NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (CDF review of TA600) [ID1683]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (CDF review of TA600) [ID1683]

Contents:

The following documents are made available to consultees and commentators:

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

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

2. **Comments on the Appraisal Consultation Document** from **MSD**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. British Thoracic Oncology Group (BTOG)

4. **Evidence Review Group critique of company comments on the ACD** prepared by ScHARR

5. **Evidence Review Group addendum of company comments on the ACD** prepared by ScHARR

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

Appraisal title

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	MSD	MSD appreciates the opportunity to respond to the Appraisal Consultation Document (ACD) for ID1683. In this response we also provide an updated economic model populated with the most recent data cut (September 2020) for the three relevant PD-L1 subgroups and the endpoints (progression-free survival (PFS), overall survival (OS) and time on treatment (ToT) from the KEYNOTE-407 study. Prior to responding in detail to the points in the ACD, MSD would like to clarify its position on three elements: 1) Population in which access is being sought in this appraisal 2) Subgroups relevant to NHS clinical practice and therefore suitable for decision making 3) Residual uncertainty in this appraisal and 4) Decision-making threshold **1) Population in which access is being sought** MSD is seeking ongoing access in the same population that had access in the Cancer Drugs Fund (CDF). That is, all patients with a PD-L1 tumour proportion score (TPS) of <50% (both TPS <1% and TPS 1% to 49%) and the subgroup of patients with TPS of 50% or more (TPS≥50%) who need an *urgent* clinical response. MSD is not seeking access in the broad TPS≥50% population. The company position is as follows: any patient with untreated, metastatic, squamous cell, non-small cell lung cancer (NSCLC) and a TPS ≥50% that *can* successfully be treated with pembrolizumab monotherapy *should* be treated with pembrolizumab monotherapy. However, in line with clinician	Comment noted. Thank you for stating your position. Thank you for clarifying the population in which access is sought. The committee discussed this at the second appraisal committee meeting. It concluded Pembrolizumab combination therapy should be considered in the same groups that had access in the Cancer Drugs Fund (see section 3.3 of the FAD).

			feedback and current access in the CDF, there is a population of patients with TPS≥50% that need an urgent clinical response. This urgent clinical need is specified in the Blueteq criteria as "*(e.g. major impending airway obstruction) so as to justify the use of the combination of pembrolizumab carboplatin and paclitaxel rather than pembrolizumab monotherapy …"*. As stated in the ACD, 'a few patients who need a rapid response may benefit from initial combination therapy with pembrolizumab chemotherapy.' This is consistent with the Final Appraisal Document in TA600 (pages 4-5), which summarises clinical expert feedback to committee in this appraisal that "*while most clinicians would use pembrolizumab monotherapy for people whose tumours express PD-L1 at 50% or higher, to avoid the additional toxicity of chemotherapy, a few people who need an urgent, rapid response may benefit from initial combination therapy with pembrolizumab and chemotherapy (for example, those with bulky central disease).*" These patients therefore require chemotherapy and as such, the comparator for TPS ≥50% patients with an urgent clinical need is chemotherapy (in line with the KEYNOTE-407 trial) and not pembrolizumab monotherapy. This position reduces uncertainty. The indirect treatment comparison (ITC) between pembrolizumab combination and pembrolizumab monotherapy becomes redundant. It also changes the decision-making threshold on the basis that these patients (i.e., the relevant population) likely meet the end of life criteria, detail provided below. **2) Subgroups relevant for decision making in line with NHS clinical practice** The company supports the conclusion on page 23 [section 3.15] of the ACD, "The committee agreed that its preferred cost-effectiveness analysis would include the weighted values for PD-L1 tumour proportion scores of less than 50% …". We note the statement on page 22 [section 3.13], "The committee recalled that it had considered this subgroup stratification [PD-L1 tumour proportion score less than 1% and 1% to 49%] not to be relevant to NHS clinical practice." Additionally, on page 12 [section 3.5], "[…the committee] would have preferred to see the economic model replicate clinical practice by basing the cost-effectiveness estimate on the PD-L1 subgroups seen in clinical practice." A consequence of this indication remaining in the CDF longer than anticipated due to delays related to COVID-19 is that there is evidence that differentiation by TPS <1% and 1% to 49% is relevant to NHS clinical policy and practice. This can be seen in both national COVID interim guidance and in routine	The committee considered the subgroups relevant for decision making at the second appraisal committee meeting. It considered it was appropriate to consider decision on the cost-effectiveness of the sub-groups based on the proportions using in the Cancer Drugs Fund. This has been reported in section 3.7 of the FAD.

use of pembrolizumab combination while in the CDF.

a. COVID interim guidance specifically identified the TPS 1-49% population for access to pembrolizumab monotherapy. This confirms that the <50% TPS population is not homogenous, and this is relevant for NHS policy making and routine clinical practice.

b. Market research data routinely collected between January 2020 up to July 2021 shows use across the three PD-L1 populations to be different to the split in the clinical trial. In routine NHS practice, the majority of pembrolizumab combination treatment in the CDF was in the 1-49% population.

Real world use of pembrolizumab combination therapy across PD-L1 TPS subgroups compared with subgroup distribution in KEYNOTE-407

PD-L1 TPS subgroup	Pembrolizumab combination therapy usage – June 2020	KEYNOTE-407 distribution
<1%	22%	35.5%
1-49%	68%	37.8%
≥50%	10%	26.7%
Source: IQVIA Market Research Data, July 2021		

On this basis the committee can be assured that using the approach of calculating the ICER weighted by PD-L1 subgroups is appropriate as it is reflective of routine NHS clinical practice. However, in order to represent the value of this indication to the NHS, the weighting of these subgroups should reflect real world usage rather than clinical trials.

This more accurate representation of value to the NHS reduces the weighted ICER for the subgroup that has a tumour proportion score of less than 50% from £33,862 to £30,943 using the ERG-preferred assumptions (based on September 2020 data cut and ERG amends to company economic model).

3) Residual uncertainty in this appraisal and the decision-making threshold

MSD is puzzled by the apparent level of uncertainty perceived by the committee and communicated in the ACD. We do not consider this an accurate reflection of the data package presented or reflective of

The committee addressed these issues of uncertainty at the second committee meeting.

			the ERG's comments on this appraisal. Page 5 of the ACD references four remaining areas of uncertainty: • uncertainty about the long-term treatment effect of pembrolizumab combination therapy on progression-free survival and overall survival • the fact that committee's preferred assumptions about subsequent immunotherapy use did not reflect experience in KEYNOTE-407 • the fact that the indirect comparison for the subgroup with a PD-L1 tumour proportion score of 50% or more presented in the company submission to the Cancer Drugs Fund review was not robust • uncertainty about whether pembrolizumab combination therapy meets NICE's end of life criteria. Taking each point in turn, the latest data cut (September 2020) provides Kaplan Meier (KM) PFS curves for more than 90% of the standard of care arm and more than 80% of the pembrolizumab combination arm. The KM OS curves are more than 80% complete for the SoC arm and more than 70% complete for the pembrolizumab combination arm. This is a mature and complete data package suitable for decision making. The ERG's conclusion as relates to MSD's survival modelling, "*The ERG does not have any major concerns regarding the company's updated modelling of OS within the overall ITT population*," ("ID1683 pembrolizumab ERG post FAC ERG report v2 170521 GK" page 45, section 4.4.2) demonstrates the company has taken a very plausible, conservative approach with any residual uncertainty is likely to favour the company's base case ICER estimates. On the very specific point of **long-term treatment effect**, we now have median follow up beyond three years. The committee's preference for treatment effect waning in PFS or OS at three years is not supported by the data. There is no structural change in the pembrolizumab KM curves at or around 36 months that would indicate loss of effect. With regards to **subsequent immunotherapy**, there are two options available. Neither is perfect. However, exploratory analyses indicate both approaches result in largely similar ICER estimates. The	

			company believes using the KEYNOTE-407 data on subsequent therapy produces ICERs that are too high, undervaluing pembrolizumab combination therapy. However, given there is no optimal way to adjust statistically to better reflect usual UK practice, the company is prepared to accept the "within trial" approach in order to expedite the conclusion of this appraisal. Any residual uncertainty is likely to favour the company's base case ICER estimates. The third point about the robustness of the **indirect treatment comparison** between pembrolizumab combination therapy and pembrolizumab monotherapy in the broad TPS ≥50% population is redundant as we are not seeking access in any patients for whom pembrolizumab monotherapy is a suitable treatment. The fourth point relates to the third. The subgroup of patients in the TPS ≥50% who have urgent clinical need represents only 11% of the population being considered in this appraisal. When the comparator is chemotherapy, and in a subgroup of patients with a need of urgent clinical response, this population is highly likely to meet the **end of life criteria.** Similarly, page 21 lists eight committee-preferred assumptions. MSD will accept six of these. The 7th point, waning of treatment effect between 3- and 5-years MSD cannot accept on the basis that we now have trial data beyond 3 years that does not show any change in PFS or OS at or around 36 months. The company does not agree with the ERG's position of treatment effect waning of OS at 5 years as there is no evidence to support this. However, the company is prepared to accept this to conclude this appraisal. Again, any residual uncertainty is likely to favour the company's base case ICER estimates. The 8th point, stratification around TPS of 50% is not reflective of the COVID-reality where we have seen that differentiation between <1% & 1-49% is relevant for UK clinical decision making and both national policy and market research data support this. **4) Decision making threshold** Given there is very little residual uncertainty and that there is improved clarity regarding the relevant population and therefore eligibility for the end of life criteria in the subgroup of TPS≥50%, MSD believes that the correct threshold against which to make a decision for this appraisal is £50,000, the end of life threshold. The company is confident that we are already below this threshold taking the above into account.	
2	Company	MSD	MSD is encouraged that the Appraisal Consultation Document acknowledges the following:	Comment noted. Thank you.

			• Data from the KEYNOTE-407 clinical trial demonstrates that pembrolizumab with carboplatin and paclitaxel [pembrolizumab combination therapy] is "…likely to be clinically effective compared with platinum-based chemotherapy for people with PD-L1 tumour proportion score of less than 50%" [page 10 section 3.4] and "effective at increasing progression-free survival in all PD-L1 subgroups." • People with untreated metastatic squamous NSCLC and their treating clinicians would welcome the continued availability of pembrolizumab combination therapy given the lack of other effective therapies for metastatic squamous NSCLC. • The committee recognised that for untreated metastatic squamous NSCLC, there is a high unmet need for both patients and healthcare professionals, and that pembrolizumab combination therapy is likely to be clinically effective. • The committee judged the company's economic model and choice of parametric models for overall and progression-free survival to be generally robust and appropriate for decision making. • The committee found that both the extension to life criterion and the short life expectancy criterion have both been likely met for the subgroup with PD-L1 scores of less than 50% MSD welcomes the comments above. In addition to the points made in the section 1, there are a number of issues we will respond to. We structure our response as follows: 1) Updated base case analysis with most recent data cut 2) Comments on the 'Why the committee made these recommendations' sections 3) Response to the 'outstanding areas of uncertainty' from page 5 of the ACD. 4) Additional points of clarification from the ACD	
3	Company	MSD	**<u>Updated economic model using ERG-preferred base case and Sept 2020 data cut</u>** **September 2020 additional data cut** The delay in this CDF review due to COVID-19 gave sufficient time for an additional data cut to be submitted. The September 2020 data provides a median time from randomization to data cut-off of 40.1	Comment noted.

months (33.1-49.4) and reveals results consistent with those from the Final Analysis (May 2019), as shown in Table 1 below.

Table 1 – Comparison of Overall Survival for ITT population: Final Analysis vs September 2020 data cut

	Final analysis (May 2019)	**September 2020 data cut**
Overall survival HR (95% CI)	0.71 (0.58-0.88)	0.71 (0.59-0.86)
Median OS – Pembro combo	17.1 months	17.2 months
Median OS – SoC Chemo	11.6 months	11.6 months

Using the ITT to illustrate the completeness of this dataset now: In the ITT analysis of the September 2020 data cut, OS and PFS events had occurred in 73.4% and 83.1% respectively in patients treated with pembrolizumab combination therapy and in 81.9% and 91.5% respectively of patients treated with standard chemotherapy. The equivalent proportion of events at the time pembrolizumab combination therapy was recommended to the CDF was 30.6% and 54.7% of OS and PFS events respectively, in patients treated with pembrolizumab combination therapy, and 42.7% and 70.1% of events for patients treated with chemotherapy. The evidence base now available to the committee is sufficiently robust and mature such that the cost-effectiveness estimates are no longer associated with any important uncertainty.

Updated economic model

MSD has fully updated the economic model for the three PD-L1 TPS subgroups with OS, PFS and ToT data from the September 2020 data cut. Cost-effectiveness results are shown below in Table 3 reflecting all the ERG's preferred assumptions and including the confidential discount for pembrolizumab and excluding confidential comparator discounts. We understand the committee preference includes an assumption for treatment effect waning in PFS and OS starting at 3 years that is not supported by the data nor reflects the ERG's preference. We do not include that assumption in any analysis presented herein.

MSD has aligned with the ERG's conservative base case survival modelling assumptions specified at the conclusion of TA600. The starting point of company's base case for this CDF Review uses conservative clinical estimates around progression-free-survival as agreed by the committee in appraisal TA600, termed "ERG's pessimistic analysis 6b". The ERG have not identified any plausible alternative survival assumptions

.

The committee considered the company's choice of parametric

and have noted that the company's survival models are the most clinically plausible.

The company conducted a comprehensive curve fitting exercise for the three subgroups with the Sept 2020 data cut. Coincidentally, the same parametric survival model parametric survival model, the log-logistic, was suitable for the ITT analysis as well as for the <1% and 1-49% TPS subgroups. The log-logistic, and to some extent log-normal, also provides good statistical fit according to AIC/BIC of the six parametric survival models considered, as shown below in **Error! Reference source not found.**.

Table 2 - Statistical fit to overall survival Kaplan-Meier data by PD-L1 TPS subgroup (September 2020 data cut)

Fitted Function	PD-L1 TPS <1%		Fitted Function	PD-L1 TPS 1-49%	
	AIC	BIC		AIC	BIC
Exponential	[redacted]	[redacted]	Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	Weibull	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	LogNormal	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	LogLogistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	Gompertz	[redacted]	[redacted]
GenGamma	[redacted]	[redacted]	GenGamma	[redacted]	[redacted]

Overlaying the log-logistic to the OS KM curves for the <1% and 1-49% TPS subgroups (see Figure 1 and Figure 2 below) highlights the good visual fit to the most mature survival data from KEYNOTE-407 for both treatment arms.

Figure 1 - Overall Survival in 1-49% TPS subgroup: KM data with log-logistic parametric survival model (September 2020 data cut)

[redacted]

models for overall and progression-free survival are appropriate for decision making (see section 3.8 of the FAD). The committee discussions around cost-effectiveness estimates are reported in section 3.14 of the FAD.

Figure 2 - Overall Survival in <1% TPS subgroup: KM data with log-logistic parametric survival model (September 2020 data cut)

Importantly, the cost-effectiveness estimates are not sensitive to the choice of log-logistic versus lognormal, and there is agreement between the ERG and the company that log-logistic is the most appropriate for the ITT analysis, on the basis that it is the most clinically plausible.

The results of the ERG preferred base case updated with the Sept 2020 data cut is provided below.

Table 3 – ERG-preferred base case cost-effectiveness results with confidential pembrolizumab discount and comparators at list price, September 2020 data cut

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
ITT population							
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]				
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,361
PD-L1 TPS <1%							
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]				
Pembrolizumab +	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,262

			Chemotherapy [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] **PD-L1 TPS 1-49%** Trial Chemotherapy Arm [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] Pembrolizumab + Chemotherapy [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] £30,639 **PD-L1 TPS ≥50%** Trial Chemotherapy Arm [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] Pembrolizumab + Chemotherapy [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] £26,213 The ICERs are stable for the ITT population and subgroups using ERG-preferred assumptions and comparing the September 2020 data cut with the Final Analysis (May 2019) data cut. Given the confirmatory results in the cost-effectiveness estimates based on the more mature September 2020 data in the updated economic model, MSD believes that any remaining uncertainty in the cost-effectiveness estimates is minimal likely to favour the company's base case ICER estimates.	
4	Company	MSD	**Why the committee made these recommendations:** The points in this section the company wishes to respond to are: 1) The lack of availability of nab-paclitaxel and any intimation this is a meaningful uncertainty in the economic evaluation 2) Comparing pembrolizumab combination therapy with pembrolizumab monotherapy, in the population with TPS ≥50% 3) Using subgroups as the basis for decision making 4) Eligibility for the end of life criteria **Generalisability of trial nab-paclitaxel outcomes** Page 3 of the ACD states "…in the NHS, carboplatin plus gemcitabine is the most commonly used platinum-based chemotherapy, and nab-paclitaxel is not available… So, the evidence does not capture how	Comment noted. Thank you. Thank you for clarifying the company position regarding the relevance of nab-paclitaxel. Any reference to the availability of nab-paclitaxel has been removed

			pembrolizumab combination therapy will be used in the NHS." MSD refutes the relevance of nab-paclitaxel not being available in the NHS given the statement in the Final Appraisal Document for TA600 (CDF entry for this indication): "During technical engagement, it was concluded that all standard chemotherapy treatments can be considered to be of equal efficacy, and therefore KEYNOTE-407 was relevant for decision making for this population" (NICE 2019. "Final appraisal document – Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer", page 5, section 3.2). The availability of nab-paclitaxel is not a source of uncertainty in the current CDF Review. The company requests this be removed from any future documents. **Comparing pembrolizumab combination with pembrolizumab monotherapy** We hope the company position is now clear on this point, but we will reiterate just in case. The company is not seeking access in the broad TPS ≥50% subgroup. MSD is seeking continued access for the approximately 10% of untreated, squamous, NSCLC patients that have TPS of 50% or more and *need an urgent clinical response*. As a consequence of this, the ITC for pembrolizumab combination therapy compared with pembrolizumab monotherapy becomes redundant as does paragraph 3.6 in the ACD. Clinical expert advice to MSD confirms that the urgency of clinical intervention requires chemotherapy, and therefore chemotherapy is the correct comparator for this population ([redacted] Consultant Oncologist, [redacted] South West England). Updated KEYNOTE-407 trial data for pembrolizumab combination therapy compared with chemotherapy in the TPS≥50% reports median OS of [redacted] months and [redacted] months respectively, an incremental median OS gain of [redacted] months. The population of relevance to this appraisal is a sicker subgroup of patients within the TPS≥50% population and as such they all meet the criteria of usual survival less than 24 months. If they did not, they would not have an urgent clinical need and therefore would be ineligible to receive	in the FAD. The committee discussions around treatment for metastatic squamous NSCLC are reported in section 3.2 of the FAD. Thank you section 3.6 in the original ACD has now been removed from the FAD. The committee's discussions around the end of life eligibility criteria are reported in section 3.12 and 3.13 of the FAD.

pembrolizumab combination therapy. Given the substantial benefit of pembrolizumab combination therapy compared to chemotherapy in this population, it is implausible that these patients would not have a survival gain substantial enough to warrant the full end of life modifier to be applied.

The company acknowledges it does not have the exact dataset from KEYNOTE-407 to match this real-world UK population (as this population is a product of the eligibility agreed at the point of CDF entry). However, we consider there is sufficient information and insight following use in NHS practice for two years to make the required decision.

Table 4 below reports the following PFS and OS outcomes for the TPS≥50% subgroup based on the trial data (reported as medians). For the median PFS and OS gains, pembrolizumab combination therapy is associated with a clinically meaningful benefit compared with standard chemotherapy.

Table 4 – PFS and OS outcomes for the TPS≥50% subgroup (September 2020 data)

	Median PFS	**Median OS**
Trial Chemotherapy Arm	[redacted] months	[redacted] months
Pembrolizumab + Chemotherapy	[redacted] months	[redacted] months

These outcomes result in an ICER of £26,213 per QALY gained compared with chemotherapy in a population highly likely to meet the end of life eligibility criteria. The company believes the end of life threshold is the threshold that should be used for decision making.

Subgroups as the basis for decision making

Decision making based on subgroups is a typical example of the tension in HTA decision making between maintaining the internal integrity of a clinical trial and presenting a case that is generalisable to the setting in which the technology will be delivered. What is critical is clarity regarding the scale of the resultant uncertainty.

Treatment and prognosis of squamous NSCLC are linked to PD-L1 status. There are three subgroups that

are relevant for decision making comprised of <1%, 1-49% and ≥50% TPS and this aligns with NHS policy and routine clinical use. Because of the structure of the trial, while there may be some underpowering in the subgroup analyses the results are still numerically profound, particularly considering this is an under-served patient population. The baseline characteristics provided in Appendix to this response do not indicate any differences between populations that would suggest the results are unsuitable to support decision making.

KEYNOTE-407 was stratified by <1% and ≥1% PD-L1 TPS, ensuring that treatment arms were well balanced for PD-L1 TPS. KEYNOTE-407 did not stratify for the TPS 1-49% population but the subgroup is well balanced both between arms and when compared to the population with TPS <1% (see in Appendix). This TPS≥50% subgroup was specified in the Terms of Reference for this appraisal due to the availability of a different comparator treatment available for the population with TPS≥50% and the requirement to compare to that.

The committee notes (on Page 10, section 3.4) there would be uncertainties associated with assessing the cost effectiveness for people with a PD-L1 TPS score of less <50% and ≥50% PD-L1 TPS because "*KEYNOTE-407 was not stratified in this way and any analysis that attempts to blend the subgroups can potentially break randomisation*." It is unclear why blending subgroups would potentially break randomization given the arms are well balanced across the three subgroups. Furthermore, given the size and well-balanced distribution to the <1% and 1-49% PD-L1 TPS subgroups, MSD does not believe that there are high levels of uncertainty inherent in these subgroup estimates.

Important new information that has become available due to the time this medicine has been used on the CDF is how usage across the groups differs in routine UK practice compared with the clinical trial, see again table below.

Table 5 - Real world use of pembrolizumab combination therapy across PD-L1 TPS subgroups compared with subgroup distribution in KEYNOTE-407

PD-L1 TPS subgroup	Pembrolizumab combination therapy usage – June 2020	KEYNOTE-407 distribution
<1%	22%	35.5%
1-49%	68%	37.8%
≥50%	10%	26.7%

Source: IQVIA Market Research Data, July 2021

Applying these weights gives a more accurate representation of value to the NHS of pembrolizumab combination therapy and results in an ICER estimate of £30,943 in the subgroup with TPS <50%.

Table 6 – Committee-preferred base case cost-effectiveness results for <%50 PD-L1 TPS subgroup based on real world usage data (Reflecting confidential pembrolizumab discount and comparators at list price, September 2020 data cut)

	Pembro combination therapy vs standard chemotherapy	
	Incremental QALYs	Incremental Costs
Unweighted results		
<1% PD-L1 TPS	[redacted]	[redacted]
1-49% PD-L1 TPS	[redacted]	[redacted]
Reweighted results		
<1% PD-L1 TPS	[redacted]	[redacted]
1-49% PD-L1 TPS	[redacted]	[redacted]
Weighted ICER in <50% PD-L1 TPS subgroup		
Pembrolizumab combination therapy vs standard chemotherapy		£30,943 per QALY

Given this population is eligible for end of life criteria, the company is confident this ICER would remain below the £50,000 end of life threshold when including confidential patient access scheme discounts for comparators.

Eligibility for End of Life

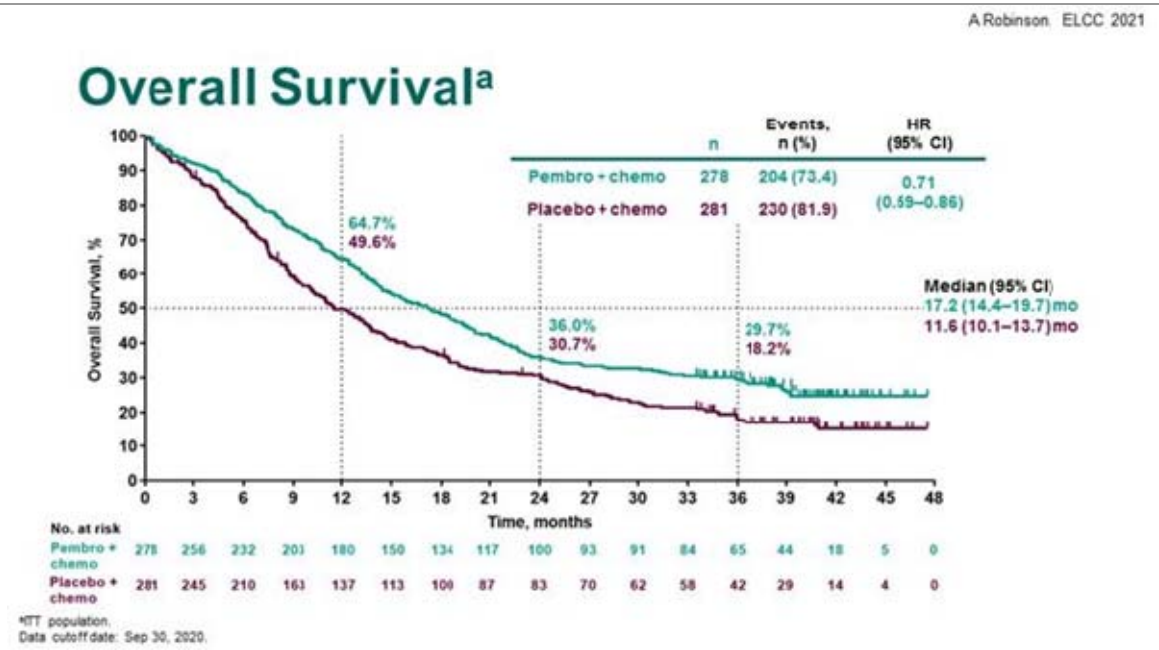
The company agrees it is highly likely that eligibility for End of Life is met for both populations with TPS <1% and TPS 1-49%. The company further asserts that the relevant population in the subgroup with TPS≥50% and urgent clinical need also meet the end of life criteria.

If the patient in this TPS ≥50% population is likely to survive more than 24 months without the addition of pembrolizumab, they explicitly do not meet the criteria for urgent clinical need. The incremental median OS difference between pembrolizumab combination therapy and chemotherapy is [redacted] months. Even accounting for the requested access in a sicker patient population, it is not plausible that the survival gain for patients

The committee further discussed eligibility for end of life at the second committee meeting. Its discussions are reported in section 3.12 and 3,13 of the FAD.

			treated with pembrolizumab combination would not be profound and suitable for application of the full end of life QALY multiplier. MSD's position is, if a person with untreated, metastatic, squamous, NSCLC can be treated with pembrolizumab monotherapy, this should be the first choice of treatment. However, patients with an urgent need for a clinical response need the immediacy of chemotherapy. The Blueteq criteria for this population in CDF states, "*the use of the combination of pembrolizumab, carboplatin and paclitaxel* ***rather than*** *pembrolizumab monotherapy*". In this, the relevant specific population requiring an urgent response, pembrolizumab monotherapy is not the appropriate comparator. Instead, chemotherapy is the appropriate comparator, and therefore comparison with chemotherapy is relevant for the assessment of end of life criteria met or not. Usage during the period in the CDF since August 2019 in over 1000 patients has enabled the committee to evaluate how many and what proportion of patients with ≥50% PD-L1 TPS actually meets the specific criteria for eligibility. The NHS England Cancer Drugs Fund Clinical Lead has confirmed in written communication that 11% of the entire cohort of squamous NSCLC patients who having received pembrolizumab combination therapy during the CDF period are ≥50% PD-L1 TPS and therefore have an urgent critical clinical need as deemed by their treating clinician ([redacted]). It is important to note that the criteria of "urgent clinical need" was introduced by NICE and NHSE at the point of entry to the CDF and did not form any part of the KEYNOTE-407 clinical trial protocol. As such, this population cannot be identified within the KEYNOTE-407 study population. However, MSD strongly assert that there is little doubt that this population meets the NICE End of Life criteria based on the following evidence: 1. Urgent clinical need implies a short survival, and there is clinical consensus that this survival would be less than 24 months in this population. By definition, if patients were not in such a severe health state they would be suitable candidates for pembrolizumab monotherapy and thus ineligible for pembrolizumab combination therapy per the current restrictions in the Cancer Drugs Fund.	

			2. The incremental OS gain in this population is profound: Median OS gain versus standard chemotherapy in KEYNOTE-407 was [redacted] months in the ≥50% PD-L1 TPS subgroup. Even if this survival gain is reduced in the ≥50% patient population with an urgent clinical need, the survival gain is highly likely to be profound and therefore suitable for application of the full end of life multiplier, compared with chemotherapy alone.	
5	Company	MSD	**<u>Responding to the remaining areas of uncertainty after then technical engagement stage:</u>** 1) Long-term treatment effect of pembrolizumab combination therapy on PFS and OS 2) Subsequent treatment 3) ITC of pembrolizumab combination therapy versus pembrolizumab monotherapy 4) Eligibility for end of life We consider points 3) and 4) to have been addressed (see above). **1) Long-term treatment effect** Page 16, section 3.9 of the Appraisal Consultation Document states "*A treatment effect lasting between 3 and 5 years is appropriate for decision making.*" As part of the Terms of Engagement, MSD submitted analysis consistent with "ERG's pessimistic analysis 6b", which included a 5-year duration of treatment effect for pembrolizumab combination therapy. Since long-term follow-up data became available from KEYNOTE-407, the committee have not reassessed the plausibility of this assumption based on a review of the OS hazards over time. Nor have the committee highlighted any evidence that a 5-year duration of treatment effect was *too* optimistic, and that a 3-year duration of treatment effect would be more plausible. Long-term OS KM data in the ITT population from the September 2020 data cut (shown below), provides no evidence that treatment effect on OS begins to wane in patients with follow-up beyond 36 months. **Figure 3 - Overall survival: ITT population in KEYNOTE-407 (September 2020 data)**	Comment noted. Thank you. Thank you for clarifying your position regarding a long-term treatment effect. The committee considered this further at the second committee meeting and these discussions are reported in section 3.10 of the FAD. It concluded a treatment effect lasting 5 years for both overall and progression-free survival is appropriate for decision making.

			 The company position is that there is no evidence to support the implementation of waning of treatment effect at 5 years, particularly not in PFS, given the maturity of this data this additional assumption is unwarranted. The company is prepared to accept the ERG's waning of treatment effect in OS at 5 years, in the absence of any supportive evidence, in order to conclude this appraisal. We note again uncertainty is more likely to favour the company ICER estimates on this point. **2) Costing of subsequent treatment assumptions** MSD acknowledges that the 15% of chemotherapy-treated patients later treated with chemotherapy as a subsequent therapy in KEYNOTE-407 represents a deviation from NHS clinical practice. Two methods for costing this second-line chemotherapy have been presented to committee. The company assumption reflects the clinical reality described unanimously by consultant oncologists in the UK that 100% of chemotherapy-treated patients who receive a second-line treatment would be treated with a PD-L1 inhibitor. The ERG assumption proposes to cost second-line chemotherapy based on treatment the pattern in the	Thank you for clarifying the company's position regarding the costing of subsequent treatments. The committee discussed this further at the second committee meeting. It concluded the Costs of subsequent treatment included in the economic model should reflect the treatments in KEYNOTE 407 (see section 3.9 of the FAD).

			clinical trial, preferring to align with the trial rather than UK clinical practice. The company has considered the use of methods adjust survival for this 15% of chemotherapy-treated patients based on the counterfactual assuming they had been able to receive a second-line PD-L1 inhibitor in the clinical trial. However, due to the small patient numbers, there is insufficient data to estimate a statistically robust adjustment to survival outcomes (e.g., via crossover adjustment methods) such that they would match what would be expected in NHS clinical practice. The ICER is moderately sensitive to the uncertainty around costing of subsequent therapies, and at a minimum, the committee should select the midpoint within the range of uncertainty between ERG and company assumptions.	
6	Company	MSD	**<u>Committee's preferred assumptions</u>** Page 21 of the ACD reports the committees eight preferred assumptions. The company can accept six of these. MSD's position is there needs to be a refinement of the assumption around stratification by PD-L1 subgroup. Rather than anchoring this around subgroups for the purposes of NICE assessment and available comparators, we think the three relevant subgroups need to be considered to align with NHS policy making, NHS clinical practice and, as stated in the ACD difference in prognosis and potential differences in the clinical effect of pembrolizumab combination, PD-L1 score. Taking account of the three subgroups is critical to ensure the correct value to the NHS is determined, as this indication is not used equally in these three subgroups <1%, 1-49% and ≥50%. The one assumption we cannot accept, discussed above, is an implementation of the waning of treatment effect at three years for either PFS or OS as we have trial data that refutes this. The important conclusion to draw here, is that while there is a point that the company considers to be counter to the available evidence, and new information has become available that allows better assessment of the value of this indication to the NHS, there is substantial acceptance of the ERG and committee's position. The evidence package is mature, the extrapolation is robust and, "the most clinically plausible 5-year and 10-year survival estimates" (page 14 section 3.7). Any suggestion that there is a high degree of uncertainty in this appraisal is not a fair reflection of the data or the modelling approach taken. Neither does	Comment noted. Thank you for clarifying the company's position regarding the committee's preferred assumptions. The committee discussed these further at the second committee meeting. Its discussions are reported in section 3.14 of the FAD.

			this recognise that pembrolizumab combination therapy is an innovative technology in the treatment of squamous NSCLC, a disproportionally under-served patient population.	
7	Company	MSD	**Poor outcomes associated with the squamous histology of NSCLC** Page 6, section 3.1 of the Appraisal Consultation Document states: "*People with squamous NSCLC often have a poor quality of life, and a potential extension to life is important to them. Outcomes tend to be worse with squamous NSCLC than with non-squamous NSCLC because people have a higher prevalence of smoking-related comorbidities. For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score less than 50%, outcomes are particularly poor.*" MSD notes the relatively poor outcomes associated with squamous NSCLC associated with smoking-related comorbidities are more likely to impact people from lower socio-economic groups given the higher rates of smoking among this population.[1] Whilst the committee did not identify any equalities issues, MSD believes there are significant equity issues, particularly for those patients with squamous disease that have a TPS of <1% or 1-49%. The committee should consider the socio-economic determinants of health inequality that lead to increased smoking rates as context to their decision making.	Comment noted. Thank you. The committee discussed these equality issues at the second committee meeting. Its discussions around equalities are documented in section 3.16 of the FAD.
8	Company	MSD	**Updated PD-L1 TPS subgroup analysis based on September 2020 data cut** Page 8, section 3.3 of the Appraisal Consultation Document states "*At response to technical engagement, the company provided additional overall survival data from a later follow up of KEYNOTE-407 (data cut September 2020). It wanted the committee to consider data only from the whole intention-to-treat population rather than from the PD-L1 subgroups.*" MSD wishes to apologise for any misunderstanding and confirm (as stated above) that we believe it to be appropriate and necessary to consider the 3 subgroup populations. We would also clarify that at the time of technical engagement, MSD was only able to provide ITT OS results from the September 2020 data cut. We have since updated the subgroup analyses within the economic model and this is submitted as part of this	Comment noted. Thank you for providing the updated subgroup analyses. The committee considered this at the second committee meeting. Its discussions and conclusion is reported in section 3.5 of the FAD.

[1] "The role of patient, tumour and system factors in socioeconomic inequalities in lung cancer treatment: population-based study." Br J Cancer. 2014 Jul 29; 111(3): 608–618.

			Appraisal Consultation Document response. Given the size and well-balanced distribution to the <1% and 1-49% PD-L1 TPS subgroups, MSD does not believe that there are high levels of uncertainty inherent in these subgroup estimates.	
9	Company	MSD	**Decision-making cost-effectiveness threshold** In the discussion pertaining to decision making thresholds in the ACD the text references NICE's guide to the methods of technology appraisal and notes that: • Above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. • The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The longer text also refers to innovation, NHS (non-health) priorities and quality of life not captured in the QALY measure. We note the ACD focus on uncertainty – we assume to drive a lower decision-making threshold. It is critical that there is understanding uncertainty works in both directions (against and in favour of company/ERG assumptions). In this case we would consider the uncertainties sufficiently well balanced, and in the context of mature data, that there is as little uncertainty in this appraisal as any NICE assessment. We also note committees have discretion to consider unmet need and inequalities in their deliberation. Squamous NSCLC patients have long been the poor relations in lung cancer treatment, and this should be explicitly acknowledged in committee decision making. The <50% PD-L1 TPS subgroup represents 89% of use of the pembrolizumab combination therapy in current clinical practice based on market research data obtained by MSD and confirmed by NHSE. Should the committee decide to use a different threshold for the subgroup with PD-L1 TPS ≥50%, a weighted threshold should be calculated based on the 89% vs 11% split between the <50% and ≥50% PD-L1 TPS	Comment noted. Thank you. The committee decisions around cost-effectiveness estimates are reported in section 3.14 of the FAD. Thank you. The committee considered these issues in its decision making. Its discussions around the clinical need for pembrolizumab combination therapy are documented in section 3.1 of the FAD. The committee's discussions around equalities are documented in section 3.16 of the FAD. Thank you. The committee's discussions around the weighted analysis of the PD-L1 <50% subgroup are reported in section 3.7 of the FAD.

			subgroups. (The <50% PD-L1 subgroup is grouped together in this calculation given the committee has agreed that End of Life criteria have been met in this population.) In a hypothetical example where the committee decides to use a £30,000/QALY threshold for the subgroup with PD-L1 TPS ≥50%, the decision-making threshold should be calculated as follows: 89% * £50,000 + 11% * £30,000 = £47,800 per QALY gained In this way, the decision-making threshold would reflect the true value for money to the NHS of a medicine which is overwhelmingly used for treatment of an end of life indication. In the event end of life criteria are not met for the ≥50% PD-L1 TPS subgroup, a conclusion MSD would strongly disagree with, MSD believes there is a clear evidence that it would be appropriate for the committee to apply a £30,000 (rather than £20,000) per QALY decision-making threshold for the ≥50% PD-L1 TPS subgroup, to be included in the weighted threshold calculation described above, based on the following evidence: • Over 2.5 years additional data collection from KEYNOTE-407 since TA600 which recommended pembrolizumab combination therapy to the Cancer Drugs Fund • High unmet need in the squamous metastatic NSCLC population • Clinically meaningful survival benefits seen with pembrolizumab combination therapy which have remained stable after 40 months median follow-up (time from randomization to data cutoff) • Possible equalities issues resulting from squamous NSCLC disproportionally affecting people in lower income socio-economic groups • Alignment between company and ERG survival modelling assumptions	
10	Company	MSD	MSD requests clarification of the text on page 22 and 23 of the ACD to ensure it is clear that the comparison that is being referred to is pembrolizumab combination therapy compared with pembrolizumab monotherapy. Given much of the rest of the document refers to a comparison to chemotherapy and given MSD's position not to seek access for pembrolizumab combination therapy in patients that can successfully be treated with pembrolizumab monotherapy, two clarifications are needed. The first, that this is not the population for whom MSD is seeking access, and the second, that the comparison is versus pembrolizumab monotherapy (for example in the discussion about south west quadrants and at the top of page 23).	Comment noted. Thank you. This section of the ACD (ACD section 3.13) referred to the committees discussions on the cost effectiveness estimates and was discussed at the first committee meeting. This section has now been updated in the FAD Please see section 3.14 in the FAD to

				reflect the committee discussions at the second committee meeting.
11	Consultee	British Thoracic Oncology Group	Page 6, section 3.1: *"the role of biomarkers such as PD-L1 to predict the cancers most likely to respond to immunotherapy is less well established in squamous NSCLC than in non-squamous NSCLC".* We do not agree with this statement. Most thoracic oncologists would view a PD-L1 negative, low (1-49%) or high (>50%) result in squamous and non-squamous as equally useful in terms of directing anti-cancer therapy. In clinical practice, there is not a significant difference between the role of PD-L1 in squamous and non-squamous lung cancer.	Comment noted. Thank you. We have now updated section 3.1 of the FAD to report the committee discussions around clinical need following the second committee meeting.
12	Consultee	British Thoracic Oncology Group	Page 10, section 3.4: *"The committee agreed that stratifying clinical evidence by these 3 PD-L1 subgroups [<1%, 1-49%, >50%] was not generalisable to NHS clinical practice".* We do not agree with this statement, which is important because it is a central tenet of the committee's reasoning. Although it is correct that current therapeutic options for squamous cell NSCLC available on the NHS only differ between PD-L1 >50% (single-agent Pembrolizumab) and PD-L1 <50% (Pembrolizumab, Paclitaxel and Carboplatin), in practice most thoracic oncologists would still categorise patients into low (<1%), weak (1-49%) and high (>50%) when assessing a patient's tumour type and making treatment decisions. Indeed, after histology sub-type (squamous vs. non-squamous) this is the most important pathological characteristic. Whether a squamous cell carcinoma is negative or weak positive would influence how an oncologist would view the relative benefits of 1st and 2nd line treatment options.	Comment noted. Thank you. Following the second committee meeting this sentence has been removed and section 3.4 of the FAD has been updated to reflect the committee discussions.
12	Consultee	British Thoracic Oncology Group	Page 10, section 3.4: *"The committee concluded that pembrolizumab combination therapy is likely to be clinically effective compared with platinum-based chemotherapy for people with PD-L1 tumour proportion score of less than 50%. However, there is uncertainty over the exact overall survival estimates because of the how the subgroups were stratified."* It seems unfair to dismiss the 3-level PD-L1 stratification (see point 2 above), which is universally used by practising oncologists, instead require a PD-L1 <50% or >50% stratification, and then focus on the uncertainty of the precise benefit of Pembrolizumab combination in the <50% group.	Comment noted. Thank you. The committee further discussed the clinical evidence for the PD-L1 subgroups at the second committee meeting. Please see section 3.4 of the FAD for the committee considerations
13	Consultee	British Thoracic Oncology Group	Page 15, section 3.8: *"But the ERG noted that this was inconsistent with the experience of people in KEYNOTE-407, in which a few people had chemotherapy alone as subsequent treatment."* There are always some patients who would not receive immunotherapy as subsequent line therapy after 1st line chemotherapy (for example, if significant auto-immune conditions). However, they would very much be in the minority and it is the case that immunotherapy is the standard of care. This is even more the case now, compared to when KEYNOTE-407 was running, because 2nd line immunotherapy was not as widely available in all countries as it is now.	Comment noted. The committee discussed the assumptions regarding the costs of subsequent treatments further at the second committee meeting. It concluded the costs of subsequent treatment included in the economic model should

			In the Committee papers provided by NICE, the details of subsequent therapies (page 44) were redacted, and so it is not possible to be more precise with respect to this objection. But it should be noted that there were a large number of chemotherapy regimens listed as 2nd line treatments given, which would not be used on the NHS. *"The ERG used an alternative approach in its preferred base case, in which the costs of chemotherapy were only applied to people who had subsequent-line treatment. This included the people in KEYNOTE-407 who had subsequent chemotherapy."* We do not agree with the approach taken by the ERG here. This does not reflect clinical practice. We agree with the Clinical Experts in this respect.	reflect the treatments in KEYNOTE 407. This is reported in section 3.8 of the FAD

NICE National Institute for Health and Care Excellence

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

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

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Name of commentator person completing form:	Carl Selya-Hammer
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	MSD appreciates the opportunity to respond to the Appraisal Consultation Document (ACD) for ID1683. In this response we also provide an updated economic model populated with the most recent data cut (September 2020) for the three relevant PD-L1 subgroups and the endpoints (progression-free survival (PFS), overall survival (OS) and time on treatment (ToT) from the KEYNOTE-407 study. Prior to responding in detail to the points in the ACD, MSD would like to clarify its position on three elements: 1) Population in which access is being sought in this appraisal 2) Subgroups relevant to NHS clinical practice and therefore suitable for decision making 3) Residual uncertainty in this appraisal and 4) Decision-making threshold **1) Population in which access is being sought** MSD is seeking ongoing access in the same population that had access in the Cancer Drugs Fund (CDF). That is, all patients with a PD-L1 tumour proportion score (TPS) of <50% (both TPS <1% and TPS 1% to 49%) and the subgroup of patients with TPS of 50% or more (TPS≥50%) who need an *urgent* clinical response. MSD is not seeking access in the broad TPS≥50% population. The company position is as follows: any patient with untreated, metastatic, squamous cell, non-small cell lung cancer (NSCLC) and a TPS ≥50% that *can* successfully be treated with pembrolizumab monotherapy *should* be treated with pembrolizumab monotherapy. However, in line with clinician feedback and current access in the CDF,

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	there is a population of patients with TPS≥50% that need an urgent clinical response. This urgent clinical need is specified in the Blueteq criteria as "*(e.g. major impending airway obstruction) so as to justify the use of the combination of pembrolizumab carboplatin and paclitaxel rather than pembrolizumab monotherapy …"*. As stated in the ACD, 'a few patients who need a rapid response may benefit from initial combination therapy with pembrolizumab chemotherapy.' This is consistent with the Final Appraisal Document in TA600 (pages 4-5), which summarises clinical expert feedback to committee in this appraisal that "*while most clinicians would use pembrolizumab monotherapy for people whose tumours express PD-L1 at 50% or higher, to avoid the additional toxicity of chemotherapy, a few people who need an urgent, rapid response may benefit from initial combination therapy with pembrolizumab and chemotherapy (for example, those with bulky central disease).*" These patients therefore require chemotherapy and as such, the comparator for TPS ≥50% patients with an urgent clinical need is chemotherapy (in line with the KEYNOTE-407 trial) and not pembrolizumab monotherapy. This position reduces uncertainty. The indirect treatment comparison (ITC) between pembrolizumab combination and pembrolizumab monotherapy becomes redundant. It also changes the decision-making threshold on the basis that these patients (i.e., the relevant population) likely meet the end of life criteria, detail provided below. **2) Subgroups relevant for decision making in line with NHS clinical practice** The company supports the conclusion on page 23 [section 3.15] of the ACD, "The committee agreed that its preferred cost-effectiveness analysis would include the weighted values for PD-L1 tumour proportion scores of less than 50% …". We note the statement on page 22 [section 3.13], "The committee recalled that it had considered this subgroup stratification [PD-L1 tumour proportion score less than 1% and 1% to 49%] not to be relevant to NHS clinical practice." Additionally, on page 12 [section 3.5], "[…the committee] would have preferred to see the economic model replicate clinical practice by basing the cost-effectiveness estimate on the PD-L1 subgroups seen in clinical practice." A consequence of this indication remaining in the CDF longer than anticipated due to delays related to COVID-19 is that there is evidence that differentiation by TPS <1% and 1% to 49% is relevant to NHS clinical policy and practice. This can be seen in

both national COVID interim guidance and in routine use of pembrolizumab combination while in the CDF.

a. COVID interim guidance specifically identified the TPS 1-49% population for access to pembrolizumab monotherapy. This confirms that the <50% TPS population is not homogenous, and this is relevant for NHS policy making and routine clinical practice.
b. Market research data routinely collected between January 2020 up to July 2021 shows use across the three PD-L1 populations to be different to the split in the clinical trial. In routine NHS practice, the majority of pembrolizumab combination treatment in the CDF was in the 1-49% population.

Real world use of pembrolizumab combination therapy across PD-L1 TPS subgroups compared with subgroup distribution in KEYNOTE-407

PD-L1 TPS subgroup	Pembrolizumab combination therapy usage – June 2020	KEYNOTE-407 distribution
<1%	22%	35.5%
1-49%	68%	37.8%
≥50%	10%	26.7%

Source: IQVIA Market Research Data, July 2021

On this basis the committee can be assured that using the approach of calculating the ICER weighted by PD-L1 subgroups is appropriate as it is reflective of routine NHS clinical practice. However, in order to represent the value of this indication to the NHS, the weighting of these subgroups should reflect real world usage rather than clinical trials.

This more accurate representation of value to the NHS reduces the weighted ICER for the subgroup that has a tumour proportion score of less than 50% from £33,862 to £30,943 using the ERG-preferred assumptions (based on September 2020 data cut and ERG amends to company economic model).

3) Residual uncertainty in this appraisal and the decision-making threshold

MSD is puzzled by the apparent level of uncertainty perceived by the committee and communicated in the ACD. We do not consider this an accurate reflection of the data package presented or reflective of the ERG's comments on this appraisal.

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	Page 5 of the ACD references four remaining areas of uncertainty: • uncertainty about the long-term treatment effect of pembrolizumab combination therapy on progression-free survival and overall survival • the fact that committee's preferred assumptions about subsequent immunotherapy use did not reflect experience in KEYNOTE-407 • the fact that the indirect comparison for the subgroup with a PD-L1 tumour proportion score of 50% or more presented in the company submission to the Cancer Drugs Fund review was not robust • uncertainty about whether pembrolizumab combination therapy meets NICE's end of life criteria. Taking each point in turn, the latest data cut (September 2020) provides Kaplan Meier (KM) PFS curves for more than 90% of the standard of care arm and more than 80% of the pembrolizumab combination arm. The KM OS curves are more than 80% complete for the SoC arm and more than 70% complete for the pembrolizumab combination arm. This is a mature and complete data package suitable for decision making. The ERG's conclusion as relates to MSD's survival modelling, "*The ERG does not have any major concerns regarding the company's updated modelling of OS within the overall ITT population*," ("ID1683 pembrolizumab ERG post FAC ERG report v2 170521 GK" page 45, section 4.4.2) demonstrates the company has taken a very plausible, conservative approach with any residual uncertainty is likely to favour the company's base case ICER estimates. On the very specific point of **long-term treatment effect**, we now have median follow up beyond three years. The committee's preference for treatment effect waning in PFS or OS at three years is not supported by the data. There is no structural change in the pembrolizumab KM curves at or around 36 months that would indicate loss of effect. With regards to **subsequent immunotherapy**, there are two options available. Neither is perfect. However, exploratory analyses indicate both approaches result in largely similar ICER estimates. The company believes using the KEYNOTE-407 data on subsequent therapy produces ICERs that are too high, undervaluing pembrolizumab combination therapy. However, given there is no optimal way to

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	adjust statistically to better reflect usual UK practice, the company is prepared to accept the "within trial" approach in order to expedite the conclusion of this appraisal. Any residual uncertainty is likely to favour the company's base case ICER estimates. The third point about the robustness of the **indirect treatment comparison** between pembrolizumab combination therapy and pembrolizumab monotherapy in the broad TPS ≥50% population is redundant as we are not seeking access in any patients for whom pembrolizumab monotherapy is a suitable treatment. The fourth point relates to the third. The subgroup of patients in the TPS ≥50% who have urgent clinical need represents only 11% of the population being considered in this appraisal. When the comparator is chemotherapy, and in a subgroup of patients with a need of urgent clinical response, this population is highly likely to meet the **end of life criteria.** Similarly, page 21 lists eight committee-preferred assumptions. MSD will accept six of these. The 7th point, waning of treatment effect between 3- and 5-years MSD cannot accept on the basis that we now have trial data beyond 3 years that does not show any change in PFS or OS at or around 36 months. The company does not agree with the ERG's position of treatment effect waning of OS at 5 years as there is no evidence to support this. However, the company is prepared to accept this to conclude this appraisal. Again, any residual uncertainty is likely to favour the company's base case ICER estimates. The 8th point, stratification around TPS of 50% is not reflective of the COVID-reality where we have seen that differentiation between <1% & 1-49% is relevant for UK clinical decision making and both national policy and market research data support this. **4) Decision making threshold** Given there is very little residual uncertainty and that there is improved clarity regarding the relevant population and therefore eligibility for the end of life criteria in the subgroup of TPS≥50%, MSD believes that the correct threshold against which to make a decision for this appraisal is £50,000, the end of life threshold. The company is confident that we are already below this threshold taking the above into account.

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2	MSD is encouraged that the Appraisal Consultation Document acknowledges the following: • Data from the KEYNOTE-407 clinical trial demonstrates that pembrolizumab with carboplatin and paclitaxel [pembrolizumab combination therapy] is "…likely to be clinically effective compared with platinum-based chemotherapy for people with PD-L1 tumour proportion score of less than 50%" [page 10 section 3.4] and "effective at increasing progression-free survival in all PD-L1 subgroups." • People with untreated metastatic squamous NSCLC and their treating clinicians would welcome the continued availability of pembrolizumab combination therapy given the lack of other effective therapies for metastatic squamous NSCLC. • The committee recognised that for untreated metastatic squamous NSCLC, there is a high unmet need for both patients and healthcare professionals, and that pembrolizumab combination therapy is likely to be clinically effective. • The committee judged the company's economic model and choice of parametric models for overall and progression-free survival to be generally robust and appropriate for decision making. • The committee found that both the extension to life criterion and the short life expectancy criterion have both been likely met for the subgroup with PD-L1 scores of less than 50% MSD welcomes the comments above. In addition to the points made in the section 1, there are a number of issues we will respond to. We structure our response as follows: 1) Updated base case analysis with most recent data cut 2) Comments on the 'Why the committee made these recommendations' sections 3) Response to the 'outstanding areas of uncertainty' from page 5 of the ACD. 4) Additional points of clarification from the ACD
3	**Updated economic model using ERG-preferred base case and Sept 2020 data cut** **September 2020 additional data cut**

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The delay in this CDF review due to COVID-19 gave sufficient time for an additional data cut to be submitted. The September 2020 data provides a median time from randomization to data cut-off of 40.1 months (33.1-49.4) and reveals results consistent with those from the Final Analysis (May 2019), as shown in Table 1 below.

Table 1 – Comparison of Overall Survival for ITT population: Final Analysis vs September 2020 data cut

	Final analysis (May 2019)	**September 2020 data cut**
Overall survival HR (95% CI)	0.71 (0.58-0.88)	0.71 (0.59-0.86)
Median OS – Pembro combo	17.1 months	17.2 months
Median OS – SoC Chemo	11.6 months	11.6 months

Using the ITT to illustrate the completeness of this dataset now: In the ITT analysis of the September 2020 data cut, OS and PFS events had occurred in 73.4% and 83.1% respectively in patients treated with pembrolizumab combination therapy and in 81.9% and 91.5% respectively of patients treated with standard chemotherapy. The equivalent proportion of events at the time pembrolizumab combination therapy was recommended to the CDF was 30.6% and 54.7% of OS and PFS events respectively, in patients treated with pembrolizumab combination therapy, and 42.7% and 70.1% of events for patients treated with chemotherapy. The evidence base now available to the committee is sufficiently robust and mature such that the cost-effectiveness estimates are no longer associated with any important uncertainty.

Updated economic model

MSD has fully updated the economic model for the three PD-L1 TPS subgroups with OS, PFS and ToT data from the September 2020 data cut. Cost-effectiveness results are shown below in Table 3 reflecting all the ERG's preferred assumptions and including the confidential discount for pembrolizumab and excluding confidential comparator discounts. We understand the committee preference includes an assumption for treatment effect waning in PFS and OS starting at 3 years that is not supported by the data nor reflects the ERG's preference. We do not include that assumption in any analysis presented herein.

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MSD has aligned with the ERG's conservative base case survival modelling assumptions specified at the conclusion of TA600. The starting point of company's base case for this CDF Review uses conservative clinical estimates around progression-free-survival as agreed by the committee in appraisal TA600, termed "ERG's pessimistic analysis 6b". The ERG have not identified any plausible alternative survival assumptions and have noted that the company's survival models are the most clinically plausible.

The company conducted a comprehensive curve fitting exercise for the three subgroups with the Sept 2020 data cut. Coincidentally, the same parametric survival model parametric survival model, the log-logistic, was suitable for the ITT analysis as well as for the <1% and 1-49% TPS subgroups. The log-logistic, and to some extent log-normal, also provides good statistical fit according to AIC/BIC of the six parametric survival models considered, as shown below in **Error! Reference source not found.**.

Table 2 - Statistical fit to overall survival Kaplan-Meier data by PD-L1 TPS subgroup (September 2020 data cut)

Fitted Function	PD-L1 TPS <1%		Fitted Function	PD-L1 TPS 1-49%	
	AIC	BIC		AIC	BIC
Exponential	[redacted]	[redacted]	Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	Weibull	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	LogNormal	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	LogLogistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	Gompertz	[redacted]	[redacted]
GenGamma	[redacted]	[redacted]	GenGamma	[redacted]	[redacted]

Overlaying the log-logistic to the OS KM curves for the <1% and 1-49% TPS subgroups (see Figure 1 and Figure 2 below) highlights the good visual fit to the most mature survival data from KEYNOTE-407 for both treatment arms.

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Figure 1 - Overall Survival in 1-49% TPS subgroup: KM data with log-logistic parametric survival model (September 2020 data cut)

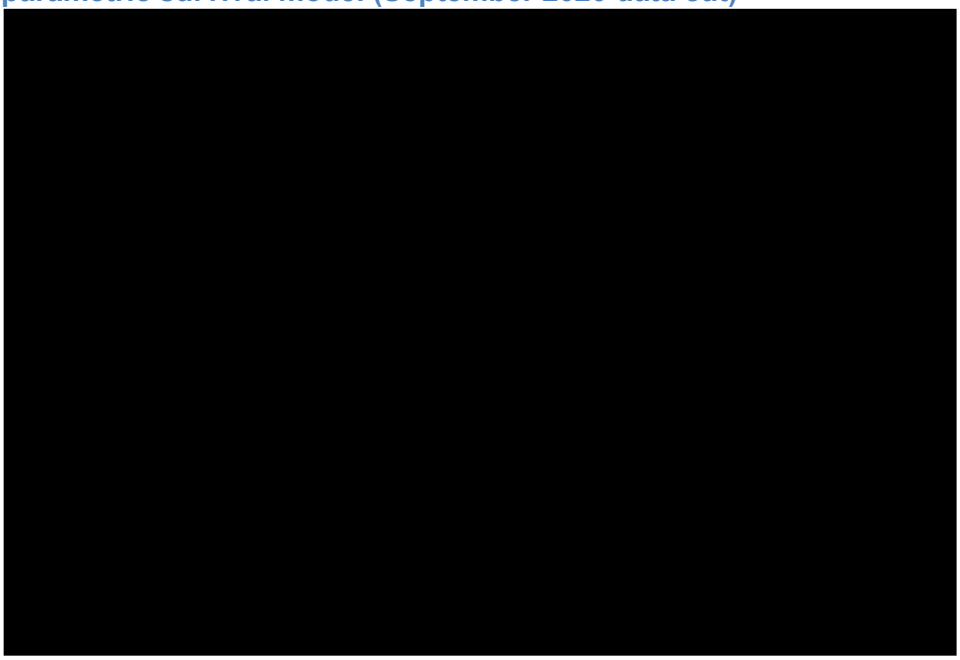

Figure 2 - Overall Survival in <1% TPS subgroup: KM data with log-logistic parametric survival model (September 2020 data cut)

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Importantly, the cost-effectiveness estimates are not sensitive to the choice of log-logistic versus lognormal, and there is agreement between the ERG and the company that log-logistic is the most appropriate for the ITT analysis, on the basis that it is the most clinically plausible.

The results of the ERG preferred base case updated with the Sept 2020 data cut is provided below.

Table 3 – ERG-preferred base case cost-effectiveness results with confidential pembrolizumab discount and comparators at list price, September 2020 data cut

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
ITT population							
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]				
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,361
PD-L1 TPS <1%							
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]				
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,262
PD-L1 TPS 1-49%							
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]				
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,639
PD-L1 TPS ≥50%							
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]				
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,213

The ICERs are stable for the ITT population and subgroups using ERG-preferred assumptions and comparing the September 2020 data cut with the Final Analysis (May 2019) data cut.

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	Given the confirmatory results in the cost-effectiveness estimates based on the more mature September 2020 data in the updated economic model, MSD believes that any remaining uncertainty in the cost-effectiveness estimates is minimal likely to favour the company's base case ICER estimates.
4	**Why the committee made these recommendations:** The points in this section the company wishes to respond to are: 1) The lack of availability of nab-paclitaxel and any intimation this is a meaningful uncertainty in the economic evaluation 2) Comparing pembrolizumab combination therapy with pembrolizumab monotherapy, in the population with TPS ≥50% 3) Using subgroups as the basis for decision making 4) Eligibility for the end of life criteria **Generalisability of trial nab-paclitaxel outcomes** Page 3 of the ACD states "…in the NHS, carboplatin plus gemcitabine is the most commonly used platinum-based chemotherapy, and nab-paclitaxel is not available… So, the evidence does not capture how pembrolizumab combination therapy will be used in the NHS." MSD refutes the relevance of nab-paclitaxel not being available in the NHS given the statement in the Final Appraisal Document for TA600 (CDF entry for this indication): "During technical engagement, it was concluded that all standard chemotherapy treatments can be considered to be of equal efficacy, and therefore KEYNOTE-407 was relevant for decision making for this population" (NICE 2019. "Final appraisal document – Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer", page 5, section 3.2). The availability of nab-paclitaxel is not a source of uncertainty in the current CDF Review. The company requests this be removed from any future documents.

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	Comparing pembrolizumab combination with pembrolizumab monotherapy We hope the company position is now clear on this point, but we will reiterate just in case. The company is not seeking access in the broad TPS ≥50% subgroup. MSD is seeking continued access for the approximately 10% of untreated, squamous, NSCLC patients that have TPS of 50% or more and *need an urgent clinical response*. As a consequence of this, the ITC for pembrolizumab combination therapy compared with pembrolizumab monotherapy becomes redundant as does paragraph 3.6 in the ACD. Clinical expert advice to MSD confirms that the urgency of clinical intervention requires chemotherapy, and therefore chemotherapy is the correct comparator for this population ([redacted] Consultant Oncologist, [redacted] South West England). Updated KEYNOTE-407 trial data for pembrolizumab combination therapy compared with chemotherapy in the TPS≥50% reports median OS of [redacted] months and [redacted] months respectively, an incremental median OS gain of [redacted] months. The population of relevance to this appraisal is a sicker subgroup of patients within the TPS≥50% population and as such they all meet the criteria of usual survival less than 24 months. If they did not, they would not have an urgent clinical need and therefore would be ineligible to receive pembrolizumab combination therapy. Given the substantial benefit of pembrolizumab combination therapy compared to chemotherapy in this population, it is implausible that these patients would not have a survival gain substantial enough to warrant the full end of life modifier to be applied. The company acknowledges it does not have the exact dataset from KEYNOTE-407 to match this real-world UK population (as this population is a product of the eligibility agreed at the point of CDF entry). However, we consider there is sufficient information and insight following use in NHS practice for two years to make the required decision. Table 4 below reports the following PFS and OS outcomes for the TPS≥50% subgroup based on the trial data (reported as medians). For the median PFS and OS gains, pembrolizumab combination therapy is associated with a clinically meaningful benefit compared with standard chemotherapy.

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Table 4 – PFS and OS outcomes for the TPS≥50% subgroup (September 2020 data)

	Median PFS	Median OS
Trial Chemotherapy Arm	***** months	***** months
Pembrolizumab + Chemotherapy	***** months	***** months

These outcomes result in an ICER of £26,213 per QALY gained compared with chemotherapy in a population highly likely to meet the end of life eligibility criteria. The company believes the end of life threshold is the threshold that should be used for decision making.

Subgroups as the basis for decision making

Decision making based on subgroups is a typical example of the tension in HTA decision making between maintaining the internal integrity of a clinical trial and presenting a case that is generalisable to the setting in which the technology will be delivered. What is critical is clarity regarding the scale of the resultant uncertainty.

Treatment and prognosis of squamous NSCLC are linked to PD-L1 status. There are three subgroups that are relevant for decision making comprised of <1%, 1-49% and ≥50% TPS and this aligns with NHS policy and routine clinical use. Because of the structure of the trial, while there may be some underpowering in the subgroup analyses the results are still numerically profound, particularly considering this is an under-served patient population. The baseline characteristics provided in Appendix to this response do not indicate any differences between populations that would suggest the results are unsuitable to support decision making.

KEYNOTE-407 was stratified by <1% and ≥1% PD-L1 TPS, ensuring that treatment arms were well balanced for PD-L1 TPS. KEYNOTE-407 did not stratify for the TPS 1-49% population but the subgroup is well balanced both between arms and when compared to the population with TPS <1% (see in Appendix). This TPS≥50% subgroup was specified in the Terms of Reference for this appraisal due to the availability of a different comparator treatment available for the population with TPS≥50% and the requirement to compare to that.

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The committee notes (on Page 10, section 3.4) there would be uncertainties associated with assessing the cost effectiveness for people with a PD-L1 TPS score of less <50% and ≥50% PD-L1 TPS because "*KEYNOTE-407 was not stratified in this way and any analysis that attempts to blend the subgroups can potentially break randomisation*." It is unclear why blending subgroups would potentially break randomization given the arms are well balanced across the three subgroups. Furthermore, given the size and well-balanced distribution to the <1% and 1-49% PD-L1 TPS subgroups, MSD does not believe that there are high levels of uncertainty inherent in these subgroup estimates.

Important new information that has become available due to the time this medicine has been used on the CDF is how usage across the groups differs in routine UK practice compared with the clinical trial, see again table below.

Table 5 - Real world use of pembrolizumab combination therapy across PD-L1 TPS subgroups compared with subgroup distribution in KEYNOTE-407

PD-L1 TPS subgroup	Pembrolizumab combination therapy usage – June 2020	KEYNOTE-407 distribution
<1%	22%	35.5%
1-49%	68%	37.8%
≥50%	10%	26.7%
Source: IQVIA Market Research Data, July 2021		

Applying these weights gives a more accurate representation of value to the NHS of pembrolizumab combination therapy and results in an ICER estimate of £30,943 in the subgroup with TPS <50%.

Table 6 – Committee-preferred base case cost-effectiveness results for <%50 PD-L1 TPS subgroup based on real world usage data (Reflecting confidential pembrolizumab discount and comparators at list price, September 2020 data cut)

	Pembro combination therapy vs standard chemotherapy	
	Incremental QALYs	Incremental Costs
Unweighted results		
<1% PD-L1 TPS	*****	*****
1-49% PD-L1 TPS	*****	*****
Reweighted results		
<1% PD-L1 TPS	*****	*****
1-49% PD-L1 TPS	*****	*****

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Weighted ICER in <50% PD-L1 TPS subgroup	
Pembrolizumab combination therapy vs standard chemotherapy	£30,943 per QALY

Given this population is eligible for end of life criteria, the company is confident this ICER would remain below the £50,000 end of life threshold when including confidential patient access scheme discounts for comparators.

Eligibility for End of Life

The company agrees it is highly likely that eligibility for End of Life is met for both populations with TPS <1% and TPS 1-49%. The company further asserts that the relevant population in the subgroup with TPS≥50% and urgent clinical need also meet the end of life criteria.

If the patient in this TPS ≥50% population is likely to survive more than 24 months without the addition of pembrolizumab, they explicitly do not meet the criteria for urgent clinical need. The incremental median OS difference between pembrolizumab combination therapy and chemotherapy is ***** months. Even accounting for the requested access in a sicker patient population, it is not plausible that the survival gain for patients treated with pembrolizumab combination would not be profound and suitable for application of the full end of life QALY multiplier.

MSD's position is, if a person with untreated, metastatic, squamous, NSCLC can be treated with pembrolizumab monotherapy, this should be the first choice of treatment. However, patients with an urgent need for a clinical response need the immediacy of chemotherapy. The Blueteq criteria for this population in CDF states, "*the use of the combination of pembrolizumab, carboplatin and paclitaxel* ***rather than*** *pembrolizumab monotherapy*". In this, the relevant specific population requiring an urgent response, pembrolizumab monotherapy is not the appropriate comparator. Instead, chemotherapy is the appropriate comparator, and therefore comparison with chemotherapy is relevant for the assessment of end of life criteria met or not.

Usage during the period in the CDF since August 2019 in over 1000 patients has enabled the committee to evaluate how many and what proportion of patients with ≥50% PD-L1

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	TPS actually meets the specific criteria for eligibility. The NHS England Cancer Drugs Fund Clinical Lead has confirmed in written communication that 11% of the entire cohort of squamous NSCLC patients who having received pembrolizumab combination therapy during the CDF period are ≥50% PD-L1 TPS and therefore have an urgent critical clinical need as deemed by their treating clinician ([redacted]). It is important to note that the criteria of "urgent clinical need" was introduced by NICE and NHSE at the point of entry to the CDF and did not form any part of the KEYNOTE-407 clinical trial protocol. As such, this population cannot be identified within the KEYNOTE-407 study population. However, MSD strongly assert that there is little doubt that this population meets the NICE End of Life criteria based on the following evidence: 1. Urgent clinical need implies a short survival, and there is clinical consensus that this survival would be less than 24 months in this population. By definition, if patients were not in such a severe health state they would be suitable candidates for pembrolizumab monotherapy and thus ineligible for pembrolizumab combination therapy per the current restrictions in the Cancer Drugs Fund. 2. The incremental OS gain in this population is profound: Median OS gain versus standard chemotherapy in KEYNOTE-407 was [redacted] months in the ≥50% PD-L1 TPS subgroup. Even if this survival gain is reduced in the ≥50% patient population with an urgent clinical need, the survival gain is highly likely to be profound and therefore suitable for application of the full end of life multiplier, compared with chemotherapy alone.
	Responding to the remaining areas of uncertainty after then technical engagement stage: 1) Long-term treatment effect of pembrolizumab combination therapy on PFS and OS 2) Subsequent treatment 3) ITC of pembrolizumab combination therapy versus pembrolizumab monotherapy 4) Eligibility for end of life We consider points 3) and 4) to have been addressed (see above).

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1) Long-term treatment effect

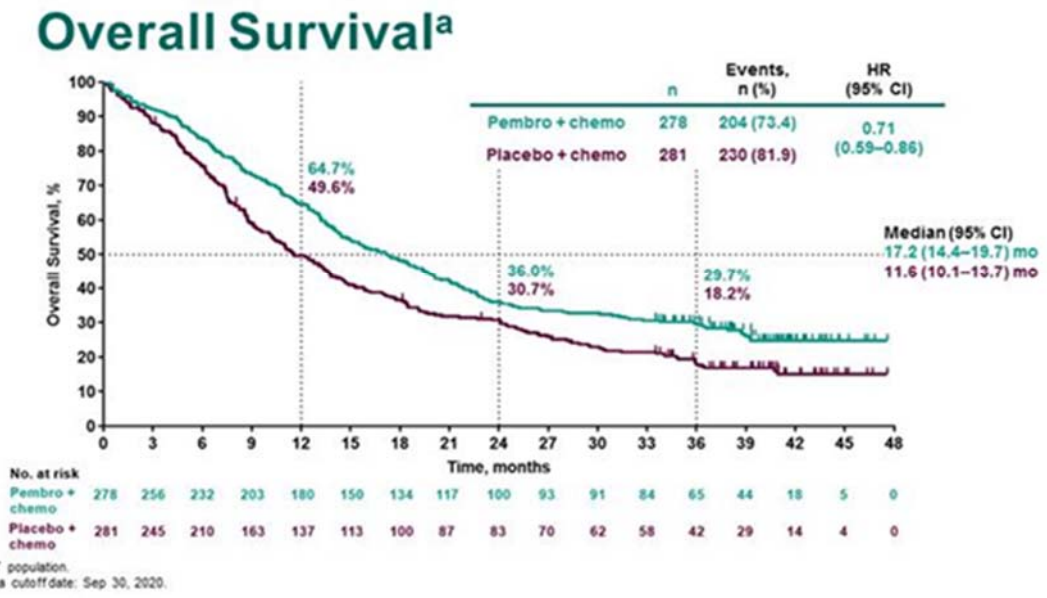
Page 16, section 3.9 of the Appraisal Consultation Document states "*A treatment effect lasting between 3 and 5 years is appropriate for decision making.*"

As part of the Terms of Engagement, MSD submitted analysis consistent with "ERG's pessimistic analysis 6b", which included a 5-year duration of treatment effect for pembrolizumab combination therapy. Since long-term follow-up data became available from KEYNOTE-407, the committee have not reassessed the plausibility of this assumption based on a review of the OS hazards over time. Nor have the committee highlighted any evidence that a 5-year duration of treatment effect was *too* optimistic, and that a 3-year duration of treatment effect would be more plausible.

Long-term OS KM data in the ITT population from the September 2020 data cut (shown below), provides no evidence that treatment effect on OS begins to wane in patients with follow-up beyond 36 months.

Figure 3 - Overall survival: ITT population in KEYNOTE-407 (September 2020 data)

A Robinson. ELCC 2021



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	The company position is that there is no evidence to support the implementation of waning of treatment effect at 5 years, particularly not in PFS, given the maturity of this data this additional assumption is unwarranted. The company is prepared to accept the ERG's waning of treatment effect in OS at 5 years, in the absence of any supportive evidence, in order to conclude this appraisal. We note again uncertainty is more likely to favour the company ICER estimates on this point. **2) Costing of subsequent treatment assumptions** MSD acknowledges that the 15% of chemotherapy-treated patients later treated with chemotherapy as a subsequent therapy in KEYNOTE-407 represents a deviation from NHS clinical practice. Two methods for costing this second-line chemotherapy have been presented to committee. The company assumption reflects the clinical reality described unanimously by consultant oncologists in the UK that 100% of chemotherapy-treated patients who receive a second-line treatment would be treated with a PD-L1 inhibitor. The ERG assumption proposes to cost second-line chemotherapy based on treatment the pattern in the clinical trial, preferring to align with the trial rather than UK clinical practice. The company has considered the use of methods adjust survival for this 15% of chemotherapy-treated patients based on the counterfactual assuming they had been able to receive a second-line PD-L1 inhibitor in the clinical trial. However, due to the small patient numbers, there is insufficient data to estimate a statistically robust adjustment to survival outcomes (e.g., via crossover adjustment methods) such that they would match what would be expected in NHS clinical practice. The ICER is moderately sensitive to the uncertainty around costing of subsequent therapies, and at a minimum, the committee should select the midpoint within the range of uncertainty between ERG and company assumptions.
5	**Committee's preferred assumptions** Page 21 of the ACD reports the committees eight preferred assumptions. The company can accept six of these. MSD's position is there needs to be a refinement of the assumption around stratification by PD-L1 subgroup. Rather than anchoring this around subgroups for the purposes of

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	NICE assessment and available comparators, we think the three relevant subgroups need to be considered to align with NHS policy making, NHS clinical practice and, as stated in the ACD difference in prognosis and potential differences in the clinical effect of pembrolizumab combination, PD-L1 score. Taking account of the three subgroups is critical to ensure the correct value to the NHS is determined, as this indication is not used equally in these three subgroups <1%, 1-49% and ≥50%. The one assumption we cannot accept, discussed above, is an implementation of the waning of treatment effect at three years for either PFS or OS as we have trial data that refutes this. The important conclusion to draw here, is that while there is a point that the company considers to be counter to the available evidence, and new information has become available that allows better assessment of the value of this indication to the NHS, there is substantial acceptance of the ERG and committee's position. The evidence package is mature, the extrapolation is robust and, "the most clinically plausible 5-year and 10-year survival estimates" (page 14 section 3.7). Any suggestion that there is a high degree of uncertainty in this appraisal is not a fair reflection of the data or the modelling approach taken. Neither does this recognise that pembrolizumab combination therapy is an innovative technology in the treatment of squamous NSCLC, a disproportionally under-served patient population.
	In the remaining form we pick up other points that need to be addressed
6	**Poor outcomes associated with the squamous histology of NSCLC** Page 6, section 3.1 of the Appraisal Consultation Document states: "*People with squamous NSCLC often have a poor quality of life, and a potential extension to life is important to them. Outcomes tend to be worse with squamous NSCLC than with non-squamous NSCLC because people have a higher prevalence of smoking-related comorbidities. For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score less than 50%, outcomes are particularly poor.*"

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	MSD notes the relatively poor outcomes associated with squamous NSCLC associated with smoking-related comorbidities are more likely to impact people from lower socio-economic groups given the higher rates of smoking among this population.[1] Whilst the committee did not identify any equalities issues, MSD believes there are significant equity issues, particularly for those patients with squamous disease that have a TPS of <1% or 1-49%. The committee should consider the socio-economic determinants of health inequality that lead to increased smoking rates as context to their decision making.
7	**Updated PD-L1 TPS subgroup analysis based on September 2020 data cut** Page 8, section 3.3 of the Appraisal Consultation Document states "*At response to technical engagement, the company provided additional overall survival data from a later follow up of KEYNOTE-407 (data cut September 2020). It wanted the committee to consider data only from the whole intention-to-treat population rather than from the PD-L1 subgroups.*" MSD wishes to apologise for any misunderstanding and confirm (as stated above) that we believe it to be appropriate and necessary to consider the 3 subgroup populations. We would also clarify that at the time of technical engagement, MSD was only able to provide ITT OS results from the September 2020 data cut. We have since updated the subgroup analyses within the economic model and this is submitted as part of this Appraisal Consultation Document response. Given the size and well-balanced distribution to the <1% and 1-49% PD-L1 TPS subgroups, MSD does not believe that there are high levels of uncertainty inherent in these subgroup estimates.
8	**Decision-making cost-effectiveness threshold** In the discussion pertaining to decision making thresholds in the ACD the text references NICE's guide to the methods of technology appraisal and notes that:

[1] "The role of patient, tumour and system factors in socioeconomic inequalities in lung cancer treatment: population-based study." Br J Cancer. 2014 Jul 29; 111(3): 608–618.

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	• Above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. • The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The longer text also refers to innovation, NHS (non-health) priorities and quality of life not captured in the QALY measure. We note the ACD focus on uncertainty – we assume to drive a lower decision-making threshold. It is critical that there is understanding uncertainty works in both directions (against and in favour of company/ERG assumptions). In this case we would consider the uncertainties sufficiently well balanced, and in the context of mature data, that there is as little uncertainty in this appraisal as any NICE assessment. We also note committees have discretion to consider unmet need and inequalities in their deliberation. Squamous NSCLC patients have long been the poor relations in lung cancer treatment, and this should be explicitly acknowledged in committee decision making. The <50% PD-L1 TPS subgroup represents 89% of use of the pembrolizumab combination therapy in current clinical practice based on market research data obtained by MSD and confirmed by NHSE. Should the committee decide to use a different threshold for the subgroup with PD-L1 TPS ≥50%, a weighted threshold should be calculated based on the 89% vs 11% split between the <50% and ≥50% PD-L1 TPS subgroups. (The <50% PD-L1 subgroup is grouped together in this calculation given the committee has agreed that End of Life criteria have been met in this population.) In a hypothetical example where the committee decides to use a £30,000/QALY threshold for the subgroup with PD-L1 TPS ≥50%, the decision-making threshold should be calculated as follows: 89% * £50,000 + 11% * £30,000 = £47,800 per QALY gained

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	In this way, the decision-making threshold would reflect the true value for money to the NHS of a medicine which is overwhelmingly used for treatment of an end of life indication. In the event end of life criteria are not met for the ≥50% PD-L1 TPS subgroup, a conclusion MSD would strongly disagree with, MSD believes there is a clear evidence that it would be appropriate for the committee to apply a £30,000 (rather than £20,000) per QALY decision-making threshold for the ≥50% PD-L1 TPS subgroup, to be included in the weighted threshold calculation described above, based on the following evidence: • Over 2.5 years additional data collection from KEYNOTE-407 since TA600 which recommended pembrolizumab combination therapy to the Cancer Drugs Fund • High unmet need in the squamous metastatic NSCLC population • Clinically meaningful survival benefits seen with pembrolizumab combination therapy which have remained stable after 40 months median follow-up (time from randomization to data cutoff) • Possible equalities issues resulting from squamous NSCLC disproportionally affecting people in lower income socio-economic groups • Alignment between company and ERG survival modelling assumptions
9	MSD requests clarification of the text on page 22 and 23 of the ACD to ensure it is clear that the comparison that is being referred to is pembrolizumab combination therapy compared with pembrolizumab monotherapy. Given much of the rest of the document refers to a comparison to chemotherapy and given MSD's position not to seek access for pembrolizumab combination therapy in patients that can successfully be treated with pembrolizumab monotherapy, two clarifications are needed. The first, that this is not the population for whom MSD is seeking access, and the second, that the comparison is versus pembrolizumab monotherapy (for example in the discussion about south west quadrants and at the top of page 23).

Insert extra rows as needed

Appendix:

Baseline characteristics by TPS subgroup (TPS <1%, 1-49%, ≥50%) from KEYNOTE-407

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Subject Characteristics
(ITT Population, TPS<1%)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	95		99		194	
Gender						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years)						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ex US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
East-Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-East Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
EU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-EU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subject Characteristics
(ITT Population, TPS<1%)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Smoking Status						
Never Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ECOG						
0	[redacted]					
1	[redacted]					
Histology						
Squamous	[redacted]					
Adenosquamous	[redacted]					
Metastatic Stage						
M1A	[redacted]					
M1B	[redacted]					
Brain Metastasis Status at Baseline						
Yes	[redacted]					
No	[redacted]					
Baseline Tumor Size						
Subjects with data	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Median	[redacted]					
Range	[redacted]					
Taxane Chemotherapy						
+Paclitaxel	[redacted]					
+Nab-Paclitaxel	[redacted]					
Prior Adjuvant/Neo-adjuvant Therapy						
Yes	[redacted]					
No	[redacted]					
Prior Radiation						
	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Yes	[redacted]					
No	[redacted]					
Prior Thoracic Radiation						
Yes	[redacted]					
No	[redacted]					
Database Cutoff Date: 03APR2018						

Source: [MK3475-KN407: adam-adsl]

Subject Characteristics
(ITT Population, TPS 1-49%)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	103		104		207	
Gender						
Male	[redacted]					
Female	[redacted]					
Age (Years)						

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian Or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ex US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
East-Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-East Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

Subject Characteristics
(ITT Population, TPS 1-49%)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
EU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-EU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking Status						
Never Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology						
Squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenosquamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Stage						
M1A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M1B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain Metastasis Status at Baseline						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Tumor Size						
Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Taxane Chemotherapy						
+Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+Nab-Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Adjuvant/Neo-adjuvant Therapy						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Prior Radiation						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Thoracic Radiation						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018						

Source: [MK3475-KN407: adam-adsl]

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

Subject Characteristics
(ITT Population, TPS ≥50%)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	73		73		146	
Gender						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years)						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ex US	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
East-Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-East Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
EU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-EU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

Subject Characteristics
(ITT Population, TPS ≥50%)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Smoking Status						
Never Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology						
Squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenosquamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Stage						
M1A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M1B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain Metastasis Status at Baseline						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Tumor Size						
Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Taxane Chemotherapy						
+Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+Nab-Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Adjuvant/Neo-adjuvant Therapy						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Radiation						

NICE National Institute for Health and Care Excellence

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

Subject Characteristics
(ITT Population, TPS ≥50%)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Thoracic Radiation						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018						

Source: [MK3475-KN407: adam-adsl]

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

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

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Page 6, section 3.1: *"the role of biomarkers such as PD-L1 to predict the cancers most likely to respond to immunotherapy is less well established in squamous NSCLC than in non-squamous NSCLC".* We do not agree with this statement. Most thoracic oncologists would view a PD-L1 negative, low (1-49%) or high (>50%) result in squamous and non-squamous as equally useful in terms of directing anti-cancer therapy. In clinical practice, there is not a significant difference between the role of PD-L1 in squamous and non-squamous lung cancer.
2	Page 10, section 3.4: *"The committee agreed that stratifying clinical evidence by these 3 PD-L1 subgroups [<1%, 1-49%, >50%] was not generalisable to NHS clinical practice".* We do not agree with this statement, which is important because it is a central tenet of the committee's reasoning. Although it is correct that current therapeutic options for squamous cell NSCLC available on the NHS only differ between PD-L1 >50% (single-agent Pembrolizumab) and PD-L1 <50% (Pembrolizumab, Paclitaxel and Carboplatin), in practice most thoracic oncologists would still categorise patients into low (<1%), weak (1-49%) and high (>50%) when assessing a patient's tumour type and making treatment decisions. Indeed, after histology sub-type (squamous vs. non-squamous) this is the most important pathological characteristic. Whether a squamous cell carcinoma is negative or weak positive would influence how an oncologist would view the relative benefits of 1st and 2nd line treatment options.
3	Page 10, section 3.4: *"The committee concluded that pembrolizumab combination therapy is likely to be clinically effective compared with platinum-based chemotherapy for people with PD-L1 tumour proportion score of less than 50%. However, there is uncertainty over the exact overall survival estimates because of the how the subgroups were stratified."* It seems unfair to dismiss the 3-level PD-L1 stratification (see point 2 above), which is universally used by practising oncologists, instead require a PD-L1 <50% or >50% stratification, and then focus on the uncertainty of the precise benefit of Pembrolizumab combination in the <50% group.
4	Page 15, section 3.8: *"But the ERG noted that this was inconsistent with the experience of people in KEYNOTE-407, in which a few people had chemotherapy alone as subsequent treatment."* There are always some patients who would not receive immunotherapy as subsequent line therapy after 1st line chemotherapy (for example, if significant auto-immune conditions). However, they would very much be in the minority and it is the case that immunotherapy is the standard of care. This is even more the case now, compared to when KEYNOTE-407 was running, because 2nd line immunotherapy was not as widely available in all countries as it is now. In the Committee papers provided by NICE, the details of subsequent therapies (page 44) were redacted, and so it is not possible to be more precise with respect to this objection. But it should be noted that there were a large number of chemotherapy regimens listed as 2nd line treatments given, which would not be used on the NHS. *"The ERG used an alternative approach in its preferred base case, in which the costs of chemotherapy were only applied to people who had subsequent-line treatment. This included the people in KEYNOTE-407 who had subsequent chemotherapy."*

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 30 September 2021. Please submit via NICE Docs.

	We do not agree with the approach taken by the ERG here. This does not reflect clinical practice. We agree with the Clinical Experts in this respect.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Please return to: **NICE DOCS**

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]

Addendum: ERG comments on the company's ACD response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Correspondence author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	7th October 2021

1. Introduction

In September 2021, the National Institute for Health and Care Excellence (NICE) issued a negative Appraisal Consultation Document (ACD) on the use of pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (NSCLC).[1] The ACD states that the KEYNOTE-407 trial[2] is not fully reflective of clinical practice in England because carboplatin plus gemcitabine is the most commonly used platinum-based chemotherapy and nab-paclitaxel is not used in the NHS. The ACD highlights uncertainty surrounding: the clinical evidence for people in the programmed death-ligand 1 (PD-L1) tumour proportion score (TPS) subgroups; the company's indirect comparison between pembrolizumab combination therapy versus pembrolizumab monotherapy in people with PD-L1 TPS ≥50%, and whether pembrolizumab combination therapy meets NICE's End-of-Life (EoL) criteria. The ACD states that the cost-effectiveness estimates are uncertain, but are likely to be higher than what NICE considers an acceptable use of NHS resources.

In October 2021, the company submitted a response to the NICE ACD.[3] The company's ACD response includes a written document and an updated economic model which includes overall survival (OS) data for the individual PD-L1 TPS subgroups from the September 2020 data-cut of KEYNOTE-407. These data had not previously been presented. The company's ACD response focusses on four main issues:

(i) Clarification on the population with PD-L1 TPS ≥50% for whom the company is seeking a positive recommendation
(ii) Subgroups relevant to NHS clinical practice and NICE decision-making
(iii) Residual uncertainty around the clinical and cost-effectiveness of pembrolizumab combination therapy
(iv) The decision-making threshold.

The main points raised in the company's ACD response are summarised in Section 2.

2. Summary of main points raised in the company's ACD response

(i) Clarification on the population of patients with PD-L1 TPS ≥50% for whom the company is seeking a positive recommendation

The company's ACD response[3] clarifies the company's position regarding the population of patients with PD-L1 TPS ≥50% for whom they are seeking a positive recommendation. The company's response (page 2) states that their position is that *"any patient with untreated, metastatic, squamous cell, non-small cell lung cancer (NSCLC) and a TPS ≥50% that can successfully be treated with pembrolizumab monotherapy should be treated with pembrolizumab monotherapy. However, in line with clinician feedback and current access in the CDF, there is a population of patients with TPS≥50% that need an urgent clinical response [from chemotherapy]."* Therefore, the company is seeking a positive recommendation only in those patients with an urgent clinical need who would otherwise receive

chemotherapy alone. The comparator for these patients would be chemotherapy rather than pembrolizumab monotherapy. The company argues that this position reduces uncertainty and renders the indirect treatment comparison (ITC) between pembrolizumab combination therapy and pembrolizumab monotherapy redundant. The company also argues that pembrolizumab combination therapy is likely meet NICE's EoL criteria in this urgent need subgroup.

(ii) Subgroups relevant to NHS clinical practice and NICE decision-making

The company's ACD response[3] argues that it is appropriate to make decisions on the basis of subgroups, but that the TPS <50% group is not homogenous and that, on the basis of prescribing data from IQVIA, the distribution of patients across the PD-L1 TPS <1%, 1-49% and ≥50% subgroups in NHS practice differs from that in the KEYNOTE-407 trial. The company argues that weighted incremental cost-effectiveness ratios (ICERs) should be calculated using the estimates from IQVIA rather than KEYNOTE-407. The company's re-analysis using weights based on the IQVIA data result in an ICER for pembrolizumab combination therapy versus chemotherapy in the PD-L1 TPS <50% subgroup of £30,943 per quality-adjusted life year (QALY) gained (note - the ERG was unable to generate this value using the company's submitted model).

(iii) Residual uncertainty

The company disagrees with statements made in the ACD regarding the magnitude and importance of uncertainty around four aspects of the appraisal:

(a) Uncertainty surrounding PFS and OS

- The company's ACD response[3] argues that the data from KEYNOTE-407[2] are mature and suitable for decision-making.
- The company's response highlights that the ERG did not have major concerns regarding the company's updated OS modelling for the intention-to-treat (ITT) population and states that the company has taken *"a very plausible, conservative approach"*.
- The company argues that the Appraisal Committee's preferred assumption of treatment effect waning is not supported by the longer-term follow-up of KEYNOTE-407.[2] The company's updated economic analyses include an assumption of treatment effect waning for OS, but not progression-free survival (PFS).
- The company also argues that whilst nab-paclitaxel is not used in the NHS, this does not limit the generalisability of the KEYNOTE-407 trial.

(b) Differences between subsequent immunotherapy use in KEYNOTE-407 and NHS clinical practice

- The company's ACD response[3] acknowledges that neither the company's original approach and the ERG's preferred approach for handling second-line immunotherapy costs

and outcomes is ideal. Page 6 of the company's response states *"the company is prepared to accept the "within trial" approach in order to expedite the conclusion of this appraisal."* However, page 20 of the company's response states that *"at a minimum, the committee should select the midpoint within the range of uncertainty between ERG and company assumptions."*

(c) Robustness of the company's ITC for patients with PD-L1 TPS ≥50%

- The company's response[3] states that the ITC of pembrolizumab combination therapy versus pembrolizumab monotherapy is redundant as the relevant target population relates specifically to patients with PD-L1 TPS ≥50% in urgent clinical need (e.g. major impending airway obstruction) who would otherwise receive chemotherapy.

(d) Uncertainty about whether pembrolizumab combination therapy meets NICE's EoL criteria.

- The company argues that the use of pembrolizumab combination therapy in the subgroup of patients with PD-L1 TPS ≥50% with urgent clinical need is highly likely to meet the EoL criteria.

(iv) Decision-making threshold

The company's ACD response[3] states that because pembrolizumab combination therapy is highly likely to meet the EoL criteria in the PD-L1 TPS ≥50% subgroup, a threshold of £50,000 per QALY gained should be used for decision-making. The company states that the PD-L1 TPS ≥50% urgent need subgroup comprises 11% of the overall target population. The company's response also states that if the Appraisal Committee determines that pembrolizumab combination therapy does not meet NICE's EoL criteria in the PD-L1 TPS ≥50% subgroup, a weighted threshold should be used based on the prevalence of the TPS subgroups in clinical practice.

(v) Company's updated economic analysis

The company's ACD response[3] includes additional survival modelling of OS for the three PD-L1 TPS subgroups using the September 2020 data-cut of KEYNOTE-407. These data have not been included for the PD-L1 TPS subgroups in previous iterations of the company's model. The company's response presents cost-effectiveness results for the ITT population and for the PD-L1 TPS <1%, 1-49% and ≥50% subgroups; these are summarised in Table 1. These analyses exclude assumptions of treatment effect waning for PFS, but include the ERG's preferred assumptions regarding second-line immunotherapy use based on the experience of the KEYNOTE-407 trial.[2] The ERG has included weighted results for the overall PD-L1 TPS <50% subgroup based on KEYNOTE-407 and IQVIA at the bottom of the table.

Table 1: ERG's preferred analysis, KEYNOTE-407 September 2020 data-cut, includes pembrolizumab PAS, excludes treatment effect waning assumptions on PFS, includes updated CMU prices from May 2021, generated by the ERG

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
ITT population							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,367**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <1%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,272**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS 1-49%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,645**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS ≥50%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£26,216**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <50%, re-weighted using KEYNOTE-407							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,956**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <50%, re-weighted using IQVIA							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,489**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; PD-L1 - programmed death-ligand 1; TPS - tumour proportion score; ITT - intention-to-treat
** Undiscounted*

3. ERG comments on the key points raised in the company's ACD response

(i) Clarification on the population of patients with PD-L1 TPS ≥50% for whom the company is seeking a positive recommendation

The ERG notes that pembrolizumab monotherapy was listed as the comparator for the PD-L1 TPS ≥50% subgroup in the original NICE scope for TA600 and in the Terms of Engagement (ToE) document for the CDF review.[4] This comparator was assumed in the company's original economic model and the CDF model. The ITC used to inform both versions of this model reflects patients recruited into KEYNOTE-407 and KEYNOTE-042 with TPS ≥50%, without any additional criteria relating to urgent need of clinical response. The ERG believes that the company's clarification of their intended target population within this TPS ≥50% subgroup is helpful. However, the company has not presented any clinical evidence or economic analysis which is relevant to this specific population. Whilst the company's ACD response[3] presents median PFS, median OS and an ICER for pembrolizumab combination therapy versus chemotherapy based on data from KEYNOTE-407 (ICER = £26,213 per QALY gained, excluding updated CMU drug costs), this reflects the broader PD-L1 TPS ≥50% subgroup and is not relevant to the company's intended target population with urgent clinical need.

The ERG also notes that whilst it may be reasonable to assume that the EoL criterion of survival normally being less than 24 months will be met within the urgent need subgroup, the company has not

presented any relevant evidence to suggest that pembrolizumab combination therapy will extend survival by at least 3 months for these patients.

(ii) Subgroups relevant to NHS clinical practice and NICE decision-making

The company's CDF submission[5] presents cost-effectiveness results for the ITT population and for three PD-L1 TPS subgroups: <1%, 1-49% and ≥50% (see Table 1). The NICE ACD[1] (Section 3.13) states that the Appraisal Committee *"would have preferred cost-effectiveness estimates for PD-L1 tumour proportion scores of less than 50% and 50% or more."* The ERG understands that the Appraisal Committee's preference for merging the two subgroups with TPS <50% provides consistency with previous NICE TAs. The company's ACD response[3] argues that patients with PD-L1 TPS <50% do not represent a homogenous population and that the weights applied for the TPS <1% and 1-49% subgroups should be applied based on NHS practice rather than the proportions from KEYNOTE-407. The submission from the British Thoracic Oncology Group (BTOG) also notes that *"in practice most thoracic oncologists would still categorise patients into low (<1%), weak (1-49%) and high (>50%) when assessing a patient's tumour type and making treatment decisions."*[6]

The ERG considers that if the Appraisal Committee wishes to consider the PD-L1 TPS <50% subgroup as a whole, it would seem reasonable to re-weight the results of the TPS <1% and 1-49% subgroups using the IQVIA data, rather than using the prevalence in KEYNOTE-407. However, the ERG is unsure whether it is appropriate to combine the results for the PD-L1 TPS <1% and 1-49% subgroups – whilst inconsistent with previous appraisals in NSCLC, it may be more appropriate consider these two subgroups separately. One of the main reasons for undertaking economic analyses across subgroups is to assess the importance of heterogeneity on the cost-effectiveness of a technology – in particular - to determine whether that technology is cost-effective in some subgroups but not others. Weighting the results across the subgroups may mask the fact that a technology is not cost-effective in one of those subgroups. Given that the company argues that the PD-L1 TPS <50% subgroup is not homogenous, this implies that the cost-effectiveness of pembrolizumab combination therapy is likely to differ between the TPS <1% and 1-49% subgroups, and this is demonstrated by the company's model results (see Table 1). It may instead be more appropriate to assess the cost-effectiveness of pembrolizumab combination therapy and the case for EoL in each PD-L1 TPS subgroup individually.

Page 15 of the company's ACD response[6] states that *"It is unclear why blending subgroups would potentially break randomization given the arms are well balanced across the three subgroups."* The ERG believes that it is the analysis of a trial dataset using subgroups that were not included as stratification factors which may break randomisation, rather than the blending of those subgroups. The ERG agrees with the company that overall the baseline characteristics appear to be generally well

balanced within the PD-L1 TPS subgroups, although there are some differences, as shown in the appendix to the company's ACD response.

(iii) Residual uncertainty

(a) Uncertainty surrounding long-term PFS and OS

The company's ACD response[3] argues that *"there is there is no evidence to support the implementation of waning of treatment effect at 5 years, particularly not in PFS, given the maturity of this data this additional assumption is unwarranted".* However, the company is prepared to accept the ERG's assumption of waning of the treatment effect on OS at 5 years – this is included in the company's results presented in Table 1. The ERG notes that the assumption of a lifetime treatment effect was not considered appropriate in the Terms of Engagement (ToE) document for this CDF review. Whilst the September 2020 data-cut of KEYNOTE-407 provides longer-term follow-up, there are no data beyond 4 years and it is unclear whether the treatment effects on PFS and/or OS would persist beyond this timepoint. The ERG does not believe that the evidence presented in the company's ACD response is conclusive in supporting an assumption of indefinite treatment effects - the OS plot presented in Figure 3 of the ACD response indicates high levels of censoring and few OS events in both groups at later timepoints. The ERG believes that it may have been more informative to present plots of the empirical hazard functions and log cumulative hazards for PFS and OS to assess whether the treatment effects persists at later timepoints.

The company believes that the evidence from KEYNOTE-407 is robust and that any suggestion that there is a high degree of uncertainty in the evidence of modelling approach in this appraisal is unfair. The ERG notes that at the time at which the NICE ACD was published, the company had not provided data from the September 2020 data-cut for the individual PD-L1 TPS subgroups. The ERG believes that this may have contributed to the Appraisal Committee's concerns regarding uncertainty in the evidence. Whilst the company has now provided these data, there remains some uncertainty surrounding long-term outcomes within the specific PD-L1 TPS subgroups. The ERG also notes that the company's updated economic analysis by PD-L1 TPS subgroup involved selecting parametric survival models for PFS and OS on the basis of statistical goodness-of-fit and visual inspection only. The company's ACD response does not include any consideration of the plausibility of the selected models within each PD-L1 TPS subgroup. This further contributes to uncertainty around the ICERs within the subgroups.

(b) Differences between subsequent immunotherapy use in KEYNOTE-407 and NHS clinical practice

The ERG's views regarding this aspect of the economic analysis are described in the ERG report[7] and the ERG's technical engagement (TE) response.[8] The company's preferred approach is to assume that all patients receiving standard chemotherapy receive second-line immunotherapy on progression, which is not consistent with the experience of KEYNOTE-407.[2] The ERG's preferred approach is to assume

the level of subsequent immunotherapy use observed in the trial, which is not consistent with current clinical practice. As noted previously in the ERG's TE response, without adjustment of outcomes, the company's preferred ICER is likely to represent an underestimate, whilst the ERG's preferred analysis is consistent with the trial but is limited in that it does not fully reflect current clinical practice. Whilst both approaches are subject to problems, the ERG believes that it is more appropriate to align health outcomes with the costs required to generate those outcomes and notes that the company's preferred analysis is inconsistent in this regard. The company's ACD response[3] states that there are insufficient data to estimate a statistically robust adjustment to the survival outcomes from the trial. Overall, the ERG's view remains unchanged and considers that taking the midpoint ICER between these two analyses, as suggested by the company, may not be particularly meaningful.

(c) Robustness of the company's ITC for patients with PD-L1 TPS ≥50%

The ERG agrees that the company's ITC and economic analyses for the PD-L1 TPS ≥50% subgroup do not reflect the population of patients who would receive pembrolizumab combination therapy. As noted above, no evidence of clinical benefit for pembrolizumab combination therapy has been presented within this specific subgroup.

(d) Uncertainty about whether pembrolizumab combination therapy meets NICE's EoL criteria.

The ERG remains unsure whether and in which subgroups pembrolizumab combination therapy meets NICE's EoL criteria. Based on the updated analyses presented in Table 1, the ERG notes the following:

[redacted]

- There is no clinical evidence for pembrolizumab combination therapy versus chemotherapy in the TPS ≥50% urgent clinical need subgroup.

(iv) Decision-making threshold

The ERG does not believe that the use of a weighted threshold across all subgroups is appropriate. Instead, the ERG suggests that it would be more appropriate to consider the cost-effectiveness of pembrolizumab combination therapy separately within each relevant PD-L1 subgroup against the relevant threshold given the Committee's view on whether the EoL criteria are met within that subgroup.

(v) Company's updated economic analysis

The ERG was able to replicate the results presented in Table 3 of the company's ACD response using the executable model provided by the company. The ERG was unable to replicate the company's weighted ICER for the PD-L1 TPS <50% subgroup reported in the ACD response.

4. References

1. National Institute for Health and Care Excellence. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer - Appraisal Consultation Document. London, UK; 2021.
2. Merck, Sharp and Dohme Ltd. Clinical study report: A randomized, double-blind, Phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell lung cancer subjects (KEYNOTE-407); 2018.
3. Merck, Sharp and Dohme Ltd. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683] - Company's response to the NICE ACD. Hertfordshire, UK; 2021.
4. National Institute for Health and Care Excellence. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA600). Terms of engagement for CDF review. London, UK; 2020.
5. Merck, Sharp and Dohme Ltd. Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated squamous non-small-cell lung cancer [ID1306]. Company's submission - Document B. Hertfordshire, UK; 2018.
6. British Thoracic Oncology Group. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (review of TA600) [ID1683] - response to the ACD; 2021.
7. Tappenden P, Navega Biz A, Uttley L, Stevens JW. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Evidence Review Group report. Sheffield, UK; 2020.
8. Tappenden P, Navega Biz A. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Addendum: ERG response to company's technical engagement response and updated analyses including the confidential PAS discount for pembrolizumab. Sheffield, UK; 2021.

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer: CDF guidance review [ID1683]

addendum: Updated analyses presented in the company's ACD response including pembrolizumab PAS

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Table 1: ERG's preferred analysis, KEYNOTE-407 September 2020 data-cut, includes pembrolizumab PAS, excludes treatment effect waning assumptions on PFS, includes updated CMU prices from May 2021 generated by the ERG

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
ITT population							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,367**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <1%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,272**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS 1-49%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,645**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS ≥50%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£26,216**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <50%, re-weighted using KEYNOTE-407							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,956**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <50%, re-weighted using IQVIA							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,489**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <50%, re-weighted using CDF							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,640**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; PD-L1 - programmed death-ligand 1; TPS - tumour proportion score; ITT - intention-to-treat
** Undiscounted*

Table 2: ERG's preferred analysis, KEYNOTE-407 September 2020 data-cut, includes pembrolizumab PAS, includes treatment effect waning assumptions on PFS, includes updated CMU prices from May 2021 generated by the ERG

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
ITT population							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,708**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <1%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,389**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS 1-49%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,273**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS ≥50%							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£26,438**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <50%, re-weighted using KEYNOTE-407							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,468**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <50%, re-weighted using IQVIA							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,071**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

PD-L1 TPS <50%, re-weighted using CDF							
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£36,131**
Chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; PD-L1 - programmed death-ligand 1; TPS - tumour proportion score; ITT - intention-to-treat
** Undiscounted*