indicating that the proportional hazards assumption for PFS might be assumed but due to the uncertainty regarding the PH assumption, pembrolizumab and BV were modelled by fitting independent parametric models to each treatment arm.

Figure 32. Comparison in cumulative hazard in BIRC-assessed Progression-free Survival over time between groups treated with pembrolizumab versus BV

Figure 33. Schoenfeld residual for graphical diagnosis of proportional hazards in BIRC-assessed Progression-free Survival between groups treated with pembrolizumab versus BV

The next step was the visual inspection of the hazard plots which suggested a change in hazard while further examination of the Chow tests (Figure 34 and Figure 35) indicated a change around week 26 (more prominent on pembrolizumab arm) and around week 52 (more prominent on BV arm but also observed in pembrolizumab arm too).

Figure 34. Plot of multiple Chow test statistics to detect break points in BIRC-assessed Progression-free Survival in group treated with pembrolizumab

Figure 35. Plot of multiple Chow test statistics to detect break points in BIRC-assessed Progression-free Survival in group treated with BV

As the change in hazard is obvious around the same time point (52 weeks) for both arms, a piecewise approach was considered in the base case. This way KM data are used until the 52 week breaking point and then parametric extrapolation is applied thereafter. A series of parametric extrapolations were fitted to PFS data for week 52 in order to identify the best fitting curve (Figure 36 and Figure 37).

Figure 36. Plot of parametric fitting and extrapolation of long-term BIRC-assessed PFS for the group treated with pembrolizumab with breaking point at Week 52, ITT population

Figure 37. Plot of parametric fitting and extrapolation of long-term BIRC-assessed PFS for the group treated with BV, with breaking point at Week 52, ITT population

Table 112 presents a summary of the AIC and BIC statistics for both arms. Please note that generalised gamma did not converge. For pembrolizumab, the AIC and BIC criteria suggest Gompertz is the best fitting model while for BV is exponential. However, log-normal was the second-best fitting model for both arms and provided a good visual fit.

Table 112. Summary of parametric fitting performances of BIRC-assessed Progression-free Survival for the group treated with pembrolizumab and BV

	Pembrolizumab				Brentuximab vedotin			
Distributions	AIC	Rank	BIC	Rank	AIC	Rank	BIC	Rank
Exponential								
Weibull								
Gompertz								
Log-logistic								
Log-normal								
Generalised gamma								

The selection of a piecewise log-normal extrapolation was also validated externally with two consultant haematologists, from different centres, who specialise in lymphomas whom were asked to discuss key issues relating to economic modelling.

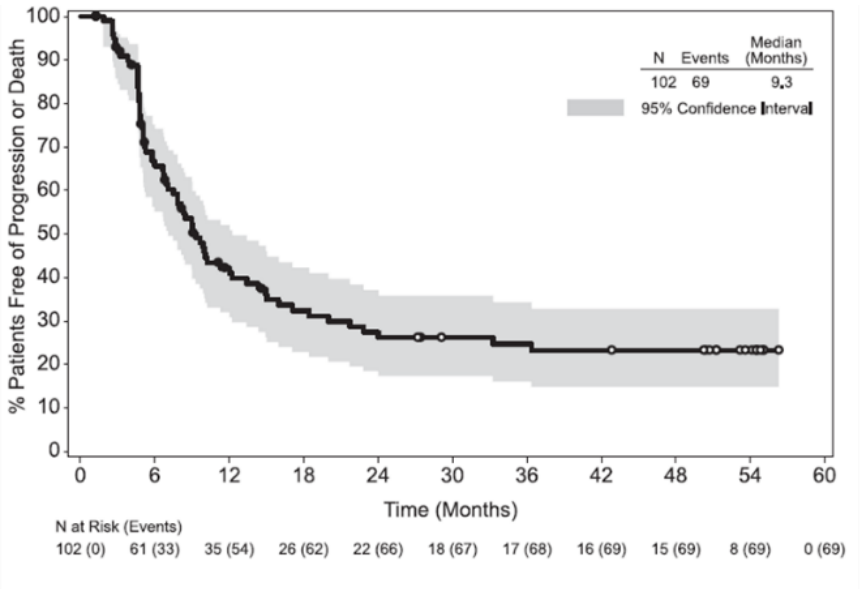
The plausibility of the approach to modelling PFS was validated by asking clinicians to estimate 5-year survival percentages for BV. The suggestions were that for patients who are R/R after ASCT (SCT+3L) the estimated PFS was approximately ~15% at 5 years while patients ineligible for transplant would have a lower PFS about ~10%. This is because patients relapsing after ASCT means they were chemo-sensitive enough initially to receive the ASCT and so would be more likely to respond to BV. Additionally, they will be younger / biologically fit (as they had an ASCT) than patients for whom ASCT is not a treatment option. It should be noted that as per the NICE scope, MSD considered the ITT as its base case however as suggested by the clinicians, the subpopulations within the trial can perform differently in clinical practice making overall estimates on PFS for the whole ITT group difficult to provide. However, it can be seen from Table 113, that the ITT modelled 5-year PFS for the BV arm is 11.5% and this is potentially a plausible estimate since it is within the 10% and 15% 5-year PFS estimates cited by the clinician for the two subgroups.

A piecewise extrapolation with breaking point at 26 weeks as well as a fully fitted parametric curve from week 0 are explored as scenario analyses in Table 140 (section B.3.8). Neither of the two were selected as the base case since the best statistical fits to the PFS KM data for each scenario resulted in low, clinically implausible 5-year PFS estimates of BV, ~2.5-3.5% for week 0 and ~8.5% for week 26.

Table 113. PFS modelled extrapolation estimates – piecewise parametric approach with breaking point at week 52

	PFS				
	1 yr	2 yr	3 yr	4 yr	5 yr
Pembrolizumab	[redacted]	36.8%	30.5%	26.6%	23.7%
BV	[redacted]	22.7%	17.2%	13.8%	11.5%

Figure 38. Progression free survival for Gopal et al 2015



In conclusion, based on the visual and statistical fit of the extrapolated curves as well as the external validation from clinical experts, the log-normal was selected as the base case with a breaking point at week 52 (Figure 39). Please note that the decline in the PFS of pembrolizumab arm after year 10 is due to a requirement applied in the model so that PFS is never higher than OS, see more details in the Overall Survival section

Figure 39. Extrapolation of modelled long-term BIRC-assessed PFS for pembrolizumab and BV with breaking point at Week 52, ITT population

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B.3.3.3 Overall survival

As discussed at the beginning of section B.3.3, due the absence of OS data from KEYNOTE-204, a conservative argument for OS is to assume that there will be similar OS for all treatment arms. The Gopal et al (2015) publication was deemed as a relevant study which provided OS data that could be digitised.

Gopal et al (2015) is a multicenter, single arm, open-label, phase 2 trial of BV in subjects with R/RcHL following. The data used in the model is based on a March 2014 data cutoff which represents a median of approximately 3 years of observation time for all patients.

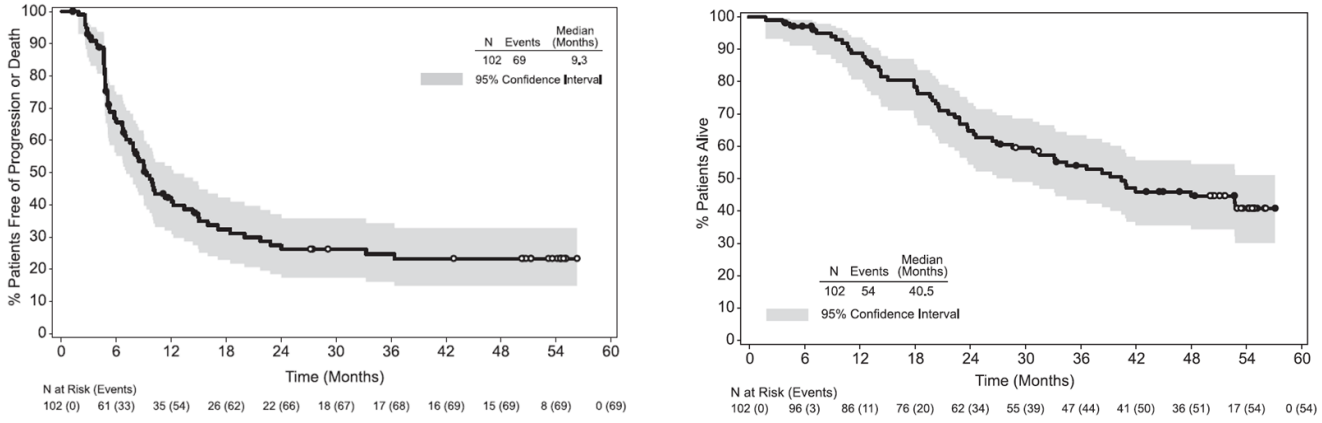
All patients enrolled in Gopal et al (2015) were R/R following ASCT (N=102), as per the indication for BV for this population. All patients participating in Gopal 2015 received BV 1.8 mg/kg IV once every 3 weeks over 30 minutes on an outpatient basis for up to 16 infusions. Eligible patients were aged 12 years or older, presented with histologic confirmation of CD30-positive Hodgkin RSC by central pathology review was required, as well as fluorodeoxyglucose, disease by positron emission tomography (PET) and measurable disease of at least 1.5 cm by computed tomography (CT).

The primary and secondary endpoints of Gopal 2015 were:

- (Primary) Overall response rate
- (Secondary) Duration of response, CR, PFS, OS, and incidence and severity of AEs

Median follow-up in this study was 33.3 months (range, 1.8 to 57.3 months); The median OS was estimated at 40.5 months and the median PFS was 9.3 months (see Figure 40).

Figure 40. Progression free survival (left) and overall survival (right) for Gopal 2015[51]



Whilst Gopal et al (2015) provides the most robust long-term OS data, a limitation is that this study was performed before the availability of newer therapies post-progression, such as pembrolizumab and nivolumab. This may underestimate the BV OS for the patient

population in current clinical practice. However, this should only provide a further conservative prediction of OS benefit and is applied equally to both the BV and pembrolizumab arms therefore not impacting the cost effectiveness results.

KM data from the Gopal et al (2015) [51] study was digitized and extrapolated to provide one-piece survival fits.

Figure 41: Gopal (2015) OS extrapolation fit

Table 114: Summary of parametric fitting performances of OS from Gopal (2015)

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

The AIC and BIC criterion suggests log-normal is the best fitting model. Upon visual inspection and long-term extrapolation, the log-normal distribution predicts a robust long-

term survival. The log-normal distribution has the best statistical fit and a plausible long-term prediction and therefore is selected as the base case.

Clinical expert opinion suggested that for patients who are at least third line with prior ASCT (subpopulation from KEYNOTE-204 which is the same population as Gopal et al.), OS at 5-years is ~45-50%. However, as mentioned before the ITT population in this model, includes patients (2L and 3L) who are ASCT-naïve to receive transplant and for these patients, clinical expert opinion suggested 5-year OS of ~20-30% so the modelled survival of 37.4% (Table 115) is a fair representation of the ITT population. Therefore, the BV modelled OS is within the range of what is expected in clinical practice.

Using this approach results in a modelled median OS of 41.9 months for all treatment arms (Figure 42), compared to a median OS of 40.5 months in the Gopal et al. clinical trial (Table 115).

Figure 42: Modelled overall survival applying log-normal extrapolation of Gopal (2015) to all treatments

Table 115. Modelled mean, median and landmark OS

			Proportion of patients alive after				
	Mean	**Median**	**1 yr**	**2 yr**	**3 yr**	**4 yr**	**5 yr**
Pembrolizumab	73.488	41.856	87.1%	69.4%	55.6%	45.3%	37.4%
BV	73.488	41.856	87.1%	69.4%	55.6%	45.3%	37.4%

As highlighted before, since no OS data are available from KEYNOTE-204 the approach to model equal OS was selected on the basis of the most conservative scenario for the cost effectiveness analysis and it is very likely that the modelled pembrolizumab OS is an underestimate of its expected true efficacy on KEYNOTE-204 . Data from KEYNOTE-087 (section B.2.6.2) (singe-arm trial) suggest that OS for patients treated with pembrolizumab post-BV was considerably higher than the conservative modelled OS in this submission

where it was assumed equal to BV. KEYNOTE-087 (Figure 43) reported 12 month OS of [redacted], 24-month OS of [redacted] and 36-month of 86.4% which confirms the expectation that pembrolizumab potentially has better outcomes in the targeted population as well. Clinical opinion has also agreed with the fact that IOs are expected to have much higher OS than modelled here.

Figure 43. Kaplan-Meier Estimates of Overall Survival (ASaT Population) – KEYNOTE-087

Overall survival is adjusted for general mortality risk at each cycle, this is estimated using general population mortality tables which considers the populations starting age and treatment duration. The mortality risks of the general population were sourced from the Office for National Statistics using the national life tables for England 2013–2015.

As discussed at the beginning of the section, alternative approaches were also explored as scenario analyses to model OS:

1) OS data from KEYNOTE-087 to model OS for all treatments (similar to base case approach but OS data source was from KEYNOTE-087 instead of Gopal et al.)

2) Predictive equation of the relationship between PFS and OS from Gopal et al. and application of the equation in both arms of KEYNOTE-204

B.3.3.3.1. Alternative approach 1: OS data from KEYNOTE-087 to model both arms in KEYNOTE-204:

Standard parametric analyses were conducted for the KEYNOTE-087 OS data. The plot of the fully parametric OS fitting from week 0 for pembrolizumab is shown in Figure 44 and Table 116 shows the summary of parametric fitting performances for each of the arms of the KEYNOTE-087 trial.

Figure 44: Plot of parametric fitting and extrapolation of OS for pembrolizumab – KEYNOTE-087

Table 116: Summary of parametric fitting performances of OS for the group treated with pembrolizumab

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]

The AIC criterion suggests log-logistic may be the best fitting model and the BIC criterion suggests exponential may be the best fitting model. Upon visual inspection in Figure 45, the

exponential fit underestimates the OS survival from the KEYNOTE-087 trial in the first 100 weeks, whereas the log-normal distribution provides a good fit to the KM data during that time period. Considering this, along with the AIC and BIC statistics being very similar between all distributions, the log-normal distribution was chosen to extrapolate the OS survival beyond the KEYNOTE-087 trial follow up period.

Using this approach results in a median OS of 171.6 months for all treatment arms (Figure 45). Whilst this might be a more plausible scenario for the pembrolizumab arm, the estimate is a significant overestimation of the expected mOS for BV since clinical experts suggested a mOS of no more than 4-5 years after the introduction of checkpoint inhibitors in the 4th line setting. However, for reference, ICERs for this scenario are presented in Table 140 section B.3.8

Figure 45: Modelled OS applying log-normal extrapolation of KEYNOTE-087 to all treatments

Alternative approach 2: Predictive equation of the relationship between PFS and OS from Gopal et al. and application of the equation in both arms of KEYNOTE-204

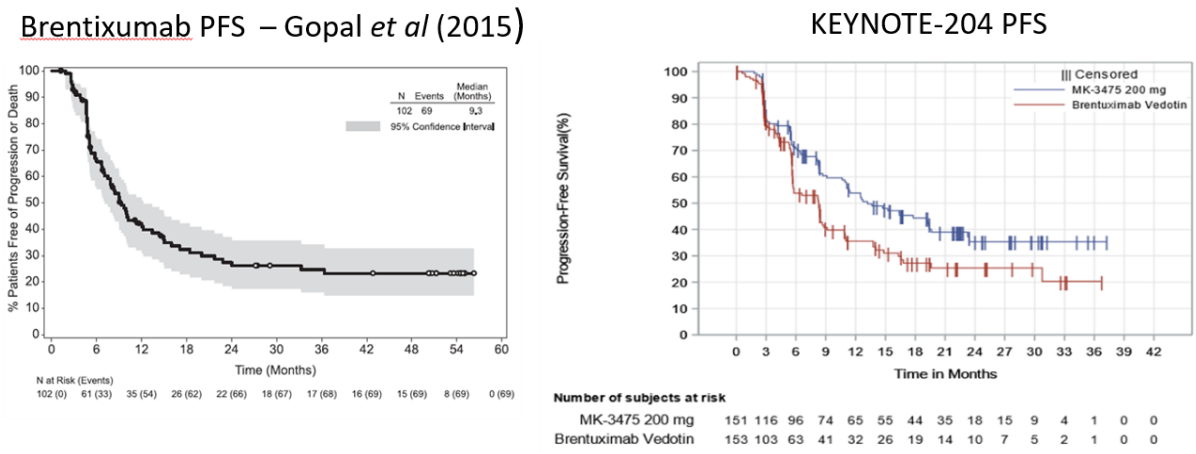
In this approach, the OS for all treatments in KEYNOTE-204 was calculated assuming that the relationship observed between PFS and OS reported in Gopal (2015) [51] will translate to KEYNOTE-204. The underlying assumption is that the PFS is a predictor of OS, independent of treatment. This relationship was captured in terms of the time-dependent ratio of cumulative hazards of OS relative to PFS, or the time-dependent instantaneous hazard ratio of OS relative to PFS. In summary, the OS and PFS data from Gopal et al. was utilized to estimate the cumulative hazard relationship between the two endpoints so that it could be applied to KEYNOTE-204 PFS and generate OS for each of the comparators.

As previously mentioned, patients from Gopal (2015) [51]are a subpopulation of the ITT population of KEYNOTE-204, i.e. Gopal (2015) only included patients who had relapsed or

were refractory to ASCT (SCT+3L+), whereas in KEYNOTE-204, patients who were ineligible to SCT and had received at least one prior salvage therapy were also included.

A comparison of PFS between the Gopal (2015) [51] and KEYNOTE-204 pembrolizumab studies revealed similar efficacy in PFS for BV, with median PFS of 9.3 months and 8.3 months, respectively (**Error! Reference source not found.** and Figure 46). Since there was some overlap in PFS outcomes and that Gopal 2015 had more mature OS data, it was assumed that the PFS and OS relationship from Gopal 2015 could be used as a proxy in the predictive equation approach to generate alternative OS curves for pembrolizumab and BV based on the PFS from KEYNOTE-204. The validation of this assumption is discussed later in this section.

Figure 46. Progression free survival for Gopal 2015 and KEYNOTE-204



Outcome of the predictive equation

Using the method described above, time varying hazard ratios were estimated and applied to the PFS to estimate the OS curves for pembrolizumab and BV for the ITT population (Figure 47).

Figure 47: Predictive equation fitted curves – Gopal 2015 (ITT population)

Validation of the predictive equation

As mentioned before, the approach of modelling OS based on the surrogacy of PFS for OS was explored as an alternative since data from KEYNOTE-204 are not yet available. Also, the availability of mature data from Gopal et al. was a robust source of evidence since the population explored comprised of a subpopulation of KEYNOTE-204. However, the predictive equation relies on a defined methodology that includes the assumption an extension of PFS will lead to an extension of OS. While literature is very sparse on OS and PFS data to validate this assumption in this indication, there is a precedent where NICE have previously accepted this. During TA524, the committee agreed with clinical experts that for patients at increased risk of relapse or progression after ASCT: "it was reasonable to assume that an extension to progression-free survival would lead to some extension in overall survival"[54]. One of clinical experts whom provided expert opinion to MSD, suggested that in the absence of other data PFS may be a good surrogate of OS. However, another clinical expert suggested that a sequence of various treatments and/or ASCT is available for patients after they progress and patients are expected to have better outcomes if they are R/R after ASCT (as per Gopal et al.) than if they never had an ASCT due to age/comorbidities or due to being chemorefractory (additionally included in the KEYNOTE-204 ITT population). Since subpopulation within the KEYNOTE-204 ITT could potentially have different outcomes, it could be considered uncertain to assume the relationship between PFS and OS, that unfortunately is not known in sufficient detail for this indication and is likely to be confounded by post-this indication treatments. Therefore, in order to

provide the committee with an alternative method to derive OS benefit in the cost effectiveness analysis, the predictive equation is explored as a scenario analysis and not as the base case.

In summary, recognising the limitations of the lack of OS data, the approach to model OS was to select the most conservative option in every step of the process. Two reasonable approaches were initially identified; however, the predictive equation would not provide enough face validity and potentially be optimistic for pembrolizumab so the most conservative option of applying OS curves from another trial was preferred. Between KEYNOTE-087 and Gopal et al., the latter was selected as the OS curves for BV would again provide the most pessimistic scenario. Additionally, since the Gopal et al. publication, a variety of subsequent treatments have been introduced in the R/RcHL pathway, like immune checkpoint inhibitors, which have improved survival and therefore, the OS curves from Gopal et are potentially underestimating the total OS gain due to the absence of follow on data. Another indication of the modelled pembrolizumab OS being conservative in the base case is the spike in the modelled PFS curve (Figure 39) as it equals OS after some years. Finally, 1, 2, and 3-year OS data from KEYNOTE-087 suggest the potential for pembrolizumab to have a substantial higher OS than the one assumed equal to the BV arm.

B.3.3.4 Time on Treatment

Time on Treatment is defined as the time between the date of first study drug dose until date of last dose. For the analysis of ToT, data collected in the KEYNOTE-204 clinical study were included until treatment discontinuation or death, or until the date of censoring. Patients in the analysis were censored at the time of visit when study discontinuation occurred, if applicable, or in the case of missing follow-up data, each subject was censored at the date of the last recorded follow-up visit.

As mentioned above a maximum treatment duration of 35 cycles (i.e.105 weeks) was assumed for both pembrolizumab and BV arms as per KEYNOTE-204 protocol. As KM data are available up until week 88, separate parametric curves were fitted to extrapolate the ToT until the maximum duration of treatment. Week 80 was selected as the cut-off point to extrapolate the ToT curves as it had an adequate number of events that occurred post-week 80, while also actual KM data are applied in the model for as much as possible. AIC/BIC based tests combined with visual inspection were used to select the best-fitted parametric distributions. The function with the lowest AIC/BIC was exponential for both arms (see Table 117). The modelled ToT curves for pembrolizumab and BV are presented in Figure 48, Figure 50 .

Table 117. Summary of parametric fitting performances of Time on Treatment for Pembrolizumab and BV, cut off Week 80

Fitted Function	Pembrolizumab		Statistical Rank	BV		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 48. Plot of parametric fitting and extrapolation of long-term ToT for pembrolizumab, cut off Week 80

Figure 49. Plot of parametric fitting and extrapolation of long-term ToT for brentuximab vedotin, cut off Week 80

Figure 50. Plot of parametric fitting and extrapolation of long-term ToT for pembrolizumab and BV with breaking point at Week 80

B.3.3.5 Adverse events

The cost and HRQoL burden related to adverse events is captured in the economic analyses. The AEs included in the economic model are restricted to events experienced while on initial therapy and not events that may result from further treatment. This is because progressive disease was evaluated as an efficacy endpoint of this trial. AEs were followed until 30 days after last dose of study treatment. Serious adverse events (SAEs) were monitored until 90 days after last dose of study treatment[3] AEs are assumed to only be applied in the first cycle of the model, as patients would discontinue initial therapy when experiencing an AE. Incidence of AEs is collected from KEYNOTE-204 population for the treatments of pembrolizumab and BV. The AEs are taken from the all subjects as treated

population grade 3-5, where there was an incidence ≥2% in one or more of the treatment groups of KEYNOTE-204[47]

Table 118: AE incidences rates for subjects with Grade 3-5 Adverse Events (Incidence ≥2% in One or More Group) (All-Subjects-as-Treated Population) from KEYNOTE-204[47]

Adverse event	Pembrolizumab	BV
Acute Kidney Injury	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL was evaluated in KEYNOTE-204 using two measures: EORTC-QLQ-C30 questionnaire (version 3.0) which was used to assess cancer-related quality of life, as well as the generic health status measure, EQ-5D-3L.

Questionnaires were completed at several time points within KEYNOTE 204: pre-dose at Cycle 1 (baseline), Cycle 3 (Week 6), Cycle 5 (Week 12), Cycle 7 (Week 18), and Cycle 9 (Week 24) and every 12 weeks thereafter until PD or up to 1 year while the subject is receiving study treatment. Questionnaires were also collected at discontinuation and at the 30-day Safety Follow-up visit. If discontinuation occurred 30 days from the last dose of study treatment, i.e., at the time of the mandatory 30-day Safety Follow-up visit, PROs do not need to be repeated. The primary analysis approach for the prespecified PRO endpoints was based on a quality of- life-related full analysis set (FAS) population, which consists of all randomized participants who received at least 1 dose of study treatment and had completed at least 1 PRO assessment.

As described in the KEYNOTE-204 Exploratory *Endpoints* section, outcomes for pembrolizumab-treated patients demonstrated improvements using both scales: Longer PFS in the pembrolizumab group was accompanied by an improvement in health related QOL, as compared to BV.

Consistently with NICE reference case, HRQoL data were reported directly from patients using the EQ-5D-3L questionnaire and the utility of the changes in QoL was based on public preferences using a choice-based method. Analysis of baseline score and EQ-5D health utility score by progression free state by IRC assessment are provided using UK algorithm, developed based on the time trade-off (TTO) technique.

When estimating utilities, two approaches were considered:

- Estimation of mean utility values (selected as base case)
- Multivariate model

Estimation of mean utility values

The health state utility values were calculated as mean values for both intervention arms and were stratified by progression status (Table 119).

Table 119 EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) - UK Algorithm (Full Analysis Set Population)

	Pembrolizumab					BV					pooled				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
Progressive	[redacted]														

Multivariate model

The purpose of the multivariate utility analysis is to investigate how UK utility values are associated with patient characteristics at baseline, such as Age, Continuous Age, centralized at 35, Gender, ECOG, Total Lines of Prior Therapies, Prior SCT Status, PDL1 and Post-Treatment SCT Status. It is also of interest to understand how some dynamic parameters were mediated potentially by the antitumor therapy interventions during the trial, such as Treatment, PFS Status Judged by IRC and Grade 3-5 AE, are related to the utility score.

The analysis was carried out by first conducting a linear-mixed effect model using the longitudinally measured UK utility value as the outcome and the individual factors of interest as the single covariate. A linear-mixed effect model was then used with all factors included as covariates. Two age-related parameters were considered represent the age effect in the multivariate models: age group with cut-off at 35 years old and continuous age centralized at 35. Given p-values and the ease of interpretation, continuous age centralized at 35 was chosen as the age parameter in the final multivariate models. Based on the statistical significance and clinical interpretations of the linear-mixed effect model, a final multi-variate linear mixed effect is chosen which includes the factors of continuous age (centralized at 35), Treatment, PFS status and Grade 3-5 AE status.

The covariates for both multi-variate models are presented in Table 120.

Table 120: Multivariate Modelling of UK UTILITY VALUE

Coefficient	Multivariate model	
	Without age	
	Estimate	SE
Intercept	[redacted]	
Treatment (Pembrolizumab=1; BV=0)	[redacted]	
PFS Status (PF=1; PD=0)	[redacted]	
Age offset (Cohort age - 35 years)	[redacted]	

B.3.4.2 Mapping

Consistently with NICE's reference case, utilities were derived from the EQ-5D 3L questionnaire which was collected directly from patients during the KEYNOTE-204 trial. As this is the preferred measure of health-related quality of life in adults by NICE, no mapping was conducted.

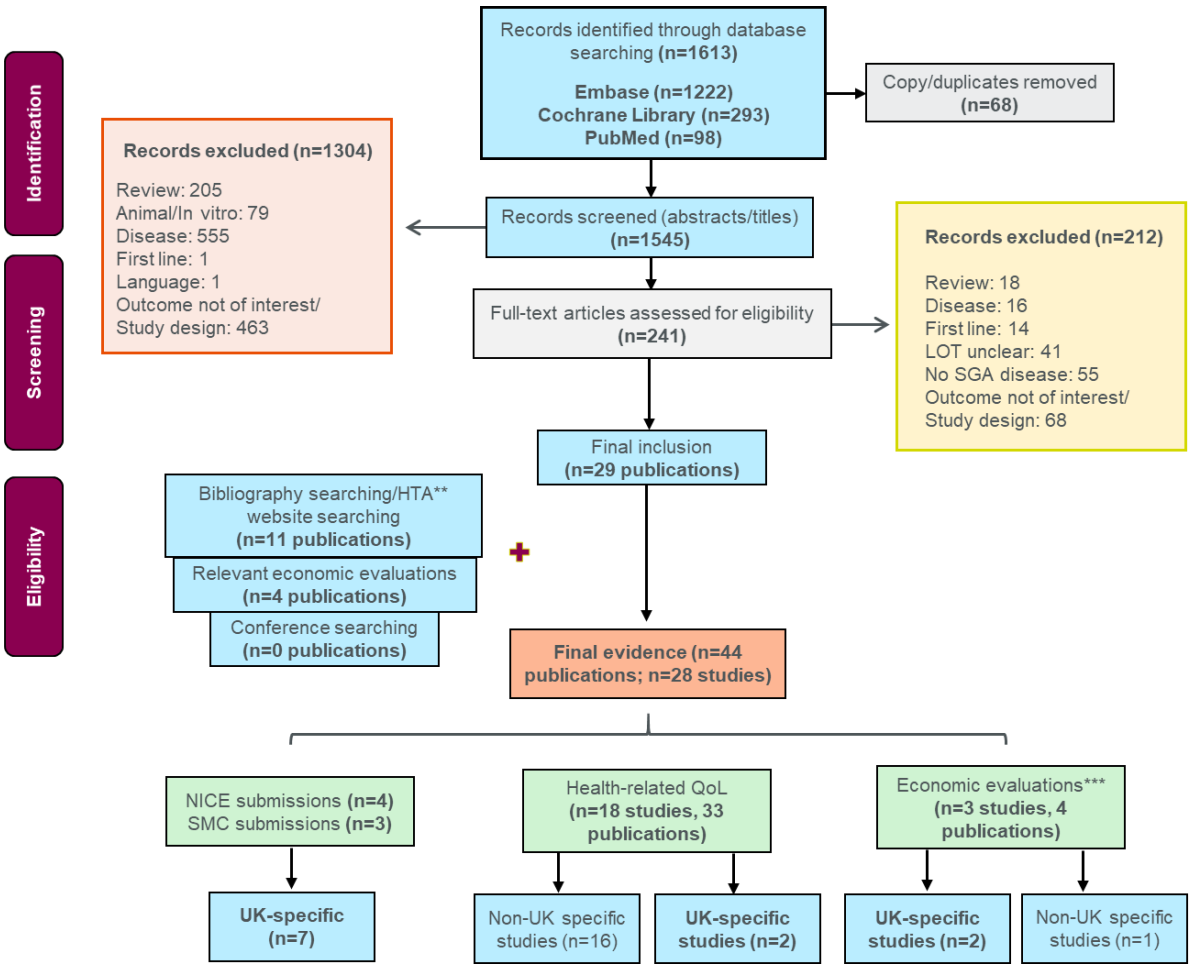
B.3.4.3 Health-related quality-of-life studies

In line with the NICE Guide to the methods of technology appraisal (2013) [44] a SLR was conducted to identify and summarize the health-related quality of life associated with the treatment of patients with R/RcHL using generic and disease-specific instruments associated with R/RcHL.

A comprehensive search strategy was designed to retrieve relevant data from published literature. The last searches were carried out on March 31st, 2020. Searches were limited to studies published from 2001-2020 and were not restricted to the English language. The original review was conducted from January 1st, 2001 to July 15th, 2016, with an update conducted in March 2020. There was no change in the eligibility criteria. Full methodology, inclusion criteria and databases searched are provided in Appendix G while the search strategy and the data extracted from the identified studies are provided in Appendix H.

Figure 51 presents a PRISMA diagram of the flow of studies through the literature review process.

Figure 51 PRISMA flow diagram for QoL studies



HTA: Health technology assessment; LOT: Line of therapy; NICE: National Institute for Health and Care Excellence; SGA: Subgroup analysis; SMC: Scottish Medicines Consortium
**HTA website searching was conducted only for NICE and SMC submissions (in-line with the guidance from NICE evidence submission template)
***The remaining 13 studies identified in Appendix G did not report utility estimates relevant to the NICE UK

The literature searches resulted in the retrieval of 1,613, possibly relevant citations. Following the pre-determined inclusion/exclusion criteria (Appendix G) detailed screening of the abstracts and full texts resulted in the inclusion of 44 citations, 29 identified through electronic database searches, and 11 through hand searching of relevant reviews, included studies, and HTA websites. Three additional citations were also identified from the systematic review of economic evaluations that reported utility estimates relevant to the existing scope (Appendix G).

The review of the published literature in the R/RcHL setting identified 18 studies from which only two were relevant to the UK (Swinburn 2015; Ramsey 2016)[55, 56]. Also, the review of the published economic evaluations (Appendix G) resulted in the identification of three cost-effectiveness studies with utility metrics reported (Parker 2017; Jones 2017; Large 2019)[57-59]: two of these studies were relevant to the healthcare setting in the UK, and one study

conducted from a US perspective was described further because of the appropriateness of the technology evaluated. In addition, the systematic search identified four NICE appraisals of treatments for R/RcHL, i.e., TA462 of nivolumab, TA540 of pembrolizumab, TA524 and TA446 of BV. The full details are provided in Appendix H

Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

The majority of the publications identified report utilities based on the response rates and progression status. Only Large et al. (2019) applied utilities elicited directly from participants in the trial. Out of 4 NICE TAs identified, only in TA462 and TA540, utilities were evaluated using EQ-5D directly from patients in the pivotal trials. Three TAs and two (Parker 2017; Large 2019) of the three cost-effectiveness studies, retrieved the utility estimates from the publication by Swinburn et al. The utility values for the PFS state in literature varies between 0.76 to 0.821 which is not too dissimilar from the utilities reported in KEYNOTE-204. However, most of the studies applied the Swinburn utilities in the progressed state (0.38) and this is considerably lower than the KEYNOTE-204 for both arms. The committee in TA540[60] (FAD) suggested that the PD value from Swinburn is unlikely to be so low in the progression state while the committee in TA462 suggested that the Swinburn utility applied in the SoC arm, is not expected to have such a large difference with the nivolumab arm which applied trial utilities (redacted from company submission but ERG scenario applied utilities from a relevant trial Checkmate-205 of 0.715). Additionally, Swinburn et al. is a vignette study and therefore is not based on the EQ-5D-3L responses as preferred according to the NICE methods guide. Finally, TA446 and TA462 applied treatment specific utility values in the PFS state and due to lack of data, pooled PD utilities based on Swinburn.

B.3.4.4 Adverse reactions

The burden of AEs on the QoL was captured in the model. The health disutility associated with a particular AE was estimated by the health utility decrement from an AE and the time spent in that AE. This is restricted to AEs experienced while on initial therapy and does not include events that may result from further treatment. Given the absence of disutilities from KEYNOTE-204 or in any R/R HL study, disutilities were identified in other oncology studies. Disutility values, for AEs that could not be sourced from the literature, used the adverse event covariate of the multivariate utility model outlined above with a 1-week (a model cycle) duration.

A summary of the AE disutilities, their duration and the sources from which these parameters were extracted is provided in Table 121 below.

Table 121. Adverse event disutilities and durations

	Disutilities	Source	Av. duration (days)	Source
Acute Kidney Injury	-0.075	-	7.00	AE covariate from the multivariate utility model [61]
Anaemia	-0.080	Average of: Beusterien (2010) [62] as used in TA344 and Nafees (2008) [63] as used in TA411	14.78	Avg of "NICE TA306" and "NICE TA476"
Diarrhoea	-0.063	Avg: Beusterien (2010) [62] from TA344 and Nafees (2008) [63] from TA395	5.53	"NICE TA360" [64]
Nausea	-0.075	-	7.00	AE covariate from the multivariate utility model [61]
Neuropathy peripheral	-0.330	Swinburn (2015) [55] from TA446 [65]	76.00	"NICE TA446" [65]
Neutropenia	-0.125	Avg: Tolley (2013) [66] from TA359 and Nafees (2008) from TA411[63]	12.26	Avg of "NICE TA306" [67] and "NICE TA476" [68]
Neutrophil count decreased	-0.125	Assumed equal to Neutropenia	12.26	Assumed equal to Neutropenia
Pneumonia	-0.200	"NICE TA561" [69]	18.19	"NICE TA561" [69]
Pneumonitis	-0.200	Assumed equal to pneumonia	18.19	Assumed equal to pneumonia
Thrombocytopenia	-0.108	Tolley (2013) [66]from TA359	15.94	Avg of "NICE TA306" [67] and "NICE TA476" [68]

Vomiting	-0.075	-	7.00	AE covariate from the multivariate utility model [70]
Weight increased	-0.075	-	7.00	AE covariate from the multivariate utility model [70]

The disutility of each AE was multiplied by the rates of treatment-related AEs as outlined in Table 118. The disutilities were front-loaded as a one-off quality-adjusted life years reduction in the first cycle of the model.

Pembrolizumab has an acceptable, well tolerated and manageable safety profile which is also favourable compared with BV in R/R cHL as demonstrated in KEYNOTE-204. Additionally, it is plausible that the available utilities account for the toxicity of therapies, so that AE associated disutilities may be double counting. Thus, a conservative scenario analysis was conducted where it was assumed that neither pembrolizumab were associated with AEs and they were set to 0.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The health utility of patients is dependent upon their disease state and so consequently, during each cycle, patients are assigned a constant health utility value equivalent to their current disease state. EQ-5D analyses based on KEYNOTE-204 data showed that patients who had progressive disease experienced a lower HRQoL than those in the pre-progression health state.

A study by Ara and Brazier (2010)[71] suggests that average utility decreases with age therefore age-adjusted utilities are applied in the model to account for the impact of age on utilities using the formula provided by Ara and Brazier(Equation 1) [71]. Decrements are calculated based on the age of the cohort in each model cycle and the proportion who are male

Equation 1: Age utility decrements

$$Utility\ decrement = 1 - (0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age\text{^}2)$$

The utility values chosen for the cost-effectiveness model are presented in Table 122.

Table 122. Summary of utility values for cost-effectiveness analysis

	Utilities				Reference in submission (section and page number)	Justification
	Pembrolizumab		BV			
	Mean	SE	Mean	SE		
Health state utilities						
PFS	[redacted]				Section B.3.4.1 page	Based on KEYNOTE-204 data, consistent with NICE Reference case
PD	[redacted]				Section B.3.4.1 page	
Adverse event disutilities						
Acute Kidney Injury	-0.075				Section B.3.4.4 page	Disutilities associated with grade 3+ treatment related AEs from published literature and from the multivariate model
Anaemia	-0.080					
Diarrhoea	-0.063					
Nausea	-0.075					
Neuropathy peripheral	-0.330					
Neutropenia	-0.125					
Neutrophil count decreased	-0.125					
Pneumonia	-0.200					
Pneumonitis	-0.200					
Thrombocytopenia	-0.108					
Vomiting	-0.075					
Weight increased	-0.075					

It should be noted that both in the pre- and post-progression state, treatment-specific utilities were applied as pembrolizumab is expected to provide improved quality of life compared to BV due to its mechanism of action. As described in the FAD TA462, for nivolumab [72], which has a similar mode of action, clinical experts suggested that pre-progression quality of life was likely to be better with the IO than with existing treatments because of its potential to improve quality of life. Additionally, for the post progression utilities the committee considered that utilities between the two arms had a very large differential which was not considered plausible. While the post progression utilities of TA462 were redacted from the publicly available FAD, post-progression utilities for the SoC was 0.38 which is considerably lower than 0.693 that was reported in KEYNOTE-204

Thus, the quality of life data derived from patients during KEYNOTE-204 was applied in the model as they better reflect the expected benefits of pembrolizumab and BV in the post-progression phase, even following cessation of therapy. This includes the potential for immune system stimulation following progression and continued B-symptom control.

Despite the expectation of improved health state utilities for pembrolizumab vs BV, scenario analyses have been undertaken to evaluate the impact of alternative utility assumptions in the post-progression state where pooled utilities for both arms from KEYNOTE-204 were assumed for both arms.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Parameters used in the cost effectiveness analysis

The full list of variables used in the cost effectiveness analysis is presented in Appendix M

B.3.5.2 Input from clinical experts

Resource use and costs used in the cost effectiveness model were mainly sourced from previous submissions and/or literature while some of the values, regarding the resource use were validated with two consultant haematologists. More information is provided in each of the sections.

B.3.5.3 Resource identification, measurement and valuation studies

As discussed in Section B.3.1, an SLR was conducted to identify and summarize costs, and healthcare resource requirement of patients with R/RcHL. A description of the methodology and the search strategy is provided in Appendix G while the identification of the cost and resource use studies, their overview and the data extracted are provided in Appendix I.

B.3.5.4 Intervention and comparators' costs and resource use

Acquisition costs

Pembrolizumab

Pembrolizumab is supplied as 100mg vials and the cost effectiveness model assumes a fixed dose of 200mg every 3 weeks (Q3W). This is aligned with the licensed dose of pembrolizumab as well as the dosing in KEYNOTE-204. The list price of a 100mg vial is £2,630.00[73]. Therefore, the drug acquisition cost for pembrolizumab per cycle is £5,260 based on two 100mg vials using the list price. [redacted]. In order to reflect the true economic impact of a positive recommendation for this indication, the base case results as well as all scenario analyses have the above PAS discount [redacted] applied.

Additionally, pembrolizumab monotherapy is also licensed at a fixed dose of 400mg every 6weeks (Q6W)[1]. A scenario analysis with the alternative dosing implemented in the model is presented in section B.3.8. Currently a simple discount patient access scheme (PAS) is operational for all pembrolizumab indications approved through baseline commissioning.

The providers will purchase pembrolizumab from MSD and MSD will supply the same at its confidential

Therefore, the NHS net discount price for all indications; will be at a [redacted] discount on MSD's list price, plus VAT where applicable. Therefore, the 200mg administration of pembrolizumab will cost [redacted]

Treatment duration

As per the proposed licence and KEYNOTE-204 protocol, patients treated with pembrolizumab are to be treated until disease progression is confirmed or unacceptable toxicities occur. To estimate the duration of treatment in the pembrolizumab, ToT data from the KEYNOTE-204 was used, to reflect both early discontinuation caused by AEs and other reasons for discontinuations before progression in addition to the additional weeks of treatment that some patients may receive until confirmation of progression. See section B.3.3 for further details regarding the use of ToT data in the model. There is no evidence regarding the optimal duration of treatment with pembrolizumab; however, the KEYNOTE-204 protocol[74] mandated a maximum of 35 cycles of pembrolizumab (2 years) therefore a cap of 35 cycles (105 weeks) was applied in the model. Finally, for patients on treatment, adjustments were made based on the actual proportion of a full treatment dose that, on average, patients receive within each 3-week treatment cycle in KEYNOTE-204. For this, data regarding dose intensity (98%) occurring within KEYNOTE-204 was implemented in the model to account for these delayed doses and 'holidays' due to AEs

Brentuximab Vedotin

BV is supplied as 50mg vials and the list price of a 100mg vial is £2,500.00[75] BV is administered in a dose of 1.8mg/kg IV every 3 weeks (21 days) in line with NICE TA524[22]. Consistently with TA446, vial wastage is considered in the base case so the cost per cycle for each treatment is a sum product of the number of vials used and respective vial price, therefore the cost of BV per patient per cycle is £7,365. The DoH has agreed a patient access scheme with the manufacturer of BV. Since this is commercial in confidence the model assumed BV list price.

Treatment duration

As per the licence[50] and KEYNOTE-204 protocol[74], patients treated with BV are to be treated until disease progression is confirmed or unacceptable toxicities occur. Consistent with the pembrolizumab arm, in order to estimate the duration of treatment in the BV arm, ToT data from the KEYNOTE-204 was used, to reflect both early discontinuation caused by AEs and other reasons for discontinuations before progression in addition to the additional weeks of treatment that some patients may receive until confirmation of progression. See section B.3.3 for further details regarding the use of TOT data in the model. A cap of 35 cycles (105 weeks) was applied in the model consistently with the KEYNOTE-204 protocol. As discussed in section B.3.2, BV licensed dosing is up to a maximum of 16 cycles[50]. A maximum doses of 35 doses was assumed in the base case for BV to reflect its efficacy from KEYNOTE-204, however a scenario analysis is presented in Table 140 (section B.3.8) where maximum dose of BV is set to 16 cycles as per its license. It should also be noted that in the FAD for TA524[54], the committee accepted the manufacturer's and ERG's mean number of BV cycles which was 8.5 cycles. This is very close to the mean modelled ToT of BV arm in the KEYNOTE -204 (approximately 8.6 cycles)

Finally, consistent with the pembrolizumab arm, the dose intensity occurring within KEYNOTE-204 (98%) was implemented in the BV arm.

Table 123 summarises the modelled drug acquisition costs of pembrolizumab and BV per cycle.

Table 123. Pembrolizumab and BV dosage, administration, treatment duration, vial size and costs – list price

Treatment	Dosage (mg)	Dosage unit	Admins per cycle	Cycle length (days)	Max cycles	Vial size (mg)	Vial (1) price, £/vial	Vials used	Cost (£) per cycle	Dose intensity	Cost (£) per cycle in base case
Pembrolizumab	200	mg	1	21	35	100	2,630	2.00	5,260	0.982	£5,165
BV	1.8	mg/kg	1	21	35	50	2,500	3.00	6,989	0.982	£6,863

Administration costs

Pembrolizumab

Pembrolizumab is administered Q3W as an intravenous infusion over 30 minutes[1].

Therefore, as per the National Tarif of Chemotherapy regimens list[76], the following HRG

code was applied in every cycle of pembrolizumab: SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance. Based on the NHS reference costs 2018-2019[77], the administration cost of SB12Z at an outpatient setting for every cycle is £183.54[77].

Brentuximab Vedotin

BV is administered as an intravenous infusion over 30 minutes every 3 weeks[50] same as pembrolizumab therefore, as per the National Tarif of Chemotherapy regimens list[76] the same HRG code (SB12Z) and NHS reference cost[77] was applied.

Table 124 summarises the use and cost, per drug administration

Table 124: Resource use and cost per drug administration

Treatment regimen	Administration costs (£)			
	HRG code	Source	Cost per administration	Source
Pembrolizumab 200mg[a]	1 x SB12Z	National Tarif of Chemoregimens List 2017/18	£183.54	NHS Reference costs 2018-2019[77]
BV[a]	1 x SB12Z	National Tarif of Chemoregimens List 2017/18	£183.54	NHS Reference costs 2018-2019[77]

Subsequent treatment costs

The model includes costs of subsequent treatment lines after treatment discontinuation or failure on the primary intervention. The costs of subsequent treatment are applied to patients in the PD health state. Subsequent treatment costs do not apply in the first cycle of the model as all patients are assumed to start in the PF health state. For the base case the ten most commonly utilized subsequent treatments from the KEYNOTE-204 trial were chosen and the proportions re-weighted to represent subsequent therapies in the treatment specific usage percentages as presented in Table 127. In clinical practice, not all patients receive subsequent treatment. The model accounted for these patients based on KEYONTE-204 estimates – referred as “none” in Table 127

The costs of subsequent treatments are presented in Table 125 and are mainly sourced from the DoH’s drugs and pharmaceutical electronic Market Information Tool (eMIT)[78]; apart from Bendamustine. Pembrolizumab, BV and Nivolumab which are sourced from the British

National Formulary (BNF)[79]. Dosing is sourced from the license of the product or from protocols identified.

The subsequent treatment administration costs are based on the National Tariff of Chemotherapy regimens list and NHS Reference costs. Table 127 details the subsequent treatment durations and usage following progression, both of which were taken from the KEYNOTE-204 trial[47].

Table 125: Subsequent treatment costs list price

Treatment mix	Individual treatment	Dosage (mg)	Dosage unit	Admins per cycle	Cycle length (days)	Vial size (mg)	Vial (1) price, £/vial	Vials used	Cost (£) per cycle
BV*	-	2	mg/kg	1	21	50	2,500	3.00	7,500
Nivolumab*	-	3	mg/kg	1	14	100	1,097	3.00	3,291
Pembrolizumab*	-	200	mg	1	21	100	2,630	2.00	5,260
Bendamustine*	-	120	mg/m²	2	28	25	2.91	9.00	58
Bendamustine* + BV	Bendamustine*	120	mg/m²	2	21	25	2.91	9.00	58
	BV	2	mg/kg	1	21	50	2,500	3.00	7,500
Etoposide + melphalan	Etoposide	200	mg/m²	3	28	100	65	4.00	35
	Melphalan	140	mg/m²	1	7	50	140	6.00	824
Cyclophosphamide + fludarabine phosphate	Cyclophosphamide	250	mg/m²	3	28	500	9.20	1	28
	Fludarabine phosphate	25	mg/m²	3	28	50	155.	1	465
Bendamustine* + gemcitabine + vinorelbine tartrate	Bendamustine*	90	mg/m²	2	21	25	2.91	7.00	41
	Gemcitabine	800	mg/m²	4	21	200	3.28	8.00	105
	Vinorelbine Tartrate	20	mg/m²	1	21	10	29.00	4.00	116
Cisplatin + cytarabine + dexamethasone	Cisplatin	100	mg/m²	1	21	10	1.99	19.00	38
	Cytarabine	2,000	mg/m²	1	21	100	3.50	38.00	133
	Dexamethasone	40	mg	4	21	1	0.07	80.00	22

Carmustine + cytarabine + etoposide + melphalan	Carmustine	300	mg/m²	1	7	100	1,000	6.00	6,000
	Cytarabine	200	mg/m²	4	21	100	3.50	6.00	56
	Etoposide	200	mg/m²	4	28	100	2.88	4.00	46
	Melphalan	140	mg/m²	1	7	50	137.37	4.00	824

Table 126: Subsequent treatment resource use per administration

Treatment	Resource use per administration	Assumption	Cost per administration (£)
BV	1 x SB12Z (£183.54)	intravenous infusion over 30 minutes, outpatient	183.5
Nivolumab	1 x SB12Z (£183.54)	intravenous administration over 30 minutes, outpatient	183.5
Pembrolizumab	1 x SB12Z (£183.54)	intravenous infusion over 30 minutes, outpatient	183.5
Bendamustine	1 x SB13Z ((£314.36)	intravenous infusion over 30 - 60 minutes, outpatient	314.4
Bendamustine + BV	1 x SB12Z (£183.54) 2 x SB15Z (£223.00)	Day 1: BV intravenous infusion over 30 minutes, outpatient Day 2: Bendamustine intravenous infusion over 30 - 60 minutes, outpatient Day 3: Bendamustine intravenous infusion over 30 - 60 minutes, outpatient	629.5
Etoposide + melphalan	1 x SB14Z (£317.73) 4 x SB15Z (£223.00)	Assumed as per the components of the BEAM regimen below Days 1-4: Etoposide IV infusion over 120 minutes Day 5: Melphalan IV infusion over 30 minutes	1,209.7
Cyclophosphamide + fludarabine phosphate[80]	1 x SB12Z (£183.54) 2 x SB15Z (£223.00)	Day 1: Cyclophosphamide Intravenous bolus over 10 minutes, Fludarabine intravenous infusion over 30 minutes, outpatient Day 2: Cyclophosphamide Intravenous bolus over 10 minutes, Fludarabine intravenous infusion over 30 minutes, outpatient Day 3: Cyclophosphamide Intravenous bolus over 10 minutes, Fludarabine intravenous infusion over 30 minutes, outpatient	629.5
Bendamustine + gemcitabine + vinorelbine tartrate[81]	1 x SB14Z (£317.73) 3 x SB15Z (£223.00)	Day 1: Gemcitabine intravenous infusion over 30 minutes, outpatient: vinorelbine Intravenous bolus over 10 minutes Day 2: Bendamustine intravenous infusion over 30 - 60 minutes, outpatient Day 3: Bendamustine intravenous infusion over 30 - 60 minutes, outpatient Day 4: Gemcitabine intravenous infusion over 30 minutes, outpatient	986.7

Cisplatin + cytarabine + dexamethasone[82]	1 x SB14Z (£317.73) 3 x SB15Z (£223.00)	Day 1-4: Dexamethasone IV, cisplatin IV infusion over 2 hours, outpatient Day 2: Cytarabine IV infusion over 3 hours, outpatient Reference:	986.7
Carmustine + cytarabine + etoposide + melphalan (BEAM)[83]	1 x SB14Z (£385.28) 5 x SB15Z (£223.00)	Day 1: Carmustin Intravenous infusion over 60 minutes Days 2,3,4,5: Cytarabine IV infusion over 60 minutes and Etoposide IV infusion over 120 minutes Day 6: Melphalan IV infusion over 30 minutes Assumed day case	1,432.7

Source: [84] *SB12Z (Chemo, OP) Deliver Simple Parenteral Chemotherapy at First Attendance = £183.54;* SB14Z: Outpatient Deliver complex chemotherapy, including prolonged infusion treatment at first attendance = £317.73; SB15Z (Chemo, OP): Deliver Subsequent Elements of a Chemotherapy Cycle = £223.00

Table 127: Subsequent treatment durations and usage[47]

Treatment	No. of days of treatment (ITT mean)	Average cycle length of regimen (in days)	Duration of subsequent treatment (in weeks)	% usage following progression	
				Pembrolizumab*	BV*
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine + BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide + melphalan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide + fludarabine phosphate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine + gemcitabine + vinorelbine tartrate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin + cytarabine + dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carmustine + cytarabine + etoposide + melphalan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clinical expert opinion elicited suggested that clinical practice in the UK is expected to be different and aligned with the treatment pathway presented in Figure 2.

For the BV arm;

- patients on salvage chemotherapy (SCT-2L) will receive BV following progression
- patients on BV ineligible for transplant (SCT-3L+) will receive pembrolizumab and

- patients on BV who were r/r after ASCT (SCT+3L) will receive nivolumab.

The split of the uptake in the ITT population for the scenario analysis was assumed as per the patients in each subpopulation in KEYNOTE-204 (SCT-2L:18%, SCT-3L:45% and SCT+3L:36%) and also it was assumed that all of the patients who progress will receive subsequent treatment

After the introduction of pembrolizumab, it was suggested by clinical expert opinion that all patients from the 3 subgroups will receive BV.

Table 128. Subsequent treatment mix as suggested by clinical expert opinion

Treatment	% usage following progression	
	Pembrolizumab*	BV*
BV	100%	18%
Nivolumab		45%
Pembrolizumab		37%

A scenario analysis with the % of usage of subsequent therapies as per UK clinical practice is presented in Table 140 section B.3.8. Also, as per the recommendation by NICE, since pembrolizumab is in the CDF for patients ineligible for ASCT post-BV treatment, an additional scenario was investigated assuming KEYNOTE-204 subsequent therapies uptake but excluding pembrolizumab from the subsequent therapies (assuming all patients will receive a subsequent treatment).

Table 129. Unit costs associated with the technology in the economic model

Items	Pembrolizumab	Reference in submission	BV	Reference in submission
Technology cost	£5,165 per cycle [redacted]	Section B.3.5	7,365 per cycle (including dose intensity 0.98)	Section B.3.5
Mean cost of technology treatment	£93,180 [redacted]	Section B.3.5	£67,880 (based on ToT from KEYNOTE-204)	Section B.3.5
Administration cost	£3,311 (based on £184 per cycle for duration equal to ToT from KEYNOTE-204)	Section B.3.5	1,692 per cycle (based on £184 per cycle for duration equal to ToT from KEYNOTE-204)	Section B.3.5
Subsequent Treatment cost	£8,344 [redacted]	Section B.3.5	£16,502	Section B.3.5
Total	£104,835 [redacted]		£28,691	

B.3.5.5 Health-state unit costs and resource use

Health state costs are applied to each weekly cycle in the model for the proportion of patients in the PF and PD health states. These costs comprise the costs of providing routine follow-up care and monitoring of patients with R/RcHL. The total cost per week is a sum product of the individual resource unit costs and weekly resource usages, which is applied in each cycle of the model throughout the entire time horizon. No disease management costs accrue in the first cycle for the PD state, as all patients being in the PF state at the start of the time horizon.

The published data exploring in detail the resource use associated with patients with previously treated R/RcHL is limited. Consequently, the main source of resource utilisation used in this submission comes mainly from published NICE TAs.

Resource usage was derived from a previous submission (TA446)[52], where clinical expert opinion was elicited to obtain disease management resource usage for R/RcHL. The unit cost sourced from NHS Schedule of Reference Costs 2018-2019 and annual resource usage ascribed to the PF and PD health states are presented in Table 130 and Table 131, respectively.

Table 130: Progression-free state costs and resource use

Resource	Unit cost (£)	Unit cost source (NHS reference costs 2018-2019 code) [77]	Weekly usage	Cost per cycle	Resource use source
Outpatient attendance	173.39	303: Clinical Haematology, Consultant led follow-up attendance, non-admitted face to face	0.20	34.56	NICE TA446 Committee papers, ERG Table 95 (p210) [52]
Blood count	2.79	DAPS05: Haematology	0.20	0.56	
Biochemistry	1.10	DAPS04: Clinical Biochemistry	0.20	0.22	
CT scan	115.56	RD26Z: Computerised Tomography Scan, three areas with contrast	0.06	6.64	
PET scan	775.51	RN03A: Positron Emission Tomography with computed Tomography (PETCT) of more than three areas, 19 years and over	0.03	22.29	
Total cost per week (£)				64.27	

Source: [65], [84]

Abbreviations: BNF: British National Formulary; CT: Computerized tomography; PETCT: Positron Emission Tomography with computed Tomography; NG: NICE guideline; NHS, National Health Service; NICE: National institute for Health and Care Excellence; eMIT: Drugs and pharmaceutical electronic market information; TA: Technology appraisal

Table 131: Progressed disease state costs and resource use

Resource	Unit cost (£)	Unit cost source (NHS reference costs 2018-2019 [84] code)	Weekly usage	Cost per cycle	Resource use source
Outpatient attendance	173.39	303: Clinical Haematology, Consultant led follow-up attendance, non-admitted face to face	0.20	34.56	NICE TA446: Committee papers, ERG Table 95 (p210)[52]
Blood count	2.79	DAPS05: Haematology	0.20	0.56	
Biochemistry	1.10	DAPS04: Clinical Biochemistry	0.20	0.22	
CT scan	115.56	RD26Z: Computerised Tomography Scan, three areas with contrast	0.06	6.64	
PET scan	775.51	RN03A: Positron Emission Tomography with computed Tomography (PETCT) of more than three areas, 19 years and over	0.03	22.29	
Total cost per week (£)				64.27	-

A scenario analysis with alternative resource use was conducted because clinical expert opinion elicited by MSD suggested that patients who progress are expected to have additional resource use compared to those who do not progress. Also, they suggested a different resource usage in the PFS state. So, according to this, patients in remission after prior treatment (PFS state) would typically be seen every 3 months in outpatient visits with blood tests at the time. Patients might have 1 scan per year. Post progression, they would be seen once every 3 weeks with blood tests each time. Scan every 2-3 months until in remission again. Therefore, this scenario analysis is presented in section B.3.8, assumed the following resource use:

Table 132. Alternative resource use of disease management based on UK clinical expert opinion, examined in scenario analysis,

	PFS state	PD state
	Weekly usage	Weekly usage
Outpatient attendance	0.08	0.32
Blood count	0.08	0.32
Biochemistry	0.08	0.32
CT scan	0.02	0.07
PET scan	0.02	0.07

Terminal care costs

. As data for the cost and resource use of R/RcHL patients in terminal care is limited; the cost of terminal care is based on Brown et al.(2013)[85] which is from locally advanced or metastatic non-small cell lung cancer patients. The cost of terminal care includes hospitalization and palliative care given to patients in the months or weeks leading up to death These costs are calculated based on a weighted mean of the unit costs corresponding to care given in a hospital, hospice, or home setting (resource location as in Table 133). The weights correspond to the proportion who receives terminal care in each setting derived from a previous submission TA531 [86] which used terminal care resource use from the systematic review conducted by Brown et al. (2013)[85].

The resource unit costs are sourced from NHS Schedule of Reference Costs 2018-2019[77] and the PSSRU 2019[87]. The cost of drugs and equipment for home care was taken from Brown et al. (2013)[85]and inflated to 2018/19 prices using the NHS cost inflation index (PSSRU, 2019)[87]

The total cost of terminal care (£4,462) is applied as a one-off cost to each death event in the model. The terminal care costs included in the analysis are presented in Table 133.

Table* 133*: Terminal care costs

Terminal care type	Resource type	Resource location per patient*	Unit cost (£)	Usage*	Total cost	Source / Assumption
Hospital		56%	4,685	1 episode (9.66 days)	4,139	"NHS reference costs 2018-19": Non-Elective Long Stay and Non-Elective Excess Bed Days, Weighted sum of HRG code DZ17L, DZ19P and DZ17T[77]
Hospice		17%	4,139	1 episode (9.66 days)	5,174	Assumed 25% increase on hospital inpatient care
Home	Community nurse	27.0%	£1,797.22	28 hours	4,685	"PSSRU 2019": Modern matron community, nurse consultant (Band 8a)[87]
	GP home visit		£476.00	7 visits		"NHS reference costs 2018-19: Non-Admitted Face-to-Face Attendance, First (WF01B)[77]
	Macmillan Nurse		£2,140.61	50 hours		Assumed to be 66.7% of community nurse cost
	Drugs and equipment		£270.94	1 (average drug and equipment usage assumption)		The value used in Brown et al' s study (2013, Marie Curie report figure of £240 increased for inflation) was inflated to 2014/15 using the PSSRU HCHS index and then to 2018/19 using PSSRU NHSCII[85]
Terminal care cost (£) per patient					4,462	

B.3.5.6 Adverse reaction unit costs and resource use

Adverse event costs (AE) ascribed in only the first cycle of the model by applying the weekly incidence of these AEs, multiplied by the respective costs, to the time on treatment curve in each treatment arm.

The analysis uses subgroup specific AEs of grade 3-5 severity with an incidence ≥2% in any treatment arm of the KEYNOTE-204[47]. The costs of managing most AEs are derived from the NHS Reference costs 2018-2019[77], with previous NICE submissions used as a guide for the appropriate HRG codes. The cost of nausea, vomiting and weight increase are sourced from the Nivolumab NICE submission[23]The costs of treating each AE and the associated HRG code and descriptions are provided in Table 134.

Table 134: Adverse event costs

AE	AE Details		Cost (£)	Source
	HRG code	Description		
Acute Kidney Injury	LA07K	Acute Kidney Injury with Interventions, with CC Score 0-5 (LA07K) non elective short stay	987	" NHS reference costs 2018-2019"[77]:
Anaemia	SA03G-H, SA04G-L, SA05G-J, SA08G-J	Haemolytic Anaemia with CC Score 0-3+; Iron Deficiency Anaemia with CC Score 0-14+; Megaloblastic Anaemia with CC Score 0-8+; Other Haematological or Splenic Disorders, with CC Score 0-6+	722	"NICE TA540": Committee papers, CS Table 99 (p216). "NHS reference costs 2018-19": weighted average of codes SA03G-H, SA04G-L, SA05G-J, SA08G-J[77, 88]
Diarrhoea	FZ49D-E, FZ49F-H, FZ49F-H, FZ91A-D, FZ91E-H, FZ91J-M	Nutritional Disorders with Interventions, with CC Score 0-2+; Nutritional Disorders without Interventions, with CC Score 0-6+; Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with CC Score 0-8+; Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 0-9+; Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-11+	1,401	"NICE TA540": Committee papers, CS Table 99 (p216). "NHS reference costs 2018-19": weighted average of codes FZ49D-E, FZ49F-H, FZ49F-H, FZ91A-D, FZ91E-H, FZ91J-M[77, 88]
Nausea	NA	Cost sourced from literature	591	"NICE TA462": Committee papers, CS Table 60 (p134).[23]
Neuropathy peripheral	WF01A-B "PSSRU 2019": physiotherapist 10 sessions;	Neurology 400 (CL) first attendance and follow up	734	"NICE TA446": Committee papers, ERG Table 98. "NHS reference costs 2018-19": WF01A and WF01B; "PSSRU 2019": physiotherapist 10 sessions; "BNF 2020": Gabapentin regimen: 3000mg/day for 42 days[52, 77]

	"BNF 2020": Gabapentin regimen: 3000mg/day for 42 days			
Neutropenia	SA08G-J	Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over	1,033	"NICE TA540": Committee papers, CS Table 99 (p216). "NHS reference costs 2018-19": weighted average of codes SA08G-J[77, 88]
Neutrophil count decreased	-	-	1,033	Assumption: equal to Neutropenia
Pneumonia	DZ11K-V	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 0-14+; Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-13+; Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-14+	494	"NHS reference costs 2019-2019": Weighted average of DZ11K-V. Lobar, Atypical or Viral Pneumonia, with single, multiple and without Interventions, with CC Score 0-14+[77]
Pneumonitis	-	-	494	Assumption: equal to Pneumonia
Thrombocytopenia	SA12G-K	Thrombocytopenia with CC Score 0-8+	674	"NICE TA540": Committee papers, CS Table 99 (p216). "NHS reference costs 2018-19": weighted average of codes SA12G-K[77, 88]
Vomiting		Cost sourced from literature	591	"NICE TA462"Committee papers, CS Table 60 (p134).[23]
Weight increased		Cost sourced from literature	591	Assumption: equal to vomiting

1 Source: [84], [87]

B.3.5.7 Miscellaneous unit costs and resource use

Stem cell transplant (SCT) costs

The percentage of patients receiving stem cell transplant (SCT) therapy was obtained from the KEYNOTE-204 trial for the ITT population[89] As discussed in section B.3.2.2, due to the paucity of data and the design of the trial, SCT was modelled as an input to the model (rather than a health state) and reflected an unquantified additional benefit.

The costs associated with auto SCT and allo-SCT are sourced from Radford et al. (2017) [90]which was identified in the economic SLR but was also preferred by the NICE committee in previous TAs[23, 88]. Radford was a retrospective analysis that studied the cost and resource use in 40 cHL patients who had failed after auto-SCT and reported costs on 15 (37.5%) patients who received chemotherapy followed by allo-SCT or a second ASCT. Due to the paucity of data it was assumed that the cost for the first and second auto-SCT would be the same. Radford and colleagues estimated that the cost of allo-SCT was £110,374 and the cost of auto-SCT was £21,612. Both costs have been inflated to 2018/19 using the NHSCII pay and prices index (PSSRU). The costs and resource use associated with SCT are presented in Table 135.

Table 135: SCT costs and resource use

Treatment	% Patients receiving Auto SCT	% Patients receiving Allo SCT	Source
	ITT population (Base case)		
Pembrolizumab	[redacted]	[redacted]	KN204 HTA PEM TTST-TTSCT report: Table 7 (Allo) and Table 8 (Auto)[89]
BV	[redacted]	[redacted]	
SCT Type	**Unit cost (£)**	**Source**	
Auto SCT	£22,368	"NICE TA540": Committee papers; based on Radford et al. (2017)[90] Inflated to 2018/19 prices using the NHSCII pay and prices index (PSSRU)[87]	
Allo SCT	£114,234		

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

The complete list of the data inputs included in the model is provided in Appendix M.

The base-case cost-effectiveness analysis reflects the NICE reference case as closely as possible

B.3.6.2 Assumptions

Assumption	Rationale
A key assumption of the base case is the equal OS efficacy of BV and pembrolizumab arm.	As discussed in section B.3.3, in the absence of OS data from KEYNOTE-087, this is approach was selected as the most conservative way to model pembrolizumab OS and demonstrate the potential for cost-effectiveness in order to enable access to patients until comparative OS data from KEYNOTE-204 become available.
Patients from Gopal et al. are assumed to have equal OS with patients in KEYNOTE-204	This assumption was made in the absence of evidence specific to the KEYNOTE-204 population. The population in Gopal et al. consists of a subpopulation from KEYNOTE-204 (SCT+3L+) and reported mature OS data therefore it was deemed as an appropriate proxy.
Baseline patient characteristics parameters are derived from KEYNOTE-204, which is assumed to be reflective of patients seen in UK clinical practice.	Sensitivity analyses (probabilistic and deterministic) have been conducted to assess the impact of variability in these parameters. Clinical experts confirmed that baseline characteristics of patients in KEYNOTE-204 is broadly reflective of patients they see in clinical practice.
BV stopping rule was applied as per the KEYNOTE-204 trial at 35 cycles.	To reflect the trial efficacy of KEYNOTE-204 as only 17/152 patients received BV for more than 12 months. A scenario analysis was conducted were the maximum number of cycles of BV was 16 as per its license.
Once patients progress, they receive subsequent therapies as experienced by patients in KEYNOTE-204.	Alternative mix and uptake was assumed based on clinical input for the clinical practice in the UK (Table 128.) An additional scenario was run to exclude pembrolizumab from the KEYNOTE-204 proportions since pembrolizumab is currently in the CDF
The efficacy of SCT was incorporated in the model as part of the true trial efficacy, assuming that pembrolizumab and BV were not used as a bridge to transplant	Only a small proportion of patients received transplant pre-progression in KEYNOTE-204 and the time to transplant was close to 2 years for both arms. Therefore, neither of the treatments included in KEYNOTE-204 were used as a bridge to transplant. (see section B.3.2.2)
AE costs are applied as a one-off cost in the first cycle of the model	Grade 3+ adverse events can potentially lead to treatment discontinuation meaning patients remaining on treatment beyond the first year will

	be likely to be tolerating treatment well and not experiencing severe adverse events
The model assumed vial wastage (i.e. the vials will be not shared among patients)	Drug wastage was assumed because vial sharing would be unlikely due to the small number of patients with r/r cHL, also since the total storage time of the solution from reconstitution to infusion should not exceed 24 hours
Terminal care costs from patients with locally advanced or metastatic non-small cell lung cancer (as reported by Brown et al.) are assumed to apply to R/RcHL patients	There is a paucity of data for terminal care costs in R/RcHL and the publication from Brown et al. provides a comprehensive estimation. It should be noted that since the terminal care costs are applied to both arms, there is no impact in the results.

B.3.7 Base-case results

The results of the economic model are presented below. In the base case analysis, the estimated LYS were 4.98 for both arms since OS was assumed equal. Patients treated with pembrolizumab accrued 4.11 QALYs compared to 3.52 QALYs for BV. Since the OS was assumed the same, the gain in QALYs for the pembrolizumab arm is stemming from the difference in utilities and PFS gains.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 136 below presents the base case incremental cost-effectiveness results for pembrolizumab incorporating the baseline PAS discount. The results show pembrolizumab to be cost-effective compared to BV as patients accrue more QALYs and it is less expensive i.e. pembrolizumab is dominant over BV.

Table 136. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs(pembro vs)	ICER incremental (£/QALY)(pembro vs.)
Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
BV	[redacted]	4.98	3.52	-24,981	0.00	0.59	Dominant

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The objective of the probabilistic sensitivity analysis (PSA) is to assess the variation in model results stemming from the uncertainty in key individual parameters used in the model. To conduct the PSA, probabilistic distributions were assigned to key parameters in the model that may be subject to variation or uncertainty. These distributions were then used to randomly sample new plausible values for parameters. The model was run with the sampled parameters and the result of the model under each new set of parameters was recorded. This process was then repeated for 1000 iterations. The PSA results were represented graphically on a scatter plot, and a cost-effectiveness plane, showing the results of each iteration in terms of total costs and QALY differentials between two treatment strategies.

The probabilistic distribution applied to each category of parameters is described in Table 137

Table 137: PSA parameter distributions

Parameter	Distribution used in the PSA	
Patient characteristics		
Female (%)	Beta	Ranges between 0 and 1
Weight (kg) - average	Log-normal	Skewed and positive data
Body surface area (m²)	Log-normal	Skewed and positive data
Clinical		
Pembrolizumab progression-free survival - Coef. 1	Multivariate normal	To capture correlation between coefficients
Pembrolizumab progression-free survival - Coef. 2	Multivariate normal	To capture correlation between coefficients
Pembrolizumab progression-free survival - Coef. 3	Multivariate normal	To capture correlation between coefficients
BV progression-free survival - Coef. 1	Multivariate normal	To capture correlation between coefficients
BV progression-free survival - Coef. 2	Multivariate normal	To capture correlation between coefficients
BV progression-free survival - Coef. 3	Multivariate normal	To capture correlation between coefficients
Gopal (2015) overall survival - Coef. 1	Multivariate normal	To capture correlation between coefficients
Gopal (2015) overall survival - Coef. 2	Multivariate normal	To capture correlation between coefficients
Gopal (2015) overall survival - Coef. 3	Multivariate normal	To capture correlation between coefficients
Pembrolizumab time to treatment discontinuation - Coef. 1	Multivariate normal	To capture correlation between coefficients

Pembrolizumab time to treatment discontinuation - Coef. 2	Multivariate normal	To capture correlation between coefficients
Pembrolizumab time to treatment discontinuation - Coef. 3	Multivariate normal	To capture correlation between coefficients
BV time to treatment discontinuation - Coef. 1	Multivariate normal	To capture correlation between coefficients
BV time to treatment discontinuation - Coef. 2	Multivariate normal	To capture correlation between coefficients
BV time to treatment discontinuation - Coef. 3	Multivariate normal	To capture correlation between coefficients
Adverse event incidence rates	Beta	Ranges between 0 and 1
Utilities		
Mean health state utility values (HSUV) (PFS) - Pembrolizumab	Beta	Ranges between 0 and 1
Mean health state utility values (HSUV) (PFS) - BV	Beta	Ranges between 0 and 1
Mean health state utility values (HSUV) (PFS) - Overall	Beta	Ranges between 0 and 1
Mean health state utility values (HSUV) (PD) - Pembrolizumab	Beta	Ranges between 0 and 1
Mean health state utility values (HSUV) (PD) - BV	Beta	Ranges between 0 and 1
Mean health state utility values (HSUV) (PD) - Overall	Beta	Ranges between 0 and 1
AE disutility	Log-normal	Skewed and positive data
AE duration	Log-normal	Skewed and positive data
SCT – rates of patients receiving stem cell therapy	Beta	Ranges between 0 and 1
Costs		
Disease management usage per week	Gamma	Ranges bounded at zero i.e. no negative values
Subsequent treatment durations	Gamma	Ranges bounded at zero i.e. no negative values
Subsequent treatment usage	Dirichlet	series of beta distributions that would still sum to 1 so that subsequent treatments do not exceed 100%
Adverse event costs	Gamma	Ranges bounded at zero i.e. no negative values

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in **Error! Not a valid bookmark self-reference.** and the corresponding scatterplot and cost-effectiveness acceptability curves are presented in Figure 52 and Figure 53. The main part of the ellipse on the SE quadrant of the cost-effectiveness plane suggests the dominance of pembrolizumab (less costly, more health gains) in most of the iterations. However, in some of the iterations pembrolizumab has less health gains even though it is still less costly (SW quadrant). Due to this fact, the CEAC (Figure 53) forms a horizontal line close to 1 which can be translated to pembrolizumab having health gains in most- but not all - iterations compared to compared to BV however it is less costly across all iterations

Table 138. Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS)

	Total cost (£)	Total LYs	Total QALYs	Incr. cost (pembro vs.)	Incr. LYs	Incr. QALYs	Cost (£) per QALY (pembro vs.)
Pembrolizumab	[redacted]	5.00	4.13				
BV	[redacted]	5.00	3.55	[redacted]	0.00	0.58	Dominant

Figure 52 Scatterplot of PSA results (1,000 simulations; results discounted, with PAS)

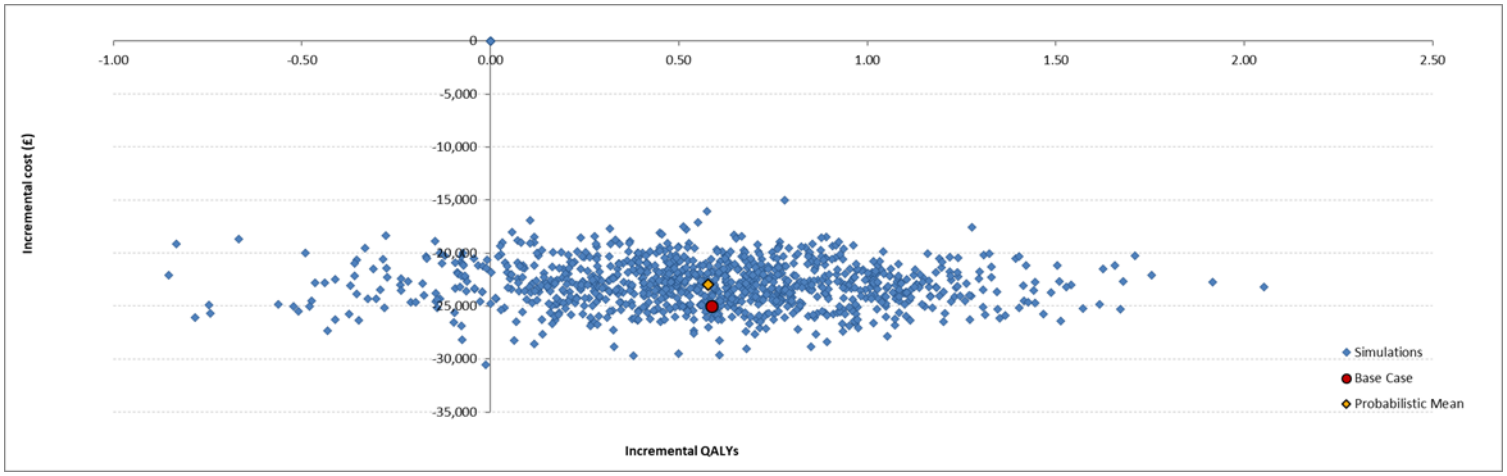
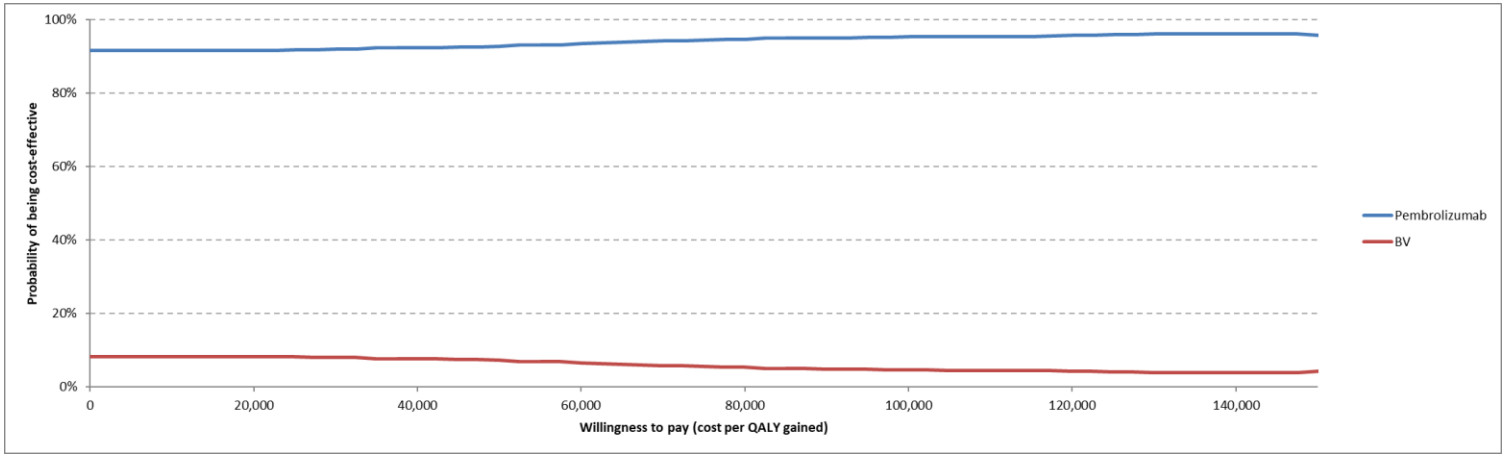


Figure 53. Cost-effectiveness acceptability curve (results discounted, with PAS)



B.3.8.2 Deterministic sensitivity analysis

In order to assess the impact of parameters on the model outcomes, deterministic sensitivity analyses have been used to vary the data inputs. Parameters were varied within their 5% and 95% confidence intervals where possible, and +/- 10% otherwise. The parameters subject to sensitivity analysis, the varied values are presented in below.

Table 139. DSA input parameters

	DSA inputs		
	Lower	Base case	Upper
Discount rate - Costs	0.00	0.035	0.06
Discount rate - Outcomes	0.00	0.035	0.06
Age (mean)	37.21	41.346	45.48
Female (%)	0.38	0.428	0.47
Body surface area (m^2)	1.71	1.900	2.09
Mean health state utility values (HSUV) (PFS) - Pembrolizumab	[redacted]	[redacted]	[redacted]
Mean health state utility values (HSUV) (PFS) - BV	[redacted]	[redacted]	[redacted]
Mean health state utility values (HSUV) (PFS) - Overall	[redacted]	[redacted]	[redacted]
Mean health state utility values (HSUV) (PD) - Pembrolizumab	[redacted]	[redacted]	[redacted]
Mean health state utility values (HSUV) (PD) - BV	[redacted]	[redacted]	[redacted]
Mean health state utility values (HSUV) (PD) - Overall	[redacted]	[redacted]	[redacted]
Disutility - Acute Kidney Injury	-0.07	-0.075	-0.08
Disutility - ALT/ALP/AST elevated	-0.05	-0.050	-0.06
Disutility - Anaemia	-0.07	-0.080	-0.09
Disutility - Diarrhoea	-0.06	-0.063	-0.07
Disutility - Fatigue	-0.11	-0.117	-0.13
Disutility - Gastrointestinal disorders	-0.07	-0.075	-0.08
Disutility - General disorders and administration site conditions	-0.07	-0.075	-0.08

Disutility - Leukocytes / Lymphocytes	-0.14	-0.150	-0.17
Disutility - Metabolism disorders	-0.07	-0.075	-0.08
Disutility - Nausea	-0.07	-0.075	-0.08
Disutility - Neuropathy peripheral	-0.30	-0.330	-0.36
Disutility - Neutropenia	-0.11	-0.125	-0.14
Disutility - Neutrophil count decreased	-0.11	-0.125	-0.14
Disutility - Other Infections	-0.20	-0.220	-0.24
Disutility - Other Nervouus system disorders	-0.07	-0.075	-0.08
Disutility - Other respiratory disorders	-0.07	-0.075	-0.08
Disutility - Pneumonia	-0.18	-0.200	-0.22
Disutility - Pneumonitis	-0.18	-0.200	-0.22
Disutility - Rash	-0.03	-0.030	-0.03
Disutility - Thrombocytopenia	-0.10	-0.108	-0.12
Disutility - Vomiting	-0.07	-0.075	-0.08
Disutility - Weight increased	-0.07	-0.075	-0.08
Adverse event incidence (grade ≥3) - Pembrolizumab - Acute Kidney Injury	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Anaemia	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Diarrhoea	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Neutropenia	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Pneumonia	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Pneumonitis	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Thrombocytopenia	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - Pembrolizumab - Weight increased	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - BV - Acute Kidney Injury	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - BV - Anaemia	[redacted]	[redacted]	[redacted]

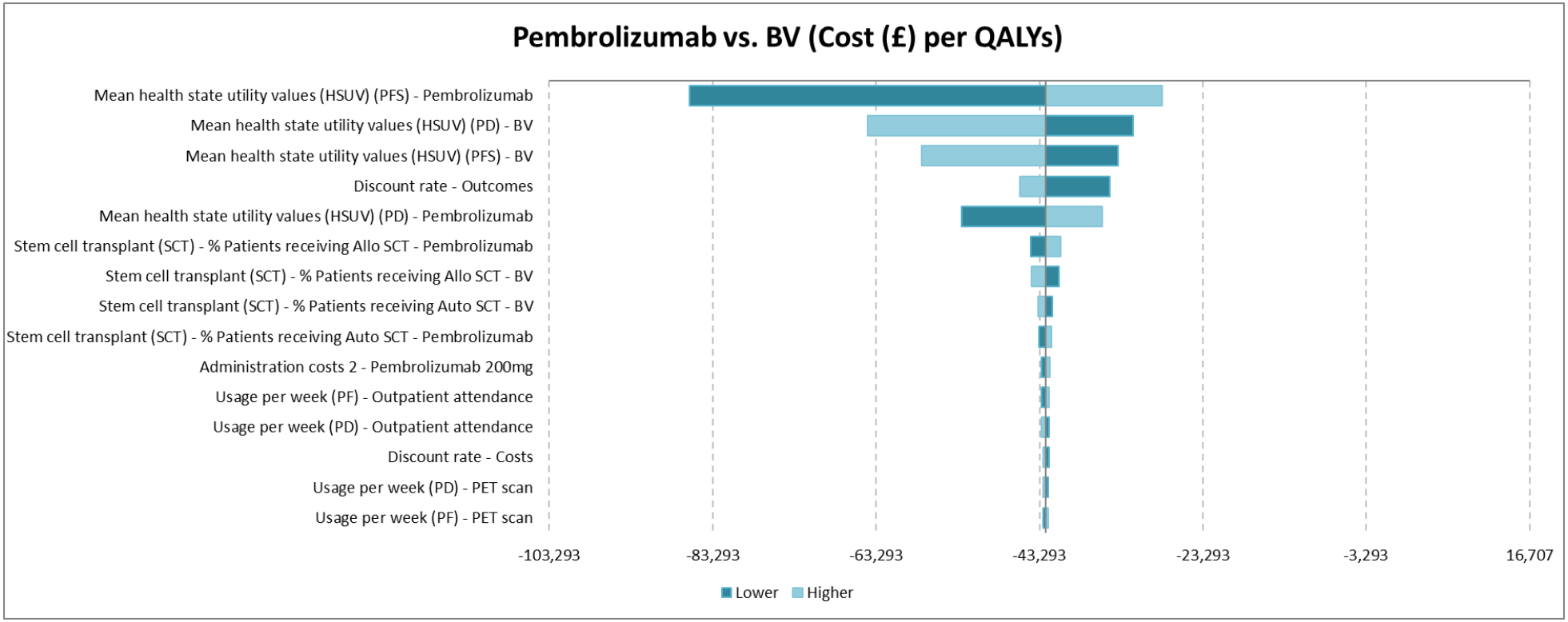
Adverse event incidence (grade ≥3) - BV - Diarrhoea	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - BV - Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - BV - Neutropenia	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - BV - Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - BV - Pneumonia	[redacted]	[redacted]	[redacted]
Adverse event incidence (grade ≥3) - BV - Pneumonitis	[redacted]	[redacted]	[redacted]
Administration costs 1 - Pembrolizumab 200mg	165.19	183.541	201.89
Administration costs 1 - BV	165.19	183.541	201.89
Administration costs 2 - Pembrolizumab 200mg	165.19	183.541	201.89
Administration costs 2 - BV	165.19	183.541	201.89
Adverse event costs - Cost (£) per event - ALT/ALP/AST elevated	449.11	499.007	548.91
Adverse event costs - Cost (£) per event - Anaemia	649.46	721.620	793.78
Adverse event costs - Cost (£) per event - Diarrhoea	1,260.60	1,400.667	1,540.73
Adverse event costs - Cost (£) per event - Fatigue	551.49	612.769	674.05
Adverse event costs - Cost (£) per event - Leukocytes / Lymphocytes	81.35	90.389	99.43
Adverse event costs - Cost (£) per event - Nausea	531.96	591.070	650.18
Adverse event costs - Cost (£) per event - Neuropathy peripheral	660.56	733.956	807.35
Adverse event costs - Cost (£) per event - Neutropenia	930.08	1,033.43	1,136.77
Adverse event costs - Cost (£) per event - Neutrophil count decreased	930.08	1,033.43	1,136.77
Adverse event costs - Cost (£) per event - Other Infections	416.74	463.04	509.35
Adverse event costs - Cost (£) per event - Pneumonia	488.69	542.99	597.29
Adverse event costs - Cost (£) per event - Pneumonitis	488.69	542.99	597.29
Adverse event costs - Cost (£) per event - Rash	160.82	178.69	196.56
Adverse event costs - Cost (£) per event - Thrombocytopenia	667.33	741.47	815.62
Adverse event costs - Cost (£) per event - Vomiting	977.13	1,085.70	1,194.27
Adverse event costs - Cost (£) per event - Weight increased	977.13	1,085.70	1,194.27
Stem cell transplant (SCT) - % Patients receiving Auto SCT - Pembrolizumab	[redacted]	[redacted]	[redacted]

Stem cell transplant (SCT) - % Patients receiving Auto SCT - BV	[redacted]	[redacted]	[redacted]
Stem cell transplant (SCT) - % Patients receiving Allo SCT - Pembrolizumab	[redacted]	[redacted]	[redacted]
Stem cell transplant (SCT) - % Patients receiving Allo SCT - BV	[redacted]	[redacted]	[redacted]
Usage per week (PF) - Outpatient attendance	0.18	0.20	0.22
Usage per week (PF) - Blood count	0.18	0.20	0.22
Usage per week (PF) - Biochemistry	0.18	0.199	0.22
Usage per week (PF) - CT scan	0.05	0.057	0.06
Usage per week (PF) - PET scan	0.03	0.029	0.03
Usage per week (PD) - Outpatient attendance	0.18	0.199	0.22
Usage per week (PD) - Blood count	0.18	0.199	0.22
Usage per week (PD) - Biochemistry	0.18	0.199	0.22
Usage per week (PD) - CT scan	0.05	0.057	0.06
Usage per week (PD) - PET scan	0.03	0.029	0.03

The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab vs. BV are presented in Figure 54 below. In all scenarios, the ICER for pembrolizumab vs BV was dominant. The inputs that most affect the ICERs are the treatment specific utilities followed by the discount rate on outcomes and the stem cell transplant rates.

Plausible alternative scenarios have further been investigated in the next section (Scenario Analysis), with all the scenarios showing dominance of pembrolizumab.

Figure 54. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most sensible variables (discounted results, with PAS)



B.3.8.3 Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions

Model structure	Scenario 1	Model horizon 50 years
	Scenario 2	Model horizon 60 years
Efficacy estimates	Scenario 3	PFS extrapolation fully fitted parametric (week 0)
	Scenario 4	PFS extrapolation – piecewise approach week 26
	Scenario 5	Modelling survival - assuming equal OS based on pembrolizumab OS curves from KEYNOTE-087
	Scenario 6	Modelling survival – predictive equation based on the relationship of PFS to OS from Gopal et al.
QoL	Scenario 7	QoL – multivariate model
	Scenario 8	QoL – pooled utilities from KEYNOTE-204 in the post-progression state
	Scenario 9	QoL – assuming no AE disutilities for both arms
Treatment costs	Scenario 10	Pembrolizumab assumed at a fixed dose of 400mg every 6weeks (Q6W)
	Scenario 11	Allow vial sharing
	Scenario 12	BV maximum number of cycles set to 16
Subsequent therapies	Scenario 13	Subsequent therapy alternative proportions: UK clinical practice based on expert opinion assumed everyone proceeds to subsequent treatment (Table 128)

	Scenario 14	Subsequent therapy alternative proportions: as per KEYNOTE-204 - excluding pembrolizumab and redistributing the KEYNOTE-204 proportions
Disease management costs	Scenario 15	Weekly usage of disease management resources assumed as per UK clinical expert opinion. (Table 132)

Table 140. Key scenario analyses

Scenario		Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--		--
	BV	[redacted]	4.98	3.52	-24,981	0.00	0.59		Dominant
Scenario 1	Pembrolizumab	93,016	5.00	4.12	--	--	--		--
Time horizon 50 years	BV	117,998	5.00	3.54	-24,981	0.00	0.59		Dominant
Scenario 2	Pembrolizumab	93,027	5.00	4.13	--	--	--		--
Time horizon 60 years	BV	118,008	5.00	3.54	-24,981	0.00	0.59		Dominant
Scenario 3	Pembrolizumab	91,797	4.98	4.08	--	--	--		--
PFS fully parametric fit	BV	116,239	4.98	3.47	-24,442	0.00	0.61		Dominant
Scenario 4	Pembrolizumab	91,885	4.98	4.10	--	--	--		--
PFS piecewise week 26	BV	116,020	4.98	3.50	-24,134	0.00	0.61		Dominant
Scenario 5	Pembrolizumab	118,745	12.20	9.71	--	--	--		--

OS based on KEYNOTE-087 curves	BV	142,897	12.20	8.21	-24,152	0.00	1.49		Dominant
Scenario 6	Pembrolizumab	109,667	10.14	8.09	--	--	--		--
OS based on predictive equation Gopal et al	BV	123,337	7.28	5.01	-13,670	2.86	3.08		Dominant
Scenario 7	Pembrolizumab	92,940	4.98	4.06	--	--	--		--
utilities based on multivariate model	BV	117,922	4.98	3.60	-24,981	0.00	0.46		Dominant
Scenario 8	Pembrolizumab	92,940	4.98	4.03	--	--	--		--
Pooled utilities post-progression	BV	117,922	4.98	3.74	-24,981	0.00	0.29		Dominant
Scenario 9	Pembrolizumab	92,940	4.98	4.11	--	--	--		--
no AE disutilities	BV	117,922	4.98	3.53	-24,981	0.00	0.59		Dominant
Scenario 10	Pembrolizumab	92,833	4.98	4.11	--	--	--		--
Pembrolizumab dosing 400mg Q6W	BV	117,922	4.98	3.52	-25,089	0.00	0.59		Dominant
Scenario 11	Pembrolizumab	92,278	4.98	4.11	--	--	--		--
No vial wastage	BV	111,848	4.98	3.52	-19,570	0.00	0.59		Dominant
Scenario 12	Pembrolizumab	92,940	4.98	4.11	--	--	--		--
BV maximum cycles set to 16	BV	108,527	4.98	3.52	-15,586	0.00	0.59		Dominant
Scenario 13	Pembrolizumab	111,057	4.98	4.11	--	--	--		--

Subsequent treatments based on UK market shares	BV	140,407	4.98	3.52	-29,350	0.00	0.59		Dominant
Scenario 14	Pembrolizumab	92,125	4.98	4.11	--	--	--		--
Subsequent treatments based on KEYNOTE--204 excluding pembrolizumab	BV	109,312	4.98	3.52	-17,188	0.00	0.59		Dominant
Scenario 15	Pembrolizumab	90,936	4.98	4.11	--	--	--		--
Resource use based on clinical expert opinion	BV	122,842	4.98	3.52	-31,906	0.00	0.59		Dominant

B.3.8.4 Summary of sensitivity analyses results

Probabilistic sensitivity analysis suggested that pembrolizumab is dominant in all scenarios

One-way sensitivity analyses showed that the inputs that most affect the ICER are those related to treatment specific utilities followed by the discount rate on outcomes and the stem cell transplant rates.

Scenario analysis showed that the cost-effectiveness of pembrolizumab is resilient to the sources of uncertainty assessed here with all scenarios showing pembrolizumab is dominant over BV.

B.3.9 Subgroup analysis

As discussed in section B.3.2 the subgroups' economic analyses are presented in the following sections

- Patients with R/RcHL who did not have at least two prior therapies when autologous stem cell transplant is not a treatment option (SCT-2L)
- Patients with R/RcHL who are at least third line with prior stem cell transplant. (SCT+3L+) and
- Patients with R/RcHL who are at least third line when autologous stem cell transplant is not a treatment option (SCT-3L+).

B.3.9.1 Patients with R/RcHL who did not have at least two prior therapies when autologous stem cell transplant is not a treatment option(-2L)

For the SCT-2L subgroup, the relevant comparator is salvage chemotherapy as per the NICE final scope[46]. As pembrolizumab has been compared head-to-head to BV only in KEYNOTE 204, an indirect treatment comparison (ITC) was needed to obtain estimates of relative efficacy of pembrolizumab versus the chemotherapy regimens. As many of these regimens have only been evaluated in single-arm trials, an anchored network meta-analysis of pembrolizumab versus chemotherapy was not possible. However, a matching-adjusted indirect comparison (MAIC) provided a method to adjust for between-study differences in patient characteristics to compare outcomes of interest between clinical trials evaluating pembrolizumab and chemoregimens. The MAIC uses the paper by Balzarotti et al. (2016): a phase II randomized, multicenter study which investigated the activity and safety of bortezomib added to IGEV compared with IGEV alone in patients with relapsed/refractory Hodgkin Lymphoma (HL). Full details of the analysis and the results of the MAIC are provided in Appendix D.1.2 an Appendix N. The chemotherapy regimen of IGEV in the Balzarotti (2016) study, represents the chemotherapy clinical data (PFS) in the SCT-2L analysis. The rationale for its choice is provided in Section B.2.9.

The clinical efficacy for this subgroup, was modelled based on PFS from the MAIC. In the absence of OS data from KEYNOTE-204, an approach consistent with the ITT population base case was applied: equal OS for both pembrolizumab and chemotherapy arm based on the extrapolation of the BV OS reported in Gopal et al.

It is highlighted that the MAIC results should be interpreted with extreme caution due to the low effective sample size obtained for KEYNOTE-204 after matching. All other variables for this subgroup analysis are presented in Appendix N.1.

Table 141. Key parameters used for ASCT-2L+ subgroup analysis

Subgroup	Treatment arm	Progression-free Survival	Overall Survival	Time on Treatment	Transplant rates	Subsequent treatments
SCT-2L+	Pembrolizumab	MAIC	OS applied from Gopal et al. 2015	80-week breaking point with exponential (stopping rule 35 cycles)	AutoSCT: [redacted] Allo-SCT: [redacted]	BV (100%) (as per UK clinical practice)
	Chemotherapy	MAIC	OS applied from Gopal et al. 2015	Set to be equal to chemotherapy PFS. Max number of cycles was applied	AutoSCT: [redacted] Allo-SCT: [redacted]	BV (100%) (as per UK clinical practice)

Since the comparison using the MAIC results for PFS (SCT-2L subgroup base case) are subject to considerable uncertainty due to lack of robust evidence, an alternative scenario is presented below in which is based on the KEYNOTE-204. In this trial comparison, chemotherapy PFS is assumed same as BV PFS from KEYNOTE-204 while OS for both chemotherapy and pembrolizumab are still based on Gopal et al. Costs were assumed as per the chemotherapy arm.

Results

Table 136 below presents the base case incremental cost-effectiveness results and scenario analysis for the SCT-2L subgroup incorporating the baseline PAS discount. The ICER for the base case of the SCT-2L subgroup analysis was £53,559 while the trial-based comparison resulted to an ICER of £35,934. Both analyses should be interpreted with extreme caution as the lack of robust evidence poses significant limitations to appropriate decision making.

Table 142. Cost effectiveness results for subgroup ASCT-2L

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case for SCT-2L	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	Chemotherapy	[redacted]	4.98	3.58	£28,019	0.00	0.52	£53,559
Alternative approach Trial based comparison	Pembrolizumab	[redacted]	4.98	4.09	--	--	--	
	Chemotherapy	[redacted]	4.98	3.49	£21,280	0.00	0.59	£35,934

B.3.9.2 Patients with R/RcHL who are at least third line with prior stem cell transplant (ASCT+3L+)

Subgroup analysis for the ASCT+3L+ population is presented below. The same survival modelling assumptions have been used as on the base case (Table 143). All other variables remain the same except from the transplant rates (subgroup specific from KEYNOTE-204) and subsequent treatments (as per UK clinical practice). Details of the survival modelling for this subgroup are presented in Appendix N

Table 143. Key parameters used for ASCT+3L+ subgroup analysis

Subgroup	Treatment arm	Progression-free Survival	Overall Survival	Time on Treatment	Transplant rates	Subsequent treatments
ASCT+3L+	Pembrolizumab	52-week breaking point with lognormal	OS applied from Gopal et al. 2015	80-week breaking point with exponential	AutoSCT: [redacted] Allo-SCT: [redacted]	BV (100%) (as per UK clinical practice)
	BV	52-week breaking point with lognormal	OS applied from Gopal et al. 2015	80-week breaking point with exponential	AutoSCT: [redacted] Allo-SCT: [redacted]	Nivolumab (100%) (as per UK clinical practice)

Results

Table 136 below presents the base case incremental cost-effectiveness results and scenario analysis for the +3L+ subgroup incorporating the baseline PAS discount. The results show that pembrolizumab dominates BV.

Table 144. Cost effectiveness results for subgroup +3L+

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.55	-41,328	0.00	0.56	Dominant
Scenario 1 BV max cycles 16	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.55	-36,358	0.00	0.56	Dominant

B.3.9.3 Patients with R/RcHL who are at least third line when autologous stem cell transplant is not a treatment option ("SCT-3L+").

Subgroup analysis for the ASCT3-L+ population is presented below. The same survival modelling assumptions have been used as on the base case (Table 143). All other variables remain the same except from the transplant rates (subgroup specific from KEYNOTE-204) and subsequent treatments (as per UK clinical practice). Two scenario analyses are provided: 1) for the maximum cycles of BV and 2) for the use of subsequent treatments from KEYNOTE-204 (excluding pembrolizumab) instead of UK clinical practice since pembrolizumab is in CDF. Details of the survival modelling for this subgroup are presented in Appendix N

Table 145. Key parameters used for SCT-3L+ subgroup analysis

Subgroup	Treatment arm	Progression-free Survival	Overall Survival	Time on Treatment	Transplant rates	Subsequent treatments
ASCT+3L+	Pembrolizumab	52-week breaking point with lognormal	OS applied from Gopal et al. 2015	80-week breaking point with exponential	AutoSCT: [redacted] Allo-SCT: [redacted]	BV (100%) (as per UK clinical practice)
	BV	52-week breaking point with lognormal	OS applied from Gopal et al. 2015	80-week breaking point with exponential	AutoSCT: [redacted] Allo-SCT: [redacted]	Pembrolizumab (100%) (as per UK clinical practice)

Results

Table 146 below presents the base case incremental cost-effectiveness results and scenario analysis for the -3L+ subgroup incorporating the baseline PAS discount. The results show that pembrolizumab dominates BV across all scenarios

Table 146. Cost effectiveness results for subgroup SCT-3L+

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-29,326	0.00	0.61	Dominant
Scenario 1 BV max cycles 16	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-19,978	0.00	0.61	Dominant
Scenario 2 (subsequent treatment from KEYNOTE-204)	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-23,356	0.00	0.61	Dominant

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

No study assessing the cost-effectiveness of pembrolizumab versus BV for the target population was identified from the systematic literature review relevant to England. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

A technical review of the cost-effectiveness model was conducted by an independent analyst who did a quality control, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code. (test like extreme conditions tests, outputs moving towards the intuitive direction, appropriate labelling of graphs, cell errors etc.) The full checklist of this quality check is provided in the References pack.

Additionally, an independent agency was commissioned to validate the technology assessment approach and the cost-effectiveness model for pembrolizumab in R/R cHL for the NICE submission. Two UK health economists received pre-read material and 2-hour blinded interviews were conducted. While the experts considered the predictive equation as a valid method to extrapolate OS, the underlying assumptions were quite uncertain and as discussed in section B.3.3.1 a more conservative approach was taken in the base case

Finally, external clinical validation was undertaken with two consultant haematologists, from different centres, who specialise in lymphomas to discuss key issues relating to economic modelling like validation of the OS, PFS, as well as resource use and model structure.

B.3.11 Interpretation and conclusions of economic evidence

The economic analysis demonstrated that pembrolizumab is a cost-effective option for the NHS and this was consistent across all scenarios that tested various assumptions. The analysis performed is based on a de novo economic model with a structure designed to reflect the R/RcHL setting in the most simplistic form while still capturing the relevant outcomes. The model structure (3-state partitioned survival model) is consistent with previous R/RcHL models and oncology indications. The model makes use of data from KEYNOTE-204 which is the first anti-PD1 study with a Phase III randomized trial that demonstrates a statistically and clinically significant improvement in PFS compared with brentuximab vedotin (BV) in R/R cHL patients. This is a key strength of the economic

analysis, at least for the PFS, as many of the trials in this disease area are single arm studies with no comparative data.

The analysis is directly applicable to clinical practice in England since:

a) the patient population in KEYNOTE-204 and the de novo economic evaluation are reflective of patients with R/RcHL

b) the economic model structure is consistent with other oncology models submitted to NICE and

c) the resource utilisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions, incorporating the committee preferences.

The full ITT population of KEYNOTE-204 was considered in the base case of the economic model however, three subpopulations were also presented:

- Patients with R/RcHL who are at second line with no prior stem cell transplant (ASCT-2L) (compared to chemotherapy via an MAIC)
- Patients with R/RcHL who are at least third line with prior stem cell transplant. (+3L+) (compared to BV) and
- Patients with R/RcHL who are at least third line when autologous stem cell transplant is not a treatment option (-3L+). (compared to BV)

While KEYNOTE-204 did not report OS in the interim analysis presented here, alternative sources were used in the economic modelling to examine the cost-effectiveness of pembrolizumab versus BV in order to make a case to allow access for patients until OS data from KEYNOTE-204 become available.

For the base case, equal OS curves for pembrolizumab and BV arms - based on the BV OS reported from Gopal et al. were assumed, while PFS was sourced from patient level data of KEYNOTE-204. Efficacy outputs were validated with two clinical experts who provided 5 - year PFS and OS estimates for BV based on their experience. The OS modelling approach was considered as the most conservative way to model cost effectiveness outcomes and it should be highlighted that that pembrolizumab OS gains are potentially underestimated. This is supported by KEYNOTE-087 OS data as well as expert opinion which indicate the expectation for better pembrolizumab outcomes in this population.

In the base case analysis, the estimated LYS were 4.98 for both arms. Patients treated with pembrolizumab accrued 4.11 QALYs compared to 3.52 QALYs for BV. Since the OS was assumed the same, the gain in QALYs for the pembrolizumab arm is stemming from the difference in utilities and PFS gains. Pembrolizumab was dominant versus BV in the base case and in all scenario analysis.

Pembrolizumab also showed dominance over BV for the third line subgroups: SCT-3L+ and SCT+3L+. For the SCT-2L subgroup, the comparison versus chemotherapy was conducted via the means of a MAIC and the results should be interpreted with extreme caution due to the low effective sample size obtained for KEYNOTE-204 after matching the populations.

Sensitivity analysis demonstrated that pembrolizumab is dominant across all methods tested however it is recognised that a key limitation is the lack of OS data which adds to the uncertainty and potentially affects model stability. The most conservative assumptions to model OS throughout this technology assessment were selected on balance, using the most relevant evidence where possible and the conclusion of the economic analysis suggests that pembrolizumab is a cost-effective option for NHS.

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Single technology appraisal

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

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
[ID1557] Clarification questions ERG pembrolizumab 051120 [ACIC]. docx	V1.	Yes	05/11/2020

Section A: Clarification on effectiveness data

Literature searches

A1. Were any specific searches completed for adverse events (in addition to the searches for clinical effectiveness systematic literature review [SLR])?

No searches were conducted specifically for adverse events; however, adverse events and serious adverse events were included in the PICOS for the clinical SLR. Specifically, the clinical SLR included the following outcomes: drug related adverse events occurring in more ≥10% of patients in any arm, grade 3-5 adverse events (overall and drug related) and discontinuations due to adverse events.

A2. The SIGN filters were used to identify randomised controlled trials in the MEDLINE and Embase searches. These filters do not include any specific terminology for single-arm prospective studies. Was the search tested to ensure the filter identified relevant single-arm prospective studies?

The search results were cross-referenced with the most recent guidelines published by the National Comprehensive Cancer Network and European Society for Medical Oncology, as well as recent technology appraisals relevant to the population of interest (TA462 and TA540) to ensure the search captured all relevant evidence.

A3. Please can you provide further details of the targeted literature search of PubMed described in D.1.2.1?

The search results were cross-referenced with the most recent guidelines published by the National Comprehensive Cancer Network and European Society for Medical Oncology, as well as recent technology appraisals relevant to the population of interest (TA462 and TA540) to ensure the search captured all relevant evidence.

Systematic review methods

A4. Table 13 of Appendix D shows 6 trials included in the UK feasibility assessment. These were identified from the set of 45 UK relevant studies found in the SLR. Additional criteria provided in Table 11 were applied to this set of 45 UK

studies to identify the 6 studies in Table 13. Table 12 only shows a list of 5 excluded pembrolizumab studies. What were the other excluded studies with reasons?

Please see the table below of the excluded studies from the UK SLR in order to determine the relevant studies included in the feasibility assessment. MSD apologises Table 12 in the submission document was included in error and did not contain the full list of excluded studies.

Trial ID	NCT code	Intervention(s)	Primary publication	Reason for exclusion from UK feasibility assessment
Armand 2019	NCT02362997	Pembrolizumab	Armand 2019[1]	ASCT-failed population
KEYNOTE-013	NCT01953692	Pembrolizumab	Armand 2016[2]	3L+ population
KEYNOTE-051	NCT02332668	Pembrolizumab	Geoerger 2020[3]	KEYNOTE-204 will be used as source of data for pembrolizumab
KEYNOTE-087	NCT02453594	Pembrolizumab	Chen 2017[4]	KEYNOTE-204 will be used as source of data for pembrolizumab
AETHERA	NCT01100502	BV	Moskowitz 2015a[5]	ASCT-failed population
Bartlett 2014	NCT00947856	BV	Bartlett 2014[6]	KEYNOTE-204 will be used as comparison to BV
Chen 2015	NCT01393717	BV	Chen 2015[7]	KEYNOTE-204 will be used as comparison to BV
FIL ONLUS	NCT02227433	BV	Stefoni 2020[8]	KEYNOTE-204 will be used as comparison to BV
Goranova-Marinova 2019	--	BV	Goranova-Marinova 2019[9]	KEYNOTE-204 will be used as comparison to BV
NCT02939014	NCT02939014	BV	NCT02939014[10]	KEYNOTE-204 will be used as comparison to BV
Ogura 2014	JapicCTI-111650	BV	Ogura 2014[11]	KEYNOTE-204 will be used as comparison to BV
Walewski 2018	NCT01990534	BV	Walewski 2018[12]	KEYNOTE-204 will be used as comparison to BV
Younes 2012b	NCT00848926	BV	Younes 2012[13]	ASCT-failed population
Kanat 2010	--	DHAP	Kanat 2010[14]	Mixed population with other malignancies, did not report patients characteristics for HL subgroup
Aparicio 1999	--	ESHAP	Aparicio 1999[15]	2L and 3L outcomes not reported separately
HD-R31	NCT01453504	Everolimus + DHAP vs DHAP	Von Tresckow 2018[16]	Fewer than 9 patients in population of interest
Gokmen 2018	--	GDP	Gokmen 2018[17]	Unclear what proportion of patients are 2L
Rybka 2015	--	Gemcitabine based treatment	Rybka 2015[18]	No 2L patients
Fields 1994	--	ICE	Fields 1994[19]	Only 3L+ population
Hertzberg 2003	--	ICE	Hertzberg 2003[20]	Mixed population with other malignancies, did not report patients characteristics for HL subgroup

Kleiner 1997	--	ICE	Kleiner 1997[21]	Mixed population with other malignancies, did not report patients characteristics for HL subgroup
Moskowitz 2010	--	ICE	Moskowitz 2010[22]	Only reported on patients who received both ICE and subsequent ASCT
Shea 2009	--	ICE	Shea 2009[23]	All patients were reported as transplant-eligible
Moskowitz 2012	NCT00255723	ICE + augmented ICE	Moskowitz 2012[24]	All patients were reported as transplant-eligible
Santoro 2007	--	IGEV	Santoro 2007[25]	Patient characteristics not reported separately for 2L population
Bishton 2007	--	IVE	Bishton 2007[26]	Mixed population with other malignancies, did not report patients characteristics for HL subgroup
Jackson 2000	--	IVE	Jackson 2000[27]	Only 11 2L relapsed patients
Proctor 2001	--	IVE	Proctor 2001[28]	8 primary refractory patients, 2L relapsed patients not separated from 3L relapsed patients
Proctor 2003	--	IVE	Proctor 2003[29]	Patient characteristics not reported separately for 2L population
Zinzani 1994	--	IVE	Zinzani 1994[30]	Fewer than 6 patients in population of interest
CA209-039	--	Nivolumab	Ansell 2015[31]	Treatment considered to be not of interest for indirect treatment comparison
Checkmate 205	NCT02181738	Nivolumab	Armand 2018[32]	Treatment considered to be not of interest for indirect treatment comparison
Fedorova 2018	--	Nivolumab	Fedorova 2018[33]	Treatment considered to be not of interest for indirect treatment comparison
Kichigina 2018	--	Nivolumab	Kichigina 2018[34]	Treatment considered to be not of interest for indirect treatment comparison
Maruyama 2017	JapicCTI-142755	Nivolumab	Maruyama 2017[35]	Treatment considered to be not of interest for indirect treatment comparison
NIVALLO	--	Nivolumab	Wong 2018[36]	Treatment considered to be not of interest for indirect treatment comparison
Brice 1999	--	ASCT	Brice 1999[37]	Treatment considered to be not of interest for indirect treatment comparison
Evens 2007	--	ASCT	Evens 2007[38]	Treatment considered to be not of interest for indirect treatment comparison
H96	--	ASCT	Sibon 2016[39]	Treatment considered to be not of interest for indirect treatment comparison

Comparators

A5. Please explain why bendamustine-based regimens are not included in the list of standard of care treatments for the SCT-2L subgroup.

Bendamustine based regimens were not included in the list of standard of care (SoC) treatments for the 2L subgroup in light of clinical expert opinion elicited by MSD, relevant guidelines and publications applicable to UK clinical practice.

Clinical expert opinion explained a variety of regimens are commonly used across the UK, the frequency of which varies across institutions. However, the clinicians did not include bendamustine based regimens in the list of SoC treatment for 2L patients with R/RcHL. ICE and GDP were highlighted as the regimens most commonly used in the UK. Clinicians were further asked to validate the list of the SoC regimens, included in the submission, for use in 2L and it was confirmed this list is representative of UK clinical practice.

There are currently no clear recommendations or guidelines for SoC for 2L R/RcHL patients. However, in the absence of recently published up to date UK specific guidance, MSD referred to the following guidelines for insight which do not list bendamustine based regimens. The Pan London Guidelines [40] state the choice of 2L regimens in patients should be based on patient factors and the familiarity of the treatment centre with the regimens. A platinum-based regimen is usually recommended, e.g. ESHAP, DHAP, GEM-P, or ICE. In addition, IGEV can be considered as an alternative. Furthermore, ESMO [41] list salvage regimens such as DHAP, IGEV or ICE to be given at in the 2L setting.

Eyre et al conducted [42] a UK-wide retrospective analysis to assess the efficacy of BV in R/RcHL patients who had not previously received ASCT. The list of 2L regimens included in the submission reflect this publication and the clinical expert opinion elicited by the company which does not include bendamustine.

Dosing

A6. Please explain why results for pembrolizumab 400mg (administered every 6 weeks) are included. It is our understanding that the SmPC only includes the [redacted].

MSD have submitted the draft SmPC as a separate document in the clarification response. This document is highly confidential until CHMP opinion.

The recommended dose as described in the SmPC is as follows:

[redacted]

[redacted]

MSD included a scenario analysis in the economic section of the submission (Document B Section B 3.8.3) since the SmPC allows for both dosing regimens for KEYTRUDA as a monotherapy in adults.

Median OS

A7. The ERG notes that the expected median overall survival (OS) in the control group of KEYNOTE-204 is 22.4 months (company submission document B, p. 63) and that, as of the data cut-off date for [redacted], the median duration of follow up for the BV group was 24.3 months (p.82). Was median OS for the BV group reached by the data cut-off date?

Please note this is an assumption which was included in the statistical analysis plan (Documents B, p 63) [redacted]

Survival/extrapolation

A8. Priority question: Please elaborate on how Week 26 and 52 were chosen as the break points for semiparametric model fits.

a) **Was there a clinical rationale for these decisions?**

Upon review of the timepoints as explained in A8b, a cutoff point of less than 6 months was avoided for various reasons related to the clinical effectiveness. First, a delayed treatment effect is common with immunooncology so treatment benefit of PFS can be well-established within 6-month of treatment follow-up. Additionally, some responses assessed initially need to be confirmed for sustainability check in subsequent assessments for determining disease progression. Finally, since the first assessment of tumour imaging data is not available until some time around 8-10 weeks following the first dose, therefore a sudden and steep drop off in PFS is observed around this early period.

b) **Figure 34 and Figure 35 in the company submission document B seem to include discontinuities at a range of time points. Were these evaluated as well as potential break points and how were these evaluated?**

Chow-test alone doesn't provide comprehensive information for determining a cutoff time point. Rather, it provides some information to detect naively the time point when the structure in survival over time after that point is different from the one before that time point. Given the survival function is non-increasing over time, this method could suggest more cutoff points than necessary, most of which may just be due to subtle changes in survival patterns that are not easily visualizable or detectable by other methods.

The cutoff timepoints were selected through a series of iterative steps and requirements. The goal was to identify appropriate time points for both Pembrolizumab and BV across all subgroups to ensure consistency between the comparators and across the subgroups.

1) We began with a review of the ITT population and identified possible time points by
    a. First reviewing the chow tests
    b. Then conducting a visual inspection of the one-piece fitting
    c. Followed by a review of the cumulative hazard plots
    d. Finally, examining the number of remaining events in the tail of the KM curve and ensured that there were sufficient events (minimum of 10) remaining post the candidate cutoff. These were inferred from the Kaplan-Meier plot and survival summary table.
2) We then reviewed the SCT-2L ineligible population and repeated steps 1a-d for this subgroup. The goal was to determine if any of the dates in the ITT population aligned with this subgroup. The same exercise for the 3L+ SCT ineligible as well as the 3L+ SCT eligible was repeated.

A9. To assist with parameter interpretation, please supply the form of the survival distribution functions showing the role of the parameters reported in the model. For example, in the model it appears 'coef. 1' for the exponential is the estimate of the log(rate), so that

S(t) = exp(-exp([coef. 1])t)

The survival functions are created through a two-step process where the hazard function is reconstructed and then the survival function is calculated. The vector of time in the formulae is represented by vt. These answers can be verified by checking the hazard_func macro in the VBA code (Note in the VBA code that Survregparameterisation is always true).

The cumulative hazards are reconstructed for each distribution using the hazard_func macro.

Exponential function:

Parameter input to hazard function	Parameter used in formula	Parameter represented

Alpha	Exp(alpha)	Log(rate)
Beta	NA	NA
Q	NA	NA

Final formula with parameters on their inputted scale:

H(i, 1) = (exp(alpha) * vt(i, 1))

Weibull function:

Parameter input to hazard function	Parameter used in formula	Parameter represented
Alpha	Exp(alpha)	Log(shape)
Beta	Exp(beta)	Log(scale)
Q	NA	NA

Final formula with parameters on their inputted scale:

H(i, 1) = ((vt(i, 1) / exp(beta)) ^ exp(alpha))

Gompertz function:

Parameter input to hazard function	Parameter used in formula	Parameter represented
Alpha	alpha	Shape
Beta	Exp(beta)	Log(rate)
Q	NA	NA

Final formula with parameters on their inputted scale:

H(i, 1) = (exp(beta) / alpha) * (Exp(alpha * vt(i, 1)) - 1)

Log-logistic function:

Parameter input to hazard function	Parameter used in formula	Parameter represented
Alpha	Exp(alpha)	Log(shape)
Beta	Exp(beta)	Log(scale)
Q	NA	NA

Final formula with parameters on their inputted scale:

H(i, 1) = -Log(1 - (1 / (1 + (vt(i, 1) / exp(beta)) ^ (-exp(alpha)))))

Log-normal function:

Parameter input to hazard function	Parameter used in formula	Parameter represented
Alpha	alpha	meanlog
Beta	Exp(beta)	Log(sdlog)
Q	NA	NA

Final formula with parameters on their inputted scale:

H(i, 1) = -Log(1 - NormSDist((Log(vt(i, 1)) - alpha) / exp(beta)))

Generalised Gamma function:

Parameter input to hazard function	Parameter used in formula	Parameter represented
Alpha	alpha	mu
Beta	Exp(beta)	Log(sigma)
Q	Q	Q

Final formula with parameters on their inputted scale:

If Abs(Q) < 0.05, then the function reduces to the lognormal parameterization.

H(i, 1) = -Log(1 - NormSDist((Log(vt(i, 1)) - alpha) / exp(beta)))

Otherwise:

If Q > 0, then ret = GammaDist(Exp(Q * (([Log(vt(i, 1))] - alpha) / exp(beta))) * (Q ^ (-2)), (Q ^ (-2)), 1, True)

Otherwise ret = 1 - GammaDist(Exp(Q * (([Log(vt(i, 1))] - alpha) / exp(beta))) * (Q ^ (-2)), (Q ^ (-2)), 1, True)

H(i, 1) = -Log(1-ret)

With the generalized gamma hazard reconstruction, there is one final check when i>2

If H(i, 1) < H(i-1, 1) Then

H(i, 1) = H(i-1, 1)

The cumulative hazards are then exponentiated as S(t) = exp ("cumulative hazards")

A10. The choice of Weibull for progression-free survival (PFS) gives poorly fitting survival curves in the Excel model 'Survival' worksheet (see PFS survival curves),

and unlikely parameter estimates (identical shape and scale parameter estimates for pembrolizumab). Please check and make any necessary corrections.

The parameters for the Weibull distribution have been corrected to include the alpha [log(shape)] values. Previously, the beta [log(scale)] values were used for both the alpha [log(shape)] and beta [log(scale)] parameters for the Weibull distribution. These errors have been rectified by amending AC7, AK7, U79 and AC79 in 'ClinicalData' sheet of the CEM model to reflect the correct alpha [log(shape)] and beta [log(scale)] parameters for the Weibull distribution. The resulting Weibull distribution for progression-free survival (PFS) now provides better fitting survival curves in the Excel model 'Survival' worksheet. The updated model (including the amendment required in question A13) is provided along with the clarification questions.

A11. Please provide further information relating to the tenability of assumptions used in survival analyses:

a) **Please provide diagnostic plots (such as Cox-Snell residuals) for all fully parametric survival curves estimated.**

Cox-snell residuals against cumulative hazards and cumulative distribution functions for the ITT population are displayed in the plot below:

b) **The company submission reports (document B p189) that "The statistical test supports the proportional hazards assumption since the result is not statistically significant (p >0.05)". Please provide further details of this test including which test was used and the results.**

Test of proportionality of hazards for all comers between pembrolizumab and brentuximab vedotin treatment arms, which is cited here, was conducted using the cox.zph function in R. See the R documentation for Test The Proportional Hazards Assumption Of A Cox Regression for details.

See test result below:

```
> survival::cox.zph(survival::coxph(survival::Surv(AVAL, 1 - CNSR) ~ TRT01P,
+                         data = subset(KN204.TTE, ITTFL == 'Y' & TRT01P != '' &
+                                               PARAMCD == 'PFSSIRC')))
                        rho  chisq     p
TRT01PMK-3475 200 mg 0.0217 0.0785 0.779
```

A12. Please provide a scenario using the piecewise approach for Time on Treatment with a cut-off point at week 26, akin to that for PFS in the base case.

As discussed during the meeting for clarification questions with the ERG, the Time on Treatment curve parameters with a Week 26 cut-off for pembrolizumab and BV for the ITT population is provided as separate document in the clarification questions.

A13. The ERG notes that the generalised gamma distribution did not converge (document B, p193) when fitted to the BV data from Weeks 0 and 52, despite the fairly large sample size (n=152). Specifying different initial values for the generalised gamma parameters (such as the estimates obtained for one of the other distributions) may assist with convergence. If so, please supply the parameter estimates and covariance matrix for the generalised gamma and the updated AIC and BIC.

The issues for week 0 and week 52 fitting arise from the optimization option chosen. After switching the option to the default, convergences achieved with generalized gamma distribution assumptions. The parameter estimates and covariance matrix for gengamma was updated in the model along with the AIC and BIC statistics. An updated

version of the model, including the amendment from question A10 is provided along the clarification questions.

Please note that while updating the model, a minor error was identified in the AE costs which had a minimal effect in the results (incremental costs changed by £21). The amended base case for the ITT population is as follows:

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
BV	[redacted]	4.98	3.52	-25,002	0.00	0.59	**Dominant**

A14. Of the 6 'standard of care' regimens shown in table 59, the comparison with IGEV from Balzarotti et al. 2016 was selected for base case MAIC, but MAIC results for the other comparators were not presented. The company state that 'This analysis [with IGEV] was selected as the base case because the Balzarotti study was the only SOC study that published KM curves for OS or PFS' (company submission p125). Please clarify if any other considerations were involved when excluding each of the other MAIC analyses from further consideration (e.g. non-correspondence with target population).

Studies including 2L ASCT naïve patients were considered within the feasibility assessment to determine whether they might provide a suitable proxy for standard of care in the patient population. The feasibility assessment focused on the distribution of study and patient characteristics that were expected to modify absolute or relative treatment effects, outcome definitions that were expected to impact relative treatment effects, and the reporting of observed absolute effects to determine which comparisons were possible.

The feasibility assessment showed that the populations in all 5 chemotherapy studies (Baetz 2003, Balzarotti 2016, Hu 2018, Josting 2002, Ramzi 2015) were not

comparable to KEYNOTE-204 in terms of ineligibility for ASCT. A small proportion of patients in the 2L ASCT population from KEYNOTE-204 did go on to receive some form of transplant ([redacted] of those treated with pembrolizumab and [redacted] of those treated with BV), likely due to their initial ineligibility being based on factors related to prior treatment as opposed to factors not related to prior treatment such as older age or presence of comorbidities. In comparison, all patients went on to receive ASCT in Baetz et al., 2003 and 9 out of 12 (75%) in Hu et al., 2018. In Josting et al., 2002, it was not clear what proportion of patients went on to receive SCT, but peripheral blood stem cells were successfully harvested in 96% of patients. In Ramzi et al 2015 all patients were aged less than 60 and were required to have adequate organ function (creatinine <1.4 mg/dl, serum aspartate or alanine aminotransferase <2.5 upper limit of normal and bilirubin <1.5 ULN), though the proportion who went on to receive SCT was not reported. Finally, a significant proportion of patients in the IGEV arm of Balzarotti et al., 2016 underwent peripheral blood stem cell mobilization (n=34); however, the exact number of patients who went on to receive subsequent transplantation is unclear from the full text publication, but at minimum was 31 (81.6%).

Given the differences in the underlying populations that could not be adjusted for, the MAICs versus all studies were deemed to be subject to significant risk of bias. However, in order to provide an indication of the relative treatment effect of pembrolizumab versus current interventions in terms of the key outcomes of PFS, the results of the comparisons with Balzarotti et al., 2016 were presented while the others were not.

A15. Please supply a histogram of the weights for the base case MAIC (IGEV-Pembrolizumab).

Figure 1. Histogram of Weights for Pembrolizumab Matching-Adjusted Indirect Comparison of Pembrolizumab (Keynote 204) vs IGEV (Balzarotti) Second Line Subjects with No Prior Stem Cell Transplant with Age < 65 Years

A16. Clinical advice suggests UK standard of care may include regimens involving bendamustine, and bendamustine, gemcitabine, vinorelbine (BEGEV) is also listed in the company decision problem form. In light of the feasibility study, please clarify the potential for MAIC analyses of these regimens.

As per the response for question A5 clinical advice elicited by MSD did not suggest bendamustine containing regimens were considered SoC for the 2L setting for patients with R/RcHL in addition to aforementioned guidelines and publications. Therefore, whilst this may have been listed in the decision problem form it was not included in the company submission in light of the expert opinion received to ensure the SoC list was relevant to clinical practice.

However, a global SLR which included bendamustine in the search was conducted. No comparisons for bendamustine or BEGEV are feasible based on the evidence collected in this overarching SLR. Two studies of these regimens were identified, neither of which feature a population which is 2L ASCT ineligible. Santoro et al, 2016 studied BEGEV as induction therapy for R/RHL patients before undergoing ASCT. Moskowitz et al. 2013 studied bendamustine monotherapy in R/R HL patients who had failed or were ineligible for ASCT; however, 75% of the patients fell into the failed category and outcomes were not available for the subgroup of ineligible patients. The population also was heavily pre-treated with a median number of prior chemotherapies of 4. Therefore, a MAIC including bendamustine or BEGEV was not feasible.

A17. Please summarise the proportion of patients in the SCT-2L subgroup of KN204 used in the MAIC, and in the selected comparator study, that went on to receive SCT. Please also summarise the information available relating to SCT eligibility (e.g. comorbidities, organ function) for each.

As described in Appendix D.1.2.1, a significant proportion of patients in the IGEV arm of Balzarotti 2016 underwent peripheral blood stem cell mobilization (n=34); however, the exact number of patients who went on to receive subsequent transplantation is unclear from the full text publication, but at minimum was 31 (81.6%). To ensure comparability as much as possible, PFS data from KEYNOTE-204 including imaging post

transplantation was used for the purposes of comparison; reported median PFS (per investigator assessment) for patients on pembrolizumab ([redacted] of whom received a subsequent transplant) and BV [redacted] of whom received a subsequent transplant) was [redacted] weeks (range [redacted]) and [redacted] weeks (range [redacted]), respectively, when including post-transplant clinical and imaging data.

The Balzarotti et al., 2016 study did not report any information related to ASCT eligibility in terms of organ function or comorbidities, but all patients were aged <65 years.

The study protocol for KEYNOTE-204 states the exclusion of patients who are eligible for allogeneic or autologous stem cell transplantation per investigator assessment.

For KEYNOTE-204, in patients who received study drug as second line, none had received prior ASCT and were those who were considered ineligible for auto SCT due to two broad categories:

1. Chemo refractory (patients who were considered refractory to 1L therapy) and

2. Non chemo refractory (this include age and comorbidities)

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Table 43 of Appendix H provides details of only 5 of the published studies of utility estimates identified from the health-related quality of life (HRQoL) SLR searches (3 cost effectiveness studies with utility metrics reported: Large, 2019; Parker, 2017; Jones, 2017; and 2 of the 18 HRQoL studies identified: Swinburn, 2014; Ramsey, 2016). Please provide details of the 16 non-UK HRQoL studies identified in the HRQoL searches.

Table 1: Additional details for non-UK studies identified in the health-related quality of life review (n=16 studies)

Study name/ Country	Patient Pop (age; cHL/HL/ sALCL)	Information on recruitment	Intervention and comparator(s)	Smp size	Response rates	Description of health states	Adverse reactions	Appropriateness of health states	Method of elicitation/valuation Consistency with the reference case	Mapping	Uncertainty around values
Younes 2016, USA, Canada, and Europe	37 (28-48) years; cHL	• Participants of checkmate 205 study • Patient-reported general health status was assessed using the 3-level version of the EQ- 5D questionnaire	• Nivolumab	80	EORTC-QLQC30 completion Week 1: 94% Week 9: 83% Week 17: 85% Week 25: 82% Week 33: 88% EORTC QLQ-C30 or EQ-5D assessment: 90%	• EQ-5D utility index increased by 0.05 units	NR	Yes	NR (Limited information reported in the study)	NR	Standard error • 0.02

Von 2019, Canada, Japan, Australia, Russia, Israel, UK, Sweden, Spain, Norway, Italy, USA, Hungary, Greece, Germany, France	35 (18-76) years; cHL	• Participants of a clinical trial (KEYNOTE-087)
		• QoL was assessed using QLQ-C30 and EQ-5D
		• EQ-5D utility scores were calculated using the published algorithms
			• Pembrolizumab	206	Compliance rates for EQ-5D questionnaire
					
					Week 12: 94%
					Week 24: 78%
						Baseline
						
						• All cohorts: 0.74
						• Responders (CR + PR): 0.74
						• Stable disease: 0.78
						• Progressive disease: 0.72
						
						Week 12
						
						• All cohorts: 0.80
						• Responders (CR + PR): 0.83
						• Stable disease: 0.81
						• Progressive disease: 0.69
							NR	Yes	The generic health statuses assessed were converted to population-based utility values using published algorithms. More specifically, US-based scoring was applied to US patients, UK-based scoring for UK patients and EU-based scoring for all other patients.
									• Consistency with NICE reference case: No
									  ○ Described using standardized and validated instrument: Yes (EQ-5D)
									  ○ TTO or SG: NR
									  ○ Representative sample of public: No
										NR	Baseline
											
											• All cohorts: 0.22
											• Responders (CR + PR): 0.22
											• Stable disease: 0.18
											• Progressive disease: 0.24
											
											Week 12
											
											• All cohorts: 0.21
											• Responders (CR + PR): 0.21
											• Stable disease: 0.19
											• Progressive disease: 0.24

Study name/ Country	Patient Pop (age; cHL/HL/ sALCL)	Information on recruitment	Intervention and comparator(s)	Smp size	Response rates	Description of health states	Adverse reactions	Appropriateness of health states	Method of elicitation/valuation Consistency with the reference case	Mapping	Uncertainty around values
Brandt 2010, Germany	43.5 (21-72) years; HL	• Participants of a retrospective observational trial • EQ-5D questionnaire was utilized. The transformation into an index value was accomplished by employing the German time-trade off (TTO) value set	• High-dose chemotherapy followed by peripheral blood stem cell transplantation • Conventional chemotherapy	98	Questionnaire completion rate • High-dose chemotherapy: 63% • Conventional chemotherapy: 65%	EQ-5D index • High-dose chemotherapy: 0.88 • Conventional chemotherapy: 0.92	NR	Yes	• German time trade off valuations for transformation into index values • Consistency with NICE reference case: No The utility data were calculated using the German TTO value set. EQ-5D responses were collected. ○ Described using standardized and validated instrument: Yes (EQ-5D) ○ TTO or SG: Yes, TTO ○ Representative sample of public: No	NR	Standard deviation • High-dose chemotherapy: 0.17 • Conventional chemotherapy: 0.13
Ruffer 2003, Germany, Switzerland, and Austria	31 (15-72) years; HL	NR	• Radiotherapy/ Combined modality treatment/ Chemotherapy	94	NR	NR	NR	NR	NR	NR	NR
Ng 2005, USA	44 (16-82) years; HL	NR	• Radiotherapy/ Chemotherapy/ Combined modality treatment	70	NR	NR	NR	NR	NR	NR	NR
Goodman 2008, USA	25 (5-47) years; HL	NR	• HDT + ASCR + Salvage therapy	218	NR	NR	NR	NR	NR	NR	NR
Magagnoli 2010, Italy	31 (NR) years; HL	NR	• IGEV + AHCT + HDCT	81	NR	NR	NR	NR	NR	NR	NR

Study name/ Country	Patient Pop (age; cHL/HL/ sALCL)	Information on recruitment	Intervention and comparator(s)	Smp size	Response rates	Description of health states	Adverse reactions	Appropriateness of health states	Method of elicitation/valuation Consistency with the reference case	Mapping	Uncertainty around values
Zsofia 2010, NR	43 (18-77) years; cHL	NR	• Radiotherapy/ Chemotherapy/ Combined modality treatment	44	NR	NR	NR	NR	NR	NR	NR
Minn 2012, USA	26 (10-63) years; HL	NR	• HDT + AHCR	154	NR	NR	NR	NR	NR	NR	NR
Semochkin 2013, NR	28 (22-41) years; HL	NR	• Dacarbazine • Vinblastine • ODPA • Radiotherapy	7	NR	NR	NR	NR	NR	NR	NR
Chen 2016, USA, Canada, and Europe	35 (18-76) years; cHL	NR	• Brentuximab vedotin	12	NR	NR	NR	NR	NR	NR	NR
Dada 2018, Saudi Arabia	26 (15-40) years; cHL	NR	• Nivolumab	10	NR	NR	NR	NR	NR	NR	NR
Ionova 2019, NR	28 (18-67) years; HL	NR	• Brentuximab vedotin	70	NR	NR	NR	NR	NR	NR	NR
Lepik 2019, NR	31 (19-62) years; cHL	NR	• Nivolumab	101	NR	NR	NR	NR	NR	NR	NR
Kreissl 2019, Germany	36 (18-60) years; HL	NR	• Chemotherapy/ Radiotherapy	97	NR	NR	NR	NR	NR	NR	NR
Shi 2019, China	33 (28-43) years; cHL	NR	• Sintilimab	96	NR	NR	NR	NR	NR	NR	NR

AHCR: Autologous haematopoietic cell rescue; AHCT: Autologous hematopoietic stem cell transplantation; ASCR: Autologous stem-cell rescue; cHL: Classical hodgkin lymphoma; CR: Complete response; HDCT: High dose chemotherapy; HDT: High dose chemoradiotherapy; HL: Hodgkin lymphoma; IGEV: Ifosfamide, gemcitabine, vinorelbine; NR: Not reported; PBSCT: Peripheral blood stem cell transplantation; PR: Partial response; SG: Standard gamble; TTO: Time trade off

B2. What filters were used for the bibliographic database searches for cost-effectiveness and health-related quality of life studies?

The search filter used for identifying economic studies is based on the SIGN (Scottish Intercollegiate Guideline Network) filter, an adaptation of the strategy designed by the National Health Service CRD York (https://www.sign.ac.uk/what-we-do/methodology/search-filters/). The quality of life search facet is based on the standard NICE guidance for literature search strategy development. We have supplemented these search words with additional QoL scale-specific measures, i.e., HL-specific QoL scales, based on the search of the existing medical literature.

B3. Does the PRISMA flow diagram (fig. 7, Appendix G) combine the results from the original search (completed July 15th 2016) and updated (March 2020) cost-effectiveness searches?

Yes, the PRISMA flow diagram is combined for the search estimates from the original and updated cost-effectiveness review.

B4. How were the update searches for cost-effectiveness completed to locate new records published since the original search? Was the same search strategy used in the original and update searches? Were the update bibliographic database searches date limited to identify new records published since July 15th 2016, or were search results deduplicated against the original search result set from July 15th 2016?

Yes, the same search strategy was used in the original and update searches (no addition or change to the search terms). We re-ran the search from the original starting date till March 2020. Records from the original search (till July 2016) were already screened and need not be reviewed again. To remove these records, we used deduplication, identified, and removed one of the matching pairs of records, leaving only new records for screening.

Utilities

B5. Please provide further clarity surrounding the estimation of utility values within the base case analysis. Please comment on the following:

a) **How was quality of life captured for patients in the progressed disease health state? The company submission (document B, page 209) states that quality of life questionnaires were completed until disease progression or up to one year of treatment. Please clarify.**

As per the trial protocol patient-reported outcomes (PROs) were assessed pre-dose at Cycle 1 (baseline), Cycle 3 (Week 6), Cycle 5 (Week 12), Cycle 7 (Week 18), and Cycle 9 (Week 24) and every 12 weeks thereafter until PD or up to 1 year while the subject is receiving study treatment. Also, PROs were obtained at discontinuation and at the 30-day Safety Follow-up Visit. If discontinuation occurred 30 days from the last dose of study treatment, i.e., at the time of the mandatory 30-day Safety Follow-up Visit, PROs were not needed to be repeated.

Patients in the progressed disease health status included any patients who had a documented PD (or Progressive Disease) during the study period. The treatment difference in the change from baseline for Quality of Life was estimated using the cLDA model. Additionally, a subgroup analysis was performed, based on progression status (yes, no) as determined by BICR where a progression was considered any time during the study, or before SCT for subjects with post-treatment SCT.

b) **What valuation set was used? Please provide a reference.**

A time trade-off (TTO) valuation technique was used to estimate the utilities based on Dolan (1997): Modelling valuations for EuroQol health states. Med Care 1997; 35(11): 1095-108

General clarification points

B6. Priority Question: The split of uptake (based on the KEYNOTE204 intention to treat [ITT] population) is stated to be 18%, 45% and 36% for the SCT-2L, SCT-3L

and SCT+3L subgroups respectively (company submission document B, page 228). Could you please confirm whether these proportions were used in the ITT economic analysis and correspond to the representation in KEYNOTE 204 of each of the three subgroups in the decision problem (SCT-2L, SCT-3L, SCT+3L)?

The split of uptake (18%, 45% and 36% for SCT-2L, SCT-3L and SCT+3L respectively) presented in document B page 228 corresponds to each of the three subgroups defined in the decision problem (i.e.18% of the ITT population is SCT-2L, 45% of the ITT is SCT-3L+ and 36% is SCT+3L+). Please note that these proportions were used in the model only as a scenario analysis in order to assign the relevant subsequent therapies to the ITT population based on clinical expert opinion (i.e. all patients on salvage chemotherapy (SCT-2L) will receive BV following progression, all patients on BV ineligible for transplant (SCT-3L+) will receive pembrolizumab and patients on BV who were r/r after ASCT (SCT+3L) will receive nivolumab).

B7. Priority Question: Please provide further information relating to the economic analyses for 3L subgroups. For both subgroups please comment on the specific list below and whether inputs or methods differ to those used in the ITT analysis:

c) **Utility values: Elicitation method and mean PFS and progressed disease values used for both treatment arms.**

Elicitation method and mean PF and PD utility values for the 3L subgroups were assumed as per the ITT population (see section B.3.4.1 of Document B)

d) **Adverse events: List of adverse events (AE) events and percentage of patients experiencing AEs in both treatment arms. Were AEs applied to the first cycle only in the model? What duration of events, disutilities and sources were used?**

The AEs and the percentage of patients experiencing AEs for the 3L subgroups were assumed as per the ITT population. For reference, a list of AEs for each 3L subgroup is provided below:

Subjects with Grade 3-5 Adverse Events
(Incidence ≥2% in One or More Group)

Subjects Who Are at Least Third Line with Prior Stem Cell Transplant (SCT+3L+)
(All-Subjects-as-Treated Population)

Study: 3475-204	Patients with Event n (%)	
System Organ Class PT	MK-3475 200 mg N[a] = 55	Brentuximab Vedotin N[a] = 56
Patients with one or more adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]

a: Number of patients: all-subjects-as-treated population.

Database Cutoff Date: [redacted]

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades are based on NCI CTCAE version 4.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

MedDRA version used is 22.1.

Subjects with Grade 3-5 Adverse Events
(Incidence ≥2% in One or More Group)
Subjects Who Are at Least Third Line Without Prior Stem Cell Transplant (SCT-3L+)

(All-Subjects-as-Treated Population)

Study: 3475-204	Patients with Event n (%)	
System Organ Class **PT**	**MK-3475 200 mg** **N[a] = 66**	**Brentuximab Vedotin** **N[a] = 69**
Patients with one or more adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]

a: Number of patients: all-subjects-as-treated population.

Database Cutoff Date: [redacted]

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades are based on NCI CTCAE version 4.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

MedDRA version used is 22.1.

AEs were applied in the first cycle of the model as per the ITT analysis. Duration of the AEs, disutilities and sources were assumed the same as per the ITT population.

e) **Treatment acquisition costs, dosing, administration and terminal care costs: Please provide inputs and assumptions used for both treatment arms and list sources.**

Treatment acquisition costs, dosing, administration cost and terminal care costs were assumed same as the ITT analysis. Please see sections B.3.5.4 and B.3.5.5 in Document B.

f) **Subsequent treatments: List of subsequent treatments used in both arms. What assumptions or sources were used to validate subsequent treatment use?**

Subsequent treatments for the 3L subgroups were assumed as per Table 143 (section B.3.9.2) and Table 145 (section B.3.9.3) for SCT+3L+, and SCT-3L+ respectively. These subsequent treatments were assumed based elicitation of clinical expert opinion.

g) **Stem cell transplant: Rates and costs used. Please list the sources used.**

Stem cell transplant rates for the 3L subgroups were based on the respective rates observed in KEYNOTE-204.

Table 2. Stem cell transplant rates for SCT+3L+ subgroup

	% Patients receiving Auto SCT	% Patients receiving Allo SCT
Pembrolizumab	[redacted]	[redacted]
BV	[redacted]	[redacted]

Table 3. Stem cell transplant rates for SCT-3L+ subgroup

	% Patients receiving Auto SCT	% Patients receiving Allo SCT
Pembrolizumab	[redacted]	[redacted]
BV	[redacted]	[redacted]

Stem cell transplant costs were based on the Radford et al (2017) [43] (as per the ITT population)

B8. The disaggregated cost table (company submission, appendix J, table 51) does not appear to include a breakdown of stem cell transplant costs. Please provide a breakdown of stem cell transplant costs for treatment arms.

Health state	Cost intervention (Pembrolizumab)	Cost comparator (BV)	Increment	Absolute increment	% Absolute increment
SCT costs	[redacted]	[redacted]	558	558	2.19%

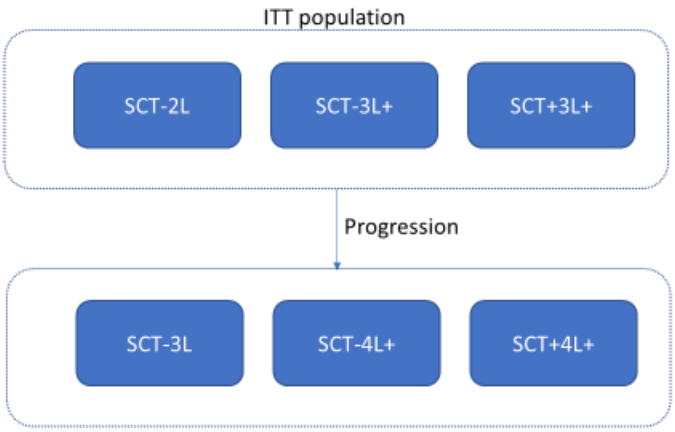
B9. Priority Question: It is unclear how the benefit of subsequent treatments is captured in the economic model. When a patient fails on primary treatment with either pembrolizumab or brentuximab vedotin, do they incur costs of subsequent treatment only, or does the model account for any subsequent treatment benefit in terms of PFS or OS apart from the degree to which that benefit is already included in the observed and extrapolated survival curves?

The benefit of subsequent treatments is included in the applied effectiveness curves and the model does not account for any other additional benefit. For example, when a patient fails on primary treatment with either pembrolizumab or BV and proceeds to subsequent treatment, they accrue the costs of the respective subsequent treatments (in ITT population, the subsequent treatments in base case were assumed as per the KEYNOTE-204 trial) while the benefit accrued is reflected in the applied effectiveness curves.

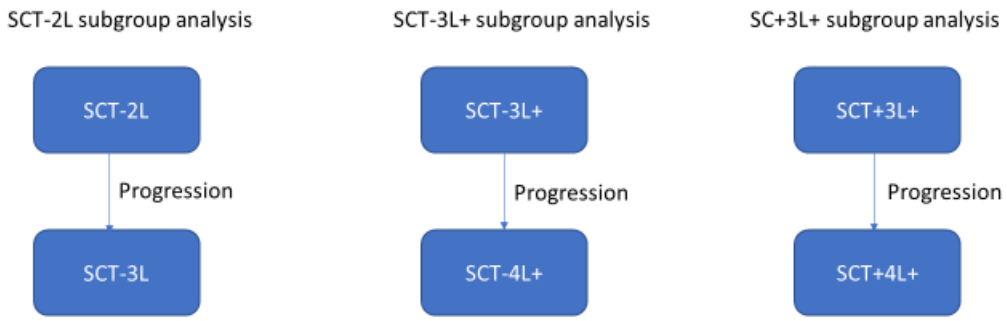
B10. Please provide a full diagram of the model explaining the cohort flow (mentioning at which line of therapy patients enter the model and how they progress thereon) for the ITT population and subgroups and highlight any differences between the ITT population and subgroups in this regard.

The ITT population is made of patients from the 3 subgroups i.e. : second line subjects with no prior stem cell transplant (“SCT-2L”), subjects who are at least third line with no prior SCT (“SCT-3L+”) and subjects who are at least third line with prior stem cell transplant (“SCT+3L+”).

In the base case the ITT population enters the model as per the lines of therapy mentioned above. Once they progress, patients proceed to the next line of therapy, ie patients in the 2L proceed to 3L, and patients in the 3L+ subgroups proceed to 4L+ lines. Please note that subsequent treatments in the base case of the ITT population were considered as per the subsequent treatments of KEYNOTE-204. A scenario analysis was run for the ITT to assign UK-specific subsequent treatments based on clinical expert opinion (see clarification question B6).



For each of the subgroup analyses the flow is as below. Please note that for simplification purposes, the subsequent treatments in each of the subgroup analysis were UK specific and based on clinical expert opinion.



B11. Please clarify the degree to which the treatment response (in terms of overall response, complete response and partial response/PR) has been captured in the model.

The effect of treatment response was not captured in the model. The model structure was based on the commonly used 3-state partitioned survival which captures the effect of OS and PFS. Further detail around the decision on model structure and health states is provided in document B.3.2.2.

B12. Please explain why the AE disutilities are applied at Cycle 0 only and not in the following cycles.

The approach of modelling AE disutilities as a one-off decrement at cycle 0 is consistent with previous cHL submissions (TA462 and TA540). The QALY loss in the model is estimated by combining data on the disutility values and mean duration of each AE. These were weighted by the respective AE incidence to give a one-off disutility applied in the first cycle of the model.

All of the AE treatment durations were shorter than one year which would make disutility*duration applied at cycle 0 equivalent to disutility applied per cycle for the duration of the AE. AE disutilities applied as a one-off decrement (disutility*duration) at cycle 0 are likely to overestimate the disutility due to discounting after the first year should the one-off disutilities be applied in later years.

Additional scenario analyses

B13. For the additional scenario analyses requested below please provide the results both with and without the pembrolizumab PAS. Please also provide the results for all subgroup analyses.

B14. It is understood that the base case economic analysis uses EU patient characteristics for several modelled parameters including weight and body surface area (company submission, document B, table 106). Please provide a

scenario analysis whereby patient characteristics from the whole ITT population are used.

Scenario analyses were run based on the patient characteristics of ITT KEYNOTE-204 population (see table below). The difference in the ICER was zero because in the base case, vial wastage is assumed for the BV and therefore, the weight does not impact the ICER.

Baseline patient characteristics in the KEYNOTE-204 trial (ITT population)

Characteristic	Mean
Age (years)	41.35
Female (%)	42.77
Weight (kg)	76.45
Body surface area (m^2)	1.9

ITT Population - With PAS

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.52	-24,981	0.00	0.59	Dominant

ITT Population - Without PAS

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.52	19,317	0.00	0.59	£32,905

SCT-2L Population - With PAS

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.58	28,018	0.00	0.52	53,558

SCT-2L Population - Without PAS

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.58	70,403	0.00	0.52	£134,578

SCT+3L+ Population - With PAS

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.55	-41,328	0.00	0.56	Dominant

SCT+3L+ Population - Without PAS

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.55	14,514	0.00	0.56	25,938

SCT-3L+ Population - With PAS

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-20,226	0.00	0.61	Dominant

SCT-3L+ Population - Without PAS

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-10,054	0.00	0.61	Dominant

B15. Priority Question: As an exploratory analysis, please incorporate a waning in pembrolizumab treatment effect over time; i.e. assume a gradual waning in treatment effect from Year 3, until there is no difference in PFS between treatments by Year 5.

MSD does not consider the application of treatment waning effect to PFS being valid or relevant to decision making and this request is inconsistent with previous submissions of immunooncology therapies where treatment waning is applied to OS only.

As detailed in document B (Table 109. Features of the economic analysis), equal OS curves were assumed for pembrolizumab and BV in the base case - based on published BV OS curves which is the most conservative way to represent the treatment effect in the absence of OS data from KEYNOTE-204 and would be more conservative than the application of a gradual treatment waning at OS after year 3 (since this would confer some benefit to the pembrolizumab arm as opposed to our approach to conservatively assume equal OS). Therefore, the application of treatment waning to PFS is not

appropriate as the base case is already at the extreme end of conservative for treatment benefits in OS and not consistent with previous ways in which treatment waning has been applied.

B16. Please provide a scenario analysis which assumes adverse events (for both pembrolizumab and brentuximab) occur for the duration of treatment.

Please see question B12. The application of AEs for the duration of the treatment may not be appropriate as AEs may resolve earlier, or continue after, treatment discontinuation. Costs and disutilities of AEs were applied - consistently with previous submissions - for the duration of the AE as a weighted average of the incidence at cycle 0.

B17. The ERG notes that 5-year OS and PFS estimates provided by clinical experts have been used for external validation of the model (company submission, document B, pages 194 and 199).

h) **Were survival estimates at other time points elicited? If so, please provide these.**

No other timepoints were elicited.

i) **The OS and PFS estimates cover both 2L and 3L patients who are ASCT-naïve. Were separate estimates for 2L and 3L patients elicited? If so, please provide these.**

Separate estimates were elicited but were not able to be provided by the clinicians since it was suggested that there is considerable uncertainty for the 2L subgroup due to the number of subsequent therapies and therapies available at later lines.

Model clarification

B18. The matrices reported in the Excel model worksheet 'Survival' (labelled 'Cholesky decomposition') do not appear to be Cholesky matrices (they are not

triangular). Please clarify and make any corrections. Are they the variance-covariance matrices? If not, please provide these.

The matrices reported in the Excel model worksheet are triangular Cholesky matrices.

An example of the generalised gamma matrix from the fully parametric fit to pembrolizumab fit is:

	Mu	Log(sigma)	Q
Mu	0.0168	~~0.0182~~	~~0.0930~~
Log(sigma)	0.0182	0.0266	~~0.1044~~
Q	0.0930	0.1044	0.6654

B19. The model user guide mentions the below:

"Two buttons for restoring default values are provided: one restores the default values within the active sheet; the other one restores all the default values in the model. These buttons can be found in the top left of any sheet which contains input cells".

However, there is no such button in any of the user input sheets. Please clarify if this is a deliberate omission.

This was an omission in the economic model. The user guide was written based on a standard template. At the time the model was finalised for NICE submission, the restore defaults functionality had not yet been programmed. The restore defaults function, as stated, would only remove the user inputs (white cells) and would not reset drop down menus.

B20. The results presented in the 'Scenario tables' sheet in the model do not seem to be aligned with results in the report even after the scenario analysis macro is re-run for the correct settings. Please clarify.

Please ignore the "Scenario tables", "Scenarios" and "Scenario results" tabs in the model. The scenarios presented in Document B section B.3.8.3 were run manually and individually for each of the scenario analyses presented.

B21. In the settings tab within the model (specifically the subgroup box), please state what patient populations subgroups 5, 6, 7 and 8 refer to.

Please ignore the subgroups 5-11 in the subgroup drop down list, this was a placeholder which should have been removed.

B22. The ERG notes that the model results for subgroups SCT-2L & SCT-3L do not match those given in the report (company submission, document B, Tables 142 & 146, respectively). This may be related to the proportions of the subsequent treatments for these subgroups.

Please check the analyses for the two subgroups and confirm the results for these.

The default results for SCT-2L & SCT-3L in the model do not match the results in Document B, because subgroups were run as scenario analyses i.e. the subsequent therapies were changed manually in the model before copying the results from the model.

When parameters are set in the model as per Table 141 (section B.3.9.1), Table 143 (section B.3.9.2) and Table 145 (section B.3.9.3) for SCT-2L, SCT+3L+, and SCT-3L+ respectively, results are:

Table 4. Cost effectiveness results for subgroup SCT-2L

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case for SCT-2L	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	Chemotherapy	[redacted]	4.98	3.58	28,018	0.00	0.52	£53,558
Alternative approach Trial based comparison	Pembrolizumab	[redacted]	4.98	4.09	--	--	--	
	Chemotherapy	[redacted]	4.98	3.49	21,279	0.00	0.59	£35,932

Table 5. Cost effectiveness results for subgroup SCT+3L+

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.55	-41,328	0.00	0.56	Dominant
Scenario 1 BV max cycles 16	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.55	-36,358	0.00	0.56	Dominant

Table 6. Cost effectiveness results for subgroup SCT-3L+

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-20,226	0.00	0.61	Dominant
Scenario 1 BV max cycles 16	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-10,878	0.00	0.61	Dominant
Scenario 2 (subsequent treatment from KEYNOTE-204)	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-26,194	0.00	0.61	Dominant

Section C: Textual clarification and additional points

C1. Please provide the following:

j) Figures with poor resolution or hard to read: Appendix N, figures 20 and 34

Figure 20. *PFS Model output for pembrolizumab vs. chemotherapy based on MAIC results*

Figure 34. Modelled OS applying log-normal extrapolation of Gopal (2015) to all treatments and modelled PFS applying a piecewise approach using a lognormal extrapolation from week 52, -3L+ subgroup

k) Missing figures: Appendix D, figures 2 and 3

Figure 2. Reconstructed Kaplan-Meier curve for OS; Balzarotti 2016

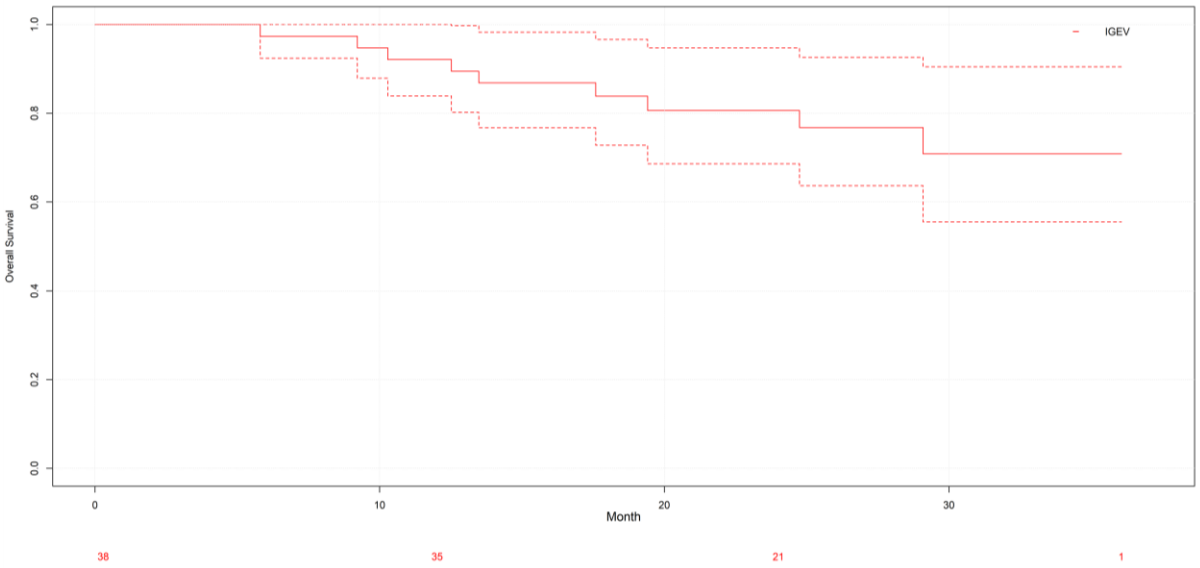
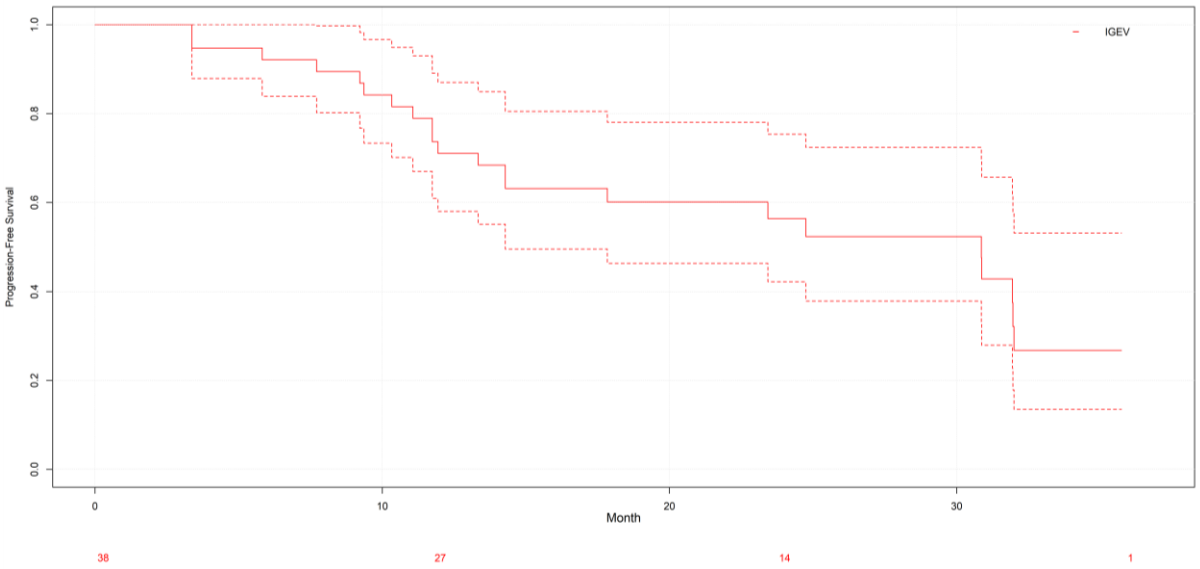


Figure 3 Reconstructed Kaplan-Meier curve for PFS; Balzarotti 2016



C2. Section D.1.1.3 states that "In addition to the 45 trials identified, the SLR identified 38 single arms, 6 RCTs, and 1 comparative trial, which were either conducted entirely in R/R HL populations or had a subgroup of R/R HL patients". The additional trials do not appear in the list of included studies, or the PRISMA

diagram (Fig 1). Please confirm that this sentence describes the 45 included studies in Table 5-9 and not additional trials.

MSD can confirm that this sentence describes the 45 included studies in Table 5-9 and not additional trials.

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Appendix to clarification questions

Please note that while updating the model for the clarification questions, a minor error was identified in the AE costs which had a minimal effect in the results (incremental costs changed by £21 for base case). Please find below the amended results for the ITT population, the subgroups as well as the scenario analyses run in section B.3.8.3 of the original submission.

Table 1. Cost effectiveness results– ITT population

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER incremental (£/QALY)**
Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
BV	[redacted]	4.98	3.52	-25,002	0.00	0.59	**Dominant**

Table 2. . Cost effectiveness results for subgroup ASCT-2L

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case for SCT-2L	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	Chemotherapy	[redacted]	4.98	3.58	28,030	0.00	0.52	£53,581
Alternative approach Trial based comparison	Pembrolizumab	[redacted]	4.98	4.09	--	--	--	
	Chemotherapy	[redacted]	4.98	3.49	21,292	0.00	0.59	£35,952

Table 3. Cost effectiveness results for subgroup +3L+

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.55	-41,349	0.00	0.56	Dominant
Scenario 1 BV max cycles 16	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	
	BV	[redacted]	4.98	3.55	-36,379	0.00	0.56	Dominant

Table 4. Cost effectiveness results for subgroup SCT-3L+

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG (pembro vs.)	Incremental QALYs (pembro vs)	ICER incremental (£/QALY) (pembro vs.)
Base case	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-20,248	0.00	0.61	Dominant
Scenario 1 BV max cycles 16	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-10,900	0.00	0.61	Dominant
Scenario 2 (subsequent treatment from KEYNOTE-204)	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	
	BV	[redacted]	4.98	3.49	-26,216	0.00	0.61	Dominant

Table 5. Key scenario analyses

Scenario		Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
	BV	[redacted]	4.98	3.52	-25,002	0.00	0.59	Dominant
Scenario 1 Time horizon 50 years	Pembrolizumab	[redacted]	5.00	4.12	--	--	--	--
	BV	[redacted]	5.00	3.54	-25,002	0.00	0.59	Dominant
Scenario 2 Time horizon 60 years	Pembrolizumab	[redacted]	5.00	4.13	--	--	--	--
	BV	[redacted]	5.00	3.54	-25,002	0.00	0.59	Dominant
Scenario 3 PFS fully parametric fit	Pembrolizumab	[redacted]	4.98	4.08	--	--	--	--
	BV	[redacted]	4.98	3.47	-24,464	0.00	0.61	Dominant
Scenario 4 PFS piecewise week 26	Pembrolizumab	[redacted]	4.98	4.10	--	--	--	--
	BV	[redacted]	4.98	3.50	-24,155	0.00	0.61	Dominant
Scenario 5 OS based on KEYNOTE-087 curves	Pembrolizumab	[redacted]	12.20	9.71	--	--	--	--
	BV	[redacted]	12.20	8.21	-24,173	0.00	1.49	Dominant
Scenario 6 OS based on predictive equation Gopal et al	Pembrolizumab	[redacted]	10.14	8.09	--	--	--	--
	BV	[redacted]	7.28	5.01	-13,691	2.86	3.08	Dominant
Scenario 7 utilities based on multivariate model	Pembrolizumab	[redacted]	4.98	4.06	--	--	--	--
	BV	[redacted]	4.98	3.60	-25,002	0.00	0.46	Dominant
Scenario 8 Pooled utilities post-progression	Pembrolizumab	[redacted]	4.98	4.03	--	--	--	--
	BV	[redacted]	4.98	3.74	-25,002	0.00	0.29	Dominant
Scenario 9 no AE disutilities	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
	BV	[redacted]	4.98	3.53	-25,002	0.00	0.59	Dominant
Scenario 10 Pembrolizumab dosing 400mg Q6W	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
	BV	[redacted]	4.98	3.52	-25,110	0.00	0.59	Dominant

Scenario 11	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
No vial wastage	BV	[redacted]	4.98	3.52	-19,591	0.00	0.59	Dominant
Scenario 12	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
BV maximum cycles set to 16	BV	[redacted]	4.98	3.52	-15,607	0.00	0.59	Dominant
Scenario 13	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
Subsequent treatments based on UK market shares	BV	[redacted]	4.98	3.52	-29,371	0.00	0.59	Dominant
Scenario 14	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
Subsequent treatments based on KEYNOTE--204 excluding pembrolizumab	BV	[redacted]	4.98	3.52	-22,837	0.00	0.59	Dominant
Scenario 15	Pembrolizumab	[redacted]	4.98	4.11	--	--	--	--
Resource use based on clinical expert opinion	BV	[redacted]	4.98	3.52	-31,927	0.00	0.59	Dominant

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma [ID1557]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Merck Sharp & Dohme - NA Takeda - £30,000 (support for information and education activities)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients	We have used information from UK-respondents to the Lymphoma Coalition's 2020 Global Patient Survey, which seeks to understand patient experience in lymphomas as well as the impact of treatment and care. A total of 679 people from the UK responded to the patient survey, 10% of whom had Hodgkin lymphoma. An additional 64 people responded to the caregiver survey, 6% of whom cared for a person with Hodgkin lymphoma.

and carers to include in your submission?	We also sent a survey to our network of patients and carers asking about specifically about their experience of current treatment for relapsed and refractory Hodgkin lymphoma and their opinions on pembrolizumab, with particular emphasis on quality of life. We received two responses from patients with relapsed or refractory Hodgkin lymphoma who had had at least two previous treatments, which we have used in this submission. We have also included information based on our prior experience with patients with Hodgkin lymphoma.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Around 2,100 people in the UK are diagnosed with Hodgkin lymphoma each year. The most common symptoms are swollen lymph nodes, often in the neck, armpit or groin but they can be in the chest, causing breathlessness. Symptoms can vary depending on where the lymphoma is growing. Systemic symptoms are common, including fevers, night sweats, unexplained weight loss, fatigue, loss of appetite and severe itching. Hodgkin lymphoma is treated with the aim of cure. Most people are treated with chemotherapy regimens ABVD or BEACOPPesc. However, around 10% of patients with early-stage disease and 20–30% with advanced disease are refractory to treatment or relapse after initial treatment. These patients are likely to be treated with salvage chemotherapy followed by stem cell transplant in patients who are able to tolerate it. For patients who relapse again, treatment options include more chemotherapy, brentuximab vedotin, nivolumab or pebrolizumab. Hodgkin lymphoma and its treatment significantly affect patients' quality of life. Just over half of patients report that symptoms and side effects of treatment negatively impact their social lives and the everyday activities they are able to do. Fatigue is the most commonly reported symptom, affecting around 3 in 4 people, and it can persist for many years. Patients report that this affects their work, physical activity and social activities. Fatigue, nausea and vomiting and infections are considered to be the most troublesome side effects. One patient who had had chemotherapy, radiotherapy, a stem cell transplant and nivolumab for Hodgkin lymphoma said, "The fatigue is the most difficult to manage over the long term – it may be from the lymphoma or the treatment. The fatigue and stress have often made it very difficult to contribute normally at work. I have no energy to do anything in the evening – my fatigue then can be overwhelming." Hodgkin lymphoma can also have a financial impact on patients and their families. One patient, who had been treated with ABVD and bretuximab vedotin (available second-line during the coronavirus pandemic), said, "I have not worked

	for almost 12 months, though fortunately the financial impact has been mitigated by insurance and a good company sick pay scheme." The emotional impact of lymphoma is also considerable. Around a third of patients experience depression, anxiety, isolation and loss of self-esteem, with even more (>40%) reporting fear of lymphoma progression or relapse. Over a quarter of patients say they feel overwhelmed by managing their lymphoma and many fee they do not get enough emotional or financial support to help them. About half of patients with Hodgkin lymphoma report needing information on psychological support and counselling, with around 1 in 3 listing that access to support for their families would be beneficial. One patient with relapsed Hodgkin lymphoma said, "There were periods earlier when I felt death was very near, and that was a very difficult time emotionally. I have also had to deal with a lot of uncertainty, and although my condition is now stable, fear can overtake me when I experience even mild symptoms." From a practical viewpoint, patients with Hodgkin lymphoma find the treatments and associated blood tests and waiting times a huge time commitment. Travel costs and transport logistics can also be an issue for patients who live some distance away from their treatment centre. The impact of Hodgkin lymphoma extends beyond the patient to their carers and families. One patient said, "Having two small children, the impact on myself and my family has been huge." Carers provide emotional support, practical support with transport, help with personal care, errands and household chores, and many also take responsibility for managing finances and healthcare appointments. They provide an essential role in supporting people affected by lymphoma, but this is a huge psychological and emotional burden. Almost all caregivers report feeling worried or anxious, and scared by the prospect of their loved ones' lymphoma relapsing. One patient with relapsed Hodgkin lymphoma told us how stressful it was for their partner trying to manage their work around treatment and increased childcare responsibilities, and how their partner had really suffered emotionally.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current	Most people with Hodgkin lymphoma are treated with chemotherapy, sometimes followed by radiotherapy. High-dose chemotherapy regimens might be used. For relapsed or refractory Hodgkin lymphoma, salvage chemotherapy followed by stem cell transplant is the most common treatment option. Treatment is very intense and some people are not able to tolerate it. People who experience a subsequent relapse might be treated with more chemotherapy or targeted

treatments and care available on the NHS?	treatments such as brentuximab vedotin, nivolumab or pebrolizumab. At present, these less toxic options are only available for people who have either relapsed after a stem cell transplant or who are not able to have a stem cell transplant. One patient who had received multiple lines of treatment for Hodgkin lymphoma said, "I am grateful for the treatment I have received on the NHS, but I have found it inadequate on multiple occasions." In particular, the patient felt that more effective, better tolerated – and less risky – treatment options should be available earlier in the treatment pathway and that at many points in their pathway, the options available on the NHS were very limited. When they experienced a relapse after an autologous stem cell transplant, the patient resorted to private treatment to enable them to access a combination of brentuximab vedotin and nivolumab rather than undergo an allogeneic stem cell transplant on the NHS. Patients feel that current treatment options for relapsed or refractory Hodgkin lymphoma are difficult to cope with. Most patients experience significant side effects, such as fatigue, nausea, pain and hair loss, and many go on to develop late effects. One patient told us how treatment left them unable to care for their children – with emotional as well as physical consequences. Treatment has a long-lasting impact on physical and mental wellbeing. However, patients are grateful that treatment has given them another chance. One patient described how daunted they feel at the prospect of a stem cell transplant, which will be an inevitable part of their treatment once they achieve a remission.
8. Is there an unmet need for patients with this condition?	Patients feel there is a definite unmet need for an effective, less demanding treatment with fewer side effects and will therefore allow a better quality of life. One patient commented, "Many of the options after failure of initial treatment do not have especially high success rates. This is not very reassuring." The three most important factors patients with lymphoma rate in a treatment are, in order: effectiveness (in terms of improved survival or response rates); quality of life; and tolerability.
Advantages of the technology	

9. What do patients or carers think are the advantages of the technology?	Patients feel that the high response rate to pembrolizumab, combined with its tolerability profile, offer a significant advantage over many other treatments. Patients feel that pembrolizumab has a more favourable side effect profile than most other treatments for relapsed and refractory Hodgkin lymphoma, which 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. It is also likely to have a much lower impact on family life, since it does not require prolonged hospital stays and the less troublesome side effects allow patients to carry on with day-to-day activities. Two patients who had been treated with a similar checkpoint inhibitor experienced far less onerous side effects with the checkpoint inhibitor than with the radiotherapy, chemotherapy or stem cell transplant they had previously had. The targeted treatment allowed them to carry on with a more 'normal' family life. One commented, "I don't know how I would have managed my son's school years on those other treatments."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all treatments, patients were concerned about the potential side effects. One noted that many of the potential side effects are similar to lymphoma symptoms, which can make it hard for a patient to feel reassured that treatment is working. This can have an emotional impact. Another felt the uncertainty of a long-term remission was a disadvantage, although felt that this was partly offset by the high short-term response rate.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	One patient felt that people who found it hard to tolerate chemotherapy side effects might in particular benefit from pembroizumab.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	Given the current coronavirus pandemic, it is more important than ever to consider the potential benefits of well tolerated treatments that can be safely administered in the outpatient setting.
14. What is the proportion of people with relapsed or refractory Hodgkin's lymphoma who did not have at least two prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option and for whom brentuximab vedotin is not licenced? And what treatment would they be given?	

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • Relapsed or refractory Hodgkin lymphoma is rare – but when it develops, it has a significant physical, psychological and financial impact on patients and their families. • Current treatments for relapsed or refractory Hodgkin lymphoma are typically very intensive and incur serious side effects and late effects. • Targeted treatments are generally not available early in the treatment pathway and more toxic treatments (such as stem cell transplants) place a huge burden on patients and their families. • Patients feel that pembrolizumab has the potential to offer a convenient, outpatient treatment with high response rates. • The favourable tolerability profile of pembrolizumab is viewed as a significant advantage over many other treatment options.

Thank you for your time.

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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

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
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Author Contributions:

Maxwell S. Barnish	Project managed the ERG team and critiqued the clinical effectiveness evidence.
Brian O'Toole	Critical appraisal of the economic evidence, writing and editorial input, and co-supervised the final report
David Packman	Critical appraisal of the economic evidence, checked and re-analysed the economic model, carried out further scenario analyses, and drafted economic sections of the report
Madhusubramanian Muthukumar	Critical appraisal of the economic evidence, checked and re-analysed the economic model, carried out further scenario analyses, and drafted economic sections of the report
Justin Matthews	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report
Naomi Shaw	Critical appraisal of the search methods and editorial input.
Claudius Rudin	Clinical advice and review of draft report.
Louise Crathorne	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report. Guarantor of the report.

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Abbreviations

AEs	Adverse events
AFT	Accelerated failure time
AIC	Akaike's information criterion
ASaT	All Subjects as Treated
ASCT	Autologous stem cell transplantation
AUC	Area under the curve
-ben	Bendamustine
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BV	Brentuximab vedotin
CAA	Commercial access agreement
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
ChiVPP	Chlorambucil with vinblastin, procarbazine and prednisolone
CI	Confidence interval
CR	Complete response
CS	Company submission
DHAP	D – dexamethasone; HA – high dose Ara C, also known as cytarabine; P – cisplatin
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EQ-5D	EuroQol 5 dimensio
ERG	Evidence Review Group
ESHAP	E – etoposide; S – solu-medrone (also called methylprednisolone); HA – high dose cytarabine, also known as Ara C; P – cisplatin
ESR	Erythrocyte sedimentation rate
ESS	Effective sample size
GDP	G – gemcitabine, d - dexamethasone, C – cisplatin
-Gen Gam / -GG	Generalised gamma
HL	Hodgkin's lymphoma
HR	Hazard ratio

HRQoL	Health-related quality of life
HTA	Health technology assessment
ICE	I – ifosfamide; C – carboplatin; E – etoposide
ICER	Incremental cost-effectiveness ratio
IGEV	I – ifosfamide; G – gemcitabine; V – vinorelbine
IPD	Individual patient data
ITT	Intention to treat
IWG	International Working Group
KM	Kaplan-Meier
LY	Life year(s)
MAIC	Matched adjusted indirect comparison
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
-nivo	nivolumab
NMA	Network meta-analysis
NR	Not reported
NS	Not stated
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD	Progressed disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
pembro	pembrolizumab
PET	Positron emission tomography
PET-CT	Positron emission tomography and computed tomography (scan)
PFS	Progression free survival
PICOS	Population Intervention, Comparator, Outcomes, Study Design
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services

PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
R/R	Relapsed/refractory
R/RcHL	Relapsed/refractory classic Hodgkin's lymphoma
SCT	Stem cell transplantation
SCT-2L	Patients with R/RcHL who did not have at least two prior therapies when autologous stem cell transplant is not a treatment option
SCT+3L+	Patients with R/RcHL who are at least third line with prior stem cell transplant.
SCT-3L+	Patients with R/RcHL who are at least third line when autologous stem cell transplant is not a treatment option
SG	subgroup
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TA	Technology appraisal
TAG	Technology Appraisal Guidance
TLR	Targeted literature review
ToT	Time on treatment
TTO	Time trade off
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
vs	Versus
WTP	Willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3, 1.4, 1.5, and 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1. Overview of the ERG's key issues

A brief overview of the key issues identified by the ERG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

Broadly speaking the key clinical issues related to immaturity of overall survival data, the matched-adjusted indirect comparison (MAIC) and the generalisability to UK clinical practice of the intention to treat (ITT) analyses. In terms of cost effectiveness issues, the ERG noted uncertainty surrounding the extrapolation of OS and PFS, estimation of base case utility values (particularly the PD health state), inclusion of SCT rates, assumptions relating to subsequent treatment usage and calculation of time on treatment (ToT) costs as well as health state resource use costs for the PD health state.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
Key Issue 1: Immaturity of overall survival data	The immaturity of OS data in the key trial, meaning no directly observed comparative OS data were available for use in the economic model	Section 3.2.5.1
Key Issue 2: How reliable is the comparison of pembrolizumab with standard of care made by the MAIC	The matched adjusted indirect comparison (MAIC) analysis was only conducted with regard to one potential 2L salvage chemotherapy regimen (IGEV) and is therefore not generalizable to the full range of	Section 3.3

for the SCT-2L subgroup?	regimens used in clinical practice in the UK	
Key Issue 3: Generalisability of the intention to treat (ITT) population to UK clinical practice	The intention to treat (ITT) analysis is not generalizable to the UK treatment pathway, since there are three clear subgroups (SCT-2L, SCT-3L+ and SCT+3L+), not all of which have BV as a relevant comparator.	Section 3.2.1
Key Issue 4: Uncertainty in PFS estimation in the SCT-2L subgroup	There are no head-to-head data comparing pembrolizumab to chemotherapy within this subgroup. The company has therefore conducted a MAIC to estimate clinical effectiveness.	Section 4.2.6.2
Key Issue 5: Uncertainty in the maintenance of PFS benefit associated with pembrolizumab after treatment discontinuation in Year 2	The incremental QALY gain associated with pembrolizumab was driven by the difference in PFS between treatments. A key assumption (which is applied in all subgroups) is that after treatment discontinuation (Year 2), PFS will not be affected i.e. the proportion of patients in the PFS health state will continue to follow the chosen extrapolation curve over time.	Sections 3.2.5.2 and Section 6.2.1.3
Key Issue 6: Utility values used in the progressed disease (PD) health state for pembrolizumab	There is uncertainty surrounding the base case pembrolizumab PD health state utility value, which appears to lack plausibility.	Sections 4.2.7 and 6.2.1.1
Key Issue 7: Uncertainty in subsequent treatments and assumed proportions in the company's base case analysis	There is uncertainty surrounding the company's base case assumptions with respect to subsequent treatment usage.	Sections 4.2.8.3 and 6.2.1.13
Key Issue 8: Gopal et al. (2015) should not be used as the primary source of OS for all subgroups	It was assumed that OS from Gopal et al. (2015)[1] was generalisable to all subgroups. However, given that patients in Gopal et al. (2015), were those who had a prior SCT (reflecting the SCT+3L+ subgroup) there was some concern surrounding the generalisability of OS estimates to the subgroups.	Section 3.2.5.1
Key Issue 9: Time on treatment (ToT) for BV in SCT-3L+ and SCT+3L+ subgroups	The company assumed that patients treated with BV will receive the same maximum ToT as pembrolizumab (35 cycles). However, as per the SmPC for BV, treatment should be provided for a maximum of 16 cycles.	Section 4.2.8.2

Abbreviations: BV, brentuximab vedotin; ITT intention to treat; MAIC, matched adjusted indirect comparison; OS, overall survival; PD, progressed disease; PFS, progression free survival; SCT, stem cell transplant; ToT, time on treatment

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and ERG's preferred assumptions

	Company's preferred assumption	ERG preferred assumption	Report Sections
Population	The company has presented an ITT analysis as the base case for consideration (with subgroup analyses results provided for information)	The ERG preferred to individually appraise each subgroup.	Sections 4.2.3 and 4.2.4
OS	The company prefer to use one clinical study (Gopal et al., 2015)[1] to estimate OS for all subgroups.	The ERG preferred to use Balzarotti et al. (2016)[2] for SCT-2L and SCT-3L+, and Gopal et al. (2015)[1] for SCT+3L+	Section 4.2.6.1
PFS	The company preferred to model PFS using a 52-week cut point (ITT population and SCT-3L subgroups).	The ERG preferred to model PFS using a 26-week cut point.	Section 4.2.6.2
Utilities	The company prefer to use treatment specific QoL data from KEYNOTE-204[3] to estimate both the PFS and PD health state utilities.	The ERG preferred to assume no difference in PD utility between treatments (applying the same value to both treatment arms).	Section 4.2.7
ToT	The company preferred to model ToT using an 80-week cut point.	The ERG preferred to model ToT using a 26-week cut point.	Section 4.2.8.2
Maximum number of treatment cycles	The company preferred to assume that BV would require a similar maximum number of treatment cycles to pembrolizumab (35 cycles).	The ERG preferred the SmPC estimate of a maximum of 16 cycles to be used for BV.	Section 4.2.8.1
SCT rates	The company preferred to use SCT rates from KEYNOTE-204.[3]	The ERG preferred to remove differences in SCT rates between treatments from the model.	Section 4.2.8.4

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ITT intention to treat; OS, overall survival; PD, progressed disease; PFS, progression free survival; QoL, quality of life; SCT, stem cell transplant; SmPC, summary of product characteristics; ToT, time on treatment

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Improving the quality of life of patients in both the PFS and PD health states. The model estimates that patients receiving pembrolizumab have a higher utility value in both the PFS and PD states compared to the comparator (BV). The incremental QALY gain associated with pembrolizumab is therefore due to a higher proportion of patients remaining progression free and the associated higher quality of life with being in both the PFS and PD health state, versus the comparator.
- Increasing the proportion of patients in the PFS health state. The model estimated a higher proportion of patients on pembrolizumab would remain progression free compared to those receiving the comparator treatment (brentuximab vedotin [BV]).
- The ERG noted that the model does not estimate pembrolizumab to have an effect on OS, compared to the comparator treatment (BV). Due to the OS modelling approach adopted by the company, whereby a single OS curve was assumed to apply to both treatments, pembrolizumab does not result in an incremental life year (LY) gain versus the comparator treatment.

Overall, the technology is modelled to affect costs by:

- Lowering medicine acquisition costs, compared to BV, in ITT, SCT-3L+ and SCT+3L+ subgroups. The model therefore assumes that, at list price, pembrolizumab as a treatment strategy will be cheaper than BV.
- Including a two-year stopping rule for pembrolizumab which assumes that patients do not continue on treatment after this time point. Treatment costs are therefore capped at two years in the model.
- Subsequent treatment usage. Modelled results are sensitive to subsequent treatment assumptions.

The modelling assumptions that have the greatest effect on the ICER are:

- Base case utility values.
- The distribution of subsequent treatments, which may vary between clinical practice, treatments that are relevant for this appraisal (e.g. CDF-only treatments) and trial data. For SCT-3L+, pembrolizumab is positioned as a subsequent treatment but is a CDF-only drug and is thus not routinely commissioned.
- The assumption of a long-term PFS benefit for pembrolizumab, in interaction with utility values. A key model assumption relates to the maintenance of pembrolizumab treatment benefit (with respect to PFS state membership) over time, despite treatment discontinuation at Year 2.

1.3. The decision problem: summary of the ERG's key issues

The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal, and identified no key issues with the decision problem.

1.4. The clinical effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the clinical effectiveness and safety evidence presented in the CS, and identified the following key issues for consideration by the committee.

Key Issue 1: Immaturity of overall survival data

Report sections	**3.2.5.1**
Description of issue and why the ERG has identified it as important	No mature OS data were provided from the pivotal KEYNOTE-204[3,4] trial since median OS had not been reached. This meant that no directly comparative OS data for pembrolizumab and BV were available to inform the economic model.
What alternative approach has the ERG suggested?	The ERG conducted additional scenario analyses using OS data from published studies including KEYNOTE 087,[5] Balzarotti et al. (2016)[2] and Gopal et al. (2015)[1]
What is the expected effect on the cost-effectiveness estimates?	The impact of these scenario analyses on the ICER was minimal, given that the same data are used to model OS for both pembrolizumab and comparator treatment arms (see Section 3.2.5.1).
What additional evidence or analyses might help to resolve this key issue?	Mature OS data from KEYNOTE-204[3,4] will be key to resolving this uncertainty.

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; OS, overall survival

Key Issue 2: How reliable is the comparison of pembrolizumab with standard of care made by the MAIC for the SCT-2L subgroup?

Report sections	3.3
Description of issue and why the ERG has identified it as important	The company carried out unanchored MAIC for SCT-2L subgroup for pembrolizumab vs salvage chemotherapy. However, this analysis is susceptible to bias arising from any missing prognostic factors or effect modifiers and is limited by a small effective sample size and the inclusion of only one salvage chemotherapy regimen.
What alternative approach has the ERG suggested?	The ERG has not carried out additional MAIC analyses given the limitations of the analysis and the available data.
What is the expected effect on the cost-effectiveness estimates?	The impact on cost-effectiveness estimates is uncertain.
What additional evidence or analyses might help to resolve this key issue?	An analysis that draws on a richer data set with larger sample size, for example routinely collected data, may produce a more robust analysis and resolve remaining uncertainty in the impact of pembrolizumab as compared to salvage chemotherapy regimens.

Abbreviations: ERG, Evidence Review Group; MAIC, matched adjusted indirect comparison; SCT, stem cell transplant; SoC, standard of care

Key Issue 3: Generalisability of the intention to treat (ITT) population to UK clinical practice

Report sections	3.2.1
Description of issue and why the ERG has identified it as important	The company presented intention to treat (ITT) results from KEYNOTE-204[3,4] as the primary clinical effectiveness data to inform its economic model. The ITT analysis included SCT-2L, SCT-3L+ and SCT+3L+ patients. These three patient groups do not have a common comparator – since salvage chemotherapy is the relevant comparator for the SCT-2L group and BV is the relevant comparator for the other 2 groups. This means that the ITT population does not generalise to the UK treatment pathway in clinical practice.
What alternative approach has the ERG suggested?	Due to the concern surrounding the plausibility of an overall ITT population, the ERG was of the opinion that each subgroup should be assessed individually.
What is the expected effect on the cost-effectiveness estimates?	The company has provided cost effectiveness results for each subgroup. The ICER presented for each subgroup differs to the ITT ICER due to

	differences in comparator, clinical effectiveness data and subsequent treatment usage.
What additional evidence or analyses might help to resolve this key issue?	Additional clinical advice to confirm the generalisability of the trial and its subgroups to UK clinical practice would resolve uncertainty. In addition, clinical evidence targeted at subgroups relevant to UK clinical practice (e.g. for SCT-2L) would reduce uncertainty about generalisability.

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival; PFS, progression free survival

1.5. The cost effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the economic model and cost-effectiveness evidence presented in the CS, and identified the following key issues for consideration by the committee.

Key Issue 4: Uncertainty in PFS estimation in the SCT-2L subgroup

Report sections	**4.2.6.2**
Description of issue and why the ERG has identified it as important	There are no head-to-head data comparing pembrolizumab to chemotherapy within this subgroup. The company has therefore conducted a MAIC to estimate clinical effectiveness. The ERG noted that the PFS benefit associated with pembrolizumab is being driven by an imprecise HR, due to the small sample size of patients within the MAIC. There is considerable uncertainty surrounding the pembrolizumab treatment effect within this subgroup.
What alternative approach has the ERG suggested?	The ERG noted that although the clinical effectiveness results are highly uncertain, the company appears to have used best available evidence to generate treatment effect for this subgroup. The ERG acknowledged that a scenario analysis which removes the pembrolizumab PFS benefit could be conducted. However, given that a conservative assumption has already been adopted by the company with respect to OS modelling, this scenario would be considered overly pessimistic.
What is the expected effect on the cost-effectiveness estimates?	A scenario which assumed no difference in PFS between treatments would result in a cost minimisation analysis, given that the incremental QALY gain associated with pembrolizumab stems from improved PFS alone. However, pembrolizumab would not be considered a cost

	saving treatment in this scenario. The ERG did not consider this to be a plausible scenario.
What additional evidence or analyses might help to resolve this key issue?	Conducting a cost minimisation analysis would address uncertainty surrounding the long-term benefit of pembrolizumab with respect to PFS, however, the scenario analysis lacks validity. Therefore, the ERG considered that the issue should be noted as an area of significant uncertainty and that the results for the SCT-2L subgroup should be interpreted with caution. Additional, more robust clinical evidence considering the range of salvage chemotherapies and additional sources of real-world data would assist in resolving this uncertainty.

Abbreviations: ERG, Evidence Review Group; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival; PFS, progression free survival

Key Issue 5: Uncertainty in the maintenance of PFS benefit associated with pembrolizumab after treatment discontinuation in Year 2

Report sections	**3.2.5.2 and 6.2.1.3**
Description of issue and why the ERG has identified it as important	The ERG noted that the incremental QALY gain associated with pembrolizumab was driven by the difference in PFS between treatments. A key assumption (which is applied in all subgroups) is that after treatment discontinuation (Year 2), PFS will not be affected i.e. the proportion of patients in the PFS health state will continue to follow the chosen extrapolation curve over time. The ERG considered this assumption to be highly uncertain, given a lack of long-term clinical effectiveness data supporting this assumption.
What alternative approach has the ERG suggested?	Clinical opinion to the ERG has noted that it may be plausible for some patients to continue receive PFS benefit after stopping treatment, however the extent of this benefit in terms of duration is not clear. The ERG requested the company provide a scenario analysis which incorporated a waning in pembrolizumab treatment effect from Year 3, until no difference was assumed between treatments in Year 5. The company did not provide this analysis citing a lack of precedent for this type of scenario and that a conservative approach had already been adopted in the base case analysis with respect to OS. As an exploratory analysis the ERG has conducted this scenario.

What is the expected effect on the cost-effectiveness estimates?	This scenario analysis resulted in an increased ICER for pembrolizumab, given that PFS, in interaction with utility values, is a driver of the incremental QALY gain within the model.
What additional evidence or analyses might help to resolve this key issue?	Longer term data are required to address uncertainty surrounding maintenance of treatment effect.

Abbreviations: ERG, Evidence Review Group; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year

Key Issue 6: Utility values used in the progressed disease (PD) health state for pembrolizumab

Report sections	**4.2.7 and 6.2.1.1**
Description of issue and why the ERG has identified it as important	The ERG considered utility values were uncertain due to the following; • Small patient numbers and limited QoI data collection with respect to the estimation of PD values. • Clinical opinion to the ERG, outlined that the value used in the pembrolizumab PD health state was somewhat high and lacked face validity. Furthermore, patients in this health state have a higher quality of life than those on BV, who are progression free. Due to the uncertainty surrounding the pembrolizumab PD utility value, the incremental QALY gain associated with pembrolizumab appears to be overestimated.
What alternative approach has the ERG suggested?	The ERG conducted a scenario analysis that applies the BV PD utility value ([redacted]) to both treatment arms. See Section 4.2.7.
What is the expected effect on the cost-effectiveness estimates?	This scenario analysis resulted in a reduction in incremental QALYs for pembrolizumab (and increased ICER).
What additional evidence or analyses might help to resolve this key issue?	Additional data and more robust estimation of utility values post-progression, alongside a clear clinical rationale for differential utilities post-progression, would assist in resolving this uncertainty.

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; PD, progressed disease; QALY, quality adjusted life year; QoL, quality of life

Key Issue 7: Uncertainty in subsequent treatments and assumed proportions in the company's base case analysis

Report sections	4.2.8.3 and 6.2.1.13
Description of issue and why the ERG has identified it as important	• The ERG did not consider an ITT population to be appropriate for decision making therefore the subsequent treatments and proportions used for this analysis should be interpreted with caution. • For the SCT-3L+ subgroup, the company assumed that patients who failed on BV go on to receive pembrolizumab. The ERG noted that pembrolizumab is a CDF treatment, therefore it is not routinely commissioned and this assumption is not appropriate. • For the SCT+3L+ subgroup, the company assumed that 100% of patients who failed on pembrolizumab go on to receive BV. However, the ERG understood that nivolumab is the most appropriate subsequent treatment for use. Therefore, the company's base case assumption potentially underestimates costs for pembrolizumab. ERG preference for Nivolumab as subsequent therapy in this subgroup was based on the current treatment pathway, however clinical opinion to the ERG noted that BV could potentially be used. • There were some discrepancies between modelled subsequent treatments and those reported in the CS.
What alternative approach has the ERG suggested?	The ERG undertook scenario analyses using alternative subsequent treatment assumptions. See Section 6.2.1.13.
What is the expected effect on the cost-effectiveness estimates?	Altering subsequent treatments had a substantial impact on the subgroup results, resulting in increased ICERs for pembrolizumab.
What additional evidence or analyses might help to resolve this key issue?	In subgroups where subsequent treatments are poorly understood, routinely collected data could inform more realistic assumptions.

Abbreviations: BV, brentuximab vedotin; CDF, Cancer Drugs Fund; CS, company submission; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention to treat

Key Issue 8: Gopal et al. (2015) should not be used as the primary source of OS for all subgroups

Report sections	3.2.5.1
Description of issue and why the ERG has identified it as important	It is assumed that OS from Gopal et al. (2015)[1] is generalisable to all subgroups. However, given that patients in Gopal et al. (2015), were those had a prior SCT (reflecting the SCT+3L+ subgroup) there was some concern surrounding the generalisability of OS estimates to the subgroups. Furthermore, based on clinical opinion to the ERG (and clinical opinion provided to the company), it may be reasonable for OS to differ according to subgroup.
What alternative approach has the ERG suggested?	The ERG has sought to validate the company's modelled base case OS estimates via clinical expert opinion. See Section 4.2.6.1 In addition, the ERG proposed that the following sources be used to estimate OS within the submission: • SCT-2L: Balzarotti et al. (2016)[2] • SCT+3L+: Gopal et al. (2015)[1] • SCT-3L+: Balzarotti et al. (2015)[2] The ERG was aware that OS data from KEYNOTE 087[5] are available and have therefore conducted additional scenario analyses using this study (see Section 6.2.1.10).
What is the expected effect on the cost-effectiveness estimates?	Given that a conservative approach to modelling OS has been adopted the use of alternative data sources for OS as outlined by the ERG may not have a material impact on the ICER, but may improve the plausibility of estimates for life-years gained and thus QALYs gained. PFS is the key driver in this submission.
What additional evidence or analyses might help to resolve this key issue?	Mature OS data from KEYNOTE-204 along with clinical validation of OS estimates would address outstanding uncertainty surrounding OS extrapolation. In the absence of mature OS data, exploration of larger and more robust datasets (e.g. routinely collected data) that could inform OS assumptions may inform a more appropriate range of scenarios for OS.

Abbreviations: ERG, Evidence Review Group

Key Issue 9: Time on treatment (ToT) for BV in SCT-3L+ and SCT+3L+ subgroups

Report sections	4.2.8.2
Description of issue and why the ERG has identified it as important	The company assumed that patients treated with BV receive the same maximum ToT as pembrolizumab (35 cycles). However, as per the SmPC for BV, treatment should be provided for a maximum of 16 cycles. The ERG considered the company's base case assumption to be inappropriate and leads to an overestimation of BV treatment costs.
What alternative approach has the ERG suggested?	Assuming a maximum number of treatment cycles of 16 is the ERG's preferred assumption. The ERG conducted this scenario analysis. For completeness, the ERG also conducted a number of ToT scenarios including use of KM data only (no extrapolation) and the use of alternative extrapolation points (26 weeks and 52 weeks).
What is the expected effect on the cost-effectiveness estimates?	Assuming a maximum number of 16 cycles (for BV) will result in lower acquisition costs for BV and an increased ICER for pembrolizumab.
What additional evidence or analyses might help to resolve this key issue?	Data reflecting the use of BV in clinical practice, including in terms of 'real-world' utilisation of BV by subgroups relevant to UK clinical practice, would inform more realistic ICER estimates.

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ToT, time on treatment

1.6. Other key issues: summary of the ERG's views

No other key issues were identified.

1.7. Summary of ERG's preferred assumptions and resulting ICER

A summary of ERG's preferred assumptions and resulting ICER is provided for each subgroup in Table 3 (SCT-2L), Table 4 (SCT-3L+), and Table 5 (SCT+3L+).

Table 3: Summary of ERG's preferred assumptions and ICER (SCT-2L)- includes pembrolizumab PAS

Preferred assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Company base-case deterministic	[redacted]	[redacted]	£53,581
ERG corrected company base case (deterministic)	[redacted]	[redacted]	£53,099

ERG corrected company base case (probabilistic)	[redacted]	[redacted]	£56,446
ERG corrected company base case used as start point for ERG analyses, below			
Scenario 14: Balzarotti et al (2016) used as the data source for estimating OS for both pembrolizumab and chemotherapy (IGEV) - Key Issue 8	[redacted]	[redacted]	£41,007
Scenario 1: Utility value for PD health state set to [redacted] for both treatment arms - Key Issue 6	[redacted]	[redacted]	£94,319
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	£89,930
Scenario 5: No difference in SCT rates between treatment arms (apply pembrolizumab allo-SCT and auto SCT rate to both arms)	[redacted]	[redacted]	£109,876
Scenario 6: Dose intensity for pembrolizumab assumed to be 100%	[redacted]	[redacted]	£112,387
Scenario 8: Time horizon increased to 50 years	[redacted]	[redacted]	£112,284
Scenario 11: 26-week data cut point for ToT	[redacted]	[redacted]	£202,428
ERG base case (deterministic)*	[redacted]	[redacted]	£202,428
ERG base case (probabilistic)	[redacted]	[redacted]	£176,859

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; SCT, stem cell transplant

Notes: * ERG base case combines all preferred scenarios

Table 4: Summary of ERG's preferred assumptions and ICER (SCT-3L+)- includes pembrolizumab PAS

Preferred assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Company base-case	[redacted]	[redacted]	Dominant (-£33,316)
Company base case used as start point for ERG analyses, below			
Scenario 14: Balzarotti et al (2016) used as the data source for estimating OS for both pembrolizumab and chemotherapy- Key Issue 8	[redacted]	[redacted]	Dominant (-£24,450)
Scenario 22: Semi parametric approach to modelling PFS (cut point for PFS set at 26 weeks)	[redacted]	[redacted]	Dominant (-£27,163)
Scenario 1: Utility value for PD health state set to [redacted] for both treatment arms - Key Issue 6	[redacted]	[redacted]	Dominant (-£61,670)
Scenario 18: Subsequent treatment assumed to reflect UK practice: 100% of patients who fail pembrolizumab go on to receive BV AND 100%	[redacted]	[redacted]	£24,265

of patients who fail on BV go on to receive bendamustine alone - Key Issue 7			
Scenario 19: Maximum ToT for brentuximab set to 16 cycles (not 35 as per base case) - Key Issue 9	[redacted]	[redacted]	£52,006
Scenario 11: Cut-off for ToT to reflect PFS data cut point (26 weeks)	[redacted]	[redacted]	£79,232
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	£67,399
Scenario 5: No difference in SCT rates between treatment arms (pembrolizumab allo-SCT and auto-SCT rate to both arms)	[redacted]	[redacted]	£62,226
Scenario 6: Dose intensity for pembrolizumab 100%	[redacted]	[redacted]	£65,018
Scenario 8: Time horizon increased to 50 years	[redacted]	[redacted]	£64,124
ERG base case (deterministic)*	[redacted]	[redacted]	£64,124
ERG base case (probabilistic)	[redacted]	[redacted]	£58,738

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; SCT, stem cell transplant

Notes: * ERG base case combines all preferred scenarios

Table 5: Summary of ERG's preferred assumptions and ICER (SCT+3L+)- includes pembrolizumab PAS

Preferred assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Company base-case	[redacted]	[redacted]	Dominant (-£73,896)
Company base case used as start point for ERG analyses, below			
Scenario 22: Semi parametric approach to modelling PFS (cut point for PFS set at 26 weeks)	[redacted]	[redacted]	Dominant (-£57,940)
Scenario 1: Utility value for PD health state set to [redacted] for both treatment arms - Key Issue 6	[redacted]	[redacted]	Dominant (-£79,339)
Scenario 19: Maximum ToT for brentuximab set to 16 cycles (not 35 as per base case) - Key Issue 9	[redacted]	[redacted]	Dominant (-£68,202)
Scenario 11: Cut-off for ToT to reflect PFS data cut point (26 weeks)	[redacted]	[redacted]	Dominant (-£49,001)
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	Dominant (-£61,514)

Scenario 5: No difference in SCT rates between treatment arms (pembrolizumab allo-SCT and auto-SCT rate to both arms)	[redacted]	[redacted]	Dominant (-£66,889)
Scenario 6: Dose intensity for pembrolizumab 100%	[redacted]	[redacted]	Dominant (-£64,127)
Scenario 8: Time horizon increased to 50 years	[redacted]	[redacted]	Dominant (-£63,904)
Scenario 18: Subsequent treatment assumed to reflect UK practice: 100% of patients who fail pembrolizumab go on to receive nivolumab AND 100% of patients who fail on BV go on to receive nivolumab - Key Issue 7	[redacted]	[redacted]	Dominant (-£33,849)
ERG base case (deterministic)*	[redacted]	[redacted]	Dominant (-£33,849)
ERG base case (probabilistic)	[redacted]	[redacted]	Dominant (-£34,156)

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; SCT, stem cell transplant

Notes: * ERG base case combines all preferred scenarios

Modelling errors identified and corrected by the ERG are described in Section 5.3. For further details of the exploratory and sensitivity analyses done by the ERG, see Sections 5.2 and 6.2.

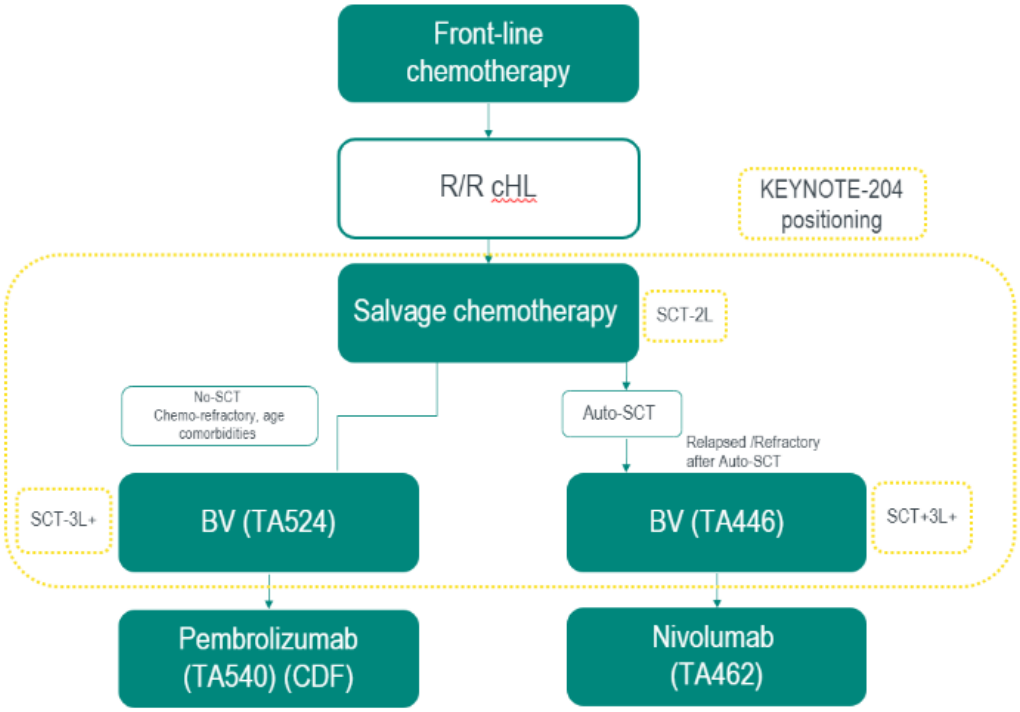
2. INTRODUCTION AND BACKGROUND

2.1. Introduction

Hodgkin's lymphoma (HL) is a form of cancer of the lymphatic system, which is an important component of the immune system. HL accounts for around 20% of all lymphomas.[6] A rare malignant proliferation of cells from the lymphoreticular system, HL mainly affects lymph node tissues, spleen, liver and bone marrow.[7] Survival with HL in England between 2013 and 2017 was 90.6% at one year and 75% at 10 years.[8] However, those considered to be relapsed or refractory (R/R) have considerably worse prognosis than the wider HL population.[9,10] The majority (59%) of HL cases occur in males and the condition is associated with a bimodal age distribution with the first peak between 20 and 24 years and the second peak between 75 and 79 years.[11] The Evidence Review Group (ERG) considered that the Company Submission (CS) offered an acceptable description of the condition; its pathophysiology, natural course and epidemiology; and the current treatment options available.

No National Institute for Health and Care Excellence (NICE) clinical guideline for the management of HL was cited in the CS, and the ERG did not identify a relevant NICE guideline. Instead, the CS depicts a treatment algorithm summary for relapsed or refractory classic HL (R/RcHL) in the UK, which is reproduced in Figure 1.

Figure 1: Treatment algorithm summary for patients with R/RcHL



Source: CS, Document B, Figure 2, p.19

The CS also outlines the relevant NICE-approved comparators for this indication (CS Document B.1.3, p.21):

- BV is recommended as an option for treating CD30-positive HL in adults with R/R disease,[12] only if:
  - They have already had autologous stell cell transplant (ASCT) or
  - They have already had at least two previous therapies when ASCT or multi-agent chemotherapy are not suitable and,
  - The company provides BV according to the commercial agreement.
- Nivolumab is recommended, within its marketing authorization, as an option for treating R/RcHL in adults after ASCT and treatment with BV.[13]
- Pembrolizumab is recommended, within its marketing authorization, for use within the Cancer Drugs Fund as an option for treating R/RcHL in adults who have had BV and cannot have ASCT.[14]

2.2. Background

Pembrolizumab is a monoclonal antibody of the IgG4/Kappa isotope designed to exert dual ligand blockade of the programmed cell death protein 1 (PD-1) pathway by directly blocking the interaction between PD-1 and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), which appear on antigen-presenting or tumour cells. Pembrolizumab is currently used for a range of other cancer indications in current practice. The ERG considered that the company's intended positioning, as compared to current standard of care, was appropriate and generally well-described.

The company's intended positioning for pembrolizumab can be conceptualised as three specific sub-populations:

- Patients with R/RcHL who did not have at least two prior therapies when autologous stem cell transplant is not a treatment option (SCT-2L)
- Patients with R/RcHL who are at least third line with prior stem cell transplant. (SCT+3L+)
- Patients with R/RcHL who are at least third line when ASCT stem cell transplant is not a treatment option (SCT-3L+)

For the SCT+3L+ and SCT-3L+ groups, this is the position in the treatment pathway currently occupied by brentuximab vedotin (BV), while for the SCT-2L group, this is the position in the treatment pathway currently occupied by salvage chemotherapy. Clinical advice to the ERG was that these were broadly the appropriate comparators, although the company's use of exclusively IGEV (ifosfamide; gemcitabine; vinorelbine)[2] as a chemotherapy regimen in the economic modelling did not reflect the diversity of regimens used in clinical practice. Clinical advice to the ERG indicated that various combination regimens have some evidence of efficacy, although the regimens have not been compared head-to-head. This means it is difficult to determine whether it is appropriate to assume comparable efficacy between treatments. Furthermore, the selection of chemotherapy regimen is largely a matter of centre and clinician preference.

2.3. Critique of company's definition of decision problem

The ERG considered that the company's definition of the decision problem generally matched the decision problem in the NICE scope.[15]

Table 6: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with relapsed or refractory classical Hodgkin lymphoma who have received: • autologous stem cell transplant or • at least one prior therapy when autologous stem cell transplant (ASCT) is not a treatment option	As per final scope	Not applicable	The ERG considered that the company decision problem was generally well matched to the NICE scope. However, the ERG noted that the company systematic literature review (SLR) specified patients should be at least 3 years of age, whereas the company economic model excluded the paediatric population. Therefore, the company submission was narrower in age range than the company decision problem. Whereas the NICE scope said patients should have received ASCT, the company submission (CS) specified patients should have failed ASCT not solely received it.
Intervention	Pembrolizumab	As per final scope	Not applicable	As per the scope for the appraisal.
Comparator(s)	Brentuximab vedotin (BV) For people who did not have at least two prior therapies when autologous stem cell transplant is not a treatment option	As per final scope	Not applicable	The ERG agreed that BV and chemotherapy are the comparators of interest in this appraisal. The ERG, however, noted that the company SLR listed BV monotherapy, nivolumab

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• Chemotherapy regimens			monotherapy, standard of care chemotherapy regimens and ASCT as interventions as opposed to comparators. It also listed placebo or best supportive care, any intervention of interest, any treatment that facilitates an indirect comparison and no intervention as comparators.
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival • response rates • proportion receiving subsequent stem cell transplant • adverse effects of treatment • health-related quality of life.	[redacted]	[redacted]	The ERG agreed that the outcome measures are comparable between the NICE final scope and company submission. However, it is important to note that OS measures used in the company model were not directly observed from an included trial, and instead modelled from BV data in the Gopal et al. (2015)[1] study.
Economic analysis	If the evidence allows the following subgroups may be considered • people who could have a subsequent stem cell transplant (autologous or allogeneic) if they respond to treatment	Post-hoc efficacy analyses for PFS and ORR are presented for 3 subpopulations; second line subjects with no prior stem cell transplant ("SCT-2L") subjects who are at least third line with no prior SCT ("SCT-3L+")	Patients who were considered ineligible for auto SCT included patients who could have a subsequent stem cell transplant if they respond to treatment and patients whom stem cell transplant is contraindicated because of comorbidities and age.	The ERG agreed that the economic subgroup analyses presented are aligned with the reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• people for whom stem cell transplant is contraindicated because of comorbidities	subjects who are at least third line with prior stem cell transplant ("SCT+3L+")		
Subgroups	If the evidence allows the following subgroups may be considered • people who could have a subsequent stem cell transplant (autologous or allogeneic) if they respond to treatment • people for whom stem cell transplant is contraindicated because of comorbidities	Post-hoc efficacy analyses for PFS and ORR are presented for 3 subpopulations; second line subjects with no prior stem cell transplant ("SCT-2L") subjects who are at least third line with no prior SCT ("SCT-3L+") subjects who are at least third line with prior stem cell transplant ("SCT+3L+")	Patients who were considered ineligible for auto SCT included patients who could have a subsequent stem cell transplant if they respond to treatment and patients whom stem cell transplant is contraindicated because of comorbidities and age.	The ERG considered that the sub-groups in the company decision problem to be appropriate and clinically relevant, although specified differently than in the NICE final scope. The ERG considered the fact that the 'third-line' subgroups included patients who were at least third-line rather than solely third-line to be a minor issue in terms of generalizability, but to be reasonable in the circumstances.
Special considerations including issues related to equity or equality	NS.	MSD does not envisage any equality issues with the use of pembrolizumab for the treatment of R/RcHL who have received: ASCT or at least one prior therapy when ASCT is not a treatment option.	NA.	NA.

Abbreviations ASCT, Autologous stem cell transplant; BV, brentuximab vedotin; CS, Company submission; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; NA, Not applicable; NS, Not stated; OS, Overall survival; SLR, Systematic literature review.

Source: CS, Document B, Table 1, p.13; CS, Document B, Section 1.4, p.20.

3. CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of pembrolizumab for [redacted] The ERG reviewed the details provided on:

- Methods implemented to identify, screen, data extract and assess the risk of bias in relevant evidence
- Clinical efficacy of pembrolizumab
- Safety profile of pembrolizumab
- Assessment of comparative clinical effectiveness of pembrolizumab against relevant comparators

A detailed description of an aspect of the CS is only provided where the ERG disagreed with the company's assessment or proposal, or where the ERG identified a particular area of concern that the ERG considered necessary to highlight for the Committee.

The ERG identified three key issues in the clinical effectiveness evidence:

- The immaturity of OS data in the key trial meaning no directly observed comparative OS data were available for use in the economic model.
- The matched adjusted indirect comparison (MAIC) analysis was only conducted with regard to one potential 2L salvage chemotherapy regimen (IGEV) and is therefore not generalisable to the full range of regimens used in clinical practice in the UK.
- The intention to treat (ITT) analysis is not generalizable to the UK treatment pathway, since there are three clear subgroups (SCT-2L, SCT-3L+ and SCT+3L+), not all of which have BV as a relevant comparator.

3.1. Critique of the methods of review(s)

The company undertook a systematic review to identify relevant publications on the efficacy and safety of pembrolizumab monotherapy, compared to BV monotherapy, nivolumab monotherapy, standard of care chemotherapy regimens, ASCT, BSC and placebo, for adult and paediatric patients aged three years or older with R/RcHL who have failed ASCT or following at least one prior therapy when ASCT is not a treatment option. The company considered BV and, in the

case of 3L+ ASCT-ineligible patients: R/RcHL patients who have not had an ASCT and received more than 1 prior line of therapy, standard of care chemotherapy regimens, to be the most relevant comparators.

In total, 98 publications (describing 45 unique trials) were included in the SLR. Most studies identified in the SLR were single arm and therefore offered no comparative effectiveness data for pembrolizumab. One open-label phase III RCT (KEYNOTE-204)[3,4] was identified that included the target population and formed the pivotal trial for this appraisal. There were two further single-arm studies (KEYNOTE-087[5] and Gopal et al. (2015)[1]) that the company included as clinical effectiveness sources in the economic model. The identified evidence, with a focus on the pivotal trial, is critiqued in Section 3.2.

Table 7: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D.1.1.2	The ERG was broadly satisfied with the search methods but noted the following limitation: the SIGN RCT filter applied to database searches may not have retrieved all relevant single-arm prospective studies, Despite this limitation, the ERG was satisfied that the clinical effectiveness searches identified all relevant trial evidence.
Inclusion criteria	Appendix D.1.1.2	The ERG was generally satisfied with the robustness of the inclusion criteria. There were some potential limitations. Differences in aspects of how the population, interventions and comparators were defined are outlined above in Table 6. A total of 98 publications were included, representing 45 unique trials. The ERG was satisfied that important trials are likely to have been identified.
Screening	Appendix D.1.1.3	The ERG was satisfied with the screening process. Two independent reviewers were used with a third reviewer to adjudicate disagreements.
Data extraction	Appendix D.1.1.3	The ERG was satisfied with the data extraction process. Two independent reviewers were used with a third reviewer to adjudicate disagreements. Standardised extraction forms were used.
Tool for quality assessment of included study or studies	Appendix D.1.2.3	The ERG was satisfied with the risk of bias assessment. The Newcastle-Ottawa scale was used for single-arm studies, and the NICE risk of bias tool (a modification of the

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		Cochrane tool) was used for comparative studies.
Evidence synthesis	Document B.2.8; Document B.2.9; Appendix D.1.2	No meta-analysis of pembrolizumab trials was conducted since there was only one Phase III RCT. The ERG considered this to be appropriate. The ERG's critique of the matched adjusted indirect comparison (MAIC) is found in Section 3.4.

Abbreviations: CS, Company submission; ERG, Evidence Review Group

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Of 45 studies included in the SLR, only one study (KEYNOTE-204[3,4]) – an open-label RCT compared pembrolizumab with BV directly – and therefore forms the pivotal trial in the clinical effectiveness evidence.

3.2.1. Study design

The key trial included from the company's SLR, and the only source of directly comparative evidence to inform the economic model, is a Phase III, open label RCT (KEYNOTE-204[3,4]) evaluating pembrolizumab in patients with R/RcHL who have previously received at least one multi-agent chemotherapy regimen from countries including the UK, USA, Japan, Italy, Sweden, Australia, Poland and Russia (although details on UK sites were not provided). The clinical effectiveness data in the CS are principally from the intention-to-treat (ITT) population, although post-hoc subgroup results from the three subgroups as outlined in Section 2.2 are also provided in CS Appendix L. The ERG considered the subgroups as opposed to the ITT population to be appropriate for decision making (Section 4.2.3), since the population comprises three subgroups (SCT-2L, SCT-3L+ and SCT+3L+) which do not all share a common relevant comparator in the UK treatment pathway. The company has presented a cost effectiveness scenario analysis using clinical effectiveness inputs from one other pembrolizumab trial (KEYNOTE-087[5]), although this was single-arm in nature and was not used in the company base case. The ERG considered this to be appropriate and therefore did not present further critique of this study. The ERG critique of clinical effectiveness results therefore focuses on KEYNOTE-204.[3,4]

The population, intervention and outcomes presented in KEYNOTE-204[3,4] were broadly consistent with the NICE decision problem, although it is important to note that mature OS data

were not available from KEYNOTE-204[3,4] and were therefore mapped from a single-arm BV study (Section 4.2.6.1).[1]

No specific dose of pembrolizumab was stated in the NICE decision problem for this appraisal. At the clarification stage, the company clarified to the ERG that the doses included in the CS for adult patients – 200 mg administered every three weeks and 400 mg administered every six weeks [redacted]. However, the key trial (KEYNOTE-204[3,4]) utilised only the 200 mg every three weeks dose (CS, Document B, Table 3, p.23), and this was therefore the dose used in the company base case economic model. The 400 mg every six weeks dose was considered separately in a scenario analysis.

Clinical advice to the ERG indicated that the doses of pembrolizumab and BV were appropriate with regard to UK clinical practice. However, for the SCT-2L sub-group, the company's economic model did not consider a full range of salvage chemotherapy regimens, and instead focused on IGEV, which the clinical advisor to the ERG considered to be only one of multiple potential chemotherapy regimens in clinical practice. There is likely to be some regional and/or centre-level variation in terms of chemotherapy regimen use. Clinical advice to the ERG indicated a preference for bendamustine-based regimens, whereas the clarification response from the company indicated that clinical advice received by the company did not support including such regimens on the standard of care list.

3.2.2. Randomisation stages and protocol amendments

The KEYNOTE-204[3,4] trial involved the randomisation of patients (1:1) to either pembrolizumab monotherapy (200 mg every three weeks) or BV. The ERG considered that randomisation was carried out appropriately. It was stratified by prior auto-SCT status and HL status.

KEYNOTE-204[3,4] was subject to seven protocol amendments (CS, Document B, Table 55, p.118). However, the ERG did not identify any protocol amendments that it considered likely to have introduced a high risk of bias in addition to the potential bias inherent in an open-label trial design.

3.2.3. Quality assessment of the trials of the technology of interest

The company reported a generally favourable assessment of study quality for KEYNOTE-204[3,4] as well as for the single-arm pembrolizumab studies KEYNOTE-013,[16] KEYNOTE-087[5] and KEYNOTE-051,[17] of which KEYNOTE-087[5] was used to inform a scenario analysis in the economic model. These three single-arm studies did not inform the MAIC. The complete quality assessment is available in Appendix D of the CS (Tables 29 and 30). The company

acknowledged appropriately the limitations of the open-label nature of KEYNOTE-204.[3,4] The company evaluated RCTs using the NICE Risk of Bias Tool, which is a modified version of the Cochrane tool, and evaluated single-arm studies using the Newcastle-Ottawa Scale,[18] which the ERG considered to be appropriate for this purpose. The ERG considered risk of bias using the published literature as well as the data presented in the CS and accompanying documents specifically for the outcomes from KEYNOTE-204[3,4] that informed the economic model (primarily PFS, response rates, proportion receiving subsequent transplant, adverse events and health-related quality of life).

While the ERG noted some strengths of trial quality such as appropriate randomisation and broadly similar baseline characteristics across arms, the ERG notes the limitations associated with the open label nature of KEYNOTE-204,[3,4] whereby neither investigators nor patients were blinded to the treatment allocation. However, the different mode of administration for pembrolizumab as an immunotherapy versus BV as a chemotherapy would make blinding difficult to achieve. While ITT analysis is typically a strength of trials in terms of internal validity, in the context of this appraisal it has substantial limitations in terms of external validity given the existence of three clear sub-groups (SCT-2L, SCT-3L+ and SCT+3L+), not all of which have BV as a relevant comparator. Additionally, the ERG identified a risk of attrition bias in the KEYNOTE-204[3,4] trial given [redacted]. A further limitation to the external validity of the KEYNOTE-204[3,4] trial in the context of this appraisal is the immaturity of OS data, precluding the use of directly observed comparative OS data as a clinical effectiveness input to the economic model.

3.2.4. Baseline characteristics

Baseline characteristics for patients included in the KEYNOTE-204[3,4] study were reported in the CS (Document B, Table 7, pp.33-36) for the ITT population. Baseline characteristics were not provided in the CS for the subgroup populations (SCT-2L, SCT-3L+ and SCT+3L+) that the ERG considered to be most relevant for decision-making. Considering the ITT population, the ERG agreed with the company's assertion that the baseline characteristics in KEYNOTE-204[3,4] were generally well-balanced between the pembrolizumab and BV arms. While the ERG noted a tendency for ECOG score of 1 and high-risk features such as bulky disease, baseline B symptoms and baseline bone marrow involvement to be more prevalent in the pembrolizumab arm than the BV arm, the ERG considered there to be no major baseline imbalances between the two arms of the KEYNOTE-204[3,4] trial. The ERG noted that in the company base case economic model the patient characteristics from European sites only were used for some

variables rather than the international population in an attempt to better reflect the UK population, while for other variables the full international ITT population was used. The ERG however considered that the international population may be more suitable, given the population of Europe as a whole is less ethnically diverse than the UK population. Baseline characteristics for selected variables for the European population in KEYNOTE-204[3,4] were presented in the CS, Document B, Table 106, p.177. Ethnicity was not reported in the European population, however age and gender appeared comparable with the international ITT population.

3.2.5. Clinical effectiveness results

Data in the target population were presented for PFS, response rates, proportion of patients receiving subsequent stem cell transplant, health-related quality of life and adverse events. It is important to note that no OS data were available from the KEYNOTE-204[3,4] trial. Statistical analyses were broadly appropriate. The primary analysis population in the CS was the ITT population for all efficacy outcomes and the All Subjects as Treated (ASaT) population for safety outcomes. The ERG has explained above how the ITT population has generalisability problems in the context of the UK treatment pathway, and that sub-group analyses are preferable for decision-making. Therefore, the clinical effectiveness efficacy results that the ERG considered to be most relevant are those presented in Section 3.2.5.5.

3.2.5.1. Overall survival

Mature OS data were not available from the KEYNOTE-204[3,4] trial (Section 4.2.6.1). Therefore, clinical effectiveness inputs for OS parameters in the company economic model were not based on directly observed comparative data.

3.2.5.2. Progression-free survival

PFS was assessed per IWG 2007[19] by blinded independent central review. Statistical analysis was conducted using the stratified Log-rank test for testing and a stratified Cox model with Efron's tie handling method for estimation. The main analysis used the primary censoring rule (CS, Document B, Table 16, p.66) for handling missing data. PFS curves were estimated using the non-parametric Kaplan-Meier (KM) method.

In the ITT population, based on a median (range) follow-up time of [redacted] months, median PFS of 13.2 (95% CI 10.9, 19.4) months in the pembrolizumab arm compared favourably with median PFS of 8.3 (95% CI 5.7, 8.8) months in the BV arm, with a hazard ratio (HR) of 0.65 (95% CI 0.44, 0.88), one-sided Log-rank test p=0.00271.

3.2.5.3. Response rate

Objective response rate (ORR) was assessed per IWG 2007[19] by blinded independent central review. Statistical analysis was conducted using the stratified Miettinen and Nurminen method.[20] Participants with missing data were classed as non-responders.

In the ITT population, there was a numerical difference in ORR in favour of pembrolizumab (ORR 65.6%, 95% CI [redacted]) over BV (ORR 54.2%, 95% [redacted]), although the difference was [redacted].

3.2.5.4. Health-related quality of life

Health-related quality of life (HRQoL) was assessed in KEYNOTE-204[3,4] using two measures - EORTC-QLQ-C30 questionnaire (version 3.0)[21] which was used to assess cancer-related quality of life, as well as the generic health status measure, EQ-5D-3L.[22] Questionnaires were completed at several time points within KEYNOTE-204: pre-dose at Cycle 1 (baseline), Cycle 3 (Week 6), Cycle 5 (Week 12), Cycle 7 (week 18), and Cycle 9 (Week 24) and then every 12 weeks until PD or up to one year while the subject is receiving study treatment. Questionnaires were also collected at discontinuation and at the 30-day safety follow-up visit.

EQ-5D-3L is the standard HRQoL measure for NICE appraisals, and following the NICE reference case, HRQoL data were reported directly from patients using the EQ-5D-3L questionnaire and the utility of the changes in QoL in the company base case economic model was based on public preferences using a choice-based method.

There was a statistically significant benefit for pembrolizumab over BV in terms of EQ-5D-3L utility scores of [redacted] points, 95% CI [redacted], [redacted], at 24 weeks. There was a statistically significant benefit for pembrolizumab over BV in terms of EQ-5D-3L visual analogue (VAS) scores of [redacted] points, 95% CI [redacted], [redacted], at 24 weeks.

3.2.5.5. Subgroup analyses

The CS reports both pre-specified and post-hoc subgroup analyses for the pivotal KEYNOTE-204 trial.[3,4]

Pre-specified subgroup analyses were conducted to assess efficacy within each category of the following classification variables:

- Prior ASCT

- Disease status following first-line therapy (refractory vs relapsed within 12 months vs relapsed after 12 months)
- Sex
- Age (binary split at 65)
- ECOG status (0 vs 1)
- Geographic region
- Prior BV status (Yes vs No)

Post-hoc subgroup analyses were conducted, dividing the population into three cohorts:

- SCT-2L
- SCT-3L+
- SCT+3L+

The results of the pre-specified and post-hoc subgroup analyses can be found in CS (Appendix L). The ERG considered the factors selected by the company for consideration in subgroup analysis to be appropriate. However, the ERG considered that the three cohorts considered in the post-hoc subgroup analysis should have been pre-specified analyses, given their relevance to clinical treatment pathways and decision-making.

In the post-hoc subgroup analysis, results in the primary analysis favoured pembrolizumab over BV for both PFS and ORR in all three cohorts. However, p-values or confidence intervals for the between-arm difference were not reported. This made it difficult for the ERG to comment on the robustness of the efficacy of pembrolizumab in each of these three cohorts. PFS in the pembrolizumab arm was highest in the SCT-2L subgroup ([redacted], 95% CI [redacted] vs [redacted], 95% CI [redacted] for BV). Notwithstanding the lack of information regarding statistical significance, the mean difference between arms was also highest in the SCT-2L subgroup, and lowest in the SCT+3L+ subgroup (pembrolizumab [redacted], 95% CI [redacted]; BV [redacted], 95% CI [redacted]).

3.2.5.6. Adverse effects

Adverse events (AEs) in the KEYNOTE-204 trial[3,4] were reported in the CS B.2.10. AEs were considered in the ASaT population, which formed the primary safety analysis population. Overall, the ERG agreed with the company that pembrolizumab had an acceptable safety

profile. AEs were very common with nearly all participants experiencing at least one AE and the majority in each treatment arm experiencing treatment-related AEs. The ERG agreed with the company that the incidence of AEs both overall and in specific AE categories was comparable between the treatment arms. The ERG agreed with the company that the biggest difference was noted with regard to serious adverse events (SAEs, pembrolizumab [redacted] vs BV [redacted]), and accepts the company's explanation of this in terms of differing duration of exposure (pembrolizumab median [redacted] days vs BV median [redacted] days).

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As stated in Section 2.2 the appropriate comparator for the SCT-2L subgroup is 'standard of care' (SoC), which is salvage chemotherapy but not BV. The pivotal trial (KEYNOTE-204[3,4]) did not contain a head-to-head comparison of pembrolizumab vs SoC, and therefore the company carried out an indirect comparison, with adjustment for known prognostic or effect-modifying covariates by MAIC.

The company identified a retrospective study of UK clinical practice (Eyre et al., 2017[23]) and received clinical advice (CS, Appendix D1.2.1, pp35-36), and thereby identified the following SoC regimens in the UK with associated trial evidence (CS, Document B, Table 58): GDP (gemcitabine, dexamethasone, cisplatin), IGEV, ICE (ifosfamide; carboplatin; etoposide), ICE + panobinostat, DHAP (dexamethasone; high dose Ara C [cytarabine]; cisplatin), ESHAP (etoposide; solu-medrone [also called methylprednisolone]; high dose Ara C [cytarabine]; cisplatin).

Investigational regimens and combinations with other agents were excluded on the basis that these were 'not considered representative of SoC in the UK' (CS, Document B, p36).

Clinical advice received by the ERG suggested that there were local preferences for these SoC regimens in different UK centres and each had some track record of efficacy, but they had not been compared head-to-head. They also commented that the company's selection seemed comprehensive, other than the omission of bendamustine or bendamustine-containing regimens. This omission was raised in clarification and the company explained that these were not included by their clinical advisors for clinical practice, nor were they suggested by guidelines or a retrospective study (see clarification response A5). Furthermore, the company stated that a MAIC analysis of bendamustine regimens would not have been feasible with the information available (clarification response A16).

The company carried out a targeted literature review (TLR), to identify potential prognostic or effect-modifying variables, viz.: 1.) disease status (early relapse vs late relapse vs refractory), 2.) age, 3.) ECOG 0 vs 1, 4.) presence of bulky disease, 5.) prior radiotherapy, 6.) sex, and 7.) presence of B symptoms. The company also stated that "The following patient characteristics were considered as potential prognostic factors but were either considered to have significant overlap with the aforementioned covariates, or were deemed to be less relevant from a clinical perspective: refractory relapse vs sensitive relapse, serum albumin levels, haemoglobin levels, white cell count, and lymphocyte count." (CS, Appendix D1.2.3 p52). The clinical advisor to the ERG assessed the company's list of variables and was largely satisfied, though suggested the addition of erythrocyte sedimentation rate (ESR).

With the six selected trials believed to represent UK practice the company inspected the available outcomes (Precision report table 13)[24] and available covariates (CS, Appendix D, Table 23). On this basis, and in particular because only Balzarotti et al. (2016)[2] provided KM data for PFS assessment, the company did not present results from the other five trials. The company further elaborated (clarification question A14) that the study populations were not comparable in terms of ASCT ineligibility, though Balzarotti et al. (2016)[2] was retained (further details below). The ERG did not receive any evidence that IGEV is not a suitable proxy for SoC in the UK, but generalisability of the results is not assured.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

The company assembled six MAIC analyses for a pembrolizumab vs SoC comparison. However, as detailed in Section 3.3, the company presented only one of these (pembrolizumab vs IGEV using Balzarotti et al. (2016)[2]) in the CS, now described.

The company base case analysis for this subgroup was "pembrolizumab vs. IGEV in second line subjects without prior stem cell transplant (SCT) based on the KEYNOTE-204 and Balzarotti 2016 studies." (CS, Document B, pp125-6). The base case analysis was restricted to patients aged <65 years to conform with the IGEV population, but a sensitivity analysis was also described without this restriction.

The company matched pembrolizumab (from KEYNOTE-204, individual patient data [IPD] available) to IGEV (Balzarotti et al. (2016)[2]) aggregate data available for some covariates, and pseudo-IPD data for PFS) with an 'unanchored' MAIC since there was no common comparator between these studies. The numbers of participants available in each trial was low ([redacted], KEYNOTE-204 pembrolizumab arm; [redacted], Balzarotti et al. trial IGEV arm) and under matching

the effective sample size (ESS) was lower again ([redacted]). The company provided a histogram of MAIC weights in response to clarification question A15. There was only one observation with zero or very small weight, indicating very substantial overlap between the two samples (but with a known *lack of overlap in age already accounted for* by exclusion of >65 year olds when forming the base case).

The company presented MAIC-adjusted results for CR, PR, OR (CR or PR) and PFS. The last of these is relevant from an economic perspective. OS was not analysed because it is not yet available from the KN204 trial. After matching, the estimated base case PFS [redacted] (CS, Document B, Table 61). Under the sensitivity analysis (which did not restrict the age of participants in KEYNOTE-204) the estimate for PFS was [redacted], Doc B Table 66). The result is not significant under either analysis (base case or sensitivity) though the directions of the point estimates differ. The estimates were made with Cox regression but the ERG questions whether proportional hazards would be supported in the company's base case (Doc B fig 27). For clinical outcomes, in the base case the company reported significantly improved PR (RR= [redacted]) (CS, Document B, Table 64) but the result for CR (RR= [redacted]) (CS, Document B, Table 63) was not significant.

The purpose of the MAIC in this instance is to reweight participants in the pembrolizumab trial (KN-204) so that its aggregate covariate values match those of the IGEV trial. Characteristics before and after matching are shown in Tables 60 and 65 (CS, Document B), showing that the MAIC correctly adjusted for these covariates. Nevertheless, the ERG notes that the interpretation of the resulting estimate is of the effect of pembrolizumab vs IGEV *in the population of the IGEV trial*. The IGEV trial was carried out in specialist centres in Italy, and it is important to consider whether this is a suitable representation of the 'target population', SCT-2L in UK clinical practice. For example, the Balzarotti et al. (2016)[2] sample contained no patients over 65 (even though "age was not specifically an exclusion criterion in the comparator study", Doc B p126) compared with [redacted] of the pembrolizumab (KN-204) sample. The ERG suggests this may indicate a less age-diverse study population in the IGEV trial than in KEYNOTE-204 or UK clinical practice.

Because the base case MAIC is unanchored, an assumption must be made that all effect modifiers and prognostics have been accounted for. The company acknowledged this was a strong assumption and in the ERG's view correctly warned of a potential for bias. ECOG score was a known prognostic variable that, because it was not reported in the comparator study, could not be adjusted for in the MAIC. Another important prognostic not incorporated to the

company's MAIC was SCT eligibility. In the KEYNOTE-204 subgroup no participants had received prior ASCT, and these were treated as ASCT-ineligible, whereas "none of the comparator studies explicitly limited enrolment to ASCT-ineligible patients". The company indicated that information was limited on this and relevant patient characteristics "for example comorbidities was not well-described in publications beyond a requirement for 'adequate organ function'" (CS, Document B, p137). The clinical advisor explained to the ERG that ASCT eligibility can be a dynamic characteristic in some patients. The company outlined (in the CS and clarification A14) that there were differences in the proportions of patients from subgroup SCT-2L who subsequently went on to receive SCT: much lower in KN-204 ([redacted] and [redacted] in each arm) compared to Balzarotti et al. (2016)[2] (at least 81%).

Conclusion: Only one SoC regimen was available for MAIC analysis with respect to PFS (IGEV). The ERG noted that a number of other salvage treatments are used in clinical practice but these could not in the company's view be analysed by MAIC. On the other hand, the ERG did not receive any evidence that IGEV was an unsuitable proxy for SoC. The ERG agreed with the company that the results of this unanchored MAIC (Pembrolizumab vs IGEV) should be treated with caution. The MAIC accounted for a number of important prognostic/effect-modifying variables, but may contain residual bias from others unadjusted for, and in particular was known not to adjust for SCT eligibility or ECOG. Furthermore, the ESS was low, leading to estimates with poor precision. Finally, the estimate of effect is with reference to the population in the IGEV trial rather than UK clinical practice.

3.5. Additional work on clinical effectiveness undertaken by the ERG

None.

3.6. Conclusions of the clinical effectiveness section

The ERG considered that the company had identified all relevant clinical evidence for this appraisal. Data were not available for the OS outcome included in the NICE final scope for this appraisal.[15] Requisite information regarding the methodology and outcomes for clinical effectiveness was available in the CS, and was generally reasonably described.

There was one pivotal RCT comparing pembrolizumab and BV (KEYNOTE-204[3,4]) that could provide directly comparative evidence for the base case economic model. A further single arm pembrolizumab trial (KEYNOTE-087[5]) informed a company scenario analysis. While there were several strengths to the KEYNOTE-204 trial,[3,4] the open-label nature of the trial was a key limitation, although the extent to which blinding could be achieved was limited by the different

modes of administrative of the immunotherapy pembrolizumab and the chemotherapy BV. The ERG was satisfied that there was evidence of a benefit for pembrolizumab over BV in terms of PFS and ORR. In the absence of directly comparative evidence for pembrolizumab versus salvage chemotherapy (the relevant comparator for the SCT-2L subgroup), MAIC analysis was conducted. The base case MAIC that informed the economic model included two trials. Limitations of the MAIC included the fact that it was unanchored.

The three key issues in the clinical effectiveness evidence are as follows:

- The immaturity of OS data in the key trial meaning no directly observed comparative OS data were available for use in the economic model
- The matched adjusted indirect comparison (MAIC) analysis was only conducted with regard to one potential 2L salvage chemotherapy regimen (IGEV) and is therefore not generalizable to the full range of regimens used in clinical practice in the UK
- The intention to treat (ITT) analysis is not generalizable to the UK treatment pathway, since there are three clear subgroups (SCT-2L, SCT-3L+ and SCT+3L+), not all of which have BV as a relevant comparator.

4. COST-EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

The company conducted a single systematic literature review with the overall objective being to identify and summarize a) the published cost-effectiveness analysis, b) health-related quality of life associated with the treatment healthcare costs, and c) and resource requirements of patients with R/RcHL.

Table 8: Summary of ERG's critique of the methods implemented by the company to identify health economic evidence: Cost-effectiveness studies

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix G.1 and Appendix G.5	The ERG was broadly satisfied with the search methods.
Inclusion criteria	Appendix G.2, Appendix G, Table 32	Appropriate. Studies including adults and children with R/RcHL were eligible for inclusion. No restriction was placed in respect of pharmacological interventions other than line of therapy, second- or later line therapies (although the latter distinction was not noted in the PICOS table but in the supporting narrative). Study designs specified were relevant for the objective of the review (economic evaluations). Only full texts available in English language were included. Included studies were grouped: UK and non-UK setting. A total of 16 studies met the eligibility criteria for the review: of these, 2 were UK-specific. In addition, 7 UK-specific HTA submissions (4 NICE and 3 SMC). The company noted that two were conducted in a UK setting and no studies compared pembrolizumab versus brentuximab or chemotherapy in the population of interest in the UK setting.
Screening	Appendix G.3	Appropriate. Studies were dual screened independently at title/abstract and full-text screening stages.
Data extraction	Appendix G.4	Appropriate. Data extraction was completed by two reviewers independently and checked by a third reviewer.
QA of included studies	Not reported	Quality appraisal of identified studies reporting economic evaluations was not reported. Given the absence from the CS, the ERG assumed that QA of included studies was not undertaken by the company.

Abbreviations: cHL, classical Hodgkin lymphoma; CS, Company Submission; ERG, Evidence Review Group; QA, quality assessment; R/R, relapsed, refractory

Table 9: Summary of ERG's critique of the methods implemented by the company to identify health economic evidence: Health-related quality of life

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix H	The ERG was broadly satisfied with the search methods.
Inclusion criteria	Doc B, Section B.3.4.3, Appendix H (cross references detail in Appendix G.2, Appendix G, and Table 32)	Broadly appropriate. Studies including adults and children with R/RcHL that reported HRQoL using disease-specific and generic instruments or directly reported health state utility values were eligible for inclusion. No restriction was placed in respect of pharmacological interventions other than line of therapy, second- or later line therapies (although the latter distinction was not noted in the PICOS table but in the supporting narrative). Only full texts available in English language were included. Included studies were grouped: UK and non-UK setting. A total of 21[a] studies (in 37 publications) were identified in the review. Of these, the company reported in detail on 5 of the studies as directly relevant to the submission. Of the 5 studies, 4 were relevant to the UK setting and 1 was conducted from a US perspective but had evaluated pembrolizumab. In addition, 7 previous HTAs were identified (4 NICE and 3 SMC). The company discussed the included studies and commented on the utility estimates identified in context of the KEYNOTE-204 data.
Screening	Appendix H cross references detail in Appendix G.3	Appropriate. Studies were dual screened independently at title/abstract and full-text screening stages.
Data extraction	Appendix H cross references detail in Appendix G.4	Appropriate. Data extraction was completed by two reviewers independently and checked by a third reviewer.
QA of included studies	Not reported	Quality appraisal of identified studies reporting HRQoL/utility data was not reported. Given the absence from the CS, the ERG assumed that QA of included studies was not undertaken by the company.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; HTA,s, health technology assessment; NICE, National Institute of Health and Care Excellence; QA, quality assessment; SMC, Scottish Medicines Consortium

Notes:

a 18 studies (in 33 publications) were identified in the review and an additional 3 studies (in 4 publications) were identified as relevant from the cost-effectiveness review.

Table 10: Summary of ERG's critique of the methods implemented by the company to identify health economic evidence: Healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix I	The ERG was broadly satisfied with the search methods.
Inclusion criteria	Appendix I (cross references detail in Appendix G.2, Appendix G, and Table 32)	Broadly appropriate. Studies including adults and children with R/RcHL that reported healthcare costs and/or resource use were eligible for inclusion in the review. No restriction was placed in respect of pharmacological interventions other than line of therapy, second- or later line therapies (although the latter distinction was not noted in the PICOS table but in the supporting narrative). Only full texts available in English language were included. Included studies were grouped: UK and non-UK setting. A total of 25[a] studies were included. Of these, the company considered that two of the studies were UK specific. The company did, however, also tabulate findings from the included non-UK specific studies. In addition, 7 previous HTAs were identified (4 NICE and 3 SMC). Identified evidence relevant to the UK setting was used to inform model parameters with the exception of Parker (2017)[25] (Scotland).
Screening	Appendix I cross references detail in Appendix G.3	Appropriate. Studies were dual screened independently at title/abstract and full-text screening stages.
Data extraction	Appendix I cross references detail in Appendix G.4	Appropriate. Data extraction was completed by two reviewers independently and checked by a third reviewer.
QA of included studies	Not reported	Quality appraisal of identified studies reporting healthcare resource use and cost data was not reported. Given the absence from the CS, the ERG assumed that QA of included studies was not undertaken by the company.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HTAs, health technology assessment; NICE, National Institute of Health and Care Excellence; QA, quality assessment; SMC, Scottish Medicines Consortium

Notes:

a 21 studies were identified in the literature search and four studies identified as eligible for inclusion from the review of cost-effectiveness analyses

4.2. Summary and critique of company's submitted economic evaluation by the ERG

4.2.1. NICE reference case checklist

Table 11: NICE reference case checklist

Attribute	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Only direct health effects were captured in the model. Carer disutility and wider societal benefits were not considered. The company's appraoch seems reasonable.
Perspective on costs	NHS and PSS	An NHS perspective was adopted as appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The time horizon used in the base case was 40 years. At this time point [redacted] of patients were still alive in the model (in both treatment arms). The ERG considered using a longer time horizon within their preferred base case.
Synthesis of evidence on health effects	Based on systematic review	For the base case analysis (ITT population) and subgroup analyses (SCT-3L+ and SCT+3L+), treatment efficacy with respect to PFS was derived directly from KEYNOTE-204.[3,4] For the SCT-2L subgroup, treatment efficacy was based on a MAIC. OS for all subgroups were based on a published study by Gopal et al.[1]
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs were used as appropriate. The EQ-5D-3L was used, which is considered the preferred health related quality of life measure in adults.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Values were elicited directly from patients in KEYNOTE-204.[3,4]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Dolan et al. (1997)[26] was used, which is considered a valid source.

Attribute	Reference case	ERG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	There were no equity concerns.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	PSSRU (2018/19) and NHS reference costs were used as appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits were discounted at 3.5%, as appropriate.

Key: EQ-5D, EuroQol 5 dimension; ERG, Evidence Review Group; HRQoL: health-related quality of life; ITT, intention to treat; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

The company submitted a partitioned survival model, also known as an area under the curve (AUC) model which consisted of three mutually exclusive health states, Progression free survival (PFS), progressed disease (PD) and death. Patients entered the model in the PFS health state and the proportion of patients remaining progression free over time was determined by the slope of the PFS curve. Membership in the PD health state was estimated based on the difference between the OS and PFS curves. The ERG acknowledged that AUC models are frequently used within the area of oncology. Clinical opinion to the ERG has confirmed that PFS and OS are considered the key outcomes for patients with RR cH/L.

The ERG noted that the company's modelling approach differed to previous models submitted to NICE for Hodgkin's lymphoma with respect to SCT. Within the current submission the company confirmed that pembrolizumab would not be used as a bridge to transplant, where the aim is to control the disease, and possibly elicit a disease response to allow for SCT. The company also stated that within this submission SCT was not modelled as an explicit health state, but rather as a model input due to the study design of KEYNOTE 204[3,4] and paucity of data. However in previous NICE TAs, including TA540[14] and TA462,[13] treatments were modelled as bridge to transplant and included survival, cost and Qol implications associated with SCT. The ERG noted that the current model for pembrolizumab only includes costs associated with SCT, which represents a departure from prior modelling approaches. Furthermore, based on TA524,[12] the ERG understood that pembrolizumab has the potential to be used by clinicians as a bridge to transplant in 'fitter' patients.

The cycle length used in the model was one week, which appeared to sufficiently capture progression and clinically important events. Given that pembrolizumab and brentuximab are administered on a three-weekly basis, a longer modelled cycle length (reflecting frequency of administration) could have been considered by the company. However, weekly cycles were considered appropriate.

4.2.3. Population

The company presented base case results for the ITT population in KEYNOTE-204[3,4] which included second-line patients (SCT-2L) and patients who were third-line or higher (SCT-3L+ and SCT+3L+). Several patient characteristics used within the model including weight and body surface area (BSA) were based on European patient characteristics, whilst age and sex reflected the entire ITT population. The company did not provide rationale as to why separate characteristics were used for certain model parameters. However, the ERG noted that the company's model had a function which allowed for characteristics to be changed to reflect the ITT characteristics only. During the clarification process, the company provided updated results using ITT patient characteristics only, however this did not impact on the ICER.

The ERG note that cost-effectiveness results were not provided for a paediatric population, [redacted]. As such it is unclear whether the results reported in Section 5.1 are generalisable to a paediatric population.

4.2.4. Interventions and comparators

For the SCT-2L subgroup, the company assumed the comparator most likely to be displaced is salvage chemotherapy (specifically IGEV). The company assumed that the clinical efficacy associated with IGEV (from the MAIC) is representative of other chemotherapy regimens. The ERG noted that this assumption is uncertain and has not been supported by clinical evidence. Furthermore, based on clinical opinion to the ERG, other potentially relevant treatment regimens appear to have been omitted, including bendamustine. The company was asked to comment on why the regimen was omitted and noted that clinical opinion and published literature searches did not identify bendamustine as a plausible treatment. The ERG did not consider the company's rationale to be accurate or reasonable, given that clinical response to the ERG has outlined a strong preference for using bendamustine.

With respect to the SCT-3L+ and SCT+3L+ subgroups the company assumed BV to be the comparator most likely displaced. The ERG considered this to be appropriate based on current treatment algorithm depicted in Section 2.1.

Within the ITT base case economic analysis BV was selected as the primary comparator. However, based on the clinical treatment pathway for R/RcHL patients (Section 2.1), comparators differed according to whether patients are being treated second-line or third-line. BV does not appear to be the most appropriate comparator for the SCT-2L population, given that salvage chemotherapy is the appropriate comparator for this subgroup.[15] The ERG did not consider there to be a single comparator applicable to all patient subpopulations, therefore each subgroup is assessed by the ERG separately within this appraisal. The ERG considered that the ITT analysis and results should be interpreted with caution and that the subgroup analyses results should be considered most relevant for decision making.

4.2.5. Perspective, time horizon and discounting

A 40-year time horizon was used in the economic model. The company justified the time horizon on the basis that most of the modelled patients are estimated to have died by this time point (with [redacted] of patients alive at 40 years). Based on a review of NICE TA540[14] (pembrolizumab for relapsing or refractory classical Hodgkin's Lymphoma), the ERG preferred a 50-year time horizon. However, a shorter time horizon (40 years) has been used and accepted previously in TA524[12] (BV for CD30- positive Hodgkin's Lymphoma). In order to ensure that all patients have died in the model, an additional scenario analysis was conducted in which the time horizon was increased to 50 years (Section 6.2.1.8). However, given the small proportion of patients alive at this time point, this did not have a major impact on results (see Section 6.2.1.8)

No issues were identified with respect to perspective or discouting. An NHS perspective was adopted which is considered appropriate. Costs and benefits were discounted at 3.5%, as per NICE guidance.

4.2.6. Treatment effectiveness and extrapolation

As previously mentioned, the key driver of pembrolizumab incremental QALYs within the model was PFS and associated assumptions surrounding this parameter. Given that the company assumed no difference in OS between pembrolizumab and IGEV in the SCT-2L subgroup or versus BV in the SCT-3L+ and SCT+3L+ subgroups, pembrolizumab was not associated with an incremental LY gain. Although this approach may be considered somewhat conservative, there were limitations surrounding the company's handling of OS within the model, which are discussed below.

4.2.6.1. Overall survival

OS data from KEYNOTE-204[3,4] were not mature. Therefore, for the base case ITT analysis the company estimated OS for both pembrolizumab and BV based on BV Kaplan Meier data from a published study (Gopal et al. (2015)[1]). The ERG acknowledged that eligible patients within this study were those who were 12 years or older with relapsed or refactory HL after prior auto-SCT. Median OS within the study was [redacted] months.

ITT population and subgroup analyses

OS data for BV were assumed to be representative of OS for pembrolizumab patients; i.e. OS was the same in both treatment arms. In order to model long-term survival estimates, the company extrapolated OS using a fully parametric modelling approach, whereby a log normal curve was fitted to the Gopal et al. (2015)[1] KM data (see Figure 2). The company justified the use of the log normal curve on the basis that it produced the lowest AIC/BIC statistics and produced plausible long term survival estimates. Based on this approach, five-year OS was estimated to be [redacted] for both pembrolizumab and BV.

Figure 2. Modelled OS (ITT population and subgroups)

Abbreviations: BV, brentuzimab vedotin; OS, overall survival

The ERG acknowledged that assuming no difference in survival between treatment arms may be considered a conservative assumption and could potentially underestimate the impact of pembrolizumab on OS. However, as noted above, the company assumed that OS from Gopal et al. (2015)[1] would be generalizable to all subgroups. Given that patients in Gopal et al. (2015)[1] were those had a prior SCT (reflecting the SCT+3L+ subgroup) the ERG consider that there was some concern surrounding the generalisability of OS estimates to the subgroups. Furthermore, based on clinical opinion to the ERG (and clinical opinion provided to the company), it may be reasonable for OS to differ according to subgroup. Therefore, in order to

estimate more plausible OS estimates for each subgroup, the ERG conducted additional scenario analyses whereby Balzarotti et al. (2016)[2] was used to estimate OS for the SCT-2L and SCT-3L+ subgroups. As patients in Balzarotti et al. (2016)[2] were considered to be more representative of these subgroups given that they had not received prior SCT, this source has been selected for use within the ERG preferred base case for this subgroup. See Section 6.2.1.14 for results.

In order to explore the impact of using an alternative OS data source on the ICER, the company also carried out 'Alternative approach 1' (CS Document B section 3.3.3.1, company scenario 5) in which the same assumption of equal OS between arms was made, but OS data were instead derived from KEYNOTE-087[5], a non randomised, phase II, single arm study which assessed the effectiveness of pembrolizumab in patients with R/R cHL. It should be noted that KEYNOTE-087[5] was the only other alternative data source used in the model to estimate OS. The study included 3 cohorts of R/R cHL patients. Cohort 1 were patients who failed to achieve a response or progressed after autologous stem cell transplant (auto-SCT) and relapsed after treatment with, or failed to respond to treatment with BV. Cohort 2 were patients who were unable to achieve a complete response or partial response to salvage chemotherapy and did not receive auto-SCT, but relapsed after treatment with, or failed to respond to treatment with BV. Cohort 3 were patients who failed to achieve a response to, or progressed after, auto-SCT, and had not received BV after auto-SCT and did or did not, receive BV as part of primary treatment or salvage treatment. The ERG noted that the scenario analysis results were based on the KEYNOTE-087[5] ITT patient population (results were not provided using OS rates from each individual cohort).

The ERG understood that this scenario analysis (which was provided for the ITT population only) caused the incremental QALY gain for pembrolizumab to increase, as pembrolizumab resulted in higher 5 year OS compared to 5 year OS for BV as reported in Gopal et al. (2015)[1] ([redacted] versus [redacted] respectively). Therefore the use of Gopal et al. (2015)[1] for the ITT population in the base case, could be considered somewhat conservative. Overall the ERG found KEYNOTE-087[5] to lack robustness given that it is a non randomised and single arm study, however it was useful to determine the impact of using an alternative OS data source on the ICER. As the company did not provide results for each subgroup the ERG subsequently conducted scenaro analyses for the SCT-2L, SCT-3L+ and SCT+3L+ subgroups using KEYNOTE-087[5] as the relevant OS source for both treatment arms. It was not possible for the ERG to obtain OS data for each individual cohort within KEYNOTE-087[5], therefore results are based on the ITT population within KEYNOTE-087[5]. Results are outlined in section 6.2.2.

A further approach investigated by the company ('Alternative approach 2', Doc B section 3.3.3.1, company scenario 6) was to use a predictive equation (predicting OS from PFS). The hazard ratio of OS:PFS from Gopal et al. (2015)[1] was applied to the PFS hazard in KEYNOTE-204 to obtain estimates of the OS hazard in KEYNOTE-204. The full details of the approach were not supplied e.g. use of both a ratio of hazards and a ratio of cumulative hazards are mentioned. The company indicated that a previous appraisal (TA524[12]) accepted the plausibility of an association between PFS and OS. However the company also acknowledged that Gopal et al. (2015)[1] most closely generalises to a subgroup (SCT+3L+) of the KEYNOTE-204 population only, and furthermore (Document B p205) "since the Gopal et al. publication, a variety of subsequent treatments have been introduced in the R/RcHL pathway, like immune checkpoint inhibitors". The ERG anticipates there may be further inconsistencies between the populations that might require adjustment. The ERG agrees with the company that this approach lacked face validity.

Additional limitations surrounding the modelling of OS

- The company did not provide sensitivity analysis using alternative parametric fits for OS extrapolation. As such it is unclear what impact alternative fits have on the ICER. In order to address uncertainty, the ERG conducted additional scenario analysis for the SCT-3L- and SCT-3L+ subgroups using the log logistic curve for extrapolation in both treatment arms. See Section 6.2.1.21 and 6.2.2.

- A single set of distribution parameters informs the OS curves in both treatment arms and, as a result, these curves are varied in exactly the same way in the probabilistic sensitivity analysis. The ERG noted that this may not adequately reflect uncertainty surrounding the OS parameters: this uncertainty would be captured better by using two sets of OS parameters, one for each arm. These sets contained identical values in the deterministic analysis, but were varied separately in the ERG probabilistic analysis (see Section 6.2.3.1).

4.2.6.2. Progression free survival

SCT-2L subgroup

In the company's base case, PFS for chemotherapy (IGEV) was based on pseudo-IPD, obtained from a digitized Kaplan-Meier curve in Balzarotti et al. (2016)[2] using a method developed by Guyot et al. (2012).[27]

Parametric distributions were fully-fitted to the pseudo-IPD, for the purpose of interpolation and extrapolation in the chemotherapy arm. The ERG noted an inconsistency here when compared

with the piecewise approach favoured by the company in PFS modelling elsewhere. The following parametric distributions were considered: the exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma.

The relative statistical fit of the distributions was assessed using AIC and BIC scores, with the log-normal providing the best fit. PFS in the pembrolizumab arm was then modelled by applying the hazard ratio obtained from the MAIC to the PFS curve for IGEV. The hazard rate from the MAIC is obtained by Cox regression, with an implicit assumption of proportional hazards. The ERG noted that the inferred survival function for pembrolizumab (Appendix N.1 p202) also depends on an assumption of proportional hazards. The Weibull is a proportional hazards model but the log-normal is not. Also, the Weibull provided the second-best fit to the pseudo-IPD after the log-normal with only a slightly reduced relative fit (difference in AIC of [redacted]) (Appendix N table 77). The ERG considered the use of the fully-fitted Weibull distribution for modelling PFS in a scenario.

The ERG noted potential concerns surrounding the use of clincal effectiveness data from the MAIC to generate cost-effectiveness results for this subgroup. As noted in Section 3.4 the MAIC was associated with several limitations which introduce uncertainty and imprecision surrounding the reported HR for pembrolizumab (imprecision expressed by the wide confidence interval). Furthermore, it was unclear whether the assumption of proportional hazards held. The company acknowledged this (see p203 and p204 of the company's Appendices document) and therefore conducted a scenario using clinical data derived from a post hoc subgroup analysis of KEYNOTE-204.[3]

The ERG further noted that the company had assumed the clinical effectiveness of IGEV is generalisable to all chemotherapies, however clinical data was not supplied to support this assumption. Due to these uncertainties, the base case cost effectiveness results for this subgroup should be interpreted with caution.

As noted previously, a trial-based scenario analysis was also presented, with clinical data derived from a post hoc subgroup analysis of KEYNOTE-204.[3] For this scenario analysis, independent semi-parametric models were fitted to each arm, with BV used as a proxy for the chemotherapy comparator. The same method was used to identify break-points as for the other subgroups, with a break-point at Week 26 chosen based on visual inspection of the cumulative hazards plot. The best fitting distribution to the data beyond Week 26, the exponential, was not chosen for the parametric extrapolation, because the hazards were not found to be constant.

The log-normal, the second-best fitting distribution for the comparator arm, was chosen for the trial-based scenario.

Although this scenario anlaysis was useful, the ERG noted that assuming comparable efficacy between BV and IGEV was a major simplifying assumption that was not underpinned by clinical clincal data, and therefore preferred the company's base case proportional hazards approach, despite its limitations.

SCT-3L+ and SCT+3L+ subgroups

Clinical data used to estimate PFS for both pembrolizumab and BV were derived from post-hoc subgroup analyses of KEYNOTE-204.[3] The ERG noted that small patient numbers within each of these subgroups may introduce uncertainty in the results, however direct comparative data versus a relevant comparator was considered a strength.

In order to model long-term PFS, the assumption of proportional hazards was assessed. The log-cumulative hazards for each arm were plotted and the ratio of hazards was not found to be constant with respect to time. Hence, the company opted to fit independent semi-parametric models, where data from a Kaplan-Meier curve was used up to a cutpoint after which a parametric curve was employed, to each treatment arm, an approach discussed by e.g. Latimer et al. (2011).[28]

Chow tests were conducted at multiple time points to detect structural changes in PFS. The ERG noted that while the Chow test can be used to assess whether a single structural-break occurs at a known time point, it is not recommended for detecting time points at which structural-breaks may occur.[29] The break-points were identified through visual inspection of the test statistics plotted against time for each treatment. As the degrees of freedom or reference lines were not shown on the plots, the ERG could not determine whether the test statistics were statistically significant. Prominent changes in the plotted test statistics were identified at Weeks 26 and 52 for the pembrolizumab arm and at Week 52 for the BV arm.

Cumulative hazards plots were reviewed before the break-points were selected. The ERG noted a substantial increase in hazard around Week 12 in both arms, with smaller increases approximately every subsequent 12 weeks. This may be due to the dates of the tumour imaging data assessment (the first of which occurs around eight to 10 weeks after the initial dose), and subsequent checks for sustained response, rather than periodic increases in the proportion of patients with progressed disease. It could be argued that a smoother modelling approach for the trial period would be preferable in order to prevent sudden steep drops in modelled PFS, which would be unlikely to occur in clinical practice with this patient population.

A delayed treatment effect was suspected for pembrolizumab based on prior immunological knowledge, with the full benefit believed to well-established within the first six months, and so break-points of less than 24 weeks were avoided. However, an investigation of the hazards in the first six months might have indicated a time point by which the treatment effect had become fully-established, with a break-point of less than 24 weeks separating the time period in which the effect was fully established from that in which it was not. The Kaplan-Meier plots were also reviewed to ensure that at least 10 events occurred following the potential break-points.

A semi-parametric piecewise modelling approach was used in the company's base case and SCT-3L+ & SCT+3L+ subgroup analysis, with a break-point at Week 52. The KEYNOTE-204 Kaplan-Meier estimators were used to model PFS directly until Week 52, with a log-normal distribution fitted to the data beyond Week 52 used for parametric extrapolation. Scenarios with break-points at Week 0 or Week 26 (Scenarios 3 and 4, respectively) were considered, along with the following alternative distributions: the exponential, Weibull, Gompertz, log-logistic and generalised gamma.

The ERG noted that, with a break-point at either Week 26 or Week 52, the differences among the distributions in AIC and BIC scores were small, indicating that there was little difference in the relative statistical fit to the data (according to Burnham and Anderson (2002)[30] a rule of thumb is that models with differences in AIC of less than 2 cannot be distinguished). But the results of scenario analyses using alternative distributions for modelling PFS were not presented in the submission.

A break-point at Week 0 or at Week 26 was not selected for the company's base case involving the KEYNOTE-204 ITT population, since the modelled five-year PFS obtained with the best fitting distribution at those break-points (prior to convergence of the generalized gamma for the BV arm) was lower than expected: the clinical experts consulted by the company gave five-year PFS estimates of 15% for patients with prior ASCT and 10% for those ineligible for transplant. These estimates were higher than the five-year PFS estimate of 5% for third-line patients, suggested by the clinical expert consulted by the ERG.

Week 52 was chosen as the break-point in the SCT-3L+ and SCT+3L+ subgroup analysis by the company for consistency with the company's base case. This means that, while the Kaplan-Meier estimators were used directly for a longer period, fewer trial data informed the parametric extrapolation than would have been the case had an earlier break-point been selected.

The log-normal was the second-best fitting distribution to the data beyond Week 52 based on AIC and BIC scores. The best fitting distribution, the exponential, was not chosen for the

parametric extrapolation, because the company stated that the hazards were not found to be constant. This was also the case for the data beyond Week 26.

In the ERG base-case, the log-normal distribution fitted to the data beyond Week 26 was selected. The ERG regarded that this was a reasonable and appropriate choice of distribution across both 3L+ subgroups, balancing parsimony in model fit and across subgroups and accounting for the pattern of hazards following the cutpoint. The earlier break-point means that more of the trial data inform the parametric extrapolation, which may introduce less uncertainty. Since these data were collected after the first six months of the trial, the treatment effect should have been well-established (company response A8a).

The semi-parametric piecewise modelling approach was used in the ERG base case, as the log-cumulative hazard plots for the SCT-3L+ & SCT+3L+ subgroups could not be well approximated by straight lines (see Figure 3 and Figure 4).

Figure 3. Log-cumulative hazard plot for the SCT+3L+ subgroup

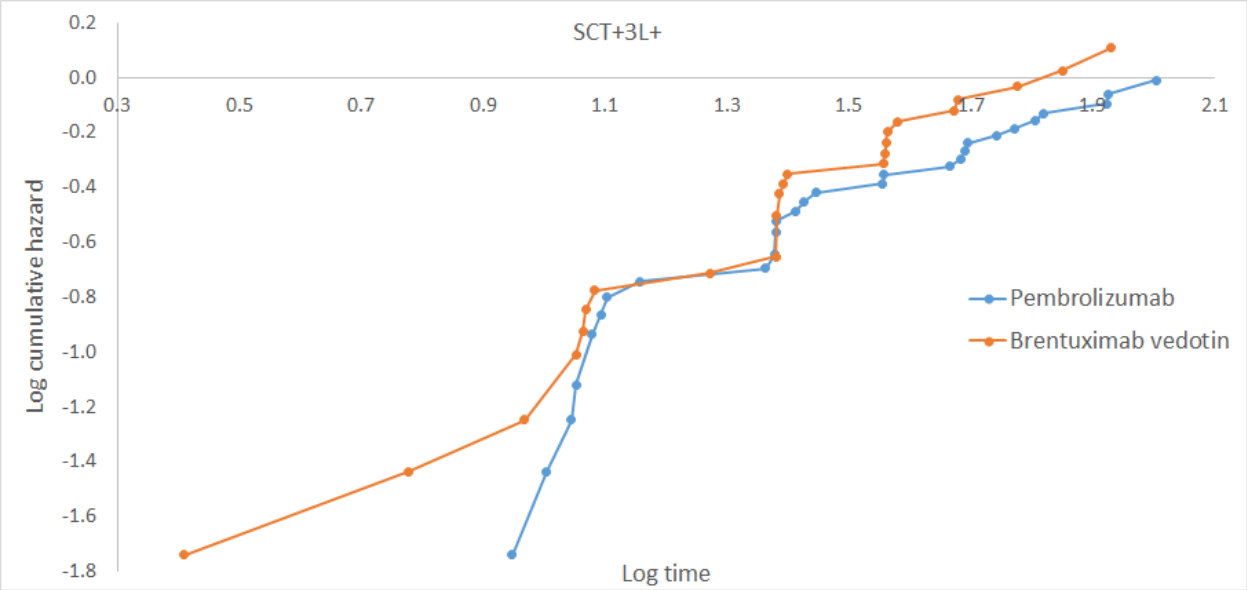
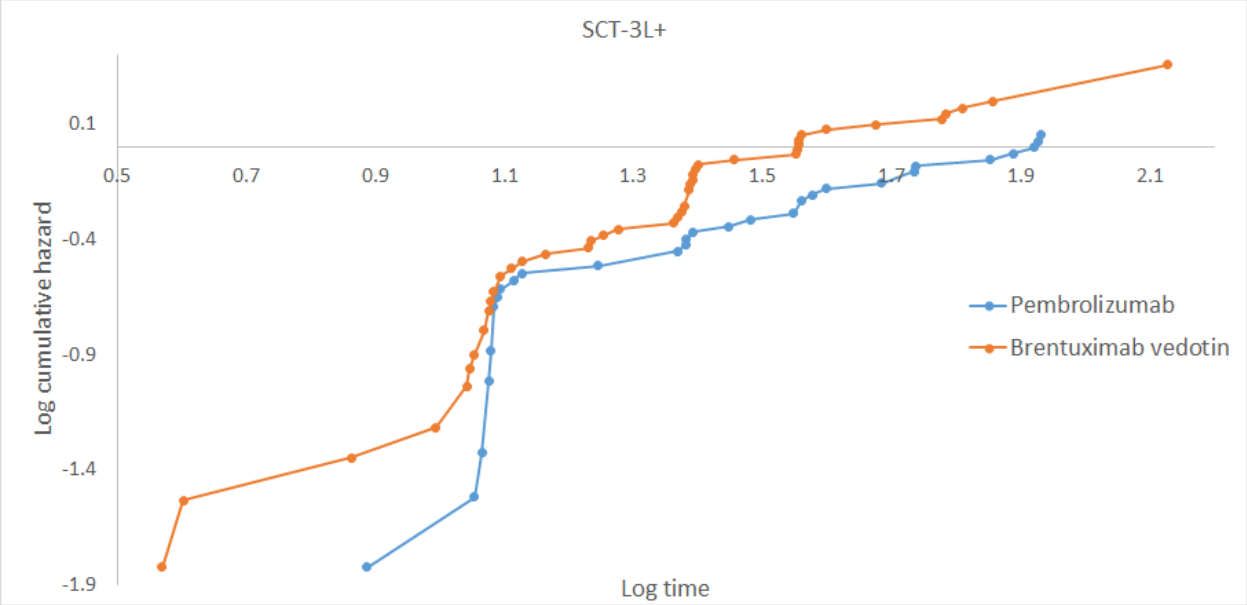


Figure 4. Log-cumulative hazard plot for the SCT-3L+ subgroup



An alternative approach would be to use a more flexible model, such as the distributions proposed by Jackson et al. (2010),[31] of which the generalized gamma is a special case. The generalized gamma provided a much better statistical fit to the full SCT-3L+ subgroup data than the other parametric distributions considered (as assessed by AIC and BIC statistics), as well as the best fit to full SCT+3L+ subgroup data for the pembrolizumab arm. The ERG conducted a scenario with PFS modelled by full-fitted generalized gamma distributions for each arm (i.e. with a break-point at Week 0).

In the company's SCT-3L+ subgroup analysis, the modelled five-year PFS was [redacted] and [redacted] for pembrolizumab and BV, respectively. For the SCT+3L+ subgroup, the modelled five-year PFS was [redacted] and [redacted] for pembrolizumab and BV, respectively.

Uncertainty surrounding the maintenance of pembrolizumab treatment effect on PFS

In the base case the company assumed that after patients discontinue treatment in Year 2, PFS for pembrolizumab would be maintained i.e. efficacy did not diminish after stopping treatment. Due to the lack of clinical data supporting this assumption, the ERG asked the company to provide a scenario analysis which incorporated a waning in PFS treatment effect for pembrolizumab after treatment discontinuation (from Year 3) until no difference in PFS was observed between treatments by Year 5. A similar approach had been used in NICE TA655[32] for assessing uncertainty surrounding OS, given limited long term clinical evidence.

However, the company did not provide this analysis, and stated that the scenario would not be appropriate to conduct on the basis that a highly conservative approach was already adopted in the modeling of OS. The ERG acknowledged that the company's base case approach of assuming no diffference in OS could be considered conservative, however, as noted above there is uncertainty surrounding the maintenance of pembrolizumab PFS benefit after patients stop treatment. The ERG was of the opinion that exploratory analyses incorporating a waning in pembrolizumab PFS treatment effect would be useful and therefore have conducted this scenario analysis for each subgroup (see Section 6.2.1.3).

4.2.7. Health-related quality of life

The company's base case analysis included disutilities associated with grade 3-5 adverse events, which are outlined on p212 and p213 of the CS. Due to the absence of disutility data from KEYNOTE 204,[3,4] the list of events and durations were based on previous NICE TAs and published literature. Disutilities for several adverse events including anaemia, diarrhoea and neutropenia were based on the average of values reported accross different data sources. To derive treatment specific disutility for both pembrolizumab and the comparator, disutilities associated with each adverse event were multiplied by the treatment specific rates from the ITT population in KEYNOTE 204 (see Table 118 in the CS). For the SCT-2L subgroup, chemotherapy (IGEV) adverse event rates were derived from NICE TA462[13] for Nivolumab, based on published study by Santoro (2007).[33] Santoro et al. (2007)[33] was an Italian prospective study designed to assess response rates, toxicity and stem cell mobilisation in 91 patients with refractory or relapsed Hodgkins Lymphoma.

The ERG noted that the company had applied the ITT adverse event rates to the SCT-3L+ and SCT+3L+ subgroups. Given the availability of subgroup data, it could be argued that these data should have been used. The ERG noted that adverse event rates were broadly similar between pembrolizumab and BV (based on subgroup data provided by the company during the clarification process), although for the SCT+3L+ subgroup, patients on pembrolizumab appeared to experience more infections and infestations compared to those on BV ([redacted] vs [redacted] respectively).

Overall, adverse events and associated disutilities did not appear to be a key driver of incremental QALYs within this submission, due in part to the 'front loading' of disutilities, whereby they were applied to Cycle 0 only. The company justified this approach on the basis that it has been used previously in NICE TA462[13] and TA540.[14] During the clarification process, the company noted an error surrounding the application of adverse events within base case the economic model and therefore provided updated results which are reflected in 5.1.1.

The company undertook a systematic literature review to identify studies reporting health-related quality of life or utility values (Section 4.1). However, determined the use of utility values from the KEYNOTE-204[3,4] study to be most aligned with the NICE reference case. Utility values used in the company's base case were derived from the ITT population within the KEYNOTE-204 study (Table 12). Values were elicited directly from patients using the EQ-5D-3L, which is considered an appropriate quality of life measure and reflects NICE guidance. Questionnaires were completed every 12 weeks from Cycle 1 (baseline) until disease progression or up till one year whilst the patient is on treatment. The valuation set used to convert the EQ-5D-3L health states into a single summary index (utility value) was based on UK public preferences using the time trade off (TTO) method from Dolan et al. (1997),[26] which elicited values from 3,395 members of the UK population.

Table 12: Base case utility values

Treatment	PFS utility	PD utility
Pembrolizumab	[redacted]	[redacted]
BV	[redacted]	[redacted]
Pooled utilities	[redacted]	[redacted]

Abbreviations: BV, brentuximab vedotin; PD, progressed disease; PFS, progression-free survival

The ERG acknowledged that using utility values elicited directly from patients within KEYNOTE-204[3,4] (as opposed to published literature sources) may be considered a strength; however, there are several uncertainties surrounding the approrpiateness of the progressed disease utility values which should be highlighted. These include the following:

- Utility values for progressed disease based on only two time points within 30 days:

  As patients in KEYNOTE-204 completed EQ-5D-3L questionnaires up to one year or until progression, it was unclear how the company captured utility for those in the progressed disease health state. The company was asked to comment and subsequently noted that patient reported outcomes (PRO's) were obtained at discontinuation and at the 30-day safety follow up visit. The ERG noted that the 30-day time frame used to estimate PD utility is short and unlikely to sufficiently capture changes in QoL.

- PD utility values were derived from fewer patients than the progression free health state:

  Values for the progressed disease health state were based on [redacted] patients in the pembrolizumab arm and [redacted] patients in the BV arm. This is considerably lower than the patient numbers used to estimate values for the progression free health state ([redacted] patients

and [redacted] patients in the pembrolizumab and BV arms respectively). As such, due to the relatively small patient numbers, utility values for the progressed disease health state may be associated with increased uncertainty.

- The progressed disease utility value for pembrolizumab appears to lack face validity:

  Clinical opinion to the ERG noted that the progressed disease utility value for pembrolizumab did not appear to be plausible. It was acknowledged that the utility decrement of moving from the progression free to the progressed disease health state is likely to be considerably higher than ([redacted]). Therefore, the value may not reflect the true quality of life burden associated with disease progression.

Given the concerns outlined above surrounding the progressed disease utlity value for pembrolizuamb, the ERG was of the opinion that the base case incremental QALY gain associated with pembrolizumab was subject to uncertainty and likely to be overestimated. The company provided a scenario analysis for the ITT population, which used the pooled value of [redacted] for the progressed disease health state (applied to both treatment arms). This resulted in a [redacted] incremental QALY gain reduction for pembrolizumab (from [redacted]). Although this served as a useful analysis, scenario analyses were not provided for the individual subgroups, which was considered a major limitation. Furthermore, the pooled value may not be appropriate to use for both treatments given that the progression free utility value for BV is [redacted]. This suggests a minimal reduction in quality of life upon disease progression for BV patients, which lacks plausibility.

The ERG noted that in NICE TA524[12] a lower utility value was used for the estimation of PD i.e. 0.38, which was derived from a published study by Swinburn et al. (2015).[34] Within this study utility was estimated for patients with R/R Hodgkin lymphoma and anaplastic large cell lymphoma. The ERG found that the PD utility value estimated by Swinburn et al. (2015),[34] was not particularly robust, given that they were not elicited directly from patients but rather from a relatively small sample of the UK population (n=100) using vignettes. Therefore the company's decision to not use Swinburn et al. (2015),[34] within their base case analysis seems justifiable. In TA524,[12] a scenario analysis was provided which estimated PD utility based on the Checkmate205[35] study, a single-arm study of nivolumab in patients with cHL following failure of ASCT. Within the study QoL data were collected from nivolumab treated patients using the EQ-5D. The PD value for these patients was estimated to be 0.715 and is outlined in SMC 1240/17.[36]

Given the limitations surrounding the PD utility value for pembrolizumab and in order to adequately test uncertainty, the ERG suggested a more reasonable approach was to remove the

difference in PD utility between treatments (whilst retaining in the PFS health state) (Section 6.2.1.2). This approach retained the treatment specific utility associated with pembrolizumab and BV in the PFS health state (observed in KEYNOTE-204[3,4]), whilst addressing uncertainty surrounding the PD state value. For this scenario the BV value for PD (was applied to both treatment arms) as it appeared to better reflect the QoL of patients whose disease had progressed and is similar to the value reported in SMC 1240/17.[36]

As an exploratory analysis, the ERG conducted an additional scenario anlaysis for each subgroup which removed treatment specific utility differences from the model (by applying BV utilities from KEYNOTE 204[3,4] to both treatment arms). This analysis was considered to be somewhat pessimistic given that direct QoL trial data are ignored (see Section 6.2.1.1).

4.2.8. Resources and costs

4.2.8.1. Medicine acquisition costs

The company noted that pembrolizumab is supplied in 100 mg vials and the list price per vial is £2,630. The ERG confirmed that this was reflective of BNF pricing. Treatment costs in the model were based on a fixed dose of 200 mg every three weeks resulting in a cost of £5,260. The dosing schedule appeared to be in line with pembrolizumab dosing in KEYNOTE-204[3,4] and the SmPC.

A patient access scheme (PAS) was submitted by the company, which reduced the price of pembrolizumab by [redacted]. The company stated that the current CAA discount in place for pembrolizumab is [redacted], however, as the discount will increase to [redacted], on TAG publication of pembrolizumab ID1140 for untreated metastatic or unresectable recurrent squamous cell head and neck cancer, the [redacted] will be used and is considered appropriate. The cost of pembrolizumab per three-week treatment cycle (with PAS) was therefore estimated to be [redacted].

The company provided scenario analysis results for the ITT population using a dose of 400 mg administered every six weeks, which did not have a meaningful impact on the ICER (see p250 of the CS). The company stated this this alternative dose forms part of draft SMPC, which has yet to receive CHMP opinion. For completeness, the ERG has considered this alternative dose within a scenario analysis for each subgroup (see Section 6.2.1.7).

Within the economic model, treatment costs were further adjusted to reflect the dose intensity within KEYNOTE-204 (98%). This was applied to both the pembrolizumab and BV treatment arms. For completeness the ERG conducted a scenario analysis for each subgroup assuming 100% dosing intensity in both treatment arms (Section 6.2.1.6).

For BV, the list price was estimated to be £2,500 per 50mg vial, as per the BNF. The company estimated the cost per cycle based on the sum product of the number of vials used and cost per vial. The ERG understood that a patient would therefore require 3 vials (administered at 1.8 mg/kg and assuming patient weight of 77 kg). The cost per treatment cycle used in the economic analysis was estimated to be £7,365, when adjusted for trial based dose intensity (see p220 of the CS). The company assumed drug wastage in the model, which was considered reasonable. Based on clinical opinion to the ERG, it was noted that vial sharing is unlikely to reflect current practice given concerns surrounding treatment shelf life/storage and small patient numbers.

For the SCT-2L subgroup, the company acknowledged that there is range of multi agent chemotherapy agents available for use within this subgroup of patients and that frequency of use is likely to differ across UK centres. The company therefore used a published study by Eyre et al. (2017)[23] to inform the list of potential regimens. The ERG note that this study was relatively recent (2017) and UK based, which is considered a strength. However, patients included in the study had two prior lines of chemo therapy and had received BV. It is therefore unclear whether treatment regimens from this study are fully generalisable to the SCT-2L population (see Table 82, p210 of the company's Appendices document for list of chemotherapy regimens used in the company's base case).

The proportion of patients receiving each treatment regimen was based on Eyre et al. (2017),[23] but amended using clinical opinion to reflect recent changes in treatment use (see Table 83 on p211 of the company's Appendices document). Clinical opinion to the ERG noted that bendamustine is used in the UK within this patient population. However, the company did not include this as a plausible treatment option, which somewhat limits the validity of the company's treatment list. Treatment acquisition costs were derived from the drugs and pharmaceutical electronic Market Information Tool (eMIT) and seemed to be largely accurate. The ERG noticed a minor error with respect to the cost of vinorelbine, which the company estimated to be £3.67 per 10 mg/1ml solution; however, the price in eMIT was £36.71. For completeness the ERG has amended this cost to reflect eMIT pricing, which is included in the ERG preferred base case (see Section 5.3). Furthermore, it was not possible to verify the cost of chlorambucil (£1.71) using eMIT. When crosschecked with the BNF, the price was higher (£42.87).

As noted in 4.2.8.3, for the ITT analysis, the unit costs of subsequent treatments were included and derived using eMIT (see p224 of the CS). Overall, costs were largely accurate though several costs could not be validated using eMIT. The ERG considered that potential variation in unit cost estimates for chemotherapy treatments, may not be a primary concern given the minor nature of these costs (with respect to the relatively high acquisition cost of pembrolizumab) and that the

ITT analysis and list of subsequent treatments is not considered to be reflective of each subgroup. See Section 4.2.8.3 for further commentary on subsequent treatment use.

4.2.8.2. Time on treatment (ToT)

According to the SmPC for pembrolizumab,[37] treatment should be continued until progression or unacceptable toxicity. However, it is worth noting that the economic model incorporates a two-year stopping rule, whereby all patients were assumed to discontinue treatment after two years. The company highlighted that this was in line with the KEYNOTE-204 protocol, where treatment was mandated to stop at 35 cycles/105 weeks. The ERG noted that this assumption was used in previous NICE technology appraisal guidance including TA428 (pembrolizumab for PD-L1 NSCLC after chemotherapy).[38] Within TA428, clinical experts commented that the decision to stop treatment would be made between the clinician and the patient, and that the number of patients likely to have treatment after two years would be small. Clinical opinion to the ERG advised that the stopping rule is likely to be adhered to in practice, given that it is part of the marketing authorization for pembrolizumab. Overall, the inclusion of a two-year stopping rule appeared to be consistent with previous NICE technology appraisals and clinical opinion.

SCT-2L subgroup

The same approach was used for modelling ToT in the pembrolizumab arm of the SCT-2L subgroup as for the other subgroups. Due to the lack of ToT data for chemotherapy (IGEV), ToT was set equal to PFS for the comparator. Given the lack of available evidence, the ERG considered this to be reasonable and used the same approach for the ERG base case.

SCT-3L+ and SCT+3L+ subgroups

ToT was modelled separately for the pembrolizumab and BV arms using a semi-parametric approach, which allowed ToT to be extrapolated beyond that observed in KEYNOTE-204[3,4] until the maximum duration of treatment (assumed to be 35 cycles/100 weeks). The company used the same modelling approach for the SCT-3L+ and SCT+3L+ subgroup analyses as for the ITT population, differing only in the portion of the data used. The KEYNOTE-204 Kaplan-Meier estimators were used directly until Week 80, with an exponential distribution fitted to the data beyond Week 80 used for parametric extrapolation.

The break-point at Week 80 was chosen as KM data for the ITT population was available until Week 88: the company wished to use the KM estimators to model ToT directly for as long a period as possible, while ensuring that what was considered to be an adequate number of events remained for fitting a parametric distribution for extrapolation. The ERG noted that while KM data

were available at least until Week 88 for the SCT-3L+ subgroup, the last recorded event in the BV arm for the SCT+3L was at 82.6 weeks.

The company selected the exponential distribution for extrapolation on the basis that it produced the lowest AIC & BIC statistics. Information on the assessment of hazards for ToT was not available in the CS.

Uncertainty surrounding the company's ToT modelling approach

The company assumed a maximum treatment duration of 35 cycles (105 weeks) for both pembrolizumab and BV in the SCT-3L+ and SCT+3L+ subgroups, which does not appear appropriate. Although the use of 35 cycles was consistent with the two-year pembrolizumab stopping rule, based on the SmPC for BV, the maximum number of cycles that treatment should be given is 16. Assuming 35 cycles for BV therefore potentially overestimates the medicine costs. The company did conduct a scenario analysis which assumed a maximum treatment duration of 16 cycles for BV (this was applied to costs only as efficacy was assumed to be maintained for 35 cycles (see p253 in the CS), The ERG considered that 16 cycles should be used and therefore this assumption forms part of the ERG's base case (Section 6.2.1.19 and Section 6.2.2).

It was recognised that using KM data to Week 80 may reduce extrapolation uncertainty; however, in order to be consistent with the company's PFS modelling approach, the ERG considered that estimating ToT using a 26-week cut point preferable. This was because ToT should be largely coterminous with PFS, as progression would often trigger a change in treatment. In order to determine the impact of alternative ToT assumptions on the results, the ERG conducted additional scenario analyses whereby ToT is based on KM data from KEYNOTE-204, as well as using an alternative cut point at 26 weeks. Parameters for ToT with cut point at 26 weeks was provided only for the ITT population during clarification; still, the ERG regarded that this would present more reliable and appropriate estimates (Section 6.2.1.10, Section 6.2.1.11 and Section 6.2.2).

The company did not provide scenario analyses using alternative distributions for ToT. Although the exponential distribution selected by the company exhibited the lowest AIC/BIC score, there was minimal difference between the scores for each distribution. For completeness, the ERG conducted additional scenario analyses using alternative ToT distributions (Section 6.2.1.12 and Section 6.2).

4.2.8.3. Subsequent treatment costs

The ERG noted that subsequent treatment costs were likely to have an impact on the ICER for pembrolizumab (see Sections 6.2.1.18 and 6.2.2). Subsequent treatment costs were included in the model and were assumed to apply once patients entered the PD health state. For the ITT analysis, the list of subsequent treatments was based on the ten most commonly used subsequent treatments within KEYNOTE-204.[3,4] The list of subsequent treatments and proportion of patients receiving each are outlined in Table 13. When estimating subsequent treatments and proportions for each subgroup, the company assumed these to reflect UK clinical practice (see Table 14). Overall, the ERG noted several concerns surrounding the company's base case subsequent treatment estimates which introduce uncertainty and may not reflect appropriate treatments provided in within current clinical practice.

Table 13. Base case subsequent treatments (ITT analysis)

Subsequent treatment(s)	After failing	
	Pembrolizumab	BV
BV	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]
Bendamustine + BV	[redacted]	[redacted]
Etoposide+melphalan	[redacted]	[redacted]
Cyclophosphamide + fludarabine phosphate	[redacted]	[redacted]
Bendamustine + gemcitabine + vinorelbine tartrate	[redacted]	[redacted]
Cisplatin + cytarabine + dexamethasone	[redacted]	[redacted]
Carmustine + cytarabine + etoposide + melphalan	[redacted]	[redacted]
None	[redacted]	[redacted]

Abbreviations: BV, brentuximab vedotin; ITT, intention to treat

Table 14: Base case subsequent treatment assumptions (subgroup analyses)

	Subsequent treatments
SCT-2L	
Pembrolizumab	100% receive BV
IGEV	
SCT-3L+	

	Subsequent treatments
Pembrolizumab	100% BV
BV	100% pembrolizumab
SCT+3L+	
Pembrolizumab	100% BV
BV	100% nivolumab

Abbreviations: BV, brentuximab vedotin

The ERG highlighted uncertainties surrounding subsequent treatments, as follows:

- As noted previously in Section 4.2.3, the ERG did not consider an ITT population to be appropriate for decision making, therefore the subsequent treatments and proportions used for this analysis should be interpreted with caution.

- The ERG noted discrepancies between the subsequent treatment assumptions applied in the model and those outlined in the CS for two key subgroups (SCT-2L and SCT-3L+), which led to differences between the modelled results and those reported in the CS. The company was asked to comment and noted that the default results for SCT-2L and SCT-3L+ in the model did not match the CS results as subsequent therapies were changed manually in the model, before copying results. The ERG considered the company's response helpful and that it clarifies the disparity between results.

- There was concern surrounding the use of pembrolizumab as the subsequent treatment for patients who fail on BV in the SCT -3L+ subgroup. As pembrolizumab at this line of treatment is included within the Cancer Drugs Fund (CDF), clinical opinion was sought to determine what treatment would be given to patients who did not have the option to be treated with pembrolizumab. It was suggested that further chemotherapy (typically with a regimen that does not contain an anthracycline) should be considered. Such options included bendamustine alone, bendamustine+gemcitabine+vinorelbine, gemcitabine with Cis- or carboplatin and dexamethasone, ChlVPP (chlorambucil with vinblastin, procarbazine and prednisolone) or similar combinations. The ERG conducted a scenario analysis for this subgroup, which assumed that 100% of patients who failed BV went on to receive 'bendamustine' only (Section 6.2.1.18).

- The ERG noted that the handling of subsequent treatment in the SCT+3L+ subgroup appeared to be inappropriate, as the company assumed that 100% of patients who failed on pembrolizumab went on to receive BV, whilst 100% of patients who failed BV went on to

receive nivolumab. Based on a review of the treatment pathway for this subgroup, patients in both treatment arms should receive nivolumab as subsequent treatment (Section 6.2.1.18).

4.2.8.4. Monitoring, administration and resource use costs

The ERG acknowledged that monitoring and resource use were not considered to be a key cost driver within this submission. However, there were concerns surrounding the estimation of resource use for the PD health state, which requires comment.

The company stated that data pertaining to resource use for patients with R/RcHL were limited and therefore estimates were derived from a previously published NICE appraisal TA446 for BV.[39] Resource use costs were valued using 2018/19 NHS reference costs, which was an appropriate source. However, the ERG considered the company's PET scan cost (£775.51) to be higher than the cost quoted in the NHS reference cost guidance, which was estimated to be £506. Using a lower PET scan cost is unlikely to have any material impact on the ICER, and is therefore not a key concern.

Annual resource use for patients in the PFS health state was based on clinical expert opinion. Estimates therefore may be subject to some degree of uncertainty. The total cost per cycle was £64.27 (see Table 16 below for granularity). In TA446[39] resource use for the PD health state was assumed to be the same as for the PFS health state. The company has adopted the same assumption within the current submission, therefore the cost per cycle associated with progressed disease is also estimated to be £64.27. The ERG considered this to be a simplifying assumption which may not reflect current practice. Clinical opinion to the ERG noted that PD health state costs would be expected to be higher due to deterioration in quality of life and requirement for additional monitoring.

The company acknowledged this limitation within the CS and provided a scenario analysis which assumed patients in the PD health state would require higher resource use, based on clinical opinion to the company (see p232 of the CS). However, the ERG noted that results were provided for the ITT analysis only and not for each subgroup. Furthermore, the scenario analysis assumed that resource use would also decrease simultaneously for patients in the PFS state. Although health state resource use was not considered a key driver of the ICER, the ERG considered that the company's scenario analysis potentially underestimates monitoring and resource use costs for pembrolizumab, whilst overestimating these costs in the comparator arm. For completeness, the ERG conducted a scenario analysis for each subgroup, which applied higher resource estimates to the PD state only.

Table 15: Base case PFS and PD health state costs

Resource	Unit cost (£)	Unit cost source (NHS reference costs 2018-2019 code)[40]	Weekly usage	Cost per cycle	Resource use source
Outpatient attendance	173.39	303: Clinical Haematology, Consultant led follow-up attendance, non-admitted face to face	0.20	34.56	NICE TA446 Committee papers,[39] ERG Table 95 (p210)
Blood count	2.79	DAPS05: Haematology	0.20	0.56	
Biochemistry	1.10	DAPS04: Clinical Biochemistry	0.20	0.22	
CT scan	115.56	RD26Z: Computerised Tomography Scan, three areas with contrast	0.06	6.64	
PET scan	775.51	RN03A: Positron Emission Tomography with computed Tomography (PETCT) of more than three areas, 19 years and over	0.03	22.29	
Total cost per week (£)				**64.27**	

Abbreviations: CT, computed tomography; ERG, Evidence Review Group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PET, positron emission tomography; TA, technology appraisal

Administration costs

For the SCT-2L subgroup, the company has outlined the unit costs for chemotherapy administration in Table 84 on p211 of the Appendices document. The ERG considered the unit costs to be reflective of NHS reference costs 2018/19 and appropriate for use.

Administration costs were calculated in the model by multiplying the number of administrations for each treatment regimen (accounting for both the first and subsequent administrations per cycle) by the relevant cost per administration. For the SCT-3L+ and SCT+3L+ subgroups, the company assumed that both pembrolizumab and BV were administered via IV infusion over 30 minutes (as per the SmPC for each treatment) and used the National Tariff of Chemotherapy Regimens List and NHS reference costs 2018/19, to estimate costs associated with administration. Overall, the company's handling of administration costs within the CS seemed reasonable.

Adverse event costs

On p235 of the CS, the company state that subgroup specific grade 3-5 AEs from KEYNOTE 204[3,4] (with an incidence of ≥2% in any arm) were used to estimate adverse event costs in the base case. The complete list of adverse events are outlined in Table 134 on p236 of the CS. NHS reference costs 2018/19 were used as appropriate to estimate the unit cost of each event,

however NICE TA462[13] was used to estimate the cost associated with nausea vomiting and weight increase.

During the clarification stage the company noted that several AE costs within the model including pneumonia, pneumonitis, rash, thrombocytopenia, vomiting and increased weight) were different from those specified in the CS (Document B, Section B.3.5.6, pp.235-36). The company presented corrected results for the ITT population in response to clarification question A13. Overall, the ERG noted that adverse event costs were only applied to cycle 0 in the model and therefore did not have a material impact on results.

Stem Cell Transplant

In terms of stem cell transplant (SCT), patients in the PFS health state were eligible to undergo either auto-SCT or allo-SCT, based on treatment specific rates from the pivotal study KEYNOTE-204.[3,4] SCT rates used in the base case analysis were derived from subgroup data and are outlined in Table 16. The ERG noted that patient numbers within each subgroup were small, therefore the rates may be subject to uncertainty. The cost associated with an auto-SCT and allo-SCT was estimated to be £22,368 and £114,234 respectively. Costs were based on a published study by Radford et al. (2017),[41] which reported cost and resource use in 40 cHL patients who had failed after auto SCT. Radford et al. (2017)[41] was considered to be the preferred source in TA462[13] for nivolumab. The ERG also noted that this study has been used previously in NICE TA540[14] for pembrolizumab. Costs were inflated to reflect 2018/19 prices as appropriate.

Table 16: Base case SCT rates (derived from KEYNOTE 204 subgroup data)

	Auto-SCT	Allo-SCT
SCT-2L		
Pembrolizumab	[redacted]	[redacted]
IGEV (assumed to equal BV)	[redacted]	[redacted]
SCT-3L+		
Pembrolizumab	[redacted]	[redacted]
BV	[redacted]	[redacted]
SCT+3L+		
Pembrolizumab	[redacted]	[redacted]
BV	[redacted]	[redacted]

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; SCT, stem cell transplantation

Due to the uncertainty surrounding the validity of the base case SCT rates, the ERG considered it pertinent to undertake further sensitivity analysis. SCT rate is a notable, but not central, factor

affecting ICERs. A scenario analysis has therefore been conducted for each subgroup which sets SCT rates equal between groups (see Section 6.2.1.5). Given that base case SCT rates are subject to uncertainty and are associated with high costs, the ERG's preferred base case was to set these rates equal to each other between arms. See Section 6.2.1.5 for further discussion on how this scenario analysis impacts incremental costs and QALYs in each subgroup.

Terminal care costs

The company applied a once off cost of £4,462 to each death event in the model. The cost was based on a published study by Brown et al. (2013)[42] and represents the weighted average of hospital, hospice and home setting costs. Brown et al has been used to estimate terminal care costs previously in NICE TA540[14] and have been updated. The ERG noted that terminal care costs were not considered a key driver within the model.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

5.1.1.1. ITT population

Results of the company's base case analysis were presented as an ICER for pembrolizumab compared to BV. The results presented in the CS (Document B, Section B.3.7.1, p240) were based on incorrect costs for the AEs: the costs incurred for AEs (pneumonia, pneumonitis, rash, thrombocytopenia, vomiting and increased weight), applied in the model were different from those specified in the CS (Document B, Section B.3.5.6, pp.235-36). The company presented corrected results for the ITT population in response to clarification question A13. The model version submitted to the ERG following this correction is referred to as "revised model" in the sections below. The total and incremental costs, life years (LYs), and QALYs, and the ICER were replicated in Table 17 below. A patient access scheme (PAS) of [redacted] was applied to the acquisition cost of pembrolizumab.

Table 17: Company base case deterministic results

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

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

Source: Company "revised model" (clarification response 5 November 2020)

Based on the results, pembrolizumab was considered the dominant treatment when compared to BV resulting in an incremental QALY gain of [redacted] and incremental savings of [redacted]. Incremental savings were mainly due to lower medicines acquisition costs associated with pembrolizumab. As noted throughout this report, pembrolizumab was not associated with a survival gain, therefore incremental QALYs versus BV stem primarily from a higher proportion of patients remaining in the progression free health state.

5.1.1.2. Subgroup results

The results for the subgroups following model revision, were also presented by the company in an appendix to its response to clarification questions.

SCT-2L

For the SCT-2L subgroup, results of the company's base case analysis were presented as an ICER for pembrolizumab compared to salvage chemotherapy (IGEV). Total and incremental costs, life years (LYs), and QALYs were presented in the CS (Document B, Section B.3.9.1, p257); however, they were subsequently updated as per the company's "revised model" as replicated in (Table 18) below. A PAS of [redacted] was applied to the acquisition cost of pembrolizumab.

Table 18: Company base case deterministic results: SCT-2L

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	Lys	QALYs	
Company base case (deterministic)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	[redacted]	-	
IGEV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,581

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

Source: Company "revised model" (clarification response 5 November 2020)

As noted above, pembrolizumab resulted in an ICER of £53,581 compared to salvage chemotherapy based on incremental costs of [redacted] and an incremental QALY gain of [redacted]. Incremental costs were mainly due to higher medicines acquisition costs associated with pembrolizumab. Pembrolizumab was not associated with a survival gain, therefore incremental QALYs versus IGEV stem primarily from a higher proportion of patients remaining in the progression free health state.

SCT-3L+

For the SCT-3L+ subgroup results, the company's base case analysis were presented as an ICER for pembrolizumab compared to BV. Total and incremental costs, life years (LYs), and QALYs were presented in the CS (Document B, Section B.3.9.3, p260), and were subsequently updated as per the company's "revised model" as replicated in (Table 19) below. A patient PAS of [redacted] is applied to the acquisition cost of pembrolizumab.

Table 19: Company base case deterministic results: SCT-3L+

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

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

Source: Company "revised model" (clarification response 5 November 2020)

For this subgroup pembrolizumab was considered to dominate BV resulting in incremental savings of [redacted] and an incremental QALY gain of [redacted]. Incremental savings were mainly due to lower medicines acquisition costs associated with pembrolizumab. Pembrolizumab was not associated with a survival gain, therefore incremental QALYs versus BV stem primarily from a higher proportion of patients remaining in the progression free health state.

SCT+3L+

For the SCT+3L+ subgroup results, results of the company's base case analysis were presented as an ICER for pembrolizumab compared to BV. Total and incremental costs, life years (LYs), and QALYs were presented in the CS (Document B, Section B.3.9.2, p260); however, they were subsequently updated as per the company's "revised model" as replicated in (Table 20) below. A PAS of [redacted] is applied to the acquisition cost of pembrolizumab.

Table 20: Company base case deterministic results: SCT+3L+

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

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

Source: Company "revised model" (clarification response 5 November 2020)

For this subgroup pembrolizumab was considered to dominate BV resulting in incremental savings of [redacted] and an incremental QALY gain of [redacted]. Incremental savings were mainly due to lower medicines acquisition costs associated with pembrolizumab. Pembrolizumab was not associated with a survival gain, therefore incremental QALYs versus BV stem primarily from a higher proportion of patients remaining in the progression free health state.

5.2. Company's sensitivity analyses

In addition to exploring the role of parameter uncertainty on the model results, the CS also reported several sensitivity analyses which explored the impact of alternative settings and assumptions. These are discussed further below.

Overall, the ERG considered the approach taken for sensitivity analysis to be appropriate.

5.2.1. One-way sensitivity analysis

The company conducted a deterministic one-way sensitivity analysis (OWSA) with the included parameters as presented in CS (Document B, Table 139). The CS stated that where data were available, parameters were varied using 95% confidence intervals, otherwise upper and lower bounds were varied by a standard error of 10% of the mean (base case) value.

A tornado plot was used to present the OWSA results in the CS (Document B, Figure 55) for pairwise comparison of pembrolizumab vs. BV for the ITT population, with the ICER as the outcome of interest. The plot showed the results were most sensitive to the PFS and PD health state utility values of pembrolizumab and BV and disount rate for outcomes. However, the OWSA results for the subgroups were not presented in the CS.

The ERG noted that the OWSA results were not impacted by the changes to the company's revised model.

5.2.2. Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) to explore the impact of parameter uncertainty when the model parameters' were varied as per the respective distributions (CS, Document B, Table 137). The PSA was run for 1,000 iterations.

The company's "revised model" presented updated PSA results provided in Table 21.

Table 21: Company PSA

Arm	Totals		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Company presented probabilistic base case					
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	
BV	[redacted]	[redacted]	[redacted]	[redacted]	34,540
Company probabilistic base case – using correct model settings					
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	
BV	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-39,266)

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

The ERG noted that the incremental costs were positive in the PSA and not aligned with the deterministic base case results. The ERG investigated the PSA macro but did not identify any errors and assumed that it might be due to incorrect model settings while running the PSA. Therefore, the PSA was re-run by the ERG using the correct settings and the results following the re-run are provided in (Table 21) above.

Further, as per the revised model, the company stated that at a willingness-to-pay threshold of £30,000 per QALY gained, the probability of pembrolizumab being cost-effective versus BV for the ITT population was 40%. However, the ERG noted that, when re-running the PSA with the correct model settings applied (as indicated above), the probability of pembrolizumab being cost-effective versus BV for ITT population changed to 92%.

In addition, the ERG noted that the PSA results were not presented for the subgroups in the CS. Details on the PSA for subgroups carried out as part of ERG additional analyses are given in Section 6.2.3.

5.2.3. Company's scenario analyses

The company conducted several scenario analyses to assess the impact of alternative settings and assumptions and the structural uncertainties on the base case results. Scenario analysis results were provided in the CS (Document B, Table 140).

Scenarios with alternative OS data increased the incremental QALYs of pembrolizumab vs BV whereas the scenario with pooled post-progression utility decreased the incremental QALYs. Scenarios with no vial sharing, alternative maximum number of cycles with BV and subsequent treatments based on KEYNOTE-204[3,4] excluding pembrolizumab increased the incremental costs whereas the scenarios with alternative resource use, subsequent treatments based on UK

market shares and alternative dosing for pembrolizumab decreased the incremental costs. In all the scenarios presented pembrolizumab remained dominant versus BV, in line with the base case.

The scenario analyses presented were limited in number and focused on the ITT population, with none exploring the differences in modelling the PFS and OS across the subgroups considered. The results of the scenario analyses did, however, highlight the influence of the data used to model and extrapolate overall survival, alternative assumptions on utilities and subsequent treatments.

5.3. Model validation and face validity check

The ERG found the company's cost-effectiveness model to be mostly free of errors, however some minor issues were noted; for example, use of inconsistent labelling of the Cholesky matrices, duplication of a parameter for Weibull fit, non-convergence with generalized gamma. These errors were either fixed by the company during clarification and were incorporated in the "revised model" provided in the clarification response or were found not to have any impact on the model results.

Briefly, the errors corrected are listed below:

- An error in the chemotherapy (IGEV) PFS meant that the proportion of patients progression-free in each arm at each time point did not correspond to the hazard at that time point. This error affected the SCT-2L subgroup analysis.
- An error in the maximum treatment cycle reference for BV meant that the maximum treatment cycle for pembrolizumab was used for both arms, regardless of the model settings. This affected the ITT population and SCT-3L+ and SCT+3L+ subgroups. However, the results for the company's base case and subgroup analysis remain unchanged, since the same maximum number of cycles was selected for both arms. Hence, these fixes are not shown in Table 22 below.
- As noted in Section 4.2.8.1, a minor error was noted in the company's model with respect to unit cost for vinorelbine. This error affected the SCT-2L subgroup analysis.

Table 22: ERG corrections to the company's subgroup analysis case

Preferred assumption	ICER when applied individually	Cumulative ICER £/QALY
SCT-2L subgroup (pembrolizumab compared to salvage chemotherapy (IGEV))		
Company base case	£53,581	£53,581
Error in chemotherapy PFS	£53,276	£53,276
Amended vinorelbine cost	£53,403	£53,099
ERG corrected company base case	£53,099	–

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1. Exploratory and sensitivity analyses undertaken by the ERG

The ERG carried out a number of exploratory and sensitivity analyses. Table 23 summarises the scenario analyses as applied to each of the three subgroups: (SCT-2L, SCT-3L+, and SCT+3L+).

Table 23. Summary of scenario analyses by subgroup

		Subgroups		
#	**Scenario**	**SCT -2L**	**SCT -3L+**	**SCT +3L+**
1	Utility value for the PD health state	●	●	●
2	Equal PFS and PD utility values	●	●	●
3	Waning of pembrolizumab PFS treatment effect	●	●	●
4	Higher resource use in the PD health state	●	●	●
5	No difference in SCT rates between treatment arms	●	●	●
6	Dose intensity for pembrolizumab assumed to be 100%	●	●	●
7	Pembrolizumab administered 400 mg (every six weeks)	●	●	●
8	Time horizon increased to 50 years	●	●	●
9	KEYNOTE-087 source for OS data (pembro & comparator[a])	●	●	●
10	ToT for pembrolizumab based on KM data only	●	●	●
11	Alternative cut points for modelling ToT (26 wks)	●	●	●
12	Alternate parametric fit (log normal) for ToT (pembro & comparator[a])	●	●	●
13	Subsequent Tx based on subgroup data from KEYNOTE-204	●	●	●
14	Balzarotti et al. (2016) used to estimate OS (pembro & comparator[a])	●	●	NA
15	Balzarotti et al. (2016) for OS + alternative parametric fit	●	●	NA
16	Alternative parametric fit for PFS, applied to both pembro and IGEV	●	NA	NA
17	Combined analysis: PFS (fully parametric) and OS (KEYNOTE 087)	●-W	●-GG	●-GG
18	Subsequent treatments assumed to reflect UK practice	NA	●-ben[b]	●-nivo[c]
19	Reduction in maximum number of cycles of BV	NA	●	●
20	Fully parametric approach to model PFS (generalised gamma curve)	NA	●	●
21	Log-logistic parametric fit for Gopal et al. (2015) OS data (pembro & BV)	NA	●	●
22	Model PFS using different data cut point (26 weeks)	NA	●	●

Abbreviations: -ben, bendamustine; BV, brentuximab vedotin; CTx, chemotherapy; -GG, generalised gamma; NA, not applicable; -nivo, nivolumab; OS, overall survival; pembro, pembrolizumab; PFS, progression free survival; SCT, stem cell transplantation; ToT, time on treatment; Tx, treatment; -W, Weibull; wks, weeks

Notes: a Comparator: SCT-2L = IGEV; SCT-3L+ & SCT+3L+ = BV; b 100% of patients who fail pembro go on to receive BV AND 100% of patients who fail BV go on to receive bendamustine alone; c 100% of patients who fail pembro go on to receive BV AND 100% of patients who fail on BV go on to receive bendamustine alone

The following adjustments were relevant to the PSA and are not associated with a deterministic ICER:

- OS modelled separately for both pembrolizumab and the comparator treatment
- PFS HR varied using the 95% confidence interval from the MAIC.

6.2. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The scenario analyses described in Section 6.1 are described in turn below. The impact on the ICER (Section 6.3) refers to the company's base case ICER including the ERG corrections detailed in Section 5.3.

6.2.1. Scenario analyses

6.2.1.1. Scenario 1: Utility value for the PD health state

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

The company's base case utility value for the pembrolizumab PD state was associated with uncertainty and considered implausibly high (see Section 4.2.7). This scenario analysis removes the difference in treatment specific values in the PD health state by applying the BV PD health state value ([redacted]) to both pembrolizumab and the comparator (IGEV [SCT-2L] and BV [SCT-3L+ and SCT+3L+]). The ERG considered this value to better reflect the quality of life for patients with PD. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.2. Scenario 2: Equal PFS and PD utility values

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

In this scenario it was assumed that pembrolizumab and the comparator treatment (IGEV [SCT-2L] and BV [SCT-3L+ and SCT+3L+]), were associated with the same PFS and PD utility values i.e. pembrolizumab was not associated with a treatment specific utility gain. Utilities were based on BV values within KEYNOTE-204.[3,4] The ERG recognised that this assumption may be highly conservative given that QoL data reported within the pivotal study detected treatment specific differences in utility. However, given the uncertainties surrounding these trial-based utilities (Section 4.2.7), and the sensitivity of the ICER to changes in utility, the ERG considered this

scenario analysis would address further uncertainty. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.3. Scenario 3: Waning of pembrolizumab PFS treatment effect

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

As noted in Section 4.2.6, due to the lack of long-term clinical effectiveness data, there is some uncertainty surrounding the maintenance of pembrolizumab treatment effect with respect to PFS (after patients discontinue). The ERG noted that in the absence of long-term clinical efficacy data, scenario analyses which incorporate a waning in treatment effect are helpful to address uncertainty, although this assumption appears to have only been applied to OS previously (NICE TA655[32] and TA428[38]). For this scenario analysis, a waning in pembrolizumab PFS treatment effect was applied at Year 3 until no difference in hazards was assumed by Year 5. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.4. Scenario 4: Higher resource use in the PD health state

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

Based on clinical advice, the ERG considered it was implausible for patients to have identical costs in both the PFS and PD health state (Section 4.2.8.4). This scenario analysis applied higher resource use assumptions to the PD health state, which were derived from clinical opinion to the company reported within the CS (see Section 4.2.8.4). As such, weekly outpatient visits, blood count and biochemistry tests increased from 0.20 in the company's base case to 0.32, whilst weekly CT and PET scan usage increased from 0.06 and 0.03 respectively to 0.07. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.5. Scenario 5: No difference in SCT rates between treatment arms

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

As noted in Section 4.2.8.4, SCT is not a central model driver as pembrolizumab is not being used as a bridge to transplant, though it may be associated with meaningful shifts to the ICER. However, SCT rates are associated with considerable uncertainty given that they are based on small patient numbers. This scenario analysis assumed no difference in SCT rates between

treatment arms i.e. the pembrolizumab allo-SCT and auto SCT rates are applied to both arms). The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.6. Scenario 6: Dose intensity for pembrolizumab assumed to be 100%

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

As highlighted in Section 4.2.8.1, the company estimated the base case dose intensity for pembrolizumab to be 98%. However, the ERG understood that the dose intensity in practice could potentially be higher than the 98% witnessed in KEYNOTE-204,[3,4] and therefore were interested in determining whether assuming a 100% dosing intensity is likely to impact on the ICER. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.7. Scenario 7: Pembrolizumab administered 400 mg (every six weeks)

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

The company's base case used the licensed dose of 200 mg (every three weeks) which is appropriate (Section 4.2.8.1). However, given the availability of an alternative dose (400 mg administered every six weeks), the ERG conducted an analysis to determine the impact of using this alternative dosing option on the ICER. Given that treatment acquisition costs are a key driver of costs, this scenario is unlikely to have a material impact on the ICER. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.8. Scenario 8: Time horizon increased to 50 years

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

The model predicted that a small proportion of patients remained alive at 40 years (Section 4.2.5). For completeness the ERG considered the model should be run until all patients have died. This scenario is unlikely to have a material impact on results given the small proportion of patients alive at 40 years. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.9. Scenario 9: KEYNOTE-087 as the source for OS data in both treatment arms

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

Given the availability of OS data within KEYNOTE-087[5] (Section 4.2.6.1), the ERG was interested in using available data from this single arm study of pembrolizumab in order to generate OS for both treatment arms (SCT-2L: pembrolizumab and IGEV; SCT-3L+ and SCT+3L+: pembrolizumab and BV). The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.10. Scenario 10: ToT for pembrolizumab based on KM data only

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

As noted in Section 4.2.8.2, there was some uncertainty regarding the company's base case approach to modelling treatment costs. In order to reduce extrapolation uncertainty, the ERG considered that estimating costs using relevant KM data only from KEYNOTE-204[3,4] would accurately reflect trial-based treatment costs. In this scenario (for the SCT-2L subgroup), ToT for pembrolizumab was estimated based on KM data from the ITT population in KEYNOTE 204. Given that KM data were not available for IGEV, ToT was set to equal PFS (26 weeks) for the comparator. For the SCT-3L+ and SCT+3L+ subgroups KM data were available for both pembrolizumab and BV and these were subsequently used to estimate treatment costs. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.11. Scenario 11: Alternative cut-points for modelling ToT (26 weeks)

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

The company estimated treatment costs in the base case by extrapolating ToT at 80 weeks (Section 4.2.8.2). The ERG understood the company's rationale of using as much KM data as possible before extrapolation; however, the company did not provide sensitivity analyses exploring the use of alternative cut points. The ERG considered the use of a 26-week cut point as the most appropriate time for modelling ToT, given that ToT should be largely coterminous with PFS. ITT data were used to undertake this analysis (as opposed to by subgroup) as this was what was provided by the company during clarification. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.12. Scenario 12: Alternate parametric fit (log normal) for ToT (pembrolizumab and comparator)

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

The company did not provide scenario analyses using alternative distributions for ToT (Section 4.2.8.2). Although the exponential distribution selected by the company exhibited the lowest AIC/BIC score, there was minimal difference between the scores for each distribution. This scenario analyses used the log-normal distribution as it resulted in the second lowest AIC/BIC scores in both treatment arms (SCT-2L: pembrolizumab and IGEV; SCT-3L+ and SCT+3L+: pembrolizumab and BV). The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.13. Scenario 13: Subsequent treatments based on subgroup data from KEYNOTE-204

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	✓

In the base case analysis, subsequent treatment costs for each subgroup were based on the company's understanding of current UK clinical practice. However, the ERG noted several concerns surrounding the base case assumptions (Section 4.2.8.3). It is worth highlighting that subsequent treatment data for the SCT-2L and SCT-3L+ subgroups were also available from KEYNOTE-204[3,4] detailing the list of treatments and the associated uptake rates from the study. This scenario therefore used direct subgroup trial data to estimate subsequent treatment costs for these subgroups. Subsequent treatment data were not available for the SCT+3L+ subgroup, therefore treatments and uptake rates, for patients who failed pembrolizumab and BV, were derived from the ITT population (Table 13 in Section 4.2.8.3). Although this scenario is useful, the ERG outlined concerns surrounding the use of these data to estimate subsequent treatment costs (see Section 4.2.8.3). The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.14. Scenario 14: Balzarotti et al. (2016) used to estimate OS (pembrolizumab and comparator)

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	×

As noted in Section 4.2.6.1, the ERG did not consider Gopal et al. (2015)[1] to be the most appropriate data source to derive OS estimates for the SCT-2L and SCT-3L+ subgroups.

Patients in Balzarotti et al. (2016)[2] (patients with HL who are R/R to firstline chemotherapy), appeared to better reflect these subgroups. This scenario analysis is unlikely to have a material impact on the ICER given that the same OS data are applied to both arms (SCT-2L: pembrolizumab and IGEV; SCT-3L+ and SCT+3L+: pembrolizumab and BV). The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.15. Scenario 15: Balzarotti et al. (2016) for OS and alternative parametric fit applied

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	✓	SCT+3L+	×

In addition to Section 6.2.1.14, the ERG considered there was some uncertainty surrounding the impact of using an alternative parametric fit on the ICER (as the company did not provide sensitivity analysis using alternative parametric fits). This scenario analysis aims to explore OS uncertainty by using an alternative data source considered more generalisable to the SCT-2L and SCT-3L+ subgroup (Balzarotti et al., 2016[2]), as well as an alternative parametric fit (log-logistic). The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.16. Scenario 16: Alternative parametric fit (Weibull) for PFS, applied to both pembrolizumab and IGEV treatment arms

Applicable to subgroup:	SCT-2L	✓	SCT-3L+	×	SCT+3L+	×

To extrapolate PFS in its base case, the company applied a log normal curve to both treatment arms (Section 4.2.6.2). Given that the company did not provide sensitivity analysis results using alternative fits, this scenario estimates the impact of using the next best curve fit on the ICER. The Weibull produced the lowest AIC/BIC scores and therefore was selected as the appropriate fit for this scenario. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.17. Scenario 17: Combined analysis: PFS (fully parametric) and OS (KEYNOTE-087)

Applicable to subgroup:	**SCT-2L**	✓ Weibull	**SCT-3L+**	✓ Gen Gam	**SCT+3L+**	✓ Gen Gam

The ERG considered that it may be useful to conduct a combined scenario analysis to explore the combined effect of alternative PFS and OS assumptions on the ICER. This scenario analysis models OS using an alternative data source (KEYNOTE 087[5]) and uses an alternative fully parametric fit (Weibull was used for SCT-2L and generalised gamma for both SCT-3L+ and SCT+3L+), for PFS for both pembrolizumab and comparator (SCT-2L: IGEV, and SCT-3L- and SCT+3L+ BV. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.18. Scenario 18: Subsequent treatments assumed to reflect UK practice

Applicable to subgroup:	**SCT-2L**	×	**SCT-3L+**	✓ BV > BEN	**SCT+3L+**	✓ Pembro > NIVO

Subsequent treatments included in the model are considered to have a large impact on the base case ICER, given the associated treatment acquisition costs.

As noted in Section 4.2.8.3, there were a number of concerns surrounding the company's base assumptions with respect to subsequent treatments in both the SCT-3L+ and SCT+3L+ subgroups.

SCT-3L+ subgroup: In the base case analysis the company assumed that patients who fail on BV go on to receive pembrolizumab (Section 4.2.8.3). However, the ERG noted that as pembrolizumab is within the Cancer Drugs Fund (CDF), it may therefore may not be routinely available. Based on clinician response to the ERG, bendamustine was suggested a plausible treatment option for these patients. Therefore, this scenario assumes that 100% of patients who fail on BV go on to receive bendamustine. It is anticipated that this scenario analysis will have a large upward impact on the ICER, as subsequent treatment costs for the comparator arm have decreased, relative to the base case.

SCT+3L+ subgroup: In the base case analysis the company assumed that patients who fail on pembrolizumab go on to receive BV, whilst 100% of patients who failed BV went on to receive

nivolumab. Based on a review of the treatment pathway for this subgroup, patients in both treatment arms should receive nivolumab as subsequent treatment (Section 4.2.8.3).

For this scenario analysis, subsequent treatment assumptions were as outlined in Table 24, which more appropriately reflect UK clinical practice. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

Table 24: ERG preferred subsequent treatments

	Subsequent treatment
SCT-3L+	
Pembrolizumab	100% receive BV
BV	100% receive bendamustine only
SCT+3L+	
Pembrolizumab	100% receive nivolumab
BV	100% receive nivolumab

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group

6.2.1.19. Scenario 19: Reduction in maximum number of cycles of BV

Applicable to subgroup:	SCT-2L	×	SCT-3L+	✓	SCT+3L+	✓

As noted in Section 4.2.8.2, the company assumed a maximum treatment duration of 35 cycles (105 weeks) for both pembrolizumab and BV in both the SCT-3L and SCT+3L subgroups, which did not appear appropriate. Although 35 cycles were consistent with the two-year pembrolizumab stopping rule, based on the SmPC for BV, the maximum number of cycles should be given is 16. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.20. Scenario 20: Fully parametric approach to model PFS (using the generalised gamma curve)

Applicable to subgroup:	SCT-2L	×	SCT-3L+	✓	SCT+3L+	✓

As noted in Section 4.2.6.2, the generalised gamma provided a superior statistical fit to the full SCT-3L+ subgroup data compared with the other parametric distributions (as assessed by AIC and BIC statistics), as well as the best fit to full SCT+3L+ subgroup data for the pembrolizumab arm. Therefore, this scenario analysis models PFS by applying full-fitted generalised gamma

distributions to each arm (i.e. with a break-point at Week 0). The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.21. Scenario 21: Alternative parametric fit (log-logistic) for Gopal et al. (2015) OS data for both pembrolizumab and BV

Applicable to subgroup:	SCT-2L	×	SCT-3L+	✓	SCT+3L+	✓

As noted in Section 4.2.6.1 the company did not provide sensitivity analysis using alternative distributions. For this scenario the ERG selected the log-logistic curve for use on the basis that it produces the next best fit, based on AIC/BIC statistics. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.1.22. Scenario 22: Model PFS using different data cut point (26 weeks)

Applicable to subgroup:	SCT-2L	×	SCT-3L+	✓	SCT+3L+	✓

In the base case analysis, the company extrapolated PFS using a 52-week cut point (see Section 4.2.6.2). For this scenario analysis, the log-normal distribution was fitted to the data at Week 26. Using a 26-week break-point means that more robust trial data is used to inform the parametric extrapolation, leading to less uncertain estimates. This is the ERG's preferred cut point. The incremental results and impact on the company base case are presented in Section 6.2.2 by subgroup.

6.2.2. Impact of scenario analyses on the ICER

The impact of each scenario on the ICER is provided for each of the subgroups: SCT-2L (Table 25), SCT-3L+ (Table 26), and SCT+3L+ (Table 27).

Table 25: Impact on the ICER of additional analyses undertaken by the ERG: SCT-2L

Subgroup	**Subgroup: SCT-2L**			
Scenario	Incr costs £	Incr QALYs	ICER £/QALY	+/-
ERG corrected company base case	[redacted]	[redacted]	53,099	-
Scenario 1: Utility value PD health state	[redacted]	[redacted]	94,284	[redacted]
Scenario 2: Equal PFS and PD utility value	[redacted]	[redacted]	799,995	[redacted]
Scenario 3: Waning of pembro PFS Tx effect	[redacted]	[redacted]	58,559	[redacted]
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	50,627	[redacted]
Scenario 5: No difference in SCT rates	[redacted]	[redacted]	64,332	[redacted]

Subgroup	Subgroup: SCT-2L			
Scenario 6: Dose intensity for pembro 100%	[redacted]	[redacted]	54,513	[redacted]
Scenario 7: Pembro 400 mg Q6W	[redacted]	[redacted]	53,742	[redacted]
Scenario 8: Time horizon 50 years	[redacted]	[redacted]	52,891	[redacted]
Scenario 9: KN-087 OS data (**pembro and IGEV**)	[redacted]	[redacted]	20,205	[redacted]
Scenario 10: ToT pembro based on KM data only	[redacted]	[redacted]	52,172	[redacted]
Scenario 11: 26-week cut-point for modelling ToT	[redacted]	[redacted]	103,052	[redacted]
Scenario 12: Log-normal fit for ToT (**pembro and IGEV**)	[redacted]	[redacted]	53,319	[redacted]
Scenario 13: Subsequent Tx based on SG data KN-204	[redacted]	[redacted]	57,148	[redacted]
Scenario 14: Balzarotti (2016) for OS (**pembro and IGEV**)	[redacted]	[redacted]	41,007	[redacted]
Scenario 15: Balzarotti (2016) for OS + log-logistic	[redacted]	[redacted]	44,996	[redacted]
Scenario 16: Weibull for PFS (**pembro & IGEV**)	[redacted]	[redacted]	53,745	[redacted]
Scenario 17: Combined PFS (**Weibull**) and OS (**KEYNOTE-087**) pembro and IGEV	[redacted]	[redacted]	20,799	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; incr, incremental; KN, KEYNOTE; OS, overall survival; PD, progressed disease; pembro, pembrolizumab; PFS, progression free survival; Q6W, every 6 weeks; QALYs, quality adjusted life years; SCT, stem cell transplant; SG, subgroup; ToT, time on treatment; Tx, treatment

Table 26: Impact on the ICER of additional analyses undertaken by the ERG: SCT-3L+

Subgroup	Subgroup: SCT-3L+			
Scenario	Incr costs £	Incr QALYs	ICER £/QALY	+/-
ERG corrected company base case	[redacted]	[redacted]	Dominant (-33,316)	-
Scenario 1: Utility value PD health state	[redacted]	[redacted]	Dominant (-52,833)	[redacted]
Scenario 2: Equal PFS and PD utility value	[redacted]	[redacted]	Dominant (-168,907)	[redacted]
Scenario 3: Waning of pembro PFS Tx effect	[redacted]	[redacted]	Dominant (-34,253)	[redacted]
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	Dominant (-40,840)	[redacted]
Scenario 5: No difference in SCT rates	[redacted]	[redacted]	Dominant (-36,184)	[redacted]
Scenario 6: Dose intensity for pembro 100%	[redacted]	[redacted]	Dominant (-32,154)	[redacted]
Scenario 7: Pembro 400 mg Q6W	[redacted]	[redacted]	Dominant (-33,314)	[redacted]
Scenario 8: Time horizon 50 years	[redacted]	[redacted]	Dominant (-33,234)	[redacted]
Scenario 9: KN-087 OS data (**pembro and BV**)	[redacted]	[redacted]	Dominant (-10,962)	[redacted]

Subgroup	Subgroup: SCT-3L+			
Scenario 10: ToT pembro based on KM data only	[redacted]	[redacted]	Dominant (-31,229)	[redacted]
Scenario 11: 26-week cut-point for modelling ToT	[redacted]	[redacted]	Dominant (-52,121)	[redacted]
Scenario 12: Log-normal fit for ToT (**pembro and BV**)	[redacted]	[redacted]	Dominant (-33,183)	[redacted]
Scenario 13: Subsequent Tx based on SG data KN-204	[redacted]	[redacted]	Dominant (-43,136)	[redacted]
Scenario 14: Balzarotti (2016) for OS (**pembro and BV**)	[redacted]	[redacted]	Dominant (-24,450)	[redacted]
Scenario 15: Balzarotti (2016) for OS + log-logistic	[redacted]	[redacted]	Dominant (-26,254)	[redacted]
Scenario 16: Weibull for PFS (**pembro and BV**)	[redacted]	[redacted]	Dominant (-33,316)	[redacted]
Scenario 17: Combined PFS (**generalised gamma**) and OS (**KEYNOTE-087**) pembro and BV	[redacted]	[redacted]	Dominant (-12,622)	[redacted]
Scenario 18: Subsequent treatments assumed to reflect UK practice (**100% bendamustine** on BV failure)	[redacted]	[redacted]	15,703	[redacted]
Scenario 19: Reduction in maximum number of BV cycles	[redacted]	[redacted]	Dominant (-17,935)	[redacted]
Scenario 20: Fully parametric approach to model PFS (generalised gamma curve)	[redacted]	[redacted]	Dominant (-35,005)	[redacted]
Scenario 21: Alternative parametric fit (**log logistic**) for Gopal et al. (2015) OS data (pembro and BV)	[redacted]	[redacted]	Dominant (-33,110)	[redacted]
Scenario 22: 26-week data cut point for PFS	[redacted]	[redacted]	Dominant (-36,396)	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; incr, incremental; KN, KEYNOTE; OS, overall survival; PD, progressed disease; pembro, pembrolizumab; PFS, progression free survival; Q6W, every 6 weeks; QALYs, quality adjusted life years; SCT, stem cell transplant; SG, subgroup; ToT, time on treatment; Tx, treatment

Table 27: Impact on the ICER of additional analyses undertaken by the ERG: SCT+3L+

Subgroup	Subgroup: SCT+3L+			
Scenario	Incr costs £	Incr QALYs	ICER £/QALY	+/-
ERG corrected company base case	[redacted]	[redacted]	Dominant (-73,896)	-
Scenario 1: Utility value PD health state	[redacted]	[redacted]	Dominant (-107,883)	[redacted]
Scenario 2: Equal PFS and PD utility value	[redacted]	[redacted]	Dominant (-458,591)	[redacted]
Scenario 3: Waning of pembro PFS Tx effect	[redacted]	[redacted]	Dominant (-75,473)	[redacted]
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	Dominant (-79,965)	[redacted]

Subgroup	Subgroup: SCT+3L+			
Scenario 5: No difference in SCT rates	[redacted]	[redacted]	Dominant (-78,183)	[redacted]
Scenario 6: Dose intensity for pembro 100%	[redacted]	[redacted]	Dominant (-72,152)	[redacted]
Scenario 7: Pembro 400 mg Q6W	[redacted]	[redacted]	Dominant (-74,342)	[redacted]
Scenario 8: Time horizon 50 years	[redacted]	[redacted]	Dominant (-73,726)	[redacted]
Scenario 9: KN-087 OS data (**pembro and BV**)	[redacted]	[redacted]	Dominant (-29,418)	[redacted]
Scenario 10: ToT pembro based on KM data only	[redacted]	[redacted]	Dominant (-73,374)	[redacted]
Scenario 11: 26-week cut-point for modelling ToT	[redacted]	[redacted]	Dominant (-139,123)	[redacted]
Scenario 12: Log-normal fit for ToT (**pembro and BV**)	[redacted]	[redacted]	Dominant (-73,967)	[redacted]
Scenario 13: Subsequent Tx based on SG data KN-204	[redacted]	[redacted]	Dominant (-28,585)	[redacted]
Scenario 17: Combined PFS (**generalised gamma**) and OS (**KEYNOTE-087**) pembro and BV	[redacted]	[redacted]	Dominant (-30,704)	[redacted]
Scenario 18: Subsequent treatments assumed to reflect UK practice (**100% nivolumab** on pembro failure)	[redacted]	[redacted]	Dominant (-45,625)	[redacted]
Scenario 19: Reduction in maximum number of BV cycles	[redacted]	[redacted]	Dominant (-65,013)	[redacted]
Scenario 20: Fully parametric approach to model PFS (generalised gamma curve)	[redacted]	[redacted]	Dominant (-54,360)	[redacted]
Scenario 21: Alternative parametric fit (**log-logistic**) for Gopal et al. (2015) OS data (pembro and BV)	[redacted]	[redacted]	Dominant (-74,240)	[redacted]
Scenario 22: 26-week data cut point for PFS	[redacted]	[redacted]	Dominant (-57,940)	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; incr, incremental; KN, KEYNOTE; OS, overall survival; PD, progressed disease; pembro, pembrolizumab; PFS, progression free survival; Q6W, every 6 weeks; QALYs, quality adjusted life years; SCT, stem cell transplant; SG, subgroup; ToT, time on treatment; Tx, treatment

6.2.3. Adjustment to the probabilistic sensitivity analysis

In the company's analysis, a single set of distribution parameters informs the OS curves in both treatment arms and, as a result, these curves are varied in exactly the same way in the probabilistic sensitivity analysis (PSA).

The ERG noted that this may not adequately reflect uncertainty surrounding the OS parameters: this uncertainty would be captured better by using two sets of OS parameters, one for each arm.

These sets contained identical values in the deterministic analysis, but were varied separately in the ERG probabilistic analysis. The same Cholesky matrix was used for each set to account for the correlation among the parameters in that set, but the matrix was multiplied by a different random vector for each set, the values of which were drawn from an inverse Normal distribution.

The choice of OS distribution based on the data from Balzarotti et al. (2016)[2] needed to be specified for the PSA in the ERG probabilistic analysis for the SCT-2L and SCT-3L+ subgroups.

The PSA sample mean for the PFS hazard ratio (HR) obtained from the MAIC was also missing from the company's model. In the ERG and corrected company probabilistic analysis for the SCT-2L subgroup, the HR was varied using a log-normal distribution, with a standard error based on the 95% confidence interval obtained from the MAIC.

6.3. ERG's preferred assumptions

The ERG's preferred base case analysis for each subgroup comprised alternative assumptions and amended model errors and settings

Table 28: ERG's preferred model assumptions (SCT-2L)

Preferred assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Company base-case	[redacted]	[redacted]	£53,581
ERG corrected company base case	[redacted]	[redacted]	£53,099
Scenario 14: Balzarotti et al (2016) used as the data source for estimating OS for both pembrolizumab and chemotherapy (IGEV)	[redacted]	[redacted]	£41,007
Scenario 1: Utility value for PD health state set to [redacted] for both treatment arms	[redacted]	[redacted]	£94,319
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	£89,930
Scenario 5: No difference in SCT rates between treatment arms (apply pembrolizumab allo-SCT and auto SCT rate to both arms)	[redacted]	[redacted]	£109,876
Scenario 6: Dose intensity for pembrolizumab assumed to be 100%	[redacted]	[redacted]	£112,387
Scenario 8: Time horizon increased to 50 years	[redacted]	[redacted]	£112,284
Scenario 11: 26-week data cut point for ToT	[redacted]	[redacted]	£202,428

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; SCT, stem cell transplant

Table 29: Comparison of company and ERG results (SCT-2L)

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
ERG corrected company base case (deterministic)							
Pembro	[redacted]	[redacted]	[redacted]	-	-	-	-
IGEV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,099
ERG base case (deterministic)							
Pembro	[redacted]	[redacted]	[redacted]	-	-	-	-
IGEV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£202,428
ERG corrected company base case (probabilistic)							
Pembro	[redacted]	[redacted]	[redacted]	-	-	-	
IGEV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,446
ERG base case (probabilistic)							
Pembro	[redacted]	[redacted]	[redacted]	-	-	-	-
IGEV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,859

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; Pembro, pembrolizumab; QALY, quality adjusted life year

Note: It was not possible to obtain LY results from the cost-effectiveness model

Table 30: ERG's preferred model assumptions (SCT-3L+)

Preferred assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Company base-case[a]	[redacted]	[redacted]	**Dominant (-£33,316)**
Scenario 14: Balzarotti et al (2016) used as the data source for estimating OS for both pembrolizumab and chemotherapy	[redacted]	[redacted]	Dominant (-£24,450)
Scenario 22: Semi parametric approach to modelling PFS (cut point for PFS set at 26 weeks)	[redacted]	[redacted]	Dominant (-£27,163)
Scenario 1: Utility value for PD health state set to [redacted] for both treatment arms	[redacted]	[redacted]	Dominant (-£61,670)
Scenario 18: Subsequent treatment assumed to reflect UK practice: 100% of patients who fail pembrolizumab go on to receive BV AND 100% of patients who fail on BV go on to receive bendamustine alone	[redacted]	[redacted]	£24,265
Scenario 19: Maximum ToT for brentuximab set to 16 cycles (not 35 as per base case)	[redacted]	[redacted]	£52,006
Scenario 11: Cut-off for ToT to reflect PFS data cut point (26 weeks)	[redacted]	[redacted]	£79,232

Preferred assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	£67,399
Scenario 5: No difference in SCT rates between treatment arms (pembrolizumab allo-SCT and auto-SCT rate to both arms)	[redacted]	[redacted]	£62,226
Scenario 6: Dose intensity for pembrolizumab 100%	[redacted]	[redacted]	£65,018
Scenario 8: Time horizon increased to 50 years	[redacted]	[redacted]	£64,124

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; SCT, stem cell transplant

Note:

a ERG corrected company base case not applicable for this subgroup (see Section 5.3)

Table 31: Comparison of company and ERG results (SCT-3L+)

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)[a]							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£33,316)
ERG base case (deterministic)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,124
Company base case (probabilistic)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£31,773)
ERG base case (probabilistic)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,738

Abbreviations: BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year

Note:

It was not possible to obtain LY results from the cost-effectiveness model

a ERG corrected company base case not applicable for this subgroup (see Section 5.3)

Table 32: ERG's preferred model assumptions (SCT+3L+)

Preferred assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Company base-case	[redacted]	[redacted]	**Dominant (-£73,896)**
Scenario 22: Semi parametric approach to modelling PFS (cut point for PFS set at 26 weeks)	[redacted]	[redacted]	Dominant (-£57,940)
Scenario 1: Utility value for PD health state set to [redacted] for both treatment arms	[redacted]	[redacted]	Dominant (-£79,339)
Scenario 19: Maximum ToT for brentuximab set to 16 cycles (not 35 as per base case)	[redacted]	[redacted]	Dominant (-£68,202)
Scenario 11: Cut-off for ToT to reflect PFS data cut point (26 weeks)	[redacted]	[redacted]	Dominant (-£49,001)
Scenario 4: Higher resource use in the PD health state	[redacted]	[redacted]	Dominant (-£61,514)

Preferred assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Scenario 5: No difference in SCT rates between treatment arms (pembrolizumab allo-SCT and auto-SCT rate to both arms)	[redacted]	[redacted]	Dominant (-£66,889)
Scenario 6: Dose intensity for pembrolizumab 100%	[redacted]	[redacted]	Dominant (-£64,127)
Scenario 8: Time horizon increased to 50 years	[redacted]	[redacted]	Dominant (-£63,904)
Scenario 18: Subsequent treatment assumed to reflect UK practice: 100% of patients who fail pembrolizumab go on to receive nivolumab AND 100% of patients who fail on BV go on to receive nivolumab	[redacted]	[redacted]	Dominant (-£33,849)

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; SCT, stem cell transplant

Note: a ERG corrected company base case not applicable for this subgroup (see Section 5.3)

Table 33: Comparison of company and ERG results (SCT+3L+)

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)[a]							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£73,896)
ERG base case (deterministic)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£33,849)
Company base case (probabilistic)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£66,098)
ERG base case (probabilistic)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£34,156)

Abbreviations: BV, brentuximab vedotin; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year

Note:

It was not possible to obtain LY results from the cost-effectiveness model

a ERG corrected company base case not applicable for this subgroup (see Section 5.3)

6.4. Conclusions of the cost-effectiveness section

6.4.1. SCT-2L

The company's base case results (ERG corrected for errors) indicated that pembrolizumab resulted in an ICER of £53,099 when compared to salvage chemotherapy (IGEV). The ERG acknowledged that this result was subject to uncertainty due to concerns surrounding the use of MAIC data in the economic analysis, which was used to estimate the clinical effectiveness of pembrolizumab. As such results should be interpreted with caution.

Using the ERG's preferred assumptions, the ICER for pembrolizumab increased to £202,428 based on an incremental cost of [redacted] and an incremental QALY gain of [redacted]. Based on this analysis, pembrolizumab does not appear to be a cost-effective treatment option for patients with R/RcHL who did not have at least two prior therapies when autologous stem cell transplant is not a treatment option, when compared to salvage chemotherapy. The ERG conducted a large number of scenario analyses to test uncertainty surrounding key modelled parameters. As outlined in Table 28, the ICER was particularly sensitive to several ERG preferred assumptions including the use of alternative utility and ToT assumptions.

6.4.2. SCT-3L+ and SCT+3L+

For the SCT-3L+, the company's base case results (ERG corrected for errors) indicated that pembrolizumab was the dominant treatment when compared to BV. Using the ERG's preferred assumptions, pembrolizumab resulted in an ICER of £64,124 based on an incremental cost of [redacted] and an incremental QALY gain of [redacted]. The ERG conducted scenario analyses to test uncertainty surrounding key modelled parameters. The ICER was particularly sensitive to several preferred ERG assumptions including alternative subsequent treatments, reduced maximum ToT for BV and the use of an earlier cut point for ToT (26 weeks).

For the SCT+3L+ subgroup, the company's base case results (ERG corrected for errors) indicated that pembrolizumab remained dominant when compared to BV. Using the ERG's preferred assumptions, pembrolizumab remained dominant resulting in incremental savings of [redacted] and an incremental QALY gain of [redacted]. Incremental results were most sensitive to alternative ERG preferred assumptions including utility and subsequent treatments as noted in section 6.3.

7. END OF LIFE

Pembrolizumab does not meet NICE's end of life criteria outlined below.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months; and
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 1 prior therapy [ID1557]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 16 December 2020** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38, "In the ITT population, based on a medium (range) follow-up time of [redacted] months,	In the ITT population, based on the ***median*** (range) follow up of [redacted] months in the pembrolizumab group	The word "medium" is not factually correct. The values quoted within this sentence are for the pembrolizumab arm only,	The ERG has corrected the typographical error, replacing 'medium' by 'median' (Refer to ERG Report, Section 3.2.5.2, p.38). The ERG Report already clearly states "in the pembrolizumab arm" in the next clause of the sentence. No amendment required.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40 "This made it difficult for the ERG to comment on the robustness of the efficacy of pembrolizumab in each of these three cohorts. PFS in the pembrolizumab arm was highest in the SCT-2L subgroup ([redacted], 95% CI [redacted] vs [redacted], 95% CI [redacted] for BV).	This made it difficult for the ERG to comment on the robustness of the efficacy of pembrolizumab in each of these three cohorts. PFS in the pembrolizumab arm was highest in the SCT-2L subgroup ([redacted] 95% CI [redacted] vs [redacted], 95% CI [redacted] for BV).	The CS states estimated median time in weeks, not months. The value stated for the confidence interval was incorrect in the ERG report.	The ERG has made the proposed amendment (Refer to ERG Report, Section 3.2.5.5, p.40).

Issue 3

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>The pooled utilities in Table 12 page 62 should be a row instead of a column
Table 1: Base case utility values
<table>
<tr><th>Treatment</th><th>PFS utility</th><th>PD utility</th><th>Pooled values</th></tr>
<tr><td>Pembrolizumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>BV</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Table 2: Base case utility values
<table>
<tr><th>Treatment</th><th>PFS utility</th><th>PD utility</th></tr>
<tr><td>Pembrolizumab</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>BV</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Pooled utilities</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>The pooled utility values presented here reflect the pooling of the two arms per health state.</td>
<td>This is not a factual inaccuracy; however the ERG has amended the Table as per the company’s request (refer to ERG Report, Section 4.2.7, p63).</td>
</tr>
</table>

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The company assumed that patients treated with BV will receive the same maximum ToT as pembrolizumab (35 cycles). However, as per the SmPC for BV, treatment should be provided for a maximum of 16 cycles.	The company assumed that patients treated with BV will receive a maximum of 35 cycles, as per the KEYNOTE-204 protocol. However, as per the SmPC for BV, treatment should be provided for a maximum of 16 cycles. It should be noted though that the trial efficacy of the BV arm is based on a maximum of 35 cycles.	The assumption regarding the BV max ToT was based on the KEYNOTE-204 trial protocol. MSD provided a scenario analysis for which a maximum of 16 doses of BV were assumed acknowledging the BV SmPC. What is not explicitly reflected in the ERG report though is the fact that whilst costs were assigned to BV for a max of 16 doses, the benefit of BV is reflected in the efficacy of the comparator arm for a max of 35 doses.	This is not a factual inaccuracy. However, the ERG has amended the report to reflect that the company conducted a scenario analysis which assumed a maximum ToT of 16 cycles for BV. Furthermore, it has also been noted that this scenario analysis assumed that the benefit/efficacy of BV is reflected for a maximum of 35 cycles (refer to ERG Report, Section 4.2.8.2, p68).

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Based on a review of the treatment pathway for this subgroup, patients in both treatment arms should receive nivolumab as subsequent treatment	Patients on pembrolizumab should receive BV as subsequent therapy.	The ERG assumption may not accurately reflect the potential pathway after the introduction of pembrolizumab, as the evidence for IOs used in consecutive lines of treatment is limited. Clinical opinion elicited by MSD suggested that if pembrolizumab is given in the 3L patients after failing transplant, then at 4L they would receive BV, not nivolumab. Whilst the nivolumab NICE TA does not explicitly prohibit any prior use of Ios, the pivotal trial of this indication, Checkmate-205, excluded patients with prior IO use. (https://ascopubs.org/doi/suppl/10.1200/JCO.2017.76.0793/suppl_file/protocol_2017.760793.pdf)	This is not a factual inaccuracy. The ERG acknowledge the company's comment that there is likely to be uncertainty surrounding subsequent treatment usage in the 3L setting. However, it was considered that the most appropriate subsequent treatment for this patient population should be nivolumab, which is reflective of the treatment pathway.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.49 The time horizon used in the base case was 40 years. At this time point [redacted] of patients were still alive in the model (in both treatment arms). The ERG	The time horizon used in the base case was 40 years. At this time point [redacted] of patients were still alive in the model (in both treatment arms). The ERG	The OS in the model base case (see pembro trace tab) at 40 years is [redacted] ([redacted])	The ERG has made the proposed amendment (Refer to ERG Report, Section 4.2.1, p.49).

considered using a longer time horizon within their preferred base case.	considered using a longer time horizon within their preferred base case.		

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.49 Dolan et al. (1997)[26] was used, which is considered an a valid source.	Dolan et al. (1997)[26] was used, which is considered **a** valid source.	Syntax error	The ERG has made the proposed amendment (Refer to ERG Report, Section 4.2.1, Table 11, p.49).

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.61 A similar approach had been used in NICE TA655[32] for assessing uncertainty surrounding OS, given limited long term clinical evidence.	A similar approach had been used in NICE TA655[32] for assessing uncertainty surrounding OS, but not PFS given limited long term clinical evidence	No treatment waning in PFS has been applied in TA655, or in any other cHL submission.	This is not a factual inaccuracy. On p84 of the ERG report it is stated that in TA655 efficacy waning appears to have been only applied to OS. No edit required.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
However, the ERG understood that the dose intensity in practice could potentially be higher than the 98% witnessed in KEYNOTE-204,[3,4] and therefore were interested in determining whether assuming a 100% dosing intensity is likely to impact on the ICER.	n/a	It is not clear why the ERG understood that in practice dose intensity could be potentially higher than the 98% observed in KEYNOTE-204. The dose intensity is calculated from the trial as the number of actual versus expected number of doses and it is common in patients treated with IOs to delay doses due to AEs therefore accounting for this should be implemented in the model.	This is not a factual inaccuracy. The ERG understand that a dose intensity of 98% is representative of KEYNOTE 204; however, it is unclear whether this can be generalised to all patients in clinical practice. As a means of addressing uncertainty and in order to determine the impact on the ICER if a higher dosing intensity was used, the ERG considered that assuming 100% dose intensity (as part of the ERG base case) would be more reasonable.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **Friday 5 February 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**MSD**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Immaturity of overall survival data	**YES- PFS2 data**	MSD acknowledges that the immaturity of the OS data results in uncertainty about the long-term effectiveness. However, the economic model outcomes suggest that pembrolizumab is a cost-effective option for the NHS across most scenarios even when OS is conservatively assumed to be equal between the two arms. This base case assumption was selected as the most conservative way to model pembrolizumab OS and demonstrate the potential for cost-effectiveness in order to enable access to patients until OS data from KEYNOTE-204 become available [redacted] MSD considers this modelling approach (setting OS to be equal in both arms), to mitigate for any uncertainty due to the immaturity of the OS data. As such, whilst MSD initially considered pembrolizumab a candidate for the CDF, on the basis of further data collection in the pivotal clinical trial (KEYNOTE-204) and the plausibility of pembrolizumab being cost effective, we think the strength of the updated ICER estimates may not require this indication to go into CDF. In the absence of mature OS data from the pivotal trial, MSD sought clinical expert opinion on the impact of immunotherapies (IOs) on OS expectations in cHL. Clinicians describe the introductions of

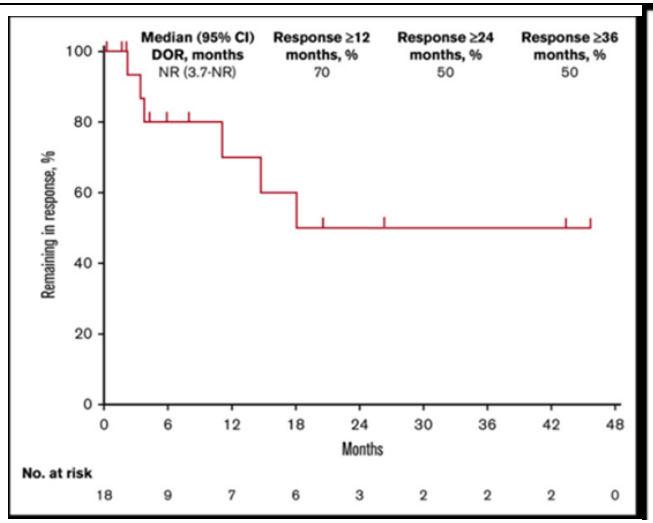
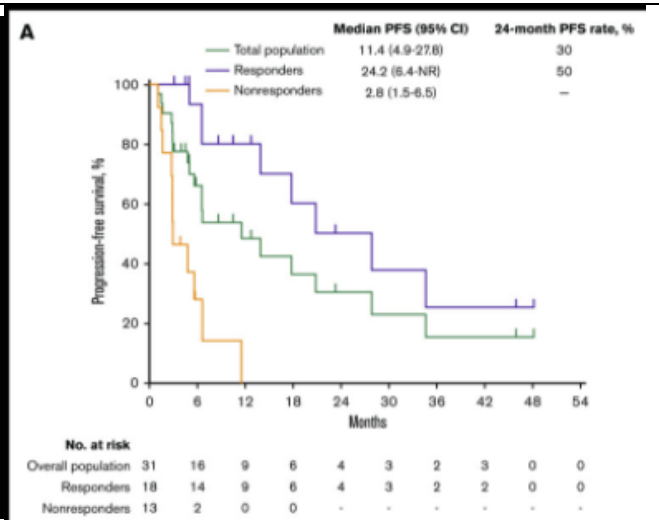
		IOs [1,2] in cHL having had a large impact on OS in the cHL space, where patients previously have had limited options specifically those who are unfit for transplant with advanced age and comorbidities. Despite this insight being drawn from IO use in later lines of therapy, compared to the patient population relating to this appraisal, in the absence of OS data it is reasonable to assume that a survival benefit will also be seen in these patients. Furthermore, expert opinion described that the PFS benefit seen in KEYONTE-204 is indicative of an significant OS benefit specifically of patients who are ineligible to receive transplant due to age or comorbidities: early relapse is a poor prognostic factor and patients who are progression free for a continued period of time are more likely to survive longer. In addition, the life expectancy of this ineligible group is very low (the majority of them leave for less than 2 years) and clinicians would value the introduction of pembrolizumab at an earlier point in the pathway. Experts explained this relationship is observed with IOs later on in the pathway and they expect the same earlier in the pathway. KEYNOTE-204 reported improvement in the exploratory endpoint, PFS2 (defined as the time from randomisation to subsequent disease progression after the initiation of subsequent oncologic therapy(-ies), or death from any cause, whichever occurs first.) which has been highlighted by EMA [3] as a reliable endpoint when OS data is not available. Since the subsequent treatments have a major influence in the OS outcomes, PFS2 provides useful information about the expected benefit on patients' survival. The PFS2 at 24 months was [redacted] for pembrolizumab versus [redacted] for BV whilst median PFS2 [redacted] for any arm (ITT HR [redacted]). In the absence of comparative data for the patient population in question MSD would also like to reiterate the value of longer-term evidence in all treated participants, from KEYNOTE-087. With a

		median follow-up duration of 39.5 months (range, 1.0-44.8), the median OS for pembrolizumab was not reached and the OS rates at 12 and 24 months were [redacted], and [redacted] respectively. In contrast, the conservative OS outcomes from the economic model suggest 87.1% and 69.4% of patients alive at 12 and 24 months respectively. Considering patients in KEYNOTE-087 are one line of therapy later in the pathway than KEYNOTE-204, it may be possible to assume improved OS benefit in KEYNOTE-204. As the ERG acknowledged, assuming no difference in survival between treatment arms may be considered a conservative assumption and could potentially underestimate the impact of pembrolizumab on OS therefore even though OS data is immature. It is plausible that pembrolizumab is cost effective.
Key issue 2: How reliable is the comparison of pembrolizumab with standard of care made by the MAIC for the SCT-2L subgroup?	**NO**	Considering the recent communication to NICE regarding the change in the proposed wording for this indication that this issue is now not relevant for this appraisal and is now resolved.
Key issue 3: Generalisability of the intention to treat (ITT) population to UK clinical practice	**YES**	According to the ERG report, the ITT population of KEYNOTE-204 is not generalisable to the UK due to inclusion of 2L patients who have a different comparator in clinical practice. MSD communicated to NICE a change in the proposed label for this indication [redacted] which excludes 2L population. Since the SCT-3L+ and SCT+3L+ subgroups have a common comparator, which is also the trial comparator, it was agreed during the technical engagement call, that it is appropriate for the committee to consider the updated target population ('3L+') i.e. ITT excluding 2L, in its totality to

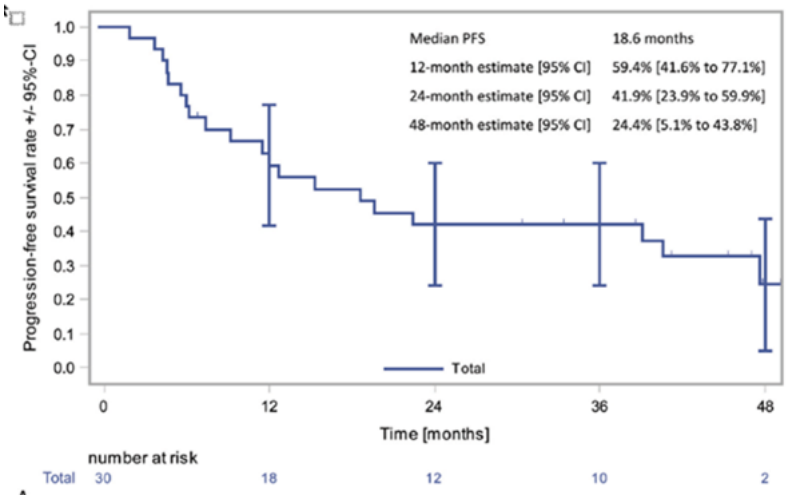
		increase the robustness of the outcomes compared to those of 3L+ subgroups separately. The updated results of the cost effectiveness model suggest the dominance of pembrolizumab over BV across all scenarios tested (see New Evidence Form).
Key issue 4: Uncertainty in PFS estimation in the SCT-2L subgroup	**NO**	Considering the recent communication to NICE regarding the change in the proposed wording for this indication that this issue is now not relevant for this appraisal and is now resolved.
Key issue 5: Uncertainty in the maintenance of PFS benefit associated with pembrolizumab after treatment discontinuation in Year 2	**YES - provided here**	MSD disagrees with the ERG approach to implement a treatment waning effect for PFS and considers the 3-5 year assumption for this indication uncertain, and inconsistent with all previous cHL submissions to NICE. Implementing PFS waning contradicts the existing evidence (detailed below) and has the potential to not only penalize pembrolizumab but also impact long term patient care in this already conservative submission. NICE has not taken into consideration any treatment waning – neither to PFS or OS – for pembrolizumab or for nivolumab in cHL before, neither for the comparator of this indication, BV, so it is queried what the evidence is behind the introduction in this specific cHL submission. MSD acknowledges that NICE has previously accepted a 3-5 treatment waning effect in other indications like NSCLC (the ERG report also refers to TA655 and TA428 which are NSCLC indications), however, in these submissions, the waning effect was applied only to OS. Checkpoint inhibitors are a well-established treatment option in R/R cHL with response rates of 65% to 84% [4]. This is the highest reported among all malignancies and this is the result of the distinctive biology of cHL which is characterized by the malignant Hodgkin Reed-Sternberg (HRS) cells [4] ; these cells harbour a gene alteration (9p24.1 gene alteration/amplification) which results in overexpression of PD-L1/PD-L2. This profile is associated with very high response rates and durable PFS with anti-PD-1 therapy [5] making cHL uniquely sensitive to anti-PD-1 agents. Results

		from KEYNOTE-204 and also longer-term data from other cHL IO studies such as KEYNOTE-087, KEYNOTE-013 and Checkmate-205 (presented below) confirm the high response rates and also confirm that the responses are durable; patients continue to receive benefit over an extended period. On this basis, it is not considered appropriate to apply the arbitrary 3-5 year PFS waning. There is clear clinical rational and evidence from long term follow up of current pivotal studies to suggest this is not appropriate in cHL. In KEYNOTE-204 the ORR was 65.6% for pembrolizumab vs 54.2% for the BV arm with 24.5% achieving CR and [redacted] seeing a PR in the pembrolizumab arm. Duration of response favoured the pembrolizumab arm, with an increase of 6.9 months when compared with BV (20.7 months vs 13.8 months). Whilst the number of patients at risk after 2 years are very limited, a plateau starts to form and is observed approximately after that time point. Pembrolizumab also showed an improved PFS effect after 2 years sustained until 39 months.

		  KEYNOTE-013 evaluated pembrolizumab monotherapy in haematologic malignancies. In the cHL cohort, the trial enrolled cHL patients who experienced relapse after, were ineligible for, or declined autologous stem cell transplantation and experienced progression with or did not respond to brentuximab vedotin. The median follow-up was 52.8 months. CR rate was 19%, and median duration of response (DOR) was not reached; Response durations at ≥24 months and ≥36 months were both 50% by the Kaplan-Meier method. As can be seen on the graphs below, pembrolizumab achieves sustained effect in PFS for at least 4 years whilst there is a plateau after 3 years.

		  In KEYNOTE-087, there was again a sustained treatment effect. With a median follow-up duration of 39.5 months, the ORR by BICR was 71.0% (95% CI: 64.3, 77.0), including achievement of CR in 27.6% of participants, based on IWG response criteria. Response durations of ≥12 and ≥24months were observed in [redacted] by KM estimation and [redacted] by KM estimation participants, respectively (see Figure showing Objective Response Duration). Additionally, the PFS rates at 12 and 24months by BICR were [redacted] and [redacted], respectively, by KM estimation there is a plateau if PFS starting before 3 years as can be seen in the figure showing PFS below.

		[redacted]  Checkmate-205: with a median observation time of 43 months, reports a median PFS of 18.6 months and 12-, 24- and 48-months PFS estimates of 59.4% [95% CI 41.6%–77.1%], 41.9% [95% CI 23.9%–59.9%] and 24.4% [95% CI 5.1%–43.8%], respectively (graph below). ORR was 84% (25/30) with best response being complete response (CR) and partial response (PR) in 8 (27%) and 17 (57%) patients, respectively.

		 In conclusion, apart from the lack of precedence in exploring PFS waning in cHL there is evidence to suggest that pembrolizumab, due to its mode of action in cHL, provides sustained response and prolonged PFS. MSD wishes to remind the Appraisal Committee of the conservative nature of OS modelling (no OS benefit considered for this submission) and as per the ERG report: "given that a conservative assumption has already been adopted by the company with respect to OS modelling, this scenario (PFS waning) would be considered overly pessimistic". Any uncertainty of PFS, may be more appropriate to be tested via alternative parametric curves and not by implementing an arbitrary threshold of waning effect to drive the PFS downwards where there is no clinical rationale.
Key issue 6: Utility values used in the progressed disease (PD) health state for pembrolizumab	NO	MSD disagrees with the ERG approach about the utilities for two main reasons:

		1. The ERG preferred to remove the difference in the PD state between pembrolizumab and BV. However, pembrolizumab outcomes and adverse events (AE) in cHL suggest that the quality of life post-progression can be significantly different between arms: BV's common side effect is neuropathy. Peripheral neuropathy is a frequent AE of BV treatment, affecting the majority of the patients, with literature reporting between 48%[6] up to 70% of patients[7] experiencing the event. Neuropathy can be debilitating since patients report difficulty with balance, pain after periods of long sitting or when getting up in the morning and a reliance on family members for tasks they can no longer perform. This AE is also persistent, and it does not resolve quickly so patients who received BV, and experience the AE, carry its cumulative effect even in the post progressed state. Whilst pembrolizumab can also cause immune-related AEs, such as hypothyroidism, these are well documented, managed more easily and less debilitating on average on patients' quality of life. Therefore, it is rational to assume that the PD quality of life *is* different between arms in the PD state too. Additionally, the PFS for pembrolizumab in KEYNOTE-204 was significantly better than BV which means that patients on pembrolizumab stay in remission longer. For Hodgkin's lymphoma, the time to relapse is a prognostic factor of poorer outcomes and therefore, patients who progress faster are expected to have poorer quality of life on average in the PD state, since their third line treatment failed faster. 2. The ERG preferred to apply the BV utility in both arms in the PD state. The value was 0.693 however, as mentioned in the ERG report the utility reported for nivolumab in Checkmate-205 was outlined as 0.715 in SMC submission 1240/17 [8] (value redacted from the NICE submission). This ERG assumption suggests the expected utility for R/R cHL patient treated with immunotherapy at a later line of therapy (4L) is superior to 3L R/R cHL patients

		which appears unlikely. Patients in Checkmate-205 received more lines of therapy and this can be a significant factor that affects patients' quality of life, mostly because of the cumulative effect of failure on all the previous lines of therapies. Therefore, it is not valid to assume that quality of life in a 3L patient (0.693) is lower than a patient in the 4L (0.715). MSD considers the treatment specific values from the trial should be used in the PD state. If not, then the utility value should not be lower than utilities for patients on a later line of therapy. This is in line with clinical expert opinion.
Key issue 7: Uncertainty in subsequent treatments and assumed proportions in the company's base case analysis	**YES**	MSD disagrees with the ERG approach on the subsequent treatments. SCT+3L+ subgroup: the ERG preferred to assume that if patients fail on pembrolizumab, they will receive nivolumab as a subsequent therapy. The TA for nivolumab (TA462) [2] reads: "Nivolumab is recommended, within its marketing authorisation, as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults after autologous stem cell transplant and treatment with brentuximab vedotin". Whilst the TA does not explicitly preclude the use of prior IO, previous use of BV is mandated in the recommendation. Therefore, if a patient receives pembrolizumab in the 3L setting instead of BV, then the nivolumab TA recommendation does not allow nivolumab to be used subsequently. Additionally, the pivotal trial of nivolumab in this indication Checkmate-205 [9] excluded patients who received prior IO therefore there is no evidence for re-challenging patients who failed with nivolumab. The assumption that SCT+3L patients who fail pembrolizumab will receive BV subsequently, was also validated with clinical experts in the UK who would clearly consider BV as a subsequent treatment to pembrolizumab and not nivolumab.

		SCT-3L+ subgroup: The ERG assumed in their base case that patients who fail BV will receive Bendamustine monotherapy as a subsequent treatment. However, as per the ERG report, patients might also receive other chemotherapies such as bendamustine+gemcitabine+vinorelbine, gemcitabine with Cis- or carboplatin and dexamethasone, ChlVPP (chlorambucil with vinblastin, procarbazine and prednisolone) or similar combinations. Clinical experts highlighted a Clinical Commissioning Policy Statement by NHS England, published in October 2020, (Bendamustine for relapsed/refractory classical Hodgkin lymphoma (all ages) [1828] [Publication reference: 200701P]) [10] which reviews all evidence on Bendamustine and concludes that "There is very limited evidence about the effects of using bendamustine for relapsed/refractory classical Hodgkin lymphoma. It is not possible to have any level of confidence about either the effectiveness or the toxicity of Bendamustine in this group of patients." "Therefore, Bendamustine is not recommended as a treatment option for R/R cHL." In order to better reflect the UK clinical practice, it would be more reasonable to also include in the subsequent treatments of BV, a mix of relevant chemotherapies since clinical expert opinion to MSD suggested Bendamustine is not the most efficacious agent. Additionally, the ERG's assumption is extremely conservative since Bendamustine is considerably cheaper than the other treatments and therefore a mix including the other chemotherapy agents would provide a more balanced estimate. Whilst there was not enough time to amend the mix of subsequent treatments mentioned above in the model, within the timeframe agreed with the ERG and NICE during technical engagement, MSD provides a scenario (see scenario 10 in the new Evidence Form) which assumes 100% use of the most expensive chemotherapy regimen so that the committee is aware of a possible range of ICERs within which the true value might be.

		Finally, MSD would like to highlight the unmet need within the treatment pathway for R/R cHL patients with no prior ASCT. The subsequent treatment choice of chemotherapy in this group varies nationally as there is no established standard of care (single or combination chemotherapy) and based on clinical expert opinion a proportion of these patients who are considered unfit (age & co-morbidities) would be unsuitable for chemotherapy thus no efficacious available treatment. Introduction of pembrolizumab at 3L will expand the choice within this subpopulation and patients considered unfit will have a choice of approved treatments such as BV in R/R cHL rather than the limited option of investigational therapies.
Key issue 8: Gopal et al. (2015) should not be used as the primary source of OS for all subgroups	**NO**	Whilst Gopal et al.[11] is based on the pivotal trial of BV post-ASCT, MSD suggests that it is a conservative and relevant source. MSD do not believe it is realistic nor appropriate to use Balzarotti et al. (2015 [12]) as a suitable source to estimate OS for the SCT-3L+ subgroup. The trial population in the Balzarotti et al. (2015) [12] study is not comparable to the SCT-3L+ subgroup from KEYNOTE-204, due to the fact the patients in the Balzarotti et al. cannot be considered ineligible based on the most commonly given reasons by clinicians. The objective of the Balzarotti study was to investigate the activity of IGEV in association with B-IGEV as pre-transplantation induction in patients with R/R cHL after first line treatment. Therefore, the population in the study is in the 2L and the intervention was chemotherapy – rather than BV- and as a result not reflective of the SCT-3L+ patients in the pivotal trial relating to this indication. The NCT page for the trial, NCT00636311, specifically highlights the preclusion of patients with inadequate organ function from enrolling. In addition, patients were only eligible to be included in the

		study if they were <65 years of age. Therefore, it is reasonable to assume that the population in the Balzarotti et al.[12] are on the whole eligible for a SCT. A substantial proportion of the patients in the Balzarotti study (approximately 81% (minimum)) went onto transplantation therefore it could be assumed that not many patients in the paper would be truly "ineligible". This proportion is higher than the SCT -3L+ subpopulation for which OS is being estimated for. Based on the points above it is not appropriate to assume the population in the Balzarotti et al. (2015)[12] study would give accurate estimates for the subpopulation in the KN204 trial.
Key issue 9: Time of treatment (ToT) for BV in SCT-3L+ and SCT+3L+ subgroups	**NO**	MSD acknowledges that the maximum doses of BV, as per its SmPC, are 16 rather than 35 as per the KEYNOTE-204 protocol. Whilst the implementation of a max of 16 doses was preferred by the ERG according to its license, it should be noted that this amendment is not balanced since it only affects the costs – in favour of BV. MSD wishes to point out that these patients in the BV arm will also accrue the benefit of more doses than they would actually receive in UK clinical practice and therefore this ERG preferred assumption is conservative. [redacted] (overall ITT population) in KEYNOTE-204 received more than 16 cycles. By investigator assessment, [redacted] maintained or achieved partial or complete remission after Cycle 16. The majority of AEs, [redacted], were among those stated in the BV prescribing information: "Table 6: Adverse Reactions Reported in ≥10% of Patients with Relapsed Classical Hodgkin Lymphoma (Study 1)" (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125388s100lbl.pdf).

		There was no pronounced incidence of severe toxicity, with [redacted] reporting at least one AE equal to Grade 3 or higher during extended treatment. [redacted] This means that patients who got more than 16 cycles of BV in the trial, tolerated the drug as expected and accrued clinical benefit which is not adjusted for in the ERG amendment. MSD wishes to point out that this is a conservative amendment and provides a higher ICER which is not a fair representation of the clinical practice.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Please note that a full list of all the variables amended for the base case in the updated economic model is provided in the New Evidence Form			

Key issue 3	ITT population	3L+ population	Dominant
Key issue 7	Subsequent treatments as per KEYNOTE-204	Pembrolizumab arm → 100% BV BV arm → 55.2% bendamustine 44.8% nivolumab The subsequent treatments in the BV arm are based on the split of 3L+ between SCT-3L+ and SCT+3L+ in KEYNOTE-204	Dominant
Key issue 9	BV max doses as per KEYNOTE-204	BV max doses as per its license	Dominant
Dominant	Incremental QALYs: 0.59	Incremental costs:-£11,872	Dominant

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Technical engagement proposed new evidence form (company only)

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 1 prior therapy [ID1557]

As the company for this appraisal, you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses will be used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting. As part of your response, you may intend to provide new evidence to address some or all of the key issues identified in the executive summary of the ERG report (that is, evidence that has not already been provided during the appraisal).

We would like to understand the extent of new evidence that you propose to provide in your response to technical engagement. This will help the ERG to plan its critique of your response. You do not have to provide new evidence in response to every issue. However, in general, any new evidence provided should have the purpose of addressing a key issue identified in the executive summary of the ERG report. Decisions about whether NICE will accept new evidence will be made on a case by case basis. Please note that NICE may need to extend timelines and reschedule the appraisal committee meeting to allow new evidence to be considered. Therefore, it is important that you notify NICE about new evidence in advance by completing this form as comprehensively as possible. Please be aware that NICE will not routinely accept new evidence provided after the deadline for technical engagement responses.

Deadline for returning this form: **Friday 22 January 2021**

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses.
- Please ensure your response clearly identifies which key issue from the executive summary of the ERG report your proposed new evidence is intended to address. Please use the same issue numbers that have been used in the executive summary of the ERG report.
- If you intend to provide new evidence to address issues in the ERG report that have not been identified as key issues, please make this clear.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink.

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Summary of proposed new evidence

Please use the table below to provide details of any proposed new evidence that you intend to submit in response to technical engagement.

Please be as comprehensive as possible.

Key issue(s) that the new evidence will address	Summary of the proposed new evidence (short title)	How will the new evidence address the key issue(s)?	Is the new evidence expected to alter the company's base-case ICER?	Additional details about the proposed new evidence (if available)
Key Issue 3: Generalisability of the intention to treat (ITT) population to UK clinical practice	"3L+ subpopulation"	The updated population in the model is representative of the proposed licensed population and generalisable to clinical practice as all 3L+ patients will receive BV in the UK, which is the trial comparator.	**YES**	Clinical evidence of the 3L+ population as well as an updated version of the model for the 3L+ population are provided to demonstrate the clinical and cost effectiveness of pembrolizumab versus BV

N/A

“3L+ subpopulation’

1. Clinical effectiveness

Clinical data for the 3L+ subpopulation from KEYNOTE-204 are presented for baseline characteristics, PFS, response rates, health-related quality of life and adverse events.

1.1. Baseline Characteristics

Table 1 Demographic and Baseline Characteristics Subjects Who Are at Least Third Line (Intention-to-Treat Population)

	Study: 3475-204	
	MK-3475 200 mg [redacted]	**Brentuximab Vedotin** [redacted]
Gender		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Race		
American, Indian or Alaska Native	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Multiple	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]
White	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Ethnicity		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]

Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Pooled Race Group 1		
White	[redacted]	[redacted]
All Others	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Pooled Age Group 1 (years)		
< 65	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]
Pooled Age Group 2 (years)		
< 65	[redacted]	[redacted]
≥ 65 to < 75	[redacted]	[redacted]
≥ 75 to < 85	[redacted]	[redacted]
Geographic location: US		
US	[redacted]	[redacted]
Ex-US	[redacted]	[redacted]
Geographic location: EU		
EU	[redacted]	[redacted]
Ex-EU	[redacted]	[redacted]
Geographic location: World		
Europe	[redacted]	[redacted]
Japan	[redacted]	[redacted]
North America	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]
Disease Subtype		
Classical Hodgkin Lymphoma	[redacted]	[redacted]

Lymphocyte Depleted		
Classical Hodgkin Lymphoma Lymphocyte Rich	[redacted]	[redacted]
Classical Hodgkin Lymphoma Mixed Cellularity	[redacted]	[redacted]
Classical Hodgkin Lymphoma Nodular Sclerosis	[redacted]	[redacted]
Missing	[redacted]	[redacted]
ECOG performance status at screening		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Strata Prior SCT		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Strata Disease Status After 1L		
Primary Refractory	[redacted]	[redacted]
Relapsed < 12 Months	[redacted]	[redacted]
Relapsed >= 12 Months	[redacted]	[redacted]
Refractory or Relapsed Aft Any Line		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
PD-L1 Status		
<1%	[redacted]	[redacted]
≥1%	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Prior Use of Brentuximab Vedotin		

Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior Radiation		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Bulky Disease		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Baseline B symptoms		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Baseline Bone Marrow Involvement		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Country Name		
Australia	[redacted]	[redacted]
Brazil	[redacted]	[redacted]
Canada	[redacted]	[redacted]
Czech Republic	[redacted]	[redacted]
France	[redacted]	[redacted]
Germany	[redacted]	[redacted]
Hong Kong	[redacted]	[redacted]
Israel	[redacted]	[redacted]
Italy	[redacted]	[redacted]
Japan	[redacted]	[redacted]
Korea, Republic of	[redacted]	[redacted]

New Zealand	[redacted]	[redacted]
Poland	[redacted]	[redacted]
Russian Federation	[redacted]	[redacted]
South Africa	[redacted]	[redacted]
Sweden	[redacted]	[redacted]
Turkey	[redacted]	[redacted]
Ukraine	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]
United States	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Median [Min; Max]	[redacted]	[redacted]
Weight (Kg)		
Subjects with data	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median [Min; Max]	[redacted]	[redacted]
Height (cm)		
Subjects with data	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median [Min; Max]	[redacted]	[redacted]
BSA (m2)		
Subjects with data	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median [Min; Max]	[redacted]	[redacted]

1.2. PFS

In line with the ITT population results presented in the submission for this appraisal, PFS was longer in the pembrolizumab arm compared with the BV arm in 3L+ patients from the KEYNOTE-204 pivotal trial (**Error! Reference source not found.**). In addition, PFS assessed by the investigator using IWG 2007 criteria showed a more marked PFS benefit than PFS as assessed by BICR (Table 3), again showing a similar trend in benefit as the ITT population. Table 4, reports the exploratory endpoint of second progression-free survival which is defined as the time from the randomisation date to the subsequent disease progression date after initiation of new anti-cancer therapy, or death from any cause, whichever occurs first. The results for the 3L+ subgroup for estimated mean time to second progression-free survival favour pembrolizumab in line with the primary analysis for PFS.

Table 2. Estimated Median and Mean Progression Free Survival Based on Central Review per IWG 2007 (Primary Analysis) Subjects Who Are Least Third Line (Intention-to-Treat Population)

Study: 3475-204[a] Treatment	N	Number of Events (%)	Estimated Median Time in weeks	95% CI of Estimated Median Time in weeks	Estimated Mean Time in weeks	SE of Estimated Mean Time in weeks	95% CI of Estimated Mean Time in weeks
MK-3475 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a: Database Cutoff Date: [redacted] For the primary PFS analysis, clinical and imaging data following auto-SCT or allo-SCT are included. Estimated mean and median of Time to Event is from product-limit (Kaplan-Meier) method. Time to event analyses are expressed in weeks.							

Table 3 Estimated Median and Mean Progression Free Survival Based on Investigator Review per IWG 2007 (Primary Analysis) Subjects Who Are at Least Third Line

(Intention-to-Treat Population) **Study: 3475-204[a] Treatment**	**N**	**Number of Events (%)**	**Estimated Median Time in weeks**	**95% CI of Estimated Median Time in weeks**	**Estimated Mean Time in weeks**	**SE of Estimated Mean Time in weeks**	**95% CI of Estimated Mean Time in weeks**
MK-3475 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a: Database Cutoff Date: [redacted] For the primary PFS analysis, clinical and imaging data following auto-SCT or allo-SCT are included. Estimated mean and median of Time to Event is from product-limit (Kaplan-Meier) method. Time to event analyses are expressed in weeks.							

Table 4. Estimated Median and Mean Second Progression-Free Survival Time Subjects Who Are at for Least Third Line (Intention-to-Treat Population)

Study: 3475-204[a] Treatment	**N**	**Number of Events (%)**	**Estimated Median Time in weeks**	**95% CI of Estimated Median Time in weeks**	**Estimated Mean Time in weeks**	**SE of Estimated Mean Time in weeks**	**95% CI of Estimated Mean Time in weeks**
MK-3475 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a: Database Cutoff Date: [redacted] Estimated mean and median of Time to Event is from product-limit (Kaplan-Meier) method.							

Time to event analyses are expressed in weeks.
Second progression-free survival is defined as the time from the randomisation date to the subsequent disease progression date after initiation of new anti-cancer therapy, or death from any cause, whichever occurs first.

1.3. Response rates

In line with the response rates reported for the ITT population submitted to NICE, the results for the 3L+ subpopulation in Table *5* show the ORR based on BICR increased in favour of pembrolizumab. Results of ORR assessed by the investigator were consistent with ORR based on BICR, Table 6, similarly to the ITT results submitted to NICE.

Table 5 *Summary of Best Overall Response Based on Central Review per IWG 2007 Subjects Who Are at Least Third Line (Intention-to-Treat Population)*

Study: 3475-204[a]	**MK-3475 200 mg** [redacted]		**Brentuximab Vedotin** [redacted]	
Response Evaluation	**n[b]**	**Percentage[b] [95 %-CI][c]**	**n[b]**	**Percentage[b] [95 %-CI][c]**
Objective Response	[redacted]	[redacted]	[redacted]	[redacted]
Complete Response	[redacted]	[redacted]	[redacted]	[redacted]
Partial Response	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]
Non-Evaluable	[redacted]	[redacted]	[redacted]	[redacted]
No Assessment	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
b: Subjects with event.
c: Based on binomial exact confidence interval method for binomial data.
Excludes data after autologous SCT or allogeneic SCT.

Table 6. *Summary of Best Overall Response Based on Investigator Review per IWG 2007 Subjects Who Are at Least Third Line*

(Intention-to-Treat Population)

Study: 3475-204[a]	MK-3475 200 mg [redacted]		Brentuximab Vedotin [redacted]	
Response Evaluation	**n[b]**	**Percentage[b] [95 %-CI][c]**	**n[b]**	**Percentage[b] [95 %-CI][c]**
Objective Response	[redacted]	[redacted]	[redacted]	[redacted]
Complete Response	[redacted]	[redacted]	[redacted]	[redacted]
Partial Response	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]
No Assessment	[redacted]	[redacted]	[redacted]	[redacted]
a: Database Cutoff Date: [redacted]				
b: Subjects with event.				
c: Based on binomial exact confidence interval method for binomial data.				
Excludes data after autologous SCT or allogeneic SCT.				

1.4. Health related quality of life

Longer PFS in the pembrolizumab group was accompanied by an improvement in health related QOL, as compared to BV in the 3L+ population, consistently with the overall ITT population.

Table 7. Baseline EQ-5D Health Utility Scores - UK Algorithm Subjects Who Are at Least Third Line (Full Analysis Set Population)

Study: 3475-204[a]	MK-3475 200 mg [redacted]					Brentuximab Vedotin [redacted]					Pooled [redacted]				
	n[†]	m[‡]	Mean	SE	95% CI	n[†]	m[‡]	Mean	SE	95% CI	n[†]	m[‡]	Mean	SE	95% CI
Baseline	[redacted]														

[redacted]

a: Database Cutoff Date: [redacted]
n† = Number of patients with non-missing EQ-5D score.
m‡ = Number of records with non-missing EQ-5D score.

Table 8. EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) - UK Algorithm Subjects Who Are at Least Third Line (Full Analysis Set Population)

Study: 3475-204[a]	MK-3475 200 mg [redacted]					Brentuximab Vedotin [redacted]					Pooled [redacted]				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Before SCT	[redacted]														
After SCT	[redacted]														
Progressive	[redacted]														
Before SCT	[redacted]														

a: Database Cutoff Date: [redacted]
n† = Number of patients with non-missing EQ-5D score.
m‡ = Number of records with non-missing EQ-5D score.
Progression-free off treatment utility data for subjects that did not have a SCT are classified as 'before SCT'.

Clinical and imaging data following auto-SCT or allo-SCT are included to determine Progression-free status.
EQ-5D score during baseline is not included.

1.5. Adverse events

As per the results reported for the ITT population, patients in the pembrolizumab arm were on treatment for approximately twice as long compared with the BV arm in the 3L+ subpopulation Table 9. Similar proportions of patients in both arms experience one or more adverse events in the 3L+ subpopulation, as reported in the ITT population. For the 3L+ subpopulation the most frequently reported Grade 3-5 AEs (incidence ≥5%) in the pembrolizumab arm were Infections and infestations ([redacted]) and blood and lymphatic system disorders ([redacted]) in the BV arm, Table 11.

Table 9. Estimated Median and Mean Time On Treatment Subjects Who Are at Least Third Line (All-Subjects-as-Treated Population)

Study: 3475-204[a] Treatment	**N**	**Number of Events (%)**	**Estimated Median Time in weeks**	**95% CI of Estimated Median Time in weeks**	**Estimated Mean Time in weeks**	**SE of Estimated Mean Time in weeks**	**95% CI of Estimated Mean Time in weeks**
MK-3475 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brentuximab Vedotin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: [redacted]
Estimated mean and median of Time to Event is from product-limit (Kaplan-Meier) method. Time to event analyses are expressed in weeks.
Time on Treatment is defined as the time from the date of initial dose until the date of last dose.
Number of Events is defined as number of subjects who had discontinued or completed primary study treatment at the database cutoff date.

Table 10. Subjects with Grade 3-5 Adverse Events (Incidence ≥2% in One or More Group) Subjects Who Are at Least Third Line

(All-Subjects-as-Treated Population)

Study: 3475-204	Patients with Event n (%)	
System Organ Class **PT**	**MK-3475 200 mg**	**Brentuximab Vedotin**
Patients with one or more adverse events		
Blood and lymphatic system disorders		
Neutropenia		
Anaemia		
Thrombocytopenia		
Leukopenia		
Cardiac disorders		
Gastrointestinal disorders		
Diarrhoea		
General disorders and administration site conditions		
Hepatobiliary disorders		
Infections and infestations		
Pneumonia		
Injury, poisoning and procedural complications		
Infusion related reaction		
Investigations		
Neutrophil count decreased		
Alanine aminotransferase increased		
Metabolism and nutrition disorders		
Hypokalaemia		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		

Nervous system disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]

a: Number of patients: all-subjects-as-treated population.
Database Cutoff Date: [redacted]
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.
MedDRA version used is 22.1.

Table 11. Subjects with Grade 3-5 Adverse Events (Incidence ≥5% in One or More Group) Subjects Who Are at Least Third Line (All-Subjects-as-Treated Population)

Study: 3475-204	**Patients with Event n (%)**	
System Organ Class	**MK-3475 200 mg**	**Brentuximab Vedotin**
PT	[redacted]	[redacted]
Patients with one or more adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]

Neutropenia	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]

a: Number of patients: all-subjects-as-treated population.
Database Cutoff Date: [redacted]
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.
MedDRA version used is 22.1.

2. Cost effectiveness

2.1. Economic model

The cost effectiveness model was updated for the 3L+ population and the key parameters for the updated base case were:
Table 12. Key parameters set in the updated model

Parameter	3L+ population model inputs	Consistency with ITT base case submitted originally
Population	3L+	Yes
Time horizon	50 years	No – as per ERG's preferred assumption
Discount rates (cost / outcomes)	3.5%	Yes

Half-cycle correction	Yes	Yes
Patient characteristics	Updated for the 3L+ population	No, however it does not affect the ICERs
PFS	2-piece approach: KM data and lognormal extrapolation after week 52	Yes same method- data updated for the 3L+ subpopulation. Further details are described below
OS	Gopal et al. (lognormal extrapolation)	Yes
ToT	KM up to week 80 and exponential extrapolation after week 80	Yes same method- data updated for the 3L+ subpopulation
AE incidence	Grade 3-5 AEs with incidence >2% - patients 3L+	No, updated for the 3L+ population
Utilities	Mean utilities – treatment specific in Progression-Free and Progressed Disease state	Yes
Apply age-related utility decrement	Yes	Yes
Disutilities and disutility duration	Based on previous NICE TAs and literature	Yes
Pembrolizumab discount	[redacted]	[redacted]
Dose intensity	98% for both arms based on KEYNOTE-204 (ITT population)	Yes
BV maximum doses	16	No- as per ERG's preferred assumption
Administration costs	Based on National Tariff of Chemotherapy Regimens List and NHS reference costs 2018/19	Yes
Stem cell transplant rates	Updated for the 3L+ population – applied same rates for both arms as per the ERG's preference	NO – updated for 3L+ population, as per ERG's preferred assumption
Resource use	Higher resource use in the PD health state	No – as per ERG's preferred assumption
Terminal care	Based on previous submission	Yes
Subsequent treatments	Pembrolizumab arm → 100% BV BV arm → 55.2% bendamustine 44.8% nivolumab The subsequent treatments in the BV arm are based on the split of 3L+ between SCT-3L+ and SCT+3L+ in KEYNOTE-204	No – based on clinical expert opinion
Costs of AEs	Based on previous submissions and NHS reference costs	Yes

2.2. Extrapolation of PFS

The extrapolation of PFS for the 3L+ population followed the structure of the ITT population submitted originally.

Survival analyses for PFS were conducted using approaches outlined by the Decision Support Unit (DSU) by NICE: The first step was the assessment of the proportional hazards (PH) assumption judged via the plotting of the log-cumulative hazard function (Figure 1) and associated residual plots (Figure 2): when comparing the PFS outcomes observed in the pembrolizumab and BV, PH may not hold based on the visual assessment of the log-cumulative hazards plot. The plots are parallel, they merge and separate in a couple of time points. The statistical test supports the PH assumption since the result is not statistically significant ($p > 0.05$) indicating that the PH assumption for PFS might be assumed but due to the uncertainty regarding the PH assumption, pembrolizumab and BV were modelled by fitting independent parametric models to each treatment arm.

Figure 1. Comparison in cumulative hazard in BIRC-assessed Progression-free Survival over time between groups treated with pembrolizumab versus BV for 3L+

Figure 2. Schoenfeld residual for graphical diagnosis of proportional hazards in BIRC-assessed Progression-free Survival between groups treated with pembrolizumab versus BV for 3L+

Visual inspection of the 3L+ hazard plots in Figure 1 shows that they are very similar to the ITT population and a change in hazard can be seen for cut off points similar to the ones identified in the ITT population plots i.e. week 26 and week 52. For consistency but also in order to use as much as possible of the observed KM data, week 52 was selected as the cut-off point. Additionally, it provided more clinically plausible estimates compared to week 26 since the latter results in low 5year PFS estimates. Therefore, KM data are used until the 52-week breaking point and then parametric extrapolation is applied thereafter. A series of parametric extrapolations were fitted to PFS data for week 52 in order to identify the best fitting curve (Figure 3 and Figure 4).

Figure 3. Plot of parametric fitting and extrapolation of long-term BIRC-assessed PFS for the group treated with pembrolizumab with breaking point at Week 52, 3L+ population

Figure 4. Plot of parametric fitting and extrapolation of long-term BIRC-assessed PFS for the group treated with BV with breaking point at Week 52, 3L+ population

Table 13 presents a summary of the AIC and BIC statistics for both arms. For pembrolizumab, the AIC and BIC criteria suggest Gompertz is the best fitting model while for BV is gengamma. However, log-normal was the second-best fitting model for pembrolizumab arm and third for BV arm and provided a good visual fit therefore it was selected as the best fitting curve.

Table 13. Summary of parametric fitting performances of BIRC-assessed Progression-free Survival for the group treated with pembrolizumab and BV, 3L+ population

	Pembrolizumab				Brentuximab vedotin			
Distributions	AIC	Rank	BIC	Rank	AIC	Rank	BIC	Rank
Exponential	[redacted]							
Weibull	[redacted]							
Gompertz	[redacted]							
Log-logistic	[redacted]							
Log-normal	[redacted]							
Generalised gamma	[redacted]							

The selection of a piecewise log-normal extrapolation was also in accordance with the external validation that was conducted for the original submission with two consultant haematologists, from different centres, who specialise in lymphomas whom were asked to discuss key issues relating to economic modelling. The plausibility of the approach to modelling PFS was validated by asking clinicians to estimate 5-year survival percentages for BV. The suggestions were that for patients who are R/R after ASCT (SCT+3L) which estimated PFS was approximately ~15% at 5 years while patients ineligible for transplant would have a lower PFS about ~10%.

It can be seen from Table 15, that the ITT modelled 5-year PFS for the BV arm is 11.5% and this is potentially a plausible estimate since it is within the 10% and 15% 5-year PFS estimates cited by the clinician for the two subgroups.

A piecewise extrapolation with breaking point at 26 weeks as well as a fully fitted parametric curve from week 0 are explored as scenario analyses. Neither of the two were selected as the base case since the best statistical fits to the PFS KM data for each scenario resulted in much higher, clinically implausible 5-year PFS estimates of BV, ~17-17.5%.

Table 14. PFS modelled extrapolation estimates – piecewise parametric approach with breaking point at week 52, 3L+ population

	PFS				
	1 yr	2 yr	3 yr	4 yr	5 yr
Pembrolizumab	50.5%	35.6%	29.7%	26.0%	23.4%
BV	32.6%	21.7%	16.4%	13.3%	11.1%

Table 15. PFS modelled extrapolation estimates – piecewise parametric approach with breaking point at week 26, 3L+ population

	PFS				
	1 yr	2 yr	3 yr	4 yr	5 yr
Pembrolizumab	51.3%	37.0%	29.6%	24.9%	21.6%
BV	36.3%	21.5%	14.9%	11.1%	8.6%

In conclusion, based on the visual and statistical fit of the extrapolated curves as well as the external validation from clinical experts, the log-normal was selected as the base case with a breaking point at week 52 (Figure 5). Please note that the decline in the PFS of pembrolizumab arm after year 10 is due to a requirement applied in the model so that PFS is never higher than OS, see more details in the Overall Survival section

Figure 5. Extrapolation of modelled long-term BIRC-assessed PFS for pembrolizumab and BV with breaking point at Week 52, 3L+ population

2.3. Time on Treatment

For the updated population the ToT was preferred to be consistent with the original submission, i.e. extrapolate based on a 2-piece extrapolation. Since KM data for the pembrolizumab arm in the 3L+ population is available up to week 103 (i.e. almost all doses up to the stopping rule at 104 weeks) it is more appropriate to use as much of the actual KM data by extrapolating at week 80 is the most robust approach. For the BV arm, a maximum of 16 doses is applied in the updated model (as per BV's license) and therefore it makes more sense to use the actual KM data too and not to extrapolate by week 26 as per the ERG preferred assumption. As per Table 16 the exponential had the best fit for both arms and was selected for the extrapolation of ToT.

Table 16. Summary of parametric fitting performances of Time on Treatment for Pembrolizumab and BV, cut off Week 80, 3L+ population

	Pembrolizumab				Brentuximab vedotin			
Distributions	AIC	Rank	BIC	Rank	AIC	Rank	BIC	Rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.4. Base case results

Table 17 below presents the base case incremental cost-effectiveness results for pembrolizumab incorporating the updated baseline PAS discount. The results show pembrolizumab to be cost-effective compared to BV as patients accrue more QALYs and it is less expensive i.e. pembrolizumab is dominant over BV.

Table 17. Updated population base case deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Pembrolizumab	[redacted]	5.00	4.13	--	--	--		--
BV	[redacted]	5.00	3.54	-11,872	0.00	0.59		Dominant

2.5. Probabilistic sensitivity analysis

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 18 and the corresponding scatterplot and cost-effectiveness acceptability curves are presented in Figure 6 and Figure 7. The main part of the ellipse on the SE quadrant of the cost-effectiveness plane suggests the dominance of pembrolizumab (less costly, more health gains) in most of the iterations.

Table 18. Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS), 3L+ population

	Total cost (£)	Total LYs	Total QALYs	Incr. cost (pembro vs.)	Incr. LYs	Incr. QALYs	Cost (£) per QALY (pembro vs.)
Pembrolizumab	[redacted]	5.026	4.141				
BV	[redacted]	5.026	3.575	11,558	0.00	0.57	Dominant

Figure 6. Scatterplot of PSA results (1,000 simulations; results discounted, with PAS)

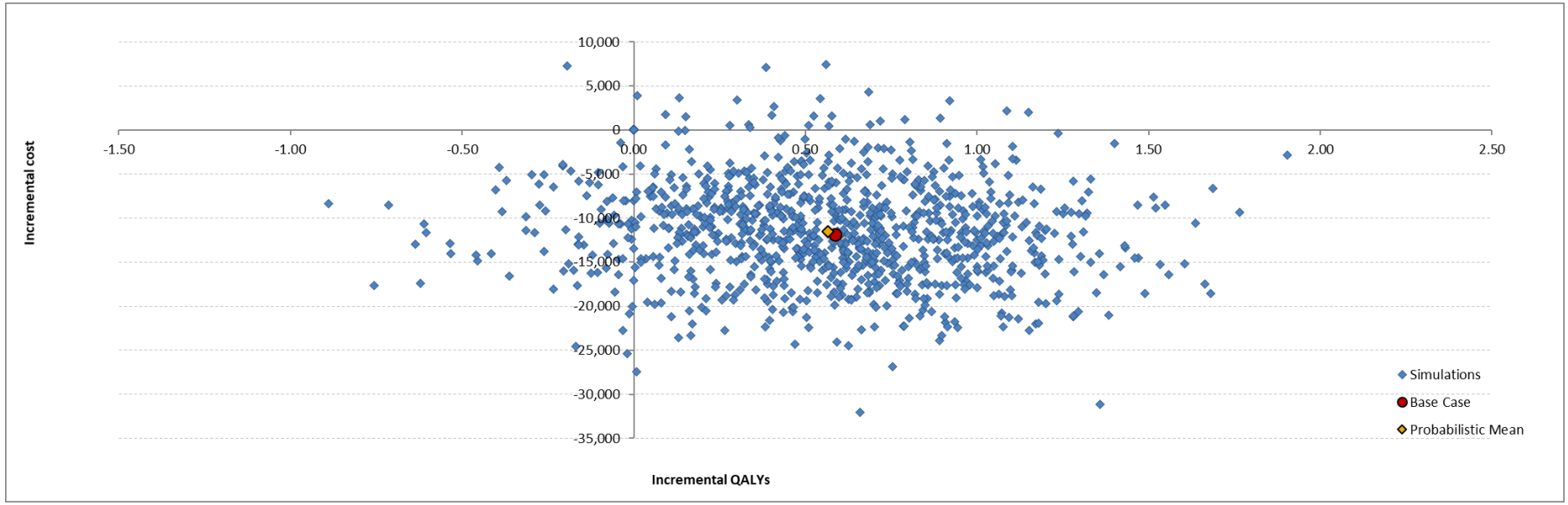
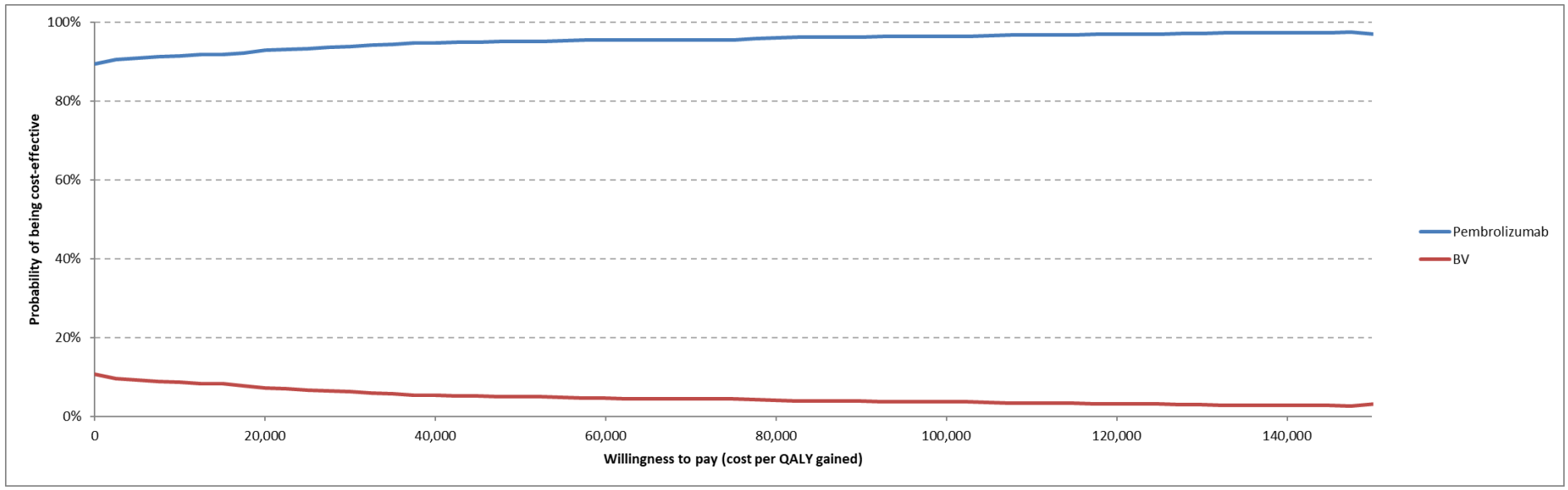


Figure 7. Cost-effectiveness acceptability curve (results discounted, with PAS)



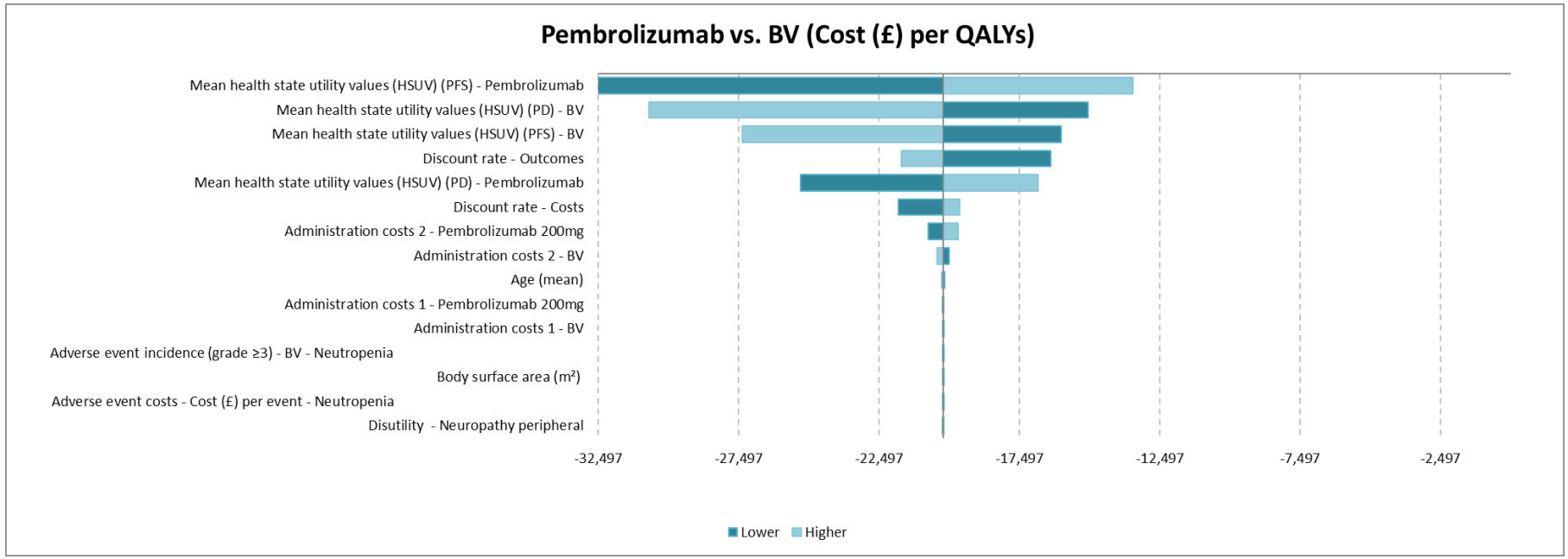
2.6. Deterministic sensitivity analysis

The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab vs. BV are presented in Figure 8 below.

In all scenarios, the ICER for pembrolizumab vs BV was dominant. The inputs that most affect the ICERs are the treatment specific utilities followed by the discount rate on outcomes and the stem cell transplant rates.

Plausible alternative scenarios have further been investigated in the next section (Scenario Analysis), with all the scenarios showing dominance of pembrolizumab.

Figure 8. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most sensible variables (discounted results, with PAS), 3L+ population



2.7. Scenario analyses

Scenario		Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Base case	Pembrolizumab	[redacted]	5.00	4.13	--	--	--		--
	BV	[redacted]	5.00	3.54	-11,872	0.00	0.59		Dominant
Scenario 1	Pembrolizumab	[redacted]	5.00	3.95	--	--	--		--
Utility same in PD state 0.693	BV	[redacted]	5.00	3.54	-11,872	0.00	0.40		Dominant
Scenario 2	Pembrolizumab	[redacted]	5.00	4.13	--	--	--		--
Dose intensity 100%	BV	[redacted]	5.00	3.54	-12,198	0.00	0.59		**Dominant**
Scenario 3	Pembrolizumab	[redacted]	5.00	4.13	--	--	--		--
Pembro 400 mg Q6W	BV	[redacted]	5.00	3.54	-12,183	0.00	0.59		**Dominant**
Scenario 4	Pembrolizumab	[redacted]	12.52	9.89	--	--	--		--
OS based on KEYNOTE-087	BV	[redacted]	12.52	8.39	-7,854	0.00	1.51		**Dominant**
Scenario 5	Pembrolizumab	[redacted]	5.00	4.13	--	--	--		--
PFS piecewise week 26	BV	[redacted]	5.00	3.54	-24,981	0.00	0.59		Dominant
Scenario 6 26-week cut-point for modelling ToT	Pembrolizumab	[redacted]	5.00	4.13	--	--	--		--
	BV	[redacted]	5.00	3.52	-13,016	0.00	0.61		Dominant
Scenario 7	Pembrolizumab	[redacted]	5.00	4.14	--	--	--		--

Gompertz for PFS- 52 weeks	BV	[redacted]	5.00	3.61	-10,090	0.00	0.53		**Dominant**
Scenario 8	Pembrolizumab	[redacted]	5.00	4.14	--	--	--		--
Gengamma for PFS – 52 weeks	BV	[redacted]	5.00	3.62	-9,745	0.00	0.52		**Dominant**
Scenario 9	Pembrolizumab	[redacted]	5.00	4.13	--	--	--		--
BV 35 max cycles	BV	[redacted]	5.00	3.54	-20,304	0.00	0.59		**Dominant**
Scenario 10	Pembrolizumab	[redacted]	5.00	4.13	--	--	--		--
Subsequent treatment - most expensive chemo post-BV in the SCT-3L+	BV	[redacted]	5.00	3.54	-12,416	0.00	0.59		**Dominant**

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 5 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens and current treatment options	
About you	
1. Your name	**Elizabeth Phillips**
2. Name of organisation	**The Christie NHS Trust and University of Manchester**
3. Job title or position	**Consultant Haematologist and Senior Clinical Lecturer**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with classical Hodgkin's lymphoma? ☒ a specialist in the clinical evidence base for classical Hodgkin's lymphoma or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ I don't know if they submitted one

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
The aim of treatment for relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	There are 2 different groups of patients, with very different goals and treatment pathways, depending on whether the patient is fit enough to receive subsequent consolidation with SCT. For transplant-fit patients: to achieve complete metabolic response, in order to facilitate subsequent SCT and potentially cure For transplant-unfit patients: to prolong quality and quantity of life (cure is unlikely to be achieved) Many clinical trials recruit 'transplant-ineligible' patients, which include a combination of both groups- transplant-fit patients who have not achieved satisfactory disease control, and those that are transplant-unfit.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	It depends whether the patient is fit for SCT consolidation For transplant-fit patients: complete metabolic response (CMR) as this defines eligibility for subsequent SCT For transplant-unfit patients: at least partial response- progression-free/overall survival and quality of life are much more important

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens?	Yes For transplant-fit patients: there is a need to improve CMR rates with 2L therapy and to provide effective 3L options for those that fail intensive salvage chemotherapy. Pembrolizumab monotherapy will only assist with the latter. Most transplant-unfit patients: there is no standard of care and no effective chemotherapy options for 2L treatment. There is a clear need for early access to novel agents from 2L+ (currently 3L+ via CDF).
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSH guidelines were published in 2014 (Collins *et al*, Brit J Haem). These are currently being revised, but treatment pathways have not significantly changed apart from the more widespread use of novel agents: brentuximab vedotin (BV) as 3L and PD-1 inhibitors as 4L currently
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**2L treatment:** Transplant-fit patients: standard of care is intensive multi-agent chemotherapy, although there is widespread variation in preferred regimen around the UK: examples include IGEV, ESHAP, ICE, GDP. Retrospective data in Hodgkin lymphoma (unpublished real-world data from 11 UK centres), and randomised trials in other lymphomas, suggest that CMR rates are similar with all of these regimens. For transplant-unfit patients, the treatment pathway is currently undefined. The 2014 BSH guidelines suggest single-agent chemotherapy and/or palliation in this group

	3L treatment: Some centres have access to BV plus bendamustine (Wales, selected centres in England). This regimen is only applicable to transplant-fit patients. It induces high CMR rates and is likely to be preferred to single-agent pembrolizumab in these centres. However, most English centres only have access to BV as monotherapy, irrespective of whether the patient is transplant-fit or -unfit. The Keynote-204 trial therefore applies to current practice in most centres for 3L treatment.
• What impact would the technology have on the current pathway of care?	It will alter the sequence of treatments for relapsed and refractory Hodgkin lymphoma. For transplant-unfit patients, it will mean that clinicians have better 2L options and no longer feel obliged to offer toxic and fairly ineffective chemotherapy as a bridge to novel agents (which are only available from 3L+). For transplant-fit patients, it will provide earlier access to PD-1 inhibition, prior to BV and at a point when most patients are still eligible for autoSCT. Currently, PD-1 inhibition is more commonly used as a bridge to alloSCT
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Compared with BV monotherapy- very little difference in terms of use of outpatient resources as these agents are both delivered every 21 days as intravenous infusions. For transplant-unfit patients, the duration of pembrolizumab therapy is likely to be longer than with alternative treatments (such as BV), but this is largely due to more durable responses and better tolerability
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary/tertiary centres only
• What investment is needed to introduce the	None- this treatment is already in widespread use via the CDF

technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	For transplant-unfit patients: yes, there is no standard of care For transplant-fit patients: not clear. The survival benefit will be for the small proportion of patients that do not achieve CMR by other means, assuming that PD-1 inhibitors are not available later in therapy, via the CDF or otherwise.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes- for most patients (transplant-unfit, or 3L+ if transplant-fit). The Keynote-204 trial demonstrated a QoL benefit over single-agent BV Whether pembrolizumab improves QoL when compared with intensive chemotherapy for transplant-fit patients as 2L treatment is less clear. The toxicity of pembrolizumab is much lower than with chemotherapy. However, treatment pathways are longer if using 2L pembrolizumab, and the majority of patients (i.e. those that do not achieve CMR) will still require intensive chemotherapy at a later date
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As 2L treatment, CMR rates are lower with pembrolizumab than with intensive chemotherapy. This is important, as fewer patients will therefore be eligible for SCT consolidation with pembrolizumab as 2L treatment. The sequencing of PD-1 inhibition and SCT is another important consideration for transplant-fit patients. Autologous SCT is essentially a vehicle to deliver high-dose chemotherapy consolidation. The established view is that patients require evidence of prior chemosensitivity to derive benefit. The benefit of autologous SCT directly after 2L/3L PD-1 inhibition is unclear, given that most patients will not have demonstrated chemosensitivity to traditional chemotherapy agents. Published data on autologous SCT after anti-PD-1

	therapy are limited to a small case series (N=13). Allogeneic SCT is usually not considered until subsequent lines of therapy (4L, or 3L with suboptimal response) and/or failure of autologous SCT. Nevertheless, PD-1 inhibition can increase the toxicity of allogeneic SCT, so there is a potential advantage for bringing pembrolizumab into the treatment pathway earlier, at a point when autologous SCT is still an option. The optimal sequencing of therapies for SCT-fit patients is unclear.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Monitoring for immune-related adverse effects is required, including regular thyroid function tests Pembrolizumab is a low-intensity outpatient regimen that is generally easy to deliver- either on a par or easier than other treatment options, depending on the patient group and line of therapy that it is applied to
16. Will any rules (informal or formal) be used to start or stop treatment with the technology?	It is standard practice to perform regular response assessment by PET-CT after 12 weeks It is well documented that pembrolizumab and similar agents can cause pseudo-progression, resulting in indeterminate responses on PET assessment. Therefore, it will be important to allow clinicians to continue treatment

Do these include any additional testing?	with pembrolizumab if there is potential radiological progression but no clinical signs of PD, as per LyRIC criteria (Cheson et al, Blood 2016). Otherwise, overt PD or unacceptable toxicity are the usual criteria for stopping therapy
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. Amplification of PD-1 ligands is now known to be a defining feature of Hodgkin lymphoma. Checkpoint inhibitors have unprecedented single agent efficacy in this disease. The optimum use of PD-1 inhibitors is yet to be defined, but there is a strong pre-clinical rationale for bringing them into the treatment pathway earlier, at a point when patients are less immunosuppressed and able to mount effective anti-tumour immune responses

• Does the use of the technology address any particular unmet need of the patient population?	Yes, for transplant-unfit patients in particular See previous comments about transplant-fit patients- it depends on which line of therapy it is applied to
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Immune-related side effects cause significant morbidity for a minority of patients (~5%). In rare instances, these toxicities may render patients ineligible for subsequent treatment, such as further salvage therapy or SCT consolidation. In general, pembrolizumab has a favourable toxicity profile. See comments on Q13 re: quality of life
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	Keynote-204 reflects current UK practice for 3L treatment of Hodgkin lymphoma
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free survival, quality of life and overall survival are important for both groups. CMR rates are important for the transplant-fit as these define treatment failure and the need for subsequent lines of therapy. All of these outcomes were measured.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The primary outcome measure for Keynote-204 was PFS. Arguably, this is a surrogate for OS, although it is also clinically meaningful in its own right. It may not be possible to identify an OS benefit for pembrolizumab in Keynote-204, given a potential element of crossover at relapse
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The adverse effects of checkpoint inhibitors are already well described
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA524?	No
23. How do data on real-world experience compare with the trial data?	There are few mature datasets on real-world experience with PD-1 inhibition for Hodgkin lymphoma. Patient populations are heterogeneous, tend to be more heavily pre-treated and include patients with relapse after SCT. Many of these series describe patients treated with nivolumab, rather than pembrolizumab, or a variety of PD-1

	inhibitors. In general, overall response rates of 60-70%, CMR rates 20-25% with median PFS >1 year. Results from Keynote-204 and other pembrolizumab trials are broadly consistent with these results
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the issues below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Immaturity of overall survival data	PFS2 data from Keynote-204 are encouraging, and suggest that the benefit of early pembrolizumab continues beyond treatment failure. An element of crossover in therapies after treatment failure will reduce any OS benfit I expect that any OS benefit will be greater in the transplant-unfit population where there are no standard treatment options at relapse, than in those who are transplant-fit (auto or allo SCT)
How reliable is the comparison of pembrolizumab with standard of care made by the MAIC for the SCT-2L subgroup?	Unreliable and uninterpretable. Patient numbers are small in both groups. This comparison does not reflect the breadth of standard chemotherapy regimens used in standard practice Only randomised trials will resolve this issue. Real-world data may provide more information on outcomes with standard chemotherapy, but uncertainty about outcomes with 2L pembrolizumab will remain, given the small numbers of patients in this group in Keynote-2014

Generalisability of the intention to treat (ITT) population to UK clinical practice	I agree that BV is only a relevant comparator for 3L treatment, or 2L if transplant-unfit (the latter according to interim CDF access during the COVID pandemic) Please note that the subgroups described throughout this appraisal (according to line of therapy and prior receipt of SCT) do not adequately reflect clinical practice- fitness for SCT consolidation is key in determining treatment pathways
Uncertainty in PFS estimation in the SCT-2L subgroup	I agree with the panel's concerns
Uncertainty in the maintenance of PFS benefit associated with pembrolizumab after treatment discontinuation in Year 2	I agree with the panel's concerns
Utility values used in the progressed disease (PD) health state for pembrolizumab	I agree that it is difficult to assume ongoing benefit at PD
Uncertainty in subsequent treatments and assumed proportions in the company's base case analysis	I disagree that nivolumab is a valid treatment option after failure of pembrolizumab. It does not make logical sense to use one PD-1 inhibitor after failure of another given that the mechanism of action presumably does not differ; I am not aware of any data to support this I note that subsequent access to BV and pembrolizumab at treatment failure is currently reliant on CDF access rather than routine commissioning. However, I do believe that it is reasonable to assume these are the next 'standard' treatment options where available- there are very little data to support alternative options beyond 3L

Gopal et al. (2015) should not be used as the primary source of OS for all subgroups	I agree that it is not possible to extrapolate these data to other patient groups
Time of treatment (ToT) for BV in SCT-3L+ and SCT+3L+ subgroups	ToT for BV is generally limited by cumulative development of peripheral neuropathy, for those that are transplant-unfit. This often occurs prior to completing treatment- therefore it is unreasonable to assume that patients will receive >16 cycles. I note the median number of cycles in Keynote-204 was only 7. For transplant-fit patients, most patients will only receive 4-8 cycles
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Treatment pathways need to take account of fitness for subsequent stem cell transplant
- For transplant-unfit patients, where there are no standard 2L or 3L treatment options, pembrolizumab offers clear benefits in terms of both quality of life and PFS.
- For transplant-fit patients, the optimum sequencing of therapies is unclear
- Response rates are an important consideration for transplant-fit patients
- Available data support use of pembrolizumab where BV is a valid comparator (i.e. 3L)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 5 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens and current treatment options	
About you	
1. Your name	**Graham Collins**
2. Name of organisation	**Oxford University Hospitals NHS Foundation Trust**
3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with classical Hodgkin's lymphoma? ☐ a specialist in the clinical evidence base for classical Hodgkin's lymphoma or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	It depends on the population being treated. 1. Elderly and / or co-morbid who are not fit for a stem cell transplant. The aim is to induce a durable remission, maintain good quality of life and prolong survival 2. Younger / fit patient who is not currently eligible for a stem cell transplant as they are not in a good enough remission. The aim is to induce a stable remission to bridge them to a potentially curative stem cell transplant (autologous or allogeneic) 3. Younger / fit patient relapsing after an autologous stem cell transplant. The aim for most patients is induce a stable remission so as to bridge them to a potentially curative allogeneic stem cell transplant. Some patients may not be fit for (or may decline) an allogeneic transplant in which case, a prolonged remission, prolonged survival with good quality of life is the aim
9. What do you consider a clinically significant treatment	Reduction in tumour by 50% is generally accepted as a treatment response for patients lymphoma and I would regard this as clinically meaningful. This would normally correlate with a reduction in any lymphoma symptoms the

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	patient was experiencing prior to treatment. It is also a good enough response to proceed to an allogeneic stem cell transplant (although generally for an autologous transplant, deeper remissions are desirable).
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory classical Hodgkin's lymphoma after 1 or more multi-agent chemotherapy regimens?	Yes. Current options are: - Brentuximab vedotin. This is an important agent in the treatment of this condition but only complete responses (seen in 25-30% patients) are durable; partial responses are most less stable - For younger patients, alternative combination chemo is an option, although as patients have failed 2 types of combination chemo (frontline chemo and 1st lines relapse) by this point, different combination chemo will have limited benefit generally and be associated with significant toxicity - For older patients, combination chemo is poorly tolerated. BV is the current option but remission for most are short and toxicities (neutropenia, fatigue) can be significant in this frailer group of patients
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Brentuximab vedotin (BV) is the most commonly used agent. Although BV is only licensed and commissioned as a single agent, some centres combine it with other chemotherapy agents (e.g. Bendamustine). These combinations are more effective but many centres are unable to use them due to inconsistent funding across England specifically and the UK more generally.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The current BSH guidelines are rather out of date and new ones are being written. No other treatment guidelines is specifically being used.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes it can vary and there are differences of opinion: - Although single agent BV is the most popular treatment; some centres in England would combine BV with other agents (even though it's not routinely funded) and some centres would try alternative multi-agent chemotherapy - For this younger fitter group not suitable for SCT due to poor remission, some centres would use 2nd line relapse treatment to try to get the patient to autologous transplant, some to try to get them to allogeneic transplant. - For older / frail patients, most centres would use BV as 2nd line - For patients relapsing after an autologous transplant, some centres would use BV if the patient was BV naïve or if they had prior BV to which they responded and tolerated well; others would combine BV with a chemotherapy agent (not licensed or routinely funded). Most centres would use the treatment to bridge to an allogeneic stem cell transplant; others would keep treating with pembrolizumab until progression and only then aim to re-induce remission and take to allogeneic transplant.
• What impact would the technology have on the current pathway of care?	Currently PD1 inhibitors (nivolumab or pembrolizumab) can be used but only AFTER brentuximab. If this NICE appraisal is adopted, pembrolizumab could be used BEFORE BV. BV could still be used in the event of pembrolizumab failure.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently we can only use pembrolizumab in patients who have failed 2 lines of treatment and BV and are not suitable for a stem cell transplant. This technology appraisal would enable us to use the agent higher in the treatment pathway (note: for patients relapsing after a stem cell transplant AND BV we currently can use nivolumab which is a very similar agent to pembrolizumab).
• How does healthcare resource use differ between the technology and current care?	Negligible – it simply moves where we can pembrolizumab in the pathway.
• In what clinical setting should the technology be	Secondary care, in chemotherapy day treatment units.

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Keynote 204 demonstrated prolonged PFS and improved QoL compared to BV. So yes I would expect clinically meaningful benefit both: - For when the patient is on the drug (improved QoL) - As a bridge to potentially curative therapy
• Do you expect the technology to increase length of life more than current care?	No, as currently we can use pembrolizumab (or the very similar agent nivolumab) after BV; this appraisal moves it to before BV but both can still be used)
• Do you expect the technology to increase health-related quality of life more than current care?	Yes as this was demonstrated I think convincingly by Keynote 204.
14. Are there any groups of people for whom the technology would be more or less effective	There are small groups of patients in whom this is contra-indicated eg. Active autoimmune disease; following a solid organ transplant

(or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	PD1 inhibitors do require an awareness of immune related toxicities (e.g. thyroid disorders, pancreatitis, hypophysitis etc). However PD1 inhibitors are in widespread use in oncology and are already in use further down the Hodgkin pathway. So units are already delivering these agents and are used to the practical implications.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Responses should be assessed on treatment with CT or PET scanning. Although limited treatment can occur post-progression on a scan (and has showed in some cases to re-induce remission) generally treatment would be stopped if progression is seen on 2 consecutive scans.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	When used as a bridge to a potentially curative stem cell transplant, the technology is being used as part of a curative pathway. Cure has a major impact on QALY.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	PD1 inhibitors are hugely innovative and have revolutionsed cancer medicine. This appraisal however is more about defining their place in the pathway.
• Is the technology a 'step-change' in the management of the condition?	Yes – but as above, this appraisal is more about defining the role of PD1 inhibitors (pembrolizumab) in the pathway as they are already in use in relapsed Hodgkin.
• Does the use of the technology address any particular unmet need of the patient population?	It enables a high rate of durable responses earlier on the treatment pathway, and a bridge to transplant for younger patients.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Pembrolizumab is generally very well tolerated. It can cause very severe immune related reactions but these are uncommon. Examples include pneumonitis, colitis, thyroid dysfunction. When they occur they can seriously affect the patient's quality of life detrimentally.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Keynote 204 compared single agent BV with pembrolizumab. This reflects UK practise. However, BV could be used up to 35 cycles which is not UK practise (which is up to 16). However not many patients on the BV arm received over 16 cycles. Furthermore, the UK generally uses allogeneic stem cell transplants more than, for example, North America. So fewer patients were bridged to this in the trials compared to UK practise.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	CMR rate is an important outcome as it allows effective bridging and is associated with longer remission. This was measured. PFS is also a very relevant endpoint for patients as is QoL. These were measured. OS is also important and was measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No – pembro is used widely in solid tumour oncology so the side effect prolife is well established.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA524?	No
23. How do data on real-world experience compare with the trial data?	I am not aware of significant real world data of pembrolizumab use in this setting.
Equality	
24a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the issues below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Immaturity of overall survival data	Hodgkin lymphoma is generally a disease of modest tempo so OS data takes a long time to mature. I would also not expect an OS difference from Keynote 204 as it is effectively a cross over trial (if patients fail BV on trial they would probably get a PD1i as standard afterwards and vice versa)
How reliable is the comparison of pembrolizumab with standard of care made by the MAIC for the SCT-2L subgroup?	My understanding is that this appraisal is only focusing on use in 3L (i.e. failed front line and then 1st relapse treatment).

Generalisability of the intention to treat (ITT) population to UK clinical practice	I assume you mean the Keynote 204 population? It is a mixture of patients who would not be considered fit for a stem cell transplant if they achieved a suitable remission; and patients relapsing after a SCT and those who have not achieved a suitable remission for a SCT to be performed. This mixture of patients reflects clinical practise in the UK
Uncertainty in PFS estimation in the SCT-2L subgroup	My understanding is that this appraisal is only focusing on use in 3L (i.e. failed front line and then 1st relapse treatment).
Uncertainty in the maintenance of PFS benefit associated with pembrolizumab after treatment discontinuation in Year 2	The issue here is whether there is expected to be an increase in relapses seen when pembrolizumab stops after 2 years. My view is that there is likely to be a modest increase in the relapse rate. This is because I have not seen convincing data that pembrolizumab cure patients. So when the therapeutic effect of the drug is removed, I would expect residual disease to start progressing.
Utility values used in the progressed disease (PD) health state for pembrolizumab	When a patient progresses, it is always associated with extreme psychological distress. In my view, relapses on pembrolizumab would be associated with slightly better utility values than relapses on BV as BV is associated with worse QoL and a higher rate of side effects such as neuropathy. Pembrolizumab is overall slightly better tolerated.
Uncertainty in subsequent treatments and assumed proportions in the company's base case analysis	Patients failing BV currently will get nivolumab. However, I understand that in a NICE appraisal we are not supposed to consider this as it is within the CDF. That is very odd as in reality this is most will get. However, if nivo is not available then there is no standard of care and treatments vary greatly from single agent chemotherapy (e.g. gemicitabine, vinblastine) to palliative oral combination regimens (e.g. PEP-C, DECC) to palliative radiotherapy and steroids.

Gopal et al. (2015) should not be used as the primary source of OS for all subgroups	This is a perfectly reasonable source for OS in patients who have relapsed after a SCT and had BV. Nowadays patients failing BV would get nivo (although again this probably isn't supposed to be considered). Data is much less good for patients not suitable for SCT. Eyre et al (2017) is reasonable, albeit formally low quality, data for survival for stem cell transplant naïve patients treated with BV although all these patients were deemed fit for SCT. OS survival in these groups would likely be less than in Gopal (2015).
Time of treatment (ToT) for BV in SCT-3L+ and SCT+3L+ subgroups	BV is licensed and funded for up to 16 cycles. - SCT- 3L+: for patients fit for transplant, only 4-8 cycles of BV would usually be given before going for transplant, or before switching to alternative therapy; for unfit patients, treatment would be ongoing to progression or toxicity; it is unusual in this instance to get to 16 cycles, a typical median number would be 8. - SCT+3L+: most of these patients will be being bridged to a transplant. In this situation most patients receive 6-8 cycles of BV
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- This appraisal would change the line of treatment where PD1 inhibition can be used
- Brentuximab is a relevant UK comparator
- The UK is generally more likely to bridge people to stem cell transplantation compared to other countries and the trial population

- There is no standard of care following 3rd line of treatment; approaches vary widely
- Any relapse is associated with intense psychological and emotional distress so prolonging PFS is very important

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **Friday 5 February 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Takeda UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Immaturity of overall survival data	**NO**	No comment.
Key issue 2: How reliable is the comparison of pembrolizumab with standard of care made by the MAIC for the SCT-2L subgroup?	**NO**	On 28 January 2021, the European Medicines Agency (EMA) CHMP issued the following opinion for pembrolizumab:[1] *KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.* We note that the CHMP opinion above does not include first salvage/second-line patients (SCT-2L subgroup).
Key issue 3: Generalisability of the intention to treat (ITT) population to UK clinical practice	**NO**	We agree with the ERG that the ITT analysis from the KEYNOTE-204 pivotal trial includes three distinct patient subgroups with different prognostic outcomes. Given the subgroups have different comparators and divergent patient characteristics, it is therefore inappropriate to pool these subgroups, and they should instead be assessed individually. • **SCT-2L:** We note that the SCT-2L population may no longer be considered relevant for the appraisal. These patients, who are defined as not having at least two prior therapies when ASCT is not a treatment option, are not

		included in the recent CHMP opinion (28 January 2021) for pembrolizumab, and are not expected to be included in the updated marketing authorisation.[1] • **SCT-3L+ and SCT+3L+:** Despite the exclusion of the SCT-2L subgroup, it remains inappropriate to pool the SCT-3L+ and SCT+3L+ subgroups: o Patients who are ASCT ineligible (SCT-3L+) and patients who are eligible and have received prior ASCT (SCT+3L+) are prognostically very different. As noted in the company submission for pembrolizumab, a patient's eligibility status for ASCT is assessed following failure of chemotherapy, and patients who are ineligible for ASCT are deemed so due to poor fitness (i.e. advanced age, presence of comorbidities, or poor performance status) and are expected to be worse performers than their counterparts who are deemed fit for an ASCT. A 2020 review of therapeutic strategies in Hodgkin's lymphoma described the expected outcome of ASCT-ineligible patients (i.e. SCT-3L+) to be worse than those experiencing disease progression or relapse following ASCT (i.e. SCT+3L+).[2] The resultant heterogeneity in fitness and therefore outcomes between the SCT-3L+ and SCT+3L+ subgroups indicate it would be flawed to consider this group of patients to be the same and more accurate to assess each subgroup individually. o These two patient subgroups also follow different treatment pathways, in terms of prior and subsequent treatments, as noted in Key Issue 7 which may impact their outcomes and the associated costs. • The subgroups should be appraised separately to ensure an aligned and consistent approach with prior NICE appraisals and guidance in relapsed/refractory (r/r) Hodgkin's lymphoma.

		○ The NICE appraisal for brentuximab vedotin (BV) in CD30-positive r/r Hodgkin's lymphoma (ID1366/TA524) considered the SCT-3L+ and SCT+3L+ populations separately and made independent recommendations.[3] The populations were modelled and presented separately at NICE's request due to the underlying difference in the patient subgroups, place in treatment pathway and outcomes. The Committee considered each group individually.
Key issue 4: Uncertainty in PFS estimation in the SCT-2L subgroup	**NO**	Please note our response to Issue #1 in light of the recent CHMP opinion (28 January 2021) for pembrolizumab.[1]
Key issue 5: Uncertainty in the maintenance of PFS benefit associated with pembrolizumab after treatment discontinuation in Year 2	**NO**	No comment.
Key issue 6: Utility values used in the progressed disease (PD) health state for pembrolizumab	**NO**	No comment.
Key issue 7: Uncertainty in subsequent treatments and assumed proportions in the company's base case analysis	**NO**	We agree with the ERG that there is notable uncertainty surrounding the company's base case assumptions for subsequent treatment usage. • **SCT-3L+:** The company base case assumed 100% of patients receiving BV in the SCT-3L+ subgroup would receive pembrolizumab as subsequent treatment. However, as noted by the ERG, pembrolizumab is currently recommended for use in the CDF, rather than for routine commissioning, for the treatment of r/r classical Hodgkin lymphoma in adults who are ASCT-ineligible and have failed BV.[4] The 2019 Position Statement from NICE clearly outlines that treatments recommended for use in the CDF are not considered established practice, and should therefore not be used as

		comparators or be included in a treatment sequence in appraisals or economic models.[5] It is against NICE guidance to consider pembrolizumab, a CDF funded medicine, as a subsequent treatment for patients treated with BV, instead only routinely commissioned medicines should be considered. • **SCT+3L+:** The company base case assumed 100% of patients receiving pembrolizumab in the SCT+3L+ subgroup would receive BV as subsequent treatment, whereas the ERG scenario assumed 100% of patients would receive nivolumab. o We note the clinical opinion to the ERG which stated that either nivolumab or BV could be used as subsequent treatment following treatment with pembrolizumab in SCT+3L+ patients, and this aligns with what is stated on page 20 of the company submission, and in the following NICE recommendations: ▪ BV is recommended as an option for adults with r/r CD30-positive Hodgkin's lymphoma if they have already had ASCT (TA524)[3] ▪ Nivolumab is recommended as an option for adults with r/r classical Hodgkin's lymphoma after ASCT and treatment with BV (TA462)[6] o Therefore the subsequent treatment pathway of BV followed by nivolumab should be modelled for SCT+3L+ patients, to comprehensively represent subsequent treatments following pembrolizumab. Including just one treatment (either BV or nivolumab) may underestimate the comprehensive costs associated with the SCT+3L+ pathway.

		We would also like to note that BV is provided with a simple discount PAS. Given the BV PAS is confidential, the company and ERG presented ICERs do not include the net price of BV, and therefore do not reflect true cost-effectiveness estimates.
Key issue 8: Gopal et al. (2015) should not be used as the primary source of OS for all subgroups	**YES**	We agree with the ERG that it is inappropriate to assume OS data from Gopal *et al.* (2015)[7] is generalisable to all subgroups in the pembrolizumab appraisal. The patients in Gopal *et al.* (2015) had all received prior ASCT, representing the SCT+3L+ subgroup only. It is not appropriate to use the same OS data for patients in the SCT-3L+ subgroup, who are ineligible for ASCT; as discussed above for Key Issue 3, SCT-3L+ patients are prognostically very different and likely to have worse outcomes compared to patients who were deemed fit for ASCT. We also believe that use of the Gopal *et al.* (2015) OS data for pembrolizumab is not a conservative assumption. The 5-year results from this pivotal phase 2 trial (published in Chen *et al.* 2016)[8] for BV reported 33% (34/102) of patients achieved a complete response (CR); 38% of these CR patients (13/34) remained in remission at study closure, therefore representing long-term disease control and potential cure. Although the pivotal Phase 2 trial for BV is not directly comparable to KEYNOTE-204, the patients in KEYNOTE-204 demonstrated a lower CR rate of 24.5% in the pembrolizumab arm and 24.2% in the BV arm. The results for BV in the KEYNOTE-204 trial are likely to be confounded by the imbalance in baseline characteristics; the median prior lines of therapy was 2 in pembrolizumab arm and 3 in the BV arm,[9] favouring the pembrolizumab arm as pembrolizumab patients were likely healthier at baseline and anticipated to have a better response. In addition, there are more mature OS data available for the pivotal phase 2 trial of BV, published in Chen *et al.* 2016.[8] The 3-year follow-up published in Gopal *et al.* (2015) reported 54 deaths (54/102 patients, median OS 40.5 months),[7] and the 5-year follow-up published in Chen *et al.* 2016 reported only 3 additional deaths in the two-year time period (57/102 patients),[8] which further highlights that use of

		these OS data for pembrolizumab should not be considered a conservative assumption. Due to differences observed in patient populations and anticipated outcomes associated with different drugs, it is more accurate to use separate sources of OS data for pembrolizumab and BV, and we believe the following would provide a more accurate reflection of anticipated long-term response, and thus cost-effectiveness: • KEYNOTE-087 for pembrolizumab • Chen *et al.* 2016 for BV

Key issue 9: Time on treatment (ToT) for BV in SCT-3L+ and SCT+3L+ subgroups	**YES**	It is not appropriate and would be off-label to assume patients treated with BV will receive 35 cycles of treatment (per the KEYNOTE-204 trial) as done by the company submission. The EMA marketing authorisation for relapsed or refractory Hodgkin's Lymphoma and the BV SmPC, indicate patients should receive a maximum of 16 cycles of BV.[10] BV is not approved for use beyond 16 cycles in any indication. The NICE recommendation[3] and NHS Treatment Criteria,[4] outlining the funding requirements in England, clearly state no more than 16 cycles of BV should be administered per patient. Furthermore, it should be noted that the number of cycles administered to patients in clinical practice in the UK is in fact notably less than maximum allowed 16 cycles: • **SCT-3L+ and SCT+3L+:** The median ToT in the pivotal KEYNOTE-204 trial was 146.5 (range 1–794) days for patients in the BV arm, which equates to approximately **7** three-week cycles.[11] • **SCT-3L+:** Data from real-world use of BV in England on the CDF indicates the mean number of cycles is **4.1** (95% CI 3.7–4.6) in patients who received two prior lines of therapy and were ineligible for ASCT.[12] • **SCT+3L+:** The pivotal phase 2 trial for BV in r/r Hodgkin's lymphoma following ASCT (Gopal *et al.* 2015) reported that the median number of cycles for patients is as low as **7** (range 1–16) in non-responders; **13.5** (range 4–16) in patients in remission and **10** (range 3–16) in all other responders.[7] In summary, it is inappropriate to assume patients will receive more than 16 cycles of BV. The Committee should consider that the number of cycles of BV used in clinical practice is in fact likely to be substantially lower than 16. Scenarios using median durations of treatment of BV from local clinical practice and the CDF data cited above should also be considered.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Takeda UK has no additional issues to raise.

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

A Single Technology Appraisal

Requests for clarification on company's response to Technical Engagement Response

February 2021

Further to receipt of the company's response to technical engagement (date 25 January 2021), the ERG has reviewed the information provided by the company and to enable it to fully review and comment on the response – specifically to provide updated results for the 3L population – the following clarifications are required:

1. Could you please explain why pooling the 3L+ population (removing 2L patients) results in a slight increase in PFS utility compared to the ITT values. The ERG assumed that when 2L patients are removed, health state utility values are likely to decrease given that these patients may be considered 'fitter' than 3L+ patients.

This is an analysis directly from the clinical trial data and reflects patients' experiences however, this slight difference in utilities has not been explored in detail for a clinical rational. In general, 2L patients in KEYONTE-024 were ineligible for transplant due to age or comorbidities or they were chemo refractory and these patients are considered less fit so it is likely that they have lower quality of life than 3L+.

2. Please outline why a number of AE's (e.g. Gastrointestinal and Metabolism disorders) were not observed in ITT population, but were recorded in the pooled SCT 3L+ subgroup?

Please disregard the ITT population AEs, some of the categories were not appropriately transferred in the model. The AEs for 3L+ should be applied in the model as per Table 10. Subjects with Grade 3-5 Adverse Events (Incidence ≥2% in One or More Group) Subjects Who Are at Least Third Line (All-Subjects-as-Treated Population) in the document ID1557 Technical Engagement_New evidence form for company [ACIC]

3. Please outline why the trial-based subsequent treatment usage in the pooled 3L+ population does not correspond with that reported for the SCT-3L+ and SCT+3L+ subgroups. In particular, certain subsequent treatments that were used

in both subgroups (in both arms of KEYNOTE-204) do not appear to have been recorded in the pooled 3L population (in either arm), e.g. etoposide + melphalan.

The number of different subsequent therapies from KEYNOTE-204 (especially chemotherapy regimens) was too high and therefore a pragmatic approach needed to be considered in the economic model. Whilst in the original trial reports from KEYNOTE-204, the subgroups' subsequent therapies add up to the 3L+ population, when the economic model was updated for the 3L+, the subsequent treatments were adjusted to focus in a variety of countries outside of the UK. Please note that in the results provided by MSD for the 3L+, the KEYNOTE-204 subsequent therapies were not taken into consideration, as the base case reflected the ERG preferred scenario which is relevant to the UK clinical practice.

4. The company have provided distributions fitted to the PFS and ToT data for the pooled 3L+ subgroup, including PFS distributions with a break-point at Week 26. The impact of modelling PFS using a log-normal distribution with a break-point at Week 26 is considered in the scenario analysis in section 2.7 of the new evidence form (Scenario 5).

The results for Scenario 5 appear to have been accidentally interchanged with the results for Scenario 6, in which ToT is modelled with a break-point at Week 26.

MSD confirms that results of Scenario 5 " PFS piecewise week 26" were accidentally interchanged with Scenario 6. The correct results for scenario 5 are:

Scenario 6 PFS piecewise week 26	Pembrolizumab	[redacted]	5.00	4.13	--	--	--	--
	BV	[redacted]	5.00	3.52	-13,016	0.00	0.61	Dominant

The ERG have been unable to replicate these results, though, as the parameters for the 3L+ ToT distributions with a break-point at Week 26 do not appear in the model.

Scenario 6 should be omitted as the results presented were an error. As the ERG rightly points out, the ToT distributions for cutoff at week 26 were not included in the model. This is because MSD does not believe that week 26 is the best option to extrapolate ToT because selecting the cutoff point at Week 80 provides considerably more KM data than week 26. For transparency though, the parameters for the 3L+ ToT distributions with a break point at week 26 are provided in the file: "3L+ all model clinical data (PFS_ToT)"

It is written in the update guide that the 3L+ survival outputs can be found in the Excel file "3L+ all model clinical data (PFS_ToT)", but this file was not received by the ERG.

The file "3L+ all model clinical data (PFS_ToT)" is also provided along these clarification responses.

Please would the company provide the parameters for the 3L+ ToT distributions with a break-point at Week 26?

As discussed, ToT distributions are provided in the file mentioned above.

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 Company's Response to Technical Engagement Response

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This TE response 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]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2020.

1. INTRODUCTION

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of pembrolizumab for treating relapsed or refractory classical Hodgkin's lymphoma after one or more multi-agent chemotherapy regimens [ID1557]. Each of the issues outlined in the technical report are discussed in further detail in Section 2.

The company has presented some additional data, including clinical effectiveness data for the 3L+ subpopulation, to reflect the revised proposed licensed population. Additional clinical effectiveness data are discussed in Section 2.

The company has also made changes to the economic model and provided a revised PAS. The ERG critique and the preferred ERG base case are presented in Section 4.

2. ERG CRITIQUE OF ADDITIONAL EVIDENCE

In its response to Technical Engagement (TE), the company provided two types of additional clinical effectiveness evidence. Firstly, the company provided PFS2 data – defined as the time from randomisation to subsequent disease progression after the initiation of subsequent oncologic therapy(-ies), or death from any cause, whichever occurs first – as an alternative efficacy endpoint, in the absence of mature OS data. Secondly, the company provided data for a combined 3L+ subpopulation (SCT-3L+ combined with SCT+3L+), since the company has now excluded the SCT- 2L subgroup that was included in its originally submitted intention to treat (ITT) population, to reflect the revised proposed licensed population.

In the combined 3L+ subpopulation, PFS was longer in the pembrolizumab arm than in the brentuximab vedotin (BV) arm, in line with the ITT results from the original company submission. However, it was notable that the effect in favour of pembrolizumab over BV was greater for investigator-assessed PFS (median PFS [redacted]) than for PFS assessed by blinded independent review committee (BICR, median PFS [redacted] Response rate data showed an advantage in favour of pembrolizumab over BV (BICR objective response [redacted]), consistent with the ITT population. An improvement in health-related quality of life was found for pembrolizumab over BV (mean EQ-5D [redacted]), consistent with the ITT population. Similar proportions of patients in the two arms experienced at least one adverse event in the 3L+ subpopulation, consistent with the ITT population. The longer time on treatment in the pembrolizumab arm compared to the BV arm should be taken into account in the interpretation. However, the ERG noted that there were adverse event categories – gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders and nervous system disorders – which were not recorded in the relevant table for the ITT population in the company submission (CS, Section B.3.3.5, Table 118) and for which the number of events was zero in the model, but for which events were recorded in the 3L+ subpopulation in the company's TE response. Following a request for clarification, the company indicated that the original ITT adverse event results were incorrect and should therefore be disregarded, in favour of those in the TE response.

PFS2 was significantly higher for pembrolizumab than for BV at 24 months ([redacted] ITT HR [redacted]). The ERG considered that the fact that median PFS2 [redacted]

[redacted] to be a substantial limitation to the use of PFS2 as an alternative endpoint for decision-making.

The ERG remained of the view that it is preferable to consider the SCT-3L+ and SCT+3L+ subgroups separately for decision-making as opposed to as one combined 3L+ population. This was due to the differences in subsequent treatment that can be expected in routine clinical practice as well as differential uncertainty regarding ICERs.

3. ERG REVIEW OF KEY ISSUES

Key issue 1: Immaturity of overall survival data

The Evidence Review Group (ERG) considered the immaturity of overall survival (OS) data to be a key issue in this appraisal, as there were no directly observed comparative OS data for use in the economic model. The ERG noted in its initial report that mature OS data from KEYNOTE-204[1,2] will be key to resolving this uncertainty. In its response to TE, the company was unable to provide mature OS data from this pivotal trial. The company provided PFS2 data, which may provide a reliable endpoint if OS data are not available.[3] Nevertheless, the absence of directly observed comparative OS data to inform the clinical inputs to the economic concern remained a key concern for the ERG. Moreover, median PFS2 [redacted] which limited the usefulness of PFS2 as an alternative endpoint for decision-making.

Key issue 2: How reliable is the comparison of pembrolizumab with standard of care made by the MAIC for the SCT-2L subgroup?

The ERG noted that the company has withdrawn the SCT-2L subgroup from this appraisal, to reflect the revised proposed licensed population. Therefore, the ERG no longer considered this to be a key issue in this appraisal.

Key issue 3: Generalisability of the intention to treat (ITT) population to UK clinical practice

The ERG noted concerns in its initial report regarding the generalisability of the ITT population to UK clinical practice. A key aspect of this was that the SCT-2L subgroup had a different comparator. The ERG noted that the company withdrew the SCT-2L subgroup from this appraisal, to reflect the revised proposed licensed population. The exclusion of the SCT-2L subgroup addressed the ERG's concerns regarding generalisability. However, the ERG maintained its preference to consider the SCT-3L+ and SCT+3L+ subgroups separately, given the likelihood of differing subsequent treatments for these two subgroups in clinical practice.

Key issue 4: Uncertainty in PFS estimation in the SCT-2L subgroup

The ERG noted that the company withdrew the SCT-2L subgroup from this appraisal, to reflect the revised proposed licensed population. Therefore, the ERG no longer considered this to be a key issue in this appraisal.

Key issue 5: Uncertainty in the maintenance of PFS benefit associated with pembrolizumab after treatment discontinuation in Year 2

The ERG agreed with the company that there was a lack of precedent (within published TAs) regarding the application of a waning effect to PFS and acknowledged this in its initial report, stating that a waning in treatment effect appeared to have been applied previously to OS only. Given the lack of long-term data, the ERG judged that this scenario was helpful to explore uncertainty surrounding the assumption of a continued treatment effect (with respect to PFS), as it was unclear whether patients will continue to experience benefit once treatment has stopped. The ERG agreed that the company had adopted a conservative approach with respect to OS in the model and that to further apply a waning in PFS would 'penalise' pembrolizumab. Therefore, the ERG did not consider this scenario as part of its preferred base case, but rather presented it to highlight uncertainty.

Key issue 6: Utility values used in the progressed disease (PD) health state for pembrolizumab

The company's comments with respect to progressed disease utility were noted. The ERG acknowledged that there may be potential for a differential treatment effect on HRQoL whilst in the PD health state; however, the ERG considered that the QoL data reported in KEYNOTE-204 were subject to uncertainty i.e. small patient numbers and the short 30-day time frame used to estimate PD utility were insufficient to capture changes in QoL. Therefore, to reduce uncertainty, the preferred ERG approach was to assume no difference in PD utility between treatments. Additionally, clinical advice to the ERG noted face validity concerns surrounding the base case PD utility value for pembrolizumab, which further supported the ERG's decision to adopt a more conservative approach to PD utility estimation.

The ERG acknowledged the company's comment regarding the use of the BV PD utility value for both pembrolizumab and BV i.e. that using a utility value of [redacted] for progressed disease was lower than the progressed disease utility value reported in a prior HTA submission of nivolumab for this indication (SMC 1240/17). Checkmate-205, the study used to derive the nivolumab PD utility value of 0.71 included 3L patients (identified as cohort B) also included patients who received additional lines of therapy (identified as cohort C). However, the [redacted] PD utility value remains the ERG's preferred PD utility on the basis that it is derived using relevant (albeit limited) HRQoL data from KEYNOTE-204. It should be noted that when the ERG conducted an exploratory analysis using a utility value of 0.71 for the PD state (in both treatment arms), the incremental QALY gain for pembrolizumab decreased across all subgroups,

indicating that a higher PD value utility value would reduce the overall health benefit of pembrolizumab (and work in favour of BV).

Key issue 7: Uncertainty in subsequent treatments and assumed proportions in the company's base case analysis

Subsequent treatments in both 3L subgroups remained an area of considerable uncertainty requiring further discussion from NICE committee members. The ERG acknowledged the company's concerns regarding the ERG's preferred subsequent treatment (nivolumab) for patients who fail on pembrolizumab in the SCT+3L+ subgroup, and agreed that there may be some disparity between the treatment provided by clinicians in practice and the treatment deemed appropriate by the treatment algorithm summary (Figure 1 in the initial ERG report). However, given the uncertainty surrounding subsequent treatments, the ERG considered that using the treatment algorithm to select subsequent treatment for the SCT+3L+ subgroup was a more robust approach. Nivolumab was therefore selected by the ERG as the appropriate subsequent treatment for this patient subgroup.

With respect to the SCT-3L+ subgroup, the ERG agreed with the company that chemotherapy treatments (other than bendamustine) were likely used in clinical practice and that choice would vary depending on physician preference and centre of treatment. The ERG's decision to use bendamustine as the primary subsequent treatment for patients who had failed on BV was informed by clinical advice.

The ERG acknowledged the additional scenario analysis provided by the company (for the pooled 3L subgroup), which assumed 100% use of the most expensive chemotherapy regimen. [redacted]

Key issue 8: Gopal et al. (2015) should not be used as the primary source of OS for all subgroups

The ERG acknowledged the company's concerns regarding the appropriateness of the ERG's preferred assumption that Balzarotti et al. should be used as the primary source of OS for the SCT-3L+ population. However, the ERG remained convinced that OS data from Gopal et al., which included patients with prior SCT, were not adequately generalisable to this subgroup (see p.54 in the initial ERG report). The ERG recognised the limitations surrounding Balzarotti et al. put forward by the company; however, given the lack of robust published OS data for this

subgroup (and the concerns surrounding the generalisability of patients within Gopal et al.), Balzarotti et al. was deemed a reasonable source for the SCT-3L+ subgroup.

Key issue 9: Time of treatment (ToT) for BV in SCT-3L+ and SCT+3L+ subgroups

The ERG acknowledged the company's comment that using a maximum ToT for BV of 16 cycles reduces the overall cost of BV (whilst still capturing the benefits of BV per KEYNOTE-204, where a proportion of patients remained on treatment beyond 16 cycles). For transparency (as per the ERG's response to the FAC), the initial report was amended to reflect that the scenario analysis provided by the company which assumed 16 cycles for BV, still included the benefit/efficacy of BV for a maximum of 35 cycles.

As noted in the initial report, 16 cycles reflected the licensed indication of BV and therefore was considered the most appropriate maximum duration of treatment by the ERG. Furthermore, the ERG noted that a relatively small proportion of patients (in the overall ITT population in KEYNOTE-204) received more than 16 cycles (approximately [redacted]). In the SCT+3L+ subgroup approximately [redacted] received more than 16 cycles.

4. UPDATED COMPANY AND ERG BASE CASE ANALYSES

In response to the technical engagement report, the company presented updated analyses for a pooled 3L population. The ERG acknowledged that the company's revised base case results included a number of alterations as outlined in Table 1. Table 2 and Table 3 report the results of the company's base case and probabilistic sensitivity analysis. It should be noted that the ERG did not consider the pooled 3L analysis to be the analysis most suitable for decision-making given that two distinct subgroups exist (SCT-3L+ and SCT+3L+) based on differences in subsequent treatments. Furthermore, a meaningful differential in uncertainty exists between these subgroups. For completeness, results for the pooled 3L population have been presented here.

Table 1: List of revised parameters used to estimate base case results for Pooled 3L analysis

Parameter	Change from ITT analysis
Population	Updated (reflects Pooled 3L patients)
Time horizon	Updated to 50 years as per the ERG preferred assumption
Discount	N/A
Half cycle correction	N/A
Patient characteristics	N/A
PFS	Same approach as per ITT, however data updated to reflect pooled 3L population
OS	Gopal et al (Log normal extrapolation)
ToT	Same approach as per ITT, however data updated to reflect pooled 3L population
AE incidence	Updated to reflect pooled 3L population
Utilities	N/A
Apply age related decrements	N/A
Pembrolizumab discount	[redacted]
Dose intensity	N/A
BV maximum doses	Updated to reflect ERG preferred assumption (max 16 cycles)
Administration costs	N/A
Stem cell transplant rates	Updated to reflect pooled 3L population (and no difference in SCT rates between arms as per ERG assumption
Resource use	Updated to reflect ERG preferred assumption (assumes higher resource use in the PD state)

Terminal care	N/A
Subsequent treatments	Updated Pembrolizumab arm at 100% BV BV arm at 55.2% bendamustine and 44.8% nivolumab
Costs of AE's	NA

N/A indicates that the parameter reflects what was used in the ITT population i.e. the parameter has not been changed within this analysis

Table 2: Company base case results (Pooled 3L analysis)

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Pembrolizumab	[redacted]	5.00	4.13	-	-	-	
BV	[redacted]	5.00	3.54	-11,872	0.00	0.59	Dominant

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

Source: Company New Evidence Form v0.1

Table 3: Company PSA (Pooled 3L analysis)

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company presented probabilistic base case							
Pembrolizumab	[redacted]	5.03	4.14	-	-	-	
BV	[redacted]	5.03	3.58	-11,558	0.00	0.57	Dominant

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

4.1. ERG preferred base case assumptions

As noted above, the company submitted revised clinical data for the pooled 3L population. Based on a review of the revised clinical data and additional information provided by the company within the New Evidence form, the list of ERG preferred assumptions for this pooled population differs to the assumptions outlined in the ERG report (for the individual 3L

subgroups). The ERG considered the following assumptions reasonable for inclusion in the ERG preferred base case for the pooled 3L population, and reflects these changes in Table 4.

- OS data for the pooled 3L population to be based on Gopal et al. The ERG accepted the company's assumption that Gopal et al was the most appropriate source for deriving OS data for this population (given that patients in Balzarotti better reflected 2L patients). The ERG did consider the possibility of using a mixture model using data from both Gopal et al. and Balzarotti et al.; however, this would have introduced further uncertainty and therefore was not conducted.

- PFS data for the pooled 3L subgroup used. Given that the company's revised analysis provides cost-effectiveness results for the pooled 3L population, the ERG agreed that PFS for both pembrolizumab and BV should reflect the pooled 3L estimates. As per the ERG's preferred base case assumption in the initial report, a 26-week cut point was selected to model PFS.

- Subsequent treatments were based on the company's revised assumption i.e. 100% of patients who fail on pembrolizumab receive BV and for patients who fail on BV (55.2% assumed to receive bendamustine and 44.8% receive nivolumab). Overall, the ERG considered the company's assumptions may be used for the purposes of this analysis; however, the ERG did not consider that there was an appropriate overall subsequent treatment for this pooled 3L population, given that subsequent treatments are likely to differ in clinical practice according to whether a patient has followed a SCT-3L+ or SCT+3L+ pathway. The ERG therefore considered this assumption to be associated with considerable uncertainty.

- Health state utility values (HSUVs) and AEs based on the pooled 3L population. The ERG noted several anomalies surrounding the company's revised HSUV and AE data for the pooled 3L population (outlined below), which required clarification from the company.

  HSUVs The ERG noted that removing 2L patients (and pooling the 3L population) resulted in slightly increased HSUVs for the PFS state in both treatment arms, when compared to the ITT values outlined in the CS. Given that 2L patients are likely to be somewhat fitter than 3L patients, the ERG expected that utility values based on pooled 3L patients only would decrease. The company were asked to explain these results and noted that in general 2L patients were ineligible for transplant (due to age or comorbidities) or were

chemotherapy-refractory, therefore it is likely that they had lower HRQoL than 3L+ patients. The ERG did not consider the company's response entirely satisfactory or robust, however agreed on balance the use of pooled 3L data was reasonable for this analysis as it reflected the relevant population under review.

AEs. It was not clear to the ERG why a number of AEs (e.g. Gastrointestinal and Metabolism disorders) were not observed in ITT population, but were recorded in the pooled SCT 3L+ subgroup. When asked to clarify, the company noted that the AEs occurring in the ITT population should be disregarded as some categories were not appropriately transferred in the model. The ERG acknowledged the company's error and accepted the use of pooled 3L population AE data for this analysis.

- ToT based on pooled 3L data (parameters for the pooled 3L population ToT distributions based on 26-week cut point). The ERG noted that initially the company did not provide these distributions but these were subsequently provided during clarification. The choice of parametric distribution made little difference to the 3L+ results: the ICER varied by around 2% when different distributions were selected (with the exception of the Gompertz, which provided a relatively poor fit to the pooled 3L+ ToT data from Week 26). In their clarification response the company further stated that they do not believe 26 weeks to be the most reasonable cut point to model ToT on the basis that selecting a ToT cut point of 80 weeks uses more observed data (as reflected by the KM curve). The ERG acknowledged the company's comment however maintained that a 26-week cut point is the most appropriate choice for extrapolating ToT given that after this time point, there is a regularisation of hazards. Furthermore, 26 weeks is coterminous with the preferred ERG PFS extrapolation point.
- Dosing intensity of 100% has been applied to both arms (pembrolizumab and BV). It should be noted that in the initial report, this assumption was applied only to the pembrolizumab arm. However, the ERG acknowledged the company's comments that this assumption should apply to both treatment arms.

Table 4: ERG's preferred model assumptions (Pooled 3L analysis)

Preferred assumption	Incr. Costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Company base case[a]	-11,872	0.59	Dominant

			(-20,201)
Semi parametric approach to modelling PFS (cut point for PFS set at 26 weeks)- based on pooled 3L data	-13,016	0.61	Dominant (-21,353)
Utility value for PD health state set to [redacted] for both treatment arms	-13,016	0.40	Dominant (-32,051)
Cut-off for ToT to reflect PFS data cut point (26 weeks) based on pooled 3L data	-5,385	0.41	Dominant (-13,260)
Dose intensity for both pembrolizumab and BV set to 100%	-5,587	0.41	Dominant (-13,757)

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; SCT, stem cell transplant; ToT, time on treatment

In light of the new/revised evidence submitted, the ERG acknowledged that several ERG preferred assumptions outlined in the initial report (for the SCT-3L+ and SCT+3L+ subgroups) should be updated to reflect data for the pooled 3L population, on the basis that these data appeared more generalisable to the individual subgroups than data from the ITT population. The tables below (Table 5 and Table 6) therefore reflect the ERG's preferred base case assumptions for both subgroups.

Table 5: Updated ERG SCT-3L+ Base Case

SCT-3L+	Incr. Costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Previous ERG base case	21,839	0.34	64,124
New pembrolizumab PAS discount	16,429	0.34	48,239
Dose intensity for BV also set to 100%	15,361	0.34	45,103
Health state utility values and AEs based on pooled 3L data	15,394	0.35	44,215
Cut-off for ToT to reflect PFS data cut point (26 weeks)- based on pooled 3L data	15,572	0.35	44,725

Abbreviations: AEs, adverse events; BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; ToT, time on treatment

Table 6: Updated ERG SCT+3L+ Base Case

SCT+3L+	Incr. Costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Previous ERG base case	-15,186	0.45	-33,849
New pembrolizumab PAS discount	-22,274	0.45	-49,647
Dose intensity for BV also set to 100%	-23,537	0.45	-52,463
Health state utility values and AE's based on pooled 3L data	-23,504	0.46	-51,481
Cut-off for ToT to reflect PFS data cut point (26 weeks)- based on pooled 3L data	-23,248	0.46	-50,920

Abbreviations: BV, brentuximab vedotin; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year;

5. UPDATED ERG SCENARIO ANALYSES

The scenario analyses outlined in Table 7 largely reflect the scenario analyses conducted in the ERG report. However based on the revised/additional evidence provided by the company for the pooled 3L analysis, several scenarios were altered or removed.

Table 7: Updated ERG scenario analyses (Pooled 3L analysis)

Subgroup	**Pooled 3L analysis**			
Scenario	**Incr. costs**	**Incr. QALYs**	**ICER (£/QALY)**	**+/-**
Company base-case	-11,872	0.59	Dominant (-20,201)	-
Error! Reference source not found.: Utility value PD health state	-11,872	0.40	Dominant (-29,321)	-45%
Error! Reference source not found.: Equal PFS and PD utility value	-11,872	0.13	Dominant (-92,758)	-359%
Error! Reference source not found.: Waning of pembro PFS Tx effect	-10,247	0.57	Dominant (-18,075)	11%
Error! Reference source not found.: Dose intensity for pembro and BV 100%	-12,198	0.59	Dominant (-20,756)	-3%
Error! Reference source not found.: Pembro 400 mg Q6W	-12,183	0.59	Dominant (-20,730)	-3%
Error! Reference source not found.: KN-087 OS data (**pembro and BV**)	-7,854	1.51	Dominant (-5,218)	74%
Error! Reference source not found.: ToT pembro based on KM data only	-11,865	0.59	Dominant (-20,191)	0.05%
Error! Reference source not found.: 26-week cut-point for modelling ToT	-4,241	0.59	Dominant (-7,216)	64%
Error! Reference source not found.: Log-normal fit for ToT (**pembro and BV**)	-11,877	0.59	Dominant (-20,210)	-0.05%
Error! Reference source not found.: Subsequent Tx based on pooled 3L data KN-204	-24,924	0.59	Dominant (-42,411)	-110%
Error! Reference source not found.: Combined PFS (**generalised gamma**) and OS (**KEYNOTE-087**) pembro and BV	-13,750	1.56	Dominant (-8,829)	56%
Error! Reference source not found.: Fully parametric approach to model PFS (generalised gamma curve)	-13,895	0.62	Dominant (-22,588)	-12%
Error! Reference source not found.: Alternative parametric fit (**log-logistic**) for Gopal et al. (2015) OS data (pembro and BV)	-11,505	0.58	Dominant (-19,851)	2%
Error! Reference source not found.: 26-week data cut point for PFS	-13,016	0.61	Dominant (-21,353)	-6%

Scenario 23: Health state utilities and AE's based on ITT population	-11,905	0.59	Dominant (-20,176)	0.1%

Abbreviations: ICER, incremental cost effectiveness ratio; incr, incremental; KN, KEYNOTE; OS, overall survival; PD, progressed disease; pembro, pembrolizumab; PFS, progression free survival; Q6W, every 6 weeks; QALYs, quality adjusted life years; SCT, stem cell transplant; SG, subgroup; ToT, time on treatment; Tx, treatment

6. CONCLUSIONS

Based on the updated evidence for the pooled 3L analysis, pembrolizumab resulted in ERG preferred incremental savings of £5,587 and an incremental QALY gain of 0.41. However, the appropriateness of the pooled 3L subgroup is subject to considerable uncertainty, given that subsequent treatments provided to patients in clinical practice will differ according to whether they are SCT-3L+ and SCT+3L+. The ERG was of the opinion that two distinct subgroups exist for 3L patients and that the pooled 3L analysis should be interpreted with caution.

7. REFERENCES

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3. European Medicines Agency. Answers from the CHMP Scientific Advisory Group (SAG) for Oncology for Revision of the anticancer guideline. 2012.