NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

The Evidence Review Group appendices discussing the confidential comparator commercial agreement in this appraisal are completely confidential and have therefore not been included in these papers.

Contains AIC ,CIC

Pre-meeting briefing

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

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.

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

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

Common abbreviations			
AE	Adverse event	K-M	Kaplan-Meier
AIC	Akaike information criterion	LS	Least squares
ALK	Anaplastic lymphoma kinase	LYG	Life years gained
ASaT	All subjects as treated	NMA	Network meta-analysis
BIC	Bayesian information criterion	NSCLC	Non-small cell lung cancer
BICR	Blinded independent central review	ORR	Objective response rate
CAA	Commercial access agreement	OS	Overall survival
CDF	Cancer Drugs Fund	PAS	Patient access agreement
CHMP	Committee for Medicinal Products for Human Use	PD	Progressed disease
CR	Complete response	PD-L1/2	Programmed death-ligand 1/2
CS	Company submission	PFS	Progression-free survival
CSR	Clinical study report	PH	Proportional hazards
DCR	Disease control rate	PR	Partial response
EAMS	Early Access to Medicines Scheme	PS	Performance score
ECOG	Eastern Cooperative Oncology Group	PSA	Probabilistic sensitivity analysis
EGFR	Epidermal growth factor receptor	PSS	Personal and Social Services
EMA	European Medicines Agency	Q3W	Every 2 weeks
EORTC	European Organisation for the Treatment of Cancer	QALY	Quality adjusted life year
EQ-5D	European Quality of Life - 5 Dimensions Questionnaire	QLQ	Quality of life questionnaire
ERG	Evidence Review Group	RCT	Randomised controlled trial
FAS	Full analysis set	RECIST	Response Evaluation Criteria In Solid Tumors
HR	Hazard ratio	RPSFT	Rank preserving structural failure time
HRQoL	Health-related quality of life	RR	Response rate
iA1	First interim analysis	sd	Standard deviation
IA2	Second interim analysis	SD	Stable disease
ICER	Incremental cost effectiveness ratio	SAE	Serious adverse event
IHC	Immunohistochemistry	SmPC	Summary of product characteristics
IPCW	Inverse Probability of Censoring Weighting	SOC	Standard of care
ITT	Intention-to-treat	TK	Tyrosine kinase
KEYNOTE-024	Key trial that informs the clinical effectiveness and cost effectiveness evidence	TPS	Tumour proportion score

Disease background & management

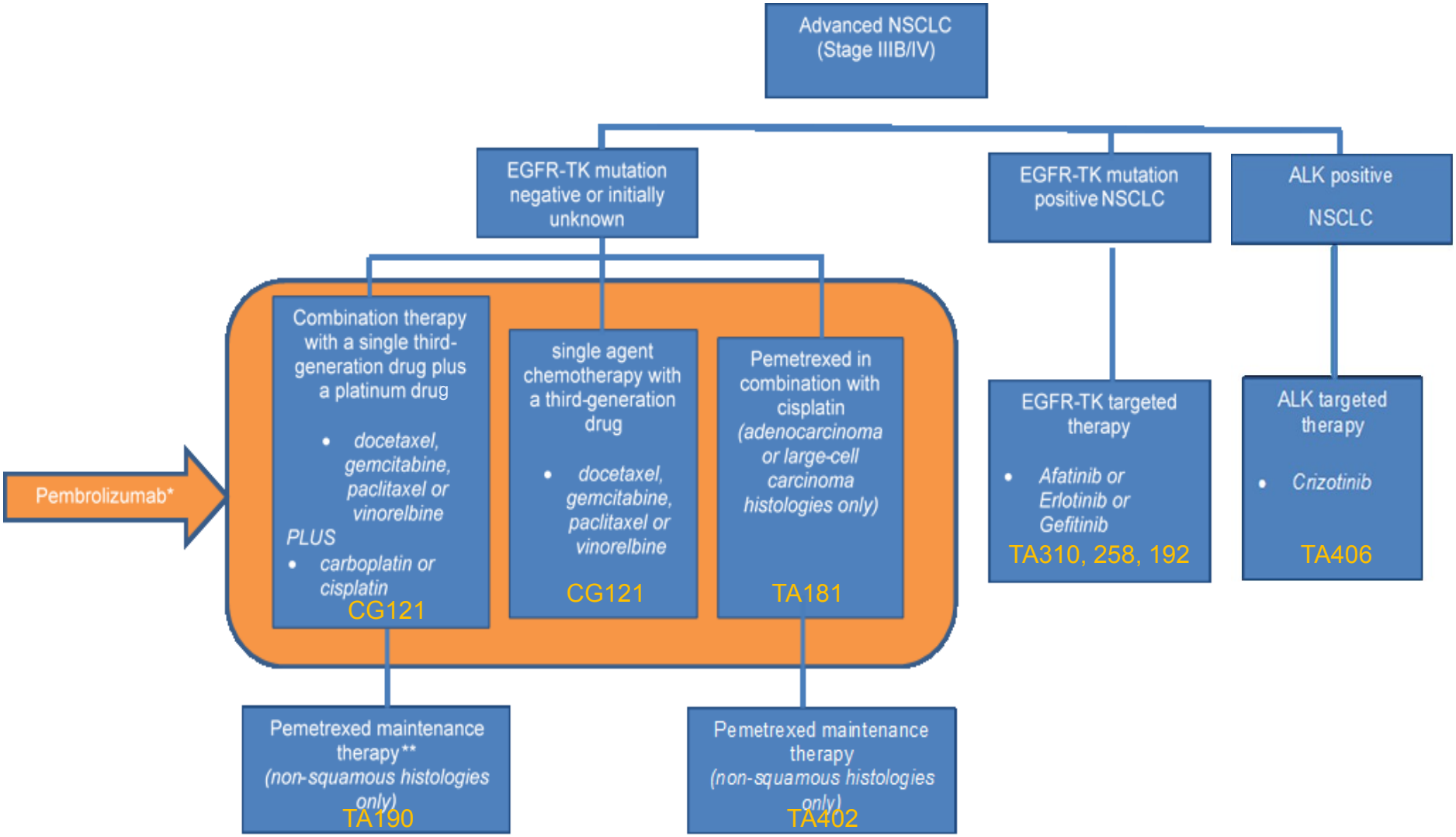
- In the UK, more than 45,000 people are diagnosed with lung cancer and over 35,000 people die from the condition each year. NSCLC accounts for up to 85 to 90% of lung cancer cases.
- More than half of people with NSCLC present with incurable advanced local or metastatic disease at the time of diagnosis
  - Estimated 5-year survival rate of around 10%
- 2 major histological subtypes
  - Squamous cell carcinoma (25 to 30% of diagnoses)
  - Non-squamous cell carcinoma
    - Adenocarcinoma (30 to 40%)
    - Large-cell carcinoma (10 to 15%)
    - Other cell types (5%)
- Management for untreated mutation negative NSCLC is platinum based chemotherapy (CG121) or pemetrexed & cisplatin (TA181)
- Targeted therapy is a growing part of cancer regimens
  - Between 23 and 28% of people with advanced NSCLC have tumours which strongly express PD-L1 (tumour proportion score [TPS] ≥50%)

DETAILS OF THE TECHNOLOGY

Technology	Pembrolizumab (KEYTRUDA)
Proposed marketing authorisation	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
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 [redacted]
Acquisition cost	100 mg vial: • List price: £2,630 per 100 mg vial • PAS price: [redacted] per 100 mg vial [redacted]
Cost of a course of treatment	Average time on treatment: 6.76 months (equivalent to 9.80 cycles) based on KEYNOTE-024: • Average cost of a course of treatment at list price: £51,548 (9.8 * 5,260) • PAS price: [redacted]

- The company estimates that in England, approximately 1500 patients per year would be eligible for treatment with pembrolizumab (Source: Company submission, p234)
- The ERG considers this estimate to be reasonable

Treatment pathway



** People with advanced NSCLC 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)*

Source: Company submission, figure 3 (p38)

Patients and carers comments

Roy Castle Lung Cancer Foundation

- *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 is currently the first line therapy option.*

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

- *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.*

- *… 'end of life' considerations are very important to this patient group…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*

- *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.*

Clinical expert comments

- Submissions from: x2 clinical experts

- *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, it is generally much better tolerated than the current standards.*

- *Currently PDL-1 testing is in progress to support the EAMS. If the treatment were approved by NICE, the amount of testing would need to be scaled up. Around seven centers are currently testing in England and Wales. These centres may be able to cope with the increased demand or a small number of additional centers could be commissioned. New centers would need personnel to be trained in reporting the PDL-1 test. A training scheme is also in place.*

NHS England comments

- *…there are no substantial issues as to generalisability of the trial data into clinical practice in England as long as patients receiving pembrolizumab are of performance status 0 or 1 and have at least 50% PD-L1 expression. If NICE recommends this indication, NHE England would ensure that treating clinicians will have to certify the performance status of the patient (0 or 1) at the time of registration of seeking funding and also state the result of the PD-L1 expression test*.
- *The evidence base for 1st line use is founded on a trial design which capped the treatment duration at 2 years and hence NHSE will institute a treatment cap at 2 years on the basis of implementing evidenced-based practice. In addition, if NICE recommends pembrolizumab in this indication and its assessment of cost effectiveness is also based on a maximum of 2 years treatment, that will also be the foundation for NHSE's commissioning position in that if Trusts continue treatment beyond 2 years for individual patients, NHSE will not reimburse Trusts for this non-commissioned use of drug.*
- *…in drugs such as pembrolizumab/nivolumab, when benefits to patients occur when there is sufficient recruitment of the immune system against the cancer, that this recruitment of the immune system and consequent patient benefit may not require continued treatment until disease progression*
- *...the potentially eligible population for 1st line pembrolizumab is large, being about 1500 patients/year.*

COMPANY'S DECISION PROBLEM & DEVIATIONS FROM FINAL SCOPE (1)

	Final NICE scope	Company submission	Rationale	ERG comments
Population	People with PD-L1 positive metastatic non-small-cell lung cancer (NSCLC) not treated with chemotherapy in the metastatic setting	Patients with stage IV NSCLC lacking EGFR and/or ALK mutation; whose tumours express PD-LI (TPS ≥ 50%), with no prior systemic chemotherapy treatment	In line with the KEYNOTE-024 trial population and the anticipated licence.	Matches the population in the KEYNOTE-024 trial & in line with anticipated marketing authorisation. No clinical effectiveness evidence for patients with untreated metastatic NSCLC with: • a PD-L1 TPS <50% • a PD-L1 TPS ≥50% whose tumours also test positive for EGFR or ALK mutations.
Subgroups	By tumour histology (squamous or non-squamous) and level of PD-L1 expression (strong positive or weak positive)	The following subgroups have been considered: • Tumour histology (squamous or non-squamous) • Comparator therapy regimen (pemetrexed-containing versus non-pemetrexed containing)	The KEYNOTE-024 trial only included patients with TPS ≥ 50% .	The ERG notes that 18% of patients in the KEYNOTE-024 trial were of squamous histology. Clinical advice to the ERG is that in NHS clinical practice, approximately 30% - 40% of patients have squamous disease.
Intervention	Pembrolizumab	Pembrolizumab 200 mg, Q3W	In line with the marketing authorisation.	

COMPANY'S DECISION PROBLEM & DEVIATIONS FROM FINAL SCOPE (2)

	Final NICE scope	Company submission	Rationale	ERG comments
Comparator	1) Platinum doublet chemotherapies (docetaxel, gemcitabine, paclitaxel, vinorelbine) with or without pemetrexed maintenance 2) Platinum doublet pemetrexed (adenocarcinoma or large cell carcinoma only) with or without pemetrexed maintenance 3) Single chemotherapy (docetaxel, gemcitabine, paclitaxel, vinorelbine); if platinum combination therapy not appropriate.	1) KEYNOTE-024 trial: Pembrolizumab (PMB) vs. 'standard of care' (SOC): platinum doublet chemotherapy (gemcitabine or paclitaxel, or (for non-squamous NSCLC) platinum doublet pemetrexed. Indirect evidence (NMA): PMB vs. platinum doublet chemotherapies (docetaxel, gemcitabine, paclitaxel, vinorelbine). 2) Subgroup analysis of KEYNOTE-24 trial: PMB vs. pemetrexed-containing and non-pemetrexed-containing SOC. Indirect evidence (NMA): PMB vs. platinum doublet pemetrexed (non-squamous/adenocarcinoma histology subgroup only). 3) No evidence presented for single agent chemotherapy	1) The SOC chemotherapy regimens in KEYNOTE-024 are reflective of current clinical practice in England. 1&2) Comparisons with a specific chemotherapy included in NMA. 3) No evidence available.	1) The ERG agrees that analysis by the individual treatments in the KEYNOTE-024 trial would be uninformative due to small numbers for each treatment. The NMA compared a population of patients whose tumours strongly express PD-L1 with a population of patients whose PD-L1 status is unknown. 3) Clinical advice to the ERG is that single agent docetaxel is predominantly used as second-line chemotherapy rather than as a first-line therapy. Approximately 15% of NCSLC patients treated with single chemotherapy first-line.

COMPANY'S DECISION PROBLEM & DEVIATIONS FROM FINAL SCOPE (3)

	Final NICE scope	Company submission	ERG comments
Outcome	• overall survival (OS) • progression-free survival (PFS) • response rates (RRs) • adverse effects (AEs) of treatment • health-related quality of life (HRQoL)	In line with the final scope.	Because of the immaturity of the data in KEYNOTE-24 (only 35% of the expected OS events had occurred and median OS had not been reached in either arm), combined with patient crossover (43.7% of patients switched from SOC to pembrolizumab), the true effect of pembrolizumab on OS is difficult to ascertain.
Economic analysis	The time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The use of pembrolizumab is conditional on the presence of 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	In line with the final scope. The time horizon considered is 20 years. Costs are considered from an NHS and PSS perspective. The company's economic model includes the costs associated with testing strategies to identify patients with PD-L1 expressing tumours	

Clinical effectiveness evidence

Company submission section 4

Clinical evidence for pembrolizumab: KEYNOTE-024 (1)

Clinical evidence supporting the use of pembrolizumab as a treatment for adult patients with was presented from a single phase III RCT KEYNOTE-024

Trial design	Open label, phase III RCT; n=305 with 1:1 randomisation based on geography (East Asia/non-East Asia), ECOG (0/1), histology (squamous/non-squamous) 149 sites in 16 countries including 8 UK sites; n=21
Intervention (n=154)	Pembrolizumab 200 mg, i.v., Q3W
Comparator (n=151)	Standard of care comprised of one of the following: • Pemetrexed 500 mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (non-squamous histologies only) • Pemetrexed 500 mg/m^2 Q3W and cisplatin 75 mg/m^2 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (for non-squamous histologies only) • Gemcitabine 1250 mg/m^2 days 1 and 8 and cisplatin 75 mg/m^2 day 1 Q3W for 4-6 cycles • Gemcitabine 1250 mg/m^2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles • Paclitaxel 200 mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q 3W for 4-6 cycles followed by optional pemetrexed maintenance (pemetrexed maintenance for non-squamous histologies only)
Population	• Histologically or cytologically confirmed diagnosis of NSCLC, is stage IV, does not have an EGFR sensitizing (activating) mutation or ALK translocation, and has not received prior systemic chemotherapy treatment for their metastatic PD-L1 strong tumour as determined by IH at a central laboratory.(i.e. Tumour Proportion Score ≥50%) • Measurable disease (based on RECIST 1.1) as determined by the site • ECOG Performance status of 0 or 1

Clinical evidence for pembrolizumab: KEYNOTE-024 (2)

Study duration	Treatment on study continued until one of the following: • Disease progression (according to RECIST 1.1) • Unacceptable adverse event(s) • Intercurrent illness that prevented further administration of treatment • Investigator's decision to withdraw the subject • Noncompliance with trial treatment or procedures requirements • Subject had received 35 treatments of study medication (pembrolizumab arm only) • Administrative reasons Subjects randomised to the control arm who had documented progression of disease could crossover to pembrolizumab. Treatment was limited to 35 administrations of pembrolizumab Final PFS analysis was planned at 20 months from the start of the study Final OS analysis was planned at 28 months from the start of the study
Outcomes (ITT population)	Primary: Progression-free survival (based on RECIST 1.1) assessed by blinded independent central radiologist review Secondary: Safety and tolerability; overall survival; overall response rate
Pre-planned subgroups	• Age category (≤65, >65 years) • Sex (female, male) • Race (white, non-white) • ECOG status (0, 1) • Geographic region of enrolling site (East Asia, non-East Asia) • Histology (squamous, non-squamous) • Smoking status (never, former, current) • Brain metastasis status (baseline brain metastasis, no baseline brain metastasis) • Investigators' choice of SOC chemotherapy

KEYNOTE-024: Baseline characteristics (ITT population)

	Pembrolizumab (n=154)	Standard of care (n=151)
Male n (%)	92 (59.7)	95 (62.9)
Age, years, mean (SD)	63.9 (10.1)	64.6 (9.5)
ECOG PS n (%)		
0	54 (35.1)	53 (35.1)
1	99 (64.3)	98 (64.9)
2	1 (0.6)	0 (0)
Cancer stage at screening n (%)		
IIIb	1 (0.6)	1 (0.7)
IV	153 (99.4)	150 (99.3)
Geographic region of enrolling site n (%)		
Non-East Asia	133 (86.4)	132 (87.4)
East Asia	21 (13.6)	19 (12.6)
Histology		
Squamous	29 (18.8)	27 (17.9)
Non-squamous	125 (81.2)	124 (82.1)
Smoking status n (%)		
Current	34 (22.1)	31 (20.5)
Former	115 (74.7)	101 (66.9)
Never	5 (3.2)	19 (12.6)
Brain metastasis at baseline n (%)		
Yes	18 (11.7)	10 (6.6)
No	136 (88.3)	141 (93.4)
Baseline tumour size		
Patients with data	151	150
Mean (sd)	90.9 (53.4)	99.7 (63.4)
Prior adjuvant therapy n (%)		
Yes	6 (3.9)	3 (2.0)
No	148 (96.1)	148 (98)
Prior neo-adjuvant therapy n (%)		
Yes	3 (1.9)	1 (0.7)
No	151 (98.8)	150 (99.3)
Source: Adapted from table 15, p76, company submission		

KEYNOTE-024: Chemotherapy regimens in standard of care arm

Chemotherapy regimen	Squamous histology n=27	Non-squamous histology n=123
Carboplatin+gemcitabine	15	5
Cisplatin+gemcitabine	7	4
Carboplatin+paclitaxel	5	12
Carboplatin+pemetrexed with pemetrexed maintenance	NA	28
Carboplatin+pemetrexed without pemetrexed maintenance	NA	38
Cisplatin+pemetrexed with pemetrexed maintenance	NA	18
Cisplatin+pemetrexed without pemetrexed maintenance	NA	18
Number of treatment cycles received		
Median (range)	4 (1 to 6)	4 (1 to 6)
<4 cycles (n)	11	42
4 cycles (n)	3	47
5 cycles (n)	0	7
6 cycles (n)	13	27
Source: Adapted from company submission, figure 7 (p 75)		

ERG critique of KEYNOTE-024 trial

- Agree with company that baseline characteristics are generally well balanced across treatment arms and participants are broadly representative of a population of patients with advanced NSCLC
- However in KEYNOTE-024, only 18% of patients had squamous disease. Clinical advice to the ERG is that in NHS clinical practice, approximately 30% - 40% of patients have squamous disease. The ERG notes that treatment options for patients with non-squamous disease include platinum plus vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed. Treatment options for patients with squamous disease are limited to platinum plus vinorelbine, gemcitabine, docetaxel or paclitaxel
- In clinical practice in the NHS, optimal treatment for patients with non-squamous tumours is platinum plus pemetrexed followed by pemetrexed maintenance treatment. In the KEYNOTE-024 trial, only 37% of the patients with non-squamous tumours were treated with platinum plus pemetrexed followed by pemetrexed maintenance

ERG: KEYNOTE-24 post-trial treatments

- In response to clarification, the company provided details of the post-trial treatments given to patients after disease progression. The information provided did not include the 66 patients from the SOC arm of the KEYNOTE-024 trial who had crossed over to treatment with pembrolizumab
  - Clinical advice to the ERG is that in the NHS, docetaxel monotherapy or docetaxel plus nintedanib is standard of care after disease progression on first-line chemotherapy. The ERG notes that very few patients from the KEYNOTE-024 trial received post-progression treatment with docetaxel and none received post-progression treatment with nintedanib.

KEYNOTE-024: PFS, OS and ORR ITT population

	Endpoint	Pembrolizumab n=154	Standard of care n=151
Primary endpoint	**PFS (BICR)**		
	Median, months (95% CI)	10.3 (6.7 to -)	6.0 (4.2 to 6.2)
	HR (95% CI)	0.50 (0.37 to 0.68) p<0.001	
	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	47.7%	15.0%
Secondary endpoints	**OS**		
	Median (months)	Not reached	Not reached
	HR (95% CI)	HR 0.60 (0.41 to 0.89) p=0.005	
	Number of events n (%)	44 (28.6)	64 (42.4)
	Person months	1402	1227.5
	Event rate/100 person months	3.1	5.2
	OS rate at 6 months	80.2%	72.4%
	OS rate at 12 months	69.9%	54.2%
	ORR (BICR)		
	Confirmed ORR (95% CI)	44.8% (36.8 to 53)	27.8% (20.8 to 35.7)
	Difference in % pembrolizumab compared with standard of care	16.6 (6.0 to 27.0) p=0.0011	

Source: Company submission, tables 17, 18 and 25 (p80, 81 and 93)

Progression-free survival: ITT population Kaplan-Meier

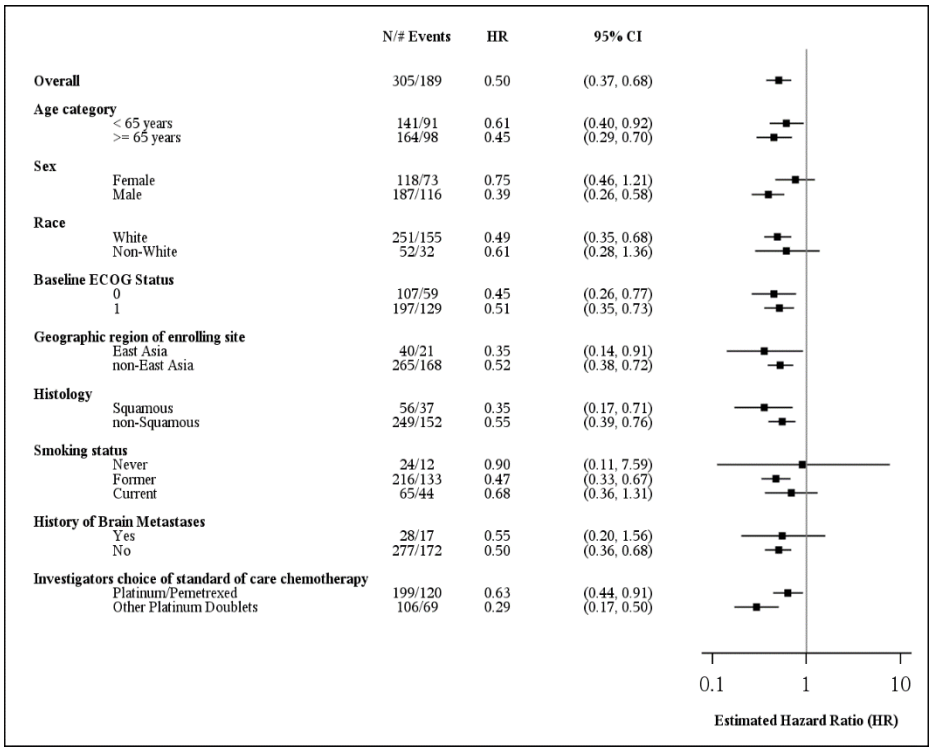
Based on BICR assessment per RECIST 1.1

Pre-meeting briefing document

Summary and subgroups: Progression free survival

- 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

- Pembrolizumab was statistically significantly better compared with SOC for the two subgroups considered in the company submission:

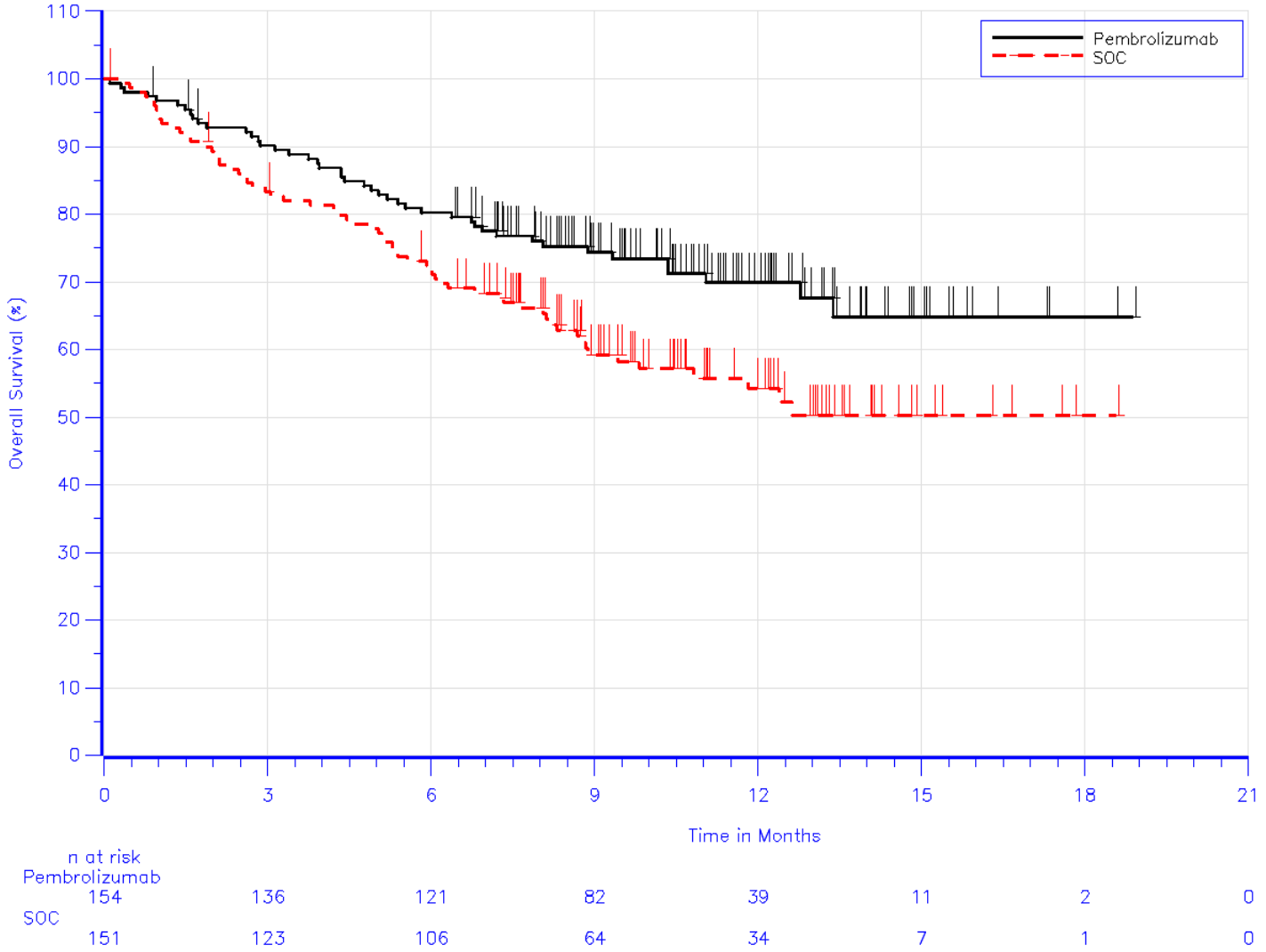


- squamous disease
  HR=0.35; 95% CI 0.17 to 0.71
- non-squamous disease
  HR=0.55; 95% CI 0.39 to 0.76

- platinum+pemetrexed
  HR=0.63; 95% CI 0.44 to 0.91
- non-pemetrexed platinum doublets
  HR=0.29; 95% CI 0.17 to 0.50

Source: Company submission figure 15, p98 (HR according to BICR assessment per RECIST 1.1

Overall survival: ITT population Kaplan-Meier



Subgroup analyses: Overall survival

OS subgroup analysis demonstrated a statistically significant benefit of pembrolizumab over SOC for the two subgroups considered in the company submission:

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

Source: Company submission figure 16, p99

Summary: Overall survival

- 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 of the KEYNOTE-024 trial crossed over to receive pembrolizumab:

Method of OS adjustment	HR (95%CI)
No adjustment	0.60 (0.41; 0.89)
RPSFT	0.57 (0.32; 0.86)
IPCW	0.55 (0.34; 0.87)
2-stage	**0.50 (0.34; 0.76)**

The 2-stage adjustment considered the most appropriate.

- The OS results show that 108 (35.4%) deaths had occurred at the time of the IA2; these events represent 64% of the target number of events at final analysis (170 deaths)
- Median OS had not been reached in either the intervention or the comparator arm
- No one assigned to the pembrolizumab arm had been treated long enough to complete therapy (two years).

ERG critique: Systematic review methods and evidence available

- Satisfied with the systematic review methods
- Although only 1 RCT (KEYNOTE-024) was identified, this is a small, well-conducted, open-label trial
  - The ERG did not identify any additional relevant trials
- The trial Data and Safety Monitoring Committee recommended that the trial should be stopped early for benefit at IA2:
  - At this time, only 35% of the total number of expected OS events had occurred and median OS had not been reached in either of the trial arms
  - The ERG is aware of published evidence that shows that several trials that have been stopped early for benefit have not delivered the anticipated survival gain estimated at the time stopping
- The immaturity of the OS data and the high level of patient crossover (43.7%) limit the reliability of the OS data from the KEYNOTE-024 trial
- The results of the subgroup analyses should be interpreted with caution given the small numbers of patients and the small numbers of events in each subgroup

ERG critique: Cross-over adjustment of OS in KEYNOTE-24 trial

- Agree the 2-stage model was the most appropriate method to adjust for treatment crossover, however the ERG considers that results generated all 3 methods are unreliable
- All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional.
- There is no direct evidence of the clinical effectiveness to allow a comparison of pembrolizumab compared with the individual comparators listed in the final scope issued by NICE

ERG critique: Progression free survival

- The company provided PFS results as assessed by blinded independent central review (BICR), and at clarification also provided the results of an exploratory analysis of PFS based on investigator assessment
- The PFS results for patients in the SOC arm were similar, irrespective of method of assessment. However, the PFS results for patients in the pembrolizumab arm were different

PFS (months)	Pembrolizumab	SOC
BICR	10.3	6
Investigator	[redacted]	[redacted]

- The ERG is uncertain of the reasons for, or the implications of, the [redacted] difference between the BICR-assessed PFS and investigator-assessed PFS results for patients treated with pembrolizumab.

ERG critique: PD-L1 testing

- In the draft SmPC for pembrolizumab, it is stipulated that treatment should be initiated only after a validated laboratory test has confirmed the tumour expression of PD-L1.
- Information is only provided on the binary assessment of the immunohistochemical marker PD-L1. In addition to validation of the test, the ERG considers that further information is likely to emerge on PD-L1 as a continuous predictive biomarker
- Clinical advice to the ERG is that, at present, there is no established or validated test for PD-L1 expression and testing for PD-L1 expression is not routinely available in NHS treatment centres. The ERG notes that, in the NHS, there is currently no standard means of identifying patients whose tumours strongly express PD-L1

KEYNOTE-024 adverse events:

	Pembrolizumab		SOC	
	n	%	n	%
Subjects in population	**154**		**150**	
with one or more adverse events	148	96.1	145	96.7
with no adverse event	6	3.9	5	3.3
with drug-related† adverse events	113	73.4	135	90.0
with toxicity grade 3-5 adverse events	82	53.2	109	72.7
with toxicity grade 3-5 drug-related adverse events	41	26.6	80	53.3
with serious adverse events	68	44.2	66	44.0
with serious drug-related adverse events	33	21.4	31	20.7
who died	9	5.8	7	4.7
who died due to a drug-related adverse event	1	0.6	3	2.0
discontinued‡ due to an adverse event	14	9.1	21	14.0
discontinued due to a drug-related adverse event	11	7.1	16	10.7
discontinued due to a serious adverse event	13	8.4	11	7.3
discontinued due to a serious drug-related adverse event	10	6.5	7	4.7

† 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 was monitored until 90 days after last dose
Source: Adapted from company submission table 41 (p137)

Summary of adverse events (AEs)

- There were comparable numbers of subjects with one or more AEs in the pembrolizumab arm (148, 96.1%) compared to the SOC arm (145, 96.7%).
- Fewer had Grade 3-5 drug-related AEs in the pembrolizumab arm (26.6%) than in the SOC arm (53.3%). SAE in the pembrolizumab and SOC arms (44.2% and 44%, respectively), and drug-related SAEs were comparable in both treatment groups (21% each).
- The most frequently reported drug-related AEs were follows:
  - In the pembrolizumab arm: diarrhoea (14.3%), fatigue (10.4%), and pyrexia (10.4%; approximately double the incidence observed in the SOC arm)
  - In the SOC arm: anaemia (44.0%), nausea, (43.3%), fatigue (28.7%), decreased appetite (26.0%), neutropaenia (22.7%), vomiting (20.0%), diarrhoea (13.3%), neutrophil count decreased (13.3%), platelet count decreased (12.0%), stomatitis (12.0%), constipation (11.3%), thrombocytopaenia (11.3%), white blood cell count decreased (10.7%), dysgeusia (10.0%), and blood creatinine increased (10.0%). The incidence AE listed above with the exception of diarrhoea were more than double the incidence observed in the pembrolizumab arm.
- A total of 35 (23%) subjects (14 [9.1%] in the pembrolizumab arm and 21 [14.0%] in the SOC arm) discontinued due to an AE; of which, 27 (17.8%) discontinued due to a drug-related AE (11 [7.1%] in the pembrolizumab arm and 16 [10.7%] in the SOC arm)
- There were 9 (5.8%) deaths reported in the pembrolizumab arm; of which, 1 (0.6%) death was assessed to be a drug-related SAE. In the SOC arm, 7 (4.7%) deaths were reported and 3 (2%) of these deaths were assessed as drug related SAEs
- The safety profile for SOC was as expected

ERG critique: Safety and monitoring

- The ERG notes that 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. They may also have greater variation in available social support.
- The ERG considers that AEs arising from treatment with immunotherapy (i.e., pembrolizumab) in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related.

KEYNOTE-024: Health-related quality of life

- HRQoL outcomes were measured using the:
  - European Organisation for Research and Treatment Cancer Quality of Life questionnaire (EORTC-QLQ-C30)
  - EORTC Quality of Life questionnaire designed specifically to collect information from patients with lung cancer (EORTC-QLQ-LC13)
  - EuroQoL EQ-5D 3L tool
- Outcomes from all 3 questionnaires favour treatment with pembrolizumab
- The results of the EQ-5D 3L analyses were used in the company's economic model

EQ-5D 3L results at week 15

EQ-5D utility score

	Baseline		Week 15		Change from baseline at week 15	
Treatment	n	Mean (SD)	n	Mean (SD)	n	LS Mean (95% CI)
EQ-5D utility scores						
Pembrolizumab	144	0.72 (0.242)	108	0.80 (0.224)	150	0.05 (0.01 to 0.09)
SOC	137	0.71 (0.214)	92	0.76 (0.184)	147	-0.00 (-0.04 to 0.04)
Pairwise Comparison				Difference in LS means (95% CI)		p-value
Pembrolizumab compared with SOC				0.06 (0.00 to 0.11)		0.036
Source: Company submission, table 28 (p96)						

Visual analogue scale

	Baseline		Week 15		Change from baseline at week 15	
Treatment	n	Mean (SD)	n	Mean (SD)	n	LS mean (95% CI)†
Pembrolizumab	144	68.72 (21.099)	108	75.52 (17.166)	150	4.25 (0.72 to 7.77)
SOC	137	69.71 (19.279)	92	72.73 (17.123)	147	0.39 (-3.33 to 4.11)
Pairwise Comparison				Difference in LS Means (95% CI)		p-value
Pembrolizumab vs. SOC				3.85 (-0.72 to 8.42)		0.098
Source: Company submission, table 29 (p96)						

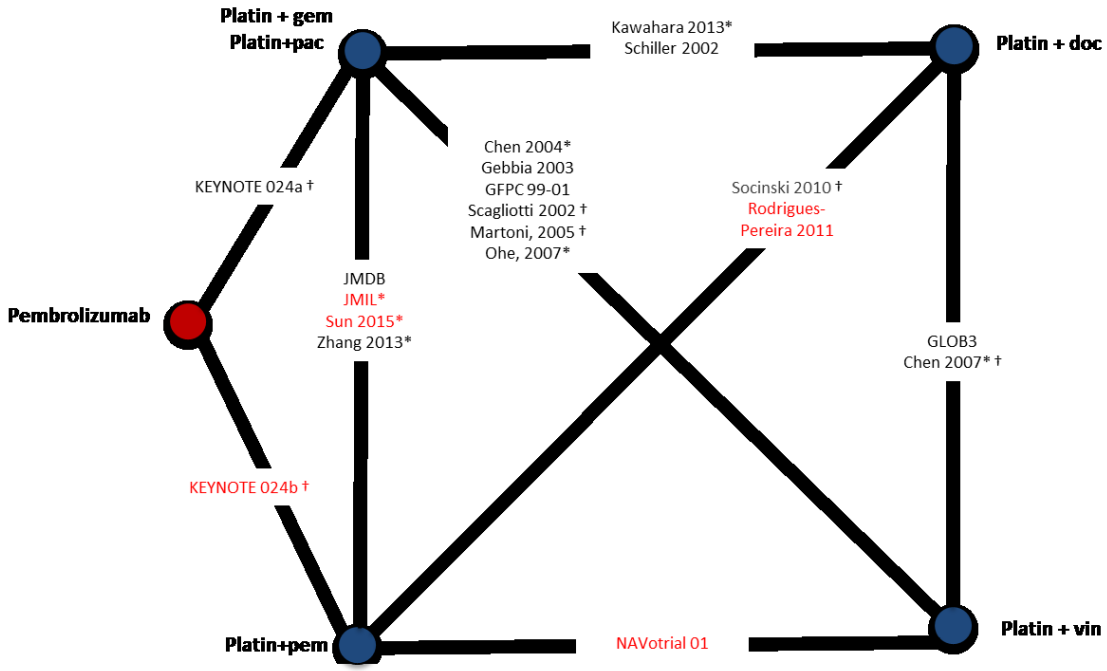
Non-controlled trials: KEYNOTE-001

- F1 cohort of a phase 1 dose escalation study (KEYNOTE-001) of pembrolizumab in patients with NSCLC provides evidence of the longer-term clinical efficacy of pembrolizumab in the treatment of patients with advanced NSCLC (median follow-up duration was 22.2 months [range 17.8 to 30.5 months]):
  - Of the 101 patients with untreated stage IV NSCLC PD-L1 positive tumours enrolled into the F1 cohort study, only 27 (26.7%) had a TPS ≥50%
  - None of the three doses of pembrolizumab administered in the F1 cohort study (2 mg/kg Q3W, 10 mg/kg Q3W or 10 mg/kg Q2W) match the 200 mg Q3W dose in the KEYNOTE-024 study in line with the anticipated marketing authorisation for pembrolizumab
- The ERG:
  - F1 cohort study is of minimal relevance to the company's decision problem given: i) the small number of patients with a TPS of ≥50% and ii) that the doses of pembrolizumab administered.
  - The patient population of the F1 cohort matches the population in the final scope issued by NICE, i.e. patients with PD-L1 positive NSCLC not treated with chemotherapy in the metastatic setting.

Network meta-analyses (NMA)

- The systematic review identified 13 trials comparing the standard of care regimens in KEYNOTE-024 to other interventions of interest and 8 trials comparing non-pemetrexed-containing and pemetrexed-containing KEYNOTE 024 standard of care interventions
- The outcomes of interest were overall survival and progression free-survival (AE and HRQoL were reported inconsistently so were not included in the NMA)
- The population included all patients with advanced or metastatic NSCLC other than those in trials in exclusively EGFR or ALK positive patients.
- With the exception of the KEYNOTE-024 trial, PD-L1 status was not reported in the included trials
- The populations of KEYNOTE-024 considered in the all-comers network were:
  - KEYNOTE-024a: pembrolizumab versus non-pemetrexed-containing SOC, mixed histology
  - KEYNOTE-024b: pembrolizumab versus pemetrexed-containing SOC, all non-squamous
- Two analyses were performed in a Bayesian framework:
  1. NMA based on reported hazard ratios assuming proportional hazards between treatments, and
  2. NMA based on the scanned Kaplan-Meier curves anticipating that hazard ratios can vary over time according to a certain parametric function

Networks of evidence for progression-free survival (constant hazard ratios): All histologies



†HR calculated from KM
Trials in red: non-squamous
Trials in black: all histologies
Trials with 100% Asian patients denoted with *
KEYNOTE 024a: Patients assigned to platinum + gem or platinum + pac before randomization
KEYNOTE 024b: Patients assigned to platinum + pemetrexed before randomization (non-squamous)

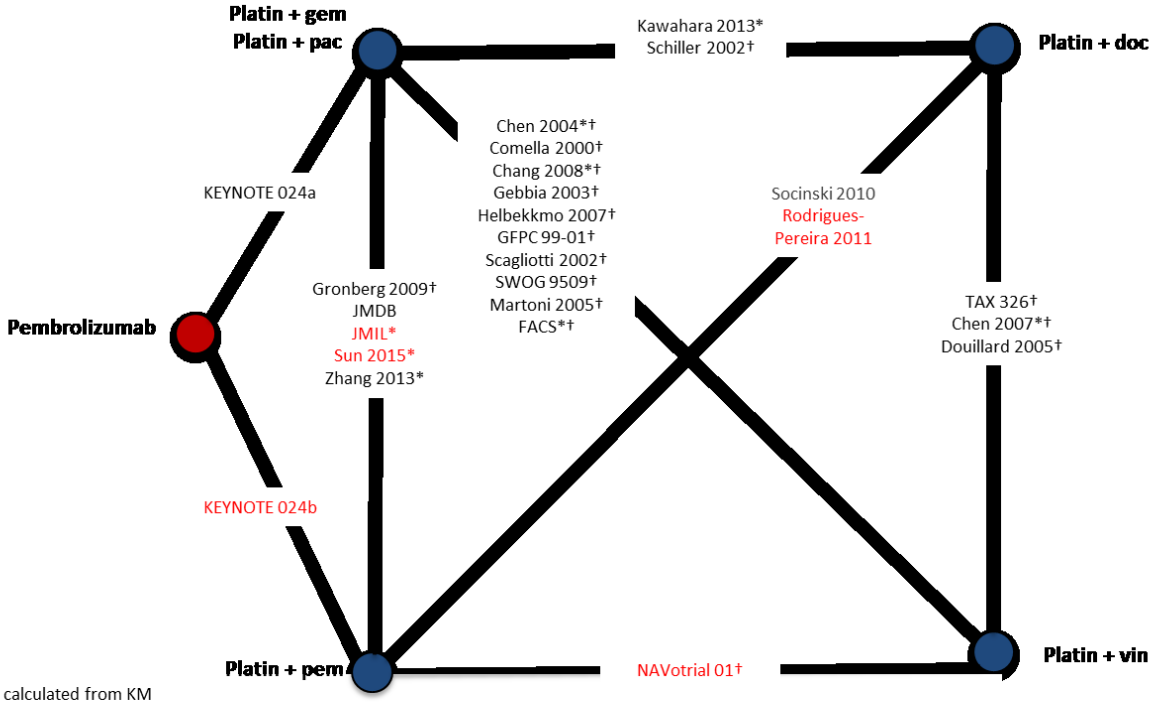
Source: Company submission figure 18 (p120)

Results of fixed effects network meta-analysis based on constant hazard ratio assumption: Progression-free survival; all histologies

Platin + gem or pac	1.03 (0.95, 1.12)	1.00 (0.90, 1.11)	0.94 (0.83, 1.07)	**2.06 (1.50, 2.81)**
0.97 (0.90, 1.05)	Platin + pem	0.97 (0.86, 1.09)	0.92 (0.81, 1.05)	**2.00 (1.47, 2.71)**
1.00 (0.90, 1.12)	1.03 (0.92, 1.16)	Platin + doc	0.95 (0.83, 1.08)	**2.06 (1.49, 2.84)**
1.06 (0.94, 1.20)	1.09 (0.96, 1.24)	1.05 (0.93, 1.20)	Platin + vin	**2.18 (1.58, 2.99)**
0.49 (0.36, 0.67)	**0.50 (0.37, 0.68)**	**0.48 (0.35, 0.67)**	**0.46 (0.34, 0.63)**	Pembro
All bold values are statistically meaningful at the 0.05 significance level				
Source: Company submission table 34 (p120)				

- Pembrolizumab offered better OS than every other intervention of interest, and was the only intervention better than the reference treatment of platinum plus gemcitabine/paclitaxel (HR 0.49, 95% CrI 0.36-0.67)
- Pembrolizumab was also superior to all other interventions of interest

Networks of evidence for overall survival (constant hazard ratios): All histologies



†HR calculated from KM
Trials in red: non-squamous
Trials in black: all histologies
Trials with 100% Asian patients denoted with *
KEYNOTE 024a: Patients assigned to platinum + gem or platinum + pac before randomization
KEYNOTE 024b: Patients assigned to platinum + pemetrexed before randomization (non-squamous)

Source: Company submission figure 19 (p122)

Results of fixed effects network meta-analysis based on constant hazard ratio assumption: Overall survival; all histologies

Platin + gem or pac	1.03 (0.95, 1.13)	0.96 (0.87, 1.06)	**0.90 (0.82, 0.99)**	**1.65 (1.11, 2.46)**
0.97 (0.89, 1.05)	Platin + pem	0.93 (0.83, 1.04)	**0.87 (0.78, 0.97)**	**1.60 (1.08, 2.36)**
1.04 (0.94, 1.15)	1.08 (0.96, 1.20)	Platin + doc	0.94 (0.86, 1.03)	**1.72 (1.14, 2.57)**
1.11 (1.01, 1.22)	**1.15 (1.03, 1.28)**	1.07 (0.97, 1.17)	Platin + vin	**1.83 (1.23, 2.73)**
0.61 (0.41, 0.90)	**0.63 (0.42, 0.93)**	**0.58 (0.39, 0.87)**	**0.55 (0.37, 0.81)**	Pembro
All bold values are statistically meaningful at the 0.05 significance level.				
Source: Company submission table 35 (p122)				

- Pembrolizumab offered better OS than every other intervention of interest, and was the only intervention better than the reference treatment of platinum plus gemcitabine/paclitaxel (HR 0.61, 95% CrI 0.41-0.90).
- Platinum plus pemetrexed showed a lower HR than platinum plus vinorelbine
- No other comparisons between platinum-based regimens were statistically meaningful

ERG critique: Network meta-analyses

- Appropriate for the company to conduct NMA to support the existing direct evidence comparing pembrolizumab with the comparators of interest
- Satisfied that the clinical assumptions to construct the networks are reasonable and the methodology used to conduct the main NMA (all-comers) is appropriate, however the ERG considers the results to be unreliable because:
  - There is extensive heterogeneity between the included trials: e.g., only the KEYNOTE-024 includes patients with TPS ≥50%, and all KEYNOTE-024 patients have stage IV disease whereas other studies included patients with stage III and IIIb disease
  - The company's unadjusted and adjusted treatment crossover results are very similar raising concerns over the accuracy of the results
- The ERG notes that the results of the NMA were not used to inform the company's cost effectiveness base case

Cost-effectiveness evidence

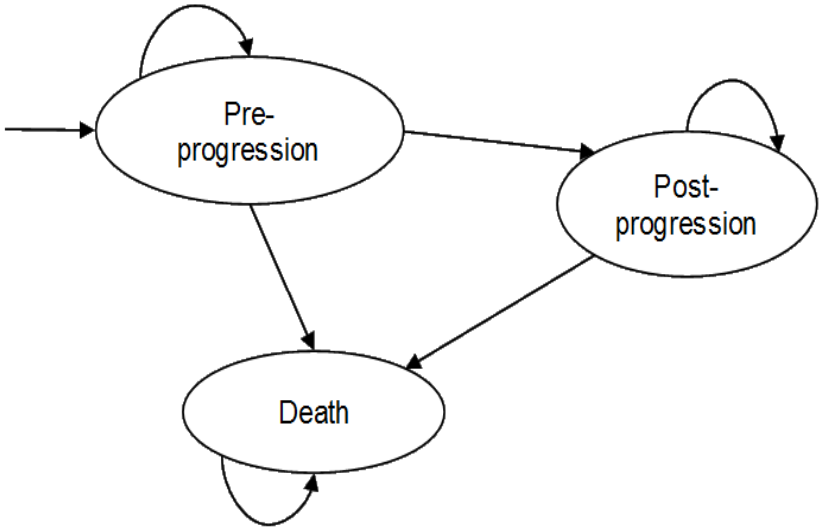
company submission chapter 5

Company's 3-state partitioned survival model

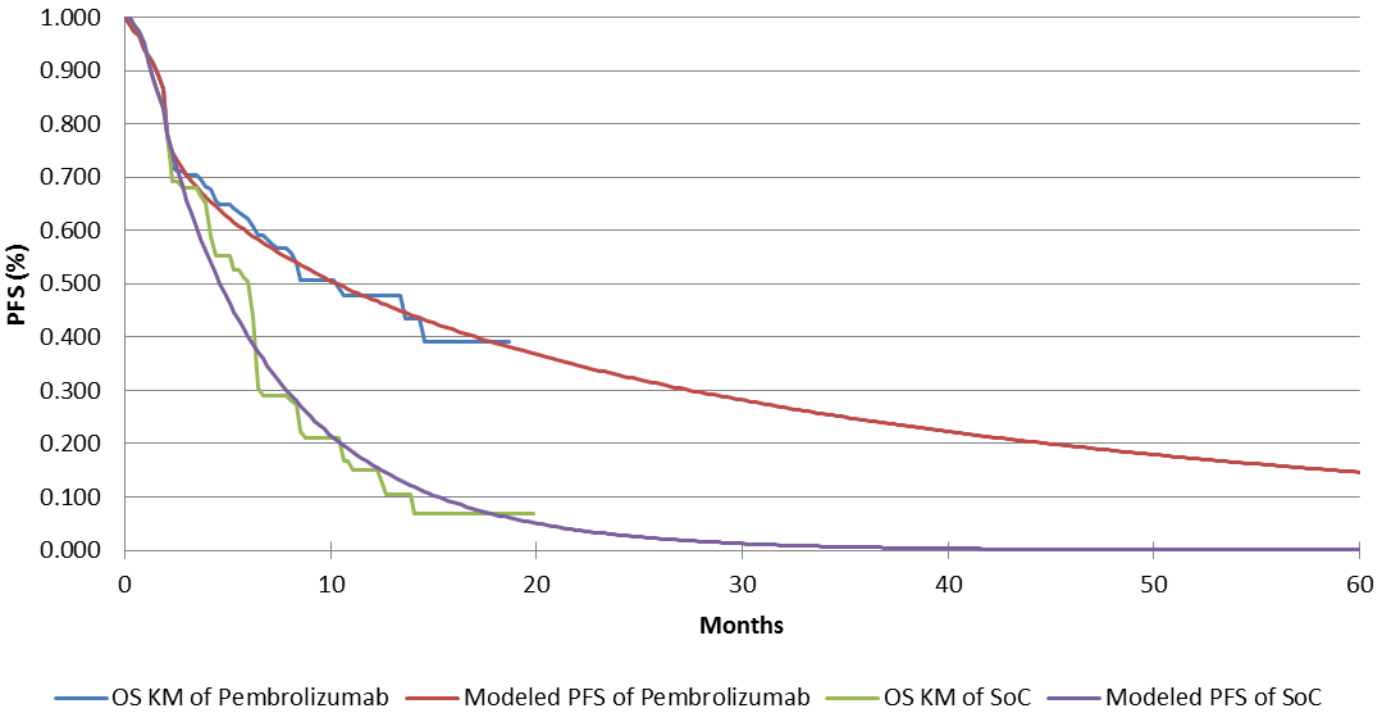
Lifetime horizon 20 years; cycle length 1 week; half-cycle correction

The clinical evidence was derived from KEYNOTE-024:

- Quality-adjusted life years (QALYs) estimated using time-to-death utilities from EQ-5D data
- PFS and OS for pembrolizumab and SOC (SOC OS has two-stage cross-over adjustment) we modelled using a 2-phase piecewise approac
  - For PFS, Kaplan-Meier data was used du the first 9 weeks, to reflect the protocol d fall in PFS observed at the first radiologic assessment. This was followed by extrapolating using a Weibull distribution
  - For OS, Kaplan-Meier data was used dur the first 22 weeks, on the basis of the changes to cumulative hazards, and an exponential model was fitted afterwards following standard parametric approaches.

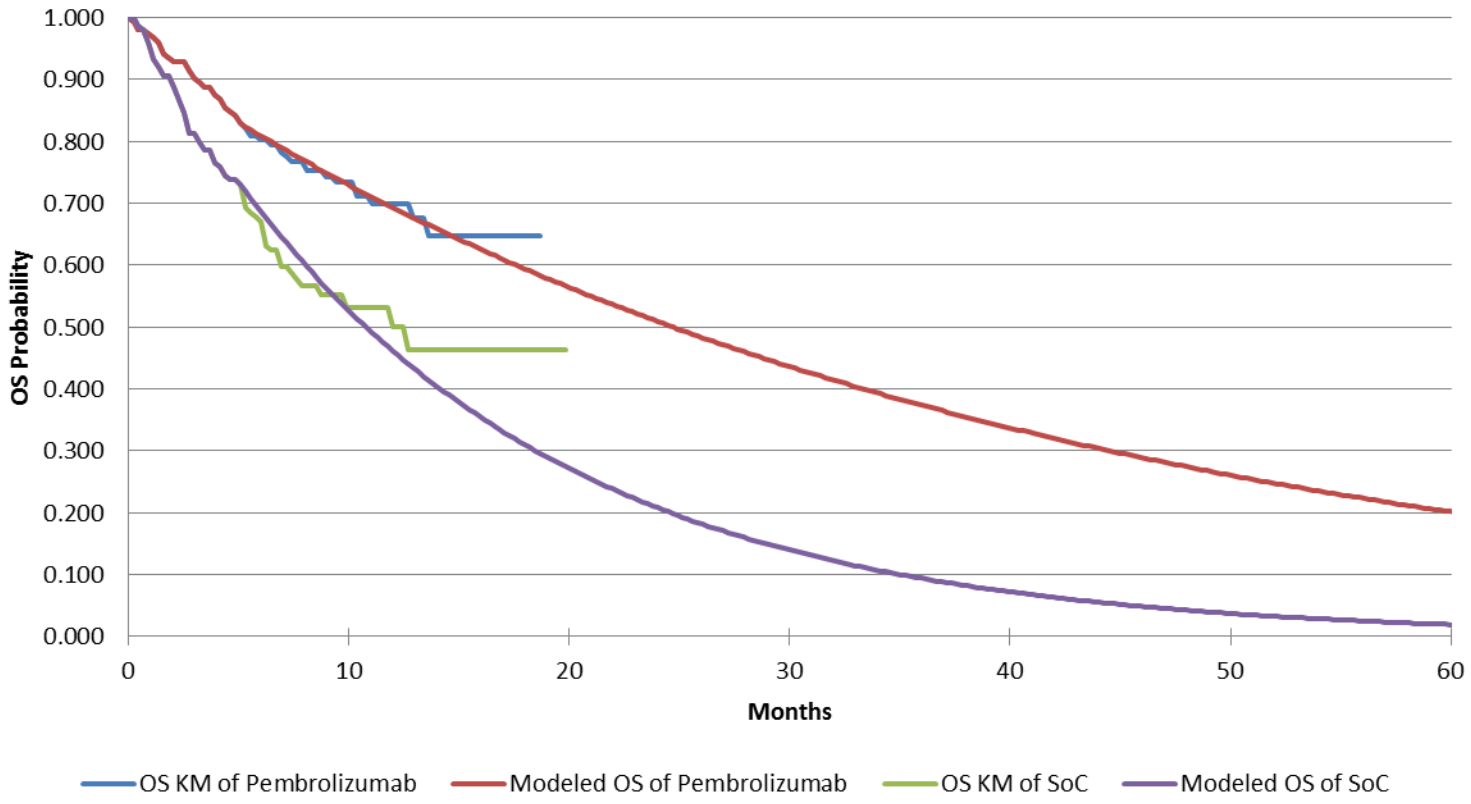


Kaplan-Meier curves and fitted 2-phase piecewise models for pembrolizumab and standard of care: Progression-free survival



Source: Company submission figure 38, p180

Kaplan-Meier curves and fitted 2-phase piecewise models for pembrolizumab and standard of care: Overall survival



Source: Company submission, figure 31, p175

Company model: analyses considered

1. Base case: The comparator was based on the distribution of SOC chemotherapy options in the KEYNOTE-024 trial
2. In additional analyses, relating to the NMA all histologies population, pembrolizumab was indirectly compared to individual platinum-based chemotherapies containing gemcitabine or paclitaxel, docetaxel, vinorelbine or pemetrexed based on the results of the NMA
3. Using data from the KEYNOTE-024 trial, the company also considered the cost effectiveness of treatment with pembrolizumab for subgroups of patients treated with specific regimens:
   - non-squamous population (pemetrexed and non-pemetrexed chemotherapy combinations) and squamous population (non-pemetrexed chemotherapy combinations)
   - non-pemetrexed only (squamous and non-squamous population) and pemetrexed only (squamous only population)

Company model: treatment duration

- Time on treatment data from KEYNOTE-024 were used to estimate treatment duration for patients treated with pembrolizumab and SOC. Independent Weibull and Gamma parametric curves were selected using AIC/BIC-based tests and visual inspection to represent patient level data in the pembrolizumab and SOC arms, respectively.
- Treatment with pembrolizumab was assumed to continue until disease progression or intolerable toxic effects resulting in discontinuation, with maximum treatment duration of 35 cycles (105 weeks).
- In line with the relevant SmPCs and UK clinical practice, patients prescribed SOC, were assumed to receive treatment up to disease progression or intolerable toxic effects resulting in discontinuation, with maximum treatment duration of six cycles (18 weeks).
- Patients treated with pemetrexed maintenance therapy were assumed to be treated until disease progression or unacceptable toxicity
- It was assumed that, in line with UK clinical practice and NICE guidance, all patients in the pembrolizumab arm received docetaxel in the second-line setting. Second-line therapy for all patients in the SOC arm was also assumed to be docetaxel

Company model: utilities

- The mean EQ-5D utility scores were pooled from the pembrolizumab and SOC treatment arms of KEYNOTE-024 because there were no statistically significant or clinically meaningful differences between arms. UK preference-based scores were used for all patient data in KEYNOTE-024.

Time to death (days)	Mean	95% CI
≥360*	0.808	(0.767, 0.850)
180 to 360	0.712	(0.663, 0.762)
30 to 180	0.598	(0.547, 0.648)
<30	0.48	(0.324, 0.637)

* This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days.
Source: Company submission Table 65, p195

- Utility scores for all patients were adjusted over time using the annual utility decrement of 0.0045 (Kind et al., 1999). Based on the baseline age, the decrement was applied annually from the age of 65 to 75 years to reflect the natural decrease in utility associated with age.
- Utility decrements: Grade 3 to 5 AEs were associated with utility of 0.719 (0.683 to 0.755), compared those who did not experience any AEs 0.793 (0.777 to 0.809). Utility decrements were applied during the first cycle based on grade 3+ AE incidence rates and the corresponding mean duration across them.

Company model: AE and PD-L1 testing

- The company model includes 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 in the first cycle of the model for each treatment arm
- The company model includes the cost of PD-L1 testing to identify patients who are eligible for treatment with pembrolizumab. The company estimates that approximately 11.6% of patients with NSCLC who have stage IV disease will also have >50% PD-L1 expression. Thus 8.6 patients will need to be tested for PD-L1 expression to identify 1 patient eligible to receive pembrolizumab. The company estimates that a single PD-L1 test will cost £40.50 per patient, which equates to a total cost of £348.21 relative to each patient that eventually receives pembrolizumab

Company model: Cost (1)

- Body surface area measurements used to calculate drug cost per administration were based on a weighted mean average of 1.83 m^2 from male and female patients recruited at European sites in KEYNOTE-024
- It is assumed that there was full vial sharing and no wastage for the comparator drugs and the cost of combination therapies was equal to the sum of the individual component drug costs
- The company model includes a dose intensity adjustment designed to reflect the proportions of patients in the KEYNOTE-024 trial who did not receive the full doses of study treatment (0.79% of patients in the pembrolizumab arm and 2.95% of patients in the SOC arm)
- Pemetrexed maintenance therapy was included for the same proportion of patients in the KEYNOTE-024 trial who received this therapy. There is currently a Commercial Access Agreement (CAA) in place for the administration of pemetrexed as maintenance therapy (results with a range of possible CAA discounts for pemetrexed were presented)

Company model: Cost (2)

- The costs of treatment with pembrolizumab after SOC were not accounted for in the company's base case analysis (when a statistical approach to adjust for patient crossover was implemented). All patients in the SOC arm were assumed to receive docetaxel as second-line (same assumption as for the pembrolizumab arm). The duration of second-line treatment with docetaxel is assumed to be 3 cycles (9 weeks) and 8.7 cycles (26.1 weeks) for patients whose first-line therapy was SOC and pembrolizumab respectively, based on data from the KEYNOTE-024 trial.
- The cost of subsequent therapy was incorporated in the model as a one-off cost in the post-progression state which was derived by weighting by the proportion of patients receiving docetaxel or pembrolizumab and taking into account the assumed treatment durations. The administration cost associated with treatment with docetaxel was assumed to be equal to that associated with treatment with pembrolizumab.

Company model: Summary

Assumption	Company approach
Treatment continuation	KEYNOTE-024: 2-year stopping rule applied based
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.
OS extrapolation	KEYNOTE-024: Separate exponential models were fitted at week 22, 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).
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).
Long-term treatment effect	treatment effect beyond 2 years was limited
Treatment switching	2-stage adjustment (43.7% of patients switched from SOC to pembrolizumab)
Utilities	KEYNOTE-024: Quality-adjusted life years (QALYs) estimated using time-to-death utilities from EQ-5D data.
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.
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

Company base case (discounted, with PAS)

Deterministic results

Technologies	Total			Incremental		ICER per QALY gained
	Costs	LYG	QALYs	Costs	QALYs	
SOC	£22,278	1.22	0.86			
Pembrolizumab	£76,462	2.75	2.06	£54,185	1.21	£44,896

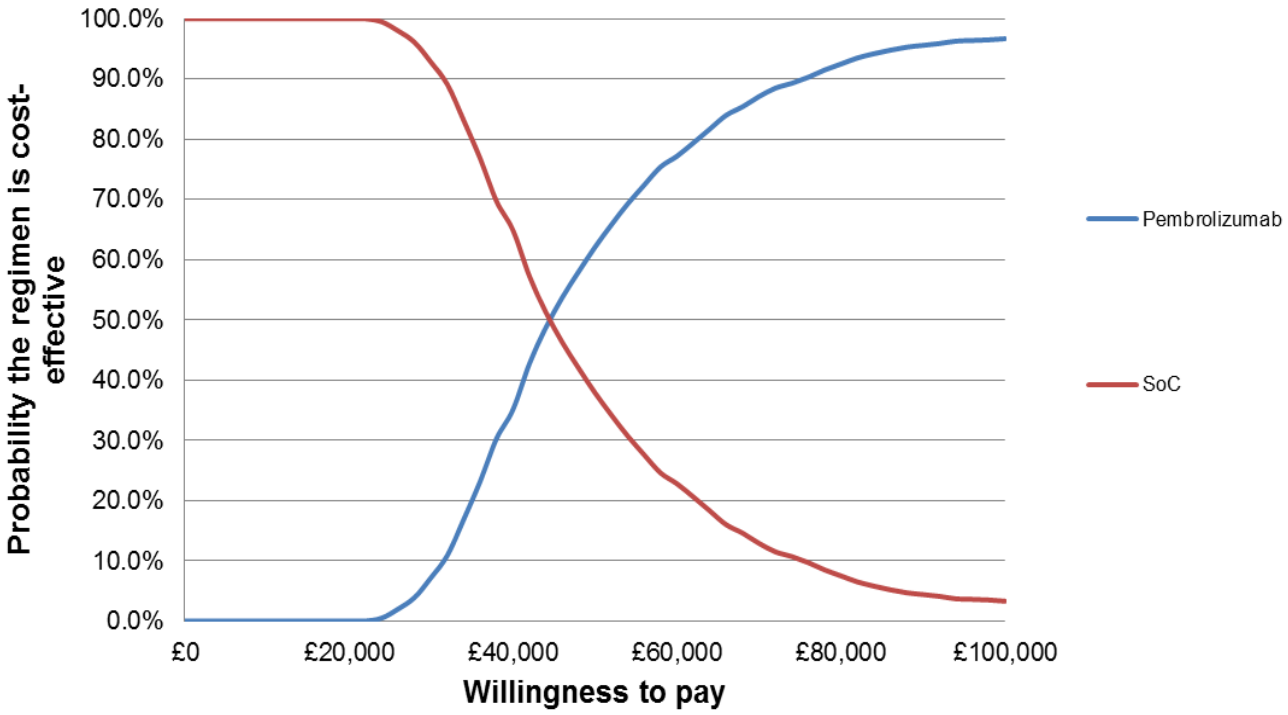
Source: Company submission, table 80 (p217)

Probabilistic results

Technologies	Total		Incremental		ICER per QALY gained
	Costs	QALYs	Costs	QALYs	
SOC	£22,666	0.87	-	-	-
Pembrolizumab	£77,005	2.09	£54,339	1.22	£44,394

Source: Company submission table 87 (p223)

Cost effectiveness acceptability curve



Source: Company submission figure 46 (p224)

- The chance of pembrolizumab being cost effective at a threshold of £50,000 per QALY gained is approximately 62%

ICERs for pembrolizumab versus SOC using a range of different discounts to reflect possible values for the current pemetrexed CAA (discounted, with PAS)

Discount to pemetrexed price	ICER per QALY gained
0%	£44,896
10%	£45,167
20%	£45,437
30%	£45,708
40%	£45,979
50%	£46,250
60%	£46,520
70%	£46,791
80%	£47,062
90%	£47,332
Source: Company submission table 81 (p217)	

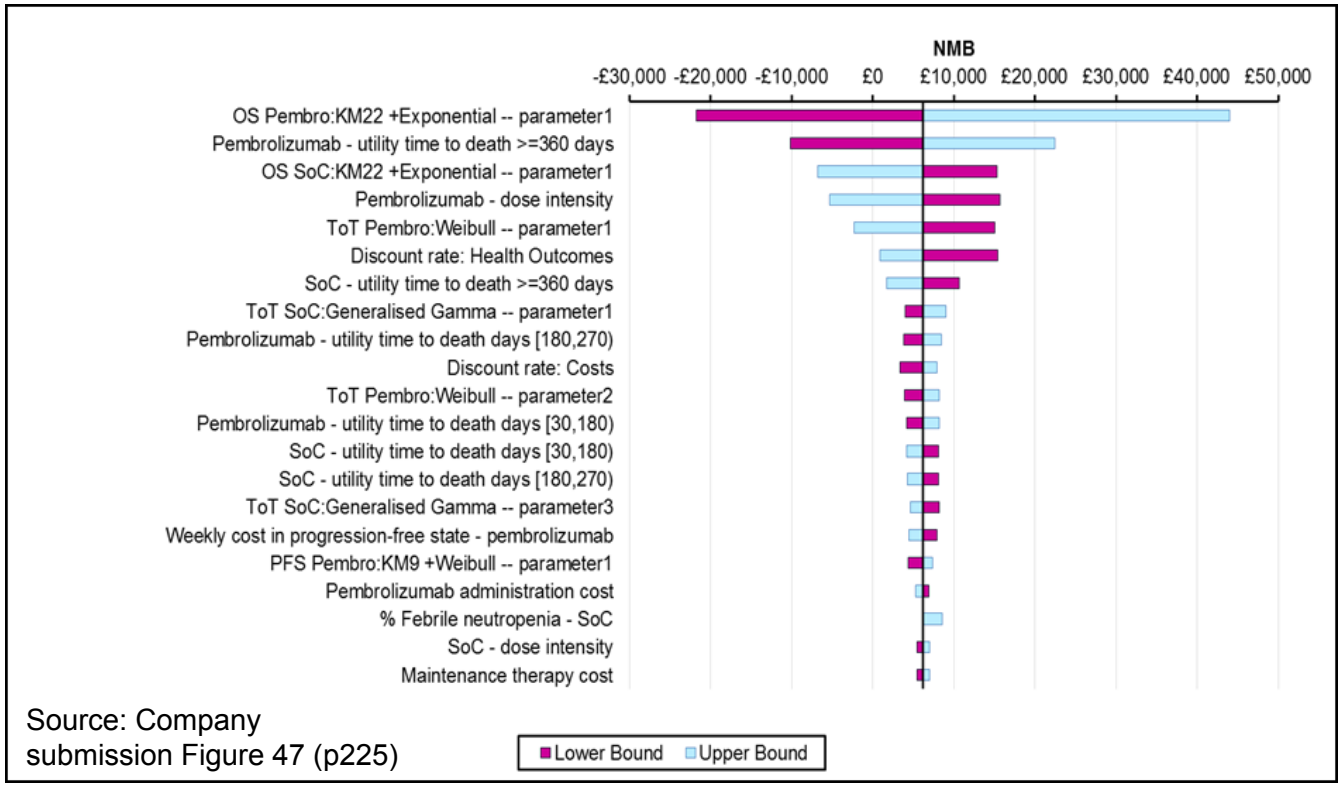
Pairwise cost effectiveness comparisons based on NMA results (discounted, with PAS)

Technologies	Total			Incremental		ICER per QALY gained
	Costs	LYG	QALYs	Costs	QALYs	
Platinum+gemcitabine or paclitaxel	£18,238	1.277	0.899	£58,224	1.163	£50,080
Platinum+docetaxel*	£17,721	1.262	0.892	£58,741	1.17	£50,206
Platinum+vinorelbine	£18,987	1.179	0.823	£57,476	1.239	£46,377
Platinum+pemetrexed	£24,003	1.359	0.964	£52,460	1.098	£47,786
Pembrolizumab	£76,462	2.752	2.062	-	-	-

*Company corrected values, there were errors in the original CS table

Sources: Company submission table 85 (p222) company submission and ERG report table 49 (p98)

Company deterministic sensitivity analysis: 10 parameters with greatest influence



Source: Company submission Figure 47 (p225)

The three most influential parameters were:

- the extrapolation of OS in pembrolizumab arm
- utility values for long-term survivors, and
- the extrapolation of OS in SOC arm

Company scenario analysis (with PAS)

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
Base case	**£54,185**	**1.21**	**£44,896**
Crossover – ITT (no adjustment)	£39,981	0.99	£40,547
Crossover- RPSFT adjustment	£54,908	1.30	£42,295
Crossover- IPCW adjustment	£54,274	1.22	£44,447
OS cut-off – 4 weeks	**£52,409**	**0.95**	**£55,244**
OS cut-off – 0 week (i.e. fully fitted parametric)	**£52,283**	**0.93**	**£55,952**
PFS cut-off – 18 weeks	£54,644	1.21	£45,277
PFS cut-off – 27 weeks	£55,502	1.21	£45,988
SOC PFS extrapolation based on exponential	£54,148	1.21	£44,865
No half cycle correction	£54,183	1.21	£44,900
SOC as for UK market shares	£53,744	1.21	£44,531
Utilities – progression-based (pooled)	£54,185	1.16	£46,705
Utilities – time to death (per treatment arm)	£54,185	1.17	£46,280
Utilities – progression-based (per treatment arm)	£54,185	1.22	£44,586
No age-related disutilities	£54,185	1.24	£43,865
Source: Adapted from company submission, table 88 (p228)			

Subgroup analyses: Histology (with PAS)

Histology	Treatment		
	Pembrolisumab (n=154)	SOC (n=151)	Total (n=305)
Non-Squamous	[redacted]	[redacted]	[redacted]
Squamous	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	incremental QALYs	ICER per QALY gained
Base case (all population)	£54,185	1.21	£44,896
non-squamous histology subgroup			
Two stage crossover adjustment	£52,965	1.21	£43,716
No cross over adjustment (ITT)	£39,000	1.02	£38,281
RPSFT	£55,596	1.54	£36,117
IPCW	£54,133	1.36	£39,815
squamous histology subgroup			
Two stage crossover adjustment*	NA	NA	NA
No cross over adjustment (ITT)	£47,929	0.83	£57,721
RPSFT	£61,077	0.92	£66,715
IPCW	£59,416	0.71	£83,707

*The two-stage adjustment could not be implemented in this population

Source Company Appendix 29 page 567

Subgroup analyses: Pemetrexed treatment regiment (with PAS)

Treatment Regimen	Treatment		
	Pembrolisumab (n=154)	SOC (n=151)	Total (n=305)
Containing Pemetrexed	[redacted]	[redacted]	[redacted]
Without Pemetrexed	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
Base case (all population)	£54,185	1.21	£44,896
pemetrexed-containing chemotherapies			
Two stage crossover adjustment	£44,344	0.87	£51,146
No cross over adjustment (ITT)	£30,816	0.73	£42,475
RPSFT	£45,175	0.97	£46,435
IPCW	£46,021	1.08	£42,674
non-pemetrexed-containing chemotherapies			
Two stage crossover adjustment*	NA	NA	NA
No cross over adjustment (ITT)	£56,543	1.43	£39,676
RPSFT*	NA	NA	NA
IPCW	£69,152	1.44	£47,941

*The two-stage adjustment and RPSFT could not be implemented in this population

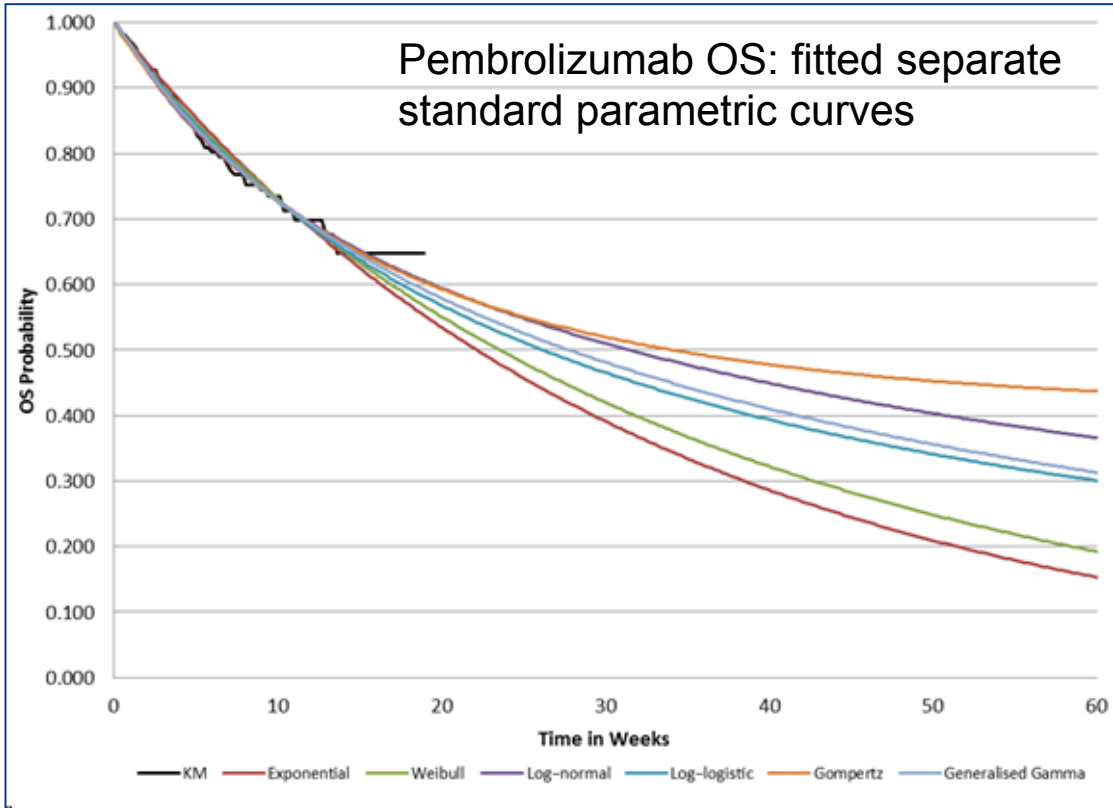
Source Company Appendix 29 page 570

ERG critique: Cost effectiveness evidence

- No relevant papers have been missed during the literature review and that the searches were adequate and well reported
- The economic model was well constructed but noted 4 fundamental issues which cast substantial doubt on the reliability of the company's base case cost effectiveness results for the comparison of treatment with pembrolizumab versus SOC:
  1. The extrapolation of OS in the pembrolizumab arm of the KEYNOTE-024 is uncertain due to only 35.4% of the total events having occurred
  2. Compared to survival data in registry and published studies the extrapolation of OS in the SOC arm of the KEYNOTE-024 trial is overly pessimistic
  3. The 2-years stopping rule for treatment continuation
  4. The utility values derived from KEYNOTE-024 trial are implausibly high

ERG critique: Pembrolizumab arm extrapolation

- Company assumed a constant mortality rate for both pembrolizumab and SOC after week 22. This is higher for SOC than pembrolizumab for the 20 year time horizon of the model and means that pembrolizumab continues to have a treatment effect many years after treatment could have stopped.
- In addition, there is uncertainty in the projections that exist even at just 2 years after treatment commenced (50.9% to 58.4% depending on the distribution chosen).
- Analysis carried out by the ERG shows that, of the 2.06 QALYs generated in the pemb. arm, 1.76 QALYs (85.4%) are generated after 22 weeks i.e., during the period that a statistical distribution is used to represent patient survival. Further, 1.18 QALYs are generated beyond 18 months. This means that over 57% of the QALYs attributable to treatment with pemb. are generated during a period in which there is no direct evidence of effect from any clinical trials.



Source: CS Figure 30 (p174)

ERG critique: SOC arm extrapolation, 2-years stopping rule

1. The extrapolated survival for patients treated with SOC at 5 years is 1.9%, whereas National Lung Cancer Audit (NCLA) data suggest that 5-year survival for all patients with stage IV NSCLC is 5%. Given that not all patients in the NCLA dataset received chemotherapy (which has been shown to extend life), an extrapolation method that predicts 5.0% survival at 5 years will overestimate the ICER (versus SOC).

   Published figures suggest that OS at 5 years for patients receiving SOC could be as high as 13%.

2. The cost of pembrolizumab is calculated on the basis that treatment ceases after 2 years (35 cycles) in line with the KEYNOTE-024 trial protocol. However, for patients with untreated PD-L1 positive metastatic NSCLC, the [redacted]. The ERG believes treatment would not be stopped after 2 years if a patient was receiving clinical benefit from pembrolizumab

ERG critique: utilities

The utility values derived from the KEYNOTE-024 trial, are implausibly high, notably for the period 360 days before death when these values are higher than the UK population norm for people of the same age.

The company submission states:

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

Source: Company submission, p36

Summary of the ERG's exploratory and sensitivity analyses

Due to the extreme uncertainty around any projection of OS for patients receiving pembrolizumab, the ERG has not made any revisions to the company's projection.

The following changes were implemented:

1. removing 2 years (35 cycle) stopping rule on the number of cycles of pembrolizumab that can be administered
2. altering the OS extrapolation for patients receiving SOC such that 5% and 13% of patients are alive at 5 years
3. limiting the magnitude of the utility values used in the model so that they are no higher than the UK population norm for people of the same age

The ERG considers that the last 2 of these amendments are conservative.

ERG analyses

Scenario/ERG amendment	Incremental costs		ICER	
	Cost	QALY	£/QALY	Change
Company base case	£54,185	1.21	**£44,896**	
R1) Removal of 35 cycle limit for pemb.	£111,268	1.21	**£92,194**	+£47,298
R2) 5% 5-year OS survival for SOC	£52,345	0.98	**£53,479**	+£8,583
R3) 13% 5-year OS survival for SOC	£48,833	0.54	**£89,727**	+£44,831
R4) Utility value for >360 days to death set to population norm	£54,185	1.18	**£45,900**	+£1,004
R5) Nafees et al., 2008 utility values	£54,185	1.01	**£53,896**	+£9,000
ERG preferred scenario (R1, R2 & R4)	£109,428	0.96	**£114,291**	+£69,395

Source: Table 53, page 115 ERG report

Years of treatment (cycles)	% still expected on treatment at end of year	ICER
2 yrs (35 cycles, company base case)	30.7%	**£44,896**
3 yrs (52 cycles)	22.6%	**£56,502**
4 yrs (70 cycles)	17.4%	**£65,421**
5 yrs (87 cycles	13.7%	**£71,476**
10 yrs (174 cycles)	5.3%	**£88,024**
Total over lifetime (348 cycles; R1)	100.0%	**£92,194**

Source: Table 52, page 105 ERG report

The ERG's amendments to the company's OS extrapolation for patients receiving SOC and to the utility values employed in the model are very conservative and the ERG's revised cost effectiveness results should be interpreted as a lower bound estimate of the ICER per QALY gained for this comparison

End of life considerations

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 was not reached. However, the average life expectancy for a patient with NSCLC (regardless of histology) receiving chemotherapy SOC is estimated to be between 9.9 and 13.9 months, based on the following: 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. Squamous patients have lower life expectancy as evident from the SQUIRE trial reporting a median OS of 9.9 months for the gemcitabine + cisplatin arm.
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: The average number of months of life gained with pembrolizumab as estimated by the economic model is 29 months, compared to 14.6 months with SOC In KEYNOTE-001 trial, the median OS for the treatment naïve NSCLC pembrolizumab arm was 22.1 months (95% CI, 16.8 to 27.2)
Source: Company submission table 49, p157	

ERG critique: End of life considerations

- The ERG agrees with the company that average patient life expectancy is less than 24 months
  - The mean OS for patients treated with SOC generated using the ERG adjusted company model (based on 5% survival at 5 years) is 1.86 years (22.3 months). The undiscounted difference in mean survival between patients treated with pembrolizumab versus SOC estimated by the ERG amended model is 1.07 years (12.8 months)
- Although there is considerable uncertainty around the validity of the representations of OS in the company model, the ERG is satisfied that the evidence is sufficient to suggest that the OS of patients treated with pembrolizumab is likely to be, on average, at least 3 months more than that of patients treated with SOC.
- The ERG, therefore, considers that pembrolizumab meets the end of life criteria for the target patient population

Innovation

- The company considers that pembrolizumab is an innovative treatment because:
  - patients can be selected for targeted treatment based on their PD-L1 status
  - treatment with pembrolizumab offers a significant survival benefit and is better tolerated than treatment with chemotherapy
  - the US Food and Drug Administration granted pembrolizumab Breakthrough Therapy Designation and priority review for the first-line treatment of patients with advanced NSCLC whose tumours express PD-L1
  - pembrolizumab received Promising Innovative Medicines designation (Early Access to Medicines Scheme) in November 2015, and in March 2016 pembrolizumab was granted a positive Scientific Opinion by the Medicines and Healthcare Products Regulatory Agency's (EAMS number 00025/0001) for the treatment of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test

Equality issues

- No equality or equity issues were identified by the company or the ERG

Clinical effectiveness issues

1. Does KEYNOTE-024 trial represent current clinical practice in the UK?
    - Chemotherapies used in the standard of care arm
    - Patients with stage 4 PDL-1 >50% NSCLC were included (NOT PD-L1 positive metastatic NSCLC patients)
2. Is the trial data sufficiently robust given that the study was stopped early?
3. What is the committee's view of the clinical plausibility of using a 2 year stopping rule?
4. What is the committee's view of the [redacted] difference between the BICR and investigator PFS assessment?
5. PD-L1 testing is a requirement for treatment with pembrolizumab but is not currently considered standard clinical practice.

Cost-effectiveness issues

1. What is the committee's view of the assumptions in the company's economic model?
   - Are the assumptions appropriate and clinically plausible?
   - Has the model captured all relevant costs and benefits associated with pembrolizumab?
   - Are the company's scenario analyses informative for decision making?
2. Is the extrapolation of OS in the pembrolizumab and standard of care arms of the KEYNOTE-24 suitable for decision making?
3. Are the utility values used in the model plausible?
4. What are the most plausible ICERs for pembrolizumab?

Authors

- **Marcela Haasova**
  Technical Lead
- **Fay McCracken**
  Technical Adviser
- with input from the Lead Team (Andrew Black and Susanne Dutton)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for untreated PD-L1 positive metastatic non-small-cell lung cancer.

Background

Lung cancer falls into two main histological categories: around 85–90% are non-small-cell lung cancers (NSCLC) and the remainder are small cell lung cancers[1,2]. NSCLC can be further classified into 3 histological sub-types of large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma. Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV). In 2013, approximately 26,800 people were diagnosed with NSCLC in England, of whom 13% had stage IIIA, 10% had stage IIIB and 46% had stage IV disease[2].

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

The median survival of people with lung cancer (all stages) is approximately 8 months[2]. Around a third of people with lung cancer, and a fifth of people with stage IV disease, survive for more than 1 year after diagnosis[3].

For the majority of people with NSCLC, the aims of treatment are to prolong survival and improve quality of life. Treatment choices are influenced by the presence of biological markers (such as mutations in epidermal growth factor receptor-tyrosine kinase (EGFR-TK), anaplastic-lymphoma-kinase (ALK) or PD-L1 status), histology (squamous or non-squamous) and previous treatment experience. NICE clinical guideline 121 (CG121) recommends platinum-based chemotherapy (that is, cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel, or vinorelbine) as an option for people with previously untreated stage III or IV NSCLC and good performance status. Alternatively, people may receive pemetrexed in combination with cisplatin if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (NICE technology appraisal guidance 181). For people who are unable to tolerate a platinum combination, the clinical guideline

recommends single-agent chemotherapy with docetaxel, gemcitabine, paclitaxel, or vinorelbine. Best supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated. For non-squamous NSCLC that has not progressed immediately following initial therapy with a NICE-recommended platinum-based chemotherapy regimen, maintenance treatment with pemetrexed is recommended as an option (NICE technology appraisal guidance 190 and draft final NICE guidance from the review of technology appraisal 309 [CDF rapid reconsideration process]).

The technology

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

Pembrolizumab does not have a marketing authorisation in the UK for untreated PD-L1 positive metastatic NSCLC. It has been studied in clinical trials, compared with platinum-based chemotherapy, in adults with PD-L1 positive advanced or metastatic NSCLC who have not had chemotherapy for their metastatic disease.

Intervention(s)	Pembrolizumab
Population(s)	People with PD-L1 positive metastatic non-small-cell lung cancer (NSCLC) not treated with chemotherapy in the metastatic setting

Comparators	• 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 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)

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The 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. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	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. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer (2014) NICE technology appraisals guidance 309. Review ongoing (CDF rapid reconsideration process ID1005). Publication expected August 2016.

	Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010) NICE technology appraisals guidance 190. Static guidance list (review decision December 2014). Pemetrexed for the first-line treatment of non-small-cell lung cancer (2009) NICE technology appraisals guidance 181. Static guidance list (review decision December 2014). **Appraisals in development:** Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy NICE technology appraisals guidance [ID840]. Publication expected January 2017. **Related Guidelines:** The diagnosis and treatment of lung cancer (2011). NICE guideline 121. Review of guideline ongoing (review decision March 2016). Publication date to be confirmed. **Related Quality Standards:** Quality standard for lung cancer (2012). NICE quality standard 17 http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp **Related NICE Pathways:** Lung cancer. Pathway created: Mar 2012. http://pathways.nice.org.uk/pathways/lung-cancer
Related National Policy	Department of Health, Improving Outcomes: A strategy for cancer, fourth annual report, Dec 2014 https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report NHS England, Manual for prescribed specialised services, chapter 105: specialist cancer services (adults), May 2016. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health, NHS Outcomes Framework 2016-20167, April 2016. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

	Department of Health, Cancer commissioning guidance, Dec 2009. http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_110115

References

1 Cancer Research UK (2011 data) Lung cancer incidence statistics. Accessed May 2016.

2 Health and Social Care Information Centre (2014) National Lung Cancer Audit: 2013 patient cohort. Accessed May 2016.

3 Cancer Research UK (2010–12 data) Lung cancer survival statistics. Accessed May 2016.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company Merck Sharp & Dohme (pembrolizumab) Patient/carer groups • Black Health Agency • British Lung Foundation • Cancer Black Care • Cancer Equality • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Roy Castle Lung Cancer Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus • UK Lung Cancer Coalition Professional groups • Association of Anaesthetists • Association of Cancer Physicians • Association of Respiratory Nurse Specialists • Association of Surgeons of Great Britain and Ireland • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Thoracic Oncology Group • British Thoracic Society	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Accord Healthcare (cisplatin, carboplatin, docetaxel, gemcitabine, paclitaxel) • Allergan (docetaxel, gemcitabine, paclitaxel, pemetrexed, vinorelbine) • Celgene (paclitaxel) • Dr Reddy's Laboratories (docetaxel) • Hospira UK (cisplatin, carboplatin, docetaxel, gemcitabine, paclitaxel) • Lilly UK (gemcitabine, pemetrexed) • Medac GmbH (docetaxel, gemcitabine, paclitaxel, vinorelbine) • Peckforton Pharmaceuticals (paclitaxel) • Pierre Fabre (vinorelbine) • Sun Pharma (carboplatin, gemcitabine)

Consultees	**Commentators (no right to submit or appeal)**
• Cancer Research UK • National Lung Cancer Forum for Nurses • Primary Care Respiratory Society • Royal College of Anesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS Eastbourne, Hailsham and Seaford CCG • NHS Greater Preston CCG • NHS England • Welsh Government	• Sandoz (cisplatin) • Sanofi (docetaxel) • Seacross pharmaceuticals (docetaxel) <u>Relevant research groups</u> • Cochrane Lung Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

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

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

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

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

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

Commentators

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

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Merck Sharp & Dohme

Evidence submission

File name	Version	Contains confidential information	Date
		Yes	18 October 2016

Contents

Tables and figures

Abbreviations

AE	Adverse Event
AEOSI	Adverse events of special interest
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ASaT	All Subjects as Treated
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central review
BOR	Best Overall Response
BSA	Body surface area
BSC	Best Supportive Care
BTD	Breakthrough Therapy Designation
CAA	Commercial access agreement
CDF	Cancer Drugs Fund
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CR	Complete response
CSR	Clinical Study Report
CTA	Clinical Trial Assay
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DCR	Disease control rate
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMit	Electronic Market Information Tool
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire
EQ-5D	EuroQoL 5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food and Drug Administration
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA1	First Interim-Analysis
IA2	Second Interim-Analysis
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INV	Investigator evaluation
IPCW	Inverse probability censoring weighted
irAEs	Immune-related AEs
IRC	independent review committee
irRC	Immune-related response criteria
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat

IV	Intravenous
IVRS/IXRS	Interactive Voice Response System/ Interactive Voice and Web Response System
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
MedDRA	Medical Dictionary of Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
MK-3475	Pembrolizumab - *Keytruda*®
MRA	Market Ready Assay
MSD	Merck Sharp and Dohme Ltd
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PA	Prototype Assay
PAS	Patient Access Scheme
PbR	Payment by results
PD	Progressive Disease
PD-1	Programmed death 1 protein
PD-L1	Programmed cell death 1 ligand 1
PFR	Progression-free rate
PFS	Progression free survival
PH	Proportional hazards
PIM	Promising Innovative Medicines
PK	Pharmacokinetics
PPS	Post-progression state
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcomes
PS	Performance status
PSSRU	Personal and Personal and Social Services Research Unit
PT-DC	Platinum-based doublet chemotherapy
QALY(s)	Quality-Adjusted Life Year(s)
Q3W	Every 3 weeks
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank-preserving structural failure time
RR	Response rate
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable Disease
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SOC	Standard of Care
STA	Single technology assessment
TA	Technology Appraisal
TC	Tumour cells
TNM	Tumour, Node, and Metastases

TOT	Time on treatment
TPS	Proportion of tumour cells staining for PD-L1
TTD	Time to death
TTO	Time trade off
UK	United Kingdom of Great Britain and Northern Ireland
US	United States of America
VAS	Visual Analogue Scale
VAT	Value-Added Tax

1. Executive summary

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] In the United Kingdom (UK), each year more than 45,000 people are diagnosed with lung cancer and over 35,000 die from the condition.[2] More than half of non-small cell lung cancer (NSCLC) patients present with incurable advanced local or metastatic disease at the time of diagnosis,[2] with an estimated five-year survival rate around 10%.[2]

Despite the benefits associated with platinum-based chemotherapy or a targeted therapy, survival remains poor for patients with advanced NSCLC.[3] Treatment approaches to advanced NSCLC have evolved over the last decade, to incorporate predictive markers of benefit from treatment (such as sensitising EGFR mutation); this has resulted in improvements in clinical outcomes and reduced treatment toxicity. However, the use of targeted therapies is limited to specific subpopulations. All patients with stage IV NSCLC inevitably develop resistance to chemotherapy and experience disease progression.[4]

In the face of such poor prognosis, there remains a critical unmet medical need for more effective first-line therapy options. There is additionally a desire to identify and validate more predictive biomarkers that will allow clinicians to tailor therapies to treat those who will benefit most from them.

Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging with its ligands PD-L1 and PD-L2. The drug first received a marketing authorisation for use in patients with metastatic melanoma in 2015 was subsequently recommended for use in the NHS by NICE for this patient population. In 2016, the marketing authorisation for pembrolizumab was expanded to authorise its use for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 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 pembrolizumab. A submission to NICE covering this patient population is currently under review [ID840], with final guidance due in February 2017.

With this submission, pembrolizumab is proposed to be used as a first-line treatment option for adult patients with metastatic 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 [TPS ≥ 50%])[5] and no EGFR or ALK positive tumour mutation. Between 23-28% of patients with advanced NSCLC are estimated to have tumours with TPS ≥50%.[6, 7] Studies have shown that patients whose

tumour(s) express PD-L1 respond better to PD-1 inhibitors than those who have tumour(s) without PD-L1 expression%[6-9] and increased levels of PD-L1 expression on tumour cells correlate with improved response to treatment with PD-1 inhibitors.[10]

KEYNOTE-024 is a phase III randomised controlled trial (median follow up of 11.2 months; range 6.3 to 19.7 months) which serves as the primary evidence base for the efficacy of pembrolizumab in the patient population of relevance to this submission. The results from the second interim analysis (IA2) of KEYNOTE-024 demonstrate both statistically significant and clinically meaningful benefit for patients. On the basis of these results, the external data and safety monitoring committee (DSMC) recommended that KEYNOTE-024 be stopped early to give the patients who were receiving standard of care chemotherapy regimens (SOC) the opportunity to receive pembrolizumab.

The results from IA2 of KEYNOTE-024 demonstrate that first-line therapy with pembrolizumab 200 mg Q3W significantly prolongs overall survival (OS) (HR 0.60; 95% CI: 0.41, 0.89; p=0.005) and progression-free survival (PFS) (HR 0.50; 95% CI: 0.37, 0.68; p<0.001) compared with SOC (which was inclusive of pemetrexed maintenance for patients with non-squamous tumours).The significant OS improvement associated with pembrolizumab 200 mg Q3W occurred despite the low number of deaths (35.4%) observed at the time of the database cut-off and the potentially confounding impact of crossover from SOC to pembrolizumab (43.7% in-study crossover), and was shown to persist after applying statistical methods to adjust for crossover. Survival improvement was demonstrated across all relevant subgroups. Additionally, compared to SOC, pembrolizumab 200 mg Q3W was associated with both a higher response rate (44.8% vs. 27.8%), and a longer median duration of response (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+]).

Supportive data from KEYNOTE-001 (Cohort F1) provides additional evidence for the long term survival benefit associate with pembrolizumab in the treatment-naïve NSCLC population (median follow-up duration 22.2 months; range, 17.8-30.5 months).

In KEYNOTE-024, AEs of grade 3-5 severity attributed to treatment occurred in twice as many patients treated with SOC compared with pembrolizumab (53.3% vs. 26.6%); and fewer discontinuations due to drug-related AEs occurred among patients in the pembrolizumab 200 mg Q3W arm compared to the SOC arm. Overall, the safety profile of pembrolizumab remains consistent with previously reported findings in patients with advanced NSCLC[6, 7] and other tumour types.[11-15] The enhanced efficacy and safety profile of pembrolizumab versus SOC demonstrated in KEYNOTE-024 is corroborated by improvements in HRQoL

The 200 mg Q3W fixed dose is shown to be an efficacious and simplified dosing regimen for patients with previously untreated NSCLC, and offers clinicians more convenience and reduces the potential for dosing errors. A fixed dosing scheme also reduces complexity in the logistical chain at treatment facilities and reduces wastage.

The cost-effectiveness of pembrolizumab was evaluated through the development of a three-state partitioned survival model, with the three states being PFS, post-progression and death, in line with the modelling approach taken in previous HTAs concerning advanced NSCLC reviewed by NICE (see section 5.2). The model projected health outcomes (i.e. OS and PFS) to estimate patients' health-related quality of life (HRQoL) and costs. Quality-adjusted life years (QALYs) were estimated by considering time-to-death utilities derived from EQ-5D data collected in KEYNOTE-024. Clinical and economic outcomes were projected over a 20-year time horizon to cover the anticipated lifetime of the population initiating first line therapy and assessed as part of this submission.

We utilised a two-part piecewise approach constructed on the basis of KEYNOTE-024 data, following the NICE DSU guidance and recent NICE submissions. The results demonstrate that pembrolizumab, as an end of life therapy, meets the NICE criteria to be considered a cost-effective use of NHS resources. The model estimates that patients treated with pembrolizumab gain 1.21 additional QALYS compared to SOC. The incremental cost-effectiveness ratio (ICER) when comparing pembrolizumab to SOC is £44,896. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is therefore 62%.

Results from multiple sensitivity analyses showed the ICER to be consistently below £50,000 per QALY (discounted, with the PAS). The main drivers of the cost-effectiveness analyses were related to the extrapolation of OS, utilities for long-term survivors, time on treatment and dose intensity. The sensitivity analyses conducted demonstrated that the cost-effectiveness of pembrolizumab is resilient to the different sources of uncertainty assessed.

The availability of pembrolizumab as a first-line treatment option in England, for adult patients with advanced NSCLC whose tumours express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutation, will represent a step-change in the treatment options available and will provide patients and clinicians with a transformative new treatment alternative. The proposed positioning of pembrolizumab, as a targeted first-line treatment for a distinct population comprising patients with advanced NSCLC, with TPS≥50%, aims to ensure usage is reserved for those patients most likely to derive clinical benefit from the drug. Pembrolizumab is expected to displace the use of traditional platinum-based doublet chemotherapy regimens as first-line therapy in this patient population.

1.1 Statement of decision problem

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

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with 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 data from the supporting clinical trial (KEYNOTE-024) anticipated licence and with the final NICE scope.
Intervention	Pembrolizumab	Pembrolizumab 200 mg Q3W	In line with the anticipated 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)		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

	(for people with adenocarcinoma or large cell carcinoma only) ○ with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only; subject to ongoing NICE 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)		quality of life. 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. In line with the final scope, comparisons with specific chemotherapeutic agents have also been included via a network meta-analysis.
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS) • response rates (RRs) • adverse effects (AEs) of treatment • health-related quality of life (HRQoL)	The outcome measures considered include: • OS • PFS • RRs • AEs of treatment • HRQoL	In line with NICE final scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	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

	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

1.2 Description of the technology being appraised

The technology being appraised is described in Table 2 below:

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Marketing authorisation/CE mark status	Pembrolizumab currently has a marketing authorisation covering the following indications: • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 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.
Indications and any restriction(s) as described in the summary of product characteristics	Indication to which this submission relates: KEYTRUDA is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 (tumour proportion score [TPS] ≥50%) with no EGFR or ALK positive tumour mutations.
Method of administration and dosage	200 mg every three weeks (Q3W); intravenous (IV) infusion.

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

The route of administration for pembrolizumab is IV infusion, over a 30 minute period. The anticipated licensed dosing regimen for patients with previously untreated NSCLC is 200 mg Q3W (for patients with melanoma or previously treated NSCLC, the recommended dose remains as 2 mg/kg Q3W, as per the current product licence). Treatment with pembrolizumab continues until disease progression or unacceptable toxicity, whichever occurs first. The list price of pembrolizumab is £2,630 per 100 mg vial [redacted]

PD-L1 testing is an immunohistochemistry (IHC) test. IHC is part of routine pathology practice. MSD is currently supporting the development of PD-L1 testing reference centres, which will provide the capacity to enable the tumours from patients with advanced NSCLC to be tested for PD-L1 status. It is anticipated that after the recommendation by NICE of pembrolizumab for patients with advanced NSCLC, PD-L1 testing of all patients with advanced NSCLC will become part of routine clinical practice - we anticipate that PD-L1 testing will be added to the current panel of EGFR and ALK tests for NSCLC.

In May 2015 the EMA granted marketing authorisation for pembrolizumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. In 2015 the National Institute for Health and Care Excellence (NICE) published two pieces of guidance (TA357[16] and TA366[17]) recommending pembrolizumab as an option for treatment of advanced (unresectable or metastatic) melanoma.

In August 2016, the EMA approved a variation to the marketing authorisation for pembrolizumab,[18] to include an additional indication for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 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. NICE is currently reviewing a submission for this indication [ID840], with an anticipated guidance publication date of February 2017.

A regulatory variation to the product licence for pembrolizumab is currently under review by the EMA, to broaden the eligible NSCLC population for this drug. The anticipated approval date for this variation is Q1 2017, and the anticipated licence indication is “KEYTRUDA is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 (tumour proportion score [TPS] ≥50%) with no EGFR or ALK positive tumour mutations”.

The innovative nature of pembrolizumab has been recognised on a number of occasions. Most recently in September 2016 the United States (US) Food and Drug Administration

(FDA) granted the drug Breakthrough Therapy Designation (BTD) and priority review for the first-line treatment of patients with advanced NSCLC whose tumours express PD-L1. [19] The FDA's Breakthrough Therapy Designation is intended to expedite the availability of promising new therapies that are planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates substantial improvement over existing therapies on one or more clinically significant endpoints. Pembrolizumab has previously been granted breakthrough status for specific patients with advanced melanoma, metastatic NSCLC in previously treated patients, microsatellite instability high metastatic colorectal cancer, and relapsed or refractory classical Hodgkin Lymphoma. [19]

In the UK, pembrolizumab received Promising Innovative Medicines (PIM) designation (Early Access to Medicines Scheme (EAMS) Step 1) in November 2015, and in March 2016 pembrolizumab was granted a positive Scientific Opinion by the Medicines and Healthcare Products Regulatory Agency's (MHRA) (MHRA EAMS number 00025/0001)[20] for the treatment of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test (see section 2.5). EAMS aims to give earlier access to promising new unlicensed or 'off label' medicines to UK patients that have a high unmet clinical need. In order to facilitate patient access to pembrolizumab in the period prior to EMA approval of the new indication to broaded the NSCLC patient population eligible to receive this drug, MSD is offering pembrolizumab free of charge under EAMS. Currently 231 patients are registered under EAMS across 49 enrolling centres.

1.3 Summary of the clinical effectiveness analysis

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

The clinical evidence presented in this submission is derived primarily from the second interim analysis (IA2) of KEYNOTE-024;[5, 21] an adequately powered phase III randomised controlled trial (RCT) of pembrolizumab 200 mg Q3W (anticipated licence dose and schedule, relevant to this submission) versus standard of care (SOC) chemotherapy regimens, in a patient population relevant to the anticipated label, comprising previously untreated patients with advanced NSCLC whose tumours strongly express PD-L1 (based on a Tumour Proportion Score (TPS) of ≥50%: TPS is the percentage of viable tumour cells showing partial or complete immunohistochemistry (IHC) membrane staining) (see section 4.7). Previous studies have demonstrated that approximately 23% to 28% of patients with advanced NSCLC have a PD-L1 TPS ≥50%).[6, 7] As the comparator arm in KEYNOTE-024

comprised a mix of various SOC regimens, an indirect and mixed treatment comparison was performed through a Network Meta-Analysis (NMA) to estimate the efficacy of pembrolizumab versus specific chemotherapy regimes, and the results are provided (see section 4.10). Evidence is also provided from KEYNOTE-001, which was a phase I study (due to its initial dose escalation component), that evolved into multiple phase II-like sub-studies through a series of expansion cohorts. Of relevance to this submission, cohort F1 provides supportive evidence for the additional survival benefit seen with pembrolizumab in previously untreated patients with advanced NSCLC (see section 4.11).

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 anticipated to receive pembrolizumab in UK clinical practice (see section 4.5).

The results from IA2 of KEYNOTE-024[5, 21] demonstrate that first-line treatment with pembrolizumab significantly prolonged overall survival (OS) (HR 0.60; 95% CI: 0.41, 0.89; p=0.005) and progression-free survival (PFS) (HR 0.50; 95% CI: 0.37, 0.68; p<0.001) compared with SOC (inclusive of pemetrexed maintenance for patients with non-squamous tumours). The magnitude of benefit observed in the SOC group was consistent with that previously observed for platinum-doublet regimens and pemetrexed maintenance.

The significant OS improvement for pembrolizumab as compared with SOC occurred despite the low number of deaths (35.4%) observed at the time of the database cut-off (09-May-2016) and the potentially confounding impact of crossover from SOC to pembrolizumab (43.7% in-study crossover). Three alternative crossover adjustment methods were applied to adjust for the crossover observed in KEYNOTE-024 (see section 4.7). All methods adjusting for direct crossover in the SOC arm provide treatment estimates that are larger (HR in a range of 0.50 to 0.57) than the ITT estimate (HR=0.60). Survival improvement was observed across all key subgroups. In addition, pembrolizumab was associated with both a higher response rate compared to SOC group (44.8% vs. 27.8% respectively), and a longer median duration of response (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+]).

The improved survival benefit associated with pembrolizumab as compared to SOC in the population studied is corroborated by improvements in health-related quality of life (HRQoL). Results from key patient-reported outcome (PRO) analyses indicated that when assessing change from baseline to Week 15, there was an improvement of almost 8 points in the EORTC QLQ-C30 global health status/QoL score for the pembrolizumab arm compared to SOC (difference in LS means = 7.82; 95% CI: 2.85, 12.79; nominal p=0.002).

Pembrolizumab also prolonged the time to true deterioration in the EORTC QLQ-LC13 composite endpoint of cough, dyspnea, and chest pain compared to SOC (HR 0.66; 95% CI: 0.44, 0.97; nominal p=0.029). These findings, along with results from supportive PRO analyses, suggest that health-related QoL and symptoms were improved or maintained to a greater degree with pembrolizumab than with SOC in this NSCLC subject population.

The observed safety profile of the pembrolizumab arm was consistent with the safety profile for pembrolizumab established to date. The chemotherapy safety profile was also as expected. Based on the mechanism of action of pembrolizumab, immune-mediated adverse-events (AEs), including pneumonitis, occurred at greater frequency with pembrolizumab. Most immune-mediated events were of Grade 1 or 2 severity and none led to death. Pembrolizumab was better tolerated than chemotherapy and AEs were easily managed.

The evidence provided is robust and consistently demonstrates both a statistically significant and clinically meaningful benefit of pembrolizumab compared to SOC for adults with previously untreated advanced NSCLC, without EGFR and/or ALK mutation, whose tumours strongly express PD-L1. These data underscore the substantial benefit of pembrolizumab as initial therapy for this patient group.

1.4 Summary of the cost-effectiveness analysis

The cost-effectiveness of pembrolizumab was assessed against SOC in 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.

Cost-effectiveness was evaluated through the development of a three-state partitioned survival model, with the three states being PFS, post-progression and death, in line with the modelling approach taken in previous HTAs concerning advanced NSCLC reviewed by NICE (see section 5.2). The analysis was conducted in line with the NICE reference case, i.e. from the perspective of the NHS and Personal and Social Services (PSS). A discount rate of 3.5% per annum was applied to both costs and benefits. Clinical and economic outcomes were projected over a 20-year time horizon to cover the anticipated lifetime of the population here assessed, initiating first line therapy. The analysis was run using 1-week model cycles. The model projected health outcomes (i.e. OS and PFS) to estimate patients' health-related quality of life (HRQoL) and costs. Quality-adjusted life years (QALYs) were estimated by using time-to-death utilities derived from EQ-5D data collected in KEYNOTE-024.

The clinical evidence used to populate the pembrolizumab and SOC arms was derived from the pivotal KEYNOTE-024 trial. For the SOC, OS was estimated by adjusting for crossover using two-stage adjustment method.

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

- For OS, KEYNOTE-024 KM data was used during the first 22 weeks, on the basis of the changes to cumulative hazards, and an exponential model was fitted afterwards following standard parametric approaches.
- For PFS, KEYNOTE-024 KM data was used during the first 9 weeks, to reflect the protocol driven fall in PFS observed at the first radiologic assessment. This was followed by extrapolating using a Weibull distribution.

Section 5 details the development of the de novo economic model for pembrolizumab, with Table 3 below presenting the results for the main population of patients with advanced NSCLC considered in the submission (see above).

The model estimates that patients treated with pembrolizumab gain 1.21 additional QALYS compared to SOC. The incremental cost-effectiveness ratio (ICER) when comparing pembrolizumab to SOC is £44,896. The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 62%.

Results from multiple sensitivity analyses showed the ICER to be consistently below £50,000 per QALY (discounted, with the PAS). The main drivers of the cost-effectiveness analyses were related to the extrapolation of OS, utilities for long-term survivors, time on treatment and dose intensity. The sensitivity analyses conducted demonstrated that the cost-effectiveness of pembrolizumab is resilient to the different sources of uncertainty assessed.

Table 3: Incremental cost-effectiveness results – Base case, main population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SOC	£22,278	1.22	0.86	-	-	-
Pembrolizumab	£76,462	2.75	2.06	£54,185	1.21	£44,896
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

2. The technology

2.1 Description of the technology

Brand name: KEYTRUDA®

Generic name: pembrolizumab

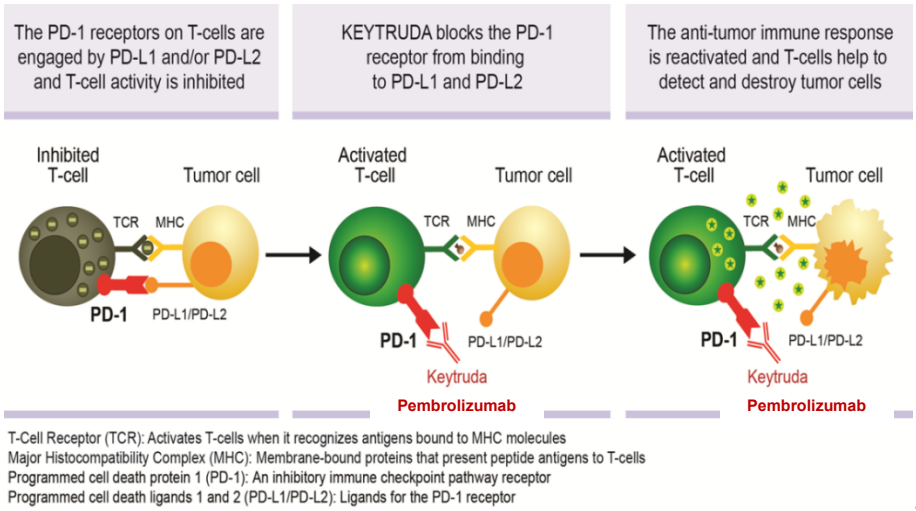
Therapeutic class: BNF Category "Other immunomodulating drugs" (08.02.04).[22]

Brief overview of mechanism of action:

Programmed death 1 protein (PD-1) is an immune-checkpoint receptor that is expressed on antigen-presenting T cells. PD-1 acts to initiate downstream signalling, which in turn inhibits the proliferation of T cells as well as cytokine release and cytotoxicity.[23] The PD-1 ligands, PD-L1 and PD-L2, are frequently upregulated on the surface of many tumour cell surfaces.[24]

Pembrolizumab (Keytruda®) is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype[23] designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells (Figure 1). By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour immunity (Figure 1).

Figure 1: Pembrolizumab – mechanism of action



Source: MSD data on file.

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1: Current UK regulatory status

- Application submitted: July 2016
- CHMP Opinion expected: December 2016
- Estimated date of Marketing Authorisation: February 2017

2.2.2: Anticipated indication in the UK

KEYTRUDA is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 (tumour proportion score [TPS] ≥50%) with no EGFR or ALK positive tumour mutations.

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

Please see Appendix 1.

2.2.4: Draft SmPC

The draft SmPC has been included as an appendix – see Appendix 1. Please note this draft SmPC includes provisional indication wording which will be subject to change as the regulatory review progresses. Therefore the final approved indication wording, as well as other sections of the SmPC, may differ compared to the one presented in Appendix 1.

2.2.5 Draft EMA assessment report

The draft EMA assessment report is currently unavailable.

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

Not applicable – public assessment report currently unavailable

2.2.7: Anticipated date of availability in the UK

Pembrolizumab is already available as a first- and second-line treatment option to patients with advanced NSCLC in the UK under the Early Access to Medicines Scheme (EAMS) – see section 2.5.

The anticipated commercial launch date following regulatory approval is February 2017.

2.2.8: Details of regulatory approval outside of the UK

Not applicable

2.2.9: Other health technology assessments in the UK

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

2.3 Administration and costs of the technology

Table 4: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Powder for concentrate for solution for infusion	Draft SmPC (see Appendix 1)
Acquisition cost (excluding VAT) *	List price: 100mg vial = £2,630. A PAS is under discussion with the Department of Health. The proposed scheme aims to provide a simple discount ([redacted] to the list price of pembrolizumab. The NHS acquisition cost (excl. VAT) is: 100mg vial = [redacted]	Pending confirmation with the Department of Health
Method of administration	Intravenous infusion	Draft SmPC (see Appendix 1)
Doses	Induction dose: 200mg	Draft SmPC (see Appendix 1)
Dosing frequency	200mg every 3 weeks until disease progression or unacceptable toxicities	Draft SmPC (see Appendix 1)
Average length of a course of treatment	Based on KEYNOTE-024 trial, the average time on therapy per patient is 6.76 months, equivalent to 9.80 cycles received per patient treated with pembrolixumab 200mg Q3W during a course of treatment	CSR KEYNOTE-024
Average cost of a course of treatment	The average cost per treatment course is: £51,548 at list price	KEYNOTE-024
Anticipated average interval between courses of treatments	Treatment is continuous until disease progression or unacceptable toxicity leading to discontinuation	CSR KEYNOTE-024
Anticipated number of repeat courses of treatments	Repeated treatment is not anticipated	Draft SmPC (see Appendix 1)
Dose adjustments	No dose adjustment is expected	Draft SmPC (see Appendix 1)
Anticipated care setting	Pembrolizumab is anticipated to be administered in a hospital setting	
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

2.4 Changes in service provision and management

2.4.1 Additional tests or investigations needed

Pembrolizumab is anticipated to be licensed as first-line therapy for patients with metastatic NSCLC with PD-L1 Tumour Proportion Score (TPS) ≥50%, defined as membranous PD-L1 expression on at least 50% of tumour cells, regardless of staining intensity.

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

PD-L1 expression is tested using a qualitative immunohistochemical (IHC) assay to detect PD-L1 protein in NSCLC tissue.

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

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

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

2.4.3 Additional infrastructure in the NHS

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

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

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

2.4.5 Concomitant therapies administered with the technology

No concomitant therapies are required.

2.5 Innovation

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

In the treatment of NSCLC, customising therapy based on histology, i.e. squamous and non-squamous, and molecular typing (EGFR-TK and ALK mutations) has become the standard of care. Platinum-based chemotherapy regimens remain the foundation of treatment for the majority of patients with first-line NSCLC.[25] However, over the last decade, those therapies have not significantly improved the 1-year and 5-year survival rates, even with the introduction of newer targeted therapies and combination approaches most patients relapse and die as a consequence of their NSCLC.[3, 26-29]

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

Due to its distinct mechanism of action, pembrolizumab has demonstrated significant survival benefit and improved tolerability profile compared to chemotherapy regimens and is expected to provide a durable response for a proportion of patients with advanced NSCLC.[21] Furthermore, pembrolizumab represents a “step-change” in the management of patients with advanced NSCLC, as it is the first PD-1 inhibitor to be reviewed by NICE for the first-line treatment of patients with advanced NSCLC whose tumours express PD-L1. The selection of patients for treatment with pembrolizumab on the basis of PD-L1 expression will enable pembrolizumab to be used in patients most likely to benefit, prevent unnecessary exposure to pembrolizumab for those patients who are less likely to benefit, and ultimately save costs to the overall healthcare system.

The innovative nature of pembrolizumab was first recognised by the US Food and Drug Administration (FDA) in January 2013 by granting it Breakthrough Therapy Designation (BTD) for advanced melanoma.[30] The FDA’s BTD is intended to expedite the development and review of a drug that is planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoint.[31] In October 2014 the FDA granted pembrolizumab BTD for the treatment of patients with advanced (metastatic) NSCLC whose disease has progressed

after other treatments.[31] In October 2015 pembrolizumab was granted accelerated approval for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.[31] The innovative nature of pembrolizumab was again recognised by the FDA in September 2016 by granting it BTD and priority review for the first-line treatment of patients with advanced non–small cell lung cancer whose tumours express PD-L1.[19]

In the UK, in March 2015 pembrolizumab became the first medicine to be granted positive scientific opinion under the MHRA's Early Access to Medicines Scheme (EAMS) for the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care.[32] Pembrolizumab received Promising Innovative Medicines (PIM) designation (EAMS Step 1) in November 2015, and in March 2016 a positive Scientific Opinion was granted (MHRA EAMS number 00025/0001) for "*the treatment as monotherapy of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation or whose disease has progressed on or after platinum-containing chemotherapy. Patients who have an EGFR sensitising mutation or an ALK translocation should also have had disease progression on approved therapies for these aberrations prior to receiving pembrolizumab*".[20] EAMS aims to give earlier access to promising new unlicensed or 'off label' medicines to UK patients that have a high unmet clinical need. This validates MSD's position that pembrolizumab should be considered innovative in its potential to make a significant and substantial impact on health-related benefits in an area of high unmet need.

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

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

The term *lung cancer* is used for tumours arising from the respiratory epithelium (bronchi, bronchioles, and alveoli). According to the World Health Organization classification, epithelial lung cancers consist of two major cell types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[33]

NSCLC accounts for up to 85-90% of lung cancer cases in the UK[34] and includes two major histological subtypes: squamous cell carcinoma (25% to 30%) and non-squamous cell carcinoma, including adenocarcinoma (30% to 40%), large-cell carcinoma (10% to 15%), and other cell types (5%).[35, 36] The histological subtype of NSCLC correlates generally with the cancer's site of origin, reflecting the variation in respiratory tract epithelia (Figure 2). Squamous cell carcinoma develops from the flat, surface covering cells in the airways. It tends to originate in the central bronchi. This type of tumour is found most commonly in men and is closely correlated with a smoking history.[33, 37] Adenocarcinoma is the most common form of NSCLC in many countries. It develops from mucus making cells in the lining of the airways and lesions are usually peripherally located. Adenocarcinoma is found most commonly in women and never smokers.[33, 37] Large cell carcinomas tend to occur peripherally and are defined as poorly differentiated carcinomas of the lung composed of larger malignant cells without evidence of squamous, glandular differentiation, or features of small cell carcinoma by light microscopy. These tumours are associated with a poor prognosis because of their tendency to spread to distant sites early in their course.[33, 37]

NSCLC is staged according to the Tumour-Node-Metastasis (TNM) classification, based on the primary tumour size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M).[38] This information is combined to assign an overall stage of 0, I, II, III, or IV: In stage 0 the cancer is found only in the top layers of cells lining the air passages. In stages I and II NSCLC, an invasive cancer has formed but has not spread to lymph nodes or distant sites. In stage III the NSCLC has spread to lymph nodes in the middle of the chest, also described as locally advanced disease. Stage III has two subtypes: If the cancer has spread only to lymph nodes on the same side of the chest where the cancer started, it is called stage IIIA. If the cancer has spread to the lymph nodes on the opposite side of the chest, or above the collar bone, it is called stage IIIB. In stage IV

NSCLC the cancer has spread to distant lymph nodes or to other organs such as the liver, bone, or brain.

Lung cancer cells harbour multiple chromosomal abnormalities, including mutations, amplifications, insertions, deletions, and translocations.[33, 36, 39] Molecular aberrations in genes encoding signalling proteins that drive initiation and maintenance of tumour cells are important markers of prognosis and response to treatment. More than 50% of NSCLC tumours test positive for at least one molecular biomarker; most commonly mutations in Kirsten rat sarcoma (KRAS) (15-20%),[40-43] epidermal growth factor receptor (EGFR) (17%; more frequent in women (69.7%), in patients who had never smoked (66.6%), and in those with adenocarcinomas (80.9%)),[43, 44] and translocations involving anaplastic lymphoma kinase (ALK) (2-7%).[43, 45, 46] ALK translocations occur most commonly in patients with non-squamous NSCLC.[43]

Figure 2: Primary Histologic Subtypes of NSCLC

Non-squamous-cell carcinoma

Adenocarcinoma

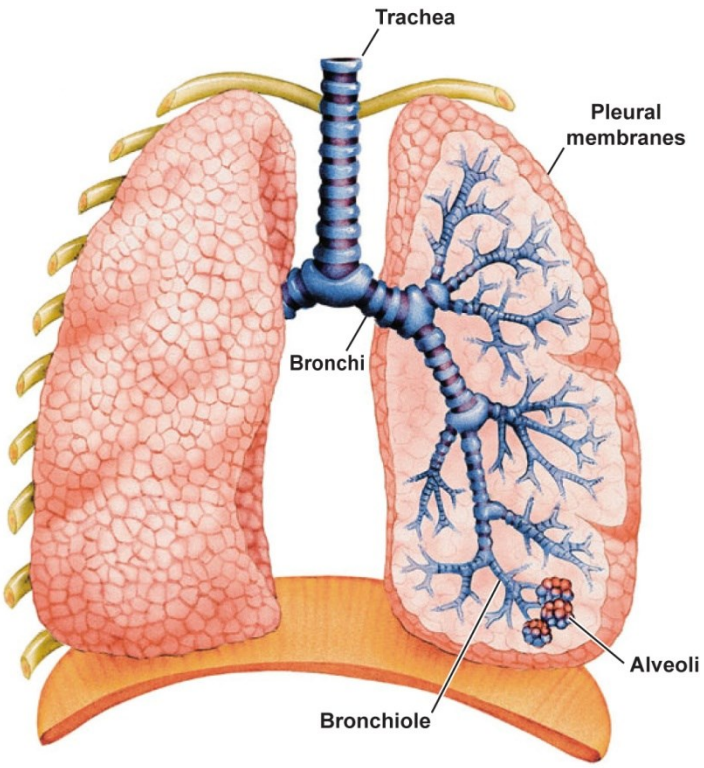
- Most common type of lung cancer in women and nonsmokers
- Lesions are usually peripherally located
- Arises from bronchi, bronchioles, or alveolar walls
- Worldwide incidence increasing

Large-cell carcinoma

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

Squamous-cell carcinoma

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



NSCLC = non-small cell lung cancer.
Source: Adapted from Teaching Times, 2016.[47].

As research continues, more biomarkers are being discovered. Programmed cell death ligand 1 (PD-L1), the ligand of PD-1 receptor, is a cell surface protein that has recently been studied in a number of resected NSCLC specimens; the findings of previous studies have shown that the percentage of patients with advanced NSCLC whose tumours strongly

express PD-L1, defined as tumour proportion score [TPS] ≥50% is between 23% and 28%.[6, 7] Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging with its ligands PD-L1 and PD-L2. The binding of PD-1 to PD-L1 (or to PD-L2) can inhibit a cytotoxic T-cell response, but by disrupting the engagement of the PD-1 receptor with its ligands, pembrolizumab serves to impede inhibitory signals in T cells, resulting in cytotoxic T cells recognising and destroying the tumour cells (see section 2.1).[6]

Studies have shown that PD-L1 is a predictive biomarker for anti–PD-1 and anti–PD-L1 therapies: patients whose tumours express PD-L1 respond better to PD-1 inhibitors than those patients with tumours without PD-L1 expression;[6-9] and patients with increasing PD-L1 expression on tumour cells respond better to PD-1 inhibitors.[10]

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

NSCLC is often asymptomatic in the early stages, with the majority of patients diagnosed at a late stage (stages IIIB-IV) when prognosis is poor and curative treatment is no longer viable.[48]

One of the reasons for delayed diagnosis is that the most common symptoms of NSCLC (e.g. cough, shortness of breath and chest pain) are similar to those associated with conditions such as smoking and chronic bronchitis, making early diagnosis extremely difficult. Unfortunately, more than half of all patients diagnosed with NSCLC present with locally advanced or metastatic disease at the time of diagnosis that is not amenable to the surgery which offers patients the best chance of cure. To date, prevention, rather than screening, has been the most effective strategy for reducing the burden of NSCLC in the long term. The majority of lung cancer cases (85.6%) occur as a result of tobacco smoking (including environmental smoke exposure) and progress in smoking cessation is now reflected in declining lung cancer rates and mortality.[49]

The pathway leading to the confirmation and communication of diagnosis is often a very frustrating experience for patients due to experienced delays, lack of information and support, and uncertainty regarding next steps.[50] Additionally, patients diagnosed at stage IV present a very low 5-year OS of 3% and there has not been a significant change in the survival of advanced NSCLC in England in the past decade.[51, 52]

Patients with NSCLC have reported the highest prevalence levels of psychological distress (three times more than in other cancers),[53] which can lead to a poorer prognosis and greater patient burden. [54, 55] Increased levels of psychological distress are reported by patients undergoing oncological treatment and by those approaching death.[53]

Patients with advanced NSCLC are in need of help from caregivers, particularly in the period leading to death. Furthermore, informal caregivers are increasingly recognised as recipients of care themselves, [56] as they have to deal with the distressing nature of the patient's symptoms. Unmet need is more prevalent among caregivers of patients with lung cancer, who report concerns in terms of reducing stress in the patient, understanding the experience of the cancer patient and even accessible, affordable, hospital parking. [57]

Advanced NSCLC imposes a substantial burden to society, not only in terms of years of life lost (YLL) due to premature death, but also due to the corresponding loss of contribution to the economy and the substantial health care costs associated with its prevention and management. Lung cancer costs the UK economy an estimated £2.4 billion per year, highest among the four most prevalent cancer types in the UK (considering breast cancer, prostate cancer and colorectal cancer).[58] Informal care and healthcare costs account for 16% and 35% of the cost of lung cancer respectively whilst due to the high burden of the poor 5 year survival prognosis associated with NSCLC (3%), £1.2 billion of the annual loss to the economy can be attributed to wage losses due to premature deaths of patients with lung cancer, who were previously in employment.[58, 59] According to Cancer Research UK, the average cost per lung cancer patient is £9,071 to the healthcare system annually, where an average cost per cancer patient in the UK totals £2,776.[58]

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

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

According to current NICE guidance, patients whose tumours test positive for anaplastic lymphoma kinase (ALK) mutation are eligible to recive first-line treatment with crizotinib (TA406).[60] Patients whose tumours test positive for epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation are eligible to receive first-line treatment with an EGFR-TK inhibitor: afatinib (TA 310),[61] erlotinib (TA 258)[62] or gefitinib (TA 192).[63] For patients with negative or unknown EGFR status (EGFR wild-type) and good performance status

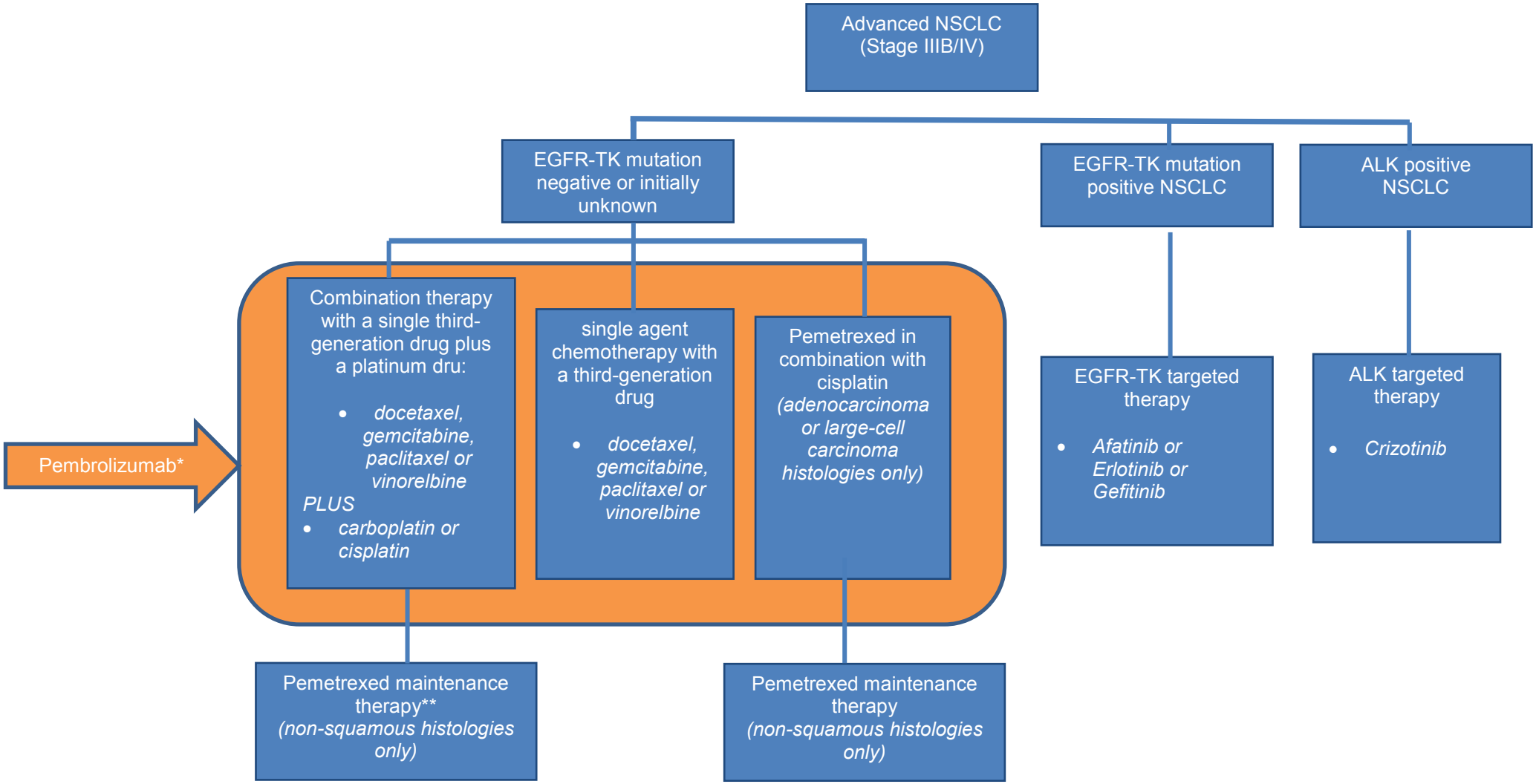
(WHO 0, 1 or a Karnofsky score of 80–100) chemotherapy should be offered; where the chemotherapy should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) (NICE CG 121).[64] Patients who are unable to tolerate such combination may be offered single-agent chemotherapy with a third-generation drug.[64] Pemetrexed in combination with cisplatin is also recommended if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (TA 181). [65]

Platinum-based doublet chemotherapy (PT-DC) as first-line treatment for NSCLC is associated with an ORR of between 15%-32%, and median progression-free survival (PFS) and overall survival (OS) of 4.0 to 5.1 and 8.1 to 10.3 months, respectively.[66] Despite the benefits associated with platinum-based chemotherapy or a targeted therapy, survival remains poor for patients with advanced NSCLC.[3] Over the past decade, the treatment approach to advanced NSCLC has evolved to incorporate predictive markers of benefit from treatment (such as sensitising EGFR mutation), allowing for improvements in clinical outcomes and treatment toxicity. However, the use of targeted therapies is limited to specific subpopulations, and all patients eventually experience disease progression through primary or acquired resistance.[67] Similarly all patients with stage IV NSCLC inevitably develop resistance to chemotherapy and experience disease progression[4]. Consequently, there remains a critical unmet medical need for more effective first-line therapy options, as the majority of patients continue to face a very poor prognosis. In addition, there is an urgent need to identify and validate more predictive biomarkers that will allow clinicians to tailor therapies to treat those who will benefit most from them.

With this submission, pembrolizumab is proposed to be used as a first-line treatment option for adult patients with metastatic NSCLC with PD-L1 TPS ≥50% and no EGFR or ALK positive tumour mutation.

The proposed positioning of pembrolizumab in the treatment pathway (Figure 3) is expected to displace the use of platinum-doublet chemotherapy, single agent chemotherapy or pemetrexed in combination with cisplatin (latter for the subgroup of adenocarcinoma patients only) as a first-line treatment option for patients with advanced stage IV NSCLC who have received no prior therapy. In addition, PD-L1 expression will be used as a predictive biomarker for the identification of patients with advanced NSCLC most likely to experience significant clinical benefit from treatment with pembrolizumab.

Figure 3: First-line treatment algorithm for advanced NSCLC with proposed positioning of pembrolizumab



** 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)*

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

In the UK, lung cancer is the most common cause of cancer death. Over 35,000 people die from lung cancer each year, accounting for more than 1 in 5 cancer deaths.[68]

NSCLC is potentially curable when diagnosed at an early stage; however over half of those diagnosed with lung cancer present at stage IV which is associated with a poor prognosis.[69]

Treatment for patients with advanced NSCLC aims to prolong OS and improve HRQoL by improving symptoms. Patients with a good performance status have been shown to benefit from first-line therapy however approximately 55% of patients will continue to second line therapy due to disease progression.[70-73] There are limited treatment options for advanced NSCLC after disease progression, and these are subject to tumour histology and presence of mutations (see section 3.3). Despite recent advances in therapy, patients with NSCLC have a poor prognosis that has not changed significantly over the past decade.[52] The median survival is only 6 to 10 months; duration of response is limited, and almost all patients relapse and die,[26-29] the corresponding 5-year OS rate for these stage IV patients is 3%.[73].

The number of expected cases of NSCLC for 2017 in England is 27,215; of which 12,441 are expected to be stage IV. In total, 1,447 patients are expected to be eligible for treatment with pembrolizumab (see Table 5 and section 6.2).

Table 5: Estimated patient numbers for England, 2017-2021

Year	2017	2018	2019	2020	2021
Total NSCLC cases	27,215	27,324	27,433	27,543	27,653
Total NSCLC stage IV cases	12,441	12,491	12,541	12,591	12,641
Total 1L stage IV patients with NSCLC that is >50% PD-L1 positive	1,769	1,776	1,783	1,790	1,798
Total 1L EGFR/ALK negative, >50% PD-L1 positive patients eligible for pembrolizumamb	1,447	1,453	1,459	1,464	1,470

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

According to the NICE guideline for the diagnosis and treatment of lung cancer (CG121)[64] published in April 2011, chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100). Specifically for patients with advanced NSCLC, a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) should be offered. For patients intolerant to platinum combination therapy, single-agent chemotherapy with a third generation drug should be offered.

Details of relevant NICE guidance published for the first-line treatment of patients with advanced NSCLC, are provided below:

- TA181:[65] In September 2009, NICE recommended pemetrexed (Alimta, Eli Lilly and Company Limited) in combination with cisplatin as an option for the first-line treatment of patients with locally advanced or metastatic NSCLC only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.
- TA192:[63] In July 2010, NICE recommended Gefitinib (Iressa, AstraZeneca) as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.
- TA258:[62]In June 2012, NICE recommended Erlotinib (Tarceva, Roche Products) as a possible treatment option for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and the company provides erlotinib with the discount agreed in the patient access scheme.
- TA 310:[61] In April 2014 NICE recommended afatinib (Giotrif®, Boehringer-Ingelheim) as an option for treating adults with locally advanced or metastatic NSCLC if the tumour tests positive for EGFR mutation and the patient has not previously had an EGFR-TK inhibitor, and only if the manufacturer provides afatinib with the discount agreed in the PAS.

- TA406:[60] In September 2016, NICE recommended crizotinib as as an option for untreated ALK-positive advanced NSCLC in adults, and only if the manufacturer provides crizotinib with the discount agreed in the PAS

Additionally, in 2012 NICE published Quality Standards (NICE QS17)[74] that define clinical best practice regarding the diagnosis and management of lung cancer in adults, and the supportive care provided to people with lung cancer. Quality statement 12 on "Systemic therapy for advanced NSCLC" states that people with stage IIIB or IV NSCLC and eligible performance status are offered systemic therapy (first- and second-line) in accordance with NICE guidance, that is tailored to the pathological sub-type of the tumour and individual predictive factors.[74]

NICE diagnostic guidance (DG9[75]) has recommended a number of methods for EGFR mutation testing in adults with previously untreated, locally advanced or metastatic NSCLC, that are clinically and cost effective for informing treatment decisions as currently recommended by NICE.

3.6: Details of other clinical guidelines and national policies

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

European Society for Medical Oncology (ESMO)[76]

ESMO has recently published updated clinical practice guidelines concerning the diagnosis, treatment and follow-up of metastatic NSCLC.

For patients with Eastern Cooperative Oncology Group performace status (ECOG PS) 0-2, the recommended first-line treatment option is platinum-based doublet chemotherapy.[76] The guideline also states that the incorporation of pemetrexed and bevacizumab into individual treatment schedules should be considered. For patients with ECOG PS ≥2, platinum-based (preferably carboplatin) doublets should be considered in eligible PS 2 patients. Single-agent chemotherapy with gemcitabine, vinorelbine and docetaxel represents an alternative treatment option. Poor PS (3– 4) patients should be offered BSC in the absence of documented activating (sensitising) EGFR mutations or ALK rearrangements.

In patients with activating EGFR mutations, first-line treatment with a tyrosine kinase inhibitors (TKI) such as afatinib, erlotinib, or gefitinib, should be considered as front-line

therapy .[67] Similarly, patients with NSCLC harbouring an ALK rearrangement should be considered for treatment with crizotinib.

The guideline describes the range of appropriate treatment options for patients in the second-line setting. Based on the KEYNOTE-010 trial data,[7] pembrolizumab 2 mg/kg Q3W is specified[76] as an appropriate option in pretreated patients with platinum-pretreated, advanced NSCC expressing PD-L1.

National Comprehensive Cancer Network (NCCN) (2016) [77]

The recently updated NCCN guideline (version 1.2017) states that for patients who test positive for PD-L1, first line therapy with permbrolizumab is appropriate. The guideline describes that in the context of first-line pembrolizumab therapy, PD-L1 expression levels of ≥50% are considered a positive test result. For patients with EGFR mutation, the NCCN guideline recommends erlotinib, afatinib or gefitinib as first-line treatment options. For patients with ALK rearrangement, crizotinib is the recommended first-line treatment option. 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 performace status (ECOG PS) 0 - 2; or BSC if ECOG PS 3 or 4.

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

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

3.8: Equality issues

We do not anticipate any equity or equality issues.

4. Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1: Systematic Review

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

4.1.2: Search strategy description

A systematic literature search was conducted May 10, 2016 in Medline, EMBASE, and Cochrane Central Register of Controlled Trials databases, from inception to present. The database searchs were supplemented with manual searches of the clinical trial registry (US National Institute of Health's (NIH) ClinicalTrial.gov) and conference proceedings from the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) Annual Meetings (for the past two years); and the company's own records to identify additional study information that had not yet been published in a peer-reviewed journal.

The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design (PICOS criteria presented in Table 6), using a combination of the search terms such as *carcinoma*, *lung cancer*, *non-small cell*, *metastatic*, *advanced*, within the restriction limit of "randomised controlled trials" (RCTs) (see Appendix 2 for full details of the search strategy by database). To meet the requirements of different regulatory authorities, all the comparators recommended for treatment of advanced NSCLC were included in the search strategy (see Appendix 2). However, to address the decision problem set by NICE, only studies with comparators relevant to the UK setting have been included (see PICOS eligibility criteria in Table 6).

4.1.3: Study selection

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

Two investigators working independently screened all titles and abstracts identified in the literature that could potentially meet the inclusion criteria (see Table 6). Full articles were retrieved for further detailed assessment by the same reviewers. Discrepancies occurring

between the two investigators were resolved by involving a third investigator and reaching consensus.

For selection of pembrolizumab specific studies, only the RCTs comparing pembrolizumab with any of the relevant comparators were included (see Table 6). For selection of studies for indirect and mixed treatment comparisons we included RCTs with comparisons between any of the interventions of interest (see section 4.10.1).

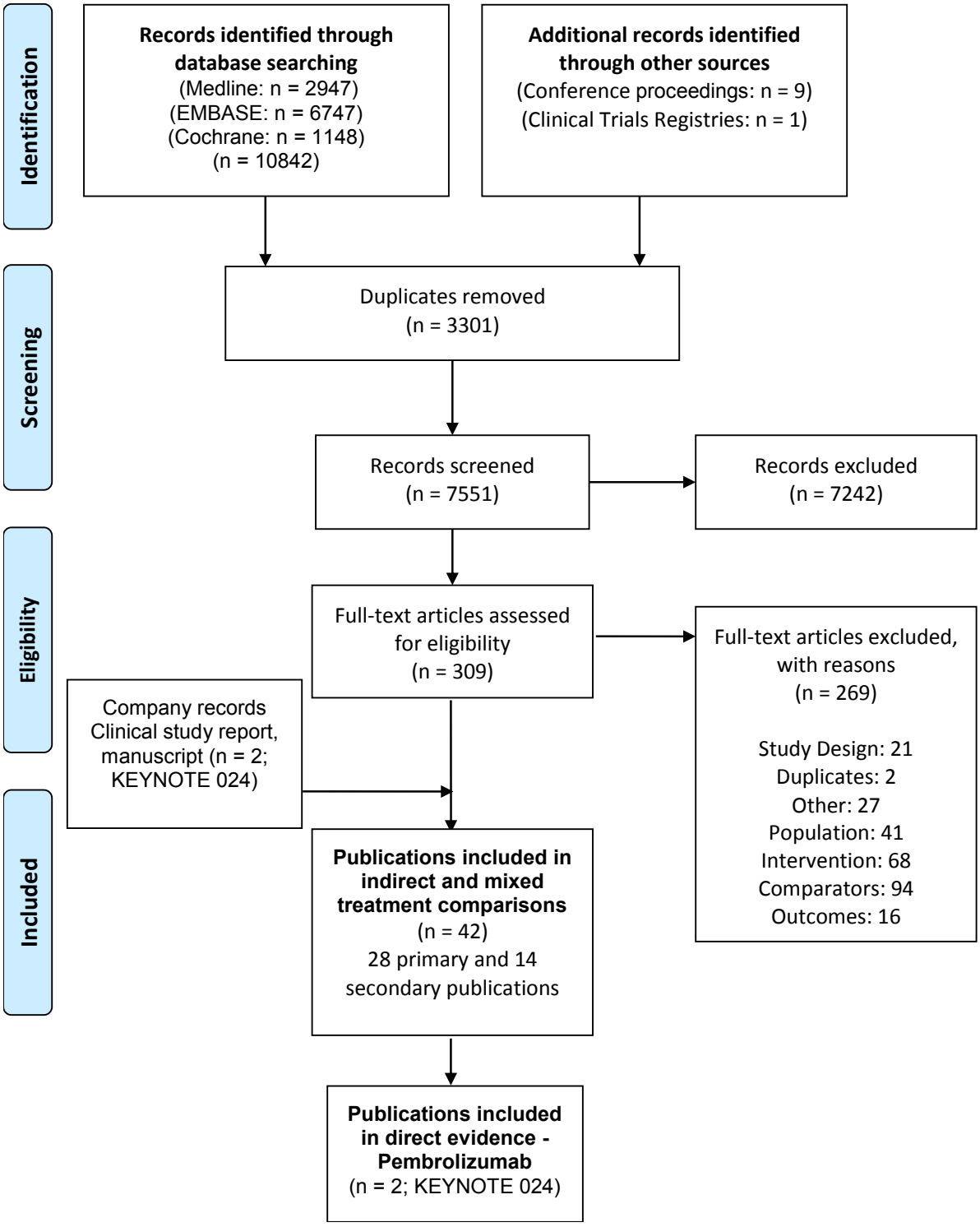
Table 6: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with metastatic NSCLC who were previously untreated with systemic therapy for their metastatic disease	
Intervention	Pembrolizumab / MK-3475	Any other intervention
Comparators	• Platinum (Carboplatin or Cisplatin) + pemetrexed (non-squamous only) • Platinum (Carboplatin or Cisplatin) + pemetrexed, followed by pemetrexed maintenance (non-squamous only) • Platinum (Carboplatin or Cisplatin) + docetaxel • Platinum (Carboplatin or Cisplatin) + paclitaxel • Platinum (Carboplatin or Cisplatin) + gemcitabine • Platinum (Carboplatin or Cisplatin) + vinorelbine • Non-pemetrexed platinum (Carboplatin or Cisplatin) doublet, followed by pemetrexed switch maintenance (non-squamous only)	Any other comparison
Outcomes	At least one of the following outcomes$: • Overall survival (OS) • Progression-free survival (PFS) • Overall response rate • Health-related quality of life • Grade 3 and above adverse events	Other efficacy and safety outcomes to be considered for analysis, but each study must include at least one of those presented to the left
Study design	Randomised controlled trials (RCTs)	Non-randomised clinical trials, prospective and retrospective observational studies, case studies
Language restrictions	English	Any other language
Time	1995 onwards	
$ No network meta-analysis was proposed for adverse events or HRQoL, as these are inconsistently reported across trials, both in terms of grouping of adverse events and in terms of criteria for reporting (ie. percent prevalence as a cutoff point for inclusion in publication).		

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

The electronic search yielded 10,842 citations (Medline: n = 2947; EMBASE: n = 6747; Cochrane Clinical Trial Registry: n = 1148) through the database searches, following which nine conference abstracts, and one clinical trial registry from the manual search were added. Of these, 309 were selected for full text review; 269 were excluded for not meeting the PICOS criteria. Two company records were added at this stage (KEYNOTE 024 clinical study report and manuscript)[5, 21] giving rise to 42 studies (28 primary and 14 secondary publications) that were included in the evidence base for the network of indirect evidence (see section 4.10). As shown in the PRISMA flow diagram (Figure 4) one study, KEYNOTE-024, (reported in one clinical study report [CSR][21] and one publication[5]) met the inclusion/exclusion criteria of the systematic review (Table 6), and provides the evidence base for the direct evidence of pembrolizumab in the population covered by the decision problem. A complete reference list of the included studies has been provided in Appendix 3.

Figure 4: PRISMA flow diagram of the systematic review process



4.1.5: Single study data drawn from multiple sources

A list of studies relevant to the decision problem is given in Table 7:

- KEYNOTE-024 data consists of one CSR[21] and one publication[5] (in addition to an entry in clinicaltrials.gov [78]).

4.1.6: Complete reference list for excluded studies

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

4.2 List of relevant randomised controlled trials

4.2.1: List of relevant RCTs involving the intervention of interest

Table 7: List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
KEYNOTE-024	• Histologically or cytologically confirmed diagnosis of NSCLC, is stage IV, does not have an EGFR sensitizing (activating) mutation or ALK translocation, and has not received prior systemic chemotherapy treatment for their metastatic PD-L1 strong tumour as determined by IH at a central laboratory.(i.e. Tumour Proportion Score (TPS*) of ≥50%) • Measurable disease (based on RECIST 1.1) as determined by the site • ECOG Performance status of 0 or 1 *TPS is the percentage of viable tumour cells showing partial or complete IHC membrane staining.	Pembrolizumab 200 mg IV Q3W	SOC (comprised of one of the following): • *Pemetrexed 500 mg/m2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (this arm was permitted for non-squamous histologies only)* • *Pemetrexed 500 mg/m2 Q3W and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (this arm was permitted for non-squamous histologies only)* • *Gemcitabine 1250 mg/m2 days 1 and 8 and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles* • *Gemcitabine 1250 mg/m2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles* • *Paclitaxel 200 mg/m2 Q3W and carboplatin AUC 5-6 day 1 Q 3W for 4-6 cycles followed by optional pemetrexed maintenance (pemetrexed maintenance was permitted for non-squamous histologies only)*	• ClinicalTrials.gov reference: NCT02142738 (78) • KEYNOTE-024 Clinical Study Report (21) • Reck M et al (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer *N Engl J Med* DOI: 10.1056/NEJMoa1606774

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1: Key aspects of listed RCTs

KEYNOTE-024[5, 21]

Trial design:

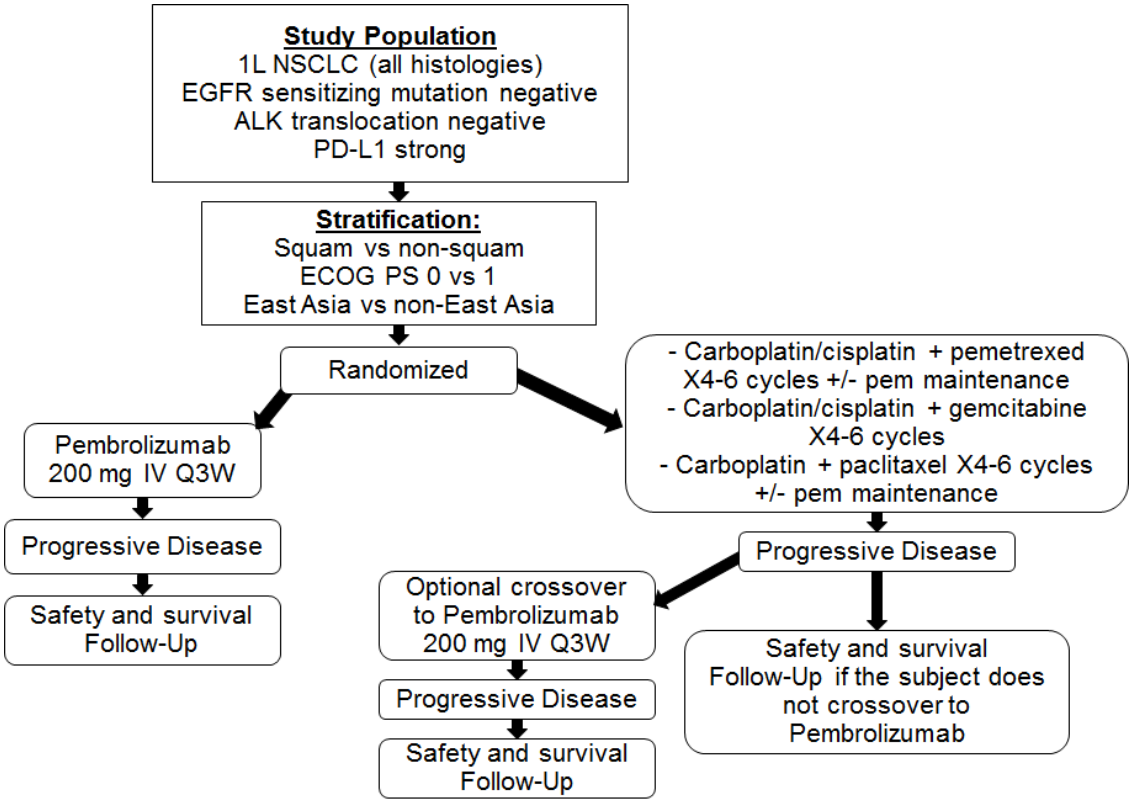
KEYNOTE-024 was a multicentre, international, randomised, open label, controlled phase III trial of intravenous (IV) pembrolizumab monotherapy versus the choice of multiple standard of care platinum based chemotherapies in subjects previously untreated for their stage IV, PD-L1 strong (defined as Tumour Proportion Score [TPS] ≥ 50%), non-small cell lung cancer (NSCLC). Please see Appendix 4 for further information regarding the rationale for PD-L1 as a predictive biomarker

Enrolled subjects had tumours which were classified as PD-L1 strong, who lacked an EGFR sensitizing mutation and were ALK translocation negative non-small cell lung cancer (NSCLC). Subjects were randomised in a 1:1 ratio to receive pembrolizumab 200 mg IV every 3 weeks (Q3W) or standard of care (SOC), which comprised of the investigator's choice of one of the platinum doublets listed below:

- Pemetrexed 500 mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (this arm was permitted for non-squamous histologies only)
- Pemetrexed 500 mg/m^2 Q3W and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (this arm was permitted for non-squamous histologies only)
- Gemcitabine 1250 mg/m^2 days 1 and 8 and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles
- Gemcitabine 1250 mg/m^2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles
- Paclitaxel 200 mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q 3W for 4-6 cycles followed by optional pemetrexed maintenance (pemetrexed maintenance was permitted for non-squamous histologies only)

The design of KEYNOTE-024 is depicted in Figure 5 below:

Figure 5: Study design of KEYNOTE-024



Furthe details concerning the dose selection and timing of dose administration for the pembrolizumab arm is provided in Appendix 5.

After a screening phase of up to 42 days, eligible subjects were randomised in a 1:1 ratio to either to pembrolizumab or SOC. Randomisation occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS).

Randomisation was stratified according to the following factors:

- Geography: East Asia vs non-East Asia
- ECOG PS: 0 vs 1.
- Histology: squamous vs non-squamous

The specific platinum doublet (including whether pemetrexed maintenance was to be offered for those subjects with non-squamous histologies) as well as the dose to be administered must have been identified prior to randomisation. While pemetrexed maintenance was optional, it was strongly recommended in subjects with non-squamous histologies, with the study protocol advising it should have been administered unless toxicity or decline in performance status precluded its administration, and radiographic imaging did not demonstrate PD after completion of at least 4 cycles of platinum doublet.

Subjects who received one of the platinum doublets above in the neoadjuvant or adjuvant setting were not permitted to receive the same platinum doublet in this trial if randomised to the control arm, unless a known contraindication prohibited treatment with another platinum doublet. Subjects received assigned treatments during a 3-week (Q3W) dosing cycle (for both the control and pembrolizumab arms).

Subjects were evaluated every 9 weeks (63 +/- 7 days) with radiographic imaging to assess response to treatment. All imaging obtained on study was submitted for a central radiologists' review, who assessed the images using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 for determination of objective response rate (ORR) and progression-free survival (PFS).

Treatment on study continued until one of the following:

- Disease progression (according to RECIST 1.1)
- Unacceptable adverse event(s)
- Intercurrent illness that prevented further administration of treatment
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedures requirements
- Subject had received 35 treatments of study medication (pembrolizumab arm only)
- Administrative reasons

When a subject discontinued/withdrew from participation in the trial, all applicable activities scheduled for the final trial visit were performed at the time of discontinuation.

Subjects receiving pembrolizumab who attained a complete response (CR) were permitted to consider stopping trial treatment if they met criteria for suspending therapy. These subjects, in addition to subjects receiving pembrolizumab who stopped drug administration

after receiving 35 trial treatments for reasons other than disease progression or intolerability, may have been eligible for re-treatment in the Second Course Phase after they experienced radiographic disease progression, at the discretion of the investigator. Response or progression in the Second Course Phase did not count towards the ORR and PFS of the primary endpoint in this trial. The decision to re-treat was at the discretion of the investigator, and only if the patient met the criteria for retreatment and the trial was still ongoing. Retreatment was limited to 17 cycles.

Subjects randomised to the control arm who experienced documented progression of disease (PD) per RECIST 1.1 by blinded independent central radiology review and met all crossover criteria outlined in the study protocol (see Appendix 6) had the opportunity to crossover to pembrolizumab. Treatment was limited to 35 administrations of pembrolizumab during the crossover phase. Crossover subjects who subsequently achieved a CR per RECIST 1.1 had the option to suspend pembrolizumab therapy. A crossover subject was permitted to receive treatment in a second course phase if they meet the pre-defined crossover criteria (see Appendix 6). Subjects had post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up

After the end of treatment each subject was followed for a minimum of 30 days for adverse event (AE) monitoring. Serious adverse events (SAE) and Events of Clinical Interest (ECI) were collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiated new anticancer therapy, whichever was earlier.

One PFS analysis was planned during the course of the trial. OS analysis was also performed at this final PFS analysis. A final OS analysis was planned for after about 170 deaths had occurred between the pembrolizumab arm and control, and was expected to occur approximately 14 months after enrollment completion. In addition, it was prespecified that the trial may be stopped early at the recommendation of the Data Monitoring Committee (DMC) if the risk/benefit ratio to the trial population as a whole was unacceptable.

Eligibility criteria:

Participation in this trial was dependent upon supplying tumour tissue from locations that had not been radiated. Formalin-fixed specimens obtained either at the time of or after the subject had been diagnosed with metastatic disease were required for determination of PD-L1 status. Biopsies obtained prior to receipt of neoadjuvant/adjuvant chemotherapy was permitted. The specimen was evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only subjects whose tumours expressed PD-L1 at a

predefined cut point (TPS ≥ 50%) as determined by the central laboratory facility were eligible for randomisation.

Key inclusion criteria:

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

- Histologically or cytologically confirmed diagnosis of NSCLC, is stage IV, does not have an EGFR sensitizing (activating) mutation or ALK translocation, and has not received prior systemic chemotherapy treatment for their metastatic NSCLC.
- Measurable disease (based on RECIST 1.1) as determined by the site.
- ≥18 years of age on day of signing informed consent.
- Life expectancy of ≥3 months
- Eastern Cooperative Oncology Group (ECOG) Performance status of 0 or 1
- PD-L1 strong tumour as determined by IHC at a central laboratory (tumour proportion score [TPS] ≥50%).

Key Exclusion Criteria

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

- EGFR sensitizing mutation and/or an ALK translocation.
- Received systemic therapy for the treatment of their stage IV NSCLC (completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease).
- Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.
- Tumour specimen is not evaluable for PD-L1 expression by the central laboratory.
- Received systemic steroid therapy < 3 days prior to the first dose of trial treatment or received any other form of immunosuppressive medication.

- Subject is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent for NSCLC, radiation therapy, and/or surgical resection).
- Received prior systemic cytotoxic chemotherapy, biological therapy, OR major surgery within 3 weeks of the first dose of trial treatment; received thoracic radiation therapy of > 30 Gy within 6 months of the first dose of trial treatment.
- Received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
- Untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on the baseline brain imaging obtained during the screening period OR identified prior to signing the ICF.
- Active autoimmune disease that has required systemic treatment in past 2 years. Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Has interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or IV steroids.

Settings and locations where the data were collected:

This was a global study conducted in 16 countries: Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, UK, USA.

21 patients from the UK participated in the study at 9 UK sites.

Trial drugs and concomitant medications:

Subjects were randomised in a 1:1 ratio to receive IV pembrolizumab 200 mg Q3W or SOC, which comprised the investigator's choice of one of the platinum doublets listed below:

- Pemetrexed 500 mg/m2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (this arm was permitted for non-squamous histologies only)

- Pemetrexed 500 mg/m2 Q3W and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (this arm was permitted for non-squamous histologies only)
- Gemcitabine 1250 mg/m2 days 1 and 8 and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles
- Gemcitabine 1250 mg/m2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles
- Paclitaxel 200 mg/m2 Q3W and carboplatin AUC 5-6 day 1 Q 3W for 4-6 cycles followed by optional pemetrexed maintenance (pemetrexed maintenance was permitted for non-squamous histologies only)

For the control chemotherapy options, the choice of platinum doublet and the respective dose of each chemotherapeutic agent must have been decided and recorded prior to randomisation. If a subject received a platinum doublet as part of neoadjuvant/adjuvant therapy that doublet may not have been chosen as a standard of care chemotherapy control option for this trial unless a contraindication precluded treatment with an alternate regimen. Pemetrexed was not permitted as a treatment for subjects with squamous histologies.

Concomitant medications

All treatments that the investigator considered necessary for a subject's welfare could be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication was recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. Palliative and supportive care was permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery for tumour control or symptom management was not permitted during the study. Palliative radiotherapy was permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion was not a RECIST 1.1 defined target lesion and was not administered for tumour control. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy. The specifics of the radiation treatment, including the location, were to be recorded.
All concomitant medications received within 30 days before the first dose of trial treatment through the Safety Follow-up Visit should be recorded. Further details of acceptable and prohibited concomitant Medications are provided in Appendix 7.

Primary, secondary and tertiary objectives

Primary objectives:

- To compare the PFS per RECIST 1.1 as assessed by blinded independent central radiologists' (BICR) review in subjects with PD-L1 strong, 1L metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapies.

PFS was defined as the time from randomisation to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occured first.
Tumours staining for PD-L1 with 50% or greater were considered strong expressers (TPS ≥50%).

Secondary objectives:

- Evaluate the safety and tolerability profile of pembrolizumab in subjects with 1L metastatic PD-L1 strong NSCLC.
- Evaluate the overall survival (OS) in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies
- Evaluate the overall response rate (ORR) as assessed by RECIST 1.1 by BICR review in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies

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

ORR was defined as the proportion of the subjects in the analysis population who had either a complete response (CR) or partial response (PR). Responses were based upon blinded independent central radiologists' review per RECIST 1.1.

Exploratory objectives:

- To evaluate PFS per immune-related response criteria (irRC) in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies
- Evaluate the PFS as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab compared to SOC chemotherapies.
- To evaluate ORR per irRC in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.
- To evaluate response duration per RECIST 1.1 by BICR review in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.
- To evaluate response duration per irRC in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.
- To evaluate patient-reported treatment effects at pre-specified time points while on treatment and post-discontinuation as measured by changes from baseline in all domains and single items of the QLQ-C30 and LC13, with particular emphasis on QLQ-C30 QoL domain, chest pain (LC13 question 10), cough (LC13 ques tion 1) and dyspnea domain (LC13 questions 3-5) in previously untreated advanced NSCLC subjects receiving either pembrolizumab or comparator.
- To summarize and compare by treatment arm, the number and proportion of subjects who improved, worsened or remained stable for all domains and single items of the QLQ-C30 and LC13.
- To describe by treatment arm, the proportion of subjects reporting “no”, “some”, or “extreme” EQ-5D health state profiles at pre-specified time points.
- To evaluate within each treatment arm, quality-adjusted survival using the Quality-adjusted Time without Symptoms or Toxicity (Q-TWiST) approach.
- To evaluate within each treatment arm, the difference in patient reported outcome (PRO) score for progressed subjects compared to subjects with no radiographic evidence of tumour progression.
- To evaluate genomic signatures that predict for response in subjects treated with pembrolizumab.

Clinical Procedures/ Assessments

Biomarker assessment

PD-L1 expression was assessed in formalin-fixed tumour samples at a central laboratory using the IHC 22C3 pharmDx assay (Dako North America, Carpinteria, CA). Tumour samples were obtained from core needle or excisional biopsies or resected tissue collected at the time metastatic disease was diagnosed. Fine-needle aspirates or samples collected from irradiated sites or before administration of (neo)adjuvant were not permitted.[79, 80]

Tumours staining for PD-L1 with 50% or greater were considered strong expressers (TPS ≥50%).

Response Assessment: Tumour imaging

The initial tumour imaging was performed within 30 days of randomisation date. The subject must have had at least one radiographically measurable lesion per RECIST 1.1 per local reading. On-study imaging was performed every 9 weeks (63 ± 7 days) from the date of randomisation or more frequently if clinically indicated.

If RECIST 1.1 defined progression was documented by blinded independent central radiology review, then the subject could have discontinued trial treatment unless, in the opinion of the investigator, the subject was deriving clinical benefit from the therapy and the subject did not have any signs or symptoms of clinically instability. Clinical stability was defined as:

- Absence of symptoms and signs indicating clinical significant progression of disease (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease or progressive tumour at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Immune related response criteria (irRC) assessed by the blinded independent radiology review was provided to the investigator at the time of RECIST 1.1 defined progression in order to aid in decisions regarding treatment continuation. If treatment was continued beyond RECIST 1.1 defined tumour progression, subsequent imaging assessments were based upon modified RECIST criteria. Modified RECIST 1.1 is an adapted form of RECIST 1.1 to account for the unique tumour response seen in this class of therapeutics.

In modified RECIST 1.1, if imaging showed PD, tumour assessment could have been repeated ≥ 4 weeks later at the site in order to confirm PD with the option of continuing treatment for clinically stable subjects.

In determining whether or not the tumour burden had increased or decreased, investigators considered all target lesions as well as non-target lesions. Subjects deemed clinically unstable were not required to have repeat imaging for confirmation. If radiologic progression was confirmed at the subsequent scan then the subject was discontinued from trial treatment unless, if in the opinion of the investigator, the subject was deriving clinical benefit and upon consultation with the Sponsor. If radiologic progression was not confirmed, then the subject was to resume/continue trial treatment and have their next scan according to the every 9 weeks (63 ± 7 days) schedule.

Observation phase: Imaging

Imaging during the observation phase was obtained every 9 weeks (63 ± 7 days) until the subject experienced disease progression that had been confirmed by blinded independent central radiology review or started a new antineoplastic therapy.

Subjects who move into the Second Course Phase continued to have scans performed every 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment for Year 1 and every 3 months thereafter.

Brain Imaging

For patients with no previous history of brain metastases, screening brain imaging needed to be obtained. This scan could have been collected up to 42 days prior to randomization. If lesions were identified, the lesions had to be treated, regardless of symptoms.

Patient Reported Outcomes (PROs)

The EuroQol EQ-5D-3L, EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were administered by trained site personal and completed electronically by the subjects prior to all other study procedures and receiving results of any tests.

Tumour Tissue Collection

Tumour tissue for biomarker analysis from formalin fixed paraffin embedded tumour tissue sample or newly obtained formalin fixed biopsy of a tumour lesion not previously irradiated was required to be provided in the form of a tissue block or unstained slides and received by the central vendor before randomisation. Only subjects whose tumours demonstrate strong PD-L1 expression were eligible for enrollment.

Populations used for analysis:

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

4.3.2: Comparative summary of the methodology of the RCTs

Table 8: Comparative summary of trial methodology

Trial number (acronym)	**KEYNOTE-024**
Location	Global study conducted in 16 countries: Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, UK, and USA.
Trial design	Randomised, open label, controlled phase III trial of intravenous (IV) pembrolizumab monotherapy versus the choice of multiple standard of care platinum based chemotherapies in subjects previously untreated for their stage IV, PD-L1 strong, non-small cell lung cancer (NSCLC). Tumour response centrally reviewed by blinded independent radiologists.
Key eligibility criteria for participants	• Histologically or cytologically confirmed diagnosis of NSCLC, is stage IV, does not have an EGFR sensitizing (activating) mutation or ALK translocation, and has not received prior systemic chemotherapy treatment for their metastatic • PD-L1 strong tumour as determined by IH at a central laboratory.(i.e. Tumour Proportion Score (TPS*) of ≥50%) • Measurable disease (based on RECIST 1.1) as determined by the site • ECOG performance status of 0 or 1
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as out-patients.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=) and comparator(s) (n=)** **Permitted and disallowed concomitant medication**	Subjects were randomised in a 1:1 ratio to receive IV pembrolizumab 200 mg Q3W (n = 154) or SOC (n = 151), which comprised the investigator's choice of one of the platinum doublets listed below: • Pemetrexed 500 mg/m2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (this arm was permitted for non-squamous histologies only) • Pemetrexed 500 mg/m2 Q3W and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (this arm was permitted for non-squamous histologies only) • Gemcitabine 1250 mg/m2 days 1 and 8 and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles • Gemcitabine 1250 mg/m2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles • Paclitaxel 200 mg/m2 Q3W and carboplatin AUC 5-6 day 1 Q 3W for 4-6 cycles followed by optional pemetrexed maintenance (pemetrexed maintenance was permitted for non-squamous histologies only) Disallowed concomitant medicines: • Immunotherapy not specified in this protocol. • Chemotherapy not specified in this protocol. • Investigational agents other than pembrolizumab. • Surgery for symptom management or tumour control • Radiation therapy for tumour control • Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. • Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest, use as a pre-medication for chemotherapeutic agents specified in the protocol, or for use as a pre-medication in subjects with a known history of an IV contrast allergy administered as part of CT radiography.

	• For control arm subjects, concomitant meds should be prohibited as per local standard of care practices and/or the respective package insert details. • Bisphosphonates and/or RANKL inhibitor therapies cannot be initiated after informed consent has been signed. These therapies may be continued IF treatment with an agent from one of these two classes was initiated PRIOR to signing informed consent. Exclusion criteria list provides further details of other medications prohibited in this trial.
Primary outcomes (including scoring methods and timings of assessments)	Primary objective: To compare the Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded independent central radiologists' review in subjects with PD-L1 strong, 1L metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies. PFS was defined as the time from randomisation to the first documented disease progression per RECIST 1.1 based on blinded independent central radiologists' review or death due to any cause, whichever occurred first. ITT population served as the primary population for the analyses of PFS and OS. On-study imaging was performed every 9 weeks (63 ± 7 days). If RECIST 1.1 defined progression was documented by blinded independent central radiology review, the subject could have discontinued trial treatment unless, the investigator believed the subject continued to derive clinical benefit from treatment. While continuing trial treatment, patients continued to be scanned according to the every 9 weeks (63 ± 7 days) schedule Subjects randomised to the control arm who experienced PD per RECIST 1.1 and met all protocol defined crossover criteria had the opportunity to crossover to pembrolizumab. Treatment was limited to 35 administrations of pembrolizumab during the crossover phase; a cross over subject was permitted to receive treatment in a second course phase if they meet the pre-defined crossover criteria Subjects receiving pembrolizumab who attained a CR in addition to subjects receiving pembrolizumab who stopped drug administration after receiving 35 trial treatments for reasons other than PD/intolerability, may have been eligible for re-treatment in the Second Course Phase after experiencing PD, at the discretion of the investigator. Response or progression in the Second Course Phase did not count towards the ORR and PFS of the primary endpoint in this trial. Retreatment was limited to 17 cycles in the second course phase.
Secondary/ tertiary outcomes (including scoring methods and timings of assessments)	The secondary objectives were as follows: • To evaluate the safety and tolerability profile of pembrolizumab in subjects with 1L metastatic PD-L1 strong NSCLC. • To evaluate the overall survival (OS) in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies • To evaluate the overall response rate (ORR) as assessed by RECIST 1.1 by blinded independent central radiology review in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies OS was defined as the time from randomisation to death due to any cause.

	Subjects without documented death at the time of the final analysis were censored at the date of the last follow-up. ORR was defined as the proportion of the subjects in the analysis population who had either a complete response (CR) or partial response (PR). Responses were based upon blinded independent central radiologists' review per RECIST 1.1.
Pre-planned subgroups	Subgroup analyses based on clinically relevant baseline patient or tumour characteristics as per study protocol: • Age category (≤65, >65 years) • Sex (female, male) • Race (white, non-white) • ECOG status (0, 1) • Geographic region of enrolling site (East Asia, non-East Asia) • Histology (squamous, non-squamous) • Smoking status (never, former, current) • Brain metastasis status (baseline brain metastasis, no baseline brain metastasis) • Investigators' choice of SOC chemotherapy
ASaT= All Subjects as Treated; DCR = Disease Control Rate; FAS = full analysis set; ITT = intention to treat; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RR = response rate;	

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

4.4.1: Statistical analysis:

KEYNOTE-024[5, 21]

Primary hypothesis

The study primary hypothesis was as follows:

Pembrolizumab prolongs PFS by RECIST 1.1 (blinded independent central radiologists' review) in subjects with PD-L1 strong NSCLC compared to SOC chemotherapies.

Tumours staining for PD-L1 with 50% or greater were considered strong expressers (TPS ≥50%).

Analysis and stopping guidelines

KEYNOTE-024 study was initiated on 05 September 2014. There was one planned analysis of ORR (IA1), one planned analysis of PFS (IA2) and two planned analyses of OS (IA2, and final analysis if efficacy bound was not crossed at IA2). Table 9 provides the summary of the OS interim analysis strategy assuming that ~110 OS events were observed at the time of the final PFS analysis.

Table 9: Summary of PFS and OS Analysis Strategies

ORR, PFS and OS Analyses	Key Endpoints	Expected Timing of Analysis	Sample size expected at time of analysis	Primary Purpose of Analysis
ORR analysis	• ORR	~16 months from study start	First 191 subjects have at least 6 months follow up	Demonstrate superiority of pembrolizumab in ORR
Final PFS analysis Interim OS analysis	• PFS (primary) • OS	~20 months from study start	~ 175 PFS (~110 OS) events between the pembrolizumab arm and the chemotherapy arm	Demonstrate superiority of pembrolizumab in PFS Examine OS effect of pembrolizumab
Final OS analysis	• OS	~28 months from study start	~170 OS events between the pembrolizumab arm and the chemotherapy arm	Examine OS effect of pembrolizumab

The data cut-off date for the IA2 results presented in this report is 09-May-2016 (report date 11-July-2016).

Sample size

KEYNOTE-024 was event-driven and planned to randomise approximately 300 subjects with 1:1 ratio into the pembrolizumab arm and the SOC arm.

The planned PFS analysis was to be conducted after approximately 175 PFS events were observed between the pembrolizumab arm and control. The sample size calculation was based on the following assumptions:

- PFS follows an exponential distribution with a median of 5.5 months in the control arm,
- Hazard ratio between pembrolizumab and control is 0.55,

- An enrollment period of 14 months and at least 6 months PFS follow-up after enrollment completion, and
- A dropout rate of 10% per year.

The overall type I error rate for this study is strictly controlled at 2.5% (one-sided). With ~175 PFS events, the study had ~98%/97% power to detect a hazard ratio of 0.55 at alpha = 2.5%/2% (one-sided) at the final PFS analysis. A p-value less than 2.5%/2% (one-sided) for PFS approximately corresponds to an empirical hazard ratio of < 0.744/0.738 (or approximately at least 7.4/7.5 months of median PFS in pembrolizumab vs. 5.5 months of median PFS in SOC

The final OS analysis was planned to be conducted after approximately 170 deaths had occurred between the pembrolizumab arm and control. The final OS analysis was expected to occur 14 months after enrollment completion. The calculation was based on the following assumptions:

- overall survival follows an exponential distribution with a median of 13 months in the control arm,
- hazard ratio between pembrolizumab and control is 0.7,
- an enrollment period of 14 months and 14-15 months follow-up after enrollment completion, and
- a dropout rate of 0.005 per month.

With ~110 OS events at interim OS analysis, the study had ~90% power to observe a hazard ratio < 1 when the true hazard ratio is 0.7, assuming that half of the subjects in the control arm cross over to pembrolizumab at the time of analysis. The final OS analysis was planned to be conducted after approximately 170 deaths have occurred between the pembrolizumab arm and control. With 170 OS events at final OS analysis, the study had ~75% power to observe a hazard ratio < 1 assuming that ~70% of the subjects in the control arm cross over to pembrolizumab. With two planned OS analyses, i.e., ~110 OS events at final PFS analysis and ~170 OS events at the final OS analysis, the study had approximately 60%/57% power to detect a hazard ratio of 0.7 at the level of 2.5%/2.0% (one-sided). However, due to the anticipated high crossover rate, it was acknowledged that the actual power could be substantially lower

Statistical methods used to compare groups for primary and secondary outcomes

The statistical methods and analysis strategy for the primary and secondary efficacy endpoints are summarised in the Table 10 below.

Table 10: KEYNOTE-024 - Analysis strategy for key efficacy endpoints

Endpoint (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary			
PFS (RECIST 1.1 by blinded independent central radiology review)	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based
Secondary			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method for estimation	ITT	Model based
ORR (RECIST 1.1 by blinded independent central radiology review)	Stratified Miettinen & Nurminen method	ITT	Subjects with missing data are considered non-responders
ITT = intention-to-treat			

The Kaplan-Meier (KM) method was used to estimate the PFS curve in each treatment group. The hazard ratio (HR) and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported.

Since disease progression is assessed periodically, progressive disease (PD) could have occurred any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event.

The KM method will be used to estimate the survival curves. The HR and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. Since subjects in the control arm were expected to discontinue from the study earlier compared to

subjects in the pembrolizumab arm because of earlier onset of PD and the opportunity to switch to the pembrolizumab treatment after the confirmed PD, the Rank Preserving Structural Failure Time (RPSFT) model was pre-specified to adjust for the effect of crossover on OS. The 95% confidence intervals of the hazard ratio for OS after adjustment of the cross-over effect were planned to be provided.

A 95% confidence interval for the difference in response rates (RR) between the pembrolizumab arm and the control as well as the p-value were planned to be provided.

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

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

- Age category (≤65, >65 years)
- Sex (female, male)
- Race (white, non-white)
- ECOG status (0, 1)
- Geographic region of enrolling site (East Asia, non-East Asia)
- Histology (squamous, non-squamous)
- Smoking status (never, former, current)
- Brain metastasis status (baseline brain metastasis, no baseline brain metastasis)
- Investigators' choice of standard of care chemotherapy

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

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

KEYNOTE-024[5, 21]

Trial population

The intention-to-treat (ITT) population that included all randomised subjects served as the primary population for the analyses of efficacy data in this trial.

Missing data approach and censoring methods

The approach for dealing with missing data in KEYNOTE-024 is described in Table 11 below:

Table 11: KEYNOTE-024: Approach for dealing with missing data

Endpoint (Description, Time Point)	Missing Data Approach
PFS (RECIST 1.1 by blinded independent central radiology review)	Model based
OS	Model based
ORR (RECIST 1.1 by blinded independent central radiology review)	Subjects with missing data are considered non-responders

In order to evaluate the robustness of the PFS endpoint, two sensitivity analyses were performed with a different set of censoring rules. Sensitivity analysis 1 was the same as the primary analysis except that it censored at the last disease assessment without PD when PD or death was documented after more than one missed disease assessment.

Sensitivity analysis 2 was the same as the primary analysis except that it considered discontinuation of treatment or initiation of new anticancer treatment, whichever occured later, to be a PD event for subjects without documented PD or death.

The censoring rules for primary and sensitivity analyses are summarised in Table 12:

Table 12: Censoring rules for Primary and Sensitivity Analyses of PFS

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

Subjects in the control arm were expected to discontinue from the study earlier compared to subjects in the pembrolizumab arm because of earlier onset of PD. As such patients may have switched to pembrolizumab treatment after the confirmed progressive disease, use of the Rank Preserving Structural Failure Time (RPSFT) model was pre-specified to adjust for the effect of crossover on OS.

The Kaplan-Meier estimates of the OS rate at time points of interest were planned to be compared between the two treatment groups to explore the confounding effect of subsequent treatments.

4.4.3: Statistical tests used in primary analysis

Table 13: Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KEYNOTE-024	Primary hypothesis: Pembrolizumab prolongs PFS by RECIST 1.1 (blinded independent central radiologists' review) in subjects with PD-L1 strong NSCLC compared to SOC chemotherapies	The ITT population served as the primary population for the analyses of efficacy data in this trial . The overall type I error rate was strictly controlled at 2.5% (one-sided). The study had ~98%/97% power to detect a hazard ratio of 0.55 at alpha = 2.5%/2% (one-sided) at the final PFS analysis. The sample size calculation was based on the following assumptions: • PFS follows an exponential distribution with a median of 5.5 months in the control arm, • Hazard ratio between pembrolizumab	Event-driven study which and planned to randomise approximately 300 subjects with 1:1 ratio into the pembrolizumab arm and the SOC arm. The sample size calculation was based on the following assumptions: 1) PFS follows an exponential distribution with a median of 5.5 months in the control arm, 2) HR between pembrolizumab and control is 0.55, 3) An enrolment period of 14 months and at least 6 months PFS follow-up after enrolment completion 4) A dropout rate of 10% per year. The assumption for the median PFS of 5.5 months in the control arm did not take into account potential prognostic implications in a biomarker selected population. As such, the control median may have been more or less than 5.5 months	Each patient participated in the trial from the time h/she signed the informed consent form through the final protocol-specified contact. Treatment on study continued until one of the following: • Disease progression (according to RECIST 1.1) • Unacceptable adverse event(s) • Intercurrent illness that prevents further administration of treatment • Investigator's decision to withdraw the subject • Noncompliance with trial treatment or procedures requirements • Subject had received 35 treatments of study medication (pembrolizumab arm only), • Administrative reasons. If a patient discontinued/ withdrew prior to study completion, all applicable activities scheduled for the final

		and control is 0.55, • An enrolment period of 14 months and at least 6 months PFS follow-up after enrolment completion, and • A dropout rate of 10% per year.		study visit were performed at the time of discontinuation.

4.5 Participant flow in the relevant randomised controlled trials

4.5.1: Number of patients eligible to enter each trial

KEYNOTE-024[5, 21]

The first subject was allocated to treatment on 19-September-2014 and the last subject included in this report was assigned treatment on 29-October-2015. The second interim analysis (IA2) was performed after 189 events of progression or death and 108 deaths had occurred and was based on a data cut-off date of 09-May-2016.

The data and safety monitoring committee (DSMC) reviewed the results on 08-June-2016 and 14-June-2016. Because pembrolizumab was superior to SOC with respect to OS at the prespecified multiplicityadjusted, one-sided alpha level of 1.18%, the external DSMC recommended that KEYNOTE-024 be stopped early to give the patients who were receiving SOC the opportunity to receive pembrolizumab.

The disposition of subjects in the ITT population from randomisation through to analysis is presented in Figure 6. Overall, 1934 patients from 142 sites in 16 countries were screened for enrollment, including 1729 who submitted samples for PD-L1 assessment. Of the 1653 patients whose samples were evaluable for PD-L1, 500 (30.2%) had a PD-L1 tumour proportion score ≥50%. The PD-L1 distribution in screen subjects is shown in Table 14.

Between September 19, 2014, and October 29, 2015, 305 patients were randomly allocated to receive pembrolizumab (n=154) or investigator-choice chemotherapy (n=151). Within the chemotherapy group, the most common regimen was carboplatin plus pemetrexed (n=67).

Table 14: Distribution in screened subjects: IA2

PD-L1 Status Among Screened Subjects	n	%
Total screened subjects With PD-L1 Samples	1729	
PD-L1 PS>=50%	500	29
PD-L1 PS 1-49%	646	37
PD-L1 PS<1%	507	29
Not Evaluable	76	4
No Data	205	12
(Database Cutoff Date: 09MAY2016).		

Figure 7 depicts the breakdown of therapies received in the chemotherapy group by tumour histology.

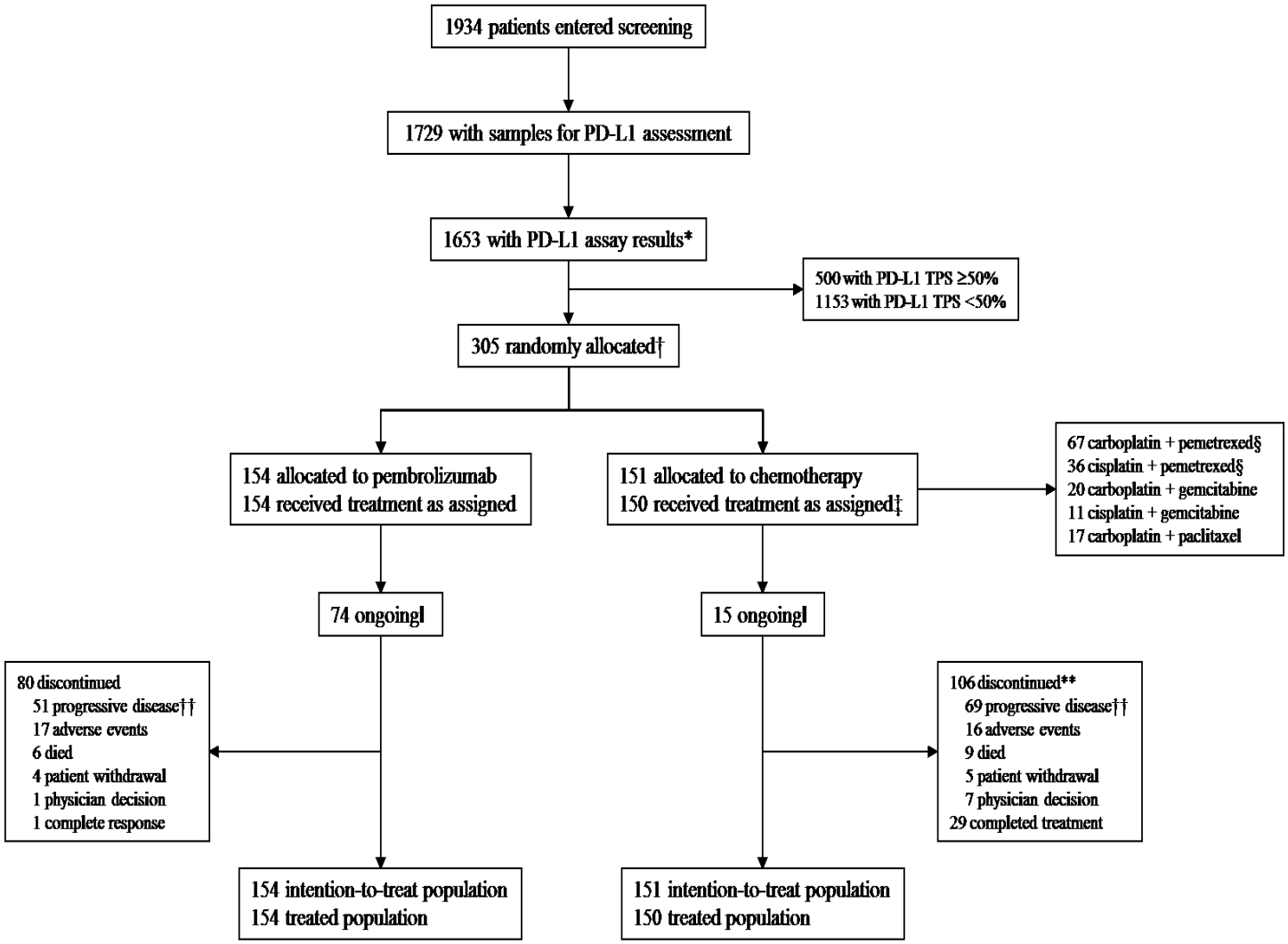
All patients in the pembrolizumab group received study treatment (Figure 6). In the chemotherapy group, one patient withdrew consent before receiving planned study treatment (Figure 6), and 46 patients received pemetrexed maintenance therapy (Figure 6).

More subjects (48.1%) randomised to pembrolizumab continue to receive the drug on study compared to subjects randomised to SOC (10.0%), which consists of pemetrexed maintenance therapy after the four to six cycles of platinum doublet chemotherapy.

More subjects randomised to SOC (42.0%) discontinued treatment for PD than subjects randomised to pembrolizumab (29.9%). A similar proportion of subjects across the two arms discontinued study medication due to AEs, clinical progression of disease, and withdrawal by subjects. More subjects in the SOC arm discontinued due to death (6.0% vs. 3.9%) and physician decision (4.7% vs. 0.6%) compared to the pembrolizumab arm. Only subjects assigned to SOC who received the protocol specified maximum of four to six cycles of platinum doublet therapy and had no evidence of disease progression could have the disposition of “completed.”

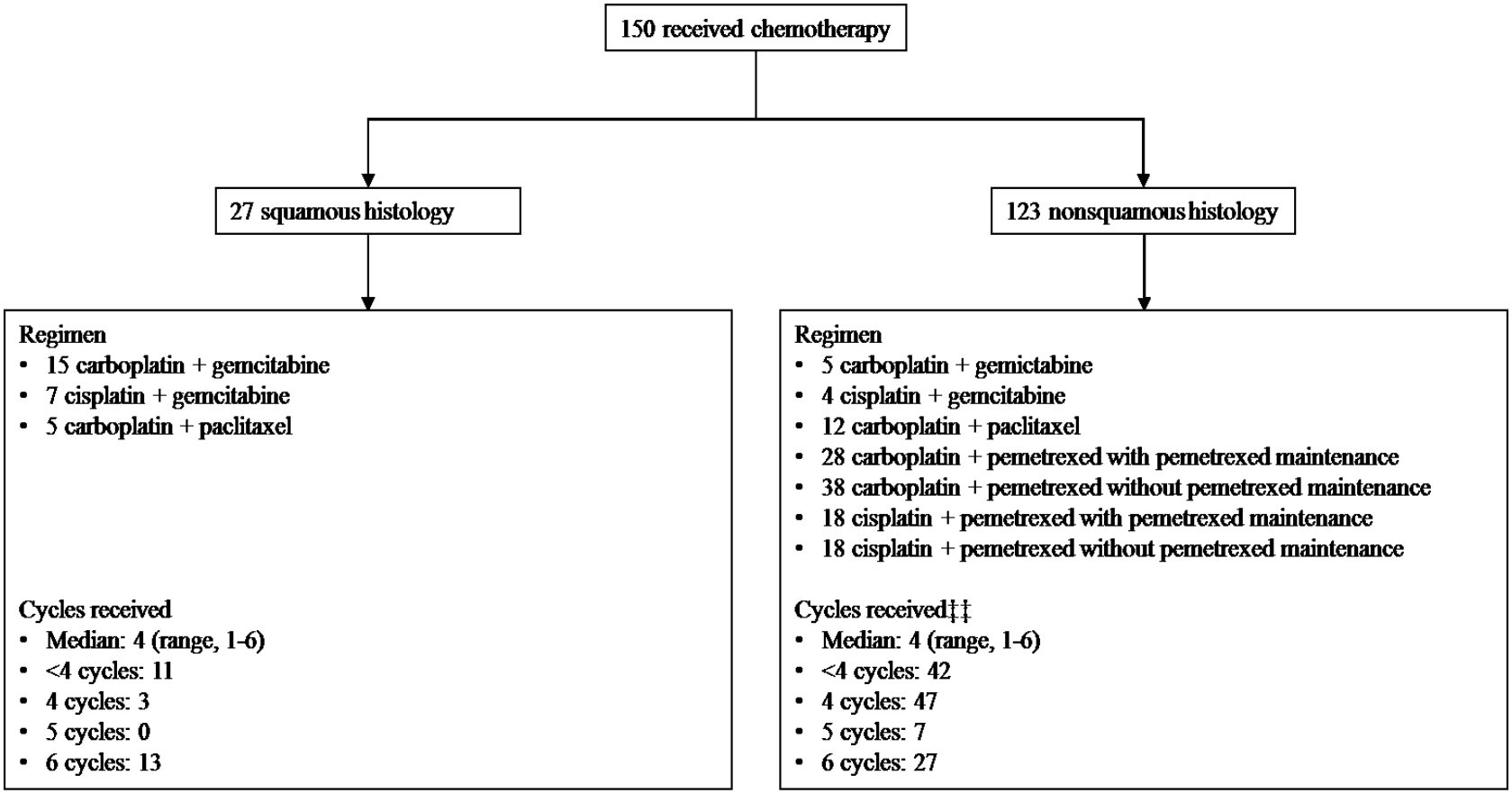
No one assigned to pembrolizumab had been treated long enough to complete therapy (two years).

Figure 6: CONSORT diagram – KEYNOTE-024 (database cutoff date: 09 May 2016)[5]



PD-L1 denotes programmed death ligand 1, TPS tumour proportion score.
**Reasons for nonevaulable samples were insufficient tumour cells (n=62), excluded sample collection method or sample type (n=11), and sample contained bone that was at least partially decalcified (n=3).*
†Reasons for screen failure were untreated brain metastases (n=59); sensitizing EGFR mutation or ALK translocation (n=30); Eastern Cooperative Oncology Group performance status of 2 or 3 (n=27); inadequate organ function (n=19); intercurrent condition prohibited by protocol or that would prevent full study participation (n=16); no histological or cytological confirmation of non–small-cell lung cancer (n=13); written, informed consent not provided (n=11); life expectancy <3 months (n=6); previous malignancy other than basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or underwent potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy (n=3); treatment with other systemic or localized antineoplastic therapy expected while on study (n=3); incorrect interpretation of PD-L1 results (n=2); lack of measurable disease per RECIST (n=2); previous systemic therapy for stage IV disease (n=2); previous systemic chemotherapy, biological therapy, or major surgery within 3 weeks or thoracic radiation >30 Gy within 6 months of first dose of study treatment (n=2); and participation within another clinical trial within 30 days of first dose of study treatment (n=1).
‡One patient who was to receive carboplatin + pemetrexed followed by pemetrexed maintenance therapy withdrew consent before receiving the first dose of study treatment.
§28 (42.4%) patients who received carboplatin + pemetrexed and 18 (50.0%) who received cisplatin + pemetrexed received pemetrexed maintenance therapy.
‖Patients without a completed study medication discontinuation form.
***Includes 66 patients who crossed over to receive pembrolizumab as part of the study.*
††Includes clinical progression.

Figure 7: Therapy received in the chemotherapy group by tumour histology[5]



4.5.2: Characteristics of participants at baseline for each trial

KEYNOTE-024[5, 21]

Baseline characteristics of the ITT population were as expected for patients with advanced NSCLC (Table 15). The majority of subjects were male (61.3%), White (82.3%), non-Hispanic (92.5%), and non-East Asian (86.9%). Most of the subjects had Stage IV adenocarcinoma (69.5%), NSCLC with no prior neo-adjuvant (98.7%), or adjuvant (97%) chemotherapy. The majority of subjects had an ECOG 1 at baseline (64.6%). The treatment arms were generally well balanced by all baseline characteristics. An imbalance was noted in the baseline smoking status; more "never-smokers" were randomised to the SOC arm as compared to pembrolizumab (12.6% vs. 3.2%, respectively). In addition, more subjects with baseline brain metastases were randomised to the pembrolizumab arm as compared to SOC (11.7% vs. 6.6%, respectively). These differences were not statistically significant.

Table 15: KEYNOTE-024 - Baseline Characteristics - ITT Population

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		151	
Gender				
Male	92	(59.7)	95	(62.9)
Female	62	(40.3)	56	(37.1)
Age (Years)				
< 65	77	(50.0)	64	(42.4)
>= 65	77	(50.0)	87	(57.6)
Mean	63.9		64.6	
SD	10.1		9.5	
Median	64.5		66.0	
Range	33 to 90		38 to 85	
ECOG				
0	54	(35.1)	53	(35.1)
1	99	(64.3)	98	(64.9)
2	1	(0.6)	0	(0.0)
Cancer Stage at Screening				
IIIB	1	(0.6)	1	(0.7)
IV	153	(99.4)	150	(99.3)
Geographic Region of Enrolling Site				
Non-East Asia	133	(86.4)	132	(87.4)
East Asia	21	(13.6)	19	(12.6)
Histology				
Squamous	29	(18.8)	27	(17.9)
Non-Squamous	125	(81.2)	124	(82.1)

Smoking Status				
Current	34	(22.1)	31	(20.5)
Former	115	(74.7)	101	(66.9)
Never	5	(3.2)	19	(12.6)
Brain Metastasis Status at Baseline				
Y	18	(11.7)	10	(6.6)
N	136	(88.3)	141	(93.4)
Baseline Tumour Size (mm)				
Subjects with data	151		150	
Mean	90.9		99.8	
SD	53.4		63.4	
Median	82		84	
Range	14 to 322		14 to 369	
Baseline Weight (kg)				
Subjects with data	154		151	
Mean	68.8		72.7	
SD	13.7		17.2	
Median	69		70	
Range	38 to 110		39 to 132	
Prior Adjuvant Therapy				
Yes	6	(3.9)	3	(2.0)
No	148	(96.1)	148	(98.0)
Prior Neo-adjuvant Therapy				
Yes	3	(1.9)	1	(0.7)
No	151	(98.1)	150	(99.3)
(Database Cutoff Date: 09MAY2016).				

4.6 Quality assessment of the relevant randomised controlled trials

A complete quality assessment for each trial is included in Appendix 8.

A tabulated summary of the quality assessment results is presented in Table 16 below.

Table 16: Quality assessment results for parallel group RCTs

Trial	KEYNOTE-024
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination	

4.7 Clinical effectiveness results of the relevant randomised controlled trials

KEYNOTE-024 Results – Interim Analysis 2 (IA2): data cut-off 09-May-2016[5, 21]

The KEYNOTE-024 IA2 was performed on the primary (PFS), secondary (OS and ORR), and exploratory (time to response/response duration and PRO) endpoints. The primary and secondary endpoints were evaluated in the ITT population. The primary efficacy endpoint, PFS per RECIST 1.1 by blinded independent central radiologist (BICR), is presented based on the primary censoring analysis; PFS per RECIST 1.1 by BICR using the sensitivity analysis 1, which uses different censoring rules, is also provided (See Appendix 9).

OS data were analysed using the ITT approach, as planned in the CSR analyses. A number of patients (n=66, 43.7%) in the SOC arm switched to pembolizumab after RECIST-defined disease progression (Figure 6), as was allowed in the study protocol (direct switching). Of the patients who crossed over, 57.6% remained on pembrolizumab at the time of data cut-off. In addition, 9 patients in the SOC arm switched to an anti-PD1 treatment, after the protocol treatment (indirect switching). Additional analyses using a variety of modelling approaches have been presented within this section, to adjust for treatment switching.

The data cut-off date for this analysis was 09-May-2016. At this time, subjects had a median duration of follow-up of 11.2 months (range 6.3 to 19.7 months) and 48.1% of patients in the pembrolizumab group and 10.0% of patients in the SOC group remained on assigned study treatment (Figure 5). Median duration of exposure was 7.0 months (range, 1 day-18.7 months) for pembrolizumab and 3.5 months (range, 1 day-16.8 months) for chemotherapy. The median number of cycles of platinum-doublet chemotherapy was 4 cycles for both squamous and non-squamous histology (Figure 5).

A summary of the clinical efficacy outcome results based on IA2 of KEYNOTE-024 for pembrolizumab 200 mg IV Q3W vs SOC is presented in Table 17 below:

Table 17: KENOTE-024 - Summary of efficacy endpoints

	Treatment-naïve NSCLC	
Number Patients - ITT population	Pembrolizumab 200 mg N=154	SOC N= 151
Primary endpoints		
PFS (BICR per RECIST 1.1) – ITT population		
Median (95% CI), [months]	10.3 (6.7, --)	6.0 (4.2, 6.2)
	HR 0.50 (95% CI 0.37, 0.68); *p < 0.001.*	
PFS rate at 6 months	62.1%	50.3%
PFS rate at 12 months	47.7%	15.0%
Secondary endpoints		
OS - ITT population		
Median (95% CI), [months]	not reached	not reached
	HR 0.60 (95% CI 0.41, 0.89); *p=0.005*	
OS rate at 6 months	80.2%	72.4%
OS rate at12 months	69.9%	54.2%
ORR (BIRC per RECIST 1.1) - ITT Population		
Confirmed ORR %	44.8%	27.8%
Time to Response		
Number of responders (n) Median [months] Range [months]	69 2.2 (1.4 – 8.2)	42 2.2 (1.8 – 12.2)
Response Duration (BIRC assessment) - ITT Population		
Median [months] Range [months]	not reached (1.9+ - 14.5+)	6.3 (2.1+ - 12.6+)
% of subjects who achieved an overall response (CR + PR)	44.8%	27.8%
% of subjects who achieved a CR	4%	1%
Disease control rate	69.5%	67.5%

Efficacy results are presented in more detail below:

Primary Endpoints

- *Progression Free Survival Based on BICR Assessment per RECIST 1.1*

  Primary Analysis

Table 18 presents the analysis of PFS based on BICR assessment per RECIST 1.1 in the ITT population. 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. A total of 189 PFS events were reported at the time of the data cut-off date. Per the primary analysis method the HR of PFS was 0.50 (95% CI: 0.37, 0.68) with a one-sided p-value of <0.001, favoring pembrolizumab, with median PFS of 10.3 months for pembrolizumab and 6.0 months for SOC. The PFS rates at 6 months were 62.1% and 50.3% for pembrolizumab and SOC, respectively. The 12-month PFS rates are 47.7% and 15.0% for the pembrolizumab and SOC arms, respectively.

Table 18: KEYNOTE-024 Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population)

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	73 (47.4)	1000.2	7.3	10.3 (6.7, .)	62.1 (53.8, 69.4)	---	---
SOC	151	116 (76.8)	785.6	14.8	6.0 (4.2, 6.2)	50.3 (41.9, 58.2)	0.50 (0.37, 0.68)	<0.001

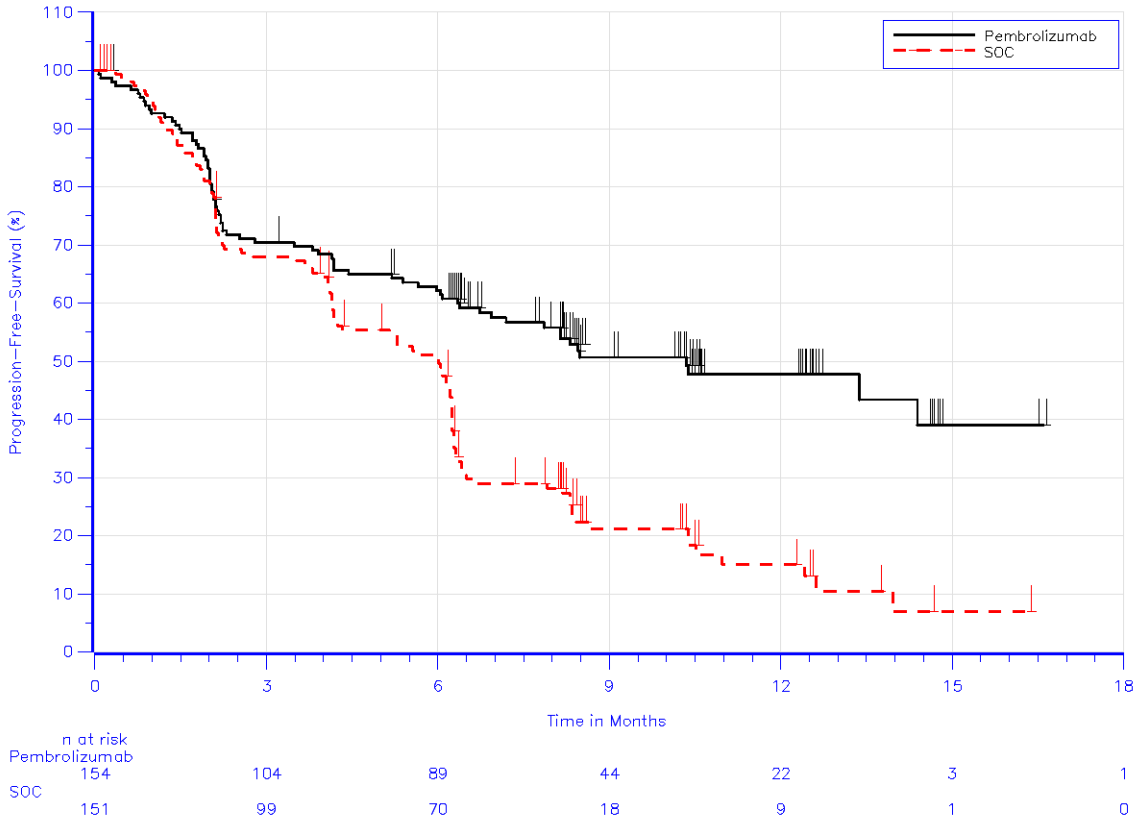
Progression-free survival is defined as time from randomisation to disease progression, or death, whichever occurs first.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous).
‡‡ One-sided p-value based on log-rank test.
(Database Cutoff Date: 09MAY2016)

Figure 8 provides the Kaplan-Meier estimates of PFS based on the BICR assessment per RECIST 1.1 in the ITT population. The PFS Kaplan-Meier (KM) curves separate early at approximately 4 months, with continuous separation between the two curves over the course of follow-up. The median PFS of 6.0 months observed for the SOC arm is consistent with that previously observed for platinum-doublet regimens and pemetrexed maintenance.

Sensitivity analysis 1 was performed with a different censoring rule to evaluate the robustness of the PFS endpoint. This sensitivity analysis was the same as the primary analysis except that it censored at the last disease assessment without PD when PD or death was documented after more than one missed disease assessment.

The result of the sensitivity analysis 1 was consistent with the primary PFS analysis results by BICR assessment, demonstrating the robustness of PFS results (See Appendix 9).

Figure 8: KEYNOTE-024 - KM of PFS based on BICR assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population)



Secondary endpoints:

- *Overall Survival*

  Primary Analysis

Table 19 and Figure 9 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. The treatment difference in OS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference between the treatment arms.

There was a total of 108 (35.4%) deaths at the time of data cutoff. In those instances where subjects were confirmed to be alive on the visit cut-off date of 09-May-2016, survival was censored as of 09-May-2016. The HR for OS was 0.60 (95% CI: 0.41, 0.89) with a one sided p-value of 0.005, favoring 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 stiudy sponsor unblinding. The median OS had not been reached for either arm. The 6-month OS rates were 80.2% and 72.4% for pembrolizumab and SOC arms, respectively. The 12-month OS rates are 69.9% and 54.2% for the pembrolizumab and SOC arms, respectively.

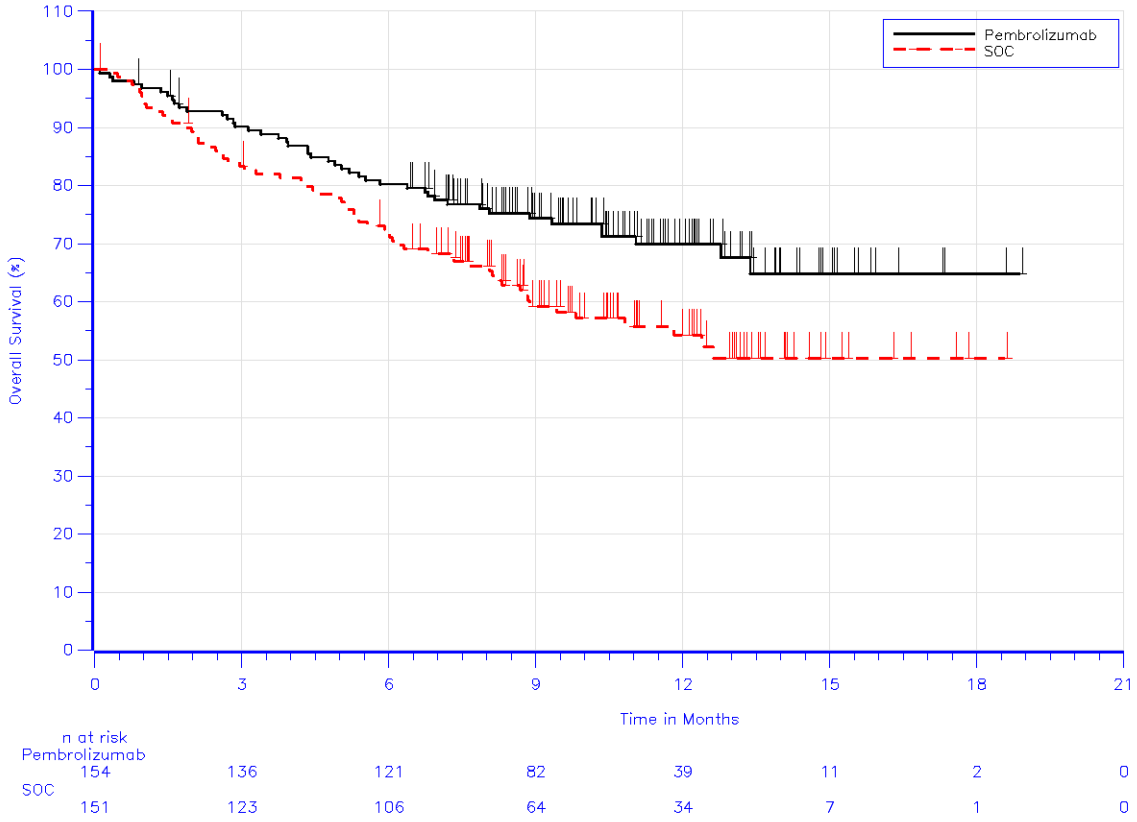
Table 19: Analysis of Overall Survival (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	154	44 (28.6)	1402.0	3.1	Not Reached (., .)	80.2 (72.9, 85.7)	---	---
SOC	151	64 (42.4)	1227.5	5.2	Not Reached (9.4, .)	72.4 (64.5, 78.9)	0.60 (0.41, 0.89)	0.005

† 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: 09MAY2016)

The curves (Figure 9) 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 low number of deaths (35.4%) observed at the time of the database cutoff and the potential confounding impact of crossover from chemotherapy to pembrolizumab. A 43.7% (n=66) crossover rate from chemotherapy to pembrolizumab (after disease progression) was observed at the time of the database cutoff in the SOC arm as shown in Figure 6.

Figure 9: KM of OS (ITT Population)



- *Modelling approaches on OS analysis after adjusting for switching*

Overall survival (OS) data were analysed using the ITT approach, as planned in the CSR analyses. ITT results of the OS analysis result in a hazard ratio of 0.60, p=0.009 (2-sided), (95% CI: 0.41; 0.89) corresponding to a substantial reduction of 40% in hazard (see Table 19).

A number of patients (n=66, 43.7%) in the SOC arm switched to pembolizumab, as was allowed in the study protocol (direct switching). An additional 9 patients in the SOC arm switched to an anti-PD1 treatment, after the protocol treatment (indirect switching).

The breakdown of the disposition of the SoC group is depicted in Figure 10.

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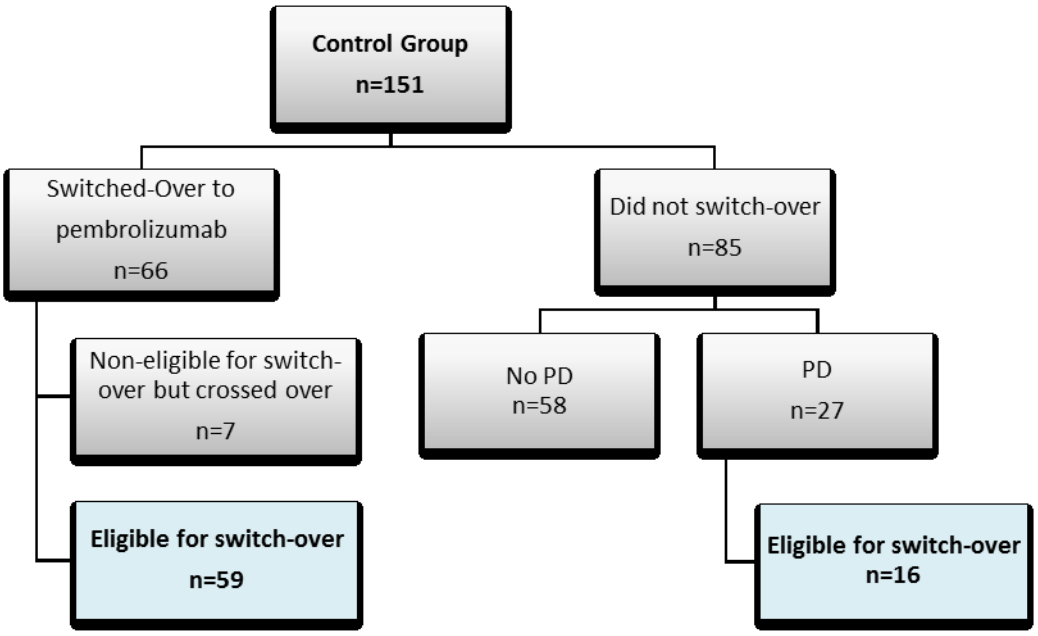
Figure 10: Disposition of patients in the KEYNOTE-024 SOC group according to switch



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.

As the survival benefit associated with pembrolizumab is diluted due to switching, conventional survival analysis will underestimate the survival benefit associated with pembrolizumab. Therefore, for the estimation of the OS in the SOC arm, OS was adjusted, using alternative crossover adjustment methods, to reflect the actual benefit of patients receiving SOC in the absence of crossover to pembrolizumab, as it is reflective of clinical practice in England for the previously treated PD-L1 positive NSCLC population. Three statistical methods were applied to adjust for treatment switching: the rank preserving structural failure time method (RPSFT),[81] the simplified 2-stage method[82] and the inverse probability of censoring weighting method (IPCW).[83] The methods were applied to account for direct switching (primary) and to account for direct and indirect switching (secondary).

The RPSFT method had been pre-specified in the study protocol to adjust for the anticipated crossover effect in advance of the availability of trial based information needed to determine the clinical validity of the approach, which should be assessed a posteriori. Following the NICE DSU recommendations for the adjustment of crossover in clinical trials,[84] additional crossover adjustments (two-stage and the IPCW) were implemented to better understand the SOC-related OS in the absence of crossover.

RPSFT adjustment

The RPSFT method is based on the assumption of common treatment effect, a strong assumption that cannot be formally tested based on the data. It assumes that the multiplicative treatment effect of pembrolizumab is constant, irrespective of the time of initiation of the treatment (at randomisation or switch). Under this assumption, the adjusted estimated hazard ratio was 0.57 (95% CI: 0.32; 0.86). This result is fairly close to ITT one. It is obtained through a common acceleration factor of 1.90, estimated under the common treatment effect. If the common treatment assumption holds, the estimated hazard ratio is correct. In other cases, it is biased as it averages different treatment effects.

The common treatment effect was explored numerically using two-stage estimates. The post-progression treatment of pembrolizumab estimated through the 2-stage methodology (acceleration factor of 4.05, [95% CI: 1.39; 16.44]) was compared with the overall effect of pembrolizumab adjusted for switching (acceleration factor of 2.11, [95% CI: 1.49; 2.99]). The acceleration factor is the multiplicative factor quantifying the increase in survival time due to pembrolizumab compared to SOC. Although this comparison may be prone to some bias, it suggests that there is numerical evidence against the common treatment assumption.

Two-stage adjustment

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. These conditions were met in KEYNOTE-024. In stage 1, the switch effect was estimated after adjustment for other covariates. The estimated post-progression treatment estimate was 4.05 (95% CI: 1.39; 16.44). This point estimate suggests that switching to pembrolizumab increases survival time by a factor of 4.05. In parallel, it is important to note that the estimate is not very precise due to the limited number of patients (n=16) who were eligible to switch and did not switch. Adjustment of survival time based on this factor had a strong impact on survival. In addition, re-censoring using this factor would reduce the information and provide less reliable results. Therefore, the two-stage methodology was finally used without re-censoring. The estimated hazard ratio of 0.50 (95% CI: 0.34; 0.76) from the two-stage simplified method is consistent with the survival adjustment resulting from the stage 1 estimate.

IPCW adjustment

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, 28.1% of events (18 observed deaths over 64) 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 0.55 (95% CI 0.34, 0.87) – a 45% statistically significant reduction in hazard of mortality. The two more conservative sensitivity analyses produced a smaller reduction in hazard of mortality of 36% and 30% respectively.

Based on the small sample size (compared to the observational datasets for which the IPCW was designed), it was uncertain whether the IPCW method could be a potentially valid, alternative method to adjust for crossover and would result in clinically valid results.[85] However, the results are aligned with those from the other adjustment methods.

The results from the ITT approach and results from the methods adjusting for direct switching are summarized in Table 20 below. The three adjustment methods provided estimated hazard ratios smaller than the HR derived from the ITT analysis (larger treatment effect), within a narrow range of 0.57 to 0.50. The results from the ITT approach and results from the methods adjusting for direct + indirect switching are summarized in Table 21.

In summary, the three methods adjusting for direct switchover in the SOC arm provide treatment estimates that are larger (HR in a range of 0.50 to 0.57) than the ITT estimate (HR=0.60). There is evidence that the common treatment effect assumption does not hold in this trial as the treatment effect appears to be numerically larger post progression than at randomisation. The IPCW method is likely to be biased due to the small sample size. Based on the trial characteristics, the switching mechanism, the proportion of patients switching and the clinical validity of the outputs obtained,[84] the two-stage adjustment was found to be the most appropriate method for this adjustment (see section 5.3.2). The assumptions required for it to be valid (i.e. potential to switch determined by disease progression and potential confounders measured until this point) were met.

Table 20: Summary Results of OS Analyses (direct switching)

Crossover correction method	Pembrolizumab 200 mg mg Q3W vs. SOC		
	Hazard Ratio	95% CI	P-value (2-sided)
ITT	0.60	(0.41; 0.89)	0.0009
Simplified two-stage (no re-censoring)[$]	0.50	(0.34; 0.76)	0.0009*
RPSFT	0.57	(0.32; 0.86)	0.0009*
IPCW	0.55	(0.34; 0.87)	0.0150

** 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 = 0.44 (95% CI: 0.20, 1.07); p = 0.0094

Table 21: Summary Results of OS Analyses (direct + indirect switching)

Crossover correction method	Pembrolizumab 200 mg mg Q3W vs. SOC		
	Hazard Ratio	95% CI	P-value (2-sided)
ITT	0.60	(0.41; 0.89)	0.0009
Simplified two-stage (no re-censoring)	0.50	(0.33; 0.76)	0.0009*
RPSFT	0.53	(0.31; 0.85)	0.0009*
IPCW	0.59	(0.36; 0.98)	0.0350

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

A summary of the median OS in the pembrolizumab study arm and SOC study arm, with and without various crossover correction methods applied, is summarised below in Table 22.

Table 22: Analysis of median OS using Two-stage, RPSFT and IPCW methods

Crossover correction method	Median OS (months) (95% CI)
SOC (no crossover correction)	Not Reached (9.4 , ---)
SOC - Simplified two-stage correction (no re-censoring)*	12.6 (7.6, .)
SOC – RPSFT correction	Not Reached (6.9, ---)
SOC – IPCW correction	11.8 (9.8 , ---)
Pembrolizumab 200 mg Q3W	Not Reached (--- , ---)

**SOC- Two stage correction (with re-censoring) Median OS = Not Reached (95% CI: 3.8, .)*

Figure 11: Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using 2-stage analysis - No recensoring (ITT Population)

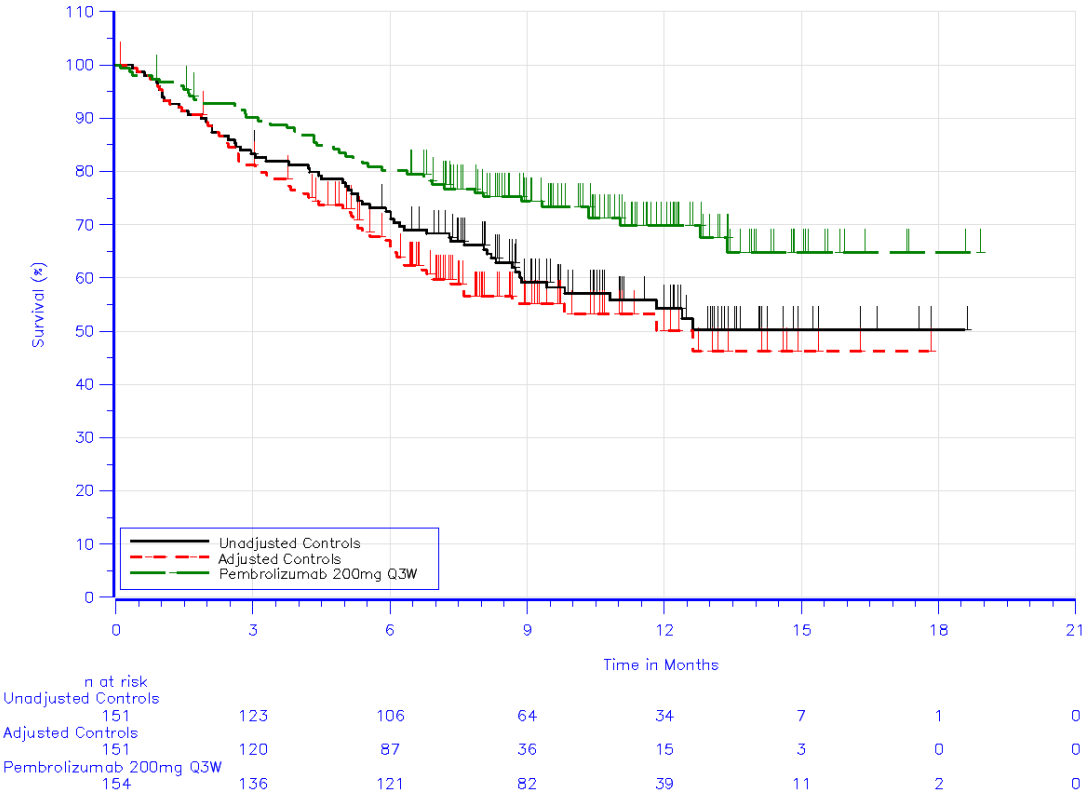


Figure 12: Analysis of Overall Survival with RPSFT Correction (ITT population)

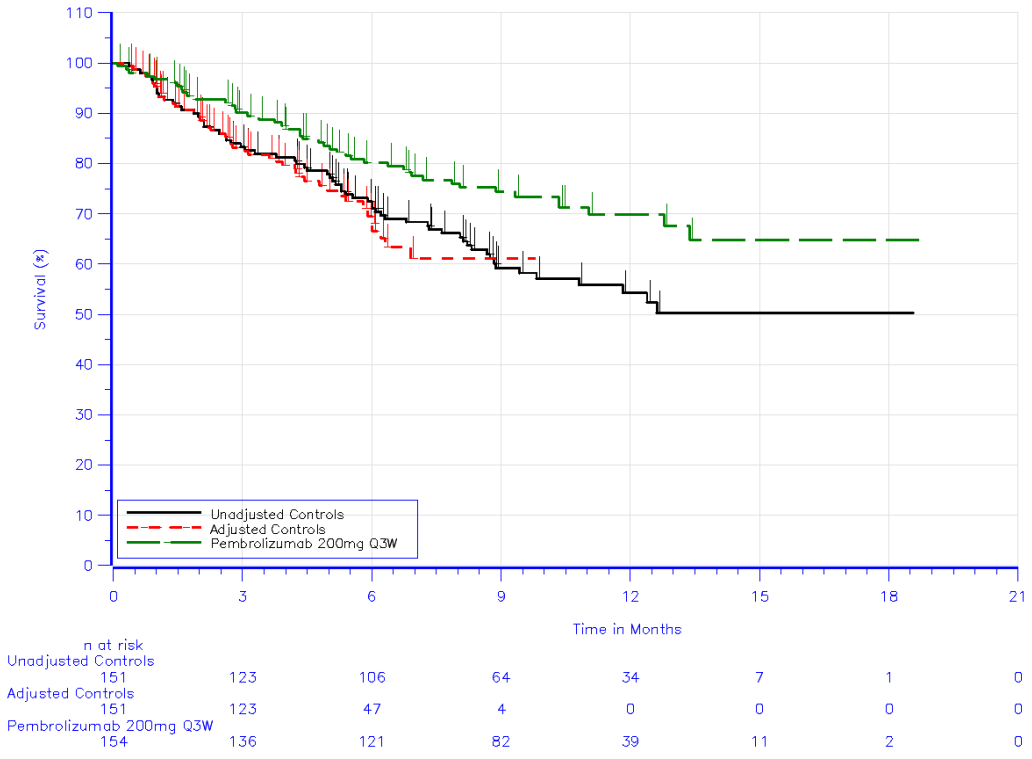
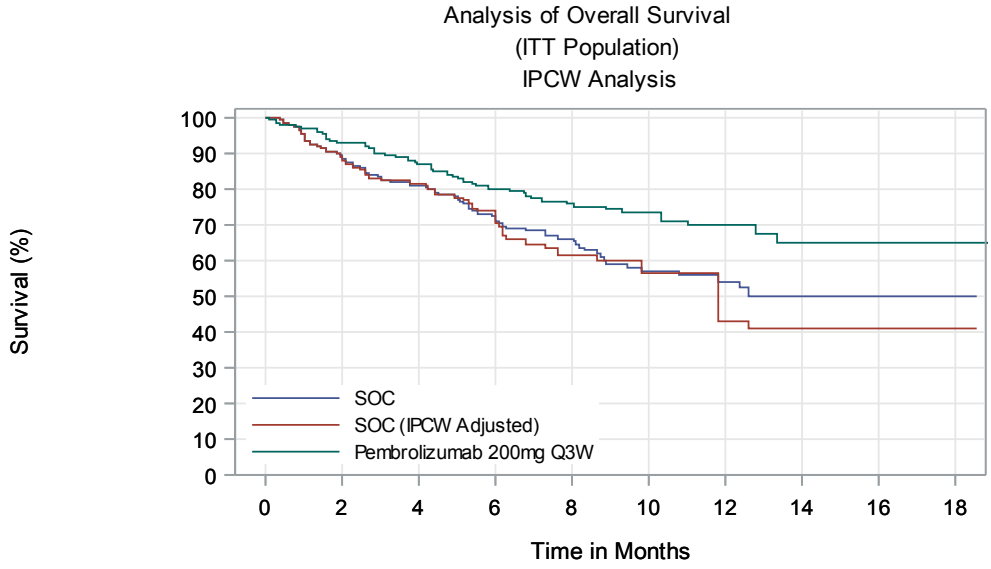


Figure 13: Analysis of Overall Survival with IPCW correction (ITT population)



Number of Subjects at Risk

SOC	151	133	120	106	83	51	34	13	5	1
SOC (IPCW Adjusted)	151	132	111	87	46	29	15	7	2	0
Pembrolizumab 200mg Q3W	154	140	131	121	98	71	39	17	5	2

Inverse-Probability-of-Censoring Weights (IPCW) applied from study entry to all subjects in the SOC arm
(Database Cutoff Date: 09MAY2016)

- *Objective Response Rate (ORR) Based on BICR Assessment per RECIST 1.1*

Table 23 presents the analysis of confirmed ORR based on BICR assessment per RECIST 1.1 in the ITT population. Objective response rate was not formally tested for statistical significance at IA2. 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 (44.8%) compared to SOC (27.8%); nominal p=0.0011. The confirmed ORR difference was 16.6% for pembrolizumab vs. SOC. The ORR of 27.8% observed for SOC is consistent with that previously observed for platinum-doublet regimens and pemetrexed maintenance.

Table 23: Analysis of Objective Response with confirmation based on BICR assessment per RECIST 1.1 (ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab vs. SOC	
				Estimate (95% CI)†	p-Value††
Pembrolizumab	154	69	44.8 (36.8,53.0)	16.6 (6.0,27.0)	0.0011
SOC	151	42	27.8 (20.8,35.7)		

† 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: 09MAY2016)

Exploratory endpoints

Exploratory analyses included Time to response and response duration, best overall response, and patient-reported outcomes (PROs) analyses.

- *Time to Response and Response Duration Based on BICR Assessment per RECIST 1.1*

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 24 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 69 responders were observed in the pembrolizumab arm with a median time to response of 2.2 months (range 1.4 to 8.2 months), and the median duration of response was not reached. There were 42 responders in the SOC arm with a median time to response of 2.2 months (range 1.8 to 12.2 months) and a median duration of response of 6.3 months (range 2.1+ to 12.6+ months). Figure 14 demonstrates the prolonged duration of response of pembrolizumab relative to the SOC among responders in the ITT population.

Table 24: Summary of time to response and response duration for subjects with objective response based on BICR assessment (ITT Population)

	Pembrolizumab (N=154)	SOC (N=151)
Number of Subjects with Response†	69	42
Time to Response† (months)		
Mean (SD)	3.0 (1.4)	3.2 (2.2)
Median (Range)	2.2 (1.4-8.2)	2.2 (1.8-12.2)
Response Duration‡ (months)		
Median (Range)§	Not reached (1.9+ - 14.5+)	6.3 (2.1+ - 12.6+)
Number of Subjects with Response ≥ 2 months(%)‡	68(100.0)	42(100.0)
Number of Subjects with Response ≥ 4 months(%)‡	59(93.6)	33(89.3)
Number of Subjects with Response ≥ 6 months(%)‡	43(88.0)	16(59.4)
Number of Subjects with Response ≥ 9 months(%)‡	15(81.9)	4(36.2)

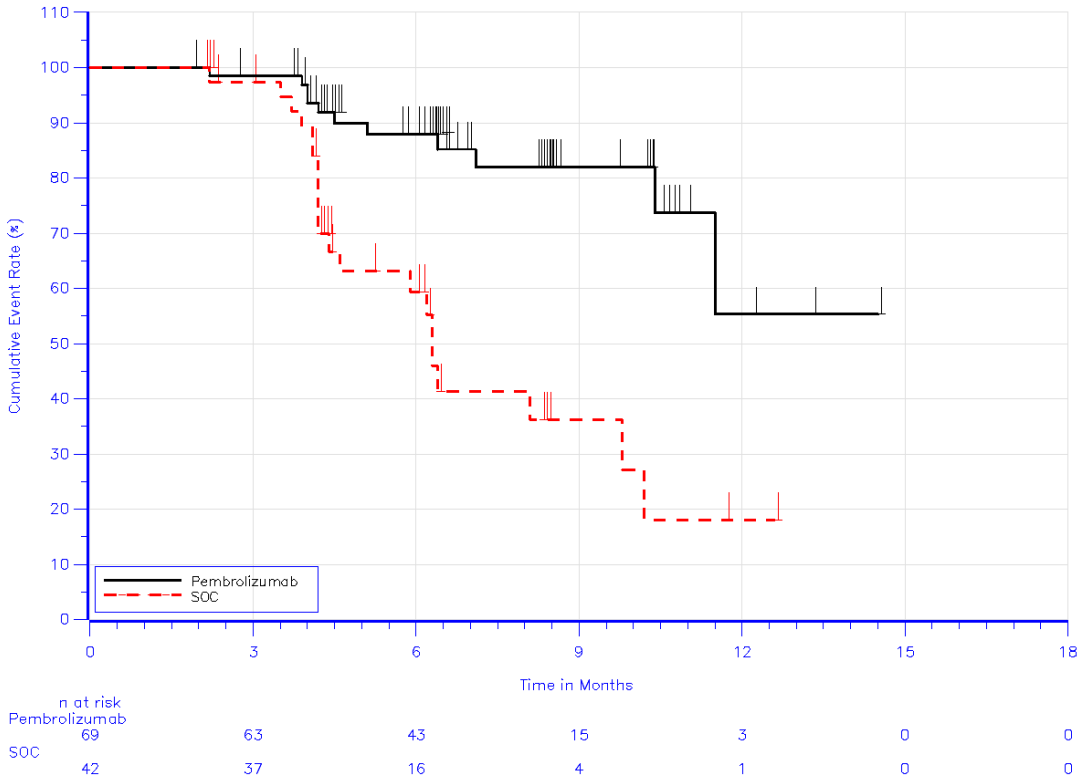
† Analysis on time to response and response duration are based on Subjects with a best overall response as confirmed complete response or partial response only.

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

§ "+" indicates the response duration is censored.

(Database Cutoff Date: 09MAY2016)

Figure 14: Summary of response duration for subjects with objective response based on BICR assessment (ITT Population)



- *Best Overall Response*

A summary of confirmed BOR based on BICR assessment in the ITT population is presented in Table 25. Results show that 44.8% of subjects treated with pembrolizumab achieved a confirmed CR/PR compared to 27.8% of subjects treated with SOC. Four percent (n=6) of subjects treated with pembrolizumab had a CR as compared to only 1% (n=1) observed for SOC. The disease control rate (percentage of subjects who achieved CR, PR, and stable disease [StD]) was similar between the pembrolizumab (69.5%) and SOC (67.5%) arms.

Table 25: Summary of best overall response based on BICR assessment RECIST 1.1 with confirmation (ITT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Number of Subjects in Population	154		151	
Complete Response (CR)	6	3.9	1	0.7
Partial Response (PR)	63	40.9	41	27.2
Overall Response (CR + PR)	**69**	**44.8**	**42**	**27.8**
Stable Disease (SD)	38	24.7	60	39.7
Disease Control (CR + PR + SD)	**107**	**69.5**	**102**	**67.5**
Progressive Disease (PD)	34	22.1	28	18.5
Not Evaluable (NE)	4	2.6	6	4.0
No Assessment	9	5.8	15	9.9

BICR = Blinded Independent Central Review
Responses are based on BICR best assessment across timepoints, with confirmation.
(Database Cutoff Date: 09MAY2016).

- *Patient Reported Outcome (PRO) Analyses*

Three questionnaires, administered electronically, were included in this study. Endpoints from these questionnaires are neither pure efficacy nor pure safety endpoints as they are affected by both disease progression and treatment tolerability.

The primary approach for analysis of the pre-specified exploratory PRO endpoints was based on a PRO-specific full analysis set (FAS) population following the ITT principle and ICH-E9 guidelines. The PRO FAS population consisted of all randomised subjects who received at least one dose of study medication and completed at least one PRO instrument.
The treatment effect on PRO score change from baseline was evaluated at Week 15 using constrained longitudinal data analysis (cLDA). Week 15 was selected to minimize loss of data due to death or disease progression while allowing comparisons in scores while subjects in both arms were still on treatment.

- *EORTC QLQ-C30 and EORTC QLQ-LC13 Compliance Rate and Completion Rate*

The PRO completion rate was defined as the proportion of subjects who completed at least one PRO questionnaire to obtain a valid PRO score at each visit among the whole PRO FAS population. The PRO compliance rate was defined as the proportion of subjects who completed at least one PRO questionnaire to obtain a valid PRO score among those who were expected to complete these questionnaires at each visit according to their individual status. These rates exclude subjects from the denominator who are missing certain visits by design (e.g., due to death, discontinuation due to progression, discontinuation due to AE, other discontinuation of treatment, translations not being available or no visit being scheduled). Visits of "treatment discontinuation" and "safety follow-up" were mapped to different time points according to the actual visit time window.

The sample size of the PRO FAS population (n=299) was slightly smaller than the ITT population (n=305) due to 6 subjects not satisfying the PRO FAS definition previously described. Compliance rates for EORTC QLQ-C30 at baseline were above 90% in both treatment arms (96% pembrolizumab; 92.6% SOC) and close to 80% at Week 15 (84.5% pembrolizumab; 78.6% SOC), although compliance in the SOC arm was slightly lower than the pembrolizumab arm. The EORTC QLQ-LC13 compliance rates were nearly identical to those of EORTC QLQ-C30. As expected, completion rates continued to decrease at each time point as more and more subjects discontinued the study due to disease progression, physician decision, AEs, or death.

- *EORTC QLQ-C30 Score Change from Baseline to Week 15*

Table 26 summarises the EORTC QLQ-C30 global health status/QoL score at baseline and at Week 15, and presents the observed mean (standard deviation [SD]) and least squares (LS) mean (95% CI) of the score change from baseline to Week 15 for each of the treatment groups.

The baseline global health status/QoL score was similar for both treatment arms. There was an improvement of 6.94 points (95% CI: 3.29, 10.58) compared to baseline in the pembrolizumab arm, and a worsening of -0.88 point (95% CI: -4.78, 3.02) in the SOC arm at Week 15. The difference in LS means between pembrolizumab and SOC at Week 15 was 7.82 points (95% CI: 2.85, 12.79; two-sided nominal p=0.002). Mean differences of 10 points or more have been widely viewed as being clinically significant when interpreting the results of randomised trials employing EORTC QLQ-C30; however, minimally important differences as low as 4 points have been reported for EORTC QLQ-C30 in NSCLC trials. [86-88]

Table 26: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at week 15 (FAS Population)

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab	145	62.24 (22.267)	109	70.95 (21.234)	150	6.94 (3.29, 10.58)
SOC	137	59.85 (22.306)	92	63.68 (20.546)	147	-0.88 (-4.78, 3.02)
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. SOC					7.82 (2.85, 12.79)	0.002

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous)) as covariates.

For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

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- *Time to Deterioration Analysis of EORTC QLQ-LC13 Composite Endpoint of Cough, Chest Pain, and Dyspnea*

The time to deterioration endpoint was a composite of cough (QLQ-LC13 question [Q]1), chest pain (QLQ-LC13 Q10), and dyspnea (QLQ-LC13 Q3 to Q5) and was defined as the time to the first onset of a 10-point or greater score decrease from baseline in any one of these three symptoms, confirmed by a second adjacent 10-point or greater score decrease from baseline. Subjects with no confirmed decrease from baseline were censored at the date of their last observation. Pembrolizumab prolonged the time to true deterioration when compared to SOC (HR=0.66; 95% CI: 0.44, 0.97; two-sided nominal p=0.029) (Table 27)

Table 27: Time to true deterioration for cough (LC13-Q1) chest pain (LC13-Q10) and dyspnea (LC13-Q3-5) (FAS Population)

			Pembrolizumab vs. SOC	
Treatment	N	Deterioration (Events) %	Hazard Ratio† (95% CI)†	p-Value‡
Pembrolizumab	151	46 (30.5)	---	---
SOC	148	58 (39.2)	0.66 (0.44, 0.97)	0.029

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

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

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

(Database Cutoff Date: 09MAY2016)

- *Summary of EQ-5D-3L Analysis*

The EQ-5D provides data for use in economic models and analyses on health utilities or QALY. The EQ-5D change from baseline to Week 15 in utility and visual analog scale (VAS) scores are provided in Table 28 and Table 29, respectively. Results from EQ-5D analyses were consistent with the results of EORTC QLQ-C30 analyses

Table 28: Analysis of change from baseline in EQ-5D utility score (Using European Algorithm) at week 15 (FAS Population)

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab	144	0.72 (0.242)	108	0.80 (0.224)	150	0.05 (0.01, 0.09)
SOC	137	0.71 (0.214)	92	0.76 (0.184)	147	-0.00 (-0.04, 0.04)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. SOC	0.06 (0.00, 0.11)	0.036

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous)) as covariates.

For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

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Table 29: Analysis of change from baseline in visual analog scale (VAS) at week 15 (FAS Population)

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab	144	68.72 (21.099)	108	75.52 (17.166)	150	4.25 (0.72, 7.77)
SOC	137	69.71 (19.279)	92	72.73 (17.123)	147	0.39 (-3.33, 4.11)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. SOC	3.85 (-0.72, 8.42)	0.098

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (geographic region (East Asia vs. non-East Asia), ECOG PS (0 vs. 1) and histology (squamous vs. non-squamous)) as covariates.

For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Database Cutoff: 09MAY2016

4.8 Subgroup analysis

KEYNOTE-024[21]

Subgroup analyses

The baseline characteristics of the following patient subgroups are provided in Appendix 10. All randomised subjects were included in the analyses according to the treatment group to which they were randomised (ITT population).

- Patients with pre-selected pemetrexed containing regimens. Pemetrexed containing regimens include the following pre-selected chemotherapies: 'Pemetrexed and Carboplatin' and 'Pemetrexed and Cisplatin'. These regimens are referred to as "Platinum/Pemetrexed", in line with terminology used in the clinical study report (CSR).

- Patients with pre-selected non-pemetrexed containing regimens. Non-pemetrexed containing regimens include the following pre-selected chemotherapies: 'Paclitaxel and Carboplatin', 'Gemcitabine and Carboplatin' and 'Gemcitabine and Cisplatin'. These regimens are referred to as "Other Platinum Doublets", in line with terminology used in CSR

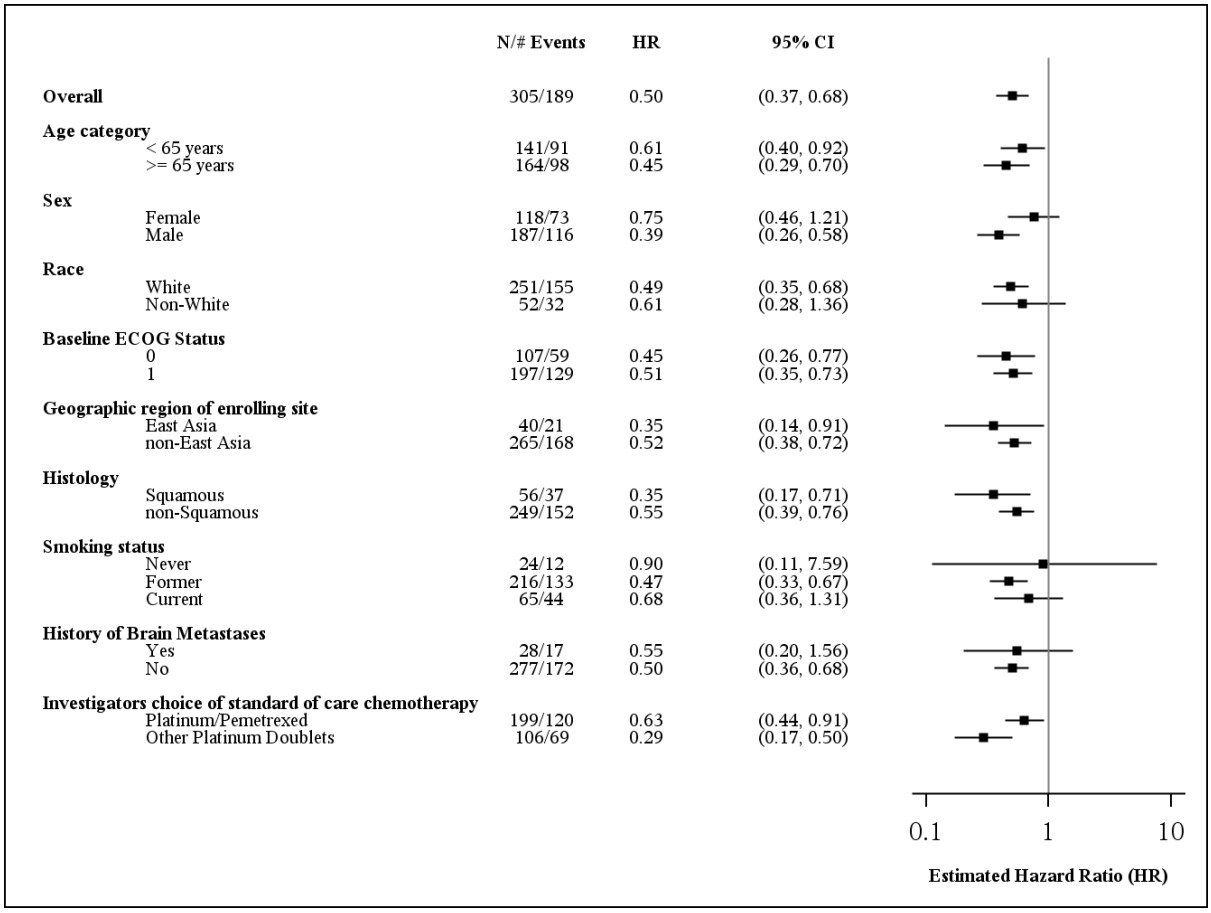
- Squamous patients.

- Non-squamous patients.

Figure 15 (forest plot) provides the results of the subgroup analyses of PFS according to BICR assessment per RECIST 1.1 by pembrolizumab arm vs. pooled SOC. The forest plot analyses demonstrated consistent benefit for the improved HR of pembrolizumab vs. SOC.

The improvement was independent of subject age, sex, ECOG performance status, tumour histology, region of enrollment, 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 0.9, resulting from the small number of subjects in this subgroup.

Figure 15: KEYNOTE-024 - Forest plot of PFS hazard ratio by subgroup factor BICR assessment (primary censoring rule)



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: 09MAY2016).

Figure 16 (forest plot) provides the results of the subgroup OS analysis between pembrolizumab arm and pooled SOC. The forest plot of subgroup analysis demonstrated a consistent benefit of pembrolizumab over SOC, with consistent point estimates for the HR in important subgroups of histology, type of SOC, and geography. [redacted]

Figure 16: KEYNOTE-024 - Forest plot of OS hazard ratio by subgroup factor

[redacted]

Analysis of Overall Survival Adjusting for Treatment Switch – Subgroup Analysis

Additional subgroup analyses were conducted in thesubgroups of subjects defined by cancer histology (non-squamous, squamous) and by use of type of the treatment regimen (containing pemetrexed, without pemetrexed):

- To estimate the treatment difference (hazard ratio) between pembrolizumab 200 mg Q3W and standard of care in OS, adjusting for the protocol-permitted switch-over of control arm subjects to pembrolizumab 200 mg Q3W using the RPSFT model , a simplified two-stage survival analysis model and the IPCW model.

- To estimate the OS curve for the standard of care treatment group, adjusted for the adjusting for the protocol permitted treatment switch-over of control arm subjects to pembrolizumab 200 mg Q3W using using RPSFT model, simplified two-stage survival analysis model and Inverse Probability of Censoring Weighting (IPCW) model.

Full details of the analyses undertaken (methods and results) are presented in Appendix 11.

Table 30 summarises the main findings in subgroups of patients defined by histology (non-squamous, squamous).

[redacted]

Table 30: Analysis of OS adjusting for treatment switch: subgroups of patients defined by histology (non-squamous, squamous).

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]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	2-stage§	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	IPCW	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
Squamous	ITT	SOC	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	2-stage§	[redacted]					
	IPCW	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[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

Table 31 summarises the main findings in subgroups of patients defined by treatment regimen (containing pemetrexed, without pemetrexed).

[redacted]

Table 31: Analysis of OS adjusting for treatment switch: subgroups of patients defined by treatment regimen (containing pemetrexed, without pemetrexed)

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]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	2-stage§	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	IPCW	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
Treatment regimen without pemetrexed	ITT	SOC	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	RPSFT¶	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	
	2-stage§	[redacted]					
	ICPW	SOC adjusted	[redacted]	[redacted]	[redacted]		[redacted]
		Pembrolizumab	[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 [redacted]

[redacted]

[redacted]

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4.9 Meta-analysis

There is only one randomised controlled trial for the intervention versus a relevant comparator (KEYNOTE-024). KEYNOTE-001 Cohort F1[89] (see section 4.11) was an uncontrolled study which did not include a comparator of relevance to the decision problem. A meta-analysis was not conducted as it was deemed inappropriate to pool pembrolizumab data from these two studies, given their different designs. The key baseline characteristics of participants from both studies are presented below (see Table 33). The total number of patients in the treatment naïve population of KEYNOTE-001 (Cohort F1) was 101, but a smaller proportion (n=27) represent those with TPS ≥50% (see section 4.11). Patients in Cohort F1 of KEYNOTE-001 were treated with different dosing regimes (pembrolizumab 10 mg/kg Q2W and pembrolizumab 10 mg/kg Q3W) compared to patients in the pembrolizumab arm of KEYNOTE-024 (pembrolizumab 200 mg Q3W).

Table 33: Comparison of baseline characteristics of patients treated with pembrolizumab in KEYNOTE-024 and KEYNOTE-001 (Cohort F1)

	KEYNOTE-024$ [5]	KEYNOTE-001 Cohort F1 [90]
	Pembrolizumab 200 mg/kg Q3W n=154 (%)	Overall treatment naïve population* n=101 (%)
Gender		
Male	92 (59.7)	60 (59.4)
Age (Years)		
Median (Range)	64.5 (33 to 90)	68.0 (39 to 93)
ECOG		
[0] [1]	54 (35.1) 99 (64.3)	44 (43.6) 57 (56.4)
Histology		
Squamous Non-Squamous Other/not specified	29 (18.8) 125 (81.2)	19(18.8) 79(78.2) 3 (3.0)
Smoking Status		
Never Current or former	5 (3.2) 149 (96.8)	11(10.9) 90 (89.1)

* Database Cut-off Date: 18SEP2015
$ITT Population. Database Cutoff Date: 09MAY2016

4.10 Indirect and mixed treatment comparisons

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 has been conducted to enable a comparison to be made for the purposes of this submission.[91-93]

4.10.1: Search strategy

A systematic literature review was conducted according to a previously prepared protocol, to identify relevant studies to inform both direct and indirect comparisons between the interventions of interest. The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design. Details of the search strategy are presented in section 4.1. Full description of the search strategy by database is presented in Appendix 2.

4.10.2: Details of treatments

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

- Pembrolizumab
- Platinum + pemetrexed (non-squamous/adenocarcinoma histology subgroup only)
- Platinum + gemcitabine
- Platinum + paclitaxel
- Platinum + docetaxel
- Platinum + vinorelbine

4.10.3: Criteria used in trial selection

The inclusion and exclusion criteria and the study selection process are described in section 4.1 (see Table 6 PICOS eligibility criteria and Figure 4 PRISMA flow diagram).
For selection of studies for indirect and mixed treatment comparisons we included RCTs with comparisons between any of the interventions of interest.

4.10.4: Summary of trials

A summary of included trals is provided in Table 34 below.

Table 34: Summary of the trials

Trial ID	NCT number	Principal publication (n = 28)	Secondary publications (n = 14)	Arm 1	Arm 2	Arm 3	Arm 4
KEYNOTE 024 trial							
KEYNOTE 024[21]	NCT02142738	--	Reck et al, 2016[5]	Pembrolizumab	Standard of care (carboplatin + paclitaxel/pemetrexed/ gemcitabine or cisplatin + pemetrexed/gemcitabine)		
Trials comparing KEYNOTE 024 SOC regimens to other interventions of interest							
Chang et al., 2008	NCT00021060	Chang et al, 2008[94]		Cisplatin + gemcitabine	Cisplatin + vinorelbine	--	--
Chen et al., 2004	NCT01303926	Chen et al, 2004[95]	--	Cisplatin + paclitaxel	Cisplatin + vinorelbine	--	--
Comella et al., 2000	--	Comella et al, 2000a[96]	Comella et al, 2000b; Comella et al 2000c[97]	Cisplatin + gemcitabine + vinorelbine	Cisplatin + gemcitabine	Cisplatin + vinorelbine	--
FACS	--	Ohe et al, 2007[98]	Takeda et al, 2003[99]; Kubota et al, 2004[100]; Goto et al, 2006[101]	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine	
Gebbia et al., 2003	--	Gebbia, 2003[102]	--	Cisplatin + gemcitabine	Vinorelbine + cisplatin	--	--
GFPC 99-01	--	Thomas et al, 2006[103]	--	Carboplatin + gemcitabine	Cisplatin + vinorelbine	--	--
Helbekkmo et al., 2007	--	Helbekkmo et al, 2007[104]	--	Carboplatin + vinorelbine	Carboplatin + gemcitabine	--	--
Kawahara et al., 2013	--	Kawahara et al, 2013[105]	--	Carboplatin + docetaxel	Carboplatin + paclitaxel	--	--
Khodadad et al., 2014	NCT00948675	Khodadad et al, 2014[106]	--	Cisplatin + docetaxel	Paclitaxel + carboplatin	--	--
Scagliotti et al., 2002	--	Scagliotti et al.,	--	Cisplatin + gemcitabine	Carboplatin + paclitaxel	Cisplatin +	--

Trial ID	NCT number	Principal publication (n = 28)	Secondary publications (n = 14)	Arm 1	Arm 2	Arm 3	Arm 4
		2002[107]				vinorelbine	
Schiller et al., 2002	--	Schiller et al, 2002[108]	--	Cisplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + docetaxel	Carboplatin + paclitaxel
Sumanth et al., 2008	--	Sumanth et al, 2008[109]	--	Carboplatin + docetaxel	Carboplatin + gemcitabine	--	--
SWOG-9509	--	Kelly, 2001[110]	Moinpour et al. 2002[111]	Cisplatin + vinorelbine	Paclitaxel + carboplatin	--	--
Trials comparing non-pemetrexed-containing and pemetrexed-containing KEYNOTE 024 SOC interventions							
Gronberg et al., 2009	--	Gronberg, 2009[112]	--	Carboplatin + pemetrexed	Carboplatin + gemcitabine	--	--
JMDB	NCT00087711	Scagliotti, 2008[113]	Syrigos et al, 2010[114]; Novello, 2010[115]; Yang, 2010[116]	Cisplatin + pemetrexed	Cisplatin + gemcitabine	--	--
JMIL	NCT01005680	Wu, 2010[117]	NCT01005680	Cisplatin + pemetrexed	Cisplatin + gemcitabine	--	--
NAVotrial 01	--	Bennouna et al, 2014[118]	--	Cisplatin + pemetrexed	Cisplatin + vinorelbine	--	--
Rodrigues-Pereira et al., 2011	NCT00520676	Rodrigues-Pereira et al, 2011[119]	--	Pemetrexed + carboplatin	Carboplatin + docextal	--	--
Socinski et al., 2010	NCT00308750	Socinski et al, 2010[120]	Raju et al, 2009	Carboplatin + docetaxel	Carboplatin + pemetrexed	carboplatin + pemetrexed + enzastaurin	--
Sun et al., 2015	NCT01401192	Sun et al, 2015[121]	--	Cisplatin + pemetrexed	Cisplatin + gemcitabine	--	--
Zhang et al., 2013	--	Zhang et al, 2013[122]	--	Cisplatin + pemetrexed	Cisplatin + gemcitabine	--	--
Trials comparing interventions of interest not in KEYNOTE 024							
Chen et al., 2007	--	Chen et al, 2007[123]	--	Cisplatin + vinorelbine	Cisplatin + docetaxel	--	--
Douillard et al., 2005	--	Douillard et al, 2005[124]	--	Cisplatin + docetaxel	Cisplatin + vinorelbine	--	--

Trial ID	NCT number	Principal publication (n = 28)	Secondary publications (n = 14)	Arm 1	Arm 2	Arm 3	Arm 4
GLOB3	--	Tan et al, 2009[125]	--	Cisplatin + vinorelbine	Cisplatin + docetaxel	--	--
GOIM 2608	--	Gebbia et al, 2010[126]	--	Cisplatin + docetaxel	Cisplatin + vinorelbine	--	--
Martoni et al., 2005	--	Martoni et al, 2005[127]	--	Cisplatin + vinorelbine	Cisplatin + gemcitabine	--	--
TAX 326	--	Belani, 2001[128]	Fossella et al, 2003[129]; Belani, 2006[130]	Cisplatin + docetaxel	Carboplatin + docetaxel	Cisplatin + vinorelbine	--

4.10.5 Trials identified in search strategy

Table 34 presents a full list of included trials. The KEYNOTE-024 trial[5, 21] evaluated pembrolizumab compared to standard-of care (SOC) platinum-based chemotherapies: carboplatin + paclitaxel, carboplatin + pemetrexed, cisplatin + pemetrexed, carboplatin + gemcitabine, and cisplatin + gemcitabine. In addition to KEYNOTE-024, there are 13 trials that had KEYNOTE-024 standard-of-care (SOC) regimens or cisplatin + paclitaxel to other interventions of interest. Eight trials had KEYNOTE-024 SOC interventions with or without pemetrexed regimens, and six trials had interventions of interest not in the KEYNOTE-024 trial.

4.10.6 Rationale for choice of outcome measure chosen

The outcomes of interest for the NMA were:

- OS (time-varying HR and constant HR)
- PFS (time-varying HR and constant HR)

Both OS and PFS are clinically relevant outcomes that were referenced in the final scope for this appraisal and the decision problem. OS is the gold standard endpoint to demonstrate superiority of antineoplastic therapy. PFS is an acceptable scientific endpoint for a randomised phase III trial to demonstrate superiority of a new antineoplastic therapy, especially if it is believed that the median time to OS with the new therapy may be significantly longer than that seen with standard of care. No network meta-analysis was conducted for adverse events or HRQoL, as these are inconsistently reported across trials, both in terms of grouping of adverse events and in terms of criteria for reporting (ie. percent prevalence as a cutoff point for inclusion in publication).

4.10.7 Populations in the included trials

The population of interest includes first-line patients with advanced or metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥ 50%), and are EGFR wild-type, and ALK negative. As no trial to date has been conducted in this set of patients, the population in scope for this analysis includes all patients with advanced or metastatic NSCLC other than those in trials in exclusively EGFR or ALK positive patients, under the assumption that the included interventions of interest do not vary in efficacy based on EGFR or ALK status.

The primary population of interest was the population of all-comers (all histologies combined). Analyses concerning the non-squamous/adenocarcinoma subgroup and squamous subgroup are presented in Appendix 18.

Data for KEYNOTE-024 was obtained from the relevant clinical study report and study publication;[5, 21] the construction of analysis scenarios was limited by the availability of robust data. All outcomes of KEYNOTE-024 were available for the comparison of pembrolizumab versus SOC, which combined platinum + pemetrexed with platinum + gemcitabine and platinum + paclitaxel. Data was also made available stratified by pre-randomisation SOC assignment: pemetrexed-containing regimen versus non-pemetrexed-containing regimen. In terms of histology, results for non-squamous and squamous histology were only available for pembrolizumab versus the combined SOC regimens. However, all patients who were assigned to platinum+pemetrexed were non-squamous.

In order to combine pembrolizumab to the network of evidence spanned by the other interventions of interest, the populations of KEYNOTE-024 considered in the all-comers network were:

- KEYNOTE-024a: pembrolizumab versus non-pemetrexed-containing SOC, mixed histology
- KEYNOTE-024b: pembrolizumab versus pemetrexed-containing SOC, all non-squamous

4.10.8 Apparent or potential differences in patient populations between the trials

Trial characteristics of the included RCTs are summarized in Table 34 and Appendix 12. The earliest trial began in 2000 (Comella et al, 2000[96]), and all trials are complete. Most trials were two-arm and open label. The study inclusion criteria and the information on prior treatment are provided in Appendix 12. The majority of trials recruited stage IIIB and IV chemotherapy naïve patients, who were 18 years or older. Eight trials recruited patients with ECOG performance status of 0 or 1, four trials recruited patients with an ECOG performance status of 0, 1 or 2, three trials recruited patients with WHO performance status of 0, 1 or 2. Histology of NSCLC (i.e. squamous vs non-squamous) was not part of inclusion criteria for most studies, but there were four trials that recruited patients with non-squamous NSCLC only.

With the exception of the KEYNOTE-024 trial, PD-L1 status was not reported in the included trials.

Treatment details in each of the RCTs are provided in Appendix 12. For the majority of the trials, the treatment regimen consisted of planned cycles of six with each cycle of 21 days. Some trials allowed for additional therapies for patients with tumour response (complete or partial response) with no progressive disease and/or at the local physicians' discretion.

Baseline patient characteristics are summarized in Appendix 13. Baseline age, gender, and race/ethnicity are also provided and illustrated graphically in Appendix 13. Baseline smoking status, ECOG performance status, disease stage, and histology are provided in tabulated and graphical format in Appendix 13

Baseline age was reasonably similar between trials; the mean age ranged from 50.6 to 64.9 years, and the median age ranged from 54 to 67.5 years. Most patient populations were male; one of the treatment arms in Rodrigues-Pereira et al. 2011[119] (docetaxel + carboplatin: 47%; 50/105) trials consisted of less than 50% of men, but the overall male population was 50% or more. Both treatment arms in Khodadad et al, 2014[106] had less than 50% of men (cisplatin + docetaxel: 42%; 21/50; carboplatin + paclitaxel: 34%; 17/50). For race/ethnicity, there were noticeable variation between trials; eight trials only had Asian patients, while two other trials had less than 20% of Asian patients (KEYNOTE-024 and JMDB.[21, 113])

For trials comparing non-pemetrexed and pemetrexed-containing KEYNOTE-024 SOC interventions, current and former smokers made up a majority of the patient populations. There were two notable exceptions; JMDB and Sun et al, 2015 trials[113, 121] were made up of at least 40% of never smokers. All other trials with the exception of KEYNOTE-024 did not report smoking status. ECOG performance status of 0 or 1 was most commonly reported. However, Khodadad et al. 2014[106] had 50% or more of ECOG 2 patients (50% in the docetaxel + cisplatin arm and 66% in the paclitaxel + carboplatin arm).

The percentage of patients diagnosed with adenocarcinoma ranged from 31% (Gebbia et al, 2003[102] cisplatin + vinorelbine: 34%; 47/140, cisplatin + gemcitabine: 31%; 43/138) to 98% across trials (Sun et al, 2015[121] cisplatin + gemcitabine: 98%; 152/155, cisplatin + pemetrexed 99%; 158/160). The percentage of patients diagnosed with squamous cell carcinoma ranged from 0% (JMIL[117] cisplatin + gemcitabine: 0%; 0/130, cisplatin +

pemetrexed: 0%; 0/126) to 52% (Gebbia et al, 2003[102] cisplatin + vinorelbine: 52%; 73/140, cisplatin + gemcitabine: 42%; 72/138).

With the exception of the KEYNOTE-024 trial, PD-L1 status was not reported in the included trials.

In combining direct and indirect evidence in an NMA, trials must be reasonably similar. Patients are randomised only within trials, not across trials, so there is a risk that patients participating in different trials differ with respect to demographic, disease or other characteristics. In addition, features of the trials themselves may differ. If these trial or patient characteristics are effect modifiers, i.e. they affect the treatment effects of an intervention versus a control, then there are systematic differences in treatment effects across trials. Systematic differences in known and unknown effect-modifiers among studies comparing the same interventions in direct fashion result in between-study heterogeneity. An imbalance in the distribution of effect modifiers between studies comparing different interventions will result in transitivity or consistency violations and therefore biased indirect comparisons.[91, 131-133]

In order to gauge the appropriateness of proceeding with an NMA.1 the feasibility assessment included: 1) an assessment of whether the RCT evidence for the interventions of interest formed one evidence network and 2) an assessment of the distribution of study and patient characteristics that may have affected treatment effects across direct comparisons of the evidence networks.

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

As mentioned above, trial characteristics of included studies are presented in Appendix 12 and baseline patient characteristics are summarized in Appendix 13.

The reported outcomes from included trials are also summarised in Appendix 14.

A summary of the quality assessment of included trials is provided in Appendix 14. KEYNOTE-024 had low risk for sequence generation and incomplete outcome data domains, and unclear risk for allocation concealment and blinding of participants, personnel, and outcome assessors. The other trials generally presented a low risk of bias with regards to sequence generation, incomplete outcome data, and other sources of bias. For several studies, there was unclear risk of bias for allocation concealment, due to being open trials

and having the different methods of drug administration between the treatment arms that prevented allocation concealment. Most trials had unclear risk or high risk for the domain of blinding of participants, personnel and outcome assessors, and unclear risk for selective outcome report as study protocol was accessible for limited number of studies.

For all studies, we assessed the validity of individual trials using the Risk of Bias instrument, endorsed by the Cochrane Collaboration.[134] This instrument was used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The risk of bias instrument can be used to assign summary assessments of within-study bias; low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high-risk of bias (high-risk of bias for one or more key domains). Any disagreements between reviewers were resolved by discussion with a third reviewer.

4.10.12 Methods of analysis and presentation of results

In Appendix 15, an overview of concepts and models for NMA are provided.

Based on the findings of the feasibility assessment, the results of the RCTs that are part of one evidence network and deemed sufficiently similar were synthesized by means of NMAs by outcome of interest. Under the assumption of consistency, the NMA model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared to control. Based on these basic parameters, the relative treatment effects between each of the contrasts in the network were obtained.

Models, likelihood, priors

All analyses were performed in the Bayesian framework and involved a model with parameters, data and a likelihood distribution, and prior distributions. For response outcomes, a standard binomial setup was used. For analysis of survival outcomes, two sets of models were used: 1) NMA based on reported HRs assuming proportional hazards between treatments; and 2) NMA based on the scanned KM curves anticipating that HRs can vary over time according to a certain parametric function.

- *PFS and OS using reported HRs*

The NMA of reported HRs in terms of PFS and OS was performed using a fixed and random effects regression model with a contrast-based normal likelihood for the log HR of each trial in the network according to [91, 131] using normal non-informative prior distributions for the parameters to be estimated with a mean of 0 and a variance of 10,000.

- *Fixed and random effects*

For the NMA based on reported HRs both fixed and random effects models were considered. For the random effects models one parameter for the between-study heterogeneity was used, making the assumption that the between-study heterogeneity is the same for each intervention relative to the overall reference treatment of choice. Based on the findings that the fixed effects model was considered more parsimonious than the random effects model, a fixed effects model was used for the NMA based on KM curves anticipating time-varying treatment effects. This was considered appropriate because any differences between trials regarding follow-up time, potentially causing between-study heterogeneity, was captured with time-related parameters in the model. For response outcomes, fixed effect models were used. Results from using a random effects model for the NMA are also provided as supporting evidence.

- *PFS and OS using published KM curves*

Traditional NMA for survival outcomes are based on hazard ratio (HR) estimates and rely on the proportional hazards assumption, which is implausible if the hazard functions of competing interventions cross. The hazard function describes the instantaneous event (e.g. death) rate at any point in time. Ouwens et al and Jansen have presented methods for network meta-analysis of survival data using a multidimensional treatment effect as an alternative to the synthesis of the constant HRs.[92, 135] The hazard functions of the interventions in a trial are modeled using known parametric survival functions or fractional polynomials and the difference in the parameters are considered the multidimensional treatment effect, which are synthesised (and indirectly compared) across studies. With this approach, the treatment effects are represented by multiple parameters rather than a single parameter. The model introduced by Jansen was used for the NMA of PFS and OS.[92, 136]

For PFS and OS the following competing survival distributions were considered using the multivariate NMA framework (See Appendix 15): Weibull, Gompertz, and 2nd order fractional polynomials with power p_1=0 and 1 and power p_2= 0 and 1. In essence, these 2nd order fractional polynomial models are extensions of the Weibull and Gompertz model, and allow

arc- and bathtub shaped hazard functions. For the relative treatment effects in the 2nd order fractional polynomial framework we assumed that treatment only has an impact on two of the three parameters describing the hazard function over time (i.e. one scale and 1 shape parameter). The fixed effects versions of these flexible survival models presented in Appendix 15 were used for the evidence synthesis. Model 1, presented here below, is the fixed effects model assuming that the survival times follow a Weibull (p=0) or Gompertz (p=1) distribution. Model 2 is an extension of Model 1 with a covariate to explain between-trial heterogeneity (regarding proportion of non-squamous or non-squamous patients in each trial, depending on the scenario). Model 3 is the 2nd order fractional polynomial model considered.

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

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

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

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\end{pmatrix}=\begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} & if\ k=b, b\in\{A,B,C\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}+\beta X_{j}\\ d_{1Ak}-d_{1Ab}\end{pmatrix} & if\ k\succ b \text{ and } b=A\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\end{pmatrix} & if\ k\succ b \text{ and } b\neq A\end{cases} \tag{2}$$

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

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\\ \beta_{2jk}\end{pmatrix}=\begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix} & if\ k=b, b\in\{A,B,C\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\\ 0\end{pmatrix} & if\ k\succ b\end{cases} \tag{3}$$

For each treatment arm of each study in the NMA, the reported Kaplan-Meier curves were digitised (DigitizeIt; http://www.digitizeit.de/). The Kaplan-Meier curves can be divided into *q*

consecutive intervals over the follow-up period: [t_1, t_2], (t_2, t_3], …, (t_q, t_{q+1}] with t_1=0. For each time interval m=1,2,3,….,q, extracted survival proportions were used to calculate the patients at risk at the beginning of that interval and incident number of deaths (See Appendix 16). [136] A binomial likelihood distribution of the incident events for every interval can be described according to:

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

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

The prior distributions for model 1 are:

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

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

For model 2, the additional prior distribution for the covariate is $\beta \sim normal(0, 10^4)$. For model 3 the prior distributions for the study effects are:

$$\begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} \sim normal\left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \mathrm{T}_\mu \right) \qquad \mathrm{T}_\mu = \begin{pmatrix} 10^4 & 0 & 0 \\ 0 & 10^4 & 0 \\ 0 & 0 & 10^4 \end{pmatrix}$$

- *Model selection*

The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing survival models.[137] DIC provides a measure of model fit that penalizes model complexity according to $DIC = \overline{D} + pD$, $pD = \overline{D} - \hat{D}$. $\overline{D}$ ("Dbar") is the posterior mean residual deviance, pD is the effective number of parameters, and $\hat{D}$ is the deviance evaluated at the posterior mean of the model parameters. In general, a more complex model

will result in a better fit to the data, demonstrating a smaller residual deviance. The model with the better trade-off between fit and parsimony has a lower DIC. A difference in DIC of about 5 points can be considered meaningful.

Results of the NMA based on the constant reported HRs can be defended when the results of the time varying HR analysis suggests no statistically meaningful changes in the HRs over time

- *Presentation of results*

The results of the NMA for PFS and OS are presented with estimates for treatment effects of each intervention relative to docetaxel in terms of scale and shape parameters. Based on these parameter estimates, plots of the HR as a function of time of each intervention relative to docetaxel are presented. The posterior distributions of relative treatment effects and modeled outcomes are summarized by the median and 95% credible intervals (CrIs), which are constructed from the 2.5th and 97.5th percentiles of the posterior distributions.

The results of the NMA based on reported HRs are presented with cross-tables with relative treatment effect estimates (HRs) between all interventions of interest along with 95%CrI.

4.10.13 Programming language

The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the OpenBUGS software package.[137, 138] A first series of iterations from the OpenBUGS sampler was discarded as 'burn-in', and the inferences were based on additional iterations using two chains. All analyses were performed using R version 3.3.1 (http://www.r-project.org/) and OpenBugs version 3.2.3 (OpenBUGS Project Management Group). The OpenBUGS code used in the analysis is presented in Appendix 17.

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

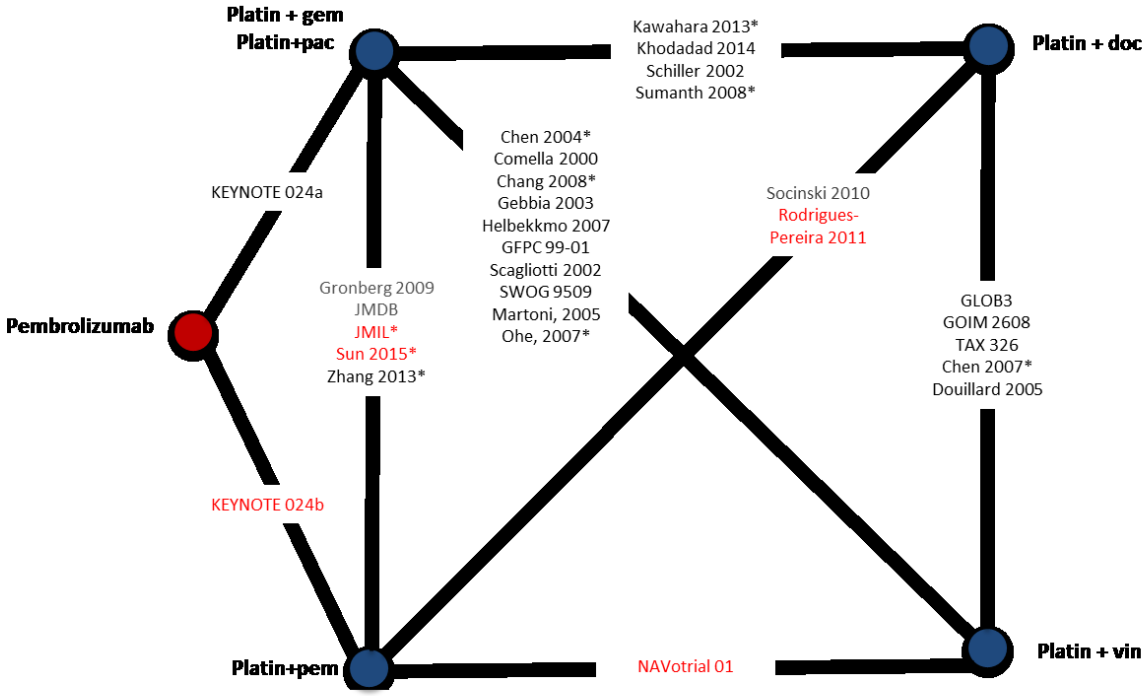
The results of the NMA for PFS and OS are presented with estimates for treatment effects of each intervention relative to docetaxel in terms of scale and shape parameters. Based on these parameter estimates, plots of the HR as a function of time of each intervention relative to docetaxel are presented. The posterior distributions of relative treatment effects and modeled outcomes are summarized by the median and 95% credible intervals (CrIs), which are constructed from the 2.5th and 97.5th percentiles of the posterior distributions.

The results of the NMA based on reported HRs are presented with cross-tables with relative treatment effect estimates (HRs) between all interventions of interest along with 95%CrI.

Networks of evidence

Given the scope of the NMA, the resulting network of evidence is shown in Figure 18. The comparability of the included trials was assessed in terms of histology and other potential prognostic factors. One trial (Khodadad 2014[106]) was conducted exclusively in patients with ECOG 2; as KEYNOTE-024 allowed only patients with ECOG 0 or 1, it was decided to remove Khodadad 2014[106] from the analysis set.

Figure 18: Complete network of evidence



Trials in red: non-squamous
Trials in black: all histologies
Trials with 100% Asian patients denoted with *
KEYNOTE 024a: Patients assigned to platinum + gem or platinum + pac before randomization
KEYNOTE 024b: Patients assigned to platinum + pemetrexed before randomization (non-squamous)

- *All-histologies network*

In order to assess the interventions of interest in a population of mixed histology, Figure 18 was used as the network of evidence. KEYNOTE-024a and KEYNOTE-024b were included separately, as this allowed for pemetrexed-containing SOC regimens to be considered as separate from non-pemetrexed-containing regimens. In order to adjust for differences in the distribution of histology between trials, a covariate was included which represented the proportion of non-squamous patients in each trial. This covariate was centered at the

proportion of non-squamous patients in KEYNOTE-024, in order to estimate relative treatment effects in a population that reflects KEYNOTE-024.

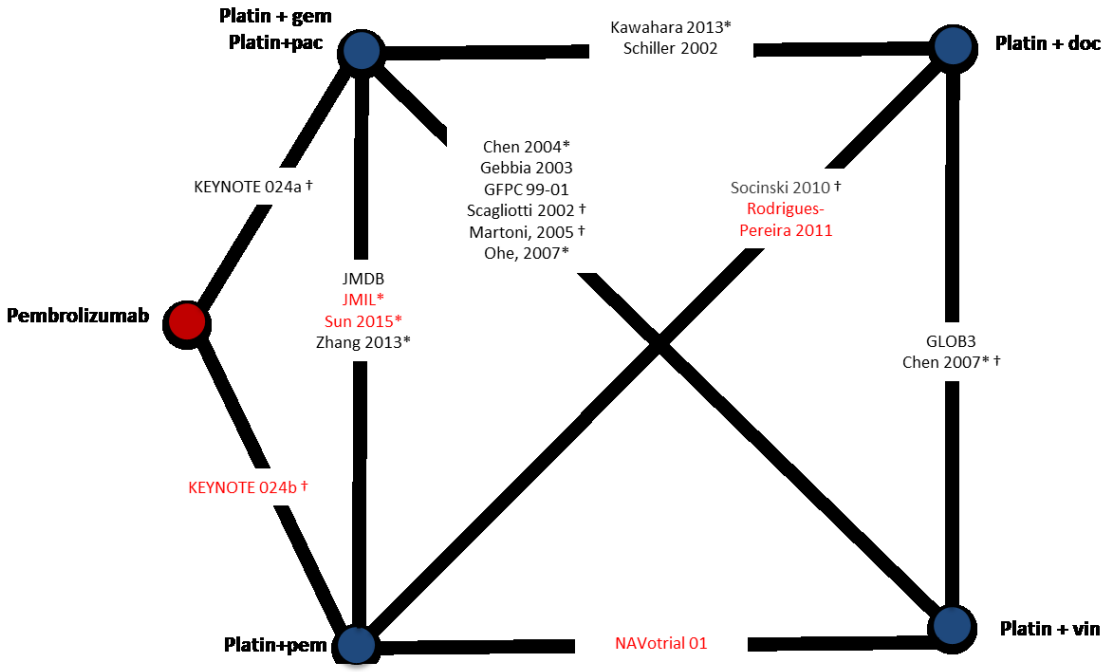
Addditional networks were constructed to look at the following specific sub-populations. Full details of these networks and corresponding NMA results can be found in Appendix 18.

- Non-squamous population – including mixed-histology trials
- Non-squamous population – pure network (only includes trials conducted in purely non-squamous population)
- Squamous population – including mixed-histology trials
- Squamous population – pure network (only includes trials conducted in purely squamous population)

NMA Results: PFS - All histologies

The network of evidence for PFS using reported HRs in the all-histologies population is presented in Figure 19. For each trial in the network, the HR, along with the log(HR) and associated SE are presented in Appendix 18. A fixed-effects NMA was conducted on the log(HR)s with a covariate encoding the proportion of squamous patients in each trial; the results are presented in Table 35. Under this model, pembrolizumab has the lowest HR versus platinum + gemcitabine/paclitaxel (HR 0.49, 95% CrI 0.36-0.67). Pembrolizumab was also superior to all other interventions of interest. None of the platinum-based regimens differed from each other. The random-effects analysis produced similar results (Appendix 18), as did the sensitivity analysis removing trials with 100% Asian patients (Appendix 18); in this scenario pembrolizumab had an HR of 0.52 (95% CrI 0.37-0.72).

Figure 19: Network of evidence for progression-free survival (constant HR); all histologies



†HR calculated from KM
Trials in red: non-squamous
Trials in black: all histologies
Trials with 100% Asian patients denoted with *
KEYNOTE 024a: Patients assigned to platinum + gem or platinum + pac before randomization
KEYNOTE 024b: Patients assigned to platinum + pemetrexed before randomization (non-squamous)

Table 35: Results of fixed effects network meta-analysis based on constant hazard ratio assumption; progression-free survival; all histologies; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals

Platin + gem or pac	1.03 (0.95, 1.12)	1.00 (0.90, 1.11)	0.94 (0.83, 1.07)	**2.06 (1.50, 2.81)**
0.97 (0.90, 1.05)	**Platin + pem**	0.97 (0.86, 1.09)	0.92 (0.81, 1.05)	**2.00 (1.47, 2.71)**
1.00 (0.90, 1.12)	1.03 (0.92, 1.16)	**Platin + doc**	0.95 (0.83, 1.08)	**2.06 (1.49, 2.84)**
1.06 (0.94, 1.20)	1.09 (0.96, 1.24)	1.05 (0.93, 1.20)	**Platin + vin**	**2.18 (1.58, 2.99)**
0.49 (0.36, 0.67)	**0.50 (0.37, 0.68)**	**0.48 (0.35, 0.67)**	**0.46 (0.34, 0.63)**	**Pembro**

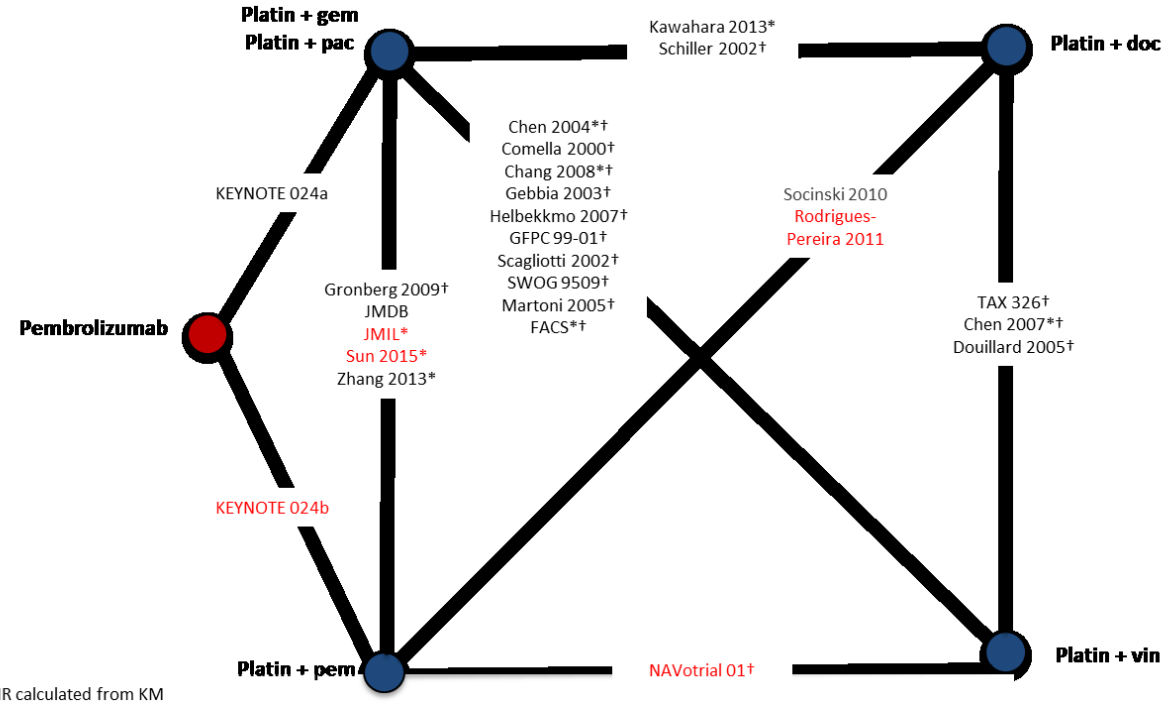
Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 31.12; Deviance: 27.11

In order to allow relative treatment effects to vary over time, an analysis was conducted using data from Kaplan Meier (KM) curves; these results are presented in Appendix 18. Different models were fit to the data, assuming that PFS times follow a Weibull distribution, a Gompertz distribution, or 2nd order fractional polynomial (FP) models. As can be seen in Appendix 18, the HRs of each intervention versus platin + gemcitabine/paclitaxel do not change over time, except for pembrolizumab, which suggests that the constant HR model may not adequately capture the relative treatment effect of pembrolizumab versus other interventions. Results of the random-effects models along with results of the sensitivity analysis excluding trials in 100% Asian populations are presented in Appendix 18: results of these analyses differed little from those of the primary analysis.

NMA Results: OS - All histologies

Figure 20 presents the network of evidence for OS (assuming constant HRs) in the all-histologies population; the corresponding data is shown in Appendix 18. The results of the NMA are given in Table 36. Pembrolizumab offered better OS than each other intervention of interest, and was the only intervention better than the reference treatment of platinum + gemcitabine/paclitaxel (HR 0.61, 95% CrI 0.41-0.90). In addition, platinum + pemetrexed showed a lower HR than platinum + vinorelbine. No other comparisons between platinum-based regimens were statistically meaningful. Under the random-effects model (Appendix 18), similar results were drawn, although the comparison between platinum + vinorelbine and platinum + pemetrexed was not statistically meaningful. In the sensivity analysis removing trials with entirely Asian populations, results were similar to that in the base case analysis (see Appendix 18).

Figure 20: Network of evidence for overall survival (constant HRs); all histologies



†HR calculated from KM
Trials in red: non-squamous
Trials in black: all histologies
Trials with 100% Asian patients denoted with *
KEYNOTE 024a: Patients assigned to platinum + gem or platinum + pac before randomization
KEYNOTE 024b: Patients assigned to platinum + pemetrexed before randomization (non-squamous)

Table 36: Results of fixed effects network meta-analysis based on constant hazard ratio assumption; overall survival; all-histologies; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals

Platin + gem or pac	1.03 (0.95, 1.13)	0.96 (0.87, 1.06)	**0.90 (0.82, 0.99)**	**1.65 (1.11, 2.46)**
0.97 (0.89, 1.05)	**Platin + pem**	0.93 (0.83, 1.04)	**0.87 (0.78, 0.97)**	**1.60 (1.08, 2.36)**
1.04 (0.94, 1.15)	1.08 (0.96, 1.20)	**Platin + doc**	0.94 (0.86, 1.03)	**1.72 (1.14, 2.57)**
1.11 (1.01, 1.22)	**1.15 (1.03, 1.28)**	1.07 (0.97, 1.17)	**Platin + vin**	**1.83 (1.23, 2.73)**
0.61 (0.41, 0.90)	**0.63 (0.42, 0.93)**	**0.58 (0.39, 0.87)**	**0.55 (0.37, 0.81)**	**Pembro**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 31.07; Deviance: 27.06

As with PFS, an NMA was performed allowing HRs to vary over time, using digitized KM curves (network presented in Appendix 18). The HRs for each intervention do not change appreciably over time; therefore the assumption of constant HRs is reasonable in this population for OS. However, the width of the CrIs can be seen to vary, particularly for pembrolizumab. Results of the random-effects models and results of the sensitivity analysis excluding trials in 100% Asian populations are also provided in Appendix 18.

Discussion and conclusion

The objective of NMA was to assess the efficacy of pembrolizumab relative to competing interventions for first-line treatment of advanced NSCLC in patients whose tumours express PD-L1 and are sensitising EGFR mutation and ALK translocation negative. Information concerning the efficacy and safety of pembrolizumab was obtained from KEYNOTE-024. It was of interest to compare pembrolizumab to relevant comparators in a mixed-histology population. Additional analyses specifically in non-squamous and squamous subgroups are presented in Appendix 18.

A key assumption required in order to connect KEYNOTE-024 to the network of relevant comparators was that of the comparability of the SOC regimens used as comparators in KEYNOTE-024. The design of the KEYNOTE-024 trial and availability of trial data limited the granularity of results that would have allowed pembrolizumab to be compared to each of the five SOC regimens individually. Previous work[139-141] has suggested that combinations of cisplatin or carboplatin and gemcitabine or paclitaxel were equivalently efficacious in both squamous and non-squamous populations. However, platinum + pemetrexed has been shown to demonstrate greater benefit in non-squamous patients than platinum + gemcitabine or paclitaxel.[139-141] In order to assess these assumptions with the most up-to-date evidence base, an additional NMA was performed comparing platinum combinations with gemcitabine, paclitaxel, and pemetrexed in both an all-histologies and non-squamous populations (see Appendix 19). These results supported the equivalence of platinum + gemcitabine or paclitaxel regardless of histology for OS, although the SOC regimens did differ somewhat for PFS (Appendix 19). The analysis also confirmed the increased efficacy of platinum + pemetrexed regimens in non-squamous populations (Appendix 19).

In the mixed-histology population, pembrolizumab was the only one of the included interventions to offer better PFS or OS than platinum + gemcitabine/paclitaxel. Pembrolizumab was statistically superior to all of the included platinum-based regimens; none of the other interventions were found to differ significantly from each other in terms of PFS. In the analysis

allowing HRs to vary (Appendix 18), pembrolizumab was more efficacious than all other regimens after 9 months of treatment. Pembrolizumab produced favorable HRs compared to all other regimens in terms of OS. Platinum + pemetrexed showed benefit over platinum + vinorelbine in terms of OS, although this is likely due to high proportion of non-squamous patients receiving pemetrexed. Platinum + vinorelbine was statistically worse than platinum + gemcitabine/paclitaxel. In the time-varying HR analysis, pembrolizumab showed statistical benefit over all other regimens after 6 months of treatment. In this population, the assumption of constant HR is reasonable for OS; for PFS, however, the HR of pembroliuzmab versus the reference treatments decreases over time, and the time-varying HR model should be preferred over the simpler constant HR model. In all populations, a sensitivity analysis removing trials in 100% Asian patients was conducted (see Appendix 18); in all cases results were nearly identical to those of the base case analyses.

The proportional hazards assumption is key when conducting NMA for OS and PFS based on the constant HR; this is implausible if the hazard functions of competing interventions cross. When we use a constant HR in the context of NMA we implicitly assume that the log hazard functions of all treatments in the network run parallel, which may be considered unrealistic. As an alternative to the constant HR, which is a univariate treatment effect measure, we can also use a multivariate treatment effect measure that describes how the relative treatment effect (e.g. HR) develops over time. Ouwens et al and Jansen presented methods for NMA of survival data using a multi-dimensional or multivariate treatment effect as an alternative to the synthesis of one treatment effect (e.g. the constant HRs).[92, 142] The hazard functions of the interventions in a trial are modeled using known parametric survival functions, and the difference in the parameters are considered the multi-dimensional treatment effect, which are synthesized (and indirectly compared) across studies. With this approach, the treatment effects are represented by multiple parameters rather than a single parameter. By incorporating additional parameters for the treatment effect, the proportional hazards assumption is relaxed and the NMA model can be fitted more closely to the available data. In the context of the analysis, the results of the time-varying HR analyses suggested that the HRs for the included interventions are stable over time for OS and therefore the more parsimonious constant HR analysis may be used to draw inference with minimal risk of added bias. For PFS, the HR of pembrolizumab versus the reference treatment (platinum + gemcitabine/paclitaxel or platinum + gemcitabine/paclitaxel/pemetrexed) decreased over time (indicating higher relative efficacy with increasing time on treatment); this suggests that the constant HR model may not be appropriate

in this population and the time-varying model should be preferred. It should be noted that for the constant HR analysis of PFS, many of the HRs used for analysis were calculated from KM curves, as most included trials did not publish HRs for PFS. These data points cannot be considered to be as accurate as HRs obtained from the true individual patient-level data within each trial, so these results should be interpreted with some caution.

In summary, based on currently-available RCT evidence, pembrolizumab demonstrates benefit in terms of PFS and OS compared to combinations of carboplatin or cisplatin and gemcitabine, paclitaxel, docetaxel, vinorelbine, or pemetrexed.

4.10.17 Justification for the choice of random or fixed effects model

For the NMA based on reported HRs and the NMA based on KM curves anticipating time-varying treatment effects, both fixed and random effects models were considered.Results are presented in this section and Appendix 18.

4.10.18 and 4.10.19 Heterogeneity between results of pairwise comparisons and inconsistencies between direct and indirect evidence

Please refer to the Discussion section presented above.

4.11 Non-randomised and non-controlled evidence

4.11.1 - Non-controlled evidence

KEYNOTE-001[89, 90, 143]

Methods:

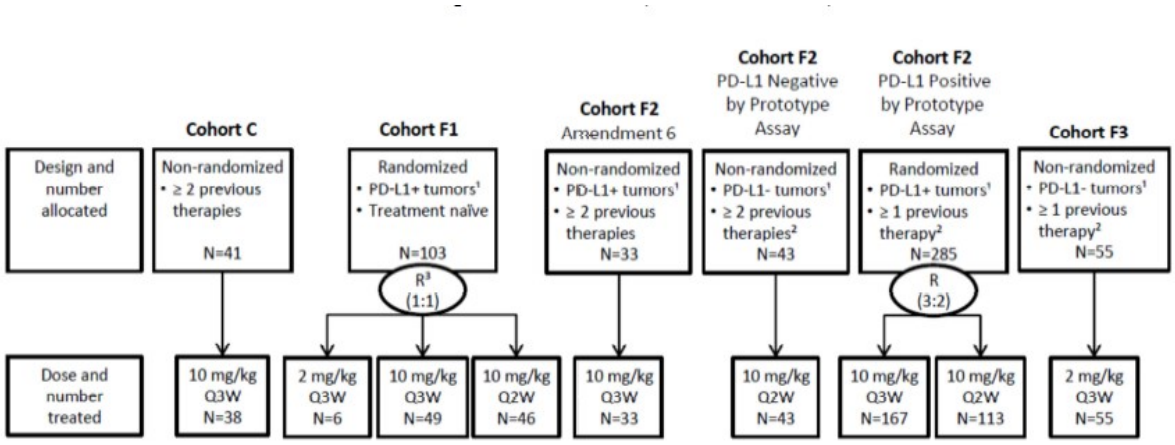
KEYNOTE-001 is a phase I multi-centre, open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumour activity of pembrolizumab in adult patients with progressive locally advanced or metastatic carcinomas, including melanoma or NSCLC.

Although KEYNOTE-001 is a phase I study due to its initial dose escalation component, it evolved into multiple phase II-like sub-studies in melanoma and NSCLC through a series of expansion cohorts, all of which have completed enrolment: Part A, which included subjects with NSCLC as part of a broader solid tumour population, evaluated dose escalation of pembrolizumab. Parts B and D were phase II-like expansion cohorts to study safety and efficacy in patients with melanoma.

Parts C and F (divided into cohorts F1, F2 and F3) were expansion cohorts specifically designed to evaluate the efficacy and safety of pembrolizumab in patients with locally advanced or metastatic NSCLC: Cohort F1 enrolled treatment–naïve patients with stage IV NSCLC, and is relevant to the decision problem. All patients enrolled in Part C, Cohort F2, and Cohort F3 had received at least one line of prior therapy which must have included platinum-based chemotherapy and demonstrated disease progression before initiating pembrolizumab; therefore these cohorts are not relevant to the decision problem.

Further details on Parts C and F are provided in Figure 21 below. The quality assessment of Cohort F1 (randomised) of KEYNOTE-001 is provided in Appendix 8.

Figure 21: KEYNOTE-001 NSCLC expansion cohorts (n = 560 allocated)



[1]Tumor PD-L1 expression was determined by a prototype assay to inform enrollment. Samples were independently reanalyzed using a clinical trial/market-ready immunohistochemistry assay.
[2]Including ≥ therapy with platinum-containing doublet.
[3]First 11 subjects randomized to 2mg/kg Q3W or 10 mg/kg Q3W. The remaining 92 subjects were randomized to 10mg/kg Q2W or Q3W.

PD-L1 expression was assessed with the following assays, both of which used the murine 22C3 anti–human PD-L1 antibody:

- A prototype immunohistochemistry assay (QualTek Molecular Laboratories, Goleta, CA, USA)
    - This assay informed study enrollment. PD-L1 positivity was defined as membrane staining on ≥1% of cells within tumour nests, including both neoplastic cells and intercalated mononuclear inflammatory cells, or a distinctive pattern of staining caused by mononuclear inflammatory cells infiltrating the stroma, forming a banding pattern adjacent to tumour nests
- A clinical trial immunohistochemistry assay (early version of the PD-L1 22C3 IHC pharmDx assay, Dako North America, Carpinteria, CA, USA)..
    - This assay was used to analyse the relationship between PD-L1 expression and efficacy. Tumours were categorized based on TPS (i.e. the percentage of tumour cells demonstrating membranous PD-L1 staining).

Further details of the PD-L1 expression assays used in the study and antigen stability are provided in Appendix 20.

The inclusion/exclusion criteria applied to the treatment-naïve cohort F1 of KEYNOTE-001 are described below:

Cohort F1 inclusion criteria:

- Histologically or cytologically confirmed stage IV NSCLC
- Age ≥18 years
- Wild-type EGFR and negative ALK translocation status (not required for the first 11 patients enrolled under an earlier protocol version)
- Measurable disease per investigator-assessed irRC
- ECOG performance status of 0 or 1
- Completion of adjuvant therapy >1 year prior to recurrent/metastatic disease
- New tumour sample available for assessment of PD-L1 expression was required for all randomised patients.

Cohort F1 exclusion criteria:

- Active, untreated brain metastases or carcinomatous meningitis
- Prior systemic therapy
- History of noninfectious pneumonitis or autoimmune disease requiring steroid therapy
- Prior therapy targeting the PD-1 pathway.

The first 11 subjects were randomised (1:1) to either pembrolizumab 2 mg/kg Q3W or 10 mg/kg Q3W. Following a protocol amendment, the subsequent subjects (n=90) were randomly assigned 1:1 to either pembrolizumab 10 mg/kg Q3W or every 2 weeks (Q2W). The changes to the dosing schedule were based on evolving data with the dose and schedule in subjects with melanoma.

Pembrolizumab was administered over 30 minutes as an IV infusion. Treatment was continued until disease progression per investigator-assessed irRC, unacceptable toxicity, physician decision, or patient withdrawal.

Patients who experienced confirmed complete response per irRC after ≥6 months of treatment could discontinue pembrolizumab, provided they received ≥2 doses beyond initial complete response; eligible patients who experienced disease progression were permitted to remain on treatment until a confirmatory scan 4–6 weeks later.

Primary efficacy endpoint (related to NSCLC):

Objective response rate (ORR) served as the primary efficacy endpoint to demonstrate the anti-tumour activity of pembrolizumab in the study population enrolled under Cohort F1. Tumour imaging was conducted every 9 weeks and reviewed centrally. Response was assessed per RECIST v1.1 by independent central review (primary end point for efficacy) and per irRC by investigator (primary end point for clinical decision-making).

Secondary efficacy endpoints:

Secondary endpoints included duration of response, disease control rate (defined as complete response + partial response + stable disease + noncomplete response/nonprogressive disease [defined as patients without measurable disease per central review at baseline who did not experience complete response or disease progression]), PFS, OS, and relationship between PD-L1 expression and antitumour activity.

Results: KEYNOTE-001 (Cohort F1) - Data cut-off 18-September 2015 [90, 143]

Below are presented the updated safety and efficacy data concerning first-line pembrolizumab therapy and the correlation between PD-L1 expression and clinical activity in treatment-naive patients with advanced NSCLC enrolled in KEYNOTE-001.

At the time of data cut-off (18-September-2015), the median follow-up duration was 22.2 months (range, 17.8-30.5) for treatment-naïve patients.[90]. As of this date, 36 (35.6%) patients were alive without new anticancer therapy, and 13 (13%) were still receiving pembrolizumab.

The results presented focus on the results in the All Subjects as Treated (ASaT) dataset as the more conservative evaluation of treatment effect. Subjects who received at least one dose of study treatment were included in the ASaT dataset.

Between 01-March-2013 and 26-March-2014, at total of 101 treatment-naive patients with advanced NSCLC from 8 countries enrolled and were randomly assigned to receive pembrolizumab 2 mg/kg Q3W (n = 6), 10 mg/kg Q3W (n = 49), or 10 mg/kg Q2W (n = 46). The participant flow is depicted in Figure 22.

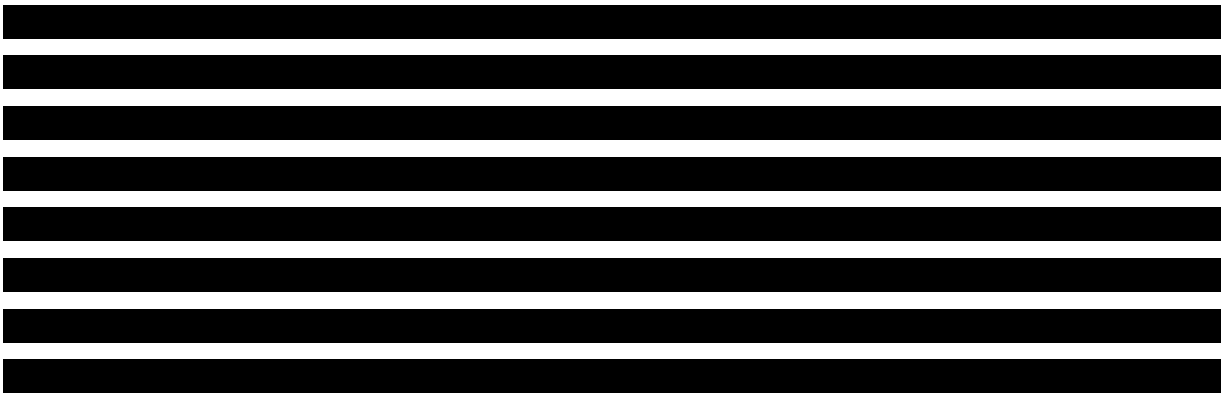


Figure 22: Consort diagram[143] - KEYNOTE-001 Cohort F1 (treatment-naïve population) - database cut-off 18-Sep-2015.

Patient baseline characteristics are presented in Table 37.

Table 37: KEYNOTE-001 Cohort F1: Baseline characteristics in the intent-to-treat[90]

Characteristic	Overall (N=101)
Age, years	
Median	68.0
Range	39-93
Sex, n (%)	
Male	60 (59)
Female	41 (41)
ECOG performance status,* n (%)	
0	44 (44)
1	57 (56)
Histology, n (%)	
Non-squamous	79 (79)
Squamous	19 (19)
Smoking history, n (%)	
Current or former	90 (89)
Never	11 (11)
EGFR mutation, n (%)	
Yes	3 (3)
No	95 (94)
Unknown	3 (3)

Objective response rate (ORR)[143]

[redacted]

Table 38: KEYNOTE 001 Cohort F1: Summary of efficacy by dose (ASaT population)

n (%) [95% CI]	Overall	2 mg/kg Q3W	10 mg/kg Q3W	10 mg/kg Q2W
CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Non CR/non PD	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable*	[redacted]	[redacted]	[redacted]	[redacted]
No assessment	[redacted]	[redacted]	[redacted]	[redacted]
ORR	[redacted]	[redacted]	[redacted]	[redacted]
DCR†	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; CR=complete response; DCR=disease control rate; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.
95% CI based on binomial exact confidence interval method.
**Accounts for patients who were non-evaluable, withdrew consent, were withdrawn by the investigator, died, or started new anticancer therapy before the first tumour assessment and therefore did not have response evaluated.*
†Includes (CR + PR + SD + NonCR/NonPD).

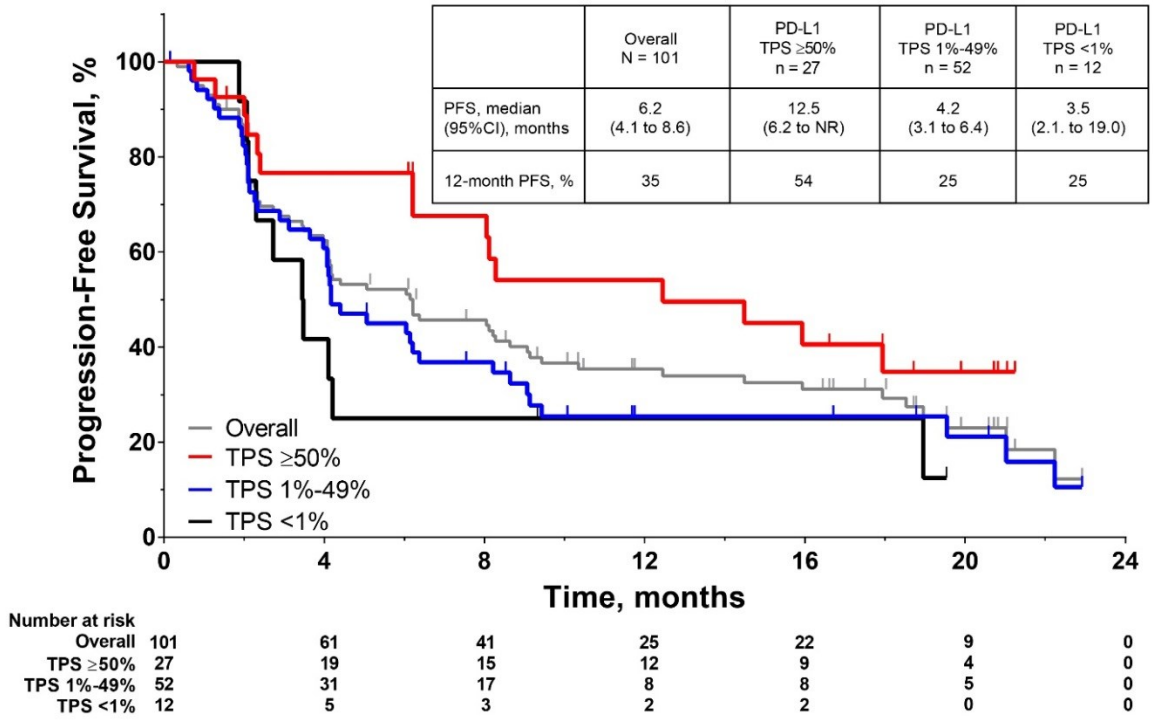
Time to response and duration of response[143]

[redacted]

Progression-Free Survival[90]

Median PFS was 6.2 months (95% CI, 4.1–8.6 months) in the overall population, with a 12-month PFS rate of 35%. Among patients with TPS ≥50%, the median PFS was 12.5 months (95% CI, 6.2 months to not reached) and 12-month PFS rate was 54% (Figure 23).

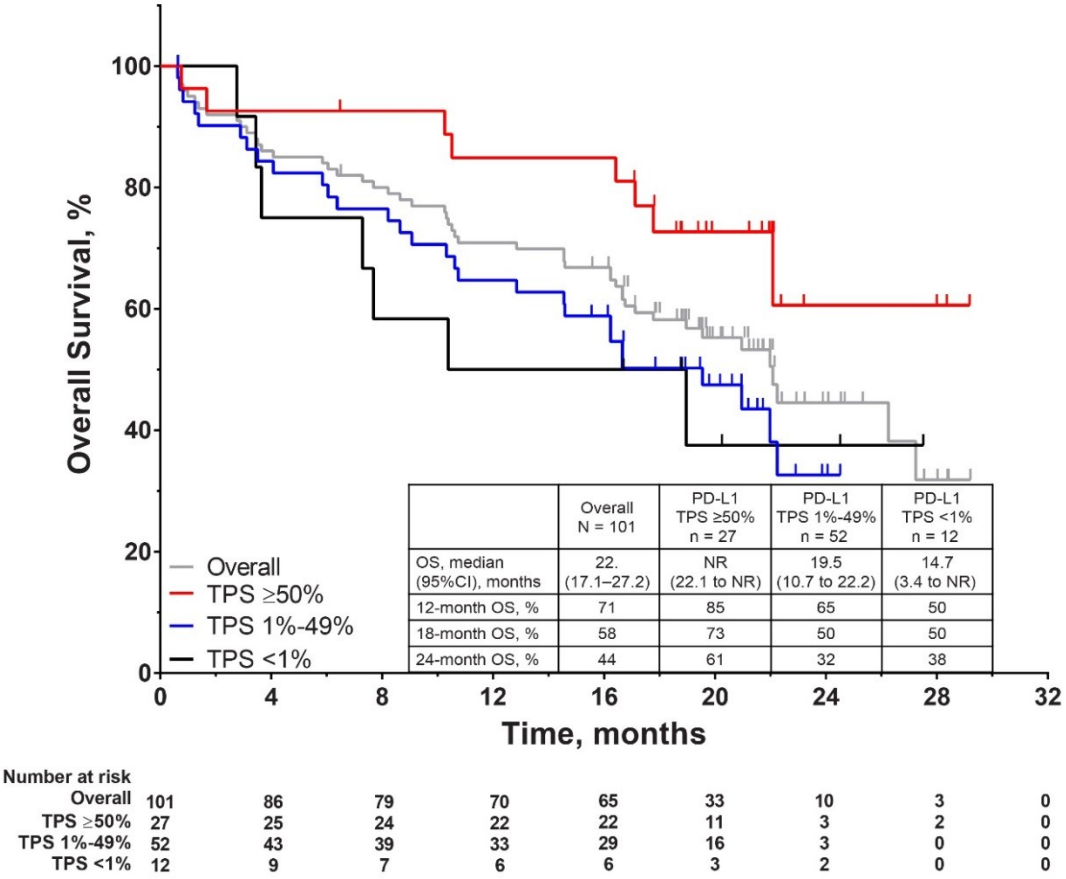
Figure 23: KM estimates of PFS per RECIST v1.1 by independent central review by PD-L1 expression level.



Overall Survival[90]

Median OS was 22.1 months in the overall population (95% CI, 17.1–27.2 months). In the TPS ≥50% group, median OS was not reached (95% CI, 22.1 months to not reached) (Figure 24).

Figure 24: KM estimates of OS per RECIST v1.1 by independent central review by PD-L1 expression level.



The results presented provide supportive evidence on the longer term clinical benefit of pembrolizumab in patients with advanced NSCLC whose tumours strongly express PD-L1, and help provide a comprehensive assessment of clinical efficacy.

Subgroup analyses[143]

Subgroup analyses were performed based on major demographic factors and potentially important prognostic factors for patients with advanced NSCLC. [redacted]

4.12 Adverse reactions

4.12.2 Adverse reactions reported in RCTs listed in section 4.2

KEYNOTE-24 Adverse reactions[21]

Safety analyses were conducted in the 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. No subjects took incorrect trial treatment for the entire treatment period

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 09-May-2016.

Summaries and listings of overall AEs include events from the first dose to 30 days after the last dose of study drug. Summaries and listings of SAEs and AEOSIs (summaries, counts, listings, and tables including non-serious AEs [NSAEs]) were collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiated new anticancer therapy, whichever was earlier. Therefore, the incidence of SAEs in overall AE summary tables differs slightly from the incidence of SAEs in later sections, where SAEs that were captured up to 90 days after the last dose of study treatment are described.

- *Extent of Exposure*

Table 39 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 (66 [44%]). The vast majority of subjects with non-squamous NSCLC were administered a pemetrexed containing doublet (102 [83%]). Forty-six (37%) subjects with non-squamous NSCLC received pemetrexed maintenance. More subjects with squamous NSCLC received gemcitabine in combination with carboplatin (55.6%) as compared to gemcitabine in combination with cisplatin (26%) or paclitaxel in combination with carboplatin (18.5%).

Table 39: KEYNOTE-024 Breakdown of chemotherapy by histology

Actual Study Medication	Non-squamous N (%)	Squamous N (%)	Total N (%)
Gemcitabine and carboplatin	5 (3.33)	15 (10)	20 (13.33)
Gemcitabine and cisplatin	4 (2.67)	7 (4.67)	11 (7.33)
Paclitaxel and carboplatin without pemetrexed maintenance	12 (8.00)	5 (3.33)	17 (11.33)
Pemetrexed and carboplatin with pemetrexed maintenance	28 (18.67)	0 (0)	28 (18.67)
Pemetrexed and carboplatin without pemetrexed maintenance	38 (25.33)	0 (0)	38 (25.33)
Pemetrexed and cisplatin with pemetrexed maintenance	18 (12.00)	0 (0)	18 (12.00)
Pemetrexed and cisplatin without pemetrexed maintenance	18 (12.00)	0 (0)	18 (12.00)
Total	123 (82.00)	27 (18.00)	150 (100.00)
N = number Frequency missing = 1			

Table 40 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 mean days on therapy in the pembrolizumab arm was 205.73 days compared to 120.83 days in the SOC arm.

Table 40: KEYNOTE-024 Summary of drug exposure (ASaT population)

	Pembrolizumab	SOC
	N=154	N=150
Study Days On-Therapy (days)		
Mean	205.73	120.83
Median	214.00	106.00
SD	144.93	105.94
Range	1.00 to 568.00	1.00 to 511.00
(Database Cutoff Date: 09MAY2016).		

Table 41 displays a summary of exposure to treatment by duration in the ASaT population. Overall, 87 subjects in the pembrolizumab arm received treatment for ≥6 months compared to 29 subjects in the SOC arm.

Table 41: KEYNOTE-024 Exposure by duration (ASaT population)

Duration of Exposure	Pembrolizumab (N=154)		SOC (N=150)	
	n	Subject Years	n	Subject Years
> 0 m	154	86.7	150	49.6
≥ 1 m	130	86.2	119	48.9
≥ 3 m	108	82.8	84	43.1
≥ 6 m	87	74.5	29	23.9
≥ 12 m	23	27.3	5	5.7
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: 09MAY2016).				

- *Adverse Events (AEs)*

Table 42 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 almost double mean exposure to pembrolizumab as compared to SOC.

Results show that there were comparable numbers of subjects with one or more AEs in the pembrolizumab arm (148 [96.1%]) compared to the SOC arm (145 [96.7%]). Fewer subjects had Grade 3 to 5 drug-related AEs in the pembrolizumab arm (26.6%) than in the SOC arm (53.3%). Serious adverse events reported in the pembrolizumab and SOC arms were comparable (44.2% and 44%, respectively). Drug-related SAEs were also comparable in both treatment groups (21% each). There were 9 (5.8%) deaths reported in the pembrolizumab arm; of which, 1 (0.6%) death was assessed to be a drug-related SAE. In the SOC arm, 7 (4.7%) deaths were reported and 3 (2%) of these deaths were assessed as drug related SAEs. A total of 35 (23%) subjects (14 [9.1%] in the pembrolizumab arm and 21 [14.0%] in the SOC arm) discontinued due to an AE; of which, 27 (17.8%) discontinued due to a drug-related AE (11 [7.1%] in the pembrolizumab arm and 16 [10.7%] in the SOC arm).

Table 42: KEYNOTE-024 Adverse Event summary (ASaT population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	148	(96.1)	145	(96.7)
with no adverse event	6	(3.9)	5	(3.3)
with drug-related† adverse events	113	(73.4)	135	(90.0)
with toxicity grade 3-5 adverse events	82	(53.2)	109	(72.7)
with toxicity grade 3-5 drug-related adverse events	41	(26.6)	80	(53.3)
with serious adverse events	68	(44.2)	66	(44.0)
with serious drug-related adverse events	33	(21.4)	31	(20.7)
who died	9	(5.8)	7	(4.7)
who died due to a drug-related adverse event	1	(0.6)	3	(2.0)
discontinued‡ due to an adverse event	14	(9.1)	21	(14.0)
discontinued due to a drug-related adverse event	11	(7.1)	16	(10.7)
discontinued due to a serious adverse event	13	(8.4)	11	(7.3)
discontinued due to a serious drug-related adverse event	10	(6.5)	7	(4.7)

† 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: 09MAY2016).

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

- In the pembrolizumab arm: dyspnoea (22.1%), diarrhoea (20.8%), constipation (20.8%), fatigue (20.8%), and decreased appetite (20.1%).
- In the SOC arm: anemia (52.7%), nausea (46.7%), fatigue (35.3%), decreased appetite (32.7%), neutropaenia (24%), vomiting (24%), constipation (22.7%), and diarrhoea (22%).
- The incidence of pruritus, rash, and nasopharyngitis in the pembrolizumab arm were more than double the incidence observed in the SOC arm.

The incidence of nausea, anemia, vomiting, neutropaenia, blood creatinine increased, stomatitis, thrombocytopaenia, dysgeusia, neutrophil count decreased, platelet count decreased, and white blood cell count decreased in the SOC arm were more than double than 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 43. 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 43: KEYNOTE-024 Subjects with Adverse Events by decreasing incidence (incidence ≥10% in one or more treatment groups) (ASaT population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	148	(96.1)	145	(96.7)	293	(96.4)
with no adverse events	6	(3.9)	5	(3.3)	11	(3.6)
Nausea	30	(19.5)	70	(46.7)	100	(32.9)
Anaemia	20	(13.0)	79	(52.7)	99	(32.6)
Fatigue	32	(20.8)	53	(35.3)	85	(28.0)
Decreased appetite	31	(20.1)	49	(32.7)	80	(26.3)
Constipation	32	(20.8)	34	(22.7)	66	(21.7)
Diarrhoea	32	(20.8)	33	(22.0)	65	(21.4)
Dyspnoea	34	(22.1)	24	(16.0)	58	(19.1)
Vomiting	12	(7.8)	36	(24.0)	48	(15.8)
Cough	26	(16.9)	21	(14.0)	47	(15.5)
Back pain	20	(13.0)	21	(14.0)	41	(13.5)
Arthralgia	24	(15.6)	15	(10.0)	39	(12.8)
Neutropaenia	2	(1.3)	36	(24.0)	38	(12.5)
Pyrexia	24	(15.6)	14	(9.3)	38	(12.5)
Oedema peripheral	16	(10.4)	15	(10.0)	31	(10.2)
Blood creatinine increased	10	(6.5)	20	(13.3)	30	(9.9)
Alanine aminotransferase increased	17	(11.0)	11	(7.3)	28	(9.2)
Dizziness	16	(10.4)	12	(8.0)	28	(9.2)
Pruritus	23	(14.9)	5	(3.3)	28	(9.2)
Rash	22	(14.3)	6	(4.0)	28	(9.2)
Asthenia	10	(6.5)	16	(10.7)	26	(8.6)
Stomatitis	7	(4.5)	18	(12.0)	25	(8.2)
Thrombocytopaenia	2	(1.3)	20	(13.3)	22	(7.2)
Dysgeusia	3	(1.9)	18	(12.0)	21	(6.9)
Neutrophil count decreased	1	(0.6)	20	(13.3)	21	(6.9)
Platelet count decreased	1	(0.6)	19	(12.7)	20	(6.6)
Nasopharyngitis	16	(10.4)	2	(1.3)	18	(5.9)
White blood cell count decreased	1	(0.6)	16	(10.7)	17	(5.6)

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: 09MAY2016).

Appendix 22 provides a detailed summary of the incidence, number of episodes and duration of episodes of grade 3-5 AEs and grade 2-5 diarrhoea AEs in the following sub-populations of interest from KEYNOTE-024:

- Patients with pre-selected pemetrexed containing regimens (i.e "Platinum/Pemetrexed" group)
- Patients with pre-selected non-pemetrexed containing regimens (i.e "Other Platinum Doublets" group)
- Squamous patients
- Non-squamous patients

- *Drug-Related Adverse Events*

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 44 displays the number and percentage of subjects with drug-related AEs (incidence ≥10%) by decreasing incidence (based on the total incidence) in the ASaT population. 248 (81.6%) subjects reported a drug-related AE: 113 (73.4%) 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 (14.3%), fatigue (10.4%), and pyrexia (10.4%).
- In the SOC arm: anaemia (44.0%), nausea, (43.3%), fatigue (28.7%), decreased appetite (26.0%), neutropaenia (22.7%), vomiting (20.0%), diarrhoea (13.3%), neutrophil count decreased (13.3%), platelet count decreased (12.0%), stomatitis (12.0%), constipation (11.3%), thrombocytopaenia (11.3%), white blood cell count decreased (10.7%), dysgeusia (10.0%), and blood creatinine increased (10.0%).

The incidence of pyrexia in pembrolizumab arm was approximately double the incidence observed in the SOC arm.

The incidence 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 hematologic toxicities observed in the SOC arm were consistent with bone marrow suppression which is expected with chemotherapy.

Table 44: KEYNOTE-024 Subjects with drug-related Adverse Events by decreasing incidence (incidence ≥10% in one or more treatment groups) (ASaT population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	113	(73.4)	135	(90.0)	248	(81.6)
with no adverse events	41	(26.6)	15	(10.0)	56	(18.4)
Nausea	15	(9.7)	65	(43.3)	80	(26.3)
Anaemia	8	(5.2)	66	(44.0)	74	(24.3)
Fatigue	16	(10.4)	43	(28.7)	59	(19.4)
Decreased appetite	14	(9.1)	39	(26.0)	53	(17.4)
Diarrhoea	22	(14.3)	20	(13.3)	42	(13.8)
Neutropaenia	1	(0.6)	34	(22.7)	35	(11.5)
Vomiting	4	(2.6)	30	(20.0)	34	(11.2)
Pyrexia	16	(10.4)	8	(5.3)	24	(7.9)
Constipation	6	(3.9)	17	(11.3)	23	(7.6)
Stomatitis	4	(2.6)	18	(12.0)	22	(7.2)
Neutrophil count decreased	0	(0.0)	20	(13.3)	20	(6.6)
Blood creatinine increased	3	(1.9)	15	(10.0)	18	(5.9)
Platelet count decreased	0	(0.0)	18	(12.0)	18	(5.9)
Thrombocytopaenia	0	(0.0)	17	(11.3)	17	(5.6)
White blood cell count decreased	1	(0.6)	16	(10.7)	17	(5.6)
Dysgeusia	1	(0.6)	15	(10.0)	16	(5.3)

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: 09MAY2016).

- *Drug-Related Grade 3 to 5 Adverse Events*

Table 45 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 (3.9%), pneumonitis (2.6%), and anaemia (1.9%).
- In the SOC arm: anemia (19.3%), neutropaenia (13.3%), platelet count decreased (6.0%), and thrombocytopaenia (5.3%).

The overall incidence of drug-related Grade 3 to 5 AEs in the SOC arm (53.3%) was approximately double than in the pembrolizumab arm (26.6%).

Table 45: KEYNOTE-024 Subjects with Grade 3-5 drug-related Adverse Events by decreasing incidence (incidence ≥1% in one or more treatment groups) (ASaT population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	41	(26.6)	80	(53.3)	121	(39.8)
with no adverse events	113	(73.4)	70	(46.7)	183	(60.2)
Anaemia	3	(1.9)	29	(19.3)	32	(10.5)
Neutropaenia	0	(0.0)	20	(13.3)	20	(6.6)
Platelet count decreased	0	(0.0)	9	(6.0)	9	(3.0)
Diarrhoea	6	(3.9)	2	(1.3)	8	(2.6)
Thrombocytopaenia	0	(0.0)	8	(5.3)	8	(2.6)
Fatigue	2	(1.3)	5	(3.3)	7	(2.3)
Neutrophil count decreased	0	(0.0)	6	(4.0)	6	(2.0)
Pneumonitis	4	(2.6)	1	(0.7)	5	(1.6)
Decreased appetite	0	(0.0)	4	(2.7)	4	(1.3)
Hypoalbuminaemia	2	(1.3)	2	(1.3)	4	(1.3)
Asthenia	1	(0.6)	2	(1.3)	3	(1.0)
Febrile neutropaenia	0	(0.0)	3	(2.0)	3	(1.0)
Lymphocyte count decreased	0	(0.0)	3	(2.0)	3	(1.0)
Nausea	0	(0.0)	3	(2.0)	3	(1.0)
Pancytopaenia	0	(0.0)	3	(2.0)	3	(1.0)
Pneumonia	0	(0.0)	3	(2.0)	3	(1.0)
White blood cell count decreased	0	(0.0)	3	(2.0)	3	(1.0)
Acute kidney injury	0	(0.0)	2	(1.3)	2	(0.7)
Aspartate aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)
Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Epistaxis	0	(0.0)	2	(1.3)	2	(0.7)
Leukopaenia	0	(0.0)	2	(1.3)	2	(0.7)

Lower respiratory tract infection	2	(1.3)	0	(0.0)	2	(0.7)
Lung infection	0	(0.0)	2	(1.3)	2	(0.7)
Stomatitis	0	(0.0)	2	(1.3)	2	(0.7)
Transaminases increased	2	(1.3)	0	(0.0)	2	(0.7)

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: 09MAY2016).

- *Drug-Related Serious Adverse Events (SAEs)*

Table 46 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 were comparable between the pembrolizumab (21.4%) and SOC (20.7%) arms. The most common drug-related SAEs by decreasing incidence were as follows:

- In the pembrolizumab arm: pneumonitis (4.5%) and diarrhoea (1.9%).
- In the SOC arm: anaemia (2.7%), febrile neutropaenia (2.0%), pancytopaenia (2.0%), pneumonia (2.0%), and thrombocytopaenia (2.0%).

Table 46: KEYNOTE-024 Subjects with Drug-Related serious Adverse Events by decreasing Incidence (incidence >0% in one or more treatment groups) (ASaT population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	154		150		304	
with one or more adverse events	33	(21.4)	31	(20.7)	64	(21.1)
with no adverse events	121	(78.6)	119	(79.3)	240	(78.9)
Pneumonitis	7	(4.5)	1	(0.7)	8	(2.6)
Anaemia	1	(0.6)	4	(2.7)	5	(1.6)
Diarrhoea	3	(1.9)	1	(0.7)	4	(1.3)
Febrile neutropaenia	0	(0.0)	3	(2.0)	3	(1.0)
Pancytopaenia	0	(0.0)	3	(2.0)	3	(1.0)
Pneumonia	0	(0.0)	3	(2.0)	3	(1.0)
Thrombocytopaenia	0	(0.0)	3	(2.0)	3	(1.0)
Acute kidney injury	0	(0.0)	2	(1.3)	2	(0.7)
Alanine aminotransferase increased	2	(1.3)	0	(0.0)	2	(0.7)
Colitis	2	(1.3)	0	(0.0)	2	(0.7)

Diabetes mellitus	2	(1.3)	0	(0.0)	2	(0.7)
Epistaxis	0	(0.0)	2	(1.3)	2	(0.7)
Lower respiratory tract infection	2	(1.3)	0	(0.0)	2	(0.7)
Lung infection	0	(0.0)	2	(1.3)	2	(0.7)
Acute hepatic failure	1	(0.6)	0	(0.0)	1	(0.3)
Aspartate aminotransferase increased	1	(0.6)	0	(0.0)	1	(0.3)
Bilirubin conjugated increased	1	(0.6)	0	(0.0)	1	(0.3)
Cellulitis	0	(0.0)	1	(0.7)	1	(0.3)
Cerebrovascular accident	1	(0.6)	0	(0.0)	1	(0.3)
Death	0	(0.0)	1	(0.7)	1	(0.3)
Diabetic ketoacidosis	1	(0.6)	0	(0.0)	1	(0.3)
Enterocolitis	1	(0.6)	0	(0.0)	1	(0.3)
Face oedema	1	(0.6)	0	(0.0)	1	(0.3)
Fatigue	1	(0.6)	0	(0.0)	1	(0.3)
Gait disturbance	0	(0.0)	1	(0.7)	1	(0.3)
Gastric ulcer	1	(0.6)	0	(0.0)	1	(0.3)
Hepatic enzyme increased	1	(0.6)	0	(0.0)	1	(0.3)
Hyperthyroidism	1	(0.6)	0	(0.0)	1	(0.3)
Hypophysitis	1	(0.6)	0	(0.0)	1	(0.3)
Hypovolaemia	1	(0.6)	0	(0.0)	1	(0.3)
Infusion related reaction	1	(0.6)	0	(0.0)	1	(0.3)
Leukocytosis	0	(0.0)	1	(0.7)	1	(0.3)
Lichenoid keratosis	1	(0.6)	0	(0.0)	1	(0.3)
Malignant neoplasm progression	0	(0.0)	1	(0.7)	1	(0.3)
Musculoskeletal pain	1	(0.6)	0	(0.0)	1	(0.3)
Nausea	0	(0.0)	1	(0.7)	1	(0.3)
Neutropenic sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Oedema peripheral	1	(0.6)	0	(0.0)	1	(0.3)
Organising pneumonia	1	(0.6)	0	(0.0)	1	(0.3)
Pancreatitis	1	(0.6)	0	(0.0)	1	(0.3)
Pericarditis	1	(0.6)	0	(0.0)	1	(0.3)
Platelet count decreased	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(0.7)	1	(0.3)
Pulmonary embolism	1	(0.6)	0	(0.0)	1	(0.3)
Pulmonary sepsis	0	(0.0)	1	(0.7)	1	(0.3)
Pyrexia	0	(0.0)	1	(0.7)	1	(0.3)
Rash	1	(0.6)	0	(0.0)	1	(0.3)
Respiratory tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Skin infection	0	(0.0)	1	(0.7)	1	(0.3)
Stomatitis	0	(0.0)	1	(0.7)	1	(0.3)
Sudden death	1	(0.6)	0	(0.0)	1	(0.3)
Transaminases increased	1	(0.6)	0	(0.0)	1	(0.3)
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.7)	1	(0.3)
Vasospasm	0	(0.0)	1	(0.7)	1	(0.3)
Vomiting	1	(0.6)	0	(0.0)	1	(0.3)

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: 09MAY2016).

- *Adverse Events of Special Interest*

An immune-related adverse event (irAE) was defined as an AE that was consistent with an immune phenomenon and was temporally associated with drug exposure. This definition was designed as a sensitive, although perhaps not specific, screening tool for AEs with potential immune etiology analysis.

The analysis of AEOSI was the primary method of assessing irAEs for this study and was based on a compiled list of preferred AE terms potentially associated with an immune etiology. This list was developed by the Sponsor through ongoing monitoring of the pembrolizumab safety profile during the development program. The AEOSI identified as potential risks for pembrolizumab, as well as events that are being monitored by the Sponsor to determine whether they may be immune-mediated AEs associated with pembrolizumab treatment have been included.

The AEOSI are presented regardless of Investigator-assessed causality and generally include all AE grades (with the exception of severe skin reactions). In an attempt to capture all informative data, the list of terms is intentionally broad; consequently, some reported terms may not have an obvious immune mechanism. The list of terms is updated periodically based on emerging pembrolizumab safety data.

Table 47 displays the summary of AEOSI in the ASaT population. Adverse events of special interest were more common among pembrolizumab-treated subjects compared to SOC-treated subjects (29.2% vs. 4.7%, respectively). A majority of these events were Grade 1 or 2 in severity, as only 9.7% of pembrolizumab-treated subjects experienced Grade 3 to 5 AEOSI. There were no deaths reported due to AEOSI in either treatment group. Six (3.9%) subjects discontinued due to drug-related AEOSI in the pembrolizumab arm and none in the SOC arm. Table 48 displays the subjects with AEOSI (incidence >0% in one or more treatment groups) by AEOSI category.

Table 47: KEYNOTE-24 Adverse Event summary AEOSI (ASaT population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more adverse events	45	(29.2)	7	(4.7)
with no adverse event	109	(70.8)	143	(95.3)
with drug-related† adverse events	39	(25.3)	3	(2.0)
with toxicity grade 3-5 adverse events	15	(9.7)	1	(0.7)
with toxicity grade 3-5 drug-related adverse events	13	(8.4)	1	(0.7)
with serious adverse events	17	(11.0)	1	(0.7)
with serious drug-related adverse events	16	(10.4)	1	(0.7)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	6	(3.9)	0	(0.0)
discontinued due to a drug-related adverse event	6	(3.9)	0	(0.0)
discontinued due to a serious adverse event	5	(3.2)	0	(0.0)
discontinued due to a serious drug-related adverse event	5	(3.2)	0	(0.0)

† 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: 09MAY2016).

Table 48: KEYNOTE-024 Subjects with Adverse Events by AEOSI category (incidence > 0% in one or more treatment groups) (ASaT population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	154		150	
with one or more AEOSI	45	(29.2)	7	(4.7)
with no AEOSI	109	(70.8)	143	(95.3)
Colitis	**3**	**(1.9)**	**0**	**(0.0)**
Colitis	2	(1.3)	0	(0.0)
Enterocolitis	1	(0.6)	0	(0.0)
Hyperthyroidism	**12**	**(7.8)**	**2**	**(1.3)**
Hyperthyroidism	12	(7.8)	2	(1.3)
Hypophysitis	**1**	**(0.6)**	**0**	**(0.0)**
Hypophysitis	1	(0.6)	0	(0.0)
Hypothyroidism	**14**	**(9.1)**	**2**	**(1.3)**
Hypothyroidism	14	(9.1)	2	(1.3)
Infusion Reactions	**7**	**(4.5)**	**2**	**(1.3)**
Drug hypersensitivity	0	(0.0)	1	(0.7)

Hypersensitivity	4	(2.6)	0	(0.0)
Infusion related reaction	3	(1.9)	1	(0.7)
Myositis	**3**	**(1.9)**	**0**	**(0.0)**
Myopathy	1	(0.6)	0	(0.0)
Myositis	2	(1.3)	0	(0.0)
Nephritis	**1**	**(0.6)**	**0**	**(0.0)**
Tubulointerstitial nephritis	1	(0.6)	0	(0.0)
Pancreatitis	**1**	**(0.6)**	**0**	**(0.0)**
Pancreatitis	1	(0.6)	0	(0.0)
Pneumonitis	**9**	**(5.8)**	**1**	**(0.7)**
Interstitial lung disease	1	(0.6)	0	(0.0)
Pneumonitis	8	(5.2)	1	(0.7)
Skin	**6**	**(3.9)**	**0**	**(0.0)**
Psoriasis	1	(0.6)	0	(0.0)
Rash	2	(1.3)	0	(0.0)
Rash generalised	1	(0.6)	0	(0.0)
Rash maculo-papular	1	(0.6)	0	(0.0)
Toxic skin eruption	1	(0.6)	0	(0.0)
Thyroiditis	**4**	**(2.6)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(0.6)	0	(0.0)
Thyroiditis	3	(1.9)	0	(0.0)
Type 1 Diabetes Mellitus	**1**	**(0.6)**	**0**	**(0.0)**
Diabetic ketoacidosis	1	(0.6)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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: 09MAY2016).

KEYNOTE-001 – Cohort F1: Adverse Events[143]

Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, ECG measurements, and vital signs reported during the treatment period up to the data cut-off 18-September-2015. Adverse events (AEs) were collected throughout the study and for 30 days thereafter (90 days for serious AEs).

The safety data is presented below for KEYNOTE-001 Cohort F1. [redacted]

[redacted]

Table 49: KEYNOTE-001 Cohort F1: Grade 3-4 treatment-related AEs (ASaT population)

n (%)	Overall [redacted]	2 mg/kg Q3W [redacted]	10 mg/kg Q3W [redacted]	10 mg/kg Q2W [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The safety findings from KEYNOTE-001 Cohort F1 demonstrate that pembrolizumab monotherapy was generally well tolerated in the first-line treatment of NSCLC, with low occurrence of grade 3/4 toxicity and without any treatment-related death. [redacted]

4.12.3 Studies that report additional adverse reactions to those reported in section 4.2

The search strategy used to identify studies which reported AEs was consistent with that described in section 4.1 (see Appendix 2). No additional studies were identified in addition to those described in section 4.2, 4.7 and 4.11

4.12.4 Brief overview of the safety of the technology in relation to the decision problem

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

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 approximately twice that of SOC (206 days in pembrolizumab and 121 days in SOC). Fewer subjects discontinued pembrolizumab due to a drug-related AE compared to subjects on SOC (7.1% vs. 10.7, respectively), and drug-related Grade 3 to 5 AEs occurred less frequently among pembrolizumab-treated subjects than SOC-treated subjects (26.6% vs. 53.3%, respectively).

Deaths ascribed to drug-related AEs were also infrequent, occurring in 0.6% of pembrolizumab-treated subjects compared to 2.0% of SOC-treated subjects. Among subjects treated with pembrolizumab as initial therapy, the most common AEs were dyspnea (22.1%), diarrhoea (20.8%), constipation (20.8%), fatigue (20.8%), and decreased appetite (20.1%). These AEs were generally mild and tolerable, and infrequently led to treatment discontinuations.

The main AEOSIs were the potential immune-mediated AEs consistent with the currently approved product licence. In the ASaT population, 45 (29.2%) subjects treated with pembrolizumab as initial treatment and 7 (4.7%) 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 45 (29.2%) pembrolizumab-treated subjects who experienced an AEOSI, less than half (15 [9.7%]) had an AEOSI that was Grade 3 to 5 in severity. Furthermore, only 6 (3.9%) pembrolizumab-treated subjects discontinued therapy due to an AEOSI.

The most common AEOSI in the pembrolizumab arm, included hypothyroidism (9.1%) and hyperthyroidism (7.8%). All cases were Grade 1 to 2. Hypothyroidism responded to thyroid replacement. The majority of the hyperthyroidism cases were Grade 1, did not require treatment interruption or steroid therapy, and responded to anti-thyroid therapy. Seven

subjects (4.5%) had both hypothyroidism and hyperthyroidism; in all cases hyperthyroidism preceded the hypothyroidism. Nine (5.8%) subjects treated with pembrolizumab experienced pneumonitis in KEYNOTE-024. A majority of cases were Grade 1 to 2 in nature, with less than half (4 [2.6%]) of the pneumonitis cases Grade 3 to 4 in severity. Adverse events of special interest that were Grade 2 and higher in severity were managed with treatment interruption and corticosteroids. There were no fatal cases of pneumonitis or any other AEOSIs observed in KEYNOTE-024.

Overall the safety profile of pembrolizumab remains consistent with previously reported findings when used as a treatment option for patients with advanced NSCLC[6, 7] and other tumour types.[11-15] This demonstrates that pembrolizumab is well tolerated and the safety profile is acceptable for an advanced NSCLC population; and favourable when compared to SOC regimens.

4.13 Interpretation of clinical effectiveness and safety evidence

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

The efficacy results from IA2 of KEYNOTE-024[5, 21] are robust and demonstrate substantial, clinically meaningful benefit of pembrolizumab compared to SOC for all efficacy endpoints including PFS, OS, and ORR in previously untreated patients with NSCLC, without EGFR sensitizing mutations or ALK translocations, and whose tumours strongly express PD-L1 (TPS ≥50%). On the basis of data from the second interim analysis (IA2) of KEYNOTE-024, the data and safety monitoring committee (DSMC) recommended that the trial be stopped and that patients remaining in the chemotherapy group be offered pembrolizumab.

A summary of the main clinical effectiveness findings is provided below:

- **Pembrolizumab 200 mg Q3W significantly prolongs PFS and OS, and results in higher ORR and longer duration of response compared to chemotherapy SOC**

The results from IA2 of KEYNOTE-024[5, 21] demonstrate that first-line treatment with pembrolizumab significantly prolonged PFS (HR 0.5, p< 0.001) and OS (HR 0.6, p = 0.005) compared with SOC (which included maintenance pemetrexed for patients with non-squamous tumours) in patients with advanced NSCLC (TPS≥ 50%). The PFS curves began to separate around month 4 with continuous separation over the course of follow-up, and the

improvement in PFS was observed across all subgroups analysed. The significant OS improvement for pembrolizumab as compared with SOC is noteworthy given a high crossover rate (43.7%) from SOC to pembrolizumab as allowed by the protocol and the low number of OS events (35.4%) observed at the time of the database cut-off. Survival improvement was observed across all key subgroups. The few HRs close to one correspond to subgroups with small numbers of events and, thus, less precise estimates. Pembrolizumab also resulted in a higher confirmed ORR compared to SOC (44.8% vs. 27.8% respectively). The median response duration was 6.3 months for the SOC arm and not reached for the pembrolizumab arm.

The results from KEYNOTE-024 are supported by the results from the NMA conducted in the mixed-histology population to compare the relative treatment effects of pembrolizumab to each specific chemotherapy regimen of interest in the UK setting (platinum + pemetrexed [non-squamous/adenocarcinoma histology subgroup only]; platinum + gemcitabine; platinum + paclitaxel; platinum + docetaxel; platinum + vinorelbine). The NMA demonstrates that pembrolizumab was statistically superior to all of the included platinum-based regimens in terms of both PFS and OS.

The available data underscore the substantial treatment effect of pembrolizumab administered as a first-line therapy in patients with previously untreated, advanced NSCLC expressing PD-L1 at a TPS>50%.

- **Pembrolizumab 200 mg Q3W improves HRQoL compared to chemotherapy SOC**

The improved benefit as assessed by PFS, OS, ORR, and response duration for pembrolizumab as compared to SOC in the KEYNOTE-024 population is corroborated by improvements in HRQoL. Results from key PRO analyses indicated that when assessing change from baseline to Week 15, there was an improvement of almost 8 points in the EORTC QLQ-C30 global health status/QoL score for the pembrolizumab arm compared to SOC (difference in LS means = 7.82; 95% CI: 2.85, 12.79; nominal p=0.002). While mean differences of 10 points or more have been widely viewed as being clinically meaningful, [86, 87] minimally important differences as low as 4 points have been reported for EORTC QLQ-C30 in NSCLC trials].[88] Pembrolizumab also prolonged the time to true deterioration in the EORTC QLQ-LC13 composite endpoint of cough, dyspnea, and chest pain compared to SOC (HR 0.66; 95% CI: 0.44, 0.97; nominal p=0.029). These findings, along with results from supportive PRO analyses, suggest that health-related QoL and symptoms were

improved or maintained to a greater degree with pembrolizumab than with SOC chemotherapy in this NSCLC subject population

- **Pembrolizumab 200 mg Q3W has a favourable AE profile and is more tolerable in treatment naïve patients, compared with SOC**

Pembrolizumab was well-tolerated by patients with previously untreated metastatic NSCLC with PD-L1 TPS ≥ 50%. The majority of AEs among the pembrolizumab treated subjects were Grade 1 and 2 in severity; relatively few patients discontinued therapy due to AEs. Incidences of AEs were similar between the pembrolizumab and SOC arms despite a longer median duration of subject exposure to pembrolizumab as compared to SOC (214 days vs. 106 days, respectively). Among pembrolizumab-treated patients, the most common AEs were dyspnea (22.1%), diarrhoea (20.8%), constipation (20.8%), fatigue (20.8%), and decreased appetite (20.1%). These AEs were generally mild and tolerable. In the SOC arm, anemia (52.7%), nausea (46.7%), fatigue (35.3%), decreased appetite (32.7%), neutropaenia (24%), vomiting (24%), constipation (22.7%), and diarrhoea (22%) were the most common AEs.

Fewer patients discontinued pembrolizumab due to a drug-related AE as compared to patients on SOC (7.1% vs. 10.7%, respectively), and drug-related Grade 3 to 5 AEs occurred less frequently among pembrolizumab-treated patients than those treated with SOC (26.6% vs. 53.3%, respectively). Deaths due to drug-related AEs were also infrequent, occurring in 0.6% of pembrolizumab-treated patients compared to 2% of SOC treated subj patients ects. Of the 45 (29.2%) of pembrolizumab-treated patients who experienced an AEOSI, less than half (15 [9.7%]) were Grade 3 to 5 in severity. Furthermore, only 6 (3.9%) pembrolizumab-treated patients discontinued therapy due to an AEOSI. There were no fatal cases of any AEOSI observed in KEYNOTE-024.

- **The 200 mg fixed dose offers a simplified dosing regimen as a first-line treatment option for patients with advanced NSCLC**

KEYNOTE-024 is the first trial to incorporate a fixed dose of pembrolizumab of 200 mg. Based on pharmacokinetic modelling, the 200-mg fixed dose of pembrolizumab is expected to provide exposure similar to the weight-based dosing regimens used in previous studies of pembrolizumab.[144] The results from KEYNOTE-024 demonstrate the efficacy of the 200 mg Q3W fixed dose treatment regimen for previously untreated patients with advanced NSCLC, and are consistent with results observed in patients enrolled in the KEYNOTE-001 trial who

had previously untreated NSCLC with tumours that stongly expressed PD-L1 (TPS ≥ 50%) and who were treated with pembrolizumab at a dose of 10 mg/kg.[90] These results support that in the previously untreated patient population, 200 mg is an appropriate dose of pembrolizumab. The fixed dose provides a simplified dosing regimen which will be more convenient for clinicians and reduces the potential for dosing errors. A fixed dosing scheme also reduces complexity in the logistical chain at treatment facilities and reduces wastage.

4.13.2 Discussion of the strengths and limitations of the clinical evidence base for the technology

Internal Validity

KEYNOTE-024 is a multicentre, randomised, open-label phase III trial of pembrolizumab 200 mg Q3W versus SOC in previously untreated adults with advanced NSCLC, without EGFR sensitizing mutations or ALK translocations, and whose tumours strongly express PD-L1 (TPS ≥50%). Randomisation was stratified by ECOG performance status (0 vs. 1), geographic region of the enrolling site (East Asia vs. non-East Asia) and histology (squamous vs non-squamous).

The primary efficacy endpoint was PFS, with OS as a secondary endpoint. Both are clinically relevant endpoints that were directly referenced in the final scope for this appraisal and the decision problem. The endpoints selected are consistent with those used in studies of other therapeutic agents in the population of advanced NSCLC. The definition of progression when evaluating the primary endpoint of PFS in KEYNOTE-024 followed an established response evaluation criteria (RECIST 1.1) in the primary efficacy analysis, in line with European guidance.[145]

HRQoL was an exploratory endpoint of the KEYNOTE-024 study, with changes from baseline in patients treated with pembrolizumab compared to patients treated with SOC recorded using both the preferred measure of EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC-QLQC30 (see section 5.4).

Although KEYNOTE-024 was conducted as an open-label study, the independent radiologists who performed the central imaging review were blinded to treatment assignment, in order to minimise bias. The treatment arms were well balanced by all baseline characteristics, with the exception that there were more patients who never smoked and fewer patients with brain metastases randomised to the SOC arm than the

pembrolizumab arm, which may suggest that patients in the SOC arm could have been favoured in terms of expected prognosis as compared to the patients administered pembrolizumab.

Part F1 of KEYNOTE-001 was a phase II-like cohort in previously untreated patients with advanced NSCLC. Although KEYNOTE-001 does not provide comparative efficacy data versus the comparator of interest, it provides useful longer term data supporting the clinical benefit of pembrolizumab in patients with advanced NSCLC who express PD-L1, and helps provide a comprehensive assessment of the clinical efficacy of pembrolizumab. In addition, KEYNOTE-001 study provides data on the validation of the Clinical Trial Assay (CTA) used to test PD-L1 expression; therefore, the assay used in KEYNOTE-024 was rigorously evaluated and validated before the study began.

External validity

KEYNOTE-024 was a global study conducted in 149 academic medical centres in 16 countries. 49 out of the 63 sites were in Europe. Of the 305 patients with advanced NSCLC participating in this study, 158 (52%) were enrolled at sites in Europe (including 21 patients from the UK).

Baseline characteristics of patients enrolled in KEYNOTE-024 were as expected for patients with advanced NSCLC. The majority of patients were male, white, with mean age around 64 years old. Most patients were current or former smokers and had tumour of non-squamous histology (Table 15). Nevertheless subgroup analyses confirm the benefit of pembrolizumab versus SOC in patients of all histologies. The pembrolizumab benefit observed in patients with squamous histology is notable given the limited treatment options available for these patients.

The observed safety profile of pembrolizumab in KEYNOTE-024 was consistent with that seen previously with pembrolizumab for the treatment of advanced NSCLC [6, 7] and other types of tumours.[11-15]

All the patients enrolled in KEYNOTE-024 had a PD-L1 tumour proportion score of 50% or greater. The 50% cutoff point was determined based on KEYNOTE-001 trial data which showed a significantly increased ORR in this population[6] The prevalence of a tumour proportion score of 50% or greater in the KEYNOTE-024 screened population (30.2%) was consistent with the prevalence observed in the KEYNOTE-001 trial among previously untreated patients (24.9%) and in the KEYNOTE-010 trial among previously treated patients (28%).[6, 7] Further clinical trials which are currently ongoing, including the Phase III KEYNOTE-042 study, will assess the benefit of pembrolizumab over chemotherapy in a wider patient population, encompassing previously untreated patients who have PD-L1 postive tumours (i.e. TPS ≥ 1%).

Life expectancy of people with advanced NSCLC in England

Full details concerning the life expectancy of UK patients with advanced NSCLC have been provided in section 3.4 of the submission and are summarised in Table 50 below. Information concerning the estimated number of people with the particular therapeutic indication for which the technology is being appraised is also presented in section 3.4.

Please note that according to the new CDF TA process the criterion of small patient population does no longer apply [146].

Table 50: 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 was not reached. However, the average life expectancy for a patient with NSCLC (regardless of histology) receiving chemotherapy SOC is estimated to be between 9.9 and 13.9 months, based on the following: • 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.[147] • Squamous patients have lower life expectancy as evident from the SQUIRE trial reporting a median OS of 9.9 months for the gemcitabine + cisplatin arm.[148]
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: • The average number of months of life gained with pembrolizumab as estimated by the economic model is 29, compared to 14.6 months with SoC • In KEYNOTE-001 trial, the median OS for the treatment naïve NSCLC pembrolizumab arm was 22.1 months (95% CI, 16.8-27.2)

4.14 Ongoing studies

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

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

5. Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Strategies used to retrieve cost-effectiveness studies relevant to decision-making in England

Relevant cost-effectiveness studies from the published literature were identified through a systematic literature search carried out on 26th May 2016, for untreated patients with advanced NSCLC. Given the evolving treatment landscape over the last decade, electronic database searches and additional hand-searches were restricted to the last 10 years, as older cost data may not be considered representative of the current economic environment.

The first stage in the review was to identify all relevant economic evidence for the comparator treatments by implementing comprehensive searches. The following research questions were posed in accordance with the decision problem:

- What is the cost-effectiveness of comparator therapies to pembrolizumab in untreated patients with advanced NSCLC?
- What is the health related quality of life (in terms of utilities) associated with first line treatment of patients with advanced NSCLC?
- What are the resource requirements and costs associated with the first line treatment of advanced NSCLC in the UK?

A comprehensive literature search relative to these three research questions was carried out using several databases:

- MEDLINE and EMBASE (using EMBASE.com): 2005-2016
- MEDLINE In-Process (using PubMed.com): 2005-2016
- EconLit (using EBSCO.com): 2005-2016
- The Cochrane Library including:
    - NHS Economic Evaluation Database (NHS EED): No limit
    - Health Technology Assessment Database (HTAD): No limit

Manual searches were also performed on the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) conference proceedings and International Society for Pharmacoeconomics and Outcomes Research (ISPOR); Annual European and International Congress, with additional papers identified from the reference list of included papers. The manual searches were constrained to the most recent 2 years.

In addition to the formal literature search and manual searches, the National Institute for Health and Care Excellence (NICE) website was searched to identify relevant information from previous submissions not otherwise captured. A bibliographic search of the relevant, published systematic reviews, economic models and HTAs was also conducted to ensure that all studies of relevance to the review had been captured in the initial searches.

All retrieved studies were reviewed by two independent researchers and assessed against the eligibility criteria set out in the final protocol and presented in **Table 51** below.

Table 51: Inclusion and exclusion criteria for cost-effectiveness studies

Criteria	Inclusion	Exclusion	Rationale
Population	Untreated adults with advanced NSCLC	• Healthy volunteers • Previously treated NSCLC patients • Patients under the age of 18	The relevant patient population
Intervention/ Comparator	Studies comparing pembrolizumab vs. any other pharmacological treatment	Non-drug treatments (e.g. surgery, radiotherapy)	To allow all papers with relevant pharmacological interventions to be captured
Outcomes	Studies including a comparison of benefits and costs between the intervention and comparator arms. Results should be expressed in incremental costs and QALYs, and any other measure of effectiveness reported together with costs	Cost-only outcomes	To identify relevant cost-effectiveness studies
Study type	Full economic evaluation comparing at least two interventions in terms of: • cost-consequence • cost-effectiveness • cost-utility • cost-benefit evaluations	Burden of illness studies, Cost-minimisation and Budget impact analysis	To identify relevant cost-effectiveness studies
Publication type	Economic evaluations	Letters, editorials and review studies	To identify primary study articles
Time limit	Studies published in last 10 years will be included	Studies published before 2005	To ensure recent economic models are included and limit the number of studies identified to those most relevant to the decision problem
Language	Studies for which a full text version is available in	Not available in English	To ensure the studies can be correctly understood

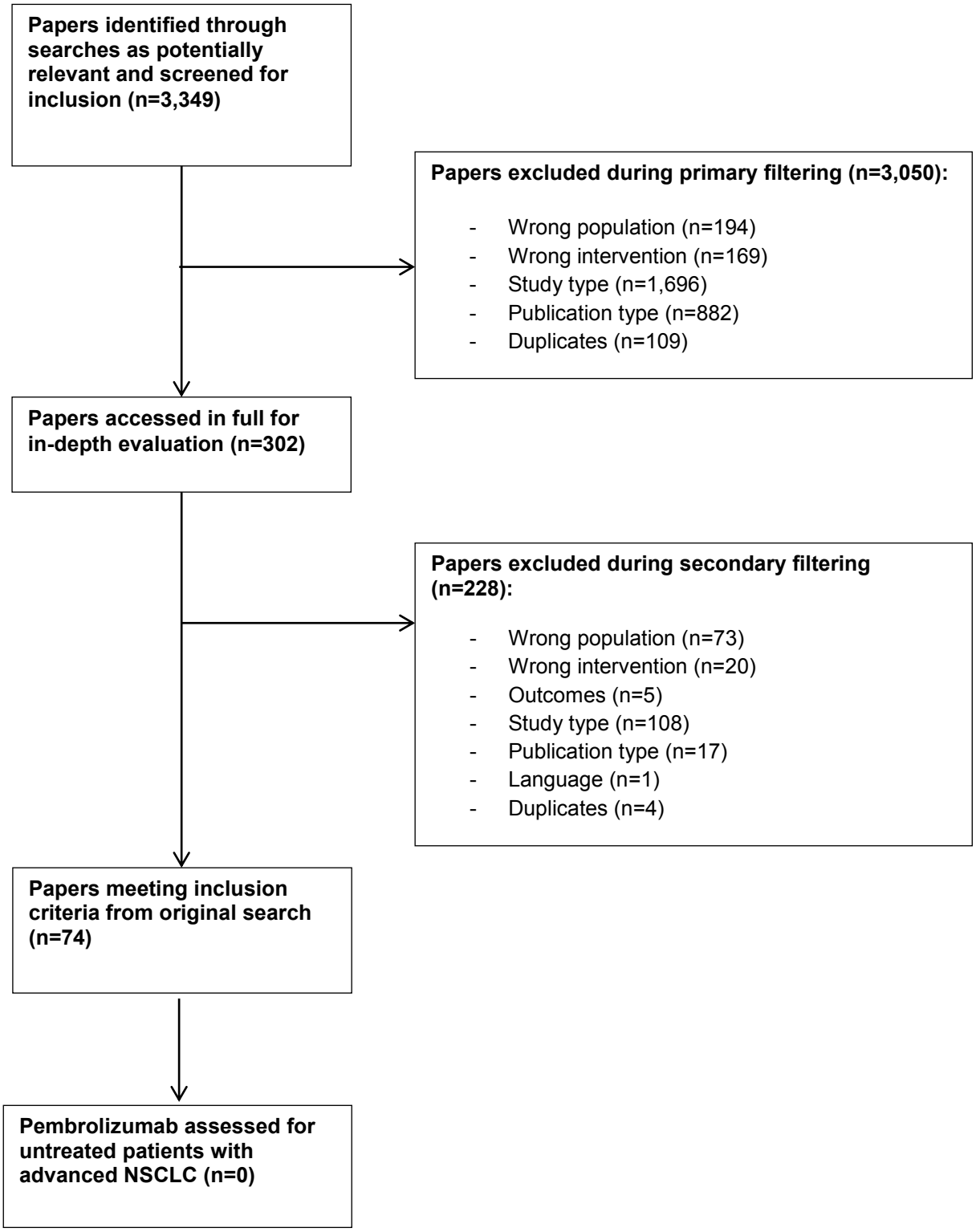
Criteria	Inclusion	Exclusion	Rationale
	English		and interpreted
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed The study's data and results must be extractable	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated Studies that fail to present extractable results	To ensure data can be extractable To ensure methods can be replicated To ensure results can be validated
Key: NSCLC, Non-small cell lung cancer; QALYs, Quality adjusted life years.			

The search strategy is provided in Appendix 23 and was conducted following the methodology for systematic review developed and published in 2009 by the Centre for Reviews and Dissemination (University of York). [149]

5.1.2 Brief description of identified cost-effectiveness studies

Of a total of 3,349 papers identified in the cost-effectiveness search, 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. The PRISMA flow diagram is presented in Figure 25.

Figure 25: PRISMA diagram for cost-effectiveness studies



Key: n, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

5.1.3 Complete quality assessment for each relevant cost-effectiveness study identified

This is not applicable as no cost-effectiveness study meeting all the inclusion criteria was identified, indicating a de novo cost-effectiveness model is required to assess the cost-effectiveness of pembrolizumab compared with relevant comparators.

5.2 De novo analysis

5.2.1 Patient population

The patient population included in the economic evaluation consisted of patients with advanced NSCLC 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 anticipated licence indication and with the final NICE scope.[150]

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.[5]

The baseline characteristics of the patients included in the model are presented in Table 52.

Table 52. 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.

5.2.2 Model structure

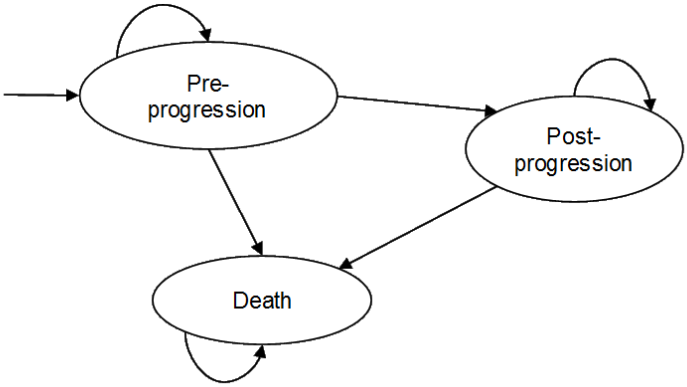
Consistent with the majority of economic models previously developed for recent NICE oncology submissions in advanced NSCLC, [151] [61, 152]a de-novo economic analysis was built as a 'partitioned-survival' area-under-the-curve model. The model consisted of three health states: pre-progression, post-progression and death (see Figure 26). 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. [5, 21] A cycle length of one week was considered sufficient to reflect the patterns of treatment administration and the transitions to disease progression and death. In line with previous submissions, a half-cycle correction was implemented to mitigate bias.[60, 61, 151, 153-156]

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.[154, 157]

Disease progression was defined per RECIST v1.1 as assessed by BICR (which was the primary endpoint in KEYNOTE-024). [5, 21]

Figure 26. Model structure



The partitioned-survival model was developed by fitting survival curves to trial data for progression free survival (PFS) and overall survival (OS). In partitioned survival models, health transitions are derived directly from the proportion of patients that are reflected by the areas under the PFS and OS curves, rather than using transition probabilities (as would be the case with standard Markov models),. The area underneath the OS curve represented the proportion of patients that were still alive (both in pre-progression and post-progression) at different points in time, while the proportion of patients in the pre-progression state were identified by the patients located underneath the PFS curve. The area between the PFS and the OS represented the proportion of post-progression patients, i.e. those who were in the 'post progression' health state.

The definition of the health states used in the model was based on the definitions conventionally used in oncology clinical trials and, specifically, the ones used in the pembrolizumab KEYNOTE-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.[158, 159]
- 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 additional analyses, pembrolizumab was indirectly compared to platinum-based chemotherapies either containing gemcitabine or paclitaxel, docetaxel, vinorelbine or pemetrexed. Furthermore, to reflect the planned subgroup analyses in KEYNOTE-024, the following comparisons were conducted:

- Pembrolizumab was compared against SOC in the subgroup of patients with NSCLC of squamous and non-squamous histology, independently.
- Pembrolizumab was compared against pemetrexed-containing chemotherapies in the subgroup of patients with non-squamous NSCLC.
- Pembrolizumab was compared against non-pemetrexed-containing chemotherapies among patients of any histology.

Please see Table 55 in section 5.2.4 below for clarification on the type of comparisons assessed in the cost-effectiveness model.

In the model, patients in the pembrolizumab arm were assumed to be eligible to receive treatment until progression, in line with the anticipated licence for pembrolizumab for advanced NSCLC patients. This is consistent with the protocol of the KEYNOTE-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. [5, 21] In the base case model, a maximum treatment duration of 35 cycles was applied, in line with the KEYNOTE-024 protocol (see section 5.2.5 below).[159]

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 5.5.5). 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.

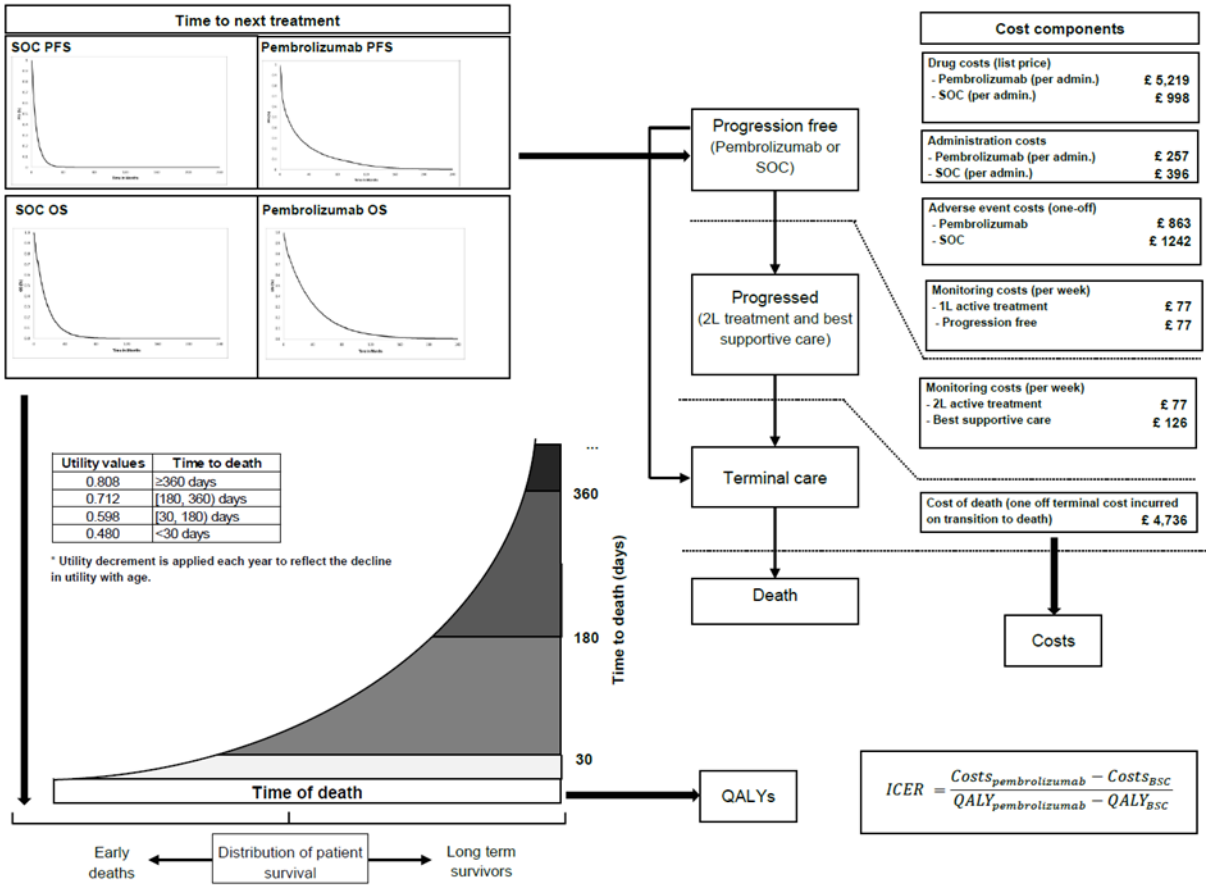
Since patients in KEYNOTE-024 could receive subsequent oncologic therapies after treatment discontinuation, the costs of these subsequent treatments are included in the

economic evaluation according to the proportion of patients receiving them after treatment discontinuation:

- Based on UK clinical practice and NICE guidance, it was assumed that all patients in the pembrolizumab arm received docetaxel as second line treatment.
- Crossover from the SOC arm to the pembrolizumab arm was allowed during the trial.
    - In KEYNOTE-024, 43.7% of the patients treated with SOC crossed over to pembrolizumab after treatment discontinuation. To better reflect the expected OS in the absence of switching, the adjusted OS for SOC, using a simplified two-stage adjustment, was applied in the model (see section 4.7). Whenever crossover adjustments were implemented, the costs of pembrolizumab after SOC were not accounted for. For consistency between the adjustment for crossover and the estimation of the subsequent treatment costs, all patients in the SOC arm were assumed to receive docetaxel as second line treatment (same assumption as the pembrolizumab arm) when crossover adjustments were considered.
    - In additional analyses, when crossover adjustments were not implemented, patients were assumed to receive pembrolizumab based on the proportion of patients crossing over, with the rest of the patients assumed to receive docetaxel.

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 27.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 implemented 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. (140)

Figure 27: Model diagram describing the estimation of QALYs and costs



5.2.3 Key features of the de novo analysis

Table 53: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	20 years	Lifetime horizon for the defined target population (0.2% of patients alive after this period in the base case) In line with most recent advanced or metastatic NSCLC NICE submissions/id}[151, 153, 155, 156, 160]
Cycle length	1 week	Sufficient to model the patterns of treatment administration, transitions to disease progression and OS. In line with a recent NICE submission in advanced NSCLC. [161]
Half-cycle correction	Yes	In line with previous submissions and to mitigate bias[151, 153, 155, 156, 160]

Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case[162] 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[163]
Discount of 3.5% for utilities and costs	Yes	NICE reference case[162]
Perspective (NHS/PSS)	Yes	NICE reference case[162] 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. [65, 151, 152, 164]
PSS, personal social services; QALYs, quality-adjusted life years		

5.2.4 Intervention technology and comparators

The intervention (i.e. pembrolizumab) was implemented in the model as per the anticipated licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200 mg over 30 minutes every 3 weeks [Q3W]). The anticipated licence states that pembrolizumab is to be administered until disease progression or unacceptable toxicities, although there is no evidence regarding the optimal duration of treatment with pembrolizumab, particularly since the KEYNOTE-024 protocol established that treatment should continue until documented disease progression, toxicities leading to discontinuation, physician's decision or a maximum of 35 cycles of pembrolizumab.

We anticipate pembrolizumab to be considered 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 (see section 4.3.1), 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.

- 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 (see section 4.10), 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 54. 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%
Vinorelbine/carboplatin	0%	17%
Vinorelbine/cisplatin	0%	10%
Pemetrexed/carboplatin	44%	17%
Pemetrexed/cisplatin	24%	26%
% Total	100%	100%

Source: Ipsos 2016. Data on file. [165]

The dosing and administration frequencies for these comparators were implemented 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 55.

Table 55. 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	✓	✓	✓	✓
NMA comparisons – All histologies	▪ Gemcitabine or paclitaxel + platinum ▪ Docetaxel + platinum ▪ Vinorelbine + platinum ▪ Pemetrexed + platinum	NMA	✓	×	×	×
Subgroup – NSQ	▪ SOC (reflected by pemetrexed and non-pemetrexed chemotherapy combinations)	KEYNOTE-024	✓	✓	✓	✓
Subgroup – SQ	▪ SOC (reflected by combination of non-pemetrexed chemos)	KEYNOTE-024	✓	×	✓	✓
Subgroup – Non-pemetrexed-based (both SQ and NSQ)*	▪ SOC (reflected by non-pemetrexed only)	KEYNOTE-024	✓	×	×	✓
Subgroup – Pemetrexed-based (only NSQ)	▪ SOC (reflected by pemetrexed only)	KEYNOTE-024	✓	✓	✓	✓

ITT = intention to treat; NMA = network meta-analysis; NSQ = non-squamous; SOC = standard of care; SQ = squamous;

5.2.5 Discontinuation rules

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.[159] In the cost-effectiveness model, the survival estimates of OS and PFS are based on KEYNOTE-024 data, thus reflecting the implementation 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.[166]

Patients treated with pemetrexed maintenance are assumed to be treated until disease progression or unacceptable toxicity.[153]

5.3 Clinical parameters and variables

5.3.1 Overall method of modelling survival

The primary data source for the economic model was the data derived from the KEYNOTE-024 clinical trial. The follow-up period in KEYNOTE-024 was shorter than the time horizon of the economic model. Therefore, extrapolation of the OS and PFS from KEYNOTE-024 was required for the area-under-the-curve (AUC) partitioned survival approach.

The guidance from the NICE DSU was followed to identify base case parametric survival models for OS and PFS.[85] 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:
    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. A comprehensive range of pooled parametric survival models were explored. Here, data from both treatment arms were used within the same model. All standard

parametric models (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma) were considered and compared. 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.

5.3.2 Modelling overall survival

To adjust OS for switching in the SOC arm, a simplified two-stage approach[84, 85] was identified as the most appropriate method, as mentioned in section 4.7. The OS KM curve for SOC adjusted for treatment switching using the two-stage model compared to the unadjusted OS is shown in Figure 11 above. Based on the feedback received during the validation of the model, the two-stage OS-adjusted curve looked reasonable, even if the experts expected a more impactful adjustment than the one observed, in line with the high proportion of patients crossing over.

Standard parametric curves were initially fitted to the full KM OS data. When the PH assumption was tested, this did not hold, based on the cumulative hazard plot (see **Figure 28**), the log-cumulative hazard plot (see **Figure 29**) and the Schoenfeld residuals plot (see **Figure 30**). As shown in Figure 29, the two lines crossed towards the beginning of the log-cumulative hazard plot. Additionally, for the Schoenfeld residuals plot (see Figure 30), there is a clear deviation from the y=0 line. Therefore, separate models were subsequently fitted based on the individual patient data from KEYNOTE-024.[85]

Figure 28. Cumulative hazard plot of OS for pembrolizumab and SOC based on KEYNOTE-024

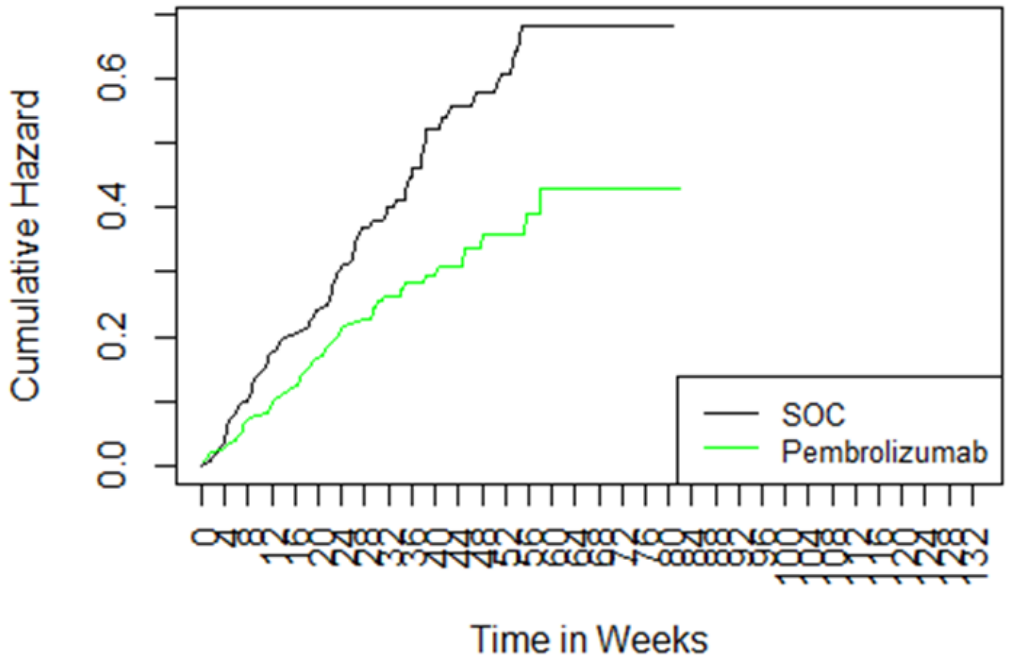


Figure 29. Log-cumulative hazard plot of OS for pembrolizumab and SOC based on KEYNOTE-024

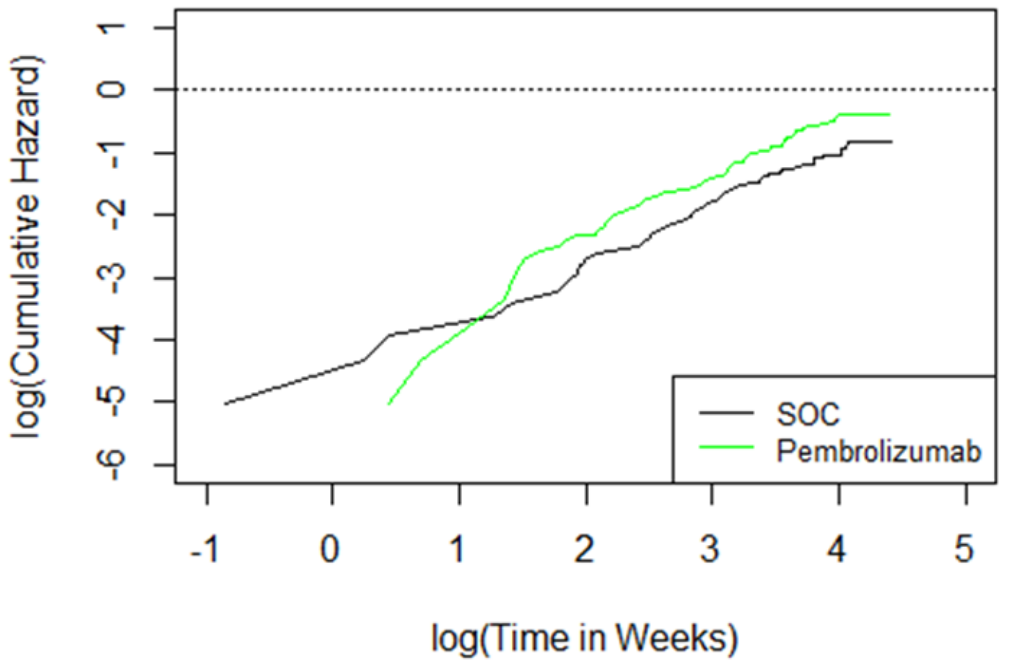
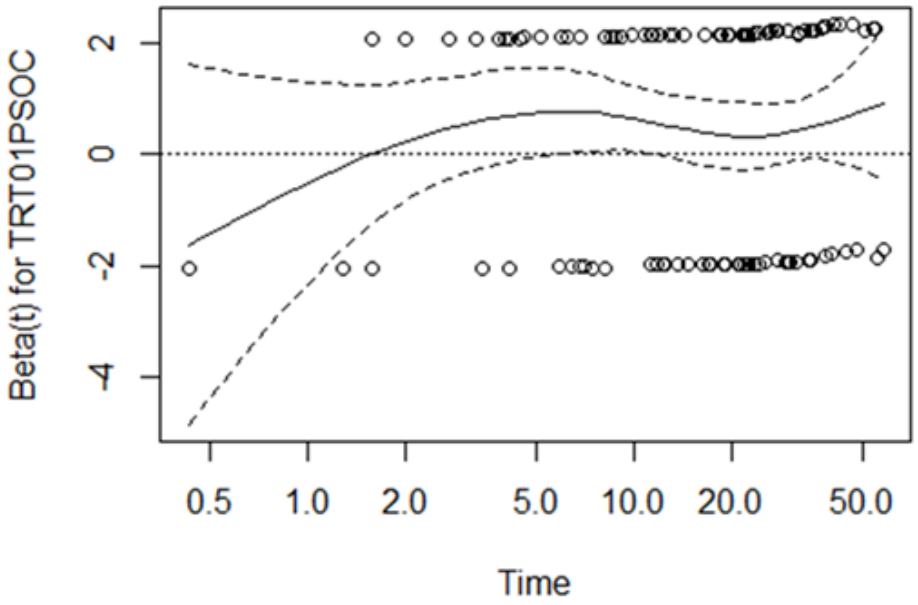


Figure 30. Schoenfeld residuals plot of OS for pembrolizumab and SOC based on KEYNOTE-024

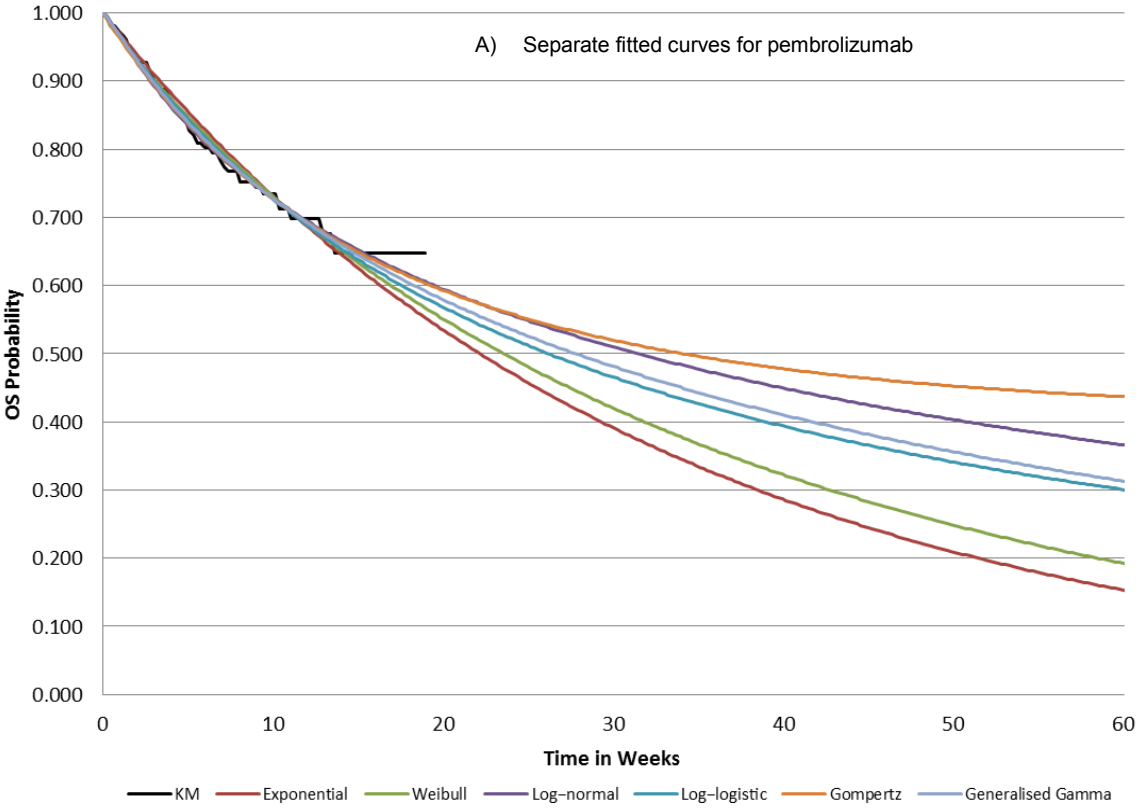


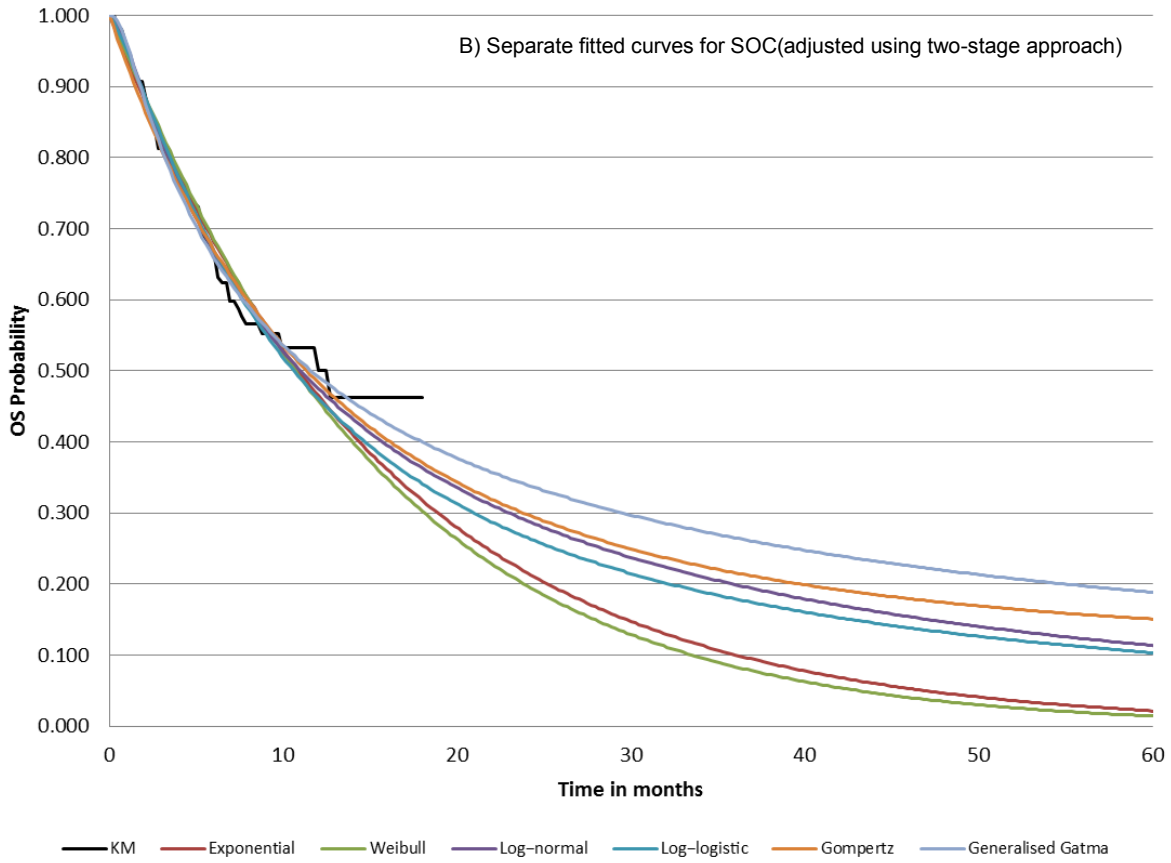
The fitted separate standard parametric curves are presented in **Figure 31**. For the pembrolizumab arm, the exponential curve is the closest statistical fit to the data, based on the AIC/BIC goodness of fit statistics. For the SOC parametric adjustment, the curves presenting the closest statistical fit to the data (i.e. log-normal distribution followed by generalized gamma) resulted in an overestimation of the OS at 5 years (i.e. higher than 10% and up to almost 20%, which is well above the 5% OS rate reported by the NLCA for patients with stage IV and PS 0-1).[51] These were therefore discarded as clinically implausible.

Table 56. Fitted exponential curves for the fully fitted parametric approach for OS

Fitted Function	Pembrolizumab		SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC
Exponential	523.9	527	670	673
Weibull	525.6	531.7	671.8	677.8
LogNormal	525.1	531.1	665.7	671.7
LogLogistic	525	531	668.5	674.5
Gompertz	524.8	530.9	671.2	677.3
GenGamma	526.8	535.9	666.7	675.7

Figure 31. Fitted separate standard parametric curves for the OS of pembrolizumab (A) and SOC (B)





The cumulative hazard plot (see Figure 28) demonstrates that the change in hazard is not constant over time (i.e. the OS curves start separating from week 4, while there is clear change in the slope after around 22 weeks). This suggests that a piecewise model is more appropriate than the use of single parametric curves. Given the precedence of the use of 2-phase piecewise models (KM plus exponential) in recent NICE appraisals in advanced NSCLC,[151, 160, 167, 168] we decided to implement a 2-phase piecewise model as the most appropriate method to extrapolate OS.

For the 2-phase piecewise approach, the second phase exponential models were fitted using a 22-week cut-off point, based on the cumulative hazard plot (see Figure 28) and the sufficient numbers of patient at-risk at this point. The fitted 2-phase piecewise models are presented in Figure 32. These provide a good balance of KM data to be used directly in the first phase and enough remaining KM data to be used to fit an exponential curve in the second phase. Additionally, it results in a plausible visual fit.

Figure 32. OS KM curves vs. fitted 2-phase piecewise models for the OS of pembrolizumab and SOC based on KEYNOTE-024

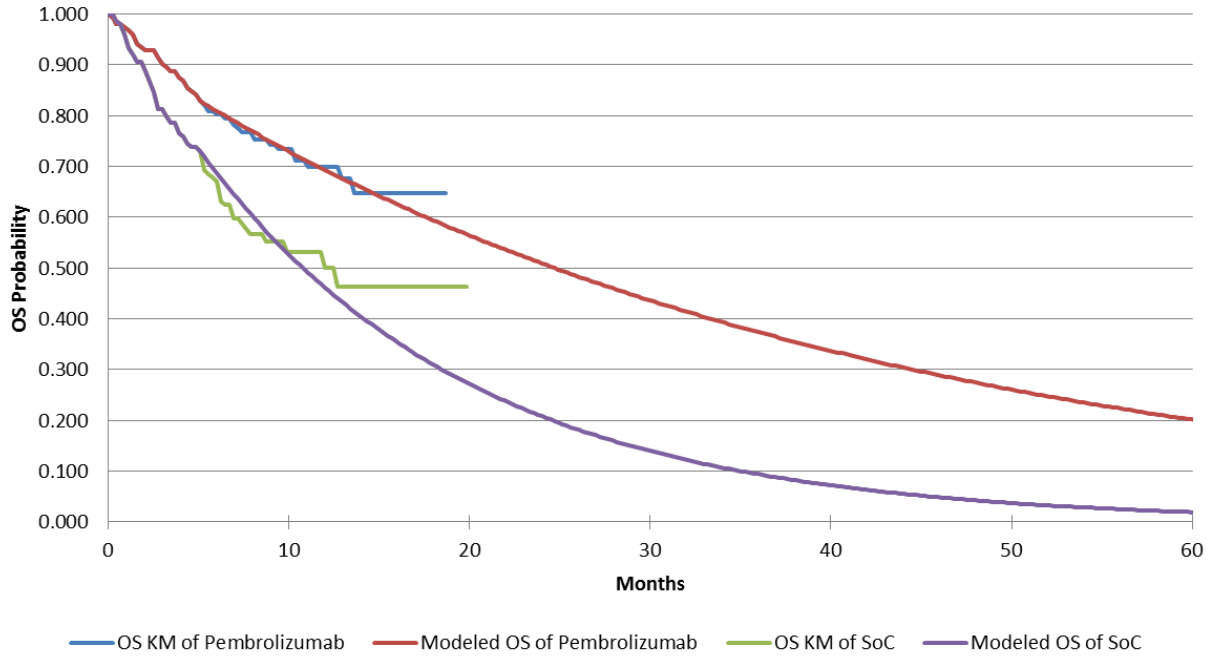


Table 57. Fitted exponential curves for the 2-phase piecewise approach for OS

	Exponential curve parameters	
Cut-off (weeks)	Pembrolizumab	SOC
22	5.126	4.4125

5.3.3 Modelling progression free survival

Based on the trial protocol of KEYNOTE-024, the first tumour assessment was performed at week 9 and this is demonstrated by the overlapping PFS for the first 9 weeks in Figure 33. This resulted in a protocol-driven drop of PFS between weeks 0 and 9, which did not allow the fitting of a full parametric curve. As a consequence, the KM data were used directly for the first 9 weeks of the model time horizon and parametric functions were fitted from then onwards. Since the proportional hazard assumption was not supported, separate models were used for pembrolizumab and SOC. To identify the most plausible survival curves among the standard parametric curves, the guidance from the NICE DSU[85] was followed.

The PH assumption was tested using the Schoenfeld residual test. Although based on the test result (p = 0.0974) the PH assumption could not be rejected at the 10% significance level, the visual inspection of the Schoenfeld residual plot and the log-cumulative hazard plot (see below Figure 35 and Figure 36) did not support this assumption. The log-cumulative hazard plots of pembrolizumab and SOC appeared to converge at the beginning and diverge towards the end, which suggests the implausibility of the PH assumption. The Schoenfeld residuals plot deviated from the y=0 horizontal line, which is an indication of a potential violation of the PH assumption. Therefore, separate models were used based upon the pembrolizumab and SOC data separately for the projection of the PFS using a 2-part piecewise extrapolation. Following DSU guidance[169], only similar types of parametric curves (with 'type' defined as the same parametric distribution) were considered for the pembrolizumab and SOC arms.

Figure 33. KM survival plot for PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and SOC based on KEYNOTE-024

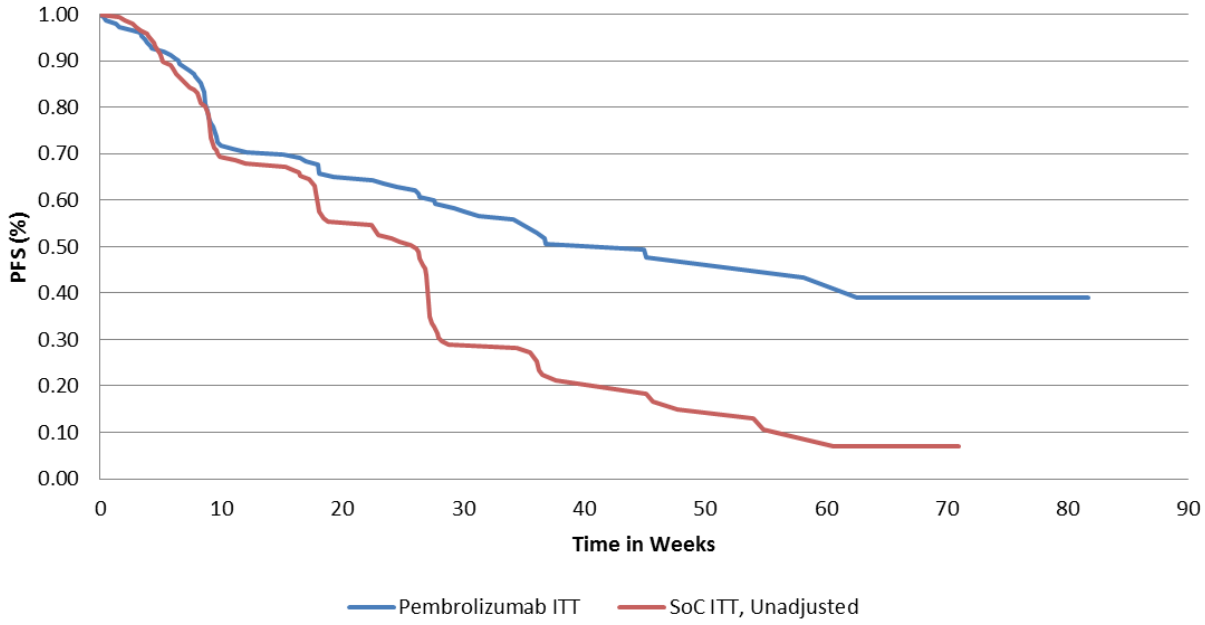


Figure 34. Cumulative hazard plot of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and SOC based on KEYNOTE-024

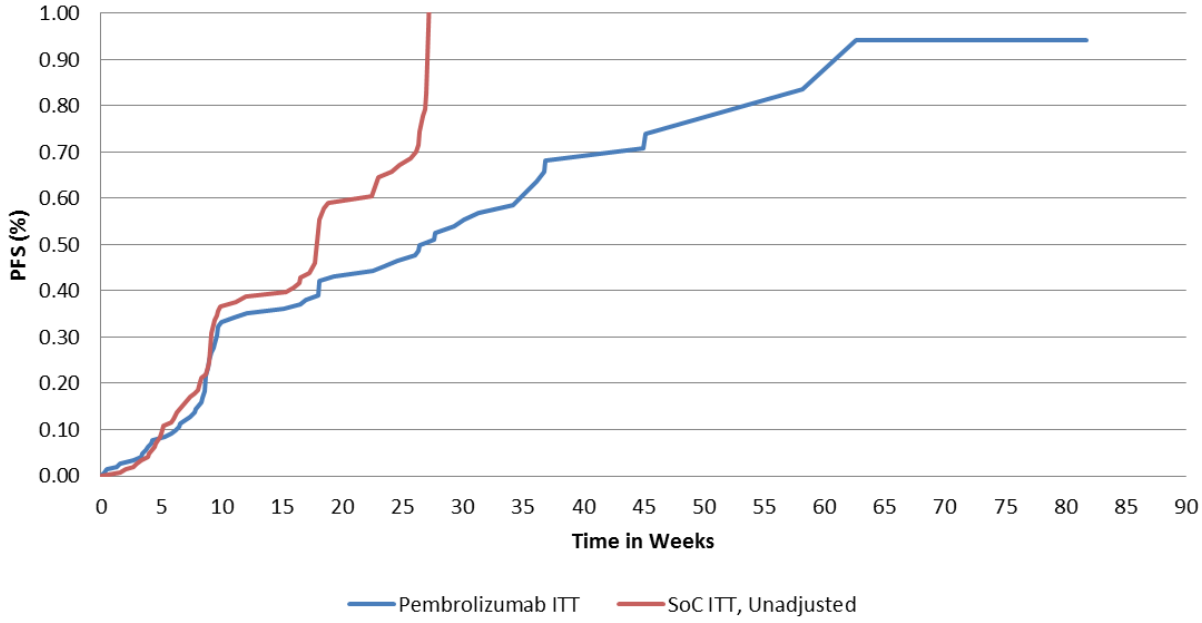


Figure 35. Log-cumulative hazard plot of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and SOC based on KEYNOTE-024

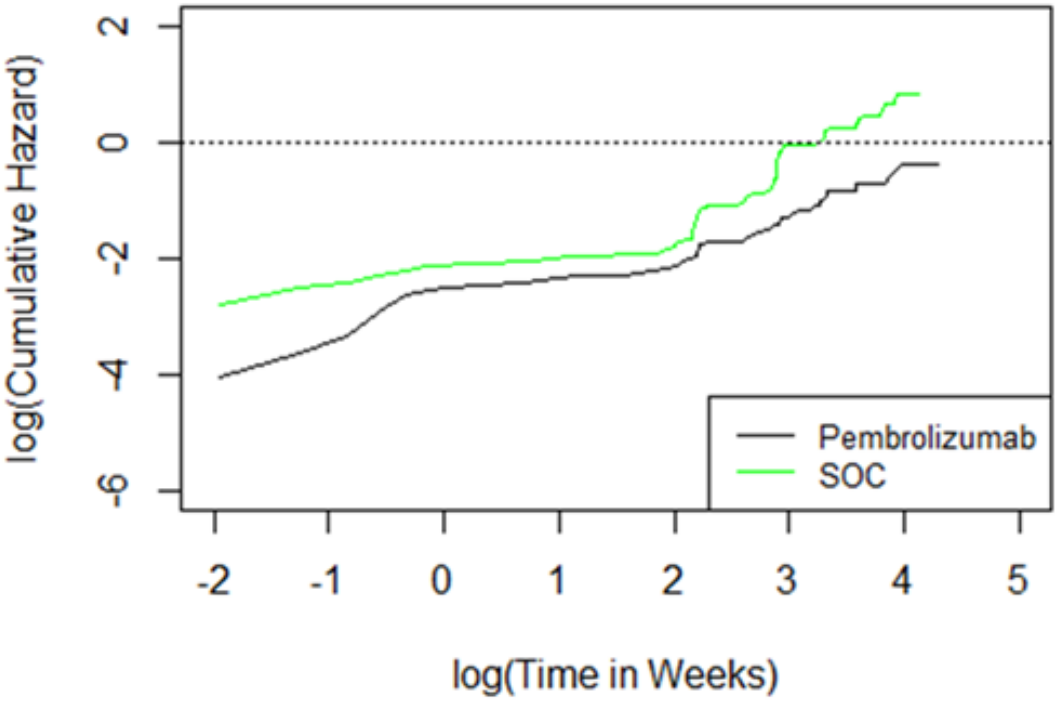


Figure 36. Schoenfeld residual plot of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and SOC based on KEYNOTE-024

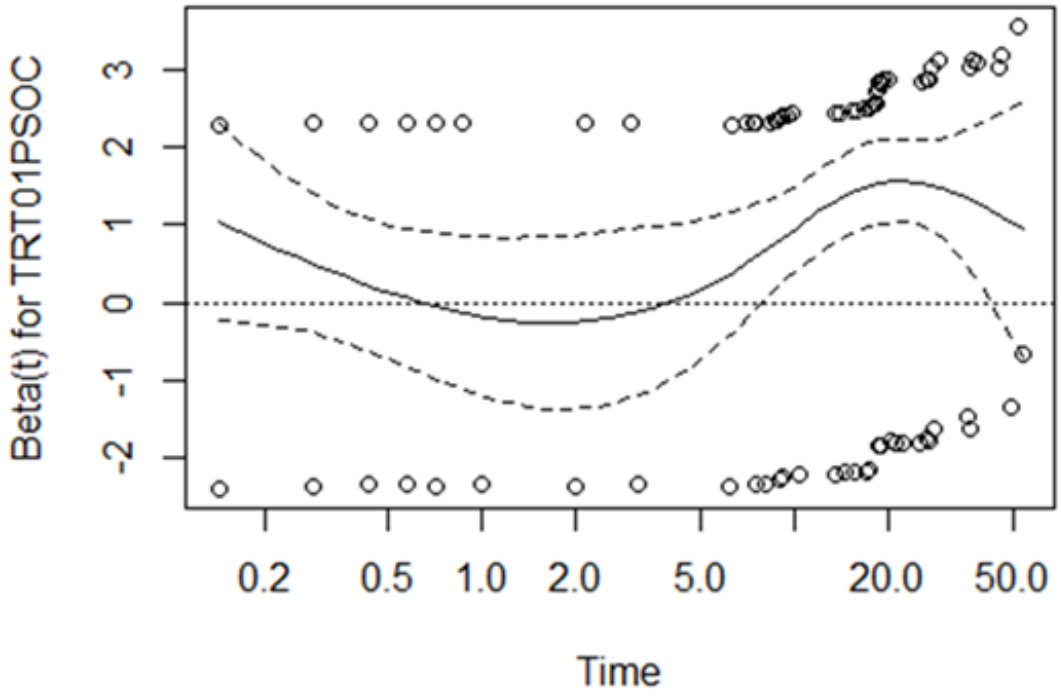


Table 58 reports the AIC/BIC statistics for the second part of the PFS two-part curve fit for pembrolizumab based on KEYNOTE-024 PFS data. A Weibull distribution was the best fit to the pembrolizumab PFS data based both on AIC/BIC criteria and visual fit (see Figure 37). For SOC, there is no clear best statistical fit, with the exponential distribution presenting the lowest BIC value while the generalized gamma the lowest AIC value. Based on visual inspection (see Figure 38), the Weibull distribution is close to both the exponential and the generalised gamma distributions, and it also has a good visual fit to the KM data. Consequently, it was selected for the extrapolation of PFS for SOC to maintain consistency with the best fit identified for pembrolizumab.

Table 58. Goodness-of-fit measures for PFS defined per RECIST v1.1 as assessed by BICR, with cut-off of 9 weeks, for pembrolizumab and SOC based on KEYNOTE-024

	Pembrolizumab		SOC	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	430.1	432.8	718	**720.8**
Weibull	**424.1**	**429.6**	719.4	724.9
Log-Normal	427.3	432.8	749.2	754.7
Log-Logistic	425.4	430.9	735.1	740.6
Gompertz	430.1	435.6	719	724.4
Generalised Gamma	425.3	433.5	**714.4**	722.6
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria.				

Figure 37. PFS KM curve vs. fitted 2-phase piecewise models for the PFS defined per RECIST v1.1 as assessed by BICR, with cut-off of 9 weeks, of pembrolizumab based on KEYNOTE-024

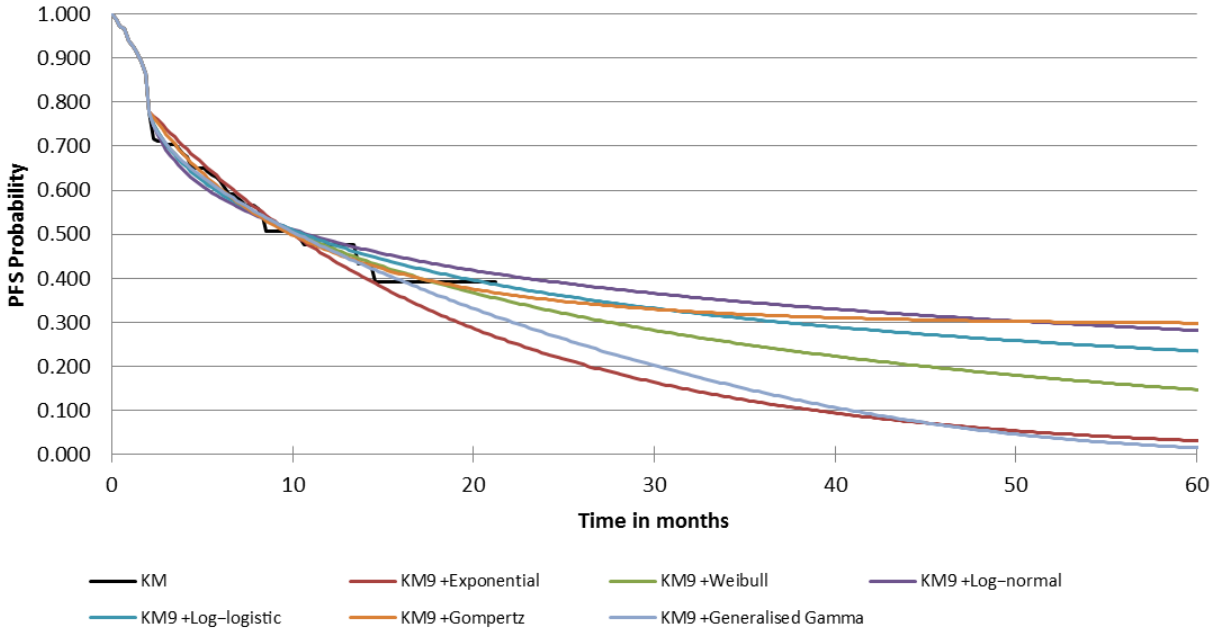
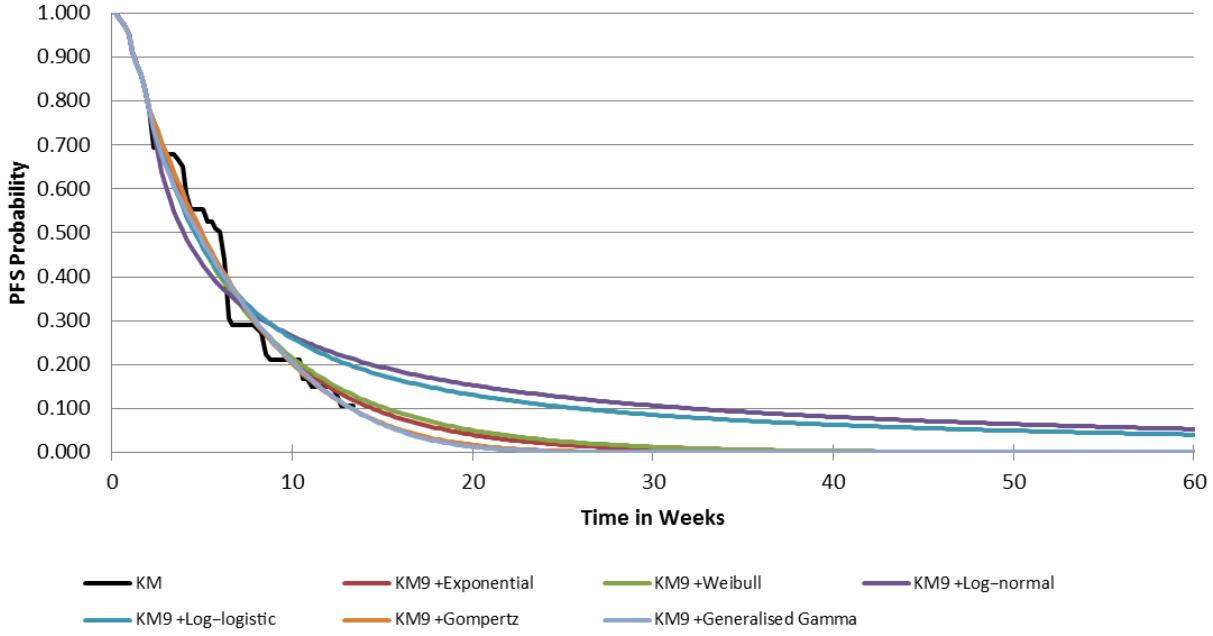
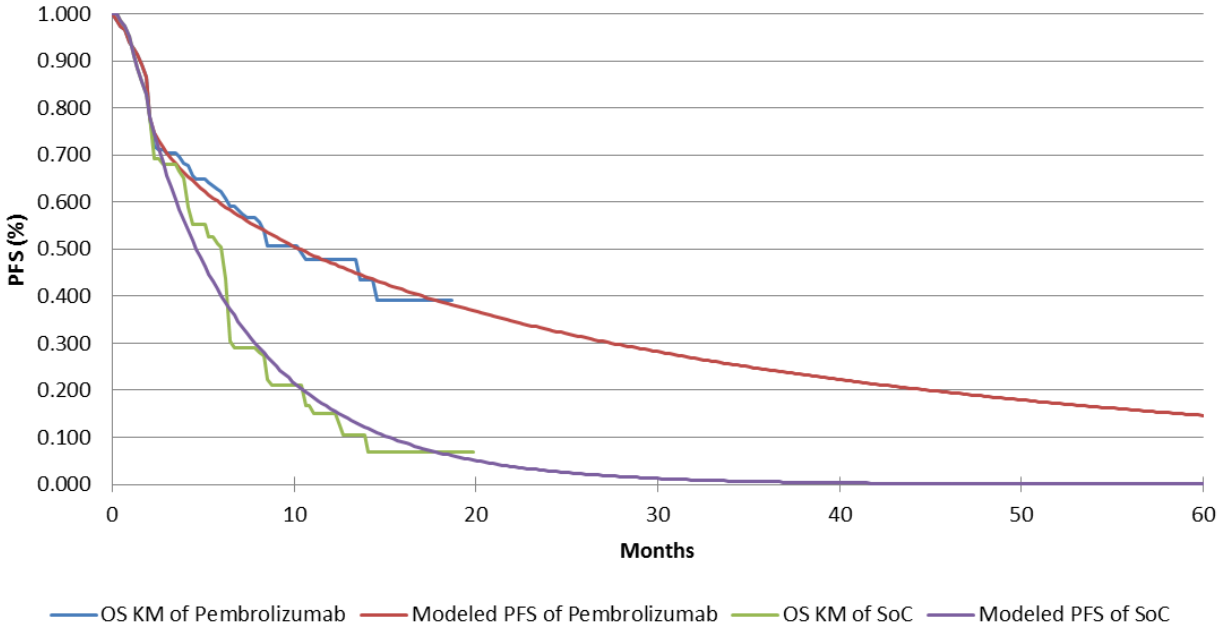


Figure 38. PFS KM curve vs. fitted 2-phase piecewise models for the PFS defined per RECIST v1.1 as assessed by BICR, with cut-off of 9 weeks, of SOC based on KEYNOTE-024



The modelled PFS curves based on the approach above are presented in Figure 39 below.

Figure 39. Fitted base case 2-phase piecewise models for PFS of pembrolizumab and SOC based on KEYNOTE-024



5.3.4 Modelling indirect comparisons

As stated in the NICE DSU technical support document 14[84], a PH assumption is required for indirect comparisons if the HR from an indirect comparison is to be used for the entire modelled period. Since based on KEYNOTE-024 data, there was evidence that the PH assumption did not hold between pembrolizumab and SOC, it was found more appropriate to implement the NMA approach using time-varying HRs. As reported in section 4.10, the fixed effects model was considered more parsimonious than the random effects model.

Although the 2nd order FP models seemed to be more flexible, these models were very sensitive to limited data at the end of the available follow-up of the trials. The estimated treatment effects were uncertain and resulted in flat PFS and OS curves beyond the available data that were implausible.

Therefore, the results of the fixed effects model using a Weibull distribution, based on KM curves anticipating time-varying treatment effects, were used in the cost-effectiveness model. This was considered appropriate because any differences between trials regarding follow-up time, potentially causing between-study heterogeneity, were captured with time-related parameters in the model.

Based on the results of the NMA, and considering the network related to all comers (i.e. all histologies), pembrolizumab was indirectly compared against the following comparators in additional analyses:

- Gemcitabine or paclitaxel combined with a platinum (carboplatin or cisplatin)
- Docetaxel combined with a platinum (carboplatin or cisplatin)
- Vinorelbine combined with a platinum (carboplatin or cisplatin)
- Pemetrexed-containing chemotherapy

5.3.5 Adverse events

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients (at any grade) in either treatment arm, with two exceptions:

- Diarrhoea Grade 2 is also included to be consistent with previous NICE appraisals.[167, 170]
- 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.[151, 170]

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

The incidence of AEs was taken from the KEYNOTE-024 trial for each treatment arm (see Table 59). It should be noted that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on AEs of any grade. The unit cost and the disutility associated with the individual AEs were assumed to be the same for all treatment arms, therefore the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 59. This was consistent with the methods used in previous submissions[161, 167] and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting.

In the base case, the impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost. These were then applied in the first cycle of the model for each treatment arm. AE-related disutilities were considered as part of the base case since this was the preferred approach by the committee assessing the ongoing submission for pembrolizumab for the treatment of patients with advanced NSCLC and PD-L1 positive tumours who have been previously treated.[160]

Table 59. 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	0.0%	2.7%
Anaemia	4.5%	23.3%
Fatigue	1.3%	4.7%
Decreased appetite	1.3%	3.3%
Constipation	0.6%	0.7%
Diarrhoea	3.9%	2.0%
Diarrhoea (Grade 2+)	2.6%	2.7%
Dyspnoea	1.9%	2.7%
Vomiting	0.6%	2.0%
Back pain	1.3%	3.3%
Arthralgia	0.0%	0.7%
Neutropaenia	0.0%	14.0%
Oedema peripheral	0.6%	0.0%
Blood creatinine increased	0.0%	0.7%
Alanine aminotransferase increased	1.3%	0.0%
Dizziness	0.6%	0.0%
Rash	1.3%	0.0%
Asthenia	0.6%	2.7%
Chest pain	0.0%	1.3%
Stomatitis	0.0%	1.3%
Hyponatraemia	3.2%	4.7%
Thrombocytopaenia	0.0%	6.0%
Neutrophil count decreased	0.0%	4.0%
Abdominal pain	0.6%	0.0%
Aspartate aminotransferase increased	1.3%	0.0%
Hyperglycaemia	2.6%	0.7%
Platelet count decreased	0.0%	6.0%
Musculoskeletal pain	0.6%	0.7%
Pneumonia	1.9%	7.3%
White blood cell count decreased	0.0%	2.0%
Haemoptysis	0.6%	0.7%
Pain in extremity	0.6%	0.0%
Urinary tract infection	0.6%	1.3%
Blood alkaline phosphatase increased	0.6%	0.0%
Dry skin	0.0%	1.3%
Pleural effusion	3.9%	2.7%
Neuropathy peripheral	0.0%	0.7%
Leukopaenia	0.0%	1.3%
Epistaxis	0.0%	1.3%
Chronic obstructive pulmonary disease	3.9%	0.7%
Pneumonitis	2.6%	0.7%
Febrile neutropaenia	0.0%	2.0%

5.3.6 Subsequent treatment

Given the advanced nature of the disease and the lack of data on multiple lines of therapy beyond the second line treatment, only one line of subsequent therapy is modelled. Based on UK clinical practice and NICE guidance,[64, 152] it was assumed all patients in the pembrolizumab arm receive docetaxel as second line treatment. For patients in the SOC arm, patients are assumed to receive pembrolizumab based on the proportion of patients who crossed over in KEYNOTE-024 (43.7%), 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)[152] and 8.7 cycles (i.e., 26.1 weeks) for pembrolizumab based on data observed in KEYNOTE-024. For consistency between the approach taken to adjust for crossover and the costing of subsequent treatments, in the base case all patients in the SOC arm were assumed to receive docetaxel as the only second line treatment when crossover adjustments for the SOC arm were considered.

Table 60 presents the distribution of subsequent therapies for the pembrolizumab and SOC arms.

Table 60. 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%	56.3%*
Pembrolizumab	0%	0%	43.7%

Key: SOC, standard of care.
*Based on calculation (100%-43.7%).

5.3.7 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 5 year and 10 year survival percentages from the extrapolation approach.

5.4 Measurement and valuation of health effects

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

HRQoL was evaluated in the KEYNOTE-024 trial using the EuroQoL EQ-5D-3L (see sections 4.3 and 4.7 above). All trial-based HRQoL analyses conducted for the purpose of the economic section were derived from this trial and the estimated utilities were used in the

cost-effectiveness model. Evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case.[162]

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 anticipated licenced indication and the treatment arms included for the estimation of PFS, OS and safety from KEYNOTE-024 included in the economic model, as stated in section 5.3 above (cut-off date: 9th May 2016).

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 NSCLC patients receiving palliative radiotherapy[171] and in advanced melanoma patients.[172-174] Time to death was demonstrated as more relevant than progression-based utilities since by considering more health states it offers a better HRQoL data fit.[172-174]

  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 61.

Table 61. Compliance of EQ-5D by visit and by treatment (FAS Population, TPS ≥ 1%)

Treatment Visit	Category	Pembrolizumab	SOC
		N = 151	N = 148
		n (%)	n (%)
Baseline	Expected to complete questionnaires	151	148
	Completed	144	137
	Compliance(completed per protocol)*	95.4%	92.6%
Week 3	Expected to complete questionnaires	144	138
	Completed	127	122
	Compliance(completed per protocol)*	88.2%	88,4%
Week 6	Expected to complete questionnaires	138	131
	Completed	120	110
	Compliance(completed per protocol)*	87.0%	84.0%

Treatment Visit	Category	Pembrolizumab	SOC
		N = 151	N = 148
		n (%)	n (%)
Week 15	Expected to complete questionnaires	129	117
	Completed	108	92
	Compliance(completed per protocol)*	83.7%	78.6%
Week 24	Expected to complete questionnaires	111	92
	Completed	98	75
	Compliance(completed per protocol)*	88.3%	81.5%
*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: 09 May 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.[175]

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. There were no statistically significant or clinically meaningful differences in EQ-5D scores by treatment arm; therefore, the scores from the pooled treatment groups were used.

The estimated utilities are presented in Table 62 and Table 63 below.

Table 62: 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*	32	66	0.796	0.032	(0.732, 0.859)	22	43	0.828	0.02	(0.787, 0.869)	54	109	0.808	0.021	(0.767, 0.850)
[180, 360)	10	21	0.735	0.04	(0.652, 0.818)	16	36	0.699	0.031	(0.636, 0.763)	26	57	0.712	0.025	(0.663, 0.762)
[30, 180)	27	54	0.555	0.045	(0.465, 0.645)	41	93	0.622	0.031	(0.561, 0.684)	68	147	0.598	0.026	(0.547, 0.648)
<30	9	9	0.574	0.099	(0.346, 0.803)	12	12	0.41	0.108	(0.173, 0.647)	21	21	0.48	0.075	(0.324, 0.637)

† 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 63: 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	131	528	0.802	0.01	(0.782, 0.822)	125	412	0.747	0.011	(0.725, 0.769)	256	940	0.778	0.008	(0.763, 0.793)
Progressive	66	106	0.66	0.031	(0.598, 0.722)	86	142	0.674	0.026	(0.622, 0.726)	152	248	0.668	0.02	(0.629, 0.707)

† 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

5.4.2 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.[162]

5.4.3 Systematic searches for relevant HRQoL data

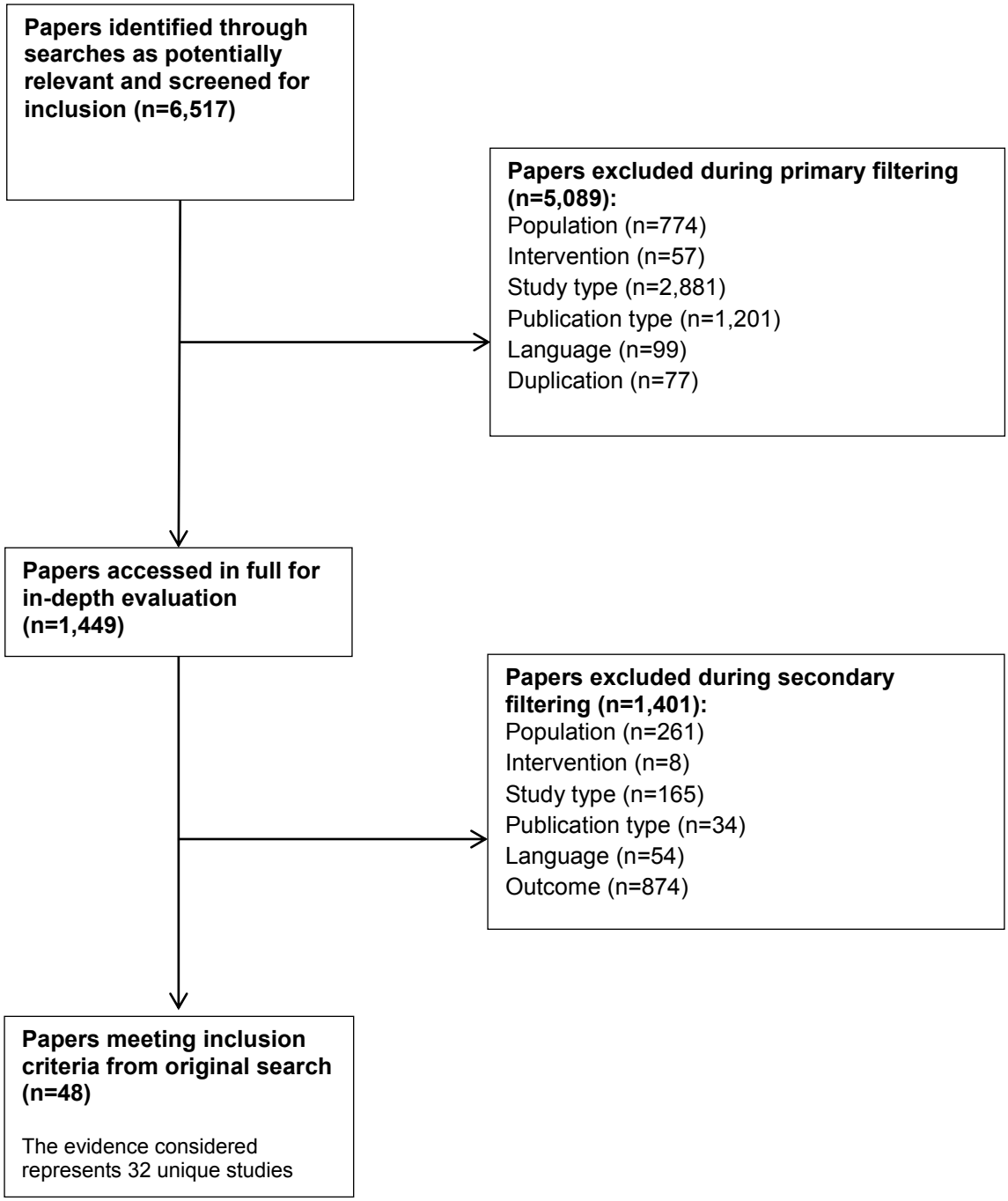
The relevant HRQoL data from the published literature were identified through a systematic literature search carried out on 14th June 2016, for untreated patients with advanced NSCLC, (see Appendix 24 for more details). The objective was to identify HRQoL (in terms of utilities) associated with advanced NSCLC in line with the research question posed in section 5.1.

A comprehensive literature search was carried out using the different databases presented in section 5.1.1. The electronic database searches for utility studies were not limited by any specific publication year or date. Conference searches were also performed to identify potentially relevant conference abstracts or posters of interest (see section 5.1.1). These searches were restricted to abstracts published during the last 2 years

Appendix 24 provides details of the search strategies for HRQoL and utilities along with the eligibility criteria set out in the final protocol.

Systematic database searches identified 6,517 records. Primary screening of abstracts and titles was performed for 6,440 records after removing 77 duplicates. The majority of the records were excluded on the basis of study type (2,881), followed by review/editorial (1,201). After primary screening, 1,428 records were included for secondary screening. Additionally, 21 studies were identified from the economic modelling review, which reported utility values. After secondary screening of full texts, 48 publications were included, multiple reports of the same study were linked together and data for 32 unique studies were extracted into the same data extraction grids. Conference searches did not retrieve any relevant study for utility data.

Figure 40: PRISMA Diagram: HRQoL and Utility studies



Key: HRQoL, Health-related quality of life.

5.4.4 Provide details of the studies in which HRQoL was measured

Please see Appendix 25 for the details of the identified studies.

5.4.5 Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

Table 64 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 64: 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	0.65-0.784	Chevalier et al. (2013); [176] Chouaid et al. (2012); [177]Lee et al.,(2014)*; [178] NICE[TA227], (2011) [179]; NICE[TA258], (2012) ; [62] NICE[TA310], (2014); [61] Wu et al.,(2011); [180] Zeng et al., (2014); [181]Zeng et al.,(2013) [182]
Progression-free (iv/oral)	-0.0425 (iv)/- 0.0139 (oral) from baseline 0.67	NICE[TA192], (2010); [63] Zeng et al., (2014) [181]
Treatment cycle	Cycle 3-4: 0.03 from baseline Cycle 0-2/ >6 : 0.4099 - 0.7758	Galetta et al. (2015); [183] Gridelli et al. (2012); [184]NICE[TA309] (2014) [185]
Progressed disease	0.31–0.68	Chevalier et al. (2013);[176] Chouaid et al. (2012);[177] Joerger et al., (2011);[186] Klein et al., (2009);[187] Lee et al., (2014)*;[178] Matter-Walstra et al., (2012);[188] NICE[TA181], (2009)*;[65] NICE[TA192], (2010);[63] NICE[TA227], (2011);[179] NICE[TA310], (2014);[61] Schluckebier et al., (2015);[189] Ting et al., (2015);[190] NICE [ID835] ;[151] Zeng et al.,(2013) [182]
Near death	0.18-0.35	Klein et al., (2009); [187] NICE[TA181], (2009)* [65]
Other utilities identified from the systematic review		
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	Brown et al. (2013)*;[140] Chouaid et al. (2011);[191] Griebsch et al. (2014);[192] Khan et al. (2015); [193] Solomon et al. (2014);[194]Verduyn et al. (2012); [195] Lopes et al. (2012)*; [196] Djalalov et al. (2014)*; [197] NICE[TA190], (2010); [198] NICE[TA227] (2011)* [179]

Health state	Range of values	References
	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	
Stable disease	0.49–0.84.	Joerger et al., (2011); [186] Klein et al., (2009); [187] Matter-Walstra et al., (2012); [188] Nafees et al. (2016); [199] NICE[TA181], (2009)*; [65] Ting et al.,(2015); [190] NICE[TA310] (2014) [61]
AEs	Rash:-0.0325 Neutropaenia:-0.46	Nafees et al. (2016); [199] NICE[TA181], (2009)*; [65] NICE[TA192] (2010); [63]
Placebo	Pre progression: 0.6438 Post progression: 0.5760	Khan et al. (2015) [193]
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); [200]Tongpak et al. (2012); [201] NICE[TA181], (2009)* [65]
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[202], 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[185] 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.[65, 187] However it is unclear if these values were reflective of the HRQoL of the patients in a period of <30 days to death.

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.[176-178, 185, 193]

It should be noted that the majority of the economic evaluation studies[62, 63, 65, 140, 178, 179, 182, 189, 196, 197] calculated utility values using an algorithm by Nafees et al. (2008)[202] 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.[203-205] 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, the NICE reference case stipulates the use of utility values directly derived from the patients.

5.4.6 Describe how adverse reactions affect HRQoL

The impact of AEs on HRQoL was assessed by examining the EQ-5D health utilities of patients who experienced AEs (grade 3-5) compared to those who did not experience AEs in the progression-free health state.

For this assessment, the time points associated with grade 3-5 AEs for each patient were identified. EQ-5D scores collected at these time points were then used to estimate the utility of the progression-free state with grade 3-5 AEs. EQ-5D scores collected at other time points were used to estimate the utility associated with the progression-free health state in the absence of grade 3-5 AEs. The utility values for patients experiencing grade 3-5 AEs were significantly lower (0.719; 95% CI: 0.683, 0.755) than those of patients not experiencing grade 3-5 AEs (0.793; 95% CI: 0.777, 0.809; see Table 65).

It has been assumed for the purposes of the modelling that any impact of AEs on HRQoL will be expressed in terms of a disutility of AEs applied based on AE incidence rates and the corresponding mean duration across them (i.e. 31.5 days of duration across grade 3+ AEs, as estimated from KEYNOTE-024).

Table 65: 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	33	66	0.746	0.032	(0.682, 0.810)	59	124	0.704	0.022	(0.661, 0.748)	92	190	0.719	0.018	(0.683, 0.755)
Progression -Free w/o Grade3+ AE	122	462	0.81	0.011	(0.789, 0.831)	100	288	0.765	0.013	(0.740, 0.791)	222	750	0.793	0.008	(0.777, 0.809)

5.4.7 Definition of the health states in terms of HRQoL in the cost-effectiveness analysis.

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, 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. 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).

5.4.8 Clarification on whether HRQoL is assumed to be constant over time in the cost-effectiveness analysis

A constant value for HRQoL is applied in each cycle taking into account whether patients were considering time to death or in the pre- or post-progression health states. An age-related utility decrement of 0.0045 is applied per year, from the age of 65 until 75, to reflect the natural decrease in utility associated with increasing age.[206]

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.[206], 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.

5.4.9 Description of whether the baseline HRQoL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states

Not applicable.

5.4.10 Description of how and why health state utility values used in the cost-effectiveness analysis have been adjusted, including the methodologies used

The health state utility values have not been amended; however, as explained above, a yearly utility decrement applies as patients get older.

5.4.11 Identification of any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis

No health effects on patients were excluded from 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. As mentioned in section 5.2.3, 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. [163]

5.4.12 Summary of utility values chosen for the cost-effectiveness analysis

The utility values chosen for the cost-effectiveness model are presented in Table 66.

Table 66: Summary of utility values for cost-effectiveness analysis

	Utilities**		Reference in submission (section and page number)	Justification
	Mean	95% CI		
By time-to-death (days) - 4 categories				
≥360*	0.808	(0.767, 0.850)	Section 5.4.1 Table 62 Page 187	Utility values from KEYNOTE-024
[180, 360)	0.712	(0.663, 0.762)		
[30, 180)	0.598	(0.547, 0.648)		
<30	0.48	(0.324, 0.637)		
Progression based utilities				
Progression-Free	0.778	(0.763, 0.793)	Section 5.4.1 Table 62 Page 187	Alternative utility values from KEYNOTE-024
Progressed	0.668	(0.629, 0.707)		

** This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days.*
*** Utilities from KEYNOTE-024 are pooled utilities*

5.4.13 Details of clinical expert assessment of the applicability of the health state utility values available

The applicability of the selected health state utility values was not assessed by clinical experts as these values were in line with those identified in the published literature and overall consistent with the NICE reference case.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Parameters used in the cost effectiveness analysis

A summary of the variables used in the cost estimation is presented in Appendix 26

5.5.2 Resource identification, measurement and valuation studies

The type of costs considered in the economic model included the drug and administration costs related to the intervention and comparator, including the costs related to subsequent therapies (see section 5.5.5), the monitoring and management of the disease (see section 5.5.6), the management of adverse events (AEs) (see section 5.5.7), and the costs related to terminal care (see section 5.5.6). In addition, for patients treated with pembrolizumab, the costs of testing for PD-L1 expression were also included (see section 5.5.5).

A systematic literature review was conducted to identify costs and resource use in the treatment and on-going management of advanced NSCLC patients from a UK perspective. The population criteria considered in the systematic review was limited to include only untreated adult patients with advanced NSCLC. The searches conducted for resource use data and the selection criteria followed for the identification and inclusion of relevant studies are provided in Appendix 27.

From 3,893 references identified from the search strategy as potentially relevant, 16 publications from 15 unique studies were included for cost and/or resource use data extraction. Figure 41 below presents the PRISMA diagram for the resource use and cost literature searches and a summary displaying the details of the included studies is available in Appendix 28.

Of the studies identified, 11 are economic evaluations where a wide range of resource use and costs data were reported including costs for drugs, inpatients/outpatients, GPs/nurses, palliative and terminal care, and indirect costs. Although all studies included were UK-specific, two reported costs in Euro currency and one study did not report any costs at all as it was a health care resource utilisation study.[207-209]. The remaining 12 studies reported costs in terms of sterling pounds (GBP £).

A variety of monetary costs relating to drug price and administration were identified. SOC drug costs, including pemetrexed and non-pemetrexed containing regimens, were sourced primarily from the BNF. Although the studies included were published in the last 10 years, they may not represent the most current drug prices in the UK.

The main use of resources by patients with advanced NSCLC relate to hospital episodes, terminal care, time required for dispensing, inpatient and outpatient episodes' duration and patients' visits to different health care professionals. The identified studies reported a variety of resource use related to hospital episodes, ranging from 4.3 days in NICE TA181 (2009) [65] to 20 days in Fleming et al (2008) [210].

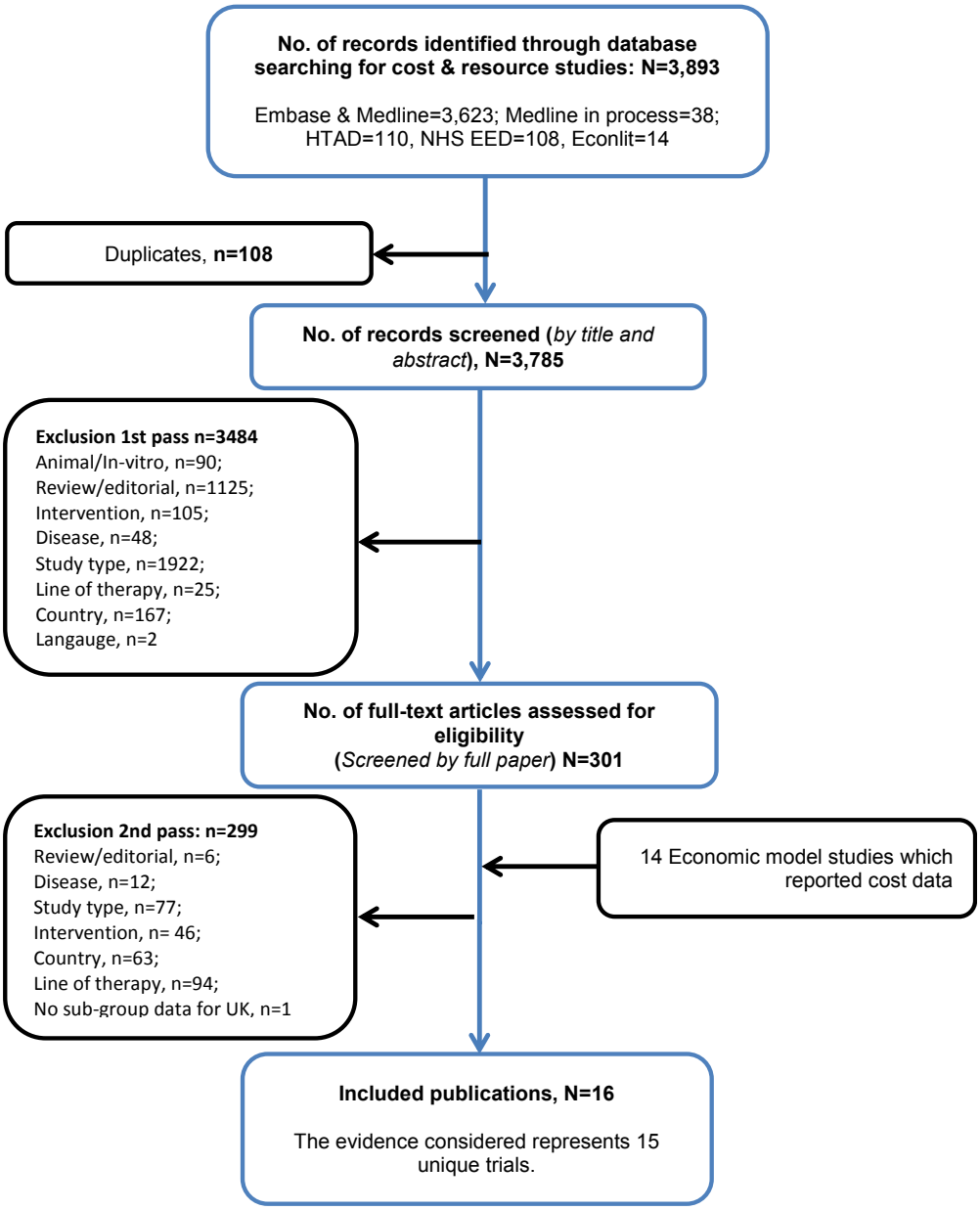
Of the studies identified, there were 9 that reported adverse events and all were associated with a variety of unit costs. For example an incident of diarrhoea cost between £261[179] and £867[65] whilst an incident of fatigue ranged broadly between £39[140] and £2537[65]. Brown et al (2013)[140] reported the total AE costs for docetaxel, paclitaxel, gemcitabine and pemetrexed as £773, £751, £733 and £409 respectively. The cost of AEs with a placebo spanned between £0.83[193] and £181[185].

Additionally, a number of studies reported follow-up costs for health states. NICE TA227 (2011) reported a total cost for progression free health state of £684 compared with a disease progression cost of £9,061 for the non-squamous population on BSC. The cost of monthly progression free supportive care ranged between £362[179] and £181[62] whilst the cost of terminal care was reported to be between £2,588[62] and £2,825[185].Lastly, TA181 reported a cost of specialist palliative care to be £3,236.[65]

The identified resource use and cost studies provide some useful information for the de novo cost-effectiveness model regarding the quantity and frequency of the use of resources and the monetary unit costs for AEs and follow up health state costs. A limitation of the resource use and cost data identified from these studies is that the values are not consistent across the studies as the regimens compared vary widely so caution is required when interpreting these results and their implications for clinical practice.

The final resource use and costs inputs applied in the model are presented in sections 5.5.4 to 5.5.7 with details and rationale for the sources used.

Figure 41: PRISMA diagram for included cost and resource use studies



Key: HTAD, Health Technology Assessment Database; NHS EED, NHS Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

5.5.3 Use of NHS reference costs or payment-by-results (PbR) tariffs

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing pembrolizumab. Details about the cost estimation of treatment with pembrolizumab in terms of acquisition and administration are reported below. As previously agreed with NHS England (personal communication, 9th December 2014) for the single technology assessment (STA) submission of pembrolizumab for advanced melanoma),[16] the administration cost of pembrolizumab can be reflected through NHS Reference Cost code SB12Z[211], since this corresponds to the administration of a simple therapy (i.e. involving the administration of only one agent without IV anti-emetics), with the infusion only lasting half an hour.

5.5.4 Input from clinical experts

The above costing approach was validated with clinical experts.

5.5.5 Intervention and comparators' costs and resource use

Drug costs

The drug acquisition costs per treatment are presented below, with the unit costs for comparators being taken from the latest electronic market information tool (eMit)[212] 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)[213] 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 1). The expected 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[212] apart from pemetrexed, for which the corresponding drug costs are only available from MIMS.[213] 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,[159] whenever available. Dosing for the remaining drugs not included in KEYNOTE-024 was based on SmPC or Brown et al (2013).[140, 214, 215]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 67). 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 67: 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 68: 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[214]	eMit[212]
Gemcitabine	1250mg/m^2	Q3W	2250mg	£0.01	£21.65	KEYNOTE-024[21]	eMit[212]
Paclitaxel	200mg/m^2	Q3W	360mg	£0.07	£25.78	KEYNOTE-024[21]	eMit[212]
Vinorelbine	27.5mg/m^2	Q1W	49.5mg	£0.36	£53.48	SmPC[215]	eMit[212]
Carboplatin	400mg/m^2	Q3W	720mg	£0.04	£30.30	Brown 2013[140]	eMit[212]
Cisplatin	75mg/m^2	Q3W	135mg	£0.11	£14.26	KEYNOTE-024[21]	eMit[212]
Pemetrexed	500mg/m^2	Q3W	915mg	£1.60	£1,464.00	KEYNOTE-024[21]	MIMS[213]

* 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 69). This approach reflected the recommendation of the health economic experts consulted for the validation of the de novo cost-effectiveness model, Table 70 summarises the drug costs per administration for the comparators used in the economic model.

Table 69: 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 70: Summary of the drug costs per administration for the comparators used in the base case

	All	Squamous	Non-squamous
Overall platinum-based chemotherapy	£998.43	£47.91	£930.59
Non-pemetrexed containing platinum-based therapy	£49.07	£47.91	£50.57
Pemetrexed containing platinum-based therapy	£1,445.18	n/a	£1,448.28
Gemcitabine or paclitaxel plus platinum	£49.07	£47.91	£50.57
Docetaxel plus platinum	£38.89	£38.89	£38.89
Vinorelbine plus platinum	£76.79	£81.98	£66.83

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

As per the anticipated licence, patients treated with pembrolizumab are expected to be treated until disease progression is confirmed. To estimate the duration of treatment in the

pembrolizumab and comparator arms, time on treatment (TOT) data from KEYNOTE-024 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.

Separate parametric curves were fitted to the patient level treatment duration data from KEYNOTE-024 to represent ToT in the economic model (see Figure 42 and Figure 43). AIC/BIC based tests combined with visual inspection were used to select the best-fitted parametric distributions. The function with the lowest AIC/BIC is Weibull for pembrolizumab, and GenGamma for SOC (see Table 71). The Weibull produces the most conservative estimates, not only as it estimates higher ToT than the GenGamma but the impact is also higher in the pembrolizumab arm.

Table 71: Goodness of fit measures for ToT

Fitted Function	Pembrolizumab		SOC	
	AIC	BIC	AIC	BIC
Exponential	815.7	818.8	1127.9	1130.9
Weibull	778.8	784.9	1127.5	1133.6
LogNormal	783.6	789.7	1186	1192
LogLogistic	781.2	787.2	1169.3	1175.3
Gompertz	800	806.1	1128.7	1134.7
GenGamma	780.4	789.5	1115.3	1124.3

Figure 42. Standard parametric curves for ToT of pembrolizumab

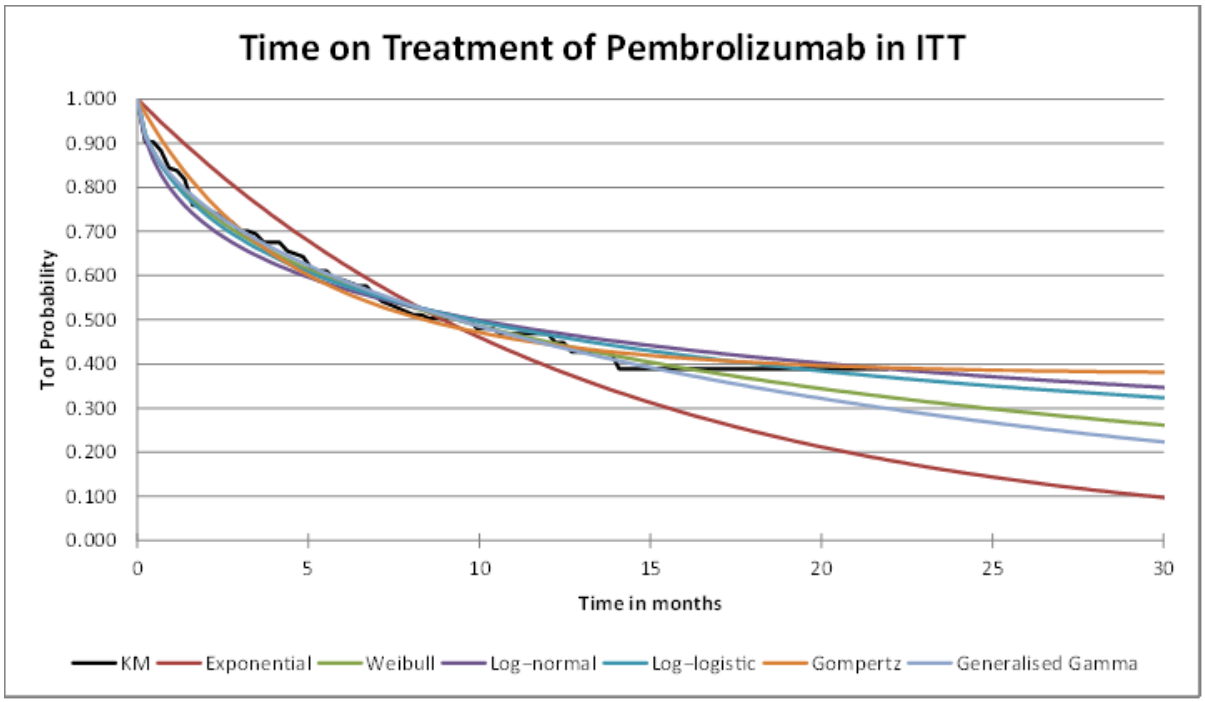
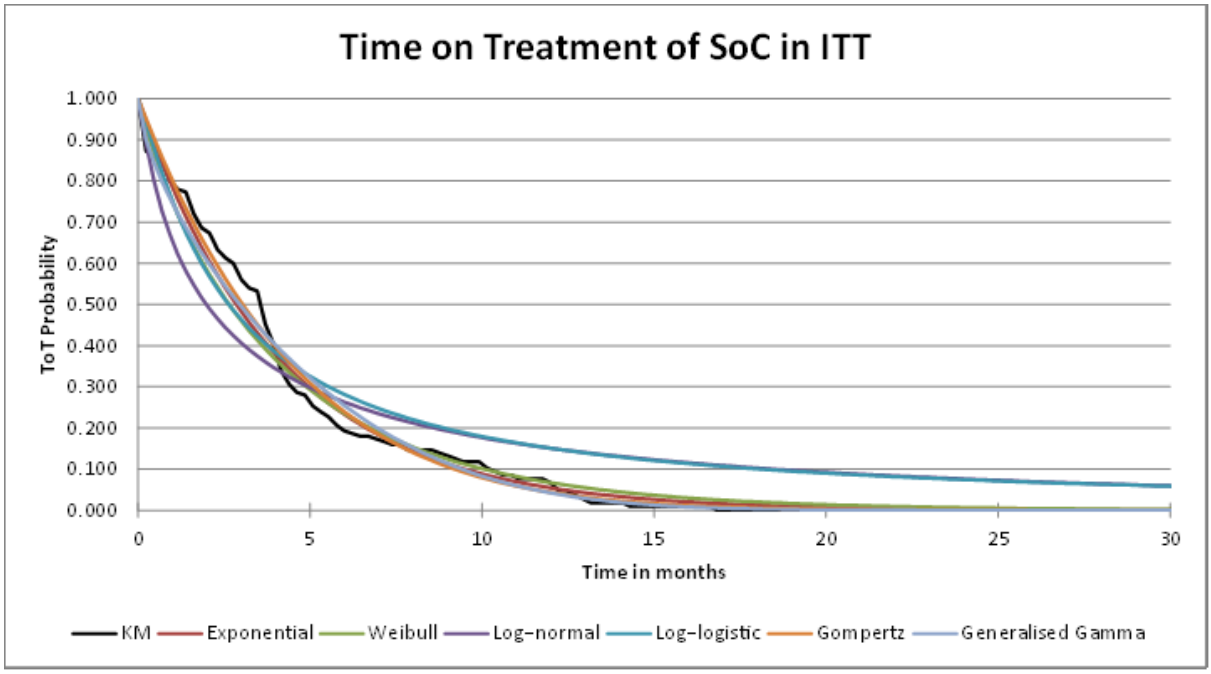


Figure 43. Standard parametric curves for ToT of SOC



In the base case model, a maximum treatment duration of 35 cycles (i.e., 105 weeks or 2 years) was assumed for pembrolizumab, in line with the KEYNOTE-024 protocol.[159] 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[159] and clinical practice in England. The average numbers of cycles received per patient in KEYNOTE-024 were 5.05 (range 4-6) for all platinum-based therapy, pemetrexed-containing platinum-based therapy and non-pemetrexed-containing platinum-based therapy respectively. Following first line therapy, all patients who remain progression-free will be eligible for pemetrexed maintenance therapy until disease progression or unacceptable toxicity.[153]

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, 99.21% of patients on pembrolizumab and 97.05% 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 2014-2015 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.[16]

Platinum-based combination therapy

The administration costs required for platinum-based therapies were based on previous NICE submissions in NSCLC first line treatment.[63, 65, 152]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 of chemotherapy administration cycle was taken from national reference costs 2014/15.[211] Table 72 summarises the administration costs used in the economic model.

Table 72. Administration costs of pembrolizumab and platinum-based chemotherapy

	Assumptions	Unit costs	Reference
Gemcitabine + carboplatin	1 x SB12Z (outpatient)	£257.11	ID840[170]
Gemcitabine + carboplatin	1 x SB14Z (outpatient) 1 x SB15Z (outpatient)	£530.41	TA181[65]
Gemcitabine + cisplatin	1 x SB14Z (Day case and regular day/night) 1 x SB15Z (outpatient)	£618.05	TA181[65]
Paclitaxel + carboplatin	1 x SB14Z (outpatient)	£325.94	TA192[63]
Paclitaxel + cisplatin	1 x SB14Z (Day case and regular day/night)	£413.58	Assumption
Docetaxel + carboplatin	1 x SB14Z (outpatient)	£325.94	Assumption
Docetaxel + cisplatin	1 x SB14Z (Day case and regular day/night)	£413.58	TA181[65]
Vinorelbine + carboplatin	1 x SB14Z (Outpatient) 1 x SB15Z (Day case and regular day/night)	£688.31	Assumption
Vinorelbine + cisplatin	1 x SB14Z (Day case and regular day/night) 1 x SB15Z (Day case and regular day/night)	£775.95	TA192[63]

	Assumptions	Unit costs	Reference
Pemetrexed + carboplatin	1 x SB14Z (outpatient)	£325.94	TA406[152]
Pemetrexed + cisplatin	1 x SB14Z (Day case and regular day/night)	£413.58	TA181[65]

Similar to the drug costs for the comparators, the administration 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 therapies) 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 73 summarises the drug administration costs for the comparators used in the economic model.

Table 73. Summary of the drug administration costs for the comparators used in the base case

	All
Overall platinum-based chemotherapy	£395.66
Non-pemetrexed containing platinum-based therapy	£478.08
Pemetrexed containing platinum-based therapy	£356.87
Gemcitabine or paclitaxel plus platinum	£478.08
Docetaxel plus platinum	£369.76
Vinorelbine plus platinum	£720.86

Costs associated with PD-L1 testing

Pembrolizumab is anticipated to be licensed for the first line treatment of advanced NSCLC in adults whose tumours express PD-L1, as assessed by a validated test.

Based on the information and calculations presented in section 6.2, we estimate that 11.6% 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, 8.6 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 £348.21 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 74). This cost was applied only to the pembrolizumab arm of the model.

Table 74: 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	11.6%
PD-L1 test cost	£40.5
Total PD-L1 costs	£348.21

*Sources: see Section 6.2.

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[153] following the first line active chemotherapy treatment. The proportion of patients receive 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.[153]

The drug cost for pemetrexed maintenance therapy is shown in Table 70 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. Furthermore, it was assumed an additional CT scan every 12 weeks is required due to pemetrexed maintenance treatment based on an assumption made by the manufacturer in the TA402 submission.[153]

Costs associated with subsequent therapies received by patients after treatment discontinuation

The method and assumptions for modelling subsequent therapies were discussed in Section 5.3.6. It was assumed that all patients in the pembrolizumab arm receive docetaxel as second line treatment. In the SOC arm, patients are assumed to receive pembrolizumab based on the proportion of patients crossed over in KEYNOTE-024 (43.7%) with the remaining proportion of patients to receive docetaxel. The duration of the second line treatment for docetaxel is assumed to be 3 cycles (i.e., 9 weeks)[152] and 8.7 cycles (i.e., 26.1 weeks) for pembrolizumab based on data observed in KEYNOTE-024 [21]. For consistency between crossover adjustment and subsequent treatment costs, all patients in the SOC arm were assumed to receive docetaxel as the only second line treatment when crossover adjustments for the SOC arm were made.

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 an average duration of treatment of 9 weeks and 26.1 weeks for docetaxel and pembrolizumab, respectively. 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.

5.5.6 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 all regimens currently approved by NICE and licensed across Europe for the systemic treatment of patients with advanced NSCLC.[140] 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 75 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,[140] 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 76 presents the unit costs for individual resource use items, which were updated based on the latest NHS reference costs 2014-2015 and the Personal and Personal and Social Services Research Unit (PSSRU) 2015 report.[211, 216] The estimated per week

monitoring and disease management costs were £76.75 and £125.87 respectively for the PFS and PPS periods.

Table 75: Resource use frequency for progression-free and progressed health states (based on Brown et al study[140])

Resource	PFS	PPS	Unit	Source quoted in Brown 2013
Outpatient visit	9.61	7.91	per annum	Big Lung Trial[217]
Chest radiography	6.79	6.5	per annum	Big Lung Trial[217]
CT scan (chest)	0.62	0.24	per annum	Big Lung Trial[217]
CT scan (other)	0.36	0.42	per annum	Big Lung Trial[217]
ECG	1.04	0.88	per annum	Big Lung Trial[217]
Community nurse visit	8.7	8.7	visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG81,[218] Marie Curie report[219]
Clinical nurse specialist	12	12	hours contact time per patient	Appendix 1 of NICE Guideline CG81[218]
GP surgery	12	0	consultations per patient	Appendix 1 of NICE Guideline CG81[218]
GP home visit	0	26.09	per annum (fortnightly)	Marie Curie report[219]
Therapist visit	0	26.09	per annum (fortnightly)	Appendix 1 of NICE Guideline CG81[218]

* 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 76. Unit costs of disease monitoring and supportive care

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£177.83	per visit	NHS Reference Costs 2014–2015, Consultant Led, Non-Admitted Face to Face Attendance, First, 800 clinical oncology[211]
Chest radiography	£26.39	per case	NICE technology appraisal TA199; TAG report, p.328 (£24.04 in 2009)[220]
CT scan (chest)	£121.68	per case	NHS Reference Costs 2014–2015, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)[211]
CT scan (other)	£124.10	per case	NHS Reference Costs 2014–2015, Diagnostic Imaging, Outpatient, HRG code RD26Z (three areas with contrast)[211]
ECG	£174.91	per case	NHS Reference Costs 2014–2015, 800 Clinical Oncology, Outpatient, HRG code EY51Z[211]
Community nurse visit	£67.00	per hour	PSSRU 2015, p.169: Cost per hour of patient-related work (including qualifications)[216]
Clinical nurse specialist	£91.00	per contact hour	PSSRU 2015, p.175: Cost per contact hour (including qualifications)[216]
GP surgery visit	£44.00	per visit	PSSRU 2015, p.177: Cost per patient contact lasting 11.7 minutes, including direct care staff costs (including qualifications)[216]
GP home visit	£88.92	per visit	PSSRU 2015, p.177-178: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel[216]
Therapist visit	£44.00	per hour	PSSRU 2015, p.191: Cost per hour for community occupational therapist (including training)[216]

* 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.[140] The estimated one-off terminal costs were £4,735.73 and are assumed to be the same for all treatment arms (see Table 77).

Table 77: Unit costs of terminal care patients (based on Brown et al study[140])

Resource	Unit cost	Number of consumption	% of patients in each care setting	Assumptions / Reference
Community nurse visit	£67.00 per hour	28.00 hours	27%	PSSRU 2015, p.169: Cost per hour of patient-related work (including qualifications)[216]
GP Home visit	£88.92 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[216]
Macmillan nurse	£60.70 per hour	50.00 hours	27%	Assumed to be 66.7% of community nurse cost[140]
Drugs and equipment	£546 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 2014/15 using the PSSRU HCHS index[140, 216]
Terminal care in hospital	£3,760.46 per episode	1 episode (9.66 days)	56%	NHS Reference Costs 2014–2015, 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[211] Assumed that unit cost is = £3518.46 + 0.92 excess days at £263.05 per day[140]
Terminal care in hospice	£4,700.58 per episode	1 episode (9.66 days)	17%	Assumed 25% increase on hospital inpatient care[140]
Total cost	£4,735.73 (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

5.5.7 Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section 5.3.5. The approach used to consider the HRQoL impact of AEs as part of the cost-effectiveness assessment is described in section 5.4.6.

The unit costs related to the management of AEs were mainly derived from the Brown et al study and from the previous NICE STA submissions.[140, 151, 160, 221])[63, 167] When unit costs were not available or the management costs were trivial, zero cost was applied. All unit costs were inflated to 2014/15 prices using the hospital and community health services (HCHS) index published by PSSRU for 2015.[216] Table 78 below presents only the unit costs per AE that costing was applied in the cost-effectiveness model.

Table 78: Unit cost per AE used in the de novo model

Adverse Event	Unit costs	Reference
Nausea	£967.99	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[140, 216]
Anaemia	£2,610.66	NICE ID840[160]
Fatigue	£2,768.35	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[140, 216]
Diarrhoea (grade 2)	£442.76	NICE ID840[160]
Diarrhoea (grade 3-4)	£967.99	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[140, 216]
Dyspnoea	£571.06	NICE TA403[221]
Vomiting	£764.71	NICE TA192 (inflated to 2014/15 using PSSRU inflation indices)[63] [216]
Neutropaenia	£117.31	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[140, 216]
Alanine aminotransferase increased	£598.85	TA347 (inflated to 2014/15 using PSSRU inflation indices)[167] [216]
Rash	£123.34	Brown (inflated to 2014/15 using PSSRU inflation indices)[140, 216]
Asthenia	£2,768.35	Brown (inflated to 2014/15 using PSSRU inflation indices)[140, 216]
Thrombocytopaenia	£758.50	NICE ID865[152]
Neutrophil count decreased	£179.83	NICE ID840[160]
Aspartate aminotransferase increased	£342.78	NICE TA347 (inflated to 2014/15 using PSSRU inflation indices)[167, 216]
Pneumonia	£3,008.41	NICE ID835[151]
White blood cell count decreased	£560.08	NICE ID840[160]
Urinary tract infection	£2,225.03	NICE TA347 (inflated to 2014/15 using PSSRU inflation indices)[167] [216]
Neuropathy peripheral	£19.76	NICE TA162[220]
Pneumonitis	£3,008.41	Assumed to be same as pneumonia
Febrile neutropaenia	£6,831.00	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[140, 216]

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

5.5.8 Miscellaneous unit costs and resource use

There are no additional costs included in the model apart from those outlined in the previous sections.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Tabulated variables included in the cost-effectiveness analysis

A table summarising the full list of variables applied in the economic model is presented in Appendix 26.

Additionally, Table 79 below presents a summary of the clinical inputs and data sources used in the economic model.

Table 79. Summary of clinical inputs and data sources used in the economic model

Clinical evidence and source	Brief description	Use in the model
KEYNOTE-024[21]	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.	• 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, PFS and ToT parametric curves for both pembrolizumab and SOC arms. • Patient level data from the SOC arm was used to perform crossover adjustments for the SOC OS. • OS KM data were used to model OS in the first phase of the OS before parametric curves were applied. • PFS KM data were used to model PFS in the first 9 weeks before parametric curves were applied. • Patient level data were used to calculate 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. • 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. • Used as part of the NMA to compare the relative effectiveness in terms of OS and PFS for pembrolizumab and SOC regimens in additional analyses.
General population mortality[222]	Latest national life table in England & Wales providing age- and gender-specific general population mortality.	Applied throughout the modelled time horizon as background mortality (i.e., general population mortality is applied when modelled mortality is lower than the gender- and age-matching general population mortality).

Key: AE, adverse event; HR, hazard ratio; IV, intravenous; KM, Kaplan-Meier; NLCA, National Lung Cancer Audit; NMA, network meta-analysis; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression free survival; Q3W, every 3 weeks; RCT, randomised controlled trial; TPS, proportion of tumour cells staining for PD-L1.

5.6.2 For the base-case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible

The base-case cost-effectiveness analysis reflects the NICE reference case as closely as possible.

5.6.3 List of all assumptions used in the de novo economic model with justifications for each assumption

Table 80 summarises the assumptions used in the economic model.

Table 80: 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. Patients in the SOC arm are assumed not to receive pembrolizumab when a crossover adjustment is implemented in the cost-effectiveness model, since their OS efficacy estimates are adjusted to control for the impact of crossing over to pembrolizumab. An 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.[151, 153, 155, 156, 160]
Efficacy	Use unadjusted KM data for the first 22 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, ID811) or has been used by an assessment group for a recent NICE MTA (TA374). For the first 22 weeks OS KM data provides the more robust and reliable estimate and at that point patient numbers are sufficient to implement parametric fitting based on KEYNOTE-024 data. The 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).[154, 156]
Costs	PD-L1 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.	If pembrolizumab were to be recommended by NICE, testing for PD-L1 status would become standard practice. Based on the information and calculations presented in section 6.2, we estimate that 11.6% 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.

5.7 Base-case results

5.7.1 Base-case cost effectiveness analysis results

The results of the economic model are presented in Table 81 below. In the base case analysis, the estimated mean overall survival was 2.75 years with pembrolizumab and 1.22 years with SOC. At the end of the 20-year time horizon there were 0.3 % patients still alive in the pembrolizumab cohort and 0% in the SOC cohort. Patients treated with pembrolizumab accrued 2.06 QALYs compared to 0.86 among patients in the SOC cohort.

5.7.2 Base-case incremental cost effectiveness analysis results

Table 81 below presents the base case incremental cost-effectiveness results, incorporating the PAS. 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 is compared to SOC was

£44,896.This ICER should be considered in the context of pembrolizumab being an end of life technology that presents an innovative nature (see Section 2.5 and Section 4.13).

Table 81: Base-case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SOC	£22,278	1.22	0.86			
Pembrolizumab	£76,462	2.75	2.06	£54,185	1.21	£44,896
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Since there is a current commercial access agreement (CAA) for the administration of pemetrexed as maintenance therapy,[153] we have presented in Table 82 below the ICERs for comparisons of pembrolizumab and SOC considering a range of possible CAA-equivalent simple discounts for pemetrexed administered as maintenance therapy.

Table 82: ICERs from the pairwise comparison for pembrolizumab vs. SOC (discounted, with PAS for pembrolizumab, and considering a range of potential simple discounts, equivalent to the current CAA for pemetrexed administered as maintenance therapy)

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

5.7.3 Clinical outcomes from the model

In Table 83 the outcomes of the pembrolizumab and SOC arms of the KEYNOTE-024 trial, have been compared to the outcomes from the model. The model estimates similar percentages of patients in pre-progression and surviving at different points in time to those reported in the KEYNOTE-024 trial (see Table 83), suggesting that, for the trial period, the model is able to replicate the results of KEYNOTE-024.

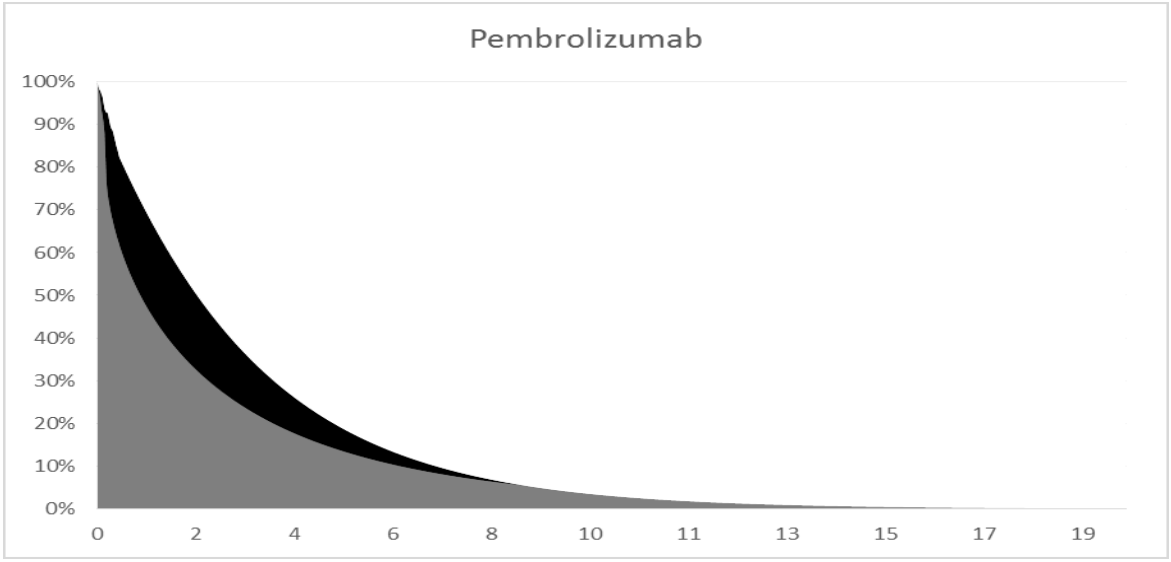
Table 83: Comparison of model and trial outcomes

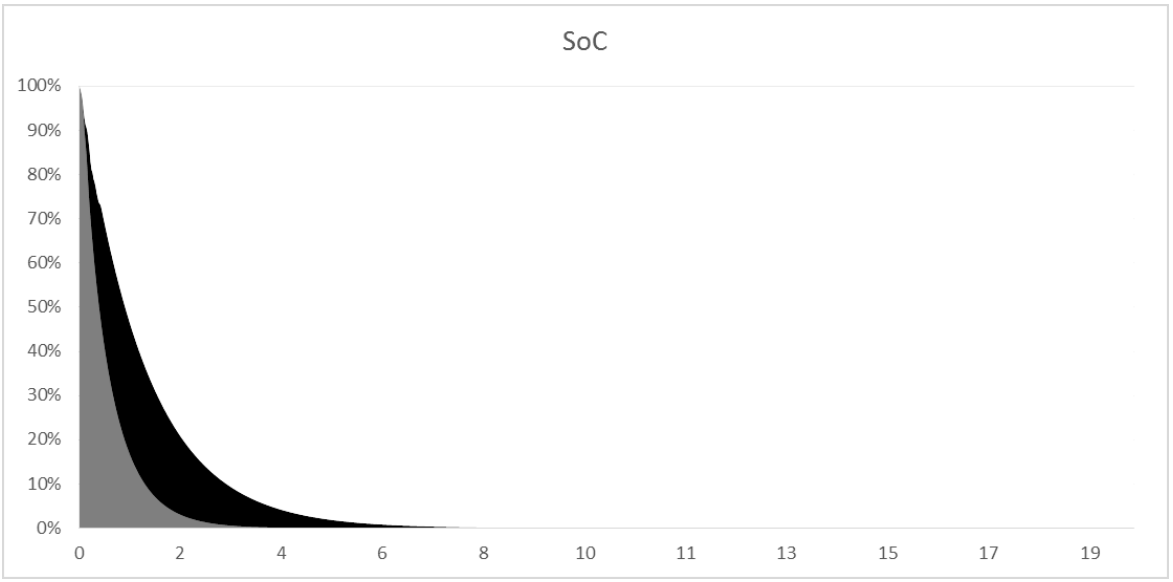
	Pembrolizumab		SOC	
Outcome	Base case	KEYNOTE-024	Base case	KEYNOTE-024
Median PFS (months)	10.1	10.3	4.6	6.0
6-month PFS	59.3%	62.1%	39.3%	50.3%
Median OS (months)	24.6	Not reached	10.8	Not reached
6-month OS	80.6%	80.2%	68.1%	72.4%
1-year OS	69.1%	-	45.7%	-
2-year OS	50.7%	-	20.6%	-
5-year OS	19.9%	-	1.9%	-
10-year OS	4.2%	-	0%	-

5.7.4 Markov traces

Figure 44 below illustrates how patients move through the model states over time when treated with pembrolizumab or SOC, respectively. The diagrams show that patients spend longer in the pre-progression health state on pembrolizumab compared the SOC and that patients also survive for longer.

Figure 44: Markov trace for pembrolizumab and SOC

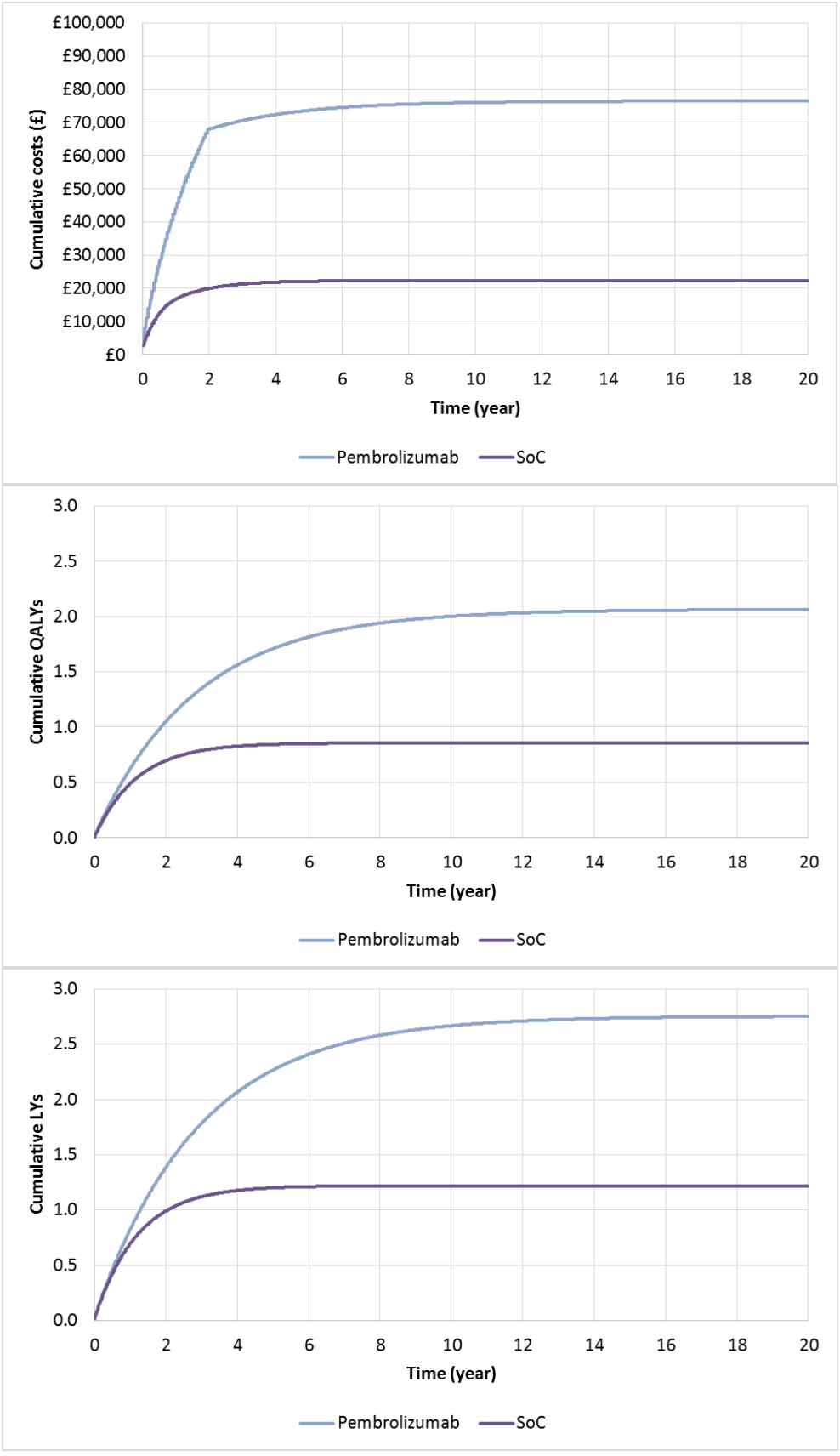




5.7.5 Accrual of costs, QALYs and LYs over time

Figure 45 shows how the costs, QALYs and life years accumulate over time, respectively. In the base case, QALYs are accrued over time according to the time to death utilities approach, as previously reported (see sections 5.2.2 and 5.4).

Figure 45: Cumulative costs, QALYs and LYs over time



5.7.6 Disaggregated results of the base case incremental cost effectiveness analysis

Table 84 shows the disaggregated life years by health state. This shows that patients on pembrolizumab spend longer in both the pre- and post-progression health states compared to patients receiving SOC. Table 85 shows that the majority of costs in the pembrolizumab cohort are associated with treatment.

Table 84: Disaggregated life-years by health state (discounted)

	Pre-progression	Post-progression	Total
Pembrolizumab	2.02	0.73	2.75
SOC	0.56	0.66	1.22

Table 85: Summary of predicted resource use by category of cost

	Pembrolizumab	SOC	Incremental	Absolute increment	% absolute increment
PD-L1 test cost	£348	£0	£348	£348	0.55%
Drug acquisition cost	£53,347	£4,030	£49,317	£49,317	77.85%
Drug administration cost	£4,380	£1,597	£2,783	£2,783	4.39%
Demetrexed maintenance cost	£0	£3,909	-£3,909	£3,909	6.17%
Disease management cost	£12,476	£6,155	£6,320	£6,320	9.98%
Subsequent treatment (2L) cost	£765	£808	-£42	£42	0.07%
Terminal care cost	£4,283	£4,537	-£254	£254	0.40%
AE cost	£863	£1,242	-£379	£379	0.60%
Total	£76,462	£22,278	£54,184	£63,352	100%

5.7.7 Cost-effectiveness results based on the NMA

Pairwise cost-effectiveness comparisons of pembrolizumab compared to the comparators included in the NMA are presented in **Table 86**, and the incremental cost-effectiveness results when considering all interventions together are presented in **Table 87**.

These results should be interpreted with caution due to the high levels of heterogeneity observed across the studies in terms of the assessed population (i.e. squamous and non-squamous populations are likely to present different underlying risks) and interventions for which not all patients included in the studies would be eligible (i.e. pemetrexed-based combinations not being appropriate for patients with NSCLC of squamous histology). The presence of this type of heterogeneity may have biased these results and therefore, may have compromised the results of the NMA. Consequently, the comparisons of pembrolizumab vs. SOC directly derived from KEYNOTE-024 data are considered more

reliable given that they are based on a randomised assessment of patients comparable at baseline.

Table 86: Base case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) pairwise comparison pembrolizumab vs. comparator (QALYs)
Platinum + gemcitabine or paclitaxel	£18,238	1.277	0.899	£58,224	1.163	£50,080
Platinum + docetaxel	£15,988	0.985	0.673	£60,474	1.389	£43,541
Platinum + vinarelbine	£18,987	1.179	0.823	£57,476	1.239	£46,377
Platinum + pemetrexed	£24,003	1.359	0.964	£52,460	1.098	£47,786
Pembrolizumab	£76,462	2.752	2.062	-	-	-
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 87. Incremental cost-effectiveness analysis based on NMA (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) pairwise comparison pembrolizumab vs. comparator (QALYs)
Platinum + gemcitabine or paclitaxel	£15,988	0.99	0.67			
Platinum + docetaxel	£18,238	1.28	0.90	£2,250	0.23	£9,943
Platinum + vinarelbine	£18,987	1.18	0.82	£748	-0.08	£20,044
Platinum + pemetrexed	£24,003	1.36	0.96	£5,016	0.14	£27,531
Pembrolizumab	£76,462	2.75	2.06	£52,460	1.10	£43,541
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix 26.

Table 88: Incremental cost-effectiveness results based on probabilistic sensitivity analysis (discounted, with PAS)

Technologies	*Total costs (£)*	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab	£77,005	2.09	-	-	-
SOC	£22,666	0.87	£54,339	1.22	£44,394
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 88, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 46 and Figure 47.

The cost-effectiveness acceptability curve shows that there is an approximately 62% chance of pembrolizumab to be cost-effective when compared to SOC at the £50,000 per QALY threshold.

Figure 46: Scatterplot of PSA results (1,000 simulations; results discounted, with PAS)

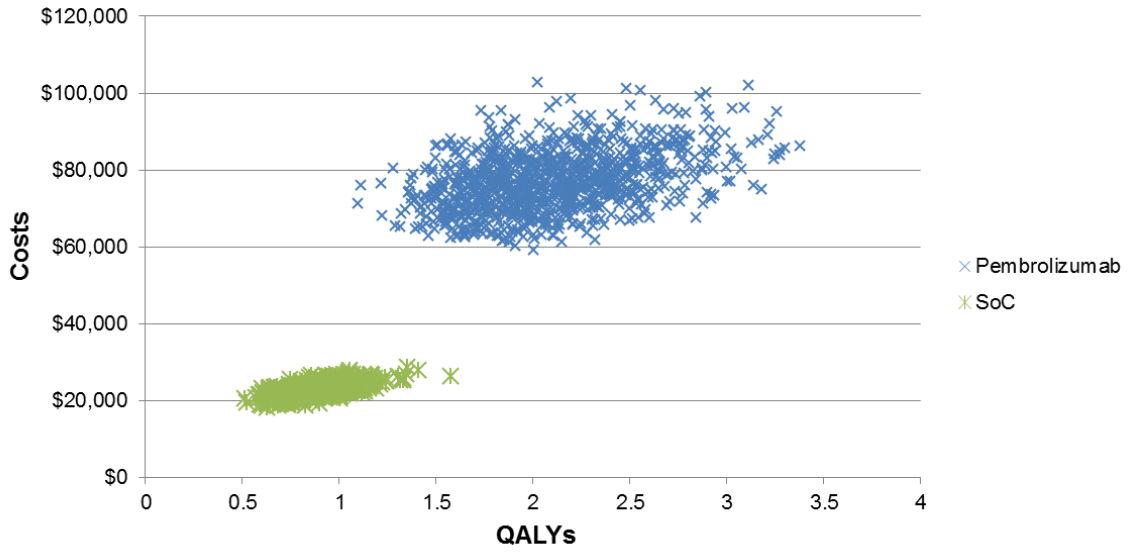


Figure 47: Cost-effectiveness acceptability curve (results discounted, with PAS)

5.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

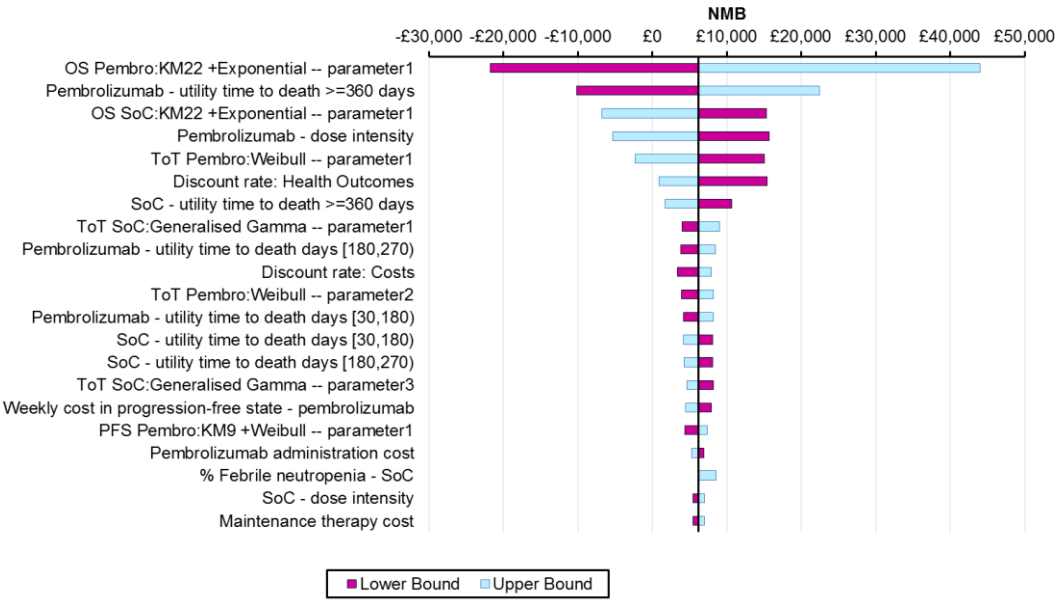
- Baseline characteristics (i.e. body surface area)
- Administration costs
- Costs of the PD-L1 test
- Resource utilisation
- Proportion of patients actually receiving the expected dose
- Subsequent treatment costs and mean duration of subsequent treatment
- Health-state related costs when on active 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 48 below. These are presented with the PAS for pembrolizumab.

The inputs that most affect the ICERs are those related to the extrapolation of the OS (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 48).

Figure 48: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables (discounted results, with PAS)



5.8.3 Scenario analyses

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

- Impact of implementing different crossover adjustments (scenario 1), including:
  - No crossover adjustment (scenario 1.a)
  - RPSFT adjustment (scenario 1.b)
  - IPCW adjustment (scenario 1.c)

- Alternative cut-off for the estimation of the exponential curve in the second phase of the piecewise approach used to extrapolate OS (scenario 2):
    - Considering a 4-week cut-off (scenario 2.a), time at which the OS KM curves for pembrolizumab and SOC started separating. The validity of this approach is questionable given that it does not allow full use of the OS KM data. Since a clear change in slope occurs later at week 22, a more appropriate approach is that presented in the base case, whereby accurate KM data are used up to week 22 to maximise the use of the trial data and to reduce the period to which extrapolation is to be applied.
    - Using a fully fitted parametric approach to the whole trial data (scenario 2.b). As previously mentioned, this approach was not considered to be appropriate because it did not make optimal use of the OS KM data and it did not fit the data.
- Alternative cut-off for the estimation of the parametric curve in the second phase of the piecewise approach used to extrapolate PFS (scenario 3):
    - Considering an 18-week cut-off (i.e. second radiologic assessment; scenario 3.a)
    - Considering a 27-week cut-off (i.e. third radiologic assessment; scenario 3.b).
- Using a different parametric function to extrapolate SOC PFS (since exponential seemed a better fit than Weibull in terms of AIC/BIC statistics, although Weibull was used in the base case to be consistent with the parametric approach used for pembrolizumab; scenario 4).
- Assessing the impact of the half-cycle correction (scenario 5).
- 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 6).
- Using progression-based utilities as an alternative approach to estimate QALYs based on KEYNOTE-024 (scenario 7).
- Using utilities derived per treatment arm instead of pooled utilities from KEYNOTE-024 (scenario 8):

    - With the time to death approach (scenario 8.a)
    - With the progression-based approach (scenario 8.b)
- Removing the age-related disutilities (scenario 9).

Table 89: Results from the scenario analyses

All population										
		Pembrolizumab			SOC			Pembro vs SOC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Base case		£76,462	2.75	2.06	£22,278	1.22	0.86	£54,185	1.21	£44,896
Scenario 1.a	Crossover – ITT (no adjustment)	£76,462	2.75	2.06	£36,481	1.50	1.08	£39,981	0.99	£40,547
Scenario 1.b	Crossover- RPSFT adjustment	£76,462	2.75	2.06	£21,554	1.11	0.76	£54,908	1.30	£42,295
Scenario 1.c	Crossover- IPCW adjustment	£76,462	2.75	2.06	£22,188	1.21	0.84	£54,274	1.22	£44,447
Scenario 2.a	OS cut-off – 4 weeks	£74,652	2.42	1.80	£22,242	1.21	0.85	£52,409	0.95	£55,244
Scenario 2.b	OS cut-off – 0 week (i.e. fully fitted parametric)	£74,728	2.43	1.81	£22,446	1.25	0.88	£52,283	0.93	£55,952
Scenario 3.a	PFS cut-off – 18 weeks	£77,014	2.75	2.06	£22,369	1.22	0.86	£54,644	1.21	£45,277
Scenario 3.b	PFS cut-off – 27 weeks	£77,496	2.75	2.06	£21,993	1.22	0.86	£55,502	1.21	£45,988
Scenario 4	SOC PFS extrapolation based on exponential	£76,462	2.75	2.06	£22,315	1.22	0.86	£54,148	1.21	£44,865
Scenario 5	No half cycle correction	£76,495	2.76	2.07	£22,312	1.23	0.86	£54,183	1.21	£44,900
Scenario 6	SOC as for UK market shares	£76,462	2.75	2.06	£22,718	1.22	0.86	£53,744	1.21	£44,531
Scenario 7	Utilities – Progression based (pooled)	£76,462	2.75	2.02	£22,278	1.22	0.86	£54,185	1.16	£46,705
Scenario 8.a	Utilities – Time to death (per treatment arm)	£76,462	2.75	2.04	£22,278	1.22	0.87	£54,185	1.17	£46,280
Scenario 8.b	Utilities – Progression-based (per treatment arm)	£76,462	2.75	2.07	£22,278	1.22	0.85	£54,185	1.22	£44,586
Scenario 9	No age-related disutilities	£76,462	2.75	2.10	£22,278	1.22	0.86	£54,185	1.24	£43,865

5.8.4 Summary of sensitivity analyses results

The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 62%.

One-way sensitivity analyses showed that the inputs that most affect the ICERs are those related to the extrapolation of the OS, utilities for long-term survivors, parameters of the extrapolation function for time on treatment and dose intensity considered to estimate the cost of pembrolizumab.

Scenario analysis showed that the cost-effectiveness of pembrolizumab is resilient to the sources of uncertainty assessed, including: incidence of AEs, PFS extrapolation, utility values for shorter term survivors, health-related costs, and assumptions around age-related disutilities. The two scenarios evaluating different approaches for extrapolation of OS are the only outliers (see Table 89).

5.9 Subgroup analysis

5.9.1 Types of subgroups that are not considered relevant

The results of the clinical analyses on the subgroups of patients with advanced NSCLC by histology and those by type of SOC combination regimen are presented in Appendix 29. The subgroup analyses have been conducted because these were pre-specified in the protocol. However, due to the small numbers of patients per subgroup, we do not believe these are 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 applies to comparisons of pembrolizumab against non-pemetrexed combinations administered to patients with non-squamous NSCLC.

5.9.2 Analysis of subgroups

Further details on the statistical analyses of these subgroups are presented in section 4.8 and in Appendices 11 and 29.

5.9.3 Definition of the characteristics of patients in the subgroup

See section 4.8 and Appendices 11 and 29.

5.9.4 Description of how the statistical analysis was carried out

See section 4.8 and Appendices 11 and 29.

5.9.5 Results of subgroup analyses

See Appendix 29.

5.9.6 Identification of any obvious subgroups that were not considered

Not applicable.

5.10 Validation

5.10.1 Methods used to validate and quality assure the model

Clinical benefit

Comparing the model outcomes to clinical trial outcomes

The outcomes of the pembrolizumab 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 section 5.7.3.

Expert validation

The model approach and inputs have been validated by two external health economists (Dr. Laura Bojke, from the Centre for Health Economics, University of York and Professor Alistair Grey). These individuals were selected as leading experts in health economic practice and methodology development in the UK. Dr Bojke is a regular member of NICE ERG's. The model structure, selection of appropriate dataset, the survival analysis undertaken and assumption regarding extrapolation and the utility values used were all discussed.

Both experts were in agreement that the current model structure and key assumptions are valid and are consistent with previous submissions in this indication. 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 implemented, the experts agreed that it is 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 will also help 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.

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 implementation and programming of the model was verified via internal quality control processes using an internal quality control checklist, available in Appendix 30.

5.11 Interpretation and conclusions of economic evidence

5.11.1 Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab for the treatment of patients with advanced NSCLC 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. 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.

No study assessing the cost-effectiveness of pembrolizumab for the target population identified above was identified from the systematic literature review. It was therefore not

possible to compare the results of the economic model developed in this submission with any available publication.

5.11.2 Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the advanced NSCLC population eligible for pembrolizumab as per the anticipated licence. As mentioned previously (see section 5.3.1), the KEYNOTE-024 trial, which assessed patients in line with the anticipated licenced indication, was used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab as first line therapy.

5.11.3 Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in KEYNOTE-024 and the de novo economic evaluation are reflective of patients with advanced NSCLC in the UK. 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.

- 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 were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs.

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

5.11.4 Strengths and weaknesses of the evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model.

- OS: Head-to-head data from the KEYNOTE-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.[48] [141, 223]

- 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.

- Estimation of utilities: Utility values were obtained from EQ-5D KEYNOTE-024 data. Four time categories were used for the time-to-death approach.

- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to 35 cycles, as defined as part of the KEYNOTE-024 protocol.

- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from recent NICE appraisals.

Extensive sensitivity analyses were conducted to inform the uncertainty around the above limitations, which helped in understanding what key variables could potentially have a major impact on the cost-effectiveness results.

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.

5.11.5 Further analyses

See section 4.14.

6 Assessment of factors relevant to the NHS and other parties

6.1 Analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness

The level of PD-L1 expression is correlated with efficacy outcomes in patients with previously treated advanced and previously untreated NSCLC (Garon, NEJM, 2015). [224] Testing with a validated PD-L1 test is an efficient use of resources due to increased efficacy with pembrolizumab in PD-L1–positive patients (more targeted therapy). By testing for PD-l1 expression, treatment with pembrolizumab can be targeted to patients who will benefit the most from treatment with pembrolizumab.

This can result in a more efficient use of NHS resources derived from not treating patients that are PD-L1 non-expressers.

6.2 Number of people eligible for treatment in England

In total, 1,447 patients with advanced NSCLC who have a PD-L1 tumour proportion score of 50% or greater, with no sensitising EGFR mutations or ALK translocations and who have undergone no previous systemic therapy are estimated to be eligible for treatment with pembrolizumab in 2017 (see Table 90 below). The steps followed to estimate these values are described below.

Table 90: Number of untreated, advanced NSCLC patients eligible for treatment with pembrolizumab in first line

	Year 1	Year 2	Year 3	Year 4	Year 5
	2017	2018	2019	2020	2021
Number of patients	1,447	1,453	1,459	1,464	1,470

The estimated number of NSCLC incident cases by stage in England was obtained for 2013 from the National Lung Cancer Audit (assuming that 94% of the cases registered in NLCA for England and Wales related to England).[73] To reflect the increase in the number of new diagnosed cases of NSCLC over time an annual incidence growth rate of 0.40% was applied.[225]

In 2017 12,441 new cases of NSCLC stage IV are expected.[73] Approximately 55% of these patients are expected to receive first line therapy (6,843 patients in total.[72] In total, 85.5% of these patients are estimated to have tumour samples that are assessable for PD-L1

expression and 30.2% of these are expected to have a PD-L1 tumour proportion score of 50% or greater.[5] Patients with NSCLC with no sensitising EGFR mutations or ALK translocations who have undergone no previous systemic therapy for metastatic disease are anticipated to be eligible for therapy with pembrolizumab in first line. The proportion of patients estimated to have no sensitising EGFR mutations or ALK translocations is 81.2%.[225]

Table 91: Estimates of incident population

	England	Sources
Proportion of NSCLC cases reported in NLCA that reflect those in England	94%	HSCIC (2014)[73]
NSCLC annual incidence growth rate	0.40%	Mavroudis-Chocholis et al (2015)[225]
Proportion of NSCLC patients that have squamous tumours	40%	Mavroudis-Chocholis et al (2015)[225]
Proportion of NSCLC patients that are EGFR/ALK positive mutations	Adenocarcinomas: - 19% EGFR positive - 6% ALK positive Squamous: - 3% EGFR positive - 5% ALK positive	Mavroudis-Chocholis et al (2015)[225]
Proportion of patients treated in 1L	55%	MSD Data on file (2015)[72]
Proportion of patients with assessable samples	85.5%	Reck et al (2016)[5]
Proportion of patients with PD-L1 positive expression (among those with assessable samples)	30.2%	Reck et al (2016) [5]

We have estimated the maximum number of patients eligible for pembrolizumab in 1st assuming that all eligible patients are treated with pembrolizumab in first line (see Table 90).

6.3 Assumptions that were made about current treatment options and uptake of technologies

The budget impact compares two alternative scenarios:

- The existing treatment scenario, reflecting SOC in current clinical practice (i.e. without pembrolizumab), where patients can be treated with a platinum-based chemotherapy or a pemetrexed combination, the latter only in case of non-squamous histology.
- The new treatment scenario (with pembrolizumab assumed to be used as part of clinical practice).

The main assumptions formulated to estimate the number of patients eligible to receive pembrolizumab in 1L are:

- The budget impact model considers the following costs: testing, treatment pre-progression, administration and management of AEs.
- A total of 11.6% of patients with NSCLC stage IV will be eligible for treatment with pembrolizumab in 1L.
- For each patient identified as a PD-L1 positive expresser in at least 50% of their tumour cells (and potentially eligible for treatment with pembrolizumab), 8.6 patients would need to be tested.
- Patients treated with pembrolizumab receive the anticipated licensed dose of 200 mg for an average of 205.73 days (i.e. for 9.8 cycles), as reported in KEYNOTE-024.
- The following inputs are based on outcomes from KEYNOTE-024:
    - The mean treatment duration (see Table 92)
    - The average number of vials per patient for SOC, which was based on the BSA of patients recruited at European sites (detailed in section 5.5.2).
    - The proportion of patients receiving the expected dose
- No patients are assumed to be treated through clinical trials
- Only the costs related to pre-progression is considered as part of the budget impact estimation (i.e. for simplification, it is assumed that after progression costs will be similar independent of the subsequent therapies administered).
- It is assumed that pembrolizumab is introduced in the market in 2017.

Table 92. Time on treatment and number of administrations

	Pembrolizumab 200 mg Q3W	SOC
Time on therapy (months)	6.76	3.97
Number of administrations (cycles)	9.80	5.75
Sources	KEYNOTE-024[21]	

6.4 Assumptions that were made about market shares in England

We have assumed that all eligible patients will get treatment with pembrolizumab in first line once pembrolizumab is introduced into the market, and after a positive recommendation by NICE. This reflects, therefore, the maximum number of patients that could be expected to receive pembrolizumab.

6.5 Other significant costs associated with treatment that may be of interest to commissioners

Technology costs and other significant costs associated with treatment with pembrolizumab are identical to those assumed in the cost-effectiveness model and are described in section 5.5.

6.6 Unit costs assumed and how they were calculated

All unit costs considered here estimate the annual budget to the NHS in England and are based upon the ones included in the economic in section 5.5.

6.7 Estimates of resource savings

See section 6.1.

6.8 State the estimated annual budget impact on the NHS in England.

The introduction of pembrolizumab to the market in England is expected to displace the use of SOC chemotherapy regimens in first line for the particular group of patients with advanced NSCLC and a PD-L1 tumour proportion score of 50% or greater. The estimated budget impact on the NHS in England of all PD-1 agents is presented in Table 93. This is presented with the PAS for pembrolizumab. MSD has not attempted to estimate the share of pembrolizumab in first line but rather has presented the potential maximum budget impact, assuming that all eligible patients would receive treatment with pembrolizumab.

Table 93: Estimated budget impact of pembrolizumab over 5 years (with PAS for pembrolizumab)

[redacted]

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

See section 6.1.

6.10 Highlight the main limitations within the budget impact analysis.

A number of assumptions were made in terms of proportion of patients treated in 1st line, which introduced uncertainty into the estimates here presented. Additionally, the model is based on a closed cohort of patients based on the eligible population presented in Table 90. As a limitation to this approach, there may be a small proportion of patients who are eligible for therapy and has not been considered in these projections. Furthermore, consideration of

the maximum amount of number of patients potentially treated with pembrolizumab in first line does not allow for an accurate estimation of the budget impact specifically related to pembrolizumab, since some patients may still get treated with some of the standard SOC regimens once pembrolizumab becomes available.

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Single technology appraisal

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

Dear [redacted],

The Evidence Review Group, Liverpool Reviews and Implementation Group, and the technical team at NICE have looked at the submission received on 18 October 2016 from Merck Sharp and 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 24 November 2016. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Helen Powell, Technical Lead (Helen.Powell@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

KEYNOTE-024: trial methodology

A1. **Priority request**: The statistical methods used to analyse overall survival (OS) and progression-free survival (PFS) data from the KEYNOTE-024 trial are only valid if failure hazards in both treatment arms are proportional over time. Please clarify whether any formal testing was undertaken to check whether OS and PFS hazards were proportional and, if testing was undertaken, please provide the results.

A2. **Priority request:** Page 86 of the company submission states that the two-stage adjustment method was not re-censored using the post-progression treatment estimate because it would provide less reliable results. However, this introduces bias in the analysis. Please provide results from the two-stage adjustment including re-censoring, for comparison with the results in the submission.

A3. Page 86 of the company submission states that the two-stage adjustment model was estimated after adjustment for other covariates. Please provide details of the other covariates that were adjusted for in the model.

A4. Phase III trial data are usually analysed using two-sided hypothesis testing. Please justify using one-sided hypothesis testing in KEYNOTE-024. Please also justify why the sample size calculation was carried out using a one-sided p-value; the sample size required is likely to be smaller as a result of using a one-sided hypothesis test.

A5. Table 8 of the company submission includes a list of the drug regimens used in the KEYNOTE-024 trial. Patients with non-squamous histology who were treated with a platinum doublet chemotherapy (PDC) that included pemetrexed or paclitaxel were eligible to receive maintenance treatment with pemetrexed. Patients treated with gemcitabine were not eligible to receive maintenance treatment with pemetrexed. Please explain the rationale for the restriction of pemetrexed maintenance to the treatment of patients with non-squamous histology treated with PDC that included pemetrexed or paclitaxel.

KEYNOTE-024: trial results

A6. Please provide results of the primary endpoint (PFS) from the KEYNOTE-024 trial that are based on investigator assessment.

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A7. Please provide the p-values for the interaction tests in the subgroup analyses presented in Figures 15 and 16 of the company submission (forest plots of PFS and OS hazard ratio by subgroup factor, KEYNOTE-024 trial).

A8. Please provide details of any crossover or subsequent therapies received by patients in the intervention and control arms of the KEYNOTE-024 trial. Please provide the number (and proportion) of patients who received subsequent treatment on progression for each arm, with a breakdown of subsequent treatments received. Please provide details, using the table provided, of the number of patients switching to pembrolizumab treatment after disease progression in the standard of care (SoC) arm, stratified by the number of weeks between time of disease progression and the time of treatment switch.

Time to treatment switch from disease progression	**Standard of Care (SoC) arm**
	N
0- 1 weeks	
> 1 to 2 weeks	
> 2 to 3 weeks	
> 3 to 4 weeks	
…etc	

Network meta-analyses (NMA)

A9. **Priority request:** Please provide details of the feasibility assessment that was undertaken to ascertain whether it was appropriate to conduct a NMA.

A10. **Priority request:** Please clarify whether the OS data from the KEYNOTE-024 trial that were included in the NMA were adjusted or unadjusted for treatment switching. If the data were adjusted, please provide the results of the NMA for OS using unadjusted data. If the data were unadjusted, please provide the results of the NMA for OS using adjusted data.

A11. Please clarify whether, when conducting the NMA, any adjustments for multi-arm trials were made and what criteria were used to select the arms that were included in the NMA.

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Section B: Clarification on cost-effectiveness data

Kaplan-Meier data

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

Trial data set: KEYNOTE-024
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 B2
Population: ITT population including all patients lost to follow-up or withdrawing from the trial

a. Time to death from any cause (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 SoC arm of the trial stratified by whether patients crossed over and received pembrolizumab

c. Time to study treatment discontinuation Kaplan-Meier analysis.

B2. Priority request: Please provide the Kaplan-Meier analyses listed in a and b below for the following three populations:

1. *Rank-preserving structural failure time (RPSFT) adjusted population*
2. *Two-stage adjusted population (including re-censoring, see question A2)*
3. *Inverse probability of censoring weighting (IPCW) adjusted population*

To the following specifications:

Trial data set: KEYNOTE-024
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

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a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (pembrolizumab versus SoC)

b. Time to study treatment discontinuation Kaplan-Meier analysis

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

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Utility data

B3. Priority request: Please complete the table below using data collected during the KEYNOTE-024 trial and valued using the UK time trade off (TTO) value set.

Utility values	Pembrolizumab		Standard of care		Average	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline						
>360 days to death						
>180-360 days to death						
30-180 days to death						
<30 days to death						

Adverse events

B4. Priority request. Please provide tables showing Grade 3+ adverse events occurring in greater than 5% of patients, using data from the most recent data cut of the KEYNOTE-024 trial. Please provide the number of episodes per patient affected and mean duration per episode in days, stratified by treatment arm.

Subgroups

B5. 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 staining ≥50%). The NICE appraisal committee will appraise the technology within the full boundaries of its marketing authorisation in untreated metastatic NSCLC. In the event that the marketing authorisation includes tumours with weak PD-L1 expression, please comment on whether pembrolizumab is likely have similar clinical and cost-effectiveness regardless of the level of PD-L1 expression (strong positive or weak positive).

Comparators

B6. Single agent chemotherapy is a comparator in the final scope issued by NICE, but appears to have been excluded from the company's NMA and economic model. Please provide full justification for excluding this comparator.

Section C: Textual clarifications and additional points

C1. Please clarify why the results in Table 85 and Table 86 of the company submission do not match the results provided in the 'Results' sheet of the model and identify which are the correct results.

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C2. Some of the confidentiality marking is not in line with the instructions on marking confidential information in the NICE guide to the processes of technology appraisals (sections 3.1.24–3.1.29). Some of the confidentiality marking requires lifting to enable the committee to see the evidential basis of the decision and to keep the amount of confidential data to an absolute minimum. A separate letter will be sent with specific requests regarding this.

MSD
Hertford Road
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EN11 9BU, UK
Telephone +44 (0)1992 452644
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24th November 2016

Dear Helen,

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

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

KEYNOTE-024: trial methodology

A1. **Priority request**: The statistical methods used to analyse overall survival (OS) and progression-free survival (PFS) data from the KEYNOTE-024 trial are only valid if failure hazards in both treatment arms are proportional over time. Please clarify whether any formal testing was undertaken to check whether OS and PFS hazards were proportional and, if testing was undertaken, please provide the results.

We can confirm that no formal testing was undertaken to check whether OS and PFS hazards were proportional, as the KEYNOTE-024 statistical analysis plan did not pre-specify any tests for checking the proportional hazards assumption.

Section 5.3 of the submission document explains the rationale for applying time varying hazard ratios in the economic modelling: Standard parametric curves were initially fitted to the full KM OS data. When the PH assumption was tested, this did not hold, based on the cumulative hazard plot (see Figure 27 of the submission document), the log-cumulative hazard plot (see Figure 28 of the submission document) and the Schoenfeld residuals plot (see Figure 29 of the submission document). As shown in Figure 28 of the submission document, the two lines crossed towards the beginning of the log-cumulative hazard plot. Additionally, for the Schoenfeld residuals plot (see Figure 29 of the submission document), there is a clear deviation from the y=0 line. Therefore, separate models were subsequently fitted based on the individual patient data from KEYNOTE-024.

A2. **Priority request:** Page 86 of the company submission states that the two-stage adjustment method was not re-censored using the post-progression treatment estimate because it would provide less reliable results. However, this introduces bias in the analysis. Please provide results from the two-stage adjustment including re-censoring, for comparison with the results in the submission.

Please note that Tables 20 and 22 in the submission document (re-numbered below as **Table** 1 and Table 2 for this response) provided results of OS analyses and median OS using the simplified two-stage correction method, with re-censoring. The requested information has been highlighted in red text and the tables have been provided again below for ease of reference.

Table 1: Summary Results of OS Analyses (direct switching)

Crossover correction method	Pembrolizumab 200 mg mg Q3W vs. SOC		
	Hazard Ratio	95% CI	P-value (2-sided)
ITT	0.60	(0.41; 0.89)	0.0009
Simplified two-stage (no re-censoring)[$]	0.50	(0.34; 0.76)	0.0009*

RPSFT	0.57	(0.32; 0.86)	0.0009*
IPCW	0.55	(0.34; 0.87)	0.0150

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

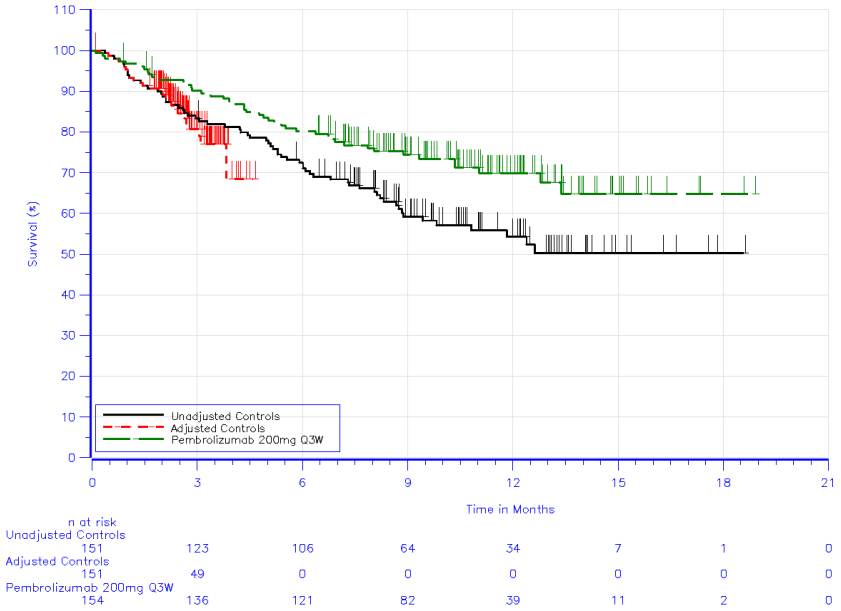
$When Two-stage (with re-censoring) crossover correction method is applied, resultant HR = 0.44 (95% CI: 0.20, 1.07); p = 0.0094

Table 2: Analysis of median OS using Two-stage, RPSFT and IPCW methods

Crossover correction method	Median OS (months) (95% CI)
SOC (no crossover correction)	Not Reached (9.4 , ---)
SOC - Simplified two-stage correction (no re-censoring)*	12.6 (7.6, .)
SOC – RPSFT correction	Not Reached (6.9, ---)
SOC – IPCW correction	11.8 (9.8 , ---)
Pembrolizumab 200 mg Q3W	Not Reached (--- , ---)
**SOC- Two stage correction (with re-censoring) Median OS = Not Reached (95% CI: 3.8, .)*	

The Kaplan-Meier estimates of OS depicting the estimation of treatment effect with the re-censoring procedure applied is provided below (Figure 1):

Figure 1: Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using 2-stage analysis - ITT Population



(Database Cutoff Date: 09 MAY 2016)

A3. Page 86 of the company submission states that the two-stage adjustment model was estimated after adjustment for other covariates. Please provide details of the other covariates that were adjusted for in the model.

The assumption that patients are at a similar stage of disease progression and that the switching and non-switching groups are similar was assessed by comparing the characteristics of switchers and non-switching patients amongst patients from the control arm who were considered eligible for switch-over. This involved both variables measured at baseline and those measured at the secondary baseline. The following variables were described and compared between the two groups:

- At baseline
    - Clinically relevant variables:
        - Age
        - Sex
        - Metastatic staging (M1b/others)
    - Other important characteristics:
        - Histology (squamous/non-squamous)
        - Geographic region (East Asian/non-East Asian)
        - Smoking status (3 categories: current/former/never)
- At secondary baseline
    - Clinically relevant variables:
        - ECOG performance status (0/1 or higher),
        - Tumour size
        - Time to Progression
    - Other important characteristics:
        - BMI (Body mass index)
        - Haemoglobin

To assess ECOG, tumour size, BMI and haemoglobin at the time of switch, the last measurement of each variable before or at the time of progression (+3 days) were used as secondary baseline assessments.

A4. Phase III trial data are usually analysed using two-sided hypothesis testing. Please justify using one-sided hypothesis testing in KEYNOTE-024. Please also justify why the sample size calculation was carried out using a one-sided p-value; the sample size required is likely to be smaller as a result of using a one-sided hypothesis test.

One-sided test at 0.025 type I error rate is asymptotically equivalent to two-sided test at 0.05 type I error rate in the case of log-rank test statistics. In the context of the trial where direction of the treatment effect is expected to favour the experimental drug, using one-sided test at 0.025 was statistically sound and would not result in smaller sample size.

A5. Table 8 of the company submission includes a list of the drug regimens used in the KEYNOTE-024 trial. Patients with non-squamous histology who were treated with a platinum doublet chemotherapy (PDC) that included pemetrexed or paclitaxel were eligible to receive maintenance treatment with pemetrexed. Patients treated with gemcitabine were not eligible to receive maintenance treatment with pemetrexed. Please explain the rationale for the restriction of pemetrexed maintenance to the treatment of patients with non-squamous histology treated with PDC that included pemetrexed or paclitaxel.

When designing the study it was assumed that the majority of the gemcitabine/platinum combination therapy regimen would be used for patients with squamous histologies only, for which pemetrexed maintenance is not permitted.

Investigators were aware that pemetrexed maintenance was not permitted for patients assigned to receive gemcitabine/platinum combinations. Because multiple platinum doublet options were available, investigators could have administered a pemetrexed/platinum or carboplatin/paclitaxel combination therapy regimen, both of which permitted subsequent pemetrexed maintenance therapy.

KEYNOTE-024: trial results

A6. Please provide results of the primary endpoint (PFS) from the KEYNOTE-024 trial that are based on investigator assessment.

As per the KEYNOTE-024 study protocol, sensitivity analyses were performed for comparison of PFS based on investigator's assessment. Please find below the results of the evaluation of PFS by investigator review (Table 3 and Figure 2).

Table 3: Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) - ITT Population

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]	[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 Cut-off Date: 09MAY2016)

Figure 2: Kaplan-Meier of Progression-Free-Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) ITT population

(Database Cutoff Date: 09MAY2016)

PFS by investigator assessment was assessed using the same RECIST criteria as the PFS by BICR assessment. As BICR is the only recognised assessment method by which to assess PFS from a regulatory stand point, this was the rationale why BICR assessment was included as an endpoint rather than the investigator assessment. PFS assessed per RECIST by BICR is also considered more robust than PFS based on investigator assessment, especially for an open label trial.

A7. Please provide the p-values for the interaction tests in the subgroup analyses presented in Figures 15 and 16 of the company submission (forest plots of PFS and OS hazard ratio by subgroup factor, KEYNOTE-024 trial).

Table 4 and
Table 5 presented below provide the requested p-values for the interaction tests in the subgroup analyses presented in Figures 15 and 16 of the submission document:

Table 4: Analysis of Progression-Free Survival (PFS) based on IRC assessment per RECIST 1.1 for subgroups (Intention-to-Treat Population)

Study: P024	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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender								
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race								
Non-White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG status								
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic region of enrolling site								
Non-East Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
East Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology								
Squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status								
Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of Brain Metastases								
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator's choice of standard of care chemotherapy								
Platinum/Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Platinum Doublets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Number of patients: all-patients-as-treated

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: 09MAY2016)

Table 5: Analysis of Overall Survival (OS) for subgroups (Intention-to-Treat Population)

Study: P024	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]							
≥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: all-patients-as-treated

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: 09MAY2016)

A8. Please provide details of any crossover or subsequent therapies received by patients in the intervention and control arms of the KEYNOTE-024 trial. Please provide the number (and proportion) of patients who received subsequent treatment on progression for each arm, with a breakdown of subsequent treatments received.

Table 6 below provides details of subsequent therapies received by patients in the intervention and control arms of the KEYNOTE-024 trial.

This table does not include within trial crossover from the standard of care (SOC) arm to pembrolizumab, which consisted of 66 patients who crossed over following SOC to subsequently receive pembrolizumab as second-line therapy.

Table 6: Summary of New Oncologic Therapies after Discontinuing from Study Treatment Intention-to-Treat Population

	Pembrolizumab (N=154) n (%)	SoC (N=151) n (%)	Pembrolizumab + SoC Pooled (N=305) n (%)
With one or more new Systemic Therapies	**35**	**25**	**60**
2L	**35**	**14**	**49**
bevacizumab + pemetrexed	1 (2.9%)	0 (0.0%)	1 (2.0%)
cabozantinib	1 (2.9%)	0 (0.0%)	1 (2.0%)
carboplatin + gemcitabine	4 (11.4%)	1 (7.1%)	5 (10.2%)
carboplatin + paclitaxel	3 (8.6%)	1 (7.1%)	4 (8.2%)
carboplatin + paclitaxel + bevacizumab	4 (11.4%)	0 (0.0%)	4 (8.2%)
carboplatin + pemetrexed	11 (31.4%)	0 (0.0%)	11 (22.4%)
carboplatin + pemetrexed + bevacizumab	1 (2.9%)	0 (0.0%)	1 (2.0%)
carboplatin + vinorelbine	1 (2.9%)	0 (0.0%)	1 (2.0%)
cisplatin + gemcitabine	2 (5.7%)	0 (0.0%)	2 (4.1%)
cisplatin + pemetrexed	5 (14.3%)	0 (0.0%)	5 (10.2%)
cisplatin + pemetrexed + bevacizumab	1 (2.9%)	0 (0.0%)	1 (2.0%)
docetaxel	0 (0.0%)	1 (7.1%)	1 (2.0%)
nivolumab	0 (0.0%)	5 (35.7%)	5 (10.2%)
paclitaxel	0 (0.0%)	1 (7.1%)	1 (2.0%)
pembrolizumab	0 (0.0%)	3 (21.4%)	3 (6.1%)
pemetrexed	0 (0.0%)	2 (14.3%)	2 (4.1%)
platinum + pemetrexed	1 (2.9%)	0 (0.0%)	1 (2.0%)
2M	**8**	**1**	**9**
bevacizumab	1 (12.5%)	0 (0.0%)	1 (11.1%)
bevacizumab + pemetrexed	1 (12.5%)	0 (0.0%)	1 (11.1%)
erlotinib	1 (12.5%)	1 (100.0%)	2 (22.2%)
pemetrexed	5 (62.5%)	0 (0.0%)	5 (55.6%)
3L	**2**	**12**	**14**
carboplatin + paclitaxel	0 (0.0%)	1 (8.3%)	1 (7.1%)

carboplatin + pemetrexed + bevacizumab	1 (50.0%)	0 (0.0%)	1 (7.1%)
dexamethasone + docetaxel	0 (0.0%)	1 (8.3%)	1 (7.1%)
dexamethasone + docetaxel + nintedanib	1 (50.0%)	0 (0.0%)	1 (7.1%)
docetaxel	0 (0.0%)	8 (66.7%)	8 (57.1%)
luminespib	0 (0.0%)	1 (8.3%)	1 (7.1%)
nivolumab	0 (0.0%)	1 (8.3%)	1 (7.1%)
4L	**0**	**3**	**3**
cabozantinib	0	1 (33.3%)	1 (33.3%)
gemcitabine	0	2 (66.7%)	2 (66.7%)

Please provide details, using the table provided, of the number of patients switching to pembrolizumab treatment after disease progression in the standard of care (SoC) arm, stratified by the number of weeks between time of disease progression and the time of treatment switch.

In KEYNOTE-024, 151 patients were randomised to the SOC control arm. A total of 66 out of 151 patients (43.7%) switched over to pembrolizumab 200 mg Q3W. Table 7 summarises the number of patients by weekly intervals of time to switch-over from disease progression. Half of the patients switched-over within 4 weeks following disease progression and most of them (n=54) switched-over within 3 months after disease progression.

Time to switch-over from disease progression is categorised in weekly intervals. The number of patients who switched-over within each interval is displayed below.

Table 7: Time to switch-over from disease progression (switching-over patients from SOC arm to pembrolizumab 200 mg Q3W)

Study: KEYNOTE-024 **Time to Switch over from Disease Progression (weeks)**	**Switchers from SOC to Pembrolizumab 200 mg Q3W** **N = 66**
<=1 week	0
>1 to 2 weeks	12
>2 to 3 weeks	12
>3 to 4 weeks	12
>4 to 5 weeks	8
>5 to 6 weeks	2
>6 to 7 weeks	2
>7 to 8 weeks	1
>8 to 9 weeks	0
>9 to 10 weeks	0
>10 to 11 weeks	1
>11 to 12 weeks	4
>=12 weeks	9
Missing (No Disease Progression reported)	3
(Database Cutoff Date: 09MAY2016).	

Network meta-analyses (NMA)

A9. Priority request: Please provide details of the feasibility assessment that was undertaken to ascertain whether it was appropriate to conduct a NMA.

Our submission document stated that in order to gauge the appropriateness of proceeding with an NMA, a feasibility assessment was undertaken which included: 1) an assessment of whether the RCT evidence for the interventions of interest formed one evidence network and 2) an assessment of the distribution of study and patient characteristics that may have affected treatment effects across direct comparisons of the evidence networks.

The scope of the feasibility assessment and data availability were described within section 4.10.7 of the submission document (populations in the included trials), and the evidence network and analyses generated following feasibility assessment was described in section 4.10.14 of the submission document (Networks of evidence). For ease of reference, the relevant sections have been described again below:

The population of interest includes first-line patients with advanced or metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥ 50%), and are EGFR wild-type, and ALK negative. As no trial to date (other than KEYNOTE-024) has been conducted in this set of patients, the population in scope for this analysis includes all patients with advanced or metastatic NSCLC other than those in trials in exclusively EGFR or ALK positive patients, under the assumption that the included interventions of interest do not vary in efficacy based on EGFR or ALK status.

The primary population of interest was the population of all-comers (all histologies combined). Analyses concerning the non-squamous/adenocarcinoma subgroup and squamous subgroup are presented in Appendix 18 of the submission document.

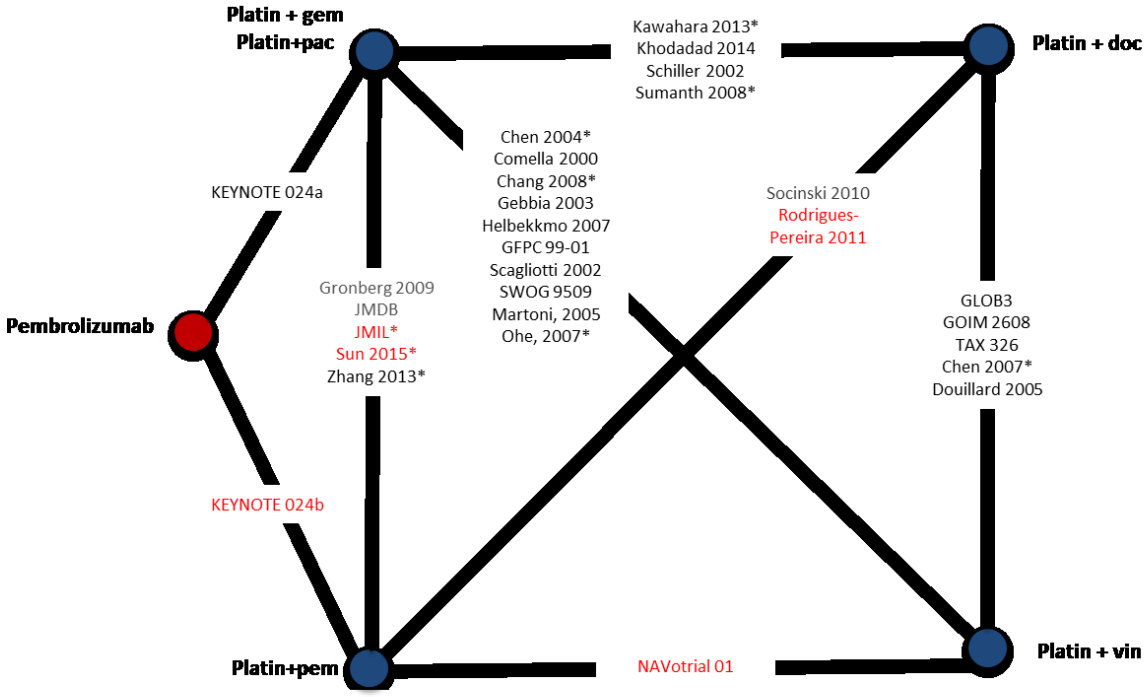
Data for KEYNOTE-024 was obtained from the relevant clinical study report and study publication; the construction of analysis scenarios was limited by the availability of robust data. All outcomes of KEYNOTE-024 were available for the comparison of pembrolizumab versus SOC, which combined platinum + pemetrexed with platinum + gemcitabine and platinum + paclitaxel. Data was also made available stratified by pre-randomisation SOC assignment: pemetrexed-containing regimen versus non-pemetrexed-containing regimen. In terms of histology, results for non-squamous and squamous histology were only available for pembrolizumab versus the combined SOC regimens. However, all patients who were assigned to platinum+pemetrexed were non-squamous.

In order to combine pembrolizumab to the network of evidence spanned by the other interventions of interest, the populations of KEYNOTE-024 considered in the all-comers network were:

- KEYNOTE-024a: pembrolizumab versus non-pemetrexed-containing SOC, mixed histology
- KEYNOTE-024b: pembrolizumab versus pemetrexed-containing SOC, all non-squamous

Given the scope of the NMA, the resulting network of evidence is shown in Figure 3. The comparability of the included trials was assessed in terms of histology and other potential prognostic factors. One trial (Khodadad 2014) was conducted exclusively in patients with ECOG 2; as KEYNOTE-024 allowed only patients with ECOG 0 or 1, it was decided to remove Khodadad 2014 from the analysis set.

Figure 3: Complete network of evidence



Trials in red: non-squamous
Trials in black: all histologies
Trials with 100% Asian patients denoted with *
KEYNOTE 024a: Patients assigned to platinum + gem or platinum + pac before randomization
KEYNOTE 024b: Patients assigned to platinum + pemetrexed before randomization (non-squamous)

- *All-histologies network*

In order to assess the interventions of interest in a population of mixed histology, Figure 3 was used as the network of evidence. KEYNOTE-024a and KEYNOTE-024b were included separately, as this allowed for pemetrexed-containing SOC regimens to be considered as separate from non-pemetrexed-containing regimens. In order to adjust for differences in the distribution of histology between trials, a covariate was included which represented the proportion of non-squamous patients in each trial. This covariate was centered at the proportion of non-squamous patients in KEYNOTE-024, in order to estimate relative treatment effects in a population that reflects KEYNOTE-024.

A10. Priority request: Please clarify whether the OS data from the KEYNOTE-024 trial that were included in the NMA were adjusted or unadjusted for treatment switching. If the data were adjusted, please provide the results of the NMA for OS using unadjusted data. If the data were unadjusted, please provide the results of the NMA for OS using adjusted data.

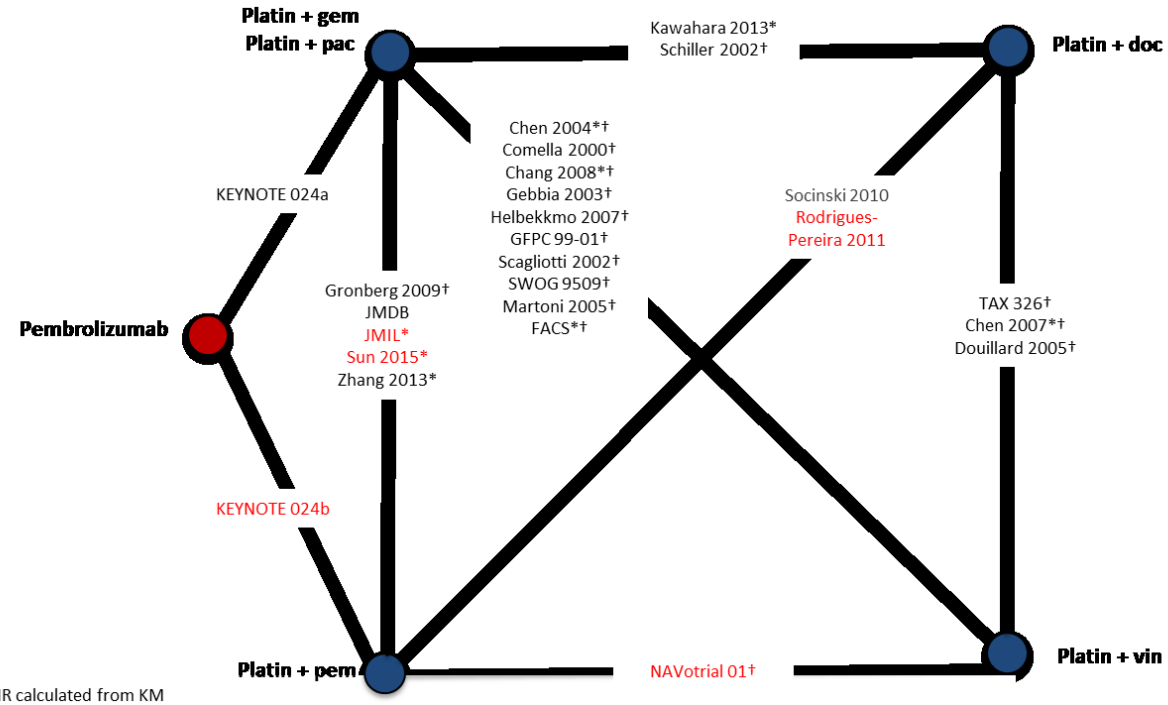
We can confirm that the NMA presented in our submission included OS data from KEYNOTE-024 that were unadjusted for treatment switching.

An alternative analysis has been conducted for OS, incorporating the 2-stage model for the arm of KEYNOTE-024 assigned to pemetrexed-containing SOC prior to randomisation (i.e. KEYNOTE-024b; see Figure 4). In this model, the survival time of patients who received SOC but then switched to pembrolizumab was adjusted using an acceleration factor. Given the small sample size of comparison group for the 1st stage model, the adjustment using the simplified 2-stage model could not be performed in the subgroup of patients who received a treatment regimen without pemetrexed, so the unadjusted results from KEYNOTE-024a were used.

Figure 4 presents the network of evidence for OS (assuming constant HRs) in the all-histologies population under this alternative analysis; the corresponding data is shown in Table 8. The results of the fixed-effects NMA are given in Table 9. Pembrolizumab offered better OS than all other interventions of interest, and was the only intervention better than the reference treatment of platinum + gemcitabine/paclitaxel (HR 0.54, 95% CrI 0.35-0.82). In addition, platinum + pemetrexed showed a lower HR than platinum + vinorelbine. No other comparisons between platinum-based regimens were statistically meaningful. Under the random-effects model (Table 10), similar results were drawn, although the comparison between platinum + vinorelbine and platinum + pemetrexed was not statistically meaningful.

In order to allow HRs to vary over time, an NMA was performed using digitised KM curves (network presented in Supplementary Appendix 1; Figure 1). Of the models fit to the data, the most parsimonious was the 2nd order FP model with p1=1 and p2=0 (Supplementary Appendix 1; Table 1). Under this model, pembrolizumab is statistically better than platinum+gemcitabine/paclitaxel and all other interventions of interest after approximately 4 months (Supplementary Appendix 1; Figure 4). The HRs for each intervention do not change appreciably over time; therefore the assumption of constant HRs is reasonable in this population for OS. Results of the random-effects models were similar to those of the fixed-effect analysis, although the resulting credible intervals (CrIs) were wider. The best-fitting models were the 2nd order FP models with p1=0, p2=1 and p1=1, p2=0 (Supplementary Appendix 1; Figures 7 and 8).

Figure 4: Network of evidence for overall survival (constant HRs); all histologies – alternative analysis 1



†HR calculated from KM
Trials in red: non-squamous
Trials in black: all histologies
Trials with 100% Asian patients denoted with *
KEYNOTE 024a: Patients assigned to platinum + gem or platinum + pac before randomization
KEYNOTE 024b: Patients assigned to platinum + pemetrexed before randomization (non-squamous)

Table 8: Constant hazard ratios for overall survival; all histologies – alternative analysis 1

Study	Reference	Intervention	HR	logHR(SE)
Chang 2008	Platin + gem or pac	Platin + vin	1.23	0.21 (0.25)
Chen 2004	Platin + gem or pac	Platin + vin	1.05	0.05 (0.19)
Chen 2007	Platin + doc	Platin + vin	1.08	0.08 (0.27)
Comella 2000	Platin + gem or pac	Platin + vin	1.27	0.24 (0.22)
Douillard 2005	Platin + doc	Platin + vin	1.14	0.13 (0.14)
Gebbia 2003	Platin + gem or pac	Platin + vin	0.84	-0.17 (0.12)
GFPC 99-01	Platin + gem or pac	Platin + vin	1.05	0.05 (0.22)
Gronberg 2009	Platin + gem or pac	Platin + pem	1.02	0.02 (0.1)
Helbekkmo 2007	Platin + gem or pac	Platin + vin	0.98	-0.02 (0.1)
JMDB	Platin + gem or pac	Platin + pem	0.94	-0.06 (0.06)
JMIL	Platin + gem or pac	Platin + pem	1.00	0 (0.15)
Kawahara 2013	Platin + gem or pac	Platin + doc	0.77	-0.26 (0.25)
KEYNOTE 024a	Platin + gem or pac	Pembrolizumab	0.42	-0.87 (0.35)
KEYNOTE 024b	Platin + pem	Pembrolizumab	0.62	-0.48 (0.27)
Martoni 2005	Platin + gem or pac	Platin + vin	0.94	-0.06 (0.12)
NAVotrial 01	Platin + pem	Platin + vin	1.08	0.08 (0.19)
FACS	Platin + gem or pac	Platin + vin	1.19	0.17 (0.12)

Study	Reference	Intervention	HR	logHR(SE)
Rodrigues-Pereira 2011	Platin + pem	Platin + doc	0.99	-0.01 (0.17)
Scagliotti 2002	Platin + gem or pac	Platin + vin	1.38	0.32 (0.09)
Schiller 2002	Platin + gem or pac	Platin + doc	1.01	0.01 (0.07)
Socinski 2010	Platin + pem	Platin + doc	1.49	0.4 (0.2)
Sun 2015	Platin + gem or pac	Platin + pem	0.88	-0.13 (0.17)
SWOG 9509	Platin + gem or pac	Platin + vin	1.06	0.06 (0.11)
TAX 326	Platin + doc	Platin + vin	1.03	0.03 (0.06)
Zhang 2013	Platin + gem or pac	Platin + pem	1.09	0.09 (0.16)

Table 9: Results of fixed effects network meta-analysis based on constant hazard ratio assumption; overall survival; all-histologies; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals – alternative analysis 1

Platin + gem or pac	1.03 (0.95, 1.13)	0.96 (0.87, 1.06)	**0.90 (0.82, 0.99)**	**1.87 (1.22, 2.85)**
0.97 (0.89, 1.05)	**Platin + pem**	0.93 (0.83, 1.04)	**0.87 (0.79, 0.97)**	**1.81 (1.19, 2.73)**
1.04 (0.94, 1.15)	1.07 (0.96, 1.20)	**Platin + doc**	0.94 (0.86, 1.03)	**1.94 (1.27, 2.96)**
1.11 (1.01, 1.22)	**1.15 (1.03, 1.27)**	1.07 (0.97, 1.17)	**Platin + vin**	**2.07 (1.36, 3.14)**
0.54 (0.35, 0.82)	**0.55 (0.37, 0.84)**	**0.52 (0.34, 0.79)**	**0.48 (0.32, 0.74)**	**Pembro**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 30.26; Deviance: 26.25

Table 10: Results of random-effects network meta-analysis based on constant hazard ratio assumption; overall survival; all-histologies; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals – alternative analysis 1

Platin + gem or pac	1.03 (0.91, 1.16)	0.96 (0.83, 1.10)	0.90 (0.79, 1.01)	**1.86 (1.18, 2.95)**
0.97 (0.86, 1.10)	**Platin + pem**	0.93 (0.80, 1.09)	0.87 (0.75, 1.00)	**1.81 (1.16, 2.84)**
1.04 (0.91, 1.20)	1.07 (0.92, 1.25)	**Platin + doc**	0.93 (0.82, 1.06)	**1.94 (1.22, 3.07)**
1.12 (0.99, 1.27)	1.15 (1.00, 1.33)	1.07 (0.95, 1.22)	**Platin + vin**	**2.08 (1.32, 3.29)**
0.54 (0.34, 0.85)	**0.55 (0.35, 0.86)**	**0.52 (0.33, 0.82)**	**0.48 (0.30, 0.76)**	**Pembro**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 31.56; Deviance: 22.51; SD: 0.08

A11. Please clarify whether, when conducting the NMA, any adjustments for multi-arm trials were made and what criteria were used to select the arms that were included in the NMA.

The standard OpenBUGS code did include adjustment for multi-arm trials. For any individual trial, only arms representing interventions of interest were included in the NMA. No trial contributed more than two nodes to the analysis.

Section B: Clarification on cost-effectiveness data

Kaplan-Meier data

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

Trial data set:	*KEYNOTE-024*
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 B2*
Population:	*ITT population including all patients lost to follow-up or withdrawing from the trial*

a. Time to death from any cause (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 SoC arm of the trial stratified by whether patients crossed over and received pembrolizumab

c. Time to study treatment discontinuation Kaplan-Meier analysis.

The requested analyses are presented in Tables 11 to 16.

In the primary analyses in KEYNOTE-024, patients without documented death at the time of the final analyses were censored at the date of last follow-up if it occurred before the data cut-off; otherwise, patients were censored at the database cut-off date.

We consider this approach to be appropriate given that the date of censoring is based on a confirmed OS status, rather than on an assumed OS status at the time of data cut-off.

The consequence of applying the alternative censoring rule requested by the ERG is that, as noted below, it will marginally modify the OS benefit in favour of the comparator (SOC) arm, at the expense of disregarding confirmed OS data.

By definition, the number of events and censored observations remain unchanged as compared to the primary censoring rule defined in the CSR [redacted]

[redacted]. A full report, describing the methodology and results when applying the altenative censoring rule, is provided as an appendix (Appendix 2) to this response document.

Table 11. Time to death from any cause (OS) KM – pembrolizumab

[Please see Table 11 presented in Appendix 3 (see: 'MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'OS ITT – Pembro']

Table 12. Time to death from any cause (OS) KM – SOC

[Please see Table 12 presented in Appendix 3 (see: 'MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'OS ITT – SOC']

Table 13. Time to death from any cause (OS) KM – SOC stratified: patients who crossed over to pembrolizumab

[Please see Table 13 presented in Appendix 3 (see: 'MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'OS ITT – SOC switch']

Table 14. Time to death from any cause (OS) KM – SOC stratified: patients who did not crossed over to pembrolizumab

[Please see Table 14 presented in Appendix 3 (see: 'MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'OS ITT – SOC no switch']

Table 15. Time to study treatment discontinuation KM -pembrolizumab

[Please see Table 15 presented in Appendix 3 (see: 'MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'TTD – Pembro']

Table 16. Time to study treatment discontinuation - SoC

[Please see Table 15 presented in Appendix 3 (see: 'MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'TTD – SOC']

B2. Priority request: Please provide the Kaplan-Meier analyses listed in a and b below for the following three populations:

1. *Rank-preserving structural failure time (RPSFT) adjusted population*
2. *Two-stage adjusted population (including re-censoring, see question A2)*
3. *Inverse probability of censoring weighting (IPCW) adjusted population*

To the following specifications:

Trial data set: KEYNOTE-024

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*

a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (pembrolizumab versus SoC)

b. Time to study treatment discontinuation Kaplan-Meier analysis

Table 17. RPSFT- adjusted OS: Time to death from any cause (OS) KM – pembrolizumab

[Please see Table 17 presented in Appendix 3 (see: '(MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'RPSFT - Pembro']

Table 18. RPSFT- adjusted OS: Time to death from any cause (OS) KM - SOC

[Please see Table 18 presented in Appendix 3 (see: '(MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'RPSFT - SOC']

Table 19. Two-stage- adjusted OS: Time to death from any cause (OS) KM – pembrolizumab

[Please see Table 19 presented in Appendix 3 (see: '(MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: '2-stage - Pembro']

Table 20. Two-stage - adjusted OS: Time to death from any cause (OS) KM – SOC

[Please see Table 20 presented in Appendix 3 (see: '(MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: '2-stage - Pembro']

Table 21. IPCW- adjusted OS: Time to death from any cause (OS) KM – pembrolizumab

[Please see Table 21 presented in Appendix 3 (see: '(MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'IPCW - Pembro']

Table 22. IPCW- adjusted OS: Time to death from any cause (OS) KM – SOC

[Please see Table 22 presented in Appendix 3 (see: '(MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'IPCW - SOC']

Table 23. Time to study treatment discontinuation KM – pembrolizumab

[Please see Table 15 presented in Appendix 3 (see: '(MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'TTD – Pembro']

Table 24. Time to study treatment discontinuation KM - SOC

[Please see Table 15 presented in Appendix 3 (see: '(MS)D response - ID990 pembrolizumab clarification letter - Appendix 3 - Tables B1 & B2', worksheet: 'TTD – SOC']

Utility data

B3. Priority request: Please complete the table below using data collected during the KEYNOTE-024 trial and valued using the UK time trade off (TTO) value set.

The table has been completed as requested:

Utility values	Pembrolizumab		Standard of care		Average	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	144	0.72 (0.242)	139	0.71 (0.214)	283	0.716(0.275)
>360 days to death	32	0.796(0.258)	22	0.828(0.133)	54	0.808(0.217)
>180-360 days to death	10	0.735(0.182)	16	0.699(0.189)	26	0.712(0.186)
30-180 days to death	27	0.555(0.331)	41	0.622(0.297)	68	0.598(0.311)
<30 days to death	9	0.574(0.297)	12	0.410(0.373)	21	0.480(0.344)

N = Number of patients with at least one non-missing record

Please note this information was presented as part of the submission (see Tables 28 and 61 in the original submission).

Adverse events

B4. Priority request. Please provide tables showing Grade 3+ adverse events occurring in greater than 5% of patients, using data from the most recent data cut of the KEYNOTE-024 trial. Please provide the number of episodes per patient affected and mean duration per episode in days, stratified by treatment arm.

Table 25 summarises the incidence, average number of episodes and average duration of episodes for grade 3-5 adverse events occurring at an incidence of at least 5% in one of the treatment groups. The number and percentage of patients with at least one episode is provided. The number of episodes by patient is summarised by treatment group using means and standard errors. Duration of an episode is also summarised by treatment group using means and standard errors. For patients with multiple episodes of the same adverse event, the average duration has first been calculated within the patient.

Overall, more patients in the SOC treatment arm experienced grade 3-5 adverse events as compared to patients in the pembrolizumab treatment arm (72.7% versus 53.2%, respectively). No grade 3-5 adverse event occurred in the pembrolizumab group at an incidence greater than 5%. In the SOC treatment arm, most frequently grade 3 to 5 adverse events were anaemia (23.3%) and neutropenia (14.4%).

Table 25: Subjects with Grade 3-5 Adverse Events by decreasing incidence (incidence >5% in one or more treatment groups) (ASaT Population)

	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 adverse event	82	(53.2)	2.1 (0.2)	75.0 (12.8)	109	(72.7)	2.7 (0.2)	114.4 (11.5)	191	(62.8)	2.4 (0.1)	97.5 (8.7)
Anaemia	7	(4.5)	1.4 (0.4)	105.1 (48.6)	35	(23.3)	1.1 (0.0)	211.0 (26.7)	42	(13.8)	1.1 (0.1)	193.4 (24.2)
Neutropenia	0	(0.0)	/ (/)	/ (/)	21	(14.0)	1.7 (0.2)	30.2 (14.6)	21	(6.9)	1.7 (0.2)	30.2 (14.6)
Pneumonia	3	(1.9)	1.3 (0.3)	13.0 (4.4)	11	(7.3)	1.0 (0.0)	65.4 (36.5)	14	(4.6)	1.1 (0.1)	54.1 (29.0)
Platelet count decreased	0	(0.0)	/ (/)	/ (/)	9	(6.0)	1.1 (0.1)	13.8 (1.6)	9	(3.0)	1.1 (0.1)	13.8 (1.6)
Thrombocytopenia	0	(0.0)	/ (/)	/ (/)	9	(6.0)	1.7 (0.2)	63.1 (32.9)	9	(3.0)	1.7 (0.2)	63.1 (32.9)

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: 09MAY2016).

Subgroups

B5. 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 staining ≥50%). The NICE appraisal committee will appraise the technology within the full boundaries of its marketing authorisation in untreated metastatic NSCLC. In the event that the marketing authorisation includes tumours with weak PD-L1 expression, please comment on whether pembrolizumab is likely have similar clinical and cost-effectiveness regardless of the level of PD-L1 expression (strong positive or weak positive).

The only first-line NSCLC data that we will have at the time of regulatory approval comes from KEYNOTE-024, which was conducted exclusively in patients with TPS ≥ 50%.

We anticipate the first-line NSCLC indication will be restricted to the population of patients with TPS ≥50%. The anticipated indication wording relating to the first-line treatment of NSCLC is as follows:

"KEYTRUDA is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations."

Comparators

B6. Single agent chemotherapy is a comparator in the final scope issued by NICE, but appears to have been excluded from the company's NMA and economic model. Please provide full justification for excluding this comparator.

NICE clinical guideline 121 recommends single-agent chemotherapies for people who are unable to tolerate a platinum combination. In KEYNOTE-024, eligible patients had to be able to tolerate platinum combination chemotherapy. Consequently there is no evidence concerning pembrolizumab in patients who are only suitable for single agent chemotherapy. Due to the lack of available evidence for this subgroup of patients, single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine; for people for whom platinum combination therapy is not appropriate) was not included as a relevant comparator in this submission. This position was additionally supported by the fact that based on recent market shares observed in the UK, less than 3% of patients in the UK are unsuitable to receive platinum containing chemotherapy as first-line therapy.

Section C: Textual clarifications and additional points

C1. Please clarify why the results in Table 85 and Table 86 of the company submission do not match the results provided in the 'Results' sheet of the model and identify which are the correct results.

The results presented in the 'Results' sheet of the model are the correct results. We apologise for the typo presented as part of Tables 85 and 86 in the submission. We are

presenting below the updated tables (re-numbered below as Table 26 and Table 27 for this response), based on the correct results:

Table 26: Base case results (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) pairwise comparison pembrolizumab vs. comparator (QALYs)
Platinum + gemcitabine or paclitaxel	£18,238	1.277	0.899	£58,224	1.163	£50,080
Platinum + docetaxel	£17,721	1.262	0.892	£58,741	1.170	£50,223
Platinum + vinarelbine	£18,987	1.179	0.823	£57,476	1.239	£46,377
Platinum + pemetrexed	£24,003	1.359	0.964	£52,460	1.098	£47,786
Pembrolizumab	£76,462	2.752	2.062	-	-	-

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

Table 27: Incremental cost-effectiveness analysis based on NMA (discounted, with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental analysis	Removing extendedly dominated	Incremental analysis after removing extendedly dominated
Platinum + docetaxel	£17,721	1.262	0.892	-	-	-	-	-
Platinum + gemcitabine or paclitaxel	£18,238	1.277	0.899	£517	0.007	£73,857	£73,857	Extendedly dominated
Platinum + vinarelbine	£18,987	1.179	0.823	£749	-0.076	Dominated	Dominated	Dominated
Platinum + pemetrexed	£24,003	1.359	0.964	£5,765	0.065	£88,692	Extendedly dominated	Extendedly dominated
Pembrolizumab	£76,462	2.752	2.062	£52,459	1.098	£47,777	£50,064	£50,206

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

C2. Some of the confidentiality marking is not in line with the instructions on marking confidential information in the NICE guide to the processes of technology appraisals (sections 3.1.24–3.1.29). Some of the confidentiality marking requires lifting to enable the committee to see the evidential basis of the decision and to keep the amount of confidential data to an absolute minimum. A separate letter will be sent with specific requests regarding this.

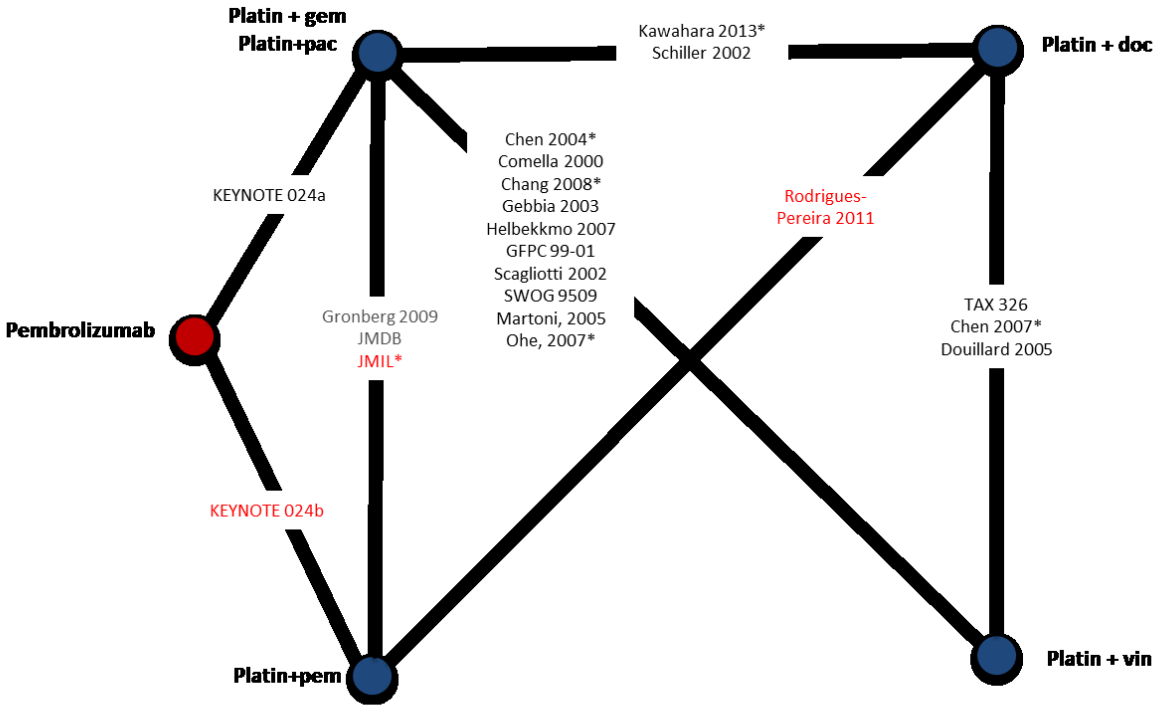
Please find enclosed an updated version of the submission document and appendices with revised confidentiality markings, and updated redacted versions of both documents. The original Appendix H (Checklist of confidential information), that was submitted with the original version of the submission on 18 October 2016, still applies to the updated versions of the submission document and appendices. A new Appendix H has been provided in relation to the contents of this response document concerning the clarification questions.

SUPPLEMENTARY APPENDICES

APPENDIX 1: NMA using digitised KM curves – alternative analysis

In order to allow HRs to vary over time, an NMA was performed using digitised KM curves (Figure 1). Of the models fit to the data, the most parsimonious was the 2nd order FP model with p1=1 and p2=0 (Table 1). Under this model, pembrolizumab is statistically better than platinum+gemcitabine/paclitaxel and all other interventions of interest after approximately 4 months (Figure 4). The HRs for each intervention do not change appreciably over time; therefore the assumption of constant HRs is reasonable in this population for OS. Results of the random-effects models were similar to those of the fixed-effect analysis, although the resulting CrIs were wider. The best-fitting models were the 2nd order FP models with p1=0, p2=1 and p1=1, p2=0 (Figures 7 and 8).

Figure 1: Network of evidence for overall survival (KM curves); all histologies – alternative analysis 1



Trials in red: non-squamous
Trials in black: all histologies
Trials with 100% Asian patients denoted with *
KEYNOTE 024a: Patients assigned to platinum + gem or platinum + pac before randomization
KEYNOTE 024b: Patients assigned to platinum + pemetrexed before randomization (non-squamous)

Table 1: Model fit estimates for fixed-effects network meta-analysis with parametric survival models for overall survival; all histologies – alternative analysis 1

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5428.22	54.78	5483
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5600.02	54.98	5655
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5198.06	76.94	5275
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5173.37	77.63	5251
2nd order FP with p1=1, p2=0, treatment effects on 1 scale (d0) and 1 shape parameter (d1)	**5172.8**	**77.2**	**5250**
2nd order FP with p1=1, p2=1, treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5219.59	77.41	5297

Figure 2: Results of fixed-effects network meta-analysis of overall survival; all histologies; treatment effects as hazard ratio over time relative to platinum + gemcitabine/paclitaxel (Weibull model) – alternative analysis 1

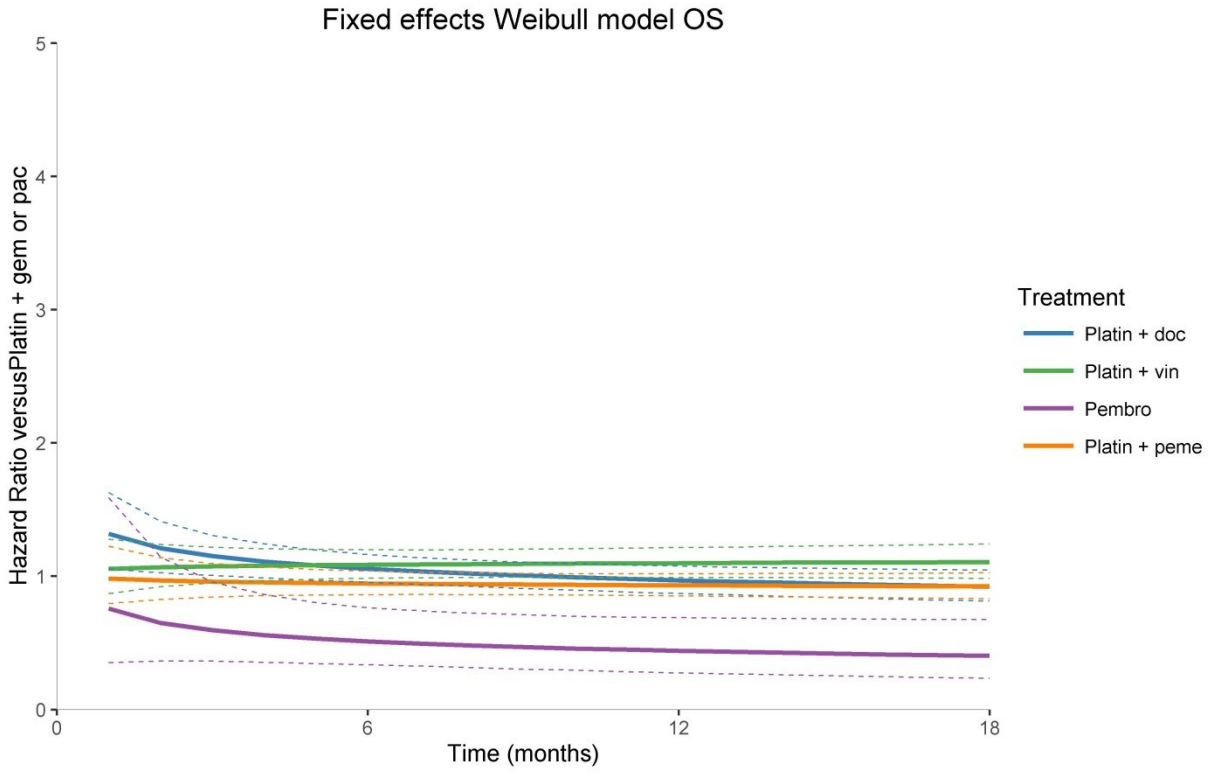


Table 2: Basic parameter estimates of Weibull model; overall survival; all histologies – alternative analysis 1

	d0 estimate	d0 variance	d1 estimate	d1 variance	Correlation
Platin + gem or pac	Reference		Reference		
Platin + doc	0.275450	0.0121553	-0.12340	0.0023434	-0.8948
Platin + vin	0.054710	0.0097099	0.01539	0.0017242	-0.8710
Pembro	-0.277300	0.1495187	-0.21925	0.0297215	-0.8412
Platin + peme	-0.017075	0.0121547	-0.02183	0.0020887	-0.9174

Figure 3: Results of fixed-effects network meta-analysis of overall survival; all histologies; treatment effects as hazard ratio over time relative to platinum + gemcitabine/paclitaxel (Gompertz model) – alternative analysis 1

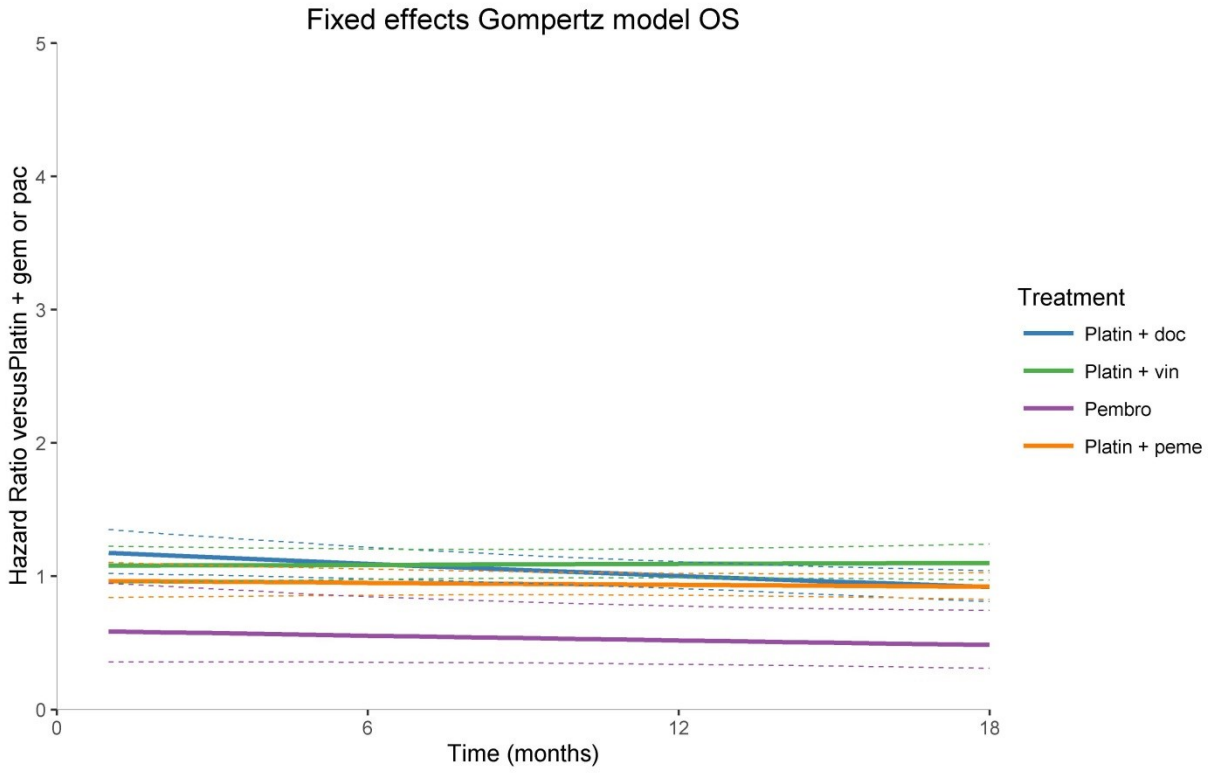


Table 3: Basic parameter estimates of Gompertz model; overall survival; all histologies – alternative analysis 1

	d0 estimate	d0 variance	d1 estimate	d1 variance	Correlation
Platin + gem or pac	Reference		Reference		
Platin + doc	0.174500	0.0057779	-0.014370	0.00002939	-0.7456
Platin + vin	0.074645	0.0047905	0.001131	0.00002218	-0.6894
Pembro	-0.523600	0.0667805	-0.011190	0.00015808	-0.5802
Platin + peme	-0.034685	0.0054786	-0.002638	0.00002567	-0.7974

Figure 4: Results of fixed-effects network meta-analysis of overall survival; all histologies; treatment effects as hazard ratio over time relative to platinum + gemcitabine/paclitaxel; 2nd order FP model (p_1=1, p_2=0) – alternative analysis 1

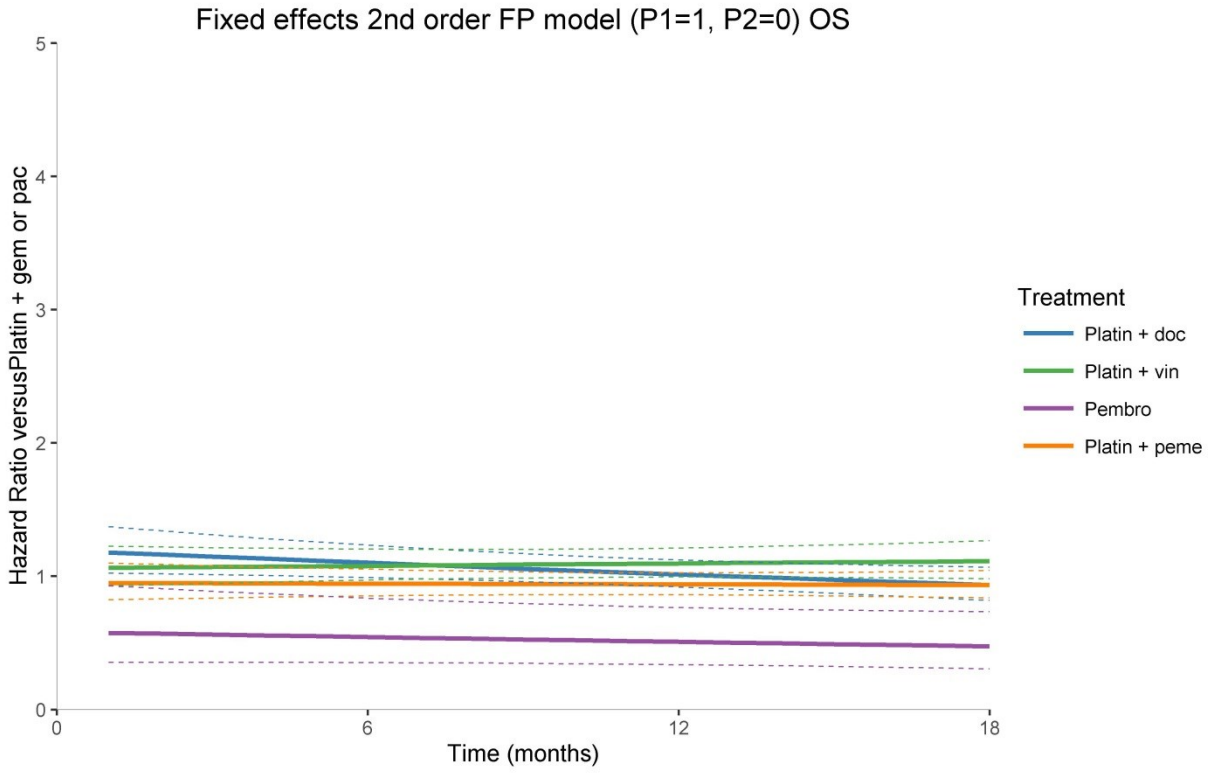


Table 4: Basic parameter estimates of 2nd order FP model (p_1=1, p_2=0); overall survival; all histologies – alternative analysis 1

	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Platin + gem or pac	Reference		Reference		
Platin + doc	0.1801	0.006989	-0.01392	0.0000397	-0.79726
Platin + vin	0.0590	0.006154	0.00273	0.0000303	-0.74980
Pembro	-0.6917	0.113579	-0.00454	0.0001230	-0.72384
Platin + peme	-0.0312	0.006056	-0.00256	0.0000288	-0.81487

Table 5: Model fit estimates for random-effects network meta-analysis with parametric survival models for overall survival; all histologies – alternative analysis 1

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5424.44	58.56	5483
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5596.13	58.87	5655
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5197.23	79.77	5277
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	**5171.62**	**80.38**	**5252**
2nd order FP with p1=1, p2=0, treatment effects on 1 scale (d0) and 1 shape parameter (d1)	**5171.82**	**80.18**	**5252**
2nd order FP with p1=1, p2=1, treatment effects on 1 scale (d0) and 1 shape parameter (d1)	5217.96	81.04	5299

Figure 5: Results of random-effects network meta-analysis of overall survival; all histologies; treatment effects as hazard ratio over time relative to platinum + gemcitabine/paclitaxel (Weibull model) – alternative analysis 1

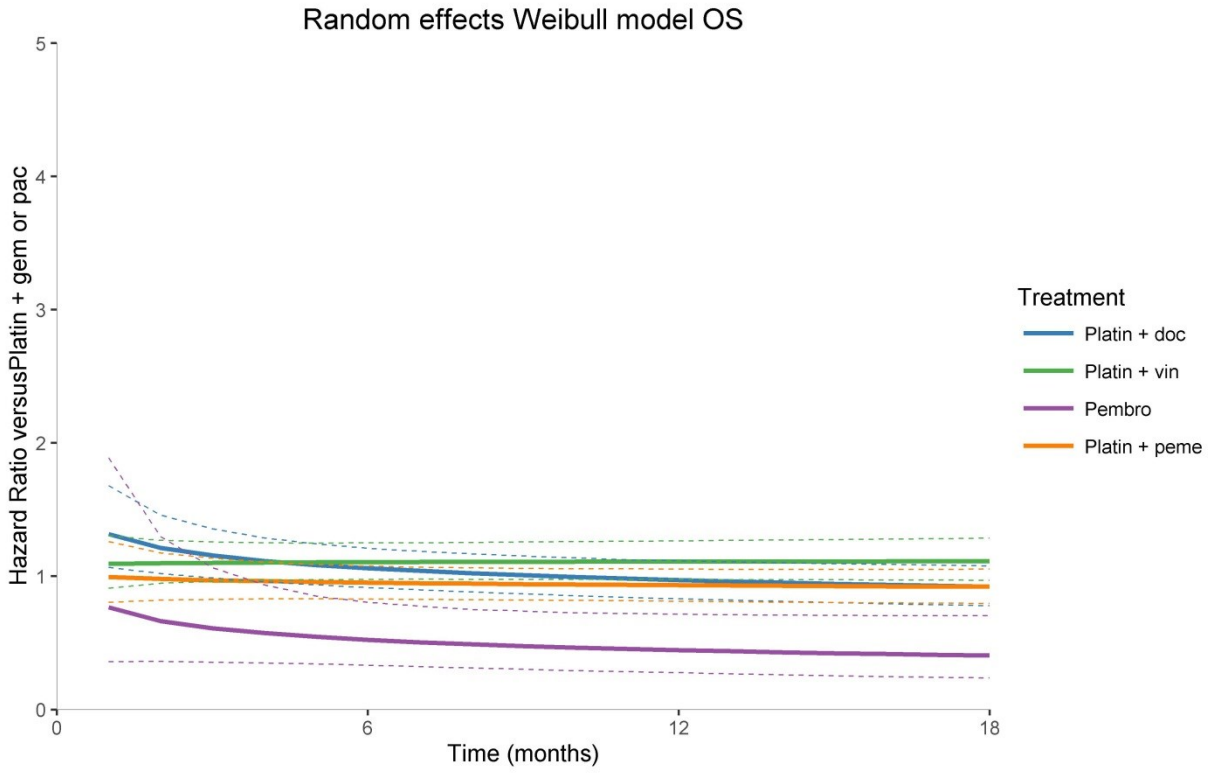


Table 6: Basic parameter estimates of random-effects Weibull model; overall survival; all histologies – alternative analysis 1

	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Platin + gem or pac	Reference		Reference		
Platin + doc	0.27480	0.0129022	-0.12440	0.0021064	-0.7868
Platin + vin	0.08842	0.0087165	0.00636	0.0013258	-0.7404
Pembro	-0.26600	0.1739185	-0.22010	0.0321428	-0.8434
Platin + peme	-0.00583	0.0122151	-0.02951	0.0017479	-0.8121

Figure 6: Results of random-effects network meta-analysis of overall survival; all histologies; treatment effects as hazard ratio over time relative to platinum + gemcitabine/paclitaxel (Gompertz model) – alternative analysis 1

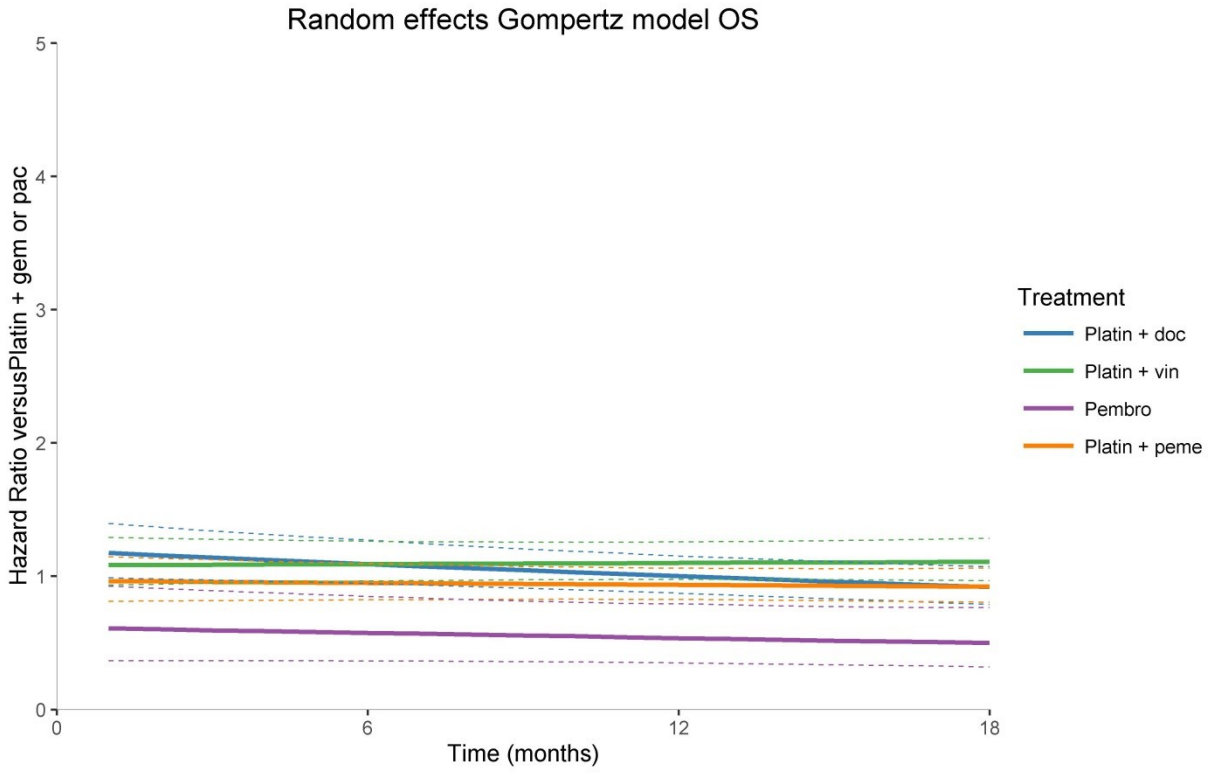


Table 7: Basic parameter estimates of random-effects Gompertz model; overall survival; all histologies – alternative analysis 1

	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Platin + gem or pac	Reference		Reference		
Platin + doc	0.17490	0.00824816	-0.0146150	0.000029177	-0.6521
Platin + vin	0.07874	0.00709901	0.0012460	0.000024400	-0.6448
Pembro	-0.48600	0.06749345	-0.0117700	0.000150661	-0.5687
Platin + peme	-0.03475	0.00794848	-0.0023535	0.000026000	-0.7087

Figure 7: Results of random-effects network meta-analysis of overall survival; all histologies; treatment effects as hazard ratio over time relative to platinum + gemcitabine/paclitaxel; 2nd order FP model (p_1=0, p_2=1) – alternative analysis 1

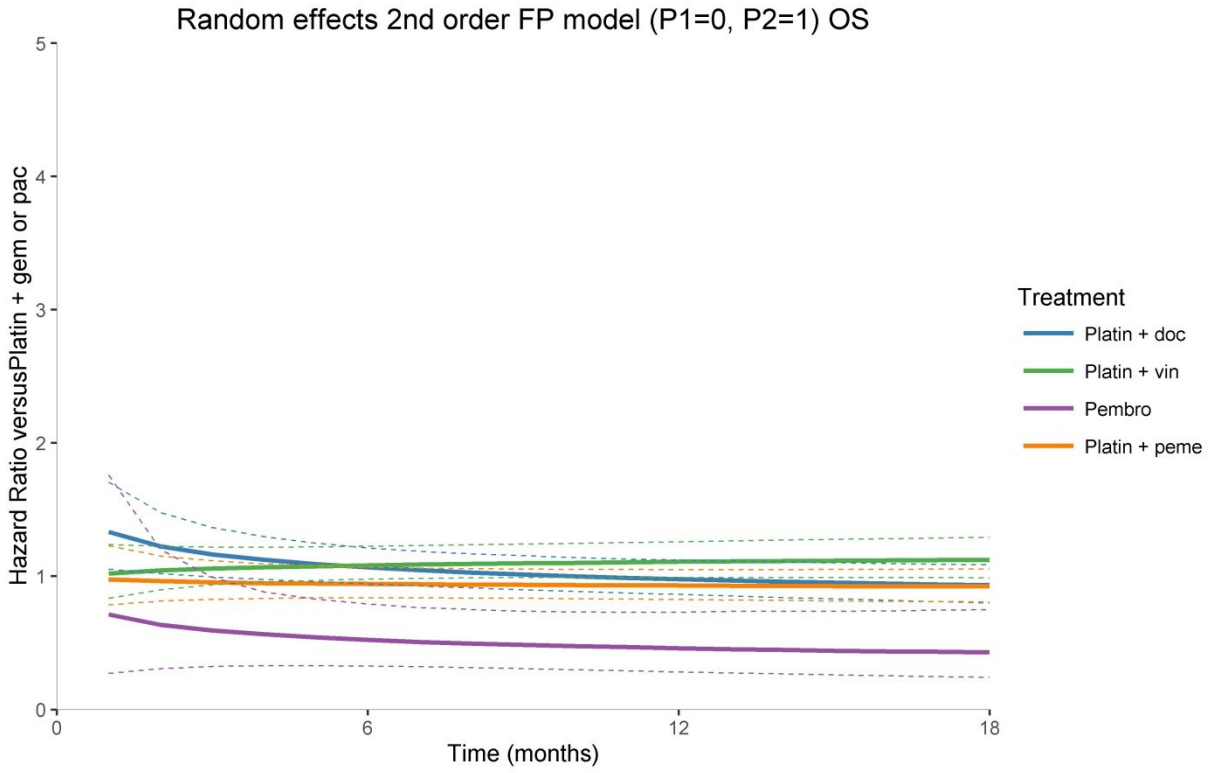


Table 8: Basic parameter estimates of random-effects 2nd order FP model (p_1=0, p_2=1); overall survival; all histologies – alternative analysis 1

	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Platin + gem or pac	Reference		Reference		
Platin + doc	0.28710	0.01723	-0.12290	0.0031670	-0.8834
Platin + vin	0.01919	0.00921	0.03225	0.0015668	-0.8094
Pembro	-0.33775	0.23241	-0.17710	0.0450865	-0.8899
Platin + peme	-0.02429	0.01255	-0.01975	0.0019873	-0.8539

Figure 8: Results of random-effects network meta-analysis of overall survival; all histologies; treatment effects as hazard ratio over time relative to platinum + gemcitabine/paclitaxel; 2nd order FP model (p_1=1, p_2=0) – alternative analysis 1

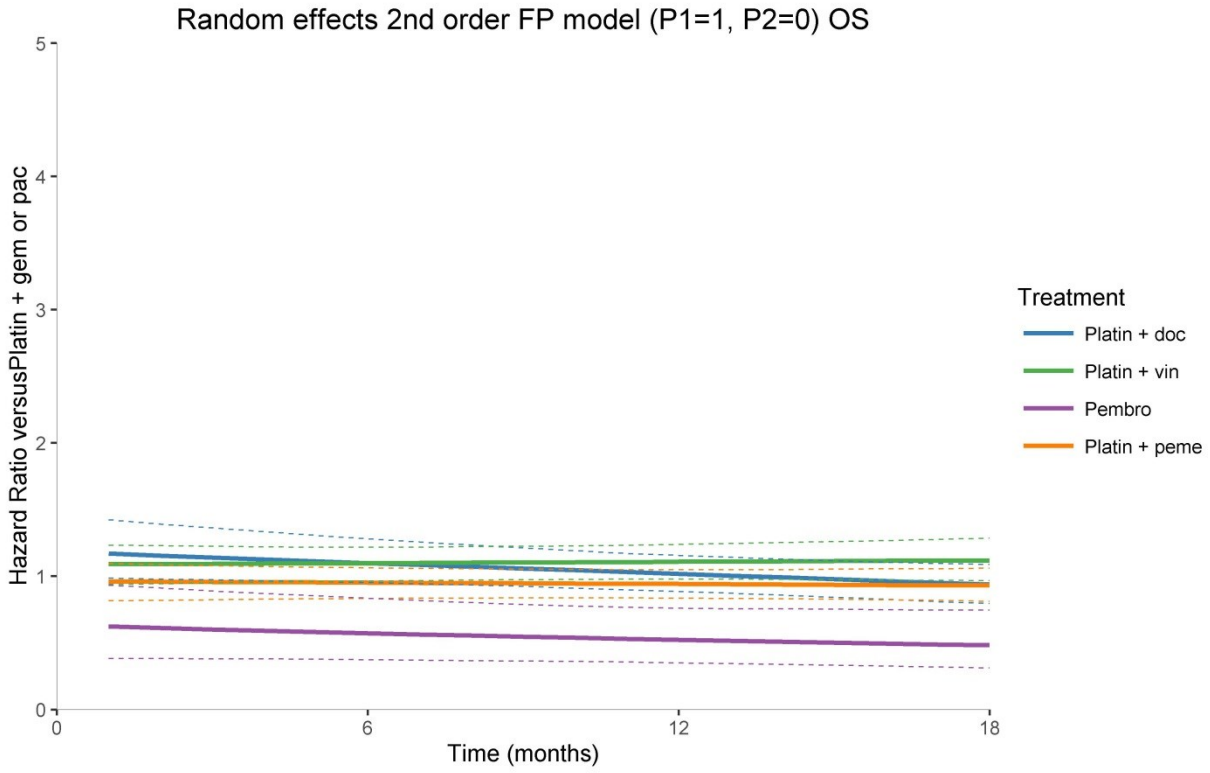


Table 9: Basic parameter estimates of random-effects 2nd order FP model (p_1=1, p_2=0); overall survival; all histologies – alternative analysis 1

	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Platin + gem or pac	Reference		Reference		
Platin + doc	0.17080	0.00901074	-0.013340	0.00004043	-0.7270
Platin + vin	0.08513	0.00626695	0.001606	0.00002731	-0.6568
Pembro	-0.45755	0.05264610	-0.013230	0.00015061	-0.5217
Platin + peme	-0.03843	0.00641251	-0.001848	0.00002485	-0.6886

APPENDIX 2: Analysis of Overall Survival – Additional tables using alternative censoring rule

Keytruda (MK-3475) First-line NSCLC HTA Submission

UK - Protocol 024

Analysis of Overall Survival

Additional tables using Alternative Censoring Rule

Table of contents

1 OBJECTIVE

As requested by NICE, an alternative censoring rule is defined censoring patients alive and still at risk of the target event at database cut-off date. Using this alternative censoring rule:

- To estimate the treatment difference between pembrolizumab 200 mg Q3W and standard of care in overall survival.

- To estimate the treatment difference between pembrolizumab 200 mg Q3W and standard of care in overall survival, adjusted for the by-protocol allowed treatment switch-over of control arm subjects to pembrolizumab 200 mg Q3W using a simplified two-stage survival analysis model, the Rank-Preserving Structure Failure Time (RPSFT) model and Inverse Probability of Censoring Weighting (IPCW) model.

2 STATISTICAL ANALYSIS

2.1 Endpoints

2.1.1 Overall Survival – ITT analysis

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 May 9, 2016 are censored at the cutoff date.

2.1.2 Overall Survival in the 2-stage model

In the 2-stage model, OS is defined similarly as in ITT, but the survival time of the SOC arm subjects switching to pembrolizumab 200 mg Q3W is adjusted. Specifically, the survival time after the secondary baseline of SOC subjects who switched-over to pembrolizumab is adjusted multiplicatively by an acceleration factor determined in stage 1, using a regression model applied to post progression survival data.

2.1.3 Overall Survival in the RPSFT model

In the RPSFT model, the overall survival is defined similarly as in ITT, but the survival time of the SOC arm subjects switching to pembrolizumab 200 mg Q3W is adjusted. Specifically, the survival time after switching of SOC subjects who switched-over to pembrolizumab 200 mg Q3W is adjusted multiplicatively by an acceleration factor determined by g-estimation in a first step, based on the common treatment effect assumption. A re-censoring process is also applied to OS to all control subjects to account for the adjustment of the OS.

2.1.4 Overall Survival in the IPCW model

In the IPCW model, the overall survival (OS) is defined similarly as in ITT, but the survival time of the SOC arm subjects who switched-over to pembrolizumab 200 mg Q3W is censored at switching time. Individual observations are weighted in the final proportional hazards model,

using the inverse probability of censoring weights estimated from the multiple logistic regression models.

2.2 Analysis Populations

The intention-to-treat (ITT) population is used for the analysis of OS. All randomized subjects are included in the analyses according to the treatment group they were randomized to.

2.3 Data Used in the Analysis

The present report covers the statistical analysis based on protocol 024 in the non-small cell first line lung cancer (NSCLC) indication. Database lock/Study completion information is provided in Table 28.

Table 28

List of Protocols and DBLs Used in the Submission

MK Number	Protocol number	Database Cut-off date Database Lock date (DBL)
MK-3475	P024	May 9, 2016 (DB cutoff) June 3, 2016 (DBL)

2.4 Treatment arms

Protocol 024 is a randomized, open-label phase III trial of pembrolizumab (MK-3475) 200 mg Q3W versus platinum based chemotherapy (standard of care or SOC) in subjects previously untreated for their stage IV, PDL-1 strong, non-small cell lung cancer. Patients randomized to the standard of care arm may receive pembrolizumab 200 mg Q3W after documented disease progression.

2.5 Statistical Methods

A full description of each method used can be found in the report provided on 11-Oct-2016, “MK3475_prot024_RPSFT_2stage_ICPW_report_subgroups_FINAL.docx”. This report included OS adjusted analyses using the censoring rule as defined in the CSR.
The analysis under alternative censoring rule for overall survival endpoint presented here are:

- Analysis overall survival (ITT analysis)
- Adjustment using RPSFT model with re-censoring
- Adjustment using 2-stage model without re-censoring
- Adjustment using 2-stage model with re-censoring

- Adjustment using IPCW model where all observations were weighted from study entry

3 RESULTS

3.1 Impact of alternative definition of censoring rule

Table 29 presents the impact of using the alternative censoring rule for overall survival by treatment group. By definition, the number of events and censored observations remain unchanged as compared to the primary censoring rule defined in the CSR [redacted]

3.2 Overall survival – ITT

Table 30 and Figure 5 present the results of the OS analysis and Kaplan-Meier estimates of OS in the ITT population. There were a total of [redacted] deaths at the time of data cutoff (09 May 2016).
The HR for OS [redacted] with a two-sided p-value of [redacted] for the comparison of pembrolizumab 200 mg Q3W arm vs. the SOC arm.
Figure 6 shows the Kaplan Meier curve of overall survival in control group split by switch-over status.

3.3 Overall Survival using 2-stage model

In protocol 24, 151 patients were randomized to control arm. A total of 66/151 (43.7%) patients switched over to pembrolizumab 200 mg Q3W including 59 patients meeting the eligibility criteria for switch-over. In 85 non-switched over patients, 16 patients met the eligibility criteria for switch-over. A total of [redacted] were included in the first stage model to estimate the acceleration factor.
The lognormal distribution was selected for the parametric model for the survival time post progression based on the AIC criteria. The parametric model was fitted to the post progression survival of the [redacted] from control arm eligible for switch-over. The model was adjusted for covariates as defined in the SAP and was convergent.
The acceleration factor is estimated based on the effect of switching from control to pembrolizumab and its 95%CI was estimated based on the 1000 bootstrap samples. Among models in the 1000 bootstrap samples, 994 models did converge and were kept in the analysis. The estimated acceleration factor and its 95%CI are presented in Table 31 and are equal to [redacted] This acceleration factor was used to adjust survival times or censored survival times of the [redacted] who were eligible for switch-over and who actually switched from control arm to pembrolizumab 200 mg Q3W.

3.3.1 Without re-censoring

Table 31 and Figure 7 present the results of the analysis of OS adjusting for treatment switch from control arm to pembrolizumab including Kaplan-Meier estimates of OS and estimation of treatment effect without re-censoring procedure applied.
Without re-censoring, the number of events in control arm is the same in the adjusted analysis as in the unadjusted ITT analysis (here[redacted]). The adjusted HR for OS is [redacted] with a two-sided p-value of [redacted] in the pembrolizumab 200 mg Q3W arm vs. the control arm.

3.3.2 With re-censoring

Table 32 and Figure 8 present the results of the analysis of OS adjusting for treatment switch from control arm to pembrolizumab including Kaplan-Meier estimates of OS and estimation of treatment effect with the re-censoring procedure applied.
Re-censoring procedure applied to all control patients. Applying the re-censoring procedure, [redacted] events have been re-censored and the number of exposed person-months [redacted] person-months in the unadjusted analysis vs. [redacted] person-months in the adjusted one. In view of the high value of acceleration factor, it is recommended to present results without re-censoring procedure.
The adjusted HR for OS is [redacted] with a two-sided p-value of [redacted] in the pembrolizumab 200 mg Q3W arm vs. the control arm.

3.4 Overall Survival using RPSFT model

Table 33 and Figure 9 present the results of the OS analysis adjusting for treatment switch from control arm to pembrolizumab 200 mg Q3W using RPSFT model.
A total of 66/151 (43.7%) of control patients switched to pembrolizumab 200 mg Q3W.
Following the re-censoring procedure applied to all control patients, the number of events in the control arm was [redacted] from 64 events in the unadjusted ITT analysis to [redacted] events, corresponding to a proportion of [redacted] of events being recensored. Similarly, the re-censoring had an impact on the number of person-months in the control arm, [redacted] from to [redacted] person-months in the unadjusted analysis vs. [redacted] person-months in the adjusted analysis.

The adjusted HR for OS is [redacted] with a two-sided p-value of [redacted] in the pembrolizumab 200 mg Q3W vs. the control arm.

3.5 Overall Survival using IPCW model

The IPCW-adjusted median survival under the current censoring rule remains at 11.8 months, whilst the median survival in the unadjusted SOC arm and the pembrolizumab arm were not reached.
The IPCW-adjusted hazard ratio of death is [redacted] with a 1000-replication bootstrap p-value of [redacted] (Table 34 and Figure 10).

4 TABLES AND FIGURES

4.1 Impact of alternative definition of censoring rule

Table 29

Impact of Definition of censoring rule for Overall Survival
(ITT population)

	Standard of Care N=151	Pembrolizumab N=154
Primary censoring rule		
Number (%) of events		
Events	64 (42.4)	44 (28.6)
Censored observations	87 (57.6)	110 (71.4)
Time to Overall Survival (days)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	253.0 (1.0-565.0)	286.0 (3.0-574.0)
Alternative censoring rule		
Number (%) of events		
Events	[redacted]	[redacted]
Censored observations	[redacted]	[redacted]
Time to Overall Survival (days)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
(Database Cutoff Date: 09MAY2016)		

4.2 Overall survival – ITT

Table 30

Analysis of Overall Survival
Sensitivity analysis on alternative censoring rule
ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	Pembrolizumab vs. SOC	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Standard of Care	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab 200mg Q3W	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

† From product-limit (Kaplan-Meier) method for censored data. Patients who were lost to follow-up or who withdrew are censored at the date recorded. Patients alive and still at risk of the target event at the date of database cut-off are censored at the date of database cut-off
‡ 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).
‡‡ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 09MAY2016)

Figure 5

Kaplan-Meier of Overall Survival
Sensitivity analysis on alternative censoring rule
ITT Population

(Database Cutoff Date: 09MAY2016)

Figure 6

Kaplan-meier of Overall Survival
Sensitivity analysis on alternative censoring rule
ITT population

(Database Cutoff Date: 09MAY2016)

4.3 Overall Survival using 2-stage model

4.3.1 Without re-censoring

Table 31

Analysis of Overall Survival | No Recensoring
Sensitivity analysis on alternative censoring rule
ITT Population
Comparison Pembrolizumab 200 mg Q3W versus Standard of Care (SOC)
Adjusting for Treatment switch to Pembrolizumab 200 mg Q3W in SOC arm using 2-stage analysis

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in %† (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‖
Standard of Care	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care, Adjusted ¶	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab 200 mg Q3W	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 1 model††							Acceleration factor‡‡	
§ Controls eligible to cross-over to Pembrolizumab 200mg Q3W, Patients switching vs Patients not switching							[redacted]	

¶ Survival times shrunk for the patients eligible to cross-over and who actually crossed-over to Pembrolizumab 200mg Q3W treatment.

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

‡ Based on Cox regression model with treatment as a covariate, stratified by histology (squamous/non squamous), geography (East Asia/ non East Asia) and ECOG status at baseline (0/1). The 95% CI is based on bootstrap samples on the ITT population, stratified for treatment arm and SOC arm

‖ Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for treatment switch.

†† Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: age, sex, metastatic staging (M1B vs others), geography (East Asia/ non East Asia), squamous tumor type, smoking status (Current/ Former/ Never) at baseline and ECOG performance status (0/1), tumour size, BMI and hemoglobin at time of progression (defined as the secondary baseline) and time to disease progression.

§ Patients were eligible to switch if they had documented progression, did not stop chemotherapy for any other reason than progressive disease, had a 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.

‡‡ Acceleration factor used to shrink the survival time of SOC patients eligible to cross-over and who actually crossed-over to Pembrolizumab 200mg Q3W. The 95% CI is based on the same bootstrap samples as for the Cox regression model

(Database Cutoff Date: 09 MAY 2016).

Figure 7

Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using 2-stage analysis
No recensoring
ITT Population

(Database Cutoff Date: 09 MAY 2016)

4.3.2 With re-censoring

Table 32

Analysis of Overall Survival
Sensitivity analysis on alternative censoring rule
ITT Population
Comparison Pembrolizumab 200 mg Q3W versus Standard of Care (SOC)
Adjusting for Treatment switch to Pembrolizumab 200 mg Q3W in SOC arm using 2-stage analysis

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 9 in %† (95% CI)	Treatment vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‖
Standard of Care	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care, Adjusted ¶	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab 200 mg Q3W	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 1 model††							Acceleration factor‡‡	
§ Controls eligible to cross-over to Pembrolizumab 200mg Q3W, Patients switching vs Patients not switching							[redacted]	

¶ Survival times shrunk for the patients eligible to cross-over and who actually crossed-over to Pembrolizumab 200mg Q3W treatment. Re-censoring procedure was applied to adjusted survival times.

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

‡ Based on Cox regression model with treatment as a covariate, stratified by histology (squamous/non squamous), geography (East Asia/ non East Asia) and ECOG status at baseline (0/1). The 95% CI is based on bootstrap samples on the ITT population, stratified for treatment arm and SOC arm.

‖ Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for treatment switch.

†† Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: age, sex, metastatic staging (M1B vs others), geography (East Asia/ non East Asia), squamous tumor type, smoking status (Current/ Former/ Never) at baseline and ECOG performance status (0/1), tumour size, BMI and hemoglobin at time of progression (defined as the secondary baseline) and time to disease progression.

§ Patients were eligible to switch if they had documented progression, did not stop chemotherapy for any other reason than progressive disease, had a 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.

‡‡ Acceleration factor used to shrink the survival time of SOC patients eligible to cross-over and who actually crossed-over to Pembrolizumab 200mg Q3W. The 95% CI is based on the same bootstrap samples as for the Cox regression model

(Database Cutoff Date: 09 MAY 2016).

Figure 8

Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch using 2-stage analysis
ITT Population

(Database Cutoff Date: 09 MAY 2016)

4.4 Overall Survival using RPSFT model

Table 33

Analysis of Overall Survival with RPSFT Correction
Sensitivity Analysis on Alternative Censoring Rule
(ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	Survival Rate at Month 9† (95% CI)	Treatment vs. Control		
							Hazard Ratio‡ (95% CI)§	p-Value‖	p-Value¶
SOC (No RPSFT Correction)	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
SOC	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Pembrolizumab	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Rank-preserving structural failure model (RPSFT) model is used to adjust for the effect of cross-over from SOC to Pembrolizumab in overall survival analysis
† From product-limit (Kaplan-Meier) method
‡ Based on Cox regression model corrected by RPSFT, with treatment as covariate and stratified by geographic region (East Asia vs non-East Asia) / ECOG (0 vs 1) and histology (squamous vs non-squamous)
§ Obtained by fitting the Cox regression model to the bootstrap samples corrected by RPSFT
‖ Two-sided p-value based on Cox regression model
¶ Two-sided p-value based on log-rank test
(Database Cutoff Date: 09MAY2016)

Figure 9

Analysis of Overall Survival with RPSFT Correction
(ITT population)

(Database Cutoff Date: 09 MAY 2016)

4.5 Overall Survival using IPCW model

Table 34

Analysis of Overall Survival
(ITT Population)
Comparison between Pembrolizumab and Standard of Care (SOC)

Inverse-Probability-of-Censoring Weights (IPCW) applied from study entry to all subjects in the SOC arm

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	Treatment vs. Control		
						Hazard Ratio†† (95% CI)	p-Value§	p-Value§§
SOC	151	[redacted]	[redacted]	[redacted]	[redacted]			
SOC (IPCW Adjusted)	151	[redacted]	[redacted]	[redacted]	[redacted]			
Pembrolizumab 200mg Q3W	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data, if the median OS is reached.
†† HR based on Cox regression model with treatment as a covariate stratified by baseline ECOG, histology of squamous/non-squamous, and geographical region, and bootstrap 95% CI.
§ Two-sided p-value based on the IPCW log-rank test.
§§ Two-sided p-value based on bootstrap percentiles.
(Database Cutoff Date: 09MAY2016).

Figure 10

Submission from **Roy Castle Lung Cancer Foundation,** for consideration by NICE, in their review of **Pembrolizumab** for untreated PD-L1 strong-positive metastatic non small cell lung cancer [**ID990**].

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being 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 is currently the first line therapy option.

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. 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, will ensure a more segmented population.

2. Improvement in survival
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available.

   However, we note the Phase 3, KEYNOTE-024 study, presented at the European Society of Medical Oncology meeting and published in the New England Journal of Medicine. This study was undertaken in 305 patients with advanced NSCLC, who had not yet received treatment and whose biopsy specimens showed no EGFR or ALK mutations and showed high expression of PD-L1. In this study, Pembrolizumab was compared with platinum based doublet chemotherapy. Median Progression Free Survival was 10,3 months for Pembrolizumab and 6 months for platinum chemotherapy. overall survival at 6 months was 80% for Pembrolizumab and 72% for platinum chemotherapy. At one year, overall survival was 70% and 54% respectively. [Note, crossover rate of 50%, - patients in the chemotherapy group, given Pembrolizumab on disease progression]

   We understand that about 30% of NSCLC tumours show PD-L1 expression at 50% or more (this was the cut off figure used in the trial). It should be noted that the patient populations which benefit from Targeted Therapies (EGFR and ALK) are quite different. Most patients in KEYNOTE-024 were male, more than 90% were current or former smokers and around 20% were squamous cell. This compares to the trials for Targeted Therapies, where 90% of the oncogenic drivers (EGFR mutations, ALK rearrangement) were found in patients with adenocarcinoma. Most were women and non smokers. Thus, patients with tumours showing mutations, should be treated first line with Target Therapies.

   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.

We note in KEYNOTE-024, toxicity was lower with Pembrolizumab than platinum based chemotherapy. (Grade 3/4 adverse events – 27% versus 53%) and the incidence of all adverse events was lower with Pembrolizumab.

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 represents a new option with better overall survival and fewer side effects, in this very selected, high PD-L1 patient group.

[redacted]

December 2016.

NHS England comment in January 2017 on the NICE appraisal of pembrolizumab as 1st line treatment of advanced/metastatic non small cell lung cancer (NSCLC)

1. KEYNOTE-024 is an open label randomised trial in patients with previously untreated and advanced squamous and non-squamous NSCLC whose tumours had Tumour Proportion Scores of 50% or more for PD-L1 expression. Patients with treatable oncogenic aberrations such as those with activated EGFR or ALK mutations were excluded from this study.
2. 305 patients were randomised to receive a maximum of 2 years of treatment with a fixed 200mg dose of 3-weekly pembrolizumab or 4-6 cycles of standard chemotherapy regimens for non-squamous and squamous NSCLC. These standard regimens were the combination of carboplatin or cisplatin with pemetrexed or the combination of carboplatin or cisplatin with gemcitabine or the combination of carboplatin with paclitaxel. Maintenance pemetrexed was used as appropriate for non-squamous NSCLC in patients whose disease had not progressed with 1st line therapy. Crossover between arms was allowed.
3. Patients had to be of performance status 0 or 1 to enter the trial.
4. In the protocol-specified 2nd interim analysis of KEYNOTE-024, there had been 189 PFS events. Pembrolizumab offered a statistically significant and clinically meaningful delay in disease progression: with a median duration of follow-up of 11.2 months, the PFS hazard ratio (HR) for the intention to treat population (TPS ≥50%) was 0.50 for the fixed dose pembrolizumab arm when compared with standard chemotherapies (95% CI 0.37-0.68). Follow-up is still short but the Kaplan-Meier PFS curves have separated widely with some suggestion that there may be plateauing beyond 12 months although numbers of patients at risk at this point are small. Nevertheless, a similar phenomenon was observed in the second line pembrolizumab setting (now NICE-approved).
5. In the 2nd interim survival analysis, there had been 108 deaths. Pembrolizumab significantly improved median overall survival (OS), 80% of patients receiving pembrolizumab being alive at 6 months whereas the figure for chemotherapy was 72% (HR 0.60, 95%CI 0.41-0.89). Cross over had occurred in 44% of patients at the time of this 2nd interim analysis.
6. All grade treatment related adverse events were less in the pembrolizumab arm (73% vs 90%) and grade 3-5 treatment related adverse events were also less (27% vs 53%). The main (as expected) side-effects of pembrolizumab were diarrhoea, fatigue, pyrexia and rarely pneumonitis.
7. In summary, pembrolizumab offers more efficacious and less toxic 1st line treatment than standard chemotherapy in treatment-naïve patients with both squamous and non-squamous advanced NSCLC with PD-L1 expression of at least 50%. Follow-up is still short but crossover is likely to blur the survival benefit.
8. NHS England perceives that there are no substantial issues as to generalisability of the trial data into clinical practice in England as long as patients receiving pembrolizumab are of performance status 0 or 1 and have at least 50% PD-L1 expression. If NICE recommends this indication, NHE England would ensure that treating clinicians will have to certify the performance status of the patient (0 or 1) at the time of registration of seeking funding and also state the result of the PD-L1 expression test. The latter can be verified as Public Health England is supplied with the results of routine molecular genetic testing. These mechanisms will ensure that a patient exhibiting between 1 and 49% PD-L1 expression are not treated

with 1st line pembrolizumab although such patients would be eligible for 2nd line pembrolizumab after progressing on 1st line chemotherapy.

9. Approximately 30% of advanced NSCLC patients will have at least 50% expression of PD-L1. Approximately 5500 patients/year with advanced NSCLC have 1st line chemotherapy and most of these are of performance status 0 or 1. Thus the potentially eligible population for 1st line pembrolizumab is large, being about 1500 patients/year.
10. Since 2nd line pembrolizumab has interim funding from the CDF and will shortly be funded from baseline commissioning, most of 1st line pembrolizumab patients would have potentially received pembrolizumab at relapse under current NICE recommendation/guidance. However the doses of pembrolizumab are different in these 2 lines of treatment: there is a 200 mg fixed dose in the 1st line setting as opposed to the 2mg/kg dose in the 2nd line setting. Since the median weight for NSCLC patients in the second line setting is likely to be 75Kg or less, 1st line pembrolizumab will represent a 33% rise in dose administered versus 2nd line use. In addition, the treatment duration for 1st line use is likely to be greater than in 2nd line treatment. A third factor is that the attrition to health and survival associated with advanced lung cancer means that more patients with at least 50% PD-L1 expression will receive pembrolizumab as 1st line treatment than currently as 2nd line treatment. Thus 1st line pembrolizumab will substantially increase the cost of drug used in the NHS for this particular group of patients, perhaps by about 50% when combining all these issues of implementation.
11. Another issue that NHSE wishes to comment on is the treatment duration of pembrolizumab and what would happen at 2 years if patients remain free of disease progression and have continued to tolerate the drug. The evidence base for 1st line use is founded on a trial design which capped the treatment duration at 2 years and hence NHSE will institute a treatment cap at 2 years on the basis of implementing evidenced-based practice. In addition, if NICE recommends pembrolizumab in this indication and its assessment of cost effectiveness is also based on a maximum of 2 years treatment, that will also be the foundation for NHSE's commissioning position in that if Trusts continue treatment beyond 2 years for individual patients, NHSE will not reimburse Trusts for this non-commissioned use of drug.
12. NHSE again notes the fixed dose of pembrolizumab (200mg) given at each administration. It urges the manufacturer to create a 200mg vial as the present vial size is 50mg and thus with a 200mg vial, oncology pharmacies will have to reconstitute one vial rather than 4.
13. NHSE notes that all the cytotoxic drugs used in the KEYNOTE-024 trial as the comparator treatments have generic preparations in use in the NHS.
14. Standard practice in NHSE is to give 4 cycles of combination chemotherapy as 1st line chemotherapy with maintenance pemetrexed following only in non squamous NSCLC and those patients not progressing on 1st line treatment. The comparison in the cost effectiveness analyses therefore for this appraisal needs to reflect 4 cycles of chemotherapy, not 6 cycles which were permitted in the KEYNOTE-024 trial design.
15. NHSE wishes to inform NICE that current clinical opinion is changing rapidly as to the assessment as to the optimal duration of treatment with checkpoint inhibitors in cancer. Until very recently, treatment with pembrolizumab/nivolumab would have been considered to be optimal when continued to the time of either disease progression or unacceptable toxicity. However, ipilimumab in melanoma is already given for a fixed duration of treatment only. Recent evidence suggests that (at least in melanoma where use of such

drugs has been the greatest and longest), patients who discontinue checkpoint inhibitors for reasons other than disease progression (mainly toxicity) derive the same OS benefit as those that continue on treatment until disease progression (eg S Hodi et al, Proc Amer Soc Clin Oncol 2016: abstract 9518). Clinical experience is also pointing to the same conclusion ie that in drugs such as pembrolizumab/nivolumab, when benefits to patients occur when there is sufficient recruitment of the immune system against the cancer, that this recruitment of the immune system and consequent patient benefit may not require continued treatment until disease progression. There are thus trials underway in melanoma and renal cancer which are randomising patients to fixed durations of treatment of checkpoint inhibitors (eg for 1 year) versus treatment to disease progression. However, this type of trial design has already been implemented in the setting of squamous and non-squamous non small cell lung cancer previously treated with chemotherapy in a 1380 patient trial which has randomised patients still on treatment at 1 year to continue on therapy with nivolumab or discontinue treatment at that stage. The trial has completed recruitment and is in its follow up phase. Given that recruitment has been completed, results of the randomisation of treatment duration would be expected to be reported within the next 1-2 years.

[redacted]

[redacted]

January 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Paul Cane

Name of your organisation: Royal College of Pathologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? NO
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? YES, member
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

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Single Technology Appraisal (STA)

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

My area of expertise is around selection of patients for treatment using biomarker testing. Patients expressing the marker PDL-1 do much better on this treatment than those that do not. Testing is available at a handful of centres across the country at present supporting the EAMS.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

No comment.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts**.**

I do not see any barriers to equitable availability of this treatment.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No comment

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

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Single Technology Appraisal (STA)

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Currently PDL-1 testing is in progress to support the EAMS. If the treatment were approved by NICE, the amount of testing would need to be scaled up. Around seven centers are currently testing in England and Wales. These centres may be able to cope with the increased demand or a small number of additional centers could be commissioned. New centers would need personnel to be trained in reporting the PDL-1 test. A training scheme is also in place.

The test is currently funded by MSD to support its EAMS. If NICE were to approve the treatment, consideration needs to given to how testing would be funded within the NHS.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Martin Forster

Name of your organisation: NCRI-RCP-RCR-ACP

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

Currently, patients diagnosed with advanced NSCLC who are fit enough to receive systemic therapy are initially investigated with tissue assays including EGFR, ALK and increasingly PD-L1 testing. Molecular testing for EGFR is well established, ALK testing becoming more universally standard and PD-L1 increasing, but PD-L1 testing may be variable in the current climate where pembrolizumab is only available as second line therapy.

Patients with EGFR activating mutations or ALK translocations are treated with the relevant targeted therapies. These patients have a much better prognosis than other patients with NSCLC, but unfortunately their disease remains incurable and they will go on to have disease progression. Patients with EGFR or ALK activation who have exhausted targeted therapies are then treated with platinum-based combination chemotherapy. This therapeutic approach is delivered fairly consistently across the UK with little variation in medical opinion on the treatment options.

Other fit patients with NSCLC bearing no targetable oncogenic drivers are offered platinum based combination chemotherapy for 4-6 cycles, with or without subsequent maintenance therapy (currently in UK limited to maintenance pemetrexed in patients with non-squamous lung cancer, who remain fit after combination chemotherapy and whose tumours remain controlled). This therapeutic approach is delivered fairly consistently across the UK, with little variation in medical opinion on the options.

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). The availability of pembrolizumab is

relatively new, only NICE approved in late 2016, and so there may be more variability in this use at present, although it is increasing rapidly. There is no evidence that I'm aware of significant use off protocol.

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, it is generally much better tolerated than the current standards. Caution needs to be taken when considering use of the technology in patients on steroids or other immunosuppressants, with auto-immune disease or chronic infections.

The technology will be predominantly be delivered in tertiary care centres, due to the prescribing governance and requirement for adequate experience of the agent. All patients will have advanced lung cancers and it unlikely the technology will significantly change the requirements for symptom and social support, although these may be reduced in patients which significantly reduced tumour burden following therapy.

This sequence of therapy is approved in US and European Advanced NSCLC treatment algorithms.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use? I think that it is likely that PD-L1 testing will become more extensive performed at diagnosis once pembrolizumab becomes available as first line therapy. This should not cause delays in the patient pathway as other histological tests are already being performed and awaited for. However, the proportion of patients with advanced NSCLC available for pembrolizumab as first line therapy is likely to only be 15-25% patients. It is likely that for these patients therapy will be easier to deliver, with fewer concomitant medication than current chemotherapy, although for responders treatment will go on for much longer than current chemotherapy schedules.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation. The optimal duration of pembrolizumab therapy remains uncertain, although the studies that have led to

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approval limited therapy to 2 years. I think that this is reasonable, with no suggestion that longer therapy has better outcomes that I am aware of. There is a recognised possibility of pseudo-progression, which although very uncommon 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.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

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.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No inequalities that I'm aware of

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No, data are all available with the public arena

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Since pembrolizumab is now available for relapsed NSCLC with PD-L1 expression >1% appropriate training will be in place before this assessment is completed.

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Patient/carer expert statement (STA)

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

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Carol A Davies
Name of your nominating organisation: NLCFN
Do you know if your nominating organisation has submitted a statement?

☐ Yes x No

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you

- a patient with the condition?

☐ Yes x No

a carer of a patient with the condition?

☐ Yes x No

- a patient organisation employee or volunteer?

x Yes ☐ No

Do you have experience of the treatment being appraised?

x Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: no

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

PD1 positive test result

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

No experience

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Research suggests small proportion of people with Lung Cancer benefit from this treatment

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

•

ID990 STA Pembrolizumab

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

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

3rd January 2017

CONTAINS CIC/AIC

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

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Contributions of authors:

Janette Greenhalgh	Project lead, critique of the clinical evidence, drafted the clinical results section and supervised the final report
James Mahon	Checking and validation of the economic model and critique
Angela Boland	Critical appraisal of the clinical and economic evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence
Ashma Krishan	Critical appraisal of the statistical evidence
Ahmed Abdulla	Critical appraisal of the economic evidence
Rabeea'h Aslam	Critique of the clinical evidence, drafted the clinical results section
Eleanor Kotas	Cross-check of the company submission search strategy
Lindsay Banks	Critical appraisal of the company submission
John Green	Clinical advice and critical appraisal of the clinical evidence

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

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LIST OF ABBREVIATIONS

AE	adverse event
AEOSI	adverse event of special interest
AIC	Akaike information criterion
ALK	anaplastic lymphoma kinase
ASaT	all subjects as treated
BIC	Bayesian information criterion
BICR	blinded independent central review
BSA	body surface area
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CR	complete response
CS	company submission
CSR	clinical study report
DCR	disease control rate
DoR	duration of response
DSMC	Data and Safety Monitoring Committee
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC	European Organisation for the Treatment of Cancer
EQ-5D	European Quality of Life - 5 Dimensions Questionnaire
ERG	Evidence Review Group
FAD	final appraisal determination
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
IA2	second interim analysis
ICER	incremental cost effectiveness ratio
IHC	immunohistochemistry
ITT	Intention-to-treat
KEYNOTE-024	key trial that informs the clinical effectiveness and cost effectiveness evidence
K-M	Kaplan-Meier
NMA	network meta-analysis
NLCA	National Lung Cancer Audit
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressed disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PH	proportional hazards
PPS	post-progression survival
PR	partial response
PS	performance score
PSA	probabilistic sensitivity analysis
PSS	Personal and Social Services
PTDS	post-treatment discontinuation survival
QALY	quality adjusted life year
RCT	randomised controlled trial
sd	standard deviation
SD	stable disease
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	summary of product characteristics
TPS	tumour proportion score
TTD	time to treatment discontinuation

1 SUMMARY

1.1 Scope of the submission

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) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Merck, Sharp & Dohme to support the use of pembrolizumab (Keytruda®) for the treatment of patients with untreated programmed death-ligand 1 (PD-L1) positive metastatic non-small cell lung cancer (NSCLC).

1.2 Critique of the decision problem in the company submission

Intervention

The intervention described in the final scope issued by NICE and discussed in the company submission (CS) is pembrolizumab. On December 15th 2016, the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending the use of pembrolizumab as a first-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no epidermal growth factor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations. The Summary of Product Characteristics (SmPC) states [redacted]

At present, there is no established or validated test for PD-L1 expression, and testing for PD-L1 expression is not routinely carried out in UK NHS treatment centres.

Pembrolizumab is administered intravenously over a 30-minute period. The licensed dose of pembrolizumab for patients with untreated PD-L1 positive metastatic NSCLC is anticipated to be 200mg every 3 weeks.

Population

The population described in the final scope issued by NICE is people with PD-L1 positive NSCLC who have not been treated with chemotherapy in the metastatic setting. The population discussed in the CS is a subset of this population, namely patients with untreated metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutations. The company has not presented clinical effectiveness evidence for the use of pembrolizumab in patients with untreated metastatic NSCLC with a PD-L1 TPS <50% or for patients with a PD-L1 TPS ≥50% whose tumours also test positive for EGFR or ALK mutations.

Comparators

The comparators listed in the final scope issued by NICE are:

- 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 (for people with squamous NSCLC) pemetrexed maintenance treatment
- pemetrexed in combination with a platinum drug (for people with adenocarcinoma or large cell carcinoma only) with or without pemetrexed maintenance treatment
- single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) for people for whom platinum combination therapy is not appropriate.

The company has provided results from 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). After four to six cycles of chemotherapy, patients with tumours of non-squamous histology who were treated with platinum+paclitaxel or platinum+pemetrexed had the option to receive maintenance treatment with pemetrexed. Patients in the SOC arm were able to cross over and receive treatment with pembrolizumab when their disease progressed.

Clinical results from the KEYNOTE-024 trial are 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 comes from a subgroup analysis. The company has 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. The company has not discussed the clinical effectiveness of pembrolizumab compared with single agent chemotherapy.

Outcomes

Clinical evidence is presented in the CS for all five outcomes specified in the final scope issued by NICE: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL).

The results described in the CS were generated as part of the KEYNOTE-024 trial second interim analysis (IA2). At this point only 35% of the expected OS events had occurred and median OS had not been reached in either of the trial arms.

Other considerations

An agreed Patient Access Scheme (PAS) is in place for pembrolizumab. However, the company reports (CS, p29) that it is currently discussing an updated PAS arrangement with the Department of Health.

Equality and End of Life considerations

The company has not identified any equality issues. However, the company has presented a case for pembrolizumab to be assessed against the NICE End of Life criteria.

1.3 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company conducted a broad literature search and did not identify any relevant randomised controlled trials (RCTs) other than the ongoing phase III KEYNOTE-024 trial. The KEYNOTE-024 trial included 305 patients with untreated stage IV NSCLC whose tumours strongly expressed PD-L1 (TPS ≥50%) and were not EGFR sensitising (activating) mutations or had ALK translocation. In the trial, treatment with pembrolizumab was compared with SOC.

The company presents results from the IA2 of the KEYNOTE-024 trial. The PFS results presented in the CS are based on data from the blinded independent central review (BICR) and the primary censoring analysis. Median PFS was found to be statistically significantly longer for patients in the pembrolizumab arm compared to median PFS for patients in the SOC arm, 10.3 months versus 6 months (hazard ratio [HR]=0.50; 95% CI 0.37 to 0.68, p<0.001).

Several subgroup analyses were carried out as per the final scope issued by NICE. Results showed that median PFS for patients treated with pembrolizumab was improved compared with median PFS for patients treated with SOC for all of the specified subgroups e.g., patients with squamous disease (HR=0.35; 95% CI 0.17 to 0.71), patients with non-squamous disease (HR=0.55; 95% CI 0.39 to 0.76) and patients treated with non-pemetrexed platinum doublets (HR=0.29; 95% CI 0.17 to 0.50) and patients treated with platinum+pemetrexed (HR= 0.63; 95% CI 0.44 to 0.91).

Patients in the SOC arm were permitted to cross over and receive pembrolizumab after RECIST-defined disease progression. Nearly half (43.7%) of the patients randomised to the SOC arm of the KEYNOTE-024 trial crossed over to receive pembrolizumab. The OS results show that 108 (35.4%) deaths had occurred at the time of the IA2; these events represent 64% of the target number of events at final analysis (170 deaths). The ERG notes that median OS had not been reached in either the intervention arm or the comparator arm. The company

assessed the suitability of three different methods to adjust for treatment crossover. The company selected the 2-stage approach to be the most appropriate. The OS HR result for the comparison of treatment with pembrolizumab versus SOC without adjusting for treatment switching indicates a statistically significant treatment benefit for patients treated with pembrolizumab compared with those treated with SOC (HR=0.60; 95% CI 0.41 to 0.89 p=0.005), the crossover adjusted HR also indicates a statistically significant treatment benefit (HR=0.50; 95% CI 0.34 to 0.76, p=0.0009).

Results from subgroup analyses for OS [redacted]

HRQoL outcomes using the European Organisation for Research and Treatment Cancer (EORTC) Quality of Life, the EORTC Quality of Life in Lung Cancer and the EuroQoL EQ-5D 3L questionnaires favour treatment with pembrolizumab. The safety data demonstrate that the numbers of patients who experienced any AE or any serious AE (SAE) were similar in both arms of the trial. Compared with the pembrolizumab arm, drug-related AEs (including grade 3 to 5 AEs) were more frequent in the SOC arm as were discontinuations due to AEs and drug-related AEs. A higher proportion of patients in the pembrolizumab arm discontinued treatment due to SAEs (8.4% versus 7.3%) and drug-related SAEs (6.5% versus 4.7%) than in the SOC arm.

Indirect evidence

In the population of interest, there are no RCTs comparing the clinical effectiveness of pembrolizumab with the other comparators identified in the final scope issued by NICE. The company therefore conducted a series of NMAs to compare PFS and OS for five different comparators. The primary population of interest was the population of all-comers (all histologies combined). The company constructed additional networks to independently consider the squamous and non-squamous populations.

Results from the all-comers (all histologies combined) network show that treatment with pembrolizumab statistically significantly improves PFS and OS compared to all other comparators of interest.

The results from these NMAs were **not** used in the company's base case cost effectiveness analyses.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

The ERG considers that the KEYNOTE-024 trial was a small, well-conducted, open-label, RCT. However, when the results of IA2 were made available, the trial Data and Safety Monitoring Committee (DSMC) recommended that the KEYNOYE-024 trial should be stopped early for benefit; at this time, only 35% of the total number of expected OS events had occurred and median OS had not been reached in either of the trial arms. The ERG is aware of published evidence that shows that several trials that have been stopped early for benefit have not delivered the anticipated survival gain estimated at the time stopping. The protocol for the KEYNOTE-024 trial allowed patients receiving SOC to cross over at disease progression to receive pembrolizumab and, at the time of IA2, 43.7% of patients from the SOC arm had crossed over. The ERG considers that the immaturity of the OS data and the high level of patient crossover limit the reliability of the OS data from the KEYNOTE-024 trial. Furthermore, the ERG considers that the results of the patient subgroup analyses from the KEYNOTE-024 trial should be interpreted with caution given the small numbers of patients and the small numbers of events in each subgroup.

The company considered three different methods to adjust the trial OS data for the effect of crossover (2-stage method, rank preserving structural failure time [RPSFT] method and the inverse probability of censoring weighting method [IPCW]). Of the methods considered to adjust for treatment crossover, the ERG agrees with the company that the 2-stage model was the most appropriate. However, the ERG considers that results generated from the 2-stage adjustment method (and the RPSFT and ICPW methods]) are unreliable. All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. This (initial) HR is only reliable if the OS hazards for the two trial datasets are proportional. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. As the (initial) HR result is uncertain, all adjustments to it should be viewed with caution.

The company provided PFS results as assessed by BICR. In response to the ERG's request, the company provided the results of an exploratory analysis of PFS based on investigator assessment. The PFS results for patients in the SOC arm were similar, irrespective of method of assessment ([redacted]). However, the PFS results for patients in the pembrolizumab arm were different ([redacted]). The ERG is uncertain of the reasons for, or the implications of, the [redacted] difference between the BICR-assessed PFS and investigator-assessed PFS results for patients treated with pembrolizumab. Clinical advice to the ERG is that the difference between investigator-assessed and BICR-assessed PFS may be the result of the inexperience of the trial investigators with the use of pembrolizumab in treating NSCLC. The ERG notes that in the event that pembrolizumab is recommended for use in the NHS, very few clinicians are likely to be experienced in the use of pembrolizumab for treating NSCLC.

Indirect evidence

The ERG considers that it was appropriate for the company to conduct an indirect treatment comparison to support the existing direct evidence comparing pembrolizumab with the comparators of interest. In the main body of the CS, the company presents the results of NMAs undertaken using fractional polynomials; these results are not used to inform the company's cost effectiveness base case. The ERG is satisfied that the clinical assumptions made by the company to construct the evidence networks are reasonable.

Although the ERG considers that the methodology used to conduct the main NMA (all-comers) is appropriate, the ERG's view is that the results are unreliable. First, there is extensive heterogeneity between the included trials (e.g., only the KEYNOTE-024 trial includes a population of patients whose tumours strongly express PD-L1 and the KEYNOTE-024 trial includes only patients with stage IV disease whereas there are patients with stage III and IIIb disease in the other included studies). Second, the company's unadjusted and adjusted treatment crossover results are very similar raising concerns over the accuracy of the results. Third, there is the possibility that the company may have double-counted patients in the pembrolizumab arm of the KEYNOTE-024 trial in the NMAs, which could lead to over inflation of the results and produce biased estimates of OS.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with pembrolizumab versus SOC for untreated patients with advanced NSCLC whose tumours strongly express PD-L1. The model comprises three mutually exclusive health states: pre-progression, post-progression, and dead. All patients

enter the model in the pre-progression health state and remain in this state until disease progression. The model time horizon is set at 20 years and has a 1-week cycle length. The model perspective is that of the UK NHS. Outcomes were measured in quality adjusted life years (QALYs), and both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE.

Data from the KEYNOTE-024 trial were used to estimate patient survival and to estimate patient utility. 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.

The company modelled OS using a 2-phase piecewise model with an exponential distribution appended to K-M data from the KEYNOTE-024 trial. The K-M data were adjusted in the SOC arm, using the 2-stage approach, for crossover. Separate exponential models were fitted to data from each arm of the trial, at week 22, to extrapolate survival up to 20 years. The company's base case analysis prediction is a mean of 1.22 life years gained (LYG) for patients receiving SOC and 2.75 LYG for patients receiving pembrolizumab.

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 mean EQ-5D utility scores by time to death used in the company base case are ≥360 days: 0.808; ≥180 to <360 days: 0.712; ≥30 to <180 days: 0.598; and <30 days: 0148.

The company base case incremental cost effectiveness ratio (ICER) for the comparison of treatment with pembrolizumab versus SOC is £44,896 per QALY gained; pembrolizumab generates 1.21 additional QALYs at an additional cost of £54,185. The company carried out a wide range of deterministic sensitivity analyses. The most influential parameters are related to the extrapolation of OS for patients treated with pembrolizumab, the utility associated with long-term survival and the extrapolation of OS for patients treated with SOC. The company's probabilistic sensitivity analysis (PSA) results show that when the cost effectiveness of treatment with pembrolizumab is compared with SOC there is a 62% probability of treatment with pembrolizumab being cost effective at a threshold of £50,000 per QALY gained. The company carried out nine scenario analyses and results from these demonstrated that the cost effectiveness of treatment with pembrolizumab versus SOC was only sensitive to two scenarios, both of which employed alternative methods of extrapolating OS.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers that there are 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.

First, any extrapolation of OS data from patients in the pembrolizumab arm of the KEYNOTE-024 will be highly uncertain due to only 35.4% of the total events having occurred.

Second, the company's extrapolation of OS data from patients in the SOC arm of the KEYNOTE-024 trial is overly pessimistic compared to survival results available from registry data and published studies describing patients with stage IV NSCLC treated with chemotherapy. Survival, predicted by the company extrapolation, for patients treated with SOC at 5 years is 1.9%, whereas National Lung Cancer Audit (NLCA) data suggest that 5-year survival for all patients with stage IV NSCLC is 5%. Given that not all patients in the NCLA dataset received chemotherapy (which has been shown to extend life), the ERG considers that using an extrapolation method that predicts 5.0% survival at 5 years will still lead to a conservative estimate of the ICER per QALY gained for the comparison of treatment with pembrolizumab versus SOC.

Third, 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, for patients with untreated PD-L1 positive metastatic NSCLC, [redacted] The ERG, therefore, considers 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.

Fourth, the ERG considers that the utility values incorporated into the company model, which were derived from data collected as part of the KEYNOTE-024 trial, are implausibly high, notably for the period 360 days before death when these values are higher than the UK population norm.

1.7 Summary of company's case for End of Life criteria being met

The company has put forward a case that pembrolizumab meets NICE's End of Life criteria based on the following points:

- available data from the SOC arm of the KEYNOTE-024 trial, in conjunction with NCLA data (11.3 months for patients with stage IIIb/IV, PS 0 to 1 and receiving

chemotherapy) suggest that the median OS for the population under consideration in this appraisal is less than 24 months

- the results of the company's economic modelling suggest a mean OS gain of over 14 months for patients treated with pembrolizumab compared with SOC.

1.8 ERG commentary on End of Life criteria

The ERG agrees with the company that average patient life expectancy is less than 24 months. The mean OS for patients treated with SOC generated using the ERG adjusted company model (based on 5% survival at 5 years) is 1.86 years (22.3 months). The undiscounted difference in mean survival between patients treated with pembrolizumab versus SOC estimated by the ERG amended model is 1.07 years (12.8 months). Although there is considerable uncertainty around the validity of the representations of OS in the company model, the ERG is satisfied that the evidence is sufficient to suggest that the OS of patients treated with pembrolizumab is likely to be, on average, at least 3 months more than that of patients treated with SOC.

The ERG, therefore, considers that pembrolizumab meets the End of Life criteria for the target patient population presented by the company in the CS.

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical evidence

- The company provided a detailed submission. Requests for further clinical information were fulfilled to a good standard
- HRQoL data were collected during the KEYNOTE-024 trial
- The company conducted a good quality systematic review to inform the direct and indirect evidence comparisons
- The company has explored alternative methods to assess the effects of treatment crossover on OS.

Cost effectiveness evidence

- The economic model was well constructed
- The company carried out a comprehensive range of deterministic sensitivity and scenario analyses.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- The KEYNOTE-024 trial was an open-label trial that was stopped early for benefit. At the time of stopping, median OS had not been reached in either arm of the trial. It is unknown whether the OS benefit observed at IA2 will be observed in the longer-term

- The impact on OS of patient crossover from the SOC arm to treatment with pembrolizumab is unclear even after the company's extensive exploration of alternative methods to assess the effects of treatment crossover
- The company carried out Cox proportional hazards modelling for OS but did not check the proportional hazards assumption for validity as it was not pre-specified. After checking, the ERG identified that the assumption of proportional hazards was invalid and therefore the OS results should be interpreted with caution
- There is no direct evidence of the clinical effectiveness to allow a comparison of pembrolizumab compared with the individual comparators listed in the final scope issued by NICE
- The ERG is uncertain of the reasons for, or the implications of, the [redacted] difference between the BICR-assessed PFS and the investigator-assessed PFS for patients in the pembrolizumab arm of the KEYNOTE-024 trial [redacted].
- The ERG considers that the results of the company NMAs are unreliable for the following reasons:
    - there is extensive heterogeneity between included studies (e.g., PD-L1 status, disease stage, race/ethnicity)
    - the unadjusted and adjusted NMA results are 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
- Information is only provided on the binary assessment of the immunohistochemical marker PD-L1. In addition to validation of the test, the ERG considers that further information is likely to emerge on PD-L1 as a continuous predictive biomarker
- In the draft SmPC for pembrolizumab, it is stipulated that treatment should be initiated only after a validated laboratory test has confirmed the tumour expression of PD-L1. Clinical advice to the ERG is that, at present, there is no established or validated test for PD-L1 expression and testing for PD-L1 expression is not routinely available in NHS treatment centres. The ERG notes that, in the NHS, there is currently no standard means of identifying patients whose tumours strongly express PD-L1
- Clinical advice to the ERG is that AEs arising from treatment with immunotherapy (i.e., pembrolizumab) in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.

Cost effectiveness evidence

- The long-term OS of patients treated with pembrolizumab is highly uncertain. Even though the company chose the most pessimistic extrapolation from those considered in the submission, it may be that this is still an overly optimistic extrapolation – especially if the actual survival curve has multiple phases
- The company's OS projection for patients treated with SOC results is overly pessimistic and results in survival at 5-years being only 1.9%. The ERG considers that published evidence points to survival being at least 5% at 5 years
- The company assumes an arbitrary stopping rule for treatment with pembrolizumab after 35 cycles (2 years). The ERG considers 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

- Utility values in the model, which were derived from data collected during the KEYNOTE-024 trial, are implausibly high, with the value for patients who are a year away from death being higher than the UK population norm for people of the same age.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

Due to the extreme uncertainty around any projection of OS for patients receiving pembrolizumab, the ERG has not made any revisions to the company's projection. However, the ERG has implemented the following changes to the model:

- removing the arbitrary 2 years (35 cycle) limit on the number of cycles of pembrolizumab that can be administered
- altering the OS extrapolation for patients receiving SOC such that 5% of patients are alive at 5 years
- limiting the magnitude of the utility values used in the model so that they are no higher than the UK population norm for people of the same age.

The ERG considers that the last two of these amendments are conservative. Published figures suggest that OS at 5 years for patients receiving SOC could be as high as 13%. Utility values for patients with metastatic NSCLC are likely to be lower than those in the general UK population of the same age.

1.11 Cost effectiveness conclusions

Application of the ERG model amendments results in an ICER for the comparison of treatment with pembrolizumab versus SOC of £114,291 per QALY gained. Given that the amendments made by the ERG to the company's OS extrapolation for patients receiving SOC and to the utility values employed in the model are very conservative, the ERG's revised cost effectiveness results should be interpreted as a lower bound estimate of the ICER per QALY gained for this comparison.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section 3.1 of the company submission (CS[1]) includes an overview of non-small cell lung cancer (NSCLC). Section 3.2 of the CS includes a description of the effects of the disease on patients, carers and society. Information about the life expectancy of this population in England is presented in Section 3.4 of the CS. Key points from these sections are included as bulleted items in Box 1 and Box 2. The Evidence Review Group (ERG) considers that these points appropriately summarise the underlying health problems. The ERG notes that the patient population of interest to the company is a subset of the overall NSCLC PD-L1 population, i.e. patients with untreated metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥50%). At present there are few data available that are specific to patients whose tumours express PD-L1.

Box 1 Company overview of NSCLC

Disease types and staging

- NSCLC accounts for up to 85-90% of lung cancer cases in the UK(34) and includes two major histological subtypes: squamous cell carcinoma (25% to 30%) and non-squamous cell carcinoma, including adenocarcinoma (30% to 40%), large-cell carcinoma (10% to 15%), and other cell types (5%).
- NSCLC is staged according to the Tumour-Node-Metastasis (TNM) classification, based on the primary tumour size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M). This information is combined to assign an overall stage of 0, I, II, III, or IV.
- If the cancer has spread to the lymph nodes on the opposite side of the chest, or above the collar bone, it is called stage IIIB. In stage IV NSCLC the cancer has spread to distant lymph nodes or to other organs such as the liver, bone, or brain.
- More than 50% of NSCLC tumours test positive for at least one molecular biomarker; most commonly mutations in Kirsten rat sarcoma (KRAS) (15-20%) epidermal growth factor receptor (EGFR) (17%), and translocations involving anaplastic lymphoma kinase (ALK) (2-7%).
- Programmed cell death ligand 1 (PD-L1), the ligand of PD-1 receptor, is a cell surface protein that has recently been studied in a number of resected NSCLC specimens; the findings of previous studies have shown that the percentage of patients with advanced NSCLC whose tumours strongly express PD-L1, defined as tumour proportion score [TPS] ≥50% is between 23% and 28%.

Epidemiology and prognosis

- In the UK, lung cancer is the most common cause of cancer death. Over 35,000 people die from lung cancer each year, accounting for more than 1 in 5 cancer deaths.
- NSCLC is potentially curable when diagnosed at an early stage; however over half of those diagnosed with lung cancer present at stage IV which is associated with a poor prognosis.
- Treatment for patients with advanced NSCLC aims to prolong OS and improve HRQoL by improving symptoms. Patients with a good performance status have been shown to benefit from first-line therapy however approximately 55% of patients will continue to second line therapy due to disease progression.
- Despite recent advances in therapy, patients with NSCLC have a poor prognosis that has not changed significantly over the past decade. The median survival is only 6 to 10 months; duration of response is limited, and almost all patients relapse and die. The corresponding 5-year overall survival rate for stage IV patients is 3%.

The ERG notes that tumours classified as stage IIIB or stage IV are referrred to as advanced and/or metastatic tumours. The population discussed in the CS is patients who have stage IV disease. Clinical advice to the ERG is that EGFR and ALK positivity are mutually exclusive and have therapeutic implications for NICE approved targeted therapy. There are no current treatment implications for tumours of KRAS status.

Box 2 Company's overview of the effects of NSCLC on patients, carers and society

Effects of NSCLC on patients, carers and society

- The pathway leading to the confirmation and communication of diagnosis is often a very frustrating experience for patients due to delays, lack of information and support, and uncertainty regarding next steps
- Patients with NSCLC have reported the highest prevalence levels of psychological distress (three times more than in other cancers), which can lead to a poorer prognosis and greater patient burden. Increased levels of psychological distress are reported by patients undergoing oncological treatment and by those approaching death
- Patients with advanced NSCLC are in need of help from caregivers, particularly in the period leading to death
- Informal caregivers are increasingly recognised as recipients of care themselves, as they have to deal with the distressing nature of the patient's symptoms. Unmet need is more prevalent among caregivers of patients with lung cancer, who report concerns in terms of reducing stress in the patient, understanding the experience of the cancer patient and even accessible, affordable, hospital parking
- Advanced NSCLC imposes a substantial burden to society, not only in terms of years of life lost due to premature death, but also due to the corresponding loss of contribution to the economy and the substantial health care costs associated with its prevention and management
- Lung cancer costs the UK economy an estimated £2.4 billion per year, highest among the four most prevalent cancer types in the UK (considering breast cancer, prostate cancer and colorectal cancer)
- Informal care and healthcare costs account for 16% and 35% of the cost of lung cancer respectively
- £1.2 billion of the annual loss to the economy can be attributed to wage losses due to premature deaths of patients with lung cancer, who were previously in employment.
- According to Cancer Research UK, the average cost per lung cancer patient is £9,071 to the healthcare system annually, whereas an average cost per cancer patient in the UK is £2,776.

2.2 Critique of company's overview of current service provision

An overview of current service provision is presented in Section 3.3 of the CS. The company correctly observes that treatment for patients with advanced NSCLC is guided by tumour histology, tumour genotype and by patient performance status (PS). The ERG notes that, at present there are no specific treatments available for patients with advanced or metastatic NSCLC whose tumours express PD-L1 (i.e. the patient population identified in the final scope[2] issued by NICE). Clinical advice to the ERG is that the relationship between PD-L1 status and tumour histology and/or genotype is not fully understood.

The company summarises the current treatment pathway for patients in the NHS with advanced or metastatic NSCLC according to NICE guideline CG121[3] and published NICE guidance[4-8] (Table 1). The ERG notes that NICE guidance also recommends the use of pemetrexed monotherapy as a maintenance treatment for patients with tumours of non-

squamous histology whose disease has not progressed after four cycles of platinum doublet chemotherapy with docetaxel, paclitaxel, gemcitabine (TA190[9]) or pemetrexed (TA402[10]).

Table 1 Company summary of NICE guidelines and guidance

NICE guideline or guidance	Summary of NICE recommendation
CG121[3] (2011)	• For patients with tumours of negative or unknown EGFR status and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) chemotherapy should be offered; where the chemotherapy should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) • Patients who are unable to tolerate combination therapy may be offered single-agent chemotherapy with a third-generation drug
TA181[4] (2009)	• Pemetrexed in combination with cisplatin is recommended if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma
TA192[5] (2010)	• Patients whose tumours test positive for EGFR tyrosine kinase mutation are eligible to receive first-line treatment with gefitinib
TA258[6] (2012)	• Patients whose tumours test positive for EGFR tyrosine kinase mutation are eligible to receive first-line treatment with erlotinib
TA310[7] (2014)	• Patients whose tumours test positive for EGFR tyrosine kinase mutation are eligible to receive first-line treatment with afatinib
TA406 [8](2016)	• patients whose tumours test positive for anaplastic lymphoma kinase (ALK) mutation are eligible to receive first-line treatment with crizotinib

EGFR=epidermal growth factor receptor; WHO=World Health Organisation
Source: CS, p36 and p40

The company has presented a treatment algorithm outlining the existing treatment pathway for patients in the NHS with advanced or metastatic NSCLC (Figure 1). The company positions pembrolizumab as a first-line treatment for patients with metastatic NSCLC whose tumours have a PD-L1 TPS≥50% and no EGFR or ALK positive mutations (CS, p37). The company considers pembrolizumab is an alternative treatment to platinum doublet chemotherapy, single agent chemotherapy or pemetrexed+cisplatin in appropriate patients. The ERG notes that the algorithm presented by the company broadly reflects current clinical practice and would capture the treatment pathway in the event that pembrolizumab were to be recommended by NICE for use in the NHS.

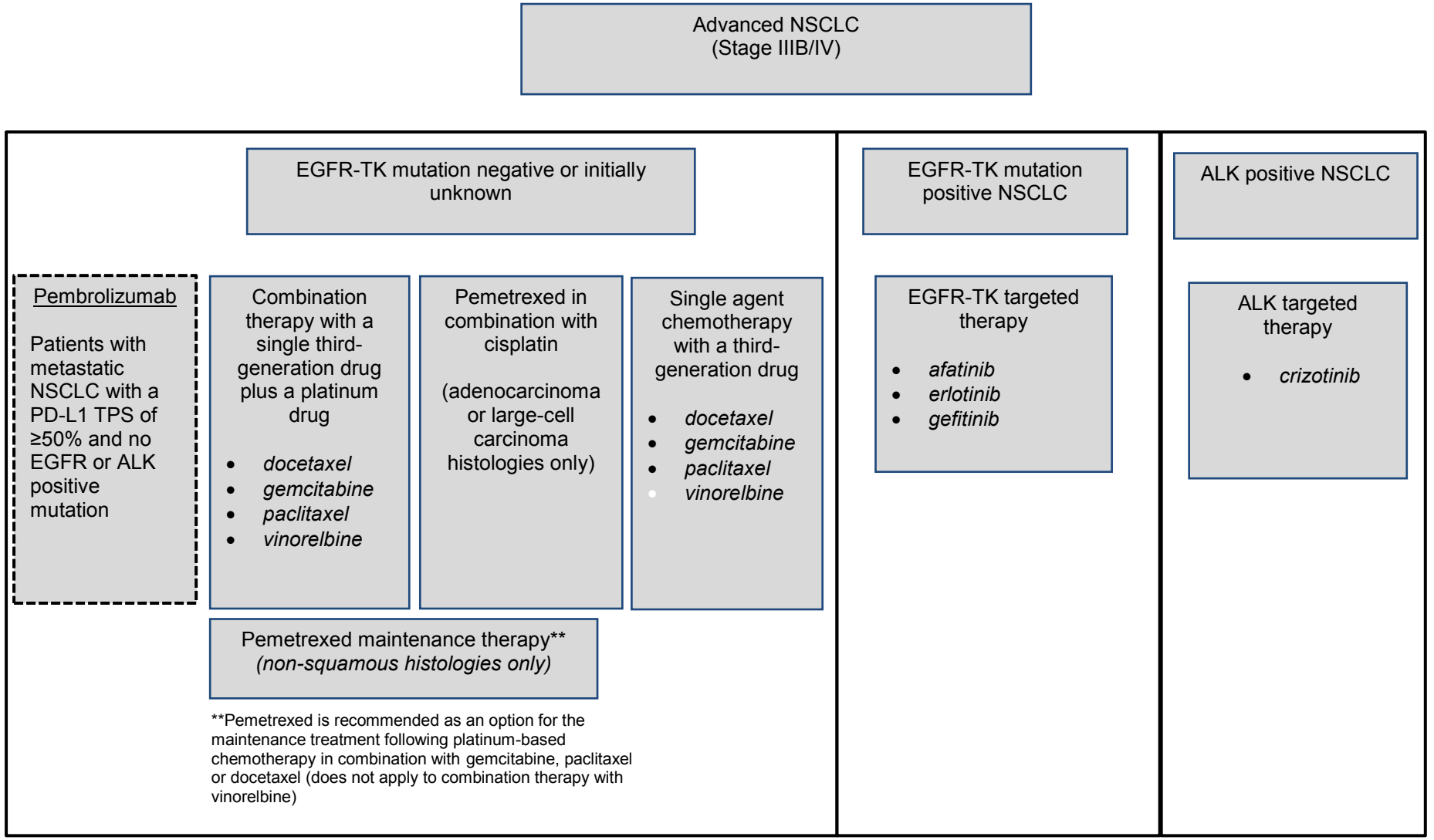


Figure 1 Company's treatment algorithm with proposed position of pembrolizumab

Source: CS, Figure 3

2.2.1 Testing for PD-L1 expression in the NHS

PD-L1 expression is assessed in a laboratory through immunohistochemistry (IHC) staining. The ERG is aware that, in the NHS, there is currently no established test for PD-L1 expression and that routine testing for PD-L1 expression in the NHS is not available. [redacted]

2.3 Innovation

The company considers that pembrolizumab is an innovative treatment and reports (CS, p31) that:

- patients can be selected for targeted treatment based on their PD-L1 status
- treatment with pembrolizumab offers a significant survival benefit and is better tolerated than treatment with chemotherapy
- the US Food and Drug Administration granted pembrolizumab Breakthrough Therapy Designation and priority review for the first-line treatment of patients with advanced NSCLC whose tumours express PD-L1[11]
- pembrolizumab received Promising Innovative Medicines designation (Early Access to Medicines Scheme (EAMS) Step 1) in November 2015, and in March 2016 pembrolizumab was granted a positive Scientific Opinion by the Medicines and Healthcare Products Regulatory Agency's (MHRA) (MHRA EAMS number 00025/0001) for the treatment of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test.[12]

2.4 Number of patients eligible for treatment with pembrolizumab

The company estimates that in England, approximately 1500 patients per annum would be eligible for treatment with pembrolizumab. The company's method for calculating the patient numbers is described in the CS (CS, p234).

The ERG considers the company's estimate of approximately 1500 patients to be reasonable.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem described by the company in the CS in relation to the final scope[2] issued by NICE is presented in Table 2. A summary comparison between the decision problem outlined in final scope and that addressed within the CS is also presented in Table 2. Each parameter in Table 2 is discussed in more detail in the text following the table.

Table 2 NICE scope and company's decision problem

NICE scope Parameter and specification	**Decision problem addressed in the company submission**
Population People with PD-L1 positive NSCLC not treated with chemotherapy in the metastatic setting	• The evidence presented in the CS is relevant to a subset of patients identified in the final scope issued by NICE • The population discussed in the CS is previously untreated patients with metastatic (stage IV) NSCLC whose tumours **strongly** express PD-L1 with no EGFR or ALK positive mutations Strong expression of PD-L1 is defined in the CS as: membranous PD-L1 expression on at least 50% of tumour cells, regardless of the staining intensity. The patient population discussed in the CS has a tumour proportion score (TPS) of 50% or greater
Intervention Pembrolizumab	Pembrolizumab
Comparators • 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 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)	Direct evidence presented in the CS • In the KEYNOTE-024[13] trial pembrolizumab is compared with 'standard of care' (SOC). The SOC regimens comprise platinum doublet chemotherapy of either gemcitabine or paclitaxel, or (for patients with non-squamous NSCLC), platinum doublet pemetrexed Patients with non-squamous NSCLC without disease progression after treatment were eligible for maintenance treatment with single agent pemetrexed. Results are presented for overall SOC treatment. The results of a subgroup analysis of PFS and OS outcomes for patients treated with platinum doublet regimens that included, or did not include, pemetrexed are also presented in the CS • No direct evidence is presented in the CS for the comparison of pembrolizumab with platinum doublet docetaxel, gemcitabine, paclitaxel or vinorelbine Indirect evidence presented in the CS • Pembrolizumab is compared with all platinum doublet chemotherapies listed in the final scope issued by NICE (docetaxel, gemcitabine, paclitaxel, vinorelbine) and platinum doublet pemetrexed in non-selected populations of patients with advanced or metastatic NSCLC No evidence presented • The company has not considered treatment with single agent chemotherapy
Outcomes OS PFS RR AEs HRQoL	As per the NICE scope
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	As per the NICE scope The time horizon considered is 20 years

NICE scope Parameter and specification	**Decision problem addressed in the company submission**
The use of pembrolizumab is conditional on the presence of 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	
Other considerations 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 company has presented a subgroup analysis by tumour histology (squamous or non-squamous). The company was not able to undertake a subgroup analysis by level of PD-L1 expression as the KEYNOTE-024[13] trial (the main source of clinical effectiveness evidence) included only patients whose tumours were defined as strongly expressing PD-L1 (i.e., TPS ≥50%).

AE=adverse event; ALK=anaplastic lymphoma kinase; BSC=best supportive care; CDF=cancer drugs fund; EGFR=epidermal growth factor receptor; HRQoL=health-related quality of life; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; OS=overall survival; PD=platinum doublet; PFS=progression-free survival; PD-L1=programmed death ligand 1; QALY=quality adjusted life year; RR=response rate; SOC=standard of care; TPS=tumour proportion score
Source: CS, Table 1

3.1 Pembrolizumab clinical evidence

The main evidence for the clinical effectiveness of pembrolizumab is derived from a small randomised controlled trial (RCT) known as the KEYNOTE-024[14] trial. The currently available OS data from the KEYNOTE-024 trial are based on a second interim analysis (IA2), when only 35% of the expected events had occurred. Median follow-up was 11.2 months. Median OS has not been reached in either arm of the KEYNOTE-024 trial.

In the KEYNOTE-024 trial, patients in the SOC arm were able to cross over to treatment with pembrolizumab when their disease had progressed and, at IA2, 43.7% of patients from the SOC arm had received treatment with pembrolizumab. The ERG considers that the level of patient crossover and the immaturity of the available OS data mean that the available data are difficult to interpret.

The KEYNOTE-024 trial was stopped early for benefit at IA2 by the trial Data and Safety Monitoring Committee (DSMC). The ERG is aware that there is evidence that some trials that have been stopped early for benefit have not delivered the anticipated survival gain estimated at the time of stopping.[15-17]

The KEYNOTE-024 trial was designed to compare the clinical effectiveness and safety of treatment with pembrolizumab compared with 'standard of care' (SOC). SOC is used as a global term for chemotherapies that include platinum doublet chemotherapy and gemcitabine, paclitaxel or, for patients with non-squamous histology, pemetrexed. The trial results are

presented as comparisons of the effectiveness and safety of treatment with pembrolizumab versus SOC.

The company has conducted network meta-analyses (NMAs to allow the effectiveness of treatment with pembrolizumab to be compared with all of the comparator platinum doublet chemotherapies listed in the final scope issued by NICE).

3.2 Population

The population described in the final scope issued by NICE is people with PD-L1 positive NSCLC who have not been treated with chemotherapy in the metastatic setting. The population discussed in the CS is a subset of this population, namely patients with untreated metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutations. The ERG notes that the patient population discussed in the CS matches the patient population in the KEYNOTE-024 trial and is expected to match the patient population indicated in the anticipated marketing authorisation soon to be issued by the EMA.

On December 15th 2016, the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency EMA issued a positive opinion[18] recommending the use of pembrolizumab as a first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 (TPS≥50%) with no EGFR or ALK positive tumour mutations.

The ERG notes that there is no clinical effectiveness evidence presented in the CS for the use of pembrolizumab in patients with untreated metastatic NSCLC with a PD-L1 TPS <50%, or for patients with a PD-L1 TPS ≥50% whose tumours also test positive for EGFR or ALK mutations.

The company has presented the results of patient subgroup analyses. The subgroups included age (≤65 versus >65 years), sex, race (white versus non-white), ECOG status (0 versus 1), geographic region of enrolling site (East Asia versus non-East Asia), histology (squamous versus non-squamous), smoking status (never versus former versus current), brain metastasis status (baseline brain metastasis versus no baseline brain metastasis), investigators choice of standard of care chemotherapy.

Pembrolizumab is currently licensed in Europe for the treatment of advanced (unresectable or metastatic) melanoma[19] and for the treatment of locally advanced or metastatic NSCLC[19] in patients whose tumours express PD-L1 (TPS ≥1%) and who have received at least one prior chemotherapy regimen. For the latter indication, patients with EGFR or ALK positive tumour mutations should have received prior therapy.

The ERG is aware that NICE is currently appraising pembrolizumab as a treatment for PD-L1 positive NSCLC after platinum chemotherapy (ID840[20]). NICE expects to publish final guidance in January 2017.

The company reports (CS, p28) that patients in the NHS are able to receive treatment with pembrolizumab under the Early Access to Medicines Scheme (EAMS).[21] It is stated within the EAMS Public Assessment Report[21] that pembrolizumab can be used to treat patients with metastatic NSCLC whose tumours express PD-L1 (as determined by a validated test) and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation.

3.3 Intervention

The intervention specified in the final scope issued by NICE, and discussed in the CS, is pembrolizumab. Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging with its ligands PD-L1 and PD-L2 (CS, p14). It is administered as an intravenous infusion. The treatment regimen for pembrolizumab in the first-line setting is a 200mg intravenous infusion administered over 30 minutes every 3 weeks (Q3W) until [redacted]

It is reported (CS, p62) that the number of pembrolizumab treatments in the KEYNOTE-024 trial is limited to 35, i.e., treatment duration of approximately 2 years. The company states (CS, p73) that at the time that the CS was written, none of the patients in the KEYNOTE-024 trial had received 35 treatments. In the company's economic model, patients can receive up to 35 treatments with pembrolizumab. The ERG notes from the draft SmPC[1] for pembrolizumab that [redacted]

Testing for PD-L1 expression

In the draft SmPC[1] for pembrolizumab, it is stipulated that treatment should be initiated only after a validated laboratory test has confirmed the tumour expression of PD-L1. Clinical advice to the ERG is that, at present, there is no established or validated test for PD-L1 expression and testing for PD-L1 expression is not routinely available in NHS treatment centres.

PD-L1 expression is determined from IHC staining of a tumour sample collected via a biopsy. [redacted]

[redacted]

3.4 Comparators

The comparators specified in the final scope issued by NICE are:

- 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 (people with adenocarcinoma or large cell carcinoma only) with or without pemetrexed maintenance treatment
- single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) for people for whom platinum combination therapy is not appropriate).

Clinical advice to the ERG is that, in the NHS, patients with NSCLC are rarely treated with platinum+vinorelbine, and, that single agent docetaxel is predominantly used as second-line chemotherapy rather than as a first-line therapy. The ERG notes that pemetrexed is only licensed for use with cisplatin; however, clinical advice to the ERG is that, in the NHS, patients are also treated with carboplatin+pemetrexed, in view of the more favourable toxicity profile of carboplatin.

The direct evidence presented in the CS is derived from the KEYNOTE-024 trial in which treatment with pembrolizumab is compared with a 'standard of care' (SOC) chemotherapy regimen. The SOC regimen included a choice of platinum doublet treatments: gemcitabine, paclitaxel or, for patients with non-squamous histology, pemetrexed. Patients with tumours of non-squamous histology, who were treated with platinum doublet paclitaxel or platinum doublet pemetrexed, but not platinum doublet gemcitabine, also had the option to receive single agent pemetrexed maintenance therapy if their disease had not progressed after four to six cycles of platinum doublet chemotherapy.

There is no direct evidence available from the KEYNOTE-024 trial for the clinical effectiveness of pembrolizumab versus platinum+docetaxel, platinum+gemcitabine, platinum+paclitaxel or platinum+vinorelbine; however there is evidence presented (albeit from a subgroup analysis) for the clinical effectiveness of pembrolizumab versus platinum+pemetrexed. The company has stated (and the ERG agrees) that analysis by the individual treatments available in the KEYNOTE-024 trial (i.e. platinum+gemcitabine and platinum+paclitaxel) would be uninformative as the number of individual treatments allocated to patients is small.

In the absence of any direct evidence for the clinical effectiveness of pembrolizumab versus the individual platinum doublet chemotherapy regimens specified in the final scope issued by NICE, the company has conducted NMAs. The company has, therefore, in the main analysis,

chosen to compare the outcomes of treatment from a population of patients whose tumours strongly express PD-L1 with a population of patients whose PD-L1 status is unknown. The ERG is uncertain whether the outcomes of unselected patients with NSCLC can reasonably be compared with the outcomes of patients whose tumours strongly express PD-L1.

No evidence is presented in the CS (either direct or indirect) to allow a comparison of the clinical effectiveness of pembrolizumab with any of the single agent chemotherapies specified in the final scope issued by NICE. The rationale for this omission is not provided in the CS. Clinical advice to the ERG is that approximately 15% of NHS patients with NCSLC are treated with single agent chemotherapy in the first-line setting.

3.5 Outcomes

Clinical evidence from the KEYNOTE-024 trial is reported for all five outcomes specified in the final scope issued by NICE: progression-free survival (PFS), overall survival (OS), response rate (reported as objective response rate [ORR], best overall response rate, disease control rate), adverse events (AEs) of treatment and health-related quality of life (HRQoL). The ERG notes that, at IA2, median OS had not been reached in either arm of the trial. An additional problem when interpreting OS data from the KEYNOTE-024 trial is that the protocol[22] allowed patients in the SOC arm to switch to treatment with pembrolizumab after their disease had progressed; at the time of IA2, 47.3% of patients switched from SOC to pembrolizumab. The immaturity of the data, combined with patient crossover, means that the true impact of treatment with pembrolizumab on OS is difficult to ascertain.

The outcomes of PFS and OS are reported from the company's NMAs that compare pembrolizumab with each of the platinum doublet chemotherapies listed in the final scope issued by NICE.

3.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 20-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective. The company's economic model includes the costs associated with testing strategies to identify patients with PD-L1 expressing tumours.

3.7 Subgroups

Two subgroup analyses are identified in the final scope issued by NICE: i) analysis by tumour histology (squamous or non-squamous) and ii) level of PD-L1 expression (strong positive or weak positive). The CS includes an analysis of the outcomes of patients from the KEYNOTE-

024 trial according to histology; the ERG notes that 18% of patients in the KEYNOTE-024 trial were of squamous histology. The company has not conducted a subgroup analysis based on level of PD-L1 expression as only data from patients with strongly expressing tumours are available from the KEYNOTE-024 trial.

3.8 Other relevant factors

The company did not identify any equity or equality issues. The ERG is aware that an agreed Patient Access Scheme (PAS) is in place for pembrolizumab; however, the company reports (CS, p29) that it is currently discussing an updated PAS arrangement with the Department of Health. In the CS, the company has used the currently agreed PAS price for pembrolizumab. The list prices of docetaxel, gemcitabine, paclitaxel, vinorelbine and pemetrexed are used in all of the cost effectiveness analyses presented in the CS.

4 CLINICAL EFFECTIVENESS

This section provides a structured summary and critique of the clinical effectiveness evidence submitted by the company in support of the use of pembrolizumab for untreated PD-L1 positive metastatic NSCLC.

4.1.1 Systematic review methods

The company conducted a systematic review to identify studies of relevance to this appraisal. The company conducted a systematic search for RCTs to inform direct and indirect comparisons of the interventions. Separate searches were conducted for the retrieval of cost effectiveness evidence. Full details of the strategies used to locate clinical effectiveness evidence are reported in Section 4.1 and Appendix 2 of the CS. A summary of the systematic review methods employed by the company, with accompanying ERG comments, is presented in Table 3.

Overall, the ERG is satisfied that the company's systematic review methods were of an adequate standard, were relevant to the final scope issued by NICE and to the company's decision problem.

The company's literature searches were conducted in May 2016. The ERG has conducted its own searches (up to 2nd November 2016). An examination of the findings from the searches conducted by the ERG did not identify any relevant trials additional to those reported in the CS.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses[23] (PRISMA) diagram presented in the CS (CS, Figure 4) shows the results of the company's inclusion process. The company states (CS, p45) that the search of electronic databases, conference proceedings and clinical trial registries yielded 3301 non-duplicate references. Of these, 309 articles were selected for full text review and 269 articles were excluded following the application of the inclusion and exclusion criteria. Two company records (a clinical study report [CSR][24] and publication manuscript[13]) relevant to the KEYNOTE-024 trial were provided by the company at this stage. A total of 42 publications, representing 28 trials were selected for inclusion in the company's systematic review. Only one[13,24] of the 28 included RCTs (the KEYNOTE-024 trial) provides direct evidence for the clinical effectiveness of pembrolizumab versus any of the comparators identified in the final scope issued by NICE.

Table 3 Summary of and ERG comment on the systematic review methods used by the company

Review method	ERG comment
Searching	
• RCT only data searches • Databases searched included MEDLINE, MEDLINE in Process, Embase and CENTRAL (search strategies are described in Appendix 2 of the CS) from inception to 10th May 2016 • Grey literature was searched for clinical studies and conference abstracts	• The company states that all comparators recommended for the treatment of advanced NSCLC were included in the search strategy. However, only papers that described comparators relevant to the UK were included in the company's systematic review. The ERG considers this is appropriate. • The company states that, due to lack of data specific to the PD-L1 population described in the CS, the search was carried out to include metastatic NSCLC regardless of PD-L1 status. The ERG considers that it was appropriate to widen the search criteria • The ERG was able to replicate the electronic database searches • The company searched the appropriate conference abstracts • The ERG is confident that no relevant studies were missed
Eligibility criteria	
• Two independent assessors assessed study eligibility based on the criteria presented in Table 6 of the CS	• Use of two independent assessors improves the quality of reviews • Only articles published with full-text in the English language were considered • The ERG is satisfied that the eligibility criteria were relevant to the scope
Data extraction	
• Two independent assessors extracted data • A pre-defined extraction form was used	• The company has not reported the method used to extract study data. Quality assurance regarding data extraction is, therefore, uncertain
Quality assessment and risk of bias	
• Descriptive critical appraisal of all included RCTs and non-RCTs was undertaken using the NICE recommended methods	• Risk of bias was assessed using NICE recommended methods (NICE minimum criteria and the Cochrane Collaboration's Risk of Bias tool) • Two independent assessors carried out the risk of bias exercise

CS=company submission; ERG=Evidence Review Group; NSCLC=non-small cell lung cancer; PD-L1=programmed death ligand 1; RCT=randomised controlled trial
Source: CS, p43 to p47

4.1.2 Evidence synthesis

The company's search for RCT evidence identified one trial (the KEYNOTE-024[24] trial) that was eligible for inclusion in the systematic review.

The company did not conduct a search for non-randomised studies; however, details of a dose-ranging study, the F1 cohort study/KEYNOTE-001[25] study are described in the CS. Results from the KEYNOTE-024 trial and the F1 cohort study are presented narratively in the CS.

The company reports (CS, p106) that the designs of the two studies are too different to allow any pooling of the data. The doses of pembrolizumab administered in the KEYNOTE-024 trial and the F1 cohort study are different and only a small subset of patients (n=27) in the F1

cohort study had tumours with a TPS ≥50%. The ERG agrees with the company that pooling data from the KEYNOTE-024 trial and the F1 cohort study is inappropriate.

To compare the clinical effectiveness of treatment with pembrolizumab with the platinum doublet chemotherapy comparators listed in the final scope issued by NICE, the company has conducted NMAs.

4.2 Critique, analysis and interpretation of trials of the technology

4.2.1 Identified studies presented in the company submission

Key trial

The company presents evidence from the KEYNOTE-024 trial for the clinical effectiveness of treatment with pembrolizumab. The patients recruited to the RCT had untreated stage IV NSCLC and their tumours strongly expressed PD-L1 (TPS ≥50%) with no sensitising EGFR mutations or ALK translocations. Patients were randomised to receive either pembrolizumab 200mg Q3W or SOC chemotherapy. Details relevant to the KEYNOTE-024 trial are reported in the CS, in the trial CSR and in a published paper.[13]

Other studies

In the dose-ranging F1 cohort study, 101 patients with untreated stage IV NSCLC whose tumours expressed PD-L1 with no EGFR mutations or ALK translocations were randomised to one of three different pembrolizumab treatment regimens, 2mg/kg Q3W, 10mg/kg Q3W or 10mg/kg Q2W. Details of the F1 cohort study are described in the CS, in the trial CSR[26] and in a manuscript currently under review by an oncology journal.[26] The company considers that the data from the F1 cohort study provide supportive evidence for the survival benefit of pembrolizumab over a longer period of follow-up (22 months) than is currently available from the KEYNOTE-024 trial (11 months).

The ERG considers that the results of the F1 cohort study are of minimal relevance to the company's decision problem given that only 27 patients in the study had tumours with a TPS of ≥50% and that the doses of pembrolizumab administered in the F1 cohort are different to the dose of pembrolizumab administered in the KEYNOTE-024 trial. The ERG notes that the licensed dose of pembrolizumab is likely to match the 200mg dose used in the KEYNOTE-024 trial.

A summary of the details of the F1 cohort study is presented in Appendix 1 of this ERG report.

Network meta-analysis

The company identified 28 trials for inclusion in the NMAs. The ERG's summary and critique of the company's NMAs is presented in Section 4.9 of this ERG report.

4.3 Characteristics of the KEYNOTE-024 trial

The key characteristics of the KEYNOTE-024 trial are summarised in Table 4. The trial was conducted internationally and included 305 patients who were randomised in a 1:1 ratio to receive either pembrolizumab or SOC. The SOC treatment administered to each patient was decided by the investigator at each trial site prior to randomisation. Randomisation was stratified by ECOG PS (0 versus 1), geographic region of enrolling site (East Asia versus non-East Asia) and histology (squamous versus non-squamous).

Eligibility criteria for entry into the KEYNOTE-024 trial were provided by the company (CS, p53). Clinical advice to the ERG is that the eligibility criteria are reasonable. Twenty-one patients from eight treatment centres based in the UK were included in the trial.

The SOC treatments are described in detail in Table 4. As part of the clarification process, the ERG asked the company (Question A5) to explain why patients in the KEYNOTE-024 trial whose disease had not progressed after four cycles of platinum+gemcitabine were not able to receive pemetrexed maintenance treatment. The ERG is aware that pemetrexed maintenance is available to patients in the NHS whose tumours are of non-squamous histology and whose disease has not progressed after four cycles of platinum+gemcitabine, docetaxel, paclitaxel or pemetrexed (TA190[9] & TA402[10]).

The company explained that in the planning stages of the KEYNOTE-024 trial, it was envisaged that platinum+gemcitabine would be used mainly to treat patients with squamous disease. Trial investigators knew that squamous patients treated with platinum+gemcitabine would not be eligible to receive pemetrexed as a maintenance treatment. Trial investigators also knew that the alternative SOC treatments (i.e., platinum+paclitaxel or platinum+pemetrexed) could be followed by pemetrexed maintenance (in patients with non-squamous disease). The ERG notes that in the KEYNOTE-024 trial, nine patients with non-squamous disease were treated with platinum+gemcitabine only.

Table 4 Characteristics of the KEYNOTE-024 trial

Location	UK, Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, and USA
Design	Phase III randomised, controlled, open-label
Population	• Histologically or cytologically confirmed diagnosis of NSCLC, stage IV, no EGFR sensitising (activating) mutation or ALK translocation, no systemic chemotherapy treatment for metastatic disease. PD-L1 strong tumour (TPS ≥50%) • Life expectancy of ≥3 months • ECOG PS 0 or 1
Intervention	Pembrolizumab 200mg Q3W (n=154)
Comparators	SOC (n=151) Trial investigator's choice of platinum doublet: • Pemetrexed 500mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q3W followed by optional pemetrexed 500mg/m^2 Q3W (non-squamous histology only) • Pemetrexed 500mg/m^2 Q3W and cisplatin 75mg/m^2 day 1 Q3W followed by optional pemetrexed 500mg/m^2 Q3W (non-squamous histology only) • Gemcitabine 1250mg/m^2 days 1 and 8 and cisplatin 75mg/m^2 day 1 Q3W • Gemcitabine 1250mg/m^2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W • Paclitaxel 200mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q3W followed by optional pemetrexed maintenance (pemetrexed maintenance permitted for non-squamous histology only) All platinum doublets administered were 4-6 cycles of treatment
Treatment - limitations, continuation and crossover	Treatment on study continued until one of the following events occurred: • Disease progression (according to RECIST 1.1) • Unacceptable AEs • Intercurrent illness that prevented further administration of treatment • Investigator's decision to withdraw the subject • Noncompliance with trial treatment or procedures requirements • Patient had received 35 treatments of study medication (pembrolizumab) • Administrative reasons Patients receiving pembrolizumab who attained a CR in addition to patients receiving pembrolizumab who stopped drug administration after receiving 35 trial treatments for reasons other than progressive disease or intolerability, may have been eligible for re-treatment in the second course phase after experiencing progressive disease. Response or progression in the second course phase did not count towards the ORR and PFS of the primary endpoint. Retreatment was limited to 17 cycles Patients randomised to the SOC arm who experienced progressive disease per RECIST 1.1 and met all protocol defined crossover criteria had the opportunity to crossover to pembrolizumab. Treatment was limited to 35 administrations of pembrolizumab in the crossover phase; patients who crossed over were permitted to receive treatment in the second course phase if they met the pre-defined crossover criteria
Primary outcome	PFS (based on RECIST 1.1) assessed by blinded independent central radiologist review
Secondary outcomes	OS, Safety, ORR
Study duration	Final PFS analysis planned at 20 months from the start of the study Final OS analysis planned at 28 months from the start of the study

AE=adverse events; ALK=ankylosing lymphoma kinase; AUC=area under the curve; CR=complete response; ECOG; EGFR epidermal growth factor receptor; PS=Eastern Oncology Group Performance Status; IHC=immunohistochemistry; NSCLC=non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PD-L1= programmed death ligand 1; PFS=progression free survival; Q3W=every 3 weeks; RECIST=response evaluation criteria in solid tumours; SOC=standard of care; TPS=tumour proportion score. Source: CS, Table 8 and CS, p51

4.4 Characteristics of patients included in the KEYNOTE-024 trial

The key baseline characteristics of patients included in the KEYNOTE-024 trial are listed in Table 5. The ERG agrees with the company that the baseline characteristics are generally well balanced across the treatment arms. The company reports (CS, p78) that the majority of patients had stage IV adenocarcinoma (69.5%), were male (61.3%), white (82.3%) of non-Hispanic and non-East Asian ethnicity. The company considers (CS, p78) that the patients recruited to the KEYNOTE-024 trial are broadly representative of a population of patients with advanced NSCLC. The ERG agrees with the company's opinion. However, in the trial, only 18% of patients had squamous disease and clinical advice to the ERG that is that, in NHS clinical practice, approximately 30% to 40% of patients have squamous disease. The ERG notes that treatment options for patients with non-squamous disease include platinum+ vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed. Treatment options for patients with squamous disease are limited to platinum+vinorelbine, gemcitabine, docetaxel, paclitaxel.

Table 5 Baseline characteristics of patients recruited to the KEYNOTE-024 trial

	Pembrolizumab	SOC
N	154	151
Male n (%)	92 (59.7)	95 (62.9)
Age, years, mean (SD)	63.9 (10.1)	64.6 (9.5)
ECOG PS n (%)		
0	54 (35.1)	53 (35.1)
1	99 (64.3)	98 (64.9)
2	1 (0.6)	0 (0)
Cancer stage at screening n (%)		
IIIb	1 (0.6)	1 (0.7)
IV	153 (99.4)	150 (99.3)
Geographic region of enrolling site n (%)		
Non-East Asia	133 (86.4)	132 (87.4)
East Asia	21 (13.6)	19 (12.6)
Histology		
Squamous	29 (18.8)	27 (17.9)
Non-squamous	125 (81.2)	124 (82.1)
Smoking status n (%)		
Current	34 (22.1)	31 (20.5)
Former	115 (74.7)	101 (66.9)
Never	5 (3.2)	19 (12.6)
Brain metastasis at baseline n (%)		
Yes	18 (11.7)	10 (6.6)
No	136 (88.3)	141 (93.4)
Baseline tumour size		
Patients with data	151	154
Mean (sd)	90.9 (53.4)	99.7 (63.4)
Prior adjuvant therapy n (%)		
Yes	6 (3.9)	3 (2.0)
No	148 (96.1)	148 (98)
Prior neo-adjuvant therapy n (%)		
Yes	3 (1.9)	1 (0.7)
No	151 (98.8)	150 (99.3)

ECOG PS=Eastern Cooperative Oncology Group Performance Status; sd=standard deviation; SOC=standard of care
Source: CS Table 15

4.4.1 Chemotherapy treatments administered in the KEYNOTE-024 trial

The company provides details of the specific chemotherapy treatments administered to patients in the SOC arm of the KEYNOTE-024 trial. The numbers of patients receiving each treatment are provided in Table 6 by tumour histology (squamous or non-squamous).

The ERG notes that in clinical practice in the NHS, optimal treatment for patients with non-squamous tumours is platinum+pemetrexed followed by pemetrexed maintenance treatment. In the KEYNOTE-024 trial, 37% of the patients with non-squamous tumours were treated with platinum+pemetrexed followed by pemetrexed maintenance.

Table 6 Chemotherapy treatments administered in the KEYNOTE-024 trial

Chemotherapy regimen	**Squamous histology N=27**	**Non-squamous histology N=123**
Carboplatin+gemcitabine	15	5
Cisplatin+gemcitabine	7	4
Carboplatin+paclitaxel	5	12
Carboplatin+pemetrexed with pemetrexed maintenance	NA	28
Carboplatin+pemetrexed without pemetrexed maintenance	NA	38
Cisplatin+pemetrexed with pemetrexed maintenance	NA	18
Cisplatin+pemetrexed without pemetrexed maintenance	NA	18
Number of treatment cycles received:		
Median	4 (range 1 to 6)	4 (range 1 to 6)
<4	11	42
4	3	47
5	0	7
6	13	27

NA=not applicable
Source: CS, Figure 7

4.4.2 Treatments administered after the KEYNOTE-024 trial

In response to the ERG's clarification request (Question A8), the company provided details of the post-trial treatments given to patients after disease progression (Table 7). The company points out that the information provided in Table 7 does not include the 66 patients from the SOC arm of the KEYNOTE-024 trial who had crossed over to treatment with pembrolizumab.

Clinical advice to the ERG is that, in the NHS, docetaxel monotherapy[3] or docetaxel+nintedanib[27] is standard of care after disease progression on first-line chemotherapy. The ERG notes from Table 7 that very few patients from the KEYNOTE-024 trial received post-progression treatment with docetaxel and none received post-progression treatment with nintedanib.

Table 7 Post-trial treatments

	Pembrolizumab N=154 n (%)	SOC N=151 n (%)
Patients with one or more new systemic therapies	**35**	**25**
Second-line	**35**	**14**
Bevacizumab+pemetrexed	1 (2.9%)	0 (0.0%)
Cabozantinib	1 (2.9%)	0 (0.0%)
Carboplatin+gemcitabine	4 (11.4%)	1 (7.1%)
Carboplatin+paclitaxel	3 (8.6%)	1 (7.1%)
Carboplatin+paclitaxel + bevacizumab	4 (11.4%)	0 (0.0%)
Carboplatin pemetrexed	11 (31.4%)	0 (0.0%)
Carboplatin+pemetrexed + bevacizumab	1 (2.9%)	0 (0.0%)
Carboplatin+vinorelbine	1 (2.9%)	0 (0.0%)
Cisplatin+gemcitabine	2 (5.7%)	0 (0.0%)
Cisplatin+pemetrexed	5 (14.3%)	0 (0.0%)
Cisplatin+pemetrexed+bevacizumab	1 (2.9%)	0 (0.0%)
Docetaxel	0 (0.0%)	1 (7.1%)
Nivolumab	0 (0.0%)	5 (35.7%)
Paclitaxel	0 (0.0%)	1 (7.1%)
Pembrolizumab	0 (0.0%)	3 (21.4%)
Pemetrexed	0 (0.0%)	2 (14.3%)
Platinum+pemetrexed	1 (2.9%)	0 (0.0%)
Second-line maintenance	**8**	**1**
Bevacizumab	1 (12.5%)	0 (0.0%)
Bevacizumab+pemetrexed	1 (12.5%)	0 (0.0%)
Erlotinib	1 (12.5%)	1 (100.0%)
Pemetrexed	5 (62.5%)	0 (0.0%)
Third-line	**2**	**12**
Carboplatin+paclitaxel	0 (0.0%)	1 (8.3%)
Carboplatin+pemetrexed+bevacizumab	1 (50.0%)	0 (0.0%)
Dexamethasone+docetaxel	0 (0.0%)	1 (8.3%)
Dexamethasone+docetaxel+nintedanib	1 (50.0%)	0 (0.0%)
Docetaxel	0 (0.0%)	8 (66.7%)
Luminespib	0 (0.0%)	1 (8.3%)
Nivolumab	0 (00.0%)	1 (8.3%)
Fourth-line	**0**	**3**
Cabozantinib	0	1 (33.3%)
Gemcitabine	0	2 (66.7%)

SOC=standard of care
Source: Company clarification response QA8

4.4.3 Statistical approach adopted for the conduct and analysis of data from included studies

A full description and critique of the KEYNOTE-024 trial is presented in this section of the ERG report. Information relevant to the statistical approach taken by the company to analyse data

from this trial has been taken directly from the CSR, the protocol and the statistical analysis plan (SAP)[22] and from the CS.

Trial population

Data from the intention-to-treat (ITT) population were used to determine PFS, OS and ORR results. The data were analysed according to the treatment group to which patients were initially randomised, regardless of which treatment they actually received. All safety data analyses were performed using the 'All Subjects as Treated' (ASaT) population, consisting of data from all randomised patients who received at least one dose of study treatment.

Outline of analyses

An outline of the strategies used to implement the planned interim analyses (interim analysis 1 [IA1] and IA2), and their purpose is provided in Table 8. The company states that the KEYNOTE-024 trial was initiated on 05 September 2014 and was stopped for efficacy after 20 months and is therefore no longer recruiting patients. The data cut-off for the IA2 results was 09 May 2016. Results presented in the CS are those generated from data available on this date. At the time of IA2, the median duration of follow-up was 11.2 months (range 6.3 months to 19.7 months). Data from the ITT population have been used as the basis for calculating PFS, OS and ORR.

Table 8 Summary of the strategies used for KEYNOTE-024 interim analyses

ORR, PFS and OS Analyses	Key endpoints	Expected timing of analysis	Sample size expected at time of analysis	Primary purpose of analysis
ORR analysis	ORR	~16 months from study start	First 191 subjects have at least 6 months follow up	Demonstrate superiority of pembrolizumab in ORR
Final PFS analysis Interim OS analysis	PFS (primary) OS	~20 months from study start	~175 PFS (~110 OS) events between the pembrolizumab arm and the chemotherapy arm	Demonstrate superiority of pembrolizumab in PFS Examine OS effect of pembrolizumab
Final OS analysis	OS	~28 months from study start	~170 OS events between the pembrolizumab arm and the chemotherapy arm	Examine OS effect of pembrolizumab

ORR=objective response rate; OS=overall survival; PFS=progression-free survival
Source: CS, Table 9

The KEYNOTE-024 trial was stopped early for benefit. Early closure of trials may lead to exaggerated treatment effects that are not borne out in the longer term.[15,17,28] Although IA2 was conducted after 108/170 (63.5%) OS events had occurred, the ERG is concerned that

relative survival between the trial arms is based on immature data (35.4% of the anticipated OS events had occurred). Median OS has not been reached for either of the treatment arms. The company reports that the results from the final analysis will be available in June 2018 when the 170 expected death events will have occurred; however, the ERG notes that the OS data are limited by patient crossover.

Efficacy outcomes

The definitions and methods used to analyse the primary and secondary efficacy outcomes from the KEYNOTE-024 trial are presented in Table 9.

Table 9 Analysis strategy used to generate key efficacy endpoints (KEYNOTE-024 trial)

Endpoint	Definition	Statistical method
Primary outcome		
PFS	Time from randomisation to the first documented disease progression as per RECIST 1.1 based on blinded independent central radiologists' review or death due to any cause, whichever occurred first	**Testing:** Stratified log-rank test **Estimation:** K-M method was used to estimate the PFS curve in each treatment group. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported
Secondary outcome		
OS	Time from randomisation to death due to any cause. Subjects without documented death at the time of the final analysis were censored at the date of the last follow-up	**Testing:** Stratified log-rank test **Estimation:** K-M method was used to estimate the OS curve in each treatment group. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported
ORR	Proportion of the subjects in the analysis population who had either a CR or PR. Responses were based upon blinded independent central radiologists' review per RECIST 1.1	Stratified Mietten & Nurminen method

CI=confidence interval; CR=complete response; HR=hazard ratio; K-M=Kaplan-Meier; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response
Source: CS, Table 8 and 10

The stratified log-rank test and stratified Cox model used the following randomisation stratification factors: geography (East Asia versus non-East Asia), ECOG PS (0 versus 1) and histology (squamous versus non-squamous).

The company states that, as disease progression could occur at any point between assessments, the date of progression was approximated as the date of the first assessment at which disease progression was objectively documented using RECIST 1.1 criteria, regardless of study drug discontinuation. Death is always considered as a confirmed progressive disease event.

The ERG is satisfied that all outcomes were pre-specified in the trial SAP and were fully reported in the CSR

Censoring methods

To evaluate the robustness of the PFS endpoint, the company presents censoring rules for the primary analysis and performs two sensitivity analyses with alternative censoring rules. A summary of the censoring rules for the primary analysis and sensitivity analyses are shown in Table 10.

Table 10 Censoring rules for the primary and sensitivity analyses of PFS

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

PD=progressive disease; PFS=progression-free survival
Source: CS, Table 12

Proportional hazards

The analyses carried out by the company to generate PFS and OS hazard ratios (HRs) from the KEYNOTE-024 trial data were conducted using Cox proportional hazards (PH) modelling. The validity of this method relies on the assumption that the hazards of the two treatments being compared are proportional.

No details are provided in the CS or in the SAP to suggest that any testing has been carried out to ascertain whether the assumption of PHs holds for the PFS or OS data. As part of the clarification process, the ERG requested details of any PH testing that the company had carried out. The company clarified that they did not perform any formal testing to check whether OS and PFS hazards were proportional, as the KEYNOTE-024 trial SAP did not pre-specify any tests for checking the PH assumption.

The ERG investigated whether the PH assumption employed by the company to calculate OS HR holds by using the OS data requested by the ERG during the clarification process and plotting the cumulative hazard associated with pembrolizumab versus the cumulative hazard

associated with SOC (cumulative hazard versus cumulative hazard [H-H] plot) for the ITT population. The OS H-H plot suggests that the PH assumption does not hold for OS and therefore, the OS HR result must be interpreted with caution. The ERG was unable to test the PH assumption for PFS as the PFS data were not requested during the clarification process and the quality of the K-M plot in Figure 8 of the CS was not adequate for the ERG to digitise the data and generate the H-H plots for comparison.

Crossover adjustment methods

Patients in the SOC arm were permitted to cross over and receive pembrolizumab after RECIST-defined disease progression. Nearly half of the patients (n=66, 43.7%) randomised to the SOC arm of the KEYNOTE-024 trial had crossed over to receive pembrolizumab at the time of IA2. An additional nine patients in the SOC arm had also switched to an anti-PD1 treatment. None of the patients in the pembrolizumab arm switched to any other treatment.

It was pre-specified in the trial protocol that the rank-preserving structural failure time (RPSFT) method would be used to adjust OS estimates to take into account the impact of crossover. The company explains that trial based information was required to assess the clinical validity of the crossover adjustment method and that any assessment should be made *a posteriori.* Following the recent crossover adjustment guidelines issued by the NICE Decision Support Unit (DSU),[29] the company decided that additional crossover adjustments, namely the inverse probability of censoring weighting (IPCW) method and the 2-stage method, would also be used to estimate OS in the SOC arm.

The company used three methods to account for direct switching (the primary analysis) and also to account for direct and indirect switching (the secondary analysis). The company defines direct switching as treatment switching from SOC to pembrolizumab as per the study protocol, whereas indirect switching is defined as treatment switching after the protocol treatment has come to an end. The company states that, having considered the switching mechanism (which in this instance was typically related to disease progression and, therefore, non-random), trial characteristics, the proportion of patients switching and the clinical validity of the outputs, the 2-stage method was considered to be the most suitable crossover adjustment method.

ERG's assessment of suitability of RPSFT method

The company states that the RPSFT method is only valid if the assumption of common treatment effect holds, i.e. that the effect of treatment with pembrolizumab is constant, irrespective of the point in time that the therapy was initiated (baseline or switch).

The company explored the validity of the common treatment effect numerically, using two-stage estimates. Under this assumption, if the common treatment effect holds then the post-progression estimate of pembrolizumab (without switching) and the treatment effect of pembrolizumab adjusted for switching should be the same. The post-progression treatment estimate of pembrolizumab (acceleration factor of 4.05, [95% CI 1.39 to 16.44]) was compared with the overall effect of pembrolizumab adjusted for switching (acceleration factor of 2.11, [95% CI 1.49 to 2.99]). The acceleration factor is the multiplicative factor quantifying the increase in survival time that occurs when treatment with pembrolizumab is compared to SOC. Although this factor could be prone to some bias as it averages different treatment effects, it does imply that there is a clear difference between the two results, suggesting that patients initially treated with pembrolizumab experience a different treatment effect to patients who crossed over to receive pembrolizumab on disease progression.

The ERG agrees with the company that the assumption of a common treatment effect does not hold and, therefore, it is not appropriate to use the RPSFT method to adjust for the effect of crossover.

Suitability of the IPCW method

The company explains that the IPCW method is unsuitable due to the relatively small number of patients participating in the KEYNOTE-024 trial (compared to the observational datasets for which this method was designed). This method is also reliant on the key assumption of no unmeasured confounders, which is that data must be available on baseline and time-dependent variables that predict both treatment switching and prognosis.[29] The company does not provide any details to suggest that they have verified this assumption. The ERG considers that these are important limitations and that both the RPSFT method and the 2-stage method are more appropriate methods to use to adjust data for the effect of treatment switching when the sample size is small and when there is potential bias due to insufficient data on confounders.

Suitability of the 2-stage method

The 2-stage method requires the following criteria to be valid to be a suitable approach:

- switching only occurred after disease progression

- there is no known time-dependent confounding between the time of disease progression and time of treatment switching
- prognostic covariates collected at the time of disease progression are known.

As these requirements have been fulfilled, the ERG agrees with the company that the 2-stage method is the preferred choice over the RPSFT and IPCW methods.

The ERG notes that the company performed a simple model by estimating the switch effect after adjusting for the baseline covariates. The company did not specify which prognostic covariates were adjusted, and, as part of the clarification process, the ERG requested these details (Question A3). This information is important as some covariates can have an impact on the likelihood of switching and overall outcome. The company clarified that, at baseline, the model was adjusted for age, gender, metastatic staging (M1b/others), histology, geographic region and smoking status; at secondary baseline, the company adjusted for ECOG PS (0/1 or higher), tumour size, time to progression, body mass index (BMI) and haemoglobin.

The estimated adjusted post-progression treatment effect (acceleration factor) is 4.05 (95% CI 1.39 to 16.44). This point estimate suggests that switching to treatment with pembrolizumab increases survival time by a factor of 4.05. However, it is important to note that this estimate may not be precise due to the small number of patients who were eligible to switch but did not switch (n=16).

Another important factor to consider is re-censoring of survival time. Re-censoring is important in the 2-stage method as a positive or negative treatment effect can increase or decrease the probability that the survival time of an individual is censored and, where treatment switching occurs, the treatment received is likely to be linked to prognosis. Re-censoring involves breaking the dependence between censoring time and treatment received by re-censoring adjusted survival and censoring times at the minimum of the censoring times observed for the patients. Although re-censoring can avoid the bias associated with adjusted censoring times being related to prognosis, it usually involves a loss of longer-term information. This can be important if extrapolating survival data for use in economic analyses. Furthermore, re-censoring can lead to biased estimates of the “average” treatment effect in circumstances where the PH assumption does not hold, due to longer-term data on the effect of treatment being lost. [29]

The company argues that the data included in the 2-stage model were not re-censored using the post-progression treatment estimate because doing so would provide less reliable results. However, the company provides the HR results using the simplified 2-stage method with and

without re-censoring for comparison, 0.44 (95% CI 0.20 to 1.07) and 0.50 (95% CI 0.34 to 0.76), respectively. The ERG is concerned that there is a difference between the results obtained with and without re-censoring. The ERG considers that this difference could be due to the PH assumption not being valid, which is known to affect the results obtained from re-censoring. However, it is unclear why the results for re-censoring highlight a statistically significant p-value (p=0.0094) when the 95% CI includes 1. The ERG considers that the company may have presented incorrect results.

In conclusion, the ERG considers that despite ed from the 2-stage adjustment method (and the two other methods considered by the company [RPSFT and ICPW methods]) are unreliable. All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. This (initial) HR is only reliable if the OS hazards for the two trial data-sets are proportional. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. As the (initial) HR result is uncertain, all adjustments to it should be viewed with a similar level of caution.

ERG assessment of statistical approach

A summary of the ERG's assessment of the statistical approach used to analyse data from the KEYNOTE-024 trial is presented in Table 11.

Table 11 ERG assessment of the statistical approach used to analyse KEYNOTE-024 trial data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CS (pages 64 and 65)	The ERG considers that the methods used to calculate the sample size are appropriate
Protocol amendments	Provided in the CSR (Section 9.7.1)	The ERG notes that the changes detailed in the protocol amendments were unlikely to have been driven by the results of the trial and are, therefore, not a cause for concern
Missing data approach	The company reports that a model-based approach was used to handle missing data for both OS and PFS. For ORR, patients with missing data were considered to be non-responders	The ERG is satisfied that the company took a suitable approach to handling missing data
Subgroup analyses for OS and PFS	Pre-specified subgroup analyses: • Age category (≤65 versus >65 years) • Sex (female versus male) • Race (white versus non-white) • ECOG status (0 versus 1) • Geographic region of enrolling site (East Asia versus non-East Asia) • Histology (squamous versus non-squamous) • Smoking status (never versus former versus current) • Brain metastasis status (baseline brain metastasis versus no baseline brain metastasis) • Investigators choice of standard of care chemotherapy	The ERG is satisfied that the results of all subgroup analyses are provided in the CS/CSR
Sensitivity analyses for the primary outcome	Pre-specified sensitivity analyses in the SAP: Sensitivity analysis 1 is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment Sensitivity analysis 2 is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death.	The ERG is satisfied that the results for sensitivity analysis 1 are provided in the CSR. However, results for sensitivity analysis 2 are not provided in the CS or CSR
Adverse events	Safety was assessed through summaries of AEs, SAEs and AEs of special interest	The ERG is satisfied that the results of all the AE data analyses are provided in the CSR
Health-related quality of life	• EORTC-QLQ-C30 • EORTC QLQ-LC13 • EQ-5D-3L questionnaire	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate

AE=adverse event; CS=company submission; CSR=clinical study report; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; EORTC QLQ-LC13= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 items; EQ-5D-3L=EuroQol-5 Dimension-3 level; ERG=Evidence Review Group; HRQoL=health-related quality of life; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; SAE=serious adverse event; SAP=statistical analysis plan
Source: CS and ERG comment

4.5 Risk of bias assessment for the KEYNOTE-024 trial

The company conducted two risk of bias assessments for the KEYNOTE-024 trial, one using the criteria recommended in the NICE Methods Guide[30] (in the direct evidence section) and the other (as part of the indirect comparison) using the risk of bias tool recommended in the Cochrane Handbook of Systematic Reviews.[31] The results from the former are presented in Table 12. The ERG agrees with the company's overall risk of bias assessment, but notes that an element of blinding was in place in the KEYNOTE-024 trial as the analyses of PFS and ORR were based on BICR.

The ERG considers that the risk of bias for the KEYNOTE-024 trial is low for the majority of the criteria in Table 12. However, the ERG notes that trial was open-label but with blinded independent central review of the primary outcome of PFS. The ERG also notes that the trial protocol allowed patients in the SOC arm to receive treatment with pembrolizumab after their disease had progressed and that the KEYNOTE-024 trial was stopped early for benefit. The impacts of patient crossover and the early closure of the trial on the OS results are unclear.

Table 12 Company's risk of bias assessment for the KEYNOTE-024 trial and ERG comment

Criterion	Company's judgement and rationale	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Agree; however, analysis of PFS and ORR were based on BICR
Were there any unexpected imbalances in drop-outs between groups?	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree

PFS=progression-free survival; ORR=objective response rate; blinded independent central review; ITT=intention to treat
Source: CS Table 16

4.6 Results from the KEYNOTE-024 trial

Results from the KEYNOTE-024 trial for the ITT population are summarised in Table 13. The company reports (CS, p79) that the results are based on the data examined during IA2. The data cut for IA2 was 9th May 2016.

Table 13 Results from the KEYNOTE-024 trial (ITT population)

Endpoint	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)
HR (95% CI)	0.50 (0.37 to 0.68) p<0.001	
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	47.7%	15.0%
Secondary endpoints		
OS		
Median (months)	Not reached	Not reached
HR (95% CI)	HR 0.60 (0.41 to 0.89) p=0.005	
Number of events n (%)	44 (28.6)	64 (42.4)
Person months	1402	1227.5
Event rate/100 person months	3.1	5.2
OS rate at 6 months	80.2%	72.4%
OS rate at 12 months	69.9%	54.2%
ORR (BICR)		
Confirmed ORR (95% CI)	44.8% (36.8 to 53)	27.8% (20.8 to 35.7)
Difference in % pembrolizumab vs SOC	16.6 (6.0 to 27.0) p=0.0011	

BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; SOC=standard of care
Source: CS, Table 17, Table 18 and Table 25

4.6.1 Progression-free survival

The PFS results presented in Table 13 are based on the BICR and the primary censoring analysis (see Table 10 of this ERG report for details of the censoring analyses). Results based on sensitivity analysis 1 (SA1) are presented in Appendix 9 of the CS. The ERG agrees with the company that the results of SA1 are consistent with the results of the primary censoring analysis.

Median PFS was statistically significantly longer for patients in the pembrolizumab arm compared to patients in the SOC arm, 10.3 months versus 6 months (HR=0.50; 95% CI 0.37 to 0.68, p<0.001). The company reports (CS, p82 and Figure 8) that the Kaplan-Meier (K-M) curves separate at approximately 4 months and remain separated for the duration of follow up (approximately 16 months) indicating that after 4 months of treatment, the probability of disease progression is greater in the SOC arm than in the pembrolizumab arm. The ERG notes (from an examination of Figure 8 of the CS) that the majority of PFS events in the

KEYNOTE-024 trial had occurred by 9 months; at this time, only 44 patients remained at risk in the pembrolizumab arm and 18 patients remained at risk in the SOC am.

In response to the ERG's clarification request (Question A6), the company provided the results of an exploratory analysis of investigator-assessed PFS (Table 14). The ERG notes that there appears to be a difference of [redacted] in median PFS between the investigator-assessed results and the results reported for BICR-assessed PFS ([redacted]). Median PFS in the SOC arm appears to be similar between the two analyses ([redacted]). The ERG is uncertain of the reasons for, or the implications of, the [redacted] difference between the BICR-assessed PFS and investigator-assessed PFS.

Table 14 Exploratory analysis of investigator-assessed PFS from the KEYNOTE-024 trial

	Pembrolizumab N=154	SOC N=151
Primary endpoint **PFS (Investigator assessment)**		
Median, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Number of events n (%)	[redacted]	[redacted]
Person months	[redacted]	[redacted]
Event rate/100 person months	[redacted]	[redacted]
PFS rate at 6 months	[redacted]	[redacted]

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival
Source: Company clarification response, QA6

Progression-free survival sensitivity analyses

The company pre-specified that two sensitivity analyses would be conducted to evaluate the robustness of the PFS endpoint. The results from SA1 are consistent with the primary PFS analysis results [redacted] However, the ERG is concerned that the results from the planned sensitivity analysis 2 (SA2) have not been presented in the CS and the impact of varying assumptions on the PFS result cannot be fully assessed.

Progression-free survival subgroup analysis

The results of the subgroup analyses undertaken by the company, using data from the ITT population of the KEYNOTE-024 trial, are presented in Figure 15 of the CS. A list of the subgroup analyses is provided in Table 11 of this ERG report.

The results, presented as a forest plot, demonstrate that, when compared with SOC, treatment with pembrolizumab confers benefit, in terms of HR, in the following subgroup analyses: age, sex, ECOG PS, tumour histology, region of enrolment, presence of brain metastases at baseline, smoking history/status, and SOC regimen administered. However, the ERG notes that for some of the subgroups only a small number of events had occurred (for example,

never smoking [n=12] and presence of brain metastases at baseline [n=17]), meaning that there are wide confidence intervals (CIs) which preclude an accurate interpretation of the treatment effect.

During the clarification process, the ERG requested the p-values for the tests for interaction for all performed subgroup analyses (Question A7). [redacted]

However, the ERG considers that the results from the subgroup analysis should be interpreted with caution as over 60% of the patients in the population were male and on platinum/pemetrexed treatment.

Several subgroup analyses were carried out as per the final scope issued by NICE. Results showed that median PFS for patients treated with pembrolizumab was improved compared with median PFS for patients treated with SOC for all of the specified subgroups e.g., patients with squamous disease (HR=0.35; 95% CI 0.17 to 0.71), patients with non-squamous disease (HR=0.55; 95% CI 0.39 to 0.76) and patients treated with non-pemetrexed platinum doublets (HR=0.29; 95% CI 0.17 to 0.50) and patients treated with platinum+pemetrexed (HR= 0.63; 95% CI 0.44 to 0.91).

[redacted]

4.6.2 Objective response rate

The company reports (CS, p90) that no formal statistical testing was carried out on the ORR results. The ORR (Table 13) was higher in the pembrolizumab arm than in the SOC arm (44.8% versus 27.8%, nominal p=0.0011). The company reports (CS, p90 that the confirmed difference in ORR was 16.6%.

4.6.3 Time to response, response duration and disease control rate (exploratory endpoints)

The results of the exploratory outcomes from the KEYNOTE-024 trial are presented in Table 15. The table shows that 69 patients in the pembrolizumab arm responded to treatment (median time to response 2.2 months; range, 1.4 to 8.2) and the median duration of response was not reached in the pembrolizumab arm. In the SOC arm, 42 patients responded to treatment (median time to response 2.2 months; range, 1.8 to 12.2) and the median duration of response was 6.3 months.

Table 15 KEYNOTE-024 trial exploratory endpoints

Endpoint	Pembrolizumab N=154	SOC N=151
Time to response (BIRC)		
Number of responders	69	42
Median (months)	2.2	2.2
Range (months)	1.4 to 8.2	1.8 to 12.2
Response duration (BIRC) Median (range), months	Not reached (1.9+ to 14.5+)	6.3 (2.1+ to 12.6+)
Disease control rate (CR+PR+SD)	107 (69.5%)	102 (67.5%)
Progressive disease	34 (22.1%)	28 (18.5%)

BIRC=blinded independent central review; CR=complete response; PR=partial response; SD=stable disease
Source: CS, Table 23, Table 24 and Table 25

4.6.4 Overall survival

The OS results presented are from the first of two planned OS analyses: IA2 and the final analysis. The final trial report is due to be published in June 2018 (CS, p159).

IA2 was performed approximately 20 months after the start of study, when it was expected that approximately 110 OS events would have been observed. A total of 108 patients had died (35.4%) by the time the IA2 analysis was undertaken, representing 64% of the target number of events at final analysis (170 deaths). Patients who were still alive after the IA2 data cut-off date (09 May 2016) were censored on this date. Details of treatment exposures and treatment switching at IA2 are provided in Table 16.

Table 16 Treatment exposures and treatment switching in KEYNOTE-024 at IA2

	Pembrolizumab	SOC
Patients remaining on allocated study treatment	48.1%	10%
Median duration of treatment exposure	7 months (range, 1 day to 18.7 months)	3.5 months (range, 1 day to 16.8 months)
Median number of platinum doublet chemotherapy cycles	NA	4
Patients in the SOC arm who had switched to treatment with pembrolizumab	NA	66 (43%)
Patients in the SOC arm who switched to an anti PD-L1 treatment after the protocol treatment (indirect switching)	NA	9 (6%)

SOC=standard of care
Source: CS, p81

The HR for OS indicates a statistically significant treatment benefit for patients treated with pembrolizumab compared with OS for patients treated with SOC (HR=0.60; 95% CI 0.41 to 0.89 p=0.005). The company provides unadjusted OS K-M data (CS, Figure 9). The K-M data highlight that there has been a large amount of censoring, and that there are only a small number of patients at risk beyond 9 months. The ERG considers that the results from this

analysis should be interpreted with caution as the median OS has not been reached for the intervention or for the control group.

During the clarification process, the ERG asked the company to provide further details on formal testing undertaken to assess the PH assumption. The company confirmed that no formal testing of PH for OS data had been undertaken.

For OS, the ERG assessed the PH assumption by plotting the cumulative hazard associated with pembrolizumab versus the cumulative hazard associated with SOC. The plot suggested that the PH assumption is invalid and therefore, the ERG considers that the OS results should be interpreted with caution.

Overall survival subgroup analysis

The results of the company's subgroup analyses for the ITT population of the KEYNOTE-024 trial are presented in Figure 16 of the CS. A list of these subgroup analyses is provided in Table 11 of this ERG report. [redacted]

The results, presented as a forest plot, demonstrate that, when compared with SOC, treatment with pembrolizumab [redacted]

Results from subgroup analyses for OS [redacted]

During the clarification process, the ERG requested the corresponding p-values for the tests for interaction for the subgroup analyses (Question A7). No statistically significant p-values for interaction were observed across any of the subgroups.

4.6.5 Overall survival: crossover adjustment analyses

Results using different crossover methods

The estimates for crossover adjusted OS using each of the methods considered by the company are provided in Table 17, alongside the unadjusted OS results for the two KEYNOTE-024 trial treatment arms. The results from the RPSFT analysis are consistent with those from the unadjusted analysis.

A slightly greater treatment effect between arms is observed in results from the RPSFT adjusted analysis compared with results from the unadjusted analysis. Figures relating to unadjusted results indicated that median OS has not been reached in either of the pembrolizumab or SOC arms. The ERG considers that the results from the 2-stage method should be interpreted with caution due to the change in results between the re-censoring and no re-censoring approaches.

Table 17 Analysis of median overall survival in KEYNOTE-024

Treatment	Crossover correction	Median OS (months) (95% CI)	Hazard ratio (95% CI) p-value
SOC	None	NR (9.4 to NR)	0.60 (0.41 to 0.89) p=0.0009
SOC	Simplified two-stage correction (no re-censoring)	12.6 (7.6 to NR)	0.50 (0.34 to 0.76) p=0.0009*
SOC	Simplified two-stage correction (with re-censoring)	NR (3.8 to NR)	0.44 (0.20 to 1.07) p=0.0094
SOC	RPSFT correction*	NR (6.9 to NR)	0.57 (0.32 to 0.86) p=0.0009*
SOC	IPCW correction	11.8 (9.8 to NR)	0.55 (0.34 to 0.87) p=0.0150
Pembrolizumab	Not applicable	NR (NR to NR)	---

* p-value retained from the ITT analysis based on distribution of the test statistics under the null hypothesis of no treatment effect
CI=confidence interval; IPCW=inverse probability of censoring weighting; ITT=intention-to-treat; NR=not reached; OS=overall survival; RPSFT=rank preserving structural failure time; SOC=standard of care
Source: CS, adapted from Table 20 and Table 22

The company also provides the results from the OS analyses that consider both direct and indirect switching (CS, Table 21).

4.7 Health-related quality of life

The company reports (CS, p93) that the (exploratory) HRQoL outcomes (referred to in the CS as 'patient reported outcomes' [PRO]) were measured during the KEYNOTE-024 trial using

the European Organisation for Research and Treatment Cancer Quality of Life questionnaire[32] (EORTC-QLQ-C30), the EORTC Quality of Life questionnaire designed specifically to collect information from patients with lung cancer[33] (EORTC-QLQ-LC13) and the EuroQoL EQ-5D 3L tool.[34] The company states (CS, p95) that all questionnaires were administered electronically.

The analyses of HRQoL were based on responses obtained from patients in the PRO-specific full analysis set (PRO FAS) population, i.e. all patients who were randomised to the KEYNOTE-024 trial who received at least one study treatment and who completed at least one PRO questionnaire. The effects of treatment were assessed by comparing baseline scores with scores at week 15, at which point the sample size of the PRO FAS was 299.

The ERG notes that the results should be interpreted with caution since contributor scores were elicited from trial participants (rather than from patients in NHS clinical practice) and that only HRQoL over the first 15 weeks of treatment was considered.

Results from the EORTC-QLQ-C30 and EORTC-QLQ-LC13 questionnaires

The company reports (CS, p94) that the compliance rates for the EORTC QLQ-C30 questionnaire were:

- Baseline: 96% in the pembrolizumab arm and 92.6% in the SOC arm
- Week 15: 84.5% in the pembrolizumab arm and 78.6% in the SOC arm.

Similar compliance rates were recorded for the EORTC QLQ-LC13 questionnaire (CS, p94).

The results of the analysis of patient responses to the EORTC QLQ-C30 questionnaire are presented in Table 18. The company observes that the baseline scores were similar for patients in both arms of the trial and, at Week 15, patients in the pembrolizumab arm had an improved HRQoL score (+6.94 points) whilst patients in the SOC arm had a reduced HRQoL score (-0.88 points). The difference in least squares (LS) mean between the two arms of the trial was 7.82 (95% CI 2.85 to 12.79, p=0.002). The company observes that a mean difference of >10 points is considered clinically significant in trials that have used the EORTC QLQ-C30 questionnaire but, in trials of patients with NSCLC a mean difference of four points has been considered clinically significant. It is unclear to the ERG if the results of the analysis are clinically important.

Table 18 Results of EORTC-QLQ-C-30 questionnaire

Treatment	Baseline		Week 15		Change from baseline at week 15	
	N	Mean (sd)	N	Mean (sd)	N	LS mean (95% CI)
Pembrolizumab	145	62.24 (22.27)	109	70.95 (21.23)	150	6.94 (3.29 to 10.58)
SOC	137	59.85 (22.31)	92	63.68 (20.55)	147	-0.88 (-4.78 to 3.02)
Pairwise comparison					Difference in LS means (95% CI)	p-value
Pembrolizumab vs SOC					7.82 (2.85 to 12.79)	0.002

CI=confidence interval; LS=least squares; SOC=standard of care; sd=standard deviation; vs=versus
Source: CS, Table 26

Results from the EORTC-QLQ-LC13 questionnaire

The company provides an analysis of 'time to deterioration', a composite endpoint based on patients' responses to question 1 (cough), question 10 (chest pain) and questions 3 to 5 (dyspnoea) of the EORTC QLQ-LC13 questionnaire (Table 19). The company reports that the results of the analysis demonstrate that patients in the pembrolizumab arm experienced symptom deterioration later than patients in the SOC arm (HR=0.66; 95% CI 0.44 to 0.97, p=0.029).

Table 19 Time to true deterioration, cough, chest pain, dyspnoea (EORTC-QLQ-LC13)

Treatment	N	Deterioration (events) %	Pembrolizumab vs SOC	
			HR (95% CI)	p-value
Pembrolizumab	151	46 (30.5)	0.66 (0.44 to 0.97)	0.29
SOC	148	58 (39.2)		

CI=confidence interval; HR=hazard ratio; SOC=standard of care
Source: CS, Table 27

Results from the EQ-5D 3L questionnaire

The company reports (CS, p96) that the results from the analyses of patients' responses to the EQ-5D 3L questionnaire (Table 20 and Table 21) are consistent with the results from the EORTC QLQ-30 analyses. The ERG agrees with the company that the findings from the EQ-5D 3L analyses appear to favour treatment with pembrolizumab and are consistent with the results observed using the EORTC measures of HRQoL. The company highlights that the results from the EQ-5D 3L analyses are used to inform the company's economic model.

Table 20 Analysis of change from baseline in EQ-5D utility score at week 15

Treatment	Baseline		Week 15		Change from baseline at week 15	
	N	Mean (sd)	N	Mean (sd)	N	LS mean (95% CI)
Pembrolizumab	144	0.72 (0.24)	108	0.80 (0.22)	150	0.05 (0.01 to 0.09)
SOC	137	0.71 (0.21)	92	0.76 (0.18)	147	-0.00 (-0.04 to 0.4)
Pairwise comparison					Difference in LS means (95% CI)	p-value
Pembrolizumab vs SOC					0.06 (0.00 to 0.11)	0.036

CI=confidence interval; LS=least squares; SOC=standard of care; SD=standard deviation; vs=versus
Source: CS, Table 28

Table 21 Analysis of change from baseline in visual analogue scale (VAS) at week 15

Treatment	Baseline		Week 15		Change from baseline at week 15	
	N	Mean (sd)	N	Mean (sd)	N	LS mean (95% CI)
Pembrolizumab	144	68.72 (21.01)	108	75.52 (17.17)	150	4.25 (0.72 to 7.77)
SOC	137	69.71 (19.28)	92	72.73 (17.12)	147	0.39 (-3.33 to 4.11)
Pairwise comparison					Difference in LS means (95% CI)	p-value
Pembrolizumab vs SOC					3.85 (-0.72 to 8.42)	0.10

CI=confidence interval; LS=least squares; SOC=standard of care; sd=standard deviation; vs=versus
Source: CS, Table 29

4.8 Adverse events

ERG comment on AEs arising from the use of pembrolizumab in NSCLC

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. 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.

Reporting of AEs in the KEYNOTE-024 trial

The company has reported the AEs arising from the KEYNOTE-024 trial (CS, p136 to p153). Data were collected for the ASaT population. The ASaT population included all patients who received at least one study treatment (n=304). The AEs reported in the CS were events that

occurred from the dose of study drug to 30 days after the last dose of study drug. Data relating to serious adverse events (SAEs) were collected for up to 90 days post-treatment (or 30 days in the case of patients who had a follow-on treatment for their disease).

Mean duration of treatment (CS, Table 39) with pembrolizumab was 205 days (range 1 to 568) and 120 days (range 1 to 511) for SOC. This means that AE data were collected for a longer period of time for patients treated with pembrolizumab compared with patients treated with SOC. The company observes (CS, Table 40) that 87 patients in the pembrolizumab arm and 29 patients in the SOC arm received treatment for ≥6 months.

In the CS (CS, p140 to p147), AEs from the KEYNOTE-024 trial are reported as: AEs with an incidence rate of ≥10%, drug-related AEs, drug-related grade 3 to grade 5 AEs, drug-related grade 3 to grade 5 AEs and drug-related SAEs. In addition, the company presents data related to adverse events of special interest (AEOSI) that were reported during the KEYNOTE-024 trial (CS, p148 to p150).

4.8.1 Summary of adverse events

A summary of the AEs and SAEs recorded during the KEYNOTE-024 trial is presented in Table 22. The ERG agrees with the company that the numbers of patients who experienced any AE or any SAE were similar in both arms of the trial; however, the ERG notes that there are differences in the type and predictability of the AEs recorded.

Compared with the pembrolizumab arm, drug-related AEs (including grade 3 to 5 AEs) were more frequent in the SOC arm as were treatment discontinuations due to AEs and drug-related AEs. A higher percentage of patients in the pembrolizumab arm discontinued treatment due to SAEs (8.4% versus 7.3%) and drug-related SAEs (6.5% versus 4.7%) than in the SOC arm. There were nine (5.8%) deaths in the pembrolizumab arm, one of these was considered to be

drug-related. In the SOC arm seven (4.7%) deaths occurred, three of which were considered to be drug-related.

Table 22 Summary of adverse events from the KEYNOTE-024 trial

Adverse event type	Pembrolizumab N=154		SOC N=150	
	n	%	n	%
One or more AE	148	96.1%	145	96.7%
No AE	6	3.9%	5	3.3%
Drug related AE	113	73.4%	135	90%
Grade 3 to 5 AE	82	53.2%	109	72.7%
Grade 3 to 5 drug-related AE	41	26.6%	80	53.3%
SAE	68	44.2%	66	44.0%
Serious drug-related AE	33	21.4%	31	20.7%
Death	9	5.8%	7	4.7%
Death due to drug-related AE	1	0.6%	3	2.0%
Discontinued due to AE	14	9.1%	21	14.0%
Discontinued due to drug-related AE	11	7.1%	16	10.7%
Discontinued due to SAE	13	8.4%	11	7.3%
Discontinued sue to serious drug-related AE	10	6.5%	7	4.7%

AE=adverse event; SAE=serious adverse event; SOC=standard of care
Source: CS, Table 41

4.8.2 Adverse events with an incidence rate of ≥10%

The company presents full details of AEs with an incidence rate of ≥10% recorded from the KEYNOTE-024 trial in Table 42 of the CS. The company has summarised the AEs in terms of those that occurred at levels above 20% (CS, p 139) and reports that:

- in the pembrolizumab arm, AEs that occurred in more than 20% of patients included dyspnoea (22%), diarrhoea (20.8%), constipation (20.8%) fatigue (20.8%) and decreased appetite (20.1%)
- in the SOC arm, AEs that occurred in more than 20% of patients included anaemia (52.7%), nausea (46.7%), fatigue (35.3%), decreased appetite (32.7%), neutropenia (24%), vomiting (24%, constipation (22.7%) and diarrhoea (22%).

The ERG agrees with the company's summary of AEs, but notes that fatigue and dyspnoea can be difficult to manage in patients with NSCLC.

The company points out that in the SOC arm, the incidences of particular AEs (i.e., nausea, anaemia, vomiting, neutropenia, blood creatinine increased, stomatitis, thrombocytopenia, dysgeusia, decreases in neutrophil count, platelet count and white blood cell count) were more than twice those recorded in the pembrolizumab arm. Clinical advice to the ERG is that the AEs reported in the pembrolizumab arm (for example, endocrine toxicities) are less predictable and are more difficult to manage in the NHS compared with the AEs reported in the SOC arm.

4.8.3 Drug-related adverse events

All drug-related adverse events

The company presents full details of all AEs from the KEYNOTE-024 trial that were considered to be drug-related in Table 43 of the CS. The company reports that:

- in the pembrolizumab arm, the AEs considered to be drug-related were: diarrhoea (14.3%), fatigue (10.4%), and pyrexia (10.4%)
- in the SOC arm, the AEs considered to be drug-related were: anaemia (44.0%), nausea, (43.3%), fatigue (28.7%), decreased appetite (26.0%), neutropenia (22.7%), vomiting (20.0%), diarrhoea (13.3%), decreased neutrophil count (13.3%), decreased platelet count (12.0%), stomatitis (12.0%), constipation (11.3%), thrombocytopenia (11.3%), decreased white blood cell count (10.7%), dysgeusia (10.0%), and increased blood creatinine (10.0%).

The company observes that most of the drug-related AEs recorded in the SOC arm were haematological AEs that are known to be associated with chemotherapy treatment.

Drug-related serious adverse events

Full details of the drug-related SAEs from the KEYNOTE-024 trial are reported in Table 45 of the CS. The company observes that the incidence of SAEs is similar between the pembrolizumab and SOC arms (21.4% and 20.7%).

The company reports that the most common SAEs in the pembrolizumab arm were pneumonitis (4.5%) and diarrhoea (1.9%). In the SOC arm, the most commonly occurring SAEs were anaemia (2.7%), febrile neutropenia (2.0%), pancytopenia (2.0%), pneumonia (2.0%) and thrombocytopenia (2.0%).

The ERG agrees with the company's summary of drug-related AEs.

Grade 3 to 5 drug-related AEs

The company presents full details of grade 3 to grade 5 drug-related AEs from the KEYNOTE-024 trial in Table 44 of the CS. The company reports that the incidence of grade 3 to grade 5 drug-related AEs was 26.6% in the pembrolizumab arm and 53.3% in the SOC arm.

The most common events in the pembrolizumab arm were diarrhoea (3.9%), pneumonitis (2.6%), and anaemia (1.9%).

The most common events in the SOC arm were anaemia (19.3%), neutropenia (13.3%), decreased platelet count (6.0%), and thrombocytopenia (5.3%).

4.8.4 Adverse events of special interest

The company has reported the AEOSIs that occurred in the KEYNOTE-024 trial (Table 23). The company defines an AEOSI as an AE that is consistent with an immune phenomenon and is temporally associated with drug exposure (CS, p146). The company observes that more AEOSIs were recorded in the pembrolizumab arm than in the SOC arm (29.2% versus 4.7%). The company points out that most of the AEOSIs were grade 1 or grade 2; 9.7% of patients in the pembrolizumab arm reported AEOSIs of grades 3 to 5. No deaths due to AEOSIs occurred in either arm of the KEYNOTE-024 trial.

The ERG considers that, in the less supervised environment of the UK community, the AEOSIs experienced by patients in the pembrolizumab arm, (9.7% of which were grade 3 to 5), may have greater serious and fatal complications compared to those experienced in the trial environment.

Table 23 Adverse events of special interest in the KEYNOTE-024 trial (incidence>0%)

	Pembrolizumab N=154		SOC N=150	
Adverse event type	**n**	**%**	**n**	**%**
One or more AE	45	29.2%	7	4.7%
No AE	109	70.8%	143	95.3%
Drug related AE	39	25.3%	3	2%
Grade 3 to 5 AE	15	9.7%	1	0.7%
Grade 3 to 5 drug-related AE	13	8.4%	1	0.7%
SAE	17	11%	1	0.7%
Serious drug-related AE	16	10.4%	1	0.7%
Death	0	0%	0	0%
Death due to drug-related AE	0	0%	0	0%
Discontinued due to AE	6	3.9%	0	0%
Discontinued due to drug-related AE	6	3.9%	0	0%
Discontinued due to SAE	5	3.2%	0	0%
Discontinued sue to serious drug-related AE	5	3.2%	0	0%

AE=adverse event; SAE=serious adverse event; SOC=standard of care
Source: CS, Table 46

The AEOSIs recorded in the KEYNOTE-024 trial are shown in Table 24. The ERG notes that hyperthyroidism and hypothyroidism are the two most frequently experienced AESOIs in the pembrolizumab arm (9.1% and 7.8% respectively).

Table 24 Adverse events of special interest in the KEYNOTE-024 trial

	Pembrolizumab N=154	SOC N=150
Adverse event	**n (%)**	**n (%)**
Colitis	3 (1.9%)	0 (0.0%)
Colitis	2 (1.3%)	0 (0.0%)
Enterocolitis	1 (0.6%)	0 (0.0%)
Hyperthyroidism	12 (7.8%)	2 (1.3%)
Hypophysitis	1 (0.6%)	0 (0.0%)
Hypothyroidism	14 (9.1%)	2 (1.3%)
Infusion reactions	7 (4.5%)	2 (1.3%)
Drug hypersensitivity	0 (0.0)	1 (0.7%)
Hypersensitivity	4 (2.6%)	0 (0.0%)
Infusion related reaction	3 (1.9%)	1 (0.7%)
Myositis	3 (1.9%)	0 (0.0%)
Myopathy	1 (0.6%)	0 (0.0%)
Myositis	2 (1.3%)	0 (0.0%)
Nephritis	1 (0.6%)	0 (0.0%)
Tubulointerstitial nephritis	1 (0.6%)	0 (0.0%)
Pancreatitis	1 (0.6%)	0 (0.0%)
Pneumonitis	9 (5.8%)	1 (0.7%)
Interstitial lung disease	1 (0.6%)	0 (0.0%)
Pneumonitis	8 (5.2%)	0 (0.0%)
Skin	6 (3.9%	0 (0.0%)
Psoriasis	1 (0.6%)	0 (0.0%)
Rash	2 (1.3%)	0 (0.0%)
Rash generalised	1 (0.6%)	0 (0.0%)
Rash maculo-papular	1 (0.6%)	0 (0.0%)
Toxic skin eruption	1 (0.6%)	0 (0.0%)
Thyroiditis	4 (2.6%)	0 (0.0%)
Autoimmune thyroiditis	1 (0.6%)	0 (0.0%)
Thyroiditis	3 (1.9%)	0 (0.0%)
Type 1 Diabetes mellitus	1 (0.6%)	0 (0.0%)
Diabetic ketoacidosis	1 (0.6%)	0 (0.0%)

SOC=standard of care
Source: CS, Table 47

4.9 Critique of trials identified and included in the indirect comparison

The company identified 28 RCTs for inclusion in the NMAs. A search carried out by the ERG did not identify any additional trials that met the company's eligibility criteria. A summary of the key characteristics of the trials included in the NMAs is provided in Table 25.

Table 25 Summary of trials included in the NMA

Trial	Intervention and comparator
KEYNOTE-024[1]	Pembrolizumab Standard of care
Trials comparing KEYNOTE-024 trial SOC regimens to other interventions of interest	
Chang 2008[35]	Cisplatin+gemcitabine Cisplatin+vinorelbine
Chen 2004[36]	Cisplatin+paclitaxel Cisplatin+vinorelbine
Comella 2000[37]	Cisplatin+gemcitabine Cisplatin+gemcitabine + vinorelbine Cisplatin+vinorelbine
FACs[38]	Carboplatin+paclitaxel Cisplatin+gemcitabine Cisplatin+vinorelbine
Gebbia 2003[39]	Cisplatin+vinorelbine Cisplatin+gemcitabine
GFPC 99-01 2006 [40]	Carboplatin+gemcitabine Cisplatin+vinorelbine
Helbekkmo 2007[41]	Carboplatin+gemcitabine Carboplatin+vinorelbine
Kawahara, 2013[42]	Carboplatin+docetaxel Carboplatin+paclitaxel
Khodadad 2014[43]	Cisplatin+docetaxel Carboplatin+paclitaxel
Scagliotti, 2002[44]	Cisplatin+gemcitabine Carboplatin+paclitaxel Cisplatin+vinorelbine
Schiller 2002[45]	Cisplatin+doceteaxel Cisplatin+gemcitabine Cisplatin+paclitaxel Carboplatin+paclitaxel
Sumanth 2008[46]	Carboplatin+docetaxel Carboplatin+gemcitabine
SWOG-9509[47]	Carboplatin+paclitaxel Cisplatin+vinorelbine
Trials comparing non-pemetrexed-containing and pemetrexed-containing KEYNOTE-024 trial SOC interventions	
Gronberg 2009[48]	Carboplatin+gemcitabine Carboplatin+pemetrexed
JMDB[49]	Cisplatin+gemcitabine Cisplatin+pemetrexed
JMIL[50]	Cisplatin+gemcitabine Cisplatin+pemetrexed
NAVotrial 01[51]	Cisplatin+pemetrexed Cisplatin+vinorelbine

Rodrigues-Pereira 2011 [52]	Carboplatin+docetaxel Carboplatin+pemetrexed
Socinski 2010[53]	Carboplatin+docetaxel Carboplatin+pemetrexed
Sun 2015[54]	Cisplatin+gemcitabine Cisplatin+pemetrexed
Zhang 2013[55]	Cisplatin+gemcitabine Cisplatin+pemetrexed
Trials comparing interventions of interest not in the KEYNOTE-024 trial	
Chen 2007[56]	Cisplatin+docetaxel Cisplatin+vinorelbine
Douillard 2005[57]	Cisplatin+docetaxel Cisplatin+vinorelbine
GLOB3 [58]	Cisplatin+docetaxel Cisplatin+vinorelbine
GOIM 2608 [59]	Cisplatin+vinorelbine Cisplatin+docetaxel
Martoni 2005[60]	Cisplatin+gemcitabine Cisplatin+vinorelbine
TAX 326[61]	Cisplatin+docetaxel Carboplatin+docetaxel Cisplatin+vinorelbine

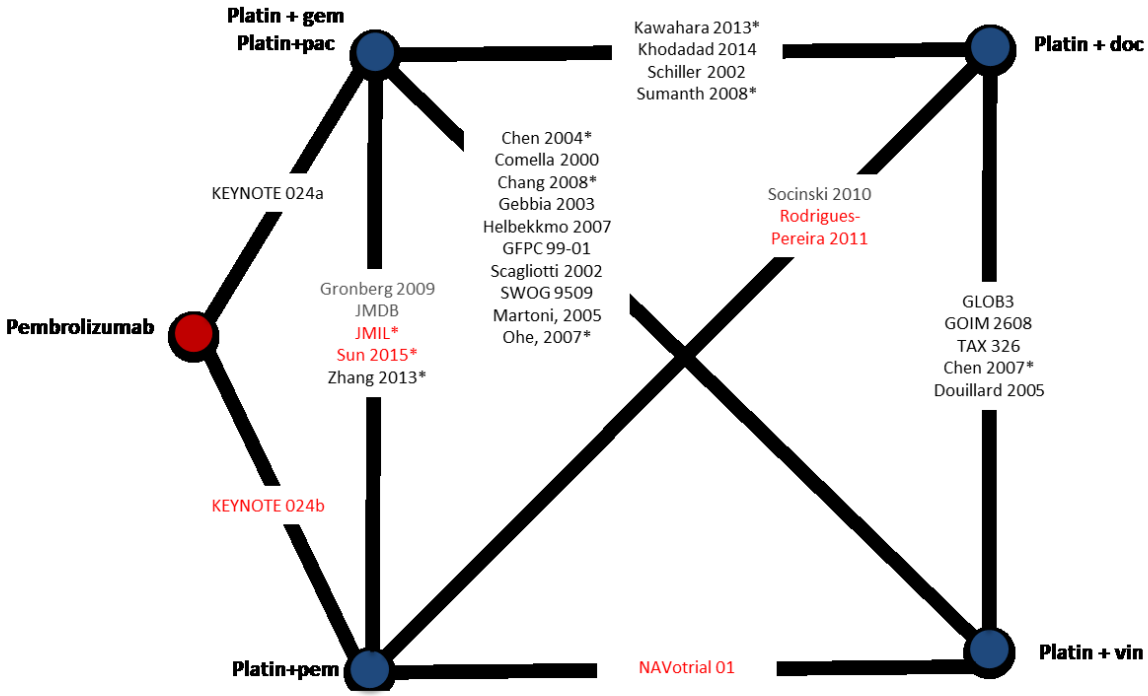
Source: CS, Table 33

Several of the trials listed in Table 25 have more than two treatment arms. The ERG asked the company (via the clarification process) whether any adjustments for multi-arm trials were made and what criteria were used to select the arms that were included in the NMAs (Question A11). The company confirmed that the analyses included adjustment for multi-arm trials and that only the trial arms representing interventions of interest were included in the NMA; no trial contributed more than two nodes to any analysis.

Networks of evidence

The company conducted five NMAs in total; however, the company's main focus is on just one NMA, an all-comers network that includes squamous and non-squamous patients. The main network is shown in Table 26. Results from specific sub-populations are reported in Appendix 18 of the CS. The results from the sub-populations are discussed in Section 4.10.4 of the ERG report.

Table 26 Overview of the main NMA and related assumptions and limitations

Scenario	Outcomes	Network of evidence	Assumptions / limitations
1 All-histologies	PFS OS		KEYNOTE-024a and KEYNOTE-024b included separately in NMA, as this allows for pemetrexed-containing SOC regimens and non-pemetrexed-containing regimens to be considered separately. The Khodadad 2014[43] trial was removed from the analysis set as it was conducted only in patients with ECOG status 2 and the KEYNOTE-024 trial included only patients with ECOG status 0 or 1. The KEYNOTE-024 trial allowed patients to crossover, however report OS results without crossover adjustment so represent relative treatment effects without crossover. Covariate in model to adjust for between trial differences in the distribution of histology which represents the proportion of non-squamous patients in each trial

Doc=docetaxel; ECOG=eastern cooperative oncology group; Gem=gemcitabine; OS=overall survival; pac=paclitaxel; pem=pemetrexed; PFS=progression-free survival; platin=platinum; SOC=standard of care; vin=vinorelbine
Source: CS, Figure 18

4.9.1 Summary of the company's network meta-analyses

An overview of the company's NMAs is presented in Box 3.

Box 3 Company overview of NMA

- To supplement the direct evidence for pembrolizumab from the KEYNOTE-024 trial, 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 NMAs of RCTs has been conducted
- The company identified 28 RCTs for inclusion in the NMAs. A search carried out by the ERG did not identify any additional trials that met the company's eligibility criteria.
- The company conducted five networks in total and focuses on one network, an all-comers (all-histologies network) including squamous and non-squamous patients.
- The outcomes of interest for the NMAs were OS (time-varying HR and constant HR) and PFS (time-varying HR and constant HR).
- The population of interest includes first-line patients with advanced or metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥ 50%), and are EGFR wild-type, and ALK negative.
- As no trial to date has been conducted in this set of patients, the population in scope for this analysis includes all patients with advanced or metastatic NSCLC other than those in trials in exclusively EGFR or ALK positive patients, under the assumption that the included interventions of interest do not vary in efficacy based on EGFR or ALK status.
- The primary population of interest was the population of all-comers (all histologies combined).
- The KEYNOTE-024 trial was the only trial included in the NMA which comprised patients whose tumours strongly express PD-L1. All other studies included in the NMA enrolled patients whose PD-L1 status was unknown.
- All outcomes of the KEYNOTE-024 trial were available for the comparison of pembrolizumab versus SOC.
- The company was also interested in assessing the outcomes of patients with squamous and non-squamous histologies. Therefore, the company split the KEYNOTE-024 trial into two populations in order to compare pembrolizumab to the different SOC populations:
    - KEYNOTE-024a: pembrolizumab versus non-pemetrexed-containing SOC, mixed histology
    - KEYNOTE-024b: pembrolizumab versus pemetrexed-containing SOC, all non-squamous histology
- The trial characteristics of the included RCTs are summarised in Table 33 and Appendix 12 of the CS. Apart from the KEYNOTE-024 trial, PD-L1 status was not reported in the included trials so the NMAs include unselected populations.
- Baseline differences are present for age between trials with mean age ranging between 50.6 to 64.9 years. In most of the trials, over 50% of the patient populations were male. Regarding race/ethnicity, there were noticeable variations between trials; for example, five trials have over 80% of Caucasian patients, whereas eight trials include only Asian patients with a further 13 trials not specifying the race/ethnicity of the patients participating in the trials. Only 25% of the trials reported smoking status; the majority of the patient populations were current/former smokers. 21 of the trials including the KEYNOTE-024 trial included patients with ECOG PS 0 or 1 with only one trial reporting that ≥ 50% of the patients reported an ECOG PS of 2.

Source: CS, Section 4.10

4.9.2 Network meta-analysis methodology

The company conducted the NMA for the population of interest presented in Table 26 to provide results for PFS and OS. The OS data from the KEYNOTE-024 trial were originally adjusted for treatment switching. The ERG asked during the clarification process whether the OS data from the KEYNOTE-024 trial included in the NMA were adjusted or unadjusted for treatment switching. The company confirmed that the results presented for OS from the KEYNOTE-024 trial were unadjusted for treatment switching. On request, the company presented the results for the OS data adjusted for treatment switching.

The company explains that instead of undertaking the NMAs using methods that rely on the PH assumption (which is often violated or implausible), a multivariate treatment effect measure was used as this method describes how the HR develops over time. The company refers to a paper by Jansen,[62] which describes a NMA method using fractional polynomials, which models HRs with a two-dimensional treatment effect. The company then considered the Weibull, Gompertz and 2nd order fractional polynomial distributions to estimate relative treatment effects between interventions. This fractional polynomial method allows the incorporation of curves that describe PFS and OS over time into the NMAs.

Each NMA was undertaken in the Bayesian framework. The company used OpenBUGS to implement the Markov Chain Monte Carlo (MCMC) method to provide estimates of the model parameters.

4.9.3 Quality assessment

The company carried out a risk of bias assessment for the trials included in the NMA using the risk of bias assessment tool for RCTs recommended by the Cochrane Collaboration.[31] The criteria assessed within the Cochrane risk of bias tool[31] are random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting of outcomes and any other sources of bias. The judgement for each criterion is: low risk of bias, high risk of bias, or unclear risk of bias.

Full results of the company's risk of bias assessment for the trials in the NMA are presented in Appendix 14 of the CS. The company also presents a narrative summary of the results as shown in Table 27 of the ERG report.

The ERG notes that company's summary of the risk of bias assessment for the KEYNOTE-024 trial does not correspond with the detail provided in Appendix 14 of the CS. The ERG notes that the trial by Martoni[60] is not included in the table presented in Appendix 14. In

Appendix 14, the company has rated the KEYNOTE-024 trial as being at low risk of bias for all criteria, except for selective reporting (unclear risk) whereas in the text, the company also described allocation concealment and blinding as being unclear.

The ERG considers that the KEYNOTE-024 trial is at low risk of bias across most of the assessment criteria, but that the risk is unclear for the criterion of 'other sources of bias.' The ERG notes that the trial was stopped early for benefit and was funded by the company who markets pembrolizumab; both factors could be considered as possible sources of bias.

For all the other trials included in the company's NMAs, the ERG agrees with the company's risk of bias assessment for the criterion of allocation concealment, blinding (participant and outcome), incomplete outcome data and selective reporting. The ERG notes that for the criterion of random sequence generation, the company considers that most of the included trials are at low risk of bias. The ERG agrees with the company's rating of each individual trial as presented in Appendix 14. However, as the company has rated 14 of the 26 trials to be at unclear risk, the ERG considers that this is a more appropriate descriptor. The ERG notes that the company allocated a rating of low risk for the criterion of 'other sources of bias'. The ERG notes that the authors of 13 of the 27 included trials reported that the trials were funded by pharmaceutical companies; this source of funding could be considered to be a possible source of bias and therefore the ERG considers this criterion to be at unclear risk.

Table 27 Company's risk of bias assessment and ERG comment

Risk of bias criterion	KEYNOTE-024	ERG comment	Summary of all other included trials	ERG comment
Random sequence generation	Low risk	Agree	Low risk (generally)	Disagree. Unclear risk. The company has rated 14 of the 26 trials as 'unclear risk' (see Appendix 14 of the CS)
Allocation concealment	Unclear risk	Disagree. Low risk. Randomisation was carried out centrally using IVRS. The ERG notes that in Appendix 14, the company has rated the trial as low risk for this criterion	For several studies, there was unclear risk of bias due to being open trials and having the different methods of drug administration between the treatment arms that prevented allocation concealment	Agree. However, the ERG considers that the meaning of risk of bias for this criterion is whether patients or physicians could have predicted before randomisation which treatment arm the patient would be randomised to rather than post-randomisation treatment
Blinding of participants	Unclear risk	Disagree. Low risk. The trial was open-label; however, blinded assessment was used in the analysis of PFS. The ERG notes that in Appendix 14, the company has rated the trial as low risk for this criterion	Most trials had unclear risk or high risk	Agree
Blinding of outcome assessment	Low risk	Agree	Most trials had unclear risk or high risk	Agree
Incomplete outcome data	Low risk	Agree	Low risk	Agree
Selective reporting	Unclear risk (due to the unavailability of CSR or trial publication	Disagree. Low risk. The CSR and trial protocol are now available	Unclear risk as the study protocol was accessible for a limited number of studies	Agree
Other sources of bias	Low risk	Disagree. Unclear risk. The trial was funded by the pharmaceutical company that markets pembrolizumab. The trial was stopped early for benefit	Low risk	Disagree. Unclear risk. 13 of the 26 trials reported sponsorship from pharmaceutical companies

CSR=clinical study report; ERG=Evidence Review Group; IVRS=interactive voice response system; PFS=progression-free survival
Source: CS, p112 and CS Appendix 14

4.10 Results of the network meta-analyses

4.10.1 Progression-free survival

The PFS results from the fixed effects NMA are provided in Table 28. The results are presented as constant HRs between all competing interventions along with 95% credible intervals (CrI). The NMA was performed on the log hazard ratios with a covariate included to represent the proportion of squamous patients in each trial. Treatment with pembrolizumab was found to statistically significantly improve PFS in comparison to platinum+gemcitabine or paclitaxel (HR=0.49; 95% CrI 0.36 to 0.67). Treatment with pembrolizumab was also found to statistically significantly improve PFS in comparison to all other therapies of interest. None of the platinum-based therapies were statistically significantly different from each other in terms of PFS. The random effects analysis produced similar results for the comparison of pembrolizumab versus platinum+gemcitabine or paclitaxel (HR=0.47; 95% CrI 0.31 to 0.68). The company also conducted a sensitivity analysis by removing trials from the NMA that included 100% Asian patients. The results from this analysis were similar to the overall results (HR=0.52; 95% CrI 0.37 to 0.72).

Table 28 PFS results from the fixed effects NMA based on constant HR assumption (all histologies)

Platinum+gemcitabine or paclitaxel	1.03 (0.95 to 1.12)	1.00 (0.90 to 1.11)	0.94 (0.83 to 1.07)	**2.06 (1.50 to 2.81)**
0.97 (0.90 to 1.05)	**Platinum+ pemetrexed**	0.97 (0.86 to 1.09)	0.92 (0.81 to 1.05)	**2.00 (1.47 to 2.71)**
1.00 (0.90 to 1.12)	1.03 (0.92 to 1.16)	**Platinum+ docetaxel**	0.95 (0.83 to 1.08)	**2.06 (1.49 to 2.84)**
1.06 (0.94 to 1.20)	1.09 (0.96 to 1.24)	1.05 (0.93 to 1.20)	**Platinum+ vinorelbine**	**2.18 (1.58 to 2.99)**
0.49 (0.36 to 0.67)	**0.50 (0.37 to 0.68)**	**0.48 (0.35 to 0.67)**	**0.46 (0.34 to 0.63)**	**Pembrolizumab**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level
Source: CS, Table 34

4.10.2 Overall survival

The OS results from the fixed effects NMA are provided in Table 29. The results are presented as constant HRs between all competing interventions along with 95% CrI. The results showed that, compared with treatment with platinum+gemcitabine or paclitaxel, treatment with pembrolizumab statistically significantly improves OS (HR=0.61; 95% CrI 0.41 to 0.90). Treatment with pembrolizumab also offered better OS than all other therapies of interest. None of the platinum-based therapies statistically significantly differed from each other. The random effects analysis produced similar results for the comparison of treatment with pembrolizumab versus platinum+gemcitabine or paclitaxel (HR=0.61; 95% CrI 0.40 to 0.93). The company

also conducted a sensitivity analysis by removing trials from the NMA that included 100% Asian patients. The results from this sensitivity analysis were similar to the overall results (HR=0.60; 95% CrI 0.40 to 0.90).

Table 29 OS results of fixed effects NMA based on constant hazard ratio assumption (all histologies)

Platinum+gemcitabine or paclitaxel	1.03 (0.95 to 1.13)	0.96 (0.87 to 1.06)	**0.90 (0.82 to 0.99)**	**1.65 (1.11 to 2.46)**
0.97 (0.89 to 1.05)	**Platinum+ pemetrexed**	0.93 (0.83 to 1.04)	**0.87 (0.78 to 0.97)**	**1.60 (1.08 to 2.36)**
1.04 (0.94 to 1.15)	1.08 (0.96 to 1.20)	**Platinum+ docetaxel**	0.94 (0.86 to 1.03)	**1.72 (1.14 to 2.57)**
1.11 (1.01 to 1.22)	**1.15 (1.03 to 1.28)**	1.07 (0.97 to 1.17)	**Platinum+ vinorelbine**	**1.83 (1.23 to 2.73)**
0.61 (0.41 to 0.90)	**0.63 (0.42 to 0.93)**	**0.58 (0.39 to 0.87)**	**0.55 (0.37 to 0.81)**	**Pembrolizumab**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
Source: CS, Table 35

Patients in the SOC arm of the KEYNOTE-024 trial were allowed to cross over to receive pembrolizumab after disease progression, if

- chemotherapy was not stopped for any other reason than progressive disease
- patient ECOG PS was 0 or 1 at time of progression and
- the patient survived for at least 30 days post-progression.

In response to a clarification request from the ERG (Question A10), the company confirmed that the results of the NMA presented in the CS were unadjusted for treatment switching. The company also provided the ERG with results from an analysis that had been adjusted for treatment switching. The results of the adjusted analysis are presented in Table 30. The ERG notes that the OS results (adjusted and unadjusted for treatment switching) are similar. The similarity is concerning as it suggests that adjusting the model for treatment switching had little difference on NMA results. Therefore, the ERG considers that both the adjusted and unadjusted results should be interpreted with caution.

The ERG considers that it is important to note that 25% of the patients crossed over from the SOC arm to receive pembrolizumab at around 8 weeks. This leads to bias and, therefore, the results that were adjusted for treatment switching should be interpreted with caution.

Table 30 OS results of fixed effects NMA based on constant hazard ratio assumption (all histologies – adjusted for treatment switching)

Platinum+gemcitabine or paclitaxel	1.03 (0.95 to 1.13)	0.96 (0.87 to 1.06)	**0.90 (0.82 to 0.99)**	**1.87 (1.22 to 2.85)**
0.97 (0.89 to 1.05)	**Platinum+ pemetrexed**	0.93 (0.83 to 1.04)	**0.87 (0.79 to 0.97)**	**1.81 (1.19 to 2.73)**
1.04 (0.94 to 1.15)	1.07 (0.96 to 1.20)	**Platinum+ docetaxel**	0.94 (0.86 to 1.03)	**1.94 (1.27 to 2.96)**
1.11 (1.01 to 1.22)	**1.15 (1.03 to 1.27)**	1.07 (0.97 to 1.17)	**Platinum+ vinorelbine**	**2.07 (1.36 to 3.14)**
0.54 (0.35 to 0.82)	**0.55 (0.37 to 0.84)**	**0.52 (0.34 to 0.79)**	**0.48 (0.32 to 0.74)**	**Pembroliumab**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
Source: Clarification response, Table 9

4.10.3 ERG critique of the network meta-analyses

Heterogeneity between included trials

The ERG has concerns about the comparability of the patient populations in the included trials.

First, the company compares PFS and OS from the KEYNOTE-024 trial, which includes a population of patients whose tumours express PD-L1 on at least 50% of their tumour cells, to other included trials that recruited unselected populations. The ERG considers that, due to the differences in these patient populations, it is inappropriate to synthesise these data in the NMAs.

Second, the ERG notes that 46 (37%) of the patients in the KEYNOTE-024 trial had received pemetrexed maintenance treatment after platinum doublet chemotherapy. The ERG notes (CS, Appendix 12, Table 3) that pemetrexed maintenance treatment was only available in one other trial (the NAVotrial[51]) that was included in the company's NMAs.

Third, patients in the KEYNOTE-024 trial all had stage IV disease, whereas all other trials included in the NMAs recruited a mix of patients with stage IIIb and stage IV disease.

Fourth, the ERG notes that there are noticeable variations in race/ethnicity between trials included in the company NMAs with eight trials including 100% Asian patients and a further five trials including over 80% of Caucasian patients. The company conducted sensitivity analyses to assess the effect of removing trials with 100% Asian patients and the ERG was satisfied that this approach had no effect on results. However, the ERG still has concerns as a further 13 trials included in the NMA do not report the race/ethnicity of patients. Therefore, there is still the possibility that race/ethnicity may affect results.

In view of all the reasons mentioned, the ERG does not consider that any reliable estimates of comparative survival are possible when treatment with pembrolizumab is compared with the comparators identified in the final scope issued by NICE.

Methodology

To generate the results of the NMAs in the context of non-proportional hazards, the company has applied a complex analytical method (fractional polynomial modelling of hazard ratios) aimed at better reflecting variations in HRs over time in the component trials of the evidence network. The true test of the appropriateness of applying such a technique to the evidence available for this appraisal is to compare the estimated HRs with those available directly from the trials. However, the ERG is unable to compare the HR of pembrolizumab versus SOC from the KEYNOTE-024 trial with the HR obtained from the main NMA based on the fractional polynomials method as the ERG considers that the OS estimates from the NMA are not accurate due to the similarity in results when comparing the adjusted and unadjusted for treatment switching results. The ERG considers that the comparison of HRs will not generate any accurate results that will be able to demonstrate whether the results from the NMA are accurate.

ERG interpretation of network meta-analysis findings

Although, the ERG considers that the methodology used to conduct the NMAs is reasonable, the ERG has identified several key concerns that should be taken into account when assessing the reliability of results generated by the NMAs.

First, it is important to note that it is unclear whether the company double counts the patients in the pembrolizumab arm when they split the KEYNOTE-024 trial. If the company has double counted then this could give the NMA additional power it does not have and hence produce biased results as this makes the PFS and OS results look more consistent than they would be if they were independent trials and so the links out to the rest of the network are artificially better. The ERG considers this to be a cause for concern and advises that the results from the NMA should be interpreted with caution. Second, the adjusted and unadjusted for treatment switching OS results from the KEYNOTE-024 trial are similar; this raises concerns over the validity of the results. Third, there is heterogeneity present in the baseline and trial characteristics; this raises concerns over the similarity of the trials combined within the NMAs.

To conclude, the ERG has several key concerns regarding the NMAs conducted by the company, and has reason to consider that the results of the NMAs cannot provide valid treatment effect estimates for pembrolizumab versus the relevant comparators. However, the ERG notes that the results of the NMAs are only used to inform the cost effectiveness of

pembrolizumab in some of the scenario analyses and not in the base case comparison. Therefore, the limitations of the NMA methodology do not have a major impact on the quality of evidence provided in the CS.

4.10.4 Additional networks of sub-populations

Additional networks of sub-populations have also been constructed with full details and corresponding NMA results provided in Appendix 18 of the CS. The sub-populations include:

- non-squamous population – including mixed-histology trials
- non-squamous population – pure network (only includes trials conducted in purely non-squamous population)
- squamous population – including mixed-histology trials
- squamous population - pure network (only includes trials conducted in purely squamous population).

The results for PFS for the sub-populations are very similar to the results obtained from the complete network, with statistically significant differences observed for treatment with pembrolizumab versus platinum+gemcitabine or paclitaxel. However, for OS, the results for the sub-populations vary, with statistically significant differences between treatment with pembrolizumab versus platinum+gemcitabine or paclitaxel only observed for the non-squamous populations for both the pure network (only non-squamous patients) and the mixed histology trials (trials including squamous and non-squamous patients). The OS results for the squamous populations showed no statistically significant differences for treatment with pembrolizumab versus platinum+gemcitabine or paclitaxel. The credible intervals are also very wide due to the small size of the population of patients with squamous disease.

4.11 Conclusions of the clinical effectiveness section

The evidence from the KEYNOTE-024 phase III RCT presented in the CS in support of the clinical effectiveness evidence of pembrolizumab for treating stage IV untreated metastatic NSCLC tumours that express PD-L1 (TPS ≥50) suggests that pembrolizumab may be a promising treatment for this population.

Direct evidence – key issues and uncertainties

The population described in the final scope issued by NICE is people with PD-L1 positive NSCLC who have not been treated with chemotherapy in the metastatic setting. The population discussed in the CS is a subset of the population described in the scope, namely, patients with untreated metastatic NSCLC whose tumours **strongly** express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutations. This means that there is no clinical effectiveness evidence for the use of pembrolizumab in patients with untreated metastatic

NSCLC with a PD-L1 TPS <50%, or for patients with a PD-L1 TPS ≥50% whose tumours also test positive for EGFR or ALK mutations.

On December 15th 2016, the CHMP of the EMA issued a positive opinion[18] recommending the use of pembrolizumab as a first-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutations.

The KEYNOTE-024 trial compares treatment with pembrolizumab with SOC chemotherapies in 305 patients. The trial was stopped early for benefit at IA2. At this point, median OS had not been reached. The trial protocol allowed patients in the SOC arm to cross over to receive treatment with pembrolizumab when their disease had progressed and, at IA2, 43.7% of patients from the SOC arm had received treatment with pembrolizumab. The immaturity of the OS data and the level of patient crossover mean that the available data are difficult to interpret. The ERG is aware that there is evidence that trials that have been stopped early for benefit have not delivered the anticipated survival gain estimated at the time of stopping.[15,17,28]

The company has considered three different methods to adjust the trial OS data for the effect of crossover. Of the methods considered for adjusting for treatment crossover, the ERG agrees with the company that the 2-stage model was the most appropriate.

However, the ERG considers that, in spite of the 2-stage adjustment method being the most appropriate method to use, the results generated from the 2-stage adjustment method (and the two other methods considered by the company [RPSFT and ICPW methods]) are unreliable. All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. This (initial) HR is only reliable if the OS hazards for the two trial datasets are proportional. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. As the (initial) HR result is uncertain, all adjustments to it should be viewed with a similar level of caution.

The ERG notes that the unadjusted OS results (HR=0.60) and those generated using the company's preferred method (the 2-stage method, HR=0.50) are very similar.

For patients treated with pembrolizumab, there appears to be a difference of [redacted] in median PFS between the investigator-assessed results and the results based on the BICR assessment ([redacted]. The reasons for, or the importance of, this difference between the two PFS estimates are unclear. Median PFS in the SOC arm is similar between the two analyses ([redacted]). The ERG is concerned that

the difference between investigator-assessed and BICR-assessed PFS may be the result of trial investigators being inexperienced with the use of pembrolizumab in treating NSCLC. The ERG notes that in the event that pembrolizumab is recommended for use in the NHS, very few clinicians are likely to be experienced in the use of pembrolizumab for treating NSCLC.

There is no direct evidence available from the KEYNOTE-024 trial for the clinical effectiveness of pembrolizumab versus platinum+docetaxel, platinum+gemcitabine, platinum+paclitaxel or platinum+vinorelbine. However, there is evidence presented (albeit from a subgroup analysis) for the clinical effectiveness of pembrolizumab versus platinum+pemetrexed.

There is no direct or indirect evidence presented in the CS to allow a comparison of the clinical effectiveness of pembrolizumab versus any of the single agent chemotherapies specified in the final scope issued by NICE.

Indirect evidence – key issues and uncertainties

The company carried out NMAs using fractional polynomials. The ERG has several key concerns regarding the NMAs conducted by the company, and has reason to believe that the results of the NMAs cannot provide valid treatment effect estimates for pembrolizumab versus the relevant comparators.

The ERG is concerned regarding the level of heterogeneity between the included trials within the NMAs. The KEYNOTE-024 trial includes a population of patients whose tumours express PD-L1 on at least 50% of their tumour cells whereas the other included trials recruited patients from unselected populations. The ERG considers that, due to the differences in these patient populations, it is inappropriate to synthesise these data in the NMAs.

The ERG notes that patients in the KEYNOTE-024 trial all had stage IV disease, whereas all other trials included in the NMA recruited a mix of patients with stage IIIb and stage IV disease.

Additionally, there are noticeable variations in race/ethnicity between trials included in the company NMAs. The company conducted sensitivity analyses to assess the effect of removing trials with 100% Asian patients and the ERG was satisfied that this approach had no effect on results. However, the ERG still has concerns as a further 13 trials included in the NMA do not report the race/ethnicity of patients. Therefore, there is still the possibility that race/ethnicity may affect results.

The company conducted the NMA for OS without adjusting for treatment crossover. However, during the clarification process, the company presented the results adjusted for treatment

crossover. The ERG is unclear why the overall conclusions and results do not change when the adjusted and unadjusted for treatment crossover results are compared.

The company split the patients from the KEYNOTE-024 trial into two groups: KEYNOTE-024a: pembrolizumab versus non-pemetrexed-containing SOC, mixed histology; and KEYNOTE-024b: pembrolizumab versus pemetrexed-containing SOC, all non-squamous. The ERG is uncertain whether the company has double counted the patients in the pembrolizumab arm when splitting the patient population in the KEYNOTE-024 trial. The ERG is concerned that if the company has double counted patients, then this could give the NMA additional power that it does not have and hence produce biased results.

Therefore, due to these reasons, the ERG does not consider that any reliable estimates of comparative survival are possible when treatment with pembrolizumab is compared with the comparators identified in the final scope issued by NICE.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of pembrolizumab for patients with untreated PD-L1 (TPS ≥50%) positive metastatic NSCLC. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.2 ERG comment on company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company conducted a systematic review to identify relevant cost effectiveness studies from the available published literature describing untreated patients with advanced NSCLC. The searches were carried out on 26th May 2016. Searching of electronic database searches and additional hand-searches was restricted to the last 10 years. The databases searched and the initial time horizon for each search are summarised in Table 31.

Table 31 Database search details

Database searched	Time horizon
Medline (via OVID SP)	2005 to 2016
Medline In-process (via OVID SP)	
EMBASE	2005 to 2016
The Cochrane Library (including the NHS EED and HTA databases)	No limit
Econ-Lit	2005 to 2016

EED=economic evaluation database; HTA=health technology assessment

Manual searches of the American Society of Clinical Oncology (ASCO) conference proceedings, the European Society for Medical Oncology (ESMO) conference proceedings and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) annual European and International Congress proceedings were also undertaken. Additional papers were identified from the reference lists of included papers. The manual searches were constrained to the most recent 2 years. In addition, the NICE website was searched to identify relevant information from previous STA submissions not otherwise captured.

5.2.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used to select studies are presented in Table 32. The ERG is satisfied that these criteria are relevant to the decision problem.

Table 32 Inclusion and exclusion criteria for cost effectiveness studies

Criteria	Inclusion	Exclusion
Population	Untreated adults with advanced NSCLC	Healthy volunteers Previously treated NSCLC patients Patients under the age of 18
Intervention/ Comparator	Studies comparing pembrolizumab vs. any other pharmacological treatment	Non-drug treatments (e.g. surgery, radiotherapy)
Outcomes	Studies including a comparison of benefits and costs between the intervention and comparator arms. Results should be expressed in incremental costs and QALYs, and any other measure of effectiveness reported together with costs	Cost-only outcomes
Study type	Full economic evaluation comparing at least two interventions in terms of cost consequence, cost effectiveness, cost utility and cost benefit evaluations	Burden of illness studies, cost minimisation and budget impact analysis
Publication type	Economic evaluations	Letters, editorials and review studies
Time limit	Studies published in last 10 years	Studies published before 2005
Language	Studies for which a full text version is available in English	Not available in English
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed The study's data and results must be extractable	Studies that fail to present sufficient methodological detail, such that the methods cannot be replicated or validated Studies that fail to present extractable results

NSCLC=non-small cell lung cancer; QALYs=quality adjusted life years
Source: CS, adapted from Table 50

5.2.3 Included and excluded studies

The company did not identify any relevant studies for inclusion in the review.

5.3 ERG critique of the company's literature review

The cost effectiveness searches include a combination of MeSH and free-text terms for the retrieval of references relating to NSCLC. A cost effectiveness filter was applied to the search along with a date limit of 2005 to 2016; the ERG considers this to be a relevant approach. Letters, editorials and literature reviews have been removed from the search results; again, the ERG considers this to be a relevant approach. The search terms and Boolean logic in the searches are considered appropriate for this type of search.

The company's search strategies supplied for The Cochrane Library and Medline in Process have sporadic numbering. However, it is possible that this is a copy and paste error as the strategies are the same as were supplied for Medline and Embase and therefore would still be adequate for retrieving cost effectiveness studies.

The search conducted in Econlit (via Ebsco) includes a cost effectiveness filter; this filter is not required for this database as it is a database of economic literature. It would have been

pertinent for the company to carry out the same search as was used for The Cochrane Library. However, the ERG considers that no relevant papers have been missed and the searches were adequate and well reported.

5.3.1 NICE Reference Case checklist

Table 33 NICE Reference Case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – most of the comparators listed in the scope are included in the economic evaluation
Perspective costs	NHS and PSS	Partial - the model only includes NHS costs. PSS costs have not been considered
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial - patient related direct health effects are considered
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 20 year time horizon
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily taken from the KEYNOTE-024 trial
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	Yes – reported directly by patients in the KEYNOTE-024 trial
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes - benefits and costs have been discounted at an annual rate of 3.5%
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	

EQ-5D=EuroQol-5 dimension; HRQoL=health related quality of life; PSS=personal social services; QALY=quality adjusted life year

5.3.2 Drummond checklist

Table 34 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Key costs and outcomes were identified
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	Costs of pembrolizumab were arbitrarily limited by stopping treatment in the model at 35 cycles
Were costs and consequences adjusted for differential timing?	Yes	Discount rate of 3.5% per annum
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost effectiveness ratios (ICERs) were calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	The results are presented and discussed in detail

5.3.3 Model structure

The cost effectiveness model presented by the company is based on a partitioned survival model, which is consistent with many oncology models submitted to NICE. The model comprises three mutually exclusive health states: pre-progression representing progression free survival (PFS), post-progression representing post-progression survival (PPS), and dead. All patients enter the model in the pre-progression health state and remain in that state until disease progression. At the beginning of each time period, patients either remain in the same health state or move to a worse health state. For example, patients in the pre-progression health state can move to the post-progression health state or to the dead health state, whilst patients in the post-progression state can only move to the dead health state. The dead health state is an 'absorbing' state i.e. a state that, once entered, cannot be left. In the base case, the company model generates results for a comparison of the cost effectiveness of treatment with pembrolizumab versus SOC. A schematic of the company model is presented in the CS and reproduced in Figure 2.

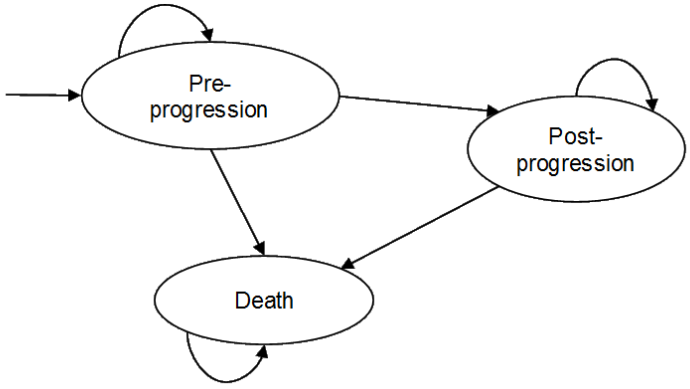


Figure 2 Schematic of the company model

The model, developed in MS Excel, uses the partitioned survival method (also known as area under the curve or AUC) to determine the proportion of patients in each of the three health states during each model cycle. The proportion of patients in the PPS state is estimated as the difference between OS and PFS. Estimates of OS and PFS are based on K-M data from the KEYNOTE-024 trial. Health effects in the company model are measured using QALYs.

5.3.4 Population

The patient population reflected in the company model is patients with advanced NSCLC whose tumours express PD-L1 on at least 50% of their tumour cells (strong expressors), with no sensitizing EGFR mutation or ALK translocation and who received no prior systemic chemotherapy treatment. The baseline characteristics of the modelled population reflect the characteristics of the KEYNOTE-024 trial baseline population and are reproduced in Table 35.

Table 35 Model baseline patient characteristics

Patient characteristic	Mean value	Source
Age	65 years	KEYNOTE-024 trial
Proportion of male patients	64.6%	KEYNOTE-024 trial
Average BSA (m^2)	1.83	KEYNOTE-024 trial (European patients)

BSA=body surface area
Source: CS, Table 51

5.3.5 Interventions and comparators

In the base case the intervention was pembrolizumab, and the comparator was SOC (therapies used in the two arms of the KEYNOTE-024 trial). Pembrolizumab was implemented in the model as per the anticipated licensed dosing regimen, i.e. administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks.

In the base case, the comparator was based on the distribution of SOC chemotherapy options prescribed to patients participating in the KEYNOTE-024 trial (Table 36). In additional analyses, relating to the NMA all histologies population, pembrolizumab was indirectly compared to individual platinum-based chemotherapies containing gemcitabine or paclitaxel, docetaxel, vinorelbine or pemetrexed based on the results of the NMA.

Using data from the KEYNOTE-024 trial, the company also considered the cost effectiveness of treatment with pembrolizumab for subgroups of patients treated with specific regimens:

- non-squamous population: pemetrexed and non-pemetrexed chemotherapy combinations
- squamous population: non-pemetrexed chemotherapy combinations
- squamous and non-squamous population: non-pemetrexed only
- squamous only population: pemetrexed only.

Table 36 Distribution of platinum-based chemotherapy combinations prescribed to patients in the KEYNOTE-024 trial and market shares

Chemotherapy combinations	KEYNOTE-024 trial	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%
Vinorelbine+carboplatin	0%	17%
Vinorelbine+cisplatin	0%	10%
Pemetrexed+carboplatin	44%	17%
Pemetrexed+cisplatin	24%	26%
% Total	100%	100%

Source: CS, Table 53

Treatment duration

In line with the KEYNOTE-024 trial protocol, treatment with pembrolizumab was assumed to continue until disease progression or intolerable toxic effects resulting in discontinuation, with maximum treatment duration of 35 cycles.

Similarly, in line with the KEYNOTE-024 trial protocol, the relevant SmPCs[63-65] and UK clinical practice, patients prescribed SOC, were assumed to receive treatment up to disease progression or intolerable toxic effects resulting in discontinuation, with maximum treatment duration of six cycles. Patients treated with pemetrexed maintenance therapy were assumed to be treated until disease progression or unacceptable toxicity.

Subsequent treatment and treatment switching

In the KEYNOTE-024 trial, 43.7% of the patients treated with SOC crossed over to receive pembrolizumab after treatment discontinuation. A simplified 2-stage adjustment was applied to take into account the effects of treatment switching on OS. This adjusted survival was used as the basis for projecting OS.

In the company model it was assumed that, in line with UK clinical practice and NICE guidance[3,66] all patients in the pembrolizumab arm received docetaxel in the second-line setting. Second-line therapy for all patients in the SOC arm was also assumed to be docetaxel.

5.3.6 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and Personal Social Services. The time horizon was set at 20 years and, in line with the NICE Methods Guide to Technology Appraisal,[30] both costs and outcomes were discounted at 3.5% per annum.

5.3.7 Treatment effectiveness and extrapolation

The primary data source for the company model was the KEYNOTE-024 trial. The follow-up period over which data were available was shorter than the time horizon of the economic model. Therefore, extrapolation of the OS and PFS from KEYNOTE-024 was required.

Overall survival

Since the PH assumption was violated when tested, a pooled parametric model was deemed unsuitable. Visual inspection and the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics were used to identify the most plausible independent parametric distributions. The company projected OS using a 2-phase piecewise model appended to K-M data from the KEYNOTE-024 trial. Separate exponential models were fitted at week 22 to extrapolate survival for both patients receiving pembrolizumab and those receiving SOC to take into account the estimated OS rate (5%) as reported in the National Lung Cancer Audit[67] (NLCA) for patients with stage IV and PS 0-1 disease. The time point of 22 weeks was chosen based on the shape of the cumulative hazard plot and there being sufficient numbers of patients at risk at this point.

Progression-free survival

K-M data from the KEYNOTE-024 trial were used directly for the first 9 weeks of the model time horizon and then separate parametric models were used based upon the pembrolizumab and SOC data separately for the projection of PFS using a 2-part piecewise extrapolation. A Weibull distribution was the best fit to the pembrolizumab PFS data based both on AIC/BIC criteria and visual fit. For SOC, there was no clear best statistical fit, with the exponential

distribution presenting the lowest BIC value while the generalised gamma had the lowest AIC value. Based on visual inspection, the Weibull distribution is close to both the exponential and the generalised gamma distributions, and it also had a good visual fit to the K-M data. Consequently, it was selected by the company for the extrapolation of PFS for SOC to maintain consistency with the best fit identified for pembrolizumab.

Modelling indirect comparisons

Since the PH assumption did not hold between pembrolizumab and SOC arms of the KEYNOTE-024 trial, the company implemented a NMA approach using time-varying HRs to model the indirect comparisons. The company used a fixed effects model with a Weibull distribution to take into account time-varying treatment effects. Treatment with pembrolizumab was compared with the following comparators in additional scenario analyses:

- gemcitabine or paclitaxel combined with a platinum (carboplatin or cisplatin)
- docetaxel combined with a platinum (carboplatin or cisplatin)
- vinorelbine combined with a platinum (carboplatin or cisplatin)
- pemetrexed-containing chemotherapy.

5.3.8 Health-related quality of life

HRQoL data were collected as part of KEYNOTE-024 trial using the EQ-5D 3L[34] tool. The company employed utility estimates in the model based on the time-to-death approach rather than utility estimates based on whether patients have progressed disease, since progression related utilities do not show a large difference between pre and post-progression utilities (0.778 and 0.668 respectively). Time-to-death sub-states were used to capture patients' HRQoL as a function of length of time until death using four categories: <30 days to death and ≥30 days to 180; ≥180 to 360 days, and ≥360 days. All patients, including censored patients, were included in the analysis for the category of 360 or more days to death.

In the base case analysis, the mean EQ-5D utility scores were pooled from the pembrolizumab and SOC treatment arms since there were no statistically significant or clinically meaningful differences in EQ-5D scores by treatment arm. UK preference-based scores were used for all patient data analysed from the KEYNOTE-024 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique. The utility values used in the company model are outlined in Table 37.

Table 37 Mean EQ-5D utility scores by time to death (KEYNOTE-024 trial data)

Time to death (days)	Mean utility (pooled across treatment arms)	95% CI
≥360*	0.808	(0.767 to 0.850)
≥180 to <360	0.712	(0.663 to 0.762)
≥30 to <180	0.598	(0.547 to 0.648)
<30	0.48	(0.324 to 0.637)

*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
Source: CS, Table 61

Within the company model, utility scores for all patients were adjusted over time using the annual utility decrement of 0.0045 that has been calculated based on figures from the publication by Kind et al.[68] Based on the baseline age of patients included in the KEYNOTE-024 trial, this decrement was applied annually from the age of 65 to 75 years to reflect the natural decrease in utility associated with increasing age.

The company's systematic review to identify studies reporting HRQoL for previously untreated patients with advanced NSCLC identified 32 unique studies. Only one relevant report was identified (NICE TA309).[10] In this report utility values were estimated by treatment arm, progressed state and time to death. However, the values presented cannot be directly compared with the utility values from the KEYNOTE-024 tial which do not adjust for the impact of disease progression on the time to death utility values and thus were not used in the company model. The company considers that, overall, the utilities derived from the KEYNOTE-024 trial are comparable to the study found from the literature search.

Impact of adverse events on health-related quality of life

The company took into account the impact of AEs on HRQoL by examining the EQ-5D-based health utility, in the PFS state, of patients who experienced grade 3 to 5 AEs (0.719; 95% CI 0.683 to 0.755) with the utility of those who did not experience any AEs in the progression-free health state (0.793; 95% CI 0.777, 0.809). Utility decrements as a result of AEs were applied during the first cycle in the company model based on AE incidence rates and the corresponding mean duration across them (i.e. 31.5 days of duration across grade 3+ AEs, as estimated from the KEYNOTE-024 trial).

5.3.9 Resources and costs

Drug costs

Pembrolizumab is administered as a 200mg fixed dose via a 30 minute IV infusion every 3 weeks (Q3W). The expected list price of a 100mg vial is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260. [redacted]

[redacted]

Drug costs for the comparator regimen, SOC, were taken from the electronic medicines information tool (eMIT)[69] for individual drugs included in the platinum-based combination therapies except for the cost of pemetrexed which was taken from the Monthly Index of Medical Specialties (MIMS) (Table 39). When multiple vial/package sizes were available, the cheapest price per mg was applied as a conservative assumption. The company did not include the costs of concomitant therapies.

Body surface area (BSA) measurements used to calculate drug cost per administration were based on a weighted mean average of 1.83m^2 from male and female patients recruited at European sites in the KEYNOTE-024 trial (Table 38). Dosing for the individual drugs was based on the KEYNOTE-024 protocol, as available. Dosing for the remaining drugs that were not included in KEYNOTE-024 protocol, was based on information in the relevant SmPC)[70,71] or from the HTA publication by Brown et al.[72] As a conservative assumption, in the company model, it is assumed that there was full vial sharing and no wastage for the comparator drugs and the cost of combination therapies was equal to the sum of the individual component drug costs. The cost per administration for the individual comparator drugs is outlined in Table 39.

Table 38 Baseline body surface area of patients recruited from European sites (KEYNOTE-024 trial)

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

BSA=body surface area
Source: CS, Table 66

Table 39 Dosing costs per administration for comparator drugs

Drug*	Dosing /m^2	Frequency	Total dose	Cost per mg	Cost per administration (assuming no wastage)	Reference for dosing	Reference for drug costs
Docetaxel	75mg	Q3W	137.25mg	£0.13	£17.42	SmPC[70]	eMit[69]
Gemcitabine	1250mg	Q3W	2287.5mg	£0.01	£22.01	KEYNOTE-024[14]	eMit[69]
Paclitaxel	200mg	Q3W	366mg	£0.07	£26.21	KEYNOTE-024[14]	eMit[69]
Vinorelbine	27.5mg	Q1W	50.33mg	£0.36	£54.37	SmPC[71]	eMit[69]
Carboplatin	400mg	Q3W	720mg	£0.04	£30.81	Brown 2013[72]	eMit[69]
Cisplatin	75mg	Q3W	135mg	£0.11	£14.49	KEYNOTE-024[14]	eMit[69]
Pemetrexed	500mg	Q3W	915mg	£1.60	£1,464.00	KEYNOTE-024[14]	MIMS[73]

*This table was amended using values from the company model as Table 67 in the CS contains dosing errors
mg=milligram; Q1W=every week; Q3W=every three weeks
Source: CS, adapted from Table 67 and company model

In the base case analysis, overall drug costs for the SOC arm were based on the weighted sum of the individual treatment costs according to the distribution of their use in the KEYNOTE-024 trial. Drug costs based on UK market shares were used in a scenario analysis. The drug costs per administration for the comparators used in the economic model are outlined in Table 40.

Table 40 Summary of the drug costs per administration for the SOC comparators

Therapy	All	Squamous	Non-squamous
Overall platinum-based chemotherapy	£998.43	£47.91	£930.59
Non-pemetrexed containing platinum-based therapy	£49.07	£47.91	£50.57
Pemetrexed containing platinum-based therapy	£1,445.18	n/a	£1,448.28
Gemcitabine or paclitaxel + carboplatin or cisplatin	£49.07	£47.91	£50.57
Docetaxel + carboplatin or cisplatin	£38.89	£38.89	£38.89
Vinorelbine + carboplatin or cisplatin	£76.79	£81.98	£66.83

Source: CS, Table 69

Treatment duration

Time on treatment (TOT) data from the KEYNOTE-024 trial were used, in the company model, to estimate treatment duration for patients treated with pembrolizumab and SOC. Independent Weibull and Gamma parametric curves were selected using AIC/BIC based tests and visual inspection to represent patient level data in the pembrolizumab and SOC arms, respectively. Maximum treatment durations of 35 cycles (105 weeks) and six cycles (18 weeks) were assumed for patients receiving pembrolizumab and SOC correspondingly. These limits are in line with the KEYNOTE-024 trial protocol.

Dose intensity

The company model also includes a dose intensity adjustment which was designed to reflect the proportions of patients in the KEYNOTE-024 trial who did not receive the full doses of study treatment (0.79% of patients in the pembrolizumab arm and 2.95% of patients in the SOC arm).

Administration costs

The Healthcare Resource Groups (HRG) code for 'simple parenteral chemotherapy – outpatient' based on the latest NHS Reference Costs 2014-2015[74] was used to reflect administration costs associated with treatment with pembrolizumab. The company assumed an administration time of 30 minutes.

The administration costs associated with treatment with platinum-based combination therapies were based on previous NICE STA submissions relating to the first-line treatment of patients with NSCLC (see Table 41). As with the costing of drugs for patients receiving SOC, in the company model, the administration costs of the platinum-based therapies are the weighted sum of the administration costs of the individual combination treatments where weights, in the base case, were based on use in the KEYNOTE-024 trial and UK market share in a scenario analysis (

Table 42).

Table 41 Administration costs of pembrolizumab and platinum-based chemotherapy

Drug	Assumptions	Unit costs	Reference
Pembrolizumab	SB12Z (Outpatient)	£257.11	-
Gemcitabine+carboplatin	SB12Z (Outpatient)	£257.11	ID840[75]
Gemcitabine+carboplatin	SB14Z (Outpatient) SB15Z (Outpatient)	£530.41	TA181[4]
Gemcitabine+cisplatin	SB14Z (Day case and regular day/night) SB15Z (Outpatient)	£618.05	TA181[4]
Paclitaxel+carboplatin	SB14Z (Outpatient)	£325.94	TA192[5]
Paclitaxel+cisplatin	SB14Z (Day case and regular day/night)	£413.58	Company assumption
Docetaxel+carboplatin	SB14Z (Outpatient)	£325.94	Company assumption
Docetaxel+cisplatin	SB14Z (Day case and regular day/night)	£413.58	TA181[4]
Vinorelbine+carboplatin	SB14Z (Outpatient) SB15Z (Day case and regular day/night)	£688.31	Company assumption
Vinorelbine+cisplatin	SB14Z (Day case and regular day/night) SB15Z (Day case and regular day/night)	£775.95	TA192[5]
Pemetrexed+carboplatin	SB14Z (Outpatient)	£325.94	TA402[10]
Pemetrexed+cisplatin	SB14Z (Day case and regular day/night)	£413.58	TA181[4]

Source: CS, adapted from Table 71

Table 42 Summary of the drug administration costs for the SOC regimens

SOC regimen	Administration costs
Overall platinum-based chemotherapy	£395.66
Non-pemetrexed containing platinum-based therapy	£478.08
Pemetrexed containing platinum-based therapy	£356.87
Gemcitabine or paclitaxel+carboplatin or cisplatin	£478.08
Docetaxel+carboplatin or cisplatin	£369.76
Vinorelbine+carboplatin or cisplatin	£720.86

Source: CS, Table 72

PD-L1 testing

The company model includes the cost of PD-L1 testing to identify patients who are eligible for treatment with pembrolizumab. The company estimates that approximately 11.6% of patients with NSCLC who have stage IV disease will also have >50% PD-L1 expression. Thus 8.6 patients will need to be tested for PD-L1 expression to identify one patient eligible to receive pembrolizumab. The company estimates that a single PD-L1 test will cost £40.50 per patient, which equates to a total cost of £348.21 relative to each patient that eventually receives pembrolizumab.

Pemetrexed maintenance therapy

Pemetrexed maintenance therapy was included in the company model for the same proportion of patients in the KEYNOTE-024 trial who received this therapy. The administration costs for

pemetrexed-containing therapy regimens are outlined in Table 41. There is currently a Commercial Access Agreement (CAA) in place for the administration of pemetrexed as maintenance therapy.[10]

Subsequent therapies and treatment switching

The costs of treatment with pembrolizumab after SOC were not accounted for in the company's base case analysis (when a statistical approach to adjust for patient crossover was implemented). All patients in the SOC arm were assumed to receive docetaxel as second-line (same assumption as for the pembrolizumab arm). The duration of second-line treatment with docetaxel is assumed to be three cycles (9 weeks) and 8.7 cycles (26.1 weeks) for patients whose first-line therapy was SOC and pembrolizumab respectively. These duration figures were based on data from the KEYNOTE-024 trial. The cost of subsequent therapy was incorporated in the model as a one-off cost in the post-progression state which was derived by weighting by the proportion of patients receiving docetaxel or pembrolizumab and taking into account the assumed treatment durations. The administration cost associated with treatment with docetaxel was assumed to be equal to that associated with treatment with pembrolizumab.

Monitoring and disease management costs

The costs of patient monitoring and disease management were applied to the PFS and PPS health states based on the resource use and cost data reported in the Brown et al study[72] and updated based on the latest NHS Reference Costs[74] and the Personal and Social Services Research Unit (PSSRU) 2015 report[76] (Table 43 and Table 44). In the company model, a cost of £76.75 per week was applied for all patients in the PFS state and for patients receiving active treatment in the PPS state. Post-progression costs of £125.87 per week were only applied to patients who were not receiving subsequent treatment whilst in the PPS state. A one-off terminal care cost of £4,735.73 was also applied to all patients in the model upon death. The company model also included the assumption that patients receiving pemetrexed

also require additional CT scanning every 12 weeks based on a previous NICE submission (TA402).[10]

Table 43 Resource use frequency for monitoring and disease management costs by state

Resource	PFS	PPS	Unit	Source quoted in Brown 2013
Outpatient visit	9.61	7.91	Per annum	Big Lung Trial[77]
Chest radiography	6.79	6.5	Per annum	Big Lung Trial[77]
CT scan (chest)	0.62	0.24	Per annum	Big Lung Trial[77]
CT scan (other)	0.36	0.42	Per annum	Big Lung Trial[77]
ECG	1.04	0.88	Per annum	Big Lung Trial[77]
Community nurse visit	8.7	8.7	Visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG81,[78] Marie Curie report[79]
Clinical nurse specialist	12	12	Hours contact time per patient	Appendix 1 of NICE Guideline CG81[78]
GP surgery	12	0	Consultations per patient	Appendix 1 of NICE Guideline CG81[78]
GP home visit	0	26.09	Per annum (fortnightly)	Marie Curie report[79]
Therapist visit	0	26.09	Per annum (fortnightly)	Appendix 1 of NICE Guideline CG81[78]

PFS=progression-free state; PPS=post-progression state; GP=general practitioner; CT=computerised tomography; ECG=electrocardiogram; NICE=National Institute for Health and Care Excellence
Source: CS, Table 74

Table 44 Disease management costs

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£177.83	Per visit	NHS Reference Costs 2014–2015[74]
Chest radiography	£26.39	Per case	TA199[80]
CT scan (chest)	£121.68	Per case	NHS Reference Costs 2014–2015[74]
CT scan (other)	£124.10	Per case	NHS Reference Costs 2014–2015[74]
ECG	£174.91	Per case	NHS Reference Costs 2014–2015[74]
Community nurse visit	£67.00	Per hour	PSSRU 2015[76]
Clinical nurse specialist	£91.00	Per contact hour	PSSRU 2015[76]
GP surgery visit	£44.00	Per visit	PSSRU 2015[76]
GP home visit	£88.92	Per visit	PSSRU 2015[76]
Therapist visit	£44.00	Per hour	PSSRU 2015[76]

GP=general practitioner; CT=computerised tomography; ECG=electrocardiogram; PSSRU=Personal Social Services Research Unit; NICE=National Institute for Health and Care Excellence; HRG=Healthcare Resource Groups; TA=Technology Appraisal
Source: CS, Table 75

Adverse events costs

The company model includes grade 3+ AEs experienced by more than 5% of patients at any grade in either arm of the KEYNOTE-024 trial. The company also included diarrhoea (grade 2) so as to be consistent with previous NICE appraisals[81,82] and febrile neutropenia due to its impact on quality of life and costs. Incidence data were taken from the KEYNOTE-24 trial. 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. The costs of AEs are detailed in Table 45.

Table 45 Adverse event costs

Adverse Event	Unit costs	Reference
Nausea	£967.99	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[72,76]
Anaemia	£2,610.66	NICE ID840[20]
Fatigue	£2,768.35	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[72,76]
Diarrhoea (grade 2)	£442.76	NICE ID840[20]
Diarrhoea (grade 3 to 4)	£967.99	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[72,76]
Dyspnoea	£571.06	NICE TA403[83]
Vomiting	£764.71	NICE TA192 (inflated to 2014/15 using PSSRU inflation indices)[5 76]
Neutropaenia	£117.31	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[72,76]
Alanine aminotransferase increased	£598.85	NICE TA347 (inflated to 2014/15 using PSSRU inflation indices)[84 76]
Rash	£123.34	Brown (inflated to 2014/15 using PSSRU inflation indices)[72,76]
Asthenia	£2,768.35	Brown (inflated to 2014/15 using PSSRU inflation indices)[72,76]
Thrombocytopaenia	£758.50	NICE ID865[66]
Neutrophil count decreased	£179.83	NICE ID840[20]
Aspartate aminotransferase increased	£342.78	NICE TA347 (inflated to 2014/15 using PSSRU inflation indices)[76,84]
Pneumonia	£3,008.41	NICE ID835[85]
White blood cell count decreased	£560.08	NICE ID840[20]
Urinary tract infection	£2,225.03	NICE TA347 (inflated to 2014/15 using PSSRU inflation indices)[84 76]
Neuropathy peripheral	£19.76	NICE TA162[80]
Pneumonitis	£3,008.41	Assumed to be same as pneumonia
Febrile neutropaenia	£6,831.00	Brown 2013 (inflated to 2014/15 using PSSRU inflation indices)[72,76]

PSSRU=Personal Social Services Research Unit; WBC=white blood cell; TA=Technology Appraisal
Source: CS, Table 77

5.3.10 Cost effectiveness results

Total costs, life years gained (LYG), QALYs and the incremental cost effectiveness ratio (ICER) per QALY gained for the cost effectiveness comparison of treatment with pembrolizumab versus SOC are shown in Table 46. In the base case, treatment with pembrolizumab generates 1.21 additional QALYs at an additional cost of £54,185. The company base case ICER for the comparison of treatment with pembrolizumab versus SOC is £44,896 per QALY gained.

Table 46 Base case cost effectiveness results (discounted, with PAS)

Technologies	Total			Incremental		ICER per QALY gained
	Costs	LYG	QALYs	Costs	QALYs	
SOC	£22,278	1.22	0.86			
Pembrolizumab	£76,462	2.75	2.06	£54,185	1.21	£44,896

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years; SOC-standard of care
Source: CS, Table 80

The company presented a range of ICERs to take into account the current CAA for the administration of pemetrexed as maintenance therapy[84] and the subsequent impact of the discount size (Table 47).

Table 47 ICERs for pembrolizumab versus SOC using a range of different discounts to reflect possible values for the current pemetrexed CAA (discounted, with PAS)

Discount to pemetrexed price	ICER per QALY gained
0%	£44,896
10%	£45,167
20%	£45,437
30%	£45,708
40%	£45,979
50%	£46,250
60%	£46,520
70%	£46,791
80%	£47,062
90%	£47,332

CAA=commercial access agreement; ICERs=incremental cost effectiveness ratios; PAS=patient access scheme; QALY=quality adjusted life year
Source: CS, Table 81

A summary of the predicted drug, drug administration and disease management costs is presented in Table 48. Just over three-quarters of the difference in costs between the intervention and comparator technologies is due to differences in acquisition costs.

Table 48 Summary of predicted resource use by category of cost

Category	Pembrolizumab	SOC	Incremental	Absolute increment	% absolute increment
PD-L1 test cost	£348	£0	£348	£348	0.55%
Drug acquisition cost	£53,347	£4,030	£49,317	£49,317	77.85%
Drug administration cost	£4,380	£1,597	£2,783	£2,783	4.39%
Pemetrexed maintenance cost	£0	£3,909	-£3,909	£3,909	6.17%
Disease management cost	£12,476	£6,155	£6,320	£6,320	9.98%
Subsequent treatment (2L) cost	£765	£808	-£42	£42	0.07%
Terminal care cost	£4,283	£4,537	-£254	£254	0.40%
AE cost	£863	£1,242	-£379	£379	0.60%
Total	£76,462	£22,278	£54,184	£63,352	100%

2L=second line; AE=adverse event; SOC=standard of care
Source: CS, Table 84

Pairwise cost effectiveness comparisons based on NMA results

Results of the pairwise comparisons using the comparators included in the company's NMA are outlined in Table 49. The company states that these results should be interpreted with caution due to the observed heterogeneity between studies.

Table 49 Pairwise cost effectiveness results (discounted, with PAS)

Technologies	Total			Incremental		ICER per QALY gained
	Costs	LYG	QALYs	Costs	QALYs	
Platinum+gemcitabine or paclitaxel	£18,238	1.277	0.899	£58,224	1.163	£50,080
Platinum+docetaxel*	£17,721	1.262	0.892	£58,741	1.17	£50,206
Platinum+vinorelbine	£18,987	1.179	0.823	£57,476	1.239	£46,377
Platinum+pemetrexed	£24,003	1.359	0.964	£52,460	1.098	£47,786
Pembrolizumab	£76,462	2.752	2.062	-	-	-

*Company corrected values, there were errors in the original CS table
ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, Table 85

5.3.11 Sensitivity analyses

Deterministic sensitivity analyses

The company carried out a wide range of deterministic sensitivity analyses for base case comparison of treatment with pembrolizumab versus SOC. The three most influential parameters were related to the extrapolation of OS for patients receiving pembrolizumab, utility values for long-term survivors and the extrapolation of OS for patients receiving SOC. Results from the analyses involving the ten parameters which, when varied, had the most influence on the company's base case results analyses are displayed in the CS in a Tornado diagram (reproduced in Figure 3)

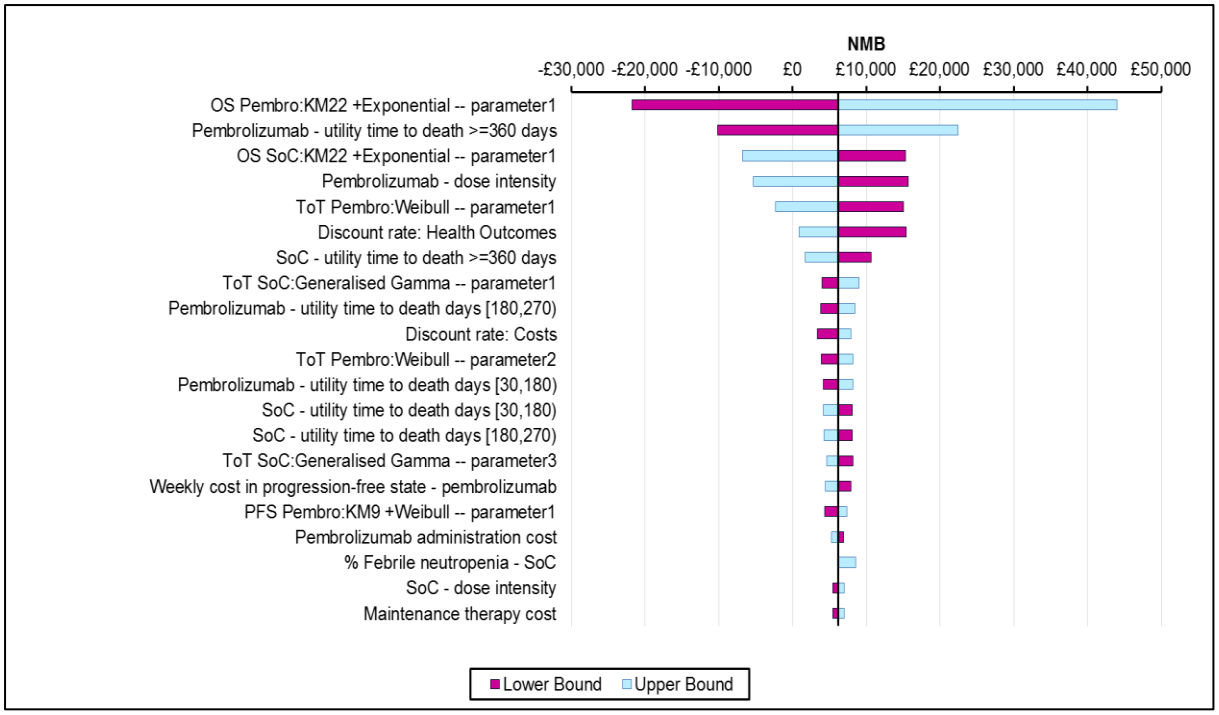


Figure 3 Deterministic sensitivity analysis (discounted results, with PAS)

Source: CS, Figure 47

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to assess the uncertainty surrounding the parameter values used in the model. Results from this analysis are displayed in Table 50 and show an ICER per QALY gained that is slightly lower than the deterministic analysis. The analysis involved running the company model 1000 times. The scatterplot of PSA results and the cost effectiveness acceptability curve (CEAC) are presented in Figure 4 and Figure 5. Examination of the CEAC shows that the chance of pembrolizumab being cost effective at a threshold of £50,000 per QALY gained is approximately 62%.

Table 50 Base case PSA ICER (discounted, with PAS)

Technologies	Total		Incremental		ICER per QALY gained
	Costs	QALYs	Costs	QALYs	
Pembrolizumab	£77,005	2.09	-	-	-
SOC	£22,666	0.87	£54,339	1.22	£44,394

ICER=incremental cost effectiveness ratio; QALYs=quality adjusted life years; SOC=standard of care
Source: CS, Table 87

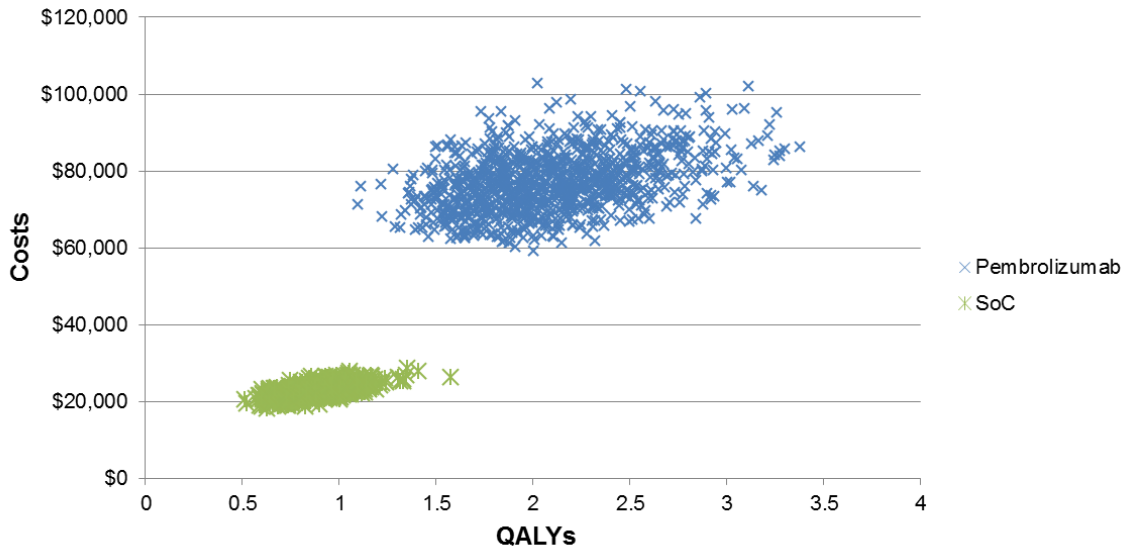


Figure 4 Scatterplot of PSA results (1,000 simulations; results discounted, with PAS)

Source: CS, Figure 45

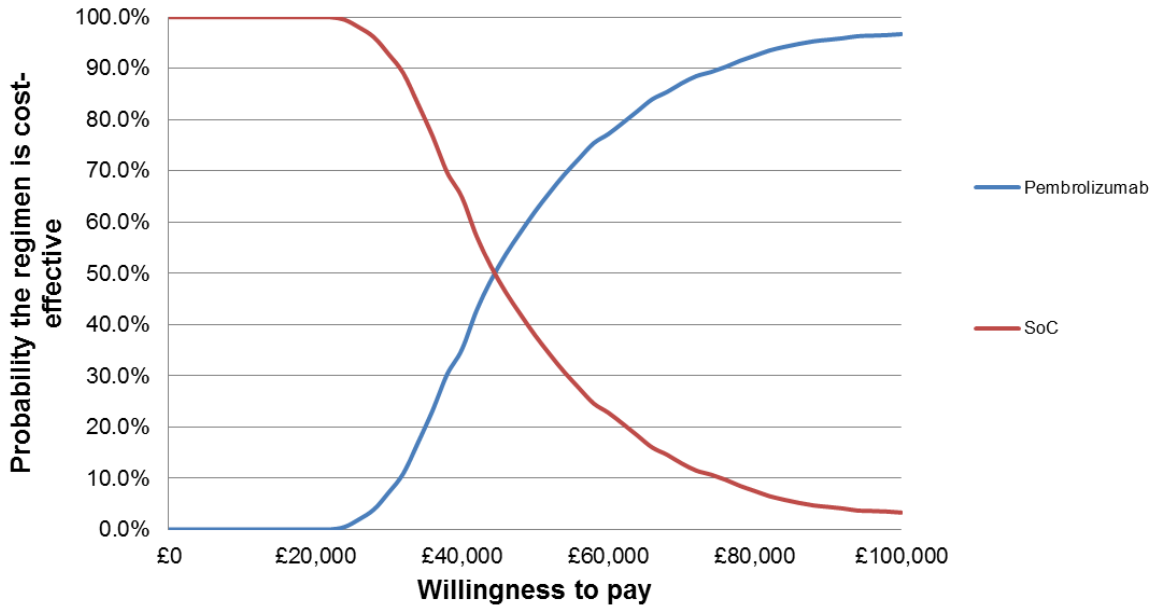


Figure 5 Cost effectiveness acceptability curve (results discounted, with PAS)

Source: CS, Figure 46

Scenario analysis

The company undertook nine scenario analyses to assess the structural and methodological assumptions implemented in the model. Results from these analyses showed that the cost effectiveness of treatment with pembrolizumab was only sensitive to two scenarios, and both of these involved employing different methods of extrapolating KEYNOTE-024 trial OS data (see Table 51).

Table 51 Scenario analyses (discounted, PAS)

Scenario	Criteria	Incremental costs	Incremental QALYs	ICER per QALY gained
Base case		£54,185	1.21	£44,896
Scenario 1.a	Crossover – ITT (no adjustment)	£39,981	0.99	£40,547
Scenario 1.b	Crossover- RPSFT adjustment	£54,908	1.30	£42,295
Scenario 1.c	Crossover- IPCW adjustment	£54,274	1.22	£44,447
Scenario 2.a	OS cut-off – 4 weeks	£52,409	0.95	£55,244
Scenario 2.b	OS cut-off – 0 week (i.e. fully fitted parametric)	£52,283	0.93	£55,952
Scenario 3.a	PFS cut-off – 18 weeks	£54,644	1.21	£45,277
Scenario 3.b	PFS cut-off – 27 weeks	£55,502	1.21	£45,988
Scenario 4	SOC PFS extrapolation based on exponential	£54,148	1.21	£44,865
Scenario 5	No half cycle correction	£54,183	1.21	£44,900
Scenario 6	SOC as for UK market shares	£53,744	1.21	£44,531
Scenario 7	Utilities – progression-based (pooled)	£54,185	1.16	£46,705
Scenario 8.a	Utilities – time to death (per treatment arm)	£54,185	1.17	£46,280
Scenario 8.b	Utilities – progression-based (per treatment arm)	£54,185	1.22	£44,586
Scenario 9	No age-related disutilities	£54,185	1.24	£43,865

ICER=incremental cost effectiveness ratio; IPCW=inverse probability censored weighting; ITT=intention to treat; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; QALY=quality adjusted life year; RPSFT=rank preserving structural failure time; SOC=standard of care
Source: CS, adapted from Table 88

5.3.12 Model validation and face validity check

Clinical benefit

The company compared outcomes from the KEYNOTE-024 trial with outcomes generated by their model and considered them to be similar.

Expert validation

The company reports that the model was validated by several experts including an external health economist, a leading expert in health economics practice and methodology development in the UK and a member of a NICE ERG. In addition, the accuracy of the implementation and programming of the model was verified via internal quality control processes using an internal quality control checklist.

5.4 Detailed critique of the company's economic model

The ERG's assessments of the structure of the company model and the data used to populate it are provided in Section 5.5.1 and Sections 5.5.2 to 5.5.4 contain details about the three issues that have a major impact on the cost effectiveness results generated by the company model, namely:

- limiting the number of cycles of pembrolizumab treatment
- OS projections
- utility values.

5.4.1 Summary of model structure and included data

The company provided a model in MS Excel. The ERG considers that the model is well constructed, there are no obvious flaws in the algorithms used to generate base case results and it is straightforward to use. In addition to the well-constructed model, the ERG welcomes the following model design choices made by the company:

- use of TTD (time to treatment discontinuation) data as the basis for estimating the cost of treating patients with pembrolizumab
- direct use of K-M data, where available
- use of utilities based on time to death rather than on disease state.

5.4.2 Number of cycles of pembrolizumab

The company has limited the number of cycles of pembrolizumab that patients can receive to 35 (approximately 2 years). This is in line with the details provided in the KEYNOTE-024 trial protocol. The ERG considers this limit to be inappropriate because:

1. no patients in the KEYNOTE-024 trial reached 2 years of treatment. The impact of stopping pembrolizumab treatment for responding or stable patients after 2 years is, therefore, unknown
2. [redacted]

[redacted]

The ERG considers that it is clinically implausible that clinicians would stop treatment at an arbitrary time point, not mentioned in the SmPC,[1] if they considered that patients were still benefiting from treatment. Further, as no patients in the KEYNOTE-024 trial completed 2 years of treatment, the OS extrapolation for pembrolizumab from this trial is based on patients who were treated in line with the KEYNOTE-024 trial protocol to a time-point before 2 years i.e., to progression or unacceptable toxicities. The ERG considers that the same approach would be taken in NHS clinical practice. Therefore, the company's OS extrapolations for patients receiving pembrolizumab, while uncertain, are at least based on a reasonable approximation of what would happen to patients should treatment with pembrolizumab become the standard of care. In contrast, the modelled costs of treatment with pembrolizumab are based on a time limiting stopping rule outlined in the KEYNOTE-024 trial protocol that was not applied to any patients participating in the trial and is not mentioned in the draft SmPC.[1]

The ERG has removed the limit on the number of cycles of treatment with pembrolizumab from the company model. This ERG amendment increases the total costs associated with treatment with pembrolizumab from £76,462 in the company base case to £133,546, and increases the ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC by £47,298 to £92,194 per QALY gained (see Table 53).

Continuing treatment with pembrolizumab beyond 35 cycles has an impact on treatment and administration costs. Table 52 shows the acquisition and administration costs of treatment with pembrolizumab that are generated by the company model, assuming treatment continues beyond 35 cycles [redacted] These figures are based on the KEYNOTE-024 trial TTD data and the extrapolation of these data undertaken by the company.

The data in Table 52 show that just under half (49.7%) of the potential acquisition and administration costs of pembrolizumab are excluded from the cost effectiveness results if treatment is assumed to discontinue at 2 years. Due to a long tail of patients remaining on treatment, by the end of 5 years the company model predicts that 13.7% of patients will still be on treatment, although by this point 78.5% of the total potential pembrolizumab costs will have been realised. Even if all treatment is arbitrarily stopped at 3 years rather than 2 years, the ICER per QALY gained for the comparison of pembrolizumab versus SOC would increase beyond £50,000 to £56,502 per QALY gained (see Table 53).

Table 52 Pembrolizumab acquisition and administration costs over time

Years of treatment (cycles)	Percentage of patients still expected on treatment at end of year	Mean discounted cost per patient of acquisition and administration to the end of the year	Percentage of mean discounted total acquisition and administration costs incurred to the end of the year	ICER per QALY gained vs SOC if all pembrolizumab treatment stopped at the end of the year
2 years (35 cycles) (company base case)	30.7%	£57,727	50.3%	£44,896
3 years (52 cycles)	22.6%	£71,734	62.5%	£56,502
4 years (70 cycles)	17.4%	£82,499	71.9%	£65,421
5 years (87 cycles	13.7%	£90,133	78.5%	£71,476
10 years (174 cycles)	5.3%	£109,778	95.6%	£88,024
Total over lifetime (348 cycles)	**100.0%**	**£114,810**	**100.0%**	**£92,194**

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

The final appraisal determination (FAD)[20] for the STA considering the use of pembrolizumab for treating advanced or recurrent PD-L1 positive NSCLC after progression with platinum-based chemotherapy was published on 2 December 2017. It is stated within the FAD[20] that the Appraisal Committee concluded that the ICERs were highly sensitive to a continued treatment effect after stopping treatment with pembrolizumab. The ERG notes the impact on the ICER of continuing treatment beyond 2 years was limited in this aforementioned appraisal. As shown in Table 52, in the current appraisal of pembrolizumab in the first-line setting, the impact on the ICER is significant if treatment continues past 2 years. It is likely that this is due to patients in the first-line setting having higher OS and PFS than patients in the second-line setting. The higher OS and PFS mean that the proportion of patients receiving pembrolizumab in the first-line setting will be higher at 2 years than the proportion of patients in the second-line setting who are still receiving pembrolizumab.

5.4.3 Overall survival

Pembrolizumab

Analysis carried out by the ERG shows that, of the 2.06 QALYs generated in the pembrolizumab arm, 1.76 QALYs (85.4%) are generated after 22 weeks i.e., during the period that a statistical distribution is used to represent patient survival. Further, 1.18 QALYs are generated beyond 18 months. This means that over 57% of the QALYs attributable to treatment with pembrolizumab are generated during a period in which there is no direct evidence of effect from any clinical trials. Confidence in the method used to extrapolate OS data from patients treated with pembrolizumab is, therefore, key to confidence in the QALY gain associated with this treatment and, thus, confidence in the estimated ICER per QALY gained.

The ERG's primary concern with the method employed by the company to extrapolate trial data is the scale of the uncertainty around the OS projections. The company extrapolations of OS K-M data from the KEYNOTE-024 trial (CS Figure 30, reproduced in Figure 6) together with AIC and BIC tests undertaken by the company (CS, p173) show that all of the standard distributions that could be selected to extrapolate the trial data are, essentially, each as statistically likely (or unlikely) as each other. There are some distributions (such as those that have implausibly long tails leading to some patients living well into their hundreds) that can be discounted as clinically implausible. However, within the confines of the range of clinically plausible distributions, there is no way to confidently pick the most likely distribution and confidence in any distribution diminishes as time from the last available trial data point increases.

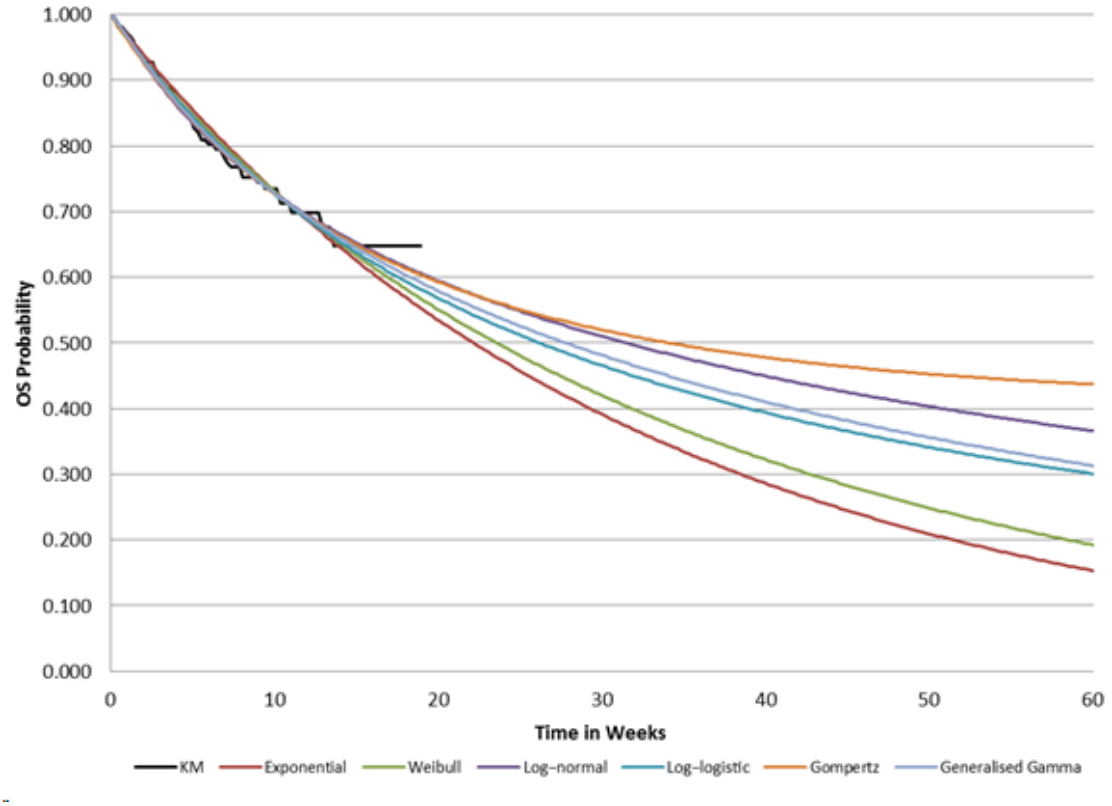


Figure 6 Company projections of KEYNOTE-024 trial K-M OS data (pembrolizumab arm)
Source: CS, Figure 30

By using an exponential distribution for extrapolation from week 22 the company has assumed a constant mortality rate for both pembrolizumab and SOC after week 22. This mortality rate is higher for SOC than pembrolizumab for the 20 year time horizon of the model and effectively means that pembrolizumab continues to have a treatment effect many years after treatment could have stopped. While the ERG considers this to be potentially implausible, it is a minor

concern compared to the uncertainty in the projections that exist even at just 2 years after treatment commenced (50.9% to 58.4% depending on the distribution chosen).

Although the company has chosen to employ the most pessimistic of the generated distributions, the ERG considers that, given the immaturity of the OS data, there is no distribution that can be considered reliable. The ERG has, therefore, not suggested an alternative representation of OS for patients treated with pembrolizumab. Instead, the ERG cautions that the extrapolation implemented in the company model should be interpreted as illustrative rather than as an expectation and, until further OS data become available, there is no way of knowing whether the company has been overly or insufficiently pessimistic in their chosen projection.

Standard of care

As stated in Section 4.4.3 of this ERG report, the ERG considers that the method for adjustment for crossover in the SOC treatment arm of the KETNOTE-024 trial produces unreliable results. Even if the crossover adjustment was reliable, the ERG considers that the company has been too pessimistic in estimating 5-year survival rates for patients with stage IV NSCLC and PS 0 to 1 receiving SOC.

The 5-year survival rate of patients treated with SOC in the company model is 1.9%. This is below the NLCA 5-year survival rate (5%) for patients with stage IV NSCLC.[67] It is also below the lower bound of the 2% to 13% 5-year survival range reported by Cancer Research UK[86] and referenced by the company in support of the following statement made in the CS:

> More than half of non-small cell lung cancer (NSCLC) patients present with incurable advanced local or metastatic disease at the time of diagnosis, with **an estimated five-year survival rate around 10%**. (CS p14, emphasis added)

The ERG considers that the actual 5-year survival rate for patients with stage IV NSCLC and PS 0 to 1 who are treated with chemotherapy should be at least the 5% reported in the NLCA dataset.[67] The ERG considers that, in clinical practice, the 5-year survival rate is likely to be closer to the higher (13%), rather than lower (2%), bound figures quoted by Cancer Research UK[86] as the NLCA 5-year survival rate[67] has been derived from data from all patients, regardless of whether the patient received chemotherapy.

Figures from the latest (2015) NLCA report[87] indicate that only 58% of patients with stage IIIb/IV NSCLC received chemotherapy in 2014 and this rate was higher than in previous years. If chemotherapy improves life expectancy, then the 5% 5-year survival figure reported by the

NLCA will be lower than the rate expected for patients in the SOC arm of the company model as all patients in the SOC arm of the company model were assumed to receive chemotherapy.

Evidence from the NLCA[67] suggests that chemotherapy treatments make a significant difference to OS estimates with 12-month survival for patients with stage IIIb/IV NSCLC who received chemotherapy being 47% compared with 25% for patients who did not receive chemotherapy. This difference is supported by findings from a US study[88] that examined the long-term survival of patients with NSCLC who had stage IIIb/IV disease, with PS 0 to 2, who did and did not receive chemotherapy. The findings from this study[88] suggest that the survival rate, at 4 years, for patients receiving chemotherapy (around 20% of the study population) is approximately twice that of patients who did not receive chemotherapy.

Taking all the above into account, the ERG considers that the company's extrapolation of OS K-M data from patients in the SOC arm of the KEYNOTE-024 trial, which results in 1.9% of patients being alive at 5 years, is too pessimistic.

Being primarily concerned that modelled OS should reflect published survival rates from the NLCA[67] dataset, the ERG took the parsimonious approach of simply adjusting the value of the exponential parameter employed in the company base case so that modelled survival at 5 years was 5%, i.e., in line with the NLCA[67] figure for the survival for all patients with stage IV NSCLC and PS 0-1. The ERG considers a higher estimate than 5% is more plausible since all patients in the SOC arm received chemotherapy and so this amendment should be considered to be conservative.

In a separate scenario analysis, the ERG explored the impact on the ICER per QALY gained of a 5-year survival rate of 13% (the upper bound of the Cancer Research UK[86] range). Again, the ERG modified the value of the exponential parameter used in the company base case to facilitate this survival adjustment. The ERG's alternative OS projections for patients treated with SOC, the company's base case projections for patients treated with SOC and the company's base case projections for patients treated with pembrolizumab are shown in Figure 7.

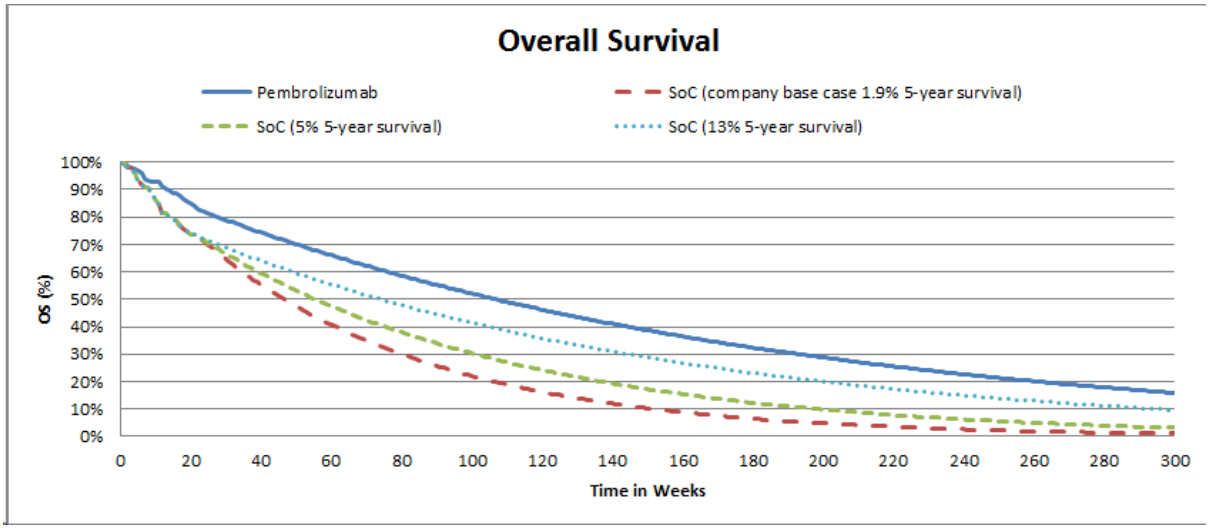


Figure 7 ERG amended and company base case OS projections

Source: ERG remodelled SOC OS

The impact of assuming the survival rate at 5 years for patients treated with SOC is 5% is to increase the QALYs for this arm from 0.86 in the company base case to 1.08, and changes the difference between treatment arms (pembrolizumab versus SOC) from 1.21 QALYs in the company base case to 0.98 QALYs. This model amendment increases the company's base case ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC by £8,583 to £53,479 per QALY gained (see Table 53).

Scenario analysis

When OS at 5 years is modelled to be 13% for patients receiving SOC, the company's base case ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC increases by £44,831 to £89,727 per QALY gained (see Table 53).

5.4.4 Utility values used in the model

The ERG considers that the utility values chosen by the company for inclusion in the company model appear to be implausibly high. This is most notably for the 12-month period before death when the values used in the company model are always higher than the UK population norms,[68] regardless of patient age. The ERG notes the following two extracts, from the CS, describing the HRQoL of patients with stage IV NSCLC:

> One of the reasons for delayed diagnosis is that the most common symptoms of NSCLC (e.g. cough, shortness of breath and chest pain) are similar to those associated with conditions such as smoking and chronic bronchitis. (CS, p35)

> Patients with NSCLC have reported the highest prevalence levels of psychological distress (three times more than in other cancers), which can lead

> to a poorer prognosis and greater patient burden. Increased levels of psychological distress are reported by patients undergoing oncological treatment and by those approaching death. (CS p35 and 36)

Even if these issues are alleviated somewhat by treatment, the company needs to justify the claim that patients with stage IV NSCLC achieve higher levels of HRQoL life than those achieved by people of the same age in the general UK population.

The reason why the utility values from the KEYNOTE-024 trial are so high for the time period >360 days to death is unclear. The ERG accepts that the KEYNOTE-024 trial EQ-5D completion rates were reasonably high. However, as data were only collected up to week 24, only a very small number of patients provided information for each of the periods to death that were measured. For example, only 54 patients provided data that contributed to the utility estimate for the period >360 days from death, and only 26 patients provided data to inform the utility estimate for the period 180 to 360 days to death. This means that the confidence intervals around the utility estimates are wide, indicating significant uncertainty around the calculated figures and that the high mean utility values may just be a statistical artefact of a small sample size. In the absence of further evidence on the time to death utility values, the ERG has carried out two scenario analyses.

First, a scenario was constructed in which the utility value >360 days before death was set to be no greater than that of the general UK population of the same age. This resulted in a reduction in the >360 days before death value from 0.808 to 0.79. This is still a conservative scenario, as it relies on the assumption that having metastatic NSCLC, with the associated quality of life issues stated in the CS and repeated above, does not lower patient utility below that of the general UK population of the same age. This scenario results in a reduction in the QALYs generated for both the pembrolizumab arm (from 2.06 in the company base case to 2.03) and the SOC arm (from 0.86 in the company base case to 0.85). Implementing this change in the company model increases the ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC by £1,004 to £45,900 per QALY gained (see Table 53).

The second scenario examined the impact of using utility values published in the Nafees 2008 paper.[89] The values from the Nafees[89] publication have previously been used in other NICE STAs, including the appraisal of pemetrexed for the first-line treatment of NSCLC (TA181[4]). While these utilities are representations of the HRQoL of patients in the stable, responding and progressive disease states, the ERG considers that, as an explorative analysis, the value for responding disease with no side effects (0.673) could be used for all values for time to

death >180 days, and the value for progressive disease (0.473) for time to death <180 days. To reiterate, this analysis is explorative and has only been carried out to highlight the impact on the ICER per QALY gained of using values broadly in line with those accepted by the Appraisal Committee when considering previous appraisals for this patient group. Using the Nafees[89] values results in a reduction in the QALYs generated in both the pembrolizumab arm (from 2.06 in the company base case to 1.73) and the SOC arm (from 0.86 in the company base case to 0.73), resulting in increasing the ICER by £9,000 to £53,896 per QALY gained for the comparison of pembrolizumab versus SOC (see Table 53).

The ERG considers that the second scenario is more likely to represent actual utilities for patients within the scope of this submission. However, as the utility values from the Nafees[89] paper are not directly transferable to the health states in the model, the ERG amended base case has used values from the first scenario.

Minor issues

The ERG identified seven minor issues in the model. Correcting these issues makes less than a one per cent difference to the company's base case ICER per QALY gained and, therefore, these amendments have not been included in the ERG's adjusted model results table (Table 53).

Body surface area of UK patients

The ERG considers that the company should have calculated costs of SOC treatments using the average BSA of UK patients with NSCLC rather than the average BSA of patients participating in the international KEYNOTE-024 trial. As UK patients potentially have a lower average BSA,[90] the costs of SOC treatment would be lower, again increasing the size of the ICER per QALY gained.

Alternative censoring approach to OS

As part of the clarification process, the ERG requested OS K-M data generated by censoring patients at data cut-off, rather than when last known to be alive. The company provided this information but it was almost identical to the K-M data using the company's preferred censoring method. This means that using the alternative censoring method had minimal impact on OS over the period for which K-M data were available and did not significantly change the parameters of the distributions used to extrapolate OS beyond the available K-M data. While it was important to explore the impact of the alternative censoring approaches, in this case the ERG is satisfied that the choice of censoring approach has not made an important difference to the size of the ICER per QALY gained and the ERG has, therefore, not

incorporated the K-M data using the ERG's preferred approach to censoring into the company model.

Discount rates

Within the company model, discounting is applied weekly starting from the first week of the model. The NICE Methods Guide[30] recommends that all costs and benefits in each year should be aggregated and the discount rate applied to the yearly totals, with the first discount applied to costs and benefits in the second year.

The company approach has overly discounted both costs and benefits in the model in the first year and has under discounted costs and benefits from the second year onwards. Without rebuilding the company model (a task that is beyond the remit of the ERG) it is not possible to calculate the impact of this error. The ERG considers that the company's approach to discounting has resulted in an underestimate of the ICER for the comparison of treatment with pembrolizumab versus SOC, but it is unlikely to have made a large enough difference such that conclusions of overall cost effectiveness of pembrolizumab would be different if discounting had been applied correctly.

Disutility values

Within the company model disutility values are added to the underlying utility value when an AE is experienced. However, the utility values used in the company base case were derived directly from patients in the KEYNOTE-024 trial. This means that there is potential 'double counting' as the utility values calculated from patients in the trial should already include any reduction in utility due to AEs averaged across all patients.

The severity of an AE may have meant that patients did not complete an EQ-5D form whilst experiencing the event. It is, therefore, possible that utility values for patients experiencing an AE are either (i) not included in the company's average utility values or (ii) these values are under-represented. If either of these occurred then, although 'double counting' is theoretically possible, in practice it may not have happened and so disutilities to account for the impact of AEs would need to be applied.

As the AEs included in the model are relatively rare and short lived, the impact on the ICER of any potential 'double counting' increases the company's base case ICER by less than £200. As such, and given the uncertainty that the 'double counting' has occurred, the ERG has not amended the model to remove the disutility adjustments associated with experiencing an AE.

PD-L1 testing

Within the company model, PD-L1 testing has been incorporated as part of the cost based on an assumption that approximately eight people will need to be tested to identify one patient whose tumours strongly express the PD-L1 gene. The ERG considers this appropriate, but notes that the effectiveness of pembrolizumab and the costs of testing per patient are based upon the sensitivity and specificity of the PD-L1 test used in the KEYNOTE-024 trial. Routine testing for the PD-L1 gene does not currently occur in the NHS. For the cost effectiveness results presented by the company, or after the ERG amendments, to hold, the PD-L1 test employed routinely in the NHS should be at least as sensitive and specific as that employed in the KEYNOTE-024 trial.

Probabilistic sensitivity analysis

The ERG notes that while the model parameter distributions used for the company's PSA are provided in Appendix 26 of the CS, no justification is supplied to support the choice of distributions. This means that the choices appear to be arbitrary. This lack of justification limits the confidence that can be placed in the company's PSA results.

6 SUMMARY OF ADDITIONAL WORK UNDERTAKEN BY THE ERG

This section summarises the impact of the ERG's amendments to the company base case results for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC. The ERG amendments only relate to issues that have a major impact on the size of the company's base case cost effectiveness results. The amendments that have been made are:

- removing the limit on the number of cycles of treatment with pembrolizumab
- remodelling the OS projections for patients treated with SOC such that 5-year survival is 5%
- altering utility values so that they are no higher than the UK population norms.

The impact of the ERG's amendments on the costs and QALYs of treatment with pembrolizumab and on the ICER per QALY gained are shown in Table 53. Compared to the values generated by the company base case, the ERG amendments increase the costs of pembrolizumab by £57,084 per patient whilst reducing the QALYs associated by pembrolizumab by 0.03. These changes increase the size of the company base case ICER from £44,896 to £114,291 per QALY gained.

For completeness, the effects of the ERG amendments on the ICERs from the company scenario analyses (i.e., pembrolizumab versus specific chemotherapy regimens) are presented in Appendix 2. However, the ERG does not consider that the results from the company's NMAs, which underpin the effectiveness evidence for specific chemotherapy regimens, are reliable and, therefore, these results are only presented for completeness and should be interpreted with caution.

Table 53 ERG adjustments to company base case: pembrolizumab versus SOC (discounted, with PAS)

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	***£76,462***	***2.06***	***2.75***	***£22,278***	***0.86***	***1.22***	***£54,185***	***1.21***	***1.53***	***£44,896***	
R1) Removal of 35 cycle limit for patients treated with pembrolizumab	£133,546	2.06	2.75	£22,278	0.86	1.22	£111,268	1.21	1.53	£92,194	+£47,298
R2) 5% 5-year OS survival for patients treated with SOC	£76,462	2.06	2.75	£24,117	1.08	1.51	£52,345	0.98	1.24	£53,479	+£8,583
R3) 13% 5-year OS survival for patients treated with SOC	£76,462	2.06	2.75	£27,630	1.52	2.06	£48,833	0.54	0.70	£89,727	+£44,831
R4) Utility value for >360 days to death set to population norm	£76,462	2.03	2.75	£22,278	0.85	1.22	£54,185	1.18	1.53	£45,900	+£1,004
R5) Nafees[89] utility values	£76,462	1.73	2.75	£22,278	0.73	1.22	£54,185	1.01	1.53	£53,896	+£9,000
B. ERG preferred scenario (R1, R2 and R4)	**£133,546**	**2.03**	**2.75**	**£24,117**	**1.07**	**1.51**	**£109,428**	**0.96**	**1.24**	**£114,291**	**+£69,395**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; SOC=standard of care; OS=overall survival

6.1 Conclusions of the ERG's cost effectiveness review

The ERG considers that there are four issues that cast substantial doubt on the reliability of the ICER per QALY gained estimated by the company for the comparison of treatment with pembrolizumab versus SOC.

First, the extrapolation of OS for pembrolizumab is highly uncertain due to the relatively short-term clinical effectiveness evidence that is currently available from the KEYNOTE-024 trial.

Second, the extrapolation of OS for SOC is overly pessimistic compared to that which would be expected when using registry data or published studies describing patients with stage IV NSCLC treated with chemotherapy. The company extrapolation predicted OS at 5 years for patients treated with SOC to be 1.9%, whereas NLCA[67] data suggest that 5-year survival for all patients with stage IV NSCLC is 5%. However, the NLCA[67] data include at least 40% of patients who did not have chemotherapy and results from other published studies show that chemotherapy increases life expectancy for stage IV NSCLC patients. In the base case, the ERG has amended survival at 5 years to be 5% for patients treated with SOC. However, in clinical practice, a greater percentage of patients receiving chemotherapy would be expected to still be alive at 5 years - possibly as many as 13%. The ERG therefore considers that the amendment made still produces a conservative estimate of the ICER per QALY gained for the comparison of treatment with pembrolizumab versus SOC.

Third, the company calculated the cost of pembrolizumab on the basis that treatment would cease after 35 cycles (2 years) as this approach fitted with the treatment approach described in the KEYNOTE-024 trial protocol. [redacted] The ERG therefore considers it implausible that treatment would be stopped at an arbitrary time point in a clinical setting if a patient were deemed to still be deriving clinical benefit from treatment with pembrolizumab.

None of the patients in the KEYNOTE-024 trial stopped treatment at 2 years as the data-cut was carried out before that point. The company has no clinical evidence to support the decision to stop treatment at 2 years and all projections of OS and PFS are only based upon treatment to progression before 2 years. The ERG considers that the only plausible costing scenario for pembrolizumab is to remove the limit on the number of cycles of pembrolizumab in the company model.

Fourth, the ERG considers that the utility values incorporated into the company models are implausibly high, notably for the period 360 days before death as these values are higher than the UK population norms.[68]

In summary, application of the ERG amendments to remove the limit on the number of pembrolizumab cycles, increase OS when treating patients with SOC and apply more plausible utility values resulted in an ICER of £114,291 per QALY gained for pembrolizumab compared to SOC. Given that the amendments made by the ERG for SOC OS and the utility values were cautious, this ICER should be interpreted as a lower bound estimate of the ICER per QALY gained for treatment with pembrolizumab versus SOC.

7 END OF LIFE CRITERIA

The company puts forward the case (CS, Section 4.13) that pembrolizumab as a first-line treatment for stage IV NSCLC meets the NICE End of Life criteria.[91]

The NICE criteria for applying a less restrictive assessment of cost effectiveness for End of Life are that:

- treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment and

The company claims that pembrolizumab in the indication for this submission meets the NICE End of Life criteria for the reasons set out Table 54.

Table 54 Company's End of Life criteria assessment

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 was not reached. However, the average life expectancy for a patient with NSCLC (regardless of histology) receiving chemotherapy SOC is estimated to be between 9.9 and 13.9 months, based on the following: According to the PARAMOUNT[92] 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. Squamous patients have lower life expectancy as evident from the SQUIRE trial reporting a median OS of 9.9 months for the gemcitabine + cisplatin arm.[93]
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: The average number of months of life gained with pembrolizumab as estimated by the economic model is 29 months, compared to 14.6 months with SOC In KEYNOTE-001[25] trial, the median OS for the treatment naïve NSCLC pembrolizumab arm was 22.1 months (95% CI, 16.8 to 27.2)

Source: CS, Table 49

The ERG agrees with the company that available data from the SOC arm of the KEYNOTE-024 trial, in conjunction with NLCA[67] data (11.3 months for patients with Stage IIIb/IV, PS 0-1 and receiving chemotherapy, suggest that the median OS for the population under consideration in this appraisal is less than 24 months. The mean OS for SOC from the ERG adjusted company model (5% survival at 5 years) is 1.51 years (18.1 months).

The difference in mean survival between patients treated with pembrolizumab versus SOC estimated using the ERG amended model is 1.24 years (14.9 months). While there is considerable uncertainty around the validity of the representations of OS in the company model, the ERG is satisfied that the evidence is sufficient to suggest that the OS of patients treated with pembrolizumab is likely, on average, to be at least 3 months more than that of patients treated with SOC.

The ERG, therefore, considers that pembrolizumab meets the End of Life criteria for the target patient population of this submission.

8 OVERALL CONCLUSIONS

Clinical effectiveness evidence

- The company has provided evidence from a small phase III un-blinded RCT (the KEYNOTE-024 trial) to support the use of pembrolizumab in patients with untreated, metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥50%). This trial was designed to compare the clinical effectiveness and safety of treatment with pembrolizumab versus SOC.
- The population in the KEYNOTE-024 trial is patients with untreated metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutations. This is a subset of the population described in the final scope issued by NICE (i.e., people with PD-L1 positive NSCLC not treated with chemotherapy in the metastatic setting).
- The KEYNOTE-024 trial was stopped early for benefit. The currently available OS data from the KEYNOTE-024 trial were obtained at IA2. At this point, only 35% of the expected OS events had occurred. Median OS had not been reached in either arm of the trial. Furthermore, the ERG has concerns that the trial based OS HR result may be inaccurate as the assumption of proportional hazards that underpins this calculation is invalid.
- The protocol for the KEYNOTE-024 trial allowed patients receiving SOC to cross over at disease progression to receive pembrolizumab and, at the time of IA2, 43.7% of patients from the SOC arm had crossed over. The company considered three different methods to adjust the trial OS data for the effect of treatment crossover. Of the methods considered, the ERG agrees with the company that the 2-stage model is the most appropriate.
- All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. This (initial) HR is only reliable if the OS hazards for the two trial data-sets are proportional. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. As the (initial) HR result is uncertain, all adjustments to it should be viewed with a similar level of caution.
- The ERG notes that the unadjusted OS results (HR=0.60) and the HR generated using the company's preferred method (the 2-stage method, HR=0.50) are very similar.
- The ERG is uncertain of the reasons for, or the implications of, the [redacted] difference between the BICR-assessed PFS and investigator-assessed PFS for patients in the pembrolizumab arm of the KEYNOTE-024 trial ([redacted]).
- In the draft SmPC[1] for pembrolizumab, it is stipulated that treatment should be initiated only after a validated laboratory test has confirmed the tumour expression of PD-L1. Clinical advice to the ERG is that, at present, there is no established or validated test for PD-L1 expression and testing for PD-L1 expression is not routinely available in NHS treatment centres. The ERG notes that, in the NHS, there is currently no standard means of identifying patients whose tumours strongly express PD-L1.
- In the absence of any direct evidence for the clinical effectiveness of treatment with pembrolizumab versus individual platinum doublet chemotherapy regimens specified in the final scope issued by NICE, the company conducted a series of NMAs. However, due to concern that patients in the KEYNOTE-024 trial may have been double counted, similarity between adjusted and unadjusted NMA OS results, mix of patients with and

without tumours that express PD-L1 and high levels of heterogeneity between included studies, the ERG considers that results from the company's NMAs should be interpreted with caution.

- The ERG notes that 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. They may also have greater variation in available social support. The ERG considers that AEs arising from treatment with immunotherapy (i.e., pembrolizumab) in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.
- The company reports that the KEYNOTE-042 RCT is currently underway. This trial has been designed to compare treatment with pembrolizumab versus SOC in a population of patients with PD-L1 positive advanced or metastatic NSCLC. Final data collection for OS is planned for February 2018. The results of the KEYNOTE-042 trial will provide evidence for the clinical effectiveness of pembrolizumab in patients whose tumours express PD-L1, regardless of the level of expression.

Cost effectiveness evidence

- To model survival for patient lifetime the company has extrapolated KEYNOTE-024 survival data. However, the ERG considers that:
    - Any extrapolation of OS data from patients in the pembrolizumab arm of the KEYNOTE-024 trial will be highly uncertain due to only 35.4% of the expected OS events having occurred.
    - The company's extrapolation of OS data from patients in the SOC arm of the KEYNOTE-024 trial is overly pessimistic compared to survival results available from registry data and published studies describing patients with stage IV NSCLC treated with chemotherapy. Survival, predicted by the company extrapolation for patients treated with SOC at 5 years is 1.9%, whereas NLCA[67] data suggest that 5-year survival for all patients with stage IV NSCLC is 5%.
- The company calculated the cost of pembrolizumab on the basis that treatment would cease after 35 cycles (2 years) as this is in line with details published in the KEYNOTE-024 trial protocol. However, for patients with untreated PD-L1 positive metastatic NSCLC, [redacted]
  The ERG therefore considers 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.
- The ERG considers that the utility values incorporated into the company model are implausibly high, notably for the period 360 days before death when these values are higher than the UK population norms.
- The ERG made three changes to the company model: altering the OS extrapolation for patients receiving SOC such that 5% of patients are alive at 5 years; removing the arbitrary 35 cycle limit on the number of cycles of pembrolizumab that can be administered; and limiting the magnitude of the utility values used in the model so that they are no higher than the population norms for people of the same age.
- Using the PAS price, application of the ERG model amendments results in an ICER for the comparison of treatment with pembrolizumab versus SOC of £114,291 per QALY gained. The ERG's amendments to the company's OS extrapolation for patients receiving SOC and to the utility values employed in the model are very conservative

and the ERG's revised cost effectiveness results should be interpreted as a lower bound estimate of the ICER per QALY gained for this comparison.

End of Life criteria

- The ERG agrees with the company that the average life expectancy of the population of interest is less than 24 months.
- Although there is considerable uncertainty around the validity of the representations of OS in the company model, the ERG is satisfied that the evidence is sufficient to suggest that the OS of patients treated with pembrolizumab is likely, on average, to be at least 3 months more than that of patients treated with SOC.
- The ERG, therefore, considers that pembrolizumab meets the End of Life criteria for the target patient population of this submission.

8.1 Implications for research

- Currently, there is no routine testing of tumours for PD-L1 expression in NHS clinical practice. Findings from a recent meta-analysis[94] suggest prognosis may be poorer for patients with tumours expressing PD-L1 than those without, but the sample sizes of the included studies were small, treatments were not considered and studies were not restricted to patients with stage IV disease (in four of the studies no patients with stage IV disease were included). The results of a small observational study (n=204) did not demonstrate a prognostic value of PD-L1 in patients with advanced NSCLC.[95] Further research is required to determine the prognostic value of PD-L1 expression for NSCLC patients with stage IV disease.
- The company carried out a series of NMAs to determine the relative clinical effectiveness of treatment with pembrolizumab versus the platinum doublet therapies specified in the final scope issued by NICE. These NMAs suffered from severe methodological limitations rendering results unreliable. Primary research is required to determine the relative effectiveness of pembrolizumab versus platinum doublet chemotherapies in the patient population of interest.
- The ERG considers that research is required to explore the competing ethical interests of allowing patients in the comparator arm of a trial to cross over to receive the intervention with the interests of the wider patient population for whom this practice means that the true benefit of the intervention relative to the trial comparator will never be certain.

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10 APPENDICES

Appendix 1 The F1 cohort of the KEYNOTE-001 study

The company reports results from a dose ranging cohort study of pembrolizumab in a population of patients with NSCLC, the F1 cohort study[25] of a phase 1 dose escalation study (KEYNOTE-001). The company states that the results of the F1 cohort study provide evidence of the longer-term clinical efficacy of pembrolizumab in the treatment of patients with advanced NSCLC (CS, p23). However, the company reports (CS, p104) that:

Of the 101 patients with untreated stage IV NSCLC PD-L1 positive tumours enrolled into the F1 cohort study, only 27 (26.7%) had a TPS ≥50% and are therefore of relevance to the patient population discussed in the CS.

None of the three doses of pembrolizumab administered in the F1 cohort study, i.e., 2mg/kg Q3W, 10mg/kg Q3W or 10mg/kg Q2W match the 200mg Q3W dose that was used in the KEYNOTE-024 study and the 200mg dose that is likely to be be stipulated in the EMA's marketing authorisation for pembrolizumab.

The ERG considers that the results of the F1 cohort study are of minimal relevance to the company's decision problem given: i) the small number of patients with tumours with a TPS of ≥50% and ii) that the doses of pembrolizumab administered in the F1 cohort study are different to the dose of pembrolizumab administered in the KEYNOTE-024 trial (and therefore the dose that is expected to be stipulated in the EMA's marketing authorisation). The ERG notes that the patient population of the F1 cohort matches the population in the final scope issued by NICE, i.e. patients with PD-L1 positive NSCLC not treated with chemotherapy in the metastatic setting.

The company presents full details of the F1 cohort study (CS, p126 to p135 and CS, p148 and 149).

10.1.1 Patient characteristics from the F1 cohort study

The key baseline characteristics of patients included in the F1 cohort study trial are listed in Table 1.

Table 1 Characteristics of patients included in the F1 cohort study

Characteristic	Overall study population (N=101)
Age (years) median (range)	68 (39 to 93)
Male n (%)	60 (59%)
ECOG PS n (%)	
0	44 (44%)
1	57 (56%)
Histology n (%)	
Non-squamous	79 (79%)
Squamous	19 (19%)
Smoking history n (%)	
Current or former	90 (89%)
Never	11 (11%)
EGFR mutation n (%)	
Y	3 (3%)
N	95 (94%)
unknown	3 (3%)

ECOG PS= Eastern Cooperative Oncology Group Performance Status; EGFR=epidermal growth factor receptor
Source: CS, Table 36

Results from the F1 cohort study

The results presented in the CS are from the data cut of 18th September 2015. At this time the median length of patient follow-up was 22.2 months (range 17.8 to 30.5 months), 35.6% of patients were alive without new cancer therapy and 13% of patients continued to receive pembrolizumab.

10.1.2 Progression-free survival

The PFS results (based on independent central review) from the F1 study cohort are presented in Figure 1. Results are given for the overall study population and by levels of PD-L1 expression. The ERG notes the small numbers of patients in each of the subgroups. The company reports (CS, p134) that median PFS in the overall population was 6.2 months (95% CI: 4.1 to 8.6) while in the subgroup of patients with PD-L1 TPS ≥50%, median PFS was 12.5 months (95% CI: 6.2 to NR).

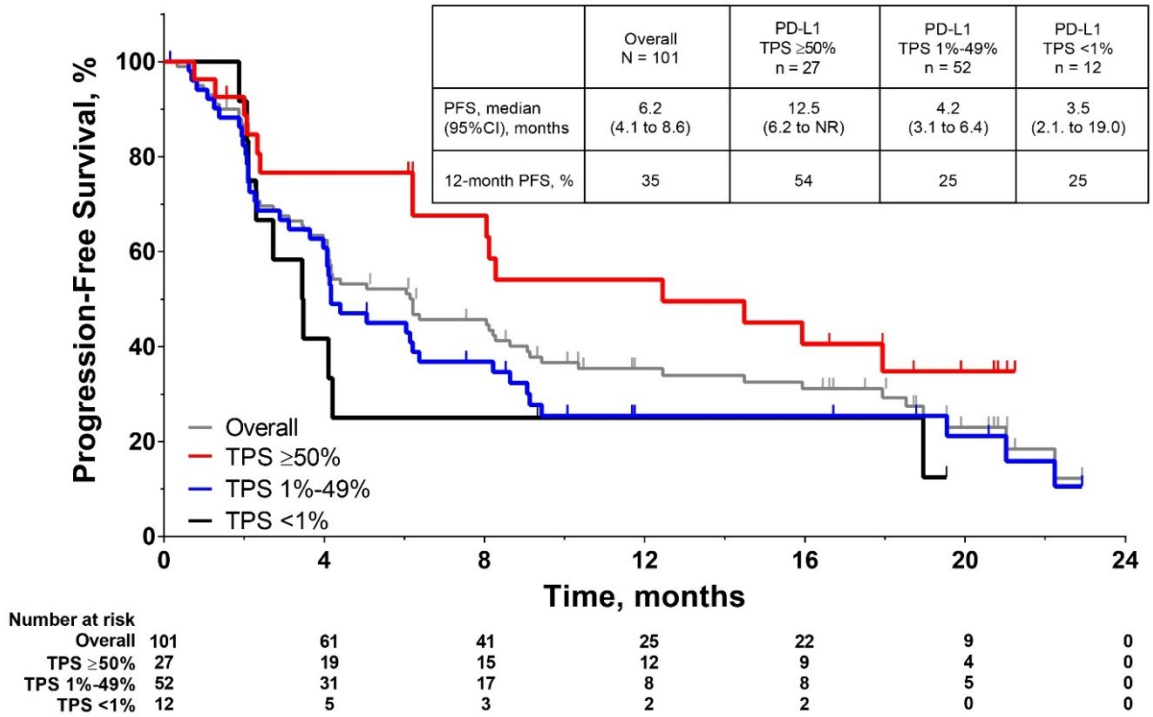

Figure 1 The F1 cohort study: K-M estimates of PFS (independent central review)

Source: CS, Figure 22

10.1.3 Overall survival

The OS results from the F1 cohort study are presented in Figure 2. Results are given for the overall study population and by levels of PD-L1 expression. The ERG notes the small numbers of patients in each of the subgroups. The company reports that median OS in the overall study population was 22.1 months (95% CI: 17.1 to 27.2), whilst in the subgroup of PD-L1 TPS ≥50% patients, median OS was not reached (95% CI: 22.1 months to NR).

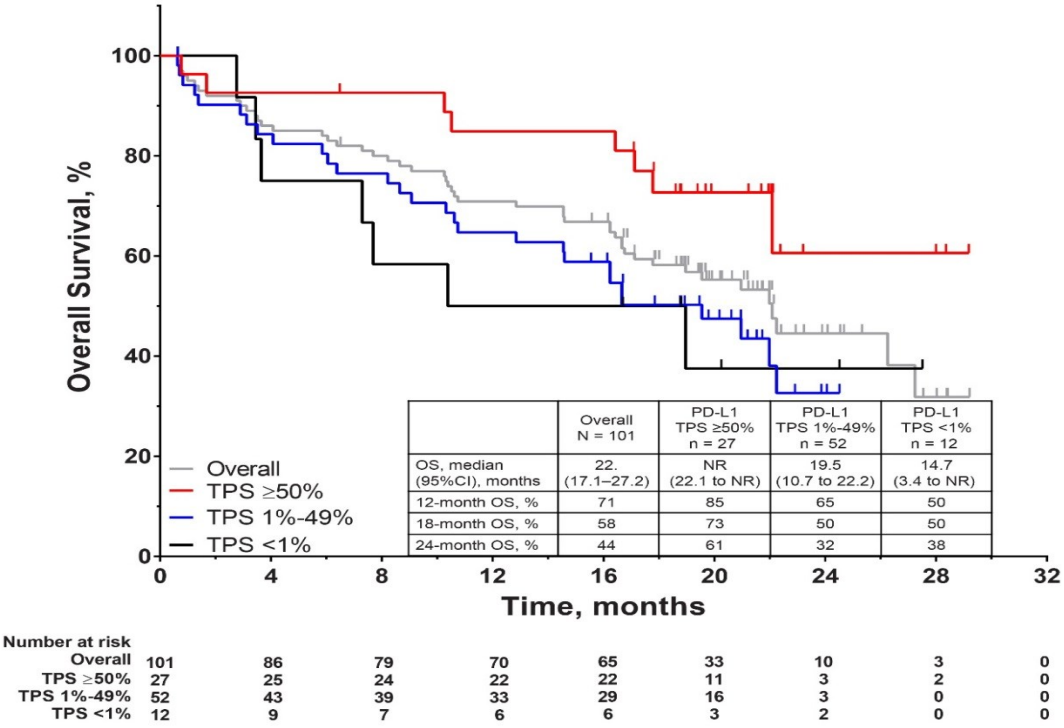

Figure 2 The F1 cohort study: K-M estimates of PFS (independent central review)

Source: CS, Figure 23

10.1.4 Adverse events

The company reports (CS, p149) that [redacted]

Appendix 2 The effects of the ERG amendments on the ICERs from the company scenario analyses

Table 1 ERG adjustments to company base case: pembrolizumab versus platinum+docetaxel (based upon NMA, discounted with PAS)

Scenario/ERG amendment	Pembrolizumab			Platinum+docetaxel			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£76,462***	***2.06***	***2.75***	***£17,721***	***0.89***	***1.26***	***£58,741***	***1.17***	***1.49***	***£50,206***	
R1) Removal of 35 cycle limit for patients treated with pembrolizumab	£133,546	2.06	2.75	£17,721	0.89	1.26	£115,825	1.17	1.49	£98,996	+£48,790
R2) 5% 5-year OS survival for patients treated with SoC	£76,462	2.06	2.75	£18,333	0.96	1.35	£58,129	1.1	1.4	£52,845	+£2,639
R3) 13% 5-year OS survival for patients treated with SoC	£76,462	2.06	2.75	£22,067	1.41	1.91	£54,395	0.65	0.84	£83,685	+£33,479
R4) Utility value for >360 days to death set to population norm	£76,462	2.03	2.75	£17,721	0.88	1.26	£58,741	1.14	1.49	£51,325	+£1,119
R5) Nafees utility values	£76,462	1.73	2.75	£17,721	0.76	1.26	£58,741	0.97	1.49	(60,558)	+£10,352
B. ERG preferred scenario (R1, R2 and R4)	**£133,546**	**2.03**	**2.75**	**£18,333**	**0.95**	**1.35**	**£115,213**	**1.08**	**1.49**	**£106,679**	**+£56,473**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; OS=overall survival; NMA=network meta-analysis

Table 2 ERG adjustments to company base case: pembrolizumab versus platinum+gemcitabine or paclitaxel (discounted, with PAS)

Scenario/ERG amendment	Pembrolizumab			Platinum+gemcitabine or paclitaxel			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£76,462***	***2.06***	***2.75***	***£18,238***	***0.90***	***1.28***	***£58,224***	***1.17***	***1.49***	***£50,193***	
R1) Removal of 35 cycle limit for patients treated with pembrolizumab	£133,546	2.06	2.75	£18,238	0.90	1.28	£115,308	1.16	1.49	£99,403	+£49,210
R2) 5% 5-year OS survival for patients treated with SoC	£76,462	2.06	2.75	£19,073	1.00	1.40	£57,390	1.06	1.4	£53,991	+£3,798
R3) 13% 5-year OS survival for patients treated with SoC	£76,462	2.06	2.75	£22,648	1.43	1.93	£53,815	0.63	0.82	£84,944	+£34,751
R4) Utility value for >360 days to death set to population norm	£76,462	2.03	2.75	£18,238	0.89	1.28	£58,224	1.14	1.49	£51,205	+£1,012
R5) Nafees utility values	£76,462	1.73	2.75	£18,238	0.77	1.28	£58,224	0.97	1.49	£60,136	+£9,943
B. ERG preferred scenario (R1, R2 and R4)	**£133,546**	**2.03**	**2.75**	**£19,074**	**0.99**	**1.40**	**£114,472**	**1.04**	**1.36**	**£110,069**	**+£59,876**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; OS=overall survival

Table 3 ERG adjustments to company base case: pembrolizumab versus platinum+vinorelbine (discounted, with PAS)

Scenario/ERG amendment	Pembrolizumab			Platinum+ vinorelbine			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£76,462***	***2.06***	***2.75***	***£18,987***	***0.82***	***1.18***	***£57,475***	***1.24***	***1.57***	***£46,351***	
R1) Removal of 35 cycle limit for patients treated with pembrolizumab	£133,546	2.06	2.75	£18,987	0.82	1.18	£114,559	1.24	1.57	£92,386	+£46,035
R2) 5% 5-year OS survival for patients treated with SoC	£76,462	2.06	2.75	£20,106	0.96	1.34	£56,356	1.1	1.41	£51,233	+£4,882
R3) 13% 5-year OS survival for patients treated with SoC	£76,462	2.06	2.75	£23,863	1.41	1.91	£52,599	0.65	0.84	£80,922	+£34,571
R4) Utility value for >360 days to death set to population norm	£76,462	2.03	2.75	£18,987	0.81	1.18	£57,475	1.22	1.57	£47,111	+£760
R5) Nafees utility values	£76,462	1.73	2.75	£18,987	0.70	1.18	£57,475	1.03	1.57	£55,801	+£9,450
B. ERG preferred scenario (R1, R2 and R4)	**£133,546**	**2.03**	**2.75**	**£20,106**	**0.94**	**1.34**	**£113,440**	**1.09**	**1.41**	**£104,073**	**+£57,722**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; OS=overall survival

Table 4 ERG adjustments to company base case: pembrolizumab versus platinum+pemetrexed (discounted, with PAS)

Scenario/ERG amendment	Pembrolizumab			Platinum+ pemetrexed			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£76,462***	***2.06***	***2.75***	***£24,003***	***0.96***	***1.36***	***£52,459***	***1.10***	***1.39***	***£47,690***	
R1) Removal of 35 cycle limit for patients treated with pembrolizumab	£133,546	2.06	2.75	£24,003	0.96	1.36	£109,543	1.10	1.39	£99,585	+£51,895
R2) 5% 5-year OS survival for patients treated with SoC	£76,462	2.06	2.75	£24,540	1.03	1.44	£51,922	1.03	1.31	£50,410	+£2,720
R3) 13% 5-year OS survival for patients treated with SoC	£76,462	2.06	2.75	£27,908	1.43	1.94	£48,554	0.63	0.81	£77,070	+£29,380
R4) Utility value for >360 days to death set to population norm	£76,462	2.03	2.75	£24,003	0.95	1.36	£52,459	1.08	1.39	£48,573	+£883
R5) Nafees utility values	£76,462	1.73	2.75	£24,003	0.82	1.36	£52,459	0.91	1.39	£57,647	+£9,957
B. ERG preferred scenario (R1, R2 and R4)	**£133,546**	**2.03**	**2.75**	**£24,540**	**1.02**	**1.44**	**£109,006**	**1.01**	**1.31**	**£107,927**	**+59,967**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; OS=overall survival

Appendix 3 ERG Revisions to the company's model

ERG Section 6 results table revision	Associated detail	Implementation instructions
R1. Removal of 35 cycle limit for patients treated with pembrolizumab		In Sheet 'Model Settings' Set value in cell I99 = 400
R2. 5% 5-year OS survival for patients treated with SoC		In Sheet 'SoC OS' Set value in cell BE62 = 4.485 **For individual chemo regimens** In Sheet 'NMA OS' Set value in cell AJ32 = 0.179 Set value in cell AJ36 = 0.134 Set value in cell AJ38= 0.228 Set value in cell AJ40= 0.236

ERG Section 6 results table revision	Associated detail	Implementation instructions
R3. 13% 5-year OS survival for patients treated with SoC		In Sheet 'SoC OS' Set value in cell BE62 = 4.925 **For individual chemo regimens** In Sheet 'NMA OS' Set value in cell AJ32 = 0.612 Set value in cell AJ36 = 0.566 Set value in cell AJ38= 0.658 Set value in cell AJ40= 0.667
R4. 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
R5. Nafees utility values		In Sheet 'utility inputs' Set value in cell D15 = 0.673 Set value in cell D16 = 0.673 Set value in cell D17 = 0.473 Set value in cell D18 = 0.473 Set value in cell E15 = 0.673 Set value in cell E16 = 0.673 Set value in cell E17 = 0.473 Set value in cell E18 = 0.473

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 [ID990]

You are asked to check the ERG report from Liverpool Reviews and Implementation Group (LRiG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm**, on **Friday 13 January 2017** 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 PD-L1 test

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8, Section 1.2 (sub-heading "Intervention"): ERG report states: "At present, there is no established or validated test for PD-L1 expression, and testing for PD-L1 expression is not routinely carried out in UK NHS treatment centres."	This sentence should be removed from each identified section.	Currently, there is a test that has been accepted for use by NHS England, which at present is available in 7 centres. NHSE has agreed that this test will be funded by them from 01 April 2017. This test is the agreed test for use to identify patients who are suitable for treatment with pembrolizumab for 2L NSCLC, recently recommended by NICE. *Background information below:* *The PD-L1 IHC 22C3 pharmDx is a CE-IVD marked companion diagnostic test indicated to aid the identification of NSCLC patients for pembrolizumab.* *PD-L1 IHC 22C3 pharmDx provides reproducible results, without the extensive burden of validation that lab-developed tests require. PD-L1 IHC 22C3 pharmDx includes the only clinically validated scoring guidelines relevant for KEYTRUDA* [1, 2] *There are 7 reference centres in the UK routinely testing for PD-L1 expression to define patient eligibility for pembrolizumab at treatment for NSCLC under the Early Access to Medicines Scheme (EAMS). PD-L1 testing has been operational at the 7 reference centres from April 2016. To date over 3800 PD-L1 tests have been conducted across the 7*	Thank you for the updated information re testing for PD-L1 expression in the NHS. The text in the ERG report was factually accurate at the time of submission (3/1/2017). No amendment to the ERG report is required.
Page 17,Section 1.9.2 (sub-heading "Weaknesses and areas of uncertainty"); Page 28, Section 3.3 (sub-heading "Testing for PD-L1 expression"); Page 117, Section 8 (sub-heading "Clinical effectiveness evidence") ERG report states: "Clinical advice to the ERG is that, at present, there is no established or validated test for PD-L1 expression and testing for PD-L1 expression is not			Thank you for the updated information re testing for PD-L1 expression in the NHS. The text in the ERG report was factually accurate at the time of submission (3/1/2017). No amendment to the ERG report is required.

routinely available in NHS treatment centres.”		*reference centres.* *In addition to this, pembrolizumab received a positive FAD for previously treated NSCLC on 2nd December 2016, with final NICE guidance published on 11 January 2017 (TA428). The licensed indication defines patient eligibility for treatment by ≥1% level of PD-L1 expression. As such PD-L1 testing has been introduced as routine clinical practice England.* *MSD have supported the funding of PD-L1 testing through the network of 7 reference laboratories and will continue to do so 01 April 2017 – at which point NHSE have confirmed that PD-L1 testing reflex testing will be funded as an exclusion to tariff as per the Monitor Guidelines.* *References:* *1: PD-L1 IHC 22C3 pharmDx - Package Insert* *2: Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-1550.*	
Page 111, Section 5.4.4 (sub-heading ‘Minor issues’/ ‘PD-L1 testing’); ERG report states: “Routine testing for the PD-L1 gene does not currently occur in the NHS”			Thank you for the updated information re testing for PD-L1expression in the NHS. The text in the ERG report was factually accurate at the time of submission (3/1/2017). No amendment to the ERG report is required.

Issue 2 Appropriateness of single-agent chemotherapy as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	
Page 9, Section 1.2 (sub-heading "Comparator"): ERG report states: "The company has not discussed the clinical effectiveness of pembrolizumab compared with single agent chemotherapy".	Please revise text as follows: "The company has not discussed the clinical effectiveness of pembrolizumab compared with single agent chemotherapy, **as there is no available evidence concerning pembrolizumab in patients who are only suitable for single agent chemotherapy (i.e. those patients who are unable to tolerate a platinum combination)."**	Although the company submission did not include the rationale for not considering single agent chemotherapy, the current text in the ERG report does not reflect the fact that a rationale was provide when responding to clarification questions. The following had been included in MSD's response to the clarification questions: "NICE clinical guideline 121 recommends single-agent chemotherapies for people who are unable to tolerate a platinum combination. In KEYNOTE-024, eligible patients had to be able to tolerate platinum combination chemotherapy. Consequently there is no evidence concerning pembrolizumab in patients who are only suitable for single agent chemotherapy. Due to the lack of available evidence for this subgroup of patients, single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine; for people for whom platinum combination therapy is not appropriate) was not included as a relevant comparator in this submission. This position was additionally supported by the fact that based on recent market shares observed in the UK, less than 3% of patients in the UK are unsuitable to receive platinum containing	This is an error on our part. The ERG report has been amended accordingly: <u>The company reports that there is no evidence available for the use of pembrolizumab in patients for whom platinum combination therapy is not appropriate</u>.
Page 30, section 3.4 (sub-heading "Comparators") ERG report states: "No evidence is presented in the CS (either direct or indirect) to allow a comparison of the clinical effectiveness of pembrolizumab with any of the single agent chemotherapies specified in the final scope issued by NICE. The rationale for this omission is not provided in the CS."	Please revise text as follows: "No evidence is presented in the CS (either direct or indirect) to allow a comparison of the clinical effectiveness of pembrolizumab with any of the single agent chemotherapies specified in the final scope issued by NICE. The rationale for this omission is not provided in the CS; **however in response to clarification questions, the company justified that NICE clinical guideline 121 recommends single-agent chemotherapies for people who are unable to tolerate a platinum combination. In KEYNOTE-024, eligible patients had to be able to tolerate platinum combination chemotherapy. Consequently there is no**		This is an error on our part. The ERG report has been amended accordingly: <u>The company explains (via the clarification process) that there is no evidence for the use of pembrolizumab in people who are intolerant of treatment with platinum doublet chemotherapy as all patients recruited to the KEYNOTE-024 trial were required to be treated with platinum doublet chemotherapy.</u>

	evidence concerning pembrolizumab in patients who are only suitable for single agent chemotherapy.."	chemotherapy as first-line therapy."	

Issue 3 Proportional hazards assumption and switching adjustment

Description of problem	Description of proposed amendment	Justification for amendment	
Page 12, section 1.4 (sub-heading "Summary of the ERG's critique of clinical effectiveness evidence submitted – Direct evidence") ERG report states: "… however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. As the (initial) HR result is uncertain, all adjustments to it should be viewed with caution."	Please remove the following: "As the (initial) HR result is uncertain, all adjustments to it should be viewed with caution."	To reflect the fact that the validity of the switching adjustments does not depend on the proportional hazards assumption holding.	Thank you for the clarification. The text has been removed as suggested.

Page 47, section 4.4.3 (sub-heading "Suitability of the 2-stage method"); Page 77, section 4.11 (sub-heading "Direct evidence – key issues and uncertainties"; Page 117, section 8 (sub-heading "Clinical effectiveness evidence" ERG report states: "…however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. As the (initial) HR result is uncertain, all adjustments to it should be viewed with a similar level of caution"	Please remove the following: "As the (initial) HR result is uncertain, all adjustments to it should be viewed with a similar level of caution."		

Issue 4 Clinical experience with pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	
Page 13, section 1.4 (sub-heading "Summary of the ERG's critique of clinical effectiveness evidence submitted – Direct evidence") ERG report states: "The ERG notes that in the event that pembrolizumab is recommended for use in the NHS,	This sentence should be removed.	Seven hospitals in England actively recruited patients into the KEYNOTE-024 study for first-line treatment of NSCLC. Within our Early Access to Medicines Scheme (EAMS), 201 first-line patients have accessed	This is a matter of opinion rather than factual inaccuracy. The ERG's statement is based on clinical advice and the report text has been updated to make this clear: Clinical advice to the ERG is that the difference between

very few clinicians are likely to be experienced in the use of pembrolizumab for treating NSCLC.”		pembrolizumab treatment thus far across 42 hospitals in England (seven of these hospitals have never treated patients with immunotherapy agents before and the medical team from MSD ensured that all hospitals were trained accordingly). In total, approximately 90 UK centres are trained with our EAMS scheme, and 153 previously-treated patients have also been treated as part of EAMS. We therefore dispute the ERG comment that “*very few clinicians are likely to be experienced in the use of pembrolizumab”*.	investigator-assessed and BICR-assessed PFS may be the result of the inexperience of the trial investigators with the use of pembrolizumab in treating NSCLC and, that in the event that pembrolizumab is recommended for use in the NHS, very few clinicians are likely to be experienced in the use of pembrolizumab for treating NSCLC.

Issue 5 Incorporation of pembrolizumab data into the NMA

Description of problem	Description of proposed amendment	Justification for amendment	
Page 13, section 1.4 (sub-heading “Summary of the ERG’s critique of clinical effectiveness evidence submitted – Indirect evidence”) ERG report states:	Please remove this sentence.	Patients in the pembrolizumab arm have not been double counted when the KEYNOTE-024 trial was split for the purpose of the NMA. When developing the NMA, the estimates used for each	Thank you for the clarification. The ERG report has been amended. All text regarding double counting has been removed.

"Third, there is the possibility that the company may have double-counted patients in the pembrolizumab arm of the KEYNOTE-024 trial in the NMAs, which could lead to over inflation of the results and produce biased estimates of OS."		pembrolizumab arm (KEYNOTE-024a and KEYNOTE-024b) were consistent with those from the ITT populations described in the subgroup analyses presented in the company submission. Please refer to the following for verification: • Table 31 (Analysis of OS adjusting for treatment switch: subgroups of patients defined by treatment regimen [containing pemetrexed, without pemetrexed]) within the company submission • Table 22 (Constant hazard ratios for overall survival; all histologies) within Appendix 18 (Network Meta-Analysis: Results and Discussion) The number of pembrolizumab patients within each subgroup represent patients who had been pre-assigned by the investigator (prior to randomisation) to receive either platinum+pemetrexed or other platinum doublets, in the event that the patient had been randomised to the SOC arm, but were instead randomised to pembrolizumab.	
Page 75, section 4.10.3 (sub-heading "ERG interpretation of network meta-analysis findings") ERG report states: "First, it is important to note that it is unclear whether the company double counts the patients in the pembrolizumab arm when they split the KEYNOTE-024 trial. If the company has double counted then this could give the NMA additional power it does not have and hence produce biased results as this makes the PFS and OS results look more consistent than they would be if they were independent trials and so the links out to the rest of the network are artificially better. The ERG considers this to be a cause for concern and advises that the results from the NMA should be	Please remove this paragraph		

interpreted with caution.”			
Page 79, section 4.11 (sub-heading “Indirect evidence – key issues and uncertainties”) ERG report states: “The company split the patients from the KEYNOTE-024 trial into two groups: KEYNOTE-024a: pembrolizumab versus non-pemetrexed-containing SOC, mixed histology; and KEYNOTE-024b: pembrolizumab versus pemetrexed-containing SOC, all non-squamous. The ERG is uncertain whether the company has double counted the patients in the pembrolizumab arm when splitting the patient population in the KEYNOTE-024 trial. The ERG is concerned that if the company has double counted patients, then this could give the NMA additional power that it does not have and hence produce biased results.”	Please remove the following two sentences from this paragraph: “The ERG is uncertain whether the company has double counted the patients in the pembrolizumab arm when splitting the patient population in the KEYNOTE-024 trial. The ERG is concerned that if the company has double counted patients, then this could give the NMA additional power that it does not have and hence produce biased results”		

Page 118, section 8 (sub-heading "Clinical effectiveness evidence") ERG report states: "• In the absence of any direct evidence for the clinical effectiveness of treatment with pembrolizumab versus individual platinum doublet chemotherapy regimens specified in the final scope issued by NICE, the company conducted a series of NMAs. However, due to concern that patients in the KEYNOTE-024 trial may have been double counted, similarity between adjusted and unadjusted NMA OS results, mix of patients with and without tumours that express PD-L1 and high levels of heterogeneity between included studies, the ERG considers that results from the company's NMAs should be interpreted with caution."	Please remove the following from this paragraph: "concern that patients in the KEYNOTE-024 trial may have been double counted,"		

Issue 6 Current licensed indication

Description of problem	Description of proposed amendment	Justification for amendment	
Page 27, section 3.2 (sub-heading "Population") ERG report states: "Pembrolizumab is currently licensed in Europe for the treatment of advanced (unresectable or metastatic) melanoma[19] and for the treatment of locally advanced or metastatic NSCLC[19] in patients whose tumours express PD-L1 (TPS ≥1%) and who have received at least one prior chemotherapy regimen. For the latter indication, patients with EGFR or ALK positive tumour mutations should have received prior therapy"	The text should be revised as follows: ".....For the latter indication, patients with EGFR or ALK positive tumour mutations should **also** have received **approved** therapy **for these mutations prior to receiving pembrolizumab"**	The revised text is in line with current licenced indication wording, which was the licensed wording in place at the time the ERG were developing their report. Please note that we are anticipating additional minor changes to the indication wording for 2L NSCLC, based on CHMP Opinion of 15th December 2016, as per the below: "…For the latter indication, patients with EGFR or ALK positive tumour mutations should **also** have received **targeted approved** therapy **before receiving pembrolizumab**	This is a factual error. The ERG report has been amended accordingly: <u>For the latter indication, patients with EGFR or ALK positive tumour mutations should have received approved therapy for these mutations prior to receiving pembrolizumab.</u>

Issue 7 Pembrolizumab as a treatment for PD-L1 positive NSCLC after platinum chemotherapy (ID840)

Description of problem	Description of proposed amendment	Justification for amendment	
Page 27, section 3.2 (sub-heading "Population")	-	Please note that this ERG comment has been superceded by events given that TA428 was published on	Thank you for the update. No amendment to the ERG

ERG report states: "The ERG is aware that NICE is currently appraising pembrolizumab as a treatment for PD-L1 positive NSCLC after platinum chemotherapy (ID840[20]). NICE expects to publish final guidance in January 2017"		11 January 2017	report is necessary.

Issue 8 Population included in NMA

Description of problem	Description of proposed amendment	Justification for amendment	
Page 30, section 3.4 (sub-heading "Comparators") ERG report states: "In the absence of any direct evidence for the clinical effectiveness of pembrolizumab versus the individual platinum doublet chemotherapy regimens specified in the final scope issued by NICE, the company has conducted NMAs. The company has, therefore, in the main	Please substitute with: "In the absence of any direct evidence for the clinical effectiveness of pembrolizumab versus the individual platinum doublet chemotherapy regimens specified in the final scope issued by NICE, the company has conducted NMAs. **The evidence available for inclusion in the NMA only permitted a comparison of** the outcomes of treatment from a population of patients whose tumours strongly express PD-L1 with a population of patients whose PD-L1 status is unknown. The ERG is uncertain whether the outcomes of unselected patients with NSCLC can reasonably be compared with the outcomes	The current text inaccurately suggests that MSD chose to compare the outcomes of treatment from a population of patients whose tumours strongly express PD-L1 with a population of patients whose PD-L1 status is unknown, rather than comparing outcomes in matching population, when the latter was in fact not a feasible possibility given the available data. The NMA was conducted in order to attempt to address the decision problem, by providing comparative efficacy estimates versus each chemotherapy regimen rather than	This is not a factual inaccuracy; however, the ERG agrees that the statement can be qualified in line with the company's suggestion. <u>In the absence of any direct evidence for the clinical effectiveness of pembrolizumab versus the individual platinum doublet chemotherapy regimens specified in the final scope issued by NICE, the company has conducted NMAs. The evidence available for inclusion in the NMA only permitted a</u>

analysis, chosen to compare the outcomes of treatment from a population of patients whose tumours strongly express PD-L1 with a population of patients whose PD-L1 status is unknown. The ERG is uncertain whether the outcomes of unselected patients with NSCLC can reasonably be compared with the outcomes of patients whose tumours strongly express PD-L1."	of patients whose tumours strongly express PD-L1."	a bundled SOC arm as seen in KEYNOTE-024. The available evidence meant the only way in which an NMA could be conducted was if data from a PD-L1 strong population (KEYNOTE-024) was compared with data from patients with unknown PD-L1 status (other trials included in NMA). If we had restricted the NMA to only those patients who strongly express PD-L1, a network would not have been feasible.	<u>comparison of the outcomes of treatment from a population of patients whose tumours strongly express PD-L1 with a population of patients whose PD-L1 status is unknown. The ERG is uncertain whether the outcomes of unselected patients with NSCLC can reasonably be compared with the outcomes of patients whose tumours strongly express PD-L1.</u>

Issue 9 Percentage of patients switching from SOC to pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	
Page 30, section 3.5 (sub-heading "Outcomes") ERG report states: "An additional problem when interpreting OS data from the KEYNOTE-024 trial is that the protocol[22] allowed patients in the SOC arm to switch to treatment	Sentence to be corrected as follows: "An additional problem when interpreting OS data from the KEYNOTE-024 trial is that the protocol[22] allowed patients in the SOC arm to switch to treatment with pembrolizumab after their disease had progressed; at the time of IA2, **43.7%** of patients switched from SOC to pembrolizumab.."	Correction of a typographical error: The ERG has reported an incorrect percentage for the proportion of patients switching from SOC to pembrolizumab.	Thank you for highlighting this typographical error. The ERG report has been amended accordingly.

with pembrolizumab after their disease had progressed; at the time of IA2, 47.3% of patients switched from SOC to pembrolizumab."			

Issue 10 Reference to unpublished study

Description of problem	Description of proposed amendment	Justification for amendment	
Page 34, section 4.2.1 (sub-heading "Identified studies presented in the company submission") ERG report states: "Details of the F1 cohort study are described in the CS, in the trial CSR[26] and in a manuscript currently under review by an oncology journal.[26]." Page 121 – list of references: Reference #26	Ref 26 (unpublished manuscript) – please can the details of this manuscript be highlighted and underlined as confidential in the list of references, as we had requested in the CS that these details remain confidential prior to publication of the study. See comment under justification column. Additionally, please note that Ref 26 assigned against the CSR in this section appears to be the incorrect reference. We believe this should state Ref 25, based on the details provided in the list of references.	Ref 26 (unpublished manuscript) – please can the details of this manuscript be highlighted and underlined as confidential as we had requested in the CS that these details remain confidential prior to publication of the study	We apologise for omitting to mark the reference to the manuscript as confidential and for the incorrect assignment of Ref 26. The ERG report has been amended accordingly.

Issue 11 OS subgroup analysis results

Description of problem	Description of proposed amendment	Justification for amendment	
Page 54 section 4.6.4 (sub-heading “Overall survival subgroup analysis”) ERG report states: “Results from subgroup analyses for OS [redacted]	Paragraph to be completed as follows: Results from subgroup analyses for OS [redacted]	Sentence stops abruptly, which we believe is in error.	Thank you for identifying this a copying error. The ERG report has been amended accordingly.

[redacted]			

Issue 12 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	
Page 59 section 4.8 (sub-heading "Adverse events") ERG report states: "In the CS (CS, p140 to p147), AEs from the KEYNOTE-024 trial are reported as: AEs with an incidence rate of ≥10%, drug-related AEs, drug-related grade 3 to grade 5 AEs, drug-related grade 3 to grade 5 AEs and drug-related SAEs. In addition, the company presents data related to adverse events of special interest (AEOSI) that were reported during the KEYNOTE-024 trial (CS, p148 to p150)."	Please substitute with: "In the CS (CS, p140 to p147), AEs from the KEYNOTE-024 trial are reported as: AEs with an incidence rate of ≥10% **in one or more treatment group**, drug-related AEs **with an incidence rate of ≥10% in one or more treatment group**, drug-related grade 3 to grade 5 AEs **with an incidence rate of ≥1% in one or more treatment group**, and drug-related SAEs **with an incidence rate of ≥0% in one or more treatment group**. In addition, the company presents data related to adverse events of special interest (AEOSI) that were reported during the KEYNOTE-024 trial (CS, p148 to p150)."	When reading this parargraph, one of the reviewers within the company had interpreted the quoted ≥10% incidence rate as applying to all categories of AEs mentioned. To avoid reader error, textual changes have been suggested. Please note there is also a duplication of wording in relation to "drug-related grade 3 to grade 5 AEs" in the current text.	This is not an error. However, the ERG recognises that the text suggested by the company helps to avoid misunderstandings and , therefore, has amended the report accordingly

Issue 13 Agreed Patient Access Scheme (PAS)

Description of problem	Description of proposed amendment	Justification for amendment	
Page 8, Section 1.2 (subheading 'Other considerations'), ERG report states: "An agreed Patient Access Scheme (PAS) is in place for pembrolizumab. However, the company reports (CS, p29) that it is currently discussing an updated PAS arrangement with the Department of Health."	-	The updated PAS has been approved.	Thank you for the updated information re the PAS. This is not a factual error. No amendment to the ERG report is required.
Page 89, Section 5.3.9 (subheading 'Other considerations'), ERG report states: "There is an updated PAS currently being discussed."	-		Thank you for the updated information re the PAS. This is not a factual error. No amendment to the ERG report is required.

Issue 14 2-year stopping rule

Description of problem	Description of proposed amendment	Justification for amendment	
Page 15, Section 1.6 'Summary of the ERG's critique of cost	MSD suggests to remove the word 'arbitrary'.	The selection of the 2-year stopping rule was not arbitrary but based on	The ERG considers the word 'arbitrary' appropriate and

effectiveness evidence submitted'. ERG report states: "[…], for patients with untreated PD-L1 positive metastatic NSCLC, [redacted]The ERG, therefore, considers 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."	On the assumption that the ERG agrees with the removal of the word arbitrary, MSD suggests that the next sentence in the paragraph is redundant and should therefore be removed.	the following: 1. 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 (i.e. 2 years). 2. The FDA has recommended pembrolizumab for the treatment of patients with metastatic NSCLC to be administered until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. 3. Reflecting on the points above and the dynamic clinical programme for PD-L1s in general, NHSE suggested a 2-year stopping rule for pembrolizumab in 2L NSCLC. This was subsequently incorporated into the NICE guidance for pembrolizumab for treating PD-L1-positive NSCLC after chemotherapy (TA428).	notes that 1) The FDA decision to approve the use of pembrolizumab is based upon the results of the KEYNOTE-024 trial. 2) The KEYNOTE-024 trial had a stopping rule of 2 years but the clinical justification for this was not made clear in the CS. Although NHSE have suggested a 2 year stopping rule for second-line patients, this does not mean that the same stopping rule would or need be applied to first-line patients. Ultimately, the company has no evidence, at any time point, on the effect that stopping treatment has on patients who are still perceived as receiving clinical benefit. However, the word 'arbitrary' has been removed as it is subjective and does not materially affect the stopping rule arguments presented by the ERG.
Page 17, Section 1.9.2 (sub-heading 'Cost effectiveness	Please see comment above concerning the word 'arbitrary'.		ERG response as for page 15 <u>The company assumes a</u>

evidence '). ERG report states: "The company assumes an arbitrary stopping rule for treatment with pembrolizumab after 35 cycles (2 years). The ERG considers 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"			stopping rule for treatment with pembrolizumab after 35 cycles (2 years). The ERG considers 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
Page 18, Section 1.10 (sub-heading 'Summary of exploratory and sensitivity analyses undertaken by the ERG'). ERG report states: "[…] removing the arbitrary 2 years (35 cycle) limit on the number of cycles of pembrolizumab that can be administered"	Please see comment above concerning the word 'arbitrary'.		ERG response as for page 15 removing the 2 year (35 cycle) limit on the number of cycles of pembrolizumab that can be administered
Page 102, Section 5.4.2 (sub-heading 'Number of cycles of pembrolizumab); ERG report states: "The ERG considers that it is clinically implausible that clinicians	Please see comment above concerning the word 'arbitrary'.		ERG response as for page 15 The ERG considers that it is clinically implausible that clinicians would stop treatment at a time point, not mentioned in the SmPC,[1] if they

would stop treatment at an arbitrary time point, not mentioned in the SmPC,[1] if they considered that patients were still benefiting from treatment."			considered that patients were still benefiting from treatment.
Page 114, Section 6.1 (sub-heading 'Conclusions of the ERG's cost effectiveness review'); ERG report states: "[…] [redacted] The ERG therefore considers it implausible that treatment would be stopped at an arbitrary time point in a clinical setting if a patient were deemed to still be deriving clinical benefit from treatment with pembrolizumab."	Please see comment above concerning the word 'arbitrary'.		ERG response as for page 15 The ERG considers it implausible that treatment would be stopped at 2 years if a patient were deemed to still be deriving clinical benefit from treatment with pembrolizumab.
Page 118, Section 8 (sub-heading 'Cost effectiveness evidence). ERG report states: "[…] [redacted] The ERG therefore considers 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	Please see comment above concerning the word 'arbitrary'.		ERG response as for page 15 The ERG considers it implausible that, in NHS clinical practice, treatment would be stopped at 2 years if a patient were deemed to still be deriving clinical benefit from treatment with pembrolizumab. The ERG made three changes to the company

benefit from treatment with pembrolizumab. […] The ERG made three changes to the company model: […] removing the arbitrary 35 cycle limit on the number of cycles of pembrolizumab that can be administered […].“			model: altering the OS extrapolation for patients receiving SOC such that 5% of patients are alive at 5 years; removing the 35 cycle limit on the number of cycles of pembrolizumab that can be administered;

Issue 15 HRQoL and utilities in cost-effectiveness assessment

Description of problem	Description of proposed amendment	Justification for amendment	
Page 87, Section 5.3.8 (sub-heading ‘Health-related quality of life’); ERG report states: “The company employed utility estimates in the model based on the time-to-death approach rather than utility estimates based on whether patients have progressed disease, since progression related utilities do not show a large difference between pre and post-progression utilities (0.778 and 0.668 respectively).	Please substitute with: “The company employed utility estimates in the model based on the time-to-death approach rather than utility estimates based on whether patients have progressed disease, **since in KEYNOTE-024, data for post-progression was only 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.”**	The ERG has made an assumption that the reason we selected time-to-death utilities was because there was not a large difference between pre- and post-progression utilities. As noted on page 185 of our submission, the rational was as follows: “[…] 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	We apologise for the incorrect interpretation of the company’s rationale. The ERG report has been updated as follows: The company employed utility estimates in the model based on the time-to-death approach.

		death. This leads to an overestimation of the utility in the post-progression state."	
Page 88, Section 5.3.8 (sub-heading 'Health-related quality of life'); ERG report states: "The company considers that, overall, the utilities derived from the KEYNOTE-024 trial are comparable to the study found from the literature search."	Please substitute with: ""The company considers that, overall, the utilities derived from the KEYNOTE-024 trial are **in line with the utilities observed in the published literature**."	To correct for what we believe is a typo in the sentence.	Thank you for this observation. The ERG report has been updated accordingly: The company considers that, overall, the utilities derived from the KEYNOTE-024 trial are in line with the utilities observed in the published literature.
Page 108, Section 5.4.4 (sub-heading 'Utility values used in the model'); ERG report states: "The ERG accepts that the KEYNOTE-024 trial EQ-5D completion rates were reasonably high. However, as data were only collected up to week 24, only a very small number of patients provided information for each of the periods to death that were measured.	Please substitute with: "The ERG accepts that the KEYNOTE-024 trial EQ-5D completion rates were reasonably high. However, only a small number of patients provided information for each of the periods to death that were measured."	To reflect accurately the data collection period for EQ-5D data in KEYNOTE-024. We would like to emphasise that, 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 (see page 184 of the submission). Therefore, EQ-5D data was collected during the full follow-up period, rather than for only for 24 weeks, as long as patients remained on treatment. We apologise for any confusion derived from reporting compliance rates	Thank you for this observation. The ERG report has been updated accordingly: The ERG accepts that the KEYNOTE-024 trial EQ-5D completion rates were reasonably high. However, only a very small number of patients provided information for each of the periods to death that were measured.

		only until week 24.	

Issue 16 Search strategies supplied as part of cost effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	
Page 81, section 5.3 'ERG critique of the company's literature review'; ERG report states: "The company's search strategies supplied for The Cochrane Library and Medline in Process have sporadic numbering. However, it is possible that this is a copy and paste error as the strategies are the same as were supplied for Medline and Embase and therefore would still be adequate for retrieving cost effectiveness studies."	-	We would like to confirm this is a typo that did not impact the running of the searches. We apologise for the reported typo.	Thank you for the confirmation. No change has been made to the ERG report.

Issue 17 NICE Reference Case checklist

Description of problem	Description of proposed amendment	Justification for amendment	
Table 33; Page 82, Section 5.3.1 (sub-heading 'NICE Reference Case checklist'). In the ERG report, the following two attributes: - Source of preference data for valuation of changes in HRQoL - Sensitivity analysis have not been completed.	The empty cells should be completed.	The answers for these two attributes are missing in the table. We believe the lack of completeness could be interpreted as a failure of the manufacture to comply with the NICE reference case.	Thank you for pointing this out. Table 33 has been completed. The missing responses are 'yes' in both cases.

Issue 18 Valuation of costs for pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	
Table 34; page 83, Section 5.3.2 (sub-heading 'Drummond checklist'). For the question: - "Were the cost and consequences valued credibly?"	MSD suggests to remove the word 'arbitrary'. On the assumption that the ERG agrees with the removal of the word arbitrary, MSD suggests the revision of the critical appraisal answer to this question.	The selection of the 2-year stopping rule was not arbitrary, but based on the following: 1. 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	This is not a factual error. However, in line with the ERG response to Issue 14, the word 'arbitrary' has been removed from Table 34 of the ERG report

the critical appraisal answer was "No" and the ERG comment was the following: "Costs of pembrolizumab were arbitrarily limited by stopping treatment in the model at 35 cycles"		treatment duration of 35 cycles (i.e. 2 years). 2. The FDA has recommended pembrolizumab for the treatment of patients with metastatic NSCLC to be administered until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. 3. Reflecting on the points above and the dynamic clinical programme for PD-L1s in general, NHSE suggested a 2-year stopping rule for pembrolizumab in 2L NSCLC. This was subsequently incorporated into the NICE guidance for pembrolizumab for treating PD-L1-positive NSCLC after chemotherapy (TA428).	

Issue 19 Minor text correction related to subgroup analyses implemented in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	
Page 85, Section 5.3.5 (sub-heading 'Interventions and	To update fourth bullet point to reflect: "**non-**squamous only population; pemetrexed only."	To correct a typo.	Thank you for highlighting this typographical error. The ERG report has been amended

comparators'); ERG states: "Using data from the KEYNOTE-024 trial, the company also considered the cost effectiveness of treatment with pembrolizumab for subgroups of patients treated with specific regimens: […] • squamous only population: pemetrexed only."			accordingly.

Issue 20 Overall survival

Description of problem	Description of proposed amendment	Justification for amendment	
Page 105, Section 5.4.3 (sub-heading 'Overall survival'/ 'Standard of care'); ERG report states: "More than half of non-small cell lung cancer (NSCLC) patients present with incurable advanced local or metastatic disease at the time of diagnosis, with **an estimated five-year survival rate around 10%**. (CS p14,	Remove emphasis and insert complete paragraph.	The emphasis is inappropriate because it implies to the reader that the 10% five-year survival rate applies to metastatic disease. We would like to clarify that it applies to the total population diagnosed with lung cancer in England and Wales, as for the CRUK website (which was the original reference). The website states: "A tenth (10%) of people diagnosed	Thank you for the observation. The ERG agrees that the company's suggested text adds clarity and has amended the report accordingly: <u>More than half of non-small cell lung cancer (NSCLC) patients present with incurable advanced local or metastatic disease at the time of</u>

emphasis added)		with lung cancer in England and Wales survive their disease for five years or more (2010-11)." If this sentence is to be presented, it should be as part of the full paragraph presented in the submission (without emphasis), to avoid misinterpretation. The full paragraph in the submission stated the following: "Lung cancer is the leading cause of cancer-related mortality worldwide.[1] In the United Kingdom (UK), each year more than 45,000 people are diagnosed with lung cancer and over 35,000 die from the condition.[2] More than half of non-small cell lung cancer (NSCLC) patients present with incurable advanced local or metastatic disease at the time of diagnosis,[2] with an estimated five-year survival rate around 10%."	diagnosis, with an estimated five-year survival rate around 10%. (CS p14) The ERG considers that the key issue for 5-year survival is the range reported by CRUK and, more importantly, that from the NLCA register.

ID990 STA Pembrolizumab

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

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CONTAINS CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This document contains erratum in respect of the ERG report following the factual accuracy check by Merck, Sharp & Dohme.

Changes made to the original text in the ERG report are highlighted in grey.

Comparators

The comparators listed in the final scope issued by NICE are:

- 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 (for people with squamous NSCLC) pemetrexed maintenance treatment
- pemetrexed in combination with a platinum drug (for people with adenocarcinoma or large cell carcinoma only) with or without pemetrexed maintenance treatment
- single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) for people for whom platinum combination therapy is not appropriate.

The company has provided results from 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). After four to six cycles of chemotherapy, patients with tumours of non-squamous histology who were treated with platinum+paclitaxel or platinum+pemetrexed had the option to receive maintenance treatment with pemetrexed. Patients in the SOC arm were able to cross over and receive treatment with pembrolizumab when their disease progressed.

Clinical results from the KEYNOTE-024 trial are 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 comes from a subgroup analysis. The company has 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. The company reports that there is no evidence available for the use of pembrolizumab in patients for whom platinum combination therapy is not appropriate.

Outcomes

Clinical evidence is presented in the CS for all five outcomes specified in the final scope issued by NICE: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL).

The results described in the CS were generated as part of the KEYNOTE-024 trial second interim analysis (IA2). At this point only 35% of the expected OS events had occurred and median OS had not been reached in either of the trial arms.

Results from the all-comers (all histologies combined) network show that treatment with pembrolizumab statistically significantly improves PFS and OS compared to all other comparators of interest.

The results from these NMAs were **not** used in the company's base case cost effectiveness analyses.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

The ERG considers that the KEYNOTE-024 trial was a small, well-conducted, open-label, RCT. However, when the results of IA2 were made available, the trial Data and Safety Monitoring Committee (DSMC) recommended that the KEYNOYE-024 trial should be stopped early for benefit; at this time, only 35% of the total number of expected OS events had occurred and median OS had not been reached in either of the trial arms. The ERG is aware of published evidence that shows that several trials that have been stopped early for benefit have not delivered the anticipated survival gain estimated at the time stopping. The protocol for the KEYNOTE-024 trial allowed patients receiving SOC to cross over at disease progression to receive pembrolizumab and, at the time of IA2, 43.7% of patients from the SOC arm had crossed over. The ERG considers that the immaturity of the OS data and the high level of patient crossover limit the reliability of the OS data from the KEYNOTE-024 trial. Furthermore, the ERG considers that the results of the patient subgroup analyses from the KEYNOTE-024 trial should be interpreted with caution given the small numbers of patients and the small numbers of events in each subgroup.

The company considered three different methods to adjust the trial OS data for the effect of crossover (2-stage method, rank preserving structural failure time [RPSFT] method and the inverse probability of censoring weighting method [IPCW]). Of the methods considered to adjust for treatment crossover, the ERG agrees with the company that the 2-stage model was the most appropriate. However, the ERG considers that results generated from the 2-stage adjustment method (and the RPSFT and ICPW methods]) are unreliable. All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. This (initial) HR is only reliable if the OS hazards for the two trial datasets are proportional. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. TEXT REMOVED

The company provided PFS results as assessed by BICR. In response to the ERG's request, the company provided the results of an exploratory analysis of PFS based on investigator assessment. The PFS results for patients in the SOC arm were similar, irrespective of method of assessment ([redacted]). However, the PFS results for patients in the pembrolizumab arm were different ([redacted]). The ERG is uncertain of the reasons for, or the implications of, the [redacted] difference between the BICR-assessed PFS and investigator-assessed PFS results for patients treated with pembrolizumab. Clinical advice to the ERG is that the difference between investigator-assessed and BICR-assessed PFS may be the result of the inexperience of the trial investigators with the use of pembrolizumab in treating NSCLC and, that in the event that pembrolizumab is recommended for use in the NHS, very few clinicians are likely to be experienced in the use of pembrolizumab for treating NSCLC.

Indirect evidence

The ERG considers that it was appropriate for the company to conduct an indirect treatment comparison to support the existing direct evidence comparing pembrolizumab with the comparators of interest. In the main body of the CS, the company presents the results of NMAs undertaken using fractional polynomials; these results are not used to inform the company's cost effectiveness base case. The ERG is satisfied that the clinical assumptions made by the company to construct the evidence networks are reasonable.

Although the ERG considers that the methodology used to conduct the main NMA (all-comers) is appropriate, the ERG's view is that the results are unreliable. First, there is extensive heterogeneity between the included trials (e.g., only the KEYNOTE-024 trial includes a population of patients whose tumours strongly express PD-L1 and the KEYNOTE-024 trial includes only patients with stage IV disease whereas there are patients with stage III and IIIb disease in the other included studies). Second, the company's unadjusted and adjusted treatment crossover results are very similar raising concerns over the accuracy of the results. Text removed

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with pembrolizumab versus SOC for untreated patients with advanced NSCLC whose tumours strongly express PD-L1. The model comprises three mutually exclusive health states: pre-progression, post-progression, and dead. All patients

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers that there are 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.

First, any extrapolation of OS data from patients in the pembrolizumab arm of the KEYNOTE-024 will be highly uncertain due to only 35.4% of the total events having occurred.

Second, the company's extrapolation of OS data from patients in the SOC arm of the KEYNOTE-024 trial is overly pessimistic compared to survival results available from registry data and published studies describing patients with stage IV NSCLC treated with chemotherapy. Survival, predicted by the company extrapolation, for patients treated with SOC at 5 years is 1.9%, whereas National Lung Cancer Audit (NLCA) data suggest that 5-year survival for all patients with stage IV NSCLC is 5%. Given that not all patients in the NCLA dataset received chemotherapy (which has been shown to extend life), the ERG considers that using an extrapolation method that predicts 5.0% survival at 5 years will still lead to a conservative estimate of the ICER per QALY gained for the comparison of treatment with pembrolizumab versus SOC.

Third, 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, for patients with untreated PD-L1 positive metastatic NSCLC, [redacted] The ERG, therefore, considers 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.

Fourth, the ERG considers that the utility values incorporated into the company model, which were derived from data collected as part of the KEYNOTE-024 trial, are implausibly high, notably for the period 360 days before death when these values are higher than the UK population norm.

1.7 Summary of company's case for End of Life criteria being met

The company has put forward a case that pembrolizumab meets NICE's End of Life criteria based on the following points:

- available data from the SOC arm of the KEYNOTE-024 trial, in conjunction with NCLA data (11.3 months for patients with stage IIIb/IV, PS 0 to 1 and receiving

- The impact on OS of patient crossover from the SOC arm to treatment with pembrolizumab is unclear even after the company's extensive exploration of alternative methods to assess the effects of treatment crossover
- The company carried out Cox proportional hazards modelling for OS but did not check the proportional hazards assumption for validity as it was not pre-specified. After checking, the ERG identified that the assumption of proportional hazards was invalid and therefore the OS results should be interpreted with caution
- There is no direct evidence of the clinical effectiveness to allow a comparison of pembrolizumab compared with the individual comparators listed in the final scope issued by NICE
- The ERG is uncertain of the reasons for, or the implications of, the [redacted] difference between the BICR-assessed PFS and the investigator-assessed PFS for patients in the pembrolizumab arm of the KEYNOTE-024 trial ([redacted]).
- The ERG considers that the results of the company NMAs are unreliable for the following reasons:
    - there is extensive heterogeneity between included studies (e.g., PD-L1 status, disease stage, race/ethnicity)
    - the unadjusted and adjusted NMA results are very similar
    - text removed
- Information is only provided on the binary assessment of the immunohistochemical marker PD-L1. In addition to validation of the test, the ERG considers that further information is likely to emerge on PD-L1 as a continuous predictive biomarker
- In the draft SmPC for pembrolizumab, it is stipulated that treatment should be initiated only after a validated laboratory test has confirmed the tumour expression of PD-L1. Clinical advice to the ERG is that, at present, there is no established or validated test for PD-L1 expression and testing for PD-L1 expression is not routinely available in NHS treatment centres. The ERG notes that, in the NHS, there is currently no standard means of identifying patients whose tumours strongly express PD-L1
- Clinical advice to the ERG is that AEs arising from treatment with immunotherapy (i.e., pembrolizumab) in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.

Cost effectiveness evidence

- The long-term OS of patients treated with pembrolizumab is highly uncertain. Even though the company chose the most pessimistic extrapolation from those considered in the submission, it may be that this is still an overly optimistic extrapolation – especially if the actual survival curve has multiple phases
- The company's OS projection for patients treated with SOC results is overly pessimistic and results in survival at 5-years being only 1.9%. The ERG considers that published evidence points to survival being at least 5% at 5 years
- The company assumes a stopping rule for treatment with pembrolizumab after 35 cycles (2 years). The ERG considers 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

- Utility values in the model, which were derived from data collected during the KEYNOTE-024 trial, are implausibly high, with the value for patients who are a year away from death being higher than the UK population norm for people of the same age.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

Due to the extreme uncertainty around any projection of OS for patients receiving pembrolizumab, the ERG has not made any revisions to the company's projection. However, the ERG has implemented the following changes to the model:

- removing the 2 year (35 cycle) limit on the number of cycles of pembrolizumab that can be administered
- altering the OS extrapolation for patients receiving SOC such that 5% of patients are alive at 5 years
- limiting the magnitude of the utility values used in the model so that they are no higher than the UK population norm for people of the same age.

The ERG considers that the last two of these amendments are conservative. Published figures suggest that OS at 5 years for patients receiving SOC could be as high as 13%. Utility values for patients with metastatic NSCLC are likely to be lower than those in the general UK population of the same age.

1.11 Cost effectiveness conclusions

Application of the ERG model amendments results in an ICER for the comparison of treatment with pembrolizumab versus SOC of £114,291 per QALY gained. Given that the amendments made by the ERG to the company's OS extrapolation for patients receiving SOC and to the utility values employed in the model are very conservative, the ERG's revised cost effectiveness results should be interpreted as a lower bound estimate of the ICER per QALY gained for this comparison

presented as comparisons of the effectiveness and safety of treatment with pembrolizumab versus SOC.

The company has conducted network meta-analyses (NMAs to allow the effectiveness of treatment with pembrolizumab to be compared with all of the comparator platinum doublet chemotherapies listed in the final scope issued by NICE).

3.2 Population

The population described in the final scope issued by NICE is people with PD-L1 positive NSCLC who have not been treated with chemotherapy in the metastatic setting. The population discussed in the CS is a subset of this population, namely patients with untreated metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutations. The ERG notes that the patient population discussed in the CS matches the patient population in the KEYNOTE-024 trial and is expected to match the patient population indicated in the anticipated marketing authorisation soon to be issued by the EMA.

On December 15th 2016, the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency EMA issued a positive opinion[18] recommending the use of pembrolizumab as a first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 (TPS≥50%) with no EGFR or ALK positive tumour mutations.

The ERG notes that there is no clinical effectiveness evidence presented in the CS for the use of pembrolizumab in patients with untreated metastatic NSCLC with a PD-L1 TPS <50%, or for patients with a PD-L1 TPS ≥50% whose tumours also test positive for EGFR or ALK mutations.

The company has presented the results of patient subgroup analyses. The subgroups included age (≤65 versus >65 years), sex, race (white versus non-white), ECOG status (0 versus 1), geographic region of enrolling site (East Asia versus non-East Asia), histology (squamous versus non-squamous), smoking status (never versus former versus current), brain metastasis status (baseline brain metastasis versus no baseline brain metastasis), investigators choice of standard of care chemotherapy.

Pembrolizumab is currently licensed in Europe for the treatment of advanced (unresectable or metastatic) melanoma[19] and for the treatment of locally advanced or metastatic NSCLC[19] in patients whose tumours express PD-L1 (TPS ≥1%) and who have received at least one prior chemotherapy regimen. For the latter indication, patients with EGFR or ALK positive tumour mutations should have received approved therapy for these mutations prior to receiving pembrolizumab.

[redacted]

3.4 Comparators

The comparators specified in the final scope issued by NICE are:

- 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 (people with adenocarcinoma or large cell carcinoma only) with or without pemetrexed maintenance treatment
- single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) for people for whom platinum combination therapy is not appropriate).

Clinical advice to the ERG is that, in the NHS, patients with NSCLC are rarely treated with platinum+vinorelbine, and, that single agent docetaxel is predominantly used as second-line chemotherapy rather than as a first-line therapy. The ERG notes that pemetrexed is only licensed for use with cisplatin; however, clinical advice to the ERG is that, in the NHS, patients are also treated with carboplatin+pemetrexed, in view of the more favourable toxicity profile of carboplatin.

The direct evidence presented in the CS is derived from the KEYNOTE-024 trial in which treatment with pembrolizumab is compared with a 'standard of care' (SOC) chemotherapy regimen. The SOC regimen included a choice of platinum doublet treatments: gemcitabine, paclitaxel or, for patients with non-squamous histology, pemetrexed. Patients with tumours of non-squamous histology, who were treated with platinum doublet paclitaxel or platinum doublet pemetrexed, but not platinum doublet gemcitabine, also had the option to receive single agent pemetrexed maintenance therapy if their disease had not progressed after four to six cycles of platinum doublet chemotherapy.

There is no direct evidence available from the KEYNOTE-024 trial for the clinical effectiveness of pembrolizumab versus platinum+docetaxel, platinum+gemcitabine, platinum+paclitaxel or platinum+vinorelbine; however there is evidence presented (albeit from a subgroup analysis) for the clinical effectiveness of pembrolizumab versus platinum+pemetrexed. The company has stated (and the ERG agrees) that analysis by the individual treatments available in the KEYNOTE-024 trial (i.e. platinum+gemcitabine and platinum+paclitaxel) would be uninformative as the number of individual treatments allocated to patients is small.

In the absence of any direct evidence for the clinical effectiveness of pembrolizumab versus the individual platinum doublet chemotherapy regimens specified in the final scope issued by NICE, the company has conducted NMAs. Text removed

The evidence available for inclusion in the NMA only permitted a comparison of the outcomes of treatment from a population of patients whose tumours strongly express PD-L1 with a population of patients whose PD-L1 status is unknown. The ERG is uncertain whether the outcomes of unselected patients with NSCLC can reasonably be compared with the outcomes of patients whose tumours strongly express PD-L1.

No evidence is presented in the CS (either direct or indirect) to allow a comparison of the clinical effectiveness of pembrolizumab with any of the single agent chemotherapies specified in the final scope issued by NICE. The company explains (via the clarification process) that there is no evidence for the use of pembrolizumab in people who are intolerant of treatment with platinum doublet chemotherapy, as all patients recruited to the KEYNOTE-024 trial were required to be treated with platinum doublet chemotherapy. Clinical advice to the ERG is that approximately 15% of NHS patients with NCSLC are treated with single agent chemotherapy in the first-line setting.

3.5 Outcomes

Clinical evidence from the KEYNOTE-024 trial is reported for all five outcomes specified in the final scope issued by NICE: progression-free survival (PFS), overall survival (OS), response rate (reported as objective response rate [ORR], best overall response rate, disease control rate), adverse events (AEs) of treatment and health-related quality of life (HRQoL). The ERG notes that, at IA2, median OS had not been reached in either arm of the trial. An additional problem when interpreting OS data from the KEYNOTE-024 trial is that the protocol[22] allowed patients in the SOC arm to switch to treatment with pembrolizumab after their disease had progressed; at the time of IA2, 43.7% of patients switched from SOC to pembrolizumab. The immaturity of the data, combined with patient crossover, means that the true impact of treatment with pembrolizumab on OS is difficult to ascertain.

The outcomes of PFS and OS are reported from the company's NMAs that compare pembrolizumab with each of the platinum doublet chemotherapies listed in the final scope issued by NICE.

3.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 20-year time period (equivalent to a lifetime horizon) and

costs were considered from an NHS perspective. The company's economic model includes the costs associated with testing strategies to identify patients with PD-L1 expressing tumours.

3.7 Subgroups

Two subgroup analyses are identified in the final scope issued by NICE: i) analysis by tumour histology (squamous or non-squamous) and ii) level of PD-L1 expression (strong positive or weak positive). The CS includes an analysis of the outcomes of patients from the KEYNOTE-024 trial according to histology; the ERG notes that 18% of patients in the KEYNOTE-024 trial were of squamous histology. The company has not conducted a subgroup analysis based on level of PD-L1 expression as only data from patients with strongly expressing tumours are available from the KEYNOTE-024 trial.

3.8 Other relevant factors

The company did not identify any equity or equality issues. The ERG is aware that an agreed Patient Access Scheme (PAS) is in place for pembrolizumab; however, the company reports (CS, p29) that it is currently discussing an updated PAS arrangement with the Department of Health. In the CS, the company has used the currently agreed PAS price for pembrolizumab. The list prices of docetaxel, gemcitabine, paclitaxel, vinorelbine and pemetrexed are used in all of the cost effectiveness analyses presented in the CS.

cohort study had tumours with a TPS ≥50%. The ERG agrees with the company that pooling data from the KEYNOTE-024 trial and the F1 cohort study is inappropriate.

To compare the clinical effectiveness of treatment with pembrolizumab with the platinum doublet chemotherapy comparators listed in the final scope issued by NICE, the company has conducted NMAs.

4.2 Critique, analysis and interpretation of trials of the technology

4.2.1 Identified studies presented in the company submission

Key trial

The company presents evidence from the KEYNOTE-024 trial for the clinical effectiveness of treatment with pembrolizumab. The patients recruited to the RCT had untreated stage IV NSCLC and their tumours strongly expressed PD-L1 (TPS ≥50%) with no sensitising EGFR mutations or ALK translocations. Patients were randomised to receive either pembrolizumab 200mg Q3W or SOC chemotherapy. Details relevant to the KEYNOTE-024 trial are reported in the CS, in the trial CSR and in a published paper.[13]

Other studies

In the dose-ranging F1 cohort study, 101 patients with untreated stage IV NSCLC whose tumours expressed PD-L1 with no EGFR mutations or ALK translocations were randomised to one of three different pembrolizumab treatment regimens, 2mg/kg Q3W, 10mg/kg Q3W or 10mg/kg Q2W. Details of the F1 cohort study are described in the CS, in the trial CSR[25] and in a manuscript currently under review by an oncology journal.[26] The company considers that the data from the F1 cohort study provide supportive evidence for the survival benefit of pembrolizumab over a longer period of follow-up (22 months) than is currently available from the KEYNOTE-024 trial (11 months).

The ERG considers that the results of the F1 cohort study are of minimal relevance to the company's decision problem given that only 27 patients in the study had tumours with a TPS of ≥50% and that the doses of pembrolizumab administered in the F1 cohort are different to the dose of pembrolizumab administered in the KEYNOTE-024 trial. The ERG notes that the licensed dose of pembrolizumab is likely to match the 200mg dose used in the KEYNOTE-024 trial.

A summary of the details of the F1 cohort study is presented in Appendix 1 of this ERG report.

without re-censoring for comparison, 0.44 (95% CI 0.20 to 1.07) and 0.50 (95% CI 0.34 to 0.76), respectively. The ERG is concerned that there is a difference between the results obtained with and without re-censoring. The ERG considers that this difference could be due to the PH assumption not being valid, which is known to affect the results obtained from re-censoring. However, it is unclear why the results for re-censoring highlight a statistically significant p-value (p=0.0094) when the 95% CI includes 1. The ERG considers that the company may have presented incorrect results.

In conclusion, the ERG considers that despite the 2-stage adjustment method being the most appropriate method to use, the results generated from the 2-stage adjustment method (and the two other methods considered by the company [RPSFT and ICPW methods]) are unreliable. All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. This (initial) HR is only reliable if the OS hazards for the two trial data-sets are proportional. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. TEXT REMOVED

ERG assessment of statistical approach

A summary of the ERG's assessment of the statistical approach used to analyse data from the KEYNOTE-024 trial is presented in **Error! Reference source not found.**.

During the clarification process, the ERG asked the company to provide further details on formal testing undertaken to assess the PH assumption. The company confirmed that no formal testing of PH for OS data had been undertaken.

For OS, the ERG assessed the PH assumption by plotting the cumulative hazard associated with pembrolizumab versus the cumulative hazard associated with SOC. The plot suggested that the PH assumption is invalid and therefore, the ERG considers that the OS results should be interpreted with caution.

Overall survival subgroup analysis

The results of the company's subgroup analyses for the ITT population of the KEYNOTE-024 trial are presented in Figure 16 of the CS. A list of these subgroup analyses is provided in **Error! Reference source not found.** of this ERG report. [redacted]

The results, presented as a forest plot, demonstrate that, when compared with SOC, treatment with pembrolizumab [redacted]

Results from subgroup analyses for OS [redacted]* (*text added following company factual accuracy check)

During the clarification process, the ERG requested the corresponding p-values for the tests for interaction for the subgroup analyses (Question A7). No statistically significant p-values for interaction were observed across any of the subgroups.

occurred from the dose of study drug to 30 days after the last dose of study drug. Data relating to serious adverse events (SAEs) were collected for up to 90 days post-treatment (or 30 days in the case of patients who had a follow-on treatment for their disease).

Mean duration of treatment (CS, Table 39) with pembrolizumab was 205 days (range 1 to 568) and 120 days (range 1 to 511) for SOC. This means that AE data were collected for a longer period of time for patients treated with pembrolizumab compared with patients treated with SOC. The company observes (CS, Table 40) that 87 patients in the pembrolizumab arm and 29 patients in the SOC arm received treatment for ≥6 months.

In the CS (CS, p140 to p147), AEs from the KEYNOTE-024 trial are reported as: AEs with an incidence rate of ≥10% in one or more treatment group, drug-related AEs with an incidence rate of ≥10% in one or more treatment group, drug-related grade 3 to grade 5 AEs with an incidence rate of ≥1% in one or more treatment group, and drug-related SAEs with an incidence rate of ≥0% in one or more treatment group. In addition, the company presents data related to adverse events of special interest (AEOSI) that were reported during the KEYNOTE-024 trial (CS, p148 to p150).

4.8.1 Summary of adverse events

A summary of the AEs and SAEs recorded during the KEYNOTE-024 trial is presented in **Error! Reference source not found.**. The ERG agrees with the company that the numbers of patients who experienced any AE or any SAE were similar in both arms of the trial; however, the ERG notes that there are differences in the type and predictability of the AEs recorded.

Compared with the pembrolizumab arm, drug-related AEs (including grade 3 to 5 AEs) were more frequent in the SOC arm as were treatment discontinuations due to AEs and drug-related AEs. A higher percentage of patients in the pembrolizumab arm discontinued treatment due to SAEs (8.4% versus 7.3%) and drug-related SAEs (6.5% versus 4.7%) than in the SOC arm. There were nine (5.8%) deaths in the pembrolizumab arm, one of these was considered to be

In view of all the reasons mentioned, the ERG does not consider that any reliable estimates of comparative survival are possible when treatment with pembrolizumab is compared with the comparators identified in the final scope issued by NICE.

Methodology

To generate the results of the NMAs in the context of non-proportional hazards, the company has applied a complex analytical method (fractional polynomial modelling of hazard ratios) aimed at better reflecting variations in HRs over time in the component trials of the evidence network. The true test of the appropriateness of applying such a technique to the evidence available for this appraisal is to compare the estimated HRs with those available directly from the trials. However, the ERG is unable to compare the HR of pembrolizumab versus SOC from the KEYNOTE-024 trial with the HR obtained from the main NMA based on the fractional polynomials method as the ERG considers that the OS estimates from the NMA are not accurate due to the similarity in results when comparing the adjusted and unadjusted for treatment switching results. The ERG considers that the comparison of HRs will not generate any accurate results that will be able to demonstrate whether the results from the NMA are accurate.

ERG interpretation of network meta-analysis findings

Although, the ERG considers that the methodology used to conduct the NMAs is reasonable, the ERG has identified two key concerns that should be taken into account when assessing the reliability of results generated by the NMAs.

First, the adjusted and unadjusted for treatment switching OS results from the KEYNOTE-024 trial are similar; this raises concerns over the validity of the results. Second, there is heterogeneity present in the baseline and trial characteristics; this raises concerns over the similarity of the trials combined within the NMAs.

To conclude, the ERG has key concerns regarding the NMAs conducted by the company, and has reason to consider that the results of the NMAs cannot provide valid treatment effect estimates for pembrolizumab versus the relevant comparators. However, the ERG notes that the results of the NMAs are only used to inform the cost effectiveness of

NSCLC with a PD-L1 TPS <50%, or for patients with a PD-L1 TPS ≥50% whose tumours also test positive for EGFR or ALK mutations.

On December 15th 2016, the CHMP of the EMA issued a positive opinion[18] recommending the use of pembrolizumab as a first-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutations.

The KEYNOTE-024 trial compares treatment with pembrolizumab with SOC chemotherapies in 305 patients. The trial was stopped early for benefit at IA2. At this point, median OS had not been reached. The trial protocol allowed patients in the SOC arm to cross over to receive treatment with pembrolizumab when their disease had progressed and, at IA2, 43.7% of patients from the SOC arm had received treatment with pembrolizumab. The immaturity of the OS data and the level of patient crossover mean that the available data are difficult to interpret. The ERG is aware that there is evidence that trials that have been stopped early for benefit have not delivered the anticipated survival gain estimated at the time of stopping.[15,17,28]

The company has considered three different methods to adjust the trial OS data for the effect of crossover. Of the methods considered for adjusting for treatment crossover, the ERG agrees with the company that the 2-stage model was the most appropriate.

However, the ERG considers that, in spite of the 2-stage adjustment method being the most appropriate method to use, the results generated from the 2-stage adjustment method (and the two other methods considered by the company [RPSFT and ICPW methods]) are unreliable. All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. This (initial) HR is only reliable if the OS hazards for the two trial datasets are proportional. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. Text removed

The ERG notes that the unadjusted OS results (HR=0.60) and those generated using the company's preferred method (the 2-stage method, HR=0.50) are very similar.

For patients treated with pembrolizumab, there appears to be a difference of [redacted] in median PFS between the investigator-assessed results and the results based on the BICR assessment ([redacted]). The reasons for, or the importance of, this difference between the two PFS estimates are unclear. Median PFS in the SOC arm is similar between the two analyses ([redacted]). The ERG is concerned that

crossover. The ERG is unclear why the overall conclusions and results do not change when the adjusted and unadjusted for treatment crossover results are compared.

Text removed

Therefore, due to these reasons, the ERG does not consider that any reliable estimates of comparative survival are possible when treatment with pembrolizumab is compared with the comparators identified in the final scope issued by NICE.

pertinent for the company to carry out the same search as was used for The Cochrane Library. However, the ERG considers that no relevant papers have been missed and the searches were adequate and well reported.

5.3.1 NICE Reference Case checklist

Table 1 NICE Reference Case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – most of the comparators listed in the scope are included in the economic evaluation
Perspective costs	NHS and PSS	Partial - the model only includes NHS costs. PSS costs have not been considered
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial - patient related direct health effects are considered
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 20 year time horizon
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily taken from the KEYNOTE-024 trial
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	Yes – reported directly by patients in the KEYNOTE-024 trial
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes - benefits and costs have been discounted at an annual rate of 3.5%
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Yes

EQ-5D=EuroQol-5 dimension; HRQoL=health related quality of life; PSS=personal social services; QALY=quality adjusted life year

5.3.2 Drummond checklist

Table 2 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Key costs and outcomes were identified
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	Costs of pembrolizumab were limited by stopping treatment in the model at 35 cycles
Were costs and consequences adjusted for differential timing?	Yes	Discount rate of 3.5% per annum
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost effectiveness ratios (ICERs) were calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	The results are presented and discussed in detail

5.3.3 Model structure

The cost effectiveness model presented by the company is based on a partitioned survival model, which is consistent with many oncology models submitted to NICE. The model comprises three mutually exclusive health states: pre-progression representing progression free survival (PFS), post-progression representing post-progression survival (PPS), and dead. All patients enter the model in the pre-progression health state and remain in that state until disease progression. At the beginning of each time period, patients either remain in the same health state or move to a worse health state. For example, patients in the pre-progression health state can move to the post-progression health state or to the dead health state, whilst patients in the post-progression state can only move to the dead health state. The dead health state is an 'absorbing' state i.e. a state that, once entered, cannot be left. In the base case, the company model generates results for a comparison of the cost effectiveness of treatment with pembrolizumab versus SOC. A schematic of the company model is presented in the CS and reproduced in **Error! Reference source not found.**.

In the base case, the comparator was based on the distribution of SOC chemotherapy options prescribed to patients participating in the KEYNOTE-024 trial (Table 3). In additional analyses, relating to the NMA all histologies population, pembrolizumab was indirectly compared to individual platinum-based chemotherapies containing gemcitabine or paclitaxel, docetaxel, vinorelbine or pemetrexed based on the results of the NMA.

Using data from the KEYNOTE-024 trial, the company also considered the cost effectiveness of treatment with pembrolizumab for subgroups of patients treated with specific regimens:

- non-squamous population: pemetrexed and non-pemetrexed chemotherapy combinations
- squamous population: non-pemetrexed chemotherapy combinations
- squamous and non-squamous population: non-pemetrexed only
- non-squamous only population: pemetrexed only.

Table 3 Distribution of platinum-based chemotherapy combinations prescribed to patients in the KEYNOTE-024 trial and market shares

Chemotherapy combinations	KEYNOTE-024 trial	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%
Vinorelbine+carboplatin	0%	17%
Vinorelbine+cisplatin	0%	10%
Pemetrexed+carboplatin	44%	17%
Pemetrexed+cisplatin	24%	26%
% Total	100%	100%

Source: CS, Table 53

Treatment duration

In line with the KEYNOTE-024 trial protocol, treatment with pembrolizumab was assumed to continue until disease progression or intolerable toxic effects resulting in discontinuation, with maximum treatment duration of 35 cycles.

Similarly, in line with the KEYNOTE-024 trial protocol, the relevant SmPCs[63-65] and UK clinical practice, patients prescribed SOC, were assumed to receive treatment up to disease progression or intolerable toxic effects resulting in discontinuation, with maximum treatment duration of six cycles. Patients treated with pemetrexed maintenance therapy were assumed to be treated until disease progression or unacceptable toxicity.

Subsequent treatment and treatment switching

Based on visual inspection, the Weibull distribution is close to both the exponential and the generalised gamma distributions, and it also had a good visual fit to the K-M data. Consequently, it was selected by the company for the extrapolation of PFS for SOC to maintain consistency with the best fit identified for pembrolizumab.

Modelling indirect comparisons

Since the PH assumption did not hold between pembrolizumab and SOC arms of the KEYNOTE-024 trial, the company implemented a NMA approach using time-varying HRs to model the indirect comparisons. The company used a fixed effects model with a Weibull distribution to take into account time-varying treatment effects. Treatment with pembrolizumab was compared with the following comparators in additional scenario analyses:

- gemcitabine or paclitaxel combined with a platinum (carboplatin or cisplatin)
- docetaxel combined with a platinum (carboplatin or cisplatin)
- vinorelbine combined with a platinum (carboplatin or cisplatin)
- pemetrexed-containing chemotherapy.

5.3.8 Health-related quality of life

HRQoL data were collected as part of KEYNOTE-024 trial using the EQ-5D 3L[34] tool. The company employed utility estimates in the model based on the time-to-death approach. Time-to-death sub-states were used to capture patients' HRQoL as a function of length of time until death using four categories: <30 days to death and ≥30 days to 180; ≥180 to 360 days, and ≥360 days. All patients, including censored patients, were included in the analysis for the category of 360 or more days to death.

In the base case analysis, the mean EQ-5D utility scores were pooled from the pembrolizumab and SOC treatment arms since there were no statistically significant or clinically meaningful differences in EQ-5D scores by treatment arm. UK preference-based scores were used for all patient data analysed from the KEYNOTE-024 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique. The utility values used in the company model are outlined in Table 5.

Table 4 Mean EQ-5D utility scores by time to death (KEYNOTE-024 trial data)

Table 5 Mean EQ-5D utility scores by time to death (KEYNOTE-024 trial data)

Time to death (days)	Mean utility (pooled across treatment arms)	95% CI
≥360*	0.808	(0.767 to 0.850)
≥180 to <360	0.712	(0.663 to 0.762)
≥30 to <180	0.598	(0.547 to 0.648)
<30	0.48	(0.324 to 0.637)

*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
Source: CS, Table 61

Within the company model, utility scores for all patients were adjusted over time using the annual utility decrement of 0.0045 that has been calculated based on figures from the publication by Kind et al.[68] Based on the baseline age of patients included in the KEYNOTE-024 trial, this decrement was applied annually from the age of 65 to 75 years to reflect the natural decrease in utility associated with increasing age.

The company's systematic review to identify studies reporting HRQoL for previously untreated patients with advanced NSCLC identified 32 unique studies. Only one relevant report was identified (NICE TA309).[10] In this report utility values were estimated by treatment arm, progressed state and time to death. However, the values presented cannot be directly compared with the utility values from the KEYNOTE-024 trial which do not adjust for the impact of disease progression on the time to death utility values and thus were not used in the company model. The company considers that, overall, the utilities derived from the KEYNOTE-024 trial are in line with the utilities observed in the published literature.

Impact of adverse events on health-related quality of life

The company took into account the impact of AEs on HRQoL by examining the EQ-5D-based health utility, in the PFS state, of patients who experienced grade 3 to 5 AEs (0.719; 95% CI 0.683 to 0.755) with the utility of those who did not experience any AEs in the progression-free health state (0.793; 95% CI 0.777, 0.809). Utility decrements as a result of AEs were applied during the first cycle in the company model based on AE incidence rates and the corresponding mean duration across them (i.e. 31.5 days of duration across grade 3+ AEs, as estimated from the KEYNOTE-024 trial).

5.3.9 Resources and costs

Drug costs

Pembrolizumab is administered as a 200mg fixed dose via a 30 minute IV infusion every 3 weeks (Q3W). The expected list price of a 100mg vial is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260. [redacted]

[redacted]

The ERG considers that it is clinically implausible that clinicians would stop treatment at a time point, not mentioned in the SmPC,[1] if they considered that patients were still benefiting from treatment. Further, as no patients in the KEYNOTE-024 trial completed 2 years of treatment, the OS extrapolation for pembrolizumab from this trial is based on patients who were treated in line with the KEYNOTE-024 trial protocol to a time-point before 2 years i.e., to progression or unacceptable toxicities. The ERG considers that the same approach would be taken in NHS clinical practice. Therefore, the company's OS extrapolations for patients receiving pembrolizumab, while uncertain, are at least based on a reasonable approximation of what would happen to patients should treatment with pembrolizumab become the standard of care. In contrast, the modelled costs of treatment with pembrolizumab are based on a time limiting stopping rule outlined in the KEYNOTE-024 trial protocol that was not applied to any patients participating in the trial and is not mentioned in the draft SmPC.[1]

The ERG has removed the limit on the number of cycles of treatment with pembrolizumab from the company model. This ERG amendment increases the total costs associated with treatment with pembrolizumab from £76,462 in the company base case to £133,546, and increases the ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC by £47,298 to £92,194 per QALY gained (see **Error! Reference source not found.**).

Continuing treatment with pembrolizumab beyond 35 cycles has an impact on treatment and administration costs. Table 6 shows the acquisition and administration costs of treatment with pembrolizumab that are generated by the company model, assuming treatment continues beyond 35 cycles [redacted] These figures are based on the KEYNOTE-024 trial TTD data and the extrapolation of these data undertaken by the company.

The data in Table 6 show that just under half (49.7%) of the potential acquisition and administration costs of pembrolizumab are excluded from the cost effectiveness results if treatment is assumed to discontinue at 2 years. Due to a long tail of patients remaining on treatment, by the end of 5 years the company model predicts that 13.7% of patients will still be on treatment, although by this point 78.5% of the total potential pembrolizumab costs will have been realised. Even if all treatment is arbitrarily stopped at 3 years rather than 2 years, the ICER per QALY gained for the comparison of pembrolizumab versus SOC would increase beyond £50,000 to £56,502 per QALY gained (see **Error! Reference source not found.**).

Table 6 Pembrolizumab acquisition and administration costs over time

concern compared to the uncertainty in the projections that exist even at just 2 years after treatment commenced (50.9% to 58.4% depending on the distribution chosen).

Although the company has chosen to employ the most pessimistic of the generated distributions, the ERG considers that, given the immaturity of the OS data, there is no distribution that can be considered reliable. The ERG has, therefore, not suggested an alternative representation of OS for patients treated with pembrolizumab. Instead, the ERG cautions that the extrapolation implemented in the company model should be interpreted as illustrative rather than as an expectation and, until further OS data become available, there is no way of knowing whether the company has been overly or insufficiently pessimistic in their chosen projection.

Standard of care

As stated in Section 4.4.3 of this ERG report, the ERG considers that the method for adjustment for crossover in the SOC treatment arm of the KETNOTE-024 trial produces unreliable results. Even if the crossover adjustment was reliable, the ERG considers that the company has been too pessimistic in estimating 5-year survival rates for patients with stage IV NSCLC and PS 0 to 1 receiving SOC.

The 5-year survival rate of patients treated with SOC in the company model is 1.9%. This is below the NLCA 5-year survival rate (5%) for patients with stage IV NSCLC.[67] It is also below the lower bound of the 2% to 13% 5-year survival range reported by Cancer Research UK[86] and referenced by the company in support of the following statement made in the CS:

> More than half of non-small cell lung cancer (NSCLC) patients present with incurable advanced local or metastatic disease at the time of diagnosis, with an estimated five-year survival rate around 10%. (CS p14)

The ERG considers that the actual 5-year survival rate for patients with stage IV NSCLC and PS 0 to 1 who are treated with chemotherapy should be at least the 5% reported in the NLCA dataset.[67] The ERG considers that, in clinical practice, the 5-year survival rate is likely to be closer to the higher (13%), rather than lower (2%), bound figures quoted by Cancer Research UK[86] as the NLCA 5-year survival rate[67] has been derived from data from all patients, regardless of whether the patient received chemotherapy.

Figures from the latest (2015) NLCA report[87] indicate that only 58% of patients with stage IIIb/IV NSCLC received chemotherapy in 2014 and this rate was higher than in previous years. If chemotherapy improves life expectancy, then the 5% 5-year survival figure reported by the

> to a poorer prognosis and greater patient burden. Increased levels of psychological distress are reported by patients undergoing oncological treatment and by those approaching death. (CS p35 and 36)

Even if these issues are alleviated somewhat by treatment, the company needs to justify the claim that patients with stage IV NSCLC achieve higher levels of HRQoL life than those achieved by people of the same age in the general UK population.

The reason why the utility values from the KEYNOTE-024 trial are so high for the time period >360 days to death is unclear. The ERG accepts that the KEYNOTE-024 trial EQ-5D completion rates were reasonably high. However, only a very small number of patients provided information for each of the periods to death that were measured. For example, only 54 patients provided data that contributed to the utility estimate for the period >360 days from death, and only 26 patients provided data to inform the utility estimate for the period 180 to 360 days to death. This means that the confidence intervals around the utility estimates are wide, indicating significant uncertainty around the calculated figures and that the high mean utility values may just be a statistical artefact of a small sample size. In the absence of further evidence on the time to death utility values, the ERG has carried out two scenario analyses.

First, a scenario was constructed in which the utility value >360 days before death was set to be no greater than that of the general UK population of the same age. This resulted in a reduction in the >360 days before death value from 0.808 to 0.79. This is still a conservative scenario, as it relies on the assumption that having metastatic NSCLC, with the associated quality of life issues stated in the CS and repeated above, does not lower patient utility below that of the general UK population of the same age. This scenario results in a reduction in the QALYs generated for both the pembrolizumab arm (from 2.06 in the company base case to 2.03) and the SOC arm (from 0.86 in the company base case to 0.85). Implementing this change in the company model increases the ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC by £1,004 to £45,900 per QALY gained (see **Error! Reference source not found.**).

The second scenario examined the impact of using utility values published in the Nafees 2008 paper.[89] The values from the Nafees[89] publication have previously been used in other NICE STAs, including the appraisal of pemetrexed for the first-line treatment of NSCLC (TA181[4]). While these utilities are representations of the HRQoL of patients in the stable, the value for responding disease with no side effects (0.673) could be used for all values for time to

6.1 Conclusions of the ERG's cost effectiveness review

The ERG considers that there are four issues that cast substantial doubt on the reliability of the ICER per QALY gained estimated by the company for the comparison of treatment with pembrolizumab versus SOC.

First, the extrapolation of OS for pembrolizumab is highly uncertain due to the relatively short-term clinical effectiveness evidence that is currently available from the KEYNOTE-024 trial.

Second, the extrapolation of OS for SOC is overly pessimistic compared to that which would be expected when using registry data or published studies describing patients with stage IV NSCLC treated with chemotherapy. The company extrapolation predicted OS at 5 years for patients treated with SOC to be 1.9%, whereas NLCA[67] data suggest that 5-year survival for all patients with stage IV NSCLC is 5%. However, the NLCA[67] data include at least 40% of patients who did not have chemotherapy and results from other published studies show that chemotherapy increases life expectancy for stage IV NSCLC patients. In the base case, the ERG has amended survival at 5 years to be 5% for patients treated with SOC. However, in clinical practice, a greater percentage of patients receiving chemotherapy would be expected to still be alive at 5 years - possibly as many as 13%. The ERG therefore considers that the amendment made still produces a conservative estimate of the ICER per QALY gained for the comparison of treatment with pembrolizumab versus SOC.

Third, the company calculated the cost of pembrolizumab on the basis that treatment would cease after 35 cycles (2 years) as this approach fitted with the treatment approach described in the KEYNOTE-024 trial protocol. [redacted] The ERG considers it implausible that treatment would be stopped at 2 years if a patient were deemed to still be deriving clinical benefit from treatment with pembrolizumab.

None of the patients in the KEYNOTE-024 trial stopped treatment at 2 years as the data-cut was carried out before that point. The company has no clinical evidence to support the decision to stop treatment at 2 years and all projections of OS and PFS are only based upon treatment to progression before 2 years. The ERG considers that the only plausible costing scenario for pembrolizumab is to remove the limit on the number of cycles of pembrolizumab in the company model.

8 OVERALL CONCLUSIONS

Clinical effectiveness evidence

- The company has provided evidence from a small phase III un-blinded RCT (the KEYNOTE-024 trial) to support the use of pembrolizumab in patients with untreated, metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥50%). This trial was designed to compare the clinical effectiveness and safety of treatment with pembrolizumab versus SOC.
- The population in the KEYNOTE-024 trial is patients with untreated metastatic NSCLC whose tumours strongly express PD-L1 (TPS ≥50%) with no EGFR or ALK positive tumour mutations. This is a subset of the population described in the final scope issued by NICE (i.e., people with PD-L1 positive NSCLC not treated with chemotherapy in the metastatic setting).
- The KEYNOTE-024 trial was stopped early for benefit. The currently available OS data from the KEYNOTE-024 trial were obtained at IA2. At this point, only 35% of the expected OS events had occurred. Median OS had not been reached in either arm of the trial. Furthermore, the ERG has concerns that the trial based OS HR result may be inaccurate as the assumption of proportional hazards that underpins this calculation is invalid.
- The protocol for the KEYNOTE-024 trial allowed patients receiving SOC to cross over at disease progression to receive pembrolizumab and, at the time of IA2, 43.7% of patients from the SOC arm had crossed over. The company considered three different methods to adjust the trial OS data for the effect of treatment crossover. Of the methods considered, the ERG agrees with the company that the 2-stage model is the most appropriate.
- All three methods adjust the HR that has been generated by comparing OS K-M data from the two arms of the KEYNOTE-024 trial. This (initial) HR is only reliable if the OS hazards for the two trial data-sets are proportional. The company did not carry out any testing of proportionality; however, tests carried out by the ERG indicate that the trial data OS hazards are not proportional and thus the company's (initial) HR result should be viewed with caution. Text removed
- The ERG notes that the unadjusted OS results (HR=0.60) and the HR generated using the company's preferred method (the 2-stage method, HR=0.50) are very similar.
- The ERG is uncertain of the reasons for, or the implications of, the [redacted] difference between the BICR-assessed PFS and investigator-assessed PFS for patients in the pembrolizumab arm of the KEYNOTE-024 trial ([redacted]).
- In the draft SmPC[1] for pembrolizumab, it is stipulated that treatment should be initiated only after a validated laboratory test has confirmed the tumour expression of PD-L1. Clinical advice to the ERG is that, at present, there is no established or validated test for PD-L1 expression and testing for PD-L1 expression is not routinely available in NHS treatment centres. The ERG notes that, in the NHS, there is currently no standard means of identifying patients whose tumours strongly express PD-L1.

In the absence of any direct evidence for the clinical effectiveness of treatment with pembrolizumab versus individual platinum doublet chemotherapy regimens specified in the final scope issued by NICE, the company conducted a series of NMAs. However, due to concern about the similarity between adjusted and unadjusted NMA OS results, the mix of patients with and

- without tumours that express PD-L1 and high levels of heterogeneity between included studies, the ERG considers that results from the company's NMAs should be interpreted with caution.
- The ERG notes that 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. They may also have greater variation in available social support. The ERG considers that AEs arising from treatment with immunotherapy (i.e., pembrolizumab) in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.
- The company reports that the KEYNOTE-042 RCT is currently underway. This trial has been designed to compare treatment with pembrolizumab versus SOC in a population of patients with PD-L1 positive advanced or metastatic NSCLC. Final data collection for OS is planned for February 2018. The results of the KEYNOTE-042 trial will provide evidence for the clinical effectiveness of pembrolizumab in patients whose tumours express PD-L1, regardless of the level of expression.

Cost effectiveness evidence

- To model survival for patient lifetime the company has extrapolated KEYNOTE-024 survival data. However, the ERG considers that:
    - Any extrapolation of OS data from patients in the pembrolizumab arm of the KEYNOTE-024 trial will be highly uncertain due to only 35.4% of the expected OS events having occurred.
    - The company's extrapolation of OS data from patients in the SOC arm of the KEYNOTE-024 trial is overly pessimistic compared to survival results available from registry data and published studies describing patients with stage IV NSCLC treated with chemotherapy. Survival, predicted by the company extrapolation for patients treated with SOC at 5 years is 1.9%, whereas NLCA[67] data suggest that 5-year survival for all patients with stage IV NSCLC is 5%.
- The company calculated the cost of pembrolizumab on the basis that treatment would cease after 35 cycles (2 years) as this is in line with details published in the KEYNOTE-024 trial protocol. However, for patients with untreated PD-L1 positive metastatic NSCLC, [redacted] The ERG therefore considers 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.
- The ERG considers that the utility values incorporated into the company model are implausibly high, notably for the period 360 days before death when these values are higher than the UK population norms.
- The ERG made three changes to the company model: altering the OS extrapolation for patients receiving SOC such that 5% of patients are alive at 5 years; removing the 35 cycle limit on the number of cycles of pembrolizumab that can be administered; and limiting the magnitude of the utility values used in the model so that they are no higher than the population norms for people of the same age.

Using the PAS price, application of the ERG model amendments results in an ICER for the comparison of treatment with pembrolizumab versus SOC of £114,291 per QALY gained. The ERG's amendments to the company's OS extrapolation for patients receiving SOC and to the utility values employed in the model are very conservative

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26th January 2017

Dear Helen,

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

Please find below updated cost-effectiveness analysis results including [redacted]

Please note that the AiC/CiC information have been highlighted, respectively.

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

Kind regards,

[redacted]

Base-case deterministic and probabilistic cost-effectiveness analysis of pembrolizumab compared with SOC

Please find below in **Table 1** the deterministic and probabilistic cost-effectiveness results for MSD's preferred base case (i.e. extrapolation based on piecewise model as estimated from the KEYNOTE-024 KM data for both pembrolizumab and SOC and considering a maximum treatment duration of 2 years), and in

Table 1. Base case incremental cost-effectiveness results (discounted, with updated PAS)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Deterministic					
Pembrolizumab	£72,017	2.06	£49,739	1.21	£41,213
SOC	£22,278	0.86	-	-	-
Probabilistic					
Pembrolizumab	£72,571	2.09	£49,905	1.22	£40,771
SOC	£22,666	0.87	-	-	-

The probability of pembrolizumab being cost-effective at a £50,000 per QALY threshold is estimated to be 70.4% with the updated value proposition.

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

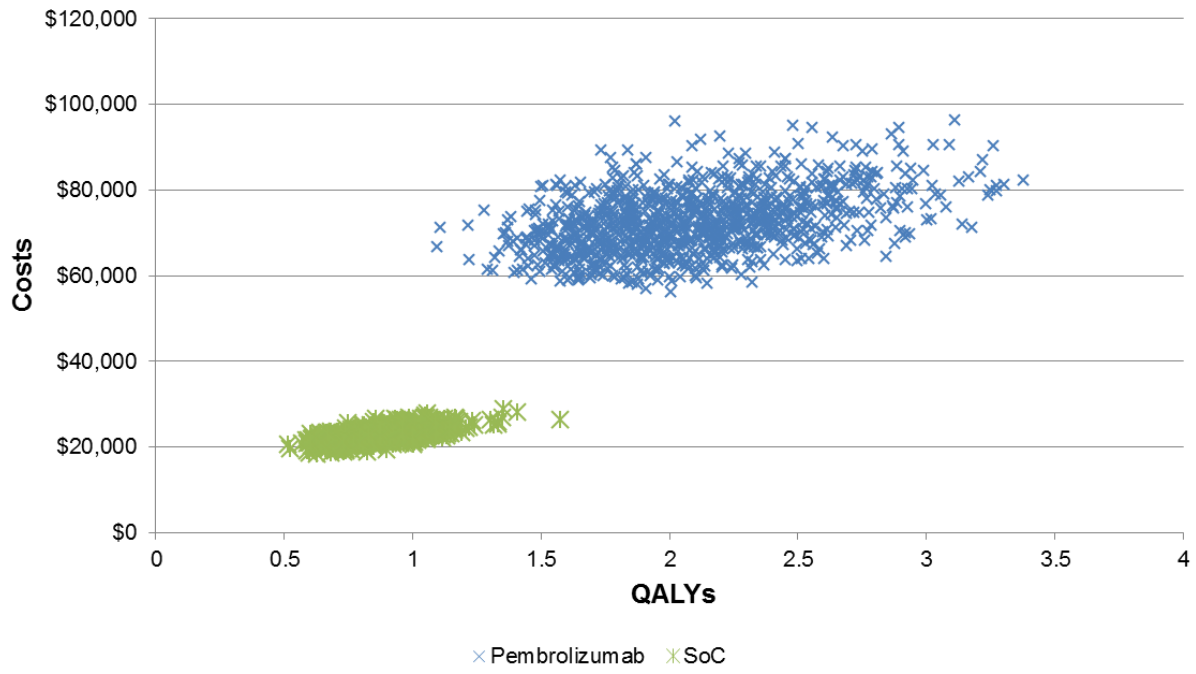
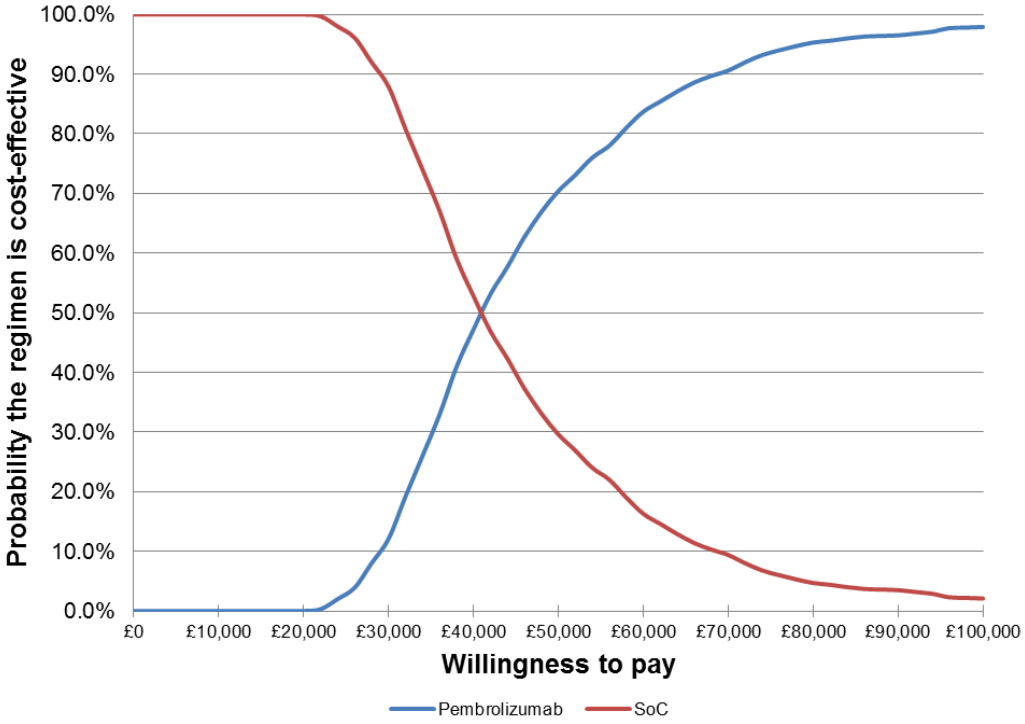


Figure 2: Cost-effectiveness acceptability curve (results discounted, with updated PAS)



ID990 STA Pembrolizumab Addendum 1

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

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

Completed 30th January 2017

DOES NOT CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

At the request of the NICE team, the ERG has updated Table 52 and Table 53 from ERG Report to reflect the new PAS discount for pembrolizumab (Table 1 and Table 2).

Table 1 Pembrolizumab acquisition and administration costs over time

Years of treatment (cycles)	Percentage of patients still expected on treatment at end of year	Mean discounted cost per patient of acquisition and administration to the end of the year	Percentage of mean discounted total acquisition and administration costs incurred to the end of the year	ICER per QALY gained vs SOC if all pembrolizumab treatment stopped at the end of the year
2 years (35 cycles) (company base case)	30.7%	£53,282	50.3%	£41,213
3 years (52 cycles)	22.6%	£66,210	62.5%	£51,925
4 years (70 cycles)	17.4%	£76,146	71.9%	£60.157
5 years (87 cycles	13.7%	£83,191	78.5%	£65,955
10 years (174 cycles)	5.3%	£101,324	95.6%	£81,020
Total over lifetime (348 cycles)	**100.0%**	**£105,969**	**100.0%**	**£84,868**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; SOC=standard of care
Source: ERG Report Table 52

Table 2 ERG adjustments to company base case: pembrolizumab vs SOC (discounted with updated PAS)

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	***£72,017***	***2.06***	***2.75***	***£22,278***	***0.86***	***1.22***	***£49,739***	***1.21***	***1.53***	***£41,213***	
R1) Removal of 35 cycle limit for patients treated with pembrolizumab	£124,704	2.06	2.75	£22,278	0.86	1.22	£102,426	1.21	1.53	£84,650	+£43,437
R2) 5% 5-year OS survival for patients treated with SOC	£72,017	2.06	2.75	£24,117	1.08	1.51	£47,900	0.98	1.24	£48,878	+£7,665
R3) 13% 5-year OS survival for patients treated with SOC	£72,017	2.06	2.75	£27,630	1.52	2.06	£44,387	0.54	0.70	£82,198	+£40,985
R4) Utility value for >360 days to death set to population norm	£72,017	2.03	2.75	£22,278	0.85	1.22	£49,739	1.18	1.53	£42,152	+£939
R5) Nafees[89] utility values	£72,017	1.73	2.75	£22,278	0.73	1.22	£49,739	1.01	1.53	£49,247	+£8,034
B. ERG preferred scenario (R1, R2 and R4)	**£124,704**	**2.03**	**2.75**	**£24,117**	**1.07**	**1.51**	**£100,587**	**0.96**	**1.24**	**£104,778**	**+£63,565**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; SOC=standard of care; OS=overall survival
Source: ERG Report Table 53

ID990 STA Pembrolizumab Addendum 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Following the Appraisal Committee meeting on 31st January 2017, NICE requested that the ERG provide the results of a further scenario analysis which involved combining scenario R2 (5% 5-year OS survival for patients treated with SOC) and R4 (utility value for >360 days to death set to population norm). The result from this scenario is shown in Table 2.

All results reflect the impact of the new patient access scheme (PAS) discount for pembrolizumab.

Table 1 Pembrolizumab acquisition and administration costs over time

Years of treatment (cycles)	Percentage of patients still expected on treatment at end of year	Mean discounted cost per patient of acquisition and administration to the end of the year	Percentage of mean discounted total acquisition and administration costs incurred to the end of the year	ICER per QALY gained vs SOC if all pembrolizumab treatment stopped at the end of the year
2 years (35 cycles) (company base case)	30.7%	£53,282	50.3%	£41,213
3 years (52 cycles)	22.6%	£66,210	62.5%	£51,925
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5 years (87 cycles	13.7%	£83,191	78.5%	£65,955
10 years (174 cycles)	5.3%	£101,324	95.6%	£81,020
Total over lifetime (348 cycles)	**100.0%**	**£105,969**	**100.0%**	**£84,868**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; SOC=standard of care
Source: ERG Report Table 52

Table 2 ERG adjustments to company base case: pembrolizumab (discounted with updated PAS) vs SOC

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	***£72,017***	***2.06***	***2.75***	***£22,278***	***0.86***	***1.22***	***£49,739***	***1.21***	***1.53***	***£41,213***	
R1) Removal of 35 cycle limit for patients treated with pembrolizumab	£124,704	2.06	2.75	£22,278	0.86	1.22	£102,426	1.21	1.53	£84,650	+£43,437
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R4) Utility value for >360 days to death set to population norm	£72,017	2.03	2.75	£22,278	0.85	1.22	£49,739	1.18	1.53	£42,152	+£939
R5) Nafees[89] utility values	£72,017	1.73	2.75	£22,278	0.73	1.22	£49,739	1.01	1.53	£49,247	+£8,034
B. ERG preferred scenario (R1, R2 and R4)	**£124,704**	**2.03**	**2.75**	**£24,117**	**1.07**	**1.51**	**£100,587**	**0.96**	**1.24**	**£104,778**	**+£63,565**
C. AC requested scenario (R2 and R4)	**£72,017**	**2.03**	**2.75**	**£24,117**	**1.07**	**1.51**	**£47,900**	**0.96**	**1.24**	**£50,028**	**+£8,915**

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; SOC=standard of care; OS=overall survival
Source: ERG Report Table 53

ID990 STA Pembrolizumab Addendum 3

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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

Completed 21st April 2017

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

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

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

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

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

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

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

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

NICE team request 1 and 2

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

Table 1 Company base case (Company Table 2)

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

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

Table 2 Appraisal Committee preferred assumptions (Company Table 6)

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

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

NICE team request 3

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

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

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

SOC=standard of care

1.2 ERG modifications to Table 2 and Table 6

NICE team request 4

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

Table 4 Company Table 2 with utilities capped at population norm

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

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

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

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

Completed 22nd March 2017

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A MEMBER OF THE RUSSELL GROUP

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

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

1 ERG RESPONSE TO MSD'S RESPONSE TO THE ACD

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

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

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

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

1.1 OS projection for patients receiving pembrolizumab

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

1.2 Utility values

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

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

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

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

1.3 OS projection for patients receiving SOC

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

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

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

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

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

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

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