NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Contents:

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- How is pembrolizumab expected to be used in clinical practice?

- The company has not provided comparisons with all comparators listed in the scope (docetaxel is the main comparator for the full population and nintedanib plus docetaxel for the adenocarcinoma population). The ERG agrees with the company's rationale. However, should best supportive care also be included as a comparator?

- PD-L1 testing is not currently considered standard clinical practice and is a requirement for determining suitability for treatment with pembrolizumab. Are there training and monitoring factors that need to be taken into account?

- The key clinical effectiveness evidence for pembrolizumab compared with docetaxel was from in the KEYNOTE-010, KEYNOTE-001 and LUME-LUNG- 1 trials. Only KEYNOTE-010 included a patient population relevant to the decision problem addressed by the company. How generalizable are the results?

- The company suggests that treatment with pembrolizumab would be stopped at 2 years even if people have not progressed. What is the committees view on the clinical plausibility this 2 year stopping rule?

- What is the committee's view on progression/pseudo progression in patients receiving pembrolizumab in this indication?

- What is the committee's view of the PD-L1 subgroup analysis presented by the company (In the clinical trials people were stratified by PD-L1 status)?

- The company carried out a network meta-analysis (NMA) based on data from KEYNOTE-010 and LUME-LUNG-01. The trial was not powered to assess PD-L1 status or EGFR status. How reliable are the results of the NMA given the differences in population (LUME-LUNG-01 was an adenocarcinoma population)?

Cost effectiveness

- What is the Committee's view on the company's modelling assumption that all patients will stop treatment with pembrolizumab at 2-years?

- The company used a piecewise approach to estimate overall survival, and a cut-off time of 52 weeks was used to switch from Kaplan Meier data to parametric curves. The cost effectiveness results were sensitive to the cut-off time. Is base case 1 or 2 most appropriate for decision making? Is the cut-off time of 52 appropriate? In the company's modelling, 82% of the overall survival gain occurs post-progression after treatment has ended (based on base case 2). What is the

committees view on the plausibility of continued survival gain after treatment with pembrolizumab has ended?

- In the model, progression free survival from KEYNOTE-010 was used as a proxy for time on pembrolizumab and docetaxel treatment. The company calculated HRs for time on treatment compared with progression free survival to estimate the proportions of patients on treatment, based on proportion of patients who are progression-free in each cycle for pembrolizumab and docetaxel. What is the committee's view on the use of progression-free survival as a proxy for time on treatment?

- Treatment switching during the trial was not allowed in the study protocol of KEYNOTE-010. However, a total of 50 patients switched to other PD-1 treatments after treatment discontinuation. The company used a two-stage adjustment to account for treatment switching. What is the Committee's view on the method used and the impact on the cost effectiveness results?

Other considerations

- The company proposes that pembrolizumab should be considered as an end-of-life treatment. Are the end-of-life criteria met for this appraisal?

1 Remit and decision problem

1.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for treating advanced or recurrent Programmed cell death 1 ligand PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with advanced non-small-cell lung cancer that is PD-L1 positive: • whose disease has progressed after platinum-containing doublet chemotherapy • whose disease has progressed on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours	People with advanced NSCLC that is PD-L1 positive: • whose disease has progressed after platinum-containing doublet chemotherapy. • Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations.	In line with the anticipated licence and with the NICE final scope.	In line with the anticipated licence and with the NICE final scope.
Int.	Pembrolizumab			
Com.	• Docetaxel monotherapy • Nintedanib with docetaxel (for people with adenocarcinoma histology) • Afatinib or erlotinib (if no previous EGFR-TKI therapy received due to delayed or unknown	• Docetaxel monotherapy • Nintedanib with docetaxel (for people with adenocarcinoma histology)	• Nivolumab is not a relevant comparator because it has not yet been recommended by NICE for second-line NSCLC. • Ceritinib is not a relevant comparator because it has not yet	The ERG noted that the decision problem deviated from the NICE scope but agreed with the company's rationale that these appraisals were still ongoing at the time of submission

	mutation status in the circumstances described in TA374) • Crizotinib (only for patients with ALK positive mutation status, not recommended by NICE but available via the CDF) • Nivolumab (subject to ongoing NICE appraisal) • Ramucirumab with docetaxel (subject to ongoing NICE appraisal) • Best supportive care		been recommended by NICE. • Ramucirumab with docetaxel is not a relevant comparator because it has not yet been recommended by NICE. • BSC, outside of the context of being offered alongside of systemic anti-cancer therapies is the option when there is no other active treatment available. • Pembrolizumab as a second or third line therapy, by definition would be offered subsequent to platinum-based, and where appropriate and EGFR or ALK targeted therapy. • At these points in the care pathway docetaxel is considered and appropriate treatment option	

Out.	• overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life			The outcomes considered in the company submission are in line with those detailed in the NICE final scope.
Subgroups	If the evidence allows, consideration will be given to subgroups based on cancer histology and biological markers (PD-L1, EGFR, and ALK).	People with NSCLC of adenocarcinoma histology	As part of the cost-effectiveness model, subgroup analysis on patients with NSCLC of adenocarcinoma type was conducted, where pembrolizumab was compared against nintedanib in combination with docetaxel and against docetaxel monotherapy.	Adenocarcinoma is an important histological sub-type of the NSCLC, which accounts for 30-40% of the NSCLC. The ERG agrees with the company's decision to perform a subgroup analysis for people with adenocarcinoma histology. The company, however, has not provided any reason for not considering subgroup analyses according to biological markers (PD-L1, EGFR, and ALK).
Special considerations	If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices.	The cost of testing for PD-L1 expression, required to assess patients' eligibility to treatment with pembrolizumab, has been included as part of the cost-effectiveness assessment.	In line with NICE final scope	The decision problem addressed by the company differs from the NICE final scope but is considered appropriate and clinically relevant by the ERG

Source: Final scope, company submission (table 1) and ERG report				

2 The technology and the treatment pathway

2.1 Pembrolizumab (Keytruda, Merck Sharp and Dohme) is a humanised monoclonal antibody which acts on the 'programmed death 1' protein (PD-1). This protein is part of the immune checkpoint pathway, and blocking its activity may promote an anti-tumour immune response. Pembrolizumab has been studies in the treatment of advanced non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 and who have disease progression on or after prior chemotherapy as per the scope of this appraisal. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations should also have disease progression on approved therapy for these aberrations prior to receiving. Pembrolizumab is available through the UK Medicines and Healthcare products Regulatory Agency's Early Access to Medicines Scheme.

Table 2 Technology

	Pembrolizumab	**Docetaxel monotherapy**	**Nintedanib with docetaxel (for people with adenocarcinoma)**
Anticipated marketing authorisation	Indicated for the treatment of advanced NSCLC in adults whose tumours express PD-L1 and who have disease progression on or after prior chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations prior to receiving pembrolizumab.	Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.	Indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

Administration method	2 mg/kg every three weeks (Q3W); intravenous (IV) infusion.		Administered on day 1 of a 21 day cycle at a dose of 75 mg/m2. If required doses can be reduced to 60 mg/m2; intravenous infusion (IV).	Administered orally at 200 mg twice daily on days 2–21 of a standard 21 day docetaxel cycle. Dose adjustments to 150 mg or 100 mg twice daily are permitted in patients who experience adverse events.
Acquisition cost[1]	List price: 50mg vial: £1315.00	PAS price: 50mg vial: [redacted]	Docetaxel 10 mg/mL 2-mL vial = £138.33 8-mL vial = £454.53 16-mL vial = £1069.50; Docetaxel 20 mg/mL 1-mL vial = £160.00 4-mL vial = £530.00 7-mL vial = £900.00[1]	£2,151.10 per month (30-day pack)[1]
Average cost of a course of treatment[1]	List price: £29,114	PAS price: [redacted] (mean treatment duration: 7.20 cycles)[2].	Cannot be determined using the company submission/model	Cannot be determined using the company submission/model

1: List prices taken from British national formulary online (accessed April 2016). Nintedanib has a confidential patient access scheme, which cannot be reported in this document. 2: Company estimates. NICE technology appraisal guidance 347.

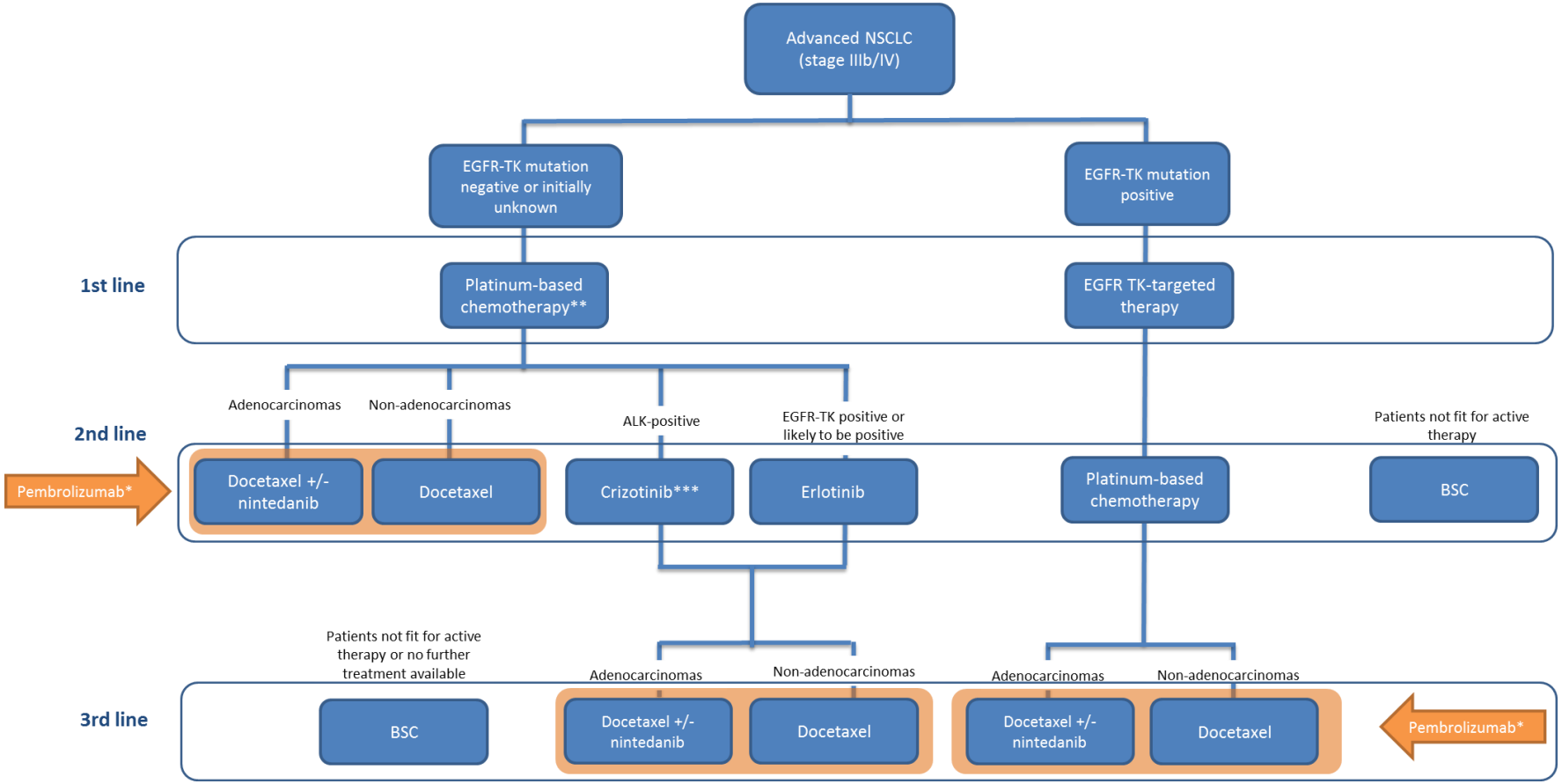
See summary of product characteristics for details on adverse reactions and contraindications.

IV, intravenous; PAS, patient access scheme

2.2 Treatment options for non-small cell lung cancer (NSCLC) include biological therapy, chemotherapy and radiotherapy. Cancers with a mutation in the EGFR and ALK gene may be treated with a targeted therapy. For people with locally advanced or metastatic NSCLC whose disease has progressed after chemotherapy, NICE technology appraisals 347, 310 and 374 recommend docetaxel monotherapy, nintedanib, afatinib and erlotinib respectively as options in some circumstances. In clinical practice, NSCLC tumours that progress after treatment with EGFR-targeted therapies may be treated with platinum in combination with gemcitabine, vinorelbine, pemetrexed or a taxane. Best supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated.

2.3 The company anticipates that pembrolizumab will be used in people whose tumours express PD-L1 and whose disease has progressed on or after prior chemotherapy. In addition it will be considered for people with EGFR or ALK genomic tumour aberrations whose disease has progressed on approved therapy for these aberrations prior to receiving pembrolizumab (Figure 1). PD-L1 expression testing is currently not standard practice in the NHS. The company have included the cost of testing in the economic model.

Figure 1 - Treatment pathway



Taken from the company submission, figure 3 (page 38).

3 Comments from consultees

3.1 Clinical and patient experts emphasised that the current outlook for patients with non-small cell lung cancer (NSCLC), who have relapsed after platinum based chemotherapy is poor. They noted that active treatment options, after previous chemotherapy treatment, are limited in this patient group. Consultees noted that improvement in symptoms is important for people with NSCLC. Consultees highlighted that people with relapsed NSCLC have multiple and distressing symptoms. They concluded that this is an area of high unmet need.

3.2 Clinical experts commented that the majority of patients with NSCLC who are fit enough for systemic treatment will receive platinum based combination chemotherapy. They noted that the arrival of immune checkpoint inhibitors (such as pembrolizumab) is therefore strongly welcomed for the management of this population with significant unmet need. Clinical experts noted that there is a clear correlation between tumour PD-L1 expression and the anti-tumour activity of pembrolizumab. Consultees commented that as PD-L1 analysis will be required to establish eligibility for this treatment, this might lead to a more complicated patient pathway compared to current alternatives. Clinical experts highlighted that there are a number of PD-L1 IHC assays available, but none are in routine use, and therefore a degree of histopathology training will be required.

3.3 Both clinical and patient experts noted that pembrolizumab is generally very well tolerated and causes less frequent mild and severe toxicities than currently available docetaxel-based alternatives. Pembrolizumab is delivered as a short infusion, similar to docetaxel, and does not require specific supportive medication as standard. As a biological agent it can occasionally cause an anaphylactic reaction, which needs to be managed accordingly. Clinical experts also highlighted that in addition to training of oncologists, further training in administration and monitoring will also be

required for healthcare professionals who have had limited experience with this agent, or others in its class. The evaluation of response to immune checkpoint inhibitors is also more complex than for conventional cytotoxic toxicities. It is recognised that in a small proportion of patients, tumours may appear to increase initially before subsequently responding, a phenomenon known as pseudo-progression. This will require additional training for some thoracic radiologists involved in evaluating the effectiveness of pembrolizumab for NSCLC and education of oncologists to differentiate patients with progressing disease from those with pseudo-progression

3.4 In addition to training of oncologists, many of who will have had limited experience with this agent, or others in its class, members of the extended multi-disciplinary team will also need training.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review identified 3 randomised control trials which were relevant to the decision problem. These were:

- KEYNOTE-010, a phase II/III head-to-head RCT that compared pembrolizumab with docetaxel
- KEYNOTE-001 (Parts C and F) a phase I trial due to its initial dose escalation, which evolved into multiple phase II-like sub-studies through a series of expansion cohorts that assessed the effects and safety of pembrolizumab (no comparator)
- LUME-LUNG-1, a phase III trial that compared docetaxel plus nintedanib with docetaxel plus placebo.

KEYNOTE-010

KEYNOTE-010 was a randomised, multicentre (including centres in the UK), phase III open label trial comparing pembrolizumab 10 mg/kg every 3 weeks (n=346) or 2 mg/kg every 3 weeks (n=339) with docetaxel 75 mg/m^2 every 3 weeks for 4 doses (n=343). Pembrolizumab therapy continued until progression, complete response or unacceptable toxicity, up to a maximum of 2 years. The study was conducted in adults with histologically or biologically confirmed NSCLC with at least one measureable lesion, determined radiographic progression per The Response Evaluation Criteria in Solid Tumours (RECIST 1.1), and after treatment with at least two cycles of a platinum-containing doublet for NSCLC stage IIIB/IV or recurrent disease. People with an EGFR-TK or ALK mutation were eligible for pembrolizumab if disease had progressed after targeted therapy. People were evaluated for expression status of PD-L1 in a prospective manner using a qualitative immunohistochemical (IHC) assay to detect PD-L1 protein in NSCLC tissue. PD-L1 protein expression is determined by using Tumour Proportion Score (TPS), which is the percentage of viable tumour cells showing partial or complete membrane staining. Tumours staining for PD-L1 with 1% or greater were considered expressers (TPS≥1%), with a further analysis of those expressing 50% or greater (TPS≥50%). Tumours with <1% cells for PD-L1 staining were considered non-expressers (TPS<1%). Only people whose tumours expressed PD-L1 (based on a Tumour Proportion Score (TPS) of ≥1%) were eligible for randomisation in this study. People previously treated with docetaxel, prior chemotherapy and biological therapy were excluded.

The primary outcomes in KEYNOTE-010 were progression-free survival and overall survival for previously-treated patients with NSCLC whose tumours express PD-L1. Two types of patient population were used to estimate the treatment effect for the primary outcomes: the Intention-To-Treat (ITT) population in the TPS≥50% stratum and in the TPS>1%

(people with tumours who had a TPS above 1% are considered PD-L1 expressers. Patients whose tumours had <1% tumour cells positive for PD-L1 staining are considered non-expressers) overall population served as the primary population for the analyses of progression-free survival (PFS) and overall survival (OS). Secondary outcomes included overall response rate, response duration and health-related quality of life. Results were analysed at 2 planned interim analyses, after 10 months from study start (June 2014) and after 19 months from study start (March 2015).

The company noted that cross-over was not permitted within the trial. However they reported that 50 people switched to other PD-1 treatments after treatment discontinuation (43 of which were from the control arm). The company argued that since patients in the docetaxel arm were expected to discontinue treatment earlier compared to patients in the pembrolizumab arms, and that patients discontinued from docetaxel treatment may receive other anti-PD-1 treatments similar to pembrolizumab after discontinuation, the Rank Preserving Structural Failure Time (RPSFT) model was used to control for receipt of non-study treatment. The company also presented a two-stage adjustment which assumes that at the time of disease progression all patients are in a similar health state. The company also highlighted that that in KEYNOTE-010 the mean duration of study treatment was nearly 2-fold longer in the pembrolizumab 2 mg/kg every three weeks Q3W arm (151.1 days) compared with the docetaxel 75 mg/m2 Q3W arm (81.6 days).

KEYNOTE-001

KEYNOTE-001 was a combined phase I and II open label study, comprising an initial dose-escalation study (part A) followed by a group of phase II sub-studies (parts C and F divided into cohorts F1, F2 and F3). Parts C, F2 and F3 reflect the patient population included in KEYNOTE-010 and are relevant to the decision problem for this appraisal'. All patients enrolled in Part C, Cohort F2, and Cohort F3 had received at least one line of prior therapy which must have included platinum-based

chemotherapy and demonstrated disease progression before receiving pembrolizumab. The study was conducted in adults with histologically or biologically confirmed NSCLC who have previously been treated with platinum-based chemotherapy and whose disease has progressed.
In Part C people received pembrolizumab at 10 mg/kg every 3 weeks (n=38) and included people who experienced disease progression after at least two prior systemic anti-tumour regimens. Tumour samples were retrospectively collected to determine PD-L1 status.

In Cohort F2 people received pembrolizumab at 10mg/kg every 2 or 3 weeks (n=285) and included people who had locally advanced or metastatic NSCLC whose tumours expressed PD-L1 (retrospective determination) and whose disease had progressed after at least one prior systemic antineoplastic regimen, at least one of which was required to be a platinum-containing doublet. If a sensitizing EGFR-TK mutation or ALK gene rearrangement was present, progression of disease after initiating the appropriate tyrosine kinase inhibitor was required.
In Cohort F3 people received pembrolizumab at 2 mg/kg every 3 weeks (n=55) and included people locally advanced or metastatic NSCLC whose tumours expressed PD-L1 (retrospective determination) and had experienced progression of disease after at least one prior systemic antineoplastic regimen, at least one of which was a platinum-containing doublet.

Table 3 - KEYNOTE-001 total number treated, dosing and PD-L1 status for expansion cohorts C & F

Cohort	Dose	Dose frequency	Randomised	PD-L1 status	Total treated
C	10mg/Kg	Q3W	No	All comers	38
F2	10mg/Kg	Q3W	No	Positive	356
		Q3W	Yes	Positive	
		Q2W	Yes	Positive	

		Q3W	No	Negative	
F3	2mg/Kg	QSW	No	Positive	55
Source: company submission, table 9 (page 55)					

The company stated that patient characteristics were well balanced across treatment arms (Table 3). Full details of the study methods for KEYNOTE-001 and KEYNOTE-010 can be found in sections 4.3-4.6 (pages 46–56) of the company submission.

Table 4 - Patient characteristics in KEYNOTE-010 from the ITT Population (TPS ≥ 1%) and KEYNOTE-001 (part C and F) from the Total Previously Treated Efficacy Population by Dose (APaT)

	KEYNOTE-010			**KEYNOTE-001**	
	Docetaxel 75 mg/m2 Q3W n= 343	Pembrolizumab 2 mg/kg Q3W n= 344	Pembrolizumab 10 mg/kg Q3W n= 346	Pembrolizumab 10 mg/kg Q3W n=238	Pembrolizumab 10 mg/kg Q2W n=156
Age: median (range), years	62 (33 – 82)	63 (29 – 82)	63 (20 to 88)	63 (28 – 85)	62 (32 – 82)
Sex: % male	60.9%	61.6%	61.6%	48.3%	59%
ECOG status: % ECOG 0	33.8%	32.6%	34.7%	37%	26.9%
PD-L1 status: % positive	44.3%	40.4%	43.6%	N/A	N/A
EGFR Mutation – wild type	85.7%	85.2%	83.2%	N/A	N/A
ALK translocation status – wild type	90.4%	89.2%	88.2%	78.2%	96.2%
Lines of prior therapy: % 0 1 2	0.9% 68.5% 21.9%	1.7% 70.6% 19.2%	2.0% 67.9% 19.9%	18.1% 31.5%	15.4% 27.6%
Prior chemotherapy - yes	98.8%	97.4%	97.4%	N/A	N/A
Prior EGFR TKI therapy -	99.7%	88.4%	83.8%	N/A	N/A

no					
Prior ALK inhibitor therapy - no	99.4%	99.1%	98.6%	N/A	N/A
ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death 1 ligand; Q2W, every 2 weeks; Q3W, every 3 weeks Source: Company submission, table 17 (page 82) and table 18 (page 85)					

LUME –LUNG 1

4.2 In the LUME-LUNG 1 study people were randomised in a 1:1 ratio to receive either docetaxel 75mg/m2 plus nintedanib, 400mg Q3W (n=655) or docetaxel 75 mg/m2 plus placebo Q3W (n=659). Nintedanib was given as 200 mg twice daily orally and docetaxel 75 mg/m2 was administered as an intravenous infusion over 1 hour Q3W. The study included adult patients with advanced NSCLC whose disease had progressed on or after treatment with only 1 prior chemotherapy regimen. This study presented subgroup analyses including patients with adenocarcinoma (approximately 50% of the study population). Neither PD-L1 expression nor EGFR mutation status were assessed in LUME-LUNG 1 study.

ERG comments

4.3 The ERG stated that KEYNOTE-010 was well designed and well conducted. It considered that the population was representative of patients seen in the UK NHS, and patient characteristics were well balanced across treatment groups. However, it did note that although all three trials included participants with advanced NSCLC, whose disease has recurred after platinum-containing chemotherapy, only KEYNOTE-010 included a patient population relevant to the decision problem addressed by the company.

- In KEYNOTE-010 trial included adults with PD-L1 positive advanced NSCLC whose disease has progressed after appropriate targeted therapy for EGFR or ALK positive tumours.

- In KEYNOTE-001 not all included patients presented with a PD-L1 positive NSCLC.
- In LUME-LUNG-1 neither PD-L1 expression nor EGFR mutation status were assessed among included patients with advanced NSCLC.

4.4 The ERG noted that among the patient population in KEYNOTE-010, there was a higher proportion of patients with a TPS of 1-49% compared with those with a TPS of ≥50% (55.7% versus 44.3% in the docetaxel group and 59.7% versus 40.4% in the pembrolizumab group). Apart from metastatic staging (M1B) and brain metastasis, the ERG noted that there were no significant differences in other baseline characteristics between the overall population and the TPS≥50% stratum and between treatment groups in each stratum.

4.5 The ERG stated that the KEYNOTE-001 parts C, F2 and F3 cohorts was generally well designed and well conducted. The ERG commented that safety data from the non-randomised non-controlled cohorts of KEYNOTE-001 (part C, F2 and F3) would be relevant to address the decision problem. The ERG noted that not all of the participants within the safety population were PD-L1 positive; 18.5% of the participants had a TPS less than 1%.

Clinical trial results

KEYNOTE-010

4.6 Pembrolizumab was associated with a statistically significant increase in median overall survival (OS) compared with docetaxel (10.4 months, 95% CI: 9.4, 11.9 compared with 8.5 months, 95% CI: 7.5, 9.8 respectively). There was a 29% reduction in the risk of death for patients on pembrolizumab (HR: 0.71; 95% CI: 0.58, 0.88, p=0.00076). Pembrolizumab appears to improve progression free survival, but there's no evidence of a difference between treatments. Pembrolizumab was

associated with statistically significantly higher overall response rates compared with docetaxel ($p<0.05$).

4.7 There were no significant differences in progression-free survival, overall survival or overall response rates between the 2 pembrolizumab dosing regimens in the TPS≥1% population ($p>0.05$). In the TPS≥50% population the median OS for pembrolizumab 2 mg/kg was 14.9 months, compared with 8.2 months for docetaxel (HR 0.54; 95% CI: 0.38, 0.77; p-value=0.00024). Full details of the results can be found in section 4.7 of the company submission (page 87–106).

4.8 The secondary endpoints of KEYNOTE-010 were overall response rate (ORR), response duration and time to response by IRC assessment per RECIST 1.1.

- In the TPS≥1% population pembrolizumab 2 mg/kg Q3W was associated with an 18% ORR compared to 9.3% in the docetaxel group (p=0.00045).
- In the TPS≥50% population, pembrolizumab 2 mg/kg Q3W produced an ORR of 30.2%, compared to 7.9% in the docetaxel arm.
- In the TPS≥1% population there were 62 responders in the pembrolizumab 2 mg/kg Q3W arm and the median time to response was 65 days (range 38 to 127 days). There were 32 responders in the docetaxel arm and the median time to response was 65 days (range 41 to 250 days).
- In the TPS≥50% stratum, there were 42 responders in the pembrolizumab 2 mg/kg Q3W arm and the median time to response was 65 days (range 38 to 141 days). There were 12 responders in the docetaxel arm and the median time to response was 65 days (range 59 to 247 days)

4.9 Pre-specified subgroup analyses were presented for PD-L1 biomarker subgroups (i.e. (TPS≥50% stratum vs. overall population TPS≥1%)

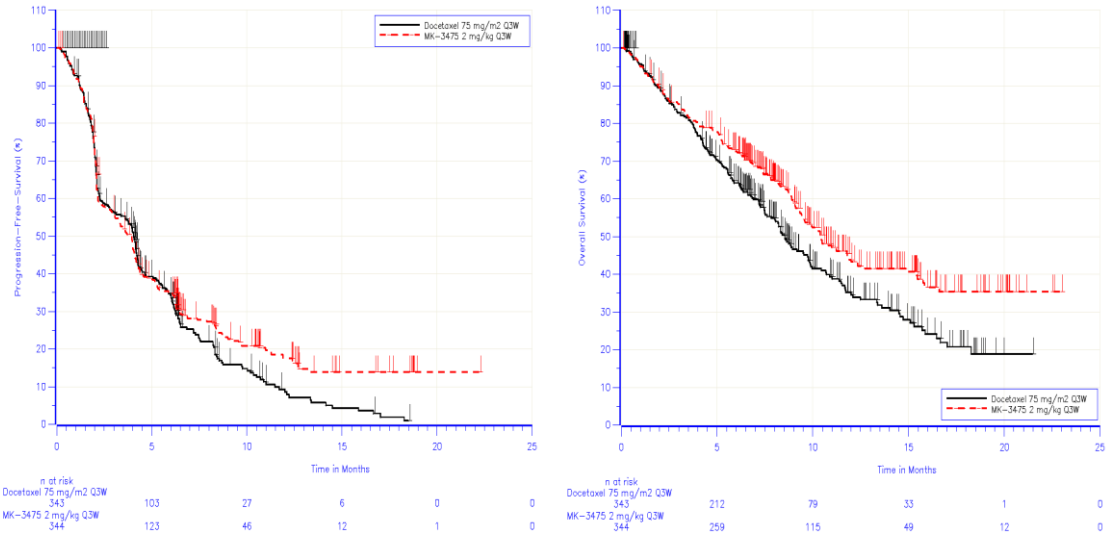
clinically relevant baseline patient or tumour characteristics. The company noted that pembrolizumab was associated with greater efficacy compared with docetaxel in the majority of the subgroups.

Table 5 Clinical effectiveness outcomes in KEYNOTE-010

	Pembrolizumab	**Docetaxel**
	2 mg/kg Q3W n=344	**75 mg/m2 Q3W** n=343
Primary endpoints		
Overall survival – ITT population		
Median: months (95% CI)	10.4 (9.4, 11.9)	8.5 (7.5, 9.8)
Hazard ratio (95% CI)	HR 0.71 (95% CI 0.58, 0.88); p=0.00076	
12 month overall survival rate (%)	43%	35%
Progression-free survival – ITT population		
Median: months: (95% CI)	3.9 (3.1, 4.1)	4.0 (3.1, 4.2)
Progression-free survival rate at 12 months (%)	18%	9%
Secondary endpoints		
Overall response rate (ORR) – ITT population		
Overall response rate (95% CI)	18% (14.1, 22.5)	9% (6.5, 12.9)
Time to response – ITT population		
Median: days Range: days	65 (38-217)	65 (41-250)
Response duration - ITT population		
Median: days Range: days	NR (20+ - 610+)	189 (43+ - 268+)
% of responses ongoing among responders	73%	34%
CI, confidence interval; Q2W, every 2 weeks; Q3W, every 3 weeks; NR, not recorded Source: company submission, table 20 (page 87)		

Figure 2 Progression-free survival and overall survival in KEYNOTE-010

A, Overall survival in the ITT population; **B**, progression-free survival in the ITT population (per RECIST 1.1)



Source: Company submission, figures 8 (page 81) and 11 (page 87)

KEYNOTE-001

4.10 The primary outcome in KEYNOTE-001 was the overall response rate (ORR) in the previously treated efficacy population. ORR was 37.4% (95% CI 27.9%, 47.7%) in the TPS>50% stratum and 11.8% (95% CI 6.8%, 18.7%) in the TPS 1-49% stratum. The median follow-up time was 16.2 months, ranging from 10.9 months to 32.3 months. In the TPS>50% stratum the median progression free survival was 5.8 months and the 3 and 6 month survival rates were 55.1% and 49.9%, respectively. The median overall survival was 7.8 months in the TPS 1-49% stratum and 15.5 months in the TPS>50% stratum. The 6 and 12 month overall survival rates were 57.3% and 43.2%, respectively, in the TPS 1-49% stratum and 71.6% and 56%, respectively, in the TPS>50% stratum. Full details of the efficacy analyses can be found in section 4.7 of the company submission (page 106–115).

ERG comments

4.11 The ERG stated that the data provided by the company to assess the efficacy and safety of pembrolizumab in patients with advanced PD-L1 positive NSCLC (TPS>1% and TPS>50%) was consistent. The ERG noted that in the overall population (TPS>1%) and in the TPS>50% stratum, pembrolizumab 2mg/kg Q3W showed a superior overall survival (OS) compared with docetaxel. In patients with a TPS>50%, pembrolizumab demonstrated statistically significant benefits in terms of progression free survival (PFS) compared with docetaxel. The ERG noted that pembrolizumab treatment did not significantly improve OS or PFS in patients with a TPS between 1-49%. However, they did note that KEYNOTE-010 was powered to detect a difference in the population with a TPS>50% and in the overall TPS>1% population. The company did not present a power calculation for the TPS 1-49% population. However, this seems to be irrelevant since the results (point estimates and precision of the confidence intervals) are now available. The ERG commented that pembrolizumab had a good safety profile.

4.12 Two different doses of pembrolizumab were tested (2 mg/kg and 10 mg/kg) in KEYNOTE-010 and interim analyses were undertaken and adjusted for. The ERG believed that the pembrolizumab 2 mg/kg results were considered most relevant and in line with the anticipated licensed dose regimen.

4.13 The ERG concluded that there was a lack of methodological details provided when adjusting overall survival for treatment switching, which prevented them from making a complete assessment, and other suitable techniques for adjusting for treatment switching (as indicated by the NICE DSU TSD 16),72 were not considered. The ERG noted that treatment switching during the trial was not allowed in the study protocol of KEYNOTE-010. However, a total of 50 patients switched to other PD-1 treatments after treatment discontinuation. The majority of the patients who did switch treatment were from the control arm (43/50). The company

used the Rank Preserving Structural Failure Time (RPSFT) and a two-stage adjustment to account for treatment switching. Results of overall survival (OS) were similar between techniques (unadjusted HR 0.71 95% CI 0.55, 088; RPSFT HR 0.71 95% CI 0.55, 0.87; 2-stage adjusted OS full model 0.69 95% CI 0.56, 0.85; 2-stage adjusted OS simple model 0.69 95% CI 0.55, 0.85). Due to the assumptions made by each technique the company opted to use the 2-stage adjusted values in the cost-effectiveness analysis. The ERG concluded that after adjusting for treatment switching, the estimates of treatment effect were very similar to the unadjusted results. Full details of the methods used to adjust for treatment switching can be found in section 4.7 of the company submission.

Health-related quality of life

4.14 Health-related quality of life was measured in KEYNOTE-010, using the European Organisation for Research and Treatment Cancer Quality of Life Questionnaire (EORTC QLQ-30) and the EuroQol EQ-5D. The EQ-5D questionnaire was administered at treatment cycles 1, 2, 3, 5, 9 and 13 (up to 13 cycles) and was based on the full analysis set (FAS) population of the pembrolizumab 2 mg/kg Q3W arm and docetaxel arm in KEYNOTE-010. EQ-5D was administered when patients were on treatment, at the discontinuation visit and 30 days after. When estimating utilities, 3 approaches were considered, estimation of utilities based on time-to-death; estimation of utilities based upon whether or not patients have progressive disease and combination of time-to-death and progression-based utilities.

4.15 Patients' health-related quality of life was estimated as a function of length of time until death; these were considered separately for pre-progression and post-progression health states in the model. The results showed that there was no statistically significant difference between pembrolizumab and docetaxel but that global health status and quality of life was better in the pembrolizumab group compared to the docetaxel group (see section

4.7, page 103 of the company submission). The company noted that the results from the EQ-5D were used to inform the economic model.

ERG comments

4.16 The ERG considered the company's approach in estimating patients' health-related quality of life as a function of length of time until death separately for pre-progression and post-progression to be appropriate. In addition, the ERG found the systematic review of relevant health-related quality of life data to be helpful.

Subgroup analyses

4.17 As part of the cost-effectiveness model the company presented subgroup analysis on patients with non-small cell lung cancer (NSCLC) adenocarcinoma. The company presented results which indicated pembrolizumab was superior across the vast majority of subgroups in the TPS≥1% population. The few HRs close to or greater than one correspond to subgroups with small numbers of events and thus, less precise estimates. Pembrolizumab provided survival benefit compared with docetaxel irrespective of whether archival or new tumour samples were used to assess PD-L1 expression (Figure 25, page 116 of the company submission). There was a significant survival benefit for patients with non-squamous (adenocarcinoma) disease. For those with squamous disease, the difference was not statistically significant (probably because of the small population size), but the data suggest a clinical benefit in this group also was superior compared to docetaxel. See section 4.8 (page 116 – 117) for full details of the subgroup analyses of overall survival and progression-free survival for pembrolizumab Q3W arm vs. docetaxel.

ERG comments

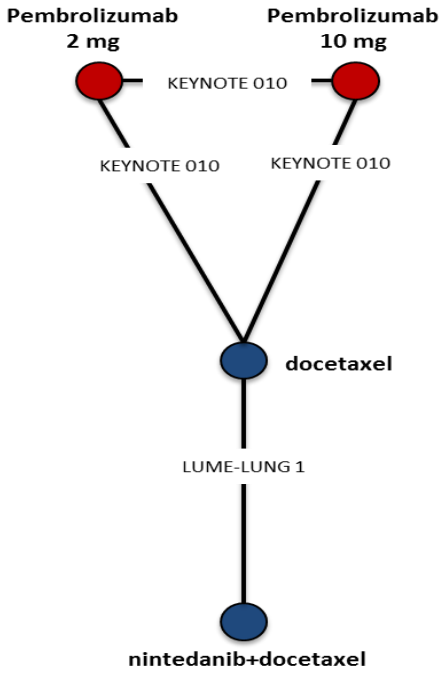
4.18 The ERG agreed that adenocarcinoma is an important histological sub-type of the NSCLC, which accounts for 30-40% of the NSCLC. Therefore, the ERG agrees with the company's decision to perform a subgroup

analysis for people with adenocarcinoma histology. The company noted that KEYNOTE-010 was not powered to undertake subgroup analyses by EGFR status and, as expected, the number of patients with NSCLC that had EGFR positive mutation status was very small. Additionally, only 8% of the patients included in KEYNOTE-010 were EGFR-mutation positive and only 0.8% of the patients included had tumours with ALK translocations (see Table 17, page 83 in the company submission).

Network meta-analyses

In the absence of head to head trials of pembrolizumab with appropriate comparators the company presented an indirect treatment comparison (ITC) by means of a network meta-analysis (NMA). The analysis was performed in a Bayesian framework using a fixed-effects model. It was based on data from KEYNOTE-010 and LUME-LUNG 1 identified in the systematic review (figure 3) which focussed on 2 advanced NSCLC populations: all NSCLC histologies population (previously treated) and an adenocarcinoma population (previously treated). For all NSCLC histologies population, the company identified KEYNOTE-010 as the only RCT comparing pembrolizumab with docetaxel and, therefore, no further analysis was deemed necessary. With regard to the adenocarcinoma subpopulation, both KEYNOTE-010 and LUME-LUNG-1 included docetaxel as a comparator forming a connected network for the indirect comparison. The company noted that there was a degree of heterogeneity between the two trials due to the differences in patient characteristics. Full details of the network meta-analysis methods and assumptions can be found in section 4.10 (page 119–132) and appendix 19 of the company submission.

Figure 3: Network of evidence for comparison of pembrolizumab to nintedanib+docetaxel - NSCLC of adenocarcinoma histology



Source: Company submission, figure 27 (page 128)

4.19 The company stated that the network meta-analysis showed that of pembrolizumab compared with the combination of nintedanib and docetaxel shows no evidence of a significant difference in terms of either overall survival (HR 0.81, 95% CI 0.59, 1.10) or progression free survival (HR 1.04, 95% CI 0.79, 1.36). The NMA shows a beneficial effect in favour of pembrolizumab with a 42% reduction in the odds of discontinuing treatment due to adverse event (OR 0.58, 95% CI 0.34, 0.99) and a 36% reduction in the odds of having a Grade 3 or 4 adverse events (OR 0.64, 95% CI 0.44, 0.94).Pembrolizumab also offered a more favourable safety profile in terms of discontinuations due to AEs and Grade 3 or 4 AEs. It noted that when the treatment effects were extrapolated, pembrolizumab appeared to be beneficial after 1 year of follow-up. Full results can be found in section 4.10 (page 126 - 132) and appendix 19 of the company submission.

ERG comments

4.20 The ERG commented that the network meta-analysis (NMA) was limited as there were only two trials included in the comparison of two treatments, therefore the heterogeneity between KEYNOTE-010 and LUME-LUNG-1 could not be estimated. Additionally, as LUME-LUNG-1 was the only trial identified by the company that provided evidence for nintedanib in combination with docetaxel, any estimation of the relative effectiveness of nintedanib in combination with docetaxel compared with pembrolizumab should be interpreted with caution. (see section 4.20 for more details).

4.21 The ERG commented that they could not replicate the company's NMA results using the programs supplied in the company submission. The ERG calculated the indirect comparison using the Bucher method (since it is equivalent to undertaking a NMA with fixed effects comparing two treatments and three trials) and were able to confirm the results for all outcomes assessed. They also noted that a network meta-analysis with fractional polynomial models would have been a more adequate approach due to the progression free survival Kaplan Meier curves violating the proportional hazards assumption.

4.22 The ERG noted that the company did not consider data for the all NSCLC histologies population from LUME-LUNG-1. According to the decision problem, nintedanib in combination with docetaxel is the recommended treatment only in people with NSCLC of adenocarcinoma histology. The ERG agrees with the company's decision of not including data for the all NSCLC histologies population from LUME-LUNG-1. The company noted that both trials were at overall low risk of bias, but he ERG did not agree as KEYNOTE-010 was an open label trial in which only outcome assessors were blinded but not patients and/or study personnel.

Adverse effects of treatment

4.23 The company presented detailed adverse event data from KEYNOTE-010 in section 4.12.2 (page 132–146) of its submission. These results are

summarised in Table 6. The company stated that pembrolizumab was generally well tolerated with fewer drug-related adverse events, drug-related Grade 3-5 adverse events (AE); and fewer discontinuations due to drug-related adverse events occurring in patients in the pembrolizumab 2 mg/kg Q3W arm compared to the docetaxel arm. The most common treatment-related adverse events with pembrolizumab and docetaxel were fatigue, decreased appetite, nausea and rash. There were 2 drug-related deaths with pembrolizumb and 1 death with docetaxel.

4.24 The company presented adverse event data from KEYNOTE-001 in section 4.12.2 (page 132–146) of its submission. These results are summarised in Table 7. The most common drug-related AEs were fatigue, pruritus, decreased appetite, rash, and arthralgias. The most prevalent adverse event across arms was fatigue (22.6% in the pembrolizumab 10mg/kg Q3W arm and 6.6% in the pembrolizumab 2mg/kg Q3W arm). The most common drug-related Grade 3 to 5 AE in the all NSCLC patient population in KEYNOTE-001 was pneumonitis . All other drug-related Grade 3 to 5 AEs occurred in less than 1% of patients.

Table 6 Summary of adverse events in KEYNOTE-010 (all patients as treated population) (TPS ≥ 1%)

	Docetaxel 75mg/m2 Q3W		Pembrolizumab 2mg/kg Q3W	
	n	%	n	%
N	309		339	
Patients with 1 or more AE	251	81.2%	215	63.4%
Toxicity grade 3–5 AE	173	56%	158	46.6%
SAE	107	34.6%	115	33.9%
Discontinued due to an AE	42	13.6%	32	9.4%
Drug-related AEs	251	81.2%	215	63.4%
Patients with 1 or more AE	109	35.3%	43	12.7%
Patients with no adverse events	200	64.7%	296	87.3%
Fatigue	76	24.6%	46	13.6%
Diarrhoea	56	18.1%	24	7.1%
Rash	14	4.5%	25	7.4%
Pruritus	5	1.6%	29	8.6%

Discontinued due to an AE	42	13.6%	28	8.3%

AE, adverse event; SAE, serious adverse event
Source: company submission, tables 53–57 (page 134–142)

Table 7 KEYNOTE-001 - Patients with drug-related AEs (incidence ≥ 5% in one or more treatment groups). All patients with NSCLC by dose

	Pembrolizumab 2 mg/kg Q3W		Pembrolizumab 10 mg/kg Q3W		Pembrolizumab 10 mg/kg Q2W	
	n	(%)	n	(%)	n	(%)
N	61		287		202	
Patients in population	61		287		202	
with one or more AEs	31	50.8%	201	70.0%	148	73.3%
with no AEs	30	49.2%	86	30.0%	54	26.7%
Toxicity grade 3–5 AE	26	42.6%	130	45.3%	94	46.5%
SAE	27	44.3%	108	37.6%	82	40.6%
Discontinued due to an AE	9	14.8%	40	13.9%	30	14.9%
Drug-related AEs	6	9.8%	23	8.0%	13	6.4%
Fatigue	4	6.6%	65	22.6%	35	17.3%
Pyrexia	4	6.6%	12	4.2%	9	4.5%
Decreased appetite	4	6.6%	36	12.5%	16	7.9%
Pruritus	4	6.6%	33	11.5%	22	10.9%
Rash	2	3.3%	30	10.5%	18	8.9%

AE, adverse event; SAE, serious adverse event
Source: company submission, tables 60 and 61 (page 145 and 146)

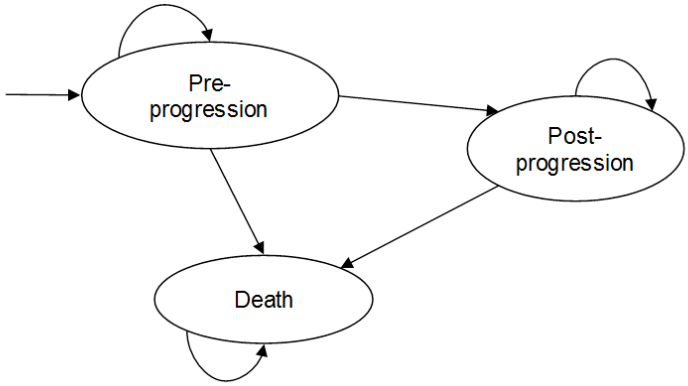
Cost-effectiveness evidence

4.25 The company presented a *de novo* economic model comparing pembrolizumab (at its licensed dose of 2 mg/kg every 3 weeks) with docetaxel (at a dose of 5 mg/m2 Q3W, with maximum treatment duration of 18 weeks) in people with advanced NSCLC that is PD-L1 positive, whose disease has progressed after platinum-containing doublet chemotherapy. As well as in people with EGFR or ALK genomic tumour aberrations have disease progression on approved therapy for these aberrations. The company also provided additional subgroup analyses in the adenocarcinoma population comparing pembrolizumab with docetaxel monotherapy and nintedanib in combination with docetaxel.

Model structure

4.26 The company presented a partitioned survival model with 3 states: pre-progression, post-progression and death (Figure 4). All patients entered the model in the pre-progression state. From the pre-progression state, patients could remain in that health state or progress and move to the post-progression state. Patients could move to the death state from both the pre-progression and the post-progression health states. Patients received treatment with pembrolizumab until disease progression, in line with the anticipated licence and consistent with the protocol of the KEYNOTE-010 trial. The model used a cycle length of 1 week and had a time horizon of 30 years (lifetime). The model perspective was the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

Figure 3 Company's model structure



ERG comments

4.27 The ERG's believed the company's model was generally consistent with the NICE reference case, although it did not include costs for Personal Social Services or any impact on carers. The ERG also noted that many of the comparators listed in the NICE scope were excluded from the economic evaluation. The company stated that the comparators set out in the scope were still ongoing appraisals and were therefore not eligible to be included. The ERG agreed with this rationale presented by the company. The ERG commented that only docetaxel monotherapy and nintedanib in combination with docetaxel (for the adenocarcinoma sub-group) were compared with pembrolizumab. The ERG considered the model structure to be reasonable, however, there were substantial uncertainties associated with the OS survival estimates in the longer-term.

4.28 The ERG noted that patients in the pembrolizumab arm were eligible for treatment until disease progression and maximum treatment duration for the base case analysis was assumed to be 2 years. These are in line with the anticipated licence and consistent with KEYNOTE-010. Patients in the docetaxel arm were restricted to maximum treatment duration of 18 weeks, in line with current practice in England. The company's model also accounted for the effects of treatment switching using a two-stage adjustment approach.

Model details

4.29 Pembrolizumab was assumed to be administered according to the anticipated license at 2mg/kg by IV infusion over 30 minutes every three weeks. Patients are expected to receive continuous treatment until disease progression or unacceptable toxicities, for a maximum duration of two years. Docetaxel monotherapy was assumed to be administered at a dose of 75mg/m2 three weekly for a maximum duration of 18 weeks. Nintedanib was assumed to be administered at a dose of 200 mg (or a reduced dose of 150 mg) twice daily; no stopping rule was applied to nintedanib and people could remain on treatment after discontinuation of docetaxel for as long as clinical benefit is observed. Time on treatment was based on progression-free survival (PFS), which was used as a proxy for time on pembrolizumab and docetaxel monotherapy. The company calculated the hazard ratio for time on treatment compared with PFS, to account for patients who experienced treatment discontinuation due to adverse events (AEs) and other reasons. This hazard ratio was applied to PFS in each cycle to estimate the proportion of patients on treatment.

4.30 The proportion of people in the each health state in each cycle was based on estimates of progression-free survival and overall survival (OS) from KEYNOTE-010, using a partitioned-survival (or 'area under the curve') approach. For the full summary of the company's base case survival modelling approaches see Table 24 (page 96) of the company submission. Progression-free survival (PFS) was estimated as follows:

- The company used data from KEYNOTE-010 for the extrapolation of PFS for patients in the pembrolizumab and the docetaxel monotherapy arms. The company concluded that the proportional hazards assumption did not hold and that separate models should be fitted to data from the pembrolizumab and docetaxel arms from KEYNOTE-010.
- The company fitted separate parametric curves (exponential, Weibull, log-normal, log-logistic, Gompertz a generalised gamma distributions) to the two arms of the observed PFS data from KEYNOTE-010. The

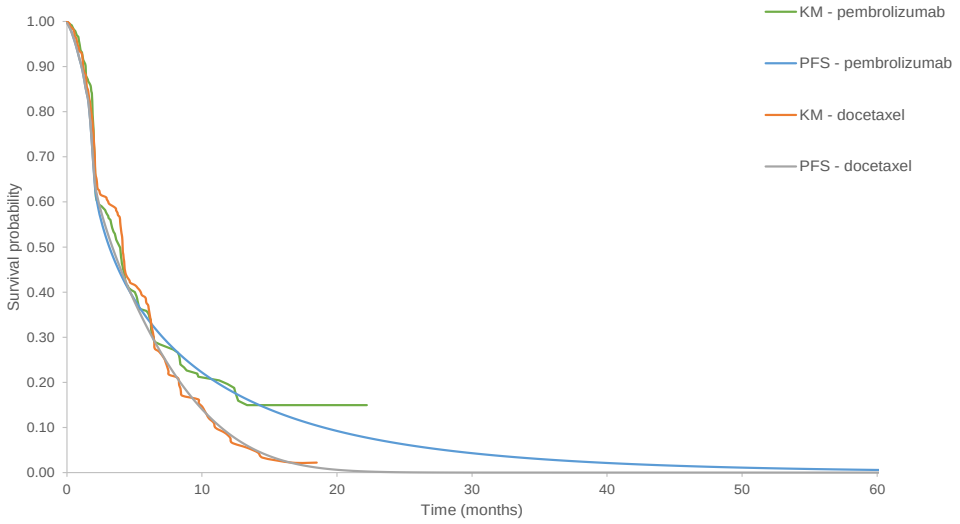
company considered the generalised gamma distribution to best fit the data. As a result, KEYNOTE-010 KM data were used to week 9 and generalised gamma curves fitted to KEYNOTE-010 were used from week 9 onwards. The fitted PFS data for both treatment arms is shown in Figure 5.

Overall-survival was estimated as follows:

- The company used a piecewise model using Kaplan Meier data from KEYNOTE-010 and external data from non-comparative studies with longer-term follow up. This was deemed appropriate and logical as the proportional hazards assumption was not found to hold and when separate parametric curves were fitted this resulted in clinically implausible outcomes with a poor visual fit. Based on different approaches to OS extrapolation, two base cases were assessed (Figures 6 and 7):
  - Base case 1: In the pembrolizumab arm, the KM data from KEYNOTE-010 up to the first 52 weeks was used. In the second phase, an exponential curve fitted to data from KEYNOTE-001 was used from 52 weeks onwards. In the docetaxel arm, the KM data from KEYNOTE-010 up to the first 52 weeks were used. In addition, adjustment for switching using a two stage method was also applied. In the second phase, an exponential curve was fitted to data from KEYNOTE-010 was used from 52 weeks onwards.
  - Base case 2: In the pembrolizumab arm, the KM data from KEYNOTE-010 up to the first 52 weeks were used which was similar to base case 1. In the second phase, contrary to base case 1, an exponential curve fitted to data from KEYNOTE-010 was used from 52 weeks onwards. For the docetaxel arm, the extrapolation approach used remains the same as that to base case 1.

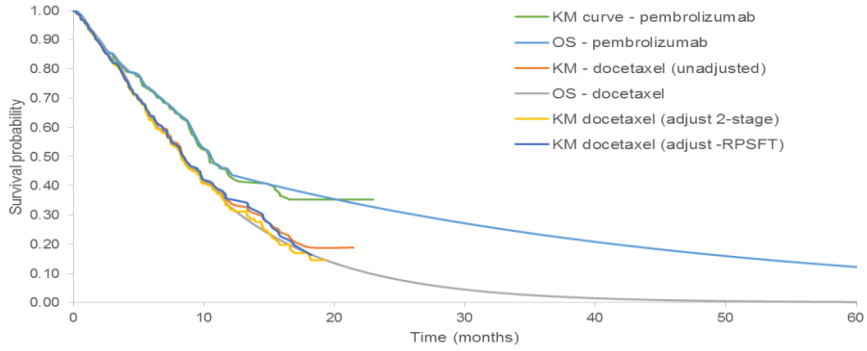
– For both base cases, adjustment to switching to other PD-L1 treatments following treatment discontinuation was also applied to the docetaxel monotherapy arm. For the nintedanib with docetaxel arm, PFS and OS were estimated by applying the estimated hazard ratio from the NMA to the docetaxel monotherapy curves. Only data from the adenocarcinoma patients within KEYNOTE-010 were used

Figure 5 Base case 2-phase piecewise models for PFS of pembrolizumab and docetaxel based on KEYNOTE-010



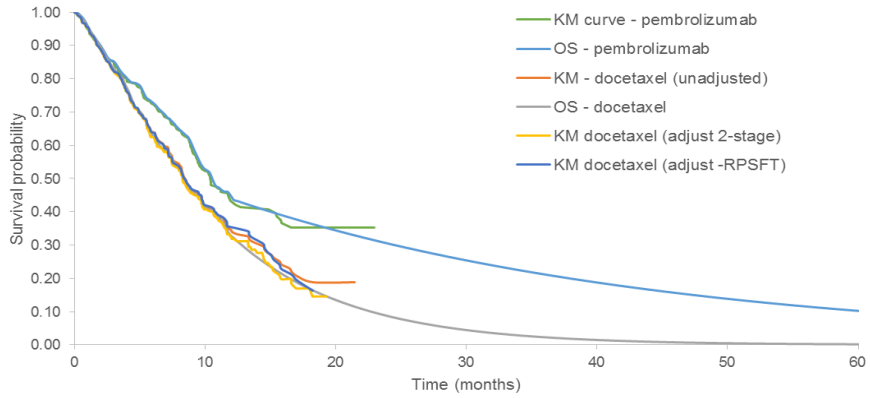
Source: Figure 48, page 179, of the company submission

Figure 6 Base case 1 – KM+exponential+projection based on KEYNOTE-001 for pembrolizumab arm vs. KM+exponential for docetaxel arm, with OS for docetaxel adjusted using the two-stage method.



Source: Figure 38, page 172, of the company submission

Figure 7 Base case 2 – KM+exponential for both pembrolizumab and docetaxel arms, with OS for docetaxel adjusted for switching using the two-stage method



Source: Figure 39, page 173, of the company submission

4.31 The company presented health-related quality of life (HRQOL) data from EuroQol EQ-5D questionnaires completed by the KEYNOTE-010 patients. People completed the EQ-5D questionnaires 6 times during treatment and once after treatment discontinuation. People's health-related quality of life was estimated as a function of length of time until death; these were considered separately for pre-progression and post-progression health states. As a result, four health states were used to estimate QALYs in the model: pre-progression and <30 days to death; pre-progression and >30 days to death; post-progression and <30 days to death; and post-progression and >30 days to death. A summary of these utilities is presented in Table 26. The company applied an age related annual utility decrement of 0.0044 from the age of 62 to 75 years to reflect the natural decrease in health utilities with increasing age. No decrement was added for patients over the age of 75 as the original data source used for this adjustment (Kind et al 1999) reported the same disutility values to be applicable to patients aged 75 and above. In the model, the company assumed that any utility decrements associated with adverse events (AEs) would have been already captured in the EQ-5D scores from KEYNOTE-010; therefore no further utility decrements were applied to the model.

Table 8 Mean utility scores informing the company model

Base case analysis		
	Mean	95% CI
Pre-progression		
≥ 30 days	0.763	(0.751, 0.774)
< 30 days	0.284	(0.136, 0.433)
Post-progression		
≥ 30 days	0.675	(0.644, 0.705)
< 30 days	0.320	(0.052, 0.588)
Source: ERG report, Table 26 (page 118)		

4.32 The model included the drug and administration costs related to the intervention and comparator, including the costs related to subsequent therapies, the monitoring and management of the disease, the management of adverse events and the costs related to terminal care. The resource use and cost estimates used to inform the model were based on data from KEYNOTE-010 and other published sources. In addition, for patients treated with pembrolizumab, the costs of testing for PD-L1 expression were also included in the model. The company stated that a single PD-L1 test was estimated to be £40.50. The company estimated that 12% of NSCLC stage IIIB/IV to be eligible for treatment with pembrolizumab in England, and that to identify one patient eligible for treatment, 8.39 would need to be tested for PD-L1. This equates to £337.51 per patient with advanced NSCLC whose tumour expresses PD-L1 and eligible for second- or third-line pembrolizumab (Table 87, page 210 and section 6.3, page 254 of the company submission). Treatment costs where appropriate, were based on patients' weight in KEYNOTE-010 and assumed no vial sharing. Pembrolizumab has a confidential patient access scheme (PAS) included in the model but a confidential a patient access scheme for nintedanib was not known and therefore not included. As a result the list price for nintedanib was used however, the company did present a series of pairwise comparisons for pembrolizumab compared with nintedanib and docetaxel. The company presented a range of potential simple discounts with corresponding ICER's for

nintedanib in the adenocarcinoma subgroup. In base case 1, the ICER's ranged from £34,997 when 0% discount was applied to £58,364 when a 95% discount was applied. In base case 2 the ICER's ranged from £24,424 when 0% discount was applied to £38,434 when a 95% discount was applied. For full details of the ICERs from the pairwise comparison for pembrolizumab compared with nintedanib plus docetaxel (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts for nintedanib) in the adenocarcinoma subgroup, see Table 32 (page 115) of the ERG report.

ERG comments

4.33 The ERG noted that the population included in the economic model was consistent with the population specified in the NICE scope and baseline characteristics were similar compared with KEYNOTE-010. The ERG stated that there was a lack of clarity in the company submission on how trial and external data had been incorporated into the model.

4.34 The ERG noted that in the economic model, there is an inconsistency to implementing stopping rules. The model assumes maximum treatment duration for pembrolizumab and docetaxel, but not to nintedanib. The ERG commented that the company did not provide any justification for this. The ERG also noted that it is assumed in the modelling that all people will stop treatment at 2 years. Given that there is no data support this estimates of cost-effectiveness appear unreasonably optimistic. It would have been more appropriate to taper the treatment effect beyond the stopping of treatment at 2 years.

4.35 The ERG was satisfied that the company had followed the general approach to survival analysis and extrapolation of individual participant data recommended by the NICE decision support unit (DSU). However, due to the absence of long-term survival data comparing pembrolizumab with docetaxel, uncertainty remains around the estimated overall survival OS. The ERG noted that a piecewise approach was used to estimate OS.

A cut-off time of 52 weeks was used to switch from Kaplan Meier (KM) data to parametric curves. Both the company and the ERG have explored the impact of using different cut-off times. The results of the cost-effectiveness were sensitive to the cut-off times. The results of the cost-effectiveness analyses were highly sensitive to the OS extrapolation of pembrolizumab. Based on the current assumptions, 82% of the overall survival gain occurs post-progression (based on base case 1) 79% in base case 2. The results of the cost-effectiveness analyses were highly sensitive to the estimated hazard ratio of time on treatment to PFS for pembrolizumab.

4.36 The ERG noted that the company submission provided a summary of the key differences between the utility values derived from the literature and those reported in KEYNOTE-010. For the progression-free health state, the estimated health utilities were generally consistent from the two sources. However, greater differences in estimated health utilities were found for the post-progression health state. In particular, two studies reported health utilities of 0.217 and 0.22 for progressed health states. However, the company attributed this to the studies assessing utilities from healthy volunteers instead of NSCLC patients. The ERG considers the company's approach in estimating patients' health-related quality of life as a function of length of time until death separately for pre-progression and post-progression to be appropriate. In addition, the ERG found the systematic review of relevant health-related quality of life data to be helpful.

4.37 The ERG noted that treatment costs (including the cost of PD-L1 testing) represented 84% and 85% of the incremental costs in base cases 1 and 2, respectively. Therefore, only the cost of treatment and the duration of treatment could result in any meaningful impact on the incremental costs between the treatments.

Company's base-case results and sensitivity analysis

4.38 The company presented base-case results using the PAS price for pembrolizumab and the list prices for all other drugs. The company presented 2 separate base cases which were based on different approaches to the extrapolation of overall survival. For base case 1, in the pembrolizumab arm, Kaplan Meier data from KEYNOTE-010 up to the first 52 weeks were used. In the second phase, an exponential curve fitted to data from KEYNOTE-001 was used from 52 weeks onwards. In the docetaxel arm, Kaplan Meier data from KEYNOTE-010 up to the first 52 weeks were used. In addition, adjustment for switching (the company considered the two-stage method to be the most appropriate) was also applied. In the second phase, an exponential curve was fitted to data from KEYNOTE-010 was used from 52 weeks onwards. For base case 2, in the pembrolizumab arm, Kaplan Meier data from KEYNOTE-010 up to the first 52 weeks were used; this was similar to base case 1. In the second phase, contrary to base case 1, an exponential curve fitted to data from KEYNOTE-010 was used from 52 weeks onwards. For the docetaxel arm, the extrapolation approach used remains the same as that to base case 1.

4.39 In base case 1 for pembrolizumab compared with docetaxel, pembrolizumab was associated with an additional 0.70 QALYs at an additional cost of £30,242, giving an ICER of £43,351 per QALY gained. (Table 9).

4.40 In base case 2 for pembrolizumab compared with docetaxel, pembrolizumab was associated with an additional 0.61 QALYs at an additional cost of £30,016, giving an ICER of £49,048 per QALY gained. (Table 9).

4.41 The company presented cost-effectiveness results for the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1.

- In base case 1 for pembrolizumab compared with nintedanib plus docetaxel, pembrolizumab was associated with an additional 0.529 QALYs at an additional cost of £18,506 giving ICER of £34,997 per QALY gained. (Table 10).
- In base case 2 for pembrolizumab compared with nintedanib plus docetaxel , pembrolizumab was associated with an additional 0.823 QALYs at an additional cost of £19,282, giving ICER of £23,424 per QALY gained. (Table 10).

4.42 Full details of the base case results, including clinical outcomes and disaggregated costs, can be found in section 5.7 (page 218–219) of the company submission; details of the deterministic and probabilistic analyses can be found in sections 5.8.2 (page 235–238) and 5.8.1 (page 229–234).

Table 9 Company results for base case 1 and base case 2 (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£41,509	1.90	1.30	-	-	-
Docetaxel	£11,267	0.87	0.60	£30,242	0.70	£43,351
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£41,283	1.77	1.22	-	-	-
Docetaxel	£11,267	0.87	0.60	£30,016	0.61	£49,048
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years Source: Company submission, Table 96 (page 219)						

Table 10 Company results for adenocarcinoma subgroup (incremental analysis; discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER (£) vs. comparator	Incremental analysis
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£42,238	1.988	1.364	-	-	-	-
Nintedanib + Docetaxel	£23,732	1.204	0.836	£18,506	0.529	£34,997	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£29,444	0.660	£44,597	£44,597
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£43,014	2.442	1.659	-	-	-	-
Nintedanib + Docetaxel	£23,732	1.204	0.836	£19,282	0.823	£23,424	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£30,220	0.955	£31,657	£31,657

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: Company submission, Table 97 (page 219)

4.43 The company presented both deterministic and probabilistic sensitivity analyses. The deterministic results showed that, when comparing pembrolizumab with docetaxel, the model results were most sensitive to extrapolation of overall survival based on KEYNOTE-001, the assumptions around time on treatment, and dose intensity considered to estimate the cost of pembrolizumab. The discount rate for QALYs also had an impact on the cost-effectiveness estimates. In the subgroup analyses for adenocarcinoma patients, inputs with the greatest impact on the incremental cost-effectiveness ratio (ICER) included; the extrapolation of the overall survival using KEYNOTE-001 data, the assumptions around time on treatment and dose intensity considered to estimate the cost of pembrolizumab. The results of the probabilistic sensitivity analysis showed that the probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 81.1% or 56% (see company submission, pages 231 and 232, figures 61 and 63).

In the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is between 71.1% and 97.2% (see company submission, page 234 and 235, figures 65 and 66).

ERG comments

4.44 The ERG commented on the piecewise modelling approach to estimating overall survival (OS). In base case 1, data from KEYNOTE-001 were used. This base case is based on a non-randomised comparison of pembrolizumab from KEYNOTE-001 with the docetaxel arm from KEYNOTE-010. The ERG noted that the cost-effectiveness assessment of the adenocarcinoma sub-group was primarily based on data from the adenocarcinoma sub-group in KEYNOTE-010. The sample size of this sub-group is small and parameter estimates were associated with substantial uncertainty with the results.

4.45 The company noted that base case 2 was considered the most cost conservative analysis presented. The ERG noted that the company did not explain how it was conservative. THE ERG stated that it was only conservative in relation to the other base case. The ERG stated that they preferred base case 2 compared with base case 1 as they felt it was more plausible.

4.46 The ERG considered the most important uncertainty relates to the estimates of the OS in the model. The cost-effectiveness estimates are based on significant gains in post-progression survival with pembroluzimab with a greater proportion of patients receiving pembroluzimab surviving to 5, 10 and 20 years (12.15%, 2.46%, 0.1%, base case 2) compared to docetaxel (0.57%, 0%, 0%). These extrapolations are inevitably uncertain given the current trial follow-up (median 13 months, maximum 24 months).

4.47 The ERG commented that the network meta-analysis (NMA) presented by the company showed no evidence of a difference in overall survival and progression-free survival between pembrolizumab and nintedanib plus docetaxel. The ERG also highlighted concern about the reliability of the NMA results due to the fact that only two trials, which included different clinical populations, were included in the NMA. The ERG noted that they were unable to replicated the results presented by the company because the model used was too complex.

4.48 The ERG concluded that pembrolizumab compared with docetaxel significantly improved overall survival in previously treated adults with advanced NSCLC whose tumours express PD-L1 (TPS>1% overall population and TPS>50% stratum). Progression-free survival was also improved, in a statistically significant way but only in the pembrolizumb TPS>50% stratum and not in the overall TPS>1% population. In the TPS 1-49% stratum pembrolizumab was not shown to be superior to docetaxel in terms of overall survival and progression-free survival (however KEYNOTE-010 was not powered to detect differences in this sub-population). In a number of subgroups analyses for both primary outcomes, there was no significant difference between pembrolizumab and docetaxel.

Company scenarios

4.49 The company presented 11 scenarios exploring a number of assumptions, including:

- Using alternative approaches to extrapolate overall survival (OS) (2 scenarios)
- Assessing the impact of vial sharing in clinical practice (1 scenario)
- Changing the type of approach used to estimate utilities from KEYNOTE-010 (2 scenarios)
- Adverse event-related disutilities (1 scenario)
- In relation to the age-adjustment of utilities (1 scenario)

- Exploring a 52 week cut-off using Kaplan Meier and exponential curves (1 scenario)
- Alternative cut-off for the estimation of the exponential curve in Phase 2 of the piecewise approach (3 scenarios)

4.50 The company stated that the results of the scenario analysis showed that the cost-effectiveness of pembrolizumab is robust to the sources of uncertainty assessed, including: extrapolation approaches used to estimate OS and PFS in the longer term, utility approach used to estimate QALYs and assumptions around disutilities related to AE and to ageing. Full details of the company scenario analyses can be found in section 5.8.3 (page 239 - 245) of the company submission.

ERG additional analyses

4.51 The ERG conducted further analyses regarding the extrapolation of overall survival. In particular, this was found to be very sensitive to the choice of "cut-point" with cut-points before 52 weeks (the earliest cut-point used in the company submission) leading to a marked reduction in incremental survival benefit. The ERG noted that when earlier cut-off points were used this had a significant effect on the ICER and that overall survival decreases gradually. The ERG highlighted that the company model suggests that once people discontinue treatment there is assumed to be an overall survival gain which is extrapolated over 20 years. The incremental gain in the discounted pre-progression survival is 0.19 years and the incremental gain in post-progression survival is 0.85 years. Therefore, 82% of the overall survival gain of 1.03 years occurs post-progression after treatment has ended. Given the uncertainty in the long term extrapolations of survival and uncertainty in prognosis for patients who stop treatment at the two year times the estimates of cost-effectiveness unreasonably optimistic.

Innovation

4.52 The company considered pembrolizumab to be innovative for the following reasons:

- It was granted Promising Innovative Medicines (PIM) designation in the UK in November 2015, and in March 2016 a positive EAMS Scientific Opinion was granted.
- it represents a “step-change” in the management of patients with advanced NSCLC, as it is the first PD-1 inhibitor to be licensed and reviewed by NICE for the treatment of patients with advanced NSCLC whose tumours express PD-L1.
- It has a novel and innovative model of action, and meets an important unmet medical need by offering an additional treatment option for a life-threatening and debilitating condition.
- It will add to the currently available treatment options and, due to its innovative mechanism of action; this PD-1 immune checkpoint inhibitor is expected to provide a durable response for a proportion of NSCLC patients.

5 End-of-life considerations

5.1 The company considered that pembrolizumab fulfils the criteria to be considered as an end-of-life treatment (Table 6).

Table 6 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is lower than 24 months: • Patients with advanced NSCLC have a short life expectancy of less than 24 months (Health and Social Care Information Centre 2014).

<table>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>
<table>
<tr><th></th><th>Pembrolizumab</th><th>Docetaxel</th></tr>
<tr><td colspan="3">Primary endpoints</td></tr>
<tr><td colspan="3">Overall survival – ITT population</td></tr>
<tr><td>Median: months (95% CI)</td><td>10.4 (9.4, 11.9)</td><td>8.5 (7.5, 9.8)</td></tr>
<tr><td colspan="3">Progression-free survival – ITT population</td></tr>
<tr><td>Median: months: (95% CI)</td><td>3.9 (3.1, 4.1)</td><td>4.0 (3.1, 4.2)</td></tr>
</table>
</td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>The number of patients eligible for treatment with pembrolizumab in 2017 is expected to be:
1,795 patients with NSCLC that is PD-L1 positive - see section 6.2
1,121 patients with advanced melanoma previously untreated with ipilimumab</td></tr>
<tr><td colspan="2">Source: Company submission, table 62 (page 152)</td></tr>
</table>

6 Equality issues

6.1 No equality issues were raised during the scoping process. The company stated that it did not believe there were any issues relating to equality for this appraisal.

7 Authors

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with input from the Lead Team (Susan Griffin, Malcolm Oswald and Professor Oluwafemi Oyebode).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy.

Background

Lung cancer falls into two main histological categories: around 85–90% are non-small-cell lung cancers (NSCLC) and the remainder are small cell lung cancers. NSCLC can be further classified into 3 histological sub-types of large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma. Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV). In 2013, approximately 28,500 people were diagnosed with NSCLC in England and Wales, of whom 13% had stage IIIA, 10% had stage IIIB and 46% had stage IV disease.[1]

Cancer cells expressing an immunologic marker called programmed cell death 1 ligand (PD-L1) are believed to suppress certain immune responses and cause increased tumor aggressiveness. The proportion of NSCLC that is PD-L1 positive in England is unknown.

Lung cancer caused approximately 28,000 deaths in England in 2012.[2] The median survival of people with lung cancer (all stages) is approximately 6 months; 35% of people with lung cancer survive for more than 1 year after diagnosis.

For the majority of people with NSCLC, the aims of treatment are to prolong survival and improve quality of life. Treatment choices may be influenced by the presence of biological markers (such as mutations in epidermal growth factor receptor-tyrosine kinase (EGFR-TK), anaplastic-lymphoma-kinase (ALK) or PD-L1 status), histology (squamous or non-squamous) and previous treatment experience. NICE clinical guideline 121 (CG121) recommends platinum-based chemotherapy as an option for people with previously untreated stage III or IV NSCLC and good performance status. For people with locally advanced or metastatic NSCLC whose disease has progressed after chemotherapy, NICE recommends docetaxel monotherapy, nintedanib, afatinib and erlotinib as options in some circumstances (CG121, technology

appraisal 347, 310 and technology appraisal 374 respectively). In clinical practice, ALK-positive NSCLC tumours that progress after treatment with platinum doublet therapy may be treated with a targeted therapy such as crizotinib (not recommended by NICE but available via the Cancer Drugs Fund at the time of issuing the scope). EGFR-TK positive NSCLC tumours that progress after treatment with targeted therapy may be treated with a platinum agent in combination with gemcitabine, vinorelbine, pemetrexed or a taxane. Best supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated.

The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, anti-programmed cell death 1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Pembrolizumab does not have a marketing authorisation in the UK for treating non-small cell lung cancer. It has been studied in clinical trials, in adults with NSCLC that is PD-L1 positive, whose disease has recurred after receiving platinum-containing doublet chemotherapy, compared with docetaxel.

Intervention(s)	Pembrolizumab
Population(s)	People with advanced non-small-cell lung cancer that is PD-L1 positive: • whose disease has progressed after platinum-containing doublet chemotherapy. • whose disease has progressed on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours.

Comparators	• Docetaxel monotherapy • Nintedanib with docetaxel (for people with adenocarcinoma histology) • Afatinib or erlotinib (if no previous EGFR-TKI therapy received due to delayed or unknown mutation status in the circumstances described in TA374) • Crizotinib (only for patients with ALK positive mutation status, not recommended by NICE but available via the CDF) • Nivolumab (subject to ongoing NICE appraisal) • Ceritinib (only for patients with ALK positive mutation status, subject to ongoing NICE appraisal) • Ramucirumab with docetaxel (subject to ongoing NICE appraisal) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.

Other considerations	If the evidence allows, consideration will be given to subgroups based on cancer histology and biological markers (PD-L1, EGFR, ALK). If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer' (2015). NICE technology appraisal 347. Review date July 2018. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (2014). NICE technology appraisal guidance 310. Review Proposal Date Apr 2017. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175; 2015). NICE technology appraisal guidance 374. Review Proposal Date December 2018. Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (2013). NICE technology appraisal guidance 296. Review Proposal Date May 2016. Appraisals in development: 'Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer'. NICE technology appraisal guidance [ID729]. Expected date of publication TBC. 'Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer'. NICE technology appraisal guidance [ID811]. Expected date of publication May 2016.

	'Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer'. NICE technology appraisal guidance [ID900]. Expected date of publication September 2016 'Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer'. NICE technology appraisal [ID838]. Expected date of publication August 2016. Related Guidelines: The diagnosis and treatment of lung cancer (2011). NICE clinical guideline 121. Review date June 2015. Related Quality Standards: 'Quality standard for lung cancer (2012). NICE quality standard 17. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways: Lung cancer. Pathway created: Mar 2012. http://pathways.nice.org.uk/pathways/lung-cancer
Related National Policy	Department of Health, Improving Outcomes: A strategy for cancer, third annual report, Dec 2013 https://www.gov.uk/government/publications/the-national-cancer-strategy-3rd-annual-report--2 NHS England, Manual for prescribed specialised services, chapter 105: specialist cancer services (adults), Jan 2014. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2013-2014, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf Department of Health, Cancer commissioning guidance, Dec 2009. http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_110115

Questions for consultation

- Have all the relevant comparators for pembrolizumab been included in the scope?
- Where do you consider pembrolizumab will fit into the existing NICE pathway, lung cancer.

References

1. National Lung Cancer Audit: 2013 Patient Cohort. Published 2014 [accessed March 2015]

2. Cancer Research UK (2013) Lung cancer survival and mortality statistics. [accessed March 2015]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy [ID840]

Final matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Merck Sharp & Dohme (pembrolizumab) Patient/carer groups • Roy Castle Lung Cancer Foundation Professional groups • Association of Cancer Physicians • British Thoracic Oncology Group • British Thoracic Society • Cancer Research UK • National Lung Cancer Forum for Nurses • Royal College of Physicians • Royal College of Radiologists Others • Department of Health • NHS England • Welsh Government	General • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland Comparator companies • *Accord Healthcare (docetaxel) (CAU not returned, not participating)* • *Actavis UK (docetaxel) (CAU not returned, not participating)* • *Boehringer Ingelheim (nintedanib, afatinib) (CAU not returned, not participating)* • *Dr. Reddy's Laboratories (docetaxel) (CAU not returned, not participating)* • *Hospira UK (docetaxel) (CAU not returned, not participating)* • Lilly UK (ramucirumab) • *Medac GmbH (docetaxel) (CAU not returned, not participating)* • *Novartis (ceritinib) (CAU not returned, not participating)* • Roche Products (erlotinib) • *Sanofi (docetaxel) (CAU not returned, not participating)* • Pfizer (crizotinib) • *Bristol-Myers Squibb (nivolumab) (CAU not returned, not participating)* Relevant research groups • National Cancer Research Institute Associated Public Health Groups None

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy [ID840]

Merck Sharp & Dohme: Evidence submission

24th March 2016

File name	Version	Contains confidential information	Date
		Yes	

Contents

Tables and figures

Abbreviations

AE	Adverse Event
AEOSI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
APaT	All Patients as Treated
BOR	Best Overall Response
BSC	Best Supportive Care
BTD	Breakthrough Therapy Designation
CDF	Cancer Drugs Fund
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CR	Complete response
CSR	Clinical Study Report
CTA	Clinical Trial Assay
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DCR	Disease control rate
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMit	Electronic Market Information Tool
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
EQ-5D	EuroQoL 5 Dimensions
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food and Drug Administration
HR	Hazard Ratio
HRQoL	Health-related quality of life
IA1	First Interim-Analysis
IA2	Second Interim-Analysis
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INV	Investigator evaluation
irAEs	Immune-related AEs
IRC	independent review committee
irRC	Immune-related response criteria
ITT	Intention-to-treat
IV	Intravenous
IVRS/IXRS	Interactive Voice Response System/ Interactive Voice and Web Response

	System
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
MedDRA	Medical Dictionary of Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MK-3475	Pembrolizumab - *Keytruda*®
MRA	Market Ready Assay
MSD	Merck Sharp and Dohme Ltd
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
ORR	Overall Response Rate
OS	Overall Survival
PA	Prototype Assay
PAS	Patient Access Scheme
PD	Progressive Disease
PD-1	Programmed death 1 protein
PD-L1	Programmed cell death 1 ligand 1
PFR	Progression-free rate
PFS	Progression free survival
PIM	Promising Innovative Medicines
PK	Pharmacokinetics
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcomes
QALY(s)	Quality-Adjusted Life Year(s)
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank-preserving structural failure time
RR	Response rate
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable Disease
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SOC	Standard of Care
TA	Technology Appraisal
TC	Tumour cells
TNM	Tumour, Node, and Metastases
TPS	Proportion of tumour cells staining for PD-L1
UK	United Kingdom of Great Britain and Northern Ireland
US	United States of America
VAS	Visual Analogue Scale
VAT	Value-Added Tax

1. Executive summary

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] In the United Kingdom (UK), each year more than 44,000 people are diagnosed with lung cancer and over 35,000 die from the condition.[2] More than half of non-small cell lung cancer (NSCLC) patients present with incurable advanced local or metastatic disease at the time of diagnosis,[2] with an estimated five-year survival rate around 5%.[3]

Despite the benefits associated with platinum-based chemotherapy or targeted therapy, survival remains poor for patients with advanced NSCLC (see section 3.3). For advanced NSCLC patients who have progressed after first-line chemotherapy and targeted therapy the prognosis is even worse. There are limited treatment options for these patients; the response rate for currently approved agents in this population is less than 15%; duration of response is limited, and almost all patients relapse and die as a consequence of their NSCLC,[4-7] and therefore there is a need for new and more effective therapies. In, recent years, in the field of NSCLC, the development of targeted treatments for patients with Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK) genomic tumour aberrations has demonstrated the utility of such an approach

Programmed death 1 protein (PD-1) is an immune-checkpoint receptor that is expressed on antigen-presenting T cells. PD-1 acts to initiate downstream signalling, which in turn inhibits the proliferation of T cells as well as cytokine release and cytotoxicity.[8] The PD-1 ligands, PD-L1 and PD-L2, are frequently upregulated on the surface of many tumour cell surfaces.[9] Pembrolizumab is a potent and highly selective humanised monoclonal antibody designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour immunity

Pembrolizumab received a marketing authoristation for use in patients with metastatic melanoma in 2015 and has been recommended for use in the NHS by NICE for this patient population.

Within this submission, pembrolizumab is proposed to be used as second or third-line treatment option for adult patients with advanced NSCLC whose tumours express PD-L1 and who have disease progression on or after prior platinum-based chemotherapy and, if

EGFR or ALK mutation positive, also experience disease progression on approved therapies for these aberrations prior to receiving pembrolizumab.

The efficacy of pembrolizumab has been evaluated primarily through the KEYNOTE-010 study, a phase II/III randomized controlled trial (median follow up of 13 months, range 6 to 24 months) in a patient population relevant to this submission. The results demonstrate both a statistically significant as well as clinically meaningful benefit for patients. For overall survival, compared to docetaxel, there was a 29% reduction in the risk of death (hazard ratio (HR) 0.71, p=0.00076), based on the final analysis. Supportive data from KEYNOTE-001 provides additional evidence for the long term survival benefit of pembrolizumab treatment (median follow up 16.2 months; range 10.9 to 32.3 months).

The results from KEYNOTE-010 also demonstrate improved progression free survival (based on independent review committee (IRC) per RECIST 1.1) for pembrolizumab compared to docetaxel (HR 0.88, p=0.06758). Because of the unique pattern of response associated with immunotherapy, there are more progression events based on RECIST 1.1 than irRC (generally due to new lesions classified as progressive disease per RECIST 1.1[10]). PFS when assessed by irRC may be a better reflection of the benefit of immunotherapies to patients (HR 0.76, p=0.00174 in the pembrolizumab 2 mg/kg Q3W arm vs. the docetaxel arm).

Fewer drug-related AEs, drug-related Grade 3-5 AEs; and fewer discontinuations due to drug-related AEs occurred among patients in the pembrolizumab 2 mg/kg Q3W arm compared to the docetaxel arm. Immune-related AEs were typically Grade 1 to 2, and were generally reversible with treatment discontinuation and/or use of corticosteroids. Overall, the safety profile of pembrolizumab remains consistent with previously reported findings in patients with advanced melanoma, showing that pembrolizumab is well tolerated and the safety profile is acceptable for an advanced NSCLC population; and favourable when compared to chemotherapy.

Cost-effectiveness was evaluated through the development of a three-state partitioned survival model, with the three states being PFS, post-progression and death, in line with the modelling approach taken in previous HTAs concerning advanced NSCLC reviewed by NICE (see section 5.2). The model projected health outcomes (i.e. OS and PFS) to estimate patients' health-related quality of life (HRQoL) and costs. Quality-adjusted life years (QALYs) were estimated by using an approach that considered time-to-death and progression-based utilities derived from EQ-5D data. Clinical and economic outcomes were projected over a 20-year time horizon to cover the anticipated lifetime of the target population initiating second or third line therapy.

A number of approaches have been taken to evaluating the cost-effectivess of pembrolizumab with the two more conservative selected as the primary analyses for this submission. The results demonstrate that pembrolizumab meets the NICE criteria to be considered a cost-effective use of NHS resources.

In the two base case analyses, the model estimates that patients treated with pembrolizumab gain 0.70 additional QALYS (base case 1) or 0.61 QALYs (base case 2), compared to docetaxel monotherapy. The incremental cost- effectiveness ratio (ICER) when comparing pembrolizumab to docetaxel is respectively £43,351 and £49,048. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is therefore 81.1% or 56%.

In patients with NSCLC of adenocarcinoma histology, the model estimates that treatment with pembrolizumab results in a gain of additional 0.529 (base case 1) or 0.823 QALYs (base case 2), compared to nintedanib combined with docetaxel. The ICER when comparing pembrolizumab to nintedanib in combination with docetaxel combination is respectively £34,997 and £23,424. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is therefore 71.1% and 97.2%.

The availability of pembrolizumab for the treatment of patients with advanced NSCLC that is PD-L1 positive, whose disease has progressed after platinum-containing doublet chemotherapy (and, if EGFR or ALK positive mutations, after disease progression on an approved therapy for these aberrations) in England will represent a step-change in the treatment options available and will provide patients and clinicians with a transformative new treatment option.

Clinicians view pembrolizumab, the first of a new class of immuno-oncology agents for use in patients with advanced NSCLC whose tumours express PD-L1, as a step change in treatment, as it validates the use of PD-L1 expression for optimal treatment selection in patients with advanced NSCLC. Pembrolizumab, alongside other targeted therapies, is expected by them to displace the use of docetaxel in this patient population.

1.1 Statement of decision problem

The decision problem addressed in the submission is presented in the Table 1 below.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with advanced non-small-cell lung cancer that is PD-L1 positive: ▪ whose disease has progressed after platinum-containing doublet chemotherapy. ▪ whose disease has progressed on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours.	People with advanced NSCLC that is PD-L1 positive, whose disease has progressed after platinum-containing doublet chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations.	In line with the anticipated licence and with the final NICE scope.
Intervention	Pembrolizumab	Pembrolizumab 2mg/kg Q3W	In line with the anticipated licence and with the final NICE scope.
Comparator (s)	▪ Docetaxel monotherapy ▪ Nintedanib with docetaxel (for people with adenocarcinoma histology) ▪ Nivolumab (subject to ongoing NICE appraisal) ▪ Ceritinib (only for patients with ALK positive mutation status, subject to ongoing NICE appraisal) ▪ Ramucirumab with docetaxel (subject to ongoing NICE appraisal) ▪ Best supportive care (BSC)	▪ Docetaxel monotherapy ▪ Nintedanib with docetaxel (for people with adenocarcinoma histology)	▪ Nivolumab is not a relevant comparator because it has not yet been recommended by NICE for second-line NSCLC. ▪ Ceritinib is not a relevant comparator because it has not yet been recommended by NICE. ▪ Ramucirumab with docetaxel is not a relevant comparator because it has not yet been recommended by NICE. ▪ BSC, outside of the context of being offered alongside of systemic anti-cancer therapies is the option when there is no other active treatment available. ▪ Pembrolizumab as a second or third line therapy, by definition would be offered subsequent to platinum-based, and where appropriate and EGFR or ALK targeted therapy.

			At these points in the care pathway docetaxel is considered and appropriate treatment option
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS) • response rates (RRs) • adverse effects (AEs) of treatment • health-related quality of life (HRQoL)	The outcome measures considered include: • OS • PFS • RRs • AEs of treatment • HRQoL	In line with NICE final scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the comparator technologies should be taken into account.	• The cost-effectiveness is expressed in terms of an incremental cost per quality-adjusted life year (QALY) • The time horizon considered is 20 years • Costs are considered from an NHS and PSS perspective •	In line with NICE final scope
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on cancer histology and biological markers (PD-L1, EGFR, ALK).	• People with NSCLC of adenocarcinoma histology	▪ As part of the cost-effectiveness model, subgroup analysis on patients with NSCLC of adenocarcinoma type was conducted, where pembrolizumab was compared against nintedanib in combination with docetaxeland against docetaxel monotherapy.
Special considerations including issues related to equity or equality	If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices.	• The cost of testing for PD-L1 expression, required to assess patients' eligibility to treatment with pembrolizumab, has been included as part of the cost-effectiveness assessment.	In line with NICE final scope

1.2 Description of the technology being appraised

The technology being appraised is described in Table 2 below:

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Marketing authorisation/CE mark status	Pembrolizumab has a marketing authorization for use in patients with metastatic melanoma. MSD anticipates a licence indication for advanced NSCLC in the UK later this year.
Indications and any restriction(s) as described in the summary of product characteristics	Indication to which this submission relates: KEYTRUDA is indicated for the treatment of advanced NSCLC in adults whose tumours express PD-L1 and who have disease progression on or after prior chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations prior to receiving pembrolizumab.
Method of administration and dosage	2 mg/kg every three weeks (Q3W); intravenous (IV) infusion.

Pembrolizumab is a highly selective humanized monoclonal antibody against programmed death-1 (PD-1) receptor, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab activates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates antitumour immunity (see section 2.1).

The route of administration for pembrolizumab is IV infusion, over a 30 minute period; and the anticipated licensed dose regimen is 2 mg/kg Q3W. Treatment with pembrolizumab continues until disease progression or unacceptable toxicity, whichever occurs first. The list price of pembrolizumab is £1,315 per 50 ml vial ([redacted]). Each vial contains 50 mg of pembrolizumab. After reconstitution, 1 mL of solution contains 25 mg of pembrolizumab.

Testing for PD-L1 status is not routinely undertaken in the NHS. MSD is currently supporting the development of PD-L1 testing reference centres, which will provide the capacity to enable all advanced NSCLC patients' tumours to be tested for PD-L1 status. It is anticipated that after the recommendation by NICE of pembrolizumab for patients with advanced

NSCLC, PD-L1 testing of all advanced NSCLC patients will become part of routine clinical practice.

Pembrolizumab is currently under review by the European Medicines Agency (EMA), with a licence anticipated in June 2016. The anticipated licence indication is "treatment of advanced NSCLC in adults whose tumours express PD-L1 and who have disease progression on or after prior chemotherapy. Patients with epidermal growth factor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations should also have disease progression on approved therapy for these aberrations prior to receiving pembrolizumab". In May 2015 the EMA granted marketing authorization for pembrolizumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. In 2015 the National Institute for Health and Care Excellence (NICE) published two pieces of guidance (TA357[11] and TA366[12]) recommending pembrolizumab as an option for treatment of advanced (unresectable or metastatic) melanoma.

The innovative nature of pembrolizumab was recognised by the United States (US) Food and Drug Administration (FDA) in October 2014 by granting it Breakthrough Therapy Designation (BTD) for the treatment of patients with advanced (metastatic) NSCLC whose disease has progressed after other treatments.[13] The FDA's BTD is intended to expedite the development and review of a drug that is planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.[13]

In the UK, pembrolizumab received Promising Innovative Medicines (PIM) designation (Early Access to Medicines Scheme (EAMS) Step 1) in November 2015, and in March 2016 pembrolizumab was granted a positive Scientific Opinion by the Medicines and Healthcare Products Regulatory Agency's (MHRA) (MHRA EAMS number 00025/0001) for the treatment of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test [14] (see section 2.5). EAMS aims to give earlier access to promising new unlicensed or 'off label' medicines to UK patients that have a high unmet clinical need. In order to facility patient access to pembrolizumab in the period following the presentation of the KEYNOTE-010 results, MSD is offering pembrolizumab free of charge under EAMS. MSD anticipates that a minimum of 25 UK centres will be involved in the pembrolizumab EAMS.

1.3 Summary of the clinical effectiveness analysis

A systematic literature review was conducted to identify relevant clinical trials from the published literature (see section 4.1).

The clinical evidence presented in this submission is derived primarily from the final analysis of KEYNOTE-010; an adequately powered phase II/III randomised controlled trial (RCT) of pembrolizumab 2mg/Kg Q3W (anticipated licence dose and schedule, relevant to this submission) and 10mg/Kg Q3W versus docetaxel, in a patient population relevant to the anticipated label (previously treated patients with advanced NSCLC whose tumours express PD-L1) (see section 4.7). KEYNOTE-001 is a phase I study due to its initial dose escalation component, that evolved into multiple phase II-like sub-studies through a series of expansion cohorts. Cohorts C, F2 and F3 provide supportive evidence for the additional survival benefit seen with pembrolizumab; and for the comparative effectiveness of pembrolizumab in patients with advanced NSCLC whose tumours express PD-L1 (based on a Tumour Proportion Score (TPS) of ≥1%: TPS is the percentage of viable tumour cells showing partial or complete immunohistochemistry (IHC) membrane staining) and patients whose tumours do not express PDL-1 (TPS<1%) (see section 4.7). Since there is no direct clinical evidence comparing the clinical effect of pembrolizumab with nintedanib in combination with docetaxel for adenocarcinoma patients, an indirect and mixed treatment comparison was performed and the results are also provided (see section 4.10).

The baseline characteristics of the patients included in KEYNOTE-010 and KEYNOTE-001 were as expected for patients with advanced NSCLC, and representative of the patients who are anticipated to receive pembrolizumab in UK clinical practice (see section 4.5).

The evidence provided is robust and consistently demonstrates both a statistically significant and clinically meaningful benefit of pembrolizumab compared to docetaxel for adults with advanced NSCLC whose tumours express PD-L1, who have experienced disease progression after at least a platinum-containing systemic therapy:

In previously treated patients with advanced NSCLC whose tumours express PD-L1 (TPS≥1%), pembrolizumab 2mg/kg Q3W demonstrated superior OS compared to docetaxel, with a 29% reduction in the risk of death (hazard ratio (HR) 0.71, p=0.00076), based on the final analysis of KEYNOTE-010 (median follow up of 13 months, range 6 to 24 months) (see section 4.7). The OS curve of the pembrolizumab arm began to separate from the docetaxel arm around Month 4, the separation from the curve of docetaxel increased over time without crossing (see section 4.7). Supportive data from KEYNOTE-001 provides additional evidence for the long term survival benefit of pembrolizumab treatment (median follow up

16.2 months; range 10.9 to 32.3 months) (see section 4.7). In the Total Previously Treated Efficacy Population of KEYNOTE-001, the median OS for pembrolizumab was 11.1 months in patients with advanced NSCLC who express PD-L1 (TPS≥1%); similar to the median OS observed in KEYNOTE-010 patients (10.4 months, 95% CI 9.4, 11.9 months). This represents a clinically meaningful improvement compared to the 8.6 months median OS observed in the KEYNOTE-001 patients with advanced NSCLC whose tumours do not express PD-L1 (TPS<1%) (OS HR 0.81; 95% CI 0.57, 1.14 for PD-L1 expressers vs. PD-L1 non-expressers); or the median OS observed in the docetaxel arm of the KEYNOTE-010 (median OS 8.5 months) (see section 4.7). These results support the use of PD-L1 expression for the identification of advanced NSCLC patients that benefit the most from treatment with pembrolizumab.

In previously treated patients with advanced NSCLC whose tumours express PD-L1 (TPS≥1% population), pembrolizumab 2mg/kg Q3W also improved PFS (based on independent review committee (IRC) per RECIST 1.1) [10] compared to docetaxel (HR 0.88, p=0.06758) (see section 4.7). Because of the unique pattern of response associated with immunotherapy, there are more progression events based on RECIST 1.1 than irRC (generally due to new lesions classified as progressive disease per RECIST 1.1[10]). PFS when assessed by irRC may be a better reflection of the benefit of immunotherapies to patients (HR 0.76, p=0.00174 in the pembrolizumab 2 mg/kg Q3W arm vs. the docetaxel arm). These results support the robustness of KEYNOTE-010 PFS data in previously treated patients with advanced NSCLC whose tumours express PD-L1.

In KEYNOTE-010, the mean duration of study treatment was nearly 2-fold longer on pembrolizumab 2 mg/kg Q3W arm compared to docetaxel arm, therefore crude percentages of adverse events (AEs) are likely to underestimate the differences in safety in favour of the docetaxel arm (see section 4.12). Despite this, fewer drug-related AEs, drug-related Grade 3-5 AEs; and fewer discontinuations due to drug-related AEs occurred among patients in the pembrolizumab 2 mg/kg Q3W arm compared to the docetaxel arm. Immune-related AEs were typically Grade 1 to 2, and generally reversible with treatment discontinuation and/or use of corticosteroids. Overall, the safety profile of pembrolizumab remains consistent with previously reported findings in patients with advanced melanoma, showing that pembrolizumab is well tolerated and the safety profile is acceptable for an advanced NSCLC population; and favourable when compared to chemotherapy.

In both KEYNOTE-010 and KEYNOTE-001 there were no meaningful differences in efficacy or safety between the two pembrolizumab regimens, 2 mg/kg Q3W and 10 mg/kg Q3W. Clinical efficacy results for pembrolizumab presented in this submission focus on the

anticipated licensed dose and schedule of 2mg/kg Q3W, with results including the 10mg/Kg dosage arm provided as an appendix (Appendix 11).

1.4 Summary of the cost-effectiveness analysis

The cost-effectiveness of pembrolizumab was assessed against docetaxel in patients with advanced NSCLC whose tumours express PD-L1, whose disease has progressed after platinum-containing doublet chemotherapy (and, if EGFR or ALK positive mutations, after disease progression on an approved therapy).

Cost-effectiveness was evaluated through the development of a three-state partitioned survival model, with the three states being PFS, post-progression and death, in line with the modelling approach taken in previous HTAs concerning advanced NSCLC reviewed by NICE (see section 5.2). The model projected health outcomes (i.e. OS and PFS) to estimate patients' health-related quality of life (HRQoL) and costs. Quality-adjusted life years (QALYs) were estimated by using an approach that considered time-to-death and progression-based utilities derived from EQ-5D data. Clinical and economic outcomes were projected over a 20-year time horizon to cover the anticipated lifetime of the target population initiating second or third line therapy.

The clinical evidence used to populate the pembrolizumab and docetaxel arms in the first instance was taken from the pivotal KEYNOTE-010 trial.

PFS and OS for pembrolizumab and docetaxel were modelled using a piecewise approach:

- During the first year the KEYNOTE-010 KM data was used.
- Between years 1 and 2 OS was extrapolated using standard parametric approaches.
- After year 2 either KEYNOTE-001 data was used, or published UK registry data that reflected the expected OS for patients with stage IIIb/IV treated with chemotherapy.

Based on additional information provided by lung clinical experts related to the uncertainty around the OS benefit of pembrolizumab in the longer term, we examined an additional conservative base case analysis that is even more conservative in terms of the predicted OS benefit related to pembrolizumab. This approach utilises the KM data from KEYNOTE-010 until year one, followed by an exponential adjustment after week 52 onwards. Analyses are also presented for the subgroup of NSCLC patients of adenocarcinoma histology. For this, the HR from the comparison between nintedanib and docetaxel combination versus docetaxel chemotherapy (as estimated by results of the NMA; see section 1.3 and section

4.10) was used, assuming proportional hazards. For this analysis, the cohort of patients treated with either pembrolizumab or docetaxel monotherapy were modelled as stated above, using data specific for the adenocarcinoma group within KEYNOTE-010.

Section 5 details the development of the de novo economic model for pembrolizumab, with Table 3 and Table 4 below presenting the results for the overall population considered in the submission and for the subgroup of patients with NSCLC of adenocarcinoma histology, respectively.

In the two base case analyses, the model estimates that patients treated with pembrolizumab gain 0.70 additional QALYS (base case 1) or 0.61 QALYs (base case 2), compared to docetaxel monotherapy. The incremental cost- effectiveness ratio (ICER) when comparing pembrolizumab to docetaxel is respectively £43,351 and £49,048. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is therefore 81.1% or 56%.

In patients with NSCLC of adenocarcinoma histology, the model estimates that treatment with pembrolizumab results in a gain of additional 0.529 (base case 1) and 0.823 QALYs (base case 2), compared to nintedanib combined with docetaxel. The ICER when comparing pembrolizumab to nintedanib in combination with docetaxel combination is respectively£34,997 and £23,424. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is between 71.1% and 97.2%.

Table 3: Incremental cost-effectiveness results – Base case 1 and base case 2, overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£41,509	1.90	1.30	-	-	-
Docetaxel	£11,267	0.87	0.60	£30,242	0.70	£43,351
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£41,283	1.77	1.22	-	-	-
Docetaxel	£11,267	0.87	0.60	£30,016	0.61	£49,048
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 4: Incremental cost-effectiveness results for the subgroup of patients with advanced NSCLC of adenocarcinoma histology

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER (£) versus next less costly and less effective	Incremental analysis
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£42,238	1.988	1.364	-	-	-	-
Nintedanib + Docetaxel	£23,732	1.204	0.836	£18,506	0.529	£34,997	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£29,444	0.660	£44,597	£44,597
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£43,014	2.442	1.659	-	-	-	-
Nintedanib + Docetaxel	£23,732	1.204	0.836	£19,282	0.823	£23,424	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£30,220	0.955	£31,657	£31,657
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years **Compared to the next less costly treatment* ***Compared to the next less effective treatment*							

2. The technology

2.1 Description of the technology

Brand name: KEYTRUDA®

Generic name: pembrolizumab

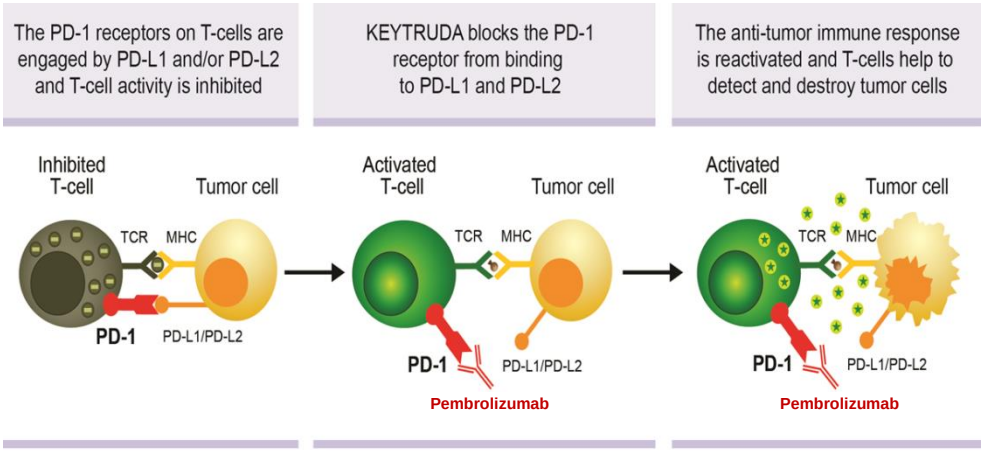
Therapeutic class: BNF Category "Other immunomodulating drugs" (08.02.04).[15]

Brief overview of mechanism of action:

Programmed death 1 protein (PD-1) is an immune-checkpoint receptor that is expressed on antigen-presenting T cells. PD-1 acts to initiate downstream signalling, which in turn inhibits the proliferation of T cells as well as cytokine release and cytotoxicity.[8] The PD-1 ligands, PD-L1 and PD-L2, are frequently upregulated on the surface of many tumour cell surfaces.[9]

Pembrolizumab (Keytruda®) is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype.[8] designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells (Figure 1). By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour immunity (Figure 1)

Figure 1: Pembrolizumab – mechanism of action



T-Cell Receptor (TCR): Activates T-cells when it recognizes antigens bound to MHC molecules
Major Histocompatibility Complex (MHC): Membrane-bound proteins that present peptide antigens to T-cells
Programmed cell death protein 1 (PD-1): An inhibitory immune checkpoint pathway receptor
Programmed cell death ligands 1 and 2 (PD-L1/PD-L2): Ligands for the PD-1 receptor

Source: Merck data on file.

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1: Current UK regulatory status

- Application submitted: January 2016
- CHMP Opinion expected 28 April 2016
- Estimated date of Marketing Authorization: June 2016

2.2.2: Anticipated indication in the UK

The anticipated licence indication in the UK is as follows: "*KEYTRUDA is indicated for the treatment of advanced non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have disease progression on or after prior chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations prior to receiving pembrolizumab*".

2.2.3: Anticipated restrictions or contraindications that are likely to be included in the draft summary of product characteristics (SmPC)

Please see Appendix 1.

2.2.4: Draft SmPC

The draft SmPC has been included as an appendix – see Appendix 1. Please note this draft SmPC will be subject to change as the regulatory review progresses and therefore the final version may differ compared to the one presented in Appendix 1.

2.2.5 Draft EMA assessment report

The draft EMA assessment report is currently unavailable.

2.2.6: Summary of the main issues discussed by the regulatory authorities

Not applicable – public assessment report currently unavailable

2.2.7: Anticipated date of availability in the UK

Pembrolizumab is already available in the UK under the Early Access to Medicines Scheme (EAMS) – see section 2.5.

The anticipated commercial launch date following regulatory approval is July 2016

2.2.8: Details of regulatory approval outside of the UK

To date, pembrolizumab has received regulatory approval for the treatment of patients with advanced NSCLC whose tumours express PD-L1 (TPS≥1%) in the following country on the date provided below.

- Malaysia: March 2015

2.2.9: Other health technology assessments in the UK

MSD will be making a submission to the Scottish Medicines Consortium (SMC) in May 2016 for the anticipated licence indication.

2.3 Administration and costs of the technology

Table 5: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Powder for concentrate for solution for infusion	Draft SmPC (see Appendix 1)
Acquisition cost (excluding VAT) *	List price: 50mg vial = £1,315 A PAS is under discussion with the Department of Health. The proposed scheme aims to provide a simple discount ([redacted]) to the list price of pembrolizumab. The NHS acquisition cost (excl. VAT) is: 50mg vial = [redacted]	Pending confirmation with Department of Health
Method of administration	Intravenous infusion	Draft SmPC (see Appendix 1)
Doses	Induction dose: 2mg/kg every 3 weeks	Draft SmPC (see Appendix 1)
Dosing frequency	Induction: 2mg/kg every 3 weeks until disease progression or unacceptable toxicities	Draft SmPC (see Appendix 1)
Average length of a course of treatment	Based on the KEYNOTE-010 trial, the average time on therapy per patient is 4.97 months, equivalent to 7.20 cycles received per patient treated with pembrolizumab 2mg/kg Q3W during a course of treatment.	Clinical trial – CSR KEYNOTE-010[16]
Average cost of a course of treatment	The average cost per treatment course is: £29,114 at list price.	KEYNOTE-010
Anticipated average interval between courses of treatments	Treatment regimen is continuous until disease progression or unacceptable toxicity leading to discontinuation	CSR KEYNOTE-010
Anticipated number of repeat courses of treatments	Repeated treatment is not anticipated	Draft SmPC (see Appendix 1)
Dose adjustments	No dose adjustment is expected	Draft SmPC (see Appendix 1)
Anticipated care setting	Pembrolizumab is anticipated to be administered in the hospital setting.	

* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

2.4 Changes in service provision and management

2.4.1 Additional tests or investigations needed

Pembrolizumab is anticipated to be licensed for patients with advanced NSCLC whose tumours express PD-L1. The SmPC requires patients with advanced NSCLC to be selected for treatment with pembrolizumab based on the presence of positive PD-L1 expression confirmed by a validated test (see draft SmPC in Appendix 1).

PD-L1 expression is tested using a qualitative immunohistochemical (IHC) assay to detect PD-L1 protein in NSCLC tissue. PD-L1 protein expression is determined by using Tumour Proportion Score (TPS), which is the percentage of viable tumour cells showing partial or complete membrane staining

2.4.2 Main resource use to the NHS associated with the technology being appraised

Pembrolizumab is administered until disease progression or unacceptable toxicity. The main resource use to the NHS associated with the use of pembrolizumab is therefore expected to be related to the management of patients in the pre-progression period.

The administration of pembrolizumab will take place in a secondary care (i.e. hospital setting) with no inpatient stay required. Patients will receive pembrolizumab as an outpatient on a 3-weekly cycle, with a duration of administration of 30 minutes per infusion.

2.4.3 Additional infrastructure in the NHS

Pembrolizumab is not anticipated to require any additional infrastructure in the NHS to be put in place.

2.4.4 Extent that the technology will affect patient monitoring compared with established clinical practice in England

Pembrolizumab is expected to provide durable benefit for a proportion of patients treated. These patients can be anticipated to receive ongoing follow-up including scanning.

2.4.5 Concomitant therapies administered with the technology

No concomitant therapies are required.

2.5 Innovation

2.5.1 State whether and how the technology is a 'step-change' in the management of the condition

Over the last decade, therapies for advanced NSCLC have not significantly improved the 1-year and 5-year survival rates, even with the introduction of newer targeted therapies and combination approaches. [3] For patients who have progressed after first-line chemotherapy and targeted therapy for molecular alterations, the prognosis is even worse. In the UK there are limited treatment options for these patients; the response rate for currently approved agents in this population is <15%; duration of response is limited, and almost all patients relapse and die as a consequence of their NSCLC. [4-7]

There is currently a high unmet need for new NSCLC therapies that improve survival without greatly increasing the toxicity or significantly compromising the quality of life of patients. In addition, there is an urgent need to identify and validate more predictive biomarkers that will allow clinicians to tailor therapies to treat those who will benefit most from them.

Pembrolizumab is the first immunotherapy, and the first PD-1 inhibitor, to be approved for the treatment of advanced NSCLC patients whose tumours express PD-L1. Pembrolizumab will add to the currently available treatment options and, due to its innovative mechanism of action; this PD-1 immune checkpoint inhibitor is expected to provide a durable response for a proportion of NSCLC patients.

Furthermore, pembrolizumab represents a “step-change” in the management of patients with advanced NSCLC, as it is the first PD-1 inhibitor to be licensed and reviewed by NICE for the treatment of patients with advanced NSCLC whose tumours express PD-L1. The selection of patients for treatment with pembrolizumab on the basis of PD-L1 expression will enable pembrolizumab to be used in patients most likely to benefit, prevent unnecessary exposure to pembrolizumab for those patients who are unlikely to benefit, and ultimately save costs to the overall healthcare system.

The innovative nature of pembrolizumab was first recognised by the US Food and Drug Administration (FDA) in January 2013 by granting it Breakthrough Therapy Designation for advanced melanoma.[17] In the UK, in March 2015 pembrolizumab became the first medicine to be granted positive scientific opinion under the MHRA’s Early Access to Medicines Scheme (EAMS) for the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care.[18]

In October 2014 the FDA granted pembrolizumab Breakthrough Therapy Designation for the treatment of patients with advanced (metastatic) NSCLC whose disease has progressed after other treatments.[13] The FDA’s BTD is intended to expedite the development and review

of a drug that is planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoint.[13] In October 2015 pembrolizumab was granted accelerated approval for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.[13]

In the UK, pembrolizumab received Promising Innovative Medicines (PIM) designation (EAMS Step 1) in November 2015, and in March 2016 a positive Scientific Opinion was granted (MHRA EAMS number 00025/0001) for "*the treatment as monotherapy of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation or whose disease has progressed on or after platinum-containing chemotherapy. Patients who have an EGFR sensitising mutation or an ALK translocation should also have had disease progression on approved therapies for these aberrations prior to receiving pembrolizumab"*.[14] EAMS aims to give earlier access to promising new unlicensed or 'off label' medicines to UK patients that have a high unmet clinical need. This validates MSD's position that pembrolizumab should be considered innovative in its potential to make a significant and substantial impact on health-related benefits in an area of high unmet need.

3. Health condition and position of the technology in the treatment pathway

3.1: Brief overview of the disease/condition for which the technology is being used

The term *lung cancer* is used for tumours arising from the respiratory epithelium (bronchi, bronchioles, and alveoli). According to the World Health Organization classification, epithelial lung cancers consist of two major cell types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[19]

NSCLC accounts for up to 85-90% of lung cancer cases in the UK[2] and includes two major histological subtypes: squamous cell carcinoma (25% to 30%) and non-squamous cell

carcinoma, including adenocarcinoma (30% to 40%), large-cell carcinoma (10% to 15%), and other cell types (5%).[20;21] The histological subtype of NSCLC correlates generally with the cancer's site of origin, reflecting the variation in respiratory tract epithelia (Figure 2). Squamous cell carcinoma develops from the flat, surface covering cells in the airways. It tends to originate in the central bronchi. This type of tumour is found most commonly in men and is closely correlated with a smoking history.[19;22] Adenocarcinoma is the most common form of NSCLC in many countries. It develops from mucus making cells in the lining of the airways and lesions are usually peripherally located. Adenocarcinoma is found most commonly in women and never smokers.[19;22] Large cell carcinomas tend to occur peripherally and are defined as poorly differentiated carcinomas of the lung composed of larger malignant cells without evidence of squamous, glandular differentiation, or features of small cell carcinoma by light microscopy. These tumours are associated with a poor prognosis because of their tendency to spread to distant sites early in their course.[19;22]

NSCLC is staged according to the Tumour-Node-Metastasis (TNM) classification, based on the primary tumour size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M).[23] This information is combined to assign an overall stage of 0, I, II, III, or IV: In stage 0 the cancer is found only in the top layers of cells lining the air passages. In stages I and II NSCLC, an invasive cancer has formed but has not spread to lymph nodes or distant sites. In stage III the NSCLC has spread to lymph nodes in the middle of the chest, also described as locally advanced disease. Stage III has two subtypes: If the cancer has spread only to lymph nodes on the same side of the chest where the cancer started, it is called stage IIIA. If the cancer has spread to the lymph nodes on the opposite side of the chest, or above the collar bone, it is called stage IIIB. In stage IV NSCLC the cancer has spread to distant lymph nodes or to other organs such as the liver, bone, or brain.

Lung cancer cells harbour multiple chromosomal abnormalities, including mutations, amplifications, insertions, deletions, and translocations.[19;21;25] Molecular aberrations in genes encoding signalling proteins that drive initiation and maintenance of tumour cells are important markers of prognosis and response to treatment. More than 50% of NSCLC tumours test positive for at least one molecular biomarker; most commonly mutations in Kirsten rat sarcoma (KRAS) (15-20%)[26-29] epidermal growth factor receptor (EGFR) (17%; more frequent in women (69.7%), in patients who had never smoked (66.6%), and in those with adenocarcinomas (80.9%)),[29;30], and translocations involving anaplastic lymphoma kinase (ALK) (2-7%).[29;31;32] ALK translocations occur most commonly in non-squamous NSCLC patients.[29]

Figure 2: Primary Histologic Subtypes of NSCLC

Non-squamous-cell carcinoma

Adenocarcinoma

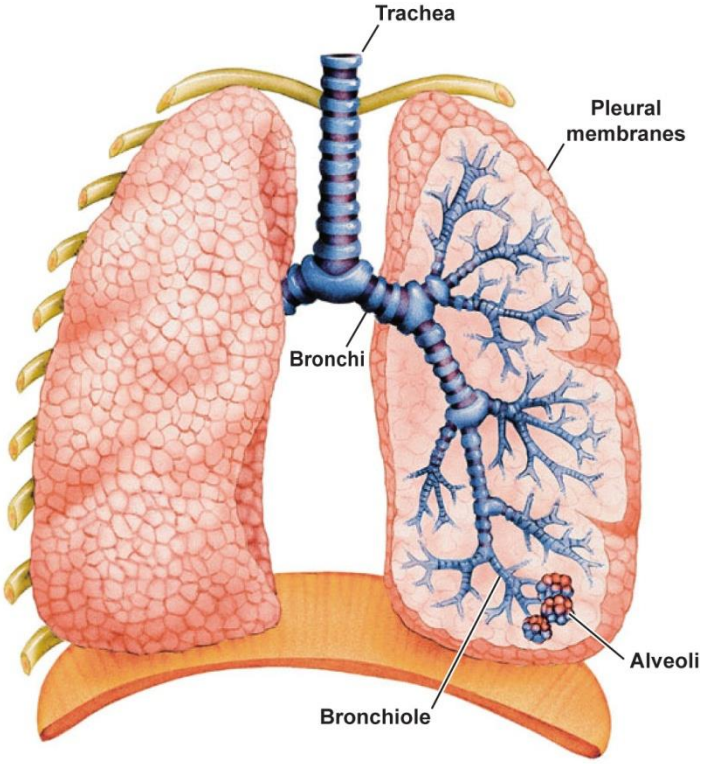
- Most common type of lung cancer in women and nonsmokers
- Lesions are usually peripherally located
- Arises from bronchi, bronchioles, or alveolar walls
- Worldwide incidence increasing

Large-cell carcinoma

- Very primitive, undifferentiated cells
- Lesions are usually peripherally located
- High tendency to metastasize

Squamous-cell carcinoma

- Most commonly found in men
- Closely correlated with smoking (dose-dependent)
- Arises from large central bronchi
- Tends to spread locally
- More readily detected in sputum



NSCLC = non-small cell lung cancer.
Source: Adapted from Teaching Times, 2016.[24]

As research continues, more biomarkers are being discovered. Programmed cell death ligand 1 (PD-L1), the ligand of PD-1 receptor, is a cell surface protein that has recently been studied in a number of resected NSCLC specimens, and has been observed in approximately 25%–40% of cases, underscoring the potential role for PD-1-based therapy.[33;34] The binding of PD-1 to PD-L1 (or to PD-L2) can inhibit a cytotoxic T-cell response. Pembrolizumab can disrupt the engagement of the PD-1 receptor with its ligands and impede inhibitory signals in T cells, resulting in cytotoxic T cells recognising and destroying the tumour cells (see section 2.1).[35] Studies have shown that PD-L1 is a predictive biomarker for anti–PD-1 and anti–PD-L1 therapies: patients whose tumours express PD-L1 respond better to PD-1 inhibitors than those patients with tumours without PD-L1 expression;[16;35-37] and patients with increasing PD-L1 expression on tumour cells and/or tumour-infiltrating immune cells respond better to PD-L1 inhibitors.[38]

The prognostic significance of PD-L1 expression in NSCLC remains controversial, with inconsistencies likely attributable to PD-L1 assay variability (i.e., differing antibodies, staining protocol, scoring, definition of cut point for positivity), relatively small study sizes, and differing baseline patient characteristics, including stage of disease at the time of tumour sample acquisition.[33;34;39-45] In an effort to clarify the prognostic significance of PD-L1

expression in NSCLC, large retrospective cohort studies were sponsored by Merck in Denmark[46] and Korea[47]. No statistically significant association was observed between PD-L1 expression and age, sex, smoking history, histology, or clinical outcomes in advanced or metastatic NSCLC.[46;47]

3.2: Effects of the disease/condition on patients, carers and society

NSCLC is often diagnosed late and is associated with a very poor prognosis.

One of the reasons for delayed diagnosis is that the most common symptoms of NSCLC (e.g. cough, shortness of breath and chest pain) are similar to those associated with conditions such as smoking and chronic bronchitis, making early diagnosis extremely difficult. Unfortunately, more than half of all patients diagnosed with NSCLC present with locally advanced or metastatic disease at the time of diagnosis that is not amenable to the surgery which offers patients the best chance of cure. To date, prevention, rather than screening, has been the most effective strategy for reducing the burden of NSCLC in the long term. The majority of lung cancer cases (87.3%) occur as a result of tobacco smoking (including environmental smoke exposure), with only one fifth of cases in the UK being attributable to diet and occupational exposures.[48] Progress in smoking cessation is now reflected in declining lung cancer rates and mortality.

The pathway leading to the confirmation and communication of diagnosis is often a very frustrating experience for patients due to experienced delays, lack of information and support, and uncertainty regarding next steps.[49] Patients diagnosed at stage IIIb/IV present a very low 5-year OS, between 3% and 7% depending on the stage (for stages IV and IIIb, respectively).[50] Additionally, there has not been a significant change in the survival of advanced NSCLC in England in the past decade.[51]

Patients with NSCLC have reported the highest prevalence levels of psychological distress (three times more than in other cancers),[52] which can lead to a poorer prognosis and greater patient burden.[53;54] Increased levels of psychological distress are reported by patients undergoing oncological treatment and by those approaching death.[52]

Patients with advanced NSCLC are in need of help from caregivers, particularly in the period leading to death. Furthermore, informal caregivers are increasingly recognised as recipients of care themselves,[55] as they have to deal with the distressing nature of the patient's symptoms and increasing social isolation as death approaches. Unmet need is more prevalent among caregivers of lung cancer patients, who report concerns in terms of

reducing stress in the patient, understanding the experience of the cancer patient and even accessible, affordable, hospital parking.[56]

Advanced NSCLC imposes a substantial burden to society, not only in terms of years of life lost (YLL) due to premature death, but also due to the corresponding loss of contribution to the economy and the substancial health care costs associated with its prevention and management. Lung cancer has been found to have the highest economic cost among four most prevalent cancer types in the UK (considering breast cancer, prostate cancer and colorectal cancer). The annual cost of lung cancer is almost 2.5 billion per year.[57] These costs account for unpaid care provided by relatives or friends of patients (i.e. informal care), lost earnings after premature death and costs associated with individuals who temporarily or permanently left employment because of illness. Inpatient care was the major component of health-care costs in lung cancer in the UK, representing 66% of all health-care costs). Additionally, the highest productivity losses attributable to mortality are associated to lung cancer (i.e. 23% of all the productivity losses associated to these four cancer types). The costs of informal care are also highest among patients with lung cancer (i.e. 16% of the total informal care provided). This high burden associated with NSCLC is due to the poor 5 year survival prognosis of lung cancer, at approximately 5%, where about 60% of the total economic costs attributed to lung cancer come from potential wage losses due to premature deaths from people in employment. Each lung cancer patient has a cost of £9,071 to the healthcare system annually, where an average cost per cancer patient in the UK totals £2,776. [57]

3.3: Clinical pathway of care showing the context of the proposed use of the technology

The clinical care pathway for patients with advanced NSCLC is determined by the tumour's histological subtype, genotype, and the performance status of the patient.

According to current NICE guidance, patients whose tumours test positive for EGFR tyrosine kinase (TK) mutation are eligible to receive first-line treatment with an EGFR-TK inhibitor: afatinib (TA 310)[58], erlotinib (TA 258)[59] or gefitinib (TA 192)[60]. For patients with negative or unknown EGFR status (EGFR wild-type) and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) chemotherapy should be offered; where the chemotherapy should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) (NICE CG 121).[61] Patients who are unable to tolerate such combination may be offered single-agent chemotherapy with a third-generation drug.[61] Pemetrexed in combination with cisplatin is

also recommended if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (TA 181)[62].

For patients with advanced NSCLC in whom relapse has occurred after prior chemotherapy, second-line treatment with docetaxel monotherapy should be considered (NICE CG 121).[61] Nintedanib in combination with docetaxel is also recommended as a second-line treatment option for locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology (TA 347)[63].
If the tumour tests positive for an EGFR mutation and the patient has not previously received treatment with an EGFR-TK inhibitor, afatinib is recommended as an alternative to docetaxel as a second-line treatment option for patients with NSCLC (TA 310)[58]. Erlotinib is recommended as a possible treatment for patients with locally advanced or metastatic NSCLC that has previously been treated with non-targeted chemotherapy because of delayed confirmation of EGFR mutation status, if their cancer tests positive for the EGFR mutation; or it is not known if the cancer is EGFR positive, but the cancer is very likely to be EGFR positive and it responds to the first 2 cycles of treatment with erlotinib (TA 374)[64].
Crizotinib is not recommended by NICE for the treatment of adults with previously treated ALK positive advanced NSCLC (TA 296)[65], but is available via the Cancer Drugs Fund (CDF)[66].

Supportive care should be provided to patients with cancer and their carers throughout the patient pathway, from pre-diagnosis onwards, to help the patient maximise the benefits of treatment and to live as well as possible with the effects of the disease.[67] Palliative care should also be considered for patients with advanced, progressive illness, who cannot be offered curative treatment. The goal of palliative care is to achieve the best quality of life for patients and their families.[67]

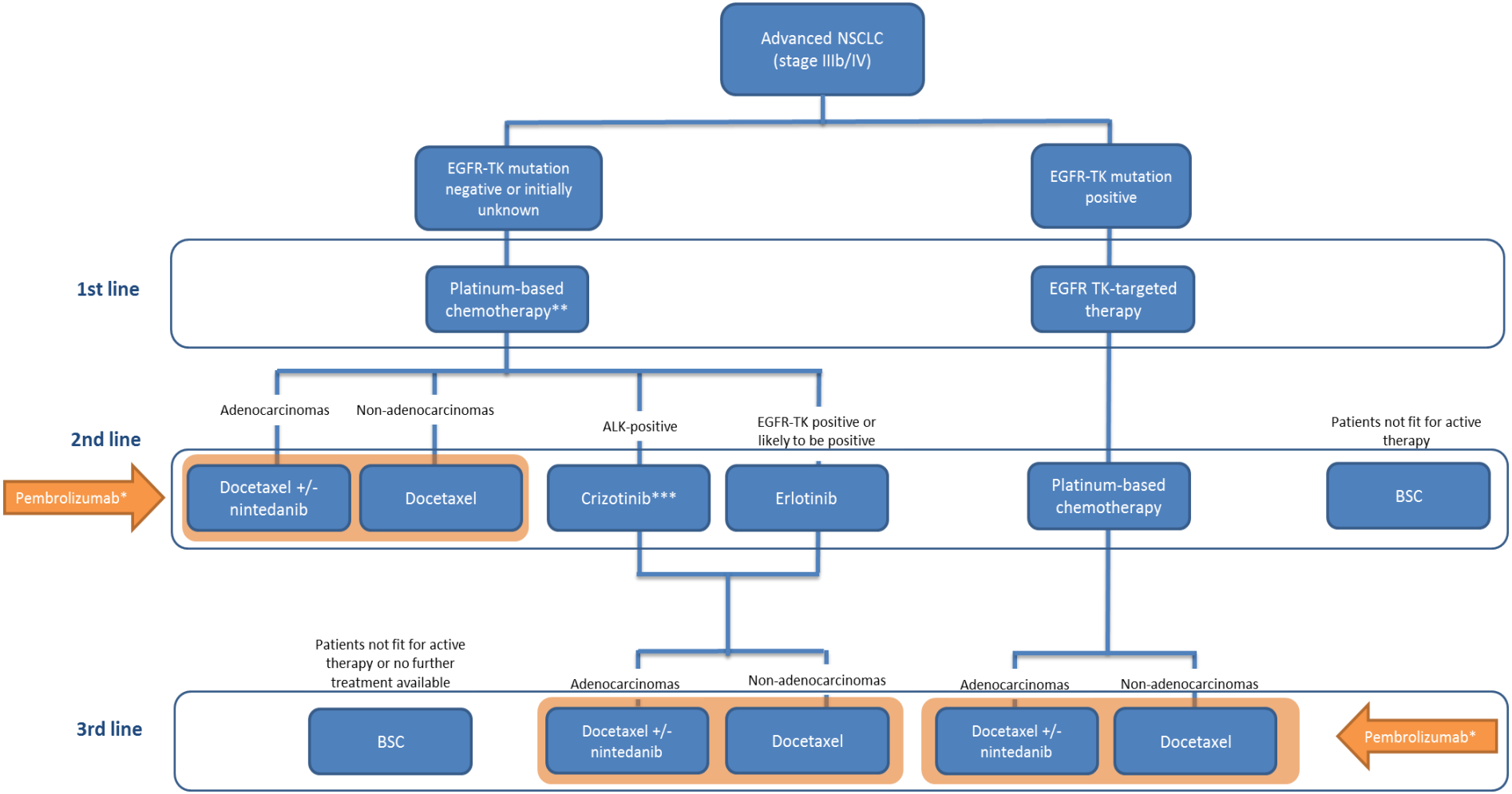
Despite the benefits associated with platinum-based chemotherapy or a targeted therapy, survival remains poor for patients with advanced NSCLC. [3] Over the past decade, the treatment approach to advanced NSCLC has evolved to incorporate predictive markers of benefit from treatment (such as EGFR mutation), allowing for improvements in clinical outcomes and treatment toxicity. However, the use of targeted therapies is limited to specific subpopulations, and all patients eventually experience disease progression through primary or acquired resistance.[68] For advanced NSCLC patients who relapse after first-line chemotherapy and targeted therapy the prognosis is even worse. There are limited treatment options for these patients; the response rate for currently approved treatments in this population is less than 15% and median survival is only 6 to 10 months; duration of response is limited, and almost all patients relapse and die as a consequence of their

NSCLC.[4-7] Consequently, there remains a critical unmet medical need for more effective therapies, as the majority of patients continue to face a very poor prognosis. In addition, there is an urgent need to identify and validate more predictive biomarkers that will allow clinicians to tailor therapies to treat those who will benefit most from them.

With this submission, pembrolizumab is proposed to be used as a second or third-line treatment option for adult patients with advanced NSCLC whose tumours express PD-L1 and who have disease progression on or after prior platinum-based chemotherapy and, if EGFR or ALK mutation positive, also experience disease progression on approved target therapies prior to receiving pembrolizumab (see Figure 3 below).

The proposed positioning in the treatment pathway is particularly relevant for these patients, who currently have limited treatment options. As a consequence, pembrolizumab is expected to displace the use of docetaxel and the use of nintedanib in combination with docetaxel (for the subgroup of adenocarcinoma patients) for advanced NSCLC patients experiencing disease progression. In addition, PD-L1 expression will be used as a predictive biomarker for the identification of advanced NSCLC patients most likely to experience significant clinical benefit from treatment with pembrolizumab.

Figure 3: Treatment algorithm for advanced NSCLC with proposed positioning of pembrolizumab



* People with advanced non-small-cell lung cancer that is PD-L1 positive
**Platinum-based chemotherapy includes: pemetrexed + cisplatin
***Not recommended by NICE but funded through the CDF

3.4: Information about the life expectancy of people with the disease or condition in England and the source of the data

In the UK, lung cancer is the most common cause of cancer death, with over 35,000 people dying from lung cancer each year, accounting for more than 1 in 5 cancer deaths,[69]

NSCLC is potentially curable when diagnosed at an early stage; however more than half of the patients are diagnosed with advance disease stage, with a poor related prognosis.[70]

Treatment for patients with advanced NSCLC aims to prolong OS and improve HRQoL by improving symptoms. Patients with a good performance status have been shown to benefit from first line therapy.[71;72] Approximately 55% of patients will receive second line therapy due to disease progression,[73;74] and for these patients life expectancy is very low. There are a limited treatment options for advanced NSCLC after disease progression, and these are subject to tumour histology and presence of mutations (see section 3.3). Despite recent advances in therapy, patients with NSCLC have a poor prognosis that has not changed significantly over the past decade.[51] The median survival is only 6 to 10 months; duration of response is limited, and almost all patients relapse and die.[4-7] The corresponding 5-year OS rates for these patients vary between 3% (stage IV)to 7% (stage IIIb).[74]

The number of expected cases of NSCLC stage IIIb/IV for 2017 in England is 27,215; 16,050 of which are expected to be stage IIIb/IV. In total, 1,795 patients are expected to be eligible for treatment with pembrolizumab (see Table 6 and section 6.2).

Table 6: Estimated patient numbers for England, 2017-2021

Year	2017	2018	2019	2020	2021
Total NSCLC cases	27,215	27,324	27,433	27,543	27,653
Total NSCLC stage IIIb/IV cases	15,050	15,111	15,171	15,232	15,293
Total stage IIIb/ IV NSCLC that is PD-L1 positive and eligible for pembrolizumab in 2L+	1,795	1,802	1,809	1,817	1,824

3.5: Details of relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used

According to the NICE guideline for the diagnosis and treatment of lung cancer (CG121) published in April 2011, docetaxel monotherapy should be considered if second-line

treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy.[61]

Details of relevant NICE guidance published afterwards are provided below:

- In April 2014 NICE recommended afatinib (Giotrif®, Boehringer-Ingelheim) as an option for treating adults with locally advanced or metastatic NSCLC if the tumour tests positive for EGFR mutation and the patient has not previously had an EGFR-TK inhibitor, and only if the manufacturer provides afatinib with the discount agreed in the PAS (TA 310).[58]
- In July 2015 NICE further recommended the use of nintedanib in combination with docetaxel (Vargatef®, Boehringer-Ingelheim) as an option for treating locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy, only if the company provides nintedanib with the discount agreed in the patient access scheme (PAS) (TA 347).[63]
- In December 2015 the NICE technology appraisal guidance for erlotinib (Tarceva®, Roche) for the treatment of NSCLC (NICE TA162) was updated and replaced by NICE TA374)[64]: Erlotinib is now recommended as a possible treatment for people with locally advanced or metastatic NSCLC that has already been treated with non-targeted chemotherapy because of delayed confirmation of EGFR mutation status, if their cancer tests positive for the EGFR mutation; or it is not known if the cancer is EGFR positive because of problems with the test, but the cancer is very likely to be EGFR positive and it responds to the first 2 cycles of treatment with erlotinib, and the company provides erlotinib with the discount agreed in the patient access scheme revised in the context of NICE TA 258. Erlotinib is not recommended in people with tumours that are EGFR mutation negative.

Additionally, in 2012 NICE published Quality Standards that define clinical best practice regarding the diagnosis and management of lung cancer in adults, and the supportive care provided to people with lung cancer (NICE QS17).[75] Quality statement 12 on “Systemic therapy for advanced NSCLC” states that people with stage IIIB or IV NSCLC and eligible performance status are offered systemic therapy (first- and second-line) in accordance with NICE guidance, that is tailored to the pathological sub-type of the tumour and individual predictive factors.[75]

NICE diagnostic guidance has recommended a number of tests for EGFR mutation testing in adults with previously untreated, locally advanced or metastatic NSCLC, that are clinically and cost effective for informing treatment decisions as currently recommended by NICE.[76]

3.6: Details of other clinical guidelines and national policies

Details of other clinical guidelines and national policies are summarised below:

European Society for Medical Oncology (ESMO)[68;77]

ESMO has published two clinical guidelines for diagnosis, treatment and follow-up of NSCLC: one for early and locally advanced NSCLC and another for metastatic NSCLC[68;77]:

In patients clinically or radiologically progressing after first-line chemotherapy with Eastern Cooperative Oncology Group (ECOG) [78] performance status (PS) 0–2, the ESMO guidelines, recommend single-agent second-line treatments such as docetaxel or pemetrexed (non-squamous only).[68;77] Patients with unknown EGFR status or wild-type EGFR patients should receive an EGFR TKI (afatinib, erlotinib or gefitinib) in any line of therapy, if not received previously. Similarly, patients with NSCLC harbouring an ALK rearrangement should receive treatment with crizotinib, if not received previously.[68;77]

National Comprehensive Cancer Network (NCCN) (2016) [79]

In patients with advanced NSCLC after failure of first-line treatment, the NCCN guideline recommends single-agent second-line treatments such as docetaxel, pemetrexed (non-squamous only), erlotinib, gemcitabine, nivolumab, and ramucirumab in combination with docetaxel, and best supportive care (BSC).[79] For patients with EGFR mutation, the NCCN guideline recommends subsequent therapy with afatinib. For patients with ALK rearrangements who have progressed following first line systemic therapy, crizotinib is recommended. Ceritinib is recommended by the NCCN for patients with ALK rearrangements who have disease progression on, or are intolerant to, crizotinib.[79]
In the 2016 update (version 4.0) of this guideline,[80] the NCCN Panel revised the recommendation for pembrolizumab from category 2A ("based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate") to category 1 ("based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate") as subsequent therapy for patients with metastatic non-squamous or squamous NSCLC and PD-L1 expression, based on data from KEYNOTE-010 study. In addition, the NCCN Panel recommends immune checkpoint inhibitors, such as pembrolizumab and nivolumab, as preferred agents for subsequent therapy.[80]

3.7: Issues relating to current clinical practice, including variations or uncertainty about established practice

We are not aware of any issues relating to current clinical practice. Comprehensive NICE guidance regarding treatment of NSCLC is available (see section 3.5 above) and provides clear recommendations.

3.8: Equality issues

We do not anticipate any equity or equality issues.

4. Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1: Systematic Review

A systematic literature review was conducted according to a previously prepared protocol, to identify relevant studies to inform both direct and indirect comparisons between the interventions included in this submission. Further details are provided below.

4.1.2: Search strategy description

A systematic literature search was conducted February 9, 2016 in Medline, EMBASE, and Cochrane Central Register of Controlled Trials databases, from inception to present. The search was supplemented with a search in clinical trial registries (using the US National Institute of Health's (NIH) ClinicalTrial.gov), with searches in the proceedings from the European Society for Medical Oncology Annual Meeting (September 2015), the European Lung Cancer Conference (April 2015) and the World Congress of Lung Cancer (September 2015); and the company's own records to identify additional study information that had not yet been published in a peer-reviewed journal.

The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design (PICOS criteria presented in Table 7), using a combination of the search terms such as *carcinoma*, *lung cancer*, *non-small cell*, *metastatic*, *advanced*, within the restriction limit of "randomised controlled trials" (RCTs) (see Appendix 2 for full details of the search strategy by database). To meet the requirements of different regulatory authorities, all the comparators recommended for treatment of advanced NSCLC were included in the search strategy (see Appendix 2). However, to address the decision problem set by NICE, only studies with comparators relevant to the UK setting have been included (see PICOS eligibility criteria in Table 7).

4.1.3: Study selection

Description of the inclusion and exclusion selection criteria, language restrictions, and the study selection process

Two investigators working independently screened all titles and abstracts identified in the literature that could potentially meet the inclusion criteria (see Table 7). Full articles were retrieved for further detailed assessment by the same reviewers. Discrepancies occurring between the two investigators were resolved by involving a third investigator and reaching consensus.

For selection of studies for head-to-head comparisons, only the RCTs comparing pembrolizumab with any of the relevant comparators (docetaxel or nintedanib in combination with docetaxel) were included. For selection of studies for indirect and mixed treatment comparisons we included RCTs with comparisons between any of the interventions of interest (see Table 7) and RCTs with other interventions that have been compared to at least two of the interventions of interest (see section 4.10.1).

Table 7: Eligibility criteria used in the search strategy

Clinical effectiveness	**Inclusion criteria**	**Exclusion criteria**
Population	Patients with advanced non-small-cell lung cancer (NSCLC), whose disease has progressed after platinum-containing doublet chemotherapy	
Intervention	Pembrolizumab / MK-3475	Any other intervention
Comparators	• Docetaxel monotherapy • Nintedanib in combination with docetaxel (for people with adenocarcinoma histology only)	Any other comparison
Outcomes	At least one of the following outcomes:* • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	Other efficacy and safety outcomes to be considered for analysis, but each study must include at least one of those presented to the left
Study design	Randomised controlled trials (RCTs)	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language restrictions	English	Any other language
**Note: the scope of the review included extraction of safety outcomes, but for selection of relevant studies the focus was on efficacy outcomes.*		

4.1.4: Flow diagram of the numbers of studies included and excluded at each stage

The electronic search yielded 9016 citations. Of these, 2441 duplicates were removed and 6369 were excluded during abstract screening, which led to 206 articles being included in the full text screening phase. Further details are provided in the below PRISMA flow diagram (Figure 4).

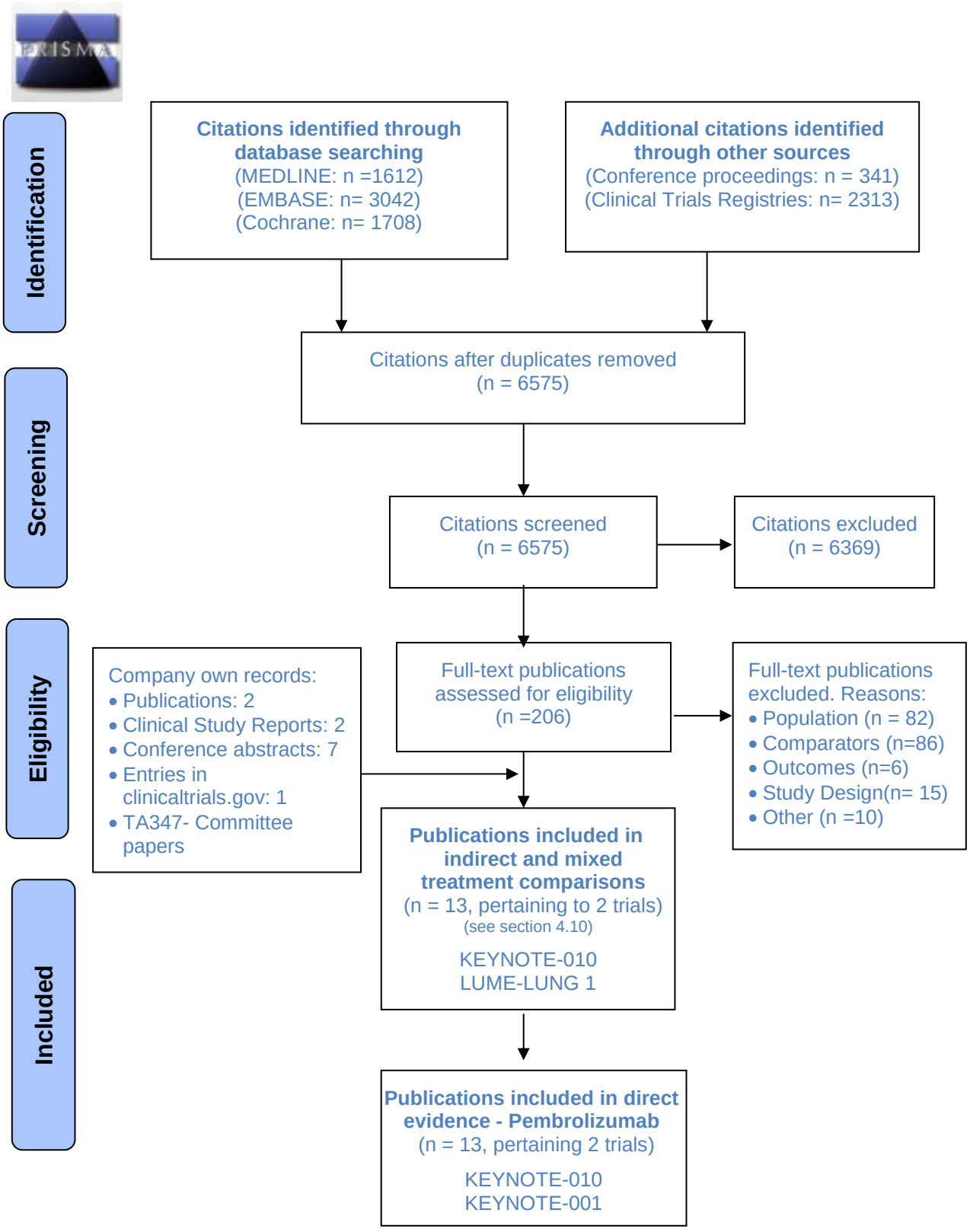


Figure 4: PRISMA flow diagram of the systematic review process

As shown in the PRISMA flow diagram, 3 studies (reported in 19 publications and 2 clinical study reports [CSR]) met the inclusion/exclusion criteria of the systematic review (Table 7). Of these, 2 studies provided data explicitly for the direct evidence of pembrolizumab in the population covered by the decision problem: KEYNOTE-010 and KEYNOTE-001; and two studies provided data to inform the indirect and mixed treatment comparisons: KEYNOTE-010 and LUME-LUNG 1 (see section 4.10.1). A complete reference list of the included studies has been provided in Appendix 3.

4.1.5: Single study data drawn from multiple sources

A list of studies relevant to the decision problem is given in Table 8:

- KEYNOTE-010 data consists of one protocol, one CSR, one entry in clinicaltrials.gov, one conference abstract and one peer reviewed publication.[16;81-84]
- KEYNOTE-001 (Parts C and F) data consists of one protocol, one CSR, one entry in clinicaltrials.gov, 6 conference abstracts and one peer reviewed publication.[35;85-93]

4.1.6: Complete reference list for excluded studies

A complete reference list for excluded studies (and the reason for exclusion) has been provided in Appendix 3.

4.2 List of relevant randomised controlled trials

4.2.1: List of relevant RCTs involving the intervention of interest

Table 8: List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
KEYNOTE-010	Patients with histologically or cytologically confirmed diagnosis of NSCLC stage IIIB/IV, and • whose tumours express PD-L1 based on a Tumour Proportion Score (TPS*) of ≥1%, • who have experienced disease progression per RECIST 1.1 after treatment with a platinum-containing systemic therapy, • who have experienced disease progression on the respective TKI targeted against an identified EGFR mutation or ALK translocation. *TPS is the percentage of viable tumour cells showing partial or complete IHC membrane staining.	Pembrolizumab 2 mg/kg Q3W Pembrolizumab 10 mg/kg Q3W	Docetaxel 75 mg/m2 Q3W	• ClinicalTrials.gov reference: NCT01905657[83] • CLINICAL STUDY REPORT P010V01[82] • Herbst, R.S.; et al. (2015)[16]
KEYNOTE-001 Part C, F*	Patients with histologically or cytologically confirmed diagnosis of NSCLC stage IIIB/IV, and • who have previously been treated with platinum-based chemotherapy and demonstrated disease progression before initiating pembrolizumab. (*Parts C, F2 and F3 reflect the patient population included in KEYNOTE-010, of interest for this submission)	Pembrolizumab 10 mg/kg Q3W or Pembrolizumab 10 mg/kg Q2W Pembrolizumab 2 mg/kg Q3W		• ClinicalTrials.gov reference: NCT01295827[89] • CLINICAL STUDY REPORT P001V04[85] • Garon, E.B.; et al. (2015)[35]

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1: Key aspects of listed RCTs

KEYNOTE-010[16;81-83]

Trial design:

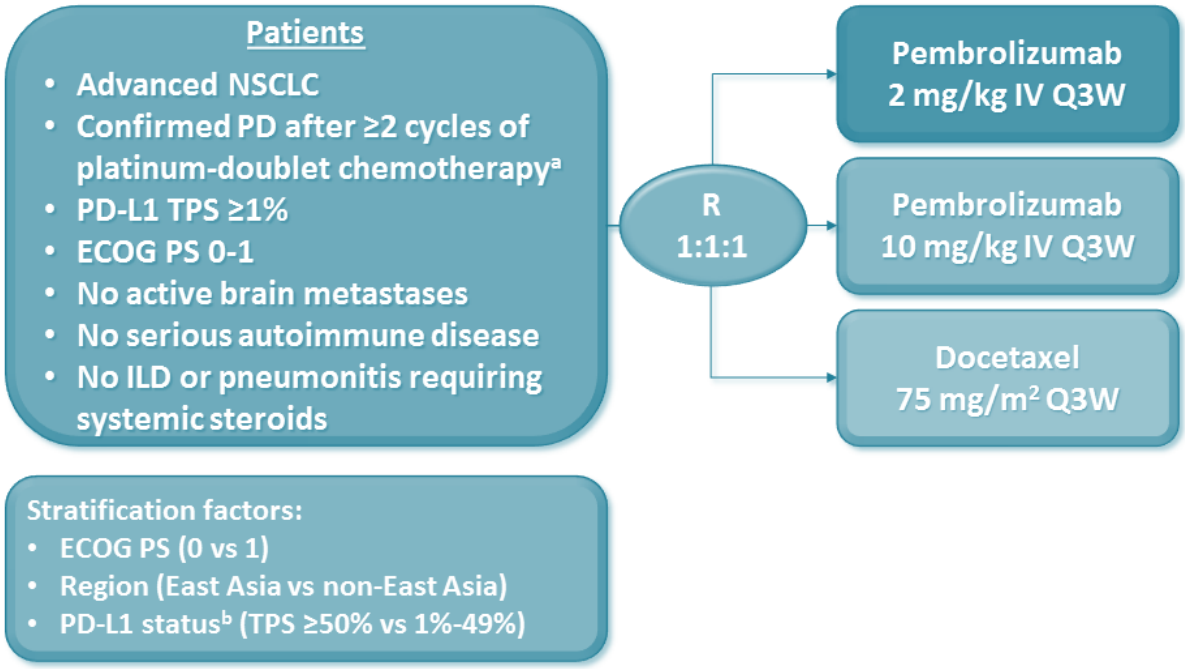
KEYNOTE-010 was a multicentre, randomised, adaptively designed phase II/III trial of intravenous (IV) pembrolizumab at two doses versus docetaxel in adults with advanced non-small cell lung cancer (NSCLC) whose tumours express PD-L1 (based on a Tumour Proportion Score (TPS) of ≥1%: TPS is the percentage of viable tumour cells showing partial or complete IHC membrane staining), and who have experienced disease progression after at least platinum-containing chemotherapy.

This was an open-label trial; therefore, the study sponsor, investigator and patient were aware of the treatment administered. However, response was assessed by independent central review (for efficacy: response and the co-primary endpoint of progression-free survival) without knowledge of patient treatment assignment.

Patients were randomised via a central Interactive Voice Response System (IVRS)/Interactive Voice and Web Response System (IXRS) in a 1:1:1 ratio to receive either pembrolizumab at 10 mg/kg every 3 weeks (Q3W), 2 mg/kg Q3W, or docetaxel at 75 mg/m^2 Q3W (Figure 5). The allocation schedule was generated by the system vendor using a computerised randomised list generator.
Initially, randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1)[78] and geographic region of the enrolling site (East Asia vs. non-East Asia). A third stratification factor, extent of tumour PD-L1 expression (TPS>50% vs. TPS=1-49%), was added in Protocol Amendment 08 (see details in Appendix 4). A total of 441 patients were randomised prior to the implementation of the third stratification factor.

The design of KEYNOTE-010 is depicted in Figure 5 below:

Figure 5: Study design of KEYNOTE-010



R = Randomisation; ECOG PS= Eastern Cooperative Oncology Group performance status; ILD=interstitial lung disease; IV=intravenously; NSCLC=non-small cell lung cancer; PD=progressive disease; Q3W=every 3 weeks; R=randomized; TPS=tumour proportion score
[a]An appropriate tyrosine kinase inhibitor was required for patients whose tumours had an *EGFR* sensitizing mutation or an *ALK* translocation. [b]Added after 441 patients enrolled and the PD-L1 IHC assay cut point was established.

KEYNOTE-010 used an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. Two formal interim analyses were performed during the conduct of the study (more details in section 4.4.1). In addition, the study could be stopped early at the recommendation of the DMC if the benefit/risk ratio to the population as a whole was unacceptable.

Eligibility criteria:

Participation in this study was dependent upon the patient supplying tumour tissue for PD-L1 analysis.

Initially, an archival or a new tissue sample was permitted for PD-L1 testing. The study protocol was later amended (see details of Protocol Amendment 08 in Appendix 4) to require a new tissue sample for PD-L1 testing (except when attempting to take a biopsy would be too risky). In addition, no new systemic antineoplastic therapy could have been administered between the PD-L1 biopsy to obtain new tissue and initiation of study medication. A total of 456 patients were enrolled on the basis of archival samples.

The specimen was evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only patients whose tumours expressed PD-L1 were eligible for randomisation in this study.

Key inclusion criteria:

A patient must have met all of the following criteria to be eligible to participate in this study:

1) Provide written informed consent/assent for the trial.

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

3) Life expectancy of at least 3 months.

4) Histologically or cytologically confirmed diagnosis of NSCLC and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST 1.1).[10]

5) Investigator determined radiographic progression per RECIST 1.1[10] after treatment with at least two cycles of a platinum-containing doublet for NSCLC stage IIIB/IV or recurrent disease.

a. Patients with an EGFR sensitising mutation or an ALK translocation able to demonstrate progression of disease on the EGFR TKI (either erlotinib, gefitinib or afatinib) or crizotinib, respectively.

b. Patients may have been treated previously with the TKI separately from the platinum-containing doublet; the order of treatment did not matter, but progression of disease as determined by RECIST 1.1 must have been demonstrated for both regimens.

6) ECOG Performance status of 0 or 1.[78]

7) Adequate organ function.

8) Recent biopsy of a tumour lesion for PD-L1 biomarker analysis; no previous irradiation and no systemic antineoplastic therapy between the PD-L1 biopsy and initiating study medication.

a. Documentation of the EGFR mutation status or ALK translocation status (not required if a patient with non-squamous NSCLC is known to have a mutation in KRAS or if a patient is known to have a tumour of predominantly squamous histology).

b. Patients would not be randomised until EGFR mutation and ALK translocation status was available in source documentation at the site.

9) PD-L1 positive (TPS of ≥1%) tumour as determined by immunohistochemistry (IHC) at a central laboratory.

10) Resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If patient received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

11) Female patient of childbearing potential must have had a negative urine or serum pregnancy test.

12) Female patients of childbearing potential and male patients with a female partner(s) of child-bearing potential must have agreed to use either 2 adequate barrier methods or a

barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity throughout the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of pembrolizumab, or through 180 days after the last dose of docetaxel.
If their partner is pregnant, males must have agreed to use a condom and no additional method of contraception was required for the pregnant partner.

Key exclusion criteria:

Patients who met any of the following criteria were not eligible to participate in this study:

1) Prior therapy with docetaxel for NSCLC.
2) Currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of this study treatment.
3) On systemic steroid therapy within three days prior to the first dose of study treatment or on any other form of immunosuppressive medication (corticosteroid use for management of events of clinical interest or as a pre-medication for docetaxel is allowed).
4) Expected to require any other form of systemic or localized antineoplastic therapy while on study.
5) Prior systemic cytotoxic chemotherapy, antineoplastic biological therapy, major surgery within 3 weeks of the first dose of study treatment; thoracic radiation therapy of > 30 Gy within 6 months of the first dose of study treatment; prior TKI therapy or completed palliative radiotherapy within 7 days of the first dose of study treatment.
6) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
7) History of a malignancy (other than NSCLC) within 5 years since initiation of study therapy, except if the patient had undergone potentially curative therapy with no evidence of recurrence for 5 years. The time requirement also did not apply to patients who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cervical cancers.
8) Active central nervous system (CNS) metastases and/or carcinomatous meningitis; patients with previously treated brain metastases were eligible provided they were stable.
9) Active autoimmune disease or history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patients that required inhaled steroid or local steroid injections were not excluded from the study. Patients with hypothyroidism not from autoimmune disease and stable on hormone replacement were not excluded from the study.
10) History of an allogeneic tissue/solid organ transplant.

11) Interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids; lymphangitic spread of the NSCLC was not exclusionary.
12) Has received a live vaccine within 30 days prior to the first administration of study medication; seasonal flu vaccines that do not contain live virus are permitted.
13) Active infection requiring intravenous systemic therapy.
14) History of Human Immunodeficiency Virus (HIV).
15) Active Hepatitis B or C.
16) Known psychiatric or substance abuse disorder
17) Regular user (including "recreational use") of illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
18) Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.
19) Required treatment with a strong inhibitor of CYP3A4.
20) History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or was not in the best interest of the patient to participate.

Settings and locations where the data were collected:

This was a global study conducted in 202 academic medical centres in 24 countries: Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Lithuania, Netherlands, Portugal, Russia, South Africa, South Korea, Spain, Taiwan, UK, and USA

Trial drugs and concomitant medications:

Patients were assigned to receive intravenous (IV) pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks (Q3W), or docetaxel 75mg/m^2 Q3W.

- Pembrolizumab was administered as a 30 minute IV infusion at two doses (2 mg/kg Q3W and 10 mg/kg Q3W). These two doses were selected on the basis of pharmacological models, given that when this study was designed the lowest effective dose of pembrolizumab was unknown, and the importance of PD-L1 staining was being validated. If one dose arm of pembrolizumab was dropped due to lack of efficacy (evaluated at Interim Analysis 1), per the Investigator's discretion the patients could continue to be treated with the other dose.

- Docetaxel 75 mg/m^2 was administered as an IV infusion over 1 hour Q3W. Pre-medication(s) for docetaxel were given as per standard of care. Corticosteroid pre-treatment and/or post treatment of docetaxel was acceptable in concordance with the local label or standard of care.

Treatment with pembrolizumab or docetaxel may have been continued until two years of therapy have been administered (or 35 administrations of pembrolizumab / or maximum number of cycles of docetaxel permitted by the local regulatory authority; whichever occurs later), confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the patient, patient withdrawal, pregnancy of the patient, noncompliance with trial treatment or procedure requirements, or administrative reasons.

Concomitant medications

Treatments specifically prohibited in the exclusion criteria were not allowed during the ongoing study. All treatments that the investigator considered necessary for a patient's welfare may have been administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications received within 30 days before the first dose of the study treatment through the "Safety Follow-up Visit" were recorded (see details on study Clinical Procedures/Assessments below). Further details of acceptable and prohibited concomitant Medications are provided in Appendix 5.

Primary, secondary and tertiary objectives

Primary objectives:

- To evaluate overall survival (OS) and progression free survival (PFS) (per RECIST 1.1 by independent radiologists') of previously-treated patients with NSCLC whose tumours express PD-L1 (TPS≥1%) and are treated with pembrolizumab compared to docetaxel.
- To evaluate OS and PFS (per RECIST 1.1 by independent radiologists') of previously-treated patients with NSCLC in the TPS≥50% stratum treated with pembrolizumab compared to docetaxel.
- To evaluate the safety and tolerability profile of pembrolizumab in previously treated patients with NSCLC in the TPS≥50% stratum and in the overall TPS≥1% population.

PFS was defined as the time from randomisation to the first documented disease progression (based on confirmed assessment by an Independent Review Committee [IRC] using Response Evaluation Criteria in Solid Tumours, RECIST 1.1[10]; or death due to any cause, whichever occurred first.

OS was defined as the time from randomisation to death due to any cause. Patients without documented death at the time of the final analysis were censored at the date of the last follow-up.

Secondary objectives:

- To evaluate the overall response rate (ORR), time to response and response duration in patients with NSCLC in in the TPS≥50% stratum and in the overall TPS≥1% population treated with pembrolizumab compared to docetaxel.

ORR was defined as the proportion of the patients in the analysis population who had either a complete response (CR) or partial response (PR). Responses were based on confirmed assessments by independent radiologists' using RECIST 1.1.[10]

Time to response was defined as the time from randomisation to the first assessment of a CR or PR; and response duration was defined as the time from first documented CR or PR until confirmed disease progression or death. The response duration for patients who have not progressed or died at the time of analysis was censored at the date of their last tumour assessment.
Only confirmed CR or PRs were included in the analyses for time to response and response duration. Responses were based on confirmed assessments by independent radiologists' using RECIST 1.1.[10]

Exploratory objectives:

- To evaluate ORR, PFS and Response duration per immune-related response criteria (irRC) by investigators' review (INV), in the TPS≥50% stratum and in the overall TPS≥1% population. treated with pembrolizumab compared to docetaxel.
- To evaluate changes in health-related quality-of-life (HRQoL) assessments from baseline in previously-treated patients with NSCLC in the TPS≥50% stratum and the TPS≥1% population treated with pembrolizumab compared to docetaxel using the electronic European Organization for Research and Treatment of Cancer Quality of

Life Questionnaire Core 30 items (eEORTC QLQ-C30) and eEORTC QLQ Lung Cancer 13 items (eEORTC QLQ-LC13).

- To characterize utilities in previously-treated subjects with NSCLC in the TPS≥50% stratum and the TPS≥1% population treated with pembrolizumab compared to docetaxel using the electronic European Quality of Life 5 Dimensions (eEQ-5D).
- To evaluate the influence of age of tumour specimen (archival vs. new) submitted for PD-L1 analysis on the primary endpoints of PFS and OS.
- To explore the correlation of tumour volumetric changes with OS in previously-treated patients with NSCLC in the TPS≥50% stratum with pembrolizumab compared to docetaxele
- To evaluate tumour volumetric changes of previously-treated patients with NSCLC in the TPS≥50% stratum treated with pembrolizumab compared to docetaxel
- To characterize healthcare resource utilization in previously-treated patients with NSCLC in the TPS≥50% stratum treated with pembrolizumab compared to docetaxel.

Clinical Procedures/ Assessments

Biomarker assessment

PD-L1 expression was assessed at a central laboratory with an immunohistochemistry (IHC) assay (Dako Clinical Trial Assay (CTA); Carpinteria, CA, USA) with the murine 22C3 anti-human PD-L1 antibody (Merck; Kenilworth, NJ, USA). NSCLC tumour tissue for biomarker analysis was received by the central vendor before randomisation. All scoring was performed by pathologists.

Tumours staining for PD-L1 with 1% or greater were considered expressers (TPS≥1%), with a further analysis of those expressing 50% or greater (TPS≥50%). Tumours with <1% cells for PD-L1 staining were considered non-expressers (TPS<1%).

Response Assessment

Response was assessed as per RECIST version 1.1[10] by IRC and as per irRC by investigator (to inform treatment decisions).

Response assessments were obtained as follows:

- Treatment Phase

The initial tumour imaging was obtained within 30 days prior to the first dose of study treatment; and then every 9 weeks (63 ± 7 days) (calculated from the study treatment start day) until the patient experienced confirmed disease progression or started a new

antineoplastic therapy. Per protocol, patients in the docetaxel group were not permitted to cross over to receive pembrolizumab.

After the first documentation of disease progression per irRC, confirmatory scans were performed between 4 and 6 weeks later (alternatively, the scan performed at the subsequent scheduled time point – every 9 weeks - could be used). Required progression confirmation was based on the regulatory agency feedback and for the IRC to account for possibility of tumour flare.
If progression was not confirmed, the patient should have continued the study treatment and tumour imaging every 9 weeks. If progression was confirmed, the patient should have discontinued the study treatment.

For patients who discontinued study treatment for reasons other than disease progression, imaging during the follow-up period was repeated every 9 weeks (63 ±7 days) until the patient experienced confirmed disease progression or started a new antineoplastic therapy.

- Post-Treatment Follow-up Phase

Each patient had a Safety Follow-Up Visit approximately 30 days after the last dose of study treatment (regardless of start of new antineoplastic therapy) for adverse event (AE) monitoring. Serious adverse events (SAEs) were collected for up to 90 days after the end of treatment unless the patient started a new anticancer therapy between days 31 and 90.

Once disease progression was confirmed or the patient started a new antineoplastic therapy, they would move into the Survival Follow-up Phase and would be contacted by telephone every 2 months to assess for survival status, post-study treatments and their response to them.

Patient Reported Outcomes (PROs) were completed electronically by patients prior to study drug administration, AE evaluation and disease status notification, in the following order: EuroQol EQ-5D first, then EORTC QLQ C-30, and lastly the EORTC LC-13 (details are provided in the Trial Flow Chart from the study protocol)[81].

Populations used for analysis:

The study population used for analysis of each endpoint is defined in section 4.4.2.

KEYNOTE-001 (Parts C and F)[35;85;86;89]

Trial design:

KEYNOTE-001 is a phase I multi-centre, open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumour activity of pembrolizumab in adult patients with progressive locally advanced or metastatic carcinomas, including melanoma or NSCLC.

Although KEYNOTE-001 is a phase I study due to its initial dose escalation component, it evolved into multiple phase II-like sub-studies in melanoma and NSCLC through a series of expansion cohorts, all of which have completed enrolment: Part A, which included subjects with NSCLC as part of a broader solid tumour population, evaluated dose escalation of pembrolizumab. Parts B and D were phase II-like expansion cohorts to study safety and efficacy in patients with melanoma.
Parts C and F (divided into cohorts F1, F2 and F3) were expansion cohorts specifically designed to evaluate the efficacy and safety of pembrolizumab in patients with locally advanced or metastatic NSCLC: Cohort F1 enrolled treatment–naïve patients with stage IV NSCLC, and therefore is not relevant to the decision problem. All patients enrolled in Part C, Cohort F2, and Cohort F3 had received at least one line of prior therapy which must have included platinum-based chemotherapy and demonstrated disease progression before initiating pembrolizumab.

Further details on Part C and F are provided in Table 9 below:

Table 9: Part C and F of KEYNOTE-001

Cohort	Histology	Dose	Dose Frequency	Randomised	Prototype PD-L1 status[1]	Total Allocated[2]		Total Treated	
C	NSCLC	10mg/Kg	Q3W	No	All comers	41		38	
F1	NSQCC	2mg/Kg[3]	Q3W	Yes	Positive	6	103	6	101
	NSQCC & NSCLC	10mg/Kg[3]	Q3W			50		49	
	NSCLC		Q2W			47		46	
F2	NSQCC	10mg/Kg[4]	Q3W	No	Positive	33	361	33	356
	NSCLC		Q3W	Yes	Positive	172		167	
	NSCLC		Q2W			113		113	
	NSCLC		Q3W	No	Negative	43		43	
F3	NSCLC	2mg/Kg	Q3W	No	Positive	55		55	

NSCLC = non-small cell lung cancer; NSQCC = Non Squamous Cell Carcinoma; PD-L1 = programmed cell death ligand-1; Q2W = every 2 weeks; Q3W = every 3 weeks.
1 Based on results of the PD-L1 prototype assay. 2 Data cut-off: 23-Jan-2015
3 The first 11 patients (under Amendment 06) were randomised to either 2 mg/kg Q3W or 10 mg/kg Q3W, and then subsequent patients were randomised to either 10 mg/kg Q3W or 10 mg/kg Q2W.

4 The first 33 patients (under Amendment 06) were treated in a non-randomised fashion at 10 mg/kg Q3W, and then subsequently, patients (under Amendment 07) with a positive PD-L1 status were randomised to either 10 mg/kg Q3W or 10 mg/kg Q2W in a 3:2 fashion.

Part C included 38 patients with locally advanced or metastatic NSCLC who experienced disease progression after at least two prior systemic anti-tumour regimens. These patients were treated with pembrolizumab 10 mg/kg Q3W. Tumour samples for these patients were collected for retrospective analysis of PD-L1 expression.

Cohort F2 was initiated to confirm the activity observed in Part C in previously-treated patients. In Cohort F2, the first 33 patients allocated and treated (Protocol Amendment 06) were required to have experienced disease progression after two prior systemic therapies for non-squamous NSCLC and a pre-treatment tumour biopsy was required to demonstrate PD-L1 expression by the Prototype Assay (PA). These patients were treated at 10 mg/kg Q3W.
Cohort F2 (Protocol Amendment 07 and greater) allocated 285 patients with locally advanced or metastatic NSCLC (all histologies) whose tumours expressed PD-L1 by the PA and had experienced progression of disease after at least one prior systemic antineoplastic regimen, at least one of which was required to be a platinum-containing doublet. If a sensitizing EGFR mutation or ALK gene rearrangement was present, progression of disease after initiating the appropriate tyrosine kinase inhibitor was required. These patients were randomised between pembrolizumab 10 mg/kg Q3W or Q2W. Two hundred eighty patients were treated.
The last F2 cohort (Amendment 07 and greater) included 43 patients (allocated and treated) with locally advanced or metastatic NSCLC whose tumours did not express PD-L1 by the PA and had experienced progression of disease after at least two prior systemic antineoplastic regimens, at least one of which was a platinum-containing doublet. These patients were treated with 10 mg/kg Q2W.

Cohort F3 enrolled patients for further safety, tolerability, and efficacy assessment of pembrolizumab at a dose of 2 mg/kg Q3W. Cohort F3 included 55 patients with locally advanced or metastatic NSCLC whose tumours expressed PD-L1 by the PA and had experienced progression of disease after at least one prior systemic antineoplastic regimen, at least one of which was a platinum-containing doublet. If a sensitizing EGFR mutation or ALK gene rearrangement was present, progression of disease after initiating the appropriate TKI was required. Because enrolment in Cohort F3 commenced last, this cohort has the shortest follow-up (Protocol Amendment 09).

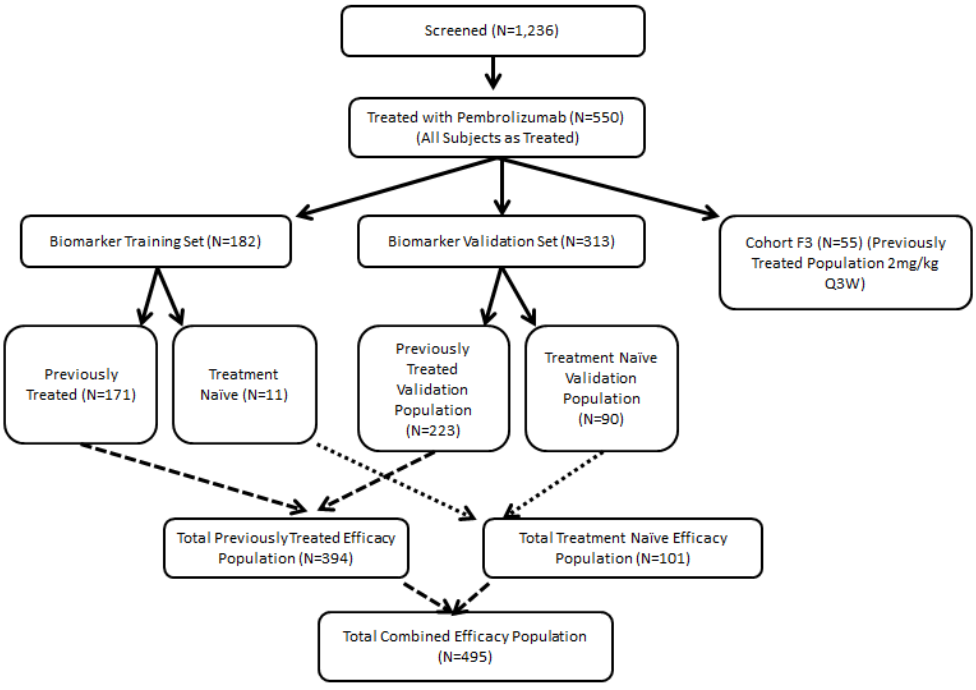
To confirm the utility of tumour PD-L1 protein expression in identifying patients most likely to benefit from pembrolizumab, Part C and Cohorts F1 and F2 were then split into two analysis sets:

- Biomarker Training Set - to identify the tumour PD-L1 protein expression cut point for a higher probability of pembrolizumab response based on PD-L1 assessed using the Dako Clinical Trial Assay (CTA) – ultimately determined to be the proportion of neoplastic cells demonstrating membranous PD-L1 staining (TPS) of 50% or more.
- Biomarker Validation Set - to validate the cut point for PD-L1 expression, confirming the response rate in the patients with advanced NSCLC with a TPS≥50% using the Market Ready Assay (MRA).

Further details of the Biomarker Sets, the PD-L1 expression assays used in the study and antigen stability are provided in Appendix 6. Figure 1 in Appendix 6 outlines which cohorts of KEYNOTE-001 contributed to the Biomarker Training and Validation sets: no patient in the Biomarker Validation Set was counted in the Biomarker Training Set.

The derivation of the efficacy analysis populations from the Biomarker Training set and Biomarker validation set is shown in Figure 6 below:

Figure 6: Derivation of the efficacy analysis populations from the Biomarker Training Set and Biomarker Validation Set of KEYNOTE-001



N = number of patients; Q3W = every 3 weeks. Data cut-off: 23-Jan-2015

A total of 1,236 patients with NSCLC signed informed consent for the study for Parts C and F. Five hundred fifty patients received at least one dose of study medication and were included in the “All Patients With NSCLC” population. A population of 223 previously treated

patients and 90 treatment-naïve patients comprised the Biomarker validation set. Of these, the 61 previously treated patients identified as TPS≥50% comprise the primary efficacy population of the NSCLC portion of KEYNOTE-001. Details of the study populations used for analysis of each endpoint are provided in section 4.4.2.

In the KEYNOTE-001 randomised cohorts (see Table 9 above) treatment assignment was based on a computer-generated allocation schedule generated in-house to maintain randomness.

KEYNOTE-001 is an open-label trial; therefore, the study sponsor, investigator and patient were aware of the treatment administered; although they were unaware of the patient's PD-L1 status. Patients, investigators, and the study sponsor were blinded to PD-L1 scores from the Biomarker Training set until all patients had ≥19 weeks of follow-up; and were blinded to PD-L1 scores from the Biomarker Validation set until final analysis. The imaging vendor was blinded to PD-L1 scores, just as the vendor scoring tumour tissues was blinded to clinical outcome.

Eligibility criteria:

Inclusion criteria

In Part C and Part F of KEYNOTE-001 patients must have met all the following criteria to be eligible to participate in the study:

1) Provide written informed consent for the trial
2) ≥18 years of age on day of signing informed consent
3) Life expectancy of at least 12 weeks
4) Histologically or cytologically confirmed diagnosis of NSCLC with locally advanced or metastatic disease
5) Measurable disease as defined per irRC
6) Tumour amenable to biopsy.
7) Patient must have agreed to a newly obtained biopsy of tumour (biopsied based on Investigator's assessment) and to providing the tissue for biomarker analysis; no previous irradiation and no systemic antineoplastic therapy between the PD-L1 biopsy and initiating study medication.
8) ECOG Performance status of 0 or 1.[78]
9) Adequate organ function.
10) Female patients of childbearing potential must have had a negative urine or serum pregnancy test.

11) Female patients of childbearing potential must have agreed to use either 2 adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 120 days after the last dose of study therapy.
Male subjects must have agreed to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study therapy.

In Part C of the study, patients must also have experienced progression of disease after two prior systemic antineoplastic regimens (adjuvant therapy counted as a regimen if administered within 1 year before the relapse).

In Cohorts F2 and F3 patients must also have met the following criteria:
a) Tumours expressing PD-L1 (TPS≥1%) as determined by a central vendor (except for the 43 patients enrolled in Cohort F-2 whose tumours did not express PD-L1).
b) Known EGFR mutation and ALK gene rearrangement status (under Part F Amendments 07 and beyond); not required for a patient with non-squamous NSCLC known to have a mutation in KRAS or if a patient was known to have a tumour of predominately squamous histology).
c) Investigator determined radiographic progression per RECIST 1.1 following treatment with a platinum-containing chemotherapy and, if sensitising EGFR mutation of ALK positive, a TKI (only erlotinib, gefitinib, or afatinib, or crizotinib, respectively). There was no preferred order of treatment with TKI or platinum doublet therapy, only that progression had been documented on both treatments.

- Under Amendment 06, patients must have experienced disease progression after at least two prior systemic antineoplastic regimens.
- Under Amendments 07 and beyond, patients whose tumours express PD-L1 (TPS≥1%) must have experienced disease progression after at least 1 prior systemic antineoplastic regimen, at least 1 of which must have been a platinum-containing doublet. PD-L1 non-expressers (TPS<1%) in Cohort F2 must have received at least two prior lines of systemic therapy.

d) If patients received prior thoracic radiation of >30 Gy, they must have waited at least 26 weeks from the date of completion of the thoracic radiation before the first dose of pembrolizumab.
e) Patients with a tumour lesion at a critical anatomic location should have had that lesion radiated prior to treatment with pembrolizumab.

Exclusion criteria

Patients who met any of the following criteria were not eligible to participate in this study:

1) Chemotherapy, radioactive or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who had not recovered to Grade 1 or better from the AEs due to cancer therapeutics administered more than 4 weeks earlier.

2) Erlotinib, gefitinib, afatinib, or crizotinib within 1 week prior to the first dose of study therapy, or who had not recovered to Grade 1 or better from the AEs due to any of these drugs administered more than 1 week earlier.

3) Currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of administration of study treatment.

4) Expected to require any other form of antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC).

5) Medical condition that required chronic systemic steroid therapy or any other form of immunosuppressive medication (physiologic replacement doses of hydrocortisone, or its equivalent, were allowed).

6) Risk factors for bowel obstruction or bowel perforation.

7) History of a hematologic malignancy, malignant primary brain tumour or malignant sarcoma, or of another malignant primary solid tumour (other than NSCLC) within 5 years since initiation of study therapy, unless the patient had undergone potentially curative therapy with no evidence of recurrence for 5 years. The time requirement also did not apply to patients who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

8) Active central nervous system metastases and/or carcinomatous meningitis; patients with previously treated brain metastases are eligible provided they are stable.

9) History of a severe hypersensitivity reaction to treatment with another mAb.

10) History of non-infectious pneumonitis that required a course of oral or IV steroids to assist with recovery, or interstitial lung disease.

11) Active autoimmune disease or a documented history of autoimmune disease or syndrome that required systemic steroids or immunosuppressive agents.

12) Patients that required inhaled steroids or local steroid injections were not excluded from the study. Patients with hypothyroidism not from autoimmune disease and stable on hormone replacement were not excluded from the study.

13) Prior treatment targeting PD-1: PD-L1 axis or CTLA 4 (with exception of ipilimumab in study Part B and Part C), or previously randomised in any pembrolizumab trial.

14) Active infection requiring therapy.

15) Positive for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active Hepatitis B or Hepatitis C.

16) History or current evidence of any condition, therapy, or laboratory abnormality that might have confounded the results of the study, interfered with the patient's participation for the full duration of the study, or was not in the best interest of the subject to participate.
17) Known psychiatric or substance abuse disorder
18) Regular user (including "recreational use") of illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
19) Symptomatic ascites or pleural effusion, unless patient was clinically stable following treatment for these conditions.
20) Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

Settings and locations where the data were collected:

The KEYNOTE-001 study enrolled patients with NSCLC in the following countries: Australia, Canada, France, Italy, Norway, South Korea, Spain, Taiwan, UK and USA.

Trial drugs and concomitant medications:

In KEYNOTE001 Part C and F pembrolizumab was administered at the allocated dose (2mg/kg or 10 mg/kg depending on the assigned treatment group) in the clinic by site personnel via a 30-minute infusion once every two weeks (Q2W) or every three weeks (Q3W) depending on the assigned treatment group. Please see Table 9 for further detail on the number of patients treated at each dose and schedule of pembrolizumab.

Study treatment was continued until disease progression by irRC or unacceptable toxicity or tolerability.

Concomitant medications

All treatments that the investigator considered necessary for a patient's welfare may have been administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications received within 30 days before the first dose of the study treatment and 30 days after the last infusion of the study treatment were recorded. Further details of acceptable and prohibited concomitant medications are provided in Appendix 7.

Primary secondary and tertiary outcomes

Primary objectives:

- To evaluate anti-tumour activity of pembrolizumab per RECIST 1.1[10] in adult patients with NSCLC with at least 1 prior systemic therapy whose tumours express a high level of PD-L1 at baseline.
- To evaluate and characterise the tolerability and safety profile of pembrolizumab in adult patients with unresectable advanced NSCLC.

Responses were based on confirmed assessment by independent central review per RECIST 1.1[10], (Independent Radiology Committee [IRC]).

Secondary objectives:

- To evaluate the response rate (RR) of patients whose tumours express a high level of PD-L1 based on Investigator (INV) assessment per immune-related response criteria (irRC).
- To evaluate response duration, progression free survival (PFS) and overall survival (OS) of patients with NSCLC who are treated with pembrolizumab.

Overall Response rate (ORR) was defined as the proportion of the patients in the analysis population who had either a complete response (CR) or partial response (PR).

Response Duration: For patients who demonstrated confirmed CR or PR, response duration was defined as the time from first documented evidence of CR or PR until disease progression or death. The response duration for patients who have not progressed or died at the time of analysis was censored at the date of their last tumour assessment.

PFS was defined as the time from randomisation to the first documented disease progression or death due to any cause, whichever occurred first.

OS was defined as the time from randomisation to death due to any cause. Patients without documented death at the time of the final analysis were censored at the date of the last follow-up.

Response Assessment

For Parts C and F, tumour response was determined in real time by the Investigator's assessment with irRC; however, an independent central review using both RECIST 1.1[10] and irRC occurred retrospectively.

In all patients, baseline tumour imaging (CT or magnetic resonance imaging [MRI], with a preference for CT) was performed within 30 days before initiating pembrolizumab therapy. The same imaging technique as used at baseline had to be used throughout the study.

Following radiological tumour assessment at screening, imaging and radiological assessment of tumour response was performed every 9 weeks (±1 week) from the first administration of pembrolizumab, unless clinical indication warranted earlier imaging. If a CR, PR, or PD was observed, repeat imaging at least 4 weeks from the last scan was requested to confirm the assessment.

If confirmatory imaging indicated an objective response or stable disease relative to baseline, treatment with pembrolizumab was continued/resumed and the next imaging studies were conducted every 9 weeks from initiating pembrolizumab. If repeat imaging confirmed PD, then patients were discontinued from study therapy.

4.3.2: Comparative summary of the methodology of the RCTs

Table 10: Comparative summary of trial methodology

Trial number (acronym)	KEYNOTE-010	KEYNOTE-001 (Part C and F)
Location	Global study conducted in 24 countries: Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Lithuania, Netherlands, Portugal, Russia, South Africa, South Korea, Spain, Taiwan, UK, and USA.	Parts C and F of KEYNOTE- 001 study were conducted across the following countries: Australia, Canada, France, Italy, Norway, South Korea, Spain, Taiwan, UK, USA
Trial design	Randomised, phase II/III study of pembrolizumab versus docetaxel in in adults with non-small cell lung cancer (NSCLC) whose tumours express PD-L1 who have experienced disease progression after at least a platinum-containing systemic therapy. Open-label trial, blinded for PD-L1 status. Tumour response centrally reviewed by blinded independent radiologists.	Phase I open-label study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and anti-tumour activity of pembrolizumab in patients with locally advanced or metastatic melanoma (ipilimumab-naïve or previously treated with or refractory to ipilimumab) and NSCLC. A series of expansion cohorts (phase II-like sub-studies) were conducted. Parts C and F were expansion cohorts specifically designed to evaluate the efficacy and safety of pembrolizumab in patients with advanced or metastatic NSCLC. All patients enrolled in Part C, Cohort F2, and Cohort F3 had previously been treated with platinum-based chemotherapy and demonstrated disease progression before initiating pembrolizumab. These represent the population of interest for this submission.
Key eligibility criteria for participants	• Histologically or cytologically confirmed diagnosis of NSCLC stage IIIB/IV or recurrent disease • PD-L1 positive tumour (TPS≥1%) • Progression per RECIST 1.1 after treatment with at least two cycles of a platinum-containing doublet chemotherapy • Patient with EGFR mutation/ALK translocation must also demonstrate progression of disease on a EGFR TKI or Crizotinib • ECOG performance status of 0 or 1	Parts C and F: • Histologically or cytologically confirmed diagnosis of NSCLC with locally advanced or metastatic disease (Parts C and F) • Tumour amenable to biopsy • Progression per RECIST 1.1 after treatment with platinum-containing doublet chemotherapy • ECOG performance status of 0 or 1 Part F only: • Known EGFR/ALK status • Patient with EGFR mutation/ALK translocation must also demonstrate progression of disease on a EGFR TKI or Crizotinib
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as day care patients	The study was run in specialist oncology departments. Patients received treatment as day care patients
Trial drugs (the interventions for	Patients were randomised in a 1:1:1 ratio to receive one of the following	Part C (non-randomised): • Pembrolizumab 10 mg/kg Q3W

each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=) and comparator(s) (n=)** **Permitted and disallowed concomitant medication**	regimens: • Pembrolizumab 2 mg/kg Q3W • Pembrolizumab 10 mg/kg Q3W • Docetaxel at 75 mg/m2 Q3W Disallowed concomitant medicines: • Any other investigational agent • Any other systemic antineoplastic therapy or immunotherapy not specified in the protocol • Radiation therapy • Initiation of bisphosphonate or anti-RANKL mAb • Glucocorticoids for any purpose other than adverse event management or as a pre-medication for docetaxel • Live vaccines within 30 days prior to the first dose of study medication and while participating in the study • Strong inhibitors of the CYP3A4 enzymes • Prior treatment with any other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody	(n=38) Part F: F2 PDL1 expressers (randomised)* • Pembrolizumab 10 mg/kg Q2W (n=113) • Pembrolizumab 10 mg/kg Q3W (n=167) F2 PDL1non-expressers (non-randomised)* • Pembrolizumab 10 mg/kg Q2W (n=43) F2 PDL1 expressers (non-randomised)* • Pembrolizumab 10 mg/kg Q3W (n=33) F3 PDL1 expressers (non-randomised) • Pembrolizumab 2 mg/kg Q3W (n=55) Disallowed concomitant medicines: • Any other investigational agent • Any other form of antineoplastic therapy • Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. • Corticosteroids at a dose of 10 mg of prednisone (or its equivalent) per day.
Primary outcomes (including scoring methods and timings of assessments)	The co-primary objectives of this study were as follows: • PFS: defined as the time from randomisation to the first documented disease progression or death due to any cause, whichever occurs first • OS: defined as the time from randomisation to death due to any cause PFS was based on assessment from a central imaging vendor, Independent Review Committee (IRC) per RECIST 1.1 criteria. ITT population served as the primary population for the analyses of PFS and OS. On-study imaging was performed every 9 weeks (63 ± 7 days) until the patient experienced confirmed disease progression or started a new antineoplastic therapy. After the end of treatment, each patient was followed for a minimum of 30 days for adverse event monitoring (90 days for serious adverse events).	Primary efficacy endpoint: • Overall RR (ORR, complete response [CR] plus partial response [PR]) based on independent central review per RECIST 1.1 (IRC) on the FAS population. Assessment of tumour response was performed every 9 weeks (±1 week) unless clinical indication warranted earlier imaging.

	Patients had post-treatment follow-up for disease status, including initiating a non-study cancer treatment, disease progression, withdrawing consent, until death, or becoming lost to follow up.	
Secondary/ tertiary outcomes (including scoring methods and timings of assessments)	The secondary objectives were as follows: • ORR (IRC per RECIST 1.1) • Time to response and Response duration (IRC per RECIST 1.1) The exploratory objectives were as follows: • ORR, PFS and Response Duration by irRC • HRQoL changes from baseline using the EORTC-QLQC30 • Patient utilities using the EuroQoL EQ-5D • Tumour volumetric changes • Healthcare resource utilization in the in the TPS≥50% stratum.	Secondary efficacy endpoints: • ORR (IRC per RECIST 1.1) Based on IRC per RECIST 1.1 and INV per irRC: • Response duration • PFS • OS Analyses of secondary endpoints were based on the APaT population.
Pre-planned subgroups	• PD-L1 biomarker subgroups (i.e. (TPS≥50% stratum vs. overall population TPS≥1%) • Subgroup analyses of primary endpoints were also performed based on clinically relevant baseline patient or tumour characteristics	Not Applicable

APaT= All Patients as Treated; DCR = Disease Control Rate; FAS = full analysis set; ITT = intention to treat; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RR = response rate; *F2 cohort is composed of randomized and non-randomised sub-cohorts.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1: Statistical analysis

KEYNOTE-010[16;81-83]

Primary hypothesis

The study primary hypotheses were as follows:

- Pembrolizumab prolongs OS in previously-treated patients with NSCLC whose tumours express PD-L1 (TPS≥1%) compared to docetaxel.

- Pembrolizumab prolongs PFS per RECIST 1.1[10] by independent radiologists' review in previously-treated patients with NSCLC whose tumours express PD-L1 (TPS≥1%) compared to docetaxel.

- Pembrolizumab prolongs OS in previously-treated patients with NSCLC in the in the TPS≥50% stratum compared to docetaxel.

- Pembrolizumab prolongs PFS per RECIST 1.1[10] by independent radiologists' review in previously-treated patients with NSCLC in in the TPS≥50% stratum compared to docetaxel.

The study is considered to have met its primary objective if at least one pembrolizumab arm is superior to docetaxel either in PFS or in OS at an interim analysis or the final analysis, in the overall study population whose tumours express PD-L1 (TPS≥1%) or in the in the TPS≥50% stratum.

Interim analysis and stopping guidelines

KEYNOTE-010 study was initiated on 28-Aug-2013 and completed enrolment 27-Feb 27-2015. There were 2 planned interim analyses in this trial, as summarised in Table 11 below. Accrual was to be continued without a hold during the interim analyses.
The first interim analysis (IA1), planned to be performed after 120 patients in the TPS≥50% stratum had ≥3 months of follow-up and designed to compare efficacy between pembrolizumab arms and to assess futility, occurred in November 2014. The second interim analysis (IA2), planned to occur after approximately 175 PFS events and 120 deaths occurred across the three arms in the TPS ≥50% stratum and designed to assess superiority of pembrolizumab for PFS in the TPS ≥50% stratum at the 0.25% significance level using the Hochberg procedure, occurred in July 2015.
After both interim analyses, the DMC recommended continuing the study until the final analysis. The data cut-off date for the final analysis presented in this report was 30-Sep-2015.

Table 11: KEYNOTE-010 - Summary of interim analysis strategy

Interim Analysis number	Key Endpoints for Interim Analysis	Anticipated approximate timing of Interim Analysis (from study start)	Sample size included for the analysis (three arms)	Purpose of analysis
Interim Analysis 1 (IA1)	ORR	App. 10 months	120 in the in the TPS≥50% stratum with 3 months of minimum follow-up	• Discontinue one pembrolizumab arm for lack of efficacy OR discontinue both arms for futility
Interim Analysis 2 (IA2) **(primary PFS analysis and interim OS analysis)**	PFS/OS	App. 19 months	App. 414 (around 175 PFS events across three arms); (around 120 OS events across three arms) in the in the TPS≥50% stratum	• Demonstrate superiority of pembrolizumab in PFS • Demonstrate superiority of pembrolizumab in OS
Final Analysis	OS/PFS	App. 30 months	App. 460 (around 200 OS events across three arms) in the in the TPS≥50% stratum	• Demonstrate superiority of pembrolizumab in OS • Demonstrate long-term PFS effect of pembrolizumab

App. = approximately; ORR = overall response rate; OS = overall survival; PD-L1 = programmed cell death 1 ligand 1; PFS = progression-free survival.

Sample size

The sample size for patients with PD-L1 expression (TPS≥50%) was targeted at approximately 460, and the overall sample size was projected to be approximately 920. The protocol of the study acknowledged that the study was event driven and would be complete after approximately 200 deaths had been observed across the three arms in the TPS≥50% stratum (approximately 140 deaths between one pembrolizumab arm and the docetaxel arm under the alternative hypothesis).

The sample size calculation was based on the following assumptions for patients in the TPS≥50% stratum:

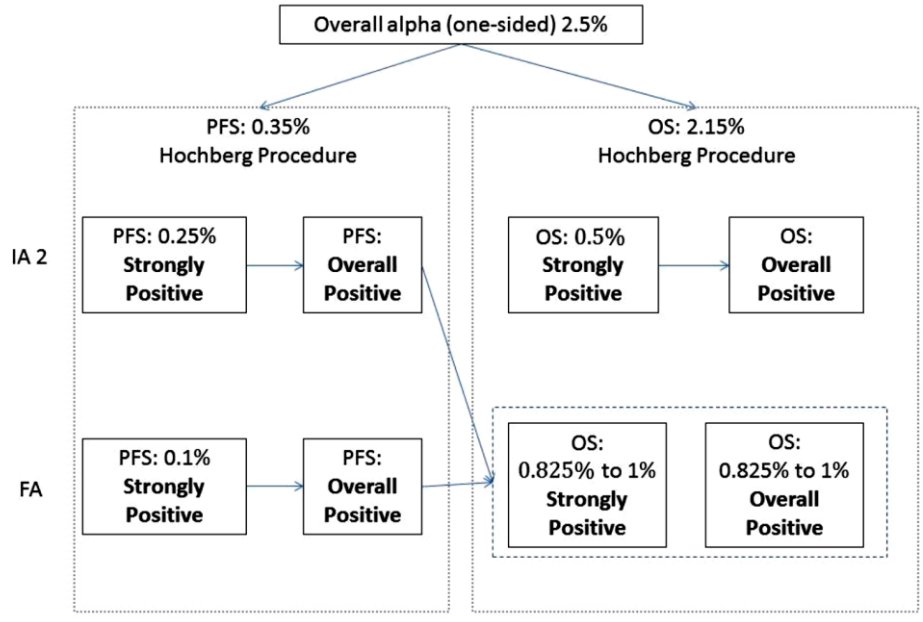
1) OS follows an exponential distribution with a median of 9 months in the docetaxel group (based on previous studies)[5],
2) the hazard ratio (HR) between pembrolizumab and control is 0.60,
3) an enrolment period of 16 months and a minimum of 8 months follow-up after enrolment completion; and
4) a dropout rate of 2% in 12 months.

At the final analysis, with approximately 140 deaths between one pembrolizumab arm and the docetaxel arm, the study had over 81% power to detect a 0.55 HR at alpha=0.825% (one-sided) in the TPS≥50% stratum under a Hochberg procedure for the two pembrolizumab vs. docetaxel comparisons. In the overall study population whose tumours express PD-L1 (TPS≥1%), it was expected that approximately 550 deaths would have been observed across three arms in the final analysis. With 378 deaths observed between two treatment arms, the study had over 80% power to detect a 0.70 HR at alpha=0.825% (one-sided) in the overall study population whose tumours express PD-L1 (TPS≥1%).

An analysis of long-term PFS was planned to be carried out at the final analysis at 0.1% alpha (one-sided) in the TPS≥50% stratum. With approximately 345 PFS events observed across the three arms in the TPS≥50% stratum (approximately 240 PFS events between one pembrolizumab arm and the docetaxel arm under the alternative hypothesis), the study had 88% power to detect a 0.6 HR at alpha=0.1%.

The strategy to address multiplicity planned for this study is summarised in Figure 7 below:

Figure 7: KEYNOTE-010 - Multiplicity strategy



The Hochberg step-up procedure was to be used for multiple comparisons on an efficacy endpoint if both pembrolizumab arms continued to study completion. The type I error rates were all one-sided. The one-sided hypothesis testing was pre-specified in the protocol, and is usually preferred in a superiority trial. The overall type I error rate was strictly controlled at 2.5% (one -sided) with 0.35% allocated to PFS and 2.15% allocated to OS hypothesis. If both pembrolizumab arms demonstrated superior PFS or OS in the TPS≥50% stratum, PFS

or OS would be tested sequentially in the overall population whose tumours express PD-L1 (TPS≥1%) at the same alpha level. At the final analysis, a Bonferroni correction would be used to adjust for the OS tests in the TPS≥50% stratum and in the overall study population whose tumours express PD-L1 (TPS≥1%).

Statistical methods used to compare groups for primary and secondary outcomes

The statistical methods and analysis strategy for the primary and secondary efficacy endpoints are summarised in the Table 12 below. The study statistician remained blinded to treatment assignment until the final analysis was completed.

Table 12: KEYNOTE-010 - Analysis strategy for key efficacy endpoints in the TPS≥50% stratum and the overall population of PD-L1 expressers (TPS≥1%)

Endpoint (description, time point)	Statistical Method	Analysis Population	Missing Data Approach
Primary			
PFS	Kaplan-Meier (KM) method for PFS curve estimation in each treatment group. Stratified Log-rank test and stratified Cox model with Efron's tie handling method to estimate treatment difference (HR).*	ITT	Model based
OS	KM method for OS curve estimation in each treatment group. Stratified Log-rank test and stratified Cox model with Efron's tie handling method to estimate treatment difference (HR).*	ITT	Model based
Secondary			
ORR	Stratified M&N[$] method	ITT	Patients with missing data are considered non-responders
Response Duration	Summary statistics using KM method	All responders in ITT	Non-responders are excluded in analysis

* Applying the same stratification factors used for randomisation [$] Miettinen & Nurminen method; ITT = intention-to-treat.

Methods for additional analyses, such as subgroup analyses and adjusted analyses

To determine whether the treatment effect is consistent across various subgroups, the study protocol specified that the estimate of the between-group treatment effect for the primary endpoint would be estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)

- Sex (female, male)
- Race (white, non-white)
- ECOG status (0 vs. 1)[78]
- Geographic region of enrolling site (East Asia, non-East Asia)
- Ethnicity (East Asian, non-East Asian)
- Previous chemotherapy regimen (types with greater than 10% subjects in the control group)
- ALK translocation status (translocated vs. wild type)
- EGFR mutation status (wild type vs. mutant)
- Age of tumour specimen (archival vs. new)

Post-hoc exploratory subgroup analyses were also conducted by tumour histology.
All subgroup analyses were to be carried out in the in the TPS≥50% stratum and the overall study population whose tumours express PD-L1 (TPS≥1%).

Since patients in the control arm were expected to discontinue treatment earlier compared to patients in the pembrolizumab arm (and could receive other PD-1 treatments similar to pembrolizumab after discontinuation); exploratory analyses of OS adjusting for the confounding effect of subsequent anti-cancer therapy were planned.

In order to evaluate the robustness of the PFS estimates, three sensitivity analyses were planned for this study, with a different set of censoring rules and PD event definitions under various scenarios (see section 4.4.2 for details on censoring rules for these sensitivity analyses).

KEYNOTE-001 (Parts C and F)[35;85;86;89]

Primary hypothesis

The study primary hypothesis was as follows:

Pembrolizumab will show a clinically meaningful response rate per RECIST 1.1[10] in patients with NSCLC with at least 1 prior systemic therapy whose tumours express a high level of PD-L1.

Interim analysis and stopping guidelines

The first patient was allocated to treatment on 08-May-2012 and the last patient included in this interim analysis was assigned treatment on 13-Jul-2014. The database cut-off used in this submission was 23-Jan-2015.

Sample size

Considering data from the Biomarker Training Set, the sample size calculation was based on the assumption that half of samples from patients in the Biomarker Validation Set would have PD-L1 expression above the cut point and that previously treated patients whose samples were above the cut point would have an ORR ≥30%. Conservatively assuming a 15% ORR with standard second-line chemotherapy based on historical controls, [4-7] 75 previously treated patients receiving pembrolizumab 10 mg/kg Q3W would yield 85% power to exclude an ORR ≤15% in patients whose samples were above the cut point with a one sided *p* value of 0.025, which approximately corresponds to an empirical response rate of 25% (i.e., the lower bound of the 95% CI for an empirical response rate at 25% excluded 15%).

Per protocol, data from previously treated patients who received pembrolizumab 10 mg/kg Q3W could be combined with previously treated patients who received 10 mg/kg Q2W. Furthermore, the protocol also stipulated that if similar response rates were observed regardless of line of therapy, those cohorts could also be combined. Finally, if the ORR outcome was positive with the PD-L1 cut point of TPS≥50%, an analysis of all patients whose tumours express PD-L1 (TPS≥1%) would be performed.

Statistical methods used to compare groups for primary and secondary outcomes

A 95% CI for ORR was provided for each population and by dose/schedule as applicable. Descriptive statistics were also provided for analyses of response duration and tumour volumetric changes. In addition, Kaplan-Meier (KM) curves and descriptive statistics of PFS and OS were provided. In order to adjust for the shorter follow-up in Cohort F3, the KM estimate of cumulative RR at the longest follow-up time-point served as an estimate of the ORR.

Methods for additional analyses, such as subgroup analyses and adjusted analyses

Subgroup analyses were performed based on major demographic factors and potentially important prognostic factors for patients with advanced NSCLC. These subgroups were not pre-specified, but were performed in post-hoc analyses to show consistency in ORR for

major subgroups who might be treated with pembrolizumab in future clinical trials or in future clinical practice. All analyses were based on ORR as determined by central review per RECIST 1.1[10] in the APaT population.

4.4.2: Trial population included in primary analysis of the primary outcome and methods to take account of missing data

KEYNOTE-010 [16;81-83]

Trial population

The intention-to-treat (ITT) population in the TPS≥50% stratum and the TPS>1% population served as the primary population for the analyses of PFS and OS in KEYNOTE-010. Patients were included in the treatment group to which they were randomised for the analysis of efficacy data using the ITT population. A supportive analysis was conducted in the Full analysis set (FAS) population, which excluded those who did not meet the key eligibility criteria or discontinued before receiving any dose of assigned treatment.

Missing data approach and censoring methods

The approach for dealing with missing data in KEYNOTE-010 has been described in Table 12 of section 4.4.1.

For OS, data for patients who were alive or lost to follow-up were censored at the time of last confirmed contact. For PFS, data for patients without documented PD/death or who were lost to follow-up were censored at the time of last tumour assessment. Since disease progression was assessed periodically, PD could occur any time in the interval between the last assessment where PD was not documented and the assessment when PD was documented. For the primary analysis, for the patients who had PD, the true date of disease progression was approximated by the date of first assessment at which PD was objectively documented per RECIST 1.1[10], regardless of discontinuation of study treatment. Death was always considered as a confirmed PD event.

For ORR, patients with missing data were considered non-responders. For duration of response, data for patients whose response was ongoing at the time of the analysis or who discontinued the study without radiological evidence of progression were censored at the time of the last radiological assessment showing response, data for patients who had radiological disease progression after missing two radiological assessments were censored at the time of the last radiological assessment showing response; and data for patients who

initiated new cancer treatment without radiological evidence of disease progression were censored at the time of starting their new treatment.

In order to evaluate the robustness of the PFS estimates, three sensitivity analyses were planned for this study, with a different set of censoring rules and PD event definitions under various scenarios. The first sensitivity analysis was the same as the primary analysis except that it censored at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis was the same as the primary analysis except that it considered discontinuation of treatment or initiation of new anticancer treatment, whichever occurred later, to be a PD event for patients without documented PD or death. The third sensitivity analysis was the same as the second sensitivity analysis except that it censored at the last disease assessment when there was no PD and no death and new anticancer treatment is initiated. The censoring rules for primary and sensitivity analyses are summarized in Table 13 below:

Table 13: KEYNOTE-010 - Censoring rules for primary and sensitivity analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2	Sensitivity Analysis 3
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment	Censored at last disease assessment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death

KEYNOTE-001 (Parts C and F)[35;85;86;89]

Trial population

The KEYNOTE-001 study populations used for the efficacy and safety analyses supporting the use of pembrolizumab in a patient population comparable to the population included in KEYNOTE-010 study are described in Table 14 below:

Table 14: KEYNOTE-001 (Parts C and F) - Populations for analyses

Population	Efficacy (E) or Safety (S)	APaT (N)	FAS (N)
Primary Efficacy Population (TPS≥50% within Stability Window) Patients in the randomised part of Cohort F2 comprising the Biomarker Validation Set, who had tumour PD-L1 expression with a TPS of ≥50% at baseline, as determined by an IHC assay using the 22C3 clone (MRA).	E	61	57
Supportive Efficacy/Safety Populations			
Total Previously Treated Efficacy Population Patients from Cohort C or F2, who experienced PD after at least platinum-based chemotherapy, who are part of the Biomarker Training or Validation Set.	E	394	360
Previously Treated Validation Population Patients from Cohort F2, who experienced PD after at least platinum-based chemotherapy, who are part of the Biomarker Validation Set.	E	223	208
Previously Treated Population, 2 mg/kg Q3W Patients in Cohort F3, who experienced PD after at least platinum-based chemotherapy. These patients were treated at 2 mg/kg Q3W.	E, S	55	52
All Patients With NSCLC Patients who received at least one dose of pembrolizumab.	S	550	502

APaT = All Patients as Treated; FAS = Full Analysis Set; MRA = Market Ready Assay; N = Number of patients; NSCLC = non-small cell lung cancer; TPS = proportion score;
Data cut-off: 23-Jan-2015

All patients in the study populations used for the efficacy analyses had previously received a platinum-based chemotherapy and experienced progression of NSCLC after initiating the platinum-based chemotherapy. Patients with a sensitizing EGFR mutation or ALK gene rearrangement must have experienced disease progression after initiating treatment with the appropriate TKI.

The Full Analysis Set (FAS) was the pre-specified population used for analysis of the primary endpoint of this study. Patients who received at least one dose of study treatment and met the requirement of measurable disease at baseline were included in the FAS population.

The other efficacy analyses are based on the All Patients as Treated (APaT) dataset, which is defined as all patients who received at least one dose of pembrolizumab. Using the APaT population for the efficacy analysis is considered a more conservative approach than using the FAS population.

Prior to assessment of tumour PD-L1 expression by the MRA in the Biomarker Validation Set, data from ongoing antigen stability studies at Dako showed a maximum of 6 months of stability for the PD-L1 antigen on a glass slide. Therefore, the Sponsor requested newly cut material from the same block scored by the PA for samples cut >6 months prior to staining with the MRA (for details please see Appendix 6).

It was pre-specified before unblinding the database that the primary efficacy analyses would be conducted using only data from patients with tumour samples that were within the stability window of the PD-L1 assay.

Missing data approach and censoring methods

A pre-specified sensitivity analysis was conducted to evaluate the potential impact of the missing data on the ORR. Those patients with slides that were beyond the six-month cut-off and not replaced with a valid tumour tissue sample were considered non evaluable in the primary analysis. Sensitivity analyses including these patients with expired samples as well as other patients with non-evaluable samples were conducted to confirm that the missing information did not substantially bias the outcome in favour of the population with evaluable samples.

4.4.3: Statistical tests used in primary analysis

Table 15: Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KEYNOTE-010	1) Pembrolizumab prolongs OS in previously-treated patients with NSCLC compared to docetaxel. 2) Pembrolizumab prolongs PFS per RECIST 1.1 by independent radiologists' review in previously-treated patients with NSCLC compared to docetaxel.	The ITT population served as the primary population for the analyses of PFS and OS. A supportive analysis was conducted in the the FAS population. The overall type I error rate was strictly controlled at 2.5% (one-sided), allowing the trial to declare positive in either OS or PFS in the TPS≥50% stratum. Strong control of Type I error was also extended to the analysis of OS in the overall population whose tumours express PD-L1 (TPS≥1%).	OS event driven study. The sample size for patients in the TPS≥50% stratum was targeted at approximately 460, and the overall sample size was projected to be 920. The sample size calculation was based on the following assumptions for patients in the TPS≥50% stratum: 1) OS follows an exponential distribution with a median of 9 months in the control arm, 2) the HR between pembrolizumab and control is 0.60, 3) an enrolment period of 16 months and a minimum of 8 months follow-up after enrolment completion; and 4) a dropout rate of 2% in 12 months. It was expected that approximately 550 patients would die by the final analysis, giving the study at least 80% power to detect an HR of 0.70 for OS in the total population.	Each patient participated in the trial from the time h/she signed the informed consent form through the final protocol-specified contact. Treatment continued until two years of therapy have been administered, confirmed disease progression, unacceptable toxicity, a decision by investigators, or withdraw consent. If a patient discontinued/ withdrew prior to study completion, all applicable activities scheduled for the final study visit were performed at the time of discontinuation.

KEYNOTE-001 (Parts C and F)	Pembrolizumab will show a clinically meaningful RR per RECIST 1.1 in patients with NSCLC with at least 1 prior systemic therapy whose tumours express a high level of PD-L1.	The primary efficacy analysis was based on the FAS population. Other efficacy analyses are based on the APaT population.	The sample size calculation was based on the assumption that half of samples from patients in the Biomarker Validation Set would have PD-L1 expression above the cut point and that previously treated subjects whose samples were above the cut point would have an ORR ≥30%. Assuming a 15% ORR with standard second-line chemotherapy, 75 previously treated patients receiving pembrolizumab 10 mg/kg Q3W would yield 85% power to exclude an ORR ≤15% in patients whose samples were above the cut point with a one sided *p* value of 0.025.	Patients were permitted to withdraw at any time or be dropped from the study at the discretion of the Investigator should any untoward effects occurred. In addition, a patient could be withdrawn by the Investigator or the study Sponsor if he/she violated the study plan or for administrative and/or other safety reasons. When a patient discontinued/withdrew prior to study completion, all applicable activities scheduled for the final study visit were performed at the time of discontinuation. No patient from Parts C or F was replaced.

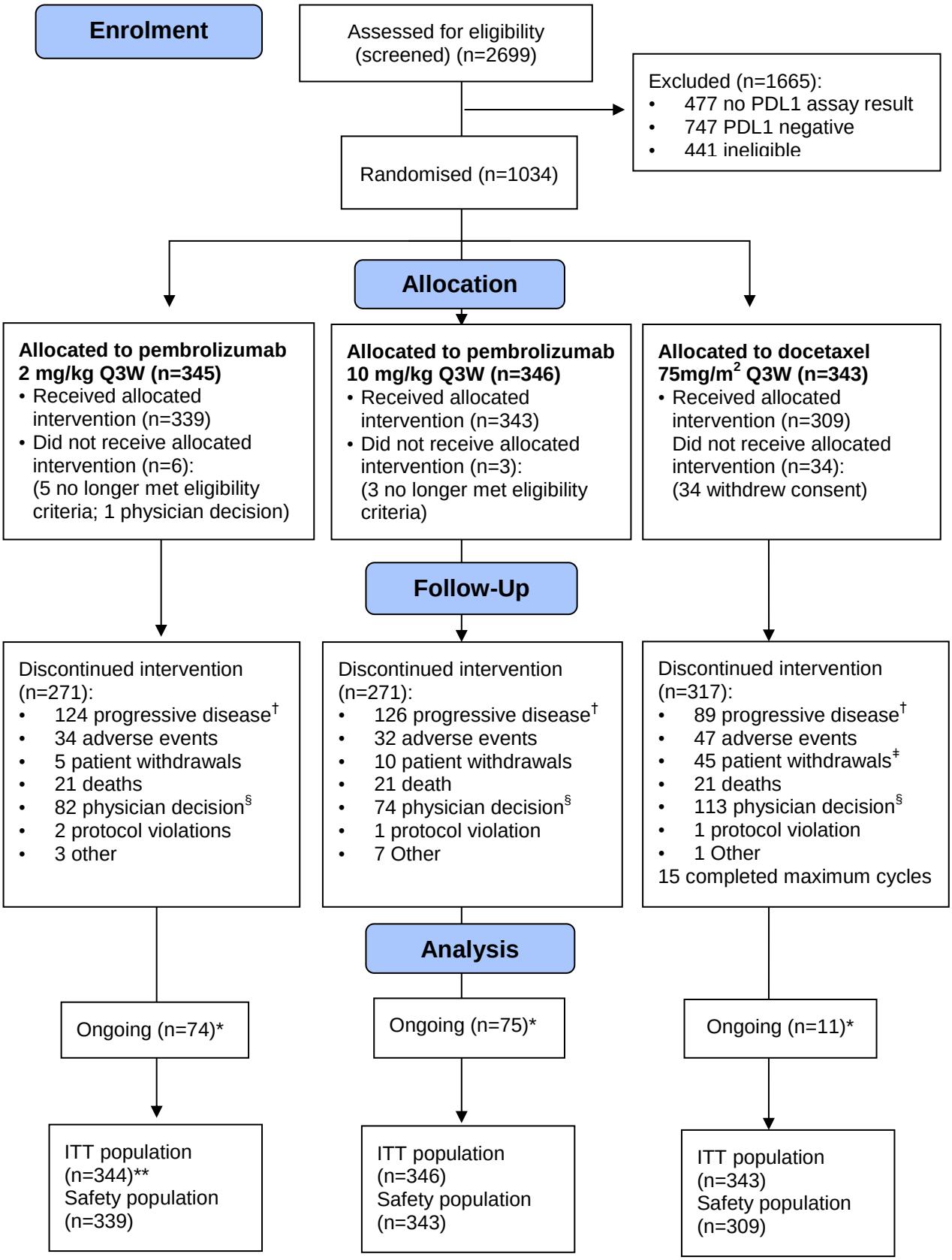
4.5 Participant flow in the relevant randomised controlled trials

4.5.1: Number of patients eligible to enter each trial

KEYNOTE-010[16;81-83]

The disposition of patients from randomisation through to last analysis (Final analysis cut-off date 30-Sep-2015) is presented in Figure 8 below:

Figure 8: CONSORT diagram – KEYNOTE-010



†Includes only disease progression observed on radiologic imaging. §Mainly clinical disease progression **Patients without a completed discontinuation form. **One patient was permitted to remain on treatment and was included in the safety analysis population, but because it would not be possible to adequately assess tumour response, the patient was excluded from the efficacy analysis population.* ‡ Includes 34 patients that withdrew consent and did not receive allocated intervention.

Of the 2222 patients whose tumour samples were assessable for PD-L1 expression, 1475 (66%) had PD-L1 expression on at least 1% of tumour cells, including 633 (28%) with PD-L1 expression on at least 50% of tumour cells. A total of 1034 patients met the eligibility criteria and were enrolled in the study. Of these, 47% were patients enrolled at sites in Europe (including 56 patients from the UK).

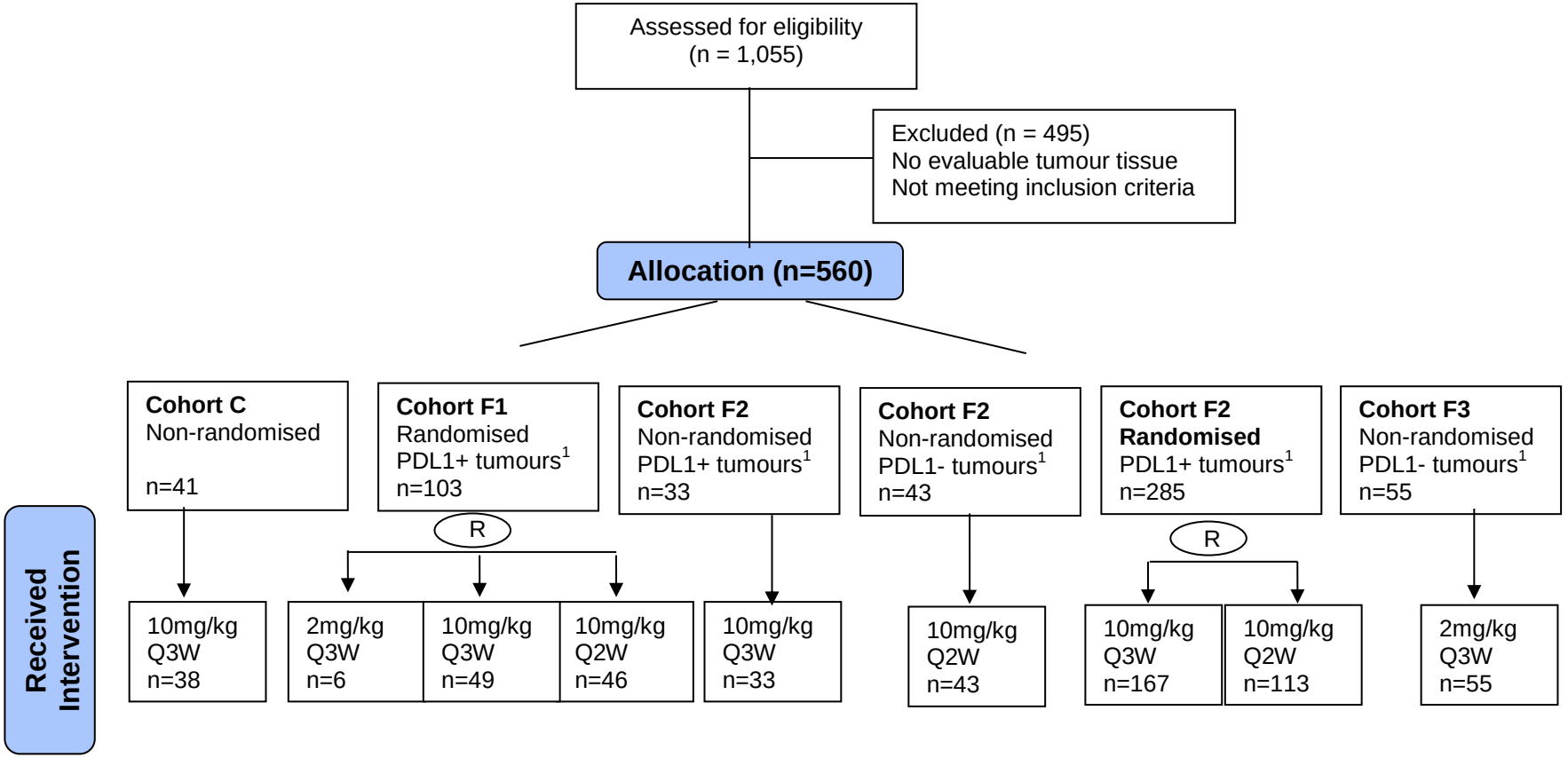
In the docetaxel arm 34 (9.9%) patients withdrew consent after learning they were allocated to the docetaxel group and did not receive the intervention. The baseline characteristics of these patients (see Table 1 in Appendix 8) did not differ significantly from the overall docetaxel population (Table 17), suggesting that the comparability of the study groups was not significantly imbalanced and that the risk of bias is low.

KEYNOTE-001 (Parts C and F)[35;85;86;89]

The disposition of patients from enrolment through to last analysis (cut-off date 23-Jan-2015) is presented in Figure 9 and Table 16. A total of 560 patients with NSCLC were allocated to Parts C and F in this study. Of these, 550 patients received at least one dose of pembrolizumab.

The derivation of the efficacy analysis populations from parts C and F of KEYNOTE-001 is described in Figure 6 and Figure 1 of Appendix 6). Table 16 presents the disposition of patients during follow up in the Total Previously Treated Efficacy Population (Cohort C and F2 from Biomarker Training or Validation Set) and the Previously Treated Population (Cohort F3, 2 mg/kg Q3W). The designation of “unknown” disposition accounts for patients who continued on treatment with pembrolizumab at the time of the database cut-off (23-Jan-2015).

Figure 9: CONSORT diagram – KEYNOTE-001 for NSCLC expansion cohorts



The disposition of patients during follow up in the Total Previously Treated Efficacy Population (Cohort C and F2) and the Previously Treated Population (Cohort F3) is described in Table 16.

PD-L1 = programmed cell death-1 ligand-1; Q2W = every 2 weeks; Q3W = every 3 weeks; R = randomized

[1]Tumour PD-L1 expression was determined by a prototype assay to inform enrolment. Samples were independently reanalysed using a clinical trial/market-ready immunohistochemistry assay. See section 4.3.1 for further description.
Data cut-off: 23JAN2015

Table 16: KEYNOTE-001 - Disposition of patients - Total Previously Treated Efficacy Population by PD-L1 and Previously-Treated Population

	Total Previously Treated Efficacy Population (Cohort C and F2, N=394) (Biomarker Training and Validation sets)	Previously Treated Population (Cohort F3, N=55)
	n (%)	n (%)
Patient Study Medication Disposition		
Discontinued	329 (83.5)	40 (72.7)
Adverse Event	91(23.1)	12 (21.8)
Physician Decision	23 (5.8)	3 (5.5)
Progressive Disease	189 (48.0)	20 (36.4)
Protocol Violation	16 (4.1)	2 (3.6)
Withdrawal By Patient	10 (2.5)	3 (5.5)
Unknown	65 (16.5)	15 (27.3)
Database Cut-off Date: 23JAN2015		

4.5.2: Characteristics of participants at baseline for each trial

KEYNOTE-010[16;81-83]

Baseline characteristics were as expected for patients with advanced NSCLC and balanced between groups (Table 17). The majority of patients were male, white, with mean age around 62 years old. Most patients were current or former smokers and had tumours of non-squamous histology. Few patients had EGFR-mutant or ALK-translocated tumours. In the study, 29% of the patients had received at least two lines of previous systemic therapy. The baseline characteristics of the 442 patients in the TPS≥50% stratum in the ITT population were similar to the overall population TPS≥1% (Appendix 8).

Table 17: KEYNOTE-010 - Baseline Characteristics - ITT Population (TPS ≥ 1%)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W		Pembrolizumab 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	343		344		346		1,033	
Gender								
Male	209	(60.9)	212	(61.6)	213	(61.6)	634	(61.4)
Female	134	(39.1)	132	(38.4)	133	(38.4)	399	(38.6)
Age (Years)								
<65	209	(60.9)	201	(58.4)	194	(56.1)	604	(58.5)
>=65	134	(39.1)	143	(41.6)	152	(43.9)	429	(41.5)
Mean	61.6		62.1		62.3		62.0	
SD	9.8		9.6		9.7		9.7	
Median	62.0		63.0		63.0		63.0	
Range	33 to 82		29 to 82		20 to 88		20 to 88	
Ethnicity								
Hispanic Or Latino	13	(3.8)	23	(6.7)	16	(4.6)	52	(5.0)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W		Pembrolizumab 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Not Hispanic Or Latino	307	(89.5)	303	(88.1)	293	(84.7)	903	(87.4)
Not Reported	14	(4.1)	7	(2.0)	25	(7.2)	46	(4.5)
Unknown	3	(0.9)	10	(2.9)	10	(2.9)	23	(2.2)
Missing	6	(1.7)	1	(0.3)	2	(0.6)	9	(0.9)
Race								
East Asian	66	(19.2)	61	(17.7)	64	(18.5)	191	(18.5)
Non-East Asian	266	(77.6)	276	(80.2)	271	(78.3)	813	(78.7)
Missing	11	(3.2)	7	(2.0)	11	(3.2)	29	(2.8)
Geographic Region								
US	77	(22.4)	73	(21.2)	74	(21.4)	224	(21.7)
EX US	266	(77.6)	271	(78.8)	272	(78.6)	809	(78.3)
Region								
Non-East Asian	281	(81.9)	280	(81.4)	282	(81.5)	843	(81.6)
East Asian	62	(18.1)	64	(18.6)	64	(18.5)	190	(18.4)
Smoker								
Never Smoker	67	(19.5)	63	(18.3)	60	(17.3)	190	(18.4)
Current/Ex-Smoker	269	(78.4)	279	(81.1)	285	(82.4)	833	(80.6)
Missing	7	(2.0)	2	(0.6)	1	(0.3)	10	(1.0)
ECOG								
0	116	(33.8)	112	(32.6)	120	(34.7)	348	(33.7)
1	224	(65.3)	229	(66.6)	225	(65.0)	678	(65.6)
2	1	(0.3)	3	(0.9)	1	(0.3)	5	(0.5)
3	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
MISSING	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
Cancer Stage								
IA	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
IB	1	(0.3)	1	(0.3)	0	(0.0)	2	(0.2)
IIB	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
IIIA	8	(2.3)	5	(1.5)	4	(1.2)	17	(1.6)
IIIB	22	(6.4)	21	(6.1)	26	(7.5)	69	(6.7)
IV	312	(91.0)	315	(91.6)	316	(91.3)	943	(91.3)
Metastatic Staging								
M0	31	(9.0)	29	(8.4)	30	(8.7)	90	(8.7)
M1	80	(23.3)	95	(27.6)	80	(23.1)	255	(24.7)
M1A	62	(18.1)	62	(18.0)	65	(18.8)	189	(18.3)
M1B	170	(49.6)	158	(45.9)	171	(49.4)	499	(48.3)
Baseline Tumour Size (mm)								
Subjects with data	308		335		338		981	
Mean	91.6		98.7		94.2		94.9	
SD	54.9		61.0		55.4		57.3	
Median	78.0		86.0		80.0		81.0	
Range	13 to 290		10 to 345		11 to 326		10 to 345	
Brain Metastasis								
Yes	48	(14.0)	56	(16.3)	48	(13.9)	152	(14.7)
No	295	(86.0)	288	(83.7)	298	(86.1)	881	(85.3)
Non-small Cell Histology								
SQUAMOUS	66	(19.2)	76	(22.1)	80	(23.1)	222	(21.5)
NON-SQUAMOUS	240	(70.0)	240	(69.8)	244	(70.5)	724	(70.1)
MIXED	4	(1.2)	3	(0.9)	3	(0.9)	10	(1.0)
OTHER	6	(1.7)	6	(1.7)	3	(0.9)	15	(1.5)
UNKNOWN	27	(7.9)	19	(5.5)	16	(4.6)	62	(6.0)
PD-L1 Status								
TPS1-49%	191	(55.7)	205	(59.6)	195	(56.4)	591	(57.2)
TPS≥50%	152	(44.3)	139	(40.4)	151	(43.6)	442	(42.8)
EGFR Mutation								

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W		Pembrolizumab 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
MUTANT	26	(7.6)	28	(8.1)	32	(9.2)	86	(8.3)
WILD TYPE	294	(85.7)	293	(85.2)	288	(83.2)	875	(84.7)
UNDETERMINED	13	(3.8)	15	(4.4)	17	(4.9)	45	(4.4)
Missing	10	(2.9)	8	(2.3)	9	(2.6)	27	(2.6)
ALK Translocation Status								
MUTANT	2	(0.6)	2	(0.6)	4	(1.2)	8	(0.8)
WILD TYPE	310	(90.4)	307	(89.2)	305	(88.2)	922	(89.3)
UNDETERMINED	20	(5.8)	22	(6.4)	26	(7.5)	68	(6.6)
Missing	11	(3.2)	13	(3.8)	11	(3.2)	35	(3.4)
Prior Lines of Systemic Therapy								
ADJUVANT	3	(0.9)	6	(1.7)	7	(2.0)	16	(1.5)
NEO ADJUVANT	0	(0.0)	1	(0.3)	1	(0.3)	2	(0.2)
FIRST LINE	235	(68.5)	243	(70.6)	235	(67.9)	713	(69.0)
SECOND LINE	75	(21.9)	66	(19.2)	69	(19.9)	210	(20.3)
THIRD LINE	20	(5.8)	18	(5.2)	27	(7.8)	65	(6.3)
FOURTH LINE	6	(1.7)	6	(1.7)	3	(0.9)	15	(1.5)
FIFTH LINE OR GREATER	3	(0.9)	3	(0.9)	4	(1.2)	10	(1.0)
Missing	1	(0.3)	1	(0.3)	0	(0.0)	2	(0.2)
Prior Adjuvant/Neo-adjuvant Therapy								
Y	18	(5.2)	20	(5.8)	26	(7.5)	64	(6.2)
N	325	(94.8)	324	(94.2)	320	(92.5)	969	(93.8)
Prior Chemotherapy†								
Y	339	(98.8)	335	(97.4)	337	(97.4)	1,011	(97.9)
N	4	(1.2)	9	(2.6)	9	(2.6)	22	(2.1)
Prior Immunotherapy†								
Y	1	(0.3)	2	(0.6)	1	(0.3)	4	(0.4)
N	342	(99.7)	342	(99.4)	345	(99.7)	1,029	(99.6)
Prior EGFR TKI Therapy†								
Y	47	(13.7)	40	(11.6)	56	(16.2)	143	(13.8)
N	296	(86.3)	304	(88.4)	290	(83.8)	890	(86.2)
Prior ALK inhibitor Therapy†								
Y	2	(0.6)	3	(0.9)	5	(1.4)	10	(1.0)
N	341	(99.4)	341	(99.1)	341	(98.6)	1,023	(99.0)

†Prior systemic therapy (Database Cut-off Date: 30SEP2015).

KEYNOTE-001- Part C and F[35;85;86;89]

Table 18 displays the baseline characteristics of the Total Previously Treated Efficacy Population (Cohort C and F2) by dose (APaT population). The Baseline characteristics of the patients in the Total Previously Treated Efficacy Population of KEYNOTE-001 were generally similar to characteristics of the population in KEYNOTE-010, and were balanced between treatment groups. For both arms the median age was 60 years. Most patients were current or former smokers and had tumours of non-squamous histology. Few patients had EGFR-mutant or ALK-translocated tumours. In this study population, 83% of the patients had received at least two lines of previous systemic therapy.

Table 18: KEYNOTE-001 - Baseline Characteristics – Total Previously Treated Efficacy Population by Dose (APaT)

	Pembrolizumab 10 mg/kg Q3W n=238	Pembrolizumab 10 mg/kg Q2W n=156	Total n=394
Gender			
Male	48.3%	55.1%	51.0%
Age (Years)			
< 65	54.6%	59.0%	56.3%
Mean (SD)	60.9 (11.4)	61.8 (9.6)	61.3 (10.7)
Median (Range)	63.0 (28 to 85)	62.0 (32 to 82)	62.0 (28 to 85)
Race			
Asian	17.6%	9.0%	14.2%
Black Or African American	5.0%	4.5%	4.8%
White	76.9%	85.3%	80.2%
Ethnicity			
Hispanic Or Latino	7.1%	3.8%	5.8%
Not Hispanic Or Latino	92.0%	96.2%	93.7%
Region			
Australia	5.0%	1.9%	3.8%
Canada	4.2%	8.3%	5.8%
EU	16.8%	17.3%	17.0%
East Asia	6.3%	5.8%	6.1%
US	67.6%	66.7%	67.3%
ECOG			
[0]	37.0%	26.9%	33.0%
[1]	63.0%	71.8%	66.5%
Unknown	0.0%	1.3%	0.5%
Cancer Staging			
III	2.5%	3.2%	2.8%
IV	97.5%	96.8%	97.2%
Metastatic Staging			
M0	2.5%	2.6%	2.5%
M1a	25.2%	26.3%	25.6%
M1b	72.3%	71.2%	71.8%
Brain Metastasis			
Yes	11.8%	12.8%	12.2%
Number of Unique Prior Systemic Therapies			
1	18.1%	15.4%	17.0%
2	31.5%	27.6%	29.9%
3	26.1%	28.8%	27.2%
4 or more	24.4%	28.2%	25.9%
Baseline Tumour Size (mm)			
Patients with data	216	144	360
Mean (SD)	111 (89)	123 (80)	116 (86)
Median (Range)	90 (11 to 548)	102 (10 to 419)	98 (10 to 548)
Histology			
Squamous	12.6%	23.1%	16.8%
Non-Squamous	85.7%	75.6%	81.7%
Adenosquamous	1.3%	1.3%	1.3%
Unknown	0.4%	0.0%	0.3%

	Pembrolizumab 10 mg/kg Q3W n=238	Pembrolizumab 10 mg/kg Q2W n=156	Total n=394
Smoking Status			
Never	32.8%	23.7%	29.2%
Former	63.4%	67.3%	65.0%
Current	3.8%	9.0%	5.8%
EGFR Mutation			
Yes	18.9%	16.0%	17.8%
No	75.6%	83.3%	78.7%
Unknown	5.5%	0.6%	3.6%
KRAS Mutation			
Yes	17.6%	16.0%	17.0%
Unknown	35.7%	37.2%	36.3%
ALK Gene Rearrangement			
Wild Type	78.2%	96.2%	85.3%
Unknown	18.5%	3.8%	12.7%
Database Cut-off Date: 23 JAN 2015			

4.6 Quality assessment of the relevant randomised controlled trials

A complete quality assessment for each trial is included in Appendix 9.

A tabulated a summary of the quality assessment results is presented in Table 19 below.

Table 19: Quality assessment results for parallel group RCTs

Trial	KEYNOTE-010	KEYNOTE- 001 (Part C and F)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	Yes	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	No
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

4.7 Clinical effectiveness results of the relevant randomised controlled trials

KEYNOTE-010 Results: Final Analysis - data cut-off 30-Sep-2015[16;81-83]

Clinical effectiveness results are presented in this section for pembrolizumab 2mg/Kg Q3W (anticipated licence dose and schedule, relevant to this submission) versus docetaxel in the ITT population of patients whose tumours express PD-L1 (TPS≥1%). Details on the rationale for the selection of the 2mg/Kg dose for the NSCLC indication are provided in Appendix 10. Full results for all three study arms (including pembrolizumab 10mg/Kg Q3W) and results in the TPS≥50% stratum are presented as an appendix (see Appendix 11).

The data cut-off date for this analysis was 30-Sep-2015. These patients had a median duration of follow up of 13 months (range 6 to 24 months).

Summary:

A summary of the clinical efficacy outcome results based on the Final Analysis of KEYNOTE-010 for pembrolizumab 2 mg/kg Q3W versus docetaxel is presented in Table 20 below:

Table 20: KENOTE-010 - Summary of efficacy endpoints for pembrolizumab in advanced NSCLC

	Previously Treated NSCLC Population (TPS≥1%)	
Number Patients - ITT population	Pembrolizumab 2 mg/kg Q3W N=344	Docetaxel 75 mg/m2 Q3W N= 343
Primary endpoints		
OS - ITT population		
Median (95% CI), [months]	10.4 (9.4, 11.9)	8.5 (7.5, 9.8)
	HR 0.71 (95% CI 0.58, 0.88); *p=0.00076*	
12 month OS rate (%)	43%	35%
PFS (IRC per RECIST 1.1) – ITT population		
Median (95% CI), [months]	3.9 (3.1, 4.1)	4.0 (3.1, 4.2)
	HR 0.88 (95% CI 0.73, 1.04); *p=0.06758*	
PFS rate at 12 months	18%	9%
Secondary endpoints		
ORR (IRC per RECIST 1.1) - ITT Population		
ORR % (95% CI) (with confirmation)	18% (14.1,22.5)	9% (6.5,12.9)
Time to Response		
Median, [days] Range, [days]	65 (38-217)	65 (41-250)

	Previously Treated NSCLC Population (TPS≥1%)	
Number Patients - ITT population	Pembrolizumab 2 mg/kg Q3W N=344	Docetaxel 75 mg/m2 Q3W N= 343
Primary endpoints		
Response Duration (IRC per RECIST 1.1) - ITT Population		
Median, [days] Range, [days]	NR (20+ - 610+)	189 (43+ - 268+)
% of responses ongoing among responders	73%	34%

Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only. "+" indicates non-PD at the last assessment (censored) for the patient with the minimum and maximum response duration within the treatment group. Ongoing response includes all responders who are alive, progression free, did not initiate new anti-cancer therapies and have not been determined to be lost to follow-up. NR= Not reached. Database Cut-off Date: 30 September 2015

Efficacy results are presented in more detail below:

Primary Endpoints

- OS in the TPS≥1% population (ITT population)

In the ITT population the median OS for pembrolizumab was 10.4 months, which represents a clinically meaningful improvement compared to 8.5 months for docetaxel in patients with a TPS≥1% (Table 21). The OS HR for pembrolizumab 2 mg/kg vs. docetaxel was 0.71 (95% CI: 0.58, 0.88) with a p-value of 0.00076 (Table 21).

There was no difference between the two pembrolizumab arms compared to each other (HR 1.17; 95% CI 0.94, 1.4; p=0.15511) in the TPS≥1% population (see Appendix 11). In the TPS≥50% stratum the median OS for pembrolizumab 2 mg/kg was 14.9 months, compared to 8.2 months for docetaxel (HR 0.54; 95% CI: 0.38, 0.77; p-value=0.00024) (see Appendix 11).

Table 21: KEYNOTE-010 analysis of OS in the TPS≥1% population (ITT population)

Treatment	N	Number Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in % † (95% CI)	Treatment vs.	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	343	193 (56.3)	2411.2	8.0	8.5 (7.5, 9.8)	46.6 (40.5, 52.5)	-	-
Pembrolizumab 2mg/kg Q3W	344	172 (50.0)	2928.7	5.9	10.4 (9.4, 11.9)	59.2 (53.5, 64.5)	0.71 (0.58, 0.88)	0.00076

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

‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (TPS≥50% TPS≥1% , TPS1-49% , and Unknown PD-L1 status)

§ One-sided p-value based on log-rank test. Database Cut-off Date: 30SEP2015

The Kaplan-Meier plot for the pembrolizumab 2mg/Kg arm began to separate from the docetaxel arm around Month 4 and remained separated from the curve of the docetaxel arm over time without crossing (Figure 10).

The separation of the OS curves is reflected by a 6 month OS rate of 72.5% (95% CI; 67.4%, 76.9%) in the pembrolizumab 2mg/Kg arm, compared to 64.2% (95%CI; 58.6%, 69.2%) in the docetaxel arm, and a 12-month OS rate of 43.2% (95% CI; 37.0%, 49.3%) in the pembrolizumab 2mg/Kg arm, compared to 34.6% (95%CI; 28.4%, 40.8%) in the docetaxel arm (Table 22).

KEYNOTE-010 was considered to have met its primary objective, demonstrating superior overall survival for pembrolizumab 2mg/Kg Q3W over docetaxel at the final analysis was conducted at database lock: 30SEP2015. Patients treated with pembrolizumab 2mg/Kg Q3W will however continue to be followed up for an additional 6 months for survival (results available May 2016).

Figure 10: KEYNOTE-010 - Kaplan-Meier of OS - patients treated with docetaxel and pembrolizumab 2mg/Kg Q3W - ITT Population (TPS≥1%)

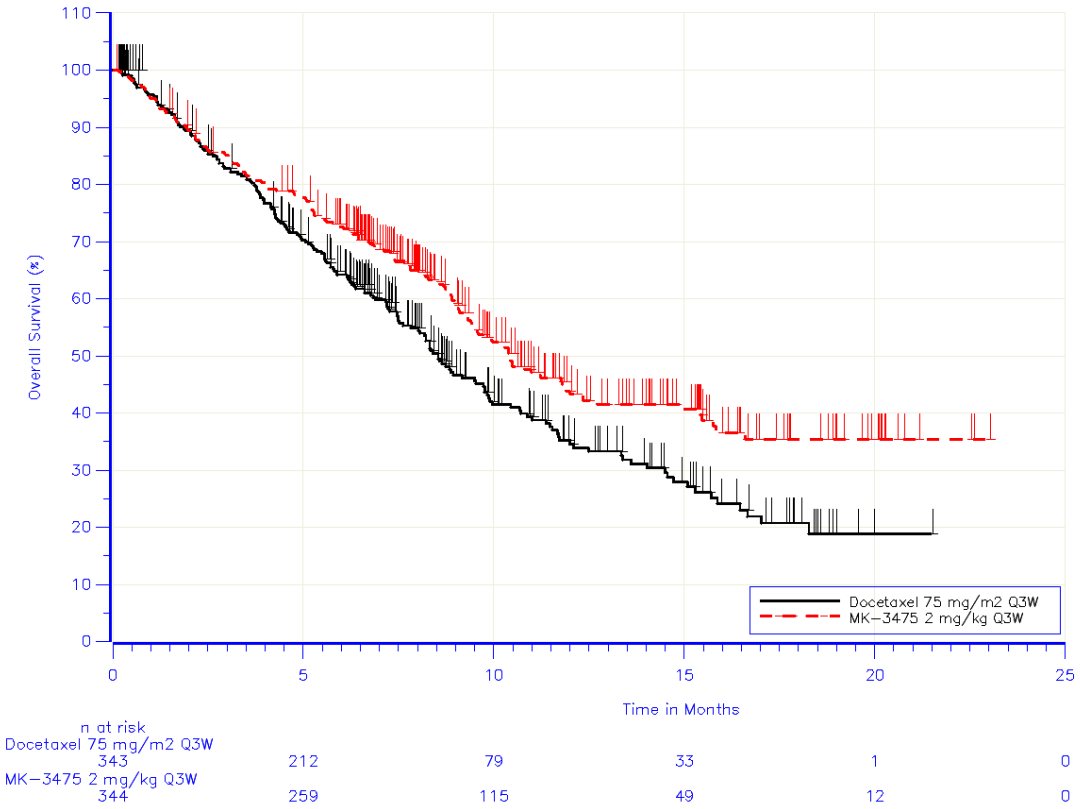


Table 22: KEYNOTE-010 - OS rate at fixed time-points in the TPS≥1% population (ITT population)

	Docetaxel 75 mg/m2 Q3W (N=343)	Pembrolizumab 2 mg/kg Q3W (N=344)
OS rate at 6 Months (95% CI)†	64.2 (58.6, 69.2)	72.5 (67.4, 76.9)
OS rate at 9 Months (95% CI)†	46.6 (40.5, 52.5)	59.2 (53.5, 64.5)
OS rate at 12 Months (95% CI)†	34.6 (28.4, 40.8)	43.2 (37.0, 49.3)

† From the product-limit (Kaplan-Meier) method for censored data.
Database Cut-off Date: 30SEP2015

OS analysis after adjusting for switching - the TPS≥1% population (ITT population)

Crossover was not permitted within the study design of KEYNOTE-010. However, a total of 50 patients switched to other PD-1 treatments after treatment discontinuation: 1 patient (0.3%) in the pembrolizumab 2 mg/kg Q3W group, 6 patients (1.7%) in the pembrolizumab 10 mg/kg Q3W group and 43 patients (12.5%) in the docetaxel 75 mg/m2 Q3W group (Table 23). Figure 11 presents the post-progression survival curves for the docetaxel arm of the KEYNOTE-010 trial, stratified according to whether patients switched to an anti-PD-1 agent or not. Patients receiving docetaxel who did not switch experienced a shorter survival than those switching.

Figure 11: Post-progression OS for the docetaxel arm according to whether patients switched or not

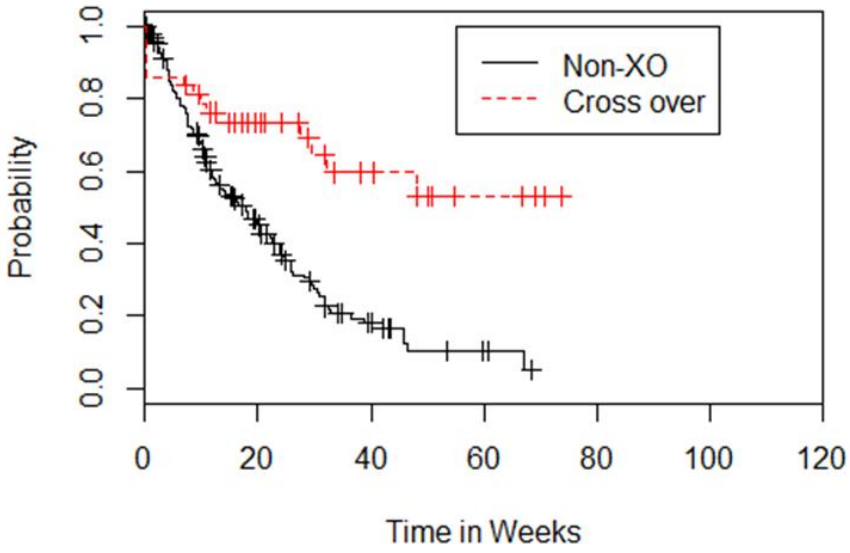


Table 23: KEYNOTE-010 – Patients switching to anti-PD-1 after disease progression

	Docetaxel 75 mg/m2 Q3W	Pembrolizumab 2 mg/kg Q3W	Pembrolizumab 10 mg/kg Q3W	Total
	n (%)	n (%)	n (%)	n (%)
Patients in population	343 (100.0)	344 (100.0)	346 (100.0)	1033 (100.0)
Switching to anti-PD1	42 (12.2)	1 (0.3)	6 (1.7)	49 (4.7)
Switching to CTLA4 inhibitor + anti-PD1	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Total patients switching to anti-PD-1	43 (12.5)	1 (0.3)	6 (1.7)	50 (4.8)

In the protocol of KEYNOTE-010 it was stated that, since patients in the docetaxel arm were expected to discontinue treatment earlier compared to patients in the pembrolizumab arms, and that patients discontinued from docetaxel treatment may receive other anti-PD-1 treatments similar to pembrolizumab after discontinuation, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis[94] was to be used to control for receipt of non-study treatment. RPSFT provides a randomisation based estimate of treatment effect corrected for the bias induced by treatment switch. This method was pre-specified in the study without considering a number of the factors that determine the validity of the approach, which should be assessed *a posteriori*.

We examined whether or not the RPSFT assumption looked likely to hold as follows.

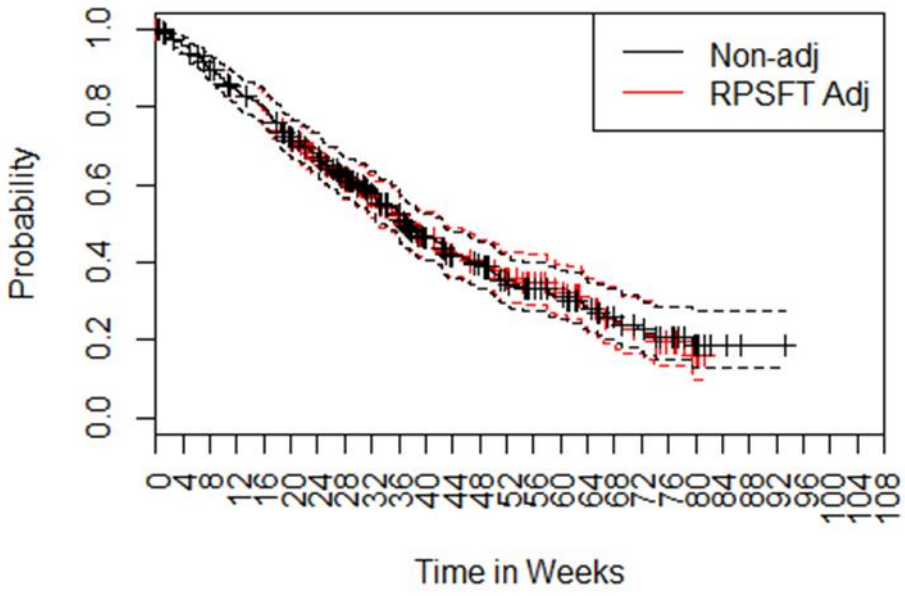
For the comparison of pembrolizumab 2 mg/kg Q3W with docetaxel 75 mg/m2 Q3W, RPSFT-adjusted results were generally consistent with the primary ITT analyses, indicating that the RPSFT method did not appreciably adjust OS in the control group, i.e., the counterfactual control group was essentially unchanged (Table 24 and Figure 12).

Table 24: KEYNOTE-010 – Analysis of pembrolizumab versus docetaxel – adjustment for switching to anti-PD-1s using RPSFT (ITT population)

	Pembrolizumab 2 mg/kg Q3W			Docetaxel 75 mg/m2 Q3W			Pembrolizumab 2 mg/kg Q3W vs. Docetaxel 75 mg/m2 Q3W	
KEYNOTE-010 ITT population	**N[a]**	**Patients with Event n (%)**	**Median Time[b] in months [95 %-CI]**	**N[a]**	**Patients with Event n (%)**	**Median Time[b] in months [95 %-CI]**	**Hazard Ratio[c] [95 %-CI]**	**p-Value[c,d]**
Unadjusted OS	344	172 (50.0)	10.4 [9.4;11.9]	343	193 (56.3)	8.5 [7.5, 9.8]	0.71 [0.55;0.88]	0.00076
RPSFT[e] Adjusted Survival	344	172 (50.0)	10.4 [9.4;11.9]	343	186 (54.2)	8.4 [7.5;9.8]	0.71 [0.55;0.87]	0.002
a: Number of patients: intention-to-treat								

b: From product-limit (Kaplan-Meier) method
c: Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), geographic region (East Asian vs. non-East Asian) and PD-L1 status (Strongly Positive , Weakly Positive, and Unknown Positive). Confidence interval Obtained by fitting the Cox regression model to the bootstrap samples corrected by RPSFT
d: Two-sided p-value (Wald test); not adjusted for cross-over.
e: Rank preserving structural failure time (RPSFT) model is used to adjust for the effect of cross-over from docetaxel to other PD-1 treatments in overall survival analysis.
CI: confidence interval

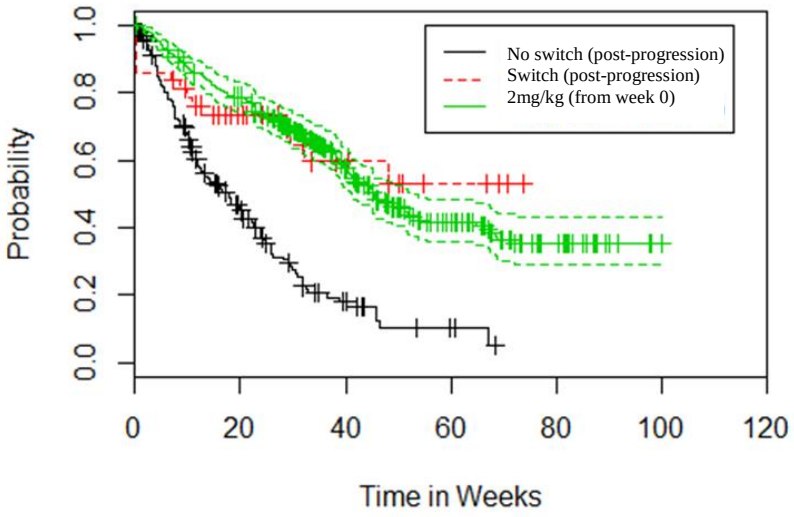
Figure 12: KEYNOTE-010 - KM of OS using RPSFT adjustment vs. unadjusted OS (ITT population)



It is unclear if the 'common treatment effect' adjustment holds, since patients receiving pembrolizumab seem to benefit more in the shorter term than patients receiving an anti-PD-1 agent after progression with docetaxel. In the longer term this treatment effect is less clear due to censoring and low number of patients at the tail for the crossover group (see Figure 13 below). This lack of common treatment effect is expected since the magnitude of the treatment effect is anticipated to be higher for immunotherapies such as pembrolizumab compared to common chemotherapies such as docetaxel.

The RPSFT validity relies on the 'common treatment effect' assumption, which requires that the relative treatment effect of the intervention is equal for all patients, independent on when the intervention is received. The graph above questions the validity of this assumption and therefore, using the RPSFT approach may not reflect the true treatment effect of docetaxel after adjusting for switching to anti-PD-1 therapies.

Figure 13: OS (from week 0) for the pembrolizumab arm vs. post-progression OS for the docetaxel arm (the latter according to whether patients switched or not)



Given that the validity of the RPSFT is in doubt in relation to whether the common treatment effect assumption holds, and after reviewing the NICE Decision Support Unit (DSU) recommendations for the adjustment of crossover in clinical trials,[95] an additional crossover adjustment (two-stage) was implemented to better understand the docetaxel-related OS in the absence of switching. The two-stage adjustment method performs well across the majority of scenarios and often produces less bias than the other adjustment methods. It is less sensitive to the switching proportion than other methods, such as the Inverse Probability of Censoring Weights (IPCW) or structural nested models (SNMs), both of which were rejected during the examination of the appropriate method for cross-over adjustment.[95;96](see sections 4.7 and 5.3.2).

Two-stage adjustment

The two-stage approach was developed in accordance to the type of switching often observed in oncology trials in patients with metastatic disease.[96] Disease progression is often the trigger to switch, and therefore it can be used as a secondary baseline for patients in the control group. It assumes that at the time of disease progression all patients are in a similar health state. The two-stage model is expected to produce an accurate estimate of the treatment effect on patients who switched as long as:

- the model fits the data,
- there are no unmeasured confounders at the point of the secondary baseline
- switching occurs soon after the secondary baseline

The two-stage adjustment methods have been demonstrated to perform better and produce less bias than other adjustment methods, particularly when switching proportions are moderate or low and the common treatment effect assumption does not hold.

In KEYNOTE-010, the majority of the patients initially treated with docetaxel who switched to an anti-PD-1 therapy after progression disease did so within the month following progression, and key potential confounders including ECOG, tumour size and LDH levels at disease progression; metastatic stage, sex and age were measured until that point. This reflects the appropriateness of considering disease progression as the secondary baseline.

For the two-stage crossover analysis, two models were run:

- The first model (complete model) adjusted for all relevant covariates (including: switching; ECOG, tumour size and LDH levels at disease progression; metastatic stage, sex and age)
- A second, simple model only incorporated statistically significant predictors (i.e. ECOG, tumour size and LDH levels at disease progression).

As presented in Table 25, the two-stage adjustment slightly improved the OS HRs for pembrolizumab compared to the adjusted docetaxel arm, independent of the model used (complete vs. simple), since both models led to similar results. Additionally, the median OS obtained from the two-stage adjustment was 8.3 months in the docetaxel adjusted arm (see Table 26), slightly lower than compared to the unadjusted median OS or the median OS adjusted using RPSFT. However, this value is still higher than that expected for patients of these characteristics being treated with docetaxel (i.e. rarely exceeding 8 months).[4;5;7;97;98].

Table 25: KEYNOTE-010 – Analysis of pembrolizumab versus docetaxel – adjustment for switching to anti-PD-1s

	Pembrolizumab 2 mg/kg Q3W vs. Docetaxel 75 mg/m2 Q3W	
KEYNOTE-010 ITT population	**Hazard Ratio [95 %-CI]**	**p-Value**
Unadjusted OS	0.71 [0.55;0.88]	0.00076
2-stage adjusted OS - full model	0.69 [0.560; 0.85]	0.0004
2-stage adjusted OS – simple model	0.69 [0.552; 0.85]	0.0004

Figure 14: KEYNOTE-010 - Two- stage crossover analysis - All covariates

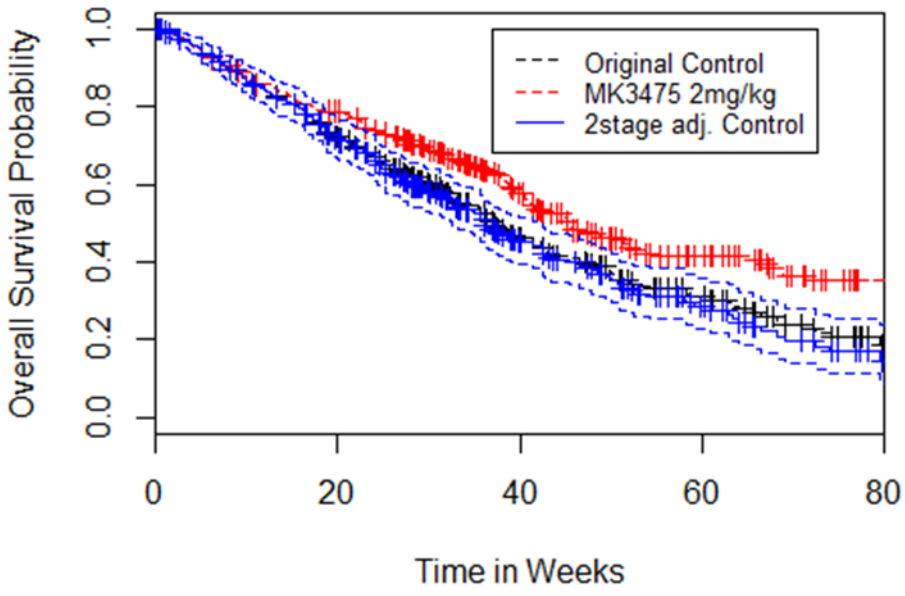
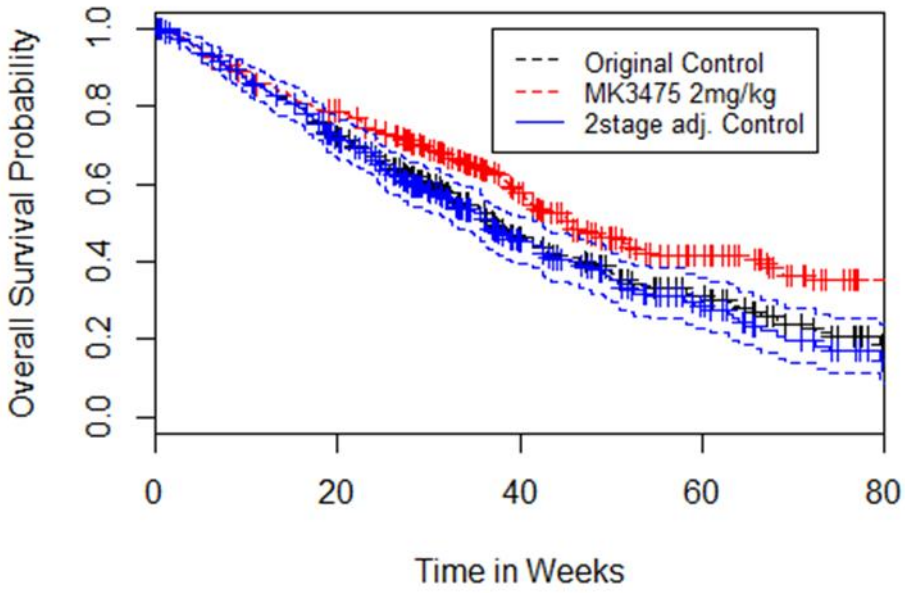


Figure 15: KEYNOTE-002 - Two-stage crossover analysis - Simple model



Comparisons of implemented methods to assess appropriateness of switching adjustments

The results of the different methods used are presented in Table 26 below.

Table 26: KEYNOTE-010 - Analysis of Median OS using RPSFT and two-stage methods

Treatment	Median OS (Months) (95% CI)
Docetaxel (no switching correction)	8.5 (7.5, 9.8)
Control (RPSFT correction)	8.4 (7.5;9.8)
Control (Two-stage correction - Simple model)	8.3 (7.4, 9.5)

Treatment	Median OS (Months) (95% CI)
Control (Two-stage correction – All covariates)	8.3 (7.4, 9.5)
Pembrolizumab 2 mg/kg Q3W (no switching correction)	10.4 (9.4, 11.9)

Based on the trial characteristics, the switching mechanism, the proportion of patients switching and the clinical validity of the outputs obtained,[95] the two-stage adjustment was found to be the most appropriate method for this adjustment (see section 5.3.2).

The two-stage crossover analysis gave more clinically valid results, even although the adjusted OS for docetaxel was still higher than that observed in previously published studies.[4;5;7;97;98] Both models implemented as part of this approach (one which adjusted for all potentially relevant covariates and a second, simple model which only adjusted for statistically significant predictors) demonstrated a larger separation between the pembrolizumab and the adjusted docetaxel arm, and led to similar results (see Table 25). Moreover, the median OS obtained from the two-stage adjustment was approximately 8.3 months (see Table 26). These results are still higher than what would be expected from patients with advanced NSCLC stage IIIb/IV treated with docetaxel after platinum-based chemotherapy based on available evidence (not higher than 8 months).[4;5;7;97;98] Based on the adjusted OS considering the two-stage approach, the median OS for patients treated with docetaxel in KEYNOTE-010 was 2 to 2.1 months shorter than that for patients treated with pembrolizumab.

- PFS by IRC assessment per RECIST 1.1 in the TPS≥1% population (ITT population)

Table 27 and Figure 16 present the analyses of PFS based on IRC assessment per RECIST 1.1 in the TPS≥1% population. Pembrolizumab 2mg/Kg Q3W treatment resulted in a higher PFS rate compared to docetaxel. This difference did not reach statistical significance at the 0.001 level (alpha) required per protocol (HR 0.88; 95% CI: 0.73, 1.04; *p-value=0.06758*). The median PFS was 3.9 months in the 2mg/Kg Q3W pembrolizumab arm and 4.0 months in the docetaxel arm (Table 27). From around Month 6 the PFS curve of pembrolizumab arm began to separate from the docetaxel arm and remained separated from the curve of docetaxel all the way towards the tail end when the majority of patients in the docetaxel arm had PFS events (Figure 16). This is reflected by a 6 month PFS rate of 35.1% (95%CI: 30.0%, 40.3%) in the pembrolizumab 2mg/Kg Q3W arm, compared to 34.3% (95%CI: 28.8%, 39.8%) in the docetaxel arm; and a 12-month PFS rate of 17.5% (95%CI: 13.1%, 22.4%) in the pembrolizumab 2mg/Kg Q3W arm, compared to 8.6% (95%CI: 5.1%, 13.1%)

in the docetaxel arm (Table 28). The mean PFS up to a certain follow-up time also provides meaningful additional information compared to the median PFS in this situation. Comparison of restricted mean survival times (RMST) of PFS provides an alternative estimate of the treatment effect over a time interval that is robust to the proportional hazard assumption. The RMST at Month 6 was 3.71 for pembrolizumab 2 mg/kg, compared to 3.76 for docetaxel; but the RMST values for the pembrolizumab 2 mg/kg arm continued to increase and differentiate from the docetaxel arm at each subsequent time point, with an RMST of 5.60 months in the 2mg/Kg Q3W pembrolizumab arm and RMST 5.03 months in the docetaxel arm at the time of the 15-month response assessment in the TPS≥1% ITT population (Table 7 Appendix 11).

Table 27: KEYNOTE-010- analysis of PFS based on IRC assessment per RECIST 1.1 in the TPS≥1% population (ITT population)

Treatment	N	Number Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 9 in % † (95% CI)	Pembrolizumab vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2	343	257 (74.9)	1368.1	18.8	4.0 (3.1, 4.2)	15.9 (11.5, 20.9)	-	-
Pembrolizumab 2 mg/kg Q3W	344	266 (77.3)	1676.2	15.9	3.9 (3.1, 4.1)	23.1 (18.4, 28.0)	0.88 (0.73, 1.04)	0.06758

IRC: Independent Review Committee.
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian)and PD-L1 status (TPS≥50% TPS≥1% , TPS1-49% , and Unknown PD-L1 status)
§ One-sided p-value based on log-rank test. *Database Cut-off Date: 30SEP2015*

Figure 16: KEYNOTE-010 - Kaplan-Meier of PFS based on IRC assessment per RECIST 1.1 - patients treated with docetaxel and pembrolizumab 2mg/Kg Q3W - ITT Population (TPS≥1%)

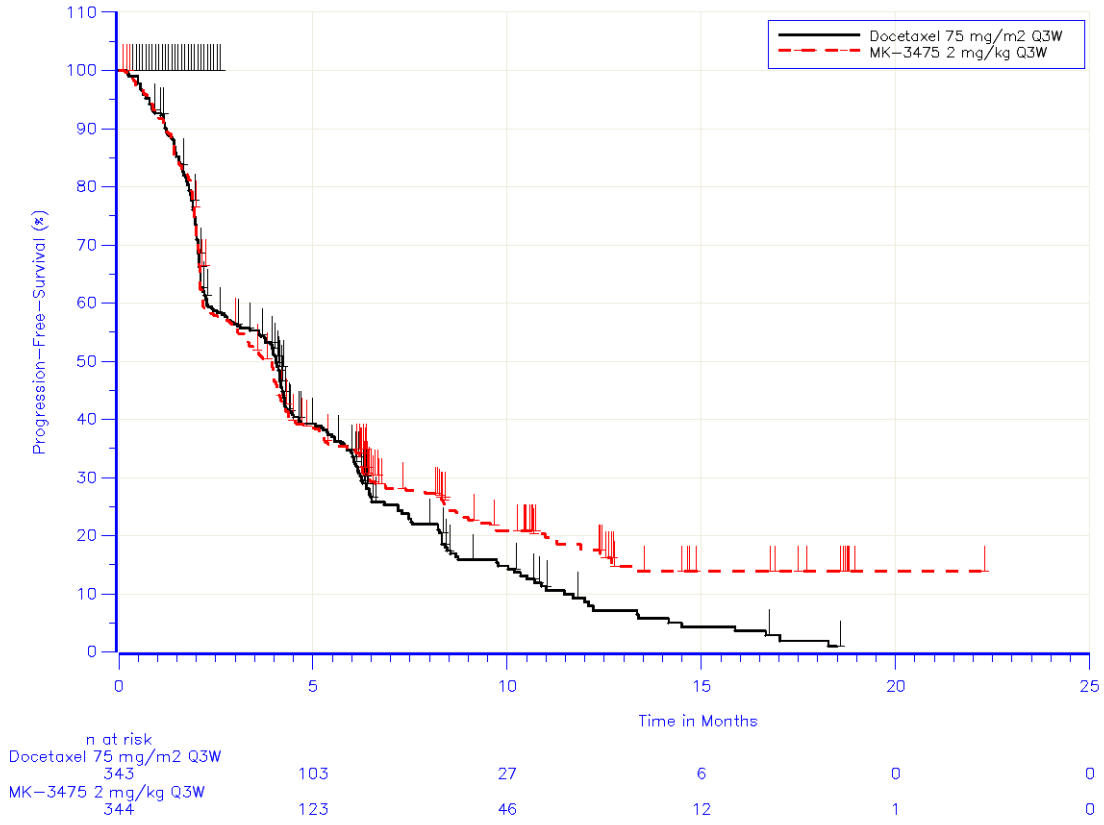


Table 28: KEYNOTE-010 - PFS rate at fixed time-points based on IRC assessment per RECIST 1.1 in the TPS≥1% population (ITT population)

	Docetaxel 75 mg/m2 Q3W (N=343)	Pembrolizumab 2 mg/kg Q3W (N=344)
PFS rate at 6 Months (95% CI)†	34.3 (28.8, 39.8)	35.1 (30.0, 40.3)
PFS rate at 9 Months (95% CI)†	15.9 (11.5, 20.9)	23.1 (18.4, 28.0)
PFS rate at 12 Months (95% CI)†	8.6 (5.1, 13.1)	17.5 (13.1, 22.4)

† From the product-limit (Kaplan-Meier) method for censored data. Database Cut-off Date: 30SEP2015

Overall, the PFS results using sensitivity censoring rules (section 4.4.2 Table 13) were similar to the primary PFS analysis results, demonstrating the robustness of PFS results.

In the TPS≥50% stratum, the median PFS was 5.2 months in the 2mg/Kg Q3W pembrolizumab arm and 4.1 months in the docetaxel arm (HR 0.58; 95% CI: 0.43, 0.77; *p-value=0.00009*) (Appendix 11).

The results of OS and PFS analyses for the TPS≥1% and for the TPS≥50% stratum were generally similar between the ITT and the FAS populations; supporting the robustness of the data from the ITT population in demonstrating the superiority of pembrolizumab over docetaxel for patients with NSCLC tumours having TPS≥1%.

Secondary endpoints

The secondary endpoints of KEYNOTE-010 were ORR, response duration and time to response by IRC assessment per RECIST 1.1.

- ORR (IRC per RECIST 1.1) in the TPS≥1% population (ITT population)

In the TPS≥1% population, pembrolizumab 2 mg/kg Q3W produced an ORR of 18.0%, compared to 9.3% in the docetaxel arm, based on IRC assessment per RECIST 1.1 with confirmation of response (Table 29). The confirmed ORR difference was 8.7% for pembrolizumab 2 mg/kg Q3W vs. docetaxel (one-sided *p-value 0.00045*) (Table 29). In the TPS≥50% stratum, pembrolizumab 2 mg/kg Q3W produced an ORR of 30.2%, compared to 7.9% in the docetaxel arm (Appendix 11).

Table 29: KEYNOTE-010: Analysis of ORR (IRC per RECIST 1.1) – ITT population (TPS≥ 1%)

Treatment	N	Number Overall Responses	Overall Response Rate (%) (95% CI)	Difference in % vs. Docetaxel	
				Estimate 95% CI†	p-Value††
TPS≥ 1% population					
Docetaxel 75 mg/m2 Q3W	343	32	9.3 (6.5,12.9)	---	
Pembrolizumab 2 mg/kg Q3W	344	62	18.0 (14.1,22.5)	8.7 (3.6,13.9)	0.00045

IRC = Independent Review Committee
Responses are based on IRC assessments per RECIST 1.1 with confirmation.
† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (TPS≥50% TPS≥1% , TPS1-49% and Unknown PD-L1 status) ; if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
§ Two-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % ≠ 0. Database Cut-off Date: 30SEP2015

Table 30 provides a summary of best overall response based on IRC assessment per RECIST 1.1 (with or without confirmation) in the TPS≥1% population. Nearly a quarter (23.0%) of the patients treated with pembrolizumab 2mg/Kg Q3W achieved a PR compared to 13.4% of subjects treated with docetaxel. There were no CRs reported. The disease control rate was greater in the pembrolizumab 2mg/Kg Q3W arm (54.1%) compared with 48.7% for the docetaxel arm.

Table 30: KEYNOTE-010: Summary of best overall response (IRC per RECIST 1.1) – ITT population (TPS≥ 1%)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Number of Patients in Population	**343**		**344**	
Complete Response (CR)	0	(0.0)	0	(0.0)
Partial Response (PR)	46	(13.4)	79	(23.0)
Overall Response (CR+PR) *	**46**	**(13.4)**	**79**	**(23.0)**
Confirmed Response (CR+PR)**	32	(9.3)	62	(18.0)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Stable Disease (SD)	121	(35.3)	107	(31.1)
Disease Control (CR+PR+SD)	**167**	**(48.7)**	**186**	**(54.1)**
Progressive Disease (PD)	98	(28.6)	111	(32.3)
Not Evaluable (NE)	9	(2.6)	10	(2.9)
No Assessment	69	(20.1)	34	(9.9)

IRC = Independent Review Committee
* Responses are based on IRC best assessment across time points, without confirmation.
** The best overall response cannot be calculated for patients without confirmed response since per KEYNOTE-010 imaging charter the response by RECIST 1.1 does not require confirmation, therefore not all responses had corresponding confirmation. An additional row for the confirmed responses only has been included.
Not Evaluable (NE) - a scan was obtained but it was not evaluable to make an interpretation of disease status (e.g. the image received did not contain the index lesion to make an assessment based on RECIST 1.1 criteria)
Database Cut-off Date: 30SEP2015

- Response duration and time to response (IRC per RECIST 1.1) in the TPS≥1% population (ITT population)

Table 31 presents the time to response and response duration in the TPS≥1% population, based on IRC assessment per RECIST 1.1 for each treatment arm individually. The first scheduled disease assessment occurred at Week 9 (around day 63), as reflected by the median times to response across the treatment arms.

In the TPS≥1% population, there were 62 responders in the pembrolizumab 2 mg/kg Q3W arm and the median time to response was 65 days (range 38 to 217 days). There were 32 responders in the docetaxel arm and the median time to response was 65 days (range 41 to 250 days). Note that late responses from 200 days were observed across both arms of the study (Table 31).

In the TPS≥50% stratum, there were 42 responders in the pembrolizumab 2 mg/kg Q3W arm and the median time to response was 65 days (range 38 to 141 days). There were 12 responders in the docetaxel arm and the median time to response was 65 days (range 59 to 247 days) (Appendix 11).

The analysis of response duration was performed only on patients with a confirmed CR or PR. In the TPS≥1% population, the median duration of response was not reached (range 20+ to 610+ days) in the pembrolizumab 2 mg/kg Q3W arm, compared to 189 days (range 43+ to 268+ days) in the docetaxel arm (Table 31). Figure 5 in Appendix 11 demonstrates the prolonged duration of response relative to docetaxel of pembrolizumab in patients in the TPS≥1% population. Among the responders in the TPS≥1% population, 73% of responses in the pembrolizumab-treated patients were ongoing compared to 34% of the docetaxel population at the time of data cut-off.

In the TPS≥50% stratum, the median duration of response was not reached (range 20+ to 512+ days) in the pembrolizumab 2 mg/kg Q3W arm, compared to 246 days (range 63+ to 268+ days) in the docetaxel arm (see Appendix 11).

Table 31: KEYNOTE-010 - Analysis of Time to Response and Response Duration – ITT population (TPS≥ 1%)

	TPS≥ 1% population	
	Docetaxel 75 mg/m2 Q3W (N=343)	**Pembrolizumab 2 mg/kg Q3W (N=344)**
IRC Assessment per RECIST 1.1		
Number of Patients with Response[†]	32	62
Time to Response [†] (DAYS)		
Mean (SD)	99 (60)	86 (36)
Median	65	65
Range of time to response	(41-250)	(38-217)
Response Duration[‡] (DAYS)		
Median	189	NR
Range of response duration[§]	(43+ - 268+)	(20+ - 610+)
Number of Response Ongoing[‖] (%)	11 (34)	45 (73)
Investigator Assessment per irRC		
Number of Patients with Response[†]	35	72
Time to Response [†] (DAYS)		
Mean (SD)	84 (43)	85 (46)
Median	62	64
Range of time to response	(41-197)	(35-317)
Response Duration[‡] (DAYS)		
Median	150	NR
Range of response duration[§]	(32+ - 450+)	(20+ - 547+)
Number of Response Ongoing [‖] (%)	12 (34)	51 (71)

[†] Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only. [‡] From product-limit (Kaplan-Meier) method for censored data. [§] "+" indicates there is no progressive disease by the time of last disease assessment.
[‖] Ongoing response includes all responders who are alive, progression free, did not initiate new anti-cancer therapies and have not been determined to be lost to follow-up. NR= Not reached.
Database Cut-off Date: 30SEP2015

Exploratory endpoints

Exploratory analyses included ORR, PFS and Response duration per irRC by investigators' review (INV), as well as PROs analyses.

In general, the ORR and response duration results based on INV assessment by irRC were similar to the results by IRC assessment per RECIST 1.1, both in the TPS≥1% population and in the TPS≥50% stratum.

The results of analyses of PFS for the TPS≥1% population by Investigator assessment by irRC in the ITT population are provided in Table 32 and Figure 17 below. Because of the

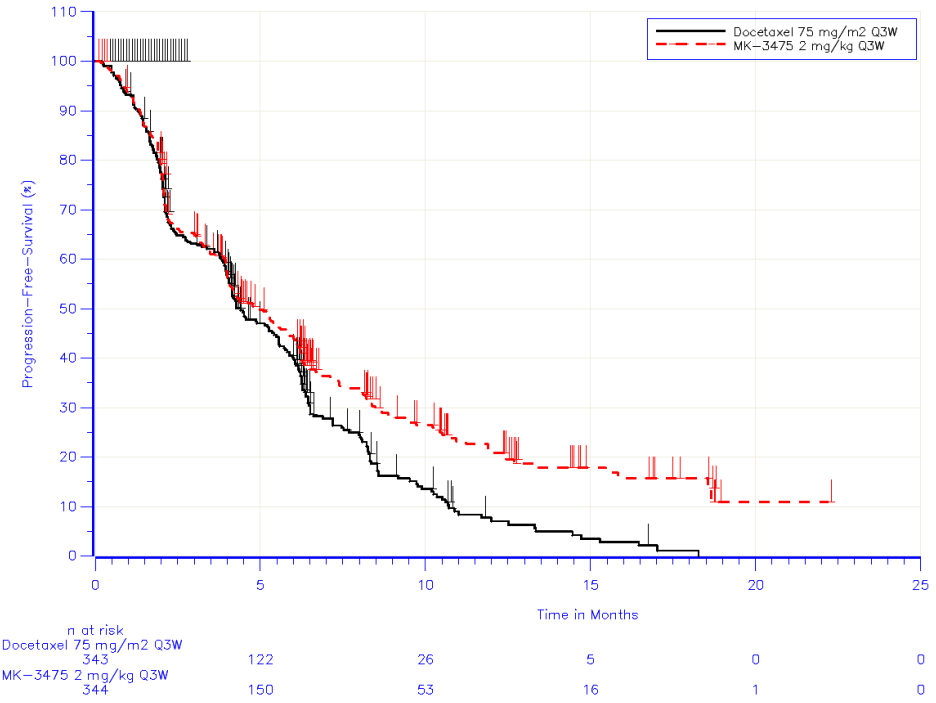
unique pattern of response associated with immunotherapy, there are more progression events based on RECIST 1.1 (generally due to new lesions classified as progressive disease) than irRC. PFS when assessed by irRC may be a better reflection of the benefit of immunotherapies to patients (HR 0.76; 95% CI: 0.64, 0.92 with a one-sided p-value of 0.00174 in the pembrolizumab 2 mg/kg Q3W arm vs. the docetaxel arm). These results support the robustness of the data of the primary endpoint PFS by IRC assessment per RECIST 1.1 in the ITT population with TPS≥1%.

Table 32: KEYNOTE-010 - Analysis of PFS Based on INV per irRC - ITT Population (TPS ≥ 1%)

Treatment	N	Number Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 9 in % † (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	343	253 (73.8)	1450.5	17.4	4.4 (4.0, 5.5)	16.2 (11.7, 21.2)	---	---
Pembrolizumab 2 mg/kg Q3W	344	244 (70.9)	1858.3	13.1	4.9 (4.0, 5.9)	28.4	0.76 (0.64, 0.92)	0.00174

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data. ‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (TPS≥50% TPS≥1% , TPS1-49% , and Unknown PD-L1 status) if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
§ One-sided p-value based on log-rank test. ‖ Two-sided p-value based on log-rank test. Database Cut-off Date: 30SEP2015

Figure 17: KEYNOTE-010 - Kaplan-Meier of PFS Based INV per irRC - patients treated with docetaxel and pembrolizumab 2mg/Kg Q3W - - ITT Population (TPS ≥ 1%)

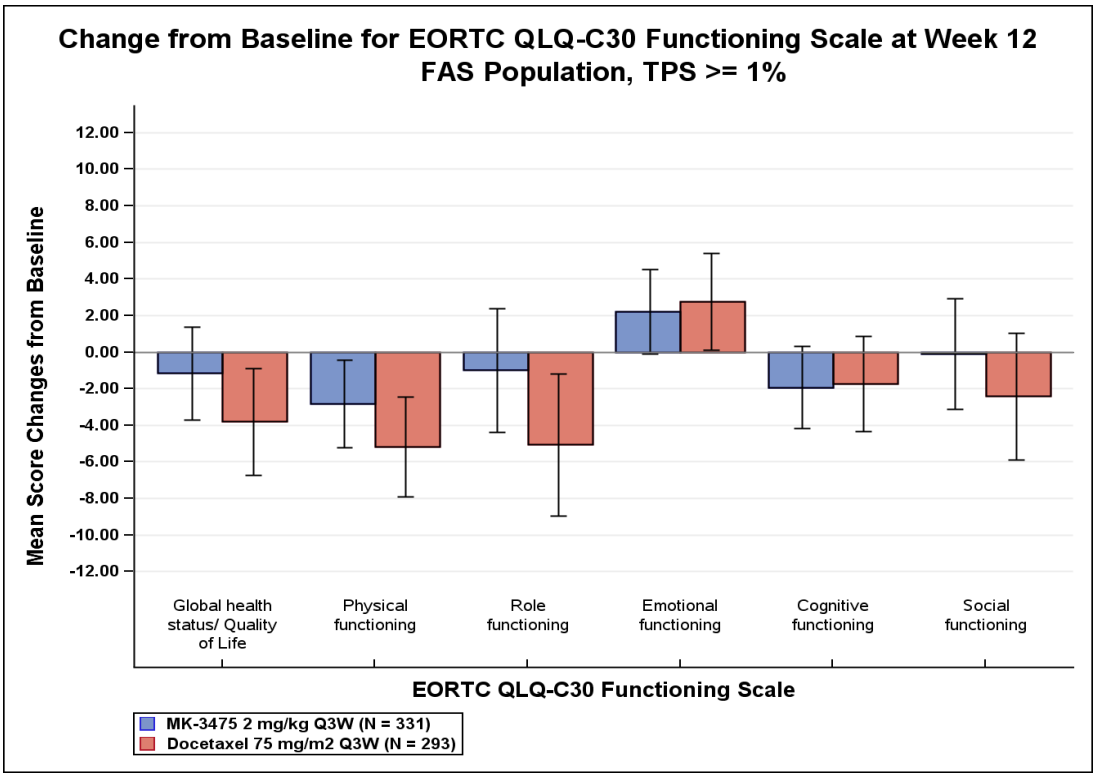


The analyses of the pre-specified exploratory PRO endpoints were based on a quality of life related FAS population following the ITT principle and ICH E9 guidelines. The PRO FAS population consisted of all randomised patients who received at least one dose of study medication and completed at least one PRO assessment.

Compliance rates at baseline were above 90% in all three treatment arms. At week 12, the key PRO time point, compliance was slightly lower for both the docetaxel (85.0%) and pembrolizumab 2 mg/kg Q3W (88.1%) arms. As expected, completion rates continued to decrease at each time point, with the main reasons being disease progression, physician decision, AE, or death.

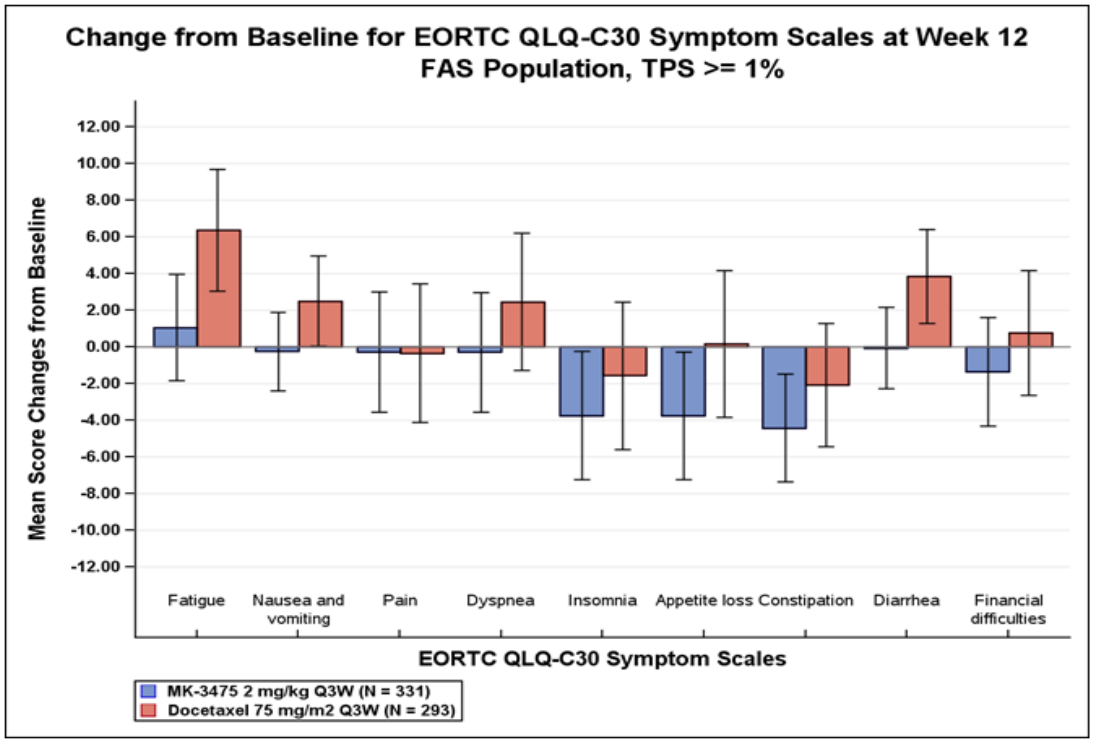
When assessing changes from baseline to week 12, there was either a numerical improvement in or less worsening of global health status/quality of life score for the pembrolizumab 2mg/Kg Q3W arm compared to the docetaxel arm (Figure 18). Additionally, there was numerical improvement in most functioning and EORTC symptom domains in the pembrolizumab arms. For docetaxel, there was a numerical worsening in most functioning and EORTC symptom domains (Figure 19). The results were similar in the TPS≥50% stratum.[82]

Figure 18: Change from Baseline eEORTC QLQ-C30 Functioning Scale/Global Health Status/Quality of Life at Week 12* (FAS population with TPS>1%)



*For global health status/quality of life score and all functional scales, a higher score denotes better HRQoL or function, and a higher negative score denotes worse HRQoL or functions.

Figure 19: Change from Baseline eEORTC QLQ-C30 Symptoms Scales at week 12* (FAS population with TPS>1%)

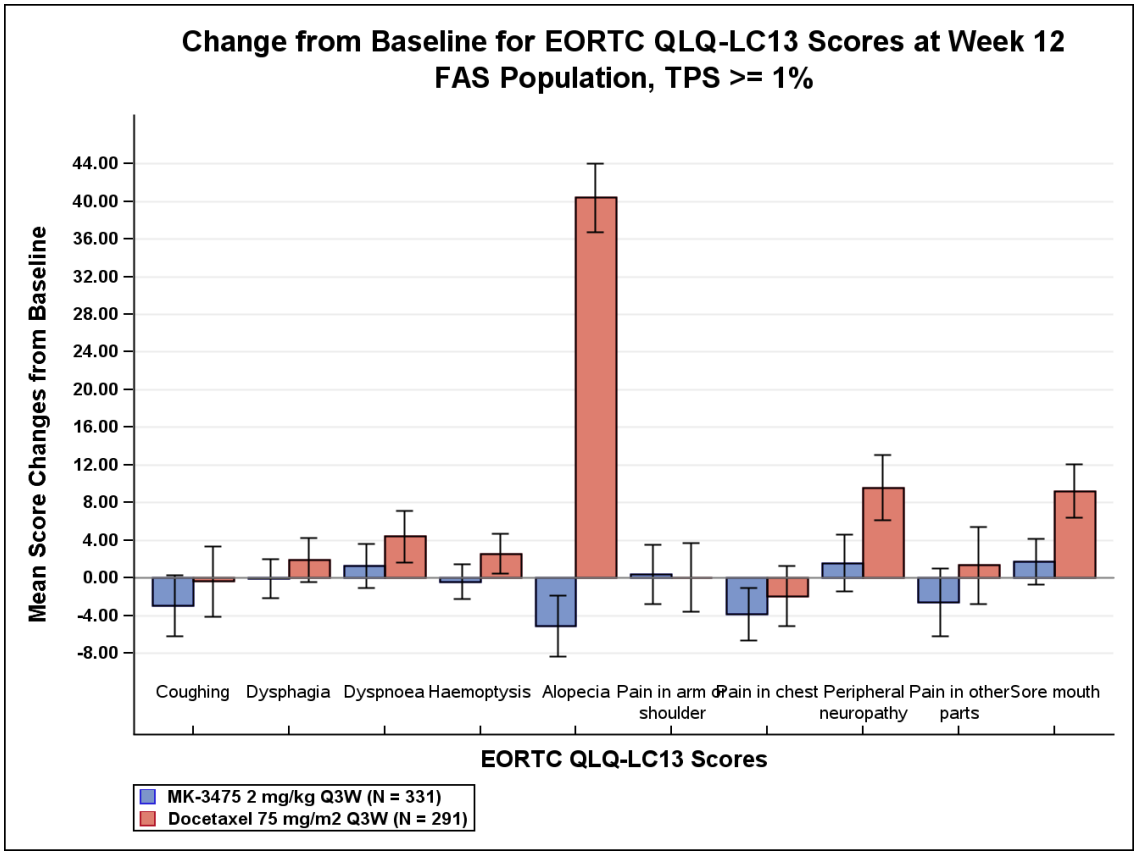


*For different symptoms scales, a higher score denotes worse symptoms.

Patients in both pembrolizumab arms had a numerical improvement from baseline to week 12 in most EORTC lung cancer symptoms (Figure 20). This improvement was more pronounced for the 2 mg/kg dose in the TPS≥50% stratum. In contrast, patients in the docetaxel arm had a numerical worsening from baseline in most EORTC lung cancer symptoms (Figure 20).

Compared to docetaxel, pembrolizumab also increased the time to true deterioration in the QLQ-LC13 composite endpoint of cough, dyspnoea and chest pain.

Figure 20: Change from Baseline for eEORTC QLQ-LC13 Symptoms at Week 12* (FAS population with TPS>1%)



**For different lung cancer symptoms, a higher score denotes worse symptoms.*

Results of eEQ-5D compliance and change from baseline to week 12 in utility and visual analogue scale (VAS) analyses are consistent with the results of EORTC QLQ-C30 analyses (Table 33 and Table 34).

Table 33: Analysis of Change from Baseline of eEuroQol (EQ)-5D Utility Score (Using European Algorithm) at week 12 (FAS Population with TPS>1%)

Treatment	N†	Baseline Mean(SD)	N†	Week 12 Mean(SD)	EuroQol (EQ)-5D Utility Score (Using European Algorithm) Change from Baseline at Week 12		
					N††	Mean(SD)	LS Mean (95% CI)‡
Pembrolizumab 2 mg/kg Q3W	290	0.74 (0.21)	199	0.78 (0.19)	191	-0.00 (0.19)	-0.00 (-0.03, 0.02)
Docetaxel 75 mg/m2 Q3W	230	0.71 (0.20)	133	0.74 (0.21)	120	-0.01 (0.20)	-0.02 (-0.05, 0.01)

Pairwise Comparison	Difference in LS Means (95% CI)	p-value
Pembrolizumab 2 mg/kg Q3W vs. Docetaxel 75 mg/m2 Q3W	0.01 (-0.03, 0.05)	0.5208

† N = Number of subjects in Full Analysis Set population with each time point observation; †† N = Number of subjects in Full Analysis Set population with Baseline and Week 12 observations; ‡ Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (extent of tumoral PD-L1 expression (TPS≥50% TPS≥1%, TPS1-49% , and Unknown PD-L1 status), Geographic region of the enrolling site (East Asia vs. non-East Asia) and ECOG (0 vs. 1), if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison) as covariates. SD: Standard deviation; LS Mean: Least square mean; CI: Confidence interval

Table 34: Analysis of Change from Baseline of VAS at week 12 (FAS Population with TPS>1%)

Treatment	N†	Baseline Mean(SD)	N†	Week 12 Mean(SD)	EQ-VAS Change from Baseline at Week 12		
					N††	Mean(SD)	LS Mean (95% CI)‡
Pembrolizumab 2 mg/kg Q3W	290	69.82 (18.39)	199	74.77 (14.93)	192	2.52 (17.43)	1.47 (-0.66, 3.60)
Docetaxel 75 mg/m2 Q3W	228	67.53 (19.59)	133	68.75 (17.24)	118	-0.8 (18.64)	-1.25 (-3.75, 1.25)
Pairwise Comparison						**Difference in LS Means (95% CI)**	**p-value**
Pembrolizumab 2 mg/kg Q3W vs. Docetaxel 75 mg/m2 Q3W						2.72 (-0.41, 5.84)	0.0880

† N = Number of subjects in Full Analysis Set population with each time point observation; †† N = Number of subjects in Full Analysis Set population with Baseline and Week 12 observations; ‡ Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (extent of tumoral PD-L1 expression (TPS≥50% , TPS1-49% , and Unknown PD-L1 status), Geographic region of the enrolling site (East Asia vs. non-East Asia) and ECOG (0 vs. 1), if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison) as covariates. SD: Standard deviation; LS Mean: Least square mean; CI: Confidence interval

The utility values derived from the EQ5D data presented above (Table 33) are presented in the cost-effectiveness section (section 5.4).

KEYNOTE-001 Results: Data cut-off 23-January-2015[35;85;86;89]

Summary:

In this section we present the results of the Total Previously Treated Efficacy Population (Cohort C and F2), with the longest follow-up period for patients treated with pembrolizumab 10mg/Kg Q3W or Q2W (median follow up 16.2 months; range 10.9 to 32.3 months); followed by data regarding the activity of pembrolizumab at 2mg/Kg Q3W dose in previously treated patients with NSCLC (Cohort F3). The results presented provide supportive evidence to the longer term clinical benefit of pembrolizumab in patients with advanced NSCLC whose tumours express PD-L1, and help provide a comprehensive assessment of clinical efficacy.
For completeness, full results for the Previously Treated Primary Efficacy Population (TPS≥50%) are presented as an appendix (Appendix 11).

Patients were included in the Total Previously Treated Efficacy Population regardless of inclusion in the Biomarker Training and Validation Sets. Therefore, results by Biomarker Status in this submission always refer to those by the CTA/MRA, unless otherwise specified. Patients who had tumour tissue on a slide that was assessed by the MRA outside the 6-

month antigen stability window and not replaced with a valid tumour tissue sample are classified as Unknown PD-L1 status for those results tagged “within Stability Window” (for details please see Appendix 6).

Patients with tumours who had a TPS above 1% are considered PD-L1 expressers. Patients whose tumours had <1% tumour cells positive for PD-L1 staining are considered non-expressers.

A summary of PFS and OS from cohorts C and F2 of KEYNOTE-001, termed the Total Previously Treated Efficacy Population, is provided in Table 35 below:

Table 35: KEYNOTE-001 Part C and F2- Summary of efficacy endpoints for pembrolizumab in advanced NSCLC

	KEYNOTE-001 Total Previously-Treated Efficacy Population (Cohort C and F2) (APaT) (N=394)		
	TPS≥1% (N=226) (PD-L1 within stability window)	**TPS<1% (N=68)** (PD-L1 within stability window)	**TPS Unknown (N=100)** (PD-L1 within stability window)
PFS (IRC per RECIST 1.1)			
Median (95% CI), [months]	2.9 (2.1, 4.1)	2.1 (2.0, 4.0)	4.0 (2.3, 5.0)
PFS rate at 6 months	36.1%	23.2%	36.4%
OS			
Median (95% CI), [months]	11.1 (8.0, 15.5)	8.6 (5.5, 12.0)	14.3 (8.5, 16.5)
6 month OS rate (%)	63.5%	57.1%	65.9%
12 month OS rate (%)	48.8%	38.3%	55.9%

Database Cut-off Date: 23JAN2015

Efficacy results are presented in more detail below:

Primary Endpoints

The primary efficacy endpoint for this study was ORR using RECIST 1.1 criteria. The primary analysis method was review of the images by IRC. The protocol specified that the primary endpoint would be assessed for the FAS dataset and the other efficacy analyses would be based on the APaT population. However, the ORR results for the APaT dataset are presented to provide a more complete and clinically meaningful summary of the response rate. Using the APaT population for the efficacy analysis is considered a more conservative approach than using FAS population.

The data cut-off date for this analysis was 23-Jan-2015, which provides a minimum of 6.4 months of follow up for all cohorts. The Total Previously Treated Efficacy Population (Cohorts C and F2) had a median duration of follow up of 16.2 months (range 10.9 to 32.3

months). Because enrolment in Cohort F3 commenced last, this cohort has the shortest follow-up (median duration of follow-up of 7.7 months with a range of 6.4 to 9.7 months).

Overall Response Rate (IRC per RECIST 1.1)

- Total Previously Treated Efficacy Population

The Total Previously Treated Efficacy population included patients from Cohort C and F2 of KEYNOTE-001, who experienced PD after at least platinum-based chemotherapy, and who are part of the Biomarker Training or Validation Set. These patients were treated with pembrolizumab 10 mg/kg Q3W or Q2W.

The ORR by central independent review per RECIST 1.1 for the 394 patients treated with pembrolizumab in the Total Previously Treated Efficacy Population (within stability window) was 19.3% (95% CI: 15.5, 23.5). Response rates by PD-L1 expression can be found in appendix 12.

Assessment via a different methodology with irRC by the Investigator did not impact the observed response rate (Table 36).

Table 36: KEYNOTE-001- Best Overall Response in the Total Previously Treated Efficacy Population, with confirmation – APaT (IRC per RECIST 1.1 and INV per irRC)

	Total Previously Treated Efficacy Population (APaT) (N=394)					
Response Evaluation	**IRC per RECIST 1.1**			**INV per irRC**		
	n	**%**	**95% CI†**	**n**	**%**	**95% CI†**
Complete Response (CR)	3	0.8	(0.2, 2.2)	2	0.5	(0.1, 1.8)
Partial Response (PR)	73	18.5	(14.8, 22.7)	86	21.8	(17.8, 26.2)
Overall Response (CR+PR)	**76**	**19.3**	**(15.5, 23.5)**	**88**	**22.3**	**(18.3, 26.8)**
Stable Disease (SD)	87	22.1	(18.1, 26.5)	141	35.8	(31.0, 40.7)
NonCR/NonPD (NN)	18	4.6	(2.7, 7.1)			
Disease Control (CR+PR+SD+NN)	**181**	**45.9**	**(40.9, 51.0)**	**229**	**58.1**	**(53.1, 63.0)**
Progressive Disease (PD)	152	38.6	(33.7, 43.6)	111	28.2	(23.8, 32.9)
Non-evaluable (NE)	8	2.0	(0.9, 4.0)			
No Assessment	53	13.5	(10.2, 17.2)	54	13.7	(10.5, 17.5)

Only confirmed responses are included in this table. † Based on binomial exact confidence interval method.
Database Cut-off Date: 23JAN2015

- Previously Treated Population 2mg/Kg Q3W (Cohort F3)

Cohort F3 was added with the last amendment to the protocol of KEYNOTE-001 to study the likely dose for pembrolizumab in patients with advanced NSCLC, i.e., 2 mg/kg Q3W. So

follow-up is shorter in these patients (median follow-up time was 7.7 months with a range of 6.4 to 9.7 months). All patients had a minimum of 27-Weeks of follow-up.

The inclusion and exclusion criteria for Cohort F3 were very similar to the previously treated advanced NSCLC population in Cohort F2 (see section 4.3.1). Therefore, comparative analyses of the response rate over time for the two cohorts were performed to demonstrate comparability between the two doses of pembrolizumab (2 mg/kg Q3W in F3 and 10 mg/kg Q3W and Q2W in F2). As the patients in Cohort F3 were required to be PD-L1 positive by the PA, comparative analyses were restricted to patients in Cohort F2 positive by the PA. The response rate by time point for each population is similar as shown in Table 37 below.

Table 37: KEYNOTE-001 - Cumulative Overall Response Rate by IRC per RECIST v1.1 over Time – APaT (Cohort F2 and Cohort F3)

Response Rate	Randomised Cohort F2 PD-L1 Positive by PA 10 mg/kg (n=280)	Cohort F3 PD-L1 Positive by PA 2 mg/kg (n=55)
RR at 9 Weeks in % (95% CI)†	8.7 (5.9, 12.7)	10.9 (5.1, 22.7)
RR at 18 Weeks in % (95% CI)†	17.8 (13.8, 22.9)	12.7 (6.3, 24.9)
RR at 27 Weeks in % (95% CI)†	21.1 (16.8, 26.5)	14.7 (7.6, 27.3)
RR at 36 Weeks in % (95% CI)†	22.3 (17.8, 27.7)	NR
RR at 90 Weeks in % (95% CI)†	NR	NR

Response includes both confirmed partial response and confirmed complete response. † From the product-limit (Kaplan-Meier) method for censored data. Database Cut-off Date: 23JAN2015

The results presented in Table 37 show that treatment of patients with NSCLC with pembrolizumab dosages of 2 mg/kg Q3W, or 10 mg/kg Q2W or 10 mg Q3W is associated with clinically significant and robust anti-tumour efficacy, with no clear discrimination between the dosages encompassing a broad range of pembrolizumab exposure levels. This data supports the 2 mg/kg Q3W dose of pembrolizumab proposed for this indication.

Secondary endpoints

Based on IRC per RECIST 1.1 and Investigator assessment per irRC:

Time to response and response duration (RECIST 1.1 and irRC) – APaT population

The median time to response in the Total Previously Treated Efficacy Population (within stability window) based on the IRC assessment per RECIST 1.1 was 2.1 months (coincident with the first protocol-specified imaging efficacy assessment at 9 weeks), with best

responses observed as early as 1.4 months and as late as 19.4 months from initiating pembrolizumab (Table 38). The median duration of response based on the IRC assessment per RECIST 1.1 in this population was 23.3 (range 1.0+ to 23.3+ months) (Table 38). The responses were durable, 78% of the patients with objective responses had ongoing responses at the time of the data cut-off.

The results were similar irrespective of the response system used to evaluate patients, i.e., whether by irRC or RECIST 1.1 (Table 38).

Table 38: Summary of Time to Response and Response Duration (IRC per RECIST 1.1 and INV per irRC), patients with confirmed response – Total Previously Treated Efficacy Population - APaT

	Total Previously Treated Efficacy Population (APaT) (N=394)	
	IRC per RECIST 1.1	**INV per irRC**
Number of Patients with Response†	76	88
Time to Response† (months)		
Mean (SD)	3.4 (3.0)	3.1 (2.0)
Median	2.1	2.1
Range of Time to Response	(1.4-19.4)	(1.6-12.2)
Response Duration‡ (months)		
Median	23.3	NR
Range of response duration§	(1.0+ - 23.3+)	(1.5+ - 29.0+)
Number of Non-progressing (non-PD)		
Patients (%)	59 (78)	72 (82)

† Analysis on time to response and response duration are based on subjects with a best overall response as confirmed complete response or partial response only. NR= Not reached ‡ From product-limit (Kaplan-Meier) method for censored data. § "+" indicates non-PD at the last assessment (censored) for the patient with the minimum and maximum response duration within the treatment group. Database Cut-off Date: 23JAN2015

PFS (RECIST 1.1 and irRC) – APaT population

- Total Previously Treated Efficacy Population

Table 39 and Figure 21 display the PFS estimates based on IRC assessment per RECIST 1.1 in the Total Previously Treated Efficacy Population (APaT), by PD-L1 status (within stability window). The median PFS in the 226 patients with advanced NSCLC who were treated at 10mg/Kg Q2W or 10mg/Kg Q3W and who express PD-L1 (TPS≥1%; within stability window) was 2.9 months, and the PFS rate at 6 months was 36.1% (Table 39). The median PFS in the 68 patients with advanced NSCLC who do not express PD-L1 (TPS<1%; within stability window) was 2.1 months, with a PFS rate at 6 months of 23.2% (Table 39). The PFS KM curve of the group of patients with advanced NSCLC who express PD-L1 (TPS≥1%; within stability) began to separate from the curve of the group of patients with advanced NSCLC whose tumours do not express PD-L1 (TPS<1%; within stability window)

around Month 4 and remained separated over time without crossing (Figure 21) (HR 0.71; 95% CI 0.53, 0.95).

The PFS estimates based on investigator assessment per irRC are provided in Table 4 and Figure 3 in Appendix 12. The median PFS was 4.1 months in the 226 patients with TPS≥1% (within stability window), and 3.0 months in the 68 patients with TPS<1% (within stability window). The PFS HR for advanced NSCLC patients with TPS≥1% vs. TPS<1% (within stability window) was 0.80 (95% CI 0.59, 1.08).

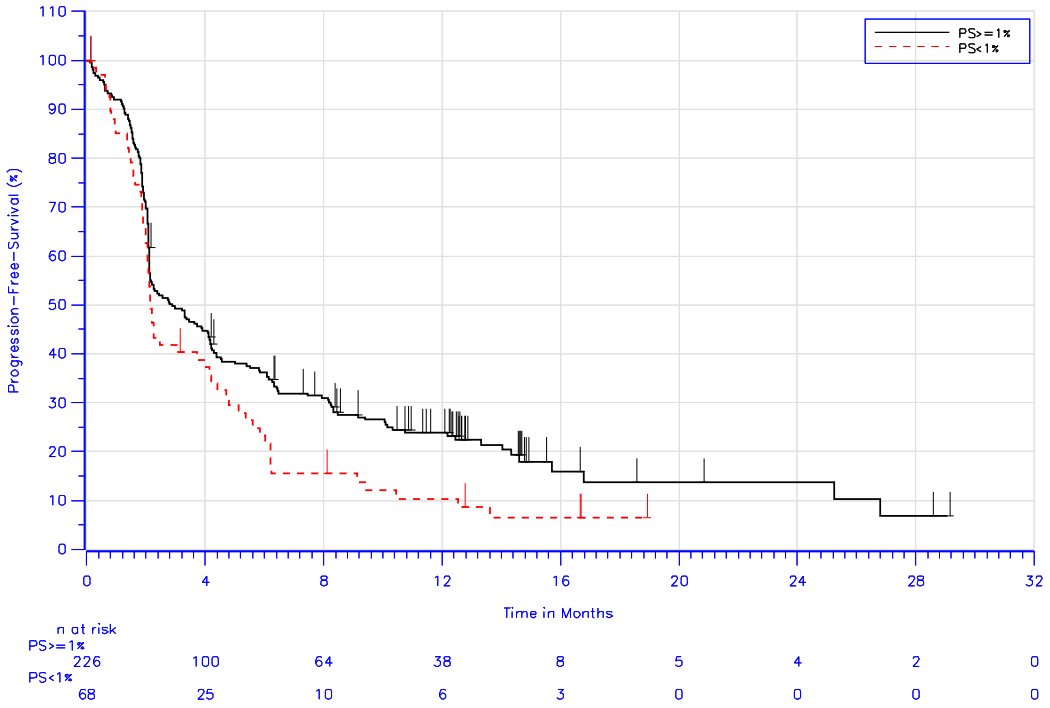
These results provide additional support for the clinical benefit of pembrolizumab treatment in patients with advanced NSCLC who express PD-L1 ≥1%.

Table 39: KEYNOTE-001 - Summary of PFS (IRC per RECIST 1.1) - Total Previously Treated Efficacy Population by PD-L1 (within stability window) – APaT

	PS>=1% (N=226)	PS<1% (N=68)	Unknown (N=100)	Total (N=394)
Number (%) of PFS Events	178 (78.8)	61 (89.7)	74 (74.0)	313 (79.4)
Person-Months	1260	279	552	2091
Event Rate/100 Person-Months (%)	14.1	21.8	13.4	15.0
Median PFS (Months)[§]	2.9	2.1	4.0	3.0
95% CI for Median PFS[§]	(2.1,4.1)	(2.0,4.0)	(2.3,5.0)	(2.2,4.0)
PFS rate at 3 Months in % [§]	49.2	41.8	54.6	49.3
PFS rate at 6 Months in % [§]	36.1	23.2	36.4	34.0

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
[§] From product-limit (Kaplan-Meier) method for censored data. Database Cut-off Date: 23JAN2015.

Figure 21: KEYNOTE-001 - Kaplan-Meier Estimates of PFS (per RECIST 1.1) - Total Previously Treated Efficacy Population by PD-L1 Expression (TPS≥1% vs. TPS<1%) – APaT



Database Cutoff Date: 23JAN2015
Data Source: [16.4]

- Previously Treated Population 2mg/Kg Q3W (Cohort F3)

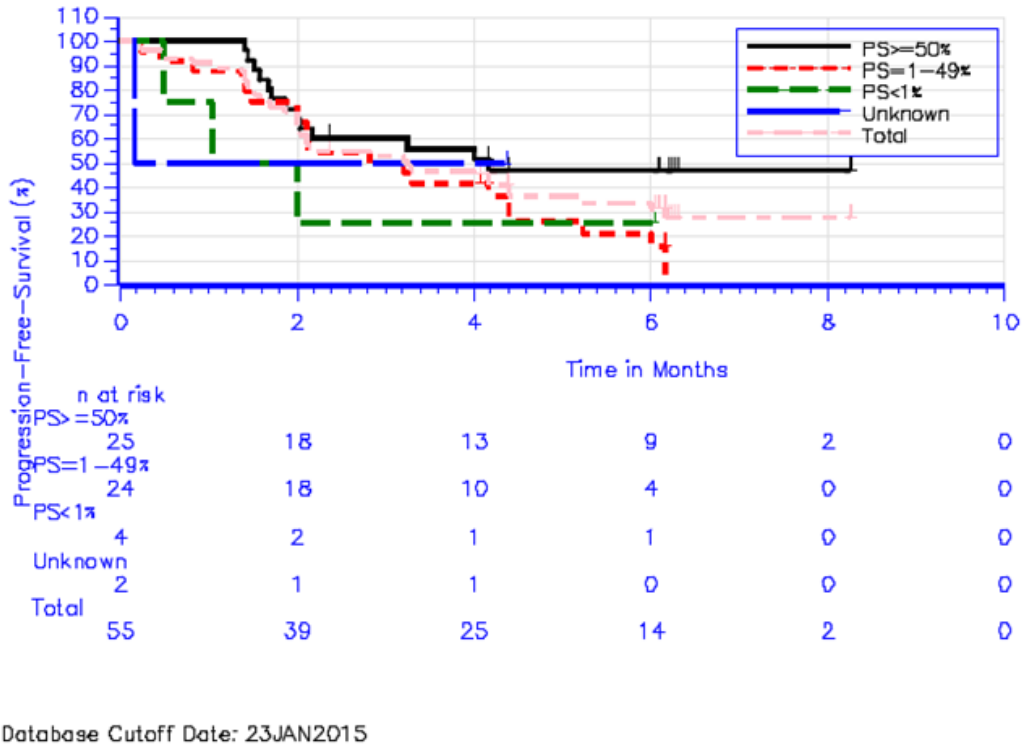
The PFS estimates from Cohort F3 PD-L1 positive patients treated with pembrolizumab 2mg/Kg Q3W (Table 40 and Figure 22) were similar to the estimates in the Total Previously Treated Efficacy Population with TPS≥1% (within stability window), supporting the proposed 2 mg/kg Q3W dose recommended for this indication. As a result of the shorter follow up in Cohort F3, the number of patients with progression disease is smaller than that observed in KEYNOTE-10 patients treated with pembrolizumab 2mg/Kg Q3W.

Table 40: KEYNOTE-001 - Summary of PFS (IRC per RECIST 1.1 and INV per irRC) in the Previously Treated Population 2mg/Kg Q3W (Cohort F3) – APaT

	Cohort F3 PD-L1 Positive 2 mg/kg (n=55) (APaT)	
	IRC per RECIST 1.1	**INV per irRC**
Number (%) of PFS Events	37 (67.3)	35 (63.6)
Person-Months	190	206
Event Rate/100 Person-Months (%)	19.5	17.0
Median PFS (Months)§	3.3	4.4
95% CI for Median PFS§	(2.0,4.4)	(2.1,16.0)
PFS rate at 3 Months in % §	52.7	56.2
PFS rate at 6 Months in % §	33.6	40.9

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first. § From product-limit (Kaplan-Meier) method for censored data. Database Cut-off Date: 23JAN2015

Figure 22: KEYNOTE-001 - Kaplan-Meier Estimates of PFS (per RECIST 1.1) - Previously Treated Population 2mg/Kg Q3W (Cohort F3) – APaT population



Database Cutoff Date: 23JAN2015

OS – APaT population

- Total Previously Treated Efficacy Population

Table 41 and Figure 23 display the OS estimates in the Total Previously Treated Efficacy Population with (APaT), by PD-L1 status (within stability window). The median OS in the 226 patients with advanced NSLC who express PD-L1 (TPS≥1%; within stability window) was 11.1 months when combining both pembrolizumab schedules (Table 41), and the OS rate at 12 months was 48.8% (Table 41). The median OS in the 68 patients with advanced NSCLC who do not express PD-L1 (TPS<1%; within stability window) was 8.6 months, with an OS rate at 12 months of 38.3% (Table 41). The OS estimates in the subpopulation of patients with advanced NSCLC whose tumours do not express PD-L1 (TPS<1%) are similar to the OS estimates observed in the docetaxel arm of the KEYNOTE-010 study (median OS 8.5 months and 12 months OS rate of 35%). These results provide supporting evidence for the longer term survival benefit of pembrolizumab treatment observed in KEYNOTE-010, and confirm that selecting patients by PD-L1 expression is predictive in identifying those likely to benefit the most from treatment with pembrolizumab.

The OS KM curve of the group of patients with advanced NSCLC who are PD-L1 expressers (TPS≥1%; within stability window) separates from the curve of the group of patients with

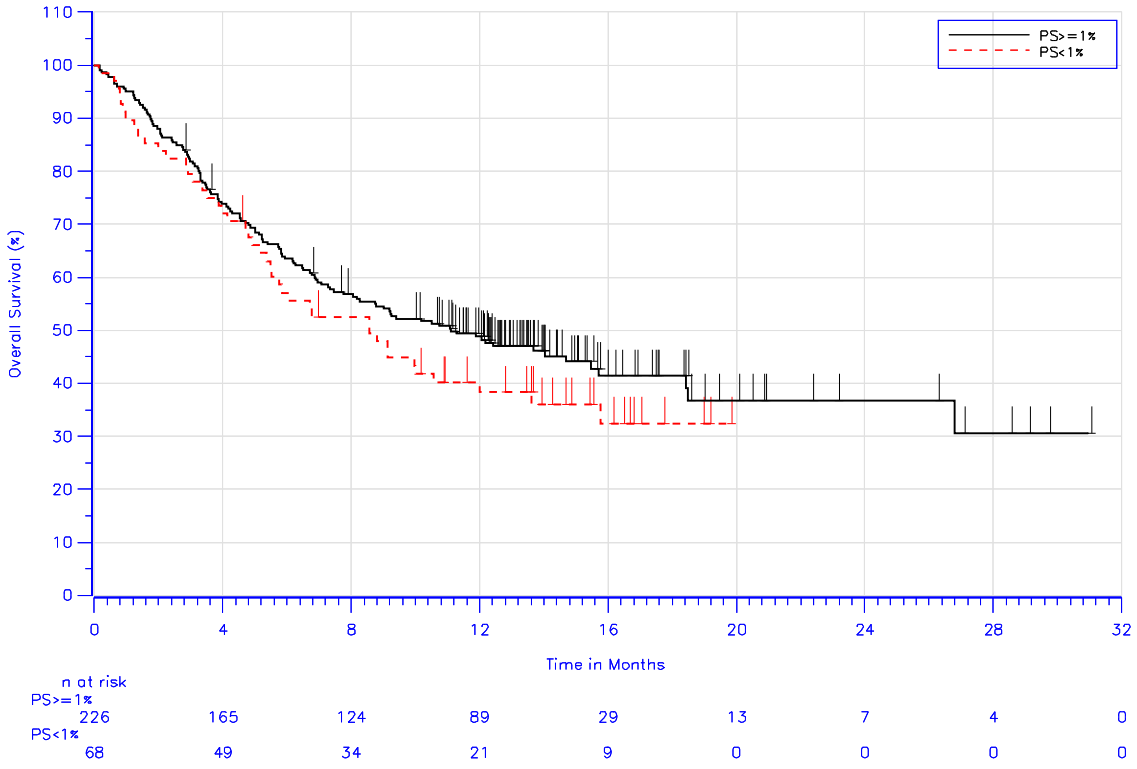
advanced NSCLC who are non expressers (TPS<1%; within stability) (Figure 23) (HR 0.81; 95% CI 0.57, 1.14).

Table 41: KEYNOTE-001 - Summary of OS - Total Previously Treated Efficacy Population by PD-L1 (within stability window) – APaT

	PS>=1% (N=226)	PS<1% (N=68)	Unknown (N=100)	Total (N=394)
Death (%)	125 (55.3)	43 (63.2)	55 (55.0)	223 (56.6)
Median Survival (Months)[§]	11.1	8.6	14.3	11.3
95% CI for Median Survival[§]	(8.0,15.5)	(5.5,12.0)	(8.5,16.5)	(8.8,14.0)
OS rate at 6 Months in % [§]	63.5	57.1	65.9	63.0
OS rate at 12 Months in % [§]	48.8	38.3	55.9	48.7

OS: Overall survival.
[§] From product-limit (Kaplan-Meier) method for censored data. Database Cut-off Date: 23JAN2015.

Figure 23: KEYNOTE-001 - Kaplan-Meier estimates of OS - Total Previously Treated Efficacy Population by PD-L1 (TPS≥1% vs. TPS<1%) – APaT



Database Cutoff Date: 23JAN2015
Data Source: [16.4]

- Previously Treated Population 2mg/Kg Q3W (Cohort F3)

The OS estimates from Cohort F3 PD-L1 positive patients treated with pembrolizumab 2mg/Kg Q3W (Table 42 and Figure 23) also support the 2 mg/kg Q3W dose of

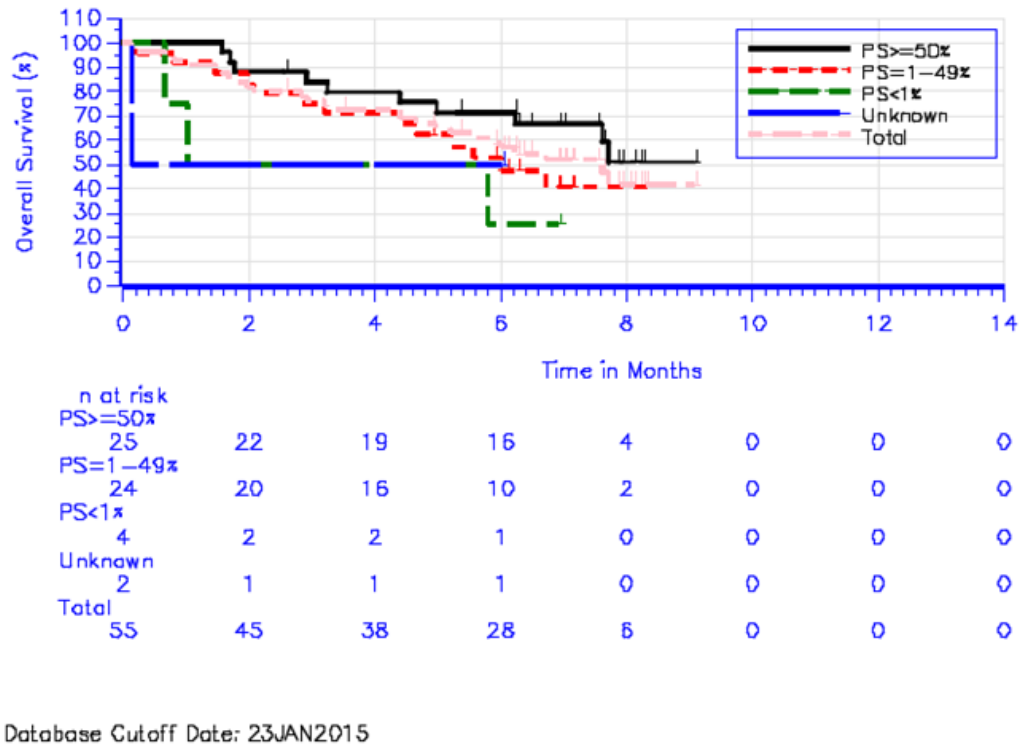
pembrolizumab proposed for this indication, even considering the shorter follow-up in these patients (pembrolizumab 2mg/Kg Q3W OS rate at 6 months 58.8%; Table 42).

Table 42: KEYNOTE-001 - Summary of OS in the Previously Treated Population 2mg/Kg Q3W (Cohort F3) – APaT

	Cohort F3 PD-L1 Positive 2 mg/kg (n=55) (APaT)
Death (%)	27 (49.1)
Median Survival (Months)[§]	7.6
95% CI for Median Survival [§]	(5.2, ..)
OS rate at 6 Months in % [§]	58.8
OS rate at 12 Months in % [§]	NR

OS: Overall survival. [§] From product-limit (Kaplan-Meier) method for censored data.
Database Cut-off Date: 23JAN2015

Figure 24: KEYNOTE-001 - Kaplan-Meier estimates of PFS (per RECIST 1.1) - Total Previously Treated Efficacy Population by PD-L1 (TPS≥1% vs. TPS<1%) – APaT



Database Cutoff Date: 23JAN2015

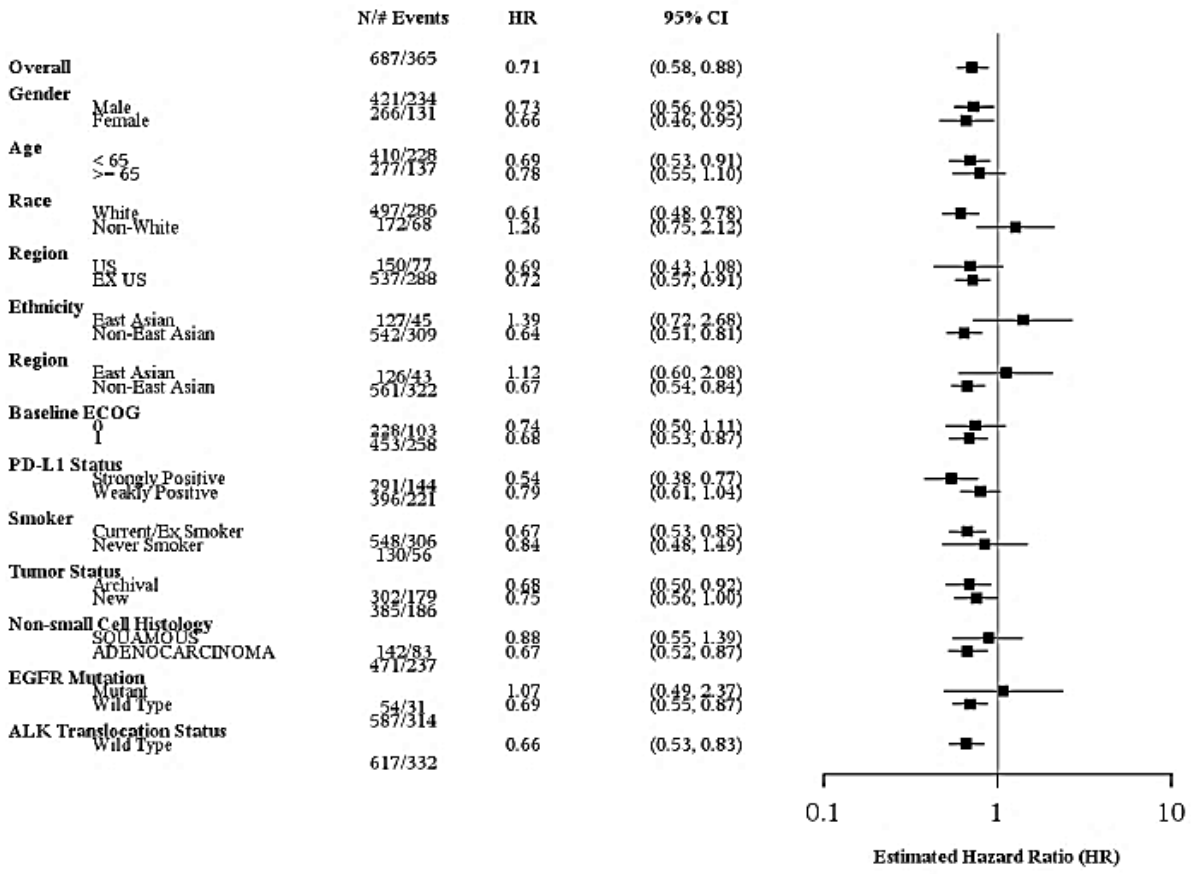
4.8 Subgroup analysis

KEYNOTE-010[16;81-83]

Subgroup analyses

Figure 25 and Figure 26 provide, respectively, the results of the subgroup analyses of OS and PFS (by IRC assessment per RECIST 1.1) for pembrolizumab 2 mg/kg Q3W arm vs. docetaxel.

Figure 25: KEYNOTE-010 - Forest Plot of OS HR by Subgroup Factors - pembrolizumab 2 mg/kg Q3W versus Docetaxel- ITT Population (TPS≥1%)

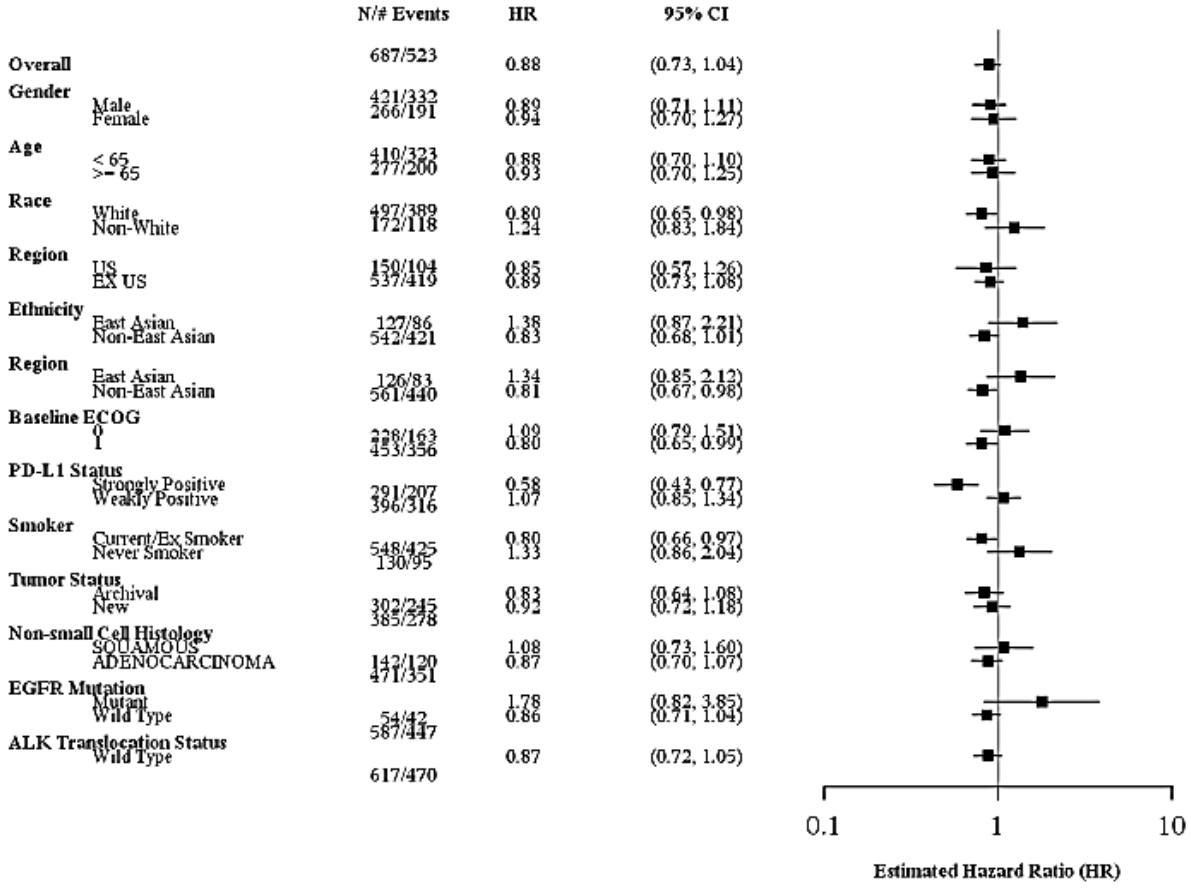


Database Cutoff Date: 30SEP2015

The subgroup results indicate consistency in the superiority of pembrolizumab compared to docetaxel across the vast majority of subgroups in the TPS≥1% population. The few HRs close to or greater than one correspond to subgroups with small numbers of events and thus, less precise estimates. Pembrolizumab provided survival benefit compared with docetaxel irrespective of whether archival or new tumour samples were used to assess PD-L1 expression (Figure 25). There was a significant survival benefit for patients with non-squamous (adenocarcinoma) disease. For those with squamous disease, the difference was

not statistically significant (probably because of the small population size), but the data suggest a clinical benefit in this group also (Figure 25). The p-values for the tests for interaction for the OS subgroup analysis presented in Figure 25 are provided in Appendix 13.

Figure 26: KEYNOTE-010 - Forest Plot of PFS (IRC per RECIST 1.1) HR by Subgroup Factors - pembrolizumab 2 mg/kg Q3W versus Docetaxel- ITT Population (TPS≥1%)



Database Cutoff Date: 30SEP2015

The results of the Forest plot analyses of OS and PFS by subgroup factors for the pooled pembrolizumab arms (to increase sample size and increase the interpretability of the results), and for the TPS≥50% stratum are provided in Appendix 13.

KEYNOTE-001 (Parts C, F2 and F3)[35;85;86;89]

Subgroup analyses

Subgroup analyses were performed based on major demographic factors and potentially important prognostic factors for patients with advanced NSCLC. These subgroups were not

pre-specified, but were performed in post-hoc analyses to show consistency in ORR for major subgroups, as determined by central review per RECIST 1.1 in the APaT population.

In general, all subgroups in the Total Previously Treated Efficacy Population responded similarly to pembrolizumab, with the exception of never smokers (BOR 10.4%; 95% CI: 5.5, 17.5) who did not respond as well as patients with a history of prior smoking (BOR 22.9%; 95% CI: 18.1, 28.3). These subgroup analyses support the conclusion that the efficacy of pembrolizumab is consistent across all major baseline demographic and prognostic factors. Further details are provided in Appendix 14.

4.9 Meta-analysis

There is only one randomised controlled trial for the intervention versus a relevant comparator (KEYNOTE-010). KEYNOTE-001 Part C and F2 did not include a comparator of relevance to the decision problem. A meta-analysis was not conducted as it was deemed inappropriate to pool pembrolizumab data from these two studies, given their different designs and differences in patient baseline characteristics between both studies (see Table 43). In KEYNOTE-001 the Total Previously Treated Efficacy Population treated with pembrolizumab might have had a slightly poorer overall prognosis due to higher proportion of patients with stage M1b disease (71.8%), which carries a minimally worse prognosis than M1a disease. Moreover, these patients also represent a heavily pre-treated advanced NSCLC population (83% received at least two lines of previous treatment).

Table 43: Comparison of baseline characteristics of patients treated with pembrolizumab in KEYNOTE-010 and KEYNOTE-001

	KEYNOTE-010	KEYNOTE-001
	Pembrolizumab 2 mg/kg Q3W n=344 (%)	**Total Previously Treated Efficacy Population n=394 (%)**
Gender		
Male	61.6	51.0
Age (Years)		
< 65 Mean (SD) Median (Range)	58.4 62.1 (9.6) 63.0 (29 to 82)	56.3 61.3 (10.7) 62.0 (28 to 85)
ECOG		
[0] [1] Unknown	32.6 66.6 0.0	33.0 66.5 0.5
Cancer Staging		
III IV	7.6 91.6	2.8 97.2
Metastatic Staging		

	KEYNOTE-010	KEYNOTE-001
	Pembrolizumab 2 mg/kg Q3W n=344 (%)	Total Previously Treated Efficacy Population n=394 (%)
M0 M1a M1b	8.4 18.0 **45.9**	2.5 25.6 **71.8**
Brain Metastasis		
Yes	16.3	12.2
Number of Unique Prior Systemic Therapies		
1 2 3 4 or more	70.6 **19.2** **5.2** **2.6**	17.0 **29.9** **27.2** **25.9**
Baseline Tumour Size (mm)		
Patients with data Mean (SD Median (Range)	335 98.7 (61.0) 86.0 (10 to 345)	360 116 (86) 98 (10 to 548)
Histology		
Squamous Non-Squamous Adenosquamous Unknown	22.1 69.8 0.9 5.5	16.8 81.7 1.3 0.3
Smoking Status		
Never Former / Current	18.3 81.1	29.2 70.8
EGFR Mutation		
Yes No Unknown	8.1 85.2 4.4	17.8 78.7 3.6
ALK Gene Rearrangement		
Wild Type Unknown	89.2 6.4	85.3 12.7
Database Cut-off Date: 23 JAN 2015		

4.10 Indirect and mixed treatment comparisons

In the absence of head to head RCTs of pembrolizumab versus competing interventions, an indirect treatment comparison (ITC) by means of a network meta-analysis (NMA) of RCTs has been conducted to enable a comparison to be made for the purposes of this submission.[99-101]

4.10.1: Search strategy

A systematic literature review was conducted according to a previously prepared protocol, to identify relevant studies to inform both direct and indirect comparisons between the interventions of interest. The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design. Details of the search strategy are

presented in section 4.1. Full description of the search strategy by database is presented in Appendix 2.

4.10.2: Details of treatments

The decision problem addressed in this submission is presented in section 1.1. The following advanced NSCLC populations and comparators of interest were identified:

- All NSCLC histologies population (previously treated)
    - pembrolizumab vs. docetaxel
- Adenocarcinoma population (previously treated)
    - pembrolizumab vs. docetaxel
    - pembrolizumab vs. nintedanib in combination with docetaxel

4.10.3: Criteria used in trial selection

The inclusion and exclusion criteria and the study selection process are described in section 4.1 (see Table 7 PICOS eligibility criteria and Figure 4 PRISMA flow diagram).
For selection of studies for indirect and mixed treatment comparisons we included RCTs with comparisons between any of the interventions of interest and RCTs with other interventions that have been compared to at least two of the interventions of interest.

4.10.4: Summary of trials

Table 44: Summary of the trials

References of trial	Treatment 1	Treatment 2	Treatment 3
KEYNOTE-010[16;81-84]	Pembrolizumab, IV 2mg/Kg Q3W (n=344)	Pembrolizumab, IV 10mg/Kg Q3W (n=346);	Docetaxel IV, 75 mg/m2 (n=343)
LUME-LUNG-1[6;102-109]	Docetaxel IV, 75 mg/m2 plus Nintedanib, PO 400mg Q3W (n=655)	Docetaxel IV, 75 mg/m2 (n=659) plus Placebo	

4.10.5 Trials identified in search strategy

Two studies were identified by the systematic literature review and form the base for the indirect treatment comparison: KEYNOTE 010[16;81-84] and LUME-LUNG 1. [6;102-109]

In the all NSCLC histologies population, KEYNOTE-010 is the only RCT that compares pembrolizumab to docetaxel; therefore no further analysis is necessary. The results of KEYNOTE-010 study have been presented in section 4.7.

In the adenocarcinoma subpopulation, one RCT (KEYNOTE-010) assessed pembrolizumab, and one RCT (LUME-LUNG 1) assessed nintedanib in combination with docetaxel. Both the studies included docetaxel as a comparator, forming a connected network (see Figure 27 below), so an indirect treatment comparison can be performed.

KEYNOTE-010 included three treatment arms: docetaxel 75 mg/m2 Q3W, pembrolizumab 2 mg/kg, and pembrolizumab 10 mg/kg. LUME-Lung 1 assessed docetaxel 75 mg/m2 Q3W and the combination docetaxel 75 mg/m2 Q3W with nintedanib 400 mg on days 2-21 of a 3-week cycle. Both the studies were multicentre, phase III RCTs. KEYNOTE 010 was conducted as an open-label study, although the analyses of PFS and ORR were based on blinded independent central review; while LUME-LUNG 1 was conducted as a double-blinded study. The two studies were similar in terms of eligibility criteria (see details in Appendix 15). In KEYNOTE-010, per protocol, crossover was not permitted, although patients could receive antineoplastic therapy after discontinuation of study treatment. In LUME-Lung 1 crossover was not permitted, but patients were allowed to discontinue docetaxel and continue with either nintedanib monotherapy or placebo, while patients on nintedanib were permitted to continue docetaxel monotherapy if they experienced intolerable adverse events due to nintedanib.

4.10.6 Rationale for choice of outcome measure chosen

The outcomes of interest for the NMA were:

- OS (time-varying HR and constant HR)
- PFS (time-varying HR and constant HR)
- Discontinuations due to adverse events
- Adverse events Grade 3 or 4

Both OS and PFS are clinically relevant outcomes that were referenced in the final scope for this appraisal and the decision problem. OS is the gold standard endpoint to demonstrate superiority of antineoplastic therapy. PFS is an acceptable scientific endpoint for a randomised phase III trial to demonstrate superiority of a new antineoplastic therapy, especially if it is believed that the median time to OS with the new therapy may be significantly longer than that seen with standard of care.

4.10.7 Populations in the included trials

The population of interest for the decision problem addressed in this submission is people with advanced NSCLC that is PD-L1 positive:

- whose disease has progressed after platinum-containing doublet chemotherapy.

- whose disease has progressed on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours.

This reflects the patient population included in KEYNOTE-010, which compares pembrolizumab to the comparator of interest (docetaxel).

For the adenocarcinoma subpopulation the search strategy identified two RCTs. KEYNOTE-010 presented subgroup analyses including patients with adenocarcinoma histology, whose tumours express PD-L1 (approximately 70% of the study population) (see section 4.8). LUME-LUNG 1 study included adult patients with advanced NSCLC whose disease had progressed on or after treatment with only 1 prior chemotherapy regimen. This study presented subgroup analyses including patients with adenocarcinoma (approximately 50% of the study population). Neither PD-L1 expression nor EGFR mutation status were assessed in LUME-LUNG 1 study.

4.10.8 Apparent or potential differences in patient populations between the trials

The distributions of baseline patient characteristics within and between comparisons are presented in Appendix 15. Characteristics such as age, proportion of current or former smokers, proportion of patients that are white, and proportion of patients with ECOG scores of 0 or 1 were similar in KEYNOTE-010 and LUME-LUNG 1. Differences in patient characteristics suggest some degree of heterogeneity across trials: LUME-Lung 1 included a larger proportion of males than KEYNOTE-010 (73% vs. 55%) and a smaller proportion of Stage IV NSCLC patients than KEYNOTE-010 (61% compared to 91%). Data on EGFR mutation or PD-L1 expression was not routinely collected in the LUME-Lung 1 study. However, data was not available on the distribution of all patient characteristics within the adenocarcinoma subgroups of LUME-LUNG 1, so it is not possible to fully ascertain the comparability of the two populations.

4.10.9; 4.10.10; 4.10.11 Methods, outcomes, baseline characteristics, risk of bias of each trial

Full details can be found in Appendix 15, including full detail of the quality assessment of the included studies. Both studies presented overall low risk of bias.

4.10.12 Methods of analysis and presentation of results

In Appendix 16, an overview of concepts and models for NMA are provided.

Models, likelihood, priors

All analyses were performed in the Bayesian framework and involved a model with parameters, data and a likelihood distribution, and prior distributions. For response and safety outcomes, a standard binomial setup was used. For analysis of survival outcomes, two sets of models were used: 1) NMA based on reported HRs assuming proportional hazards between treatments; and 2) NMA based on the scanned KM curves anticipating that HRs can vary over time according to a certain parametric function.
Reported KM curves were digitized in order to obtain the survival proportion over time, and PFS and OS proportions were extracted at two-month increments. Extracted PFS and OS proportions were used to calculate the incident number of events for each interval and patients at risk at the beginning of that interval.

- PFS and OS using reported HRs

The ITC of reported HRs in terms of PFS and OS was performed using a fixed effect regression model with a contrast-based normal likelihood for the log HR of each trial in the network according to Dias *et al*.[99] using normal non-informative prior distributions for the parameters estimated with a mean of 0 and a variance of 10,000.

- PFS and OS using scanned KM curves

Traditional ITC or NMA for survival outcomes are based on hazard ratio (HR) estimates and rely on the proportional hazards assumption, which is implausible if the hazard functions of competing interventions cross. The hazard function describes the instantaneous event (e.g. death) rate at any point in time. Jansen *et al* and have presented methods for network meta-analysis of survival data using a multidimensional treatment effect as an alternative to the synthesis of the constant HRs.[100;110] The hazard functions of the interventions in a trial are modeled using known parametric survival functions or fractional polynomials and the difference in the parameters are considered the multidimensional treatment effect, which are synthesized (and indirectly compared) across studies. With this approach, the treatment effects are represented by multiple parameters rather than a single parameter. The model introduced by Jansen was used for the ITC of PFS and OS.[100;110]
For PFS and OS the following competing survival distributions were considered using the multivariate ITC framework: Weibull, Gompertz, and 2nd order fractional polynomials with power p_1=0 and 1 and power p_2= 0 and 1. In essence, these 2nd order fractional polynomial models are extensions of the Weibull and Gompertz model, and allow arc- and bathtub shaped hazard functions. For the relative treatment effects in the 2nd order fractional polynomial framework we assumed that treatment only has an impact on two of the three

parameters describing the hazard function over time (i.e. one scale and 1 shape parameter). The fixed effects versions of these flexible survival models were used for the evidence synthesis. Model 1, presented here below, is the fixed effects model assuming that the survival times follow a Weibull (p=0) or Gompertz (p=1) distribution. Model 2 is the 2nd order fractional polynomial model considered.

$$\ln(h_{jkt}) = \beta_{0jk} + \beta_{1jk} t^{p} \qquad \text{with } t^0 = \log(t), \quad p \in \{0,1\}$$

$$\begin{pmatrix} \beta_{0jk} \\ \beta_{1jk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} & if\ k = b, b \in \{A,B,C\} \\ \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} + \begin{pmatrix} d_{0Ak} - d_{0Ab} \\ d_{1Ak} - d_{1Ab} \end{pmatrix} & if\ k \succ b \end{cases} \qquad (1)$$

$$\ln(h_{jkt}) = \begin{cases} \beta_{0jk} + \beta_{1jk} t^{p_1} + \beta_{2jk} t^{p_2} & p_1 \neq p_2 \\ \beta_{0jk} + \beta_{1jk} t^{p_1} + \beta_{2jk} t^{p_1} (\log t) & p_1 = p_2 \end{cases} \qquad \text{with } t^0 = \log(t)$$

$$\begin{pmatrix} \beta_{0jk} \\ \beta_{1jk} \\ \beta_{2jk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} & if\ k = b, b \in \{A,B,C\} \\ \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} + \begin{pmatrix} d_{0Ak} - d_{0Ab} \\ d_{1Ak} - d_{1Ab} \\ 0 \end{pmatrix} & if\ k \succ b \end{cases} \qquad (2)$$

For each treatment arm of each study in the ITTC, the reported KM curves were digitized (DigitizeIt; http://www.digitizeit.de/). The KM curves can be divided into q consecutive intervals over the follow-up period: $[t_1, t_2]$, $(t_2, t_3]$, …, $(t_q, t_{q+1}]$ with t_1=0. For each time interval m=1,2,3,….,q, extracted survival proportions were used to calculate the patients at risk at the beginning of that interval and incident number of deaths.[110] A binomial likelihood distribution of the incident events for every interval can be described according to:

$$r_{jkt} \sim bin(p_{jkt}, n_{jkt})$$

where r_{jkt} is the observed number of events in the mth interval ending at time point t_{m+1} for treatment k in study j. n_{jkt} is the number of subjects at risk just before the start of that interval adjusted for the subjects censored in the interval. p_{jkt} is the corresponding underlying event probability. When the time intervals are relatively short, the hazard rate h_{jkt} at time point t for treatment k in study j can be assumed to be constant for any time point within the corresponding mth time interval. The hazard rate corresponding to p_{jkt} for the mth interval can be standardized by the unit of time used for the analysis (e.g. months) according to

$h_{jkt} = -\ln(1 - p_{jkt}) / \Delta t_{jkt}$ where Δt_{jkt} is the length of the interval. For the model estimation, we assigned this underlying hazard to time point t_{m+1}.

The prior distributions for model 1 are:

$$\begin{pmatrix} \mu_{0\,jb} \\ \mu_{1\,jb} \end{pmatrix} \sim normal\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \mathrm{T}_{\mu} \right) \qquad \mathrm{T}_{\mu} = \begin{pmatrix} 10^4 & 0 \\ 0 & 10^4 \end{pmatrix}$$

$$\begin{pmatrix} d_{0\,Ak} \\ d_{1\,Ak} \end{pmatrix} \sim normal\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \mathrm{T}_{d} \right) \qquad \mathrm{T}_{d} = \begin{pmatrix} 10^4 & 0 \\ 0 & 10^4 \end{pmatrix}$$

- Safety outcomes

For safety analysis, the all- comers population in both studies was used, as no subgroup data was available, and histology is not believed to be an effect modifier for safety outcomes. For safety outcomes, the ITC was performed on the proportion of patients experiencing the event of interest using a fixed effect regression model with a binomial likelihood and logit link. Normal non-informative prior distributions for the parameters were used with a mean of 0 and a variance of 10,000.

- Model selection

The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing survival models. DIC provides a measure of model fit that penalizes model complexity according to $DIC = \overline{D} + pD,\ pD = \overline{D} - \hat{D}$. $\overline{D}$ ("Dbar") is the posterior mean residual deviance, *pD* is the effective number of parameters, and $\hat{D}$ is the deviance evaluated at the posterior mean of the model parameters. In general, a more complex model will result in a better fit to the data, demonstrating a smaller residual deviance. The model with the better trade-off between fit and parsimony has a lower DIC. A difference in DIC of about 5 points can be considered meaningful.
Results of the ITC based on the constant reported HRs can be defended when the results of the time varying HR analysis suggests no statistically meaningful changes in the HRs over time.

Presentation of results

The results of the ITC for PFS and OS are presented with estimates for treatment effects of each intervention relative to docetaxel in terms of scale and shape parameters. Based on

these parameter estimates, plots of the HR as a function of time of each intervention relative to docetaxel are presented. The posterior distributions of relative treatment effects and modeled outcomes are summarized by the median and 95% credible intervals (CrIs), which are constructed from the 2.5th and 97.5th percentiles of the posterior distributions.

The results of the ITC based on reported HRs, and those for safety outcomes are presented with cross-tables with relative treatment effect estimates (HRs or ORs) between all interventions of interest along with 95% CrI.

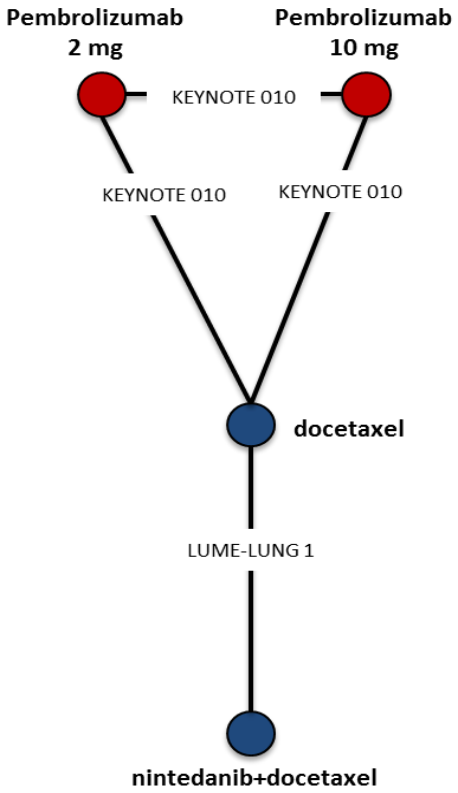
4.10.13 Programming language

The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the OpenBUGS software package.[111;112] A first series of iterations from the OpenBUGS sampler was discarded as 'burn-in', and the inferences were based on additional iterations using two chains. All analyses were performed using R version 3.2.2 (http://www.r-project.org/) and OpenBugs version 3.2.3 (OpenBUGS Project Management Group). Programming language has been provided in Appendix 17.

4.10.14; 4.10.15; 4.10.16 Results of analysis and results of statistical assessment of heterogeneity

Figure 27 presents the network of evidence for comparison of pembrolizumab to nintedanib in combination with docetaxelin previously treated patients with advanced NSCLC of adenocarcinoma histology. The results of the NMA are presented for pembrolizumab 2mg/Kg Q3W (anticipated licence dose and schedule, relevant to this submission). Full results including pembrolizumab 10mg/Kg Q3W are presented as an appendix (see Appendix19).

Figure 27: Network of evidence for comparison of pembrolizumab to nintedanib+docetaxel - NSCLC of adenocarcinoma histology



- Overall survival

The study-specific KM curves for OS based on extracted source data used for the NMA are presented in Appendix 18. A series of different NMA models were fit to the data, assuming that OS times follow a Weibull distribution, a Gompertz distribution, or 2nd order fractional polynomials (see results in Appendix 19). The relative treatment effects do not change significantly over time; the credible intervals for each intervention can contain a horizontal line, which indicates that the constant HR assumption is plausible.

As the constant HR assumption appears to be reasonable for OS with the interventions of interest, we conducted an NMA using the (constant) HRs as reported for each trial. The analysis was performed using the HRs for the adenocarcinoma subgroup as presented in KEYNOTE-010 clinical study report (separately by dose of pembrolizumab) (Table 45). The HRs obtained from the fixed-effects NMA are given in (Table 46). The estimated OS HR favoured pembrolizumab 2 mg Q3W compared with nintedanib in combination with docetaxel (HR 0.81, 95% CrI 0.59-1.10), but this difference was not statistically meaningful (Table 46).

Table 45: OS HRs reported in the studies included in the NMA

Study	Comparison	HR	logHR(SE)
KEYNOTE 010	Pembrolizumab 2mg Q3W vs. Docetaxel	0.67	-0.40 (0.13)
LUME-Lung 1	Nintedanib+Docetaxel vs. Docetaxel	0.83	-0.19 (0.09)

Table 46: Constant HRs for OS from fixed effects NMA

Docetaxel	1.49 (1.15, 1.93)	1.21 (1.01, 1.43)
0.67 (0.52, 0.87)	**Pembrolizumab 2 mg**	0.81 (0.59, 1.10)
0.83 (0.70, 0.99)	1.24 (0.91, 1.69)	**Nintedanib+docetaxel**
Each cell represents the comparison of the row treatment versus the column treatment. Cells highlighted in light blue represent direct evidence, unshaded cells represent indirect evidence		

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- Progression free survival (PFS)

Appendix 18 presents the study specific KM curves for PFS that were reconstructed from extracted source data. As for OS, different NMA models were fit to the data, including Weibull, Gompertz, and 2nd order fractional polynomial models (see Appendix 19). In all three models, nintedanib in combination with docetaxel was statistically worse than pembrolizumab after approximately 10 months (as can be seen by the non-overlapping credible intervals).

The PFS KM curves from the follow up analysis of the LUME-LUNG 1 study (February 2013)[109] crossed after approximately 1 year, violating the proportional hazards assumption. Therefore, any indirect treatment comparison with this study assuming constant HRs is associated with uncertainty. Despite this, a NMA using constant (HR) was conducted for completeness. The results are presented below, but should be interpreted with caution. The analysis was performed using the HRs for the adenocarcinoma subgroup as presented in KEYNOTE-010 clinical trial report (separately by dose of pembrolizumab) (Table 47). The HRs obtained from the fixed-effects NMA are given in (Table 48). No statistically meaningful differences were found between the estimated PFS of pembrolizumab 2 mg Q3W and nintedanib in combination with docetaxel (Table 48).

Table 47: PFS HRs reported in the studies included in the NMA

Study	Comparison	HR	logHR(SE)
KEYNOTE 010	Pembrolizumab 2mg Q3W vs. docetaxel	0.81	-0.21 (0.11)
LUME-Lung 1	Nintedanib+Docetaxel vs. docetaxel	0.84	-0.17 (0.09)

Table 48: Constant HRs for PFS from fixed effects NMA

Docetaxel	1.15 (0.93, 1.42)	1.19 (1.00, 1.41)
0.87 (0.70, 1.08)	**Pembrolizumab 2 mg**	1.04 (0.79, 1.36)
0.84 (0.71, 1.00)	0.96 (0.73, 1.27)	**Nintedanib+Docetaxel**

Each cell represents the comparison of the row treatment versus the column treatment.
Cells highlighted in light blue represent direct evidence, unshaded cells represent indirect evidence.

- Discontinuation of treatment due to adverse events (AEs)

The number and percentage of patients in each study arm discontinuing treatment due to AEs are given in Table 49. Nintedanib in combination with docetaxel had higher odds of discontinuations to due AEs than pembrolizumab 2mg/Kg Q3W. The results from the fixed-effect NMA are presented in Table 50. Pembrolizumab 2mg/Kg Q3W showed lower odds of treatment discontinuation due to AEs than nintedanib in combination with docetaxel (Table 50). The modelled probabilities of discontinuations due to AEs and the corresponding rankogram are presented in Appendix 19. Pembrolizumab 2mg/Kg Q3W is most likely the best of the studied interventions, while nintedanib in combination with docetaxel most likely the worst.

Table 49: Number and proportion of patients discontinuing treatment due to AEs

Trials	Docetaxel	Pembrolizumab 2mg	Nintedanib+docetaxel
KEYNOTE 010	47/309 (15.2%)	34/339 (10%)	
LUME-Lung 1	142/659 (21.5%)		148/655 (22.6%)
Values presented in this table are the number of events over the sample size for each arm			

Table 50: Results of fixed effects NMA of treatment discontinuations due to AEs (odds ratios with 95% credible intervals)

Docetaxel	1.61 (1.01, 2.58)	0.94 (0.73, 1.22)
0.62 (0.39, 0.99)	Pembrolizumab 2 mg	0.58 (0.34, 0.99)
1.06 (0.82, 1.38)	1.71 (1.01, 2.94)	Nintedanib+docetaxel
Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. Cells highlighted in light blue represent direct evidence, unshaded cells represent indirect evidence. DIC: 9.42; Deviance: 4.39		

- Adverse events Grade 3 or 4

Table 51 presents the number and percentage of patients experiencing Grade 3 or 4 adverse events in each study arm. The results from the fixed-effect NMA are presented in

Table 52. Nintedanib in combination with docetaxel had higher odds of AEs Grade 3 or 4 than pembrolizumab 2mg/Kg Q3W.

The modelled probabilities of AEs Grade 3 or 4 and the corresponding rankogram are presented in Appendix 19. Pembrolizumab 10 mg and pembrolizumab 2 mg are likely the best and 2nd-best treatments; nintedanib in combination with docetaxel is almost certainly the worst.

Table 51: Number and proportion of patients experiencing Grade 3 or 4 AEs

Trials	Docetaxel	Pembrolizumab 2 mg	Nintedanib+docetaxel
KEYNOTE 010	168/309 (54.4%)	155/339 (45.7%)	
LUME-Lung 1	344/659 (52.2%)		358/655 (54.7%)

Values presented in this table are the number of events over the sample size for each arm

Table 52: Results of fixed effects NMA of AEs Grade 3 or 4 in the all comers, all-histologies population (odds ratios with 95% credible intervals)

Docetaxel	1.42 (1.03, 1.93)	0.91 (0.73, 1.13)
0.71 (0.52, 0.97)	**Pembrolizumab 2 mg**	0.64 (0.44, 0.94)
1.10 (0.88, 1.37)	1.56 (1.07, 2.28)	**Nintedanib+Docetaxel**

Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. Cells highlighted in light blue represent direct evidence, unshaded cells represent indirect evidence. DIC: 9.34; Deviance: 4.35

Discussion and conclusion

In the NMA conducted to compare the relative treatment effects of pembrolizumab to nintedanib in combination with docetaxel in the adenocarcinoma population, pembrolizumab 2mg/Kg Q3W showed a non-statistically significant benefit for OS comparable to nintedanib in combination with docetaxel (HR 0.81; 95% CrI 0.59-1.10), and the reverse was the case for PFS (HR 1.04; 95% CrI 0.79, 1.36). Pembrolizumab also offered a more favourable safety profile in terms of discontinuations due to AEs and Grade 3 or 4 AEs. This comparison was limited by the fact that no assessment of inconsistency or adjustment for differences between trial populations was possible due to the evidence base consisting of only two trials.

The proportional hazards assumption is key when conducting a NMA for OS and PFS based on the constant HR; this is implausible if the hazard functions of competing interventions cross. When we use a constant HR in the context of NMA we implicitly assume that the log hazard functions of all treatments in the network run parallel, which may be considered unrealistic. As an alternative to the constant HR, which is a univariate treatment effect measure, we can also use a multivariate treatment effect measure that describes how the relative treatment effect (e.g. HR) develops over time. Jansen *et al* and presented methods for NMA of survival data using a multi-dimensional or multivariate treatment effect as an alternative to the synthesis of one treatment effect (e.g. the constant HRs).[100] The hazard functions of the interventions in a trial are modeled using known parametric survival functions, and the differences in the parameters are considered the multi-dimensional treatment effect, which are synthesized (and indirectly compared) across studies. With this approach, the treatment effects are represented by multiple parameters rather than a single parameter. By incorporating additional parameters for the treatment effect, the proportional hazards assumption is relaxed and the NMA model can be fitted more closely to the available data. In terms of PFS for nintedanib in combination with docetaxel, the assumptiom of proportional hazards is inconsistent with the reported survival curve. As such, any comparative estimates between nintedanib in combination with docetaxel and any other interventions assuming constant HRs ignore this fact and thereby may not reveal all information. Ignoring the impact of time on the HRs may lead to bias in the NMA estimates.

There are other important limitations to the indirect comparison performed. Only two RCTs were available to comprise the evidence base for this analysis. This meant that no meta-regression was possible to adjust for heterogeneity in patients characteristics across trials. In addition, only a fixed-effect indirect comparison could be conducted as between-study heterogeneity could not be estimated; random-effect models are deemed more plausible but rely on stable estimation of a heterogeneity parameter. Moreover, the KEYNOTE 010 study enroled patients with advanced NSCLC who expressed PD-L1; while PD-L1 expression was not routinely collected in the LUME-Lung 1 study. In essence, this means that the indirect comparison relies on the assumption that the efficacy of nintedanib in combination with docetaxel does not depend on PD-L1 expression and that the reported trial subgroups were comparable.

4.10.17 Justification for the choice of random or fixed effects model

In general, the assumptions of random effects models are more plausible than fixed effect models. However, for this analysis only fixed-effects models were considered, as each

contrast was described by only a single trial. This means that a between-study heterogeneity parameter cannot be estimated, and a random effects model cannot be used.

4.10.18 and 4.10.19 Heterogeneity between results of pairwise comparisons and inconsistencies between direct and indirect evidence

Please refer to Figure 27 (network) and see section 4.10.17 above. Since there is no closed loop in the network of evidence that contains the two treatments of interest, it is not possible to assess inconsistency. Nor is it possible to adjust for differences in patient characteristics between the two trials via meta-regression or other method.

4.11 Non-randomised and non-controlled evidence

4.11.1 Non-randomised evidence

KEYNOTE-001[35;85;86;89] study includes the following non-randomised and non-controlled NSCLC expansion cohorts:

- Part C (non-randomised): Pembrolizumab 10 mg/kg Q3W (n=38)
- Part F2 PD-L1 non-expressers (non-randomised): Pembrolizumab 10 mg/kg Q2W (n=43)
- Part F2 PD-L1 expressers (non-randomised): Pembrolizumab 10 mg/kg Q3W (n=33)
- Part F3 PD-L1 expressers (non-randomised): Pembrolizumab 2 mg/kg Q3W (n=55)

Figure 1 in Appendix 6 outlines which cohorts contributed to the Biomarker Training or Validation sets, and Figure 6 in section 4.3.1 describes the derivation of the efficacy analysis populations of KEYNOTE-001 from these Biomarker sets. Based on this, data from patients in Parts C and F2 (including randomised and non-randomised sub-cohorts) have been pooled for the purpose of analysis, and the results are presented in section 4.7 (efficacy) and section 4.12 (safety). Data from Cohort F3 (pembrolizumab 2mg/Kg Q3W) is presented in section 4.7 for comparative analyses of the two doses of pembrolizumab (2 mg/kg Q3W in cohort F3 and 10 mg/kg Q3W and Q2W in cohort F2).

The methodology of the non-randomised and non-controlled cohorts of KEYNOTE-001 has been presented in section 4.3 to 4.5. The quality assessment of the Cohorts C, F2 (non-randomised) and F3 of KEYNOTE-001 is provided in Appendix 9.

4.12 Adverse reactions

4.12.2 Adverse reactions reported in RCTs listed in section 4.2

KEYNOTE-010: Adverse reactions[16;81-83]

As per information regarding clinical efficacy results, the safety results are presented in this section for pembrolizumab 2mg/Kg Q3W (anticipated licence dose and schedule) versus docetaxel. Full results for all three study arms (including pembrolizumab 10mg/Kg Q3W) are presented as an appendix (see Appendix 20).

The primary safety analysis in KEYNOTE-010 was based on the overall population of patients whose tumours express PD-L1 (TPS≥1%) in the APaT population. The APaT population consists of all randomised patients who received at least one dose of study treatment. Patients were included in the treatment group corresponding to the study treatment they actually received.

Safety and tolerability were assessed by clinical and statistical review of adverse events (AEs) and laboratory values reported during the treatment period, up to the data cut-off date of 30-Sep-2015. To assess change from baseline, a baseline measurement was also required.
Summaries of AEs, counts, listings, and tables include events from the first dose of study treatment to 30 days following the last dose of study treatment, or up to the data cut-off date of 30-Sep-2015 if the patient was still on study treatment.
Serious adverse event (SAE) counts and listing tables include events from the first dose of study treatment to 90 days after the last dose to account for the extended safety follow-up period for SAEs. In the AE summary tables, all AEs, including SAEs, are reported up to 30 days after the last dose of study drug. Therefore, the incidence of SAEs in AE summary tables differs slightly from the incidence of SAEs in later sections, where SAE tables by system organ class (SOC) include SAEs captured up to 90 days after the last dose of study treatment.

All AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 17.0,[113] and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[114]
AEs considered by the Investigator to be “possibly,” “probably,” or “definitely” related to study medication were classified as “drug-related AEs.”

Table 53 presents a summary of treatment exposure and AEs for the overall (TPS≥1%) population. The duration of exposure was measured from the date of the first dose, to 30 days after the last dose, of study drug.

Table 53: Summary of Exposure and AEs - APaT Population (TPS ≥ 1%)

	Previously Treated NSCLC Population (TPS≥1%)	
Number Patients – APaT population	Docetaxel 75 mg/m2 Q3W n = 309	Pembrolizumab 2 mg/kg Q3W n = 339
Exposure, days		
• Median	62.0	106.0
• Range of exposure	1.0 to 416.0	1.0 to 681.0
• Mean (SD)	81.5 (72.3)	151.1 (143.9)
Number of Administrations		
• Median (range)	3.0 (1.0 to 18.0)	6.0 (1.0 to 26.0)
• Mean (SD)	4.6 (3.2)	7.8 (6.4)
Patients in TPS ≥ 1% population		
with one or more adverse events	297 (96.1%)	331 (97.6%)
with drug-related† AEs	251 (81.2%)	215 (63.4%)
with toxicity grade 3-5 AE	173 (56.0%)	158 (46.6%)
with toxicity grade 3-5 drug-related AEs	109 (35.3%)	43 (12.7%)
with serious AEs	107 (34.6%)	115 (33.9%)
with serious drug-related AEs	42 (13.6%)	32 (9.4%)
who died	15 (4.9%)	17 (5.0%)
who died due to a drug-related AE	5 (1.6%)	3 (0.9%)
discontinued‡ due to an AE	42 (13.6%)	28 (8.3%)
discontinued due to a drug-related AE	31 (10.0%)	15 (4.4%)
discontinued due to a SAE	19 (6.1%)	24 (7.1%)
discontinued due to a drug-related SAE	11 (3.6%)	11 (3.2%)

† Determined by the investigator to be related to the drug. ‡ Study medication withdrawn.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose. Database Cut-off Date: 30SEP2015

Overall, the mean duration of treatment in the pembrolizumab 2 mg/kg Q3W arm was 151.1 days (maximum treatment duration 681 days) compared to 81.6 days for patients in the docetaxel arm (maximum treatment duration 416 days). Despite the longer duration on pembrolizumab compared to docetaxel, overall AE counts were similar across both arms. However, fewer drug-related AEs and drug-related Grade 3-5 AEs occurred among patients in the pembrolizumab 2 mg/kg Q3W arm compared to the docetaxel arm; and fewer discontinuations due to AEs or drug-related AEs occurred among patients in the pembrolizumab arm compared to the docetaxel arm. Deaths due to drug-related SAEs were infrequent across treatment arms.

No meaningful differences occurred in the safety profile of pembrolizumab-treated patients, regardless of dose or degree of PD-L1 expression. (Appendix 20)

- Drug-Related Adverse Events

Table 54 displays the number and percentage of patients in the overall APaT population (TPS≥1%) with drug-related AEs (incidence ≥5% in one or more treatment groups). Overall, more drug-related AEs occurred among patients in the docetaxel arm than the pembrolizumab arm (81.2% vs. 63.4%). The most common drug-related AEs in the pembrolizumab 2 mg/kg Q3W arm included: fatigue (13.6%), decreased appetite (13.6%), nausea (10.9%), and rash (8.6%). In the docetaxel 75 mg/m2 Q3W arm, the most common drug-related AEs included: alopecia (32.7%), fatigue (24.6%), and diarrhoea (18.1%).

Table 54: Drug-Related AEs (Incidence ≥ 5% in One or More Treatment Groups) - APaT Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Patients in population	309		339	
with one or more AEs	251	(81.2)	215	(63.4)
with no AEs	58	(18.8)	124	(36.6)
Blood and lymphatic system disorders	**87**	**(28.2)**	**19**	**(5.6)**
Anaemia	40	(12.9)	10	(2.9)
Neutropenia	44	(14.2)	1	(0.3)
Endocrine disorders	**1**	**(0.3)**	**35**	**(10.3)**
Hypothyroidism	1	(0.3)	25	(7.4)
Gastrointestinal disorders	**132**	**(42.7)**	**87**	**(25.7)**
Diarrhoea	56	(18.1)	24	(7.1)
Nausea	45	(14.6)	37	(10.9)
Stomatitis	43	(13.9)	13	(3.8)
Vomiting	24	(7.8)	12	(3.5)
General disorders and administration site conditions	**149**	**(48.2)**	**79**	**(23.3)**
Asthenia	35	(11.3)	20	(5.9)
Fatigue	76	(24.6)	46	(13.6)
Oedema peripheral	21	(6.8)	5	(1.5)
Pyrexia	17	(5.5)	10	(2.9)
Infections and infestations	**34**	**(11.0)**	**17**	**(5.0)**
Investigations	**42**	**(13.6)**	**41**	**(12.1)**
Neutrophil count decreased	24	(7.8)	0	(0.0)
White blood cell count decreased	16	(5.2)	0	(0.0)
Metabolism and nutrition disorders	**63**	**(20.4)**	**63**	**(18.6)**
Decreased appetite	49	(15.9)	46	(13.6)
Musculoskeletal and connective tissue disorders	**57**	**(18.4)**	**39**	**(11.5)**
Arthralgia	18	(5.8)	13	(3.8)
Myalgia	29	(9.4)	9	(2.7)
Nervous system disorders	**80**	**(25.9)**	**28**	**(8.3)**
Dysgeusia	16	(5.2)	4	(1.2)
Neuropathy peripheral	28	(9.1)	2	(0.6)
Paraesthesia	17	(5.5)	3	(0.9)
Respiratory, thoracic and mediastinal disorders	**44**	**(14.2)**	**44**	**(13.0)**
Skin and subcutaneous tissue disorders	**127**	**(41.1)**	**64**	**(18.9)**

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Alopecia	101	(32.7)	3	(0.9)
Pruritus	5	(1.6)	25	(7.4)
Rash	14	(4.5)	29	(8.6)
Vascular disorders	**16**	**(5.2)**	**6**	**(1.8)**

Every patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose. (Database Cut-off Date: 30SEP2015).

The most common Grade 3 to 5 AEs (incidence >1%) reported for patients in the TPS≥1% population that received pembrolizumab 2 mg/kg Q3W were pneumonia (4.1%), dyspnoea (3.8%) and fatigue (3.5%). In the docetaxel 75 mg/m2 Q3W arm the most common Grade 3 to 5 AEs reported were neutropenia (13.6%), neutrophil count decreased (6.5%), fatigue (5.5%), febrile neutropenia (5.5%), and pneumonia (5.5%).

- Drug-Related Grade 3 to 5 Adverse Events

Table 55 displays the number of patients in the TPS≥1% population with drug-related Grade 3 to 5 AEs (incidence >0% in one or more treatment groups). The most common drug-related Grade 3 to 5 AEs (incidence >1%) in the pembrolizumab 2 mg/kg Q3W arm was fatigue (1.2%). In the docetaxel 75 mg/m2 Q3W arm, the most common drug-related Grade 3 to 5 AEs (incidence >1%) were neutropenia (12.3%), neutrophil count decreased (6.1%), and febrile neutropenia (4.9%).

No meaningful differences in safety profile occurred for pembrolizumab-treated patients, regardless of dose or degree of PD-L1 expression (Appendix 20).

Table 55: Grade 3-5 Drug-Related AEs (Incidence > 0% in One or More Treatment Groups) - APaT Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Patients in population	309		339	
with one or more AEs	109	(35.3)	43	(12.7)
with no AEs	200	(64.7)	296	(87.3)
Blood and lymphatic system disorders	**55**	**(17.8)**	**3**	**(0.9)**
Anaemia	5	(1.6)	3	(0.9)
Bone marrow failure	1	(0.3)	0	(0.0)
Febrile neutropenia	15	(4.9)	0	(0.0)
Granulocytopenia	1	(0.3)	0	(0.0)
Leukopenia	8	(2.6)	0	(0.0)
Microcytic anaemia	0	(0.0)	0	(0.0)
Neutropenia	38	(12.3)	0	(0.0)
Thrombocytopenia	1	(0.3)	0	(0.0)
Cardiac disorders	**3**	**(1.0)**	**0**	**(0.0)**
Arteriosclerosis coronary artery	1	(0.3)	0	(0.0)
Atrial fibrillation	2	(0.6)	0	(0.0)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Atrioventricular block complete	0	(0.0)	0	(0.0)
Cardiac failure acute	1	(0.3)	0	(0.0)
Myocardial infarction	0	(0.0)	0	(0.0)
Pericardial effusion	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**
Tinnitus	0	(0.0)	0	(0.0)
Vertigo	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**1**	**(0.3)**
Adrenal insufficiency	0	(0.0)	0	(0.0)
Hyperthyroidism	0	(0.0)	0	(0.0)
Hypopituitarism	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**14**	**(4.5)**	**6**	**(1.8)**
Abdominal pain upper	1	(0.3)	0	(0.0)
Colitis	0	(0.0)	3	(0.9)
Colitis ischaemic	1	(0.3)	0	(0.0)
Diarrhoea	7	(2.3)	2	(0.6)
Dysphagia	0	(0.0)	1	(0.3)
Gastritis	0	(0.0)	0	(0.0)
Gastrointestinal inflammation	1	(0.3)	0	(0.0)
Nausea	1	(0.3)	1	(0.3)
Stomatitis	3	(1.0)	0	(0.0)
Vomiting	2	(0.6)	0	(0.0)
General disorders and administration site conditions	**23**	**(7.4)**	**6**	**(1.8)**
Adverse drug reaction	1	(0.3)	0	(0.0)
Asthenia	6	(1.9)	1	(0.3)
Fatigue	11	(3.6)	4	(1.2)
General physical health deterioration	1	(0.3)	0	(0.0)
Infusion site extravasation	1	(0.3)	0	(0.0)
Mucosal inflammation	1	(0.3)	0	(0.0)
Oedema	2	(0.6)	0	(0.0)
Pyrexia	1	(0.3)	1	(0.3)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(0.3)**
Autoimmune hepatitis	0	(0.0)	1	(0.3)
Cholestasis	0	(0.0)	0	(0.0)
Infections and infestations	**13**	**(4.2)**	**3**	**(0.9)**
Laryngitis	1	(0.3)	0	(0.0)
Lung infection	1	(0.3)	0	(0.0)
Mucosal infection	1	(0.3)	0	(0.0)
Phlebitis infective	1	(0.3)	0	(0.0)
Pneumonia	4	(1.3)	3	(0.9)
Pneumonia bacterial	1	(0.3)	0	(0.0)
Rash pustular	0	(0.0)	0	(0.0)
Respiratory tract infection	1	(0.3)	0	(0.0)
Sepsis	1	(0.3)	0	(0.0)
Septic shock	1	(0.3)	0	(0.0)
Upper respiratory tract infection	2	(0.6)	0	(0.0)
Urinary tract infection	2	(0.6)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.3)**	**1**	**(0.3)**
Femur fracture	1	(0.3)	0	(0.0)
Pneumonitis chemical	0	(0.0)	1	(0.3)
Investigations	**25**	**(8.1)**	**2**	**(0.6)**
Alanine aminotransferase increased	0	(0.0)	2	(0.6)
Amylase increased	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	0	(0.0)	2	(0.6)
Blood albumin increased	0	(0.0)	0	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)
Gamma-glutamyl transferase increased	1	(0.3)	0	(0.0)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Lymphocyte count decreased	1	(0.3)	0	(0.0)
Neutrophil count decreased	19	(6.1)	0	(0.0)
Platelet count decreased	1	(0.3)	0	(0.0)
Transaminases increased	0	(0.0)	0	(0.0)
Weight decreased	0	(0.0)	0	(0.0)
White blood cell count decreased	10	(3.2)	0	(0.0)
White blood cell count increased	1	(0.3)	0	(0.0)
Metabolism and nutrition disorders	**8**	**(2.6)**	**8**	**(2.4)**
Decreased appetite	3	(1.0)	3	(0.9)
Dehydration	3	(1.0)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)
Diabetic ketoacidosis	0	(0.0)	0	(0.0)
Hyperamylasaemia	0	(0.0)	0	(0.0)
Hypercalcaemia	0	(0.0)	1	(0.3)
Hyperglycaemia	0	(0.0)	0	(0.0)
Hypertriglyceridaemia	0	(0.0)	1	(0.3)
Hypokalaemia	1	(0.3)	1	(0.3)
Hyponatraemia	0	(0.0)	1	(0.3)
Hypophosphataemia	1	(0.3)	0	(0.0)
Iron deficiency	1	(0.3)	0	(0.0)
Type 1 diabetes mellitus	0	(0.0)	1	(0.3)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.3)**
Arthralgia	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	1	(0.3)
Back pain	0	(0.0)	1	(0.3)
Bone pain	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.3)**
Malignant neoplasm progression	0	(0.0)	0	(0.0)
Paraneoplastic syndrome	0	(0.0)	1	(0.3)
Nervous system disorders	**4**	**(1.3)**	**2**	**(0.6)**
Cerebrovascular accident	0	(0.0)	1	(0.3)
Dizziness	1	(0.3)	0	(0.0)
Myelitis transverse	0	(0.0)	0	(0.0)
Neuropathy peripheral	1	(0.3)	0	(0.0)
Polyneuropathy	2	(0.6)	0	(0.0)
Toxic leukoencephalopathy	0	(0.0)	1	(0.3)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.3)**
Confusional state	0	(0.0)	1	(0.3)
Disorientation	0	(0.0)	0	(0.0)
Renal and urinary disorders	**1**	**(0.3)**	**2**	**(0.6)**
Acute kidney injury	1	(0.3)	1	(0.3)
Tubulointerstitial nephritis	0	(0.0)	1	(0.3)
Reproductive system and breast disorders	**0**	**(0.0)**	**0**	**(0.0)**
Pruritus genital	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**8**	**(2.6)**	**10**	**(2.9)**
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.3)
Dyspnoea	4	(1.3)	2	(0.6)
Hypoxia	0	(0.0)	0	(0.0)
Interstitial lung disease	1	(0.3)	0	(0.0)
Pleural effusion	2	(0.6)	1	(0.3)
Pneumonia aspiration	1	(0.3)	0	(0.0)
Pneumonitis	1	(0.3)	6	(1.8)
Pulmonary embolism	0	(0.0)	1	(0.3)
Skin and subcutaneous tissue disorders	**4**	**(1.3)**	**3**	**(0.9)**
Alopecia	2	(0.6)	0	(0.0)
Drug eruption	0	(0.0)	0	(0.0)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Lichen planus	0	(0.0)	0	(0.0)
Onycholysis	1	(0.3)	0	(0.0)
Pruritus	1	(0.3)	0	(0.0)
Psoriasis	0	(0.0)	1	(0.3)
Rash	0	(0.0)	1	(0.3)
Rash maculo-papular	0	(0.0)	1	(0.3)
Vascular disorders	**1**	**(0.3)**	**0**	**(0.0)**
Embolism	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)
Hypotension	1	(0.3)	0	(0.0)
Peripheral ischaemia	0	(0.0)	0	(0.0)

Every patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose. (Database Cut-off Date: 30SEP2015).

- Drug-Related Serious Adverse Events

Table 56 displays drug-related SAEs up to 90 days after the last dose of study medication (incidence >0% in one or more treatment groups) for patients in the TPS≥1% population. Among pembrolizumab-treated patients, the most common drug-related SAE was pneumonitis (2.1%); all other drug-related SAEs occurred in less than 1% of patients. By contrast, among docetaxel-treated patients, the most common drug-related SAEs were febrile neutropenia (3.2%) and pneumonia (1.3%).

No meaningful differences in safety profile occurred for pembrolizumab-treated patients, regardless of dose or degree of PD-L1 expression (Appendix 20).

Table 56: Drug-Related SAEs Up to 90 Days After Last Dose (Incidence > 0% in One or More Treatment Groups) - APaT Population (TPS ≥1%)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Patients in population	309		339	
with one or more adverse events	42	(13.6)	32	(9.4)
with no adverse events	267	(86.4)	307	(90.6)
Blood and lymphatic system disorders	**15**	**(4.9)**	**0**	**(0.0)**
Anaemia	0	(0.0)	0	(0.0)
Bone marrow failure	1	(0.3)	0	(0.0)
Eosinophilia	0	(0.0)	0	(0.0)
Febrile neutropenia	10	(3.2)	0	(0.0)
Leukopenia	1	(0.3)	0	(0.0)
Microcytic anaemia	0	(0.0)	0	(0.0)
Neutropenia	4	(1.3)	0	(0.0)
Cardiac disorders	**2**	**(0.6)**	**0**	**(0.0)**
Arteriosclerosis coronary artery	1	(0.3)	0	(0.0)
Atrial fibrillation	1	(0.3)	0	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)
Cardiac failure acute	1	(0.3)	0	(0.0)
Myocardial infarction	0	(0.0)	0	(0.0)
Pericardial effusion	0	(0.0)	0	(0.0)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Endocrine disorders	**0**	**(0.0)**	**2**	**(0.6)**
Adrenal insufficiency	0	(0.0)	0	(0.0)
Hyperthyroidism	0	(0.0)	0	(0.0)
Hypopituitarism	0	(0.0)	1	(0.3)
Hypothyroidism	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**4**	**(1.3)**	**4**	**(1.2)**
Colitis	0	(0.0)	3	(0.9)
Colitis ischaemic	1	(0.3)	0	(0.0)
Diarrhoea	2	(0.6)	0	(0.0)
Gastritis	0	(0.0)	0	(0.0)
Gastrooesophageal reflux disease	0	(0.0)	0	(0.0)
Pancreatitis	0	(0.0)	1	(0.3)
Vomiting	1	(0.3)	0	(0.0)
General disorders and administration site conditions	**4**	**(1.3)**	**1**	**(0.3)**
Asthenia	0	(0.0)	0	(0.0)
Fatigue	0	(0.0)	1	(0.3)
General physical health deterioration	1	(0.3)	0	(0.0)
Mucosal inflammation	1	(0.3)	0	(0.0)
Oedema	1	(0.3)	0	(0.0)
Pyrexia	1	(0.3)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(0.3)**
Autoimmune hepatitis	0	(0.0)	1	(0.3)
Infections and infestations	**12**	**(3.9)**	**3**	**(0.9)**
Laryngitis	1	(0.3)	0	(0.0)
Lung infection	1	(0.3)	0	(0.0)
Mucosal infection	1	(0.3)	0	(0.0)
Phlebitis infective	1	(0.3)	0	(0.0)
Infections and infestations	**12**	**(3.9)**	**3**	**(0.9)**
Pneumonia	4	(1.3)	3	(0.9)
Pneumonia bacterial	1	(0.3)	0	(0.0)
Respiratory tract infection	1	(0.3)	0	(0.0)
Sepsis	1	(0.3)	0	(0.0)
Septic shock	1	(0.3)	0	(0.0)
Upper respiratory tract infection	3	(1.0)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.3)**	**1**	**(0.3)**
Femur fracture	1	(0.3)	0	(0.0)
Pneumonitis chemical	0	(0.0)	1	(0.3)
Investigations	**1**	**(0.3)**	**1**	**(0.3)**
Alanine aminotransferase increased	0	(0.0)	1	(0.3)
Aspartate aminotransferase increased	0	(0.0)	1	(0.3)
Neutrophil count decreased	1	(0.3)	0	(0.0)
Metabolism and nutrition disorders	**4**	**(1.3)**	**2**	**(0.6)**
Decreased appetite	1	(0.3)	1	(0.3)
Dehydration	3	(1.0)	0	(0.0)
Diabetes mellitus	0	(0.0)	0	(0.0)
Diabetic ketoacidosis	0	(0.0)	0	(0.0)
Hypertriglyceridaemia	0	(0.0)	0	(0.0)
Hyponatraemia	0	(0.0)	0	(0.0)
Hypophosphataemia	0	(0.0)	0	(0.0)
Type 1 diabetes mellitus	0	(0.0)	1	(0.3)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**4**	**(1.2)**
Arthralgia	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	1	(0.3)
Muscle necrosis	0	(0.0)	1	(0.3)
Myopathy	0	(0.0)	1	(0.3)
Synovitis	0	(0.0)	1	(0.3)
Neoplasms benign, malignant and unspecified (incl	**0**	**(0.0)**	**0**	**(0.0)**

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
cysts and polyps)				
Malignant neoplasm progression	0	(0.0)	0	(0.0)
Nervous system disorders	**1**	**(0.3)**	**2**	**(0.6)**
Cerebrovascular accident	0	(0.0)	1	(0.3)
Cognitive disorder	1	(0.3)	0	(0.0)
Myelitis transverse	0	(0.0)	0	(0.0)
Toxic leukoencephalopathy	0	(0.0)	1	(0.3)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.3)**
Confusional state	0	(0.0)	1	(0.3)
Disorientation	0	(0.0)	0	(0.0)
Renal and urinary disorders	**1**	**(0.3)**	**1**	**(0.3)**
Acute kidney injury	1	(0.3)	0	(0.0)
Tubulointerstitial nephritis	0	(0.0)	1	(0.3)
Respiratory, thoracic and mediastinal disorders	**8**	**(2.6)**	**11**	**(3.2)**
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.3)
Dyspnoea	3	(1.0)	1	(0.3)
Interstitial lung disease	1	(0.3)	0	(0.0)
Pleural effusion	2	(0.6)	2	(0.6)
Pneumonia aspiration	1	(0.3)	0	(0.0)
Pneumonitis	2	(0.6)	7	(2.1)
Pulmonary embolism	0	(0.0)	1	(0.3)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**1**	**(0.3)**
Drug eruption	0	(0.0)	0	(0.0)
Rash maculo-papular	0	(0.0)	1	(0.3)
Vascular disorders	**1**	**(0.3)**	**0**	**(0.0)**
Hypotension	1	(0.3)	0	(0.0)
Peripheral ischaemia	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
SAE is monitored until 90 days after last dose. (Database Cut-off Date: 30SEP2015).

- Adverse Events of Special Interest (AEOSI)

The analysis of AEOSI was the primary method of assessing immune-related AEs (irAE) for this study and was based on a compiled list of preferred AE terms potentially associated with an immune etiology. An irAE was defined as an AE of unknown etiology, which is consistent with an immune phenomenon and is temporally associated with drug exposure.

The AEOSI are presented regardless of Investigator-assessed causality and generally include all AE grades (with the exception of severe skin reactions). In an attempt to capture all informative data, the list of terms is intentionally broad; consequently, some reported terms may not have an obvious immune mechanism.

Table 57 displays a summary of AEOSI in the overall (TPS≥1%) population. AEOSI were more common among pembrolizumab-treated patients compared to docetaxel-treated patients (20.4% vs. 4.2%, respectively), as expected, due to the immune activity of pembrolizumab.

The true incidence of AEOSI is likely overestimated since it includes events regardless of attribution by the Investigator.

Most AEOSI were Grade 1 or 2 in severity, as only 5.3% of pembrolizumab-treated patients experienced Grade 3 to 5 AEOSI (compared to 1.3% docetaxel-treated patients); and most AEOSI were manageable with corticosteroid treatment, interruption of pembrolizumab administration, or both. No meaningful differences occurred between the docetaxel and pembrolizumab arm in the rates of deaths due to AEOSI, discontinuations due to AEOSI (2.1% of patients on pembrolizumab vs. 1.6% of patients on docetaxel), or discontinuations due to AEOSI categorized as SAEs (1.5% of patients on pembrolizumab vs. 1.0% of patients on docetaxel) (Table 57).

No meaningful differences in safety profile occurred for pembrolizumab-treated patients, regardless of dose or degree of PD-L1 expression.

Table 57: Summary AEOSI - APaT Population (TPS ≥1%)

Patients in population	Docetaxel 75 mg/m2 Q3W N=309 n (%)	Pembrolizumab 2 mg/kg Q3W N=339 n (%)
with one or more AEs	13 (4.2)	69 (20.4)
with no AE	296 (95.8)	270 (79.6)
with drug-related† AEs	7 (2.3)	59 (17.4)
with toxicity grade 3-5 AEs	4 (1.3)	19 (5.6)
with toxicity grade 3-5 drug-related AEs	3 (1.0)	16 (4.7)
with serious adverse events (SAEs)	5 (1.6)	21(6.2)
with drug-related SAEs	3 (1.0)	18 (5.3)
who died	2 (0.6)	2 (0.6)
who died due to a drug-related AE	1(0.3)	2 (0.6)
discontinued‡ due to an AE	5 (1.6)	7(2.1)
discontinued due to a drug-related AE	5 (1.6)	7 (2.1)
discontinued due to a SAE	3 (1.0)	5 (1.5)
discontinued due to drug-related SAE	3 (1.0)	5 (1.5)

† Determined by the investigator to be related to the drug. ‡ Study medication withdrawn.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose. AEs of special interest per ECI guidance excluding Infusion Reactions. Database Cut-off Date: 30SEP2015

The most common AEOSI among pembrolizumab 2mg/Kg Q3W treated patients in the overall (TPS≥1%) population included hypothyroidism (8.3%), hyperthyroidism (3.5%), and pneumonitis (4.4%) (including 1.8% Grade 3 to 5 pneumonitis).

Further details on AEOSI (incidence > 0%) in One or More Treatment Groups in the TPS≥1% population are provided in Appendix 15.

Selected AEs of potential immune etiology were pre-specified in KEYNOTE-010, including:

1. Grade ≥3 diarrhoea
2. Grade ≥3 colitis
3. Grade ≥2 pneumonitis

4. Grade ≥3 hypothyroidism or hyperthyroidism

Table 58 shows a comparison of the incidence of those AEs between the pembrolizumab 2mg/kg Q3W arm and the docetaxel arm in the TPS≥1% population. Diarrhoea (Grade ≥3) occurred more in patients in the docetaxel arm (2.6%) than in the pembrolizumab 2mg/kg Q3W arm (0.9%), and pneumonitis (Grade ≥2) occurred more in patients in the pembrolizumab 2mg/kg Q3W arm (3.5%) than in the docetaxel arm (1.3%).

Table 58: Summary of pre-specified AEs of potential immune etiology - APaT Population (TPS ≥1%)

Treatment	n (%)	Difference in % vs Docetaxel 75 mg/m2 Q3W	
		Estimate (95% CI)†	p-value†
Patients in population			
Pembrolizumab 2 mg/kg Q3W Docetaxel 75 mg/m2 Q3W	339 309		
Grade ≥ 3 Diarrhoea with a potential immunologic etiology			
Pembrolizumab 2 mg/kg Q3W Docetaxel 75 mg/m2 Q3W	3 (0.9) 8 (2.6)	-1.7 (-4.3, 0.4)	0.096
Grade ≥ 2 Colitis with a potential immunologic etiology			
Pembrolizumab 2 mg/kg Q3W Docetaxel 75 mg/m2 Q3W	3 (0.9) 0 (0.0)	0.9 (-0.3, 2.7)	0.095
Grade ≥ 2 Pneumonitis with a potential immunologic etiology			
Pembrolizumab 2 mg/kg Q3W Docetaxel 75 mg/m2 Q3W	12 (3.5) 4(1.3)	2.2 (-0.3, 4.8)	0.080
Grade ≥ 3 Hypo- or hyperthyroidism with a potential immunologic etiology			
Pembrolizumab 2 mg/kg Q3W Docetaxel 75 mg/m2 Q3W	0 (0.0) 0 (0.0)	0.0 (-1.3, 1.1)	>0.999

† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (TPS≥50% , TPS1-49% and Unknown PD-L1 status). Every patient is counted a single time for each applicable specific adverse event category.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.

KEYNOTE-001: Adverse reactions[35;85;86;89]

Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, ECG measurements, and vital signs reported during the treatment period up to the data cut-off of 23-Jan-2015, which provides a minimum of 6.4 months of follow up for all cohorts.

AEs were summarised as counts and frequencies for each dose level and included events from the first dose up to 30 days after the last dose. SAEs counts and listings include events

from the first dose up to 90 days after the last dose to account for the extended safety follow-up period.

The safety data presented in this section refers to the 550 patients who received at least one dose of pembrolizumab, the All Patients with NSCLC Population.

Overall Extent of Exposure - All Patients with NSCLC (N=550)

Table 59 displays the summary of drug exposure by PD-L1 status for the All Patients with NSCLC Population. In patients with PD-L1 expression proportion score (TPS) ≥50% the median time on pembrolizumab was 171 days (range 1 to 925 days) versus 99 days for the total population of 550 patients. The median number of administrations was 10 for patients whose baseline tumours had a PD-L1 TPS≥50% compared to 5 or 6 for other PD-L1 subgroups.

Table 59: KEYNOTE-001 - Summary of Drug Exposure All Patients with NSCLC by PD-L1 (Irrespective of Stability Window) - APaT

	PS>=50%	PS=1-49%	PS<1%	Unknown	Total
	N=165	N=220	N=102	N=63	N=550
Study Days On-Therapy (days)					
Mean	207.78	148.51	141.76	182.17	168.90
Median	171.00	88.50	82.50	77.00	99.00
SD	184.40	141.38	151.74	226.50	170.11
Range	1.00 to 925.00	1.00 to 587.00	1.00 to 601.00	1.00 to 925.00	1.00 to 925.00
Number Administrations					
Mean	11.83	9.00	9.07	10.86	10.07
Median	10.00	6.00	5.00	5.00	6.00
SD	10.04	8.09	9.26	12.50	9.56
Range	1.00 to 45.00	1.00 to 42.00	1.00 to 42.00	1.00 to 45.00	1.00 to 45.00

Database Cut-off Date: 23JAN2015

Adverse Events - All Patients with NSCLC (N=550)

Table 60 shows the AE summary for All Patients with NSCLC by Dose:

Table 60: KEYNOTE-001 - Adverse Event Summary - All Patients with NSCLC by Dose - APaT

	Pembrolizumab 2 mg/kg Q3W n (%)	Pembrolizumab 10 mg/kg Q3W n (%)	Pembrolizumab 10 mg/kg Q2W n (%)	Total n (%)
Patients in population	61	287	202	550
with one or more AEs	58 (95.1)	276 (96.2)	197 (97.5)	531 (96.5)
with no AE	3 (4.9)	11 (3.8)	5 (2.5)	19 (3.5)
with drug-related† AEs	31 (50.8)	201 (70.0)	148 (73.3)	380 (69.1)
with toxicity grade 3-5 AEs	26 (42.6)	130 (45.3)	94 (46.5)	250 (45.5)
with toxicity grade 3-5 drug-related AEs	5 (8.2)	34 (11.8)	19 (9.4)	58 (10.5)
with SAEs	27 (44.3)	108 (37.6)	82 (40.6)	217 (39.5)
with drug-related SAEs	6 (9.8)	23 (8.0)	13 (6.4)	42 (7.6)
who died	2 (3.3)	7 (2.4)	6 (3.0)	15 (2.7)
who died due to a drug-related AE	1 (1.6)	1 (0.3)	0 (0.0)	2 (0.4)
discontinued‡ due to an AE	9 (14.8)	40 (13.9)	30 (14.9)	79 (14.4)
discontinued due to a drug-related AE	4 (6.6)	11 (3.8)	8 (4.0)	23 (4.2)
discontinued due to a SAE	9 (14.8)	30 (10.5)	22 (10.9)	61 (11.1)
discontinued due to a drug-related SAE	4 (6.6)	8 (2.8)	6 (3.0)	18 (3.3)

† Determined by the investigator to be related to the drug. ‡ Study medication withdrawn.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded. Database Cut-off Date: 23JAN2015

In general, pembrolizumab was well tolerated with 10.5% of patients experiencing a Grade 3 5 treatment related AE. Only 4.2% of patients discontinued due to a treatment related adverse event. There were 2 deaths reported due to treatment-related AEs (cardiorespiratory arrest and interstitial lung disease). The 2 mg/kg dose has a lower overall incidence of AEs in the current data set; however, this is most likely due to the much shorter duration of safety follow-up in this subpopulation.

- Drug Related AEs (≥5%)

Table 61 displays the incidence of specific drug-related AEs (≥5%) in All Patients with NSCLC (N=550) who received at least one dose of pembrolizumab, by dose. Drug-related AEs occurred in 69.1% of patients. The most common drug-related AEs were fatigue (18.9%), pruritus (10.7%), decreased appetite (10.2%), rash (9.1%), and arthralgias (8.9%). The drug-related AE rates are lower in the 2 mg/kg group relative to the 10 mg/kg groups, likely because the duration of follow-up for the 2 mg/kg group is not as mature as for the 10 mg/kg groups.

Table 61: KEYNOTE-001 - Patients with Drug-Related AEs (Incidence ≥ 5% in One or More Treatment Groups) All Patients with NSCLC by Dose - APaT

	Pembrolizumab 2 mg/kg Q3W		Pembrolizumab 10 mg/kg Q3W		Pembrolizumab 10 mg/kg Q2W		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	61		287		202		550	
with one or more AEs	31	(50.8)	201	(70.0)	148	(73.3)	380	(69.1)
with no AEs	30	(49.2)	86	(30.0)	54	(26.7)	170	(30.9)
Blood and lymphatic system disorders	**1**	**(1.6)**	**13**	**(4.5)**	**13**	**(6.4)**	**27**	**(4.9)**
Anaemia	1	(1.6)	10	(3.5)	10	(5.0)	21	(3.8)
Endocrine disorders	**4**	**(6.6)**	**23**	**(8.0)**	**21**	**(10.4)**	**48**	**(8.7)**
Hypothyroidism	4	(6.6)	16	(5.6)	20	(9.9)	40	(7.3)
Gastrointestinal disorders	**11**	**(18.0)**	**67**	**(23.3)**	**47**	**(23.3)**	**125**	**(22.7)**
Diarrhoea	5	(8.2)	27	(9.4)	15	(7.4)	47	(8.5)
Nausea	1	(1.6)	25	(8.7)	15	(7.4)	41	(7.5)
General disorders and administration site conditions	**12**	**(19.7)**	**101**	**(35.2)**	**62**	**(30.7)**	**175**	**(31.8)**
Asthenia	4	(6.6)	12	(4.2)	15	(7.4)	31	(5.6)
Fatigue	4	(6.6)	65	(22.6)	35	(17.3)	104	(18.9)
Pyrexia	4	(6.6)	12	(4.2)	9	(4.5)	25	(4.5)
Infections and infestations	**0**	**(0.0)**	**11**	**(3.8)**	**10**	**(5.0)**	**21**	**(3.8)**
Investigations	**3**	**(4.9)**	**38**	**(13.2)**	**26**	**(12.9)**	**67**	**(12.2)**
Metabolism and nutrition disorders	**7**	**(11.5)**	**44**	**(15.3)**	**20**	**(9.9)**	**71**	**(12.9)**
Decreased appetite	4	(6.6)	36	(12.5)	16	(7.9)	56	(10.2)
Musculoskeletal and connective tissue disorders	**3**	**(4.9)**	**43**	**(15.0)**	**39**	**(19.3)**	**85**	**(15.5)**
Arthralgia	2	(3.3)	25	(8.7)	22	(10.9)	49	(8.9)
Nervous system disorders	**3**	**(4.9)**	**18**	**(6.3)**	**14**	**(6.9)**	**35**	**(6.4)**
Respiratory, thoracic and mediastinal disorders	**6**	**(9.8)**	**37**	**(12.9)**	**23**	**(11.4)**	**66**	**(12.0)**
Skin and subcutaneous tissue disorders	**9**	**(14.8)**	**77**	**(26.8)**	**48**	**(23.8)**	**134**	**(24.4)**
Dry skin	0	(0.0)	8	(2.8)	11	(5.4)	19	(3.5)
Pruritus	4	(6.6)	33	(11.5)	22	(10.9)	59	(10.7)
Rash	2	(3.3)	30	(10.5)	18	(8.9)	50	(9.1)

Every Patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. (Database Cut-off Date: 23JAN2015)

The most common drug-related Grade 3 to 5 AE in the All Patients with NSCLC population was pneumonitis (1.8%). All other drug-related Grade 3 to 5 AEs occurred in less than 1% of patients. The overall incidence of drug-related SAEs in the All Patients with NSCLC population was relatively low (8.4%). The most common drug-related SAE was pneumonitis (2.5%). All other drug-related SAEs were reported in less than 1% of patients.

4.12.3 Studies that report additional adverse reactions to those reported in section 4.2

The search strategy used to identify studies which reported AEs was consistent with that described in section 4.1 (see Appendix 2). No additional studies were identified.

4.12.4 Brief overview of the safety of the technology in relation to the decision problem

Safety data from KEYNOTE-010 demonstrates a favourable safety profile for pembrolizumab compared to docetaxel, with fewer treatment-related AEs of all severities.

Pembrolizumab is well-tolerated by patients with previously treated advanced NSCLC whose tumour cells express PD-L1; few patients required discontinuation of pembrolizumab due to an AE, and deaths due to drug-related AEs were rare. The most common AEOSI in the overall (TPS≥1%) population treated with pembrolizumab 2mg/Kg Q3W included hypothyroidism (8.3%), hyperthyroidism (3.5%), and pneumonitis (4.4%). Most AEOSI were Grade 1 or 2 in severity and were manageable with corticosteroid treatment, interruption of pembrolizumab administration, or both. Only 7 (2.1%) patients treated with pembrolizumab 2mg/Kg Q3W discontinued treatment due to an AEOSI.

No clinically meaningful difference in the safety profile was observed for patients treated with pembrolizumab at 2 mg/kg Q3W vs. 10 mg/kg Q3W, regardless of degree of PD-L1 expression.

Safety data from KEYNOTE-001 demonstrates that pembrolizumab is well tolerated across all doses and schedules tested, 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Safety was also equivalent between the two PD-L1 cut points tested in the study (TPS≥50% stratum and TPS≥1% population).

Overall the safety profile of pembrolizumab remains consistent with previously reported findings in patients with advanced melanoma, showing that pembrolizumab is well tolerated and the safety profile is acceptable for an advanced NSCLC population; and favourable when compared to chemotherapy.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Statement of principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

A summary of the main clinical effectiveness findings is provided below:

- **Pembrolizumab 2 mg/kg Q3W significantly prolonged OS compared to docetaxel.**

In the KEYNOTE-010 previously treated patients with advanced NSCLC who express PD-L1 (TPS≥1%), pembrolizumab 2mg/kg Q3W demonstrated superior OS compared to docetaxel, with a 29% reduction in the risk of death (HR 0.71, *p=0.00076*), based on the final analysis of KEYNOTE-010 (median follow up of 13 months, range 6 to 24 months). The median OS was 10.4 months for pembrolizumab 2 mg/kg Q3W and 8.5 months for docetaxel. The OS curve of pembrolizumab began to separate from the docetaxel arm around Month 4, the separation from the curve of docetaxel increased over time without crossing. The OS superiority of pembrolizumab compared to docetaxel was found to be consistent across subgroups based on key prognostic factors for patients with advanced NSCLC.

Supportive data from KEYNOTE-001 provides supportive evidence of the longer term survival benefit of pembrolizumab treatment, after a median follow up of 16.2 months (range 10.9 to 32.3 months). In the Total Previously Treated Efficacy Population of KEYNOTE-001 (Cohorts C and F2) the median OS was 11.1 months for pembrolizumab patients with advanced NSLC who express PD-L1 (TPS≥1%), and the OS rate at 12 months was 48.8%.

In the NMA conducted to compare the relative treatment effects of pembrolizumab to nintedanib in combination with docetaxel in the adenocarcinoma population, pembrolizumab 2mg/Kg Q3W showed a non-statistically significant benefit for OS comparable to nintedanib in combination with docetaxel (HR 0.81; 95% CrI 0.59-1.10), and the reverse was the case for PFS (HR 1.04; 95% CrI 0.79, 1.36). Pembrolizumab also offered a more favourable safety profile in terms of discontinuations due to AEs and Grade 3 or 4 AEs. However, this comparison was limited by the fact that assessment of inconsistency assessment or adjustment for differences between trial populations was not possible due to the evidence base consisting of only two trials; and the fact that the proportional hazards assumption is not supported by the LUME-Lung 1 data. As the LUME-Lung 1 study is the only included trial providing evidence for nintedanib in combination with docetaxel, any estimation of the relative effectiveness of nintedanib in combination with docetaxel compared with pembrolizumab (that is a calculated hazard ratio) will lack credibility and invalidate the comparison. Moreover, the NMA relies on the assumption that that the efficacy of nintedanib in combination with docetaxel does not depend on PD-L1 expression and that the reported trial subgroups were comparable.

- **Pembrolizumab 2 mg/kg Q3W improved PFS compared to docetaxel.**

In the KEYNOTE-010 previously treated patients with advanced NSCLC who express PD-L1 (TPS≥1%), pembrolizumab provided numerically superior benefit in PFS (based on IRC based on RECIST 1.1) compared to docetaxel (HR 0.88, *p=0.06758*). Median PFS was 3.9

months for pembrolizumab 2mg/Kg Q3W and 4.0 months for docetaxel. From around Month 6 the PFS curve of pembrolizumab arm began to separate from the docetaxel arm and remained separated from the curve of docetaxel all the way towards the tail end when the majority of patients in the docetaxel arm had PFS events. This is reflected by a 6 month PFS rate of 35.1% (95%CI: 30.0%, 40.3%) in the pembrolizumab 2mg/Kg Q3W arm, compared to 34.3% (95%CI: 28.8%, 39.8%) in the docetaxel arm; and a 12-month PFS rate of 17.5% (95%CI: 13.1%, 22.4%) in the pembrolizumab 2mg/Kg Q3W arm, compared to 8.6% (95%CI: 5.1%, 13.1%) in the docetaxel arm.

The median PFS with pembrolizumab was longer when progression was assessed by irRC (median PFS 4.9 months for pembrolizumab 2mg/Kg and 4.0 months for docetaxel) and may be a better reflection of the PFS benefit with pembrolizumab (HR 0.76, *p=0.00174* in the pembrolizumab 2 mg/kg Q3W arm vs. the docetaxel arm).

- **Pembrolizumab 2 mg/kg Q3W resulted in a higher ORR and longer response duration compared to docetaxel.**

In the KEYNOTE-010 previously treated patients with advanced NSCLC who express PD-L1 (TPS≥1%), pembrolizumab 2 mg/kg Q3W produced a clinically meaningful and significant superior confirmed ORR (IRC per RECIST 1.1) of 18.0% compared to 9.3% in the docetaxel arm; with a median duration of response not reached (range 20+ - 610+) in the pembrolizumab 2 mg/kg Q3W arm compared to 189 days (range 43+ to 268+ days) for the docetaxel arm. Among the responders in the TPS≥1% population, at the time of data cut-off for the final analysis of KEYNOTE-010, 73% of responses in the pembrolizumab treated patients were ongoing compared to 34% of the docetaxel treated patients.

These results are supported by data first observed from KEYNOTE-001: ORR (IRC per RECIST 1.1) of 19.3% (95% CI: 15.5, 23.5) among the 394 advanced NSCLC patients in the Total Previously Treated Efficacy Population (Cohorts C and F2).

- **Pembrolizumab 2 mg/kg Q3W is well-tolerated by patients with previously treated NSCLC; and better tolerated than docetaxel.**

In KEYNOTE-010, the mean duration of study treatment was nearly 2-fold longer on pembrolizumab 2 mg/kg Q3W arm (151.1 days) compared to docetaxel arm (81.6 days). Despite the longer duration of exposure, fewer drug-related AEs and drug-related Grade 3-5 AEs; and fewer discontinuations due to AEs or drug-related AEs occurred among patients in the pembrolizumab 2 mg/kg Q3W arm compared to the docetaxel arm.

The most common AEOSI among pembrolizumab-treated patients in the overall (TPS≥1%) population included hypothyroidism (8.3%), hyperthyroidism (3.5%), and pneumonitis

(4.4%). Most of the AEOSIs were Grade 1 to 2 in severity and were manageable with corticosteroid treatment, interruption of pembrolizumab administration, or both.

- **There were no meaningful differences in efficacy or safety between the two pembrolizumab regimens, 2 mg/kg Q3W and 10 mg/kg Q3W.**

The primary efficacy results from KEYNOTE-010 demonstrate that pembrolizumab at either dose results in a similar, substantial, and clinically meaningful improvement in OS, PFS and ORR compared to docetaxel in previously treated patients with advanced NSCLC who express PD-L1 (TPS≥1%). The lack of a dose-response relationship corroborates prior results from KEYNOTE-001 advanced NSCLC data. The safety profile was also not notably different between patients treated with pembrolizumab at 2 mg/kg Q3W or 10 mg/kg Q3W.

- **PD-L1 is a biomarker which identifies patients more likely to benefit from treatment with pembrolizumab.**

In the KEYNOTE-001 previously treated patients with advanced NSCLC who express PD-L1 (TPS≥1%) from the Total Previously Treated Efficacy Population (Cohort C and F2), the median OS for pembrolizumab was 11.1 months - similar to the median OS observed in the KEYNOTE-010 patients (10.4 months, 95% CI 9.4, 11.9 months). This represents a clinically meaningful improvement compared to the 8.6 months median OS observed in the KEYNOTE-001 patients with advanced NSCLC who do not express PD-L1 (TPS<1%) (OS HR 0.81; 95% CI 0.57, 1.14 for PD-L1 expressers vs. PD-L1 non-expressers); or the median OS observed in the docetaxel arm of the KEYNOTE-010 (median OS 8.5 months) (see section 4.7). These results demonstrate that PD-L1 is a biomarker which identifies advanced NSCLC patients more likely to benefit from treatment with pembrolizumab.

4.13.2 Discussion of the strengths and limitations of the clinical evidence base for the technology

Internal Validity

KEYNOTE-010 was a multicentre, randomised, open label phase II/III trial of pembrolizumab at two doses versus docetaxel in adults with advanced NSCLC whose tumours express PD-L1 (based on prospective measure of more than one percent of viable tumour cells showing partial or complete IHC membrane staining; TPS ≥1%), who have experienced disease progression after at least a platinum-containing systemic therapy.

Randomisation was stratified by ECOG performance status (0 vs. 1)[78], geographic region of the enrolling site (East Asia vs. non-East Asia) and extent of tumour PD-L1 expression (TPS>50% vs. TPS=1-49%).

Because of uncertainty at the time of study design as to which dose schedule would have the better efficacy and safety profile in previously-treated patients with advanced NSCLC, two dosing schedules of pembrolizumab were tested in this study, 10 mg/kg Q3W and 2 mg/kg Q3W, with an opportunity to drop one dose early in the study based on Interim Analysis 1.

The primary efficacy endpoints were OS and PFS. Both are clinically relevant endpoints that were directly referenced in the final scope for this appraisal and the decision problem. OS is the gold standard endpoint to demonstrate superiority of antineoplastic therapy.

Although KEYNOTE-010 was conducted as an open-label study, to minimise bias, the independent radiologists who performed the central imaging review were blinded to treatment assignment. In addition, the study statistician remained blinded to treatment assignment until the final analysis was completed.

The treatment arms were well balanced by all baseline characteristics. KEYNOTE-010 was designed and powered to allow each pembrolizumab arm to independently demonstrate significant benefit versus docetaxel in both the TPS≥50% stratum and the overall study population whose tumours express PD-L1 (TPS≥1%) (see section 4.4.1).

Parts C, F2 and F3 of KEYNOTE-001 were phase II-like cohorts in previously treated patients with advanced NSCLC. Although KEYNOTE-001 does not provide comparative efficacy data, it provides useful longer term data supporting the clinical benefit of pembrolizumab in advanced NSCLC patients who express PDL1, and helps provide a comprehensive assessment of the clinical efficacy of pembrolizumab. In addition, KEYNOTE-001 study provides data on the validation of the Clinical Trial Assay (CTA) used to test PD-L1 expression; therefore, the assay used in KEYNOTE-010 was rigorously evaluated and validated before the study began.

External validity

KEYNOTE-010 was a global study conducted in 202 academic medical centres in 24 countries. Of the patients with advanced NSCLC included in this study, 47% patients were enrolled at sites in Europe (including 56 patients from the UK).

Baseline characteristics of patients enrolled in KEYNOTE-010 were as expected for patients with advanced NSCLC. The majority of patients were male, white, with mean age around 62 years old. Most patients were current or former smokers and had tumour of non-squamous histology (Table 17). It is important to note that almost one-third of patients in KEYNOTE-010 received at least two lines of previous treatment; consequently these patients might

have had a slightly poorer overall prognosis than those who would be expected to receive pembrolizumab in UK clinical practice, and therefore superior survival than that observed in KEYNOTE-010 is expected when expanding the use of pembrolizumab to the wider, eligible population in UK clinical practice.

Life expectancy of people with advanced NSCLC in England

Full details concerning the life expectancy of UK patients with advanced NSCLC have been provided in section 3.4 of the submission and are summarised in Table 62 below. Information concerning the estimated number of people with the particular therapeutic indication for which the technology is being appraised is also presented in section 3.4.

Table 62: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is lower than 24 months: • Patients with advanced NSCLC have a short life expectancy of less than 24 months (Health and Social Care Information Centre 2014).[74]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Pembrolizumab offers an extension to life of at least 3 months compared to docetaxel: • The average number of months of life gained with pembrolizumab as estimated by the economic model is between 21.2 and 22.8, compared to 10.4 months with docetaxel (see Table 100). • In the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the extension in OS gained by patients treated with pembrolizumab over their life time compared to those treated with nintedanib in combination with docetaxel is estimated to be at least 9.4 months (see Table 102)
The treatment is licensed or otherwise indicated for small patient populations	The number of patients eligible for treatment with pembrolizumab in 2017 is expected to be: - 1,795 patients with NSCLC that is PD-L1 positive - see section 6.2 - 1,121 patients with advanced melanoma previously untreated with ipilimumab[115]

4.14 Ongoing studies

Results provided in this submission are from the final analysis of KEYNOTE-010. Patients in KEYNOTE-010 treated with pembrolizumab 2mg/Kg Q3W continued to be followed up and a further survival analysis for the pembrolizumab 2mg/Kg Q3W arm will be conducted at the end of April with results available in May 2016.

5. Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Strategies used to retrieve cost-effectiveness studies relevant to decision-making in England

Relevant cost-effectiveness studies from the published literature were identified through a systematic literature search carried out during the period of 14th May 2015 and 15th May 2015, and updated in March 2016, for patients with advanced non-small cell lung cancer (NSCLC), following platinum-containing chemotherapy. The target population in this submission is focussed upon patients with advanced NSCLC previously treated with a platinum-based chemotherapy and whose tumours express PD-L1. However, the scope of the review was broadened in order to identify all relevant data that could inform the development and population of the model.

The first stage in the review was to identify all relevant economic evidence for the comparator treatments by implementing comprehensive searches. The following research questions were posed in accordance with the decision problem:

- What is the cost-effectiveness of comparator therapies to pembrolizumab in treating patients with advanced NSCLC, following platinum-containing chemotherapy?
- What is the health related quality of life (in terms of utilities) associated with advanced NSCLC, following platinum-containing chemotherapy?
- What are the resource requirements and costs associated with the treatment of advanced NSCLC, following platinum-containing chemotherapy?

A comprehensive literature search relative to these three research questions was carried out using several databases:

- MEDLINE and MEDLINE In-process (using Embase.com) - 1995 to 2016
- EconLit: No limit
- EMBASE (using Embase.com) – 1995 to 2016
- The Cochrane Library, including NHS EED and HTA databases – 1995 to 2016

Manual searches were also performed on the American Society of Clinical Oncology (ASCO) conference proceedings and ISPOR, with additional papers identified from the reference list of included papers. The manual searches were constrained to the most recent 3 years.

In addition to the formal literature search and manual searches, the National Institute for Health and Care Excellence (NICE) website was searched to identify relevant information from previous submissions not otherwise captured.

Table 63 provides details relative to the eligibility criteria for the cost-effectiveness literature search. Details of the search strategies conducted for the health related quality of life and utilities and resource and costs are provided in Appendix 23 and Appendix 26.

To determine which studies were eligible, explicit inclusion and exclusion criteria were applied when evaluating the literature search results. These selection criteria are detailed below for the cost-effectiveness search. The other two literature searches relative to the health related quality of life and utilities and resource and costs are provided Appendix 23 and Appendix 26 and are detailed in sections 5.4 and 5.5.

Table 63: Inclusion and exclusion criteria for cost-effectiveness studies

Criteria	Inclusion	Exclusion	Rationale
Population	Previously treated adults with advanced NSCLC, following platinum-containing chemotherapy	Treatment naïve advanced NSCLC Patients under the age of 18	The relevant patient population
Intervention/ Comparator	Studies comparing pembrolizumab vs. any other pharmacological treatment	Non-drug treatments (e.g. surgery, radiotherapy)	To allow all papers with relevant pharmacological interventions to be captured
Outcomes	Studies including a comparison of costs between the intervention and comparator arms. Results should be expressed in incremental costs and QALYs, and any other measure of effectiveness reported together with costs	Cost-only outcomes (without a cost-minimisation argument)	To identify relevant cost-effectiveness studies
Study type	Full economic evaluation comparing at least two interventions in terms of: cost-consequence cost-minimisation cost-effectiveness cost-utility and cost-benefit evaluations)	Burden of illness studies	To identify relevant cost-effectiveness studies
Publication type	Economic evaluations	Letters, editorials and review studies	To identify primary study articles
Language	Studies for which a full text version is available in	Not available in English	To ensure the studies can be correctly understood

Criteria	Inclusion	Exclusion	Rationale
	English		and interpreted
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed The study's data and results must be extractable	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated Studies that fail to present extractable results	To ensure data can be extractable To ensure methods can be replicated To ensure results can be validated
Key: *QALY, Quality-adjusted life year.*			

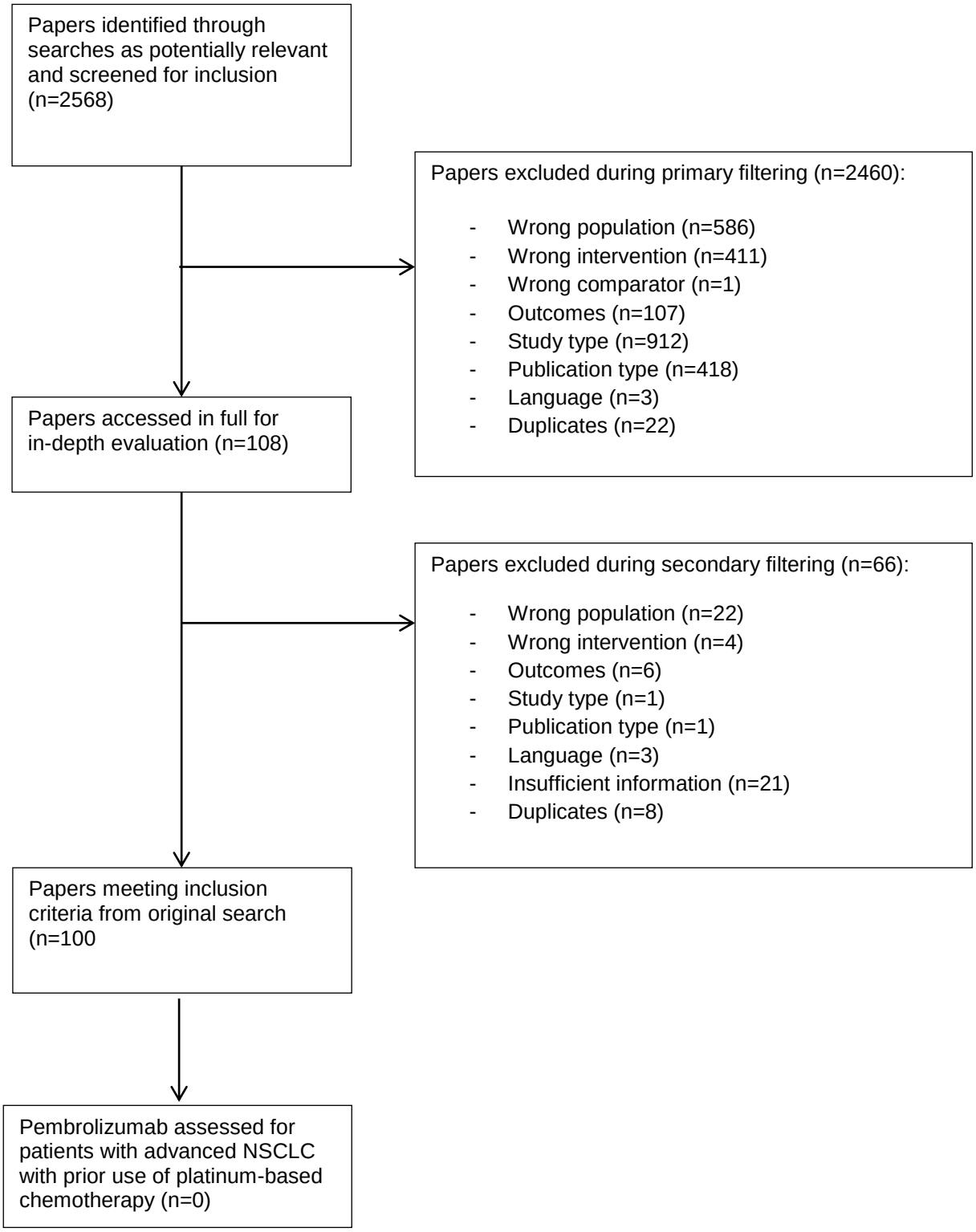
The above searches were conducted following the methodology for systematic review developed and published in 2009 by the Centre for Reviews and Dissemination (University of York).[116]

5.1.2 Brief description of identified cost-effectiveness studies

Of a total of 2,568 papers identified in the cost-effectiveness search, no cost-effectiveness studies assessing pembrolizumab for patients with advanced NSCLC, who had previously used platinum-containing chemotherapy, were found that met all the inclusion criteria (see Figure 28).

A summary list of published cost-effectiveness studies has not been compiled as no cost-effectiveness studies assessing pembrolizumab for patients with advanced NSCLC following platinum-containing chemotherapy, that met all the inclusion criteria, were identified.

Figure 28: PRISMA diagram: CEA studies*



Key: n, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**From the updated search conducted in March 2016, 290 additional hits were identified, none of them was included.

5.1.3 Complete quality assessment for each relevant cost-effectiveness study identified

This is not applicable as no cost-effectiveness study meeting all the inclusion criteria was identified, indicating a de novo cost-effectiveness model is required to assess the cost-effectiveness of pembrolizumab compared with relevant comparators.

5.2 De novo analysis

5.2.1 Patient population

The patient population included in the economic evaluation consisted of patients with advanced NSCLC that is PD-L1 positive, whose disease has progressed after platinum-containing doublet chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations.. This is in line with the anticipated licence indication and with the final NICE scope.[117]

The main body of clinical evidence for pembrolizumab was derived from the KEYNOTE-010, where patients included had received at least two cycles of a platinum-containing doublet for NSCLC stage IIIB/IV or recurrent disease. In addition, patients with an EGFR sensitising mutation or an ALK translocation should have demonstrated progression of disease on an EGFR TKI (either erlotinib, gefitinib or afatinib) or crizotinib, respectively.[16]

The baseline characteristics of the patients included in the model are presented in Table 64.

Table 64. Baseline characteristics of patients include in the model

Patient Characteristics	Mean	Measurement of uncertainty and distribution	Reference / Source
Average age	62	-	KEYNOTE-010
Proportion male	61.4%	-	KEYNOTE-010
Average weight (kg)	73.1	Normal (71.8, 74.5)	KEYNOTE-010
Average BSA (m^2)	1.84	Normal (1.82, 1.85)	KEYNOTE-010

5.2.2 Model structure

Based upon the previous cost-effectiveness models submitted to NICE within advanced or metastatic NSCLC, a de-novo economic analysis was built as a 'partitioned-survival' area-under-the-curve model. For the main analysis, two treatment arms were compared, including pembrolizumab and docetaxel. In additional analyses, focused on the adenocarcinoma

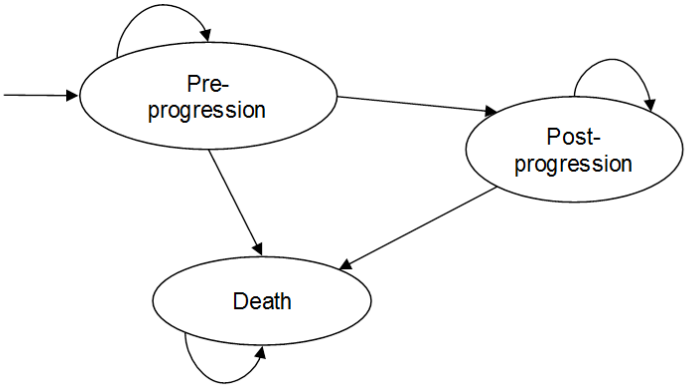
population, pembrolizumab was compared against docetaxel monotherapy and nintedanib combined with docetaxel.

Consistent with the majority of economic models previously developed for recent NICE oncology submissions in advanced NSCLC,[63;64;118] the model consisted of three health states: pre-progression, post-progression and death (see Figure 29). This approach was also in line with the clinical endpoints assessed in the pembrolizumab clinical trials, in which OS and PFS were either primary[16] or secondary endpoints.[85] A cycle length of one week was considered sufficient to reflect the patterns of treatment administration and the transitions to disease progression and death. In line with previous submissions, a half-cycle correction was implemented to mitigate bias.[63;118]

Health states were mutually exclusive, meaning that patients could only be in one state at a time. All patients started in the pre-progression state. Transitions to the death state could occur from either pre-progression or post-progression, while death was an 'absorbing state'. Patients could not transition to an improved health state (i.e. from post-progression to pre-progression), which is consistent with previous economic modelling in NSCLC.[63;119]

Disease progression was defined by RECIST v1.1 by central review (which was one of the primary endpoints in KEYNOTE-010).[16;82]

Figure 29. Model structure



The partitioned-survival model was developed by fitting survival curves to trial data for progression free survival (PFS) and overall survival (OS). In partitioned survival models, health transitions are derived directly from the proportion of patients that are reflected by the areas under the PFS and OS curves, rather than using transition probabilities (as would be the case with standard Markov models),. The area underneath the OS curve represented the proportion of patients that were still alive (both in pre-progression and post-progression) at different points in time, while the proportion of patients in the pre-progression state were

identified by the patients located underneath the PFS curve. The area between the PFS and the OS represented the proportion of post-progression patients, i.e. those who were in the 'post progression' health state.

The definition of the health states used in the model was based on the definitions conventionally used in oncology clinical trials and, specifically, the ones used in the pembrolizumab KEYNOTE-010 trial:

- Progressive disease was defined following the RECIST 1.1 criteria, i.e., at least a 20% increase in the sum of diameters of target lesions, and an absolute increase of at least 5 mm, or appearance of one or more new lesions.[10;81]
- Non-progressive disease reflected patients being alive and not in progressive disease (which included patients with complete response, partial response and stable disease).
- Death (absorbing health state).

In the model, patients in the pembrolizumab arm were assumed to be eligible to receive treatment until progression, in line with the anticipated licence for pembrolizumab for advanced NSCLC patients. This is consistent with the protocol of the KEYNOTE-010 trial, where patients remained on treatment until disease progression or intolerable toxic effects resulting in discontinuation, with maximum treatment duration of 24 months.[16] In the base case model, a maximum treatment duration of 2 years was assumed, in line with the KEYNOTE-010 protocol[81] (see section 5.2.5 below).

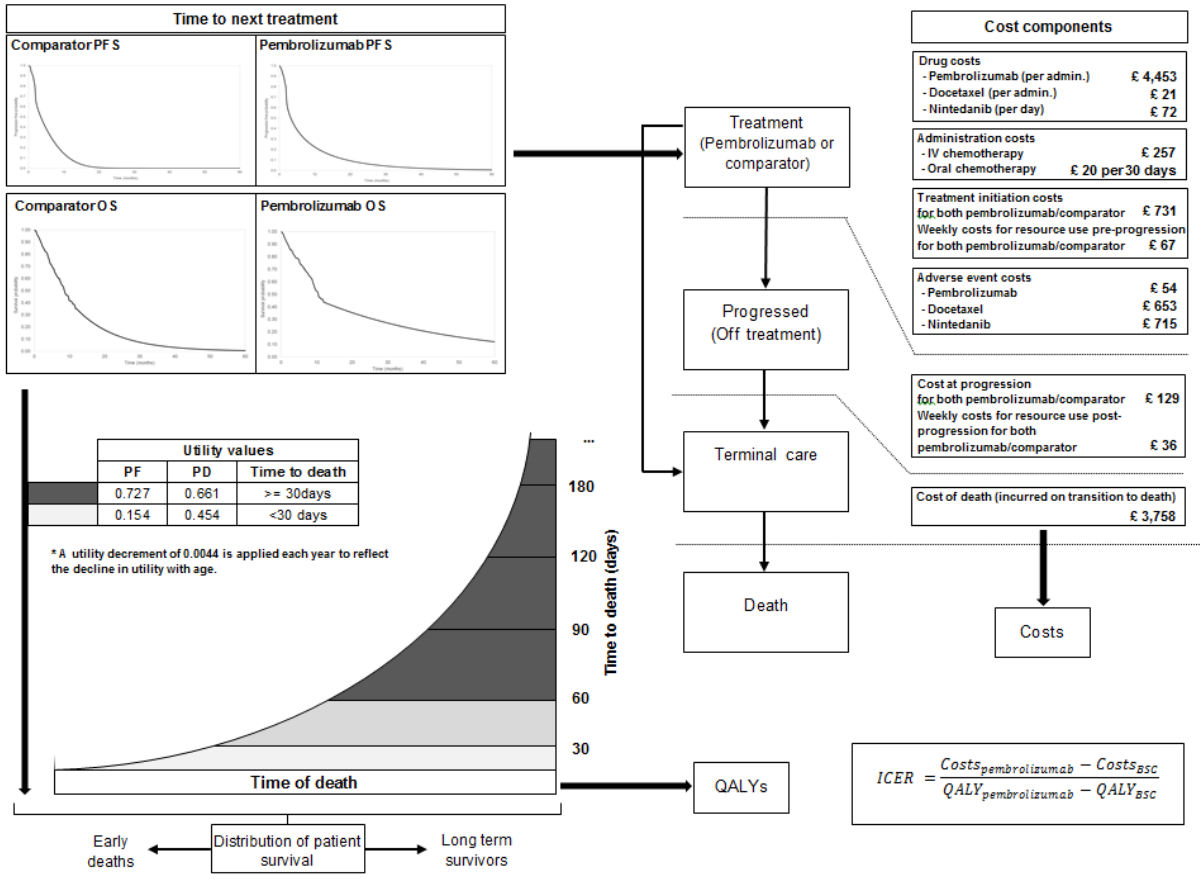
Patients treated with docetaxel were also assumed to receive treatment until a maximum number of cycles, aimed to reflect clinical practice in England (see section 5.5.5).

Treatment switches to subsequent therapies were incorporated in the model by reflecting the proportion of patients in KEYNOTE-010 that were treated with either pembrolizumab 2mg/kg Q3W or docetaxel and received subsequent oncologic therapies after treatment discontinuation. The costs of these subsequent treatments are included in the economic evaluation. It should be noted that 12.5% of the patients treated with docetaxel in KEYNOTE-010 switched to an anti-PD-1 agent after treatment discontinuation. To better reflect the expected OS in the absence of switching, the adjusted OS for docetaxel, using the two-stage adjustment, was considered in the model (see section 4.7).

To capture more accurately the impact of pembrolizumab upon quality of life, the measurements considered in the base case analysis were based on a combination of time-to-death and progression status, as shown in Figure 30.

Time-to-death sub-health states were used to capture patients' quality of life as a function of how much lifetime patients had left until they eventually died as predicted in the model. This approach was justified on the basis that NSCLC patients have been shown to have markedly decreased utilities towards the end of life.[120] The use of time-to-death sub-health states was implemented considering two health states: <30 days to death and ≥30 days to death. These were divided into pre- and post-progression. Therefore, in the base case, four health states are used for the estimation of QALYs in the model (pre-progression and <30 days to death, pre-progression and ≥30 days to death, post-progression and <30 days to death and pos-progression and ≥30 days to death) each associated with a specific utility value. Resource utilisation use and costs are captured based on the pre-progression and post-progression health states.

Figure 30: Model diagram describing the estimation of QALYs and costs



5.2.3 Key features of the de novo analysis

Table 65: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	20 years	Lifetime horizon for the defined target population (0.1% of patients alive after this period in base case 1; 0.04% with base case 2) In line with most recent advanced or metastatic NSCLC NICE submissions[63;118]
Cycle length	1 week	Sufficient to model the patterns of treatment administration, transitions to disease progression and OS. In line with a recent NICE submission in advanced NSCLC.[121]
Half-cycle correction	Yes	Yes, in line with previous submissions and to mitigate bias[63;118]
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case[122]
Discount of 3.5% for utilities and costs	Yes	NICE reference case[122]
Perspective (NHS/PSS)	Yes	NICE reference case[122]
PSS, personal social services; QALYs, quality-adjusted life years		

5.2.4 Intervention technology and comparators

The intervention (i.e. pembrolizumab) was implemented in the model as per the anticipated licensed dosing regimen (i.e. 2 mg/kg as an IV infusion over 30 minutes every 3 weeks [Q3W]). The anticipated licence establishes that pembrolizumab is to be administered until disease progression or unacceptable toxicities. However, there is no evidence regarding the optimal duration of treatment with pembrolizumab, particularly since the KEYNOTE-010 protocol established that treatment should continue until disease progression, toxicities leading to discontinuation, physician's decision or 2 years of uninterrupted delivery of pembrolizumab.

We expect pembrolizumab to be considered as an option for people with relapsed NSCLC for whom docetaxel is also an appropriate treatment option and whose tumours express PD-L1. Based on this, the appropriate comparators for pembrolizumab are as follows:

- Docetaxel, independent of the tumour histology. This is the current standard of care in pre-treated patients and is the treatment most likely to be displaced by the introduction of pembrolizumab.

- Nintedanib combined with docetaxel, which is currently recommended by NICE for the treatment of people with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma type that has progressed after first-line chemotherapy.[63]

The dosing and administration frequencies for these comparators were implemented in the model in line with their marketing authorisations and UK clinical practice.

5.2.5 Discontinuation rules

In KEYNOTE-010, patients were to continue pembrolizumab until disease progression, unacceptable toxicity or 2 years of uninterrupted delivery of pembrolizumab.[82] In line with this, in the base case we consider that pembrolizumab is discontinued after 2 years of uninterrupted delivery. In the cost-effectiveness model, the survival estimates of OS and PFS are based on KEYNOTE-010 data, thus reflecting the implementation of the within-trial maximum treatment duration.

In the case of docetaxel monotherapy, feedback from UK clinical experts has indicated that most centres will recommend up to 6 cycles (although the majority of patients will not get this number, mainly due to the toxicity caused by docetaxel). A small number of centres may limit the number of cycles to 4, also because of concerns regarding toxicity. Therefore, in the base case analysis we have assumed a maximum treatment duration for docetaxel monotherapy of 18 weeks (i.e. a maximum of 6 cycles) without adjusting efficacy (OS and PFS), as observed in the KEYNOTE-010 trial. In practical terms, in the cost-effectiveness model, patients treated with docetaxel received, on average, less than four treatment cycles (see section 5.5.5).

For the additional analyses that consider nintedanib in combination with docetaxel for the adenocarcinoma subgroup population, no treatment stopping rule was applied to nintedanib since this agent may be continued after discontinuation of docetaxel for as long as clinical benefit is observed.[121;123] The same maximum number of cycles assumed for docetaxel monotherapy were applied to docetaxel administered as part of this treatment combination (see above and section 5.5.5).

5.3 Clinical parameters and variables

5.3.1 Overall method of modelling survival

The primary data source for the economic model was the data derived from the pivotal KEYNOTE-010 clinical trial. The follow-up period in KEYNOTE-010 was shorter than the time horizon of the economic model (20 years to represent a lifetime horizon). Therefore,

extrapolation of the OS and PFS from KEYNOTE-010 was required for the area-under-the-curve (AUC) partitioned survival approach.

Initially, the guidance from the NICE DSU was followed to identify base case parametric survival models for OS and PFS.[124] In summary, the steps that were followed include:

1. Testing the proportional hazard (PH) assumption – the log cumulative hazards plots were assessed to determine if the data from the KEYNOTE-010 indicate proportional effects between pembrolizumab and docetaxel. This was done by visual inspection to determine that the curves for pembrolizumab and docetaxel arms did not cross.

2. If the PH assumption holds, a comprehensive range of pooled parametric survival models are to be explored. Here, data from both treatment arms are used within the same model, with the treatment arm (pembrolizumab arm) assigned a value of 1 and the docetaxel arm (chosen as the reference category) used as a covariate. The parametric models included the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma models. In these pooled models, pembrolizumab and docetaxel share the same intercept and other parameters of the parametric curves vary based on the estimated coefficient of the treatment arm covariate.

3. If the PH assumption does not hold, independent separate survival models are to be explored. In this case, models are separately fitted to each treatment arm using data from the relevant treatment arm. In the separate models, all parameters of the parametric curves are allowed to vary between pembrolizumab and docetaxel.

4. Within the various parametric survival models explored, visual inspection is used to assess the fit of the fitted curves to the observed clinical trial data. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics are calculated to help identify the most plausible survival models.

5. Lastly, the choice of base case parametric models is validated in terms of clinical plausibility of both short-term and long-term extrapolations.

Among alternative standard parametric curves (e.g., Weibull vs log-normal), the final choice of base case parametric survival models should be a balance between the statistical fit (based on AIC/BIC values), visual inspection and the clinical plausibility of the extrapolated model.

When the standard parametric approach was used to extrapolate OS in the long term, neither pooled nor separate parametric standard models were found to fit the KEYNOTE-010 trial data based upon:

- The proportional hazard assumption between pembrolizumab and docetaxel did not hold.
- The fitted curves obtained when implementing separate standard parametric models to the KM data of pembrolizumab and docetaxel resulted in clinically inplausible projections, since they underestimated OS for both pembrolizumab and docetaxel during the first year, and did not provide a good visual fit in the long term either (see section 5.3.2).

The cumulative hazard plot suggested that a more complex curve fitting was most appropriate (i.e. piecewise model fitting). Therefore, standard parametric curves for OS were not implemented in the economic model.

For OS, a KM plus exponential 2-phase piecewise model fit has been preferred by the ERG in recent NICE appraisals, where unadjusted trial KM data were used for the first phase followed by projections of long-term OS using an exponential model (i.e., assuming constant mortality rate) based on remaining trial KM data in the second phase.[63;121] In these previous appraisals, standard parametric models were applied as part of the original manufacturer submissions. This approach was criticised by the ERG, which suggested the use of a 2-phase piecewise model for OS. The 2-phase piecewise approach was also the method used to model OS for the EGFR-unknown population by the NICE Assessment Group (AG) in the recent erlotinib/gefitinib multiple technology appraisal (MTA).[64]

The KEYNOTE-010 trial has a relatively large sample size (344 and 343 patients for the pembrolizumab 2mg/kg and docetaxel arms respectively) and therefore the unadjusted KM OS data provide a robust representation of the relative efficacy between pembrolizumab and docetaxel when patient numbers remain relatively large. Given the precedent in recent NICE appraisals and the relative large sample size of the KEYNOTE-010 trial, the decision was made to use a KM plus exponential 2-phase piecewise approach to model OS in the base case.

To estimate the long-term OS beyond the trial period, we considered the following sources of data:

- The KEYNOTE-001 trial, which provides a longer follow up for advanced NSCLC patients previously treated (median follow up = 16.2, and up to 32.3 months of maximum follow up), although only for patients treated with pembrolizumab.

- The National Lung Cancer Audit (NLCA) registry OS data in England[50] includes up to almost 6 years of OS data for Stage IIIB and Stage IV NSCLC, stratified by stage and by whether patients received chemotherapy or not according to their performance status.

We used these alternative sources of information above to implement different plausible extrapolation scenarios for OS in the long term.

It adds to the complexity of the submission; however it was decided that providing two conservative base case scenarios with further approaches presented as sensitivity analyses to enable the exploration of different views on the survival benefit attached to pembrolizumab in the longer term.

5.3.2 Modelling overall survival for the first 2 years

Standard parametric curves were initially fitted to the full KM OS data. When the PH assumption was tested, this did not hold, based on the log-cumulative hazard plot and the Schoenfeld residuals plot. As shown in Figure 32, the two lines crossed towards the beginning and appear to diverge towards the end for the log-cumulative hazard plot. Additionally, there is a clear downward slope for the Schoenfeld residuals plot (see Figure 33). Therefore, separate models were subsequently fitted based on the individual patient data from KEYNOTE-010.[124]

The fitted separate standard parametric curves are presented in Figure 34. These separate parametric curves do not have a good visual fit compared to the 2-phase piecewise method as shown in Figure 36. For the pembrolizumab arm, all separate parametric curves underestimate the observed OS up to approximately month 9, and then they mostly overestimate observed OS between month 9 and month 15. The cumulative hazard plot (see Figure 36.A) shows that the change in hazard is not constant over time (i.e. there is a different slope before and after around 52 weeks for the pembrolizumab arm). This suggests that a piecewise model is more appropriate than the use of single parametric curves. Given the strong precedence of the use of 2-phase piecewise models (KM plus exponential) in recent NICE appraisals in previously treated advanced NSCLC, we decided to implement a 2-phase piecewise model as the most appropriate method for modelling OS in the long term.

Figure 31. Cumulative hazard plot of OS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

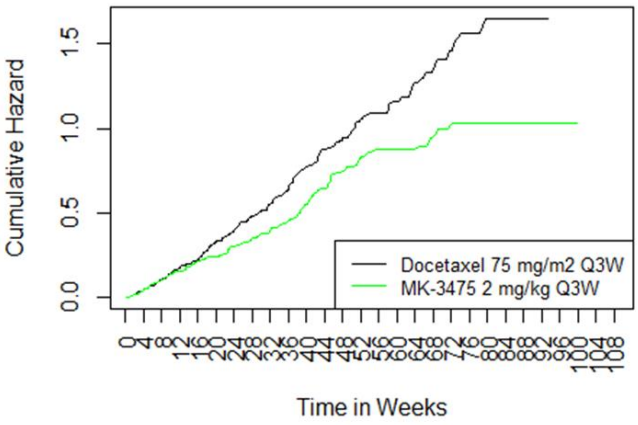


Figure 32. Log-cumulative hazard plot of OS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

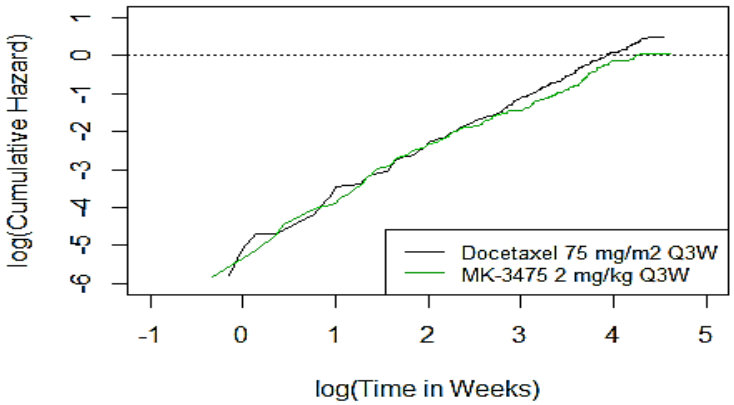


Figure 33. Schoenfeld residuals plot of OS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

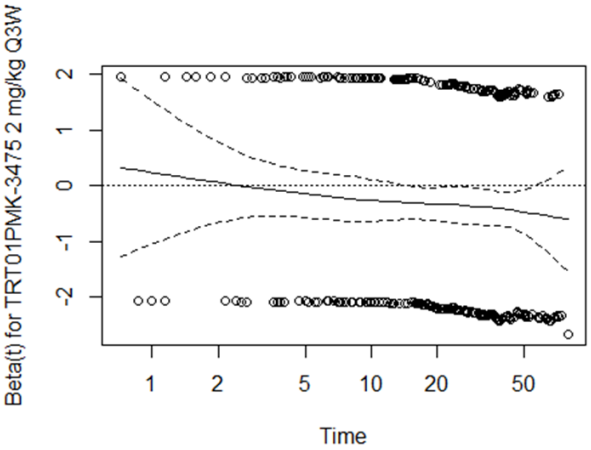


Figure 34. Fitted separate standard parametric curves for the OS of pembrolizumab (A) and docetaxel (B) in all PD-L1 positive population

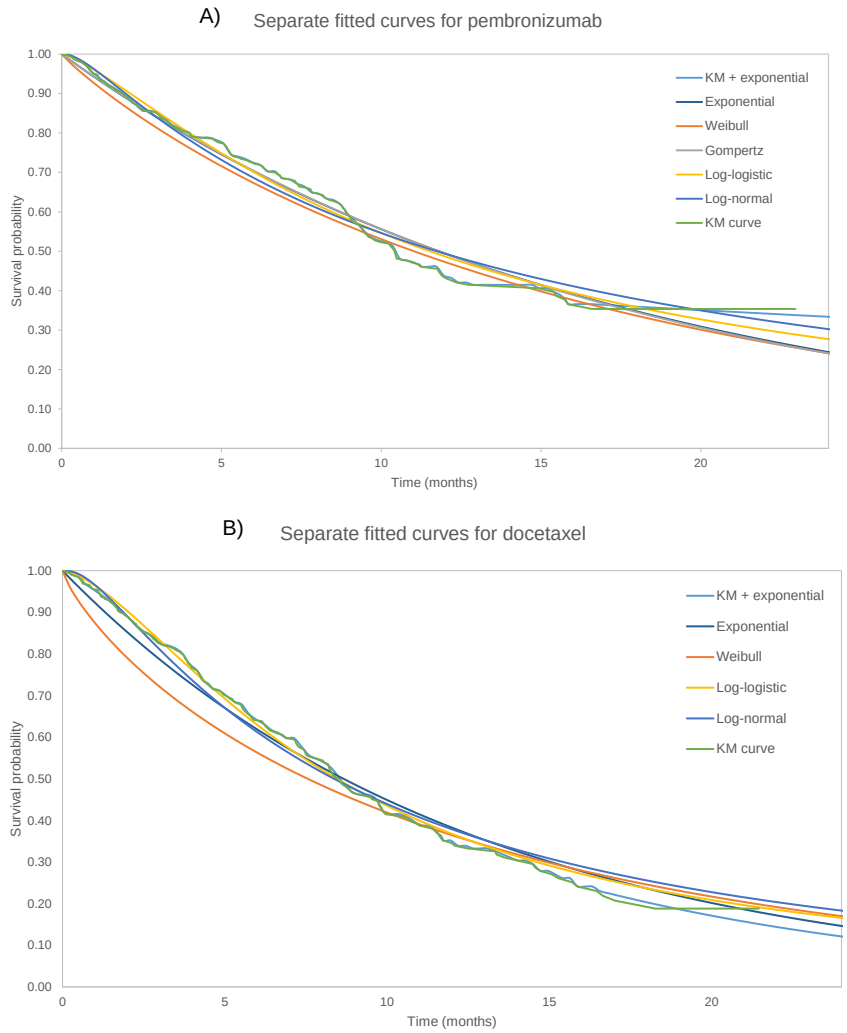


Figure 35 shows the Kaplan-Meier (KM) survival plot for OS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010. For the base case 2-phase piecewise approach, the second phase exponential models were fitted using three alternative cut-off points of 52 (1 year), 62 and 72 weeks. These cut-off points were selected as the at-risk patient numbers start to become small and therefore, the KM data becomes increasingly less reliable after these cut-off points. The at-risk patient numbers are 77, 69 and 35 for pembrolizumab and 59, 41 and 21 for docetaxel at the cut-off points of 52, 62 and 72 weeks respectively. The fitted 2-phase piecewise models for the first 2 years are presented in Figure 36. The cut-off at 52 weeks is used in the base case model because it provides a good balance of robust KM data to be used directly in the first phase and enough remaining KM data to be used to fit an exponential curve in the second phase. Additionally, it results in a plausible visual fit. A cut-off of 52 weeks also provides the most conservative estimates among the three alternative cut-off time points (see Section 5.8.3 where the cost-effectiveness results using 62 and 72 weeks are reported as part of the scenario analyses).

Figure 35. KM survival plot for OS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

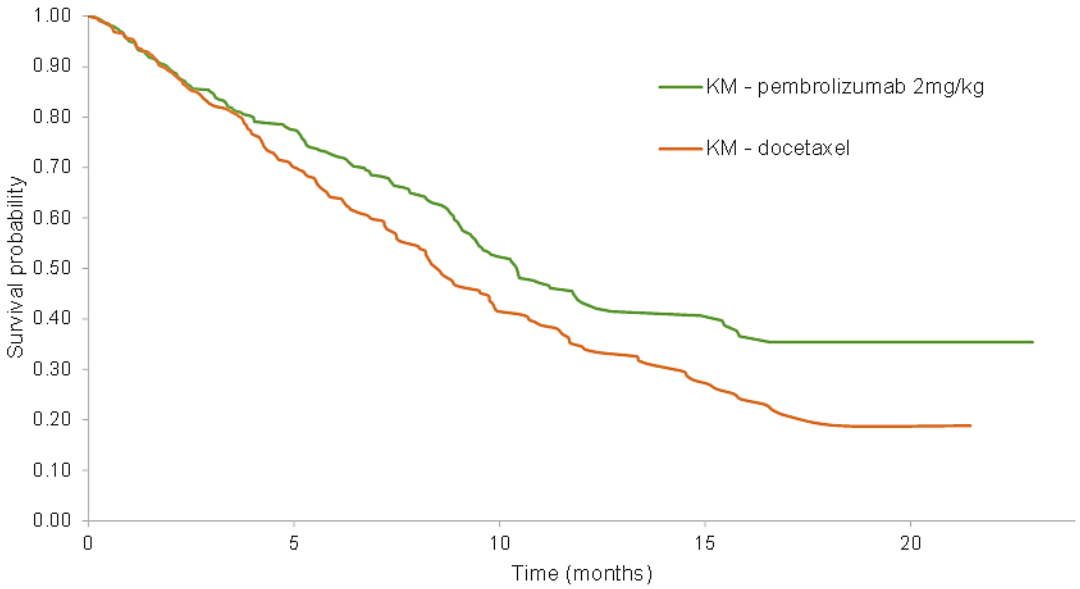


Figure 36. Fitted 2-phase piecewise models for the OS of pembrolizumab and docetaxel in all PD-L1 positive population based on Keynote-010

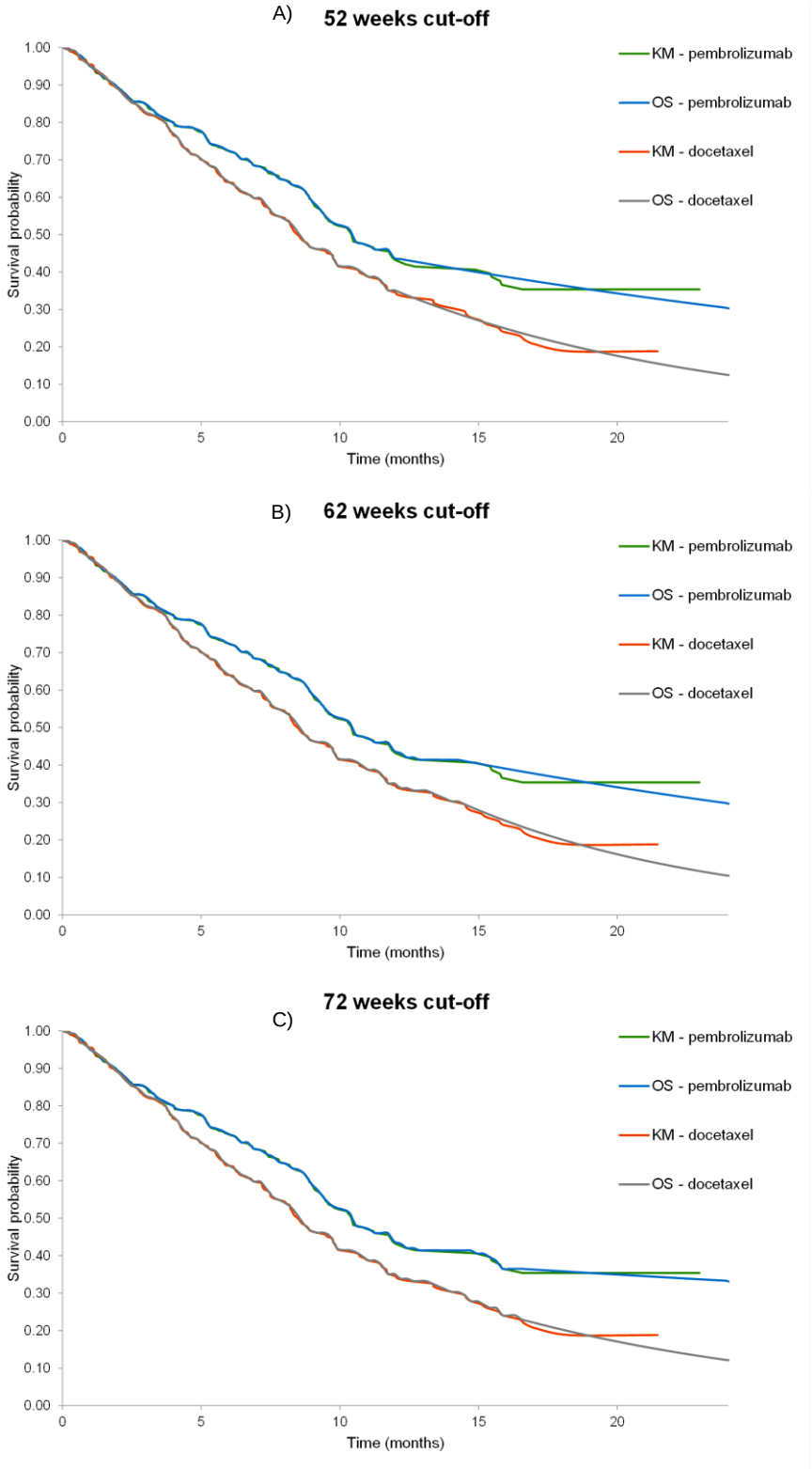


Table 66. Fitted exponential curves for the 2-phase piecewise approach for OS for the overall PD-L1 positive population

	Patients at risk		Exponential curve parameters	
Cut-off (weeks)	Pembrolizumab	Docetaxel	Pembrolizumab	Docetaxel
52	77	59	4.964741	3.923387
62	69	41	4.856485	3.68465
72	35	21	5.863225	3.921502

5.3.3 Modelling long-term overall survival beyond 2 years

The median follow-up period of KEYNOTE-010 trial is 13 months (range: 6 to 24 months). Therefore, there is considerable uncertainty regarding the long-term extrapolation of OS beyond the trial period, especially for pembrolizumab, which as an immunotherapy, is expected to significantly increase long-term survival for a proportion of patients.

It should be noted that the long-term OS benefit associated to immunotherapies such as pembrolizumab has been demonstrated in other cancer patients. For example, a recent pooled study of long-term survival data for advanced melanoma patients treated with ipilimumab showed a plateau around year 3 in the OS curve, with 21% of patients surviving at this point. This survival trend extended up to 10 years in some patients.[125] This evidence suggests that immunotherapies have a higher potential to improve OS in the long term compared to usual chemotherapies.

We have identified two main sources of non-comparative, non-RCT data that can be used to extrapolate OS beyond the KEYNOTE-010 trial period:

- The KEYNOTE-001 phase I trial for pembrolizumab on advanced NSCLC patients, with up to 32.3 months of follow-up, which can be used to extrapolate the pembrolizumab arm in the long term.
- The OS collected on the National Lung Cancer Audit (NLCA) registry,[50] which would reflect more closely the expected long-term OS in the docetaxel arm.

The following two base cases are assessed:

- **Base case 1:** For pembrolizumab, the KM curve from KEYNOTE-010 is used for the first 52 weeks, followed by the most plausible exponential curve based on the evidence available, which is the KM data from the KEYNOTE-001 trial. This exponential fitting of the KEYNOTE-001 KM data is used from 52 weeks onwards. For docetaxel, we use the 2-phase piecewise method for the entire time horizon,

based on KEYNOTE-010 (i.e. use KM data up to 52 weeks followed by an exponential curve afterwards).

The KEYNOTE-001 OS for previously treated PD-L1 patients is presented in Figure 23. Standard parametric curves were fitted to the KM data from week 52 onwards and the fitted curves and AIC/BIC results are presented in Figure 37 and Table 67.

- **Base case 2:** The 2-phase piecewise method is used (i.e. we use KM data up to 52 weeks followed by an exponential curve afterwards) for both treatment arms for the entire time horizon. This is the most conservative scenario regarding the long-term survival benefit of pembrolizumab, because OS declines to baseline more rapidly for the pembrolizumab arm due to the use of the exponential curve derived from the KEYNOTE-010 data, which reflects a shorter follow up than that in KEYNOTE-001.

Figure 37. Fitted standard parametric curves for KEYNOTE-001 OS (rebased at week 52)

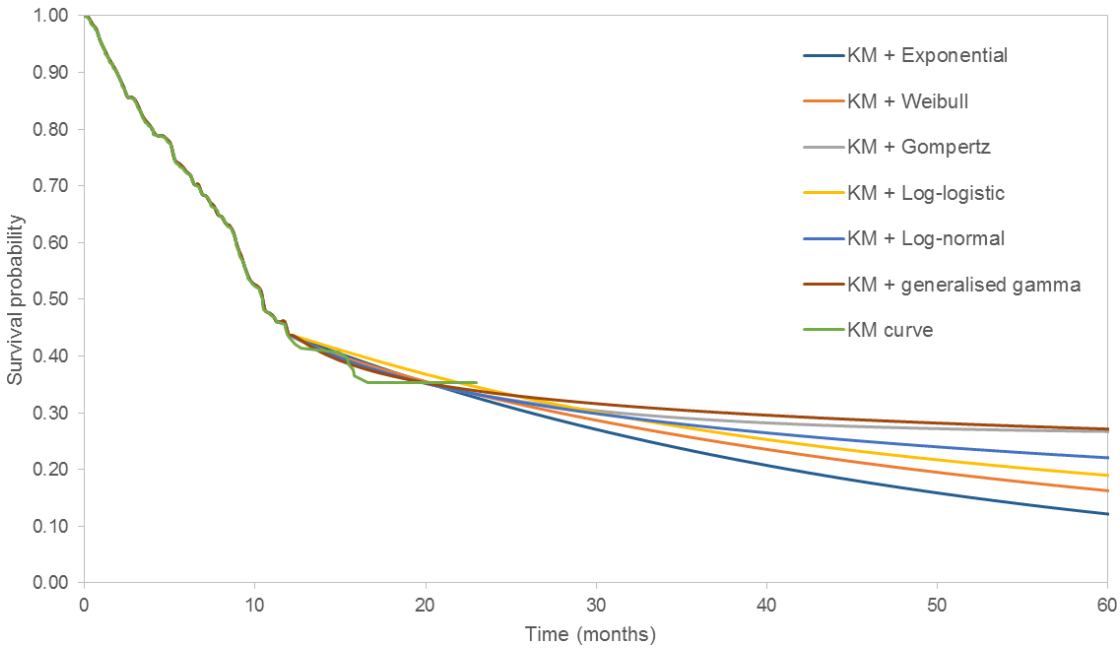


Table 67. Goodness-of-fit measures for KEYNOTE-001 OS (rebased at week 52)

	Pembrolizumab	
	AIC	**BIC**
Exponential	**123.8820142**	**126.3706506**
Log-normal	124.5470584	129.5243311
Gompertz	125.1850664	130.1623392
Log-logistic	125.328511	130.3057837
Weibull	125.5304956	130.5077684
Generalised Gamma	126.0807718	133.5466809

Switching adjustments for the docetaxel arm

The OS treatment effect estimate of the docetaxel arm was adjusted to correct for the bias induced by treatment switch. A number of factors contributed to the conclusion that the RPSFT assumption did not hold (see section 4.7):

Firstly, the method seemed to fail to adjust for crossover, as demonstrated by the similarity between the curves obtained for the control arm before and after the RPSFT correction was applied (see Figure 12). The median RPSFT-adjusted OS was 8.4 months, while that associated with patients with advanced NSCLC stage III/IV treated with docetaxel after platinum-based chemotherapy rarely exceeds 8 months.[4;5;7;97;98]

Figure 11 presents the post-progression survival curves for the docetaxel arm of the KEYNOTE-010 trial, stratified according to whether patients switched to an anti-PD-1 agent or not. Patients receiving docetaxel who did not switch experienced a shorter survival than those switching.

The adjusted results estimated by the RPSFT method were therefore considered to be implausible and not in line with observed data from previous trials on patients with stage IIIb/IV NSCLC treated with docetaxel 75mg/m^2

Figure 38. Projected OS for pembrolizumab and docetaxel – Base case 1 (KM+exponential+projection based on KEYNOTE-001 for pembrolizumab arm vs. KM+exponential for docetaxel arm, with OS for docetaxel adjusted using the two-stage method)

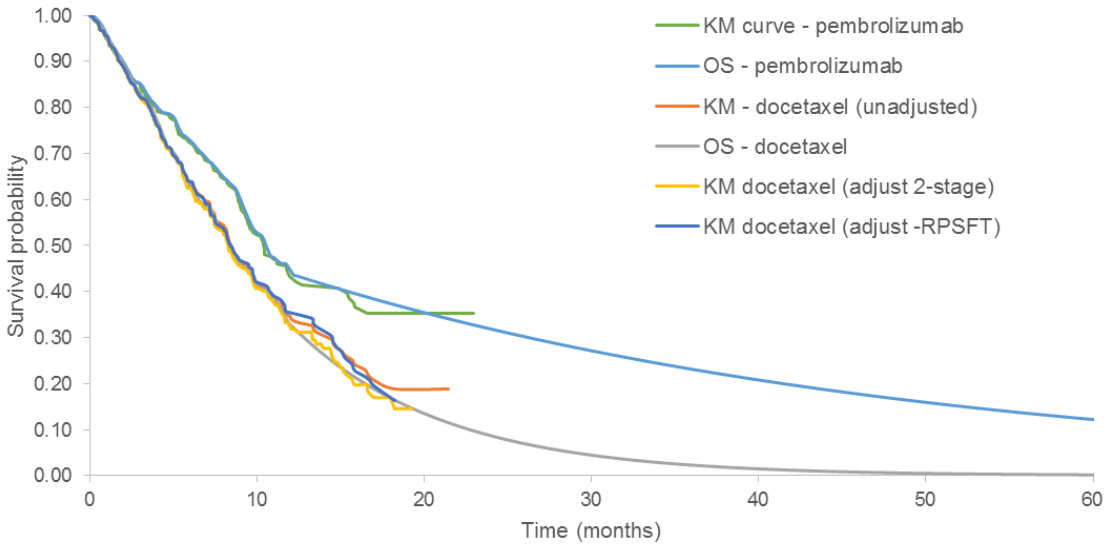
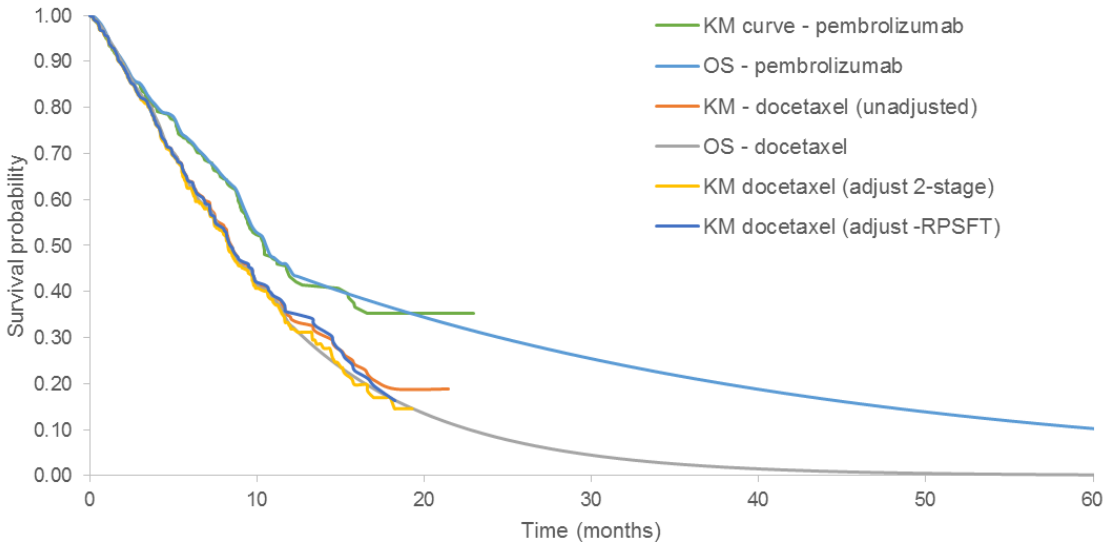


Figure 39. Projected OS for pembrolizumab and docetaxel – Base case 2 (KM+exponential for both pembrolizumab and docetaxel arms, with OS for docetaxel adjusted using the two-stage method)



Additional extrapolation scenarios modelled as part of sensitivity analyses

In scenario analyses, we used the 2-phase piecewise method for the first 2 years for both treatment arms. From year 2 onwards, parametric curves based on the NLCA registry OS were fitted and the most plausible curves (based on statistical goodness of fit, visual fit and clinical plausibility) were used for all treatment arms. These scenarios use the conditional survival for advanced NSCLC patients (conditional to patients who are alive at year 2 in the model) based on evidence from the NLCA registry OS.

Two datasets were used from the NLCA registry to model long-term OS from year 2 onwards, beyond the trial follow-up. The reported OS registry data for NSCLC patients in England by disease stage is presented in Figure 40, and that reported for patients with NSCLC stage IIIb/IV treated with chemotherapy is reported in Figure 41.[50]

Figure 40. NLCA OS registry data for NSCLC patients in England by stage[50]

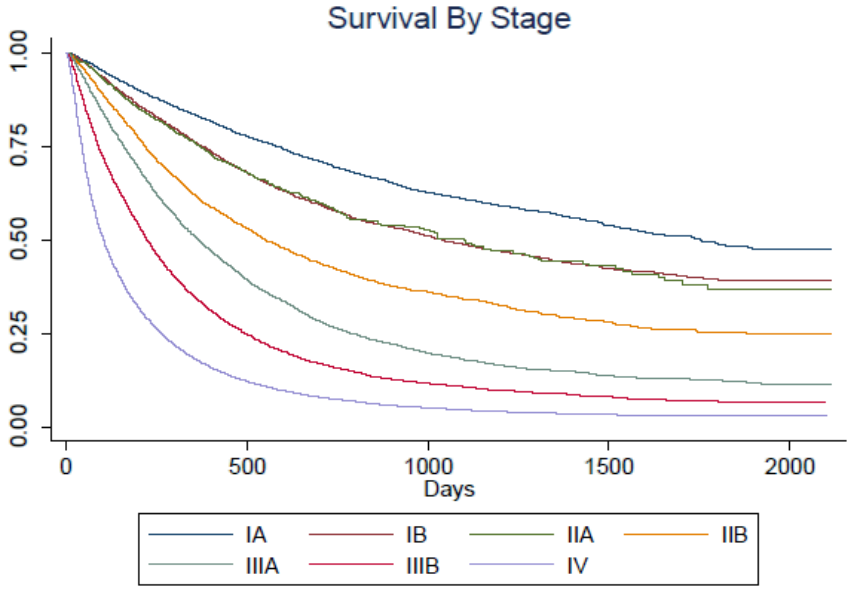
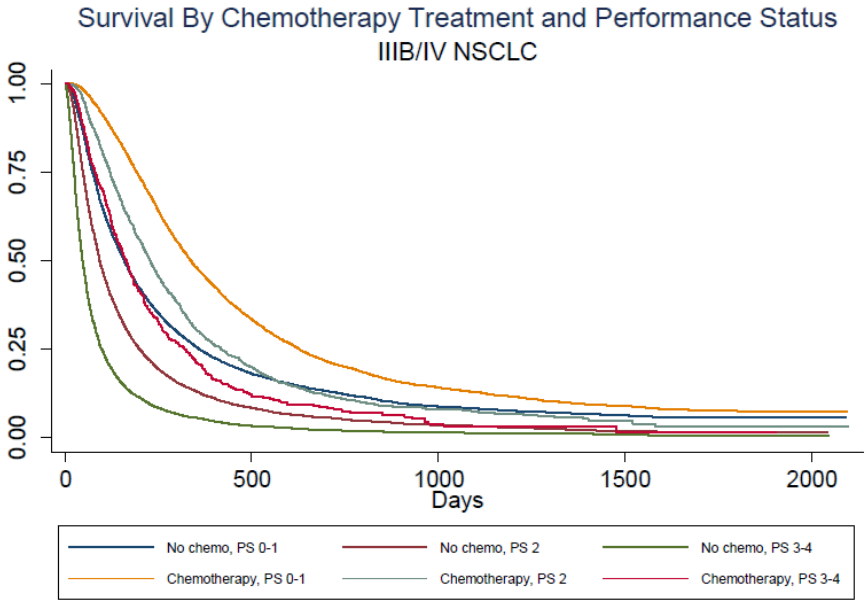


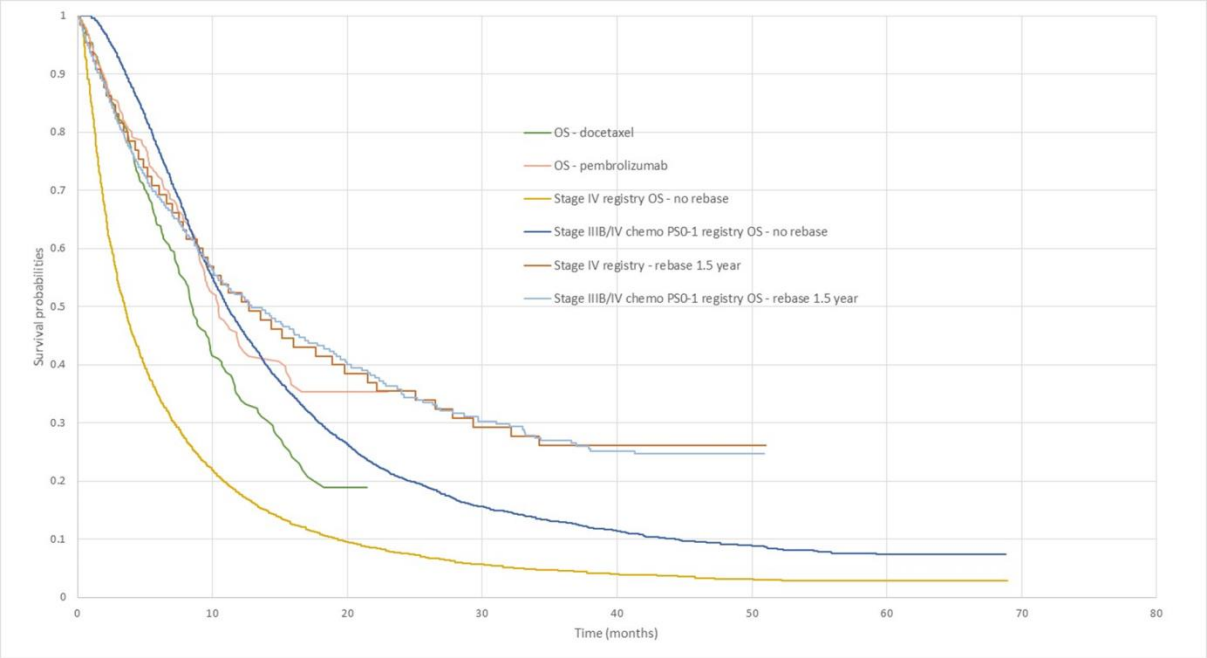
Figure 41. NLCA OS registry data for patients with NSCLC stage IIIb/IV treated with chemotherapy in England by performance status[50]



The NLCA OS registry data is defined from the time of diagnosis. Initially, to apply the registry OS from year 2 onwards in the model, the registry data were 'rebased' at 2 years. In order to 'rebase' at 2 years, only patients with OS times >2 years were included in the analyses, and the survival times of those included were recalculated as: "OS time rebased = OS time – 2 years". After rebasing, the reported KM data for Stage IIIB and IV were digitised using the Guyot 2012 method[126] where the survival probability at rebased year 0 (i.e., year 2 in Figure 40) was set to 1. Standard parametric curves were then fitted to the pseudo individual patient level data.

Since rebasing the data resulted in OS projections in the short term that were higher than expected (see), we decided to implement the registry data without considering a rebase.

Figure 42. NLCA OS registry data[50] projections according to whether rebase at 1.5 years was used or not to account for time from diagnosis



The fitted parametric curves (rebased at year 2) are presented in Figure 43; and the AIC/BIC goodness-of-fit measures of the fitted models are presented in Table 68. The generalized gamma parametric curve has been selected in the base case as the most plausible curve because it has the best AIC/BIC for Stage IV patients, who represent 93.2% of the patients in KEYNOTE-010 trial (see Table 68). Details of the method of digitisation and model fitting of the NLCA registry OS is described in Appendix 28.

For the implementation of registry OS in the model, the proportions of patients in KEYNOTE-010 who are Stage IIIB and Stage IV were used (6.8% and 93.2% for Stage IIIB and Stage IV respectively) to calculate the weighted average OS of combined Stage IIIB and Stage IV (i.e., advanced NSCLC) patients and applied in the economic model from year 2 onwards. The same registry OS is applied to all modelled arms.

For both base cases and scenario analyses presented, the latest UK gender-age specific general population mortality was applied throughout the modelled time horizon as background mortality (i.e., general population mortality is applied when modelled mortality is lower than the gender and age matching general population mortality). The general population mortality data was not applied on top of the registry OS because the NLCA registry OS data includes all-cause mortality.

Figure 43. Fitted standard parametric curves for: A) Stage IIIB and B) Stage IV OS based on NLCA registry OS (rebased at year 2)

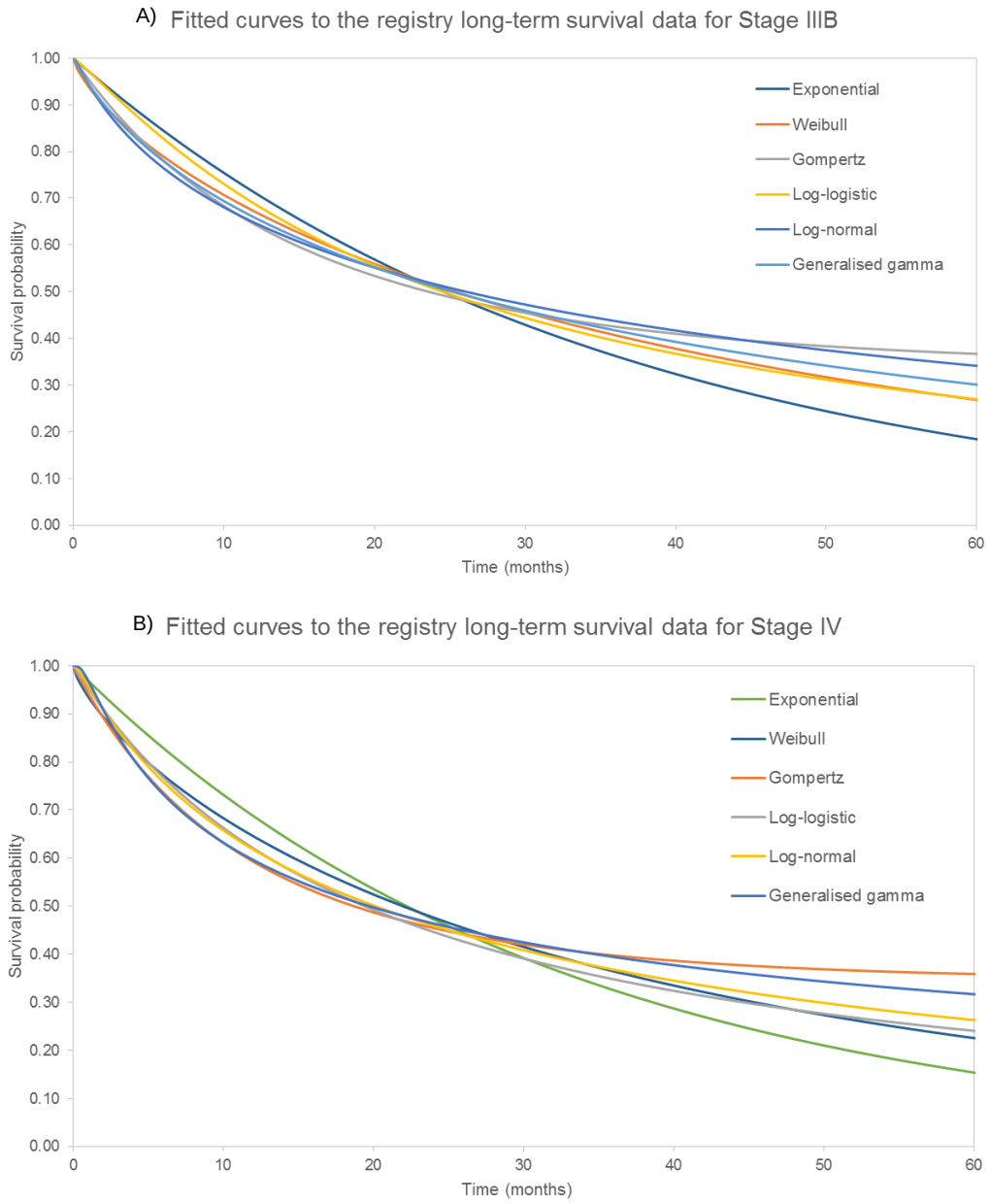
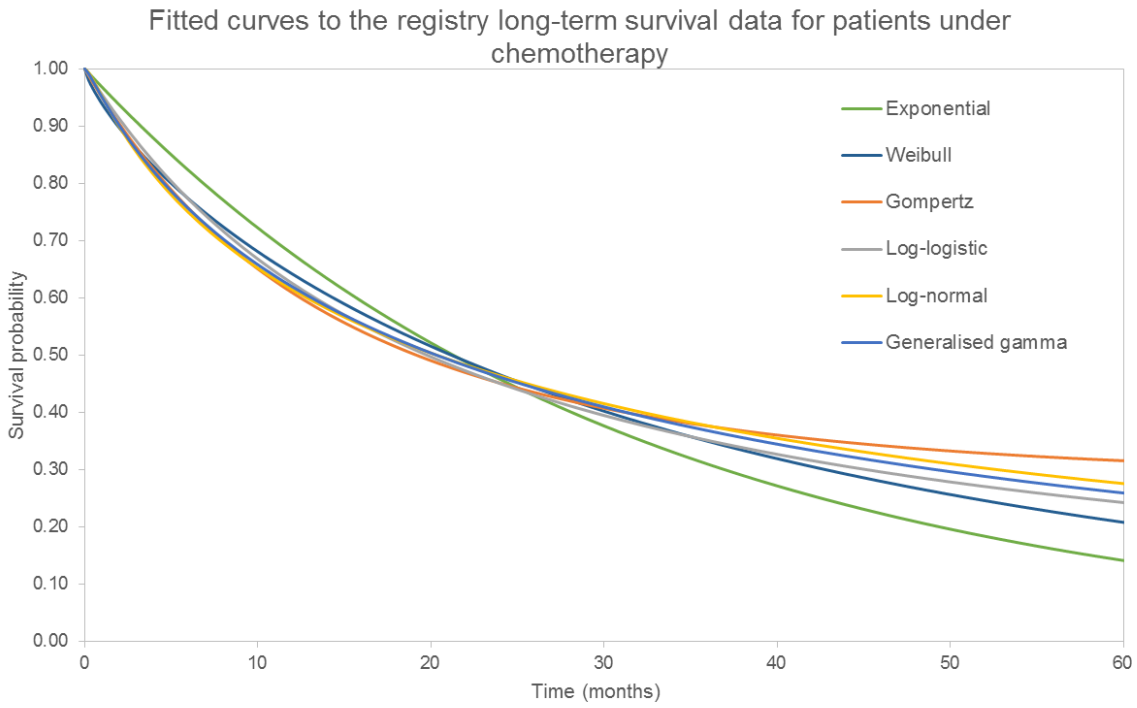


Table 68. Goodness-of-fit measures for OS for Stage IIIB and Stage IV OS based on NLCA registry OS (rebased at year 2)

	Stage IIIB			Stage IV		
Model	**AIC**	**BIC**	**Rank**	**AIC**	**BIC**	**Rank**
Exponential	14070.46	14075.98	6	34435.63	34441.97	6
Weibull	13956.65	13967.69	4	34180.41	34193.08	5
Gompertz	13919.64	13930.68	1	33755.06	33767.73	2
Log-Normal	13960.97	13972.01	5	33817.11	33829.78	3
Gen. Gamma	**13939.21**	**13955.76**	**3**	**33694.90**	**33713.91**	**1**
Log-Logistic	13928.10	13939.14	2	33932.01	33944.69	4

Key: AIC, Akaike information criteria; BIC, Bayesian information criteria.

Figure 44. Standard parametric curves for to the NLCA registry data for patients with NSCLC stage IIIb/IV receiving chemotherapy



5.3.4 Modelling progression free survival

Based on the trial protocol of KEYNOTE-010, the first tumour assessment was performed at week 9 and this is demonstrated by the overlapping PFS for the first 9 weeks in Figure 45. To identify the most plausible survival curves among the standard parametric curves, the guidance from the NICE DSU[124] was followed. Figure 45 shows the PFS KM survival plot for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010. The log-cumulative hazard plot and the Schoenfeld residuals plot are presented in Figure 46 and Figure 47. These show that the PH assumption does not hold (PH test: p = 0.00213). Therefore, separate parametric curves were fitted. Following DSU guidance,[127] only similar types of parametric curves (with 'type' defined as the same parametric distribution) were considered for the pembrolizumab and docetaxel arms.

Generalised gamma parametric curves were chosen to be used in the base case because they have the best AIC/BIC (see Table 69). Generalised gamma also provides a good visual fit to the trial KM data and plausible long-term projections (see Figure 48).

Figure 45. KM survival plot for PFS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

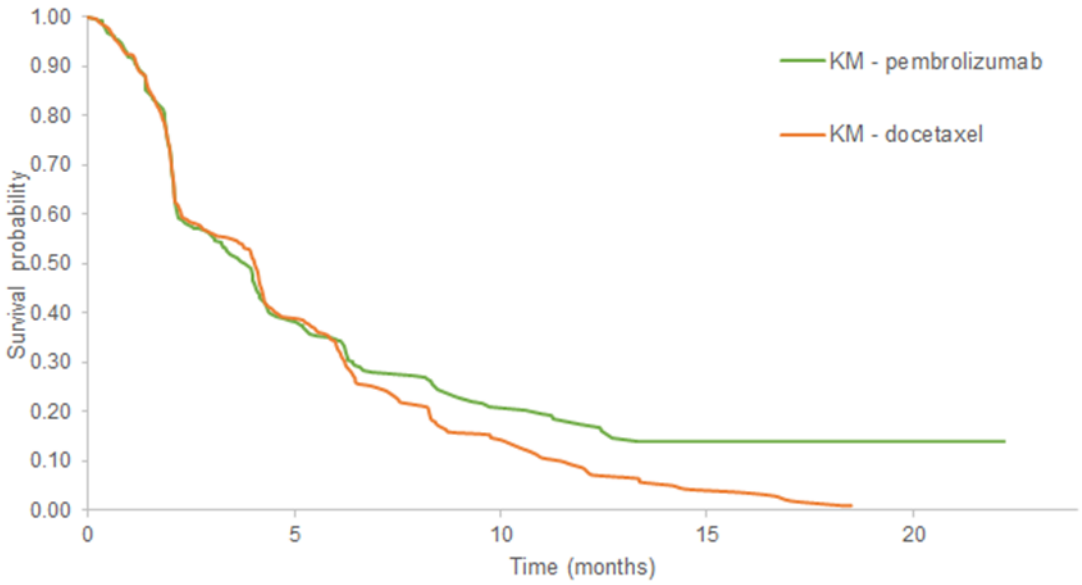


Figure 46. Log-cumulative hazard plot of PFS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

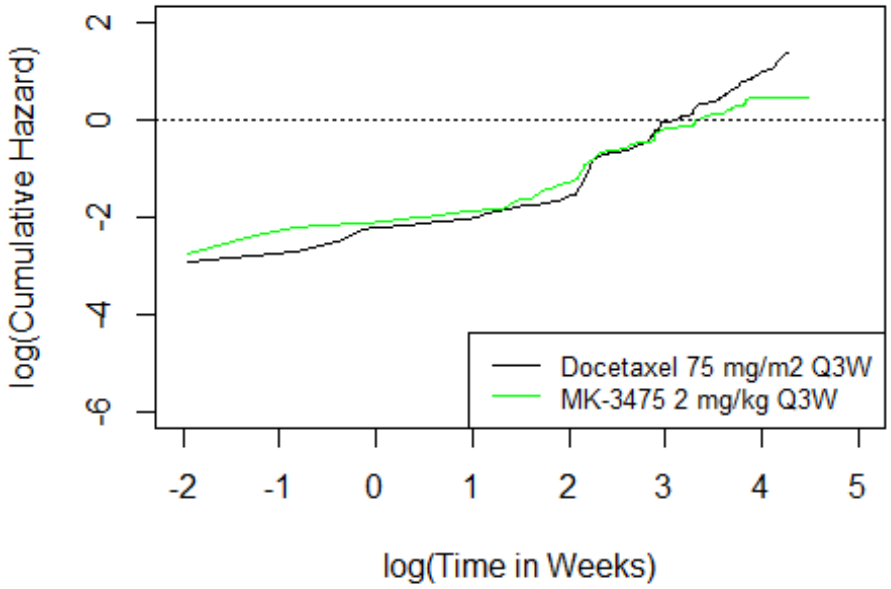


Figure 47. Schoenfeld residual plot of PFS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

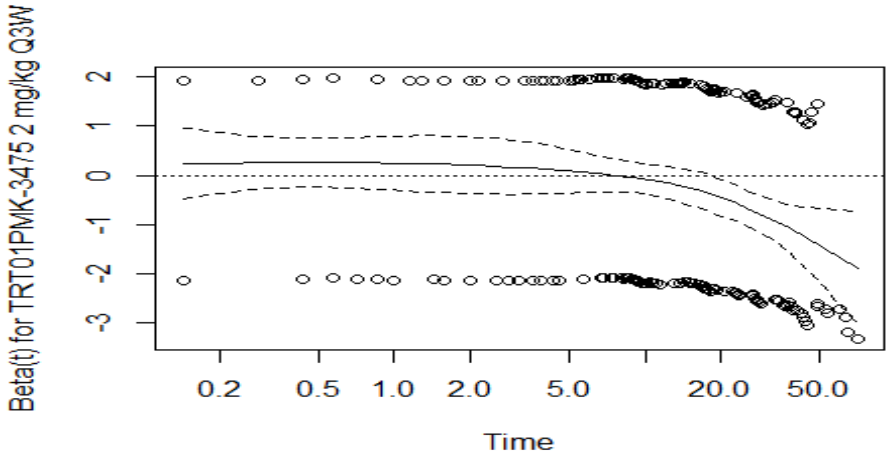


Figure 48. Fitted base case 2-phase piecewise models for PFS of pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

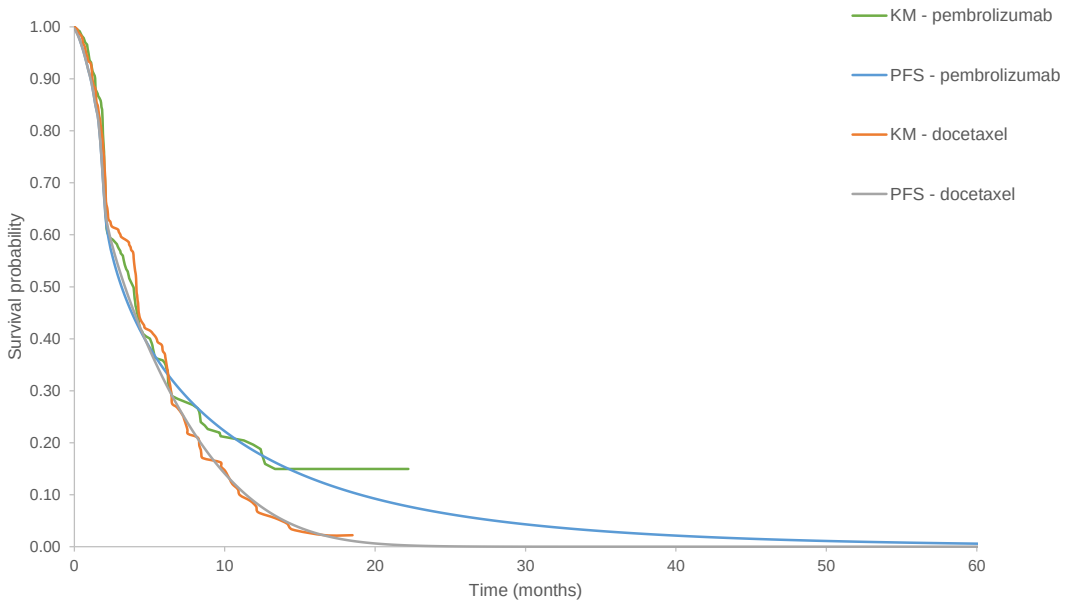


Table 69. Goodness-of-fit measures for PFS with cut-off of 9 weeks for the overall PD-L1 positive population

	Pembrolizumab		Docetaxel	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1340.9	1340.3	1262.9	1262.2
Weibull	1311.7	1314.5	1264.7	1267.3
Log-Normal	1327.6	1330.4	1319.2	1321.9
Log-Logistic	1318.6	1321.4	1296.8	1299.4
Gompertz	1317.7	1324.5	1258.7	1265.3
Generalised Gamma	1309.5	1314.4	1252.9	1257.5
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria.				

5.3.5 Adverse events

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients (at any grade) in either treatment arm, with two exceptions:

- Diarrhoea Grade 2 is also included to be consistent with previous NICE appraisal.[63]
- Febrile neutropenia (with a 4.9% incidence in the docetaxel arm) is also included as clinicians have suggested that this AE has significant impact on quality of life and costs. The inclusion of febrile neutropenia is also consistent with recent NICE appraisals.[63;64;121]

The AEs included in the economic model were validated by clinical experts.

The incidence of AEs was taken from the KEYNOTE-010 trial for each treatment arm (see Table 70). It should be noted that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on AEs of any grade. The unit cost and the disutility associated with the individual AEs were assumed to be the same for all treatment arms, therefore the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 70. This was consistent with the methods implemented in previous submissions[63;121] and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting.

In the base case, the impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost. These were then applied in the first cycle of the model for each treatment arm. However, AE-related disutilities were not considered as part of the base case since it could be considered that these were already accounted for as part of the EQ-5D utility values estimated from KEYNOTE-010 (see section 5.4.1). In sensitivity analysis we assessed the impact of including disutilities due to AEs derived from the published literature (see section 5.8.3).

Table 70. Grade 3+ AE rates for AEs included in the economic model based on Keynote-01 data

Adverse Event	Rate for pembrolizumab (Grade 3+)	Rate for docetaxel (Grade 3+)
Alopecia/ Hair loss	0.0%	0.6%
Anaemia	0.9%	1.6%
Asthenia	0.3%	1.9%
Decreased appetite	0.9%	1.0%
Diarrhea (grade 2)	2.9%	5.8%
Diarrhea	0.6%	2.3%

Adverse Event	Rate for pembrolizumab (Grade 3+)	Rate for docetaxel (Grade 3+)
Fatigue	1.2%	3.6%
Febrile neutropenia	0.0%	4.9%
Nausea	0.3%	0.3%
Neuropathy peripheral	0.0%	0.3%
Neutropenia	0.0%	12.3%
Neutrophil count decreased	0.0%	6.1%
Pruritus	0.0%	0.3%
Pyrexia	0.3%	0.3%
Rash	0.3%	0.0%
Stomatitis	0.0%	1.0%
Vomiting	0.0%	0.6%
WBC count decreased	0.0%	3.2%

5.3.6 Subsequent treatment

Given the advanced nature of the disease and the lack of data on further subsequent lines of therapy, only one line of subsequent therapy is modelled. Data from KEYNOTE-010 was used to estimate the proportions of patients in each treatment arm receiving different types of subsequent therapies. Table 71 presents the major categories of subsequent therapies for the pembrolizumab and docetaxel arms and the proportions of patients receiving each category of them. The complete list of subsequent therapies is presented in Appendix 29.

In the economic model, patients in the progressed disease health state were assumed to incur the costs of subsequent anti-neoplastic therapies as observed in the KEYNOTE-010 trial but with the clinical benefit, if any, being incorporated as part of the analysis derived from KEYNOTE-010. This is to ensure that the relevant cost of treatment for a progressed patient in different modelled treatment arms is accurately represented. A mean duration of 3.3 months was applied to all subsequent treatments, which is based on the previous nintedanib NICE appraisal.[63] For the docetaxel arm, since a switching adjustment was implemented as part of the OS projections, adjusting by the effect of anti-PD-1 agents, the cost related to these therapies was not accounted for in the model.

Table 71. Type and distribution of subsequent anti-neoplastic therapy based on Keynote-010

Adverse Event	Pembrolizumab arm	Docetaxel
Chemotherapy	34.6%	27.1%
Immunotherapy	0.6%	13.1%*
- Anti-PD-L1s	0.3%	12.5%
- Other	0.3%	0.6%
EGFR-TKI	8.4%	12.2%

ALK inhibitor	0.6%	1.2%
Other	4.1%	3.2%

Key: EGFR-TKI, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.
*Since the projected OS for docetaxel was adjusted, using the two-stage method, to reflect more accurately the impact of docetaxel in the absence of subsequent treatment with an anti-PD-1 agent, the cost of anti-PD-1s (12.5% of patients) was not accounted for as part of the costing.

5.3.7 Inputs from clinical experts

The timeframe for developing the submission in relation to the submission deadline restricted the opportunity to gain structured input.

We were able to arrange meetings with two clinical clinical oncologists working in lung cancer to discuss key issues.We tested the plausibility of the approach to modelling OS by asking the clinicians review the 5 year and 10 year survival percentages from the different approaches.

Table 72. Comparison of the OS rates at 5, 10 and 20 years with the alternative extrapolation scenarios included in the cost-effectiveness model

	Base case 1 Based on KEYNOTE-001 data (KM up to week52+Exponential up to 2 years +KEYNOTE-001 projection afterwards; Exponential best AIC/BIC fit)		**Base case 2** Conservative (KM+exponential only)	
	Pembro	**Docetaxel**	**Pembro**	**Docetaxel**
-5-year OS	12.15%	0.16%	10.18%	0.16%
-10-year OS	2.46%	0.00%	1.65%	0.00%
-20-year OS	0.10%	0.00%	0.04%	0.00%
	NLCA - Chemo PS0-1 patients stage IIIb/IV No rebase		**NLCA - Stage IIIb/IV patients** No rebase	
	Pembro	**Docetaxel**	**Pembro**	**Docetaxel**
-5-year OS	11.45%	3.25%	12.04%	3.42%
-10-year OS	8.86%	2.51%	7.70%	2.18%
-20-year OS	6.29%	1.78%	4.85%	1.38%

Pembrolizumab:

- The 5 year survival estimates from the two base case and the first two scenario analyses were agreed to all likely fall within the range expected by them (between 10% and 20%).
- The 10 year survival estimates were believed to be too low in both base cases, too high in the first of the scenario analyses and plausible in the second of the scenario analyses.

Docetaxel:

- For the 5 year survival estimate a figure of 2% to 3% would have been considered acceptable.
- For the 10 year survival estimate a figure of 0% as reflected in the two base cases was considered realistic.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

HRQoL was evaluated in the KEYNOTE-010 trial using the EuroQoL EQ-5D (see sections 4.3 and 4.7 above). All trial-based HRQoL analyses conducted for the purpose of the economic section were derived from this trial and the estimated utilities were used in the cost-effectiveness model. Evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case.[122]

In KEYNOTE-010, the EQ-5D questionnaire was administered at treatment cycles 1, 2, 3, 5, 9 and 13 (up to 13 cycles) when patients were on treatment. Additionally, it was administered at the discontinuation visit, and 30 days after (during the Safety Follow-up visit). The EQ-5D analyses presented below are based on the FAS population for the pembrolizumab 2mg/kg and the docetaxel arms, to be consistent with the anticipated licenced indication and the treatment arms included for the estimation of PFS, OS and safety from KEYNOTE-010 included in the economic model, as stated in section 5.3 above (cut-off date: 30th September 2015).

When estimating utilities, three approaches were considered:

- Estimation of utilities based on time-to-death.

  This approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease. The approach has been previously used in the estimation of HRQoL in NSCLC patients receiving palliative radiotherapy[120] and in advanced melanoma patients.[128-130] Time to death was demonstrated as more relevant than progression-based utilities since by considering more health states it offers a better HRQoL data fit.[128-130]

  Based on KEYNOTE-010 EQ-5D data, time to death was categorized into the following groups:

  - 360 or more days to death

- 180 to 360 days to death
- 30 to 180 days to death
- Under 30 days to death.

Additional analyses considered two categories for the estimation of time to death utilities:[131]

- 30 or more days to death
- Under 30 days to death.

EQ-5D scores collected within each time category were used to estimate mean utility associated with that category.

The analyses of the intervals related to time to death lower than 360 days focused on patients with observed death dates. The justification to exclude patients whose death dates were censored was that their EQ-5D values could not be linked to their time-to-death category. However, for the category of 360 or more days to death, patients with censored death date of 360 days or longer were also included since their EQ-5D data related to a survival of at least 360 days, independent of when the death date was censored.

- Estimation of utilities based upon whether or not patients have progressive disease.

  Another approach, more commonly seen in previous oncology economic modelling literature, is to define health states based on time relative to disease progression. While this approach generates results to fit the economic model by health state, there is a practical issue with the KEYNOTE-010 trial-based utility, where the utility data was collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit, but no further. Therefore, the utility data for post-progression is very limited as it is usually collected right after progression, thus missing the utility data as patients' HRQoL deteriorates when getting closer to death. This leads to an overestimate of the utility in the post-progression state. Another limitation to this approach is that progression is usually determined based on some relative change in tumour size from the baseline. However, baseline tumour sizes across studies can vary within a wide range and disease progression can be determined using different criteria within a same study and/or across studies. This makes it difficult to transfer utility results across studies, or even across disease phases.

  Following this approach, the date of progression used to estimate progression-based utilities was determined by IRC per RECIST.

- To estimate utilities for the progression-free health state, EQ-5D scores collected at all visits before the progression date were used.
- Utilities for the progressive state were based on the EQ-5D scores collected at all visits after the progression date.

- Combination of time-to-death and progression-based utilities.

  The progression-based and time-to-death approaches are not mutually exclusive but complementary, since patients suffer from both progression-related disutility and end-of-life disutility.[132] Therefore, this approach estimated the most appropriate utilities and was used in the base case analysis.

For each of the utility approaches, mean EQ-5D utility scores by health status were estimated per treatment arm (pembrolizumab 2mg/kg and docetaxel arms), and pooled for both arms. In addition, 95% confidence intervals were obtained for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was tested.

The level of EQ-5D compliance through time is presented in Table 73.

Table 73. Compliance of EQ-5D by visit and by treatment (FAS Population, TPS ≥ 1%)

Treatment Visit	Category	Pembrolizumab 2 mg/kg Q3W	Docetaxel 75 mg/m2 Q3W
		N = 345	N = 343
		n (%)	n (%)
Baseline	Expected to complete questionnaires	345	343
	Completed	321	278
	Compliance(completed per protocol)*	93.00%	81.00%
Week 3	Expected to complete questionnaires	340	334
	Completed	293	247
	Compliance(completed per protocol)*	86.20%	74.00%
Week 6	Expected to complete questionnaires	322	305
	Completed	276	215
	Compliance(completed per protocol)*	85.70%	70.50%
Week 12	Expected to complete questionnaires	282	257
	Completed	212	154
	Compliance(completed per protocol)*	75.20%	59.90%
Week 24	Expected to complete questionnaires	188	161
	Completed	122	72
	Compliance(completed per protocol)*	64.90%	44.70%
Week 36	Expected to complete questionnaires	118	86
	Completed	57	13
	Compliance(completed per protocol)*	48.30%	15.10%

Treatment Visit	Category	Pembrolizumab 2 mg/kg Q3W	Docetaxel 75 mg/m2 Q3W
		N = 345	N = 343
		n (%)	n (%)
*Compliance is the proportion of subjects who completed the PRO questionnaire among those who are expected to complete it at each time point (excludes those missing by design).			

UK preference-based scores were used for all patients analysed from the KEYNOTE-010 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique (see Appendix 22).[133]

A diagnostic analysis conducted to compare baseline EQ-5D utility scores, collected at the first visit (treatment cycle 1), showed that there was no significant difference in baseline utilities across the two treatment arms (see Appendix 22).

The estimated utilities are presented in Table 74 to Table 76 below.

Table 74: EQ-5D health utility scores by time-to-death

	Pembrolizumab 2 mg					Docetaxel					Pembrolizumab 2 mg and Docetaxel Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
All treated population															
≥360*	69	221	0.823	0.014	(0.794, 0.851)	45	135	0.781	0.015	(0.752, 0.810)	114	356	0.807	0.011	(0.786, 0.827)
[180, 360)	67	174	0.709	0.021	(0.666, 0.751)	58	140	0.726	0.018	(0.690, 0.762)	125	314	0.717	0.014	(0.688, 0.745)
[30, 180)	95	208	0.598	0.022	(0.554, 0.642)	97	201	0.655	0.019	(0.617, 0.693)	192	409	0.626	0.015	(0.596, 0.655)
<30	21	24	0.212	0.078	(0.049, 0.374)	14	15	0.429	0.093	(0.230, 0.629)	35	39	0.295	0.062	(0.170, 0.420)
† n=Number of patient with non-missing EQ-5D score															
‡ n=Number of records with non-missing EQ-5D score															
EQ-5D score during baseline is not included															
*This time-to-death category includes the records of the patients whose death dates were observed or censored ≥ 360 days after the report of EQ-5D scores. Other categories only include the records of patients with an observed death date.															

Table 75: EQ-5D health utility scores by progression status

	Pembrolizumab 2 mg					Docetaxel					Pembrolizumab 2 mg and Docetaxel Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
All treated population															
Progression free	296	976	0.765	0.008	(0.749, 0.782)	253	692	0.736	0.009	(0.719, 0.754)	549	1668	0.753	0.006	(0.741, 0.765)
Progressive	171	291	0.661	0.019	(0.624, 0.699)	102	139	0.669	0.022	(0.625, 0.714)	273	430	0.664	0.015	(0.635, 0.693)
† n=Number of patients with non-missing EQ-5D score															
‡ n=Number of records with non-missing EQ-5D score															
EQ-5D score during baseline is not included															

Table 76: EQ-5D health utility scores by progression status and time-to-death

	Pembrolizumab 2 mg					Docetaxel					Pembrolizumab 2 mg and Docetaxel Pooled				
	n[†]	n[‡]	Mean	SE	95% CI	n[†]	n[‡]	Mean	SE	95% CI	n[†]	n[‡]	Mean	SE	95% CI
All treated population															
Progression free															
≥360*	68	206	0.825	0.014	(0.796, 0.853)	45	126	0.780	0.016	(0.749, 0.811)	113	332	0.808	0.011	(0.787, 0.829)
[180, 360)	65	153	0.705	0.023	(0.660, 0.750)	55	118	0.733	0.019	(0.695, 0.770)	120	271	0.717	0.015	(0.687, 0.747)
[30, 180)	71	126	0.630	0.027	(0.576, 0.683)	85	158	0.681	0.021	(0.639, 0.722)	156	284	0.658	0.017	(0.625, 0.691)
<30	15	15	0.198	0.096	(-0.008, 0.404)	12	12	0.393	0.107	(0.158, 0.627)	27	27	0.284	0.072	(0.136, 0.433)
Progressive															
≥360*	13	15	0.793	0.070	(0.643, 0.944)	6	9	0.790	0.031	(0.718, 0.862)	19	24	0.792	0.045	(0.699, 0.885)
[180, 360)	15	21	0.738	0.065	(0.603, 0.874)	15	22	0.692	0.055	(0.577, 0.807)	30	43	0.714	0.042	(0.629, 0.799)
[30, 180)	54	82	0.548	0.038	(0.472, 0.624)	33	43	0.559	0.045	(0.467, 0.650)	87	125	0.552	0.029	(0.494, 0.610)
<30	9	9	0.234	0.142	(-0.094, 0.563)	3	3	0.577	0.199	(-0.279, 1.432)	12	12	0.320	0.122	(0.052, 0.588)

[†] n=Number of patient with non-missing EQ-5D score

[‡] n=Number of records with non-missing EQ-5D score

EQ-5D score during baseline is not included

*This time-to-death category includes the records of the patients whose death dates were observed or censored ≥ 360 days after the report of EQ-5D scores. Other categories only include the records of patients with an observed death date.

5.4.2 Mapping

Not applicable as HRQoL was derived from the KEYNOTE-010 EQ-5D data.

Utilities were evaluated using EQ-5D directly from patients from the KEYNOTE-010 trial, which is consistent with the NICE reference case.

5.4.3 Systematic searches for relevant HRQoL data

The relevant HRQoL data from the published literature were identified through a systematic literature search carried out during the period of 14th May 2015 and 15th May 2015 and updated in March 2016, for patients with advanced NSCLC, regardless of whether or not they were previously treated with platinum-containing chemotherapy (see Appendix 23 for more details). The objective was to identify HRQoL (in terms of utilities) associated with advanced NSCLC (see section 5.1).

A comprehensive literature search was carried out using the different databases presented in section 5.1: MEDLINE and MEDLINE In-process (using Ovid platform); EMBASE; The Cochrane Library which included the NHS EED and HTA database. In addition, manual searches were also performed. Such manual searches were performed on the American Society of Clinical Oncology (ASCO) conference proceedings and ISPOR, with additional papers identified from the reference list of included papers. The manual searches were constrained to the most recent 3 years (2013 to 2015). Further to the formal literature search and hand searches, the NICE website was searched to identify relevant information from previous submissions not otherwise captured.

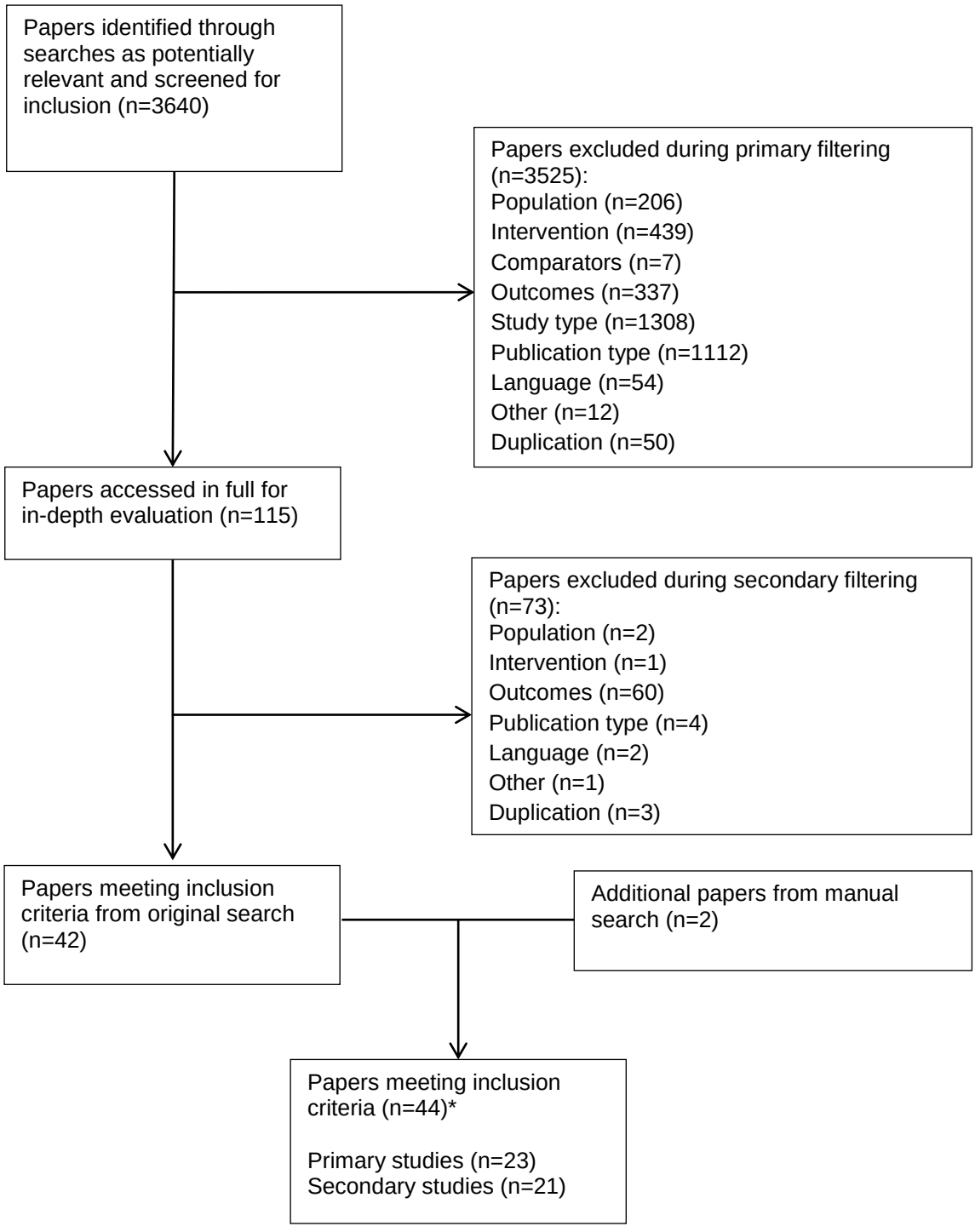
Appendix 23 provides details relative to the eligibility criteria for the HRQoL literature search along with details of the search strategy for HRQoL and utilities.

A total of 3,640 papers were identified as potentially relevant in the HRQoL and utilities search, with two additional papers being retrieved from the manual search. Figure 49 below displays the PRISMA diagram for the HROoL and utility literature search.

To ensure all relevant evidence was captured, the search was widened to patients with advanced NSCLC. In total, 44 studies were identified meeting the inclusion criteria, including 23 primary utility studies and 21 secondary utility studies (mainly cost-effectiveness studies where utilities were taken from other studies). Details of the identified primary and secondary studies are presented in Table 77 below and Appendix 24, respectively.
The search was updated in March 2016 to identify new studies published since the initial searches were conducted. Given that sufficient evidence was available in terms of HRQoL from the original search (see Table 77), the identification of new studies focused on those

reporting HRQoL using EQ-5D, to conform with the NICE reference case.[122] One additional study was identified from this search.[134]

Figure 49: PRISMA Diagram: HRQoL and Utility studies*



Key: *HRQoL, Health-related quality of life.*

*From the updated search conducted in March 2016, 432 additional hits were identified, one of them was included and is not accounted for in the above prisma diagram. The study was a primary study.

5.4.4 Provide details of the studies in which HRQoL was measured

Table 77: Characteristics of the primary HRQoL and utility studies identified

Reference	Publication type	Setting (patients)	Population	Previous treatment	Method of elicitation	Utilities included
Billingham et al. (2011)[135]	Abstract	UK	Advanced NSCLC	Platinum based chemotherapy (Gemcitabine + cisplatin or carboplatin)	EORTC QLQ-C30, LC13 and EQ-5D.	Baseline utility = 0.66 based on EQ-5D
Blackhall et al. (2014)[136]	Full text	Not reported	Previously treated patients with ALK-positive advanced NSCLC	Platinum based chemotherapy	EORTC QLQ-C30, LC-13, EQ-5D	Treatment arm (baseline/on treatment): Crizotinib 0.73/0.82 Pemetrexed 0.73/0.74 Docetaxel 0.67/0.66 Chemotherapy 0.70/0.73. Based on EQ-5D
Chevalier et al. (2013)[137]	Abstract	Multi-country	Advanced NSCLC	Not reported/ some 1st line patients	EQ-5D (French tariff)	Treatment line (progression-free/progressed): 1st 0.690/0.608 2nd 0.697/0.550 3rd / 4th 0.609/0.418
Chouaid et al. (2012)[138]	Abstract	Multi-country	Advanced NSCLC	1st to 4th treatment line patients	EQ-5D	Treatment line (progression free/progressed): 1st 0.71/0.68 2nd 0.72/0.59 3rd/4th 0.62/0.46
Chouaid et al. (2013b)[139]	Full text	Multi-country	Advanced NSCLC	1st to 4th treatment line patients	EQ-5D	Treatment line (progression free/progressed):All patients 0.66 1st 0.71/0.67 2nd 0.74/0.59 3rd/4th 0.62/0.46 PF 0.70 PD 0.58
Dooms et al. (2006)[140]	Full text	Belgium	Symptomatic advanced NSCLC	Gemcitabine or cisplatin–vindesine	Lung Cancer Symptom Score (LCSS)	Baseline utility 0.39 Average utility over 24 weeks: Cisplatin-vindesine 0.34 Gemcitabine 0.42

Reference	Publication type	Setting (patients)	Population	Previous treatment	Method of elicitation	Utilities included
Doyle et al. (2008)[141]	Full text	UK	Advanced, metastatic non-small cell lung cancer (assessed by a healthy population)	N/A	EQ-5D	Baseline utility 0.91 Treatment response plus no AE 0.712 SD plus no AE 0.626 SD plus cough 0.580 SD plus dyspnoea 0.576 SD plus pain 0.557 SD plus cough, dyspnoea and pain 0.461
Galetta et al. (2015)[142]	Full text	Italy	Chemotherapy-naive Stage IIIB/IV histologically or cytologically proven non-squamous NSCLC	N/A	EQ-5D	Cycles of treatment or time after initial treatment (stated as change from baseline, baseline not stated): After 3 cycles -0.011/-0.019 After 6 cycles -0.033/-0.063 After 12 weeks maintenance -0.041/-0.177 After 18 weeks maintenance 0.004/-0.091 Treatment arm: cisplatin with pemetrexed/carboplatin with paclitaxel and bevacizumab
Gridelli et al. (2012)[143]	Full text	Multi-country	Patients previously untreated with systemic chemotherapy who had advanced (Stage IIIB/IV) non-squamous NSCLC	Pemetrexed-cisplatin	EQ-5D	Baseline utility/induction treatment: Cycle 1 0.70/0.70 Cycle 2 0.72/0.73 Cycle 3 0.72/0.75 Cycle 4 0.73/0.76 See figure in the data extraction table for maintenance treatment.
Horgan et al. (2011)[144]	Full text	Not reported	Pre-treated advanced NSCLC	1 or 2 prior chemotherapy regimens including platinum	FACT-L	Treatment arm, change in utility with time.
Iyer et al. (2013)[145]	Full text	France & Germany	Advanced (Stage IIIB/IV) NSCLC	Not reported	FACT-L, LCSS and EQ-5D	Nationality, treatment line, overall utility. Mean health utility 0.58 (German 0.57, French 0.59) 1st line 0.63 2nd line 0.53. Based on EQ-5D.
Lee et al. (2011)[146]	Full text	Taiwan	NSCLC patients compared with healthy controls	Not reported	WHOQOL-BREF	WHOQOL-BREF values stated (72.5 ± 32.7 [5–100] for NSCLC group) but these were not mapped to utility values.

Reference	Publication type	Setting (patients)	Population	Previous treatment	Method of elicitation	Utilities included
Lewis et al. (2010)[147]	Full text	UK	Previously treated advanced NSCLC (assessed by a healthy population)	Second to third line treatment patients (1 or 2 prior chemotherapy regimes)	EQ-5D	Progression free (oral therapy) 0.451 Progression free (iv) 0.426 Disease progression 0.217 AE: Rash 0.4 Diarrhoea 0.32 Fatigue - Equal to progression free health state Anorexia - Equal to progression free health state Grade 4 neutropenia 0.32 Febrile neutropenia 0.19 Nausea 0.32 Infection - Equal to progression free health state Stomatitis 0.32 Neuropathy 0.31
Nafees et al. (2006)[148]	Abstract	UK	Previously treated advanced NSCLC (assessed by a healthy population)	N/A	EQ-5D	Stable disease with no toxicity (considered as base state) 0.66 Responding disease with no toxicity 0.67 Progressive disease 0.47 17 health states but most not described and utility not stated in abstract.
Nafees et al. (2008)[149]	Full text	UK	Different stages of NSCLC and different grade III-IV toxicities (assessed by a healthy population)	N/A	EQ-5D & SG	Intercept 0.6532 SD 0 (Stated as 0, but given as 0.653). Other health states given in relation to SD. Progressive -0.1798 Response 0.0193 Neutropenia -0.08973 Febrile neutropenia -0.09002 Fatigue -0.07346 Nausea & vomiting -0.0468 Diarrhoea -0.0468 Hair loss -0.04495 Rash -0.03248. Based on EQ-5D. Also gives Lloyd et al., utilities for metastatic breast cancer not related to NSCLC

Reference	Publication type	Setting (patients)	Population	Previous treatment	Method of elicitation	Utilities included
Reck et al. (2015)[134]	Abstract	Multi-country (CheckMate 017)	Second line, advanced squamous NSCLC patients	Not reported (but known to be heavily pretreated patients)	EQ-5D index and EQ-VAS	EQ-5D index scores: BL mean (sd): - Nivolumab: 0.683 (0.208)/ docetaxel: 0.663 (0.284) EQ-5D index was reported to improve significantly from BL at weeks 16 to 30 and weeks 42 to 54 (p≤0.05), with changes at weeks 42 to 54 large than the minimally important difference (i.e. 0.08)
Roughley et al. (2014)[150]	Abstract	France & Germany	Advanced NSCLC	Not reported.	EQ-5D	Site of metastasis: Brain metastasis 0.52 Contralateral lung metastasis 0.69 Adrenal glands 0.83 Liver 0.71 Bone metastasis 0.53
Schuette et al. (2012)[151]	Full text	Germany & Austria	Stage III/IV NSCLC patients who initiated second-line pemetrexed	Patients enrolled were about to start second line therapy.	EQ-5D	Baseline utility 0.66 2nd treatment cycle = Increase 0.02 6th treatment cycle = Increase 0.11 Other values were presented in the paper
Socinski et al. (2013)[152]	Poster abstract	Not reported	Primary chemo-radiotherapy resistant Stage III NSCLC	Platinum based chemotherapy, and radiotherapy.	EQ-5D	Baseline utility 0.79 Before to after treatment: Tecemotide -0.102 Placebo -0.136
Stopeck et al. (2013)[153]	Full text	Not reported	Castration resistant prostate cancer, breast cancer, and NSCLC	Not reported	EQ-5D	Baseline utility for NSCLC patients: 0.560
Tabberer et al. (2006)[154]	Full text	UK	NSCLC (assessed by a healthy population)	N/A	EQ-5D	Near-death (0.15) Progressed disease (0.22) Stable disease receiving IV therapy (0.43) Stable disease receiving oral therapy (0.45) Stable disease (0.46) Treatment response (0.49)

Reference	Publication type	Setting (patients)	Population	Previous treatment	Method of elicitation	Utilities included
Tongpak et al. (2012)[155]	Abstract	Thailand	Previously untreated Stage IIIB and IV NSCLC	Treatment naïve	Thai EQ-5D	Baseline utility for different stages of NSCLC disease: Stage IIIb 0.473 Stage IV 0.392 Overall 0.419
Trippoli et al. (2001)[156]	Full text	Italy	NSCLC	Not reported	SF-36, EuroQoL and EuroQoL VAS	Gender: M (0.58) F (0.67) Previous treatment: Surgery: Y (0.56) N (0.59) Chemotherapy: Y (0.59) N (0.57) Radiotherapy: Y (0.53) N (0.60) Metastasis: Present (0.53) Absent (0.68) Age: <65y (0.64) ≥65y (0.54) Time since diagnosis <12 months (0.61) ≥12 months (0.50). Based on EuroQol.
Verduyn et al. (2012)[157]	Full text	The Netherlands	Previously untreated EGFR M + NSCLC	Treatment naïve	FACT-L	Baseline utility 0.74 (EGFR M + patients) Other utility values from separate sources: SD 0.653 Objective response 0.053 IV/oral treatment decrement 0.043/ 0.014 AE decrement: Rash (0.03), Neutropenia (0.09)

Key: AE (Adverse event), BSC (Best supportive care), EGFR M+ (Epidermal growth factor receptor mutation positive), EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30), FACT-L (Functional Assessment of Cancer Therapy – Lung), LC13 (Lung cancer 13), LCSS (Lung cancer symptom scale), NSCLC (non-small cell lung cancer), SD (Stable disease), SF-36 (Short form-36), VAS (Visual analogue scale), WHOQOL-BREF (Short version of World Health Organisation quality of life assessment).

5.4.5 Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

Table 78 summarises utilities by health state that are potentially relevant for the de novo cost-effectiveness model, as identified from the systematic review, and the corresponding range of utility values reported for each health state. The reported utility values for the progression-free health state are generally consistent across different studies. However, for the progressed disease health state, the studies by Lewis et al. (2010)[147] and Tabberer et al. (2006)[154] reported much lower values (0.217 and 0.22, respectively) than the other studies. A potential explanation is that these two studies both assessed utilities from healthy volunteers, while the utilities from other studies were based on NSCLC patients.

Table 78: Summary of utilities by health states identified from the literature search and the references

Health state	Range of values	References
Potentially relevant for the de novo cost-effectiveness model		
Progression-free	0.69-0.70. PF utility reduced after multiple lines of therapy (4th line PF = 0.61)	Chevalier et al. (2013),[137] Chouaid et al. (2013b),[139] Lewis et al. (2010)[147]
Treatment cycle	0.70-0.73	Galetta et al. (2015),[142] Gridelli et al. (2012),[143] Schuette et al. (2012)[151]
Progression-free (iv/oral)	PF IV: 0.426, PF Oral: 0.451	Lewis et al. (2010)[147]
Progressed disease	0.217–0.608	Chevalier et al. (2013),[137] Chouaid et al. (2013b),[139] Lewis et al. (2010),[147] Nafees et al. (2006),[148] Nafees et al. (2008),[149] Tabberer et al. (2006)[154]
Near death	0.15	Tabberer et al. (2006)[154]
Other utilities identified from the systematic review		
Treatment line	PFS 1st 0.71 4th 0.62. PD 1st 0.67 4th 0.46	Chevalier et al. (2013),[137] Iyer et al. (2013),[145] Trippoli et al. (2001)[156]
Treatment arm	Varies depending on time recording. Dooms et al., CIS-Vin 0.34, GEM 0.42. Crizotinib 0.82, Chemo 0.73, PEM 0.73, DOC 0.74.	Blackhall et al. (2014),[136] Dooms et al. (2006),[140] Galetta et al. (2015),[142] Horgan et al. (2011)[144]
Stable disease	0.46–0.653. All values between 0.626–0.653 except Tabberer et al.	Doyle et al. (2008),[141] Nafees et al. (2006),[148] Nafees et al. (2008),[149] Tabberer et al. (2006),[154] Verduyn et al. (2012)[157]
Stable disease (iv/oral)	IV: 0.43, Oral: 0.45.	Tabberer et al. (2006),[154] Verduyn et al. (2012)[157]
BSC	Not evaluable. n = too small	Chouaid et al. (2013b)[139]
Site of metastasis/disease stage	Brain 0.52 - adrenal glands 0.83/overall NSCLC 0.419, Stage IIIb 0.473, Stage IV 0.392.	Roughley et al. (2014),[150] Tongpak et al. (2012)[155]
Key: BSC, best supportive care; CIS-Vin, cisplatin–vindesine; IV, intravenous; DOC, docetaxel; GEM, gemcitabine; PEM, pemetrexed; PD, Programme cell death; PF, progression free.		

Utilities based on the combination of progression-based and time-to-death utilities in the base case of the de novo cost-effectiveness model allow a better reflection of the HRQoL experienced by patients through time according to their health state (pre- vs. post-progression; see section 5.4.1 and Table 80). The values from this approach could not be directly compared to those of other advanced NSCLC NICE submissions since, to the best of our knowledge, the combined approach considering progression-based and time-to-death utilities has been previously used only in NICE submissions on advanced melanoma[11;12;131;158] but not until now in advanced NSCLC.

In a published Dutch study focused on stage IIIa/b and IV NSCLC patients treated with palliative chemotherapy, EQ-5D was estimated as a function of the time since randomisation.[120] The HRQoL of these patients remained relative stable until 3 months prior to death (although some variation was observed due to more severe patients dying earlier and therefore dropping out of the analysis). Towards the end of life, average EQ-5D utilities markedly decreased. This pattern in the HRQoL over time is in line with the time-to-death utility approach used in this submission. Additionally, the EQ-5D utility values reported for patients towards the end of life are consistent with those estimated in KEYNOTE-010 for patients with less than 30 days of life (around 0.3 or less, as reported in Figure 2 in the paper[120] and in line with the values for patients with less than 30 days of life in KEYNOTE-010, reported in Table 80 below). The ERG of the NICE submission for nivolumab in advanced NSCLC patients of squamous histology considered the utility values of this study as reflective of those for patients in the progressive health state. It should be noted that the patient population included in this study has some significant differences from that of KEYNOTE-010, mainly: patients in the Dutch study had more severe disease (stage IV or stage IIIa-IIIb with weight loss or ECOG 2+) and they had not been treated with chemotherapy but rather with radiotherapy for palliative purposes.

Table 79 presents a comparison of progression-based utility values from KEYNOTE-010 and those from previous NICE submissions in previously treated, advanced NSCLC patients, focusing on those with a population similar to that included in this submission (i.e. patients with EGFR/ALK positive mutations should have previously received therapy EGFR/TKI). Progression-based utility values estimated from KEYNOTE-010 are in line with those presented by manufacturers in previous NICE submissions in advanced NSCLC,[63;118] and with those reported in previous controlled trials of advanced NSCLC patients previously treated.[138;139]

Table 79. Progression-based utilities presented in recent advanced NSCLC submissions vs. those estimated from KEYNOTE-010

	Nintedanib+ docetaxel (TA347)[63;157]	Nivolumab [ID811][118;157]	Nafees et al. (2008) (Utilities preferred by the ERG during the appraisal of nivolumab)	Chouiaid et al. (2013)	KEYNOTE-010 [ID840]
Pre-progression	0.71 (week 0) to 0.661 (week 30)	0.75	0.65	0.74	0.753
Post-progression	0.64	0.592	0.43	0.46	0.664

It should be noted that cancer patients have been reported to value health states higher than the general population.[159-161] A potential reason for these high values may be related to chronically unwell, individuals having more to gain from an improvement in quality of life. Patients who have been regularly of ill health may perceive their improved health state, or a better hypothetical health state, of greater value.

During the appraisal of nivolumab for the treatment of advanced NSCLC patients with squamous histology the ERG, instead of accepting the EQ-5D utilities estimated directly from the study, preferred to use utilities derived from the general population usinga standard gamble utility method. [122] The ERG approach did not reflect the NICE reference case and, more importantly, it is likely to have resulted in an underestimation of the HRQoL valuation as opposed to that derived from patients themselves.

5.4.6 Describe how adverse reactions affect HRQoL

The impact of AEs on HRQoL was assessed by examining the EQ-5D health utilities of patients who experienced AEs (grade 3-5) compared to those who did not experience AEs in the progression-free health state.

For this assessment, the time points associated with grade 3-5 AEs for each patient were identified. EQ-5D scores collected at these time points were then used to estimate the utility of the progression-free state with grade 3-5 AEs. EQ-5D scores collected at other time points were used to estimate the utility associated with the progression-free health state in the absence of grade 3-5 AEs. The utility values for patients experiencing grade 3-5 AEs were significantly lower (0.68; 95% CI: 0.638, 0.722) than those of patients not experiencing grade 3-5 AEs (0.765; 95% CI: 0.752, 0.777; see Appendix 22).

It has been assumed for the purposes of the modelling that any impact of AEs on HRQoL has already been captured within the EQ-5D scores obtained from KEYNOTE-010 and

therefore no further decrement has been applied. This is a conservative assumption given that the overall AE profile of pembrolizumab is favourable compared with that of docetaxel.

5.4.7 Definition of the health states in terms of HRQoL in the cost-effectiveness analysis.

EQ-5D analyses based on KEYNOTE-010 data showed that patients who had progressive disease experienced a lower HRQoL than those in the pre-progression health state. However, due to the limited post-progression data available from the trial, progression related utilities do not show a large difference between pre and post-progression utilities, indicating that progression status alone is unlikely to be sufficiently reflective of changes in quality of life. When time-to-death was considered, HRQoL decreased over time as patients progressed closer to death. To capture HRQoL more appropriately, the pre- and post-progression health states were divided in sub-health states that reflected the time to death according to two categories (i.e. <30 days and ≥ 30 day).

5.4.8 Clarification on whether HRQoL is assumed to be constant over time in the cost-effectiveness analysis

A constant value for HRQoL is applied in each cycle taking into account whether patients were in the pre- or post-progression health states and considering time to death. An age-weighted utility decrement of 0.0044 is applied per year, from the age of 62 until 75, to reflect the natural decrease in utility associated with increasing age.[162]

5.4.9 Description of whether the baseline HRQoL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states

Not applicable.

5.4.10 Description of how and why health state utility values used in the cost-effectiveness analysis have been adjusted, including the methodologies used

The health state utility values have not been amended; however, as explained above, a yearly utility decrement applies as patients get older (above 62 until 75).

5.4.11 Identification of any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis

No health effects were excluded from the cost effectiveness analysis. HRQoL in the base case scenario is based upon both progression and time to death as clinical opinion has suggested that there is a decline in HRQoL associated to both progressive disease and the final months of life of advanced NSCLC patients.

5.4.12 Summary of utility values chosen for the cost-effectiveness analysis

The utility values chosen for the cost-effectiveness model are presented in Table 80.

Table 80: Summary of utility values for cost-effectiveness analysis

	Utilities**		Reference in submission (section and page number)	Justification
	Mean	95% CI		
Base case analysis – By progression status and time-to-death (days) – 2 categories				
Pre-progression				Utility values from KEYNOTE-010 with categories similar to those presented during the NICE appraisal of nivolumab[121]
≥30	0.763	(0.751, 0.774)		
<30*	0.284	(0.136, 0.433)		
Post-progression				
≥30	0.675	(0.644, 0.705)		
<30 **	0.320	(0.052, 0.588)		
By progression status and time-to-death (days) (KEYNOTE-010) – 4 categories				
Pre-progression			Section 5.4.1 Table 76 Page 188	Reported EQ-5D utilities in line with NICE reference case.[122] Use of progression-based and time to death utilities since approaches are complementary.[132]
≥360*	0.808	(0.787, 0.829)		
[180, 360)	0.717	(0.687, 0.747)		
[30, 180)	0.658	(0.625, 0.691)		
<30	0.284	(0.136, 0.433)		
Post-progression				
≥360*	0.792	(0.699, 0.885)		
[180, 360)	0.714	(0.629, 0.799)		
[30, 180)	0.552	(0.494, 0.610)		
<30	0.32	(0.052, 0.588)		
By time-to-death (days) (KEYNOTE-010) – 4 categories				
≥360*	0.807	(0.786, 0.827)	Section 5.4.1 Table 74 Page 187	Alternative utility values from KEYNOTE-010
[180, 360)	0.717	(0.688, 0.745)		
[30, 180)	0.626	(0.596, 0.655)		
<30	0.295	(0.170, 0.420)		
Progression based utilities (KEYNOTE-010)				
Progression-Free	0.753	(0.741, 0.765)	Section 5.4.1 Table Page	Alternative utility values from KEYNOTE-010
Progressed	0.664	(0.635, 0.693)		
By time-to-death (days) – 2 categories				
≥30	0.747	(0.735, 0.758)		Alternative utility values from KEYNOTE-010 with categories similar to those presented during the NICE appraisal of nivolumab[121]
<30	0.295	(0.170, 0.420)		

** This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days.*
*** Utilities from KEYNOTE-010 are pooled utilities*

5.4.13 Details of clinical expert assessment of the applicability of the health state utility values available

A European Advisory Panel was held in Dublin in February 2015 to discuss the Global approach to economic evaluation KEYNOTE-010. It was attended by three health economists and three oncologists.

When exposed to the trial based utility values, there was consensus on their credibility in relation to the population within the study.

Two UK oncologists consulted were not confident to offer an opinion as it was believed quality of life was too individual a value to arrive at a population value.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Parameters used in the cost effectiveness analysis

A summary of the variables used in the cost estimation is presented in Appendix 25.

5.5.2 Resource identification, measurement and valuation studies

The type of costs considered in the economic model included the drug and administration costs related to the intervention and comparator, including the costs related to subsequent therapies (see section 5.5.5), the monitoring and management of the disease (see section 5.5.6), the management of AEs (see section 5.5.7), and the costs related to terminal care (see section 5.5.6). In addition, for patients treated with pembrolizumab, the costs of testing for PD-L1 expression were also included (see section 5.5.5).

A systematic literature review was conducted to identify costs and resource use in the treatment and on-going management of advanced NSCLC patients from a UK perspective. The population criteria considered in the systematic review was not limited to include those with prior use of platinum-containing chemotherapy, to ensure the review captured sufficient relevant information to be of use to populate the economic model. The searches conducted for resource use data and the selection criteria followed for the identification and inclusion of relevant studies are provided in Appendix 26.

From 2,568 references identified from the search strategy as potentially relevant, and an additional six studies identified from manual searches and the updated searches conducted in March 2016, 14 studies were included for cost and/or resource use data extraction. Only seven of these studies specifically reported on resource use and costs of patients who had

prior use of platinum-containing chemotherapy. Figure 50 below presents the PRISMA diagram for the resource use and cost literature searches and a summary displaying the details of the included studies is available in Appendix 27.

Most studies are primary cost-effectiveness studies where a wide range of resource use and costs data were reported including costs for drugs, inpatients/outpatients, GPs/nurses, palliative and terminal care, and indirect costs. All included studies were in the UK setting, and therefore the reported costs are in terms of sterling pounds (GBP £).

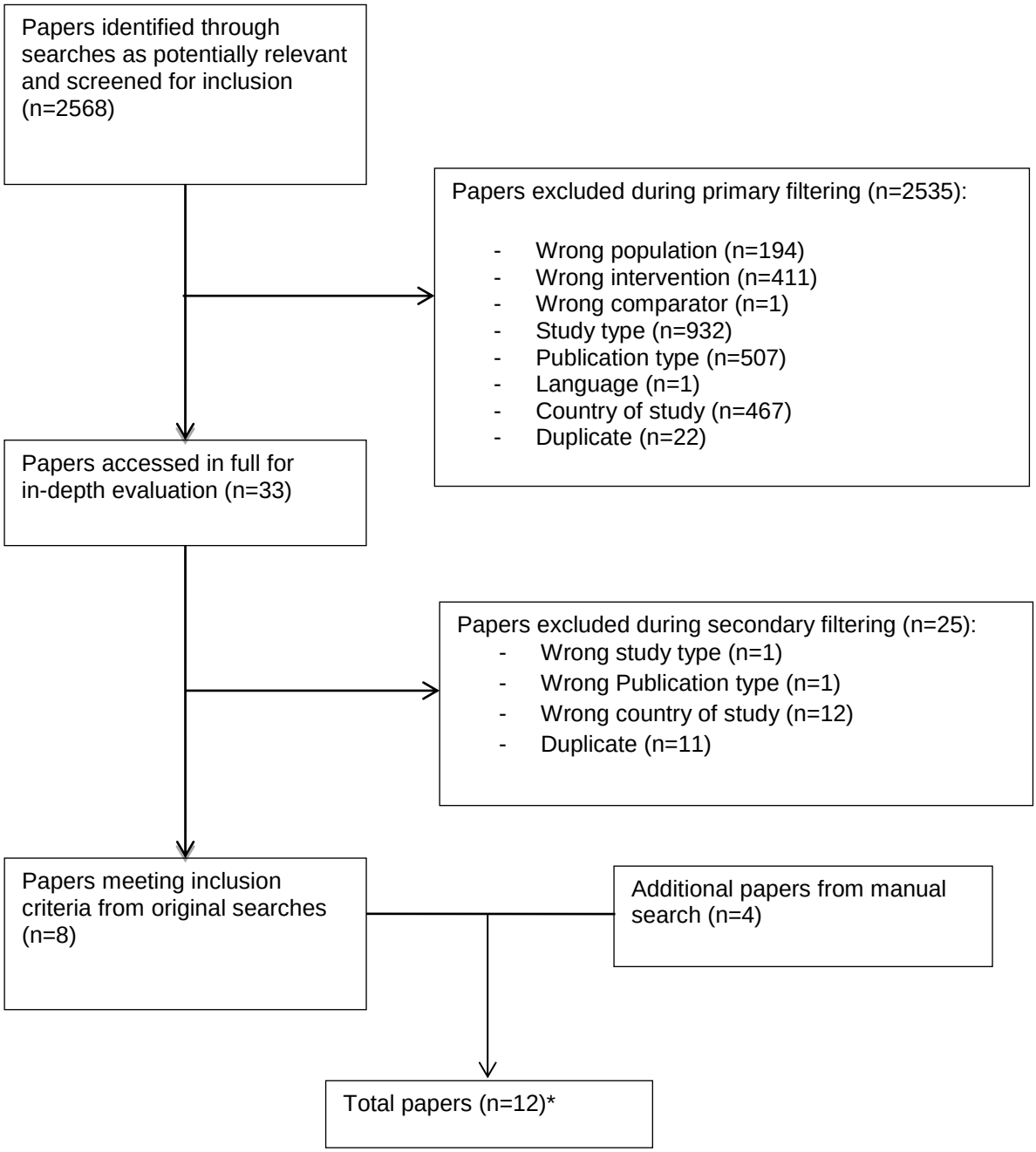
A variety of monetary costs relating to drug price, AEs and follow-up costs were identified. Docetaxel drug cost was reported to be between £4,338[163] and £5,022,[164] while its AE cost ranged between £374[164] and £760.[147] The studies were performed between 2004 and 2010 and may not represent current drug prices in the UK and costs for management AEs based on current UK clinical practice.

Additionally, a number of studies reported follow-up costs for health states. Lewis et al. (2010)[147] reported a total cost for progression free health state of £1,201 compared with disease progression health state of £6,151 for the docetaxel arm. McLeod et al. (2009)[164] presented different estimates for the pre- and post-progression health states of patients treated with docetaxel (£859 and £5,444, respectively). Lastly, Dickson et al. (2011) reported a cost of best supportive care in post progression survival of £1,405.[165]

The identified resource use and cost studies provide some useful information for the de novo cost-effectiveness model regarding the quantity and frequency of the use of resources and the unit monetary costs for AEs and follow up health state costs. However, a limitation of the resource use and cost data identified from these studies is that, due to the nature of resource use data, where prices and/or clinical practice may change over time, a large number of these studies may be considered out of date and not applicable in the current UK setting.

The final resource use and costs inputs applied in the model are presented in sections 5.5.4 to 5.5.7 with details and rationale for the sources used.

Figure 50: PRISMA diagram: resource use and cost studies



Key: N, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

*From the updated search conducted in March 2016, 290 additional hits were identified, one of them was included and is not accounted for in the above prisma diagram.

5.5.3 Use of NHS reference costs or payment-by-results (PbR) tariffs

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing pembrolizumab. Details about the cost estimation of treatment with pembrolizumab in terms of acquisition and administration are reported below. As previously agreed with NHS England (personal communication, 9th December 2014), the administration cost of pembrolizumab can be reflected through NHS Reference Cost code SB12Z, since this corresponds to the administration of a simple therapy (i.e. involving the administration of only one agent without IV anti-emetics), with the infusion only lasting half an hour.

5.5.4 Input from clinical experts

Clinical experts were not consulted due to time pressures.

5.5.5 Intervention and comparators' costs and resource use

Drug costs

The drug acquisition costs per treatment are presented below, with the unit costs for comparators being taken from the electronic market information tool (eMit), the British National Formulary and the Monthly Index of Medical Specialties (MIMS).

Pembrolizumab

As per the anticipated licence, the model uses a 2mg/kg dose of pembrolizumab, administered as a 30minute IV infusion every three weeks (Q3W) (see the SmPC in Appendix 1). The list price of a 50mg vial is £1,315.00.

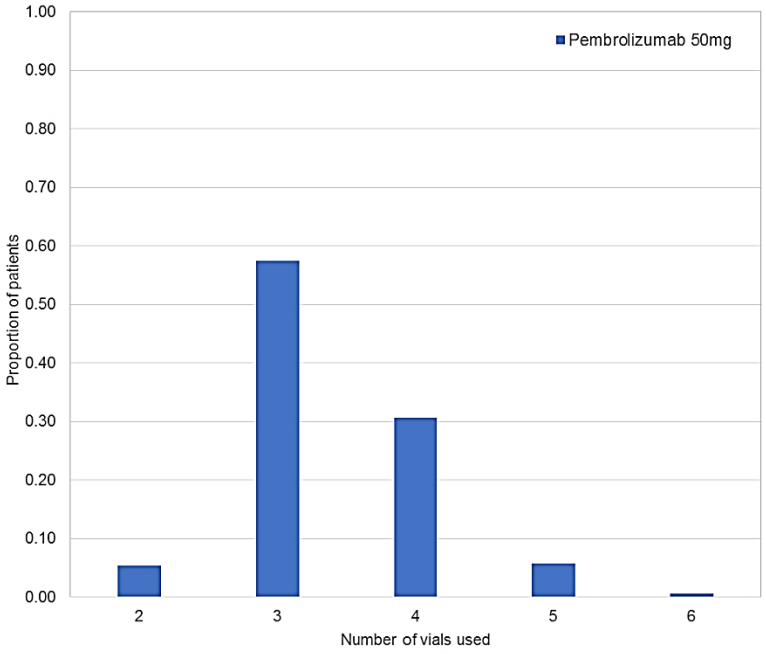
Data on the typical weight distribution of patients with NSCLC was not available for the UK. Therefore, the weight distribution from patients recruited from European sites in the KEYNOTE-010 clinical trial was used to estimate the distribution of the number of vials required for patients treated with pembrolizumab (see Table 81). No vial sharing is assumed within the model. Based on this assumption, the average number of vials required per patient per cycle was 3.39 (see Table 81). Based on the list price of pembrolizumab, the total drug cost per patient per administration is £4,453.13.

Table 81: Weight distribution from European patients* in KEYNOTE-010 and number of vials required for patietns treated with pembrolizumab

Weight Categories	Frequency	%	Total dose per administration (mg)	Vial required (assuming maximum weight in the band)	Cost per infusion (list price)
0-50kg	28	5.4%	0 to 100	2	
50-75kg	296	57.5%	100 to 150	3	
75-100kg	158	30.7%	150 to 200	4	
100-125kg	30	5.8%	200 to 250	5	
125-130kg	3	0.6%	250 to 300	6	
Total	**515**	**100.0%**		**3.39**	**£4,453.13**

*European patients are from the following countries: Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Portugal, Russian Federation, Spain, United Kingdom

Figure 51. Proportion of patients requiring different vial numbers per cycle (according to KEYNOTE-010 weight distribution by sex)



Docetaxel

For docetaxel, the model assumes that a dose of 75kg/m2 should be administered per cycle.[166] The prices of the docetaxel formulations available in the UK are presented inTable 82. The model uses the cheapest option regarding price per mg, which is based on the price of a 7ml (140mg) vial as reported in eMIT (pack price £20.95 and unit price £0.15 per mg), which is significantly lower than the price reported in MIMS. The weighted average BSA considering men and women recruited in European sites from KEYNOTE-010 was considered to estimate the average cost per dose of docetaxel per patient (see Table 83).[167]

Also, as a conservative assumption, full vial sharing is assumed for the administration of docetaxel. The total drug cost per patient per administration for docetaxel is £20.60.[167]

Table 82: Drug costs for docetaxel according to available vial sizes and sources

Concentration	Vial volume	Dose (mg/MU) per vial	MIMS[168]		eMIT[169]	
			Price per pack	Price per mg/MU	Price per vial/ pack	Price per mg/MU
20 mg/ml	1 ml	20	£153.47	£7.67	£4.55	£0.23
20 mg/ml	4 ml	80	£504.27	£6.30	£12.39	£0.15
20 mg/ml	7 ml	140	-	-	£20.95	£0.15
20 mg/ml	8 ml	160	£1,008.54	£6.30	£44.84	£0.28

Table 83: Estimation of the dose per cycle per patient based on the baseline body surface area (BSA) from KEYNOTE-010 patients (EU Patients)

Gender	Mean BSA in m^2	% of patients	Dose per infusion
Female	1.7	38.6%	127.5
Male	1.92	61.4%	144.0
Weighted average	1.85	100%	137.63

*European patients are from the following countries: Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Portugal, Russian Federation, Spain, United Kingdom

Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1

Nintedanib

Nintedanib is administered orally as 200mg twice daily in a soft capsule.[123] The list price of nintedanib according to the pack size is presented in Table 84.

Table 84. Drug costs for nintedanib (at list prices) according to available pack sizes

Concentration	Number of pills	Dose per pack	MIMS[168]	
			Price per pack	Price per mg
100 mg	120	12000	£2,151.10	£0.18
150 mg	60	9000	£2,151.10	£0.24

A patient access scheme (PAS) is in place for nintedanib. The level of discount presented in this scheme is unknown; therefore, the list price is presented in Table 84.

Following the feedback provided by the ERG for the nintedanib NICE submission,[167] in clinical practice tablets are dispensed to patients at the time of docetaxel administration in

blister packs sufficient to self-treat until the date of the next docetaxel dose (i.e. for days 2 to 21 of each cycle). Any missing doses are unlikely to affect the dispensing pattern. Therefore, missed doses will not alter the amount and cost of the product dispensed.

It is assumed that patients on the standard dose of 200mg twice per day use the 30-day pack of 100 mg capsules (120 pills) and patients on the reduced dose of 150mg twice per day use the 30-day pack of 150 capsules (60 pills). As both packs cost the same (£2,151.10), the daily cost per patient is the same, which is £71.70 per day, regardless of standard dose or reduced dose of 150mg twice per day. A further reduced dose of 100mg twice daily is also possible in patients who experience adverse events. The proportion of patients in the UK who would be on this dose of nintedanib is unknown and the model did not take into this dose level for the calculation of nintedanib drug costs. Therefore, the nintedanib drug cost per patient per day used in the model is £71.70.

Number of administrations required, unit costs and total drug costs per treatment per cycle

As per the anticipated licence, patients treated with pembrolizumab are expected to be treated until disease progression is confirmed. Therefore, PFS has been used as a proxy for the time on treatment with pembrolizumab. For both pembrolizumab and docetaxel arms in KEYNOTE-010, time on treatment is shorter than PFS due to discontinuation caused by AEs and other reasons for discontinuations before progression. To account for the difference between time on treatment and PFS, HRs for time on treatment versus PFS were calculated and used to calculate proportions of patients on treatment based on proportion of patients who are progression-free in each model cycle for pembrolizumab and docetaxel arm. The HRs are presented in Table 85.

Table 85: Hazard ratios for time on treatment versus progression free survival for pembrolizumab 2mg/kg and docetaxel based on KEYNOTE-010

Hazard ratio (time on treatment vs progression free survival)	Mean	Confidence interval
Pembrolizumab (2mg/kg) – overall population	1.039	(0.876, 1.232)
Docetaxel - overall population	2.078	(1.751, 2.466)
Pembrolizumab (2mg/kg) – adenocarcinoma	1.033	(0.839, 1.271)
Docetaxel - adenocarcinoma	1.982	(1.611, 2.439)

For patients who are on treatment, adjustments were made based on the actual proportion of patients receiving the planned dose within KEYNOTE-010. For this, data regarding dose interruption occurring within KEYNOTE-010 was analysed and incorporated into the model per administered cycle of pembrolizumab and docetaxel. These analyses showed that, on

average, 90.75% of patients on pembrolizumab and 77.15% of patients on docetaxel received their planned doses.

In the base case analysis we assumed a maximum treatment duration of 18 weeks for docetaxel monotherapy, to reflect clinical practice in England (i.e. a maximum of 6 cycles; see section 5.2.5). After accounting for the adjustments mentioned above, the average number of docetaxel cycles received per patient was 3.64, which was lower than that reported as part of KEYNOTE-010 (i.e. 3.88 cycles on average per patient treated in the docetaxel arm).[82]

For the analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, we assumed that patients receiving nintedanib in combination with docetaxel would continue treatment with nintedanib after discontinuation of docetaxel for as long as they remained progression-free (assuming that being progression-free reflects clinical benefit, to reflect the recommended posology for nintedanib).[123] The same maximum number of docetaxel cycles was assumed for the combination with nintedanib (see above).

Administration costs

Pembrolizumab

Given the time required for the administration of pembrolizumab is 30 minutes, the code for 'simple parenteral chemotherapy – outpatient' SB12Z was used to reflect administration costs.[170] This was considered an appropriate approach as it had been previously agreed with NHS England (personal communication, 9th December 2014).

Docetaxel

According to the SmPC, the time required per administration is 60minutes every 3 weeks, and so along with pembrolizumab, the code considered appropriate to reflect administration costs for docetaxel is 'simple parental chemotherapy – outpatient' SB12Z.[170]

Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1

For the analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the same administration costs as that used for docetaxel as monotherapy were assumed.

Nintedanib

As nintedanib is taken orally, it is not associated with any additional administration costs[167] as long as patients are still receiving docetaxel. Once docetaxel is discontinued and patients continue treatment with nintedanib (i.e., after a maximum of six cycles of docetaxel), the administration cost of for nintedanib is assumed to be 12 minutes of pharmacist time every 30 days.

Table 86 summarised the administration costs used in the model.

Table 86: Administration costs used in the model[170]

Treatment	Type of Administration Required	NHS Code	Cost
Pembrolizumab	Simple Chemotherapy	SB12Z	£257.11 per administration
Docetaxel*	Complex chemotherapy	SB12Z	£257.11 per administration
For additional analyses on the subpopulation of NSCLC patients with tumours that are PD-L1 positive and of adenocarcinoma histology			
Nintedanib	Oral chemotherapy (dispensed while patients receive docetaxel)	-	£0.00
	Oral chemotherapy (after discontinue of docetaxel)		

*It applies independent of whether docetaxel is administered as monotherapy or as combination therapy with nintedanib.

Costs associated with PD-L1 testing

Pembrolizumab is anticipated to be licensed for patients with NSCLC that is PD-L1 positive, as assessed by a validated test.

Based on the information and calculations presented in section 6.2, we estimate that 12% of patients with NSCLC stage IIIB/IV will be eligible for treatment with pembrolizumab in England. This means that to identify one patient with NSCLC stage IIIB/IV eligible for treatment with pembrolizumab, 8.39 total patients will need to be tested for PD-L1 expression.

A single PD-L1 test will cost £40.5 per patient tested, which equates to a cost of £337.51 per patient with NSCLC whose tumour expressesPD-L1 and therefore eligible for treatment with pembrolizumab in either second or third line therapy (see Table 87 and Section 6.2). This cost was applied only to the pembrolizumab arm of the model.

Table 87: Cost of PD-L1 testing per patient eligible for treatment with pembrolizumab

% of people eligible for treatment with pembrolizumab among patients with NSCLC stage IIIb/IV	12%
PD-L1 test cost	£40.5
Total PD-L1 costs	£337.51

*Sources: see Section 6.2.

Costs associated with subsequent therapies received by patients after treatment discontinuation

The average cost of subsequent treatment was calculated by weighting the proportions of patients receiving each subsequent treatment and the unit cost of each subsequent treatment (see Section 5.3.6 and Appendix 5.3.6), assuming an average duration of treatment of 3.3 months (14.4 weeks).[63] This weighted cost was applied during 14.4 cycles to patients who moved to the post-progression health state.

5.5.6 Health-state unit costs and resource use

There is relatively limited published literature that explores in detail the resource use associated with patients with NSCLC previously treated. Consequently, the main source of resource utilisation per health state used in this submission is the the nintedanib submission (TA347).[63]

Monitoring and disease management costs

There are three health states included in the model, Progression free (PF), Progressed (PD) and death.

Patients incur disease management costs for as long as they remain on treatment, and potentially longer. The unit costs of treatment are consistent over cycle lengths; however the frequency of resource consumption per cycle varies depending on the health state.

Table 88 shows the resource use for monitoring and disease management in the progression-free health state, and the resource use for the progressive disease health state is displayed in Table 89. Table 92 displays the unit costs for both PF and PD health states.

Table 88: Resource use for progression-free health states[63]

Resource	No. required per 3 weeks	% of patients requiring resource	Unit cost	Cost per 3 weeks
GP outpatient visit (for docetaxel only)	0.28	100%	£38.00	£10.64
Oncologist	1.00	100%	£167.12	£167.12
Full blood test	1.00	100%	£3.01	£3.01

Resource	No. required per 3 weeks	% of patients requiring resource	Unit cost	Cost per 3 weeks
Electrolytes	1.00	100%	£1.19	£1.19
Liver function test	1.00	100%	£1.19	£1.19
Renal function test	1.00	100%	£1.19	£1.19
CT scan (thorax or abdominal)	0.28	100%	£92.03	£25.77
Total cost per week (excluding GP outpatient visits)	£66.49 per week			

GP, general practitioner; CT, computerised tomography; PF, progression free;

Table 89: Resource use for progressed disease health state[63]

Resource	No. required per 3 weeks	% of patients requiring resource	Unit cost	Cost per 3 weeks
Oncologist	0.46	100%	£167.12	£76.88
Full blood test	1.00	100%	£3.01	£3.01
Electrolytes	0.46	100%	£1.19	£0.55
Liver function test	0.46	100%	£1.19	£0.55
Renal function test	0.46	100%	£1.19	£0.55
CT scan (thorax or abdominal)	0.28	100%	£92.03	£25.77
Total cost per week	£35.64 per week			

GP, general practitioner; CT, computerised tomography; PD, progressed disease;

Costs at treatment initiation and at the time of progression

One-off costs for treatment initiation (see Table 90) and upon disease progression (see Table 91) were also included in the model. Table 92 displays the sources considered for the estimation of these one-off costs.

Table 90: Resource use for treatment initiation (one-off costs) based on Iain et al, 2015

Resource	% patients	Resource use	Unit costs
GP outpatient visit	4%	2.00	£37.00
Oncologist	81%	3.60	£167.12
Radiotherapist (brain)	6%	2.30	£131.97
Palliative care	1%	1.00	£118.30
Psychologist	1%	1.00	£139.24
Full blood test	100%	1.20	£3.01
Complete metabolic panel	100%	1.20	£1.19
Lactate dehydrogenase test	100%	1.20	£1.19
CT scan (thorax or abdominal)	100%	1.00	£92.03
99Tc bone scintigraphy scan	17%	1.00	£201.12
X-ray	18%	1.00	£30.23

Resource	% patients	Resource use	Unit costs
Echography	5%	1.00	£55.63
MRI of brain	15%	1.00	£150.37
PET scan	5%	1.00	£150.37
Oncology/general ward per day (Treatment initiation)	6%	2.80	£302.96
Total cost	£730.88 (one-off cost)		

Table 91: Resource use upon disease progression (one-off costs)[63]

Resource	% patients	Resource use	Unit costs
CT scan (thorax or abdominal)	100%	1.00	£92.03
CT scan (brain)	40%	1.00	£92.03
Total cost	£128.84 (one-off cost)		

Table 92: Unit costs

Resource	Unit cost	Source
GP outpatient visit	£37.00	PSSRU 2015: Per patient contact lasting 11.7 minutes, including direct care staff costs, without qualification costs (p177)
Oncologist	£167.12	NHS reference costs 2014-15: WF01A, Non-Admitted Face to Face Attendance, Follow-up, 370, Medical Oncology
Radiotherapist (brain)	£131.97	NHS reference costs 2014-15: WF01A, Non-Admitted Face to Face Attendance, Follow-up, 800, Clinical Oncology (Previously Radiotherapy)
Radiotherapist (bone)	£131.97	NHS reference costs 2014-15: WF01A, Non-Admitted Face to Face Attendance, Follow-up, 800, Clinical Oncology (Previously Radiotherapy)
Palliative care	£118.30	NHS reference costs 2014-15: Weighted sum of SD04A (Outpatient, Medical Specialist Palliative Care Attendance, 19 years and over) and SD05A (Outpatient, Non-Medical Specialist Palliative Care Attendance, 19 years and over) by activity.
Psychologist	£139.24	Unit cost of clinical psychologist per hour of client contact in PSSRU 2014 (p183) was inflated to 2014/15 using the PSSRU HCHS index (Curtis, 2015); 1 hour visit assumed.
Full blood test	£3.01	NHS reference costs 2014-15: Direct Access Pathology Services, DAPS05, Haematology
Electrolytes	£1.19	NHS reference costs 2014-15: Direct Access Pathology Services, DAPS04, Clinical Biochemistry
Liver function	£1.19	NHS reference costs 2014-15: Direct

Resource	Unit cost	Source
		Access Pathology Services, DAPS04, Clinical Biochemistry
Renal function	£1.19	NHS reference costs 2014-15: Direct Access Pathology Services, DAPS04, Clinical Biochemistry
Complete metabolic panel	£1.19	NHS reference costs 2014-15: Direct Access Pathology Services, DAPS04, Clinical Biochemistry
Lactate dehydrogenase test	£1.19	NHS reference costs 2014-15: Direct Access Pathology Services, DAPS04, Clinical Biochemistry
CT scan (thorax or abdominal)	£92.03	NHS reference costs 2014-15: HRG data, RD20A, Computerised Tomography Scan of one area, without contrast, 19 years and over
CT scan (brain)	£92.03	NHS reference costs 2014-15: HRG data, RD20A, Computerised Tomography Scan of one area, without contrast, 19 years and over
99Tc bone scintigraphy scan	£201.12	NHS reference costs 2014-15: HRG data, RN16A, Nuclear Bone Scan of other phases, 19 years and over
X-ray	£30.23	NHS reference costs 2014-15, Direct Access Plain Film, DAPF
Echography	£55.63	NHS Reference costs 2013-14 Average of RA23Z/RA24Z/RA25Z/RA26Z/RA27Z, inflated to 2014/15 using the PSSRU HCHS index (Curtis, 2015)
MRI of brain	£150.37	NHS Reference costs 2013-14 Average of RA01A/RA02A/RA03Z, inflated to 2014/15 using the PSSRU HCHS index (Curtis, 2015)
PET scan	£150.37	NHS Reference costs 2013-14 Average of RA01A/RA02A/RA03Z, inflated to 2014/15 using the PSSRU HCHS index (Curtis, 2015)
Oncology/general ward - inpatient per day (Treatment initiation)	£302.96	NHS reference costs 2014-15: Weighted average of excess bed days for elective and non-elective inpatients for all HRGs by activity

GP, general practitioner; CT, computerised tomography; PF, progression free; PD, progressed disease;

Cost of terminal care

A one-off cost is applied to those patients at the moment of dying to reflect the cost of terminal care. The resource consumption reflects treatment received in various care settings, and is based on the values used in the NICE MTA for erlotinib and gefitinib (TA374).[64] These costs are assumed to be the same for all treatments (see Table 93).

Table 93: Unit costs of terminal care patients

Resource	Unit cost	Number of consumption	% of patients in each care setting	Total cost	Reference
Community nurse visit (per hour)	£67.00	28.00 hours	27%	£512.15	PSSRU 2014: Cost per hour of patient-related work (p187)
GP Home visit	£88.92	7.00 visits	27%	£169.93	PSSRU 2014: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel (p194-195)
Macmillan nurse	£44.69	50.00 hours	27%	£610.00	Assumption used in the Erlotinib MTA (ID620, 2015)
Drugs and equipment	£518.76	Average drug and equipment usage	27%	£141.62	The value used in Erlotinib MTA (Marie Curie report figure of £240 increased for inflation) was inflated to 2013/14 (ID620, 2015)
Terminal care in hospital	£3,021.44	1 episode (8.93 days)	56%	£1,685.96	The value used in Erlotinib MTA (£2,716.53 + 0.84 excess days @ £232.90 per day) was inflated to 2013/14 (ID620, 2015)
Terminal care in hospice	£3,776.80	1 episode (8.93 days)	17%	£638.28	Assumption used in the Erlotinib MTA (25% increase on hospital IP care) (ID620, 2015)
Total cost	£3,757.94 (one-off cost)				

5.5.7 Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section 5.3.5. The approach used to consider the impact of AEs as part of the cost-effectiveness assessment is described in section 5.4.6.

The unit costs related to the management of AEs were mainly derived from a previous NICE MTA (TA374)[64] and were inflated to 2014/15 prices using the hospital and community health services (HCHS) index published by the Personal and Personal and Social Services Research Unit for 2015.[171] When unit costs are not available from TA374,[64] data from other recent NICE appraisals was used.[63;121]

Table 94: Unit cost per AE as used in previous submissions and values used in the de novo model

	Erlotinib & gefitinib TA374[64] (NICE), 2015 183 /id}	Nivolumab (ID811)[172]	Nintedanib (TA347)[63]	Unit costs used in the de novo model	Sources
Unit used to inflated to 2014-15 using PSSRU HCHS indices	**1.04**	**1.00**	**1.02**		*Curtis and Burns (2015)* [171]
Alopecia/ Hair loss	£0.00			£0.00	TA374[64]
Anaemia			£2,610.66	£2,610.66	*TA347*[63]
Asthenia		£3,015.13		£2,317.20	*ID811*[121]
Decrease appetite				£0.00	Assumed 0
Diarrhea (grade 2)			£442.76	£442.76	TA374[64]
Diarrhea (grade 3-4)	£1,090.19		£2,108.73	£1,090.19	TA374[64]
Fatigue	£2,317.20	£3,015.13	£2,610.66	£2,317.20	TA374[64]
Nausea	£1,090.19		£2,038.34	£1,090.19	TA374[64]
Neuropathy peripheral				£0.00	Assumed 0
Neutropenia	£179.83	£354.72	£560.08	£179.83	TA374[64]
Neutrophile count decreased				£179.83	Assumed to be the same as neutropenia
Pruritus					Assumed 0
Pyrexia				£0.00	Assumed 0
Rash	£113.89		£2,433.15	£113.89	TA374[64]
Stomatitis				£0.00	Assumed 0
Vomiting			£2,038.34	£2,038.34	TA347[63]
WBC count decreased			£560.08	£560.08	TA347[63]
Febrile neutropenia	£7,331.78		£2,339	£7,331.78	TA374[64]

5.5.8 Miscellaneous unit costs and resource use

There are no additional costs included in the model apart from those outlined in the previous sections.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Tabulated variables included in the cost-effectiveness analysis

A table summarising the full list of variables applied in the economic model is presented in Appendix 25.

5.6.2 For the base-case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible

The base-case cost-effectiveness analysis reflects the NICE reference case as closely as possible.

5.6.3 List of all assumptions used in the de novo economic model with justifications for each assumption

Table 95 summarised the assumptions used in the economic model.

Table 95: List of assumptions used in the economic model

Area	Assumption	Justification
Comparator	Docetaxel monotherapy is the appropriate comparator and reflects UK clinical practice. Nintedanib in combination with docetaxel is the additional comparator for the population with NSCLC of adenocarcinoma histology.	Docetaxel monotherapy is the standard second line treatment of advanced NSCLC in the UK and is therefore the key comparator. Nintedanib in combination with docetaxel has been approved for treating advanced NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy (TA347) and therefore is only a relevant comparator for this population subgroup.
Treatment pathway	Once patients progress they receive subsequent therapies as experienced by patients in KEYNOTE-010.	The use of subsequent treatments as observed in KEYNOTE-010 trial is consistent with the OS efficacy inputs used in the model which are based patients receiving these subsequent treatments. Patients in the docetaxel arm are assumed not to receive anti-PD-1 agents since their OS efficacy estimates are adjusted to control for the impact of switching to these agents.

Area	Assumption	Justification
Time horizon	20 years	The average age of patients in the model is 62. A lifetime horizon is in line with NICE reference case. A duration of 20 years is considered long enough to reflect the difference in costs and outcomes between pembrolizumab and docetaxel monotherapy as assessed in this submission. This duration is in line with a recent NICE submission assessing an immunotherapy for NSCLC patients of squamous histology.[121]
Population	Endpoints obtained from patients treated with pembrolizumab 2mg/kg Q3W in KEYNOTE-010 are applicable to the target population, as for the anticipated licence	Only data for patients treated with pembrolizumab 2mg/kg Q3W as part of the KEYNOTE-010 trial is used for the analysis. This is consistent with the anticipated licenced dose of pembrolizumab for treating NSCLC in PD-L1 expressers in the UK. The KEYNOTE-010 trial is also the most relevant trial for the population identified as part of the decision problem (see section 1.1).
Efficacy	Use unadjusted KM data for the first 52 weeks from KEYNOTE-010 trial to model OS for pembrolizumab and docetaxel	The 2-phase piecewise method (KM plus exponential) has been suggested as the most appropriate approach by ERGs in recent NICE STAs (TA347, ID811) or has been used by an assessment group for a recent NICE MTA (TA374). Patient numbers in KEYNOTE-010 are large and OS KM data provides the more robust and reliable estimate for the first 52 weeks (1 year). Furthermore, standard parametric curves do not provide good visual fit compared to the 2-phase piecewise method. The cumulative hazard plot also suggests that piecewise model may be preferred.
	The efficacy of nintedanib in combination with docetaxel for PD-L1 expressers is similar to that observed for advanced patients with NSCLC of adenocarcinoma histology.	There is no evidence on the efficacy of nintedanib in combination with docetaxel on patients with advanced NSCLC that are PD-L1 expressers. Therefore, to enable comparisons across treatments for this subpopulation, similar efficacy to that of the population with NSCLC of adenocarcinoma type had to be assumed.
	Proportional hazard is assumed to hold for nintedanib in combination with docetaxel versus docetaxel for the efficacy estimates associated with advanced patients with NSCLC of adenocarcinoma histology	Patient level data is not available for the trial assessing nintedanib in combination with docetaxel. Therefore, an indirect treatment comparison was performed using aggregate outcomes from LUME-Lung 1 and KEYNOTE-010 trial to estimate OS and PFS HRs for nintedanib in combination with docetaxel versus docetaxel. This indirect treatment comparison relied on the proportional hazards assumption.
HRQoL	The quality of life of patients is appropriately captured by considering time to death and progression-based utilities rather based on progression-based utilities alone or time-to-death utilities alone	Clinical opinion suggests there is a decline in HRQL in the final months of life of advanced NSCLC patients which may not appropriately be captured solely through the use of progression-based health state. This was supported by the feedback provided by the ERG of previous NICE oncology submissions, which supported the use of a complementary approach (including both progression-based and time to death utilities) rather than considering these approaches independently. In sensitivity analyses, the impact of considering alternative approaches (e.g. progression-based only and time-to-death independently) was considered.

Area	Assumption	Justification
Safety	The incidence of AEs from KEYNOTE-010 trial was assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-010 trial (i.e. grade 3-5 AEs (incidence≥5% in one or more treatment groups, considering any grade)). The same method and criteria were applied in recent NICE appraisals for previously treated advanced NSCLC patients (TA347, ID811).
Costs	PD-L1 test cost is based on 12% of patients with NSCLC stage IIIB/IV being eligible for treatment with pembrolizumab in England, i.e., 8.39 tests are required to identify 1 patient who is eligible to be treated with pembrolizumab.	If pembrolizumab were to be recommended by NICE, testing for PD-L1 status would become standard practice. Based on the information and calculations presented in section 6.2, we estimate that 12% of patients with NSCLC stage IIIB/IV will be eligible for treatment with pembrolizumab in England. This means that to identify one patient with NSCLC stage IIIB/IV that is eligible for treatment with pembrolizumab, 8.39 patients will need to be tested for PD-L1 expression.

5.7 Base-case results

5.7.1 Base-case cost effectiveness analysis results

The results of the economic model are presented in Table 96 below.

For **base case 1**, the estimated mean overall survival was 1.90 years for pembrolizumab and 0.87 years for the docetaxel monotherapy arm. At the end of the 20-year time horizon there were 0.10 % patients still alive in the pembrolizumab cohort and 0% in the docetaxel monotherapy cohort. Patients treated with pembrolizumab accrued 1.30 QALYs compared to 0.60 among patients in the docetaxel monotherapy cohort.

When **base case 2** was considered, pembrolizumab resulted in an estimated mean overall survival of 1.77 years compared to 0.87 years for patients treated with docetaxel monotherapy. The proportion of patients still alive in the pembrolizumab cohort was 0.04%, and 0% in the docetaxel monotherapy cohort after 20 years. Patients treated with pembrolizumab accrued 1.22 QALYs compared to 0.60 among patients in the docetaxel monotherapy cohort.

5.7.2 Base-case incremental cost effectiveness analysis results

Table 96 below presents the base case incremental cost-effectiveness results for both base case 1 and 2, incorporating our PAS. The results show pembrolizumab to be cost-effective compared to docetaxel monotherapy when considering a willingness to pay threshold of £50,000 per QALY, regardless of the base case considered. In base case 1, the corresponding incremental-cost-effectiveness ratio (ICER) when pembrolizumab is compared to docetaxel monotherapy was £43,351, while in base case 2, the estimated ICER

for this comparison is £49,048. These should be considered in the context of pembrolizumab being an end of life technology that presents an innovative nature (see Section 2.5 and Section 4.13).

Table 96: Base-case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£41,509	1.90	1.30	-	-	-
Docetaxel	£11,267	0.87	0.60	£30,242	0.70	£43,351
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£41,283	1.77	1.22	-	-	-
Docetaxel	£11,267	0.87	0.60	£30,016	0.61	£49,048
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1

Table 97 presents the results of comparisons of pembrolizumab against nintedanib in combination with docetaxel and against docetaxel monotherapy for patients with NSCLC that is PD-L1 positive and of adenocarcinoma histology. These results show pembrolizumab to be cost-effective compared to nintedanib in combination with docetaxel, regardless of the base case considered, for a willingness to pay threshold of £50,000 per QALY. Pembrolizumab resulted in 0.529 additional QALYs at an increased cost of £18,506 in base case 1, and in 0.823 additional QALYs at an increased cost of £19,282 in base case 2, compared to nintedanib in combination with docetaxel. The cost per additional QALY gained against nintedanib in combination with docetaxel was £35,049 in base case 1 (£23,429 in base case 2). These ICERs should also be considered in the context of pembrolizumab being an end-of-life therapy (see Section 2.5 and Section 4.13).

Table 97: Cost-effectiveness results (incremental analysis; discounted, with PAS) – adenocarcinoma subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER (£) vs. comparator	Incremental analysis
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£42,238	1.988	1.364	-	-	-	-

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER (£) vs. comparator	Incremental analysis
Nintedanib + Docetaxel	£23,732	1.204	0.836	£18,506	0.529	£34,997	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£29,444	0.660	£44,597	£44,597
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£43,014	2.442	1.659	-	-	-	-
Nintedanib + Docetaxel	£23,732	1.204	0.836	£19,282	0.823	£23,424	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£30,220	0.955	£31,657	£31,657
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years **Compared to the next less costly treatment* ***Compared to the next less effective treatment*							

In base case 1 the ICER of pembrolizumab compared to nintendanib + docetaxel remains under a threshold of £50,000 per QALY even when considering a wide range of possible discounts for nintedanib (up to 60% of discount, approximately; see Table 98), while this is always the case under base case 2.

Table 98: ICERs from the pairwise comparison for pembrolizumab vs. nintedanib + docetaxel (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts for nintedanib) – adenocarcinoma subgroup

Discount	Base case 1	Base case 2
0%	£34,997	£23,424
5%	£36,227	£24,214
10%	£37,457	£25,004
15%	£38,687	£25,794
20%	£39,917	£26,584
25%	£41,146	£27,374
30%	£42,376	£28,164
35%	£43,606	£28,954
40%	£44,836	£29,744
45%	£46,066	£30,534
50%	£47,295	£31,324
55%	£48,525	£32,114
60%	£49,755	£32,904
65%	£50,985	£33,694
70%	£52,215	£34,484
75%	£53,444	£35,274
80%	£54,674	£36,064
85%	£55,904	£36,854
90%	£57,134	£37,644
95%	£58,364	£38,434

5.7.3 Clinical outcomes from the model

In Table 99 the outcomes of the pembrolizumab 2mg/kg and docetaxel arms of the KEYNOTE-010 trial, and those of the KEYNOTE-001 trial for the previously treated population assessed, have been compared to the outcomes from the model. The model estimates similar percentages of patients in pre-progression and surviving at different points in time to those reported in the KEYNOTE-010 and KEYNOTE-001 trials (see Table 99), suggesting that, for the trial period, the model is able to replicate the results of the KEYNOTE-010 and the KEYNOTE-001 trials.

Table 99: Comparison of model and trial outcomes

	Pembrolizumab				Docetaxel		
Outcome	**Base case 1**	**Base case 2**	**KEYNOTE-010**	**KEYNOTE-001**	**Base case 1**	**Base case 2**	**KEYNOTE-010**
% patients with PFS at 6 months	34.99%	34.99%	35.1%	36.10%	33.28%	33.28%	34.3%
% patients with PFS at 1 year	18.82%	18.82%	18%	-	9.23%	9.23%	9%
Median PFS (in months)	3.45	3.45	3.9	2.9	3.91	3.68	4
Median OS (months)	10.81	10.58	10.4	11.10	8.51	8.51	8.5
6-month OS	72.5%	72.5%	72.5%	64%	63%	0.6	64.2%
1-year OS	44%	44%	43%	49%	33%	33%	35%

5.7.4 Markov traces

Figure 52 and Figure 53 below illustrate how patients move through the model states over time when treated with pembrolizumab or docetaxel monotherapy, respectively. The diagrams show that patients spend longer in the pre-progression health state on pembrolizumab compared the BSC and that patients also survive for longer.

Figure 52: Base case 1 - Markov trace for pembrolizumab and docetaxel

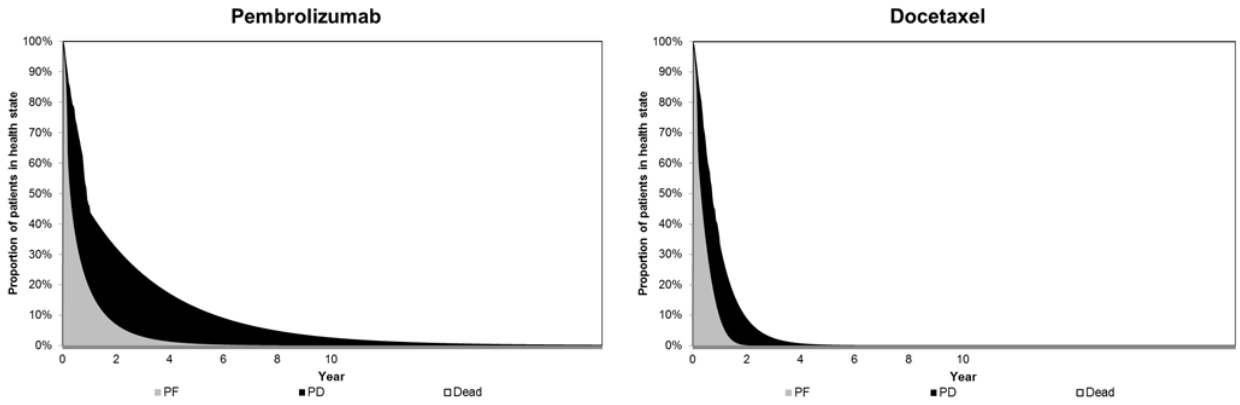
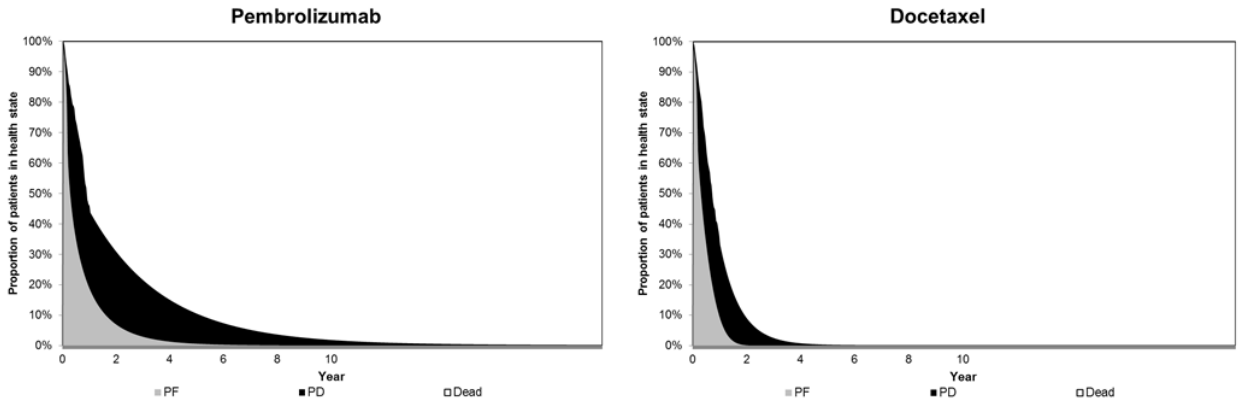


Figure 53: Base case 2 - Markov trace for pembrolizumab and docetaxel



Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1

For the analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the corresponding Markov traces for pembrolizumab, nintedanib in combination with docetaxel and docetaxel monotherapy are presented in Figure 54 for base case 1, and in Figure 55 for base case 2.

Figure 54: Base case 1 - Markov trace for pembrolizumab, docetaxel monotherapy and nintedanib in combination with docetaxel – adenocarcinoma subgroup

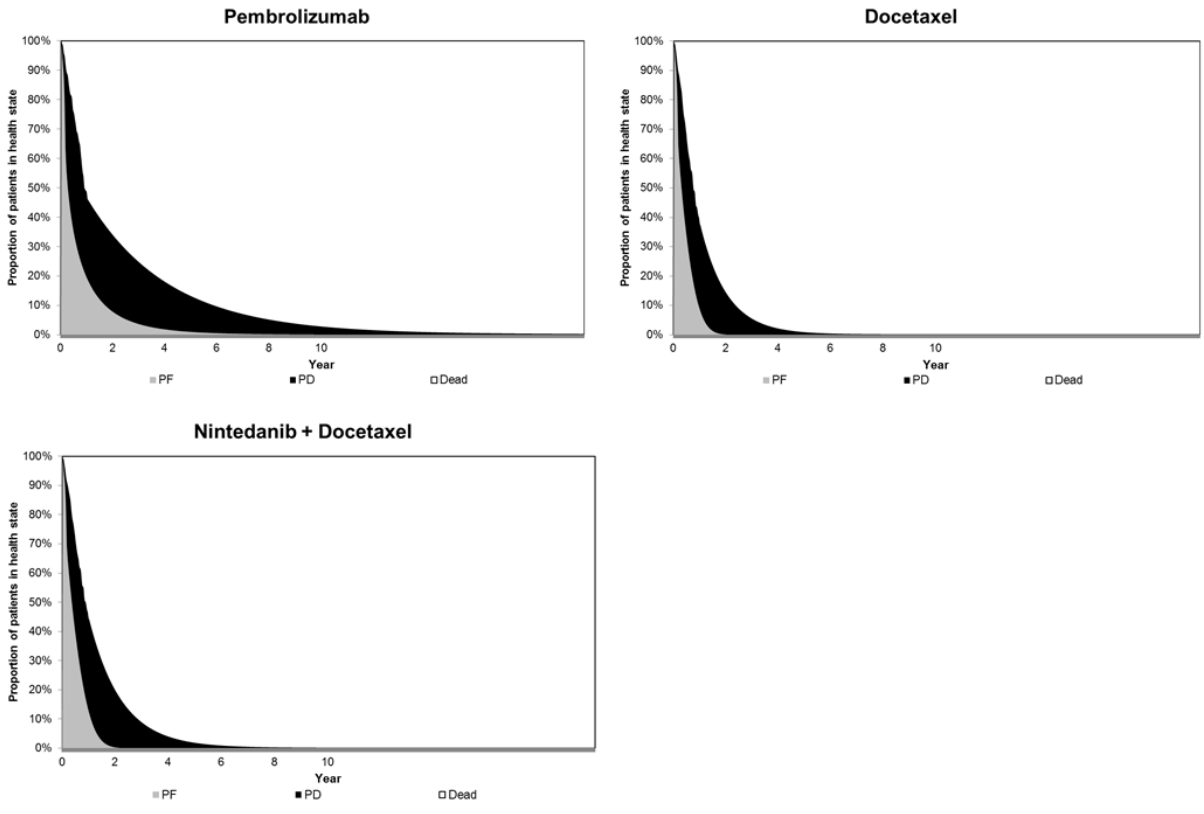
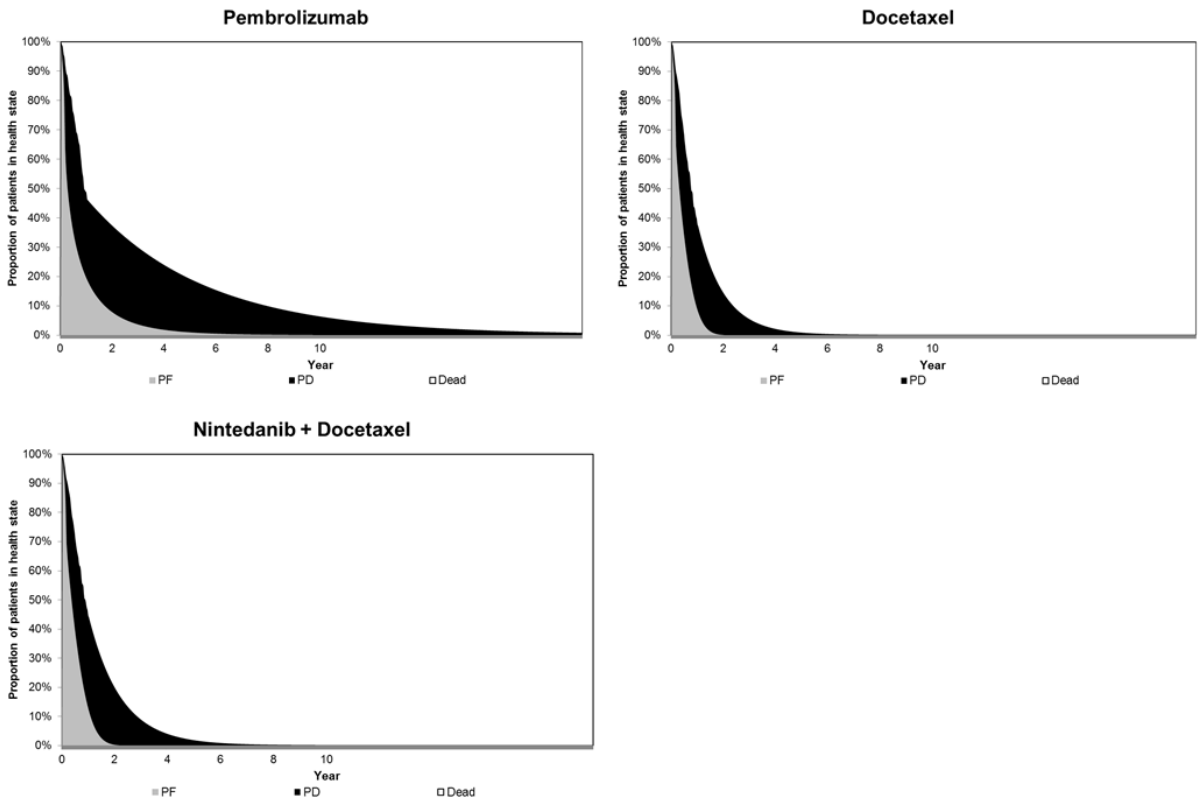


Figure 55: Base case 2 - Markov trace for pembrolizumab, docetaxel monotherapy and nintedanib in combination with docetaxel – adenocarcinoma subgroup



5.7.5 Accrual of costs, QALYs and LYs over time

Figure 56 and Figure 57 shows how the costs, QALYs and life years accumulate over time, respectively. In the base case QALYs are accrued over time according to the complementary approach considering progression-based and time to death utilities, as previously reported (see sections 5.2.2 and 5.4).

Figure 56: Base case 1 - Cumulative costs, QALYs and LYs over time

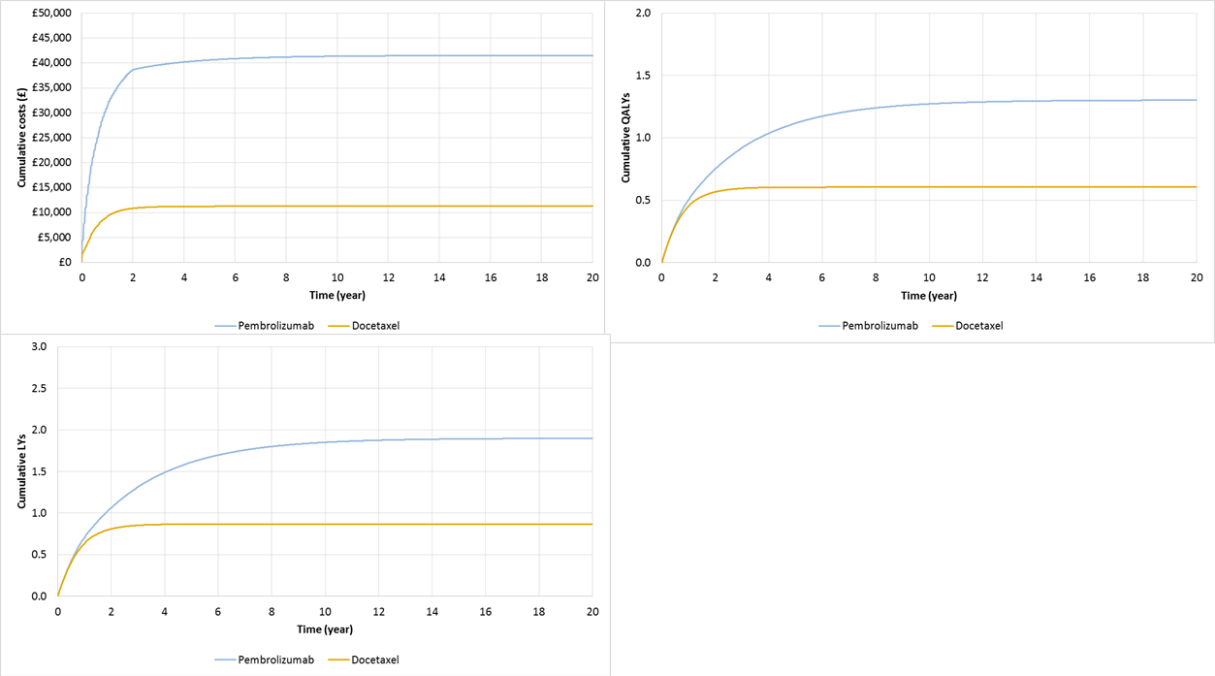
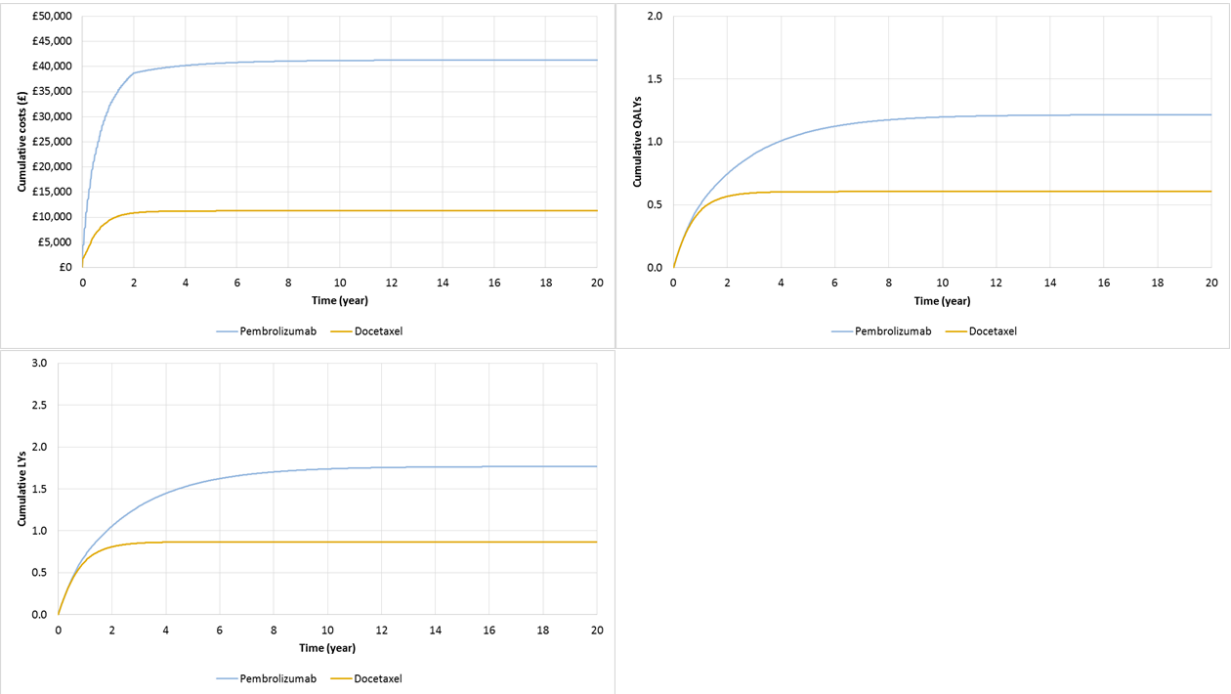


Figure 57: Base case 2 - Cumulative costs, QALYs and LYs over time



Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1

For the analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the costs, QALYs and life years accrued over time are presented in Figure 58 for base case 1, and in Figure 59 for base case 2.

Figure 58: Base case 1 - Cumulative costs, QALYs and LYs over time –adenocarcinoma subgroup

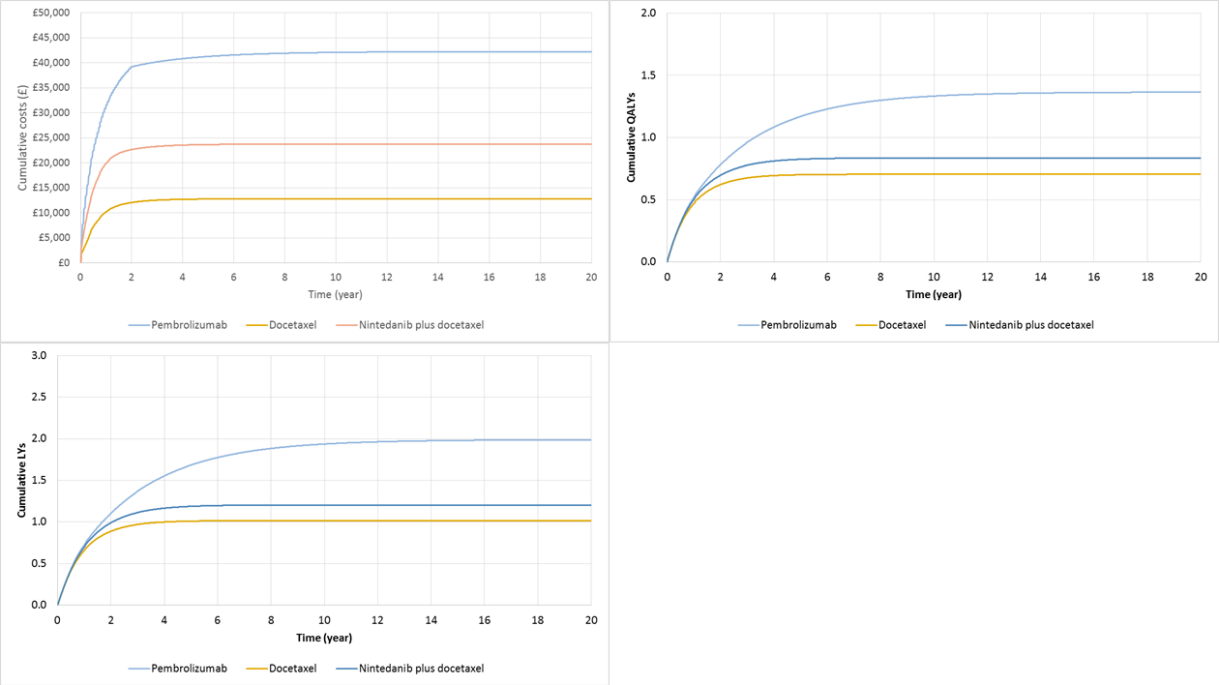
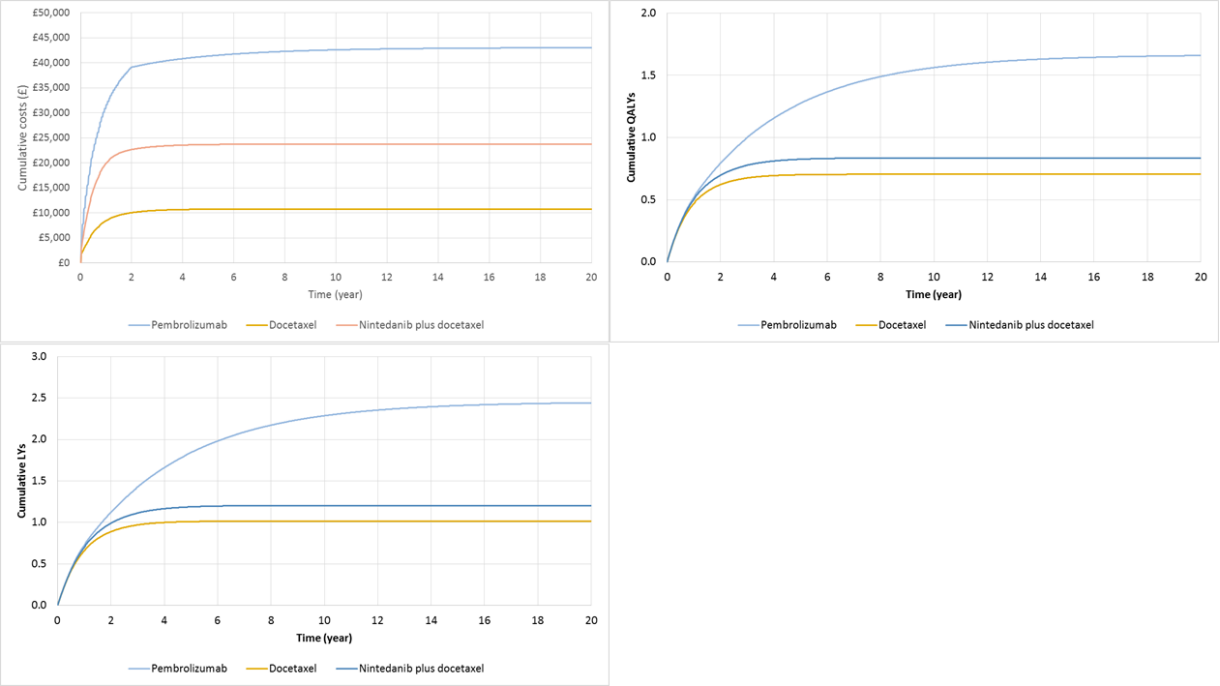


Figure 59: Base case 2 - Cumulative costs, QALYs and LYs over time –adenocarcinoma subgroup



5.7.6 Disaggregated results of the base case incremental cost effectiveness analysis

Table 100 shows the disaggregated life years by health state. This shows that patients on pembrolizumab spend longer in both the pre and post progression health states compared to patients receiving docetaxel monotherapy. Table 101 shows that the majority of costs in the pembrolizumab cohort are associated with treatment.

Table 100: Disaggregated life-years by health state (discounted)

	Pre-progression	Post-progression	Total
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)			
Pembrolizumab	0.6095	1.2889	1.898
Docetaxel	0.4208	0.4462	0.867
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)			
Pembrolizumab	0.6095	1.1574	1.767
Docetaxel	0.4208	0.4462	0.867

Table 101: Summary of predicted resource use by category of cost

	Pembrolizumab	Docetaxel	Incremental	Absolute increment	% absolute increment
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)					
Treatment Costs*	£27,504	£58	£27,447	£27,447	84%
Administration	£2,430	£933	£1,498	£1,498	5%
Subsequent line treatment	£2,307	£2,812	-£505	£505	2%
Treatment initiation	£1,068	£730	£337	£337	1%
Follow-up	£4,637	£2,439	£2,198	£2,198	7%
Terminal care	£3,508	£3,643	-£135	£135	0%
AE costs	£54	£652	-£599	£599	2%
Total	£41,509	£11,267	£30,242	£32,719	100%
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)					
Treatment Costs*	£27,504	£58	£27,447	£27,447	85%
Administration	£2,430	£933	£1,498	£1,498	5%
Subsequent line treatment	£2,307	£2,812	-£505	£505	2%
Treatment initiation	£1,068	£730	£337	£337	1%
Follow-up	£4,393	£2,439	£1,954	£1,954	6%
Terminal care	£3,526	£3,643	-£117	£117	0%
AE costs	£54	£652	-£599	£599	2%
Total	£41,283	£11,267	£30,016	£32,456	100%
*The costs of PD-L1 testing associated with treatment with pembrolizumab are included under this category (more specifically, as part of treatment initiation)					

Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1

For the analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the corresponding disaggregated life years by health state and the predicted cost by cost category for pembrolizumab compared to nintedanib in combination with docetaxel are presented in Table 102 and Table 103, and for the comparison between pembrolizumab and docetaxel monotherapy in Table 102 and Table 104, respectively.

Table 102: Disaggregated life-years by health state – adenocarcinoma subgroup

	Pre-progression	Post-progression	Total
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)			
Pembrolizumab	0.6447	1.3431	1.9878
Docetaxel	0.4231	0.5929	1.0160
Nintedanib + Docetaxel	0.4872	0.7171	1.2043
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)			
Pembrolizumab	0.6447	1.7976	2.4424
Docetaxel	0.4231	0.5929	1.0160
Nintedanib + Docetaxel	0.4872	0.7171	1.2043

Table 103: Summary of predicted resource use by category of cost: pembrolizumab vs. nintedanib + docetaxel – adenocarcinoma subgroup

	Pembrolizumab	Nintedanib + docetaxel	Incremental	Absolute increment	% absolute increment
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)					
Treatment Costs*	£28,200	£13,081	£15,118	£15,118	75%
Administration	£2,492	£1,291	£1,201	£1,201	6%
Subsequent line treatment	£2,068	£1,166	£903	£903	5%
Treatment initiation	£1,068	£730	£337	£337	2%
Follow-up	£4,860	£3,150	£1,710	£1,710	9%
Terminal care	£3,497	£3,600	-£103	£103	1%
AE costs	£54	£714	-£661	£661	3%
Total	£42,238	£23,732	£18,506	£20,034	100%
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)					
Treatment Costs*	£28,200	£13,081	£15,118	£15,118	72%
Administration	£2,492	£1,291	£1,201	£1,201	6%
Subsequent line treatment	£2,068	£1,166	£903	£903	4%
Treatment initiation	£1,068	£730	£337	£337	2%
Follow-up	£5,706	£3,150	£2,555	£2,555	12%
Terminal care	£3,427	£3,600	-£172	£172	1%
AE costs	£54	£714	-£661	£661	3%
Total	£43,014	£23,732	£19,282	£20,948	100%
*The costs of PD-L1 testing associated with treatment with pembrolizumab are included under this category (more specifically, as part of treatment initiation)					

Table 104: Summary of predicted resource use by category of cost: pembrolizumab vs. docetaxel monotherapy – adenocarcinoma subgroup

	Pembrolizumab	Docetaxel	Incremental	Absolute increment	% absolute increment
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)					
Treatment Costs*	£28,200	£59	£28,140	£28,140	81%
Administration	£2,492	£956	£1,536	£1,536	4%
Subsequent line treatment	£2,068	£4,052	-£1,983	£1,983	6%
Treatment initiation	£1,068	£730	£337	£337	1%
Follow-up	£4,860	£2,720	£2,140	£2,140	6%
Terminal care	£3,497	£3,624	-£128	£128	0%
AE costs	£54	£652	-£599	£599	2%
Total	£42,238	£12,794	£29,444	£34,863	100%
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)					
Treatment Costs*	£28,200	£59	£28,140	£28,140	79%
Administration	£2,492	£956	£1,536	£1,536	4%
Subsequent line treatment	£2,068	£4,052	-£1,983	£1,983	6%
Treatment initiation	£1,068	£730	£337	£337	1%
Follow-up	£5,706	£2,720	£2,986	£2,986	8%
Terminal care	£3,427	£3,624	-£197	£197	1%
AE costs	£54	£652	-£599	£599	2%
Total	£43,014	£12,794	£30,220	£35,777	100%
*The costs of PD-L1 testing associated with treatment with pembrolizumab are included under this category (more specifically, as part of treatment initiation)					

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix 25.

Table 105: Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS)

Technologies	*Total costs (£)*	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)					
Pembrolizumab	£41,538	1.304			
Docetaxel	£14,212	0.671	£27,326	0.634	£43,134
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)					
Pembrolizumab	£41,246	1.220			
Docetaxel	£11,283	0.604	£29,963	0.616	£48,667
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Base case 1

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis for base case 1 are presented in Table 105, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 60 and Figure 61.

The cost-effectiveness acceptability curve shows that there is an approximately 81.1% chance of pembrolizumab to be cost-effective when compared to docetaxel at the £50,000 per QALY threshold.

Figure 60: Scatterplot of PSA results (1,000 simulations; results discounted, with PAS)

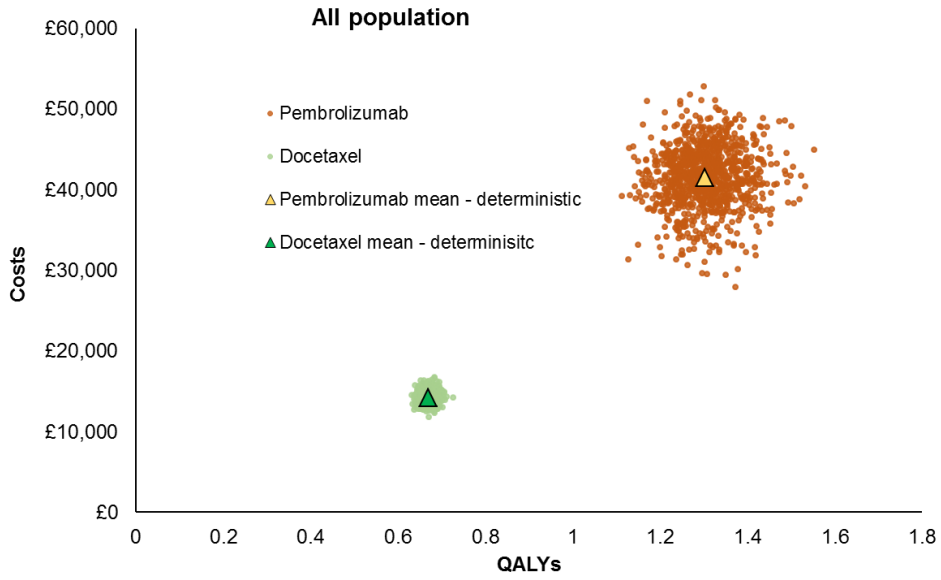
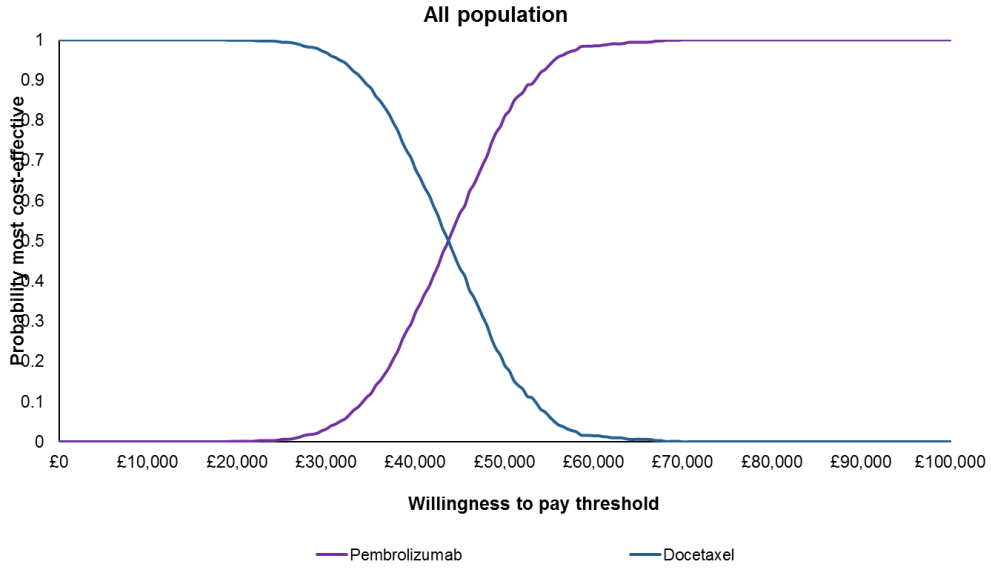


Figure 61: Cost-effectiveness acceptability curve (results discounted, with PAS)



Base case 2

The cost-effectiveness acceptability curve shows that there is approximately a 57.8% chance of pembrolizumab to be cost-effective when compared to docetaxel at the £50,000 per QALY threshold.

Figure 62: Scatterplot of PSA results (1,000 simulations; results discounted, with PAS)

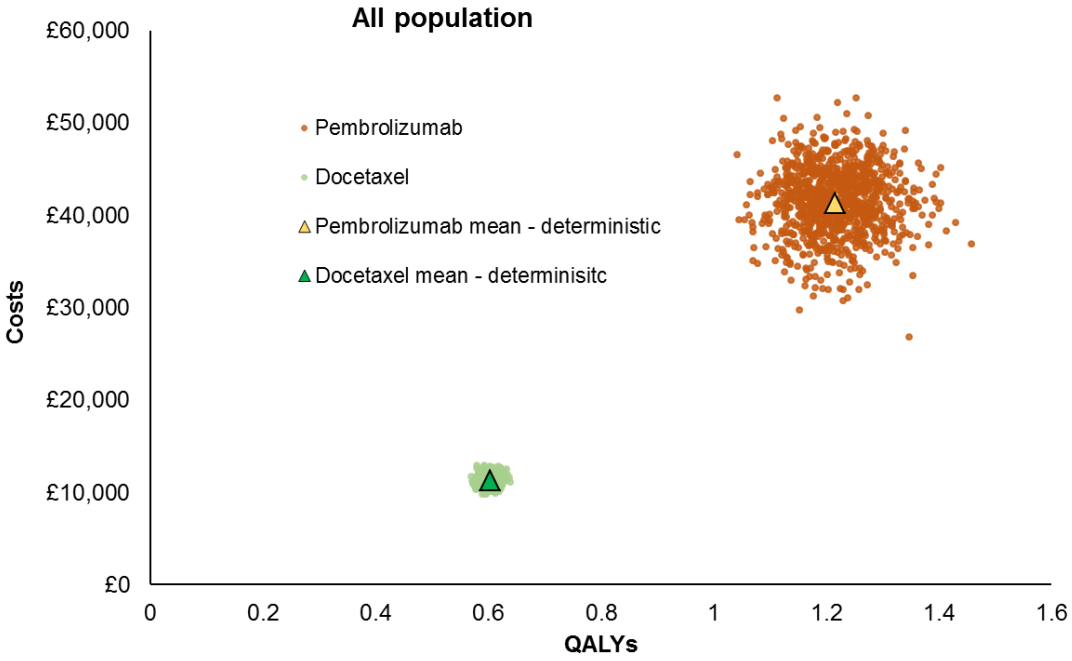
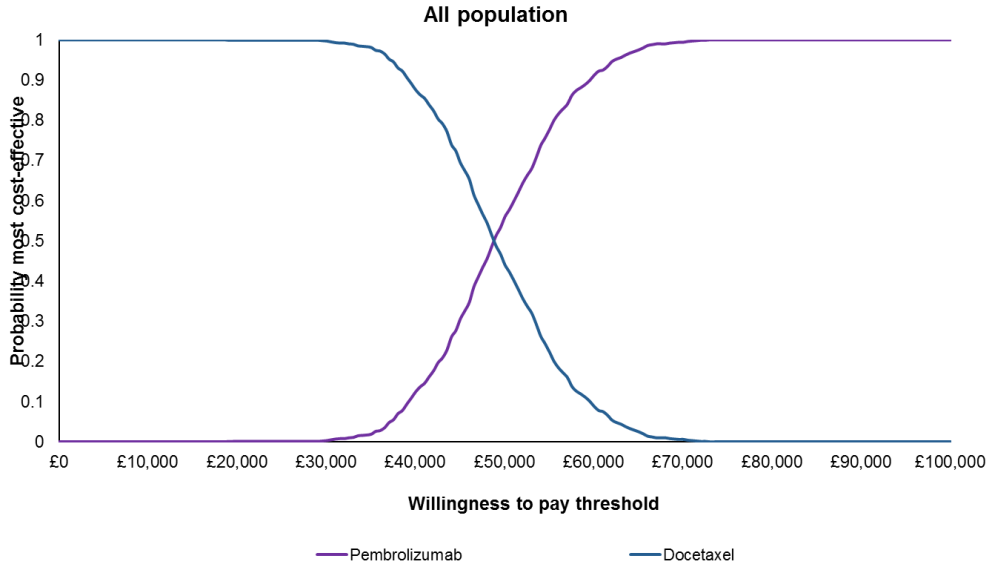


Figure 63: Cost-effectiveness acceptability curve (results discounted, with PAS)



Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1

For the analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the incremental cost-effectiveness results obtained from the probabilistic sensitivity analyses for base case 1 and base case 2 are presented in Table 106 and Figure 60.

Table 106: Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS) – adenocarcinoma subgroup

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER (£) versus baseline	Incremental analysis
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£42,705	1.370				
Nintedanib + Docetaxel	£23,851	0.838	£18,854	0.532	£35,472	Extendedly dominated
Docetaxel	£12,803	0.705	£29,902	0.665	£44,964	£44,964
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£43,598	1.673				
Nintedanib + Docetaxel	£12,782	0.706	£30,816	0.967	£31,858	Extendedly dominated
Docetaxel	£23,922	0.839	£19,677	0.834	£23,590	£23,590

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**Compared to the next less costly treatment*

***Compared to the next less effective treatment*

Base case 1

The scatterplot corresponding to the probabilistic sensitivity analysis related to base case 1 is presented in Figure 64, and the cost-effectiveness acceptability curve is presented in Figure 65.

The cost-effectiveness acceptability curve (see Figure 65) shows that there is an approximately 71.1% chance of pembrolizumab to be cost-effective when compared to either nintedanib in combination with docetaxel or docetaxel monotherapy at the £50,000 per QALY threshold.

Figure 64: Scatterplot of PSA results (1,000 simulations; results discounted, with PAS) – adenocarcinoma subgroup

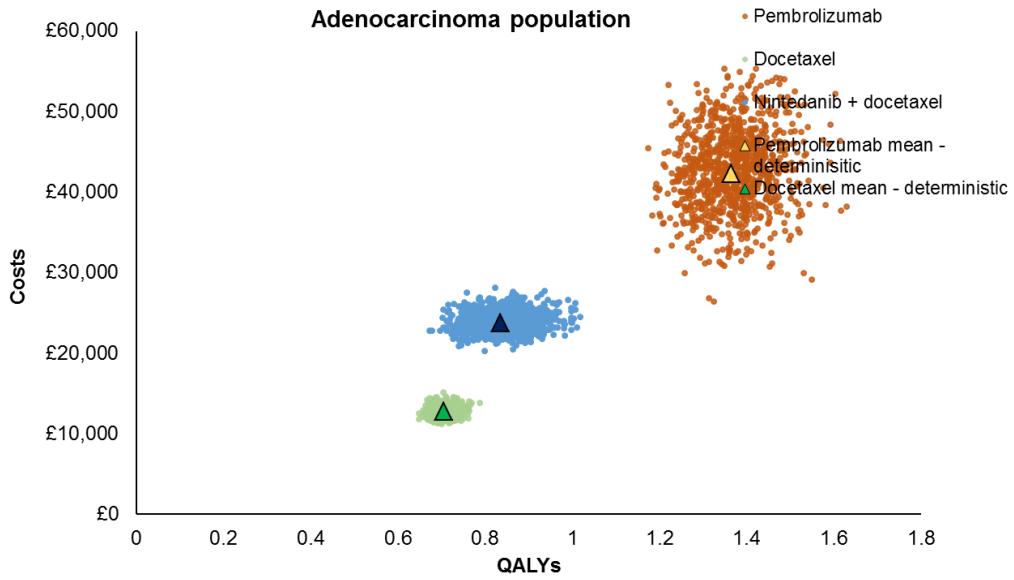
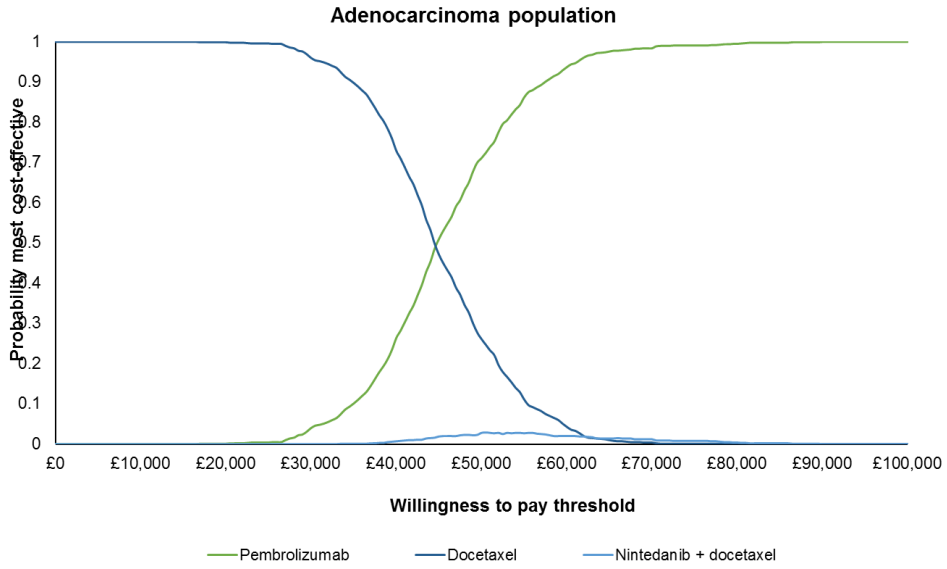


Figure 65: Cost-effectiveness acceptability curve (results discounted, with PAS) – adenocarcinoma subgroup



Base case 2

Figure 66 presents the scatterplot corresponding to the probabilistic sensitivity analysis related to base case 2.

The cost-effectiveness acceptability curve shows that there is an approximately 97.2% chance of pembrolizumab to be cost-effective when compared to either nintedanib in combination with docetaxel or docetaxel monotherapy at the £50,000 per QALY threshold.

Figure 66: Scatterplot of PSA results (1,000 simulations; results discounted, with PAS) – adenocarcinoma subgroup

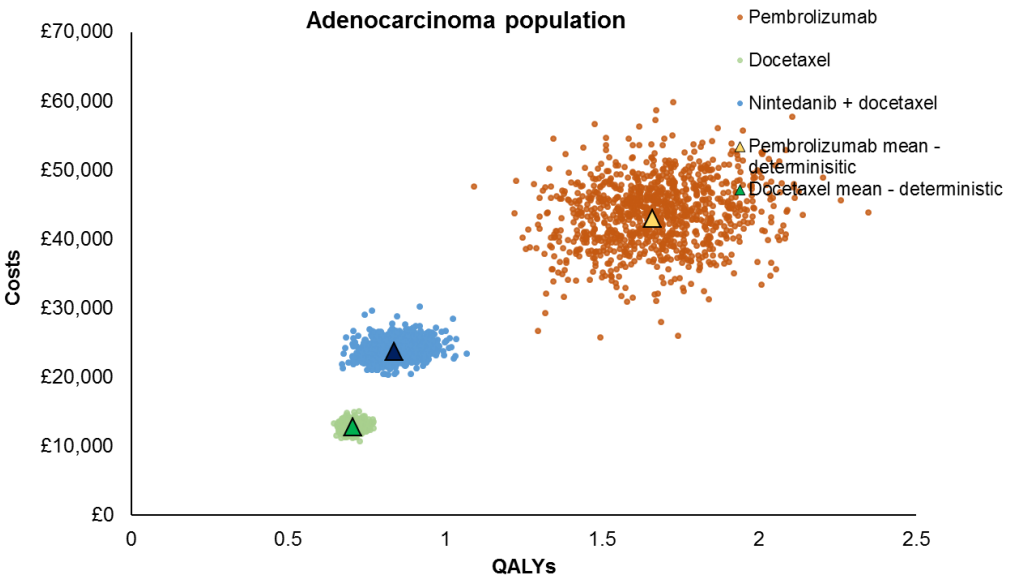
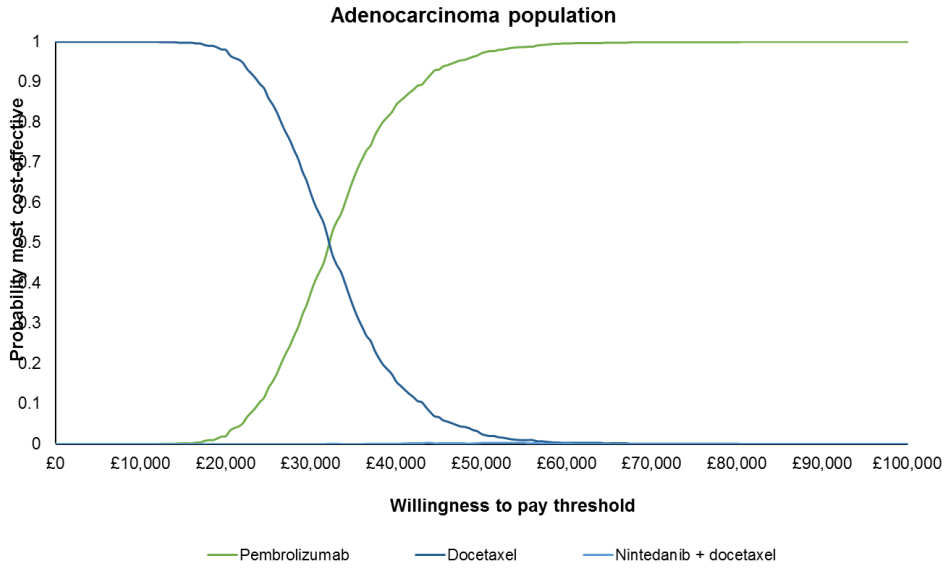


Figure 67: Cost-effectiveness acceptability curve (results discounted, with PAS) – adenocarcinoma subgroup



5.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

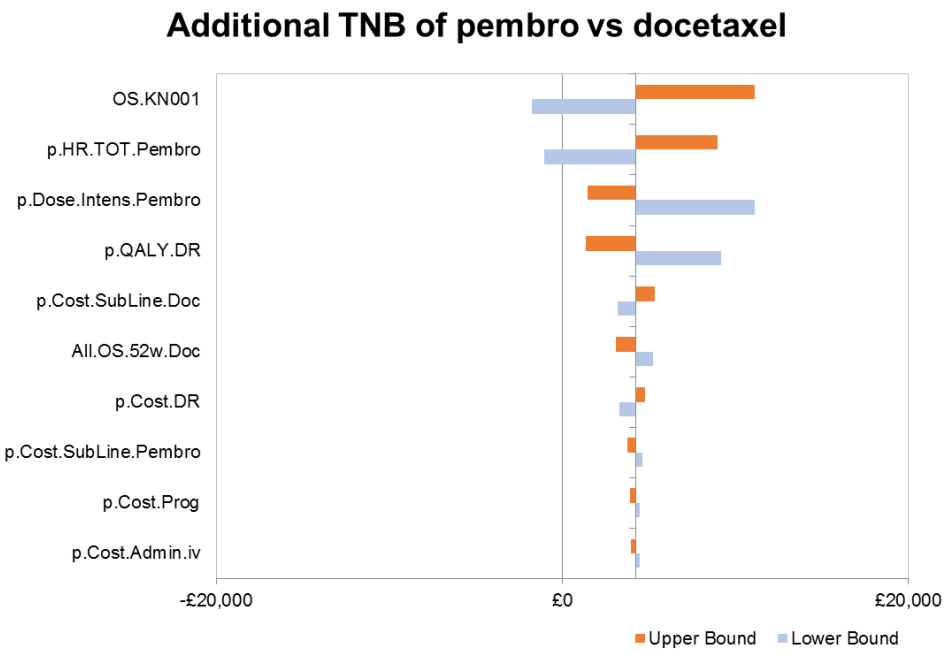
- Baseline characteristics (including proportion of males/females, patient weight and body surface area)
- Administration costs
- Resource utilisation
- Proportion of patients actually receiving the expected dose
- Administration costs
- Subsequent treatment costs and mean duration of subsequent treatment
- Follow up costs for progression free and progressed
- One-off costs for treatment initiation, upon disease progression and terminal care costs
- Costs of proportions of Stage IIIB/IV patients eligible for pembrolizumab and PD-L1 unit test cost

- Proportion of patients experiencing AEs for pembrolizumab and docetaxel
- Hazard ratio of AEs for nintedanib in combination with docetaxel versus docetaxel
- Costs of AEs
- Duration of AEs
- Combination of progression-based and time-to-death utilities
- OS and PFS hazard ratios for nintedanib in combination with docetaxel versus docetaxel
- Hazard ratios for time on treatment versus PFS for pembrolizumab and docetaxel
- All fitted pparametric curves used for OS and PFS.
- Discount rate (0% and 6%)

The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab vs. docetaxel are presented in Figure 68 below. These are presented with the PAS for pembrolizumab.

The inputs that most affect the ICERs are those related to the extrapolation of the OS (mainly consideration of KEYNOTE-001 data to extrapolate OS in the longer term), followed by the assumptions around time on treatment and dose intensity considered to estimate the cost of pembrolizumab. The discount rate for QALYs has also impact on the cost-effectiveness estimates (Figure 68).

Figure 68: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables (discounted results, with PAS)



OS.KN001 = Extrapolation of pembrolizumab OS based on KEYNOTE-001; p.HR.TOT.Pembro = HR ToT vs. PFS for pembrolizumab; p.Dose.Intens.Pembro = Dose intensity for pembrolizumab; p.QALY.DR = Discount rate applied to QALYs; p.Cost.SubLine.Doc = Cost of subsequent treatments for the docetaxel arm; All.OS.52w.Doc = Exponential extrapolation of OS considering a 52 week cut-off; p.Cost.DR = Discount rate applied to costs; p.Cost.SubLine.Pembro = Cost of subsequent treatments for the pembrolizumab arm; p.Cost.Prog = Weekly cost associated to the post-progression health state; p.Cost.Admin.iv = administration costs assumed for pembrolizumab and docetaxel.

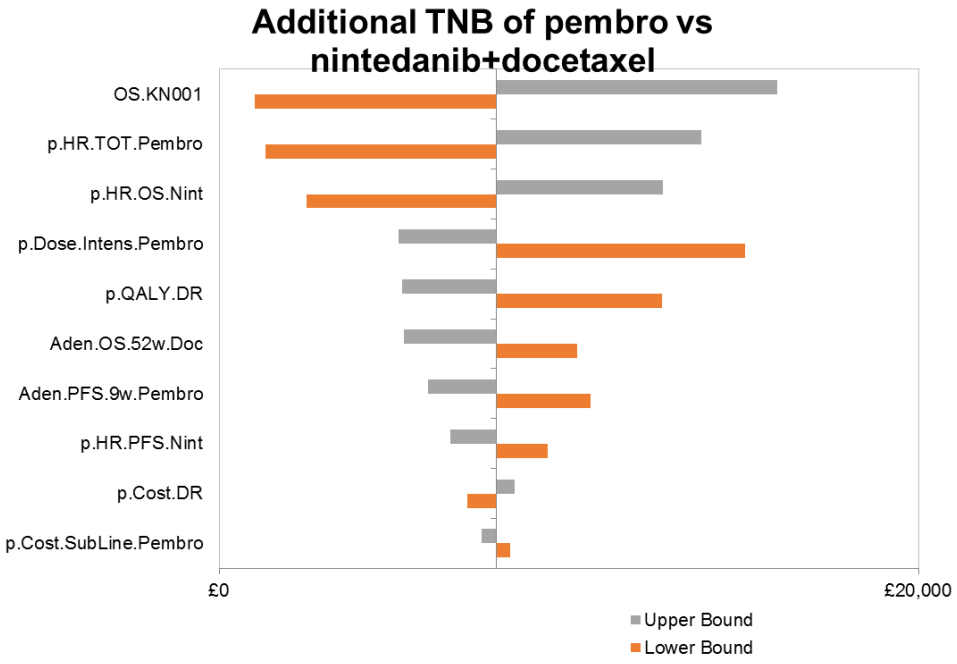
Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1

For the analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the tornado diagrams presenting the results of the deterministic sensitivity analyses are presented in Figure 69 for pairwise comparisons of pembrolizumab versus the combination of nintedanib in combination with docetaxel, and in Figure 70 for comparisons of pembrolizumab against docetaxel in this patient subgroup.

The results of the comparisons between pembrolizumab and nintedanib in combination with docetaxel are presented with the PAS for pembrolizumab and at list price for nintedanib since the PAS discount is unknown. In these comparisons, the inputs that most affect the ICER are again those related to the extrapolation of the OS using KEYNOTE-001 data and the assumptions around time on treatment and dose intensity considered to estimate the cost of pembrolizumab. Additionally, some of the parameters specific to the adenocarcinoma subgroup have a relevant impact on the results, such as the HRs derived from the NMA and the value of the parameters related to the extrapolation of OS and PFS for the

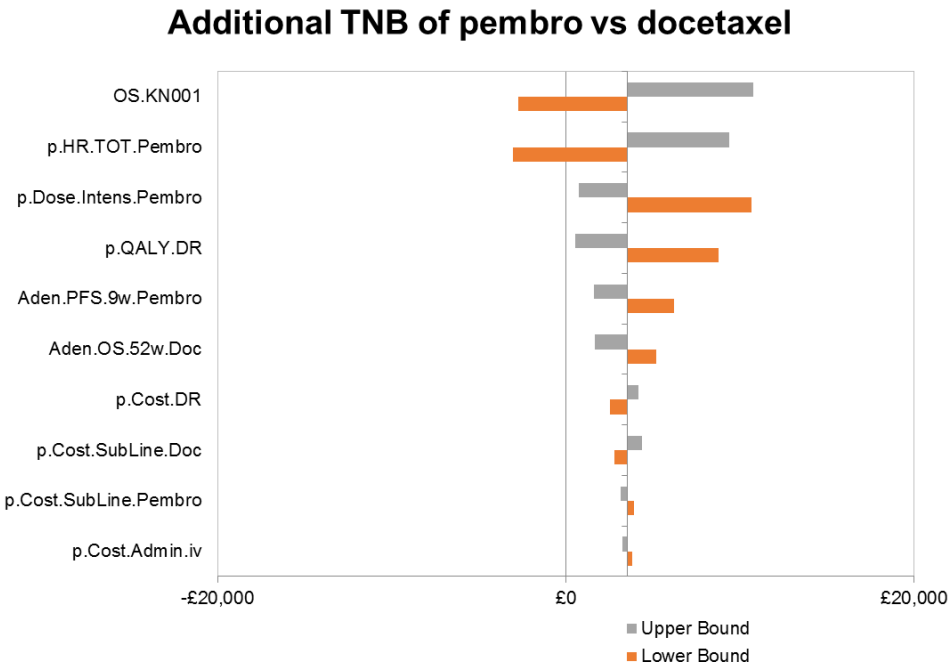
adenocarcinoma population. The discount rate for QALYs has also impact on the cost-effectiveness estimates.

Figure 69: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables comparing pembrolizumab vs. nintedanib in combination with docetaxel (discounted results, with PAS)



OS.KN001 = Extrapolation of pembrolizumab OS based on KEYNOTE-001; p.HR.TOT.Pembro = HR ToT vs. PFS for pembrolizumab; p.HR.OS.Nint = OS HR for nintedanib+docetaxel vs. docetaxel; p.Dose.Intens.Pembro = Dose intensity for pembrolizumab; p.QALY.DR = Discount rate applied to QALYs; Aden.OS.52w.Doc = Exponential extrapolation of OS considering a 52 week cut-off; Aden.PFS.9w.Doc = Exponential extrapolation of of PFS considering a 9 week cut-off; p.HR.PFS.Nint = PFS HR for nintedanib+docetaxel vs. docetaxel; p.Cost.DR = Discount rate applied to costs; p.Cost.SubLine.Pembro = Cost of subsequent treatments for the pembrolizumab arm

Figure 70: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables comparing pembrolizumab vs. docetaxel monotherapy (discounted results, with PAS)



OS.KN001 = Extrapolation of pembrolizumab OS based on KEYNOTE-001; p.HR.TOT.Pembro = HR ToT vs. PFS for pembrolizumab; p.Dose.Intens.Pembro = Dose intensity for pembrolizumab; p.QALY.DR = Discount rate applied to QALYs; Aden.PFS.9w.Doc = Exponential extrapolation of of PFS considering a 9 week cut-off; Aden.OS.52w.Doc = Exponential extrapolation of OS considering a 52 week cut-off; p.Cost.DR = Discount rate applied to costs; p.Cost.SubLine.Pembro = Cost of subsequent treatments for the pembrolizumab arm; p.Cost.Admin.iv = administration costs assumed for pembrolizumab and docetaxel.

When pembrolizumab and docetaxel were compared through deterministic sensitivity analyses, the results showed that the cost-effectiveness results are less affected by variations in the parameter values considered, although the same parameters identified above as most sensitive for analyses on the overall population were found to be sensitive, although at a lesser extent, in these comparisons. The most sensitive parameters were again those related to the extrapolation of OS and PFS, the estimation of the cost of pembrolizumab and the discount rate used for QALYs in the analysis.

5.8.3 Scenario analyses

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions.

The original intention in the submission was to present a case based primarily around utilising UK registry data (NLCA). We now present this in the form of two scenarios (labelled scenario 1 and 2 below). We did this because although the 5- and 10-year survival rates for

pembrolizumab were considered plausible, the 20-year rate was considered perhaps optimistic.

- Using alternative approaches to extrapolate OS
    - NLCA registry data for chemotherapy dataset (stage IIIb/IV PS0-1; scenario 1).
    - NLCA registry data for stage IIIb/IV dataset (scenario 2).
- Assessing the impact of vial sharing in clinical practice:
    - Full vial sharing (based on a cost per mg; scenario 3).
- Changing the type of approach used to estimate utilities from KEYNOTE-010:
    - Using time to death utilities only (scenario 4).
    - Using progression-based utilities only (scenario 5).
- Regarding AE-related disutilities:
    - Considering disutilities estimated based on KEYNOTE-010 (scenario 6).
- In relation to the age-adjustment of utilities:
    - Removing the age-adjustment for utilities (scenario 7).
- Alternative cut-off for the estimation of the exponential curve in Phase 2 of the piecewise approach:
    - KM+exponential considering a 52-week cut-off (scenario 9)
    - KM+exponential considering a 62-week cut-off (scenario 10)
    - KM+exponential considering a 72-week cut-off (scenario 11)

Table 107: Results from the scenario analyses

All population										
		Pembrolizumab			Docetaxel			Pembro vs doc		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 1		£41,509	1.8984	1.3017	£11,267	0.8670	0.6041	£30,242	0.6976	£43,351
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£42,300	2.4260	1.6317	£11,772	1.1783	0.8035	£30,528	0.8282	£36,861
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£42,148	2.3217	1.5666	£11,731	1.1500	0.7859	£30,417	0.7807	£38,959
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£39,639	1.8984	1.3017	£11,267	0.8670	0.6041	£28,372	0.6976	£40,670
Scenario 4	Progression-based utilites	£41,509	1.8984	1.2976	£11,267	0.8670	0.6118	£30,242	0.6858	£44,096
Scenario 5	Time to death utilities	£41,509	1.8984	1.3821	£11,267	0.8670	0.6269	£30,242	0.7552	£40,045
Scenario 6	Consider AE-related disutilities	£41,509	1.8984	1.2984	£11,267	0.8670	0.5693	£30,242	0.7290	£41,482
Scenario 7	Exclude age-related disutility	£41,509	1.8984	1.3189	£11,267	0.8670	0.6054	£30,242	0.7135	£42,386
Scenario 8	KM + exponential 52-week cut-off	£41,509	1.8984	1.3017	£11,267	0.8670	0.6041	£30,242	0.6976	£43,351
Scenario 9	KM + exponential 62-week cut-off	£41,517	1.9031	1.3048	£11,210	0.8342	0.5823	£30,307	0.7226	£41,943
Scenario 10	KM + exponential 72-week cut-off	£41,400	1.8352	1.2599	£11,214	0.8363	0.5836	£30,186	0.6763	£44,633
Scenario 11	PFS KM+exponential 28-week cut-off	£42,110	1.8984	1.3092	£11,287	0.8670	0.6042	£30,823	0.7050	£43,723
Base case 2		£41,283	1.7669	1.2160	£11,267	0.8670	0.6041	£30,016	0.6120	£49,048
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£42,191	2.3600	1.5889	£11,772	1.1783	0.8035	£30,419	0.7854	£38,731
Scenario 2	NLCA Registry data –	£42,046	2.2602	1.5266	£11,731	1.1500	0.7859	£30,315	0.7407	£40,925

	Stage IIIb/IV dataset (no rebase for time for diagnosis)									
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£37,543	1.7669	1.2160	£11,267	0.8670	0.6041	£26,276	0.6120	£42,937
Scenario 4	Progression-based utilites	£41,283	1.7669	1.2135	£11,267	0.8670	0.6118	£30,016	0.6017	£49,881
Scenario 5	Time to death utilities	£41,283	1.7669	1.2870	£11,267	0.8670	0.6269	£30,016	0.6601	£45,470
Scenario 6	Consider AE-related disutilities	£41,283	1.7669	1.2127	£11,267	0.8670	0.5693	£30,016	0.6434	£46,652
Scenario 7	Exclude age-related disutility	£41,283	1.7669	1.2301	£11,267	0.8670	0.6054	£30,016	0.6246	£48,053
Scenario 8	KM + exponential 52-week cut-off	£41,509	1.8984	1.3017	£11,267	0.8670	0.6041	£30,242	0.6976	£43,351
Scenario 9	KM + exponential 62-week cut-off	£41,517	1.9031	1.3048	£11,210	0.8342	0.5823	£30,307	0.7226	£41,943
Scenario 10	KM + exponential 72-week cut-off	£41,400	1.8352	1.2599	£11,214	0.8363	0.5836	£30,186	0.6763	£44,633
Scenario 11	PFS KM+exponential 28-week cut-off	£41,884	1.7669	1.2235	£11,287	0.8670	0.6042	£30,597	0.6193	£49,407
Adenocarcinoma subgroup										
		Pembrolizumab			**Nintedanib + docetaxel**			**Pembro vs ninte+doc**		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 1		£42,238	1.9878	1.3644	£23,732	1.2043	0.8356	£18,506	0.5288	£34,997
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£43,074	2.5455	1.7132	£24,739	1.8299	1.2349	£18,336	0.4783	£38,333
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£42,913	2.4353	1.6444	£24,645	1.7657	1.1948	£18,268	0.4496	£40,634
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£38,404	1.9878	1.3644	£23,732	1.2043	0.8356	£14,672	0.5288	£27,747
Scenario 4	Progression-based	£42,238	1.9878	1.3592	£23,732	1.2043	0.8392	£18,506	0.5200	£35,591

	utilites									
Scenario 5	Time to death utilities	£42,238	1.9878	1.4479	£23,732	1.2043	0.8765	£18,506	0.5715	£32,383
Scenario 6	Consider AE-related disutilities	£42,238	1.9878	1.3610	£23,732	1.2043	0.7977	£18,506	0.5634	£32,849
Scenario 7	Exclude age-related disutility	£42,238	1.9878	1.3826	£23,732	1.2043	0.8394	£18,506	0.5431	£34,071
Scenario 8	KM + exponential 52-week cut-off	£42,238	1.9878	1.3644	£23,732	1.2043	0.8356	£18,506	0.5288	£34,997
Scenario 9	KM + exponential 62-week cut-off	£42,368	2.0628	1.4139	£23,585	1.1190	0.7791	£18,783	0.6349	£29,585
Scenario 10	KM + exponential 72-week cut-off	£42,252	1.9956	1.3696	£23,744	1.2113	0.8402	£18,507	0.5294	£34,959
Scenario 11	PFS KM+exponential 28-week cut-off	£37,802	1.9878	1.3538	£24,067	1.2043	0.8365	£13,734	0.5173	£26,552
		Pembrolizumab			**Docetaxel**			**Pembro vs doc**		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 1		£42,238	1.9878	1.3644	£12,794	1.0160	0.7041	£29,444	0.6602	£44,597
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£43,074	2.5455	1.7132	£13,558	1.4894	1.0068	£29,516	0.7064	£41,784
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£42,913	2.4353	1.6444	£13,491	1.4434	0.9781	£29,422	0.6663	£44,160
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£38,404	1.9878	1.3644	£12,794	1.0160	0.7041	£25,610	0.6602	£38,790
Scenario 4	Progression-based utilites	£42,238	1.9878	1.3592	£12,794	1.0160	0.7099	£29,444	0.6493	£45,348
Scenario 5	Time to death utilities	£42,238	1.9878	1.4479	£12,794	1.0160	0.7371	£29,444	0.7108	£41,424
Scenario 6	Consider AE-related disutilities	£42,238	1.9878	1.3610	£12,794	1.0160	0.6695	£29,444	0.6916	£42,575
Scenario 7	Exclude age-related disutility	£42,238	1.9878	1.3826	£12,794	1.0160	0.7066	£29,444	0.6760	£43,556
Scenario 8	KM + exponential 52-week cut-off	£42,238	1.9878	1.3644	£12,794	1.0160	0.7041	£29,444	0.6602	£44,597

Scenario 9	KM + exponential 62-week cut-off	£42,368	2.0628	1.4139	£12,697	0.9602	0.6671	£29,670	0.7469	£39,727
Scenario 10	KM + exponential 72-week cut-off	£42,252	1.9956	1.3696	£12,801	1.0202	0.7069	£29,451	0.6627	£44,438
Scenario 11	PFS KM+exponential 28-week cut-off	£37,802	1.9878	1.3538	£12,813	1.0160	0.7046	£24,989	0.6491	£38,494
		Pembrolizumab			**Nintedanib + docetaxel**			**Pembro vs ninte+doc**		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 2		£43,014	2.4424	1.6587	£23,732	1.2043	0.8356	£19,282	0.8232	£23,424
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£43,340	2.7070	1.8179	£24,739	1.8299	1.2349	£18,602	0.5830	£31,909
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£43,163	2.5857	1.7421	£24,645	1.7657	1.1948	£18,519	0.5473	£33,833
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£39,180	2.4424	1.6587	£23,732	1.2043	0.8356	£15,448	0.8232	£18,767
Scenario 4	Progression-based utilites	£43,014	2.4424	1.6482	£23,732	1.2043	0.8392	£19,282	0.8089	£23,836
Scenario 5	Time to death utilities	£43,014	2.4424	1.7750	£23,732	1.2043	0.8765	£19,282	0.8985	£21,460
Scenario 6	Consider AE-related disutilities	£43,014	2.4424	1.6554	£23,732	1.2043	0.7977	£19,282	0.8578	£22,480
Scenario 7	Exclude age-related disutility	£43,014	2.4424	1.6898	£23,732	1.2043	0.8394	£19,282	0.8504	£22,674
Scenario 8	KM + exponential 52-week cut-off	£43,014	2.4424	1.6587	£23,732	1.2043	0.8356	£19,282	0.8232	£23,424
Scenario 9	KM + exponential 62-week cut-off	£41,966	1.8296	1.2620	£23,585	1.1190	0.7791	£18,381	0.4830	£38,058
Scenario 10	KM + exponential 72-week cut-off	£43,439	2.6971	1.8216	£23,744	1.2113	0.8402	£19,695	0.9814	£20,067
Scenario 11	PFS KM+exponential 28-week cut-off	£38,578	2.4424	1.6481	£24,067	1.2043	0.8365	£14,511	0.8116	£17,879
		Pembrolizumab			**Docetaxel**			**Pembro vs doc**		
		Total costs	Total LYs	Total	Total costs	Total LYs	Total	Inc. costs	Inc. QALYs	ICER

				QALYs			QALYs			
Base case 2		£43,014	2.4424	1.6587	£12,794	1.0160	0.7041	£30,220	0.9546	£31,657
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£43,340	2.7070	1.8179	£13,558	1.4894	1.0068	£29,782	0.8110	£36,721
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£43,163	2.5857	1.7421	£13,491	1.4434	0.9781	£29,672	0.7640	£38,836
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£39,180	2.4424	1.6587	£12,794	1.0160	0.7041	£26,387	0.9546	£27,641
Scenario 4	Progression-based utilites	£43,014	2.4424	1.6482	£12,794	1.0160	0.7099	£30,220	0.9383	£32,208
Scenario 5	Time to death utilities	£43,014	2.4424	1.7750	£12,794	1.0160	0.7371	£30,220	1.0379	£29,118
Scenario 6	Consider AE-related disutilities	£43,014	2.4424	1.6554	£12,794	1.0160	0.6695	£30,220	0.9860	£30,650
Scenario 7	Exclude age-related disutility	£43,014	2.4424	1.6898	£12,794	1.0160	0.7066	£30,220	0.9833	£30,735
Scenario 8	KM + exponential 52-week cut-off	£43,014	2.4424	1.6587	£12,794	1.0160	0.7041	£30,220	0.9546	£31,657
Scenario 9	KM + exponential 62-week cut-off	£41,966	1.8296	1.2620	£12,697	0.9602	0.6671	£29,269	0.5949	£49,195
Scenario 10	KM + exponential 72-week cut-off	£43,439	2.6971	1.8216	£12,801	1.0202	0.7069	£30,638	1.1148	£27,484
Scenario 11	PFS KM+exponential 28-week cut-off	£38,578	2.4424	1.6481	£12,813	1.0160	0.7046	£25,765	0.9435	£27,309

5.8.4 Summary of sensitivity analyses results

The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 81.1% or 56%. In the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1, the probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is between 71.1% and 97.2%.

One-way sensitivity analyses showed that the inputs that most affect the ICERs are those related to the extrapolation of the OS (mainly consideration of KEYNOTE-001 data to extrapolate OS in the longer term), followed by the assumptions around time on treatment and dose intensity considered to estimate the cost of pembrolizumab, and discount rate for QALYs.

Scenario analysis showed that the cost-effectiveness of pembrolizumab is robust to the sources of uncertainty assessed, including: extrapolation approaches used to estimate OS and PFS in the longer term, utility approach used to estimate QALYs and assumptions around disutilities related to AE and to ageing (see Table 107).

5.9 Subgroup analysis

5.9.1 Types of subgroups that are not considered relevant

Analyses on the subgroup of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1 are presented in sections 5.7 and 5.8.

5.9.2 Analysis of subgroups

See above.

5.9.3 Definition of the characteristics of patients in the subgroup

See above.

5.9.4 Description of how the statistical analysis was carried out

See above.

5.9.5 Results of subgroup analyses

See above.

5.9.6 Identification of any obvious subgroups that were not considered

See above.

5.10 Validation

5.10.1 Methods used to validate and quality assure the model

Clinical benefit

Comparing the model outcomes to clinical trial outcomes

The outcomes of the pembrolizumab 2mg/kg and docetaxel arms of the KEYNOTE-010 trial have been compared to the outcomes from the model. For more details comparing the results generated from the model to the outcomes from the model please refer to section 5.7.3.

Table 108 presents a comparison of the OS outcomes of the different extrapolation scenarios implemented in the model.

Table 108: OS projections according to the alteranative extrapolation scenarios implemented in the cost-effectiveness model

	Base case 1		**Base case 2**	
	Based on KEYNOTE-001 data		Conservative	
	(KM up to week52+Exponential up to 2 years +KEYNOTE-001 projection afterwards è Exponential best AIC/BIC fit)		(KM+exponential only)	
	Pembro	**Docetaxel**	**Pembro**	**Docetaxel**
-5-year OS	12.15%	0.16%	12.15%	0.57%
-10-year OS	2.46%	0.00%	2.46%	0.00%
-20-year OS	0.10%	0.00%	0.10%	0.00%
	NLCA - Chemo PS0-1 patients		**NLCA - Stage IIIb/IV patients**	
	stage IIIb/IV			
	No rebase		No rebase	
	Pembro	**Docetaxel**	**Pembro**	**Docetaxel**
-5-year OS	11.97%	3.25%	12.59%	3.42%
-10-year OS	9.26%	2.51%	8.05%	2.18%
-20-year OS	6.57%	1.78%	5.07%	1.38%
	NLCA - Chemo PS0-1 patients		**NLCA - Stage IIIb/IV patients**	
	stage IIIb/IV			
	Rebase (180 weeks)		Rebase (180 weeks)	
	Pembro	**Docetaxel**	**Pembro**	**Docetaxel**
-5-year OS	26.80%	7.27%	23.92%	6.50%
-10-year OS	24.72%	6.71%	18.09%	4.91%
-20-year OS	17.53%	4.76%	12.11%	3.29%

Expert validation

The model approach and inputs have been validated by two external health economists (Dr. Laura Bojke, from the Centre for Health Economics, University of York and Professor Alistair Grey). These individuals were selected as leading experts in health economic practice and methodology development in the UK. Dr Bojke is a regular member of NICE ERG's. The model structure, selection of appropriate dataset, the survival analysis undertaken and assumption regarding extrapolation and the utility values used were all discussed.

Both experts were in agreement that the current model structure and key assumptions are valid and are consistent with previous submissions in this indication.

Opinion from the experts in OS and PFS was sought to identify the most appropriate approach to select the best OS and PFS fitted curve. According to the experts' suggestions, the best curve was selected based on AIC/BIC and justified based on clinical opinion, registry data, observed and the impact on the ICER.

Both experts agreed that there is no clear cut-off to switch from KM to the Exponential curve for the OS 2-piece curve fitting approach. Therefore various scenarios with the cut-off of 52 weeks, 62 weeks and 72 weeks were considered in our model.

The experts concerned the uncertainty around the cut-off of 9 weeks for PFS, even though 9 weeks was agreed to be a reasonable assumption, and suggested exploring other cut-off points where the pembrolizumab and docetaxel PFS curves start to diverge to look at the impact on the ICER.

Both experts agreed that the same type of parametric curves should be used for the pembrolizumab and docetaxel arms for both PFS and OS (e.g., if exponential curve is selected for the pembrolizumab arm for PFS, then exponential curve should also be used for the docetaxel arm for PFS) to avoid unnecessary complexity and to comply with the NICE DSU guidance.

Both experts were in agreement that assuming ToT = PFS is reasonable based on the KM data for TOT and PFS, which are close to each other, for the overall PD-L1 population. Prof Gray noted that it is unrealistic to assume that all patients stop treatment at 2 years.

Based on the experts' comment on costs, the administration cost of oral chemotherapy was applied to the cycle when a full pack of tablets is dispatched to patients (i.e., every 30 days for nintedanib); and the subsequent treatment cost was assumed to occur over the

subsequent treatment period (currently assumed to be 3.3 months based on data reported in the nintedanib appraisal) rather than applying a one-off cost.

The experts agreed with the current approach to consider utilities and that the base case should be utilities derived from the trial. They also agreed with combining the weight of all European patients is a sensible approach given the small UK patient numbers.

According to the experts' recommendation, the resource use and any assumptions used to calculate AE costs were validated with a clinician.

The accuracy of the implementation and programming of the model was verified via internal quality control processes using an internal quality control checklist, available in Appendix 30.

5.11 Interpretation and conclusions of economic evidence

5.11. 1 Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab for the treatment of patients with advanced NSCLC whose tumours express PD-L1 and who have progressed following platinum-containing chemotherapy (and, if EGFR or ALK mutation positive, also after disease progression on an approved therapy for these aberrations). The economic evaluation reflects patients assessed in KEYNOTE-010 and is relevant to all groups of patients who could potentially use the technology, as identified in the decision problem.

No study assessing the cost-effectiveness of pembrolizumab was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

5.11.2 Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the advanced NSCLC population eligible for pembrolizumab as per the anticipated licence. As mentioned previously (see section 5.3.1), the KEYNOTE-010 trial, which assessed patients in line with the anticipated licenced indication, was used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab.

5.11.3 Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in KEYNOTE-010 and the de novo economic evaluation are mostly reflective of patients with advanced NSCLC in the UK. Although some minor differences were identified by a clinician between patients included in KEYNOTE-010 and those expected to be treated in clinical practice in England (mainly related to age and proportion of squamous patients), these differences were considered to be minor and not to affect the benefit expected for patients treated in clinical practice.

- The economic model structure is consistent with other oncology models and previous NSCLC submissions to NICE.

- The resource utilitisation and unit costs are reflective of those of UK clinical practice and were mainly derived from previous NICE submissions, accounting for the feedback provided by the ERGs in the most recent NICE appraisals.

- Extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs.

- The OS projections of the model were validated against available UK sources to ensure the clinical plausibility of the model and its applicability to UK clinical practice.

5.11.4 Strengths and weaknesses of the evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model.

- OS: Head-to-head data from the KEYNOTE-010 trial comparing pembrolizumab to docetaxel monotherapy was used in the economic evaluation. Data from KEYNOTE-001 was used in the base case 1 to extrapolate pembrolizumab's OS in the longer term. Alternative extrapolation scenarios were implemented utilising other available sources of OS data.

- Switching adjustments: The two-stage adjustment method was deemed to be the most appropriate to adjust for the effect of switching to anti-PD-L1 agents from the docetaxel arm in KEYNOTE-010.

- Estimation of utilities: Utility values were obtained from EQ-5D KEYNOTE-010 data. Two time categories were used for the time-to-death and progression-based combined approach, since these resulted in the most conservative utility estimates, compared to the four time categories initially implemented in the model.

- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to 2 years, as established as part of the KEYNOTE-010 protocol.

- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from previous NICE appraisals, accounting for the feedback provided by ERGs in the most recent submissions.

- Subgroup analyses focused on the population with NSCLC of adenocarcinoma histology: HRs from the NMA were used for the estimation of the impact of nintedanib in combination with docetaxel on OS and PFS. There were several important limitations with the indirect comparisons performed, namely: only two RCTs were available and only a fixed-effect indirect comparison could be conducted as between-study heterogeneity could not be estimated: the proportional hazards assumption was violated for PFS comparisons; no meta-regression was possible to adjust for heterogeneity in patients characteristics across trials. Furthermore, the indirect comparison relies on the assumption that the efficacy of nintedanib in combination with docetaxel does not depend on PD-L1 expression and that the reported trial subgroups were comparable, but there is no available evidence to support this assumption. Therefore, caution should be taken when interpreting the results of these analyses.

Extensive sensitivity analyses were conducted to inform the uncertainty around the above limitations, which helped understanding what key variables could potentially have a major impact on the cost-effectiveness results.

Since the approaches taken for modelling are mostly considered to be conservative, the results here presented support the conclusion that, within the context of innovative end-of-life therapies, pembrolizumab is a cost-effective therapeutic option for the treatment of patients with advanced NSCLC whose tumours express PD-L1.

5.11.5 Further analyses

The evidence base for this economic analysis was derived from the final analyses of KEYNOTE-010. Patients treated with pembrolizumab are being followed up after this final analysis, and additional OS data for these patients is expected to be available in May 2016. This additional OS data is expected to confirm the data already presented here, and is expected to support the extrapolation approaches implemented for OS. Therefore, MSD are unaware of any further analyses that could be performed with the existing available data to inform the current economic modelling approach.

6 Assessment of factors relevant to the NHS and other parties

6.1 Analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness

The level of PD-L1 expression is correlated with efficacy outcomes in patients with previously treated advanced and previously untreated NSCLC (Garon, NEJM, 2015). Testing with a validated PD-L1 test is an efficient use of resources due to increased efficacy with pembrolizumab in PD-L1–positive patients (more targeted therapy). By testing for PD-l1 expression, treatment with pembrolizumab can be targeted to patients who will benefit the most from treatment with pembrolizumab.

This can result in a more efficient use of NHS resources derived from treating patients who are PD-L1 non-expressers with therapies that may achieve similar benefits at a lower cost. This additional efficiency associated with pembrolizumab is not reflected as part of the economic assessments presented in this submission.

6.2 Number of people eligible for treatment in England

In total, 1,795 patients are estimated to be eligible for treatment with pembrolizumab (after platinum-based chemotherapy) in 2017: 1,665 as part of second line therapy and 130 as part of third line therapy (see Table 109 below). The steps followed to estimate these values are described below.

Table 109: Number of NSCLC patients, stage IIIb/IV eligible for treatment with pembrolizumab after platinum-based chemotherapy

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
	2016	2017	2018	2019	2020	2021
In 2L	1,659	1,665	1,672	1,679	1,685	1,692
In 3L	129	130	130	131	131	132
Total	1,788	1,795	1,802	1,809	1,817	1,824

The estimated number of NSCLC incident cases by stage in England was obtained for 2013 from the National Lung Cancer Audit (assuming that 94% of the cases registered in NLCA for England and Wales related to England).[74] To reflect the increase in the number of new diagnosed cases of NSCLC over time an annual incidence growth rate of 0.40% was applied.[173]

In 2017 15,050 new cases of NSCLC stage IIIb/IV are expected.[74] Approximately 55% of these patients are expected to receive first line therapy (8,278 patients in total), and 45% of those will go on to be treated in second line (3,725 patients).[73] In total, 82% of these patients are estimated to have tumour samples that are assessable for PD-L1 expression and 66% of these are expected to have PD-L1 expression on at least 1% of tumour cells.[16] Patients who do not have EGFR or ALK positive mutations and who have PD-L1 positive tumours are eligible for therapy with pembrolizumab in 2L (after receiving first line, platinum-based chemotherapy). The proportion of patients estimated to have EGFR or ALK positive mutations is 18%.[173] As for the anticipated licence, these patients need to be treated with an EGFR/TKI inhibitor in addition to a platinum-based chemotherapy before being eligible for treatment with pembrolizumab as part of third line therapy.

Table 110: Estimates of incident population

	England	Sources
Proportion of NSCLC cases reported in NLCA that reflect those in England	94%	HSCIC (2014)[74]
NSCLC annual incidence growth rate	0.40%	Mavroudis-Chocholis et al (2015)[173]
Proportion of NSCLC patients that have squamous tumours	40%	Mavroudis-Chocholis et al (2015)[173]
Proportion of NSCLC patients that are EGFR/ALK positive mutations	Adenocarcinomas: - 19% EGFR positive - 6% ALK positive Squamous: - 3% EGFR positive - 5% ALK positive	Mavroudis-Chocholis et al (2015)[173]
Proportion of patients treated in 1L	55%	MSD Data on file (2015)[73]
Proportion of patients in 1L that go on to be treated in 2L	45%	MSD Data on file (2015)[73]
Proportion of patients in 2L that go on to be treated in 3L	35%	MSD Data on file (2015)[73]
Proportion of patients with assessable samples	82%	Herbst et al. (2015)[16]
Proportion of patients with PD-L1 positive expression (among those with assessable samples)	66%	Herbst et al. (2015)[16]

Based on the estimated PD-1 class share (MSD internal forecasting), we have estimated the maximum number of patients eligible for pembrolizumab in 2nd or 3rd line that could receive pembrolizumab. We have not broken this down further to shares for individual drugs within the class for transparency purposes (see Table 111).

Table 111: Estimated maximum number of patients stage IIIb and IV with PD-L1 positive expression tumours treated with pembrolizumab in either 2L or 3L per year

	Year 0*	Year 1	Year 2	Year 3	Year 4	Year 5
	2016	2017	2018	2019	2020	2021
Estimated class share - PD-1 class	10%	23%	35%	40%	41%	41%
Maximum number of patients	30	413	631	724	745	748

*It assumes treatment will be available from November 2016 onwards.

6.3 Assumptions that were made about current treatment options and uptake of technologies

The budget impact compares two alternative scenarios:

- The existing treatment scenario, reflecting current clinical practice (i.e. without pembrolizumab), where patients can either be treated with docetaxel or with a combination of nintedanib and docetaxel, the later if tumours are of adenocarcinoma type.
- The new treatment scenario (with pembrolizumab assumed to be implemented as part of clinical practice).

The main assumptions formulated to estimate the number of patients eligible to receive pembrolizumab in 2L or 3L are:

- The budget impact model considers the following costs: testing, treatment pre-progression, administration and management of AEs.
- A total of 12% of patients with NSCLC stage IIIb/IV will be eligible for treatment with pembrolizumab.
- For each patient identified as a PD-L1 positive expresser (and potentially eligible for treatment with pembrolizumab), 8.39 patients would need to be tested.
- Patients receive the licensed dose of 2mg/kg until disease progression.
- The following inputs are based on outcomes from KEYNOTE-010:
    - The mean treatment duration (see Table 112)
    - The average number of vials per patient (assuming no vial sharing) used was based on European patient weights (detailed in section 5.5.2).
    - The proportion of patients receiving the expected dose
- No patients are assumed to be treated through clinical trials
- Only the costs related to pre-progression is considered as part of the budget impact estimation (i.e. for simplification, it is assumed that after progression costs will be similar independent of the subsequent therapies administered).

- It is assumed that pembrolizumab is introduced in the market in November 2016.

Table 112. Time on treatment and number of administrations

	Pembro 2mg/kg Q3W	Docetaxel	Nintedanib
Time on therapy (months)	4.97	2.68	5.53
Number of administrations (cycles)	7.20	3.88	7.99
Sources	KEYNOTE-010[82]		Manufacturer submission TA347 (nintedanib submission; pg 196)[63;82]

6.4 Assumptions that were made about market shares in England

Market shares are based on MSD forecasting, as explained in section 6.2 and are presented in Table 111. We assume that once pembrolizumab is introduced into the market, and in case of a positive recommendation by NICE, pembrolizumab will take proportionally market shares from both alternative treatments (docetaxel and nintedanib combined with docetaxel). The market shares here presented (see Table 111) reflect the estimated share at the class level for PD-1 therapies. This reflects, therefore, the maximum number of patients that could be expected to receive pembrolizumab.

6.5 Other significant costs associated with treatment that may be of interest to commissioners

Technology costs and other significant costs associated with treatment with pembrolizumab are identical to those assumed in the cost-effectiveness model and are described in section 5.5.

As mentioned in section 5 some patients may experience long-term survival. Mean overall survival is currently based on extrapolation method and the true mean overall survival observed in the population is not yet known. Although the assumptions used in the model are conservative there may be a significant number of patients treated with pembrolizumab who will be experiencing long term survival benefit and therefore long-term treatment with pembrolizumab.

In addition, pembrolizumab is administered every 3 weeks, which is lower than compared to some of the available chemotherapies and the administration time required per cycle is shorter than for some other chemotherapies (i.e. 30 minutes instead of 60 minutes or longer).

6.6 Unit costs assumed and how they were calculated

All unit costs considered here estimate the annual budget to the NHS in England and are based upon the ones included in the economic in section 5.5.

6.7 Estimates of resource savings

See section 6.1.

6.8 State the estimated annual budget impact on the NHS in England.

The introduction of pembrolizumab in the market in England is expected to displace the use of docetaxel (either as monotherapy or in combination with nintedanib) to subsequent treatment lines. The estimated budget impact on the NHS in England of all PD-1 agents is presented in Table 113. This is presented at list prices. MSD has not attempted to estimate the pembrolizumab share of the PD-1 class, therefore, the figures presented reflect the potentially maximum budget impact.

Table 113: Estimated budget impact of pembrolizumab over 5 years

	Year 0*	Year 1	Year 2	Year 3	Year 4	Year
	2016	2017	2018	2019	2020	202
Total stage IIIb-IV patients treated with pembrolizumab for 2L+	298	1,795	1,802	1,809	1,817	
World without pembrolizumab						
Total costs of testing	£0	£0	£0	£0	£0	
Total treatment costs	£1,810,566	£10,906,849	£10,950,477	£10,994,278	£11,038,256	£11,082
Total administration costs	£76,607	£461,481	£463,327	£465,180	£467,041	£468
Total adverse event costs	£89,454	£538,868	£541,023	£543,188	£545,360	£547
Total world without	£1,976,627	£11,907,198	£11,954,827	£12,002,646	£12,050,657	£12,098
World with pembrolizumab						
Total costs of testing	£124,921	£752,524	£755,534	£758,556	£761,590	£764
Total treatment costs	£2,496,959	£15,041,683	£15,101,850	£15,162,257	£15,222,906	£15,283
Total administration costs	£76,607	£401,489	£347,495	£325,626	£322,258	£323
Total adverse event costs	£82,929	£429,512	£366,307	£340,613	£336,522	£337
Total world with	£2,781,416	£16,625,207	£16,571,186	£16,587,052	£16,643,277	£16,709
Difference between the world with and the world without pembrolizumab						
Total costs of testing	£124,921	£752,524	£755,534	£758,556	£761,590	£764
Total treatment costs	£686,393	£4,134,834	£4,151,373	£4,167,979	£4,184,651	£4,201
Total administration costs	£0	-£59,993	-£115,832	-£139,554	-£144,783	-£145
Total adverse event costs	-£6,524	-£109,356	-£174,716	-£202,575	-£208,839	-£209
Total budget impact	£804,790	£4,718,009	£4,616,359	£4,584,406	£4,592,620	£4,610

*It assumes treatment will be available from November 2016 onwards.

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

See section 6.1.

6.10 Highlight the main limitations within the budget impact analysis.

A number of assumptions were made in terms of proportion of patients treated in 1st, 2nd and 3rd lines, which introduced uncertainty into the estimates here presented. Additionally, the model is based on a closed cohort of patients based on the eligible population presented in Table 111. As a limitation to this approach, there may be a small proportion of patients who are eligible for therapy not considered in these projections. Furthermore, consideration of the market shares at the class level does not allow an accurate estimation of the budget impact specifically related to pembrolizumab. However, for transparency purposes it was decided to present the maximum expected budget impact instead.

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Single technology appraisal

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Dear Ana and Chris,

The Evidence Review Group, Aberdeen HTA Group, and the technical team at NICE have looked at the submission received on 24 March 2016 from Merck Sharp & Dohme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **3 May 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

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If you have any queries on the technical issues raised in this letter, please contact Stuart Wood, Technical Lead (Stuart.Wood@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on clinical effectiveness data

A1. **PRIORITY.** The company submission includes direct effectiveness data comparing pembrolizumab 2mg/kg versus docetaxel 75mg/m^2 from KEYNOTE-010. Primary and secondary efficacy outcomes are reported for participants whose tumours express PD-L1 with TPS ≥1% (page 88, section 4.7) and for those with TPS of ≥50% or greater (Appendix 11 of the submission) but not for those with TPS 1-49%. Please provide clinical effectiveness results for participants with a PD-L1 **TPS 1-49%**

A2. **PRIORITY.** Section 4.14, page 152 of the company submission (ongoing studies) states that "*Results provided in this submission are from the final analysis of KEYNOTE-010. Patients in KEYNOTE-010 treated with pembrolizumab 2mg/Kg Q3W continued to be followed up and a further survival analysis for the pembrolizumab 2mg/Kg Q3W arm will be conducted at the end of April with results available in May 2016."* If available, please provide these new survival analyses

A3. **PRIORITY.** With regard to the network meta-analysis (pages 128 and 129 of the company submission), please further explain the use of constant hazard ratios, assuming proportional hazards, instead of fractional polynomial models

A4. **PRIORITY.** Results for the comparison pembrolizumab versus docetaxel presented in Table 48 (page 129 of the company submission) (HR = 0.87; 0.70 to 1.08) do not seem to match those presented for the same comparison in Table 47 (HR=0.81). Please clarify why these results are different.

A5. **PRIORITY.** Table 57 (page 142 of the company submission) shows the number of patients who died due to drug-related AEs. One death is reported for the docetaxel arm and 2 for the pembrolizumab arm. However, in the KEYNOTE-010 published paper, 5 deaths are reported among participants receiving docetaxel, and 3 among participants receiving pembrolizumab. Please clarify this difference.

A6. **PRIORITY.** Table 70 (page 180 of the company submission) shows the adverse events included in the economic modelling. Please clarify why endocrine disorders and respiratory, thoracic and mediastinal disorders (e.g. pneumonitis),which have been categorised as adverse events of special interest (AEOSI) in Appendix 20, Table 5, of the submission (page 411) have not been included in the economic modelling.

A7. Please provide a table similar to Table 43 (page 118 of the company submission) with the baseline characteristics of the subgroup with adenocarcinoma in KEYNOTE-010.

A8. In Appendix 19, Table 7, of the company submission, the model with the lowest deviance information criterion DIC doesn't seem to be presented. Please explain why

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you chose to present only the results for the model in bold 2nd order fractional polynomials with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1) and not the model with two shape parameters?

A9. One of the most relevant issues in immunotherapy is the necessary duration of therapy. The company submission states (page 161) that "*The anticipated licence establishes that pembrolizumab is to be administered until disease progression or unacceptable toxicities. However, there is no evidence regarding the optimal duration of treatment with pembrolizumab, particularly since the KEYNOTE-010 protocol established that treatment should continue until disease progression, toxicities leading to discontinuation, physician's decision or 2 years of uninterrupted delivery of pembrolizumab."* This would place considerable pressure on the pharmacy, nursing and oncology services with patients attending for an intravenous drip every 3 weeks for up to two years. Please clarify the following issues:

a. Does the company have data on the need for such long duration?

b. If not, is there intent to establish through clinical trials whether shorter courses are equally effective?

c. Given the relatively short interval between the drug being prepared and delivered, is there any possibility of home therapy being investigated?

Section B: Clarification on cost-effectiveness data

B1. **PRIORITY.** Please provide a summary of the clinical inputs and data sources used in the economic model as these are not clear.

B2. **PRIORITY.** Please provide anonymised survival data from the Keynote-010 trial in order to validate the extrapolation of survival data in the model. Please provide details of treatment assignment, time of progression, time of death, time of censoring, time of treatment discontinuation, PD-L1 expression (TPS 1-49%; ≥50%), and EGFR mutation status (mutant; wildtype).

B3. **PRIORITY.** If the request in B2 is not feasible please provide:

a. Time to treatment discontinuation (TTD) curves (including a table of detailing number of patients at risk at selected time points).

b. Kaplan Meier plots showing post-progression survival from time of progression by treatment for patients reaching progression.

B4. **PRIORITY.** Please provide results for different time points for switching between Kaplan Meier and parametric curves.

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B5. **PRIORITY.** In the model, the assumptions for using the registry data to extrapolate overall survival beyond two years needs further clarification. It is unclear whether the company has looked at survival curves for patients on the registry who have discontinued/progressed following platinum-based chemotherapy.

Please provide a table summarising the baseline characteristics of the English registry data, for the Stage IIIb and Stage IV groups. Please include patients' performance status, the proportion of patients who are PD-L1 positive and progressed after platinum chemotherapy.

B6. **PRIORITY.** Table 99 (page 221 of the company submission): Please clarify:

a. why the model predicted median overall survival (OS) of 8.51 in the docetaxel arm under base cases 1 and 2, when it is stated that the adjusted survival data from KEYNOTE-010 were used - where median OS is stated to be 8.3 years.

b. why the median OS is slightly higher in the pembrolizumab arm under base case 1 and 2 compared with the survival data of KEYNOTE-010 (e.g. OS of 10.81 for base case 1 versus 10.4 from KEYNOTE-010).

B7. **PRIORITY.** In Appendix 17 only the WinBugs programming language used in the analysis for safety outcomes, overall survival and progression free survival constant hazard ratio models has been provided. Please can you provide the data files and initial values for the Bayesian network meta-analysis described in Appendix 17.

B8. **PRIORITY.** The model spreadsheet includes link to another spreadsheet "*MSD Pembro NSCLC Model V4_22Mar2016-BC1 updates.xlst*". Please provide this sheet or update the links appropriately.

B9. **PRIORITY.** The MainMenu sheet includes a button labelled "*Survival Data*" which does not work. Please correct this error.

B10. The company submission states (page 174) that "*the registry data were 'rebased' at 2 years*". However, Figure 42 shows the registry data projections for rebase at 1.5 years. Please clarify which is correct - 2 years or 1.5 years.

B11. Figures 42 and 44 (pages 175 and 177 of the company submission) do not appear to be cited in the text of the submission. Please clarify what these figures are showing and provide comments on their interpretation.

B12. Please clarify why subgroups defined by PD-L1 expression level and EGFR mutation status were not considered in the cost-effectiveness analyses. If possible, please provide separate subgroup analyses by PD-L1 status (1-49%; ≥50%) and EGFR mutation status (mutant; wildtype).

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B13. Table 99 (page 221 of the company submission): Please clarify what accounts for the small difference in reported median OS for base case scenarios 1 and 2 in the pembrolizumab arm - when both use the KM data to 12 months.

B14. Section 5.4.1 (page 183 of the company submission): Please clarify whether the health state utility analysis informing the economic model adjusts for non-independence of repeated measures in individuals.

B15. Please clarify why the annual age decrement in utility is stopped at age 75 years in the company's economic model.

B16. In the company's economic model, a no stopping rule is applied for nintedanib in patients remaining progression free, whereas a stopping rule of 2 years is applied for pembrolizumab. Please provide further justification as to why different assumptions should be applied for the two drugs.

B17. The company submission Appendix 28 (page 465) states that "*The Gompertz model provided the best fitting curve for stage IV registry data (based on lowest AIC/BIC values, plausibility of the extrapolation and consistency with the curve chosen for Stage IIIB registry data) and was subsequently used in the economic modelling. The generalised gamma model provides the best fitting curve for Stage IV registry data based on AIC/BIC and is used for the base case economic model."* Please clarify which model was used.

B18. Figure 28, PRISMA diagram (page 156 of the company submission): Please clarify the number of papers that met the inclusion criteria from original search (108 minus 66 should give 42); and how further exclusions resulted in no papers (n=0) identified.

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3rd May 2016

Dear Helen,

Re. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Please find enclosed the MSD answers to the clarification questions from the ERG and the NICE technical team.

We believe that we have addressed all of the questions but should you or theERG require any further clarification please do let me know..

Best regards,

[redacted], [redacted] HTA and OR

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Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Section A: Clarification on clinical effectiveness data

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Please see below the clinical effectiveness results of KEYNOTE-010 patients in the PD-L1 TPS1-49% stratum (database cut-off 30 September 2015). It should be noted that KEYNOTE-010 study was designed and powered to compare efficacy between pembrolizumab and docetaxel in the TPS≥50% stratum and in the TPS≥1% overall population (with Bonferroni adjustment between the two tests). Therefore, the results within the TPS 1-49% stratum are possibly informative and should not be interpreted in the context of a well-controlled statistical testing strategy.

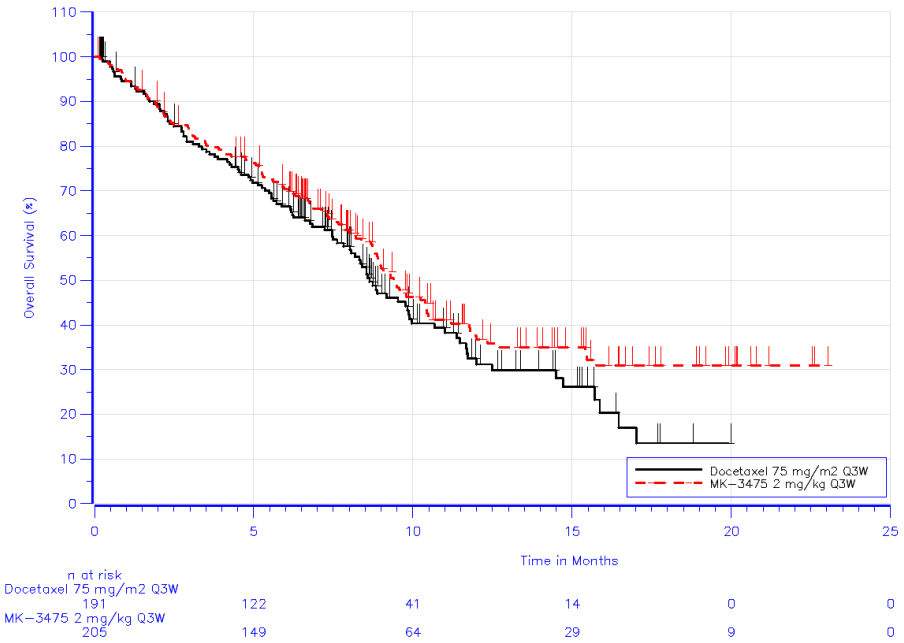
Table 1: KEYNOTE-010 analysis of OS in the TPS 1-49% population (ITT population)

Treatment	N	Number Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in % † (95% CI)	Treatment vs.	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2 Q3W	191	107 (56.0)	1319.6	8.1	8.6 (7.8, 9.9)	47.0 (38.8, 54.8)	---	---
Pembrolizumab 2 mg/kg Q3W	205	114 (55.6)	1707.7	6.7	9.4 (8.7, 10.5)	53.3 (45.7, 60.3)	0.79 (0.61, 1.04)	0.04434

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡	p-Value‖
Pembrolizumab 2 mg/kg Q3W vs. Pembrolizumab 10 mg/kg Q3W	1.15 (0.88, 1.52)	0.30825

† From product-limit (Kaplan-Meier) method for censored data. ‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (TPS≥50%, TPS≥1% , TPS1-49% , and Unknown PD-L1 status) § One-sided p-value based on log-rank test.
‖ Two-sided p-value based on log-rank test. Database Cut-off Date: 30SEP2015

Figure 1: KEYNOTE-010 - Kaplan-Meier of OS - patients treated with docetaxel and pembrolizumab 2mg/Kg Q3W - ITT Population (TPS 1-49%)



(Database Cutoff Date: 30SEP2015)

Table 2: KEYNOTE-010 - OS rate at fixed time-points in the TPS 1-49% population (ITT population)

	Docetaxel 75 mg/m2 Q3W (N=191)	Pembrolizumab 2 mg/kg Q3W (N=205)
OS rate at 6 Months (95% CI)†	66.5 (59.0, 72.9)	70.5 (63.6, 76.3)
OS rate at 9 Months (95% CI)†	47.0 (38.8, 54.8)	53.3 (45.7, 60.3)
OS rate at 12 Months (95% CI)†	31.2 (22.9, 39.8)	36.7 (29.1, 44.4)

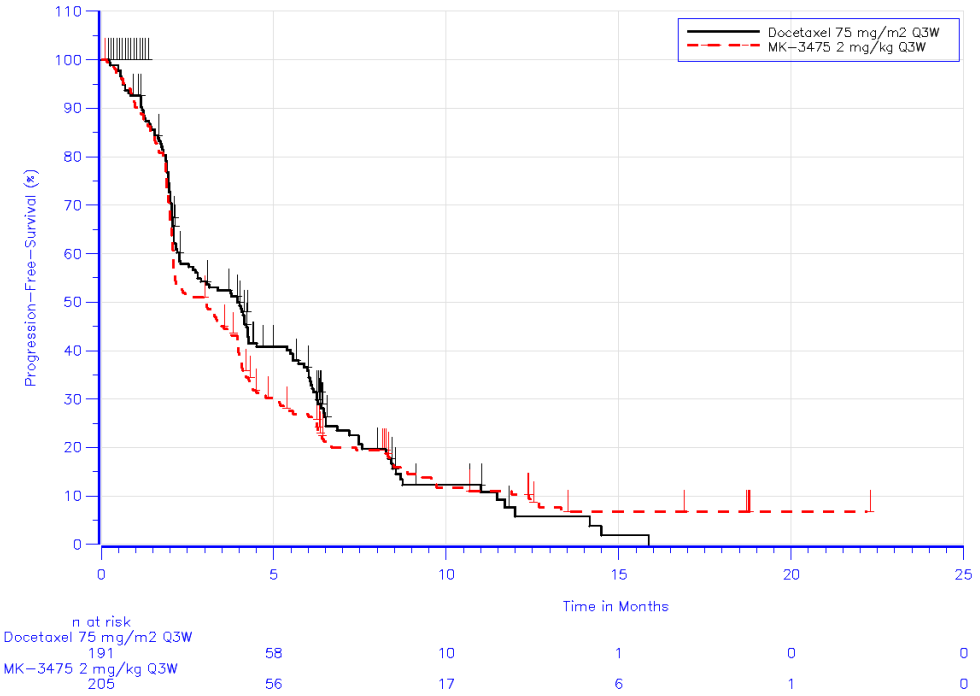
† From the product-limit (Kaplan-Meier) method for censored data.
Database Cut-off Date: 30SEP2015

Table 3: KEYNOTE-010- analysis of PFS based on IRC assessment per RECIST 1.1 in the TPS 1-49% population (ITT population)

Treatment	N	Number Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 9 in % † (95% CI)	Pembrolizumab vs. Docetaxel	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Docetaxel 75 mg/m2	191	139 (72.8)	719.9	19.3	3.9 (2.5, 4.3)	12.3 (7.0, 19.1)	-	-
Pembrolizumab 2 mg/kg Q3W	205	177 (86.3)	872.5	20.3	3.1 (2.1, 3.8)	14.6 (9.8, 20.3)	1.07 (0.85, 1.34)	0.71850

IRC: Independent Review Committee.
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian)and PD-L1 status (TPS≥50% TPS≥1% , TPS1-49% , and Unknown PD-L1 status)
§ One-sided p-value based on log-rank test. *Database Cut-off Date: 30SEP2015*

Figure 2: KEYNOTE-010 - Kaplan-Meier of PFS based on IRC assessment per RECIST 1.1 - patients treated with docetaxel and pembrolizumab 2mg/Kg Q3W - ITT Population (TPS 1-49%)



(Database Cutoff Date: 30SEP2015)

Table 4: KEYNOTE-010 - PFS rate at fixed time-points based on IRC assessment per RECIST 1.1 in the TPS 1-49% population (ITT population)

	Docetaxel 75 mg/m2 Q3W (N=191)	Pembrolizumab 2 mg/kg Q3W (N=205)
PFS rate at 6 Months (95% CI)†	35.8 (28.4, 43.3)	27.0 (21.0, 33.3)
PFS rate at 9 Months (95% CI)†	12.3 (7.0, 19.1)	14.6 (9.8, 20.3)
PFS rate at 12 Months (95% CI)†	5.8 (1.9, 12.7)	10.4 (6.3, 15.6)

† From the product-limit (Kaplan-Meier) method for censored data. Database Cut-off Date: 30SEP2015

Table 5: KEYNOTE-010: Analysis of ORR (IRC per RECIST 1.1) – ITT population (TPS 1-49%)

Treatment	N	Number Overall Responses	Overall Response Rate (%) (95% CI)	Difference in % vs. Docetaxel	
				Estimate 95% CI†	p-Value††
TPS 1-49% population					
Docetaxel 75 mg/m2 Q3W	191	20	10.5 (6.5,15.7)	---	
Pembrolizumab 2 mg/kg Q3W	205	20	9.8 (6.1,14.7)	-0.6 (-6.8,5.5)	0.57192

IRC = Independent Review Committee
Responses are based on IRC assessments per RECIST 1.1 with confirmation.
† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (TPS≥50% TPS≥1% , TPS1-49% and Unknown PD-L1 status) ; if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
§ Two-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % ≠ 0. Database Cut-off Date: 30SEP2015

Table 6: KEYNOTE-010: Summary of best overall response (IRC per RECIST 1.1) – ITT population (TPS 1-49%)

	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	(%)	n	(%)
Number of Patients in Population	**191**		**205**	
Complete Response (CR)	0	(0.0)	0	(0.0)
Partial Response (PR)	27	(14.1)	30	(14.6)
Overall Response (CR+PR)	**27**	**(14.1)**	**30**	**(14.6)**
Stable Disease (SD)	69	(36.1)	70	(34.1)
Disease Control (CR+PR+SD)	**96**	**(50.3)**	**100**	**(48.8)**
Progressive Disease (PD)	53	(27.7)	79	(38.5)
Not Evaluable (NE)	6	(3.1)	4	(2.0)
No Assessment	36	(18.8)	21	(10.2)

IRC = Independent Review Committee. Responses are based on IRC best assessment across time points, without confirmation.
Not Evaluable (NE) - a scan was obtained but it was not evaluable to make an interpretation of disease status (e.g. the image received did not contain the index lesion to make an assessment based on RECIST 1.1 criteria)
Database Cut-off Date: 30SEP2015

Table 7: KEYNOTE-010 - Analysis of Time to Response and Response Duration – ITT population (TPS 1-49%)

	TPS≥ 1% population	
	Docetaxel 75 mg/m2 Q3W (N=191)	**Pembrolizumab 2 mg/kg Q3W (N=205)**
IRC Assessment per RECIST 1.1		
Number of Patients with Response†	20	20
Time to Response ‡ (WEEKS)		
Mean (SD)	15 (9)	13 (6)
Median	9	9
Range of time to response	(6-36)	(7-31)
Response Duration‡ (WEEKS)		
Median	26	46
Range of response duration§	(6+ - 31)	(9+ - 87+)
Number of Response Ongoing‖ (%)	12 (60)	13 (65)
Investigator Assessment per irRC		

Number of Patients with Response[†]	17	26
Time to Response [†] (WEEKS)		
Mean (SD)	12 (6)	13 (7)
Median	9	9
Range of time to response	(6-27)	(5-31)
Response Duration[‡] (WEEKS)		
Median	21	NR
Range of response duration[§]	(5+ - 55)	(9+ - 78+)
Number of Response Ongoing [‖] (%)	9 (53)	19 (73)

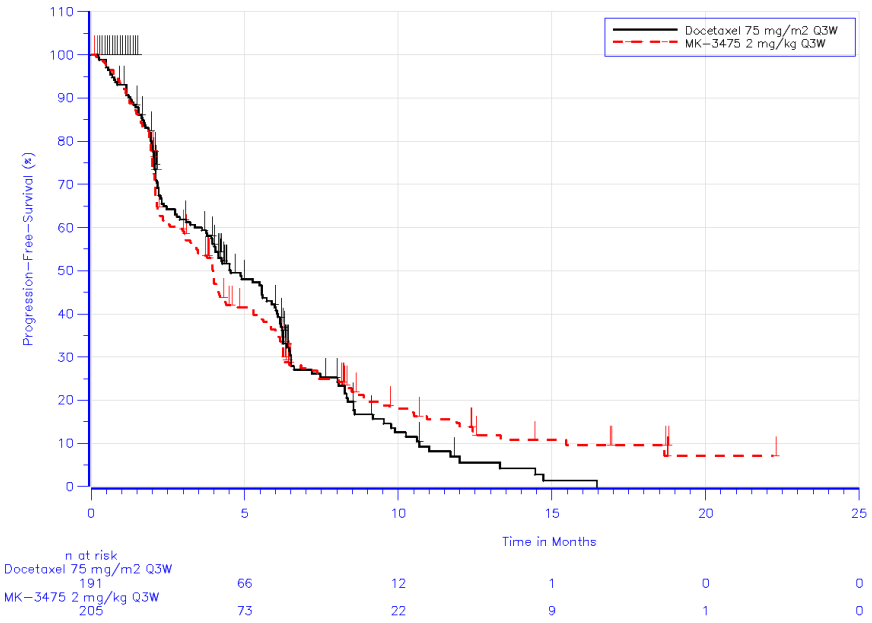
[†] Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only. [‡] From product-limit (Kaplan-Meier) method for censored data. [§] "+" indicates there is no progressive disease by the time of last disease assessment.
[‖] Ongoing response includes all responders who are alive, progression free, did not initiate new anti-cancer therapies and have not been determined to be lost to follow-up. NR= Not reached.
Database Cut-off Date: 30SEP2015

Table 8: KEYNOTE-010 - Analysis of PFS Based on INV per irRC - ITT Population (TPS 1-49%)

Treatment	N	Number Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 9 in % [†] (95% CI)	Treatment vs. Docetaxel	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Docetaxel 75 mg/m2 Q3W	191	137 (71.7)	784.8	17.5	4.5 (3.9, 5.9)	16.7 (10.7, 23.9)	---	---
Pembrolizumab 2 mg/kg Q3W	205	162 (79.0)	986.7	16.4	4.0 (3.1, 4.4)	20.4 (14.6, 26.9)	0.97 (0.77, 1.22)	0.38647

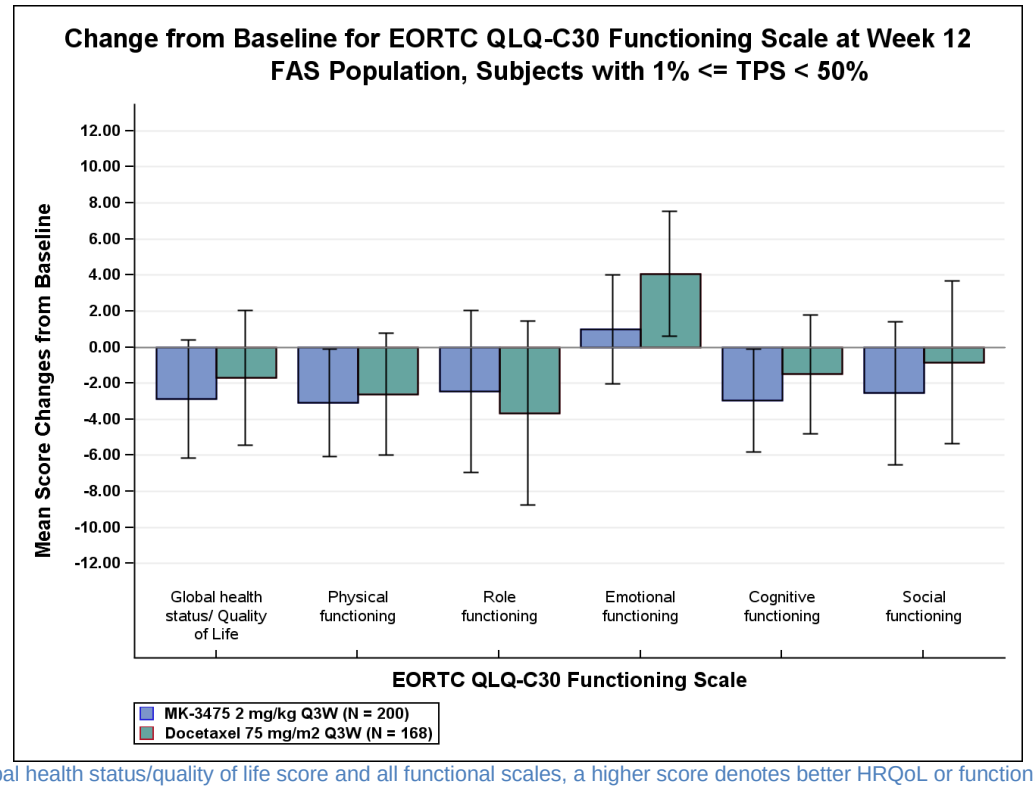
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
[†] From product-limit (Kaplan-Meier) method for censored data.[‡] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (TPS≥50% TPS≥1% , TPS1-49% , and Unknown PD-L1 status) if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

Figure 3: KEYNOTE-010 - Kaplan-Meier of PFS Based INV per irRC - patients treated with docetaxel and pembrolizumab 2mg/Kg Q3W - - ITT Population (TPS 1-49%)



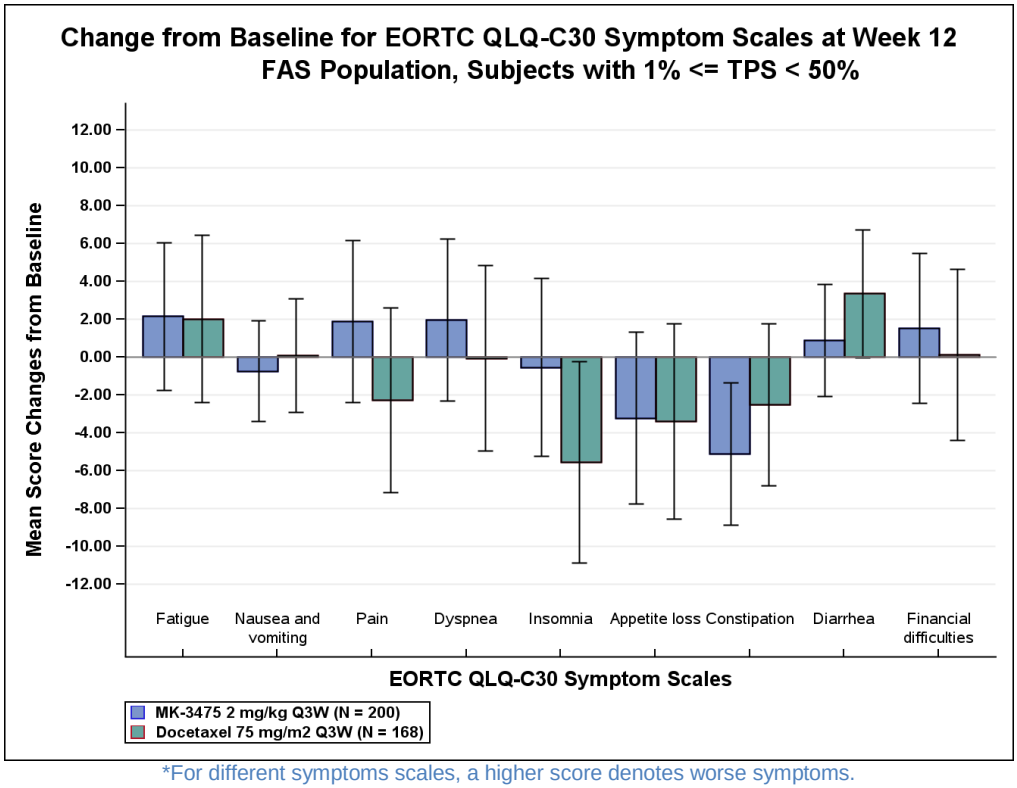
(Database Cutoff Date: 30SEP2015)

Figure 4: Change from Baseline eEORTC QLQ-C30 Functioning Scale/Global Health Status/Quality of Life at Week 12* (FAS population with TPS1-49%)



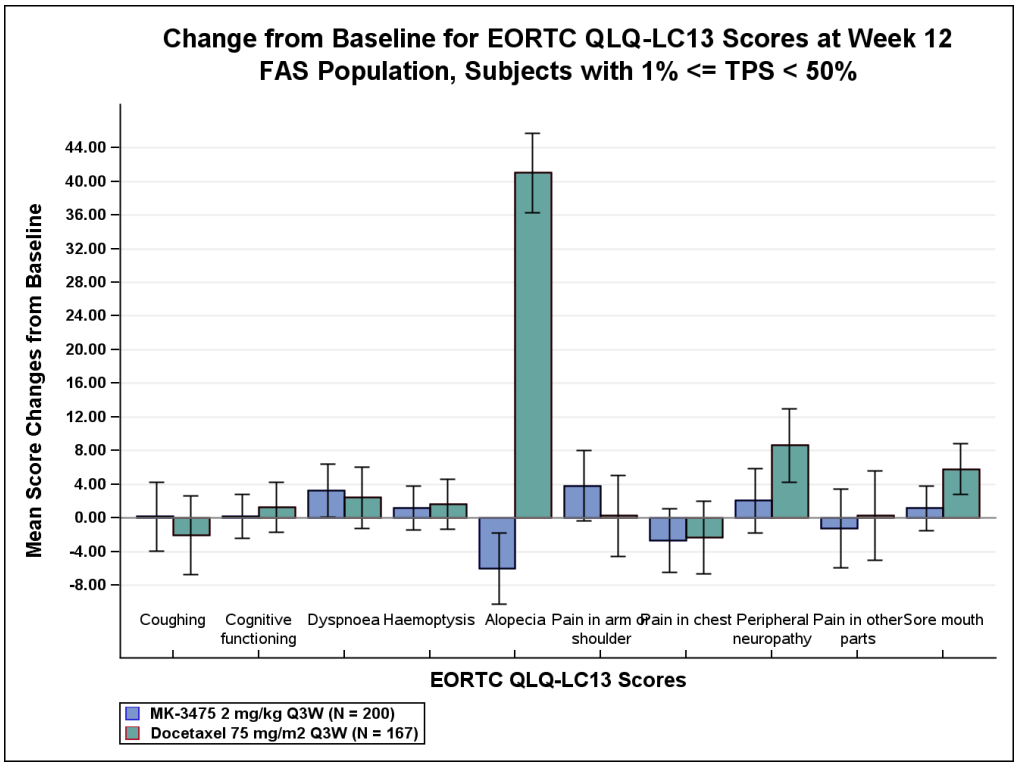
*For global health status/quality of life score and all functional scales, a higher score denotes better HRQoL or function, and a higher negative score denotes worse HRQoL or functions.

Figure 5: Change from Baseline eEORTC QLQ-C30 Symptoms Scales at week 12* (FAS population with TPS1-49%)



*For different symptoms scales, a higher score denotes worse symptoms.

Figure 6: Change from Baseline for eEORTC QLQ-LC13 Symptoms at Week 12* (FAS population with TPS1-49%)



For different lung cancer symptoms, a higher score denotes worse symptoms.

Table 9: Analysis of Change from Baseline of EuroQol (EQ)-5D Utility Score (Using European Algorithm) at week 12 (FAS Population with TPS1-49%)

Treatment	N†	Baseline Mean(SD)	N†	Week 12 Mean(SD)	EuroQol (EQ)-5D Utility Score (Using European Algorithm) Change from Baseline at Week 12		
					N††	Mean(SD)	LS Mean (95% CI)‡
Pembrolizumab 2 mg/kg Q3W	170	0.75 (0.19)	110	0.78 (0.18)	106	0.01(0.19)	0.00 (-0.03, 0.03)
Docetaxel 75 mg/m2 Q3W	129	0.69 (0.22)	77	0.73 (0.22)	69	0.01 (0.21)	-0.00 (-0.04, 0.03)
Pairwise Comparison					Difference in LS Means (95% CI)		p-value
Pembrolizumab 2 mg/kg Q3W vs. Docetaxel 75 mg/m2 Q3W					0.00 (-0.04, 0.05)		0.8446

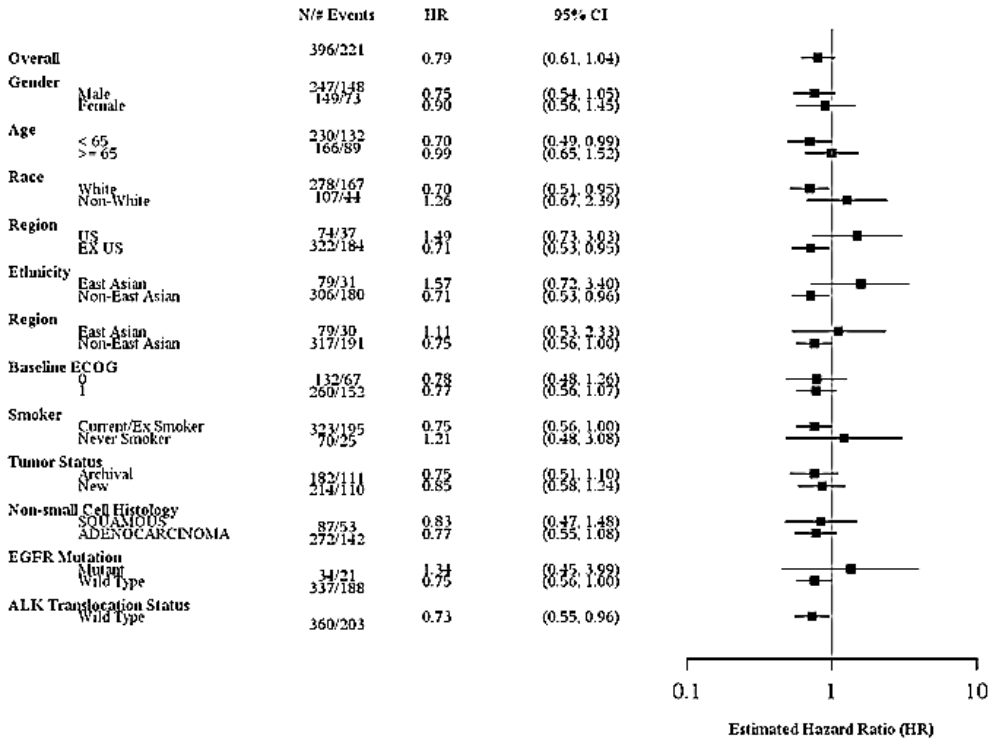
† N = Number of subjects in Full Analysis Set population with each time point observation; †† N = Number of subjects in Full Analysis Set population with Baseline and Week 12 observations; ‡ Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (extent of tumoral PD-L1 expression (TPS≥50% TPS≥1%, TPS1-49% , and Unknown PD-L1 status), Geographic region of the enrolling site (East Asia vs. non-East Asia) and ECOG (0 vs. 1), if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison) as covariates. SD: Standard deviation; LS Mean: Least square mean; CI: Confidence interval

Table 10: Analysis of Change from Baseline of VAS at week 12 (FAS Population with TPS 1-49%)

Treatment	N†	Baseline Mean(SD)	N†	Week 12 Mean(SD)	EQ-VAS Change from Baseline at Week 12		
					N††	Mean(SD)	LS Mean (95% CI)‡
Pembrolizumab 2 mg/kg Q3W	170	70.10 (18.44)	110	73.29 (15.00)	107	0.80 (16.91	-0.25 (-3.10, 2.60)
Docetaxel 75 mg/m2 Q3W	129	67.25 (21.21)	77	69.99 (17.57)	69	3.35 (20.14)	1.19 (-2.14, 4.52)
Pairwise Comparison					Difference in LS Means (95% CI)		p-value
Pembrolizumab 2 mg/kg Q3W vs. Docetaxel 75 mg/m2 Q3W					-1.44 (-5.59, 2.72)		0.4969

† N = Number of subjects in Full Analysis Set population with each time point observation; †† N = Number of subjects in Full Analysis Set population with Baseline and Week 12 observations; ‡ Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (extent of tumoral PD-L1 expression (TPS≥50% , TPS1-49% , and Unknown PD-L1 status), Geographic region of the enrolling site (East Asia vs. non-East Asia) and ECOG (0 vs. 1), if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison) as covariates. SD: Standard deviation; LS Mean: Least square mean; CI: Confidence interval

Figure 7: Forest Plot of OS HR by subgroup factors – pembrolizumab 2mg/Kg Q3W versus docetaxel – ITT population (TPS 1-49%)



Database Cut-off Date: 30SEP2015

A2. **PRIORITY.** Section 4.14, page 152 of the company submission (ongoing studies) states that "Results provided in this submission are from the final analysis of KEYNOTE-010. Patients in KEYNOTE-010 treated with pembrolizumab 2mg/Kg Q3W continued to be followed up and a further survival analysis for the pembrolizumab 2mg/Kg Q3W arm will be conducted at the end of April with results available in May 2016." If available, please provide these new survival analyses

The database cut-off for this analysis is end of April 2016. Data will become available during May and will be provided as soon as possible.

A3. **PRIORITY.** With regard to the network meta-analysis (pages 128 and 129 of the company submission), please further explain the use of constant hazard ratios, assuming proportional hazards, instead of fractional polynomial models.

For OS, the results of the network meta-analysis support the use of constant hazard ratios (HRs), assuming proportional hazards, which are applied in the cost-effectiveness model of MSD original submission [ID840]. The time-varying HRs are nearly horizontal (and indeed, a horizontal line can be contained in any of the 95% CrIs for each treatment), which means that the assumption of constant HRs is reasonable for this outcome. The constant HR model has fewer parameters to be estimated, and therefore is considered more parsimonious in the need for data.

For PFS, the assumption of constant HR does not seem to hold, as a horizontal line cannot be contained in the 95% CrI for pembrolizumab 10 mg in any of the presented

models, nor in the 95% CrI for pembrolizumab 2 mg in the Gompertz model (and some of the 2nd-order FP models that were not presented).

The analyses presented as base cases in the submission did not account for the violation of the constant HR assumption and used instead constant HRs. The expectation was that, in terms of health benefits, this was a conservative assumption since a constant benefit was assumed in terms of PFS for the combination of nintedanib and docetaxel compared to docetaxel monotherapy (HR=0.84), while the fractional polynomials approach predicts a higher hazard after around month 5.

MSD has now implemented the time-varying HR models in the cost-effectiveness model (using factional polynomial models). The results of the updated analyses are provided in Table 11 and demonstrate that there was a minor impact on the cost-effectiveness results after implementing this approach.

Table 11: Cost-effectiveness results (incremental analysis; discounted, with PAS for pembrolizumab and at list price for nintedanib) when considering time-dependent HRs using the fractional polynomials approach – adenocarcinoma subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER (£) vs. comparator	Incremental analysis
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£42,238	1.988	1.364				
Nintedanib + Docetaxel	£23,580	1.204	0.835	£18,658	0.529	£35,242	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£29,444	0.660	£44,597	£44,597
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£43,014	£2.44	£1.66				
Nintedanib + Docetaxel	£23,580	£1.20	£0.83	£19,434	£0.82	£23,591	Extendedly dominated
Docetaxel	£12,794	£1.02	£0.70	£30,220	£0.95	£31,657	£31,657

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

**Compared to the next less costly treatment*

***Compared to the next less effective treatment*

A4. **PRIORITY.** Results for the comparison pembrolizumab versus docetaxel presented in Table 48 (page 129 of the company submission) (HR = 0.87; 0.70 to 1.08) do not seem to match those presented for the same comparison in Table 47 (HR=0.81). Please clarify why these results are different.

Please accept our apologies for the labelling error in Table 47 of MSD original submission [ID840].
MSD confirms that the correct values were used in the network-meta-analysis and the results presented in Table 48 (page 129 of MSD submission) are correct. Table 47 is provided again below as Table 12, with the correct label.

Table 12: PFS HRs reported in the studies included in the NMA; separate doses of pembrolizumab

Study	Comparison	HR	logHR(SE)
KEYNOTE 010	Pembrolizumab **2mg** Q3W vs. docetaxel	0.87	-0.14 (0.11)
KEYNOTE 010	Pembrolizumab **10mg** Q3W vs. docetaxel	0.81	-0.21 (0.11)
LUME-Lung 1	Nintedanib+docetaxel vs. docetaxel	0.84	-0.17 (0.09)

A5. **PRIORITY.** Table 57 (page 142 of the company submission) shows the number of patients who died due to drug-related AEs. One death is reported for the docetaxel arm and 2 for the pembrolizumab arm. However, in the KEYNOTE-010 published paper, 5 deaths are reported among participants receiving docetaxel, and 3 among participants receiving pembrolizumab. Please clarify this difference.

Table 57 in page 142 of MSD original submission [ID840] is provided again below as Table 13. This table presents a summary of adverse events of special interest (AEOSI) in the overall (TPS≥1%) population. One patient died due to a drug-related AEOSI in the docetaxel arm and 2 patients died due to drug-related AEOSI in the pembrolizumab arm. MSD recognises that, although the title of the table (and the correspondent text in MSD submission) identifies the numbers provided as AEOSI (and not all AEs), this should have been made clearer in the body of the table. For purposes of clarity Table 57 of MSD submission is provided again below with this correction made, as Table 14.

Table 13: Summary AEOSI - APaT Population (TPS ≥1%)

Patients in population	Docetaxel 75 mg/m2 Q3W N=309 n (%)	Pembrolizumab 2 mg/kg Q3W N=339 n (%)
with one or more AEs	13 (4.2)	69 (20.4)
with no AE	296 (95.8)	270 (79.6)
with drug-related† AEs	7 (2.3)	59 (17.4)
with toxicity grade 3-5 AEs	4 (1.3)	19 (5.6)
with toxicity grade 3-5 drug-related AEs	3 (1.0)	16 (4.7)
with serious adverse events (SAEs)	5 (1.6)	21(6.2)
with drug-related SAEs	3 (1.0)	18 (5.3)
who died	2 (0.6)	2 (0.6)
who died due to a drug-related AE	1(0.3)	2 (0.6)
discontinued‡ due to an AE	5 (1.6)	7(2.1)
discontinued due to a drug-related AE	5 (1.6)	7 (2.1)
discontinued due to a SAE	3 (1.0)	5 (1.5)
discontinued due to drug-related SAE	3 (1.0)	5 (1.5)

† Determined by the investigator to be related to the drug. ‡ Study medication withdrawn.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose. AEs of special interest per ECI guidance excluding Infusion Reactions. Database Cut-off Date: 30SEP2015

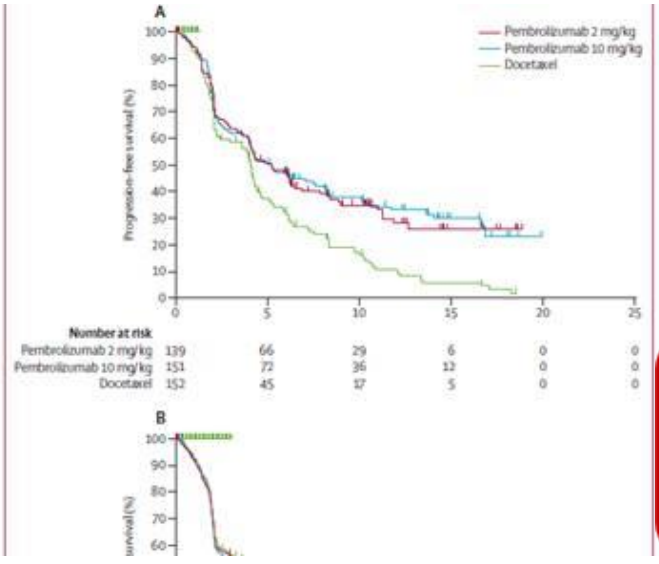
Table 14: Summary AEOSI - APaT Population (TPS ≥1%)

Patients in population	Docetaxel 75 mg/m2 Q3W N=309 n (%)	Pembrolizumab 2 mg/kg Q3W N=339 n (%)
with one or more AEOSIs	13 (4.2)	69 (20.4)
with no AEOSI	296 (95.8)	270 (79.6)
with drug-related† AEOSIs	7 (2.3)	59 (17.4)
with toxicity grade 3-5 AEOSIs	4 (1.3)	19 (5.6)
with toxicity grade 3-5 drug-related AEOSIs	3 (1.0)	16 (4.7)
with serious AEOSI	5 (1.6)	21(6.2)
with drug-related serious AEOSI	3 (1.0)	18 (5.3)
who died	2 (0.6)	2 (0.6)
who died due to a drug-related AEOSI	1(0.3)	2 (0.6)
discontinued‡ due to an AEOSI	5 (1.6)	7(2.1)
discontinued due to a drug-related AEOSI	5 (1.6)	7 (2.1)
discontinued due to a serious AEOSI	3 (1.0)	5 (1.5)
discontinued due to drug-related serious AEOSI	3 (1.0)	5 (1.5)

† Determined by the investigator to be related to the drug. ‡ Study medication withdrawn.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose. AEs of special interest per ECI guidance excluding Infusion Reactions. Database Cut-off Date: 30SEP2015

A1. Additionally, MSD would like to confirm that the number of deaths reported in the KEYNOTE-010 published paper is correct (5 deaths reported among patients receiving docetaxel, and 3 among patients receiving pembrolizumab 2mg/Kg) - please see the below image of the Lancet paper highlighting the source of this information. These numbers correspond to deaths due to all drug-related AEs (not only AEOSI). These results are presented in Table 53 of MSD submission - summary of exposure and AEs in the overall (TPS≥1%) population, provided again below as

Table 15.



score of ≥50% or greater and 6 months in the docetaxel group for all patients (appendix p 10).

In the safety population, the median duration of treatment was 3·5 months (IQR 1·4–7·2) in the pembrolizumab 2 mg/kg group, 3·5 months (1·4–7·0) in the pembrolizumab 10 mg/kg group, and 2·0 months (0·8–3·6) in the docetaxel group. Grade 3–5 adverse events attributed to study treatment occurred in 43 (13%) of 339 patients in the pembrolizumab 2 mg/kg group, 55 (16%) of 343 patients in the pembrolizumab 10 mg/kg group, and 109 (35%) of 309 patients in the docetaxel group (table 2). 15 (4%) of 339 patients, 17 (5%) of 343 patients, and 31 (10%) of 309 patients, respectively, permanently discontinued study drug because of treatment-related adverse events. Deaths attributed to study treatment occurred in three patients in the pembrolizumab 2 mg/kg group (two cases of pneumonitis and one of pneumonia), three patients in the pembrolizumab 10 mg/kg group (one case each of myocardial infarction, pneumonia, and pneumonitis), and five patients in the docetaxel group (one case each of acute cardiac failure, dehydration, febrile neutropenia, interstitial lung disease, and respiratory tract infection).

Table 15: Summary of Exposure and AEs - APaT Population (TPS ≥ 1%)

Number Patients – APaT population	Previously Treated NSCLC Population (TPS≥1%)	
	Docetaxel 75 mg/m2 Q3W n = 309	Pembrolizumab 2 mg/kg Q3W n = 339
Exposure, days		
• Median	62.0	106.0
• Range of exposure	1.0 to 416.0	1.0 to 681.0
• Mean (SD)	81.5 (72.3)	151.1 (143.9)
Number of Administrations		
• Median (range)	3.0 (1.0 to 18.0)	6.0 (1.0 to 26.0)
• Mean (SD)	4.6 (3.2)	7.8 (6.4)
Patients in TPS ≥ 1% population		
with one or more adverse events	297 (96.1%)	331 (97.6%)
with drug-related† AEs	251 (81.2%)	215 (63.4%)
with toxicity grade 3-5 AE	173 (56.0%)	158 (46.6%)
with toxicity grade 3-5 drug-related AEs	109 (35.3%)	43 (12.7%)
with serious AEs	107 (34.6%)	115 (33.9%)
with serious drug-related AEs	42 (13.6%)	32 (9.4%)
who died	15 (4.9%)	17 (5.0%)
who died due to a drug-related AE	**5 (1.6%)**	**3 (0.9%)**
discontinued‡ due to an AE	42 (13.6%)	28 (8.3%)
discontinued due to a drug-related AE	31 (10.0%)	15 (4.4%)
discontinued due to a SAE	19 (6.1%)	24 (7.1%)
discontinued due to a drug-related SAE	11 (3.6%)	11 (3.2%)

† Determined by the investigator to be related to the drug. ‡ Study medication withdrawn.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose. Database Cut-off Date: 30SEP2015

A6. **PRIORITY.** Table 70 (page 180 of the company submission) shows the adverse events included in the economic modelling. Please clarify why endocrine disorders and respiratory, thoracic and mediastinal disorders (e.g. pneumonitis),which have been categorised as adverse events of special interest (AEOSI) in Appendix 20, Table 5, of the submission (page 411) have not been included in the economic modelling.

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients (at any grade) in either treatment arm, with the exception of diarrhoea (included if Grade 2+)[1] and febrile neutropenia (included at any grade given its significant impact on quality of life and costs, as suggested by clinicians; see page 184 of the submission). This was in line with the most recent NICE submissions in patients with previously treated NSCLC (i.e. TA374[2] and ID811[3]).

- Hypothyroidism was the only AE within the endocrine disorders category with an incidence of 5% or more (of any grade) in the pembrolizumab 2mg/kg arm within KEYNOTE-010. However, none of the patients experienced Grade 3+ hypothyroidism and therefore this AE was not considered as part of the cost-effectiveness model.

- Pneumonitis was not included in the cost-effectiveness analysis since its incidence was lower than 5% (considering all grades) in either treatment arm (pembrolizumab 2mg/kg or docetaxel) in the KEYNOTE-010 trial.[4] No other respiratory, thoracic and mediastinal disorders (of any grade) occurred in at least 5% of patients and were, therefore, excluded as well from the cost-effectiveness model.

A7. Please provide a table similar to Table 43 (page 118 of the company submission) with the baseline characteristics of the subgroup with adenocarcinoma in KEYNOTE-010.

Please see below Table 16 with the baseline characteristics of the subgroup with adenocarcinoma in KEYNOTE-010 overall population (TPS≥1%).

Table 16: KEYNOTE-010 - Baseline characteristics of patients with adenocarcinoma – ITT population (TPS≥1%)

	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)
Region						
East Asian	42	(17.8)	46	(19.6)	88	(18.7)
Smoker						
Never Smoker	58	(24.6)	54	(23.0)	112	(23.8)
Current/Ex-Smoker	173	(73.3)	180	(76.6)	353	(74.9)
Missing	5	(2.1)	1	(0.4)	6	(1.3)
ECOG						
0	84	(35.6)	83	(35.3)	167	(35.5)
1	149	(63.1)	151	(64.3)	300	(63.7)
2	1	(0.4)	1	(0.4)	2	(0.4)
3	1	(0.4)	0	(0.0)	1	(0.2)
MISSING	1	(0.4)	0	(0.0)	1	(0.2)
Cancer Stage						
IIIA	6	(2.5)	4	(1.7)	10	(2.1)
IIIB	6	(2.5)	10	(4.3)	16	(3.4)
IV	224	(94.9)	221	(94.0)	445	(94.5)
Metastatic Staging						
M0	12	(5.1)	14	(6.0)	26	(5.5)
M1	60	(25.4)	60	(25.5)	120	(25.5)
M1A	42	(17.8)	44	(18.7)	86	(18.3)
M1B	122	(51.7)	117	(49.8)	239	(50.7)
Baseline Tumor Size (mm)						
Subjects with data	208		230		438	
Mean	89.5		96.4		93.1	
SD	55.3		63.9		60.0	
Median	74.0		79.0		77.0	
Range	14 to 290		10 to 345		10 to 345	
Brain Metastasis						
Yes	39	(16.5)	44	(18.7)	83	(17.6)
No	197	(83.5)	191	(81.3)	388	(82.4)
Non-small Cell Histology						
NON-SQUAMOUS	236	(100.0)	235	(100.0)	471	(100.0)
PD-L1 Status						
TPS1-49%	129	(54.7)	143	(60.9)	272	(57.7)
TPS≥50%	107	(45.3)	92	(39.1)	199	(42.3)
EGFR Mutation						

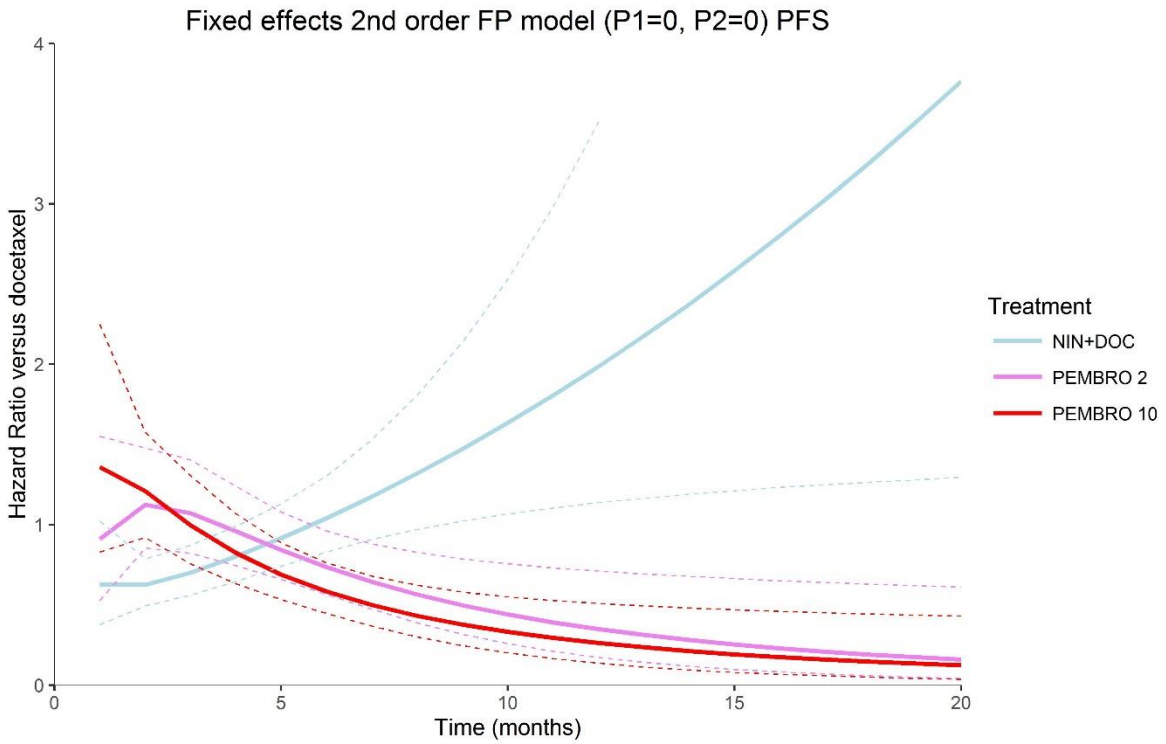
	Docetaxel 75 mg/m2 Q3W		MK-3475 2 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)
MUTANT	22	(9.3)	27	(11.5)	49	(10.4)
WILD TYPE	211	(89.4)	207	(88.1)	418	(88.7)
UNDETERMINED	2	(0.8)	0	(0.0)	2	(0.4)
Missing	1	(0.4)	1	(0.4)	2	(0.4)
ALK Translocation Status						
MUTANT	2	(0.8)	2	(0.9)	4	(0.8)
WILD TYPE	223	(94.5)	223	(94.9)	446	(94.7)
UNDETERMINED	9	(3.8)	6	(2.6)	15	(3.2)
Missing	2	(0.8)	4	(1.7)	6	(1.3)
Prior Lines of Systemic Therapy						
ADJUVANT	2	(0.8)	4	(1.7)	6	(1.3)
FIRST LINE	159	(67.4)	161	(68.5)	320	(67.9)
SECOND LINE	48	(20.3)	49	(20.9)	97	(20.6)
THIRD LINE	18	(7.6)	12	(5.1)	30	(6.4)
FOURTH LINE	6	(2.5)	6	(2.6)	12	(2.5)
FIFTH LINE OR GREATER	3	(1.3)	2	(0.9)	5	(1.1)
Missing	0	(0.0)	1	(0.4)	1	(0.2)
Prior Adjuvant/Neo-adjuvant Therapy						
Y	7	(3.0)	12	(5.1)	19	(4.0)
N	229	(97.0)	223	(94.9)	452	(96.0)
Prior Chemotherapy†						
Y	234	(99.2)	229	(97.4)	463	(98.3)
N	2	(0.8)	6	(2.6)	8	(1.7)
Prior Immunotherapy†						
Y	1	(0.4)	1	(0.4)	2	(0.4)
N	235	(99.6)	234	(99.6)	469	(99.6)
Prior EGFR TKI Therapy†						
Y	37	(15.7)	33	(14.0)	70	(14.9)
N	199	(84.3)	202	(86.0)	401	(85.1)
Prior ALK inhibitor Therapy†						
Y	2	(0.8)	3	(1.3)	5	(1.1)
N	234	(99.2)	232	(98.7)	466	(98.9)

†Prior systemic therapy (Database Cut-off Date: 30SEP2015).

A8. In Appendix 19, Table 7, of the company submission, the model with the lowest deviance information criterion DIC doesn't seem to be presented. Please explain why you chose to present only the results for the model in bold 2nd order fractional polynomials with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1) and not the model with two shape parameters?

The HRs for the model with the lowest DIC (2nd order fractional polynomials with p1=0, p2=0; treatment effects on 1 scale (d0) and 2 shape parameters) are presented below (Figure 8). The fractional polynomial models with more parameters are particularly sensitive to data in the tails. In this case, the HR for the combination nintedanib with docetaxel is trending towards infinity, and MSD does not believe this to be truly reflective of the source data. For PFS, the LUME LUNG 1 data past 8 months is extremely susceptible to a small number of events due to the sparseness of the data, and one more or fewer progression events out in the tails could have a big impact on the shape of the HR curve.

Figure 8: Results of fixed effects NMA of PFS; 2nd order fractional polynomial model (2 shape); treatment effects as HR over time relative to docetaxel



A9. One of the most relevant issues in immunotherapy is the necessary duration of therapy. The company submission states (page 161) that "*The anticipated licence establishes that pembrolizumab is to be administered until disease progression or unacceptable toxicities. However, there is no evidence regarding the optimal duration of treatment with pembrolizumab, particularly since the KEYNOTE-010 protocol established that treatment should continue until disease progression, toxicities leading to discontinuation, physician's decision or 2 years of uninterrupted delivery of pembrolizumab."* This would place considerable pressure on the pharmacy, nursing and oncology services with patients attending for an intravenous drip every 3 weeks for up to two years. Please clarify the following issues:

a. Does the company have data on the need for such long duration?

MSD has no evidence that treatment with pembrolizumab should be shorter than the maximum duration of therapy of 2 years established in KEYNOTE-010 study. It should be noted that in KEYNOTE-001 trial design treatment duration with pembrolizumab was for an unlimited period of time. However, subsequent to this, the trial design of KEYNOTE-010 restricted treatment duration to a maximum of 2 years of uninterrupted treatment with pembrolizumab.

b. If not, is there intent to establish through clinical trials whether shorter courses are equally effective?

MSD has no plans in the trial development program to look at the efficacy of shorter courses of pembrolizumab therapy.

c. Given the relatively short interval between the drug being prepared and delivered, is there any possibility of home therapy being investigated?

Yes. MSD has a small pilot study running in Manchester to investigate the possibility of home therapy for pembrolizumab and is waiting for the results of this study to assess whether this possibility should be further explored.

Section B: Clarification on cost-effectiveness data

B1. **PRIORITY.** Please provide a summary of the clinical inputs and data sources used in the economic model as these are not clear.

A summary of the key clinical inputs and data sources used in the economic model is presented in Table 17. Additionally, Table 18 below presents a summary of the extrapolation options for pembrolizumab and the comparator arms used in the cost-effectiveness model.

Table 17. Summary of clinical inputs and data sources used in the economic model

Clinical evidence and source	Brief description	Use in the model
KEYNOTE-010[4;5]	Multicentre, randomised, adaptively designed phase II/III trial of pembrolizumab 2mg/kg Q3W (n=344) versus docetaxel 75mg/m^2 Q3W (n=343) in adults with advanced NSCLC whose tumours express PD-L1 (based on a TPS of ≥1%), and who have experienced disease progression after at least platinum-containing chemotherapy.	• Used to derive the baseline patient characteristics (including average age, the proportion of male, average weight and BSA). • Patient level data were used to fit OS and PFS parametric curves for both pembrolizumab and docetaxel arms. • Patient level data for docetaxel arm were used to perform switching adjustments for the docetaxel OS. • OS KM data were used to model OS in the first phase of the OS before parametric curves were applied. • PFS KM data were used to model PFS in the first 9 weeks before parametric curves were applied. • Patient level data were used to calculate HRs for time on treatment versus PFS and proportions of patients actually receiving the planned doses for both pembrolizumab and docetaxel. • EQ-5D data collected in the trial were used to derive health state utility values (progression based, time-to-death based, and combined progression and time-to-death based) used in the model. • Used to derive the incidence of grade 3+ AEs and grade 2 diarrhoea and febrile neutropenia (all grades) for both pembrolizumab and docetaxel. • Used to derive the proportion of patients receiving subsequent treatments for both pembrolizumab and docetaxel. • Used as part of the NMA to compare the relative effectiveness in terms of OS and PFS for pembrolizumab, docetaxel and nintedanib+docetaxel in patients with NSCLC of adenocarcinoma histology.

Clinical evidence and source	Brief description	Use in the model
KEYNOTE-001[6]	Phase I multi-centre, open-label study in adult patients with progressive locally advanced or metastatic carcinomas, including patients with advanced NSCLC. It provides the longest available follow up for patients with advanced NSCLC previously treated.	Parametric survival curves were fitted using the OS data rebased at 1 year. The curve presenting the best fit (based on visual inspection, goodness of fit statistics and clinical plausibility) was used to model long-term OS for pembrolizumab from 1 year onwards in the economic model.
National Lung Cancer Audit (NLCA) registry long-term survival data[7]	NLCA registry OS data in England, which includes up to almost 6 years of OS data for NSCLC patients.	Two datasets from the NLCA registry OS (stage IIIb and stage IV OS; and combined stage IIIB/IV OS for patients with performance status 0-1 and treated by chemotherapy) were used to model the long-term OS from year 2 onwards for both pembrolizumab and docetaxel as part of scenario analyses (scenario analyses 1 and 2) in the economic model. Parametric survival curves were fitted to digitised pseudo patient level OS data rebased at year 2.
LUME-Lung 1[1]	Multicentre, double-blind, randomised phase III trial of docetaxel 75 mg/m2 Q3W and the combination docetaxel 75 mg/m2 Q3W with nintedanib 400 mg in adults with advanced NSCLC whose disease had progressed on or after treatment with only 1 prior chemotherapy regimen..	Used as part of the NMA to compare the relative effectiveness, in terms of OS and PFS, for pembrolizumab, docetaxel and nintedanib+docetaxel in patients with advanced NSCLC of adenocarcinoma histology.
General population mortality[8]	Latest national life table in England & Wales providing age- and gender-specific general population mortality.	Applied throughout the modelled time horizon as background mortality (i.e., general population mortality is applied when modelled mortality is lower than the gender- and age-matching general population mortality).

Key: AE, adverse event; HR, hazard ratio; IV, intravenous; KM, Kaplan-Meier; NLCA, National Lung Cancer Audit; NMA, network meta-analysis; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression free survival; Q3W, every 3 weeks; RCT, randomised controlled trial; TPS, proportion of tumour cells staining for PD-L1.

Table 18. Summary of extrapolation options for pembrolizumab and comparator arms

	All population		Adenocarcinoma population		
	Pembrolizumab	Docetaxel	Pembrolizumab	Docetaxel	Nintedanib + Docetaxel
Base case 1	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS:** HR applied to the docetaxel PFS curve

	All population		Adenocarcinoma population		
	Pembrolizumab	**Docetaxel**	**Pembrolizumab**	**Docetaxel**	**Nintedanib + Docetaxel**
	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001	**OS:** KEYNOTE-010 KM adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001	**OS:** KEYNOTE-010 KM adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** HR applied to the docetaxel OS curve
Base case 2	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS:** HR applied to the docetaxel PFS curve
	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** KEYNOTE-010 KM adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** KEYNOTE-010 KM adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** HR applied to the docetaxel OS curve
Scenario 1-1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1
	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001 to year 2 and the Gompertz curve fitted to the NLCA Registry data – Chemotherapy PS0-1 dataset from year 2 onwards	OS: KEYNOTE-010 KM data adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the Gompertz curve fitted to the NLCA Registry data – Chemotherapy PS0-1 dataset from year 2 onwards	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001 to year 2 and the Gompertz curve fitted to the NLCA Registry data – Chemotherapy PS0-1 dataset from year 2 onwards	OS: KEYNOTE-010 KM data adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the Gompertz curve fitted to the NLCA Registry data – Chemotherapy PS0-1 dataset from year 2 onwards	OS: Same as Base case 1

	All population		Adenocarcinoma population		
	Pembrolizumab	**Docetaxel**	**Pembrolizumab**	**Docetaxel**	**Nintedanib + Docetaxel**
Scenario 1-2	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1
	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001 to year 2 and the generalised gamma curve fitted to the NLCA Registry data – Stage IIIb/IV dataset from year 2 onwards	OS: KEYNOTE-010 KM data adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the generalised gamma curve fitted to the NLCA Registry data – Stage IIIb/IV dataset from year 2 onwards	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001 to year 2 and the generalised gamma curve fitted to the NLCA Registry data – Stage IIIb/IV dataset from year 2 onwards	OS: KEYNOTE-010 KM data adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the generalised gamma curve fitted to the NLCA Registry data – Stage IIIb/IV dataset from year 2 onwards	OS: Same as Base case 1
Scenario 1-9	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1
	OS: KEYNOTE-010 KM data to week 62, followed by the exponential curve fitted to KEYNOTE-001	OS: KEYNOTE-010 KM adjusted for switching using the two-stage method to week 62, followed by the exponential curve fitted to KEYNOTE-010	OS: KEYNOTE-010 KM data to week 62, followed by the exponential curve fitted to KEYNOTE-001	OS: KEYNOTE-010 KM adjusted for switching using the two-stage method to week 62, followed by the exponential curve fitted to KEYNOTE-010	OS: Same as Base case 1
Scenario 1-10	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1	PFS: Same as Base case 1
	OS: KEYNOTE-010 KM data to week 72, followed by the exponential curve fitted to KEYNOTE-001	OS: KEYNOTE-010 KM adjusted for switching using the two-stage method to week 72, followed by the exponential curve fitted to KEYNOTE-010	OS: KEYNOTE-010 KM data to week 72, followed by the exponential curve fitted to KEYNOTE-001	OS: KEYNOTE-010 KM adjusted for switching using the two-stage method to week 72, followed by the exponential curve fitted to KEYNOTE-010	OS: Same as Base case 1
Scenario 1-11	PFS: KEYNOTE-010 KM data to week 28, followed by the generalised gamma curve fitted to KEYNOTE-010	PFS: KEYNOTE-010 KM data to week 28, followed by the generalised gamma curve fitted to KEYNOTE-010	PFS: KEYNOTE-010 KM data to week 28, followed by the generalised gamma curve fitted to KEYNOTE-010	PFS: KEYNOTE-010 KM data to week 28, followed by the generalised gamma curve fitted to KEYNOTE-010	PFS: Same as Base case 1
	OS: Same as Base case 1	OS: Same as Base case 1	OS: Same as Base case 1	OS: Same as Base case 1	OS: Same as Base case 1

	All population		Adenocarcinoma population		
	Pembrolizumab	**Docetaxel**	**Pembrolizumab**	**Docetaxel**	**Nintedanib + Docetaxel**
Scenario 2-1	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2
	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the Gompertz curve fitted to the NLCA Registry data – Chemotherapy PS0-1 dataset from year 2 onwards	OS: KEYNOTE-010 KM data adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the Gompertz curve fitted to the NLCA Registry data – Chemotherapy PS0-1 dataset from year 2 onwards	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the Gompertz curve fitted to the NLCA Registry data – Chemotherapy PS0-1 dataset from year 2 onwards	OS: KEYNOTE-010 KM data adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the Gompertz curve fitted to the NLCA Registry data – Chemotherapy PS0-1 dataset from year 2 onwards	OS: Same as Base case 2
Scenario 2-2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2
	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the generalised gamma curve fitted to the NLCA Registry data – Stage IIIb/IV dataset from year 2 onwards	OS: KEYNOTE-010 KM data adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the generalised gamma curve fitted to the NLCA Registry data – Stage IIIb/IV dataset from year 2 onwards	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the generalised gamma curve fitted to the NLCA Registry data – Stage IIIb/IV dataset from year 2 onwards	OS: KEYNOTE-010 KM data adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010 to year 2 and the generalised gamma curve fitted to the NLCA Registry data – Stage IIIb/IV dataset from year 2 onwards	OS: Same as Base case 2
Scenario 2-9	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2
	OS: KEYNOTE-010 KM data to week 62, followed by the exponential curve fitted to KEYNOTE-010	OS: KEYNOTE-010 KM adjusted for switching using the two-stage method to week 62, followed by the exponential curve fitted to KEYNOTE-010	OS: KEYNOTE-010 KM data to week 62, followed by the exponential curve fitted to KEYNOTE-010	OS: KEYNOTE-010 KM adjusted for switching using the two-stage method to week 62, followed by the exponential curve fitted to KEYNOTE-010	OS: Same as Base case 2
Scenario 2-10	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2	PFS: Same as Base case 2
	OS: KEYNOTE-010 KM data to week 72, followed by the exponential curve fitted to KEYNOTE-010	OS: KEYNOTE-010 KM adjusted for switching using the two-stage method to week 72, followed by the exponential curve fitted to KEYNOTE-010	OS: KEYNOTE-010 KM data to week 72, followed by the exponential curve fitted to KEYNOTE-010	OS: KEYNOTE-010 KM adjusted for switching using the two-stage method to week 72, followed by the exponential curve fitted to KEYNOTE-010	OS: Same as Base case 2

	All population		Adenocarcinoma population		
	Pembrolizumab	**Docetaxel**	**Pembrolizumab**	**Docetaxel**	**Nintedanib + Docetaxel**
Scenario 2-11	PFS: KEYNOTE-010 KM data to week 28, followed by the generalised gamma curve fitted to KEYNOTE-010	PFS: KEYNOTE-010 KM data to week 28, followed by the generalised gamma curve fitted to KEYNOTE-010	PFS: KEYNOTE-010 KM data to week 28, followed by the generalised gamma curve fitted to KEYNOTE-010	PFS: KEYNOTE-010 KM data to week 28, followed by the generalised gamma curve fitted to KEYNOTE-010	PFS: Same as Base case 2
	OS: Same as Base case 2	OS: Same as Base case 2	OS: Same as Base case 2	OS: Same as Base case 2	OS: Same as Base case 2

B2. **PRIORITY.** Please provide anonymised survival data from the Keynote-010 trial in order to validate the extrapolation of survival data in the model. Please provide details of treatment assignment, time of progression, time of death, time of censoring, time of treatment discontinuation, PD-L1 expression (TPS 1-49%; ≥50%), and EGFR mutation status (mutant; wildtype).

We have provided the following documents as additional attachments:

- 'Question B2_CIC', with a description of the information provided for this question and how to access it.
- 'survival0contents_CIC', with some further details of the data provided.
- 'survival_for_NICE_from_MK_CIC', with the requested dataset.

B3. **PRIORITY.** If the request in B2 is not feasible please provide:

a. Time to treatment discontinuation (TTD) curves (including a table of detailing number of patients at risk at selected time points).

b. Kaplan Meier plots showing post-progression survival from time of progression by treatment for patients reaching progression.

Please see question B2 above.

B4. **PRIORITY.** Please provide results for different time points for switching between Kaplan Meier and parametric curves.

For this question, further clarification was requested from the ERG. The ERG clarified that they 'would like to see estimates of costs, overall survival, and QALYs for each arm for a range of cut-off points (at least every 4 months between 6 and 18 months) under the base case assumptions. This is required in order to understand the sensitivity of the model estimates.'

In the base case analyses, the OS KM data for both pembrolizumab and docetaxel arms were used during the first 52 weeks. Then, the extrapolated exponential curves were estimated by fitting exponential curves to KM data from 52-week onwards. For the additional analyses here requested by the ERG:

- We have used the same curves as in the base case analyses, and have applied them for a range of cut-off points that include different time points (at 6 months, at 10 months, at 14 months and at 18 months) to assess the sensitivity of the model estimates, as requested by the ERG.
- We have implemented these analyses only considering base case 2 (i.e. using KEYNOTE-010 data for both pembrolizumab and docetaxel arms). The reason for this was that when applying the different cut-off points to start using the KEYNOTE-001 exponential curve for the pembrolizumab arm, we obtained OS results that seemed to overestimate OS on the basis of

currently available evidence (e.g. 5-year OS was 17.4% when a 26-week cut-off point was used). On the other hand, applying this cut-off to KEYNOTE-010 data for both treatment arms (as for base case 2), resulted in results that were in line with the expected benefit of pembrolizumab in the long term (i.e. 5-year OS of approximately 12%).

The results are presented in Table 19 below.

Table 19. Costs, life years (LYs), QALYs and ICERs when considering different cut-off points for the implementation of the extrapolation of OS based on the exponential fitted curve under the base case assumptions (i.e. estimated from KM data from week 52 onwards)

Time from which the base case exponential fitted curve (week 52+) is used to extrapolate OS	Pembrolizumab			Docetaxel			Pembro vs doc		
	Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 2									
- 6 months (i.e. week 26)	£42,045	2.208	1.509	£11,249	0.857	0.597	£30,796	0.912	£33,765
- 10 months (i.e. week 43)	£41,533	1.912	1.312	£11,267	0.867	0.604	£30,266	0.708	£42,743
- 12 months (i.e. week 52; base case)	£41,283	1.767	1.216	£11,267	0.867	0.604	£30,016	0.612	£49,048
- 14 months (i.e. week 61)	£41,293	1.773	1.22	£11,293	0.882	0.614	£30,001	0.606	£49,501
- 18 months (i.e. week 78)	£41,224	1.733	1.193	£11,273	0.87	0.606	£29,951	0.587	£51,023

B5. **PRIORITY.** In the model, the assumptions for using the registry data to extrapolate overall survival beyond two years needs further clarification. It is unclear whether the company has looked at survival curves for patients on the registry who have discontinued/progressed following platinum-based chemotherapy.

Please provide a table summarising the baseline characteristics of the English registry data, for the Stage IIIb and Stage IV groups. Please include patients' performance status, the proportion of patients who are PD-L1 positive and progressed after platinum chemotherapy.

The registry data used in the model for the long-term extrapolation presented as part of scenario analyses 1 and 2 (see section 5.8.3 and Table 25) was obtained from a document reporting statistics on prognosis based on the UK National Lung Cancer Audit (NLCA) data. The survival data provided are based on data from 135,390 patients submitted to the NLCA from trusts in England (2006-2010 inclusive). The document does not provide specific numbers or proportion of patients by stage, performance status or therapy for the period covered (2006-2010). Therefore, as

reported in Appendix 28 of the submission, the following assumptions were made to conduct the analyses:

- The number of NSCLC registry patients with stage IIIB, stage IV and stage IIIB/IV chemotherapy PS 0-1 were estimated based upon the percentages of patients estimates for these stages by the National Lung Cancer Audit Report 2014 (9.6%, 45.7% and 16.2% respectively),[9] and using the total number of registry patients reported in the document (135,390).

The registry data reported in this document[7] provided OS curves from the date first seen in secondary care or the time of diagnosis:1) by stage, and 2) by performance status, according to whether patients had received chemotherapy or not. However:

- Specific OS estimates were not available for patients who had discontinued or progressed following platinum-based chemotherapy.
- PD-L1 status is not available as part of the NLCA data.

B6. **PRIORITY.** Table 99 (page 221 of the company submission): Please clarify:

a. why the model predicted median overall survival (OS) of 8.51 in the docetaxel arm under base cases 1 and 2, when it is stated that the adjusted survival data from KEYNOTE-010 were used - where median OS is stated to be 8.3 years.

The median OS in KEYNOTE-010 for patients treated in the docetaxel arm was 8.5 months, as reported in the corresponding publication of this clinical trial.[4] For docetaxel, the comparisons presented in Table 99 focused on unadjusted OS so that the results could be compared to the trial outcomes published for KEYNOTE-010.[4] When the model did not consider any switching adjustment, the median OS estimated by the model was 8.51.

When the two-stage switching adjustment was considered, the estimated adjusted median OS was 8.39. This value was estimated by linearly interpolating the proportion of patients that had died at 36 weeks (i.e. 49.01%) and those that had died a week later (51.13% in total) and was in line with the median OS adjusted for switching, using the two stage approach (i.e. 8.3 months) as reported in Table 26 in the submission.

b. why the median OS is slightly higher in the pembrolizumab arm under base case 1 and 2 compared with the survival data of KEYNOTE-010 (e.g. OS of 10.81 for base case 1 versus 10.4 from KEYNOTE-010).

The median OS estimated by the cost-effectiveness model for both base case 1 and base case 2 is 10.58. Apologies for the typo made in Table 99 (page 221) of our submission. More precisely, at 10.58 months (week 46) there were 50.25% of patients that had already died. Taking a linear interpolation between this and the previous time point within the cost-effectiveness model (i.e. 10.35 months or week 45, at which 48.15% of patients had already died), the median OS is estimated as

10.55 months. This estimate takes into account the half cycle adjustment considered in the base case, which results in a slightly higher value than the actual median OS estimated in KEYNOTE-010.

B7. **PRIORITY.** In Appendix 17 only the WinBugs programming language used in the analysis for safety outcomes, overall survival and progression free survival constant hazard ratio models has been provided. Please can you provide the data files and initial values for the Bayesian network meta-analysis described in Appendix 17.

Please see below the initials for time-varying HR analyses. For safety and constant HR analyses, *d* and *mu* initials are generated randomly from the uniform (-1,1) distribution. The data files for the Bayesian network meta-analysis are provided in separate excel files attached to this response: "*Data - OS time-varying.xlsx"*; "*Data - PFS time-varying.xlsx"* and "*Data – constant HR and safety outcomes.xlsx"*.

```
[[1]]
[[1]]$d
     [,1] [,2]
[1,]   NA   NA
[2,]   -1   -1
[3,]   -1   -1
[4,]   -1   -1

[[1]]$mu
     [,1] [,2]
[1,]   -1   -1
[2,]   -1   -1


[[2]]
[[2]]$d
     [,1] [,2]
[1,]   NA   NA
[2,]    1    1
[3,]    1    1
[4,]    1    1

[[2]]$mu
     [,1] [,2]
[1,]    1    1
[2,]    1    1
```

B8. **PRIORITY.** The model spreadsheet includes link to another spreadsheet "*MSD Pembro NSCLC Model V4_22Mar2016-BC1 updates.xlst*". Please provide this sheet or update the links appropriately.

This has been corrected and a revised version of the model is supplied to NICE. This does not impact any of the results presented in the submission.

B9. **PRIORITY.** The MainMenu sheet includes a button labelled "*Survival Data*" which does not work. Please correct this error.

The link has been updated and an updated version of the model will this button working will be shared with NICE and the ERG. This does not impact any of the results presented in the submission.

B10. The company submission states (page 174) that "*the registry data were 'rebased' at 2 years*". However, Figure 42 shows the registry data projections for rebase at 1.5 years. Please clarify which is correct - 2 years or 1.5 years.

We confirm that the registry OS data used in the economic model were rebased at 2 years, i.e., only the part of the original registry OS where OS times >2 years were used. The 'rebased' times were recalculated as: "OS time rebased = OS time – 2 years" and the survival probability at rebased year 0 (i.e., year 2 in the original registry data) was set to 1. Standard parametric curves were then fitted to the "rebased" pseudo individual patient level data (see Figure 43 and 44 in the original submission) and applied in the model from year 2 onwards for consistency. This was presented in Appendix 28 of the submission. The rationale for rebasing registry OS at 2 years is that the registry OS is only used in the model from year 2 onwards.

Figure 42 in the original submission shows registry data rebased at 1.5 years (alongside non-rebased (original) registry data, and non-rebased (original) OS for pembrolizumab and docetaxel as observed in the KEYNOTE-010 trial) for the purpose of testing the similarities between the observed OS in KEYNOTE-010 (especially for the docetaxel OS) and the registry OS. More specifically, Figure 42 was used to visually check if the observed OS for docetaxel as observed in KEYNOTE-010 (green line in Figure 42) was more in line with the non-rebased (original) registry OS or with the registry OS rebased at 1.5 years. The 1.5-year rebase was chosen because the mean time from diagnosis observed in KEYNOTE-010 is 76 weeks, i.e. 1.5 years.

Figure 42 aimed to assess whether the time from diagnosis to randomisation for patients included in KEYNOTE-010 (1.5 years) should be considered or not when using the registry OS. The conclusion from Figure 42 was that docetaxel OS observed in KEYNOTE-010 is more similar to the non-rebased (original) registry OS. Consequently, the additional rebase of 1.5 years related to the time from diagnosis was not considered when applying the registry OS in the model.

It should be noted that the use of registry OS from year 2 onwards was not included in either base case 1 or base case 2, which presented the main results of the cost-effectiveness analysis. Instead, it was only tested as part of the scenario analyses assessed in the submission.

B11. Figures 42 and 44 (pages 175 and 177 of the company submission) do not appear to be cited in the text of the submission. Please clarify what these figures are showing and provide comments on their interpretation.

The NLCA registry OS data used as part of scenario analyses in the model referred to two alternative subgroups of patients (or data sets; please see Table 25 below for further clarification):

- The first one considered patients with NSCLC stage IIIB and stage IV (independently), regardless of performance status score and independent of treatment received. This data set was presented as part of Figure 42 and Figure 43 in the submission and the cost-effectiveness results when using this data set for extrapolating OS were presented as part of scenario analysis 2 (see Table 107, page 248 in the submission). Please see the response to Question B10 above for the clarification and interpretation of Figure 42.

- The second data set reflected NSCLC patients, stage IIIB/IV and with performance status of 0 and 1 who were treated with chemotherapy. Figure 44 in the original submission presents the fitted parametric curves (rebased at year 2) for this subset of patients, and the corresponding scenario analysis was presented as scenario analysis 1 (see Table 107, page 248 in the submission). Together with the AIC/BIC (see Table 20) and considering clinical expert inputs, Figure 44 shows that the Gompertz parametric curve provided the best fit to this subset of patients within the NLCA registry among the parametric curves fitted.

Table 20. Goodness-of-fit measures for OS for stage IIIb/IV PS0-1 receiving chemotherapy OS based on NLCA registry OS (rebased at year 2)

Model	AIC	BIC	Rank
Exponential	33074.80	33081.09	6
Weibull	32888.45	32901.04	5
Gompertz	**32741.46**	**32754.06**	**1**
Log-Normal	32793.70	32806.30	4
Gen. Gamma	32787.17	32806.07	3
Log-Logistic	32781.56	32794.16	2
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria.			

Please note that the registry OS data from the two subsets of the NLCA registry patients (as shown in Figure 42 and Figure 44, respectively) was not included in the base case 1 or base case 2 and these were only tested as scenario analyses (i.e. scenario analyses 2 and 1, respectively) in the submission (see Table 107, page 248 of the submission).

B12. Please clarify why subgroups defined by PD-L1 expression level and EGFR mutation status were not considered in the cost-effectiveness analyses. If possible, please provide separate subgroup analyses by PD-L1 status (1-49%; ≥50%) and EGFR mutation status (mutant; wildtype).

Following discussion with clinicians, the MSD submission was based on the total eligible population with an associated enhanced discount.

We have now implemented additional subgroup analyses as part of the cost-effectiveness model to be able to address the request from the ERG. Please note that due to time constrains, these analyses were implemented without the corresponding switching adjustments that would have been necessary to reflect the expected OS associated with docetaxel in the absence of switching to

pembrolizumab therapy. Therefore, the estimated ICERs presented in Table 23 below are an overestimation of the expected ICERs in the absence of switching within the docetaxel arm.

- The analyses reflect subgroup-specific OS, PFS, AEs, subsequent therapies, actual doses taken as a percentage of the planned does, HR between time on treatment and PFS, and weight estimates.
- For PD-L1 strong and weak expressers, and for the EGFR wild type subgroups, a similar approach to that used in base case 1 and 2 was implemented (see Table 21).
- For the EGFR mutation positive subgroup, we could not implement a similar approach as that used in the base case due to the scarcity of OS data after 48 weeks and the fact that the parametric curves estimated based on the tail of the data were flat. Therefore, in an attempt to provide results for this patient subgroup, we implemented the standard parametric approach fitted to the full KM data and independently for the pembrolizumab and the docetaxel arms. We selected the best fitting curve in terms of the AIC/BIC estimates (i.e. the generalised gamma; see Table 22).
- The OS for the docetaxel arm across subgroups has not been adjusted by switching effects.

The results of these analyses are presented in Table 23.

Table 21. Summary of extrapolation options for pembrolizumab and comparator arms for the subgroup analyses for strong and weak expressers, and for the EGFR wild type subpopulation

	For each subgroup, subgroup specific data were implemented to reflect the base cases below	
	Pembrolizumab	**Docetaxel**
Base case 1	**PFS**: Subgroup-specific KEYNOTE-010 KM data to week 9, followed by best fitted curve (i.e. generalised gamma) to KEYNOTE-010	**PFS**: Subgroup-specific KEYNOTE-010 KM data to week 9, followed by best fitted curve (i.e. generalised gamma) to KEYNOTE-010
	OS: Subgroup-specific KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001	**OS:** KEYNOTE-010 KM (not adjusted for switching) until week 52, followed by the exponential curve fitted to KEYNOTE-010
Base case 2	**PFS**: KEYNOTE-010 KM data to week 9, followed by best fitted curve (i.e. generalised gamma) to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by best fitted curve (i.e. generalised gamma) to KEYNOTE-010
	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** KEYNOTE-010 KM (not adjusted for switching) until week 52, followed by the exponential curve fitted to KEYNOTE-010

Table 22. Goodness of fit measures for KEYNOTE-010 OS (without rebase) for the EGFR mutation positive subpopulation

Pembrolizumab	Exp	Weibull	Gaus	Logist	LogNorm	LogLogist	Gompertz	GenGamma
AIC	171.6	171.3	179.8	180.6	167.9	168.8	169.4	164.1
BIC	169	169.9	178.4	179.3	166.6	167.4	172.1	164.8

Docetaxel	Exp	Weibull	Gaus	Logist	LogNorm	LogLogist	Gompertz	GenGamma
AIC	155.8	154.7	163	163	151.8	151.2	153.3	149.8
BIC	153.1	153.3	161.5	161.6	150.4	149.8	155.8	150.3

Table 23. Costs, life years (LYs), QALYs and ICERs when considering different subgroups (strong and weak expressers and by EGFR mutation status)

Time from which the exponential fitted curve is used to extrapolate OS	Pembrolizumab			Docetaxel			Pembro vs doc		
	Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Strong expressers									
Base case 1	£54,113	2.195	1.53	£14,590	1.021	0.707	£39,523	0.824	£47,988
Base case 2	£53,768	1.995	1.4	£14,590	1.021	0.707	£39,177	0.693	£56,538
Weak expressers									
Base case 1	£34,207	1.702	1.156	£13,704	0.906	0.628	£20,503	0.528	£38,840
Base case 2	£34,045	1.608	1.095	£13,704	0.906	0.628	£20,341	0.467	£43,571
EGFR wild type									
Base case 1	£41,124	1.914	1.307	£14,100	0.959	0.664	£27,024	0.642	£42,082
Base case 2	£40,730	1.686	1.158	£14,100	0.959	0.664	£26,630	0.494	£53,899
EGFR mutation positive									
Generalised gamma	£37,261	2.09	1.386	£15,452	0.982	0.679	£21,810	0.707	£30,851

Please note that the results of these subgroup analyses should be interpreted with caution.

- The anticipated marketing authorisation for pembrolizumab in advanced NSCLC patients is expected to cover all patients who have tumours that express PD-L1, independent of the PD-L1 threshold used. As shown by the subgroup analyses presented in KEYNOTE-010, patients treated with pembrolizumab experienced a benefit in terms of OS independent of the level of PD-L1 expression of their tumours (see Figure 9). Within the subgroup of strong expressers, the proportion of patients in the pre-progression health state over time is high (as indicated by the significant improvement in PFS experienced by this patient subgroup), consequently increasing the treatment cost in this subgroup and the resulting ICER.

- It should be also noted that patients treated with pembrolizumab may experience clinical benefit even after progressive disease is documented. This clinical benefit may not be appropriately captured through the use of PFS measured by RECIST. However, this benefit is demonstrated by the significant improvements in OS experienced by all PD-L1 expressers in KEYNOTE-010.

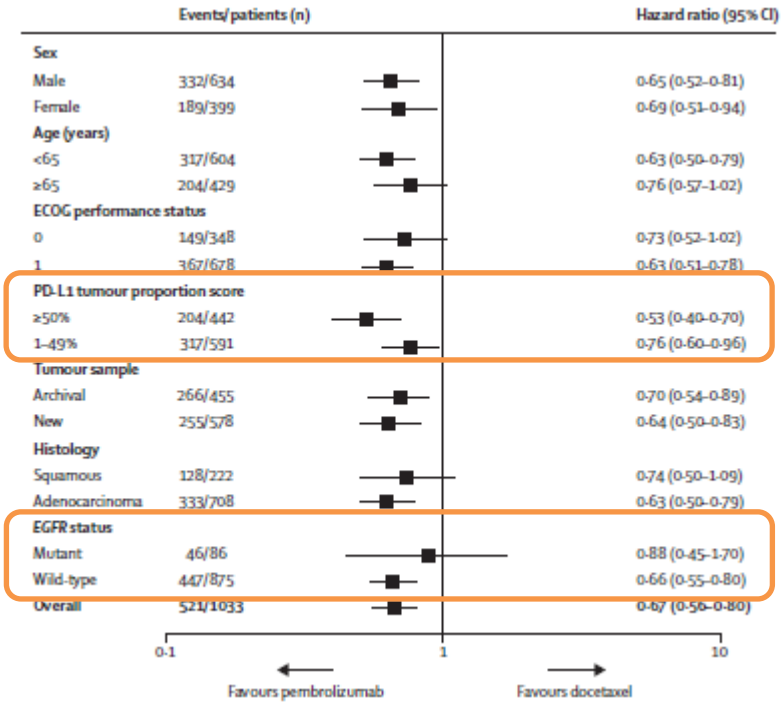
- Additionally, the KEYNOTE-010 trial was not powered to undertake subgroup analyses by EGFR status and, as expected, the number of patients with

NSCLC that had EGFR positive mutation status was very small. The subgroup analyses conducted are essentially descriptive in nature and should not be interpreted in the context of a well-powered hypothesis testing exercise. For subgroups with small number of events, such as EGFR mutant patients, the HR estimates are less precise and therefore they should be interpreted with caution.

- Finally, as mentioned above, the OS of patients initially treated with docetaxel was not adjusted to reflect the actual OS in the absence of switching to pembrolizumab. Therefore, the results here presented should be considered conservative.

We would like to note that MSD has offered an enhanced discount to update the simple discount offered through the patient access scheme currently applied along with TA 357[10] and TA366[11] for the use of pembrolizumab in patients with advance melanoma. The aim of enhancing this discount at the start of the 2L NSCLC submission process is to ensure that the cost of pembrolizumab is not seen as an obstacle to achieving a positive recommendation for the total eligible population given the significant need for more effective treatments. The alternative of limiting the eligible population to one or more subgroups to maintain a higher price was not considered appropriate and it should be noted that the company is also aware that this enhanced discount will also apply to the patients covered by TA357 and TA366 from the point of the publication of a positive recommendation for the current submission.

Figure 9: KEYNOTE-010 subgroup analyses of OS[4]



B13. Table 99 (page 221 of the company submission): Please clarify what accounts for the small difference in reported median OS for base case scenarios 1 and 2 in the pembrolizumab arm - when both use the KM data to 12 months.

Please see answer to question B6.b) presented above.

B14. Section 5.4.1 (page 183 of the company submission): Please clarify whether the health state utility analysis informing the economic model adjusts for non-independence of repeated measures in individuals.

The estimation of mean health state utilities were based on the EQ-5D values collected from KEYNOTE-010 and did not adjust for non-independence of repeated measures in individuals. The estimation of mean utilities was based on descriptive statistics according to the EQ-5D values collected at different time points. Details of the analyses conducted were reported in Appendix 22 within the submission.

Please note that there were not any significant differences between the pembrolizumab 2mg/kg Q3W and the docetaxel arms in terms of the estimated utilities, as reported in section 5.4.1 and Appendix 22 in the submission. Therefore, the estimated utility values based on pooled data from both treatment arms were used in the cost-effectiveness model, independent of the treatment arm. Since a violation of independence does not impact the estimate of the mean utility values but the confidence intervals and these were applied to both treatment arms, we considered irrelevant to adjust for non-independence of repeated measures when estimating EQ-5D utilities. Additionally, compliance rates were high across both treatment arms; consequently, EQ-5D values were considered to be representative of the patients included in KEYNOTE-010 and therefore, accounting for dependence of the repeated measures was not deemed necessary during the imputation.

B15. Please clarify why the annual age decrement in utility is stopped at age 75 years in the company's economic model.

The annual age-related utility decrement applied in the model is based on the age and gender-specific UK general population utility norms presented by Kind et al.,[12] which reported average utility values for males and females under 25, 25-34, 35-44, 45-54, 55-64, 65-74 and 75+ respectively. It was assumed that the utilities for 75+ reported by Kind et al. (0.75 and 0.71 for males and females, respectively) apply to all patients who are 75 years and above. Therefore, no further age-related decrement in utility was applied in the model when patients aged over 75 years. This means that patients aged 75 and above had the same age-related utility decrement in the cost-effectiveness model. A similar approach was adopted in the NICE submissions for pembrolizumab in patients with advanced/unresectable melanoma.[10;11]

B16. In the company's economic model, a no stopping rule is applied for nintedanib in patients remaining progression free, whereas a stopping rule of 2 years is applied for pembrolizumab. Please provide further justification as to why different assumptions should be applied for the two drugs.

For the combination of nintedanib plus docetaxel we did not consider appropriate to apply the same stopping rule of 2 years used for pembrolizumab in our model for the following reasons:

- In KEYNOTE-010 the protocol clearly established that patients were to continue pembrolizumab until disease progression, unacceptable toxicity or 2 years of uninterrupted delivery of pembrolizumab.[5] Therefore, no patients were treated beyond this period and there will not be evidence available to support therapy beyond this treatment duration.
- The protocol of the LUME-Lung 1 trial comparing nintedanib in combination with docetaxel versus docetaxel did not have a similar stopping rule regarding maximum duration of treatment. The median duration of nintedanib treatment in patients with adenocarcinoma tumour histology in the LUME-Lung-1 trial was 4.2 months.[1]
- Additionally, in our cost-effectiveness model, only 0.33% of patients in the nintedanib plus docetaxel combination arm were still in the pre-progression health state at 2 years. Therefore, the impact of the stopping rule on this treatment arm would have been minor.

Therefore, we did not apply the same stopping rule for the combination of nintedanib and docetaxel since we did not have a clear rationale to do so.

We have run an analysis to assess the impact of considering a 2-year stopping rule also for nintedanib. The results (at list prices for nintedanib and with the PAS for pembrolizumab) are presented in the table below. As can be seen, there is a minimal impact when a 2-year stopping rule is also implemented for nintedanib.

Table 24: Incremental cost-effectiveness ratios (ICERs) comparing pembrolizumab (discounted, with PAS) versus nintedanib (discounted, at list prices) – adenocarcinoma subgroup

	Base case 1	Base case 2
Original submission (i.e. no 2-year stopping rule for nintedanib)	£34,997	£23,424
Sensitivity analysis considering a 2-year stopping rule for nintedanib	£35,026	£23,442

B17. The company submission Appendix 28 (page 465) states that "The Gompertz model provided the best fitting curve for stage IV registry data (based on lowest AIC/BIC values, plausibility of the extrapolation and consistency with the curve chosen for Stage IIIB registry data) and was subsequently used in the economic modelling. The generalised gamma model provides the best fitting curve for Stage IV registry data based on AIC/BIC and is used for the base case economic model." Please clarify which model was used.

There is a typo in the sentence identified by the ERG in this question. We apologise for any confusion this typo may have caused. The sentence should have read:

"The **generalised gamma** model provided the best fitting curve for stage IV registry data (based on lowest AIC/BIC values, plausibility of the extrapolation and consistency with the curve chosen for Stage IIIB registry data) and was subsequently used in the economic modelling **because it has the lowest AIC/BIC for stage IV patients, who represent the majority of patients (93.2%) in the phase III trial**."

For clarification purposes, Table 25 below is presented to identify the models that were used per dataset analysed within the NCLA registry as part of the scenario analyses 1 and 2.

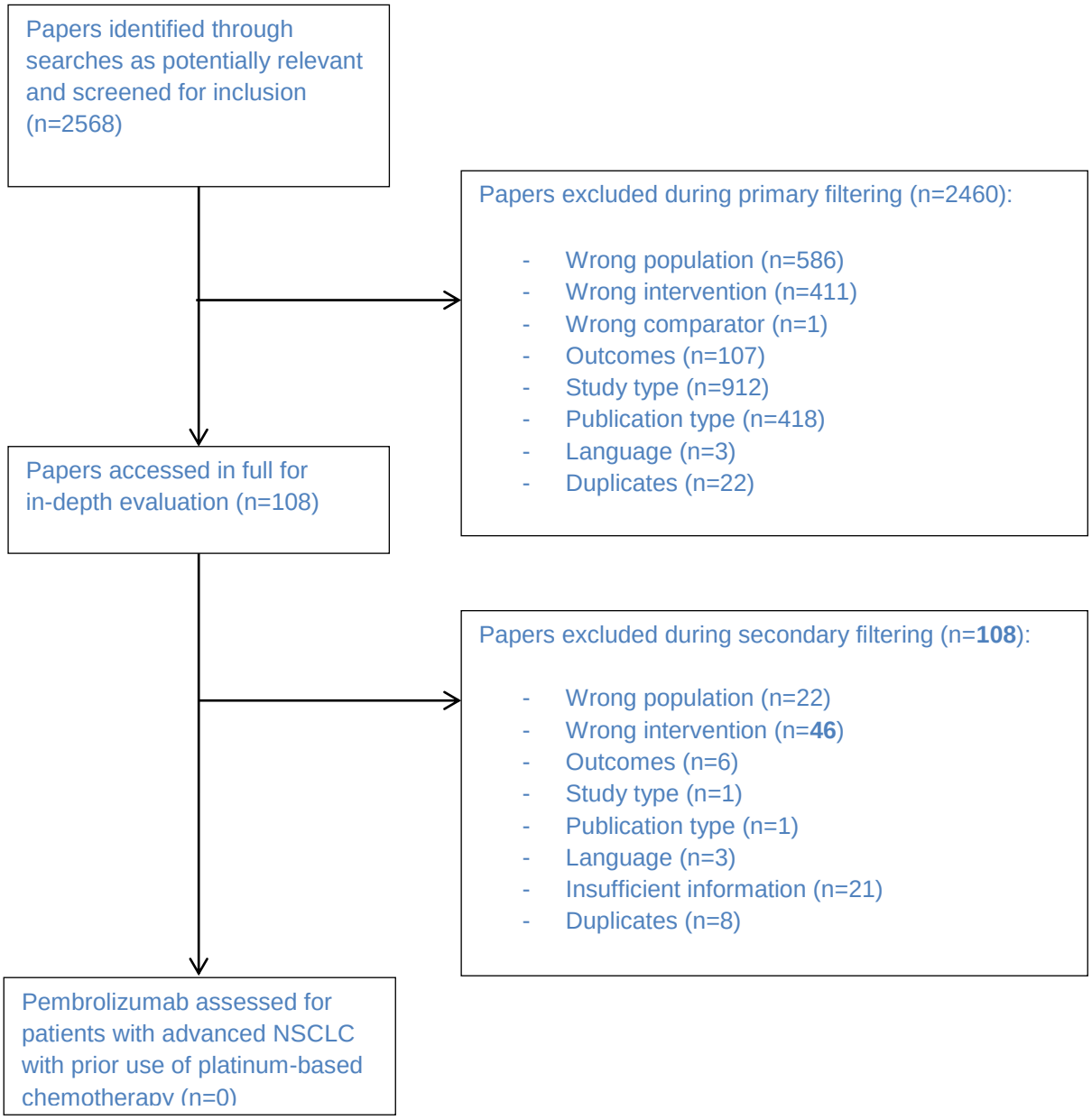
Table 25: Registry data: Best fitting curves, selected model and rationale for each subset used in the economic model

<table>
<tr><th></th><th>Best fitting curve (based on AIC/BIC)</th><th>Used in the cost-effectiveness model</th><th>Rationale</th></tr>
<tr><td colspan="4">NLCA registry data for patients with NSCLC stage IIIb/IV and performance status 0-1 who received chemotherapy</td></tr>
<tr><td>Chemotherapy patients, stage IIIb/IV and PS0-1</td><td>Gompertz</td><td>Gompertz</td><td>Best fit based on lowest AIC/BIC values, plausibility of the extrapolation and consistency with the registry data.
This dataset was used as part of scenario analysis 1.</td></tr>
<tr><td colspan="4">NLCA registry data for patients with NSCLC stage either IIIb or IV</td></tr>
<tr><td>Stage IIIb</td><td>Gompertz</td><td>General gamma</td><td rowspan="2">The generalised gamma had the lowest AIC/BIC for stage IV patients, who represented the majority of the patients in the KEYNOTE-010 trial (93.2% of the patients).
The generalised gamma model presented also a good statistical fit for stage IIIb patients.
The fit was plausible and consistent with the registry data.
This dataset was used as part of scenario analysis 2.</td></tr>
<tr><td>Stage IV</td><td>General gamma</td><td>General gamma</td></tr>
</table>

B18. Figure 28, PRISMA diagram (page 156 of the company submission): Please clarify the number of papers that met the inclusion criteria from original search (108 minus 66 should give 42); and how further exclusions resulted in no papers (n=0) identified.

The updated PRISMA diagram is presented below, after correcting for two typos (in bold below). We apologise for any confusion this may have caused.

Updated Figure 28 (in submission): PRISMA diagram: CEA studies*



Key: n, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**From the updated search conducted in March 2016, 290 additional hits were identified, none of them was included.

References

(1) National Institute for Health and Care Excellence (NICE). Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer. NICE technology appraisal guidance [TA347]. 2015 Available from: URL:http://www.nice.org.uk/guidance/ta347 [Accessed January 2016]

(2) National Institute for Health and Care Excellence (NICE). Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy. NICE technology appraisal guidance [TA374]. 2015 Available from: URL:https://www.nice.org.uk/guidance/ta374 [Accessed January 2016]

(3) National Institute for Health and Care Excellence. Nivolumab for previously treated locally advanced or metastatic squamous non-small cell lung cancer. Appraisal Consultation Document. 2015 Available from: URL:http://www.nice.org.uk/guidance/GID-TAG506/documents/appraisal-consultation-document; accessed on: 4th March 2016.

(4) Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2015.

(5) Merck Sharp & Dohme. A Phase II/III randomized trial of two doses of MK-3475 (SCH900475) versus docetaxel in previously treated subjects with non-small cell lung cancer (NSCLC). Clinical study report P010V01. 10-12-2015.

(6) Merck Sharp & Dohme. Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma (NSCLC). Clinical Study Report P001V04. 25-11-2015.

(7) Beckett P, Callister M, Slade M, Harrison R, Draffan J, Franks K et al. Sharing information with lung cancer patients: guidance for health care professionals discussing options for patients who have lung cancer. British Thoracic Society Reports. 5[Issue 1]. 2013.

(8) Office for National statistics. Interim life tables. 2014 Available from: URL:http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables [Accessed on: 10/03/2015]

(9) Health and Social Care Information Centre. National Lung Cancer Audit Report 2014. 2014 Available from: URL:http://www.hscic.gov.uk/searchcatalogue?productid=16517&q=title%3a%22Lung+cancer%22&infotype=0%2fAudit&sort=Relevance&size=10&page=1#top; accessed on: 10th March 2016.

(10) National Institute for Health and Care Excellence (NICE). Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. NICE technology appraisal guidance [TA357]. 2015 Available from: URL:https://www.nice.org.uk/guidance/ta357 [Accessed January 2016]

(11) National Institute for Health and Care Excellence (NICE). Pembrolizumab for advanced melanoma not previously treated with ipilimumab. NICE technology appraisal guidance [TA366]. 2015 Available from: URL:https://www.nice.org.uk/guidance/ta366 [Accessed January 2016]

(12) Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. The University of York Centre for Health Economics. 1999 Available from: URL:https://ideas.repec.org/p/chy/respap/172chedp.html [Accessed on: 10/04/2015]

Submission from **Roy Castle Lung Cancer Foundation,** for consideration by NICE, in their review of **Pembrolizumab** in the treatment of lung cancer (non small cell, PD-L1-positive), after platinum chemotherapy **[ID840]**.

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being only 7%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of Non Small Cell Lung Cancer (NSCLC).

General Points

1. The current outlook for patients with NSCLC, who have relapsed after platinum based chemotherapy, is poor. In this scenario, improving quality of life and even small extensions in duration of life are of considerable significance to the individual and their family.

2. Active treatment options, after previous chemotherapy treatment, are limited in this patient group. Outcomes remain relatively poor from traditional second line chemotherapy, with many patients being unable to tolerate the side effects. There is, therefore, massive unmet need in this patient group.

3. With such a poor outlook, 'end of life' considerations are very important to this patient group. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with relapsed NSCLC are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief. The reality, however, is that few active options currently exist.

This Product

1. New and Innovative Therapy
   At the time of this submission, there are currently no immunotherapy agents routinely available for use in lung cancer patients in the NHS.
   A different immunotherapy agent, Nivolumab, is currently undergoing NICE appraisal for use in lung cancer – currently licenced for squamous cell NSCLC (note - NICE Appraisal Committee decision was negative).

   Pembrolizumab is therefore, the second immunotherapy agent being developed in lung cancer treatment. Both of these agents works by harnessing the ability of the immune system to find and fight cancer. They are described as PD-1 (Programmed Death-1) Immune Checkpoint Inhibitors.

   By blocking PD-1, Pembrolizumab prevents its binding to PD-L1 on the surface of the tumour cells, hence restoring the capacity of T-cells to fight cancer cells. Pembrolizumab works best if the tumour exhibits a certain level of PD-L1. Thus, a diagnostic test prior to Pembrolizumab, which measures the PD-L1 expression levels of the patient's tumour, will ensure a more segmented population.

2. Improvement in survival
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available.

   However, we note the Phase 2/3, KEYNOTE-010 study, published in the Lancet in December 2015. This study compared Pembrolizumab (in two differing doses) with Docetaxel in previously treated, PD-L1 positive advanced NSCLC. In both the study population (all levels of PD-L1 expression) and in patients with higher levels of PD-L1 (50% or more), overall survival was superior for both doses of Pembrolizumab.

   Patients with relapsed advanced/metastatic NSCLC are a group with significant unmet medical need. Thus, existing chemotherapy has provided these patients with a modest improvement in survival. Immunotherapy provides an additional option which can significantly extend survival.

3. Side effects
   Pembrolizumab is administered as a three weekly intravenous injection.

   We understand that where side effects occur, for the majority of patients, these are mild to moderate. The most common side effects associated with Pembrolizumab include fatigue, shortness of breath, decreased appetite and cough. More serious side effects, though uncommon, can occur if the immune system attacks healthy tissues in the body, such as the lungs, colon, liver, kidneys or hormone producing glands. In the anecdotal patient experience reported to us, it appears well tolerated – in particular, when compared with current standard second line cytotoxic therapy for NSCLC.

4. As noted above, even relatively small benefits can be disproportionately large for patients.

Our observations come from a combination of one-to-one discussion with lung cancer patients, published research and our patient information helpline.

In summary

Patients with advanced and metastatic lung cancer, which have relapsed after chemotherapy are in a particularly devastating situation. With the currently recommended options, the outlook for the majority is poor. It is for this reason that the availability of additional options is very important. Pembrolizumab represents a new and innovative therapy option, for this patient group.

[redacted] [redacted] **RCLCF.**

April 2016.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI/RCP/ACP/RCR/BTOG

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? [redacted]
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

What is the expected place of the technology in current practice?

Currently patients with metastatic non-small-cell-lung cancer (NSCLC) have very poor outcomes with real world median survival in the UK of less than 12 months from diagnosis. Two sub-populations have a significantly different outcome, those with either an activating EGFR mutation or an EML4-ALK translocation, where survival is more than double the 'wild-type' population, if patients receive therapy with an appropriate EGFR targeted therapy (NICE approved as first line therapy) or ALK targeted therapy (not NICE approved but crizotinib currently available via CDF post platinum based chemotherapy and ceritinib under NICE review for use post crizotinib) respectively. Newer generation targeted drugs are also licensed for patients who progress on these agents, with durable disease control demonstrated (osimertinib in T790M EGFR mutation driven NSCLC & ceritinib in EML4-ALK translocation driven NSCLC respectively).

The majority of patients with NSCLC (>80%) will have neither of these actionable alterations and those fit enough for systemic treatment will receive platinum based combination chemotherapy. This practice is reasonably consistent across the UK. When patients develop disease progression following platinum-based chemotherapy a significant proportion (up to 50%; with significant variation across clinicians) receive no further therapy. This is generally due to the rapid decline of patients with relapsed disease and the perceived high toxicity and relatively small benefit of the current therapeutic options. Following the recent removal of approval for erlotinib for patients with relapsed EGFR wild-type NSCLC, patients currently have the option of docetaxel (any NSCLC histology) or, more recently, docetaxel & nindetanib (non-squamous histology only). Both options are associated with significant side effects and patients need to have good reserves to tolerate them, therefore uptake for their use is variable. Docetaxel & nindetanib has been shown to give better outcomes than docetaxel alone in patients with non-squamous NSCLC and will be increasingly used in preference to docetaxel for patients eligible for its use. Patients considered not fit enough for docetaxel would generally be managed currently with best supportive care only.

The arrival of immune checkpoint inhibitors is therefore strongly welcomed for the management of this patient population with significant unmet need. In addition to pembrolizumab, the technology under appraisal, nivolumab, another PD-1 inhibitor, is licensed for relapsed NSCLC and is also currently under NICE evaluation. These are monoclonal antibodies delivered by a short IV infusion. As they are biological agents and can cause anaphylactic reactions they currently need to be delivered within a cancer centre / unit by staff with appropriate expertise and experience.

Pembrolizumab has been developed in parallel with the evaluation of PD-L1 expression analysis from tumour samples. Whilst it is recognised that this may not be an optimal predictive biomarker, a clear correlation between tumour PD-L1 expression and the anti-tumour activity of pembrolizumab has been demonstrated, leading to the licensed approval in PD-L1 expressing tumours only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Pembrolizumab is generally well tolerated. Given the outcome benefits seen with pembrolizumab, in comparison to docetaxel, within this submission, coupled with better tolerability, it is expected that pembrolizumab will replace docetaxel as treatment of choice for patients with PD-L1 positive NSCLC progressing post platinum-based chemotherapy. Due to the toxicity profile of pembrolizumab, it is also likely that some patients who would not be considered fit enough to tolerated docetaxel (and would therefore currently receive best supportive care only) may be considered fit enough for pembrolizumab.

There are a few patient populations where there is more limited clinical experience. Due to the mechanism of action of pembrolizumab, patients with active auto-immune disease are potentially at higher risk of side effects, and these patients have been excluded from clinical studies to date. Therefore, with the data currently available, these patients would be unlikely to be offered pembrolizumab.
Patients with EGFR or ALK driven disease have been included in clinical trials with pembrolizumab, as long as patients have had previous exposure to the appropriate targeted therapies. However, it should be noted that as these are uncommon patient populations, the number of patients included within the studies to date has been small and therefore the absolute benefit for these sub-populations is not fully established.

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

The advantages and disadvantages of the technology

As mentioned above, it is expected that given the improved outcome seen with pembrolizumab, coupled with better tolerability, it will replace docetaxel as treatment of choice for patients with PD-L1 positive NSCLC progressing post platinum-based chemotherapy and may also be offered to some patients who would not be considered fit enough for docetaxel. The suggestion that a sub-population of patients appear to have very durable disease control with pembrolizumab therapy is likely to make it especially attractive to both patients and clinicians alike.

Pembrolizumab is delivered as a short infusion, not dissimilar to docetaxel. It does not require specific supportive medication as standard. As a biological agent it can occasionally cause an anaphylactic reaction, which needs to be managed accordingly, but unlike docetaxel, it does not require regular steroids for delivery.

Pembrolizumab is generally very well tolerated and causes less frequent mild and severe toxicities than currently available docetaxel-based alternatives. It has a very similar toxicity profile to nivolumab and can also cause immune-related toxicities. There is now a broad experience of pembrolizumab across multiple clinical trials and therefore extensive descriptions of these immune-related toxicities. Although they are not common, they are important to appreciate and will be a new experience for many clinicians and will require education for a broader population, including GPs, emergency department and acute oncology staff as well as patients themselves.

The requirement for PD-L1 analysis before establishing eligibility for pembrolizumab therapy will require a more complicated patient pathway than current alternatives. Testing can be performed on archival tissue but tumour tissue is not always readily available in patients with lung cancer, particularly if molecular analysis has been performed. Taking new biopsies may be technically challenging and lead to delays in starting treatment. PD-L1 testing itself may also cause a potential delay in starting pembrolizumb, depending on locality of testing availability. There are a number of PD-L1 IHC assays available, but none are in routine use, and therefore a degree of histopathology training will be required.

The evaluation of response to immune checkpoint inhibitors is also more complex than for conventional cytotoxic toxicities. It is recognised that in a small proportion of patients, tumours may appear to increase initially before subsequently responding, a phenomenon known as pseudo-progression. This will require additional training for some thoracic radiologists involved in evaluating the effectiveness of pembrolizumab for NSCLC and education of oncologists to differentiate patients with progressing disease from those with pseudo-progression.

It is felt that the evidence from the clinical trial data fairly reflects clinical practice. Eligible patients were required to be fit (performance status 0-1), but real-world patients do need good reserves to tolerate docetaxel. The clinical trial did not use docetaxel & nindetanib in the control arm, as this was not a standard of care at that time.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Unquestionably, the most important clinical outcomes for pembrolizumab were not the response rate or median progression free survival, which underestimate the benefits of the therapy. More important are the duration of response in responders, associated with the increased proportion of patients with disease control and survival benefit at later timepoints. In a proportion of patients there is an significantly prolonged period of disease control associated with dramatically increased overall survival.

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

I am not aware of any new significant data relevant to this submission.

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Implementation issues

As discussed above, there will be huge enthusiasm to access pembrolizumab within this indication, but the incorporation of pembrolizumab into standard care in the UK will require several additional education and training programs.

In addition to training of oncologists, many of who will have had limited experience with this agent, or others in its class, members of the extended multi-disciplinary team will also need training, including pathologists, nurses and respiratory physicians. Broader education for GPs, Emergency Department and Acute Oncology staff regarding the possible immune-related side effects will also be required.

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

There are no patient populations inappropriately excluded from consideration for pembrolizumab therapy within this appraisal.

The use of a PD-L1 expression cut off level for eligibility is an attempt to select patients most likely to gain benefit from the therapy and hence improve cost effectiveness of the treatment. It should be noted however that patients with lower PD-L1 expression levels may also respond to pembrolizumab, albeit with reduced frequency than those with higher expression, and these patients would not have the opportunity to receive pembrolizumab within this appraisal indication.

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 this appraisal:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

- *Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
- *Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*
- *Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities*

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

NHS England comment on NICE appraisal on pembrolizumab in 2nd/3rd line treatment of advanced/metastatic non small cell lung cancer

1. NHSE agrees that the correct comparators for pembrolizumab are docetaxel (in the overall non small cell lung cancer[NSCLC] group) and docetaxel plus nintedanib (in the adenocarcinoma group of patients within NSCLC). Pembrolizumab's position in the patient pathway would mainly be as 2nd line therapy for the majority of patients with NSCLC ie as 2nd line treatment for those without EGFR and ALK mutations. Pembrolizumab's position would be as 3rd line treatment for those with EGFR mutations and potentially as 4th line in those with ALK mutations. For all of these groups, the above two comparators apply.
2. NHSE notes that the maximum likely duration of administration of docetaxel is 6 cycles and this reflects clinical practice in England. The EPAR states that the duration of treatment with docetaxel in the Keynote 010 trial was open to a maximum of 2 years but this does not reflect clinical practice in England. The maximum 2 year duration of treatment in Keynote 010 with pembrolizumab is also observed (see later).
3. NHSE notes the practical consequences of the need for PD Ligand 1 testing and the fact that archival tissue can be used for this.
4. In the main phase 3 trial, pembrolizumab offers a significant but modest proportion of patients the chance of delaying disease progression, the PFS curves separating at 6 months with the possibility of a degree of plateauing in PFS beyond 12 months. The difficulty is that the median duration of follow up is only 13 months in Keynote 010 and thus the number of patients at risk beyond 12 months is very small. The longer term data on the impact of pembrolizumab on PFS is uncertain in NSCLC but is of very great interest as a proportion of patients do seem to gain much greater benefit with pembrolizumab: a similar phenomenon has been observed in advanced /metastatic melanoma with the use of pembrolizumab. The big question is ascertaining more exactly what the degree of this benefit is.
5. Pembrolizumab improves median overall survival (OS) but by only 2 months. The overall survival curves separate at about 5 months and the OS curves (as with PFS) then show a significant but larger proportion of patients (than with PFS) appearing to gain a much greater benefit in survival. The uncertainty as to survival after 15 months is great as follow up is short and the number of patients at risk after 15 months is small. There are no patients at all beyond 24 months of follow up. NHSE notes that the phase 1/2 trial data did not have follow up for very much longer than Keynote 010 (overall the median duration of follow up was 15 months in Keynote 001 but according to the EPAR the median follow up in cohort F in Keynote 001 was only 8 months). Modelling of OS beyond 15 months and the accompanying assumptions for the determination of clinical and cost effectiveness are thus very important.
6. NHSE notes that the OS benefit is driven by the effect of pembrolizumab in the subgroup of patients with PD L1 Tumour Proportion Score ≥50% and OS analysis in this subgroup was pre-planned. NHSE observes that a formal analysis was not pre-planned in the TPS 1-49% subgroup and the trial was not powered for the analysis of OS in this subgroup. NHSE agrees with the EPAR that visual inspection of the OS curves for the TPS 1-49 subgroup shows a separation although this does not achieve statistical significance. NHSE agrees with the te manufacturer's case for the clinical and cost effectiveness being assessed for the whole TPS 1-100 population ie the one that represented all the patients in the Keynote 010 study.

7. Thus, pembrolizumab is an exciting drug in the 2nd line treatment of NSCLC as no other drug (bar other checkpoint inhibitors) offers this potentially much longer term survival benefit. Nevertheless, this longer term benefit is uncertain. There are no other clinical trials of other checkpoint inhibitors with long enough follow up to help reduce this uncertainty.
8. It is noted in the manufacturer's submission for the 1st TAC meeting that there was a modelled 5 year OS rate of 12% with P vs 0.5% for docetaxel. This is a very large OS benefit for this group of patients. It might be real, it might be optimistic.
9. The same submission shows a tail in the manufacturer's modelled PFS curve for pembrolizumab which indicates that about 8% of patients are still free of disease progression at 24 months ie this 8% would stop treatment with pembrolizumab with a stopping rule at 24 months. In practice stopping rules are difficult to implement in practice, particularly when treatment is being given in the palliative setting, when the treatment is reasonably well tolerated, when the SPC states that treatment should continue until disease progression and when the only parallel in oncology is in melanoma when pembrolizumab is continued until disease progression (with significant tails observed in both PFS and OS). In addition, NHSE notes that the EPAR, although recognising the trial design of a maximum pembrolizumab treatment duration of 2 years, made no comment on treatment duration other than to include wording in the SPC to continue pembolizumab until disease progression.
10. NHSE could commission a stopping rule at 2 years for what is likely to be a very small minority of patients treated with pembrolizumab but this will be very difficult to ensure implementation and will cause disquiet from patients and clinicians and will rebound on NHSE, NICE and the manufacturer especially as we do not know the consequences of discontinuation at 2 years in terms of the impact on those patients. Keynote 010 had a trial design which allowed patients achieving a complete response to pembrolizumab to discontinue treatment but at further disease progression to re-start pembrolizumab for 12 months. The numbers of such patients eligible for such treatment would have been tiny and so no lesson can be learned as to the consequences of stopping treatment whilst it is still benefitting.
11. NHSE notes that the duration of treatment with pembroliuzumab is assumed to be the duration of PFS. NHSE recommends that NICE examines whether there is a difference between the K-M curves for PFS and treatment duration. Scans were done on a very regular 9-week basis in the Keynote 010 trial and such scanning frequency is unlikely to be replicated in clinical practice in England. There is therefore a rationale for assuming that treatment duration will be longer than that for PFS when considering the above, especially as pembrolizumab is a relatively well tolerated treatment and only 8% discontinued pembrolizumab on account of an adverse event.
12. NHSE notes that the clinical effectiveness of pembrolizumab is only robust when compared with docetaxel though it recognises the need for an indirect comparison with the combination of docetaxel plus nintedanib. There is no comparative data for pembrolizumab vs best supportive care and thus a positive recommendation by NICE for the use of pembrolizumab in 2nd/3rd line systemic therapy of NSCLC should only be in patients fit for docetaxel-containing chemotherapy and of performance status 0 or 1.
13. In summary, pembrolizumab is an exciting drug in the palliation of NSCLC as it could offer the potential of much greater benefit than standard chemotherapy treatment options and

with less toxicity, albeit for a significant but modest proportion of patients. However the current position is that this degree of benefit is very uncertain although more mature follow up of the Keynote 010 trial would address the question of uncertainty.

[redacted]

[redacted]

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Single Technology Appraisal (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Martin Forster

Name of your organisation: NCRI/RCP/ACP/RCR/BTOG

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? [redacted]
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Currently patients with metastatic non-small-cell-lung cancer (NSCLC) have very poor outcomes with real world median survival in the UK of less than 12 months from diagnosis. Two sub-populations have a significantly different outcome, those with either an activating EGFR mutation or an EML4-ALK translocation, where survival is more than double the 'wild-type' population, if patients receive therapy with an appropriate EGFR targeted therapy (NICE approved as first line therapy) or ALK targeted therapy (not NICE approved but crizotinib currently available via CDF post platinum based chemotherapy and ceritinib under NICE review for use post crizotinib) respectively. Newer generation targeted drugs are also licensed for patients who progress on these agents, with durable disease control demonstrated (osimertinib in T790M EGFR mutation driven NSCLC & ceritinib in EML4-ALK translocation driven NSCLC respectively).

The majority of patients with NSCLC (>80%) will have neither of these actionable alterations and those fit enough for systemic treatment will receive platinum based combination chemotherapy. This practice is reasonably consistent across the UK. When patients develop disease progression following platinum-based chemotherapy a significant proportion (up to 50%; with significant variation across clinicians) receive no further therapy. This is generally due to the rapid decline of patients with relapsed disease and the perceived high toxicity and relatively small benefit of the current therapeutic options. Following the recent removal of approval for erlotinib for patients with relapsed EGFR wild-type NSCLC, patients currently have the option of docetaxel (any NSCLC histology) or, more recently, docetaxel & nindetanib (non-squamous histology only). Both options are associated with significant side effects and patients need to have good reserves to tolerate them, therefore uptake for their use is variable. Docetaxel & nindetanib has been shown to give better outcomes than docetaxel alone in patients with non-squamous NSCLC and will be increasingly used in preference to docetaxel for patients eligible for its use. Patients considered not fit enough for docetaxel would generally be managed currently with best supportive care only.

The arrival of immune checkpoint inhibitors is therefore strongly welcomed for the management of this patient population with significant unmet need. In addition to pembrolizumab, the technology under appraisal, nivolumab, another PD-1 inhibitor, is licensed for relapsed NSCLC and is also currently under NICE evaluation. These are monoclonal antibodies delivered by a short IV infusion. As they are biological agents and can cause anaphylactic reactions they currently need to be delivered within a cancer centre / unit by staff with appropriate expertise and experience.

Pembrolizumab has been developed in parallel with the evaluation of PD-L1 expression analysis from tumour samples. Whilst it is recognised that this may not be an optimal predictive biomarker, a clear correlation between tumour PD-L1 expression and the anti-tumour activity of pembrolizumab has been demonstrated, leading to the licensed approval in PD-L1 expressing tumours only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab is generally well tolerated. Given the outcome benefits seen with pembrolizumab, in comparison to docetaxel, within this submission, coupled with better tolerability, it is expected that pembrolizumab will replace docetaxel as treatment of choice for patients with PD-L1 positive NSCLC progressing post platinum-based chemotherapy. Due to the toxicity profile of pembrolizumab, it is also likely that some patients who would not be considered fit enough to tolerated docetaxel (and would therefore currently receive best supportive care only) may be considered fit enough for pembrolizumab.

There are a few patient populations where there is more limited clinical experience. Due to the mechanism of action of pembrolizumab, patients with active auto-immune disease are potentially at higher risk of side effects, and these patients have been excluded from clinical studies to date. Therefore, with the data currently available, these patients would be unlikely to be offered pembrolizumab.
Patients with EGFR or ALK driven disease have been included in clinical trials with pembrolizumab, as long as patients have had previous exposure to the appropriate targeted therapies. However, it should be noted that as these are uncommon patient populations, the number of patients included within the studies to date has been small and therefore the absolute benefit for these sub-populations is not fully established.

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

As mentioned above, it is expected that given the improved outcome seen with pembrolizumab, coupled with better tolerability, it will replace docetaxel as treatment of choice for patients with PD-L1 positive NSCLC progressing post platinum-based chemotherapy and may also be offered to some patients who would not be considered fit enough for docetaxel. The suggestion that a sub-population of patients appear to have very durable disease control with pembrolizumab therapy is likely to make it especially attractive to both patients and clinicians alike.

Pembrolizumab is delivered as a short infusion, not dissimilar to docetaxel. It does not require specific supportive medication as standard. As a biological agent it can occasionally cause an anaphylactic reaction, which needs to be managed accordingly, but unlike docetaxel, it does not require regular steroids for delivery.

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Unquestionably, the most important clinical outcomes for pembrolizumab were not the response rate or median progression free survival, which underestimate the

benefits of the therapy. More important are the duration of response in responders, associated with the increased proportion of patients with disease control and survival benefit at later timepoints. In a proportion of patients there is an significantly prolonged period of disease control associated with dramatically increased overall survival.

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

There are no patient populations inappropriately excluded from consideration for pembrolizumab therapy within this appraisal.

The use of a PD-L1 expression cut off level for eligibility is an attempt to select patients most likely to gain benefit from the therapy and hence improve cost effectiveness of the treatment. It should be noted however that patients with lower PD-L1 expression levels may also respond to pembrolizumab, albeit with reduced frequency than those with higher expression, and these patients would not have the opportunity to receive pembrolizumab within this appraisal indication.

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 this appraisal:

- *Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
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- *Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities*

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

I am not aware of any new significant data relevant to this submission.

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

As discussed above, there will be huge enthusiasm to access pembrolizumab within this indication, but the incorporation of pembrolizumab into standard care in the UK will require several additional education and training programs.

In addition to training of oncologists, many of who will have had limited experience with this agent, or others in its class, members of the extended multi-disciplinary team will also need training, including pathologists, nurses and respiratory physicians. Broader education for GPs, Emergency Department and Acute Oncology staff regarding the possible immune-related side effects will also be required.

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Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Karen Clayton
Name of your nominating organisation: NLCFN
Do you know if your nominating organisation has submitted a statement?

☐ Yes ☐ No N/A

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

No

- a carer of a patient with the condition? No

- a patient organisation employee or volunteer?

☐ Yes

Do you have experience of the treatment being appraised?

☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: none

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

none

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Quality of life and symptom burden, to be able to enjoy life with least

symptoms or side effects

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

none

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

All above

Please explain any advantages that you think this treatment has over other NHS treatments in England.

No comment

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

none

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

No comment

Please list any concerns you have about the treatment being appraised.

No comment

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

no

6. Patient population

Do you think some patients might benefit more from the treatment than

others? If so, please describe them and explain why.

not sure

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

not sure

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

No comment

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

less invasive in its administration and more targeted to tumor type

Is there anything else that you would like the Appraisal Committee to consider?

no

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

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Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

Marianne Nicolson has chaired and served on Advisory Boards for BMS (Nivolumab), Merck (Pembrolizumab), Roche (Atezolizumab) and AZ (Durvalumab). Sha has also received funding from MSD/Merck for clinical trials in NSCLC using pembrolizumab in the first and subsequent lines of treatment. The remaining authors have no competing interests to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Miriam Brazzelli acted as project lead for this appraisal; contributed to the critique and review of the clinical effectiveness evidence, and supervised the work throughout the project. Neil Hawkins, Nicola McMeekin, and Olivia Wu acted as health economists; critiqued and reviewed the cost-effectiveness evidence presented in the submission, checked and re-analysed the economic model and performed further analyses. Beatriz Goulao and David Cooper acted as statisticians; critiqued the statistical methods presented in the submission, checked the numerical results, tables, and figures related to the review of the clinical effectiveness evidence. Pawana Sharma acted as systematic reviewers; critiqued the clinical effectiveness methods.

Cynthia Fraser acted as information scientist; critiqued the methods used for identifying relevant studies in the literature and conducted additional searches. Marianne Nicolson acted as clinical expert; provided clinical advice and general guidance. All authors contributed to the writing of the report and approved its final version.

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AE	Adverse effects
AEOSI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
BSC	Best supportive care
CDF	Cancer Drugs Fund
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
ERG	Evidence Review Group
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicine Agency
EQ-5D	EuroQol-5D
EORTC QLQ	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food and Drug Administration
HR	Hazard Ratio
HRQOL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRC	Independent research committee
irRC	Immune-related response criteria
ITT	Intention to treat
KM	Kaplan-Meier
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer

NICE	National Institute for Health and Clinical Excellence
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PC	Physician's choice
PD-L1	Programmed cell death 1 ligand
PFS	Progression free survival
PR	Partial response
QALY	Quality adjusted life year
QoL	Quality of life
Q3W	Every three weeks
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFT	Rank-preserving structural failure time
RR	Response rate
SAE	Serious adverse event
SPC	Summary of Product Characteristics
TA	Technology Appraisal
TKI	Tyrosin kinase inhibitor
TPS	Tumour Proportion Score
VEGF	Vascular endothelial growth factor

1 Summary

1.1 Critique of the decision problem in the company submission

The NICE scope considered the clinical and cost-effectiveness of pembrolizumab (KEYTRUDA, Merck Sharp and Dohme Limited, Hertfordshire, United Kingdom) within its marketing authorisation for the treatment of adults with advanced or recurrent PD-L1 positive non-small cell lung cancer i) whose disease has progressed after platinum-containing doublet chemotherapy and ii) whose disease has progressed on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours.

Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody that blocks the interaction between PD-1 and PD-L1 receptors thereby potentiating the expression of T cells including anti-tumour response. It is administered intravenously. Pembrolizumab was granted marketing authorisation by the European Medicine Agency (EMA) and recommended by NICE in 2015 for the treatment of advanced (unresectable or metastatic) melanoma in adults.

The decision problem addressed in the company submission deviated from the NICE final scope in that the company did not consider nivolumab, ceritinib (for people with ALK positive tumour), ramucirumab with docetaxel and best supportive care (BSC) as relevant comparators. The company's rationale for this omission was that clinical guidance on nivolumab, ramucirumab with docetaxel and ceritinib has not yet been issued by NICE. The ERG agrees that at the time the company submission was finalised, these pharmacological treatments were still ongoing NICE appraisals. Anticipated publication date for NICE guidance on ramucirumab and nivolumab is August 2016 and September 2016, respectively. BSC is commonly recommended when there is no other active treatment available and therefore the company's decision to exclude BSC from the current assessment appears to be appropriate. The comparators considered by the company were: docetaxel monotherapy and nintedanib in combination with docetaxel (for people with adenocarcinoma histology). The ERG is of the opinion that these pharmacological treatments are valid comparators against pembrolizumab for the treatment of advanced NSCLC.

Adenocarcinoma is an important histological sub-type of the NSCLC, which accounts for 30-40% of the NSCLC. The ERG agrees with the company's decision to perform a subgroup analysis for people with adenocarcinoma histology. The company, however, has not provided any reason for not considering subgroup analyses according to biological markers (PD-L1, EGFR, ALK).

The outcomes considered in the company submission are in line with those detailed in the NICE final scope.

The decision problem addressed by the company differs from the NICE final scope but is considered appropriate and clinically relevant by the ERG.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence included in the company submission consisted of three RCTs: KEYNOTE-010, a phase II/III head-to-head RCT that compared pembrolizumab with docetaxel; KEYNOTE-001 (Parts C and F) a phase I trial due to its initial dose escalation, which evolved into multiple phase II-like sub-studies through a series of expansion cohorts that assessed the effects and safety of pembrolizumab (no comparator; and LUME-LUNG-1, a phase III trial that compared docetaxel plus nintedanib with docetaxel plus placebo.

Although all three trials included participants with advanced NSCLC, whose disease has recurred after platinum-containing chemotherapy, only KEYNOTE-010 included a patient population relevant to the decision problem addressed by the company. KEYNOTE-010 trial included adults with PD-L1 positive advanced NSCLC whose disease has progressed after appropriate targeted therapy for EGFR or ALK positive tumours. In KEYNOTE-001 not all included patients presented with a PD-L1 positive NSCLC, while in LUME-LUNG-1 neither PD-L1 expression nor EGFR mutation status were assessed among included patients with advanced NSCLC.

1.2.1 KEYNOTE-010 results

Two different doses of pembrolizumab were tested (2 mg/kg and 10 mg/kg) in KEYNOTE-010 and interim analyses were undertaken and adjusted for. For the purposes of this assessment we have focused specifically on the pembrolizumab 2

mg/kg results as these were considered most relevant by the company and in line with the anticipated licensed dose regimen.

In KEYNOTE-010 median follow-up was 13 months, range 6 to 24 months.

The primary outcome of the KEYNOTE-010 trial study was overall survival (OS), progression free survival (PFS), safety and tolerability of pembrolizumab compared with docetaxel. KEYNOTE-010 considered all these outcomes in the whole population with a tumour proportion score (TPS) of 1% or greater and presented results for this stratum and, separately, for the TPS≥50% stratum. The ERG requested the results for the TPS 1-49% stratum at clarification.

In KEYNOTE-010 the median overall survival (OS) in the whole population (TPS≥1%) was 10.4 months for pembrolizumab and 8.5 months for docetaxel, which represents a 29% reduction in the risk of death (HR 0.71, 95% CI 0.58, 0.88; p=0.00076). For patients with a TPS≥50% the median OS survival was 14.9 months for pembrolizumab and 8.2 months for docetaxel. This represents a 46% reduction in the risk of death (HR 0.54, 95% CI 0.38, 0.77; p=0.00024). In the TPS 1-49% stratum, the median OS was 9.4 months for pembrolizumab and 8.6 months for docetaxel with no difference between pembrolizumab and docetaxel (HR 0.79, 95% CI 0.61, 1.04).

In the overall TPS≥1% population the median progression free survival (PFS) was 3.9 for pembrolizumab and 4.0 months for docetaxel (HR 0.88, 95% CI 0.73, 1.04; p=0.06758). In the TPS≥50% stratum, the median PFS was 5.2 months for pembrolizumab and 4.1 months for docetaxel, which represent a 42% reduction in disease progression for patients receiving pembrolizumab (HR 0.58, 95% CI 0.43, 0.77; p=0.00009). In the TPS 1-49% stratum the median PFS was 3.1 months for pembrolizumab and 3.9 months for docetaxel (HR 1.07, 95% CI 0.85, 1.34; p=0.7185).

A number of subgroups analyses for OS and PFS for pembrolizumab versus docetaxel were presented in the submission. For a number of subgroups there was no evidence of a difference between pembrolizumab and do**ceta**xel. However, few subgroups had

small numbers of events and, therefore, less precise estimates with wider confidence intervals. There was evidence of survival benefits (OS and PFS) for pembrolizumab in the 'strongly positive PD-L1 status' subgroup.

Treatment switching during the trial was not allowed in the study protocol of KEYNOTE-010. However, a total of 50 patients switched to other PD-1 treatments after treatment discontinuation. The majority of the patients who did switch treatment were from the control arm (43/50). The company used the Rank Preserving Structural Failure Time (RPSFT) and a two-stage adjustment to account for treatment switching. Results of OS were similar between techniques (unadjusted HR 0.71 95% CI 0.55, 088; RPSFT HR 0.71 95% CI 0.55, 0.87; 2-stage adjusted OS full model 0.69 95% CI 0.56, 0.85; 2-stage adjusted OS simple model 0.69 95% CI 0.55, 0.85). Due to the assumptions made by each technique the company opted to use the 2-stage adjusted values in the cost-effectiveness analysis.

The company reports that in KEYNOTE-010 the mean duration of study treatment was nearly 2-fold longer in the pembrolizumab 2 mg/kg Q3W arm (151.1 days) compared with the docetaxel 75 mg/m2 Q3W arm (81.6 days).

The proportion of patients with at least one adverse event (AE) was 35.3% in the docetaxel 75 mg/m2 Q3W arm compared with 12.7% in the pembrolizumab 2mg/kg Q3W arm. In general, fewer drug-related AEs and drug-related Grade 3-5 AEs; and fewer discontinuations due to AEs or drug-related AEs occurred among patients in the pembrolizumab 2 mg/kg Q3W arm compared with the docetaxel arm. The most common adverse event (AE) in patients receiving pembrolizumab was pneumonitis and in patients receiving docetaxel neutropenia. The most frequent serious adverse event (SAE) among patients treated with pembrolizumab was pneumonitis and among those treated with docetaxel febrile neutropenia. There was a higher prevalence of Adverse Events of Special Interest (AEOSI) in the pembrolizumab 2mg/kg Q3W, arm compared with the docetaxel 75 mg/m2 Q3W arm (20.4% and 4.2%, respectively). Grade 3 to 5 drug-related AEOSI occurred in 4.7% of patients treated with pembrolizumab and in 1.0% of patients treated with docetaxel. Most of the AEOSIs were reported by the company to be Grade 1 to 2 in severity and manageable with corticosteroid treatment, interruption of pembrolizumab administration, or both.

1.2.2 Network meta-analysis results

For the indirect and mixed treatment comparisons the company identified two RCTs, KEYNOTE-010 and LUME-LUNG-1, which focused on the following advanced NSCLC populations:

- All NSCLC histologies population (previously treated);
- Adenocarcinoma population (previously treated).

For all NSCLC histologies population, the company identified KEYNOTE-010 as the only RCT comparing pembrolizumab with docetaxel and, therefore, no further analysis was deemed necessary. With regard to the adenocarcinoma subpopulation, both KEYNOTE-010 and LUME-LUNG-1 included docetaxel as a comparator forming a connected network for the indirect comparison

The network meta-analysis (NMA) of pembrolizumab compared with the combination of nintedanib and docetaxel shows no evidence of a significant difference in terms of either overall survival (HR 0.81, 95% CI 0.59, 1.10) or progression free survival (HR 1.04, 95% CI 0.79, 1.36). The NMA shows a beneficial effect in favour of pembrolizumab with a 42% reduction in treatment discontinuation due to adverse event (HR 0.58, 95% CI 0.34, 0.99) and a 36% reduction in the number of Grade 3 or 4 adverse events (HR 0.64, 95% CI 0.44, 0.94).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG is of the opinion that the data provided by the company to assess the efficacy and safety of pembrolizumab in patients with advanced PD-L1 positive NSCLC (TPS≥1% and TPS≥50%) are consistent. The company did not initially report in their submission results of the TPS 1-49% stratum but provided these at clarification. In the overall population (TPS≥1%) and in the TPS≥50% stratum, pembrolizumab 2mg/kg Q3W showed a superior OS compared with docetaxel. In patients with a TPS≥50%, pembrolizumab demonstrated statistically significant benefits in terms of PFS compared with docetaxel. The ERG noted that pembrolizumab treatment did not significantly improve OS or PFS in patients with a TPS between 1-49%. However, it worth pointing out that KEYNOTE-010 was not

powered to detect differences in this subgroup of patients. The ERG opinion is that pembrolizumab demonstrates a good safety profile.

The company states to have used three different sensitivity scenarios for PFS (obtaining similar results) but does not report these results in the submission. For the OS analysis, no sensitivity analyses were presented. Both these sensitivity analyses would have been helpful in terms of testing the robustness of the results obtained.

The company adjusted for treatment switching after treatment discontinuation. The majority of patients who switched treatment were in the control arm and the results were similar between different methods applied. The ERG is of the opinion that ideally the company should have considered presenting additional treatment adjustment analyses to test the robustness of their results. The company did not provide important methodological details regarding the two-stage adjustment, which would have allowed a more thorough critique of its analysis and results.

The ERG considers the methods used for the analyses of KEYNOTE-010 and for the network meta-analysis generally appropriate and correctly applied.

The company presents a network meta-analysis of fixed effects, in the subpopulation with an adenocarcinoma histology. Because only two trials, KEYNOTE-010 and LUME-LUNG-1, were included with the aim of comparing two treatments, between-study heterogeneity could not be estimated. The ERG noted some clinical differences between the populations included in these two trials. KEYNOTE-010 included patients with PD-L1 positive advanced NSCLC whose disease has progressed after platinum-containing doublet chemotherapy or whose disease has progressed on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours, whereas LUME-LUNG-1 included adult patients with advanced NSCLC whose disease had progressed on or after treatment with only 1 prior chemotherapy regimen. Neither PD-L1 expression nor EGFR mutation status were assessed in LUME-LUNG-1.

1.4 Summary of cost effectiveness submitted evidence by the company

The company presented cost-effectiveness evidence comparing pembrolizumab with docetaxel in patients with advanced NSCLC whose tumours express PD-L1, and whose disease had progressed after platinum-based chemotherapy (and for patients EGFR or ALK positive mutations, after disease progression on approved therapy). In addition, the company also presented a sub-group analysis on patients with adrenocarcinoma. In this sub-group, an additional comparator – nintedanib with docetaxel was also considered.

The company developed a *de novo* partitioned survival model which comprised of three health states: pre-progression, post-progression and death. All patients entered the model at the pre-progression health state and can move to the post-progression and death state over time. Weekly cycles were applied to the model over a time horizon of 20 years. Both costs and health effects accrued were discounted at 3.5%.

In the model, pembrolizumab was assumed to be administered according to the anticipated license at 2mg/kg by IV infusion over 30 minutes every three weeks. Patients are expected to receive continuous treatment until disease progression or unacceptable toxicities, for a maximum duration of two years. Docetaxcel monotherapy was assumed to be administered at a dose of 75mg/m^2 three weekly for a maximum duration of 18 weeks. Nintedanib was assumed to be administered at a dose of 200 mg (or a reduced dose of 150 mg) twice daily; no stopping rule was applied to nintedanib.

Time on treatment was based on PFS, which was used as a proxy for time on pembrolizumab and docetaxel monotherapy. The company calculated the hazard ratio for time on treatment vs PFS, to account for patients who experienced treatment discountinuation due to AEs and other reasons. This hazard ratio was applied to PFS in each cycle to estimate the proportion of patients on treatment.

An area under curve approach was used to estimate the proportions of patients in each of the health states over time. In the model, the company used a piecewise approach to estimate progression-free survival (PFS) and overall survival (OS):

- For PFS, KM data from KEYNOTE-010 were used to week 9, after which the generalized gamma curve fitted to KEYNOTE-010 was used.
- For OS, the company explored two extrapolation approaches and presented base case 1 and base case 2. For base case 1, KM data from KEYNOTE-010 were used to week 52, after which the exponential curve fitted to KEYNOTE-001 (pembrolizumab arm) or KEYNOTE-010 (docetaxel monotherayp arm) were used. For base case 2, KM data from KEYNOTE-010 were used to week 52, after which the exponential curve fitted to KEYNOTE-010 (both pembrolizumab and docetaxel monotherapy arm). The company considered this a conservative approach.
- For both base cases, adjustment to switching to other PD-L1 treatments following treatment discontinuation was also applied to the docetaxel monotherapy arm.

For the nintedanib with docetaxel arm, PFS and OS were estimated by applying the estimated hazard ratio from the NMA to the docetaxel monotherapy curves. Only data from the adrenocarcinoma patients within KEYNOTE-010 were used.

Quality-adjusted life years (QALYs) were estimated by taking into account time-to-death and progression-based utilities. Resource use and costs were estimates were based on data from KEYNOTE-010 and published sources. The company has proposed a patients access scheme (PAS) which is subject to Department of Health approval. All cost-effectiveness results presented in the submission took into account this PAS.

In base case 1, the company estimated that compared with docetaxel monothearpy, pembrolizumab was associated with an additional 1.03 life year and 0.70 QALY at an additional cost of £30,242 per patient. The incremental cost per QALY gained for pembrolizumab compared with docetaxel monotherapy was £43,351. Results from base case 2 were consistent with base case 1, with an incremental cost-effectiveness ratio (ICER) of £49,048.

For the sub-group of patients with adenocarcinoma, nintedanib with docetaxel monotherapy was extendedly dominated. In base case 1, compared with docetaxel monotherapy, pembrolizumab was associated with an additional 0.66 QALYs at an

additional cost of £29,444, giving an ICER of £44,597. In base case 2, the estimated ICER was lower at £31,657.

The company performed a range of scenario analysis to assess model uncertainty. For the pembrolizumab and docetaxel monotherapy comparison, the ICERs ranged from £36,861 to £49,407. For the adrenoarcinoma sub-group, the pembrolizumab and nintedanib with docetaxel comparison, the ICERs ranged from £17,879 to £40,634.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG has some concerns around the assumptions on effectiveness modelling, which has a significant impact on the results.

As mentioned previously, the estimated survival in base case 2 is based on the assumption that there is a material ongoing incremental reduction in the risk of death with pembroluzimab that continues after treatment has ceased and is maintained for the lifetime of the analysis

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The submission was generally coherent and clear and appropriate methods were used for the review of clinical evidence.

The ERG considers the cost-effectiveness evidence to be reasonable. Although the original company submission lacked clarity in some of the analyses, the company was helpful in their response to clarification and provided all the relevant data that ERG requested. The Microsoft Excel model was sound and confirmed the methodologies applied as stated in the submission.

The cost-effectiveness estimates are based on significant gains in post-progression survival with pembroluzimab with a greater proportion of patients receiving pembroluzimab surviving to 5, 10 and 20 years (12.15%, 2.46%, 0.1%, base case 2) compared to Docetaxel (0.57%, 0%, 0%). These extrapolations are inevitably uncertain given the current trial follow-up (median 13 months, maximum 24 months).

There are also uncertain given it is assumed in the modelling that all patients will stop treatment at 2 years. In the currently available dataset, no patients have stopped treatment reached and stopped treatment 2 years so there are no empirical data on their subsequent survival. Given the uncertainty in the long term extrapolations of survival and uncertainty in prognosis for patients who stop treatment at the two year times the estimates of cost-effectiveness unreasonably optimistic. It would have been more appropriate to taper the treatment effect beyond the cessation of treatment at 2 years.

1.6.2 Weaknesses and areas of uncertainty

- KEYNOTE-010 trial was an open-label trial where only radiologist and statisticians were blinded to treatment assignment but not participants or study investigators.
- In KEYNOTE-010 results (i.e. OS, PFS) were not consistent among subpopulations according to PD-L1 status (patients with a TPS≥1% - overall population, patients with a TPS 1-49% and patients with a TPS≥50%). There was no evidence of a difference between pembrolizumab and docetaxel in the TPS 1-49% stratum but there was evidence of a difference, favouring pembrolizumab, in the overall population and in the TPS≥50% stratum. KEYNOTE-010 was only powered to detect a difference in OS in the subpopulation with a TPS≥50%. Results in the TPS 1-49% population should therefore be interpreted with caution.
- In KEYNOTE-001 not all included patients had a positive PD-L1 status. The trial did not provide comparative efficacy data.
- The company's NMA was based on only two trials, KEYNOTE-010 and LUME-LUNG-1, which included different clinical populations. In KEYNOTE-010 the patient population had a positive PD-L1 status, whereas PD-L1 status or EGFR mutation were not assessed in LUME-LUNG-1.
- The NMA relied on the assumption that that the efficacy of nintedanib in combination with docetaxel did not depend on PD-L1 expression and that the reported subgroups were comparable. Moreover, the proportional hazards assumption was not supported by the LUME-LUNG-1 data.

- In the economic model, there is an inconsistency to implementing stopping rules. The model assumes maximum treatment duration for pembrolizumab and docetaxel, but not to nintedanib.
- A piecewise approach was used to estimate OS. A cut-off time of 52 weeks was used to switch from KM data to parametric curves. Both the company and the ERG have explored the impact of using different cut-off times. The results of the cost-effectiveness were sensitive to the cut-off times.
- The results of the cost-effectiveness analyses were highly sensitive to the OS extrapolation of pembrolizumab. Based on the current assumptions, 82% of the overall survival gain occurs post-progression (based on base case 2).
- The results of the cost-effectiveness analyses were highly sensitive to the estimated hazard ratio of time on treatment to PFS for pembrolizumab.
- The cost-effectiveness assessment of the adrenocarcinoma sub-group was primarily based on data from the adrenocarinoma sub-group in KEYNOTE-010. The sample size of this sub-group is small and parameter estimates were associated with substantial uncertainty with the results.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Further analyses were conducted regarding the extrapolation of overall survival. In particular, this was found to be very sensitive to the choice of "cut-point" with cut-points before 52 weeks (the earliest cut-point employed in the submission) leading to a marked reduction in incremental survival benefit.

2 Background

2.1 Critique of company's description of underlying health problems

The company's description of advanced non-small-cell lung cancer (NSCLC) in terms of histology, prognosis, and prevalence appears accurate and appropriate to the decision problem. Lung cancer is characterised by a tumour growth on the respiratory epithelium (bronchi, bronchioles, and alveoli), which consists of two major categories: NSCLC and small cell lung cancer (SCLC). The company states that NSCLC accounts for up to 85-90% of lung cancer and consists of two histological sub-types: squamous cell carcinoma (25% to 30%) and non-squamous cell carcinoma, including adenocarcinoma (30% to 40%), large-cell carcinoma (10% to 15%), and other cell types (5%).[1] The company further states that adenocarcinoma is the most common form of NSCLC and is more commonly found in women and never smokers.

Squamous cell carcinoma is more commonly found in men and is correlated with smoking. Tobacco smoking (including environmental smoke exposure) is the main cause of lung cancer in the UK, accounting for approximately 90% of cases.[2] The most common symptoms of NSCLC are worsening cough, shortness of breath and chest pain. The other symptoms include haemoptysis, malaise, significant weight loss, dyspnoea and voice loss.[3]

Lung cancer is the third most common cancer in the UK (2013) which accounts for

13% of all new cases.[4] It is the most common cause of cancer death in the UK accounting for more than 1 in 5 cancer deaths.[4] In the UK, lung cancer caused 35,371 deaths in 2012, of which approximately 28,000 deaths were recorded in England.[4] According to data from National Lung Cancer audit report, around 28,500 were diagnosed with NSCLC in England and Wales in 2013.[5]

The company describes that NSCLC are often diagnosed at an advanced stage when the cancer has spread to lymph nodes (stage III) or distant sites (stage IV). Description of stages of NSCLC provided by the company is given in Table 1 below. Data suggest that 23% of cases are diagnosed when the cancer has advanced locally or regionally

(stage III B) and 46% of cases are diagnosed when metastasised (stage IV).[5, 6] The company states that more than half of the patients with NSCLC are diagnosed with advanced diseased stage thus resulting in a poor prognosis (Cancer Research UK, lung cancer incidence by stage at diagnosis). The median survival for people with all stages of lung cancer is around 6 months. Approximately 32% of those with lung cancer survive for at least one year after diagnosis which is predicted to fall to 9% surviving for 5 years and 5% surviving beyond 10 years.[4] For patients with stage IV NSCLC, 5-years survival rate ranges from 2 to 13% and median survival (for stage IV NSCLC treated with platinum-based therapy) is 8 to 12 months.[5, 7] The company submission indicates that in patients with NSCLC, the median survival is only 6 to 10 months and 5 years survival rates vary between 3% to 7% (depending on the stage of cancer) and duration of response is limited with high rates of relapse and death.

Table 1 Stages of NSCLC[8]

Stages	Description
0	The cancer is found only in the top layers of cells lining the air passages.
I/II	An invasive cancer has formed but has not spread to lymph nodes or distant sites.
III	The cancer has spread to lymph nodes in the middle of the chest (locally advanced disease)
IIIA	The cancer has spread only to the lymph nodes on the same side of the chest where the cancer started.
IIIB	The cancer has spread to the lymph nodes on the opposite side of the chest, or above the collar bone.
IV	The cancer has spread to distant lymph nodes or to other organs such as the liver, bone, or brain.

The company states that NSCLC is often diagnosed late and is associated with a very poor prognosis. High prevalence of psychological distress has been reported in patients with NSCLC compared to other types of cancer.[9] In particular, increased psychological distress were reported among those patients with NSCLC who were undergoing chemotherapy and were approaching death.[9] The company submission reports that the annual cost of lung cancer is almost 2.5 billion per year, which is the

highest economic cost among most prevalent cancer types in the UK (breast cancer, prostate cancer and colorectal cancer).[10]

2.2 Critique of company's overview of current service provision

Primary aim of treatment for advanced and metastatic NSCLC is to prolong overall survival, control disease related symptoms and improve quality of life. Treatments are influenced by tumour histology (adenocarcinomas or non-adenocarcinomas), molecular pathology (e.g., epidermal growth factor receptor mutation), performance status, comorbidities, patient's age and preferences.[11] The discovery of important biological markers such as epidermal growth factor receptor (EGFR), Kirsten rat sarcoma (KRAS), anaplastic lymphoma kinase (ALK) and recently, programmed cell death 1 ligand (PD-L1) in lung cancer has led to the development of targeted treatment.[12] The company submission describes that more than 50% of the NSCLC tumours test positive for at least one type of biomarker including 15-20% KRAS, 17% EGFR, 2-7% ALK and 25-40% PD-L1. Treatment options for NSCLC include single or combination therapy with 'cytotoxic agents' that directly inhibit the growth of tumour cell, 'targeted therapies' that inhibits small-molecules to slow the growth of cancer and with 'immune checkpoint inhibitors' that inhibits expression of T cells thereby inhibiting the proliferation of tumour (see Table 2).[11]

Table 2 Treatments considered in advanced NSCLC

Drug class	Drug	Mechanism of action
Cytotoxic agent	Cisplatin	Antitumour activity; platinum-based chemotherapeutic agent
	Carboplatin	Antitumour activity; platinum-based chemotherapeutic agent
	Docetaxel	Antitumour activity; third generation drug
	Paclitaxel	Antitumour activity; third generation drug
	Vinorelbine	Antitumour activity; third generation drug
	Gemcitabine	Antitumour activity; third generation drug
Antifolate agent	Pemetrexed disodium	Disrupt folate –dependent metabolic activity
Targeted therapy	Gefitinib	Selective inhibitor of EGFR- tyrosine kinase (TK)
	Erlotinib	Selective inhibitor of EGFR-TK
	Afatinib	An irreversible tyrosine kinase inhibitor
	Nintedanib	Small molecule tyrosine-kinase inhibitor
	Crizotinib	ALK receptor tyrosine kinase inhibitor
	Ceritinib	ALK receptor tyrosine kinase inhibitor
Immune checkpoint inhibitors	Nivolumab	Inhibit the PD-1 pathway by blockade of the PD-1 and PD-L1 interaction
	Pembrolizumab	Inhibit the PD-1 pathway by blockade of the PD-1 and PD-L1 interaction
	Ramucirumab	Blocks the activation of vascular endothelial growth factor (VEGF) by targeting and binding with the VEGF receptor-2

It is worth highlighting that drug comparators considered by the NICE scope for treating advanced or recurrent PD-L1 positive NSCLC after progression with platinum-based chemotherapy for this appraisal are docetaxel monotherapy, nintedanib with docetaxel (for people with adenocarcinoma histology), ceritinib (only

for patients with ALK positive mutation status), nivolumab, and ramucirumab with docetaxel.

The current NICE guideline for the diagnosis and treatment of lung cancer (CG121) published in April 2011, recommends that chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0,1 or Karnofsky score of 80-100). The NICE recommendations for treating advanced NSCLC are as follows:[13]

i. First line chemotherapy for advanced or metastatic NSCLC

- Chemotherapy for advanced NSCLC should start with a combination of a single third generation drug (**docetaxel, gemcitabine, paclitaxel or vinorelbine**) plus a platinum drug (**carboplatin or cisplatin**) considering their toxicities, efficacy and convenience.(CG121)[14]
- Patients who are not tolerable to a platinum combination may be offered single-agent chemotherapy with a third-generation drug.(CG121)[14]
- Patients whose tumours test positive for EGFR-TK mutations are eligible to receive first line treatment with an EGFR-TK inhibitor including **afatinib** (TA 310),[15] **erlotinib** (TA 192),[16] or **gefitinib.**(TA192)[16]
- **Pemetrexed in combination with cisplatin** is recommended as a possible treatment for locally advanced or metastatic NSCLC if the cancer is an adenocarcinoma or large cell carcinoma and the person has not had any treatment for NSCLC before.(TA181)[17]

ii. Second line chemotherapy for advanced or metastatic NSCLC

- If second line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy, **docetaxel monotherapy** should be considered.(CG121)[14]
- **Nintedanib in combination with docetaxel** is recommended as second line treatment for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first line chemotherapy.(TA347)[18]
- **Erlotinib** is recommended as an option for treating locally advanced or metastatic NSCLC that has progressed in people who have had non-targeted

> chemotherapy because of delayed confirmation that their tumour is EGFR-TK mutation-positive or tumours of unknown EGFR-TK mutations in certain cases (due to an inadequate tissue sample or poor-quality DNA, the treating clinician considers that the tumour is very likely to be EGFR-TK mutation positive and the person's disease responds to the first 2 cycles of treatment with erlotinib). (TA374)[19]

Table 3 below details all the NICE technology appraisal guidelines (published or in development) for treating advanced NSCLC (including both first and second line treatment for NSCLC). The company adequately refers to relevant NICE guidelines including CG121, TA310, TA347, TA374, TA296, and NICE QS17 in their submission.[14, 15, 18-21] The company mantains that "*If the tumour tests positive for an EGFR mutation and the patient has not previously received treatment with an EGFR-TK inhibitor, afatinib is recommended as an alternative to docetaxel as a second-line treatment option for patients with NSCLC.*"[15] The ERG noted that NICE has not recommended afatinib for second line treatment of these patients.[13] According to the NICE TA310 guidance, afatinib is recommended as an option for treating adults with locally advanced or metastatic non-small-cell lung cancer if the tumour tests positive for the EGFR-TK mutation and the person has not previously had an EGFR-TK inhibitor. The company also states that although crizotinib is not recommended by NICE for the treatment of adults with previously treated ALK positive advanced NSCLC; but it is available via the Cancer Drugs Funds (CDF). The ERG agrees with the company's statement.

Table 3 NICE guidelines (published or in development) for treating advanced NSCLC

NICE guidance	Chemotherapy	Recommendations
CG121,[14] April 2011	Third generation drugs plus a platinum drug	A combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (carboplatin or cisplatin) is recommended for advanced NSCLC.
CG121,[14] April 2011	Docetaxel	Docetaxel monotherapy is recommended in patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy.
TA310,[15] April 2014	Afatinib	Afatinib is recommended as an option for treating adults with locally advanced or metastatic non-small-cell lung cancer if the tumour tests positive for the EGFR-TK mutation and the person has not previously had an EGFR-TK inhibitor.
TA374,[19] Dec 2015	Erlotinib	Erlotinib is recommended as an option for treating locally advanced or metastatic NSCLC that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR-TK mutation-positive or tumours of unknown EGFR-TK mutations in certain cases.
TA258,[22] June 2012	Erlotinib	Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if they test positive for the EGFR-TK mutation.
TA227,[23] June 2011	Erlotinib monotherapy	Erlotinib monotherapy is not recommended for maintenance treatment in people with locally advanced or metastatic NSCLC who have stable disease after platinum-based first-line chemotherapy.
TA374,[19] Dec 2015	Gefitinib	Gefitinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-positive.
TA192,[16] July 2010	Gefitinib	Gefitinib is recommended as a possible first-line treatment for people with locally advanced or metastatic NSCLC if they test positive for the EGFR-TK mutation and who have not had drug treatment for NSCLC before.

NICE guidance	Chemotherapy	Recommendations
TA181,[17] Sept 2009	Pemetrexed combination therapy	Pemetrexed in combination with cisplatin is recommended as a possible treatment for locally advanced or metastatic NSCLC if the cancer is adenocarcinoma or large cell carcinoma and the person has not had any treatment for NSCLC before.
TA309,[24] April 2014	Pemetrexed maintenance treatment	Pemetrexed is not recommended for the maintenance treatment of locally advanced or metastatic non-squamous non-small-cell lung cancer (NSCLC) in people whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin.
TA190,[25] June 2010	Pemetrexed maintenance treatment	Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.
TA124,[26] Aug 2007	Pemetrexed	Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small-cell lung cancer.
TA347,[18] July 2015	Nintedanib	Nintedanib in combination with docetaxel is recommended as an option for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy.
TA296,[20] Sept 2013	Crizotinib	Crizotinib is not recommended by NICE but it is available via the Cancer Drugs Fund. Crizotinib has received marketing authorisation for the treatment of adults with previously treated anaplastic-lymphoma-kinase-positive advanced non-small-cell lung cancer.
TAG478[27]	Ceritinib	Appraisal suspended.
TAG524[28]	Nivolumab	It is not yet recommended. Appraisal is ongoing. Expected publication date September 2016.
TAG527[29]	Ramucirumab	It is not yet recommended. Appraisal is ongoing. Expected publication date August 2016.
TA10010[6]	Pembrolizumab	It is not yet recommended. Appraisal is ongoing. Expected publication date Jan 2017.

The company also appropriately refers to the recommendations from other clinical guidelines and national policies:

- **European Society for Medical Oncology (ESMO) Clinical Practice Guideline - Metastatic non-small-cell lung cancer**.[11] In patients clinically or radiologically progressing after first-line chemotherapy with performance status 0–2, the ESMO recommends second-line chemotherapy such as pemetrexed (for a non-squamous histology only) or docetaxel. In patients with unknown EGFR status or wild-type EGFR status, erlotinib can be considered a potential option. Any patient with a tumour bearing an activating (sensitising) EGFR mutation are recommended an EGFR TKI (afatinib, erlotinib or gefitinib) as second-line therapy, if not received previously. Any patient with NSCLC harbouring an ALK fusion are recommended crizotinib as second-line therapy, if not received previously.
- **National Comprehensive Cancer Network (NCCN) - Non-small cell lung cancer** [30]

  In patients with advanced or metastatic NSCLC who have experienced disease progression either during or after first-line therapy, the NCCN recommends subsequent therapy with second line agents such as docetaxel, pemetrexed (adenocarcinoma and large cell carcinoma), erlotinib, ramucirumab with docetaxel, nivolumab, pembrolizumab and best supportive care. For patients with EGFR mutation, the NCCN guideline recommends subsequent therapy with afatinib. Crizotinib is recommended for patients with ALK rearrangements who have disease progression with first line systemic therapy. Ceritinib is recommended to those who are intolerant to crizotinib. In the 2016 update of the NCCN guideline, pembrolizumab and nivolumab are recommended as preferred therapies for patients with metastatic non-squamous or squamous NSCLC and PD-L1 expression.

ERG also identified the following clinical guidelines, which were not mentioned in the company submission:

- **American Society of Clinical Oncology (ASCO) Clinical Practice Guideline - Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer** [31]

  For patients with stage IV NSCLC, recommendations for second line treatment include docetaxel, erlotinib, gefitinib, or pemetrexed for patients with non-squamous cell carcinoma. For patients with squamous cell carcinoma treatment

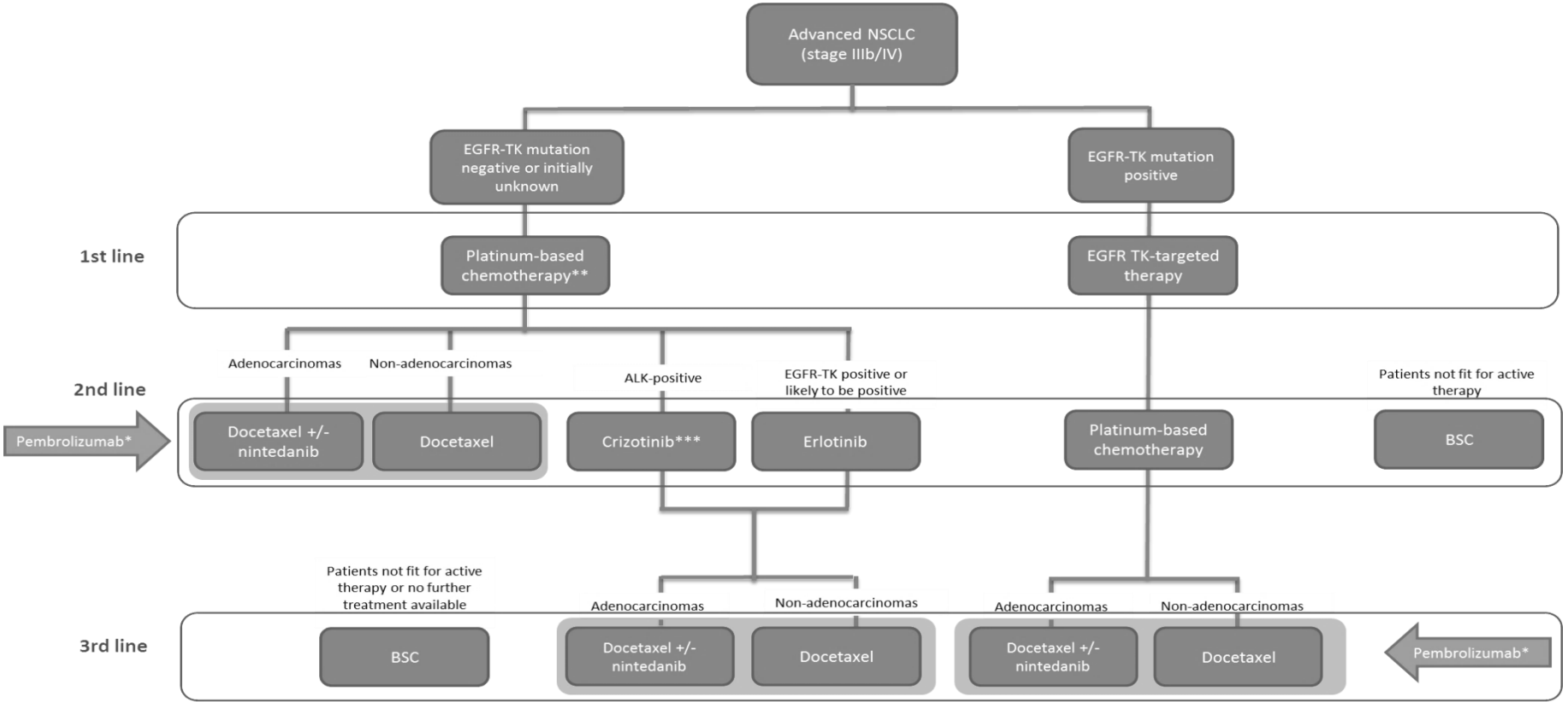
with docetaxel, erlotinib, or gefitinib are recommended. For those with sensitizing EGFR mutations who did not respond to a first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, combination cytotoxic chemotherapy is recommended. For those with *ALK* rearrangement who experience progression after crizotinib, ceritinib is recommended. In the third-line setting, for patients who have not received erlotinib or gefitinib and have PS 0 to 3, treatment with erlotinib is recommended.

- **Scottish Intercollegiate Guidelines Network 137 - Management of lung cancer**[32]

  For patients with performance status 0-2 recurrent NSCLC who have been previously treated with first line systemic anticancer therapy (SACT) for advanced disease, second line SACT with single agent docetaxel or erlotinib are recommended. For patients with advanced non-squamous cell NSCLC who have been previously treated with first line SACT for advanced disease, second line SACT with pemetrexed is recommended.

The company highlights that the use of the targeted therapies is limited to specific sub-populations and the relapse rates are high after first line chemotherapy and targeted therapy. The company further states that for advanced and recurrent NSCLC, the median survival is only 6 to 10 months and response rate is less than 15% and there are limited treatment options available for these patient.[33-36] Therefore, they propose that "*pembrolizumab can be used as a second or third line treatment option for adult patients with advanced NSCLC whose tumours express PD-L1 and who have disease progression on or after prior platinum-based chemotherapy and, if EGFR or ALK mutation positive, also experience disease progression on approved targeted therapies prior to receiving pembrolizumab*". A treatment algorithm for advanced NSCLC with the company's proposed positioning of pembrolizumab is shown in Figure 1 below, which reproduces Figure 3 of the company submission.

In conclusion, the company's description of advanced non-small-cell lung cancer and details of relevant clinical guidelines, clinical pathway and current service provision, are accurate and well-presented.



* People with advanced non-small-cell lung cancer that is PD-L1 positive

**Platinum-based chemotherapy includes: pemetrexed + cisplatin

***Not recommended by NICE but funded through the CDF

Figure 1 Treatment algorithm for advanced NSCLC with proposed positioning of pembrolizumab by the company

3 Critique of the company's definition of the decision problem

3.1 Population

Both the NICE final scope and the company's submission specify the relevant population for this appraisal as "*people with advanced NSCLC that is PD-L1 positive: i) whose disease has progressed after platinum-containing doublet chemotherapy and ii) patients with EGFR or ALK positive tumours whose disease has progressed after both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours.*"

3.2 Intervention

Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype).[37] PD-1 is a type of transmembrane protein receptor that is expressed on activated immune cell types including antigen-presenting T cells. PD-1 receptor is a negative regulator of T-cell activity and is involved in inhibitory signal transmission in the control of T cell immune response. Of the two known ligands of PD-1 (PD-L1 and PDL-2), PD-L1 is the major ligand and is expressed on many tumours. PD-1 and PD-L1 interact with each other and then inhibit expression of T cells thereby inhibiting the proliferation, survival and effector function of cytotoxic T lymphocyte.[38] Pembrolizumab binds to PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2 which potentiates T-cell responses, including anti-tumour responses, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[37]

The brand name of pembrolizumab is KEYTRUDA (Merck Sharp and Dohme Limited, Hertfordshire, United Kingdom), which is available as a 50mg powder for concentrate for solution for infusion which is administered intravenously. The recommended dose of pembrolizumab is 2 mg/kg over 30 minutes every 3 weeks. The company submission states that the average length of a course of treatment per patient is 4.97 months, equivalent to 7.20 cycles received per patient treated with pembrolizumab 2 mg/kg Q3W during a course of treatment. It is recommended that patients should be treated with pembrolizumab until disease progression or unacceptable toxicity and repeated treatment at progression is not anticipated.[37]

According to the company, at present testing for PDL-1 status is not routinely undertaken in the NHS. The ERG clinical expert confirms that, at present, testing for PDL-1 cannot be regarded as standard practice.

3.2.1 Special population

During treatment with pembrolizumab, no dose adjustment is anticipated in special population including elderly patients, patients with mild or moderate renal impairment, and patients with mild hepatic impairment. No data on safety and efficacy are available in patients aged <18 years, in patients with severe renal impairment and in patients with moderate or severe hepatic impairment. The administration of pembrolizumab during pregnancy may cause harm to the foetus, increasing rates of abortion or stillbirth. Therefore, pembrolizumab is not recommended to be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab. Women of child bearing potential should avoid pregnancy during and up to 4 months after the last dose of treatment with pembrolizumab. It is unknown whether pembrolizumab is secreted in breast milk, thus decision should be made whether to discontinue pembrolizumab or to discontinue breastfeeding, if the benefits are thought to outweigh associated risks.[37]

3.2.2 Indications

Pembrolizumab as monotherapy is indicated for the treatment of advanced (unrescetable or metastatic) melanoma in adults.[37] Pembrolizumab for the treatment of advanced (unresectable or metastatic) melanoma in adults was granted marketing authorisation by the European Medicine Agency (EMA) and recommended by NICE in 2015.[39, 40] The company submission states that pembrolizumab is currently under review by the EMA with a license anticipated in June 2016.

The anticipated licensed indication for advanced NSCLC in the UK will be "*... for the treatment of advanced non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have disease progression on or after prior chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations prior to receiving pembrolizumab*".

3.2.3 Known adverse effects

The common adverse reactions such as fatigue, rash, pruritus, diarrhoea, arthralgia and nausea of Grade 1 or 2 severity have occurred in patients treated with pembrolizumab. The most serious known adverse reactions were immune-related adverse reactions and severe infusion-related reactions. Patients should be closely monitored for signs and symptoms of any immune-related adverse reactions including immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies or any other immune-related adverse reactions (such as uveitis, arthritis, myositis, pancreatitis, severe skin reactions) and infusion related reactions. Most of these adverse reactions should be reversible and may be managed with interruptions of pembrolizumab and administration of corticosteroids and/or supportive care. A permanent discontinuation of pembrolizumab is recommended in the following cases: i) grade 4 toxicity except for endocrinopathies that are controlled with replacement hormones ii) treatment related toxicity that does not resolve to Grade 0-1 within 12 weeks after last dose of pembrolizumab iii) if any event occurs a second time at Grade≥3 severity and iv) corticosteroids dosing that cannot be reduced to ≤10 mg prednisolone within 12 weeks.[37]

A list of treatment-associated adverse reactions of pembrolizumab is presented in Table 4. Adverse reactions are presented by system organ class and are defined as: very common (≥ 10%); common (≥ 1% to < 10%); uncommon (≥ 0.1% to < 1%); rare (≥ 0.01% to < 0.1%); very rare (< 0.01%). [37]

Table 4 Adverse reactions reported in patients with advanced melanoma (n=1567) treated with pembrolizumab in clinical trials[37]

System organ class	Frequency (all grades)	Adverse reactions
Infections and infestations	Uncommon	Diverticulitis, pneumonia, conjunctivitis, herpes zoster, candida infection, influenza, urinary tract infection, oral herpes, nasopharyngitis, folliculitis
Neoplasms benign, malignant and unspecified	Uncommon	Tumour pain
	Rare	Acrochordon, neoplasm swelling
Blood and lymphatic system disorders	Common	Anaemia, thrombocytopenia
	Uncommon	Neutropenia, lymphopenia, leukopenia, eosinophilia
	Rare	Immune thrombocytopenic purpura, haemolytic anaemia, pancytopenia
Immune system disorders	Rare	Autoimmune disorder
Endocrine disorders	Common	Hypophysitis*, hyperthyroidism, hypothyroidism
	Uncommon	Adrenal insufficiency, thyroiditis*
Metabolism and nutrition disorders	Common	Decreased appetite, dehydration
	Uncommon	Type 1 diabetes mellitus, hyponatraemia, hypokalaemia, hyperglycaemia, hypophosphataemia, hypoalbuminaemia, hypertriglyceridaemia, hypocalcaemia, hypomagnesaemia, hypercholesterolaemia, hypercalcaemia, hyperuricaemia
Psychiatric disorders	Uncommon	Confusional state*, insomnia, anxiety, libido decreased, depression
	Rare	Affective disorder, agitation, hallucination, trance

System organ class	Frequency (all grades)	Adverse reactions
Nervous system disorders	Common	Headache, dysgeusia, neuropathy peripheral, dizziness, paraesthesia
	Uncommon	Hypoaesthesia, lethargy, neuralgia, peripheral sensory neuropathy, hypogeusia, restless legs syndrome, hypotonia, memory impairment, tremor, balance disorder, disturbance in attention, hyperaesthesia, hypersomnia
	Rare	Brain oedema, encephalopathy, epilepsy, meningitis noninfective, myasthenic syndrome, convulsion, dysarthria, syncope, partial seizures,
Eye disorders	Common	Dry eye
	Uncommom	Uveitis
Vascular disorders	Uncommon	Hypertension
Respiratory, thoracic and mediastinal	Common	Pneumonitis, dyspnea, cough
Gastrointestinal disorders	Very common	Diarrhea, nausea
	Common	Colitis, vomiting, abdominal pain, constipation, dry mouth
	Uncommon	Pancreatitis
Hepatobiliary disorders	Common	Hepatitis
Skin and subcutaneous tissue disorders	Very common	Rash, pruritis, vitiligo
	Common	Severe skin reactions, ecema, erythema, dry skin, hair colour changes, alopecia
	Uncommon	Lichenoid keratosis, psoriasis, dermatitis acneiform, dermatitis, papule, erythema nodosum

System organ class	Frequency (all grades)	Adverse reactions
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
	Common	Myositis, musculoskeletal pain, pain in extremity, arthritis
	Uncommon	Tenosynovitis
Renal and urinary disorders	Uncommon	Nephritis
General disorders	Very common	Fatigue
	Common	Oedema, asthenia, pyrexia, influenza like illness, chills
Investigations	Common	Increased aspartate aminotransferase, alanine aminotransferase, blood bilirubin and blood alkaline
	Uncommon	Amylase increased, blood creatinine increased,

*A group of related events that describe a medical condition rather than a single event

3.3 Comparators

The NICE final scope specifies docetaxel monotherapy, nintedanib with docetaxel (for people with adenocarcinoma histology), nivolumab, ceritinib (for people with ALK positive tumour), ramucirumab with docetaxel and BSC as the relevant comparators for pembrolizumab. The company submission considers only two main comparators: docetaxel monotherapy and the combination therapy of nintedanib with docetaxel (for people with adenocarcinoma histology).

Docetaxel, a third generation drug, is a cytotoxic agent that works by acting directly on the tumour. Docetaxel monotherapy is a recommended second-line treatment for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy.[14] Nintedanib, a small molecule tyrosine-kinase inhibitor, is a targeted therapy that blocks 3 receptor classes that promote angiogenesis and tumour growth. Nintedanib in combination with docetaxel has a UK marketing authorisation for the treatment of adults with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy.[18] The ERG is of the opinion that docetaxel monotherapy and nintedanib with docetaxel are valid comparators against pembrolizumab for treating locally advanced, metastatic or recurrent NSCLC.

Nivolumab, an alternative immunotherapy, which has a similar mechanism of action as pembrolizumab and works by inhibiting the PD-1 pathway by blocking PD-1 and PD-L1 interactions, and ramucirumab, another targeted therapy, which works by binding with the VEGFR-2 and blocks the activation of VEGF, were not considered by the company as a relevant comparators for this assessment. In the decision problem table (Table 1, page 15 of the company submission), the company states that NICE had not yet issued clinical guidance on nivolumab and on ramucirumab with docetaxel and therefore these drugs cannot be considered relevant comparators. The ERG agrees that at the time the company submission was finalised, these pharmacological treatments were still ongoing NICE appraisals. Anticipated publication date for NICE guidance on ramucirumab and nivolumab is August 2016 and September 2016, respectively.

Nivolumab is recommended by the National Comprehensive Cancer Network (NCCN) guidelines on NSCLC as second –line therapy for patients with metastatic NSCLC.[30] In a trial comparing nivolumab against docetaxel for the treatment of NSCLC, patients treated with nivolumab had improved median overall survival and suffered fewer grade 3 to 5 adverse events compared with those treated with docetaxel.[41] Ramucirumab in combination with docetaxel is considered as an option for second-line therapy by the NCCN guideline.[30] However, high rates of adverse events (more than 70%) reported in a trial comparing ramucirumab/docetaxel versus docetaxel have raised a concern on the use of this drug.[42]

Ceritinib, ALK receptor tyrosine kinase inhibitor, was recently approved by the FDA and SMC for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.[30] [43] Ceritinib is not yet recommended by NICE for second-line NSCLC and, therefore, was not considered in the company submission. The ERG agrees with company's decision. Crizotinib, another ALK receptor tyrosine kinase inhibitor is not currently recommended by NICE for the treatment of adults with previously treated ALK positive advanced NSCLC[20] but it is available through the Cancer Drugs Fund.[44] Within NHS Scotland, Crizotinib has been approved for the treatment of adults with previously treated ALK positive advanced NSCLC.[43]

The ERG agrees with the company that best supportive care would have been the standard option if there had not been other active treatment available.

3.4 Outcomes

The outcomes considered in the company submission are in line with those detailed in the NICE final scope. The company assessed: overall survival (OS), progression-free survival (PFS), response rates, adverse effects (AE) of treatment and health-related quality of life (HRQOL).

3.5 Other relevant factors

The NICE final scope indicates that subgroups based on cancer histology and biological markers (PD-L1, EGFR, ALK) should be considered if sufficient evidence is available. The company states that they considered people with NSCLC of adenocarcinoma histology and conducted a subgroup analysis on patients with

NSCLC adenocarcinoma as a part of their economic evaluation. The ERG identifies that adenocarcinoma is an important histological sub-type of the NSCLC, which accounts for 30-40% of the NSCLC. Therefore, the ERG agrees with the company's decision to perform a subgroup analysis for people with adenocarcinoma histology. The company, however, has not provided any reasons for not considering subgroup analyses according to biological markers (PD-L1, EGFR, ALK).

The company's specification for considering costs and implications of additional testing for biological markers is in line with NICE final scope. In the statement of decision problem (Table 1, page 15 of the company submission), the company stated that '*they considered the cost of testing for PDL-1 expression, required to assess patient's eligibility to treatment with pembrolizumab, as part of the cost-effectiveness assessment*'. The ERG is of the opinion that incorporating cost of testing for PDL-1 expression as part of the cost-effectiveness assessment is a valid choice.

The decision problem addressed by the company differs from the NICE final scope but is considered appropriate and clinically relevant by the ERG.

Table 5 illustrates the discrepancies between the NICE final scope and the decision problem addressed by the company in their submission and includes for clarity the company as well as the ERG's comments.

Table 5 Comparison of the NICE final scope and the decision problem addressed in the company submission

	Final scope issued by NICE	Decision problem addressed in the company submission	Comment from the company	Comment from the ERG
Population	People with advanced non-small-cell lung cancer that is PD-L1 positive: ▪ whose disease has progressed after platinum-containing doublet chemotherapy. ▪ whose tumours has progressed on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours.	People with advanced NSCLC that is PD-L1 positive, whose disease has progressed after platinum-containing doublet chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations.	The company stated that the population considered was as per the final NICE scope.	The ERG agreed with the company's comment.
Intervention	Pembrolizumab	Pembrolizumab 2mg/kg Q3W	The company stated that the intervention was in line with the anticipated licence and with the final NICE scope.	The ERG agreed with the company's comment.
Comparator (s)	▪ Docetaxel monotherapy ▪ Nintedanib with docetaxel (for people with	▪ Docetaxel monotherapy ▪ Nintedanib with docetaxel (for people with	Company provided following rationales for choosing comparators:	The ERG noted that the company did not include nivolumab, ceritinib, and

	Final scope issued by NICE	Decision problem addressed in the company submission	Comment from the company	Comment from the ERG
	adenocarcinoma histology) ▪ Nivolumab (subject to ongoing NICE appraisal) ▪ Ceritinib (only for patients with ALK positive mutation status, subject to ongoing NICE appraisal) ▪ Ramucirumab with docetaxel (subject to ongoing NICE appraisal) ▪ Best supportive care (BSC)	adenocarcinoma histology)	▪ Nivolumab is not a relevant comparator because it has not yet been recommended by NICE for second-line treatment of NSCLC. ▪ Ceritinib is not a relevant comparator because it has not yet been recommended by NICE. ▪ Ramucirumab with docetaxel is not a relevant comparator because it has not yet been recommended by NICE. ▪ BSC, outside of the context of being offered alongside of systemic anti-cancer therapies. It is the option when there is no other active treatment available. ▪ Pembrolizumab as a second or third line therapy, by definition would be offered subsequent to	ramucirumab with docetaxel as comparators because they have not yet been recommended by NICE and their use is not standard practice within the NHS. The ERG agreed with the company's decision and rationale of not including BSC as a relevant comparator.

	Final scope issued by NICE	Decision problem addressed in the company submission	Comment from the company	Comment from the ERG
			platinum-based, and where appropriate EGFR or ALK targeted therapy. At these points in the care pathway docetaxel is considered an appropriate treatment option	
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS) • response rates (RRs) • adverse effects (AEs) of treatment • health-related quality of life (HRQoL)	The outcome measures considered include: • OS • PFS • RRs • AEs of treatment • HRQoL	The company stated that the outcome measures considered were in line with NICE final scope	The ERG agreed with the company's comment.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	• The cost-effectiveness is expressed in terms of an incremental cost per quality-adjusted life year (QALY)	In line with NICE final scope.	The ERG agreed that the economic analysis addressed in the company's submission were as per the NICE final scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Comment from the company	Comment from the ERG
	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the comparator technologies should be taken into account.	• The time horizon considered is 20 years • Costs are considered from an NHS and PSS perspective		
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on cancer histology and biological markers (PD-L1, EGFR, ALK).	• People with NSCLC of adenocarcinoma histology	Company stated that 'as part of the cost-effectiveness model, subgroup analysis on patients with NSCLC of adenocarcinoma type was conducted, where pembrolizumab was compared	ERG agreed with the inclusion of subgroup analysis of people with NSCLC of adenocarcinoma histology. ERG noted that the company

	Final scope issued by NICE	Decision problem addressed in the company submission	Comment from the company	Comment from the ERG
			against nintedanib in combination with docetaxel and against docetaxel monotherapy.'	submission has not provided reasons for not considering subgroup analysis of biological markers.
Special considerations including issues related to equity or equality	If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices.	• The cost of testing for PD-L1 expression, required to assess patients' eligibility to treatment with pembrolizumab, has been included as part of the cost-effectiveness assessment.	In line with NICE final scope	ERG agreed with the company's comment.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The submission provides full details of the searches undertaken by the company to identify the included studies for their review of clinical evidence. Major relevant databases such as MEDLINE EMBASE and CENTRAL were searched on 9th February 2016. No date restrictions were imposed. Additional searches were undertaken in Clinical Trials.gov for details of ongoing trials and in three conference proceedings for 2015. The company's own records were also consulted for additional study information.

The search strategies for the main electronic databases are documented in full in Appendix 2 of the submission and are reproducible. The comparators specified in the search strategies include several drugs that were subsequently excluded from the current submission. The company clarifies that the search strategies were designed to meet the requirements for different regulatory authorities and therefore included several comparators. The following comments, however, are confined to the sections of the search strategies which are relevant for the decision problem addressed by the current submission.

The MEDLINE and EMBASE searches combine three search facets using the Boolean operator AND: pembrolizumab or the comparator interventions (nintedanib, docetaxel); non small cell lung cancer; and randomised controlled trials. The search in the Cochrane Library excluded the study design facet, which was appropriate. No further details are provided for the searches undertaken in other databases.

The structure of the search strategies and range of terms used are broadly appropriate although some syntax changes would have been beneficial (such as specifying searching in the keyword and CAS registry fields for the drug terms; inclusion of the term 'keytruda'; inclusion of addition cancer free text terms most notably 'tumor 'and 'adenocarcinoma' and replacing the truncation symbol ? with $ to capture all variations of the term 'metastatic' or 'metastasis').

A scoping search undertaken by the ERG identified additional records from the LUME LUNG-1 study, most of which are published as conference abstracts. These additional records were not retrieved by the company probably due to the fact that their search strategies included a narrow range of free text terms relating to cancer.

4.1.2 Inclusion criteria

The company conducted a systematic review of clinical evidence, which focused on the efficacy and safety of pembrolizumab in patients with advanced NSCLC whose disease has progressed after platinum-containing doublet chemotherapy.

The comparators specified in the NICE final scope and considered in the company submission were docetaxel monotherapy and nintedanib with docetaxel (for people with adenocarcinoma histology). Nivolumab, ceritinib (only for patients with ALK positive mutation status), ramucirumab with docetaxel and best supportive care (BSC) were listed as relevant comparators for pembrolizumab in the NICE final scope but were not included in the current submission. The company's justification for not considering nivolumab, ceritinib, and ramucirumab with docetaxel is considered appropriate by the ERG as these pharmacological treatments are not yet recommended by NICE. BSC is commonly recommended when there is no other active treatment available and therefore the company's decision to exclude BSC from the current assessment appears to be appropriate. The company's inclusion criteria for the review of clinical evidence are presented in Table 6 below.

Table 6 Inclusion and exclusion criteria of the clinical studies

Clinical effectiveness	Inclusion criteria stated in the company submission	Exclusion criteria stated in the company submission
Population	Patients with advanced non-small-cell lung cancer (NSCLC), whose disease has progressed after platinum-containing doublet chemotherapy	None stated
Intervention	Pembrolizumab / MK-3475	Any other intervention
Comparators	• Docetaxel monotherapy • Nintedanib in combination with docetaxel (for people with adenocarcinoma histology only)	Any other comparison
Outcomes	At least one of the following outcomes:* • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	Other efficacy and safety outcomes to be considered for analysis, but each study must include at least one of those presented to the left
Study design	Randomised controlled trials (RCTs)	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language restrictions	English	Any other language
**Note: the scope of the review included extraction of safety outcomes, but for selection of relevant studies the focus was on efficacy outcomes.*		

4.1.3 Critique of data extraction

The methods used by the company to select and assess current relevant clinical evidence are considered to be appropriate. Two reviewers independently screened all titles and abstracts identified by the literature searches. The same two reviewers assessed full text papers. Any disagreement between the two reviewers was referred to a third reviewer and resolved by consensus. Two different criteria were applied for the selection of studies: i) for head to head comparisons, only RCTs comparing pembrolizumab with any of the relevant comparators (docetaxel monotherapy or nintedanib with docetaxel) were considered suitable for inclusion while ii) for indirect and mixed treatment comparisons, RCTs with comparisons between any of the interventions of interest (see Table 6) and RCTs with other interventions that have been compared with at least two of the interventions of interest were deemed suitable for inclusion. The company followed the NICE Guide to the Methods of Technology Appraisal (REF) to assess the risk of bias of included studies. It is unclear how many reviewers were involved in the data extraction process and in the assessment of the risk of bias of selected studies. The company provides detailed and accurate information of the data extracted from the included studies.

Three clinical trials were considered relevant to the decision problem addressed by the company submission:

i) KEYNOTE-010 (pembrolizumab versus docetaxel) - published data consist of a study protocol (clinicaltrials.gov), a clinical study report, a conference abstract[45] and a peer reviewed publication.[46]
ii) KEYNOTE-001 (Parts C, F2 and F3 cohorts) (pembrolizumab only) - published data consist of a study protocol, a clinical study report, six conference abstracts[47-52] and a peer reviewed publication.[53]
iii) LUME-LUNG-1 (docetaxel plus nintedanib versus docetaxel plus placebo) - published data consist of a study protocol, six conference abstracts,[54-59] and two peer reviewed publications.[35, 60]

The company maintains that KEYNOTE-010 and KEYNOTE-001 provide direct evidence for assessing the effects of pembrolizumab while KEYNOTE-010 and LUME-LUNG-1 provide relevant data for the indirect comparison between pembrolizumab and competing interventions. KEYNOTE-001 was a phase I trial due

to its initial dose escalation, which evolved into multiple phase II-like sub-studies through a series of expansion cohorts. The company has included non-randomised, uncontrolled data from cohorts C, F2 and F3 of KEYNOTE-001, to provide additional evidence of the comparative effectiveness and safety of pembrolizumab in patients with advanced NSCLC, whose tumours express PD-L1 (based on a TPS $\geq$ 1%). Although inclusion of non-randomised evidence was not one of the criteria specified by the company for study selection, the ERG agrees that the safety data provided by this trial are relevant to the decision problem addressed by the submission.

A scoping search undertaken by the ERG identified few additional publications on nintedanib and docetaxel from the original LUME LUNG-1 trial that did not appear among the included studies identified by the company. These additional publications include a peer reviewed publication[61] and six conference abstracts.[62-67] The peer reviewed publication is an extended analysis of the LUME LUNG-1 trial, which provide a post-hoc subgroup analysis of safety data by tumour histology (adenocarcinoma and squamous cell carcinoma). Assessment of these publications by the ERG confirms that they do not provide any additional data relevant to the decision problem addressed by the submission.

4.1.4 Quality assessment

For the risk of bias assessment of included RCTs the company followed the recommendations of the York Centre for Reviews and Dissemination (CRD)[68] and of the Cochrane Handbook for Systematic Reviews of Interventions.[69] Risk of bias of non-randomised evidence (cohorts C, F2 and F3 of KEYNOTE-001) was assessed using the Newcastle-Ottawa Scale (NOS). Full details of the quality assessment of included studies are given in Appendix 9 (Tables 1 and 2) and Appendix 15 (Tables 6 and 7) of the company submission. KEYNOTE-010 and LUME-LUNG-1 were judged to be at overall low risk of bias by the company. The ERG noted, however, that KEYNOTE-010, which is an open-label trial where study sponsor, investigators and patients were aware of treatment allocation and only outcome assessors (statisticians and radiologists) were blinded to treatment allocation, was judged to be at low risk of bias for the overall blinding domain (Table 6 of the company submission). It would have been more accurate to assess and report 'blinding of personnel/participants' separately from 'blinding of outcome assessors'. The ERG

performed a broad assessment of the methods used by the company for the systematic review of clinical effectiveness using the CRD criteria (Table 7 below). In general, the quality of the systematic review was good apart from the non-blinding of participants and study personnel as described above.

Table 7 Quality assessment of the company's systematic review

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	No*
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

* Although included studies were assessed using validated tools, blinding of participants and study personnel was incomplete.

4.1.5 Evidence synthesis

The company did not conduct any meta-analyses as only one head to head RCT of pembrolizumab versus docetaxel was identified (KEYNOTE 010).[46] Another trial included in the review of clinical effectiveness, KEYNOTE-001 (cohorts C and F), did not include a comparator relevant to the decision problem.[53]

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company submission focuses on a single phase II/III RCT, KEYNOTE -010, which compares intravenous pembrolizumab at two doses with docetaxel. As described in the company submission, KEYNOTE-010 includes "*patients with histologically or cytologically confirmed diagnosis of NSCLC stage IIIB/IV, and*

- *whose tumours express PD-L1 based on a Tumour Proportion Score (TPS) of ≥1%,*
- *who have experienced disease progression per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) after treatment with a platinum-containing systemic therapy,*

- *and who have experienced disease progression on the respective TKI targeted against an identified EGFR mutation or ALK translocation.*"

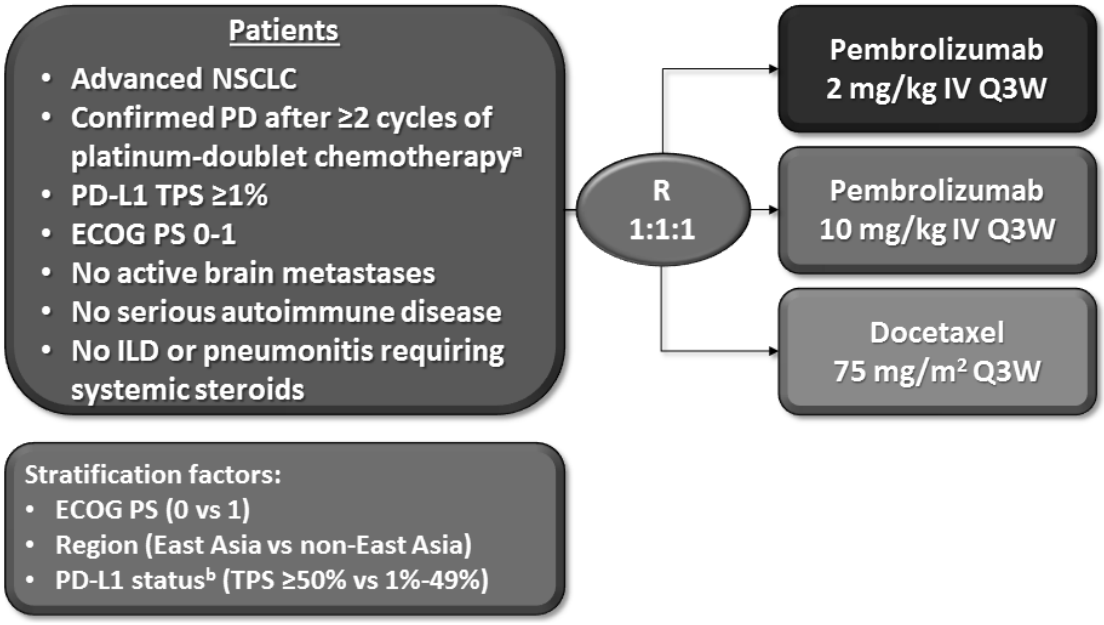
In addition, the company includes KEYNOTE-001, a phase I multi-centre, open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumour activity of pembrolizumab in adults with progressive locally advanced or metastatic carcinomas, including melanoma or NSCLC.

The company states that Parts C, F2 and F3 of KEYNOTE-001 were expansion cohorts specifically designed to evaluate the efficacy and safety of pembrolizumab in patients with advanced NSCLC, whose disease has recurred after platinum-containing chemotherapy. The characteristics of included trials are described in sections 4.2.1 and 4.2.2 below.

4.2.1 Characteristics and critique of KEYNOTE-010

Between Aug 28, 2013 and Feb 27, 2015, KEYNOTE-010 trial recruited 1034 participants from 202 academic medical centres in 24 countries. Of the total patients enrolled, 47% were patients enrolled at sites in Europe (including 56 patients from the UK). Participants were randomised in a 1:1:1 ratio to receive either pembrolizumab 10 mg/kg every 3 weeks (Q3W) (n=346), 2 mg/kg Q3W (n=345), or docetaxel at 75 mg/m2 Q3W (n=343). Pembrolizumab was administered as a 30 minute intravenous infusion at two doses (2 mg/kg Q3W and 10 mg /kg Q3W) and docetaxel 75 mg/m2 was administered as an intravenous infusion over 1 hour Q3W.

The study design of KEYNOTE-010 is shown in Figure 2 below, which reproduces Figure 5 of the company submission.



R = Randomisation; ECOG PS= Eastern Cooperative Oncology Group performance status; ILD=interstitial lung disease; IV=intravenously; NSCLC=non-small cell lung cancer; PD=progressive disease; Q3W=every 3 weeks; R=randomized; TPS=tumour proportion score

[a]An appropriate tyrosine kinase inhibitor was required for patients whose tumours had an *EGFR* sensitizing mutation or an *ALK* translocation. [b]Added after 441 patients enrolled and the PD-L1 IHC assay cut point was established.

Figure 2 Study design of KEYNOTE-010

Primary outcomes of KEYNOTE-010 were overall survival (OS), progression free survival (PFS), safety and tolerability of pembrolizumab compared to docetaxel. OS was defined as the time from randomisation to death due to any cause. PFS was defined as the time from randomisation to the first documented disease progression [based on confirmed assessment by an Independent Review Committee (IRC) using RECIST 1.1[70] or death due to any cause whichever occurred first].

Secondary outcomes considered in KEYNOTE-010 were overall response rate (ORR), time to response and response duration. ORR was defined as the proportion of the patients in the analysis population who had either a complete response (CR) or partial response (PR) (based on confirmed assessment by radiologists using RECIST 1.1).[70] Time to response was defined as the time from randomisation to the first assessment of a confirmed CR or PR; while response duration was defined as the

time from first documented and confirmed CR or PR until disease progression or death.

Other exploratory outcomes include ORR, PFS and response duration per immune-related response criteria (irRC) by investigators' review (INV), changes in HRQoL (assessed using EORTC QLQ-C30 and EORTC QLQ Lung Cancer 13 items), to characterise utilities (assessed using eEQ-5D) and to characterise healthcare resource utilisation.

KEYNOTE-010 considered all these outcomes in the following two strata of people:

1) previously treated patients with advanced NSCLC, whose tumours express PD-L1 with TPS≥1%
2) previously treated patients with advanced NSCLC, whose tumours express PD-L1 with TPS≥50%

A summary of the KEYNOTE-010 characteristics is presented in Table 8, which reproduces Table 10 of the company submission.

Table 8 Summary of the characterisitcs of KEYNOTE-010

Trial number (acronym)	**KEYNOTE-010**
Location	Global study conducted in 24 countries: Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Lithuania, Netherlands, Portugal, Russia, South Africa, South Korea, Spain, Taiwan, UK, and USA.
Trial design	Randomised, phase II/III study of pembrolizumab versus docetaxel in adults with non-small cell lung cancer (NSCLC) whose tumours express PD-L1 who have experienced disease progression after at least a platinum-containing systemic therapy. Open-label trial, blinded for PD-L1 status. Tumour response centrally reviewed by blinded independent radiologists.
Key eligibility criteria for participants	• Histologically or cytologically confirmed diagnosis of NSCLC stage IIIB/IV or recurrent disease • PD-L1 positive tumour (TPS≥1%) • Progression per RECIST 1.1 after treatment with at least two cycles of a platinum-containing doublet chemotherapy • Patient with EGFR mutation/ALK translocation must also demonstrate progression of disease on a EGFR TKI or Crizotinib • ECOG performance status of 0 or 1
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as day care patients
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) and	Patients were randomised in a 1:1:1 ratio to receive one of the following regimens: • Pembrolizumab 2 mg/kg Q3W • Pembrolizumab 10 mg/kg Q3W • Docetaxel at 75 mg/m2 Q3W Disallowed concomitant medicines: • Any other investigational agent • Any other systemic antineoplastic therapy or immunotherapy

Trial number (acronym)	KEYNOTE-010
comparator(s) Permitted and disallowed concomitant medication	not specified in the protocol • Radiation therapy • Initiation of bisphosphonate or anti-RANKL mAb • Glucocorticoids for any purpose other than adverse event management or as a pre-medication for docetaxel • Live vaccines within 30 days prior to the first dose of study medication and while participating in the study • Strong inhibitors of the CYP3A4 enzymes • Prior treatment with any other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody
Primary outcomes (including scoring methods and timings of assessments)	The co-primary objectives of this study were as follows: • PFS: defined as the time from randomisation to the first documented disease progression or death due to any cause, whichever occurs first • OS: defined as the time from randomisation to death due to any cause PFS was based on assessment from a central imaging vendor, Independent Review Committee (IRC) per RECIST 1.1 criteria. ITT population served as the primary population for the analyses of PFS and OS. On-study imaging was performed every 9 weeks (63 ± 7 days) until the patient experienced confirmed disease progression or started a new antineoplastic therapy. After the end of treatment, each patient was followed for a minimum of 30 days for adverse event monitoring (90 days for serious adverse events). Patients had post-treatment follow-up for disease status, including initiating a non-study cancer treatment, disease progression, withdrawing consent, until death, or becoming lost to follow up.
Secondary/ tertiary outcomes (including scoring methods and	The secondary objectives were as follows: • ORR (IRC per RECIST 1.1) • Time to response and Response duration (IRC per RECIST 1.1).

Trial number (acronym)	KEYNOTE-010
timings of assessments)	The exploratory objectives were as follows: • ORR, PFS and Response Duration by irRC • HRQoL changes from baseline using the EORTC-QLQC30 • Patient utilities using the EuroQoL EQ-5D • Tumour volumetric changes • Healthcare resource utilization in the in the TPS≥50% stratum.
Pre-planned subgroups	• PD-L1 biomarker subgroups (i.e. (TPS≥50% stratum vs. overall population TPS≥1%) • Subgroup analyses of primary endpoints were also performed based on clinically relevant baseline patient or tumour characteristics

Subgroup analyses were pre-specified by age, sex, Eastern Oncology Cooperative Group (EOCG) performance status, EGFR mutation status and age of tumour sample.

Considering KEYNOTE-010 presented results for the whole population with TPS of 1% or greater and also for participants with a TPS of 50% or greater, the ERG requested the results for participants with a TPS of 1-49%. At clarification the company provided the clinical effectiveness results within the TPS 1-49% stratum and further clarified that:

'It should be noted that KEYNOTE-010 study was designed and powered to compare efficacy between pembrolizumab and docetaxel in the TPS≥50% stratum and in the TPS≥1% overall population (with Bonferroni adjustment between the two tests). Therefore, the results within the TPS 1-49% stratum are possibly informative and should not be interpreted in the context of a well-controlled statistical testing strategy.'

Two different doses of pembrolizumab were tested in KEYNOTE-010 (2 mg/kg and 10 mg/kg) and interim analyses were undertaken and adjusted for. For the purpose of this assessment we focus specifically on the pembrolizumab 2 mg/kg Q3W results as

these were considered most relevant by the company and in line with the anticipated licensed dose regimen.

The study was designed with the aim of showing a difference in overall survival in patients with a TPS of 50% or greater, even though the overall population enrolled in the trial had a TPS of 1% or greater.

In KEYNOTE-010 two types of patient population were used to estimate the treatment effect for the primary outcomes: the Intention-To-Treat (ITT) population in the TPS≥50% stratum and in the TPS>1% overall population served as the primary population for the analyses of PFS and OS. Patients were included in the treatment group to which they were randomised for the analysis of efficacy data using the ITT population. A supportive analysis was conducted in the Full Analysis Set (FAS) population, which excluded those who did not meet the key eligibility criteria or discontinued before receiving any dose of assigned treatment. The primary safety analysis in KEYNOTE-010 was based on the treated TPS≥1% population (all randomised patients who received at least one dose of study treatment). Patients were included in the treatment group corresponding to the study treatment they actually received.

The participants had a median duration of follow-up of 13 months (range from 6 to 24 months).

For overall survival, data for patients who were alive or lost to follow-up were censored at the time of last confirmed contact. For progression-free survival, data for patients who had not progressed or were lost to follow-up were censored at the time of last tumour assessment. For overall response rate, patients with missing data were considered non-responders. For duration of response, data for patients whose response was on going at the time of the analysis, or who discontinued the study without radiological evidence of progression, were censored at the time of the last radiological assessment showing response. Data for patients who had radiological disease progression after missing two radiological assessments were censored at the time of the last radiological assessment showing response, and data for patients who initiated

new cancer treatment without radiological evidence of disease progression were censored at the time of starting their new treatment.

The company states (page 74 of the submission) that three sensitivity analyses with a different set of censoring rules and progressive disease definitions were undertaken to evaluate the robustness of the PFS estimates. In the clinical-effectiveness section of the submission (section 4.7, page 98) the company maintains that "*Overall, the PFS results using sensitivity censoring rules were similar to the primary PFS analysis results, demonstrating the robustness of PFS results".* However, these results are not fully presented in the submission and therefore the ERG was not in the position to critique them.

The CONSORT diagram showing the flow of participants in KEYNOTE-010 is given in Figure 3 below, which reproduces Figure 8 of the company submission. The baseline characteristics of overall participants (TPS≥1%) and TPS≥50% stratum comparing pembrolizumab 2mg/kg versus docetaxel 75 mg/m^2 are presented in Table 9 below (reproduced from Table 17 and Appendix 8 of the company submission). The ERG noted that among the patient population in KEYNOTE-010, there was a higher proportion of patients with a TPS of 1-49% compared with those with a TPS of ≥50% (55.7% versus 44.3% in the docetaxel group and 59.7% versus 40.4% in the pembrolizumab group). Apart from metastatic staging (M1B) and brain metastasis, the ERG noted that there were no significant differences in other baseline characteristics between the overall population and the TPS≥50% stratum and between treatment groups in each stratum. There were slightly higher proportions of patients with metastasis staging MIB stage and brain metastasis in the pembrolizumab arm of the TPS≥50% stratum compared with those in the pembrolizumab arm of the TPS≥1% stratum. Within the TPS≥50% stratum, the proportion of patients with MIB stage and brain metastasis was higher in the docetaxel group compared with the pembrolizumab group.

Approximately 10% of patients in the docetaxel group withdrew consent before receiving treatment. Baseline characteristics of these participants were provided in Table 1, Appendix 8 of the company submission. The company submission states that there was no significant differences in the baseline characteristics of these patients

compared with those of the overall docetaxel population. The ERG noted that there was a slightly different proportion of patients with stage IIIA cancer (2.3% in the docetaxel group in the trial versus 5.9% in the withdrawals), metastatic stage M1 (23.3% in the docetaxel group in the trial versus 38.2% in the withdrawals), M1A (18.1% in the docexatel group in the trial versus 23.5% in the withdrawals) and brain metastasis (86% in the docexatel participants in the trial versus 91.2% in the withdrawals).

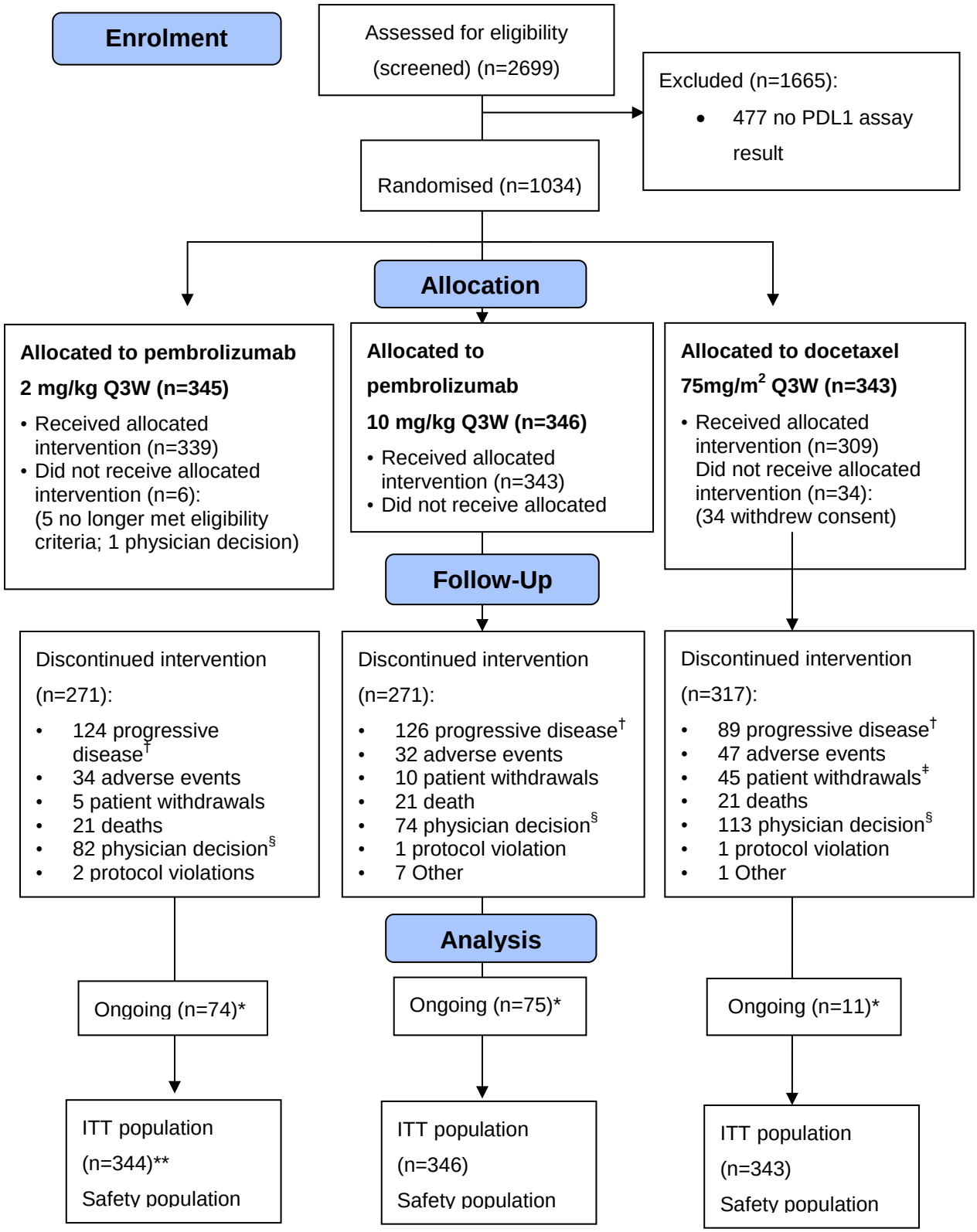


Figure 3 KEYNOTE-010 - CONSORT diagram

Table 9 KEYNOTE-010 - Baseline characteristics of the overall TPS≥1% population and of the patients with a TPS of ≥50% (reproduced from Table 17 and Appendix 8 of the company submission)

	TPS≥1%				TPS≥50%			
	Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W		Docetaxel 75 mg/m2 Q3W		Pembrolizumab 2 mg/kg Q3W	
	n	%	n	(%)	n	(%)	n	(%)
Patients	343		344		152			139
Male sex	209	60.9	212	61.6	93	61.2	81	58.3
Median age (range), years	62.0 (33-82)		63.0 (29-82)		60 (33-82)		62 (30-82)	
Smoker								
Never smoker	67	19.5	63	18.3	34	22.4	26	18.7
Current/Ex-smoker	269	78.4	279	81.1	113	74.3	112	80.6
Missing	7	2.0	2	0.6	5	3.3	1	0.7
ECOG performance status								
0	116	33.8	112	32.6	49	32.2	47	33.8
1	224	65.3	229	66.6	102	67.1	91	65.5
2	1	0.3	3	0.9	1	0.7	1	0.7
3	1	0.3	0	0.0	-	-	-	-
Missing	1	0.3	0	0.0	-	-	-	-

Cancer Stage								
IA	0	0.0	1	0.3	-	-	-	-
IB	1	0.3	1	0.3	1	0.7	1	0.7
IIB	0	0.0	1	0.3	-	-	-	-
IIIA	8	2.3	5	1.5	4	2.6	1	0.7
IIIB	22	6.4	21	6.1	9	5.9	6	4.3
IV	312	91.0	315	91.6	138	90.8	131	94.2
Metastatic Staging								
M0	31	9.0	29	8.4	14	9.2	8	5.8
M1	80	23.3	95	27.6	40	26.3	36	25.9
M1A	62	18.1	62	18.0	22	14.5	20	14.4
M1B	**170**	**49.6**	**158**	**45.9**	**76**	**50.0**	**75**	**54.0**
Median baseline tumour size, (range), mm	78.0 (13-290)		86.0 (10-345)		90 (13-290)		82 (10-345)	
Brain metastasis	**48**	**14.0**	**56**	**16.3**	**23**	**15.1**	**32**	**23.0**
Non-small Cell Histology								
Squamous	66	19.2	76	22.1	26	17.1	29	20.9
Non-squamous	240	70.0	240	69.8	111	73.0	95	68.3
Mixed	4	1.2	3	0.9	2	1.3	0	0.0

Other	6	1.7	6	1.7	3	2.0	4	2.9
Unknown	27	7.9	19	5.5	10	6.6	11	7.9
PD-L1 Status								
TPS1-49%	191	55.7	205	59.6	0		0	
TPS≥50%	152	44.3	139	40.4	152	100	139	100
EGFR Mutation								
Mutant	26	7.6	28	8.1	12	7.9	8	5.8
Wild Type	294	85.7	293	85.2	131	86.2	119	85.6
Undetermined	13	3.8	15	4.4	4	2.6	7	5.0
Missing	10	2.9	8	2.3	5	3.3	5	3.6
ALK Translocation Status								
Mutant	2	0.6	2	0.6	1	0.7	2	1.4
Wild Type	310	90.4	307	89.2	137	90.1	120	86.3
Undetermined	20	5.8	22	6.4	7	4.6	11	7.9
Missing	11	3.2	13	3.8	7	4.6	6	4.3
Prior Lines of Systemic Therapy								
Adjuvant	3	0.9	6	1.7	3	2.0	2	1.4
Neo Adjuvant	0	0.0	1	0.3	0		0	
First line	235	68.5	243	70.6	109	71.7	97	69.8
Second line	75	21.9	66	19.2	25	16.4	30	21.6
Third line	20	5.8	18	5.2	11	7.2	9	6.5

Fourth line	6	1.7	6	1.7	2	1.3	1	0.7
Fifth line or greater	3	0.9	3	0.9	2	1.3	0	
Missing	1	0.3	1	0.3	-		-	
Prior adjuvant/neo adjuvant therapy	18	5.2	20	5.8	9	5.9	7	5.0
Prior chemotherapy	339	98.8	335	97.4	149	98	137	98.6
Prior immunotherapy	1	0.3	2	0.6	0		1	0.7
Prior EGFR TKI therapy	47	13.7	40	11.6	21	13.8	14	10.1
Prior ALK inhibitor therapy	2	0.6	3	0.9	1	0.7	3	2.2
Note: Prior systemic therapy (Database Cut-off Date: 30SEP2015).								

4.2.2 Results of KEYNOTE-010

Table 10 shows the summary results for the primary, secondary and remaining efficacy outcomes in the ITT population in KEYNOTE-010.

The ERG noted that the estimate for overall survival in the TPS 1-49% stratum reported in the submission, HR 0.79 (95% CI 0.61, 1.04); p=0.04434, does not appear to be correct as the confidence interval and p-value are conflicting with each other (assuming that the confidence interval is correct, it is possible that the p-value quoted by the company refers to a one-sided hypothesis rather than a two-sided hypothesis).

In the whole population the median overall survival (OS) was 10.4 months for pembrolizumab and 8.5 months for docetaxel, which represents a 29% reduction in the risk of death (HR 0.71, 95% CI 0.58, 0.88; p=0.00076). For patients with a TPS≥50% the median OS survival was 14.9 months for pembrolizumab and 8.2 months for docetaxel. This represents a 46% reduction in the risk of death (HR 0.54, 95% CI 0.38, 0.77; p=0.00024). In the TPS 1-49% stratum, the median OS was 9.4 months for pembrolizumab and 8.6 months for docetaxel with no evidence of a difference between pembrolizumab and docetaxel (HR 0.79, 95% CI 0.61, 1.04). The OS rates were higher for those receiving pembrolizumab in all strata (36.7% compared with 31.2% in the TPS 1-49% stratum, 53.4% compared with 38% in the TPS>50% stratum and 43.2% compared with 34.6% in the whole TPS≥1% population).

In the overall TPS≥1% population the median progression free survival (PFS) was 3.9 for pembrolizumab and 4.0 months for docetaxel. The difference did not reach statistical significance at the 0.001 level (alpha) required by the study protocol (HR 0.88, 95% CI 0.73, 1.04; p=0.06758). In the TPS≥50% stratum, the median PFS was 5.2 months for pembrolizumab and 4.1 months for docetaxel indicating a 42% reduction in disease progression for patients receiving pembrolizumab (HR 0.58, 95% CI 0.43, 0.77; p=0.00009). In the TPS 1-49% stratum the median PFS was 3.1 months for pembrolizumab and 3.9 months for docetaxel. The HR of 1.07 (95% CI 0.85, 1.34; p=0.7185) does not indicate a significant difference between the treatments. In both sub-populations and in the whole population, the PFS rates were higher for patients receiving pembrolizumab (10.4% compared with 5.8% in the TPS 1-49% stratum,

28.2% compared with 10.7% in the TPS>50% stratum, and 17.5% compared with 8.6% in the whole TPS≥1% population).

The company states that the results of OS and PFS analyses for the TPS≥1% and for the TPS≥50% stratum were generally similar between the ITT and the FAS populations but does not provide details of these results in the submission.

A number of subgroups analyses for OS and PFS for pembrolizumab versus docetaxel were presented in the submission (see section 4.8 of the company submission). For OS there was no evidence of a difference between pembrolizumab and docetaxel for the following subgroups: non-White race, East Asian ethnicity and region, baseline ECOG, weakly positive PD-L1 status, never smokers, squamous cell histology, and mutant EGFR. However, few subgroups had small numbers of events and, therefore, less precise estimates with wider confidence intervals. For PFS, the overall estimate of effect showed no evidence of a difference between pembrolizumab and docetaxel and there was not a clear superiority of pembrolizumab in a number of subgroups but again number of events was small in few subgroups. There was a clear survival benefit for pembrolizumab for those in the 'strongly positive PD-L1 status' subgroup.

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Table 10 Summary of the clinical effectiveness results according to TPS rate

	TPS 1-49%		**TPS ≥ 50%**		**TPS ≥ 1% (overall population)**	
	Pembrolizumab 2mg/kg N=205	Docetaxel 75 mg/m2 Q3W N=191	Pembrolizumab 2mg/kg N=139	Docetaxel 75 mg/m2 Q3W N=152	Pembrolizumab 2mg/kg N=344	Docetaxel 75 mg/m2 Q3W N=343
Primary endpoints						
OS – ITT population						
Median (95% CI, months)	9.4 (8.7, 10.5)	8.6 (7.8, 9.9)	14.9 (10.4-not reached)	8.2 (6.4-10.7)	10.4 (9.4, 11.9)	8.5 (7.5, 9.8)
	HR 0.79 (95% CI 0.61, 1.04); p=0.04434		HR 0.54 (0.38, 0.77); P=0.00024		HR 0.71 (95% CI 0.58, 0.88); p=0.00076	
12 month OS rate (%)	36.7 (29.1, 44.4)	31.2 (22.9, 39.8)	53.4 (43.1, 62.6)	38.0 (28.9, 47.1)	43.2 (37.0, 49.3)	34.6 (28.4, 40.8)
PFS (IRC per RECIST 1.1) – ITT population						
Median (95% CI, months)	3.1 (2.1, 3.8)	3.9 (2.5, 4.3)	5.2 (4.0, 6.5)	4.1 (3.6, 4.3)	3.9 (3.1, 4.1)	4.0 (3.1,4.2)
	HR 1.07 (0.85, 1.34); p=0.71850		HR 0.58 (0.43, 0.77); p=0.00009		HR 0.88 (95% CI 0.73, 1.04), p=0.06758	
PFS rate at 12 months	10.4 (6.3, 15.6)	5.8 (1.9, 12.7)	28.2 (19.5, 37.5)	10.7 (5.6, 17.5)	17.5 (13.1, 22.4)	8.6 (5.1, 13.1)

Secondary endpoints						
ORR % (95% CI) (with confirmation)	9.8 (6.1,14.7)	10.5 (6.5,15.7)	30.2 (22.7, 38.6)	7.9 (4.1, 13.4)	18 (14.1,22.5)	9.3 (6.5,12.9)
Time to response						
Median, days	9	9	65	65	65	65
Range	7-31	6-36	38 – 141	59-247	38-127	41-250
Response duration (IRC per RECIST 1.1) – ITT population						
Median, days	46	26	Not reached	246	Not reached	189
Range, days	9+ - 87+	6+ - 31	20+ - 512+	(63+ - 268+)	20+ - 610+	43+ - 268+
% of responses on going among responders	13	12	Not available	33	73	34
EQ-5D (week 12)	0.78 (0.18)	0.73 (0.22)	Not available	Not available	0.78 (0.19)	0.74 (0.21)

OS – Overall survival
PFS – Progression free survival
ORR – Overall response rate
IRC – Independent review committee

4.2.3 Switching adjustments

Cross-over was not allowed within KEYNOTE-010. Nevertheless, a total number of 50 participants switched to other PD-1 treatments after treatment discontinuation. The prevalence of treatment switching in KEYNOTE-010 by treatment arm is presented in Table 11.

Table 11 KEYNOTE-010 - Treatment switching to anti PD-1 after disease progression

	Pembrolizumab 2 mg/kg Q3W	**Docetaxel 75 mg/m2 Q3W**	**Total**
	n (%)	n (%)	n (%)
Patients in population	344 (100.0)	343 (100.0)	1033 (100.0)
Switching to anti-PD1	1 (0.3)	42 (12.2)	49 (4.7)
Switching to CTLA4 inhibitor + anti-PD1	0 (0.0)	1 (0.3)	1 (0.1)
Total patients switching to anti-PD-1	1 (0.3)	43 (12.5)	50 (4.8)

In the study protocol, it was initially planned to adjust for treatment switching using the Rank Preserving Structural Failure Time (RPSFT) described by Robins and Tsiatis.[71] RPSFT-adjusted results are presented in the submission (Table 24 of the submission). The company, however, questioned the validity of the RPSFT 'common treatment effect' assumption and opted for another approach: the two-stage adjustment, which was developed in accordance to the type of switching often observed in oncology trials in patients with metastatic disease.[72] For clarity, the results of both techniques are presented in Table 12 below.

Table 12 Results of overall survival in the control group after using no switching adjustment, the RPSFT correction and the two-stage correction

Treatment	Median OS, months (95% CI)
Docetaxel (no switching correction)	8.5 (7.5,9.8)
Control (RPSFT correction)	8.4 (7.5,9.8)
Control (Two-stage correction - simple model)	8.3 (7.4,9.5)
Control (Two-stage correction - all covariates)	8.3 (7.4, 9.5)
Pembrolizumab 2mg/kg Q3W (no switching correction)	10.4 (9.4, 11.9)

The company didn't present any other analysis to adjust for treatment switching such as the Inverse Probability of Censoring Weights (IPCW). Given the fact that the RPSFT 'common treatment assumption' was not verified, as explained by the company in section 4.7 of the submission, the IPCW would have been a natural possibility since it doesn't make a that assumption. In addition the company recognises that the IPCW is more sensitive to the switching proportion, even though the proportion observed in this case is not low (12.5% of switching occurred from the control arm to another treatment). The company recognises (page 93 of the submission) that the two-stage adjustment method *"…is less sensitive to the switching proportion than other methods, such as the Inverse Probability of Censoring Weights (IPCW) or structural nested models (SNMs), both of which were rejected during examination of the appropriate method for cross-over adjustment."* No further justification is given on why other methods were not implement. However, presentation of several different analyses, which take into consideration different assumptions, is usually considered good practice. It is worth pointing out that the submission presents no information regarding the time point that defined the secondary baseline or the distribution of time from the secondary baseline to the switching, as well as the convergence of the model, which are all important methodological elements for assessing the quality of the modelling and the compliance with the assumptions made. However, this lack of information is not of particular concern as most of the switching observed was in the direction of the control treatment to a different drug, potentially diluting the treatment effect of

pembrolizumab. Moreover, after adjusting for treatment switching, the estimates of treatment effect were very similar to the unadjusted results.

4.2.4 Characteristics and critique of KEYNOTE-001

From May 2012 through January 2015, KEYNOTE-001 phase I trial included 495 participants. The company explains that although originally KEYNOTE-001 was a phase I trial, it evolved into a series of expansion cohorts of which parts C, F2 and F3 were relevant to the decision problem addressed by the submission. Part C, F2 and F3 cohorts assessed the efficacy and safety of pembrolizumab in patients with locally advanced or metastatic NSCLC, whose disease recurred after prior therapy with platinum-based chemotherapy. PD-L1 status was unknown among participants in part C cohort, all the participants in part F3 cohort had tumours that expressed PD-L1 while part F2 cohort included a mix of participants with PD-L1 status positive and PD-L1 status negative. Part C, F2 and F3 of KEYNOTE-001 included 38, 356 and 55 participants, respectively. Participants in part C and F2 received a dose of 10 mg/Kg of pembrolizumab Q3W and those in part F3 received 2 mg/Kg of pembrolizumab Q3W. A summary of the characteristics of KEYNOTE-001 (parts C and F) is presented in Table 13, which reproduces Table 10 of the company submission.

Table 13 Summary of the characteristics of KEYNOTE-001

Trial number (acronym)	KEYNOTE-001 (Parts C and F)
Location	Parts C and F of KEYNOTE- 001 study were conducted across the following countries: Australia, Canada, France, Italy, Norway, South Korea, Spain, Taiwan, UK, USA
Trial design	Phase I open-label study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and anti-tumour activity of pembrolizumab in patients with locally advanced or metastatic melanoma (ipilimumab-naïve or previously treated with or refractory to ipilimumab) and NSCLC. A series of expansion cohorts (phase II-like sub-studies) were conducted. Parts C and F were expansion cohorts specifically designed to evaluate the efficacy and safety of pembrolizumab in patients with advanced or metastatic NSCLC. All patients enrolled in Part C, Cohort F2, and Cohort F3 had previously been treated with platinum-based chemotherapy and demonstrated disease progression before initiating pembrolizumab. These represent the population of interest for this submission.
Key eligibility criteria for participants	<u>Parts C and F:</u> Histologically or cytologically confirmed diagnosis of NSCLC with locally advanced or metastatic disease (Parts C and F) Tumour amenable to biopsy Progression per RECIST 1.1 after treatment with platinum-containing doublet chemotherapy ECOG performance status of 0 or 1 <u>Part F only:</u> Known EGFR/ALK status Patient with EGFR mutation/ALK translocation must also demonstrate progression of disease on a EGFR TKI or Crizotinib
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as day care patients
Trial drugs (the interventions for each group with	Part C (non-randomised): Pembrolizumab 10 mg/kg Q3W (n=38)

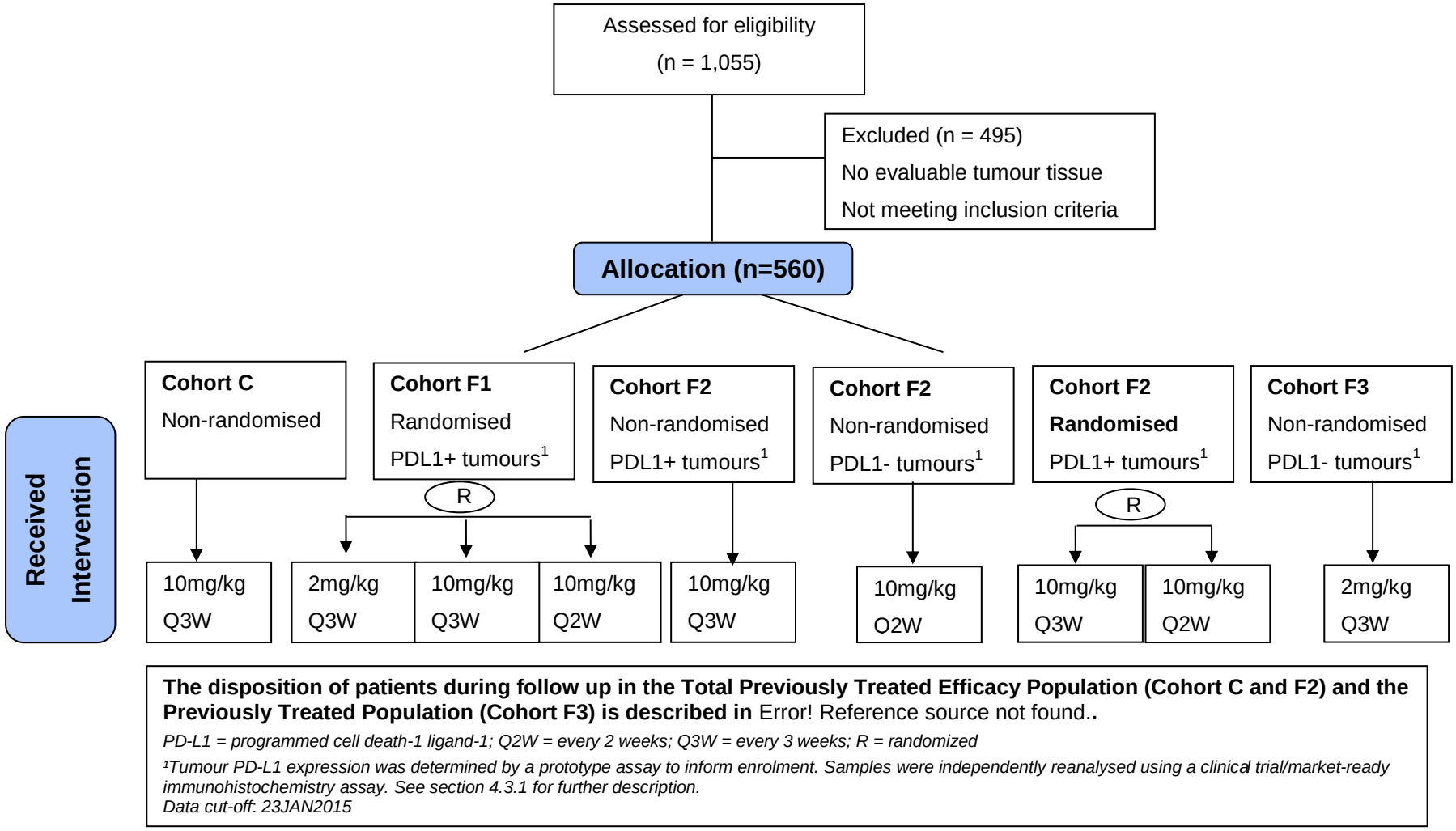
Trial number (acronym)	KEYNOTE-001 (Parts C and F)
sufficient details to allow replication, including how and when they were administered) Intervention(s) and comparator(s) Permitted and disallowed concomitant medication	Part F: F2 PDL1 expressers (randomised)* Pembrolizumab 10 mg/kg Q2W (n=113) Pembrolizumab 10 mg/kg Q3W (n=167) F2 PDL1non-expressers (non-randomised)* Pembrolizumab 10 mg/kg Q2W (n=43) F2 PDL1 expressers (non-randomised)* Pembrolizumab 10 mg/kg Q3W (n=33) F3 PDL1 expressers (non-randomised) Pembrolizumab 2 mg/kg Q3W (n=55) Disallowed concomitant medicines: Any other investigational agent Any other form of antineoplastic therapy Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Corticosteroids at a dose of 10 mg of prednisone (or its equivalent) per day.
Primary outcomes (including scoring methods and timings of assessments)	Primary efficacy endpoint: Overall RR (ORR, complete response [CR] plus partial response [PR]) based on independent central review per RECIST 1.1 (IRC) on the FAS population. Assessment of tumour response was performed every 9 weeks (±1 week) unless clinical indication warranted earlier imaging.
Secondary/ tertiary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints: ORR (IRC per RECIST 1.1) Based on IRC per RECIST 1.1 and INV per irRC: Response duration PFS

Trial number (acronym)	KEYNOTE-001 (Parts C and F)
	OS Analyses of secondary endpoints were based on the APaT population.
Pre-planned subgroups	Not Applicable

Figure 4, which reproduces Figure 9 of the company submission, shows the CONSORT diagram for the flow of participants in KEYNOTE-001. The ERG considers the methodological quality of the non-randomised, non-controlled parts C, F2 and F3 cohorts generally good. Baseline characteristics of KEYNOTE-001 are given in Table 18 of the company submission. The ERG noted that the company only reported baseline characteristics of pembrolizumab 10 mg/kg and not of pembrolizumab 2 mg/kg. The company presents results on overall survival, progression free survival, response rate and adverse events from cohorts C, F2 and F3. As highlighted earlier, cohorts C and F2 included the total previously treated efficacy population (from biomarker training and validation set), but not all patients had tumours that expressed PD-L1 while cohort F3 included the previously treated population (see Table 14 of the company submission for more details). All patients in the study populations used for the efficacy analyses had previously received a platinum-based chemotherapy and experienced progression of NSCLC after initiating the platinum-based chemotherapy. The ERG holds that safety data from the non-randomised non-controlled cohorts of KEYNOTE-001 would be relevant to address the decision problem. The company states that the safety data were presented for all participants with NSCLC who received at least one dose of pembrolizumab (n=550). The ERG noted that not all of the participants within the safety population were PD-L1 positive; 18.5% of the participants had a TPS less than 1%.

In KEYNOTE-001, the median progression free survival was 2.3 months with a 3 month survival rate of 44.7% and a 6 month survival rate of 25.3% in the 1-49% TPS stratum. In the TPS>50% stratum the median progression free survival was 5.8 months and the 3 and 6 month survival rates were 55.1% and 49.9%, respectively. The median overall survival was 7.8 months in the TPS 1-49% stratum

and 15.5 months in the TPS>50% stratum. The 6 and 12 month overall survival rates were 57.3% and 43.2%, respectively, in the TPS 1-49% stratum and 71.6% and 56%, respectively, in the TPS>50% stratum. The primary outcome in KEYNOTE-001 was the overall response rate (ORR) in the previously treated efficacy population. ORR was 37.4% (95% CI 27.9%, 47.7%) in the TPS>50% stratum and 11.8% (95% CI 6.8%, 18.7%) in the TPS 1-49% stratum. The median follow-up time was 16.2 months, range from 10.9 months to 32.3 months.



The disposition of patients during follow up in the Total Previously Treated Efficacy Population (Cohort C and F2) and the Previously Treated Population (Cohort F3) is described in Error! Reference source not found.**.**

PD-L1 = programmed cell death-1 ligand-1; Q2W = every 2 weeks; Q3W = every 3 weeks; R = randomized

[1]Tumour PD-L1 expression was determined by a prototype assay to inform enrolment. Samples were independently reanalysed using a clinical trial/market-ready immunohistochemistry assay. See section 4.3.1 for further description.
Data cut-off: 23JAN2015

Figure 4 KEYNOTE-001 - CONSORT diagram

4.2.5. Adverse events

Adverse events of KEYNOTE-010

The CSR of KEYNOTE-010 reports that the mean duration of treatment in the pembrolizumab 2mg/kg Q3W arm was 151.1 days (1.0 – 681.0) compared with 81.5 (1.0 – 416.0) in the doxetacel 75 mg/m2 Q3W arm.

Table 54 (page 135 of the company submission) displays the proportion of patients in the overall TPS≥1% population with drug-related adverse events (AEs) with an incidence ≥5% in one or more treatment groups. In general, more drug-related AEs occurred among patients receiving docetaxel than those receiving pembrolizumab (81.2% and 63.4%, respectively). The most common drug-related AEs in the pembrolizumab 2 mg/kg Q3W arm included: fatigue (13.6%), decreased appetite (13.6%), nausea (10.9%), and rash (8.6%). The most common drug-related AEs included in the docetaxel 75 mg/m2 Q3W arm included: alopecia (32.7%), fatigue (24.6%), and diarrhoea (18.1%).

Table 14 below displays the number of patients in the TPS>1% population with drug-related Grade 3 to 5 adverse events. Only the most frequent adverse events are reported. Patients with at least one adverse event were more frequent in the docetaxel 75 mg/m2 Q3W arm than in the pembrolizumab 2 mg/kg Q3W arm (35.3% versus 12.7%, respectively). The most prevalent adverse event in the pembrolizumab 2 mg/kg Q3W arm was pneumonitis (1.8%) and in the docetaxel 75 mg/m2 Q3W arm neutropenia (12.3%). A more detailed description of the adverse events is given by the company in Table 55, page 136 of the submission.

Table 14 Summary of Grade 3-5 adverse events up to 30 days following the last dose of study treatment (all patients as treated population)

Type of AD	Pembrolizumab 2mg/kg Q3W (n=339)	Docetaxel 75 mg/m2 Q3W (n=309)
One or more AEs	43 (12.7)	109 (35.3)
With no AEs	296 (87.3)	200 (64.7)
Fatigue	4 (1.2)	11 (3.6)
Pneumonitis	6 (1.8)	1 (0.3)
Neutropenia	0 (0.0)	38 (12.3)
Neutrophil count decreased	0 (0.0)	19 (6.1)
Febrile neutropenia	0 (0.0)	15 (4.9)

Table 15 displays drug-related serious adverse events (SAEs) up to 90 days after the last dose of study medication (incidence >0% in one or more treatment groups) for patients in the TPS≥1% population. Only most frequent SAEs are shown. The most prevalent SAE in the pembrolizumab 2 mg/kg Q3W arm was pneumonitis and in the docetaxel 75 mg/m2 Q3W arm febrile neutropenia. A more detailed list of drug-related SAEs is presented in Table 56, page 139 of the company submission.

Table 15 Summary of drug-related serious adverse events up to 90 days after last dose of study treatment (all patients as treated population)

Type of SAE	Pembrolizumab 2mg/kg Q3W (n=339)	Docetaxel 75 mg/m2 Q3W (n=309)
One or more SAEs	32 (99.4)	42 (13.6)
With no SAEs	267 (86.4)	307 (90.6)
Pneumonitis	7 (2.1)	2 (0.6)
Colitis	3 (0.9)	0 (0.0)
Pneumonia	3 (0.9)	4 (1.3)
Febrile neutropenia	0 (0.0)	10 (3.2)

Table 16 displays a summary of Adverse Events of Special Interest (AEOSI) in the overall (TPS≥1%) population. Most prevalent AEOSI are presented for each treatment arm. There was a higher prevalence of AEOSI in the pembrolizumab 2mg/kg Q3W,

arm, due to its immune activity, compared with the docetaxel 75 mg/m2 Q3W arm (20.4% and 4.2%, respectively). Grade 3 to 5 drug-related AEOSI occurred in 4.7% of patients treated with pembrolizumab and in 1.0% of patients treated with docetaxel while serious adverse events AEOSI occurred in 6.2% of patients treated with pembrolizumab and in 1.6% of patients treated with docetaxel. Two deaths due to drug-related AEs were observed in the pembrolizumab 2mg/kg Q3W arm compared to one death in the docetaxel arm. The proportion of patients who discontinued treatment due to drug-related AEs (2.1% versus 1.6%) or to SAEs (1.5% versus 1%) was similar between pembrolizumab and doxetacel. Most of the AEOSIs were reported by the company to be Grade 1 to 2 in severity and manageable with corticosteroid treatment, interruption of pembrolizumab administration, or both.

Table 16 Summary of adverse events of special interest (AEOSI) for the TPS 1% population (all patients as treated population), n(%)

Patients in population	Pembrolizumab 2mg/kg Q3W (n=339)	Docetaxel 75 mg/m2 Q3W (n=309)
With one or more AEs	69 (20.4)	13 (4.2)
With no AE	270 (79.6)	296 (95.8)
With drug-related AEs	59 (17.4)	7 (2.3)
With toxicity grade 3-5 AEs	19 (5.6)	4 (1.3)
With toxicity grade 3-5 drug-related AEs	16 (4.7)	3 (1.0)
With serious adverse events (SAEs)	21(6.2)	5 (1.6)
With drug-related SAEs	18 (5.3)	3 (1.0)
Who died	2 (0.6)	2 (0.6)
Who died due to a drug-related AE	2 (0.6)	1 (0.3)
Discontinued due to an AE	7 (2.1)	5 (1.6)
Discontinued due to a drug-related AE	7 (2.1)	5 (1.6)
Discontinued due to a SAE	5 (1.5)	3 (1.0)
Discontinued due to a drug-related SAE	5 (1.5)	3 (1.0)

Adverse events of KEYNOTE-001

Table 17 below, which reproduces Table 61 of the company submission shows the incidence of specific drug-related AEs (≥5%) in all patients with NSCLC (N=550) who received at least one dose of pembrolizumab, according to dose regimen in KEYNOTE-001. Drug- related AEs occurred in 69.1% of patients. The most common drug-related AEs were fatigue (18.9%), pruritus (10.7%), decreased appetite (10.2%), rash (9.1%), and arthralgias (8.9%). The most prevalent adverse event across arms was fatigue (22.6% in the pembrolizumab 10mg/kg Q3W arm and 6.6% in the pembrolizumab 2mg/kg Q3W arm). Rates of drug-related AEs were lower in the

pembrolizumab 2 mg/kg Q3W compared with the 10 mg/kg groups and a higher proportion of people in the pembrolizumab 2 mg/kg Q3W arm had no AEs .

The most common drug-related Grade 3 to 5 AE in the all NSCLC patient population in KEYNOTE-001 was pneumonitis (1.8%). All other drug-related Grade 3 to 5 AEs occurred in less than 1% of patients. The overall incidence of drug-related SAEs in the all NSCLC patient population was relatively low (8.4%). The most common drug-related SAE was pneumonitis (2.5%). All other drug-related SAEs were reported in less than 1% of patients.

Table 17 KEYNOTE-001 - Patients with drug-related AEs (incidence ≥ 5% in one or more treatment groups). All patients with NSCLC by dose

	Pembrolizumab 2 mg/kg Q3W		**Pembrolizumab 10 mg/kg Q3W**		**Pembrolizumab 10 mg/kg Q2W**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients in population	61		287		202	
with one or more AEs	31	(50.8)	201	(70.0)	148	(73.3)
with no AEs	30	(49.2)	86	(30.0)	54	(26.7)
Blood and lymphatic system disorders	**1**	**(1.6)**	**13**	**(4.5)**	**13**	**(6.4)**
Anaemia	1	(1.6)	10	(3.5)	10	(5.0)
Endocrine disorders	**4**	**(6.6)**	**23**	**(8.0)**	**21**	**(10.4)**
Hypothyroidism	4	(6.6)	16	(5.6)	20	(9.9)
Gastrointestinal disorders	**11**	**(18.0)**	**67**	**(23.3)**	**47**	**(23.3)**
Diarrhoea	5	(8.2)	27	(9.4)	15	(7.4)
Nausea	1	(1.6)	25	(8.7)	15	(7.4)
General disorders and administration site conditions	**12**	**(19.7)**	**101**	**(35.2)**	**62**	**(30.7)**
Asthenia	4	(6.6)	12	(4.2)	15	(7.4)
Fatigue	4	(6.6)	65	(22.6)	35	(17.3)

	Pembrolizumab 2 mg/kg Q3W		**Pembrolizumab 10 mg/kg Q3W**		**Pembrolizumab 10 mg/kg Q2W**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Pyrexia	4	(6.6)	12	(4.2)	9	(4.5)
Infections and infestations	**0**	**(0.0)**	**11**	**(3.8)**	**10**	**(5.0)**
Investigations	**3**	**(4.9)**	**38**	**(13.2)**	**26**	**(12.9)**
Metabolism and nutrition disorders	**7**	**(11.5)**	**44**	**(15.3)**	**20**	**(9.9)**
Decreased appetite	4	(6.6)	36	(12.5)	16	(7.9)
Musculoskeletal and connective tissue disorders	**3**	**(4.9)**	**43**	**(15.0)**	**39**	**(19.3)**
Arthralgia	2	(3.3)	25	(8.7)	22	(10.9)
Nervous system disorders	**3**	**(4.9)**	**18**	**(6.3)**	**14**	**(6.9)**
Respiratory, thoracic and mediastinal disorders	**6**	**(9.8)**	**37**	**(12.9)**	**23**	**(11.4)**
Skin and subcutaneous tissue disorders	**9**	**(14.8)**	**77**	**(26.8)**	**48**	**(23.8)**
Dry skin	0	(0.0)	8	(2.8)	11	(5.4)
Pruritus	4	(6.6)	33	(11.5)	22	(10.9)
Rash	2	(3.3)	30	(10.5)	18	(8.9)

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

In the absence of head to head RCTs compering pembrolizumab versus competing interventions, the company conducted an indirect treatment comparison (ITC) by means of a network meta-analysis (NMA) of RCTs. The company identified two RCTs, which formed the base of the indirect treatment comparison: KEYNOTE-010 and LUME-LUNG-1. These trials focused on the following advanced NSCLC populations:

- All NSCLC histologies population (previously treated);
- Adenocarcinoma population (previously treated).

KEYNOTE-010 compared pembrolizumab with docetaxel in patients with advanced and recurrent NSCLC who express PD-L1 (TPS≥1%) and who have experienced disease progression after chemotherapy or chemotherapy plus targeted therapy (for EGFR or ALK positive tumours). LUME-LUNG-1 assessed docetaxel 75 mg/m2 Q3W and the combination docetaxel 75 mg/m2 Q3W with nintedanib 400 mg on days 2-21 of a 3-week cycle in patients with advanced NSCLC whose disease had progressed on or after treatment with only 1 prior chemotherapy regimen. Both trials conducted analyses in the adenocarcinoma subpopulation and reported results relevant to the decision problem addressed by the submission. With regard to the all NSCLC histologies population, the company identified KEYNOTE-010 as the only RCT comparing pembrolizumab with docetaxel and, therefore, no further analysis was deemed necessary. With regard to the adenocarcinoma subpopulation, both KEYNOTE-010 and LUME-LUNG-1 included docetaxel as a comparator forming a connected network for the indirect comparison (see Figure 5 below). The ERG noted that the company did not consider data for the all NSCLC histologies population from LUME-LUNG-1. It is worth noting that according to the decision problem, nintedanib in combination with docetaxel is the recommended treatment only in people with NSCLC of adenocarcinoma histology. Hence, the ERG agrees with the company's decision of not including data for the all NSCLC histologies population from LUME-LUNG-1.

The company judged both trials at overall low risk of bias. The ERG, however, does not agree entirely with the company's judgement as KEYNOTE-010 was an open label trial in which only outcome assessors were blinded but not patients and/or study personnel, while LUME-LUNG-1 was a proper double blinded trial (see section 4.1.4 above).

An overview of the study design characteristics of KEYNOTE-010 and LUME-LUNG-1 is shown in Table 18 below, which reproduces Table 1, Appendix 15 of the company submission.

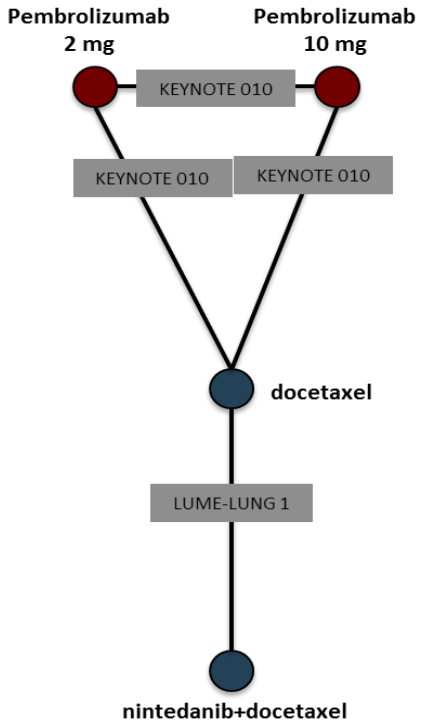


Figure 5 Network of evidence for pembrolizumab and nintedanib plus docetaxel for people with NSCLC of adenocarcinoma histology (reproduced from Figure 27 of the company submission)

Table 18 Comparative overview of the characteristics of KEYNOTE-010 and LUME-LUNG-1 included in the indirect treatment comparison

Trial ID	Phase of trial	Duration of trials	Masking	Region	Inclusion criteria	Treatments
KEYNOTE 010[45, 46]	II/III	2013 to 2015	Open-label	Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Korea, Lithuania, Netherlands, Portugal, Russian Federation, South Africa, Spain, Taiwan, United Kingdom, United States	NSCLC stage IIIb or IV PDL1 expressers (TPS≥1%) ≥18 years ECOG 0-1 1 prior chemotherapy regimen	Pembrolizumab, IV 2mg/kg Q3W (n=344) Pembrolizumab, IV 10mg/kg Q3W (n=346) Docetaxel IV, 75 mg/m2 (n=343)
LUME-LUNG-1[35, 54-60]	III	2008 to 2014	Double-blind	Austria, Belarus, Belgium, Bulgaria, China, Croatia, Czech Republic, Denmark, France, Georgia, Germany, Greece, India, Israel, Italy, Korea, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, South Africa, Spain, Switzerland, Ukraine, UK	NSCLC stage IIIb or IV ≥18 years ECOG 0-1 1 prior chemotherapy regimen	Docetaxel IV, 75mg/m2 plus nintedanib, PO 400mg Q3W (n=655) Docetaxel IV, 75 mg/m2 (n=659) plus placebo

4.3.1 Characteristics and critique of KEYNOTE-010

Please see section 4.2.1 above for the critique of KEYNOTE-010.

4.3.2 Characteristics and critique of LUME-LUNG-1

Between Dec 2008 and Feb 2014, LUME-LUNG-1 trial recruited 1314 participants from 211 academic medical centres in 27 countries (23 of which were European countries). Patients were randomised in a 1:1 ratio to receive either docetaxel 75mg/m2 plus nintedanib, 400mg Q3W (n=655) or docetaxel 75 mg/m2 plus placebo Q3W (n=659). Nintedanib was given as 200 mg twice daily orally and docetaxel 75 mg/m^2 was administered as an intravenous infusion over 1 hour Q3W.

The company provides baseline data for the adenocarcinoma subpopulation from both KEYNOTE-010 and LUME-LUNG-1 in Appendix 15 of their submission (Table 2a), which is reproduced as Table 19 below. The ERG noted that the only baseline information for the adenocarcinoma sub-groups related to the number of current/former smokers and never smokers. All other baseline data related to the all NSCLC population of LUME-LUNG-1. The company did recognise in their submission that there were not sufficient information on the baseline characteristics of the adenocarcinoma subgroups of LUME-LUNG-1.

Table 19 Baseline characteristics of the adenocarcinoma subpopulation from KEYNOTE-010 and from the overall NSCLC population from LUME-LUNG-1

	KEYNOTE-010 (adenocarcinoma population)		LUME-LUNG 1 (overall NSCLC)	
	Docetaxel (n=236)	**Pembrolizumab 2mg/kg (n=235)**	**Docetaxel (n=336)**	**Nintedanib + Docetaxel (n=322)**
Age, median(range)	60 (34-81)	62 (29-82)	60 (54-66)	60 (53-67)
Males, n (%)	129 (55)	127 (54)	(73)	(73)
Smoking status, n (%)				
Current/Former smokers	173 (73)	180 (77)	(66)	(64)
Never smokers	58 (25)	54 (23)	(34)	(36)
Unknown	5 (2)	1 (0.4)	--	--
Race, n(%)				
White	172 (73)	166 (71)	(80)	(81)
Black	5 (2)	8 (3)	(1)	(1)
Asian	48 (20)	51 (22)	(19)	(18)
Other	8 (3)	4 (2)	--	--
Unknown	3 (1)	6 (3)		
ECOG, n (%)				
0	84 (36)	83 (35)	(29)	(29)
1	149 (63)	151 (64)	(71)	(71)
2	1 (0.4)	1 (0.4)	(0)	(0)
Stage, n (%)				
IIIa	6 (3)	4 (2)	--	--
IIIb	6 (3)	10 (4)	(23)	(22)
IV	224 (95)	221 (94)	(61)	(62)
Brain metastasis	39 (16.5)	44 (18.7)	38 (5.8)	38 (5.8)

Note: Only highlighted data refers to the adenocarcinoma subpopulation, as no data was available for the subgroup of adenocarcinoma from LUME-LUNG-1.

The main difference between the two trials relates to the included patient population: KEYNOTE-010 included only patients with advanced NSCLC whose tumours

express PD-L1 and who have progressed after appropriate targeted therapy for EGFR or ALK positive tumours; while in LUME-LUNG-1 neither PD-L1 expression nor EGFR mutation status were assessed among included patients with advanced NSCLC. With regard to the proportion of patients with adenocarcinoma histology, LUME-LUNG-1 had approximately 50% of the patients with adenocarcinoma histology while KEYNOTE-010 had approximately 70% of patients with adenocarcinoma histology. The company identified some degree of clinical heterogeneity across these two trials including a higher proportion of male participants and lower proportion of those with stage IV NSCLC in LUME-LUNG-1 compared with KEYNOTE-010. The ERG further noted that LUME-LUNG-1 had a lower proportion of patients with brain metastasis compared with KEYNOTE-010.

In LUME-LUNG-1, the median duration of treatment with nintedanib plus docetaxol was 3.4 months (IQR 1.4-6.2) and with docetaxel plus placebo was 2.8 months (IQR 1.4-5.4). The CSR of KEYNOTE-010 specifies that the mean duration of study treatment for the safety population was 151.1 days for pembrolizumab and 81.6 days for doxetacel. At present, one of the most relevant issues in immunotherapy is to establish the optimal duration of therapy. The company submission states that (page 161):

"*The anticipated licence establishes that pembrolizumab is to be administered until disease progression or unacceptable toxicities. However, there is no evidence regarding the optimal duration of treatment with pembrolizumab, particularly since the KEYNOTE-010 protocol established that treatment should continue until disease progression, toxicities leading to discontinuation, physician's decision or 2 years of uninterrupted delivery of pembrolizumab.*"

The ERG is of the opinion that this would place considerable pressure on the pharmacy, nursing and oncology services with patients attending for an intravenous drip every 3 weeks for up to two years. At clarification the company explained that:

"MSD has no evidence that treatment with pembrolizumab should be shorter than the maximum duration of therapy of 2 years established in KEYNOTE-010 study. It should be noted that in KEYNOTE-001 trial design treatment duration with pembrolizumab was for an unlimited period of time. However, subsequent to this, the

trial design of KEYNOTE-010 restricted treatment duration to a maximum of 2 years of uninterrupted treatment with pembrolizumab. MSD has no plans in the trial development program to look at the efficacy of shorter courses of pembrolizumab therapy."

Given the relatively short interval between the drug being prepared and the drug being delivered, the ERG enquired whether there was any plan from the company to investigate the possibility of home therapy. At clarification the company clarified that:

"MSD has a small pilot study running in Manchester to investigate the possibility of home therapy for pembrolizumab and is waiting for the results of this study to assess whether this possibility should be further explored."

4.3.3 Results of the NMA

The outcomes considered for the indirect comparison of pembrolizumab and nintedanib in combination with docetaxel were overall survival, discontinuation of treatment due to adverse events and adverse events Grade 3 or 4.

Table 20 summarises the main results of the NMA. The network meta-analysis of pembrolizumab compared with the combination of nintedanib and docetaxel shows no evidence of a significant difference in terms of either overall survival (HR 0.81, 95% CI 0.59, 1.10) or progression free survival (HR 1.04, 95% CI 0.79, 1.36). The network meta-analysis does, however, show a beneficial effect in favour of pembrolizumab with a 42% reduction in treatment discontinuation due to adverse event (HR 0.58, 95% CI 0.34, 0.99) and a 36% reduction in the number of Grade 3 or 4 adverse events (HR 0.64, 95% CI 0.44, 0.94).

Table 20 Summary of the NMA results for relevant outcomes

Source	Type of NMA	Outcome	No. of studies in the NMA	Pembrolizumab versus nintedanib + docetaxel
Company submission	**Fixed effects**	OS (HR (95% CrI))	**2**	**HR 0.81 (0.59,1.10)**
Company submission	**Fixed effects**	PFS (HR (95% CrI))	**2**	**HR 1.04 (0.79,1.36)**
Company submission	**Fixed effects**	Discontinuing due to AE (OR (95% CrI))	**2**	**OR 0.58 (0.34, 0.99)**
Company submission	**Fixed effects**	AE grades 3 or 4 (OR (95% CrI)	**2**	**OR 0.64 (0.44,0.94)**

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

The company presents a network meta-analysis of fixed effects in the subpopulation with adenocarcinoma. Since only two trials were included with the aim of comparing two treatments, between-study heterogeneity could not be estimated. The company also undertook a fractional polynomial network meta-analysis based on scanned Kaplan Meier curves. This choice is usually justified if the proportional hazards assumption does not hold, which was the case for the progression free survival.

The NMA was limited by the fact that any assessment of inconsistency or adjustment for differences between the trials' populations was not possible because the evidence base consisting of only two trials and by the fact that the proportional hazards assumption was not supported by the LUME-LUNG-1 data. As LUME-LUNG-1 was the only trial identified by the company that provided evidence for nintedanib in combination with docetaxel, any estimation of the relative effectiveness of nintedanib in combination with docetaxel compared with pembrolizumab should be interpreted with caution. Moreover, as stated in the company submission, the NMA relied on the assumption that that the efficacy of nintedanib in combination with docetaxel did not depend on PD-L1 expression and that the reported subgroups were comparable.

When conducting the NMA the company used the recommended WinBUGS program from the NICE DSU TSD 2.[73] It is worth mentioning that the company could have

used an indirect treatment comparison instead of a fixed effects network meta-analysis. Their code appeared to be excessively complex for the purpose of this assessment (including code for multi-arm trials).

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG was not able to replicate the company's NMA results using the programs supplied in Appendix 17 of the company submission. Nevertheless, the ERG calculated the indirect comparison using the Bucher method (since it is equivalent to undertaking a NMA with fixed effects comparing two treatments and three trials) and was able to confirm the results for all outcomes assessed.

As progression free survival Kaplan Meier curves violated the proportional hazards assumption, a network meta-analysis with fractional polynomial models would have been a more adequate approach. It is worth noting that originally the company presented fractional polynomial models only in Appendix 19 of the submission but did not implemented them in the economic model. At clarification, the company provided updated analyses using fractional polynomial models (Table 11 of the company's response), showing that the impact on the cost-effectiveness results, after implementation of this approach, was modest.

4.6 Conclusions of the clinical effectiveness section

The ERG is of the opinion that the methods used in the analysis of the KEYNOTE-010 trial and in the network meta-analysis were generally appropriate and correctly applied.

With regard to the analyses of trials' results, the main uncertainties relate to the lack of methodological details provided when adjusting overall survival for treatment switching, which prevented the ERG from making a complete assessment, and to the fact that other suitable techniques for adjusting for treatment switching (as indicated by the NICE DSU TSD 16),[72] were not considered. Nevertheless, this lack of information is not of particular concern as most of the switching observed was in the direction of the control treatment to a different drug, potentially diluting the treatment effect of pembrolizumab. Moreover, after adjusting for treatment switching, the estimates of treatment effect were very similar to the unadjusted results. The company

states to have used three different sensitivity scenarios for progression free survival but does not report the results in the submission. For the overall survival analysis, no sensitivity analyses were presented. Both these sensitivity analyses would have been helpful in terms of testing the robustness of the results obtained.

5 Cost effectiveness

This chapter details a structured description and critique of the cost-effectiveness evidence submitted by Merk Sharp & Dohme. The submitted evidence includes:

- a systematic review of the published literature, and
- a *de novo* economic evaluation with an accompanying economic model in Microsoft Excel.

5.1 ERG comment on the company's review of cost effectiveness evidence

5.1.1 State objectives of the cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The company carried out a systematic search to identify cost-effectiveness studies of pembrolizumab for patients with advanced NSCLC following platinum-containing chemotherapy. Details of the search strategies are reported in Appendix 21 of the company submission.

Reports of cost effectiveness and resource use were sought by searching MEDLINE, EMBASE, NHS Economics Evaluation Database (NHS EED), HTA database, DARE and EconLit in May 2015 and further updated in March 2016 for reports published from 1995 and in English. In addition ISPOR and ASCO conference proceedings were manually searched for the previous 3 years. The NICE website was also consulted for relevant reports. The search strategies are documented in full in Appendix 21.

The searches (with the exception of Econlit) combine two search facets using the Boolean operator AND: non-small cell lung cancer; and study design (economic evaluations or costing studies). Econlit excluded the study design facet which was appropriate. The ERG believes use of study design terms for the HTA database and NHS EED was unnecessary as these are databases of economic and HTA studies and risked reducing the sensitivity of the searches.

While an appropriate range of terms was used, the NSCLC facet of the search was restricted by the inclusion of staging/ metastasis/advanced cancer related terms. This may have failed to pick up relevant data which fails to mention the stage(s) of cancer under consideration in the title or abstract. Indeed, four of the identified cost studies were found from manual searches.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

The company used explicit inclusion and exclusion criteria, with rationale to determine eligibility of studies to be included in the review. These are presented in Table 21.

Table 21 Inclusion and exclusion criteria for cost-effectiveness studies

Criteria	Inclusion	Exclusion	Rationale
Population	Previously treated adults with advanced NSCLC, following platinum-containing chemotherapy	Treatment naïve advanced NSCLC Patients under the age of 18	The relevant patient population
Intervention/ Comparator	Studies comparing pembrolizumab vs. any other pharmacological treatment	Non-drug treatments (e.g. surgery, radiotherapy)	To allow all papers with relevant pharmacological interventions to be captured
Outcomes	Studies including a comparison of costs between the intervention and comparator arms. Results should be expressed in incremental costs and QALYs, and any other measure of effectiveness reported together with costs	Cost-only outcomes (without a cost-minimisation argument)	To identify relevant cost-effectiveness studies
Study type	Full economic evaluation comparing at least two	Burden of illness studies	To identify relevant cost-effectiveness

Criteria	Inclusion	Exclusion	Rationale
	interventions in terms of: cost-consequence, cost-minimisation, cost-effectiveness, cost-utility and cost-benefit evaluations		studies
Publication type	Economic evaluations	Letters, editorials and review studies	To identify primary study articles
Language	Studies for which a full text version is available in English	Not available in English	To ensure the studies can be correctly understood and interpreted
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed The study's data and results must be extractable	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated. Studies that fail to present extractable results	To ensure data can be extractable To ensure methods can be replicated To ensure results can be validated
Key: QALY, Quality-adjusted life year.			

Source: Table 63, page 154, of the company submission

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies.

Overall, the search resulted in 2568 potentially relevant papers; however, none met the inclusion criteria. No cost-effectiveness studies were reviewed.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The systematic search for cost-effectiveness studies did not identify any existing studies on the cost-effectiveness of pembrolizumab for patients with advanced NSCLC following platinum-containing chemotherapy. The ERG considers the search strategies and the study selection criteria undertaken by the company to be appropriate.

5.2 Summary and critique of company's submitted economic evaluation by the ERG suggested research priorities

The company's economic evaluation generally follows the NICE Reference Case. The main deviation from the reference case relates to the choice of comparators. Many of the comparators listed in the NICE scope were excluded from the economic evaluation as shown in Table 22.

5.2.1 NICE reference case checklist (Table only)

Table 22 NICE reference case checklist

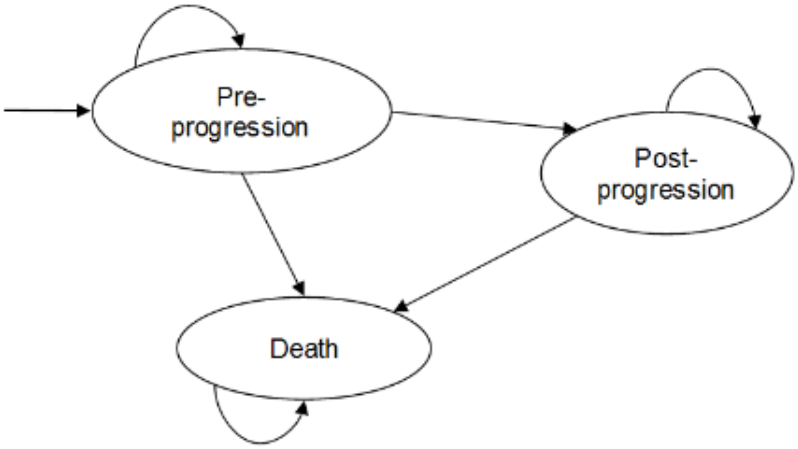
Attribute	Reference case and TA methods guidance	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	No – only **docetaxel monotherapy** and **nintedanib with docetaxel** (for patients with adenocarcinoma histology) were included in the economic evaluation. **Nivolumab, ceritinib and ramucirumab**, which are subject to ongoing NICE appraisal, were not included. **Best supportive care** was not considered by the company to be a relevant comparator.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Partial – direct health effects related to patients were considered, but impact on carers has not been considered.

Attribute	Reference case and TA methods guidance	Does the de novo economic evaluation match the reference case?
Perspective on costs	NHS and Personal Social Services (PSS)	Partial – costs to the NHS were included, but PSS costs have not been considered.
Type of economic analysis	Cost-utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 20-year time horizon
Synthesis of evidence on health effects	Based on systematic review	Partial – for the main analysis, data were primarily taken from one trial (KEYNOTE-010). For the analysis relating to the adenocarcinoma sub-group, a network meta-analysis was carried out to estimate the relative effects between pembrolizumab and nintedanib with docetaxel.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes – the EQ-5D was used to collect health-related quality of life data, and health effects were expressed in QALYs.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes – HRQoL data was collected as part of KEYNOTE-010 from patients.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes – all QALYs have the same weight.

Attribute	Reference case and TA methods guidance	Does the de novo economic evaluation match the reference case?
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes – NHS costs were valued using NHS and PSS prices.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
Probabilistic modelling	Include probabilistic modelling	Yes – the base cases were modelled probabilistically and deterministically.
Sensitivity analysis	Include sensitivity analysis	Yes

5.2.2 Model structure

The company presented a partitioned-survival model. The model comprised three mutually exclusive health states: pre-progression, post-progression and death. The model structure is presented in Figure 6. All patients entered the model in the pre-progression state. From the pre-progression state, patients could remain in that health state or progress and move to the post-progression state. Progression was defined by the RECIST v1.1 criteria, according to KEYNOTE-010. Patients could move to the death state from both the pre-progression and the post-progression health states. The company submission states that this three-state modelling approach is consistent with previous NICE submissions in advanced NSCLC.[18, 19, 74]



Source: Company submission, Figure 29, page 158

Figure 6 Model structure

In the partitioned-survival model, the areas under survival curves are used to estimate the proportion of patients in each health state at any time. The area under the overall survival (OS) curve from KEYNOTE-010 was used to estimate the proportion of patients in the death state. The area under the progression-free survival (PFS) curve from KEYNOTE-010 was used to estimate the proportion of patients in the pre-progression health state. The area between the OS and PFS curves was used to determine the proportion of patients in the post-progression health state.

In the model, patients in the pembrolizumab arm were eligible for treatment until disease progression. In the base case, the maximum treatment duration was assumed to be two years. These are in line with the anticipated licence and consistent with KEYNOTE-010. Patients in the docetaxel arm were restricted to maximum treatment duration of 18 weeks, in line with current practice in England. The company's model also accounted for the effects of treatment switching using a two-stage adjustment approach. This takes into account patient receiving subsequent oncologic therapies after treatment discontinuation with pembrolizumab or docetaxel; this was observed in KEYNOTE-010.

Time-to-death sub-health states were used to capture patients' health-related quality of life as a function of length of time until death; these were considered separately for pre-progression and post-progression health states. As a result, four health states were

used to estimate QALYs in the model: pre-progression and <30 days to death; pre-progression and >30 days to death; post-progression and <30 days to death; and post-progression and >30 days to death.

Resource use and costs were allocated based on pre and post-progression states. The costs of subsequent treatment following discontinuation were also included in the model. The model adopted a cycle length was one week, and half-cycle correction was also implemented over a time horizon of 20 years. The model adopted the perspective of the NHS; costs and effect were both discounted at 3.5% annually.

5.2.3 Population

The model considers patients with advanced NSCLC that is PD-L1 positive, and whose disease had progressed after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should also have disease progression on approved therapy for these aberrations prior to receiving pembrolizumab. This is consistent with the population specified in the NICE scope. The baseline characteristics of the model population were based on characteristics of participants at baseline for KEYNOTE-010 and are summarised in Table 23.

Table 23 Baseline characteristics of patients included in the model

Patient Characteristics	Mean	PSA distribution
Average age (years)	62	-
Proportion male	61.4%	-
Average weight (kg)	73.1	Normal (71.8, 74.5)
Average BSA (m^2)	1.84	Normal (91.82, 1.85)

Source: Adapted from Table 64 of the company submission. Average weight and average BSA were based on data from patients from KEYNOTE-010 European sites only.

Sub-group analysis in KEYNOTE-010 showed significant survival benefit for patients with adenocarcinoma (Figure 25, page 116, of the company submission). In addition to the whole population as per NICE scope, the company presented additional analyses on the sub-group of patients with adenocarcinoma. For these patients, pembrolizumab was compared with docetaxel monotherapy and nintedanib combined with docetaxel.

5.2.4 Intervention and comparators

The intervention was pembrolizumab 2 mg/kg IV infusion over 30 minutes every 3 weeks; this is in line with anticipated licensed dosing regimen. The anticipated licence stopping rules are that pembrolizumab will be administered until disease progression or unacceptable toxicities. The company states that there is no evidence on the optimal duration of treatment with pembrolizumab. In KEYNOTE-010, patients could receive uninterrupted treatment for up to two years.

The comparator was docetaxel monotherapy; this is in line with the NICE scope. The docetaxel dose considered was 75 mg/m^2 Q3W, with maximum treatment duration of 18 weeks (six cycles) based on advice from clinical experts. In KEYNOTE-010, patients received on average of less than four treatment cycles.

Nintedanib combined with docetaxel was included as an additional comparator for the sub-group of patients with advanced NSCLC of adenocarcinoma histology whose tumours express PD-L1. Nintedanib is added to docetaxel monotherapy at a dose of 200 mg or at a reduced dose of 150 mg twice daily. No stopping rules were applied to nintedanib; patients can remain on treatment after discontinuation of docetaxel for as long as clinical benefit is observed. The justification for not implementing a stopping rule similar to that of pembrolizumab (maximum treatment of two years) was not clear in the company submission. In response to the ERG's request for clarification, the company responded with the following reasoning:

- This assumption is in line with the LUME-Lung 1 trial comparing nintedanib in combination with docetaxel with docetaxel monotherapy. This trial did not include a similar stopping rule on the maximum duration of treatment. The mean duration of nintedanib treatment in patients with adrenocarinoma in LUME-Lung 1 trial was 4.2 months.
- In the economic model, only 0.33% of patients in the nintedanib plus docetaxel arm were still in the pre-progression state at two years. The company suggested that the impact of stopping rule on this treatment arm would be minor.

The company also provided a scenario analysis of implementing a 2-year stopping rule for the nintedanib plus docetaxel arm. The impact on the ICERs was shown to be very small (company clarification response, Table 24).

The company excluded other comparators that were listed in the NICE scope for the following reasons:

- Nivolumab, ramucirumab with docetaxel, and ceritinib (only for patients with ALK positive mutations) were not considered to be relevant comparators because they are subject to ongoing NICE appraisal and have not yet been recommended by NICE.
- Best supportive care was not considered to be a relevant comparator because it is only offered when no other active treatments are available.

The ERG's clinical advisor is satisfied with the justifications provided by the company and is in agreement with the exclusion of these comparators.

5.2.5 Perspective, time horizon and discounting

The company states that the economic evaluation has adopted an NHS and Personal Social Services perspective. However, outcomes and costs related to personal and social services had not been considered. The time horizon was set at 20 years to capture costs and outcomes over lifetime. In the base case, over 99% of the modelled population have died by the end of the 20-year time horizon. In line with the NICE reference case, costs and outcomes were discounted at 3.5% per annum.

5.2.6 Treatment effectiveness and extrapolation

For the base case, the relative treatment effectiveness between pembrolizumab and docetaxel was based on data from KEYNOTE-010. For the sub-group of patients with adrenocaricnoma, a network meta-analysis as carried out to estimate the relative treatment effectiveness between pembrolizmab, docetaxel, and nintedanib with docetaxel. The ERG considered the approach to the NMA appropriate. However, the NMA was limited by a small number of available studies and uncertainties about the heterogeneity between the included studies.

Overall, the ERG considers a lack of clarity in the company submission on how trial and external data have been incorporated into the model. The company provided a response to the ERG's request for further information via the clarification process. A summary of the company's base case survival modelling approaches is presented in Table 24.

Table 24 Summary of the company's base case survival modelling approaches

	All population		Adenocarcinoma population		
	Pembrolizumab	**Docetaxel**	**Pembrolizumab**	**Docetaxel**	**Nintedanib + Docetaxel**
Base case 1	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS:** HR applied to the docetaxel PFS curve
	OS: KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001	**OS:** KEYNOTE-010 KM adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** KEYNOTE-010 KM data to week 52, followed by the exponential curve fitted to KEYNOTE-001	**OS:** KEYNOTE-010 KM adjusted for switching using the two-stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010	**OS:** HR applied to the docetaxel OS curve
Base case 2	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS**: KEYNOTE-010 KM data to week 9, followed by the generalised gamma curve fitted to KEYNOTE-010	**PFS:** HR applied to the docetaxel PFS curve
	OS: KEYNOTE-010 KM data to week 52, followed by the	**OS:** KEYNOTE-010 KM adjusted for switching using the two-	**OS:** KEYNOTE-010 KM data to week 52, followed by the	**OS:** KEYNOTE-010 KM adjusted for switching using the two-	**OS:** HR applied to the docetaxel OS curve

	All population		Adenocarcinoma population		
	Pembrolizumab	**Docetaxel**	**Pembrolizumab**	**Docetaxel**	**Nintedanib + Docetaxel**
	exponential curve fitted to KEYNOTE-010	stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010	exponential curve fitted to KEYNOTE-010	stage method to week 52, followed by the exponential curve fitted to KEYNOTE-010	

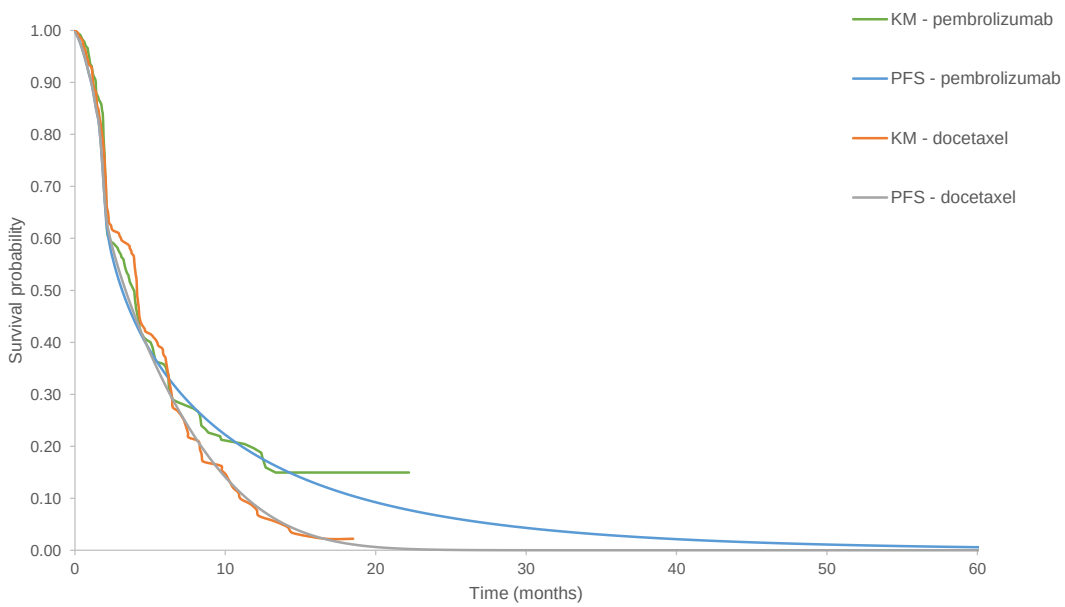
Source: adapted from company response to ERG clarification request, Table 18

Progression-free survival

The company used data from KEYNOTE-010 for the extrapolation of PFS for patients in the pembrolizumab and the docetaxel monotherapy arms. The company first tested the proportional hazard assumption, and concluded that the assumption did not hold and that separate models should be fitted to data from the pembrolizumab and docetaxel arms from KEYNOTE-010.

In KEYNOTE-010, the first tumour assessment was performed at week 9; therefore, the PFS of pembrolizumab and docetaxel overlap for the first nine weeks. The company fitted separate parametric curves (exponential, Weibull, log-normal, log-logistic, Gompertz a generalised gamma distributions) to the two arms of the observed PFS data from KEYNOTE-010. Model fit was assessed using visual inspection and the Akaike Information Criterion (AIC)/Bayesian Information Criterion (BIC) statistics. The company considered the generalised gamma distribution to best fit the data. As a result, KEYNOTE-010 KM data were used to week 9 and generalised gamma curves fitted to KEYNOTE-010 were used from week 9 onwards. This cut-off point of nine weeks was subsequently tested in a scenario analysis (scenario 11) and appears to have minimal impact on the ICER. The fitted PFS data for both treatment arms is shown in Figure 7.

In the sub-group analysis of patients with adrenocarcinoma, PFS for the nintedanib with docetaxel arm was calculated by applying the hazard ratio estimated from the NMA to the docetaxel monotherapy PFS curve.



Source: Figure 48, page 179, of the company submission

Figure 7 Base case 2-phase piecewise models for PFS of pembrolizumab and docetaxel based on KEYNOTE-010

Overall survival

The company first tested the proportional hazard assumption, and concluded that the assumption did not hold and that separate models should be fitted to data from the pembrolizumab and docetaxel arms from KEYNOTE-010. However, the fitting of separate standard parametric curves resulted in clinically implausible projections and did not provide good visual fit. Subsequently, a piecewise model – using KM data from KEYNOTE-010 and external data from non-comparative studies with longer-term follow up – was adopted and deemed appropriate.

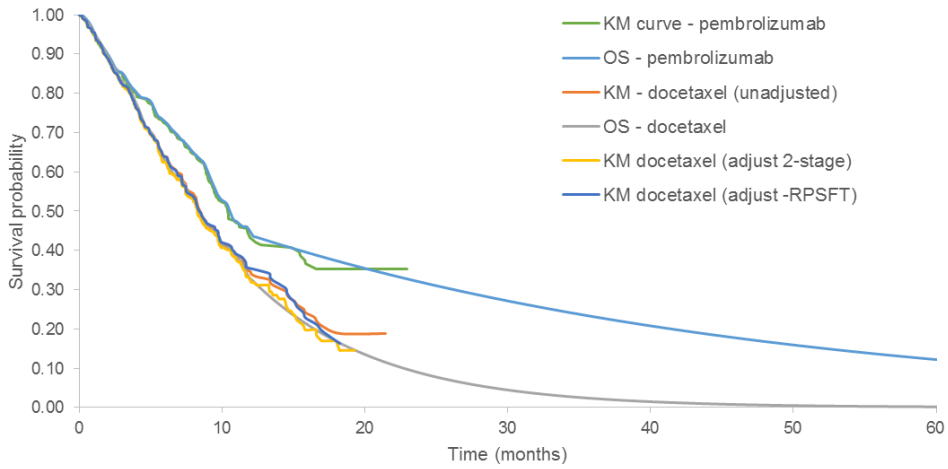
Based on different approaches to OS extrapolation, two base cases were assessed (Figures 8 and 9):

- ***Base case 1*** In the pembrolizumab arm, the KM data from KEYNOTE-010 up to the first 52 weeks were used. In the second phase, an exponential curve fitted to data from KEYNOTE-001 was used from 52 weeks onwards. In the docetaxel arm, the KM data from KEYNOTE-010 up to the first 52 weeks were used. In addition, adjustment for switching (the company considered the two-stage method

to be the most appropraite) was also applied. In the second phase, an exponential curve was fitted to data from KEYNOTE-010 was used from 52 weeks onwards.

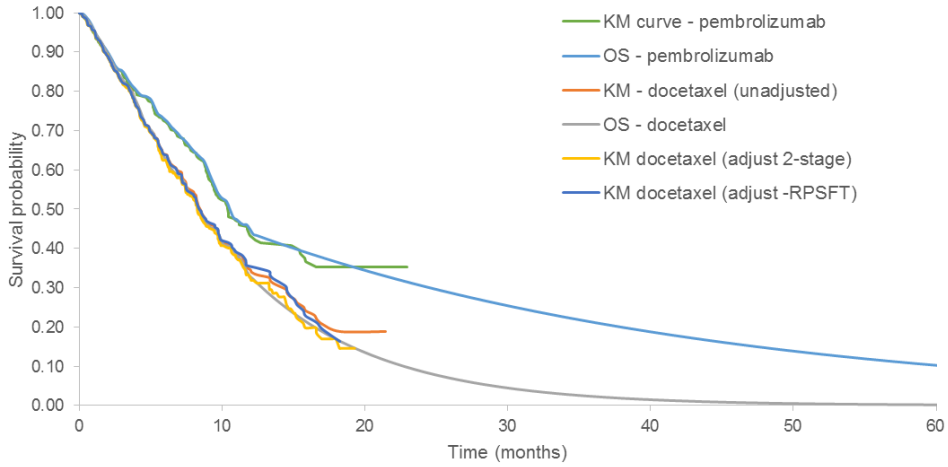
- ***Base case 2*** In the pembrolizumab arm, the KM data from KEYNOTE-010 up to the first 52 weeks were used; this was similar to base case 1. In the second phase, contrary to base case 1, an exponential curve fitted to data from KEYNOTE-010 was used from 52 weeks onwards. For the docetaxel arm, the extrapolation approach used remains the same as that to base case 1.

The ERG is satisfied that the company has followed the general approach to survival analysis and extrapolation of individual participant data recommended by NICE DSU. However, due to the absence of long-term survival data comparing pembrolizumab with docetaxel, much uncertainty remains with the estimated OS.



Base case 1 – KM+exponential+projection based on KEYNOTE-001 for pembrolizumab arm vs. KM+exponential for docetaxel arm, with OS for docetaxel adjusted using the two-stage method. Source: Figure 38, page 172, of the company submission

Figure 8 Projected OS for pembrolizumab and docetaxel – Base case 1



Base case 2 – KM+exponential for both pembrolizumab and docetaxel arms, with OS for docetaxel adjusted for switching using the two-stage method. Source: Figure 39, page 173, of the company submission

Figure 9 Projected OS for pembrolizumab and docetaxel – Base case 2

The 52-week cut-off point at which KM data switched to parametric curves was arbitrary. The company explored alternative cut-off points to the 52-week cut-off used in the base cases (1 and 2), for switching from KM data to parametric curves. Cut-off points of 62 and 72 weeks were also explored. As the time to the KM cut-off point increased, the number of at-risk patients reduced. The company stated that the 52-week cut-off "*provided a good balance of robust KM data to be used in the first phase and enough remaining KM data to be used to fit an exponential curve in the second phase*". The fitted 2-phase piecewise models for these cut-off points are shown in Figure 36, page169, of the company submission. Further, the company described this cut-off to provide a plausible visual fit and the most conservative estimates. The impact of alternative cut-off points on ICERs was inconsistent. These were presented in scenario analysis 9 (62-week cut off) and scenario 10 (72-week cut off).

In addition to KEYNOTE-010, OS extrapolation based on an alternative longer-term OS data source was tested in a scenario analysis. In this scenario analysis, the company used the two-phase piecewise method for OS extrapolation for the first two years as per the base case. From year 2 onwards, parametric curve-fitted data based on the National Lung Cancer Audit (NLCA) registry was used.

Firstly, the number of NSCLC registry patients with stage IIB, IV and IIB/IV were estimated from the NLCA audit report. Secondly, OS curves from the NLCA were digitised to generate pseudo patient-level data from published literature. Thirdly, the registry data were 'rebased' at two years – i.e. only patients with OS >2 years were included in the analysis; OS time rebased is the difference between OS time minus two years. Finally, parametric curves were fitted to this data.

For the sub-group analysis of the patients with adrenocarinoma, the OS in the nintedanib with docetaxel arm was estimated by applying the hazard ratio from the NMA to the docetaxel monotherapy OS curve.

Adverse events

The company's model included all Grade 3+ AEs and those that occurred in at least 5% of patients in KEYNOTE-010. In addition, consistent with previous NICE appraisals, the model also included diarrhoea Grade 2. Febrile neutropenia was also included based on clinical advice suggesting potential significant impact on quality of life and costs. Incidences of AEs are detailed in Table 70, page180, of the company submission.

Costs and disutilities were assumed to be the same for each individual AE for both treatment arms, in line with previous NICE submissions. Adverse events costs were incorporated in the model by estimating the weighted average costs per patient and applying this as a one-off cost in the first cycle of the model. Health disutilities as a result of AEs were assumed to be accounted for in the EQ-5D utility values from KEYNOTE-010. The ERG considers this a reasonable approach to account for AEs in the model.

Subsequent treatment

Only one line of subsequent treatment was modelled, the company justified this to be due to the advanced nature of NSCLC and the lack of data on subsequent lines. Data from KEYNOTE-010 was used to estimate the proportion of patients receiving various subsequent treatment in each arm. The type and distribution of subsequent treatments observed in KEYNOTE-010 are detailed in Table 71 (page 181 of the company submission). In the economic model, patients in the progressed health state

were assumed to incur the cost of subsequent treatment as observed in KEYNOTE-010 at a mean duration of 3.3 months. Clinical benefits were assumed to be accounted for in the analysis of KEYNOTE-010 data. Since the OS projection for docetaxel accounted for switching adjustment in the model, the costs of anti-PD1 agents in this arm were not included in the model.

Validation from clinical experts

The 5-year, 10-year and 20-years OS extrapolation from the company's model is shown in Table 25. The company presented these data to two clinical experts and there were agreement that the 5-year survival estimates for pembrolizumab and docetaxel, and 10-year survival estimates for docetaxel were acceptable and in line with their expectations. However, there were inconsistencies between their views on the 10-year survival estimates for pembrolizumab.

Table 25 Comparison of the OS rates at 5, 10 and 20 years with the alternative extrapolation scenarios included in the cost-effectiveness model

	Base case 1 Based on KEYNOTE-001 data (KM up to week52+Exponential up to 2 years +KEYNOTE-001 projection afterwards; Exponential best AIC/BIC fit)		**Base case 2** Conservative (KM+exponential only)	
	Pembro	**Docetaxel**	**Pembro**	**Docetaxel**
-5-year OS	12.15%	0.16%	10.18%	0.16%
-10-year OS	2.46%	0.00%	1.65%	0.00%
-20-year OS	0.10%	0.00%	0.04%	0.00%
	NLCA - Chemo PS0-1 patients stage IIIb/IV No rebase		**NLCA - Stage IIIb/IV patients** No rebase	
	Pembro	**Docetaxel**	**Pembro**	**Docetaxel**
-5-year OS	11.45%	3.25%	12.04%	3.42%
-10-year OS	8.86%	2.51%	7.70%	2.18%
-20-year OS	6.29%	1.78%	4.85%	1.38%

Source: Table 108, page 247, of the company submission.

5.2.7 Health-related quality of life

Health-related quality of life was derived from EuroQol EQ-5D questionnaires completed by the KEYNOTE-010 patients. The EQ-5D was administered up to six times whilst patients were receiving treatment (at treatment cycles 1, 2, 3, 5, 9 and 13) and once after treatment discontinuation (30 days after discontinuation). Data from the full analysis set population, of the pembrolizumab 2 mg/kg Q3W arm and docetaxel arm in KEYNOTE-010 were analysed (cut-off date 30 September 2015). Only completed records were used in the analysis. Missing data at baseline was 7% in the pembrolizumab arm and 19% in the docetaxel arm. At week 36, 51.7% was missing in the pembrolizumab arm and 84.9% in the docetaxel arm.

Patients' health-related quality of life was estimated as a function of length of time until death; these were considered separately for pre-progression and post-progression health states. As a result, four health states were used to estimate QALYs in the model: pre-progression and <30 days to death; pre-progression and >30 days to death; post-progression and <30 days to death; and post-progression and >30 days to death. A summary of these utilities is presented in Table 26.

Table 26 Mean utilities scores

Base case analysis		
	Mean	**95% CI**
Pre-progression		
≥ 30 days	0.763	(0.751, 0.774)
< 30 days	0.284	(0.136, 0.433)
Post-progression		
≥ 30 days	0.675	(0.644, 0.705)
< 30 days	0.320	(0.052, 0.588)

In the base case, time to death utilities were pooled values from the pembrolizumab 2 mg/kg Q3W and docetaxel arms from KEYNOTE-010. The company justified this approach based on no statistical or clinical significant differences in quality of life between these two arms. An age-adjusted annual utility decrement of 0.0044 was applied annually from the age of 62 to 75 years to reflect the natural decrease in

health utilities with increasing age. At the request of the ERG during the clarification process, the company clarified that no additional annual decrements were added to patients above 75 years. This implies that patients aged 75 years and above would have the same age-related utility decrements.

Reports of HRQoL were sought by searching MEDLINE, EMBASE, NHS Economics Evaluation Database (NHS EED), HTA database, DARE and EconLit in May 2015 and updated in March 2016 for studies published from 1995 in English. In addition, ISPOR and ASCO conference proceedings were manually searched for the previous 3 years. The NICE website was also consulted for relevant reports. The search strategies are documented in full in Appendix 23 of the company submission. The searches combined two search facets using the Boolean operator AND: non small cell lung cancer; and HRQoL and utilities. A comprehensive range of terms were included in the search strategies although the NSCLC facet of the search was restricted by the inclusion of staging/ metastasis/advanced cancer related terms

The original search carried out in 2015 identified 44 studies; an updated search was carried out in 2016 focused on studies reporting health-related quality of life using EQ-5D found one additional study. Details of these studies are presented in Table 77 (pages 191-195 of the company submission). The company submission provided a summary of the key differences between the utility values derived from the literature and those reported in KEYNOTE-010. For the progression-free health state, the estimated health utilities were generally consistent from the two sources. However, greater differences in estimated health utilities were found for the post-progression health state. In particular, two studies reported health utilities of 0.217 and 0.22 for progressed health states.[75, 76] However, the company explained that this may be due to the studies assessing utilities from healthy volunteers instead of NSCLC patients.

The search did not identify any utilities combining time to death and progression status in the search. This approach has only previously been used in patients with melanoma. The company reported that a Dutch study[77] has reported similar declines in health-related quality of life for NSCLC patients towards the final three months of life to be consistent with patients from KEYNOTE-010 who were <30 days to death.

However, the company also highlighted some '*significant differences*' in patient characteristics between the Dutch study and KEYOTE-010.

The company also presented utility results from previous NICE submissions, with similar patient populations to this submission and KEYNOTE-010. This is shown in Table 27. Health utility for the pre-progression states from KEYNOTE-010 was in line with those reported in other NICE submissions. However, for the post-progression state, health utilities from previous submissions tend to be lower than that reported in KEYNOTE-010.

Table 27 Progression-based utilities presented in recent advanced NSCLC submissions vs. those estimated from KEYNOTE-010

	Nintedanib+ docetaxel (TA347)	Nivolumab [ID811]	Nafees et al.[78] (Utilities preferred by the ERG during the appraisal of nivolumab)	Chouiaid et al[79].	KEYNOTE-010 [ID840]
Pre-progression	0.71 (week 0) to 0.661 (week 30)	0.75	0.65	0.74	0.753
Post-progression	0.64	0.592	0.43	0.46	0.664

Source: Table 79, page 198, of the company submission.

The ERG considers the company's approach in estimating patients' health-related quality of life as a function of length of time until death separately for pre-progression and post-progression to be appropriate. In addition, the ERG found the systematic review of relevant health-related quality of life data to be helpful.

Adverse events

The company's model included grade 3+ AEs and any grade AEs occurred in at least 5% of patients in either treatment arm. There were two exceptions: diarrhoea grade 2 and febrile neutropenia. In the model, it was assumed that any utility decrements associated with AEs would have been already captured in the EQ-5D scores from KEYNOTE-010; therefore no further utility decrements were applied to the model. The company considered this approach to be conservative and favours the docetaxel arm, which has higher occurrences of AEs. The company also carried out a scenario

analysis in which AE-related health disutilies were considered; this resulted in a lower ICER than base case.

5.2.8 Resource use and costs

The costs considered in the model included: drug and administration costs, cost of PD-L1 expression testing for patients treated with pembrolizumab, costs of subsequent therapies, monitoring and management of the disease, management of AEs and the costs related to terminal care.

The company carried out a systematic review to identify resource use and costs associated with the treatment of advanced NSCLC from the UK perspective. The search strategy that was used to identify cost-effectiveness studies (detailed in Section 5.2.1) was also used to identify resource use and costs data. The study inclusion and exclusion criteria, with rationale, are listed in Appendix 26 of the submission.

The company reported 14 studies included in the review, which are described in Appendix 27 of the submission. However, this was not consistent with the PRISMA diagram from Figure 50, page 203, of the company submission, which reported 12 studies from original 2015 search plus one additional study from the updated search in 2016.

Overall, these studies reported a wide range of resource use and costs data related to the management of advanced NSCLC in the UK setting. The company commented that these studies were undertaken between 2004 and 2010. Therefore, the resource use and cost data reported in many of these studies may be considered to be out of date and not applicable to the current UK setting.

Drug acquisition costs

Pembrolizumab was assumed to be administered as per the anticipated licence, at a dose of 2 mg/kg as a 30-minute IV infusion, every 3 weeks until disease progression or unacceptable toxicity. The list price of a 50mg vial is £1315. The model assumes no vial sharing. Based on the weight distribution of KEYNOTE-010 patients from the European sites, it was estimated that the mean number of vials per patient per cycle is 3.39; this corresponds to a total drug cost of £4453.13 per patient per administration.

In the model, the maximum pembrolizumab treatment duration was assumed to be two years.

The company is offering a Patient Access Scheme (PAS). This is a simple discount of [redacted] to the list price of pembrolizumab. This results in a drug cost per patient, per cycle of [redacted]. The PAS price of pembrolizumab is used in all of the company's cost-effectiveness analysis.

Docetaxel was assumed to be administered at a dose of 75mg/m^2 per cycle. The prices of docetaxel formulations available in the UK vary according to dose per vial. The company used the price based on a 140mg vial (£20.95 as reported in eMIT) to estimate the cost of docetaxel. Compared with other available dosages per vial and with the prices reported in MIMS, this gave the lowest docetaxel price per mg. In addition, full vial sharing was assumed; the company described this as a conservative assumption. Based on the average BSA of KEYNOTE-010 patients from the European sites and weighted according to sex, it was estiatmed that the total drug cost of docetaxel per patient per administration was £20.60. In the model, the maximum docetaxel treatment duration was assumed to be 18 weeks (of six cycles).

In the model, PFS from KEYNOTE-010 was used as a proxy for time on pembrolizumab and docetaxel treatment. The exception is when discontinuation due to AEs and other reasons occur before disease progression. In KEYNOTE-010, the time on treatment was 4.97 months in the pembrolizumab arm and 2.66 months in the docetaxel arm. The company calculated HRs for time on treatment vs PFS (Table 28); these were used to estimate the proportions of patients on treatment based on proportion of patients who are progression-free in each cycle for pembrolizumab and docetaxel. On average, 90.75% of patients on pembrolizumab and 77.15% of patients on docetaxel received their planned dose.

Table 28 Hazard ratios for time on treatment versus progression free survival for pembrolizumab 2mg/kg and docetaxel based on KEYNOTE-010

Hazard ratio (time on treatment vs progression free survival)	Mean	Confidence interval
Pembrolizumab (2mg/kg) – overall population	1.039	(0.876, 1.232)
Docetaxel - overall population	2.078	(1.751, 2.466)
Pembrolizumab (2mg/kg) – adenocarcinoma	1.033	(0.839, 1.271)
Docetaxel - adenocarcinoma	1.982	(1.611, 2.439)

Source: Table 85, page 207, of the company submission

Nintedanib

For the sub-group of patients with adenocarcinoma histology, the company also considered nintedanib in combination with docetaxel. Nintedanib was assumed to be administered at a dose of 200 mg (standard dose) or 150 mg (reduced dose) twice daily, orally. The list price of nintedanib is £2151.10 for 100 mg x120-pill pack, and for 150 mg x 60-pill pack. Regardless of standard dose or reduced dose, the cost per patient per day is £71.70; this was the cost used in the model. Although a lower dose of 100 mg twice daily is available to patients with AEs, the proportion of patients who would be on this dose is unknown; this was not taken into account in the model. A patient access scheme (PAS) is currently in place for nintedanib, but the level of discount is unknown. Patients on nintedanib combined with docetaxel were assumed to take nintedanib until disease progression in the model.

In the model, the company assumed that patients would continue to receive nintedanib after discontinuation of docetaxel for as long as they remain progression-free. The same maximum number of docetaxel cycles was assumed for the combination.

The ERG notes that treatment costs (including the costs of PD-L1 testing) represents 84% and 85% of the incremental costs in base cases 1 and 2, respectively. Therefore, only the cost of treatment and the duration of treatment could result in any meaningful impact on the incremental costs between the treatments.

Administration costs

Pembrolizumab and docetaxel are both administered via IV infusion, for 30 and 60 minutes, respectively, every 3 weeks. The company assumed the same administration costs for both treatments at £257.11 per administration. This was based on NHS Reference costs 2014/15 (SB12Z code for delivering 'simple parenteral chemotherapy – outpatient). Nintedanib is taken orally, while patients are taking docetaxel, there are assumed to be no costs associated with administering nintedanib. However, once docetaxel treatment has stopped the administrative costs of patients continuing with nintedanib is assumed to be 12 minutes of pharmacist time every 30 days at a cost of £20. The ERG considers these costs to be appropriate.

PD-L1 test costs

The company anticipates that pembrolizumab will be licenced to treat NSCLC patients that are PD-L1 positive, as identified by a valid test. The costs of PD-L1 tests were included in the model. The company estimated that 12% of NSCLC stage IIIB/IV to be eligible for treatment with pembrolizumab in England, and that to identify one patient eligible for treatment, 8.39 would need to be tested for PD-L1. A single test was estimated to be £40.50, which equates to £337.51 per patient with advanced NSCLC whose tumour expresses PD-L1 and eligible for second- or third-line pembrolizumab (Table 87 and Section 6.2 of the company submission).

Subsequent therapies after treatment discontinuation

On discontinuation of treatment, patients may receive subsequent oncologic therapies; this was observed in KEYNOTE-010. A weighted average cost of subsequent treatment was calculated from the weight proportion of patients with each subsequent treatment and unit cost for a treatment duration of 14.4 weeks. This weighted cost was applied during 14.4 cycles to those who moved to post-progression health states.

Monitoring and disease management costs

The company used data from TA374 (NICE MTA for erlotinib and fefitinib) to estimate costs of each of the three health states in the model.[19] The company assumed weekly costs of £66.49 for pre-progression health state. This includes visits to oncologist, blood and biochemical tests and CT scans; in the docetaxel arm, an

additional £10.64 GP visit was also included. Details are provided in Table 88, page 210, of the company submission). The company assumed weekly cost of £35.64 for post-progression health states. This includes visit to oncologist, blood and biochemical tests and CT scans. Details are provided in Table 89, page 211, of the company submission. One-off costs at treatment initiation (£730.88 -Table 90, page 211, of the company submission), upon disease progression (£128.84 - Table 91, page 212 of the company submission) and for terminal care at the moment of dying (£3757.94 - Table 93, page 214, of the company submission) were also included in the model. Although the source of these costs were provided in Appendix 27 of the company submission, the ERG was unable to verify the source for the one-off treatment initiation cost

The resource use for treatment initiation, a one off cost, is presented in Table 29 below and is sourced from Iain et al, 2015. The ERG notes that there was no reference number for this study in the report and it wasn't included in Appendix 27, *Characteristics of the cost and resource utilisation studies identified*, of the submission.

Adverse events

The company includes Grade 3+ AEs observed during KEYNOTE-010 plus two others. Unit costs were mainly sourced from a previous NICE MTA (TA374)[19] and inflated to 2014/15 prices using the hospital and community health service index. When no data were available from TA374 data from two recent NICE appraisals was used (ID811, TA347).[18, 74] The unit cost per AE used in the company's model is presented below in Table 29. The ERG notes that for asthenia the model cost reported in the table below was £2,317.20; however, in the model the cost used was £3,015.13 – the cost reported for ID811in the table below. The ERG believes the impact on the ICERs would be immaterial.

Table 29 Unit cost per AE as used in previous submissions and values used in the de novo model

	Erlotinib & gefitinib TA374	Nivolumab (ID811)	Nintedanib (TA347)	Unit costs used in the de novo model	Sources
Unit used to inflated to 2014-15 using PSSRU HCHS indices	**1.04**	**1.00**	**1.02**		*Curtis and Burns (2015)* [171]
Alopecia/ Hair loss	£0.00			£0.00	TA374[64]
Anaemia			£2,610.66	£2,610.66	*TA347*[63]
Asthenia		£3,015.13		£2,317.20	*ID811*[121]
Decrease appetite				£0.00	Assumed 0
Diarrhea (grade 2)			£442.76	£442.76	TA374[64]
Diarrhea (grade 3-4)	£1,090.19		£2,108.73	£1,090.19	TA374[64]
Fatigue	£2,317.20	£3,015.13	£2,610.66	£2,317.20	TA374[64]
Nausea	£1,090.19		£2,038.34	£1,090.19	TA374[64]
Neuropathy peripheral				£0.00	Assumed 0
Neutropenia	£179.83	£354.72	£560.08	£179.83	TA374[64]
Neutrophile count decreased				£179.83	Assumed to be the same as neutropenia
Pruritus					Assumed 0
Pyrexia				£0.00	Assumed 0
Rash	£113.89		£2,433.15	£113.89	TA374[64]
Stomatitis				£0.00	Assumed 0
Vomiting			£2,038.34	£2,038.34	TA347[63]
WBC count decreased			£560.08	£560.08	TA347[63]
Febrile neutropenia	£7,331.78		£2,339	£7,331.78	TA374[64]

Source: Table 94 of the company submission

5.2.9 Cost-effectiveness results

The deterministic results for base case 1 and base case 2, taking into account the PAS are shown in Table 30. In base case 1, compared with docetaxel monotherapy, pembrolizumab was associated with an additional 1.03 life year and 0.70 QALY at an additional cost of £30,242 per patient. The incremental cost per QALY gained for pembrolizumab compared with docetaxel monotherapy was £43,351. In base case 2, compared with docetaxel monotherapy, pembrolizumab was associated with an additional 0.90 life years and 0.61 QALYs at an additional cost of £30,016. The

incremental cost per QALY gained for pembrolizumab compared with docetaxel monotherapy was £49,048.

Table 30 De novo model base-case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£41,509	1.90	1.30	-	-	-
Docetaxel	£11,267	0.87	0.60	£30,242	0.70	£43,351
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£41,283	1.77	1.22	-	-	-
Docetaxel	£11,267	0.87	0.60	£30,016	0.61	£49,048
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Source: Table 96 of the company submission.

Adenocarcinoma sub-group

For the sub-group of patients with adenocarcinoma, the deterministic results for base case 1 and base case 2, taking into account the PAS are shown in Table 31. In both base cases, nintedanit with docetaxel was extendedly dominated. Pembrolizumab, when compared with docetaxel resulted in an ICER of £44,597 in base case 1 and an ICER of £31,657 in base case 2.

Table 31 Cost-effectiveness results adenocarcinoma subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER (£) vs. comparator	Incremental analysis
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£42,238	1.988	1.364	-	-	-	-
Nintedanib + Docetaxel	£23,732	1.204	0.836	£18,506	0.529	£34,997	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£29,444	0.660	£44,597	£44,597
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)							
Pembrolizumab	£43,014	2.442	1.659	-	-	-	-
Nintedanib + Docetaxel	£23,732	1.204	0.836	£19,282	0.823	£23,424	Extendedly dominated
Docetaxel	£12,794	1.016	0.704	£30,220	0.955	£31,657	£31,657
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years **Compared to the next less costly treatment* ***Compared to the next less effective treatment*							

Source: adapted from Table 97 of the company submission.

The company also presented ICERs of pembrolizumab compared with nintedanib with docetaxel over a range of possible discounts for nintedanib. These are shown in Table 32 below. However, the ERG noted that nintedanib combined with docetaxel combination was extendedly dominated, and therefore no longer a valid comparator.

Table 32 ICERs from the pairwise comparison for pembrolizumab vs. nintedanib + docetaxel (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts for nintedanib) – adenocarcinoma subgroup

Discount	Base case 1	Base case 2
0%	£34,997	£23,424
5%	£36,227	£24,214
10%	£37,457	£25,004
15%	£38,687	£25,794
20%	£39,917	£26,584
25%	£41,146	£27,374
30%	£42,376	£28,164
35%	£43,606	£28,954
40%	£44,836	£29,744
45%	£46,066	£30,534
50%	£47,295	£31,324
55%	£48,525	£32,114
60%	£49,755	£32,904
65%	£50,985	£33,694
70%	£52,215	£34,484
75%	£53,444	£35,274
80%	£54,674	£36,064
85%	£55,904	£36,854
90%	£57,134	£37,644
95%	£58,364	£38,434

Source: Table 98, page 220, of the company submission.

The estimated clinical outcomes of the model were presented alongside data from KEYNOTE-010 in Table 33. The model was shown to result in similar PFS and OS estimates to that of KEYNOTE-010 for the trial period.

Table 33 Comparison of model and trial outcomes

	Pembrolizumab				Docetaxel		
Outcome	**Base case 1**	**Base case 2**	**KEYNOTE-010**	**KEYNOTE-001**	**Base case 1**	**Base case 2**	**KEYNOTE-010**
% patients with PFS at 6 months	34.99%	34.99%	35.1%	36.10%	33.28 %	33.28 %	34.3%
% patients with PFS at 1 year	18.82%	18.82%	18%	-	9.23%	9.23%	9%
Median PFS (in months)	3.45	3.45	3.9	2.9	3.91	3.68	4
Median OS (months)	10.58	10.58	10.4	11.10	8.51	8.51	8.5
6-month OS	72.5%	72.5%	72.5%	64%	63%	0.6	64.2%
1-year OS	44%	44%	43%	49%	33%	33%	35%

Source: Table 99, page 221, of the company submission. The median OS for pembrolizumab in base case 1 has been corrected (from 10.81 in the submission to above value) following the company's clarification response to an ERG's query.

5.2.10 Sensitivity analyses

Probabilistic sensitivity analysis

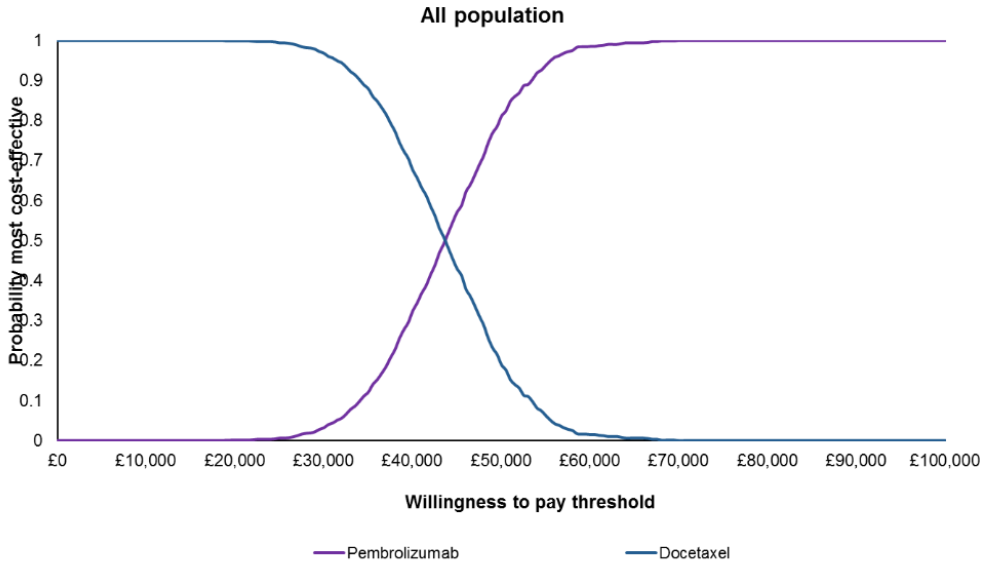
To assess the parameter uncertainty the company carried out probabilistic sensitivity analysis using 1,000 iterations. The distributions used are presented in Appendix 25 of the submission. The cost-effectiveness results (discounted, with PAS) are presented in Table 34 below.

Table 34 Cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS)

Technologies	***Total costs (£)***	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)					
Pembrolizumab	£41,538	1.304			
Docetaxel	£14,212	0.671	£27,326	0.634	£43,134
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)					
Pembrolizumab	£41,246	1.220			
Docetaxel	£11,283	0.604	£29,963	0.616	£48,667
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

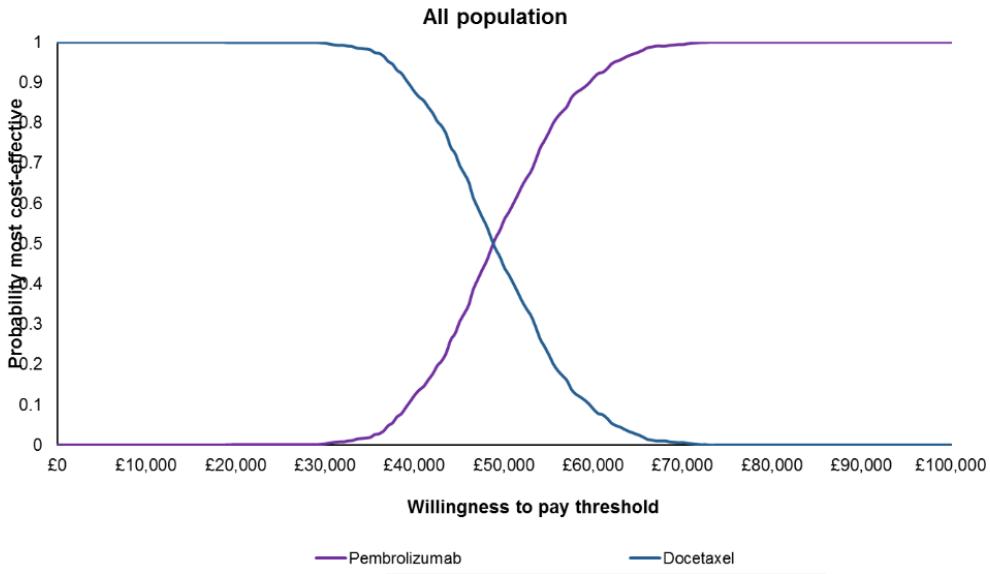
Source: Table 105, page 230, of the company submission.

For base case 1, the cost-effectiveness acceptability curve (CEAC) shows that there is an approximately 81.1% chance of pembrolizumab being cost effective compared to docetaxel at a threshold of £50,000 per QALY (Figure 10). For base case 2, the CEAC shows that there is an approximately 57.8% chance of pembrolizumab being cost effective copared to docetaxel at a threshold of £50,000 per QALY (Figure 11).



Source: Figure 61, page 231, of the company submission.

Figure 10 Cost-effectiveness acceptability curve (discounted, with PAS) base case 1



Source: Figure 63, page 232, of the company submission.

Figure 11 Cost-effectiveness acceptability curve (discounted, with PAS) base case 2

Adenocarcinoma sub-group

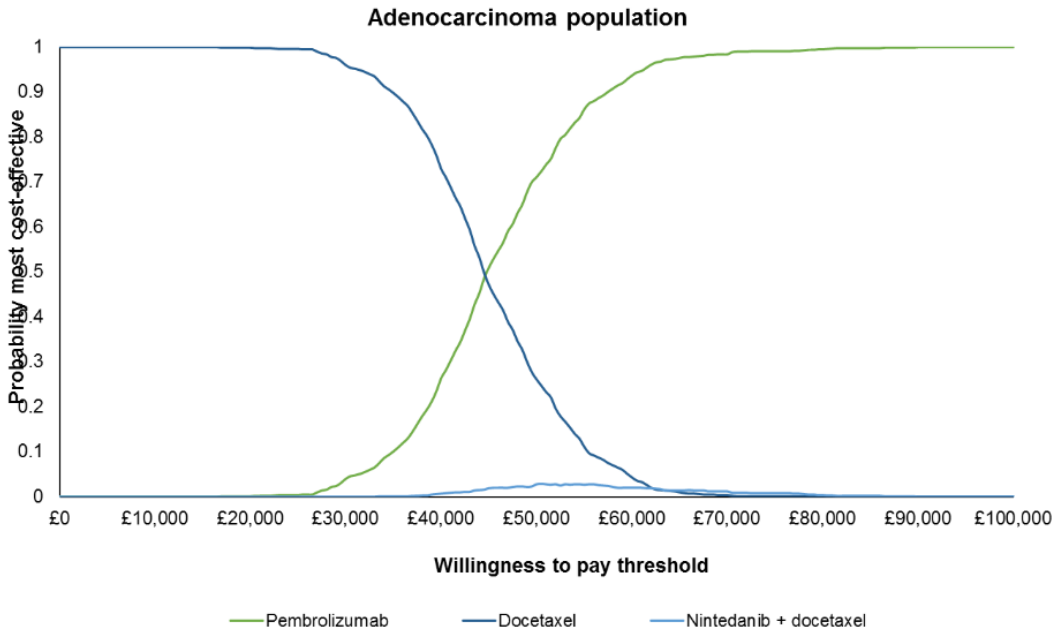
For the sub-group of patients with adenocarcinoma, the cost-effectiveness results from the probabilistic sensitivity analysis are presented in Table 35 below.

Table 35 Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS) – adenocarcinoma subgroup

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER (£) versus baseline	Incremental analysis
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£42,705	1.370				
Nintedanib + Docetaxel	£23,851	0.838	£18,854	0.532	£35,472	Extendedly dominated
Docetaxel	£12,803	0.705	£29,902	0.665	£44,964	£44,964
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)						
Pembrolizumab	£43,598	1.673				
Nintedanib + Docetaxel	£12,782	0.706	£30,816	0.967	£31,858	Extendedly dominated
Docetaxel	£23,922	0.839	£19,677	0.834	£23,590	£23,590
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years **Compared to the next less costly treatment* ***Compared to the next less effective treatment*						

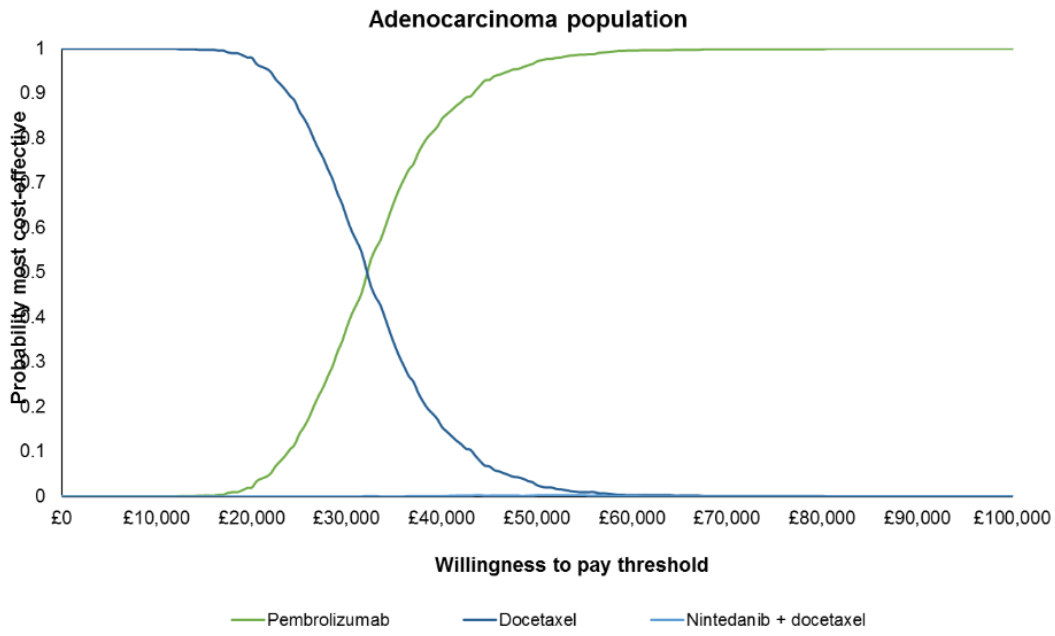
Source: Table 106 of the company submission.

In both base case 1 and base case 2 the nintedanib combined with docetaxel arm was extendedly dominated. Compared with docetaxel, pembrolizumab was associated with a QALY gain of 0.665 at an incremental cost of £29,902, resulting in an ICER of £44,964 in base case 1. In base case 2, this ICER was substantially lower at £23,590.



Source: Figure 65 of the company submission.

Figure 12 Cost-effectiveness acceptability curve base case 1 (discounted, with PAS)

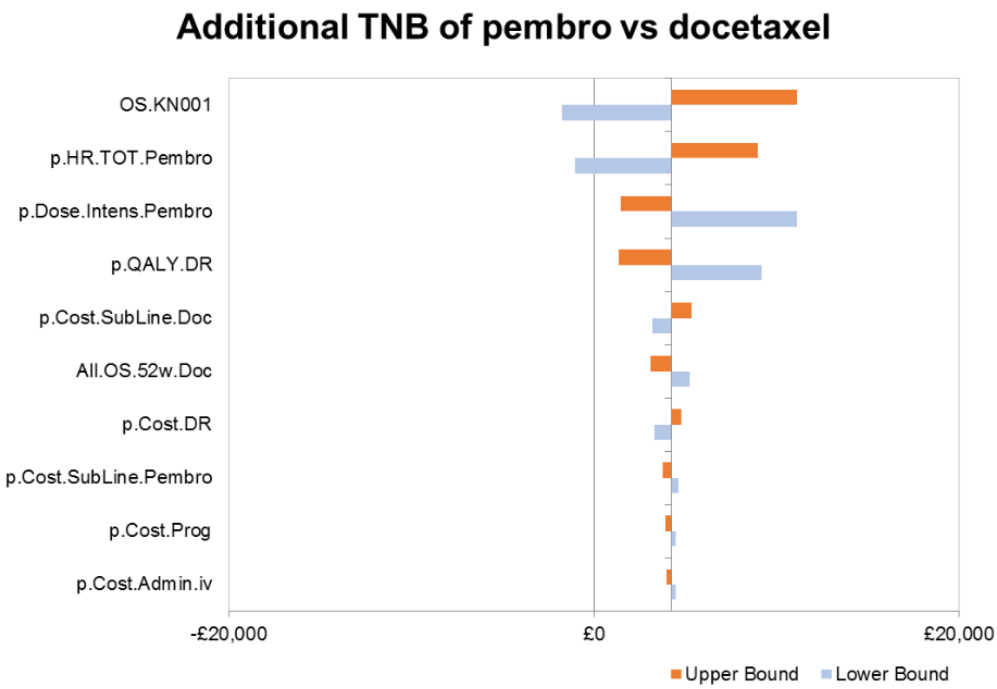


Source: Figure 67 of the company submission.

Figure 13 Cost-effectiveness acceptability curve base case 2 (discounted, with PAS)

Deterministic sensitivity analysis

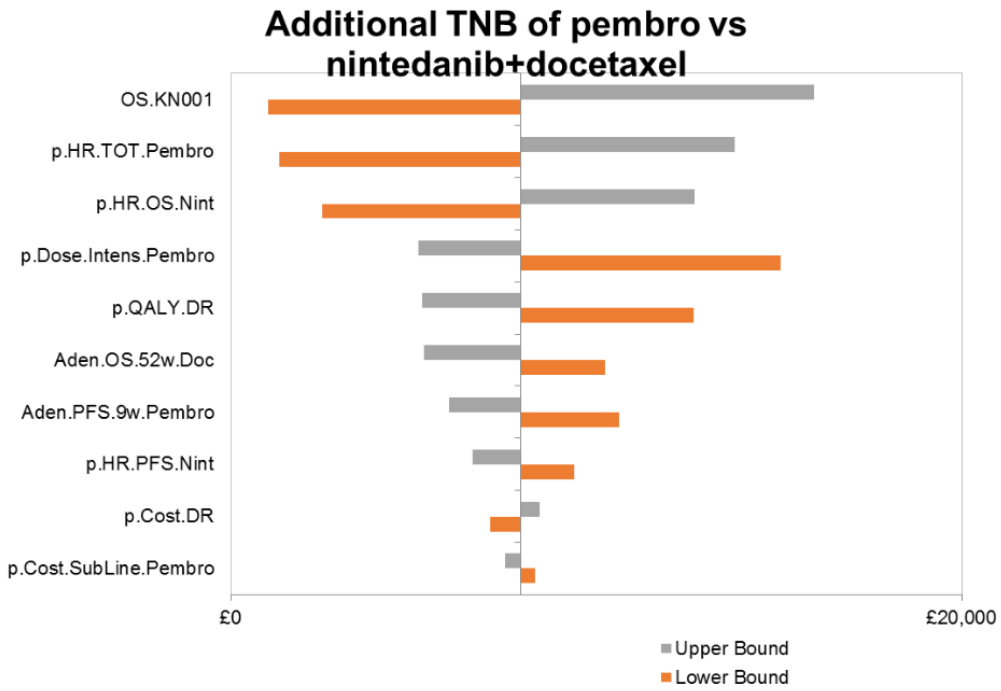
The company carried out deterministic sensitivity analyses using the 5% and 95% confidence intervals from 18 different parameters. Results for the 10 most influential parameters were presented as total net benefit in tornado diagrams for the comparison between pembrolizmab and docetaxel monotherapy (Figure 14), for the comparison between pembrolzumab and nintedanib combined with docetaxel in the adrenocarcinoma sub-group (Figure 15), and for the comparison between pembrolizumab and docetaxel monotherapy in the adrenocarcinoma sub-group (Figure 16). In each comparison, the results were most sensitive to extrapolation of pembrolizmab OS based on KEYNOTE-001, and the estimated hazard ratio for time on treatment vs PFS for pembrolizumab.



OS.KN001 = Extrapolation of pembrolizumab OS based on KEYNOTE-001; p.HR.TOT.Pembro = HR ToT vs. PFS for pembrolizumab; p.Dose.Intens.Pembro = Dose intensity for pembrolizumab; p.QALY.DR = Discount rate applied to QALYs; p.Cost.SubLine.Doc = Cost of subsequent treatments for the docetaxel arm; All.OS.52w.Doc = Exponential extrapolation of OS considering a 52 week cut-off; p.Cost.DR = Discount rate applied to costs; p.Cost.SubLine.Pembro = Cost of subsequent treatments for the pembrolizumab arm; p.Cost.Prog = Weekly cost associated to the post-progression health state; p.Cost.Admin.iv = administration costs assumed for pembrolizumab and docetaxel.

Source: Figure 68 of the company submission.

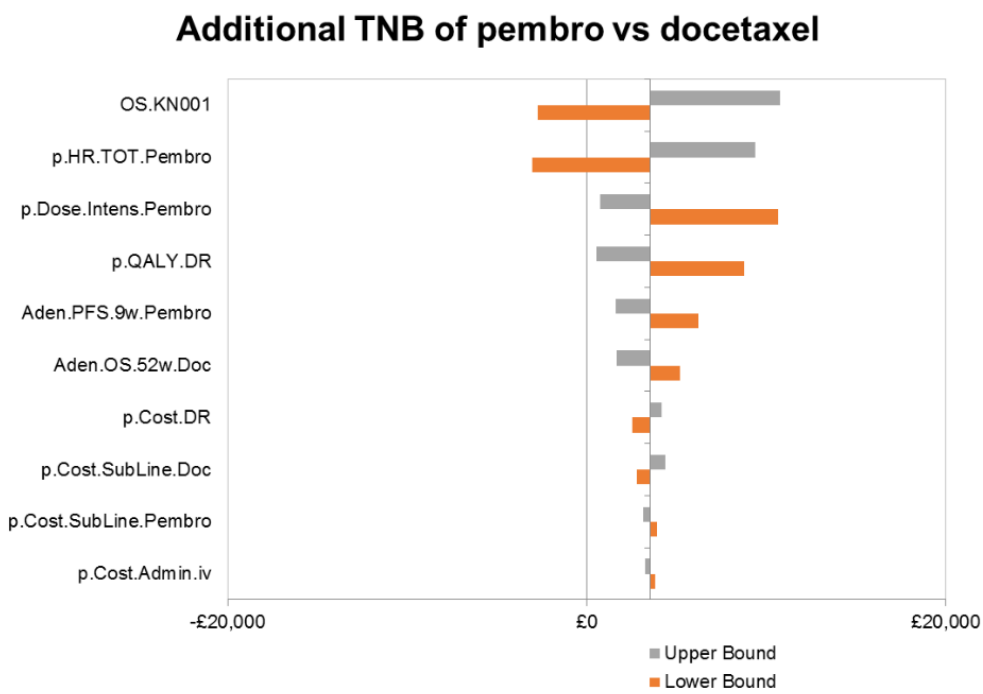
Figure 14 Tornado diagram presenting results of deterministic sensitivity analysis for 10 most sensible variables (discounted, with PAS)



OS.KN001 = Extrapolation of pembrolizumab OS based on KEYNOTE-001; p.HR.TOT.Pembro = HR ToT vs. PFS for pembrolizumab; p.HR.OS.Nint = OS HR for nintedanib+docetaxel vs. docetaxel; p.Dose.Intens.Pembro = Dose intensity for pembrolizumab; p.QALY.DR = Discount rate applied to QALYs; Aden.OS.52w.Doc = Exponential extrapolation of OS considering a 52 week cut-off; Aden.PFS.9w.Doc = Exponential extrapolation of of PFS considering a 9 week cut-off; p.HR.PFS.Nint = PFS HR for nintedanib+docetaxel vs. docetaxel; p.Cost.DR = Discount rate applied to costs; p.Cost.SubLine.Pembro = Cost of subsequent treatments for the pembrolizumab arm

Source: Figure 69 of the company submission.

Figure 15 Tornado diagram presenting results of the deterministic sensitivity analysis for 10 most sensible variables comparing pembrolizumab with nintedanib combined with docetaxel (discounted, with PAS)



OS.KN001 = Extrapolation of pembrolizumab OS based on KEYNOTE-001; p.HR.TOT.Pembro = HR ToT vs. PFS for pembrolizumab; p.Dose.Intens.Pembro = Dose intensity for pembrolizumab; p.QALY.DR = Discount rate applied to QALYs; Aden.PFS.9w.Doc = Exponential extrapolation of of PFS considering a 9 week cut-off; Aden.OS.52w.Doc = Exponential extrapolation of OS considering a 52 week cut-off; p.Cost.DR = Discount rate applied to costs; p.Cost.SubLine.Pembro = Cost of subsequent treatments for the pembrolizumab arm; p.Cost.Admin.iv = administration costs assumed for pembrolizumab and docetaxel.

Source: Figure 70 of the company submission.

Figure 16 Tornado diagram presenting deterministic sensitivity analysis results for 10 most sensible variables comparing pembrolizumab and docetaxel in the adenocarcinoma subgroup

Scenario analyses

The company carried out 11 scenario analyses to assess the uncertainty regarding some of the key assumptions of the model:

Scenario 1. Alternative approach to extrapolating OS – using NLCA registry data for chemotherapy dataset PS0-1 (no rebase for time of diagnosis)

Scenario 2. Alternative approach to extrapolating OS – using NLCA registry data for stage IIIB/IV dataset (no rebase for time of diagnosis)

Scenario 3. Cost of pembrolizumab based on full vial sharing

Scenario 4. Alternative approach to estimating utilities from KEYNOTE-010 – using progression-based utilities only

Scenario 5. Alternative approach to estimating utilities from KEYNOTE-010 – using time to death utilities only

Scenario 6. Consider disutilities associated with AEs based on KEYNOTE-010

Scenario 7. Removing age-adjustment for utilities

Scenario 8. Alternative cut-off times for the estimation of the exponential curve of the piecewise approach for OS – 52-week cut-off (base case)

Scenario 9. Alternative cut-off times for the estimation of the exponential curve of the piecewise approach for OS – 62-week cut-off

Scenario 10. Alternative cut-off times for the estimation of the exponential curve of the piecewise approach for OS – 72-week cut-off

Scenario 11. Alternative cut-off times for the estimation of the exponential curve of the piecewise approach for PFS – 28-week cut-off

Overall, these scenarios made small impact on the ICER. For base case 1, the ICERs ranged from £36,861 to £44,633. For base case 2 the ICER ranged from £38,731 to £49,881.

During the clarification process, the ERG requested further scenario analysis on different cut-off points for switching from KM data to parametric curves for OS extrapolation. The company provided additional analyses based on 26-week, 43-week, 52-week (base case), 61-week and 78-week cut-offs; this was only performed for base case 2. Details of the results are presented in the company's clarification document, Table 19.

In the adenocarcinoma, comparing pembrolizumab with docetaxel monotherapy, sub-group base case 1 the ICERs vary between £38,494 and £44,597 and base case 2 the ICERs vary between £27,309 and £49,195. There are more variations among these ICERs suggesting that they are less robust in the adenocarcinoma subgroup.

Table 36 Results from the scenario analyses

All population										
		Pembrolizumab			**Docetaxel**			**Pembro vs doc**		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 1		£41,509	1.8984	1.3017	£11,267	0.8670	0.6041	£30,242	0.6976	£43,351
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£42,300	2.4260	1.6317	£11,772	1.1783	0.8035	£30,528	0.8282	£36,861
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£42,148	2.3217	1.5666	£11,731	1.1500	0.7859	£30,417	0.7807	£38,959
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£39,639	1.8984	1.3017	£11,267	0.8670	0.6041	£28,372	0.6976	£40,670
Scenario 4	Progression-based utilites	£41,509	1.8984	1.2976	£11,267	0.8670	0.6118	£30,242	0.6858	£44,096
Scenario 5	Time to death utilities	£41,509	1.8984	1.3821	£11,267	0.8670	0.6269	£30,242	0.7552	£40,045
Scenario 6	Consider AE-related disutilities	£41,509	1.8984	1.2984	£11,267	0.8670	0.5693	£30,242	0.7290	£41,482
Scenario 7	Exclude age-related disutility	£41,509	1.8984	1.3189	£11,267	0.8670	0.6054	£30,242	0.7135	£42,386
Scenario 8	KM + exponential 52-week cut-off	£41,509	1.8984	1.3017	£11,267	0.8670	0.6041	£30,242	0.6976	£43,351
Scenario 9	KM + exponential 62-week cut-off	£41,517	1.9031	1.3048	£11,210	0.8342	0.5823	£30,307	0.7226	£41,943
Scenario 10	KM + exponential 72-week cut-off	£41,400	1.8352	1.2599	£11,214	0.8363	0.5836	£30,186	0.6763	£44,633
Scenario 11	PFS KM+exponential 28-week cut-off	£42,110	1.8984	1.3092	£11,287	0.8670	0.6042	£30,823	0.7050	£43,723
Base case 2		£41,283	1.7669	1.2160	£11,267	0.8670	0.6041	£30,016	0.6120	£49,048
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£42,191	2.3600	1.5889	£11,772	1.1783	0.8035	£30,419	0.7854	£38,731
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no	£42,046	2.2602	1.5266	£11,731	1.1500	0.7859	£30,315	0.7407	£40,925

	rebase for time for diagnosis)									
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£37,543	1.7669	1.2160	£11,267	0.8670	0.6041	£26,276	0.6120	£42,937
Scenario 4	Progression-based utilites	£41,283	1.7669	1.2135	£11,267	0.8670	0.6118	£30,016	0.6017	£49,881
Scenario 5	Time to death utilities	£41,283	1.7669	1.2870	£11,267	0.8670	0.6269	£30,016	0.6601	£45,470
Scenario 6	Consider AE-related disutilities	£41,283	1.7669	1.2127	£11,267	0.8670	0.5693	£30,016	0.6434	£46,652
Scenario 7	Exclude age-related disutility	£41,283	1.7669	1.2301	£11,267	0.8670	0.6054	£30,016	0.6246	£48,053
Scenario 8	KM + exponential 52-week cut-off	£41,509	1.8984	1.3017	£11,267	0.8670	0.6041	£30,242	0.6976	£43,351
Scenario 9	KM + exponential 62-week cut-off	£41,517	1.9031	1.3048	£11,210	0.8342	0.5823	£30,307	0.7226	£41,943
Scenario 10	KM + exponential 72-week cut-off	£41,400	1.8352	1.2599	£11,214	0.8363	0.5836	£30,186	0.6763	£44,633
Scenario 11	PFS KM+exponential 28-week cut-off	£41,884	1.7669	1.2235	£11,287	0.8670	0.6042	£30,597	0.6193	£49,407
Adenocarcinoma subgroup										
		Pembrolizumab			**Nintedanib + docetaxel**			**Pembro vs ninte+doc**		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 1		£42,238	1.9878	1.3644	£23,732	1.2043	0.8356	£18,506	0.5288	£34,997
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£43,074	2.5455	1.7132	£24,739	1.8299	1.2349	£18,336	0.4783	£38,333
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£42,913	2.4353	1.6444	£24,645	1.7657	1.1948	£18,268	0.4496	£40,634
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£38,404	1.9878	1.3644	£23,732	1.2043	0.8356	£14,672	0.5288	£27,747
Scenario 4	Progression-based utilites	£42,238	1.9878	1.3592	£23,732	1.2043	0.8392	£18,506	0.5200	£35,591
Scenario 5	Time to death utilities	£42,238	1.9878	1.4479	£23,732	1.2043	0.8765	£18,506	0.5715	£32,383
Scenario 6	Consider AE-related disutilities	£42,238	1.9878	1.3610	£23,732	1.2043	0.7977	£18,506	0.5634	£32,849

Scenario 7	Exclude age-related disutility	£42,238	1.9878	1.3826	£23,732	1.2043	0.8394	£18,506	0.5431	£34,071
Scenario 8	KM + exponential 52-week cut-off	£42,238	1.9878	1.3644	£23,732	1.2043	0.8356	£18,506	0.5288	£34,997
Scenario 9	KM + exponential 62-week cut-off	£42,368	2.0628	1.4139	£23,585	1.1190	0.7791	£18,783	0.6349	£29,585
Scenario 10	KM + exponential 72-week cut-off	£42,252	1.9956	1.3696	£23,744	1.2113	0.8402	£18,507	0.5294	£34,959
Scenario 11	PFS KM+exponential 28-week cut-off	£37,802	1.9878	1.3538	£24,067	1.2043	0.8365	£13,734	0.5173	£26,552
		Pembrolizumab			**Docetaxel**			**Pembro vs doc**		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 1		£42,238	1.9878	1.3644	£12,794	1.0160	0.7041	£29,444	0.6602	£44,597
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£43,074	2.5455	1.7132	£13,558	1.4894	1.0068	£29,516	0.7064	£41,784
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£42,913	2.4353	1.6444	£13,491	1.4434	0.9781	£29,422	0.6663	£44,160
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£38,404	1.9878	1.3644	£12,794	1.0160	0.7041	£25,610	0.6602	£38,790
Scenario 4	Progression-based utilites	£42,238	1.9878	1.3592	£12,794	1.0160	0.7099	£29,444	0.6493	£45,348
Scenario 5	Time to death utilities	£42,238	1.9878	1.4479	£12,794	1.0160	0.7371	£29,444	0.7108	£41,424
Scenario 6	Consider AE-related disutilities	£42,238	1.9878	1.3610	£12,794	1.0160	0.6695	£29,444	0.6916	£42,575
Scenario 7	Exclude age-related disutility	£42,238	1.9878	1.3826	£12,794	1.0160	0.7066	£29,444	0.6760	£43,556
Scenario 8	KM + exponential 52-week cut-off	£42,238	1.9878	1.3644	£12,794	1.0160	0.7041	£29,444	0.6602	£44,597
Scenario 9	KM + exponential 62-week cut-off	£42,368	2.0628	1.4139	£12,697	0.9602	0.6671	£29,670	0.7469	£39,727
Scenario 10	KM + exponential 72-week cut-off	£42,252	1.9956	1.3696	£12,801	1.0202	0.7069	£29,451	0.6627	£44,438
Scenario 11	PFS KM+exponential 28-week cut-off	£37,802	1.9878	1.3538	£12,813	1.0160	0.7046	£24,989	0.6491	£38,494

		Pembrolizumab			**Nintedanib + docetaxel**			**Pembro vs ninte+doc**		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 2		£43,014	2.4424	1.6587	£23,732	1.2043	0.8356	£19,282	0.8232	£23,424
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£43,340	2.7070	1.8179	£24,739	1.8299	1.2349	£18,602	0.5830	£31,909
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no rebase for time for diagnosis)	£43,163	2.5857	1.7421	£24,645	1.7657	1.1948	£18,519	0.5473	£33,833
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£39,180	2.4424	1.6587	£23,732	1.2043	0.8356	£15,448	0.8232	£18,767
Scenario 4	Progression-based utilites	£43,014	2.4424	1.6482	£23,732	1.2043	0.8392	£19,282	0.8089	£23,836
Scenario 5	Time to death utilities	£43,014	2.4424	1.7750	£23,732	1.2043	0.8765	£19,282	0.8985	£21,460
Scenario 6	Consider AE-related disutilities	£43,014	2.4424	1.6554	£23,732	1.2043	0.7977	£19,282	0.8578	£22,480
Scenario 7	Exclude age-related disutility	£43,014	2.4424	1.6898	£23,732	1.2043	0.8394	£19,282	0.8504	£22,674
Scenario 8	KM + exponential 52-week cut-off	£43,014	2.4424	1.6587	£23,732	1.2043	0.8356	£19,282	0.8232	£23,424
Scenario 9	KM + exponential 62-week cut-off	£41,966	1.8296	1.2620	£23,585	1.1190	0.7791	£18,381	0.4830	£38,058
Scenario 10	KM + exponential 72-week cut-off	£43,439	2.6971	1.8216	£23,744	1.2113	0.8402	£19,695	0.9814	£20,067
Scenario 11	PFS KM+exponential 28-week cut-off	£38,578	2.4424	1.6481	£24,067	1.2043	0.8365	£14,511	0.8116	£17,879
		Pembrolizumab			**Docetaxel**			**Pembro vs doc**		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case 2		£43,014	2.4424	1.6587	£12,794	1.0160	0.7041	£30,220	0.9546	£31,657
Scenario 1	NLCA Registry data – Chemotherapy dataset PS0-1 (no rebase for time for diagnosis)	£43,340	2.7070	1.8179	£13,558	1.4894	1.0068	£29,782	0.8110	£36,721
Scenario 2	NLCA Registry data – Stage IIIb/IV dataset (no	£43,163	2.5857	1.7421	£13,491	1.4434	0.9781	£29,672	0.7640	£38,836

	rebase for time for diagnosis)									
Scenario 3	Vial sharing - Cost of pembrolizumab estimated based on cost per mg	£39,180	2.4424	1.6587	£12,794	1.0160	0.7041	£26,387	0.9546	£27,641
Scenario 4	Progression-based utilites	£43,014	2.4424	1.6482	£12,794	1.0160	0.7099	£30,220	0.9383	£32,208
Scenario 5	Time to death utilities	£43,014	2.4424	1.7750	£12,794	1.0160	0.7371	£30,220	1.0379	£29,118
Scenario 6	Consider AE-related disutilities	£43,014	2.4424	1.6554	£12,794	1.0160	0.6695	£30,220	0.9860	£30,650
Scenario 7	Exclude age-related disutility	£43,014	2.4424	1.6898	£12,794	1.0160	0.7066	£30,220	0.9833	£30,735
Scenario 8	KM + exponential 52-week cut-off	£43,014	2.4424	1.6587	£12,794	1.0160	0.7041	£30,220	0.9546	£31,657
Scenario 9	KM + exponential 62-week cut-off	£41,966	1.8296	1.2620	£12,697	0.9602	0.6671	£29,269	0.5949	£49,195
Scenario 10	KM + exponential 72-week cut-off	£43,439	2.6971	1.8216	£12,801	1.0202	0.7069	£30,638	1.1148	£27,484
Scenario 11	PFS KM+exponential 28-week cut-off	£38,578	2.4424	1.6481	£12,813	1.0160	0.7046	£25,765	0.9435	£27,309

5.2.11 Model validation and face validity check

The company sought model validation from two external health economics experts. The following aspects of the model were considered:

- Model structure and assumptions – there was agreement that they were valid and consistent with previous submissions for this indication.
- Fitting of OS and PFS curves – the overall approach to curve fitting was based on recommendations from the experts.
- Selecting cut-off point from KM data to switch to exponential curve for OS – there was agreement that there is no clear cut-off point, as a result, other cut-off points were also tested.
- Selecting cut-off point from KM data to switch to exponential curve for PFS – there was uncertainty around the 9-week cut-off point chosen, the experts recommended exploring the impact of alternative cut-offs on the ICERs.
- The experts both agreed that the same type of parametric curve should be used for both arms for both PFS and OS, this is to 'avoid unnecessary complexity and to comply with DSU guidance'.
- Choice of parametric curves – there was agreement that same type of parametric curves should be use for pembrolizumab and docetaxel, for PFS and OS.
- Time on treatment – there was agreement that PFS was a reasonable proxy for to time on treatment. One expert noted that stopping treatment for all patients at 2 years may be unrealistic.
- Administration cost of oral chemotherapy – in the model, the costs of oral chemotherapy were applied every 30 days (when a full pack was dispatched), and subsequent treatment cost was modelled to occur over the period of subsequent treatment (3.3 months) rather than a one-off cost. This approach was based on comments from the experts.
- Approach to considering utilities – there was agreement that the approach was appropriate.
- Validation of resource use and AE costs with clinician – this was advised by the experts.

The company submission described an internal quality control process to validate model implementation and programming. However, the ERG cannot locate the checklist mentioned in the submission.

5.3 Detailed critique and exploratory analyses undertaken by the ERG

The ERG has explored the company's economic model in detail and has a number of concerns.

5.3.1 Overall survival

The company has used a piecewise approach to estimating OS. Two base cases were presented, based on different data being used to estimate OS in the longer term. In base case 1, data from KEYNOTE-001 were used. This base case is based on a non-randomised comparison of pembrolizumab from KEYNOTE-001 with the docetaxel arm from KEYNOTE-010. The internal validity of such a comparison is inherently more uncertain than a within trial comparison as there is a greater scope for factors other than treatment to vary between patients. In this case we do not think the potential benefits of improved extrapolation of survival arising from increased follow-up (maximum 32.3 months in KEYNOTE-001 vs 24 months in KEYNOTE-010) outweigh the concerns about the internal validity of the comparison.

Base case 2 was referred to as the "most conservative analysis" by the company (page 171 of the company submission). It should be noted that this is strictly relative to the other models presented. However, the analysis is not inherently conservative in the sense that it is likely to underestimate the true benefit. It was also stated in the company submission that the analysis is conservative because the OS curve based on the KEYNOTE-010 declines to baseline more rapidly than the curve based on KEYNOTE-001 due to the shorter follow-up on KEYNOTE-010. It is not axiomatic that the difference reflects differences in follow-up, it may simply reflect differences between the studies. The estimated survival in base case 2 is based on the assumption that there is a material ongoing incremental reduction in the risk of death with pembrolizumab that continues after treatment has ceased and is maintained for the lifetime of the analysis (20 years).

Table 37 presents disaggregated life-years for the pre- and post-progression health states. We can see that the incremental gain in the discounted pre-progression survival is 0.19 years and the incremental gain in post-progression survival is 0.85 years. Therefore, 82% of the overall survival gain of 1.03 years occurs post-progression after treatment has ended.

Table 37 Disaggregated life-years by health state (discounted)

	Pre-progression	**Post-progression**	**Total**
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)			
Pembrolizumab	0.6095	1.2889	1.898
Docetaxel	0.4208	0.4462	0.867
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)			
Pembrolizumab	0.6095	1.1574	1.767
Docetaxel	0.4208	0.4462	0.867

Source: Table 100, page 226, of the company submission

On examining the projected OS curves, we can see that difference in the rate of death between the two treatments from the point of departure. We can also see that the model appears to show some degree of inflexion at the point of departure at 52 weeks. This apparent point of inflexion is a result of this approach to the modelling which treats the timing of deaths up to 52 as being unrelated to the timing of deaths beyond 52 weeks. Further, the KM approach to modelling survival treats the time of each individual death as being unrelated to all other deaths. In a sense this maximises the uncertainty in the predicted curve. Overall, this can lead to estimates of survival from this form of modelling being very sensitive to the choice of cut-point. This sensitivity is illustrated below (Figure 17) which shows the original KM curve and 11 other KM curves derived from boot-strapped samples.

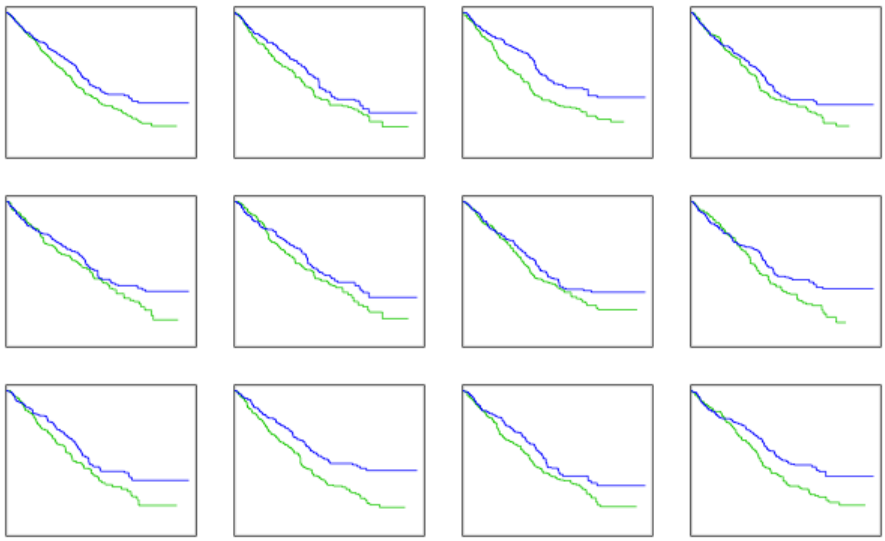


Figure 17 Boot-strapped KM curves to illustrate uncertainty

We also examined the estimated relationship between mean OS difference for the two treatments (undiscounted) over a range of breakpoints based on our own re-analysis of the KEYNOTE-010 data (Figure 18). This is not directly equivalent to the analysis in the submission as the estimates are undiscounted and we have not corrected the survival estimates for the docetaxel arm. However, it does demonstrate the potential sensitivity of survival estimates to the choice of cut-point, particularly if earlier cut-points are selected

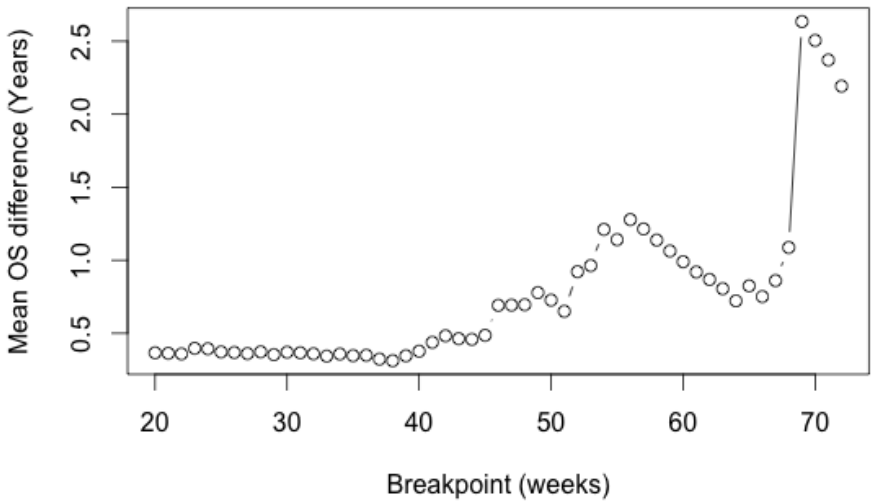


Figure 18 Estimated relationship between breakpoint and OS difference

As mentioned previously, the estimated survival in base case 2 is based on the assumption that there is a material ongoing incremental reduction in the risk of death with pembroluzimab that continues after treatment has ceased and is maintained for the lifetime of the analysis. The estimated hazard ratio from our analysis and the long-term extrapolation for different cut-points are shown below (Figure 19).

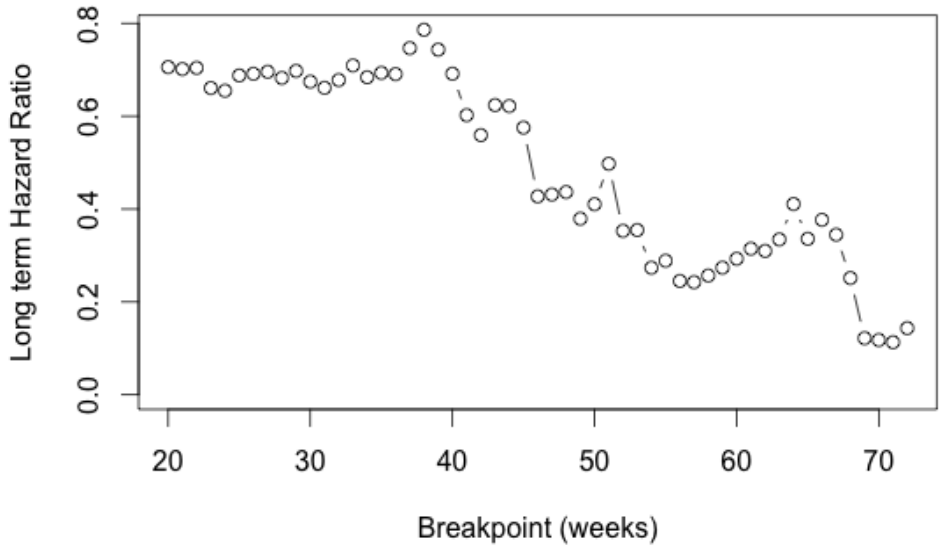


Figure 19 Estimated relationship between breakpoint and long-term hazard ratio

Again this hazard ratio is sensitive to the choice of cut-point. With the cut-point of 52 weeks used in the submission, the long-term hazard ratio is 0.35 giving an overall improvement in overall survival (undiscounted) of 0.92 years. In contrast, if the analysis were repeated with a hazard ratio of 1, representing no long-term incremental effect on survival, the incremental overall survival would be 0.18 years. Overall, the ICERs are very sensitive to assumptions regarding the maintenance of a long-term treatment effect beyond the end of the treatment period. This leads to the pronounced long-term survival in the pembroluzimab arm compared to the docetaxel arm.

5.3.2 Additional sub-group analyses

Two primary objectives of KEYNOTE-010 relates to evaluating OS, PFS, safety and tolerability in previously treated patients with NSCLC in the TPS ≥50% stratum. However, this sub-group and indeed the corresponding sub-group of TPS 1-49% were

not evaluated in the economic evaluation. Following the ERG's request during the clarification process, the company undertook three additional sub-group analyses – "strong expressers" (TPS ≥50%), "weak expressers" (TPS 1-49%) and the EGFR wild type sub-population.

These additional sub-group analyses took into consideration sub-group specific OS, PFS, AEs, subsequent therapies, actual dose taken as a percentage of the planned dose, hazard ratio between time on treatment and PFS, and weight estimates. However, the effect on OS due to treatment switching following docetaxel monotherapy discontinuation was not included due to time constraints. Therefore, the company considered these results to be over-estimation of the expected ICERs. Further, for the EGFR positive sub-group, due to the lack of OS data after 48 weeks and flat parametric curve tails observed, an alternative approach to OS modelling was used. Standard parametric curves were fitted to the full KM data and independently for the separate arms from KEYNOTE-010; the best fitting curve (the generalised gamma) was selected based on AIC/BIC statistic. Details of the additional analysis are described in the company's response to clarification (B12); the results of the sub-group analyses are shown in Table 38.

Table 38 Costs, life years (LYs), QALYs and ICERs when considering different subgroups (strong and weak expressers and by EGFR mutation status)

Time from which the exponential fitted curve is used to extrapolate OS	**Pembrolizumab**			**Docetaxel**			**Pembrolizumab vs docetaxel**		
	Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Strong expressers									
Base case 1	£54,113	2.195	1.53	£14,590	1.021	0.707	£39,523	0.824	£47,988
Base case 2	£53,768	1.995	1.4	£14,590	1.021	0.707	£39,177	0.693	£56,538
Weak expressers									
Base case 1	£34,207	1.702	1.156	£13,704	0.906	0.628	£20,503	0.528	£38,840
Base case 2	£34,045	1.608	1.095	£13,704	0.906	0.628	£20,341	0.467	£43,571
EGFR wild type									
Base case 1	£41,124	1.914	1.307	£14,100	0.959	0.664	£27,024	0.642	£42,082
Base case 2	£40,730	1.686	1.158	£14,100	0.959	0.664	£26,630	0.494	£53,899
EGFR mutation positive									
Generalised gamma	£37,261	2.09	1.386	£15,452	0.982	0.679	£21,810	0.707	£30,851

Source: company clarification to ERG response, Table 21, page 32

The company stressed that the results from these sub-group analyses should be interpreted with caution. In the strong expresser sub-group, the total cost of pembrolizumab and the associated ICERs when compared with docetaxol were greater than that of the base case for the whole population. The company's reasoning for this is that patients in this sub-group experience significant PFS improvement; therefore, the proportion of patients in pre-progressed health state over time is high resulting in high treatment costs and ICERs. The company also suggested that patients treated with pembrolizumab may continue to experience clinical benefit even after disease progression is documented; this benefit may not be appropriately captured in PFS. The ERG is not aware of existing evidence that supports this theory. The sub-groups, in particular the EGFR positive sub-group is small and estimates based on these small sub-groups may be imprecise.

5.4 Conclusions of the cost effectiveness section

Overall the company's cost-effectiveness methods were appropriate and clear.

Although the original company submission lacked clarity in some of the analyses, the company was helpful in their response to clarification and provided all the relevant data that ERG requested. The Microsoft Excel model was sound and confirmed the methodologies applied as stated in the submission.

The ERG considers the most important uncertainty relates to the estimates of the OS in the model. The cost-effectiveness estimates are based on significant gains in post-progression survival with pembroluzimab with a greater proportion of patients receiving pembroluzimab surviving to 5, 10 and 20 years (12.15%, 2.46%, 0.1%, base case 2) compared to docetaxel (0.57%, 0%, 0%). These extrapolations are inevitably uncertain given the current trial follow-up (median 13 months, maximum 24 months). There are also uncertainties given it is assumed in the modelling that all patients will stop treatment at 2 years. In the currently available dataset, no patients have stopped treatment reached and stopped treatment 2 years so there are no empirical data on their subsequent survival. Given the uncertainty in the long term extrapolations of survival and uncertainty in prognosis for patients who stop treatment at the two year times the estimates of cost-effectiveness unreasonably optimistic. It would have been more appropriate to taper the treatment effect beyond the cessation of treatment at 2 years.

6 Overall conclusions

The current submission focuses on a phase III RCT, KEYNOTE-010, sponsored by the company (KEYTRUDA, Merck Sharp and Dohme Limited, Hertfordshire, United Kingdom), which compared pembrolizumab 2mg/Kg (345 participants) with docetaxel 75 mg/m2 (343 participants). Compared with docetaxel, pembrolizumab significantly improved OS in previously treated adults with advanced NSCLC whose tumours express PD-L1 (TPS≥1% overall population and TPS≥50% stratum). PFS was improved, in a statistically significant way, only in the pembrolizumb TPS≥50% stratum but not in the overall TPS≥1% population. In the TPS 1-49% stratum pembrolizumab was not shown to be superior to docetaxel in terms of OS and PFS (but KEYNOTE-010 was not powered to detect differences in this sub-population). In a number of subgroups analyses for both primary outcomes, there was no significant difference between pembrolizumab and docetaxel.

No other head-to-head trials assessing the effects and safety of pembrolizumab versus other relevant comparators were identified. The company presents a NMA based on two RCTs, KEYNOTE-010 and LUME-LUNG 1, which compared pembrolizumab with nintedanib in combination with docetaxel. The NMA results showed no evidence of a difference in OS and PFS between pembrolizumab and nintedanib plus docetaxel.

Pembrolizumab demonstrated a significantly better safety profile in terms of Grade 3 and 4 AEs and treatment discontinuation due to AEs - in both KEYNOTE-010 against docetaxel and in the NMA against nintedanib in combination with docetaxel. AEOSI were more common in patients treated with pembrolizumab (overall TPS≥1% population) than in those treated with docetaxel. In particular AEOSI categorized as drug-related AEs, drug-related AEs with toxicity Grade 3-5, and drug-related SAEs were higher among patients treated with prembolizumab. Most of AEOSI were reported by the company to be of Grade 1 or 2 and manageable with medical treatments or interruption of pembrolizumab administration.

On the whole, the company’s systematic review of clinical evidence was well-conducted and the methods used were appropriate. There was concern, however,

about the reliability of the NMA results due to the fact that only two trials, which included different clinical populations, were included in the NMA.

The company's economic evaluation is generally appropriate for the decision problem defined in the final scope. However, it should be noted that the only docetaxel monotherapy and nintedanib with docetaxel (for the adrenocarcinoma sub-group) were compared with pembrolizumab. The *de novo* model was generally well described within the report. The ERG considers the model structure to be reasonable, however, there are substantial uncertainties associated with the OS survival estimates in the longer-term. The deterministic sensitivity analysis suggested that the key drivers of the model results are: the extrapolation of pembrolizumab OS based on KEYNOTE-001, and the hazard ratio of time on treatment relative to PFS for pembrolizumab.

The ERG considers the most important uncertainty relates to the estimates of the OS in the model. The cost-effectiveness estimates are based on significant gains in post-progression survival with pembroluzimab

6.1 Implications for research

The company presented in the submission results from the final analysis of KEYNOTE-010. It is worth noting that patients in KEYNOTE-010 treated with pembrolizumab 2mg/Kg Q3W have continued to be followed up and a further survival analysis for the pembrolizumab 2mg/Kg Q3W arm has been planned by the company.

Head-to-head trials of pembrolizumab versus relevant competing interventions (e.g.nivolumab, nintedanib in combination with docetaxel) with respect to efficacy and safety outcomes would contribute to reduce the uncertainty surrounding the clinical effectiveness of these treatments and would inform cost-effectiveness.

Future clinical trials should aim to assess the optimal duration of treatment with pembrolizumab. At present there is no evidence regarding the optimal duration of treatment with pembrolizumab, particularly since the KEYNOTE-010 protocol established that *treatment should continue until disease progression, toxicities leading to discontinuation, physician's decision or 2 years of uninterrupted delivery of*

pembrolizumab. It is possible that shorter courses of pembrolizumab are equally effective.

If in clinical practice pembrolizumab would be considered for the treatment of wider groups of patients with NSCLC, further data on the following groups are needed:

- patients with brain metastases (*Can pembrolizumab cross the blood brain barrier and reduce/delay progression of CNS disease?);*
- patients aged >75 for whom less robust or durable responses are expected;
- patients with ECOG performance status 2.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 9 June 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Subgroup analyses according to biological markers (PD-L1, EGFR, ALK)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 2: "The company, however, has not provided any reason for not considering subgroup analyses according to biological markers (PD-L1, EGFR, ALK)."	MSD proposes the removal of this comment as the easiest resolution. Alternatively, we would be comfortable with a change in the language to reflect our response to question B12 of the ERG questions.	In question B12 of the clarification questions MSD noted that: ▪ "Following discussion with clinicians, the MSD submission was based on the total eligible population with an associated enhanced discount" (in relation to the rationale not to consider subgroup analyses by PD-L1 status). ▪ "the KEYNOTE-010 trial was not powered to undertake subgroup analyses by EGFR status and, as expected, the number of patients with NSCLC that had EGFR positive mutation status was very small." Additionally, only 8% of the patients included in KEYNOTE-010 were EGFR-mutation positive (see Table 17 in the submission) and only 0.8% of the patients included had tumours with ALK translocations. At the request of the ERG, MSD provided subgroup analyses by PD-L1 status and EGFR mutation status as part of the answers to the clarification questions (please see question B12).	The comment has now been removed. See Erratum.

Issue 2 Statistical power of KEYNOTE-010 study

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10: "KEYNOTE-010 was only powered to detect a difference in OS in the subpopulation with a TPS≥50%."	KEYNOTE-010 study was designed and powered to compare efficacy between pembrolizumab and docetaxel in both the TPS≥50% stratum and in the TPS≥1% overall population (with Bonferroni adjustment between the two tests); but not within the TPS1-49% stratum.	This has been presented in MSD submission: see section 4.4 as well as in the response to clarification questions regarding the power of the analysis in the TPS1-49% stratum. MSD is concerned that the wording as it is would lead to uncertainty regarding the power of KEYNOTE-010 study to detect a difference in OS in the overall population with TPS of 1% or greater.	This sentence refers to the fact that KEYNOTE-010 was powered to detect a difference in OS in the subpopulation with a TPS≥50% and not in the TPS 1-49% subpopulation. For clarity, the text has been changed to: *KEYNOTE-010 was powered to detect a difference in the population with a TPS≥50% and in the overall TPS≥1% population. The company did not present a power calculation for the TPS 1-49% population. However, this seems to be irrelevant since the results (point estimates and precision of the confidence intervals) are now available.* It is worth noting that the KEYNOTE-010 published Lancet paper states: "*This study was designed to show a difference in overall survival in patients with a tumour proportion score of 50% or greater.*" There was a second power calculation for the overall population, based on the sample size obtained for the TPS>50% subgroup. These power

			calculations, although important, are irrelevant once a trial is over and the results for all subgroups are available. It's the effect size and precision that should be judged. In this case, for OS the 1-49% group showed an HR of 0.79 (95% CI 0.61, 1.04); the ≥50% group an HR of 0.54 (95% CI 0.38, 0.77) and the overall population an HR of 0.71 (95% CI 0.58, 0.88).

Issue 3 Design of KEYNOTE-010 study

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 49: "The study was designed with the aim of showing a difference in overall survival in patients with a TPS of 50% or greater, even though the overall population enrolled in the trial had a TPS of 1% or greater."	The TPS1% cut off was used for enrolment in KEYNOTE-010, with the first analysis conducted in the TPS50% stratum followed by a step down analysis in the overall TPS1% population.	This has been presented in MSD submission: see section 4.4. MSD is concerned that the wording as it is would lead to uncertainty regarding the power of KEYNOTE-010 study to detect a difference in OS in the overall population with TPS of 1% or greater.	The text has been changed to: "*The study was originally designed with the aim of showing a difference in overall survival in patients with a TPS of 50% or greater*". This is in line with the information reported in the KEYNOTE-010 published Lancet paper, which states: "*This study was designed to show a difference in overall survival in patients with a tumour proportion score of 50% or greater*."

Issue 4 Results of OS in the TPS 1-49% stratum

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 57: The ERG noted that the estimate for overall survival in the TPS 1-49% stratum reported in the submission, HR 0.79 (95% CI 0.61, 1.04); p=0.04434, does not appear to be correct as the confidence interval and p-value are conflicting with each other (assuming that the confidence interval is correct, it is possible that the p-value quoted by the company refers to a one-sided hypothesis rather than a two-sided hypothesis).	MSD recommends that this comment be removed in its entirety.	The results of overall survival in the TPS 1-49% stratum were provided during the clarification questions – see table 1 of MSD response to clarification questions). The footnote of Table 1 clearly states that the p value presented in the table is "[§]One-sided p-value based on log-rank test".	We may have overlooked the footnote. However, our assumption (i.e. *"It is possible that the p-value quoted by the company refers to a one-sided hypothesis rather than a two-sided hypothesis"*) appears to be correct. No revision required. It is still unclear why the company decided to present a 2-sided confidence interval alongside a 1-sided hypothesis test.

Issue 5 Minor text correction related to the use of the National Lung Cancer Audit (NLCA) registry data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 102: "Firstly, the number of NSCLC registry patients with **stage IIB, IV and IIB/IV** were estimated from the NLCA audit report."	Please substitute with: "Firstly, the number of NSCLC registry patients with stage **IIIB and IV** were estimated from the NLCA audit report."	To implement minor text correction.	Minor imprecision, which does not impact on results and conclusions. No revision required.

Issue 6 EQ-5D data collection in KEYNOTE-010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 104: "The EQ-5D was administered up to six times whilst patients were receiving treatment (at treatment cycles 1, 2, 3, 5, 9 and 13) and once after treatment discontinuation (30 days after discontinuation)."	Please substitute with: "The EQ-5D was administered at treatment cycles 1, 2, 3, 5, 9 and 13, and every 4 cycles after cycle 13 and until treatment discontinuation. It was also collected once after treatment discontinuation (30 days after discontinuation).	Apologies because this was not clearly presented as part of section 5.4.1 in the submission. The amendment is required to implement a minor text correction for this point, which had not been clearly reported as part of the submission.	This was not clearly reported in the main submission. Minor imprecision, which does not impact on results and conclusions. No revision required.

Issue 7 Age-adjusted utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 105: "At the request of the ERG during the clarification process, the company clarified that no additional annual decrements were added to patients above 75 years. This implies that patients aged 75 years and above would have the same age-related utility decrements.	Please substitute with: "At the request of the ERG during the clarification process, the company clarified that no additional annual decrements were added to patients above 75 years **since the original data source used for this adjustment (Kind et al 1999) reported the same disutility values to be applicable to patients aged 75 and above**. This implies that patients aged 75 years and above would have the same age-related utility decrements.	To clarify further why similar utilities were used for patients above 75 years.	The text has been amended according to the company's suggestion. See Erratum.

Issue 8 Updated search for resource use and costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 107: "The company reported 14 studies included in the review, which are described in Appendix 27 of the submission. However, this was not consistent with the PRISMA diagram from Figure 50, page 203, of the company submission, which reported 12 studies from original 2015 search plus one additional study from the updated search in 2016. "	-	We would like to confirm that two additional studies were identified as part of the additional searches as mentioned by the ERG, instead of one as reported in the footnote of the Prisma diagram, reported in Figure 50 of the submission. No amendment is required here.	No revision required.

Issue 9 Cost estimation of subsequent therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 110: "This weighted cost was applied during 14.4 **cycles** to those who moved to post-progression health states."	MSD suggests to change to: "This weighted cost was applied during 14.4 **weeks** to those who moved to post-progression health states."	We apologise for the typo in our submission (page 210), which has been carried through into the ERG report.	Typo in the company submission. No revision required.

Issue 10 Costs of asthenia as used in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 111: "The ERG notes that for asthenia the model cost reported in the table below was	MSD suggests to remove the comment in its entirety.	We would like to clarify that the reporting of the cost of asthenia equal to £2,317.20 reported in	Typo in the company submission. No revision required.

£2,317.20; however, in the model the cost used was £3,015.13 – the cost reported for ID811 in the table below. The ERG believes the impact on the ICERs would be immaterial."		Table 94 as part of the submission was a typo. In fact, as mentioned by the ERG, the cost of asthenia used in the model was £3,015.13, and was derived from ID811. Therefore, we can confirm that this typo did not have any impact in the estimation of the ICERs. We apologise for the reported typo.	

Issue 11 **Checklist used for the internal validation of the model**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 131: "The company submission described an internal quality control process to validate model implementation and programming. However, the ERG cannot locate the checklist mentioned in the submission."	MSD suggests either to remove the comment in its entirety or amend it to acknowledge the existence of the information provided as commercial in confidence (CiC) as part of the appendices.	Please note that we provided the checklist used for the internal validation of the model as CiC information as part of Appendix 30 of the submission.	The comment has now been removed. See Erratum.

Issue 12 **Critique of the disaggregated life years by health state**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 132: "Therefore, 82% of the overall survival gain of 1.03 years occurs post-progression after treatment has ended."	Please substitute with: "Therefore, 82% of the overall survival gain of 1.03 years **in base case 1** occurs post-progression after treatment has ended. **In base case 2, this relates to 79% of the survival gain of 0.90 years.**"	It will be helpful to clarify to what base case this result refers to and include as well the results of base case 2.	The text has been amended according to the company's suggestion. See Erratum.

Issue 13 **Critique of the extrapolation of OS (II)**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Figures 18 and 19, on pages 133 to 134, are of limited/no value without further supporting information.	The additional information that would enable the reader to understand the relevance of the figures would be: - Which parametric curves were used - How they fitted the data (AIC/BIC) - Whether clinical advice was sought on the plausibility of using different cut-offs	Presenting the figures with the current amount of information is of limited value.	The following text has been added to page 132: *"For each curve survival data are sampled from the original data with replacement allowing individual subjects to be sampled multiple times. The plotted curves are intended to illustrate the uncertainty in the form of the survival curves and hence the uncertainty in the selection of the "breakpoint" for the transition from the KM curve to the parametric extrapolation."*

Issue 14 Additional subgroup analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 135: “Following the ERG’s request during the clarification process, the company undertook **three** additional sub-group analyses – “strong expressers” (TPS ≥50%), “weak expressers” (TPS 1-49%) and the EGFR wild type sub-population.”	Please substitute with: “Following the ERG’s request during the clarification process, the company undertook **four** additional sub-group analyses – “strong expressers” (TPS ≥50%), “weak expressers” (TPS 1-49%)**,** the EGFR wild type sub-population **and EGFR mutation positive population**.”	During the clarification questions, a fourth analysis on the subpopulation of EGFR mutation positive patients was also presented at the request of the ERG. Please see MSD’s answer to question B12 for the clarification questions.	The text has been amended according to the company’s suggestion. See Erratum.

Aberdeen HTA Group

Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy

Erratum

Completed 14 June 2016

This report was commissioned by the NIHR HTA Programme as project number **15/69/02** and was supported by the Complex Reviews Support Unit, also funded by the National Institute for Health Research (project number 14/178/29).

This document is intended to replace pages 2, 10, 49, 105, 131, 132, and 135 of the of the original ERG assessment report for *Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy*, which contained a few minor inaccuracies.

The amended pages follow in order of page number below.

Adenocarcinoma is an important histological sub-type of the NSCLC, which accounts for 30-40% of the NSCLC. The ERG agrees with the company's decision to perform a subgroup analysis for people with adenocarcinoma histology.

The outcomes considered in the company submission are in line with those detailed in the NICE final scope.

The decision problem addressed by the company differs from the NICE final scope but is considered appropriate and clinically relevant by the ERG.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence included in the company submission consisted of three RCTs: KEYNOTE-010, a phase II/III head-to-head RCT that compared pembrolizumab with docetaxel; KEYNOTE-001 (Parts C and F) a phase I trial due to its initial dose escalation, which evolved into multiple phase II-like sub-studies through a series of expansion cohorts that assessed the effects and safety of pembrolizumab (no comparator; and LUME-LUNG-1, a phase III trial that compared docetaxel plus nintedanib with docetaxel plus placebo.

Although all three trials included participants with advanced NSCLC, whose disease has recurred after platinum-containing chemotherapy, only KEYNOTE-010 included a patient population relevant to the decision problem addressed by the company. KEYNOTE-010 trial included adults with PD-L1 positive advanced NSCLC whose disease has progressed after appropriate targeted therapy for EGFR or ALK positive tumours. In KEYNOTE-001 not all included patients presented with a PD-L1 positive NSCLC, while in LUME-LUNG-1 neither PD-L1 expression nor EGFR mutation status were assessed among included patients with advanced NSCLC.

1.2.1 KEYNOTE-010 results

Two different doses of pembrolizumab were tested (2 mg/kg and 10 mg/kg) in KEYNOTE-010 and interim analyses were undertaken and adjusted for. For the purposes of this assessment we have focused specifically on the pembrolizumab 2 There are also uncertain given it is assumed in the modelling that all patients will stop treatment at 2 years. In the currently available dataset, no patients have stopped

There are also uncertain given it is assumed in the modelling that all patients will stop treatment at 2 years. In the currently available dataset, no patients have stopped treatment reached and stopped treatment 2 years so there are no empirical data on their subsequent survival. Given the uncertainty in the long term extrapolations of survival and uncertainty in prognosis for patients who stop treatment at the two year times the estimates of cost-effectiveness unreasonably optimistic. It would have been more appropriate to taper the treatment effect beyond the cessation of treatment at 2 years.

1.6.2 Weaknesses and areas of uncertainty

- KEYNOTE-010 trial was an open-label trial where only radiologist and statisticians were blinded to treatment assignment but not participants or study investigators.
- In KEYNOTE-010 results (i.e. OS, PFS) were not consistent among subpopulations according to PD-L1 status (patients with a TPS≥1% - overall population, patients with a TPS 1-49% and patients with a TPS≥50%). There was no evidence of a difference between pembrolizumab and docetaxel in the TPS 1-49% stratum but there was evidence of a difference, favouring pembrolizumab, in the overall population and in the TPS≥50% stratum. KEYNOTE-010 was powered to detect a difference in OS in the subpopulation with a TPS≥50% and in the overall TPS≥1% population. The company did not present a power calculation for the TPS 1-49% population. However, this seems to be irrelevant since the results (point estimates and precision of the confidence intervals) are now available.
- In KEYNOTE-001 not all included patients had a positive PD-L1 status. The trial did not provide comparative efficacy data.
- The company's NMA was based on only two trials, KEYNOTE-010 and LUME-LUNG-1, which included different clinical populations. In KEYNOTE-010 the patient population had a positive PD-L1 status, whereas PD-L1 status or EGFR mutation were not assessed in LUME-LUNG-1.
- The NMA relied on the assumption that that the efficacy of nintedanib in combination with docetaxel did not depend on PD-L1 expression and that the reported subgroups were comparable. Moreover, the proportional hazards assumption was not supported by the LUME-LUNG-1 data.

these were considered most relevant by the company and in line with the anticipated licensed dose regimen.

The study was originally designed with the aim of showing a difference in overall survival in patients with a TPS of 50% or greater.

In KEYNOTE-010 two types of patient population were used to estimate the treatment effect for the primary outcomes: the Intention-To-Treat (ITT) population in the TPS≥50% stratum and in the TPS>1% overall population served as the primary population for the analyses of PFS and OS. Patients were included in the treatment group to which they were randomised for the analysis of efficacy data using the ITT population. A supportive analysis was conducted in the Full Analysis Set (FAS) population, which excluded those who did not meet the key eligibility criteria or discontinued before receiving any dose of assigned treatment. The primary safety analysis in KEYNOTE-010 was based on the treated TPS≥1% population (all randomised patients who received at least one dose of study treatment). Patients were included in the treatment group corresponding to the study treatment they actually received.

The participants had a median duration of follow-up of 13 months (range from 6 to 24 months).

For overall survival, data for patients who were alive or lost to follow-up were censored at the time of last confirmed contact. For progression-free survival, data for patients who had not progressed or were lost to follow-up were censored at the time of last tumour assessment. For overall response rate, patients with missing data were considered non-responders. For duration of response, data for patients whose response was on going at the time of the analysis, or who discontinued the study without radiological evidence of progression, were censored at the time of the last radiological assessment showing response. Data for patients who had radiological disease progression after missing two radiological assessments were censored at the time of the last radiological assessment showing response, and data for patients who initiated

health utilities with increasing age. At the request of the ERG during the clarification process, the company clarified that no additional annual decrements were added to patients above 75 years since the original data source used for this adjustment (i.e. Kind et al. 1999) reported the same disutility values to be applicable to patients aged 75 and above. This implies that patients aged 75 years and above would have the same age-related utility decrements. Reports of HRQoL were sought by searching MEDLINE, EMBASE, NHS Economics Evaluation Database (NHS EED), HTA database, DARE and EconLit in May 2015 and updated in March 2016 for studies published from 1995 in English. In addition, ISPOR and ASCO conference proceedings were manually searched for the previous 3 years. The NICE website was also consulted for relevant reports. The search strategies are documented in full in Appendix 23 of the company submission. The searches combined two search facets using the Boolean operator AND: non small cell lung cancer; and HRQoL and utilities. A comprehensive range of terms were included in the search strategies although the NSCLC facet of the search was restricted by the inclusion of staging/ metastasis/advanced cancer related terms

The original search carried out in 2015 identified 44 studies; an updated search was carried out in 2016 focused on studies reporting health-related quality of life using EQ-5D found one additional study. Details of these studies are presented in Table 77 (pages 191-195 of the company submission). The company submission provided a summary of the key differences between the utility values derived from the literature and those reported in KEYNOTE-010. For the progression-free health state, the estimated health utilities were generally consistent from the two sources. However, greater differences in estimated health utilities were found for the post-progression health state. In particular, two studies reported health utilities of 0.217 and 0.22 for progressed health states.[75, 76] However, the company explained that this may be due to the studies assessing utilities from healthy volunteers instead of NSCLC patients.

The search did not identify any utilities combining time to death and progression status in the search. This approach has only previously been used in patients with melanoma. The company reported that a Dutch study[77] has reported similar declines in health-related quality of life for NSCLC patients towards the final three months of life to be consistent with patients from KEYNOTE-010 who were <30 days to death.

5.3 Detailed critique and exploratory analyses undertaken by the ERG

The ERG has explored the company's economic model in detail and has a number of concerns.

5.3.1 Overall survival

The company has used a piecewise approach to estimating OS. Two base cases were presented, based on different data being used to estimate OS in the longer term. In base case 1, data from KEYNOTE-001 were used. This base case is based on a non-randomised comparison of pembrolizumab from KEYNOTE-001 with the docetaxel arm from KEYNOTE-010. The internal validity of such a comparison is inherently more uncertain than a within trial comparison as there is a greater scope for factors other than treatment to vary between patients. In this case we do not think the potential benefits of improved extrapolation of survival arising from increased follow-up (maximum 32.3 months in KEYNOTE-001 vs 24 months in KEYNOTE-010) outweigh the concerns about the internal validity of the comparison.

Base case 2 was referred to as the "most conservative analysis" by the company (page 171 of the company submission). It should be noted that this is strictly relative to the other models presented. However, the analysis is not inherently conservative in the sense that it is likely to underestimate the true benefit. It was also stated in the company submission that the analysis is conservative because the OS curve based on the KEYNOTE-010 declines to baseline more rapidly than the curve based on KEYNOTE-001 due to the shorter follow-up on KEYNOTE-010. It is not axiomatic that the difference reflects differences in follow-up, it may simply reflect differences between the studies. The estimated survival in base case 2 is based on the assumption that there is a material ongoing incremental reduction in the risk of death with pembrolizumab that continues after treatment has ceased and is maintained for the lifetime of the analysis (20 years).

Table 37 presents disaggregated life-years for the pre- and post-progression health states. We can see that the incremental gain in the discounted pre-progression survival is 0.19 years and the incremental gain in post-progression survival is 0.85 years. Therefore, 82% of the overall survival gain of 1.03 years in base case 1 occurs post-progression after treatment has ended. In base case 2, this relates to 79% of the survival gain of 0.90 years.

Table 37 Disaggregated life-years by health state (discounted)

	Pre-progression	**Post-progression**	**Total**
Base case 1: KM + exponential + projections based on KEYNOTE-001 for pembrolizumab vs. KM + exponential for docetaxel (using two-stage to adjust for switching)			
Pembrolizumab	0.6095	1.2889	1.898
Docetaxel	0.4208	0.4462	0.867
Base case 2: KM + exponential for pembrolizumab and docetaxel (using two-stage to adjust for switching)			
Pembrolizumab	0.6095	1.1574	1.767
Docetaxel	0.4208	0.4462	0.867

Source: Table 100, page 226, of the company submission

On examining the projected OS curves, we can see that difference in the rate of death between the two treatments from the point of departure. We can also see that the model appears to show some degree of inflexion at the point of departure at 52 weeks. This apparent point of inflexion is a result of this approach to the modelling, which treats the timing of deaths up to 52 as being unrelated to the timing of deaths beyond 52 weeks. Further, the KM approach to modelling survival treats the time of each individual death as being unrelated to all other deaths. In a sense this maximises the uncertainty in the predicted curve. Overall, this can lead to estimates of survival from this form of modelling being very sensitive to the choice of cut-point. This sensitivity is illustrated below (Figure 17), which shows the original KM curve and 11 other KM curves derived from boot-strapped samples. For each curve survival data are sampled from the original data with replacement allowing individual subjects to be sampled multiple times. The plotted curves are intended to illustrate the uncertainty in the form of the survival curves and hence the uncertainty in the selection of the "breakpoint" for the transition from the KM curve to the parametric extrapolation.

not evaluated in the economic evaluation. Following the ERG's request during the clarification process, the company undertook four additional sub-group analyses: "strong expressers" (TPS ≥50%), "weak expressers" (TPS 1-49%), EGFR wild type sub-population and EGFR mutation positive population.

These additional sub-group analyses took into consideration sub-group specific OS, PFS, AEs, subsequent therapies, actual dose taken as a percentage of the planned dose, hazard ratio between time on treatment and PFS, and weight estimates. However, the effect on OS due to treatment switching following docetaxel monotherapy discontinuation was not included due to time constraints. Therefore, the company considered these results to be over-estimation of the expected ICERs. Further, for the EGFR positive sub-group, due to the lack of OS data after 48 weeks and flat parametric curve tails observed, an alternative approach to OS modelling was used. Standard parametric curves were fitted to the full KM data and independently for the separate arms from KEYNOTE-010; the best fitting curve (the generalised gamma) was selected based on AIC/BIC statistic. Details of the additional analysis are described in the company's response to clarification (B12); the results of the sub-group analyses are shown in Table 38.

Table 38 Costs, life years (LYs), QALYs and ICERs when considering different subgroups (strong and weak expressers and by EGFR mutation status)

Time from which the exponential fitted curve is used to extrapolate OS	**Pembrolizumab**			**Docetaxel**			**Pembrolizumab vs docetaxel**		
	Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Strong expressers									
Base case 1	£54,113	2.195	1.53	£14,590	1.021	0.707	£39,523	0.824	£47,988
Base case 2	£53,768	1.995	1.4	£14,590	1.021	0.707	£39,177	0.693	£56,538
Weak expressers									
Base case 1	£34,207	1.702	1.156	£13,704	0.906	0.628	£20,503	0.528	£38,840
Base case 2	£34,045	1.608	1.095	£13,704	0.906	0.628	£20,341	0.467	£43,571
EGFR wild type									
Base case 1	£41,124	1.914	1.307	£14,100	0.959	0.664	£27,024	0.642	£42,082
Base case 2	£40,730	1.686	1.158	£14,100	0.959	0.664	£26,630	0.494	£53,899
EGFR mutation positive									
Generalised gamma	£37,261	2.09	1.386	£15,452	0.982	0.679	£21,810	0.707	£30,851

Source: company clarification to ERG response, Table 21, page 32

16th August 2016

Dear Helen,

Re. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

MSD welcomes the opportunity to provide the additional requested analyses.

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

Kind regards,

[redacted]

Single technology appraisal

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Dear [redacted],

Following the Committee meeting on 29th June to discuss pembrolizumab for treating locally advanced or metastatic non-small-cell lung cancer, we are writing to request some further analyses and clarifications from the company. We would be grateful if you could please include these in a supplementary appendix to your original submission, also containing your updated value proposition for pembrolizumab, in advance of the second appraisal committee meeting for this topic on 25 August 2016.

Please provide the supplementary appendix containing your updated value proposition and these analyses by **5pm** on **Tuesday 16 July 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.:

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries relating to the analyses requested in this letter, please contact Stuart Wood, Technical Lead (Stuart.Wood@nice.org.uk) or Fay McCracken, Technical Adviser (Fay.McCracken@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation
Please provide the following analyses:

Please note all the analyses in the response to the questions below have incorporated the new patient access scheme (PAS) with a discount of [redacted], which has been approved by the Department of Health.

Base case analysis:

1. Please provide a revised base-case 2 probabilistic cost-effectiveness analysis of pembrolizumab compared with docetaxel without the 2 year treatment duration assumption in the pre-progression state for pembrolizumab treatment.

   For example, the company's model assumed that at 2 years all patients in the pre-progression state would stop treatment, however the Committee noted that no 2 year treatment duration assumption is likely to be specified in the anticipated marketing authorisation for pembrolizumab. The committee was not presented with compelling evidence that such a rule would be applied in clinical practice. As a result, it would be helpful for the committee to see a cost effectiveness model of pembrolizumab compared with docetaxel with without a 2 year treatment duration assumption to determine the impact on the incremental cost-effectiveness ratio (ICER).

   MSD explored the effect of varying the maximum duration of treatment after 2 years with 0% (base-case 2), 25% (1.6% of the initial number of patients modelled), 50% (3.1% of the initial number of patients), 75% (4.7% of the initial number of patients) and 100% (6.3% of the initial number of patients) of patients remaining on treatment before disease progression. Please note that the analyses have been developed by reflecting the additional costs related to drug and administration costs. However, efficacy (OS and PFS) has not been changed from the original base-case 2. Table 1 below summarises the deterministic and probabilistic results of base-case 2 including the PAS.

Table 1. Incremental cost-effectiveness results of base-case 2 (discounted, with PAS)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,609	1.216	-	-	-
Docetaxel	£11,267	0.604	£27,342	0.612	£44,678
Probabilistic					
Pembrolizumab	£38,640	1.219	-	-	-

Docetaxel	£11,263	0.604	£27,377	0.614	£44,563
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,410	1.216	-	-	-
Docetaxel	£11,267	0.604	£28,143	0.612	£45,987
Probabilistic					
Pembrolizumab	£39,493	1.217	-	-	-
Docetaxel	£11,277	0.605	£28,216	0.612	£46,089
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,211	1.216	-	-	-
Docetaxel	£11,267	0.604	£28,944	0.612	£47,296
Probabilistic					
Pembrolizumab	£40,439	1.216	-	-	-
Docetaxel	£11,286	0.604	£29,154	0.612	£47,666
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,012	1.216	-	-	-
Docetaxel	£11,267	0.604	£29,745	0.612	£48,605
Probabilistic					
Pembrolizumab	£41,099	1.215	-	-	-
Docetaxel	£11,286	0.604	£29,814	0.611	£48,795
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,813	1.216	-	-	-
Docetaxel	£11,267	0.604	£30,546	0.612	£49,914
Probabilistic					
Pembrolizumab	£42,069	1.219	-	-	-
Docetaxel	£11,264	0.605	£30,805	0.614	£50,135
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

Scenario and sensitivity analyses:

Please apply the following to the revised base-case 2 probabilistic cost-effectiveness analysis described above:

Please note that for all analyses presented in the answers to the following questions, both deterministic and probabilistic results have been presented for 5 different scenarios:

- Assuming that no patient continues treatment after 2 years (original base case 2), in line with available evidence from KEYNOTE-010.
- Assuming that a proportion of patients (25%, 50%, 75% or 100%) continue treatment after 2 years.

Analyses assuming that a number of patients continue treatment after 2 years have been developed by reflecting the additional costs related to medication and administration. However, efficacy (OS and PFS) is unchanged from the original base-case 2.

2. Please explore the impact of adjusting for treatment switching using the rank-preserving structural failure time method in a scenario analysis.

   For example, the committee noted that the RPSFT method was specified in KEYNOTE-010 to control for people having non-study treatment, but the company did not explain why it did not do a formal analysis of a common treatment effect assumption. It also noted that the adjustment method for treatment switching may have a greater effect on projected survival, that is, the mean compared with the median overall survival estimate. As a result it would be helpful for the committee to see a scenario analysis to determine the impact on the ICER.

   Please find in Table 4 below the requested results (based on the 30th September 2015 data cut-off). As mentioned in the original submission, the assumption of the 'common treatment effect' did not hold - patients who switched to pembrolizumab after docetaxel appeared to experience a different treatment effect than those initially allocated to pembrolizumab (as shown in Figure 13 of the original submission).

   Based on the most recent data cut-off (31st March 2016), the docetaxel OS was adjusted using both the RPSFT and the two-stage methods, as implemented in the initial submission. As it can be seen from Table 2 and Table 3, the most up-to-date adjusted results support the values presented in our original submission, which were obtained using the two-stage adjustment. MSD has provided the following documents:

   - Appendix 1 (related to the RPSFT adjustment) and
   - **Error! Reference source not found.** (related ot the two-stage adjustment)

   as additional documents for validation purposes.

Table 2. KEYNOTE-010 – Analysis of pembrolizumab versus docetaxel – adjustment for switching to anti-PD-1s

	ITT population cut-off 30SEP2015	ITT population cut-off 31MAR2016
	Hazard Ratio [95 %-CI]	Hazard Ratio [95 %-CI]
Docetaxel - unadjusted OS	0.71 [0.55;0.88]	0.72 (0.60, 0.87)
Docetaxel - 2-stage adjusted OS	0.69 [0.552; 0.85]	0.64 (0.53 , 0.77)
Docetaxel - RPSFT adjusted OS	0.71 [0.55;0.87]	0.69 (0.55, 0.85)

Table 3. KEYNOTE-010 - Analysis of median OS using two-stage and RPSFT methods to adjust for switching in the docetaxel arm

	ITT population cut-off 30SEP2015	ITT population cut-off 31MAR2016
	Median OS (Months) (95% CI)	Median OS (Months) (95% CI)
Pembrolizumab 2 mg/kg Q3W	10.4 (9.4, 11.9)	10.5 (9.6, 12.4)
Docetaxel - unadjusted OS	8.5 (7.5, 9.8)	8.6 (7.9, 9.8)
Docetaxel - 2-stage adjusted OS	8.3 (7.4, 9.5)	8.1 (7.0, 9.2)
Docetaxel - RPSFT adjusted OS	8.4 (7.5;9.8)	8.3 (7.5, 9.6)

Table 4. Incremental cost-effectiveness results of base-case 2, adjusting for treatment switching using the RPSFT method (discounted, with PAS)

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,609	1.216	-	-	-
Docetaxel	£11,402	0.656	£27,207	0.560	£48,586
Probabilistic					
Pembrolizumab	£38,811	1.223	-	-	-
Docetaxel	£11,390	0.657	£27,421	0.566	£48,480

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,410	1.216	-	-	-
Docetaxel	£11,402	0.656	£28,008	0.560	£50,017
Probabilistic					
Pembrolizumab	£39,579	1.218	-	-	-
Docetaxel	£11,417	0.657	£28,162	0.561	£50,184
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,211	1.216	-	-	-
Docetaxel	£11,402	0.656	£28,809	0.560	£51,447
Probabilistic					
Pembrolizumab	£40,363	1.217	-	-	-
Docetaxel	£11,420	0.657	£28,943	0.560	£51,679
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,012	1.216	-	-	-
Docetaxel	£11,402	0.656	£29,610	0.560	£52,878
Probabilistic					
Pembrolizumab	£41,068	1.218	-	-	-
Docetaxel	£11,410	0.657	£29,657	0.561	£52,834
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,813	1.216	-	-	-
Docetaxel	£11,402	0.656	£30,411	0.560	£54,308
Probabilistic					
Pembrolizumab	£42,071	1.216	-	-	-
Docetaxel	£11,412	0.657	£30,658	0.559	£54,826
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

3. Please explore the cut-off point after which the exponential model is fitted to those patients still at risk and applied in the cost-effectiveness analysis for extrapolation. This

analysis should show the sensitivity to both earlier and later cut-off points than those originally used in base case 2.

Two additional cut-offs (at 42 weeks and at 82 weeks) have been estimated, to reflect an earlier and a later cut-off point in addition to the three cut-offs initially presented in the submission (at 52 weeks – base case-, at 62 weeks and at 72 weeks –the latter two presented as part of sensitivity analyses; see Table 107, scenarios 9 and 10 in the original submission). The results of the deterministic and probabilistic sensitivity analyses for these cut-offs are presented in Table 5.

As a reminder, the cut-off at 52 weeks was used in the base case model because:

- It is supported by the cumulative hazard and the log-cummulative hazard plots of OS for pembrolizumab and docetaxel based on KEYNOTE-010 data, as presented in the submission (see Figures 31 and 32 in the submission). These plots show that the hazard is not constant over time and presents a different slope before and after around 52 weeks.
- It resulted in a plausible visual fit (see Figure 36 in the submission).
- It provided the most conservative estimate among the three alternative cut-off time points presented in the original submission.

The results related to the cut-off at 82 weeks were considered unreliable since only 17 patients (5%) in the pembrolizumab arm and 3 patients in the docetaxel arm (1%) remained alive at that time, resulting in a flat extrapolation of the OS that is not meaningful (due to the limited number of observations and the high level of censoring).

The results related to the cut-off at 42 weeks were considered unreliable because, when considering the cumulative hazard plot for OS in the pembrolizumab 2mg Q3W arm (see Figure 31 in the original submission, presented below as Figure 1), there was a clear change in the slope happening at around week 52.

Figure 1. Cumulative hazard plot of OS for pembrolizumab and docetaxel in all PD-L1 positive population based on KEYNOTE-010

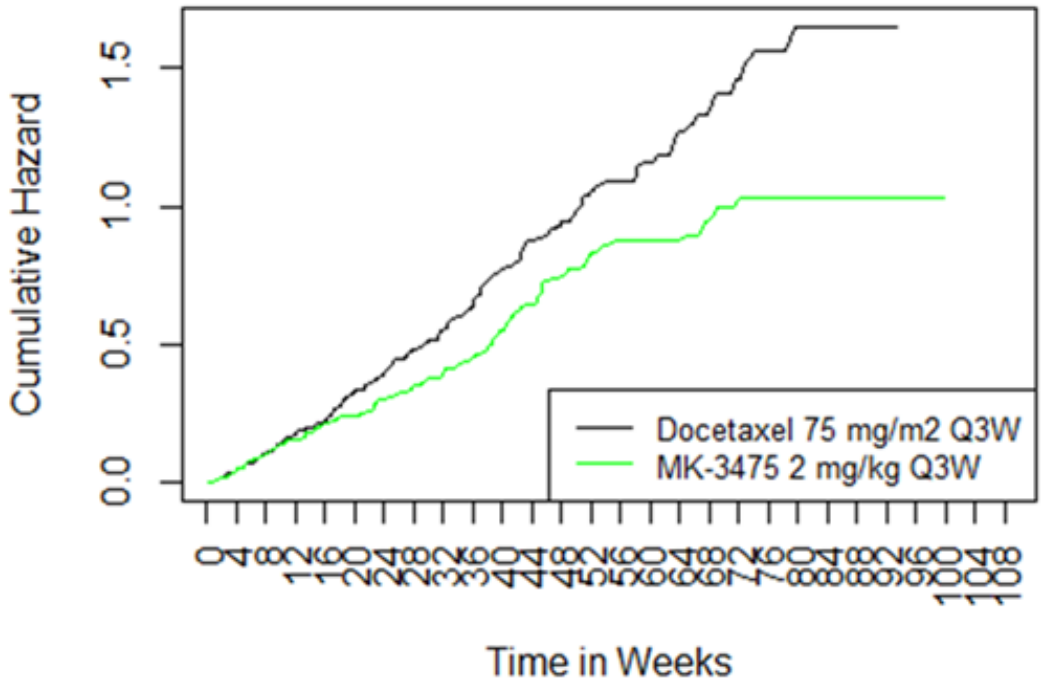


Table 5. Incremental cost-effectiveness results of base-case 2 based on deterministic and probabilistic sensitivity analyses (discounted, with PAS)

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
52-week cut-off (base case; as reported in question 1 above)					
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,609	1.216	-	-	-
Docetaxel	£11,267	0.604	£27,342	0.612	£44,678
Probabilistic					
Pembrolizumab	£38,640	1.219	-	-	-
Docetaxel	£11,263	0.604	£27,377	0.614	£44,563
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,410	1.216	-	-	-
Docetaxel	£11,267	0.604	£28,143	0.612	£45,987
Probabilistic					
Pembrolizumab	£39,493	1.217	-	-	-

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Docetaxel	£11,277	0.605	£28,216	0.612	£46,089
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,211	1.216	-	-	-
Docetaxel	£11,267	0.604	£28,944	0.612	£47,296
Probabilistic					
Pembrolizumab	£40,439	1.216	-	-	-
Docetaxel	£11,286	0.604	£29,154	0.612	£47,666
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,012	1.216	-	-	-
Docetaxel	£11,267	0.604	£29,745	0.612	£48,605
Probabilistic					
Pembrolizumab	£41,099	1.215	-	-	-
Docetaxel	£11,286	0.604	£29,814	0.611	£48,795
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,813	1.216	-	-	-
Docetaxel	£11,267	0.604	£30,546	0.612	£49,914
Probabilistic					
Pembrolizumab	£42,069	1.219	-	-	-
Docetaxel	£11,264	0.605	£30,805	0.614	£50,135
42-week cut-off					
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£37,941	0.963	-	-	-
Docetaxel	£11,366	0.642	£26,575	0.321	£82,897
Probabilistic					
Pembrolizumab	£37,979	0.963	-	-	-
Docetaxel	£11,372	0.643	£26,607	0.320	£83,127
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,742	0.963	-	-	-

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Docetaxel	£11,366	0.642	£27,376	0.321	£85,395
Probabilistic					
Pembrolizumab	£39,056	0.963	-	-	-
Docetaxel	£11,367	0.643	£27,689	0.321	£86,303
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,543	0.963	-	-	-
Docetaxel	£11,366	0.642	£28,177	0.321	£87,894
Probabilistic					
Pembrolizumab	£39,657	0.963	-	-	-
Docetaxel	£11,389	0.643	£28,268	0.321	£88,197
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,344	0.963	-	-	-
Docetaxel	£11,366	0.642	£28,978	0.321	£90,393
Probabilistic					
Pembrolizumab	£40,664	0.964	-	-	-
Docetaxel	£11,351	0.643	£29,313	0.321	£91,354
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,145	0.963	-	-	-
Docetaxel	£11,366	0.642	£29,779	0.321	£92,892
Probabilistic					
Pembrolizumab	£41,431	0.963	-	-	-
Docetaxel	£11,370	0.643	£30,060	0.320	£93,884
82-week cut-off					
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£43,653	3.229	-	-	-
Docetaxel	£13,768	1.594	£29,885	1.635	£18,276
Probabilistic					
Pembrolizumab	£43,790	3.229	-	-	-
Docetaxel	£13,812	1.594	£29,978	1.635	£18,337

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£44,454	3.229	-	-	-
Docetaxel	£13,768	1.594	£30,686	1.635	£18,766
Probabilistic					
Pembrolizumab	£44,685	3.229	-	-	-
Docetaxel	£13,767	1.594	£30,918	1.635	£18,910
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£45,255	3.229	-	-	-
Docetaxel	£13,768	1.594	£31,487	1.635	£19,256
Probabilistic					
Pembrolizumab	£45,640	3.229	-	-	-
Docetaxel	£13,763	1.594	£31,877	1.635	£19,498
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£46,056	3.229	-	-	-
Docetaxel	£13,768	1.594	£32,288	1.635	£19,746
Probabilistic					
Pembrolizumab	£45,986	3.229	-	-	-
Docetaxel	£13,776	1.594	£32,210	1.635	£19,702
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£46,857	3.229	-	-	-
Docetaxel	£13,768	1.594	£33,089	1.635	£20,236
Probabilistic					
Pembrolizumab	£47,015	3.229	-	-	-
Docetaxel	£13,761	1.594	£33,254	1.635	£20,341
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

4. Please explore alternative approaches to time to treatment using individual patient-level data and a gamma model, as used by the evidence review group (ERG), to estimate

duration. Please explain the impact of using this approach compared with the assumptions used in base case 2 [Kaplan–Meier plus an exponential model].

Table 7 below presents the deterministic and probabilistic sensitivity analyses when individual patient data and a fully parametric generalised gamma model is used to estimate treatment duration.

Figure 2 below shows the differences in the estimation of time on treatment (ToT) between the base case and the use of a generalised gamma model:

- In the base case, for the estimation of the treatment costs associated with pembrolizumab, PFS was used as a proxy for ToT with a hazard ratio applied to account for the proportion of patients that were treated until confirmed progression and for those who discontinued treatment previous to progression (see answer to question 5 below). As shown in Figure 2 below, this approach initially overestimates ToT, followed by a short period of underestimation, and then it overlaps with the KM curve for ToT for the majority of the remaining curve, except at the very end, when the number of remaining patients is very low and there are high levels of censoring and therefore higher uncertainty regarding treatment duration. On the whole, our approach reflects the treatment duration, and of note overestimates treatment duration in the initial treatment period.
- The fully parametric generalised gamma approach is not a close fit to the ToT KM curve for a large part of the curve, for which it clearly overestimates treatment duration (between month 3 and month 11; see Figure 2). During the development of the original submission, a one piece parametric approach based on ToT was not found to be appropriate for the estimate of ToT since:
    - None of the parametric models were a close fit to the data on visual grounds (see Figure 3).
    - When the AIC/BIC criteria were used to assess the goodness of fit, the models with the highest goodness of fit (i.e. lowest AIC/BIC values) were not a close fit to the data visually (see Figure 3 and Table 6 below).

Please note that time on treatment in the model is only to be used for the estimation of the costs of treatment (i.e. drug and administration costs).

Figure 2. Estimation of the time on treatment (ToT) for patients treated with pembrolizumab, comparing the ToT KM data, the ToT as estimated in the base case (KM + exponential from week 9, adjusted with the HR of ToT vs. PFS), and a fully parametric generalised gamma

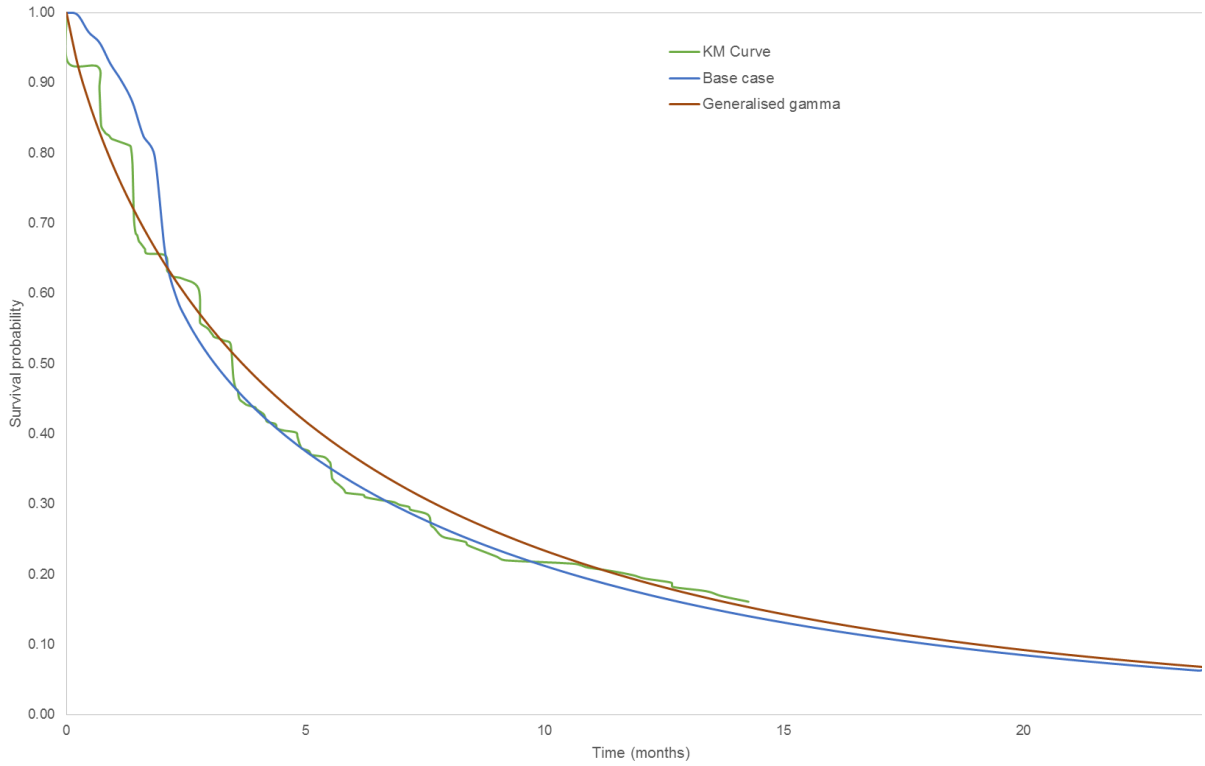


Figure 3. Duration of treatment for pembrolizumab 2mg Q3W based on fitting a fully parametric curve

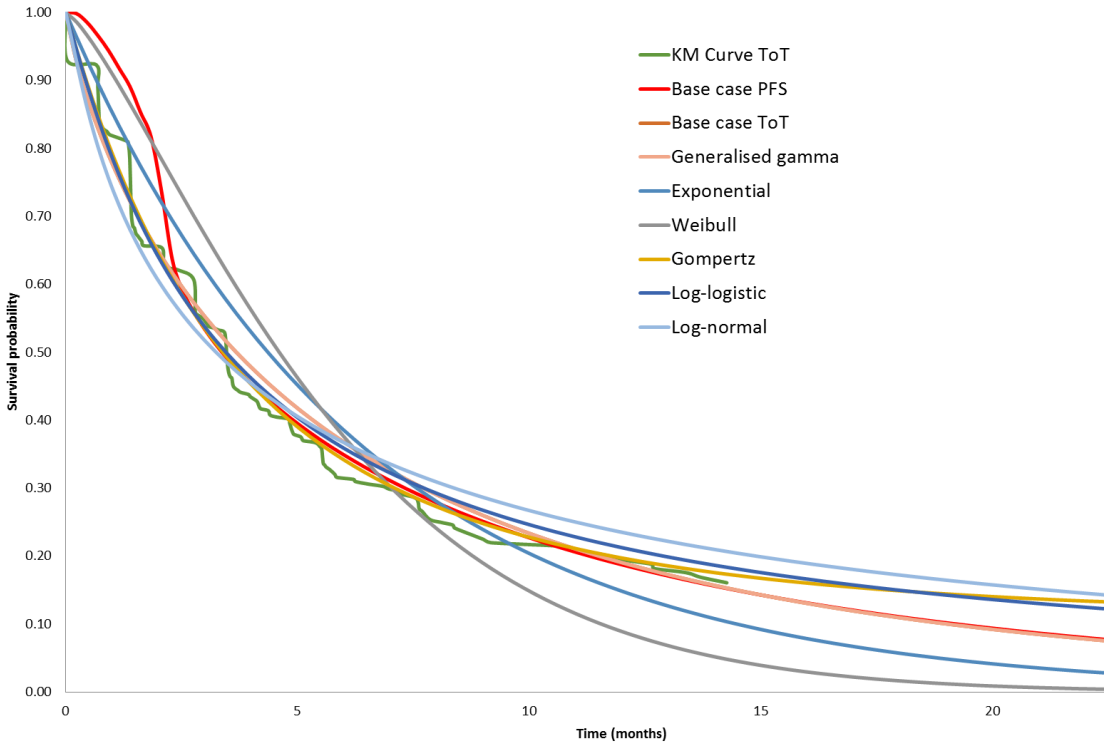


Table 6. Goodness of fit measures for ToT using a fully parametric model for the whole trial period

	Exp	Weibull	Gaus	Logist	LogNorm	LogLogist	**Gompertz**	GenGamma
AIC	2294.3	2266.3	2621.6	2597.3	2292.1	2264.0	**2256.0**	2267.1
BIC	2298.2	2274.0	2629.3	2605.0	2299.8	2271.7	**2263.6**	2278.6

Table 7. Incremental cost-effectiveness results of base-case 2, considering a fully parametric generalised gamma model (as used by the ERG) to estimate time on treatment based on deterministic and probabilistic sensitivity analyses (discounted, with PAS)

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£42,242	1.216	-	-	-
Docetaxel	£11,267	0.604	£30,975	0.612	£50,615
Probabilistic					
Pembrolizumab	£42,584	1.220	-	-	-

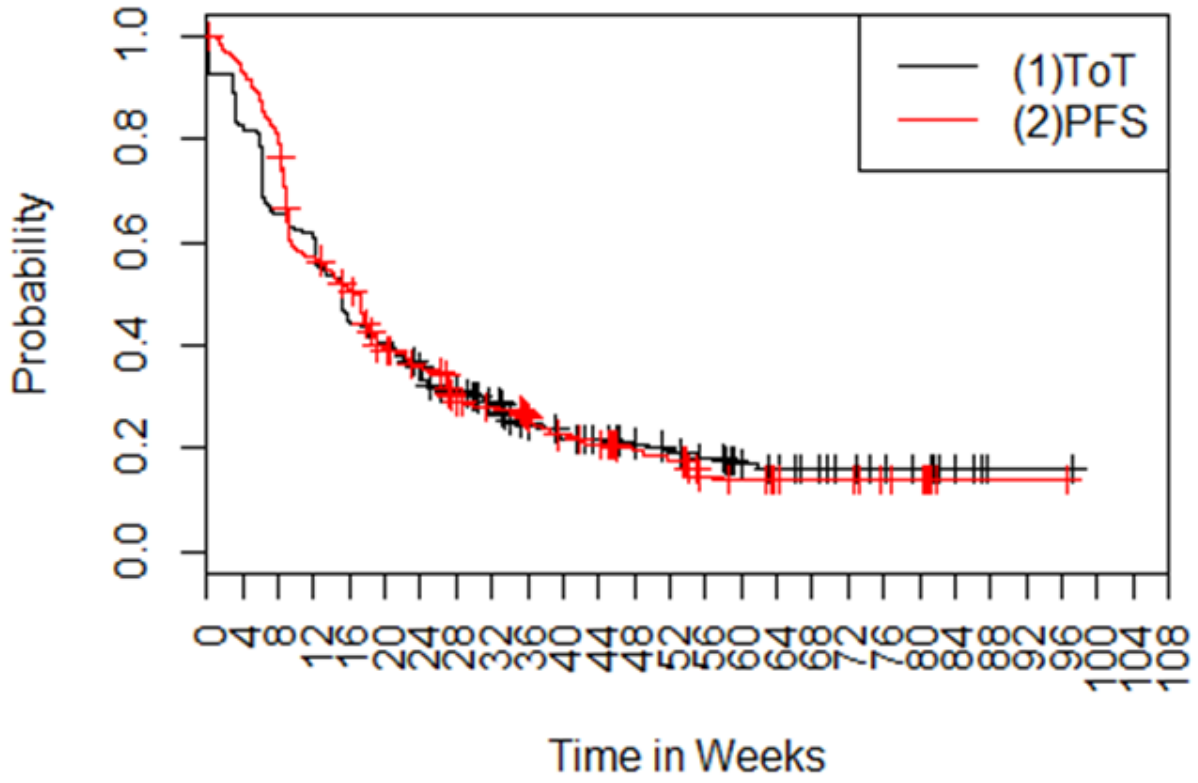
Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Docetaxel	£11,292	0.605	£31,292	0.616	£50,821
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£43,270	1.216	-	-	-
Docetaxel	£11,267	0.604	£32,003	0.612	£52,296
Probabilistic					
Pembrolizumab	£43,632	1.219	-	-	-
Docetaxel	£11,254	0.605	£32,377	0.614	£52,733
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£44,299	1.216	-	-	-
Docetaxel	£11,267	0.604	£33,032	0.612	£53,976
Probabilistic					
Pembrolizumab	£44,706	1.217	-	-	-
Docetaxel	£11,284	0.605	£33,422	0.612	£54,575
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£45,327	1.216	-	-	-
Docetaxel	£11,267	0.604	£34,060	0.612	£55,657
Probabilistic					
Pembrolizumab	£45,901	1.220	-	-	-
Docetaxel	£11,292	0.605	£34,608	0.615	£56,277
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£46,356	1.216	-	-	-
Docetaxel	£11,267	0.604	£35,088	0.612	£57,337
Probabilistic					
Pembrolizumab	£46,839	1.221	-	-	-
Docetaxel	£11,268	0.605	£35,571	0.616	£57,765
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

5. Time on treatment in the model should include the additional weeks of therapy needed (as stated in the KEYNOTE-010 protocol) to distinguish between true progression and pseudo-progression.

   For example, the committee discussed the phenomena of pseudo-progression and it was not clear how many patients in KEYNOTE-010 had confirmatory scans to check for disease progression, and what proportion of these scans confirmed true disease progression. The committee noted that a number of additional weeks of therapy were needed (as stated in the KEYNOTE-010 protocol) to distinguish between true progression and pseudo-progression in some circumstances, and this should be incorporated in the time on treatment calculation.

   MSD would like to reassure the Committee and the ERG that the duration of treatment was incorporated appropriately in the cost-effectiveness model. ToT was evaluated in the KEYNOTE-010 trial irrespective of disease progression and includes all weeks of treatment therapy.
   An adjusted PFS was used as a proxy for ToT for the estimation of drug and administration costs in the model. However, in the KEYNOTE-010 trial, RECIST 1.1 PFS would under-estimate the ToT considering that irRC generally occurs later than RECIST progression and patients could remain on treatment until confirmation of progression (4-9 weeks later).
   MSD has explored the relationship between the PFS and ToT curves. As observed in Figure 4, the two curves are close and the HR of 0.96 with 95% CI: (0.81, 1.14) demonstrates no statistically significant difference between the two curves. Thus, PFS was adjusted with the HR to account for any difference between ToT and PFS, including discontinuation due to toxicities, and additional weeks of therapy.
   Finally, MSD would like to apologise if the methodology employed in the model for the estimation of treatment costs was not clearly reported in the submission.

Figure 4. ToT vs. PFS for pembrolizumab 2mg Q3W based on KEYNOTE-010 (cut-off: 30th September 2015)



6. Please explore the impact of using a range of published post-progression utility values, as presented in the company submission (section 5.4.4, pages 191 to 195), in sensitivity analyses.

In base-case 2 analysis, the method used to estimate QALYs considered time to death (TTD) and progression based utilities. From the systematic literature review six studies were identified that included utility values for the post-progression health state. MSD has been asked to explore using these in sensitivity analyses.

The NICE reference case requires measurements of changes in HRQoL to be reported directly from patients and the utility of these to be based on public preferences using a choice-based method (see section 5.3.1. from the NICE guide to the methods of technology appraisal).[1] Based on this, the following were excluded:

- Nafees et al (2006,2008), Lewis et al (2010) and Tabberer et al (2006) were all excluded as they assessed the utility values in a healthy (or general) population.

Chevalier et al (2013) was additionally excluded as a French tariff was used.

MSD therefore explored the impact of Chouaid et al (2013b) utility values for the post progression health state, without incorporating TTD-specific utilities for the post-

progression health state (i.e. the same post-progression utility value was used independent of the TTD, since the study by Chouaid 2013b did not report post-progression utilities considering TTD). Although Chouaid 2013b does appear to meet the NICE reference case, MSD has some concerns regarding the appropriateness of using post-progression utility values to appraise pembrolizumab. The pre-progression utility value is lower than the one from KEYNOTE-010, which suggests that the inclusion by Chouaid 2013b of patients with ECOG status 0 to 2 compared to 0 to 1 from KEYNOTE-010 demonstrates a sicker population. We would also note that the EQ-5D questionnaire was administered only once to all of the patients and therefore the progressed disease utility value is derived from a different population to that of the pre-progressed.

Table 8 below summarises the utility values included in this scenario analysis; the results of the analysis are reported in Table 9.

Table 8. Summary of utility values in the post-progression health state

	KEYNOTE-010 (All)		Chouaid et al, 2013b (only progressed disease used)	
Progression-free	**Mean**	**SE**	**Mean**	**SE**
>=30 days	0.763	0.006	0.74	0.18*
<30 days*	0.284	0.072		
Progressed	**Mean**	**SE**	**Mean**	**SE**
>=0 days	0.675	0.015	0.59	0.059
<30 days^	0.32	0.122		
*n=27 patients with EQ-5D score, ^n=12 patients with EQ-5D score; *SD instead of SE				

Table 9. Incremental cost-effectiveness results of base-case 2, including the impact of post progression utilities from Chouaid et al. (2013b), based on deterministic and probabilistic sensitivity analyses (discounted, with PAS)

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,609	1.132	-	-	-
Docetaxel	£11,267	0.580	£27,342	0.551	£49,581
Probabilistic					
Pembrolizumab	£38,558	1.133	-	-	-
Docetaxel	£11,249	0.581	£27,309	0.552	£49,489

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,410	1.132	-	-	-
Docetaxel	£11,267	0.580	£28,143	0.551	£51,033
Probabilistic					
Pembrolizumab	£39,528	1.135	-	-	-
Docetaxel	£11,301	0.581	£28,227	0.554	£50,910
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,211	1.132	-	-	-
Docetaxel	£11,267	0.580	£28,944	0.551	£52,486
Probabilistic					
Pembrolizumab	£40,186	1.135	-	-	-
Docetaxel	£11,286	0.581	£28,900	0.554	£52,207
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,012	1.132	-	-	-
Docetaxel	£11,267	0.580	£29,745	0.551	£53,938
Probabilistic					
Pembrolizumab	£41,107	1.135	-	-	-
Docetaxel	£11,265	0.581	£29,842	0.554	£53,855
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,813	1.132	-	-	-
Docetaxel	£11,267	0.580	£30,546	0.551	£55,391
Probabilistic					
Pembrolizumab	£41,963	1.132	-	-	-
Docetaxel	£11,270	0.581	£30,693	0.551	£55,702
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

7. Please explore the inclusion of adverse event disutilities in a scenario analysis to demonstrate the impact on the ICER.

For example, the company stated that pooled trial utility values were used in the cost effectiveness model, however adverse-event related disutilities should have been included in base case 2. As a result, it would be helpful for the committee to see a scenario analysis to determine the impact on the ICER.

The impact of including AE-related disutilities based on the KEYNOTE-010 trial was evaluated in the original submission as part of scenario 6 (see page 240 in the submission). Table 11 below presents the deterministic and probabilistic results when AE-related disutilities based on the KEYNOTE-010 trial are incorporated in the analysis. Please note that an average disutility value was applied in this scenario as it was not possible to derive separate disutilities per AE from KEYNOTE-010. MSD has also explored the impact of specific disutilitites per AE based on published literature (see Table 10). Please find the deterministic and probabilistic results for this analysis in Table 12.

Table 10.AE disutilites based on KEYNOTE-010 vs. those derived from published literature

AE	KEYNOTE-010		Other sources		Source
	Mean	SE	Mean	SE	
Alopecia/ Hair loss	-0.085	0.009	-0.045	0.004	*Nafees et al, 2008*
Anaemia			-0.070	0.007	*TA347, 2015*
Asthenia			-0.073	0.007	*ID811, 2015*
Decrease appetite			0.000	0.000	*Assumed to be 0*
Diarrhea (grade 2)			-0.020	0.002	*TA347, 2015*
Diarrhea (grade 3-4)			-0.047	0.016	*Nafees et al, 2008*
Fatigue			-0.073	0.018	*Nafees et al, 2008*
Febrile neutropenia			-0.090	0.016	*Nafees et al, 2008*
Nausea			-0.048	0.016	*Nafees et al, 2008*
Neuropathy peripheral			0.000	0.000	*Assumed to be 0*
Neutropenia			-0.090	0.015	*Nafees et al, 2008*
Neutrophil count decreased			-0.090	0.009	*Assumed same as neutropenia*
Pruritus			0.000	0.000	*Assumed to be 0*
Pyrexia			0.000	0.000	*Assumed to be 0*
Rash			-0.032	0.012	*Nafees et al, 2008*
Stomatitis			0.000	0.000	*Assumed to be 0*
Vomiting			-0.048	0.016	*Nafees et al, 2008*
WBC count decreased			-0.050	0.005	*TA347, 2015*

Table 11. Incremental cost-effectiveness results of base-case 2, including the impact of AE-related disutilities from KEYNOTE-010 trial, based on deterministic and probabilistic sensitivity analyses (discounted, with PAS)

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,609	1.213	-	-	-
Docetaxel	£11,267	0.569	£27,342	0.643	£42,496
Probabilistic					
Pembrolizumab	£38,633	1.215	-	-	-
Docetaxel	£11,274	0.570	£27,358	0.645	£42,416
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,410	1.213	-	-	-
Docetaxel	£11,267	0.569	£28,143	0.643	£43,741
Probabilistic					
Pembrolizumab	£39,455	1.217	-	-	-
Docetaxel	£11,267	0.570	£28,189	0.647	£43,555
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,211	1.213	-	-	-
Docetaxel	£11,267	0.569	£28,944	0.643	£44,986
Probabilistic					
Pembrolizumab	£40,373	1.217	-	-	-
Docetaxel	£11,265	0.569	£29,108	0.648	£44,926
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,012	1.213	-	-	-
Docetaxel	£11,267	0.569	£29,745	0.643	£46,231
Probabilistic					
Pembrolizumab	£41,283	1.215	-	-	-
Docetaxel	£11,266	0.570	£30,017	0.645	£46,527

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,813	1.213	-	-	-
Docetaxel	£11,267	0.569	£30,546	0.643	£47,476
Probabilistic					
Pembrolizumab	£41,940	1.218	-	-	-
Docetaxel	£11,258	0.570	£30,682	0.647	£47,404
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

Table 12. Incremental cost-effectiveness results of base-case 2, including the impact of AE-related disutilities from published literature based on deterministic and probabilistic sensitivity analyses (discounted, with PAS)

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,609	1.214	-	-	-
Docetaxel	£11,267	0.574	£27,342	0.640	£42,736
Probabilistic					
Pembrolizumab	£38,644	1.213	-	-	-
Docetaxel	£11,278	0.575	£27,366	0.638	£42,879
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,410	1.214	-	-	-
Docetaxel	£11,267	0.574	£28,143	0.640	£43,988
Probabilistic					
Pembrolizumab	£39,491	1.221	-	-	-
Docetaxel	£11,268	0.575	£28,223	0.646	£43,693

Techonolgies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,211	1.214	-	-	-
Docetaxel	£11,267	0.574	£28,944	0.640	£45,240
Probabilistic					
Pembrolizumab	£40,296	1.218	-	-	-
Docetaxel	£11,273	0.575	£29,023	0.644	£45,087
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,012	1.214	-	-	-
Docetaxel	£11,267	0.574	£29,745	0.640	£46,492
Probabilistic					
Pembrolizumab	£41,210	1.215	-	-	-
Docetaxel	£11,285	0.575	£29,925	0.640	£46,748
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,813	1.214	-	-	-
Docetaxel	£11,267	0.574	£30,546	0.640	£47,744
Probabilistic					
Pembrolizumab	£42,148	1.217	-	-	-
Docetaxel	£11,281	0.575	£30,868	0.642	£48,081
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

A comment was made during the first committee meeting with regards to patients remaining on pembrolizumab treatment for longer than patients in docetaxel, and therefore, that they would experience AEs for a longer period. As observed in Table 13 below and based on the KEYNOTE-010 trial, only one patient experienced AE after one year of treatment with pembrolizumab, and this patient was accounted for as part of the estimation of the incidence of AEs from KEYNOTE-010.

Table 13: Number of patients experiencing Grade 3+ AEs of relevance for the CEM by time period, APaT Population (TPS≥1%)

Observation period of drug exposure	Control				MK-3475 2 mg/kg Q3W			
	0-3 months	3-6 months	6-12 months	Beyond 12 months	0-3 months	3-6 months	6-12 months	Beyond 12 months
AE Category								
Alopecia	2	0	0	0	0	0	0	0
Anaemia	4	3	0	0	8	1	0	1
Asthenia	6	1	1	0	3	1	0	0
Decreased appetite	6	1	1	0	5	1	0	0
Diarrhoea (grade 2)	13	2	1	0	7	5	3	0
Diarrhoea (grade 3+)	7	0	1	0	4	0	0	0
Fatigue	13	2	2	0	8	2	2	0
Febrile neutropenia	14	2	1	0	0	0	1	0
Nausea	2	0	0	0	3	3	1	0
Neuropathy peripheral	1	0	0	0	0	0	0	0
Neutropenia	69	13	4	0	0	0	0	0
Neutrophil count decreased	29	5	0	0	0	0	0	0
Pruritus	1	0	0	0	0	0	0	0
Pyrexia	3	0	0	0	2	1	0	0
Rash	0	0	0	0	0	1	0	0
Stomatitis	3	0	0	0	0	0	0	0
Vomiting	1	1	0	0	2	1	0	0
White blood cell count decreased	17	1	0	0	0	0	0	0
Database Cutoff Date: 30SEP2015								

9. Please provide a scenario in which the hazard ratio is assumed to be 1 after the trial ends (for example, those in the pembrolizumab arm are subject to the same hazard as those in the docetaxel arm).

   For example, the committee was aware that there was no model parameter to vary the treatment effect over time. It would have preferred to see an adjustment to the way the survival function is calculated at a particular point in time, by assuming that at trial end the hazard ratio is 1 (that is, people in the

pembrolizumab arm are subject to the same hazard as people in the docetaxel arm).

MSD has explored three scenarios with regards to the application of OS hazard ratio in the cost-effectiveness model, after the 52-week cut-off point. These scenarios were selected to reflect HRs going from 1 (as requested in the question) to 1.45 (which is the value that reflects the OS HR for pembrolizumab versus docetaxel estimated in KEYNOTE-010, using the two-stage adjustment for docetaxel, i.e. 0.69, continuing beyond 2 years). The results of the scenarios for HR=1.45, HR=1.2 and HR=1 can be found in Table 14 below.

Table 14. Incremental cost-effectiveness results of base-case 2 using different HRs for pembrolizumab compared to docetaxel (discounted, with PAS)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
HR=1.45					
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,006	1.365	-	-	-
Docetaxel	£11,267	0.604	£27,739	0.761	£36,460
Probabilistic					
Pembrolizumab	£39,202	1.367	-	-	-
Docetaxel	£11,299	0.605	£27,903	0.762	£36,630
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,806	1.365	-	-	-
Docetaxel	£11,267	0.604	£28,539	0.761	£37,512
Probabilistic					
Pembrolizumab	£39,823	1.364	-	-	-
Docetaxel	£11,280	0.604	£28,542	0.760	£37,569

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,607	1.365	-	-	-
Docetaxel	£11,267	0.604	£29,340	0.761	£38,565
Probabilistic					
Pembrolizumab	£40,658	1.364	-	-	-
Docetaxel	£11,281	0.604	£29,378	0.760	£38,665
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,408	1.365	-	-	-
Docetaxel	£11,267	0.604	£30,141	0.761	£39,617
Probabilistic					
Pembrolizumab	£41,533	1.364	-	-	-
Docetaxel	£11,276	0.605	£30,257	0.759	£39,858
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£42,208	1.365	-	-	-
Docetaxel	£11,267	0.604	£30,941	0.761	£40,669
Probabilistic					
Pembrolizumab	£42,461	1.366	-	-	-
Docetaxel	£11,273	0.604	£31,188	0.762	£40,940
HR=1.2					
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,112	1.028	-	-	-
Docetaxel	£11,267	0.604	£26,845	0.424	£63,258
Probabilistic					
Pembrolizumab	£38,106	1.028	-	-	-
Docetaxel	£11,288	0.604	£26,818	0.424	£63,311

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,912	1.028	-	-	-
Docetaxel	£11,267	0.604	£27,645	0.424	£65,144
Probabilistic					
Pembrolizumab	£39,035	1.029	-	-	-
Docetaxel	£11,293	0.604	£27,742	0.425	£65,299
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,713	1.028	-	-	-
Docetaxel	£11,267	0.604	£28,446	0.424	£67,031
Probabilistic					
Pembrolizumab	£39,737	1.029	-	-	-
Docetaxel	£11,285	0.605	£28,452	0.424	£67,100
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,514	1.028	-	-	-
Docetaxel	£11,267	0.604	£29,247	0.424	£68,918
Probabilistic					
Pembrolizumab	£40,817	1.027	-	-	-
Docetaxel	£11,283	0.604	£29,534	0.423	£69,824
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£41,315	1.028	-	-	-
Docetaxel	£11,267	0.604	£30,047	0.424	£70,804
Probabilistic					
Pembrolizumab	£41,605	1.028	-	-	-
Docetaxel	£11,260	0.604	£30,345	0.424	£71,596
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
HR=1.0					
0% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£37,731	0.885	-	-	-
Docetaxel	£11,267	0.604	£26,464	0.281	£94,295
Probabilistic					
Pembrolizumab	£38,014	0.884	-	-	-
Docetaxel	£11,281	0.604	£26,732	0.280	£95,371
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£38,500	0.885	-	-	-
Docetaxel	£11,267	0.604	£27,233	0.281	£97,034
Probabilistic					
Pembrolizumab	£38,560	0.884	-	-	-
Docetaxel	£11,262	0.604	£27,298	0.280	£97,509
50% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,269	0.885	-	-	-
Docetaxel	£11,267	0.604	£28,002	0.281	£99,774
Probabilistic					
Pembrolizumab	£39,416	0.885	-	-	-
Docetaxel	£11,261	0.604	£28,156	0.280	£100,493
75% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,038	0.885	-	-	-
Docetaxel	£11,267	0.604	£28,771	0.281	£102,514
Probabilistic					
Pembrolizumab	£40,166	0.884	-	-	-
Docetaxel	£11,308	0.604	£28,859	0.281	£102,870

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
100% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£40,807	0.885	-	-	-
Docetaxel	£11,267	0.604	£29,540	0.281	£105,253
Probabilistic					
Pembrolizumab	£41,102	0.885	-	-	-
Docetaxel	£11,255	0.605	£29,847	0.280	£106,633
ICER, incremental cost-effectiveness ration; QALYs, quality-adjusted life years					

MSD acknowledges that the NICE guide to the methods of technology appraisals suggests that different approaches for the duration of treatment effect should be explored (including same treatment benefits as during the treatment phase, diminishing benefits and nill treatment benefits over time; see section 5.7.7.).[1]

There is compelling evidence that patients in receipt of a checkpoint inhibitor that stop treatment before disease progression maintain clinical benefit. The distinct mechanism of action of the immune checkpoint inhibitors aims to reactivate antitumour immunity, achieving persistent survival benefit even after treatment discontinuation, as long as both the immune system and the tumour are in equilibrium state, i.e. when the immune response successfully controls tumour growth. [2,3]

Of note, no NICE HTA submission of a checkpoint inhibitor (STA268,[4] STA319,[5] STA357,[6] STA366,[7] TA384,[8] TA400,[9] ID900,[10] ID811,[11] ID853[12]) has discussed or evaluated fading of treatment effect following discontinuation of drug.

[redacted]

A1. [redacted] Additionally, based on clinical data presented in ASCO 2016 in patients with advanced melanoma in KEYNOTE-001, 61 patients experienced complete response and discontinued treatment with pembrolizumab. At the time of the analysis (median follow up 32 months) 97% (n=59) of responses were maintained and only 2 patients (3%) had experienced progressive disease (please see slides in

A2. Appendix 2

Appendix 3).

Furthermore, during the appraisals of NICE STAs of nivolomub in squamous and non-squamous lung cancer, results from the Checkmate-003 trial were presented supporting the evidence of ongoing clinical benefit following treatment discontinuation at 96 weeks. In this study, 50% of responders (n=19) that had discontinued treatment for reasons other than disease progression demonstrated persistent treatment benefit for up to 9 months from the last drug administration.[2]

In relation to ipilimumab, Schadendorf (2015) published a pooled analysis of long-term survival data from phase II and III trials of ipilimumab in unresectable or metastatic melanoma. Ipilimumab, which is licensed for only four cycles of treatment administration, has shown consistent clinical benefit. Specifically, the OS curves started to plateau approximately at year 3 and continued in some cases until year 10.[13]

Company's revised base-case 2

Reflecting on the discussions at the previous committee meeting and the questions asked in this document, MSD presents a revised base case 2 for consideration using the following assumptions:

- 25% of the patients remaing on pembrolizumab after 2 years of treatment in the original base-case 2 (i.e. 1.3% of patients who entered the model)
- Applying a 2-stage cross-over adjustment methodology for the docetaxel arm
- Using 52-week cut-off data for the exponential parametric curves
- ToT for pembrolizumab is based on HR
- Post progression utilitites based on TTD combined with progression-based utilities derived from KEYNOTE-010
- Inclusion of AE disutilities based on KEYNOTE-010
- No fading of treatment effect after the 52-week cut-off point

Table 15 below summarises MSD's preferred scenario.

Table 15. Incremental cost-effectiveness results of base-case 2 – MSD's preferred basecase (discounted, with PAS)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
25% of patients receiving treatment after 2 years					
Deterministic					
Pembrolizumab	£39,410	1.213	-	-	-

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel	£11,267	0.601	£28,143	0.612	£45,987
Probabilistic					
Pembrolizumab	£39,609	1.215	-	-	-
Docetaxel	£11,272	0.601	£28,337	0.614	£46,148

Clarifications:

Please provide further clarification on the following:

10. How many people from KEYNOTE-010 are still having pembrolizumab treatment after 2 years

    MSD can confirm that, based on the latest cut-off dataset (March 31, 2016) and additional follow-up data until July 21, 2016, no patients from the KEYNOTE-010 study have continued treatment after 2 years. In line with the KEYNOTE-010 protocol, patients discontinued treatment at 2 years of uninterrupted therapy (and no documented disease progression) or 35 treatment administrations, whichever occurred later.

11. The proportion of people in KEYNOTE-010 who had confirmatory scans and the percentage who were confirmed to have disease progression. Of these, how many continued on treatment with pembrolizumab post-progression at the clinician's discretion.

    XXXXXXXXXX

12. Please provide a summary of the hazard ratio for progression-free survival and overall survival calculated from the model results (that is, the hazard ratio based on the extrapolation).

    Based on the cost-effectiveness model, the estimated OS and PFS HRs when pembrolizumab was compared against docetaxel were:

    - OS HR = 0.46
    - PFS HR = 0.68

Of note, the HRs are estimated assuming proportional hazards, and this assumption did not hold when evaluating the PFS and OS in our submission for pembrolizumab versus docetaxel.

13. Why the rank-preserving structural failure time (RPSFT) method was disregarded and the two-stage adjustment method favoured instead. Please also clarify why why a formal analysis of a common treatment effect assumption using the RPSFT method was not carried out.

The ITT methodology underestimates the treatment effect in the presence of switchover to better treatment. Therefore methods for adjusting for switchover were indicated. The RPSFT method is assuming common treatment effect while the 2-stage method is assuming no unmeasured confounders.

As mentioned in the submission, the RPSFT method was considered inappropriate. While there is no specific test for this assumption, MSD did formally evaluate whether there was a 'common treatment effect' numerically (using two-stage estimates).

[redacted]

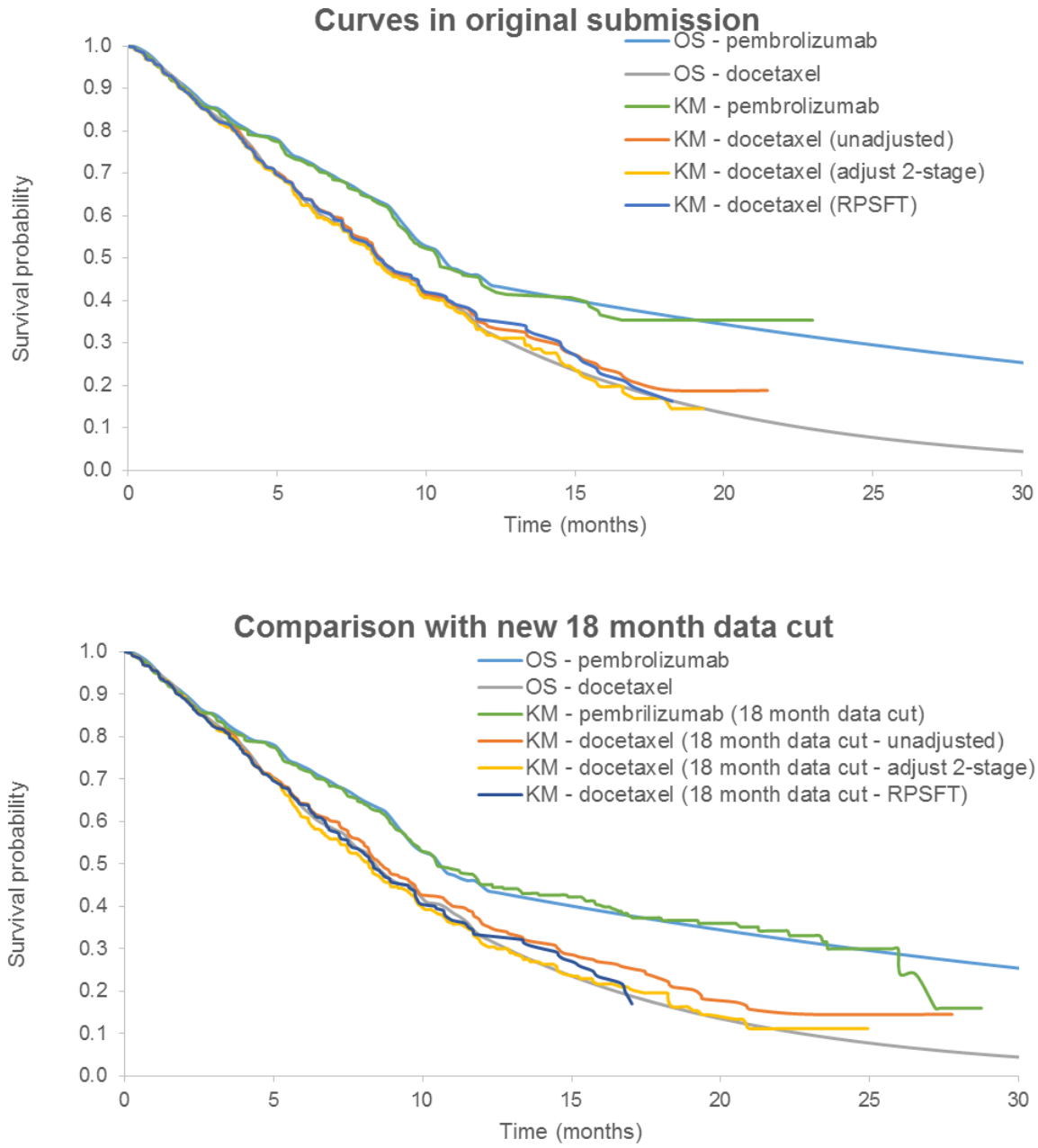
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The two-stage adjustment was found to be appropriate since:

- There was a clear secondary baseline (i.e. the time of progression).
- There were no relevant unmeasured confounders at the point of switch (measured variables included: ECOG performance status at the time of progression, age, sex, tumour size prior to progression, metastatic staging).
- Method and results replicated what was presented during our advanced melanoma submission.

MSD has implemented the two-stage and RPSFT adjustments on the latest cut-off dataset (March 2016) to provide further information to the committee. The results are presented in Table 2, Table 3 (in the answer to question 2), and Figure 5 below.

Figure 5. OS KM data and switching adjustments based on the September 2015 and the March 2016 cut-off datasets compared to the OS extrapolations from the cost-effectiveness model (base case 2)

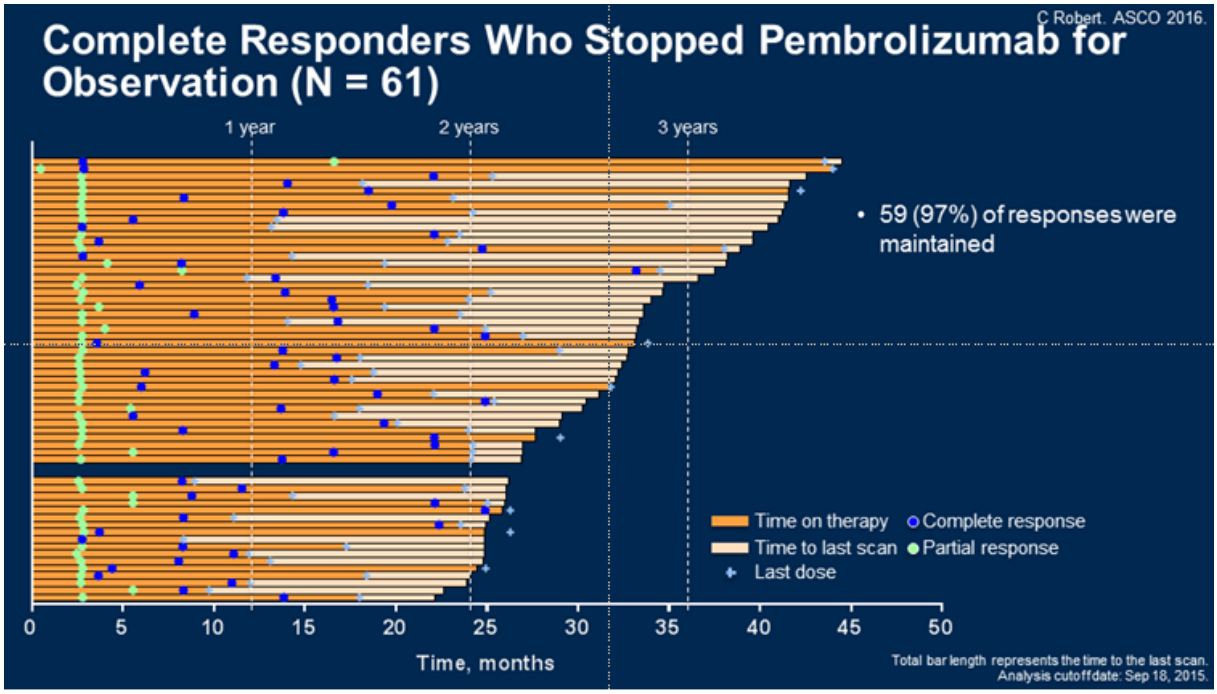


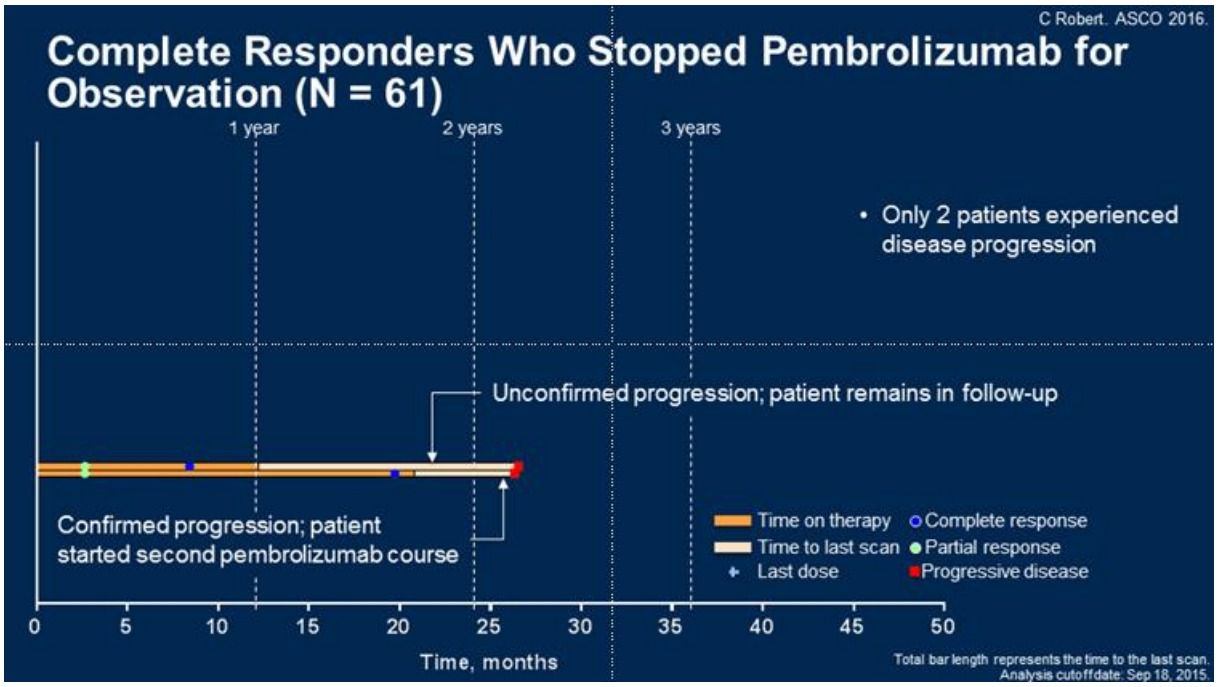
Appendix 1

Appendix 2

Appendix 3 – Evidence on persistent treatment effect of pembrolizumab

Pembrolizumab – KN001 Melanoma patients





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[1] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781; accessed on: 12th August 2016.

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[4] National Institute for Health and Care Excellence. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance [TA268]. Available at: https://www.nice.org.uk/guidance/ta268; accessed on: 12th August 2016.

[5] National Institute for Health and Care Excellence. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance [TA319]. Available at: https://www.nice.org.uk/guidance/ta319; accessed on: 12th August 2016.

[6] National Institute for Health and Care Excellence. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. NICE technology appraisal guidance [TA357] 2015. Available at: https://www.nice.org.uk/guidance/ta357; accessed on: 12th August 2016.

[7] National Institute for Health and Care Excellence. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. NICE technology appraisal guidance [TA366] 2016. Available at: https://www.nice.org.uk/guidance/ta366; accessed on: 12th August 2016.

[8] National Institute for Health and Care Excellence. Nivolumab for treating advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance [TA384]. Available at: https://www.nice.org.uk/guidance/ta384; accessed on: 12th August 2016.

[9] National Institute for Health and Care Excellence. Nivolumab in combination with ipilimumab for treating advanced melanoma. NICE technology appraisal guidance [TA400]. Available at: https://www.nice.org.uk/guidance/ta400; accessed on: 12th August 2016.

[10] National Institute for Health and Care Excellence. Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [ID900]. NICE in development [GID-TAG524]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag524; accessed on: 12th August 2016.

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https://www.nice.org.uk/guidance/indevelopment/gid-tag506; accessed on: 12th August 2016.

[12] National Institute for Health and Care Excellence. Renal cell carcinoma (metastatic, treated) - nivolumab [ID853]. NICE in development [GID-TA10037]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10037/consultation/html-content; accessed on: 12th August 2016.

13 Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, Patt D, Chen TT, Berman DM, Wolchok JD. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol. 2015 Jun 10;33(17):1889-94. doi: 10.1200/JCO.2014.56.2736. Epub 2015 Feb 9.

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23rd August 2016

Dear Helen,

Re. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Please find attached the updated answer to question 11.

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

Kind regards,

[redacted]

Single technology appraisal

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Dear [redacted],

Following the Committee meeting on 29th June to discuss pembrolizumab for treating locally advanced or metastatic non-small-cell lung cancer, we are writing to request some further analyses and clarifications from the company. We would be grateful if you could please include these in a supplementary appendix to your original submission, also containing your updated value proposition for pembrolizumab, in advance of the second appraisal committee meeting for this topic on 25 August 2016.

Please provide the supplementary appendix containing your updated value proposition and these analyses by **5pm** on **Tuesday 16 July 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.:

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries relating to the analyses requested in this letter, please contact Stuart Wood, Technical Lead (Stuart.Wood@nice.org.uk) or Fay McCracken, Technical Adviser (Fay.McCracken@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation
Please provide the following analyses:

11. The proportion of people in KEYNOTE-010 who had confirmatory scans and the percentage who were confirmed to have disease progression. Of these, how many continued on treatment with pembrolizumab post-progression at the clinician's discretion.

These analyses are all based on the KEYNOTE 010 trial with data cutoff date of September 30, 2015.

Progression was measured in two different ways for two different purposes in KEYNOTE-010

- Disease progression was measured by RECIST 1.1 criteria for the purpose of evaluation of progression as one of the trial endpoints. This was measured centrally by an Independent Review Committee (IRC) and the results were not communicated to the local investigator and therefore had no role to play in treatment decisions.

  The number of patients who had disease progression by RECIST per IRC was [redacted] of ITT population = 344). In total, [redacted] patients had confirmatory scans (i.e. [redacted] of those with disease progression by RECIST per IRC). Of these, [redacted] patients continued on treatment with pembrolizumab post-progression (RECIST per IRC).
- Disease progression was measured locally by the investigator by immune related Response Criteria (irRC) for the the purpose of deciding on whether to continue treatment with pembrolizumab.

  The number of patients who had disease progression by irRC was [redacted] of ITT population = 344). In total, [redacted] patients had confirmatory scans (i.e. [redacted] of those with disease progression by irRC). Of these, [redacted] patients continued on treatment with pembrolizumab post-progression by irRC).
- Of the ITT population (= 344 patients), [redacted] had PD by both criteria, [redacted] had no PD by both criteria, [redacted] had PD by RECIST but not by irRC, and [redacted] had PD by irRC and not by RECIST.

Please note that, as explained in response to Question 5, the HR-adjustment on PFS accounts for the additional cost of therapy for the population that remained on treatment following documented disease progression measured by RECIST per IRC. .

16-08-2016-REDACTED-FVMemo from KEYNOTE 010 –Pembrolizumab 2 mg/kg Q3W usage in relation to disease progression per RECIST 1.1 criteria based on independent review committee (IRC)

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Memo from KEYNOTE 010 –Pembrolizumab 2 mg/kg Q3W usage in relation to disease progression per irRC criteria based on investigator review (INV)

[redacted]

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Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy

Critique of the additional analyses submitted by the company after the 1st AC meeting

Produced by Aberdeen HTA Group

Date completed 23 August 2016

Contains CIC/AIC

This report provides the ERG's commentary on the additional cost-effectiveness analyses submitted by the company after the 1st AC meeting in response to a specific NICE request for further analyses and clarification. All new analyses have incorporated a new patient access scheme (PAS) of

[redacted], which has been approved by the Department of Health. The ERG received these revised analyses on 17 August 2016. The results are discussed in the following sections.

Stopping rule for pembrolizumab

The model currently forces all patients to stop treatment at 2 years regardless of whether they have progressed. This corresponds to the mandated termination of treatment at 2 years within the trial. This only affects predicted costs as there is no direct link in the model between predicted treatment duration or progression and overall survival. As a sensitivity analysis the company explored the effect of varying the proportion of those patients predicted to remain on treatment based on their predicted progression status that would continue treatment after 2 years – 0% (i.e. all patients stop at 2 years, original base-case 2), 25% (1.6% of total patients remain on treatment at 2 years), 50% (3.1% of total patients), 75% (4.7% of total patients) and 100% (6.3% of total patients). Only the impact on costs was included in the analysis; the efficacy had not been changed from the original base-case 2. In the new base-case, the company revised their stopping rule assumption from 0% to 25%, resulting in an ICER of £45,987.

The estimated costs in the original base case did correspond to drug use in the trial in that all patients stopped treatment at 2 years. The original base costs would also appear to correspond to the effectiveness of the drug as estimated from the trial. However, it should be borne in mind that the potential effect of the termination of treatment at 2 years may not be evident in the extrapolation of overall survival based on the current cut of the trial data.

If the licence or NICE mandate termination of treatment at 2 years then the original base case will reflect the cost of treatment in actual practice. If termination of treatment at 2 years is not mandated, it would seem likely that at a least some patients will continue treatment beyond two years. Due to the modelling approach used, the current sensitivity analysis provides information on the effect of costs of changes in treatment duration but not the effect on outcomes. The long term effects of terminating (or not) treatment at 2 years on long term survival remains uncertain.

Adjustment for switching with RPSFT

The company presented alternative analyses on OS, adjusting for switching using the RPSFT approach using two data cuts – 30 September 2015 (data cut used in original submission) and

31 March 2016. The differences between the OS estimates using the two sets of data were marginal, regardless of the adjustment and approaches to adjustment.

Compared with the original 2-stage adjustment, the RPSFT resulted in a smaller survival benefit (HR 0.71; 95%CI 0.55 to 0.87 compared with HR 0.69; 95%CI 0.55 to 0.85). The resultant ICER using RPSFT was £50,017 compared to £45,987 using the two part adjustment (based on the assumption that 25% of pembrolizumab patients remain on treatment beyond 2 years). The company considered the RPSFT to be inappropriate due to the assumption of common treatment effect.

A priori (i.e. before seeing the results of the analysis in terms of effects on the ICER) The ERG would also have preferred the two stage adjustment for the effects of cross-over as the assumptions of the RPSFT analysis (that treatment would have been constant pre and post progression) are more restrictive and a prior unlikely. If this assumption did hold the two analysis would on average give similar results (albeit with more uncertainty from the two part adjustment)

Cut-off point switch from KM to exponential model

The company presented cost-effectiveness analysis exploring two additional cut-off points – at 42 and 82 weeks, in addition to the 52 weeks cut-off (original base-case). The ICERs are sensitive to the cut-off point, with earlier time cut-offs resulting in higher ICERs. Based on the assumption that 25% of pembrolizumab patients remain on treatment beyond 2 years, the estimated ICERs were £85,395 and £18,766 using the 42-week and 82-week cut-offs, respectively.

The company considers 52-weeks a reasonable cut-off point, due to visual fit and the change in slope following this point. The ERG agrees that there appears to be an inflection in the survival curve at this point; however, this is less pronounced in the later 31 March 2106 data cut (presented at the previous committee meeting).

The company's area under the curve (AUC) model predicts long term overall survival solely based on the time to death observed during the trial. There is no link between time to progression or time on treatment. The company's model only considers those deaths that occur after 12 months for the long term extrapolation. The model treats the rate of death as

both constant with time after 12 months (and by implication varying with time before 12 months) and different between the two treatments. It should be noted that at the 12 month time point the patients will be heterogeneous in terms of progression and treatment status. The choice of the 12 month is based purely on the form of the observed survival curve from the trial and is not clearly related to any underlying biological or clinical process. The estimated ICER is sensitive to the selection of time points before 52 weeks. The assumption that the hazard of death for both treatments remains constant over the rest of the modelled time period as patients both progress and cease treatment is a strong assumption.

However, given the structure of the submitted model, the 52 week cut-point appears to represent the most sensible base case. Although considerable uncertainty remains, the OS curve based on the 31 March 2016 cut appears to supports the company's extrapolation based on the 52-week cut point.

Time on treatment

Following the committee's request, the company presented results of cost-effectiveness analyses that used a fully parametric generalised gamma model to estimate treatment duration. This resulted in an ICER of £52,296 (based on the assumption that 25% of pembrolizumab patients remain on treatment beyond 2 years). However, the ERG was unable to duplicate these results from the company's model.

Table 1 Incremental cost-effectiveness results of base-case 2, considering fully parametric generalised gamma model – company and ERG results (discounted, with PAS)

Technologies	0% of patients on Tx after 2 years	25% of patients on Tx after 2 years	50% of patients on Tx after 2 years	75% of patients on Tx after 2 years	100% of patients on Tx after 2 years
Company	£50,615	£52,296	£53,976	£55,657	£57,337
ERG	£46,105	£47,636	£49,166	£50,697	£52,227

The company considers the approach of using the generalised gamma model to be inappropriate, and that the original approach (using PFS as a proxy for time on treatment with a hazard ratio applied to account for discontinuation) is appropriate. The company also fitted different parametric curves to the time on treatment data, and concluded that the generalised gamma model did not provide the best model or visual fit.

The ERG view is the companies modelling is somewhat over complicated (time to progression with a constant hazard adjustment to estimate time to treatment discontinuation). We also note that there is evidence from the trial that some patents discontinued Pembrolizumab treatment before progression whilst others continued treatment beyond progression (although on average both curves appeared similar).

The ERG feel that it would be more appropriate to use the observed time to treatment discontinuation as the basis for modelling rather than time to progression with its attendant need for further adjustment. This is also in keeping with the overall model philosophy whereby other endpoints such as progression and death that are modelling independently.

Pseudo-progression

The company confirmed that they had included the costs of treatment between for those patients who were still on treatment whilst waiting for confirmation of progression as the time on treatment was evaluated in the KEYNOTE-010 irrespective of disease progression and includes all weeks of treatment therapy.

Post-progression utility

The company had identified six studies that included utility values for post-progression, but only one (Chouaid et al 2013) was considered appropriate for the scenario analysis. This resulted in an ICER of £51,033 (based on the assumption that 25% of pembrolizumab patients remain on treatment beyond 2 years).

The company reports that the study that has been included as a scenario analysis has limitations as the patient population used to elicit utility values was sicker than the KEYNOTE-010 one (ECOG status 0 to 2, compared to 0 to 1) and the pre and post-progression utilities are derived from separate populations.

Chouaid et al reported health utilities of 0.59 for second line and 0.46 for third line treatment. However, the estimates were also based on a sample size (N=47 for pre-progression 2nd line and N=17 post-progression 2nd line). The ERG considers the company's reasoning appropriate.

Adverse event disutilities

Following the committee's request, the company presented cost-effectiveness analysis exploring the impact of including disutilities in the ICER. The company presented two analyses; one using KEYNOTE-010 data and the other using published data. The ICERs for both types of data were similar; £43,741 and £43,988 respectively (based on the assumption that 25% of pembrolizumab patients remain on treatment beyond 2 years). However, the ERG was unable to duplicate these results from the company's new model, yet was able to duplicate the results for KEYNOTE-010 disutilities in the company's previous model.

Table 2 Incremental cost-effectiveness results of base-case 2, including the impact of AE-related disutilities from KEYNOTE-010 trial – company and ERG results (discounted, with PAS)

Technologies	0% of patients on Tx after 2 years	25% of patients on Tx after 2 years	50% of patients on Tx after 2 years	75% of patients on Tx after 2 years	100% of patients on Tx after 2 years
Company	£42,496	£43,741	£44,986	£46,231	£47,476
ERG	£44,678	£45,987	£47,296	£48,605	£49,914

Table 3 Incremental cost-effectiveness results of base-case 2, including the impact of AE-related disutilities from published literature – company and ERG results (discounted, with PAS)

Technologies	0% of patients on Tx after 2 years	25% of patients on Tx after 2 years	50% of patients on Tx after 2 years	75% of patients on Tx after 2 years	100% of patients on Tx after 2 years
Company	£42,736	£43,988	£45,240	£46,492	£47,744
ERG	£44,683	£45,992	£47,301	£48,610	£49,919

Long-term treatment effect

The assumption that the hazard of death for both treatments remains constant over the rest of the study period and that the difference in the hazards of death between treatments is maintained as patients both progress and cease treatment is a strong assumption. This is a clear uncertainty in both whether the differential effect of treatment on the hazard of death will be maintained as treatment is discontinued and the overall rate of death. Unfortunately, the submitted AUC model does not explicitly model the relationships between endpoints such as treatment discontinuation and progression. Therefore, we are restricted to relatively crude sensitivity analysis where the treatment effect is varied from a fixed timepoint and for all patients regardless of their status. The company supplied analysis where the incremental treatment effect was reduced by various degrees beyond the "trial" period (taken as 2 years). The EGR also conducted analyses where there assumed to be no incremental treatment effect beyond various time points.

The committee requested scenario analysis based on the assumption of no additional treatment benefit associated with pembrolizumab beyond the trial period. The company presented three scenario analyses: HR 1.45 (this reflects the OS hazard ratio for pembrolizumab versus docetaxel estimated in KETNOTE-010); HR 1.2 and HR 1.0. This resulted in an ICERs of £37,512, £65,144 and £97,034, respectively (based on the assumption that 25% of pembrolizumab patients remain on treatment beyond 2 years). However, the ERG was unable to duplicate these results from the company's model for the 1.45 hazard ratio.

Table 4 Incremental cost-effectiveness results of base-case2 using a hazard ratio of 1.45 (discounted, with PAS)

Technologies	0% of patients on Tx after 2 years	25% of patients on Tx after 2 years	50% of patients on Tx after 2 years	75% of patients on Tx after 2 years	100% of patients on Tx after 2 years
Company	£36,460	£37,512	£38,565	£39,617	£40,669
ERG	£36,513	£37,567	£38,621	£39,675	£40,729

The company argues that there is compelling evidence to suggest treatment benefit being maintained following treatment discontinuation.

The ERG carried out additional analysis on the duration of treatment effect to explore this further. The company model was adapted to enable the duration of treatment effect to be varied. This was achieved by using the pembrolizumab OS curve (KM + exponential) to the time point that treatment effect stopped and then continuing with the docetaxel OS curve following this time point. Based on the assumption that 25% of patients remain on treatment beyond 2 years, the ICERs were estimated for treatment effect being maintained to 3 years, 5 years, 10 years, 15 years and lifetime.

Although the notion that the relative treatment effect continues beyond the discontinuation of treatment (and therefore disease progression) appears bold there is evidence from other disease settings for sustained reduction in mortality. For example the Schadendorf (2015) meta-analysis pooled study data from studies where patients received ipilimumab for the treatment of in unresectable or metastatic melanoma. The meta-analysis appears to show a plateauing survival curve from 3 years (possibly continuing to 10 years although with small numbers of at risk patients).

Although the published analysis is for a different treatment and different disease area it should be borne in mind that equivalent data directly relevant to the current appraisal will not be available for at least five years. Therefore Schadendorf (2015) might be regarded as providing relevant information for the current analysis. Also, in Appendix 3 the company presents evidence of persistent treatment effect of pembrolizumab in KEYNOTE-001 for melanoma patients, this evidence shows treatment effect up to and beyond 3 years.

The ERG suggests that 3 years treatment effect duration might reasonable taking into account Schadendorf (2015) where patients showed treatment effect duration to 3 years and some to 10 years on ipilimumab, this scenario results in an ICER of £70,441. The results in Table 5 suggest that the treatment effect duration would need to last at least 10 years for the ICER to be cost-effective.

Table 5 Incremental cost-effectiveness results of base-case 2 assuming 25% of patients remain on treatment beyond 2 years and varying treatment effect duration (discounted, with PAS)

Treatment effect duration (years and months)	Treatment effect duration (weeks)	ICER
3 years	156 weeks	£70,441
5 years	260 weeks	£54,269
10 years	520 weeks	£46,914
15 years	780 weeks	£46,092
Lifetime	Lifetime	£45,987

Company's preferred scenario:

The company presents their preferred scenario as:

- 25% of the patients remaining on pembrolizumab after 2 years of treatment in the original base-case 2.
- Applying a 2-stage cross-over adjustment for treatment switching
- Using a 52 weeks cut-off for the exponential parametric curves
- ToT based on HR
- Post-progression utilities based on TTD combined with progression-based utilities from KEYNOTE-010
- Inclusion of AE disutilities from KEYNOTE-010
- No fading of treatment effect after the 52-week cut-off

Using these scenarios the company's preferred ICER is £45,987.

The ERG has calculated a 'worse-case' scenario incorporating the requests for further analysis from NICE to the company.

The scenario includes:

- 25% of the patients remaining on pembrolizumab after 2 years of treatment in the original base-case 2 which the ERG considers reasonable
- RPSFT for treatment switching; as requested by NICE
- 52 week cut-off, which the ERG considers a sensible base-case
- Gamma model for time to treatment; as requested by NICE
- Chouaid et al post-progression utilities; as requested by NICE

- Inclusion of AE disutilities from KEYNOTE-010; as requested by NICE
- Hazard ratio of 1 for duration of treatment effect; as requested by NICE

The resulting ICER incorporating all the above scenarios is £118,417. The ERG considers this ICER to be unlikely but includes it for clarification.

The ERG's preferred scenario is:

- 25% of the patients remaining on pembrolizumab after 2 years of treatment in the original base-case 2.
- Applying a 2-stage cross-over adjustment for treatment switching
- Using a 52 weeks cut-off for the exponential parametric curves
- ToT based on PFS and hazard ratio adjustment
- Post-progression utilities based on TTD combined with progression-based utilities from KEYNOTE-010
- Inclusion of AE disutilities from KEYNOTE-010
- Treatment effect duration of 3 years

The ERG preferred ICER is £65,200.

Further clarifications on ERG critique

The ERG produced commentary on the additional cost-effectiveness analyses submitted by the company after the 1st appraisal committee meeting in response to a specific NICE request for further analyses and clarification. The ERG provided NICE with these analyses on Tuesday 23 August. NICE had a number of additional queries and responses have been provided by the ERG below.

- ***Pseudo-progression: do you have an opinion on whether MSD has correctly included the additional weeks of therapy needed (as stated in the KEYNOTE-010 protocol) to distinguish between true progression and pseudo-progression? At the moment we only have MSD's assurances that they have been included. It would be really helpful for the committee to get a steer on whether they have in fact done this.***

  The company did not specifically adjust for pseudo-progression in their estimates of treatment costs. However, if patients did remain on treatment during pseudo-progression, the ToT data would reflect this. Overall, the adjusted PFS curve appeared similar to the ToT curve, the ERG is satisfied that the adjusted PFS approach did not introduce substantial bias.

  In terms of whether patients did remain on treatment during pseudo-progression:
  - the company provided data showing that [redacted] had disease progression (defined by RECIST),
  - of whom [redacted] ([redacted]) had x scans confirming disease progression (potentially consists of patients with pseudo-progression and real progression)
  - [redacted] ([redacted]) had ≥1 pembrolizumab dose between 1st and 2nd scan
  - [redacted] ([redacted]) had ≥1 dose of pembrolizumab after 2nd scan

  The company did not provide data on the proportion of scans confirming true disease progression. It is unclear whether the [redacted] who stopped treatment after between initial and second scan were due to true progression.

- ***Long term treatment effect: you refer to, 'Appendix 3' where the company presents evidence of persistent treatment effect of pembrolizumab in KEYNOTE-001 for melanoma patients, which has evidence that shows treatment effect up to and beyond 3 years.***
  Can you clarify which appendices you mean and if it refers to a different appraisal, which one.

  Apologies, we mean Appendix 3 of the most recent response from the company in reply to NICE's request for further analysis – located on page 55.

- ***Long term treatment effect: in reference to table 5, I wanted to ask why the ICER peaks at 3 years but then falls gradually to the lifetime point?***

  The ICERs do not peak at 3 years treatment effect duration, if we assume no treatment benefit after 2 years (the equivalent of the company's HR =1) the ICER is £97,034.
  3 years is the ERG's preferred assumption on treatment effect duration. The ICERs decrease the longer the treatment effect is maintained.

- ***Long term treatment effect: The company presented a scenario analyses: HR 1.45 (this reflects the OS hazard ratio for pembrolizumab versus docetaxel estimated in KEYNOTE-010).***

I am not clear as to how the HR of 1.45 reflects the OS HR for pembrolizumab versus docetaxel estimated in KEYNOTE-010, using the two-stage adjustment for docetaxel, i.e. 0.69, continuing beyond 2 years.

1.45 is the inverse of 0.69 (1/0.69). The 1.45 HR has been applied to the docetaxel arm.

- ***The company explored an 82 week cut off point to extrapolate the K-M data (as well as 42 weeks). They state it is unreliable as "only 17 patients (5%) are still alive. The modelling however predicts 12% alive at 5 years. We wanted to know if you had any thoughts on this ahead of the meeting.***

  The 12% alive at 5 years in the model reflects the assumption that treatment benefit lasts for lifetime. The ERG consider this unrealistic.