NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990]

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Merck Sharp & Dohme
   - Roy Castle Lung Cancer Foundation
   - British Thoracic Society

The Department of Health issued a 'no comments' response. None of the patient or clinical experts provided individual responses to the ACD.

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

4. **Additional evidence provided by the company, Merck Sharp & Dohme**

5. **Review of the additional evidence,** provided by the Evidence Review Group, Liverpool Reviews and Implementation Group

6. **Company updated cost-effectiveness analyses** provided by Merck Sharp & Dohme

7. **Addendum to the ERG report, including review of updated analyses,** provided by the Evidence Review Group, Liverpool Reviews and Implementation Group

8. **Responses from patient and clinical experts regarding 5-year OS rate**

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 untreated PD-L1-positive metastatic non-small-cell lung cancer

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment [sic]	Response
Merck, Sharp & Dohme	Having read the ACD, MSD UK was surprised with the provisional negative recommendation, given our confidence that pembrolizumab is a cost-effective option for previously untreated patients with PD-L1-positive metastatic non-small-cell lung cancer (NSCLC). Based on the content of the ACD, the key drivers underpinning the draft negative recommendation are uncertainty/scepticism around the following defining points, which result in a disparity between our manufacturer's base-case and the ERG's base-case: • Overall Survival (OS) data • Extrapolation of OS in the pembrolizumab and Standard of Care (SOC) arms • OS projection for patients who had SOC • Utility values • Existing commercial access agreement for pemetrexed With regards to the commercial access agreement for pemetrexed, this had been acknowledged in our submission with a variety of ICERs presented reflecting different potential discount rates for this product. For the purpose of enabling a discussion at the upcoming second appraisal committee meeting, MSD UK has assumed a 50% discount rate for pemetrexed in all ICERs presented henceforth. Our full response is provided below and firstly summarises some key points in the ACD which we believe support the approach taken by MSD in our submission, and highlight the value and clinical relevance of pembrolizumab as a valid and worthy treatment option for the patient population covered by this appraisal. Our response then addresses in turn, each of the above mentioned key drivers underpinning the draft negative recommendation. Finally, we summarise future data availability in relation to the population of interest covered by this submission.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.6, 4.10 to 4.16, and the individual responses to Merck, Sharp & Dohme's comments in the sections below.

	MSD UK has answered the Committee's concerns to the best of our ability concerning each of the key drivers identified above. In MSD UK's opinion, the primary issue influencing the variability in the ICER for pembrolizumab is OS projection for patients who had SOC. As a result of addressing this issue comprehensively, our analysis results in an MSD UK base-case ICER of £46,250 (incorporating an estimated 50% discount for pemetrexed). Were MSD to accept the ERG approach to utility values (i.e. 0.79 as population norm rather than 0.808 for those surviving at least 360 days), this would only marginally change the ICER, to £47,283 (again, incorporating an estimated 50% discount for pemetrexed). **Key points mentioned in the ACD that support the approach taken by MSD in our submission of pembrolizumab as a treatment option for patients with previously untreated PD-L1-positive metastatic NSCLC:** • The ACD states that *"the Committee concluded that pembrolizumab is an important treatment option for people with untreated metastatic PD-L1-positive NSCLC".* • The Committee agreed that "*the overall population in KEYNOTE-024 was comparable with clinical practice in England. The Committee therefore concluded that KEYNOTE-024 is generalisable to clinical practice in England*". • The clinical and patient experts agreed that "*stopping treatment at 2 years independent of disease status would be acceptable to patients*". Additionally, the Committee concluded that "*implementing a 2-year stopping rule in the model was appropriate".* • The Committee agrees with MSD that pembrolizumab *"could plausibly meet the criteria for being considered as a life-extending, end-of-life treatment".* • The Committee *"accepted the structure of the company's economic model and considered it appropriate for decision-making*".	

	• The ACD confirms that the Committee and Evidence-Review Group (ERG) *"agreed with the company that the 2-stage method was the most appropriate method for crossover adjustment".* • The Committee concluded that the company's choice of the 22-week cut-off point at which to extrapolate the Kaplan–Meier data from KEYNOTE-024 "*was plausible".*	
Merck, Sharp & Dohme	**MSD Response to key drivers underpinning the draft negative recommendation in the ACD:** • **Overall survival data** The ACD states: "*The ERG highlighted that the immaturity of the overall survival data and the high level of crossover (43.7% of standard of care arm patients had pembrolizumab at second interim analysis) limits the reliability of the survival data collected in KEYNOTE-024".* The ACD goes on to state that *"The committee concluded that although there was sufficient evidence that pembrolizumab has an important extension-to-life benefit in people with untreated stage IV metastatic PD-L1-positive NSCLC compared with standard of care, the exact size of the overall survival gain was uncertain because of the immaturity of the data"* The data from KEYNOTE-024 provided in our submission was based on a 09 May 2016 cut-off date with median 11.2 (6.3-19.7) months of follow-up. The next database lock is the per protocol criterion for defining the point at which to conduct the final OS analysis, namely, when 170 death events have occurred. As KEYNOTE-024 is an event driven study with a built-in cross-over design, this may impact actual accrual rates of death events. MSD UK was notified on 21 February 2017 that an abstract had recently been submitted for the 2017 ASCO Annual Meeting (taking place 2-6 June 2017) to evaluate the progression-free survival (PFS) as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab compared to SOC chemotherapies. PFS2 was an exploratory objective in KEYNOTE-024 and defined as the time from randomisation to disease progression on the next line of therapy, or death	Thank you for your comments and additional data. The recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD section 4.6 for more information.

	from any cause, whichever first. To provide context to the PFS2 results, updated OS results, using a data cut-off of 05 January 2017 (median 19 months of follow-up) were included in the abstract.[1] Prior to presentation at the ASCO Annual meeting, MSD UK has been permitted to share, in confidence, the updated OS results, using a data cut-off of 05 January 2017, which support the durable clinical efficacy of pembrolizumab versus standard of care (SOC). At the time of the updated data cut-off date of 05 January 2017, approximately [redacted] of the total number of expected OS events had occurred, which is an increase from the 35% of total expected OS events, based on the original data included in our submission. Appendix 1 details the analysis of OS based on the ITT population, depicts the Kaplan-Meier graph of OS.	
Merck, Sharp & Dohme	• **<u>Extrapolation of overall survival in the pembrolizumab and SOC arms</u>** The ACD states that the "*Committee agreed that based on the data available, the most appropriate method of OS extrapolation is hard to determine"*. Despite the Committee acknowledging that the company's choice of the 22-week cut-off point at which to extrapolate the KM data from KEYNOTE-024 was plausible, the ACD goes on to state that *"there is a high level of uncertainty around the extrapolation of overall survival data and the long-term treatment effect"*. Confirmation of the validity of the 22-week cut-off point is provided by the graph provided in confidence, in Appendix 2: this shows the updated OS data derived from the 05 January 2017 data cut-off (described under the above point), superimposed over the OS projections presented in our company submission. The ACD states that the Committee was *"disappointed that the company had only modelled a constant mortality rate for pembrolizumab after week 22, as this was unlikely based on current clinical understanding of disease progression"*. The ACD goes on to state that the Committee *"noted that the duration of continued of treatment effect is an area of uncertainty for new immunotherapies, and it would*	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details.

[1] Please note that there was no formal database lock associated with this analysis and no additional efficacy endpoints or safety endpoints were evaluated.

	have preferred to see scenarios in which the hazard ratio for OS was set to 1.0 at different time-points to model stopping of the continued treatment effect." In 2016 during the appraisal of pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (ID840), the same Committee (D) discussed the duration of continued treatment effect. During consultation, MSD UK had at that time confirmed that our presentation of overall survival already reflected a potential waning of treatment effect. The same approach has been taken for this appraisal (ID990), and of note, our analyses based on the combination of our Kaplan-Meier data and an exponential parametric extrapolation are in line with virtually every other recent NICE submission for oncology technologies, and has previously been accepted by the relevant ERGs and NICE Committees as the preferred basis for decision making. Given the precedent set by Committee D for this issue during the appraisal of ID840, which ultimately resulted in a positive recommendation for pembrolizumab (TA428)[(1)], MSD UK are disappointed that the Committee has raised this point again, for the same technology, in the same cancer (albeit at a different position in the care pathway), within a 6-month window.	
Merck, Sharp & Dohme	• **<u>Overall survival projection for patients who had SOC</u>** The ACD states that *"the company's OS projection for patients who had standard care was 1.9% of patients at 5 years. The ERG noted that National Lung Cancer Audit (NCLA) 2006-2010 data suggest that 5-year survival with stage IV ECOG performance status 0 to 1 NSCLC is 5% and other sources suggest it could be as high as 13%".* The ACD goes on to further discuss the different estimations in survival rates at 5 years for the SOC arm, with the conclusion that "*the NCLA estimate of 5% at 5 years was reasonable for use in decision making but this may still represent a conservative assumption based on the evidence given"*. Based on the above, the Committee appear to have assumed 13% as an upper bound for the estimate of 5-year OS in the SOC arm, and also acknowledged the validity of 5% as the most plausible estimate of 5-year OS, given their acceptance of this value from the ERG base-case analysis.	Thank you for your comments and new information. The recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD section 4.13 for more details.

	Below, MSD UK challenge the reliability and appropriateness of both the 13% and 5% OS estimates considered by the ERG and Committee. The summary of our position is as follows, which precedes our detailed justification: • The estimated 5-year OS rate of 5% for stage IV patients, presented in the 2013 publication from the British Thoracic Society (BTS)[(2)], based on data submitted to the National Lung Cancer Audit (NLCA), is unreliable and likely overestimates the true survival rate for this patient group, given the analysis was based on incomplete data. • The International Association for the Study of Lung Cancer (IASLC) 5-year OS estimate of 13% for stage IV patients, based on pathologic staging, is irrelevant to the population under consideration in our submission. • The IASLC 5-year OS estimate of 2% for stage IV patients, based on clinical staging, is likely to still represent an overestimation of the true OS rate for this patient group, given the estimation was based on a dataset which is not reflective of a UK patient cohort. The estimation is confounded by inclusion of patients more likely to have epidermal growth factor receptor (EGFR) mutated tumours which are known to have a better response rate. Subsequent IASLC analysis based on the more representative, reclassified stage IVB patient cohort, now confirms estimated 5-year OS as 0%.[(3)] ○ *National Lung Cancer Audit (NLCA) estimate of 5% OS at 5 years for patients with stage IV ECOG performance status 0 to 1 NSCLC* The 5% estimate based on NLCA data, as referred to in the ACD, is in actual fact derived from a bespoke analysis published in 2013 and conducted by the British Thoracic Society (BTS)[(2)], in a subset of the overall NLCA dataset. Survival rates are based on data from 135,390 patients submitted to the NLCA from trusts in England between 2006-2010 (inclusive) and excludes patients from Wales, Guernsey and Scotland who are routinely included in NCLA annual reports. There have been a number of NCLA annual reports published by the Royal College of Physicians, the most recent of which (2016 report)[(4)] covers the audit period 2015 (i.e. patients with lung cancer first	

	diagnosed in 2015). The 2015 audit period was the first time the NLCA had access to fully registered lung cancer case data, collected and processed by the National Cancer Registration and Analysis Service (NCRAS) which links a variety of datasets, thereby providing the most comprehensive picture of lung cancer care to date.[4] This system of data collection replaced the previous dataset (which based on the report details, we understand consisted of data from the Cancer Outcomes and Services Dataset (COSD)) submitted by trusts' multidisciplinary teams (MDTs) through a web portal (LUCADA). As a result of the change in data collection method, an "additional" 6,000 lung cancer cases in 2015 were identified, representing a 20% increase from historical LUCADA records.[4] These 6,000 cases were not previously captured when the audit relied on a single source of case identification and submission.[4] Given that audit data prior to 2016 did not have access to the linked datasets which feed the NCRAS, it is understood that a similar proportion (20%) of lung cancer cases would have been missed year on year, as they were unidentifiable via the data collection system of the time. As these "additional" cases were omitted from previous years' audit data, it should be assumed that the estimated 5-year OS from the BTS 2013 report are not robust estimates and cannot be relied upon. We discussed this with representatives of Public Health England (PHE) who are involved in the NLCA process, who expressed concern that the BTS publication should be used for purposes such as determination of survival in relation to NICE recommendations for drug treatments. The concerns stated were centred on the missing population as discussed above, and the inclusion of patients with EGFR or anaplastic lymphoma kinase (ALK) positive tumour mutations and patients enrolled in clinical trial programs. To deal with the concerns expressed above, PHE conducted an analysis of data extracted from the Cancer Analysis System via the National Cancer Registration and Analysis Service.[5] The strength of the analysis is that it is based on a dataset which includes all stage IV lung cancer patients (ICD10 codes C33-34) recorded in the National Cancer Registration System, rather than those only recorded in the NLCA (LUCADA) database, and excludes patients from the devolved nations. The limitations of the	

analysis are that it has been impossible, in the time frame available, to remove EGFR and ALK expressing patients, and/or conduct an analysis by performance status.

A summary of the analysis is presented in Tables 1 and 2 below, which details the estimated 5-year OS rate for stage IV NSCLC patients for each annual cohort (between 2001 and 2011) and for each 5-year aggregated cohort (available between 2001 and 2011) respectively. This analysis to 2011 inclusive provides the latest data available for analysis of 5-year survival rates, as 5-years' worth of follow-up is currently unavailable for patients diagnosed post 2011. The analysis shows that between 2001 and 2011, estimated survival rates have only marginally increased, with the most recent complete 5-year OS estimate being 1.6% for patients with stage IV NSCLC.

Table 1: Estimated 5-year OS rate (%) according to KM method for aggregated cohorts per year[(5)]

Year	Number of patients eligible for survival analysis	Estimate of survival rate (%) 5 years after diagnosis
2001	1,076	1.4
2002	1,081	1.3
2003	1,739	1.3
2004	1,864	1.3
2005	2,093	1.1
2006	2,452	1.0
2007	2,748	1.3
2008	3,291	1.2
2009	5,019	1.7
2010	9,489	1.5
2011	12,436	1.6

Table 2: Estimated 5-year OS rate (%) according to KM method for aggregated cohorts per 5-year period[(5)]

5-year period	Number of patients eligible for survival analysis	Estimate of survival rate (%) 5 years after diagnosis
2001-2005	7,853	1.3
2002-2006	9,229	1.2
2003-2007	10,896	1.2
2004-2008	12,448	1.2
2005-2009	15,603	1.3
2006-2010	22,999	1.4
2007-2011	32,983	1.5

- *CRUK estimate of 13% OS at 5 years for patients with stage IV ECOG performance status 0 to 1 NSCLC*

The 13% figure is attributed to "other sources" in the ACD, but during the committee meeting it was specified that the source of this figure is Cancer Research UK (CRUK). MSD UK has ascertained that CRUK quote this figure based on information in a 2007 publication of the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project[(6)] which proposed revisions to the TNM stage groupings in the then forthcoming (2009) 7th edition of the TNM classification of malignant tumours. This publication provides graphical depiction of the following:

- 5-year OS for stage IV patients by clinical stage using the proposed IASLC recommendations:[(6)]
  - Deaths/N: = 2627/2757
  - 5-year OS = 2%
- 5-year OS for stage IV patients by pathological stage using the proposed IASLC recommendations:[(6)]
  - Deaths/N: = 224/266
  - 5-year OS = 13%

It is fundamental to note that the primary purpose of the work conducted by the IASLC is to develop a robust approach to the staging of lung cancer. Their analysis was based on data from 46 contributing data

	sources in more than 19 countries, between the study period 1990 and 2000.[6] While the survival curves are useful to demonstrate the relative difference between stages, it is inappropriate to quote these as absolute levels given the nature of the data sources and analyses conducted. This was confirmed by one of the publication[6] authors (Pieter Postmus, of Vrije Universiteit University Medical Center, Amsterdam, The Netherlands) Based on the feedback regarding these analyses, MSD UK is of the opinion that neither the 2% nor the 13% 5-year IASLC OS estimates are valid. In particular we consider the 13% estimate to be irrelevant to the population under consideration in our submission, given this estimate is based on patients who were pathologically (rather than clinically) staged as stage IV. With regards to the IASLC 5-year OS estimate of 2% for stage IV patients based on clinical staging, MSD UK has concerns about the reliability of this estimate and its applicability to the population under consideration in our submission. During discussions with PHE, it was confirmed that the international patient data set on which the IASLC staging data was derived, is relatively small and not representative of a western population, being heavily weighted towards south-east Asian (mostly Japanese) patients. This is likely to have confounded OS estimates for the overall patient cohort, given the established correlation between certain ethnicities (such as Japanese) and better survival outcomes; historical data reflects the discrepancy in lung cancer (all stages) 5-year relative survival between patients from Japan (20.7% in males; 27.6% in females) and England (7.4% in males; 7.7% in females).[7] Additionally, the EGFR mutation rate in patients of Japanese origin is much higher (45%) compared to that in UK patients (12%).[8] Such patients face a better prognosis than patients in an unselected population; 5-year survival in the EGFR mutation positive NSCLC patient population has previously been estimated at 14.6%[9]. In KEYNOTE-24, eligible patients had neither an EGFR sensitizing (activating) mutation nor ALK translocation. Therefore it is inappropriate to assume comparable survival estimates between a population including EGFR-mutated patients and the population of interest covered by our submission. MSD UK would also like to draw to the Committee's attention that the 8th edition of the TNM classification for lung cancer, adopted in late 2016,[10] incorporated changes to the TNM stage IV group. These changes were proposed by the IASLC lung cancer staging project, based on analyses of cases collected by a new	

	electronic data capture system, in addition to cases contributed by individual sites (35 sources in 16 countries). For the 8th edition, the M1 category has been reclassified as M1a, M1b (representing a single metastatic lesion in one organ) and now staged as IVA, and M1c (representing multiple metastases in either single organ or multiple organs) and now staged as IVB.[3] The decision to sub-divide stage IV was taken to reflect the better prognosis for patients with single extrathoracic metastasis (stage IVA, M1a, M1b categories) than those with multiple metastatic lesions in one organ, or multiple organ involvement (new stage IVB, M1c category)[11]. The publication also confirms that stage IVB is the more common situation for stage IV patients, and such patients have a poor OS prognosis; analysis which informed the proposals for the 8th edition of the TNM staging classification system show that patients classified as stage IVB face a 5-year OS rate of 0%.[3] Given the challenges with data sets and analyses upon which the ERG preferred estimates of 5-year OS are derived, MSD UK undertook a survey of oncologists based in England (including one of the clinical experts who had provided evidence at the Committee meeting) treating patients with lung cancer, to ask them the following question (email communication provided in Appendix 3): *"In your expert opinion, for patients with untreated stage IV NSCLC, who are EGFR/ALK negative and with a performance status of 0-1, and who are representative of current clinical practice (i.e. not enrolled in clinical trials or on targeted treatment), which of the below ranges, in your opinion, best reflects the 5-year OS rate? Please answer one of the following and reply via email:* *A. 0-2%* *B. 3-5%* *C. 6-8%* *D. 9-11%* *E. Other (please specify)* From 170 oncologists in England who were sampled, we received 43 responses. The proportions of responders selecting each category were as follows:	

	A. 0-2%: 27 responses (63%) B. 3-5%: 11 responses (26%) C. 6-8%: 4 responses (9%) D. 9-11%: 1 response (2%) E. Other (please specify): 0 responses (0%) The results of this survey confirm that the 1.9% 5 year OS estimate derived from extrapolation of KEYNOTE-024 data is reasonable, given the uncertainties and challenges associated with both the BTS estimate of 5% and the IASLC estimate of 2-13%. Supportive of this, is an analysis based on data from the National Cancer Institute's North American Surveillance, Epidemiology, and End Results (SEER) database, based on people who were diagnosed with NSCLC between 1998 and 2000[12]. While we acknowledge this is likely to be based on a heavily pre-treated population, the analysis shows that the 5-year survival rate for patients with metastatic or stage IV NSCLC is approximately 1%.[12]	
Merck, Sharp & Dohme	• **<u>Utility values</u>** The ACD states that the Committee agreed with the ERG view that the utilities derived from KEYNOTE-024 were "implausibly high". The NICE reference case specifies that the EQ-5D is the preferred measure of health-related quality of life in adults. Additionally, health-related quality of life, or changes in health-related quality of life, should be measured directly by patients,[13] and the valuation of health-related quality of life measured by patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. In our submission, MSD had followed the NICE reference case by estimating utilities based on the EQ-5D data collected in KEYNOTE-024, and applying the UK tariff to reflect valuations from the UK general public. This approach fully complies with the NICE reference case and has been previously supported by committees whenever EQ-5D data directly collected from patients in the clinical trials has been available.[14-18]	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.15 for more details.

	The utility derived from KEYNOTE-024 and identified by the ERG as implausibly high is that for long-term survivors (i.e. for individuals with a survival of 360 days or more before death after treatment initiation). The value estimated from KEYNOTE-024 is 0.808, while that for the UK population norm for people of the same age (and with a level of comorbidities reflecting that of an average 64 year-old person), is 0.79, as reported by the ERG. These two values are very close to each other. As mentioned in our submission, cancer patients have been reported to value health states higher than the general population,[19-21] which may be related to chronically unwell, individuals having more to gain from an improvement in quality of life. Patients who have regularly experienced ill health may perceive their improved health state, or a better hypothetical health state, of greater value. Compared with the general population, cancer patients have consistently reported higher patient values when using a time trade off approach.[22] This is also in line with what has been observed in other previous NICE submissions, where patients' self-reported EQ-5D scores may have resulted in as high, or higher, scores than those associated to the general population.[23, 24] During the appraisal for pembrolizumab for the treatment of patients with PD-L1-positive advanced NSCLC after chemotherapy (ID840), the ERG mentioned that greater differences in estimated health utilities were found for the post-progression health state obtained from the relevant clinical trial (KEYNOTE-010) than those in the literature. However, the trial-derived utilities were finally accepted by the committee as appropriately reflecting the NICE reference case.[1]	
Merck, Sharp & Dohme	• **<u>Standard of care: existing commercial access agreement</u>** The ACD states that the Committee was aware that there is a *"commercial access agreement for pemetrexed monotherapy maintenance if used after pemetrexed and cisplatin induction therapy (one of the treatments used in the standard of care arm). Including the commercial access agreement in the company's model would further increase the ICER for pembrolizumab."* MSD would like to draw to the Committee's attention that our company submission acknowledged the existence of a current commercial access agreement (CAA) for the administration of pemetrexed as maintenance therapy, and in order to address this, we had presented a table (Table 81 in the submission document) which detailed the ICERs when comparing pembrolizumab with SOC considering a range of	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD section 4.15 for more details.

<table>
<tr>
<td></td>
<td>possible CAA-equivalent simple discounts for pemetrexed administered as maintenance therapy. This has been provided again below (as Table 3), for clarity.

Table 3: ICERs from the pairwise comparison for pembrolizumab vs. SOC (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts, equivalent to the current CAA for pemetrexed administered as maintenance therapy)

<table>
<tr><th>Discount</th><th>ICERs</th></tr>
<tr><td>0%</td><td>£44,896</td></tr>
<tr><td>10%</td><td>£45,167</td></tr>
<tr><td>20%</td><td>£45,437</td></tr>
<tr><td>30%</td><td>£45,708</td></tr>
<tr><td>40%</td><td>£45,979</td></tr>
<tr><td>50%</td><td>£46,250</td></tr>
<tr><td>60%</td><td>£46,520</td></tr>
<tr><td>70%</td><td>£46,791</td></tr>
<tr><td>80%</td><td>£47,062</td></tr>
<tr><td>90%</td><td>£47,332</td></tr>
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<td>Merck, Sharp & Dohme</td>
<td><u>Future data availability:</u>

KEYNOTE-024

The KEYNOTE-024 results presented in our original evidence submission were from the second interim analysis (IA2) of this study. The data and safety monitoring committee (DSMC) reviewed the results on 08-June-2016 and 14-June-2016. Because pembrolizumab was superior to SOC with respect to OS at the pre-specified multiplicity-adjusted, one-sided alpha level of 1.18%, the external DSMC recommended that KEYNOTE-024 be stopped early to give the patients who were receiving SOC the opportunity to receive pembrolizumab. However, patients will continue to be followed up. MSD proposes to retain the per-protocol criterion for defining the point at which to conduct the final OS analysis, namely, when 170</td>
<td>Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund.
Please see FAD section 4.20 for more details.</td>
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</table>

	death events have occurred. Based on current projections of reaching 170 death events, the proposed time lines for this study are as detailed below, but as KEYNOTE-024 is an event driven study with a built-in cross-over design, this may impact actual accrual rates of death events. • Trial completion: December 2017 • Final Report availability: June 2018 **KEYNOTE-042** KEYNOTE-042 is a multi-centre, international, randomized, open label, controlled trial of IV pembrolizumab monotherapy versus standard of care (SOC) platinum-based chemotherapy in subjects previously untreated for their advanced or metastatic, PD-L1 positive NSCLC. In this study, patients are randomised in a 1:1 ratio into the pembrolizumab arm and the SOC arm. The sample size for subjects with strongly positive PD-L1 is targeted at approximately 530, and the overall sample size for this study is projected to be approximately 1240. The number of subjects randomised in the strongly positive stratum drives the end of enrolment. KEYNOTE-042 is an event driven study (i.e., number of subjects and follow-up time are subject to change but number of events is not) and will complete after approximately 340 deaths have been observed between the two arms in the strongly positive PD-L1 stratum. With 340 deaths, the study has approximately 90% power to detect a 0.70 hazard ratio on OS at alpha=2.5% (one sided). The primary endpoints of this study are as follows: • To compare the overall survival (OS) in subjects with PD-L1 strongly positive, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	

	• To compare the OS in subjects with PD-L1 positive (strong and weak), 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapies. The secondary endpoints are as follows: • To compare the progression-free survival (PFS) by RECIST 1.1 as assessed by central independent radiologists' review in subjects with PD-L1 strongly positive, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy. • To compare the PFS as assessed by RECIST 1.1 by central independent radiologists' review in subjects with PD-L1 positive (strong and weak), 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy. • To evaluate the safety and tolerability profile of pembrolizumab in subjects with 1L advanced/metastatic PD-L1 positive NSCLC. The estimated study completion date for KEYNOTE-042 is currently February 2018.	

Comments received from commentators

Commentator	Comment [sic]	Response
Roy Castle Lung Cancer Foundation.	• We are very disappointed that the Appraisal Committee decision is not to recommend Pembrolizumab in this indication. • We note the Appraisal Committee's acknowledgement (section 4.5), of the extension of life benefit for people with untreated metastatic PD-L1 positive non small cell lung cancer (nsclc), as compared with the standard of care. We also note the Committee's conclusion that Pembrolizumab, in this indication, addresses unmet need in this debilitating disease, for which few treatment options are available. We understand the uncertainties discussed by the Committee, in the immaturity of the data (section 4.13). This, leading to uncertainty in the cost effectiveness modelling. • In our opinion, immunotherapy represents a major development in the treatment of nsclc patients. Internationally, the discovery of PD-L1 inhibition has altered practice in nsclc management. Availabillty in this untreated patient group, we believe to be of significant benefit for selected patients. Ideally, we would wish to see this achieved through routine commissioning, to ensure equity of access. However, in reducing uncertainty on issues of effectiveness, we would welcome a period of availability of access through the Cancer Drugs Fund (CDF). It is therefore regrettable that Pembrolizumab, in this indication, is not considered eligible for the CDF, whilst the data matures (section 4.17) • We note that the Appraisal Committee has reached this negative decision, based on uncertainty and cost issues. On behalf of the many lung cancer patients who would derive benefit from this therapy indication, we strongly urge constructive dialogue between the Manufacturer, NICE and NHS England. Metastatic lung cancer remains a devastating disease for many. We hope that compromise and agreement can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund.

Commentator	Comment [sic]	Response
British Thoracic Society	ACD - lung cancer (non-small-cell, metastatic, untreated, PD-L1) - pembrolizumab [ID990] Thank you for inviting comments from the British Thoracic Society on the Appraisal Consultation Document (ACD). • Has all of the relevant evidence been taken into account? Yes • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes but we would encourage negotiation with the pharmaceutical company concerned regarding an appropriate pricing structure for the NHS.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund.

Comments received from members of the public

Role*	Comment [sic]	Response
NHS Professional	I am most disappointed with the initial ACD response regarding the Pembrolizumab in the treatment of first line, PD L1 positive (greater than 50%), advanced non-small cell lung cancer. I was very much shocked at the suggestion that stage 4 non-small cell lung cancer patients have an estimated 5 year survival greater than 3%. I think this is a gross over estimation in this patient population. In my clinical experience, the only patient and that is one patient, who has managed to survive greater than 5 years is a patient who is EGFR mutation positive and are therefore not in the scope of this submission.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details.

NHS Professional	The committee considered the 5 year overall survival for patients with stage IV lung cancer to be between 5% and 13%. It also went to state that the 5% to be an over estimate because not all the patients in the NLCA received chemotherapy. I strongly disagree with this conclusion. This is based on the assumption that the use of chemotherapy significantly improves 5 year survival for these patients. There is absolutely no evidence for this, and in systemic trials with the use of chemotherapy (not targeted therapy like EGFRi and ALKi),the benefit in terms of improvement of medial overall survival is measured in terms of months. Hence I do NOT think the 5% is an over estimate. We know that the joint incidence of ALKand EGFR positives take 4 lung cancer is probably around 10%, and these are the very patients who have prolonged survival measured in terms of years, hence I suspect a significant proportion of the 5% 5 year survivors probably belong to this group. If these patients are removed from the NCLA dataset, I suspect the 5 year survival rate will drop further. Hence I think the 5% 5 year overall survival rate may in fact be an over estimate. In terms of the IALC data set which gave rise to 13%, again we can apply the same argument. A much bigger proportion of lung cancer patients in the Far East will have EGFR mutation, thus resulting in a right skew in the survival curve. Hence overall I think 5% 5 year survival rate is an over estimate, but a reasonably fair one to judge against the data available. I think the 2% quoted by MSD may in fact be closer to the true value.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details.
NHS Professional	in clinical practice 5 year survivors after chemotherapy are extremely rare even in the PS 0 or 1 subgroup. 5% feels excessive as it would imply a significant number of patients at 5 years whereas the reality is that we rarely see these pateints at 5 years - 2% 5 year survival seems far more realistic.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details.
NHS Professional	I am surprised by the contents of this ACD. The long term outcomes for this population treated with chemotherapy are very poor - really the only ones likely to be alive at 5 years are those with mutation-	Comments noted, the recommendations have changed and

	driven cancers (EGFR and the like), a group who would not be considered for 1st line pembrolizumab anyway. The long term benefits of anti-PD1 therapy are clear in the second line setting, and it seems inconsistent not to provide access in the first line setting now that data is available.	pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details.
NHS Professional	We have a dedicated immuno-oncology trials clinic and team at Barts health in London. We have treated over a 150 patients with immunotherapy as a single agent or in combination with other drugs. In lung cancer the array of treatment options is small and the patients who have received immunotherapy in both the 1st and subsequent lines of therapy have greatly benefited in terms of symptomatic as well as disease burden. It would be a shame not to be able to give patients the opportunity to receive immunotherapy in the first line setting as not only are they fit in terms of performance status at that time point, but we are also observing that these patients on progression on immunotherapy go on to have a good and extended response to chemotherapy which we wouldn't normally see with chemotherapy on its own.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund.
NHS Professional	Clinical experience and data from Goldstraw et al., JTO 2007 (TNM VII) would suggest that a 5 year OS of 5% in NSCLC is an overestimate rather than an underestimate. The 5 yr OS in lung cancer that has been staged clinically (the vast majority of patients) rather than pathologically (a small minority of patients who have undergone surgery with curative intent and then found at surgery to have metastatic disease) is 2% in this publication.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details.
NHS Professional	Comment is made that the 5 year survival for stage IV lung cancer 'could be as high as 13%'. This is completely unrealistic and does not fit with my clinical experience. The 13% figure appears to come from a surgical staging paper, which is of course not representative of stage IV lung cancer patients because few - if any - get a surgical staging.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use

	Sadly the 5 year survival for this patient group is considerably lower than 13%. NLCA quotes a figure of 5%. I think this is closer to the real figure, but is also an over-estimate, reflecting the often poor quality data that the NLCA contains. I would estimate the 5 year survival of stage IV lung cancer patients (excluding EGFR and ALK positive patients) to be around 2-4%, and this is a much more realistic figure than those used here.	in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details.
NHS Professional	It should be noted that in 2 recent reports of long-term survival in stage IV EGFR mutated NSCLC the median OS is 30.9 months and 30.8 months. Further, 14.6% and 20.52% of patients were alive at 5 years. As the proportion of EGFR mutated patients in Keynote 24 was very low consistent with the population in England it is highly unlikely that overall survival at 5 years will be in excess of 1.9%. I am oncologist who solely treats lung cancer and have a large urban cohort of patients. This new innovative treatment, pembrolizumab, for those small numbers of patients expressing high levels of the biomarker represents the most important advance in lung cancer treatments in 3 decades.	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details.
NHS Professional	As a treating clinician I would argue that is anything the 5% 5year survival rate is an over-estimate for patients with stage IV NSCLC with PS0-1 in the absence of an EGFR/ALK abnormality. Most up to data analyses from NLCA data (where data acquisition has improved over time) continues to show extremely few long term survivors and this is backed up by clinical trial data (which is likely to out-perform the real world); for an example see Treat et al JTO 2012. In my experience 5% is an over-estimate and 13% is not a tenable estimate. This is a consistent finding in studies with advanced NSCLC in patients with long term response and was seen in the Checkmates studies with nivolumab as well as the AURA studies with osimertinib. Given the psychological burden and symptom burden of NSCLC as agreed by the ERG and company it is hardly surprising that those patients who respond to treatment should rate their health related quality of life as high or higher than the general population. This represents a problem with the assessment tool rather than the analysis. I believe this guidance to be discriminatory in terms of age. The guidance assumes that all patients suitable for pembrolizumab will be suitable for combination doublet chemotherapy. Rates of treatment with platinum doublet chemotherapy drop significantly with age in the UK, and in particular over the age of 70. The reasons for this are multifactorial and are due to co-morbidities, the presence of polypharmacy, patient wishes and expectations, and the lower rates of physicians offering	Comments noted, the recommendations have changed and pembrolizumab is recommended for use in the Cancer Drugs Fund. Please see FAD sections 4.10-4.13 for more details. .

	chemotherapy. Whatever the reason the lower rates of chemotherapy use in the older age group are well established. This guidance assumes that platinum doublet chemotherapy is a valid option for all patients considered for pembrolizumab when data from the National Lung Cancer Audit and the National Cancer Intelligence Network suggest that this is not the case	

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

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Kate Moore
Technology Appraisals Project Manager - Committee D
National Institute for Health and Care Excellence

14 March 2017

Dear Kate

Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [ID990] – Response to Appraisal Consultation Document (ACD)

Having read the ACD, MSD UK was surprised with the provisional negative recommendation, given our confidence that pembrolizumab is a cost-effective option for previously untreated patients with PD-L1-positive metastatic non-small-cell lung cancer (NSCLC).

Based on the content of the ACD, the key drivers underpinning the draft negative recommendation are uncertainty/scepticism around the following defining points, which result in a disparity between our manufacturer's base-case and the ERG's base-case:

- Overall Survival (OS) data
- Extrapolation of OS in the pembrolizumab and Standard of Care (SOC) arms
- OS projection for patients who had SOC
- Utility values
- Existing commercial access agreement for pemetrexed

With regards to the commercial access agreement for pemetrexed, this had been acknowledged in our submission with a variety of ICERs presented reflecting different potential discount rates for this product. For the purpose of enabling a discussion at the upcoming second appraisal committee meeting, MSD UK has assumed a 50% discount rate for pemetrexed in all ICERs presented henceforth.

Our full response is provided below and firstly summarises some key points in the ACD which we believe support the approach taken by MSD in our submission, and highlight the value and clinical relevance of pembrolizumab as a valid and worthy treatment option for the patient population covered by this appraisal. Our response then addresses in turn, each of the above mentioned key drivers underpinning the draft negative recommendation. Finally, we summarise future data availability in relation to the population of interest covered by this submission.

MSD UK has answered the Committee's concerns to the best of our ability concerning each of the key drivers identified above. In MSD UK's opinion, the

primary issue influencing the variability in the ICER for pembrolizumab is OS projection for patients who had SOC. As a result of addressing this issue comprehensively, our analysis results in an MSD UK base-case ICER of £46,250 (incorporating an estimated 50% discount for pemetrexed). Were MSD to accept the ERG approach to utility values (i.e. 0.79 as population norm rather than 0.808 for those surviving at least 360 days), this would only marginally change the ICER, to £47,283 (again, incorporating an estimated 50% discount for pemetrexed).

Should you have any questions about the content, please do contact me.

Kind regards

[redacted]

[redacted]
Head of HTA & OR

Key points mentioned in the ACD that support the approach taken by MSD in our submission of pembrolizumab as a treatment option for patients with previously untreated PD-L1-positive metastatic NSCLC:

- The ACD states that *"the Committee concluded that pembrolizumab is an important treatment option for people with untreated metastatic PD-L1-positive NSCLC".*

- The Committee agreed that "*the overall population in KEYNOTE-024 was comparable with clinical practice in England. The Committee therefore concluded that KEYNOTE-024 is generalisable to clinical practice in England*".

- The clinical and patient experts agreed that "*stopping treatment at 2 years independent of disease status would be acceptable to patients*". Additionally, the Committee concluded that "*implementing a 2-year stopping rule in the model was appropriate".*

- The Committee agrees with MSD that pembrolizumab *"could plausibly meet the criteria for being considered as a life-extending, end-of-life treatment".*

- The Committee *"accepted the structure of the company's economic model and considered it appropriate for decision-making*".

- The ACD confirms that the Committee and Evidence-Review Group (ERG) *"agreed with the company that the 2-stage method was the most appropriate method for crossover adjustment".*

- The Committee concluded that the company's choice of the 22-week cut-off point at which to extrapolate the Kaplan–Meier data from KEYNOTE-024 "*was plausible".*

MSD Response to key drivers underpinning the draft negative recommendation in the ACD:

- **Overall survival data**

The ACD states: "*The ERG highlighted that the immaturity of the overall survival data and the high level of crossover (43.7% of standard of care arm patients had pembrolizumab at second interim analysis) limits the reliability of the survival data collected in KEYNOTE-024".* The ACD goes on to state that *"The committee concluded that although there was sufficient evidence that pembrolizumab has an important extension-to-life benefit in people with untreated stage IV metastatic PD-L1-positive NSCLC compared with standard of care, the exact size of the overall survival gain was uncertain because of the immaturity of the data"*

The data from KEYNOTE-024 provided in our submission was based on a 09 May 2016 cut-off date with median 11.2 (6.3-19.7) months of follow-up. The next database lock is the per protocol criterion for defining the point at which to conduct the final OS analysis, namely, when 170 death events have occurred. As KEYNOTE-024 is an event driven study with a built-in cross-over design, this may impact actual accrual rates of death events.

MSD UK was notified on 21 February 2017 that an abstract had recently been submitted for the 2017 ASCO Annual Meeting (taking place 2-6 June 2017) to evaluate the progression-free survival (PFS) as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab compared to SOC chemotherapies. PFS2 was an exploratory objective in KEYNOTE-024 and defined as the time from randomisation to disease progression on the next line of therapy, or death from any cause, whichever first. To provide context to the PFS2 results, updated OS results, using a data cut-off of 05 January 2017 (median 19 months of follow-up) were included in the abstract.[1]

Prior to presentation at the ASCO Annual meeting, MSD UK has been permitted to share, in confidence, the updated OS results, using a data cut-off of 05 January 2017, which support the durable clinical efficacy of pembrolizumab versus standard of care (SOC). At the time of the updated data cut-off date of 05 January 2017, approximately [redacted] of the total number of expected OS events had occurred, which is an increase from the 35% of total expected OS events, based on the original data included in our submission.

Appendix 1 details the analysis of OS based on the ITT population, depicts the Kaplan-Meier graph of OS.

- **<u>Extrapolation of overall survival in the pembrolizumab and SOC arms</u>**

The ACD states that the "*Committee agreed that based on the data available, the most appropriate method of OS extrapolation is hard to determine"*. Despite the Committee acknowledging that the company's choice of the 22-week cut-off point at which to extrapolate the KM data from KEYNOTE-024 was plausible, the ACD goes on to state that *"there is a high level of uncertainty around the extrapolation of overall survival data and the long-term treatment effect"*.

Confirmation of the validity of the 22-week cut-off point is provided by the graph provided in confidence, in Appendix 2: this shows the updated OS data derived from the 05 January 2017 data cut-off (described under the above point), superimposed over the OS projections presented in our company submission.

[1] Please note that there was no formal database lock associated with this analysis and no additional efficacy endpoints or safety endpoints were evaluated.

The ACD states that the Committee was *"disappointed that the company had only modelled a constant mortality rate for pembrolizumab after week 22, as this was unlikely based on current clinical understanding of disease progression"*. The ACD goes on to state that the Committee *"noted that the duration of continued of treatment effect is an area of uncertainty for new immunotherapies, and it would have preferred to see scenarios in which the hazard ratio for OS was set to 1.0 at different time-points to model stopping of the continued treatment effect."*

In 2016 during the appraisal of pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (ID840), the same Committee (D) discussed the duration of continued treatment effect. During consultation, MSD UK had at that time confirmed that our presentation of overall survival already reflected a potential waning of treatment effect. The same approach has been taken for this appraisal (ID990), and of note, our analyses based on the combination of our Kaplan-Meier data and an exponential parametric extrapolation are in line with virtually every other recent NICE submission for oncology technologies, and has previously been accepted by the relevant ERGs and NICE Committees as the preferred basis for decision making.

Given the precedent set by Committee D for this issue during the appraisal of ID840, which ultimately resulted in a positive recommendation for pembrolizumab (TA428)[(1)], MSD UK are disappointed that the Committee has raised this point again, for the same technology, in the same cancer (albeit at a different position in the care pathway), within a 6-month window.

- **<u>Overall survival projection for patients who had SOC</u>**

The ACD states that *"the company's OS projection for patients who had standard care was 1.9% of patients at 5 years. The ERG noted that National Lung Cancer Audit (NCLA) 2006-2010 data suggest that 5-year survival with stage IV ECOG performance status 0 to 1 NSCLC is 5% and other sources suggest it could be as high as 13%".* The ACD goes on to further discuss the different estimations in survival rates at 5 years for the SOC arm, with the conclusion that "*the NCLA estimate of 5% at 5 years was reasonable for use in decision making but this may still represent a conservative assumption based on the evidence given"*.

Based on the above, the Committee appear to have assumed 13% as an upper bound for the estimate of 5-year OS in the SOC arm, and also acknowledged the validity of 5% as the most plausible estimate of 5-year OS, given their acceptance of this value from the ERG base-case analysis.

Below, MSD UK challenge the reliability and appropriateness of both the 13% and 5% OS estimates considered by the ERG and Committee. The summary of our position is as follows, which precedes our detailed justification:

- The estimated 5-year OS rate of 5% for stage IV patients, presented in the 2013 publication from the British Thoracic Society (BTS)[(2)], based on data

submitted to the National Lung Cancer Audit (NLCA), is unreliable and likely overestimates the true survival rate for this patient group, given the analysis was based on incomplete data.

- The International Association for the Study of Lung Cancer (IASLC) 5-year OS estimate of 13% for stage IV patients, based on pathologic staging, is irrelevant to the population under consideration in our submission.
- The IASLC 5-year OS estimate of 2% for stage IV patients, based on clinical staging, is likely to still represent an overestimation of the true OS rate for this patient group, given the estimation was based on a dataset which is not reflective of a UK patient cohort. The estimation is confounded by inclusion of patients more likely to have epidermal growth factor receptor (EGFR) mutated tumours which are known to have a better response rate. Subsequent IASLC analysis based on the more representative, reclassified stage IVB patient cohort, now confirms estimated 5-year OS as 0%.[3]

    - *National Lung Cancer Audit (NLCA) estimate of 5% OS at 5 years for patients with stage IV ECOG performance status 0 to 1 NSCLC*

The 5% estimate based on NLCA data, as referred to in the ACD, is in actual fact derived from a bespoke analysis published in 2013 and conducted by the British Thoracic Society (BTS)[2], in a subset of the overall NLCA dataset. Survival rates are based on data from 135,390 patients submitted to the NLCA from trusts in England between 2006-2010 (inclusive) and excludes patients from Wales, Guernsey and Scotland who are routinely included in NCLA annual reports.

There have been a number of NCLA annual reports published by the Royal College of Physicians, the most recent of which (2016 report)[4] covers the audit period 2015 (i.e. patients with lung cancer first diagnosed in 2015). The 2015 audit period was the first time the NLCA had access to fully registered lung cancer case data, collected and processed by the National Cancer Registration and Analysis Service (NCRAS) which links a variety of datasets, thereby providing the most comprehensive picture of lung cancer care to date.[4] This system of data collection replaced the previous dataset (which based on the report details, we understand consisted of data from the Cancer Outcomes and Services Dataset (COSD)) submitted by trusts' multidisciplinary teams (MDTs) through a web portal (LUCADA).

As a result of the change in data collection method, an "additional" 6,000 lung cancer cases in 2015 were identified, representing a 20% increase from historical LUCADA records.[4] These 6,000 cases were not previously captured when the audit relied on a single source of case identification and submission.[4]

Given that audit data prior to 2016 did not have access to the linked datasets which feed the NCRAS, it is understood that a similar proportion (20%) of lung cancer cases would have been missed year on year, as they were unidentifiable via the data collection system of the time. As these "additional" cases were omitted from previous years' audit data, it should be assumed that the estimated 5-year OS from the BTS 2013 report are not robust estimates and cannot be relied upon.

We discussed this with representatives of Public Health England (PHE) who are involved in the NLCA process, who expressed concern that the BTS publication should be used for purposes such as determination of survival in relation to NICE recommendations for drug treatments. The concerns stated were centred on the missing population as discussed above, and the inclusion of patients with EGFR or anaplastic lymphoma kinase (ALK) positive tumour mutations and patients enrolled in clinical trial programs.

To deal with the concerns expressed above, PHE conducted an analysis of data extracted from the Cancer Analysis System via the National Cancer Registration and Analysis Service.[5] The strength of the analysis is that it is based on a dataset which includes all stage IV lung cancer patients (ICD10 codes C33-34) recorded in the National Cancer Registration System, rather than those only recorded in the NLCA (LUCADA) database, and excludes patients from the devolved nations. The limitations of the analysis are that it has been impossible, in the time frame available, to remove EGFR and ALK expressing patients, and/or conduct an analysis by performance status.

A summary of the analysis is presented in Tables 1 and 2 below, which details the estimated 5-year OS rate for stage IV NSCLC patients for each annual cohort (between 2001 and 2011) and for each 5-year aggregated cohort (available between 2001 and 2011) respectively. This analysis to 2011 inclusive provides the latest data available for analysis of 5-year survival rates, as 5-years' worth of follow-up is currently unavailable for patients diagnosed post 2011. The analysis shows that between 2001 and 2011, estimated survival rates have only marginally increased, with the most recent complete 5-year OS estimate being 1.6% for patients with stage IV NSCLC.

Table 1: Estimated 5-year OS rate (%) according to KM method for aggregated cohorts per year[5]

Year	Number of patients eligible for survival analysis	Estimate of survival rate (%) 5 years after diagnosis
2001	1,076	1.4
2002	1,081	1.3
2003	1,739	1.3
2004	1,864	1.3
2005	2,093	1.1
2006	2,452	1.0
2007	2,748	1.3
2008	3,291	1.2
2009	5,019	1.7
2010	9,489	1.5
2011	12,436	1.6

Table 2: Estimated 5-year OS rate (%) according to KM method for aggregated cohorts per 5-year period[5]

5-year period	Number of patients eligible for survival analysis	Estimate of survival rate (%) 5 years after diagnosis
2001-2005	7,853	1.3
2002-2006	9,229	1.2
2003-2007	10,896	1.2
2004-2008	12,448	1.2
2005-2009	15,603	1.3
2006-2010	22,999	1.4
2007-2011	32,983	1.5

- *CRUK estimate of 13% OS at 5 years for patients with stage IV ECOG performance status 0 to 1 NSCLC*

The 13% figure is attributed to "other sources" in the ACD, but during the committee meeting it was specified that the source of this figure is Cancer Research UK (CRUK). MSD UK has ascertained that CRUK quote this figure based on information in a 2007 publication of the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project[6] which proposed revisions to the TNM stage groupings in the then forthcoming (2009) 7th edition of the TNM classification of malignant tumours. This publication provides graphical depiction of the following:

- 5-year OS for stage IV patients by clinical stage using the proposed IASLC recommendations:[6]
  - Deaths/N: = 2627/2757
  - 5-year OS = 2%
- 5-year OS for stage IV patients by pathological stage using the proposed IASLC recommendations:[6]
  - Deaths/N: = 224/266
  - 5-year OS = 13%

It is fundamental to note that the primary purpose of the work conducted by the IASLC is to develop a robust approach to the staging of lung cancer. Their analysis was based on data from 46 contributing data sources in more than 19 countries, between the study period 1990 and 2000.[6] While the survival curves are useful to demonstrate the relative difference between stages, it is inappropriate to quote these as absolute levels given the nature of the data sources and analyses conducted. This was confirmed by one of the publication[6] authors (Pieter Postmus, of Vrije Universiteit University Medical Center, Amsterdam, The Netherlands)

Based on the feedback regarding these analyses, MSD UK is of the opinion that neither the 2% nor the 13% 5-year IASLC OS estimates are valid. In particular we consider the 13% estimate to be irrelevant to the population under consideration in our submission, given this estimate is based on patients who were pathologically (rather than clinically) staged as stage IV.

With regards to the IASLC 5-year OS estimate of 2% for stage IV patients based on clinical staging, MSD UK has concerns about the reliability of this estimate and its applicability to the population under consideration in our submission. During discussions with PHE, it was confirmed that the international patient data set on which the IASLC staging data was derived, is relatively small and not representative of a western population, being heavily weighted towards south-east Asian (mostly Japanese) patients. This is likely to have confounded OS estimates for the overall patient cohort, given the established correlation between certain ethnicities (such as Japanese) and better survival outcomes; historical data reflects the discrepancy in lung cancer (all stages) 5-year relative survival between patients from Japan (20.7% in males; 27.6% in females) and England (7.4% in males; 7.7% in females).[7] Additionally, the EGFR mutation rate in patients of Japanese origin is much higher (45%) compared to that in UK patients (12%).[8] Such patients face a better prognosis than patients in an unselected population; 5-year survival in the EGFR mutation positive NSCLC patient population has previously been estimated at 14.6%[9]. In KEYNOTE-24, eligible patients had neither an EGFR sensitizing (activating) mutation nor ALK translocation. Therefore it is inappropriate to assume comparable survival estimates between a population including EGFR-mutated patients and the population of interest covered by our submission.

MSD UK would also like to draw to the Committee's attention that the 8th edition of the TNM classification for lung cancer, adopted in late 2016,[10] incorporated changes to the TNM stage IV group. These changes were proposed by the IASLC lung cancer staging project, based on analyses of cases collected by a new electronic data capture system, in addition to cases contributed by individual sites (35 sources in 16 countries). For the 8th edition, the M1 category has been reclassified as M1a, M1b (representing a single metastatic lesion in one organ) and now staged as IVA, and M1c (representing multiple metastases in either single organ or multiple organs) and now staged as IVB.[3] The decision to sub-divide stage IV was taken to reflect the better prognosis for patients with single extrathoracic metastasis (stage IVA, M1a, M1b categories) than those with multiple metastatic lesions in one organ, or multiple organ involvement (new stage IVB, M1c category)[11]. The publication also confirms that stage IVB is the more common situation for stage IV patients, and such patients have a poor OS prognosis; analysis which informed the proposals for the 8th edition of the TNM staging classification system show that patients classified as stage IVB face a 5-year OS rate of 0%.[3]

Given the challenges with data sets and analyses upon which the ERG preferred estimates of 5-year OS are derived, MSD UK undertook a survey of oncologists based in England (including one of the clinical experts who had provided evidence at the Committee meeting) treating patients with lung cancer, to ask them the following question (email communication provided in Appendix 3):

"In your expert opinion, for patients with untreated stage IV NSCLC, who are EGFR/ALK negative and with a performance status of 0-1, and who are representative of current clinical practice (i.e. not enrolled in clinical trials or on targeted treatment), which of the below ranges, in your opinion, best reflects the 5-year OS rate? Please answer one of the following and reply via email:

A. 0-2%
B. 3-5%
C. 6-8%
D. 9-11%
E. Other (please specify)

From 170 oncologists in England who were sampled, we received 43 responses. The proportions of responders selecting each category were as follows:

A. 0-2%: 27 responses (63%)
B. 3-5%: 11 responses (26%)
C. 6-8%: 4 responses (9%)
D. 9-11%: 1 response (2%)
E. Other (please specify): 0 responses (0%)

The results of this survey confirm that the 1.9% 5 year OS estimate derived from extrapolation of KEYNOTE-024 data is reasonable, given the uncertainties and challenges associated with both the BTS estimate of 5% and the IASLC estimate of 2-13%. Supportive of this, is an analysis based on data from the National Cancer Institute's North American Surveillance, Epidemiology, and End Results (SEER) database, based on people who were diagnosed with NSCLC between 1998 and 2000[12]. While we acknowledge this is likely to be based on a heavily pre-treated population, the analysis shows that the 5-year survival rate for patients with metastatic or stage IV NSCLC is approximately 1%.[12]

- **<u>Utility values</u>**

The ACD states that the Committee agreed with the ERG view that the utilities derived from KEYNOTE-024 were "implausibly high".

The NICE reference case specifies that the EQ-5D is the preferred measure of health-related quality of life in adults. Additionally, health-related quality of life, or changes in health-related quality of life, should be measured directly by patients,[13] and the valuation of health-related quality of life measured by patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method.

In our submission, MSD had followed the NICE reference case by estimating utilities based on the EQ-5D data collected in KEYNOTE-024, and applying the UK tariff to reflect valuations from the UK general public. This approach fully complies with the NICE reference case and has been previously supported by committees whenever EQ-5D data directly collected from patients in the clinical trials has been available.[14-18]

The utility derived from KEYNOTE-024 and identified by the ERG as implausibly high is that for long-term survivors (i.e. for individuals with a survival of 360 days or more before death after treatment initiation). The value estimated from KEYNOTE-024 is 0.808, while that for the UK population norm for people of the same age (and with a level of comorbidities reflecting that of an average 64 year-old person), is 0.79, as reported by the ERG. These two values are very close to each other.

As mentioned in our submission, cancer patients have been reported to value health states higher than the general population,[19-21] which may be related to chronically unwell, individuals having more to gain from an improvement in quality of life. Patients who have regularly experienced ill health may perceive their improved health state, or a better hypothetical health state, of greater value. Compared with the general population, cancer patients have consistently reported higher patient values when using a time trade off approach.[22]

This is also in line with what has been observed in other previous NICE submissions, where patients' self-reported EQ-5D scores may have resulted in as high, or higher, scores than those associated to the general population.[23, 24]

During the appraisal for pembrolizumab for the treatment of patients with PD-L1-positive advanced NSCLC after chemotherapy (ID840), the ERG mentioned that greater differences in estimated health utilities were found for the post-progression health state obtained from the relevant clinical trial (KEYNOTE-010) than those in the literature. However, the trial-derived utilities were finally accepted by the committee as appropriately reflecting the NICE reference case.[1]

- **<u>Standard of care: existing commercial access agreement</u>**

The ACD states that the Committee was aware that there is a *"commercial access agreement for pemetrexed monotherapy maintenance if used after pemetrexed and cisplatin induction therapy (one of the treatments used in the standard of care arm). Including the commercial access agreement in the company's model would further increase the ICER for pembrolizumab."*

MSD would like to draw to the Committee's attention that our company submission acknowledged the existence of a current commercial access agreement (CAA) for the administration of pemetrexed as maintenance therapy, and in order to address this, we had presented a table (Table 81 in the submission document) which detailed the ICERs when comparing pembrolizumab with SOC considering a range of possible CAA-equivalent simple discounts for pemetrexed administered as maintenance therapy. This has been provided again below (as Table 3), for clarity.

Table 3: ICERs from the pairwise comparison for pembrolizumab vs. SOC (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts, equivalent to the current CAA for pemetrexed administered as maintenance therapy)

Discount	ICERs
0%	£44,896
10%	£45,167
20%	£45,437
30%	£45,708
40%	£45,979
50%	£46,250
60%	£46,520
70%	£46,791
80%	£47,062
90%	£47,332

Future data availability:

KEYNOTE-024

The KEYNOTE-024 results presented in our original evidence submission were from the second interim analysis (IA2) of this study. The data and safety monitoring committee (DSMC) reviewed the results on 08-June-2016 and 14-June-2016. Because pembrolizumab was superior to SOC with respect to OS at the pre-specified multiplicity-adjusted, one-sided alpha level of 1.18%, the external DSMC recommended that KEYNOTE-024 be stopped early to give the patients who were receiving SOC the opportunity to receive pembrolizumab. However, patients will continue to be followed up. MSD proposes to retain the per-protocol criterion for defining the point at which to conduct the final OS analysis, namely, when 170 death events have occurred. Based on current projections of reaching 170 death events, the proposed time lines for this study are as detailed below, but as KEYNOTE-024 is an event driven study with a built-in cross-over design, this may impact actual accrual rates of death events.

- Trial completion: December 2017
- Final Report availability: June 2018

KEYNOTE-042

KEYNOTE-042 is a multi-centre, international, randomized, open label, controlled trial of IV pembrolizumab monotherapy versus standard of care (SOC) platinum-based chemotherapy in subjects previously untreated for their advanced or metastatic, PD-L1 positive NSCLC.

In this study, patients are randomised in a 1:1 ratio into the pembrolizumab arm and the SOC arm. The sample size for subjects with strongly positive PD-L1 is targeted at approximately 530, and the overall sample size for this study is projected to be approximately 1240. The number of subjects randomised in the strongly positive stratum drives the end of enrolment.

KEYNOTE-042 is an event driven study (i.e., number of subjects and follow-up time are subject to change but number of events is not) and will complete after approximately 340 deaths have been observed between the two arms in the strongly positive PD-L1 stratum. With 340 deaths, the study has approximately 90% power to detect a 0.70 hazard ratio on OS at alpha=2.5% (one sided).

The primary endpoints of this study are as follows:

- To compare the overall survival (OS) in subjects with PD-L1 strongly positive, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies.

- To compare the OS in subjects with PD-L1 positive (strong and weak), 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapies.

The secondary endpoints are as follows:

- To compare the progression-free survival (PFS) by RECIST 1.1 as assessed by central independent radiologists' review in subjects with PD-L1 strongly positive, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

- To compare the PFS as assessed by RECIST 1.1 by central independent radiologists' review in subjects with PD-L1 positive (strong and weak), 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

- To evaluate the safety and tolerability profile of pembrolizumab in subjects with 1L advanced/metastatic PD-L1 positive NSCLC.

The estimated study completion date for KEYNOTE-042 is currently February 2018.

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Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Pembrolizumab for untreated, PD-L1 positive metastatic non small cell lung cancer. [ID990]

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are very disappointed that the Appraisal Committee decision is not to recommend Pembrolizumab in this indication.

- We note the Appraisal Committee's acknowledgement (section 4.5), of the extension of life benefit for people with untreated metastatic PD-L1 positive non small cell lung cancer (nsclc), as compared with the standard of care. We also note the Committee's conclusion that Pembrolizumab, in this indication, addresses unmet need in this debilitating disease, for which few treatment options are available.

  We understand the uncertainties discussed by the Committee, in the immaturity of the data (section 4.13). This, leading to uncertainty in the cost effectiveness modelling.

- In our opinion, immunotherapy represents a major development in the treatment of nsclc patients. Internationally, the discovery of PD-L1 inhibition has altered practice in nsclc management. Availabillty in this untreated patient group, we believe to be of significant benefit for selected patients. Ideally, we would wish to see this achieved through routine commissioning, to ensure equity of access. However, in reducing uncertainty on issues of effectiveness, we would welcome a period of availability of access through the Cancer Drugs Fund (CDF). It is therefore regrettable that Pembrolizumab, in this indication, is not considered eligible for the CDF, whilst the data matures (section 4.17)

- We note that the Appraisal Committee has reached this negative decision, based on uncertainty and cost issues. **On behalf of the many lung cancer patients who would derive benefit from this therapy indication, we strongly urge constructive dialogue between the Manufacturer, NICE and NHS England.** Metastatic lung cancer remains a devastating disease for many. We hope that compromise and agreement can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.

Roy Castle Lung Cancer Foundation
March 2017

British Thoracic Society

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Company Registration No. 1645201

To be submitted via NICE docs

March 2017

Dear Sir,

ACD - lung cancer (non-small-cell, metastatic, untreated, PD-L1) - pembrolizumab [ID990]

Thank you for inviting comments from the British Thoracic Society on the Appraisal Consultation Document (ACD).

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

  Yes

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

  Yes

- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
  Yes but we would encourage negotiation with the pharmaceutical company concerned regarding an appropriate pricing structure for the NHS.

Yours faithfully,

[redacted]

[redacted]
[redacted]

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

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

Comments on ACD:

I am most disappointed with the initial ACD response regarding the Pembrolizumab in the treatment of first line, PD L1 positive (greater than 50%), advanced non-small cell lung cancer.

I was very much shocked at the suggestion that stage 4 non-small cell lung cancer patients have an estimated 5 year survival greater than 3%.

I think this is a gross over estimation in this patient population.

In my clinical experience, the only patient and that is one patient, who has managed to survive greater than 5 years is a patient who is EGFR mutation positive and are therefore not in the scope of this submission.

Name	[redacted]
Role	NHS Professional
Other role	Consultant in Clnical Oncology
Organisation	
Location	England
Conflict	[redacted]
Notes	

Comments on ACD:

The committee considered the 5 year overall survival for patients with stage IV lung cancer to be between 5% and 13%. It also went to state that the 5% to be an over estimate because not all the patients in the NLCA received chemotherapy.

I strongly disagree with this conclusion. This is based on the assumption that the use of chemotherapy significantly improves 5 year survival for these patients. There is absolutely no evidence for this, and in systemic trials with the use of chemotherapy (not targeted therapy like EGFRi and ALKi),the benefit in terms of improvement of medial overall survival is measured in terms of months. Hence I do NOT think the 5% is an over estimate. We know that the joint incidence of ALKand EGFR positives take 4 lung cancer is probably around 10%, and these are the very patients who have prolonged survival measured in terms of years, hence I suspect a significant proportion of the 5% 5 year survivors probably belong to this group. If these patients are removed from the NCLA dataset, I suspect the 5 year survival rate will drop further. Hence I think the 5% 5 year overall survival rate may in fact be an over estimate.

In terms of the IALC data set which gave rise to 13%, again we can apply the same argument. A much bigger proportion of lung cancer patients in the Far East will have EGFR mutation, thus resulting in a right skew in the survival curve.

Hence overall I think 5% 5 year survival rate is an over estimate, but a reasonably fair one to judge against the data available. I think the 2% quoted by MSD may in fact be closer to the true value.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical Oncologist
Organisation	
Location	England
Conflict	None
Notes	
Comments on ACD:	
in clinical practice 5 year survivors after chemotherapy are extremely rare even in the PS 0 or 1 subgroup. 5% feels excessive as it would imply a significant number of patients at 5 years whereas the reality is that we rarely see these patients at 5 years - 2% 5 year survival seems far more realistic.	

Name	[redacted]
Role	NHS Professional
Other role	Professor, Consultant in Medical Oncology
Organisation	
Location	England
Conflict	
Notes	
Comments on ACD:	
I am surprised by the contents of this ACD. The long term outcomes for this population treated with chemotherapy are very poor - really the only ones likely to be alive at 5 years are those with mutation-driven cancers (EGFR and the like), a group who would not be considered for 1st line pembrolizumab anyway. The long term benefits of anti-PD1 therapy are clear in the second line setting, and it seems inconsistent not to provide access in the first line setting now that data is available.	

Name	[redacted]
Role	NHS Professional
Other role	medical oncology consultant
Organisation	[redacted]
Location	
Conflict	No
Notes	
Comments on ACD:	
We have a dedicated immuno-oncology trials clinic and team at Barts health in London. We have treated over a 150 patients with immunotherapy as a single agent or in combination with other drugs. In lung cancer the array of treatment options is small and the patients who have received immunotherapy in both the 1st and subsequent	

lines of therapy have greatly benefited in terms of symptomatic as well as disease burden. It would be a shame not to be able to give patients the opportunity to receive immunotherapy in the first line setting as not only are they fit in terms of performance status at that time point, but we are also observing that these patients on progression on immunotherapy go on to have a good and extended response to chemotherapy which we wouldn't normally see with chemotherapy on its own.

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

Comments on ACD:

Clinical experience and data from Goldstraw et al., JTO 2007 (TNM VII) would suggest that a 5 year OS of 5% in NSCLC is an overestimate rather than an underestimate. The 5 yr OS in lung cancer that has been staged clinically (the vast majority of patients) rather than pathologically (a small minority of patients who have undergone surgery with curative intent and then found at surgery to have metastatic disease) is 2% in this publication.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Medical Oncologist
Organisation	
Location	England
Conflict	[redacted]
Notes	

Comments on ACD:

Comment is made that the 5 year survival for stage IV lung cancer 'could be as high as 13%'. This is completely unrealistic and does not fit with my clinical experience.

The 13% figure appears to come from a surgical staging paper, which is of course not representative of stage IV lung cancer patients because few - if any - get a surgical staging.

Sadly the 5 year survival for this patient group is considerably lower than 13%. NLCA quotes a figure of 5%. I think this is closer to the real figure, but is also an over-estimate, reflecting the often poor quality data that the NLCA contains.

I would estimate the 5 year survival of stage IV lung cancer patients (excluding EGFR and ALK positive patients) to be around 2-4%, and this is a much more realistic figure than those used here.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Medical Oncology
Organisation	[redacted]

Location	England
Conflict	None
Notes	

Comments on ACD:

It should be noted that in 2 recent reports of long-term survival in stage IV EGFR mutated NSCLC the median OS is 30.9 months and 30.8 months. Further, 14.6% and 20.52% of patients were alive at 5 years. As the proportion of EGFR mutated patients in Keynote 24 was very low consistent with the population in England it is highly unlikely that overall survival at 5 years will be in excess of 1.9%.

I am oncologist who solely treats lung cancer and have a large urban cohort of patients. This new innovative treatment, pembrolizumab, for those small numbers of patients expressing high levels of the biomarker represents the most important advance in lung cancer treatments in 3 decades.

Name	[redacted]
Role	NHS Professional
Other role	Senior Lecturer and Honorary Consultant in Medical Oncology
Organisation	
Location	England
Conflict	[redacted]
Notes	

Comments on ACD:

As a treating clinician I would argue that is anything the 5% 5year survival rate is an over-estimate for patients with stage IV NSCLC with PS0-1 in the absence of an EGFR/ALK abnormality. Most up to data analyses from NLCA data (where data acquisition has improved over time) continues to show extremely few long term survivors and this is backed up by clinical trial data (which is likely to out-perform the real world); for an example see Treat et al JTO 2012. In my experience 5% is an over-estimate and 13% is not a tenable estimate.
This is a consistent finding in studies with advanced NSCLC in patients with long term response and was seen in the Checkmates studies with nivolumab as well as the AURA studies with osimertinib. Given the psychological burden and symptom burden of NSCLC as agreed by the ERG and company it is hardly surprising that those patients who respond to treatment should rate their health related quality of life as high or higher than the general population. This represents a problem with the assessment tool rather than the analysis.

I believe this guidance to be discriminatory in terms of age. The guidance assumes that all patients suitable for pembrolizumab will be suitable for combination doublet chemotherapy. Rates of treatment with platinum doublet chemotherapy drop significantly with age in the UK, and in particular over the age of 70. The reasons for this are multifactorial and are due to co-morbidities, the presence of polypharmacy, patient wishes and expectations, and the lower rates of physicians offering chemotherapy. Whatever the reason the lower rates of chemotherapy use in the older age group are well established. This guidance assumes that platinum doublet chemotherapy is a valid option for all patients considered for pembrolizumab when data from the National Lung Cancer Audit and the National Cancer Intelligence Network suggest that this is not the case.

Appendix 1: Overall Survival data (05 January 2017 data cut-off)

Table 1: Analysis of Overall Survival (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).

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

(Database Cutoff Date: 05JAN2017)

Figure 1: Kaplan-Meier of Overall Survival (ITT Population)

[redacted]

(Database Cutoff Date: 05JAN2017)

Appendix 2: Comparison of updated KEYNOTE-024 OS data with original extrapolations

Figure 1: OS projections compared with updated KEYNOTE-024 data

Appendix 3: Email communication sent to practising Oncologists based in England

From: [redacted]
Sent: 28 February 2017 14:11
To: [redacted]
Subject: Pembrolizumab in 1L Stage IV NSCLC EAMS - NICE ACD

Dear Dr [redacted],

As an oncologist who participated in the Early Access to Medicines Scheme (EAMS) for pembrolizumab in NSCLC, you may be aware that NICE have issued an Appraisal Consultation Document (ACD) for pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. The ACD states that *"pembrolizumab is not recommended, within its marketing authorisation, for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults whose tumours express PD-L1 with at least a 50% tumour proportion score and have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations"*.

In order for MSD to address a specific issue raised within the ACD I would like to ask you the following question:

In your expert opinion, for patients with untreated stage IV NSCLC, who are EGFR/ALK negative and with a performance status of 0-1, and who are representative of current clinical practice (i.e. not enrolled in clinical trials or on targeted treatment), which of the below ranges, in your opinion, best reflects the 5-year OS rate? Please answer one of the following and reply to me via email:

A. 0-2%
B. 3-5%
C. 6-8%
D. 9-11%
E. Other (please specify)

If you would like to discuss the ACD, and any of the issues raised within it, I would be happy to do so.

Please note, this NICE ACD does not affect those patients currently receiving pembrolizumab through the EAMS in this setting. MSD will continue to provide pembrolizumab until reimbursement, disease progression or until 24 months of therapy has been reached.

Kind regards

[redacted]

[redacted] February 2017

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer ID 990

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 16/108/01

Completed 22nd March 2017

DOES CONTAIN AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company, Merck, Sharp & Dohme (MSD) has provided additional evidence in response to the publication of NICE's Appraisal Consultation Document (ACD) for pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer (ID 990).

This document presents the ERG's response to the additional evidence provided by the company.

1 ERG RESPONSE TO MSD'S RESPONSE TO THE ACD

The ERG notes that the evidence presented by the company in their response to the ACD does not have any impact on the size of the incremental cost effectiveness ratios (ICERs) generated by the ERG and presented in the ERG report. In summary, the company considers that the new evidence that they have provided supports the assumptions about overall survival (OS) and utility that were made in the original company submission (CS). Thus, the company considers that the ICERs that should be considered by the Appraisal Committee (AC) are those presented in the CS.

The evidence presented by the company in their response to the ACD can be summarised as follows:

1. **OS projection for patients receiving pembrolizumab**
   Updated OS results from the KEYNOTE-024 trial are now available and show that the company's original OS projection for patients receiving pembrolizumab is valid.
2. **Utility values**
   Utility values for patients with metastatic lung cancer can be higher than the population norm utility values.
3. **OS projection for patients receiving Standard of Care (SOC)**
   Evidence from several databases and survey results demonstrate that OS for patients receiving SOC should be 1.9% at 5 years, as the company suggested in the original CS.

The ERG's response to these issues is shown in Sections 1.1 to 1.3 below.

1.1 OS projection for patients receiving pembrolizumab

Within the original ERG report, the ERG noted the uncertainty around every choice of distribution, but made no changes to the company's OS projection for patients receiving pembrolizumab. The ERG considers that the additional data provided by the company from the KEYNOTE-024 trial reduce uncertainty. However, incorporation of these data does not affect either the company's base case ICER or those ICERs generated by the ERG.

1.2 Utility values

The company has presented an argument (rather than additional evidence per se) that utility values for patients with metastatic lung cancer may be higher than utility values for the general population of the same age. The company also states that the utility values they used had been calculated using an approach that fully complied with the NICE Reference Case for calculating utility values.

The ERG accepts that, when possible, utility values should be estimated using data collected from trials and the UK valuation set. However, the resultant values must be plausible. The ERG considers, and stated in the ERG report, that the utility values chosen by the company appear high when compared with those reported by, for example, Nafees.[1] In addition, the ERG notes that whilst the utility of **individuals** with metastatic lung cancer may be higher than the population norm, **on average** the utility for that patient group would not, at any point, be higher than the population norm utility value. This line of reasoning is supported by the substantial detail that is presented by the company in the CS[2] and by the Roy Castle Foundation[3] in their submission regarding the health-related quality of life issues faced by people with the condition.

The company states, in their ACD response, that patients with cancer value health states higher than the general population values health states. This is irrelevant, as the NICE Reference Case requires that health states should be valued by society, not by patients with the condition.

The only change, within the ERG report, that the ERG made to the company's utility values was to set the value for people who were more than 360 days away from death to the population norm, as estimated by Kind.[4] The ERG highlights that the values estimated by Kind[4] were also those used by the company to estimate the age-related utility decrements used in their model. The ERG still considers that, as stated in the ERG report, the utility values chosen by the company are implausibly high and that the Kind[4] values, as used by the ERG, are still too high, but are more likely to be reflective of the patient population than those used by the company.

1.3 OS projection for patients receiving SOC

Within the ERG report, the ERG stated that the company's assumption of a 5-year survival rate of 1.9% for patients receiving SOC was likely to be too low. This is supported by National Lung Cancer Audit data[5] presented by the British Thoracic Society suggesting that the 5-year survival for patients with Stage IV lung cancer and a performance status (PS) of 0 or 1 is 5.0%. The ERG noted that this estimate was not restricted to the population receiving chemotherapy and that chemotherapy increases the life expectancy of people with the condition. The ERG highlights that, to be in-line with the trial data that are the basis of OS projections, 5-year survival estimates should be based on data collected from patients with PS 0 or 1 who are in receipt of chemotherapy.

The company has presented various data and results from a survey of oncologists to support their original position that 1.9% survival at 5 years is plausible. The ERG counters this on the following grounds:

- the new data presented by the company in their response to the ACD (Tables 1 and 2) relate to all patients, not just to those patients with PS 0 or 1 who are in receipt of chemotherapy
- the company contends that precise staging is important. Again, the ERG restates that any OS projection must be for those patients with PS 0 or 1 who are receiving chemotherapy.

The survey of oncologists carried out by the company shows that respondents were uncertain about 5-year survival rates. However, the question asked in the survey is not relevant to the current appraisal. The clinicians should have been asked for their views about 5-year survival for patients with PS 0 or 1 who were receiving chemotherapy. In addition, the company explicitly states in the question that the group of interest is patients who are representative of those in current practice and who are not enrolled in clinical trials. This is not relevant as the OS projection for SOC relates to projecting trial data and, furthermore, this projection is being compared to the (projected) experience of patients receiving pembrolizumab in a clinical trial setting.

The ERG considers the results of the company's survey show a conservative estimate, from oncologists, of the true OS of patients receiving SOC in the KEYNOTE-024 trial. Even then, a third of those surveyed considered that 5-year survival would be greater than 2% and thus the survey results can be interpreted as supporting, for the population of interest, a 5-year survival rate that is higher than the 1.9% suggested by the company.

In addition, the ERG notes that, while the company highlighted that the updated results from the KEYNOTE-024 trial support their original projection for patients receiving pembrolizumab, the company did not comment on whether those data support their OS projection for patients receiving SOC. Figure 1 in Appendix 2 of the company's response to the ACD shows the updated Kaplan-Meier (K-M) data for both SOC and pembrolizumab against the original company OS projections, i.e. the ones that the company contend are valid and should be used by the AC as the basis of decision making. [redacted]

REFERENCES

1. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008; 6:84.

2. Merck Sharp & Dohme. Pembrolizumab for untreated PD-L1 positive metastatic NSCLC ID990: Company submission to NICE. 2016.

3. Roy Castle Lung Cancer Foundation. Consultee submission to NICE: pembrolizumab for untreated PD-L1 NSCLC (ID990) 2016.

4. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Centre for Health Economics, University of York. 1999.

5. British Thoracic Society. Sharing information with lung cancer patients: guidance for healthcare professionals discussing options for patients who have lung cancer. 2013; Available from: https://www.brit-thoracic.org.uk/document-library/clinical-information/lung-cancer/sharing-information-with-lung-cancer-patients/

24th March 2017

Dear Helen,

Re. Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990]

Please find below the updated cost-effectiveness results in response to your request on 24th March 2017 to provide additional analyses. The arrangements regarding the PAS remain unchanged (as for our latest communication with NICE on 23rd January 2017) and are reflected as such as part of these analyses.

Should NICE or the ERG require any further clarification we would be more than happy to provide an answer to them.

Kind regards,

[redacted]

"Given that the new OS data was collected with a median of 19 months of follow-up (compared with the original OS collected with median of 11.2 months of follow up) we would ask you to explore various OS cut-points at which to extrapolate the KM-data in your analyses (= 22 weeks cut-point used in the original base case):

- *Please present a new company base case with the updated OS data and scenario analyses with various OS cut-points at which the extrapolate the KM data*
- *Please also update the new base case with the committee preferred assumptions:*
  - *5% 5-year OS survival for SOC*
  - *Utility value for >360 days to death set to population norm"*

Summary of results

Table 1. Summary - cost-effectiveness results for the MSD base case vs. the Committee's preferred assumptions for the base case and additional cut-offs, using updated OS data (discounted, with updated PAS)

	Base-case cut-off	Additional cut-offs	
	22-week	14-week	30-week
MSD base case: - Extrapolation based on KEYNOTE-024 data for both treatment arms - 2-stage crossover adjustment for SOC OS - Utility value for > 360 days to death estimated from KEYNOTE-024 EQ-5D data (i.e. 0.808) - Pemetrexed at list price	£42,295	£45,813	£44,150
Committee's preferred scenario: - Extrapolation based on KEYNOTE-024 data for pembrolizumab arm - 5% 5-year OS for SOC - Utility value for >360 days to death set to population norm (i.e. 0.79) - Pemetrexed at list price	£49,897	£54,577	£46,083

MSD base-case cost-effectiveness analysis of pembrolizumab compared with SOC

Please find below in

Table 2 the deterministic cost-effectiveness results for the MSD preferred base case (i.e. extrapolation based on piecewise model as estimated from the updated OS data from KEYNOTE-024 KM for both pembrolizumab and SOC, the latter adjusted using a 2-stage crossover adjustment, EQ-5D-based time-to-death utilities as estimated from KEYNOTE-024 and considering a maximum

treatment duration of 2 years). Results are provided for the base-case cut-off presented in the original submission (22 weeks), and for two additional cut-offs (14 weeks and 30 weeks (22 weeks +/- 8 weeks)).

Table 2. Incremental cost-effectiveness results for MSD's base case and additional cut-offs, using updated OS data (discounted, with updated PAS, and with list price for pemetrexed)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
22-week cut-off					
Pembrolizumab	£72,131.17	2.08	£49,415	1.17	£42,295
SOC	£22,715.97	0.91	-	-	-
14-week cut-off					
Pembrolizumab	£71,493.15	1.99	£48,671	1.06	£45,813
SOC	£22,822.55	0.92	-	-	-
30-week cut-off					
Pembrolizumab	£72,464.40	2.12	£48,893	1.11	£44,150
SOC	£23,571.21	1.02	-	-	-

In relation to the current commercial access agreement (CAA) for the administration of pemetrexed as maintenance therapy, we present, as per our original submission, in Table 3 below the ICERs for comparisons of pembrolizumab and SOC considering a range of possible CAA-equivalent simple discounts..

Table 3. ICERs from the pairwise comparison for pembrolizumab vs. SOC (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts, equivalent to the current CAA for pemetrexed administered as maintenance therapy)

Discount	ICER 22-week cut-off	ICER 14-week cut-off	ICER 30-week cut-off
0%	£42,295	£45,813	£44,150
10%	£42,575	£46,121	£44,445
20%	£42,855	£46,429	£44,740
30%	£43,134	£46,736	£45,035
40%	£43,414	£47,044	£45,330
50%	£43,694	£47,351	£45,625
60%	£43,973	£47,659	£45,920
70%	£44,253	£47,966	£46,215
80%	£44,533	£48,274	£46,510
90%	£44,812	£48,581	£46,805

One of the key drivers in the difference between the MSD base case and that preferred by the Appraisal Committee is the modelled OS for SOC. In table 4 below we have provided the 5 year OS SOC values utilising the updated clinical data as well as adding in the impact of the different cut off points.

Table 4: Model outcomes at 5 years

	Pembrolizumab			SOC		
Outcome	Base case 22-week cut-off	14-week cut-off	30-week cut-off	Base case 22-week cut-off	14-week cut-off	30-week cut-off
5-year OS	20.2%	18.3%	21.1%	2.4%	2.7%	4.5%

For validation purposes, we have provided below the probabilistic sensitivity analysis for MSD's base case in table 5 (we have assumed that one PSA analysis is sufficient for these analyses given; a) the homogeneity of all of the original probabilistic and deterministic results, and b) wanting to provide this update in time for it to be used by NICE). The probability of pembrolizumab being cost-effective at a £50,000 per QALY threshold is estimated to be 72%.

Table 5. Incremental deterministic vs. probabilistic cost-effectiveness results for the MSD base case (discounted, with updated PAS, and at list price for pemetrexed)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Deterministic					
Pembrolizumab	£72,131.17	2.08	£49,415	1.17	£42,295
SOC	£22,715.97	0.91	-	-	-
Probabilistic					
Pembrolizumab	£72,517.03	2.09	£49,450.33	1.17	£42,143
SOC	£23,066.70	0.92	-	-	-

Figure 1: Scatterplot of PSA results (1,000 simulations; results discounted, with updated PAS)

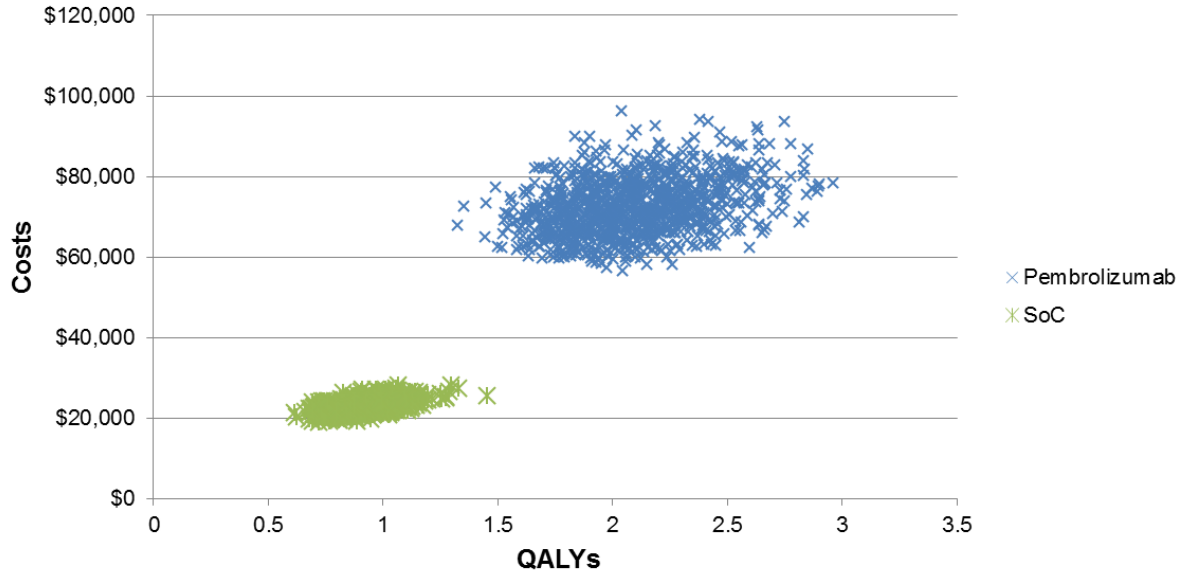

Figure 2: Cost-effectiveness acceptability curve (results discounted, with updated PAS)

Committee's preferred assumptions

Please find below in Table 6 the deterministic cost-effectiveness results considering the Committee's preferred assumptions (i.e. extrapolation based on KEYNOTE-024 KM for pembrolizumab and 5% OS projection for SOC, and utility value for >360 days to death set to population norm, i.e. 0.79; the analysis also considers a maximum treatment duration of 2 years). Results are provided for the base-case cut-off presented in the original submission (i.e. at 22 weeks), and for two additional cut-offs (i.e.

at 14 weeks and 30 weeks, i.e. 22 weeks +/- 8 weeks). Table 8 provides the approach taken to 5 year year survival to fit with the Committee preferred aassumptions.

Table 6. Incremental cost-effectiveness results for the Committee's preferred assumptions, considering additional cut-offs and using updated OS data (discounted, with updated PAS, and at list price for pemetrexed)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
22-week cut-off					
Pembrolizumab	£72,131.17	2.04	£47,908	0.96	£49,897
SOC	£24,223.10	1.08	-	-	-
14-week cut-off					
Pembrolizumab	£71,493.15	1.95	£47,229	0.87	£54,577
SOC	£24,264.44	1.09	-	-	-
30-week cut-off					
Pembrolizumab	£72,464.40	2.09	£48,668	1.06	£46,083
SOC	£23,796.65	1.03	-	-	-

In relation to the current CAA for the administration of pemetrexed as maintenance therapy, as per our original submission, we present in Table 7 below the ICERs for comparisons of pembrolizumab and SOC considering a range of possible CAA-equivalent simple discounts when the Committee's preferred assumptions are taken into account.

Table 7. ICERs from the pairwise comparison for pembrolizumab vs. SOC (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts, equivalent to the current CAA for pemetrexed administered as maintenance therapy)

Discount	ICER 22-week cut-off	ICER 14-week cut-off	ICER 30-week cut-off
0%	£49,897	£54,577	£46,083
10%	£50,237	£54,954	£46,392
20%	£50,577	£55,332	£46,701
30%	£50,918	£55,710	£47,011
40%	£51,258	£56,087	£47,320
50%	£51,598	£56,465	£47,630
60%	£51,938	£56,842	£47,939
70%	£52,279	£57,220	£48,248
80%	£52,619	£57,597	£48,558
90%	£52,959	£57,975	£48,867

Table 8: Model outcomes at 5 years

	Pembrolizumab			SOC		
Outcome	Base case 22-week cut-off	14-week cut-off	30-week cut-off	Base case 22-week cut-off	14-week cut-off	30-week cut-off
5-year OS	20.2%	18.3%	21.1%	5%		

ID990 STA Pembrolizumab Addendum 3

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer [ID990]

This report was commissioned by the NIHR HTA Programme as project number 16/108/01

Completed 21st April 2017

DOES NOT CONTAIN CIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 ERG VERIFICATION OF, AND MODIFICATIONS TO, THE COMPANY'S UPDATED COST EFFECTIVENESS RESULTS

The company, Merck, Sharp & Dohme, provided additional evidence in response to the publication of the National Institute for Health and Care Excellence (NICE) Appraisal Consultation Document (ACD) for pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer (ID990). On the 27th March 2017, the company also submitted updated cost effectiveness results to NICE. The updated cost effectiveness results were provided in the company document named 'ID990 pembrolizumab updated OS – CE analyses'.

The NICE team asked the ERG to verify the analyses presented in Table 2, Table 6 and Table 4 of the company document:

1. **Table 2 = company base case**
- *The 22-, 14- and 30-week cut off point at which to extrapolate the new overall survival (OS) data*
- *2 year stopping rule*
2. **Table 6 = committee preferred ACD assumptions**
- *The 22-, 14- and 30-week cut off point at which to extrapolate the new OS data*
- *2 year stopping rule*
- *Utilities capped at the UK population norm value*
- *5% survival range at 5 years for the standard of care arm (National Lung Cancer Audit estimate)*
3. **Table 4 = the extrapolated OS rates in the SOC arm**

The NICE team also asked the ERG to provide the following incremental cost effectiveness ratios (ICERs) per QALY gained:

4. **Scenario not included in the company document, but considered by the committee at the second appraisal committee meeting (basically updating Table 2 with utilities capped at the population norm)**
- *The 22-, 14- and 30-week cut off point at which to extrapolate the new OS data*
- *2 year stopping rule*
- *Utilities capped at the UK population norm value*
5. **Cost effectiveness results for the scenario described in scenario 4 including the Confidential Access Agreeement (CAA) price for pemetrexed (to be provided in a Confidential Appendix)**

The results of the ERG's response to the requests from the NICE team listed in 1 – 4 above are presented in this addendum to the ERG Report. As instructed by the NICE team, the ERG has provided a response to item 5 in Confidential Appendix 3.

1.1 ERG verification of company Table 2, Table 6 and Table 4

NICE team request 1 and 2

The ERG has checked Table 2 and Table 6 of the company document (Table 1 and Table 2). The ERG is satisfied that the assumptions detailed in the document have been accurately implemented in the company model and the results are reported correctly in the tables provided to NICE by the company.

Table 1 Company base case (Company Table 2)

Cut-off time	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
22-week cut-off					
Pembrolizumab	£72,131.17	2.08	£49,415	1.17	£42,295
SOC	£22,715.97	0.91	-	-	-
14-week cut-off					
Pembrolizumab	£71,493.15	1.99	£48,671	1.06	£45,813
SOC	£22,822.55	0.92	-	-	-
30-week cut-off					
Pembrolizumab	£72,464.40	2.12	£48,893	1.11	£44,150
SOC	£23,571.21	1.02	-	-	-

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years; SOC=standard of care

Table 2 Appraisal Committee preferred assumptions (Company Table 6)

Cut-off time	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
22-week cut-off					
Pembrolizumab	£72,131.17	2.04	£47,908	0.96	£49,897
SOC	£24,223.10	1.08	-	-	-
14-week cut-off					
Pembrolizumab	£71,493.15	1.95	£47,229	0.87	£54,577
SOC	£24,264.44	1.09	-	-	-
30-week cut-off					
Pembrolizumab	£72,464.40	2.09	£48,668	1.06	£46,083
SOC	£23,796.65	1.03	-	-	-

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years; SOC=standard of care

NICE team request 3

The ERG has checked the extrapolations of OS and is satisfied that these are accurately reported in Table 4 of the company document (Table 3).

Table 3 Extrapolated OS rates in the standard of care arm (Company Table 4)

	Pembrolizumab			SOC		
Outcome	Base case 22-week cut-off	14-week cut-off	30-week cut-off	Base case 22-week cut-off	14-week cut-off	30-week cut-off
5-year OS	20.2%	18.3%	21.1%	2.4%	2.7%	4.5%

SOC=standard of care

1.2 ERG modifications to Table 2 and Table 6

NICE team request 4

The ERG has modified the results from Table 2 of the company document to reflect utility values capped at the population norm. These are shown in Table 4.

Table 4 Company Table 2 with utilities capped at population norm

Cut-off time	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
22-week cut-off					
Pembrolizumab	£72,131	2.04	£49,415	1.14	£43,243
SOC	£22,716	0.90	-	-	-
14-week cut-off					
Pembrolizumab	£71,493	1.95	£48,671	1.04	£46,822
SOC	£22,823	0.91	-	-	-
30-week cut-off					
Pembrolizumab	£72,464	2.09	£48,893	1.08	£45,129
SOC	£23,571	1.00	-	-	-

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; SOC=standard of care

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Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID990]

The experts (who are not able to attend the second committee meeting) were asked the following questions:

- In you expert opinion, what would be the **5-year OS rate** for patients with untreated stage IV NSCLC, who are EGFR/ALK negative and with PS of 0-1, and who are receiving chemotherapy (including patients in clinical trials)?

- Do you think that the above estimated 5-year OS rate would change if people not receiving chemotherapy and people not included in clinical trials were included in the estimate instead? If yes, what would be the estimated **5 year OS rate** for patients with untreated stage IV NSCLC, who are EGFR/ALK negative and with PS of 0-1, and who are **NOT** receiving chemotherapy (**excluding** patients in clinical trials)?

- Would you expect the OS rate to change if patients with stage III NSCLC were also included in the first estimate? If yes, what would be the estimated **5 year OS rate** for patients with untreated **stage III - IV** NSCLC, who are EGFR/ALK negative and with PS of 0-1, and who are receiving chemotherapy (including patients in clinical trials)?

Response from clinical expert

Many thanks for this email and the opportunity to feedback on these questions. I remember the discussion at the last meeting and really don't understand the Lung audit data mentioned or other references to outcome and suspect there must be misunderstanding as to what the data represent, or a bias within the datasets that we're not aware of.

I think that the 5 year OS rate in patients with stage IV NSCLC not harbouring either EGFR or ALK molecular changes who are PS 0-1 and receiving chemotherapy is very low, probably ~1%. Of course we don't know yet how much this will be effected by the 2nd line use of pembrolizumab in patients with PD-L1 >1%.

I actually don't think this 5 year OS rate be significantly worse even if patients don't receive chemotherapy. Chemotherapy does improve the median OS of course, to around 12-13 months, in this population, but I think the impact it has out at 5 years is minimal.

However, I do think it would be a little higher I stage III disease is included. Long term outcome is actually quite different between IIIa and IIIb disease so 5 year OS rate will be a little different depending which of these you include. Stage IIIB still has a miserable longer term outcome and I would think ~5% 5 year OS rate whilst IIIa is a little better, maybe more like 15-20%. Of course these outcomes are for these stage groups alone and the influence they have on 5 year outcome of mixed stage III and IV NSCLC will depend on the proportions of each. In clinical practice, stage IV is much more common than stage III NSCLC and so I would think that the 5 year OS rate of 'real world proportions' would probably be 6-7%.

Response from patient expert

[I] have consulted with British Thoracic Oncology Group colleagues this morning. I recall the discussion at the initial Appraisal Committee meeting. From memory, the ERG thought around 15% five year survival for untreated stage IV patients. And the manufacturer under 5%.

On discussion with clinicians, we feel the true rate is more close to 5% than 15% for all patients and close to 1% for those not having chemo and 5% for those having chemo. There does not appear to be any reliable data to base this on other than clinical experience.