NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349]

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

The scope and final matrix are available on the NICE website

1. **Pre-meeting Briefing (PMB)**

2. **Company submission** from Merck Sharp and Dohme

3. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification

4. **Patient group, professional group and NHS organisation submission** from:
   - Roy Castle Lung Cancer Foundation
   - The British Thoracic Society
   - NHS England

5. **Expert personal perspectives** from:
   - Dr Martin Forster – clinical expert, nominated by NCRI-RCP-RCR-ACP
   - Professor David Snead – clinical expert, nominated by the Royal College of Pathologists
   - Mrs Lesley Holland – patient expert, nominated by National Lung Cancer Forum for Nurses

6. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRIG)

7. **Evidence Review Group response to the factual accuracy check**

8. **Evidence Review Group report erratum** prepared by Liverpool Reviews and Implementation Group (LRIG)

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

Pre-meeting briefing

Pembrolizumb for untreated PD-L1 positive metastatic non-small cell lung cancer – CDF review of TA447 [ID1349]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- 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.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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Key issues

Clinical effectiveness

- KEYNOTE-024 allowed the SOC arm to switch to other PD-L1 treatments (such as pembrolizumab or nivolumab) which have now become standard of care after chemotherapy
  - Company suggest no adjustment for crossover may be more appropriate now that trial is more similar to UK practice

Cost-effectiveness

- Company base case estimated OS by appending exponential parametric distribution to KEYNOTE-024 trial OS K-M data at 33 weeks
  - ERG used 43 weeks in exploratory analysis, based on visual fit
  - What does committee prefer?
- What is the most appropriate source for deriving the utility values?
- Most plausible ICER for pembrolizumab?
- Should pembrolizumab be considered as an End of life treatment?
- Innovation?
- Equality issues?

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Cancer Drugs Fund (CDF)

Pembrolizumab is currently available on the CDF as an option for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults, only if:

- their tumours express PD-L1 with at least a 50% tumour proportion score and have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations
- pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
- the conditions in the managed access agreement for pembrolizumab are followed.

- The committee concluded that although there was sufficient evidence that pembrolizumab had an important extension-to-life benefit compared with standard care, the exact size of the overall survival gain was uncertain because of the immaturity of the data.

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DETAILS OF THE TECHNOLOGY

Technology	Pembrolizumab (KEYTRUDA)
Marketing authorisation: January 2017	First line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a TPS ≥50% with no EGFR or ALK positive tumour mutations • TA447 recommends pembrolizumab within the CDF as a treatment option for adults with untreated PD-L1 positive (TPS≥50%) metastatic NSCLC
Mechanism of action	Humanised monoclonal antibody acts on the programmed cell death-1 (PD-1) receptor, part of the immune checkpoint pathway.
Administration	i.v. infusion in outpatient setting, 200 mg every 3 weeks until disease progression or unacceptable toxicity
Acquisition cost	100 mg vial: • List price: £2,630 per 100 mg vial • A discount courtesy of a Commercial Access Agreement has been agreed between MSD and NHS England
Cost of a course of treatment	Average time on treatment: XXXX cycles based on KEYNOTE-024: • Average cost of a course of treatment at list price: £ XXXX

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TA447: Rationale for CDF recommendation

The ICER range identified by the committee for its decision-making was **£46,083 to £61,577 per QALY gained**. This was based on:

1. All time points presented for extrapolation (22-, 14- and 30-weeks) being equally plausible because of the uncertainty around the extrapolation of OS data
2. The analyses which used an overall survival rate of 5% at 5 years for the SOC arm (based on NLCA 2006 to 2010 data)
3. The company's analysis setting the utility value for at least 360 days to death to that of the UK population norm
4. ERG's exploratory analyses with alternative (not time to death) utility values from the pemetrexed guidance (TA181), which increased the ICER by approximately £7,000 – leading to the upper estimate of the range being £61,577
   - company's ICER range (£46,083 to £54,577 per QALY gained) was considered conservative given the utilities were capped to the population norm which did not seem in line with the physical symptoms and psychological distress reported by people with NSCLC

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In an analysis of more recent data from the NLCA (2006-2011), 5-year survival of patients diagnosed at stage IV was only 3%.

Patient expert comments

- Patients with metastatic NSCLC are often debilitated with multiple and distressing symptoms – outcomes with traditional chemotherapy remains poor
- Urgent need more treatment options for people with advanced lung cancer given the very poor prognosis
- Advantages of pembrolizumab might include:
  - fewer side effects than 1st line chemotherapy (fewer hospitalisations)
  - Quick infusion time
  - Better quality of life than conventional chemotherapy
  - Fewer cases of neutropenia
- Disadvantages may include:
  - Monitoring required
  - Experience with using pembrolizumab limited but will improve the more it is used in practice

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Clinical expert comments

Testing

- Testing of tumours for PD-L1 is complex and requires adequate tissue as well as considerable expertise
- selection of PD-L1 positive tumours may show variability in observer assessment
- Limited access to testing may delay treatment

Pathway

- Pembrolizumab now widely used after chemotherapy.
- Findings of Keynote 024 trial reflects UK practice

Benefits of pembrolizumab

- Keynote 024 trial shows a median OS twice that achieved with standard care.
- Fewer adverse reactions versus standard care.
- PD-L1 inhibition is a step change in non small cell lung cancer therapy for PD-L1 positive patients

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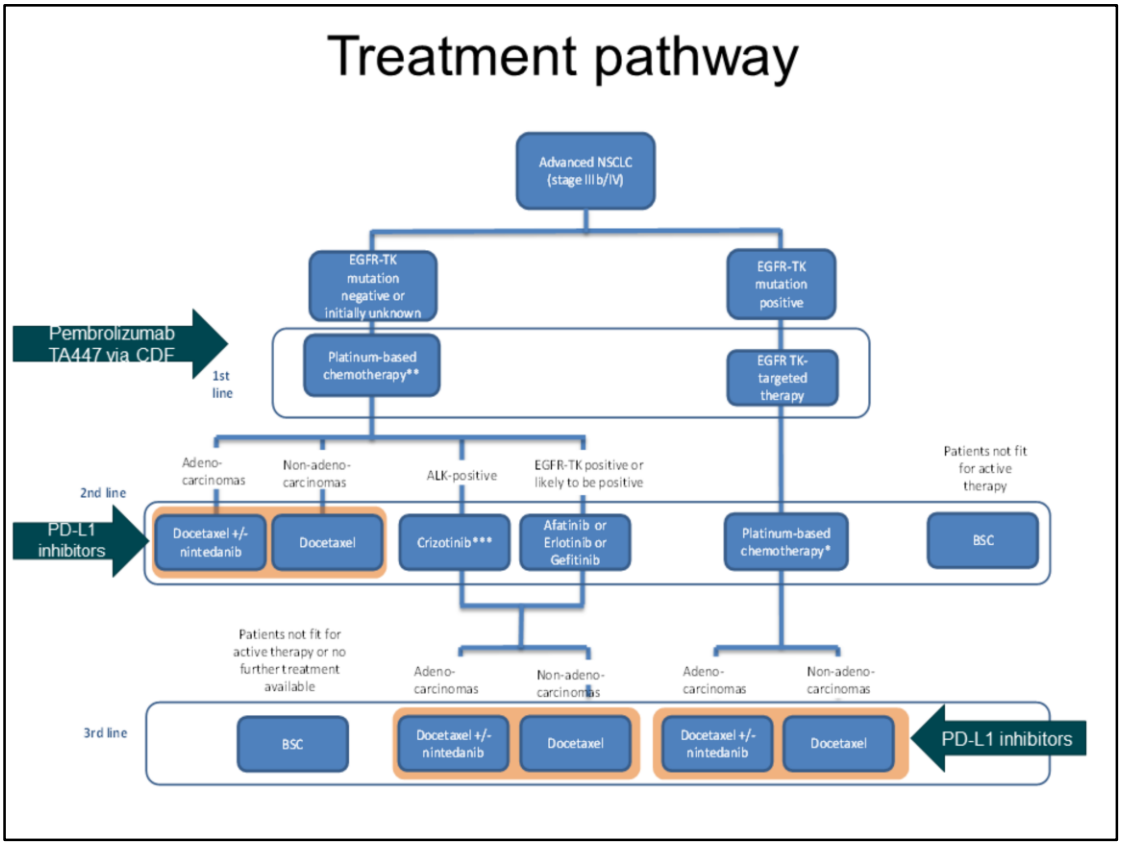

Adapted from figure 3 of Company Submission (page 19)
Since publication of TA447, as a result of NICE guidance**, pembrolizumab and nivolumab have become NHS treatment options, after chemotherapy, for many patients with locally advanced or metastatic NSCLC

TA428 (updated Sept 2017) – Pembrolizumab recommended as an option for treating locally advanced or metastatic **PD-L1 positive NSCLC in adults who have had at least one chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour), only if:
pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression, and
the company provides pembrolizumab in line with the commercial access agreement with NHS England.

**TA483 (November 2017) –Nivolumab recommended for use within the CDF as an option for treating locally advanced or metastatic squamous NSCLC lung cancer in adults after chemotherapy, only if:
nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and

the conditions in the managed access agreement are followed.

** TA484 (Nov 2017) – nivolumab recommended for use within the CDF as an option for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy, only if:
their tumours are **PD-L1 positive** and nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and the conditions in the managed access agreement are followed.

TA447 Clinical effectiveness evidence

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TA447 Clinical evidence: KEYNOTE-024

- Open-label, phase III RCT: Pembrolizumab (n=154) compared with standard of care (SOC; platinum based chemotherapy) (n=151)
- Inclusion criteria: untreated stage IV metastatic PD-L1-positive NSCLC (≥50% PD-L1 and no EGFR- or ALK-positive mutations) and an ECOG score of 0 or 1

Results were from an interim analysis: Pembrolizumab vs. SOC (ITT)

- Median OS (months): Not reached in either arms (35% of the total events had occurred):
  - OS HR: 0.60; 95% CI 0.41 to 0.89
  - OS HR (crossover adjusted): 0.50; 95% CI 0.34 to 0.76
- **A later 19 month follow up**: OS HR [redacted] of total events occurred
  - [redacted]
- Median PFS: 10.3 months vs. 6 months (p<0.001)
- ORR: 44.8% vs. 27.8%

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The baseline characteristics of the patients included in KEYNOTE-024 were as expected for patients with advanced NSCLC, and representative of the patients who are expected to receive pembrolizumab in UK clinical practice

Results:

- Median PFS was statistically significantly longer in the pembrolizumab arm compared with the SOC arm: 10.3 months versus 6 months; HR=0.50; 95% CI 0.37 to 0.68, p<0.001
- KEYNOTE-24 found statistically significant survival benefit for patients treated with pembrolizumab compared with those treated with SOC. However, 43.7% of the patients randomised to the SOC arm crossed over to receive pembrolizumab

Updated clinical effectiveness evidence: Final analysis (FA) of KEYNOTE-024 (data cut-off date: 10 July 2017)

Company submission section B.2

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Final Analysis of KEYNOTE-024: PFS, OS and ORR (ITT population) – 25.4 months median follow-up

	Number Patients (ITT)	Pembrolizumab 200 mg, N=154	SOC, N= 151
Primary endpoints	**PFS (BICR per RECIST 1.1)**		
	Median (95% CI), [months]	[redacted]	[redacted]
	Hazard Ratio; p-value	HR [redacted] (95% CI [redacted]); [redacted]	
	PFS rate at 12 months	[redacted]	[redacted]
	PFS rate at 18 months	[redacted]	[redacted]
	PFS rate at 24 months	[redacted]	[redacted]
Secondary endpoints	**OS**		
	Median (95% CI), [months]	30.0 ([redacted]	14.2 ([redacted])
	Hazard Ratio; p-value	**HR 0.63 (95% CI 0.47, 0.86); *p=0.002***	
	OS rate at 12 months	[redacted]	[redacted]
	OS rate at 18 months	[redacted]	[redacted]
	OS rate at 24 months	[redacted]	[redacted]
	OS rate at 30 months	[redacted]	[redacted]
	ORR (BIRC per RECIST 1.1)		
	Confirmed ORR % (95% CI)	45.5% (37.4, 53.7)	29.8% (22.6, 37.8)
		Difference 14.9% (4.3, 25.4); *p=0.0031*	

Source: Company submission section B.2.6.1; table 6 (p25)

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- OS data were analysed using the ITT approach, as planned in the clinical study report analyses
- Final analysis of OS was conducted following 169 death events across the study population (data cut-off date 10-July-2017).
- **Median duration of follow-up of 25.2 months** (range [redacted] months)
  - 23 (14.9%) people in the pembrolizumab group and 2 (1.3%) of patients in the SOC group remained on assigned study treatment.
- Median duration of exposure was 7.9 months (range, 1 day – 28.8 months) for pembrolizumab and 3.5 months (range, 1 day – 30.5 months) for chemotherapy.
- Mean number of cycles of pembrolizumab received was [redacted] (range [redacted] to [redacted]) (ASaT population) and chemotherapy (induction plus maintenance phases) in the SOC arm was [redacted] cycles (range [redacted] to [redacted]).
- At the time of the final analysis, [redacted]%) patients in the pembrolizumab arm had received 2 years of uninterrupted initial therapy every 3 weeks, or 35 administrations;
  - In this group, the mean duration of follow-up from the last dose of pembrolizumab to the database cut-off date was [redacted] months.
- Only [redacted] patient experienced disease progression; the median time to progression using the Kaplan-Meier method was [redacted] months. None of these patients re-initiated therapy.
- No deaths were observed in the cohort.

Progression-free survival: ITT population Kaplan-Meier

Based on BICR assessment per RECIST 1.1 (primary censoring rule)

Figure is academic in confidence

From figure 10 (pg 36 of company submission)

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The PFS Kaplan-Meier (KM) curves separate early at approximately 4 months, with continuous separation between the two curves over the time.

Company also presented results for investigator assessed as a sensitivity analysis

Summary and subgroups: Progression free survival (ITT)

- Pembrolizumab provides significant benefits in terms of PFS over SOC:
  - **Median PFS [redacted] months versus [redacted] months**
  - **HR [redacted]; 95% CI [redacted]; one-sided [redacted]**
  - A consistent benefit of pembrolizumab over SOC was also shown for the subgroups considered in the company submission:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Figure is academic in confidence

Source: Company submission document B figure 14, p47

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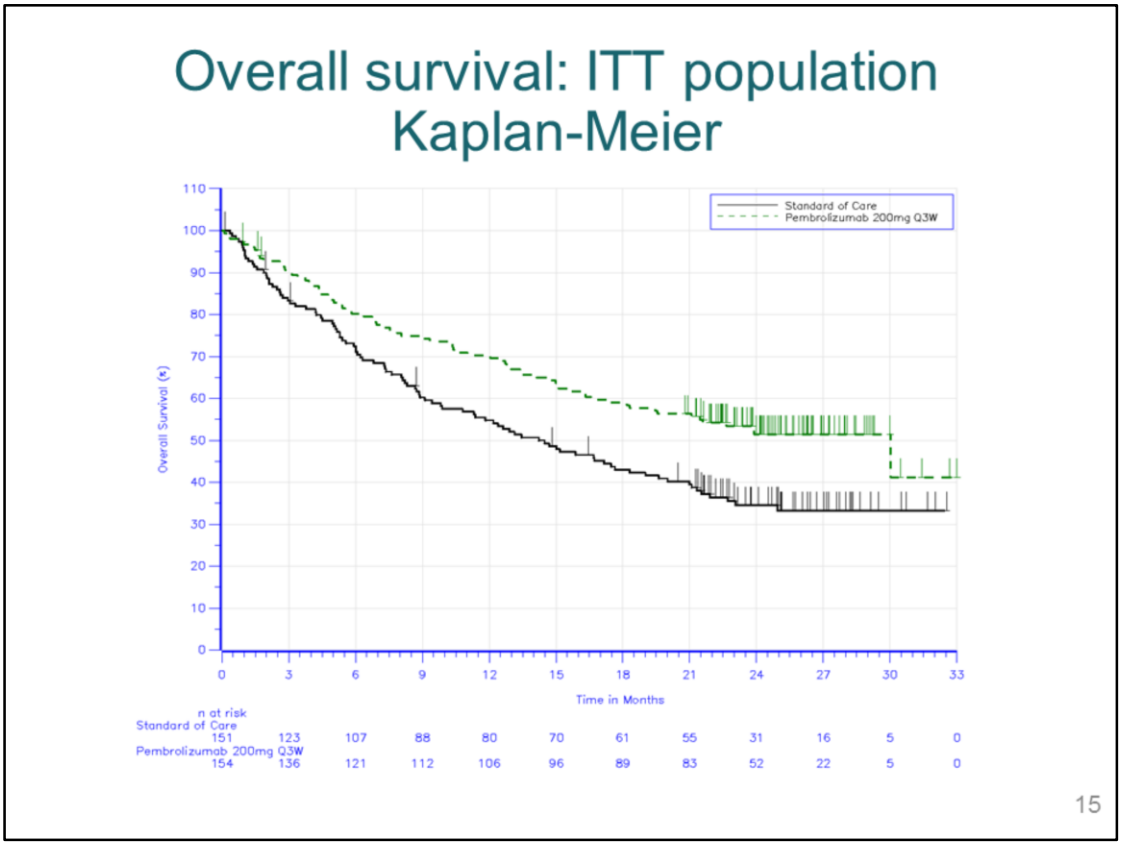
[redacted]



The curves on the KM plot began to separate by 1 month with continuous separation between the two curves over time. At no time did the curves cross. Significant improvement in OS was observed for pembrolizumab as compared to the SOC despite the potential confounding impact of crossover from chemotherapy to pembrolizumab.

At final analysis, XXXpatients (XXX%) in the SOC arm had switched to pembrolizumab, within the study cross-over, as permitted per the protocol. In addition, XXXfurther patients in the SOC arm switched to an anti-PD1 treatment (outside of within study cross-over), after the protocol treatment. Half of the patients switched within 4 weeks following disease progression and most (n=60) had switched within 3 months of disease progression.

Patients were eligible to switch if they had documented progression, did not stop chemotherapy for any other reason than progressive disease, had an ECOG score of 0 or 1 at time of progression and had at least 30 days of survival after SOC treatment. In addition, switching patients should have been initiated on pembrolizumab at least 30 days after the last dose of SOC treatment.

Summary and subgroups: Overall survival (ITT)

- Pembrolizumab provides significant benefits in terms of OS over SOC:
  - **Median OS 30 months versus 14.2 months**
  - **HR 0.63; 95% CI 0.47 to 0.86; one-sided p<0.002**
- A consistent benefit of pembrolizumab over SOC was also shown for the two subgroups considered in the company submission:

[redacted]

Figure is academic in confidence

Source: Company submission document B figure 13, p43

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[redacted]

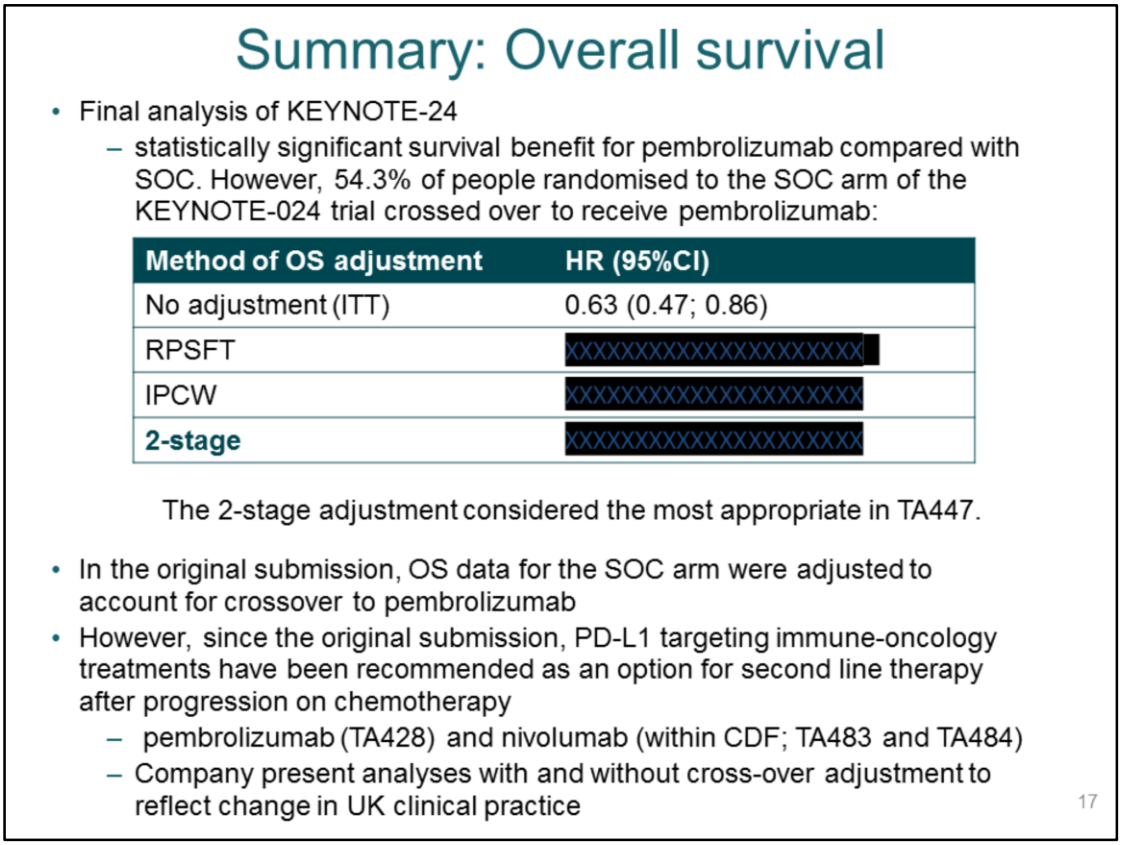

Table 9 of company submission

- The RPSFT (rank preserving structural failure time) method had been pre-specified in the study protocol to adjust for the anticipated crossover effect. It is based on the assumption of common treatment effect.

- The IPCW (the inverse probability of censoring weighting) method adjusts ITT overall survival analysis by weighting the contribution from each subject in the control arm during a particular time interval prior to switching

- The two-stage simplified model is most appropriate when patients are allowed to switch to the new treatment shortly after progression of disease and there is a clear definition of a new secondary baseline. The committee for TA447 also agreed that the 2-stage method was the most appropriate model for the cross-over adjustment.

KEYNOTE-024 Final analysis: adverse event summary (1)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued‡ due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]

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

‡ Study medication withdrawn.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded. AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose. (Database Cutoff Date: 10JUL2017).
Source: Adapted from company submission; document B table 25 (p50)

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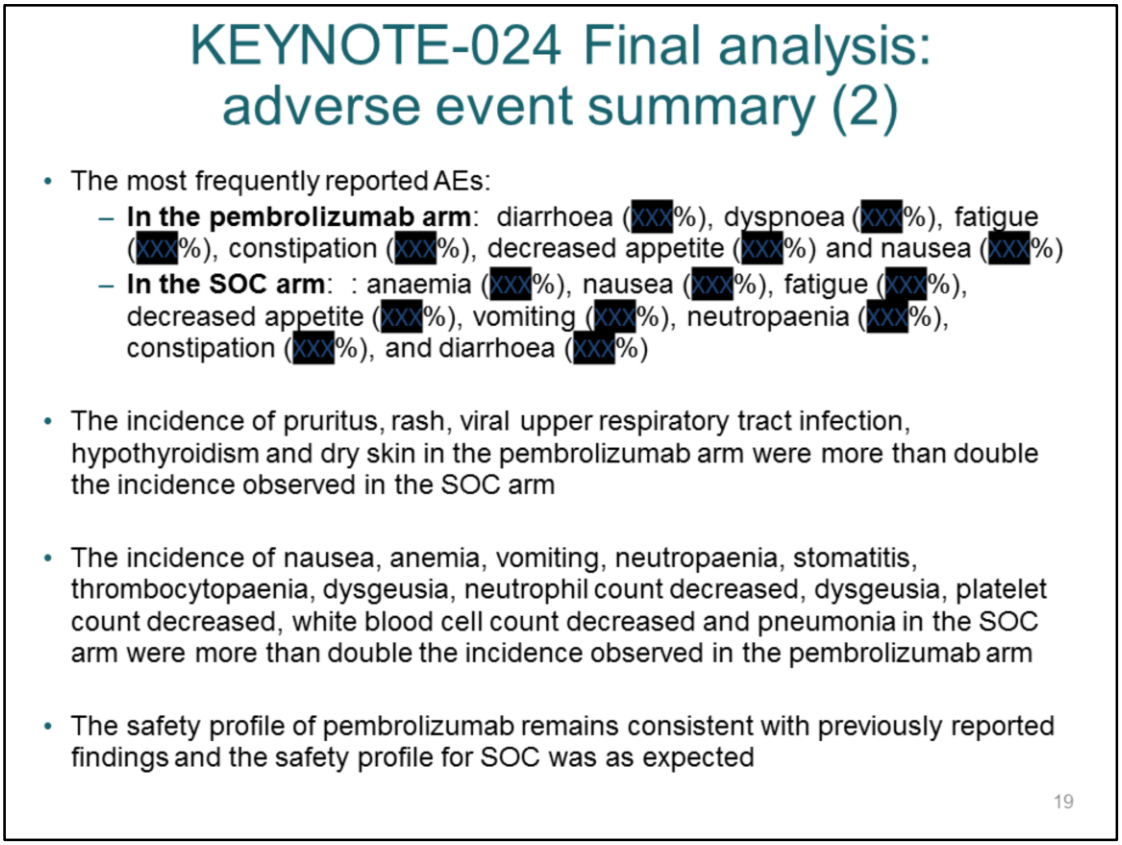
ASaT = All subjects as treated
The ASaT population consisted of all randomised subjects who received at least one dose of study treatment (n=304). Subjects were included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data.

Summaries and listing of overall AEs and SAEs include events from the first dose to 30 days or 90 days after the last dose of study medication, respectively.

- There were comparable numbers of people with ≥1 AEs in the pembrolizumab arm ([redacted]%) and the SOC arm ([redacted]%) despite people in the pembrolizumab arm had a longer mean duration of exposure to treatment (330 days in pembrolizumab and 130 days in SOC).
- Fewer people in the pembrolizumab arm had Grade 3-5 drug-related AEs ([redacted]%) than in the SOC arm ([redacted]%).
- SAE in the pembrolizumab and SOC arms ([redacted]% and [redacted]%, respectively), and drug-related SAEs were comparable in both treatment groups ([redacted]% pembrolizumab; [redacted]% SOC)
- A total of [redacted]%) people ([redacted]%] in the pembrolizumab arm and [redacted]%] in the SOC arm) discontinued due to an AE; of which, [redacted]%) discontinued due to a drug-

related AE ([redacted]%] in the pembrolizumab arm and [redacted]%] in the SOC arm)
- There were [redacted]%) deaths reported in the pembrolizumab arm; of which, [redacted]%) deaths was assessed to be a drug-related SAE. In the SOC arm, [redacted]%) deaths were reported and [redacted]%) of these deaths were assessed as drug related SAEs

SOC regimens:
- The most common regimen administered to the SOC subjects was pemetrexed in combination with carboplatin ([redacted]%]).
- Majority of subjects with non-squamous NSCLC were administered a pemetrexed containing doublet ([redacted]%]):
    - [redacted]%) subjects with non-squamous NSCLC received pemetrexed maintenance.
- More subjects with squamous NSCLC received gemcitabine in combination with carboplatin ([redacted]%) as compared to gemcitabine in combination with cisplatin ([redacted]%) or paclitaxel in combination with carboplatin ([redacted]%).



Page 51 of the company submission.

The most common AEs in the pembrolizumab arm were generally mild and tolerable, and infrequently led to treatment discontinuations.

<u>Adverse Events of Special Interest (AEOSI):</u>

- AEOSI includes immune-related adverse events (irAE) and are presented regardless of Investigator-assessed causality and generally include all AE grades (with the exception of severe skin reactions)
- AEOSI were more common among pembrolizumab-treated subjects compared to SOC-treated subjects (33.8% vs. 5.3%, respectively). This is expected, due to the general mechanism of action of the SOC agents which is anti-mitotic and not immunomodulating and it is also likely to overestimate the true frequency of immune-mediated Aes since it includes events irrespective of attribution by the Investigator
- Only 13.6% of pembrolizumab-treated subjects experienced Grade 3 to 5 AEOSI
- One death was reported due to AEOSI in the pembrolizumab treatment group, which was considered drug-related
- XXXXXX%) subjects discontinued treatment due to drug-related AEOSI in the pembrolizumab arm and XXXin the SOC arm

ERG comments

Treatment pathway

- ERG agree with company that PD-L1 therapies are becoming standard of care for people who have had prior chemotherapy

Progression-free survival

- the ERG is uncertain of the reasons for the 3.1 months difference between blinded independent central review (BICR) assessed PFS and the investigator-assessed (INV) PFS for the pembrolizumab arm of the trial (10.3 months versus 7.2 months)

Crossover adjustments

- The ERG has concerns (also described in TA447) about the reliability of approaches to crossover adjustment - results should be viewed with caution
  - Although OS HR estimates similar, variation is bigger when accounting for direct and indirect switching.

Indirect and mixed treatment comparisons

- Agreed that updated ITC and MTC results would not be useful

Adverse events

- discontinuations due to AEs and drug-related AEs have increased since the previous interim analysis

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Updated cost-effectiveness model

Company submission, section B3

Summary of company's modelling approach

Assumption	Company approach in TA447	Current approach
Treatment continuation	KEYNOTE-024: 2-year stopping rule applied	As before
Time on treatment	KEYNOTE-024: Maximum treatment durations of 35 cycles (105 weeks) and six cycles (18 weeks) were assumed for patients receiving pembrolizumab and SOC. Average time on treatment: 6.76 months (equivalent to 9.80 cycles). Once patients progress they receive subsequent therapies as experienced by patients in KEYNOTE-024.	Approach as before (ToT KM data up to 2 years was used to estimate treatment duration in the pembrolizumab arm, while parametric fitting was used to estimate ToT in the SOC arm) however: Mean number of cycles of pembrolizumab: [redacted] Mean number of cycles of chemotherapy in SOC: [redacted]
OS extrapolation	KEYNOTE-024: Separate exponential models were fitted at week 22, 14 and 30, based on the shape of the cumulative hazard plot and there being sufficient numbers of patients at risk at this point (PH assumption was violated). ▪ The 5 year extrapolated survival in the SOC arm was 2.4, 2.7, and 4.5% for the 22-week, 14-week, and 30-week cut-off points respectively	The 2-phase piecewise method (KM plus exponential) used. For the first 33 weeks OS KM data is used and at that point patient numbers are sufficient to apply parametric fitting based on KEYNOTE-024 data*. The cumulative hazard plot also suggests that a piecewise model is preferred. 23 and 43 week cut off explored in sensitivity analyses 2 base case presented:
PFS extrapolation	KEYNOTE-024: Separate Weibull models were fitted at week 9 (BICR) to reflect the protocol driven fall in PFS from baseline at the first radiologic assessment (week 9; PH assumption was violated).	KM data was used for the first 27 weeks, followed by extrapolating using an exponential distribution. Other cut offs (9 and 37 weeks) explored in sensitivity analyses

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* Company stated that the fully fitted standard parametric curves do not provide good visual fit compared to the 2-phase piecewise method. The cumulative hazard plot also suggests that a piecewise model is preferred.

Summary of company's modelling approach (2)

Assumption	Company approach in TA447	Current approach
Long-term treatment effect	treatment effect beyond 2 years was limited	Assuming the treatment effect stops 3 or 5 years after treatment initiation increases the ICERs
Treatment switching	2-stage adjustment (43.7% of patients switched from SOC to pembrolizumab)	2-stage adjustment 54.3% (82/151) of patients switched from SOC to pembrolizumab post disease progressions **Two base cases presented:** • Patient level data from the SOC arm was used to perform crossover adjustments for the SOC OS as part of the base case that reflects the original submission (for transparency purposes). • No crossover adjustments (since pembrolizumab has become SOC second line among patients who express PDL1 (TPS ≥ 1%, including strong expressers, i.e. TPS ≥ 50%).
Utilities	KEYNOTE-024: Quality-adjusted life years (QALYs) estimated using time-to-death utilities (from less than 30 days to at least 360 days) from EQ-5D data. Ranging from 0.48 to 0.808 across the 4 categories. Progressions-based utilities were explored in sensitivity*	Company model still uses same approach as previously. Capped utility for >360 days category explored as sensitivity. Utilities from pemetrexed appraisal not explored*

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* In TA447 guidance committee agreed with the ERG that the utility values from KEYNOTE-024 appeared implausible and did not seem in line with the physical symptoms described by the patient experts.
The committee made note of ERG's alternative approach of utility values from NICE's technology appraisal guidance on pemetrexed for treating nonsmall-cell lung cancer and also the approach to cap utilities for 360 days to death using the UK population norm.
Committee agreed adjusting utility to the population norm is still a conservative assumption given the clear physical symptoms and psychological distress reported by patients with NSCLC.
The committee agreed that concluded that that the ICER would likely fall between that from the analysis setting the utility for 360 days to death to that of the UK population norm and the analysis using utilities from the pemetrexed guidance

Summary of company's modelling approach (3)

Assumption	Company approach in TA447	Current approach
AE	KEYNOTE-024: Grade 3+ AEs in more than 5% of patients in either arm, plus diarrhoea (grade 2) and febrile neutropenia. Unit costs and disutility estimates are same for both arms.	As before
PD-L1 testing	The test cost is based on 11.6% of patients with NSCLC stage IV being eligible for treatment with pembrolizumab in England, i.e., 8.6 tests are required to identify 1 patient who is eligible to be treated with pembrolizumab in first line. A single PD-L1 test will cost £40.50/person, equating to a total cost of £348.121 relative to each patient that eventually receives pembrolizumab	Similar - 11.7% of people with NSCLC stage IV will be eligible for pembrolizumab treatment in England. 9.57 patients will need to be tested for PD-L1 expression to identify 1 person eligible to receive pembrolizumab. Total cost: £348.21
Costs	Drug admin costs based on BSA (weighted mean average of 1.83 m2) Full vial sharing, no wastage for comparators* Model included a dose intensity adjustment for those where planned doses for both pembrolizumab and SOC not received The cost of subsequent therapy included as a one-off cost in the post-progression state (derived by weighting the % of people receiving docetaxel or pembrolizumab and the individual unit cost, taking into account the assumed treatment durations.	As before but the company only modelled one line of subsequent therapy. Company assumed that for people having pembrolizumab after cvhemotherapy, the dose was 200mg every 3 wks**

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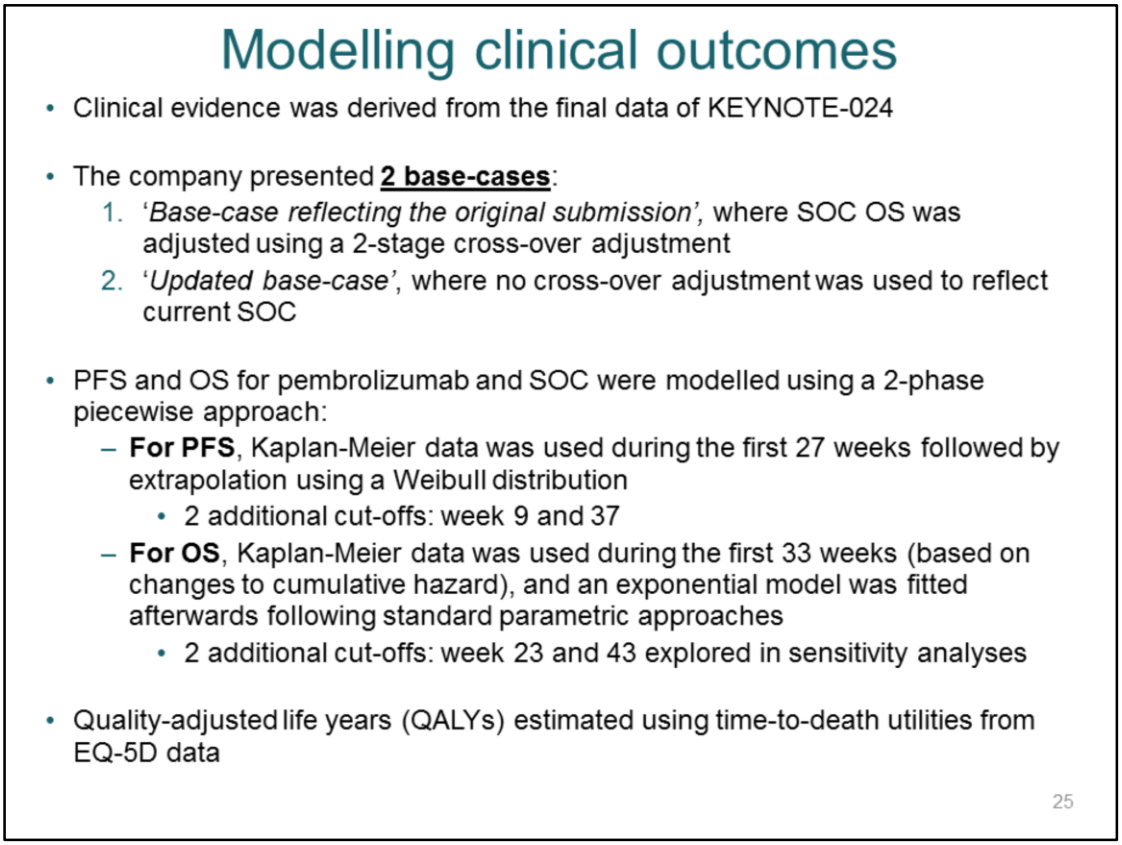
* Included as a conservative assumption

** although marketing authorisation states that for use after chemotherapy dose should be 2mg/kg



A similar approach to that of the original submission was followed for the extrapolation of OS and PFS from KEYNOTE-024, to populate the area-under-the-curve (AUC) partitioned survival approach.

The most plausible base case parametric survival models for OS and PFS were identified by following the guidance from the NICE DSU.

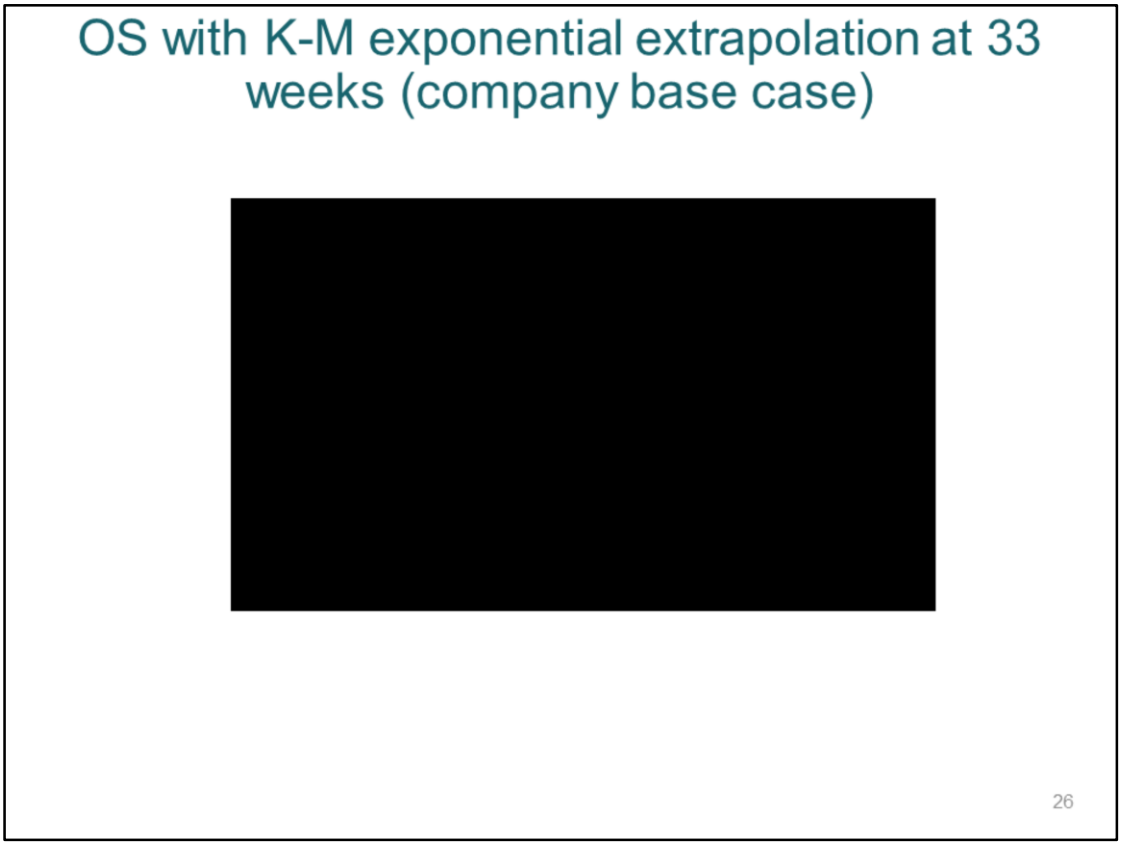
Resource use and costs were estimated based on information from the KEYNOTE-024 trial, published sources and advice from clinical experts. A Department of Health PAS discount was applied to the cost of pembrolizumab and full list prices were used to represent the cost of the comparator drugs.

HRQoL data were collected as part of the KEYNOTE-024 trial using the EQ-5D 3L tool. Collected data were pooled across both treatment arms. The company employed utility estimates in the model based on the time-to-death approach. The mean EQ-5D utility scores by time to death used in the company base case are ≥360 days: XXX; ≥180 to <360 days: XXX; ≥30 to <180 days: XXX; and <30 days: XXX

The company presented two base cases: one consistent with the original submission (also known as the ***'base case reflecting the original submission')***, and the other reflecting

current UK clinical practice (also known as the ***'updated base case'):***

- The first one reflects the base case extrapolation in the original submission, i.e. it applies the 2-stage switching adjustment, which was recognized by the ERG and the committee to be the most appropriate method for the crossover adjustment during the original appraisal:
    - The data base cut-off was week 33, after which there were still 33% remaining events in the SOC arm on which to base the parametric fitting (54% after week 23, and 17% after week 43).
- The second one reflects the current SOC, with pembrolizumab being one of the second line treatment options, after it was recommended by NICE (in January 2017) as an option for treating locally advanced or metastatic PD-L1-positive NSCLC in adults who have had at least one chemotherapy.
    - In this scenario, no crossover adjustments are accounted for in the SOC arm, reflecting the OS derived from patients initially treated with SOC who progress and then are treated with a anti-PD1 (as for NICE guidance), based on the proportion of patients who received a PD1 after progression in KEYNOTE-024.



Source: company model and presented in ERG report figure 4.
Company choice for its base case was to use an exponential distribution (joint most pessimistic option for pembrolizumab, most pessimistic option for SOC)

Company model: Utility

- The mean EQ-5D utility scores were pooled from the pembrolizumab and SOC treatment arms of KEYNOTE-024 and UK preference-based scores were used for all patient data

State	Utility value: mean (SE)	95% CI
≥360*	[redacted]	[redacted]
[180, 360)	[redacted]	[redacted]
[30, 180)	[redacted]	[redacted]
<30	[redacted]	[redacted]
Disutility per patient experiencing grade 3-5 AEs	[redacted]	-

* This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days. Source: Company submission, document B, Table 45, p93

- An age-related utility decrement of 0.0045 was applied per year, from the age of 65 until 75, and 0.75 (males) and 0.71 (females) for people over 75 years to reflect the natural decrease in utility associated with increasing age (Kind et al., 1999)
- Utility decrements: Grade 3 to 5 AEs were associated with utility of [redacted] (95% CI [redacted] to [redacted]), compared those who did not experience any AEs [redacted] (95% CI [redacted] to [redacted]). Utility decrements were applied during the first cycle based on grade 3+ AE incidence rates and the corresponding mean duration across them.

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The company explored capping the >360 days to UK norm in sensitivity analyses

The UK scoring functions were developed based on the time trade-off (TTO) technique.

The company model included grade 3+ AEs experienced by more than 5% of patients in either arm of the KEYNOTE-024 trial. The company also included diarrhoea (grade 2) and febrile neutropenia. The unit costs and disutility estimates were the same for both treatment arms and the difference in AE management costs was driven by the incidence rates from the KEYNOTE-024 trial. The impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost applied in the first cycle of the model for each treatment arm

Company model: Costs

The company only modelled one line of subsequent therapy:

- In the pembrolizumab arm: docetaxel was assumed as second line treatment
- In the SOC arm: 2 scenarios were presented:
  1. In the 'base case reflecting the original submission' (crossover adjustment for OS data), all people were assumed to receive docetaxel as the only second line treatment
  2. In the 'updated base case' (no crossover adjustments), people who progress are assumed to receive pembrolizumab based on the proportion of people who received a PD1 post-progression in KEYNOTE-024 (direct switching to pembrolizumab: [redacted]%; additional indirect switching to pembrolizumab or nivolumab: [redacted]%), with the rest assumed to receive docetaxel
     - Assumed duration of second line treatment for docetaxel and pembrolizumab are 3 cycles (9 weeks) or 9.7 cycles (29.1 weeks), respectively (based on KEYNOTE-024 FA)

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Company base case model results*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incr. QALYs	ICER (£) versus baseline (QALYs)
Base case adjusted for crossover						
SOC	£21,847	1.46	1.04	-	-	-
Pembrolizumab	£72,353	3.08	2.31	£50,506	1.27	**£39,772**
Base case unadjusted for crossover						
SOC	£43,364	1.86	1.35	-	-	-
Pembrolizumab	£72,353	3.08	2.31	£28,989	0.96	**£30,244**

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Source: Table 60, pg113 of company submission

* Discounted, with proposed discount for pembrolizumab and an assumed discount for pemetrexed administered as maintenance therapy

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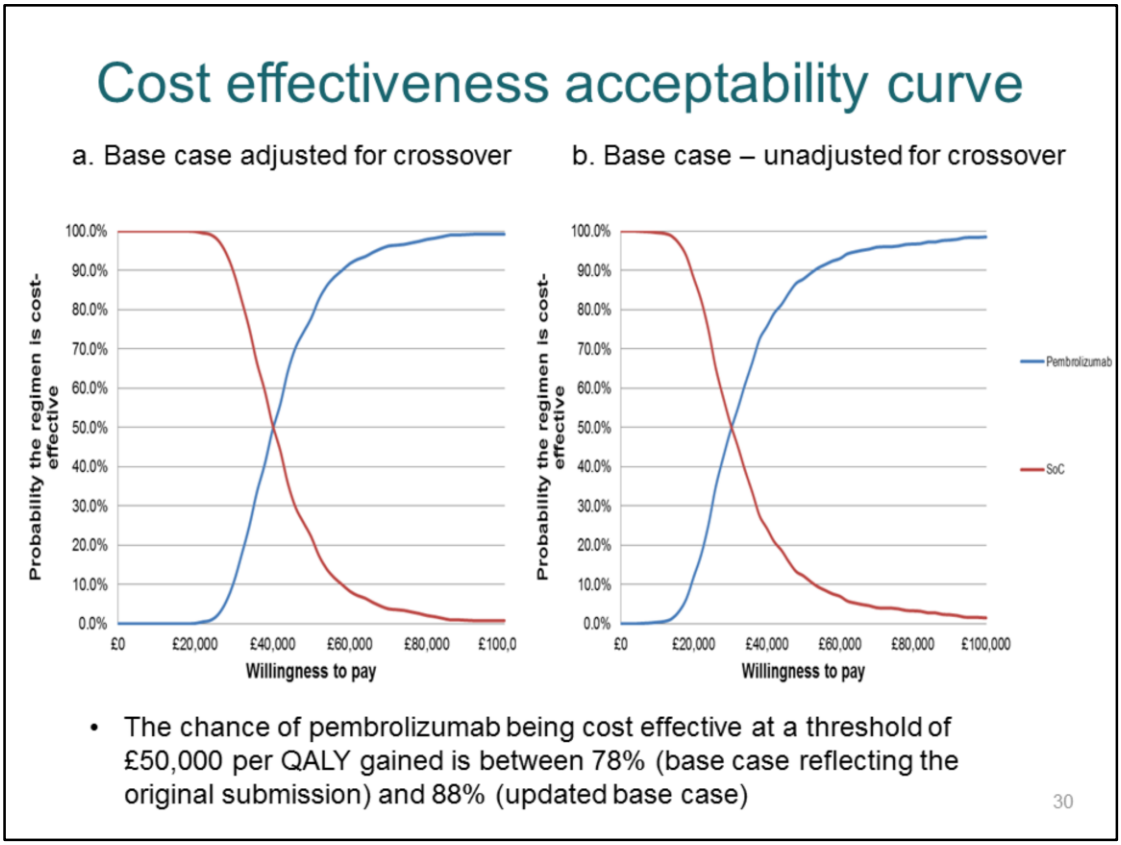
Probabilistic ICER for updated base case (based on 1,000 samples) = £30,414 per QALY gained.

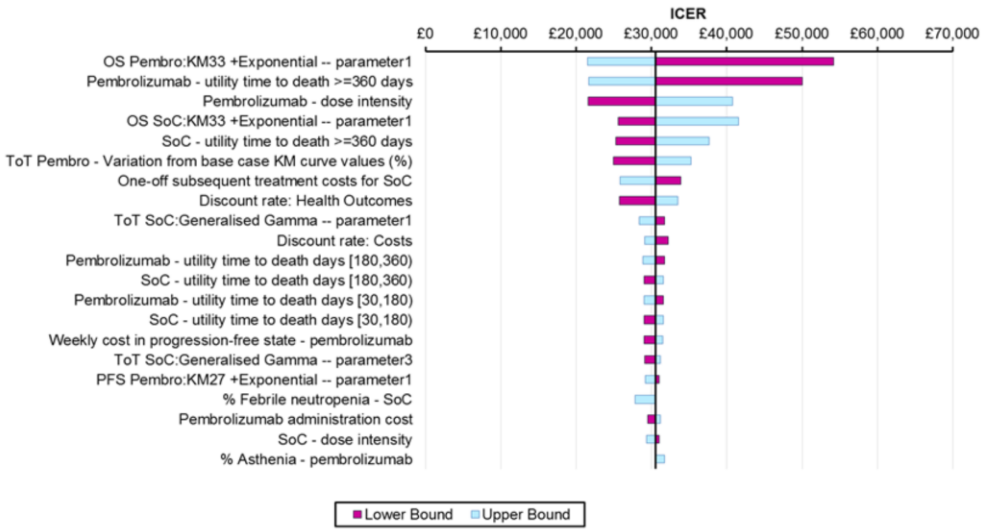
In the company submission, the company base cases are referred to as follows:

- ***'base case reflecting the original submission'***, where **crossover** adjustments were accounted for to reflect the base case analysis presented in the original submission.
- ***'updated base case'***, where **no crossover** adjustments are considered, and patients in the SOC arm who progress are assumed to receive pembrolizumab based on the proportion of patients who received a PD1 after progression in KEYNOTE-024, with the rest of the patients assumed to receive docetaxel.



Source: figure 18, pg 116 company submission
Results are discounted, with proposed discount for pembrolizumab and an assumed discount for pemetrexed administered as maintenance therapy

Company deterministic sensitivity analysis:
Updated base case – no crossover



- Three most influential parameters were: (1) the extrapolation of OS, (2) utility values for long-term survivors, and (3) assumptions around dose intensity (all in the pembrolizumab arm)

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Source: Figure 19b of company submission

Results are discounted, with proposed discount and an assumed discount for the CAA available for pemetrexed administered as maintenance therapy

The deterministic sensitivity analysis for the company's base case reflecting original submission (i.e. adjusting for crossover) parameters 1 and 2 remain the most influential and the third most influential is now dose intensity of pembrolizumab

Company scenario analysis (1): adjusted for crossover*

Scenario	Incr. costs	Incr. QALYs	ICER per QALY gained
Base case reflecting original submission	£50,506	1.27	**£39,772**
UK-specific BSA values (unadjusted by sex distribution)	£50,635	1.27	**£39,873**
UK-specific BSA values (adjusted by sex distribution)	£50,473	1.27	**£39,746**
Crossover- RPSFT adjustment	£50,661	1.29	**£39,179**
Crossover- IPCW adjustment	£49,538	1.15	**£43,065**
OS cut-off – 23 weeks	£50,829	1.31	**£38,698**
OS cut-off – 43 week	£48,522	1.02	**£47,693**
PFS cut-off – 9 weeks	£50,774	1.27	**£39,983**
PFS cut-off – 37 weeks	£50,185	1.27	**£39,519**
PFS extrapolation based on Weibull	£50,429	1.27	**£39,711**
PFS extrapolation based on GenGamma	£51,263	1.27	**£40,368**
No half cycle correction	£50,503	1.27	**£39,773**

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Source table 63 of company submission, pages 123-125

Analyses includes proposed discount for pembrolizumab and an assumed discount for pemetrexed maintenance, to account for the confidential (and therefore unknown) CAA currently available

BSA = Body surface area
In these analyses, a discount for pemetrexed maintenance is assumed, to account for the confidential (and therefore unknown) CAA currently available.

- Scenario analyses showed that the most sensitive scenarios relate to assuming treatment benefit stops at either 3 or 5 years, and the use of a 43-week cut-off to extrapolate OS
    - However, the company highlighted that there is no evidence that the treatment effect stops, as observed by the tail of the pembrolizumab KM OS based on the latest data cut (KEYNOTE-024 July 2017; see Figure 5 in company submission (document B))
    - When a 43-week cut-off is applied to extrapolate OS, there are only 17% of events left to fit the parametric adjustment in the 2-stage adjusted SOC arm, and

the scenario results in implausibly high 5-year (crossover adjusted) OS rates for the SOC (i.e. 11%, which is more than twice the value accepted by the Committee and the ERG as plausible in the original submission in the presence of adjustments for crossover).

Company scenario analysis (2): adjusted for crossover

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
SOC as for UK market shares	£50,870	1.27	**£40,059**
Utilities – Progression based (pooled)	£50,506	1.17	**£43,131**
Utilities – Time to death (per treatment arm)	£50,506	1.32	**£38,240**
Utilities – Progression-based (per treatment arm)	£50,506	1.29	**£39,255**
Utilities – Time to death by Chang et al (2017) [87]	£50,506	1.42	**£35,661**
Utilities for the time period ≥ 360 days to death equal to general population, same age	£50,506	1.25	**£40,459**
No age-related disutilities	£50,506	1.30	**£38,759**
Stop treatment effect at 3 years	£46,931	0.82	**£57,265**
Stop treatment effect at 5 years	£48,564	1.03	**£47,289**

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Source table 63 of company submission, pages 123-125

Analyses includes proposed discount for pembrolizumab and an assumed discount for pemetrexed maintenance, to account for the confidential (and therefore unknown) CAA currently available

BSA = Body surface area
In these analyses, a discount for pemetrexed maintenance is assumed, to account for the confidential (and therefore unknown) CAA currently available.

- Scenario analyses showed that the most sensitive scenarios relate to assuming treatment benefit stops at either 3 or 5 years, and the use of a 43-week cut-off to extrapolate OS
    - However, the company highlighted that there is no evidence that the treatment effect stops, as observed by the tail of the pembrolizumab KM OS based on the latest data cut (KEYNOTE-024 July 2017; see Figure 5 in company submission (document B))
    - When a 43-week cut-off is applied to extrapolate OS, there are only 17% of events left to fit the parametric adjustment in the 2-stage adjusted SOC arm, and

the scenario results in implausibly high 5-year (crossover adjusted) OS rates for the SOC (i.e. 11%, which is more than twice the value accepted by the Committee and the ERG as plausible in the original submission in the presence of adjustments for crossover).

Company scenario analysis: Updated base case (1) – no crossover adjustments

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
Base case reflecting original submission	£28,989	0.96	**£30,244**
UK-specific BSA values (unadjusted by sex distribution)	£29,117	0.96	**£30,378**
UK-specific BSA values (adjusted by sex distribution)	£28,957	0.96	**£30,210**
Crossover- RPSFT adjustment	NA	NA	**NA**
Crossover- IPCW adjustment	NA	NA	**NA**
OS cut-off – 23 weeks	£28,637	0.91	**£31,321**
OS cut-off – 43 week	£27,946	0.83	**£33,829**
PFS cut-off – 9 weeks	£29,276	0.96	**£30,543**
PFS cut-off – 37 weeks	£28,697	0.96	**£29,940**
PFS extrapolation based on Weibull	£29,017	0.96	**£30,273**
PFS extrapolation based on GenGamma	£29,761	0.96	**£31,050**
No half cycle correction	£28,989	0.96	**£30,249**

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Source table 63 of company submission, pages 123-125

BSA = Body surface area
Analyses includes proposed discount for pembrolizumab and an assumed discount for pemetrexed maintenance, to account for the confidential (and therefore unknown) CAA currently available

- Scenario analyses showed that the most sensitive scenario relate to assuming treatment benefit stops at either 3 or 5 years
    - However, the company highlighted that there is no evidence that the treatment effect stops, as observed by the tail of the pembrolizumab KM OS based on the latest data cut (KEYNOTE-024 July 2017; see Figure 5 in company submission (document B))

Company scenario analysis: Updated base case (2) - no crossover adjustments

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
SOC as for UK market shares	£29,354	0.96	**£30,624**
Utilities – Progression based (pooled)	£28,989	0.90	**£32,254**
Utilities – Time to death (per treatment arm)	£28,989	1.02	**£28,517**
Utilities – Progression-based (per treatment arm)	£28,989	1.03	**£28,266**
Utilities – Time to death by Chang et al (2017) [87]	£28,989	1.07	**£27,053**
Utilities for the time period ≥ 360 days to death equal to general population, same age	£28,989	0.94	**£30,874**
No age-related disutilities	£28,989	0.99	**£29,393**
Stop treatment effect at 3 years	£26,023	0.59	**£44,483**
Stop treatment effect at 5 years	£27,382	0.76	**£36,156**

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***Base case reflecting original submission – includes adjustment for crossover**

BSA = Body surface area
Analyses includes proposed discount for pembrolizumab and an assumed discount for pemetrexed maintenance, to account for the confidential (and therefore unknown) CAA currently available

- Scenario analyses showed that the most sensitive scenario relate to assuming treatment benefit stops at either 3 or 5 years
    - However, the company highlighted that there is no evidence that the treatment effect stops, as observed by the tail of the pembrolizumab KM OS based on the latest data cut (KEYNOTE-024 July 2017; see Figure 5 in company submission (document B))

ERG comments – cost effectiveness (1)

Treatment pathway

- The ERG agrees that current care for adv/met PD-L1 positive (≥50%) NSCLC is chemotherapy followed, on disease progression, by immunotherapy.
  - However, no trial data directly comparing efficacy of pembrolizumab in advanced or metastatic PD-L1 positive (≥50%) NSCLC for those that have and have not, received prior chemotherapy

Overall survival

- OS for the 54.3% of SOC arm who crossed over to pembrolizumab post-progression was much better than those who did not (or had not yet received) an immunotherapy
  - plausible that at least some of these patients would have immunotherapy in the future and therefore potential OS gain of this is not captured by either the OS K-M data from the KEYNOTE-024 trial or any of the OS projections
- **Treatment costs**
- Model assumes fixed dose 200 mg Q3W for pembrolizumab post chemotherapy. EMA recommends 2mg/kg Q3W: increases ICER.
- Model assumes cost of pembro after crossover is 29.1 weeks (based on trial). Cost applied at progression, however, mean of 7 weeks before starting pembrolizumab after progression and mean duration of 6 months treatment - use of a discounting model should reduce pembrolizumab costs
  - ERG state this approach likely to overestimate true discounted cost of treatment post progression

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ERG comments – cost effectiveness (2)

Utility values

Utility values used in company model (derived from KEYNOTE-024 trial data), were implausibly high

- Values for 360-day period before death were higher than the UK population norms
- company literature review does not strongly support the use of this value as studies:
  - involved patients at slightly different disease stages, were undertaken in countries other than the UK, or involved small numbers of patients
- Therefore ERG considers that it is appropriate to still limit utility values in the model to be no higher than the age-related population norms

Overall survival extrapolation

- The company chose to append a distribution at 33 weeks (because it estimated 5% of patients receiving SOC being alive at 5 years)
- ERG state that closest fit to trial data occurs when distributions are appended at 43 weeks
  - But may still underestimate the long-term survival of patients receiving SOC (9.6% of patients alive at 5 years and 1.5% alive at 10 years*)
- KEYNOTE-010 trial suggests that the company's base survival projection for SOC may be pessimistic. This casts doubt on the ICER for pembrolizumab versus SOC, and also whether pembrolizumab should be considered as an end of life treatment

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*The CS2 company base case projection suggests 9.1% of patients alive at 5 years (which is within the range previously projected) but the proportion expected to be alive at 10 years is 0.9%, which is much lower than previously estimated

TA428 (from KEYNOTE-010 trial) 5 year OS between 11.97% and 26.80% of patients receiving pembrolizumab following chemotherapy; at 10 years between 2.46% and 24.72%

Assuming that the immunotherapies received by the XXX of patients in the KEYNOTE-024 trial were all as effective as pembrolizumab in the KEYNOTE-010 trial, it would be expected that, based on the TA428 submission, the CS2 company model OS projections would show between 7.7 and 17.2% of patients alive at 5 years and between 1.6% and 15.8% alive at 10 years

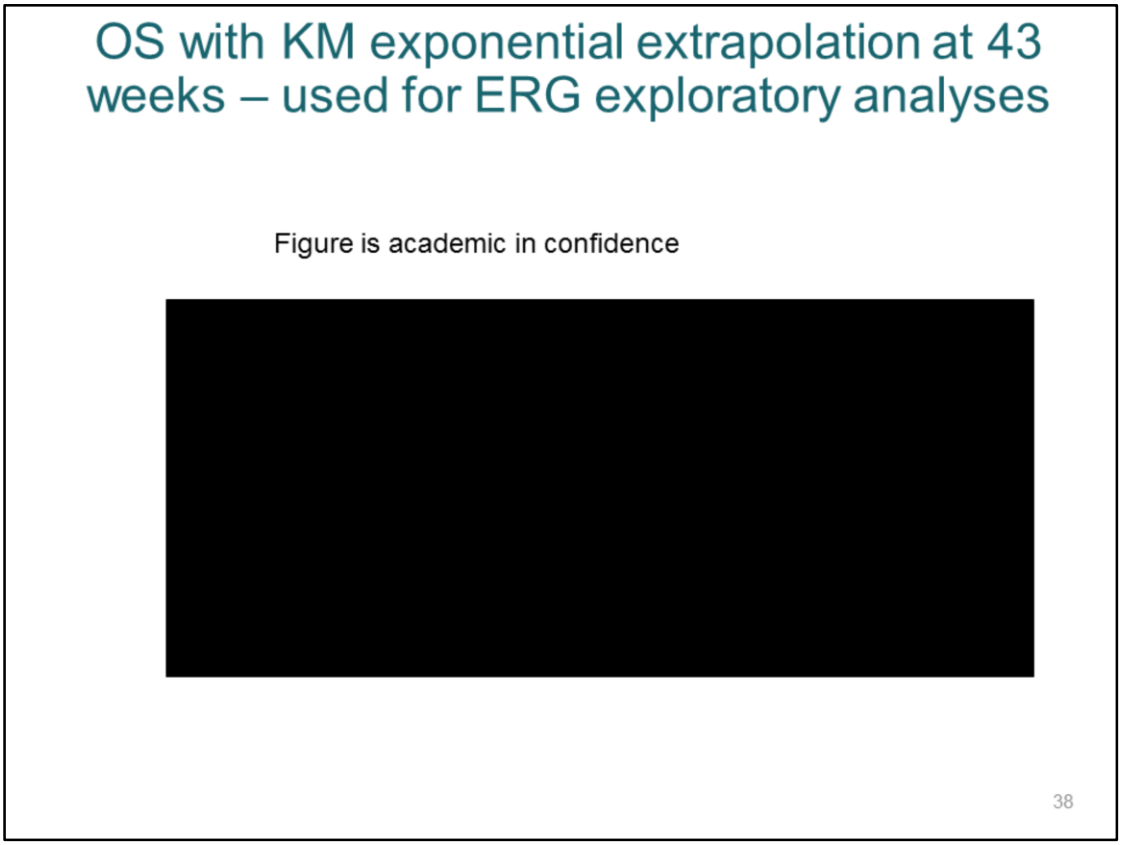

Figure 6 of ERG report (page 21)

ERG :

- Visual examination of the company's projections generated by appending exponential distributions (the company's base case choice of distribution) to K-M data at 23, 33 and 43 weeks (Figure 4, Figure 5 and Figure 6 respectively) suggests that the closest fit to the trial data occurs when distributions are appended at 43 weeks
- There is still an indication from the end of the K-M data (albeit the data becomes heavily censored from week 100) that as this approach generates estimates of 9.6% of patients alive at 5 years and 1.5% alive at 10 years this extrapolation may still underestimate the long-term survival of patients receiving SOC

ERG exploratory analyses*

Scenario/ERG amendment	Incremental		ICER	Changes from base case
	Cost	QALYs	£/QALY	£/QALY
A. Company base case	XXX	XXX	XXX	XXX
R1) Cost of pembrolizumab in SOC in line with recommended dose	XXX	XXX	XXX	XXX
R2) Utility value for >360 days to death set to population norm	XXX	XXX	XXX	XXX
R3) OS extrapolation at 43 weeks for pembrolizumab and SOC	XXX	XXX	XXX	XXX
B. ERG alternative scenario (R1-R3)	XXX	XXX	XXX	XXX

*includes proposed discount for pembrolizumab and CAA discount for pemetrexed

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Table 7 of ERG report page 23

The ERG suggested three amendments to the company model:

- applying costs associated with the recommended dose of pembrolizumab after progression on chemotherapy (more relevant to NHS)
- limiting the utility values used in the model to be no higher than the population norm (more accurate but still optimistic)
- applying exponential extrapolations to KEYNOTE-024 OS K-M data from both arms of the trial at 43 weeks

End-of-life criteria

Criterion	Company assessment	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In KEYNOTE-024 trial, median OS of 30.0 months in the pembrolizumab arm was reported compared with 14.2 months in the SOC arm. The OS of 14.2 months observed in the SOC arm is higher than reported in previous studies where median OS in patients with NSCLC (regardless of histology) receiving chemotherapy SOC ranged from 9.9 to 13.9 months: • According to the PARAMOUNT trial of pemetrexed maintenance therapy in advanced non-squamous NSCLC, the median OS was 13.9 months • Squamous patients have lower life expectancy as evidenced by the SQUIRE trial reporting a median OS of 9.9 months for the gemcitabine + cisplatin arm	The ERG's alternative approach to predicting life expectancy, i.e. applying an exponential distribution to KEYNOTE-024 trial OS K-M data at 43 weeks rather than 33 weeks, gives an estimate of mean OS of **23.4 months**, which the ERG still considers to be conservative. ERG state that it is **not certain** that the mean life expectancy of the population of interest is less than the 24 months
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 SoC: • In the final analysis of KEYNOTE-024, the difference in median OS for pembrolizumab-treated patients compared with SOC treatment patients was 15.8 months (30 months -14.2 months) • The estimated differences (based on discounted values) from the cost-effectiveness model are : o 19.4 months when the 2-stage adjustment is applied (base case reflecting the original submission) o 14.6 months when no crossover adjustment is applied (proposed new base case)	ERG had no comments in relation to extension to life of pembrolizumab compared to SOC.

Source: Adapted from company submission, document B p65

End-of-life criteria (2)

Criterion	Company assessment	ERG assessment
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 SoC: • In the final analysis of KEYNOTE-024, the difference in median OS for pembrolizumab-treated patients compared with SOC treatment patients was 15.8 months (30 months -14.2 months) • The estimated differences (based on discounted values) from the cost-effectiveness model are : o 19.4 months when the 2-stage adjustment is applied (base case reflecting the original submission) o 14.6 months when no crossover adjustment is applied (proposed new base case)	ERG had no comments in relation to extension to life of pembrolizumab compared to SOC.

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Authors

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID1349]

Document B

Merck Sharp & Dohme

Evidence submission– CDF review

November 2017

File name	Version	Contains confidential information	Date
MSD Submission Pembrolizumab (ID1349) Document B ACiC	**V1**	**Yes**	**28/11/2017**

Introduction to this document

This document represents the MSD UK evidence submission for the CDF Guidance Review of TA447 (ID1349): Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer.

As instructed in the Guidance Notes, we have not presented a full submission re-presenting all the evidence previously delivered in our original submission, but rather have focused on providing new and additional evidence relating to the uncertainties highlighted by the Committee in the original submission, along with a revised economic model incorporating the new evidence.

In our original submission in October 2016, the economic analyses conducted adjusted for the cross-over of patients in the SOC arm to pembrolizumab, reflecting the assumptions about treatment options for the SOC arm that were relevant at that time.[1] Since our original submission however, pembrolizumab has been recommended as an option for second line treatment of patients with NSCLC (TA428) and has rapidly become second-line standard of care in the UK.[1] In November 2017, nivolumab was also recommended for use within the Cancer Drugs Fund as a second-line treatment option for NSCLC (TA483)(TA484).[2 3]

To reflect this change in clinical practice, in addition to updating the original economic analyses, we are also presenting additional economic analyses which do not adjust for the cross-over and include PD-L1 targeting immune-oncology treatment as 2nd line SOC for the population covered in this submission.

Contents

Tables and figures

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

B.1.1 Decision problem

Details of the decision problem were presented in the original submission and are restated in Table 1 below for ease of reference.

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 PD-L1 positive metastatic non-small-cell lung cancer (NSCLC) not treated with chemotherapy in the metastatic setting	Previously untreated patients with metastatic (stage IV) NSCLC whose tumours strongly express PD-L1, (defined as membranous PD-L1 expression on at least 50% of tumour cells, regardless of the staining intensity (i.e., a PD-L1 tumour proportion score of 50% or greater [PD-L1 TPS ≥ 50%]) and no EGFR or ALK positive tumour mutation.	In line with the licence, with the data from the supporting clinical trial (KEYNOTE-024), and with the final NICE scope.
Intervention	Pembrolizumab	Pembrolizumab 200 mg Q3W	In line with the licence and with the final NICE scope.
Comparator(s)	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) ○ with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) ○ with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only; subject to ongoing NICE		The selection of SOC chemotherapy regimens (hereafter referred to as 'SOC') included in the comparator arm of KEYNOTE-024 is reflective of the real life choices available for patients with advanced NSCLC. Various factors such as histology and performace status are taken into consideration when deciding on the most appropriate treatment option in clinical practice, including but not restricted to tolerability, patient preference, availability of drugs, and the patient's quality of life.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	guidance from the CDF rapid reconsideration process) • Single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine; for people for whom platinum combination therapy is not appropriate)		The use of physician's choice SOC, as a comparator in KEYNOTE-024 and in this submission, reflects a pragmatic approach which enables a comparison of pembrolizumab with the variety of chemotherapy options currently available to physicians in England. The primary analysis of the KEYNOTE-024 study compares pembrolizumab with investigators choice of SOC. Subgroup analysis is also presented of the comparison between pembrolizumab versus pemetrexed-containing and non-pemetrexed-containg SOC regimens.
Outcomes	The outcome measures 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 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	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

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The use of pembrolizumab is conditional on the presence of programmed cell death 1 ligand (PD-L1). The economic modelling should include the costs associated with diagnostic testing for PD-L1 in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		
Subgroups to be considered	If evidence allows, subgroup analysis by tumour histology (squamous or non-squamous) and level of PD-L1 expression (strong positive or weak positive), will be considered.	The following subgroups have been considered: • Tumour histology (squamous or non-squamous) • Comparator therapy regimen (pemetrexed-containing versus non pemetrexed containing)	Subgroup analysis by level of PD-L1 expression has not been considered, given the submission is reflective of the population from the KEYNOTE-024 trial (i.e. patients with tumours which strongly express PD-L1, defined as those with a TPS ≥ 50%)
Special considerations including issues related to equity or equality	N/A	N/A	N/A

B.1.2 Description of the technology being appraised

Since the original submission, there have been some changes to the licensed indications for pembrolizumab, as detailed in Table 2 below.[4] These changes are also reflected in the Summary of Product Characteristics presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment
Marketing authorisation/CE mark status	Pembrolizumab was granted marketing authorisation in May 2015 by the European Medicines Agency, covering all European Markets including the UK.
Indications and any restriction(s) as described in the summary of product characteristics	Pembrolizumab (KEYTRUDA®) currently has a marketing authorisation (MA) covering the following indications: ▪ KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults (MA received May 2015). ▪ KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations prior to receiving KEYTRUDA (MA variation received August 2016). ▪ KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations (MA variation received January 2017). ▪ KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab

	vedotin (BV), or who are transplant-ineligible and have failed BV (MA variation received May 2017). ▪ KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (MA variation received August 2017). ▪ KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy (MA variation received August 2017). Contraindications included in the SmPC are listed as hypersensitivity to the active substance or to any of the following excipients: ▪ L-histidine ▪ L-histidine hydrochloride monohydrate ▪ Sucrose ▪ Polysorbate 80 ▪ Water for injections
Method of administration and dosage	KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks. The recommended dose of KEYTRUDA is: • 200 mg for NSCLC that has not been previously untreated with chemotherapy, cHL or for urothelial carcinoma. • 2 mg/kg for NSCLC that has been previously treated with chemotherapy or for melanoma. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.
Additional tests or investigations	PD-L1 testing for patients with NSCLC • Patients with NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test PD-L1 testing is an immunohistochemistry (IHC) test. IHC is part of routine pathology practice. MSD has supported the development of PD-L1 testing reference centres, which provide the capacity to enable the tumours from patients with advanced NSCLC to be tested for PD-L1 status. After the NICE recommendations for use of pembrolizumab for patients with advanced NSCLC in both first and second line, PD-L1 testing of all patients with advanced NSCLC has become part of routine clinical practice and PD-L1 testing has been added to the current panel of EGFR and ALK tests for NSCLC.[5]
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial. (incorporating PAS: [redacted])

	Based on KEYNOTE-024 trial, the average time on therapy per patient is [redacted] days, equivalent to [redacted] cycles received per patient treated with pembrolixumab 200mg Q3W during a course of treatment[6] The average cost per treatment course is [redacted] at list price [redacted]
Patient access scheme (if applicable)	[redacted]

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

A review of the disease/condition for which pembrolizumab is being used, including epidemiology, survival, clinical guidelines and pathways of care, was presented in the original submission. In this section, in response to the areas of uncertainty identified in the previous technology appraisal, we present some additional data, published since the original submission, on disease epidemiology and 5-year survival. We also present an updated clinical pathway, to better reflect current practice in the UK.

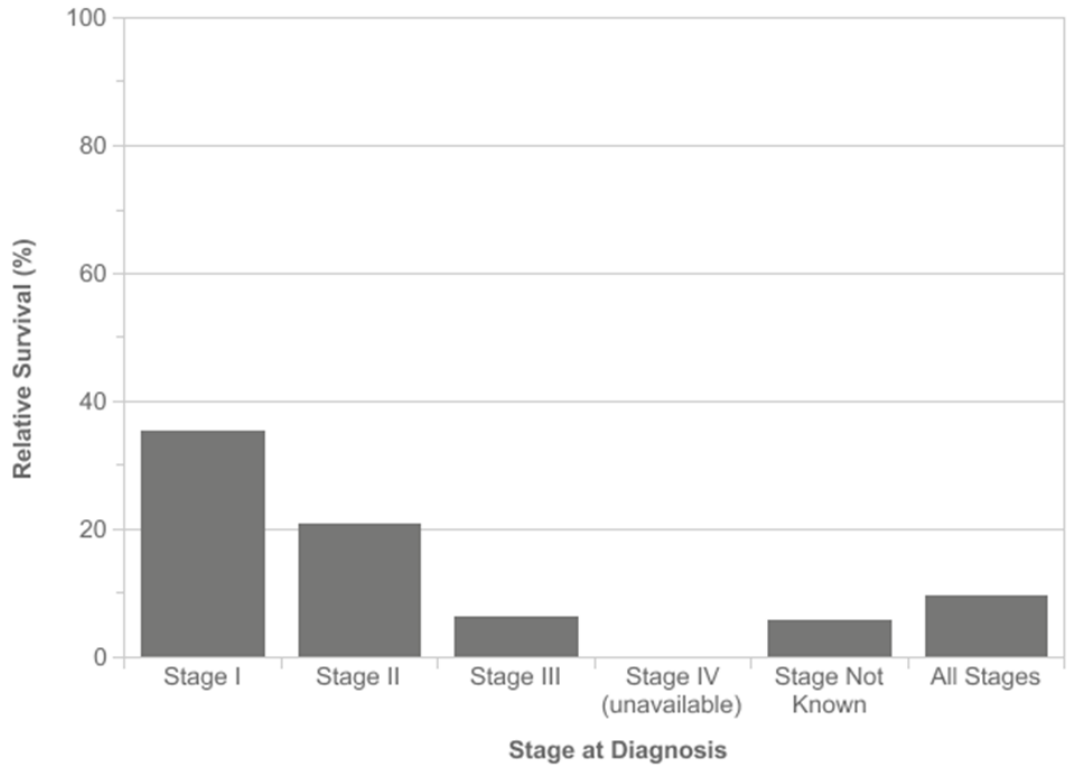
B.1.3.1: NSCLC – Incidence, prevalence and life expectancy

Lung cancer is the second most common cancer for both males and females in England. In 2015, there were a total of 37,637 cases registered, accounting for 12.5% of the total cancer registrations. [7] An estimated 57,200 people who had previously been diagnosed with lung cancer were alive in the UK at the end of 2010.[8]

The age-standardised rate for lung cancer has decreased in males from 127.9 in 1995 to 89.4 cases per 100,000 males in 2015, whilst female age-standardised rates for lung cancer have increased in this same period, from 51.4 in 1995 to 65.6 cases per 100,000 females in 2015. [7] Although the age-specific incidence of lung cancer is falling nationally as smoking prevalence falls, there has been a steady rise in the total number of lung cancer patients, partly owing to the ageing population.[9]

Based on 2010-2011 data, approximately 10% of lung cancer patients (across all stages of disease) in England and Wales survive for five years or more post diagnosis and only 5% survive for 10 years or more. [9] [10] Survival is strongly related to the stage of disease at diagnosis. An analysis of five-year survival for people diagnosed with lung cancer during 2003-2006 in the former Anglia Cancer Network showed that 35% of patients survive for 5 years or more if diagnosed at stage I compared with only 6% of those diagnosed at stage III. Five-year survival of patients diagnosed at Stage IV could not be calculated in the analysis due to the small number of people surviving beyond two years (Figure 1).[11] In an analysis of more recent data from the UK National Lung Cancer Audit (2006-2011), 5-year survival of patients diagnosed at stage IV was only 3%. [12]

Figure 1: Five-year relative survival (%) by disease stage at diagnosis in adults 15-99 years, Former Anglia Cancer Network[11]



Prepared by Cancer Research UK
Original data source:
The National Cancer Registration Service, Eastern Office. Personal communication. http://ecric.org.uk/

The number of expected cases of NSCLC for 2018 in England is 32,120; of which 15,418 are expected to be stage IV. In total, 1,799 patients are expected to be eligible for treatment with pembrolizumab (see Table 3). (See Budget Impact Model Document for additional details).

Table 3: Estimated patient numbers for England, 2018-2022

	2018	2019	2020	2021	2022
Cases of lung cancer in England	36,459	36,605	36,751	36,898	37,046
Cases of confirmed NSCLC over total lung cancer	32,120	32,249	32,378	32,507	32,637
Estimated number of incident NSCLC patients stage IV	15,418	15,479	15,541	15,604	15,666
Cases of NSCLC stage IV treated in 1L	9,867	9,907	9,946	9,986	10,026
Estimated number of NSCLC patients stage IV to be treated that are PS 0-1	8,506	8,540	8,574	8,608	8,643
Cases of NSCLC that are EGFR/ALK negative	6,958	6,985	7,013	7,041	7,070
Total EGFR/ALK negative, >50% PD-L1 positive patients eligible for pembrolizumab 1L	1,799	1,806	1,813	1,820	1,828

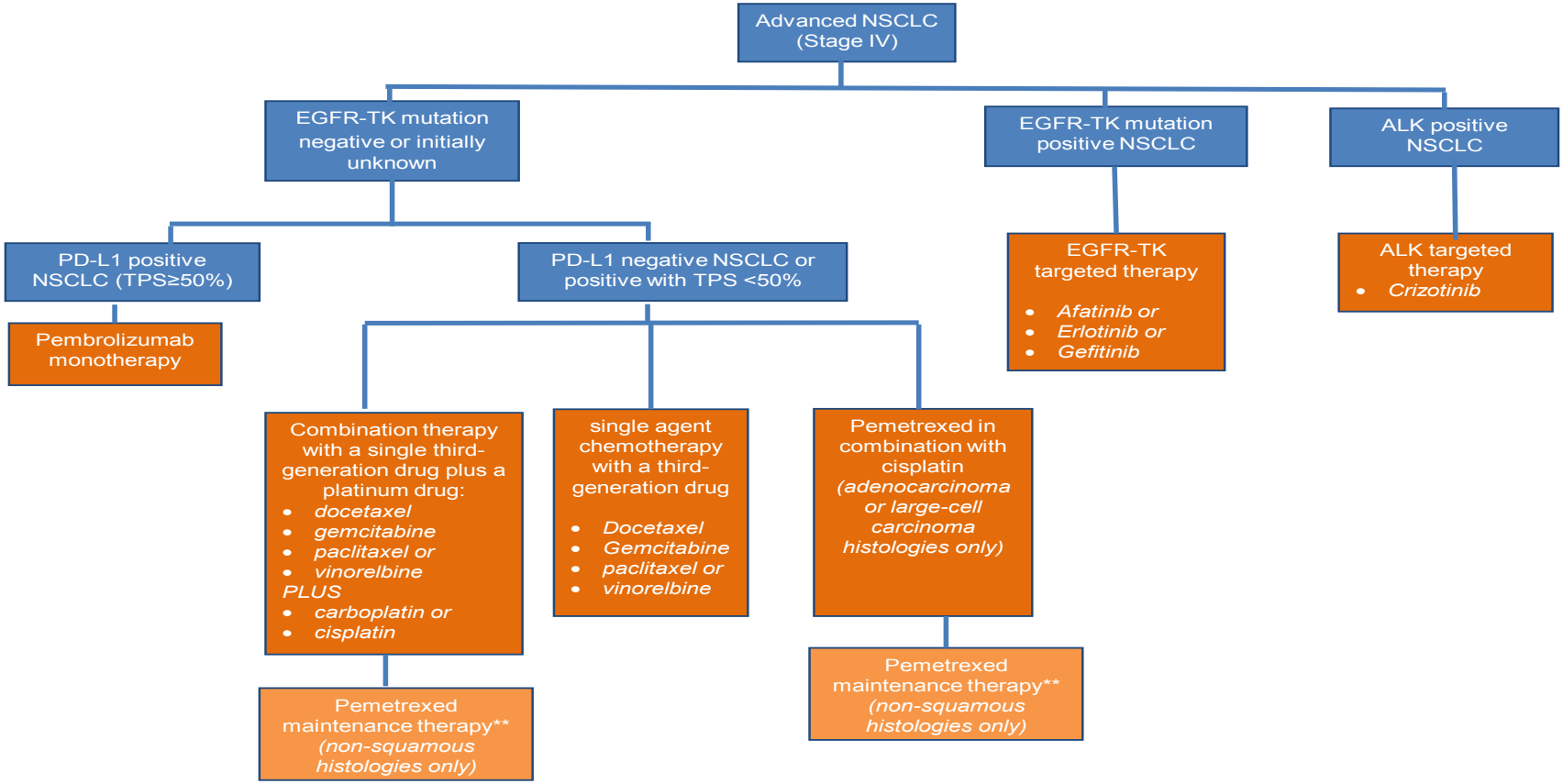
B.1.3.2: Updated UK clinical pathway of care

The original submission provided an overview of the clinical care pathway for patients with advanced NSCLC based on the relevant NICE guidelines available at that time. Since then, in addition to the recommendation for use of pembrolizumab within the CDF as an option for untreated PD-L1 positive (TPS ≥50%) metastatic NSCLC patients (TA447),[13] the drug has also been recommended for use as a treatment option for PD-L1 positive NSCLC patients after chemotherapy (TA428).[1] In November 2017, nivolumab was also recommended for use within the CDF as an option for second line treatment of both squamous and non-squamous NSCLC patients, after chemotherapy (TA483and TA484)[2 3]. Thus, PD-L1 targeting therapies are rapidly becoming standard of care in both first- and second-line treatment of eligible NSCLC patients in the UK.

Figure 2 depicts the current clinical pathway for first-line NSCLC treatment in the UK, including the most recent NICE guidance, while Figure 3 depicts the current second- and subsequent-line clinical pathway.

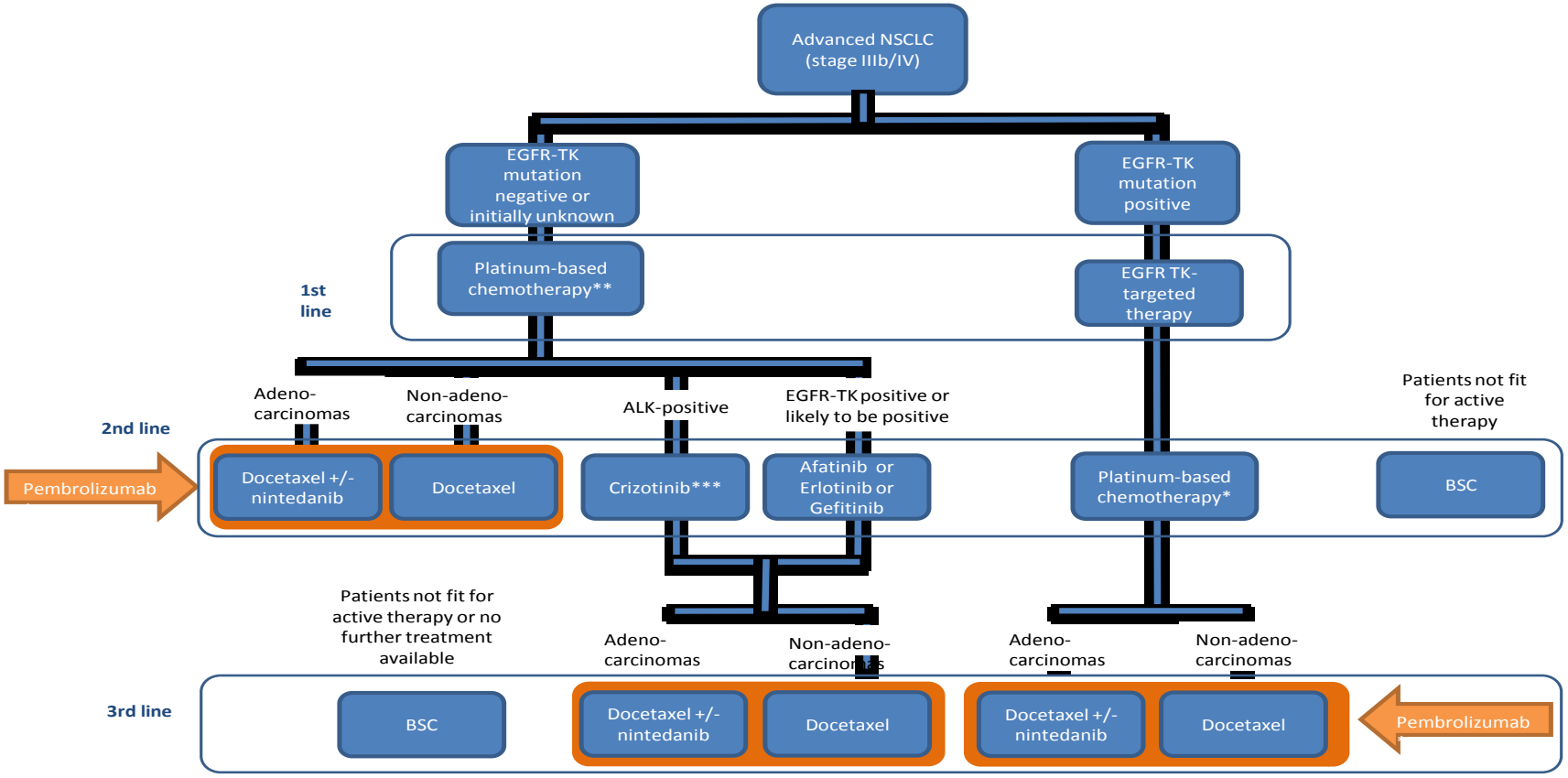
Following the NICE recommendation in June 2017 for the use of pembrolizumab first-line treatment for advanced NSCLC cases where tumour PD-L1 expression ≥50%, PD-L1 test requisition has become incorporated into hospital treatment pathways and protocols, resulting in a significant increase in the volume of PD-L1 testing across the UK. A recent analysis conducted for MSD reported a five-fold increase in the volume of PD-L1 tests conducted in the June-August 2017 period (average [redacted] tests per month) compared with the September-October 2016 period (average [redacted] tests per month).[5]

Figure 2: First-line treatment algorithm for advanced NSCLC including pembrolizumab positioning[14]



** People with advanced non-small-cell lung cancer that is strongly PD-L1 positive (TPS ≥50%); **Pemetrexed is recommended as an option for the maintenance treatment following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel (does not apply to combination therapy with vinorelbine)*

Figure 3: Second- and subsequent-line treatment options for advanced/metastatic NSCLC[14]



*Where patients develop resistance to EGFR inhibitors based on T790M mutation, treatment with osimertinib may be offered as 2nd line treatment prior to platinum-based chemotherapy

B.1.3.3: Updated clinical guidelines

The original submission included an overview of the clinical guidelines for the management of NSCLC relevant to the UK, including the guidelines from the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN). While the ESMO guidelines have not been updated since the original submission (and therefore have not been re-presented here), the NCCN guidelines have been updated and include new or updated recommendations relating to targeted therapies for metastatic NSCLC, including pembrolizumab.[15] [16] The PD-1 relevant content in the updated NCCN guidelines is summarized below.

National Comprehensive Cancer Network (NCCN) (2017)[16]

The recently updated NCCN guideline (version 5.2017) states that for patients with metastatic NSCLC who test positive for PD-L1 expression (≥50%) and who are EGFR, ALK and ROS1 negative or unknown, first line therapy with permbrolizumab is recommended (category 1). The guideline recommends IHC testing for PD-L1 expression (category 2A) before first-line treatment to assess whether patients are candidates for pembrolizumab.

For patients not meeting the above criteria, the NCCN guideline recommends first-line treatment with doublet chemotherapy or bevacizumab in combination with chemotherapy if ECOG performance status (ECOG PS) 0 - 2; or BSC if ECOG PS 3 or 4.

Post-progression following first-line chemotherapy, the guideline recommends pembrolizumab (category 1) as subsequent therapy for patients with metastatic squamous or non-squamous NSCLC and PD-L1 expression. In addition, the guideline recommends nivolumab (category 1) or atezolizumab (category 1) as subsequent therapy options for patients with metastatic NSCLC (squamous and non-squamous) that has progressed on or after first-line chemotherapy. Testing for PD-L1 expression levels is not required for prescribing nivolumab or atezolizumab, but the guidelines indicate it may provide useful information.

B.1.4 Equality considerations

As in our original submission, we do not anticipate the use of pembrolizumab in the treatment of metastatic NSCLC will raise any equity or equality issues.

B.2 Clinical effectiveness

Our original submission provided details of the identification and selection of relevant studies for the submission, listed the relevant clinical effectiveness studies included, presented the study methodologies, statistical analyses and quality assessments. None of this information has changed and therefore this section focuses on the updated clinical effectiveness results (Section B.2.6), sub-group analyses (Section B.2.7) and adverse reactions (Section B.2.10) from the Final Analysis of KEYNOTE-024.[6]

B.2.1 Identification and selection of relevant studies

Full details provided in original submission.[13]

B.2.2 List of relevant clinical effectiveness evidence

Full details provided in original submission.[13] The content in this submission is derived from the Final Analysis of study KEYNOTE-024.[6]

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

Full details provided in original submission.[13]

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

Full details provided in original submission.[13]

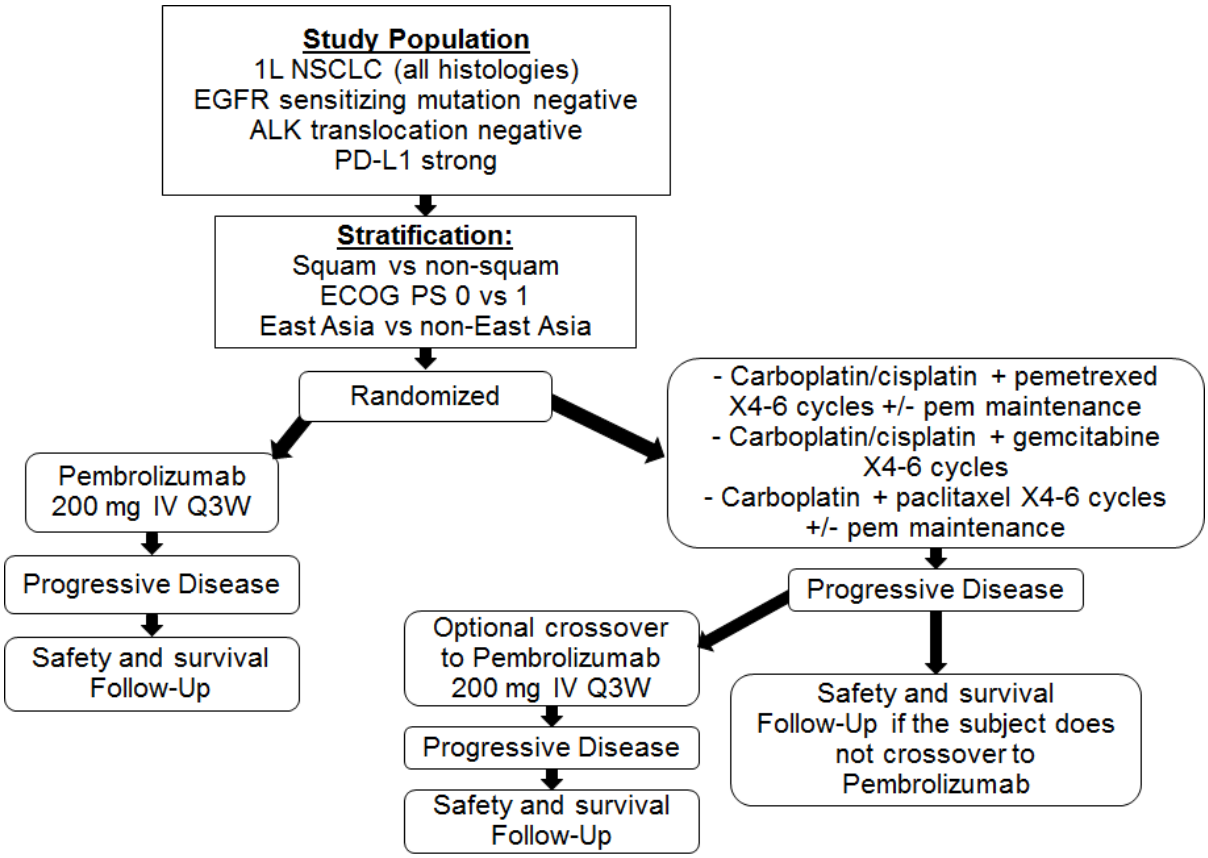
B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Full details provided in original submission.[13]

B.2.6 Clinical effectiveness results of the relevant trials

Clinical effectiveness data provided in this submission are from the final analysis of KEYNOTE-024 phase III trial of pembrolizumab versus platinum based chemotherapy in first line subjects with PD-L1 strong metastatic NSCLC.[6] Full details of the trial methodology were provided in the original submission.[13] A schematic of the study design is presented in Figure 4 below.[17]

Figure 4: Study design of KEYNOTE-024



Results provided in the original submission were from a second interim analysis (IA2) which occurred after 189 PFS events and was based on data from 09 May 2016 cut-off date.[13] Following IA2, patient follow-up continued to allow a final analysis (FA) of OS, as per the study protocol.[17]

This submission presents data from the FA of OS which was recently conducted, following 169 death events across the study population. The data cut-off date for this analysis was 10-July-2017. At this time, subjects had a median duration of follow-up of 25.2 months (range [redacted] to [redacted] months) and 23 (14.9%) patients in the pembrolizumab group and 2 (1.3%) of patients in the SOC group remained on assigned study treatment. Median duration of exposure was 7.9 months (range, 1 day – 28.8 months) for pembrolizumab and 3.5 months (range, 1 day – 30.5 months) for chemotherapy. The mean number of cycles of pembrolizumab received was [redacted] (range [redacted] to [redacted]) (ASaT population) and chemotherapy (induction plus maintenance phases) in the SOC arm was [redacted] cycles (range [redacted] to [redacted]).[6 18]

At the time of the final analysis, [redacted]/154 ([redacted]%) patients in the pembrolizumab arm had received 2 years of uninterrupted initial therapy every 3 weeks, or 35 administrations. In this group, the mean duration of follow-up from the last dose of pembrolizumab to the database

cut-off date of 10 July 2017 in this population was [redacted] months. Only [redacted] experienced disease progression; the median time to progression using the Kaplan-Meier method was [redacted] months. None of these patients re-initiated therapy. No deaths were observed in the cohort.[6]

At FA, 82 patients (54.3%) in the SOC arm had switched to pembrolizumab, within the study cross-over, as permitted per the protocol. [18] In addition, [redacted] further patients in the SOC arm switched to an anti-PD1 treatment (outside of within study cross-over), after the protocol treatment. Table 4 summarises the number of patients by weekly intervals of time to cross-over from disease progression. Half of the patients switched within 4 weeks following disease progression and most (n=60) had switched within 3 months of disease progression.[6]

Table 4: Time to cross-over from disease progression (patients from SOC arm who crossed over to pembrolizumab 200mg Q3W within permitted study cross-over) [6]

Time to switch over from disease progression (weeks)	Switchers from SOC to Pembrolizumab 200 mg Q3W N = 82
<=1 week	[redacted]
>1 to 2 weeks	[redacted]
>2 to 3 weeks	[redacted]
>3 to 4 weeks	[redacted]
>4 to 5 weeks	[redacted]
>5 to 6 weeks	[redacted]
>6 to 7 weeks	[redacted]
>7 to 8 weeks	[redacted]
>8 to 9 weeks	[redacted]
>9 to 10 weeks	[redacted]
>10 to 11 weeks	[redacted]
>11 to 12 weeks	[redacted]
>=12 weeks	[redacted]
Missing (No Disease Progression reported)	[redacted]
(Database Cutoff Date: 10Jul2017).	

Table 5 provides details of subsequent therapies received by patients following discontinuation of study treatment in the in the pembrolizumab and SOC arms of KEYNOTE-024.

Table 5: Summary of subsequent oncologic treatment following discontinuation of study treatment (ITT Population[6]

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		151	
With one or more subsequent oncologic treatment	[redacted]	[redacted]	[redacted]	[redacted]
Anti-angiogenic agent	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
ramucirumab	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
anti-GITR monoclonal antibody	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
avelumab (+) utomilumab	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab (+) nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
pembrolizumab (in study cross-over)	[redacted]	[redacted]	[redacted]	[redacted]
Oncologic surgery	[redacted]	[redacted]	[redacted]	[redacted]
Platinum doublet chemotherapy with or bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab (+) carboplatin (+) paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab (+) carboplatin (+) paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab (+) carboplatin (+)	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin (+) docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin (+) gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin (+) paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin (+) paclitaxel albumin	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin (+) pemetrexed disodium	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin (+) vinorelbine tartrate	[redacted]	[redacted]	[redacted]	[redacted]
cisplatin (+) gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
cisplatin (+) paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
cisplatin (+) pemetrexed disodium	[redacted]	[redacted]	[redacted]	[redacted]
pemetrexed disodium (+) platinum	[redacted]	[redacted]	[redacted]	[redacted]
Radiation therapy	[redacted]	[redacted]	[redacted]	[redacted]
Single agent chemotherapy with or anti-angiogenic agent	[redacted]	[redacted]	[redacted]	[redacted]
amrubicin hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab (+) paclitaxel albumin	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab (+) pemetrexed disodium	[redacted]	[redacted]	[redacted]	[redacted]
cytarabine	[redacted]	[redacted]	[redacted]	[redacted]
dexamethasone (+) docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
docetaxel (+) ramucirumab	[redacted]	[redacted]	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]	[redacted]	[redacted]
irinotecan hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]
paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
pemetrexed disodium	[redacted]	[redacted]	[redacted]	[redacted]
tegafur	[redacted]	[redacted]	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]	[redacted]	[redacted]
Single agent platinum	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Targeted therapy with or without a	[redacted]	[redacted]	[redacted]	[redacted]
cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
capmatinib	[redacted]	[redacted]	[redacted]	[redacted]
custirsen sodium (+) docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
dexamethasone (+) docetaxel (+)	[redacted]	[redacted]	[redacted]	[redacted]
docetaxel (+) nintedanib	[redacted]	[redacted]	[redacted]	[redacted]
erlotinib hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]
luminespib mesylate	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
cytarabine (+) daunorubicin (+) prednisone thioguanine	[redacted]	[redacted]	[redacted]	[redacted]

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

(Database Cutoff Date: 10JUL2017).

B.2.6.1 KEYNOTE-024 Final Analysis (FA): Summary[6 18]

The KEYNOTE-024 FA was performed principally to provide OS data; however, analyses of PFS, ORR and time to response/response duration endpoints were also conducted and are presented in this section. A summary of the results from the FA is presented in Table 6 with additional details of each analysis provided below:

Table 6: KENOTE-024 - Summary of efficacy endpoints: Final Analysis[6 18]

Number Patients - ITT population	Pembrolizumab 200 mg N=154	SOC N= 151
OS- ITT population		
Median (95% CI), [months]	30.0 [redacted]	14.2 [redacted]
Hazard Ratio; p-value	HR 0.63 (95% CI 0.47, 0.86); *p=0.002*	
OS rate at 12 months	[redacted]	[redacted]
OS rate at 18 months	[redacted]	[redacted]
OS rate at 24 months	[redacted]	[redacted]
OS rate at 30 months	[redacted]	[redacted]
PFS (BICR per RECIST 1.1) – ITT population		
Median (95% CI), [months]	[redacted]	[redacted]
Hazard Ratio; p-value	HR [redacted]	
PFS rate at 12 months	[redacted]	[redacted]
PFS rate at 18 months	[redacted]	[redacted]
PFS rate at 24 months	[redacted]	[redacted]
ORR (BIRC per RECIST 1.1) - ITT Population		
Confirmed ORR %	45.5% (37.4, 53.7)	29.8% (22.6, 37.8)
	Difference 14.9% (4.3, 25.4) *p=0.0031*	
Time to Response (BICR per RECISTS 1.1) – ITT Population		
Number of responders (n) Mean (SD) [months] Median (range) [months]	70 [redacted] 2.1 (1.4 – 14.5)	45 [redacted] 2.2 (1.8 – 10.3)
Response Duration (BICR per RECISTS 1.1) - ITT Population		
Median [months] Range [months]	not reached (1.8+ - 20.6+)	7.1 (2.1+ - 18.1+)
Best Overall Response (BICR per RECIST 1.1) – ITT Population		
% of subjects who achieved an overall response (CR + PR)	[redacted]	[redacted]
% of subjects who achieved a CR	[redacted]	[redacted]
Disease control rate	[redacted]	[redacted]

Database Cut off Date: 10 Jul 2017

B.2.6.2 Overall Survival[6 18]

Primary Analysis

Table 7 and Figure 5 present the results of the OS analysis and Kaplan-Meier estimates of OS in the ITT population, respectively. For the analysis of OS, data for patients who were alive or who were lost to follow-up were censored at the time of the last contact.

A total of 169 (55%) deaths were recorded at the time of data cutoff. The HR for OS was 0.63 (95% CI: 0.47, 0.86) with a one sided p-value of 0.002, favouring pembrolizumab. This achieved statistical significance with respect to the multiplicity strategy for OS that was specified in the supplemental statistical analysis plan finalised prior to study sponsor unblinding. The median OS was 30.0 months in the pembrolizumab arm and 14.2 months in the SOC arm. The 12-month OS rates were 70.3% and 54.8% for the pembrolizumab and SOC arms, respectively. At 24 months, OS rates were 51.5% for the pembrolizumab arm and 34.5% in the SOC arm; at 30 months, the corresponding rates were [redacted]% and [redacted]% for pembrolizumab and SOC arms, respectively.[6 18]

Table 7: Analysis of Overall Survival (ITT Population)[6 18]

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 12 in %† (95% CI)	Pembrolizumab vs. SOC Hazard Ratio‡ (95% CI)‡ p-Value‡‡
Pembrolizumab	154	73 [redacted]	[redacted]	[redacted]	30.0 (18.3, .)	70.3 [redacted]	0.63 (0.47, 0.86) *p=0.002*
SOC	151	96 [redacted]	[redacted]	[redacted]	14.2 (9.8, 19.0.)	54.8 [redacted]	

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

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

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

(Database Cutoff Date: 10JUL2017)

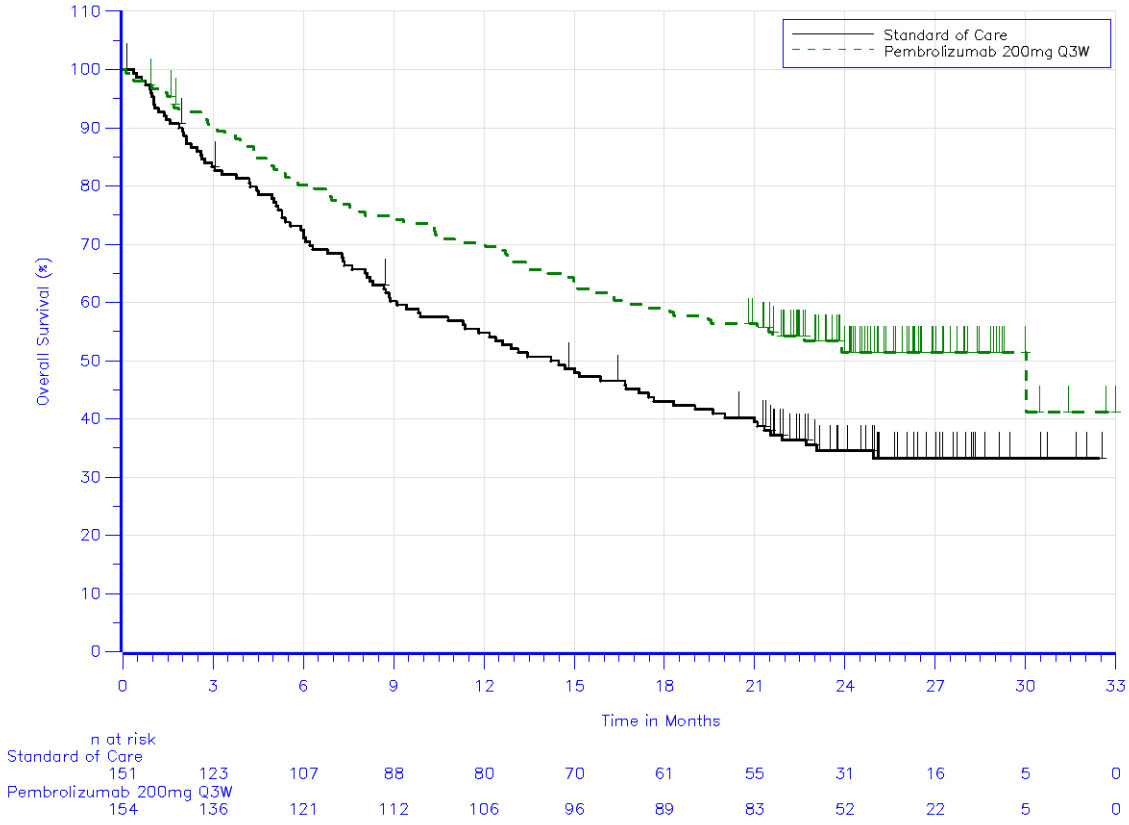
Table 8: Overall survival rate at fixed time points (ITT population)[6 18]

	Pembrolizumab (N=154)	SOC (N=151)
Rate at 12 Months in (95% CI)†	70.3 [redacted]	54.8 [redacted]
Rate at 18 Months in (95% CI)†	[redacted]	[redacted]
Rate at 24 Months in (95% CI)†	51.5 [redacted]	34.5 [redacted]
Rate at 30 Months in (95% CI)†	[redacted]	[redacted]

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

(Database Cutoff Date: 10JUL2017).

Figure 5: Kaplan-Meier of Overall Survival (ITT Population)[6 18]



Modelling approaches on OS analysis after adjusting for switching[6]

A number of patients (n=82, 54.3%) in the SOC arm switched to pembrolizumab, as permitted by the study protocol (direct switching). An additional [redacted] patients in the SOC arm switched to an anti-PD1 treatment following discontinuation of the protocol treatment (indirect switching; [redacted] switched to pembrolizumab, [redacted] switched to nivolumab).

In our original submission, the OS data for the SOC arm were adjusted to account for cross-over to pembrolizumab; this approach was accepted by the committee. For comparability with the original submission we have completed and presented the same switching analyses in this updated submission. However, given that treatment pathways have changed since the original submission, with PD-L1 targeting immune-oncology treatments now also being routinely used in second line therapy after progression on chemotherapy, there is an argument for not adjusting the SOC data as switching essentially now reflects clinical practice in the UK.

The breakdown of the disposition of patients in the SoC group is depicted in

Figure 6.

Figure 6: [redacted]

As the survival benefit associated with pembrolizumab compared to SOC is diluted due to crossover in the SOC arm (either to pembrolizumab or alternative immunotherapy), conventional survival analysis will underestimate the survival benefit associated with pembrolizumab. Therefore, the OS observed in the SOC arm was adjusted, using alternative crossover adjustment methods, to reflect the actual benefit of patients receiving SOC in the absence of crossover.

Although the two-stage was agreed as the most appropriate method of adjustment in the original submission, for consistency, we have applied the same three statistical methods as presented in the original submission: the rank preserving structural failure time method (RPSFT),[19] the simplified 2-stage method[20] and the inverse probability of censoring weighting method (IPCW).[21] The methods were applied to account for direct switching (primary) and to account for direct and indirect switching (secondary).

Full details of the methodologies adopted for each of these modelling techniques were presented in the original submission; here we present the key outputs from each approach based on the updated OS data from the KEYNOTE-024 FA.

Table 9 summarises the results of the OS analyses adjusted for direct switching, alongside the ITT analysis. Each adjustment method provided estimated hazard ratios smaller than the HR derived from the ITT analysis (larger treatment effect), within a narrow range of [redacted] Results from the analyses adjusting for both direct and indirect switching are summarised in Table 10.[6]

Table 9: Summary Results of OS Analyses (adjusted for direct switching) [6]

Crossover correction method	Pembrolizumab 200 mg mg Q3W vs. SOC		
	Hazard Ratio	95% CI	P-value (2-sided)
ITT	0.63	(0.47; 0.86)	0.003
RPSFT	[redacted]	[redacted]	[redacted]
Simplified two-stage (no re-censoring)[$]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]

** P-value retained from the ITT analysis based on distribution of the test statistic under the null hypothesis of no treatment effect*

[$]When Two-stage (with re-censoring) crossover correction method is applied, resultant HR = [redacted]

Table 10: Summary Results of OS Analyses (adjusted for direct and indirect switching) [6]

Crossover correction method	Pembrolizumab 200 mg mg Q3W vs. SOC		
	Hazard Ratio	95% CI	P-value (2-sided)
ITT	0.63	(0.47; 0.86)	0.003
RPSFT	[redacted]	[redacted]	[redacted]
Simplified two-stage (no re-censoring)[$]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]

** P-value retained from the ITT analysis based on distribution of the test statistic under the null hypothesis of no treatment effect*

[$]When Two-stage (with re-censoring) crossover correction method is applied, resultant HR = [redacted] *(95% CI:* [redacted]*); p =* [redacted]

Additional details of the crossover adjustment analyses are presented below:

Primary analyses (direct switching) [6]

RPSFT adjustment

In the primary analysis (direct switching), based on the RPSFT, the adjusted estimated hazard ratio was [redacted] (95% CI: [redacted]; *p*=[redacted]) in the pembrolizumab arm vs. the control arm.

The optimal acceleration factor, from the grid search, was estimated to be φ = 0.79. This acceleration factor was used to adjust survival times or censoring survival times of all control patients by the factor exp(-φ)=[redacted]. Using this acceleration factor, the survival period after switch-over is reduced by [redacted]% compared with the unadjusted data. Both adjusted survival times or censoring survival times and censoring status may have been modified following the re-censoring procedure in the control arm.

Based on the adjustment, the number of events in the control arm was decreased from 96 events in the unadjusted ITT analysis to [redacted] events, corresponding to [redacted]% ([redacted]/96) of

events being re-censored. Similarly, the re-censoring had an impact on the number of person-months in the control arm, decreased from [redacted] person-months in the unadjusted analysis vs .[redacted] person-months in the adjusted analysis.

Two-stage adjustment

Based on the two-stage model, the adjusted hazard ratio was [redacted] (95% CI: [redacted]; p=[redacted]) in the pembrolizumab arm vs. the control arm (without re-censoring).

The estimated acceleration factor and its 95% CI is equal to [redacted] (95% CI: [redacted]). This point estimate suggests that switching to pembrolizumab increases survival time by a factor of [redacted]. With this acceleration factor, the adjusted survival time after disease progression is reduced by [redacted]% compared with the unadjusted data.

Applying the re-censoring procedure, [redacted]/96 ([redacted]%) events were re-censored and the number of exposed person-months decreased from [redacted] person-months in the unadjusted analysis to only [redacted] person-months in the adjusted one. In view of the impact of the high value of the acceleration factor, the analysis was also conducted without re-censoring. In the analysis without recensoring, the number of events in the control arm remained the same as in the unadjusted ITT analysis (96 events).

IPCW adjustment

The IPCW-adjusted hazard ratio of mortality in the pembrolizumab arm compared to SOC was [redacted] with 95% bootstrap percentile confidence interval of [redacted] (bootstrap p-value = [redacted]).

The IPCW adjustment method adjusts ITT overall survival analysis by weighting the contribution from each subject in the control arm during a particular time interval prior to switching. Subjects who switched were censored at the time of switching. In total, [redacted]% of events ([redacted] observed deaths of 96) were lost in the SOC arm due to the informative censoring in two of the three scenarios implemented, which were consequently adjusted for using the IPC weights. In the primary analysis scenario, the IPCW-adjusted hazard ratio of mortality in the pembrolizumab arm compared to SOC was [redacted] (95% CI [redacted]) – a [redacted]% statistically significant reduction in hazard of mortality. The two more conservative sensitivity analyses produced a smaller reduction in hazard of mortality of [redacted]% and [redacted]% respectively.

Sensitivity analysis (direct plus indirect switching) [6]

To account for the overall effect of switching from SOC to any immunotherapy, sensitivity analyses were conducted to include the additional [redacted] switching patients for a total of [redacted]/151 ([redacted]%) of control patients who switched-over to any monoclonal antibody.

RPSFT adjustment

After adjustment of survival times or censoring survival times and re-censoring of control patients, the number of events in the control arm was decreased from 96 events in the unadjusted ITT analysis to [redacted] events, corresponding to a proportion of [redacted]% ([redacted]/96) of events being re-censored. Similarly, the re-censoring had an impact on the number of person-months in the control arm, decreased from to [redacted] person-months in the unadjusted analysis vs [redacted] person-months in the adjusted analysis. The resulting adjusted HR for OS is [redacted] (95%CI: [redacted]).

Two-stage adjustment

The estimated acceleration factor and its 95%CI is equal to [redacted] (95% CI: [redacted]). This acceleration factor was used to adjust survival times or censored survival times of the [redacted] patients who were eligible for switch-over and who actually switched from control arm to any monoclonal antibodies. With an acceleration factor estimated at [redacted] in the adjusted survival time, the survival period after disease progression is reduced by approximately [redacted]% compared with the unadjusted observed data.

Applying the re-censoring procedure, [redacted]/96 ([redacted]%) events have been re-censored and the number of exposed person-months decreased from [redacted] person-months in the unadjusted analysis to only [redacted] person-months in the adjusted one. The adjusted HR for OS is [redacted] (95% CI: [redacted]).

Without the re-censoring procedure applied, the adjusted HR for OS is [redacted] (95% CI[redacted]

IPCW adjustment

The IPCW-adjusted hazard ratio of pembrolizumab versus SOC is [redacted] (95% CI: [redacted]).

In the sensitivity analysis scenario, the observations were weighted in exactly the same way as in the primary analysis scenario, but subjects who switched to any anti-PD-1 therapy after the end of SOC protocol were also censored at the time of switch.

Of those who switched, [redacted]/97 ([redacted]%) subjects died after switching, and therefore [redacted]/96 ([redacted]%) observed events were lost due to censoring at the time of switch. Among those who did not switch in the SOC arm, [redacted] ([redacted]%) deaths were observed, and included in the analysis.

The IPCW-adjusted hazard ratio of pembrolizumab versus SOC is [redacted] with 95% bootstrap percentile confidence interval of [redacted] (bootstrap p-value = [redacted]).

A summary of the median OS in the pembrolizumab study arm and SOC study arm, with and without various crossover correction methods applied, is presented in Table 11. Figure 7, Figure 8 and

Figure 9 are Kaplan-Meier curves of OS, adjusting for treatment switches, using the various crossover correction methods.

Table 11: Analysis of median OS using Two-stage, RPSFT and IPCW methods[6]

Crossover correction method	**Median OS (months) (95% CI)**
SOC (no crossover correction)	14.2 (9.8, 19.0)
SOC – RPSFT correction	[redacted]
SOC - Simplified two-stage correction (no re-censoring)*	[redacted]
SOC – IPCW correction	[redacted]
Pembrolizumab 200 mg Q3W	[redacted]
**SOC- Two stage correction (with re-censoring) Median OS = Not Reached (95% CI:---., ---.)*	

Figure 7:

Figure 8: Kaplan-Meier Curves of OS adjusting for treatment switch using 2-stage correction - without re-censoring (ITT population[6]

Figure 9: [redacted][6]

B.2.6.3 Progression Free Survival[6]

As indicated above, the second interim analysis (IA2) yielded the final PFS results for the primary outcome of the study, which was presented in the original submission. Here we present the PFS data based on the FA, as summarized in Table 12 and

Figure 10 provides the Kaplan-Meier curves of PFS based on the BICR assessment per RECIST 1.1 in the ITT population, based on the primary censoring rule.

For the analysis of PFS, data for patients who were alive and had no disease progression or who were lost to follow-up were censored at the time of the last tumour assessment (primary censoring rule). A total of [redacted] PFS events were reported by the time of the data cut-off. Based on the primary censoring rule, HR of PFS was [redacted] (95% CI [redacted]) with a one-sided p-value of [redacted], favoring pembrolizumab, with median PFS of [redacted] months for pembrolizumab and [redacted] months for SOC. The PFS rates at 12 months, were [redacted] % (95% CI [redacted]) and [redacted] % (95% CI [redacted]) for pembrolizumab and SOC respectively; the corresponding PFS rates at 18 months were [redacted] % (95% CI [redacted]) and [redacted] % (95% CI [redacted]).

Table 12: Analysis of progression-free survival based on BICR assessment per RECIST 1.1 (primary censoring rule)(ITT Population) [6]

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Progression-free survival is defined as time from randomisation 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 geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on log-rank test.
(Database Cutoff Date: 10JUL2017)

Figure 10 provides the Kaplan-Meier curves of PFS based on the BICR assessment per RECIST 1.1 in the ITT population based on the primary censoring rule.

Figure 10: [redacted]

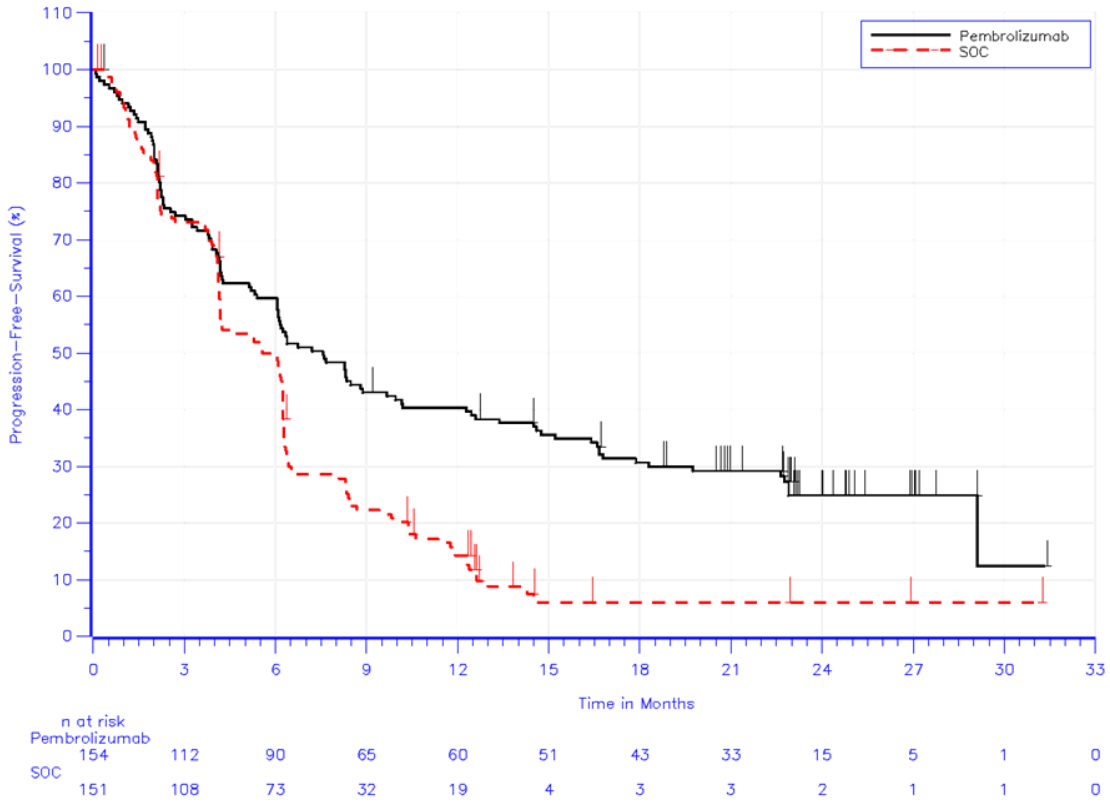
As per the KEYNOTE-024 study protocol, sensitivity analyses were performed for comparison of PFS based on investigator's assessment. Results of this analysis are presented in Table 13 and Figure 11.

Table 13: Analysis of PFS based on investigator assessment per RECIST 1.1 (primary censoring rule) (ITT Population) [6]

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Progression-free survival is defined as time from randomisation 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 geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on log-rank test.
(Database Cutoff Date: 10JUL2017)

Figure 11: Kaplan-Meier of PFS based on investigator assessment per RECIST 1.1 (primary censoring rule) (ITT Population) [6]



B.2.6.4 Objective Response Rate (ORR)[18]

Table 14 presents the analysis of confirmed ORR based on BICR assessment per RECIST 1.1 in the ITT population. The difference in ORR between the pembrolizumab arm and the SOC arm was estimated using the stratified Miettinen and Nurminen method. Pembrolizumab demonstrated a markedly higher confirmed ORR (45.5%) compared to SOC (29.8%). The confirmed ORR difference was 14.9% for pembrolizumab vs. SOC p=0.0031. The ORR of 29.8% observed for SOC is consistent with that previously observed for platinum-doublet regimens and pemetrexed maintenance

Table 14: Analysis of Objective Response with confirmation based on BICR assessment per RECIST 1.1 (ITT Population)[18]

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab vs. SOC	
				Estimate (95% CI)†	p-Value††
Pembrolizumab	154	70	45.5 (37.4, 53.7)	14.9 (4.3, 25.3)	0.0031
SOC	151	45	29.8 (22.6,37.8)		

† Based on Miettinen & Nurminen method stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). If no subjects are in one of the treatment 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.
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
(Database Cutoff Date: 10JUL2017)

B.2.6.5 Exploratory endpoints[6 18]

Exploratory analyses that were updated in the final analysis included time to response and response duration as well as best overall response.

Time to Response and Response Duration Based on BICR Assessment per RECIST 1.1[6 18]

Time to response was defined as the time from randomisation to the first assessment of a complete response (CR) or partial response (PR). Response duration was defined as the time from the first CR/PR to documented PD. Only confirmed CR/PRs were included in the analysis for time to response and response duration. Subjects who did not have PD were censored at the time of the last disease response assessment.

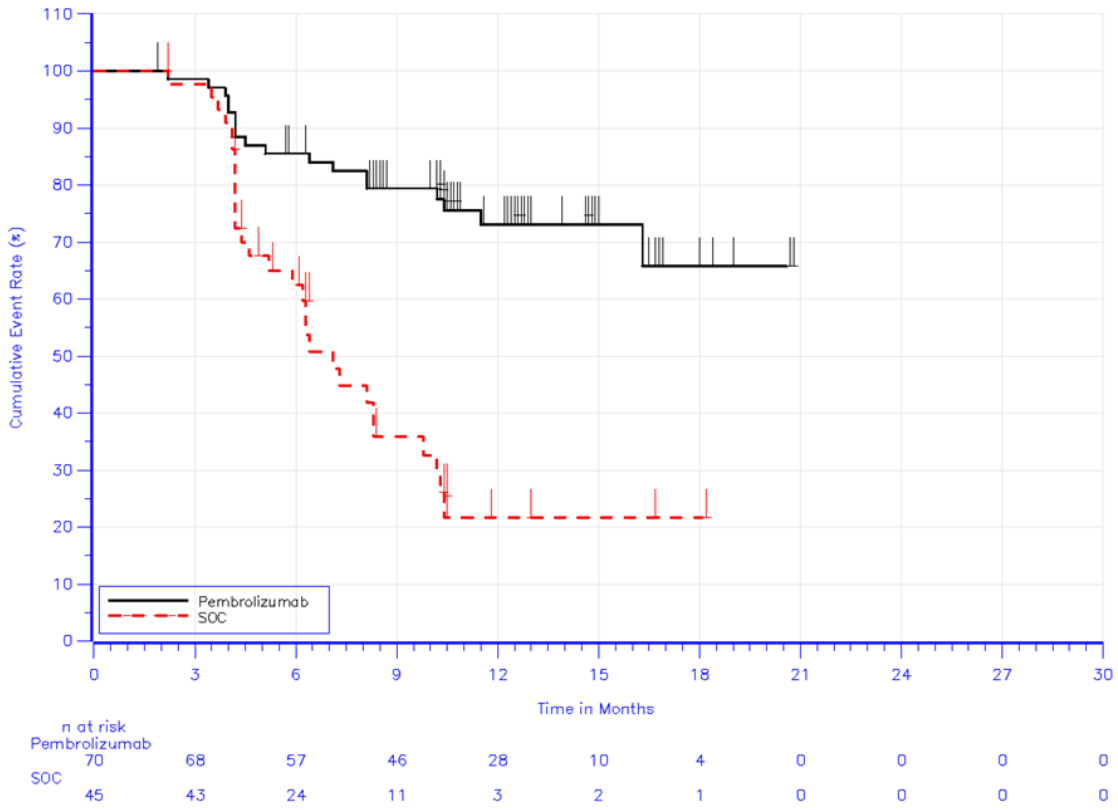
Table 15 presents the time to response and response duration among responders in the ITT population based on BICR assessment per RECIST 1.1. A total of 70 responders were observed in the pembrolizumab arm with a median time to response of 2.1 months (range 1.4 to 14.5 months), and the median duration of response was not reached (range 1.8+ to 20.6+ months). There were 45 responders in the SOC arm with a median time to response of 2.2 months (range 1.8 to 10.3 months) and a median duration of response of 7.1 months (range 2.1+ to 18.1+ months). Figure 12 demonstrates the prolonged duration of response of pembrolizumab relative to the SOC among responders in the ITT population.

Table 15: Summary of time to response and response duration for subjects with objective response based on BICR assessment (ITT Population)[6 18]

	Pembrolizumab (N=154)	SOC (N=151)
Number of Subjects with Response†	70	45
Time to Response† (months)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	2.1 (1.4-14.5)	2.2 (1.8-10.3)
Response Duration‡ (months)		
Median (Range)§	Not reached (1.8+ - 20.6+)	7.1 (2.1+ - 18.1+)
Number of Subjects with Response ≥ 6 months(%)‡	[redacted]	[redacted]
Number of Subjects with Response ≥ 12 months(%)‡	[redacted]	[redacted]
Number of Subjects with Response ≥ 18 months(%)‡	[redacted]	[redacted]

† 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.
‡ From product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates the response duration is censored.
(Database Cutoff Date: 10JUL2017)

Figure 12: Summary of response duration for subjects with objective response based on BICR assessment per RECIST 1.1 (ITT Population) [6 18]



Best Overall Response[6 18]

A summary of confirmed BOR based on BICR assessment in the ITT population is presented in Table 16. Results show that 45.5% of subjects treated with pembrolizumab achieved a confirmed CR/PR compared to 29.8% of subjects treated with SOC. [redacted]% (n=[redacted]) of subjects treated with pembrolizumab had a CR compared with [redacted]% (n=[redacted]) observed for SOC. The disease control rate (percentage of subjects who achieved CR, PR, and stable disease [StD]) was similar between the pembrolizumab ([redacted]%) and SOC ([redacted]%) arms.

Table 16: Summary of best overall response based on BICR assessment RECIST 1.1 with confirmation (ITT Population)[6 18]

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Number of Subjects in Population	154		151	
Complete Response (CR)	[redacted]	[redacted]	[redacted]	[redacted]
Partial Response (PR)	[redacted]	[redacted]	[redacted]	[redacted]
Overall Response (CR + PR)	**70**	**45.5**	**45**	**29.8**
Stable Disease (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Disease Control (CR + PR + SD)	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)				
Not Evaluable (NE)				
No Assessment				

BICR = Blinded Independent Central Review
Responses are based on BICR best assessment across timepoints, with confirmation.
(Database Cutoff Date: 10JUL2017).

B.2.7 Subgroup analysis[22]

Subgroup analyses that were pre-defined in KEYNOTE-024 are described in this section. All randomised subjects were included in the analyses according to the treatment group to which they were randomised (ITT population). The consistency of results in OS and PFS was evaluated for the different subgroups described in Table 17.

Table 17: Overview of subgroup analyses conducted for different endpoints[17]

Age Category (<65 years vs. >=65 years)
Gender (Males vs. Female)
ECOG performance status (0 vs.1)
Race (White vs. Non-White)
Region (East Asian vs. Non-East Asian)
Histology (squamous vs. non-squamous)
Smoker (current vs. former vs. never)
Brain metastasis status (Yes vs. no)
Investigator Choice of SOC: Pemetrexed doublets vs other platinum doublets

B.2.7.1 Overall survival[22]

In the primary (unadjusted for treatment switch) analysis, Pembrolizumab 200 mg Q3W was superior to SOC with regard to OS: The hazard ratio was 0.63 (95% CI: 0.47, 0.86) (based data for the cut-off date of 10-July-2017).

Table 18 presents the results of the subgroup analyses for OS between the pembrolizumab arm and pooled SOC. Figure 13 presents the results as a forest plot. The data show a consistent benefit of pembrolizumab over SOC, with consistent point estimates for the HR in important subgroups of histology, type of SOC, and geography. The small number of events in subgroups including never smokers (n=24) result in wide CIs and preclude an accurate interpretation of treatment effect.

Table 18: Analysis of OS for subgroups (ITT Population)[22]

Study: KN-024	Pembrolizumab			SOC			Pembrolizumab vs. SOC	
Overall Survival	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 for Interaction Test(I^2)
Age category								
<65	[redacted]			[redacted]				
≥65	[redacted]			[redacted]				
Gender								
Female	[redacted]			[redacted]				
Male	[redacted]			[redacted]				
Race								
Non-White	[redacted]			[redacted]				
White	[redacted]			[redacted]				
Baseline ECOG status								
0	[redacted]			[redacted]				
1	[redacted]			[redacted]				
Geographic region of enrolling site								
Non-East Asia	[redacted]			[redacted]				
East Asia	[redacted]			[redacted]				
Histology								
Squamous	[redacted]			[redacted]				
Non-Squamous	[redacted]			[redacted]				
Smoking status								
Current	[redacted]			[redacted]				
Former	[redacted]			[redacted]				
Never	[redacted]			[redacted]				
History of Brain Metastases								
Yes	[redacted]			[redacted]				
No	[redacted]			[redacted]				
Investigator's choice of standard of care chemotherapy								
Platinum/ Pemetrexed	[redacted]			[redacted]				
Other Platinum Doublets	[redacted]			[redacted]				

a: Number of patients: intention-to-treat population; b: From product-limit (Kaplan-Meier) method; c: Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs non-East Asia), ECOG PS (0 vs 1) and histology (squamous vs non-squamous), 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; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; ECOG PS: Eastern Cooperative Oncology Group Performance status; (Database Cutoff Date: 10JUL2017)

Figure 13: [redacted][22]

Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
(Database Cutoff Date: 10JUL2017).

Additional subgroup analyses based on tumour histology (non-squamous, squamous) and SOC treatment regimen (containing pemetrexed, without pemetrexed), were also undertaken to estimate the treatment difference between the pembrolizumab and SOC arms, adjusting for protocol permitted treatment cross-over of control arm subjects to pembrolizumab, based on the three cross-over models previously described (RPSFT, simplified two-stage survival, IPCW). The ITT population was used for these analyses of OS. (Full details of the methodology of these analyses was presented in the original submission).

Table 19 summarises the main findings in subgroups of patients defined by histology and Table 20 sumarises the findings by treatment regimen.

Table 19: Analysis of OS adjusting for treatment switch: subgroups of patients defined by histology (non-squamous, squamous).[22]

Subgroup	Analysis	Treatment arm	N	Number of events (%)	Number of person-months	HR‡ (95%CI) *	P-value
Non-Squamous	ITT	SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	RPSFT ¶	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	2-stage§	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	IPCW	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
Squamous	ITT	SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	RPSFT ¶	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	2-stage§	Analysis could not be carried out in the absence of comparison group in the 1st-stage model					
	ICPW	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		

¶ Re-censoring applied to all control patients; § No Re-censoring applied
* P-value retained from ITT analysis by design; †: Bootstrap p-value

Table 20: Analysis of OS adjusting for treatment switch: subgroups of patients defined by treatment regimen (containing pemetrexed, without pemetrexed)[22]

Subgroup	Analysis	Treatment arm	N	Number of events (%)	Number of person-months	HR‡ (95%CI) *	P-value
Treatment regimen containing pemetrexed	ITT	SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	2-stage§	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	IPCW	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
Treatment regimen without pemetrexed	ITT	SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]		
	2-stage§	Analysis could not be carried out given the small sample size of comparison group in the 1st-stage model					

	ICPW	SOC adjusted Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

¶ Re-censoring applied to all control patients; § No Re-censoring applied
* P-value retained from ITT analysis by design; †: Bootstrap p-value

In the overall population, the three methods adjusting for direct switch-over in the SOC arm provide treatment estimates larger (HR in a range of [redacted]) than the ITT estimate (HR=[redacted]).

In subgroups of patients with non-squamous histology, a similar trend as in the analysis in overall population was observed towards larger treatment estimates using adjustment methods versus the ITT estimate.

Subgroup analyses are exploratory and therefore have to be interpreted with caution given the small sample size especially in the subgroups of squamous histology and treatment regimen without pemetrexed. In those subgroups, it was not possible to carry out the adjustment for switching-over using the simplified two-stage model due to the limited number of patients in the comparison group in the 1st-stage model. The p-values should be interpreted as purely exploratory and within the context of the results in the overall population. Specifically, a small sample size reduces the power of the test and may generate type II errors (false negatives) while testing within several subgroups may generate type I errors (false positives).The results are associated with a high degree of uncertainty and should be interpreted with caution. The focus is on estimation with uncertainty quantified by the 95% confidence interval. Nominal p-values within subgroups are provided for completeness.

B.2.7.2 Progression-free survival[22]

In the primary (=unadjusted for treatment switch) analysis, Pembrolizumab 200 mg Q3W was superior to SOC with regard to PFS: the hazard ratio was [redacted] for the cutoff date of 10-July-2017.

Table 21 presents the results of the subgroup analyses for PFS (based on BICR assessment per RECIST 1.1) between the pembrolizumab arm and pooled SOC. Figure 14 presents the results as a forest plot. The analyses demonstrated consistent benefit for the improved HR of pembrolizumab vs. SOC across the subgroups assessed. The improvement was independent of subject age, sex, ECOG performance status, tumour histology, region of enrolment, presence of brain metastases at baseline, smoking history/status, and the SOC regimen administered. The improvement observed in the “never smokers” is difficult to interpret given the wide CI noted around the point estimate of [redacted], resulting from the small number of subjects in this subgroup.

Table 21: Subgroup analysis of PFS based on BIRC per RECIST 1.1 (ITT Population)[22]

Study: KN-024	Pembrolizumab			SOC			Pembrolizumab vs. SOC	
Progression-Free Survival	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 for Interaction Test(I^2)
Age category								
<65	[redacted]							
≥65	[redacted]							
Gender								
Female	[redacted]							
Male	[redacted]							
Race								
Non-White	[redacted]							
White	[redacted]							
Baseline ECOG status								
0	[redacted]							
1	[redacted]							
Geographic region of enrolling site								
Non-East Asia	[redacted]							
East Asia	[redacted]							
Histology								
Squamous	[redacted]							
Non-Squamous	[redacted]							
Smoking status								
Current	[redacted]							
Former	[redacted]							
Never	[redacted]							
History of Brain Metastases								
Yes	[redacted]							
No	[redacted]							
Investigator's choice of standard of care chemotherapy								
Platinum/ Pemetrexed	[redacted]							
Other Platinum Doublets	[redacted]							

a: Number of patients: intention-to-treat population; b: From product-limit (Kaplan-Meier) method; c: Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs non-East Asia), ECOG PS (0 vs 1) and histology (squamous vs non-squamous), 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; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; ECOG PS: Eastern Cooperative Oncology Group Performance status; (Database Cutoff Date: 10JUL2017)

Figure 14: [redacted])[22]

Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous). (Database Cutoff Date: 10JUL2017).

B.2.8 Meta-analysis

No meta-analysis of pembrolizumab trials was conducted either for the original submission or for this submission. Full details of the rationale and feasibility assessment that was undertaken to determine whether it was appropriate were provided in the original submission and in response to NICE clarification questions during the original appraisal.[13]

B.2.9 Indirect and mixed treatment comparisons

Uncertainties in the indirect and mixed treatment comparisons

In the original submission, in order to supplement the direct evidence for pembrolizumab from KEYNOTE-024, and in the absence of head to head RCTs of pembrolizumab versus all relevant comparators of interest, an indirect treatment comparison (ITC) by means of a network meta-analysis (NMA) of RCTs was conducted to enable a comparison to be made.[23-25] Full details of the methodology and results of the ITC and NMA were provided in the original submission.[13]

We have not updated the NMA for this submission; however, we are looking to do this for completeness and anticipate the updated analysis will be available in late December 2017.

B.2.10 Adverse reactions[18 26]

The Adverse reactions presented here have been derived from the Final Analysis.

Analyses of adverse experiences in KEYNOTE-024 were conducted in the all-subjects-as-treated (ASaT) population in this study. The ASaT population consisted of all randomised subjects who received at least one dose of study treatment (n=304). Subjects were included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data. Patients who take incorrect study treatment for the entire treatment period are included in the treatment group corresponding to the study treatment actually received.

Analyses of AE, serious AE (SAE), AE of special interest (AEOSI) were conducted and are presented in this section. Safety and tolerability were assessed by clinical and statistical review of all relevant parameters including AEs and laboratory test abnormalities during the treatment period up to the data cut-off date of 10-July-2017.[26]

B.2.10.1 Extent of Exposure

Table 22 presents the breakdown of chemotherapy administered to subjects by histology in the chemotherapy arm. The most common regimen administered to the SOC subjects was pemetrexed in combination with carboplatin ([redacted]%]). The vast majority of subjects with non-squamous NSCLC were administered a pemetrexed containing doublet [redacted]%]). [redacted]%) subjects with non-squamous NSCLC received pemetrexed maintenance. More subjects with squamous NSCLC received gemcitabine in combination with carboplatin ([redacted]%) as compared to gemcitabine in combination with cisplatin ([redacted]%) or paclitaxel in combination with carboplatin ([redacted]%).

Table 22: KEYNOTE-024 Breakdown of chemotherapy by histology[26]

Actual Study Medication	Non-squamous N (%)	Squamous N (%)	Total N (%)
Gemcitabine and carboplatin	[redacted]	[redacted]	[redacted]
Gemcitabine and cisplatin	[redacted]	[redacted]	[redacted]
Paclitaxel and carboplatin without pemetrexed maintenance	[redacted]	[redacted]	[redacted]
Pemetrexed and carboplatin with pemetrexed maintenance	[redacted]	[redacted]	[redacted]

Pemetrexed and carboplatin without pemetrexed maintenance	[redacted]	[redacted]	[redacted]
Pemetrexed and cisplatin with pemetrexed maintenance	[redacted]	[redacted]	[redacted]
Pemetrexed and cisplatin without pemetrexed maintenance	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
N = number Frequency missing = 1			

Table 23 presents the summaries of duration of exposure to treatments for the ASaT population by pooled SOC. The duration of exposure is measured from the date of the first dose to the date of last dose of treatment. The median time on therapy in the pembrolizumab arm was 7.9 months (241 days) (range 1 day to 28.8 months) compared to 3.5 months (129.70) (range 1 day to 30.5 months) days in the SOC arm.

Table 23: KEYNOTE-024 Summary of drug exposure (ASaT population)[18 26]

	Pembrolizumab	SOC
	N=154	N=150
Study Days On-Therapy (days)		
Mean	[redacted]	[redacted]
Median	241.00	106.00
SD	[redacted]	[redacted]
Range	1.00 to 878.00	1.00 to 928.00
(Database Cutoff Date: 10JUL2017).		

Table 24 displays a summary of exposure to treatment by duration in the ASaT population. Overall, [redacted] subjects in the pembrolizumab arm received treatment for ≥12 months compared to [redacted] subjects in the SOC arm.

Table 24: KEYNOTE-024 Exposure by duration (ASaT population)[26]

Duration of Exposure	Pembrolizumab (N=154)		SOC (N=150)	
	n	Subject Years	n	Subject Years
> 0 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 6 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 m	[redacted]	[redacted]	[redacted]	[redacted]
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date +1. (Database Cutoff Date: 10JUL2017).				

B.2.10.2 Adverse Events (AEs)[18 26]

Table 25 displays an overview of the numbers and percentages of subjects in the ASaT population who had AEs up to 30 days and SAEs up to 90 days after the last dose of study medication. Adverse events were collected over a longer period of time for the pembrolizumab arm as compared to SOC given the more than double mean exposure to pembrolizumab as compared to SOC.

Results show comparable numbers of subjects with one or more AEs in the pembrolizumab arm ([redacted]%]) and the SOC arm ([redacted]%]). Fewer subjects had Grade 3 to 5 drug-related AEs in the pembrolizumab arm (31.2%) than in the SOC arm (53.3%). Serious adverse events reported in the pembrolizumab and SOC arms were comparable ([redacted]% and [redacted]%, respectively). Drug-related SAEs were also comparable in both treatment groups (22.7% pembrolizumab; 20.7% SOC). There were [redacted]%) deaths reported in the pembrolizumab arm; of which, 2 (1.3%) deaths were assessed to be a drug-related SAE. In the SOC arm, [redacted]%) deaths were reported and 3 (2%) of these deaths were assessed as drug related SAEs. A total of [redacted]%) subjects ([redacted]%] in the pembrolizumab arm and [redacted]%] in the SOC arm) discontinued due to an AE; of which, 37 (12.2%) discontinued due to a drug-related AE (21 [13.6%] in the pembrolizumab arm and 16 [10.7%] in the SOC arm).

Table 25: KEYNOTE-024 Adverse event summary (ASaT Population)[26]

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued‡ due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded. AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after

The most frequently reported AEs (with an incidence of ≥20%) by decreasing incidence were as follows:

- In the pembrolizumab arm: diarrhoea ([redacted]%), dyspnoea ([redacted]%), fatigue ([redacted]%), constipation ([redacted]%), decreased appetite ([redacted]%) and nausea [redacted]%).
- In the SOC arm: anaemia ([redacted]%), nausea ([redacted]%), fatigue ([redacted]%), decreased appetite ([redacted]%), vomiting ([redacted]%), neutropaenia ([redacted]%), constipation [redacted]%), and diarrhoea ([redacted]).

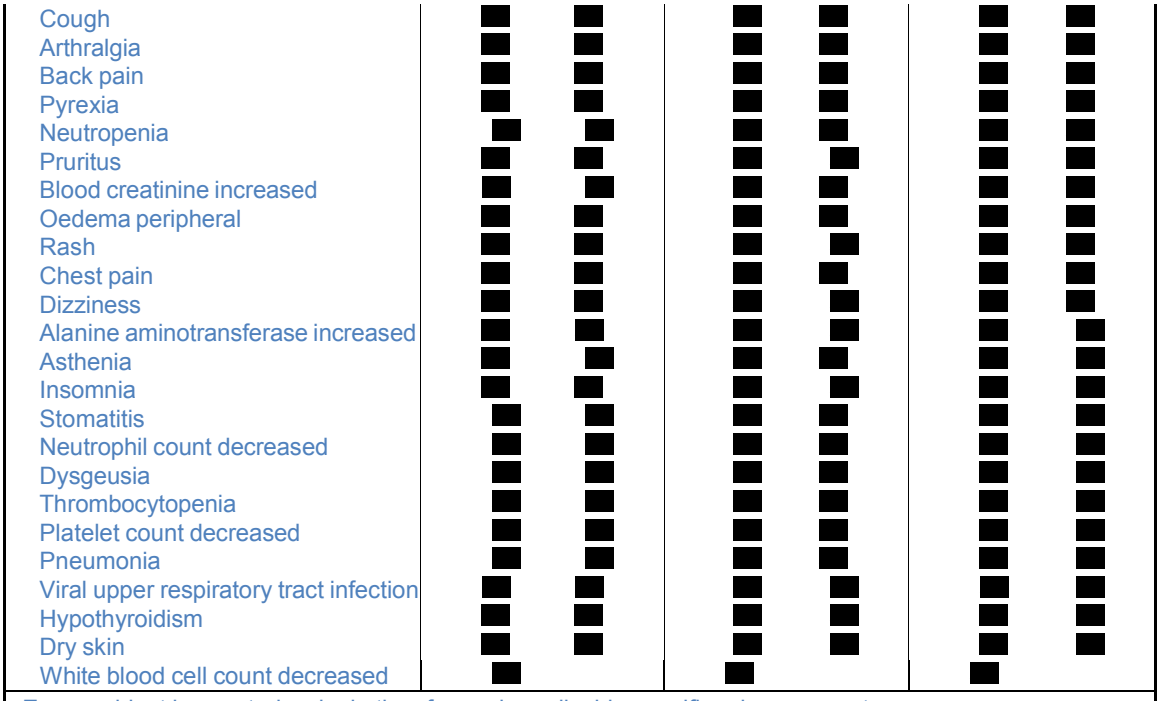
The incidence of pruritus, rash, viral upper respiratory tract infection, hypothyroidism and dry skin in the pembrolizumab arm were more than double the incidence observed in the SOC arm.

The incidence of nausea, anemia, vomiting, neutropaenia, stomatitis, thrombocytopaenia, dysgeusia, neutrophil count decreased, dysgeusia, platelet count decreased, white blood cell count decreased and pneumonia in the SOC arm were more than double the incidence observed in the pembrolizumab arm.

Analyses of subjects with AEs by decreasing incidence (incidence ≥ 10% in one or more treatment groups), are presented in Table 26. While the overall incidence of AEs (irrespective of grade) was similar across the two arms, AEs with an incidence of ≥20% were more frequent for SOC as compared to pembrolizumab. The safety profile for SOC was as expected.

Table 26: KEYNOTE-024 Subjects with Adverse Events by decreasing incidence (incidence ≥10% in one or more treatment groups) (ASaT population)[26]

	Pembrolizumab n	(%)	SOC n	(%)	Total n	(%)
Subjects in population	154		150		304	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



Every subject is counted a single time for each applicable specific adverse event.

A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded. AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose. (Database Cutoff Date: 10JUL2017).

Table 27 provides an overview of the numbers and percentages of subjects in the ASaT population with grade 3-5 adverse events (where incidence >5% in one or more treatment groups). Across both treatment arms, [redacted] patients ([redacted]%) reported at least one episode of a grade 3-5 AE; [redacted]%) in the pembrolizumab arm and [redacted] ([redacted]%) in the SOC arm. The most frequently reported grade 3-5 AEs (with an incidence of >5%) by decreasing incidence were as follows:

- In the pembrolizumab arm: anaemia ([redacted]%) and hyponatraelmia ([redacted]%),.
- In the SOC arm: anaemia ([redacted]%), neutropaenia ([redacted]%), pneumonia ([redacted]%), platelet count decreased ([redacted]%), thrombocytopaenia ([redacted]%) and fatigue ([redacted]%).

Table 28 provides details of the grade 2-5 diarrhoea adverse events across the treatment arms. The table also details the average number of episodes and average duration of episodes in the overall population. Across the study population, [redacted] patients [redacted]%) experienced at least one episode of grade 2-5 diarrhoea, including [redacted]%) in the pembrolizumab arm and [redacted]%) in the SOC arm.

Table 27: Subjects with grade 3-5 AEs (Incidence >5% in one or more treatment groups) (ASaT Population)[26]

	Pembrolizumab			SOC			Total		
	Number (%) of patients with at least one episode	Average number (SE) of episodes per patient	Average duration (SE) of episode (Days) †	Number (%) of patients with at least one episode	Average number (SE) of episodes per patient	Average duration (SE) of episode (Days) †	Number (%) of patients with at least one episode	Average number (SE) of episodes per patient	Average duration (SE) of episode (Days) †
Any type of AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specific AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
†For patients with multiple episodes of a specific adverse event, the average duration is first calculated within the patient.
AEs were followed 30 days after last dose of study treatment. (Database Cutoff Date: 10JUL2017).

Table 28: Subjects with Grade 2-5 diarrhoea adverse events (ASaT Population)[26]

	Pembrolizumab			SOC			Total		
	Number (%) of patients with at least one episode	Average number (SE) of episodes per patient	Average duration (SE) of episode (Days) †	Number (%) of patients with at least one episode	Average number (SE) of episodes per patient	Average duration (SE) of episode (Days) †	Number (%) of patients with at least one episode	Average number (SE) of episodes per patient	Average duration (SE) of episode (Days) †
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
†For patients with multiple episodes of a specific adverse event, the average duration is first calculated within the patient.
AEs were followed 30 days after last dose of study treatment. (Database Cutoff Date: 10JUL2017).

B.2.10.3 Drug-Related Adverse Events[18 26]

Adverse events considered by the Investigator to be "possibly," "probably," or "definitely" related to the study treatment are combined into the category drug-related AEs.

Table 29 displays the number and percentage of subjects with drug-related AEs (incidence ≥10% in one or more treatment groups) in the ASaT population. 253 (83.2%) subjects reported a drug-related AE: 118 (76.6%) in the pembrolizumab arm and 135 (90%) in the SOC arm. The most frequently reported drug-related AEs, by decreasing incidence, were as follows:

- In the pembrolizumab arm: diarrhoea ([redacted]%), fatigue ([redacted]%), pyrexia ([redacted]%), pruritis ([redacted]%) and rash ([redacted]%).
- In the SOC arm: anaemia ([redacted]%), nausea, ([redacted]%), fatigue ([redacted]%), decreased appetite ([redacted]%), neutropaenia ([redacted]%), vomiting ([redacted]%), diarrhoea ([redacted]%), neutrophil count decreased ([redacted]%), platelet count decreased ([redacted]%), stomatitis ([redacted]%), constipation ([redacted]%), white blood cell count decreased ([redacted]%), thrombocytopaenia ([redacted]%), dysgeusia ([redacted]%), and blood creatinine increased ([redacted]

The incidence of pyrexia, pruritis and rash in the pembrolizumab arm were more than double the incidence observed in the SOC arm.

The incidence of nausea, anemia, fatigue, decreased appetite, neutropaenia, vomiting, constipation, stomatitis, neutrophil count decreased, blood creatinine increased, platelet count decreased, thrombocytopaenia, white blood cell count decreased, and dysgeusia in the SOC arm were more than double the incidence observed in the pembrolizumab arm.

More drug-related AEs were observed with SOC as compared to pembrolizumab. Drug-related AEs observed for SOC were as expected. The predominant drug-related haematologic toxicities observed in the SOC arm were consistent with bone marrow suppression which is expected with chemotherapy.

Table 29: KEYNOTE-024 Subjects with drug-related Adverse Events by decreasing incidence (incidence ≥10% in one or more treatment groups) (ASaT population)[18] [26]

	Pembrolizumab n (%)		SOC n (%)		Total n (%)	
Subjects in population	154		150		304	
with one or more adverse events	118	(76.6)	135	(90.0)	253	(83.2)
with no adverse events	36	(23.4)	15	(10.0)	51	(16.8)
Nausea	[redacted]		[redacted]		[redacted]	
Anaemia	[redacted]		[redacted]		[redacted]	
Fatigue	[redacted]		[redacted]		[redacted]	
Decreased appetite	[redacted]		[redacted]		[redacted]	
Diarrhoea	[redacted]		[redacted]		[redacted]	
Neutropenia	[redacted]		[redacted]		[redacted]	
Vomiting	[redacted]		[redacted]		[redacted]	
Pyrexia	[redacted]		[redacted]		[redacted]	
Constipation	[redacted]		[redacted]		[redacted]	
Neutrophil count decreased	[redacted]		[redacted]		[redacted]	
Stomatitis	[redacted]		[redacted]		[redacted]	
Blood creatinine increased	[redacted]		[redacted]		[redacted]	
Pruritus	[redacted]		[redacted]		[redacted]	
Rash	[redacted]		[redacted]		[redacted]	
Platelet count decreased	[redacted]		[redacted]		[redacted]	
White blood cell count decreased	[redacted]		[redacted]		[redacted]	
Dysgeusia	[redacted]		[redacted]		[redacted]	
Thrombocytopenia	[redacted]		[redacted]		[redacted]	

Every subject is counted a single time for each applicable specific adverse event.

A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

AEs were followed 30 days after last dose of study treatment; SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 10JUL2017).

Table 30 displays the number of subjects with drug-related Grade 3 to 5 AEs (incidence ≥1% in one or more treatment groups). The most common drug-related Grade 3 to 5 AEs by decreasing incidence were as follows:

- In the pembrolizumab arm: diarrhoea ([redacted]%), pneumonitis ([redacted]%), colitis ([redacted]%) and fatigue ([redacted]%).
- In the SOC arm: anemia ([redacted]%), neutropaenia ([redacted]%), platelet count decreased ([redacted]%), and thrombocytopaenia ([redacted]%).

The overall incidence of drug-related Grade 3 to 5 AEs in the SOC arm (53.3%) was higher than in the pembrolizumab arm (31.2%).

Table 30: KEYNOTE-024 Subjects with Grade 3-5 drug-related Adverse Events by decreasing incidence (incidence ≥1% in one or more treatment groups) (ASaT population)[18 26]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	48	(31.2)	80	(53.3)	128	(42.1)
with no adverse events	106	(68.8)	70	(46.7)	176	(57.9)
Anaemia	[redacted]		[redacted]		[redacted]	
Neutropenia	[redacted]		[redacted]		[redacted]	
Platelet count decreased	[redacted]		[redacted]		[redacted]	
Diarrhoea	[redacted]		[redacted]		[redacted]	
Fatigue	[redacted]		[redacted]		[redacted]	
Thrombocytopenia	[redacted]		[redacted]		[redacted]	
Neutrophil count decreased	[redacted]		[redacted]		[redacted]	
Pneumonitis	[redacted]		[redacted]		[redacted]	
Decreased appetite	[redacted]		[redacted]		[redacted]	
Hypoalbuminaemia	[redacted]		[redacted]		[redacted]	
White blood cell count decreased	[redacted]		[redacted]		[redacted]	
Asthenia	[redacted]		[redacted]		[redacted]	
Colitis	[redacted]		[redacted]		[redacted]	
Febrile neutropenia	[redacted]		[redacted]		[redacted]	
Lymphocyte count decreased	[redacted]		[redacted]		[redacted]	
Nausea	[redacted]		[redacted]		[redacted]	
Pancytopenia	[redacted]		[redacted]		[redacted]	
Pneumonia	[redacted]		[redacted]		[redacted]	
Acute kidney injury	[redacted]		[redacted]		[redacted]	
Aspartate aminotransferase	[redacted]		[redacted]		[redacted]	
Epistaxis	[redacted]		[redacted]		[redacted]	
Hyperglycaemia	[redacted]		[redacted]		[redacted]	
Leukopenia	[redacted]		[redacted]		[redacted]	
Lower respiratory tract infection	[redacted]		[redacted]		[redacted]	
Lung infection	[redacted]		[redacted]		[redacted]	
Rash	[redacted]		[redacted]		[redacted]	
Stomatitis	[redacted]		[redacted]		[redacted]	
Transaminases increased	[redacted]		[redacted]		[redacted]	

Every subject is counted a single time for each applicable specific adverse event.

A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

AEs were followed 30 days after last dose of study treatment. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 10JUL2017).

B.2.10.4 Drug-Related Serious Adverse Events (SAEs)[18 26]

Table 31 provides a display of subjects with drug-related SAEs up to 90 days after the last dose of study medication (incidence >0% in one or more treatment groups) for subjects in the ASaT population. Overall, the incidence of drug-related SAEs was comparable between the pembrolizumab (22.7%) and SOC (20.7%) arms. The most common drug-related SAEs by decreasing incidence were as follows:

- In the pembrolizumab arm: pneumonitis ([redacted]%) and diarrhoea ([redacted]%).
- In the SOC arm: anaemia ([redacted]%), febrile neutropaenia ([redacted]%), pancytopaenia ([redacted]%), pneumonia ([redacted]%), and thrombocytopaenia ([redacted]%).

Table 31: KEYNOTE-024 Subjects with Drug-Related serious Adverse Events by decreasing Incidence (incidence >0% in one or more treatment groups) (ASaT population)[26]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	35	(22.7)	31	(20.7)	66	(21.7)
with no adverse events	119	(77.3)	119	(79.3)	238	(78.3)
Pneumonitis	[redacted]		[redacted]		[redacted]	
Anaemia	[redacted]		[redacted]		[redacted]	
Diarrhoea	[redacted]		[redacted]		[redacted]	
Febrile neutropenia	[redacted]		[redacted]		[redacted]	
Pancytopenia	[redacted]		[redacted]		[redacted]	
Pneumonia	[redacted]		[redacted]		[redacted]	
Thrombocytopenia	[redacted]		[redacted]		[redacted]	
Acute kidney injury	[redacted]		[redacted]		[redacted]	
Alanine aminotransferase	[redacted]		[redacted]		[redacted]	
Colitis	[redacted]		[redacted]		[redacted]	
Epistaxis	[redacted]		[redacted]		[redacted]	
Lower respiratory tract infection	[redacted]		[redacted]		[redacted]	
Lung infection	[redacted]		[redacted]		[redacted]	
Acute hepatic failure	[redacted]		[redacted]		[redacted]	
Aspartate aminotransferase	[redacted]		[redacted]		[redacted]	
Bilirubin conjugated increased	[redacted]		[redacted]		[redacted]	
Blood creatinine increased	[redacted]		[redacted]		[redacted]	
Cellulitis	[redacted]		[redacted]		[redacted]	
Cerebrovascular accident	[redacted]		[redacted]		[redacted]	
Death	[redacted]		[redacted]		[redacted]	
Diabetes mellitus	[redacted]		[redacted]		[redacted]	
Diabetic ketoacidosis	[redacted]		[redacted]		[redacted]	
Enterocolitis	[redacted]		[redacted]		[redacted]	
Face oedema	[redacted]		[redacted]		[redacted]	
Fatigue	[redacted]		[redacted]		[redacted]	
Gait disturbance	[redacted]		[redacted]		[redacted]	
Gastric ulcer	[redacted]		[redacted]		[redacted]	
Hepatic enzyme increased	[redacted]		[redacted]		[redacted]	
Hyperthyroidism	[redacted]		[redacted]		[redacted]	
Hypophysitis	[redacted]		[redacted]		[redacted]	
Hypovolaemia	[redacted]		[redacted]		[redacted]	
Infusion related reaction	[redacted]		[redacted]		[redacted]	
Laryngeal oedema	[redacted]		[redacted]		[redacted]	
Leukocytosis	[redacted]		[redacted]		[redacted]	
Lichenoid keratosis	[redacted]		[redacted]		[redacted]	
Malignant neoplasm progression	[redacted]		[redacted]		[redacted]	
Meningitis viral	[redacted]		[redacted]		[redacted]	
Musculoskeletal pain	[redacted]		[redacted]		[redacted]	
Nausea	[redacted]		[redacted]		[redacted]	
Neutropenic sepsis	[redacted]		[redacted]		[redacted]	
Oedema peripheral	[redacted]		[redacted]		[redacted]	
Pancreatitis	[redacted]		[redacted]		[redacted]	
Pericarditis	[redacted]		[redacted]		[redacted]	
Platelet count decreased	[redacted]		[redacted]		[redacted]	
Pulmonary alveolar haemorrhage	[redacted]		[redacted]		[redacted]	
Pulmonary embolism	[redacted]		[redacted]		[redacted]	
Pulmonary sepsis	[redacted]		[redacted]		[redacted]	
Pyrexia	[redacted]		[redacted]		[redacted]	
Rash	[redacted]		[redacted]		[redacted]	
Respiratory tract infection	[redacted]		[redacted]		[redacted]	
Skin infection	[redacted]		[redacted]		[redacted]	
Stomatitis	[redacted]		[redacted]		[redacted]	
Sudden death	[redacted]		[redacted]		[redacted]	
Transaminases increased	[redacted]		[redacted]		[redacted]	

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Tubulointerstitial nephritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vasospasm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Every subject is counted a single time for each applicable specific adverse event.

A system organ class appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.

AEs were followed 30 days after last dose of study treatment. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 10JUL2017).

B.2.10.5 Adverse Events of Special Interest[18 26]

Adverse events of special interest (AEOSI), which includes immune-related adverse events (irAE), are presented regardless of Investigator-assessed causality and generally include all AE grades (with the exception of severe skin reactions). Table 32 displays the summary of AEOSI in the ASaT population.

AEOSI were more common among pembrolizumab-treated subjects compared to SOC-treated subjects (33.8% vs. 5.3%, respectively). A majority of the AEOSI events were Grade 1 or 2 in severity, as only 13.6% of pembrolizumab-treated subjects experienced Grade 3 to 5 AEOSI. There was one death reported due to AEOSI in the pembrolizumab treatment group, which was considered drug-related. [redacted] subjects discontinued treatment due to drug-related AEOSI in the pembrolizumab arm and [redacted] in the SOC arm. Table 33 displays the subjects with AEOSI (incidence >0% in one or more treatment groups) by AEOSI category.

Table 32: Adverse Event summary AEOSI (ASaT population)[18 26]

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	52	(33.8)	8	(5.3)
with no adverse event	102	(66.2)	142	(94.7)
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued‡ due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious drug-related adverse	[redacted]	[redacted]	[redacted]	[redacted]

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

‡ Study medication withdrawn.

AEs were followed 30 days after last dose of study treatment. SAE is monitored until 90 days after last dose.

(Database Cutoff Date: 10JUL2017).

Table 33: Subjects with Adverse Events by AEOSI category (incidence > 0% in one or more treatment groups) (ASaT population)[18 26]

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	52	(33.8)	8	(5.3)
with no adverse events	102	(66.2)	142	(94.7)
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Infusion Reactions	[redacted]	[redacted]	[redacted]	[redacted]
Myositis	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Skin	[redacted]	[redacted]	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Type 1 Diabetes Mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]	[redacted]	[redacted]

Every Subjects is counted a single time for each applicable row and column.
An AEOSI category 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.
Skin-A and Skin-B categories are combined as Skin category.
AEs were followed 30 days after last dose of study treatment. SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 10JUL2017).

B.2.10.6 Brief overview of the safety of the technology in relation to the decision problem

Safety data from KEYNTE-024 demonstrates a favourable safety profile for pembrolizumab compared to SOC, with fewer treatment-related AEs of all severities.

1. Overall, AE counts observed in KEYNOTE-024 were similar between the pembrolizumab and SOC arms despite a longer mean duration of subject exposure to pembrolizumab, which was more than twice that of SOC (330 days in pembrolizumab and 130 days in SOC). Fewer subjects in the pembrolizumab arm experienced drug-related adverse events compared with the SOC arm (76.6% vs 90.0%) and fewer subjects treated with pembrolizumab experienced grade 3-5 adverse events compared with those receiving SOC [redacted]%). While more deaths were reported in the pembrolizumab versus SOC arm (n=[redacted]% vs n=[redacted]%), fewer of these deaths were ascribed to drug-related AEs in the pembrolizumab arm (n=2, 1.3%) compared with the SOC arm (n=3, 2.0%).

2. Among subjects treated with pembrolizumab as initial therapy, the most common AEs were diarrhoea ([redacted]%), dyspnoea ([redacted]%), fatigue ([redacted]%), constipation ([redacted]%), decreased appetite ([redacted]%) and nausea ([redacted]%). These AEs were generally mild and tolerable, and infrequently led to treatment discontinuations.

3. The main AEOSIs were the potential immune-mediated AEs consistent with the currently approved product licence. In the ASaT population, 52 (33.8%) subjects treated with pembrolizumab as initial treatment and 8 (5.3%) subjects treated with SOC experienced an AE consistent with the AEOSI term list of potentially immune-mediated events. The overall incidence of AEOSIs in the SOC arm was lower than that of the pembrolizumab arm, as expected, due to the general mechanism of action of the SOC agents which is anti-mitotic and not immunomodulating. This composite frequency likely overestimates the true frequency of immune-mediated AEs since it includes events irrespective of attribution by the Investigator. Of the 52 pembrolizumab-treated

subjects who experienced an AEOSI, fewer than half (21[13.6%]) had an AEOSI that was Grade 3 to 5 in severity. Furthermore, only [redacted] ([redacted]%) pembrolizumab-treated subjects discontinued therapy due to an AEOSI.

Overall the safety profile of pembrolizumab remains consistent with previously reported findings when used as a treatment option for patients with advanced NSCLC[27 28] and other tumour types.[29-33] This demonstrates that pembrolizumab is well tolerated and the safety profile is acceptable for an advanced NSCLC population; and favourable when compared to chemotherapy regimens.

B.2.11 Ongoing studies

The completion of KEYNOTE-24 occurred on 10 July 2017 (last patient, last visit) and the data base was locked on 18 August 2017. The final OS analysis for KEYNOTE-024 was presented at the International Association for the study of Lung Cancer (IASLC) conference in October 2017 and is presented in this submission. The final study report is expected to be available in late December 2017. No additional analyses are expected for this clinical trial.

KEYNOTE-042 is an ongoing phase III randomised control trial of pembrolizumab vs. SOC in 1240 treatment naïve subjects with PD-L1 positive (TPS≥1%) advanced or metastatic NSCLC. Subjects will be stratified by PD-L1 expression status (TPS ≥50% vs. TPS 1-49%) prior to randomisation and endpoints (including OS, PFS, ORR) in the trial will be assessed in subjects with TPS≥50%, TPS≥20%, and TPS≥1%. Data from the study are expected to be available in [redacted]

B.2.12 Innovation

Pembrolizumab, a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2, enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity. With this novel mode of action and as evident by the clinical and safety data presented in this submission, pembrolizumab offers a durable and well tolerated treatment option for patients considered within this submission.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Statement of principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The safety and efficacy data from the final analysis of KEYNOTE-024[6 18 26], based on median patient follow-up of 25.2 months, provide clear evidence of the substantial, clinically meaningful and durable anti-tumour activity associated with pembrolizumab treatment over standard of care in previously untreated patients with NSCLC whose tumours strongly express PD-L1 (TPS ≥50%). In addition, with median exposure of 7.9 months, (more than double that in the chemotherapy arm), safety results from KEYNOTE-024 are consistent with the established safety profile of pembrolizumab and demonstrate favourable tolerability in the target population. These data confirm that pembrolizumab should remain a standard-of-care for first-line therapy for NSCLC patients with PD-L1 expression (TPS≥50%).

The main clinical effectiveness conclusions are provided below:

- **Pembrolizumab at 200 mg Q3W provides significant benefits in terms of OS over SOC:**
    - Median OS for patients assigned to pembrolizumab arm 30.0 months (95% CI 18.3, -) versus 14.2 months (95% CI 9.8, 19.0) for SOC arm
    - HR 0.63; 95% CI 0.47-0.86; one-sided p=0.002 (primary analysis; unadjusted results)
    - HR [redacted]; 95% CI [redacted] (adjusted for SOC cross-over within study protocol, based on simplified two-stage analysis without re-censoring)
    - HR [redacted]95% CI [redacted]; p=[redacted] (adjusted for all SOC cross-over (within and outside study protocol), based on simplified two-stage analysis without re-censoring)
- **Pembrolizumab at 200 mg Q3W provides significant benefits in terms of PFS over SOC:**
    - Median PFS [redacted]months (95% CI [redacted]) versus [redacted]months ([redacted]) for SOC
    - HR [redacted]; 95% CI [redacted]; one-sided p[redacted]

- **Pembrolizumab 200 mg Q3W results in higher ORR and longer duration of response compared to chemotherapy SOC**
    - ORR of 45.5% (95% CI 37.4, 53.7) was demonstrated in the pembrolizumab arm compared with 29.8% (95% CI 22.6, 37.8) in the SOC arm; confirmed ORR difference of 14.9% (95% CI 4.3, 25.3; p=0.0031)
    - Median time to response in the pembrolizumab and SOC arms was similar at 2.1 months (range 1.4-14.5) and 2.2 months (1.8, 10.3) respectively
    - Median duration of response not reached (range 1.8+, 20.6+ months) in the pembrolizumab arm compared with 7.1 months (range 2.1+, 18.1+ months) in the SOC arm
- **Pembrolizumab 200 mg Q3W treatment effect on OS and PFS was observed in all subgroups assessed**
- **Pembrolizumab 200 mg Q3W has a favourable AE profile and is more tolerable in treatment naïve patients, compared with SOC**
- **The 200 mg fixed dose offers a simplified dosing regimen as a first-line treatment option for patients with advanced NSCLC**

Discussion of the strengths and limitations of the clinical evidence base for the technology, including internal and external validity were presented in the original submission.

Life expectancy of people with advanced NSCLC in England

Additional details of the life expectancy of UK patients with advanced NSCLC were provided in the original submission and some additional data have been provided in section B.1.3.1 These data are summarised in Table 34 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 B.1.3.1 and is incorporated into the Budget Impact Model.

Based on these data, and the OS outcomes reported in this submission, it is clear that pembrolizumab treatment offers an extension to life, normally of at least an additional 3 months compared with alternative treatment options.

Table 34: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In KEYNOTE-024 trial, median OS of 30.0 months in the pembrolizumab arm was reported compared with 14.2 months in the SOC arm. The OS of 14.2 months observed in the SOC arm is higher than reported in previous studies where median OS in patients with NSCLC (regardless of histology) receiving chemotherapy SOC ranged from 9.9 to 13.9 months: • According to the PARAMOUNT trial of pemetrexed maintenance therapy in advanced non-squamous NSCLC, the median OS was 13.9 months. This value represents the maximum survival benefit for patients in this subgroup, in the absence of pembrolizumab therapy. Please note that, pemetrexed therapy is the SoC for patients with non-squamous NSCLC.[34] • Squamous patients have lower life expectancy as evidenced by the SQUIRE trial reporting a median OS of 9.9 months for the gemcitabine + cisplatin arm.[35]

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 SoC:
	
	• In the final analysis of KEYNOTE-024, the difference in median OS for pembrolizumab-treated patients compared with SOC treatment patients was 15.8 months (30 months -14.2 months)
	• The estimated differences (based on discounted values) from the cost-effectiveness model are :
	  ○ 19.4 months when the 2-stage adjustment is applied (base case reflecting the original submission)
	  ○ 14.6 months when no crossover adjustment is applied (proposed new base case)

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature search was conducted during the original submission to identify relevant cost-effectiveness studies from the published literature evaluating interventions for untreated patients with advanced NSCLC. The search was conducted on 26th May 2016. Given the evolving treatment landscape over the last decade, electronic database searches and additional hand-searches were restricted to the last 10 years. The searches were not updated for the CDF review since this was not a source of uncertainty identified during the original appraisal.[13]

Of a total of 3,349 papers identified in the cost-effectiveness search conducted during the original submission, no cost-effectiveness studies assessing pembrolizumab for untreated patients with advanced NSCLC were found that met all the inclusion criteria. Thus, a summary list of published cost-effectiveness studies has not been compiled.

Further details of the systematic review have been reported in Appendix G.

B.3.2 Economic analysis

Since no cost-effectiveness model was identified that was of relevance for decision making in England, the cost-effectiveness model discussed during the original appraisal was updated (including: OS, PFS, time on treatment and utilities) based on the July 2017 data cut. Details of the methods followed are presented below.

Patient population

The patient population included in the economic evaluation consisted of patients with advanced NSCLC whose tumours express PD-L1 on at least 50% of their tumour cells, and who received no prior systemic chemotherapy treatment. This is in line with the licence indication and with the final NICE scope for the original appraisal.[36]

The main body of clinical evidence for pembrolizumab compared to SOC was derived from the KEYNOTE-024 study, which included previously untreated advanced NSCLC patients with PD-L1 expression on ≥50% of tumour cells and no sensitizing EGFR mutation or ALK translocation.[37]

The baseline characteristics of the patients included in the model are presented in Table 35.

Table 35. Baseline characteristics of patients included in the model

Patient Characteristics	Mean	Measurement of uncertainty and distribution	Reference / Source
Average age	65	-	KEYNOTE-024 CSR
Proportion male	64.6%	-	KEYNOTE-024 CSR
Average BSA (m^2)*	1.83	SD = 0.22	KEYNOTE-024 CSR

*These values refer to patients recruited from European sites participating in KEYNOTE-024.

During the original appraisal, the committee heard from the clinical experts that although the proportion of patients with squamous disease was smaller than expected, and stage III patients were not included in KEYNOTE-024, the overall population in KEYNOTE-024 was comparable to clinical practice in England.

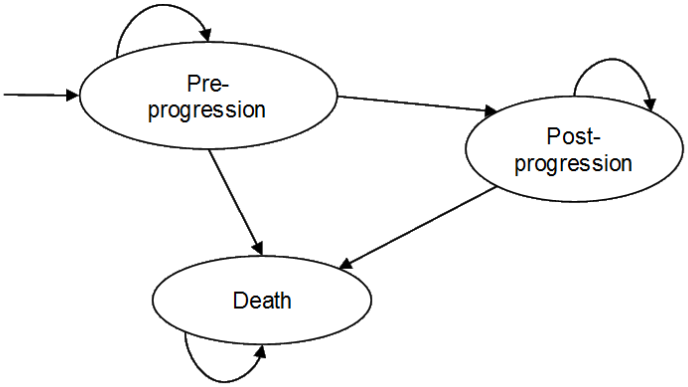
Model structure

The cost-effectiveness model presented in the original appraisal was updated for this CDF review. Consistent with the majority of economic models previously developed for recent NICE oncology submissions in advanced NSCLC, [38] [39] [40] a de-novo economic analysis was built as a 'partitioned-survival' area-under-the-curve model. The model consisted of three health states: pre-progression, post-progression and death (see Figure 15). This approach was also in line with the clinical endpoints assessed in KEYNOTE-024, in which PFS was assessed as the primary endpoint and OS as a secondary endpoint. [37] [41] 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 applied to mitigate bias.[38] [39] [42-46]

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.[44] [47]

Disease progression was defined per RECIST v1.1 as assessed by BICR (which was the primary endpoint in KEYNOTE-024). [37] [41]

Figure 15. Model structure



The partitioned-survival model was updated by fitting survival curves to trial data for progression free survival (PFS) and overall survival (OS) using the most up-to-date cut-off (i.e. July 2017). 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-024 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.[17 48]
- 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).

For the base case, and in line with the analyses conducted for KEYNOTE-024, two treatment arms were compared, including pembrolizumab and SOC.

In the model, patients in the pembrolizumab arm were assumed to be eligible to receive treatment until progression or for a maximum treatment duration of 2 years. This is consistent with the protocol of the KEYNOTE-024 trial, where patients remained on treatment until documented disease progression or intolerable toxic effects resulting in discontinuation, with maximum treatment duration of 35 cycles. [17] [37] [41] Additionally, the current NICE recommendations for the use of pembrolizumab for the treatment of advanced NSCLC states that pembrolizumab is to be stopped at 2 years of uninterrupted treatment. [1] [13]

Patients treated with SOC were also assumed to receive treatment until a maximum number of cycles, aimed to reflect clinical practice in England (see section B.3.5). For patients with advanced NSCLC of non-squamous histology treated in the SOC arm, pemetrexed maintenance therapy was optional following the first line treatment. In the base case analysis, this was reflected by accounting for the proportion of patients on pemetrexed maintenance therapy and its corresponding treatment duration, as observed during the KEYNOTE-024 trial.

Since patients in KEYNOTE-024 could receive subsequent oncologic therapies after treatment discontinuation, the costs of these subsequent treatments were included in the economic evaluation according to the proportion of patients receiving them after treatment discontinuation:

- In the original appraisal, it was assumed that all patients in the pembrolizumab arm received docetaxel as second line treatment, to reflect UK clinical practice and NICE guidance (NICE Clinical Guideline 121).[49]

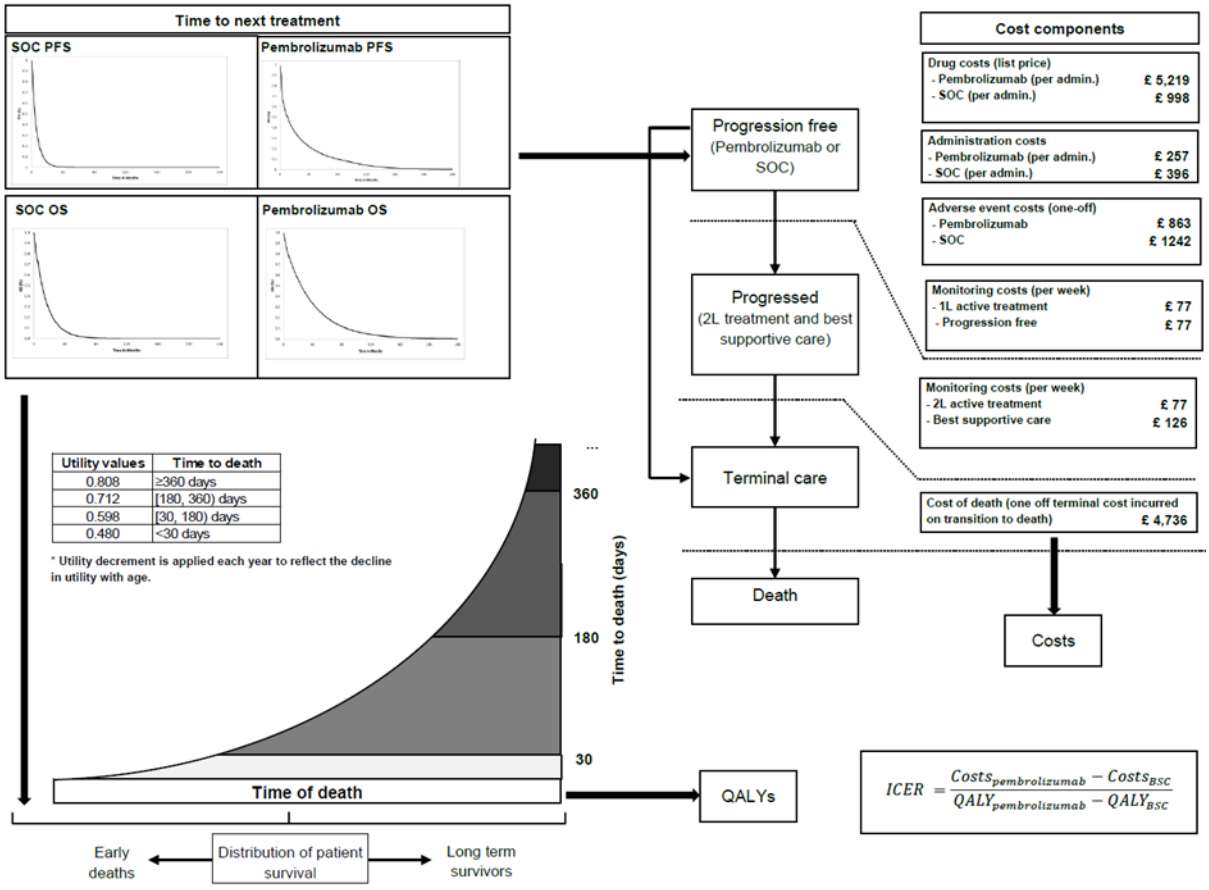
- As noted in the clinical section, clinical practice has changed between the original submission and this updated CDF submission, with now immuno-oncology drugs consistently being used in the second line setting for the population under consideration in this submission.[13] To reflect this, we are presenting now in this submission two base cases: one consistent with the original submission, and the other reflecting current UK clinical practice.
    - In the first base case, which considers crossover adjustments in order to reflect the base case analysis presented in the original submission, all patients in the SOC arm were assumed to receive doce{taxel as the only second line treatment. This scenario is identified across the submission as ***'base case reflecting the original submission'***.

To better reflect the expected OS in the absence of switching under this scenario, the adjusted OS for SOC, using a simplified two-stage adjustment, was applied in the model (see section B.2.6). Since crossover adjustments are used here, the cost of pembrolizumab after SOC is not accounted for, and all patients in the SOC arm are assumed to receive docetaxel as second line treatment (same assumption as for the pembrolizumab arm).

- In the second base case, no crossover adjustments are considered, and patients in the SOC arm who progress are assumed to receive pembrolizumab based on the proportion of patients who received pembrolizumab after discontinuation of SOC treatment in KEYNOTE-024 ([redacted]) with the rest of the patients assumed to receive docetaxel. We have named this scenario across the submission as ***'updated base case'***.

To capture more accurately the impact of pembrolizumab upon quality of life, the utilities considered in the base case analysis were based on time-to-death categories, as shown in Figure 16.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. The use of time-to-death sub-health states was applied considering four time-to-death categories: <30 days to death and ≥30 days to 180; ≥180 to 360 days, and ≥360 days. Monitoring costs were captured based on whether patients were receiving active therapy as part of first or second treatment lines, and also based on their progression status. {Brown, 2013 #411}

Figure 16: Model diagram describing the estimation of QALYs and costs



In KEYNOTE-024, patients were to continue pembrolizumab until RECIST 1.1 defined progression of disease as determined by BICR review, unacceptable toxicity or a maximum of 35 cycles of treatment with pembrolizumab.[17] In the cost-effectiveness model, the survival estimates of OS and PFS are based on KEYNOTE-024 data, thus reflecting the application of the within-trial maximum treatment duration.

In the case of SOC, it was assumed that up to a maximum of 6 cycles were administered, to reflect the protocol of KEYNOTE-024, the SmPCs and the UK clinical practice for the treatment combinations included under this comparator (e.g. up to 6 cycles allowed for pemetrexed-based combinations.[50]

Patients treated with pemetrexed maintenance are assumed to be treated until disease progression or unacceptable toxicity.[42]

3.2.3 Key features of the economic analysis

Table 36: Features of the economic analysis

	Previous appraisals		Current appraisal	
Factor	**Pemetrexed 1L (TA181)**	**Pemetrexed maintenance (TA402)**	**Chosen values**	**Justification**
Time horizon	Lifetime (6 years)	Lifetime (equivalent to 15.99 years; range: 6-20 years)	Lifetime (20 years)	Lifetime horizon for the defined target population (0.4% of patients in the pembrolizumab arm and 0% in the SOC arm were still alive after this period in the base case) In line with most recent advanced or metastatic NSCLC NICE submissions/id}[38 42 45 46 51]
Cycle length	21 days (i.e. 3 weeks)	21 days (i.e. 3 weeks)	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. [52]
Half-cycle correction	A half-cycle correction appeared to have been disabled for costs and used incorrectly for outcomes	Yes	Yes	In line with previous submissions and to mitigate bias[38 42 45 46 51]

	Previous appraisals		Current appraisal	
Factor	**Pemetrexed 1L (TA181)**	**Pemetrexed maintenance (TA402)**	**Chosen values**	**Justification**
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	Yes	NICE reference case[53] Please note that direct health effects related to patients were considered, but the impact on carers has not due to the unavailability of data to incorporate this into the model[54]
Discount of 3.5% for utilities and costs	The 'in-trial' analysis did not use discounting on either costs or outcomes, despite trial follow-up extending to more than 2 years for some patients. The ERG stated that this was an important omission, because much of the survival gain occurred after the first 12 months and would therefore be likely to be affected by discounting.	Yes	Yes	NICE reference case[53]

	Previous appraisals		Current appraisal	
Factor	**Pemetrexed 1L (TA181)**	**Pemetrexed maintenance (TA402)**	**Chosen values**	**Justification**
Perspective (NHS/PSS)	Yes	NHS	Yes	NICE reference case[53] Please note that the costs to the NHS were included, but PSS costs have not been considered due to the unavailability of data to incorporate this into the model. This is also in line with previous NICE submissions for first line therapies. [38 40 55 56]
Treatment waning effect	Not mentioned	The committee considered comments from a clinical expert mentioning that continued benefit of pemetrexed over BSC after disease progression were difficult to explain, but not further analyses seemed to have been conducted to assess the impact of this assumption.	Considered in scenario analyses	There is no evidence that treatment effect stops after discontinuation. [Please note that the term 'treatment waning' is inappropriate as applied to the analyses conducted by ERG and/or NICE technical team, which actually comprise the stopping of treatment effect at certain time points, there is no waning.]
Source of utilities	Nafees et al. (2008), which was a study commissioned by the manufacturer to study second-line treatment of NSCLC.	PARAMOUNT EQ-5D individual patient data.	KEYNOTE-024 EQ-5D individual patient data.	NICE reference case[53]

	Previous appraisals		Current appraisal	
Factor	**Pemetrexed 1L (TA181)**	**Pemetrexed maintenance (TA402)**	**Chosen values**	**Justification**
Source of costs	Patient level data from the clinical trial and resource use events from the JMDB clinical trial database	Resource use data from PARAMOUNT	Published literature, resource utilisation and costs accepted in previous NICE submissions	These reflect resource utilisation and costs accepted in previous NICE submissions.
PSS, personal social services; QALYs, quality-adjusted life years				

Intervention technology and comparators

The intervention (i.e. pembrolizumab) was included in the model as per the licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200 mg over 30 minutes every 3 weeks [Q3W]). The licence states that pembrolizumab is to be administered until disease progression or unacceptable toxicities. There is no evidence regarding the optimal duration of treatment with pembrolizumab; however, the KEYNOTE-024 protocol mandated a maximum of 35 cycles of pembrolizumab (2 years).

Pembrolizumab is currently used in England as an option for people with previously untreated advanced NSCLC with PD-L1 expression on ≥50% of tumour cells and no sensitizing EGFR mutation or ALK translocation. In line with the comparator assessed in KEYNOTE-024, SOC was considered as the comparator of relevance in the cost-effectiveness model. This was deemed to be a pragmatic approach that would allow comparisons of pembrolizumab with a variety of platinum-based chemotherapy options, most of them used in clinical practice in the UK. The clinical experts consulted during the original appraisal stated that the standard care treatments considered in KEYNOTE-024 were likely to be the same as those used in clinical practice in England.

- In the base case, distribution of SOC chemotherapies observed in KEYNOTE-024 was used to be consistent with the efficacy inputs of the model. The use of UK specific market share of SOC chemotherapies was tested in a scenario analysis.

- Pemetrexed-based combinations were shown to have a lower OS HR compared to, for example, vinorelbine-based combinations, which are also used in clinical practice in the UK. Therefore, we expect KEYNOTE-024 to provide more optimistic OS results for SOC than what would be expected for SOC in UK clinical practice, based on the proportions of patients receiving different combination chemotherapies.

Table 37. Distribution of patients according to platinum-based chemotherapy combinations in KEYNOTE-024 vs. market shares

	KEYNOTE-024 (base case)	UK market shares
Gemcitabine/carboplatin	13%	23%
Gemcitabine/cisplatin	7%	4%
Paclitaxel/carboplatin	11%	0%
Paclitaxel/cisplatin	0%	0%
Docetaxel/carboplatin	0%	2%
Docetaxel/cisplatin	0%	2%

	KEYNOTE-024 (base case)	UK market shares
Vinorelbine/carboplatin	0%	17%
Vinorelbine/cisplatin	0%	10%
Pemetrexed/carboplatin	44%	17%
Pemetrexed/cisplatin	24%	26%
% Total	100%	100%

Source: Ipsos 2017. Data on file. [57]

The dosing and administration frequencies for these comparators were applied in the model in line with their marketing authorisations and UK clinical practice.

The type of comparisons assessed in the cost-effectiveness model is presented in Table 38.

Table 38. Intervention and comparators according to the different types of analyses assessed in de novo cost-effectiveness model

Population	Intervention and comparators	Clinical evidence derived from:	OS for comparator arm			
	Pembrolizumab vs.		ITT unadjusted	Two-stage	RPSFT	IPCW
Main population	▪ SOC	KEYNOTE-024	✓	✓	✓	✓

ITT = intention to treat; SOC = standard of care

B.3.3 Clinical parameters and variables

Overall method of modelling OS and PFS

The primary data source for the economic model was the data derived from the KEYNOTE-024 clinical trial. Data from the July 2017 data cut has been used to update the clinical parameters of the cost-effectiveness model, including OS, PFS and safety. A similar approach to that of the original submission was followed for the extrapolation of the OS and PFS from KEYNOTE-024, to populate the area-under-the-curve (AUC) partitioned survival approach. For this, the guidance from the NICE DSU was followed to identify base case parametric survival models for OS and PFS.[58] In summary, the steps that were followed include:

1. Testing the proportional hazard (PH) assumption – To assess whether joint or separate statistical models were more appropriate for the pembrolizumab and SOC treatment arms with the new data cut:

    a. A statistical test of the PH assumption was performed

b. The cumulative hazard plot, the log cumulative hazard plot and the Schoenfeld residual plot were visually assessed to determine if the data from KEYNOTE-024 indicated proportional effects between pembrolizumab and SOC.

2. As for the original submission, a comprehensive range of pooled parametric survival models were explored. Data from both treatment arms were used within the same model, considering and comparing all the relevant standard parametric models (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma). Since there was evidence against the PH assumption, a pooled parametric model was deemed inappropriate.

3. Independent separate survival models were then explored. Models were separately fitted to each arm using data from the relevant treatment arm. Following the recommendation from the DSU, the same functional form was selected for the separate parametric models according to that fitting most closely the data overall.

4. Within the various parametric survival models explored, visual inspection was used to assess the fit of the curves to the observed clinical trial data. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to help identify the most plausible survival models.

5. Lastly, the choice of base case parametric models was validated in terms of clinical plausibility of both short-term and long-term extrapolations.

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

- For OS, KEYNOTE-024 KM data was used for the first 33 weeks, on the basis of the changes to cumulative hazards, and an exponential model was fitted afterwards following standard parametric approaches. Two additional cut-offs were assessed in sensitivity analyses (i.e. week 23 and week 43).
- For PFS, KEYNOTE-024 KM data was used during the first 27 weeks, to reflect the protocol driven fall in PFS observed alongside the initial radiologic assessments. This was followed by extrapolating using an exponential model. Other functional forms and two additional cut-offs were assessed in sensitivity analyses (i.e. week 9 and week 37).

As mentioned above (see section B.3.2, 'Model structure'), two alternative extrapolation scenarios were considered to project the SOC OS:

- The first one reflects the base case extrapolation in the original submission, i.e. it applies the 2-stage switching adjustment, which was recognized by the ERG and the committee to be the most appropriate method for the crossover adjustment during the original appraisal. [13] As mentioned above, the data base cut-off was week 33, after which there were still 33% remaining events in the SOC arm on which to base the parametric fitting (54% after week 23, and 17% after week 43).
- The second one reflects the current SOC, with pembrolizumab being one of the second line treatment options, after it was recommended by NICE (in January 2017) as an option for treating locally advanced or metastatic PD-L1-positive NSCLC in adults who have had at least one chemotherapy.[13] In this scenario, no crossover adjustments are accounted for in the SOC arm, reflecting the OS derived from patients initially treated with SOC who progress and then are treated with a anti-PD1 (as for NICE guidance), [1-3] based on the proportion of patients who received a PD1 after progression in KEYNOTE-024. This is the extrapolation used in the 'updated base case'.

Further details of the steps followed to select the relevant methods and data cuts for OS and PFS are presented in Appendix L, 'Modelling overall survival'.

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 appraisals. [59] [60]

- Febrile neutropaenia (with a 2% incidence in the SOC arm) is also included as clinicians have suggested that this AE has significant impact on quality of life and costs. The inclusion of febrile neutropaenia is also consistent with recent NICE appraisals.[38] [59]

The approach to identify the relevant AEs to be included in the economic model was validated in the original submission by clinical experts.

The incidence of AEs was taken from the KEYNOTE-024 trial for each treatment arm (see Table 39), and it was updated (compared to the original submission) to reflect the KEYNOTE-024 July 2017 data cut. 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 AEs occurring across treatment arms, and the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 39. This was consistent with the methods used in previous submissions[52 60] and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting.

Compared to the original submission, there were 4 additional types of AEs that met the above criteria to be accounted for in the cost-effectiveness model: [redacted]. Based on feedback provided by one of the clinical experts, [redacted] are the only of these AEs that would be treated, and the corresponding unit cost has been included in the CEM.

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. AE-related disutilities were considered as part of the base case since this was the preferred approach by the committee assessing the submission for pembrolizumab for the treatment of patients with advanced NSCLC and PD-L1 positive tumours who have been previously treated.[1]

Table 39. Grade 3+ AE rates for AEs included in the economic model based on KEYNOTE-024 data

Adverse Event	Rate for pembrolizumab (Grade 3+)	Rate for SOC (Grade 3+)
Nausea	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Diarrhoea (Grade 2+)	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Neutropaenia	[redacted]	[redacted]

Adverse Event	Rate for pembrolizumab (Grade 3+)	Rate for SOC (Grade 3+)
Oedema peripheral	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Leukopaenia	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Febrile neutropaenia	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Inputs from clinical experts

We were able to arrange meetings with two clinical oncologists working in lung cancer to discuss key issues. We validated the plausibility of the approach to modelling OS by asking the clinicians to review the projections and the 5 year, 10 and 20 year survival percentages from the extrapolation approach.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

HRQoL was evaluated in the KEYNOTE-024 trial using the EuroQoL EQ-5D-3L. All trial-based HRQoL analyses conducted for the purpose of the economic section were updated using the latest data cut from the 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.[53]

In KEYNOTE-024, the EQ-5D questionnaire was administered at treatment cycles 1, 2, 3, 6, 9 and 12 and every third cycle afterwards for as long as 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 and the SOC arms, to be consistent with the licenced indication and the treatment arms included for the estimation of PFS, OS and safety from KEYNOTE-024 included in the economic model (cut-off date: July 2017).

As for the original submission, when estimating utilities, two 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 patients with advanced NSCLC who had previously received platinum based chemotherapy[1] [61] or palliative radiotherapy[62] and in advanced melanoma patients.[63-65] Time to death has been demonstrated as more relevant than progression-based utilities since by considering more health states it offers a better HRQoL data fit.[63-65]

  Based on KEYNOTE-024 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.

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-024 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 overestimation of the utility in the post-progression state.

  Following this approach, the date of progression was determined from the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) using blinded independent central review (BICR).

  - 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.

For each of the utility approaches, mean EQ-5D utility scores by health status were estimated per treatment arm (pembrolizumab and SOC 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 40.

Table 40. Compliance of EQ-5D by visit and by treatment (FAS Population, TPS ≥ 1%)

Treatment Visit	Category	Pembrolizumab	SOC
		N = 152	N = 147
		n (%)	n (%)
Baseline	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 3	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 6	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 15	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 24	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 33	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 42	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 51	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 60	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 69	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 78	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 87	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]

Treatment Visit	Category	Pembrolizumab	SOC
		N = 152	N = 147
		n (%)	n (%)
	Compliance(completed per protocol)*	[redacted]	[redacted]
*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). Missing by design includes: death, discontinuation, translations not available, and no visit scheduled. (Database Cut-off Date: 10 Jul 2016).			

UK preference-based scores were used for all patients analysed from the KEYNOTE-024 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique.[66]

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. Based on this analysis, utilities were similar in pembrolizumab and SOC treatment groups at baseline.

The estimated utilities are presented in Table 41 and Table 42 below.

Table 41: EQ-5D health utility scores by time-to-death

Time to Overall Survival (days)	Pembrolizumab					SOC					Pembrolizumab and SOC Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
≥360*	[redacted]														
[180, 360)	[redacted]														
[30, 180)	[redacted]														
<30	[redacted]														

† n=Number of patient with non-missing EQ-5D score
‡ n=Number of records with non-missing EQ-5D score
*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 42: EQ-5D health utility scores by progression status

	Pembrolizumab					SOC					Pembrolizumab and SOC Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	[redacted]														
Progressive	[redacted]														

† 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

Mapping

Not applicable as HRQoL was derived from the KEYNOTE-024 EQ-5D data.

Utilities were evaluated using EQ-5D directly from patients from the KEYNOTE-024 trial, which is consistent with the NICE reference case.[53]

Health-related quality-of-life studies

In line with the NICE guide to the methods of technology appraisal, [53] a systematic review of the literature was conducted as part of the original submission to identify relevant studies reporting utility values. Since utility values were identified in the previous appraisal as one of the sources of uncertainty and a key driver of the cost-effectiveness results for pembrolizumab, the systematic review was updated to identify additional studies reporting utilities that may have been published since the time of the original submission. Full details of the search strategy and results can be found in Appendix H.

A total of 56 records (38 unique studies) were included in the SLR that reported health-state utility values for previously untreated patients with advanced NSCLC.

Table 43 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.

Table 43: 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	0.65-0.802	Chevalier et al. (2013); [67] Chouaid et al. (2012); [68]Lee et al.,(2014)*; [69] NICE[TA227], (2011) [70]; NICE[TA258], (2012) ; [71] NICE[TA310], (2014); [39] Wu et al.,(2011); [72] Zeng et al., (2014); [73]Zeng et al.,(2013) [74], Huang et al (2017) [75]
Progression-free (iv/oral)	-0.0425 (iv)/- 0.0139 (oral) from baseline 0.67	NICE[TA192], (2010); [76] Zeng et al., (2014) [73]
Treatment cycle	Cycle 3-4: 0.03 from baseline Cycle 0-2/ >6 : 0.4099 - 0.7758	Galetta et al. (2015); [77] Gridelli et al. (2012); [78]NICE[TA309] (2014) [79]
Progressed disease	0.31–0.69	Chevalier et al. (2013);[67] Chouaid et al. (2012);[68] Joerger et al., (2011);[80] Klein et al., (2009);[81] Lee et al., (2014)*;[69] Matter-Walstra et al., (2012);[82] NICE[TA181], (2009)*;[56]

Health state	Range of values	References
		NICE[TA192], (2010);[76] NICE[TA227], (2011);[70] NICE[TA310], (2014);[39] Schluckebier et al., (2015);[83] Ting et al., (2015);[84] NICE [ID835] ;[38] Zeng et al.,(2013); [74] Huang et al (2017); [75] Labbe et al (2017) [85]
Near death	0.18-0.35	Klein et al., (2009); [81] NICE[TA181], (2009)* [56]
Other utilities identified from the systematic review		
Time to death utilities	≥360 days: 0.805-0.904 180-360 days: 0.72-0.726 90-180 days: 0.627 30-180 days: 0.632 <30 days: 0.195-0.537	Huang et al (2017); [75] Huang et al (2017);[86] Chang et al (2016) [87]
Treatment arm	BEV-based therapy/ non BEV:0.68-0.66; AFA (change from baseline): -0.068/-0.083 ; Cis + PEM (change from baseline): -0.046/-0.062; ERL (pre/post progression):0.670,552; CRI: 0.81;CTX: 0.72; GEF:0.0528; PAX/CARB:0.0011 DOC: 0.5833; 0.6610; 0.4896 GEM: 0.6060; 0.6612; 0.4896 PAX: 0.5929; 0.6618; 0.4896 VNB: 0.5801; 0.6617; 0.4896 PEM:0.4896- 0.6614 GEF (EGFR+ ve): 0.6625; 0.6686; 0.489 PAX (EGFR+ ve): 0.5934; 0.6623; 0.4896 1L (specific treatment not identified): 0.65	Brown et al. (2013)*;[88] Chouaid et al. (2011);[89] Griebsch et al. (2014);[90] Khan et al. (2015); [91] Solomon et al. (2014);[92]Verduyn et al. (2012); [93] Lopes et al. (2012)*; [94] Djalalov et al. (2014)*; [95] NICE[TA190], (2010); [96] NICE[TA227] (2011);* [70] Taylor-Stokes 2017[97] [98]
Stable disease	0.49–0.84.	Joerger et al., (2011); [80] Klein et al., (2009); [81] Matter-Walstra et al., (2012); [82] Nafees et al. (2016); [99] NICE[TA181], (2009)*; [56] Ting et al.,(2015); [84] NICE[TA310] (2014) [39]
Stable on immunotherapy	0.80	Labbe et al (2017) [85]
Stable on other systemic treatments	0.64	Labbe et al (2017) [85]
Stable not on treatment	0.79	Labbe et al (2017) [85]
AEs	Rash:-0.0325 Neutropaenia:-0.46	Nafees et al. (2016); [99] NICE[TA181], (2009)*; [56] NICE[TA192] (2010); [76]
Placebo	Pre progression: 0.6438 Post progression: 0.5760	Khan et al. (2015) [91]
Site of metastasis/disease stage	Overall NSCLC 0.419-0.74, Stage IIIb 0.473-0.70, Stage IV 0.392-0.86.	Grutters et al. (2010); [100]Tongpak et al. (2012); [101] NICE[TA181], (2009)* [56]

Health state	Range of values	References
Key: AFA, afatinib; BEV, bevacizumab; CARB, carboplatin; CET, cetuximab; CIS, cisplatin; CRI, crizotinib; CTX, chemotherapy; DOC, docetaxel; ERL, erlotinib; GEF, gefitinib; GEM, gemcitabine; IV, intravenous; NSCLC, non-small cell lung cancer; PAX, paclitaxel; PEM, pemetrexed;		
*Utility values extracted in these studies were from economic modelling studies where it was reported as input utility values. In the economic modelling studies, this utility values were extracted from Nafees et al., 2008[102], which reported utility values for treatment in NSCLC patients		

Utilities based on time-to-death used in the base case of the cost-effectiveness model allow a better reflection of the HRQoL experienced by patients through time. A similar approach was presented in NICE TA309[79] where the manufacturer used utility values from the PARAMOUNT trial by treatment arm, progressed state and time to death. However, the values presented cannot be directly compared with the utility values from KEYNOTE-024 which do not incorporate the impact of progression on the time to death utilities. Additionally, specific utility values were used towards the end of a patient's life in the cost-effectiveness assessment of one of the included studies and a NICE submission.[56 81] However, it is unclear if these values were reflective of the HRQoL of the patients in a period of <30 days to death.

From the updated searches, two studies were included reporting time-to-death disutilities: two publications relating to quality of life data from KEYNOTE-024[75 86] and a study conducted in South Korea, with health state descriptions defined by experienced clinical oncologist and 205 participants from the general population completing the study. [87] Although these studies are not directly comparable due to differences in populations and methods used, the following can be observed:

- The sample of general public respondents from the Korean study estimated much lower utility values for patients with an expected survival of 30 days of less, compared to patients themselves in KEYNOTE-024 (0.195 versus 0.537, respectively).
- In both studies, the utility values for patients with advanced NSCLC during the period they are expected to survive for at least 360 days are between 0.805 and 0.904.

The above utility values for long-term survivors are also in line with the results of a real world study that evaluated EQ-5D-3L health utility scores from 474 outpatients with metastatic lung cancer across various disease states. As mentioned in this study, a mean HUS of 0.76 for patients with stage IV disease, and 0.79 while on chemotherapy, have been reported prior to widespread use of targeted therapies. The introduction of targeted therapies has improved patients' quality of life. In this longitudinal cohort study, patients with wild type metastatic NSCLC who were stable while receiving immunotherapy (14 patients in total) were reported

to have a utility equal to 0.80. Although it is unclear whether all patients had stage IV NSCLC, and the sample from which these utilities was small, the utility value reported for this patient group is in line with that of long-term survivors (i.e. during the period of survival of at least 360 days), as reported by patients assessed in KEYNOTE-024. This is unsurprising, since patients receiving immunotherapy not only experience improved survival but also no or milder side effects compared to those receiving chemotherapy.

A Canadian national survey conducted by the charity Lung Cancer Canada (LCC), which aimed to understand the wider impact of immunotherapy on patients' QoL, concluded that pembrolizumab allowed respondents to have a high quality of life in comparison to other available treatments such as chemotherapy. The survey included 23 patients and 14 caregivers who had experience with pembrolizumab. The majority of respondents interviewed reported no side effects to mild side effects during the period treated with pembrolizumab. Most respondents found that management of adverse events was tolerable and did not interfere with their day-to-day life. [103] The work conducted by the LCC further supports the utility values collected in KEYNOTE-024 trial.

A recent appraisal of pembrolizumab in 1L NSCLC by the Canadian Agency For Drugs and Technologies in Health (CADTH), [103] the utility values collected in the KEYNOTE-024 trial were considered appropriate for decision making. Guidance from CADTH's clinical panel confirmed that in clinical practice immunotherapy agents are better tolerated than chemotherapy, additionally supported by the information provided by patient groups such as LCC mentioned above.

Overall, the pre- and post- progression utility values from the KEYNOTE-024 trial are in line with the utilities observed in the published literature, as the pre-progression EQ-5D values were higher than the post-progression values, suggesting a worsening of HRQoL after disease progression.[67-69 79 91]

The majority of the economic evaluation studies[56 69-71 74 76 83 88 94 95] included in the systematic review calculated utility values using an algorithm by Nafees et al. (2008)[102] which is based on members of the public eliciting societal values on utilities for lung cancer patients using VAS and SG techniques. However, cancer patients have been reported to value health states higher than the general population.[104-106] 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 regularly experienced ill health may perceive their improved health

state, or a better hypothetical health state, of greater value. Additionally and importantly, the NICE reference case stipulates the use of utility values directly derived from the patients.

In the majority of these studies, EQ-5D health state descriptions were not used, and full details of the elicitation and valuation methods were not reported. As such, none of the included utility studies were deemed to be consistent with the NICE reference case for consideration for use within the health economic model. Further details of these studies are presented in Appendix H.

Adverse reactions

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. EQ-5D data from the latest data cut (July 2017) was used. The utility values for patients experiencing grade 3-5 AEs were lower [redacted] than those of patients not experiencing grade 3-5 AEs [redacted] see Table 44). Additionally, patients who were progression-free and had experienced grade 3-5 AEs, reported a higher utility while treated with pembrolizumab compared those treated with SOC [redacted] Similarly, patients who were progression-free and had not experienced grade 3-5 AEs reported higher utility values when treated with pembrolizumab compared to SOC [redacted].

In the base case, the average disutility per patient experiencing grade 3-5 AEs was [redacted] for patients treated with pembrolizumab and [redacted] for those treated with SOC.

It has been assumed for the purposes of the modelling that any impact of AEs on HRQoL is expressed in terms of a disutility of AEs applied based on AE incidence rates and the corresponding mean duration across them (i.e. [redacted] of duration across grade 3+ AEs, as estimated from KEYNOTE-024).

Table 44: Utility values for individuals with and without Grade 3+ AEs in the KN024 clinical trial

	Pembrolizumab					SOC					Pembrolizumab and SOC Pooled				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression -Free with Grade3+ AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression -Free w/o Grade3+ AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health-related quality-of-life data used in the cost-effectiveness analysis

HRQoL in the base case scenario is based upon time to death as the utility values derived from the KEYNOTE-024 trial were more sensitive than the pre-and post- progression utility values. EQ-5D analyses based on KEYNOTE-024 data showed that patients who had progressive disease experienced a lower HRQoL than those in the pre-progression health state. However, due to high level of crossover from the SOC arm to the pembrolizumab arm and due to the limitations with the data collected post-progression, progression related utilities do not show a large difference between pre and post-progression utilities, indicating that progression status 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. Therefore, to capture HRQoL more appropriately, the time-to-death utility values were further divided according to four categories (i.e. 360 or more days to death, 180 to 360 days to death, 30 to 180 days to death or under 30 days to death).

In the cost-effectiveness model, a constant value for HRQoL is applied in each cycle taking into account either time to death or progression-based health states. An age-related utility decrement of 0.0045 was applied per year, from the age of 65 until 75, to reflect the natural decrease in utility associated with increasing age.[107]

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.[107], 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 for 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.

No health effects on patients were excluded from the cost effectiveness analysis. However, the impact of pembrolizumab vs. SOC on carers has not been included in the cost-effectiveness assessment due to the unavailability of data to incorporate this into the model.[54]

The utility values chosen for the cost-effectiveness model are presented in Table 45.

Table 45: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
≥360*	[redacted]	[redacted]	Section B.3.4: Health-related quality-of-life data from clinical trials (page 83-88)	Utility values from KEYNOTE-024 (Data cut: July 2017), in line with NICE reference case
[180, 360)	[redacted]	[redacted]		
[30, 180)	[redacted]	[redacted]		
<30	[redacted]	[redacted]		
Disutility per patient experiencing grade 3-5 AEs	[redacted]	[redacted]	Section B.3.4: Adverse reactions (page 92)	
** This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days.* *** Utilities from KEYNOTE-024 are pooled utilities*				

A clinical expert assessed the applicability of the health state utility values estimated from KEYNOTE-024 and these were thought to be reasonable.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Details of the systematic review conducted as part of the original appraisal for the identification of relevant cost and health care resource use data to populate the model can be found in Appendix I. The parameters used to estimate cost effectiveness has been presented as part of Appendix L.

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)[108] published on 4 May 2016 which provides information about prices for generic drugs based on the average price paid by the NHS over the last four months. If comparators' drug costs were not available from eMIT, the costs from the Monthly Index of Medical Specialties (MIMS)[109] were used.

Pembrolizumab

As per the anticipated licence, the model uses a 200mg fixed dose of pembrolizumab, administered as a 30 minute IV infusion every three weeks (Q3W) (see the Summary of Product Characteristics [SmPC] in Appendix C). The list price of a 100mg vial is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260 based on two 100mg vials using the list price. [redacted]

Comparators

Drug acquisition costs for individual drugs included in the platinum-based combination therapies were taken from eMit[108] apart from pemetrexed, for which the corresponding drug costs are only available from MIMS.[109] When multiple vial/package sizes were available, the cheapest price per mg was applied as a conservative assumption. The costs of concomitant medications for patients receiving doublet chemotherapy (e.g. steroids, paracetamol etc.) were not taken into consideration as the costs are trivial and unlikely to affect the results.

Dosing for the individual drugs was based on the KEYNOTE-024 protocol,[17] whenever available. Dosing for the remaining drugs not included in KEYNOTE-024 was based on SmPC or Brown et al (2013).[88 110 111] Drug costs per administration were calculated based on the body surface area (BSA), which was assumed to be 1.83m^2 based on a weighted average BSA from the male and female patients recruited at European sites in KEYNOTE-024 (see

Table **46**). As a conservative assumption, full vial sharing (i.e., no wastage) is assumed for the administration of all comparator drugs. The drug costs of the platinum-based combination therapies were assumed to be equal to the sum of individual drug's costs included in a combination therapy (e.g., the drug costs for the combination pemetrexed/cisplatin therapy per administration is the sum of drug costs for pemetrexed per administration plus the drug costs for cisplatin per administration).

Table 46: Baseline body surface area (BSA) of patients recruited at European sites in KEYNOTE-024

	Mean BSA in m^2	% of patients
Female	1.68	35.4% (N=56)
Male	1.91	64.6% (N=102)
Total	1.83	100% (N=158)

Table 47: Dosing, frequency of infusion and unit costs per administration for comparator drugs

Drug	Dosing per administration	Frequency of administration	Total dose	Cost per mg	Cost per administration (assuming no wastage)	Reference for dosing	Reference for drug costs
Docetaxel	75mg/m^2	Q3W	135mg	£0.13	£17.14	SmPC[110]	eMit[108]
Gemcitabine	1250mg/m^2	Q3W	2250mg	£0.01	£21.65	KEYNOTE-024[41]	eMit[108]
Paclitaxel	200mg/m^2	Q3W	360mg	£0.07	£25.78	KEYNOTE-024[41]	eMit[108]
Vinorelbine	27.5mg/m^2	Q1W	49.5mg	£0.36	£53.48	SmPC[111]	eMit[108]
Carboplatin	400mg/m^2	Q3W	720mg	£0.04	£30.30	Brown 2013[88]	eMit[108]
Cisplatin	75mg/m^2	Q3W	135mg	£0.11	£14.26	KEYNOTE-024[41]	eMit[108]
Pemetrexed	500mg/m^2	Q3W	915mg	£1.60	£1,464.00	KEYNOTE-024[41]	MIMS[109]

* Q1W, every week; Q3W, every three weeks

The drug costs of the overall platinum-based therapy used in the economic model (i.e., all platinum-based therapy, pemetrexed-containing platinum-based therapy and non-pemetrexed-containing platinum-based therapy) are the weighted sum of the drug costs of the individual combination treatments where weights were based on the KEYNOTE-024 in the base case and UK market shares (excluding vinorelbine + platinum and docetaxel + platinum treatments which were not included in KEYNOTE-024) in the scenario analysis (Table 48). This approach reflected the recommendation of the health economic experts consulted for the validation of the de novo cost-effectiveness model, Table 49 summarises the drug costs per administration for the comparators used in the economic model.

Table 48: Distribution of the use of platinum-based chemotherapies

	KYENOTE-024 (base case)			UK market share		
	All	Squamous	Non-squamous	All	Squamous	Non-squamous
Gem + Car	13.3%	55.6%	4.1%	23.4%	52.5%	0.0%
Gem + Cis	7.3%	25.9%	3.3%	3.8%	8.5%	0.0%
Pac + Car	11.3%	18.5%	9.8%	0.0%	0.0%	0.0%
Pac + Cis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Doc + Car	0.0%	0.0%	0.0%	1.8%	0.0%	3.3%
Doc + Cis	0.0%	0.0%	0.0%	1.8%	0.0%	3.3%
Vin + Car	0.0%	0.0%	0.0%	16.6%	37.3%	0.0%
Vin + Cis	0.0%	0.0%	0.0%	9.8%	1.7%	16.3%
Pemx + Cis	44.0%	0.0%	53.7%	16.9%	0.0%	30.4%
Pemx + Car	24.0%	0.0%	29.3%	25.9%	0.0%	46.7%
Total %	100%	100%	100%	100%	100%	100%

* Gem, gemcitabine; Car, carboplatin; Cis, cisplatin; Pac, paclitaxel; Doc, docetaxel; Vin, vinorelbine; Pem, pemetrexed

Table 49: Summary of the drug costs per administration for the comparator used in the base case

	Overall population
SOC: Overall platinum-based chemotherapy	[redacted]

Number of administrations required, unit costs and total drug costs per treatment per cycle

As per the licence, patients treated with pembrolizumab are to be treated until disease progression is confirmed. To estimate the duration of treatment in the pembrolizumab and comparator arms, time on treatment (TOT) data from the KEYNOTE-024 July 2017 data-cut was used, to reflect both early discontinuation caused by AEs and other reasons for discontinuations before progression in addition to the additional weeks of treatment that some

patients may receive until confirmation of progression. See Appendix I for further details regarding the use of TOT data in the model.

In the base case model, a maximum treatment duration of 2 years was assumed for pembrolizumab, in line with the KEYNOTE-024 protocol[17] and the current recommendations for the use of pembrolizumab for the treatment of patients with advanced NSCLC.[1 13] A maximum treatment duration of 18 weeks (i.e., 6 cycles for the platinum-based therapies administrated every 3 weeks) was used for the comparator platinum-based therapies to reflect the protocol of KEYNOTE-024[17] and clinical practice in England. The average number of cycles received per patient in KEYNOTE-024 was [redacted] for all platinum-based chemotherapy. Following clinical practice in England for first line therapy, non-squamous patients who remain progression-free will be eligible for pemetrexed maintenance therapy until disease progression or unacceptable toxicity.[42]

For patients on treatment, adjustments were made based on the actual proportion of patients receiving the planned dose within KEYNOTE-024. For this, data regarding dose interruption occurring within KEYNOTE-024 was analysed and incorporated into the model per administered cycle of pembrolizumab and comparators. These analyses showed that, on average, [redacted] of patients on pembrolizumab and [redacted] of patients on overall platinum-based chemotherapy received their planned doses.

Administration costs

Pembrolizumab

Given the time required for the administration of pembrolizumab is 30 minutes, the Healthcare Resource Groups (HRG) code for 'simple parenteral chemotherapy – outpatient' SB12Z based on the latest NHS reference costs 2015-2016 was used to reflect administration costs for pembrolizumab. The assumption had been previously agreed with NHS England (personal communication, 9th December 2014) for the NICE STA submission of pembrolizumab for advanced melanoma.[112]

Platinum-based combination therapy

The administration costs required for platinum-based therapies were based on previous NICE submissions for first line treatments for NSCLC.[40 56 76] The administration costs were not identified for paclitaxel + cisplatin, docetaxel + carboplatin and vinorelbine + carboplatin. It

was assumed the administration cost for paclitaxel + cisplatin is the same as docetaxel + cisplatin pemetrexed + cisplatin; the cost for docetaxel + carboplatin is the same as the paclitaxel + carboplatin or pemetrexed + carboplatin. The administration cost for vinorelbine + carboplatin is based on the cost for vinorelbine + cisplatin but replace SB14Z (day case and regular day/night) with SB14Z (outpatient) to reflect the administration cost difference between carboplatin and cisplatin. The unit cost per cycle of chemotherapy administrated was taken from the National Reference Costs 2015/16.[113] Table 50 summarises the administration costs used in the cost-effectiveness model.

Table 50. Administration costs of pembrolizumab and platinum-based chemotherapy

	Assumptions	Unit costs	Reference
Pembrolizumab	1 x SB12Z (outpatient)	£253.00	ID840[59]
Gemcitabine + carboplatin	1 x SB14Z (outpatient) 1 x SB15Z (outpatient)	£516.00	TA181[56]
Gemcitabine + cisplatin	1 x SB14Z (Day case and regular day/night) 1 x SB15Z (outpatient)	£619.00	TA181[56]
Paclitaxel + carboplatin	1 x SB14Z (outpatient)	£304.00	TA192[76]
Paclitaxel + cisplatin	1 x SB14Z (Day case and regular day/night)	£407.00	Assumption
Docetaxel + carboplatin	1 x SB14Z (outpatient)	£304.00	Assumption
Docetaxel + cisplatin	1 x SB14Z (Day case and regular day/night)	£407.00	TA181[56]
Vinorelbine + carboplatin	1 x SB14Z (Outpatient) 1 x SB15Z (Day case and regular day/night)	£665.00	Assumption
Vinorelbine + cisplatin	1 x SB14Z (Day case and regular day/night) 1 x SB15Z (Day case and regular day/night)	£768.00	TA192[76]
Pemetrexed + carboplatin	1 x SB14Z (outpatient)	£304.00	TA406[40]
Pemetrexed + cisplatin	1 x SB14Z (Day case and regular day/night)	£407.00	TA181[56]

Similar to the drug costs for the comparators, the administration costs of the overall platinum-based therapy used in the economic model are the weighted sum of the administration costs of the individual combination treatments, where weights were based on KEYNOTE-024 in the base case and UK market share in the scenario analysis. Table 51 summarises the drug administration costs for the comparators used in the economic model.

Table 51. Summary of the drug administration costs for the comparator used in the base case

	All
SOC: Overall platinum-based chemotherapy	£380.09

Costs associated with PD-L1 testing

Pembrolizumab is licensed for the first line treatment of advanced NSCLC in adults whose tumours express PD-L1 (TPS ≥ 50%), as assessed by a validated test.

Based on the information and calculations presented as part of the Budget Impact Evidence Submission, we estimate that 11.7% of patients with NSCLC stage IV will be eligible for treatment with pembrolizumab in England. This means that to identify one patient with NSCLC stage IV eligible for treatment with pembrolizumab, 9.57 total patients will need to be tested for PD-L1 expression.

A single PD-L1 test will cost £40.50 per patient tested, which equates to a cost of £347.14 per patient with NSCLC whose tumour is >50% PD-L1 expressing and therefore eligible for treatment with pembrolizumab in the first line therapy (see Table 52). This cost was applied only to the pembrolizumab arm of the model. The PD-L1 test is currently fully reimbursed within NHS England.[114]

Table 52: Cost of PD-L1 testing per patient eligible for treatment with pembrolizumab

% of people eligible for treatment with pembrolizumab among patients with NSCLC stage IV	11.7%
PD-L1 test cost	£40.5[114]
Total PD-L1 costs	£347.14

Costs associated with pemetrexed maintenance therapy

A proportion of patients in the SOC arm receive pemetrexed maintenance therapy based on KEYNOTE-024 trial protocol and NICE guidance[42] following the first line active chemotherapy treatment. The proportion of patients receiving pemetrexed maintenance therapy is based on the data from the KEYNOTE-024 in the base case model. In a scenario analysis, it was assumed that 58.4% of progression free patients in the SOC arm receive pemetrexed maintenance therapy based on the pemetrexed maintenance NICE submission.[42]

The drug cost for pemetrexed maintenance therapy is shown in Table 49 and the administration cost was assumed to be based on a day case of simple chemotherapy (SB12Z) which is the same as pembrolizumab administration cost. Additionally, it was assumed an additional CT scan every 12 weeks is required for patients while on pemetrexed maintenance treatment based on an assumption made by the manufacturer in the TA402 submission.[42]

Health-state unit costs and resource use

The main source of resource utilisation per health state used in this submission was the Brown et al study, which compares regimens currently approved by NICE and licensed across Europe for the systemic treatment of patients with advanced NSCLC.[88] From the studies evaluated within the systematic review, MSD concludes that this study provides the most balanced and appropriate evaluation of cost and resource use given its relevance to the UK setting, recent publication and broad inclusion of treatment strategies in advanced NSCLC.

Monitoring and disease management costs

There are three health states included in the model - Progression free (PFS), 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 53 shows the resource use for monitoring and disease management in the progression-free and progressed health state. Based on the assumption used in the Brown et al study,[88] PFS costs were applied during first-line chemotherapy and while on active therapy during second-line; and PD costs were only applied when no active treatment is received. Therefore, the PFS costs in the Brown et al study were applied to the entire duration of the PF health state and the active subsequent treatment period for the PD health state in this analysis; and the post-progression state (PPS) costs in the Brown et al study were applied to the no active subsequent treatment period of the PD health state in this analysis.

Table 54 presents the unit costs for individual resource use items, which were updated based on the NHS reference costs 2015-2016 and the Personal and Personal and Social Services Research Unit (PSSRU) 2016 report.[113 115] The estimated per week monitoring and disease management costs were £76.75 and £125.87 respectively for the PFS and PPS periods.

Table 53: Resource use frequency for progression-free and progressed health states (based on Brown et al study[88])

Resource	PFS	PPS	Unit	Source quoted in Brown 2013
Outpatient visit	9.61	7.91	per annum	Big Lung Trial[116]
Chest radiography	6.79	6.5	per annum	Big Lung Trial[116]
CT scan (chest)	0.62	0.24	per annum	Big Lung Trial[116]
CT scan (other)	0.36	0.42	per annum	Big Lung Trial[116]
ECG	1.04	0.88	per annum	Big Lung Trial[116]
Community nurse visit	8.7	8.7	visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG81,[117] Marie Curie report[118]
Clinical nurse specialist	12	12	hours contact time per patient	Appendix 1 of NICE Guideline CG81[117]
GP surgery	12	0	consultations per patient	Appendix 1 of NICE Guideline CG81[117]
GP home visit	0	26.09	per annum (fortnightly)	Marie Curie report[118]
Therapist visit	0	26.09	per annum (fortnightly)	Appendix 1 of NICE Guideline CG81[117]

* PFS, progression free state; PPS, post-progression state; GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NICE, The National Institute for Health and Care Excellence

Table 54. Unit costs of disease monitoring and supportive care

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£168.00	per visit	NHS Reference Costs 2015–2016, Consultant Led, Non-Admitted Face to Face Attendance, First, 800 clinical oncology[113]
Chest radiography	£26.74	per case	NICE technology appraisal TA199; TAG report, p.328 (£24.04 in 2009)[119]
CT scan (chest)	£115.00	per case	NHS Reference Costs 2015–2016, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)[113]
CT scan (other)	£121.00	per case	NHS Reference Costs 2015–2016, Diagnostic Imaging, Outpatient, HRG code RD26Z (three areas with contrast)[113]
ECG	£226.00	per case	NHS Reference Costs 2015–2016, 800 Clinical Oncology, Outpatient, HRG code EY51Z[113]
Community nurse visit	£61.00	per hour	PSSRU 2016, p.142: Cost per hour of patient-related work Band 8a[115]
Clinical nurse specialist	£73.00	per contact hour	PSSRU 2016, p.142: Cost per contact hour Band 8b[115]
GP surgery visit	£45.63	per visit	PSSRU 2016, p.145: Cost per patient contact lasting 11.7 minutes, including direct care staff costs (including qualifications)[115]
GP home visit	£91.26	per visit	PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel[115]
Therapist visit	£44.00	per hour	PSSRU 2016, p.159: Cost per hour for community occupational therapist (including training)[115]

* GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups; TAG, Technology Assessment Group

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 also based on the values used in the Brown et al study for consistency.[88] The estimated one-off terminal costs were £4,512.04 and are assumed to be the same for all treatment arms (see Table 55).

Table 55: Unit costs of terminal care patients (based on Brown et al study[88])

Resource	Unit cost	Number of consumption	% of patients in each care setting	Assumptions / Reference
Community nurse visit	£61.00 per hour	28.00 hours	27%	PSSRU 2015, p.169: Cost per hour of patient-related work (including qualifications)[115]
GP Home visit	£91.26 per visit	7.00 visits	27%	PSSRU 2015, p.177-178: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel[115]
Macmillan nurse	£48.69 per hour	50.00 hours	27%	Assumed to be 66.7% of community nurse cost[88]
Drugs and equipment	£553 per patient	Average drug and equipment usage	27%	The value used in Brown et al' s study (2013, Marie Curie report figure of £240 increased for inflation) was inflated to 2015/16 using the PSSRU HCHS index[88 115]
Terminal care in hospital	£3,853.19 per episode	1 episode (9.66 days)	56%	NHS Reference Costs 2015–2016, Non-Elective Long Stay and Non-Elective Excess Bed Days, Weighted sum of HRG code DZ17L (Respiratory Neoplasms with Multiple Interventions, with CC Score 10+), DZ19P (Respiratory Neoplasms with Single Intervention, with CC Score 10+) and DZ17T (Respiratory Neoplasms without Interventions, with CC Score 8-12) by activity[113] Assumed that unit cost is = £3,606.87 + 0.92 excess days at £267.74 per day[88]
Terminal care in hospice	£4,816.48 per episode	1 episode (9.66 days)	17%	Assumed 25% increase on hospital inpatient care[88]
Total cost	£4,512.04 (one-off cost)			

* GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HCHS, Hospital and Community Health Service; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups

Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section B.3.3.

The unit costs related to the management of AEs were mainly derived from the Brown et al study and from the previous NICE STA submissions.[38 51 88 120)60 76] When unit costs were not available or the management costs were trivial, zero cost was applied. All unit costs were inflated to 2015/16 prices using the hospital and community health services (HCHS) index published by PSSRU for 2015.[115] Table 56 below presents the unit costs per AE for which costing was applied in the cost-effectiveness model.

Table 56: Unit cost per AE used in the de novo model

Adverse Event	Unit costs	Reference
Nausea	£980.87	Brown 2013 (inflated to 2015/16 using PSSRU inflation indices)[88 115]
Anaemia	£2,645.40	NICE TA428[1]
Fatigue	£2,805.19	Brown 2013 (inflated to 2015/16 using PSSRU inflation indices)[88 115]
Diarrhoea (grade 2)	£0.00	NICE TA428[1]
Diarrhoea (grade 3-4)	£0.00	Brown 2013 (inflated to 2015/16 using PSSRU inflation indices)[88 115]
Dyspnoea	£448.65	NICE TA403[120]
Vomiting	£980.87	NICE TA192 (inflated to 2015/16 using PSSRU inflation indices)[76 115]
Neutropaenia	£578.66	Brown 2013 (inflated to 2015/16 using PSSRU inflation indices)[88 115]
Alanine aminotransferase increased	£774.89	TA347 (inflated to 2015/16 using PSSRU inflation indices)[60 115]
Rash	£0.00	Brown (inflated to 2015/16 using PSSRU inflation indices)[88 115]
Asthenia	£0.00	Brown (inflated to 2015/16 using PSSRU inflation indices)[88 115]
Thrombocytopaenia	£118.87	NICE ID865[40]
Neutrophil count decreased	£0.00	NICE TA428[1]
Aspartate aminotransferase increased	£0.00	NICE TA347 (inflated to 2015/16 using PSSRU inflation indices)[60 115]
Pneumonia	£606.82	NICE ID835[38]
White blood cell count decreased	£0.00	NICE TA428[1]
Urinary tract infection	£124.98	NICE TA347 (inflated to 2015/16 using PSSRU inflation indices)[60 115]
Neuropathy peripheral	£2,805.19	NICE TA162[119]
Pneumonitis	£0.00	Assumed to be same as pneumonia
Febrile neutropaenia	£0.00	Brown 2013 (inflated to 2015/16 using PSSRU inflation indices)[88 115]

Adverse Event	Unit costs	Reference
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

* GP, Personal Social Services Research Unit; WBC, white blood cell.

Miscellaneous unit costs and resource use

Costs associated with subsequent therapies received by patients after treatment discontinuation

Given the advanced nature of the disease and the lack of data on multiple lines of therapy beyond the second line of treatment, only one line of subsequent therapy is modelled.

Based on UK clinical practice and NICE guidance,[40 49] it was assumed all patients in the pembrolizumab arm receive docetaxel as second line treatment.

For patients in the SOC arm, two main scenarios are presented for consistency between crossover adjustment and subsequent treatment costs (as mentioned under 'Model structure', section B.3.2):

- In the scenario identified as ***'base case reflecting the original submission'***, crossover adjustments were accounted for to reflect the base case analysis presented in the original submission. Under this scenario, all patients in the SOC arm were assumed to receive docetaxel as the only second line treatment.
- In the scenario identified as the ***'updated base case'***, no crossover adjustments are considered, and patients in the SOC arm who progress are assumed to receive pembrolizumab based on the proportion of patients who received a PD1 after progression in KEYNOTE-024 ([redacted]), with the rest of the patients assumed to receive docetaxel. The duration of the second line treatment for docetaxel is assumed to be 3 cycles (i.e., 9 weeks)[40] and 9.7 cycles (i.e., 29.1 weeks) for pembrolizumab based on data observed in KEYNOTE-024 from the July 2017 data cut.

Table 57 presents the distribution of subsequent therapies for the pembrolizumab and SOC arms.

Table 57. Type and distribution of second line subsequent chemotherapies used in the economic model

Treatment	Pembrolizumab arm	SOC arm (with crossover adjustment)	SOC arm (with no crossover adjustment)
Docetaxel	100%	100%	[redacted]
Pembrolizumab	0%	0%	[redacted]

Key: SOC, standard of care.
*Based on calculation (100%-64.4%).

The average one-off cost of subsequent treatment for each arm was calculated by weighting the proportions of patients receiving each subsequent treatment (docetaxel or pembrolizumab) and the unit cost of each subsequent treatment (including drug cost and administration cost as described above), assuming the average duration of treatment for docetaxel and pembrolizumab as reported above. For simplification purposes, we have assumed that, after progression, SOC patients receiving an anti-PD1 in second line would receive pembrolizumab, since there is a confidential CAA available for nivolumab in second line that did not have allow us to estimate accurately the cost of subsequent therapies otherwise. For docetaxel, the administration cost was assumed to be the same as the administration cost for pembrolizumab. This weighted one-off cost was applied to patients who moved to the post-progression health state only.

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A table summarising the full list of variables applied in the economic model is presented in Appendix L.

Assumptions

Table 58 below presents a summary of the clinical inputs and data sources used in the economic model, and Table 59 summarises the assumptions used in the economic model.The base-case cost-effectiveness analyses reflects the NICE reference case as closely as possible.

As previously mentioned, two base case scenarios are presented:

- The ***'base case reflecting the original submission'***, where crossover adjustments were accounted for to reflect the base case analysis presented in the original submission.
- The ***'updated base case'***, where no crossover adjustments are considered, and patients in the SOC arm who progress are assumed to receive pembrolizumab based on the proportion of patients who received a PD1 after progression in KEYNOTE-024, with the rest of the patients assumed to receive docetaxel.

Table 58. Summary of clinical inputs and data sources used in the economic model

Clinical evidence and source	Brief description	Use in the model

KEYNOTE-024[41]	Multicentre open-label, randomised, phase 3 trial of pembrolizumab 200 mg Q3W (n=154) versus SOC (n=151) in adults with untreated, advanced NSCLC whose tumours express PD-L1 in at least 50% of their tumour cells.
	Data cut: 10th July 2017
		• Used to derive the baseline patient characteristics (including average age, the proportion of males and weighted average BSA).
		• Patient level data were used to fit OS and PFS parametric curves for both pembrolizumab and SOC arms.
		• Two base case presented:
		  ○ Patient level data from the SOC arm was used to perform crossover adjustments for the SOC OS as part of the base case that reflects the original submission (for transparency purposes).
		  ○ Patient level data from the SOC arm was not used to perform crossover adjustments for the SOC OS as part of the base case that reflects current clinical practice (since pembrolizumab has become SOC second line among patients who express PDL1 (TPS ≥ 1%, including strong expressers, i.e. TPS ≥ 50%).
		• OS KM data until week 33 was 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 27 weeks before parametric curves were applied.
		• Patient level data was used to calculate the proportions of patients actually receiving the planned doses for both pembrolizumab and SOC.
		• EQ-5D data collected in the trial were used to derive health state utility values (time-to-death utility values) used in the model.
		• ToT KM data up to 2 years was used to estimate treatment duration in the pembrolizumab arm, while parametric fitting was used to estimate ToT in the SOC arm
		• Used to derive the incidence of grade 3+ AEs and grade 2 diarrhoea and febrile neutropaenia (all grades) for both pembrolizumab and SOC.
		• Used to derive the proportion of patients receiving subsequent treatments for both pembrolizumab and SOC.

General population mortality[121]	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; 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 59: List of assumptions used in the economic model

Area	Assumption	Justification
Treatment pathway	Once patients progress they receive subsequent therapies as experienced by patients in KEYNOTE-024.	The use of subsequent treatments as observed in KEYNOTE-024 trial is consistent with the OS efficacy inputs used in the model, which are based on patients receiving these subsequent treatments. Depending on the base case scenario considered, patients in the SOC arm are either: ▪ Assumed not to receive pembrolizumab, and then a crossover adjustment is applied in the cost-effectiveness model (i.e. 'base case reflecting the original submission', since their OS efficacy estimates were originally adjusted to control for the impact of crossing over to pembrolizumab). ▪ Assumed to receive pembrolizumab, and therefore no crossover adjustment is applied in the cost-effectiveness model to reflect current clinical practice (i.e. 'updated base case'). Alternative approach was used as part of sensitivity analyses to reflect more closely the costing related to SOC therapies as administered in clinical practice in the UK.
Time horizon	20 years	The average age of patients in the model is 65. 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 SOC as assessed in this submission. This duration is in line with previous NICE appraisals.[38 42 45 46 51]
Efficacy	Use unadjusted KM data for the first 33 weeks from KEYNOTE-024 trial to model OS for pembrolizumab and SOC	The 2-phase piecewise method (KM plus exponential) has been suggested as the most appropriate approach by ERGs in recent NICE STAs (TA347,[44] TA428,[1] TA447,[13] ID811)[2] or has been used by an assessment group for a recent NICE MTA (TA374). [122] For the first 33 weeks OS KM data provides the more robust and reliable estimate and at that point patient numbers are sufficient to apply parametric fitting based on KEYNOTE-024 data. The fully fitted standard parametric curves do not provide good visual fit compared to the 2-phase piecewise method. The cumulative hazard plot also suggests that a piecewise model is preferred.

Area	Assumption	Justification
HRQoL	The quality of life of patients is appropriately captured by considering time to death utilities	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 disutility associated to o the terminal stage. Since there were limitations to using a combined approach (including both progression-based and time to death utilities), and given the limitations of the progression-based approach to reflect appropriately utilities post-progression, a time to death approach was considered in the base case. In sensitivity analyses, the impact of considering an alternative approach (i.e. progression-based only) was considered.
Safety	The incidence of AEs from KEYNOTE-024 trial was assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-024 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).[44 46]
Costs	PD-L1 test cost is based on 11.7% of patients with NSCLC stage IV being eligible for treatment with pembrolizumab in England, i.e., 8.6 tests are required to identify 1 patient who is eligible to be treated with pembrolizumab in first line.	Testing for PD-L1 status has become standard practice, [redacted] Based on the information and calculations presented as part of the budget impact evidence submission, we estimate that 11.7% of patients with NSCLC stage IV will be eligible for treatment with pembrolizumab in England. This means that to identify one patient with NSCLC stage IV that is eligible for treatment with pembrolizumab in first line, 8.6 patients will need to be tested for PD-L1 expression.

B.3.7 Base-case results

The results of the economic model are presented in Table 60 below.

- In the base case reflecting the original submission, the estimated mean overall survival was 3.08 years with pembrolizumab and 1.46 years with SOC. At the end of the 20-year time horizon there were 0.44% patients still alive in the pembrolizumab cohort and 0% in the SOC cohort. Patients treated with pembrolizumab accrued 2.31 QALYs compared to 1.04 among patients in the SOC cohort.
- In the updated base case, for the SOC arm the estimated mean overall survival was 1.86 years, and 0.01% patients were estimated to be still alive at the end of the 20-year time horizon. Patients treated with SOC accrued 1.35 QALYs.

Base-case incremental cost-effectiveness analysis results

Table 60 below presents the base case incremental cost-effectiveness results for both base cases (i.e. base case reflecting the original submission versus updated base case), incorporating the proposed discount. Since there is currently a confidential (and therefore, unknown) commercial access agreement (CAA) for the administration of pemetrexed as maintenance therapy,[42] in the base case we have assumed a 50% simple discount. Additionally, we have presented in Table 61 below the ICERs for comparisons of pembrolizumab and SOC considering a range of possible CAA-equivalent simple discounts for pemetrexed administered as maintenance therapy.

The results show pembrolizumab to be cost-effective compared to SOC when considering a willingness to pay threshold of £50,000 per QALY. The corresponding incremental-cost-effectiveness ratio (ICER) when pembrolizumab was compared to SOC was £39,772 in the base case considering the original submission, and £30,244 in the updated base case.These ICERs should be considered in the context of pembrolizumab being an end of life technology that presents an innovative nature, as recognised by the Committee during the original appraisal of pembrolizumab.[13]

Table 60: Base-case results (discounted, with proposed discount and assuming a 50% discount is available as part of the CAA available for pemetrexed administered as maintenance therapy)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Base case reflecting the original submission						
SOC	£21,847	1.46	1.04	-	-	-
Pembrolizumab	£72,353	3.08	2.31	£50,506	1.27	£39,772
Updated base case						
SOC	£43,364	1.86	1.35	-	-	-
Pembrolizumab	£72,353	3.08	2.31	£28,989	0.96	£30,244
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 61: ICERs from the pairwise comparison for pembrolizumab vs. SOC (discounted, with proposed discount for pembrolizumab, and considering a range of potential simple discounts, equivalent to the current CAA for pemetrexed administered as maintenance therapy)

Discount	Base case reflecting the original submission	Updated base case
0%	£38,244	£28,220
10%	£38,549	£28,625
20%	£38,855	£29,029
30%	£39,160	£29,434
40%	£39,466	£29,839
50%	£39,772	£30,244
60%	£40,077	£30,649
70%	£40,383	£31,053
80%	£40,688	£31,458
90%	£40,994	£31,863

The estimates of the clinical outcomes included in the cost-effectiveness analysis (compared with the clinical trial results) and the tabulated, disaggregated results are presented in Appendix J.

B.3.8 Sensitivity analyses

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. In these analyses, a 50% simple discount for pemetrexed maintenance is assumed, to account for the confidential (and therefore unknown) CAA currently available. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix L.

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 62, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 17 and Figure 18.

Table 62: Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with proposed discount for pembrolizumab and assuming a 50% discount is available as part of the CAA available for pemetrexed administered as maintenance therapy)

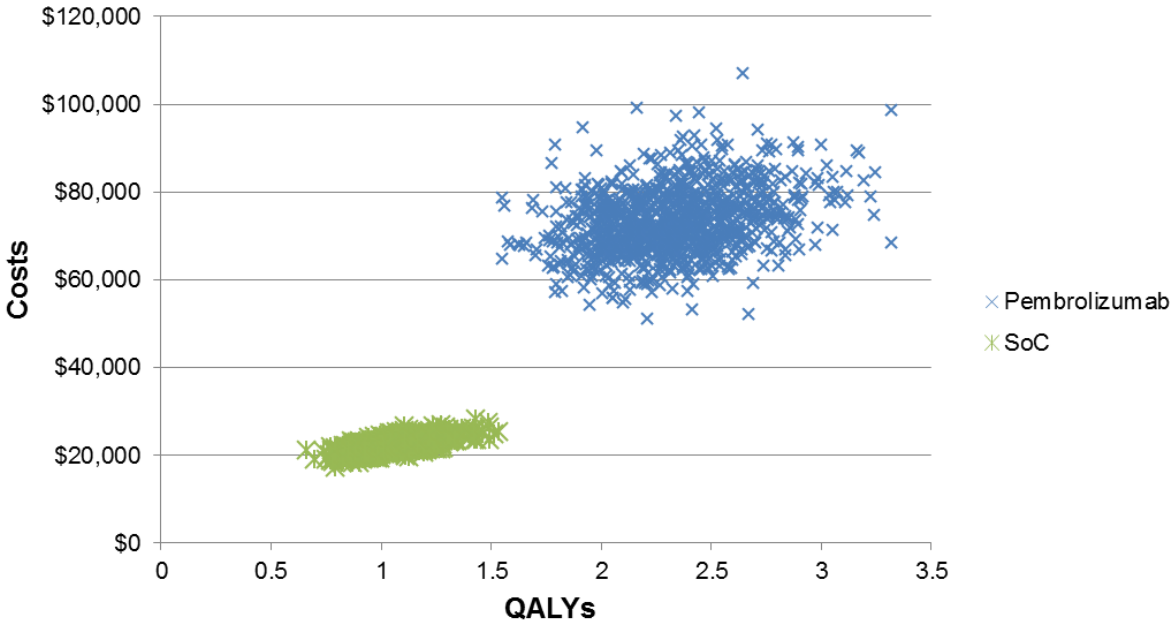
Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case reflecting the original submission					
SOC	£22,048	1.05	-	-	-
Pembrolizumab	£73,062	2.32	£51,015	1.27	£40,026
Updated base case					
SOC	£43,704	1.36	-	-	-
Pembrolizumab	£73,062	2.32	£29,359	0.97	£30,414

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

The cost-effectiveness acceptability curve shows that, for the base case reflecting the original submission versus the updated base case (respectively), there is an approximately 78% and 88% of chance of pembrolizumab being cost-effective when compared to SOC at the £50,000 per QALY threshold.

Figure 17: Scatterplot of PSA results (1,000 simulations; results discounted, with proposed discount for pembrolizumab and assuming a 50% discount is available as part of the CAA available for pemetrexed administered as maintenance therapy)

a) Base case reflecting the original submission



b) Updated base case

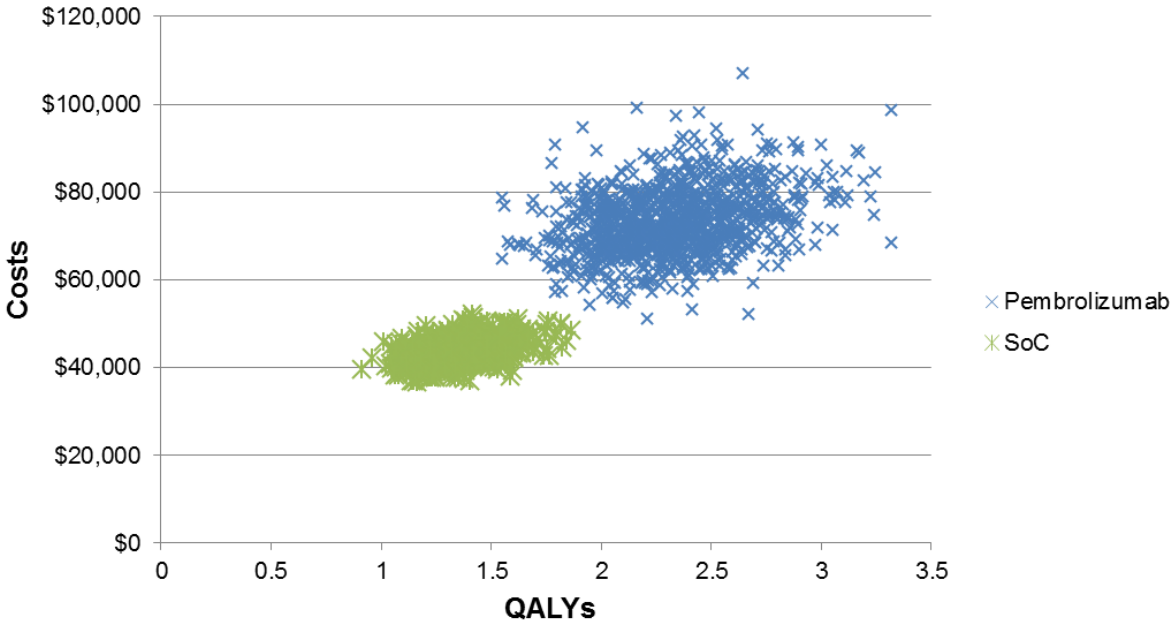


Figure 18: Cost-effectiveness acceptability curve (results discounted, with proposed discount for pembrolizumab and assuming a 50% discount is available as part of the CAA available for pemetrexed administered as maintenance therapy)

a) Base case reflecting the original submission

b) Updated base case

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 (i.e. body surface area)
- Administration costs
- Costs of the PD-L1 test
- Resource utilisation
- Proportion of patients actually receiving the expected dose
- Subsequent treatment costs and mean duration of subsequent treatment
- Health-state related costs when on active treatment, when no active treatment and for terminal care
- Health-state utility values
- Proportion of patients experiencing AEs for pembrolizumab and SOC
- Costs of AEs
- Duration of AEs
- Parameters of the parametric curves fitted to OS, PFS and ToT.
- Discount rate (0% and 6%)

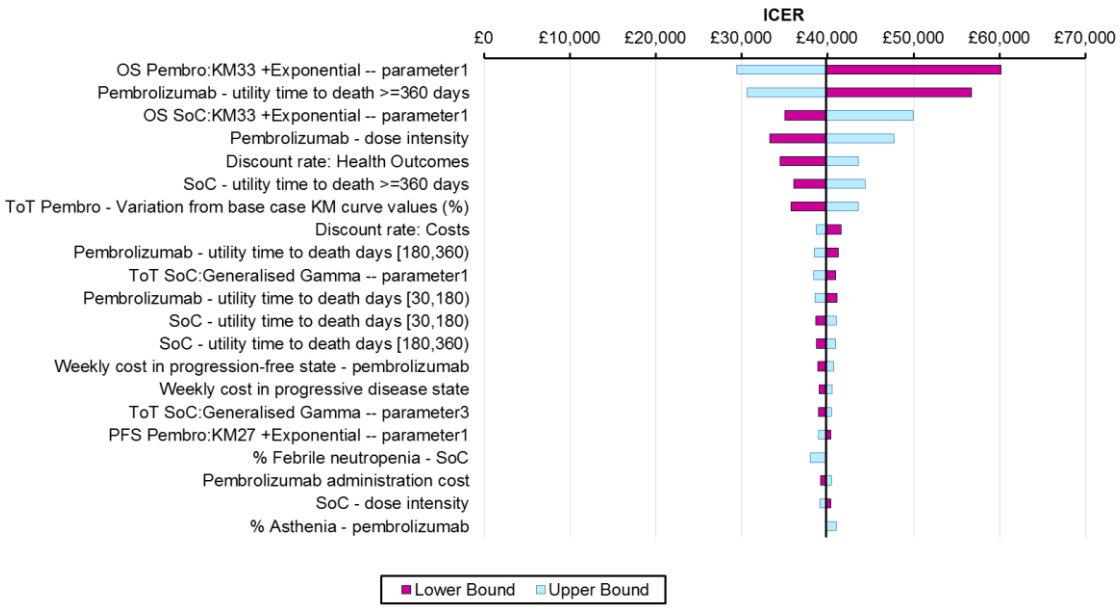
The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab vs. SOC are presented in Figure 19 below. These are presented with the confidential discount for pembrolizumab and assuming a 50% simple discount for pemetrexed maintenance, to account for the confidential (and therefore unknown) CAA currently available.

The inputs that most affect the ICERs are those related to the extrapolation of the OS (i.e. the parameter of the exponential function used for extrapolation), followed by the utility values for

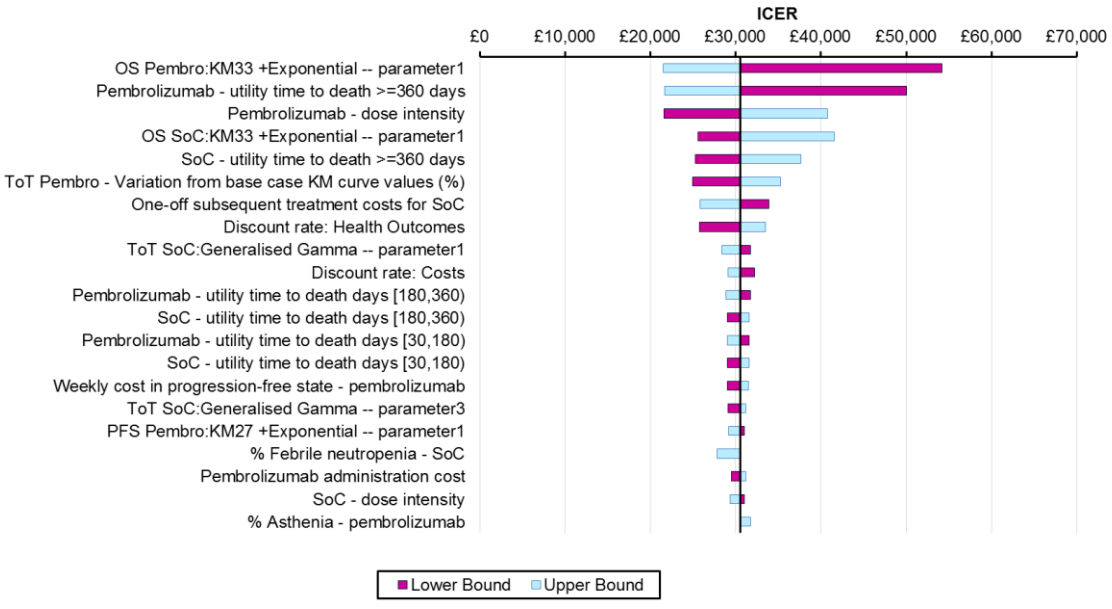
long-term survivors, assumptions around time on treatment and dose intensity considered to estimate the cost of pembrolizumab (see Figure 19).

Figure 19: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most sensible variables (discounted results, with proposed discount for pembrolizumab and assuming a 50% discount is available as part of the CAA available for pemetrexed administered as maintenance therapy)

a) Base case reflecting the original submission



b) Updated base case



Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions:

- Impact of considering UK-based BSA (i.e. 1.79),[123] as suggested by the ERG for the original submission, instead of derived from KEYNOTE-024 (i.e. 1.83), since this was one of the criticisms raised by the ERG in the original submission (scenario 1.a).
    - Since the value suggested by the ERG did not take account of the different distribution by sex of patients in the UK study versus those in KEYNOTE-024, an additional scenario was tested (i.e. scenario 1.b), where a BSA value of 1.84 was used to reflect the weighted average by sex of KEYNOTE-024 considering the mean BSA by sex from the UK study.
- Impact of using alternative crossover adjustments in addition to the 2-stage adjustment (scenario 2), including:
    - RPSFT adjustment (scenario 2.a)
    - IPCW adjustment (scenario 2.b)
- Alternative cut-offs for the estimation of the exponential curve in the second phase of the piecewise approach used to extrapolate OS (scenario 3), including:
    - A 23-week cut-off (scenario 3.a)
    - A 43-week cut-off (scenario 3.b)
- Alternative cut-offs for the estimation of the parametric curve in the second phase of the piecewise approach used to extrapolate PFS (scenario 4), including:
    - A 9-week cut-off (i.e. first radiologic assessment; scenario 4.a)
    - A 37-week cut-off (i.e. approximately the fourth radiologic assessment; scenario 4.b).
- Using a different parametric function to extrapolate PFS (since the exponential function used in the base case was not the best statistical fit, in terms of AIC/BIC, for the SOC arm; scenario 5), including:

    - Weibull (scenario 5.a)
    - Generalised Gamma (scenario 5.b)
- Assessing the impact of the half-cycle correction (scenario 6).
- Assuming the distribution of patients across different combination chemotherapies administered as part of SOC reflect UK market shares for both first line and pemetrexed maintenance (scenario 7).
- Using progression-based utilities as an alternative approach to estimate QALYs based on KEYNOTE-024 (scenario 8).
- Using utilities derived per treatment arm instead of pooled utilities from KEYNOTE-024 (scenario 9):
    - With the time to death approach (scenario 9.a)
    - With the progression-based approach (scenario 9.b)
- Using the utilities from the study by Chang et al (2017), [87] which reported alterative time-to-death utilities (scenario 10).
- Utility value for the time period of ≥360 days before death equal to that of the general UK population of the same age (i.e. 0.79 instead of 0.809, as suggested by the ERG during the original submission; scenario 11)
- Removing the age-related disutilities (scenario 12).
- Assuming that the effect of treatment stops at 3 years (scenario 13.1) or. at 5 years (scenario 13.2), with pembrolizumab presenting a similar hazard to that of the SOC arm from that point onward.

Alternative functional forms for the extrapolation of OS at 33 weeks were not explored further since, apart from the exponential distribution (used in the base case), the other functional forms presenting the best statistically fits resulted in clinically implausible results (see 'Modelling overall survival' in Appendix L).

In these analyses, a 50% simple discount for pemetrexed maintenance is assumed, to account for the confidential (and therefore unknown) CAA currently available.

Table 63: Results from the scenario analyses

		Pembrolizumab			SOC			Pembro vs SOC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case reflecting original submission		£72,353	3.08	2.31	£21,847	1.46	1.04	£50,506	1.27	£39,772
Scenario 1.a	UK-specific BSA values (unadjusted by sex distribution)	£72,352	3.08	2.31	£21,717	1.46	1.04	£50,635	1.27	£39,873
Scenario 1.b	UK-specific BSA values (adjusted by sex distribution)	£72,353	3.08	2.31	£21,880	1.46	1.04	£50,473	1.27	£39,746
Scenario 2.a	Crossover- RPSFT adjustment	£72,353	3.08	2.31	£21,692	1.44	1.02	£50,661	1.29	£39,179
Scenario 2.b	Crossover- IPCW adjustment	£72,353	3.08	2.31	£22,815	1.62	1.16	£49,538	1.15	£43,065
Scenario 3.a	OS cut-off – 23 weeks	£71,815	2.99	2.24	£20,986	1.32	0.93	£50,829	1.31	£38,698
Scenario 3.b	OS cut-off – 43 week	£71,881	3.00	2.25	£23,360	1.70	1.24	£48,522	1.02	£47,693
Scenario 4.a	PFS cut-off – 9 weeks	£72,590	3.08	2.31	£21,816	1.46	1.04	£50,774	1.27	£39,983
Scenario 4.b	PFS cut-off – 37 weeks	£71,950	3.08	2.31	£21,765	1.46	1.04	£50,185	1.27	£39,519
Scenario 5.a	PFS extrapolation based on Weibull	£71,912	3.08	2.31	£21,484	1.46	1.04	£50,429	1.27	£39,711
Scenario 5.b	PFS extrapolation based on GenGamma	£73,081	3.08	2.31	£21,818	1.46	1.04	£51,263	1.27	£40,368
Scenario 6	No half cycle correction	£72,383	3.09	2.32	£21,880	1.47	1.05	£50,503	1.27	£39,773
Scenario 7	SOC as for UK market shares	£72,353	3.08	2.31	£21,482	1.46	1.04	£50,870	1.27	£40,059
Scenario 8	Utilities – Progression based (pooled)	£72,353	3.08	2.22	£21,847	1.46	1.05	£50,506	1.17	£43,131
Scenario 9.a	Utilities – Time to death (per treatment arm)	£72,353	3.08	2.35	£21,847	1.46	1.02	£50,506	1.32	£38,240
Scenario 9.b	Utilities – Progression-based (per treatment arm)	£72,353	3.08	2.29	£21,847	1.46	1.00	£50,506	1.29	£39,255
Scenario 10	Utilities – Time to death by Chang et al (2017) [87]	£72,353	3.08	2.45	£21,847	1.46	1.03	£50,506	1.42	£35,661

		Pembrolizumab			SOC			Pembro vs SOC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Scenario 11	Utilities for the time period ≥ 360 days to death equal to general population, same age	£72,353	3.08	2.38	£21,847	1.46	1.13	£50,506	1.25	£40,459
Scenario 12	No age-related disutilities	£72,353	3.08	2.36	£21,847	1.46	1.05	£50,506	1.30	£38,759
Scenario 13.1	Stop treatment effect at 3 years	£68,778	2.50	1.86	£21,847	1.46	1.04	£46,931	0.82	£57,265
Scenario 13.2	Stop treatment effect at 5 years	£70,412	2.76	2.07	£21,847	1.46	1.04	£48,564	1.03	£47,289
Updated base case		£72,353	3.08	2.31	£43,364	1.86	1.35	£28,989	0.96	£30,244
Scenario 1.a	UK-specific BSA values (unadjusted by sex distribution)	£72,352	3.08	2.31	£43,234	1.86	1.35	£29,117	0.96	£30,378
Scenario 1.b	UK-specific BSA values (adjusted by sex distribution)	£72,353	3.08	2.31	£43,396	1.86	1.35	£28,957	0.96	£30,210
Scenario 2.a	Crossover- RPSFT adjustment	NA	NA	NA	NA	NA	NA	NA	NA	NA
Scenario 2.b	Crossover- IPCW adjustment	NA	NA	NA	NA	NA	NA	NA	NA	NA
Scenario 3.a	OS cut-off – 23 weeks	£71,815	2.99	2.24	£43,178	1.83	1.33	£28,637	0.91	£31,321
Scenario 3.b	OS cut-off – 43 week	£71,881	3.00	2.25	£43,935	1.95	1.43	£27,946	0.83	£33,829
Scenario 4.a	PFS cut-off – 9 weeks	£72,590	3.08	2.31	£43,314	1.86	1.35	£29,276	0.96	£30,543
Scenario 4.b	PFS cut-off – 37 weeks	£71,950	3.08	2.31	£43,252	1.86	1.35	£28,697	0.96	£29,940
Scenario 5.a	PFS extrapolation based on Weibull	£71,912	3.08	2.31	£42,895	1.86	1.35	£29,017	0.96	£30,273
Scenario 5.b	PFS extrapolation based on GenGamma	£73,081	3.08	2.31	£43,320	1.86	1.35	£29,761	0.96	£31,050
Scenario 6	No half cycle correction	£72,383	3.09	2.32	£43,394	1.87	1.36	£28,989	0.96	£30,249
Scenario 7	SOC as for UK market shares	£72,353	3.08	2.31	£42,999	1.86	1.35	£29,354	0.96	£30,624

		Pembrolizumab			SOC			Pembro vs SOC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Scenario 8	Utilities – Progression based (pooled)	£72,353	3.08	2.22	£43,364	1.86	1.32	£28,989	0.90	£32,254
Scenario 9.a	Utilities – Time to death (per treatment arm)	£72,353	3.08	2.35	£43,364	1.86	1.33	£28,989	1.02	£28,517
Scenario 9.b	Utilities – Progression-based (per treatment arm)	£72,353	3.08	2.29	£43,364	1.86	1.26	£28,989	1.03	£28,266
Scenario 10	Utilities – Time to death by Chang et al (2017) [87]	£72,353	3.08	2.45	£43,364	1.86	1.37	£28,989	1.07	£27,053
Scenario 11	Utilities for the time period ≥ 360 days to death	£72,353	3.08	2.38	£43,364	1.86	1.44	£28,989	0.94	£30,874
Scenario 12	No age-related disutilities	£72,353	3.08	2.36	£43,364	1.86	1.37	£28,989	0.99	£29,393
Scenario 13.1	Stop treatment effect at 3 years	£69,387	2.60	1.94	£43,364	1.86	1.35	£26,023	0.59	£44,483
Scenario 13.2	Stop treatment effect at 5 years	£70,746	2.82	2.11	£43,364	1.86	1.35	£27,382	0.76	£36,156

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 between 78% and 88%, depending on the base case scenario considered.

One-way sensitivity analyses showed that the inputs that most affect the ICERs are those related to the extrapolation of the OS for pembrolizumab and the utility for long-term survivors in the pembrolizumab arm. Some other parameters, such as the dose intensity, the discount rates and variations in the ToT for pembrolizumab, have a moderate impact.

Scenario analyses showed that the most sensitive scenarios relate to assuming treatment benefit stops at either 3 or 5 years, and the use of a 43-week cut-off to extrapolate OS when the base case analysis reflecting the original submission (i.e. using the 2-stage approach to adjust for crossover) is considered. Assuming the treatment effect stops 3 or 5 years after treatment initiation increases the ICERs to £57,265 and £47,578, respectively, in the base case reflecting the original submission, and to £44,483 and £36,434, respectively, for the updated base case. It should be noted that there is no evidence that the treatment effect stops, as observed by the tail of the pembrolizumab KM OS based on the latest data cut (KEYNOTE-024 July 2017; see Figure 5). When a 43-week cut-off is applied to extrapolate OS, the ICER increases from £40,054 up to £47,983. However, there are only 17% of events left to fit the parametric adjustment in the 2-stage adjusted SOC arm, and the scenario results in implausibly high 5-year (crossover adjusted) OS rates for the SOC (i.e. 11%, which is more than twice the value accepted by the Committee and the ERG as plausible in the original submission in the presence of adjustments for crossover. [13]

Consequently, pembrolizumab remains a cost-effective strategy when realistic scenarios are considered. The results of these sensitivity analyses show that the additional data cut, with a median follow up of 25.2 months,[18] has reduced considerably the uncertainty surrounding the clinical effectiveness and cost-effectiveness of pembrolizumab, and variations in parameter values have a much lower impact now that in the original submission.

B.3.9 Subgroup analysis

In the original submission subgroup analyses were conducted because they were pre-specified in the protocol. However, due to the small numbers of patients per subgroup, these were not clinically applicable. Additionally, subgroup analyses separating per combination chemotherapy (e.g. gemcitabine + cisplatin) were not possible due to the low numbers of patients under each of these subgroups, which also applied to comparisons of pembrolizumab against non-pemetrexed combinations administered to patients with non-squamous NSCLC.

As part of the original submission, the committee did not consider any of these subgroups clinically relevant for decision making.[13] Therefore, no subgroup analyses have been presented for this CDF evidence submission.

B.3.10 Validation

Validation of cost-effectiveness analysis

Clinical benefit

Comparing the model outcomes to clinical trial outcomes

The outcomes of the pembrolizumab 200 mg and the SOC arms of the KEYNOTE-024 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 Appendix J.

Expert validation

The model approach and inputs were validated in the original submission 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. 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 were valid and were consistent with previous submissions in this indication. Regarding the

assumption of treatment effect, they suggested that any assumptions in the model be provided with a clinical rationale.

Regarding the crossover in the clinical trial and the adjustments applied, the experts agreed that it was reasonable to perform crossover adjustment on the SOC OS given the significant proportion of patients from the SOC arm who crossed over to pembrolizumab.

The experts agreed that the two-stage approach (without re-censoring) was the most appropriate method to adjust for crossover and that it is the most recognised by ERGs. It was highlighted that the approach of presenting the ITT method as a scenario analysis also helped support the argument. The experts thought the adjusted OS HRs based on the two-stage approach seemed reasonable, and if anything, the experts expected even better adjusted HRs due to the significant crossover. The experts also noted that the fact the unadjusted HR is statistically significant is reassuring in terms of treatment efficacy and the use of crossover methods.

It should be noted that, when these experts were consulted, pembrolizumab had not been yet recommended by NICE as an option for treating locally advanced or metastatic PD-L1-positive NSCLC in adults who have had at least one chemotherapy (and targeted treatment if they have an EGFR or ALK-positive tumour). Since then, pembrolizumab has become SOC in this second line setting, and therefore, to reflect current clinical practice, the updated base case, not adjusting for crossover, was deemed more appropriate.

The experts noted that the KEYNOTE-024 trial collected good quality utility data and for a good number of patients. They agreed with the base case using utilities derived from pooling data from both treatment arms. According to their feedback, clinical rationale should be the basis for the choice between progression-based and time-to-death based utilities. They also noted that time-to-death based utilities appear to be appropriate for the pembrolizumab arm given longer survival time and utilities likely to be more dependent upon time to death. There was uncertainty regarding whether all the difference seen in values for progression free utilities between two arms can be entirely attributed to AEs.

The experts agreed with the approach to identify AEs based on a 5% cut-off at the overall AE level, and with the way the AEs have been costed. They also agreed with the approach

followed to cost the PD-L1 test, subsequent therapies and pemetrexed maintenance. For TOT for SOC, the experts suggested looking at the percentage of patients on treatment on cycle 1 to 6 from the trial and apply this directly to the model. Finally, they recommended using the distribution of patients across different SOC regimens from KEYNOTE-024 as the basis of the analysis, to maintain consistency with the efficacy inputs.

The accuracy of the model development and programming was verified via internal quality control processes using an internal quality control checklist, available in Appendix M.

The updated projections, based on the July 2017 KEYNOTE-024 data cut, were validated with two clinical experts, who agreed on the plausibility of the projections of the two base case analyses presented in this updated evidence submission. The clinicians also found the estimated utility values to be reasonable, particularly because it is expected that patients will experience an improved QoL when treated with immunotherapies compared with more toxic and less effective chemotherapies. The clinicians were asked if the approach taken by MSD for the updated base case reflected their current clinical practice and they agreed with it.

B.3.11 Interpretation and conclusions of economic evidence

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 lacking EGFR mutations and/or ALK translocations whose tumours express PD-L1 in at least 50% of their tumour cells and who have not received prior systemic chemotherapy treatment in the UK. The economic evaluation reflects patients assessed in KEYNOTE-024 and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

Only one study assessing the cost-effectiveness of pembrolizumab for the target population has been identified, although it was not relevant for decision making since it was conducted in a US setting. [86] It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

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 its marketing authorisation. As mentioned previously (see section B.3.3), the KEYNOTE-024 trial, which assessed patients in line with the marketing authorisation, was used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab as first line therapy, as identified by the Committee in the original appraisal.[13]

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-024 and the de novo economic evaluation are reflective of patients with advanced NSCLC in the UK, as recognised by the Committee for the original appraisal.[13] Some minor differences were identified between patients included in KEYNOTE-024 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 would not 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. It was also considered by the Committee as appropriate for decision making during the original submission. [13]

- The resource utilitisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of pembrolizumab.

- Extensive sensitivity analyses have been conducted in this updated evidence submission, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs, costs and long term benefits, demonstrating that pembrolizumab is a cost-effective intervention in the majority of the analyses conducted.

- The OS projections of the model were validated against available UK sources and by clinical experts, to ensure the clinical plausibility of the model and its applicability to UK clinical practice.

- The generalisability of the results was also recognised by the Committee as part of the Final Appraisal Determination of the original submission.[13]

Strengths and weaknesses of the evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model, and this updated evidence submission makes use of the final data cut for KEYNOTE-024, which has a median follow up of 25.2 months.[18]

- OS: Head-to-head data from the KEYNOTE-024 trial comparing pembrolizumab to SOC was used in the economic evaluation. The magnitude of benefit observed in the SOC group was consistent with that previously observed with platinum-based combination regimens and pemetrexed maintenance therapy.[124] [125] [126]

- Crossover adjustments: The two-stage adjustment method was deemed to be the most appropriate to adjust for the effect of switching to pembrolizumab from the SOC arm within KEYNOTE-024 during the original submission. However, given that clinical practice in second line treatment has changed after the positive NICE recommendation received by pembrolizumab for treating locally advanced or metastatic PD-L1-positive NSCLC, crossover adjustments become irrelevant and an ITT analysis (without crossover adjustment) is now reflective of the current clinical practice in England.

- Estimation of utilities: Utility values were obtained from EQ-5D KEYNOTE-024 data. Four time categories were used for the time-to-death approach, which were consistent with values published by other utility studies identified from the systematic literature review.

- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to 2 years, as defined as part of the KEYNOTE-024 protocol and recommended by NICE for pembrolizumab in both first[13] and second line. [1]

- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from recent NICE appraisals and accepted by the ERG and the Committee in the original submission. [13]

Extensive sensitivity analyses were conducted to inform the uncertainty around the above limitations, which helped in understanding the key variables that have a major impact on the cost-effectiveness results and demonstrated that pembrolizumab remains cost-effective in the majority of the analyses considered.

Since the approaches taken for modelling are, in the main, conservative, the results presented here 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 previously untreated advanced NSCLC whose tumours express PD-L1 on at least 50% of their tumour cells.

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Single technology appraisal

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349]

Dear [redacted],

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRiG), and the technical team at NICE have looked at the submission received on 28 November 2017 from March 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 **Friday 15 December 2017**. Your response and any supporting documents should be uploaded to NICE Docs.

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 on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (Ross.Dent@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk)

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

No questions

Section B: Clarification on cost-effectiveness data

Kaplan–Meier data

B1. Priority request: Please provide the Kaplan–Meier analyses, listed in a to e below, to the following specifications:

Trial data set:	*KEYNOTE-024 trial*
Censoring:	*Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, i.e. not when last known to be alive*
Format:	*Use the sample table shown below question B1*
Population:	*Intention-to-treat population including all patients lost to follow-up or withdrawing from the trial*

a. Time to death from any cause (overall survival, OS) Kaplan–Meier analysis for patients in the pembrolizumab arm of the trial

b. Time to death from any cause (OS) Kaplan−Meier analysis for patients in the standard of care (SoC) arm of the trial stratified by whether patients crossed over and received pembrolizumab and whether this was second, third or a subsequent line of therapy

c. Time from progression to initiation of treatment with pembrolizumab Kaplan−Meier analysis (SoC arm)

d. Time to study treatment discontinuation Kaplan−Meier analysis (pembrolizumab arm)

e. Time to post study treatment discontinuation Kaplan−Meier analysis (SoC arm).

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Sample table: Example of output (SAS) required from specified Kaplan–Meier analyses
- The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Section C: Textual clarifications and additional points

C1. Within the company submission, patients in the SoC arm who switched directly are differentiated from those who switched indirectly to an anti-PD1 treatment following discontinuation of the protocol treatment. Please explain the difference between direct and indirect switching.

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15th December 2017

Dear Helen,

Re. Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349]

Please find enclosed MSD's responses to the clarification questions from the ERG and the NICE technical team, concerning the clinical and cost effectiveness data for the above mentioned submission.

We believe that we have addressed all of the questions, but should you or the ERG require any further clarification, please do not hesitate to contact us.

Best regards,

[redacted]

Section A: Clarification on effectiveness data

No questions

Section B: Clarification on cost-effectiveness data

Kaplan-Meier data

B1. Priority request: Please provide the Kaplan–Meier analyses, listed in a to e below, to the following specifications:

Trial data set:	*KEYNOTE-024 trial*
Censoring:	*Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, i.e. not when last known to be alive*
Format:	*Use the sample table shown below question B1*
Population:	*Intention-to-treat population including all patients lost to follow-up or withdrawing from the trial*

a. Time to death from any cause (overall survival, OS) Kaplan–Meier analysis for patients in the pembrolizumab arm of the trial

b. Time to death from any cause (OS) Kaplan−Meier analysis for patients in the standard of care (SoC) arm of the trial stratified by whether patients crossed over and received pembrolizumab and whether this was second, third or a subsequent line of therapy

c. Time from progression to initiation of treatment with pembrolizumab Kaplan−Meier analysis (SoC arm)

d. Time to study treatment discontinuation Kaplan−Meier analysis (pembrolizumab arm)

e. Time to post study treatment discontinuation Kaplan−Meier analysis (SoC arm).

The requested analyses are presented in Appendix B1 (separate Excel file). Please note all data in Appendix B1 are provided academic in confidence.

a. Kaplan-Meier analysis of overall survival (OS) for patients in the pembrolizumab arm of the trial

Overall survival (OS) is defined as time from randomization to death due to any cause, expressed in days. Subjects without documented death and who have survival update after the data cutoff date of 10-July-2017 are censored at the cutoff date. The intention-to-treat (ITT) population is used for the analyses of overall survival (OS).

The Kaplan-Meier estimate of overall survival for patients in the pembrolizumab arm of the trial is displayed in Sheet 1 of Appendix B1.

b. Kaplan-Meier analysis of overall survival (OS) for patients in the SOC arm of the trial stratified by subsequent therapy status (no switch, direct switch to pembrolizumab, indirect switch to any PD-L1 including pembrolizumab)

As explained during our telephone discussion on December 8th, data captured relate to second line therapy received post study treatment. The Kaplan-Meier data for this analysis are presented in Sheet 2 of Appendix B1.

In Sheet 3 of Appendix B1, we have provided details of the number and proportion of patients in the SOC arm who initiated subsequent treatment with either pembrolizumab or other PD-L1s (including direct and indirect switches) overall and by whether the subsequent treatment was received within 4 weeks after disease progression or beyond 4 weeks after disease progression.

c. Time to switch-over from disease progression in the SOC arm.

Switch-over date is defined as the date of first exposure to second treatment in patients randomized to SOC arm and who switched to pembrolizumab. Time to switch-over from disease progression is calculated as the time between switch-over date and the date of the first documented disease progression per RECIST 1.1 based on blinded independent radiologists' review, expressed in days.

Sheet 4 of Appendix B1 presents the Kaplan-Meier analysis for the patients who switched to pembrolizumab within the study protocol (direct switching). Sheet 5 of Appendix B1 presents the analysis all patients who switched to pembrolizumab (including those who switched outside of the study protocol) and patients who switched to another PD-L1 therapy (direct and indirect switching)

d. Time to discontinuation of treatment in the pembrolizumab arm.

Time to discontinuation of treatment is defined as the time from the date of the first dose to the date of last exposure to treatment, expressed in days. Patients who were still on treatment at the data cutoff date of 10-July-2017 were censored at that date.

The Kaplan-Meier analysis of the time to study treatment discontinuation for the pembrolizumab arm patients is presented in Sheet 6 of Appendix B1.

e. Time to post-study discontinuation of treatment in the SOC arm.

For patients in SOC arm, the time to treatment discontinuation is time from start of SOC treatment to time of last dose of SOC for patients who did not switch or to last dose of pembrolizumab for patients who switched to pembrolizumab (either direct or indirect switch). Patients who were still on treatment at the data cutoff date of 10-July-2017 were censored at that date.
Sheet 7 in Appendix B1 presents the Kaplan-Meier analysis of the time to study treatment discontinuation in the SOC arm, while Sheet 8 provides the analysis stratified by switching status to pembrolizumab.

Section C: Textual clarifications and additional points

C1. Within the company submission, patients in the SoC arm who switched directly are differentiated from those who switched indirectly to an anti-PD1 treatment following discontinuation of the protocol treatment. Please explain the difference between direct and indirect switching.

The difference between direct and indirect switching is as follows:

- Direct switching relates to patients in the SOC arm who switched to pembrolizumab after RECIST-defined disease progression, as allowed within the study protocol (see below for switching eligibility criteria).

- Indirect switching relates to any additional patients in the SOC arm who switched to any anti-PD1 treatment (pembrolizumab or nivolumab) after the protocol treatment, but outside of the criteria defined in the study protocol.

Crossover/switching eligibility criteria

In study KEYNOTE-024, subjects in the SOC arm with documented disease progression following chemotherapy, had the opportunity to participate in the crossover arm of the trial, switching treatment to receive pembrolizumab. To be eligible to participate in the crossover arm and switch treatment to pembrolizumab, specified criteria had to be met, as defined in the trial protocol and summarised below:

- Subjects on the SOC arm will be considered for crossover to pembrolizumab after documented, progressive disease per RECIST 1.1 guidelines (based on centrally reviewed assessment). Crossover is optional and is at the discretion of the Investigator. Imaging must be completed to establish a new baseline for the Crossover Phase.
- In addition, subjects had to meet the following criteria:
    - Chemotherapy induced adverse events (except alopecia) must have improved to CTCAE (Version 4.0) ≤Grade 1
    - Have adequate organ function as per defined laboratory values.
    - If a subject is unstable as a result of a new or progressing brain metastasis(es), the subject will not be eligible for crossover.
    - ECOG Performance Status 0-1
    - Documentation of progressive disease per RECIST v1.1 by a blinded independent central review
    - Subject has not received any other systemic anticancer therapies other than the SOC platinum doublet administered during the treatment phase.
    - Subject has not received palliative radiotherapy of 30Gy or less within 7 days of the first dose of trial treatment.

At the final analysis of study KEYNOTE-024, a total of 82/151 (54.3%) of control patients had switched to pembrolizumab treatment, as allowed in the protocol (direct switching).

An additional [redacted] switch-over events occurred outside of this per-protocol scenario; including [redacted] patients who switched from SOC to pembrolizumab (without satisfying the defined crossover eligibility criteria) and [redacted] patients who switched from SOC to nivolumab (indirect switching).

Submission from **Roy Castle Lung Cancer Foundation,** for consideration by NICE, in their CDF review of TA 447, Pembrolizumab for untreated PD-L1 strong-positive metastatic non-small cell lung cancer [**1349**].

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 55 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 around 15%, 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 advanced NSCLC, remains poor. Target therapies (EGFR and ALK) have made a real difference in first line therapy to those specific patient groups. For the remainder of patients, platinum based chemotherapy has been the first line therapy option. Since Pembrolizumab has been available through the CDF, first line treatment for the subset of specified patients, has been Pembrolizumab, rather than chemotherapy.

2. Improving quality of life and even small extensions in duration of life are of considerable significance to the individual patient and their family.

3. Outcomes remain relatively poor from traditional first line chemotherapy, with many patients experiencing significant side effects. There is, therefore, massive unmet need in this patient group.

4. 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

5. Improvement in symptoms. Patients with metastatic 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.

This Product

1. New and Innovative First Line Therapy
   This is the first Immunotherapy agent seeking approval for use in untreated NSCLC patients, in the NHS. For the past year, it has been available in this indication via the CDF.
   We understand that about 30% of NSCLC tumours show PD-L1 expression at 50% or more (this indication).
   Pembrolizumab has been approved by NICE (FAD in early December 2016) in PD-L1 positive advanced NSCLC, after platinum based treatment.

   Pembrolizumab works by harnessing the ability of the immune system to find and fight cancer. It is described as a PD-1 (Programmed Death-1) Immune Checkpoint Inhibitor. 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, ensures 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 updated overall survival findings from the Phase III, KEYNOTE-024 study, presented at the World Conference in Lung Cancer in October 2017. Key findings, with an additional 6 months of data, showed a reduction in risk of death by 37% for Pembrolizumab, compared with chemotherapy, based on more than 2 years of median follow up (HR = 0.63, 95% Confidence Interval= 0.47- 0.86; nominal P=0.02). Additionally, Pembrolizumab increased overall survival by more than 1 year, more than double the overall survival for chemotherapy (30.0months [95% CI = 18.3 to not reached] versus 14.2 months [95% CI = 9.8 –19.9] respectively).

   Patients with advanced/metastatic NSCLC are a group with significant unmet medical need. Traditional platinum based chemotherapy has provided these patients with a modest improvement in survival. Immunotherapy provides an additional option which can 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 first line platinum based 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 metastatic lung cancer are in a particularly devastating situation. In the patient population being assessed, traditional platinum based chemotherapy is the first line therapy option. Pembrolizumab availability through the CDF has provided a new option with better overall survival and fewer side effects, in this very selected, high PD-L1 patient group. With updated survival data, we hope that the Appraisal Committee will now be able to make a positive recommendation in this indication.

[redacted], **RCLCF.**

January 2018.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Society**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Society (BTS) is the professional society for respiratory medicine and related health care professions. The Society exists to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care. It is a registered charity and a company limited by guarantee.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The British Thoracic Society supports the proposed appraisal. There is an urgent need more treatment options for patients with advanced lung cancer given the very poor prognosis.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the	

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be	

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

20. How do data on real-world experience compare with the trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
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Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England comment in January 2018 on the NICE re-appraisal of currently CDF-funded pembrolizumab as 1st line treatment of PD-L1 strongly positive advanced/metastatic non small cell lung cancer (NSCLC)

The commercial in confidence information in this submission has been redacted.

1. NHS England is confident that 100% of lung cancer units/centres are offering PD-L1 testing to their lung cancer patients.
2. NHS England notes the greater median duration of follow-up in this re-appraisal of the evidence, now 25 months (previously 11 months).
3. NHS England observes that cross over was allowed in this study and included a total rate of crossover of 64% from chemotherapy to anti-PD-1/PD-L1 immunotherapy. As pembrolizumab is in baseline commissioning for 2nd line use in PD-L1 positive patients, this relatively high degree of crossover in the Keynote-024 study means that the ITT trial outcomes are the most accurate indicator of outcomes associated with the current baseline-commissioned sequence of chemotherapy 1st line and pembrolizumab. NICE assessment as to the clinical and cost effectiveness of 1st line pembrolizumab should therefore be based on the outcomes analysed on an ITT basis (ie there is no need to allow for crossover from chemotherapy to immunotherapy).
4. The impact of 1st line pembrolizumab vs chemotherapy in the TPS 50-100% population is impressive: the median OS is doubled from 14 mo to 30 mo, the 30 month survival rate is 52% vs 33% and the 18 month PFS rate is 35% vs 9%.
5. NHS England notes with great concern the company's inaccurate Budget Impact Test (BIT). It states that 1043 new patients per year will commence 1st line pembrolizumab: this is wrong as NHS England knows from the CDF that the figure is and should be 1800. [redacted]
6. NHS England regards that the key question of the BIT is NHS affordability since the BIT was incorporated into the NICE Technology Appraisal process. Since February 2018 is the time at which 1st line pembrolizumab will be considered for potential inclusion in routine commissioning, NHS England regards the budget impact of 1st line pembrolizumab as triggering the need for an urgent discussion between MSD and NHS England.
7. The CDF has funded 1st line pembrolizumab since the end of May 2017 and Public Health England and the Systemic Anti Cancer Therapy (SACT) team is able to offer some analyses to compare with the population of patients entered into the Keynote-024 trial. First line pembrolizumab has been in the CDF for too short a time for the SACT team to report any worthwhile information as to treatment duration and overall survival. The data below applies to the first 957 patients entered into the CDF between late May 2017 and the end of November 2017.
8. About 150 patients per month have CDF applications made to commence 1st line pembrolizumab in NSCLC which has a TPS score of 50-100%. It took just one month for the steady state number of patients to be established in England, proof of how quickly patients, clinicians and NHS England adopt new cancer treatments.

9. The NSCLC histology ratio in the CDF was 3:1 non squamous:squamous whereas in the trial the ratio was 4:1 ie there is a greater proportion of squamous NSCLC having pembrolizumab than in the licensing trial..
10. The median age of CDF patients was 70 years whereas it was 64.5 in Keynote 24. 10% of CDF patients were in the 80+ years age group.
11. 53% of CDF patients were male as opposed to 60% in Keynote-024.
12. The performance status ratio of PS 0:1 was 1:4 in the CDF whereas in Keynote-024 the ratio was 1:2.
13. The SACT team also reports the proportions ofpatients with different PD-L1 TPS scores. The data for Keynote-024 was not in the company's submission, the NEJM paper or the EPAR.

PD-L1 tumour proportion score	Incidence in the CDF
50-59%	16%
60-69%	13%
70-79%	13%
80-89%	18%
90-100%	39%

14. SACT additionally reports the crude rates of CDF 1st line pembrolizumab use per 100,000 population. The highest rates of CDF use were in the areas of The Peninsula (3.0), Lancs and S Cumbria (2.8) and Humber (2.5). The lowest were in the areas of two National Cancer Vanguards: NW and SW London (0.7) and Greater Manchester (0.8). The 3-4 fold difference between these upper and lower CDF usage figures is likely to be explained by the availability of clinical trials investigating 1st line systemic therapy options. These numbers have to be interpreted with caution as this SACT snapshot analysis is only on 957 cases in a 6 month period and can also be affected by clinical trials opening and closing for recruitment.
15. SACT is capable too of analysing uptake of a drug for a specific indication according to indices of multiple deprivation for the GP practice in which the patient is registered. This first and early analysis is shown below. Only patients with performance status 0 or 1 are eligible for pembrolizumab and hence NHS England is encouraged by this preliminary data which shows very substantial use of pembrolizumab in NSCLC in patients from the most deprived GP practices which have the highest age-standardised rate of lung cancer.

Index of Multiple Deprivation (income) for the GP practice	Age standardised rate of lung cancer/100,000	Crude % of total CDF usage
1 least deprived	49	12%
2	61	16%
3	74	24%
4	95	22%
5 most deprived	130	25%

[redacted]

[redacted] NHS England Chemotherapy Clinical Reference Group and CDF National Clinical Lead for the Cancer Drug Fund

February 2018

NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Martin David Forster**
2. Name of organisation	[redacted]

3. Job title or position	**Clinical Senior Lecturer and Honorary Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes Minor information added here

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Primary aim is improve survival by regaining symptomatic disease control
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The experimental treatment requires 3 weekly intravenous therapy for up to 2 years and so should ideally **improve overall survival**, although this is potentially compromised by the cross over to immune checkpoint inhibitors as second line therapy. It is less toxic than standard chemotherapy and so even similar survival may be associated with better quality of life but this would need to be demonstrated.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, despite improvements in systemic therapy for lung cancer over the last decade or so patients with advanced disease without a targetable oncogenic driver still have a dreadful outlook and there is a huge unmet clinical need.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Currently patients with NSCLC without an actionable oncogenic driver receive combination platinum-based chemotherapy (cisplatin / carboplatin and either pemetrexed or gemcitabine). On progression, patients who remain fit are offered pembrolizumab (if PD-L1 >1%) for up to 2 years or docetaxel (+/- nindetanib if non-squamous and eligible, for up to 6 cycles followed by maintenance nintedanib).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, NICE, ESMO and US guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is little variation across the UK. Patients considered fit enough for combination chemotherapy wil get a platinum based combination, although the use of carboplatin / cisplatin may vary across centres.
• What impact would the technology have on the current pathway of care?	Since the techology has been available through the CDF since 2017, most centres now perform PD-L1 testing at diagnosis of advanced disease and this guides use of pembrolizumab for fit patients. This will continue if technology fully approved. If not approved patients PD-L1 testing will still be relevant for consideration of second line therapy but first line therapy will revert back to platinum-based chemotherapy.
11. Will the technology be used (or is it already used) in	As outlined above, the technology is currently being used this way via the Cancer Drugs Fund.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	No significant difference
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology will be delivered by oncology services within secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal investment required as the technology is already in use in the management of platinum resistant lung cancer and the PD-L1 testing required has been set up across multiple institutions over the last few years.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. This an outstanding treatment option for the patient population with lung cancer expressing high levels of PD-L! (>50%)
• Do you expect the technology to increase	Yes. Even though the technology can be used post platinum-based therapy the early emerging data suggest increased survival by its use as first line therapy (as submitted with this application).

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, although the QoL data are not as robust as the survival data, as toxicities are less signifcicant than current standard therapy I would expect QoL to be improved as well as survival
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As outlined within the submission the effectiveness of this therapy within this setting is limited to patients with NSCLC cancers with PD-L1 expression levels of >50%.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The technology under assessment is given intravenously every 3 weeks and the direct primary comparators are platinum-based combination chemotherapy. These are also delivered as intravenous infusions. The likelihood of benefit from the technology correlates with tumour expression levels of PD-L1, with the current evidence only demonstrating improved benefit in patients with tumours with PD-L1 expression levels >50%. Although standard chemotherapy has a reasonable disease control rate, they have only a modest response rate and responses are generally of relatively short duration. The technology has higher response rates and responses are dramatically more durable, leading to significant improvements in progression-free and overall survival. In addition, current comparators are associated with significant toxicities and whilst side effects certainly may occur with the technology,

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	it is generally much better tolerated than the current standards. They technology actually requires less routine supportive medication.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As outlined above tumours will require PD-L1 testing (already being performed) and evaluation for % staining (needs to be >50%). Although the optimal duration of pembrolizumab therapy remains uncertain, the studies that have led to approval limited therapy to 2 years. This will be a stopping point for any patients remaining on therapy for this long. The patterns of response for pembrolizumab are recognised as being different from chemotherapy, with the recognised possibility of pseudo-progression, which although very uncommon (~5%), can be difficult to establish and a proportion of patients with disease progression may be continued for a short time beyond progression before repeat confirmatory scans – this adds complexity to the radiologists reporting the scans
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this represents a dramatic step forwards for the management of NSCLC.
• Is the technology a 'step-change' in the management of the condition?	Yes, as outlined above
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as outlined above
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As well as improved survival, pembrolizumab was associated with less toxicity than chemotherapy and although education will be needed to look out for and manage the toxicity profile, it is much better tolerated than chemotherapy. The toxicity profile for this agent is well reflected within this study, although the rarer irAEs known to occur with this agent were not necessarily all experienced within this patient population. There is increasing experience of the management of this immunotherapy specific toxicities.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The study was delivered in the UK and although only a small number of patients were included from the UK, this was a global study and I think that the clinical trial reasonably reflects clinical practice within the UK. For example, real world data have recently been presented from the Netherlands, demonstrating pembrolizumab trial data to be reflected in their National experiences. This current study used the most relevant outcome for this agent, overall survival, and showed a clear improvement in comparison to standard chemotherapy.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Whilst response rates and time ot response is relevant the key outcomes for this patient population is survival (well measured) and associated QoL (reasonably measured).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	As above the toxicity profile of the technology is well established

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	As above, clinical datasets now appearing suggest similar experiences within the real world to these trial data.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- This technology is a dramatic shift in management of patients with NSCLC with high expression levels of PD-L1 offering both better survival and less toxicity.
- This technology is currently in use and clinical teams are used to delivering it and managing patients being treated by it.
- Since initial NICE submission the data from the study have matured as predicted with maintained durable benefits demonstrated
-
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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**David Snead**
2. Name of organisation	[redacted]

3. Job title or position	**Pathologist and Clinical Lead**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? X☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	X☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	X☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Overall survival Progression free survival Quality of life
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Partial response ie reduce tumour size, by 30% or greater, or complete response
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Lung cancer is the commonest cause of cancer related deaths in the UK for both sexes. The majority of patients with non small cell lung cancer present with inoperable disease, often with metastatic spread. Treatment options are limited for this group of patients. Targetable mutations in either EGFR, ALK and ROS1 are seen in less than 15% of these patients, so for the majority of patients the only treatment option is platinum based combination chemotherapy, which carries considerable morbidity and modest response rates.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Targeted therapy for patients with relevant mutations, EGFR, ALK and ROS1 translocations. Platinum based combination chemotherapy for patients without targetable mutations.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes NICE Lung cancer diagnosis and management 2011 CG121
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Clinical pathways are reasonably well defined for this disease.
• What impact would the technology have on the current pathway of care?	The biggest impact will be on correct patient selection. Testing of tumours for PD-L1 is complex and requires adequate tissue as well as considerable expertise. It critical to the correct patient selection. It is currently provided by few centres nationally with the majority of labs sending sample away for this test. As it comes into routine practice delays in getting this test done are likely to produce delay in treatment. The effective of differences in sample preparation (fixation for example) on the PD-L1 test are incompletely understood and more work is required to ensure results are accurate and reproducible discussed below.
11. Will the technology be used (or is it already used) in	The treatment is already widely used in second lie treatment, and increasingly as a first line treatment in patients with high expressing tumours.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Apart from treatment costs the key difference is around testing the tumour for PD-L1 expression. Adequate tumour cells are needed for this. It is sometime necessary to re-biopsy patients in order to acquire adequate samples for testing. Proprietary guidelines exclude alcohol based fixatives, although there is uncertainty over the validity of this advice in the pathologist community. Alcohol based fixatives are commonly used for fine needle aspirates and other cytology preparations. If these samples cannot be used for PD-L1 testing then it may mean re-biopsying some patients in order to assess PD-L1 expression.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and ideally Cancer centres
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Testing for PD-L1 expression needs to be done routinely. This will require expansion of current testing capacity in pathology laboratories, including training of staff and capital investment. More research may be needed on the range of antibodies which can be used for this test and whether exclusion of alcohol based fixatives is justified. External quality assurance schemes are essential to monitor laboratories compliance with testing. These need to be adequately resourced and contingency plans need to be in place for failing laboratories.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. In the correct patient group the treatment is more effective than standard therapy. Current data from the Keynote 024 trial shows a median OS twice that achieved with standard care. The drug is tolerated better than standard care.

• Do you expect the technology to increase length of life more than current care?	Yes, in appropriate patients OS is expected to be doubled compared to standard care.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. There are fewer adverse reactions in pembrolizumab compared to standard care.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As discussed above the therapy is only effective in those tumours which utilise the PD-L1 pathway to evade the host immune response. Current guidance indicates 50% or greater positivity as the indicator for first line care. Tumours showing less than 50% positivity show significantly less response, therefore treatment in these patients is more appropriate as second or third line therapy.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	This is not my area of expertise.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes rule based treatment is appropriate based on PD-L1 testing. Positive cases require 50% or greater positivity in the tumour cells.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Uncertain but this is possible

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. The technology offers a new treatment option which is superior to standard care in the correct patient population.
• Is the technology a 'step-change' in the management of the condition?	Yes. Immune modulation offers a new therapeutic strategy for the treatment of NSCLC
• Does the use of the technology address any particular unmet need of the patient population?	Yes it provides an additional targeted therapy as discussed above.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The drug is well tolerated in comparison to standard care.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The findings of the Keynote 024 reflect UK practise.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, progression free survival and response rate. Superior PFS survival has already been reported and reviewed in the prior NICE guidance TA447 & Reck et al NEJM 2016; 375 pp 1823-1833. Both progression free survival and tumour response rate were measured, and significantly improved OS was 30.2 in the pembrolizumab arm as opposed to 14.2 months in the standard care arm. Overall response rate was 45.5% (95% CI, 37.4-53.7) compared to 29.8% (95% CI, 22.6-37.8). IASLC conference 2017 Abstract OA 17.06 (ID 9582).

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Data relating to selection of PD-L1 positive patients may show variability in observer assessment and in the selection of the primary antibody used to mark PD-L1 ligand, may be difficult to identify in systematic reviews. Such data is relevant to implementation of testing.
21. How do data on real-world experience compare with the trial data?	The findings reported in Keynote 024 correspond well to real world experience.
Equality	
22a. Are there any potential equality issues that should be	

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your statement.

- PD-L1 inhibition is a step change in non small cell lung cancer therapy for PD-L1 positive patients
- Correct patient selection is dependent on PD-L1 testing
- Testing is complex and provides logistical challenges and requires external quality assurance
- Limited access to testing may delay treatment

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) [ID1349]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Lesley Holland**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ✓ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	National Lung Cancer Forum for Nurses
4. Did your nominating organisation submit a submission?	☐ yes, they did ✓ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ✓ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	✓ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ✓ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As a lung cancer specialist nurse I care for patients who have lung cancer. It is a disease often with no cure that can lead to complex symptoms causing considerable physical and psychological distress

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I believe patients and carers feel there are new treatments becoming available for patients with lung cancer, as long as they are eligible for the treatments.
10. Is there an unmet need for patients with this condition?	This drug is currently accessed via the Cancer Drugs Fund for patients expressing more than 50% of the PDL1 marker, and Performance Status 0-1
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Benefits of this treatment may include: • Less side effects than conventional first line chemotherapy therefore patients are hospitalised less • No IV pre medication drugs required • No Pre or post steroids required • Only require oral premedication • Infusion time is quick therefore less time in the treatment areas, means more patients can be treated, and patients will have a better overall experience • Overall the quality of life for patients who are able to receive the treatment appears to be improved • Patients also have the benefit of knowing they have a treatment that is completely targeted to their disease. • The treatment outcomes could be significant in terms of disease free progression, but more over the quality of life of palliative patients. • Patients do not become neutropenic so not so susceptible to infections during treatment • Preparation of this medication presents less handling risk as it is not a cytotoxic drug

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	• The side effects of this therapy can be complex to treat as generally the medical teams do not have so much experience of using it. The more this type of drug is used the easier this will become • There are specific blood test's required to monitor patients during treatment.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not known
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Targeted therapy
- Less side effects than conventional Chemotherapy
- Improved Pre-medication drugs required
- Quicker treatment time
- Improved outcome in respect of length of life and quality of life

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

ID1349 CDF review of TA447

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer (CDF review of TA447) ID1349

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 16/108/12

Completed 8 January 2018

CONTAINS ACADEMIC IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer (CDF review of TA447)

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Contributions of authors:

Sophie Beale	Critical appraisal of the clinical and economic evidence
James Mahon	Critical appraisal of the economic evidence
Angela Boland	Critical appraisal of the clinical evidence

All authors read and commented on draft versions of the ERG report.

1 OVERVIEW

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE). This appraisal is a review of a previous Single Technology Appraisal (STA) of the use of pembrolizumab (Keytruda®) for the treatment of untreated programmed death-ligand 1 (PD-L1) positive (≥50%) metastatic non-small cell lung cancer (NSCLC). Clinical and economic evidence was originally submitted to NICE by Merck Sharp & Dohme (MSD) in October 2016.[1] In June 2017, NICE recommended pembrolizumab (TA447) for use within the Cancer Drugs Fund (CDF) as an option for the treatment of untreated PD-L1 positive metastatic NSCLC in adults, only if:

1. patients' tumours express PD-L1 ≥50% tumour proportion score (TPS) and have no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations
2. pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
3. the conditions in the managed access agreement for pembrolizumab are followed.[2]

The company's main source of evidence for TA447 was the KEYNOTE-024 trial.[3] The original company submission (CS1)[4] provided results from an interim analysis (IA2) of trial data (9 May 2016 cut-off date). The current company submission (CS2)[5] includes data from the final analysis (10 July 2017) and cost effectiveness results that have been generated using the final dataset from the KEYNOTE-024 trial.

Although the quantity of evidence provided by the company was equivalent to that for a STA, the time period for the ERG critique was half of that for a STA. Therefore, as suggested by NICE (emailed letter dated 20 December 2017), the focus of this ERG report is on the company's economic evidence. The ERG has also provided summaries of key clinical effectiveness results alongside those from the analysis of IA2 data presented in CS1.

2 CONTEXT

2.1 Summary of ERG review of original company submission for TA447

The issues relating to KEYNOTE-024 trial design and statistical methods that were highlighted by the ERG in their original (TA447) report[6] are still relevant and are summarised here.

Direct evidence

The company's main source of effectiveness evidence was the KEYNOTE-024 trial. Patients recruited to this trial were randomised to receive either pembrolizumab or standard of care (SOC). The SOC regimens used during the trial included gemcitabine, paclitaxel or pemetrexed with a platinum therapy (cisplatin or carboplatin).

The ERG considers that the KEYNOTE-024 trial was a small, well-conducted, open-label, phase III, randomised controlled trial (RCT). However:

- clinical results from the KEYNOTE-024 trial were only presented for the comparison of treatment with pembrolizumab versus SOC
- the only direct clinical evidence for the comparison of treatment with pembrolizumab versus platinum+pemetrexed came from a subgroup analysis
- the company did not discuss the clinical effectiveness of pembrolizumab compared with single agent chemotherapy
- there was no direct evidence of the clinical effectiveness to allow a comparison of pembrolizumab with the individual comparators listed in the final scope issued by NICE[7]
- the ERG is uncertain of the reasons for, or the implications of, the 3.1 months difference between the blinded independent central review (BICR) assessed progression-free survival (PFS) and the investigator-assessed PFS for patients in the pembrolizumab arm of the KEYNOTE-024 trial (10.3 months versus 7.2 months)
- testing for PD-L1 expression was not routinely available in NHS treatment centres.

Indirect evidence

The company carried out network meta-analyses (NMAs) to generate clinical effectiveness results for comparisons of treatment with pembrolizumab versus all platinum doublet chemotherapies specified in the final scope issued by NICE. Although the ERG considered that the methodology used to conduct the main NMA (all-comers) was appropriate, the ERG considered that the results were unreliable for the following reasons:

- there was extensive heterogeneity between included studies (e.g., PD-L1 status, disease stage, race/ethnicity)
- the unadjusted and adjusted (for treatment crossover) NMA results were very similar
- repeated use of the pembrolizumab data from the KEYNOTE-024 trial may have led to over-inflation of the results due to the possible double-counting of patients in the analyses.

Cost effectiveness evidence

The ERG considered that there were four fundamental issues that cast substantial doubt on the reliability of the company's base case cost effectiveness results for the comparison of treatment with pembrolizumab versus SOC. Three of these issues are still relevant, namely:

1. any extrapolation of overall survival (OS) data from patients in the pembrolizumab arm of the KEYNOTE-024 trial was highly uncertain due to only 35.4% of the total events having occurred
2. the company calculated the cost of pembrolizumab on the basis that treatment would cease after 2 years (35 cycles) as this is in line with details published in the KEYNOTE-024 trial protocol. However, the Summary of Product Characteristics[8] does not include this time dependent stopping rule and the ERG considered it implausible that, in NHS clinical practice, treatment would be stopped at this time point if a patient were deemed to still be deriving clinical benefit from treatment with pembrolizumab
3. the ERG considered that the utility values incorporated into the company model, which were derived from data collected as part of the KEYNOTE-024 trial, were implausibly high, notably for the 360-day period before death when these values were higher than the UK population norms.

2.2 Recent developments

2.2.1 Treatment pathway

Since CS1 (October 2016), as a result of recommendations made by NICE,[9-11] pembrolizumab and nivolumab have become NHS treatment options, after chemotherapy, for many patients with locally advanced or metastatic NSCLC (see Table 1). The company states that PD-L1 targeting therapies are rapidly becoming standard of care for patients who have received prior chemotherapy. The ERG agrees with this statement.

Table 1 Relevant recommendations made by NICE

Identifier	Date	Product	Recommendation
TA428[9]	January 2017 (updated September 2017)	Pembrolizumab	As an option for treating locally advanced or metastatic **PD-L1 positive** NSCLC in adults who have had at least one chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour), only if: • pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression, and • the company provides pembrolizumab in line with the commercial access agreement with NHS England.
TA483[10]	November 2017	Nivolumab	For use within the CDF as an option for treating locally advanced or metastatic squamous NSCLC lung cancer in adults after chemotherapy, only if: • nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and • the conditions in the managed access agreement are followed.
TA484[11]	November 2017	Nivolumab	For use within the CDF as an option for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy, only if: • their tumours are **PD-L1 positive** and • nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and • the conditions in the managed access agreement are followed.

ALK=anaplastic lymphoma kinase; Cancer Drugs Fund; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1

2.2.2 Testing for PD-L1 expression in the NHS

PD-L1 expression is assessed in a laboratory through immunohistochemistry (IHC) staining. The company reports (CS2, p17) that results from a recent analysis conducted for MSD showed that there had been a 5-fold increase in the volume of PD-L1 tests conducted during the period between June and August 2017 (average [redacted] tests per month) compared with the period between September and October 2016 (average [redacted] tests per month).

2.3 Innovation

The company considers that pembrolizumab is an innovative treatment due to its novel mode of action (CS2, p62).

2.4 Number of patients eligible for treatment with pembrolizumab

The company estimates that, in England, 1799 patients would be eligible for treatment with pembrolizumab in 2018. The method used by the company to reach this estimate is described in CS2 (p16).

3 KEYNOTE-024 TRIAL RESULTS

This section provides a structured summary of the clinical effectiveness evidence submitted by the company in support of the use of pembrolizumab for untreated PD-L1 positive metastatic NSCLC. As none of the information on study methodologies, statistical analyses and quality assessment has changed since CS1, the ERG has not included a summary or critique of these aspects in this report. This section focuses on the updated clinical effectiveness results, including adjustments for crossover and adverse events (AEs), from the final analysis of the KEYNOTE-024 trial data.

3.1 Efficacy results from the KEYNOTE-024 trial

Efficacy results from the KEYNOTE-024 trial for the intention-to-treat (ITT) population are summarised in Table 2. The results provided in CS1 were based on the data examined during IA2; the data-cut for IA2 was 9th May 2016. The updated (CS2) results are based on the data examined during the final analysis; the data-cut for the final analysis was 10th July 2017.

Table 2 Results from the KEYNOTE-024 trial (ITT population)

Endpoint	IA2		Final	
	Pembrolizumab N=154	SOC N=151	Pembrolizumab N=154	SOC N=151
Primary endpoint				
PFS (BICR)				
Median, months (95% CI)	10.3 (6.7 to -)	6.0 (4.2 to 6.2)	[redacted]	[redacted]
HR (95% CI)	0.50 (0.37 to 0.68) p<0.001		[redacted]	
Number of events, n (%)	73 (47.4)	116 (76.8)		
Person months	1000.2	785.6		
Event rate/100 person months	7.3	14.8		
PFS rate at 6 months	62.1%	50.3%		
PFS rate at 12 months (95% CI)	47.7%	15.0%	[redacted]	[redacted]
PFS rate at 18 months (95% CI)	NR	NR	[redacted]	[redacted]
PFS rate at 24 months	NR	NR	[redacted]	[redacted]
Secondary endpoints				
OS				
Median, (months) (95% CI)	Not reached	Not reached	30.0 [redacted]	14.2 [redacted]
HR (95% CI)	HR 0.60 (0.41 to 0.89) p=0.005		0.63 (0.47 to 0.86) p=0.002	
Number of events, n (%)	44 (28.6)	64 (42.4)	73 [redacted]	96 [redacted]
Person months	1402	1227.5	[redacted]	[redacted]
Event rate/100 person months	3.1	5.2	[redacted]	[redacted]
OS rate at 6 months	80.2%	72.4%		
OS rate at 12 months (95% CI)	69.9%	54.2%	[redacted]	[redacted]
OS rate at 18 months (95% CI)			[redacted]	[redacted]
OS rate at 24 months (95% CI)			[redacted]	[redacted]
OS rate at 30 months (95% CI)			[redacted]	[redacted]
ORR (BICR)				
Confirmed ORR (95% CI)	44.8% (36.8%to 53%)	27.8% (20.8% to 35.7%)	45.5% (37.4% to 53.7%)	29.8% (22.6 to 37.8)
Difference: pembrolizumab vs SOC (95% CI)	16.6% (6.0% to 27.0%) p=0.0011		14.9% (4.3% to 25.4%) p=0.0031	

BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; IA2=second interim analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; SOC=standard of care
Source: CS1, Table 17, Table 18, Table 25 and CS2, Table 6, Table 7 and Table 8

The PFS results from the final analyses were similar to the results from the IA2 analyses. Using the final data-cut, median PFS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, [redacted] months versus [redacted] months. In the original ERG report, the ERG noted that there appeared to be a difference of 3.1 months in median PFS between the investigator-assessed results and the results reported for BICR-assessed PFS (7.2 months and 10.3 months respectively). Median PFS in the SOC arm appeared to be similar between the two analyses (5.5 months and 6 months). The ERG is uncertain of the reasons for, or the implications of, the 3.1 months difference between the BICR-assessed PFS and investigator-assessed PFS. No updated investigator assessed PFS data were submitted by the company in CS2.

Using the IA2 data-cut, median OS was not reached. Using the final data-cut, median OS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, 30 months versus 14.2 months.

The objective response rate (ORR) results from the final data-cut were similar to the results from the IA2 analyses. Using the final data-cut, the ORR was higher for patients in the pembrolizumab arm compared to patients in the SOC arm (45.5% versus 29.8%), with a confirmed difference in ORR of 14.9% (95% CI 4.3% to 25.4%, p=0.0031).

The results of the exploratory outcomes from the KEYNOTE-024 trial are presented in Table 3 and show that 70 patients in the pembrolizumab arm responded to treatment (median time to response 2.1 months; range, 1.4 to 14.5) and that the median duration of response was not reached in the pembrolizumab arm. In the SOC arm, 45 patients responded to treatment (median time to response 2.2 months; range, 1.8 to 10.3) and the median duration of response was 7.1 months. It is unclear why the upper bound of the time to response range for patients in the SOC arm is lower when calculated using the final dataset than it was when calculated using IA2 data (12.2 months [IA2] versus 10.3 months [final]).

Table 3 KEYNOTE-024 trial exploratory endpoints

Endpoint	IA2		Final	
	Pembrolizumab N=154	SOC N=151	Pembrolizumab N=154	SOC N=151
Time to response (BIRC)				
Number of responders	69	42	70	45
Median (months)	2.2	2.2	2.1	2.2
Range (months)	1.4 to 8.2	1.8 to 12.2	1.4 to 14.5	1.8 to 10.3
Response duration (BIRC)				
Median (months)	Not reached	6.3	Not reached	7.1
Range (months)	1.9+ to 14.5+	2.1+ to 12.6+	1.8+ to 20.6+	2.1+ to 18.1+
Disease control rate				
CR+PR+SD, n (%)	107 (69.5)	102 (67.5)	[redacted]	[redacted]
Progressive disease, n (%)	34 (22.1)	28 (18.5)	[redacted]	[redacted]

BIRC=blinded independent central review; CR=complete response; IA2=second interim analysis; PR=partial response; SD=stable disease; +=censored
Source: CS1, Table 23, Table 24, Table 25 and CS2, Table 15 and Table 16

3.2 Crossover adjustments

The company explained in their response to clarification queries that, at the time of the final analysis, and as allowed in the trial protocol, 54.3% (82/151) of patients in the SOC arm had crossed over to receive pembrolizumab (direct switching). Furthermore, an additional [redacted] 'switch-over events' occurred (indirect switching).

The company carried out four alternative methods to adjust for patient crossover. One set of analyses adjusts for direct switching and the second set of analyses adjusts for both direct and indirect switching (see

Table 4). The ERG highlights that the central hazard ratio (HR) results generated by all of the different types of adjustments for direct switching are similar; however, there is greater variation in the central estimates when the different adjustments were made for direct and indirect switching. The ERG has concerns (as described in the TA447 ERG report) relating to the reliability of all the crossover adjustment approaches employed by the company and considers that all results should be viewed with caution.

Table 4 Summary final OS results adjusted for direct and indirect switching

Crossover adjustment method	Pembrolizumab vs SOC					
	Direct switching			Direct and indirect switching		
	HR	95% CI	p-value (2-sided)	HR	95% CI	p-value (2-sided)
ITT	0.63	0.47 to 0.86	0.003	0.63	0.47 to 0.86	0.003
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Simplified two-stage (no re-censoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two-stage (with re-censoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; HR=hazard ratio; IPCW=inverse probability of censoring weighted; ITT=intention to treat; RPSFT=rank preserving structural failure time; SOC=standard of care
* p-value retained from the ITT analysis based on distribution of the test statistic under the null hypothesis of no treatment effect
Source: CS2, Table 9 and Table 10

3.3 Indirect and mixed treatment comparisons

The company offered to update the indirect and mixed treatment comparisons (ITCs and MTCs) that were presented in CS1. However, as new evidence that would ameliorate the concerns expressed in the original ERG report have yet to become available, during the clarification telephone conference, the company, the NICE team and the ERG agreed that updated ITC and MTC results would not be useful to decision-makers.

3.4 Health-related quality of life from the KEYNOTE-024 trial

No new health-related quality of life data from the KEYNOTE-024 trial were submitted as part of CS2.

3.5 Adverse events from the KEYNOTE-024 trial

Clinical advice to the ERG is that AEs arising from treatment with immunotherapy (i.e., pembrolizumab) in patients with NSCLC require careful monitoring. The use of immunotherapies such as pembrolizumab has been evaluated for several years in patients with melanoma; however, in comparison to patients with melanoma, patients with NSCLC are older and have higher rates of co-morbidities. Patients may also have greater variation in available social support. Expert advice to the ERG, presented in the TA447 ERG report, is that a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs is needed at treatment centres in the event that pembrolizumab is approved for use in the treatment of NSCLC in the NHS. Current training of senior and junior oncology medical staff as well as specialist nursing staff may be insufficient to recognise and/or deal with these complications. This approach should be integrated with triage services, and Acute Oncology Units in District General Hospitals.

The ERG has updated the most important TA447 ERG report summaries of AEs with data provided in CS2 (see Table 5); after reviewing these data, the ERG considers that there are no new safety concerns associated with treatment with pembrolizumab in patients with NSCLC. However, the ERG highlights that, for patients treated with pembrolizumab, discontinuations due to AEs and drug-related AEs have increased since the IA2 analyses.

Table 5 Summary of adverse events from the KEYNOTE-024 trial

Adverse event type	IA2		Final	
	Pembrolizumab N=154	SOC N=150	Pembrolizumab N=154	SOC N=150
One or more AE, n (%)	148 (96.1)	145 (96.7)	[redacted]	[redacted]
No AE, n (%)	6 (3.9)	5 (3.3)	[redacted]	[redacted]
Drug related AE, n (%)	113 (73.4)	135 (90.0)	[redacted]	[redacted]
Grade 3 to 5 AE, n (%)	82 (53.2)	109 (72.2)	[redacted]	[redacted]
Grade 3 to 5 drug-related AE, n (%)	41 (26.6)	80 (53.3)	[redacted]	[redacted]
SAE, n (%)	68 (44.2)	66 (44.0)	[redacted]	[redacted]
Serious drug-related AE, n (%)	33 (21.4)	31 (20.7)	[redacted]	[redacted]
Death, n (%)	9 (5.8)	7 (4.7)	[redacted]	[redacted]
Death due to drug-related AE, n (%)	1 (0.6)	3 (2.0)	[redacted]	[redacted]
Discontinued due to AE, n (%)	14 (9.1)	21 (14.0)	[redacted]	[redacted]
Discontinued due to drug-related AE, n (%)	11 (7.1)	16 (10.7)	[redacted]	[redacted]
Discontinued due to SAE, n (%)	13 (8.4)	11 (7.3)	[redacted]	[redacted]
Discontinued due to serious drug-related AE, n (%)	10 (6.5)	7 (4.7)	[redacted]	[redacted]

AE=adverse event; IA2=second interim analysis; SAE=serious adverse event; SOC=standard of care
Source: CS1, Table 41 and CS2, Table 25

4 COST EFFECTIVENESS ANALYSES

4.1 Company economic modelling

The model submitted by the company as part of CS2 is constructed in MS Excel and is identical in structure to the company CS1 model. It is a three-state partitioned survival model, with the three states being PFS, progressed disease and death.

The key elements underpinning the economic modelling presented in CS1 were:

- utility derived from the KEYNOTE-024 trial, differing by a patient's time to death
- effectiveness data for both pembrolizumab and SOC from the KEYNOTE-024 trial with the SOC arm adjusted for patients switching to immunotherapy
- resource use from the KEYNOTE-024 trial and costs from published sources.

The substantive changes to the economic modelling between CS1 and CS2 are:

- use of additional follow up data from the KEYNOTE-024 trial
- use of comparator arm data from the KEYNOTE-024 trial unadjusted for crossover to immunotherapy to model what the company considers to be current NHS care (immunotherapy after progression on chemotherapy).

The CS2 model is essentially the same, algorithmically, as that presented as part of CS1. A minor modification has been made to discounting, namely that, in the CS2 model, discounting is implemented at the start of the second year, rather than from week one, as was the case in the CS1 model. The ERG considers that this change was appropriate and in line with a minor criticism made by the ERG about the CS1 model.

In CS2, the company has provided cost effectiveness results for two scenarios. The only difference between the scenarios is the therapy that patients, whose initial treatment was chemotherapy, receive on disease progression, i.e., either docetaxel (in line with the CS1 base case scenario) or immunotherapy. In CS2, the company makes a robust case that receiving immunotherapy after chemotherapy reflects current NHS practice. It is this cost effectiveness analysis that is the focus of the ERG's critique.

However, the ERG notes that, when considering the first scenario, in the CS2 model, the proportion of patients who initially receive chemotherapy and who receive docetaxel on progression is estimated to be between 2.3% and 9.9%; depending on the methods (adjustment for treatment switching and time point at which a parametric distribution is appended to KEYNOTE-024 trial Kaplan-Meier [K-M] data) used by the company to generate the estimate. The company's updated estimates suggest that their earlier estimate, presented in CS1 (1.9% of patients alive at 5 years), was overly pessimistic. The company's revised

estimate underlines the uncertainties associated with long-term extrapolation of short term data sets and the fact that even a small amount of additional data can alter long-term survival projections.

To generate OS estimates for patients receiving SOC (immunotherapy on disease progression) the company used unadjusted data from the SOC arm of the KEYNOTE-024 trial. Two thirds of patients in this arm ([redacted]) received immunotherapy ([redacted] pembrolizumab and [redacted] other immunotherapies). In the CS2 model, it is assumed that [redacted] of patients receive pembrolizumab and the remaining [redacted] of patients receive docetaxel.

The company has estimated the cost of treatment with pembrolizumab following chemotherapy based on the average number of weeks of treatment received by patients in the SOC arm of the KEYNOTE-024 trial (29.1 weeks). The company's cost of treatment with docetaxel is estimated to be 8.5 weeks. The company state that the source for this assumed length of treatment is TA406 (Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer),[12] however, the rationale for this choice of length of treatment is not provided. Drug and drug administration costs were included in the model as a one-off cost at the time of disease progression.

The company OS estimates (for both patients treated with pembrolizumab and those receiving SOC) were derived by appending exponential distributions to KEYNOTE-024 trial data at three different time points (23, 33 and 43 weeks). The 33-week time point was used in the company base case.

The company's base case results for the comparison of the cost effectiveness of pembrolizumab versus SOC (chemotherapy followed by immunotherapy) are shown in Table 6 (exponential distributions appended to KEYNOTE-024 trial K-M data at 33 weeks). Results generated when exponential distributions are appended to KEYNOTE-024 trial data at 23 and 43 weeks are also provided.

Table 6 Company model results (CS2)

Technologies	Total			Incremental		ICER per QALY gained
	Costs	LYG	QALYs	Costs	QALYs	
Distributions appended to K-M data at 33 weeks (company base case)						
SOC (chemotherapy followed by immunotherapy)	[redacted]	1.86	1.35	-	-	-
Pembrolizumab	[redacted]	3.08	2.31	[redacted]	0.96	[redacted]
Distributions appended to K-M data at 23 weeks						
SOC (chemotherapy followed by immunotherapy)	[redacted]	1.83	1.33	-	-	-
Pembrolizumab	[redacted]	2.99	2.24	[redacted]	0.91	[redacted]
Distributions appended to K-M data at 43 weeks						
SOC (chemotherapy followed by immunotherapy)	[redacted]	1.95	1.43	-	-	-
Pembrolizumab	[redacted]	3.00	2.25	[redacted]	0.83	[redacted]

ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; LYG=life year gained; QALY=quality adjusted life year; SOC=standard of care
Source: CS2 model

4.2 ERG critique of the company economic analysis

4.2.1 Data source for standard of care (pembrolizumab following chemotherapy)

The ERG agrees with the company assessment that, in NHS clinical practice, current care for patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC is chemotherapy followed, on disease progression, by immunotherapy. However, there is currently no trial data that directly compares the efficacy of pembrolizumab in patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC who have, with those that have not, received prior chemotherapy. The company has suggested that as patients in the SOC arm of the KEYNOTE-024 trial were permitted to receive pembrolizumab (or another immunotherapy) following disease progression, these data can be considered to represent outcomes for patients receiving current NHS care.

Examination of the OS K-M data from the SOC arm of the KEYNOTE-024 trial (clarification question B1) reveals that OS for the 54.3% of SOC arm patients who received pembrolizumab following disease progression was much better than that of patients who did not (or had not yet received) an immunotherapy (

Figure 1).

Figure 1 SOC arm KEYNOTE-024 trial OS K-M data by treatment switching

The K-M data from the SOC arm of the KEYNOTE-024 trial show that [redacted] patients who did not receive immunotherapy on disease progression died within 6 months of enrolment into the trial compared to [redacted] of SOC arm patients who received immunotherapy. [redacted] receiving pembrolizumab in the SOC arm had died within the first 12 weeks of the trial compared to [redacted] of SOC arm patients who did not receive immunotherapy.

All patients in the SOC arm of the KEYNOTE-024 trial were eligible for immunotherapy following confirmed disease progression. The ERG considers that the high early mortality of patients in the SOC arm who did not receive immunotherapy is evidence that these patients died before, or shortly after disease progression and, therefore, never had the opportunity to receive any subsequent therapy (immunotherapy or docetaxel). The K-M data from the SOC arm of the KEYNOTE-024 trial also show that around [redacted] of patients who did not receive immunotherapy following progression were still alive at [redacted] weeks. These patients were eligible under the trial protocol to receive immunotherapy on disease progression; however, the reasons why they did not do so are unknown. The ERG considers it plausible that at least some of these patients would commence immunotherapy in the future and the potential OS gain from them doing so is not captured by either the OS K-M data from the KEYNOTE-024 trial or any of the current company OS projections.

In the absence of a direct head-to-head trial data comparing the efficacy of pembrolizumab in patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC who are untreated with

those previously treated with chemotherapy, the SOC arm for KEYNOTE-024 is currently the best available evidence for this comparison. However, the ERG considers there is evidence from within the KEYNOTE-024 data that using OS data from the SOC arm of that trial may underestimate the true survival of patients receiving pembrolizumab after chemotherapy.

4.2.2 Pembrolizumab treatment costs

Within the CS2 model, it is assumed that patients who receive pembrolizumab following chemotherapy are prescribed a fixed dose of 200mg every 3 weeks (Q3W). However, it is stated within the [8] issued by the European Medicines Agency that the recommended dose of pembrolizumab for patients with NSCLC who have previously been treated with chemotherapy is 2mg/kg bodyweight Q3W. Applying the cost for the recommended dose of pembrolizumab in the CS2 model (based upon the mean body weight of patients participating in the KEYNOTE-024 trial) reduces the company base case discounted costs for patients receiving SOC by [redacted] to [redacted] per patient, and increases the ICER for the comparison of pembrolizumab versus SOC to [redacted] per QALY gained.

Within the CS2 model, the cost of pembrolizumab, for those who have received prior chemotherapy, was determined by the mean time that patients in the SOC arm of the KEYNOTE-024 trial received pembrolizumab (29.1 weeks). This cost was applied as a one-off fee at disease progression. Given that data from the KEYNOTE-024 trial show that the mean length of time that patients randomised to receive SOC received pembrolizumab following disease progression was 6 months; and the mean time to treatment commencement following disease progression for these patients was 7 weeks, use of discounting in the model would be expected to slightly reduce the total cost of pembrolizumab treatment for these patients. The ERG, therefore, considers that the company's approach to costing treatment with pembrolizumab in patients previously receiving SOC is likely to overestimate the true discounted cost of this treatment. Generating a more accurate cost of treatment would require structural changes to the model that are beyond the remit of the ERG.

4.2.3 Limiting utility values to age-related population norms

In the TA447 ERG report, the ERG highlighted that the utility values in the company model seemed implausibly high for patients with metastatic NSCLC. The utility value in the CS1 and CS2 models for patients who were over 360 days from death was [redacted]. The age-related norm for people aged 65 (the age of the population at model time zero) is 0.79.[13] The ERG made the conservative suggestion that the values used in the company model should be no higher than the age-related population norms. This assumption was accepted by the NICE Appraisal Committee.

The company has undertaken a literature review (CS2, p86-90) and used results from this review to justify using a utility value of [redacted] at 360 days before death in the CS2 model. The ERG considers that results from the company literature review do not strongly support the use of this value as the cited studies either involved patients at slightly different disease stages, were undertaken in countries other than the UK, or involved small numbers of patients. The ERG, therefore, considers that it is appropriate to still limit utility values in the model to be no higher than the age-related population norms.

Adjusting the company base case by model by limiting the utility value to the age-related population norms reduces the difference in QALYs for patients treated with pembrolizumab versus SOC by 0.02 QALYs and increases the ICER for this comparison to [redacted] per QALY gained.

In the TA447 ERG report, the ERG highlighted that alternative (much lower) values for utilities to those used by the company have been used in previous NICE STAs. The ERG has carried out an exploratory analysis involving using utility values reported by Nafees[14] (0.673 for >180 days from death and 0.473 for <180 days from death). The effect on the company base case of using the Nafees utility values is to reduce the difference in QALYs for patients treated with pembrolizumab versus SOC by 0.16 QALYs and increases the ICER for this comparison to [redacted] per QALY gained.

As a point of clarification, the company states in CS2 (p90) 'Additionally and importantly, the NICE reference case stipulates the use of utility values directly derived from the patients.' The ERG highlights that the actual wording of the NICE Reference Case is '…health states drawn from patients directly with societal valuation of these health states.'

4.2.4 Extrapolation of KEYNOTE-024 trial OS data

Within the CS2 model, the company has estimated OS, both for patients initially receiving pembrolizumab and those initially receiving SOC, by appending a variety of parametric distributions to KEYNOTE-024 trial OS K-M data at different time points (23, 33 and 43 weeks). In the TA447 ERG report, the ERG explained that they considered that there was little evidence to support any particular method of extrapolating available trial data. Whilst CS2 includes 6 months more K-M data than CS1, data are still only available for approximately 10% of the model time horizon. The difficulty in choosing the most appropriate curve to use to extrapolate trial data is illustrated by the range of potential distributions considered by the company (see

Figure 2 and Figure 3).

Figure 2 Distributions considered by company to extrapolate KEYNOTE-024 trial pembrolizumab arm OS data

Figure 3 Distributions considered by company to extrapolate KEYNOTE-024 trial SOC arm OS data

Visual examination of the various distributions considered by the company to extrapolate KEYNOTE-024 trial pembrolizumab OS data suggest that the company's choice, in their base case, to use an exponential distribution is the joint most pessimistic option; with the projection generated by their Weibull distribution being essentially equivalent to that generated by their

exponential distribution. The company also chose, in their base case, to use an exponential distribution to extrapolate KEYNOTE-024 trial SOC OS data. The exponential distribution is also the most pessimistic of the considered options for extrapolating SOC arm data and leads to a substantially more pessimistic projection than any of the other distributions considered by the company.

Assuming that the same type of distribution is appended to both the pembrolizumab and SOC OS K-M data at 33 weeks, the ICER for the comparison of the cost effectiveness of pembrolizumab versus SOC varies between [redacted] per QALY gained when a generalised-gamma distribution is used to [redacted] per QALY gained when a Weibull distribution is used. The choice of distribution makes a substantial difference to the cost effectiveness of pembrolizumab versus SOC and highlights the uncertainty inherent in the long-term extrapolation of short-term trial data.

During TA428 the company provided evidence from the KEYNOTE-010 trial that, at 5 years between 11.97% and 26.80% of patients receiving pembrolizumab following chemotherapy would be alive; and at 10 years between 2.46% and 24.72% would still be alive. Assuming that the immunotherapies received by the [redacted] of patients in the KEYNOTE-024 trial were all as effective as pembrolizumab in the KEYNOTE-010 trial, it would be expected that, based on the projections provided by the company in their TA428 submission, the CS2 company model projections would show between 7.7 and 17.2% of patients alive at 5 years and between 1.6% and 15.8% alive at 10 years. The CS2 company base case projection suggests 9.1% of patients alive at 5 years (which is within the range previously projected) but the proportion expected to be alive at 10 years is 0.9%, which is much lower than previously estimated. The company's CS2 base case SOC OS projections, therefore, appear pessimistic compared with the company's previous projections.

In addition, the company has not provided any justification for their choice of time-point at which to append any distribution to KEYNOTE-024 trial data. Visual examination of the company's projections generated by appending exponential distributions (the company's base case choice of distribution) to K-M data at 23, 33 and 43 weeks (Figure 4, Figure 5 and

Figure 6 respectively) suggests that the closest fit to the trial data occurs when distributions are appended at 43 weeks. There is still an indication from the end of the K-M data (albeit the data becomes heavily censored from week 100) that as this approach generates estimates of 9.6% of patients alive at 5 years and 1.5% alive at 10 years this extrapolation may still underestimate the long-term survival of patients receiving SOC.

Figure 4 OS with K-M exponential extrapolation at 33 weeks (company base case)

Figure 5 OS with KM exponential extrapolation at 23 weeks

Figure 6 OS with KM exponential extrapolation at 43 weeks

The choice of both the distribution used to extrapolate trial data and the time at which the distribution is appended to the K-M data are essentially arbitrary. However, the ERG considers that the distributions that, visually, best fit the data from both arms of the KEYNOTE-024 trial are exponential distributions appended at 43 weeks. The long-term accuracy of the projections for patients in both arms of the trial are, however, unknown.

4.2.5 Treatment stopping at two years

Within the TA447 ERG report, the ERG suggested that some patients may receive pembrolizumab for longer than 2 years, both in the trial and in a real-world setting. As part of the clarification process, the company provided time on treatment data for patients in the KEYNOTE-024 trial who received pembrolizumab (clarification question B1). These data showed (with censoring) that all but one patient had stopped receiving pembrolizumab within 110 weeks (just over two years). However, as there is still only 2 years of follow-up data from the KEYNOTE-024 trial the impact, if any, on the long-term survival of patients who stopped pembrolizumab at 2 years for reasons unrelated to disease status is unclear.

4.3 Impact of ERG amendments on cost effectiveness

In the company CS2 base case, pembrolizumab was estimated to generate an additional 0.96 QALYs at an additional cost of [redacted] compared to SOC (where SOC involves [redacted] of patients receiving immunotherapy following disease progression), with an ICER for the comparison of the cost effectiveness of pembrolizumab versus SOC of [redacted] per QALY gained.

The ERG has suggested three amendments to the company CS2 model:

1. applying costs associated with the recommended dose of pembrolizumab after progression on chemotherapy
2. limiting the utility values used in the model to be no higher than the population norm
3. applying exponential extrapolations to KEYNOTE-025 OS K-M data from both arms of the trial at 43 weeks.

The impact of the ERG's three amendments on the costs and QALYs of treatment with pembrolizumab and on the ICER per QALY gained are shown in Table 7. Compared to the values generated by the company base case, the ERG's alternative scenario, which involves apply all three amendments, increase the incremental costs of treatment with pembrolizumab by [redacted] per patient and reduces the incremental QALYs by 0.15. These changes increase the size of the company base case ICER from [redacted] to [redacted] per QALY gained.

Details of the revisions made by the ERG to the company CS2 model can be found in Appendix 1

Table 7 ERG adjustments to company base case: pembrolizumab versus SOC (discounted, list prices)

Scenario/ERG amendment	Pembrolizumab			SOC			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]										
R1) Cost of pembrolizumab in SOC in line with recommended dose	[redacted]										
R2) Utility value for >360 days to death set to population norm	[redacted]										
R3) OS extrapolation at 43 weeks for pembrolizumab and SOC	[redacted]										
B. ERG alternative scenario (R1-R3)	[redacted]										

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

5 END OF LIFE CRITERIA

Within CS1 (Section 4.13) the company put forward a case that, for the population under consideration, pembrolizumab met NICE's End of Life criteria. However, as the treatment pathway has now changed, and treatment with pembrolizumab following chemotherapy has become a standard of care, the ERG has re-examined the End of Life criterion that patient life expectancy should be less than 24 months.

Median OS of patients in the SOC arm of the KEYNOTE-024 trial is 14.2 months (CS2, p25). The mean life expectancy predicted by the CS2 base case model is 22.3 months (CS2, p13). The ERG's alternative approach to predicting life expectancy, i.e. applying an exponential distribution to KEYNOTE-024 trial OS K-M data at 43 weeks rather than 33 weeks, produces an estimate of mean OS of 23.4 months, which the ERG still considers to be conservative. It is, therefore, not at all certain that the mean life expectancy of the population of interest is less than the 24 months.

6 ERG CONCLUSIONS

Clinical effectiveness

Results, presented in CS2, from analyses of KEYNOTE-024 final data showed that median PFS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, 8.5 months versus 6.1 months. In addition, median OS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, 30 months versus 14.2 months. No new health-related quality of life data were provided from the KEYNOTE-024 trial and there were no new safety concerns.

Cost effectiveness

The ERG suggested three amendments to the CS2 model base case:

1. applying the costs associated with the recommended dose of pembrolizumab after progression on chemotherapy
2. limiting the utility values used in the model to be no higher than the population norms
3. applying exponential extrapolations to KEYNOTE-025 trial OS K-M data, from both arms of the trial, at 43 weeks

Applying costs for the recommended dose of pembrolizumab following chemotherapy makes costs more relevant to the NHS.

The ERG considers that the amendment to the utility value provides a more accurate, but still optimistic, projection of the likely quality of life of patients with metastatic NSCLC.

In terms of OS, with trial data only available to populate 10% of the model time horizon (20-years), all survival projections, both for treatment with pembrolizumab and for treatment with SOC, are highly speculative. The ERG highlights that evidence from the KEYNOTE-010 trial suggests that the company's base survival projection for patients receiving SOC may be pessimistic. This casts doubt not only on the ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC, but also on whether pembrolizumab should be considered as an end of life treatment.

7 REFERENCES

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8 APPENDICES

Appendix 1 ERG Revisions to the CS2 company model

ERG Section 6 results table revision	Implementation instructions
R1. Cost of pembrolizumab in SOC in line with recommended dose	In Sheet 'Regimen Costs UK' Set formula in cell c125= (J22*2*'Model Inputs'!E21*(1-s.PAS.Before.Pembro))/3
R2. Utility value for >360 days to death set to population norm	In Sheet 'utility inputs' Set value in cell D15=0.79 Set value in cell E15=0.79
R3. OS extrapolation at 43 weeks for pembrolizumab and SOC	In Sheet 'Model Settings' Set value in Drop Down 40="Week 43"

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447)

You are asked to check the ERG report from Liverpool Reviews and Implementation Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 16 January 2018** 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 Confidential information

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Information has been reported in the ERG report that should be identified as ACiC, including:	For the following: ▪ Page 7, Table 2; Page 8 paragraph 1; Page 13, section 4.1; page 15, 1st and 2nd paragraphs; page 16, section 4.2.2, 1st paragraph; page 17, section 4.2.2,	This information was either identified as ACiC in the submitted documents or reported as ACiC updated clinical data in the cost-	As requested, confidentiality marking changes made to the ERG report, except that all cost and cost effectiveness numbers identified in the

▪ Page 7, Table 2, rows 20 and 22 OS rate at 12 months (Final analysis data) pembrolizumab arm xxxxx; SOC arm xxxxx OS rate at 24 months (Final analysis data) pembrolizumab arm xxxxx SOC arm xxxxx ▪ Page 8, paragraph 1 '…median PFS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, xxxx months versus xxxx months.' ▪ Page 13, section 4.1: "Two thirds of patients in this arm (xxxx) received immunotherapy (xxxx pembrolizumab and xxxx other immunotherapies). In the CS2 model, it is assumed that xxxx of patients receive pembrolizumab and the remaining xxxx of patients receive docetaxel. ▪ Page 15, Figure 1 The K-M curve of the OS data for the SOC arm in the KN024 trial, by treatment switching, was provided as ACiC and should be highlighted yellow to mark as such in the ERG report.	2nd paragraph; page 17, section 4.2.2, 3rd paragraph; page 19, 2nd paragraph**Error! Bookmark not defined.**; page 19, 3rd paragraph; page 21, section 4.3; page 22, 2nd paragraph the proposed amendments have been already reported under the field 'Description of problem'. For the following: ▪ Page 15, Figure 1; page 18, Figure 2 and Figure 3; page 20, Figure 4 and Figure 5; page 21, Figure 6 the figures should be reported as ACiC and redacted from any documents made publically available (including this document).	effectiveness model and not identified by the ERG as ACiC.	company's description of the problem (issue 1) have been marked as CIC rather than AIC

▪ Page 15, 1st paragraph: "The K-M data from the SOC arm of the KEYNOTE-024 trial show that xxxx patients who did not receive immunotherapy on disease progression died within 6 months of enrolment into the trial compared to xxxx of SOC arm patients who received immunotherapy. xxxx xxxx xxxx receiving pembrolizumab in the SOC arm had died within the first 12 weeks of the trial compared to xxxxx of SOC arm patients who did not receive immunotherapy. ▪ Page 15, 2nd paragraph: "The K-M data from the SOC arm of the KEYNOTE-024 trial also show that around xxxx of patients who did not receive immunotherapy following progression were still alive xxxx xxxx xxxx. ▪ Page 16, section 4.2.2, 1st paragraph: "Applying the cost for the recommended dose of pembrolizumab […] reduces the company base case discounted costs for patients receiving SOC by xxxxxx to xxxxxxx per patient, and increases the ICER for the comparison of pembrolizumab			

versus SOC to xxxxxxx per QALY gained. ▪ Page 17, section 4.2.2, 2nd paragraph: "Adjusting the company base case […] increases the ICER for this comparison to xxxxxx per QALY gained. ▪ Page 17, section 4.2.2, 3rd paragraph: "The effect on the company base case of using the Nafees utility values is to reduce the difference in QALYs for patients treated with pembrolizumab versus SOC by 0.16 QALYs and increases the ICER for this comparison to xxxxxx per QALY gained. ▪ Page 18 Figure 2 and Figure 3 The parametric distributions considered to extrapolate KEYNOTE 024 OS data in both the pembrolizumab and SOC arms should be highlighted yellow to mark as ACiC in the ERG report. ▪ Page 19, 2nd paragraph: "[…]the ICER for the comparison of the cost effectiveness of pembrolizumab versus SOC varies between xxxxxx per QALY gained			

when a generalised-gamma distribution is used to xxxxxx per QALY gained when a Weibull distribution is used. *(PLEASE NOTE: an additional modification is suggested for this sentence, due to a factual inaccuracy, which is reported in Issue 9 below. We have identified here the places where confidential information should be appropriately identified without accounting for the additional modifications required to eliminate factual inaccuracies here.)* ▪ Page 19, 3rd paragraph: "Assuming that the immunotherapies received by the xxxx of patients in the KEYNOTE-024 trial were all as effective as pembrolizumab in the KEYNOTE-010 trial, […]" ▪ Page 20, Figure 4 and Figure 5 The OS with K-M exponential extrapolation curves at 33 weeks and 23 weeks should be highlighted yellow to mark as ACiC in the ERG report ▪ Page 21, Figure 6 The OS with K-M exponential extrapolation curves at 43 weeks			

should be highlighted yellow to mark as ACiC in the ERG report. ▪ Page 21, section 4.3: "In the company CS2 base case, pembrolizumab was estimated to generate an additional 0.96 QALYs at an additional cost of xxxxxx compared to SOC (where SOC involves xxxx of patients receiving immunotherapy following disease progression), with an ICER for the comparison of the cost effectiveness of pembrolizumab versus SOC of xxxxxx per QALY gained." ▪ Page 22, 2nd paragraph: "Compared to the values generated by the company base case, the ERG's alternative scenario, which involves apply all three amendments, increase the incremental costs of treatment with pembrolizumab by xxxxxx per patient and reduces the incremental QALYs by 0.15. These changes increase the size of the company base case ICER from xxxxxx to £xxxxxxper QALY gained.			

Issue 2 Confidential information (2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 14, Table 6 Page 23, Table 7 The ERG is presenting the incremental costs and cost-effectiveness ratios at list price and as non-confidential data, when these should be identified as Commercial in Confidence (CiC).	It is our preference that costs and ICERs for pembrolizumab are presented, as part of the ERG report, including the proposed discount since these can be presented as non-confidential information. If the ERG decides to report ICERs at list price for pembrolizumab, all corresponding costs and ICERs within the tables should be presented in the report as CiC.	We have previously presented, in the original submission, ICERs with the proposed discounts as non-confidential information. Therefore, ICERs at list price are sensitive information and should be considered as CiC.	As suggested, CiC marking applied within the ERG report (including Table 7)

Issue 3 Factual inaccuracy (1) – PD-L1 testing

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 3, Section 2.1, sub-heading 'Direct Evidence', 6th bullet point ERG contends that 'testing for PD-L1 expression was not routinely available in NHS treatment centres' during its original TA447 report and that this issue remains valid. We contend that this is factually inaccurate as PD-L1 testing is now routinely available in the NHS.	Suggest bullet point should be removed	Inaccurate representation of current situation relating to PD-L1 testing within the NHS	The ERG does not consider this to be a factual inaccuracy. The detail in Section 2.1, as is clear from the section title, is a summary of the ERG review of CS1. No changes have been made to the ERG report

Issue 4 Factual inaccuracy (2) – Total events in KEYNOTE-024 as basis for OS extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 4, Section 2.1, Sub-heading 'Cost-effectiveness evidence', Point 1 The ERG states that: "1. any extrapolation of overall survival (OS) data from patients in the pembrolizumab arm of the KEYNOTE-024 trial was highly uncertain due to only 35.4% of the total events having occurred" This statement implies that the 35.4% total events remains applicable; this is not the case as in the final analysis of the KEYNOTE-024 data presented in CS2, xxxx events (xxxx% of the total events) had occurred.	Suggest the sentence should be removed given it has been superseded by the total number of events reported in the Final Analysis (data cut July 2017) as presented in CS2	This ERG comment has been superseded by the additional events provided in the updated evidence submission with a median follow-up of 25.2 months.[1]	The ERG does not consider this to be a factual inaccuracy. The detail in Section 2.1, as is clear from the section title, is a summary of the ERG review of CS1. No changes have been made to the ERG report

Issue 5 Factual inaccuracy (3) – Median PFS lower range data point

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 7, Table 2, Row 1 PFS (BICR); Median, months (95% CI) Pembrolizumab arm Final analysis	Transcription error should be amended as described under 'Description of problem'	Inaccurate data point presented therefore requires correction	Change requested by the company has been made to the ERG report

95% CI lower range presented as xxx rather than xx as presented in CS2 Table 12, page 35			

Issue 6 Factual inaccuracy (4) – Investigator assessed PFS data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 8, paragraph 1, line 9 The ERG states that 'No updated investigator assessed PFS data were submitted by the company in CS2'. These data were provided in CS2 on Page 36, Table 13 along with the Kaplan Meier curve in Figure 11 on Page 37.	Please remove sentence	Need to correct factual inaccuracy as investigator assessed PFS data were presented in CS2.	As requested, sentence in the ERG report has been deleted

Issue 7 Factual inaccuracy (5) – IPCW analyses p-values

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 11, Table 4, IPCW row 5 p values presented are inaccurately presented as (2-sided) xxxxxx; in CS2, the bootstrap p value was presented with a value of xxxxxx. The bootstrap p values of xxxxxx for the IPCW analyses were presented in Table 9 and Table 10 of CS2. Unfortunately, the	Please correct the p value presented as xxxxx and indicate this is a bootstrap p value (not 2-sided)	Correct factual inaccuracy	As suggested, change made to the ERG report

IPCW bootstrap p-value presented in Table 9 of CS2 was erroneously presented as p=xxxxxx but should have read p=xxxxxx as per the text on page 30, paragraph 5. We apologise for the confusion.			

Issue 8 Minor text correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 16, section 4.2.2, 1st paragraph: The ERG states that: ▪ "However, it is stated within the[8] issued by the European Medicines Agency that the recommended dose […]"	"However, it is stated within the **SmPC**[8] issued by the European Medicines Agency that the recommended dose […]"	To correct for one word missing in the sentence.	Missing word has been added to the sentence in the ERG report

Issue 9 Correction of ICER-related values for different parametric distributions at 33 week cut-off

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 19, 2nd paragraph: The ERG reported that: "Assuming that the same type of distribution is appended to both	"Assuming that the same type of distribution is appended to both the pembrolizumab and SOC OS K-M data at 33 weeks, the ICER for the comparison of the cost effectiveness of pembrolizumab versus SOC varies between	The values reported do not correspond with the actual range of ICER values provided by the model. The actual ICERs per type of distribution are reported below, at list	The ERG does not consider that this is a factual inaccuracy. The company has quoted figures that relate to changing only the

the pembrolizumab and SOC OS K-M data at 33 weeks, the ICER for the comparison of the cost effectiveness of pembrolizumab versus SOC varies between xxxxxx per QALY gained when a generalised-gamma distribution is used to xxxxxx per QALY gained when a Weibull distribution is used.	xxxxxx **per QALY gained when a Gompertz distribution** is used **to** xxxxxx **per QALY gained when an exponential distribution** is used **(at list price for pembrolizumab)**."	price (as initially reported by the ERG in the report): ▪ Exponential: xxxxxx ▪ Weibull: xxxxxx ▪ LogNormal: xxxxxx ▪ LogLogistic: xxxxxx ▪ Gompertz: xxxxxx ▪ Generalised Gamma: xxxxxx Therefore, the actual ICER range across distributions is: xxxxxx to xxxxxx, with the exponential distribution (used in the base case) being the most conservative choice.	pembrolizumab distribution. The figures in the ERG report reflect the ICERs when the same distribution is used for both pembrolizumab and SOC. No changes have been made to the ERG report

Issue 10 OS for patients receiving pembrolizumab after platinum-based chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 19, 3rd paragraph: The ERG states that: "During TA428 the company provided evidence from the KEYNOTE-010 trial that, at 5 years between 11.97% and 26.80% of patients receiving pembrolizumab following chemotherapy would be alive; and at 10 years between 2.46% and 24.72% would still be alive. Assuming that the	The paragraphs should be removed since it is misleading and irrelevant for this appraisal.	The assumption that patients treated in KN024 with pembrolizumab would have a similar response as those in KN10 is inappropriate. It is not possible to make appropriate comparisons between the OS estimates provided in TA428 and those estimated in this updated evidence submission for TA447: ▪ In KEYNOTE-010 trial, which was the main clinical evidence evaluated in	The ERG does not consider that the points made in their report are factually inaccurate. No changes have been made to the ERG report

immunotherapies received by the xxxx of patients in the KEYNOTE-024 trial were all as effective as pembrolizumab in the KEYNOTE-010 trial, it would be expected that, based on the projections provided by the company in their TA428 submission, the CS2 company model projections would show between 7.7 and 17.2% of patients alive at 5 years and between 1.6% and 15.8% alive at 10 years. The CS2 company base case projection suggests 9.1% of patients alive at 5 years (which is within the range previously projected) but the proportion expected to be alive at 10 years is 0.9%, which is much lower than previously estimated. The company's CS2 base case SOC OS projections, therefore, appear pessimistic compared with the company's previous projections." Page 25, sub-heading "Cost effectiveness", 4th paragraph: The ERG states that: "The ERG highlights that evidence from the KEYNOTE-010 trial suggests that the company's base survival projection for patients receiving SOC may be pessimistic. This casts doubt not		TA428, included patients with stage IIIb/IV NSCLC that was PD-L1 positive, and had progressed after platinum-containing doublet chemotherapy or on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours. In total, 9.1% of these patients presented EGFR/ALK mutations ▪ Patients included in KEYNOTE-024 had stage IV disease and no EGFR/ALK mutations, and therefore a poorer prognosis when considered for subsequent therapy after first line. ▪ The OS benefit reported in TA428 was associated to the pembrolizumab treatment arm, where all previously treated patients received pembrolizumab, versus xxxx of patients being treated with pembrolizumab in this first line appraisal after they received platinum-based SOC chemotherapy. Additionally, the ERG is mentioning a 5 and 10-year OS for patients receiving pembrolizumab in	

only on the ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC, but also on whether pembrolizumab should be considered as an end of life treatment.”		second/third line of 26.80% and 24.72%, respectively. The ERG seems to be taking this value out of context, especially by not providing any background information in relation to how relevant this value was for decision making in TA428. The value was derived from a sensitivity analysis that was not deemed relevant for decision making by the committee appraising TA428. Finally, it is unclear how the ERG has estimated the 5 and 10-year OS ranges here reported (i.e. 7.7 and 17.2% of patients alive at 5 years and between 1.6% and 15.8% alive at 10 years). The committee appraising TA428 considered the original modelling projections (using the September 2015 KEYNOTE-010 data and the company’s preferred assumptions), which suggested that 10.3% and 1.2% of patients in the pembrolizumab arm would be alive at 5 years and 10 years, falling to 9.6% and 1.0% respectively when incorporating the	

		March 2016 data submitted during consultation. Consultation comments from clinical experts noted that immunotherapies are expected to maintain their effect for a subgroup of people and that these values appear reasonable from clinical experience. The FAD for TA428 stated that: "the committee heard that the average number of months of life gained with pembrolizumab, as estimated by the company's economic model, is between 21.2 and 22.8 months, compared with 10.4 months with docetaxel. [This accounted for all patients in the pembrolizumab arm having being treated with pembrolizumab after platinum-based chemotherapy, as pointed out above.] It agreed that there is significant uncertainty in the overall survival gain, and that this degree of benefit is likely to be optimistic."	

Issue 11 Rationale for the choice of cut-offs and distributions as part of the updated cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 19, 4th paragraph: The ERG states that:	This sentence should be removed.	We have provided Appendix L, which details the updates conducted in the model in terms of	Page 19: sentence identified by company, and the remainder of the paragraph,

"In addition, the company has not provided any justification for their choice of time-point at which to append any distribution to KEYNOTE-024 trial data."		OS, PFS and ToT, and the rationale for the selection of the most appropriate parametric distribution and cut-off.	have been deleted and replacement text inserted as follows: *The company provided justification for their choice of time point at which to append a distribution to KEYNOTE-024 trial data in Appendix L of CS2. The company identified three points where they considered the slope of the pembrolizumab and SOC K-M data changed (23, 33 and 43 weeks). The company chose to append a distribution at 33 weeks as this approach, which included adjustment for treatment switching, led to an estimated 5% of patients receiving SOC being alive at 5 years, the level of survival that the committee, during AC1, considered plausible (33 weeks). Commencing extrapolation at 43 weeks provides a 5-year OS estimate of 10% for patients receiving SOC. The company considers this to be clinically implausible. In the original ERG report, it was stated that the ERG considered that, based on available registry data, a survival rate of 10% at 5 years for patients receiving SOC was*

Page 21, 1st paragraph: The ERG states that: "The choice of both the distribution used to extrapolate trial data and the time at which the distribution is appended to the K-M data are essentially arbitrary."			*not implausible. The ERG considers that the company's projections generated by appending exponential distributions (the company's base case choice of distribution) to K-M data at 23, 33 and 43 weeks (Figure 4, Figure 5 and Figure 6 respectively) suggest that the closest fit to the trial data (for both arms) occur when distributions are appended at 43 weeks.* Page 21: the ERG does not consider this to be a factual inaccuracy. No changes have been made to the ERG report

[1] Brahmer et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced NSCLC with PD-L1 TPS ≥ 50%. IASLC 18th World Conference on Lung Cancer 2017.

ID1349 CDF review of TA447

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer (CDF review of TA447) ID1349

Confidential until published

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CONTAINS ACADEMIC IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 11 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Not all were considered by the ERG to be factual inaccuracies but some were considered to require minor changes to the text. The pages of the ERG report that have been affected are included in this document. Please note that:

- New text added by the ERG is in *red italics and underlined*.
- Text deleted completely is struck out.
- Unaltered text, which is considered to be of relevant context to that added, amended or deleted (such as headings or sentences preceding or following the added, amended or deleted text), is presented in its original font.
- All other unaltered text is greyed out.

Table 1 Results from the KEYNOTE-024 trial (ITT population)

Endpoint	IA2		Final	
	Pembrolizumab N=154	SOC N=151	Pembrolizumab N=154	SOC N=151
Primary endpoint				
PFS (BICR)				
Median, months (95% CI)	10.3 (6.7 to -)	6.0 (4.2 to 6.2)	[redacted]	[redacted]
HR (95% CI)	0.50 (0.37 to 0.68) p<0.001		[redacted]	
Number of events, n (%)	73 (47.4)	116 (76.8)		
Person months	1000.2	785.6		
Event rate/100 person months	7.3	14.8		
PFS rate at 6 months	62.1%	50.3%		
PFS rate at 12 months (95% CI)	47.7%	15.0%	[redacted]	[redacted]
PFS rate at 18 months (95% CI)	NR	NR	[redacted]	[redacted]
PFS rate at 24 months	NR	NR	[redacted]	[redacted]
Secondary endpoints				
OS				
Median, (months) (95% CI)	Not reached	Not reached	30.0 ([redacted]	14.2 ([redacted]
HR (95% CI)	HR 0.60 (0.41 to 0.89) p=0.005		0.63 (0.47 to 0.86) p=0.002	
Number of events, n (%)	44 (28.6)	64 (42.4)	73 [redacted]	96 [redacted]
Person months	1402	1227.5	[redacted]	[redacted]
Event rate/100 person months	3.1	5.2	[redacted]	[redacted]
OS rate at 6 months	80.2%	72.4%		
OS rate at 12 months (95% CI)	69.9%	54.2%	[redacted]	[redacted]
OS rate at 18 months (95% CI)			[redacted]	[redacted]
OS rate at 24 months (95% CI)			[redacted]	[redacted]
OS rate at 30 months (95% CI)			[redacted]	[redacted]
ORR (BICR)				
Confirmed ORR (95% CI)	44.8% (36.8%to 53%)	27.8% (20.8% to 35.7%)	45.5% (37.4% to 53.7%)	29.8% (22.6 to 37.8)
Difference: pembrolizumab vs SOC (95% CI)	16.6% (6.0% to 27.0%) p=0.0011		14.9% (4.3% to 25.4%) p=0.0031	

BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; IA2=second interim analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; SOC=standard of care
Source: CS1, Table 17, Table 18, Table 25 and CS2, Table 6, Table 7 and Table 8

The PFS results from the final analyses were similar to the results from the IA2 analyses. Using the final data-cut, median PFS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, [redacted] months versus [redacted] months. In the original ERG report, the ERG noted that there appeared to be a difference of 3.1 months in median PFS between the investigator-assessed results and the results reported for BICR-assessed PFS (7.2 months and 10.3 months respectively). Median PFS in the SOC arm appeared to be similar between the two analyses (5.5 months and 6 months). The ERG is uncertain of the reasons for, or the implications of, the 3.1 months difference between the BICR-assessed PFS and investigator-assessed PFS. ~~No updated investigator assessed PFS data were submitted by the company in CS2.~~

Using the IA2 data-cut, median OS was not reached. Using the final data-cut, median OS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, 30 months versus 14.2 months.

The objective response rate (ORR) results from the final data-cut were similar to the results from the IA2 analyses. Using the final data-cut, the ORR was higher for patients in the pembrolizumab arm compared to patients in the SOC arm (45.5% versus 29.8%), with a confirmed difference in ORR of 14.9% (95% CI 4.3% to 25.4%, p=0.0031).

The results of the exploratory outcomes from the KEYNOTE-024 trial are presented in Table 3 and show that 70 patients in the pembrolizumab arm responded to treatment (median time to response 2.1 months; range, 1.4 to 14.5) and that the median duration of response was not reached in the pembrolizumab arm. In the SOC arm, 45 patients responded to treatment (median time to response 2.2 months; range, 1.8 to 10.3) and the median duration of response was 7.1 months. It is unclear why the upper bound of the time to response range for patients in the SOC arm is lower when calculated using the final dataset than it was when calculated using IA2 data (12.2 months [IA2] versus 10.3 months [final]).

Table 2 Summary final OS results adjusted for direct and indirect switching

ITT	0.63	0.47 to 0.86	0.003	0.63	0.47 to 0.86	0.003
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Simplified two-stage (no re-censoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two-stage (with re-censoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; HR=hazard ratio; IPCW=inverse probability of censoring weighted; ITT=intention to treat; RPSFT=rank preserving structural failure time; SOC=standard of care
* p-value retained from the ITT analysis based on distribution of the test statistic under the null hypothesis of no treatment effect
** This is a bootstrap p-value (not 2-sided)
Source: CS2, Table 9 and Table 10

1.1 Indirect and mixed treatment comparisons

The company offered to update the indirect and mixed treatment comparisons (ITCs and MTCs) that were presented in CS1. However, as new evidence that would ameliorate the concerns expressed in the original ERG report have yet to become available, during the clarification telephone conference, the company, the NICE team and the ERG agreed that updated ITC and MTC results would not be useful to decision-makers.

1.2 Health-related quality of life from the KEYNOTE-024 trial

No new health-related quality of life data from the KEYNOTE-024 trial were submitted as part of CS2.

1.3 Adverse events from the KEYNOTE-024 trial

Clinical advice to the ERG is that AEs arising from treatment with immunotherapy (i.e., pembrolizumab) in patients with NSCLC require careful monitoring. The use of immunotherapies such as pembrolizumab has been evaluated for several years in patients with melanoma; however, in comparison to patients with melanoma, patients with NSCLC are older and have higher rates of co-morbidities. Patients may also have greater variation in available social support. Expert advice to the ERG, presented in the TA447 ERG report, is that a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs is needed at treatment centres in the event that pembrolizumab is approved for use in the treatment of NSCLC in the NHS. Current training of senior and junior oncology medical staff as well as specialist nursing staff may be insufficient to recognise

estimate underlines the uncertainties associated with long-term extrapolation of short term data sets and the fact that even a small amount of additional data can alter long-term survival projections.

To generate OS estimates for patients receiving SOC (immunotherapy on disease progression) the company used unadjusted data from the SOC arm of the KEYNOTE-024 trial. Two thirds of patients in this arm ([redacted]) received immunotherapy ([redacted] pembrolizumab and [redacted] other immunotherapies). In the CS2 model, it is assumed that [redacted] of patients receive pembrolizumab and the remaining [redacted] of patients receive docetaxel.

The company has estimated the cost of treatment with pembrolizumab following chemotherapy based on the average number of weeks of treatment received by patients in the SOC arm of the KEYNOTE-024 trial (29.1 weeks). The company's cost of treatment with docetaxel is estimated to be 8.5 weeks. The company state that the source for this assumed length of treatment is TA406 (Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer);[12] however, the rationale for this choice of length of treatment is not provided. Drug and drug administration costs were included in the model as a one-off cost at the time of disease progression.

The company OS estimates (for both patients treated with pembrolizumab and those receiving SOC) were derived by appending exponential distributions to KEYNOTE-024 trial data at three different time points (23, 33 and 43 weeks). The 33-week time point was used in the company base case.

The company's base case results for the comparison of the cost effectiveness of pembrolizumab versus SOC (chemotherapy followed by immunotherapy) are shown in Table 6 (exponential distributions appended to KEYNOTE-024 trial K-M data at 33 weeks). Results generated when exponential distributions are appended to KEYNOTE-024 trial data at 23 and 43 weeks are also provided.

Table 3 Company model results (CS2)

Technologies	Total			Incremental		ICER per QALY gained
	Costs	LYG	QALYs	Costs	QALYs	
Distributions appended to K-M data at 33 weeks (company base case)						
SOC (chemotherapy followed by immunotherapy)	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distributions appended to K-M data at 23 weeks						
SOC (chemotherapy followed by immunotherapy)	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distributions appended to K-M data at 43 weeks						
SOC (chemotherapy followed by immunotherapy)	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; LYG=life year gained; QALY=quality adjusted life year; SOC=standard of care
Source: CS2 model

1.4 ERG critique of the company economic analysis

1.4.1 Data source for standard of care (pembrolizumab following chemotherapy)

The ERG agrees with the company assessment that, in NHS clinical practice, current care for patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC is chemotherapy followed, on disease progression, by immunotherapy. However, there is currently no trial data that directly compares the efficacy of pembrolizumab in patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC who have, with those that have not, received prior chemotherapy. The company has suggested that as patients in the SOC arm of the KEYNOTE-024 trial were permitted to receive pembrolizumab (or another immunotherapy) following disease progression, these data can be considered to represent outcomes for patients receiving current NHS care.

Examination of the OS K-M data from the SOC arm of the KEYNOTE-024 trial (clarification question B1) reveals that OS for the 54.3% of SOC arm patients who received pembrolizumab following disease progression was much better than that of patients who did not (or had not yet received) an immunotherapy (Figure 1).

Figure 1 [redacted]

The K-M data from the SOC arm of the KEYNOTE-024 trial show that [redacted] patients who did not receive immunotherapy on disease progression died within 6 months of enrolment into the trial compared to [redacted] of SOC arm patients who received immunotherapy. [redacted] receiving pembrolizumab in the SOC arm had died within the first 12 weeks of the trial compared to [redacted] of SOC arm patients who did not receive immunotherapy.

All patients in the SOC arm of the KEYNOTE-024 trial were eligible for immunotherapy following confirmed disease progression. The ERG considers that the high early mortality of patients in the SOC arm who did not receive immunotherapy is evidence that these patients died before, or shortly after disease progression and, therefore, never had the opportunity to receive any subsequent therapy (immunotherapy or docetaxel). The K-M data from the SOC arm of the KEYNOTE-024 trial also show that around [redacted] of patients who did not receive immunotherapy following progression were still alive [redacted]. These patients were eligible under the trial protocol to receive immunotherapy on disease progression; however, the reasons why they did not do so are unknown. The ERG considers it plausible that at least some of these patients would commence immunotherapy in the future and the potential OS gain from them doing so is not captured by either the OS K-M data from the KEYNOTE-024 trial or any of the current company OS projections.

In the absence of a direct head-to-head trial data comparing the efficacy of pembrolizumab in patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC who are untreated with those previously treated with chemotherapy, the SOC arm for KEYNOTE-024 is currently the best available evidence for this comparison. However, the ERG considers there is evidence

from within the KEYNOTE-024 data that using OS data from the SOC arm of that trial may underestimate the true survival of patients receiving pembrolizumab after chemotherapy.

1.4.2 Pembrolizumab treatment costs

Within the CS2 model, it is assumed that patients who receive pembrolizumab following chemotherapy are prescribed a fixed dose of 200mg every 3 weeks (Q3W). However, it is stated within the *SmPC*[8] issued by the European Medicines Agency that the recommended dose of pembrolizumab for patients with NSCLC who have previously been treated with chemotherapy is 2mg/kg bodyweight Q3W. Applying the cost for the recommended dose of pembrolizumab in the CS2 model (based upon the mean body weight of patients participating in the KEYNOTE-024 trial) reduces the company base case discounted costs for patients receiving SOC by [redacted] to [redacted] per patient, and increases the ICER for the comparison of pembrolizumab versus SOC to [redacted] per QALY gained.

Within the CS2 model, the cost of pembrolizumab, for those who have received prior chemotherapy, was determined by the mean time that patients in the SOC arm of the KEYNOTE-024 trial received pembrolizumab (29.1 weeks). This cost was applied as a one-off fee at disease progression. Given that data from the KEYNOTE-024 trial show that the mean length of time that patients randomised to receive SOC received pembrolizumab following disease progression was 6 months; and the mean time to treatment commencement following disease progression for these patients was 7 weeks, use of discounting in the model would be expected to slightly reduce the total cost of pembrolizumab treatment for these patients. The ERG, therefore, considers that the company's approach to costing treatment with pembrolizumab in patients previously receiving SOC is likely to overestimate the true discounted cost of this treatment. Generating a more accurate cost of treatment would require structural changes to the model that are beyond the remit of the ERG.

1.4.3 Limiting utility values to age-related population norms

In the TA447 ERG report, the ERG highlighted that the utility values in the company model seemed implausibly high for patients with metastatic NSCLC. The utility value in the CS1 and CS2 models for patients who were over 360 days from death was [redacted]. The age-related norm for people aged 65 (the age of the population at model time zero) is 0.79.[13] The ERG made the conservative suggestion that the values used in the company model should be no higher than the age-related population norms. This assumption was accepted by the NICE Appraisal Committee.

The company has undertaken a literature review (CS2, p86-90) and used results from this review to justify using a utility value of [redacted] at 360 days before death in the CS2 model. The

ERG considers that results from the company literature review do not strongly support the use of this value as the cited studies either involved patients at slightly different disease stages, were undertaken in countries other than the UK, or involved small numbers of patients. The ERG, therefore, considers that it is appropriate to still limit utility values in the model to be no higher than the age-related population norms.

Adjusting the company base case by model by limiting the utility value to the age-related population norms reduces the difference in QALYs for patients treated with pembrolizumab versus SOC by 0.02 QALYs and increases the ICER for this comparison to [redacted] per QALY gained.

In the TA447 ERG report, the ERG highlighted that alternative (much lower) values for utilities to those used by the company have been used in previous NICE STAs. The ERG has carried out an exploratory analysis involving using utility values reported by Nafees[14] (0.673 for >180 days from death and 0.473 for <180 days from death). The effect on the company base case of using the Nafees utility values is to reduce the difference in QALYs for patients treated with pembrolizumab versus SOC by 0.16 QALYs and increases the ICER for this comparison to [redacted] per QALY gained.

As a point of clarification, the company states in CS2 (p90) 'Additionally and importantly, the NICE reference case stipulates the use of utility values directly derived from the patients.' The ERG highlights that the actual wording of the NICE Reference Case is '…health states drawn from patients directly with societal valuation of these health states.'

1.4.4 Extrapolation of KEYNOTE-024 trial OS data

Within the CS2 model, the company has estimated OS, both for patients initially receiving pembrolizumab and those initially receiving SOC, by appending a variety of parametric distributions to KEYNOTE-024 trial OS K-M data at different time points (23, 33 and 43 weeks). In the TA447 ERG report, the ERG explained that they considered that there was little evidence to support any particular method of extrapolating available trial data. Whilst CS2 includes 6 months more K-M data than CS1, data are still only available for approximately 10% of the model time horizon. The difficulty in choosing the most appropriate curve to use to extrapolate trial data is illustrated by the range of potential distributions considered by the company (see Figure 2 and Figure 3).

Figure 2

Figure 3

Visual examination of the various distributions considered by the company to extrapolate KEYNOTE-024 trial pembrolizumab OS data suggest that the company's choice, in their base

case, to use an exponential distribution is the joint most pessimistic option; with the projection generated by their Weibull distribution being essentially equivalent to that generated by their exponential distribution. The company also chose, in their base case, to use an exponential distribution to extrapolate KEYNOTE-024 trial SOC OS data. The exponential distribution is also the most pessimistic of the considered options for extrapolating SOC arm data and leads to a substantially more pessimistic projection than any of the other distributions considered by the company.

Assuming that the same type of distribution is appended to both the pembrolizumab and SOC OS K-M data at 33 weeks, the ICER for the comparison of the cost effectiveness of pembrolizumab versus SOC varies between [redacted] per QALY gained when a generalised-gamma distribution is used to [redacted] per QALY gained when a Weibull distribution is used. The choice of distribution makes a substantial difference to the cost effectiveness of pembrolizumab versus SOC and highlights the uncertainty inherent in the long-term extrapolation of short-term trial data.

During TA428 the company provided evidence from the KEYNOTE-010 trial that, at 5 years between 11.97% and 26.80% of patients receiving pembrolizumab following chemotherapy would be alive; and at 10 years between 2.46% and 24.72% would still be alive. Assuming that the immunotherapies received by the [redacted] of patients in the KEYNOTE-024 trial were all as effective as pembrolizumab in the KEYNOTE-010 trial, it would be expected that, based on the projections provided by the company in their TA428 submission, the CS2 company model projections would show between 7.7 and 17.2% of patients alive at 5 years and between 1.6% and 15.8% alive at 10 years. The CS2 company base case projection suggests 9.1% of patients alive at 5 years (which is within the range previously projected) but the proportion expected to be alive at 10 years is 0.9%, which is much lower than previously estimated. The company's CS2 base case SOC OS projections, therefore, appear pessimistic compared with the company's previous projections.

~~In addition, the company has not provided any justification for their choice of time-point at which to append any distribution to KEYNOTE-024 trial data. Visual examination of the company's projections generated by appending exponential distributions (the company's base case choice of distribution) to K-M data at 23, 33 and 43 weeks (Figure 4, Figure 5 and Figure 6 respectively) suggests that the closest fit to the trial data occurs when distributions are appended at 43 weeks. There is still an indication from the end of the K-M data (albeit the data becomes heavily censored from week 100) that as this approach generates estimates of 9.6% of patients alive at 5 years and 1.5% alive at 10 years this extrapolation may still underestimate the long-term survival of patients receiving SOC.~~

The company provided justification for their choice of time point at which to append a distribution to KEYNOTE-024 trial data in Appendix L of CS2. The company identified three points where they considered the slope of the pembrolizumab and SOC K-M data changed (23, 33 and 43 weeks). The company chose to append a distribution at 33 weeks as this approach, which included adjustment for treatment switching, led to an estimated 5% of patients receiving SOC being alive at 5 years, the level of survival that the committee, during AC1, considered plausible (33 weeks). Commencing extrapolation at 43 weeks provides a 5-year OS estimate of 10% for patients receiving SOC. The company considers this to be clinically implausible. In the original ERG report, it was stated that the ERG considered that, based on available registry data, a survival rate of 10% at 5 years for patients receiving SOC was not implausible. The ERG considers that the company's projections generated by appending exponential distributions (the company's base case choice of distribution) to K-M data at 23, 33 and 43 weeks (Figure 4, Figure 5 and Figure 6 respectively) suggest that the closest fit to the trial data (for both arms) occur when distributions are appended at 43 weeks.

Figure 4

Figure 5

Figure 6

The choice of both the distribution used to extrapolate trial data and the time at which the distribution is appended to the K-M data are essentially arbitrary. However, the ERG considers that the distributions that, visually, best fit the data from both arms of the KEYNOTE-024 trial are exponential distributions appended at 43 weeks. The long-term accuracy of the projections for patients in both arms of the trial are, however, unknown.

1.4.5 Treatment stopping at two years

Within the TA447 ERG report, the ERG suggested that some patients may receive pembrolizumab for longer than 2 years, both in the trial and in a real-world setting. As part of the clarification process, the company provided time on treatment data for patients in the KEYNOTE-024 trial who received pembrolizumab (clarification question B1). These data showed (with censoring) that all but one patient had stopped receiving pembrolizumab within 110 weeks (just over two years). However, as there is still only 2 years of follow-up data from the KEYNOTE-024 trial the impact, if any, on the long-term survival of patients who stopped pembrolizumab at 2 years for reasons unrelated to disease status is unclear.

1.5 Impact of ERG amendments on cost effectiveness

In the company CS2 base case, pembrolizumab was estimated to generate an additional 0.96 QALYs at an additional cost of [redacted] compared to SOC (where SOC involves [redacted] of patients receiving immunotherapy following disease progression), with an ICER for the

comparison of the cost effectiveness of pembrolizumab versus SOC of [redacted] per QALY gained.

The ERG has suggested three amendments to the company CS2 model:

1. applying costs associated with the recommended dose of pembrolizumab after progression on chemotherapy
2. limiting the utility values used in the model to be no higher than the population norm
3. applying exponential extrapolations to KEYNOTE-025 OS K-M data from both arms of the trial at 43 weeks.

The impact of the ERG's three amendments on the costs and QALYs of treatment with pembrolizumab and on the ICER per QALY gained are shown in Table 7. Compared to the values generated by the company base case, the ERG's alternative scenario, which involves apply all three amendments, increase the incremental costs of treatment with pembrolizumab by [redacted] per patient and reduces the incremental QALYs by 0.15. These changes increase the size of the company base case ICER from [redacted] to [redacted] per QALY gained.

Details of the revisions made by the ERG to the company CS2 model can be found in Appendix 1

Table 4 ERG adjustments to company base case: pembrolizumab versus SOC (discounted, list prices)

Scenario/ERG amendment	Pembrolizumab			SOC			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]										
R1) Cost of pembrolizumab in SOC in line with recommended dose	[redacted]										
R2) Utility value for >360 days to death set to population norm	[redacted]										
R3) OS extrapolation at 43 weeks for pembrolizumab and SOC	[redacted]										
B. ERG alternative scenario (R1-R3)	[redacted]										

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