NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

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   - British Thoracic Oncology Group
   - Royal College of Pathologists

5. **Expert statements** from:
   - Professor Samreen Ahmed, Consultant Medical Oncologist – clinical expert, nominated by British Thoracic Oncology Group (BTOG-NCRI-ACP-RCP)
   - Dr. David Snead, Consultant and Clinical Lead Cellular Pathology – clinical expert, nominated by Royal College of Pathologists
   - Karen Clayton, Macmillan Lung Cancer CNS – patient expert, nominated by National Lung Cancer Forum for Nurses
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer [ID1173]

Pre-meeting briefing

Contains AIC and CIC

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

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Key clinical effectiveness issues

- Are the comparators used by the company relevant to NHS clinical practice?
  - Company excluded pemetrexed maintenance therapy with chemotherapy regimens
- Are the results of the company's ITC appropriate given the heterogeneity in the included studies?

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Key Cost-effectiveness issues

- Is the company's model structure appropriate?
- What is the most appropriate cut off point and extrapolation to use for OS?
  - Company = KM with 28 week cut-off then exponential distribution for both arms
  - ERG = fully fitted log-logistic curves from week 0 for both arms
- Is the time to death approach used to estimate utility values appropriate?
- Is the modelling of subsequent therapies appropriate?
- Is a life-time treatment effect appropriate?
- Is End of life criteria met?
- What is the most plausible ICER?

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Common abbreviations			
AE	Adverse event	K-M	Kaplan-Meier
ALK	Anaplastic lymphoma kinase	LS	Least squares
AIC	Akaike information criterion	LYG	Life years gained
AUC	Area under the curve	NSCLC	Non-small-cell lung cancer
BIC	Bayesian information criterion	ORR	Objective response rate
BICR	Blinded independent central review	OS	Overall survival
BNF	British national formulary	PD-1	Programmed death-1 protein
CAA	Commercial access agreement	PD-L1	Programmed cell death-1 ligand-1
DoR	Duration of response	PSA	Probabilistic sensitivity analysis
DSU TSD	Decision support unit technical support document	PSS	Personal and Social Services
ECOG	Eastern Cooperative Oncology Group	QALY	Quality adjusted life year
eMIT	Electronic market information tool	RCT	Randomised controlled trial
EGFR	Epidermal growth factor receptor	RECIST	Response Evaluation Criteria In Solid Tumours
EORTC	European Organisation for the Treatment of Cancer	RPSFT	Rank preserving structural failure time
ERG	Evidence Review Group	RR	Response rate
FAS	Full analysis set	SAE	Serious adverse event
HRQoL	Health-related quality of life	SLR	Systematic literature review
ICER	Incremental cost effectiveness ratio	TPS	Tumour proportion score
IPCW	Inverse Probability of Censoring Weighting		
ITC	Indirect treatment comparison		
KEYNOTE-189	Key trial that informs the clinical effectiveness and cost effectiveness evidence		

Disease background

- 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 85-90% of lung cancer cases
- Approximately 50% of people with NSCLC are diagnosed with incurable advanced local or metastatic disease (stage IV)
- Estimated 5-year survival rate of approximately 10%
- NSCLC: 2 major histological subtypes:
  - Squamous cell carcinoma (25 to 30%)
  - Non-squamous cell carcinoma including adenocarcinoma (30 to 40%), large-cell carcinoma (10 to 15%) and other cell types (5%)

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Pembrolizumab (KEYTRUDA) in combination with pemetrexed and platinum chemotherapy (pembrolizumab combination)

Merck, Sharpe & Dohme

Mechanism of action	Humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor, part of the immune checkpoint pathway
Anticipated marketing authorisation	KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
Administration, dosage & duration of treatment	IV infusion in outpatient setting of: • 200 mg for NSCLC that has not been previously treated with chemotherapy (when administered as monotherapy or in combination with pemetrexed and platinum chemotherapy) • 200mg for NSCLC previously treated with chemotherapy every 3 weeks until disease progression or unacceptable toxicity.
Cost (list price)	£2,630 per 100 mg vial. Average cost of treatment: [redacted] (list price).
Other NICE recommendations/ appraisals	• NICE TA531: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer • ID1210 Atezolizumab for non-squamous untreated NSCLC (1st ACM December 2018)

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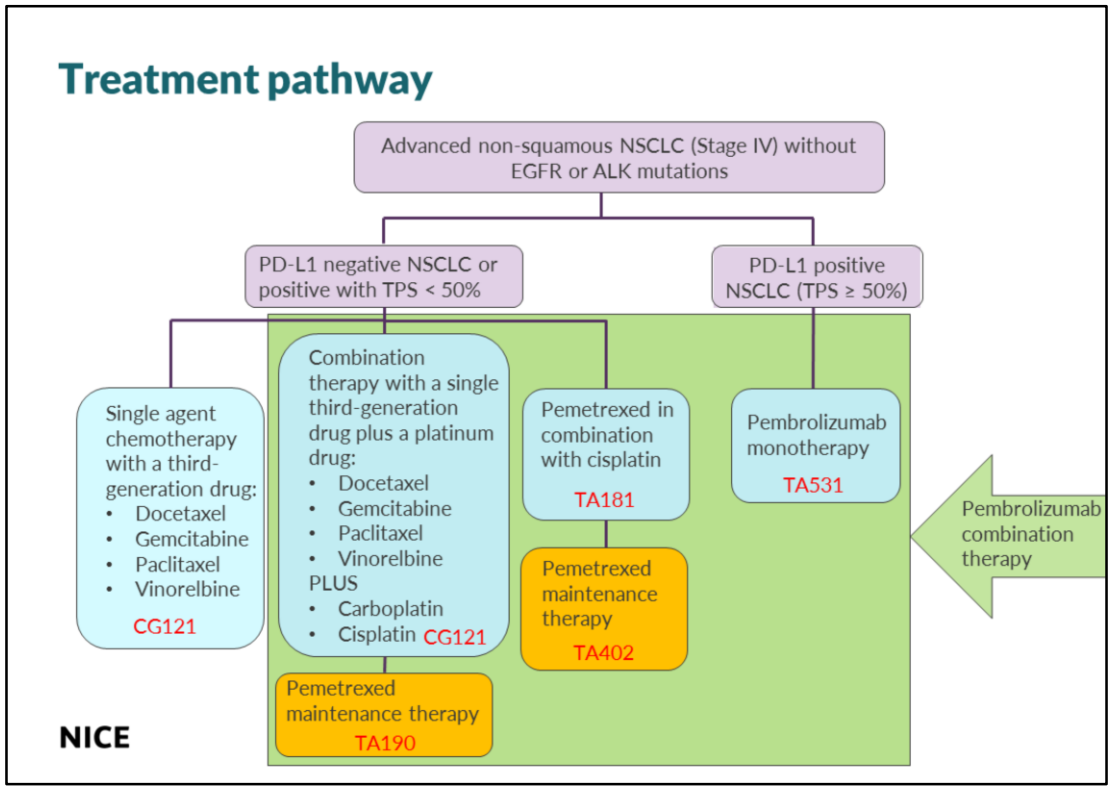

The company envisage that pembrolizumab-chemo combination therapy would displace:-

- first line use of platinum-doublet chemotherapy alone
- single agent chemotherapy or pemetrexed in combination with cisplatin (the latter is applicable for adenocarcinoma patients only)
- pembrolizumab monotherapy for patients with high levels of PDL1 expression (defined as tumour proportion score (TPS) of at least 50%).

NSCLC = Non-small cell lung cancer

EGFR-TK mutation = Epidermal growth factor receptor - Tyrosine kinase

PD-L1 = Programmed death-ligand 1

TPS = Tumour proportion score

Patients and carers comments

- None received

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Clinical expert comments

- Longer PFS with combination compared with monotherapy
- Toxicity is no greater than when chemotherapy and pembrolizumab given separately
- Experience of managing patients on combination should not be significantly different
- No greater capacity required, will actually reduce chemo suite chair numbers as both given together rather than sequentially
- Outcomes superior to standard of care
- No increased adverse event rates
- KEYNOTE 189 suggests the PD-L1 marker is irrelevant in this setting of combination therapy which would simplify patient selection.

NHS England comments

- None received

Decision problem

	Scope	Company
Population	Adults with untreated metastatic non-squamous NSCLC	As scope but lacking EGFR and/or ALK mutation
Intervention	Pembrolizumab combination	✓
Comparators	• Pemetrexed + carboplatin or cisplatin • Chemotherapy + carboplatin or cisplatin (both with or without pemetrexed maintenance) • Pembrolizumab monotherapy	✓ ✓ X ✓
Outcomes	overall survival (OS) progression-free survival (PFS) response rates (RRs) adverse effects (AEs) of treatment health-related quality of life (HRQoL) Duration of response (DOR)	✓ ✓ ✓ ✓ ✓ X Time on treatment (ToT)

ERG comments: Pemetrexed maintenance was excluded from the pair-wise comparisons with platinum plus vinorelbine, gemcitabine, docetaxel, and paclitaxel; and also that with pembrolizumab monotherapy in the company's economic modelling

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Outcomes included in the CS did not match the outcomes described in the scope, since the model included and heavily relied on the time-on-treatment outcome, and this was not included in the systematic search and review.

The comparators described in the CS aligned to the scope, except in an area of ambiguity, where pemetrexed maintenance was excluded from the pair-wise comparisons with platinum plus vinorelbine, gemcitabine, docetaxel, and paclitaxel; the same too with the pembrolizumab monotherapy comparison

Clinical effectiveness

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Clinical effectiveness

Clinical evidence for pembrolizumab in combination with chemotherapy: KEYNOTE-189

	Data from the final analysis of KEYNOTE-189 is currently anticipated in [redacted]
Trial design	Randomised, double blind, Phase III : **ONGOING**
Population	• adults with advanced or metastatic non-squamous NSCLC • No EGFR or ALK • ECOG performance score of 0 or 1
Intervention* (n=410)	Pembrolizumab 200 mg plus pemetrexed 500 mg/m2 and platinum cisplatin [75 mg/m2] or carboplatin [AUC 5 mg/mL/min] Q3W for 4 cycles, followed by pembrolizumab plus pemetrexed
Comparator* (n=206)	Saline placebo plus pemetrexed 500 mg/m2 and platinum cisplatin [75 mg/m2] or carboplatin [AUC 5 mg/mL/min] Q3W for 4 cycles, followed by saline plus pemetrexed
Outcomes	Primary: Overall survival, progression free survival Secondary: objective response rates (ORRs), adverse effects (AEs) of treatment, health-related quality of life (HRQoL), Duration of response (DOR)

*Treatment with pembrolizumab or saline placebo continued until 35 study treatments had been administered or one of the discontinuation criteria occurred.

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While KEYNOTE-189 is ongoing, data from an interim analysis (data cut-off date 08-NOV-2017) form the evidence base for this submission

AUC = Area under the curve (target area under the concentration versus time curve in mg/mL•min)

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Clinical effectiveness results

KEYNOTE-189 cut-off date for the analysis 8 November 2017

- median duration of follow-up of 10.5 months (range 0.2 to 20.4 months)

	Outcome	Pembrolizumab combination (n=410)	Control (n=206)
Primary outcomes	**Overall Survival**		
	Median, months (95% CI)	Not reached	11.3 (8.7 to 15.1)
	HR (95% CI)	**HR 0.49 (0.38 to 0.64) p < 0.00001**	
	OS rate at 6 months %	[redacted]	[redacted]
	OS rate at 12 months %	69.2%	49.4%
	Progression free survival		
	Median, months (95% CI)	8.8 (7.6 to 9.2)	4.9 (4.7 to 5.5)
	HR (95% CI)	**HR 0.52 (0.43 to 0.64) p < 0.00001**	
	PFS rate at 6 months	[redacted]	[redacted]
	PFS rate at 12 months	34.1%	17.3%

ERG comments: evidence from KEYNOTE-189 was sufficiently representative to be applied to UK clinical practice

Source: Company submission; tables 16, 17, 18 23, and 24 (p.46, 48 and 58)

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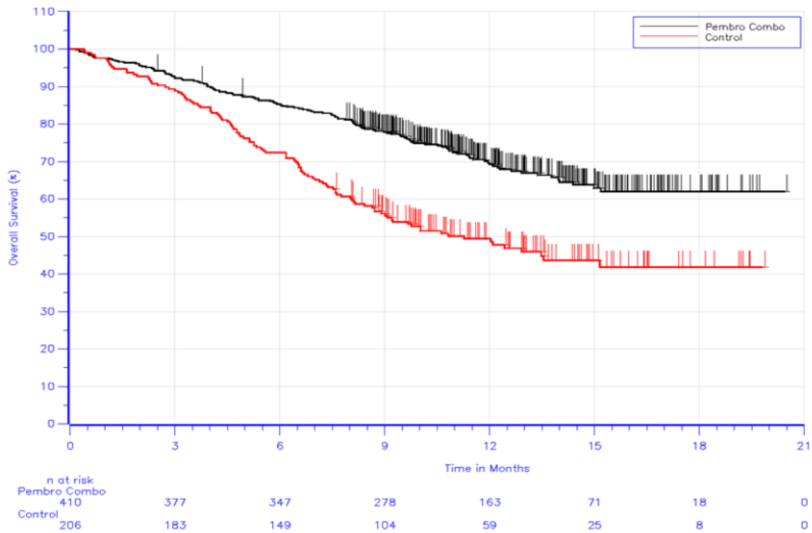
Secondary outcome results can be found in table 16, p.47 of the company submission

Overall survival: ITT population Kaplan-Meier

- Pembrolizumab combination statistically significantly improves OS vs Control



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Source: Company submission; figure 6, p.49

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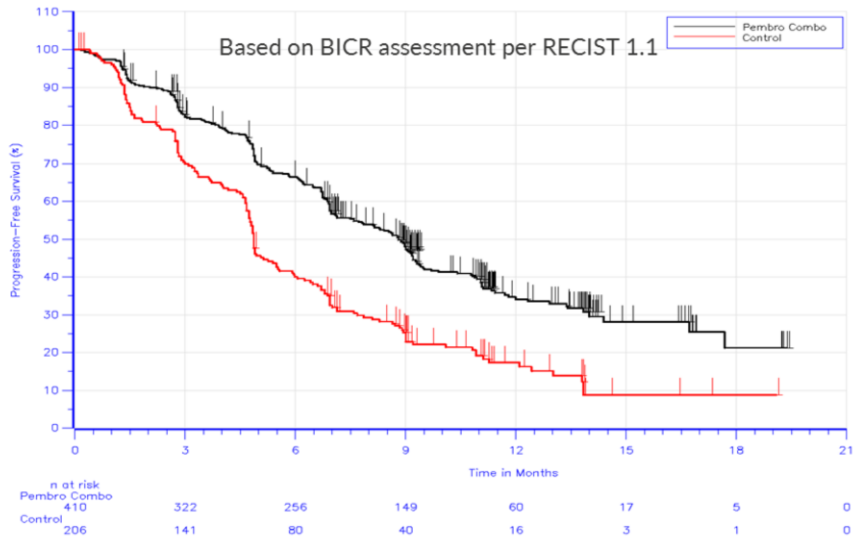
The company states that the OS projections, based on the November 2017 KEYNOTE-189 data cut, were validated with clinical experts, who agreed on the plausibility of the projections of the base case analyses presented in this submission with their estimations of SoC OS at 5 years, the majority less than 5% to somewhere between 5 and 10% (the base case for this submission estimates 2.4% SoC OS at 5 years). P.176 of submission

Progression-free survival: ITT population Kaplan-Meier

- Pembrolizumab combination statistically significantly improves PFS vs Control



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Source: Company submission figure 15, p.59

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Subgroup analyses: Overall survival (ITT population)

Tumour proportion score (TPS) <1%

Treatment	N	Median OS (months)	OS rate at 6 months %	Hazard Ratio (95% CI)
Pembrolizumab combination	127	[redacted]	[redacted]	0.59 (0.38 to 0.92)
Control	63	[redacted]	[redacted]	

TPS 1-49%

Treatment	N	Median OS (months)	OS rate at 6 months %	Hazard Ratio (95% CI)
Pembrolizumab combination	128	[redacted]	[redacted]	0.55 (0.34 to 0.90)
Control	58	[redacted]	[redacted]	

TPS≥50%

Treatment	N	Median OS (months)	OS rate at 6 months %	Hazard Ratio (95% CI)
Pembrolizumab combination	132	[redacted]	[redacted]	0.42 (0.26 to 0.68)
Control	70	[redacted]	[redacted]	

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Source: Company submission, tables 19, 20 & 21, p.51, 52 and 53

Company state that analyses based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). Patients with PD-L1 not evaluable are not included in the subgroup analysis.

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KEYNOTE-189 Adverse Events

	Pembrolizumab combination		Control	
	n	%	n	%
Type of adverse event	405		202	
drug-related adverse events	[redacted]		[redacted]	
serious drug-related adverse events	[redacted]		[redacted]	
deaths due to a drug-related adverse event	[redacted]		[redacted]	

- Most commonly reported drug-related adverse events were nausea, anaemia, fatigue and neutropenia.
- Most commonly reported drug-related serious adverse event was febrile neutropenia
- 39 died due to an AE during the trial; 27 in the pembrolizumab combination and 12 in the control group.
- Most frequently reported immune-mediated AE resulting in death was pneumonitis (3 patients)

ERG comments:
- Incidence of AEs was consistently numerically higher in the pembrolizumab combination arm than the control arm.
- Do not agree with company that the incidence of AEs between arms are 'similar'.
- Accept that the difference in AE incidence is typically modest, and is judged to be clinically acceptable.

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† Determined by the investigator to be related to the drug. For patients who crossed over to pembrolizumab from the Control group, adverse events occurred after the first dose of cross phase are excluded. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Grades are based on NCI CTCAE version 4.03

No substantial differences in the types and frequencies of AEs were reported between the treatment groups, except for higher rates of diarrhoea (30.9%) and rash (20.2%) in the pembrolizumab combination versus control (21.3%) and (11.4%) respectively.

Company's Network meta-analyses (NMA) 1

- A phase 2, open-label, multi-cohort study, KEYNOTE-021, comparing pembrolizumab combination vs pemetrexed/platinum chemotherapy was available (Cohort G1) → company did not conduct a meta-analysis due to different study design and baseline characteristics however data from KEYNOTE-021 used in NMA.
- To compare pembrolizumab combination with the chemotherapy regimes outlined in the scope an NMA was conducted.
- Both fixed and random-effects NMAs were conducted based on constant HRs (assuming proportional hazards).
- NMA assessed the overall survival (OS) and progression-free survival (PFS) for pembrolizumab combination vs:
  - Platinum + pemetrexed
  - Platinum + gemcitabine
  - Platinum + vinorelbine
  - Platinum + docetaxel
  - Platinum + bevacizumab + paclitaxel
  - Platinum + paclitaxel

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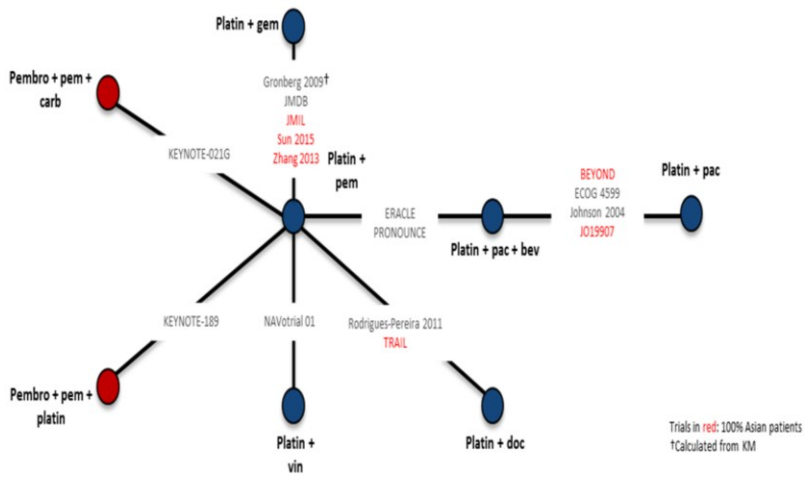
Company network for Overall survival



Source: Company submission; figure 26, p.83

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Company's NMA results: Overall survival

Pembrolizumab combination (KEYNOTE-189 data) demonstrated improved OS versus each of the comparator interventions of interest; the difference was statistically significant across all comparisons with the greatest benefit observed between pembrolizumab combination versus platinum + paclitaxel (HR 0.40, 95% CI 0.25, 0.63)

Platin + peme	**1.20 (0.91, 1.59)**	**0.89 (0.78, 1.04)**	**0.82 (0.60, 1.12)**	**1.03 (0.79, 1.33)**	**1.02 (0.63, 1.63)**	**1.68 (0.92, 3.09)**	2.03 (1.47, 2.85)
0.83 (0.63, 1.10)	Platin + doc	0.74 (0.55, 1.02)	0.68 (0.45, 1.02)	0.86 (0.58, 1.24)	0.84 (0.48, 1.48)	1.40 (0.71, 2.74)	**1.70 (1.11, 2.64)**
1.12 (0.96, 1.29)	1.34 (0.98, 1.83)	Platin + gem	0.92 (0.65, 1.28)	1.15 (0.84, 1.53)	1.14 (0.68, 1.85)	**1.88 (1.01, 3.52)**	**2.28 (1.58, 3.26)**
1.22 (0.90, 1.68)	1.47 (0.98, 2.23)	1.09 (0.78, 1.55)	Platin + pac	**1.26 (1.05, 1.49)**	1.24 (0.70, 2.19)	**2.06 (1.06, 4.08)**	**2.50 (1.59, 3.95)**
0.97 (0.75, 1.27)	1.17 (0.81, 1.72)	0.87 (0.65, 1.19)	**0.79 (0.67, 0.95)**	Platin + pac + bev	0.99 (0.57, 1.70)	1.64 (0.85, 3.16)	**1.98 (1.31, 3.03)**
0.98 (0.61, 1.59)	1.19 (0.68, 2.07)	0.88 (0.54, 1.46)	0.80 (0.46, 1.43)	1.01 (0.59, 1.74)	Platin + vin	1.65 (0.78, 3.54)	**2.01 (1.14, 3.66)**
0.60 (0.32, 1.08)	0.72 (0.37, 1.41)	**0.53 (0.28, 0.99)**	**0.49 (0.25, 0.95)**	0.61 (0.32, 1.17)	0.61 (0.28, 1.27)	Pembro + peme + carb	1.21 (0.60, 2.42)
0.49 (0.35, 0.68)	**0.59 (0.38, 0.90)**	**0.44 (0.31, 0.63)**	**0.40 (0.25, 0.63)**	**0.50 (0.33, 0.76)**	**0.50 (0.27, 0.88)**	0.82 (0.41, 1.66)	Pembro + peme + platin

Random-effects network meta-analysis based on constant hazard ratio assumption: HR (95% CI)
All bold values are statistically meaningful at the 0.05 significance level

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Source: Company submission; table 42, p.85

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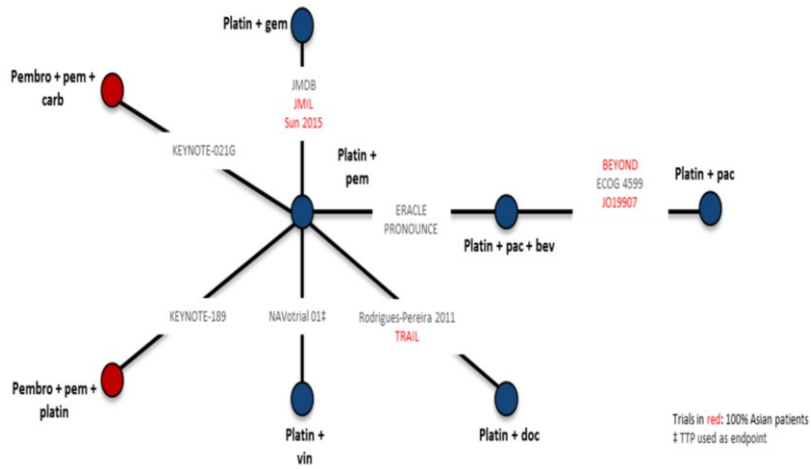
Pembrolizumab combination (based on KEYNOTE 189 data) performs better than all competing interventions, and no different to the other pembrolizumab containing regimen (based on KEYNOTE 021G data) with respect to both Overall survival and Progression-free survival.

Company's network for PFS



Source: Company submission; figure 27, p.86

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Company's NMA results: PFS

Pembrolizumab combination (KEYNOTE-189 data) demonstrated improved PFS versus each of the comparator interventions of interest; the difference was statistically significant across all comparisons with the greatest benefit observed between pembrolizumab combination versus platinum + paclitaxel (HR 0.28, 95% CI 0.13, 0.55)

Platin + peme	**0.99 (0.67, 1.46)**	**0.89 (0.66, 1.19)**	**0.54 (0.31, 0.85)**	**0.95 (0.64, 1.39)**	**0.86 (0.47, 1.55)**	**1.84 (0.94, 3.62)**	**1.92 (1.15, 3.16)**
1.01 (0.69, 1.49)	Platin + doc	0.90 (0.56, 1.46)	**0.54 (0.28, 0.98)**	0.96 (0.54, 1.64)	0.87 (0.43, 1.73)	1.86 (0.86, 3.98)	**1.94 (1.02, 3.59)**
1.12 (0.84, 1.51)	1.11 (0.68, 1.80)	Platin + gem	0.60 (0.33, 1.03)	1.07 (0.65, 1.70)	0.97 (0.50, 1.87)	**2.06 (1.00, 4.36)**	**2.16 (1.19, 3.85)**
1.86 (1.17, 3.19)	**1.85 (1.03, 3.63)**	1.65 (0.97, 3.06)	Platin + pac	**1.77 (1.33, 2.48)**	1.60 (0.76, 3.62)	**3.43 (1.54, 8.14)**	**3.56 (1.83, 7.49)**
1.05 (0.72, 1.57)	1.04 (0.61, 1.85)	0.93 (0.59, 1.55)	**0.57 (0.40, 0.75)**	Platin + pac + bev	0.91 (0.45, 1.88)	1.94 (0.91, 4.26)	**2.02 (1.08, 3.88)**
1.16 (0.65, 2.11)	1.15 (0.58, 2.34)	1.03 (0.53, 1.99)	0.63 (0.28, 1.31)	1.10 (0.53, 2.20)	Platin + vin	2.14 (0.88, 5.28)	**2.23 (1.04, 4.83)**
0.54 (0.28, 1.06)	0.54 (0.25, 1.16)	**0.48 (0.24, 0.99**	**0.29 (0.12, 0.65)**	0.52 (0.23, 1.09)	0.47 (0.19, 1.13)	Pembro + peme + carb	1.04 (0.45, 2.40)
0.52 (0.32, 0.87)	**0.52 (0.28, 0.98)**	**0.46 (0.26, 0.84)**	**0.28 (0.13, 0.55)**	**0.50 (0.26, 0.93)**	**0.45 (0.21, 0.97)**	0.96 (0.42, 2.24)	Pembro + peme + platin

Random-effects network meta-analysis based on constant hazard ratio assumption: HR (95% CI)
Base case = non squamous
All bold values are statistically meaningful at the 0.05 significance level

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Source: Company submission; table 43, p.87

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Pembrolizumab combination (based on KEYNOTE 189 data) performs better than all competing interventions, and no different to the other pembrolizumab containing regimen (based on KEYNOTE 021G data) with respect to both Overall survival and Progression-free survival.

Company's NMA 2: Pembrolizumab combination vs pembrolizumab monotherapy

- To estimate the treatment difference between pembrolizumab combination and pembrolizumab monotherapy an NMA of OS and PFS outcomes was conducted, based on data from KEYNOTE-189 and KEYNOTE-021.
- The NMA shows a numerical benefit in OS for pembrolizumab combination vs pembrolizumab monotherapy; however, the difference was not statistically significant; the HR for the comparison is [redacted].
- The results of the NMA of pembrolizumab combination vs. pembrolizumab monotherapy on PFS shows a numerical benefit in PFS for pembrolizumab combination vs pembrolizumab monotherapy, however, the result was not statistically significant [redacted].

ERG comments:

- Agrees with decision (and broadly the methodology used) to carry out an NMA of combination versus monotherapy as a separate analysis - likely to provide more robust evidence

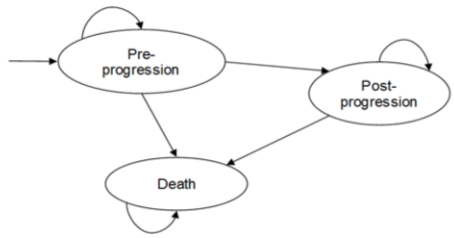
ERG critique: clinical effectiveness

Strengths	Weakness
Indirect treatment comparison (ITC) includes all relevant interventions for this patient group, and is broadly appropriate with relevant NICE DSU TSD recommendations.	Direct head-to-head trials were not available for pembrolizumab combination in comparison with most other interventions available for this treatment group, including platinum and gemcitabine and platinum and vinorelbine, which are commonly used in the UK.
An additional ITC comparing pembrolizumab combination for a sub-population of patients is presented, and conducted using individual patient data (IPD) and patient matching methods, which were judged to be of high quality.	The main ITC analysis included trials with significant heterogeneity between studies.
The direction of the effect for pembrolizumab combination is consistent between the 2 RCTs	Evidence was not presented for a number of outcomes required by the NICE scope for interventions not evaluated in direct head-to-head trials

ERG pooled the 2 RCTs results and undertook a meta-analysis: Findings support those of KEYNOTE-189 and add credibility to the consistency of the findings across settings.

Cost effectiveness

Company model structure



Factor	Chosen values
Model design	Three-state partitioned survival
Time horizon	20 years
Cycle length	1 week
Half cycle correction	Yes
Treatment waning effect	No
Discount rate	3.5%
Perspective	NHS and Personal and Social Services (PSS)
Stopping rule	2-years
Treatment effect	Lifetime

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Source: Company submission; figure 34, p.117

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Clinical evidence was derived from KEYNOTE-189

Quality-adjusted life years (QALYs) estimated using time-to-death utilities from EQ-5D data

For OS, Kaplan-Meier data was used during the first 28 weeks, on the basis of the changes to cumulative hazards, and an exponential model was fitted afterwards following standard parametric approaches.

For PFS, Kaplan-Meier data was used during the first 21 weeks, to reflect the protocol driven fall in PFS observed alongside the initial radiologic assessments. This was followed by extrapolating using a Weibull distribution.

ERG comments: Company model structure

- Structure is not a 3 health state partitioned survival model:
  - uses four states to estimate utility, based on the OS outcome, using a time-to-death approach
  - costs are based on treatment intent
  - progression status does not drive the base case
- Subsequent therapy is modelled only as far as second-line
- Structure used in TA447/531 pembrolizumab monotherapy 1st line

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Company's overall survival extrapolations (1)

- 2-phase piecewise model chosen (proportional hazards did not hold)
- For both arms, a piecewise model was fitted using the Kaplan-Meir data up to week 28 followed by an exponential distribution
- 2 additional cut offs explored in sensitivity analyses (week 18 and week 38)

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Source: Company submission; Appendix L, figure L.4, p.229 and 230

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Company's overall survival extrapolations (2)

Company's OS estimates for 3 data cut-offs

	Week 28				Week 38				Week 18			
Fitted	PC		SoC		PC		SoC		PC		SoC	
Function	5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr	5yr	10yr
Exponential	[redacted]											
Weibull	[redacted]											
LogNormal	[redacted]											
LogLogistic	[redacted]											
Gompertz	[redacted]											
GenGamma	[redacted]											

Source: Company submission; Appendix L, table L.3, p.234

ERG comments: Overall survival extrapolations (1)

- In KEYNOTE-189, median survival is only reached in the SoC arm → considerable uncertainty in the OS extrapolations
- The exponential distribution provides the *worst* statistical fit for the SoC arm of the distributions considered and results in clinically implausible OS estimates at 5 and 10 years
- Proportional hazards assumption did not hold→ exponential distribution inappropriate
- According to DSU guidance the company incorrectly:
  - Used only one cut-point of the 3 identified → *…exponential distributions with different rate parameters should be fitted to each of the time periods identified as having different (constant) hazard rates."[DSU TSU14].*
- Other distribution choices do not require the use of cut-offs in this way → *"Models other than the exponential also allow for non-constant hazards over time"*
- The use of the naïve KM curve to week 28: this is trial data so sample data. It should be used to inform the trend of the whole population, which should be a smooth trend
- Therefore ERG in its base case followed TSD14 guidance and separately fitted the log-logistic curve from Week 0 to both arms. Based on:
  - consistently good statistical fit of the curve to the observed data (AIB and BIC),
  - external face validity of SoC 5 and 10 year OS estimates (8% and 2.88%).

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ERG comments: Overall survival extrapolations (2)

- Comparison of overall survival predictions between company model, ERG preferred methods and TA447/TA531
- In TA447/531 committee accepted 8-11% as a reasonable OS for SOC

Source/Population	5-year OS	10-year OS
ID1173: Company's SoC OS predictions: KM up to 28 weeks + exponential	[redacted]	[redacted]
ID1173: ERG SOC arm OS predictions: Log-logistic from week 0	[redacted]	[redacted]
ERG preference within NICE TA447/531: SoC for untreated PD-L1-positive mNSCLC	9.60%	1.50%

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Company modelling assumptions: HRQoL

- Company modelled EQ-5D data from KEYNOTE-189
- Pooled the values for both arms
- Difference between pre and post-progression utilities is small, indicating that progression status is unlikely to be sufficiently reflective of changes in quality of life → time to death (TTD) approach used
- HRQoL decreased over time as patients progressed closer to death → to capture HRQoL more appropriately, the TTD utility values were further divided according to four categories:
  - ≥ 360 days
  - between 180 and 360 days
  - between 30 and 180 days
  - < 30 days
- 2 company scenarios:
  - Using progression-based utilities as an alternative approach to estimate QALYs based on KEYNOTE-189
  - Using utilities derived per treatment arm instead of pooled utilities from KEYNOTE-189:
    - ❖ With the time to death approach
    - ❖ With the progression-based approach

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ERG comments: HRQoL

- In TA447/531 utilities are based on TTD alone, with four HRQoL health states considered → same approach used by company here
- TTD method supported by clinical opinion gathered by the ERG that HRQoL in this population correlates better using this approach than occurrence of first progression
- ERG in its scenarios analyses explored utility values based on:
  - progression status
  - TTD with a utility decrement associated with progressive disease applied for progressed patients
  - progression status with a utility decrement associated with TTD of less than 360 days applied for patients with less than 360 days to live

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Company modelling assumptions: Subsequent treatments

- In the company base case it was assumed 43.3% of patients who discontinue 1st line therapy in the pembrolizumab combination arm, and 56.0% of patients in the SoC arm, receive second line (2L) pembrolizumab as per KEYNOTE-189
- the company adjusted the proportions to exclude the 7% patients who had pembrolizumab monotherapy *after* it had been discontinued first line (1L) in the combination arm of KEYNOTE-189

ERG comments:

- Third and subsequent lines of therapy not included in company base case
- There is uncertainty about adjustment methods used by the company in their calculation of the up-take and the distribution of therapies at second-line
- ERG in its scenario analyses explored unadjusted estimates from KEYNOTE-189 of the proportion of patients taking-up 2L treatment after 1L discontinuation (30.5% for PC, 46.6% for SoC)

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Company modelling of pembrolizumab combination vs other comparators

- For comparison with platinum plus chemotherapy (gemcitabine, vinorelbine, docetaxel and paclitaxel) effect sizes not derived from separately fitted parametric distributions but hazard ratios applied to the baseline effectiveness of the pembrolizumab combination strategy.
- Same method for OS used to determine PFS for comparator strategies, with PFS from the fitted distribution for the pembrolizumab combination arm raised to the power of a constant PFS hazard ratio in each model cycle → although PFS not used in the model

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Company modelling of subgroups

Strong expressers of PD-L1 (≥50% TPS)

- 2 comparisons of treatment strategies vs pembrolizumab combination therapy carried out for sub-population of non-squamous patients strongly expressing PD-L1: for SoC and for pembrolizumab monotherapy therapy.
- For pembrolizumab combination: same approach taken as in main comparison, but with the distributions fitted only to the sub-population data. Same selection of distributions and cut-off points made for consistency with the base case results. However, an exponential distribution has been chosen to model ToT for SoC rather than a Weibull distribution, which has been used for the overall population.
- OS for pembrolizumab monotherapy calculated by applying a constant hazard ratio to OS for pembrolizumab combination therapy. This hazard ratio is derived from the ITC of pembrolizumab combination versus pembrolizumab monotherapy for non-squamous patients with TPS ≥ 50%, using the Bucher method with population adjustment.
- For PFS the KM data from KEYNOTE-024 was used directly for ToT of the pembrolizumab monotherapy: parametric distribution was not fitted, as is the case for the pembrolizumab combination therapy using the KM data from KEYNOTE-189. No explanation given for this.

Company's base case results

- Results include the price of pembrolizumab with a confidential commercial access arrangement.
- Results do not include confidential price discount for pemetrexed maintenance therapy → presented in part 2

Base-case results vs SoC

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£42,980	1.34	0.92	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£41,344	0.89	**£46,568**

Source: Company submission; table 86, p.161

Probabilistic results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£43,527	0.93	-	-	-
Pembrolizumab combination	£84,870	1.81	£41,344	0.89	**£46,674**

Source: Company submission; table 88, p.163

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Company's results for pembrolizumab combination vs chemotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
Platinum + Paclitaxel	£25,368	1.09	0.73	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£58,956	1.08	£54,654
Platinum + Docetaxel	£27,391	1.55	1.08	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£56,932	0.73	£78,242
Platinum + Gemcitabine	£26,572	1.19	0.80	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£57,752	1.01	£57,064
Platinum + Vinorelbine	£27,663	1.33	0.91	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£56,661	0.90	£63,262
Platinum + Pemetrexed	£42,247	1.32	0.90	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£42,077	0.90	£46,504

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Source: Company submission; table 87, p.162

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Company subgroup analysis (1)

ICER results for people with TPS ≥ 50% (discounted)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£41,882	1.38	0.95	-	-	-
Pembrolizumab combination	£102,480	3.20	2.35	£60,599	1.39	£43,468

Source: Company submission; table 90, p.171

ICER results for people with TPS 1% ≥ TPS ≤ 49% (discounted)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£45,084	1.42	0.97	-	-	-
Pembrolizumab combination	£87,429	2.78	2.03	£42,346	1.05	£40,139

Source: Company submission; table 92, p.173

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Company subgroup analysis (2)

ICER results for pembrolizumab combination vs. SoC for patients with TPS <1% with crossover adjustment (discounted)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC (2 stage)	£26,432	1.15	0.77	-	-	-
Pembrolizumab combination	£62,762	1.85	1.30	£36,330	0.53	**£68,563**
SoC (RPSFT)	£26,567	1.18	0.80	-	-	-
Pembrolizumab combination	£62,762	1.85	1.30	£36,195	0.51	**£71,472**
SoC (IPCW)	£27,072	1.29	0.88	-	-	-
Pembrolizumab combination	£62,762	1.85	1.30	£35,691	0.42	**£84,501**

Source: Company submission; table 93, p.174

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Company scenario analysis (discounted)

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
UK-specific BSA values (unadjusted by sex distribution)	£41,263	0.89	£46,477
OS cut-off – 38 weeks	£40,422	0.72	£56,045
OS cut-off – 18 week	£42,080	1.01	£41,554
PFS cut-off – 11 weeks	£41,344	0.89	£46,568
PFS cut-off – 31 weeks	£41,344	0.89	£46,568
No half cycle correction	£41,302	0.89	£46,522
SoC as for UK market shares	£41,353	0.89	£46,578
Utilities – Progression based (pooled)	£41.344	0.79	£52,499
Utilities – Time to death (per treatment arm)	£41,344	0.88	£46,962
Utilities – Progression-based (per treatment arm)	£41,344	0.86	£47,868
Utilities – Time to death by Chang et al (2017)	£41,344	1.01	£40,840
No age-related disutilities	£41,344	0.90	£45,743
Assuming treatment effect stops at 5 years	£40,665	0.78	£52,333
Alternative OS distribution: LogNormal	£41,483	0.82	£50,399
Dose regimen for 2L pembrolizumab	£44,200	0.89	£49,785
Assuming a RR of 0.44 to estimate a 5 year OS for SoC of 10%	£45,408	1.54	£29,501
Inclusion of 2L pembrolizumab use as per trial proportions	£42,145	0.89	£47,470

Scenario analyses showed that the most sensitive scenarios relate to the chosen cut point for to start the parametric extrapolation from for OS with week 18 and 38 alternatives.

It should be noted that there is no evidence that the treatment effect stops.

ERG base case

- **ERG preferred base case included:**
  - Coding correction (% patients utilising 2nd line therapy; half-cycle correction)
  - Log-logistic parametric distributions for OS extrapolation from week 0
  - An adjustment for background mortality (due to the relatively short length of the trial compared to the model time horizon)
  - treatment effect is discontinued at 5 years (effect unlikely to remain over 20 year time-horizon)
  - Excluding cost of PD-L1 testing (now routine in the NHS so all in model should receive)
- **ERG scenarios included:**

Estimation of long term OS	Estimation of utilities	Estimation of high cost drug consumption
Exponential from week 0, 18, 28 and 38	TTD (Chang 2017)	Dose intensity (actual vs expected)
Log-Normal and Log-Logistic from week 0	ToT as proxy for PS	Proportion taking up 2nd line treatment after 1st line discontinuation
Generalised Gamma/Weibull/Gompertz	Combined TTD and classic progression	Less pembrolizumab at 2nd line in SoC strategy

ERG base case results

The results presented include the commercial access agreements for pembrolizumab. They do not include the confidential discount for pemetrexed maintenance therapy (presented in part 2)

Base-case results vs main comparator SoC (deterministic)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£44,409	1.74	1.22	-	-	-
Pembrolizumab combination	£86,863	3.21	2.35	£42,454	1.13	**£37,622**

Source: ERG report; table 103, p.262

Probabilistic results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£44,990	1.23	-	-	-
Pembrolizumab combination	£87,330	2.35	£42,340	1.11	**£38,075**

Source: ERG report; table 104, p.262

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ERG results for pembrolizumab combination vs other comparators

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pembrolizumab combination	£86,863	3.21	2.35				
Platinum + Gemcitabine	£27,292	1.36	0.93	£59,571	1.85	1.43	£41,710
Platinum + Vinorelbine	£28,917	1.91	1.35	£57,946	1.31	1.00	£57,939
Platinum + Docetaxel	£28,662	1.57	1.10	£58,201	1.64	1.26	£46,337
Platinum + Paclitaxel	£25,937	1.23	0.83	£60,926	1.99	1.52	£40,096

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Source: ERG report; table 105, p.263

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ERG Subgroup analysis (1)

Base case ICER results for people with TPS ≥ 50% (deterministic)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£106,292	4.19	3.11			
Pembrolizumab combination	£44,546	1.82	1.29	£61,746	1.82	£33,873
Source: ERG report; table 107, p.264						

Base case ICER results for people with TPS 1% ≥ TPS ≤ 49% (deterministic)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£88,511	3.20	2.34			
Pembrolizumab combination	£47,711	1.72	1.20	£40,800	1.14	£35,920
Source: ERG report; table 108, p.264						

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ERG Subgroup analysis (2)

Base case ICER results for people with TPS ≤ 1% (deterministic)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained
SoC	£66,904	2.45	1.77			
Pembrolizumab combination	£42,826	1.66	1.17	£24,078	0.60	£40,192
Source: ERG report; table 109, p.264						

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Impact on the ICER of additional clinical and economic analyses undertaken by ERG

	Cost per QALY gained (ICER)	Individual impact of change	%	Cumulative impact of change	Cumulative %
Company base case	£46,568				
ERG's corrections to company coding	£46,103	-£465	-1%		
ERG base case (including corrections and revisions)	£37,622	-£8,946	-19%		
Impact of revisions on company base case:					
(1) Applying background mortality	£47,814	£1,246	3%	£47,814	3%
(2) PD-L1 test cost set to zero	£46,051	-£517	-1%	£47,766	3%
(3)Log-logistic parametric function fitted for OS (both strategies, applied from week 1)	£31,463	-£15,105	-32%	£33,930	-27%
(4) Long-term waning of pembrolizumab combination from 5 years	£51,802	£5,234	11%	£37,622	-19%

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The results presented include the tentative commercial access agreements (CAAs) for pembrolizumab. They do not include existing agreements for comparators.

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ERG Scenario analyses: OS extrapolations

Company base case	Exponential from W0 (4th best stat fit to SoC KM): 5-yr OS= 3.2%; 10-yr OS= 0.1%	Exponential from W18: 5-yr OS= 2.0%; 10-yr OS= 0%	Exponential from W28 5-yr OS= 2.4%; 10-yr OS= 0.1% [Company preferred)]	Exponential from W38: 5-yr OS= 6.1%; 10-yr OS= 0.5%
£46,568	£50,569	£48,724	£53,208	£62,111
Log-Normal W0 (1st best stat fit to SoC KM): 5-yr OS= 9.5%; 10-yr OS= 3.1%	Log-Logistic (W0) (2nd best stat fit to SoC KM): 5-yr OS= 8.6%; 10-yr OS= 3.4% [ERG preferred]	Generalised Gamma (3rd best stat fit to SoC KM): 5-yr OS= 8.5%; 10-yr OS= 2.4%	Weibull (5th best stat fit to SoC KM: 5-yr OS= 1.0%; 10-yr OS= 0%	Gompertz (6th best stat fit to SoC KM): 5-yr OS= 2.7%; 10-yr OS= 0%
£33,732	£37,622	£57,045	£53,663	£68,900

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End of life considerations

Source (time in months)	Strategy		
	SoC	Pembrolizumab combination	Increment (life extension)
Mean estimated by company base case	16.61	32.17	15.56
Mean estimated by ERG base case	22.73	43.68	20.96
Mean from ERG base case of TA531	*23.4*	*38.0*	*14.6*
Median in KEYNOTE-189	11.3 (95%CI, 8.7-15.1)*	Not reached	NA
Median in KEYNOTE-024	14.2	30.0	15.8
Estimate(s) offered by the company	11.3* and 9.9 - 13.9 from other studies	13.9	NA

*KEYNOTE-189 median OS trial chemotherapy arm.

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SoC = Standard of Care

End of life consideration: ERG comments

- Considerable uncertainty around the extrapolation of overall survival beyond study follow-up
  - Median OS was not reached in the pembrolizumab combination arm of KEYNOTE-189
- Evidence from both KEYNOTE-189 and the company and ERG economic models suggest that the average overall survival on standard of care treatment is under 24 months; and the life extension offered by pembrolizumab combination is over 3 months.
- Pembrolizumab combination in this setting and population probably fulfils the criteria for end-of-life status.
- Whilst estimates of the extension to life are not robust the various point estimates are far in excess of the requirement.

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Key clinical effectiveness issues

- Are the comparators used by the company relevant to NHS clinical practice?
  - Company excluded pemetrexed maintenance therapy with chemotherapy regimens
- Are the results of the company's ITC appropriate given the heterogeneity in the included studies?

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Key cost-effectiveness issues

- Is the company's model structure appropriate?
- What is the most appropriate method for extrapolating OS?
  - Company = KM with 28 week cut-off then exponential distribution for both arms
  - ERG = fully fitted log-logistic curves from weeks 0 for both arms
  - Does the uncertainty around the extrapolation of survival beyond short follow-up periods influence decision making?
- Is a 2-year stopping rule appropriate
  - SPC does not include 2 years stopping rule
- Is a life-time treatment effect appropriate?
- What is the most plausible ICER?

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Equality and Innovation

Equality

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

Innovation (company view)

- The clinical efficacy and safety data show that pembrolizumab, when combined with chemotherapy, offers benefit in PFS and OS for all lung cancer patients, regardless of PD-L1 expression levels, with an acceptable tolerability profile.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer [ID1173]

Document B

Merck Sharp & Dohme

July 2018

File name	Version	Contains confidential information	Date
MSD Submission Pembrolizumab (ID1173) Document B.5 ACiC - Appendices	V1	Yes	06/07/2018

Introduction to this document

This document represents the MSD UK evidence submission for the review of ID1173: Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer.

Contents

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List of Figures

Abbreviations

AE – adverse events

AEOSI – adverse events of special interest

ALK – anaplastic lymphoma kinase

ASaT – all-patients-as-treated

BICR – blinded independent central review

CI – confidence interval

CR – complete response

CSR – clinical study report

DOR – duration of response

ECOG – Eastern cooperative oncology group

EGFR – epidermal growth factor receptor

EQ-5D – EuroQol 5 Dimension

HR – hazard ratio

HRQoL – health-related quality of life

ITT – intention-to-treat

IV – intravenous

KM – Kaplan-Meier

MA – marketing authorisation

NSCLC – non-small cell lung cancer

ORR – objective response rate

OD – overall survival

PD – progressive disease

PD-1 – programmed cell death 1 (receptor)

PD-L1 – programmed cell death 1 ligand 1

PD-L2 – programmed cell death 1 ligand 2

PFS – progression-free survival

PR – partial response

PRO – patient-reported outcome

Q3W – every 3 weeks

QoL – quality of life

RECIST 1.1 – response evaluation criteria on solid tumours, version 1.1

RCT – randomised controlled trial

SAE – serious adverse event

SD – standard deviation

SLR – systematic literature review

TPS – tumour proportion score

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

B.1.1 Decision problem

Details of the decision problem are presented in Table 1. The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC)	Adults with untreated metastatic non-squamous NSCLC lacking EGFR and/or ALK mutation	In line with the licence, based on the data from the supporting clinical trial KEYNOTE-189
Intervention	Pembrolizumab plus chemotherapy	Pembrolizumab in combination with pemetrexed and platinum (carboplatin or cisplatin) chemotherapy	In line with the licence

Comparator(s)	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only)
	  • with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment
	• 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
	• Pembrolizumab (PD-L1-positive only with TPS≥50%)
		As per final scope issued by NICE	Data from KEYNOTE-189 will provide comparative efficacy of pembrolizumab in combination with pemetrexed and platinum versus pemetrexed plus platinum alone.
			Data for comparative efficacy of pembrolizumab in combination with pemetrexed and platinum versus remaining comparators will be derived from indirect treatment comparison (ITC).

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	As per final scope issued by NICE	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	As per final scope issued by NICE	
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on cancer histology and biological markers (PD-L1).	The following PD-L1 subgroups have been considered: • TPS <1%, ≥1%, 1-49%, ≥50%	

B.1.2 Description of the technology being appraised

The technology being appraised is pembrolizumab in combination with pemetrexed and platinum-based chemotherapy (referred to henceforth as pembrolizumab combination), as described in Table 2 below:

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®) in combination with pemetrexed and platinum chemotherapy (pembrolizumab combination)
Mechanism of action	Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment
Marketing authorisation/CE mark status	Pembrolizumab was granted marketing authorisation in May 2015 by the European Medicines Agency, covering all European Markets including the UK.[2]
Indications and any restriction(s) as described in the summary of product characteristics	Pembrolizumab (KEYTRUDA®) currently has a marketing authorisation (MA) covering the following indications as per the SmPC[2]: ▪ KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults (MA received May 2015). ▪ KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations prior to receiving KEYTRUDA (MA variation received August 2016). ▪ KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations (MA variation received January 2017). [redacted]

	[redacted] ▪ KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin's lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV (MA variation received May 2017). ▪ KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (MA variation received August 2017). ▪ KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy (MA variation received August 2017). Contraindications included in the SmPC are listed as hypersensitivity to the active substance or to any of the following excipients: ▪ L-histidine ▪ L-histidine hydrochloride monohydrate ▪ Sucrose ▪ Polysorbate 80 ▪ Water for injections
Method of administration and dosage	KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks. The recommended dose of KEYTRUDA is: [2] • 200 mg for NSCLC that has not been previously treated with chemotherapy (when administered as monotherapy or in combination with pemetrexed and platinum chemotherapy), for cHL or for urothelial carcinoma. • 200 mg for NSCLC that has been previously treated with chemotherapy or for melanoma. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.
Additional tests or investigations	PD-L1 testing for patients with NSCLC[2] • Patients with NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test PD-L1 testing is an immunohistochemistry (IHC) test. IHC is part of routine pathology practice. MSD has supported the development of PD-L1 testing reference centres, which provide the capacity to enable the tumours from patients with advanced NSCLC to be tested for PD-L1 status. After the NICE recommendations for use of pembrolizumab for patients with advanced NSCLC in both first and second line, PD-L1 testing of all patients

	with advanced NSCLC has become part of routine clinical practice and PD-L1 testing has been added to the current panel of EGFR and ALK tests for NSCLC. [3]
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial. [redacted] Based on KEYNOTE-189 trial, the average time on therapy per patient is [redacted] days, equivalent to [redacted] cycles received per patient treated with pembrolizumab combination during a course of treatment.[4] The average cost per treatment course is [redacted] list price
Patient access scheme (if applicable)	[redacted]

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

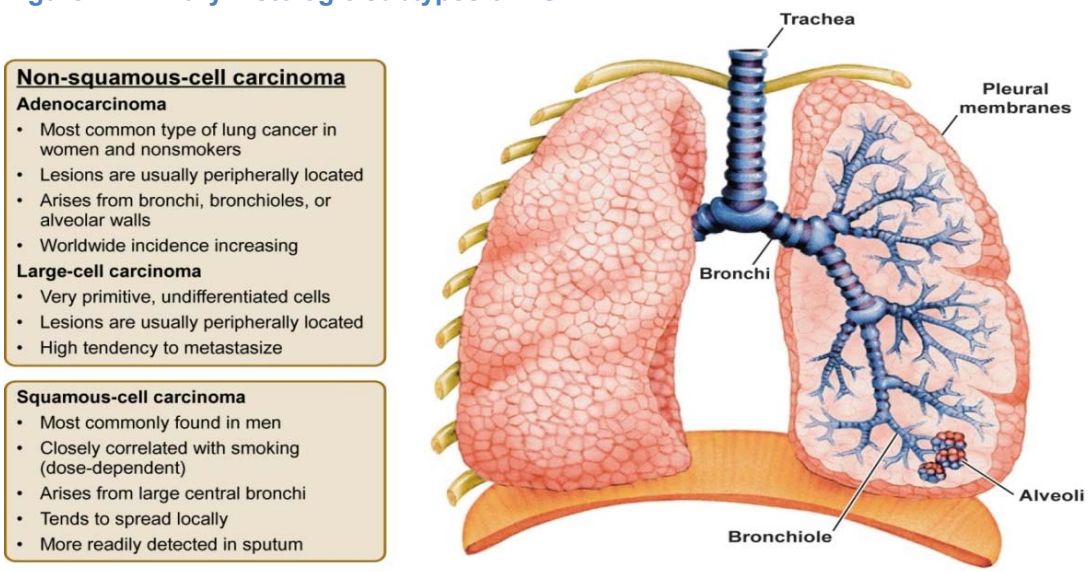
B.1.3.1 Lung cancer: an overview

Disease subtypes and classification

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).[6]

NSCLC accounts for up to 85-90% of lung cancer cases in the UK[7] 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%).[8, 9] The histological subtype of NSCLC correlates generally with the cancer's site of origin, reflecting the variation in respiratory tract epithelia (**Figure 1**). 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.[6, 10] Large cell carcinomas tend to occur peripherally and are defined as poorly differentiated lung carcinomas 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 as they often spread to distant sites early in their course.[6, 10]

Figure 1: Primary histologic subtypes of NSCLC



NSCLC=non-small cell lung cancer. Source: Adapted from Teaching Times, 2016[11].

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).[12] This information is combined to assign an overall stage of 0, I, II, III, or IV as defined below:

- Stage 0: the cancer is found only in the top layers of cells lining the air passages
- Stages I and II: an invasive cancer has formed but has not spread to lymph nodes or distant sites
- Stage III: the cancer has spread to lymph nodes in the middle of the chest, also described as locally advanced disease. Stage III has two subtypes:
    - Stage IIIA: the cancer has spread only to lymph nodes on the same side of the chest where the cancer started
    - Stage IIIB: the cancer has spread to the lymph nodes on the opposite side of the chest, or above the collar bone.
- Stage IV: the cancer has spread to distant lymph nodes or to other organs such as the liver, bone, or brain.

Molecular biomarkers

Lung cancer cells harbour multiple chromosomal abnormalities, including mutations, amplifications, insertions, deletions, and translocations.[6, 9, 13] 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%),[14-17] 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%)),[17, 18] and translocations involving anaplastic lymphoma kinase (ALK) (2-7%).[17, 19, 20] ALK translocations occur most commonly in patients with non-squamous NSCLC.[17]

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; pembrolizumab studies have shown that the percentage of patients with advanced NSCLC whose tumours express PD-L1 is between 60% and 66%. [4, 21, 22] Pembrolizumab is a highly selective, humanised monoclonal

antibody that targets programmed death 1 (PD-1) and 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.[21]

Incidence and prevalence

Lung cancer is the second most common cancer for both males and females in England. In 2016, there were a total of 36,761 cases registered, of which 88.5% were NSCLC and 53% were diagnosed with Stage IV disease.[23, 24]

The age-standardised incidence rate for lung cancer has decreased in males in recent years from 127.9 in 1995 to 89.8 cases per 100,000 males in 2016, whilst female age-standardised rates have increased in this same period, from 51.4 in 1995 to 65.5 cases per 100,000 females in 2016.[25] As the majority of lung cancer cases are related to smoking, the difference is thought to be due principally to changes in smoking prevalence in men and women in recent decades. While the age-specific incidence of smoking-related lung cancer is falling nationally as smoking prevalence falls, there has been a steady rise in the total number of lung cancer patients, partly owing to the ageing population.[23]

Diagnosis, treatment and prognosis

Diagnosis of lung cancer is based on physical examination, symptoms, smoking history and standard tests including blood tests and imaging analyses. Where lung cancer is diagnosed, pathological diagnosis of tissue biopsies is conducted to provide details of cancer subtype, disease staging and molecular markers.[26]

While NSCLC is potentially curable with surgery when diagnosed at an early stage, the majority of patients are diagnosed at an advanced stage of disease (stages IIIB-IV) when curative surgical treatment is no longer viable and prognosis is poor.[27]

Treatment for patients with advanced NSCLC aims to prolong OS and improve HRQoL by improving symptoms. The clinical care pathway for patients with advanced non-squamous NSCLC is determined by the tumour histological subtype, the molecular biomarkers present and the performance status of the patient. Section B.1.3.2 provides details of the clinical pathway of care for advanced NSCLC patients in the UK.

In the UK, lung cancer is the most common cause of cancer death. Approximately 35,620 people died from lung cancer in the UK, accounting for 21% of all cancer deaths in 2016.[28]

Based on 2010-2011 data, approximately 10% of lung cancer patients (across all stages of disease) in England and Wales survive for five years or more post diagnosis. Only 5% of lung cancer patients survive for 10 years or more post diagnosis.[7]

Survival is strongly related to the stage of disease at diagnosis. The most recent UK data from the National Cancer Registration and Analysis Service – Public Health England (based on diagnoses from 2012 to 2014) indicate one-year survival of 15% for men and 19% for women diagnosed with Stage IV lung cancer.[29] In an analysis of 2006-2011 data from the UK National Lung Cancer Audit, 5-year survival of patients diagnosed at stage IV was reported at only 3%. [30] However with the changing landscape of metastatic NSCLC with immunotherapy being available at first and second lines of treatment, the true value of 5 year survival is uncertain.

The number of expected cases of non-squamous NSCLC for 2019 in England is 25,682; of which 12,327 are expected to be stage IV. In total, 4,981 of these patients are expected to be eligible for treatment with pembrolizumab in combination with chemotherapy (Table 3). (See Budget Impact Model Document for additional details).

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

	2019	2020	2021	2022	2023
Cases of lung cancer in England	37,204	37,353	37,502	37,652	37,803
Cases of confirmed NSCLC over total lung cancer	32,925	33,057	33,189	33,322	33,455
Cases of confirmed non-squamous NSCLC over total lung cancer	25,682	25,785	25,888	25,991	26,095
Estimated number of incident NSCLC patients stage IV	12,327	12,377	12,426	12,476	12,526
Estimated number of NSCLC patients stage IV to be treated that are PS 0-1	6,641	6,668	6,695	6,721	6,748
Cases of non-squamous NSCLC that are EGFR/ALK negative (ITT population)	4,981	5,001	5,021	5,041	5,061
Total TPS>50% PD-L1 positive patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total 1≤TPS≤49% PD-L1 positive patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total TPS<1% PD-L1 negative patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TPS – tumour proportion score

B.1.3.2 UK clinical care pathway

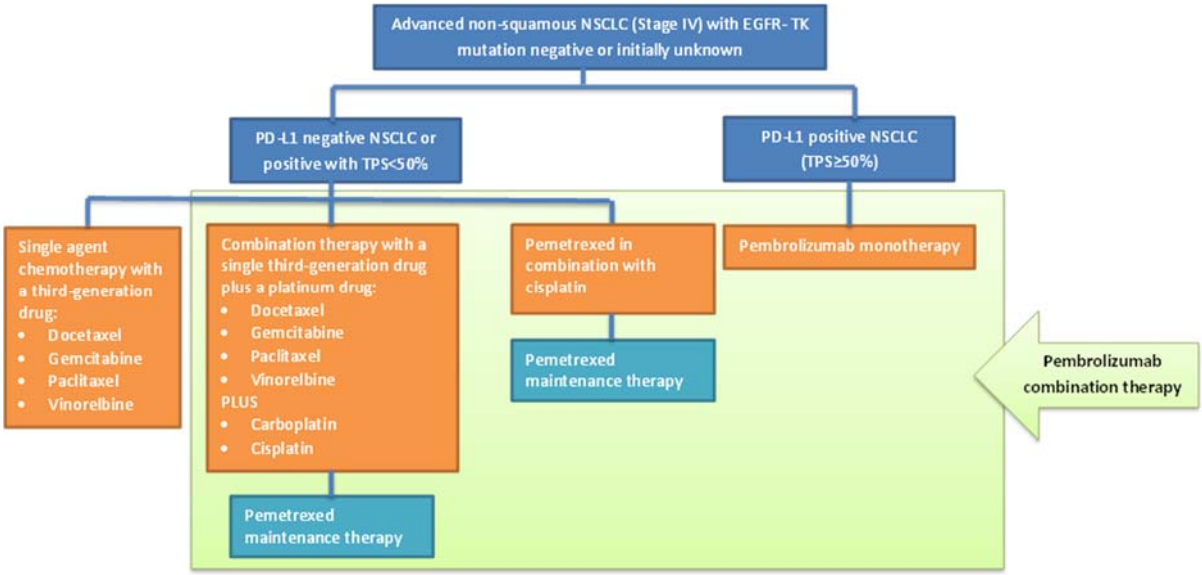
The clinical care pathway for patients with advanced NSCLC is determined by the histological subtype and genotype of the tumour, and the performance status of the patient.

Figure 2 depicts the first line treatment options which have been recommended by NICE for use in the UK, as per NICE Clinical Guideline [CG121], Lung Cancer; diagnosis and management.[31] The figure also includes the proposed positioning of pembrolizumab in combination with pemetrexed and platinum chemotherapy, as a first-line treatment option for all adult patients with advanced non-squamous NSCLC tumours that have no EGFR or ALK mutations, regardless of PD-L1 status. It is envisaged that pembro chemo combination therapy would displace first line use of platinum-doublet chemotherapy alone, single agent chemotherapy or pemetrexed in combination with cisplatin (the latter is applicable for adenocarcinoma patients only) as well as pembrolizumab monotherapy (pembrolizumab monotherapy) for patients with high levels of PDL1 expression (defined as tumour proportion score (TPS) of at least 50%).

According to current NICE guidance, patients whose tumours test positive for anaplastic lymphoma kinase (ALK) mutation are eligible to receive first-line treatment with crizotinib (TA406).[32] 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)[33], erlotinib (TA 258)[34] or gefitinib (TA 192)[35].

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 is recommended as a treatment option by NICE; 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 such combination may be offered single-agent chemotherapy with a third-generation drug.[31] Pembrolizumab monotherapy is also recommended in routine commissioning for patients with tumours expressing PD-L1 with TPS ≥50%.[36] Since the launch of pembrolizumab, PD-L1 test requisition has become incorporated into hospital treatment pathways and protocols, resulting in a significant increase in the volume of PD-L1 testing across the UK. Pemetrexed in combination with cisplatin is also recommended if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.[37]

Figure 2: First-line treatment diagram for advanced NSCLC including pembrolizumab combination positioning. [38]



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

European Society for Medical Oncology (ESMO)[39]

ESMO last published clinical practice guidelines concerning the diagnosis, treatment and follow-up of metastatic NSCLC in 2016. The landscape of NSCLC has changed significantly since then, with immunotherapies now being considered standard of care in a number of sub-populations of the disease.

For patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2, the recommended first-line treatment option is platinum-based doublet chemotherapy; the guideline 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. 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[22] pembrolizumab 2 mg/kg Q3W is specified as an appropriate option in pre-treated patients with platinum-pre-treated, advanced NSCLC expressing PD-L1.

National Comprehensive Cancer Network (NCCN) (2017)[40]

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

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

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

B.1.4 Equality considerations

We do not envisage any equity or equality issues with the use of pembrolizumab combination in the treatment of adults with untreated metastatic non-squamous NSCLC lacking EGFR and/or ALK mutation.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D1.1 for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

A systematic literature review (SLR) was conducted to identify all relevant published and unpublished randomised control trials (RCTs) and non-randomised clinical trials (non-RCTs) relating to pembrolizumab in combination with chemotherapy and relevant comparators as per the final scope described in Table 1. As the manufacturer of pembrolizumab, MSD is aware of all relevant clinical trials for pembrolizumab in combination with chemotherapy in this indication.

The full SLR methodology is presented in Appendix D1.1.2, while results are summarised in Section B.2.9. In total, 17 relevant RCTs were identified and no relevant non-RCTs: 15 trials reporting comparators included in the decision problem, and 2 studies reporting pembrolizumab in combination with chemotherapy: KEYNOTE-021[41] and KEYNOTE-189[4].

The clinical effectiveness evidence presented in this submission is focused on KEYNOTE-189, the pivotal phase III RCT assessing the safety and efficacy of pembrolizumab in combination with chemotherapy compared with saline placebo plus chemotherapy, in patients with previously untreated advanced non-squamous NSCLC (see Table 4).[4, 42] While KEYNOTE-189 is ongoing, data from an interim analysis (data cut-off date 08-NOV-2017) form the evidence base for this submission as described through Sections B2.2 to B2.6. In addition, these study data form the clinical evidence base included in the cost-effectiveness model and analyses presented in Section B.3. Data from the final analysis of KEYNOTE-189 is currently anticipated in [redacted]

KEYNOTE-189 safety and efficacy data form the basis of the regulatory application to the European Medicines Agency (EMA) for marketing authorisation of pembrolizumab combination in patients with previously untreated advanced non-squamous NSCLC. To support the EMA regulatory procedure, additional data have also been presented from KEYNOTE-021.[41] Trial details and a summary of the key efficacy and safety findings are presented below. We have also additionally provided a naive comparison of the OS and PFS benefit between KEYNOTE-21 and KEYNOTE-189 as it provides compelling evidence regarding the longer term benefit of pembrolizumab combination for this patient population.

Please note: as KEYNOTE-021 has not been included in the economic model, it is not included in Sections B.2.2 to B.2.6.

Table 4: Clinical Effectiveness Evidence – KEYNOTE-189[42]

Study	KEYNOTE-189; An ongoing, randomised, double-blind, phase III study of platinum + pemetrexed chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic non-squamous non-small cell lung cancer patients; data from interim analysis – data cut-off date 08-NOV-2017; NCT02578680				
Study design	Randomised, multi-centre, double-blind, active-controlled, parallel group study				
Population	Patients with advanced or metastatic non-squamous NSCLC who had not previously received systemic therapy for advanced disease and in whom epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-directed therapy was not indicated; an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1; no active, symptomatic, or clinically unstable central nervous system metastases; and a life expectancy of at least 3 months				
Intervention(s)	Pembrolizumab 200 mg plus pemetrexed and platinum for 4 cycles, followed by pembrolizumab plus pemetrexed				
Comparator(s)	Saline placebo plus pemetrexed and platinum for 4 cycles, followed by saline plus pemetrexed				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	KEYNOTE-189 is the pivotal trial in this indication				
Reported outcomes specified in the decision problem	**overall survival (OS)** **progression-free survival (PFS)** objective response rates (ORR) **adverse effects (AEs) of treatment** **health-related quality of life (HRQoL)** *Bolded outcomes are those included in the health economic model*				
All other reported outcomes	Duration of response (DOR)				

KEYNOTE-021 Cohort G[41]

KEYNOTE-021 is an ongoing randomised, open-label, multi-cohort, multi-centre Phase I/II study evaluating the efficacy, safety and tolerability of pembrolizumab in combination with chemotherapy, immunotherapy or tyrosine kinase inhibitor therapy, in patients with locally advanced or metastatic NSCLC. Of relevance to this submission is Cohort G (n=123), which enrolled patients with non-squamous NSCLC regardless of PD-L1 status, in whom the safety and efficacy of pembrolizumab plus pemetrexed and carboplatin chemotherapy was compared with chemotherapy alone. Patients were stratified by PD-L1 status based on Tumour Proportion Score [TPS] ≥1% or <1%. See **Table 5** for details of study design, trial population, intervention and comparator treatments and endpoints considered.

Table 5: Clinical effectiveness evidence - KEYNOTE-021 Cohort G[41]

<table>
<tr><td>Study</td><td colspan="5">KEYNOTE-021 Cohort G, an open-label, randomised phase II trial of pembrolizumab plus pemetrexed/platinum chemotherapy vs. pemetrexed/platinum chemotherapy alone in patients with previously untreated advanced non-squamous NSCLC; NCT02039674</td></tr>
<tr><td>Study design</td><td colspan="5">Randomised, multi-centre, open-label, active-controlled, multi-cohort study</td></tr>
<tr><td>Population</td><td colspan="5">Cohort G patients (N=123) with advanced (stage IIIB or IV) non-squamous NSCLC who had not previously received systemic therapy for advanced disease and whose tumours express no sensitising EGFR mutation or ALK translocation; an ECOG performance score of 0 or 1; at least one measurable lesion assessed by RECIST v1.1; and a life expectancy of at least 3 months</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Pemetrexed 500mg/m^2 plus carboplatin AUC 5mg/mL/min Q3W for 4 cycles, plus pembrolizumab 200mg Q3W for up to 2 years</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Pemetrexed 500mg/m^2 plus carboplatin AUC 5mg/mL/min Q3W for 4 cycles</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td></td></tr>
<tr><td>No</td><td></td><td>No</td><td>✓</td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">Differences in study design compared with KEYNOTE-189, in particular open label, patient characteristics and comparator chemotherapy.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">Primary endpoint: ORR
Secondary endpoints: PFS; OS; DOR; AEs</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">None</td></tr>
</table>

While enrolment to the KEYNOTE-021 study is complete, the trial is ongoing. Data from the most recent interim analysis (data cut-off date December 1 2017) based on median follow-up of 23.9 months (range 0.8 – 35.1) are summarised in Table 6. These data show that treatment with pembrolizumab plus pemetrexed and carboplatin chemotherapy provided clear survival benefit compared with pemetrexed and carboplatin alone in patients with previously untreated advanced non-squamous NSCLC, with a manageable safety profile that is overall similar to that of standard chemotherapy.[43]

Table 6: KEYNOTE-021 Cohort G Efficacy and Safety Summary[43]

Outcome	**Pembrolizumab/ Chemotherapy Combination (N=60)**	**Chemotherapy alone (N=63)**
Efficacy outcomes (ITT population)		
ORR	34 (56.7%)	19 (30.2%)
	Difference 26.4% (95% CI 8.9-42.4) p=0.0016	
DOR (median months)	Not reached (1.4+ to 29.3+)	Not reached (2.8+ to 30.1+)
Ongoing response	47.1%	31.6%
PFS (median months)	24.0 (8.5 – NR)	9.3 (6.2-14.9)
	HR 0.53 (95% CI 0.33-0.86) p= 0.00493	
OS (median months)	Not reached (24.5-NR)	21.1 (14.9-NR)*
	HR 0.56, 95% CI 0.32-0.95) p=0.01508	
Safety outcomes (All patients as treated population)		
Median exposure (range), months	10.1 (0-29)	4.9 (0-31)
Drug Related AEs	55 (93.2%)	57 (1.92%)
Grade 3-5 Drug-related AEs	24 (40.7%)	17 (27.4%)
Leading to discontinuation	10 (16.9%)	8 (12.9%)
Leading to death	1 (1.7%)	2 (3.2%)

*73% of chemotherapy arm patients received anti-PD-(L)1 therapy as subsequent treatment

Figure 3 and Figure 4 provide naïve comparisons of the OS and PFS Kaplan-Meier curves comparing KEYNOTE-021G data with that from KEYNOTE-189. These comparisons demonstrate what has been seen in KEYNOTE 002, 006, 010 and 024 that more mature data confirms the initial KM data presented at each appraisal and provides compelling evidence of the longer term benefit of pembrolizumab combination in the target patient population.

Figure 3: Kaplan-Meier curves of OS (pembrolizumab + chemotherapy arms only; KEYNOTE-189 and KEYNOTE-021G)

Figure 4: Kaplan-Meier curves of PFS (pembrolizumab + chemotherapy arms only; KEYNOTE-189 and KEYNOTE-021G)

B.2.3 Summary of methodology of KEYNOTE-189

Trial design[42]

KEYNOTE-189 is an ongoing, worldwide, randomised, active controlled, parallel-group, multi-centre, double-blind phase III study of the safety and efficacy of platinum plus pemetrexed chemotherapy with or without pembrolizumab, as first line treatment for patients with metastatic non-squamous NSCLC who lack EGFR or ALK sensitising mutations.

Participation was dependent upon supplying tumour tissue for evaluation of PD-L1 expression. The total planned enrolment was 570 patients (616 patients were ultimately randomised; 410 to the pembrolizumab chemotherapy combination arm and 206 to the control arm). Prior to randomisation, patients were stratified by programmed cell death 1 ligand 1 (PD-L1) status (Tumour Proportion Score [TPS] ≥1% vs <1%), smoking status (never vs former/current), and choice of platinum (cisplatin vs carboplatin).

Following screening, patients were randomised in a 2:1 ratio to receive either pembrolizumab 200 mg or saline placebo, combined with pemetrexed 500 mg/m2 and platinum (investigator's choice of cisplatin [75 mg/ m2] or carboplatin [AUC 5 mg/mL/min]) every 3 weeks (Q3W) for 4 cycles.

Treatment with pembrolizumab or saline placebo continued until 35 study treatments had been administered or one of the discontinuation criteria occurred. Treatment with pemetrexed also continued until one of the discontinuation criteria occurred. Treatment with platinum continued for 4 cycles or until one of the discontinuation criteria occurred. Discontinuation criteria included documented disease progression, unacceptable AEs, intercurrent illness preventing further administration of study treatment, investigator's decision to withdraw the subject, patient's decision to withdraw consent, pregnancy of the subject, noncompliance with study treatment or procedure requirements, or administrative reasons leading to discontinuation of the subject or the study. When a subject discontinued/withdrew from the study, all applicable activities scheduled for the end of treatment visit were performed at the time of discontinuation.

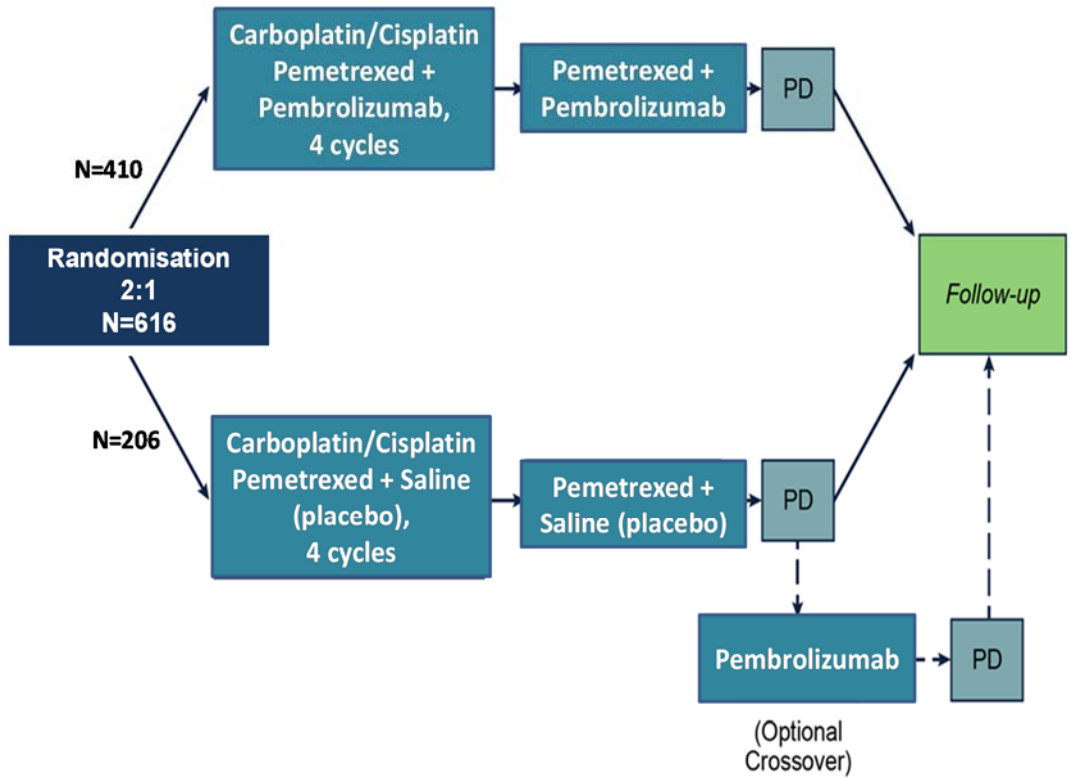
Patient's response to treatment was assessed using radiographic imaging at 6 and 12 weeks, followed by imaging every 9 weeks until week 48 and every 12 weeks for the remainder of the study. All imaging was submitted without indication of treatment assignment to a central vendor for blinded independent central review (BICR) of imaging using Response Evaluation Criteria In Solid Tumours 1.1 (RECIST 1.1) to determine PFS and ORR. Treatment decisions made by investigators could be based on immune-related

RECIST (irRECIST). Adverse events (AEs) were monitored throughout the study and severity of AEs was graded according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment with pembrolizumab or saline placebo continued until 35 study treatments had been administered or one of the discontinuation criteria occurred (documented disease progression, unacceptable AEs, intercurrent illness preventing further administration of study treatment, investigator's decision to withdraw the subject, patient's decision to withdraw consent, pregnancy of the subject, noncompliance with study treatment or procedure requirements, or administrative reasons leading to discontinuation of the subject or the study). Treatment with pemetrexed continued until one of the discontinuation criteria occurred. Treatment with platinum continued for 4 cycles or until one of the discontinuation criteria occurred.

After documented disease progression (BICR/RECIST 1.1), patients in the control arm had the opportunity to receive pembrolizumab treatment in a Crossover Phase; however, response or progression during these study periods were not considered for the analyses presented in this report. **Figure 5** illustrates the KEYNOTE-189 study design.

Figure 5: KEYNOTE-189 Study Design



Notes: PD - progressive disease; Source: Clinical Study Report[42]

Eligibility criteria [42]

Male/female patients with a diagnosis of non-squamous NSCLC, who had not received prior systemic chemotherapy treatment for their advanced or metastatic NSCLC and who did not have sensitising EGFR or ALK mutations, were eligible for enrolment in the trial. The key inclusion and exclusion criteria applied during the selection of the study population are detailed in Table 7.

Table 7: KEYNOTE-189 key eligibility criteria

Inclusion criteria
• Histologically/cytologically confirmed diagnosis stage IV (M1a or M1b) non-squamous NSCLC • Confirmation that patients do not have sensitising EGFR or ALK mutations • Measurable disease based on RECIST 1.1 as determined by local site investigator/radiology assessment • No prior systemic treatment for advanced/metastatic NSCLC at screening • Tumour tissue available from locations not radiated prior to biopsy • ≥18 years of age on day of signing informed consent • Life expectancy of at least 3 months • ECOG performance status 0 or 1
Exclusion criteria
• Predominantly squamous histology NSCLC • Received prior systemic cytotoxic chemotherapy for metastatic disease, or other targeted or biological antineoplastic therapy, before the first dose of study treatment; had a major surgery within 3 weeks prior to first dose • Received radiation therapy to the lung that is >30Gy within 6 months of first dose • Completed palliative radiotherapy within 7 days of first dose • Known history of other prior malignancy except if subject undergone potentially curative therapy with no evidence of disease recurrence for 5 years since initiation of that therapy • Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases and patients with untreated, asymptomatic brain metastases may participate if they met specific criteria • Active autoimmune disease that required systemic treatment in past 2 years • Taking chronic systemic steroids • Unable or unwilling to take folic acid or vitamin B12 supplementation • Prior treatment targeting PD-1, PD-L1/PD-L2, or other immune-regulatory receptors or mechanisms • Active infection requiring therapy • History of (non-infectious) pneumonitis that required steroids or current pneumonitis

Source: Clinical Study Report[42]

Settings and locations where the data were collected[42]

The study was conducted at 143 centres in 16 countries in North America (54 centres), Europe (71 centres, including 7 in the UK), the Middle East (6 centres), Asia (4 centres) and Australia (8 centres), as described in Table 8. All treatments were administered in secondary care centres on an out-patient basis.

30 patients from the UK participated in the study at 7 UK centres.

Table 8: Location of study centres

Country	Number of Sites
Australia	8
Austria	8
Belgium	2
Canada	6
Denmark	3
Finland	2
France	6
Germany	11
Ireland	5
Israel	6
Italy	12
Japan	4
Netherlands	3
Spain	12
UK	7
USA	48

Source: Clinical Study Report[42]

Trial drugs and concomitant medications[42]

Patients randomised to the pembrolizumab combination arm of the trial received 200 mg pembrolizumab, pemetrexed 500 mg/m2, and platinum (investigator's choice of cisplatin [75 mg/ m2] or carboplatin [AUC 5 mg/mL/min]) Q3W for 4 cycles. Patients randomised to the control arm of the trial received saline solution, pemetrexed and platinum Q3W for 4 cycles (dosing as for pembrolizumab combination arm). Dosing schedules are described in

Table 9.

Table 9: Trial treatments dosing and administration schedules

Drug	Dose/ Potency	Dose Frequency	Route of administration	Regimen/ treatment period	Use
Pembrolizumab[a]	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Experimental
Normal saline[a]	N/A	Q3W	IV infusion	Day 1 of each 21-day cycle	Placebo
Pemetrexed	500mg/m2	Q3W	IV infusion	Day 1 of each 21-day cycle	Active comparator
Cisplatin	75 mg/m2	Q3W	IV infusion	Day 1 of each 21-day cycle for 4 cycles	Active comparator
Carboplatin	AUC 5 mg/mL/min	Q3W	IV infusion	Day 1 of each 21-day cycle for 4 cycles	Active comparator

Notes: AUC – area under concentration curve; Q3W – every 3 weeks;
[a]pembrolizumab/saline placebo administered prior to chemotherapy
Source: Clinical Study Report[42]

Study blinding/masking

The study was double-blinded, but the clinical supplies were provided open-label. Therefore, an unblinded pharmacist provided the investigative staff with ready-to-use blinded pembrolizumab or saline infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion visits.

Treatment identification information was unmasked only if necessary for the welfare of the subject. Once an emergency unblinding occurred, the principal investigator, site personnel, and Sponsor personnel were unblinded so that appropriate follow-up medical care could be provided to the subject.

Concomitant medications

All treatments that the investigator considered necessary for a patient's welfare, including palliative and supportive care, could be administered at the discretion of the investigator in-keeping with the community standards of medical care. All concomitant medication used from 30 days before the first dose of study treatment through the Safety Follow-up Visit was recorded on the CRF, including all prescription, over-the-counter, herbal supplements, and intravenous (IV) medications and fluids. After the Safety Follow-up Visit, only medications taken for serious adverse events (SAEs) and events of clinical interest (ECIs) were recorded.

Patients were prohibited from receiving chemotherapy and biologic therapy not specified in the protocol, radiation, other investigational agents, live vaccines, prolonged systemic glucocorticoids (for any purpose other than to modulate symptoms from an immune-related AE), and phenytoin (while receiving platinum) during the Screening, Treatment, Crossover, and Second Course Phases of this study. There were no prohibited therapies during the Post-Treatment Follow-Up Phase.

Outcomes used in the economic model

The outcomes of overall survival (OS), progression free survival (PFS), and patient HRQoL were included within the health economic model, along with details of time on treatment (ToT) and adverse events (AEs), as reported in Section B.3. The OS and PFS outcomes were pre-specified as co-primary endpoints in KEYNOTE-189, while patient reported outcomes (PRO) as measured using the European Quality of Life Five Dimensions Questionnaire (EQ-5D), was pre-specified as an exploratory endpoint.

Full details of the objectives and hypotheses and the outcomes used in the KEYNOTE-189 study are presented below[42]:

Primary objectives and hypotheses

- To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using PFS per RECIST 1.1 as assessed by BICR of imaging.

Hypothesis: Pembrolizumab combination prolongs PFS (BICR/RECIST 1.1) compared to saline placebo/chemo combination.

- To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using OS.

Hypothesis: Pembrolizumab combination prolongs OS compared to saline placebo/chemo combination.

Secondary objectives

- To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using objective response rate (ORR) per RECIST 1.1 as assessed by BICR.
- To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using duration of response (DOR) per RECIST 1.1 as assessed by BICR.
- To evaluate the safety and tolerability profile of pembrolizumab combination therapy.

Key exploratory objectives

- To evaluate the effect of PD-L1 expression levels on the efficacy endpoints of PFS, OS, and ORR.
- To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using PFS, ORR, and DOR assessed by the investigator using RECIST 1.1.
- To evaluate changes in HRQOL assessments from baseline in the biomarker-positive strata and in the overall study population using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-Core 30 items (C30) and EORTC QLQ-Lung Cancer 13 items (LC13).
- To characterise utilities in patients treated with pembrolizumab combination compared with saline placebo/chemo combination using the EuroQoL 5 Dimension Visual Analogue Scale (EQ-5D VAS).

Patient characteristics at baseline[42]

Baseline characteristics of the patients in the Intention-to-treat (ITT) population in KEYNOTE-189 are presented in **Table 10**. As the table shows, the control group enrolled more female and younger patients, than the pembrolizumab combination. Otherwise, the treatment groups were relatively well balanced in terms of baseline characteristics. Both treatment groups had similar proportions of patients with brain metastases at baseline. PD-L1 expression indicated by TPS ≥1% and <1% was similar in both treatment groups. There

were few “never smokers” in both groups, which were equally balanced. Most of the patients received carboplatin rather than cisplatin in both treatment arms. The overall population and history of prior treatment are relevant to the UK and largely representative of UK clinical practice.

Table 10: Study subject characteristics (ITT population)

	Pembrolizumab chemo combination		**Control**	
	n	**%**	**N**	**%**
Patients in population	410		206	
Gender				
Male	254	62.0	109	52.9
Female	156	38.0	97	47.1
Age (years)				
<65	197	48.0	115	55.8
≥65	213	52.0	91	44.2
Mean	63.2		62.8	
SD	9.4		9.1	
Median	65.0		63.5	
Range	34 to 84		34 to 84	
Race				
Asian	10	2.4	8	3.9
Black or African American	11	2.7	3	1.5
White	387	94.4	194	94.2
Missing	2	0.5	1	0.5
Ethnicity				
Hispanic or Latino	5	1.2	7	3.4
Not Hispanic or Latino	384	93.7	190	92.2
Not reported	9	2.2	4	1.9
Unknown	12	2.9	5	2.4
Region				
US	85	20.7	34	16.5
Ex US	325	79.3	172	83.5
Geographic region				
East-Asian	4	1.0	6	2.9
Non-East Asian	106	99.0	200	97.1
Smoking Status				
Never smoker	48	11.7	25	12.1
Former/current smoker	362	88.3	181	87.9

	Pembrolizumab chemo combination		Control	
	n	%	N	%
ECOG				
0	186	45.4	80	38.8
1	221	53.9	125	60.7
2	1	0.2	0	0.0
Missing	2	0.5	1	0.5
Histology				
Adenocarcinoma	394	96.1	198	96.1
NSCLC NOS	10	2.4	4	1.9
Other	6	1.5	4	1.9
Brain metastasis status at baseline				
Yes	73	17.8	35	17.0
No	337	82.2	171	83.0
Baseline tumour size (mm)				
Patients with data	402		200	
Mean	97.5		105.3	
SD Median	67.5		66.5	
Range	84.0		87.2	
	11.5 to 422.1		19.3 to 466.5	
PD-L1 status				
<1%	127	31.0	63	30.6
≥1%	260	63.4	128	62.1
Not evaluable	23	5.6	15	7.3
Platinum chemotherapy				
Cisplatin	113	27.6	58	28.2
Carboplatin	297	72.4	148	71.8
Prior radiation				
Yes	84	20.5	46	22.3
No	326	79.5	160	77.7
Prior thoracic radiation				
Yes	28	6.8	20	9.7
No	382	93.2	186	90.3
Prior adjuvant therapy				
Yes	25	6.1	14	6.8
No	385	93.9	192	93.2

	Pembrolizumab chemo combination		Control	
	n	%	N	%
Prior neoadjuvant therapy				
Yes	5	1.2	6	2.9
No	405	98.8	200	97.1

Source: Clinical Study Report[42]

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

Key elements of the statistical analysis plan are summarised in **Table 11** and Source: Clinical Study Report[42]

Table 12.[42]

Table 11: Statistical analysis plan summary

Study design overview	Phase III study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy in first line metastatic non-squamous NSCLC
Treatment assignment	Approximately 570 patients to be randomised 2:1 to receive pembrolizumab combination or chemo alone. Study is double-blinded
Analysis populations	Efficacy: Intention to treat (ITT) Safety: All patients as treated (ASaT)
Primary endpoints/ hypotheses	Hypothesis 1: Pembrolizumab plus chemotherapy combination prolongs PFS by RECIST 1.1 as assessed by BICR compared to saline placebo plus chemotherapy. Hypothesis 2: Pembrolizumab plus chemotherapy combination prolongs OS compared to saline placebo plus chemotherapy. Hypothesis 3: Pembrolizumab plus chemotherapy combination improves ORR (BICR/RECIST 1.1) compared to saline placebo plus chemotherapy.
Statistical methods for key efficacy analyses	See **Source:** Clinical Study Report[42] **Table 12** below
Statistical Methods for Key Safety Analyses	Analysis of safety results follow a tiered approach; the tiers differ with respect to analyses performed. There are no Tier 1 safety parameters in this trial. All safety parameters are considered either Tier 2 or Tier 3. Tier 2 parameters assessed via point estimates with 95% confidence intervals provided for between-group

	comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment difference analysed using the Miettinen and Nurminen method. In primary safety comparison, patients who crossover to pembrolizumab censored at time of crossover (i.e., AEs occurring during treatment with pembrolizumab are excluded for control-arm patients). Exploratory safety analysis conducted for the crossover population, including all safety events starting from date of first dose of pembrolizumab.
Interim Analyses	Two interim analyses are planned in this study: Interim analysis 1: To demonstrate superiority of pembrolizumab in combination with pemetrexed/platinum in PFS and OS; ORR tested if both the PFS and OS test results were significant; to be performed after approx. 370 PFS events are observed Initerim analysis 2: To demonstrate superiority of pembrolizumab in combination with pemetrexed/platinum in PFS and OS; to be performed after approx. 468 PFS events are observed
Final Analysis	To demonstrate superiority of pembrolizumab in combination with pemetrexed/ platinum in OS; to be performed after approx. 416 death events are observed
Multiplicity	Overall Type I error rate for each endpoint in the group sequential tests is strictly controlled at 2.5% (one-sided); for both PFS and OS, this is based on the Lan-DeMets O'Brien-Fleming spending function. Between the endpoints, the type I error is controlled by the following rollover rule: The total type I error allocated to PFS (0.0095) is subject to rollover to OS if the PFS test is positive. The type I error allocated to OS (0.0155) is subject to rollover to PFS if the OS test is positive. Furthermore, the total type I error (0.025) is subject to rollover to ORR at IA1 if the PFS and OS tests are both positive.
Sample size and power	Enrolment of 570 patients assumed to occur over 12 months at 2:1 ratio between the experimental and control groups. The actual enrolment is 616 patients within 13 months. With 370 PFS events at IA1, the study has ~72% power for detecting a PFS HR of 0.7 at 0.0095 (one-sided) and ~84% power for detecting a HR of 0.7 at 0.025 (one-sided). With 468 PFS events at IA2, the study has ~90% power for detecting a HR of 0.7 at 0.0095 (one-sided) and ~96% power for detecting a HR of 0.7 at 0.025 (one-sided). The duration of PFS in the control group is assumed to follow an exponential distribution with a median of 6.5 months based on historical data. The assumed follow-up time after last patient enrolled is 13 months for IA2. An exponential dropout rate of 0.35% per month is assumed. With 242 deaths at IA1, the study has ~37% power for detecting an OS HR of

	0.7 at 0.0155 (one-sided) and ~47% power for detecting a HR of 0.7 at 0.025 (one-sided) when the PFS test is significant. With 332 deaths at IA2, the study has ~73% power for detecting a HR of 0.7 at 0.0155 (one-sided) and ~80% power for detecting a HR of 0.7 at 0.025 (one-sided) when PFS test is significant. With 416 deaths at FA, the study has ~90% power for detecting a HR of 0.7 at 0.0155 (one-sided) and ~93% power for detecting a HR of 0.7 at 0.025 (one-sided) when the PFS test is significant. The duration of OS in the control group is assumed to follow an exponential distribution with a median of 13 months based on historical data. The exponential dropout rate assumed for OS is 0.1% per month.

Source: Clinical Study Report[42]

Table 12: Analysis strategy for key efficacy endpoints

Endpoint	Statistical methods	Analysis population	Missing data approach
Primary endpoints			
PFS per RECIST 1.1 by central imaging vendor	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Primary censoring rule Sensitivity analysis 1 Sensitivity analysis 2
OS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based (censored at last known alive date)
Secondary endpoint			
ORR per RECIST 1.1 by central imaging vendor	Stratified M&N method with sample size weights	ITT	Patients without assessments are considered non-responders and conservatively included in denominator

[a]For stratified analyses, the stratification factors used for randomisation will be applied to the analysis

M&N: Miettinen and Nurminen method

Source: Clinical Study Report[42]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of KEYNOTE-189 was conducted using the Cochrane Collaboration's Risk of Bias tool.[44] Based on this analysis, the study was determined to be 'Low risk' across five of six key domains and 'Unclear risk' for the 'Incomplete Outcome Data' domain. The complete quality assessment is included in Appendix D. A tabulated summary of the quality assessment results is presented in Table **13** below.

Table 13: Quality assessment results for parallel group RCTs

Trial	KEYNOTE-189	Justification
Was randomisation carried out appropriately?	Yes	A computerized randomised list generator was utilized for sequence generation. Interactive voice response system (IVRS)/integrated web response system (IWRS) was used for randomisation
Was the concealment of treatment allocation adequate?	Yes	The Sponsor, investigator and subject were blinded to treatment allocation. The study site's unblinded pharmacist obtained each patient's study identification number and study drug assignment via the IVRS/IWRS and prepared the solutions for infusion. The unblinded pharmacist provided the investigative staff with ready-to-use blinded pembrolizumab/saline infusion solutions, packaged identically to maintain the blinding, for administration at scheduled infusion visits.
Were the groups similar at the outset of the study in terms of prognostic factors?	No	The control enrolled more female and younger patients, than the pembrolizumab combination. Otherwise, the treatment groups were relatively well balanced in terms of baseline characteristics
Were care providers, patients and outcome assessors blind to treatment allocation?	Yes	The study was double-blind, with sponsor, investigator and subject blinded to treatment allocation. In addition, radiologists who assessed the tumour images were blinded.
Were there any unexpected imbalances in drop-outs between groups?	Not clear	Number of discontinued patients were not specified explicitly with reasons due to interim analysis results provided

Trial	KEYNOTE-189	Justification
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Outcomes pre-specified in the study protocol were reported in trial results.
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 Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)		

Consideration of UK clinical practice

At present, in routine UK clinical practice, first line treatment options for the majority of patients in the UK with advanced non-squamous NSCLC lacking EGFR and/or ALK mutations are limited to chemotherapy.[31] Only those individuals whose tumour cells have high levels of PD-L1 expression (TPS score ≥50%) have routine access to innovative immuno-oncology treatment in the form of pembrolizumab monotherapy.[36] Data from KEYNOTE-189 show that pembrolizumab in combination with chemotherapy is a promising treatment option which has demonstrated efficacy, including survival benefits, in all non-squamous NSCLC patients regardless of PD-L1 expression, with a good tolerability profile.[4, 42]

Additionally, although patients with high levels of PD-L1 (TPS score ≥50%), currently have access to first line pembrolizumab monotherapy which can provide considerable benefits, pembrolizumab in combination with chemotherapy can offer a significant step change in treatment options for these patients.

There remains considerable unmet need for additional treatments which provide survival benefits for those patients who are both currently ineligible for first line immuno-oncology therapy and those who have access to immune-oncology therapy who could realise greater survival benefits with pembrolizumab combination therapy.

B.2.6 Clinical effectiveness results of the relevant trials

The clinical data presented in this submission are from IA1 of the KEYNOTE-189 phase III trial of pembrolizumab plus chemotherapy combination versus saline placebo plus chemotherapy as first line treatment in patients with advanced non-squamous NSCLC. [4, 42] For simplicity, abbreviated nomenclature for the treatment groups is used in this section as per **Table 14**:

Table 14: Treatment group nomenclature

Treatment group	Abbreviated nomenclature
Pembrolizumab/pemetrexed/platinum combination therapy	Pembrolizumab combination
Saline placebo/pemetrexed/platinum combination therapy	Control

The IA1 was performed on the primary (PFS and OS), secondary (ORR and DoR) and exploratory (PRO) efficacy endpoints, with a data cut-off date for the analysis of 8 November 2017. All efficacy analyses were conducted using the ITT population. At the IA1 data cut-off date, patients had a median duration of follow-up of 10.5 months (range 0.2 to 20.4 months) and 33.8% of patients in the pembrolizumab combination group and 17.8% of patients in the control group remained on assigned treatment. Mean duration of exposure was [redacted] days (SD [redacted] days) in the pembrolizumab combination arm compared with [redacted] days (SD [redacted] days) in the control arm. The mean number of cycles of treatment received was [redacted] (SD [redacted]) and 7 (SD [redacted]) in the pembrolizumab combination and control groups, respectively. [4, 42] (

Table 15)

Table 15: Summary of drug exposure (ASaT population) [42]

	Pembrolizumab combination (N=405)	Control (N=202)	Total (N=607)
Number of Days on Therapy (days)			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]

	Pembrolizumab combination (N=405)	Control (N=202)	Total (N=607)
Range	[redacted]	[redacted]	[redacted]
Number of Cycles			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Note: For patients who crossed over to pembrolizumab from the control group, doses administered after crossover are excluded. Source: Clinical Study Report[42]

B.2.6.1 Summary of clinical efficacy outcomes

A summary of the clinical efficacy outcome results from IA1 are presented in **Table 16** with additional details of each endpoint provided in the sub-sections B.2.6.2 to B.2.6.5 below [4, 42]

Table 16: Summary of clinical efficacy outcomes (IA1) [42]

	Treatment-naïve NSCLC	
Number Patients - ITT population	**Pembrolizumab combination N=410**	**Control N=206**
Primary endpoints		
OS - ITT population		
Median (95% CI), [months]	not reached	11.3 (8.7, 15.1)
	HR 0.49 (95% CI 0.38, 0.64) p<0.00001	
OS rate at 6 months	85.3%	72.3%
OS rate at 12 months	69.2%	49.4%
PFS (BICR per RECIST 1.1) – ITT population		
Median (95% CI), [months]	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
	HR 0.52 (95% CI 0.43, 0.64); p < 0.00001	
PFS rate at 6 months	66.4%	40.1%

	Treatment-naïve NSCLC	
Number Patients - ITT population	**Pembrolizumab combination N=410**	**Control N=206**
PFS rate at 12 months	34.1%	17.3%
Secondary endpoints		
ORR (BIRC per RECIST 1.1) - ITT Population		
Confirmed ORR (CR + PR)%	47.6% (42.6, 52.5)	18.9% (13.8-25.0)
Difference in % vs control	28.5% (21.1, 35.4) P<0.0001	
% of patients who achieved a CR	0.5%	0.5%
Disease control rate (CR+PR+SD)	84.6%	70.4%
Time to Response		
Number of responders (n) Median [months] Range [months]	[redacted] [redacted]	[redacted] [redacted]
Response Duration (BIRC assessment) - ITT Population		
Median [months] Range [months]	11.2 (1.1+ to 18.0+)	7.8 (2.1+ to 16.4+)

Source: Clinical Study Report[42]

B.2.6.2 Overall survival[4, 42]

Overall survival (OS) is defined as time from randomisation to death due to any cause, expressed in days. Patients without documented death at the time of analysis were censored at date of last known contact. Patients who had survival update after the data cut-off date were censored at the cut-off date.

At the cut-off date, 235 deaths (38%) had been reported in the study; [redacted] %) in the pembrolizumab combination group and [redacted] %) in the control group.

Table 17 and **Table 18** present the results of the OS analysis and

Figure 6 presents the Kaplan-Meier (KM) estimates of OS in the ITT population. OS was significantly higher in the pembrolizumab combination group compared with the control (HR

0.49; 95% CI: 0.38, 0.64; p<0.00001). The median OS was not reached in the pembrolizumab combination arm and was 11.3 months in the control group (

Table 17). The OS rate was higher in the pembrolizumab combination than the control at 6 months ([redacted] % vs [redacted] %) and remained higher at 12 months (69.2% vs 49.4%) (**Table 18**). The KM plot demonstrates that the pembrolizumab combination curve separated from the control curve early at Month 1, with continuous separation between the 2 curves over time (

Figure 6).

Table 17: Analysis of overall survival (ITT population) [42]

Treatment	N	Number of events (%)	Person-months	Event rate/100 person months	Median OS[a] (months)(95% CI)	OS rate at month 6 in %[a] (95% CI)	Hazard Ratio[b] (95% CI) p-value[c]
Pembrolizumab combination	410	[redacted]	[redacted]	[redacted]	Not reached (.,.)	[redacted]	0.49 (0.38, 0.64); p<0.00001
Control	206	[redacted]	[redacted]	[redacted]	11.3 (8.7, 15.1)	[redacted]	

[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model; [c]One-sided p-value based on stratified log-rank test; Source: Clinical Study Report[42]

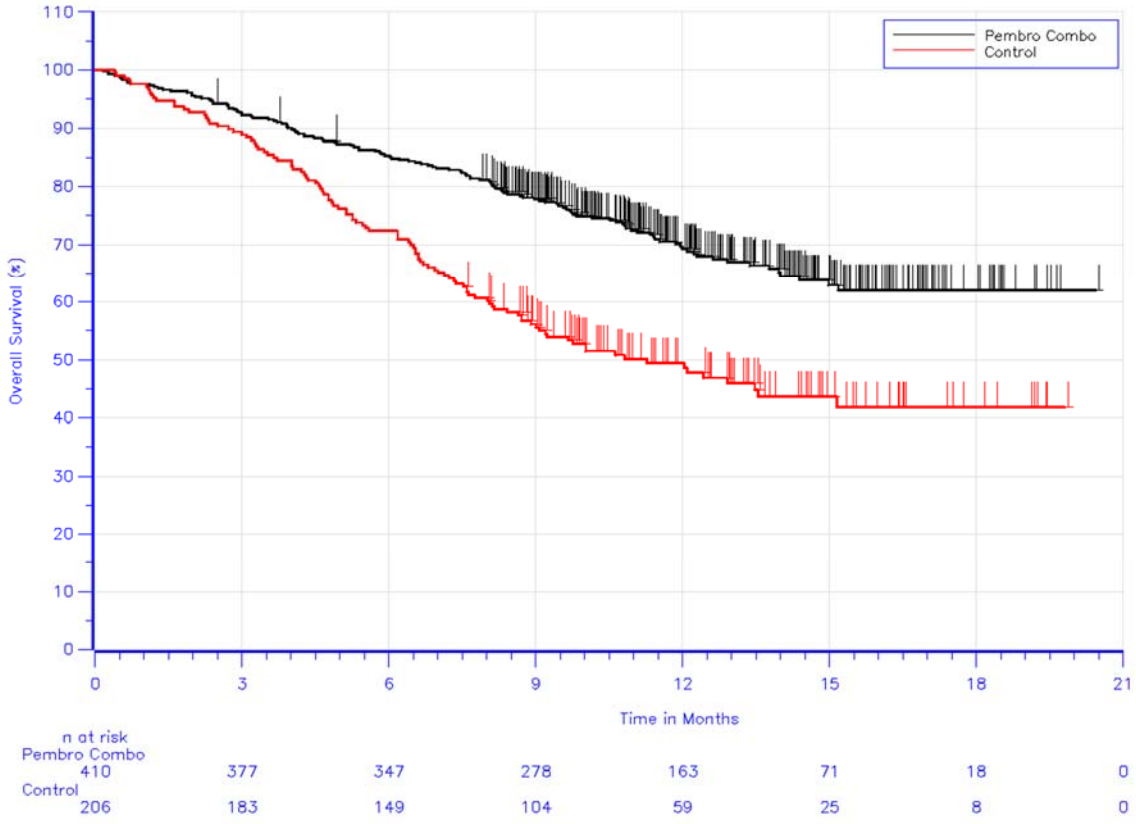
Table 18: Summary of overall survival rate over time (ITT population) [42]

	Pembrolizumab combination N=410	Control N=206
OS rate at 6 months (95% CI)a	[redacted]	[redacted]
OS rate at 9 months (95% CI)a	[redacted]	[redacted]
OS rate at 12 months (95% CI)a	69.2 (64.1, 73.8)	49.4 (42.1, 56.2)

[a]From the product-limit Kaplan-Meier method for censored data

Source: Clinical Study Report[42]

Figure 6: Kaplan-Meier estimates of overall survival (ITT population)



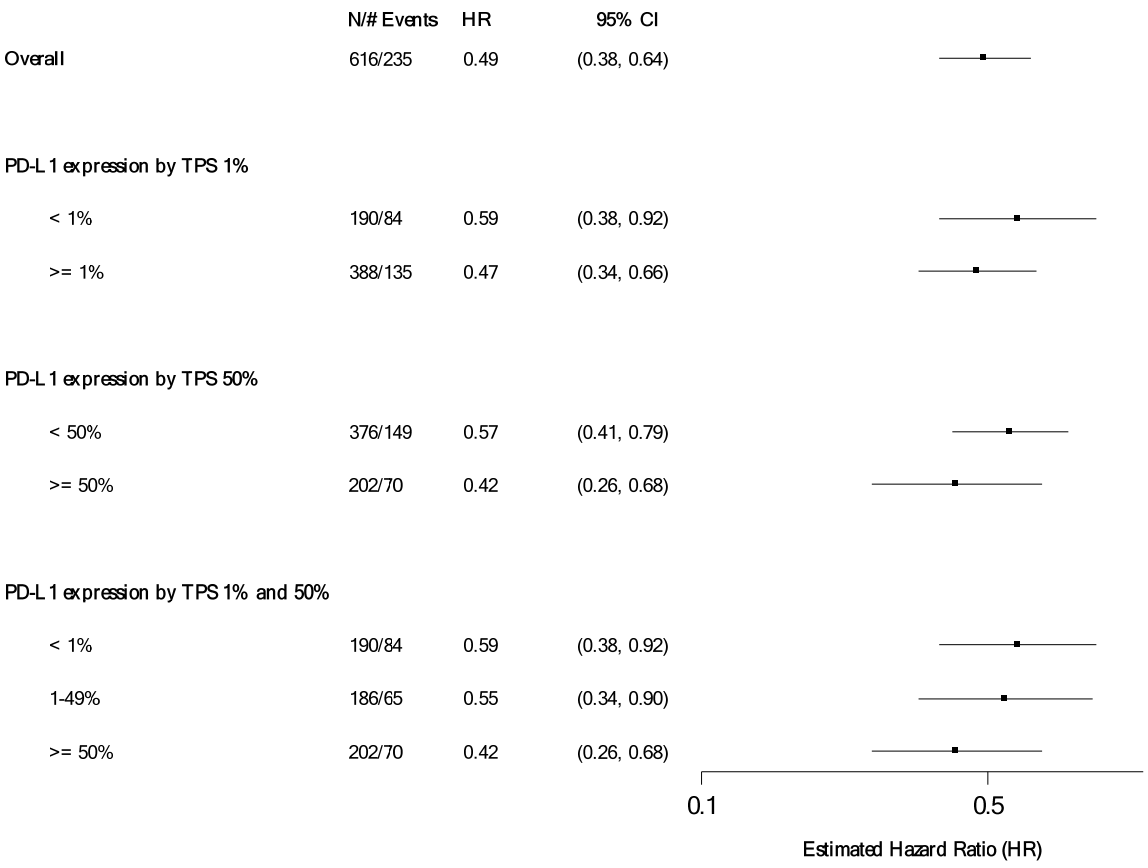
Source: Clinical Study Report[42]

At the time of data cut-off, [redacted] of the 206 patients in the control ITT population were continuing on the control treatment. Of the remaining [redacted] patients, [redacted] eligible patients with disease progression confirmed by BICR had crossed over to pembrolizumab monotherapy within the study and an additional [redacted] patients received a PD-1 antibody (pembrolizumab or nivolumab) as subsequent therapy outside of the study, resulting in an overall crossover rate of [redacted] % ([redacted] /170). Despite the high crossover rate from the control to an anti-PD-1 antibody, the OS benefit of the pembrolizumab combination treatment persisted.

OS by PD-L1 expression

The OS benefit of the pembrolizumab combination over the control was observed across all PD-L1 expression subgroups (TPS <1%, TPS 1-49%, and TPS ≥50%) (**Figure 7**). An incremental OS benefit was observed with increased PD-L1 expression, with improved HR.

Figure 7: Forest plot of OS hazard ratio by PD-L1 expression (ITT population) [42]



Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). Patients with PD-L1 not evaluable are not included in the subgroup analysis.
Source: Clinical Study Report[42]

OS was improved with the pembrolizumab combination compared to the control in PD-L1 TPS <1% (**Table 19**), TPS 1 to 49% (

Table 20), and TPS ≥50% (

Table 21) analyses with HRs of 0.59, 0.55, and 0.42, respectively. The median OS was longer in the pembrolizumab combination than the control ([redacted] months vs [redacted] months) in PD-L1 TPS <1%. In TPS 1 to 49% and TPS ≥50%, the median OS was [redacted] in the pembrolizumab combination and was [redacted] months and [redacted] months, respectively, in the control. The KM plots revealed that the pembrolizumab combination curves separated from

the control curves relatively early by Month 1, Month 5, and Month 3 in TPS <1% (**Figure 8**), TPS 1 to 49% (

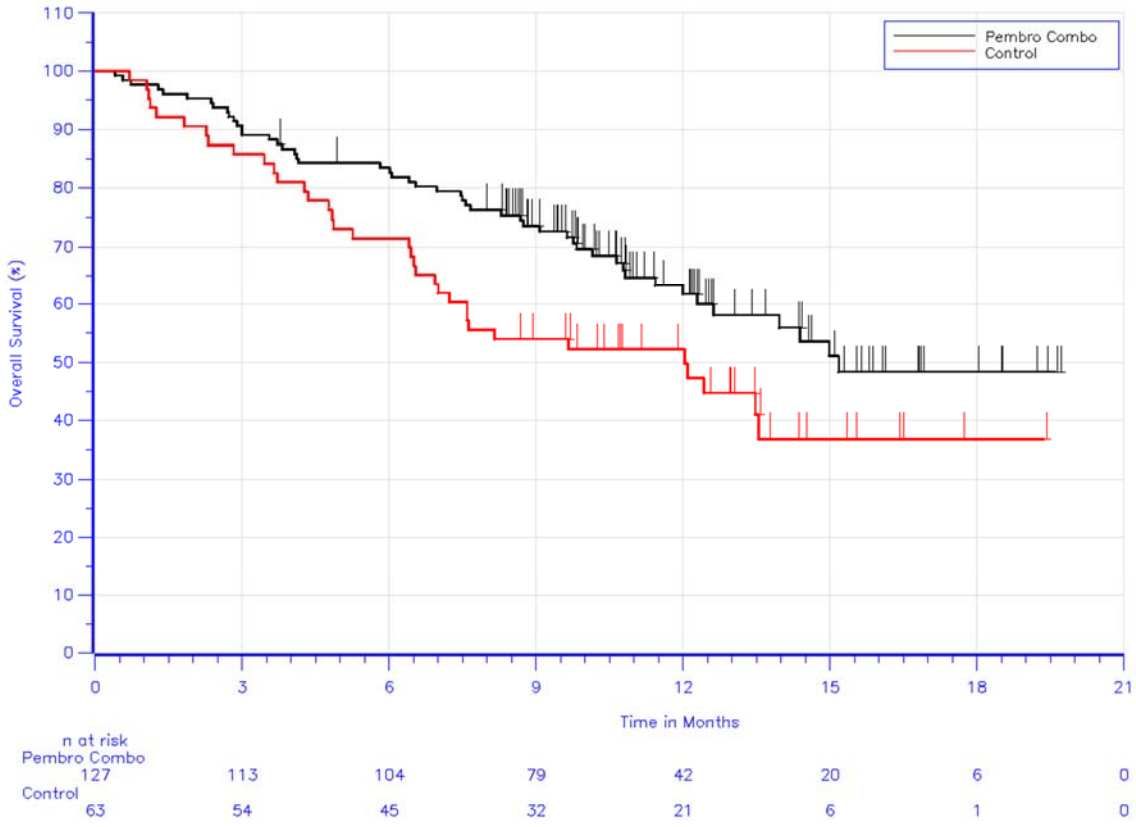
Figure 9), and TPS ≥50% (**Figure 10**), respectively; this separation of the curves was maintained throughout the remainder of the evaluation period.

Table 19: Analysis of overall survival (ITT population; TPS<1%)[42]

Treatment	N	Number of events (%)	Person-months	Event rate/ 100 person months	Median OSa (months) (95% CI)	OS rate at month 6 in %a (95% CI)	Hazard Ratiob (96% CI) p-value c
Pembrolizumab combination	127	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.59 (0.38, 0.92); p<0.00951
Control	63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current); [c]One-sided p-value based on stratified log-rank test.
Source: Clinical Study Report[42]

Figure 8: Kaplan-Meier estimates of overall survival with TPS<1% (ITT population) [42]



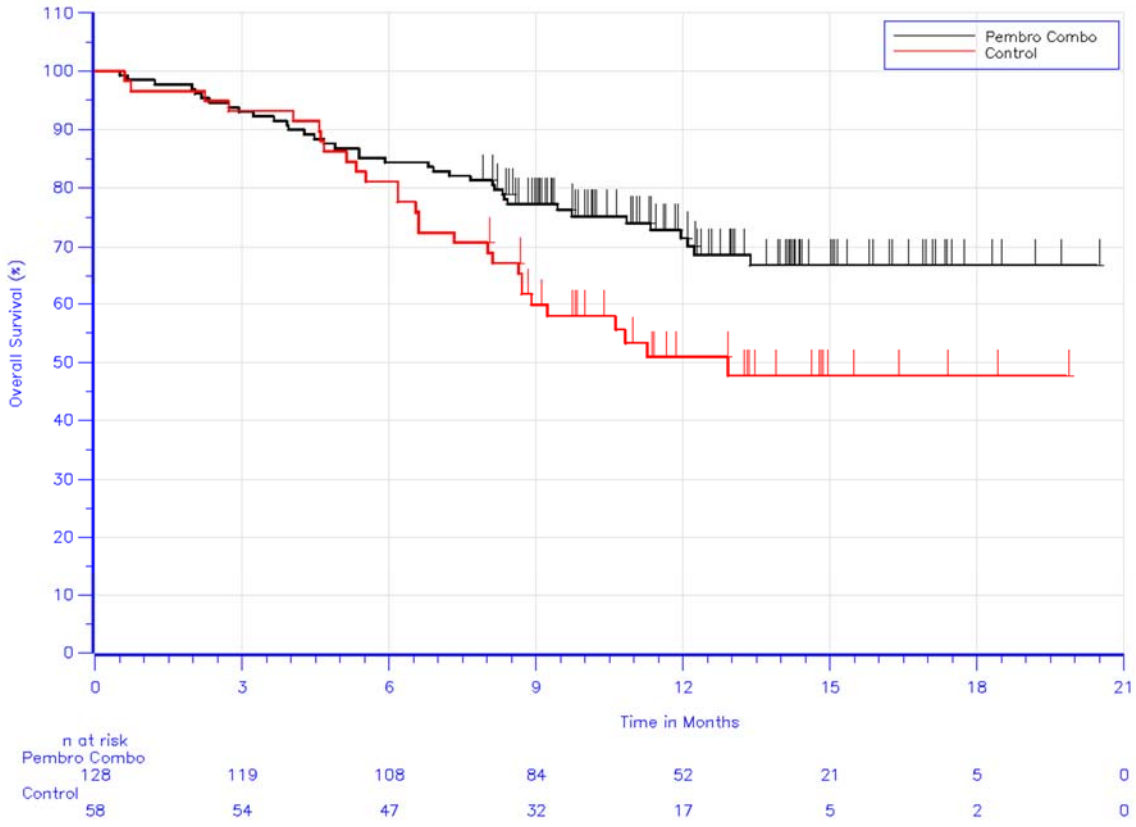
Source: Clinical Study Report[42]

Table 20: Analysis of overall survival (ITT population; TPS 1-49%)[42]

Treatment	N	Number of events (%)	Person-months	Event rate/ 100 person months	Median OS[a] (months) (95% CI)	OS rate at month 6 in %[a] (95% CI)	Hazard Ratio[b] (96% CI) p-value[c]
Pembrolizumab combination	128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.55 (0.34, 0.90); p<0.00808
Control	58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current); [c]One-sided p-value based on stratified log-rank test.
Source: Clinical Study Report[42]

Figure 9: Kaplan-Meier estimates of overall survival with TPS 1-49% (ITT population) [42]



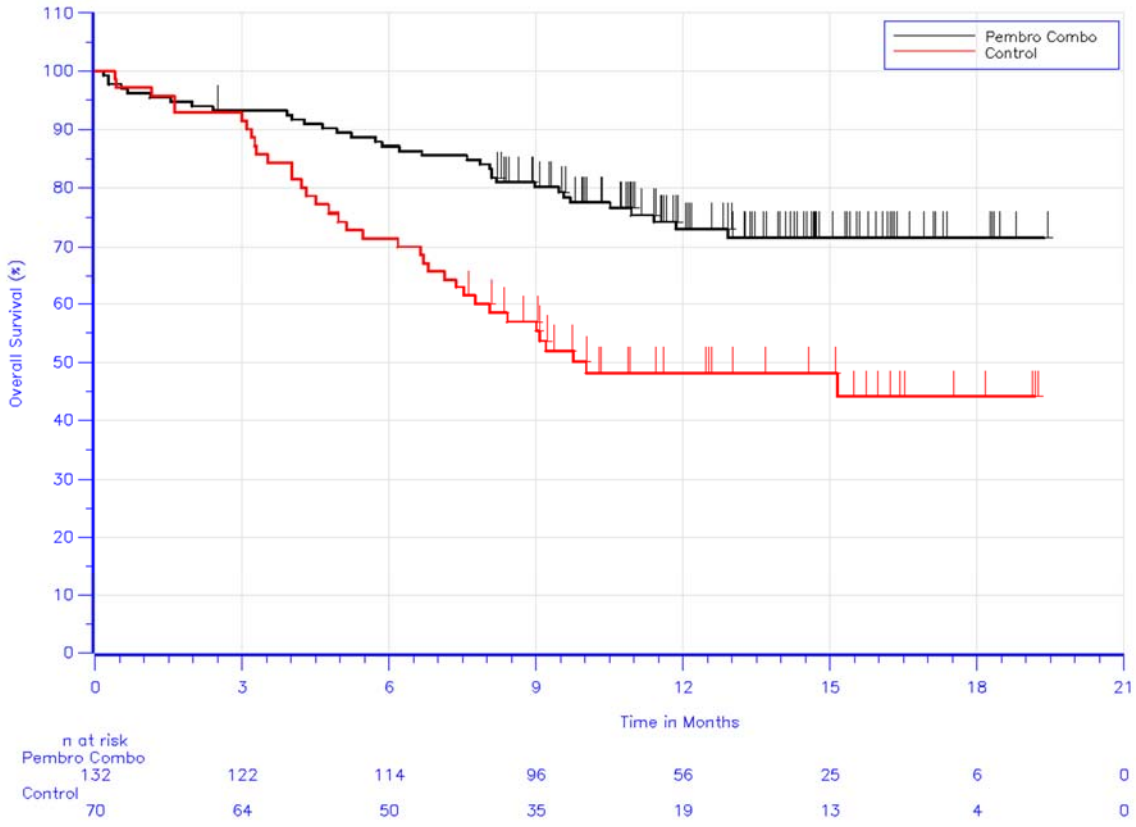
Source: Clinical Study Report[42]

Table 21: Analysis of overall survival (ITT population; TPS ≥50%)[42]

Treatment	N	Number of events (%)	Person-months	Event rate/ 100 person months	Median OSa (months) (95% CI)	OS rate at month 6 in %a (95% CI)	Hazard Ratiob (96% CI) p-value c
Pembrolizumab combination	132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.42 (0.26, 0.68); p<0.00012
Control	70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current); [c]One-sided p-value based on stratified log-rank test.
Source: Clinical Study Report[42]

Figure 10: Kaplan-Meier estimates of overall survival with TPS ≥50% (ITT population) [42]



Source: Clinical Study Report[42]

Modelling approaches on OS analysis after adjusting for crossover

This section summarises the results of the OS analyses in KEYNOTE-189, accounting for patients randomised to the control group who crossed over to pembrolizumab monotherapy or other anti-PD1/PD-L1 treatments after disease progression.

As permitted by the clinical protocol, 67 of the 206 patients randomised to the control arm crossed over to pembrolizumab monotherapy after documented disease progression. In addition, 18 patients were treated with other anti-PD1 treatment after progression. The true survival benefit associated with pembrolizumab combination is likely to be diluted by this crossover option. Therefore to adjust for the effect of crossover in the control arm, three crossover adjustment analyses have been employed: the simplified two-stage survival analysis model (two-stage adjustment)[45], the rank preserving structural failure time (RPSFT) model[46] and the inverse probability of censoring weighting (IPCW) model[47]. All three analyses have been conducted to adjust for 1) direct crossover (i.e. adjusts for patients

who crossover to pembrolizumab monotherapy as permitted by trial protocol) and 2) direct and indirect crossover (i.e adjusts for patients who crossover to pembrolizumab monotherapy as permitted by trial protocol plus patients who receive other anti-PD-1/PD-L1 therapy outside of the trial protocol).

As second line treatment with pembrolizumab is now standard of care in UK clinical practice for patients whose tumours express PD-L1, the cross-over adjustment is only relevant for those patients who would not be eligible to receive pembrolizumab treatment; i.e. those patients whose tumours do not express PD-L1 (TPS<1%). At the time of data cut-off, in patients with PD-L1 TPS<1%, [redacted] patients were randomised to the control arm and [redacted] ([redacted] %) crossed over to pembrolizumab monotherapy (direct crossover). An additional 6 patients had received PD-1 subsequent therapy outside of the study (indirect crossover).[42]

A summary of the crossover adjustment results for the TPS<1% population is presented in **Table 22**. Figures depicting the Kaplan-Meier OS curves for the unadjusted ITT population with TPS<1% and each of the primary adjustment analyses are also presented (Figures 9 to 12.) (Methodological details of the adjustment analyses are available in Appendix E.)

Table 22: Summary of OS crossover adjustment analyses in patients with PD-L1 TPS<1% (ITT population) [45-47]

Crossover adjustment method	Pembrolizumab combination vs. Control		
	Hazard Ratio	95% CI	P-value (2-sided)
ITT (TPS<1%)	[redacted]	[redacted]	[redacted]
Simplified two-stage (TPS<1%)[2]	[redacted]		
Adjusting for direct crossover only[3]	[redacted]		
Primary approach (without re-censoring)		[redacted]	[redacted]
Sensitivity 1 (with re-censoring)		[redacted]	[redacted]
Adjusting for direct and indirect crossover[4]	[redacted]		
Without re-censoring		[redacted]	[redacted]
With re-censoring		[redacted]	[redacted]
RPSFT (TPS<1%)	[redacted]		
Adjusting for direct crossover only	[redacted]		
Primary approach (without re-censoring)		[redacted]	[redacted]
Sensitivity 1 (with re-censoring)		[redacted]	[redacted]
Adjusting for direct and indirect crossover	[redacted]		

Without re-censoring With re-censoring		[redacted] [redacted]	[redacted] [redacted]
IPCW (TPS<1%)	[redacted]		
Adjusting for direct crossover Adjusting for direct and indirect crossover	[redacted]	[redacted] [redacted]	[redacted] [redacted]

[1] Two-sided p-value based on Cox regression model, ITT population, analysis not adjusted for treatment crossover

[2] Stage 1 model: Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: age, sex, brain metastasis (Yes vs. No), PD-L1 expression (<1% vs. ≥1%), smoking status (never, former/current), platinum chemotherapy (cisplatin vs. carboplatin), Region (US, EU, Rest of world) at baseline and ECOG performance status (0/1), tumour size, BMI and haemoglobin at time of progression (defined as the secondary baseline) and time to disease progression

[3] Acceleration factor: [redacted] used to shrink the survival time of control patients who crossed-over to pembrolizumab. Its estimate and the 95% CI are derived from Stage 1 Lognormal model

[4] Acceleration factor: [redacted] used to shrink the survival time of control patients who crossed-over to pembrolizumab. Its estimate and the 95% CI are derived from Stage 1 Lognormal model

[5] Bootstrap percentile confidence interval

[6] Bootstrap p-value

Source: Keytruda Analysis of Overall Survival – Adjusting to Treatment Crossover reports[45-47]

Figure 11: Kaplan-Meier curves of OS (unadjusted for crossover) in patients with PD-L1 TPS<1% (ITT population)[42]

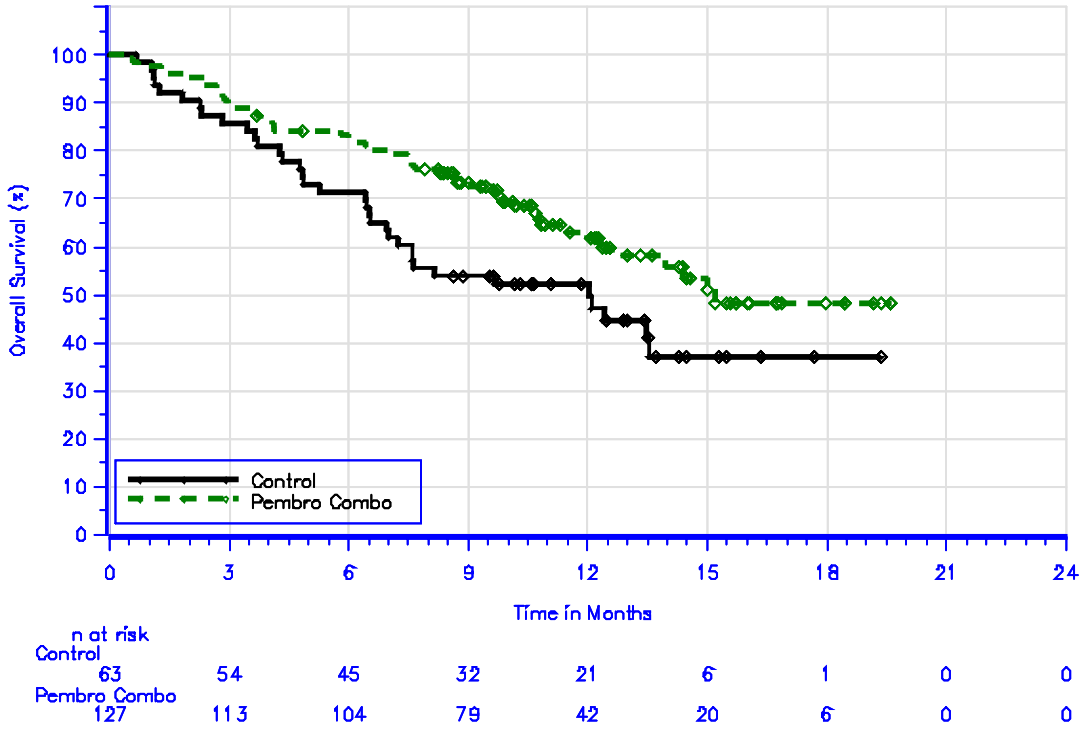
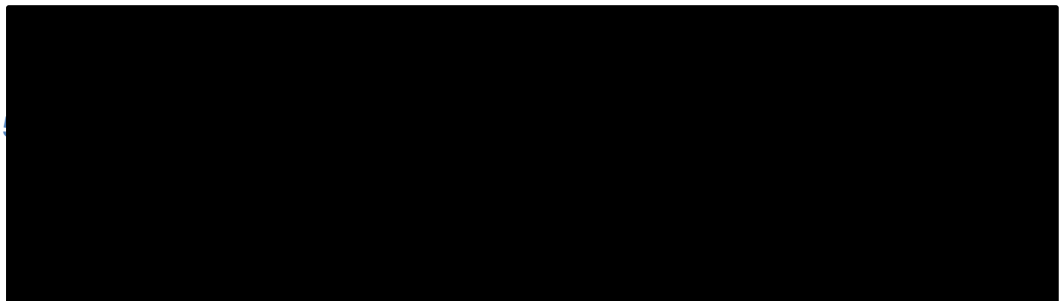


Figure 12: Kaplan-Meier curves of OS adjusting for direct crossover based on two-stage model in patients with PD-L1 TPS<1% (ITT population; primary approach)[45]

Figure 13: Kaplan-Meier curves of OS adjusting for direct crossover based on RPSFT model in patients with PPD-L1 TPS<1% (ITT population; primary approach)[46]

Figure 14: Kaplan-Meier curves of OS adjusting for direct crossover based on IPCW model in patients with PD-L1 TPS<1% (ITT population; primary approach)[47]



B.2.6.3 Progression free survival[4, 42]

Progression free survival (PFS) is defined as time from randomisation to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first, expressed in days. Patients without an event (progression or death) at the time of last tumour assessment were censored at the last disease assessment date.

A total of 410 (67%) PFS events had been reported at the time of data cut-off, [redacted]%) in the pembrolizumab combination group and [redacted]%) in the control arm. **Table 23** and

Table 24 present the results of the PFS analysis and **Figure 15** presents the Kaplan-Meier (KM) estimates of PFS in the ITT population.

Based on BICR assessment, median PFS for pembrolizumab combination was 8.8 months (95% CI 7.6, 9.2) compared with 4.9 months (95% CI 4.7, 5.5) for the control arm. This was a statistically significant and clinically meaningful benefit in PFS, equating to a 48% reduction in risk of progression or death for the pembrolizumab combination compared with the control (HR 0.52; 95% CI: 0.43, 0.64; p<0.00001) (**Table 23**). The PFS benefit for the pembrolizumab combination was maintained at 12 months; 34.1% of patients in the pembrolizumab combination and 17.3% of patients in the control were alive and progression-free (

Table 24). The KM plot for PFS based on BICR assessment demonstrated that the pembrolizumab combination curve separated early from the control curve at week 6 and was sustained throughout the remainder of the evaluation period **Figure 15**. It is worth noting that the median PFS for the pembrolizumab combination is in an area of considerable censoring, and is very likely to shift to the right with further follow-up.

Table 23: Analysis of PFS based on BICR assessment per RECIST 1.1 (primary analysis) (ITT population) [42]

Treatment	N	Number of events (%)	Person-months	Event rate/ 100 person months	Median PFS[a] (months) (95% CI)	PFS rate at month 6 in %[a] (95% CI)	Hazard Ratio[b] (96% CI) p-value [c]
Pembrolizumab combination	410	[redacted]	[redacted]	[redacted]	8.8 (7.6, 9.2)	[redacted]	0.52 (0.43, 0.64); p<0.00001
Control	206	[redacted]	[redacted]	[redacted]	4.9 (4.7, 5.5)	[redacted]	

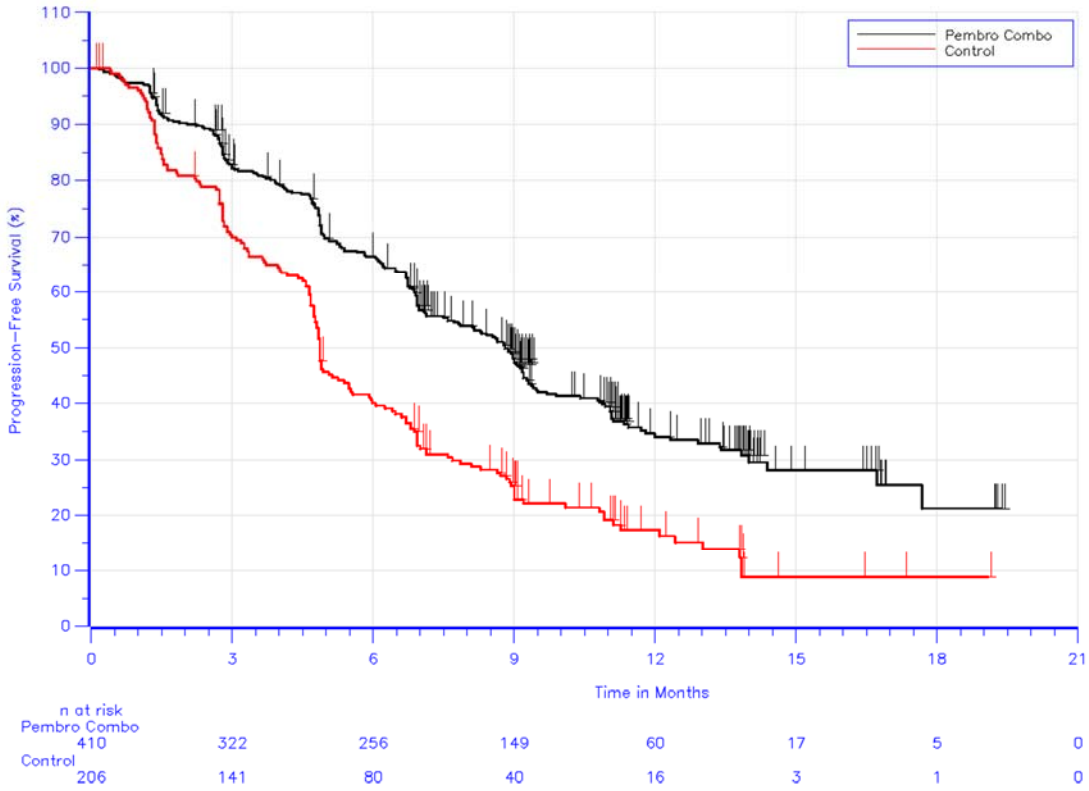
[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model; [c]One-sided p-value based on stratified log-rank test; Source: Clinical Study Report[42]

Table 24: Summary of PFS rate over time based on BICR per RECIST 1.1 (primary analysis) (ITT population) [42]

	Pembrolizumab combination N=410	Control N=206
PFS rate at 3 months (95% CI)a	[redacted]	[redacted]
PFS rate at 6 months (95% CI)a	[redacted]	[redacted]
PFS rate at 9 months (95% CI)a	[redacted]	[redacted]
PFS rate at 12 months (95% CI)a	34.1 (28.8, 39.5)	17.3 (12.0, 23.5)

aFrom the product-limit Kaplan-Meier method for censored data; Source: Clinical Study Report[42]

Figure 15: Kaplan-Meier estimates of PFS based on BICR assessment per RECIST 1.1 (primary analysis) (ITT population) [42]



Source: Clinical Study Report[42]

PFS by PD-L1 expression

The PFS benefit of the pembrolizumab combination over the control was observed across all PD-L1 expression status subgroups (

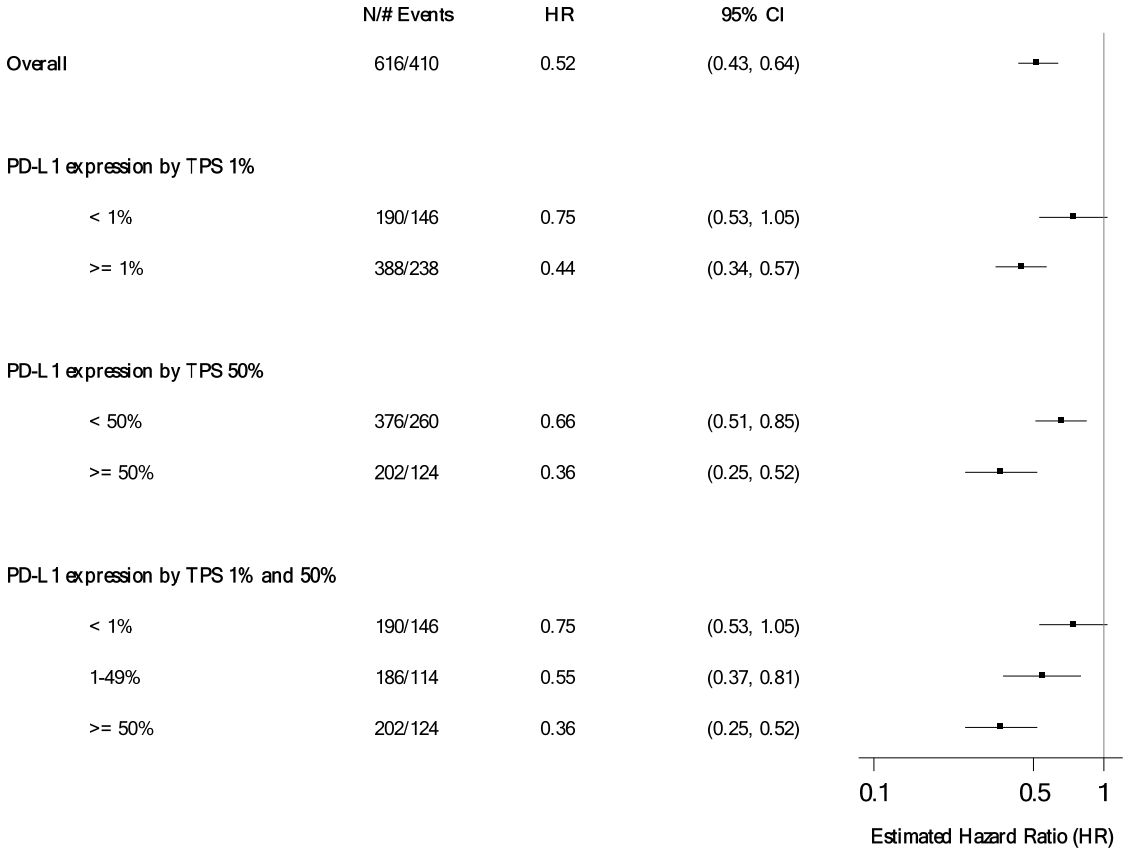
Figure 16) (TPS <1%, TPS 1-49%, and TPS ≥50%). An incremental PFS benefit was observed with increased PD-L1 expression, with improved HR.

A clinically meaningful benefit in PFS based on BICR assessment was observed with the pembrolizumab combination compared with the control in PD-L1 TPS 1 to 49% (**Table 26**) and TPS ≥50% (

Table 27) analyses with HR of 0.55 and 0.36, respectively. The KM plots revealed that the pembrolizumab combination curves for PFS based on BICR assessment separated from the control curves at week 12, about the time of the second scheduled follow-up scan, in TPS 1 to 49% (**Figure 18**) and week 6 in TPS ≥50% (**Figure 19**), which were sustained throughout the remainder of the evaluation period. The treatment effect of pembrolizumab combination was noted in the PD-L1 TPS <1%, as was reflected by the HR (**Table 25**) and KM curves

(**Figure 17**), which were directionally similar to those in the TPS 1 to 49% and TPS ≥50% PD-L1 expression categories.

Figure 16: Forest plot of PFS hazard ratio by PD-L1 expression based on BICR assessment per RECIST 1.1 (ITT population) [42]



Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). Patients with PD-L1 not evaluable are not included in the subgroup analysis.

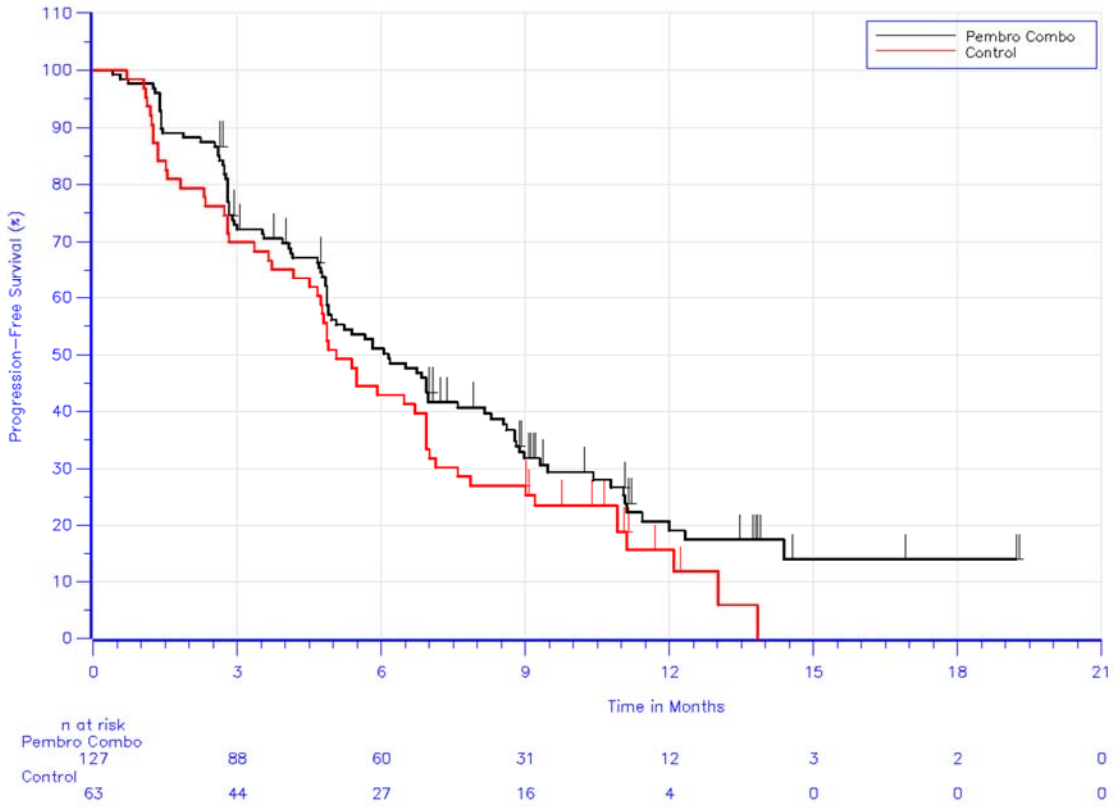
Source: Clinical Study Report[42]

Table 25: Analysis of PFS based on BICR assessment per RECIST 1.1 (ITT population; TPS<1%)[42]

Treatment	N	Number of events (%)	Person-months	Event rate/ 100 person months	Median OS[a] (months) (95% CI)	OS rate at month 6 in %a (95% CI)	Hazard Ratio[b] (96% CI) p-value[c]
Pembrolizumab combination	127	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.75 (0.53, 1.05); p=0.04756
Control	63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current); [c]One-sided p-value based on stratified log-rank test.
Source: Clinical Study Report[42]

Figure 17: Kaplan-Meier estimates of PFS (primary analysis) based on BICR per RECIST 1.1 with TPS<1% (ITT population) [42]



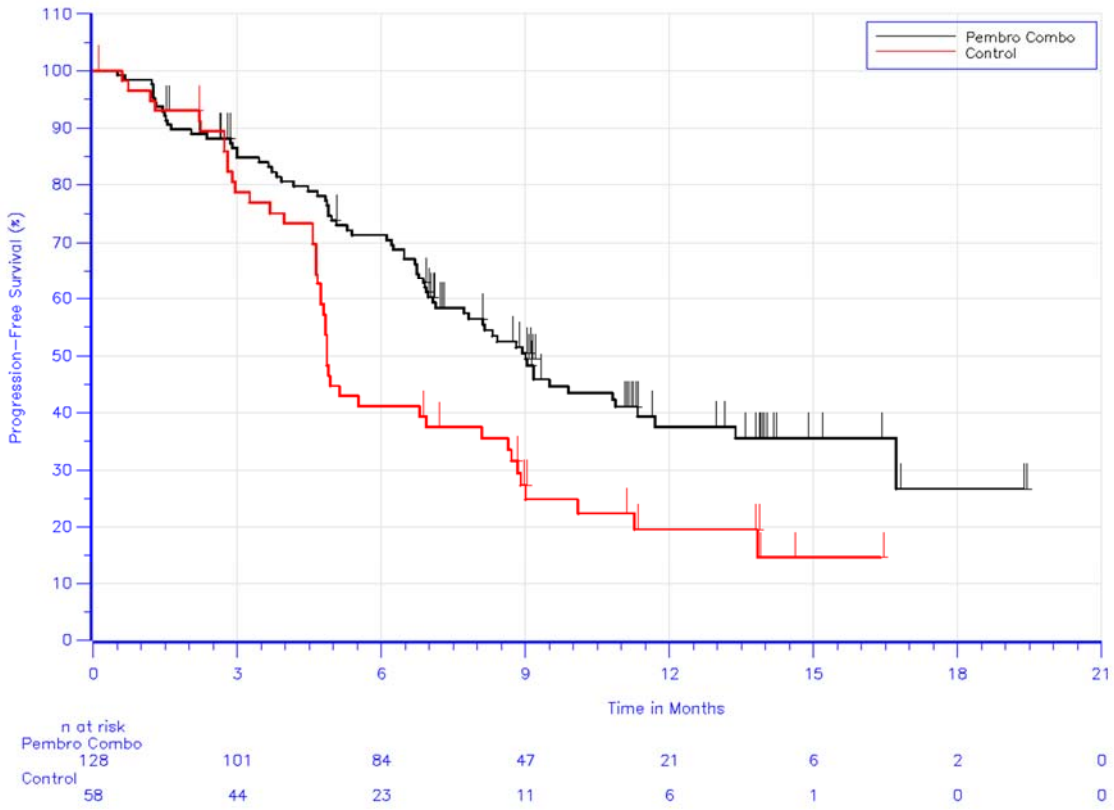
Source: Clinical Study Report[42]

Table 26: Analysis of PFS based on BICR assessment per RECIST 1.1 (ITT population; TPS 1-49%)[42]

Treatment	N	Number of events (%)	Person-months	Event rate/ 100 person months	Median OS[a] (months) (95% CI)	OS rate at month 6 in %[a] (95% CI)	Hazard Ratio[b] (96% CI) p-value[c]
Pembrolizumab combination	128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.55 (0.37, 0.81); p=0.00104
Control	58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current); [c]One-sided p-value based on stratified log-rank test.
Source: Clinical Study Report[42]

Figure 18: Kaplan-Meier estimates of PFS (primary analysis) based on BICR per RECIST 1.1 with TPS 1- 49% (ITT population) [42]



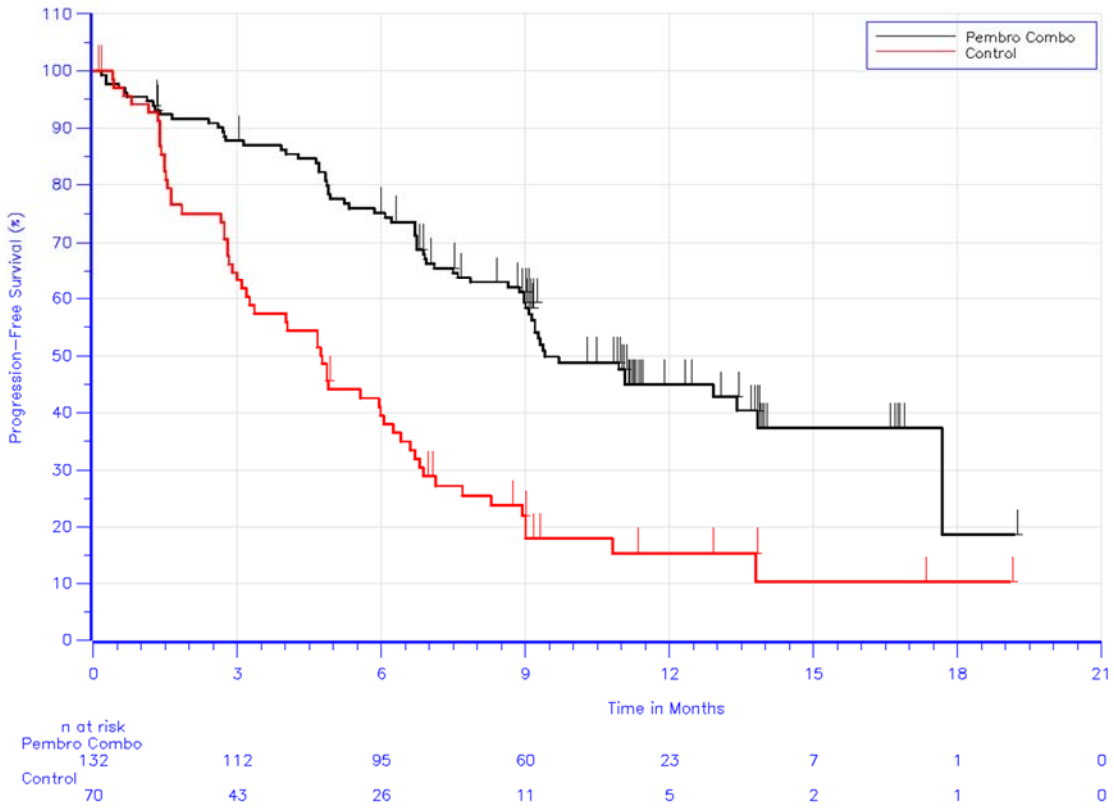
Source: Clinical Study Report[42]

Table 27: Analysis of PFS based on BICR assessment per RECIST 1.1 (ITT population; TPS ≥50%)[42]

Treatment	N	Number of events (%)	Person-months	Event rate/ 100 person months	Median OS[a] (months) (95% CI)	OS rate at month 6 in %[a] (95% CI)	Hazard Ratio[b] (96% CI) p-value[c]
Pembrolizumab combination	132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.36 (0.25, 0.52); p<0.00001
Control	70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current); [c]One-sided p-value based on stratified log-rank test.
Source: Clinical Study Report[42]

Figure 19: Kaplan-Meier estimates of PFS (primary analysis) based on BICR per RECIST 1.1 with TPS ≥50% (ITT population) [42]



Source: Clinical Study Report[42]

PFS based on investigator assessment

As per the KEYNOTE-189 study protocol, sensitivity analyses were performed for comparison of PFS based on investigator assessment (rather than BICR) per RECIST 1.1. Results of the sensitivity analyses are presented below.

Consistent with the results of the primary analysis of PFS, a statistically significant and clinically meaningful benefit in PFS was observed with the pembrolizumab combination (47% reduction in risk of progression or death) based on investigator assessment (**Table 28**), with the PFS benefit for the pembrolizumab combination group maintained at 12 months (

Table 29). The corresponding KM plot showed consistent results with the primary analysis having an early and sustained separation of the pembrolizumab combination and the control curves over time (**Figure 20**).

Table 28: PFS based on investigator assessment per RECIST 1.1 (ITT population) [42]

Treatment	N	Number of events (%)	Person-months	Event rate/ 100 person months	Median OS[a] (months) (95% CI)	OS rate at month 6 in % (95% CI)	Hazard Ratio[b] (96% CI) p-value[c]
Pembrolizumab combination	410	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53 (0.43, 0.64); p<0.00001
Control	206	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a]From product-limit (Kaplan-Meier) method for censored data; [b]Based on Cox regression model; [c]One-sided p-value based on stratified log-rank test

Source: Clinical Study Report[42]

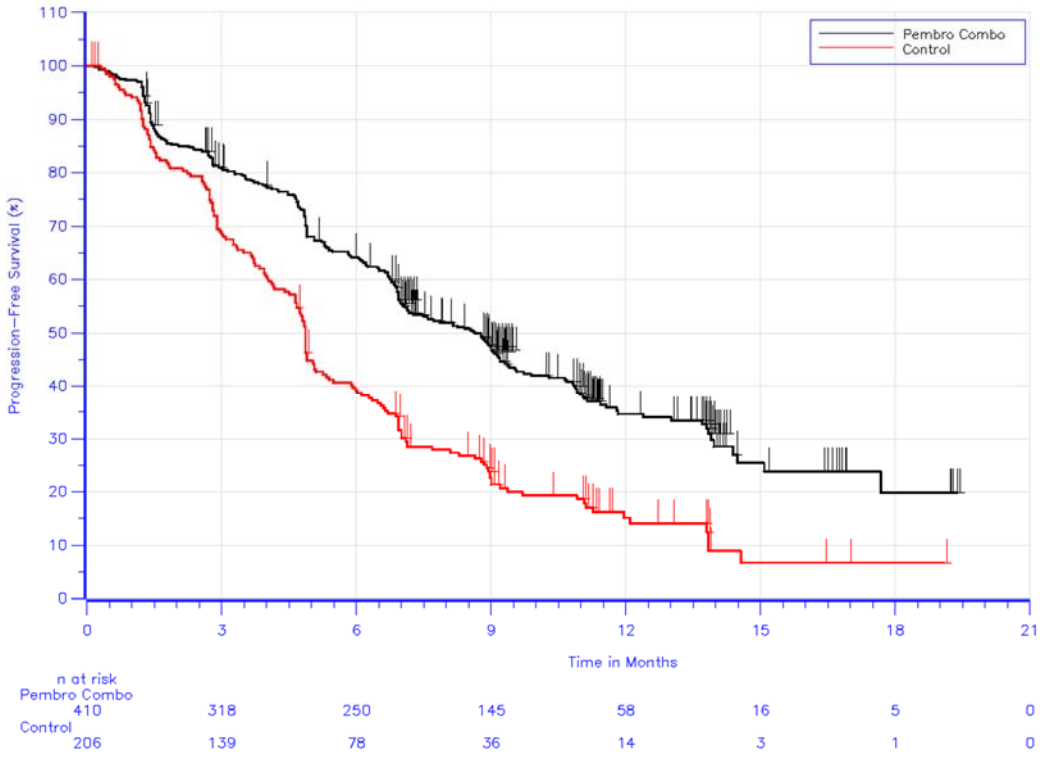
Table 29: Summary of PFS rate based on investigator assessment over time (ITT population) [42]

	Pembrolizumab combination N=410	Control N=206
PFS rate at 6 months (95% CI)a	[redacted]	[redacted]
PFS rate at 6 months (95% CI)a	[redacted]	[redacted]
PFS rate at 9 months (95% CI)a	[redacted]	[redacted]
PFS rate at 12 months (95% CI)a	[redacted]	[redacted]

[a]From the product-limit Kaplan-Meier method for censored data

Source: Clinical Study Report[42]

Figure 20: Kaplan-Meier estimates of PFS based on investigator assessment per RECIST 1.1 (ITT population) [42]



Source: Clinical Study Report[42]

B.2.6.4 Objective response rate[4, 42]

The confirmed ORR based on BICR assessment was substantially higher in the pembrolizumab combination group than the control (47.6% vs 18.9%) (**Table 30**). Statistical assessment of the difference between the treatment groups favoured the pembrolizumab combination (28.5% difference, p<0.0001) relative to the control. The rate of best overall response of PD was lower in the pembrolizumab combination (8.8%) than the control (17.5%) (**Table 31**).

Table 30: Objective response (confirmed) based on BICR assessment per RECIST 1.1 (ITT population) [42]

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control Estimate (95% CI)[a] p-value[b]
Pembrolizumab combination	410	195	47.6 (42.6,52.5)	28.5 (21.1,35.4) p<0.0001
Control	206	39	18.9 (13.8,25.0)	

[a] Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). [b]One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Source: Clinical Study Report[42]

Table 31: Summary of objective response (confirmed) based on BICR assessment per RECIST 1.1 (ITT population) [42]

	Pembrolizumab combination			Control		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Patients in Population	410			206		
Complete Response (CR)	2	0.5	[redacted]	1	(0.5)	[redacted]
Partial Response (PR)	193	(47.1)	[redacted]	38	(18.4)	[redacted]
Objective Response (CR+PR)	**195**	**(47.6)**	**(42.6, 52.5)**	**39**	**(18.9)**	**(13.8, 25.0)**
Stable Disease (SD)	152	(37.1)	[redacted]	106	(51.5)	[redacted]
Disease Control (CR+PR+SD)	**347**	**(84.6)**	[redacted]	**145**	**(70.4)**	[redacted]
Progressive Disease (PD)	36	(8.8)	[redacted]	36	(17.5)	[redacted]
Not Evaluable (NE)	10	(2.4)	[redacted]	8	(3.9)	[redacted]
Not Assessable	17	(4.1)	[redacted]	17	(8.3)	[redacted]

Note: Stable disease includes both SD and Non-CR/Non-PD. NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomisation) Not Assessable: no post-baseline assessment available for response evaluation.
Source: Clinical Study Report[42]

ORR by PD-L1 expression

The response rates in the pembrolizumab combination were consistently higher than the control for PD-L1 TPS <1% (**Table 32**), TPS 1 to 49% (**Table 33**) and TPS ≥50% (

Table 34). An incremental ORR benefit was observed with increased PD-L1 expression.

Table 32: Objective response (confirmed) based on BICR assessment per RECIST 1.1 with TPS <1% (ITT population) [42]

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control Estimate (95% CI)[a] p-value[b]
Pembrolizumab combination	127	[redacted]	[redacted]	[redacted]
Control	63	[redacted]	[redacted]	

[a] Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). [b]One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Source: Clinical Study Report[42]

Table 33: Objective response (confirmed) based on BICR assessment per RECIST 1.1 with TPS 1-49% (ITT population) [42]

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control Estimate (95% CI)[a] p-value[b]
Pembrolizumab combination	128	[redacted]	[redacted]	[redacted]
Control	58	[redacted]	[redacted]	

[a] Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). [b]One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Source: Clinical Study Report[42]

Table 34: Objective response (confirmed) based on BICR assessment per RECIST 1.1 with TPS ≥50% (ITT population) [42]

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control Estimate (95% CI)[a] p-value[b]
Pembrolizumab combination	132	[redacted]	[redacted]	[redacted]
Control	70	[redacted]	[redacted]	

[a] Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). [b]One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Source: Clinical Study Report[42]

ORR based on investigator assessment

The confirmed ORR based on investigator's assessment using RECIST 1.1 was higher with the pembrolizumab combination than the control (p<0.0001) (**Table 35**).

Table 35: Objective response (confirmed) based on investigator assessment per RECIST 1.1 (ITT population) [42]

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control Estimate (95% CI)[a] p-value[b]
Pembrolizumab combination	410	[redacted]	[redacted]	[redacted]
Control	206	[redacted]	[redacted]	

[a] Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). [b]One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Source: Clinical Study Report[42]

B.2.6.5 Duration of response[4, 42]

The median duration of response (DOR) was 11.2 months for the pembrolizumab combination and 7.8 months for the control (Table 36). The time to response was similar for the pembrolizumab combination group and the control.

Based on KM estimation, [redacted] % of responders in the pembrolizumab combination and [redacted] % of responders in the control had a response that lasted 12 months or longer (Table 36). The KM plot for DOR based on BICR assessment revealed that the pembrolizumab combination curve separated from the control curve by Month 2 with continuous separation over time (Figure 9). The median duration of response for the pembrolizumab combination is in an area of considerable censoring, and is very likely to shift to the right with further follow-up.

Table 36: Time to response and duration of response for patients with confirmed response based on BICR assessment per RECIST 1.1 (ITT population) [42]

	Pembrolizumab combination (N=410)	Control (N=206)	Total (N=616)
Number of patients with response[a]	195	39	234
Time to Response[a] (months)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Range)	2.2 (1.1-11.1)	1.4 (1.2-11.1)	1.7 (1.1-11.1)
Response Duration[b] (months)			
Median (Range)	11.2 (1.1+ - 18.0+)	7.8 (2.1+ - 16.4+)	10.7 (1.1+ - 18.0+)
Number (%[b]) of Patients with Extended Response Duration:			
≥ 3 months	[redacted]	[redacted]	[redacted]
≥ 6 months	[redacted]	[redacted]	[redacted]
≥ 9 months	[redacted]	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]	[redacted]

[a] Response: Best objective response as confirmed complete response or partial response; [b] From product-limit (Kaplan-Meier) method for censored data; "+" indicates there is no progressive disease by the time of last disease assessment. Source: Clinical Study Report[42]

Figure 21: Kaplan-Meier estimates of duration of response in patients with confirmed response based on BICR assessment per RECIST 1.1 (ITT population) [42]

Source: Clinical Study Report[42]

At the time of the data cut-off, [redacted] % of responders in the pembrolizumab combination compared to [redacted] % of responders in the control were observed to have an ongoing response to treatment (

Table 37).

Table 37: Summary of response outcome in patients with confirmed response based on BICR assessment per RECIST 1.1 (ITT population) [42]

	Pembrolizumab combination	**Control(N=206)**
Number of Patients with Response[a]	195	39
Patients who progressed or died[b] (%) Range of DoR (months)	[redacted]	[redacted]
Censored patients (%)	[redacted]	[redacted]
Patients who progressed or died after 2 or more missed visits	[redacted]	[redacted]
Patients started new anti-cancer treatment	[redacted]	[redacted]
Patients who were lost to follow-up	[redacted]	[redacted]

	Pembrolizumab combination	Control(N=206)
Patients whose last adequate assessment was ≥ 5 months prior to data cut-off date	[redacted]	[redacted]
Patients with ongoing response[c]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]
≥9 months	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]
Range of DoR (months)	[redacted]	[redacted]

[a] Response: Best overall response as confirmed complete response or partial response. [b] Include patients who progressed or died either prior to or without missing 2 or more consecutive disease assessments. [c] Ongoing response: patients who are alive, not progressed, not initiated new anti-cancer treatment, h not been determined to be lost to follow-up and whose last adequate assessment was <5 months prior to the data cut-off date. "+" indicates no progressive disease by time of last disease assessment. Source: Clinical Study Report[42]

The investigator assessment of DOR by RECIST 1.1 was similar to the BICR assessment (Table 38) (Figure 10).

Table 38: Time to response and duration of response for patients with confirmed response based on investigator assessment per RECIST 1.1 (ITT population) [42]

	Pembrolizumab combination (N=410)	Control (N=206)
Number of patients with response[a]	[redacted]	[redacted]
Time to Response[a] (months)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
Response Duration[b] (months)		
Median (Range)	[redacted]	[redacted]
Number (%[b]) of Patients with Extended Response Duration:		
≥ 3 months	[redacted]	[redacted]
≥ 6 months	[redacted]	[redacted]
≥ 9 months	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]

[a] Response: Best objective response as confirmed complete response or partial response. [b] From product-limit (Kaplan-Meier) method for censored data. "+" indicates no progressive disease by the time of last disease assessment. Source: Clinical Study Report[42]

Figure 22: Kaplan-Meier estimates of duration of response in patients with confirmed response based on investigator assessment per RECIST 1.1 (ITT population) [42]

Source: Clinical Study Report[42]

B.2.6.6 PRO endpoints[4, 42]

As described in Section B.2.3, three PRO questionnaires were employed to assess patient HRQoL in the study: EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D VAS. The PROs were analysed in the PRO FAS population (n=602), which consisted of patients who received at least 1 dose of study medication and completed at least 1 PRO assessment.

Of particular relevance to this submission is the EQ-5D VAS PRO, which was used to characterise the utility values included in the cost-effectiveness model (see Section B.3). Compliance rates for EQ-5D VAS were [redacted] % and [redacted] % at baseline for the pembrolizumab combination and control groups, respectively. Completion rates decreased at each time point post baseline as more patients discontinued the study.

EQ-5D VAS results for weeks 12 and 21 are presented in

Table 39 and

Table 40, respectively.

Table 39: Analysis of change from baseline in EQ-5D VAS at week 12 (FAS population) [42]

	Baseline		Week 12		Change from Baseline	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Week 12						
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison		Difference in LS Means (95% CI)			p-Value	
Pembrolizumab combination vs. Control		[redacted]			[redacted]	

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumour proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

For baseline and Week 12, N is the number of patients in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of patients in the analysis population in each treatment group.

p-value is based on two-sided t test

Source: Clinical Study Report[42]

Table 40: Analysis of change from baseline in EQ-5D VAS at Week 21 (FAS population) [42]

	Baseline		Week 21		Change from Baseline	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Week 21						
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembrolizumab combination vs. Control	[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumour proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

For baseline and Week 21, N is the number of patients in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of patients in the analysis population in each treatment group.

p-value is based on two-sided t test

Source: Clinical Study Report[42]

The changes in EQ-5D VAS scores from baseline to week 12 and week 21 were similar between the pembrolizumab combination and control groups of the study. However, the QoL scores in the control arm deteriorated while those in the pembro arm were maintained. There

was a difference in the EQ-5D VAS LS means at week 12 (3.82 points, 95% CI: 0.60, 7.04; two-sided nominal p=0.020) and at Week 21 (4.61 points, 95% CI: 1.03, 8.19; two-sided nominal p=0.012), favouring the pembrolizumab combination.

Section B.3.4 provides further details of the EQ-5D and utilities data used in the cost-effectiveness model. Further details of the EORTC QLQ-C30, EORTC QLQ-LC13 are presented in Section 11.5 of the KEYNOTE-189 company CSR.[42]

B.2.7 Subgroup analysis [42]

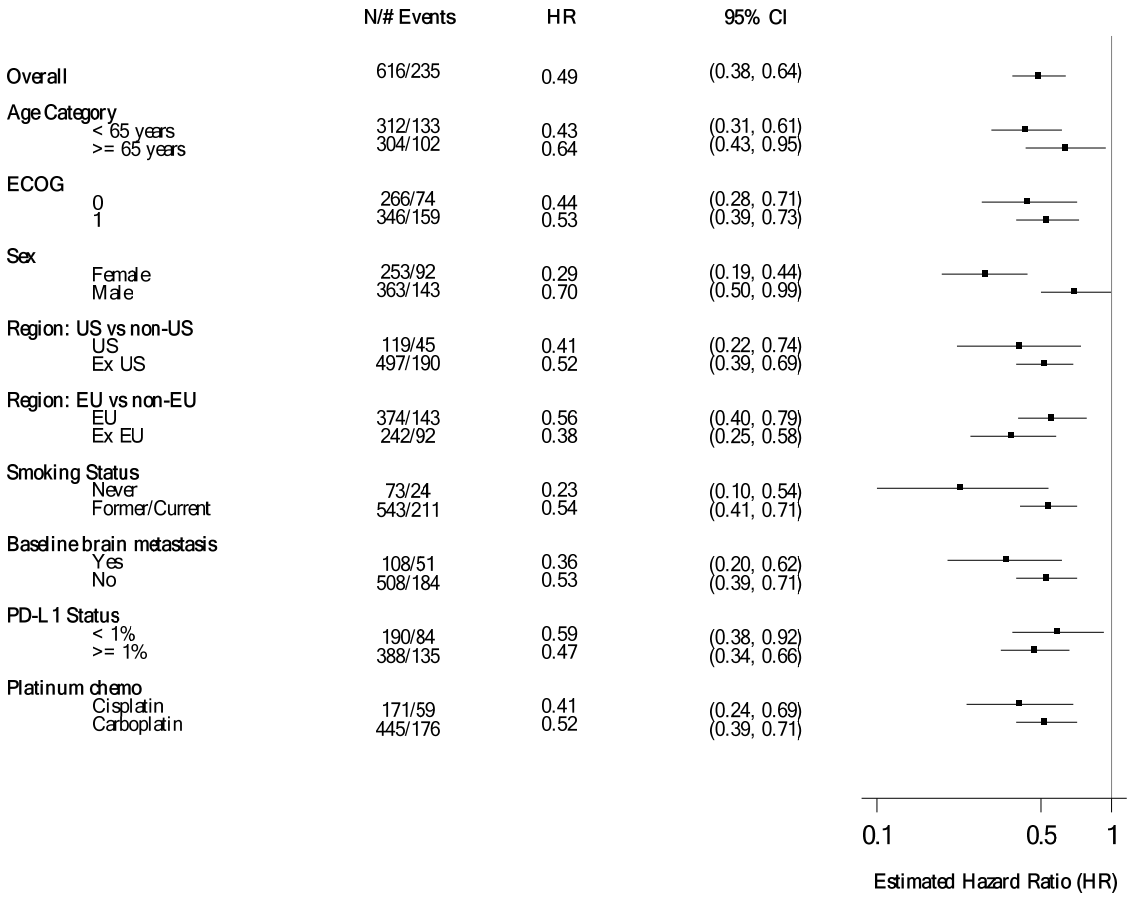
A series of subgroup analyses was pre-specified in the KEYNOTE-189 study protocol to assess the between-group treatment effect on OS, PFS and ORR of the following variables:

- Age category (<65, ≥65 years)
- ECOG Performance Scale (0, 1)
- Sex (female, male)
- Race (white, non-white)
- Geographic region (US, Ex US)
- Geographic region (EU, Ex EU)
- Smoking status (never, former/current)
- Brain metastasis status at baseline (yes, no)
- PD-L1 expression (unknown, TPS <1%, or TPS ≥1%)
- PD-L1 expression (unknown, TPS <50%, or TPS ≥50%)
- PD-L1 expression (unknown, TPS <1%, 1%≤TPS≤49%, or TPS ≥50%)
- Platinum chemotherapy (cisplatin, carboplatin)

Results of the subgroup analyses based on PD-L1 expression levels have been presented in Section B.2.6 above. In this section, we provide a summary of the results of the other subgroup analyses.

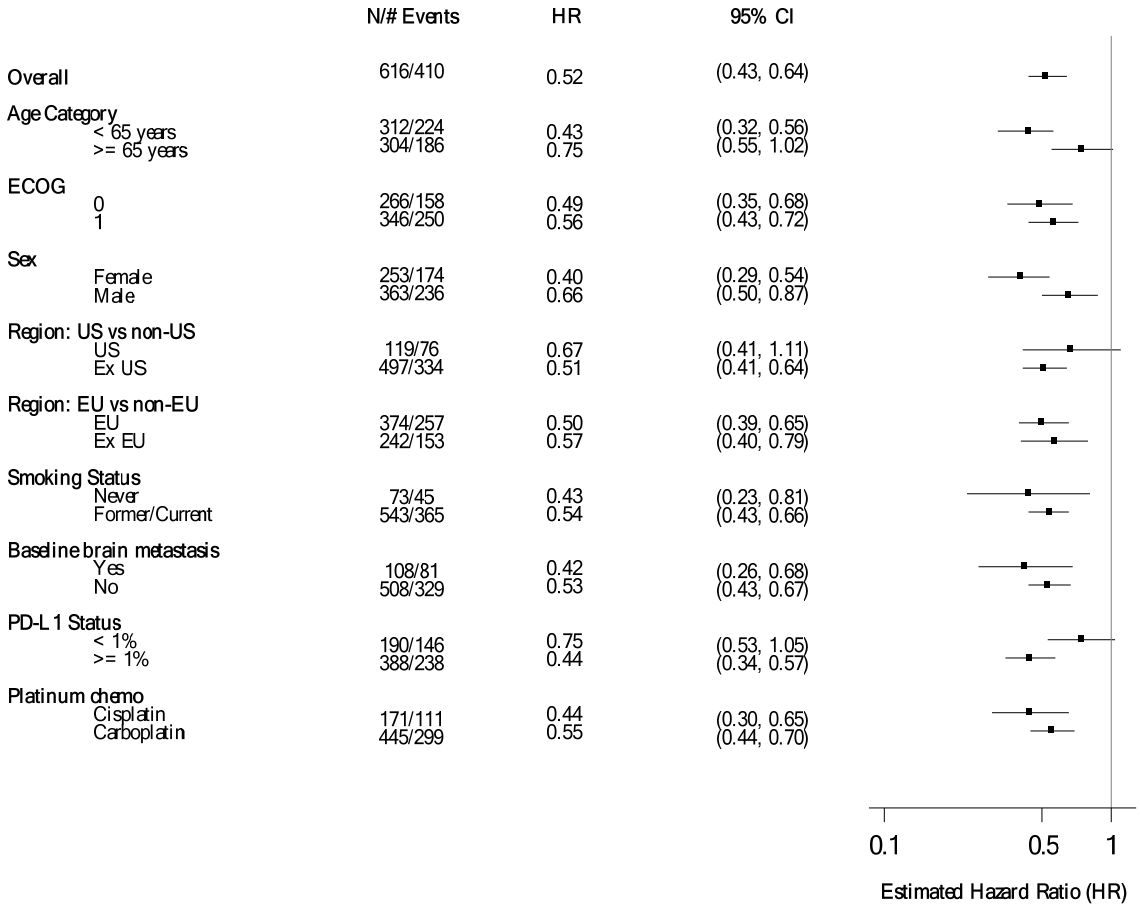
Based on the analyses conducted, the OS, PFS and ORR benefit of pembrolizumab combination over the control was observed in all subgroups, as depicted in the Forest plots in **Figure 23**, **Figure 24** and **Figure 25**. Full results of the subgroup analyses are presented in Appendix E.

Figure 23: Forest plot of OS Hazard Ratio by subgroup factors (ITT population) [42]



Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot. Patients with PD-L1 not evaluable are not included in the subgroup analysis. Source: Clinical Study Report[42]

Figure 24: Forest plot of PFS hazard ratio by subgroup factors based on BICR assessment per RECIST 1.1 (Primary censoring rule) (ITT population) [42]



Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot. Patients with PD-L1 not evaluable are not included in the subgroup analysis.Source: Clinical Study Report[42]

Figure 25: Forest plot of ORR by subgroup factors based on BICR assessments per RECIST 1.1 (ITT population) [42]

Analysis (ORR difference and 95% CI) in the overall population is based on the stratified Miettinen and Nurminen method; analysis in the subgroups is based on the unstratified Miettinen & Nurminen method. If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot. Patients with PD-L1 not evaluable are not included in the subgroup analysis. Source: Clinical Study Report[42]

B.2.8 Meta-analysis

Only one phase III, randomised, double-blind, controlled trial of pembrolizumab combination compared with a relevant comparator has been conducted: KEYNOTE-189. A second phase II, open-label, multi-cohort study, KEYNOTE-021, also included a cohort of patients in whom the efficacy and safety of pembrolizumab combination was assessed relative to chemo alone (Cohort G1), as described in Section B.2.2.

A meta-analysis has not been conducted for this submission as it was deemed inappropriate to pool pembrolizumab data from these two studies, given their different design and differences in the baseline characteristics of enrolled patients. KEYNOTE-189 is a low risk, high quality phase III trial, which included patients from the UK in 7 trial centres and which, we believe, is representative of UK clinical practice. KEYNOTE-021 is an open-label, phase II study conducted only in the USA and Japan. In addition, the performance of the control arms between the trials was different; KEYNOTE-21 Cohort G control arm performed better than historical standards while KEYNOTE-189 control arm performed in line with and at the lower end of the range of historical standards. This difference may have been related to varying gender distributions between the trials, as female gender is considered to be a positive prognostic factor in NSCLC, and KEYNOTE-021G had a higher proportion of female patients compared with KEYNOTE-189 (61% vs 41%).

While a meta-analysis has not been conducted due to the between-trial heterogeneity, data from KEYNOTE-021 Cohort G have been used to facilitate the development of a connected network in the indirect treatment comparison (ITC) presented in Section B.2.9. Furthermore, the key efficacy and safety results from this trial have also been summarised within this dossier, as they support the findings presented from the pivotal KEYNOTE-189 trial (Section B.2.2).

B.2.9 Indirect treatment comparisons

Full details of the methodology adopted in the indirect treatment comparisons described below are presented in Appendix D.

B.2.9.1 Pembrolizumab combination versus chemotherapy[48]

In the absence of head to head RCTs of pembrolizumab combination versus relevant comparators (as per the Decision Problem), an ITC was conducted. The ITC, by means of a network meta-analysis (NMA) of RCTs, assessed the relative treatment effects for the outcomes: overall survival (OS) and progression-free survival (PFS) for pembrolizumab combination versus competing interventions used routinely in UK clinical practice.

A comprehensive SLR was conducted to identify relevant studies for the ITC (details of the SLR methodology are presented in Appendix D). The SLR was initially conducted in May 2016 and subsequently updated in March 2017, November 2017, and April 2018. A total of 36 publications pertaining to 17 RCTs were considered relevant to the decision problem. Details of the identified studies and the sources of the data used in the ITC is summarised in Table 41 below.

Table 41: Summary of sources of data used in the ITC[48]

Trial	Publications	KM (OS)	KM (PFS)	HR (OS)	HR (PFS)
BEYOND	Zhou et al, 2015[49]	Figure 3A	Figure 2A	Figure 3A	Figure 2A
ECOG 4599	Sandler et al, 2006[50]	Figure 2A	Figure 2B	Figure 3	Page 2546 (text)
	Sandler et al, 2010[51]	–	–	–	–
	Tyagi et al, 2005[52]	–	–	–	–
	Gerber et al, 2013[53]	–	–	–	–
ERACLE	Galetta et al, 2015[54]	Figure 4B	Figure 4A	Figure 4B	Figure 4A
Gronberg et al, 2009	Gronberg et al, 2009[55]	Figure 3b	–	**Figure 3b**	–
	Brown et al, 2013{Brown, 2013 #308}	–	–	Table 12	–
JMDB	Scagliotti et al, 2008[56]	Figure 2	Figure 2	Figure 2	Figure 2
	Novello et al, 2010[57]	–	–	–	–
	Syrigos et al, 2010[58]	–	–	–	–
	Yang et al, 2010[59]	–	–	–	–
JMIL*	Wu et al, 2014[60]	Figure 2B	Figure 2C	Table 2	Table 2
	Eli Lilly and Company, 2013[61]	–	–	–	–
JO19907*	Niho et al, 2012[62]	Figure 2	Figure 2	Figure 2	Figure 2
Johnson et al, 2004*	Johnson et al, 2004[63]	Figure 2 Figure 4	Figure 1	**Figure 2** **Figure 4**	**Figure 1**
KEYNOTE 021G	Provided by Merck (data cut-off: May 31, 2017)	Confidential email	Confidential email	Confidential email	Confidential email
	Langer et al, 2016 (data cut-off: August 8, 2016){Langer CJ., 2016 #561}	–	–	–	–

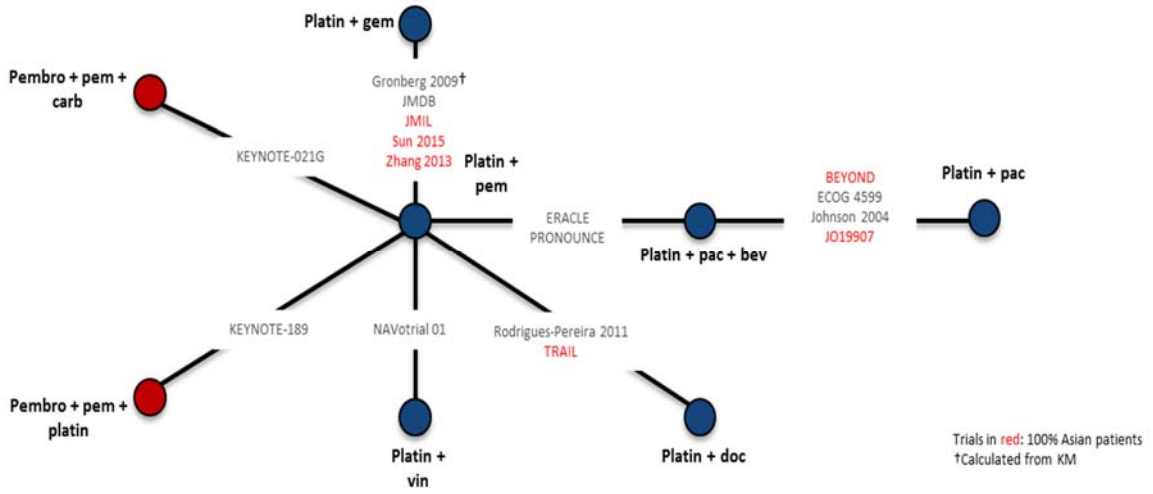
Trial	Publications	KM (OS)	KM (PFS)	HR (OS)	HR (PFS)
	Langer et al, 2016{Langer CJ, 2016 #578}	–	–	–	–
	Langer et al, 2016{Langer C, 2017 #591}	–	–	–	–
	Papadimitrakopoulou, 2017 (data cut-off: Dec 31, 2016)[64]	–	–	–	–
	Borghaei et al, 2017{Borghaei H, 2017 #592}	–	–	–	–
	Borghaei et al, 2017{Borghaei H, 2017 #593}	–	–	–	–
KEYNOTE-024†	Reck et al, 2016{Reck, 2016 #481}	Figure 2	Figure 1	Figure 2	Figure 1
	Provided by Merck (data cut-off: July 10, 2017)	--	--	--	--
	Reck et al, 2016 (supplement){Reck M, 2016 #594}	–	–	–	–
	Brahmer et al, 2017{Brahmer J, 2017 #560}	–	–	–	–
	Brahmer et al, 2017{Brahmer JR, 2017 #595}	–	–	–	–
KEYNOTE 189	Provided by Merck (data cut-off: Nov 8, 2017) [42]	Confidential email	Confidential email	Confidential email	Confidential email
	Gandhi 2018{Gandhi, 2018 #554}	–	–	–	–
NAVotrial 01	Bennouna et al, 2014[65]	Figure 3	Figure 2	Figure 3	Figure 2
PRONOUNCE	Zinner et al, 2015[66]	Figure 3C	Figure 3B	Figure 3C	Figure 3B
Rodrigues-Pereira et al, 2011	Rodrigues-Pereira et al, 2011[67]	Figure 2B	Figure 2C	Figure 2B	Figure 2C
Sun et al, 2015*	Sun et al, 2015[68]	Figure 3B	Figure 3A	Page 2453 (text)	Page 2453 (text)
TRAIL*	Park et al, 2017[69]	Figure 3C	Figure 3A	**Figure 3C**	**Figure 3A**
Zhang et al, 2013*	Zhang et al, 2013[70]	Figure 2	–	Table 2 Figure 4	–

In summary, networks of evidence were developed for both OS and PFS for a non-squamous patient population. Connected networks were feasible for both OS and PFS, and are reported below.

Overall survival

The network of evidence for OS, based on the clinical trials identified, is presented in Figure 26. Both fixed- and random-effects NMAs were conducted based on constant HRs (assuming proportional hazards). Analyses using time-varying HRs were also conducted. Results of the random-effects analysis used in the economic model (Section B.3) are shown in **Table 41.** Results of the fixed-effect NMA and time-varying HR analyses are presented in Appendix D.

Figure 26: Network of evidence for overall survival [48]



Source: Systematic literature review and meta-analysis report[48]

Pembrolizumab combination (KEYNOTE-189 data) demonstrated improved OS versus each of the comparator interventions of interest; the difference was statistically significant across all comparisons, with the greatest benefit observed between pembrolizumab versus platinum + paclitaxel (HR 0.40, 95% CI 0.25, 0.63) (Table 42). Similarly, the results for pembrolizumab combination with carboplatin (KEYNOTE-021 data) for OS demonstrated a statistically significant benefit compared with platinum + paclitaxel (HR 0.49, 95% CI 0.25, 0.95) and platinum + gemcitabine (HR 0.53, 96% CI 0.28, 0.99) (Table 42).

In addition to the random-effects NMA, a fixed-effects model was also used; see Appendix D for results. The findings of both the random- and fixed- effects models, based on KEYNOTE-189 data, were consistent, showing a statistically significant survival benefit for pembrolizumab combination therapy versus all included comparators, with the only exception being other pembrolizumab-containing regimens.

The results of the pembrolizumab combination (KEYNOTE-021) are also consistent when using either the random or fixed effects model. The results show a consistent trend of improved OS for patients; the comparisons were considered statistically significant for the pembrolizumab combination versus platinum + gemcitabine, and platinum + paclitaxel.

As shown in Figure 26, indicated in red, a number of clinical trials were conducted in an exclusively Asian population; therefore, a sensitivity analysis removing these studies was conducted. Results of the sensitivity analysis were consistent with both the random- and fixed-effects NMA results (Table 22, Appendix D), and so in an attempt to maximise the available evidence-base these trials were retained in the analysis (see Appendix D).

Table 42: Results of random-effects network meta-analysis based on constant hazard ratio assumption; overall survival; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals[48]

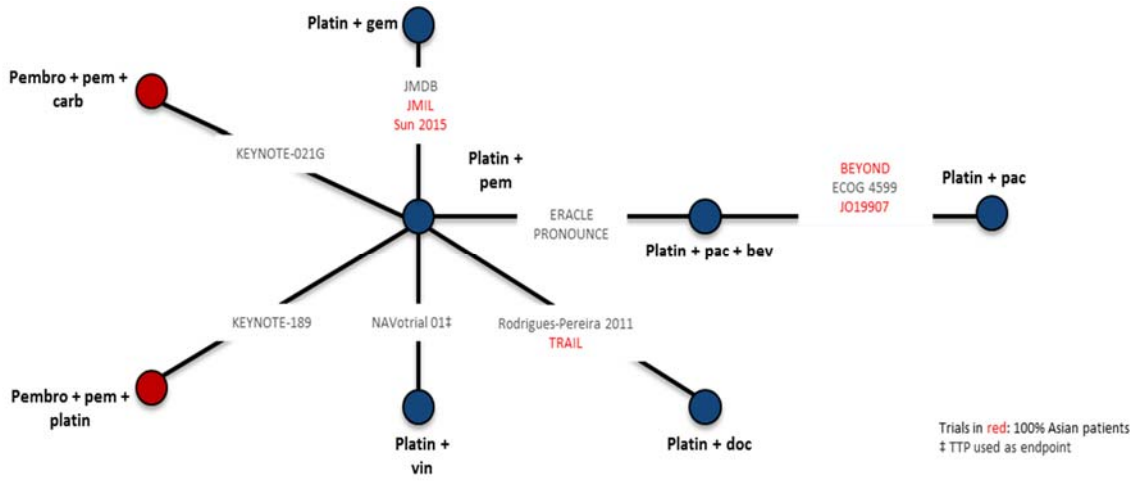
Platin + peme	1.20 (0.91, 1.59)	0.89 (0.78, 1.04)	0.82 (0.60, 1.12)	1.03 (0.79, 1.33)	1.02 (0.63, 1.63)	1.68 (0.92, 3.09)	**2.03 (1.47, 2.85)**
0.83 (0.63, 1.10)	**Platin + doc**	0.74 (0.55, 1.02)	0.68 (0.45, 1.02)	0.86 (0.58, 1.24)	0.84 (0.48, 1.48)	1.40 (0.71, 2.74)	**1.70 (1.11, 2.64)**
1.12 (0.96, 1.29)	1.34 (0.98, 1.83)	**Platin + gem**	0.92 (0.65, 1.28)	1.15 (0.84, 1.53)	1.14 (0.68, 1.85)	**1.88 (1.01, 3.52)**	**2.28 (1.58, 3.26)**
1.22 (0.90, 1.68)	1.47 (0.98, 2.23)	1.09 (0.78, 1.55)	**Platin + pac**	**1.26 (1.05, 1.49)**	1.24 (0.70, 2.19)	**2.06 (1.06, 4.08)**	**2.50 (1.59, 3.95)**
0.97 (0.75, 1.27)	1.17 (0.81, 1.72)	0.87 (0.65, 1.19)	**0.79 (0.67, 0.95)**	**Platin + pac + bev**	0.99 (0.57, 1.70)	1.64 (0.85, 3.16)	**1.98 (1.31, 3.03)**
0.98 (0.61, 1.59)	1.19 (0.68, 2.07)	0.88 (0.54, 1.46)	0.80 (0.46, 1.43)	1.01 (0.59, 1.74)	**Platin + vin**	1.65 (0.78, 3.54)	**2.01 (1.14, 3.66)**
0.60 (0.32, 1.08)	0.72 (0.37, 1.41)	**0.53 (0.28, 0.99)**	**0.49 (0.25, 0.95)**	0.61 (0.32, 1.17)	0.61 (0.28, 1.27)	**Pembro + peme + carb**	1.21 (0.60, 2.42)
0.49 (0.35, 0.68)	**0.59 (0.38, 0.90)**	**0.44 (0.31, 0.63)**	**0.40 (0.25, 0.63)**	**0.50 (0.33, 0.76)**	**0.50 (0.27, 0.88)**	0.82 (0.41, 1.66)	**Pembro + peme + platin**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically significant at the 0.05 significance level.
DIC: 22.67; Deviance: 13.26; SD: 0.08

Progression-free survival

The network of evidence for PFS is presented in Figure 27. Both random- and fixed-effects NMAs were conducted based on constant HRs (assuming proportional hazards).). Analyses using time-varying HRs were also conducted. Results of the random-effects analysis used in the economic Section B.3 are shown in Table 43 below; while the fixed-effects results and time-varying HR analyses are presented in Appendix D.

Figure 27: Network of evidence for progression-free survival [48]



Source: Systematic literature review and meta-analysis report[48]

The results of the random-effects analysis demonstrate that pembrolizumab combination therapy (KEYNOTE-189 data) provides improved PFS versus each of the comparator interventions (Table 43). These results were statistically significant favouring pembrolizumab combination therapy versus all relevant comparisons, with the greatest benefit observed between pembrolizumab chemotherapy combination versus platinum + paclitaxel (HR 0.28, 95% CI 0.13, 0.55). Pembrolizumab + pemetrexed + carboplatin (KEYNOTE-021 data) provided statistically significant improved PFS versus platinum + paclitaxel (HR 0.29, 95% CI 0.12, 0.65) and versus platinum + gemcitabine (HR 0.48, 95% CI 0.24, 0.99).

The fixed-effects NMAs reported comparable results, showing that for KEYNOTE-189 data, using either a random or fixed effects model resulted in statistically significant benefit versus all comparators. For KEYNOTE-021 data, while a direction of positive treatment effect (i.e. improved PFS) was observed for all comparisons, the results became statistically significant when using a fixed-effect model. (Table 23, Appendix D) Results of the sensitivity analysis conducted to exclude the trials with an exclusively Asian population, were consistent with findings of the fixed-effects NMA; therefore to maximise the available evidence base these trials were retained in the analysis. (Table 24, Appendix D).

Table 43: Results of random-effects network meta-analysis based on constant hazard ratio assumption; progression-free survival; base case (non-squamous); results presented as constant hazard ratios between all competing interventions along with 95% credible intervals[48]

Platin + peme	0.99 (0.67, 1.46)	0.89 (0.66, 1.19)	**0.54 (0.31, 0.85)**	0.95 (0.64, 1.39)	0.86 (0.47, 1.55)	1.84 (0.94, 3.62)	**1.92 (1.15, 3.16)**
1.01 (0.69, 1.49)	**Platin + doc**	0.90 (0.56, 1.46)	**0.54 (0.28, 0.98)**	0.96 (0.54, 1.64)	0.87 (0.43, 1.73)	1.86 (0.86, 3.98)	**1.94 (1.02, 3.59)**
1.12 (0.84, 1.51)	1.11 (0.68, 1.80)	**Platin + gem**	0.60 (0.33, 1.03)	1.07 (0.65, 1.70)	0.97 (0.50, 1.87)	**2.06 (1.00, 4.36)**	**2.16 (1.19, 3.85)**
1.86 (1.17, 3.19)	**1.85 (1.03, 3.63)**	1.65 (0.97, 3.06)	**Platin + pac**	**1.77 (1.33, 2.48)**	1.60 (0.76, 3.62)	**3.43 (1.54, 8.14)**	**3.56 (1.83, 7.49)**
1.05 (0.72, 1.57)	1.04 (0.61, 1.85)	0.93 (0.59, 1.55)	**0.57 (0.40, 0.75)**	**Platin + pac + bev**	0.91 (0.45, 1.88)	1.94 (0.91, 4.26)	**2.02 (1.08, 3.88)**
1.16 (0.65, 2.11)	1.15 (0.58, 2.34)	1.03 (0.53, 1.99)	0.63 (0.28, 1.31)	1.10 (0.53, 2.20)	**Platin + vin**	2.14 (0.88, 5.28)	**2.23 (1.04, 4.83)**
0.54 (0.28, 1.06)	0.54 (0.25, 1.16)	**0.48 (0.24, 0.99**	**0.29 (0.12, 0.65)**	0.52 (0.23, 1.09)	0.47 (0.19, 1.13)	**Pembro + peme + carb**	1.04 (0.45, 2.40)
0.52 (0.32, 0.87)	**0.52 (0.28, 0.98)**	**0.46 (0.26, 0.84)**	**0.28 (0.13, 0.55)**	**0.50 (0.26, 0.93)**	**0.45 (0.21, 0.97)**	0.96 (0.42, 2.24)	**Pembro + peme + platin**

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: 24.29; Deviance: 13.08; SD: 0.19

Conclusion

The objective of the ITC was to assess the efficacy of pembrolizumab combination therapy relative to competing interventions used in UK clinical practice for the first-line treatment of advanced NSCLC patients whose tumours had non-squamous histology and who do not have sensitising EGFR and ALK mutations, as defined in the NICE Decision Problem. Information concerning the safety and efficacy of pembrolizumab combination was obtained from KEYNOTE-189.

As described above NMA, analyses were conducted using both random- and fixed-effects models using constant hazard ratios (HR) (assuming proportional hazards assumption holds). *Note: NMA analyses using time-varying HR were also conducted but were not required for the cost-effectiveness model; see below and Appendix L for discussion*.

The evidence network for both OS and PFS was constructed by including all trials with non-squamous patients with no specific PD-L1 expression subgroups. A sensitivity analysis excluding trials conducted exclusively in Asian populations, due to potentially unknown/ unmeasured treatment effect modifiers, was conducted. Due to the limited number of trials remaining after the exclusion of Asian studies it was not possible to run random-effects NMA, as this led to an unstable estimation of the heterogeneity parameter and unreasonably wide credible intervals.

The proportional hazards assumption is key when conducting NMAs for OS and PFS based on the constant HR; this is implausible if the hazard functions of competing interventions cross. When a constant HR is used in the context of an NMA it is implicitly assumed 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).[71, 72] The hazard functions of the interventions in a trial are modelled using known parametric survival functions, and the difference in the parameters is considered the multi-dimensional treatment effect, which is synthesised (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. A horizontal line (denoting a constant HR) can be fitted between the CrIs because the change

in HR over time is not statistically significantly different from 1 as observed in time-varying NMAs. Therefore, the more parsimonious constant HR analysis may be used to draw inference with minimal risk of added bias.

Based on the results presented above, and the validity of the proportional hazards assumption, a constant HR model in this case is considered appropriate. Pembrolizumab combination using a random-effects analysis demonstrated statistically significant improvement in OS versus platin + pemetrexed, platin + docetaxel, platin + gemcitabine, platin + paclitaxel, platin + paclitaxel + bevacizumab, and platin + vinorelbine. This was unchanged when removing trials conducted in an entirely East Asian patient population. Of note, pembrolizumab combination was not significantly different to other pembrolizumab-containing regimens as seen in the base case and sensitivity analyses (Table 42).

The PFS analysis using a random-effects model also yielded statistically significant results. Based on KEYNOTE-189 data, pembrolizumab combination was superior to platin + pemetrexed, platin + docetaxel, platin + gemcitabine, platin + paclitaxel, platin + paclitaxel + bevacizumab, and platin + vinorelbine; this remained unchanged during the sensitivity analysis, i.e. removal of trials conducted in soley Asian patient populations. Similar to the result of OS, pembrolizumab combination therapy was not significantly different to other pembrolizumab-containing regimens as seen in the base case and sensitivity analyses (Table 43).

In conclusion, pembrolizumab combination (based on KEYNOTE 189 data) performs better than all competing interventions, and no different to the other pembrolizumab containing regimen (based on KEYNOTE 021G data) with respect to both OS and PFS. Additionally, sensitivity analyses which excluded exclusively Asian trials consistently did not change the results in a statistically significant manner compared to the full NMA. The results of the sensitivity analyses must be interpreted with caution, however, due to the utilisation of fixed-effects rather than random-effects models.

In all scenarios, time-varying NMAs observed that the change in HR over time is not statistically significantly different from 1, implying that the HRs can be modelled as constant over time and the proportional hazards NMA results provide the best combination of fit and parsimony.

Discussion of strengths and limitations

This study has several strengths and limitations. Among the strengths is the use of both fixed- and random-effects models as well as both constant and time-varying hazard ratios.

The consistency seen across both the fixed- and random-effects models gives confidence that the improved OS and PFS performance reported for pembrolizumab combination therapy, compared with all assessed comparator products, is reflective of expected clinical practice.

The results of our analyses show that the proportional hazards assumption holds as the change in HR over time in the time-varying NMAs was not statistically significant from 1; this provides confidence that the constant HR analysis may be used to draw inference with minimal risk of added bias.

As with all ITCs the validity of these findings are dependent on the quality of the RCTs included and the extent of any violations in the similarity and consistency assumptions across studies. In a NMA of RCTs involving multiple treatment comparisons, the randomisation holds only within the individual trials, and not across trials. If the different direct comparisons show systematic differences in study and patient characteristics, and these differences are treatment effect modifiers, then the estimates of any indirect comparison as obtained with the NMA will be biased.

Although the studies were determined to be of good quality overall (Table 28 and Table 29, Appendix D1.2.5), there were minor differences; i.e. some trials were double-blind or conducted in exclusively Asian patients. Differences in terms of race/ethnicity were accounted for by conducting a sensitivity analysis excluding exclusively Asian trials, which provided similar results to both the random- and fixed-effects NMAs. In the absence of individual patient data to adjust for differences identified, it has to be accepted that there is the risk of confounding bias if these differences act as treatment effect modifiers.

B.2.9.2 Pembrolizumab combination versus pembrolizumab monotherapytherapy[73]

To estimate the treatment difference between pembrolizumab combination and pembrolizumab monotherapy (pembrolizumab monotherapy), an ITC of OS and PFS outcomes was conducted, based on data from KEYNOTE-189 and KEYNOTE-024. Full details of the methodology adopted in this ITC are presented in Appendix D1.2.3.2. In this section, we present the results of the OS and PFS analyses.

The ITT population from both trials was used for the analysis. To provide a meaningful comparison, patients with non-squamous and strong PD-L1 expression levels (TPS ≥50%) were selected from both studies. As the control arm in KEYNOTE-189 is carboplatin/cisplatin plus pemetrexed chemotherapy, patients with the corresponding investigators' choice of SOC were selected from the KEYNOTE-024 dataset. Treatment arms and population

selection are summarised in Table 44. The ITC was performed using the Bucher method after adjusting/weighting the populations in each treatment arm using the Inverse Probability of Treatment Weighting (IPTW) method to balance out the covariates known to influence treatment outcomes (see Appendix D1.2).

Table 44: Summary of ITC patient selection[73]

KEYNOTE Trial	Treatment arms	Population Selection	Patient numbers
KEYNOTE-189	- Pembrolizumab + Chemotherapy[a] - Chemotherapy[a]	Strong PD-L1 patients (TPS ≥50%)[b]	N=202 Pembro + chemo: n=132 Chemo: n=70
KEYNOTE-024*	- Pembrolizumab - Chemotherapy[a]	Non-squamous histology patients[c]	N=199 Pembrolizumab monotherapy: n=97 Chemo: n=102

a. pemetrexed plus carboplatin/cisplatin
b. KEYNOTE-024 contains TPS ≥50% patients only, so only those patients selected from KEYNOTE-189
c. KEYNOTE-189 contains non-squamous patients only, so only those patients selected from KEYNOTE-024

* Data from KEYNOTE-024 from Final Analysis of data based on 7 July 2017 data cut-off date.

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

Overall survival

Figure 28 and Figure 29 describe the Kaplan-Meier curves for overall survival in studies KEYNOTE-189 and KEYNOTE-024, respectively while the Kaplan-Meier curves of the 4 treatment arms are displayed together in Figure 30. The Kaplan-Meier curves are based on the data as observed, prior to any population adjustment (i.e. prior to weighting approach).

Figure 28: Kaplan-Meier curves of OS in KEYNOTE-189 study population (ITT population) [73]

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

Figure 29: Kaplan-Meier curves of overall survival in KEYNOTE-024 (ITT population) [73]

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

Figure 30: Kaplan-Meier curves of OS (KEYNOTE-189 and KEYNOTE-024); Unadjusted survival curves[73]

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

Table 45 presents the results of the indirect treatment comparison of pembrolizumab combination vs. pembrolizumab monotherapy on OS after population adjustment/weighting. The ITC shows a numerical benefit in OS for pembrolizumab combination vs pembrolizumab monotherapy; however, the difference was not statistically significant; the HR for the comparison is [redacted]

Table 45: Analysis of OS (Population adjusted by weighting) (ITT population) [73]

Indirect Treatment Comparison (ITC)	Pembrolizumab + Chemotherapy[a]			Pembrolizumab monotherapy			Chemotherapy[a]					
Endpoint	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95%-CI]	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95%-CI]	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95%-CI]	Hazard Ratio[d,g] [95%-CI]	ITC Hazard Ratio[e] [95%-CI]	p-Value[f]
Overall Survival - population adjusted by weighting												
Study: P189[h]	[redacted]											
Study: P024[i]												

a: Pemetrexed and Carboplatin or Pemetrexed and Cisplatin

b: Number of patients: intention-to-treat

c: From product-limit (Kaplan-Meier) method

d: Based on weighted Cox regression model with treatment as covariate stratified by platinum chemotherapy (cisplatin vs. carboplatin), smoking status (never vs. former/current) for P189, and stratified by geographic region (East Asia vs. non-East Asia) and ECOG PS (0 vs. 1) for P024.

e: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of pembrolizumab combination (P189) vs monotherapy (P024)

f: Two-sided p-value calculated from the test statistic associated with the ITC estimate and its standard error

g: The inverse probability of treatment weighting (IPTW) method using a multinomial logistic regression was performed with covariates: platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current), ECOG PS (0 vs. 1), age, gender, metastatic stage M1B (yes vs. no), brain metastasis (yes vs. no), region (Europe, North America, Rest of World). The derived weights were used in the Cox model to adjust for population imbalance across studies and treatment arms.

h: Database Cut-off Date: 08NOV2017

i: Database Cut-off Date: 10JUL2017

CI: Confidence Interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ITC: Indirect Treatment Comparison; PD-L1: Programmed cell death 1- ligand 1.

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

Progression-free survival

Figure 31 and Figure 32 describe the Kaplan-Meier curves for PFS in studies KEYNOTE-189 and KEYNOTE-024, respectively while the Kaplan-Meier curves of the 4 treatment arms are displayed together in Figure 33. The Kaplan-Meier curves are based on the data as observed, prior to any population adjustment (i.e. prior to weighting approach).

Table 46 presents the results of the indirect treatment comparison of pembrolizumab combination vs. pembrolizumab monotherapy on PFS after population adjustment/weighting. As for OS, the ITC analysis shows a numerical benefit in PFS for pembrolizumab combination vs pembrolizumab monotherapy, however, the result was not statistically significant [redacted]

While the ITC provides evidence of a numerical benefit for pembrolizumab combination over pembrolizumab monotherapy, confidence intervals around the estimated HRs for PFS and OS were wide due to the limited sample size in the individual trials. The limited sample size was due to only a subset of the patients from each trial being included in the ITC, as previously described, in order to match patients from both studies and provide a common control arm as anchor in the ITC.

Figure 31: Kaplan-Meier curves of PFS based on BICR assessment per RECIST 1.1, KEYNOTE-189 (Primary censoring rule) (ITT population) [73]

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

Figure 32: Kaplan-Meier curves of PFS based on BICR assessment pre RECIST 1.1, KEYNOTE-024 (Primary censoring rule) (ITT population) [73]

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

Figure 33: Kaplan-Meier curves of PFS, KEYNOTE-189 and KEYNOTE-024 (unadjusted curves) [73]

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

Table 46: Analysis of PFS (Population adjusted by weighting) (ITT population) [73]

Indirect Treatment Comparison (ITC)	Pembrolizumab + Chemotherapy[a]			Pembrolizumab monotherapy			Chemotherapy[a]					
Endpoint	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95%-CI]	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95%-CI]	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95%-CI]	Hazard Ratio[d,g] [95 %-CI]	ITC Hazard Ratio[e] [95%-CI]	p-Value[f]
Progression Free Survival - population adjusted by weighting												
Study: P189[h]	[redacted]											
Study: P024[i]												

a: Pemetrexed and Carboplatin or Pemetrexed and Cisplatin

b: Number of patients: intention-to-treat

c: From product-limit (Kaplan-Meier) method

d: Based on weighted Cox regression model with treatment as a covariate stratified by platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current) for P189, and stratified by geographic region (East Asia vs. non-East Asia) and ECOG PS (0 vs. 1) for P024.

e: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of pembrolizumab combination (P189) vs monotherapy (P024)

f: Two-sided p-value calculated from the test statistic associated with the ITC estimate and its standard error

g: The inverse probability of treatment weighting (IPTW) method using a multinomial logistic regression was performed with covariates: platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current), ECOG PS (0 vs. 1), age, gender, metastatic stage M1B (yes vs. no), brain metastasis (yes vs. no), region (Europe, North America, Rest of World). The derived weights were used in the Cox model to adjust for population imbalance across studies and treatment arms.

h: Database Cut-off Date: 08NOV2017

i: Database Cut-off Date: 10JUL2017

CI: Confidence Interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ITC: Indirect Treatment Comparison; PD-L1: Programmed cell death 1- ligand 1..

Source: Indirect treatment comparison pembrolizumab combination vs pembrolizumab monotherapy[73]

B.2.10 Adverse reactions [4, 42]

In KEYNOTE-189, 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. Safety analyses were conducted in the ASaT population, which consisted of all randomised patients who received at least one dose of study treatment (n=607). Patients were included in the treatment group corresponding to the study treatment they actually received. Incidence of, causality and outcome of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AEOSI) were collected in the study. AEs were collected up to 30 days and SAEs up to 90 days after the last dose of study medication.

B.2.10.1 Extent of exposure

The duration of exposure, measured from the date of the first dose to the date of the last dose of treatment, for the ASaT population is presented in Table 47. The time on treatment was longer for the pembrolizumab combination compared with the control (median duration of exposure: [redacted] days vs. [redacted] days, respectively). The mean number of treatment cycles received was [redacted] in the pembrolizumab combination and [redacted] in the control groups.

In the pembrolizumab combination, [redacted] of 405 patients ([redacted] person-years) had duration of exposure of ≥6 months compared with [redacted] of 202 patients ([redacted] person-years) in the control. [redacted] patients in the pembrolizumab combination group received treatment for over 12 months (Table 48).

More patients in the pembrolizumab combination completed all 4 cycles of carboplatin/cisplatin than in the control. Similarly, more patients in the pembrolizumab combination received ≥5 cycles of pemetrexed (i.e., pemetrexed maintenance) than in the control, regardless of the platinum administered (Table 49 and Table 50).

Table 47: Summary of drug exposure (ASaT population) [42]

	Pembrolizumab combination (N=405)	Control (N=202)
Number of days on therapy		
Mean Median SD Range	[redacted]	[redacted]
Number of cycles		
Mean Median SD Range	[redacted]	[redacted]

For control group patients who crossed over to pembrolizumab, doses administered after crossover are excluded
Source: Clinical Study Report[42]

Table 48: Exposure by duration (ASaT population) [42]

	Pembrolizumab combination (N=405)		Control (N=202)	
	N	Person-years	n	Person-years
Duration of exposure				
>0m ≥1m ≥3m ≥6m ≥12m	[redacted]	[redacted]	[redacted]	[redacted]

Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. For control group patients who crossed over to pembrolizumab, doses administered after crossover are excluded. 1 Month = 30.4375 days. Source: Clinical Study Report[42]

Table 49: Summary of drug administration by dose regimen (ASaT population; carboplatin/pemetrexed) [4, 42]

	Pembrolizumab combination (N = 294)			Control (N = 145)		
Number of	Pembrolizumab	Pemetrexed	Carboplatin	Placebo	Pemetrexed	Carboplatin
Administrations	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1	12 (4.1)	14 (4.8)	15 (5.1)	13 (9.0)	15 (10.3)	15 (10.3)
2	22 (7.5)	23 (7.8)	23 (7.8)	16 (11.0)	16 (11.0)	16 (11.0)
3	12 (4.1)	11 (3.7)	12 (4.1)	6 (4.1)	6 (4.1)	9 (6.2)
4	16 (5.4)	23 (7.8)	244 (83.0)	13 (9.0)	14 (9.7)	105 (72.4)
>=5	232 (78.9)	223 (75.9)	0 (0.00)	97 (66.9)	94 (64.8)	0 (0.00)
Mean	10.5	9.5	3.6	7.9	7.4	3.4
SD	6.3	5.8	0.8	5.6	5.4	1.0
Median	10.0	9.0	4.0	6.0	6.0	4.0
Range	1 to 30	1 to 30	1 to 4	1 to 23	1 to 24	1 to 4

For control patients who crossed over to pembrolizumab, doses administered after crossover are excluded.
Source: Clinical Study Report[42] and Gandhi et al, 2018[4]

Table 50: Summary of drug administration by dose regimen (ASaT population; cisplatin/pemetrexed) [4, 42]

	Pembrolizumab combination (N = 294)			Control (N = 145)		
Number of	Pembrolizumab	Pemetrexed	Cisplatin	Placebo	Pemetrexed	Cisplatin
Administrations	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1	5 (4.5)	6 (5.4)	6 (5.4)	3 (5.3)	3 (5.3)	3 (5.3)
2	8 (7.2)	7 (6.3)	7 (6.3)	7 (12.3)	7 (12.3)	7 (12.3)
3	5 (4.5)	5 (4.5)	8 (7.2)	2 (3.5)	2 (3.5)	2 (3.5)
4	5 (4.5)	6 (5.4)	90 (81.1)	4 (7.0)	4 (7.0)	45 (78.9)
>=5	88 (79.3)	87 (78.4)	0 (0.00)	41 (71.9)	41 (71.9)	0 (0.00)
Mean	11.2	10.4	3.6	8.4	8.0	3.6
SD	6.8	6.6	0.8	5.8	5.1	0.9
Median	11.0	9.0	4.0	7.0	7.0	4.0
Range	1 to 26	1 to 26	1 to 4	1 to 26	1 to 19	1 to 4

For patients who crossed over to pembrolizumab from the control group, doses administered after crossover are excluded. Source: Clinical Study Report[42] and Gandhi et al, 2018[4]

B.2.10.2 Adverse events

The adverse event profile observed for pembrolizumab combination and control arms were generally consistent with the known safety profiles of the respective therapies administered. Table 51 provides a summary of overall adverse experiences in the ASaT population.

Comparable proportions of patients in the pembrolizumab combination and control experienced AEs (99.8% vs 99.0%), drug-related AEs (91.9% vs 90.6%), Grade 3-5 AEs (67.2% vs 65.8%) and SAEs ([redacted] % vs [redacted] %). Drug-related Grade 3 to 5 AEs ([redacted] % vs [redacted] %) and drug-related SAEs ([redacted] % vs [redacted] %) were observed more frequently with pembrolizumab combination than control. The greater exposure in the pembrolizumab combination (in terms of increased cycles of both pembrolizumab and pemetrexed) resulted in an increased possibility for an AE to develop and be collected.

Higher rates of discontinuation of any drug within the treatment regimen due to an AE, irrespective of AE category, occurred in the pembrolizumab combination compared with the control (27.7% vs 14.9%). Importantly, the rate of discontinuation of all drugs due to an AE was similar across both trial arms ([redacted] % vs [redacted] %). The differences in discontinuation rates between the treatment groups may be attributable to the longer duration of exposure to pembrolizumab and pemetrexed for patients in the pembrolizumab combination. Patients in the control were more likely to discontinue treatment for PD.

The number of reported deaths was similar between the 2 treatment groups (pembrolizumab combination: 6.7%; control: 5.9%).

Table 51: Adverse event summary (ASaT population) [4, 42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with one or more adverse events	404	(99.8)	200	(99.0)	604	(99.5)
with no adverse event	1	(0.2)	2	(1.0)	3	(0.5)
with drug-related† adverse events	[redacted]		[redacted]		[redacted]	
with toxicity grade 3-5 adverse events	272	(67.2)	133	(65.8)	405	(66.7)
with toxicity grade 3-5 drug-related adverse events	[redacted]		[redacted]		[redacted]	
with serious adverse events	[redacted]		[redacted]		[redacted]	
with serious drug-related adverse events	[redacted]		[redacted]		[redacted]	
who died	27	(6.7)	12	(5.9)	39	(6.4)
who died due to a drug-related adverse event	[redacted]		[redacted]		[redacted]	
discontinued any drug due to an adverse event	112	(27.7)	30	(14.9)	142	(23.4)
discontinued pembrolizumab or placebo	82	(20.2)	21	(10.4)	103	(17.0)
discontinued any chemotherapy	[redacted]		[redacted]		[redacted]	
discontinued all drugs	[redacted]		[redacted]		[redacted]	
discontinued any drug due to a drug-related adverse event	[redacted]		[redacted]		[redacted]	
discontinued pembrolizumab or placebo	[redacted]		[redacted]		[redacted]	
discontinued any chemotherapy	[redacted]		[redacted]		[redacted]	
discontinued all drugs	[redacted]		[redacted]		[redacted]	
discontinued any drug due to a serious adverse event	[redacted]		[redacted]		[redacted]	
discontinued pembrolizumab or placebo	[redacted]		[redacted]		[redacted]	
discontinued any chemotherapy	[redacted]		[redacted]		[redacted]	
discontinued all drugs	[redacted]		[redacted]		[redacted]	
discontinued any drug due to a serious drug-related adverse event	[redacted]		[redacted]		[redacted]	
discontinued pembrolizumab or placebo	[redacted]		[redacted]		[redacted]	
discontinued any chemotherapy	[redacted]		[redacted]		[redacted]	

† Determined by the investigator to be related to the drug. For patients who crossed over to pembrolizumab from the Control group, adverse events occurred after the first dose of cross phase are excluded. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Grades are based on NCI CTCAE version 4.03. Source: Clinical Study Report[42] and Gandhi et al, 2018[4]

Overall AEs

The most frequently reported AEs were nausea (pembrolizumab combination: 55.6%; control: 52.0%), anaemia (pembrolizumab combination: 46.2%; control: 46.5%), and fatigue (pembrolizumab combination: 40.7%; control: 38.1%) (Table 52). No substantial differences in the types and frequencies of AEs were reported between the treatment groups, except for higher rates of diarrhoea and rash in the pembrolizumab combination versus control. When adjusted for exposure, however, the frequencies of diarrhoea and rash were similar between the treatment groups. These events were predominantly Grade 1 or 2 and easily managed. Diarrhoea and rash are well-known AEs of both pembrolizumab and chemotherapy.

Table 52: Patients with adverse events by decreasing incidence (incidence ≥10% in one or more treatment groups) (ASaT population) [4, 42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with one or more adverse events	404	(99.8)	200	(99.0)	604	(99.5)
with no adverse events	1	(0.2)	2	(1.0)	3	(0.5)
Nausea	225	(55.6)	105	(52.0)	330	(54.4)
Anaemia	187	(46.2)	94	(46.5)	281	(46.3)
Fatigue	165	(40.7)	77	(38.1)	242	(39.9)
Constipation	141	(34.8)	64	(31.7)	205	(33.8)
Diarrhoea	125	(30.9)	43	(21.3)	168	(27.7)
Decreased appetite	114	(28.1)	61	(30.2)	175	(28.8)
Neutropenia	110	(27.2)	49	(24.3)	159	(26.2)
Vomiting	98	(24.2)	47	(23.3)	145	(23.9)
Cough	87	(21.5)	57	(28.2)	144	(23.7)
Dyspnoea	86	(21.2)	52	(25.7)	138	(22.7)
Asthenia	83	(20.5)	49	(24.3)	132	(21.7)
Rash	82	(20.2)	23	(11.4)	105	(17.3)
Pyrexia	79	(19.5)	30	(14.9)	109	(18.0)
Oedema peripheral	78	(19.3)	26	(12.9)	104	(17.1)
Thrombocytopenia	73	(18.0)	29	(14.4)	102	(16.8)
Lacrimation increased	69	(17.0)	22	(10.9)	91	(15.0)
Back pain	52	(12.8)	23	(11.4)	75	(12.4)
Alanine aminotransferase increased	49	(12.1)	18	(8.9)	67	(11.0)
Dizziness	49	(12.1)	19	(9.4)	68	(11.2)
Headache	48	(11.9)	19	(9.4)	67	(11.0)
Blood creatinine increased	47	(11.6)	16	(7.9)	63	(10.4)
Dysgeusia	46	(11.4)	19	(9.4)	65	(10.7)
Hypokalaemia	44	(10.9)	15	(7.4)	59	(9.7)
Pruritus	43	(10.6)	21	(10.4)	64	(10.5)
Upper respiratory tract infection	41	(10.1)	15	(7.4)	56	(9.2)
Pneumonia	37	(9.1)	22	(10.9)	59	(9.7)

Source: Clinical Study Report and Gandhi et al, 2018[4, 42]

Drug-related AEs

The drug-related AEs observed for patients treated with the pembrolizumab combination were generally consistent with the known safety profiles of pembrolizumab monotherapy and pemetrexed/platinum chemotherapy.

Drug-related AEs were reported for the majority of patients in both pembrolizumab combination and control groups ([redacted]% vs [redacted]%). The most commonly reported drug-related AEs were nausea (pembrolizumab combination: [redacted] %; control: [redacted] %), anaemia (pembrolizumab combination: [redacted] %; control: [redacted] %), fatigue (pembrolizumab combination: [redacted] %; control: [redacted] %), and neutropenia (pembrolizumab combination: [redacted] %; control: [redacted] %) (Table 53). No substantial differences in the types and frequencies of drug-related AEs were reported between the treatment groups, except for a higher incidence of diarrhoea ([redacted] % vs [redacted] %) and increased lacrimation ([redacted] % vs [redacted] %) in the pembrolizumab combination versus control. When adjusted for exposure, the rates of both diarrhoea and increased lacrimation were generally similar between the treatment groups. These events were predominantly Grade 1 or 2 and easily managed. Diarrhoea is a well-known AE of both pembrolizumab monotherapy and chemotherapy, and increased lacrimation has been described as a chemotherapy-related AE.

Table 53: Patients with drug-related AEs by decreasing incidence (incidence >10% in one or more treatment groups (ASaT population) [42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacrimation increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report[42]

Grade 3 to 5 AEs

A total of 405 (57.3%) patients experienced 1 or more Grade 3 to 5 AEs (Table 54). The most commonly reported Grade 3 to 5 AEs were anaemia (pembrolizumab combination: 16.3% vs. control: 15.3%) and neutropenia (pembrolizumab combination: 15.8% vs. control: 11.9%). With the exception of febrile neutropenia (pembrolizumab combination: 6.7% vs. control: 2.0%), no substantial differences in the types and frequencies of Grade 3 to 5 AEs were reported between the treatment groups. The exposure-adjusted event rate of febrile neutropenia remained higher in the pembrolizumab combination group compared with control (pembrolizumab combination: [redacted] events/100 person-months vs control: [redacted] events/100 person-months). The febrile neutropenia events most often occurred early in the course of treatment during induction when all 3 drugs were administered. By the time of data cut-off, the febrile neutropenia events had resolved, or were resolving. Febrile neutropenia and neutropenia are not known risks of pembrolizumab monotherapy in patients with NSCLC.

Table 54: Patients with grade 3-5 AEs by decreasing incidence (incidence ≥5% in one or more treatment group) (ASaT population) [4, 42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	272	(67.2)	133	(65.8)	405	(66.7)
with no adverse events	133	(32.8)	69	(34.2)	202	(33.3)
Anaemia	66	(16.3)	31	(15.3)	97	(16.0)
Neutropenia	64	(15.8)	24	(11.9)	88	(14.5)
Thrombocytopenia	32	(7.9)	14	(6.9)	46	(7.6)
Febrile neutropenia	23	(5.7)	16	(7.9)	39	(6.4)
Asthenia	25	(6.2)	7	(3.5)	32	(5.3)
Fatigue	27	(6.7)	4	(2.0)	31	(5.1)
Pneumonia	23	(5.7)	5	(2.5)	28	(4.6)
Diarrhoea	21	(5.2)	6	(3.0)	27	(4.4)
Dyspnoea	15	(3.7)	11	(5.4)	26	(4.3)

Source: Clinical Study Report and Gandhi et al, 2018[4, 42]

Drug-related Grade 3 to 5 AEs

More patients in the pembrolizumab combination had a drug-related Grade 3 to 5 AEs compared with the control (pembrolizumab combination: [redacted] %; control: [redacted] %); the most

commonly reported events were neutropenia (pembrolizumab combination: [redacted] % vs. control: [redacted] %) and anaemia (pembrolizumab combination: [redacted] % vs. control: [redacted] %) (Table 55). The frequencies and types of drug-related Grade 3 to 5 AEs reported in the pembrolizumab combination were generally consistent with the known safety profiles of pembrolizumab monotherapy and pemetrexed/platinum chemotherapy.

Table 55: Patients with drug-related grade 3 to 5 AEs by decreasing incidence (incidence ≥5% in one or more treatment groups (ASaT population) [42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report[42]

Serious AEs (SAEs)

Approximately half of the patients ([redacted] /607; [redacted] %) experienced at least 1 SAE, and a similar percentage of patients in the pembrolizumab combination experienced an SAE as in the control group ([redacted] % vs [redacted] %). The SAEs reported in the pembrolizumab combination were generally consistent with the known safety profiles of pembrolizumab monotherapy and pemetrexed/platinum chemotherapy. The incidence of febrile neutropenia was higher in the pembrolizumab combination compared with the control (pembrolizumab combination: [redacted] %; control: [redacted] %). (Table 56)

Table 56: Patients with SAEs by decreasing incidence (incidence in ≥5% one or more treatment groups) (ASaT population) [42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report[42]

Drug-related serious AEs (SAEs)

There were [redacted] ([redacted] %) patients with 1 or more drug-related SAEs. More patients in the pembrolizumab combination had a drug-related SAE than in the control (pembrolizumab combination: [redacted] %; control: [redacted] %). (Table 57) The most commonly reported drug-related SAE was febrile neutropenia, the frequency of which was higher in the pembrolizumab combination compared with the control (pembrolizumab combination: [redacted] %; control: [redacted] %). The drug-related SAEs in the pembrolizumab combination were generally consistent with the known safety profiles of pembrolizumab monotherapy and pemetrexed/platinum chemotherapy.

Table 57: Patients with drug-related SAEs by decreasing incidence (incidence in ≥5% one or more treatment groups) (ASaT population) [42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report[42]

Summary of deaths

Thirty nine patients died due to an AE during the trial; 27 in the pembrolizumab combination and 12 in the control group. The proportion of deaths due to AEs was similar between the treatment groups (pembrolizumab combination: 6.7%; control: 5.9%). Immune-mediated pneumonitis, which occurred in 3 patients (0.7%) in the pembrolizumab combination group, was the most frequently reported immune-mediated AE resulting in death; the frequency was consistent with that previously observed with pembrolizumab monotherapy in NSCLC trials.

Adverse Events of Special Interest (AEOSI)

Adverse events of special interest (AEOSIs), defined as immune-mediated events and infusion-related reactions associated with pembrolizumab, are presented regardless of investigator-reported causality.

Table 58 presents a summary of the AEOSIs in the ASaT population. There were 116/607 (19.1%) patients with 1 or more AEOSIs (pembrolizumab combination: 92/405 (22.7%); control: 24/202 (11.9%)). A total of 45/607 (7.4%) patients experienced Grade 3 or higher AEOSIs (pembrolizumab combination: 36/405 (8.9%); control: 29/202 (4.5%). Three patients (0.7%) in the pembrolizumab combination arm died due to an AEOSI of Grade 5 pneumonitis. Table 59 shows the patients with AEOSIs by AEOSI category.

In general, the frequencies and severity of the AEOSIs observed during the trial were similar to that previously described for pembrolizumab monotherapy. The exception may be nephritis and acute kidney injury, both of which are also associated with pemetrexed and platinum-based drugs and occurred with a greater frequency in this trial than in earlier trials of pembrolizumab monotherapy.

Table 58: Summary of AEOSI including all risk categories (ASaT population) [4, 42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	N	(%)
Patients in population	405		202		607	
with one or more adverse events	92	(22.7)	24	(11.9)	116	(19.1)
with no adverse event	313	(77.3)	178	(88.1)	491	(80.9)
[redacted]						
with toxicity grade 3-5 adverse events	36	(8.9)	9	(4.5)	45	(7.4)
[redacted]						
	3	(0.7)	0	(0.0)	3	(0.5)
[redacted]						

† Determined by the investigator to be related to the drug. For control group patients who crossed over to pembrolizumab, adverse events occurring after the first dose of crossover phase are excluded. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. Grades are based on NCI CTCAE version 4.03. Source: Clinical Study Report and Gandhi et al, 2018[4, 42]

Table 59: Patients with AEOSI by AEOSI category (incidence >0% in one or more treatment groups) (ASaT population) [4, 42]

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with one or more adverse events	92	(22.7)	24	(11.9)	116	(19.1)
with no adverse events	313	(77.3)	178	(88.1)	491	(80.9)
Adrenal Insufficiency	1	(0.2)	1	(0.5)	2	(0.3)
Colitis	9	(2.2)	0	(0.0)	9	(1.5)
Hepatitis	5	(1.2)	0	(0.0)	5	(0.8)
Hyperthyroidism	16	(4.0)	6	(3.0)	22	(3.6)
Hypophysitis	3	(0.7)	0	(0.0)	3	(0.5)
Hypothyroidism	27	(6.7)	5	(2.5)	32	(5.3)
Infusion Reactions	10	(2.5)	2	(1.0)	12	(2.0)
Myositis	1	(0.2)	0	(0.0)	1	(0.2)
Nephritis	7	(1.7)	0	(0.0)	7	(1.2)
Pancreatitis	3	(0.7)	0	(0.0)	3	(0.5)
Pneumonitis	18	(4.4)	5	(2.5)	23	(3.8)
Severe Skin Reactions	8	(2.0)	5	(2.5)	13	(2.1)
Thyroiditis	1	(0.2)	0	(0.0)	1	(0.2)
Type 1 Diabetes Mellitus	1	(0.2)	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column. A bolded term 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. For control group patients who crossed over to pembrolizumab, adverse events occurring after the first dose of crossover phase are excluded. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. Source: Clinical Study Report and Gandhi et al, 2018[4, 42]

B.2.11 Ongoing studies

Results provided in this submission are from IA1 of the KEYNOTE-189 clinical trial, based on a data cut-off date of 8 November 2017. As described in Section B.2.4, the timing of further analyses is event-driven, with an additional interim analysis of the study scheduled after approximately [redacted] PFS events and the final analysis of the study after [redacted] death events are observed. The final analysis is currently estimated for [redacted].

B.2.12 Innovation

Pembrolizumab, a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2 enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity. Currently, first line treatment with pembrolizumab in the UK is limited to those patients whose tumours have high levels of PD-L1 expression (TPS ≥50%).[36] The clinical efficacy and safety data presented in this submission show that pembrolizumab, when combined with chemotherapy, offers a durable benefit in PFS and OS for all lung cancer patients, regardless of PD-L1 expression levels, with an acceptable tolerability profile.[4, 42]

B.2.13 Interpretation of clinical effectiveness and safety evidence

The safety and efficacy data from IA1 of KEYNOTE-189, as presented in this submission, are robust and demonstrate substantial, clinically meaningful benefit of pembrolizumab combination compared with chemo control for all efficacy endpoints in previously untreated patients with non-squamous NSCLC. In addition, the safety results from the study are largely consistent with the established safety profile of pembrolizumab plus pemetrexed and platinum-based chemotherapy, and affirm an acceptable tolerability profile in the target population.

The key findings from the study are summarised below.

Pembrolizumab combination significantly prolongs OS and PFS and results in higher ORR and longer duration of response compared with current chemotherapy SOC

After median follow-up of 10.5 months, first line treatment with pembrolizumab combination significantly prolonged OS (HR 0.49; 95% CI 0.38, 0.64; p<0.00001) and PFS (HR 0.52; 95% CI 0.43, 0.64; p<0.00001) compared with chemotherapy control in patients with advanced non-squamous NSCLC, regardless of PD-L1 expression levels. While median OS in the pembrolizumab combination arm was not reached (11.3 months, range 8.7, 15.1 for control), median PFS was 8.8 months (range 7.6, 9.2) compared with 4.9 months (4.7, 5.5) for control. The Kaplan-Meier curves for both OS and PFS separated early at approximately month 1 and either continued (OS) or was maintained (PFS) over time. Improvements in OS and PFS were seen in all PD-L1 subgroups analysed, with incremental benefit observed with increased PD-L1 expression. Pembrolizumab combination also resulted in significantly

higher confirmed ORR compared with control (47.6% vs 18.9%). The median response duration was 11.2 months for pembrolizumab combination and 7.8 months for control.

The results of KEYNOTE-189 are supported by the results of the NMA conducted to compare the relative treatment effects of pembrolizumab combination to each specific chemotherapy regimen of interest in the UK setting. The NMA demonstrated that pembrolizumab combination was statistically superior to all non-pembrolizumab containing regimens assessed, in terms of both OS and PFS. Furthermore, an ITC comparison of pembrolizumab combination efficacy revealed a numerical benefit in both OS (HR [redacted] 95%: [redacted]) and PFS (HR [redacted], 95%: [redacted]) over pembrolizumab monotherapy; however, the results were not statistically significant.

Pembrolizumab combination treatment effect on OS, PFS and OR was observed in all subgroups assessed and regardless of PD-L1 expression levels

The benefit of pembrolizumab combination treatment over control was reported in all subgroup analyses, including age, gender, geographic region, smoking status, brain metastasis status, platinum chemotherapy option and PD-L1 expression levels.

HRQoL was maintained in pembrolizumab combination patients while patients in the chemo control group experienced deteriorating HRQoL

Analyses of HRQoL based on the PRO analyses conducted in KEYNOTE-189 indicate that the addition of pembro to chemotherapy did not exacerbate treatment-related symptoms and improved disease-related symptoms in the target patient population. Baseline HRQoL scores, based on EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D, were similar for both treatment groups. By week 12 of treatment, regardless of the instrument used, there was a slight improvement in HRQoL in the pembrolizumab combination group compared with a deterioration in the control group. Thereafter, until week 48, HRQoL were improved or maintained to a greater degree in the pembrolizumab combination group than in the control group.

Pembrolizumab combination has an acceptable tolerability profile

The AE summary profile observed for patients in the KEYNOTE-189 trial was generally consistent with the known safety profiles of pembrolizumab monotherapy and pemetrexed/platinum chemotherapy. Comparable proportions of patients in both treatment

arms experienced AEs, drug-related AEs, Grade 3 to 5 AEs and SAEs. More pembrolizumab combination patients experienced drug-related Grade 3 to 5 AEs compared with the control. The longer duration of exposure in the pembrolizumab combination group resulted in an increased possibility for an AE to develop.

The most frequently-reported AEs across both treatment groups were nausea, anaemia and fatigue. Most AEs were generally mild and easily managed. Diarrhoea and rash – both well-known AEs of pembrolizumab monotherapy and chemotherapy – were more frequently reported in the pembrolizumab combination group; however, when adjusted for exposure, the event rates were similar across the groups.

Pembrolizumab combination treatment was associated with higher rates of discontinuation of any drug, irrespective of AE category, compared with control while the rate of discontinuation of all drugs was similar in both treatment groups. The differences in discontinuation rates may be attributable to the longer duration of exposure to pembrolizumab and pemetrexed for patients in the pembrolizumab combination. Patients in the control were more likely to discontinue treatment for PD. The number of reported deaths was similar between the 2 treatment groups. As expected, the incidence of AEOSI was higher in the pembrolizumab combination groups compared with control. Of the 92 patients in the pembrolizumab combination group who experienced AEOSIs, 32 had grade 3-5 AEOSIs and 3 patients died due to the AEOSI.

Internal Validity

KEYNOTE-189 is a robust, multicentre, randomised, active-controlled, double-blind phase III trial of pembrolizumab combination versus control in previously untreated adults with advanced or metastatic non-squamous NSCLC. Treatment allocation/randomisation was stratified by PD-L1 expression (TPS ≥1% vs <1%), platinum chemotherapy (cisplatin vs carboplatin) and smoking status (never vs former/current).

The co-primary efficacy endpoints were OS and PFS. Both are clinically relevant endpoints that were directly referenced in the final scope for this appraisal and the decision problem. 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-189 followed an established response evaluation criteria (RECIST 1.1) in the primary efficacy analysis, in line with European guidance.[74]

HRQoL was an exploratory endpoint of the KEYNOTE-189 study, with changes from baseline in patients treated with pembrolizumab combination compared to control recorded using both the preferred measure of EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC QLQ-C30 and lung cancer specific EORTC QLQ-LC13 (see section 5.4).

In addition to being double blind, with both patients and clinicians blinded to treatment assignment, for PFS analysis, the independent radiologists who performed the central imaging review were also blinded to treatment assignment, in order to minimise bias.

The control enrolled more female and younger patients, than the pembrolizumab combination. Otherwise, the treatment groups were relatively well balanced in terms of baseline characteristics. Both treatment groups had similar proportions of patients with brain metastases at baseline. PD-L1 expression indicated by TPS ≥1% and <1% was similar in both treatment groups. There were few “never smokers” in both groups, which were equally balanced. Most of the patients received carboplatin rather than cisplatin in both the pembrolizumab combination and the control.

External validity

KEYNOTE-189 was a global study conducted in 143 academic medical centres in 16 countries, including 76 sites in Europe. Of the patients participating in the study, 61% were enrolled at sites in Europe (including 30 patients from the UK).

Baseline characteristics of patients enrolled in KEYNOTE-189 were as expected for patients with advanced NSCLC. The majority of patients were male, white, with mean age around 63 years old. Most patients were current or former smokers and had adenocarcinomas (Table **10**).

The observed safety profile of pembrolizumab combination in KEYNOTE-189 was consistent with that seen previously with pembrolizumab for the treatment of advanced NSCLC [21, 22] and other types of tumours.[75-79]

End-of-life criteria

An overview of published data on life expectancy of UK patients with Stage IV NSCLC was provided in Section B.1.3.1. To recap: There is a paucity of data reporting long-term survival

of NSCLC patients who are diagnosed with Stage IV disease in the UK. The most recent data identified (for 2014 followed up to 2015), reported one year survival of 15% for men and 19% for women diagnosed with Stage IV disease. We found only one publication with 5-year survival data for patients diagnosed at Stage IV, reported at only 3% (based on 2006-2011 data).

In recent years, newer treatment options have become available for NSCLC patients with advanced disease, including pembrolizumab monotherapy for patients with high levels of PD-L1 expression (TPS ≥50%) which can be expected to increase the long term survival estimates over first-line SoC patients. However, in the absence of recently published long-term survival expectations for UK Stage IV lung cancer patients, at the June 2018 ASCO meeting in the US, we conducted an informal survey of expert physicians' estimates of survival in the patient population from KEYNOTE-189. The majority of 11 physicians surveyed reported that 5 year survival remains between 2 and 5%, indicating that the first of the end-of-life criteria is met and that significant unmet need remains for life-extending treatment options for this patient population.

As the median OS of pembrolizumab combination was not reached in the latest analysis of KEYNOTE-189, it is not possible to confirm the treatment provides at least a 3 month extension to life over SoC. However, the modelled estimated differences from the cost-effectiveness analysis indicate a difference of 11.2 months (See Section B.3.3).

Table 60: 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-189 trial, median OS was [redacted] in the pembrolizumab combination arm compared with 11.3 months in the control arm. The OS of 11.3 months observed in the SoC arm is in line with previous studies where median OS in patients with NSCLC (regardless of histology) receiving chemotherapy SoC ranged from 9.9 to 13.9 months.(4) IN KEYNOTE-024 trial, median OS of 14.2 months was observed in the SOC arm (range 9.8, 19.0 months).(80) According to the PARAMOUNT trial of pemetrexed maintenance therapy in advanced non-squamous NSCLC, the median OS was 13.9 months.(81)
There is sufficient evidence to indicate that the treatment	Pembrolizumab combination offers an extension to life of at least 3 months compared to SoC: • Since median OS in the latest analysis of KEYNOTE-189 was [redacted]

Criterion	Data available
offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	[redacted], it is not possible to estimate the difference in median OS for pembrolizumab combination-treated patients compared with SoC treatment patients. [4] • However, the estimated differences (based on discounted values) from the cost-effectiveness model are: o 13.9 months (ITT base case 30.4-16.1)

B.2.14 Cancer Drugs Fund suitability

Within this submission MSD are seeking a recommendation for pembrolizumab combination (pembrolizumab combination) for use within the CDF as a treatment for adults with untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC).

The rationale for seeking a CDF recommendation is that MSD acknowledges the Committee will believe that more certainty will be required around the OS benefit given the immaturity of the data when it is known that further analyses will be conducted. This is particularly relevant given that the trial, and the MSD base case, cover the entire population irrespective of PDL1 expression.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Relevant cost-effectiveness studies from the published literature were identified through a systematic literature review carried out on the 14th April 2015, and updated twice; on the 17th September 2017 and on the 2nd April 2018. The target population in this submission is patients with untreated metastatic non-squamous non-small cell lung cancer. However, the scope of the review was broadened to patients with squamous or non-squamous NSCLC and including patients with EGFR and ALK mutations, in order to identify all relevant data that could inform the development and population of the model. The first stage in the review was to identify all relevant economic evidence for the comparator treatments by implementing comprehensive searches. The following research question was posed in accordance with the decision problem:

1. What is the cost-effectiveness of comparator therapies to pembrolizumab combination in untreated patients with metastatic non-small cell lung cancer?

The original search included studies of both first and second line metastatic non-small cell lung cancer; the updated searches only included studies of first line metastatic non-small cell lung cancer.

The original database, internet and hand searches identified 5,519 records. A total of 30 cost-effectiveness studies were included that reported on cost-effectiveness in the first line setting. Within the updated searches, 1,647 new records were identified, from which 20 cost-effectiveness studies were finally included; 17 from the first update, 3 from the second update.

A total of 50 cost-effectiveness studies for patients with first-line metastatic non-small cell lung cancer were identified, that met all the inclusion criteria. Of the 50 studies, data was extracted only from UK studies reporting the cost-effectiveness of Pembrolizumab combination of which none were identified. Therefore a summary of published cost-effectiveness studies has not been compiled.

B.3.2 Economic analysis

Of the two cost effectiveness studies assessing pembrolizumab in untreated NSCLC, both were partitioned survival models consisting of three health states (progression free, progressed and death).With this in mind, a cost-effectiveness model was developed using the PSM approach as previously used to assess the cost-effectiveness of pembrolizumab combination in combination compared with relevant comparators.

B.3.2.1 Patient population

The patient population included in the economic evaluation consisted of patients with advanced NSCLC, who received no prior systemic chemotherapy treatment. This is in line with the proposed licenced indication and with the final NICE scope [1].

The main body of clinical evidence for pembrolizumab combination compared to SoC was derived from the KEYNOTE-189 study, which included previously untreated advanced NSCLC patients with no sensitizing EGFR mutation or ALK translocation [42].

The baseline characteristics of the patients included in the model are presented in Table 61.

Table 61. Baseline characteristics of patients included in the model

Patient Characteristics	Mean	Measurement of uncertainty and distribution	Reference / Source
Average age*	62 [82]	-	KEYNOTE-189
Proportion male*	63.6%[82]	-	KEYNOTE-189
Average BSA (m^2)*	1.81[82]	SD = 0.21	KEYNOTE-189

*These values refer to patients recruited from European sites participating in KEYNOTE-189.

B.3.2.2 Model structure

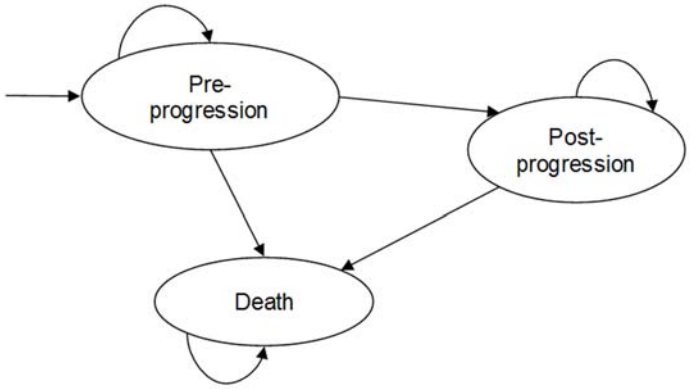
Consistent with the majority of economic models developed for recent NICE oncology submissions in advanced NSCLC [32, 83] [33], a de-novo economic analysis was built as a 'partitioned-survival' area-under-the-curve model. The model consisted of three health states: pre-progression, post-progression and death (see Figure 34). This approach was also in line with the clinical endpoints assessed in KEYNOTE-189, in which PFS and OS were assessed as primary endpoints [84]. A cycle length of one week was considered sufficient to reflect the patterns of treatment administration and the transitions to disease progression

and death. In line with previous submissions, a half-cycle correction was applied to mitigate bias [85] [86] [87] [32] [5, 88] [33] [89, 90].

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 [5, 88] [86] [91] [85, 89, 90].

Disease progression was defined per RECIST v1.1 as assessed by BICR (which was the primary endpoint in KEYNOTE-189 [84]).

Figure 34. Model structure



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 combination KEYNOTE-189 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 [84, 92].
- 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-189, two treatment arms were compared, pembrolizumab combination (pembrolizumab plus carboplatin/cisplatin + pemetrexed) and SoC (placebo plus carboplatin/cisplatin + pemetrexed).

In the model, patients in the pembrolizumab combination arm were assumed to be eligible to receive treatment until progression or for a maximum treatment duration of 2 years (consistent with the 35 cycle maximum for trial protocol) with pembrolizumab and 4 cycles with chemotherapy consistent with the KEYNOTE-189 trial protocol [93]|[42] [84]. Additionally, the current NICE recommendations for the use of pembrolizumab monotherapy for the treatment of advanced NSCLC states that pembrolizumab is to be stopped at 2 years of uninterrupted treatment [5, 88].

Patients treated with SoC were also assumed to receive treatment until a maximum number of 4 cycles, aimed to reflect clinical practice in England (see section B.3.5).

Both treatment arms were eligible for pemetrexed maintenance therapy following 1L treatment until disease progression or unacceptable toxicity. 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-189 trial.

Since patients in KEYNOTE-189 could receive subsequent oncologic therapies after treatment discontinuation, the costs of these subsequent treatments were included in the economic evaluation according to the proportion of patients receiving them after treatment

discontinuation from the trial. In addition, cross over from the SoC arm to pembrolizumab was allowed during the trial but since 2L IO therapy is standard of care in the UK for patients expressing PD-L1 [94, 95], cross over adjustment has not been implemented in the ITT base case analysis.

Subgroup analysis at different levels of PD-L1 expression (≥50%, 1%≤TPS≤49% and <1% TPS) has been conducted and within this, cross over adjustment has been made in the <1% TPS subgroup for which 2L IO therapy is not SoC in the UK in order to better reflect the OS in the absence of switching. When crossover adjustments were implemented here, 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 second line treatment in line with the proportions reported in KEYNOTE 189 (same assumption as the pembrolizumab combination arm) when crossover adjustments were considered.

Three methods for cross over adjustment in the <1% TPS subgroup have been implemented in the model – 2 stage, IPCW and RPSFTM, results of which are presented in section B.3.9. Further details of this analysis can be found in the clinical section B.2.6.

To capture more accurately the impact of pembrolizumab combination upon quality of life, the utilities considered in the base case analysis were based on time-to-death categories. Time-to-death sub-health states were used to capture patients' quality of life as a function of how much lifetime patients had left until they eventually died as predicted in the model. The use of time-to-death sub-health states was applied considering four time-to-death categories: <30 days to death and ≥30 days to 180; ≥180 to 360 days, and ≥360 days. Monitoring costs were captured based on whether patients were receiving active therapy as part of first or second treatment lines, and also based on their progression status [96].

3.2.3 Key features of the economic analysis

Table 62: Features of the economic analysis

	Previous appraisals			Current appraisal	
Factor	**Pemetrexed 1L (TA181)**	**Pemetrexed maintenance (TA402)**	**Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2017) NICE technology appraisal 447**	**Chosen values**	**Justification**
Time horizon	Lifetime (6 years)	Lifetime (equivalent to 15.99 years; range: 6-20 years)	Lifetime (20 years)	Lifetime (20 years)	Lifetime horizon for the defined target population (0% of patients in the pembrolizumab combination arm and 0% in the SoC arm were still alive after this period in the base case). In line with most recent advanced or metastatic NSCLC NICE submissions[5, 88].
Cycle length	21 days (i.e. 3 weeks)	21 days (i.e. 3 weeks)	1 week	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[5, 88].
Half-cycle correction	A half-cycle correction appeared to have been disabled for costs and used incorrectly for outcomes	Yes	Yes	Yes	In line with previous submissions and to mitigate bias[5, 88, 94, 95]

	Previous appraisals			Current appraisal	
Factor	**Pemetrexed 1L (TA181)**	**Pemetrexed maintenance (TA402)**	**Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2017) NICE technology appraisal 447**	**Chosen values**	**Justification**
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	Yes	Yes[97]	NICE reference case 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
Discount of 3.5% for utilities and costs	The 'in-trial' analysis did not use discounting on either costs or outcomes, despite trial follow-up extending to more than 2 years for some patients. The ERG stated that this was an important omission, because much of the survival gain occurred after the first 12 months and would therefore be likely to be affected by discounting.	Yes	Yes	Yes[97]	NICE reference case

	Previous appraisals			Current appraisal	
Factor	**Pemetrexed 1L (TA181)**	**Pemetrexed maintenance (TA402)**	**Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2017) NICE technology appraisal 447**	**Chosen values**	**Justification**
Perspective (NHS/PSS)	Yes	NHS	NHS	Yes[97]	NICE reference case. 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[5, 88, 94, 95].
Treatment waning effect	Not mentioned	The committee considered comments from a clinical expert mentioning that continued benefit of pemetrexed over BSC after disease progression were difficult to explain, but no further analyses seemed to have been conducted to assess the impact of this assumption.	Considered in scenario analyses	Not considered.	There is no evidence that treatment effect stops after discontinuation. Considered in scenario analyses
Source of utilities	Nafees et al. (2008), which was a study commissioned by the manufacturer to study second-line treatment of NSCLC.	PARAMOUNT EQ-5D individual patient data.	KEYNOTE-024 EQ-5D individual patient data.	KEYNOTE-189 EQ-5D individual patient	NICE reference case

	Previous appraisals			Current appraisal	
Factor	**Pemetrexed 1L (TA181)**	**Pemetrexed maintenance (TA402)**	**Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2017) NICE technology appraisal 447**	**Chosen values**	**Justification**
				data[97].	
Source of costs	Patient level data from the clinical trial and resource use events from the JMDB clinical trial database	Resource use data from PARAMOUNT	Published literature, resource utilisation and costs accepted in previous NICE submissions	Published literature, resource utilisation and costs accepted in previous NICE submissions	These reflect resource utilisation and costs accepted in previous NICE submissions.
PSS, personal social services; QALYs, quality-adjusted life years					

B.3.2.3 Intervention technology and comparators

The intervention (pembrolizumab combination) was included in the model as per the proposed licensed dosing regimen (i.e.pembrolizumab administered intravenously at a fixed dose of 200 mg over 30 minutes combined with pemetrexed 500 mg/m2 every 3 weeks (Q3W) and platinum chemotherapy (investigator's choice of cisplatin [75 mg/ m2] or carboplatin [5mg/mL/min] Q3W for 4 cycles).

The proposed licence states that pembrolizumab is to be administered until disease progression or unacceptable toxicities. There is no evidence regarding the optimal duration of treatment with pembrolizumab; however, the KEYNOTE-189 protocol mandated a maximum of 35 cycles of pembrolizumab (2 years). Treatment with pemetrexed continued until one of the discontinuation criteria occurred.

In line with the comparator assessed in KEYNOTE-189, SoC (based on the trial chemotherapy arm) 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 combination with the most commonly used platinum-based chemotherapy options in the UK. Clinical experts have suggested that these treatments are likely to be the same as those used in clinical practice in England.

- In the base case, distribution of SoC platinum based chemotherapies observed in KEYNOTE-189 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.

The following comparators were also assessed as per the NICE scope [(1)] with efficacy estimates derived from a network meta-analysis and indirect treatment comparison. Further detail available in B.2.8 and B.2.9.

- 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

- Pembrolizumab monotherapy (≥50%TPS only)

- Pemetrexed-based combinations were shown to have a lower OS HR compared to, for example, vinorelbine-based combinations, which are also used in clinical practice in the UK. Therefore, we expect KEYNOTE-189 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 63. Distribution of patients according to platinum-based chemotherapy combinations in KEYNOTE-189 vs. market shares

	KEYNOTE-189 (base case)	UK market shares
Gemcitabine/carboplatin	n/a	3.3%
Gemcitabine/cisplatin	n/a	8.0%
Paclitaxel/carboplatin	n/a	0%
Paclitaxel/cisplatin	n/a	0%
Docetaxel/carboplatin	n/a	0%
Docetaxel/cisplatin	n/a	0%
Vinorelbine/carboplatin	n/a	0%
Vinorelbine/cisplatin	n/a	10.9%
Pemetrexed/carboplatin	[redacted]	33.9%
Pemetrexed/cisplatin	[redacted]	43.9%
% Total	100%	100%

Source: Ipsos 2017 [98]

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

The type of comparisons assessed in the cost-effectiveness model is presented in Table 64.

Table 64. Intervention and comparators according to the different types of analyses assessed in de novo cost-effectiveness model

Population	**Intervention and comparators** Pembrolizumab vs.	**Clinical evidence derived from:**	**OS for comparator arm**			
			unadjusted	Two-stage	RPSFT	IPCW
ITT population	▪ Cisplatin/carboplatin + Pemetrexed	KEYNOTE-189	✓	×	×	×
ITT population	▪ Gem plus platinum ▪ Paclitaxel plus platinum ▪ Doc plus platinum ▪ Vinorelbine plus platinum	KEYNOTE-189 NMA	✓	×	×	×
Subgroups						
≥50% TPS	▪ Cisplatin/carboplatin + Pemetrexed ▪ Pembrolizumab mono	KEYNOTE-189 ITC	✓	×	×	×
1%≤TPS≤49%	▪ Cisplatin/carboplatin +	KEYNOTE-189	✓	×	×	×

	Pemetrexed					
<1% TPS	▪ Cisplatin/carboplatin + Pemetrexed	KEYNOTE-189	✓	✓	✓	✓

ITT = intention to treat

B.3.3 Clinical parameters and variables

B.3.3.1 Overall method of modelling OS and PFS

The primary data source for the economic model was the data derived from the KEYNOTE-189 clinical trial. Data from the November 2017 data cut has been used for the clinical parameters of the cost-effectiveness model, including OS, PFS and safety. To extrapolate the OS and PFS from KEYNOTE-189, to populate the area-under-the-curve (AUC) partitioned survival approach, guidance from the NICE DSU was followed to identify base case parametric survival models for OS and PFS [(99)]. In summary, the steps that were followed include:

- Testing the proportional hazard (PH) assumption – To assess whether joint or separate statistical models were more appropriate for the pembrolizumab combination and SoC treatment arms:
    - A statistical test of the PH assumption was performed
    - The cumulative hazard plot, the log cumulative hazard plot and the Schoenfeld residual plot were visually assessed to determine if the data from KEYNOTE-189 indicated proportional effects between pembrolizumab combination and SoC.
- A comprehensive range of pooled parametric survival models were explored. Data from both treatment arms were used within the same model, considering and comparing all the relevant standard parametric models (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma). Since there was evidence against the PH assumption, a pooled parametric model was deemed inappropriate.
- 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.

- 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.

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

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

- For OS, KEYNOTE-189 KM data was used for the first 28 weeks, on the basis of the changes to cumulative hazards, and an exponential model was fitted afterwards following standard parametric approaches. Two additional cut-offs were assessed in sensitivity analyses (i.e. week 38 and week 18).
- For PFS, KEYNOTE-189 KM data was used during the first 21 weeks, to reflect the protocol driven fall in PFS observed alongside the initial radiologic assessments. This was followed by extrapolating using a Weibull model. Other functional forms and two additional cut-offs were assessed in sensitivity analyses (i.e. week 11 and week 31).

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

For the other comparators included in the scope, in the absence of direct head-to-head trial data, a Bayesian network meta-analysis was conducted to obtain relative treatment effect estimates for pembrolizumab combination versus other non-trial chemotherapy regimens based on data from KN189 and other trials identified in a systematic review (please see section B.2.9). Further details on the steps to select the relevant methods for OS and PFS are also presented in Appendix L.

B.3.3.2 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 (100{National Institute for Health and Care Excellence., 2016 #504)}.
- 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 [100].

The approach to identify the relevant AEs to be included in the economic model was validated by clinical experts and has been previously accepted in other 1L NSCLC submissions [5, 88].

The incidence of AEs was taken from the KEYNOTE-189 trial for each treatment arm (see

Table 65). It should be noted that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on AEs of any grade. The unit cost and the disutility associated with the individual AEs were assumed to be the same for AEs occurring across treatment arms, and the difference in terms of AE costs and disutilities were driven by the AE rates presented in

Table 65. This was consistent with the methods used in previous submissions [101] 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 submission for

pembrolizumab for the treatment of patients with advanced NSCLC and PD-L1 positive tumours who have been previously treated [94, 95].

Table 65. Grade 3+ AE rates for AEs included in the economic model based on KEYNOTE-189 data[42]

Adverse Event	Risk for pembrolizumab combination	Risk for SoC
Nausea	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea (grade 2)	[redacted]	[redacted]
Diarrhoea (grade 3-4)	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]

Urinary tract infection	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]

B.3.3.3 Inputs from clinical experts

We were able to arrange meetings with clinical oncologists working in lung cancer to discuss key issues. We validated the plausibility of the approach to modelling OS by asking eleven clinicians to estimate 5 year survival percentages for current SoC with the majority providing estimates ranging from 0-5%, with some expecting this to be higher for patient populations where IO is available.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL was evaluated in the KEYNOTE-189 trial using the EuroQoL EQ-5D-3L. HRQoL analyses conducted from the trial data were utilitsed for the purpose of the economic section 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 [97].

In KEYNOTE-189, the EQ-5D questionnaire was administered at treatment cycles 1, 2, 3, 4, and 5 and every third cycle afterwards for as long as patients were on treatment for the first year and every fourth cycle in years 2-4. 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 combination and the SoC arms, to be consistent with the licenced indication and the treatment arms included for the estimation of PFS, OS and safety from KEYNOTE-189 included in the economic model (cut-off date: November 2017).

When estimating utilities, two approaches were considered:

- Estimation of utilities based on time-to-death

  This approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease. The approach has been previously used in the estimation of HRQoL in patients with advanced NSCLC who had previously received platinum based chemotherapy or palliative radiotherapy [102] [94, 103] and in advanced melanoma patients [104{Batty, 2012 #14}][105]. Time to death has been demonstrated as more relevant than progression-based utilities since by considering more health states it offers a better HRQoL data fit [104{Batty, 2012 #14}][105].

  Based on KEYNOTE-189 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 was 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-189 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 combination 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.

An analysis conducted to compare baseline EQ-5D utility scores, collected at the first visit (treatment cycle 1), showed that baseline utilities across the two treatment arms were similar.

The time to death utility data shows there was no evidence to suggest a statistically significant difference in EQ-5D scores by treatment arm, with the potential exception of the time to death interval of 30 to < 180 days, and therefore, scores from the pooled treatment groups for each state were used in the model.

The level of EQ-5D compliance through time is presented in

Table 66.

Table 66. Compliance of EQ-5D by visit and by treatment (FAS Population) [42]

Treatment Visit	Category	Pembrolizumab combination	SoC
		N = 402	N = 200
Baseline	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 3	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 6	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 9	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 12	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 21	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 30	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]

*Compliance is the proportion of subjects who completed the PRO questionnaire among those who are expected to complete it at each time point (excludes those missing by design).
Missing by design includes: death, discontinuation, translations not available, and no visit scheduled.
(Database Cut-off Date: November 2017).

UK preference-based scores were used for all patients analysed from the KEYNOTE-189 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique [106]. The estimated utilities are presented in Table 67 and

Table 68 below.

Table 67: EQ-5D health utility scores by time-to-death [82]

Time from EQ-5D Assessment Date to Death or Censoring Date (days)	Pembrolizumab combination					SoC					Pooled				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
≥ 360	[redacted]														
[180, 360)	[redacted]														
[30, 180)	[redacted]														
<30	[redacted]														

n† = Number of patients with non-missing EQ-5D score

m‡ = Number of records with non-missing EQ-5D score

EQ-5D score during baseline is not included

Database cut-off date: 08NOV2017

Table 68: EQ-5D health utility scores by progression status [82]

	Pembrolizumab combination					SoC					Pooled				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score

m‡ = Number of records with non-missing EQ-5D score

EQ-5D score during baseline is not included

Database cut-off date: 08NOV2017

B.3.4.2 Mapping

Not applicable as HRQoL was derived from the KEYNOTE-189 EQ-5D data.

Utilities were evaluated using EQ-5D directly from patients from the KEYNOTE-189 trial, which is consistent with the NICE reference case [97].

B.3.4.3 Health-related quality-of-life studies

In line with the NICE guide to the methods of technology appraisal [97], a systematic review of the literature was conducted to identify relevant studies reporting utility values. Full details of the search strategy and results can be found in Appendix H.

The objective was to identify HRQoL (in terms of utilities) associated with a first-line metastatic non-small cell lung cancer. The following research questions were posed in accordance with the decision problem:

1. What is the health-related quality of life (in terms of utilities) in untreated patients with metastatic non-small cell lung cancer?

Please see Appendix G.1. for details of the search strategies and databases searched for HRQoL and utilities along with the eligibility criteria set out in the final protocol. Please refer to Appendix H for further details on the HrQoL review.

The original database, internet and hand searches identified 5,691 records. In total, 4 publications were included that reported on utility values in the first line setting. Within the updated searches, 1,647 new records were identified, from which 4 studies reporting utility values were finally included, both from the first update. A total of 8 studies were identified through original and updated searches. A further 11 utility studies were found through hand searching the NICE website. Details of characteristics of the identified studies can be found in Appendix H.

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 [107] 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-189 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 NICE submissions included [37] However, it is unclear if these values were reflective of the HRQoL of the patients in a period of <30 days to death. The time to death utility approach was also used and accepted by the committee in the recent TA for pembrolizumab in 1L NSCLC[5, 88].

One study was included reporting time-to-death disutilities: two publications relating to quality of life data from KEYNOTE-024 [102, 108], a study conducted in South Korea, with health state descriptions defined by experienced clinical oncologist and 205 participants from the general population completing the study[109]. Although these studies are not directly comparable due to differences in populations and methods used, the following can be observed:

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

The above utility values for long-term survivors are also in line with the results of a real world study that evaluated EQ-5D-3L health utility scores from 474 outpatients with metastatic lung cancer across various disease states. As mentioned in this study, a mean HUS of 0.76 for patients with stage IV disease, and 0.79 while on chemotherapy, have been reported prior to widespread use of targeted therapies. The introduction of targeted therapies has improved patients' quality of life. In this longitudinal cohort study, patients with wild type metastatic NSCLC who were stable while receiving immunotherapy (14 patients in total) were reported to have a utility equal to 0.80. Although it is unclear whether all patients had stage IV NSCLC, and the sample from which these utilities were taken was small, the utility value reported for this patient group is in line with that of long-term survivors (i.e. during the period of survival of at least 360 days), as reported by patients assessed in KEYNOTE-189. This is unsurprising, since patients receiving immunotherapy not only experience improved survival but also no or milder side effects compared to those receiving chemotherapy.

A Canadian national survey conducted by the charity Lung Cancer Canada (LCC), which aimed to understand the wider impact of immunotherapy on patients' QoL, concluded that pembrolizumab allowed respondents to have a high quality of life in comparison to other

available treatments such as chemotherapy. The survey included 23 patients and 14 caregivers who had experience with pembrolizumab. The majority of respondents interviewed reported no side effects to mild side effects during the period treated with pembrolizumab. Most respondents found that management of adverse events was tolerable and did not interfere with their day-to-day life [110]. The work conducted by the LCC further supports the utility values collected in KEYNOTE-189 trial.

Overall, the pre- and post- progression utility values from the KEYNOTE-189 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.{ National Institute for Health and Care Excellence, 2013 #368;;Chouaid, 2012 #315; } [111]

The majority of the economic evaluation [37] [35] [34] [112] studies included in the systematic review calculated utility values using an algorithm by Nafees et al. (2008) [113] 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 [114] [115] [116]. A potential reason for these high values may be related to chronically unwell, individuals having more to gain from an improvement in quality of life. Patients who have regularly experienced ill health may perceive their improved health state, or a better hypothetical health state, of greater value. Additionally and importantly, the NICE reference case stipulates the use of utility values directly derived from the patients.

In the majority of these studies, EQ-5D health state descriptions were not used, and full details of the elicitation and valuation methods were not reported. As such, none of the included utility studies were deemed to be consistent with the NICE reference case for consideration for use within the health economic model. Further details of these studies are presented in Appendix H. A scenario analysis considering the time to death utility values reported by Chang et al has been considered as an alternative to the trial data.

B.3.4.4 Adverse reactions

The impact of AEs on HRQoL was assessed by examining the EQ-5D health utilities of patients who experienced AEs (grade 3-5) compared to those who did not experience AEs in the progression-free health state.

For this assessment, the time points associated with grade 3-5 AEs for each patient were identified. EQ-5D scores collected at these time points were then used to estimate the utility of the progression-free state with grade 3-5 AEs. EQ-5D scores collected at other time points were used to estimate the utility associated with the progression-free health state in the absence of grade 3-5 AEs. EQ-5D data from the latest data cut (November 2017) was used. The utility values for patients experiencing grade 3-5 AEs were lower [redacted] than those of patients not experiencing grade 3-5 AEs [redacted]; see Table 69). Additionally, patients who were progression-free and had experienced grade 3-5 AEs, reported a higher utility while treated with pembrolizumab combination compared those treated with SoC [redacted] respectively). Similarly, patients who were progression-free and had not experienced grade 3-5 AEs reported higher utility values when treated with pembrolizumab combination compared to SoC [redacted], respectively).

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

It has been assumed for the purposes of the modelling that any impact of AEs on HRQoL is expressed in terms of a disutility of AEs applied based on AE incidence rates and the corresponding mean duration across them (i.e. [redacted] days of duration across grade 3+ AEs, as estimated from KEYNOTE-189).

Table 69: Utility values for individuals with and without Grade 3+ AEs in the KN189 clinical trial[82]

	Pembrolizumab combination					SoC					Pooled				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
During Grade3+ AEs while Progression Free	[redacted]														
Progression Free without Grade3+ AE	[redacted]														

n† = Number of patients with non-missing EQ-5D score

m‡ = Number of records with non-missing EQ-5D score

EQ-5D score during baseline is not included

Database cut-off date: 08NOV2017

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

HRQoL in the base case scenario is based upon time to death as the utility values derived from the KEYNOTE-189 trial were more sensitive than the pre-and post- progression utility values. EQ-5D analyses based on KEYNOTE-189 data showed that patients who had progressive disease experienced a lower HRQoL than those in the pre-progression health state. However, due to high level of crossover from the SoC arm to the pembrolizumab arm and due to the limitations with the data collected post-progression, progression related utilities do not show a large difference between pre and post-progression utilities, indicating that progression status is unlikely to be sufficiently reflective of changes in quality of life. When time-to-death was considered, HRQoL decreased over time as patients progressed closer to death. Therefore, to capture HRQoL more appropriately, the time-to-death utility values were further divided according to four categories (i.e. 360 or more days to death, 180 to 360 days to death, 30 to 180 days to death or under 30 days to death).

In the cost-effectiveness model, a constant value for HRQoL is applied in each cycle taking into account either time to death or progression-based health states. An age-related utility decrement of 0.0044 was applied per year, from the age of 65 until 75, to reflect the natural decrease in utility associated with increasing age [117].

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 [117]., which reported average utility values for males and females under 25, 25-34, 35-44, 45-54, 55-64, 65-74 and 75+ respectively. It was assumed that the utilities for 75+ reported by Kind et al. (0.75 and 0.71 for males and females, respectively) apply to all patients who are 75 years and above. Therefore, no further age-related decrement in utility was applied in the model for patients aged over 75 years. This means that patients aged 75 and above had the same age-related utility decrement in the cost-effectiveness model.

No health effects on patients were excluded from the cost effectiveness analysis. However, the impact of pembrolizumab combination 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.

The utility values chosen for the cost-effectiveness model are presented in Table 70.

Table 70: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
≥360*	[redacted]	[redacted]	Section B.3.4: B.3.4.1 Health-related quality-of-life data from **clinical trials** (page 130-136)	Utility values from KEYNOTE-189 (Data cut: Nov 2017), in line with NICE reference case[82, 97]
[180, 360)	[redacted]	[redacted]		
[30, 180)	[redacted]	[redacted]		
<30	[redacted]	[redacted]		
Disutility per patient experiencing grade 3-5 AEs	Pembrolizumab combination: [redacted] SoC: [redacted]		Section B.3.4: Adverse reactions (page 138)	
** This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days.* *** Utilities from KEYNOTE-189 are pooled utilities*				

A clinical expert assessed the applicability of the health state utility values estimated from KEYNOTE-189 and these were thought to be reasonable.

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

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

B.3.5.1 Intervention and comparators' costs and resource use

Drug costs

The drug acquisition costs per treatment are presented below, with the unit costs for comparators being taken from the electronic market information tool (eMit [118]) 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 British National Formulary (BNF) [119] were used.

Pembrolizumab

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

Comparators and combination drugs

Drug acquisition costs for individual drugs included in the platinum-based combination therapies were taken from eMit[118] apart from pemetrexed, for which the corresponding drug costs are only available from BNF [119]. 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-189 protocol [84], whenever available. Dosing for the remaining drugs not included in KEYNOTE-189 was based on SmPC or Brown et al [120] [121] [96] (2013). Drug costs per administration were calculated based on the body surface area (BSA), which was assumed to be 1.81m^2 based on a mean BSA from the male and female patients recruited at European sites in KEYNOTE-189 (see

Table 71). 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 71: Baseline body surface area (BSA) of patients recruited at European sites in KEYNOTE-189

	Mean BSA in m^2	% of patients

Female	1.63	63.6% (N=238) [82]
Male	1.90	36.4% (N=136) [82]
Total	1.81	100% (N=374) [82]

Table 72: 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
Pembrolizumab	200mg	Q3W	200mg	£26.30	£5260	SmPC [122]	BNF
Docetaxel	75mg/m^2	Q3W	135.75mg	£0.18	£25.01	SmPC[121]	eMit[118]
Gemcitabine	1250mg/m^2	Q3W	2262.50mg	£0.01	£35.07	SmPC[123]	eMit[118]
Paclitaxel	200mg/m^2	Q3W	362mg	£0.07	£23.75	SmPC [124]	eMit[118]
Vinorelbine	27.5mg/m^2	Q1W	49.78mg	£0.10	£15.08	SmPC [120]	eMit[118]
Carboplatin	400mg/m^2	Q3W	724mg	£0.04	£30.13	KEYNOTE-189 [42]	eMit[118]
Cisplatin	75mg/m^2	Q3W	135mg	£0.09	£12.16	KEYNOTE-189 [42]	eMit[118]
Pemetrexed	500mg/m^2	Q3W	905mg	£1.60	£1,448.00	KEYNOTE-189 [42]	MIMS

* Q1W, every week; Q3W, every three weeks

The drug costs of the overall platinum-based plus pemetrexed therapy used in the economic model are the weighted sum of the drug costs of the individual combination treatments where weights were based on the KEYNOTE-189 in the base case and UK market shares (excluding treatments not included in KEYNOTE-189) in the scenario analysis (

Table **73**). Table 74 summarises the drug costs per administration for the comparators used in the economic model.

Table 73: Distribution of the use of platinum-based chemotherapies

	KEYNOTE-189 (base case)	UK market share
Gem + Car	0.0%	3.3%
Gem + Cis	0.0%	8.0%
Pac + Car	0.0%	0.0%
Pac + Cis	0.0%	0.0%

Doc + Car	0.0%	0.0%
Doc + Cis	0.0%	0.0%
Vin + Car	0.0%	0.0%
Vin + Cis	0.0%	10.9%
Pemx + Cis	[redacted]	33.9%
Pemx + Car	[redacted]	43.9%
Total %	100%	100%

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

Table 74: Summary of the drug costs per administration for the comparator used in the base case

	Overall population
SoC: Cis/Car plus Pemx	£1420.12

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

As per the licence, patients treated with pembrolizumab are to be treated until disease progression is confirmed. To estimate the duration of treatment in the pembrolizumab combination and SoC arms, time on treatment (ToT) data from the KEYNOTE-189 Nov 2017 data-cut was used, to reflect both early discontinuation caused by AEs and other reasons for discontinuations before progression in addition to the additional weeks of treatment that some patients may receive until confirmation of progression. See Appendix I for further details regarding the use of ToT data in the model.

In the base case model, a maximum treatment duration of 2 years was assumed for pembrolizumab, in line with the KEYNOTE-189 protocol[84] and the current recommendations for the use of pembrolizumab for the treatment of patients with advanced NSCLC [5, 88, 94, 95]. A maximum treatment duration of 12 weeks (i.e., 4 cycles for the platinum-based therapies administrated every 3 weeks) was used for the comparator platinum-based therapies to reflect the protocol of KEYNOTE-189[84] and clinical practice in England. The average number of cycles received in the comparator arm per patient in KEYNOTE-189 was 3.5 and 3.6[125] (range:1-4) in the pembrolizumab combination arm for carboplatin/cisplatin induction therapy.

For patients on treatment, adjustments were made based on the actual proportion of patients receiving the planned dose within KEYNOTE-189. For this, data regarding dose interruption occurring within KEYNOTE-189 was analysed and incorporated into the model per

administered cycle of pembrolizumab and comparators. These analyses showed that, on average, 95.6% of patients on pembrolizumab combination and 96.4%[125] of patients on overall platinum-based chemotherapy received their planned doses.

B.3.5.2 Administration costs

Pembrolizumab combination

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 2016-2017 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 [126].

Platinum-based combination therapy

The administration costs required for platinum-based therapies were based on previous NICE submissions for first line treatments for NSCLC [5, 87, 88, 127]. It was assumed the administration cost for paclitaxel + cisplatin is the same as docetaxel + cisplatin and pemetrexed + cisplatin; the cost for docetaxel + carboplatin is the same as the paclitaxel + carboplatin or pemetrexed + carboplatin. The administration cost for vinorelbine + carboplatin is based on the cost for vinorelbine + cisplatin but replace SB14Z (day case and regular day/night) with SB14Z (outpatient) to reflect the administration cost difference between carboplatin and cisplatin. The unit cost per cycle of chemotherapy administrated was taken from the National Reference Costs 2016/17 [128].

Table **75** summarises the administration costs used in the cost-effectiveness model.

Table 75. Administration costs of pembrolizumab and platinum-based chemotherapy

	Assumptions	Unit costs	Reference
Pembrolizumab + platinum+pemetrexed	1 x SB12Z (outpatient) 1 x weighted average based on KEYNOTE189 market share of: 1 x SB14Z (outpatient) (pemetrexed+carb) 1 x 1 x SB14Z (inpatient) (pemetrexed+cis)	£561.79	Assumption based on clinical opinion
Pembrolizumab mono	1 x SB12Z (outpatient)	£259.76	ID1349[5]
Gemcitabine +	1 x SB14Z (outpatient)	£474.95	TA181[37]

	Assumptions	Unit costs	Reference
carboplatin	1 x SB15Z (outpatient)		
Gemcitabine + cisplatin	1 x SB14Z (Day case and regular day/night) 1 x SB15Z (outpatient)	£591.08	TA181[37]
Paclitaxel + carboplatin	1 x SB14Z (outpatient)	£269.86	TA192[35]
Paclitaxel + cisplatin	1 x SB14Z (Day case and regular day/night)	£385.99	Assumption
Docetaxel + carboplatin	1 x SB14Z (outpatient)	£385.99	Assumption
Docetaxel + cisplatin	1 x SB14Z (Day case and regular day/night)	£269.86	TA181[37]
Vinorelbine + carboplatin	1 x SB14Z (Outpatient) 1 x SB15Z (Day case and regular day/night)	£602.97	Assumption
Vinorelbine + cisplatin	1 x SB14Z (Day case and regular day/night) 1 x SB15Z (Day case and regular day/night)	£719.10	TA192[35]
Pemetrexed + carboplatin	1 x SB14Z (outpatient)	£269.86	TA406[32]
Pemetrexed + cisplatin	1 x SB14Z (Day case and regular day/night)	£385.99	TA181[37]

Similar to the drug costs for the comparators, the administration costs of the overall platinum-based therapy used in the economic model are the weighted sum of the administration costs of the individual combination treatments, where weights were based on KEYNOTE-189 in the base case and UK market share in the scenario analysis. Table 76 summarises the drug administration costs for the comparators used in the economic model.

Table 76. Summary of the drug administration costs for the comparator used in the base case

	All
SoC: Cis/Carb plus Pemx	£302.03

B.3.5.3 Costs associated with PD-L1 testing

The anticipated license for pembrolizumab in combination with platinum based chemotherapy is for the first line treatment of advanced NSCLC in adults. Since pembrolizumab monotherapy already has a license in advanced NSCLC in adults who express ≥50% PDL-1 as assessed by a validated test, and that this validated test is now the standard of care, the cost of this test had been included for the whole population of patients treated with pembrolizumab combination at a cost of £40.50 per patient. For the sub-groups,

the testing cost for the full population is modelled to be borne by each of the sub-groups, as it is assumed that in order to know whether a patient in that sub-group is PDL-1 positive or not, the entire population must be tested resulting in the overall cost per patient in the table below.

Table 77 PDL-1 testing costs per patient for pembrolizumab combination therapy

	Full Population	PDL-1 TPS ≥50% Population	PDL-1 TPS 1%≤TPS≤49% Population	PDL-1 TPS <1% Population
% of all patients within population	100.0%	34.9%	32.2%	32.9%
PDL-1 test cost	£40.50	£40.50	£40.50	£40.50
PDL-1 test costs for pembrolizumab combination/patient	£40.50	£115.89	£125.85	£123.21

B.3.5.4 Costs associated with pemetrexed maintenance therapy

Three sources of data are used for modelling pemetrexed maintenance:

- ToT based on KN189 with parametric fitting and extrapolation of observed KM data for patients who have not discontinued each treatment altogether at a given time point
- Dose intensity of pembrolizumab combination (capturing patients who missed doses of both medications during the maintenance phase) and dose Intensity of SoC
- Proportion of patients remaining on treatment who utilise pemetrexed
    - In the pembrolizumab combination arm, this is the proportion of patients remaining on pembrolizumab who utilise pemetrexed maintenance in a given cycle.
    - For the SoC arm, if a patient does not receive pemetrexed maintenance in a given cycle, their non-utilisation is already captured in the dose intensity variable for SoC above (as pemetrexed is the only medication taken during the maintenance phase in this arm).

Patients sometimes miss or delay a dose which results in their actual treatment utilisation reflecting fewer cycles than if based on a strict dosing schedule. To adjust for this, data from

KEYNOTE-189 are used to determine the percentage of actual treatment cycles received, versus expected, for the pembrolizumab combination and SoC arms of the trial. These reflect receipt of any treatment dose during a given cycle while a patient is on treatment. In addition, for the pembrolizumab combination arm, the proportion of cycles in which pemetrexed maintenance therapy is utilised, among patients utilising pembrolizumab during a given cycle, is also estimated from the trial (Table 78). Analogous data were obtained from KEYNOTE-024[129] for pembrolizumab monotherapy. Drug acquisition and administration costs for these comparators are adjusted by these percentages.

Table 78 Percentage of actual treatment cycles received vs. expected, by KEYNOTE-189 trial treatment arm

Treatment arm	Actual vs. Expected
Pembrolizumab combination	[redacted]
Pemetrexed Maintenance*	[redacted]
SoC	[redacted]
Pembrolizumab monotherapy	[redacted]

* For patients in pembrolizumab combination arm only

The drug cost for pemetrexed maintenance therapy is shown in Table 74 and the administration cost was assumed to be based on a day case of simple chemotherapy (SB12Z) which is the same as pembrolizumab administration cost. Additionally, it was assumed an additional CT scan every 12 weeks is required for patients while on pemetrexed maintenance treatment based on an assumption made by the manufacturer in the TA402 submission [87].

B.3.5.5 Health-state unit costs and resource use

The main source of resource utilisation per health state used in this submission was the Brown et al study, which compares regimens currently approved by NICE and licensed across Europe for the systemic treatment of patients with advanced NSCLC [96]. From the studies evaluated within the systematic review, MSD concludes that this study provides the most balanced and appropriate evaluation of cost and resource use given its relevance to the UK setting, recent publication and broad inclusion of treatment strategies in advanced NSCLC.

Monitoring and disease management costs

There are three health states included in the model - Progression free (PFS), Progressed (PD) and death.

Patients incur disease management costs for as long as they remain on treatment, and potentially longer. The unit costs of treatment are consistent over cycle lengths; however the frequency of resource consumption per cycle varies depending on the health state.

Table 53 shows the resource use for monitoring and disease management in the progression-free and progressed health state. Based on the definitions for health states used in the Brown et al study [96] , PFS costs from Brown et al. were applied during first-line chemotherapy and for patients modelled to receive a second-line therapy following first-line treatment discontinuation. PD costs were only applied when no active treatment is received following 1st line therapy discontinuation.

Table 80 presents the unit costs for individual resource use items, which were updated based on the NHS reference costs 2016-2017 and the Personal and Personal and Social Services Research Unit (PSSRU) 2017 report [128{Curtis, 2017 #52}]. The estimated per week monitoring and disease management costs were £65.10 and £115.57 respectively for the PFS and PPS periods.

Table 79: Resource use frequency for progression-free and progressed health states (based on Brown et al study) [96]

Resource	PFS	PPS	Unit	Source quoted in Brown 2013
Outpatient visit	9.61	7.91	per annum	Big Lung Trial[130]
Chest radiography	6.79	6.5	per annum	Big Lung Trial[130]
CT scan (chest)	0.62	0.24	per annum	Big Lung Trial[130]
CT scan (other)	0.36	0.42	per annum	Big Lung Trial[130]
ECG	1.04	0.88	per annum	Big Lung Trial[130]
Community nurse visit	8.7	8.7	visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG81, Marie Curie report [131, 132]
Clinical nurse specialist	12	12	hours contact time per patient	Appendix 1 of NICE Guideline CG81[132]
GP surgery	12	0	consultations per patient	Appendix 1 of NICE Guideline CG81
GP home visit	0	26.09	per annum (fortnightly)	Marie Curie report[131, 132]

Therapist visit	0	26.09	per annum (fortnightly)	Appendix 1 of NICE Guideline CG81[132]
Macmillan nurse	0	0		Marie Curie report[131]
Drugs/equiptment	0	0		Marie Curie report[131]
Location of terminal care	0	0		Office for National Statistics death tables 5.2 [133]

* 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 80. Unit costs of disease monitoring and supportive care

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£128.00	per visit	NHS Reference Costs 2016–2017, Consultant Led, Non-Admitted Face to Face Attendance, First, 800 clinical oncology[128]
Chest radiography	£27.22	per case	NICE technology appraisal TA199; TAG report, p.328 (£24.04 in 2009) [134]
CT scan (chest)	£110.00	per case	NHS Reference Costs 2016–2017, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast) [128]
CT scan (other)	£118.00	per case	NHS Reference Costs 2016–2017, Diagnostic Imaging, Outpatient, HRG code RD26Z (three areas with contrast) [128]
ECG	£334.00	per case	NHS Reference Costs 2016–2017, 800 Clinical Oncology, Outpatient, HRG code EY51Z[128]
Community nurse visit	£62.00	per hour	PSSRU 2017, p.142: Cost per hour of patient-related work Band 8a[135]
Clinical nurse specialist	£74.00	per contact hour	PSSRU 2017, p.142: Cost per contact hour Band 8b[135]
GP surgery visit	£38.00	per visit	PSSRU 2017[135], p.145: Cost per patient contact lasting 11.7 minutes, including direct care staff costs (including qualifications)
GP home visit	£85.44	per visit	PSSRU 2017, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel[135]
Therapist visit	£45.00	per hour	PSSRU 2017, p.159: Cost per hour for community occupational therapist (including training) [135]

* 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 [96]. The estimated one-off terminal costs were £4,404.26 and are assumed to be the same for all treatment arms (see Table 81).

Table 81: Unit costs of terminal care patients (based on Brown et al study) [96]

Resource	Unit cost	Number of consumption	% of patients in each care setting	Assumptions / Reference
Community nurse visit	£62.00 per hour	28.00 hours	30%	PSSRU 2017, p.169: Cost per hour of patient-related work (including qualifications) [135]
GP Home visit	£85.44 per visit	7.00 visits	30%	PSSRU 2017, p.177-178: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel[135]
Macmillan nurse	£49.36 per hour	50.00 hours	30%	Assumed to be 66.7% of community nurse cost[96]
Drugs and equipment	£563 per patient	Average drug and equipment usage	30%	The value used in Brown et al' s study (2013, Marie Curie report figure of £240 increased for inflation) was inflated to 2016/17 using the PSSRU HCHS index[96, 131]
Terminal care in hospital	£3,737.05 per episode	1 episode (9.66 days)	62%	NHS Reference Costs 2016–2017, 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 Assumed that unit cost is = £3,606.87 + 0.92 excess days at £267.74 per day[96, 128]
Terminal care in hospice	£4,671.32 per episode	1 episode (9.66 days)	7.1%	Assumed 25% increase on hospital inpatient care[96]
Total cost	£4,404.24 (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

B.3.5.6 Adverse reaction unit costs and resource use

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

The unit costs related to the management of AEs were mainly derived from the Brown et al study and from the previous NICE STA submissions [96]. When unit costs were not available or the management costs were trivial, zero cost was applied. All unit costs were inflated to 2016/17 prices using the hospital and community health services (HCHS) index published by PSSRU for 2017 [135] Table 82 below presents the unit costs per AE for which costing was applied in the cost-effectiveness model.

Table 82: Unit cost per AE used in the de novo model

Adverse Event	Unit costs	Reference
Nausea	£998.38	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices) [96, 135]
Anaemia	£2,692.61	NICE TA428[94, 101]
Fatigue	£2,855.25	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices)[136, 137]
Decreased appetite	£0.00	TA428 inflated to 2016/17 using PSSRU inflation indices
Constipation	£0.00	Assumed to be zero
Diarrhoea (grade 2)	£456.66	NICE TA428[94] inflated to 2016/17 using PSSRU inflation indices
Diarrhoea (grade 3-4)	£998.38	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices) [96, 135]
Dyspnoea	£588.98	NICE TA403 inflated 2016/17[138]
Vomiting	£813.47	NICE TA192 (inflated to 2016/17 using PSSRU inflation indices) [35, 135]
Back pain	£0.00	Assumed to be zero
Arthralgia	£0.00	Assumed to be zero
Neutropaenia	£120.99	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices) [96, 135]
Oedema peripheral	£0.00	Assumed to be zero
Blood creatinine increased	£0.00	Assumed to be zero
Alanine aminotransferase increased	£637.03	TA347 (inflated to 2016/17 using PSSRU inflation indices) [90, 135]
Dizziness	£0.00	Assumed to be zero
Rash	£127.21	Brown (inflated to 2016/17 using PSSRU inflation indices) [96]
Asthenia	£2,805.19	Brown (inflated to 2016/17 using PSSRU inflation indices) [135]
Chest pain	£0.00	Assumed to be zero[96]
Stomatitis	£0.00	TA428, 2016[94]
Hyponatraemia	£0.00	TA357, 2015[126]

Adverse Event	Unit costs	Reference
Thrombocytopaenia	£782.31	TA406 inflated to 2016/17 using PSSRU inflation indeces [32, 135]
Dyspepsia	£0.00	Assume same as decreased appetitie
Abdominal pain	£0.00	TA395[139]
Aspartate aminotransferase increased	£364.64	NICE TA347 (inflated to 2016/17 using PSSRU inflation indices) [90, 135]
Hyperglycaemia	£0.00	TA395[139]
Pyrexia	£261.00	NHS reference costs 16/17 WJ07B Fever of unknown origin[128]
Musculoskeletal pain	£0.00	Assumed to be zero
Pneumonia	£3,102.84	TA411 2016 (inflated to 2016/17 using PSSRU inflation indeces) [83]
White blood cell count decreased	£577.66	NICE TA428 2016 inflated to PSSRU 2016/17 inflation indeces[101, 135]
Haemoptysis	£0.00	Assumed to be zero
Pain in extremity	£0.00	Assumed to be zero
Urinary tract infection	£2,366.90	NICE TA347 (inflated to 2016/17 using PSSRU inflation indices) [135] [90]
Mucosal inflamation	£0.00	Assumed to be zero
Pleural effusion	£0.00	Assumed to be zero
Upper respiratory tract infection	£171.14	Assume the same as lower respiratory tract infection
Leukopenia	£0.00	Assumed to be zero
Epistaxis	£0.00	Assumed to be zero
Conjunctivitis	£0.00	Assumed to be zero
Pneumonitis	£3,102.84	Assumed to be same as pneumonia
Febrile neutropaenia	£7,266.56	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices) [96, 135]
Bronchitis	£171.14	Assume the same as lower respiratory tract infection
Hypertension	£0.00	Assumed to be zero
Weight decreased	£0.00	Assume the same as decreased appetite
Gamma-glutamyltransferase increased	£369.42	TA347, 2015 (inflated to 2016/17 using PSSRU inflation indeces) [135] [90]
Hypokalaemia	£465.00	NHS reference costs 16/17 KC05G: Fluid or electrolyte disorders with intervention[128]
Hypomagnesaemia	£465.00	NHS reference costs 16/17 KC05G: Fluid or electrolyte disorders with intervention[128]
Dehydration	£465.00	NHS reference costs 16/17 KC05G: Fluid or electrolyte disorders with intervention[128]
Hypophosphataemia	465.00	NHS reference costs 16/17 KC05G: Fluid or electrolyte disorders with intervention[128]
Dysgeusia	£0.00	Assume the same as decreased appetite
Insomnia	£0.00	Assumed to be zero
Anxiety	£0.00	Assumed to be zero
Acute kidney injury	£377.00	Acute kidney injury with intervention (LA07K) NHS reference costs 16/17[128]

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

B.3.5.7 Miscellaneous unit costs and resource use

Costs associated with subsequent therapies received by patients after treatment discontinuation

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

It was assumed 43.3% of patients who discontinue 1st line therapy in the pembrolizumab combination arm, and 56.0% of patients in the SoC arm, receive second line treatment as per KEYNOTE-189 [42].

For patients in the SoC arm, cross over adjustment was not implemented in the ITT population since 2L immune oncology drugs are now thought to be standard of care. In subgroup analysis of the patient population with PDL1 <1%, cross over adjustments have been made. Details of which can be found in section B.2.6

Table **83** presents the distribution of subsequent therapies for the pembrolizumab combination and chemotherapy arms. Within KEYNOTE-189, pembrolizumab was utilized in 2L by 7% of patients who used a subsequent therapy following discontinuation of pembrolizumab combination. This percentage may include patients who poorly tolerated the chemotherapy component of combination therapy and continued on monotherapy after discontinuing carboplatin and/or pemetrexed, as well as a small number of patients who elected to be unblinded as they wanted to confirm they were benefitting from pembrolizumab and continue on therapy. As this could not occur in clinical practice in the UK, the proportions in the economic model have been re-weighted to exclude pembrolizumab which will slightly reduce the overall costs in the pembrolizumab arm. No adjustment was made for efficacy as the specific clinical benefit of pembrolizumab use in this position is unclear. There is no evidence that the use of pembrolizumab does or does not have a clinical benefit used in this position but it cannot be ruled out. We have included an analysis (SA #15) that retains the cost associated with retaining pembrolizumab used second line.

Table 83. Type and distribution of second line subsequent chemotherapies used in the economic model

Treatment	Pembrolizumab arm	SoC arm
Carb+Pemx	[redacted]	[redacted]

Doc+Nintedanib	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]

The average one-off cost of subsequent treatment for each arm was calculated by weighting the proportions of patients receiving each subsequent treatment and the unit cost of each subsequent treatment (including drug cost and administration cost as described above), assuming the average duration of treatment as reported above. For simplification purposes, we have assumed that, after 1st line discontinuation, SoC patients receiving an anti-PD1 in second line would receive pembrolizumab, since there is a confidential CAA available for nivolumab in second line that did not allow us to estimate accurately the cost of subsequent therapies otherwise. Administration costs per cycle were assumed to be the same as in first line therapy described above with docetaxel and docetaxel plus Nintedanib being assumed to be 1xSB12Z (deliver simple parental chemotherapy at first attendance). This weighted one-off cost was applied to patients at the point of 1st line treatment discontinuation.

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

B.3.6.1 Summary of base-case analysis inputs

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

B.3.6.2 Assumptions

Table 84 below presents a summary of the clinical inputs and data sources used in the economic model, and Table 85 summarises the assumptions used in the economic model. The base-case cost-effectiveness analyses reflects the NICE reference case as closely as possible.

Table 84. Summary of clinical inputs and data sources used in the economic model

Clinical evidence and source	Brief description	Use in the model
KEYNOTE-189	Multicentre open-label, randomised, phase 3 trial of pembrolizumab 200 mg plus cisplatin/carboplatin plus pemetrexed maintenance Q3W (n=410) versus placebo plus cisplatin/carboplatin plus pemetrexed maintenance (SoC) (n=206) in adults with untreated, advanced NSCLC. Data cut: November 2017	• Used to derive the baseline patient characteristics (including average age, the proportion of males and weighted average BSA). • Patient level data were used to fit OS and PFS parametric curves for both pembrolizumab combination and SoC arms. • Base case presented: o ITT: Patient level data from the SoC arm was not used to perform crossover adjustments for the SoC OS as part of the base case since pembrolizumab monotherapy has become SoC second line among patients who express PD-L1 (TPS ≥ 1%, including strong expressers, i.e. TPS ≥ 50%). Therefore the decision was taken not to adjust the entire ITT population despite <1% TPS PD-L1 subgroup not having access to pembrolizumab monotherapy in 2L currently. o As a subgroup analysis, patient level data from the SoC arm was used to perform crossover adjustments in the <1% TPS PD-L1 subgroup for the SoC OS. • OS KM data until week 28 was used to model OS in the first phase of the OS before parametric curves were applied. • PFS KM data were used to model PFS in the first 21 weeks before parametric curves were applied. • Patient level data was used to calculate the proportions of patients actually receiving the planned doses for both pembrolizumab combination and SoC. • EQ-5D data collected in the trial were used to derive health state utility values (time-to-death utility values) used in the model. • ToT KM data up to 2 years was used to estimate treatment duration in the pembrolizumab combination arm, while parametric fitting was used to estimate ToT in the SoC arm • Used to derive the incidence of grade 3+ AEs and grade 2 diarrhoea and febrile neutropaenia (all grades) for both pembrolizumab combination and SoC. • Used to derive the proportion of patients receiving subsequent treatments for both pembrolizumab combination and SoC.
General population mortality[140]	Latest national life table in England & Wales providing age- and gender-specific general population mortality.	Applied throughout the modelled time horizon as background mortality (i.e., general population mortality is applied when modelled mortality is lower than the gender- and age- matching general population mortality).

Key: AE, adverse event; HR, hazard ratio; IV, intravenous; KM, Kaplan-Meier; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression free survival; Q3W, every 3 weeks; RCT, randomised controlled trial; TPS, proportion of tumour cells staining for PD-L1.

Table 85: 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-189.	The use of subsequent treatments as observed in KEYNOTE-189 trial is consistent with the OS efficacy inputs used in the model, which are based on patients receiving these subsequent treatments. No crossover adjustment is applied in the base case cost-effectiveness model to reflect current clinical practice in the ITT population. It would not be possible to apply crossover adjustment in part of the ITT population only (<1% TPS PD-L1) however subgroup analysis in this group shows the cross over adjusted results.
Time horizon	20 years	The average age of patients in the model is 62. A lifetime horizon is in line with NICE reference case. Duration of 20 years is considered long enough to reflect the difference in costs and outcomes between pembrolizumab combination and SoC as assessed in this submission. This duration is in line with previous NICE appraisals [83, 85, 87, 101].
Efficacy	Use unadjusted KM data for the first 28 weeks from KEYNOTE-189 trial to model OS for pembrolizumab combination 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, TA428, TA447, ID811) [94] [5, 86, 88, 89] or has been used by an assessment group for a recent [94] NICE MTA (TA374) [141]. For the first 28 weeks OS KM data provides the more robust and reliable estimate and at that point patient numbers are sufficient to apply parametric fitting based on KEYNOTE-189 data. The fully fitted standard parametric curves do not provide good visual fit compared to the 2-phase piecewise method. The cumulative hazard plot also suggests that a piecewise model is preferred.
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.

Area	Assumption	Justification
Safety	The incidence of AEs from KEYNOTE-189 trial was assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-189 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) [86, 141].
Costs	PD-L1 test cost is assumed for the whole patient population receiving pembrolizumab combination at a cost of £40.50/patient.	Testing for PD-L1 status has become standard practice, [redacted]

B.3.7 Base-case results

The results of the economic model are presented in Table 86 below. In the base case reflecting the original submission, the estimated mean overall survival was 2.50 years with pembrolizumab combination and 1.34 years with SoC. At the end of the 20-year time horizon there were 0.00% patients still alive in the pembrolizumab combination cohort and 0.00% in the SoC cohort. Patients treated with pembrolizumab combination accrued 1.81 QALYs compared to 0.92 among patients in the SoC cohort.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Table 86 and Table 87 below presents the base case incremental cost-effectiveness results for the base case incorporating the aforementioned discount. There is currently a confidential (and therefore, unknown) commercial access agreement (CAA) for the administration of pemetrexed as maintenance therapy, in the base case we have assumed a 0% simple discount as requested by NICE.

The results show given that data are immature, pembrolizumab combination has the potential to be cost-effective compared to SoC when considering a willingness to pay threshold of £50,000 per QALY with the corresponding incremental-cost-effectiveness ratio (ICER) when pembrolizumab combination was compared to SoC was £46,568 in the base case. These ICERs should be considered in the context of pembrolizumab meeting end of life criteria and utilised in combination with the existing technology.

Table 86: Base-case results versus trial comparator SoC (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SoC	£42,980	1.34	0.92	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£41,344	0.89	£46,568
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 87: Base-case results versus NMA comparators (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Platinum + Paclitaxel	£25,368	1.09	0.73	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£58,956	1.08	£54,654
Platinum + Docetaxel	£27,391	1.55	1.08	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£56,932	0.73	£78,242
Platinum + Gemcitabine	£26,572	1.19	0.80	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£57,752	1.01	£57,064
Platinum + Vinorelbine	£27,663	1.33	0.91	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£56,661	0.90	£63,262
Platinum + Pemetrexed	£42,247	1.32	0.90	-	-	-
Pembrolizumab combination	£84,324	2.50	1.81	£42,077	0.90	£46,504
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

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

B.3.8 Sensitivity analyses

B.3.8.1 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 L.

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 35 and Figure 36.

Table 88: Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus trial comparator SoC (discounted)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
SoC	£43,527	0.93	-	-	-
Pembrolizumab combination	£84,870	1.81	£41,344	0.89	£46,674

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

The cost-effectiveness acceptability curve shows that, for the base case, there is an approximately 59% of chance of pembrolizumab combination being cost-effective when compared to SoC at the £50,000 per QALY threshold.

Figure 35: Scatterplot of PSA results (1,000 simulations) versus trial comparator SoC (discounted)

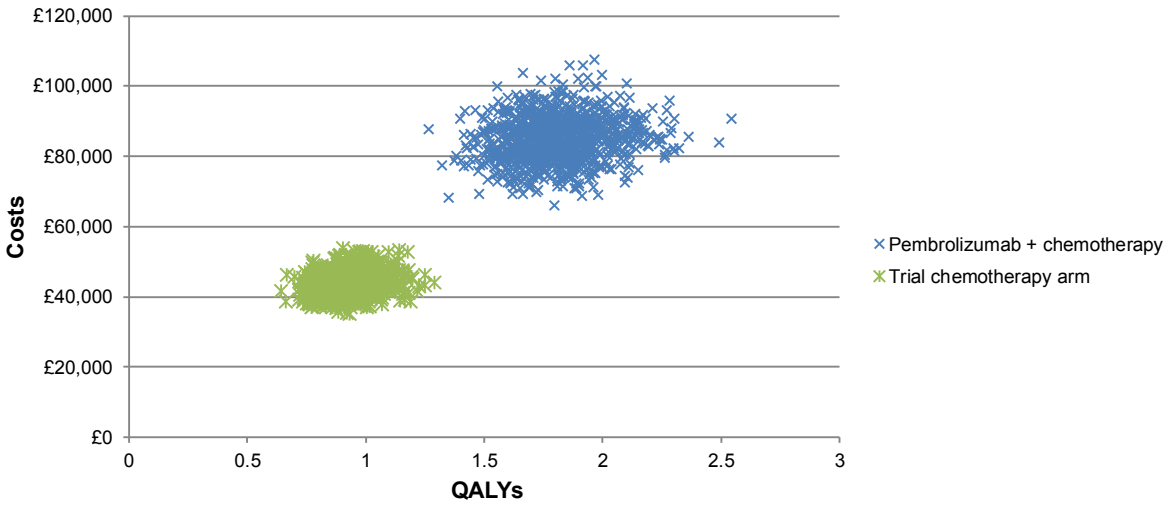
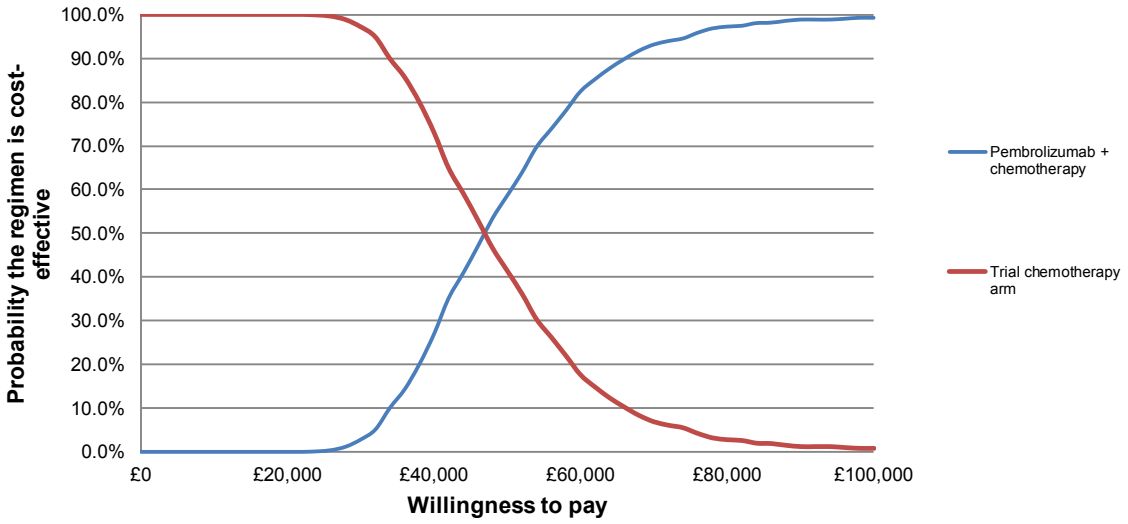


Figure 36: Cost-effectiveness acceptability curve versus trial comparator SoC (discounted)



B.3.8.2 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:

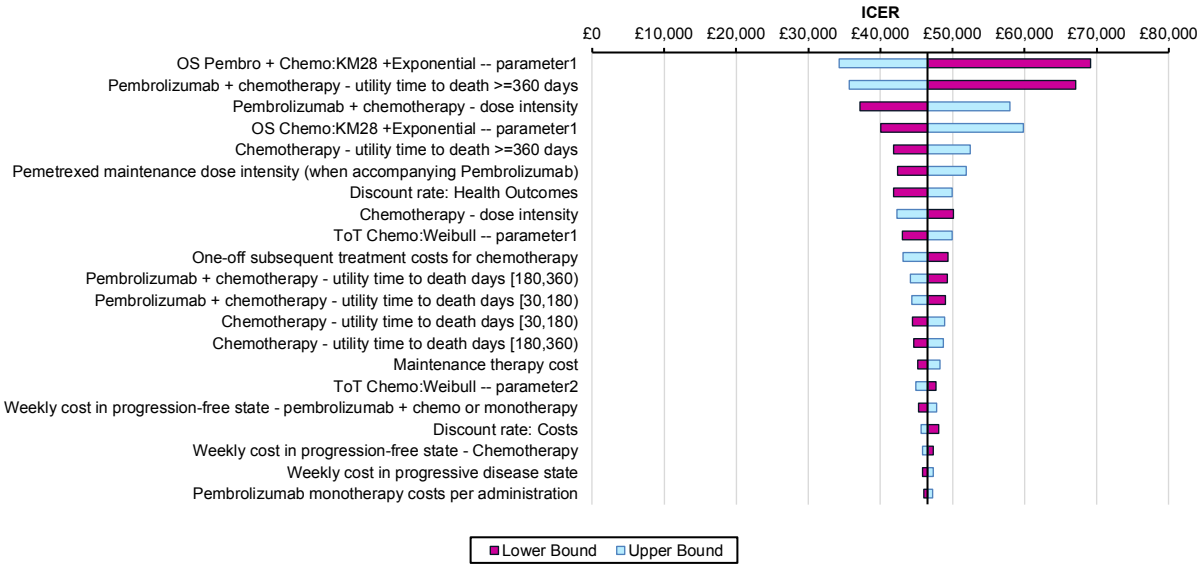
- Baseline characteristics (i.e. body surface area)
- Administration costs
- Costs of the PD-L1 test
- Resource utilisation
- Proportion of patients actually receiving the expected dose
- Subsequent treatment costs and mean duration of subsequent treatment
- Health-state related costs when on active treatment, when no active treatment and for terminal care
- Health-state utility values
- Proportion of patients experiencing AEs for pembrolizumab combination 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 combination vs. SoC are presented in Figure 37 below.

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 37).

Figure 37: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most sensible variables versus trial comparator SoC (discounted)



B.3.8.3 Scenario analysis

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

- Impact of considering UK-based BSA (i.e. 1.79) [142], as suggested by the ERG for TA [88], instead of derived from KEYNOTE-189 (scenario 1).
- Alternative cut-offs for the estimation of the exponential curve in the second phase of the piecewise approach used to extrapolate OS, including:
    - A 38-week cut-off (scenario 2.a)
    - A 18-week cut-off (scenario 2.b)
- Alternative cut-offs for the estimation of the parametric curve in the second phase of the piecewise approach used to extrapolate PFS, including:
    - A 11-week cut-off (scenario 3.a)
    - A 31-week cut-off (scenario 3.b)
- Assessing the impact of the half-cycle correction (scenario 4).
- 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 5).
- Using progression-based utilities as an alternative approach to estimate QALYs based on KEYNOTE-189 (scenario 6).
- Using utilities derived per treatment arm instead of pooled utilities from KEYNOTE-189:
    - With the time to death approach (scenario 7.a)
    - With the progression-based approach (scenario 7.b)
- Using the utilities from the study by Chang et al (2016) [109], which reported alterative time-to-death utilities (scenario 8).
- Removing the age-related disutilities (scenario 9).

- Assuming that the effect of treatment stops at 5 years (scenario 10), with pembrolizumab presenting a similar hazard to that of the SoC arm from that point onward.

- Using a different parametric function to extrapolate OS including:

    - Log Normal as the second best fitting for both arms at week 28 (scenario 11a).

- Dose regimen for 2L pembrolizumab set to fixed dose 2mg/kg (scenario 12)

- Assuming a 50% discount for pemetrexed in induction and maintenance therapy under the assumption of generic entrants to the market in the near future (scenario 13).

- Taking into account the uncertainty around SoC long term OS estimates, and those estimates preferred in recent NSCLC STAs of between 7.7 and 17.2%[5], a scenario in which a proportional relative risk (RR) or 0.44 using base case settings is applied from week 85 (end of current trial follow up) in order to produce an OS estimate for the SoC arm of 10% (more detail in Appendix L) (scenario 14).

- Assuming the trial proportions of 2L therapy usage following pembrolizumab combination treatment which includes 7% pembrolizumab monotherapy (scenario 15).

Table 89: Results from the scenario analyses versus trial comparator SoC (discounted)

		Pembrolizumab combination			SoC			Pembrolizumab combination vs SoC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Scenario 1	UK-specific BSA values (unadjusted by sex distribution)	£84,079	2.50	1.81	£42,816	1.34	0.92	£41,263	0.89	£46,477
Scenario 2.a	OS cut-off – 38 weeks	£84,477	2.53	1.83	£44,055	1.59	1.11	£40,422	0.72	£56,045
Scenario 2.b	OS cut-off – 18 week	£84,913	2.63	1.91	£42,834	1.31	0.89	£42,080	1.01	£41,554
Scenario 3.a	PFS cut-off – 11 weeks	£84,324	2.50	1.81	£42,980	1.34	0.92	£41,344	0.89	£46,568
Scenario 3.b	PFS cut-off – 31 weeks	£84,324	2.50	1.81	£42,980	1.34	0.92	£41,344	0.89	£46,568
Scenario 4	No half cycle correction	£84,323	2.51	1.82	£43,021	1.35	0.93	£41,302	0.89	£46,522
Scenario 5	SoC as for UK market shares	£84,423	2.50	1.81	£43,070	1.34	0.92	£41,353	0.89	£46,578
Scenario 6	Utilities – Progression based (pooled)	£84,324	2.50	1.72	£42,980	1.34	0.93	£41,344	0.79	£52,499
Scenario 7.a	Utilities – Time to death (per treatment arm)	£84,324	2.50	1.80	£42,980	1.34	0.92	£41,344	0.88	£46,962
Scenario 7.b	Utilities – Progression-based (per treatment arm)	£84,324	2.50	1.76	£42,980	1.34	0.90	£41,344	0.86	£47,868
Scenario 8	Utilities – Time to death by Chang et al (2017) [109]	£84,324	2.50	1.92	£42,980	1.34	0.91	£41,344	1.01	£40,840
Scenario 9	No age-related disutilities	£84,324	2.50	1.83	£42,980	1.34	0.93	£41,344	0.90	£45,743
Scenario 10	Assuming treatment effect stops at 5 years	£83,644	2.36	1.70	£42,980	1.34	0.92	£40,665	0.78	£52,333
Scenario 11	Alternative OS distribution: LogNormal	£92,540	4.31	3.19	£51,057	3.23	2.36	£41,483	0.82	£50,399
Scenario 12	Dose regimen for 2L pembrolizumab	£84,324	2.50	1.81	£40,124	1.34	0.92	£44,200	0.89	£49,785
Scenario 13	50% discount pemetrexed maintenance and	£73,337	2.50	1.81	£35,634	1.34	0.92	£37,703	0.89	£42,467

		Pembrolizumab combination			SoC			Pembrolizumab combination vs SoC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
	induction									
Scenario 14	Assuming a RR of 0.44 to estimate a 5 year OS for SoC of 10%	£90,272	3.79	2.79	£44,864	1.77	1.25	£45,408	1.54	£29,501
Scenario 15	Inclusion of 2L pembrolizumab use as per trial proportions	£85,125	2.50	1.81	£42,980	1.34	0.92	£42,145	0.89	£47,470

B.3.8.4 Summary of sensitivity analyses results

The probability of pembrolizumab combination therapy being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 59%.

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

Scenario analyses showed that the most sensitive scenarios relate to the chosen cut point for to start the parametric extrapolation from for OS with week 18 and 38 alternatives ranging from £41,554 and £56,045, respectively. It should be noted that there is no evidence that the treatment effect stops. The scenario (#14) which implements a relative risk to take into account the uncertainty around SoC long term OS estimates, was also found to be one of the most sensitive scenarios producing an ICER of £29,051.

The majority of scenario analyses produce ICERs below £50,000/QALY and therefore Pembrolizumab combination therefore should be considered a cost-effective strategy when realistic scenarios are considered

B.3.9 Subgroup analysis

The results of the cost-effectiveness analyses on the subgroups of patients with the following different levels of PD-L1 expression versus trial comparator SoC are shown below:

- ≥50% TPS
    - Versus SoC
    - Versus pembrolizumab monotherapy as the expected SoC in this patient population since the recommendation of TA447 [5, 88]
- 1%≤TPS≤49%
- <1% TPS

The subgroup analysis has been conducted because it was pre-specified in the KEYNOTE-189 trial protocol [84] and analysis by PD-L1 expression was also pre-specified in the final scope [1]. Further detail on the statistical analysis and characteristics of the subgroups can be found in section B.2 and appendix E. Due to the smaller number of patients per

subgroup, the results should be interpreted with caution versus the ITT. Base case distributions have been kept for subgroup analysis for consistency of results.

Patients whose tumours express PD-L1 with TPS≥50%

- OS cut-off point at 28 weeks (2-phase with exponential distribution based on AIC/BIC for pembrolizumab combination arm, best statistical fit and consistency with the base case. Gompertz was the best fit for SoC, however when tested gave implausibly high 5 year SoC OS of 43% and so was discarded),
- PFS cut-off point at 21 weeks (2-phase with exponential distribution based on best statistical fit)
- ToT parametric approach (exponential distribution for both arms based on best statistical fit)

Table 90 Incremental cost-effectiveness results for the pembrolizumab combination vs. SoC for patients with TPS≥50% (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SoC	£41,882	1.38	0.95	-	-	-
Pembrolizumab combination	£102,480	3.20	2.35	£60,599	1.39	£43,468
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 91 Incremental cost-effectiveness results for the pembrolizumab combination vs. pembrolizumab monotherapy for patients with TPS≥50% (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab mono	£72,319	2.17	1.57	-	-	-
Pembrolizumab combination	£102,480	3.20	2.35	£30,161	0.78	£38,699
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B.3.9.1 Patients whose tumours express PD-L1 with TPS1%≤TPS≤49%

- OS cut-off point at 28 weeks (2-phase with exponential distribution based on statistical fit).
- PFS cut-off point at 21 weeks (2-phase with Weibull distribution based on the best statistical fit for SoC and consistency with base case. The best statistical fit for pembrolizumab combination was exponential but this made no difference to the results and so the base case Weibull distribution was maintained for consistency.)
- ToT parametric approach: exponential for both arms based on best statistical fit.

Table 92 Incremental cost-effectiveness results for the pembrolizumab combination vs. SoC for patients with TPS 1%≥TPS≤49% (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SoC	£45,084	1.42	0.97	-	-	-
Pembrolizumab combination	£87,429	2.78	2.03	£42,346	1.05	£40,139
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Patients whose tumours express PD-L1 with TPS<1%

- OS cut-off point at 28 weeks 2-phase with:
  - 2 Stage: Exponential distribution based on best statistical fit
  - RPSFT: Exponential distribution based on best statistical fit with pembrolizumab combination arm. LogNormal distribution was the best fit for the SoC arm but produced implausibly high SoC OS at 5 years of 26.4%
  - IPCW: Exponential distribution as the best statistical fit.
- PFS cut-off point at 21 weeks (2-phase with Weibull distribution based on best statistical fit and consistency with base case. GenGamma was the best fit for SoC but produced implausible results and so for consistency with the base case was favoured.)
- ToT parametric approach: Exponential for SoC and Gompertz for pembrolizumab combination chosen as best statistical fit.

Table 93 Incremental cost-effectiveness results for the pembrolizumab combination vs. SoC for patients with TPS <1% with crossover adjustment (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SoC (2 stage)	£26,432	1.15	0.77	-	-	-
Pembrolizumab combination	£62,762	1.85	1.30	£36,330	0.53	£68,563
SoC (RPSFT)	£26,567	1.18	0.80	-	-	-
Pembrolizumab combination	£62,762	1.85	1.30	£36,195	0.51	£71,472
SoC (IPCW)	£27,072	1.29	0.88	-	-	-
Pembrolizumab combination	£62,762	1.85	1.30	£35,691	0.42	£84,501
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Clinical benefit

Comparing the model outcomes to clinical trial outcomes

The outcomes of the pembrolizumab combination therapy and the SoC arms of the KEYNOTE-189 trial have been compared to the outcomes from the model. For more details comparing the results generated from the model to the outcomes from the model please refer to Appendix J.

Expert validation

The model approach and inputs were validated by two external health economists (Dr. Chris Bojke, from the Centre for Health Economics, University of Leeds and Professor Alistair Grey from Oxford University). These individuals were selected as leading experts in health economic practice and methodology development in the UK. The model structure, selection of appropriate dataset, the survival analysis undertaken and assumption regarding extrapolation and the utility values used were all discussed.

Both experts were in agreement that the current model structure and key assumptions were valid and were consistent with previous submissions in this indication. Regarding the assumption of treatment effect, they suggested that any assumptions in the model be provided with a clinical rationale.

Regarding the crossover in the clinical trial and the adjustments applied, the experts agreed that it was reasonable to perform crossover adjustment on the SoC OS in the <1% TPS subgroup only, given the significant proportion of patients from the SoC arm who crossed over to pembrolizumab (33.3% in the <1% TPS subgroup) and taking into account that pembrolizumab therapy is not available in routine clinical practice as a 2L treatment for this subgroup. They also suggested inclusion of a SA which looked at crossover in the whole ITT population which was not taken into account since this is not reflective of UK clinical practice.

The HE experts agreed with the methods of extrapolation for OS, PFS and ToT and that use of the exponential distribution for OS was the most conservative option and to explore other cut points and distributions in SA. With regards to NMA/ITC comparators, it was agreed that choosing constant hazard ratios to estimate the OS and PFS for comparators that are not included in the key trial is a more intuitive and justifiable approach than using time-varying hazard ratios. It was also noted that the time varying approach would require additional extrapolation therefore increasing the uncertainty.

The experts noted that the KEYNOTE-189 trial collected good quality utility data and for a good number of patients. They agreed with the base case using time-to-death utilities derived from pooling data from both treatment arms. The experts suggested inclusion of a scenario without the age-matched general population utility cap for pembrolizumab monotherapy however this was disregarded due to comments made in previous NICE submissions.

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 with inclusion of a SA included for UK SoC market share data.

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

The OS projections, based on the November 2017 KEYNOTE-189 data cut, were validated with clinical experts, who agreed on the plausibility of the projections of the base case analyses presented in this submission with their estimations of SoC OS at 5 years, the majority less than 5% to somewhere between 5 and 10% (the base case for this submission estimates 2.4% SoC OS at 5 years). The clinicians also found the estimated utility values to be reasonable. The clinicians were asked if the approach taken by MSD for the base case reflected their current clinical practice and they agreed with it.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab combination therapy for the treatment of patients with advanced NSCLC lacking EGFR mutations and/or ALK translocations who have not received prior systemic chemotherapy treatment in the UK. The economic evaluation reflects patients assessed in KEYNOTE-189 and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

B.3.11.2 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 combination therapy as per its marketing authorisation. As mentioned previously (see section B.3.3), the KEYNOTE-189 trial, which assessed patients in line with the marketing authorisation, was used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab combination as first line therapy.

B.3.11.3 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-189 and the de novo economic evaluation are reflective of patients with advanced NSCLC in the UK as validated by clinical experts. Some minor differences were identified between patients included in KEYNOTE-189 and those expected to be treated in clinical practice in England (mainly related to age and sex). 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 combination.

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

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

B.3.11.4 Strengths and weaknesses of the evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model, and this updated evidence submission makes use of the final data cut for KEYNOTE-189, which has a median follow up of 10.5 months.

- OS: Head-to-head data from the KEYNOTE-189 trial comparing pembrolizumab combination 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 [27]. [143] [144]

- Crossover adjustments: Given that clinical practice in second line treatment for all PD-L1 expressors is different to that of non-expressors (i.e IO drugs are SoC for PD-L1 positive), it was not deemed appropriate to conduct cross over adjustment for the base case ITT population. The <1% TPS PD-L1 subgroup was adjusted for cross over.

- Estimation of utilities: Utility values were obtained from EQ-5D KEYNOTE-189 data. Four time categories were used for the time-to-death approach, which were consistent with values published by other utility studies identified from the systematic literature review.

- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to 2 years, as defined as part of the KEYNOTE-189 protocol and recommended by NICE for pembrolizumab in both first [88] and second line [94].

- 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 the key variables that have a major impact on the cost-effectiveness results and demonstrated that pembrolizumab combination therapy has the potential to offer a cost-effective option in the majority of the analyses considered.

Since the approaches taken for modelling are, in the main, conservative, the results presented here support the conclusion that, within the context of innovative therapies, pembrolizumab combination therapy is a cost-effective therapeutic option for the treatment of patients with previously untreated advanced NSCLC.

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Single Technology Appraisal

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173] – [noACIC]

Dear Christopher,

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have looked at the submission received on 6 July 2018 from Merck Sharp & Dohme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Tuesday 14 August 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK].

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 Stephen Robinson, Technical Lead (Stephen.Robinson@nice.org.uk) or Victoria Kelly, Technical Adviser (victoria.kelly@nice.org.uk). Any procedural questions should be addressed to Gemma Barnacle, Project Manager (Gemma.Barnacle@nice.org.uk).

Yours sincerely

Victoria Kelly
Technical Adviser – Appraisals

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Searching

A1. In Appendix G the second update search is reported as repeating the 1b update, however the 1b update in table G.1.2 (page 162) only includes economics search terms, not utility and resource use search terms.

- Were the utility and resource use searches also carried out as part of the second update?

A2. In Appendix G could you please explain why pembrolizumab is not included as a search term in line 2 of the 1b update (page 164)?

A3. In Appendix G, page 158 the cost/resource/utility update searches are reported as identifying 1647 studies, however the results in tables G.2, G.3 and G.4 (Appendix G pages 152 and 153) add up to 1638. Should these figures add up to 1647?

A4. In Appendix D, page 5 the manufacturer hand-searched the ESMO (European Society for Medical Oncology), WCLC (World Conference on Lung Cancer), AACR (American Association for Cancer Research) and ASCO (American Society of Clinical Oncology) conference proceedings from the last two years – could you please state if you are aware of any other conference proceedings where this disease might be discussed?

KEYNOTE-189 Trial

A5. Could you please specify the primary censoring rule used to address missing data for progression free survival (PFS) in KEYNOTE-189? Are the sensitivity analyses 1 and 2 mentioned and/or reported in the submission? (Main submission, page 42, Table 12).

Network Meta-analysis

A6. Were the PFS and overall survival (OS) effect estimates adjusted for covariates in trials other than KEYNOTE-189, and if so what were these? (Appendix D, pages 94 and 95)

A7. A process of model selection leads to a model with a second order fractional polynomial (FP) with results presented within the Appendix (Tables 25-42). For the second order FP model, parameter estimates are given (Tables 26, 29, 32, 35, 38, 41 within the appendices).

a. We believe the parameters d0 and d1 should be interpreted as they are specified in the cited paper by Jansen (2011) [BMC Med Res Meth 11:61]. Could you please confirm if this is correct?

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b. We would have expected a second order FP model to give estimates for 3 parameters, yet estimates are given for only two (d0, d1) in the tables and in the priors (Appendix D, page 95). Could you please clarify?

A8. Appendix D, page 95 states that "The prior distributions 'for model 9' are:" Could you please provide details of 'model 9'?

A9. In the network diagrams (main submission page 83 and Appendix D page 101), [Pembro + pem + carboplatin] and [Pembro + pem + platin] are given separate nodes. Could you please explain why, in this instance, carboplatin is not combined with other platinum treatments so these two become a single node? (The combining of platinum treatments seems to occur in all the other nodes).

A10. Could you please explain why KEYNOTE-021G is not included in the Pembrolizumab combination vs pembrolizumab monotherapy indirect comparison analysis within appendix D section D1.2.3.2 (pages 116 to 121)?

A11. Within Table 44, (page 91, main submission) subject characteristics are given for several potential effect modifiers for the KEYNOTE-189 and KEYNOTE-024 trials. Is the same summary information presented for KEYNOTE-021G? If this is not the case, could you please supply the information?

A12. In addition, is summary/aggregate information for these characteristics presented or available for other studies used in the network meta-analysis?

A13. Please could you provide the complete set of code used to perform the network meta-analysis?

A14. [Additional question] Please could you explain the difference between the estimate of the OS HR for KN021G in the main submission (Table 6; p.29) and the appendix (Table 20; p.91)?

Section B: Clarification on cost-effectiveness data

Extrapolation of overall survival

B1. The OS survival curve adopted by the model uses a piecewise approach. The post-follow-up phase is estimated in the base case using fitted exponential parametric distributions, for both Pembro-combo and SOC strategies.

a. Please could you provide details of the derivation of the distribution parameters? Was the fit based on all or part of the observed data, and if part, which part?

b. Was the same or a different method used to fit the alternative distributions?

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c. Please could you provide the code for this analysis?

B2. [Additional question] Please provide the long term OS estimates from each of the 11 clinical experts?

B3. [Additional question] Please specify to whom in the model the PDL1 test cost was applied? The report and model suggest that the test costs applied to only people who go on to receive pembrolizumab.

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14th August 2018

Dear Victoria,

Re. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

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,

Chris O'Regan, Head of HTA and OR

Section A: Clarification on effectiveness data

Searching

A1. In Appendix G the second update search is reported as repeating the 1b update, however the 1b update in table G.1.2 (page 162) only includes economics search terms, not utility and resource use search terms.

- Were the utility and resource use searches also carried out as part of the second update?

Table G.1.2 should read as the following below and did include the utility and resource use search terms. Table G.1.2 (now G.1.3 below) from appendix G only included the additional economics search terms to the original search.

G.1.2 Search strategy for cost-effectiveness, utility and cost/resource use studies for update 1a – original search terms

Search No.	Search Terms	No. of Articles
Disease		
#1	"Carcinoma, Non-Small-Cell Lung"[Mesh] OR non small cell lung cancer*[Title] OR nonsmall cell lung cancer*[Title] OR non small cell lung carcinoma*[Title] OR nonsmall cell lung carcinoma*[Title] OR NSCLC[Title]"english"[Language]	9,672
Economics		
#2	#1 AND ("Carcinoma, Non-Small-Cell Lung/economics"[Mesh] OR "Health Care Costs"[Mesh] OR "Hospital Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Employer Health Costs"[Mesh] OR "Drug Costs"[Mesh] OR "Cost of Illness"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Health Resources/utilization"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Fees and Charges"[Mesh] OR cost*[Title] OR economic*[Title] OR pharmacoeconomic*[Title] OR "modeling"[Text Word] OR "modelling"[Text Word] OR "Models, Economic"[Mesh] OR cost effective*[Text Word] OR "health utility"[Text Word] OR "health utilities"[Text Word] OR health stat*[Title] OR "Health Status Indicators"[Mesh] OR "Activities of Daily Living"[Mesh] or "Models, Economic"[MeSH] or "Cost-Effective"[text word] or "Quality-Adjusted Life Years"[Mesh] or cost effective*[Text Word] OR cost-effective*[Text Word] OR "modeling"[Text Word] OR "modelling"[Text Word] OR economic model*[Text Word] OR (model*[Text Word] AND (cost*[Text Word] OR costs[Text Word] OR economic*[Text Word] OR pharmacoeconomic*[Text Word])) OR "markov model"[Title] OR "markov-model"[Title] OR "decision-analytic models"[Text Word] OR cost consequence[Text Word] OR discreet event simulation[Text	195

	Word] OR "Cost-Benefit Analysis"[MeSH] OR cost utility[Text Word] OR cost-utility[Text Word] or "Models, Economic"[MeSH])"English"[Language]	
Resource use and cost studies		
#3	#1 and ("Costs and Cost Analysis"[MeSH] OR "Economics"[MeSH] OR "Economics, hospital"[MeSH] OR "Economics, medical"[MeSH] OR "Economics, nursing"[MeSH] OR "Economics, Pharmaceutical"[MeSH] OR "Health Resources/utilization"[MeSH] OR "Fees and Charges"[MeSH] OR (Economic*[Text Word] AND burden*[Text Word]) OR hospitalization*[Text Word] OR hospitalisation*[Text Word] OR economic*[Text Word] OR price*[Text Word] OR pricing[Text Word] OR cost*[Text Word] OR costs[Text Word] OR "cost analysis"[Text Word] OR cost-analysis[Text Word] OR "resource use"[Text Word] OR "resource utilization"[Text Word] OR "resource utilisation"[Text Word] OR health care cost*[Text Word] OR health-care cost*[Text Word] OR productivity[Text Word] OR "cost-minimization"[Text Word] OR "cost-minimisation"[Text Word] OR "cost-minimisation analysis"[Text Word] OR productivity cost*[Text Word] OR societal cost*[Text Word] OR economic benefit*[Text Word] OR "Employment"[MeSH] OR "Work"[MeSH] OR "employment"[Text Word] OR "unemployment"[Text Word] OR "Health Care Costs"[MeSH] OR direct cost[Text Word] or direct costs[text word] OR (direct[Text Word] AND (cost[Text Word] OR costs[Text Word])) OR indirect cost*[Text Word] OR (indirect[Text Word] AND (cost[Text Word] OR costs[Text Word]))) "English"[Language]	134
Utility studies		
#4	#1 and ("EuroQol"[Text Word] OR "standard gamble"[Text Word] OR "time trade off"[Text Word] OR "time trade-off"[Text Word] OR "time tradeoff"[Text Word] OR "TTO"[Text Word] OR "EQ5D"[Text Word] OR "EQ-5D"[Text Word] OR "health utility index"[Text Word] OR "health utilities index"[Text Word] OR (health[Text Word] AND utilit*[Text Word] AND index[Text Word) OR HUI*[Text Word] OR "SF-6D"[Text Word] OR sf6*[Text Word] OR sf 6*[Text Word] OR short form 6*[Text Word] OR shortform 6*[Text Word] OR "sf six"[Text Word] OR "sfsix"[Text Word] OR "shortform six"[Text Word] OR "short form six"[Text Word] OR "QALY"[Text Word] OR "Quality-Adjusted Life Years"[MeSH] OR Quality adjusted life year*[Text Word] OR Quality-adjusted life year*[Text Word] OR Quality adjusted life-year*[Text Word] OR Quality-adjusted life-year*[Text Word] OR	83

	"SF-36"[Text Word] OR "sf36"[Text Word] OR "sf 36"[Text Word] OR "short form 36"[Text Word] OR "shortform 36"[Text Word] OR "sf thirtysix"[Text Word] OR "sf thirty six"[Text Word] OR "shortform thirtysix"[Text Word] OR "shortform thirty six"[Text Word] OR "short form thirty six"[Text Word] OR "short form thirtysix"[Text Word] OR "short form thirty six"[Text Word] OR "Short Form Health Survey"[Text Word] OR "willingness to pay"[Text Word] OR (utilit*[Text Word] AND score*[Text Word]) OR (utilit*[Text Word] AND weight*[Text Word]) OR SF-6D[Text Word] OR "Assessment of Quality of Life"[Text Word] OR AQOL[Text Word] OR AQOL-2[Text Word] OR QWB[Text Word] OR 15D[Text Word] OR QLQ-C30[Text Word] OR "QLQ C30"[Text Word] OR "QLQC30"[Text Word] OR "Quality of life questionnaire-core 30"[Text Word] OR "Quality of life questionnaire core 30"[Text Word]) "English"[Language]	
Exclusions		
#5	"Animals"[Mesh] NOT "Humans"[Mesh]"English"[Language]	210,742
#6	"Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type] OR "Comment"[Publication Type] OR "Interview"[Publication Type]"English"[language]	242,579
Totals		
#7	((#2 or #3 or #4) NOT (#5 OR #6))"English"[language]	237

A2. In Appendix G could you please explain why pembrolizumab is not included as a search term in line 2 of the 1b update (page 164)?

The tables in appendix G should have been named more clearly. As you will see below from Table G.1.4 (formerly G.1.3 in appendix G), drug search terms were not included in the 1b update or the original search. In the original search, the reason for this was to not limit the NSCLC treatments included. In the 1b update, this was to be consistent with the original search. Table G.1.3 (formerly G.1.2 in appendix G) was to identify cost-effectiveness studies for the additional treatments of interest not only for the timeframe of the first update (2015-17) but for the entire original search period (2007 onwards).

G.1.3 Search strategy for cost-effectiveness, utility and cost/resource use studies for update 1a – additional search terms for cost-effectiveness studies including publication dates from 2007/09/01 onwards

Search No.	Search Terms	No. of Articles
Disease		
#1	"Carcinoma, Non-Small-Cell Lung"[Mesh] OR non small cell lung cancer*[Title] OR nonsmall cell lung cancer*[Title] OR non small cell lung carcinoma*[Title] OR nonsmall cell lung carcinoma*[Title] OR	28,308

	NSCLC[Title]	
Drugs		
#2	#1 AND ("Bevacizumab"[Mesh] OR bevacizumab[Title/Abstract] OR avastin[Title/Abstract] OR "Pemetrexed"[Mesh] OR pemetrexed[Title/Abstract] OR alimta[Title/Abstract] OR "LY-231514"[Title/Abstract] OR "LY 231,514"[Title/Abstract] OR "LY231514"[Title/Abstract] OR "Albumin-Bound Paclitaxel"[Mesh] OR abraxane[Title/Abstract] OR "Nab-paclitaxel"[Title/Abstract] OR "albumin bound paclitaxel"[Title/Abstract] OR "protein bound paclitaxel"[Title/Abstract] OR "ABI007"[Title/Abstract] OR "ABI-007"[Title/Abstract] OR (("necitumumab"[Supplementary Concept] OR necitumumab[Title/Abstract] OR "IMC-11F8"[Title/Abstract] OR portrazza[Title/Abstract]) AND ("Carcinoma, Non-Small-Cell Lung/drug therapy"[Majr] OR "Drug Therapy"[Majr] OR chemotherapy[Title/Abstract])))	1,624
Economics		
#3	#2 AND ("Cost-Benefit Analysis"[Majr] OR "Models, Economic"[Majr] OR "Models, Econometric"[Majr] OR "Costs and Cost Analysis"[Majr] OR "Economics"[Majr] OR "Economics, Hospital"[Majr] OR "Economics, Medical"[Majr] OR "Economics, Nursing"[Majr] OR "Economics, Pharmaceutical"[Majr] OR "Cost Savings"[Majr] OR cost effective*[Title/Abstract] OR modeling[Title] OR modelling[Title] OR economic model*[Title/Abstract] OR (model*[Title] AND (cost[Title] OR costs[Title] OR economic*[Title] OR pharmacoeconomic*[Title])) OR Markov[Title/Abstract] OR "decision analysis"[Title/Abstract] OR "decision-analytic models"[Title/Abstract] OR "cost consequence"[Title/Abstract] OR ((cost[Title] OR costs[Title]) AND (effective*[Title] OR utilit*[Title] OR benefit*[Title] OR minimi*[Title])) OR "discrete event simulation"[Title/Abstract] OR "cost analysis"[Title/Abstract] OR "cost-minimisation analysis"[Title/Abstract] OR economic benefit*[Title/Abstract] OR "cost utility"[Title/Abstract] OR costminimization[Title/Abstract] OR costminimisation[Title/Abstract] OR "cost minimization"[Title/Abstract] OR "cost minimisation"[Title/Abstract] OR "budget impact"[Title/Abstract] OR econometric[Title/Abstract] OR "economic evaluation"[Title/Abstract])	72
Exclusions		
#5	"Animals"[Mesh] NOT "Humans"[Mesh]"English"[Language]	1,046,943
#6	"Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type] OR "Comment"[Publication Type] OR "Interview"[Publication Type]	1,043,417

Totals		
#7	(#3 NOT (#4 OR #5))	71

G.1.4 Search strategy for cost-effectiveness, utility and cost/resource use studies for update 1b

Search No.	Search Terms	No. of Articles
Disease		
#1	"Carcinoma, Non-Small-Cell Lung"[Mesh] OR non small cell lung cancer*[Title] OR nonsmall cell lung cancer*[Title] OR non small cell lung carcinoma*[Title] OR nonsmall cell lung carcinoma*[Title] OR NSCLC[Title]	2,276
Economics		
#3	#2 AND ("Carcinoma, Non-Small-Cell Lung/economics"[Mesh] OR "Health Care Costs"[Mesh] OR "Hospital Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Employer Health Costs"[Mesh] OR "Drug Costs"[Mesh] OR "Cost of Illness"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Health Resources/utilization"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Fees and Charges"[Mesh] OR cost*[Title] OR economic*[Title] OR pharmacoeconomic*[Title] OR "modeling"[Text Word] OR "modelling"[Text Word] OR "Models, Economic"[Mesh] OR cost effective*[Text Word] OR "health utility"[Text Word] OR "health utilities"[Text Word] OR health stat*[Title] OR "Health Status Indicators"[Mesh] OR "Activities of Daily Living"[Mesh] OR "Models, Economic"[MeSH] OR "Cost-Effective"[text word] OR "Quality-Adjusted Life Years"[Mesh] OR cost effective*[Text Word] OR cost-effective*[Text Word] OR "modeling"[Text Word] OR "modelling"[Text Word] OR economic model*[Text Word] OR (model*[Text Word] AND (cost*[Text Word] OR costs[Text Word] OR economic*[Text Word] OR pharmacoeconomic*[Text Word])) OR "markov model"[Title] OR "markov-model"[Title] OR "decision-analytic models"[Text Word] OR cost consequence[Text Word] OR "discreet event simulation"[Text Word] OR "cost utility"[Text Word] OR "cost-utility"[Text Word])	67
Resource Use and Cost Studies		
#3	#1 AND (“Costs and Cost Analysis”[Mesh] OR “Economics”[Mesh] OR “Economics, hospital”[Mesh] OR “Economics, medical”[Mesh] OR “Economics, nursing”[Mesh] OR “Economics, Pharmaceutical”[Mesh] OR “Health Resources/utilization”[Mesh] OR “Fees and Charges”[Mesh] OR (Economic*[Text Word] AND	66

	burden*[Text Word]) OR hospitalization*[Text Word] OR hospitalisation*[Text Word] OR economic*[Text Word] OR price*[Text Word] OR pricing[Text Word] OR cost*[Text Word] OR costs[Text Word] OR "cost analysis"[Text Word] OR "resource use"[Text Word] OR "resource utilization"[Text Word] OR "resource utilisation"[Text Word] OR health care cost*[Text Word] OR productivity[Text Word] OR "cost-minimization"[Text Word] OR "cost-minimisation"[Text Word] OR productivity cost*[Text Word] OR societal cost*[Text Word] OR economic benefit*[Text Word] OR "Employment"[Mesh] OR "Work"[Mesh] OR employment[Text Word] OR unemployment[Text Word] OR "Health Care Costs"[Mesh] OR direct cost*[Text Word] OR (direct[Text Word] AND (cost[Text Word] OR costs[Text Word])) OR indirect cost*[Text Word] OR (indirect[Text Word] AND (cost[Text Word] OR costs[Text Word])))	
Utility Studies		
#4	#1 AND ("EuroQol"[Text Word] OR "standard gamble"[Text Word] OR "time trade off"[Text Word] OR "time tradeoff"[Text Word] OR "TTO"[Text Word] OR "EQ5D"[Text Word] OR "EQ-5D"[Text Word] OR "health utility index"[Text Word] OR "health utilities index"[Text Word] OR (health[Text Word] AND utilit*[Text Word] AND index[Text Word]) OR HUI*[Text Word] OR "SF-6D"[Text Word] OR sf6*[Text Word] OR sf 6*[Text Word] OR short form 6*[Text Word] OR shortform 6*[Text Word] OR "sf six"[Text Word] OR "sfsix"[Text Word] OR "shortform six"[Text Word] OR "short form six"[Text Word] OR "QALY"[Text Word] OR "Quality-Adjusted Life Years"[Mesh] OR Quality adjusted life year*[Text Word] OR "SF-36"[Text Word] OR "sf36"[Text Word] OR "sf 36"[Text Word] OR "short form 36"[Text Word] OR "shortform 36"[Text Word] OR "sf thirtysix"[Text Word] OR "sf thirty six"[Text Word] OR "shortform thirtysix"[Text Word] OR "shortform thirty six"[Text Word] OR "short form thirty six"[Text Word] OR "short form thirtysix"[Text Word] OR "short form thirty six"[Text Word] OR "Short Form Health Survey"[Text Word] OR "willingness to pay"[Text Word] OR (utilit*[Text Word] AND score*[Text Word]) OR (utilit*[Text Word] AND weight*[Text Word]) OR "Assessment of Quality of Life"[Text Word] OR AQOL[Text Word] OR "AQOL-2"[Text Word] OR QWB[Text Word] OR 15D[Text Word] OR "QLQ-C30"[Text Word] OR "QLQC30"[Text Word] OR "Quality of life questionnaire-core 30"[Text Word])	26
Exclusions		
#5	"Animals"[Mesh] NOT "Humans"[Mesh]	13,365
#6	"Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case	39,613

	Reports"[Publication Type] OR "Comment"[Publication Type] OR "Interview"[Publication Type]	
Totals		
#7	((#2 OR #3 OR #4) NOT (#5 OR #6))	103

A3. In Appendix G, page 158 the cost/resource/utility update searches are reported as identifying 1647 studies, however the results in tables G.2, G.3 and G.4 (Appendix G pages 152 and 153) add up to 1638. Should these figures add up to 1647?

The results in tables G.2, G.3 and G.4 add up to 1638. The overall number should add up to 1644 (rather than 1647) to account for the internet searches (n=6).

A4. In Appendix D, page 5 the manufacturer hand-searched the ESMO (European Society for Medical Oncology), WCLC (World Conference on Lung Cancer), AACR (American Association for Cancer Research) and ASCO (American Society of Clinical Oncology) conference proceedings from the last two years – could you please state if you are aware of any other conference proceedings where this disease might be discussed?

Additional congresses could be ESMO IO [ESMO Immuno Oncology Congress], SITC [Society for Immunotherapy of Cancer] & ELCC [European Lung Cancer Congress].

KEYNOTE-189 Trial

A5. Could you please specify the primary censoring rule used to address missing data for progression free survival (PFS) in KEYNOTE-189? Are the sensitivity analyses 1 and 2 mentioned and/or reported in the submission? (Main submission, page 42, Table 12).

Details of the censoring rules for the primary and sensitivity analyses of PFS are presented in **Table 1** below.

Table 1: 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

Results of the PFS sensitivity analyses were not presented in the submission but have been included below for your reference.

PFS Sensitivity Analysis 1

Table 2: Analysis of PFS (sensitivity analysis 1) based on BICR assessment per RECIST 1.1 (ITT population)

Treatment	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS† (Months) (95% CI)	PFS Rate at month 6 in %† (95% CI)	vs. Control	
						Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo (N=410)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control (N=206)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Figure 1: Kaplan-Meier estimates of PFS (sensitivity analysis 1) based on BICR assessment per RECIST 1.1 (ITT population)

PFS Sensitivity Analysis 2

Table 3: Analysis of PFS (sensitivity analysis 2) based on BICR assessment per RECIST 1.1 (ITT population)

Treatment	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS† (Months) (95% CI)	PFS Rate at month 6 in %† (95% CI)	vs. Control	
						Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo (N=410)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control (N=206)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Figure 2: Kaplan-Meier estimates of PFS (sensitivity analysis 2) based on BICR assessment per RECIST 1.1 (ITT population)

Network Meta-analysis

A6. Were the PFS and overall survival (OS) effect estimates adjusted for covariates in trials other than KEYNOTE-189, and if so what were these? (Appendix D, pages 94 and 95)

PFS and OS estimates were not adjusted for covariates. As shown in the feasibility assessment, the included trials were similar in study design and baseline patient characteristics. To avoid over-fitting models, no covariates were used. Additionally, this analysis only included patients with non-squamous disease. Potential effect modification was addressed by conducting a sensitivity analysis excluding trials conducted among East Asian patients only.

A7. A process of model selection leads to a model with a second order fractional polynomial (FP) with results presented within the Appendix (Tables 25-42). For the second order FP model, parameter estimates are given (Tables 26, 29, 32, 35, 38, 41 within the appendices).

a. We believe the parameters d0 and d1 should be interpreted as they are specified in the cited paper by Jansen (2011) [BMC Med Res Meth 11:61]. Could you please confirm if this is correct?

Yes, parameters d0 and d1 are interpreted as shown in Jansen (2011) [BMC Med Res Meth 11:61].

b. We would have expected a second order FP model to give estimates for 3 parameters, yet estimates are given for only two (d0, d1) in the tables and in the priors (Appendix D, page 95). Could you please clarify?

d0 reflects the relative treatment effect of the intervention versus the reference treatment (platin + pemetrexed) assuming constant log hazard ratios over time, and d1 reflects the change in the log hazard ratio over time relative to platin+ pemetrexed. d2 reflects the log hazard ratio for treatment k relative to a comparator treatment b. In this case, we assume d2 = 0 as limited data were available. Thus, parameter estimates were not shown in tables for d2 and we assume treatment only has an impact on two parameters that describe the hazard function over time: shape and scale.

A8. Appendix D, page 95 states that "The prior distributions 'for model 9' are:" Could you please provide details of 'model 9'?

Model 9 refers to a second-order fractional polynomial model including p_1=0 or 1 and p_2= 0 or 1 which incorporates the following prior distributions:

$$\begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 10^4 & 0 \\ 0 & 10^4 \end{pmatrix} \right)$$

$$\begin{pmatrix} d_{0Ak} \\ d_{1Ak} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 10^4 & 0 \\ 0 & 10^4 \end{pmatrix} \right)$$

Further details on Model 9 can be found in Jansen (2011) [BMC Med Res Meth 11:61] and in the provided BUGS code presented at the end of this document (Sections 2.3-2.4).

A9. In the network diagrams (main submission page 83 and Appendix D page 101), [Pembro + pem + carboplatin] and [Pembro + pem + platin] are given separate nodes. Could you please explain why, in this instance, carboplatin is not combined with other platinum treatments so these two become a single node? (The combining of platinum treatments seems to occur in all the other nodes).

When developing the NMA networks, it was not considered appropriate to merge the Pembro + pem + platin (KEYNOTE-189) and the Pembro + pem + carboplatin (KEYNOTE-021G) data due to differences in study design and patient demographics between the studies (see the main submission Section B.2.8 Meta-analysis; p82 for further details).

A10. Could you please explain why KEYNOTE-021G is not included in the Pembrolizumab combination vs pembrolizumab monotherapy indirect comparison analysis within appendix D section D1.2.3.2 (pages 116 to 121)?

KEYNOTE-021G was not included in the ITC analysis of OS and PFS outcomes as the study was an open-label phase 2 study comparing pembrolizumab/chemotherapy combination versus chemotherapy alone, with the primary objective of assessing ORR. While PFS and OS were captured, they were included as secondary endpoints only and as such, the study was not powered to detect changes in these endpoints.

A11. Within Table 44, (page 91, main submission) subject characteristics are given for several potential effect modifiers for the KEYNOTE-189 and KEYNOTE-024 trials. Is the same summary information presented for KEYNOTE-021G? If this is not the case, could you please supply the information?

Table 44 provided a summary of the patient selection for the ITC which did not include KEYNOTE-021G and therefore the same information was not presented in the submission, but is presented in the table below:

KEYNOTE Trial	Treatment arms	Population Selection	Patient numbers
KEYNOTE-21G	- Pembrolizumab + Chemotherapy[1] - Chemotherapy[1]	Advanced/metastatic NSCLC[2]	N=123 [ITT population] Pembro + chemo: n=60 Chemo: n=63 N=37 [TPS ≥50%] Pembro + chemo: n=20 Chemo: n=17
1. Pemetrexed plus carboplatin 2. Keynote21G contains patients primarily with non-squamous histology			

A12. In addition, is summary/aggregate information for these characteristics presented or available for other studies used in the network meta-analysis?

PD-L1 TPS ≥ 50% subgroup data was only available for KN189. Subgroup data by PD-L1 status was not available for trials evaluating non-PD-L1-directed interventions. All patients in the analysis networks had non-squamous disease.

A13. Please could you provide the complete set of code used to perform the network meta-analysis?

Provided in a separate document uploaded to NICE.docs 10 Aug 2018.

A14. [Additional question] Please could you explain the difference between the estimate of the OS HR for KN021G in the main submission (Table 6; p.29) and the appendix (Table 20; p.91)?

The OS HR for KN021G presented in Table 6; p 29 of the main submission is based on 23.9 months of follow-up (data cut-off December 1 2017) which were presented in a poster at ASCO in June 2018 (Gentzler et al. 2018)[1] and were the most recent data available at the time of our submission to NICE. The data presented in Table 20, p91 of the appendix relate to the studies identified from an SLR conducted to feed into the NMA, which was executed on April 16, 2018, and therefore did not include the ASCO Gentzler poster. The OS HR data included in the NMA, as presented in Table 20, were the latest data available at the date of the SLR and are based on 18.7 months of follow-up (data cut-off May 31 2017) as presented at WCLC in October 2017 (Borghaei et al. 2017)[2].

Section B: Clarification on cost-effectiveness data

Extrapolation of overall survival

B1. The OS survival curve adopted by the model uses a piecewise approach. The post-follow-up phase is estimated in the base case using fitted exponential parametric distributions, for both Pembro-combo and SOC strategies.

a. Please could you provide details of the derivation of the distribution parameters? Was the fit based on all or part of the observed data, and if part, which part?

Example R code and an additional document is uploaded with the response to clarification questions which provides detail of the derivation of distribution parameters. The fit was based on the KM data following the reported weekly cut-point. For the base case week 28 cut-point for OS, the fitting was based on KM data available beyond week 28.

b. Was the same or a different method used to fit the alternative distributions?

There are different functional forms for each distribution included in the model, so the methods are not the same in that sense. But the general methodology based on use of KM data up to the cut-point, and parametric fitting based on the KM data following the cut-point, was the same for each distribution

c. Please could you provide the code for this analysis?

---

[1] Gentzler RD LC, Borhaei H, et al., editor 24-Month Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed-Carboplatin Plus Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC. American Society of Clinical Oncology (ASCO); 2018 June 1-5, 2018; Chicago, Ilinois.

[2] Borghaei H, Langer C, Gadgeel S, et al. Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous nsclc: keynote-021 cohort g update. Journal of thoracic oncology. 2017;Conference: 18th world conference on lung cancer of the international association for the study of lung cancer, IASLC. 2017. Japan 12(11 Supplement 2):S1791.

Example R code for OS at a week 28 cut point has been uploaded with response to clarification questions and in addition, a document which details how the parameters of each distribution are derived.

B2. [Additional question] Please provide the long term OS estimates from each of the 11 clinical experts?

Eleven clinical experts from 11 different NHS trusts were asked to reply to the following questions (not in order to protect anonymity).

NHS Trusts that responded	[redacted]
For a patient diagnosed today with non-EGFR or ALK mutated non-squamous NSCLC, what would be the five year survival rates	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

B3. [Additional question] Please specify to whom in the model the PDL1 test cost was applied? The report and model suggest that the test costs applied to only people who go on to receive pembrolizumab.

This is correct, as a conservative assumption the PDL1 test cost was applied in the pembrolizumab combination arm. Please find below a scenario analysis in which PDL1 test cost is applied to both arms producing an ICER of £46,324 versus the company submission base case ICER of £46,370.

Intervention	Total Costs	Total LYs	Total QALY	Incremental Costs	Incremental QALYs	ICER

Pembrolizumab combination	£76,257	2.50	1.81	-	-	-
SoC	£35,129	1.34	0.92	£41,128	0.89	£46,324

NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer [ID1173]

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

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

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

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	**British Thoracic Oncology Group (BTOG)**
3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**BTOG registered charity**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**None**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve	Prolong and improve quality of life

mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Difference in progression free survival for >3 months Overall survival difference Improvement in QOL
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes Small but additive treatment improvements over the last 5 years
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Chemotherapy for PDL1 negative NSCLC Checkpoint inhibitor (PD1 Ab) for PDL1 >50%

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Treatment of NSCLC guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No great variation in treatment
• What impact would the technology have on the current pathway of care?	Both checkpoint inhibitor and chemotherapy given together rather than sequentially
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	New technology
• How does healthcare resource use differ	Given sequentially

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care: Oncologists
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No extra capacity required Likely to save chemotherapy chair time as immunotherapy and chemotherapy given together
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes Prevention of early progression of disease
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase	If disease free interval is greater than likely QOL will be improved

health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not defined
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Experience of managing patients on combination should not be significantly different Trials experience is not of increasing toxicity

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Evaluable disease on imaging and clinical benefit
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	None
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	More responders Less early progression of disease

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	None extra than those experienced with chemotherapy or Immunotherapy alone
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and OS measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	NA
19. Are you aware of any relevant evidence that might	None

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA181; TA190; TA402; TA447]?	Comparators are other PD1 antibodies
21. How do data on real-world experience compare with the trial data?	Trial likely enriched with good performance status patients likely to manage better
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None

22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Is biomarker testing (PD-L1, EGFR, ALK) standard practice in the NHS?	Yes
Key messages	

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

- Longer PFS with combination
- Likely allow those who take longer to respond to checkpoint inhibitors to benefit
- Toxicity is no greater than when chemotherapy and pembrolizumab given separately
- No greater capacity required, will actually reduce chemosuite chair numbers as both given together rather than sequentially
-

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer [ID1173]

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

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

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

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
[redacted]	[redacted]

2. Name of organisation	[redacted] **Royal College of Pathologists**
3. Job title or position	**Consultant Pathologist**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	[redacted] **The Royal College of Pathologist is a college of professional pathologists which is funded by the membership and a registered charity it's mission is maintaining the high standard of pathology in the UK.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve	Increased overall survival and improved quality of life through reducing disease burden and slowing progression.

mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction of disease volume as assessed on radiological imaging.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes metastatic NSCLC is an incurable disease and the biggest cause of cancer related deaths in men and women. There is an unmet need in therapies which provide effective response rates with good quality of life. Responses to current chemotherapy are variable and the treatment has significant co-morbidity. Many patients are ineligible for chemotherapy because of co-morbidity. There is a need for more effective treatment, curative therapy and a wider range of treatment options better suited to the patient population.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Metastatic NSCLC is treated with palliative chemotherapy the mainstay of which is has been platinum based chemotherapy. More recently permetrexed has been shown to provide superior outcomes in patients with adenocarcinoma. This has led to a change in pathology practice with immunocytochemistry now routinely used to distinguish and from squamous carcinoma on the diagnostic biopsy. Pembrolizumab has proved to be very effective as a first line treatment in NSCLC, which highly expresses the PD-L1 ligand. In

	this setting Pembrolizumab effectively blocks the PD-L1 pathway and leads to an improved host response to the tumour which has proved an effective means of slowing progression and in some cases inducing regression. Assessment of the PD-L1 expression is achieved through immunocytochemistry. A number of markers are commercially available for this but the results are not always compatible. Since response to Pembrolizumab monotherapy are dependent on the level of expression of PD-L1, correct assessment of this biomarker is the key step in patient selection. Furthermore the assessment of this marker is difficult and can be prone to error between and within observers. This is particularly likely to happen where training is incomplete or inadequate and experience is limited. It is important that the detail of how this companion diagnostic marker works is fully understood, including knowledge about expression may be altered in different sample types, tissue fixation methods, tissue processing and method of immunocytochemical staining. Variation between and within observers may suggest quantified image analysis of stain intensity is superior to human assessment. However in the KEYNOTE 189 study PD-L1 expression had no significant effect on response to combination therapy, suggesting assement of this biomarker is irrelevant in this setting. It is also important to point out that patients with metastatic NSLC will be diagnosed on small biopsies, either bronchial biopsies or EBUS samples. Such samples are very good at giving a diagnosis, but may contain relatively few cells. Since the expression of PD-L1 is known to be heterogeneous the possibility that the relatively small proportion of cells present in the biopsy may not be representative of the underlying tumour needs to be considered. Finally there have been a number of targeted treatments based on specific mutations that occur in a subset of these tumours, most often adenocarcinomas. These include mutations in the EGFR gene, and translocations of the ALK or ROS1 genes. The net result of this has been a substantial increase in the amount of testing performed on pathology samples used to make the diagnosis of NSCLC to establish suitability targeted treatment. Pathologists have responded to this by preserving tissue where this is possible for molecular and immunohistochemical testing, this is obviously important but needs to be supported by appropriate resources. With increasing numbers of genetic targets and complexity of the testing involved many laboratories have opted to out source this testing to other larger laboratories. This is resulting in delays to many patients before treatment can commence. The requirement to perform so many ancillary companion diagnostic tests leads to exhaustion of the tissue. PD-L1 tends to be performed after immunocytochesmistry to type the tumour and EGFR and ALK tests, by

	which time there may be very few tumour cells left in the biopsy sample. Some patients ay need a second biopsy simply to identify this biomarker.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidelines 24 updated 2011 The diagnosis and treatment of lung cancer. NICE Technology appraisals TA181; TA190; TA402; TA447
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined. The least clearly defined part of the pathway is tumours with low expression of PD-L1. The KEYNOTE 189 suggests this marker is irrelevant in this setting of combination therapy which would simplify patient selection.
• What impact would the technology have on the current pathway of care?	Introducing combination of permetrexed and Pembrolizumab appears to offer superior outcomes to standard of care. The pathway is likely to remain the same, as most of the existing testing is in place to select the patient groups who might benefit from this combination therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Both drugs are already routinely used in the NHS.

• How does healthcare resource use differ between the technology and current care?	Both drugs are already routinely but not in combination.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should be delivered by oncologists specialising in lung cancer treatment in the secondary care setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As stated above I do not think additional or new technology is needed to correctly identify the patient sub group. There are concerns over the quality of biopsy tissue to provide the assessment of PD-L1 expression but this is the case with current standard of care and will not be altered by combination therapy.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes results suggest this combination therapy is superior to the standard of care.
• Do you expect the technology to increase length of life more than current care?	Yes overall survival at 12 months and 21 months is superior on the combination therapy group compared to the current standard of care

• Do you expect the technology to increase health-related quality of life more than current care?	Yes, overall survival is improved and the adverse reactions rate is comparable to the existing standard of care.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	Since the PD-L1 expression did not seem to be relevant to response this will simplify patient selection.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Unable to comment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
16. Do you consider the technology to be innovative in	Yes the results suggest a significant improvement in overall survival compared to the standard of care.

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	I am not sure it really is. Definitely it's an improvement and welcome development but I am not sure it qualifies as a step change.
• Does the use of the technology address any particular unmet need of the patient population?	No.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Since this a combination with chemotherapy the side effects are comparable to the standard of care. The addition of pembrolizumab appears to be well tolerated.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, objective response, and disease progression. These were adequately assessed in the study
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA181; TA190; TA402; TA447]?	no
21. How do data on real-world experience compare with the trial data?	Yes.
Equality	
22a. Are there any potential equality issues that should be	no

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Is biomarker testing (PD-L1, EGFR, ALK) standard practice in the NHS?	Yes.
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your submission. • Outcomes superior to standard of care • PD-L1 expression is irrelevant to response to the treatment. • No increased adverse event rates • •	

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

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

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

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

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

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

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim of this combination for NSCLC would be to palliate symptoms and produce prolonged remissions. This in turn would improve survival which for advanced lung cancer ranges between 12-18 months.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant response would be improvement in symptoms. All clinical trials use RECIST criteria which is percentage reduction of tumour on CT scans, any reduction in lesions by >20% constitutes a response
9. In your view, is there an unmet need for patients and	Small incremental advances have been made over the years. It is also clear that this type of lung cancer is not one disease and can vary in response and rapidity of progression. Currently PDL1<50% receive chemotherapy and those >50% receive pembrolizumab as 1st line treatment. It is clear from trials and real life practice that

healthcare professionals in this condition?	some patients have rapid progression of disease with checkpoint inhibitors (Pembrolizumab). Combination with chemotherapy may allow rapid responses and allow checkpoint inhibitors more time to produce immunological response. Immune checkpoint inhibition may produce more sustained, prolonged responses.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	First line treatment for advanced lung cancer irrespective of predictive marker PDL1 expression. Chemotherapy and pembrolizumab will be given together. Previously they were administered sequentially. This will actually save capacity on chemotherapy suites as the treatments are administered during one visit.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE TA181: pemetrexed based chemotherapy for previously untreated non-squamous NSCLC NICE TA402: Maintenance pemetrexed for non squamous NSCLC following cisplatin/pemetrexed chemotherapy NICE TA531: Pembrolizumab for untreated NSCLC PDL1>50% NICE TA428: Pembrolizumab for NSCLC previously treated with chemotherapy PDL1<50%
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined standard of care.
• What impact would the	This would actually release capacity as both treatments are given rather then going through different lines

technology have on the current pathway of care?	of treatment. Less attendances to chemosuite but may be there for slightly longer each time as administration time longer
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Chemotherapy and pembrolizumab given together as first line treatment
• How does healthcare resource use differ between the technology and current care?	As above
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Upfront drug cost is greater but as most patients recive 2 lines of treatment the overall drug costs should not be greater. The only excess drug costs maybe that proportion of patients never receiving second line treatment due to rapid disease progression and death following first line chemotherapy.
12. Do you expect the	The Keynote 189 study reached both primary outcomes of PFS and OS at 12 months

technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes statistically significant difference noted in PFS and 12month OS 12 OS 69% in chemo/pembro vs 49% in chemo/placebo p<0.001 PFS 8.8 vs 4.9 months p<0.001
• Do you expect the technology to increase health-related quality of life more than current care?	No significant increase toxicity was noted with the combination compared to chemotherapy alone. HRQ improvement due to reduction in cancer
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	All level of PDL1 expressors derived benefit over that of chemotherapy alone
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As above Reduction in attendances on chemosuite but time spent on visits maybe greater.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	CT scan assessments every 2-3 cycles would remain SOC
16. Do you consider that the	Toxicity no greater than that over chemotherapy alone

use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	As above
• Is the technology a 'step-change' in the management of the condition?	The use immunotherapy well established in lung cancer. This is simply combining chemotherapy and immunotherapy

• Does the use of the technology address any particular unmet need of the patient population?	None
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As above
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes SOC represents UK practice
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they	Yes PFS and OS

measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Statistically significant results Met preplanned primary outcome
21. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA181;	None

TA190; TA402; TA447]?	
22. How do data on real-world experience compare with the trial data?	Caution with less fit patients required but confidence will increase once established treatment regime
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
23b. Consider whether these issues are different from issues with current care and why.	
Key messages	

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

- Better PFS and OS statistically significant despite allowing crossover in Keynote 189 (NEJM 31st May 2018 378 2078-92)
- No significant increase in toxicity with combination up front
- Allows all to have opportunity of benefit form combination and not be beholden to second line treatment
- Reduction in chemotherapy attendances as combination rather than sequential treatment
-

Thank you for your time.

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

……

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer [ID1173]

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

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

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	**University Hospitals of Coventry and Warwickshire and the Royal College of Pathologists**
3. Job title or position	**Consultant Pathologist**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**UHCW NHS Trust is an NHS Teaching Hospital. The Royal College of Pathologist is a college of professional pathologists which is funded by the membership and a registered charity it's mission is maintaining the high standard of pathology in the UK.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to	Increased overall survival and improved quality of life through reducing disease burden and slowing progression.

stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction of disease volume as assessed on radiological imaging.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes metastatic NSCLC is an incurable disease and the biggest cause of cancer related deaths in men and women. There is an unmet need in therapies which provide effective response rates with good quality of life. Responses to current chemotherapy are variable and the treatment has significant co-morbidty. Many patients are ineligible for chemotherapy because of co-morbidity. There is a need for more effective treatment, curative therapy and a wider range of treatment options better suited to the patient population.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Metastatic NSCLC is treated with palliative chemotherapy the mainstay of which is has been platinum based chemotherapy. More recently permetrexed has been shown to provide superior outcomes in patients with adenocarcinoma. This has led to a change in pathology practice with immunocytochemistry now

NICE National Institute for Health and Care Excellence

Patient expert statement

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer [ID1173]

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

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

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

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

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? x☐ a patient organisation employee or volunteer?

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

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ **x** I am drawing on others' experiences. Please specify how this information was gathered: **I am a lung cancer nurse working and supporting patient with condition and treatments**
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patient and Carers are very concerned with patient side effects and how they can help alleviate also if the treatments are working. They also worry with regards to follow up scans and what news they will bring good or bad

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Patient and carers ask with regards to new treatments and understand current treatments are offered on best practice and NICE approved they also have options of clinical trials if meet criteria
10. Is there an unmet need for patients with this condition?	Yes a lot of treatment are very toxic and most patient present with stage 4 disease and symptomatic which rules them out of the new treatments
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Unable to comment
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Unable to comment
Patient population	
13. Are there any groups of patients who might benefit	

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • Patient require options with regards to treatment plans	

- Many present late where options are limited
-
-
-
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Thank you for your time.

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NHS England submission in October 2018 on the NICE appraisal of the combination of pembrolizumab plus chemotherapy as 1st line treatment of advanced/metastatic non squamous non small cell lung cancer (NSCLC)

1. NHS England observes that this appraisal is in effect one that pitches the combination of pembrolizumab in combination with standard cytotoxic chemotherapy (a platinum compound plus pemetrexed followed by maintenance pemetrexed) as 1st line therapy followed by docetaxel at relapse **versus** the routinely commissioned options of **either** 1st line pembrolizumab monotherapy in patients who are PD-L1 50-100% positive followed at relapse by the same standard cytotoxic chemotherapy **or** the same standard cytotoxic chemotherapy 1st line followed at relapse by pembrolizumab/atezolizumab if PD-L1 positive or atezolizumab if PD-L1 negative. As a consequence NHS England expects to see the longer term survival benefit of either 1st or 2nd line immunotherapy incorporated in the longer term survival projection of the comparator treatments.
2. A platinum compound plus pemetrexed followed by maintenance pemetrexed as appropriate is by far the most commonly used standard cytotoxic chemotherapy for non squamous non small cell lung cancer in fit patients.
3. NHS England notes that the median duration of follow-up in the Keynote 189 data submitted for this appraisal is only 10.5 months. This is still very short and NHS England is aware that the next data analysis is scheduled for [redacted]. In the current analysis (data cut on 1 November 2017), there are very few patients in the survival analysis who are at risk after 15 months.
4. NHS England observes that the keynote 189 study was performed only in patients of good performance status (ECOG PS 0 or 1).
5. NHS England notes the cost effectiveness estimates presented by the company and the ERG in relation to PD-L1 status but also observes that the hazard ratios for overall survival for the PD-L1 groups of <1%, 1-49% and 50-100% are 0.59, 0.55 and 0.42, respectively. The hazard ratios for progression free survival are 0.75, 0.55 and 0.36, respectively. The link between degree of benefit and PD-L1 status is once again seen.
6. Because the follow-up is so short, NHS England is concerned that the serious, longer term toxicities of pembrolizumab (colitis, pneumonitis, hepatitis etc) may not have been fully captured in the economic model. NHS England observes that 39 deaths due to an adverse event were observed in the pembrolizumab arm whereas the corresponding figure was 12 deaths in the placebo arm.
7. The short duration of follow-up of the keynote 189 study also makes the estimated mean duration of treatment with pembrolizumab plus chemotherapy uncertain.
8. NHS England observes that the company's projection of overall survival is pessimistic for the comparator arm. This figure of [redacted] 5 year survival would have been regarded as pessimistic even before the options of immunotherapies were routinely commissioned. The fact that only patients treated in this Keynote 189 study were of ECOG performance status 0 or 1 would also point to the likelihood of higher 5 year overall survival rates.
9. The company has assumed a life time treatment effect whereas the ERG has assumed a 5 year treatment effect. NICE appraisals have previously assumed lesser durations of treatment benefit given the brevity of follow-up. This trial shares this same shortness of follow-up as ones previously appraised by NICE.

10. NHS England observes the sensitivity of the ICER when different modelling methodologies are employed which still produce similar 5 and 10 year projections: the ERG's preferred use of the log-logistic function has 5 year and 10 year estimations of 8.6% and 3.4% versus the generalised gamma function which yields 8.5% and 2.4%, respectively. Yet the ICER for the gamma function is £20K/QALY higher.
11. The company and ERG have used the wrong chemotherapy delivery tariffs although NHS England does not regard this as making a substantial difference to the ICERs.
12. NHS England is confident about being able to ensure compliance with the 2 year stopping rule for treatment with pembrolizumab.
13. NHS England will still wish patients to be tested for PD-L1 status as a full discussion with patients as to treatment options cannot be done without knowing the PD-L1 status of the lung cancer.
14. NHS England notes with great concern the company's inaccurate Budget Impact Test (BIT). It states that 1035 new patients per year will commence 1st line pembrolizumab plus chemotherapy. NHS England knows already that 1800 patients/year commence pembrolizumab monotherapy in just the PD-L1 50-100% group. NHS England considers that many patients and clinicians will opt for the combination of chemotherapy plus pembrolizumab given the attrition that lung cancer causes from line of therapy to line of therapy. The figure of 1035 patients/year by the company is a significant underestimate as over 5000 patients commence 1st line chemotherapy at present in England. NHS England regards the greatly underestimated budget impact of 1st line pembrolizumab plus chemotherapy as triggering the need for an urgent discussion between MSD and NHS England.
15. NHS England notes that atezolizumab plus chemotherapy in a similar indication is coming to NICE for appraisal and the first appraisal meeting is in December 2018

[redacted]

[redacted]

October 2018

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School, South Cloisters, St Luke's Campus, Heavitree Road, Exeter EX1 2LU
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Date completed	11/09/2018
Source of funding	This report was commissioned by the NIHR Systematic Reviews Programme as project number 17/46/14. JM was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula (NIHR CLAHRC South West Peninsula).
Declared competing interests of the authors	Dr Nicole Dorey has received educational grants from Amgen, Boehringer Ingelheim, Lilley, Roche, and Teva. Dr Adam Dangoor has received honoraria from Roche and Amgen.
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NHS, the NIHR SER programme or the Department of Health and Social Care. Any errors are the responsibility of the authors.
This report should be referenced as follows	Griffin E, Farmer C, Packman D, Nikram E, Matthews J, Barnish M, Briscoe S, Dorey N, Dangoor A, Mujica Mota M. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2018.
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Please note that text highlighted in yellow and underlined is ‘[redacted]. Text highlighted in aqua and underlined is ‘[redacted]’. Text highlighted green and underlined is ‘[redacted]’.

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Abbreviations

AE	Adverse event
AIC	Akaike information criteria
ALK	Anaplastic lymphoma kinase
ALK+	Anaplastic lymphoma kinase positive
AUC	Area under curve
BOR	Best overall response
BIC	Bayesian information criterion
BIRC	Blinded independent review committee
BSC	Best supportive care
CADTH	Canadian agency for drugs and technologies in health
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CMs	Concomitant medication
CNS	Central nervous system
CR	Complete response
CRD	Centre for reviews and dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
DOR	Duration of response
DSU	Decision support unit
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EGP	Economic guidance panel
EMA	European Medicines Agency
EoL	End of Life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EOPE	Early onset pulmonary events
EQ-5D	EuroQol 5-dimensions
ERG	Evidence review group
ESS	Effective sample size
FE	Fixed effect

HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IDCR	Intracranial disease control rate
IGF-1R	Insulin-like growth factor 1 receptor
INV	Investigator
IQR	Inter-quartile range
IPD	Individual patient data
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
K-M	Kaplan-Meier
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MMA	Marketing authorisation application
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N	Number
NA	Not available
NCI	National Cancer Institute (US)
NHS	National health service
NICE	National Institute for Health and Care Excellence
NR	Nor reached *or* Not reported
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate/ Overall response rate
OS	Overall survival
PC	Pembrolizumab combination
PD	Progressive disease
PenTAG	Peninsula Technology Assessment Group
PF	Prognostic factor
PFS	Progression-free survival
PK	Pharmacokinetics
PM	Pemetrexed maintenance
PR	Partial response
PRISMA	Preferred reporting items for systematic review and meta-analysis
PRO	Patient reported outcomes
PS	Performance status
PSS	Personal social services

Q3W	Once every three weeks
QALYs	Quality adjusted life years
QD	Once daily
QoL	Quality of Life
RCT	Randomised controlled trial
RE	Random effect
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended phase 2 dose
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
SLR	Systematic literature review
SMC	Scottish medicines consortium
SmPC	Summary of product characteristics
SoC	Standard of Care
TEAE	Treatment emergent adverse event
TEM	Treatment effect modifier
ToT	Time on treatment
TRAE	Treatment related adverse event
TSD	Technical support document
TTD	Time to death
TTR	Time to response
UK	United Kingdom

1 Summary

1.1 Critique of the decision problem in the company submission

The clinical evidence submitted by the company, and used in the cost-effectiveness analysis, matched the patient population described in the scope, notwithstanding the specification of EGFR and ALK negativity.

Detail of the intervention described in the CS matched the expectation set out in the scope. NICE clarified that the use of pemetrexed maintenance following PC was appropriate. Pembrolizumab's proposed indication for the combination intervention matched that of the model but differed to the scope in its limitation to adults whose tumours have no EGFR or ALK positive mutations.

The comparators described in the CS matched the comparators described in the scope, except that pemetrexed maintenance was excluded from the pair-wise comparisons with platinum plus vinorelbine, gemcitabine, docetaxel, and paclitaxel; and also that with pembrolizumab monotherapy. The company did not present exploratory analysis of the impact of this approach.

The main comparator, pemetrexed plus platinum described as the current standard of care in the NHS in England and Wales. This was verified by expert advisors to the ERG.

Outcomes included in the CS did not match the outcomes described in the scope. The base case cost-effectiveness analysis additionally included the time-on-treatment outcome, and this was not included in the systematic search and review. However, the use of KEYNOTE-189 as a single source of evidence for this outcome in the main comparison and sub-group analysis was reasonable given about the evidence identified in the SLR. The scope included PFS but the company did not include this outcome in their base case cost-effectiveness analysis. However, advice received by the ERG supports the clinical justification of the alternative use of: the OS-based time-to-death method for utility estimation; and time on active treatment approach for cost estimation. Technical limitations are comparable across progression-based and time-to-death based approaches.

The company did not identify any equity or equality issues in their submission.

The company put the case forward for end-of-life classification.

1.2 Summary of clinical effectiveness evidence submitted by the company

Two randomised controlled trials (RCTs) evaluating the target intervention were included in the submission: KEYNOTE-189 and KEYNOTE-021G. These trials compared Pembrolizumab Combination therapy (Pembrolizumab + Platin + Pemetrexed) with Platinum and Pemetrexed in the target patient group. In the absence of further direct head-to-head trials that compare Pembrolizumab Combination therapy with other interventions specified in the NICE scope, fourteen RCTs were included in the submission that compared other interventions with Platinum and Pemetrexed therapy (n=10) or with each other (n=4). Indirect treatment comparison (ITC) analysis was then used to compare these interventions with Pembrolizumab Combination therapy. Finally, one RCT comparing Pembrolizumab monotherapy with platinum and pemetrexed in a sub-population of the target patient group (patients with PD-L1 TPS ≥50%) was included and used to inform an indirect comparison of Pembrolizumab monotherapy and Pembrolizumab Combination therapy (using subgroup data from KEYNOTE-189) in patients with PD-L1 ≥50%.

The evidence included in this submission was identified using a systematic literature review (SLR), which was informed by a search of three scholarly bibliographic databases, plus hand-searching of several major relevant scientific conferences. Study selection was conducted by two independent researchers, following pre-specified criteria for inclusion and exclusion. Quality assessment of the included studies was evaluated using the Cochrane Risk of Bias tool. KEYNOTE-189 was an international double-blind RCT, that was rated at low risk of bias across all domains. KEYNOTE-021G was a multicentre open-label RCT, which received a low risk of bias rating for all domains except patient and care provider blinding. KEYNOTE-24, a study of pembrolizumab monotherapy in strong expressers of PD-L1, was not presented with a quality assessment. One trial evaluating other interventions was double-blind, while all others were open-label or had unclear blinding. Aside from blinding, the majority of the evidence base evaluating treatments other than Pembrolizumab were evaluated as being of good or unclear quality.

All studies identified by the SLR were included in the ITC analysis. The analysis was used to compare interventions on two clinical outcomes: overall survival (OS) and progression-free survival (PFS). Notably, evidence for Pembrolizumab Combination therapy was evaluated separately for KEYNOTE-189 and KEYNOTE-021G. For OS, Pembrolizumab Combination therapy, as evaluated in KEYNOTE-189, emerged as statistically superior to all other interventions (meta-analysed range in HR 0.40 – 0.59). The efficacy of Pembrolizumab Combination therapy for OS as evaluated in KEYNOTE-021G was consistent with those findings but demonstrated a smaller effect (meta-analysed range in HR 0.49 – 0.72), which

was only statistically significant against two of the six interventions (platinum and gemcitabine, and platinum and paclitaxel). For PFS, Pembrolizumab Combination therapy, as evaluated in KEYNOTE-189, emerged as statistically superior to all other interventions (meta-analysed range in HR 0.28 – 0.52). However again, the effect was similar but reduced in KEYNOTE-021G (meta-analysed range in HR 0.29 – 0.54), and was only statistically different for the same two of other interventions. ITC analysis was not reported for other outcomes, and the submission did not report standard meta-analysis of any data. Data from KEYNOTE-189 and KEYNOTE-021G indicated that Pembrolizumab Combination therapy was associated with a higher objective response rate (ORR) than platinum and pemetrexed. This effect was driven by a difference in partial response, as very few patients (similar in both arms) achieved a complete response to treatment. Evidence from KEYNOTE-189 further demonstrated a clinically meaningful difference in health-related quality of life (HRQoL) for patients receiving Pembrolizumab Combination therapy compared to platinum and pemetrexed (not evaluated in KEYNOTE-021G). A comparison of adverse events in KEYNOTE-189 and KEYNOTE-021G suggested that the rate of adverse events (AEs) may be modestly higher for patients receiving Pembrolizumab Combination therapy compared to platinum and pemetrexed therapy, including drug-related AEs and discontinuations due to AE. There was no conclusive evidence of a difference in duration of response (DoR; KEYNOTE-189 and KEYNOTE-021G) or time to response (TTR; KEYNOTE-189) between Pembrolizumab Combination therapy and platinum and pemetrexed therapy. The submission did not report evidence comparing Pembrolizumab Combination therapy and other interventions for DoR, TTR, AEs, HRQoL or patient-reported outcomes (PROs).

In a sub-population of patients with PD-L1 TPS ≥50%, the analysis demonstrated that Pembrolizumab Combination therapy was associated with a benefit for OS and PFS compared to Pembrolizumab monotherapy, but neither of these effects was statistically significant due to wide 95% credible intervals (CrIs) around the effects.

Overall, the clinical effectiveness evidence presented by the company in the submission suggests that Pembrolizumab Combination therapy may offer significant clinical advantages for OS and PFS compared to other available interventions for this patient group. Compared to platinum and pemetrexed therapy, the rate of partial treatment response may be greater, as may HRQoL, although there may be no difference in the DoR or TTR. There is insufficient evidence presented in the submission to determine whether Pembrolizumab Combination therapy is superior to other interventions for ORR, DoR, or HRQoL/PROs. In terms of safety, the evidence indicates that patients treated with Pembrolizumab Combination therapy are at slightly increased risk of adverse events compared to platinum and pemetrexed, but the rate of AEs compared to other interventions could not be evaluated based on the information in

or supplied with this submission. In a sub-population of patients at higher risk of progression (PD-L1 TPS ≥50%), Pembrolizumab Combination therapy may be more effective for OS and PFS than Pembrolizumab monotherapy, but further evidence is needed.

1.3 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The ERG considered the SLR to be broadly appropriate, in that the literature search, methods of study selection, and pre-specified inclusion/exclusion criteria were likely to have captured the most relevant evidence base for this submission. However, the company placed additional limits on the evidence presented in the submission beyond those specified in the pre-specified criteria and the scope. These limits were not clearly stated, but were evident by the lack of evidence that was presented in the company submission. While evidence for all outcomes specified in the NICE scope are presented for the comparison between Pembrolizumab Combination therapy and platinum and pemetrexed therapy, evidence for only two outcomes (OS and PFS) is presented for other comparisons. The data presented by the company is appropriate for the most relevant comparison in this submission; i.e. the comparison between the technology of interest and platinum and pemetrexed therapy, which is standard of care in the UK. Furthermore, OS and PFS are arguably the critical outcomes for evaluating the clinical efficacy of interventions in this patient group. However, the ERG did consider that the exclusion of outcome data for other comparators used in the UK was a significant omission from that specified by the NICE scope, and restricted the ERG's evaluation of the clinical effectiveness of the technology of interest.

The SLR identified two RCTs which evaluated the technology of interest. Both trials evaluated the clinical efficacy of Pembrolizumab Combination therapy as compared to platinum and pemetrexed therapy. However, the company argue that the trials are heterogeneous, and therefore do not pool the data from these studies in the submission. While the ERG considered these two RCTs to be a limited evidence base to support the technology, both trials were assessed as being high quality. The pivotal trial for the submission, KEYNOTE-189, is a large, high quality, double-blind RCT. KEYNOTE-021G is a smaller trial and open label, trial follow-up was considerably longer than KEYNOTE-189, and the ERG considered that evidence for objective outcomes (OS, PFS, ORR, DoR, safety) was also high quality. Both trials were considered to be broadly applicable to the UK. The majority of other studies included in the SLR are also open label RCTs, and are of mixed quality.

Due to the lack of direct head-to-head trials available for the technology, the bulk of the evidence in this submission is based on ITC analyses. The ERG considered that the ITC analyses conducted were broadly appropriate, although heterogeneity was a concern for the main ITC comparing Pembrolizumab Combination therapy with other interventions. It was unclear from the submission whether a formal feasibility assessment was rigorously conducted, and significant variability in study design and population were noted between trials. Insufficient information was reported by the company for the ERG to evaluate heterogeneity across intervention characteristics and methods of outcome assessment, which may be additional concerns. The ERG agree that the sample included in the ITC prevented the use of statistical methods to control for heterogeneity (e.g. meta-regression), and therefore the ERG considered that the findings of the ITC may be influenced by heterogeneity between trials, and should be interpreted with caution. ITC analyses providing a comparison between Pembrolizumab combination therapy and Pembrolizumab monotherapy in a sub-population of patients with PD-L1 ≥50% were conducted using individual patient data and were of high quality.

Overall, the ERG agreed that the evidence presented in the submission from the KEYNOTE-189 and KEYNOTE-021G trials demonstrates that Pembrolizumab Combination therapy is associated with a clear benefit for OS, PFS, ORR, and HRQoL as compared to platinum and pemetrexed therapy. Moreover, these benefits were associated with no evidence of significant safety concerns. Consequently, the ERG agreed that the evidence supports the use of Pembrolizumab Combination therapy over platinum and pemetrexed therapy for UK clinical practice. However, the ERG noted that there is some uncertainty about the size of the treatment effect for Pembrolizumab Combination therapy that may be achieved in this patient population in UK clinical practice. While the ERG agreed that the effect size reported in the KEYNOTE-189 trial represents the highest quality evidence, the ERG noted that the effect may be smaller when accounting for older patients and those with ECOG 2 status. Variation in the effect between KEYNOTE-189 and KEYNOTE-021G, also suggests that the effect may vary between patient populations.

The ERG considered that the evidence presented also suggests that Pembrolizumab Combination therapy may be beneficial for OS and PFS compared to other interventions, including platinum and gemcitabine and platinum and vinorelbine, which are commonly used in the UK. This is based on the findings of the ITC analyses for OS and PFS, where Pembrolizumab Combination therapy as evaluated in KEYNOTE-189 demonstrated clear benefit against all treatments, and (while not all findings were statistically significant) results for KEYNOTE-021G were consistent with this. However, the ERG considered that this evidence is of lower quality compared to evidence comparing Pembrolizumab and

pemetrexed, due to heterogeneity in the ITC analyses, and the lack of evidence presented for other outcomes (including safety).

1.4 Summary of cost-effectiveness evidence submitted by the company, with ERG critique

1.4.1 Search for and review of evidence

The company included no cost-effectiveness studies in their search for evidence. It was not necessary to limit the inclusion of cost-effectiveness studies to the UK setting since valuable information relating to health benefits, model structure, and model assumptions, can be sought from other settings. They included seven studies and one update of potential use to the utility analysis, and 11 UK NICE technology appraisals of possible relevance. The objective of the utility search specified only interventions used at first treatment line, but the HRQoL of a second-line population could inform utility scores post-progression in this model population. Indeed TA520, the appraisal of atezolizumab in adults with locally advanced EGFR or ALK-positive NSCLC who have already had chemotherapy, was included. Whilst TA428, an appraisal of pembrolizumab at second-line in the relevant population, was omitted but later used as supportive evidence. Four studies of potential use to the cost analysis were included, alongside evidence in appraisals mentioned before. Two of the four did not meet the pre-specified inclusion criteria, including a UK HTA which was used as a secondary source for modelling. Generally, included studies were relevant to the decision problem, but multiple sources of evidence used to inform quantities of health resource use were too old to accurately resemble current NHS practice.

1.4.2 The decision problem and reference case

The clinical evidence submitted by the company, and used in the cost-effectiveness analysis, matched the patient population described in the scope, notwithstanding the specification of EGFR and ALK negativity. The key trial informing the estimates of relative effectiveness of the main comparison, PC versus SoC, was KEYNOTE-189, a phase III RCT. The company provided an additional analysis of cost-effectiveness according to PD-L1 expression; and of a comparison with pembrolizumab monotherapy in strong expressers of PD-L1 only. The intervention described in the CS and modelled in the cost-effectiveness analysis matched the specification of the scope. NICE clarified that the use of pemetrexed maintenance following PC was appropriate. The comparators described in the CS aligned to the scope, except in an area of ambiguity, where pemetrexed maintenance was excluded from the pair-wise comparisons with platinum plus vinorelbine, gemcitabine, docetaxel, and paclitaxel; the same too with the pembrolizumab monotherapy comparison. The first listed

comparator, pemetrexed plus platinum, was appropriately described as the current standard of care (SoC) in the NHS in England and Wales. Therefore the pairwise comparison of PC and SoC is the main focus of the evaluation. Outcomes included in the CS did not match the outcomes described in the scope, since the model included and heavily relied on the time-on-treatment outcome, and this was not included in the systematic search and review. KEYNOTE-189 was again the single source of evidence informing this outcome. This was reasonable for the main comparison and sub-group analysis given the evidence identified in the SLR (Evidence for pembrolizumab combination is KEYNOTE-189 and KEYNOTE-021G only). The scope included the PFS outcome, the primary outcome of KEYNOTE-189, but the company did utilise PFS in their base case cost-effectiveness analysis. However, advice received by the ERG supported the company's implicit reasoning for its exclusion: that the OS-based time-to-death method for utility estimation, and time on active treatment approach for cost estimation, were best suited to the modelling of the population. The company did not identify any equity or equality issues in their submission; it did make the case for the appraisal to be given an end-of-life classification.

1.4.3 The model structure

The structure departs from the standard three health state partition survival model: it uses four states to estimate utility, based on time-to-death; costs are aligned to treatment intent; progression status does not play any role in the base case. This is not a reflection of previous models in NSCLC except the MSD model presented in NICE TA531 for pembrolizumab monotherapy for untreated PD-L1 positive metastatic NSCLC. There is some clinical merit in the structure, and in the view of the ERG and its clinical advisors it represents a reasonable simulation, with the drawback of the loss of the PFS link between costs and benefits. Pembrolizumab in combination is modelled to a stopping-rule of two years which does not reflect the license specification. Modelled costs are limited to the inclusion of second-line therapy costs and benefits since those of subsequent lines of anti-cancer therapy are assumed zero. This is a simplification since some patients in KEYNOTE-189 received third, fourth and fifth lines of anti-cancer therapy.

1.4.4 Treatment effect

The estimated effectiveness of the pembrolizumab combination treatment strategy and of the main comparator were based on the data from the relevant treatment arms of the KEYNOTE-189 clinical trial, using the November 2017 data cut. OS and PFS have been modelled by fitting parametric distributions to parts of the KM data, although PFS is not taken into consideration in the company's base case. The same source has been used to estimate treatment safety. The type and frequency of Grade 3+ AEs are used to determine a

one-off cost associated with AEs for each treatment arm, are based on observations from KEYNOTE-189, as are dis-utilities associated with AEs for each treatment arm. Parametric curves are fitted the full KM data of ToT distributions to smooth and extrapolate estimates. Guidance within NICE DSU TSD 14 was followed when fitting the distributions for OS and PFS; the assumption of proportional hazards was falsified so separate distributions for the treatment arms were fitted, which requires fewer assumptions. HRQoL estimates were based on time to death (TTD), a function of OS, and ToT is not used for the disutility of adverse events, which meant that the distributions for OS alone determine the modelled treatment effect. Here the AIC and BIC statistics, which assess goodness-of-fit and parsimony, were calculated and assessment for piecewise cut-points elicited at 28, 38 and 52 weeks. Exponential curves were then chosen for both treatment arms, despite providing a poorer statistical fit for the SoC strategy (the only one of the two reaching a median survival) compared to some of other the distributions considered. KM data was been used directly until a single cut-off point at 28 weeks, and then a single parametric curve was appended, fitted to the data beyond the cut-off point. This is despite the advice in TSD 14 that, for piecewise constant models, exponential distributions with different rate parameters should be fitted to each of time periods identified as having different (constant) hazard rates. Furthermore, with this cut-off, the exponential distribution provides the worst statistical fit for the SoC strategy of the distributions considered.

ToT has been modelled using separately fitted parametric distributions for both treatment arms. While the CS states that the distribution for the pembrolizumab combination arm was fitted to the first two years of the ToT KM data, the portion used for the SoC arm has not been specified.

1.4.5 HRQoL

The utility estimates were derived from the HRQoL analyses carried out in KEYNOTE-189, whereby patients completed the EQ-5D. Pooled estimates were used in the company's base case, so there is no difference in the utility inputs between the two treatment arms aside from those arising from serious adverse effects (applied as a one-off in the first model cycle). Utility values were calculated around a time-to-death (TTD) approach. The four alive health states were: greater than 360 days ([redacted]), between 180 and 360 days ([redacted]), between 30 and 180 days ([redacted]), or less than 30 days ([redacted]). An annual age decrement was applied, increasing to age 75 and remaining constant thereafter. The time-to-death approach used in the company base case has NSCLC precedent in MSD's recent submission for pembrolizumab monotherapy (also an untreated population). The approach is not historically standard but

clinical advice elicited by the ERG supports an approach which correlates HRQoL closer to OS/nearing death than the occurrence of first progression.

The structure of the cost analysis followed the use of active therapies, which was limited to first- and second-line anti-cancer treatment. Thereafter resources were modelled to resemble consumption aligned to non-curative intent, signified by a reduction in monitoring and an increase in community-based care (disease management costs increased after active therapy). Active treatments included the immunotherapies and systemic cytotoxic chemotherapy. Second-line treatments were attributed a fixed course. Notably, pembrolizumab was heavily taken-up at second-line in the SoC strategy, helping to equalise costs with the strategy of pembrolizumab in combination at first-line (56.5% of patients in the SoC arm receive second line treatment as per KEYNOTE-189, [redacted] of which receive pembrolizumab monotherapy). Dose intensity adjustment was small and accounted only for interruptions not dose reductions. For this previously untreated population, subsequent lines of active therapy are available after first progression and these would require similar supportive resources as first-line options; so a costing approach based on time on active anti-cancer treatment, rather than progression, is reasonable but the common link to PFS between benefits and costs is lost.

1.4.6 Resources and their cost

Pembrolizumab was costed according to the licensed dosing at first and second-line: a 200mg fixed dose administered by IV infusion every three weeks. The unit cost of 200mg was £5,260. A tentative [redacted] price ([redacted] was also tested by the ERG. All other drug acquisition unit costs were taken from the preferred sources appropriately. Similarly, the posology of non-fixed dose therapies was sourced in the first instance from KEYNOTE-189, then the drug SmPC. In a conservative assumption, vial sharing was implemented, meaning all comparator drugs carboplatin, cisplatin, gemcitabine, vinorelbine, docetaxel, and paclitaxel cost less, which impacts more profoundly on the SoC strategy. The base case carboplatin-cisplatin mix was [redacted], near opposite to UK practice, but ICERs were not sensitive to inaccuracy here. The drug acquisition cost per administration was [redacted] for pembrolizumab combination (prior to the maintenance period), and £1,420 for SoC. According to the license, patients receiving pembrolizumab are to be treated until disease, or discontinuation due to adverse events, inter-current illness, protocol compliance, or investigator or patient preference. However, in the model and in the key trial KEYNOTE-189, a stopping two-year rule was implemented. In the PC arm of the trial 14% of patients remained on treatment after this point (latest data cut: approximately 85 weeks or 1.6 years). In the model 11.8% of patients in the PC strategy remained on treatment at the 85 weeks,

but neither costs nor benefits were included for this subset of patients. For the period before, a parametric distribution was fitted to time-on-treatment KM curves using AIC and BIC goodness-of-fit statistics and visual inspection criteria; resulting in exponential and Weibull selections for PC and SoC strategies respectively. The modelled four cycles Q3W (12 weeks) of platinum-based therapy matched the protocol of KEYNOTE-189 and clinical practice in England (average number of cycles received in KEYNOTE-189 was 3.5 and 3.6 in SoC and PC strategies respectively. In the model 3.6% and 4.4%, respectively, of expected administrations were not received due to treatment interruption). The modelling of drug administration is broadly satisfactory: unit costs for administration were appropriately sourced based on setting and complexity; and summed to reflect multiple drug regimens (in any case, ICERs are insensitive to this aspect of costing). Pemetrexed maintenance, featuring in both PC (87.8%) and SoC (96.4%) strategies, was started from week 13. Only in the PC strategy did pemetrexed treatment discontinuation inform ToT, meaning that maintenance costs for a subset of patients in this strategy (those who discontinue pembrolizumab for a reason other than progression but continue maintenance therapy) are not included. This could lead to a small underestimation of the ICERs. Interruption of maintenance was 3.6% for SoC and 12.2% for PC, based on KEYNOTE-189. As mentioned, the cost of disease management varied according to active treatment status; a reasonable demarcation of resource change. But limitations in cost analysis arose from secondary sources of evidence used to populate utilisation rate estimates, which in some cases drew on observations from 12 or more years ago. However, changing all rates by +/-10% does not significantly impact the ICERs. A one-off cost was applied to all patients at the time of death for all strategies, which represented a reasoned quantity. In respect to second-line treatment, the uptake, the distribution of type, and unit cost determined a one-off cost. The company included adjustments to published figures of uptake and distribution which could not be verified, and ICERs are sensitive to these inputs. Type, patient frequency, and unit cost of serious adverse event determined a simplified one-off cost which did not capture events when they occurred in a patient more than once. Otherwise the method was reasonable since safety profiles were not much different between strategies, and ICERs were not sensitive to variation in those profiles.

1.4.7 Company results

The ICER for PC versus SoC was £46,568 per QALY gained (deterministic analysis); and £46,674 per QALY gained (probabilistic analysis) Probabilistic analysis gave the probability of PC being the most cost-effective strategy as 58%. The mean incremental LYs gained per person were 1.16, and discounted incremental QALYs gained were 0.89 over the model lifetime. The PC incurred £41,344 more resource than the SoC. The ICERs for PC versus

the platinum and chemotherapy doublet options were all more than £50,000 per QALY gained. The ICER for PC versus pembrolizumab monotherapy, for patients strongly expressing PD-L1 (>=50% TPS) was £38,699 per QALY gained. The mean incremental LYs gained per person were 1.03, and incremental discounted QALYs gained were 0.78 over the model lifetime. The PC incurred £30,161 more resource than the SoC. In the sub-group analysis, the ICERs were £42,703, £38,632, and £51,545 for TPS>=50%, 1%>=TPS<=49%, and TPS<=1% groups respectively. Deterministic sensitivity analysis revealed unsurprising sensitivity in the ICERs towards OS estimation, health state utility estimation (in particular >360 days state), and the consumption of high cost drug (in particular pembrolizumab). Company scenario tended to centre on inputs to which the ICER was insensitive, or about which uncertainty was not so high.

1.4.8 ERG results

The ERG base case incorporated preference for log-logistic distributions for OC and SoC strategies from week 0; the inclusion of background mortality to account for the immaturity of OS data from the trial, which was too short to capture increasing risk of death from other causes as patients age through the time horizon; a reduction in the relative mortality risks of PC after five years; and the removal of PD-L1 test cost since this is now routine for all new diagnoses. The ICER for PC versus SoC was £37,622 per QALY gained (deterministic analysis); and £38,075 per QALY gained (probabilistic analysis). Probabilistic analysis gave the probability of PC being the most cost-effective strategy as 69%. The mean incremental LYs gained per person were 1.47, and discounted incremental QALYs gained were 1.13 over the model lifetime. The PC incurred £42,454 more resource than the SoC. The ICERs for PC versus the platinum and chemotherapy doublet options ranged from £40,000 to £58,000 per QALY gained. The ICER for PC versus pembrolizumab monotherapy, for patients strongly expressing PD-L1 (>=50% TPS) was £40,225 per QALY gained. The mean incremental LYs gained per person were 0.98, and incremental QALYs gained were 0.74 over the model lifetime. The PC incurred £29,788 more resource than the SoC. In the sub-group analysis, the ICERs were £33,873, £35,920, and £40,192 for TPS>=50%, 1%>=TPS<=49%, and TPS<=1% groups respectively.

1.4.9 Face validity

In respect to the utility value inputs, the value for the ≥360 days state compares a little low to the two literature sources for NSCLC, but a lower estimate here is conservative. The range in values for the <30 days state is wide, but the ICERs are not sensitive to this input. Company estimates of 5 and 10-year OS (2.4% and 0.1%) for SoC are low compared to ERG estimates in TA531 (9.6% and 1.5%), the appraisal of pembrolizumab in untreated

advanced NSCLC; and low compared to our ERG too (8.6% and 3.4%). Similarly, LYs and discounted QALYs gained for SoC are lower in the company analysis (1.34 and 0.92) than the ERG adaptation (1.74 and 1.22). If ERG OS estimates are to be preferred, then these estimates of benefit follow.

1.4.10 End-of-life

PC in this comparison and setting probably fulfils the criteria for end-of-life status (ERG estimate 22.73 months mean expected survival with SoC). Whilst estimates of the extension to life are not robust the ERG estimates extension of 20.96 months.

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

- The SLR conducted by the company is generally of good quality, using methodology that is likely to have captured the evidence base for this clinical area
- The company provides clinical effectiveness evidence for the technology of interest from 2 RCTs, which compare the technology against an intervention commonly used in the UK to treat this patient group.
- Evidence from the 2 RCTs evaluating the technology of interest is of high quality for key clinical outcomes (OS, PFS, ORR, safety).
- The main ITC includes all relevant interventions for this patient group, and is broadly appropriate with relevant NICE DSU TSD recommendations.
- An additional ITC comparing the technology of interest against current treatment for a sub-population of patients is presented, and conducted using IPD and patient matching methods, which were judged to be of high quality.
- The direction of the effect for the technology of interest is consistent between the 2 RCTs presented.

1.5.2 Weaknesses and areas of uncertainty

- Direct head-to-head trials were not available for the pembrolizumab combination in comparison with most other interventions available for this treatment group, including platinum and gemcitabine and platinum and vinorelbine, which are commonly used in the UK.

- The main ITC analysis to compare the technology of interest with interventions for which there was no evidence from direct head-to-head trials was limited by significant heterogeneity between studies.
- Evidence was not presented for a number of outcomes required by the NICE scope for interventions not evaluated in direct head-to-head trials
- The submission was missing information about the study design, intervention characteristics, and methods of outcome assessment for the majority of trials identified by the SLR.
- Quality assessment of studies identified by the SLR was conducted with an appropriate, validated tool, however was not assessed by outcome, as is gold standard practice. No quality assessment was reported for one key trial (KEYNOTE-024).
- The cost-effectiveness analysis model structure had no common link between health benefits and costs; they were independently modelled.
- The cost-effectiveness analysis did not explicitly model the relative clinical effect of second-line treatment; the method of not adjusting for cross-over in KEYNOTE-189 introduces uncertainty of unknown size.
- The cost-effectiveness analysis included in the costing only two lines of anti-cancer therapy but the benefit of six lines for some patients.
- ICERs were sensitive to consumption of pembrolizumab but the level of uptake at second-line for SoC was not verifiable.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.6.1 Clinical analyses

Following review of the clinical evidence, the ERG conducted the following additional analyses:

1. Standard meta-analysis of primary outcome data (OS, PFS, ORR) pooling evidence from KEYNOTE-189 and KEYNOTE-021G. The ERG considered that evidence from these studies should have been pooled in the submission, despite some areas of heterogeneity between the studies noted by the company. Evidence from KEYNOTE-189 carried the greatest weight in all analyses, and the relative effect estimates in the meta-analyses were consistent with those reported by KEYNOTE-189.

2. The ERG calculated the relative effect of the pembrolizumab combination for the proportion of patients with extended response duration, as reported by KEYNOTE-189 and KEYNOTE-021G. While this data was reported by the company, no statistical analysis was provided to determine if there was a statistically significant difference between treatment arms. The findings indicated that there was no statistical difference in the proportion of patients with extended response duration between arms, at any time-point.

1.6.2 Economic analyses

Following review of the economic modelling, the ERG conducted an adjustment to the economic model using a set of preferred alternative inputs and approaches to the company's base case selections, as follows:

1. An adjustment for background mortality has been included in the ERG's preferred base case due to the relatively short length of the trial compared to the model time horizon and since background mortality is likely to impact the two strategies differently, due to the differences between them in estimated long-term survival.
2. The company base case was adapted to exclude PD-L1 test costs for all patients in all strategies, since testing is routine for all new NSCLC diagnoses in the NHS in England and Wales.
3. The selection of the log-logistic statistical distribution for the parametric smoothing and extrapolation of OS, for SoC and PC strategies. In preference to the selection use of a piecewise exponential fit to the individual patient level Kaplan-Meier plots of KEYNOTE-189. A preference based on best practice guidance, consistency of best statistical fit across strategies, and clinical estimates of long-term survival for SoC elicited by the company and the ERG.
4. The ERG considers this continued duration of effect to be unlikely and have instead opted for the scenario presented by the company in which the mortality rate of the PC strategy is increased to match that of the SoC strategy from year five. This has the effect of increasing the rate of convergence of the survival curves from the point.

In addition to four minor aspects of coding correction to the company model, the impact of these preferences was a reduction in the ICER of the main comparison (Table 1: PV versus SoC). Cost-effectiveness is also improved in the comparison of PC versus platinum plus chemotherapy; versus monotherapy; and versus pemetrexed plus platinum in the PD-L1 sub-groups.

Table 1 Comparison of ERG and Company estimates of cost-effectiveness

PC versus SoC (whole population)	Cost per QALY gained (ICER)
Company base case	£46,568
After ERG corrections to company coding	£46,103
ERG base case (after corrections and preferences)	£37,622

Abbreviations: ICER = Incremental cost effectiveness ratio; QALY = Quality-adjusted life year.

The ERG's cost-effectiveness analysis produces a lower ICER, and this is driven by the ERG's selection of the log-logistic distribution for the estimation of overall survival (see section 6). A set of alternative scenarios explore uncertainty in ICER around: the estimation of long-term survival; the estimation of utility (in particular the ≥360 days from death health state); and the estimation of consumption of pembrolizumab (first or subsequent lines). See section 6.4 for the full scenario set and results.

2 Background

2.1 Critique of company's description of underlying health problem

The CS presents the health condition and treatment pathway on pages 19-25.

Lung cancer can be divided into two main histological categories: non-small-cell lung cancer (NSCLC) and small cell lung cancer. NSCLC has been estimated to account for 80-90% of all lung cancer cases in the UK,(1) and can be subdivided into two major histological subtypes: squamous cell carcinoma (25-30%) and non-squamous cell carcinoma, including adenocarcinoma (30-40%), large-cell carcinoma (10-15%) and other cell types (5%).(2, 3) Lung cancer is the second most common cancer for both males and females in England with 36,761 cases registered in 2016, of which 88.5% were NSCLC and 53% were diagnosed with Stage IV disease,(4, 5) in which the cancer has spread to distant lymph nodes or to other organs such as the liver, bone or brain.(6) The age-standardised incidence rate for lung cancer has decreased in recent years in males (127.9 per 100,000 in 1995; 89.8 per 100,000 in 2016) but increased in females (51.4 per 100,000 in 1995; 65.5 per 100,000 in 2016),(7) which is considered to be largely attributable to changes in gender-specific smoking prevalence.

The population in this appraisal represents a large group of people at first-line who are diagnosed with NSCLC. The company estimates that there are 28,974 expected cases of non-squamous NSCLC in England in 2019, of which 5,620 are expected to be eligible for treatment with pembrolizumab in combination with chemotherapy under this appraisal. These are adults with non-squamous NSCLC who test negative for anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation, for which specific treatment pathways are available.

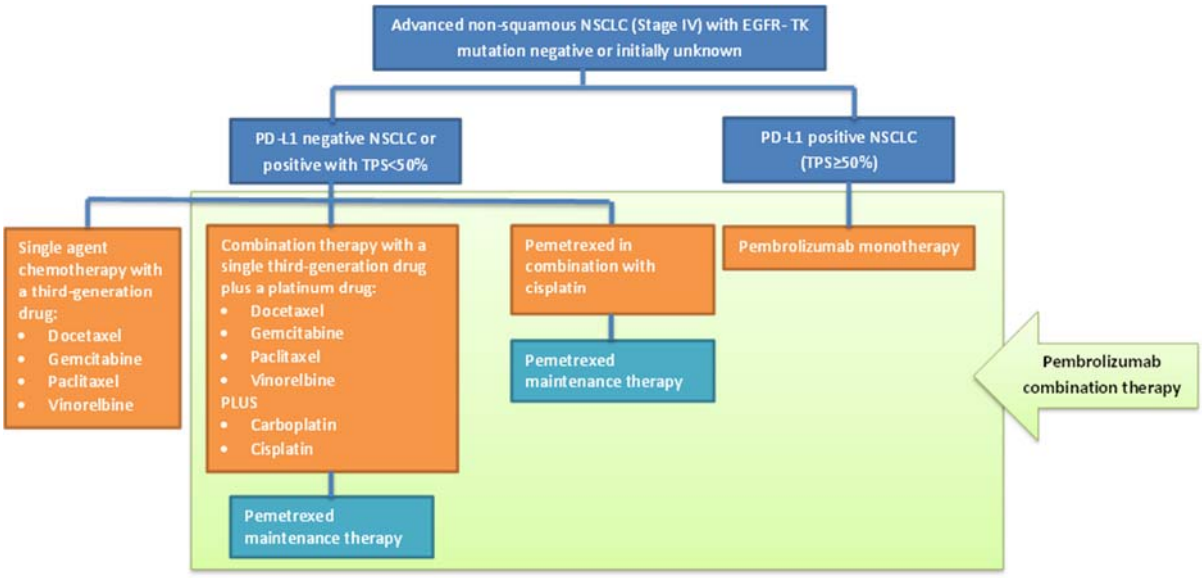
ERG comment:

- The ERG with the help of advice from clinical experts in lung oncology considered the company's description of the underlying health problem to be accurate and relevant to the decision problem under consideration.

2.2 Critique of company's overview of current service provision

The company sets out the current treatment pathway as follows:

Figure 1 First-line treatment diagram for advanced NSCLC including pembrolizumab



Source: MSD CS Document B Figure 2 page 24

The ERG and its clinical advisors consider the treatment pathway above to be reasonably representative of standard NHS treatment for advanced non-squamous advanced ALK and EGFR-negative NSCLC currently in England and Wales. The clinical advisers to the ERG consider that routine use of docetaxel and paclitaxel is limited in current NHS practice in England and Wales. The clinical advisers to the ERG note that cisplatin is typically preferred to carboplatin, if both are indicated.

Changes to service provision

If approved by NICE for routine first-line use in England and Wales, pembrolizumab combination therapy would offer an alternative to a) pembrolizumab monotherapy in PD-L1 positive patients with TPS ≥50%, and either b) pemetrexed in combination with platin chemotherapy or c) combination therapy with a third-generation drug plus platinum chemotherapy in PD-L1 negative patients or PD-L1 positive patients with TPS <50%.

ERG comment:

- The CS accurately describes the treatment landscape around the proposed position of pembrolizumab combination therapy; and fairly describes the extent of any changes that may be required to service provision (none substantial).

3 Critique of company's definition of decision problem

3.1 Population

In respect to the population to be evaluated, the company go further than the NICE final scope by reducing the population to those lacking the EGFR and/or ALK mutation. This is in-line with the draft Summary of Product Characteristics (SmPC) for pembrolizumab in combination with pemetrexed and platinum chemotherapy (provided in CS appendix C). This specification also aligns with the population of the key supporting trial KEYNOTE-189.(8), and is viewed as appropriate by the ERG.

KEYNOTE-189 was the single source of evidence informing clinical effectiveness for the main comparison (PC versus SoC). The company did not include in their effect size estimate the relevant sub-population of the open-label phase II trial KEYNOTE-021G by means of a standard meta-analysis, citing between-trial heterogeneity, but no feasibility analysis was presented (when the ERG ran this meta-analysis the impact on the ITC hazard ratio was found to be small. See section 4.5). Independent expert clinical advice confirmed the company's view that patients recruited to KEYNOTE-189 reasonably represented those treated by the NHS in England and Wales.

Multiple additional clinical trials informed an ITC network meta-analysis to estimate the clinical effect size (HRs) of the alternative whole population comparator (platinum with chemotherapies gemcitabine, vinorelbine, docetaxel, paclitaxel). The ERG found heterogeneity in the population baseline characteristics amongst these trials, which was not quantified or appropriately explored by the company (see section 4.4.1).

For the comparison with pembrolizumab monotherapy (PD-L1 ≥50% TPS), clinical effectiveness evidence was sourced also from KEYNOTE-024, with data gathered only from trial patients strongly expressing PD-L1.

ERG comment:

- The clinical evidence submitted by the company, and used in the cost-effectiveness analysis, matched the patient population described in the scope, notwithstanding the specification of EGFR and ALK negativity.

3.2 Intervention

The intervention described in the scope ('Pembrolizumab in combination with pemetrexed and platinum chemotherapy') was implemented in the model with the option for patients to follow-on with pemetrexed maintenance therapy. This important aspect of the modelling was not drawn out in the company's description of the decision problem (MSD CS Section B.1.1,

Table 1); but neither is this detail included in the scope. However, the ERG confirmed with NICE that this inclusion was reasonable and allowable; and it also aligned with the key source of evidence.

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment. Pembrolizumab was first granted marketing authorisation in May 2015 by the European Medicines Agency. Pembrolizumab should be administered as an intravenous infusion over 30 minutes every 3 weeks. The recommended dose is 200 mg for NSCLC that has not been previously treated with chemotherapy, when administered as monotherapy or in combination with pemetrexed and platinum chemotherapy (MSD CS Section B.1.2, Table2, page 16).

The indication for pembrolizumab in this evaluation is in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations (MSD CS B1.2). The brand name for pembrolizumab is KEYTRUDA®.

ERG comment:

- The intervention described in the CS matched the intervention described in the final scope, after clarification from NICE regarding the use of pemetrexed maintenance following PC.
- The proposed indication for the intervention matched that of the model, but differed to the scope in its limitation to adults whose tumours have no EGFR or ALK positive mutations.

3.3 Comparators

In their definition of the decision problem the company describe the same list of comparator treatment strategies as defined in the scope; in which two types or regimens were included for whole population evaluation.

1. 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.

The company consider this regimen as the standard of care for first-line treatment in this population. It is referred to by the company and the ERG as the standard of care (SoC) treatment strategy. Advice elicited from clinical advisors to the ERG confirmed that this comparator is representative of the current care standard in the NHS in England and Wales.

2. Chemotherapy (vinorelbine, gemcitabine, docetaxel, or paclitaxel) in combination with a platinum drug (carboplatin or cisplatin) With or without pemetrexed maintenance treatment

Note that pemetrexed maintenance is not licensed following carboplatin. Pemetrexed maintenance was excluded from the pair-wise comparisons with platinum plus vinorelbine, gemcitabine, docetaxel, and paclitaxel; a reason was not given by the company but was presumably because most trials included in the NMA pre-dated it's availability for this indication.

In an evaluation of the sub-population of strong expressers of PD-L1 only (TPS≥50%), pembrolizumab combination was compared to:

3. Pembrolizumab monotherapy.

Pemetrexed maintenance was not included for either strategy of this comparison.

ERG comment:

- The comparators described in the CS matched the comparators described in the final scope, except that pemetrexed maintenance was excluded from the pair-wise comparisons with platinum plus vinorelbine, gemcitabine, docetaxel, and paclitaxel; and also that with pembrolizumab monotherapy.
- The SoC comparator is representative of the current care standard in the NHS in England and Wales.
- The company have not presented exploratory analysis of the impact of including pemetrexed maintenance for the comparison of PC with platinum plus vinorelbine/gemcitabine/docetaxel/paclitaxel.

3.4 Outcomes

The company detail five health outcomes considered in their evaluation. This is in contrast to the six listed in the NICE final scope.

- overall survival (OS)
- progression-free survival (PFS)
- response rates

- adverse effects of treatment (AEs)
- health-related quality of life (HRQoL)

The company erroneously omitted DoR from their definition of the decision problem (CS; Table 1). In the company's review of clinical evidence, DoR was reported only for trials evaluating pembrolizumab combination therapy (see section 4.1.2), and DoR was not considered in the economic evaluation. Evidence for DoR could help in the consideration of the extent of loss of effect following discontinuation. The company consider 'waning' of effect in a scenario analysis.

In their base case model the company do not include PFS. Although described as a 'partitioned-survival' method with three health states of pre-progression, post-progression, and death; the company model is in fact driven by OS and ToT. Previous economic evaluations of interventions for this population use, in a classic approach, the PFS outcome to estimate the number of people in pre-progression and post-progression health states at any given time (with the two states representing an exclusive cost and utility). The company depart form this in two main respects: utility is estimated as a function of time from death; and costs are estimated according to treatment intend – whether or not active (anti-cancer) therapy is received (a function of ToT). The company justify the exclusion of PFS by virtue that TTD (using OS) considers more health states (4 versus 2 in this case), which offers a better data fit to declining HRQoL in the terminal phase of the disease.

Advice elicited by the ERG from clinical experts supported the underlying company assumption: that the HRQoL of patients in this population correlated better with time from death than first progression status.

The safety outcome was explored in full only for the PC and SOC, not the alternative comparators. Adverse events included in the economic evaluation of this main comparison were appropriately selected from KEYNOTE-189 (only). Data regarding the proportion of patients experiencing at least one event was included, but more detailed data about the number of events per patient, and the time of the event, was not included or presented. This led to some reasonable simplification, with subsequent loss of accuracy in the derivation of utilities and costs.

ERG comment:

- Outcomes included in the CS did not match the outcomes described in the final scope. The base case cost-effectiveness analysis included the time-on-treatment (ToT) outcomes, this was not included in the systematic review. However, the use of

KEYNOTE-189 as a single source of evidence for this outcome was reasonable given was is known about the evidence identified in the SLR.

- The scope included PFS but the company did not include this outcome in their base case cost-effectiveness analysis. However, clinical advice to the ERG supports the clinical justification of the alternative use of OS. Technical limitations are comparable across each approach.

3.5 Other relevant factors

The company did not identify any equity or equality issues in their submission.

The company economic model base case included confirmed and tentative commercial agreements about patient access schemes for pembrolizumab. The ERG provided separate confidential result sets (for company and ERG base case preferences) that included the PAS arrangement(s) for other drugs.

The company put the case forward for end-of-life classification (see Chapter 7).

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Description of clinical effectiveness searches

The search to identify clinical effectiveness studies is reported in appendix D1.1. In total, three bibliographic databases were searched including MEDLINE and EMBASE (both via the Ovid platform) and CENTRAL (via the Cochrane Library). The search strategy combines search terms for non-small cell lung cancer with search terms for pembrolizumab or relevant comparators. A combination of free text (i.e. title and abstract) and indexing terms (e.g. MeSH in MEDLINE) were used. Search results were limited to randomized controlled trials using a study type filter developed by the Scottish Intercollegiate Guidelines Network (SIGN) [https://www.sign.ac.uk/search-filters.html, last accessed 20th August 2018]. The filter was adapted to increase the precision of the search results by excluding records indexed as observational, cohort or retrospective studies. In addition, conference proceedings which are not also labelled as randomized controlled trials were excluded. Search results were limited to English language studies and to studies published from 1995 to-date. The most recent update search was carried out in April 2018.

In addition, the US National Institutes of Health Clinical Trial Registry (ClinicalTrials.gov) and the conference proceedings of ESMO (European Society for Medical Oncology), WCLC (World Conference on Lung Cancer), AACR (American Association for Cancer Research) and ASCO (American Society of Clinical Oncology) were searched to identify relevant studies not yet published in journal format. The conference proceedings were manual searched across the most recent two year period at the time of searching.

Critique of clinical searches

The MEDLINE and EMBASE searches use a wide selection of search terms including the relevant MeSH and Emtree indexing terms for non-small cell lung cancer, pembrolizumab and comparators. Free-text (i.e. title and abstract) search terms which describe non-small cell lung cancer are appropriately combined using proximity operators to increase the sensitivity of the search. In comparison, the CENTRAL search strategy uses a less comprehensive selection of indexing terms and makes no use of proximity operators. These are short-comings compared to the MEDLINE and EMBASE searches, but – in view of the more comprehensive approach taken in MEDLINE and EMBASE, and the still appropriate selection of search terms in CENTRAL – are not likely reduce the overall effectiveness of the

searches for retrieving all relevant published studies. The 1995 date limit is not explicitly justified but seems appropriate in view of historical changes to treatment strategies.

Adaptions were made to the SIGN randomized controlled trial study type filter which increase the precision of the search by excluding records indexed as observational, cohort or retrospective studies. Furthermore, conference proceedings which are not also labelled as randomized controlled trials were excluded. Because these adaptations have not been tested and validated by SIGN or, to our knowledge, the manufacturer, the effectiveness of the filter for identifying randomized controlled trials is potentially compromised. However, the adaptations are at least semantically appropriate in that the types of study which are intended to be excluded are not relevant to the clinical effectiveness section of the report.

The ClinicalTrials.gov search strategy is not reported and so cannot be critiqued which is a shortcoming of the company submission. However the searches are likely to be simple free text searches in view of the basic search interfaces of trials registries. The conference proceedings which are hand-searched are appropriate for the disease area.

ERG comment:

- Although there is some uncertainty about the effectiveness of adaptations to the SIGN RCT study type filter, overall the search for studies for the clinical effectiveness review is appropriate for the requirements of the review.

4.1.2 SLR Inclusion criteria

The inclusion criteria for the SLR as specified in the CS are summarised in Table 2. No corresponding exclusion criteria were explicitly reported.

Table 2 Eligibility Criteria for the SLR

Criterion	Inclusion criteria	Exclusion criteria
Population	Metastatic NSCLC patients who were previously untreated with systemic therapy for their metastatic non-squamous disease	NR
Interventions	• Pembrolizumab + pemetrexed + cisplatin or carboplatin • Pemetrexed + carboplatin or cisplatin with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment† • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin), with or	NR

Criterion	Inclusion criteria	Exclusion criteria
	without pemetrexed maintenance treatment • Pembrolizumab monotherapy‡	
Comparators	• Any of the above interventions and placebo. • Between any of the above interventions • Any intervention providing a link between two of the above interventions	NR
Outcomes	• Overall survival • Progression-free survival • Overall response rate (tabulations only) • Duration of response* • Health-related quality of life (tabulations only) • Grade 3 or 4 adverse events (tabulations only)	NR
Study designs	Randomised controlled trials	NR
Limits	• English language • 1995 onwards	NR

Abbreviations: NR = not reported; NSCLC = non-small-cell lung cancer.

*Note that this outcome was included in the NICE scope, but missing from the inclusion criteria specified in the CS (submission p.15)

‡In patients whose tumours express PD-L1 with at least a 50% tumour proportion score.

The ERG agreed that the SLR inclusion criteria specified by the company included all relevant populations and interventions of interest to the decision problem. However, the ERG noted that several changes had been made to the inclusion criteria from those specified in the NICE scope. Some of these were summarised and justified by the company in Chapter B.1.1; and in these cases, the ERG agreed that the amendments were consistent with the marketing authorisation for Pembrolizumab and good methodological practice. However, several other amendments had been made to the inclusion criteria, where no justification was provided in the CS (font colour blue in Table 2). These changes were:

- Limit to include evidence published since 1995

- Additional inclusion of studies of irrelevant comparators that could be used to link between relevant comparators
- Limit to English language articles
- Limit to evidence from randomised controlled trials (RCTs)
- Limit to evidence for grade 3 or 4 adverse events
- Duration of response no longer listed as an outcome of interest
- Limit to tabulated data only for overall response rate, health-related quality of life, and adverse events

The ERG considered that the restriction of evidence to articles published since 1995 was acceptable and unlikely to miss published evidence that evaluates the interventions of interest, and in more modern, applicable settings. The inclusion of evidence that 'may provide a link between included interventions' was also deemed to be an acceptable approach to identify evidence for indirect treatment comparisons between included interventions. Limiting evidence to English language articles is common and acceptable practice for SLRs conducted in the UK, although this should be noted as a limitation of this evidence base.

The ERG agreed that the restriction of the evidence base to RCTs was judged to be an acceptable approach in this SLR. Generally, the ERG consider that the inclusion of observational studies can broaden the evidence base for therapy technology; for example by providing evidence of the effect of treatment in real world clinical settings, and at frequently longer follow-up. However, clinical advice to the ERG was that RCTs were sufficient evidence for the evaluation of pembrolizumab combination therapy in this patient group.

The rationale for restricting the outcomes of interest to adverse events (AEs) of grade 3 or 4 severity is unclear. While all AE data, irrespective of grade, would be extracted for papers that were included in the SLR, it was noted that this change to the SLR protocol could lead to papers aimed at reporting other grade AEs in this population being excluded at the full text screening level.

The ERG noted that duration of response (DoR), ORR, PROs/HRQoL, and AE outcomes were only reported for trials evaluating pembrolizumab combination therapy; i.e. no data for these outcomes were reported for other comparisons included in the SLR, including pembrolizumab monotherapy. The ERG considered this to be a significant omission from the CS, and is a conflict with the NICE scope and the inclusion criteria as specified in the CS. It was also noted that DoR was missing from the inclusion criteria specified in the CS (p.15);

however, it was considered that this was likely to be a typographical error, as DoR data was nevertheless reported for both trials evaluating pembrolizumab combination therapy.

Finally, the ERG were concerned with additional criteria that only evidence presented in the form of tabulated data of ORR, HRQoL and grade 3 and 4 AEs would be included in the SLR. The decision to report data in tables or in the text of a publication has no reasonable association with the quality of the evidence, and should not be used to determine inclusion. Furthermore, this creates a lack of parity with the other clinical outcomes in the protocol. It is assumed that this approach was employed to save resource in data extraction, which is not accepted methodological practice.

ERG comment:

- The inclusion/exclusion criteria specified by the company are broadly aligned with the NICE scope, although several limitations subsequently applied by the company undermine the methodological rigor of the approach and risk excluding relevant evidence. The exclusion of evidence for key outcomes specified in the NICE scope for the majority of interventions specified in the NICE scope is a serious concern.

4.1.3 Study screening and data extraction

4.1.3.1 Study screening

A two-stage process was used to screen records identified by the literature searches [Source: Appendices D1.1.2]: two reviewers, working independently, were stated to have screened all records at both title/abstract and full text levels. It is unclear whether the same two reviewers screened records from all phases of the screening process. Discrepancies were stated to be resolved through discussion, or with the input of a third reviewer. The proportion of discrepancies recorded by reviewers was not reported. The software used to conduct screening (e.g. Excel, Endnote, and Covidence) was not reported. Appropriately, the SLR relating to outcomes inclusion criteria were used to determine inclusion only at the full-text level of screening. On the basis of the information provided, the ERG considers that the screening was conducted according to appropriate methodological practice.

ERG comment:

- The ERG considers study screening to have been conducted according to acceptable methodology.

4.1.3.2 Data extraction

The CS did not contain information about the methods used to extract data from included studies; for example, who performed data extraction, the software used to capture extracted

data, the selection of data points for extraction, and methods for data validation. It is therefore not possible for the ERG to determine whether data extraction for the SLR meets appropriate methodological standards.

ERG comment:

- The company did not report sufficient information for the ERG to evaluate the rigor of data extraction.

4.1.4 Quality assessment

All trials included in the SLR were assessed for bias using the Cochrane Collaboration's quality assessment tool, which is a validated tool for the assessment of risk of bias in RCTs [Source: Appendices D1.2.5]. The tool covers principle sources of bias in RCTs, including; randomisation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The CS reports a single risk of bias rating for studies within each domain of the tool; risk of bias ratings are therefore not provided for each outcome within the study, as is gold standard methodology. This is because the risk of bias frequently varies across outcomes. The ERG considers this to be a limitation of the submission, as the risk of bias ratings provided within submission may not apply to all clinical effectiveness, safety, and PRO data. Furthermore, no summary risk of bias rating (calculated across all domains of the tool) is derived. While this is not compulsory for adequate risk of bias assessment, and also carries itself some limitations, the derivation of overall risk of bias ratings can aid the interpretation of evidence identified, and can inform a feasibility assessment for ITC analysis. A critique of the quality assessment ratings for each study included in the SLR and ITC is provided in Sections 4.2.3 and 4.3.5.

ERG comment:

- Quality assessment was performed using a validated risk of bias checklist. However, risk of bias ratings were not reported separately for each outcome, which is not consistent with gold standard methodology.

4.1.5 Evidence Synthesis

The CS provides limited qualitative synthesis of the evidence identified by the SLR. Qualitative synthesis of the evidence provided in the CS is limited to discussion of the comparability of evidence from the KEYNOTE-189 and KEYNOTE-021G trials. The CS does not report qualitative synthesis of evidence for comparators evaluated in other trials. The CS also did not include standard meta-analysis of evidence identified by the SLR. Standard meta-analysis may have been feasible for a number of comparisons, supported by evidence

from multiple studies (pembrolizumab combination therapy vs. platinum + pemetrexed N=2; platinum + gemcitabine vs. platinum + pemetrexed N=5; platinum + docetaxel vs. platinum + pemetrexed N=2; platinum + paclitaxel vs. platinum + paclitaxel + bevacizumab N=4). The ERG's consideration of the company's rationale for not conducting standard meta-analysis is summarised in Section 4.2.5, 4.3.6.1.5, and 4.3.6.2.4.

The CS reports the findings of two indirect treatment comparisons (ITCs), which evaluate the clinical efficacy of all interventions identified in the SLR for two clinical outcomes: OS and PFS. The company states that it was not possible to perform a NMA to evaluate the efficacy of interventions for safety or HRQoL outcomes. No rationale is provided for why NMA was not reported for DoR outcome data. Two further ITCs were conducted to evaluate the efficacy of pembrolizumab combination therapy in comparison with pembrolizumab monotherapy for OS and PFS in a sub-population of patients with PD-L1 ≥50%. No explanation was reported for why other clinical outcomes specified in the NICE scope were not evaluated for this comparison.

Overall, the ERG considered that the ITC approach used in the CS was appropriate to address the research question of this submission. However, the ERG note that this approach is limited to evaluating only two of the clinical outcomes specified in the NICE scope. While NMA/ITC of other outcomes may not have been feasible, this is not clearly stated for all outcomes, and the lack of qualitative synthesis of the evidence in the CS for those outcomes where ITC was not feasible means that the research question for this submission is not fully addressed by the CS. The ERG felt that the lack of standard meta-analysis in the CS made it more difficult to compare clinical evidence from the same comparison between studies, but that this in itself did not prevent the CS from addressing the research question as specified in the NICE scope.

ERG comment:

- ITC analyses presented in the CS are appropriate for two key outcomes specified in the NICE scope: OS and PFS. Insufficient evidence synthesis, either qualitative or quantitative, is provided in the CS for other outcomes.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Excluded studies

A total of 415 publications were excluded at the full-text screening stage across the original search and all subsequent updates. A full list of excluded studies with the reasons for exclusion is provided in Appendix 1.

The CS reports reasons for exclusion solely in abstract categorical form. Across the original search and all subsequent updates, 133 publications were excluded for reason of the comparators, 105 the population, 98 the intervention, 26 the study design, 21 the outcomes, 2 for being duplicates and 30 for 'other' reasons.

No further detail was provided regarding the specific reasons for the exclusion of each publication. The exclusion of duplicates is clearly appropriate. However, the CS does not say what in particular about the comparators, population, intervention, study design or outcomes meant that each publication did not fulfil the inclusion criteria. This prevents the ERG from providing a fully informed critique of whether the exclusions at the full-text stage were fully in accordance with the SLR inclusion criteria, and whether the inclusion criteria have been implemented rigorously and consistently.

In particular, the ERG note that 30 publications, which represent 7% of those excluded at the full-text review stage, were listed as being excluded for 'other' reasons. No further detail is provided or examples of what this 'other' category represents. Therefore, the ERG cannot be sure that only appropriate reasons for exclusion are covered by this 'other' category. The ERG, therefore, cannot be fully satisfied that it is not possible that any relevant available data were excluded, especially for the comparator technologies.

ERG comment:

- Insufficient information was provided by the company about the reasons for exclusion for the ERG to evaluate the rigor of the selection process, and to determine whether no relevant studies were excluded.

4.2.2 Included studies

Two trials were identified by the SLR that evaluated the efficacy of pembrolizumab combination therapy in the target population; KEYNOTE-189(8) and KEYNOTE-021G(9). A further trial(10) was identified that evaluated the efficacy of pembrolizumab as monotherapy in combination with chemotherapy. The company stated that the methodology used in KEYNOTE-189 and KEYNOTE-021G were too dissimilar to be pooled in standard meta-analysis or within the same treatment nodes in the ITC; however this the ERG note that the trials were considered similar enough to include in the same ITC to evaluate the comparative effectiveness of treatments for patients with non-squamous metastatic NSCLC. Details of these trials are summarised below, and the ERG critique is reported in Sections 4.2.2.1 - 4.2.2.4.

KEYNOTE-189(8) is a Phase III, randomised, double-blind, active-controlled trial enrolling 646 patients worldwide. KEYNOTE-189 compares pembrolizumab and placebo, where both

arms are delivered in combination with pemetrexed and platinum (followed by pemetrexed maintenance therapy for patients who receive cisplatin). The trial is ongoing, and the evidence presented in this submission is based on an interim analysis. The evidence has been published in one journal article(8) with supplementary appendix, and additional documentation from the company (including the CSR) was also provided.

KEYNOTE-021G is a Phase I/II randomized, open-label, active-controlled trial enrolling 123 patients in centres in the US and Taiwan. KEYNOTE-021G compares pembrolizumab combination therapy with 'standard of care', which was comprised of combinations of chemotherapy and platinum therapies. The evidence for this trial that was provided in this submission is based on 'cohort G'; a sub-population of the KEYNOTE-021 trial, which was selected prior to randomisation (based on the study protocol).(9)

Of note, KEYNOTE-024, and a matching sub-population of patients from KEYNOTE-189, were analysed in a further ITC to evaluate the comparative efficacy of pembrolizumab combination and monotherapy for the treatment of patients with non-squamous metastatic NSCLC and PD-L1 ≥50%. Details and ERG critique of this trial and the analysis is reported in Section 4.3.4.2.1.

ERG comment:

- Both trials identified by the SLR that evaluate the technology of interest were considered to be consistent with the NICE scope.

4.2.2.1 Study Design

The study designs used in the trials evaluating pembrolizumab combination therapy are summarised in Table 3.

Table 3 Trials Evaluating the Technology of Interest: Study Design

	KEYNOTE-189	KEYNOTE-021G
Sample size	616 (410 intervention and 206 control)	123 (60 intervention and 63 control)
Randomisation status	Yes, randomised study	Yes, randomised study
Multi-centre trial?	Yes, multi-centre worldwide study	Yes, multi-centre study in the US and Taiwan
Blinding	Double blind	Open label
Intervention	Pembrolizumab plus pemetrexed and platinum chemotherapy	Pembrolizumab plus pemetrexed and platinum chemotherapy
Control	Active control – pemetrexed and platinum chemotherapy plus saline placebo	Active control – pemetrexed and platinum chemotherapy plus saline placebo

KEYNOTE-189 offers a considerably larger sample size than KEYNOTE-021G (n=616 vs 123); the latter forming a sub-cohort of a wider study. Both studies were randomised, although the studies differed in blinding status. KEYNOTE-021G is an open label study, whereas KEYNOTE-189 is double blind. However, in KEYNOTE-189, the medicines were initially supplied to sites open label. Therefore, “an unblinded pharmacist provided the investigative staff with ready-to-use blinded pembrolizumab or saline infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion visits” (MSD CS, p.35). Both studies were multi-centre, although KEYNOTE-189 recruited from sites worldwide, whereas KEYNOTE-021G was restricted to sites in the US and Taiwan. In both studies, the intervention was pembrolizumab at the recommended dose, plus pemetrexed and platinum chemotherapy (either cisplatin or carboplatin for KEYNOTE-189, only carboplatin for KEYNOTE-021G), while there was an active control comprising the same treatment combination of pemetrexed and platinum with active pembrolizumab

replaced by a saline placebo. KEYNOTE-021G is a subset of the larger KEYNOTE-021 study, selected so as to correspond to the population in the NICE scope for this appraisal. From the information provided in the CS, the ERG is unclear about whether or not randomisation is maintained when the subset is selected from the larger RCT population.

The primary, secondary and exploratory objectives for KEYNOTE-189 are provided in Table 4.

Table 4 Primary, secondary and exploratory objectives for KEYNOTE-189

Primary objectives and hypotheses • To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using PFS per RECIST 1.1 as assessed by blinded independent central review (BICR) of imaging in patients with metastatic non-squamous NSCLC (EGFR and ALK negative). Hypothesis: Pembrolizumab combination prolongs PFS (BICR/RECIST 1.1) compared to saline placebo/chemo combination. • To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using OS. Hypothesis: Pembrolizumab combination prolongs OS compared to saline placebo/chemo combination.
Secondary objectives • To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using objective response rate (ORR) per RECIST 1.1 as assessed by BICR. • To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using duration of response (DOR) per RECIST 1.1 as assessed by BICR. • To evaluate the safety and tolerability profile of pembrolizumab combination therapy.
Key exploratory objectives • To evaluate the effect of PD-L1 expression levels on the efficacy endpoints of PFS, OS, and ORR.

- To evaluate the anti-tumour activity of pembrolizumab combination compared with saline placebo/chemo combination using PFS, ORR, and DOR assessed by the investigator using RECIST 1.1.
- To evaluate changes in HRQOL assessments from baseline in the biomarker-positive strata and in the overall study population using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-Core 30 items (C30) and EORTC QLQ-Lung Cancer 13 items (LC13).
- To characterise utilities in patients treated with pembrolizumab combination compared with saline placebo/chemo combination using the EuroQoL 5 Dimension Visual Analogue Scale (EQ-5D VAS).

Source: Adapted from MSD CS Document B pages 36-37

The appendix of the primary publication(9) delineates the objectives and hypotheses for the original KEYNOTE-021 trial, as shown in Table 5. The aims and objectives of KEYNOTE-021 appear relevant to this appraisal, taking into consideration that only the cohort G that has a population matching the scope contributes to the evidence base for this appraisal.

Table 5 Objectives and hypotheses for KEYNOTE-021

Primary objectives

- To determine the recommended Phase II dose for pembrolizumab in combination with chemotherapy or immunotherapy in subjects with unresectable or metastatic NSCLC.
- To evaluate anti-tumour activity based on RECIST 1.1 of pembrolizumab in combination with chemotherapy or immunotherapy in NSCLC subjects using objective response rate (ORR).

Hypothesis

- Pembrolizumab in combination with chemotherapy improves ORR per RECIST 1.1 by blinded independent central review in NSCLC subjects compared to chemotherapy alone.
-

Secondary objectives

- Objective: To evaluate anti-tumour activity based on RECIST 1.1 of pembrolizumab in combination with chemotherapy in NSCLC subjects using progression-free survival (PFS).
- Cohort G1 Hypothesis: pembrolizumab in combination with chemotherapy prolongs PFS per RECIST 1.1 by blinded independent central review in NSCLC subjects compared to chemotherapy alone treatment.
- Objective: To evaluate duration of response (DOR) per RECIST 1.1 by blinded

• Independent central review in subjects with unresectable or metastatic NSCLC treated with Pembrolizumab in combination with chemotherapy or immunotherapy or chemotherapy alone. • Objective: To evaluate the overall survival (OS) in subjects with unresectable or metastatic NSCLC treated with pembrolizumab in combination with chemotherapy or immunotherapy or chemotherapy alone. • Objective: To characterize the pharmacokinetic (PK) profile of pembrolizumab when given in combination with chemotherapy or ipilimumab or TKI (gefitinib or erlotinib.) • Objective: To evaluate anti-tumour activity based on modified RECIST 1.1 of pembrolizumab in combination with chemotherapy or immunotherapy or TKI (Part 1). • Objective: To evaluate the correlation between PD-L1 expression levels and anti-tumour activity of Pembrolizumab in cohort G1.
Exploratory objectives • To evaluate PFS and OS following crossover to pembrolizumab in subjects treated with chemotherapy alone until disease progression. • To explore the correlation of tumour measurements (e.g., single longest diameter or volume) with PFS and OS in previously-treated subjects with NSCLC in subjects receiving pembrolizumab in combination with chemotherapy versus chemotherapy alone. • To investigate other biomarkers that may correlate with tumour response.

Source: Appendix of the primary publication.(9)

ERG comment:

- It is unclear whether randomisation was maintained for the selection of patients from KEYNOTE-021 for this submission (cohort 'G'). Providing that randomisation was maintained, as is implied by the primary publication(9), then both trials included in the SLR are consistent with the NICE scope for this appraisal.

4.2.2.2 Population Characteristics

KEYNOTE-189

The key inclusion and exclusion criteria for KEYNOTE-189 are shown in Table 6.

Table 6 KEYNOTE-189 Key Eligibility Criteria

Inclusion criteria
• Histologically/cytologically confirmed diagnosis stage IV (M1a or M1b) non-squamous NSCLC • Confirmation that patients do not have sensitising EGFR or ALK mutations • Measurable disease based on RECIST 1.1 as determined by local site investigator/radiology assessment

• No prior systemic treatment for advanced/metastatic NSCLC at screening • Tumour tissue available from locations not radiated prior to biopsy • ≥18 years of age on day of signing informed consent • Life expectancy of at least 3 months • ECOG performance status 0 or 1
Exclusion criteria
• Predominantly squamous histology NSCLC • Received prior systemic cytotoxic chemotherapy for metastatic disease, or other targeted or biological antineoplastic therapy, before the first dose of study treatment; had a major surgery within 3 weeks prior to first dose • Received radiation therapy to the lung that is >30Gy within 6 months of first dose • Completed palliative radiotherapy within 7 days of first dose • Known history of other prior malignancy except if subject undergone potentially curative therapy with no evidence of disease recurrence for 5 years since initiation of that therapy • Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases and patients with untreated, asymptomatic brain metastases may participate if they met specific criteria • Active autoimmune disease that required systemic treatment in past 2 years • Taking chronic systemic steroids • Unable or unwilling to take folic acid or vitamin B12 supplementation • Prior treatment targeting PD-1, PD-L1/PD-L2, or other immune-regulatory receptors or mechanisms • Active infection requiring therapy • History of (non-infectious) pneumonitis that required steroids or current pneumonitis

Source: MSD CS Document B Table 7 page 33

The distribution of study centres in KEYNOTE-189 is shown in Table 7.

Table 7 Distribution of study centres in KEYNOTE-189

Country	Number of Sites
Australia	8
Austria	8
Belgium	2
Canada	6
Denmark	3
Finland	2
France	6
Germany	11
Ireland	5

Israel	6
Italy	12
Japan	4
Netherlands	3
Spain	12
UK	7
USA	48

Source: MSD CS Document B Table 8 page 34

All centres in KEYNOTE-189 were secondary care outpatient facilities (CS, p.34). There were a total of 143 centres, of which 7 were in the UK, contributing a total of 30 patients to the study (5% of total). UK centres comprise 10% of European centres and 5% of total centres in the study. The country contributing the most centres was the USA (n=48), representing 34% of total centres.

Baseline characteristics for KEYNOTE-189 from the intention-to-treat (ITT) population are shown in Table 8.

Table 8 Population Characteristics: KEYNOTE-189 (ITT population)

	Pembrolizumab combination		**Control**	
	n	**%**	**N**	**%**
Patients in population	410		206	
Gender				
Male	254	62.0	109	52.9
Female	156	38.0	97	47.1
Age (years)				
<65	197	48.0	115	55.8
≥65	213	52.0	91	44.2
Mean	63.2		62.8	
SD	9.4		9.1	
Median	65.0		63.5	
Range	34 to 84		34 to 84	
Race				
Asian	10	2.4	8	3.9
Black or African American	11	2.7	3	1.5
White	387	94.4	194	94.2
Missing	2	0.5	1	0.5
Ethnicity				

	Pembrolizumab combination		Control	
	n	**%**	**N**	**%**
Hispanic or Latino	5	1.2	7	3.4
Not Hispanic or Latino	384	93.7	190	92.2
Not reported	9	2.2	4	1.9
Unknown	12	2.9	5	2.4
Region				
US	85	20.7	34	16.5
Ex US	325	79.3	172	83.5
Geographic region				
East-Asian	4	1.0	6	2.9
Non-East Asian	106	99.0	200	97.1
Smoking Status				
Never smoker	48	11.7	25	12.1
Former/current smoker	362	88.3	181	87.9
ECOG				
0	186	45.4	80	38.8
1	221	53.9	125	60.7
2	1	0.2	0	0.0
Missing	2	0.5	1	0.5
Histology				
Adenocarcinoma	394	96.1	198	96.1
NSCLC NOS	10	2.4	4	1.9
Other	6	1.5	4	1.9
Brain metastasis status at baseline				
Yes	73	17.8	35	17.0
No	337	82.2	171	83.0
Baseline tumour size (mm)				
Patients with data Mean SD Median Range	402 97.5 67.5 84.0 11.5 to 422.1		200 105.3 66.5 87.2 19.3 to 466.5	
PD-L1 status				

	Pembrolizumab combination		Control	
	n	**%**	**N**	**%**
<1%	127	31.0	63	30.6
≥1%	260	63.4	128	62.1
Not evaluable	23	5.6	15	7.3
Platinum chemotherapy				
Cisplatin	113	27.6	58	28.2
Carboplatin	297	72.4	148	71.8
Prior radiation				
Yes	84	20.5	46	22.3
No	326	79.5	160	77.7
Prior thoracic radiation				
Yes	28	6.8	20	9.7
No	382	93.2	186	90.3
Prior adjuvant therapy				
Yes	25	6.1	14	6.8
No	385	93.9	192	93.2
Prior neoadjuvant therapy				
Yes	5	1.2	6	2.9
No	405	98.8	200	97.1

Source: MSD CS Document B Table 10 pages 38-40

The CS notes (p.37) that "the control group enrolled more female and younger patients, than the pembrolizumab combination. Otherwise, the treatment groups were relatively well balanced in terms of baseline characteristics." The ERG largely agree with this assessment. The proportion of females in the control group is 47% vs 38% in the pembrolizumab combination group. Meanwhile, 44% of participants in the control group were aged ≥65 compared to 52% in the pembrolizumab combination group, although the ERG also note that the median ages of 63.5 and 65 respectively are only 1 ½ years apart. The ERG also note that 39% of control patients had ECOG performance status of 0 compared to 45% of patients in the pembrolizumab combination group, while 61% of control patients had ECOG of 1 compared to 54% of patients in the pembrolizumab combination group. Gender, age and ECOG status are all known prognostic markers for treatment response in this population.

KEYNOTE-021G

The ERG considered study population information about KEYNOTE-021G to not be reported in the CS to the same level of thoroughness as KEYNOTE-189, which may be representative of the company's positioning of KEYNOTE-189 as the pivotal trial in the CS.

Information provided within the submission on the eligibility criteria for KEYNOTE-021G is brief. It is stated (CS, p.28) to be a sub-cohort of the wider KEYNOTE-021 study "evaluating the efficacy, safety and tolerability of pembrolizumab in combination with chemotherapy, immunotherapy or tyrosine kinase inhibitor therapy, in patients with locally advanced or metastatic NSCLC". The Appendix of the principal publication (9) provides detailed inclusion and exclusion criteria, which are shown in Table 9, Source: The Appendix of the principal publication.(9)

Table 10 and Abbreviations:

Source: The Appendix of the principal publication.(9)

Table 11.

Table 9 Inclusion criteria for KEYNOTE-021

In order to be eligible for participation in this trial, the subject must:

1. Have a histologically-confirmed or cytologically confirmed diagnosis of stage IIIB/IV NSCLC

a) Subjects for cohort A, B, C, E, F and G should have received no prior systemic treatment for stage IIIb/IV NSCLC.

b) Subjects for cohorts D and H should have received prior treatment for NSCLC which should have been platinum based, unless EGFR mutation or ALK translocation was present. Subjects who are eligible for specific targeted therapy (e.g., EGFR mutation or ALK translocation) should have received prior treatment with the appropriate targeted agents.

c) Subjects for cohorts E and F should have confirmed activating EGFR mutation.

2. Patients who had disease progression >1yr after completing adjuvant therapy for stage IIIIA disease are eligible for Cohort A, B, C, G1 and G2, as long as no systemic therapy was given for the recurrent disease.
3. Subject must have at least one radiographically measurable lesion as per RECIST 1.1 defined as a lesion that is ≥10 mm in longest diameter or lymph node that is ≥15 mm in short axis imaged by CT scan or MRI
4. Be ≥18 years of age on day of signing informed consent.
5. Have a life expectancy of at least 3 months.
6. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status

7. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
8. Have adequate organ function
9. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication and up to 180 days after last dose of chemotherapeutic agents or TKIs.
    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
11. Male subjects of childbearing potential (Section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.7.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy and up to 180 days after last dose of chemotherapeutic agents or TKIs.
    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
12. Subject has voluntarily agreed to participate by giving written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

Source: The Appendix of the principal publication.(9)

Table 10 Values indicative of adequate organ function in KEYNOTE-021

System	Laboratory value
Haematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Haemoglobin	≥9 g/dL or ≥5.6 mmol/L– 4 weeks without transfusions
Renal	
Serum creatinine OR calculated creatinine clearance (CrCl)[a] (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for subjects with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ ULN

AST (SGOT) and ALT (SGPT)	≤ 1.5 X ULN
Alkaline Phosphatase	≤ 2.5 X ULN
Endocrine	
Thyroid stimulating hormone (TSH)	Within normal limits[b]
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy ≤1.5 X ULN unless the subject is receiving anticoagulant therapy
[a] Creatinine clearance should be calculated per institutional standard. If no local guideline is available, Creatinine Clearance should be calculated using the Cockcroft-Gault Method: CrCl = [(140-age) * weight (kg) * (0.85 for females only)] / (72 * serum creatinine) [b] If TSH is not within normal limits at baseline, the subject will still be eligible if total T3 or free T3 and free T4 are within the normal limits.	

Abbreviations:

Source: The Appendix of the principal publication.(9)

Table 11 Exclusion criteria for KEYNOTE-021

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to administration of MK-3475.
2.

a) Within 3 weeks of the first dose of trial treatment:

- Has received prior systemic cytotoxic chemotherapy
- Has received antineoplastic biological therapy (e.g., cetuximab)
- Had major surgery

b) Received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of trial treatment

c) Received prior tyrosine kinase inhibitor therapy or completed palliative radiotherapy within 7 days of the first dose of trial treatment

3. Is expected to require any other form of antineoplastic therapy while on study
4. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
5. Patients with clinically active diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis.

6. Has a known history of prior malignancy except if the patient has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.

   Note: The time requirement for no evidence of disease for 5 years does not apply to the NSCLC tumour for which a subject is enrolled in the study. The time requirement also does not apply to subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.
7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study medication.
8. Previously had a severe hypersensitivity reaction to treatment with another mAb
9. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. Subjects with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects on chronic systemic steroids would be excluded from the study.
11. Had prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms. Has participated in any other MK-3475 trial and has been treated with MK-3475.

    Examples of such antibodies include (but are not limited to) antibodies against IDO, PD-L1, IL-2R, GITR.
12. Has an active infection requiring therapy.
13. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
14. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator
16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

17. Is, at the time of signing informed consent, a regular user (including “recreational use”) of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
18. Has symptomatic ascites or pleural effusion. A subject who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
19. Has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management. Lymphangitic spread of the NSCLC is not exclusionary
20. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study
21. Subjects in cohorts E and F that require treatment with a strong inhibitor of CYP3A4 will be excluded. They may be included if there is an alternate treatment available (not a strong CYP3A4 inhibitor) and they are willing to switch prior to randomization. If a subject opts to change from a strong CYP 3A4 inhibitor to a weaker CYP 3A4 inhibitor, the subject must stop the strong CYP 3A4 inhibitor 7 days before study drug administration
22. Is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

Source: The Appendix of the principal publication.(9)

The CS states that KEYNOTE-021G is a specific sub-cohort relevant to this submission that “enrolled patients with non-squamous NSCLC regardless of PD-L1 status, in whom the safety and efficacy of pembrolizumab plus pemetrexed and carboplatin chemotherapy was compared with chemotherapy alone” (p.28). This cohort is narrower in terms of population and interventions than the complete trial, thereby corresponding to the NICE scope for this appraisal.

The ERG consider the inclusion criteria for KEYNOTE-189 and KEYNOTE-021G to be broadly comparable, although to differ in some specific details. The CS Appendix (p.89, Table 17) states that KEYNOTE-021G recruited participants from centres in the USA and Taiwan exclusively, which contrasts with the worldwide recruitment in KEYNOTE-189. There is no further information included in the submission about the number of centres in KEYNOTE-021G, and how these were subdivided between the USA and Taiwan. The principal publication (9) clarifies that recruitment was from 26 medical centres and the appendix to the publication shows that 23 of these centres (88%) were based in the USA. The number of participants recruited from each site and each country is not reported. However, it should be noted that the USA was also a major recruiting context for KEYNOTE-189; although the proportion of US sites is considerably greater in KEYNOTE-021G, and there are no UK or European participants. While KEYNOTE-021G may therefore be

considered less relevant to UK clinical practice than KEYNOTE-189, it is important to remember that only 5% of participants in KEYNOTE-189 came from UK centres.

Limited information on the baseline characteristics for KEYNOTE-021G was provided in the CS Appendix. No further baseline information specifically for cohort G is publically available. The available information is shown in Table 12.

Table 12 Population Characteristics: KEYNOTE-021G

	Pembrolizumab chemo combination		**Control**	
	n	**%**	**N**	**%**
Patients in population	60	48.8	63	51.2
Gender				
Male	22	36.7	26	41.3
Female	38	63.3	37	58.7
Age (years)				
<65	NR	NR	NR	NR
≥65	NR	NR	NR	NR
Mean	NR	NR	NR	NR
SD	NR	NR	NR	NR
Median	62.5	NA	63.2	NA
IQR	54.0-70.0	NA	58.0-70.0	NA
Range	NR	NR	NR	NR
Race				
Asian	5	8	5	8
Black or African American	4	7	0	0
White	49	82	58	92
Missing	NR	NR	NR	NR
Ethnicity				
Hispanic or Latino	NR	NR	NR	NR
Not Hispanic or Latino	NR	NR	NR	NR
Not reported	NR	NR	NR	NR
Unknown	NR	NR	NR	NR
Region				
US	NR	NR	NR	NR
Ex US	NR	NR	NR	NR
Geographic region				

	Pembrolizumab chemo combination		Control	
	n	**%**	**N**	**%**
East-Asian	NR	NR	NR	NR
Non-East Asian	NR	NR	NR	NR
Smoking Status				
Never smoker	15	25	9	14
Former/current smoker	45	75	54	86
ECOG				
0	NR	NR	NR	NR
1	NR	NR	NR	NR
0 or 1	59	98	63	100
2	NR	NR	NR	NR
Missing	NR	NR	NR	NR
Histology				
Adenocarcinoma	NR	NR	NR	NR
NSCLC NOS	NR	NR	NR	NR
Other	NR	NR	NR	NR
Brain metastasis status at baseline				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Baseline tumour size (mm)	NR	NR	NR	NR
Patients with data	NR	NR	NR	NR
Mean	NR	NR	NR	NR
SD Median	NR	NR	NR	NR
Range	NR	NR	NR	NR
PD-L1 status				
<1%	NR	NR	NR	NR
≥1%	NR	NR	NR	NR
Not evaluable	NR	NR	NR	NR
Platinum chemotherapy				
Cisplatin	NR	NR	NR	NR
Carboplatin	NR	NR	NR	NR
Prior radiation				

	Pembrolizumab chemo combination		Control	
	n	**%**	**N**	**%**
Yes No	NR NR	NR NR	NR NR	NR NR
Prior thoracic radiation				
Yes No	NR NR	NR NR	NR NR	NR NR
Prior adjuvant therapy				
Yes No	NR NR	NR NR	NR NR	NR NR
Prior neoadjuvant therapy				
Yes No	NR NR	NR NR	NR NR	NR NR
Disease stage				
Stage IIIb Stage IV	1 59	2 98	2 60	3 95

Abbreviations: NR = not reported. NA = not applicable.
Source: Adapted from MSD CS Appendix Tables 18 and 19, pages 87-90.

The ERG consider that the two arms of KEYNOTE-021G were generally comparable in terms of baseline characteristics. However, it was noted that the proportion of former/current smokers was considerably higher in the control group than in the pembrolizumab combination group (86% vs 75%).

A considerable proportion of the baseline characteristic variables available for KEYNOTE-189 are not presented for KEYNOTE-021G. This makes it difficult for the ERG to compare the baseline characteristics of these two pembrolizumab combination therapy trials to assess the extent of participant comparability. However, based on the available information, it was noted that the gender profiles of the two studies were quite different. In KEYNOTE-189, 62% of participants in the pembrolizumab combination arm and 53% of controls were male, whereas these figures were 37% and 41% respectively in KEYNOTE-021G. Based on the limited information available for KEYNOTE-021G age profiles, patient age appears to be comparable for the two studies. In terms of ethnicity, both studies recruited largely white participants, although the precise proportions differed. Almost all participants in both studies had ECOG score of 0 or 1, although KEYNOTE-021G did not provide the breakdown between these two performance grades.

The ERG also notes that the CSR for KEYNOTE-021 was not provided in the references with the submission. This limited the extent to which the ERG could explore further issues and missing information.

ERG comment:

- Population characteristics included in both KEYNOTE-189 and KEYNOTE-021G are consistent with the NICE scope for this appraisal.
- Limited information about the trial population in KEYNOTE-021G limited the ERG's evaluation of the comparability in population characteristics between the two trials, however a significant difference in gender between the two trials was noted. The ERG noted that each trial reported a statistically significant difference in a prognostic marker at baseline, which was not accounted for in subsequent statistical analysis.

4.2.2.3 Intervention Characteristics

The intervention characteristics used in the trials evaluating pembrolizumab combination therapy are summarised in Table 13. In both trials, pembrolizumab was administered according to its licence, at a dose of 200mg administered intravenously once every 3 weeks.

For patients in KEYNOTE-189, pembrolizumab and placebo were both administered prior to chemotherapy. All patients received premedication with folic acid, vitamin B12, and glucocorticoids, and additional therapies (including palliative and supportive care) were permitted at the discretion of the investigator. Mean duration of exposure was [redacted] days (SD [redacted] days) in the pembrolizumab combination arm compared with [redacted] days (SD [redacted] days) in the control arm. The mean number of cycles of treatment received was [redacted] (SD [redacted]) and [redacted] (SD [redacted]) in the pembrolizumab combination and control groups, respectively (Table 14). Limited details about background care was reported for KEYNOTE-021G, and this made it difficult for the ERG to evaluate comparability in intervention characteristics between the trials. One notable difference in intervention regimes, noted by the company in their submission, is the difference in platinum regimens used in the two pembrolizumab combination therapy trials: patients included in KEYNOTE-021G received carboplatin only; while 27.3% of patients in KEYNOTE-189 received cisplatin, rather than carboplatin (71.3%). However, contrary to licence indications in the UK, where only patients receiving cisplatin are eligible to receive pemetrexed maintenance, patients in both KEYNOTE-189 and KEYNOTE-021G received pemetrexed maintenance. The CS does not report details of how many patients in KEYNOTE-189 received pemetrexed maintenance therapy.

Table 13 Trials Evaluating the Technology of Interest: Intervention Characteristics

Drug	KEYNOTE-189	KEYNOTE-021G
Pembrolizumab	200 mg; IV infusion. Q3W; Day 1 of each 21-day cycle	200 mg; IV infusion. Q3W
Normal saline	Saline, IV infusion. Q3W; Day 1 of each 21-day cycle	Saline, IV infusion. Q3W
Pemetrexed	500mg/$m^{2;}$ IV infusion. Q3W; Day 1 of each 21-day cycle	500mg/$m^{2;}$ IV infusion. Q3W
Cisplatin	75 mg/m2; IV infusion. Q3W; Day 1 of each 21-day cycle for 4 cycles	NA
Carboplatin	AUC 5 mg/mL/min; IV infusion. Q3W; Day 1 of each 21-day cycle for 4 cycles	AUC 5 mg/mL/min; IV infusion. Q3W; for 4 cycles

Abbreviations: AUC = Area under concentration curve; IV = Intravenous; NR = Not reported; Q3W = Every 3 weeks
Source: MSC CS pages 28 and 35

Table 14 Summary of Drug Exposure (KEYNOTE-189)

	Pembrolizumab combination	Control	Total
	(N=405)	(N=202)	(N=607)
Number of Days on Therapy (days)			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of Cycles			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Abbreviations: SD = Standard deviation

Source: MSD CS page 99

ERG comment:

- Intervention characteristics used in the included trials for the technology of interest and control were consistent with licensing authorisation. Although contrary to funding indications in the UK, pemetrexed maintenance therapy was permitted for all patients, regardless of platinum administration, as opposed to only those receiving cisplatin. Interventions used across trials appeared to be comparable, except for the use of platinum (carboplatin and/or cisplatin).

4.2.2.4 Outcome Assessment

Outcome assessment methods used in trials evaluating pembrolizumab combination therapy are summarised in Table 15. All outcomes of interest specified in the NICE scope were reported in KEYNOTE-189. Methods of outcome assessment used within KEYNOTE-189 were considered to be reliable and valid measures of each of the stated outcomes. The submission provides limited details about methods of outcome assessment used in KEYNOTE-021G, and therefore it is not possible to fully evaluate the comparability of the methods of assessment used across the two trials. In particular, the ERG were concerned that it was not possible to determine from the submission whether multivariate analysis and methods for handling data were consistent between KEYNOTE-189 and KEYNOTE-021G. The ERG noted that median follow-up was considerably longer in KEYNOTE-021G than in KEYNOTE-189. Differential follow-up may affect the comparability of outcomes between trials, as a greater number of events will be captured by trials with longer follow-up. While log-rank calculated outcomes provide a standardised estimate of risk (i.e. assuming that the risk is consistent across time), trials with long follow-up may nevertheless be better able to identify any longer-term patterns in events.

The ERG noted that response to treatment was evaluated as 'best overall response' during the study follow-up; and therefore may not represent the patients' only or final treatment response. However the ERG felt that this was an acceptable measure of response in this population. Patients whose response to treatment was unknown were treated as non-responders; which the ERG considered to be a conservative but acceptable approach.

Table 15 Trials Evaluating the Technology of Interest: Outcome Assessment

Endpoint		KEYNOTE-189	KEYNOTE-021G
OS	Definition	Time from randomization to death from any cause	NR
	Time-point	Median follow-up of 10.5 months (range, 0.2 to 20.4)*	Median 23.9 months (range 0.8 – 35.1)

Endpoint		KEYNOTE-189	KEYNOTE-021G
	Statistical methods	Stratified Log-rank test; adjusted for PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). Note that estimated survival rates were derived from Kaplan-Meier analysis for time-points ≥12 months	NR; log rank test reported
	Analysis population	ITT	ITT
	Missing data approach	Model based (censored at last known alive date)	NR
PFS	Definition	Time from randomisation to first documented disease progression (RECIST 1.1) based on blinded independent central review (BICR) or death due to any cause, whichever occurred first. Data were also reported in the CS for investigator assessment of disease progression.	NR
	Time-point	Median follow-up of 10.5 months (range, 0.2 to 20.4)*	Median 23.9 months (range 0.8 – 35.1)
	Statistical methods	Stratified Log-rank test; (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). Note that estimated survival rates were derived from Kaplan-Meier	NR; log rank test reported

Endpoint		KEYNOTE-189	KEYNOTE-021G
		analysis for time-points ≥12 months	
	Analysis population	ITT	ITT
	Missing data approach	Patients censored at last disease assessment, unless in the case of documented progression or death≠	NR
ORR	Definition	Best possible response (RESCIST 1.1; complete or partial response), as determined by blinded, independent central radiologic review.	NR
	Time-point	Median follow-up of 10.5 months (range, 0.2 to 20.4)	Median 23.9 months (range 0.8 – 35.1)
	Statistical methods	Stratified M&N method, stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)	NR
	Analysis population	ITT	ITT
	Missing data approach	Patients without assessments are considered non-responders and conservatively included in denominator	NR

Endpoint		KEYNOTE-189	KEYNOTE-021G
Duration of Response	Definition	Time from first documented complete or partial response to disease progression or death. Assessed by blinded, independent central radiologic review.	NR
	Time-point	Median follow-up of 10.5 months (range, 0.2 to 20.4)	Median 23.9 months (range 0.8 – 35.1)
	Statistical methods	Median (range); proportion of patients with response ≥12 months; proportion of patients with ongoing response at time of final follow-up. No relative effect calculated	NR
	Analysis population	ITT	ITT
	Missing data approach	NR	NR
Safety	Definition	Discontinuation due to adverse events; incidence of AEs. AEs were graded according to NCI CTCAE 4.0	Drug related AEs; grade 3-5 drug-related AEs, discontinuation due to AE; AE leading to death
	Time-point	NR; AEs were collected up to 30 days and SAEs up to 90 days after the last dose of study medication.	Median 23.9 months (range 0.8 – 35.1)
	Statistical methods	NR	NR
	Analysis population	All patients as treated	All patients as treated
	Missing data approach	NR	NR

Endpoint		KEYNOTE-189	KEYNOTE-021G
HRQoL	Definition	EORTC QLQ-C30 and EQ-5D VAS; both assessed on a scale of 0-100 (better = better quality of life)	NA
	Time-point	12 weeks; 21 weeks	NA
	Statistical methods	Difference in LS means, adjusted for 'study visit interaction' and stratification factors (PD-L1 expression (1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)	NA
	Analysis population	NR; appears to be available cases only	NA
	Missing data approach	Model assumed that missing data were MAR	NA

* Note: Absolute outcome rates were reported at other time-points. ≠Sensitivity analyses were conducted with altered censoring of missing data. This included (a) an analysis that censored patients who missed 2 assessments at the time of the last documented assessment and (b) an analysis where disease progression was assumed for patients who initiated new anticancer therapy or missed 1 or more disease assessments.

Abbreviations: HRQoL, health-related quality of life; ITT, intention to treat; M&N, Miettinen and Nurminen method; MAR, missing at random; NA, not applicable; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; VAS, visual analogue scale.

Source: MSD CS pages 28-29, 40-42, 45, 47, 58, 69, 73

ERG comment:

- Methods of outcome assessment used in the trials were consistent with the NICE scope. Generally outcomes in KEYNOTE-189 were assessed according to acceptable methodological practice. Limited detail was reported concerning outcome assessment for KEYNOTE-021G, and therefore the rigor of outcome assessment in this trial could not be full evaluated.

- Except for HRQoL data, which was reported in KEYNOTE-189, no further PRO data was available.
- Differences at baseline were not accounted for in either trial, based on the information provided.

4.2.3 Quality assessment

The results of the quality assessment for KEYNOTE-189 and KEYNOTE-021G as reported by the company, and the ERG's comments, are presented in Table 16. As discussed in Section 4.1.4, the company reported quality ratings for each domain of the Cochrane Risk of Bias Tool. Quality ratings were reported across all trial outcomes; i.e. quality ratings were assumed to apply to all data reported by the study.

Overall, the ERG agreed with the quality ratings as reported by the company for KEYNOTE-189 and KEYNOTE-021G. Both trials were well-conducted, with a high risk rating for one domain in the KEYNOTE-021G trial because of the use of an open label design. Nevertheless, the open label design may have little impact on hard outcomes evaluated by the trial, including survival and progression (note that progression was evaluated using blinded, independent review). Patient reported outcomes (PROs), which may be associated with a greater risk of non-blinding, were not reported for this trial.

Table 16 Trials Evaluating the Technology of Interest: Quality Assessment

Criteria	Company Assessment	ERG Comments
KEYNOTE-189		
Was randomisation carried out appropriately?	Low risk - A computerized randomised list generator was utilized for sequence generation. Interactive voice response system (IVRS)/integrated web response system (IWRS) was used for randomisation	Low risk – The ERG agrees with the company assessment
Was the concealment of treatment allocation adequate?	Low risk - The Sponsor, investigator and subject were blinded to treatment allocation. The study site's unblinded pharmacist obtained each patient's study identification number and study drug	Low risk – The ERG agreed that the risk of selection bias due to sponsor, investigator, and subject was low. However, the ERG noted that the assignment of drugs by an unblinded pharmacist may

	assignment via the IVRS/IWRS and prepared the solutions for infusion. The unblinded pharmacist provided the investigative staff with ready-to-use blinded pembrolizumab/saline infusion solutions, packaged identically to maintain the blinding, for administration at scheduled infusion visits.	pose a risk, although this is unclear.
Were the groups similar at the outset of the study in terms of prognostic factors?*	Low risk - The control enrolled more female and younger patients, than the pembrolizumab combination. Otherwise, the treatment groups were relatively well balanced in terms of baseline characteristics	High risk – the ERG noted that differences in gender and age at baseline in the trial were not accounted for in subsequent multivariate analysis. As gender is a known prognostic marker for outcome from NSCLC, it was thought that this may pose a risk of bias to the validity of the outcome data.
Were care providers, patients and outcome assessors blind to treatment allocation?	Low risk - The study was double-blind, with sponsor, investigator and subject blinded to treatment allocation. In addition, radiologists who assessed the tumour images were blinded.	Low risk – The ERG agrees with the company assessment
Were there any unexpected imbalances in drop-outs between groups?	Unclear - Number of discontinued patients were not specified explicitly with reasons due to interim analysis results provided	Unclear – The ERG agrees with the company assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk - Outcomes pre-specified in the study protocol were reported in trial results.	Low risk – The ERG agrees with the company assessment

Other bias	Low risk: the study appears to be free of other sources of bias	Low risk – The ERG agrees with the company assessment
KEYNOTE-021G		
Was randomisation carried out appropriately?	Low risk - A computerized randomised list generator was utilized for sequence generation.	Low risk – The ERG agrees with the company assessment
Was the concealment of treatment allocation adequate?	High risk – Open label	High risk – The ERG agrees with the company assessment
Were the groups similar at the outset of the study in terms of prognostic factors?*	NR	Unclear risk – the ERG noted that there were differences at baseline in several population characteristics (ethnicity, smoking, histology), although these were marginally not statistically significant.
Were care providers, patients and outcome assessors blind to treatment allocation?	High risk – Patients and treating physicians were not blinded to study treatments. Radiologists who assessed the tumour images were blinded.	High risk – The ERG agrees with the company assessment
Were there any unexpected imbalances in drop-outs between groups?	Low risk – Number of discontinued patients and reasons were specified and accounted for.	Low risk – The ERG agrees with the company assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk - Outcomes pre-specified in the study protocol were reported in trial results.	Low risk – The ERG agrees with the company assessment
Other bias	Low risk – the study appears to be free of other sources of bias	Low risk – The ERG agrees with the company assessment

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

*Note that this is not a component of the Cochrane risk of bias tool; however this domain was reported by the company for KEYNOTE-189 and the ERG considered this to be a helpful addition to the quality assessment. This domain was not included in quality assessment of other trials in the SLR.

Source: MSD CS pages 43-44; Appendix D, Table 47 page 128

ERG comment:

- Overall, the ERG considered the evidence from both trials to be of high quality. Despite the open-label design, the principle outcomes in the trial were objective/'hard outcomes', that are less affected by blinding. Furthermore, disease progression in both trials was evaluated by independent, blinded review. Evidence of disease progression as evaluated by investigator review in KEYNOTE-021G is considered to be of lower quality, as outcome assessors were not blinded. No PRO/HRQoL outcomes were reported in KEYNOTE-021G.
- A potential cause of concern for both trials is the imbalance at baseline in prognostic markers, which was not accounted for in subsequent analysis. It is unclear how this may have affected the results.

4.2.4 Clinical effectiveness results for Pembrolizumab Combination Therapy

4.2.4.1 Clinical Efficacy

Clinical efficacy outcomes specified by the NICE scope were overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and duration of response (DoR). In addition to these outcomes, the company also reported outcome data for time to response (TTR) for patients in both KEYNOTE-189 and KEYNOTE-021G.

4.2.4.1.1 Overall Survival (OS)

The OS of patients (ITT analysis) following treatment with pembrolizumab combination therapy in KEYNOTE-189 and KEYNOTE-021G, as compared with platinum and pemetrexed therapy, is reported in Table 17.

Median survival was not reached by patients receiving pembrolizumab combination therapy in either KEYNOTE-189 or KEYNOTE-021G. Median survival for patients receiving platinum and pemetrexed therapy varied widely between the two trials, with improved survival for patients in KEYNOTE-021G (21.1 months) than in KEYNOTE-189 (11.3 months). It is likely

that differential median survival between the trials has be influenced in part by the longer follow-up of patients in KEYNOTE-021G.

Absolute rates of overall mortality were only reported in the CS for patients in KEYNOTE-189: the data indicated that [redacted] % of patients receiving pembrolizumab combination therapy had died during the follow-up period, compared to [redacted] % of patients receiving platinum and pemetrexed therapy. Estimated rates of mortality, as calculated using Kaplan-Meier, demonstrated a statistically significant beneficial effect in the risk of OS for pembrolizumab combination therapy at 6-, 9-, and 12-months from baseline. Rates of mortality were significantly lower in KEYNOTE-021G; and in this trial no difference in the rate of mortality was found. The primary publication for KEYNOTE-021G(9) reported that overall mortality was 22% in both arms of the trial, at a median follow-up comparable with KEYNOTE-189 (10.6 months).However, based on hazard ratio (HR) analysis, which accounts for censoring of data during follow-up, both trials reported that pembrolizumab combination therapy was associated with a statistically significant benefit for OS. This data indicated that pembrolizumab combination therapy was associated with a [redacted] (KEYNOTE-021G) and [redacted] (KEYNOTE-189) reduction in the risk of mortality during follow-up compared with platinum and pemetrexed therapy alone. The ERG noted that while 95% Cis around both effects were consistent with a beneficial effect of pembrolizumab combination therapy compared to platinum and pemetrexed, and the relative effect reported in KEYNOTE-021G was within the 95% Cis of the effect reported in KEYNOTE-189 (KEYNOTE-189 HR 95%CI 0.38 – 0.64; KEYNOTE 021G HR 95%CI 0.32 – 0.95). 95% Cis reported for KEYNOTE-189 are narrower than those for KEYNOTE-021G; reflecting the larger sample; although in both trials the ERG noted that the width of the confidence intervals indicated that there may be some uncertainty around the size of the effect, A Kaplan-Meier plot depicting OS in both arms of the KEYNOTE-189 trial, was provided by the company and is reproduced below (Figure 2).

Comparing between studies, the ERG noted that the relative effect of Pembrolizumab Combination therapy for OS was still smaller for patients in KEYNOTE-021G than in KEYNOTE-189. The ERG also note that, in contrast to the final follow-up data reported in the CS, at a follow-up comparable with KEYNOTE-189, no difference in OS between patients receiving pembrolizumab combination therapy and those receiving platinum and pemetrexed was found for patients in the KEYNOTE-021G (HR 0.90; 95% CI 0.42 – 1.91).

The company propose that unexpectedly high survival in the pemetrexed and platinum arm of the KEYNOTE-021G trial may have contributed to the reduced treatment effect of pembrolizumab combination therapy in KEYNOTE-021 compared to KEYNOTE-189: median survival of patients in the control arm of KEYNOTE-021G approached double that of those in

KEYNOTE-189. Clinical expert advice to the ERG supported the claim that median survival in KEYNOTE-021G was higher than would be expected for this population group. The company propose that the reason for improved survival in KEYNOTE-021G may be the higher proportion of female patients in the trial (60.1% in KEYNOTE-021G compared to 41.1% in KEYNOTE-189); stating that female patients may have more positive outcomes following treatment for NSCLC. However, the ERG note a recent meta-analysis that did not identify a consistent beneficial effect of female gender for response to anti PD-L1 therapies(11). Furthermore, the ERG notes that females were distributed equally between treatment groups in KEYNOTE-021G, such that any favourable effect of gender would apply to both treatment groups, and therefore may have limited impact on the relative treatment effect. Furthermore, subgroup analysis of OS in KEYNOTE-189 (see Table 18) suggest that the relative effect of pembrolizumab combination therapy compared to platinum and pemetrexed was stronger amongst female patients. This would suggest that the effect of pembrolizumab combination therapy relative to platinum and pemetrexed should be greater in any study with more female patients. Clinical expert advice to the ERG was that gender alone is unlikely to be responsible for the difference in survival between trials.

The company were unable to further explain the reason for the variation in treatment effect between KEYNOTE-189 and KEYNOTE-021G. Inclusion criteria for the two trials were comparable, and there were no other observable difference in baseline population characteristics between the trials. The ERG considered the possibility that variation in OS could be influenced by variation in ongoing treatment pathways following progression used across different regions in the trials. Overall, survival of patients in both KEYNOTE-189 and KEYNOTE-021G were within expectations based on reported survival across other studies included in the SLR: median survival of patients across all interventions evaluated in studies published from 2015 onwards was 14.3 months (mean 17.5; range 10.5 – 30). The ERG therefore considered that trial populations in both KEYNOTE-189 and KEYNOTE-021G may be representative of the target population, and therefore the true treatment effect may be within the range of both studies.

ERG comment:

- Overall, the ERG agreed that there is no evidence that 1st line treatment with pembrolizumab combination therapy is associated with harm to the OS of patients with metastatic non-squamous NSCLC. Rather, treatment with Pembrolizumab combination therapy is likely to be associated with a reduction in the risk of mortality compared to platinum and pemetrexed therapy. Overall effect estimates for OS reported across the two trials were large, suggesting a potentially large effect of pembrolizumab combination therapy for OS. However, the unexplained heterogeneity

in the size of the effect between the two studies, as well as the width around the confidence intervals of the effects, suggests that there is some uncertainty around the size of the effect.

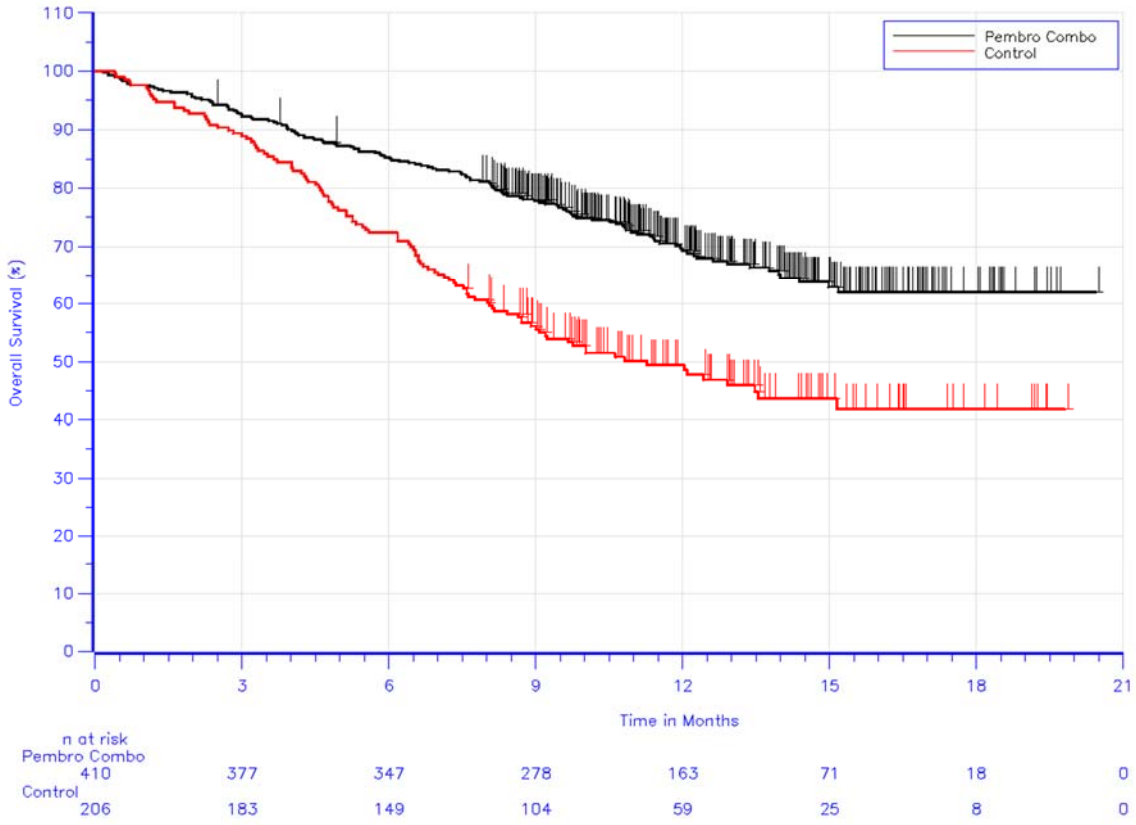
Table 17 Clinical Efficacy: Pembrolizumab Combination Therapy vs. Platinum + Pemetrexed

Outcome*	KEYNOTE-189		KEYNOTE-021G	
	Pembrolizumab Combination (N=410)	Control (N=206)	Pembrolizumab Combination	Control
	Final follow-up: median 10.5 months (range 0.2 - 20.4)		Final follow-up: median 23.9 months (range 0.8 – 35.1)	
Absolute Survival	[redacted] Extracted from the K-M method (95% CI): 6 months: [redacted] 9 months: [redacted] 12 months: 69.2% (64.1 – 73.8)	[redacted] Extracted from the K-M method (95% CI): 6 months [redacted] 9 months: [redacted] 12 months: 49.4% (42.1 – 56.2)	NR	NR
Relative survival (unadjusted)	NR		HR 0.56 (95% CI 0.32 – 0.95)≠∞	
Relative survival (adjusted)	HR 0.49 (95% CI 0.38 – 0.64)^			
Median time to death (months; 95% Cis)	Not reached	11.3 (8.7 – 15.1)	Not reached (24.5 – NR)	21.1 (14.9 – NR)
Additional analyses	[redacted]	[redacted]	NR	NR

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated. ^Covariates: PD-L1 status (Tumour Proportion Score [TPS] ≥1% vs <1%), smoking status (never vs former/current), and choice of platinum (cisplatin vs carboplatin). ≠ Unclear if analysis was adjusted. ∞ Note that data from an earlier cut-off data were used in the NMA (communication from company 14/08/18).

Source: MSD CS pages 29, 46-47, 94-95

Figure 2 KEYNOTE-189: OS Kaplan-Meier Plot



Source: MSD CS Document B Figure 9 page 49 (from KEYNOTE -189 CSR)

Subgroup Analyses

The findings of a number of subgroup analyses for OS from the KEYNOTE-189 dataset were also reported in the CS: these data are summarised in Table 18. The analyses indicated that pembrolizumab combination therapy has a statistically significant clinical benefit for OS across all population subgroups analysed. In all analyses, the relative treatment effect of pembrolizumab combination therapy for OS was large; although the ERG noted wide confidence intervals around the effects, which indicate some uncertainty around the size of the effect. Confidence intervals approached the line of null effect for patients with PD-L1 <1% and 1-49%, age ≥ 65, and of male gender.

ERG comment:

- The ERG considered that the size and consistency in the relative effect of pembrolizumab combination therapy across subgroup analyses was indicative of a clinical benefit for OS across the patient population.

Table 18 Clinical Efficacy of Pembrolizumab Combination Therapy: OS Subgroup Analyses

Outcome*	**KEYNOTE-189**
	HR (95% CI)^
PD-L1: <1%; ≥1%	<1%: 0.59 (0.38 – 0.92) ≥1%: 0.47 (0.34 – 0.66)
PD-L1: <50%; ≥50%	<50%: 0.57 (0.41 – 0.79) ≥50%: 0.42 (0.26 – 0.68)
PD-L1: <1%; 1-49%; ≥50%	<1%: 0.59 (0.38 – 0.92) 1-49%: 0.55 (0.34 – 0.90) ≥50%: 0.42 (0.26 – 0.68)
Age: < 65; ≥ 65	< 65: 0.43 (0.31; 0.61) ≥ 65: 0.64 (0.43; 0.95)
Age: < 65; 65-74	< 65: 0.43 (0.31; 0.61) 65-74: 0.51 (0.32; 0.81)
Age: <75	0.43 (0.33; 0.57)
ECOG: 0; 1	0: 0.44 (0.28; 0.71) 1: 0.53 (0.39; 0.73)
Gender: Male, female	Male: 0.70 (0.50; 0.99) Female: 0.29 (0.19; 0.44)
Ethnicity	White: 0.46 (0.35; 0.60)
Region: US; non-US	US: 0.41 (0.22; 0.74) Non-US: 0.52 (0.39; 0.69)
Region: Eu; Ex-EU	EU: 0.56 (0.40; 0.79) Non-EU: 0.38 (0.25; 0.58)
Smoker: Never; Former/Current	Never: 0.23 (0.10; 0.54) Former/Current: 0.54 (0.41; 0.71)
Brain metastasis: yes; no	Yes: 0.36 (0.20; 0.62) No: 0.53 (0.39; 0.71)
Platinum chemo: cisplatin; carboplatin	Cisplatin: 0.41 (0.24; 0.69) Carboplatin: 0.52 (0.39; 0.71)

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated. ^Based on Cox regression model with treatment as a covariate stratified by PD-L1 (≥ 1% vs <1%), platinum chemotherapy (cisplatin vs carboplatin) and smoking status (never vs former/current), if any level of a subgroup variable has fewer than 10% of the ITT population, subgroup analysis is not performed in that level of the subgroup variable.

Source: MSD CS Appendix pages 140 – 143

Patient Crossover

Patients in the platinum and pemetrexed arms of both KEYNOTE-189 and KEYNOTE-021G were permitted to crossover to pembrolizumab monotherapy following documented disease progression. Based on data from KEYNOTE-189, the CS provides the results of several analyses that adjust for this crossover in a small minority of patients with PD-L1 <1% who crossed to either pembrolizumab monotherapy ([redacted] of total control arm) or another anti-PD-L1 therapy ([redacted] source p.54 main submission). A number of other patients in the platinum and pemetrexed arm of KEYNOTE-189 were permitted to crossover to pembrolizumab monotherapy or another PD-L1 therapy, but were not included in the crossover adjustment as the company stated that these patients would be eligible for crossover under current practice in the UK. In total, [redacted] of patients in the control arm with documented disease progression crossed over to Pembrolizumab monotherapy, and an additional [redacted] % of patients received a PD-L1 antibody (pembrolizumab or Nivolumab; CS p.54). In summary, the crossover adjustment adjusts for any additional benefit of pembrolizumab monotherapy in patients who switched from the control arm in KEYNOTE-189 and who would not be eligible to do so in UK practice. The results of the crossover adjustments were comparable with the main analyses, with little change in the overall effect.

ERG comment:

- The ERG agreed that the adjustment was appropriate for exploring the effect of pembrolizumab combination therapy in a population aligned with the UK patient group. Overall, the crossover adjustments made little meaningful difference to the relative effect of treatment, albeit to broaden the 95%Cis around the effect.

4.2.4.1.2 Progression-Free Survival (PFS)

The PFS of patients following treatment with pembrolizumab combination therapy in KEYNOTE-189 and KEYNOTE-021G is reported in Table 19.

As noted in Section 4.2.2.4, progression was evaluated using RECIST 1.1 criteria based on independent, blinded radiological review in both KEYNOTE-189 and KEYNOTE-021G. Both trials demonstrated a similarly large beneficial effect of pembrolizumab combination therapy for PFS relative to control; between a 47% (KEYNOTE-021G) and 48% (KEYNOTE-189) reduction in the risk of disease progression or death. Confidence intervals indicated some uncertainty around the size of the effect, however were consistent with a statistically significant, and clinically beneficial, effect of pembrolizumab combination therapy relative to control. The CS reports estimated rates of PFS following treatment initiation (based on Kaplan-Meier analysis), which indicate a statistically significant beneficial effect in the risk of PFS for pembrolizumab combination therapy at 3-, 6-, 9-, and 12-months from baseline in KEYNOTE-189 (also see Figure 3). Both trials also demonstrated a longer median duration of PFS for patients receiving pembrolizumab combination therapy compared to control; although the difference was not statistically different for patients in KEYNOTE-021G. The data were also consistent with PFS outcome data as assessed by unblinded, investigator review (CS p. 65).

ERG comment:

- Overall, both trials demonstrate a clinically significant benefit of pembrolizumab combination therapy for PFS in this population group. While 95% Cis indicate that there may be some uncertainty in the size of the effect, the data are consistent with the conclusions of the CS.

Table 19 Clinical Efficacy of Pembrolizumab Combination Therapy: PFS

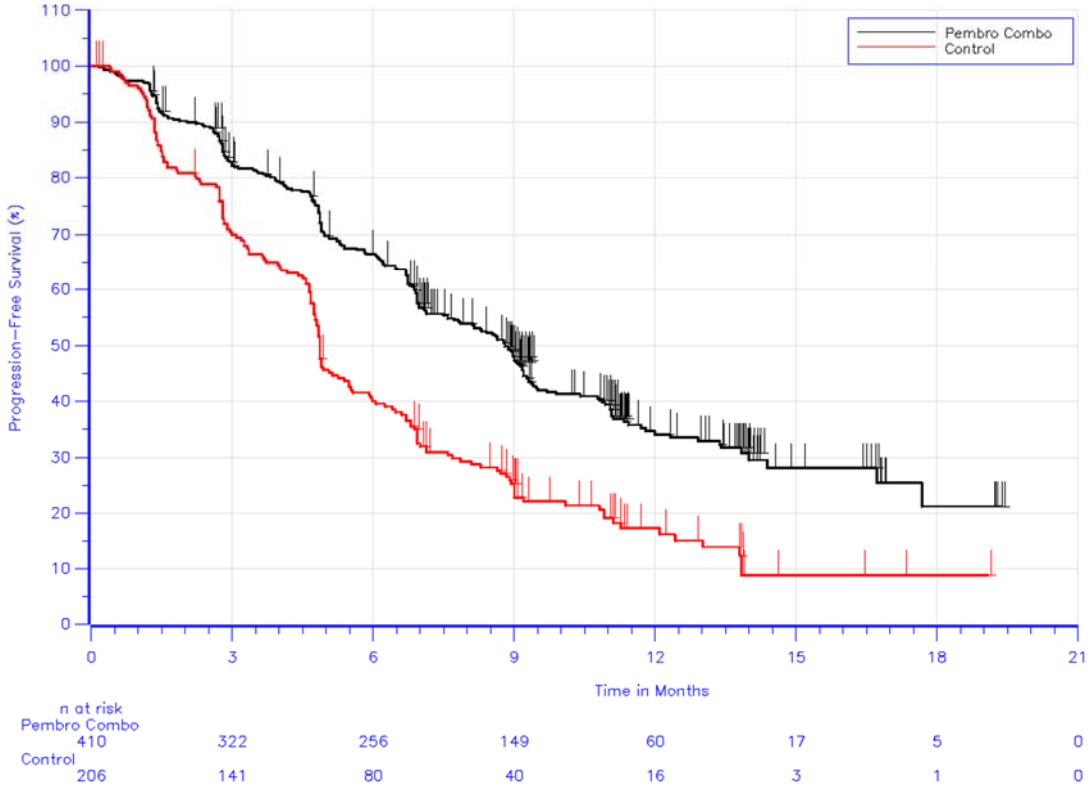
Outcome*	KEYNOTE-189		KEYNOTE-021G	
	Pembrolizumab Combination (N=410)	Control (N=206)	Pembrolizumab Combination (N=60)	Control (N=63)
	Final follow-up: median 10.5 months (range 0.2 - 20.4)		Final follow-up: median 23.9 months (range 0.8 – 35.1)	
PFS	[redacted] Patients progression-free and alive¥: (3 months: [redacted] 6 months: [redacted] 9 months: [redacted] 12 months: 34.1% (28.8 – 39.5)	[redacted] Patients progression-free and alive¥: 3 months: [redacted] 6 months: [redacted] 9 months: [redacted] 12 months: 17.3% (12.0 – 23.5)	NR	NR
Relative PFS (unadjusted)	NR		HR 0.53 (95% CI 0.33 – 0.86)≠	
Relative PFS (adjusted)	HR 0.52 (95% CI 0.43 – 0.64)^		NR	
Median PFS (months; 95% Cis)	8.8 (7.6 – 9.2)	4.9 (4.7 – 5.5)	24.0 (8.5 – NR)	9.3 (6.2 – 14.9)
Additional analyses	Events per 100 person months: [redacted]	Events per 100 person months: [redacted]	NR	NR

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated. ¥ Extracted from the K-M method (95% CI).

Source: MSD CS pages 29, 58-66, 94-95

The company provides a Kaplan-Meier plot depicting PFS in both arms of the KEYNOTE-189 trial, which is reproduced below (Figure 3)

Figure 3 KEYNOTE-189: PFS Kaplan-Meier Plot



Source: MSD CS Figure 15 page 59

Subgroup Analyses

The findings of a number of subgroup analyses for PFS from the KEYNOTE-189 dataset were also reported in the CS: this data is summarised in Table 20. Subgroup analyses of PFS data based on the KEYNOTE-021G dataset were not reported in the submission. Subgroup analyses for KEYNOTE-189 indicate that pembrolizumab combination therapy demonstrated a consistent benefit for PFS across all sub-populations. However, 95% confidence intervals crossed the line of null effect for patients with PD-L1 <1%, patients ≥65 years, and patients based in US settings. Interestingly, the effect of pembrolizumab combination therapy on PFS was shown to be more pronounced for patients with higher PD-L1 scores, younger patients, females, patients with no smoking history, those with brain metastasis, and patients who received cisplatin therapy. These findings should be interpreted with caution, however, due to the multiple analyses and small samples involved (which are represented by broader 95% confidence intervals around most effects).

ERG comment:

- The evidence demonstrated that the effect of pembrolizumab combination therapy for PFS was generally consistent across most population subgroups. There is some

evidence that the pembrolizumab combination therapy be less effective in some subgroups, but the evidence is not sufficient to demonstrate this conclusively and further research is needed.

Table 20 Clinical Efficacy of Pembrolizumab Combination Therapy: PFS Subgroup Analyses

Outcome*	**KEYNOTE-189**
	HR (95% CI)^
PD-L1: <1%; ≥1%	<1%: 0.75 (0.53 – 1.05) ≥1%: 0.44 (0.34 – 0.57)
PD-L1: <50%; ≥50%	<50%: 0.66 (0.51 – 0.85) ≥50%: 0.36 (0.25 – 0.52)
PD-L1: <1%; 1-49%; ≥50%	<1%: 0.75 (0.53 – 1.05) 1-49%: 0.55 (0.37 – 0.81) ≥50%: 0.36 (0.25 – 0.52)
Age: < 65; ≥ 65	< 65: 0.43 (0.32; 0.56) ≥ 65: 0.75 (0.55; 1.02)
Age: < 65; 65-74	< 65: 0.43 (0.32; 0.56) 65-74: 0.64 (0.45; 0.91)
Age: <75	0.47 (0.38; 0.58)
ECOG: 0; 1	0: 0.49 (0.35; 0.68) 1: 0.56 (0.43; 0.72)
Gender: Male, female	Male: 0.66 (0.50; 0.87) Female: 0.40 (0.29; 0.54)
Ethnicity	White: 0.51 (0.41; 0.62)
Region: US; non-US	US: 0.67 (0.41; 1.11) Non-US: 0.51 (0.41; 0.64)
Region: Eu; Ex-EU	EU: 0.50 (0.39; 0.65) Non-EU: 0.57 (0.40; 0.79)
Smoker: Never; Former/Current	Never: 0.43 (0.23; 0.81) Former/Current: 0.54 (0.43; 0.66)
Brain metastasis: yes; no	Yes: 0.42 (0.26; 0.68) No: 0.53 (0.43; 0.67)
Platinum chemo: cisplatin; carboplatin	Cisplatin: 0.44 (0.30; 0.65) Carboplatin: 0.55 (0.44; 0.70)

^Based on Cox regression model with treatment as a covariate stratified by PD-L1 (≥ 1% vs <1%), platinum chemotherapy (cisplatin vs carboplatin) and smoking status (never vs

former/current), if any level of a subgroup variable has fewer than 10% of the ITT population, subgroup analysis is not performed in that level of the subgroup variable.

Source: MSD CS Appendix pages 144 – 147

Sensitivity Analyses

The results of a sensitivity analysis of data from KEYNOTE-189, which conservatively codes missing patients as progressed, was provided by the company following submission (communication 14/08/2018). This analysis continues to demonstrate a statistically significant benefit of pembrolizumab combination therapy for PFS relative to platinum and pemetrexed ([redacted]). This data was not reported for KEYNOTE-021G, although considering the upper 95% CI of the effect in this trial, the ERG considered it likely that a more conservative approach to the management of missing data would result in the effect no longer being statistically significant between arms.

ERG comment:

- This analysis lends weight to the reliability of the effect estimate from KEYNOTE-189.

4.2.4.1.3 Overall Response Rate (ORR)

The ORR of patients following treatment with pembrolizumab combination therapy in KEYNOTE-189 and KEYNOTE-021G is reported in Table 21.

Absolute rates of overall response to treatment were higher for patients who received pembrolizumab combination therapy in both trials. The data indicated that 47.6% of patients in KEYNOTE-189 and 56.7% of patients in KEYNOTE-021 receiving pembrolizumab combination therapy responded during the follow-up period, compared to 18.9% and 30.2% of patients receiving platinum and pemetrexed therapy in KEYNOTE-189 and KEYNOTE-021, respectively. In both trials, response was defined as either complete or partial response. Data reported for KEYNOTE-189 in the CS indicated that almost all responses were partial (0.5% complete response rate in both arms). A breakdown of response rates into complete and partial response was not reported for KEYNOTE-021G; however the associated publication, Langer et al.(9), reported (at an earlier follow-up; median 10.6 months) that all responses were partial (55% pembrolizumab combination therapy; 29% platinum and pemetrexed therapy). The ERG noted that response rate was defined in both trials as best possible response during the follow-up period, and so does not take into consideration the duration of response. The relative difference in response rates between the arms in both trials was similar; pembrolizumab combination therapy demonstrated a 28.5% (KEYNOTE-189) and 26.4% (KEYNOTE-021G) increase in the rate of treatment response during the follow-up period.

Table 21 Clinical Efficacy of Pembrolizumab Combination Therapy: ORR

Outcome*	**KEYNOTE-189**		**KEYNOTE-021G**	
	Pembrolizumab Combination (N=410)	Control (N=206)	Pembrolizumab Combination (N=60)	Control (N=63)
	Final follow-up: median 10.5 months (range 0.2 - 20.4)		Final follow-up: median 23.9 months (range 0.8 – 35.1)	
ORR	195/410 (47.6%)	39/206 (18.9%)	34/60 (56.7%)	19/63 (30.2%)
Relative ORR	NR		% difference: 26.4% (95% CI 8.9 – 42.4)≠	
Relative ORR (adjusted)	% difference: 28.5% (95% CI: 21.1 – 35.4)^		NR	
Complete Response	2/410 (0.5%)	1/206 (0.5%)	NR	NR
Partial Response	193/410 (47.1%)	38/206 (18.4%)	NR	NR
Stable Disease	152/410 (37.1%)	106/206 (51.5%)	NR	NR
Disease Control	347/410 (84.6%)	145/206 (70.4%)	NR	NR
Progressive Disease	36/410 (8.8%)	36/206 (17.5%)	NR	NR

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated. ^ Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). ≠ Unclear if difference was adjusted for covariates, as in KEYNOTE-189.
Source: MSD CS pages 29, 66-67

The ORR rates of patients in the KEYNOTE-189 trial were also reported separately for a small number of population subgroups based on PD-L1 status: these data are summarised in Table 22. It is unclear why subgroup analyses according to the same subpopulations analysed for OS and PFS were not also conducted for ORR. No subgroup analyses were reported in the submission for the ORR of patients in KEYNOTE-021G. Overall the subgroup

analyses indicated that pembrolizumab combination therapy was associated with an increased rate of response across all PD-L1 subpopulations. The difference in the rate of response increased as PD-L1 TPS score increased: pembrolizumab combination therapy was associated with a 17.4%, 28.5%, and 38.5% increase in the rate of response for patients with PD-L1 TPS <1%, 1-49%, and ≥50%, respectively.

ERG Comment:

- The evidence demonstrates that overall response rate was higher for patients receiving Pembrolizumab combination therapy in both trials. In KEYNOTE-189, and at earlier follow-up in KEYNOTE-021G, this effect is driven by a significant difference in partial response rate. There is no evidence of a difference in complete response between arms in either trial.

Table 22 Clinical Efficacy of Pembrolizumab Combination Therapy: ORR Subgroup Analyses

Outcome*	**KEYNOTE-189**	
	Pembrolizumab Combination Therapy	Control
PD-L1: <1%	[redacted]	[redacted]
	% difference^: [redacted]	
PD-L1: 1-49%	[redacted]	[redacted]
	% difference^: [redacted]	
PD-L1: ≥50%	[redacted]	[redacted]
	% difference^: [redacted]	

* Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated. ^ Based on Miettinen and Nurminen method stratified by PD-L1 status (>=1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).

Source: MSD CS pages 67-68

4.2.4.1.4 Duration of Response (DoR)

The DoR of patients following treatment with pembrolizumab combination Therapy in KEYNOTE-189 and KEYNOTE-021G is reported in Table 23. A Kaplan-Meier plot depicting the proportion of patients exhibiting a response throughout the follow-up period is also provided by the company (Figure 4).

In KEYNOTE-189, median duration of response was reported to be 11.2 months for patients receiving pembrolizumab combination therapy (range 1.1 – 18.0) and 7.8 months for patients receiving platinum and pemetrexed (range 2.1 – 16.4). No statistical analysis of the difference in response duration was reported, however the range in DoR in the two arms suggests that there is no statistically significant difference in DoR between pembrolizumab combination therapy and platinum and pemetrexed therapy. It is interesting that median duration of response was not reached for patients in either arm of KEYNOTE-021G, despite the considerably longer follow-up compared with KEYNOTE-189.

Both studies reported the proportion of patients who experienced extended response duration (note that in KEYNOTE-189 this was based on Kaplan-Meier analysis). These data indicated that the proportion of patients with extended response duration was similar in both arms at 3 months, but became numerically greater in the pembrolizumab combination therapy arm than the platinum and pemetrexed arm at all other time-points. No statistical analysis was reported to determine if the difference in the proportion of patients was statistically significant at any time-point. The ERG independently compared these data, and found that there was no statistically significant difference in the proportion of patients with extended response duration in either trial, and at any time-point (see Section 4.5).

ERG Comment:

- The evidence from both trials did not demonstrate a statistically significant difference in the duration of response between either arms.

Table 23 Clinical Efficacy of Pembrolizumab Combination Therapy: DoR

Outcome*	**KEYNOTE-189**		**KEYNOTE-021G**	
	Pembrolizumab Combination (N=195)	Control (N=39)	Pembrolizumab Combination (N=34)	Control (N=19)
	Final follow-up: median 10.5 months (range 0.2 - 20.4)		Final follow-up: median 23.9 months (range 0.8 – 35.1)	
Median DoR (Range)	11.2 months (1.1 – 18.0)	7.8 months (2.1 – 16.4)	Not reached (1.4 – 29.3)	Not reached (2.8 – 30.1)
Relative DoR (unadjusted)	NR		NR	

Relative ORR (adjusted)	NR		NR	
Number of patients with extended response duration^	3 months: [redacted] 6 months: [redacted] 9 months: [redacted] 12 months: [redacted]	3 months: [redacted] 6 months: [redacted] 9 months: [redacted] 12 months: [redacted]	47.1%	31.6%

* Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated. ^ From product-limit (Kaplan-Meier) method for censored data.
Source: MSD CS pages 29, 69-72

Figure 4 Kaplan-Meier estimates of duration of response in patients with confirmed response based on BICR assessment per RECIST 1.1 (ITT population)

[redacted]

Source: MSD CS Figure 21 page 70

4.2.4.1.5 Additional Outcomes

The company further reported the time to response (TTR) for patients treated in the KEYNOTE-189 trial; these data are summarised in Table 24. The time to response was comparable between patients receiving Pembrolizumab Combination therapy and those receiving platinum and pemetrexed. Time to response data was not reported for patients in KEYNOTE-021G.

Table 24 Clinical Efficacy of Pembrolizumab Combination Therapy: TTR

Outcome*	**KEYNOTE-189**	
	Pembrolizumab Combination Therapy (N=[redacted])	Control (N=[redacted])
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated.
Source: MSD CS page 71

4.2.4.2 Patient-Reported Outcomes/Health-Related Quality of Life

Health-related quality of life (HRQoL) following treatment with pembrolizumab combination therapy is reported in the CS for patients in the KEYNOTE-189 trial; no patient-reported outcome data is reported for patients in KEYNOTE-021G. Evidence from KEYNOTE-189 is summarized in Table 25.

HRQoL in the KEYNOTE-189 trial was assessed using EQ-5D VAS, EORTC-QLQ C30, and EORTC QLQ-LC13; however only data for EQ-5D VAS was provided in the CS. Not all patients completed HRQoL measures, and a substantial number of patients were missing from the analysis. Patient attrition increased over time, at a similar rate between arms (although attrition was somewhat higher in the control arm). By the 21 week follow-up, data was only available for 61.0% of patients in the pembrolizumab combination arm, and 51.1% of patients in the control arm.

Based on the raw HRQoL scores, there was no statistically significant difference in the change in HRQoL in the two arms between baseline and 12 and 21 weeks follow-up. However, following adjustment for covariates (treatment by study visit interaction, PD-L1 ≥ 1% vs. <1%, platinum chemotherapy, and smoking status) and imputation to replace missing data, the analysis demonstrated a statistically significant difference in change in HRQoL between baseline and 12 and 21 weeks. This difference was clinically meaningful, based on established minimally important difference (MID) criteria for EQ-5D VAS (12). The difference

in HRQoL was driven by both increased HRQoL in the pembrolizumab combination arm and a decrease in HRQoL in the control arm, between baseline and 21 weeks. The ERG considered that the follow-up of HRQoL was relatively short, and may not capture the impact of disease progression on HRQoL. The ERG were also concerned with the high level of missing data from the HRQoL follow-up, which was not explained.

ERG comment:

- Overall, the ERG considered that the analysis was acceptable for understanding the short-term impact of pembrolizumab combination therapy, although is limited in quality due to high levels of missing data and the short follow-up time-point. Nevertheless, the ERG noted that the findings were consistent with the clinical efficacy outcome data, which shows an increased risk of progression in patients in the control group.

Table 25 HRQoL following treatment with Pembrolizumab Combination Therapy

Outcome*	**KEYNOTE-189**	
	Pembrolizumab Combination Therapy	Control
EQ-5D VAS		
Baseline Mean (SD)	[redacted] N=[redacted]	[redacted] N=[redacted]
Week 12 Mean (SD)	[redacted] N=[redacted]	[redacted] N=[redacted]
Week 21 Mean (SD)	[redacted] N=[redacted]	[redacted] N=[redacted]
Change from baseline LS Mean 0-12 weeks (95% CI)^	[redacted] N=[redacted]	[redacted] N=[redacted]
Change from baseline LS Mean 0-21 weeks (95% CI)^	[redacted] N=[redacted])	[redacted] N=[redacted]
Difference in LS means 0-12 weeks (95% CI)	[redacted]	
Difference in LS means 0-21 weeks (95% CI)	[redacted]	

*Note that all outcomes are reported as assessed in the patients who received at least 1 dose of study medication and completed at least 1 PRO assessment. ^Based on constrained longitudinal data analysis (cLDA) model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumour proportion score ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)) as covariates.

Source: MSD CS pages 73-74

4.2.4.3 Safety

The CS (pp.98-108) provides information about the safety profile of pembrolizumab combination therapy based on a full-text scholarly publication (8) and the CSR (13) for KEYNOTE-189. Information about the safety profile of this therapy using data from KEYNOTE-021G (9, 14) is provided in the CS Appendix (Appendix F, pp. 151-154).

The ERG verified the safety data included in the CS for KEYNOTE-189 against the full-text scholarly publication and the CSR, and found no apparent discrepancies. It is stated (p.98) that adverse events (AEs) were collected up to 30 days after the last dose of study medication and serious adverse events (SAEs) were collected for up to 90 days. The ERG considered this a sufficient period to capture the majority of drug-related events, as it is recognised that immunotherapy toxicity may occur weeks or months after treatment is discontinued. The ERG considered that the safety data comparing pembrolizumab combination with control in the pembrolizumab trials are thoroughly reported in the CS. However, the ERG also noted that considerable portions of the adverse event profile are based on the confidential CSR rather than on publically available data.

Adverse events (AEs) were common in both the active and control arms of KEYNOTE-189, occurring overall in 99.8% of patients in the pembrolizumab combination arm and 99% of patients in the control arm (CS, p.100). Drug-related AEs (91.9% vs 90.6%), grade 3-5 AEs (67.2% vs 65.8%) and serious adverse events (SAEs, [redacted]) were all common in both arms, although slightly more common in the pembrolizumab combination arm. The greatest difference in AEs between pembrolizumab combination therapy and control occurred for drug-related grade 3 to 5 AEs ([redacted], and drug-related SAEs ([redacted]whereby participants in the pembrolizumab combination group had an [redacted]incidence respectively of having a drug-related grade 3 to 5 AE than participants in the control arm. The CS states (p.100) that “the adverse event profile observed for pembrolizumab combination and control arms were generally consistent with the known safety profiles of the respective therapies administered”. The ERG considered this to be a reasonable assessment.

The CS states (p.100) that “higher rates of discontinuation of any drug within the treatment regimen due to an AE, irrespective of AE category, occurred in the pembrolizumab combination compared to the control (27.7% vs 14.9%)”. The ERG consider this to be accurate. However, the ERG disagree with the company’s interpretation of the data regarding discontinuation of all drugs due to an AE: the CS states that “importantly, the rate of discontinuation of all drugs due to an AE was similar across both trial arms ([redacted])”; however, the ERG note that this is a difference

[redacted], and so which may justifiably be seen as substantially higher.

The data above show that adverse events were [redacted] for the active pembrolizumab combination arm than the control arm. The CS states that the number of reported deaths is “similar” (p.101) between the two treatment groups (6.7% vs 5.9%). However, the ERG notes that deaths were numerically more common in the active arm by a relative magnitude of 14%.

Table 26 provides an overview of the adverse event profile in the KEYNOTE-189, showing total values as well as those subdivided between the active and control arms:

Table 26 KEYNOTE-189 Adverse event summary

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with one or more adverse events	404	(99.8)	200	(99.0)	604	(99.5)
with no adverse event	1	(0.2)	2	(1.0)	3	(0.5)
with drug-related† adverse events	[redacted]					
with toxicity grade 3-5 adverse events	272	(67.2)	133	(65.8)	405	(66.7)
with toxicity grade 3-5 drug-related adverse events	[redacted]					
with serious adverse events	[redacted]					
with serious drug-related adverse events	[redacted]					
who died	27	(6.7)	12	(5.9)	39	(6.4)
who died due to a drug-related adverse event	[redacted]					
discontinued any drug due to an adverse event	112	(27.7)	30	(14.9)	142	(23.4)
discontinued pembrolizumab or placebo	82	(20.2)	21	(10.4)	103	(17.0)
discontinued any chemotherapy	[redacted]					
discontinued all drugs	[redacted]					
discontinued any drug due to a drug-related adverse event	[redacted]					
discontinued pembrolizumab or placebo	[redacted]					
discontinued any chemotherapy	[redacted]					
discontinued all drugs	[redacted]					
discontinued any drug due to a serious adverse event	[redacted]					
discontinued pembrolizumab or placebo	[redacted]					
discontinued any chemotherapy	[redacted]					
discontinued all drugs	[redacted]					

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
discontinued any drug due to a serious drug-related adverse event	[redacted]					
discontinued pembrolizumab or placebo	[redacted]					
discontinued any chemotherapy	[redacted]					

Source: MSD CS Document B Table 51 page 101

As profiled in Table 27, the most frequently reported AEs were nausea (55.6% vs 52.0%), anaemia (46.2% vs 46.5%) and fatigue (40.7% vs 38.1%). The CS states (p.102) that "no substantial differences in the types and frequencies of AEs were reported between the treatment groups, except for higher rates of diarrhoea and rash in the pembrolizumab combination versus control". However, the ERG noted from Table 27 that the observed incidence was numerically greater for active pembrolizumab combination than controls for 20 out of 26 AE categories; supporting a tendency towards increased AE risk in active pembrolizumab combination therapy compared to control.

Table 27 KEYNOTE-189 Patients with adverse events by decreasing incidence (incidence ≥10% in one or more treatment groups)

	Pembrolizumab combination		**Control**		**Total**	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with one or more adverse events	404	(99.8)	200	(99.0)	604	(99.5)
with no adverse events	1	(0.2)	2	(1.0)	3	(0.5)
Nausea	225	(55.6)	105	(52.0)	330	(54.4)
Anaemia	187	(46.2)	94	(46.5)	281	(46.3)
Fatigue	165	(40.7)	77	(38.1)	242	(39.9)
Constipation	141	(34.8)	64	(31.7)	205	(33.8)
Diarrhoea	125	(30.9)	43	(21.3)	168	(27.7)
Decreased appetite	114	(28.1)	61	(30.2)	175	(28.8)
Neutropenia	110	(27.2)	49	(24.3)	159	(26.2)
Vomiting	98	(24.2)	47	(23.3)	145	(23.9)
Cough	87	(21.5)	57	(28.2)	144	(23.7)
Dyspnoea	86	(21.2)	52	(25.7)	138	(22.7)
Asthenia	83	(20.5)	49	(24.3)	132	(21.7)
Rash	82	(20.2)	23	(11.4)	105	(17.3)
Pyrexia	79	(19.5)	30	(14.9)	109	(18.0)
Oedema peripheral	78	(19.3)	26	(12.9)	104	(17.1)
Thrombocytopenia	73	(18.0)	29	(14.4)	102	(16.8)
Lacrimation increased	69	(17.0)	22	(10.9)	91	(15.0)
Back pain	52	(12.8)	23	(11.4)	75	(12.4)

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Alanine aminotransferase increased	49	(12.1)	18	(8.9)	67	(11.0)
Dizziness	49	(12.1)	19	(9.4)	68	(11.2)
Headache	48	(11.9)	19	(9.4)	67	(11.0)
Blood creatinine increased	47	(11.6)	16	(7.9)	63	(10.4)
Dysgeusia	46	(11.4)	19	(9.4)	65	(10.7)
Hypokalaemia	44	(10.9)	15	(7.4)	59	(9.7)
Pruritus	43	(10.6)	21	(10.4)	64	(10.5)
Upper respiratory tract infection	41	(10.1)	15	(7.4)	56	(9.2)
Pneumonia	37	(9.1)	22	(10.9)	59	(9.7)

Source: MSD CS Document B Table 52 page 102

Table 28 shows that only [redacted] of patients receiving active pembrolizumab combination and [redacted] of controls did not encounter any drug-related AEs. The most prevalent drug-related AEs were [redacted] Drug-related AEs were [redacted] Moreover, the observed incidence [redacted]

Table 28 KEYNOTE-189 Patients with drug-related AEs by decreasing incidence (incidence >10% in one or more treatment groups)

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with one or more adverse events	[redacted]					
with no adverse events	[redacted]					
Nausea	[redacted]					
Anaemia	[redacted]					
Fatigue	[redacted]					
Neutropenia	[redacted]					
Decreased appetite	[redacted]					
Diarrhoea	[redacted]					
Vomiting	[redacted]					
Thrombocytopenia	[redacted]					
Constipation	[redacted]					
Asthenia	[redacted]					
Lacrimation increased	[redacted]					
Rash	[redacted]					

Source: MSD CS Document B Table 53 page 103

Table 29 shows that across treatment groups, 405/607 (66.7%) patients experienced 1 or more grade 3-5 AEs, although above the table in the CS (p.104), the percentage is apparently misreported as 57.3%. Grade 3-5 AEs were more prevalent in patients receiving active pembrolizumab combination therapy than controls (67.2% vs 65.8%). The most common grade 3-5 AEs were anaemia, neutropenia and thrombocytopenia – with only the first also appearing among the most common three overall AEs. The observed incidence of grade 3-5 AEs was numerically greater for patients receiving active pembrolizumab combination therapy than controls for 7 out of 9 categories.

Table 29 KEYNOTE-189 Patients with grade 3-5 AEs by decreasing incidence (incidence ≥5% in one or more treatment group)

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	272	(67.2)	133	(65.8)	405	(66.7)
with no adverse events	133	(32.8)	69	(34.2)	202	(33.3)
Anaemia	66	(16.3)	31	(15.3)	97	(16.0)
Neutropenia	64	(15.8)	24	(11.9)	88	(14.5)
Thrombocytopenia	32	(7.9)	14	(6.9)	46	(7.6)
Febrile neutropenia	23	(5.7)	16	(7.9)	39	(6.4)
Asthenia	25	(6.2)	7	(3.5)	32	(5.3)
Fatigue	27	(6.7)	4	(2.0)	31	(5.1)
Pneumonia	23	(5.7)	5	(2.5)	28	(4.6)
Diarrhoea	21	(5.2)	6	(3.0)	27	(4.4)
Dyspnoea	15	(3.7)	11	(5.4)	26	(4.3)

Source: MSD CS Document B Table 54 page 104

More patients (CS, p.104) in the active pembrolizumab combination therapy arm ([redacted] Table 30) had a drug-related grade 3-5 AE than those in the control arm. Only four categories of drug-related grade 3-5 AE were observed with an incidence ≥5% in one or more treatment groups. Of these, the three most common were neutropenia, anaemia and thrombocytopenia. For all four AE categories, the incidence was [redacted].

Table 30 KEYNOTE-189 Patients with drug-related grade 3 to 5 AEs by decreasing incidence (incidence ≥5% in one or more treatment groups

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	[redacted]		[redacted]		[redacted]	
with no adverse events	[redacted]		[redacted]		[redacted]	
Neutropenia	[redacted]		[redacted]		[redacted]	
Anaemia	[redacted]		[redacted]		[redacted]	
Thrombocytopenia	[redacted]		[redacted]		[redacted]	
Febrile neutropenia	[redacted]		[redacted]		[redacted]	

Source: MSD CS Document B Table 55 page 105

The CS states (p.105) that "approximately half of the patients…experienced at least 1 SAE", and the ERG consider this to be accurate. The CS also states (p.105) that "a similar percentage of patients in the pembrolizumab combination experienced an SAE as in the control group ([redacted] vs [redacted]. However, the ERG note that the incidence of an SAE [redacted] Table 31 indicates that three SAE categories occurred with an incidence of ≥5% in one or more treatment groups – febrile neutropenia, pneumonia and anaemia. Febrile neutropenia as an SAE occurred [redacted]

Table 31 KEYNOTE-189 Patients with SAEs by decreasing incidence (incidence of ≥5% in one or more treatment groups)

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	[redacted]		[redacted]		[redacted]	
with no adverse events	[redacted]		[redacted]		[redacted]	
Febrile neutropenia	[redacted]		[redacted]		[redacted]	
Pneumonia	[redacted]		[redacted]		[redacted]	
Anaemia	[redacted]		[redacted]		[redacted]	

Source: MSD CS Document B Table 56 page 105

[redacted] of patients across treatment arms experienced drug-related SAEs (Table 32. This was [redacted] among patients on pembrolizumab combination than controls ([redacted]. Two drug-related SAEs were reported with incidence of ≥5% in one or more treatment groups: febrile neutropenia and anaemia. The CS states (p.106) that "the most commonly reported drug-related SAE was febrile neutropenia, the frequency of which was higher in the pembrolizumab combination compared with the control (pembrolizumab combination: [redacted] %; control: [redacted] %)".

[redacted] There were a total of 39 deaths due to an AE in the trial (p.106) – 27 in the pembrolizumab combination arm and 12 in the control group. The CS notes (p.106) that "the proportion of deaths due to AEs was similar between the treatment groups (pembrolizumab combination: 6.7%; control: 5.9%)". However, the ERG note that this value was numerically greater for pembrolizumab combination, and that the 0.8% point difference represents a 14% increase.

Table 32 KEYNOTE-189 Patients with drug-related SAEs by decreasing incidence (incidence of ≥5% in one or more treatment groups)

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: MSD CS Document B Table 57 page 106

The incidence of AEs of special interest was substantially higher for patients receiving pembrolizumab combination therapy than controls (22.7% vs 11.9%, Table 33). The most common AEs of special interest were hypothyroidism (overall 5.3%, active pembrolizumab combination 6.7%, controls 2.5%), pneumonitis (overall 3.8%, active pembrolizumab combination 4.4%, controls 2.5%) and hyperthyroidism (overall 3.6%, active pembrolizumab combination 4.0%, controls 3.0%). All of these three most common AEs were greater for pembrolizumab combination therapy than controls.

Table 33 KEYNOTE-189 Summary of Adverse Events of Special Interest including all risk categories

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	N	(%)
Patients in population	405		202		607	
with one or more adverse events	92	(22.7)	24	(11.9)	116	(19.1)
with no adverse event	313	(77.3)	178	(88.1)	491	(80.9)
[redacted]						
with toxicity grade 3-5 adverse events	36	(8.9)	9	(4.5)	45	(7.4)
[redacted]						
who died	3	(0.7)	0	(0.0)	3	(0.5)
[redacted]						

Source: MSD CS Document B Table 58 page 107

AE data from KEYNOTE-021G are presented as Appendix F in the CS (pp.147-158). This is based on Cohort G1 ASaT population. A summary of adverse events for this cohort is presented in Table 34.

Table 34 Adverse event summary for KEYNOTE-021G

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Subjects in population	59		62	
with one or more adverse events	59	(100.0)	61	(98.4)
with no adverse event	0	(0.0)	1	(1.6)
with drug-related† adverse events	55	(93.2)	56	(90.3)
with toxicity grade 3-5 adverse events	32	(54.2)	32	(51.6)
with toxicity grade 3-5 drug-related adverse events	23	(39.0)	16	(25.8)
with serious adverse events	24	(40.7)	17	(27.4)
with serious drug-related adverse events	16	(27.1)	6	(9.7)
who died	1	(1.7)	2	(3.2)
who died due to a drug-related adverse event	1	(1.7)	2	(3.2)
discontinued‡ due to an adverse event	7	(11.9)	8	(12.9)
discontinued due to a drug-related adverse event	6	(10.2)	8	(12.9)
discontinued due to a serious adverse event	6	(10.2)	3	(4.8)
discontinued due to a serious drug-related adverse event	5	(8.5)	3	(4.8)

†Determined by the investigator to be related to the drug. ‡ Study medication withdrawn. For subjects who crossed over to pembrolizumab, adverse events occurred after the first dose of crossover phase are excluded. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Grades are based on NCI CTCAE version 4.0. (Database cut-off date: 08AUG2016).
Source: MSD CS Appendix Table 55 pages 148-149

The company report that the proportions of participants in the pembrolizumab combination group reporting AEs (100% vs 98.4%), drug-related AEs (93.2% vs 90.3% and Grade 3-5 AEs (54.2% vs 51.6%) are “comparable” (p.148) in each case with those in the control group. However, the ERG note that in each case the proportion encountering AEs is higher for the pembrolizumab combination group than the control group, although the magnitude of difference is modest. The ERG agree with the company that “differences were observed”

(p.148) in terms of drug-related Grade 3-5 AEs (40.7% vs 27.4%) and drug-related SAEs (27.1% vs 9.7%) and consider this to be a rather marked increase in the pembrolizumab combination group compared to the control group.

The most frequently reported AEs in KEYNOTE-021G across the study population, with an incidence ≥25% were:

- "Pembrolizumab combination: fatigue ([redacted] %), nausea ([redacted] %), constipation ([redacted] %), dyspnoea ([redacted] %), vomiting ([redacted] %), diarrhoea ([redacted] %), anaemia ([redacted] %), decreased appetite ([redacted] %), headache ([redacted] %), and rash ([redacted] %)
- Control: anaemia ([redacted] %), nausea ([redacted] %), fatigue ([redacted] %), constipation ([redacted] %), and vomiting ([redacted] %)" (p.149)

The majority of subjects in both treatment arms reported drug-related AEs during the trial (pembrolizumab combination 93.2%, control 90.3%). The most frequently-reported drug-related AEs were:

• "Pembrolizumab combination: fatigue (64.4%), nausea (57.6%), anaemia (32.2%), rash (27.1%), vomiting (27.1%)

• Control: anaemia (53.2%), nausea (43.5%), and fatigue (40.3%)" (p.149)

Approximately half of the participants in each treatment arm reported Grade 3-5 AEs during the trial (pembrolizumab combination [redacted] %, control [redacted] %). The ERG note that this figure was slightly higher in the pembrolizumab combination group. The most frequently reported Grade 3-5 AEs with an incidence ≥5% were:

- "Pembrolizumab combination: anaemia ([redacted] %), neutrophil count decreased ([redacted] %), acute kidney injury ([redacted] %), cellulitis ([redacted] %), dehydration ([redacted] %), and syncope ([redacted] %)
- Control: anaemia ([redacted] %)" (p.149)

The ERG agree with the company that "more subjects in the pembrolizumab combination arm reported a drug-related Grade 3-5 AE during the trial" (p.149) (pembrolizumab combination [redacted] %, control [redacted] %). The most frequently reported drug-related Grade 3-5 AEs with an incidence ≥5% were:

- Pembrolizumab combination: anaemia (11.9%) and neutrophil count decreased (5.1%)
- Control: anaemia (14.5%) (pp.149-150)

The ERG note that SAEs were reported for 41 participants during the trial. More subjects in the pembrolizumab combination arm reported an SAE than in the control arm ([redacted] /59 [redacted] %] and [redacted] /62 [redacted] %], respectively). The most frequently reported SAEs with an incidence ≥2% were:

- "Pembrolizumab combination: acute kidney injury ([redacted] %), cellulitis ([redacted] %), dehydration ([redacted] %), fatigue ([redacted] %), pleural effusion ([redacted] %), pneumonia ([redacted] %), pyrexia ([redacted] %), and sepsis ([redacted] %)
- Control: nausea ([redacted] %), pancytopenia ([redacted] %), and small intestinal obstruction ([redacted] %)"(p.150)

Drug-related SAEs were reported by 22 participants during the trial. More participants in the pembrolizumab combination arm reported an SAE than in the control arm (27.1% and 9.7%, respectively). The most frequently reported drug-related SAEs with an incidence ≥2% were:

- "Pembrolizumab combination: acute kidney injury (3.4%), fatigue (3.4%), pyrexia (3.4%), and sepsis (3.4%)
- Control: nausea (3.2%) and pancytopenia (3.2%)" (p.150)

There were 3 deaths due to an AE during the trial. The company state that "one subject in the pembrolizumab combination arm died as a result of sepsis" and "two subjects in the control arm died due to an AE, one as a result of sepsis and one as a result of pancytopenia". The ERG note that the CS Appendix states that "all 3 events were considered by the Investigator to be related to study medication" (p.150).

ERG Comment:

- In summary, the CS presents a thorough profile of AEs for the pembrolizumab trials. The ERG consider that the incidence of AEs was consistently numerically higher in the pembrolizumab combination arm than the control arm. The ERG therefore does not agree with the company's assertion that the incidence of AEs between arms are 'similar'; however the ERG accepts that the difference in AE incidence is typically modest, and is judged to be clinically acceptable.

4.2.5 Meta-analysis

The company chose not to pool the evidence for pembrolizumab combination therapy as compared to platinum and pemetrexed from the KEYNOTE-189 and KEYNOTE-021G trials in a standard meta-analysis. The company state that this decision was driven by concerns about heterogeneity in study design and population characteristics between the two studies

(p.79). In particular, the company highlight that KEYNOTE-021G is an open label study, while KEYNOTE-189 is double-blind. Furthermore, the company highlight regional differences in study setting, variation in the proportion of female patients (there is a greater number of female patients in KEYNOTE-021G), and variation in platinum therapy (all patients in KEYNOTE-021G received carboplatin, compared to 71.3% of patients in KEYNOTE-189). The company further argue that the higher rate of survival in the control arm of the KEYNOTE-021G, and the lower rate of survival in KEYNOTE-189, is evidence that the study populations in the trials are heterogeneous.

The ERG did not agree that variation in blinding between the two trials was a significant concern for the primary efficacy outcomes related to survival and response; as blinding is considered to have a limited impact on 'hard' outcomes, such as survival. Furthermore, progression/response to treatment was evaluated using blinded, independent evaluation in both studies, and therefore is unlikely to vary between the trials due to treatment blinding. The company did not provide clear justification for how regional differences between the two trials were a concern for pooling. While healthcare settings and ongoing treatment pathways may vary between countries, this is also the case for trials included within the KEYNOTE-189 trial, which was conducted across multiple continents. The ERG did agree that differences in gender balance between the two trials may have impacted on a difference in treatment outcome between the trials, as subgroup analysis of data from KEYNOTE-189 indicated a favourable effect of female gender on outcome. However, the effect of gender on treatment outcome has not been found consistently across studies(11), and as gender was distributed equally between the arms in KEYNOTE-021G, it's unclear whether this would have significant impact on the relative effect between arms.

The median survival of patients in the control arms of both KEYNOTE-189 and KEYNOTE-021 were within the range of median survival rates reported in other trials identified by the SLR (median survival in studies published from 2015 onwards: 14.3 months; mean 17.5; range 10.5 – 30). Moreover, the relative treatment effect of pembrolizumab combination therapy reported in KEYNOTE-021G was within the 95%Cis around the effect reported in KEYNOTE-189. However, it was noted that the median survival rate of patients in the control arm of KEYNOTE-021G was higher than KEYNOTE-189. Expert clinical advice to the ERG also highlighted that the median survival of patients in the control arm of KEYNOTE-021G was higher than may be expected for this group of patients relative to UK clinical practice. The reasons for the disparity in median survival between KEYNOTE-021G and KEYNOTE-189 were unclear; the ERG and clinical experts to the ERG did not judge the variation in gender alone to be sufficient to cause the improved survival, and the inclusion criteria and other baseline characteristics between the trials were comparable. While variation in

outcome between trials may be an indicator of heterogeneity in the trial populations, there was no other evidence for this. It was also noted that the relative effect for pembrolizumab combination reported in KEYNOTE-021G was within the 95% Cis reported in KEYNOTE-189. In consideration of the evidence in this case the ERG felt that standard meta-analysis of data from KEYNOTE-189 and KEYNOTE-021G may have been acceptable. This is particularly true for OS, PFS, and ORR, which were evaluated using similar methodology, and may be more protected from bias due to blinding status. To assess whether pooling evidence from KEYNOTE-189 and KEYNOTE-021G altered the treatment effect for pembrolizumab combination therapy, the ERG conducted exploratory meta-analysis of data from the two trials (reported in Section 4.5).

ERG comment:

- The ERG acknowledge that there are some indications of heterogeneity between KEYNOTE-189 and KEYNOTE-021G, but did not feel that there was sufficient justification to not have pooled the data in standard meta-analysis.

4.2.6 Applicability to clinical practice

The company state that the patient population in KEYNOTE-189 and the economic evaluation were assessed by clinical experts as being reflective of the patient population treated in the UK. They do, however, note some difference between patients in the KEYNOTE-189 trial and UK patients:

"*Some minor differences were identified between patients included in KEYNOTE-189 and those expected to be treated in clinical practice in England (mainly related to age and sex). These differences were considered to be minor and would not affect the benefit expected for patients treated in clinical practice*."(CS, p.178)

As acknowledged elsewhere in the CS, gender is a prognostic marker for outcome in this patient population, and variation in treatment outcome was noted between male and female patients in subgroup analyses of KEYNOTE-189. Clinical advisors to the ERG noted that patients in KEYNOTE-189 were slightly younger (age range 34 – 84; mean 63 years) and fitter (restricted to ECOG 0/1) than the overall patient group that would be seen in clinical practice. Clinical advice to the ERG suggested that approximately 20% of patients seen in the UK will be rated as ECOG score 2. Although older patients and those with poorer performance scores (i.e. ECOG 2) may respond less well to treatment, overall on the basis of expert clinical advice, the ERG considered that the evidence from KEYNOTE-189 was sufficiently representative to be applied to UK clinical practice.

As discussed previously (section 4.2.5), median survival rates in the control arms of KEYNOTE-189 and KEYNOTE-021G vary; with patients in KEYNOTE-021G responding better than expected, and patients in KEYNOTE-189 responding "at the lower end of the range of historical standards". The company identify several differences in trial population characteristics and study design between the trials, but these cannot satisfactorily explain the disparity in outcome between the trials. The ERG considered that the heterogeneity between the two trials raises some uncertainty about the applicability of the KEYNOTE-189 trial findings beyond the population and study settings used in the trial. The company suggested that the data from KEYNOTE-189 is more applicable to clinical practice in the UK than that from KEYNOTE-021G, due to the inclusion of 7 UK sites in the trial. However, the ERG note that UK sites comprise only 5% of the overall number of study sites in KEYNOTE-189, while other regions with different healthcare systems comprise a larger body of the trial evidence (e.g. USA, which comprises 34%). The CS provides no comment on whether the effect of pembrolizumab combination therapy varied between patients treated in the UK compared to other trial locations. Subgroup analysis of data from KEYNOTE-189 (appendix, p. 141) indicated that there may be a difference in the relative effect of pembrolizumab combination therapy for OS between patients treated in non-EU compared to EU sites (EU [redacted]; I^2 = 46.6%). While the difference was not statistically significant, with wide 95%Cis around the effects, the data nevertheless suggests that study location may influence the efficacy of pembrolizumab combination therapy. The ERG also considered that greater heterogeneity reported between KEYNOTE-189 and KEYNOTE-021G for OS compared to PFS may reflect variation in ongoing treatment pathways between different regions. Overall, the ERG suggest that the true treatment effect of pembrolizumab combination therapy in UK clinical practice may vary an unknown amount from that reported in KEYNOTE-189. Subgroup analysis of outcomes reported from UK centres used in KEYNOTE-189, and evidence of the efficacy of pembrolizumab combination therapy from further studies, would have provided greater certainty of the true treatment effect in UK clinical practice.

ERG comment:

- The ERG considered that the emphasis on a single trial, KEYNOTE-189, to demonstrate the clinical efficacy of pembrolizumab combination therapy reduces the generalisability of the trial findings. The trial was largely conducted in non-UK settings, and therefore it is possible that variation in clinical healthcare settings and post-progression treatment pathways may alter the treatment effect of pembrolizumab combination therapy compared to what would be seen in UK clinical practice. Variation in treatment outcomes between KEYNOTE-189 and KEYNOTE-021G raises concerns about the stability of the treatment effect across patient

groups. While clinical advisors to the ERG agreed that the trial sample in KEYNOTE-189 were sufficiently similar to the UK patient population to permit generalisation of the treatment effect; the ERG nevertheless agreed that there is some uncertainty that the size of the effect of pembrolizumab combination therapy reported in KEYNOTE-189 would be seen in real clinical practice.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS included two ITC analyses: (A) an ITC comparing the relative efficacy of interventions for the treatment of non-squamous metastatic NSCLC in patients with negative EGFR and ALK mutations, and (B) and ITC comparing the relative efficacy of interventions for the treatment of non-squamous metastatic NSCLC in patients with negative EGFR and ALK mutations in patients with PD-L1 ≥50%. ITC (B) was an indirect comparison of pembrolizumab monotherapy based on evidence from KEYNOTE-024 and a sub-population of patients with PD-L1 ≥50% from KEYNOTE-189. Details of the identification and methodology of the studies included in the ITC analyses are described below. As agreed with NICE (communication 02/08/2018), the critique in this report places greater emphasis on those intervention strategies (platinum + gemcitabine and platinum + vinorelbine) that are commonly used in the UK. A full list of the comparators evaluated in the ITC is provided in Table 35.

4.3.1 Search strategy

Trials included in both ITCs were identified from the SLR methods described in Section 4.1. This strategy was designed to identify relevant trials for both ITCs, without the need for an additional search.

ERG comment:

- The ERG considered this approach to be appropriate for identifying relevant evidence for the ITC.

4.3.2 Feasibility assessment

4.3.2.1 (A) ITC: First line Interventions for Non-Squamous Metastatic NSCLC

The company state that a feasibility assessment was conducted for this ITC; however, details of the methodology used to assess the feasibility of ITC were not provided. Critically, it is unclear whether additional criteria were specified to select studies for inclusion in the ITC than those used for the SLR, since all 17 studies identified by the SLR are included in the ITC. Generally, the ERG note that it is good methodological practice to include as much of the evidence base in the ITC as possible, unless there is a strong reason for

exclusion.(15). Appropriate reasons for exclusion may be to respond to heterogeneity in the body of evidence, or to exclude studies evaluated as being of poor quality in quality assessment. In the CS appendices, the company discusses heterogeneity between studies in study design and population; including variation in factors that have prognostic relevance for outcome in this patient population (p. 87 – 88). However, the potential impact of heterogeneity in these factors on the outcome of the ITC is not discussed, but the CS reports that trials included in the same ITC were judged to be "sufficiently similar" (CS Appendices, p. 96). The company reports very few details concerning the study design, populations, interventions, and outcome assessment used in trials that did not evaluate pembrolizumab combination therapy, and therefore the ERG could not evaluate this assertion in any depth. The ERG were concerned with this omission given that methods to assess and control for heterogeneity in the analysis (e.g. meta-regression) were not used in the ITC, as the company states that this was not possible due to the small evidence base.

Furthermore, the company states that ITC analysis was not feasible for HRQoL or safety evidence, due to heterogeneity in methods of outcome assessment (CS Appendices, p. 88). However, the criteria used to determine inclusion in the ITC for these outcomes, and details of the specific methodology used by each study for these outcomes, is not provided in the CS. As a consequence, it was not possible for the ERG to verify this decision. Moreover, no comment is made on the feasibility of ITC for ORR or duration of response, which are also key outcomes specified by the SLR review protocol.

ERG comment:

- Insufficient information was provided in the CS to evaluate the rigor of the feasibility assessment, and for the ERG to consider the appropriateness of the studies included in the NMA.
- Insufficient information was provided in the CS to evaluate the company's decision not to conduct ITC analysis of other outcomes (ORR, DoR, HRQoL, Safety).

4.3.2.2 (B) ITC: First line Interventions for Non-Squamous Metastatic NSCLC (PD-L1 ≥50%)

The CS does not specify that a separate feasibility assessment was conducted for this ITC. Again, the CS states that trials included in the ITC were judged to be "sufficiently similar" (CS Appendices, p. 96). Further to this, the company use score-matching methodology to reduce differences in baseline characteristics, and provide evidence of comparability between the selected trial populations from KEYNOTE-024 and KEYNOTE-189, and state that the outcome definition and control arms in the trials were comparable. It is unclear why

evidence from KEYNOTE-021G, for which IPD data was available to the company, was not considered for inclusion in the ITC using similar score-matching techniques.

ERG comment:

- Insufficient information was provided in the CS to evaluate the company's process for determining inclusion in the ITC. It is likely that information regarding PD-L1 status of patients was only available for the KEYNOTE trials; however it is unclear to the ERG why data from KEYNOTE-021G was not included in the analysis.

4.3.3 Study selection criteria

4.3.3.1 (A) ITC: First line Interventions for Non-Squamous Metastatic NSCLC

The company does not state explicitly whether inclusion criteria for the ITC was the same or altered from the inclusion criteria of the original SLR (specified in Section □). The company state that methodology for the identification of literature was based on the original SLR; which would imply that inclusion and exclusion criteria were the same.

ERG comment:

- The ERG assume that the inclusion/exclusion criteria used were the same as those used for the original SLR, which was judged to be appropriate.

4.3.3.2 (B) ITC: First line Interventions for Non-Squamous Metastatic NSCLC (PD-L1 ≥50%)

The CS states that only patients evaluated as PD-L1 ≥ 50% were eligible for inclusion in this ITC; although the company does not state explicitly whether other inclusion criteria for the ITC was the same or altered from the original SLR (specified in Section □). Only two trials were selected for inclusion: KEYNOTE-024, which is conducted exclusively with patients evaluated as PD-L1 ≥ 50%; and KEYNOTE-189, which reports data for a subgroup of patients evaluated as PD-L1 ≥ 50%. It is not stated clearly whether other trials identified by the SLR were excluded from the ITC as they did not report data exclusively for patients evaluated as PD-L1 ≥ 50%; however the ERG considered it unlikely that other trials (not evaluating PD-L1 targeting therapies) will have tested patients for PD-L1, and therefore would likely be ineligible for this ITC. Evidence for other outcomes (ORR, DoR, Safety and PRO/HRQoL) is not reported from KEYNOTE-024, or for the sub-population of patients from KEYNOTE-189 with PD-L1 ≥ 50%. This implies that the inclusion criteria of the ITC were limited to OS and PFS data only, but it is unclear why this would be the case.

ERG comment:

- The ERG agree with the decision to limit inclusion in the ITC to patients with PD-L1 ≥ 50%. Insufficient information was reported in the CS to determine why inclusion was limited to OS and PFS outcomes only; this is unclear, given that other outcomes were available for both trials, and are included in the NICE scope for this submission. Furthermore, it is unclear why data from KEYNOTE-021G was not included in this analysis.

4.3.4 Included studies

4.3.4.1 (A) ITC: First line Interventions for Non-Squamous Metastatic NSCLC

An ITC was conducted to compare pembrolizumab combination therapy with a range of comparator strategies in patients with non-squamous metastatic NSCLC. A total of 17 studies were included in the ITC: KEYNOTE-189 and KEYNOTE-021G for pembrolizumab combination therapy, and 15 comparator studies. Pemetrexed and platinum was the common comparator across all studies, apart from platinum + paclitaxel + bevacizumab, which was used to provide an indirect comparison between platinum + paclitaxel and platinum + pemetrexed. Based on expert clinical advice received by the ERG, it was acknowledged that three of the intervention strategies (platinum + docetaxel, platinum + paclitaxel, and platinum + paclitaxel + bevacizumab) are not commonly used in UK clinical practice. The comparators evaluated in the ITC are summarised in Table 35, and details provided in the following sections.

Table 35 Comparators to the Technology of Interest Evaluated in (A) ITC

Intervention	Number of trials
Platinum + gemcitabine	5
Platinum + vinorelbine	1
Platinum + docetaxel	2
Platinum + bevacizumab + paclitaxel	6
Platinum + paclitaxel	4

Source: MSD CS Appendix D, pages 94-95

4.3.4.1.1 Study Design

Platinum + Gemcitabine vs. Platinum + Pemetrexed

Five studies comparing platinum and gemcitabine with platinum and pemetrexed were included in the ITC. These were Grønberg et al. (16, 17), JMDB(18), JMIL(19), Sun et al.(20) and Zhang et al. (21). Table 36 presents information about the study design of these studies.

Unlike KEYNOTE-189 and KEYNOTE-021G, four of the trials evaluating platinum and gemcitabine with platinum and pemetrexed were based in a single country only, while one study (18) was international. All trials, except for Sun et al (20) were multi-centre. Three of

the trials were listed as being open-label; while no information is provided on the blinding status of Zhang et al (21). The ERG note that JMDB (18) is also an open-label study. The ERG also note that the reported dates of trial initiation ranged from July 2004 to July 2011, indicating that these studies were not particularly recent.

ERG comment:

- The ERG agreed that all of the included trials that evaluated platinum and gemcitabine are consistent with the NICE scope. None of the included studies were based in the UK, although one trial (18) included a minority of study sites in the UK. The ERG note that some of the trials are old, and may not best represent modern day practice.

Table 36 Study Design: Studies Evaluating Platinum + Gemcitabine vs. Platinum + Pemetrexed

Trial ID	Phase	Date of trial initiation	Date of trial completion	Masking	Region	Multi-centre
Gronberg et al, 2009	III	May, 2005	July, 2007	Open-label	Norway	Yes
JMDB	III	July, 2004	March, 2008	Open label*	USA, Argentina, Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Greece, Hungary, India, Israel, Italy, Korea, Mexico, Netherlands, Poland, Portugal, Puerto Rico, Spain, Sweden, Taiwan, Turkey, UK	Yes
JMIL	III	November, 2009	--	Open-label	China	Yes
Sun et al, 2015	II	July, 2011	January, 2014	Open-label	Korea	No
Zhang et al, 2013	II	NR	November, 2010	--	China	Yes

*Reported as unclear blining in the CS.

Source: Adapted from MSD CS Appendix Table 17 page 86

Platinum + Vinorelbine vs. Platinum + Pemetrexed

Only one trial evaluating platinum and vinorelbine as compared with platinum and pemetrexed was included in the ITC: this was the NAVOtrial 01 (22). Table 37 presents information about the study design of NAVOtrial 01 as was reported in the CS: the only information reported is that NAVOtrial 01 is a phase II multi-centre RCT. Without further detail about the location, blinding, and date of the trial, it is difficult for the ERG to fully evaluate the comparability of NAVOtrial 01 with other trials included in the SLR.

ERG comment:

- The ERG agreed that one included trial that evaluated platinum and vinorelbine is consistent with the NICE scope, although little information was available about the trial design to evaluate further.

Table 37 Study design: Studies Evaluating Platinum + Vinorelbine vs. Platinum + Pemetrexed

Trial ID	Phase	Date of trial initiation	Date of trial completion	Masking	Region	Multi-center
NAVOtrial 01	II	--	--	--	--	Yes

Source: Adapted from MSD CS Appendix Table 17 page 86

Other comparisons

Platinum chemotherapy + paclitaxel was compared with platinum chemotherapy + paclitaxel + bevacizumab by four studies (BEYOND(23), ECOG 4599(24), JO19907(25) and Johnson et al.(26)). BEYOND was a Chinese, multi-centre study; JO19907 a Japanese, multi-centre study; Johnson et al. a North American multi-centre study. The recruitment locations of ECOG 4599 are not reported in the CS. BEYOND is reported in the CS as being double-blind, while no details on blinding status are provided for the rest of these other comparator trials. Platinum chemotherapy + pemetrexed was compared with platinum chemotherapy + paclitaxel + bevacizumab by two studies (ERACLE (27) and PRONOUNCE (28)), the latter including a pemetrexed maintenance phase. ERACLE is a multi-centre Italian RCT, but the blinding status is not reported in the CS. PRONOUNCE is an open-label multi-centre RCT from the USA. Platinum chemotherapy + docetaxel was compared with platinum chemotherapy + pemetrexed by two studies (Rodrigues-Pereira (29) and TRAIL(30)). Rodrigues-Pereira is a multi-centre international open-label RCT from six countries. TRAIL is a multi-centre, open-label RCT.

ERG comment

- The ERG agreed that all of the included trials that evaluated other comparators are consistent with the NICE scope.

4.3.4.1.2 Population Characteristics

The CS does not report the inclusion and exclusion criteria of studies not evaluating pembrolizumab that are included in the ITC analysis. This would have given a clearer picture of the comparability of participant eligibility across studies. Given the number of included studies, and the timeframe for this STA, it was not feasible for the ERG to independently extract the inclusion and exclusion criteria from the original study publications. A limited number of baseline characteristics of patients included in these trials was reported in the CS: these are summarised in Table 38, Table 40 and Table 41, and in the text below.

Platinum + Pemetrexed vs. Platinum + Gemcitabine

Comparative population characteristics for studies comparing platinum + pemetrexed and platinum + gemcitabine are presented in Table 38. The ERG note that baseline characteristic information reported in the CS for these studies is relatively limited. Gender profiles are relatively well balanced across the studies, and are relatively comparable with the KEYNOTE-189 intervention arm. The Grønberg et al(16) and JMIL(31) studies appear comparable with KEYNOTE-189 in terms of age; whereas the population in Zhang et al.(21) is considerably younger. Insufficient information was provided to evaluate whether the

population in Sun et al.(20) was of a similar age to that of KEYNOTE-189. Patients who had never smoked were the minority population in all studies; comprising between 5% and 49% of the study populations. The proportion for Sun et al (42% for the intervention group and 49% for controls) was considerably higher than the respective figure for KEYNOTE-189 and KEYNOTE-021G. This is an important source of heterogeneity across treatment groups and with KEYNOTE-189, as patients who have never smoked may have different outcomes following treatment (32). ECOG status was not reported in Sun et al (20). Like KEYNOTE-189, almost all participants in Zhang et al (100.0%) (21) and JMIL (99.8%) (31) were assessed as being ECOG 0 or 1. In contrast, in Grønberg, 23% in the intervention arm and 22% of controls had ECOG 2, which the ERG consider an important source of heterogeneity. As discussed above (see Table 36), three of the four trials were conducted in exclusively Asian populations, which may limit the comparability of these studies in particular with KEYNOTE-189. Disease stage data were not presented in the CS for KEYNOTE-189**,** meaning that information on this key prognostic factor cannot be compared with the comparator trials.

ERG comment:

- Baseline population characteristics for a number of important prognostic factors for the included studies are reported in the CS; however, baseline information for other prognostic markers are not reported. Across the information available to the ERG, trials evaluating platinum and gemcitabine vary in ECOG status, smoking history, age, and geographic region, which are all factors that may lead to variation in the treatment effect. It was not possible to evaluate heterogeneity between trials in terms of other factors, included disease stage and location of metastasis.

Table 38 Population characteristics: Platinum + pemetrexed vs. platinum + gemcitabine (Table 1 of 2)

Study	Grønberg et al.(16)				JMDB(18)				JMIL(31)			
	Gemcitabine plus platinum		Pemetrexed plus platinum		Gemcitabine plus platinum		Pemetrexed plus platinum		Gemcitabine plus platinum		Pemetrexed plus platinum	
	n	%	N	%	n	%	N	%	n	%	N	%
Patients in population	217	49.8	219	50.2	863	50.0	862	50.0	634	50.6	618	49.4
Gender												
Male	128	59.0	123	56.2	605	70.1	605	70.2	425	67.0	400	64.7
Female	89	41.0	96	43.8	258*	29.9*	257*	29.8*	209	33.0	218	35.3
Age (years)												
<65	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
≥65	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mean	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
SD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Median	66.0	NA	64.0	NA	61.0	NA	61.1	NA	60.0	NA	60.6	NA
IQR	25.0-84.0	NA	35.0-90.0	NA	26.4-79.4	NA	28.8-83.2	NA	NR	NR	NR	NR
Range	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Race												
Asian	NR	NR	NR	NR	104	12.1	116	13.5	634	100.0	618	100.0
Black or African American	NR	NR	NR	NR	18	2.1	18	2.1	0	0.0	0	0.0
White	NR	NR	NR	NR	680	78.8	605	70.2	0	0.0	0	0.0

Missing	NR	NR	NR	NR	NR	NR	NR	NR	0	0.0	0	0.0
Ethnicity												
Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Not Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Not reported	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Unknown	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Region												
US	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ex US	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Geographic region												
East-Asian	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Non-East Asian	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smoking Status≠												
Never smoker	11	5.1	22	10.0	122	14.1	128	14.8	105	16.6	111	18.0
Former/current smoker	204	94.0	197	90.0	647	75.0	629	73.0	447	70.5	432	70.0
ECOG≠												

0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
0 or 1	168	77.4	172	78.5	861	99.8	861	99.9	633	99.8	617	99.8
2	49	22.6	47	21.5	NR	NR	NR	NR	NR	NR	NR	NR
Missing	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Histology												
Adenocarcinoma	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NSCLC NOS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Other	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brain metastasis status at baseline												
Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baseline tumour size (mm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Patients with data	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mean	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
SD Median	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Range	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PD-L1 status												
<1%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
≥1%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Not evaluable	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Platinum chemotherapy												
Cisplatin	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Carboplatin	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Prior radiation												
Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Prior thoracic radiation												
Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Prior adjuvant therapy												
Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Prior neoadjuvant therapy												
Yes	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Disease stage≠												
Stage IIIb	61	28.1	63	28.8	210	24.3	205	23.4	144	22.7	125	20.2
Stage IV	156	71.9	156	71.2	653	75.7	657	76.2	490	77.3	493	79.8

* Hand calculated and assuming no missing data. ≠Note that not all values add up to 100%: assumed that remaining is missing data.

Table 39 Population characteristics: Platinum + pemetrexed vs. platinum + gemcitabine (Table 2 of 2)

Study	Sun et al.(20)				Zhang et al.(21)			
	Gemcitabine plus platinum		Pemetrexed plus platinum		Gemcitabine plus platinum		Pemetrexed plus platinum	
	n	%	N	%	n	%	N	%
Patients in population	155	49.2	160	50.8	124	49.4	127	50.6
Gender								
Male	91	58.7	87	54.4	77	62.1	78	61.4
Female	64	41.3	73	45.6	47	37.9	49	38.6
Age (years)								
<65	NR	NR	NR	NR	NR	NR	NR	NR
≥65	NR	NR	NR	NR	NR	NR	NR	NR
Mean	NR	NR	NR	NR	NR	NR	NR	NR
SD	NR	NR	NR	NR	NR	NR	NR	NR
Median	NR	NR	NR	NA	55.0	NA	54.0	NA
IQR	NR	NR	NR	NA	26.0-71.0	NA	33.0-73.0	NA
Range	37-79	NA	29-81	NA	NR	NR	NR	NR
Race								
Asian	155	100.0	160	100.0	124	100.0	127	100.0
Black or African American	0	0.0	0	0.0	0	0.0	0	0.0
White	0	0.0	0	0.0	0	0.0	0	0.0
Missing	0	0.0	0	0.0	0	0.0	0	0.0
Ethnicity								

Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR	NR
Not Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR	NR
Not reported	NR	NR	NR	NR	NR	NR	NR	NR
Unknown	NR	NR	NR	NR	NR	NR	NR	NR
Region								
US	NR	NR	NR	NR	NR	NR	NR	NR
Ex US	NR	NR	NR	NR	NR	NR	NR	NR
Geographic region								
East-Asian	NR	NR	NR	NR	NR	NR	NR	NR
Non-East Asian	NR	NR	NR	NR	NR	NR	NR	NR
Smoking Status								
Never smoker	65	41.9	78	48.8	NR	NR	NR	NR
Former/current smoker	90	58.1	82	51.3	NR	NR	NR	NR
ECOG								
0	NR	NR	NR	NR	NR	NR	NR	NR
1	NR	NR	NR	NR	NR	NR	NR	NR
0 or 1	NR	NR	NR	NR	124	100.0	127	100.0
2	NR	NR	NR	NR	NR	NR	NR	NR
Missing	NR	NR	NR	NR	NR	NR	NR	NR
Histology								
Adenocarcinoma	NR	NR	NR	NR	NR	NR	NR	NR
NSCLC NOS	NR	NR	NR	NR	NR	NR	NR	NR

Other	NR	NR	NR	NR	NR	NR	NR	NR
Brain metastasis status at baseline								
Yes	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR
Baseline tumour size (mm)	NR	NR	NR	NR	NR	NR	NR	NR
Patients with data	NR	NR	NR	NR	NR	NR	NR	NR
Mean	NR	NR	NR	NR	NR	NR	NR	NR
SD Median	NR	NR	NR	NR	NR	NR	NR	NR
Range	NR	NR	NR	NR	NR	NR	NR	NR
PD-L1 status								
<1%	NR	NR	NR	NR	NR	NR	NR	NR
≥1%	NR	NR	NR	NR	NR	NR	NR	NR
Not evaluable	NR	NR	NR	NR	NR	NR	NR	NR
Platinum chemotherapy								
Cisplatin	NR	NR	NR	NR	NR	NR	NR	NR
Carboplatin	NR	NR	NR	NR	NR	NR	NR	NR
Prior radiation								
Yes	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR
Prior thoracic radiation								
Yes	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR

Prior adjuvant therapy								
Yes	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR
Prior neoadjuvant therapy								
Yes	NR	NR	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR	NR	NR
Disease stage≠								
Stage IIIb	3	1.9	3	1.9	35	28.2	45	35.4
Stage IV	142	91.6	144	90.0	89	71.8	82	64.6

≠Note that not all values add up to 100%: assumed that remaining is missing data.
Abbreviations: NR = Not reported; NA = Not applicable.
Source: Adapted from MSD CS Appendix Tables 18 and 19, pages 87-90.

Platinum + Pemetrexed vs. Platinum + Vinorelbine

The population characteristics for NAVOtrial 01(22) are presented in Table 40. Only characteristics for age, gender, and disease stage were reported in the CS. Trial arms appear well balanced across these three characteristics. Overall, NAVOtrial 01 appears reasonably comparable with KEYNOTE-189 in terms of age and gender, although the proportion of men in KEYNOTE-189 is lower specifically in the control arm (62% male in intervention arm vs 52.9% male in control arm). However, without further detail on the trial population characteristics, particularly for important prognostic markers (e.g. ECOG status, metastatic progression, smoking history), it is not possible for the ERG to satisfactorily evaluate whether patients in the trial are comparable to other trial populations included in the ITC.

ERG comment:

- NAVOtrial01 appears to be comparable to KEYNOTE-189 in terms of age, gender, and disease stage. The ERG was not able to evaluate the comparability of the trial regarding other prognostic markers for treatment outcome.

Table 40 Population characteristics: Platinum + pemetrexed vs. platinum + vinorelbine (NAVOtrial01(22))

	Cisplatin plus vinorelbine		**Cisplatin plus pemetrexed**	
	n	**%**	**N**	**%**
Patients in population	100	66.2	51	33.8
Gender				
Male	62	62.0	33	64.7
Female	38	38.0	18	35.3
Age (years)				
<65	NR	NR	NR	NR
≥65	NR	NR	NR	NR
Mean	NR	NR	NR	NR
SD	NR	NR	NR	NR
Median	61.0	NA	63.8	NA
IQR	38.4-75.1	NA	40.3-75.5	NA
Range	NR	NR	NR	NR
Race				
Asian	NR	NR	NR	NR
Black or African American	NR	NR	NR	NR
White	NR	NR	NR	NR

	Cisplatin plus vinorelbine		Cisplatin plus pemetrexed	
	n	**%**	**N**	**%**
Missing	NR	NR	NR	NR
Ethnicity				
Hispanic or Latino	NR	NR	NR	NR
Not Hispanic or Latino	NR	NR	NR	NR
Not reported	NR	NR	NR	NR
Unknown	NR	NR	NR	NR
Region				
US	NR	NR	NR	NR
Ex US	NR	NR	NR	NR
Geographic region				
East-Asian	NR	NR	NR	NR
Non-East Asian	NR	NR	NR	NR
Smoking Status				
Never smoker	NR	NR	NR	NR
Former/current smoker	NR	NR	NR	NR
ECOG				
0	NR	NR	NR	NR
1	NR	NR	NR	NR
0 or 1	NR	NR	NR	NR
2	NR	NR	NR	NR
Missing	NR	NR	NR	NR
Histology				
Adenocarcinoma	NR	NR	NR	NR
NSCLC NOS	NR	NR	NR	NR
Other	NR	NR	NR	NR
Brain metastasis status at baseline				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Baseline tumour size (mm)	NR	NR	NR	NR
Patients with data	NR	NR	NR	NR
Mean	NR	NR	NR	NR

	Cisplatin plus vinorelbine		Cisplatin plus pemetrexed	
	n	**%**	**N**	**%**
SD Median	NR	NR	NR	NR
Range	NR	NR	NR	NR
PD-L1 status				
<1%	NR	NR	NR	NR
≥1%	NR	NR	NR	NR
Not evaluable	NR	NR	NR	NR
Platinum chemotherapy				
Cisplatin	NR	NR	NR	NR
Carboplatin	NR	NR	NR	NR
Prior radiation				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Prior thoracic radiation				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Prior adjuvant therapy				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Prior neoadjuvant therapy				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Disease stage≠				
Stage IIIb	8	8.0	5	9.8
Stage IV	88	88.0	45	88.2

≠Note that not all values add up to 100%: assumed that remaining is missing data.
Abbreviations: NR = Not reported; NA = Not applicable.
Source: Adapted from MSD CS Appendix Tables 18 and 19, pages 87-90

Other comparisons

Demographic and clinical baseline characteristics for the other comparisons (i.e. those not evaluating platin + vinorelbine or platin + gemcitabine) are shown in Table 41 and Table 42. The ERG, with input from expert clinical advice, considered the demographic and clinical characteristics across the studies included in the NMA for these other comparators to be broadly comparable with studies evaluating interventions more commonly used in UK clinical practice. However, the ERG noted that the TRAIL (30) and ERACLE (27) studies in

particular had a higher proportion of male participants than KEYNOTE-189 (62% intervention, 53% control), with the highest being 78% in the carboplatin + paclitaxel + bevacizumab arm of the ERACLE study and the range across all studies being 46-78%. Age profiles were generally comparable with KEYNOTE-189, although participants in the BEYOND study (23) were on average slightly younger than other studies (median age: 56 for carboplatin + paclitaxel arm; 57 for carboplatin + bevacizumab + paclitaxel arm). BEYOND and JO11907 (25) recruited exclusively Asian participants. Across studies, a large majority of participants were consistently of ECOG status 0 or 1. Smoking status was not reported by some studies, and the percentage of never smokers ranged across trial arms from 22% to 39% in the 4 trials for which this information was available. The proportion of patients with stage IV disease ranged between 69% and 100% across studies; this is a concerning factor to be heterogeneous across studies, given that disease stage is an important prognostic factor.

ERG comment:

- Overall the ERG agreed that the trials evaluating other comparisons were broadly comparable with the UK patient population. A number of factors were heterogeneous across trials, including gender, disease stage, and geographic region; all of which are prognostic markers for treatment outcome.

Table 41 Population characteristics: Other Comparisons

Trial ID	Treatment	N randomised	Age	Male	Caucasian	Black	Asian
BEYOND	carboplatin + paclitaxel	138	56.0 (23.0 - 74.0)	77 (56%)			138 (100%)
	carboplatin + bevacizumab + paclitaxel	138	57.0 (30.0 - 75.0)	75 (54%)			138 (100%)
ECOG 4599	carboplatin + paclitaxel	433		253 (58%)	378 (87%)	23 (5%)	
	carboplatin + paclitaxel + bevacizumab	417		210 (50%)	352 (84%)	22 (5%)	
ERACLE	cisplatin + pemetrexed	60	60.0 (35.0 - 72.0)	42 (70%)			

Trial ID	Treatment	N randomised	Age	Male	Caucasian	Black	Asian
	carboplatin + paclitaxel + bevacizumab	58	62.0 (41.0 - 71.0)	45 (78%)			
JO19907	carboplatin + paclitaxel	59	60.0 (38.0 - 73.0)	38 (64%)			59 (100%)
	carboplatin + paclitaxel + bevacizumab	121	61.0 (34.0 - 74.0)	77 (64%)			121 (100%)
Johnson et al, 2004	carboplatin + paclitaxel	32		24 (75%)			
	carboplatin + paclitaxel + bevacizumab (7.5 mg/kg)	32		20 (62%)			
	carboplatin + paclitaxel + bevacizumab (15 mg/kg)	35		16 (46%)			
PRONOUNCE	platinum + paclitaxel + bevacizumab, followed by bevacizumab	179	65.4 (41.2 - 86.2)	104 (58%)	157 (88%)	20 (11%)	0 (0%)
	platinum + pemetrexed, followed by pemetrexed	182	65.8 (38.4 - 84.1)	105 (58%)	165 (91%)	11 (6%)	4 (2%)
Rodrigues-Pereira et al, 2011	carboplatin + docetaxel	105	58.9 (31.4 - 78.4)	50 (48%)	35 (33%)	4 (4%)	44 (42%)
	carboplatin + pemetrexed	106	60.1 (27.9 - 83.1)	64 (60%)	39 (37%)	5 (5%)	45 (42%)
TRAIL	pemetrexed+ cisplatin	77	63.0* (8.9)	53 (69%)			

Trial ID	Treatment	N randomised	Age	Male	Caucasian	Black	Asian
	docetaxel+ cisplatin	71	63.6* (9.7)	50 (70%)			

Note: blank cells are consistent with reporting in the CS, and are assumed to represent data that was not reported by the included trials.
* - mean; ** - IQR
Abbreviations: NR = Not reported; NA = Not applicable.
Source: Adapted from MSD CS Appendix Table18, pages 87-88

Table 42 Clinical participant characteristics for other comparisons

Trial ID	Treatment	N Randomised	ECOG 0/1	ECOG 2	Current or former smoker	Never smoker	Stage IIIb	Stage IV
BEYOND	carboplatin + paclitaxel	138	138 (100%)	0 (0%)			9 (7%)	125 (91%)
	carboplatin + bevacizumab + paclitaxel	138	138 (100%)	0 (0%)			8 (6%)	126 (91%)
ECOG 4599	carboplatin + paclitaxel	433	430 (99%)				55 (13%)	337 (78%)
	carboplatin + paclitaxel + bevacizumab	417	414 (99%)				50 (12%)	310 (74%)
ERACLE	cisplatin + pemetrexed	60	60 (100%)		42 (70%)	13 (22%)	3 (5%)	57 (95%)
	carboplatin + paclitaxel + bevacizumab	58	58 (100%)		35 (60%)	16 (28%)	4 (7%)	54 (93%)
JO19907	carboplatin + paclitaxel	59	59 (100%)	0 (0%)	40 (68%)	19 (32%)	12 (20%)	42 (71%)
	carboplatin + paclitaxel + bevacizumab	121	121 (100%)	0 (0%)	83 (69%)	38 (31%)	28 (23%)	83 (69%)
Johnson et al, 2004	carboplatin + paclitaxel	32	30 (94%)	2 (6%)			6 (19%)	26 (81%)
	carboplatin + paclitaxel + bevacizumab (7.5 mg/kg)	32	31 (97%)	1 (3%)			2 (6%)	30 (94%)
	carboplatin + paclitaxel + bevacizumab (15 mg/kg)	35	31 (89%)	4 (11%)			7 (20%)	28 (80%)
PRONOUNCE	platinum + paclitaxel + bevacizumab, followed by bevacizumab	179	179 (100%)		172 (96%)		0 (0%)	179 (100%)
	platinum + pemetrexed, followed by pemetrexed	182	181 (99%)		164 (90%)		1 (1%)	181 (99%)
Rodrigues-Pereira et al, 2011	carboplatin + docetaxel	105	88 (84%)	17 (16%)	62 (59%)	41 (39%)	23 (22%)	82 (78%)
	carboplatin + pemetrexed	106	91 (86%)	15 (14%)	72 (68%)	34 (32%)	17 (16%)	89 (84%)

Trial ID	Treatment	N Randomised	ECOG 0/1	ECOG 2	Current or former smoker	Never smoker	Stage IIIb	Stage IV
TRAIL	pemetrexed+ cisplatin	51	69 (90%)	8 (10%)	37 (73%)	14 (28%)	5 (6%)	72 (94%)
	docetaxel+ cisplatin	49	64 (90%)	7 (10%)	35 (71%)	14 (29%)	3 (4%)	68 (96%)

Note: blank cells are consistent with reporting in the CS, and are assumed to represent data that was not reported by the included trials.
Source: Adapted from MSD CS Appendix Table19, pages 89-90

4.3.4.1.3 Intervention Characteristics

Platinum + Pemetrexed vs. Platinum + Gemcitabine

Table 43 profiles the intervention characteristics for the included gemcitabine studies.

ERG comment:

- The ERG considers all included trials that evaluated platinum and gemcitabine to fit the scope for this appraisal in terms of the intervention characteristics. However, the ERG also notes that no information on dosing or method of administration is provided in the CS. Information derived from publications of the trials indicated that the administration of interventions were broadly comparable with UK practice, although there was variation in the dose of interventions used between studies.

Table 43 Intervention characteristics: Platinum + Pemetrexed vs. Platinum + Gemcitabine

Trial ID	Treatment
Grønberg et al, 2009	carboplatin + gemcitabine
	carboplatin + pemetrexed
JMDB	cisplatin + gemcitabine
	cisplatin + pemetrexed
JMIL	cisplatin + gemcitabine
	cisplatin + pemetrexed
Sun et al, 2015	cisplatin + gemcitabine
	cisplatin + pemetrexed
Zhang et al, 2013	cisplatin + gemcitabine
	cisplatin + pemetrexed

Source: Adapted from MSD CS Appendix Table18, pages 87-88

Platinum + Pemetrexed vs. Platinum + Vinorelbine

Table 44 profiles the intervention characteristics used in one trial that evaluated platinum and vinorelbine and platinum and pemetrexed(22).

ERG comment:

- The ERG considers the interventions used in this trial to fit the scope for this appraisal. However, the ERG also notes that no information on dosing, method of administration, or background care is provided in the CS.

Table 44 Intervention characteristics: Platinum + Pemetrexed vs. Platinum + Vinorelbine

Trial ID	Treatment
NAVOtrial 01	cisplatin + pemetrexed
	cisplatin + vinorelbine

Source: Adapted from MSD CS Appendix Table18, pages 87-88

Other comparisons

Interventions for studies included in the NMA for other comparisons are shown in Table 45.

ERG comment:

- The ERG considered that all of these studies met the scope for this appraisal in terms of interventions evaluated. However, the ERG noted that dosing information was only provided in the CS for the Johnson et al.(26) study, while no information was provided on dosing scheduling, method of administration, or background care for any studies.

Table 45 Profile of intervention characteristics for other comparisons

Trial ID	Treatment
BEYOND	carboplatin + paclitaxel
	carboplatin + bevacizumab + paclitaxel
ECOG 4599	carboplatin + paclitaxel
	carboplatin + paclitaxel + bevacizumab
ERACLE	cisplatin + pemetrexed
	carboplatin + paclitaxel + bevacizumab

Trial ID	Treatment
JO19907	carboplatin + paclitaxel
	carboplatin + paclitaxel + bevacizumab
Johnson et al, 2004	carboplatin + paclitaxel
	carboplatin + paclitaxel + bevacizumab (7.5 mg/kg)
	carboplatin + paclitaxel + bevacizumab (15 mg/kg)
PRONOUNCE	platinum + paclitaxel + bevacizumab, followed by bevacizumab
	platinum + pemetrexed, followed by pemetrexed
Rodrigues-Pereira et al, 2011	carboplatin + docetaxel
	carboplatin + pemetrexed
TRAIL	pemetrexed + cisplatin
	docetaxel + cisplatin

Source: Adapted from MSD CS Appendix Table18, pages 87-88

4.3.4.1.4 Outcome Assessment

The CS reports OS and PFS outcome data for trials included in the ITC. Data reported for each of the included trials, where reported, were median OS/PFS and treatment effect on risk of event occurrence (HR) for OS and PFS. The CS does not report information about the methods for assessing outcomes in comparator trials. Critically, the ERG were concerned that it was not possible to evaluate comparability in the definition of outcomes and the median follow-up time. Subsequent communication with the company (date 14/08/2018) confirmed that no data included in the ITCs were adjusted for baseline covariates. Due to the limited detail reported about population baseline characteristics in the trials, as well as of

other factors that may vary between trial arms (e.g. background care), it is not possible for the ERG to determine if the use of unadjusted data may have introduced bias into the ITC.

ERG comment:

- Insufficient information was reported about outcome assessment in trials not evaluating pembrolizumab combination for the ERG to evaluate whether methods of outcome assessment were rigorous and sufficiently comparable across trials.

4.3.4.2 (B) ITC: First line Interventions for Non-Squamous Metastatic NSCLC (PD-L1 ≥50%)

4.3.4.2.1 Study Design

KEYNOTE-024 is an international multi-centre phase III RCT that recruited from 16 countries. The CS does not provide any further information on the country profile for KEYNOTE-024, including whether any UK centres were involved in the trial, and the comparability of its country profile with KEYNOTE-189. The CSR (33) clarifies that [redacted] However, as the ITC includes a sub-population of patients from both KEYNOTE-024 and KEYNOTE-189, it is unclear whether study design characteristics as described for the full trial are representative for this sample. It should also be noted that the selection of a subgroup of patients from a trial undermines the integrity of the randomisation process. While the company use population-matching techniques to address imbalance in population characteristics between and within the trials, there may be imbalance in other trial characteristics that are unknown.

The RG noted information on the blinding status of KEYNOTE-024 was contradictory between the CS and published outputs [redacted]. Table 17 in the CS appendix identifies KEYNOTE-024 as “quadruple or double-blind”. However, the ERG found this to be incorrect. All other sources (including the primary publication (10), [redacted], and slides provided with the submission from a conference abstract (34)), clearly describe KEYNOTE-024 an open label” trial. Information about the study design of KEYNOTE-024 as reported by the CS is summarised in Table 46.

ERG comment:

- The ERG considered that KEYNOTE-024 was consistent with the NICE scope, and should be considered an open label trial in the submission.

- The ERG noted that this analysis includes subgroups from each trial, who are selected post-randomisation. Aside from population characteristics that may have been adequately addressed using statistical population-matching techniques, there may be unknown sources of imbalance between the trials.

Table 46. Study design for KEYNOTE-024

Trial ID	Phase	Date of trial initiation	Date of trial completion	Masking	Region	Multi-centre
KEYNOTE 024	III	January, 2016	November, 2017	Open label	Europe, North America, East Asia, Other region (16 countries)	Yes

Source: Adapted from MSD CS Appendix Table17, pages 86

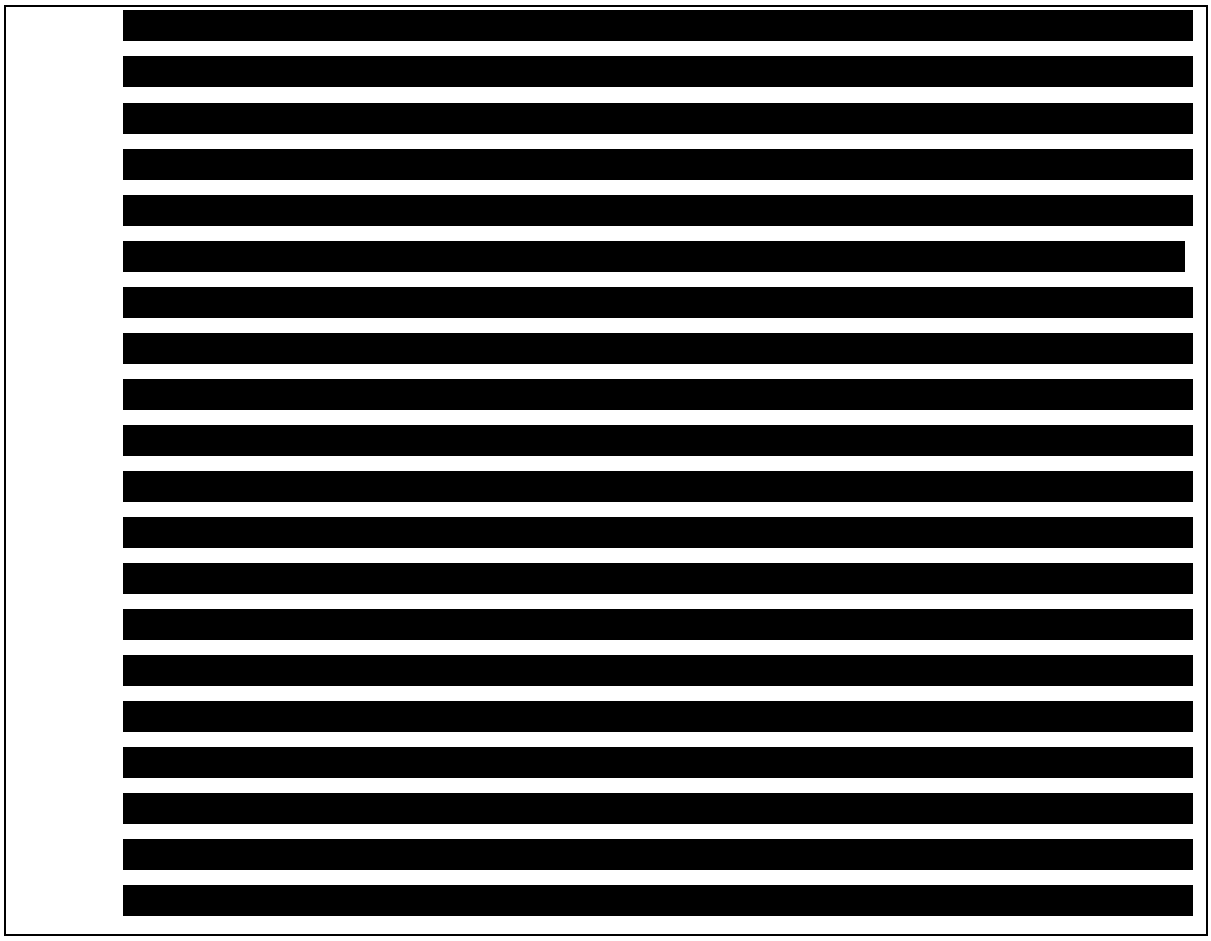
4.3.4.2.2 Population Characteristics

The inclusion and exclusion criteria for KEYNOTE-024 were not provided with the CS. However, the CSR

Table 47

Table 48 Table 49

Table 47 Inclusion criteria for KEYNOTE-024



[redacted]

1. [redacted]

Source: Adapted from KEYNOTE-024 CSR pages 56-58

Table 48 Adequate organ function laboratory values in KEYNOTE-024

[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]

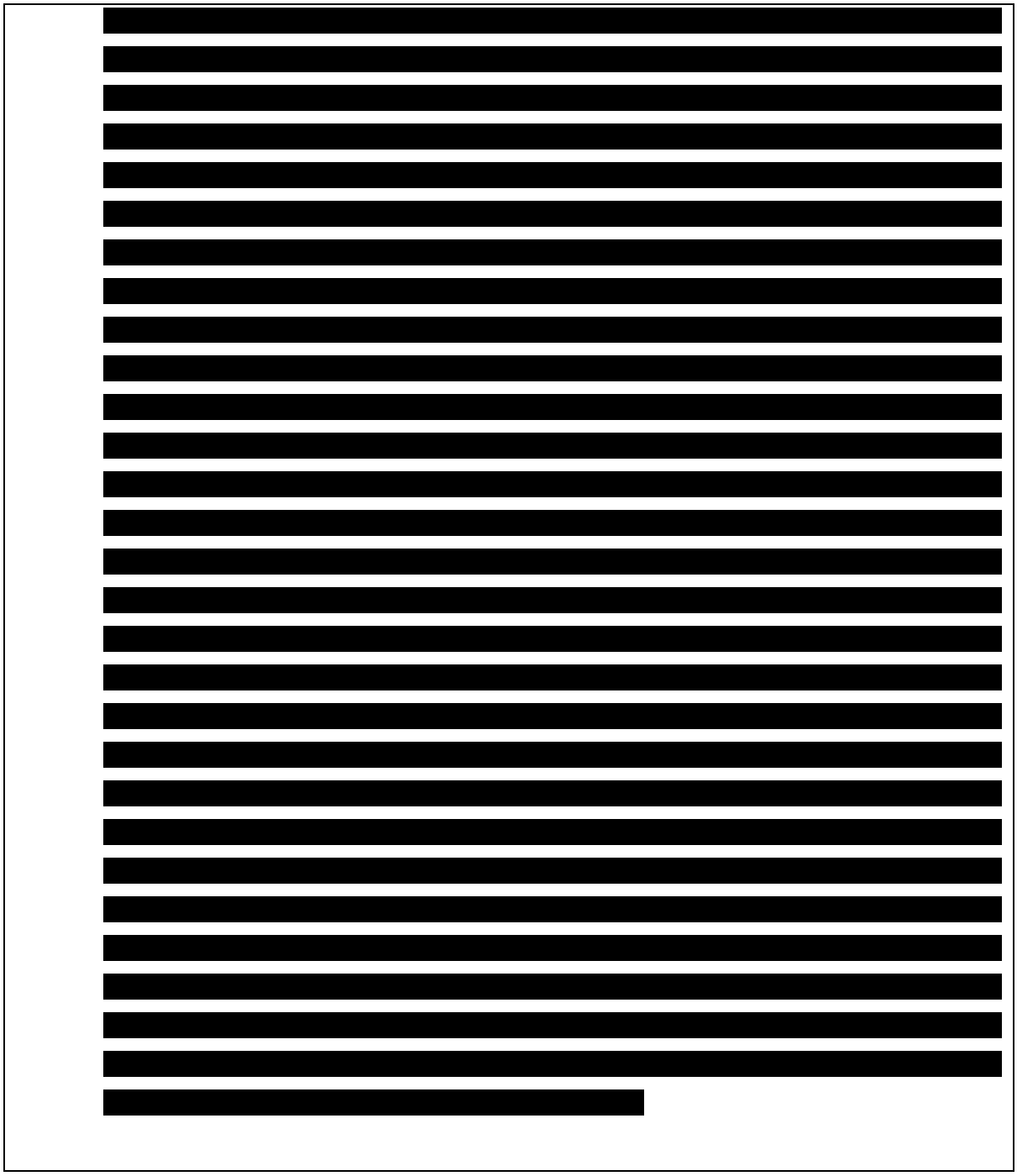
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GFR = glomerular filtration rate; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine. [a]Creatinine clearance was calculated per institutional standard. If no local guideline was available, Creatinine Clearance

was calculated using the Cockcroft-Gault Method: CrCl = ([140-age] * weight [kg] * [0.85 for females only])/(72 * creatinine).
Source: Adapted from KEYNOTE-024 CSR pages 56

[redacted]

Table 49 Exclusion criteria for KEYNOTE-024

1. [redacted]



Source: Adapted from KEYNOTE CSR pages 58-60

The ERG considered the baseline characteristic information for the full sample of KEYNOTE-024 within the CS to be relatively limited. The information provided is profiled in Table 50. Data were available for gender, age, race, smoking status, ECOG and disease stage.

Table 50 Baseline characteristics for KEYNOTE-024

	Pembrolizumab		**Control**	
	n	**%**	**N**	**%**
Patients in population	154	50.5	151	49.5
Gender				
Male	92	59.7	95	62.9
Female	62	40.3	56	37.1
Age (years)				
<65	NR	NR	NR	NR
≥65	NR	NR	NR	NR
Mean	63.9	NA	64.6	NA
SD	10.1	NA	9.5	NA
Median	NR	NR	NR	NR
IQR	NR	NR	NR	NR
Range	NR	NR	NR	NR
Race*				
Asian	25	16.2	21	13.9
Black or African American	2	1.3	2	1.3
White	125	81.2	126	83.4
Ethnicity				
Hispanic or Latino	NR	NR	NR	NR

	Pembrolizumab		Control	
	n	**%**	**N**	**%**
Not Hispanic or Latino	NR	NR	NR	NR
Not reported	NR	NR	NR	NR
Unknown	NR	NR	NR	NR
Region				
US	NR	NR	NR	NR
Ex US	NR	NR	NR	NR
Geographic region				
East-Asian	NR	NR	NR	NR
Non-East Asian	NR	NR	NR	NR
Smoking Status				
Never smoker	5	3.2	19	12.6
Former/current smoker	149	96.8	132	87.4
ECOG				
0	NR	NR	NR	NR
1	NR	NR	NR	NR
0 or 1	153	99.4	151	100
2	1	0.6	0	0
Missing	NR	NR	NR	NR
Histology				
Adenocarcinoma	NR	NR	NR	NR
NSCLC NOS	NR	NR	NR	NR
Other	NR	NR	NR	NR
Brain metastasis status at baseline				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Baseline tumour size (mm)	NR	NR	NR	NR
Patients with data	NR	NR	NR	NR
Mean	NR	NR	NR	NR
SD Median	NR	NR	NR	NR
Range	NR	NR	NR	NR
PD-L1 status				

	Pembrolizumab		Control	
	n	**%**	**N**	**%**
<1%	NR	NR	NR	NR
≥1%	NR	NR	NR	NR
Not evaluable	NR	NR	NR	NR
Platinum chemotherapy				
Cisplatin	NR	NR	NR	NR
Carboplatin	NR	NR	NR	NR
Prior radiation				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Prior thoracic radiation				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Prior adjuvant therapy				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Prior neoadjuvant therapy				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Disease stage				
Stage IIIb Stage IV	1 153	0.6 99.4	1 150	0.7 99.3

* Note that numbers may not add up to 100% of study sample; remaining numbers are assumed to be missing data.
Abbreviations: NA = Not applicable; NR = Not reported.
Source: Adapted from MSD CS Appendix Table 18 pages 91-93

Baseline population characteristics were comparable between the trial arms of KEYNOTE-024. However, it was noted that the proportion of former or current smokers was higher in the pembrolizumab arm than the control arm (97% vs 87%).

Limited reporting of baseline characteristics for KEYNOTE-024 prevents the ERG from making a full assessment of the extent to which baseline characteristics were comparable with those reported for KEYNOTE-189. However, based on the available information, the ERG did note some points of divergence. Firstly, the proportion of males in the control group was considerably higher in KEYNOTE-024 than KEYNOTE-189 (63% vs 53%). Secondly, the proportion of white participants was much higher in KEYNOTE-189 than KEYNOTE-024

(overall 94% vs 82%). Thirdly, while smoking status was comparable between the two studies for the control group, the proportion of former or current smokers in the pembrolizumab arm was considerably higher in KEYNOTE-024 than in the pembrolizumab combination arm of KEYNOTE-189 (97% vs 88%).

A total of 199 patients (102 in the platin and pemetrexed arm and 97 in the Pembrolizumab monotherapy arm) from KEYNOTE-024 with PD-L1 ≥50% were selected for inclusion in the ITC analysis. This inclusion represented a reduction of a third in the sample size from the original trial (32.5% platin and pemetrexed and 37.0% Pembrolizumab monotherapy). The population characteristics of these patients is reported Table 51, alongside the characteristics of patients with PD-L1 ≥50% selected from KEYNOTE-189 for comparison. Note that these characteristics are prior to population matching techniques were used. The ERG noted that there was an imbalance between treatment arms in KEYNOTE-024 in terms of the platinum therapy used (a higher proportion of patients in the platinum and pemetrexed arm received carboplatin therapy; [redacted]% vs. 52.6%), and smoking history (a lower proportion of patients in the platinum and pemetrexed arm were former/previous smokers). The arms appeared comparable for gender, age, ECOG status, disease stage, presence of brain metastasis, and geographic region. As compared with the KEYNOTE-189 sample of patients with PD-L1 ≥50%, patients in KEYNOTE-024 were more likely to be female, have a poorer ECOG performance score (ECOG 1 or 2), receive cisplatin, have a disease stage under M1B, and be based outside of Europe and North America. Patients with PD-L1 in both trials were comparable for age, smoking history, and presence of brain metastasis.

Table 51 Population Characteristics of Patients included in (B) ITC Analysis (prior to population matching: KEYNOTE024 and KEYNOTE-189 patients with PD-L1 ≥50%)

	Before Weighting			
	Study 189[a]		Study 024[b]	
	Pembrolizumab combination (N=132)	Control (N=70)	Pembrolizumab monotherapy (N=97)	Control (N=102)
Age (years)	64.2	64.4	63.5	64.2
Sex				
F	[redacted]	51.4	47.4	41.2
M	[redacted]	48.6	52.6	58.8
ECOG (%)				
0	[redacted]	34.8	34.0	35.3
1 or 2	[redacted]	65.2	66.0	64.7
Chemotherapy (%)				
Pemetrexed and Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed and Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]

Smoker status				
Former/Current Smoker	87.9	90.0	96.9	86.3
Never Smoker	12.1	10.0	[redacted]	13.7
Distance Metastatic Staging M1B (%)				
No	29.5	21.7	46.4	52.0
Yes	70.5	78.3	53.6	48.0
Brain Metastasis				
No	82.6	81.4	86.6	91.2
Yes	17.4	18.6	13.4	8.8
Region				
Europe	64.4	61.4	47.4	44.1
North America	21.2	28.6	19.6	16.7
Rest of World	14.4	10.0	33.0	39.2
a: Database cut-off Date: 08NOV2017; b: Database cut-off Date: 10JUL2017				

Source: MSD CS Appendix Table 26, p. 123

Following population-matching techniques were applied to the data, trial arms and characteristics between the two trials became more comparable (Table 52)

Table 52 Population Characteristics of Patients included in (B) ITC Analysis (following population matching: KEYNOTE024 and KEYNOTE-189 patients with PD-L1 ≥50%)

	After Weighting			
	Study 189[a]		Study 024[b]	
	Pembrolizumab combination (N=132)	Control (N=70)	Pembrolizumab monotherapy (N=97)	Control (N=102)
Age (years)	63.9	64.0	64.8	63.1
Sex				
F	44.3	48.7	45.9	47.3
M	55.7	51.3	54.1	52.7
ECOG (%)				
0	43.6	42.8	49.1	38.5
1 or 2	56.4	57.2	50.9	61.5
Chemotherapy (%)				
Pemetrexed and Carboplatin	68.2	73.3	68.9	67.8
Pemetrexed and Cisplatin	31.8	26.7	31.1	32.2
Smoker status				
Former/Current Smoker	89.5	87.2	88.0	88.4
Never Smoker	10.5	12.8	12.0	11.6
Distance Metastatic Staging M1B (%)				
No	40.1	33.2	38.6	39.7
Yes	59.9	66.8	61.4	60.3
Brain Metastase				

No	86.3	84.4	83.7	86.7
Yes	13.7	15.6	16.3	13.3
Region				
Europe	59.2	59.5	55.6	55.6
North America	18.0	23.5	17.1	19.5
Rest of World	22.8	17.1	27.3	24.9
a: Database cut-off Date: 08NOV2017; b: Database cut-off Date: 10JUL2017				

Source: MSD CS Appendix Table 27, p. 124

ERG comment:

- The ERG considered the inclusion criteria and population characteristics of KEYNOTE-024 to be consistent with the NICE scope. Limited information about baseline characteristics for the full sample of patients in KEYNOTE-024 was reported in the CS; however, details of important prognostic markers at baseline for patients with PD-L1 ≥50% were reported in further detail. Based on the characteristics reported, there was some variation in key markers between arms and between the two trials. However, as appropriate population matching techniques were used to control for key prognostic markers between and within studies, the ERG considered that this will have reduced the impact of any differences at baseline on the outcomes of the analyses.

4.3.4.2.3 Intervention Characteristics

No information regarding dosing, administration, or background care used in KEYNOTE-024 was reported in the CS. The ERG referred to the previous TA(NICE), 2018 #77} for pembrolizumab monotherapy in this patient population, and confirmed that dosing of pembrolizumab was consistent with the licence and with other trials included in the SLR. Following population-matching techniques, the proportion of patients receiving each platinum therapy was comparable between trial arms, and between KENYOTE-024 and KEYNOTE-189. Details of background care and length of treatment were not available for the patient cohort included in this analysis.

ERG comment:

- Dosing and administration of pembrolizumab was consistent with licencing indications and other trials in the SLR. There was insufficient information provided in the CS to evaluate the comparability of the length of treatment and background care administered to patients with PD-L1 ≥50% in KEYNOTE-024 and KEYNOTE-189.

4.3.4.2.4 Outcome Assessment

PFS and OS were the only outcomes for KEYNOTE-024 reported in the CS; details of outcome assessment used in KEYNOTE-024 are summarised in Table 53 below, alongside details of the methods used in KEYNOTE-189. Outcome definitions are matching between the two trials, and both employ time-to-event methodology to estimate treatment effects (HR), and use the ITT population datasets. For KEYNOTE-024, data is reported both for the full trial population (appendices p.94) and in a smaller sample of patients following weighting of outcome data to match sample population characteristics with the KEYNOTE-189 sample. HR analyses in the trials are adjusted for covariates, although the covariates used in the analyses differ between trials: KEYNOTE-024 effects are adjusted for geographic region (East Asia vs. non-East Asia) and ECOG status (0 or 1), and KEYNOTE-189 effects are adjusted for PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current). It's unclear whether the difference in the analysis used may affect the comparability of the estimates.

ERG comment:

- Methodology for the definition and assessment of OS and PFS appears to be comparable between KEYNOTE-024 and KEYNOTE-189; although the estimates from each trial are adjusted for different covariates, which may affect the comparability of the estimates.

Table 53 Trials Included in the ITC (B): Outcome Assessment

Endpoint		**KEYNOTE-024**	**KEYNOTE-189**
OS	Definition	Time from randomization to death from any cause	Time from randomization to death from any cause
	Time-point	NR	NR
	Statistical methods	Time-to-event (HR) stratified by geographic region (East Asia vs. non-East Asia) and ECOG status (0 vs. 1)	Time to event (HR); adjusted for PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)
	Analysis population	ITT	ITT

Endpoint		KEYNOTE-024	KEYNOTE-189
	Missing data approach	NR	Model based (censored at last known alive date)
PFS	Definition	Time from randomisation to first documented disease progression (RECIST 1.1) based on blinded independent central review (BICR) or death due to any cause, whichever	Time from randomisation to first documented disease progression (RECIST 1.1) based on blinded independent central review (BICR) or death due to any cause, whichever occurred first
	Time-point	NR	NR
	Statistical methods	Time to event (HR) stratified by geographic region (East Asia vs. non-East Asia) and ECOG status (0 vs. 1)	Time to event (HR) adjusted for PD-L1 (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)
	Analysis population	ITT	ITT
	Missing data approach	NR	Patients censored at last disease assessment, unless in the case of documented progression or death

Abbreviations: ECOG = Eastern Co-operative Oncology Group Performance score; HR = Hazard ratio; ITT = Intention to treat; NR = Not reported.
Source: MSD CS 40-42, 91-97; MSD CS Appendix D page 119

4.3.5 Quality assessment

4.3.5.1 (A) ITC: First line Interventions for Non-Squamous Metastatic NSCLC

Platinum + Pemetrexed vs. Platinum + Gemcitabine

Quality assessment of the five studies(16, 18, 20, 21, 31) that compare the relative clinical efficacy of platinum and gemcitabine therapy with platinum and pemetrexed therapy is reported in Table 54.

Generally the ERG agreed with the assessment reported by the company, although with a few exceptions. One study(18) was stated by the company to be at an unclear risk for blinding of patients and care providers; however the ERG notes that the trial is stated to be an open label trial, and therefore is at a high risk for this criteria. Another study(21) did not report blinding status and was assessed as being at unclear risk of blinding; however the ERG notes that the drug schedule used in the trial would prevent adequate blinding, and therefore the trial was assessed as being at high risk for this criteria also. The ERG considered the same study(21) to also be at high risk of reporting bias (assessed as unclear risk by the company), as the primary outcome for the trial was not reported.

Overall, all studies evaluating platinum and pemetrexed vs. platinum and gemcitabine were evaluated by the ERG as being at high risk for blinding, since all were open label or, in one case,(21) study information indicated some risk to adequate blinding. Furthermore, none of the included trials clearly stated whether outcome assessors were blinded to treatment allocation. The lack of adequate blinding by the studies means that subjective outcomes, such as HRQoL, are at a high risk of bias. However, this may have little impact on 'harder' outcomes, such as OS and disease progression, (when the latter is assessed using RECIST or objective criteria criteria). Aside from blinding, 3(18, 21, 31) of the 5 studies received one other high risk rating: one study(31) was evaluated as being at high risk due to a high number of patients missing from the analysis, and two studies(18, 21) were assessed as being at high risk due to reporting bias. All outcomes from these studies should therefore be considered at a high risk of bias. However, the ERG also noted that a high number of the criteria in the quality assessment across the studies were evaluated as being at 'unclear risk', due to insufficient information reported in the publications; with each study receiving at least one unclear rating.

ERG Comment:

- Overall, the ERG considered that the evidence base evaluating platinum and gemcitabine as compared to platinum and pemetrexed to be of low quality, and that the findings should therefore be interpreted with caution.

Table 54 Quality Assessment: Platinum + Pemetrexed vs. Platinum + Gemcitabine

Criteria	Company Assessment	ERG Comments
Gronberg et al. 2009		
Was randomisation carried out appropriately?	Low risk: Block randomisation	Low risk: The ERG agrees with the company assessment
Was the concealment of treatment allocation adequate?	Low risk: Telephone allocation	Low risk: The ERG agrees with the company assessment
Were care providers and patients blind to treatment allocation?	High risk: Open label study	High risk: The ERG agrees with the company assessment
Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication	Unclear risk: The ERG agrees with the company assessment
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data	Low risk: The ERG agrees with the company assessment, however notes that there is some minor discrepancies in patient flow, and it's not clear which patients were excluded from the analyses
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear risk: No information reported in the publication	Unclear risk: The ERG agrees with the company assessment
Other bias	Low risk: The study appears to be free of other sources of bias	Low risk: The ERG agrees with the company assessment
JMDB		
Was randomisation carried out appropriately?	Low risk: Method developed by Stuart and Pocock in 1975 (commony known as	Low risk: The ERG agrees with the company assessment

	minimization) was utilized in this trial.	
Was the concealment of treatment allocation adequate?	Unclear risk: The method of allocation concealment is not described.	Unclear risk: The ERG agrees with the company assessment
Were care providers and patients blind to treatment allocation?	Unclear risk: There is insufficient information to permit judgement of risk level.	High risk: The trial is stated to be open label in Novello et al. 2010(35)
Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication	High risk: The trial is stated to be open label in Novello et al. 2010(35)
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.	Low risk: The ERG agrees with the company assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	High risk: The study protocol is unavailable, but expected outcomes (OS, PFS, response) were reported. A pre-specified outcome in paper, time to treatment failure, was not reported as a part of trial results.	High risk: The ERG agrees with the company assessment
Other bias	Low risk: The study appears to be free of other sources of bias	Low risk: The ERG agrees with the company assessment
JMIL		
Was randomisation carried out appropriately?	Unclear risk: The sequence generation process is not described.	Unclear risk: The ERG agrees with the company assessment
Was the concealment of treatment allocation adequate?	Unclear risk: The method of allocation concealment is not described.	Unclear risk: The ERG agrees with the company assessment

Were care providers and patients blind to treatment allocation?	High risk: Open label study	High risk: The ERG agrees with the company assessment
Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication	Unclear risk: The publication(31) notes that the interim analysis was unblinded. Results were “not unblinded until the final analysis”; it’s unclear whether this implies results were unblinded prior to analysis.
Were there any unexpected imbalances in drop-outs between groups?	High risk: Reasons for exclusion from analyses and/or discontinuations were not specified. In particular, approximately 11% of GC treatment arm was not evaluated for response for unspecified reasons.	High risk: The ERG agrees with the company assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported	Low risk: The ERG agrees with the company assessment
Other bias	Low risk: The study appears to be free of other sources of bias	Low risk: The ERG agrees with the company assessment
Sun et al. 2015		
Was randomisation carried out appropriately?	Low risk: Block random assignment was used in the trial with block sizes of two or four.	Low risk: The ERG agrees with the company assessment
Was the concealment of treatment allocation adequate?	Unclear risk: The method of allocation concealment is not described.	Unclear risk: The ERG agrees with the company assessment

Were care providers and patients blind to treatment allocation?	High risk: Open label study	High risk: The ERG agrees with the company assessment
Were outcome assessors blind to treatment allocation?	Low risk: While the trial is specifically categorized as open-label, selected outcome (objective response rate) underwent independent review in order to mitigate potential bias associated with the unmasked study design. Additionally, radiological scans were reviewed in a blinded manner.	Low risk: The ERG agrees with the company assessment
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.	Low risk: The ERG agrees with the company assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.	Low risk: The ERG agrees with the company assessment
Other bias	Low risk: The study appears to be free of other sources of bias	Low risk: The ERG agrees with the company assessment
Zhang et al. 2013		
Was randomisation carried out appropriately?	Unclear risk: The sequence generation process is not described.	Unclear risk: Stratified randomisation, no further information
Was the concealment of treatment allocation adequate?	Low risk: Centralized stratified randomisation was used in this trial.	Low risk: The ERG agrees with the company assessment
Were care providers and patients blind to treatment allocation?	Unclear risk: There is insufficient information to permit judgement of risk level.	High risk: Drug schedule would prevent blinding

Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication	Unclear risk: The ERG agrees with the company assessment
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.	Low risk: The ERG agrees with the company assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.	High risk: the ERG noted that the primary outcome (progression-free survival) is not reported. The data are cited as unpublished.
Other bias	Low risk: The study appears to be free of other sources of bias	Low risk: The ERG agrees with the company assessment

Source: MSD Appendix D pages 126-133. Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

Platinum + Pemetrexed vs. Platinum + Vinorelbine

Quality assessment of the trial evaluating platinum and pemetrexed with platinum and vinorelbine is reported in Table 55 below.

Generally the ERG agreed with the company's assessment of the trial; although blinding of care providers and patients was considered to be at high risk, as the treatment schedule used in the study would prevent adequate blinding. Based on the information provided by the trial authors, the ERG agreed with the company that it was not possible to determine whether allocation concealment and outcome assessor blinding were conducted appropriately, and therefore the trial is at unclear risk for these criteria. All other criteria were assessed as being at low risk.

ERG comment:

- Due to the risk of blinding, and unclear risk associated with allocation concealment and outcome assessment, the ERG considered that the findings of the trial should be interpreted with caution.

Table 55 Quality Assessment: Platinum + Pemetrexed vs. Platinum + Vinorelbine

Criteria	Company Assessment	ERG Comments
NAVOtrial01		
Was randomisation carried out appropriately?	Low risk: Minimization procedure was used in this trial.	Low risk: The ERG agrees with the company assessment
Was the concealment of treatment allocation adequate?	Unclear risk: The method of allocation concealment is not described.	Unclear risk: The ERG agrees with the company assessment
Were care providers and patients blind to treatment allocation?	Unclear risk: Information pertaining blinding of participants and personnel was not described in this trial.	High risk: treatment schedule prevents blinding
Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication	Unclear risk: The ERG agrees with the company assessment
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.	Low risk: The ERG agrees with the company assessment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.	Low risk: The ERG agrees with the company assessment
Other bias	Low risk: The study appears to be free of other sources of bias	Low risk: The ERG agrees with the company assessment

Source: MSD CS Appendix p. 126-133. Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

Other comparisons

The quality assessment of trials evaluating other comparisons, as reported in the CS, is reported in Table 56. Within the scope of this report, it was not possible for the ERG to re-evaluate the company's quality assessment for these trials.

Only one(23) of the other trials included in the SLR was double-blind; this trial evaluated the clinical efficacy of adding bevacizumab to platinum and paclitaxel therapy. All other trials were either open label (and therefore assessed as being at high risk of blinding of patients and care providers) or did not report blinding (and were assessed as being at unclear risk for blinding). Subjective outcomes (such as HRQoL) reported by these trials should therefore be considered at a high risk of bias.

Aside from patient and care provider blinding, only one other trial(27) received a high risk rating (for missing data). However, 7 out of the 8 trials received at least one unclear rating, due to insufficient information reported by the trial publications. These were generally concerning randomisation (4 studies(25, 26, 28, 30)), allocation concealment (5 studies(24, 26-28, 30)), and blinding of outcome assessors (5 studies(24, 26, 27, 29, 30)).

ERG comment:

- Overall, the evidence base for other comparisons identified by the SLR was of limited quality. Only one trial(23) evaluating the clinical efficacy of incorporating bevacizumab into platinum and paclitaxel therapy was considered to be at low risk of bias. All other studies are considered to be at high or unclear risk of bias, and subjective outcomes particularly should be interpreted with caution.

Table 56 Quality Assessment: Other Comparisons

Criteria	Company Assessment
Platinum + Pac + Bev vs. Platinum + Pemetrexed	
ERACLE	
Was randomisation carried out appropriately?	Low risk: Randomisation was performed using permuted blocks with variable size according to the Moss-Oakford algorithm
Was the concealment of treatment allocation adequate?	Unclear risk: There is insufficient information on allocation concealment to permit judgement on risk level.
Were care providers and patients blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication

Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication
Were there any unexpected imbalances in drop-outs between groups?	High risk: While outcomes availability during randomised phase was balanced, sizable discrepancies (>20%) were seen in numbers of total subjects and available outcomes between two treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.
Other bias	Low risk: The study appears to be free of other sources of bias
PRONOUNCE	
Was randomisation carried out appropriately?	Unclear risk: The sequence generation process is not described.
Was the concealment of treatment allocation adequate?	Unclear risk: The method of allocation concealment is not described.
Were care providers and patients blind to treatment allocation?	High risk: Open label
Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.
Is there any evidence to suggest that the authors measured more	Low risk: The study protocol is unavailable, but expected outcomes were reported.

outcomes than they reported?	
Other bias	Low risk: The study appears to be free of other sources of bias
Platinum + Pac vs. Platinum + Pac + Bev	
BEYOND	
Was randomisation carried out appropriately?	Unclear risk: While the study was categorized as randomised, there is insufficient information on sequence generation to permit judgement on risk of bias.
Was the concealment of treatment allocation adequate?	Low risk: Interactive voice/web response system was used for randomisation.
Were care providers and patients blind to treatment allocation?	Low risk: Double-blind study
Were outcome assessors blind to treatment allocation?	Unclear risk: While the trial is categorized as double-blinded, there is an insufficient amount of information permitting judgement on the blinding status of outcomes assessment.
Were there any unexpected imbalances in drop-outs between groups?	Low risk: The outcomes data for this trial appeared to be complete.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported
Other bias	Low risk: The study appears to be free of other sources of bias
ECOG 4599	
Was randomisation carried out appropriately?	Low risk: Randomisation was performed using permuted blocks.

Was the concealment of treatment allocation adequate?	Unclear risk: There is insufficient information on allocation concealment to permit judgement on risk of bias.
Were care providers and patients blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication
Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.
Other bias	Low risk: The study appears to be free of other sources of bias
Johnson et al. 2004	
Was randomisation carried out appropriately?	Unclear risk: The sequence generation process is not described.
Was the concealment of treatment allocation adequate?	Unclear risk: The method of allocation concealment is not described.
Were care providers and patients blind to treatment allocation?	Unclear risk: Information pertaining blinding of participants and personnel was not described in this trial.
Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication

Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.
Other bias	Low risk: The study appears to be free of other sources of bias
JO19907	
Was randomisation carried out appropriately?	Unclear risk: The sequence generation process is not described.
Was the concealment of treatment allocation adequate?	Low risk: Centralized stratified randomisation
Were care providers and patients blind to treatment allocation?	High risk: Open label study
Were outcome assessors blind to treatment allocation?	Low risk: Outcomes assessment process for this trial is specifically described as blinded.
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.
Other bias	Low risk: The study appears to be free of other sources of bias

Platinum + Doc	
Rodrigues-Pereira 2011	
Was randomisation carried out appropriately?	Low risk: Random sequence was generated by computer in this trial.
Was the concealment of treatment allocation adequate?	Low risk: Interactive voice response system was used for randomisation.
Were care providers and patients blind to treatment allocation?	High risk: Open label study
Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.
Other bias	Low risk: The study appears to be free of other sources of bias
TRAIL	
Was randomisation carried out appropriately?	Unclear risk: The sequence generation process is not described.
Was the concealment of treatment allocation adequate?	Unclear risk: The method of allocation concealment is not described.
Were care providers and patients blind to treatment allocation?	High risk: Open label study

Were outcome assessors blind to treatment allocation?	Unclear risk: Blinding or lack thereof was not addressed in this publication
Were there any unexpected imbalances in drop-outs between groups?	Low risk: Number of discontinued patients and reasons were specified and accounted for.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk: The study protocol is unavailable, but expected outcomes were reported.
Other bias	Low risk: The study appears to be free of other sources of bias

Source: MSD CS Appendix p. 126-133. Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

4.3.5.2 (B) ITC: First line Interventions for Non-Squamous Metastatic NSCLC (PD-L1 ≥50%)

Quality assessment of KEYNOTE-024 was not reported in the CS; it is unclear why this was not reported. KEYNOTE-024 is a randomised, open label Phase III trial of pembrolizumab monotherapy in comparison with various platinum-based chemotherapy treatment options. As chemotherapy treatment options in the trial were broader than those used in the control arm of KEYNOTE-189, the company select a sub-population of patients who receive comparable chemotherapy options from KEYNOTE-024 for inclusion in the ITC. While this break in the randomisation paradigm creates a risk to the integrity of comparability between trial arms, the company conduct propensity score matching analysis to ensure balance between trial arms and between key prognostic risk factors.

ERG comment:

- As full quality assessment of KEYNOTE-024 was not reported in the CS, it was not possible for the ERG to full evaluate the quality of the evidence from KEYNOTE-024. Based on the information provided, a possible source of bias is the selection of patients post-randomisation. The use of population matching techniques may have

ensured sufficient comparability in the trial arms in the key prognostic factors; although there may be additional sources of imbalance (e.g. study design features, intervention characteristics) that are unclear from the CS due to insufficient information having been provided.

4.3.6 Clinical effectiveness results for comparators to pembrolizumab combination Therapy

4.3.6.1 (A) ITC: First line Interventions for Non-Squamous Metastatic NSCLC

4.3.6.1.1 Clinical Efficacy

The clinical efficacy of comparators to pembrolizumab combination therapy are reported in the CS appendices (p. 94-95). The company only reported outcomes for OS and PFS: no data was reported for the remaining clinical efficacy outcomes specified in the NICE scope (ORR, DoR). The company provided no comment on the clinical efficacy of these interventions as reported by the individual trials (note that the company does discuss the clinical efficacy of these therapies in comparison with pembrolizumab combination therapy on the basis of the ITC analysis: Section 4.4).

Platinum + Pemetrexed vs. Platinum + Gemcitabine

Clinical efficacy outcomes for studies comparing platinum + pemetrexed vs. platinum + gemcitabine are reported in Table 57.

All 5 studies reported median OS and OS HR. Follow-up of OS was not reported in the CS. Median OS for patients receiving platinum and pemetrexed therapy ranged widely between 7.0 and 27.3 months (range: 5.4 – 22.7); note that range in OS was not reported for 1 study(20) with the longest median survival. Median OS for patients receiving platinum and gemcitabine ranged between 7.8 and 23.7 months (range: 6.0 – 20.5; again, note that range was not reported for 1 study(20) with the longest median survival). The two studies with the poorest median survival were the oldest studies; published in 2008(18) and 2009(16). As compared with platinum and gemcitabine therapy, HRs for OS following platinum and pemetrexed therapy ranged between 0.88 and 1.00 (range of 95%Cis 0.64 – 1.35). No study reported a statistically significant difference between the two therapies.

Three studies reported median PFS and PFS HR. Median PFS for patients receiving platinum and pemetrexed therapy ranged between 4.8 and 6.0 months (range of 95% Cis: 4.6 – 8.1). As compared with platinum and gemcitabine therapy, HRs for PFS following platinum and pemetrexed therapy ranged between 0.75 – 1.05 (range of 95% Cis: 0.59 – 1.36). Only one study(20) reported a statistically significant difference between the therapies; reporting a 25% reduction in the risk of progression or death for patients receiving cisplatin

and pemetrexed compared to cisplatin and gemcitabine. However, the upper 95% confidence interval approached the line of null effect (0.95), and this finding was not replicated in the remaining 2 studies(18, 31).

ERG comment:

- Overall, across the studies there was no conclusive evidence that treatment with platinum and gemcitabine was superior to treatment with platinum and pemetrexed for OS and PFS.

Table 57 Clinical Efficacy: Platinum + Pemetrexed vs. Platinum + Gemcitabine

Trial ID	Treatment	N	Median OS (95% CI)	OS HR (95% CI)	Median PFS (95% CI)	PFS HR (95% CI)
Gronberg et al. 2009	pemetrexed +carboplatin	127	7.0 (5.4-10.1)	0.96 (0.75, 1.23)	--	--
	gemcitabine+carboplatin	121	7.8 (6.0-9.4)	--	--	--
JMDB	cisplatin+pemetrexed	862	10.3 (9.8-11.2)	0.94 (0.84, 1.05)	4.8 (4.6-5.3)	1.04 (0.94, 1.15)
	cisplatin+gemcitabine	863	10.3 (9.6-10.9)	--	5.1 (4.6-5.5)	--
JMIL	pemetrexed+cisplatin	126	17.5 (13.3-22.7)	1.00 (0.74, 1.33)	5.9 (5.0-6.5)	1.05 (0.81, 1.36)
	gemcitabine+cisplatin	130	15.5 (13.7-19.3)	--	5.8 (5.6-6.4)	--
Sun 2015	cisplatin + pemetrexed	160	27.3	0.88 (0.64, 1.23)	6.0 (3.4-8.1)	0.75 (0.59, 0.95)

Trial ID	Treatment	N	Median OS (95% CI)	OS HR (95% CI)	Median PFS (95% CI)	PFS HR (95% CI)
	cisplatin + gemcitabine	155	23.7	--	5.3 (2.5-6.7)	--
Zhang 2013	cisplatin + pemetrexed	105	16.7 (13.0-20.4)	0.95 (0.68, 1.35)	--	--
	cisplatin + gemcitabine	100	16.7 (13.6-20.5)	--	--	--

Abbreviations: CI = Confidence interval; HR = Hazard ratio; OS = Overall survival; PFS = Progression-free survival.

Source: MSD CS Appendix D pages 94-95

Platinum + Pemetrexed vs. Platinum + Vinorelbine

Clinical efficacy outcomes reported by the company for one study(22) comparing platinum and pemetrexed with platinum and vinorelbine are presented in Table 58. Median overall survival in the trial was comparable between the two arms: 10.8 months for patients receiving cisplatin and pemetrexed therapy (range 7.0 – 16.4) and 10.2 months for patients receiving cisplatin and vinorelbine (range 7.8 – 11.9). There was no statistically significant difference between the two therapies in OS according to the estimated HR. Median PFS was 4.3 months for patients receiving cisplatin and pemetrexed therapy (range 3.8 – 5.6) and 4.2 months for patients receiving cisplatin and vinorelbine (range 3.6 – 4.7). The study reported a numerically lower risk of progression or death for patients receiving cisplatin and pemetrexed than for patients receiving cisplatin and vinorelbine (HR 0.86); however the 95% CIs around the effect was wide, and the effect was not statistically significant (95% CIs 0.59 – 1.26).

ERG comment:

- Overall, one trial included in the SLR did not demonstrate conclusive evidence that treatment with platinum and vinorelbine was superior to platinum and pemetrexed for OS and PFS.

Table 58 Clinical Efficacy: Platinum + Pemetrexed vs. Platinum + Vinorelbine

Trial ID	Treatment	N	Median OS (95% CI)	OS HR (95% CI)	Median PFS (95% CI)	PFS HR (95% CI)
NAVOtrial 01	pemetrexed+cisplatin	51	10.8 (7.0-16.4)	1.00 (0.65, 1.54)	4.3 (3.8-5.6)	0.86 (0.59, 1.26)
	vinorelbine+cisplatin	100	10.2 (7.8-11.9)	--	4.2 (3.6-4.7)	--

Abbreviations: CI = Confidence interval; HR = Hazard ratio; OS = Overall survival; PFS = Progression-free survival.

Source: MSD CS Appendix D page 94

Other Comparisons

Evidence for the clinical efficacy of other comparators to pembrolizumab combination therapy are reported in Table 59. Two studies reported that there was no statistically significant difference in OS and PFS between platinum and docetaxel therapy and platinum and pemetrexed therapy.(29, 30) Two studies also reported no statistically significant difference in OS and PFS between platinum, paclitaxel and bevacizumab therapy and platinum and pemetrexed therapy. (27, 28) Four studies compared platinum and paclitaxel therapy with platinum, paclitaxel and bevacizumab therapy. Of these, two studies reported OS HR; one of these studies reported that the addition of bevacizumab to platinum and paclitaxel therapy statistically significantly reduced the risk of mortality(24), while the other study reported no statistically significant difference. (25) All three studies that evaluated PFS HR reported that the addition of bevacizumab to platinum and paclitaxel therapy statistically significantly reduced the risk of progression or death.

ERG Comment:

- The ERG considered that there was no evidence that treatment with platinum and docetaxel, or with platinum, paclitaxel and bevacizumab, was superior to treatment with platinum and pemetrexed therapy. There was some evidence that the addition of bevacizumab increased the efficacy of platinum and paclitaxel therapy for OS and PFS.

Table 59 Clinical Efficacy: Other Comparisons

Trial ID	Treatment	N	Median OS (95% CI)	OS HR (95% CI)	Median PFS (95% CI)	PFS HR (95% CI)
BEYOND	bevacizumab+paclitaxel+carboplatin	138	24.3	--	9.2 (8.4-10.7)	0.40 (0.29, 0.54)
	paclitaxel+carboplatin	138	17.7	--	6.5 (5.8-7.1)	--
ECOG 4599	carboplatin + paclitaxel + bevacizumab	417	12.3	0.79 (0.67, 0.92)	6.2	0.66 (0.57, 0.77)
	carboplatin + paclitaxel	433	10.3	--	4.5	--
ERACLE	cisplatin+pemetrexed	60	14.0 (10.5-20.3)	0.93 (0.60, 1.42)	8.1 (7.5-10.8)	0.79 (0.53, 1.17)
	carboplatin+paclitaxel+bevacizumab	58	14.4 (10.9-19.1)	1.08 (0.70, 1.67)	8.3 (6.1-11.5)	--
JO19907	carboplatin+paclitaxel	58	23.4 (17.4-28.5)	--	5.9 (4.2-6.5)	--
	carboplatin+paclitaxel+bevacizumab	117	22.8 (18.1-28.2)	0.99 (0.65, 1.50)	6.9 (6.1-8.3)	0.61 (0.42, 0.89)
Johnson 2004	carboplatin+paclitaxel	32	14.9	--	4.2	--
	carboplatin+paclitaxel (7.5 mg/kg)	32	11.6	--	4.3	--
PRONOUNCE	platinum + pemetrexed	182	10.5 (9.3-12.0)	1.07 (0.83, 1.36)	4.4 (4.2-5.3)	1.06 (0.84, 1.35)

Trial ID	Treatment	N	Median OS (95% CI)	OS HR (95% CI)	Median PFS (95% CI)	PFS HR (95% CI)
	carboplatin + paclitaxel + bevacizumab	179	11.7 (9.2-14.3)	0.93 (0.74, 1.20)	5.5 (5.0-6.0)	0.94 (0.74, 1.19)
Rodrigues-Pereira 2011	pemetrexed+carboplatin	106	14.9 (12.2-19.0)	--	5.8 (4.8-6.4)	--
	docetaxel+carboplatin	105	14.7 (10.8-19.8)	0.99 (0.70, 1.39)	6.0 (4.8-6.6)	1.04 (0.78, 1.39)
TRAIL	cisplatin + pemetrexed	77	11.7 (8.6-14.8)	--	4.7 (4.4-5.0)	--
	cisplatin + docetaxel	71	13.3 (8.1-18.5)	--	4.4 (3.7-5.1)	--

Source: MSD CS Appendix D pages 93-95

4.3.6.1.3 Patient-Reported Outcomes/Health-Related Quality of Life

No evidence for PROs or HRQoL was reported in the CS for other comparator therapies to pembrolizumab combination therapy. It is unclear to the ERG why this evidence was not presented, given that these outcomes were specified in the NICE scope as of importance. The ERG were therefore not able to consider the comparative effect of pembrolizumab combination therapy and other comparators for these outcomes.

ERG Comment:

- As this evidence was not provided in the CS, the ERG were unable to evaluate the effectiveness of pembrolizumab combination therapy for PROs and HRQoL relative to other comparator therapies.

4.3.6.1.4 Safety

No safety evidence was reported in the CS for other comparator therapies to pembrolizumab combination therapy. Again, it is unclear to the ERG why this evidence was not presented, as safety evidence is also specified in the NICE scope as of importance. Without this evidence, it is not possible, on the basis of the CS, to evaluate the comparative safety of pembrolizumab combination therapy with other available treatments.

ERG Comment:

- As this evidence was not provided in the CS, the ERG were unable to evaluate the safety of pembrolizumab combination therapy relative to other comparator therapies.

4.3.6.1.5 Meta-analysis

No standard meta-analysis was conducted of the individual trials evaluating comparators to pembrolizumab combination therapy; no rationale is presented in the CS for why this was not conducted. Given that all trials identified by the SLR for other comparators were included in the ITC for OS and PFS, the ERG agreed that this was sufficient for evaluating the relative efficacy of interventions for these outcomes. However, as the company did not conduct ITC analyses for other outcomes specified in the NICE scope (stated, for HRQoL and safety, to be due to between-trial heterogeneity in outcome reporting), the ERG believed that standard meta-analysis, where feasible, should have been presented for these outcomes for comparators to pembrolizumab combination therapy.

ERG Comment:

- It is unclear why standard meta-analysis of outcome data from these trials was not presented in the CS, particularly for those outcomes that were not evaluated using ITC analysis (where feasible).

4.3.6.2 (B) ITC: First line Interventions for Non-Squamous Metastatic NSCLC (PD-L1 ≥50%)

4.3.6.2.1 Clinical Efficacy

The clinical efficacy of pembrolizumab monotherapy as evaluated in KEYNOTE-024 is reported in the CS appendices (p.94).(8) Clinical efficacy data from KEYNOTE-024 following adjustment for population matching with KEYNOTE-189 is further reported in the main submission (p.94). Both sets of data are reported in Table 60 below. As with the other comparators in this submission, only clinical efficacy data for OS and PFS are reported; no evidence is reported for ORR or DoR.

Prior to matching, median overall survival in KEYNOTE-024(10) was reported to be 14.2 months for patients receiving platinum and pemetrexed therapy (range 9.8 – 19.0) and 30.0 months for patients receiving pembrolizumab (range 18.3 – not reached). Patients receiving pembrolizumab monotherapy demonstrated a statistically significant reduced risk of death compared to patients receiving platinum and pemetrexed therapy. Median PFS was also greater for patients receiving pembrolizumab monotherapy than those receiving platinum and pemetrexed therapy (8.5 and 6.1 months, respectively). The reduced risk of progression or death amongst patients receiving pembrolizumab monotherapy relative to platinum and pemetrexed therapy was shown to be statistically significant.

Estimated outcomes following population-matching were similar to those in the original analysis, although median survival was not reached in the pembrolizumab monotherapy arm, and overall survival was also slightly longer for patients receiving platinum and pemetrexed (median [redacted] vs. [redacted] months). There was no change in the hazard ratio effect between pembrolizumab monotherapy and platinum and pemetrexed, and the effect remained statistically significant, although 95% Cis were broader. Median PFS and the relative effect of pembrolizumab monotherapy for PFS compared to platinum and pemetrexed was also similar to the original estimate before population matching.

Compared to the full sample, median OS from the sub-population of patients with PD-L1 ≥50% in KEYNOTE-189 receiving platinum and pemetrexed (following population matching) was slightly shorter ([redacted] vs. 11.3 months), although the number of deaths was comparable ([redacted] vs. [redacted] Mortality was lower for patients receiving pembrolizumab combination therapy in the sub-population of patients with PD-L1 ≥50% than in the full sample ([redacted] % vs. [redacted] %). As with the full sample, median survival was not reached for patients receiving Pembrolizumab Combination therapy. With regards to PFS, the rate of PFS events for patients receiving pembrolizumab combination therapy was slightly lower in the sub-population than in the full sample (51.5% vs. 59.5%), although the number of events in the

platinum and pemetrexed arm remained comparable (80.0% vs. 80.6%). Median PFS for patients receiving pembrolizumab combination therapy was also slightly longer in the sub-population than in the full sample (9.4 vs 8.8 months), with no change in the median PFS of patients receiving platinum and pemetrexed (4.7 vs. 4.9 months).

Overall, based on population-adjusted data in samples from KEYNOTE-024 and KEYNOTE-189, the data indicates that the relative effect of pembrolizumab as compared to platinum and pemetrexed is more pronounced for both OS and PFS when administered as part of combination therapy than when delivered as monotherapy. pembrolizumab combination therapy was associated with a 58% and 62% reduction in the risk of OS and PFS events, respectively, compared to 36% and 45% for pembrolizumab monotherapy.

Table 60 Clinical Efficacy: Pembrolizumab Monotherapy

Trial ID	**Treatment**	**N**	**Median OS (95% CI)**	**OS Events**	**OS HR* (95% CI)**	**Median PFS (95% CI)**	**PFS Events**	**PFS HR* (95% CI)**
KEYNOTE-024	Pembrolizumab	154	30.0 (18.3 – not defined)	NR	0.63 (0.47-0.86)	8.5 (6.2-14.6)	NR	0.52 (0.42-0.69)
	Platinum + pemetrexed	151	14.2 (9.8-19.0)	NR	--	6.1 (4.2-6.2)	NR	--
Following adjustment for population weighting								
KEYNOTE-024	Pembrolizumab	97	Not reached (16.6 – not defined)	46 (47.4%)	0.64 (0.41 – 0.98)	8.1 (5.4 – 14.4)	58 (59.8%)	0.55 (0.38 – 0.81)
	Platinum + pemetrexed	102	16.7 (11.4 – 21.5)	62 (60.8%)		6.2 (5.3 – 6.4)	83 (81.4%)	--

Trial ID	Treatment	N	Median OS (95% CI)	OS Events	OS HR* (95% CI)	Median PFS (95% CI)	PFS Events	PFS HR* (95% CI)
KEYNOTE-189	Pembrolizumab Combination therapy	132	Not reached (NR)	34 (25.8%)	0.42 (0.25 – 0.69)	9.4 (9.0 – 13.8)	68 (51.5%)	0.38 – 0.26 – 0.57)
	Platinum + pemetrexed	70	10.0 (7.5 – not defined)	36 (51.4%)		4.7 (3.1 – 6.0)	56 (80.0%)	

*Based on weighted Cox regression model with treatment as covariate stratified by platinum chemotherapy (cisplatin vs. carboplatin), smoking status (never vs. former/current) for KEYNOTE-189, and stratified by geographic region (East Asia vs. non-East Asia) and ECOG (0 vs. 1) for KEYNOTE-024.

Abbreviations: NR = Not reported

Source: MSD CS Appendix D p.94

4.3.6.2.2 Patient-Reported Outcomes/Health-Related Quality of Life

No evidence for PROs or HRQoL was reported in the CS for pembrolizumab monotherapy. As with other comparators, it is unclear to the ERG why this evidence was not presented, given that these outcomes were specified in the NICE scope. The ERG were therefore not able to consider the comparative effects of pembrolizumab combination therapy and pembrolizumab monotherapy for these outcomes.

ERG comment:

- As this evidence was not provided in the CS, the ERG were unable to evaluate the relative effectiveness of pembrolizumab monotherapy and combination therapy for PROs and HRQoL outcomes.

4.3.6.2.3 Safety

No safety evidence was presented for pembrolizumab monotherapy. The ERG were therefore not able to compare the safety of pembrolizumab combination therapy and pembrolizumab monotherapy.

ERG comment:

- As this evidence was not provided in the CS, the ERG were unable to evaluate the relative safety of pembrolizumab monotherapy and combination therapy.

4.3.6.2.4 Meta-analysis

Standard meta-analysis is not applicable for this evidence, given that only one study evaluating pembrolizumab monotherapy was identified by the SLR.

4.3.7 Applicability to clinical practice

As discussed previously, studies evaluating platinum and pemetrexed, platinum and gemcitabine, platinum and vinorelbine, and pembrolizumab monotherapy were considered to be most relevant to UK clinical practice, as these interventions are most commonly used for this patient group and were identified as the primary comparators. Of the trials evaluating these interventions, no studies were reported to be based in the UK, although KEYNOTE-024 included some centres (6%) in the UK. One international study(18) included centres in Europe, and one study was based in Norway(16). Other studies in these comparisons were based in Asia(20, 21, 31) or was not reported(22). Clinical advisors to the ERG suggested that studies based in Asia may have limited applicability to practice in the UK. Centres in countries with highly different healthcare systems (e.g. the US) may also have less applicability to UK practice, and therefore evidence from this evidence base should be interpreted with caution. The ERG was advised that one trial including centres in Europe(18),

which compared platinum and gemcitabine with platinum and pemetrexed, was pivotal in informing the use of chemotherapy in this patient group in the UK. This trial was therefore highlighted as being more representative of UK care compared to other trials. Across the included studies, clinical advisors to the ERG noted that the populations included in studies were younger and fitter than would be seen in clinical practice, with some studies excluding patients with ECOG score 2 and over the age of 75 years. Clinical advisers to the ERG considered that around 20% of relevant patients in routine clinical practice have ECOG score 2, while 11 out of 17 studies (including all three KEYNOTE studies) included ≤1% of participants with this poorer performance status (and two studies did not report ECOG). It was also noted that PD-L1 data were not available for many trials, as routine testing of PD-L1 will only have begun in research and clinical practice following the use of other PD-L1 targeted-therapies (in the UK, this was approximately 2016). Furthermore, testing for EGFR and ALK biomarkers will not have been routine practice for many of the comparator trials, and therefore populations for these trials will include subpopulations of patients with these biomarkers who are excluded from the more recent trials (including KEYNOTE-189 and KEYNOTE-021G). It is unclear how these changes may have impacted on the outcome data from the included trials, and how applicable earlier studies may be to the target patient population and the current UK treatment pathway.

ERG Comment:

- Overall, the ERG considered that there is likely to be some variation between the treatment effects reported in the included studies and what would be expected in clinical practice in the UK.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 (A) ITC: First line Interventions for Metastatic Non-Squamous Metastatic NSCLC

4.4.1.1 Specification of Evidence Network

All seventeen trials identified by the SLR were included in an NMA to evaluate the comparative efficacy of interventions for OS; 13 of these trials(9, 13, 18, 20, 22-25, 27-31) also reported PFS, and were included in a second NMA to evaluate the efficacy of interventions for PFS. The evidence networks as stated by the company are shown in Figure 5for OS and in Figure 6 for PFS.

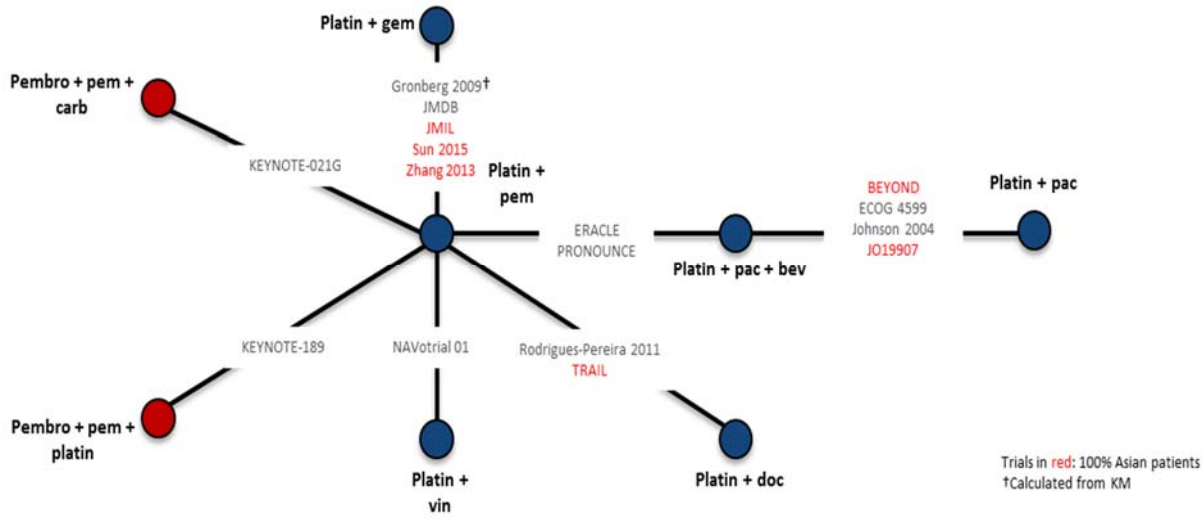
Notable aspects of the NMA are:

(i) Cisplatin, carboplatin and platinum are treated identically as ‘platinum’ therapy.

(ii) KEYNOTE-021G (Pembrolizumab + pemet + carboplatin) and KEYNOTE-189 trials (Pembrolizumab + pemet + carboplatin/cisplatin) are treated as separate nodes in the network. The company's reasoning is consistent with the company's rationale for not pooling the studies in standard meta-analysis (see discussion in Sections 4.1.5 and 4.2.5), and are discussed further in this section.

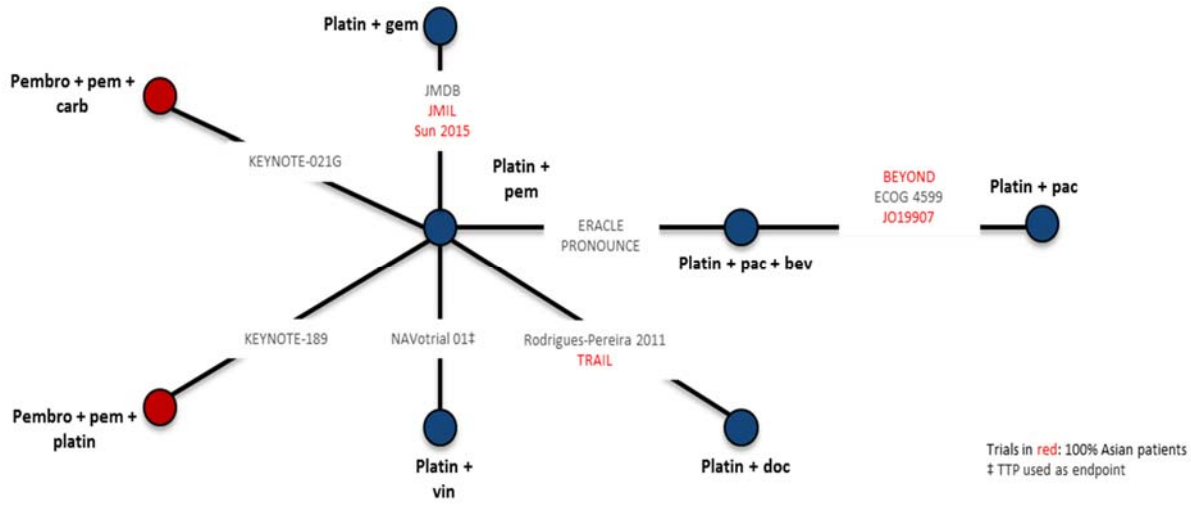
(iii) KEYNOTE-024 trial is not included in the ITC(A) but is rather included in a separate IPD analysis. [(B) ITC: First line Interventions for Metastatic Non-Squamous Metastatic NSCLC (PD-L1 ≥50%)]. The company's reasoning is detailed in Section 4.4.2 herein.

Figure 5 Network of evidence presented in CS for overall survival



Source: MSD CS Document B Figure 26 page 83

Figure 6 Network of evidence presented in CS for progression-free survival



Source: MSD CS Document B Figure 27 page 88

The justification for treating KEYNOTE-189 (Pembrolizumab + pemet + carboplatin/cisplatin) and KEYNOTE-021G (Pembrolizumab + pemet + carboplatin) as separate nodes were clarified by the company (14/8/18) as follows:

"When developing the NMA networks, it was not considered appropriate to merge the Pembro + pem + platin (KEYNOTE-189) and the Pembro + pem + carboplatin (KEYNOTE-021G) data due to differences in study design and patient demographics between the studies (see the main submission Section B.2.8 Meta-analysis; p82 for further details)."

These differences are summarised in Table 61.

Table 61 Differences noted in CS between KEYNOTE-189 and KEYNOTE-021G

	KEYNOTE-189	**KEYNOTE-021(G)**
Concealment	Double blind	Open label
Phase	Phase III	Phase II
Centres	7 centres	NR
Region	UK	USA and Japan
Baseline hazard	"performed in line with and at the lower end of the range of historical standards"	"performed better than historical standards"
Gender of sample	41% female	61% female
Reference group chemotherapy	Pemetrexed 500 mg/m² Carboplatin* AUC 5 mg/ml/min or cisplatin 75mg/m²	Pemetrexed 500 mg/m² Carboplatin AUC 5 mg/ml/min

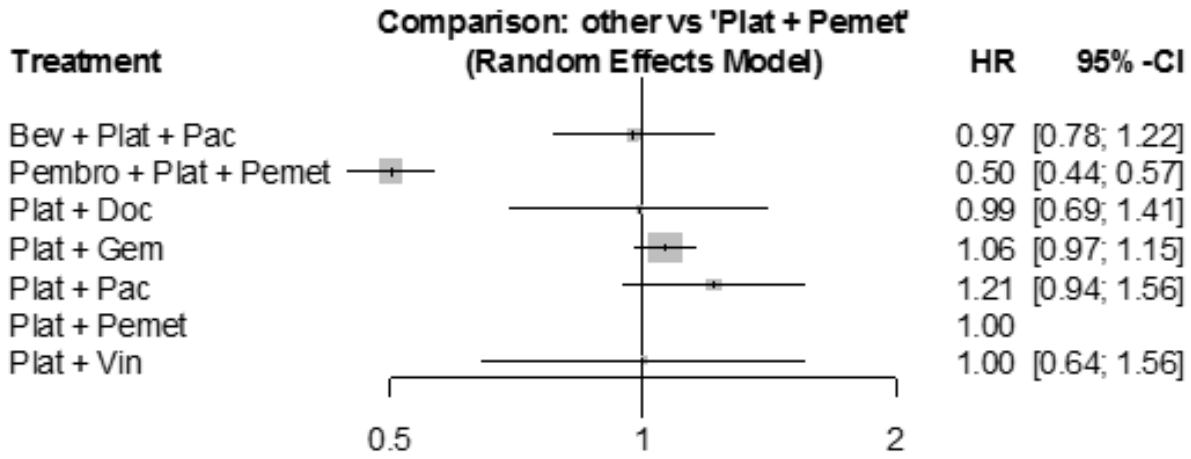
Treatment group chemotherapy	Reference group chemo plus Pembrolizumab 200mg up to 2 yrs	Reference group chemo plus Pembrolizumab 200mg up to 2 yrs

*72.2% of patients received carboplatin

The ERG questions the CS decision to split the (Pembro + Pemet + Platin) into (Pembro + Pemet + Carb) [KEYNOTE-021G] and (Pembro + Pemet + Platin) [KEYNOTE-189]. Firstly, the default NMA defines nodes on the basis of treatments, treatment combinations and dosage differences (Dias, Ades (36), p.15)(36): differences in study design and population structure are not ordinarily factors in node definition. Secondly, as shown in Figure 5 and Figure 6, in every other case the CS treats the platinum therapies (cisplatin, carboplatin, platinum) as a platinum therapy class; so for consistency a special splitting condition should not be applied to the (Pembro + Pemet + Platin) node.

As a sensitivity analysis, the ERG has repeated the NMA for OS with a single (Pembro + Pemet + Platin) node that pools the results of KEYNOTE-189 and KEYNOTE-021G. The underlying information was derived by the ERG from HR estimates and confidence intervals supplied in Table D20 (p91-2). A forest plot of this analysis is shown in Figure 7**Error! Reference source not found.**. Comparing the results with information in Table B42 shows no substantial difference in estimates for OS.

Figure 7 Forest plot [with pooling of KEYNOTE-189 and KEYNOTE-021G], excluding Johnson (dosage comparisons) and KEYNOTE024 [TSD>50% only]. Plat + Pemet as reference group.



Also in section B.2.8 the CS remarks that the control arm of KEYNOTE-021G "performed better than historical standards". Baseline hazard rates (derived by the ERG) in the reference arm are shown in Figure 7, and it does not appear that KEYNOTE-021G hazards were exceptionally low.

ERG comment:

- The approach to structuring the NMA in the CS was somewhat *ad hoc,* and the ERG draws attention to the recommendation of Salanti *et al.,* that

  "an upfront plan for investigating sources of inconsistency is advisable, and reports should distinguish planned analyses from post-hoc explorations".

However the results do not appear to be sensitive to the node splitting.

4.4.1.2 NMA Survival Model Selection

The NMA described in the CS includes investigation of a variety of survival models which extend the available forms beyond traditional parametric choices and may also be configured with both FE and RE models. The NMA is an application of the theory outlined by Jansen (37) which describes a Bayesian analysis. The models covered are a set of time-dependent survival models, specifically Gompertz, Weibull, and a set of 2nd order fractional polynomials (FP).

Under a model selection process (Appendix D) the company selects the particular 2nd order FP defined as (p1=1, p2=0) [MSD CS Appendix D, tables 31, 34, 37, 40 (pp. 106, 108, 111, 113)]. The company have clarified (14/8/18) that the notation for this model is that of Jansen (37). The company's clarification statement (14/8/18) also indicated that:

> *"…, parameter estimates were not shown in tables for d2 and we assume treatment only has an impact on two parameters that describe the hazard function over time: shape and scale."*

From this the ERG tentatively understands that the second-order time-dependent parameters are set to zero, yielding a first-order time-dependent model.

Despite selecting a time-dependent model from this process, the model selected for presentation in the main CS is rather a constant HR (time-independent) survival model. The justification for this is given as follows (p88):

> *"A horizontal line (denoting a constant HR) can be fitted between the CrIs [credible intervals] because the change in HR over time is not statistically significantly different*

from 1 as observed in time-varying NMAs. Therefore, the more parsimonious constant HR analysis may be used to draw inference with minimal risk of added bias"

The ERG cautiously accepts that the choice of a constant HR (i.e. exponentially distributed survival time) model for the CS clinical evidence is justifiable. A more formal case could have been made if the model comparisons (Tables D25, 28, 31, 34, 37 and 40) had included a constant HR model (described in Jansen 2011, p13) and if the CS provided clear justification (in terms of statistical test results) for selecting this in preference to the time-varying models.

The CS gives further support elsewhere for a time-independent model:

"The C-E model includes the option to model either a constant or a time varying HR. Exploration of modeling under both sets of assumptions led to a finding that the use of time varying HRs considerably altered the duration of time patients treated with pembrolizumab combination spent in progression-free vs. progressed disease states relative to that estimated from the analysis limited to the trial comparators (from greater time spent progression free in the trial comparator analysis to nearly a 3:1 ratio of progressed to progression free time in the NMA with time varying HRs). Therefore, for plausibility and consistency, analyses of indirect treatment comparators within document B reflect constant HRs, where this issue does not occur." (MSD CS Appendix L page 253)

The meaning of the further qualitative reasoning in is not clear to the ERG, nor the extent of its influence on the choice of a time-independent model in the main CS.

ERG comment:

- The process of selection of survival models is sometimes unclear in the CS, but the ERG judges that the final decisions are largely sound.

4.4.1.3 Results of the Base Case Analysis

4.4.1.3.1 Overall Survival

The results of the base case ITC (random-effects assuming constant hazard rate) for OS are reported in Table 62. The results demonstrate that pembrolizumab combination therapy as evaluated by KEYNOTE-189 was associated with a statistically significant benefit for OS compared to all other interventions, with the exception of pembrolizumab combination therapy as evaluated by KEYNOTE-021G. Across all other interventions, pembrolizumab combination therapy in KEYNOTE-189 was associated with a 41% - 60% reduction in the risk of all-cause mortality (range in HR 0.40 – 0.59). Although the ERG noted that the range in 95% credible intervals (CrIs) was wide: range 10% - 75%. In comparison with the main

comparators used in clinical practice in the UK, pembrolizumab combination therapy as evaluated in KEYNOTE-189 was associated with a 51% reduced risk compared to platinum and pemetrexed alone, 56% compared with platinum and gemcitabine, and 50% compared with platinum and vinorelbine.

The effect of pembrolizumab combination therapy for OS as evaluated by KEYNOTE-021G was lower when compared to other interventions than when evaluated in KEYNOTE-189. Pembrolizumab combination therapy evaluated in KEYNOTE-021G was only associated with a statistically significant benefit for OS when compared to platinum and gemcitabine and platinum and paclitaxel. For all other interventions pembrolizumab combination therapy was associated with a numerical reduction in the risk of mortality (range in HR 0.60 – 0.72), but 95% CrIs were broad, and suggested that the true effect of pembrolizumab combination therapy could be associated with a benefit or harm for OS compared to these interventions.

The ERG noted that 95%CrIs were broad for many of the comparisons reported in the CS. This may represent the small evidence base including in the ITC, and may also be indicative of heterogeneity in the network.

ERG comment:

- Evidence for pembrolizumab combination therapy from KEYNOTE-189 demonstrates a large effect for OS, compared to all other comparative therapies. This includes the principle alternatives used presently in the UK (platinum and pemetrexed, and platinum and gemcitabine, and platinum and vinorelbine). The evidence for pembrolizumab combination therapy as evaluated in KEYNOTE-021G was weaker, although still showed a consistent trend towards a large beneficial effect of pembrolizumab combination therapy for OS.

Table 62 OS Results: First line Interventions for Metastatic Non-Squamous Metastatic NSCLC

Platin + peme	1.20 (0.91, 1.59)	0.89 (0.78, 1.04)	0.82 (0.60, 1.12)	1.03 (0.79, 1.33)	1.02 (0.63, 1.63)	1.68 (0.92, 3.09)	**2.03 (1.47, 2.85)**
0.83 (0.63, 1.10)	**Platin + doc**	0.74 (0.55, 1.02)	0.68 (0.45, 1.02)	0.86 (0.58, 1.24)	0.84 (0.48, 1.48)	1.40 (0.71, 2.74)	**1.70 (1.11, 2.64)**
1.12 (0.96, 1.29)	1.34 (0.98, 1.83)	**Platin + gem**	0.92 (0.65, 1.28)	1.15 (0.84, 1.53)	1.14 (0.68, 1.85)	**1.88 (1.01, 3.52)**	**2.28 (1.58, 3.26)**
1.22 (0.90, 1.68)	1.47 (0.98, 2.23)	1.09 (0.78, 1.55)	**Platin + pac**	**1.26 (1.05, 1.49)**	1.24 (0.70, 2.19)	**2.06 (1.06, 4.08)**	**2.50 (1.59, 3.95)**
0.97 (0.75, 1.27)	1.17 (0.81, 1.72)	0.87 (0.65, 1.19)	**0.79 (0.67, 0.95)**	**Platin + pac + bev**	0.99 (0.57, 1.70)	1.64 (0.85, 3.16)	**1.98 (1.31, 3.03)**
0.98 (0.61, 1.59)	1.19 (0.68, 2.07)	0.88 (0.54, 1.46)	0.80 (0.46, 1.43)	1.01 (0.59, 1.74)	**Platin + vin**	1.65 (0.78, 3.54)	**2.01 (1.14, 3.66)**
0.60 (0.32, 1.08)	0.72 (0.37, 1.41)	**0.53 (0.28, 0.99)**	**0.49 (0.25, 0.95)**	0.61 (0.32, 1.17)	0.61 (0.28, 1.27)	**Pembro + peme + carb**	1.21 (0.60, 2.42)
0.49 (0.35, 0.68)	**0.59 (0.38, 0.90)**	**0.44 (0.31, 0.63)**	**0.40 (0.25, 0.63)**	**0.50 (0.33, 0.76)**	**0.50 (0.27, 0.88)**	0.82 (0.41, 1.66)	**Pembro + peme + platin**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically significant at the 0.05 significance level.
DIC: 22.67; Deviance: 13.26; SD: 0.08

4.4.1.3.2 Progression-Free Survival

The results of the base case ITC (random-effects assuming constant hazard rate) for PFS are reported in Table 63. The results indicate that pembrolizumab combination therapy as evaluated in KEYNOTE-189 was associated with a statistically significant benefit for PFS compared to all interventions, with the exception of pembrolizumab combination therapy as evaluated in KEYNOTE-021G. Across all other interventions, pembrolizumab combination therapy in KEYNOTE-189 was associated with a 48% - 72% reduction in the risk of progression or mortality (range in HR 0.28 – 0.52). Again, the ERG noted wide 95% CrIs around these effects (range in 95% CrIs 2% - 87%). Compared to the main comparators for pembrolizumab combination therapy as used in UK clinical practice, pembrolizumab combination therapy as evaluated by KEYNOTE-189 was associated with a 48% reduction in risk compared to platinum and pemetrexed therapy alone, a 54% reduction in risk compared to platinum and gemcitabine, and a 55% reduction in risk compared to platinum and vinorelbine.

The effect of pembrolizumab combination therapy for PFS as evaluated by KEYNOTE-021G was lower when compared to other interventions than when evaluated in KEYNOTE-189. Pembrolizumab combination therapy evaluated in KEYNOTE-021G was only associated with a statistically significant benefit for PFS when compared with platinum and gemcitabine, and platinum and paclitaxel. For all other interventions pembrolizumab combination therapy was associated with a numerical reduction in the risk of progression or mortality, but wide 95% CrIs were consistent with either a clinical benefit or harm of pembrolizumab combination therapy for PFS.

As with the ITC for OS, the ERG noted wide 95% CrIs around all of the relative effects reported from the ITC. Again this suggests a high degree of uncertainty surrounding the effect estimates.

ERG comment:

- Evidence for pembrolizumab combination therapy from KENYOTE-189 demonstrates a large effect for PFS, compared to all other comparative therapies. This includes the principle alternatives used presently in the UK (platinum and pemetrexed, and platinum and gemcitabine, and platinum and vinorelbine). The evidence for pembrolizumab combination therapy as evaluated in KEYNOTE-021G was weaker, although still showed a, while not statistically significant, consistent trend towards a large beneficial effect of pembrolizumab combination therapy for PFS.

Table 63 PFS Results: First line Interventions for Metastatic Non-Squamous Metastatic NSCLC

Platin + peme	0.99 (0.67, 1.46)	0.89 (0.66, 1.19)	**0.54 (0.31, 0.85)**	0.95 (0.64, 1.39)	0.86 (0.47, 1.55)	1.84 (0.94, 3.62)	**1.92 (1.15, 3.16)**
1.01 (0.69, 1.49)	**Platin + doc**	0.90 (0.56, 1.46)	**0.54 (0.28, 0.98)**	0.96 (0.54, 1.64)	0.87 (0.43, 1.73)	1.86 (0.86, 3.98)	**1.94 (1.02, 3.59)**
1.12 (0.84, 1.51)	1.11 (0.68, 1.80)	**Platin + gem**	0.60 (0.33, 1.03)	1.07 (0.65, 1.70)	0.97 (0.50, 1.87)	**2.06 (1.00, 4.36)**	**2.16 (1.19, 3.85)**
1.86 (1.17, 3.19)	**1.85 (1.03, 3.63)**	1.65 (0.97, 3.06)	**Platin + pac**	**1.77 (1.33, 2.48)**	1.60 (0.76, 3.62)	**3.43 (1.54, 8.14)**	**3.56 (1.83, 7.49)**
1.05 (0.72, 1.57)	1.04 (0.61, 1.85)	0.93 (0.59, 1.55)	**0.57 (0.40, 0.75)**	**Platin + pac + bev**	0.91 (0.45, 1.88)	1.94 (0.91, 4.26)	**2.02 (1.08, 3.88)**
1.16 (0.65, 2.11)	1.15 (0.58, 2.34)	1.03 (0.53, 1.99)	0.63 (0.28, 1.31)	1.10 (0.53, 2.20)	**Platin + vin**	2.14 (0.88, 5.28)	**2.23 (1.04, 4.83)**
0.54 (0.28, 1.06)	0.54 (0.25, 1.16)	**0.48 (0.24, 0.99**	**0.29 (0.12, 0.65)**	0.52 (0.23, 1.09)	0.47 (0.19, 1.13)	**Pembro + peme + carb**	1.04 (0.45, 2.40)
0.52 (0.32, 0.87)	**0.52 (0.28, 0.98)**	**0.46 (0.26, 0.84)**	**0.28 (0.13, 0.55)**	**0.50 (0.26, 0.93)**	**0.45 (0.21, 0.97)**	0.96 (0.42, 2.24)	**Pembro + peme + platin**

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: 24.29; Deviance: 13.08; SD: 0.19

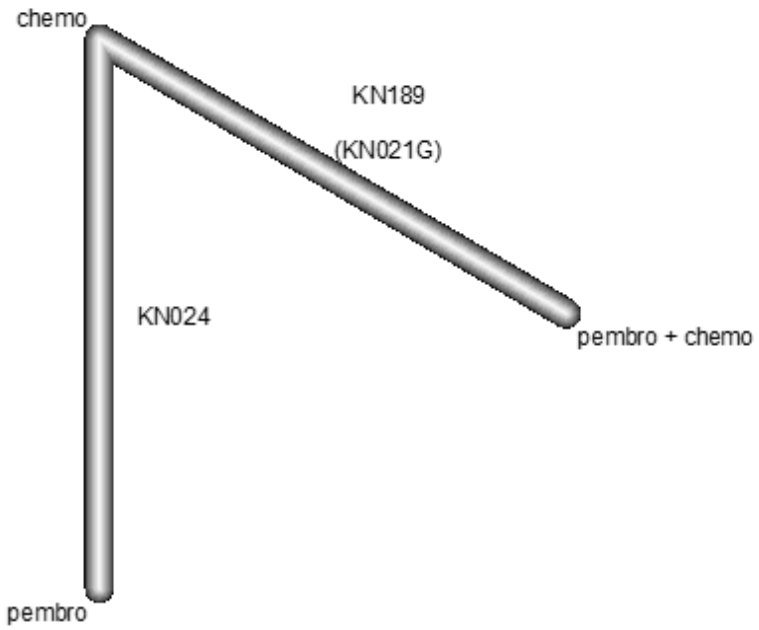
4.4.1.4 Sensitivity Analysis in NMA

Noting that certain studies were carried out in exclusively Asian centres, the company repeated the NMA without these trials and found the results to be consistent (Tables D22 (p98) and D24 (p100)).

4.4.2 (B) ITC: First line Interventions for Metastatic Non-Squamous Metastatic NSCLC (PD-L1 ≥50%)

An ITC was carried out comparing pembrolizumab combination therapy and pembrolizumab monotherapy. Two trials were used (KEYNOTE-189 and KEYNOTE-024), but a third potentially relevant trial (KEYNOTE-021G) was not; see below. A subset of the available data was taken (non-squamous patients with TPS ≥ 50%) from the two trials to improve comparability. The network is shown in Figure 8.

Figure 8 Network of evidence for (B) ITC comparing combination therapy with monotherapy



The analysis was carried out separately on IPD (section B 2.9.2, pp90 ff.) using 'Inverse Probability of Treatment Weighting' to improve balance in the subject characteristics (Table D45). The improved balance in doing so is shown when comparing CS Tables D44 and D45 (MSD CS Appendix D, pages 120-1).

The ERG agrees with the company's decision to carry out ITC of combination versus monotherapy as a separate IPD-based analysis, and the improved balance is shown by comparing tables D44 and D45 (pp120-1).

A further set of IPD is available from the KEYNOTE-021G trial, however this was not utilised in the ITC. The company clarified the underlying reason (14/8/18):

"KEYNOTE-021G was not included in the ITC analysis of OS and PFS outcomes as the study was an open-label phase 2 study comparing pembrolizumab/chemotherapy combination versus chemotherapy alone, with the primary objective of assessing ORR. While PFS and OS were captured, they were included as secondary endpoints only and as such, the study was not powered to detect changes in these endpoints."

The ERG disagrees with the company's reasoning not to include KEYNOTE-021G: an ITC does not proceed on the basis of the power of the component studies, and power is in any case altered during the syntheses. Furthermore, power is a function of the effect size of interest, and may well not be consistently defined across studies. However, the ERG recognise that the excluded trial (KEYNOTE-21G) from ITC (B) is composed of relatively few patients (n=37), and therefore would likely have added limited weight in the analysis.

ERG comment:

- The ERG agrees with the company's decision to carry out an ITC of combination versus monotherapy as a separate IPD-based analysis with a weighting method to improve covariate balance. This is likely to provide more robust evidence, with the caveat that important effect modifiers might not have been included, or may be unmeasured or unknown. The ERG believes that IPD from KEYNOTE-021G should have been included in the analysis, but does not expect that this would have had a significant impact on the final effect estimate.

4.4.2.1 Results of the Base Case Analysis

4.4.2.1.1 Overall Survival (OS)

Based on the results of the ITC, pembrolizumab combination therapy is associated with a numerically reduced risk of mortality compared with pembrolizumab monotherapy. The effect was large (HR [redacted]); however 95% CIs around the effect were very broad, and are consistent with either a greater or reduced effect of pembrolizumab combination therapy compared to monotherapy (95% Cis [redacted]).

ERG comment:

Based on this ITC, there is insufficient evidence to demonstrate that pembrolizumab combination therapy is superior for OS compared to monotherapy.

4.4.2.1.2 Progression-Free Survival (PFS)

Based on the results of the ITC, pembrolizumab combination therapy is associated with a numerically reduced risk of mortality or disease progression compared with Pembrolizumab monotherapy. The effect was also large (HR [redacted]); however again the 95% Cis around the effect were very broad, and are consistent with either a greater or reduced effect of pembrolizumab combination therapy for PFS compared to monotherapy (95% Cis [redacted]).

ERG comment:

- Based on this ITC, there is insufficient evidence to demonstrate that pembrolizumab combination therapy is superior for PFS compared to monotherapy.

4.4.3 Patient-level covariates

The patient-level covariate information supplied in the CS is shown in Table 60. Parallel information is shown across rows, and shows how the covariates were used and what was omitted in the two NMAs. The first column shows the IPD information available and summarised for KEYNOTE-189. The second column shows the information summarised and compared across trials in NMA (A). The third column shows the IPD covariates utilised in NMA (B) (and balanced for with the treatment weighting approach).

Table 64 Patient covariate information supplied

IPD data summarised for KEYNOTE-189 [a]	ITC (A) covariate information presented for comparison across trials [b]	ITC (B) covariate info used [c]
Gender	Gender	Gender
Age	Age	Age
ECOG 0,1 or 2	ECOG 0 or 1 ECOG 2	ECOG 0 ECOG 1 or 2
Former/current smoker Never smoker	Current smokers Never smoker	Former/current smoker Never smoker
-	Stage IIIb lung cancer	-
-	Stage IV lung cancer	-
Chemotherapy (carboplatin or cisplatin)	-	Chemotherapy (carboplatin or cisplatin)
	-	M1B metastatic staging
Brain metastases	-	Brain metastases (Y/N)
Region (US, exUS) Geographic region (east Asian, non-east Asian)	-	Region (Europe/ N.America/ Rest of World)
Ethnicity and Race	Race	
Histology (adenocarcinoma, NSCLC NOS, Other)	-	-
PD-L1 status <1% or >=1%	-*	Limited to >=50%
Baseline tumour size	-	-
Prior radiation	-	-
Prior thoracic information	-	-
Prior adjuvant therapy	-	-
Prior neoadjuvant therapy	-	-

Source: MSD CS Appendix, Table D44; *a source: Table B10. b source: Table D18-19. c*

* Information not available in trials prior to pembrolizumab.

ERG comment:

- The clinicians consulted by the ERG identified comorbidity, age, gender, sites of metastatic disease, and ECOG performance status as primary prognostic markers. Age, gender, and ECOG status were included in both ITC analyses, comorbidity in neither, and sites of metastatic disease crudely or partially. Clinical experts to the ERG note that age may partially account for the presence of comorbidity.
- ITC (A) and ITC (B) analyses include subsets of covariates identified in KEYNOTE-189. The reasons and consequences of omitting some variables from analyses are unclear.

4.4.4 Investigation of heterogeneity

Further details of the CS scope are given in section 4.1.2. The CS scope allowed for the inclusion of trials in which clinical judgement was permitted to determine treatment choice, and therefore treatment necessarily varied both within and between trials. This includes the use of cisplatin or carboplatin therapy, and the use of pemetrexed maintenance following cisplatin therapy. Further details of co-interventions in the trials not involving pembrolizumab were not provided in the CS, and therefore it is unclear whether there is further variation in treatment administration, dose, and delivery (see section 4.3.4.1.3).

Included trial populations may also vary with respect to prognostic or effect-modifying variables (listed in table 61). In relation to effect modification Salanti et al note that:(38)

> *"If important variables are believed to alter the effectiveness of the treatments and vary across comparisons, then it may not be reasonable to analyse the network as a whole"*

The ERG finds limited discussion of effect modification in the CS, though there is acknowledgement of it (CS, p90) "it has to be accepted that there is the risk of confounding bias if these differences act as treatment effect modifiers". In section D1.2.2 (pp84-85), the CS compares covariates across trials noting many similarities (but also some differences in, for example, patient ethnicity). In section B2.8 (p79) the CS also identifies discrepancies between KEYNOTE-189 and KEYNOTE-021G in particular (previously summarised in table 58). There is no systematic discussion of evidence for potential effect modification from previous studies (including KEYNOTE-189), though the topic is touched on in several places (e.g. "female gender is considered to be a positive prognostic factor", section B.2.8). There are attempts to achieve balance across treatments during analysis, for example in the choice

of inverse probability treatment weighting for the (B) IPD ITC, and in a sensitivity analysis in ITC (A) in which Asian-only trials are removed.

ERG comment:

- The (A) ITC comparison could be biased by imbalance in known potential effect modifiers over the network and the ERG finds only limited exploration of this issue in the CS. There may also be further unmeasured or unknown effect modifiers.

Schwarzer et al distinguish three “principal sources” of heterogeneity:(39)

- Clinical baseline heterogeneity between patients from different studies, measured, e.g. in baseline characteristics and not necessarily reflected on the outcome scale
- Statistical heterogeneity, quantified on the outcome measurement scale, that may or may not be clinically relevant and may or may not be statistically significant
- Heterogeneity from other sources, e.g. design-related heterogeneity

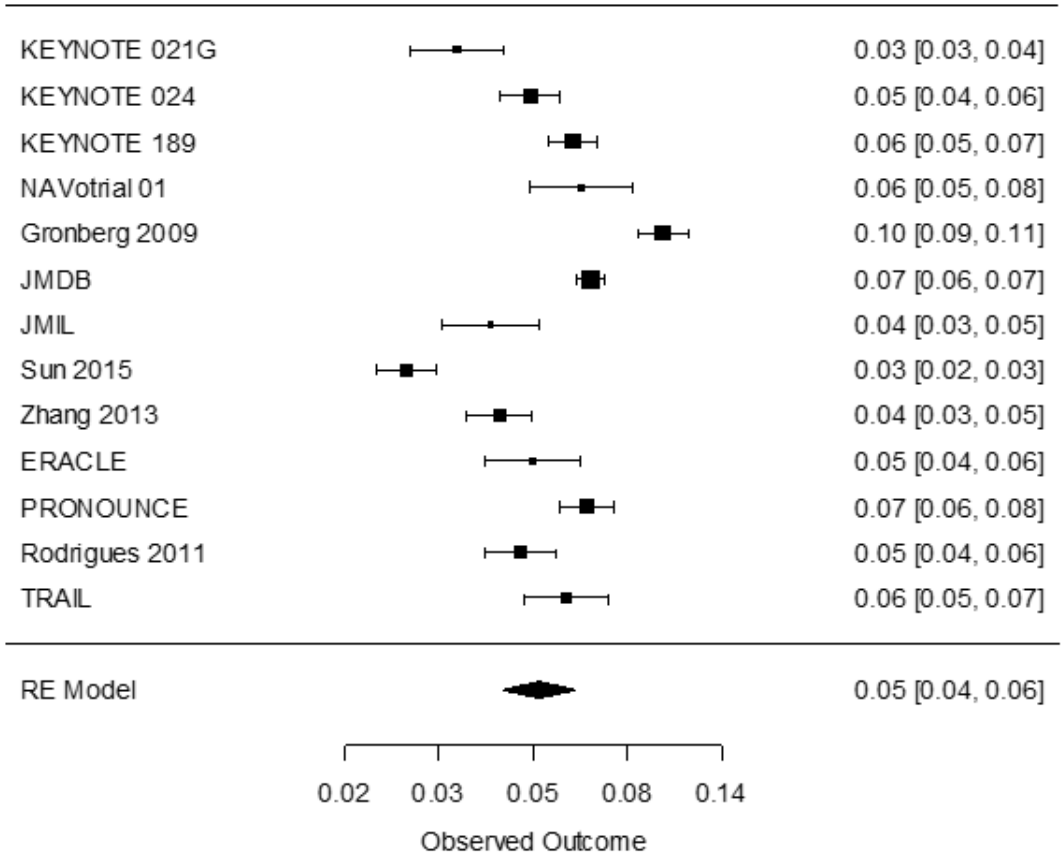
These sources of heterogeneity are now considered further.

4.4.4.1 Clinical baseline heterogeneity

The median OS survival times for patients in the reference group (platinum + pemetrexed) are supplied in Table D20 (MSD CS Appendix p 91-2). The ERG note that considerable variation in median survival time can be seen (range 7.0 from Gronberg et al. 2009 to 27.3 from Sun et al. 2015).(16, 20)

The ERG conducted an additional meta-analysis to compare baseline OS hazard rates. To facilitate this, the ERG calculated baseline hazard rates (assuming constant hazard) from the median OS times for 13 studies that evaluated platinum and pemetrexed therapy. A forest plot is shown in **Error! Reference source not found.**Figure 9 weighted by sample size. There is some evidence of clinical baseline heterogeneity as the Figure shows, and the estimate of between-trial variability for log hazards in the reference group is τ^2=0.14 (95% 0.07 to 0.38).

Figure 9 Results of meta-analysis of hazard rates in reference arm (Platinum + Pemet). Hazard rate estimates assume constant hazard rate (hazard rate = $\log_e(2)$/median survival time, with median survival time from Table D20)



4.4.4.1.1 *Heterogeneity from other sources*

An aspect of heterogeneity in NMA is that indirect and direct evidence on treatment effects may be inconsistent. However, the ERG notes that the network in this case is a star, so there is no inconsistency component to the heterogeneity. While this simplifies the conceptual interpretation of the network, it should be noted that with this type of network structure, the influence of effect modifiers through variation in between-treatment comparisons can't be detected by network analysis.

4.4.4.1.2 Statistical heterogeneity

For OS in ITC (A), the ERG calculated the total 'within-treatment' heterogeneity as Q=1.87 (df=7, p=0.96). This can be further decomposed by pairwise comparisons as shown in Table 65. There is no statistical evidence of within-treatment heterogeneity.

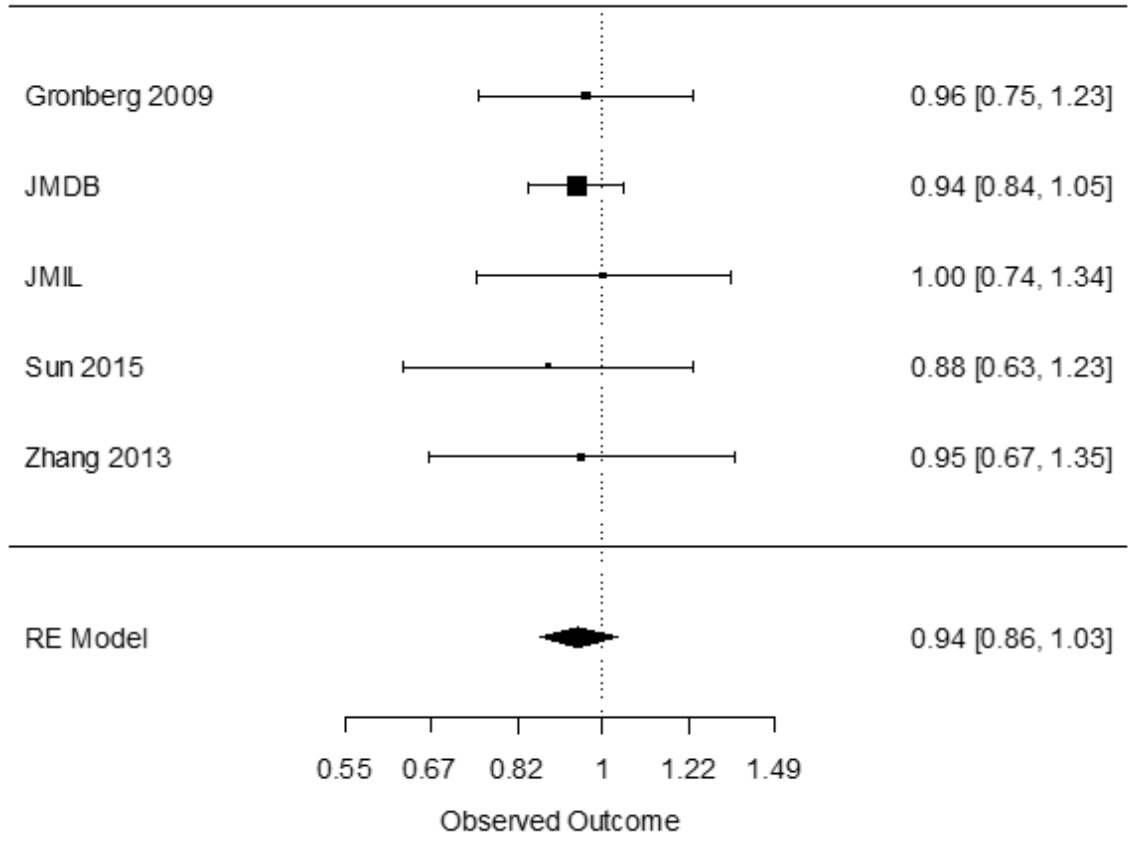
Note that most of the evidence for assessing within-treatment heterogeneity in outcomes is provided by the 5-study comparison of platinum and gemcitabine vs platinum and

pemetrexed. The associated forest plot for this comparison, calculated by the ERG, is shown in Figure 10.

Table 65 Decomposition of within-designs Q statistic by pairwise comparison

Design	Q	df	p-value
(Bev + Plat + Pac) vs (Plat + Pac)	0.93	1	0.34
(Bev + Plat + Pac) vs (Plat + Pemet)	0.30	1	0.59
(Pembro + Plat + Pemet) vs (Plat + Pemet)	0.31	1	0.58
(Plat + Gem) vs (Plat + Pemet)	0.34	4	0.99

Figure 10 Meta-analysis of "Plat + Pemet" vs "Plat + Gem"



Bayesian summary statistics for fixed and random effects models are extracted from CS and collated in Table 66 to further interpret heterogeneity. The inclusion of random effects appears to produce little or no improvement in model fit as measured by DIC, further suggesting a lack of statistical heterogeneity.

Table 66 Comparison of FE and RE model fit statistics extracted from CS

Outcome	Sources	Model	Dbar	pD	DIC
OS	Table 34	FE	3727.5	55.5	3783
	Table 37	RE	3724.9	59.1	3784
PFS	Table 25	FE	2902.4	49.6	2952
	Table 28	RE	2895.7	53.3	2949

Results are for selected model (2nd order FP with p1=1, p2=0).

Dbar = posterior mean of the deviance for the current model; pD = effective number of parameters; DIC = deviance information criterion.

ERG comment:

- The evidence in (A) ITC shows heterogeneity in baseline hazards (Figure 9) at the same time as a lack of heterogeneity in relative treatment effect (Figure 10). The ERG would like to have seen further exploration of this potentially conflicting information. It is possible for example that the observed baseline heterogeneity arises from variables that are not effect modifiers so that it is not transmitted to the relative effects. It is also possible that further studies would reveal greater heterogeneity in relative effects, since at present this information is largely obtained from a single comparison (Platinum + Pemetrexed vs Platinum + Gemcitabine,).

4.4.5 Applicability to NICE target population

All ITC analyses include studies identified by the SLR; consideration of the applicability of these studies to the NICE target population is discussed in Sections 4.2.6 and 4.3.7.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As an exploratory analysis, the ERG performed standard meta-analysis of primary outcome data (OS, PFS, and ORR) from KEYNOTE-189 and KEYNOTE-021G; the findings are presented below (Figure 11 to Figure 13). While the relative effect of pembrolizumab combination therapy for OS, PFS and ORR was slightly smaller in the KEYNOTE-021G trial, in the pooled analysis, the overall effect was comparable with the estimate reported by KEYNOTE-189 alone. As the larger of the two studies, data from KEYNOTE-189 carried the greater weight (80%) in the analyses. Despite noted difference in the population and intervention characteristics between the two trials (Section 4.2.2), heterogeneity statistics (I^2) did not reveal any statistical heterogeneity between the two trials. However, as the

calculation of I^2 is driven by the degree of overlap in 95% Cis around the effect estimates, and 95%Cis around the effect from KEYNOTE-021G were wide due to the smaller sample size, this effect may be unreliable. Inspection of the relative effect estimates suggests some variation in the relative effect of pembrolizumab combination therapy for OS between the two trials; this may be explained by the improved outcome of the control arm in KEYNOTE-021G. However, the relative effect of pembrolizumab combination therapy for PFS and ORR were similar between the two trials.

In conclusion, while the ERG agree that there are some differences in study design and population between KEYNOTE-189 and KEYNOTE-021G, pembrolizumab combination therapy had a similar effect on PFS and ORR in both trials, relative to standard of care. While the benefit of Pembrolizumab on OS was smaller in the KEYNOTE-021 trial, the ERG agreed that this may be due to the higher OS rate in the control arm of this trial, and as the smaller trial, this analysis also lends less weight to the overall analysis. In sum, the findings of the ERG meta-analysis support the findings of the KEYNOTE-189, and add credibility to the consistency of the findings across settings.

Figure 11 Standard Meta-Analysis of OS (KEYNOTE-021G and KEYNOTE-189)

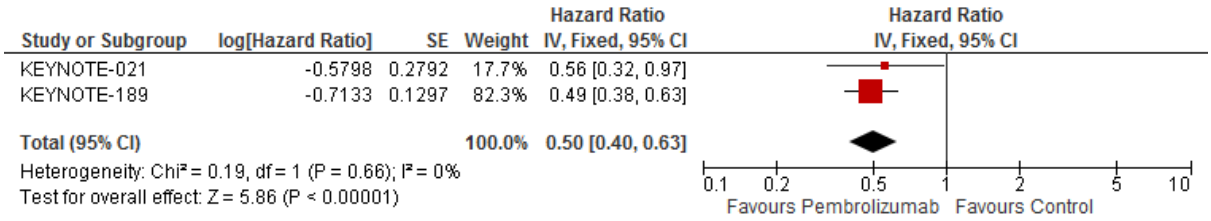


Figure 12 Standard Meta-Analysis of PFS (KEYNOTE-021G and KEYNOTE-189)

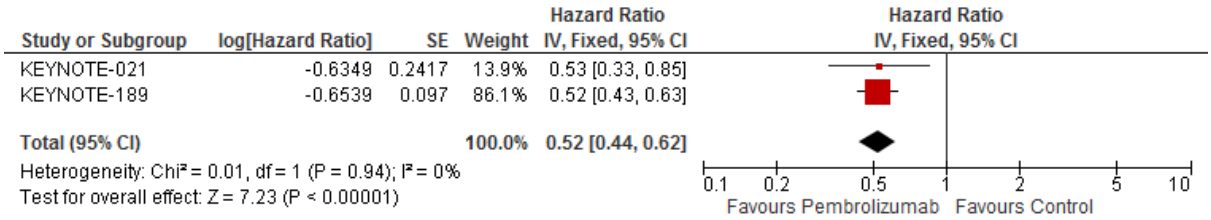
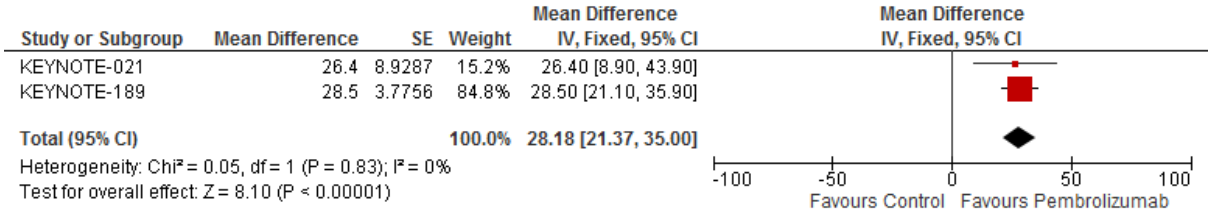
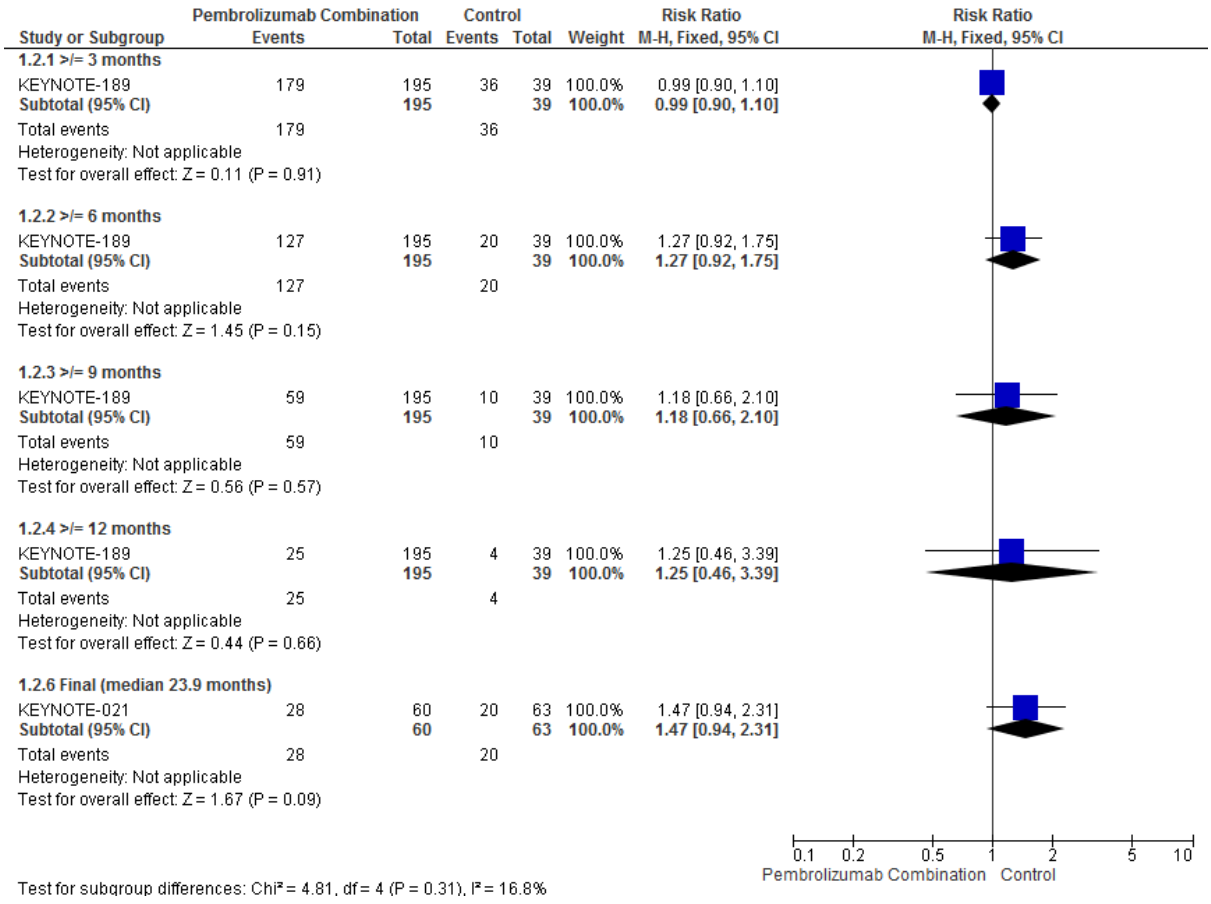


Figure 13 Standard Meta-Analysis of ORR (% difference in ORR; KEYNOTE-021G and KEYNOTE-189)



In addition, the ERG conducted additional analyses to statistically compare the proportion of patients in each arm of KEYNOTE-189 and KEYNOTE-021G who experienced extended response duration. The analyses demonstrated no statistical difference in extended response duration between trial arms at any time-point (see Figure 14).

Figure 14 Proportion of Patients with Extended Response Duration



4.6 Conclusions of the clinical effectiveness evidence

The SLR presented by the company identified 17 RCTs evaluating interventions for the 1st line treatment of metastatic non-squamous EGFR and ALK negative NSCLC, including 2 trials evaluating the technology of interest. As compared to other interventions identified by the SLR, including the principle alternatives to pembrolizumab combination therapy currently used in the UK, the evidence identified shows that 1st line treatment with pembrolizumab combination therapy could have a large beneficial effect on OS and PFS for patients with metastatic non-squamous EGFR and ALK negative NSCLC . As compared to platinum and pemetrexed therapy, which is the most relevant comparator for UK practice, pembrolizumab combination therapy was also found to be associated with benefits for the rate of partial response to treatment, and with an overall benefit to HRQoL. Furthermore, compared to platinum and pemetrexed, the evidence did not identify significant concerns for safety or toxicity. However, there is no evidence that pembrolizumab combination therapy affects the rate of complete response to treatment, the duration of treatment response, or the time to response. A limitation of the CS is that it did not present evidence of the effect of pembrolizumab combination therapy on ORR, duration of response, HRQoL, and safety as compared to other interventions in the NICE scope; including platinum and gemcitabine, or platinum and vinorelbine, which are also commonly used in the UK. Evidence compared to these interventions, therefore, is limited to the effect of pembrolizumab combination therapy on OS and PFS.

The evidence base for pembrolizumab combination therapy is small, including few patients from the UK or related healthcare settings, and with some heterogeneity in effect between the two trials.(8, 14) Furthermore, expert clinical advisors to the ERG advise that the evidence does not include patients with ECOG status 2, who comprise approximately 20% of the UK patient population, and generally have poorer outcomes. As such, the ERG considered that there is some uncertainty about the size of the effect that may be seen if pembrolizumab combination therapy were to be used with this patient population in UK clinical practice. However, the effect sizes reported for OS and PFS in the trials are large and from high quality trials, which lends confidence to the potential benefit pembrolizumab combination therapy may have. As such, the ERG considered it likely that 1st line treatment with pembrolizumab combination therapy would be associated with a benefit for OS and PFS in patients in the UK with metastatic non-squamous EGFR and ALK negative NSCLC, as compared to all other interventions.

The CS presented evidence from two trials to indirectly compare the efficacy of pembrolizumab combination therapy and pembrolizumab monotherapy for the treatment of a

sub-population of patients with metastatic non-squamous EGFR and ALF negative NSCLC who have a PD-L1 TPS score ≥50%. This evidence showed that in this population there is a trend for pembrolizumab combination therapy to have a greater beneficial effect for OS and PFS than Pembrolizumab monotherapy. However, neither of these effects was statistically significant, and with large 95% Cis that cross the line of null effect. Overall, the ERG considered that there is likely to be a beneficial effect of using pembrolizumab in combination with platinum and pemetrexed in this population, although further evidence that directly compares the two approaches is needed to confirm this. Furthermore, no evidence was presented in the CS that compared the relative difference in safety, or the effect of the treatments on other clinical outcomes.

5 Cost-effectiveness

5.1 ERG comment on companies review of cost-effectiveness evidence

5.1.1 Objective and search method

The company posed the following research questions in accordance with the decision problem, with the objective of identifying relevant evidence pertaining to cost-effectiveness in general, but also HRQoL in terms of utility and cost/resource use:

1. *What is the cost-effectiveness of comparator therapies to pembrolizumab combination in untreated patients with metastatic non-small cell lung cancer?*
2. *What is the health-related quality of life (in terms of utilities) in untreated patients with metastatic non-small cell lung cancer?*
3. *What are the resource requirements and costs associated with the first-line treatment of metastatic non-small cell lung cancer?*

The searches to identify cost-effectiveness, utility and cost/resource studies are reported in appendices G (cost-effectiveness), H (utility) and I (cost/resource). The bibliographic database searches for all three types of study are combined in one search strategy which is reported in appendix G.1. Additional information was also provided in response to clarification questions for the manufacturer.(40)

In total, seven bibliographic databases were searched including MEDLINE (via the PubMed platform), EMBASE (via Elsevier), BIOSIS (via Dialog), EconLit (via EBSCO), NHS EED, HTA and DARE (all via the Cochrane Library). The search strategy is in three parts and combines search terms for non-small cell lung cancer and cost-effectiveness, non-small cell lung cancer and utilities, and non-small cell lung cancer and cost/resource use. A combination of free text (i.e. title and abstract) and indexing terms (e.g. MeSH in MEDLINE) was used. Search results were limited to English language studies. Animal studies, editorials, commentaries and letters were excluded. The most recent update of the searches was carried out on 2nd April 2018.

A supplementary search was carried out to identify cost-effectiveness studies of the additional treatments of interest published since 1st January 2007. This uses the same search terms for non-small cell lung cancer and cost-effectiveness as the main searches, combined with search terms for bevacizumab, avastin, pemetrexed, Alimta, albumin-bound paclitaxel, abraxane nab-paclitaxel, protein bound paclitaxel, necitumumab, portrazza and

chemotherapy. The same databases were searched as the main search and last updated on 2nd April 2018.

The conference proceedings of ESMO (European Society for Medical Oncology), WCLC (World Conference on Lung Cancer), AACR (American Association for Cancer Research) and ASCO (American Society of Clinical Oncology) were manually searched to identify relevant studies not yet published in journal format. These searches were limited to the two most recent years at the time of searching. The websites of health technology assessment agencies were searched for cost-effectiveness analyses and models of first-line treatment of metastatic non-small cell lung cancer, including NICE, the Scottish Medicines Consortium, CADTH and INHAHTA.

The bibliographic database searches include the appropriate indexing term (e.g. MeSH in MEDLINE) for non-small cell lung cancer, and appropriate indexing terms for relevant types of cost, utility and resource analysis. The free-text (i.e. title and abstract) search terms are also appropriate, however terms which describe non-small cell lung cancer are only searched in the title field, whereas cost, utility and resource terms are searched in title and abstract fields. Focusing the search on title only for the disease area is likely to increase the precision of the search results, but there is a risk of failing to identify relevant studies which only mention the disease area in the abstract. This risk is mitigated by the use of the relevant indexing term.

The bibliographic databases which are searched are all appropriate and include two specialised economics databases (EconLit and NHS EED). The NHS EED database was discontinued in 2015 but it can still be searched as an archive.

The supplementary bibliographic database search to identify cost-effectiveness studies of additional treatments of interest uses the same disease area and cost-effectiveness search terms as the main search, which (as noted above) are all appropriate. Additional search terms were added to focus the search on relevant treatments, all of which are appropriate to the aim of the search. The description of the supplementary database search in the manufacturer's report states that 'a specific search (for bevacizumab, necitumumab, pemetrexed, pembrolizumab, and protein-bound paclitaxel) was conducted for economic models from the 1st of January 2007' (CS Appendix G, p154). However, there is no search term for pembrolizumab in the search strategy. In response to our clarification question on this issue, the manufacturer stated that the aim of the search was 'to identify cost-effectiveness studies for the additional treatments of interest', which would not include pembrolizumab. In view of this clarification the search is appropriate for the stated aim.

The conference proceedings and health technology assessment agencies which are searched for grey literature are appropriate for the disease area. However the search terms for the web searches of health technology assessment agencies are not reported and so cannot be critiqued. These searches are likely to be simple free-text searches for key terms due to the basic search interfaces of the websites.

5.1.2 Inclusion/exclusion criteria

Inclusion and exclusion criteria for the original search, updates 1a, 1b and 2 are given in Table 67.

Table 67 Inclusion and exclusion criteria for the original search, updates 1a, 1b and 2

Criteria	Inclusion	Exclusion
Population	Patients aged ≥ 18 years with advanced NSCLC (resource use, costs, and utility weights) • Patients aged ≥ 18 years with second-line advanced NSCLC (economic evaluations) [excluded from updates] • Patients aged ≥ 18 years with first-line metastatic NSCLC (economic evaluations)	• Patients with primarily other types of cancer/disease • Studies in animals but not humans • Patients with second-line advanced/metastatic NSCLC [updates only]
Interventions (applied to economic evaluations only)[a]	• Pembrolizumab • Bevacizumab[b] (1b and 2 only) • Necitumumab[b] (1b and 2 only) • Pemetrexed[b] (1b and 2 only) • Protein-bound paclitaxel[b] (1b and 2 only) • Nivolumab (not 1b or 2) • Atezolizumab (not 1b or 2) • Crizotinib (not 1b or 2) • Ceritinib (not 1b or 2) • Nintedanib (+ docetaxel) (not 1b or 2) • Ramucirumab (+ docetaxel) (not 1b or 2) • Any of the epidermal growth factor receptor tyrosine-kinase inhibitors small molecules (erlotinib, gefitinib, afatinib, rociletinib, AZD9291) (not 1b or 2) • Best supportive care	• Any interventions other than those identified at left
Study type	• Economic evaluations - Cost-effectiveness analyses - Cost-benefit analyses - Cost-utility analyses	• Commentaries • Letters • Consensus reports • Non-systematic reviews

Criteria	Inclusion	Exclusion
	• Prospective studies reporting costs or resource utilization (e.g., observational studies, clinical trials) • Utility studies (including studies where utility weights were mapped from other instruments, e.g., disease-specific patient-reported outcome measures) • Retrospective studies reporting costs or resource utilization (e.g., cost-of-illness, cross-sectional studies) • Systematic reviews of economic analyses, resource-use, or cost studies[b]	• Articles reporting cost estimates that are not based on data (e.g., commentaries making general reference to cost burden)

Abbreviations: ICER = Incremental cost-effectiveness ratio; NSCLC = Non-small cell lung cancer.

[a] No restrictions for interventions will be applied for utility, resource-use, and cost studies; all those that are relevant to advanced NSCLC will be included. [b] Systematic reviews will be included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening.

Source: MSD CS Appendix G, Table G60, page 155

The search for cost-effectiveness evidence included studies of both first- and second-line treatments of metastatic non-small cell lung cancer, although the updated searches (1b and 2) only included studies of first-line treatments of metastatic non-small cell lung cancer. The search for HRQoL evidence in previously untreated patients with non-squamous metastatic non-small cell lung cancer was subsequently broadened to include patients with squamous NSCLC, and including patients with EGFR and ALK mutations. The search for resource and cost evidence targeted the treatment and on-going management of untreated metastatic non-squamous non-small cell lung cancer. The type of costs for consideration included the drug and administration costs related to the intervention and comparator, costs related to subsequent therapies, the cost of monitoring and managing disease including adverse events, and the costs related to terminal care. In addition, for patients treated with pembrolizumab combination, the costs of testing for PD-L1 were included.

ERG comment:

- Pre-specified inclusion and exclusion criteria were appropriate.

5.1.3 Results

5.1.3.1 Evidence on cost-effectiveness

The original database, internet and hand searches identified 5,519 records. A total of 30 cost-effectiveness studies were included that reported on cost-effectiveness in the first line

setting. Within the updated searches, 1,647 new records were identified, from which 20 cost-effectiveness studies were finally included; 17 from the first update, 3 from the second update. A total of 50 cost-effectiveness studies for patients with first-line metastatic non-small cell lung cancer were identified, that met all the inclusion criteria. Of the 50 studies, data was extracted only from UK studies reporting the cost-effectiveness of Pembrolizumab combination, of which none were identified.

5.1.3.2 Evidence on HRQoL or utilities

From their original database, internet and hand searches the company identified 5,691 records. After removing duplicates and primary screening of abstracts and titles 587 records were included for secondary screening. After secondary screening of full texts, 4 publications were included that reported on utility values in the first-line setting. Updated searches found 1,647 new records from which another 4 studies reporting utility values were finally included. Brief detail of the seven extractions (from eight inclusions) presented by the company is given in Table 68. Also given are the additional 11 utility NICE technology appraisals of interventions for people with NSCLC, which were found through hand searching the NICE website (Table 69). All 17 extractions are presented in full in Appendix 2. Perhaps the most important of the inclusions are the studies by Huang et al,(41) and Chang et al,(42) because they provide alternative sources for TTD health state utilities.

Table 68 Studies included in the company's HRQoL/utility search findings

Study first author and year of publication	Population	Intervention
Chouaid, 2012(43)	Advanced NSCLC patients	Not specified
Pujol, 2014(44)	Eligible patients with advanced (stage IIIB/IV) non-squamous NSCLC patients who had completed 4 cycles of induction therapy, had not progressed, and had an ECOG PS of 0/1; adequate organ function, and age of 18 year or older. Additional eligibility criteria included no prior systemic chemotherapy for lung cancer, including adjuvant treatment.	pemetrexed 56%; placebo 62%

Gridelli, 2012(45) Netherlands, Poland, Portugal, Romania, Spain, Turkey, and UK	Patients were of advanced (Stage IIIB/IV) non-squamous NSCLC	PEM(I)+CIS(I) Randomised to: PEM(M)+BSC(M) Placebo(M)+BSC(M)
Iyer, 2013(46)	Eligible patients were patients with advanced (stage IIIB/IV) NSCLC in France and Germany, who were receiving drug treatment for NSCLC in non–clinical trial settings 67% of patients were male. Average age was 63 years old at the time of questionnaire completion.	
Nafees, 2016(47) UK, France, Australia, South Korea, Taiwan and China	Metastatic NSCLC patients.	Not specified
Huang, 2017(41)	Multi-country, Metastatic NSCLC with PD-L1 TPS ≥50% with no prior chemotherapy	Pembrolizumab Platinum-based chemotherapy
Chang, 2016(42)	South Korea	Health states descriptions developed by expert panel of experienced clinical oncologists and 205 participants completed the study

Source: MSD CS Appendix H

Table 69 HTAs identified on the NICE website relevant to HRQoL/utilities

NICE Appraisal	Population	Intervention
NICE TA309(48) UK	Locally advanced or metastatic (Stage IIIB/IV) non-squamous NSCLC	PEM+BSC Placebo + BSC
NICE TA181(49) UK	Patients with chemo-naive NSCLC that was not amenable to surgical resection	PEM 500mg/m2+CIS 75mg/m2 GEM 1250mg/m2+CIS 75mg/m2 GEM 1250mg/m2+CARB 500mg (for target AUC of 5mg/ml*min) DOC 75mg/m2+CIS 75mg/m2
NICE TA190(50) UK	Patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology	PEM+BSC Placebo + BSC
NICE TA192(51) UK	Patients with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK	GEF GEM+CARB PAX+CARB VNB+CIS

		GEM+CIS
NICE TA227(52) UK	Patients with both squamous and non-squamous histology of NSCLC	ERL PEM BSC
NICE TA258(53) UK	Metastatic NSCLC patients with tumours harboring an activating mutation of the EGFR TK	ERL GEF
NICE TA310(54) UK	EGFR mutation positive locally advanced or metastatic NSCLC patients	AFA GEF ERL
NICE TA411(55) UK	The model population comprised adults with advanced, metastatic, squamous NSCLC who had not had previous CTX for their lung cancer	NECI+GEM+CIS GEM+CIS GEM+CARB PAX+CARB DOC+CIS
NICE TA447(56) UK	People with PD-L1 positive metastatic non-small-cell lung cancer (NSCLC) not treated with chemotherapy in the metastatic setting	PEMBROLIZUMAB PEM + CARB induction, PEM maintenance PEM + CIS induction, PEM maintenance GEM+CIS GEM + CARB PAX + CARB
NICE TA520(57) UK	People with locally advanced or metastatic non-small-cell lung cancer whose disease has progressed after chemotherapy	ATEZOLIZUMAB DOC
NICE TA500(58) UK	People with untreated ALK+ advanced NSCLC	CERITINIB PEM + CARB induction, PEM maintenance PEM + CIS induction, PEM maintenance CRIZOTINIB (MAIC PROFILE 1014)

Source: MSD CS Appendix H

5.1.3.3 Evidence on resource use

Of the 5,691 records identified in the wider original search, 587 were included for secondary screening, after which 25 publications were included that reported on cost and healthcare resource identification in the first line setting. A further 24 studies were included from update

searches (17 from the first and 7 from the second update). However, after a limitation to studies with a UK perspective, only 2 of these 49 studies were retained as matching inclusion/exclusion criteria. However, two additional studies were included and data presented by the company despite technical exclusion. Brown *et al*. was excluded at the level 2 screen as it was a systematic review. Fleming *et al.* was excluded due to presenting a factor analysis of costs. However both studies have been reported as they provide a variety of cost and resource use information relevant to the submission. Brief detail of these four studies is presented in Table 70. A further 11 records were found in addition from hand searching of the NICE website (Table 71). All 15 extractions are presented in full in Appendix 2.

The company report that the main use of resources by patients with advanced NSCLC related to hospital episodes, terminal care, time required for dispensing, inpatient and outpatient episodes' duration and patients' visits to different health care professionals. Their identified studies reported a variety of resource use related to hospital episodes. Of the studies identified, there were 9 that reported adverse events and all were associated with a variety of unit costs. Additionally, a number of studies reported follow-up costs for health states. Perhaps the most important of the included studies was Brown et al, it being a SLR and the source of resource rate estimates in the economic model.(17)

Table 70 Studies included in the company's resource use search findings

Study first author and year of publication	Brief study description
Khan, 2015(59)	Cost-effectiveness of first-line erlotinib in patients with advanced NSCLC unsuitable for chemotherapy
Lay, 2007(60)	Comparative cost-minimisation of oral and intravenous chemotherapy for first-line treatment of NSCLC in the UK NHS system
Brown, 2013(17)	A study to evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic NSCLC: a systematic review and economic evaluation
Fleming, 2008(61)	A cost study to evaluate the factors influencing hospital costs of lung cancer patients in Northern Ireland

Source: MSD CS Appendix I

Table 71 HTAs identified on the NICE website relevant to health resourcing

NICE Appraisal and year of publication	Brief study description
NICE TA181 (2009)	A cost effectiveness analysis comparing pemetrexed plus cisplatin and gemcitabine plus cisplatin for the first line treatment of NSCLC
NICE TA190 (2009) (50)	A cost effectiveness analysis comparing pemetrexed maintenance therapy with best supportive care for the maintenance treatment of NSCLC
NICE TA192 (2010)(51)	A cost effectiveness analysis comparing gefitinib with gemcitabine and carboplatin, paclitaxel and carboplatin, vinorelbine and cisplatin, and gemcitabine and cisplatin for the first line treatment of locally advanced or metastatic NSCLC
NICE TA227 (2011)(52)	A cost effectiveness analysis comparing erlotinib with best supportive care for the maintenance treatment of NSCLC
NICE TA258 (2012)(53)	A cost effectiveness analysis comparing erlotinib with gefitinib for first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC
NICE TA309 (2013)(48)	A cost effectiveness analysis of pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer.
NICE TA310 (2014)(54)	A cost effectiveness analysis of Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic NSCLC
NICE TA411 (2016)(55)	A cost effectiveness analysis of necitumumab for the first line treatments of squamous metastatic NSCLC
NICE TA447 (2018)(56)	A cost effectiveness analysis of pembrolizumab for the first line treatment of metastatic NSCLC in patients whose tumours strongly express PD-L1 (i.e., a PD-L1 tumour proportion score of 50% or greater).
NICE TA520 (2018)(57)	A cost effectiveness analysis of atezolizumab for patients with locally advanced or metastatic non-small-cell lung cancer whose disease has progressed after chemotherapy.
NICE TA500 (2018)(58)	A cost effectiveness analysis of ceritinib for patients with untreated, ALK positive advanced non-small-cell lung cancer.

Source: MSD CS Appendix I

5.1.4 Conclusions

General cost effectiveness evidence

The company did not report conclusions from the evidence included in the review of cost-effectiveness evidence since no evidence was included in their review. The ERG is unable to

comment on findings for the same reason, but notes that the final filter (UK studies only) excluded all 50 of the previously included cost-effectiveness studies.

ERG comment:

- No evidence was included. It was not necessary to limit the inclusion of cost-effectiveness studies to the UK setting since valuable information relating to strategy benefit, model structure, and model assumptions, can be garnered from other settings.

HRQoL evidence

The company described in detail their search method and extracted and presented data from 7 studies and 11 technology appraisals but did not make conclusions in the review of HRQoL evidence.

The company identified the key NICE technology appraisal TA447 (published June 2017): the cost effectiveness analysis of pembrolizumab for the first line treatment of metastatic NSCLC in patients whose tumours strongly express PD-L1. However there was inconsistency in the inclusion implementation. Whilst the objective specified first-line treatments, TA530, an appraisal of appraisal of atezolizumab in adults with locally advanced EGFR or ALK-positive NSCLC who have already had chemotherapy, was included. Whilst TA428, an appraisal of pembrolizumab at second-line in the relevant population, was omitted but later used for supportive evidence. The ERG believe the HRQoL and utility scores of people receiving second-line treatment could be used inform model inputs or validate model outputs. Therefore two other population/intervention relevant appraisals which were not identified by the search were:

- Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428), published January 2017.(62)
- Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531), published July 2018.(63)

Since the most recent search update was carried out on 2nd April 2018, TA531 would not be captured

ERG comment:

- Included studies were relevant to the decision problem.
- NICE appraisals of interventions used at second treatment line were not intended for inclusion in the utility review, despite their potential use to post-progression utility estimation and validation. In any case, the company made no conclusions about their

findings or their content, and progression based utility estimation was not the method selected for the base case.

Cost and resource evidence

The company included and presented data from 15 sources (four UK studies and 11 NICE technology appraisals). The company did not identify NICE TA428 in their search.(62) The company conclude that the identified resource use and cost studies provided some useful information for the *de novo* cost-effectiveness model. In particular regarding the quantity and frequency of the use of resources, and the unit cost of AEs, disease monitoring and management. The company states that a limitation of the cost data identified from these studies was 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.

ERG comment:

- TA428 an appraisal of pembrolizumab at second-line in the relevant population was missed in the search but included within the modelling of costs.
- The company included in their economic model evidence from numerous studies/records, including from Brown(17) and Fleming(61) which were technically excluded using their prospective criteria for review.
- The company search for economic evidence omitted important relevant evidence which was later used in support of their economic evaluation. This suggests a lack of consistency in the prospective systematic identification and use of evidence used for the company economic evaluation.
- The company have not commented on appropriateness of use of those studies heavily depended on for their economic evaluation given the time at which the study data were collected and the backdrop of changing practices with the introduction of targeted immuno-therapies.

5.2 Summary and critique of companies submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

The issues bulleted in this table are discussed in more detail in Chapter 3. The NICE reference case is specified in detail in the NICE Guide to Methods of Technology Appraisal 2013.(64)

Table 72 NICE reference case checklist

NICE Reference Case Requirements(64)	Comments with reference to the scope(65)	Issues arising
Defining the decision problem	The company's description of their definition of the decision problem builds on the scope definition, but they do not fully replicate some details. It deviates in one noted area: the company specify a more restricted population in which EFGR and ALK mutation positive patients are excluded. The company included pemetrexed maintenance therapy in combination with pembrolizumab after 12 weeks, which neither the scope specified, nor the company explicitly recognised/discussed. The company did not model pemetrexed maintenance in the comparison of PC with platinum plus gemcitabine/vinorelbine/docetaxel/paclitaxel. The company defined the detail of a sub-group analysis.	• By reducing the population to those lacking the EGFR and/or ALK mutation the submission aligned with license and the design of KEYNOTE-189.(8) • The ERG confirmed with NICE that this was reasonable and allowable. • May not reflect current clinical practice in the NHS in England and Wales.

Comparator(s)	The company describe the same list of comparator treatment strategies as defined in the NICE final scope. The company refer to the first listed comparator treatment strategy (pemetrexed in combination with a platinum drug, with or without pemetrexed maintenance treatment) as the Standard of Care.	• Ambiguity about use or pemetrexed maintenance was removed by NICE: should be included within intervention and comparator strategies. • Clinical advice to the ERG is that pemetrexed plus platinum is the standard of care.
Perspective on outcomes	The company did not list DoR but did include it in the SLR. The full set of outcomes were included only for the main comparison; only PS and OS for the remaining comparators. The company excluded PFS from the economic evaluation.	• DoR was included in the SLR • This was a serious limitation in the search and use of evidence. • This deviates from standard practice but has some merit in this condition and treatment-line.
Perspective on costs	The company describe their perspective as NHS and PSS.	• Few costs are attributable to social care.
Type of economic evaluation	A cost-utility analysis with outcomes reported as ICERs in cost per QALY gained.	
Time horizon	A 20 year effectively lifetime horizon is used. No patients are expected to be alive in either the SoC or pembrolizumab combination strategies of the model by the end of this period. The	

	baseline age of patients starting in the model was 62 years (63 in the ITT population of KEYNOTE-189).(8)	
Synthesis of evidence on health effects	SLR for the synthesis of evidence of health effects. RCT KEYNOTE-189 is used to as a single source to inform the health effect for the main comparison; multiple trials are used in an ITC NMA to inform the comparison with platinum and vinorelbine/gemcitabine/docetaxel /paclitaxel; two RCTs are used in an ITC to inform the comparison with pembrolizumab monotherapy (KEYNOTE-189 and KEYNOTE-024).(8, 34)	• The synthesis of evidence was limited by a lack of a comprehensive pre-specified qualitative approach: evidence was not presented for outcomes other than of PFS and OS for comparators outside the main comparison. • There lacked a standard meta-analysis of evidence for the main comparison.
Measuring and valuing health effects	Utilities were estimated using time-to-death (TTD), a function of OS.	• The PFS outcomes is excluded. However, expert advice to the ERG supported the use of the TTD approach: that HRQoL is better proxied by time from death (OS) than first progression status.
Source of data for measurement of health-related quality of life	Utility data incorporated into the model came from a single source, KEYNOTE-189. The evaluation of HRQoL was based on EQ-5D (-3L) data from KEYNOTE-189.(8)	• Given KEYNOTE-189 followed patients until progression/death, estimating the PD utility using only trial data would be limited. However, the TTD approach does not have this issue. However, data is limited only to patients experiencing death or progression, or more than one year from treatment start.

Source of preference data for valuation of changes in health-related quality of life	EQ-5D UK tariff values were used to calculate utility values, and therefore utilities are representative of UK preferences. Scoring used the time trade-off (TTO) technique. Mapping was not required or used.	
Equity considerations	None.	
Evidence on resource use and costs	SLR limited to the UK setting; included also NICE technology appraisals. Unit costs were appropriately drawn from standard sources. Cost year 2016-17. Some relatively minor aspects of costing relied on data published ten or more years ago.	• Loss of accuracy across all strategies, with low impact on the ICERs.
Discounting	Annual 3.5% discount applied to costs and QALYs.	
Abbreviations: NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

5.2.2 Model structure

5.2.2.1 General structure

The company submitted an economic model to assess the cost effectiveness of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy relative to SoC for treatment of people with previously untreated non-squamous non-small-cell lung cancer.

The model described in the CS was a 'partitioned-survival' method with three health states of pre-progression, post-progression, and death (Figure 15). However, the ERG note that the actual model being used for the company's base case follows a different structure (Figure 16). It is in fact driven by OS and ToT; progression status is excluded and therefore the model is not of partitioned survival. It is of the same structure as that submitted by MSD for NICE TA531, CDF Review.(63, 66)

In this model patients are categorised based on their time-to-death. Time categories are: less than 30 days to death; between 30 and 180 days to death; between 180 and 360 days to death; and more than 360 days to death. Similar to the described structure each state is attributed an exclusive utility score, but importantly, the attribution of this score to individuals is not based on their progression status and therefore survival is not 'partitioned'. As depicted in Figure 16 patients instead transit through the different survival-based utility states until reaching the death state (zero utility). This model structure departs from the classic methods used in previous appraisals of pembrolizumab monotherapy (TA447) and pemetrexed (TA181), where the partitioned survival model with three health states have been employed for a previously untreated population.(49, 56) This structure is however tested in a scenario analysis which takes the three-state partition survival approach, utilising PFS data collected in the KEYNOTE189 trial.(8)

5.2.2.2 Benefits

The proportion of patients in each health state in any given cycle is estimated the OS outcome at weekly intervals (corrected to the mid-cycle). This is an appropriate time-unit since it allows a goof fit to treatment cycle lengths, resource consumption estimates, and the chosen utility estimation technique (See section 5.2.7).

The estimation of OS for those surviving beyond the trial follow-up period are statistically predicted using the best judged parametric distributions, which was applied to the Kaplan-Meier plots of KEYNOTE-189 (See section 5.2.6).(8) The model's time horizon is 20 years (lifetime).

Figure 15 Model structure as reported in the company submission

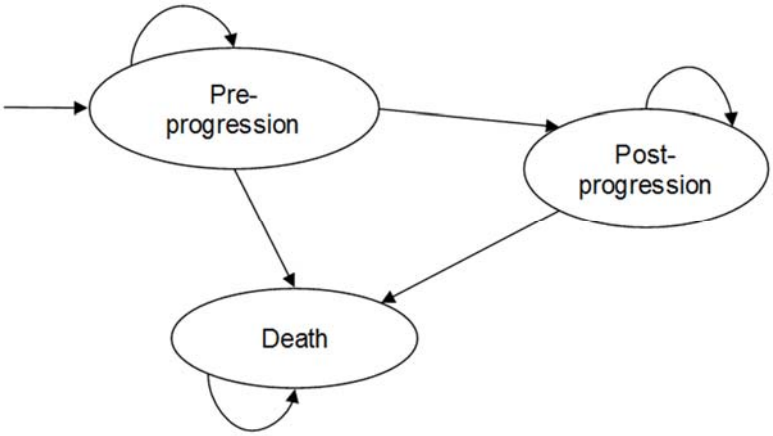
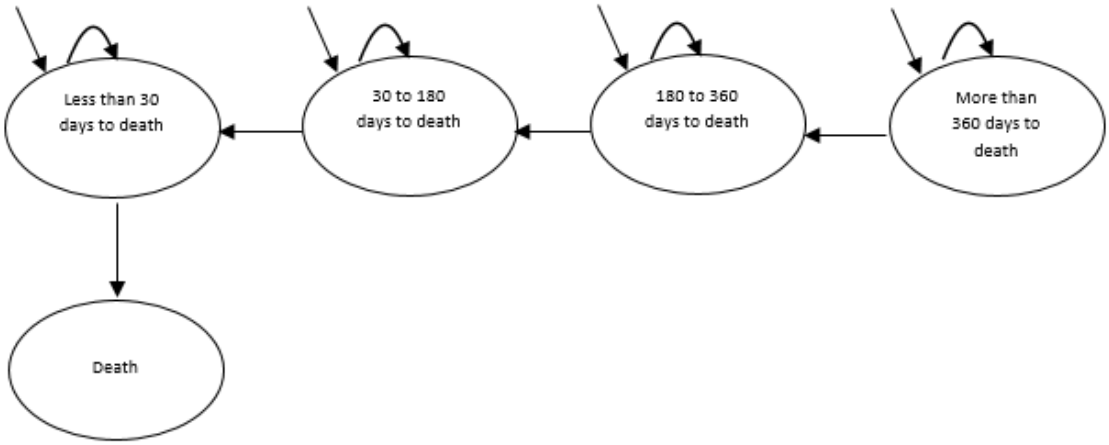


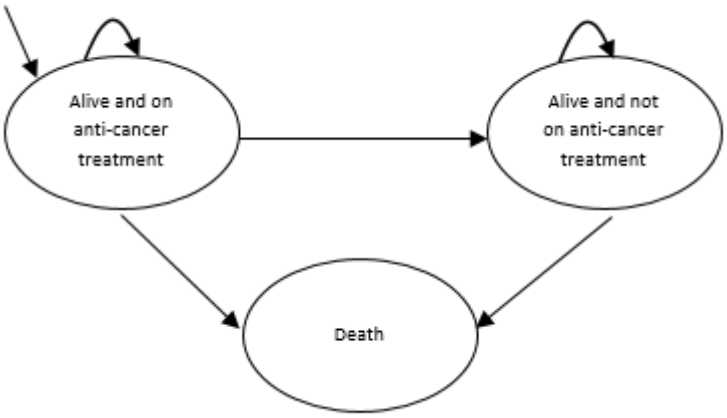
Figure 16 Actual model of the company base case, in respect to the utility evaluation



5.2.2.3 Costs

The calculation of costs in the company's base case does not overlay the utility-driven health states, but in all strategies is based on whether or not a patient remains on active anti-cancer treatment (modelled as far as second-line treatment). The cost-analysis structure depicted in Figure 17.

Figure 17: Actual model of the company base case in respect to the cost evaluation



At the point of first-line treatment discontinuation patients receive a further second-line of anti-cancer therapy. After second-line in the model, therapy is no longer considered active/anti-cancer, and at this point a second set of resources are applied.

Costs applied in a 'one-off' fashion, to the first model cycle, were the PD-L1 test cost, and those associated with the management of severe adverse events. The ERG note that the company applied PD-L1 test costs only to those patients who go on to receive pembrolizumab. Expert clinical opinion elicited by the ERG is that all patients with a new lung cancer diagnosis now routinely undergo tests for biological markers in the NHS, including the PD-L1 test; and the results are then used to help determine the treatment plan.

For patients in the pembrolizumab combination strategy pembrolizumab administration is modelled in three-weekly cycles from week 1 for up to two years. A two year stopping rule was modelled to reflect the design of KEYNOTE-189(8)). This does not reflect the licence of pembrolizumab for this indication. Pembrolizumab for the first 12 weeks combined with a fixed course of platinum-based chemotherapy and with pemetrexed (each for up to four cycles). In the model, pemetrexed maintenance therapy could then be commenced, but its discontinuation did not inform the time-on-treatment statistic (see section 5.2.8.6). Patients in the SoC strategy also received up to four cycles of platinum-based chemotherapy treatment. This was combined with 'upfront' pemetrexed and followed by pemetrexed maintenance therapy. In this strategy, the discontinuation pemetrexed maintenance did inform the time-on-treatment statistic.

5.2.2.4 Sub-group analysis

A sub-group analysis was conducted where the sub-populations were based on different levels of PD-L1 expression (≥50%, 1%≤TPS≤49% and <1% TPS). Otherwise approaches, underlying model assumptions, and estimates remained the same.

In KEYNOTE-189 patients were allowed by protocol to switch from the SoC ('trial chemotherapy' arm) to the pembrolizumab combination arm.(8) However, no adjustment in effect size was made for cross-over in the model. This approach was appropriate since alternative immune-therapy options are available as standard at second-line, and the cross-over effect in KEYNOTE-189 does to some degree approximate their benefit. For the sub-group of patients with <1% TPS there is no second-line immune-therapy option available, so in this case (only), adjustment for cross-over was included.

5.2.2.5 Comparison with platinum plus chemotherapy

Effect sizes were not derived from separately fitted parametric distributions but applied hazard ratios (gemcitabine, vinorelbine, docetaxel, paclitaxel) to the baseline performance of the PC strategy (see section **Error! Reference source not found.**).

ERG comment:

- The structure departs from the standard three health state partition survival model: it uses four states to estimate utility, based on the OS outcome, using a time-to-death approach; costs are aligned to treatment intent; progression status does not drive the base case.

- The structure has clinical merit, and in the view of the ERG represents a reasonable and appropriate simulation. There is precedence in MSD's previous submission for NICE TA531 (CDF Review).(63)
- Pembrolizumab in combination is modelled to a stopping-rule of two years. This does not reflect the license specification.
- Subsequent therapy is modelled only as far as second-line.

5.2.3 Population and sub-populations

5.2.3.1 Whole population evaluations

The NICE scope defines the population for this evaluation as *"Adults with untreated metastatic non-squamous NSCLC".(65)* The company go on to exclude people with a sensitizing EGFR mutation or ALK translocation, and specify untreated as no prior systemic chemotherapy treatment. Both refinements retain alignment with the expected licenced indication for pembrolizumab used in combination, and the populations from studies providing the clinical effectiveness evidence.

The main body of clinical effectiveness evidence for the main comparison, pembrolizumab combination versus pemetrexed in combination with carboplatin or cisplatin (SoC), was

derived from the KEYNOTE-189 study.(8) This trial also states that patients must also have an ECOG performance status 0 or 1, and had at least one metastatic lesion according to RECIST version 1.1.The staring age of patients in the model was 62 years. This compares to a mean age in the ITT population of KEYNOTE-189 of 63 years, and median age of 64 years (range 34-84 years).(8)

The evidence for the additional comparisons versus chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with carboplatin or cisplatin was derived from 16 separate trials, for which PFS and OS outcomes were considered in a network meta-analysis (see section 4.4.1). Evidence was limited to non-squamous NSCLC stage 3 or 4. There was little evidence provided on baseline characteristics which prevented the assessment of sources of heterogeneity (see section 4.4.4), including EGFR and ALK status.

5.2.3.2 Sub-population evaluations

Pembrolizumab monotherapy (PDL1 TPS ≥50%)

The evidence for comparison of pembrolizumab combination versus pembrolizumab monotherapy comprised data from the RCTs KEYNOTE-024 and KEYNOTE-189.(8, 34) The population selected from the KEYNOTE-024 were those with non-squamous histology and PD-L1 TPS ≥50%; the population from the latter was the sub-population strongly expressing PD-L1 (TPS ≥50%).

PD-L1 TPS sub-group analysis

Sub-groups were defined by different levels of PD-L1 expression (≥50%, 1%≤TPS≤49%, and <1% TPS). Evidence for this analysis was drawn from KEYNOTE-189.(8)

ERG comment:

- The modelled population matched that of the scope and is clinically relevant. The company provided an additional analysis of cost-effectiveness according to PD-L1 expression; and of a comparison with pembrolizumab monotherapy in strong expressers of PD-L1 only.
- The ITC analysis used to compare PC with platinum plus chemotherapy, for which there was no evidence from direct head-to-head trials, was limited by significant heterogeneity between studies.

5.2.4 Interventions and comparators

5.2.4.1 Intervention

The indication for pembrolizumab in this evaluation is in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations (MSD CS B1.2). The intervention is referred to by the company, and in this report, as pembrolizumab combination (PC).

The doses modelled were pembrolizumab (200mg fixed) plus cisplatin (75mg/m^2) and pemetrexed (500mg/m^2), or plus carboplatin (400mg) and pemetrexed (500mg/m^2). Pemetrexed maintenance (PM) when taken-up (cisplatin users only by license) was from week 13 (500mg/m^2). All drugs within the regimen were administered Q3W.

When used in subsequent lines of therapy, the dose of pembrolizumab remained fixed at 200mg.

5.2.4.2 Main comparator

The first comparator is the pemetrexed in combination with a platinum drug (cisplatin or carboplatin), with or without pemetrexed maintenance therapy; both in the context of the whole population, and analysed according to the level of PD-L1 expression in a sub-group analysis. This comparator is described by the company as the standard of care (SoC), and was verified as such by independent expert clinicians consulted by the ERG.

The doses used in the model were cisplatin (75mg/m^2) plus pemetrexed (500mg/m^2), or carboplatin (400mg) plus pemetrexed (500mg/m^2). These are standard doses which were not varied except for their administration frequency versus target. The platin chemotherapies were modelled to a maximum of four Q3W treatment cycles.

When pemetrexed maintenance (PM) was taken-up (cisplatin users only by license), the dose was unchanged (500mg/m^2). The uptake of pemetrexed maintenance differed by treatment strategy (87.6% for PC; 100% for SoC). Note that the scope did not specify the use or otherwise of pemetrexed maintenance after pembrolizumab combination; but did specify the option of pemetrexed maintenance as part of SoC.(65)

The comparison of pembrolizumab combination (PC) with pemetrexed in combination with pemetrexed in combination with a platinum drug (SoC) is referred to as the ‘main’ comparison.

5.2.4.3 Other comparators

The other comparators listed in the scope and modelled by the company were 'chemotherapies' in combination with a platinum drug, with the option of pemetrexed maintenance. Note that pemetrexed is also a chemotherapy. Four chemotherapies were specified: gemcitabine, vinorelbine, docetaxel, paclitaxel; and each was modelled individually by the company.(65)

The doses modelled were: Platin (75mg/m^2 cisplatin or 400mg carboplatin) plus gemcitabine (1250mg/m^2); Platin (75mg/m^2 cisplatin or 400mg carboplatin) plus vinorelbine (27.5mg/m^2); Platin (75mg/m^2 cisplatin or 400mg carboplatin) plus docetaxel (75mg/m^2); Platin (75mg/m^2 cisplatin or 400mg carboplatin) plus paclitaxel (200mg/m^2). All were administered once every three weeks (Q3W) for a maximum of four cycles.

The final comparator listed in the scope was pembrolizumab monotherapy.(65) Here the population was limited to the license of the monotherapy, which is for strong expressers of PD-L1 only (TPS score ≥50%). The dose was 200mg fixed, administered Q3W by intra-venous infusion.

ERG comment:

- The intervention was modelled with the exclusion of patients ALK+ or EGFR+; and with a two-year stopping rule. Otherwise it was modelled according to the scope and the product license.
- Comparators were modelled to the remit of the scope and their respective licenses.
- Intervention and comparators were modelled so as to align with their use in the key sources of clinical effectiveness evidence.

5.2.5 Perspective, time horizon and discounting

The company model took the perspective of the NHS and PSS as is preferred by NICE.(64) Included resources related to PSS or social care were limited to some small elements within the cost of terminal care. But overall it reasonably included all health-benefits relevant to patients that were specified in the scope.

The base-case model used a 20-years effectively lifetime horizon for the target population. Since 0% of patients in the pembrolizumab combination arm and 0% in the SoC arm were still alive after this period it was therefore long enough to capture the differences between strategies in costs and benefits. Future costs and benefits were discounted using an annual rate of 3.5%. However, some costs were simulated as one-off: those associated with adverse events were all applied at the start of treatment; and those associated with

subsequent lines of treatment (not insignificant) were applied at their initiation rather than throughout the course of therapy.

ERG comment:

- Perspective, time horizon and discounting are consistent with NICE reference case preferences.(64) Simplifications in costing were reasonable.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 General approach

The efficacy of the pembrolizumab combination treatment strategy and of the main comparator were based on the data from the relevant treatment arms of the KEYNOTE-189 clinical trial, using the November 2017 data cut.(8) OS and PFS have been modelled by fitting parametric distributions to parts of the KM data, although PFS is not taken into consideration in the company's base case, despite suggestions to the contrary in the company's report (E.g. in MSD CS B.3.2.2).

The same data has also been used to estimate treatment safety. The type and frequency of Grade 3+ AEs, which are used to determine a one-off cost associated with AEs for each treatment arm (see section 5.2.8) are based on observations from KEYNOTE-189, as is the disutility associated with AEs for each treatment arm (see section 5.2.7).(8) Treatment tolerability has been incorporated by fitting to the full KM data of ToT distributions, separate for both treatment arms and from the PFS distributions. The reasons for treatment discontinuation in the trial are given in MSD CS Appendix N.

According to the company's report (MSD CS B.3.3.1), the guidance within NICE DSU TSD 14 was followed when fitting the distributions for OS and PFS; and the first step was to test the assumption of proportional hazards.(67) The TSD states that it is preferable to fit separate distributions for the treatment arms when patient-level data is available for each, as is the case with KEYNOTE-189, since this requires fewer assumptions. The assumption of proportional hazards should be tested, though, as this will indicate whether an approach using time-varying hazards would be appropriate.

HRQoL estimates were based on time to death (TTD), and ToT is not used for the disutility of adverse events (see section 5.2.7), which means that the distributions for OS alone determine the modelled treatment effect.

5.2.6.2 Overall survival main comparator

On finding that the proportional hazards assumption does not hold for OS, the company fitted standard parametric curves to the full KM OS data (i.e. from week 0) for both treatment

arms. AIC and BIC statistics, which assess goodness-of-fit and parsimony, were calculated (MSD CS Appendix L). Exponential curves were then chosen for both treatment arms, despite providing a poorer statistical fit for the SoC strategy (the only one of the two reaching a median survival compared to some of other the distributions considered.(8)

If the curves alone were used over the time-horizon, it would imply a constant hazard ratio between the two treatment arms, an assumption the company already falsified. The company write that it would therefore be more appropriate to use a piecewise model rather than single parametric curves, although their approach could be described as using both: the KM data has been used directly until a cut-off point (at 28 weeks, in the base case) and then a single parametric curve, appended to the data beyond the cut-off point, has been used for extrapolation beyond it. In doing this, the company are implicitly assuming that the hazard ratio is constant beyond the cut-off point, despite having identified two points (at 38 and at 52 weeks) lying beyond this in the base case at which the gradient of the curves in the cumulative hazard plot change (the latter lying beyond the cut-off point in all of the scenarios considered).

This is despite the advice in TSD 14 that, for piecewise constant models, exponential distributions with different rate parameters should be fitted to each of time periods identified as having different (constant) hazard rates.(67) No explanation has been given as to why this approach was not taken. Notwithstanding the selection of the exponential distribution (which has a constant hazard rate) and the identification of four points at which the gradient of the cumulative hazard curves change, the company chose in their base case to use a piecewise model with only two phases, citing precedent for the use of such models in previous NICE appraisals (appraisals of MSD's pembrolizumab at first-line [TA447] and second-line [TA428] advanced PD-L1 positive non-squamous NSCLC; and necitumumab at first-line advanced/metastatic squamous NSCLC [TA411]).(55, 56, 62)

To support the decision to fit the same type of parametric model for both the pembrolizumab combination arm as for the SoC arm for OS, the company cite the TSD, which states that substantial justification would be required otherwise.(67) It is worth noting that this decision has a significant impact on the model results: for example, with a 28 week cut-off (as in the company's base case), choosing the distributions for OS that provided the best statistical fit for each treatment arm would result in the pembrolizumab combination strategy being dominated by SoC. With this cut-off, the exponential distribution provides the worst statistical fit for the SoC strategy of the distributions considered. Details of the ERG's preferred approach are given in section 6.1.1.

5.2.6.3 Time-on-treatment

Different types of parametric models have been selected for ToT, with no other justification than that these provided the best statistical fit, and even this has only been given for the sub-group analysis (MSD CS B.3.9). In their Appendix N the company state that a comparable methodological approach was used in the sub-group analysis as in the base case when modelling ToT. As the guidance in TSD 14 relates to survival analysis, it should be noted that ToT has been used in the company's model instead of PFS when determining disease management costs, even in the scenario in which utility is based on progression status. (There is, however, a setting in the model which allows for ToT to be set equal to PFS).

Although Table 84 (MSD CS B.3.5.1) suggests otherwise, ToT has been modelled using separately fitted parametric distributions for both treatment arms. While the CS states that the distribution for the pembrolizumab combination arm was fitted to the first two years of the ToT KM data, the portion used for the SoC arm has not been specified. Cut-off points relating to observed changes in gradient have not been considered for ToT, though an exponential distribution has been fitted for the pembrolizumab combination arm and, in both arms, ToT is used instead of PFS. (Points of treatment discontinuation have been included, as described in section 5.2.4).

5.2.6.4 Progression-free survival

Cut-off points were chosen when fitting distributions for PFS in the base case and in the scenario analyses, though these were not identified in the same way as those for OS: each is seven weeks shorter than the corresponding point for OS. This is reportedly due to a drop in observed KM PFS between weeks 0 and 6, as a result of the first tumour assessment in the trial not taking place until after the initial radiologic assessments (MSD CS B.3.3.1).

The company described that this also meant that full parametric curves could not to be fitted (MSD CS Appendix L) but, from their report, it is unclear to which portion of the KM data the curves were fitted. Upon receiving the R code and replicating the company's results, it was found that the distributions used in their base case have been fitted to the data of patients who had not progressed nor died by week 21 in the trial. The KM data has been used for PFS directly up until the cut-off point (at 21 weeks, in the base case) and the fitted curve for extrapolation beyond it. The use of cut-off points based on those for OS is despite the fact that a different type of parametric model has been chosen for PFS: the Weibull distribution, as opposed to the exponential, is used for both treatment arms. Unlike for OS, there is no option in the company's model for selecting parametric distributions for PFS without using one of three cut-off points. In some scenarios, the use of a cut-off point for OS makes a

significant difference to the results. This may also be true for PFS, although not in the company's base case, in which the PFS distributions have not been used.

5.2.6.5 Capped survival

OS has been capped by the survival rate for the general population: the mortality rate for the patient population in any given model cycle must be at least equivalent to the mortality rate from ONS life tables.(68) This also does not make a difference in the company's base case, where exponential distributions with a 28 week cut-off point have been selected for OS, although it does in other scenarios.

5.2.6.6 Duration of effect

The treatment effect, i.e. the improved OS of patients in the pembrolizumab combination arm relative to those in the SoC arm, remains evident in the base case over approximately 14 years of the 20-year time-horizon. The justification for this is that there is no evidence of the treatment effect discontinuing after patients finish treatment (MSD CS B.3.2.2, Table 62). A company scenario has been presented in which the difference in effect between arms is reduced at 5 years by introducing the mortality rate for SoC to PC (MSD CS B.3.8.3). The company's model allows for longer periods to be considered, but not shorter than 5 years. No reason has been given for this imposed limitation. Details of the ERG's preferred approach are given in section 6.1.3.

5.2.6.7 Background mortality

No adjustment of the extrapolated period was made for increasing mortality from other causes as age increases, and no justification for its omission was provided. This can be an important adjustment when extrapolation is long and based on short trial follow-up. The KEYNOTE-189 KM curves used for OS estimation were based on a median follow-up of 10.5 months(8); and were extrapolated to twenty years (although the company estimate 0.1% alive at 10 years). Inclusion of background mortality adjustment tends to impact strategies offering extended survival, and in this case its omission has led to an underestimation of the ICERs. Details of the ERG's preferred approach are given in section 6.1.2.

5.2.6.8 Clinical validation of statistical estimates

The company included in their process of distribution selection the input of eleven clinicians to estimate 5 year survival percentages for current SoC (MSD CS B.3.3.3; and Clarification response B2(69)). The question asked was:

> *For a patient diagnosed today with non-EGFR or ALK mutated non-squamous NSCLC, what would be the five year survival rates?*

Nine out of eleven clinicians responded with quantifiable answers (Table 73).

Table 73 Clinical expert advice elicited by the company

5-year OS (SoC)	Number of estimates
0%	2
1%	1
2-3%	1
3-5%	3
5-10%	2

Abbreviations: OS = Overall survival; SoC = Standard of Care.

Estimates elicited by the ERG for SoC were in the 5-10% 5-year survival range.

The company base estimates of 5- and 10-year OS are presented in Table 74, along with estimates from relevant previous NICE technology appraisals. Comparison for company base case estimates with input from expert clinicians, and the preference of the ERG of TA447,(66) would suggest that the company's selection of exponential with a single 28-week cut-point may underestimate OS on SoC.

Table 74 Comparative estimates of 5- and 10-year OS with SoC

Source/Population	5-year OS	10-year OS
SoC Company model: SoC for untreated PD-L1-positive mNSCLC	2.40%	0.10%
ERG preference within NICE TA447: SoC for untreated PD-L1-positive mNSCLC(66)	9.60%	1.50%

Abbreviations: mNSCLC = Metastatic non-small cell lung cancer; OS = Overall survival.

5.2.6.9 Second-line treatment effect

The effect of second line treatment was incorporated in the base case by not applying an adjustment for cross-over. This approach was appropriate since alternative immune-therapy options are available as standard at second-line, and the cross-over effect in KEYNOTE-189 does to some degree approximate their benefit.

5.2.6.10 Other whole population comparators

For the comparison with platinum plus chemotherapy (gemcitabine, vinorelbine, docetaxel and paclitaxel) effect sizes were not derived from separately fitted parametric distributions but rather hazard ratios were applied to the baseline performance of the pembrolizumab

combination strategy. The estimated OS of patients for the comparator strategy at any time point was taken to be equal to the OS from the fitted distribution for pembrolizumab combination at that time point raised to the power of a constant hazard ratio, derived from the NMA (see section 4.4.1). (OS HRs are presented in Table 59). The model settings also allow for the consideration of time-varying hazard ratios, but this approach was deemed to be less intuitive and more difficult to justify by the clinical experts consulted by the company, since it involved more extrapolation (MSD CS B.3.10.1).

The same method as for OS was used to determine PFS for the comparator strategies, with PFS from the fitted distribution for the pembrolizumab combination arm raised to the power of a constant PFS hazard ratio in each model cycle (PFS HRs from the NMA are presented in Table 60). ToT for the comparator strategies was taken to be the same as that for the pembrolizumab combination strategy.

5.2.6.11 Sub-populations

Strong expressers of PD-L1 (≥50% TPS)

Two comparisons of treatment strategies versus pembrolizumab combination therapy have been carried out for the sub-population of non-squamous patients strongly expressing PD-L1: for SoC and for pembrolizumab monotherapy therapy.

For the former, the same approach has been taken as in the main comparison, but with the distributions fitted only to the trial data corresponding to the sub-population. According to the company's report, the same selection of distributions and cut-off points has been made so that there is consistency with the base case results (MSD CS B.3.9). However, an exponential distribution has been chosen to model ToT for SoC rather than a Weibull distribution, which has been used for the overall population.

As with the other comparators that are not considered in KEYNOTE-189, OS for pembrolizumab monotherapy has been calculated by applying a constant hazard ratio to OS for pembrolizumab combination therapy. This hazard ratio is derived from the ITC of pembrolizumab combination therapy versus pembrolizumab monotherapy for non-squamous patients with TPS ≥ 50%, using the Bucher method with population adjustment (see section 4.4.2).

The same approach has been used for PFS. The KM data from KEYNOTE-024 has been used directly for ToT of the pembrolizumab monotherapy: a parametric distribution has not been fitted, as is the case for the pembrolizumab combination therapy using the KM data from KEYNOTE-189. No explanation has been given for this in the company's submission.

Sub-group analysis

For non-squamous patients with 1% ≤ TPS ≤ 49%, the same approach has been used to compare pembrolizumab combination therapy with SoC as for those with TPS ≥ 50%. For patients with TPS ≤ 1%, two other approaches have been considered as well for OS, which do not use a 2 phase piecewise model (MSD CS B.3.9.1). In the IPCW approach exponential distributions have been selected for both strategies, while a lognormal distribution has been chosen for SoC in the RPSFT approach. Additional subgroup analyses have also been carried out for the ITT population (for details, see MSD CS Appendix E). The ERG agrees with the company that caution should be taken when interpreting these results, due to the small sample sizes.

ERG comment:

- The distributions for OS alone determine the modelled treatment effect. The choice of curves and cut-off points for OS can therefore make significant difference to the model results.
- Modelling of the relative effect size of second-line therapy is simply approximately by not adjusting for cross-over between arms of KEYNOTE-189, the single evidence source. This simplification introduces uncertainty which has not been explored (32.5% of patients in the SoC arm had crossed over during the trial to receive pembrolizumab monotherapy *after* disease progression).
- The company base case method predicts low estimates of long-term survival for the SoC arm, and deviates from technical best practice.

5.2.7 Health-related quality of life

The utility estimates were derived from the HRQoL analyses carried out in KEYNOTE-189, whereby patients completed the EQ-5D questionnaire at baseline, particular treatment cycles, at treatment discontinuation and at the safety follow-up visit 30 days later (MSD CS B.3.4.1). Pooled estimates were used in the company's base case, so there is no difference in the utility inputs between the two treatment arms, as is preference.(64) Utility estimation was based on time-to-death (TTD) and modelled accordingly, hence, in the base case, the distributions for OS alone determine the relative HRQoL of patients in the two treatment arms.

Four alive health states for HRQoL are considered, with patients categorised accordingly to whether their TTD is greater than or equal to 360 days, between 180 and 360 days, between 30 and 180 days, or less than 30 days (henceforth referred to, using the labels from the company's model, as the ≥360, [180, 360), [30, 180) and (0, 30) states). It should be noted that each of these 'health states' have associated utility values, but not associated costs,

which were analysed using a different model structure (see section 5.2.2). As would be expected, states representing a longer TTD have a higher utility value associated with them (MSD CS B.3.4.5).

Since the time spent in all but the ≥360 state is fixed for all patients, an increase in survival would result in more time spent in this health state and a higher proportion of time alive spent in this state. Hence, an increase in survival would not only increase the QALYs gained by each patient, but also their average HRQoL per year of life. Indeed, the ICER was found to be sensitive to the utility input for this state.

A limitation of using TTD is that data from a large number of patients is not available. Data for patients remaining alive and less than one year from commencement of treatment can not inform the analysis since the do not qualify for any health state. Although a single patient's data can contribute to all four. Of six-hundred and two patients in the trial who were invited to complete questionnaires at baseline, [redacted] did so. By week 30, [redacted] completed a response. At the November 2017 data cut-off, [redacted] responses were available for the ≥360 state; [redacted] responses for the [180, 360); [redacted] for the [30, 180) state; and [redacted] for the (0, 30) state. Table 75 shows the mean estimates of the pooled results.

Table 75 Detail of utility survey and state means for TTD method

State	n†	m‡	Mean utility	SE	95% CI
≥360	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[180, 360)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[30, 180)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n† = Number of patients with non-missing EQ-5D score; m‡ = Number of records with non-missing EQ-5D score; EQ-5D score during baseline is not included.

Source: MSD CS Document B Table 67, Page 134

The estimates used in the model are presented in Table 76. An age-related utility decrement was included seperately (MSD CS B.3.4.5).

Table 76 Mean utility values for health state used in the model

State	Company model
≥360	[redacted]
[180, 360)	[redacted]
[30, 180)	[redacted]
<30	[redacted]

Source: MSD CS Document B Table 70, Page 142

A small utility decrement due to aging has, however, been applied. This varies per year lived up until an age of 75 years, beyond which the disutility due to age is constant (at approximately -0.0526). The decrement is calculated using average utility values by age category for the general population, published by Kind *et al*.(70) A one-off utility decrement associated with grade 3+ AEs has also been applied in the first model cycle (MSD CS B.3.3.2).

In the company's base case, the difference between the pooled utility values of progression-free patients who did or did not experience grade 3+ AEs, at the time points associated with these in KEYNOTE-189 (MSD CS B.3.4.4), was used as the disutility associated with a grade 3+ AE for both treatment arms. Although a pooled value for the duration of grade 3+ AEs has been used in all scenarios considered, the risks of experiencing these in each treatment arm have been used to calculate the average disutility per patient due grade 3+ AEs for each treatment arm. This is the one-off decrement associated with grade 3+ AEs and, in the company's base case, is the only difference in health effect between the treatment arms that is not caused by the OS distributions.

To explain why an approach based on TTD rather than on progression status was chosen for evaluating utility in their base case, the two studies on advanced melanoma have been cited in the company's report that are said to have shown that the former approach is more suitable.(71, 72) The first source is a poster by Batty *et al* comparing the EORTC QLQ-C30, standard gamble and SF-36 methods, which is not relevant for this appraisal.(71) Indeed, TTD was not even mentioned. The second, a paper by Hatswell *et al*, does conclude that TTD was more relevant than progression status for an advanced melanoma trial, but gives a number of reasons why similar results might not be reproducible with other datasets, including the nature of disease, the type of treatment used and the maturity of the trial (90% of patients had died on completion).(72)

According to the company's report, the two studies find that the TTD approach is more suitable because a better statistical fit is achieved by using a greater number of health states (MSD CS B.3.4.1). It is not necessarily the case that an approach with more health states will provide a better fit (this would depend on which states were more appropriate) and the paper by Hatswell *et al* recommends that statistical analysis is carried out on patient-level utility data to determine whether or not progression status alone is sufficient.(72) There is no indication in the submission that the company have done this. One of the two other studies cited as precedent, by van den Hout *et al,* does not use TTD utility scores.(73) The other, by Huang *et al*, considers TTD and progression status individually and finds that both are

strongly associated with utility deterioration for untreated metastatic NSCLC patients.(41) In TA428, the pre- and post-progression health states were divided in sub-health states reflecting TTD. Two sub-health states were used, with patients categorised accordingly to whether their TTD was greater than or equal to 30 days, or less than. However, unlike the approach based on progression status alone, this is not included as a scenario analysis in the company's report, nor there is there an option for this in the model. According to company Table 85 (MSD CS B.3.6.2), there were 'limitations to using a combined approach', but this has not been elaborated on elsewhere in the submission.

No precedents have been cited nor explanation been given for the choice of the four (alive) health states based on TTD. Huang *et al* and Chang *et al* both use the same five (alive) health states based on TTD: ≥360, [180, 360), [90, 180), [30, 90) and (0, 30).(41, 42) For company scenario 8, in which the utility values from the study by Chang *et al* have been used, the utility value for the [30, 90) state has been used for the [30, 180) state in the company's model, while the value for the [90, 180) state has been discarded. This has not been mentioned in the report (MSD CS B.3.8.3) but it is a conservative selection. It has also not been explained why the utility values from study by Huang *et al* were not considered as an alternative scenario. See section 5.2.12 for a comparison of health state utility values used in the model and other economic evaluations in NSCLC.

ERG comment:

- The time-to-death approach used in the company base case has little precedent, but is supported by the clinical opinion gathered by the ERG that HRQoL in this populations correlates better to TTD than occurrence of first progression.

5.2.8 Resources and costs

5.2.8.1 General approach

The structure of the cost analysis followed the use of active therapies, which was limited to first- and second-line anti-cancer treatment. Thereafter resources were modelled to resemble consumption aligned to non-curative intent, signified by a reduction in monitoring and an increase in community-based care. Active treatments included the immunotherapies pembrolizumab, nintedanib, and nivolumab. Nintedanib and nivolumab at second-line only. Active treatments also included the systemic cytotoxic chemotherapies.

In their description of the cost attribution the company erroneously describe a three-health state modelling in which monitoring and disease management costs are applied using 'pre-progression' and 'post-progression' labelling (MSD CS B.3.5.5). In fact, the division of this cost category is applied not at [first-] progression but at the discontinuation of active (anti-

cancer) therapy at second-line. Nonetheless, the components of on- and off- active treatment resource sets were appropriate.

The company estimate the time on active treatment by summing the time on first-line treatment (proportions extrapolated from KM curves of KEYNOTE-189) and the time-on second-line treatment (fixed estimates). See section 5.2.6.3 for the critique of the ToT methods, and section 5.2.8.9 for detail of the duration of second-line therapy. The company preferred the time on treatment approach to a progression-status approach for costing:

"…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." (MSD CS B.3.5.1)

The extent of discontinuation prior to progression, or the degree of treatment beyond progression was not presented in the CS. However, for this previously untreated population, subsequent lines of active therapy are available after first progression and these would require similar supportive resources as first-line options.

ERG comment:

- A costing approach based on time on active (anti-cancer) treatment, rather than progression, is reasonable but any direct link (E.g. via PFS) between benefits and costs is lost.

5.2.8.2 Drug acquisition cost

Pembrolizumab

Pembrolizumab was costed according to the licensed dosing when used in combination at first-line (MSD CS Appendix C), and the licensed dosing when used at second-line or as first-line monotherapy.(74) In all cases this was 200mg fixed dose administered by IV infusion every three weeks. The list price of a 100mg vial is £2,630.00 (200mg administration = £5,260). In this report, a tentative [redacted] price is also explored, the result of a commercial arrangement with the Patient Access Scheme Liaison Unit (PASLU). This equates [redacted] per administration.

Comparator drugs

The ERG are satisfied that the acquisition unit costs of adjunct and comparator drugs were taken from the preferred sources appropriately (eMIT, BNF and MIMs, in order of preference).(75, 76) See Table 77.

Dosing

Dosing of non-fixed dose therapies was sourced in the first instance from observation in the KEYNOTE-189 trial, then the drug SmPC.(8) Whilst this is a reasonable approach it should be noted that posology information in the SmPC is advisory and provide no indication as to the weight or body surface area (BSA) of recipients; and the KEYNOTE-189 trial had fewer than 5% (30/616) of participants recruited from the 7 centres in the analysis setting ('UK' NHS). As a result any variation between average international dosing trends and preferences in KEYNOTE-189 and NHS preferences will be introduced. For example, average BSA. In the model this was a weighted calculation of male and female averages of the 374 patients across the trial's European sites (1.81m^2). However, the incremental cost-effectiveness ratios of pembrolizumab versus the comparators are unlikely to be significantly sensitive to this limitation. Details of dosing frequency, unit cost and source are presented in Table 77.

Table 77 Dosing, frequency and unit costs per administration for comparator drugs

Drug	Dosing per administration	Freq. of administration	Total dose	Cost per mg	Cost per administration (assuming no wastage)	Reference for dosing	Reference for drug costs
Pembrolizumab	200mg	Q3W	200mg	£26.30	£5,260	SmPC	BNF
Docetaxel	75mg/m^2	Q3W	135.75mg	£0.18	£25.01	SmPC	eMit
Gemcitabine	1250mg/m^2	Q3W	2262.50mg	£0.01	£35.07	SmPC	eMit
Paclitaxel	200mg/m^2	Q3W	362mg	£0.07	£23.75	SmPC	eMit
Vinorelbine	27.5mg/m^2	Q1W	49.78mg	£0.10	£15.08	SmPC	eMit
Carboplatin	400mg/m^2	Q3W	724mg	£0.04	£30.13	KEYNOTE-189	eMit
Cisplatin	75mg/m^2	Q3W	135mg	£0.09	£12.16	KEYNOTE-189	eMit
Pemetrexed	500mg/m^2	Q3W	905mg	£1.60	£1,448.00	KEYNOTE-189	MIMS

Source: MSD, CS Document B, Table 72 page 146

Vial sharing

In what the company describe as a conservative assumption underlying their base case, a policy of vial sharing was implemented. This means that IV delivered drug in any part-used vials are incorporated into the administration of subsequent patients. As such potential drug

wastage is effectively reduced. This assumption applies to all comparator drugs except pembrolizumab (carboplatin, cisplatin, gemcitabine, vinorelbine, docetaxel, paclitaxel). Since the consumption of these specific drugs - as a proportion of the total strategy drug acquisition cost - is higher with the comparator strategies than the pembrolizumab combination strategy, the cost saving is most significant in these, and so the assumption is indeed conservative.

Choice of platinum drug

In respect to the clinical selection of carboplatin versus cisplatin for combination therapy strategies (I.e. all treatment strategies but pembrolizumab monotherapy), the company selected for their base case the ITT population of the KEYNOTE-198 trial as the source for a weighted estimate of platinum-therapy drug cost.(8) In the trial, [redacted]% of platinum therapy was cisplatin and [redacted]% was carboplatin. This contrasts with advice received by the ERG from independent clinical experts (cisplatin is chosen ahead of carboplatin because it allows access to pemetrexed maintenance); and varies from the UK market share of cisplatin + pemetrexed versus carboplatin + pemetrexed (43.6% to 56.4%, relatively) (MSD CS B.3.5.1, Table 73). However, the proportion of one platinum relative to the other is meaningful only to the cost analysis (not the clinical effect) and has a non-significant impact on costs or ICERs. A scenario based on expert clinical opinion (90% cisplatin) increases the ICER insignificantly.

Total drug acquisition cost per administration

The resultant combined therapy costs (strategy drug acquisition costs), per administration, are presented in Table 78.

Table 78 Drug acquisition cost per administration for treatment strategies of the main comparison (unadjusted for dose intensity)

Strategy	Overall population
Pembrolizumab combination	£6,733.16
Standard of Care (SoC)	£1420.12

Adapted from: MSD CS Document B, Table 74 page 147

5.2.8.3 Time on treatment, dose interruptions and reductions

The company state the expected licence will specify that patients receiving pembrolizumab are to be treated until disease progression is confirmed, adverse events, inter-current illness, protocol compliance, or investigator or patient preference. However, in the model and in the key trial KEYNOTE-189, a stopping rule was implemented, setting a two-year limit to

pembrolizumab treatment. Fourteen per cent of patients were still on pembrolizumab combination treatment at the cut-off date, approximately 85 weeks or 1.6 years from treatment initiation.(8) A parametric distribution was fitted to each Kaplan-Meier plot (November 2017 cut-off) of patients on treatment to smooth and extrapolate until – [effectively] all patients were discontinued from first-line active treatment. The time on second-line anti-cancer therapy was fixed added separately (see section 5.2.8.9 for detail of the modelling of subsequent treatments). Using AIC and BIC goodness-of-fit values and visual inspection, the company fitted an exponential distribution to the pembrolizumab ToT plot, and a Weibull distribution to the SoC ToT plot. The exponential extrapolation predicted approximately 12% of patients in the pembrolizumab combination strategy remained on treatment at two years, the treatment stop-point. A two-year stopping rule was implemented in KEYNOTE-189 and the company model, but has not been highlighted by in the CS as an expected specification for pembrolizumab in combination. Neither costs nor benefits are included in the model for this potential subset of patients. See section 5.2.6.3 for critique of the methods used to extrapolate time on treatment.

A maximum treatment duration of 12 weeks (equal to 4 cycles for the platinum-based therapies administrated every 3 weeks) was used for the comparator platinum-based therapies to reflect the protocol of KEYNOTE-189 and clinical practice in England. The average number of cycles received in the comparator arm per patient in KEYNOTE-189 was 3.5 and 3.6 in the pembrolizumab combination arm for carboplatin/cisplatin induction therapy.(8) In the model however, this adjustment was the proportion of patients in strategy not receiving (due to dose interruption) their planned dose of the pembrolizumab combination regimen (4.4%); or planned pemetrexed-platinum combination regimen (3.6%). Adjustment at the same level beyond week 12 and for the period of first-line active treatment. The estimates used for pemetrexed maintenance and pembrolizumab monotherapy were 12.2% and 1.0%.

Whilst this adjustment accounts for dose interruption, in their model the company do not describe any method for taking account of dose reduction. Reductions have the potential to reduce costs. Since reductions may be more frequent in recipients of systemic chemotherapy, where dosing is not fixed, this omission is may introduce a costing bias which would underestimate the ICERs (more pemetrexed maintenance is used in the SoC strategy, see section 5.2.8.6).

ERG comment:

- The assumption of vial sharing may lead to a small over-estimation of the ICERs.

- The lack of adjustment for dose reductions (other than interruptions) may lead to a small under-estimation of the ICERs.
- ICERs are insensitive to the relative proportion of cisplatin to carboplatin used at first-line.
- Treatment with pembrolizumab combination beyond two years was not modelled; the impact of a small proportion of patients remaining on treatment beyond two years is uncertain.
- In general the assumptions and approaches were appropriate.

5.2.8.4 Drug administration

Pembrolizumab (as monotherapy or in combination) is recommended as a 30 minute IV infusion, so the chosen HRG code of 'simple parenteral chemotherapy' (HRG code SB12Z) was accepted by the ERG as appropriate.(74, 77) However, in the CS the description of the selected unit cost was 'Outpatient' whereas the actual figure is the 'Day case and Regular Day/Night' average (Table 79). In the NHS year 2016/17 this selection represented 80% of all cases so is reasonable and acceptable.

Table 79 Drug administration unit costs (from National Schedule of Reference costs)(77)

Service description	Currency code	Currency description	Unit costs used in model
Chemotherapy, Day case and Regular Day/Night	SB12Z	Deliver simple parenteral chemotherapy at first attendance	£259.76
	SB14Z	Complex chemotherapy at first attendance	£385.99
	SB15Z	Subsequent doses of chemotherapy	£333.11
Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£269.86
	SB15Z	Deliver subsequent elements of a chemotherapy cycle	£205.09

Source: MSD CS Economic model, worksheet <Regimen Costs UK>

Except for the comparator pembrolizumab as monotherapy, in the subgroup of patients strongly expression PD-L1 (TPS ≥50%), treatment strategies comprise multiple elements. The model costed the administration of each individual drug separately, adding together the costs (Table 80).

Table 80 Total administration costs of therapies (based on the National Schedule of Reference costs)(77)

	Assumptions	Unit costs	Reference
Pembrolizumab + platinum+pemetrexed	1 x SB12Z (outpatient) 1 x weighted average based on KEYNOTE189 market share of: 1 x SB14Z (outpatient) (pemetrexed+carb) 1 x 1 x SB14Z (inpatient) (pemetrexed+cis)	£561.79	Assumption based on clinical opinion
Pembrolizumab mono	1 x SB12Z (outpatient)	£259.76	ID1349
Gemcitabine + carboplatin	1 x SB14Z (outpatient) 1 x SB15Z (outpatient)	£474.95	TA181(49)
Gemcitabine + cisplatin	1 x SB14Z (Day case and regular day/night) 1 x SB15Z (outpatient)	£591.08	TA181(49)
Paclitaxel + carboplatin	1 x SB14Z (outpatient)	£269.86	TA192(51)
Paclitaxel + cisplatin	1 x SB14Z (Day case and regular day/night)	£385.99	Assumption
Docetaxel + carboplatin	1 x SB14Z (outpatient)	£385.99	Assumption
Docetaxel + cisplatin	1 x SB14Z (Day case and regular day/night)	£269.86	TA181(49)
Vinorelbine + carboplatin	1 x SB14Z (Outpatient) 1 x SB15Z (Day case and regular day/night)	£602.97	Assumption
Vinorelbine + cisplatin	1 x SB14Z (Day case and regular day/night) 1 x SB15Z (Day case and regular day/night)	£719.10	TA192(51)
Pemetrexed + carboplatin	1 x SB14Z (outpatient)	£269.86	TA406(78)
Pemetrexed + cisplatin	1 x SB14Z (Day case and regular day/night)	£385.99	TA181(49)

Source: MSD CS Document B, Table 75, page 149

Table 81 Total administration cost of combination therapies

Strategy	Administration cost
Pembrolizumab combination	£561.79
Platinum, pemetrexed (SoC)	£302.03

ERG comment:

- The modelling of drug administration is broadly satisfactory.
- ICERs are insensitive to this aspect of costing.

5.2.8.5 PD-L1 testing

The PD-L1 test is described by the company as standard of care in the UK (MSD CS B.3.5.3), and this is in line with expert opinion elicited by the ERG.

For the strategy comparisons considering the whole population the company attributed the cost of the PD-L1 cost only to those patients subsequently treated with pembrolizumab. The company describe this as conservative, and a scenario analysis later provided - in which all patients receive and are attributed the cost - shows a small impact on the ICER.

In the company's subgroup analysis of PD-L1 expression, the test cost is inflated to account for respective negative results. I.e. TPS not ≥50%, not between 1% and 49%, and not <1%. However, since this test is routine for all patients, irrespective of their result, the ERG consider this cost to be applicable to all, whether pembrolizumab is limited or unlimited by PD-L1 status. Therefore a zero cost would be most appropriate.

ERG comment:

- The company incorrectly apply PD-L1 test costs to a fraction of the whole population, but the impact is very small.
- ICERs are insensitive to this aspect of costing.

5.2.8.6 Pemetrexed maintenance

Application

Pemetrexed maintenance therapy was included in both strategies of the main comparison (PC and SoC), from week 13, but not included in the platinum plus chemotherapy strategies, or the pembrolizumab monotherapy strategy. Discontinuation of maintenance in the PC strategy was independent of pembrolizumab use insofar as ToT for the PC strategy was determined by pembrolizumab. In contrast, ToT in the SoC strategy was determined by maintenance (treatment would otherwise have been limited to 12 weeks). This means that a subset of patients are created in the PC strategy for which costs are not fully accounted: those who discontinue pembrolizumab for a reason other than progression but continue to receive first-line active treatment (I.e. pemetrexed maintenance). Whilst the cost of subsequent treatments for these patients should be included properly, the cost of a proportion of their period of maintenance is excluded, which would lead to a small underestimation of the ICERs.

Dose intensity of drugs during the maintenance phase

The company introduced an acquisition cost adjustment to maintenance cost for occasions when patients missed or delayed administrations, resulting in fewer cycles being received. Table 82 details the extent of these interruptions based on observation in KEYNOTE-189. The proportions reflect the receipt of any treatment dose while on treatment, as long as a dose was received. No adjustment was made for sub-target dosing of received administrations, however, the ICER is not sensitive to a 10% reduction in the dose intensity of pemetrexed (an increase in the order of two hundred pounds).

Table 82 Percentage of actual pemetrexed treatment cycles received versus expected, by KEYNOTE-189 trial treatment arm

Strategy	Proportion of patients receiving pemetrexed (maintenance) actual vs expected dose
Pembrolizumab combination maintenance phase*	[redacted]
SoC	[redacted]

*applicable only to those still receiving pembrolizumab.

Source: MSD CS Document B, Table 78, page 151

ERG comment:

- Reduction in the cost of pemetrexed maintenance from dose reductions (above interruptions) were not included, but ERG testing shows insensitivity of the ICERs.
- Exclusion of pemetrexed maintenance costs for people who have discontinued pembrolizumab in the combination regimen may lead to the underestimation of the ICERs.

5.2.8.7 Monitoring and disease management

This type of cost varied according to the treatment status on patients within the model. Patients receiving active treatment, including subsequent active treatment (extended to second-line only in this model), were attributed a set and rate of resources labelled 'progression-free health state'. Patients discontinuing active treatment, that is, following discontinuation of second-line active therapy, were attributed a second set and rate of resources labelled 'progressed health state'. These labels are perhaps artefacts of an earlier model design, since progression status is not related to the application of these costs. Instead, their application is linked to the discontinuation of active therapy, which in the view of the ERG is an appropriate demarcation of change in resource type and rate of

consumption for this population; albeit any outcome-based link between benefits and costs is thus lost since PFS would be the common outcome.

The main difference in resource consumption between the two resource sets is a reduction in hospital and surgery setting consultations, and monitoring; and an increase in community-based care from GPs and therapists (Table 83). These differences are commensurate with the change in treatment intent signalled by the cessation of active intervention. Therefore, the ERG is satisfied with the company's base case approach. Having said that, limitations were identified in the compilation of costs which were heavily reliant on Brown *et al*.(17) This is a 2013 UK HTA assessment incorporating a systematic review of clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer. From this source the company used secondary sources to populate utilisation rate estimates, which in some cases drew on observations from 12 or more years ago E.g. The Big lung trial had a start date of January 1995 and an overall end date of December 2005.(79) This trial was used to estimate the frequency of outpatient visits, chest radiography, CT scans and ECGs.

Table 83 Resource use frequency for progression-free and progressed health states

Resource	On anti-cancer treatment	Following anti-cancer treatment	Unit	Source quoted in Brown 2013(17)
Outpatient visit	9.61	7.91	per annum	Big Lung Trial(80)
Chest radiography	6.79	6.5	per annum	Big Lung Trial(80)
CT scan (chest)	0.62	0.24	per annum	Big Lung Trial(80)
CT scan (other)	0.36	0.42	per annum	Big Lung Trial(80)
ECG	1.04	0.88	per annum	Big Lung Trial(80)
Community nurse visit	8.7	8.7	visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG81,(81) Marie Curie report(82)
Clinical nurse specialist	12	12	hours contact time per patient	Appendix 1 of NICE Guideline CG81(81)
GP surgery	12	0	consultations per patient	Appendix 1 of NICE Guideline CG81(81)
GP home visit	0	26.09	per annum (fortnightly)	Marie Curie report(82)

Therapist visit	0	26.09	per annum (fortnightly)	Appendix 1 of NICE Guideline CG81(81)
Macmillan nurse	0	0		Marie Curie report(82)
Drugs/equipment	0	0		Marie Curie report(82)
Location of terminal care	0	0		Office for National Statistics death tables 5.2(83)

Abbreviations: GP = general practitioner; CT = computerised tomography; ECG = electrocardiogram; NICE = The National Institute for Health and Care Excellence.

Source: MSD CS Document B, Table 79, page 152

Table 84 presents the unit costs of those resources identified in Table 83. Estimates except for Chest radiography have been collected from standard texts and extracted correctly.

Table 84 Unit costs of disease monitoring and supportive care (based on the National Schedule of Reference costs, and the PSSRU handbook)(77, 84)

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£128.00	per visit	NHS Reference Costs 2016–2017, Consultant Led, Non-Admitted Face to Face Attendance, First, 800 clinical oncology
Chest radiography	£27.22	per case	NICE technology appraisal TA199; TAG report, p.328 (£24.04 in 2009)
CT scan (chest)	£110.00	per case	NHS Reference Costs 2016–2017, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)
CT scan (other)	£118.00	per case	NHS Reference Costs 2016–2017, Diagnostic Imaging, Outpatient, HRG code RD26Z (three areas with contrast)
ECG	£334.00	per case	NHS Reference Costs 2016–2017, 800 Clinical Oncology, Outpatient, HRG code EY51Z(77)
Community nurse visit	£62.00	per hour	PSSRU 2017, p.142: Cost per hour of patient-related work Band 8a
Clinical nurse specialist	£74.00	per contact hour	PSSRU 2017, p.142: Cost per contact hour Band 8b
GP surgery visit	£38.00	per visit	PSSRU 2017, p.145: Cost per patient contact lasting 11.7 minutes, including direct care staff costs (including qualifications)

GP home visit	£85.44	per visit	PSSRU 2017, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel
Therapist visit	£45.00	per hour	PSSRU 2017, p.159: Cost per hour for community occupational therapist (including training)

Abbreviations: 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.

Source: MSD CS Document B, Table 80, page 152

ERG comment:

- The overarching method of cost application matched the population characteristic (i.e. previously untreated) albeit the company description was insufficient.
- Collection of unit costs is satisfactory.
- Sources used to inform the rate of consumption of resource are not recent and may be inaccurate. Inaccuracies could impact the ICERs in either direction. Changing all rates by +/-10% does not significantly impact the ICERs (approximately £600).
    - Halving the fortnightly rate of home GP and therapist visits reduces the ICERs by approximately £1,100.

5.2.8.8 Terminal care

A one-off cost was applied to all patients at the time of death (£4,404) for all strategies. This was appropriate and the construction of the point estimate was reasonable (Table 85).

Table 85 Unit costs and rate of terminal care resources (based on the National Schedule of Reference costs, and the PSSRU handbook)(77, 84, 85)

Resource	Unit cost	Number of consumption	% of patients in each care setting	Assumptions / Reference
Community nurse visit	£62.00 per hour	28.00 hours	30%	PSSRU 2017, p.169: Cost per hour of patient-related work (including qualifications)
GP Home visit	£85.44 per visit	7.00 visits	30%	PSSRU 2017, p.177-178: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel
Macmillan nurse	£49.36 per hour	50.00 hours	30%	Assumed to be 66.7% of community nurse cost

Drugs and equipment	£563 per patient	Average drug and equipment usage	30%	The value used in Brown et al' s study (2013, Marie Curie report figure of £240 increased for inflation) was inflated to 2016/17 using the PSSRU HCHS index
Terminal care in hospital	£3,737.05 per episode	1 episode (9.66 days)	62%	NHS Reference Costs 2016–2017, 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 Assumed that unit cost is = £3,606.87 + 0.92 excess days at £267.74 per day
Terminal care in hospice	£4,671.32 per episode	1 episode (9.66 days)	7.1%	Assumed 25% increase on hospital inpatient care
Total cost	£4,404.24 (one-off cost)			

Source: MSD CS Document B, Table 81 page 155

5.2.8.9 Subsequent lines of treatment

The company model included explicit costs for second-line anti-cancer treatment. The modelling of the benefit of subsequent line drugs was indirect (see the Treatment effect section 5.2.6 for comment on the benefit of second-line drugs). Observation from KEYNOTE-189 informed the proportions of patients receiving anti-cancer therapies at second-line (Table 86).(86) Information about treatment to the fifth-line was reported in the same source but treatments at third and subsequent lines were said in the CS not to be included. Similarly, the company cited KEYNOTE-189 as the source of the distribution of therapies at second-line (Table 87). The company used KEYNOTE-21G for the estimates of treatment duration, although the ERG was unable to find and verify these figures (Table 88). The ERG was unable to replicate and verify the company's estimates for

Table 86 Proportion of patients taking-up second-line treatment

Pembrolizumab combination	SoC	Pembrolizumab monotherapy
45.8%	56.5%	39.9%

Source: MSD CS Economic model worksheet <Regimen Costs>

Since subsequent lines of therapy include high cost regimens, and this proportion differs by strategy, the proportion of patients taking-up second-line therapy is important. The ERG note that the company adjusted the sourced proportions to exclude patients (7%) who took-up

pembrolizumab after discontinuation of pembrolizumab combination treatment at first-line. In a scenario analysis the company showed this adjustment to reduce the ICER by about £500. Detail of adjustment method was unspecified. In an ERG scenario analysis, using the published figures, the ICER without adjustment increased by approximately £2,200.

Table 87 Distribution of second-line therapies

Distribution of second-line therapies	Pembrolizumab combination	SoC	Pembrolizumab monotherapy
Carboplatin (400 mg) + Gemcitabine (1250 mg/m^2)	0%	0%	20%
Carboplatin (400 mg) + Pemetrexed (500 mg/m^2)	17%	0%	55%
Cisplatin (75 mg/m^2) + Pemetrexed (500 mg/m^2)	0%	0%	25%
Docetaxel (75 mg/m^2)	64%	14%	0%
Docetaxel (75 mg/m2) + Nintedanib (200 mg)	19%	0%	0%
Nivolumab (240 mg)	0%	15%	0%
Pembrolizumab (200 mg)	0%	72%	0%

Source: MSD CS Document B, Table 83 page 158; and CS Economic model worksheet <Regimen Costs>

Drug acquisition costs and associated drug administration costs were appropriately calculated, using the same unit costing as at first-line. In a simplification which partly alludes the discounting of future costs, all second-line treatment costs were applied in the model cycle (week) immediately following the discontinuation of first-line therapy – informed by the time-on-[first]-treatment statistic.

Table 88 Average treatment duration of second-line anti-cancer therapy (weeks)

Post-discontinuation regimen	Pembrolizumab combination	SoC
Chemotherapy regimens	20.9	10.3
PD1/PDL1 regimens	28.0	26.4

Maintenance regimen	12.6	7.4

Source: MSD CS Economic model worksheet <Regimen Costs>. Original source unknown.

ERG comment:

- Unit costing is satisfactory.
- There is uncertainty about adjustment methods used by the company in their calculation of the up-take and the distribution of therapies at second-line.
- Sensitivity analyses show the ICERs are sensitive to the modelling of subsequent lines of therapy.

5.2.8.10 Adverse events

Serious adverse events (grade 3 and 4) which occurred in at least 5% patients (any grade) in either arm of KEYNOTE-189 were included in the cost analysis (utility decrements were also applied – see section 5.2.7). Exceptions for grade 2 were made for diarrhoea and febrile neutropenia. For individual AE occurrences, unit costs (and utility decrements) were assumed to be the same across treatment arms, so any difference in totals were driven by AE rates (Table 89).

Table 89 Grade 3 and 4 AE rates used in the economic model (from KEYNOTE-189 clinical study report)(13)

Adverse Event	Risk for pembrolizumab combination	Risk for SoC
Nausea	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea (grade 2)	[redacted]	[redacted]
Diarrhoea (grade 3-4)	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]

Rash	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]

Source: MSD CS Document B, Table 65 page 129

AE rates for subsequent lines of treatment were not included.

The impact of AEs incorporated by estimating weighted average costs per patient were summed to a one-off cost, and these were then applied to the first cycle of the model for each treatment arm. This is a costing simplification often used since applying AE costs to patients at the time in their treatment course when it happened, for the correct duration, is

complex whilst not in most cases improving accuracy meaningfully. In another simplification, driven by the method of data capture in-trial, the impact of second or subsequent adverse events on a patient is not captured, since the measure is patients who experienced the event. I.e. If a patient experiences two episodes of febrile neutropenia, then only the half the cost (and utility decrement) is captured.

Unit cost estimates are presented in Table 90. When unit costs were not available or the management costs were trivial, zero cost was applied. Many of the unit costs were sourced from the Brown *et al*.(17) HTA, with limitations of age as described above.

Table 90 Unit costs of adverse events included in the model (based mainly on the National Schedule of Reference costs, and the PSSRU handbook)(17, 51, 62, 77, 84, 87)

Adverse Event	Unit costs	Reference
Nausea	£998.38	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices)
Anaemia	£2,692.61	NICE TA428
Fatigue	£2,855.25	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices)
Decreased appetite	£0.00	TA428 inflated to 2016/17 using PSSRU inflation indices
Constipation	£0.00	Assumed to be zero
Diarrhoea (grade 2)	£456.66	NICE TA428 inflated to 2016/17 using PSSRU inflation indices
Diarrhoea (grade 3-4)	£998.38	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices)
Dyspnoea	£588.98	NICE TA403 inflated 2016/17
Vomiting	£813.47	NICE TA192 (inflated to 2016/17 using PSSRU inflation indices)
Back pain	£0.00	Assumed to be zero
Arthralgia	£0.00	Assumed to be zero
Neutropenia	£120.99	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices)
Oedema peripheral	£0.00	Assumed to be zero
Blood creatinine increased	£0.00	Assumed to be zero
Alanine aminotransferase increased	£637.03	TA347 (inflated to 2016/17 using PSSRU inflation indices)
Dizziness	£0.00	Assumed to be zero
Rash	£127.21	Brown (inflated to 2016/17 using PSSRU inflation indices)
Asthenia	£2,805.19	Brown (inflated to 2016/17 using PSSRU inflation indices)
Chest pain	£0.00	Assumed to be zero
Stomatitis	£0.00	TA428, 2016
Hyponatraemia	£0.00	TA357, 2015
Thrombocytopenia	£782.31	TA406 inflated to 2016/17 using PSSRU inflation indices
Dyspepsia	£0.00	Assume same as decreased appetite

Abdominal pain	£0.00	TA395(88)
Aspartate aminotransferase increased	£364.64	NICE TA347 (inflated to 2016/17 using PSSRU inflation indices)
Hyperglycaemia	£0.00	TA395(88)
Pyrexia	£261.00	NHS reference costs 16/17 WJ07B Fever of unknown origin
Musculoskeletal pain	£0.00	Assumed to be zero
Pneumonia	£3,102.84	TA411 2016 (inflated to 2016/17 using PSSRU inflation indices)
White blood cell count decreased	£577.66	NICE TA428 2016 inflated to PSSRU 2016/17 inflation indices(77, 84)
Haemoptysis	£0.00	Assumed to be zero
Pain in extremity	£0.00	Assumed to be zero
Urinary tract infection	£2,366.90	NICE TA347 (inflated to 2016/17 using PSSRU inflation indices)
Mucosal inflammation	£0.00	Assumed to be zero
Pleural effusion	£0.00	Assumed to be zero
Upper respiratory tract infection	£171.14	Assume the same as lower respiratory tract infection
Leukopenia	£0.00	Assumed to be zero
Epistaxis	£0.00	Assumed to be zero
Conjunctivitis	£0.00	Assumed to be zero
Pneumonitis	£3,102.84	Assumed to be same as pneumonia
Febrile neutropenia	£7,266.56	Brown 2013 (inflated to 2016/17 using PSSRU inflation indices)
Bronchitis	£171.14	Assume the same as lower respiratory tract infection
Hypertension	£0.00	Assumed to be zero
Weight decreased	£0.00	Assume the same as decreased appetite
Gamma-glutamyltransferase increased	£369.42	TA347, 2015 (inflated to 2016/17 using PSSRU inflation indices) (84, 87)
Hypokalaemia	£465.00	NHS reference costs 16/17 KC05G: Fluid or electrolyte disorders with intervention(77)
Hypomagnesaemia	£465.00	NHS reference costs 16/17 KC05G: Fluid or electrolyte disorders with intervention(77)
Dehydration	£465.00	NHS reference costs 16/17 KC05G: Fluid or electrolyte disorders with intervention(77)
Hypophosphataemia	465.00	NHS reference costs 16/17 KC05G: Fluid or electrolyte disorders with intervention(77)
Dysgeusia	£0.00	Assume the same as decreased appetite
Insomnia	£0.00	Assumed to be zero
Anxiety	£0.00	Assumed to be zero
Acute kidney injury	£377.00	Acute kidney injury with intervention (LA07K) NHS reference costs 16/17(77)

Source: MSD CS Document B, Table 82 page 154

ERG comment:

- The side-effect profiles of treatment regimens of the main comparison (PC versus SoC) are not sufficiently different to drive the ICER.
- Methods used are simple but reasonable.

5.2.9 Cost effectiveness results

Summary results of the company's deterministic base case analysis are presented in Table 91. The deterministic model served as the company's primary analysis.

The results presented in this section include the agreed and tentative commercial access agreements (CAAs) for pembrolizumab. They do not include existing agreements for comparators.

The deterministic ICER for PC versus SoC was £46,568 per QALY gained. The mean incremental LYs gained per person were 1.16, and incremental QALYs gained were 0.89 over the model lifetime. The PC incurred £41,344 more resource than the SoC. (Table 91).

5.2.9.1 Whole population, main comparison

Table 91 Base case result of main comparison for overall population (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£84,324	2.50	1.81				
SoC	£42,980	1.34	0.92	£41,344	1.16	0.89	£46,568

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

Table 92 Base case result of main comparison for overall population (probabilistic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£84,870	NR	1.81				
SoC	£43,527	NR	0.93	£41,344	NR	0.89	£46,674

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; NR = Not reported; QALY = Quality-adjusted life year; SoC = Standard of care.

5.2.9.2 Whole population, other comparisons

The ICERs for PC versus the platinum and chemotherapy doublet options were all in excess of £50,000 per QALY gained (Table 93).

Table 93 Base-case result of primary analysis versus NMA comparators (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£84,324	2.50	1.81				
Platinum + Gemcitabine	£26,572	1.19	0.80	£57,752	1.31	1.01	£57,064
Platinum + Vinorelbine	£27,663	1.33	0.91	£56,661	1.17	0.90	£63,262
Platinum + Docetaxel	£27,391	1.55	1.08	£56,932	0.95	0.73	£78,242
Platinum + Paclitaxel	£25,368	1.09	0.73	£58,956	1.41	1.08	£54,654

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

5.2.9.3 TPS>=50% sub-population, versus pembrolizumab monotherapy

The ICER for PC versus pembrolizumab monotherapy, for patients strongly expressing PD-L1 was £38,699 per QALY gained. The mean incremental LYs gained per person were 1.03, and incremental QALYs gained were 0.78 over the model lifetime. The PC incurred £30,161 more resource than the SoC (Table 94).

Table 94 Base case result of sub-population comparison for patients with TPS>=50%, PC versus pembrolizumab monotherapy (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£102,480	3.20	2.35				
Pembrolizumab monotherapy	£72,319	2.17	1.57	£30,161	1.03	0.78	£38,699

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

5.2.9.4 Sub-group analysis (main comparison only)

In the sub-group analysis, the ICERs were £42,703, £38,632, and £51,545 for TPS>=50%, (Table 95); 1%>=TPS<=49% (Table 96); and TPS<=1% (Table 97) groups respectively.

Table 95 Base case result of main comparison for patients with TPS>=50% (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£102,480	3.20	2.35				
SoC	£42,949	1.38	0.95	£59,532	1.81	1.39	£42,703

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

Table 96 Base case result of main comparison for patients with 1%>=TPS<=49% (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£87,429	2.78	2.03				
SoC	£46,673	1.42	0.97	£40,756	1.37	1.05	£38,632

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

Table 97 Base case result of main comparison for patients with TPS<=1% (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£64,982	1.85	1.30				
SoC	£41,285	1.24	0.84	£23,697	0.60	0.46	£51,545

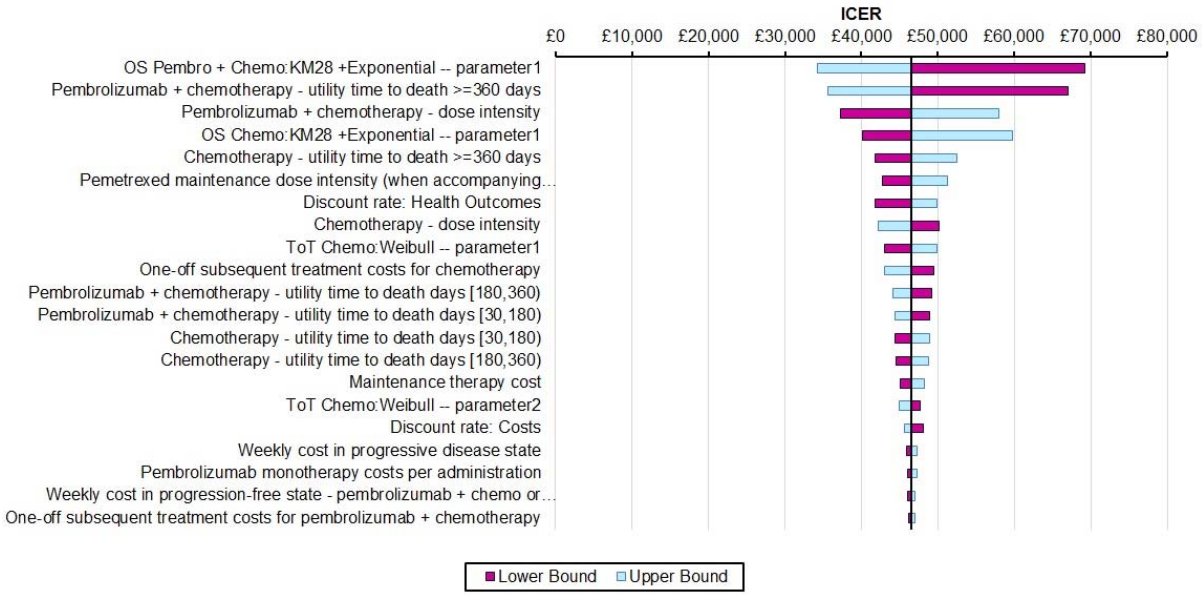
Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

5.2.10 Sensitivity analyses

Univariate deterministic sensitivity analyses were conducted by the company to explore the impact of changes in key parameters on the ICER. Variables and their impact on the ICER of the main comparison can be seen in Figure 18 in the form of a tornado diagram. The ICER is most sensitive to:

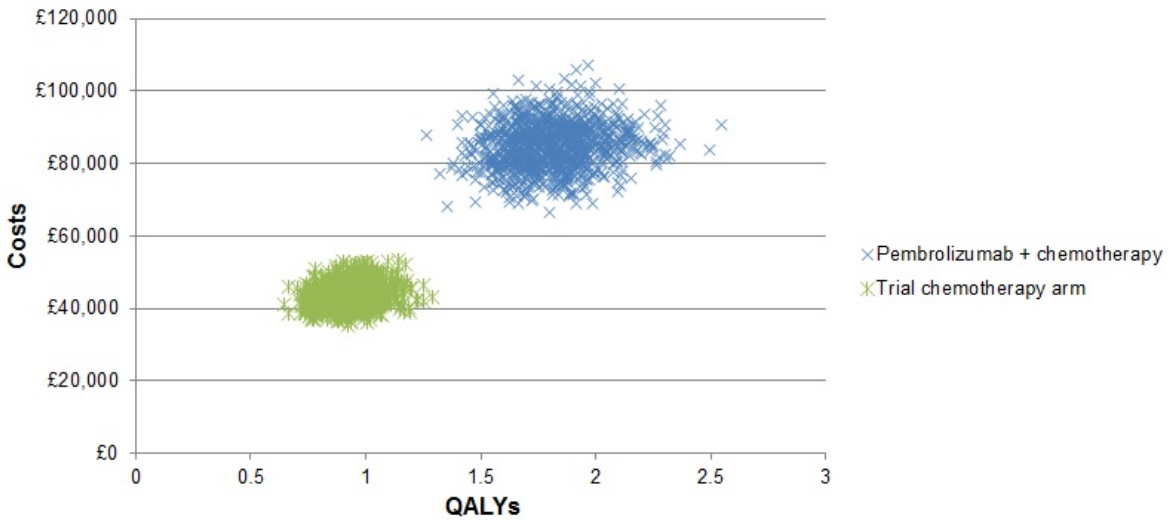
1. the parameters informing the shape and scale of the exponential parametric distribution used to estimate long-term overall survival;
2. the utility estimate used for the period when patients are more than a year from death (both strategies);
3. the amount of pembrolizumab received in terms of target treatment cycles missed / dose interruptions (referred to in the CS as 'dose intensity': 95.6% in the base case).

Figure 18 Tornado diagram: deterministic sensitivity analyses results, PC versus SoC



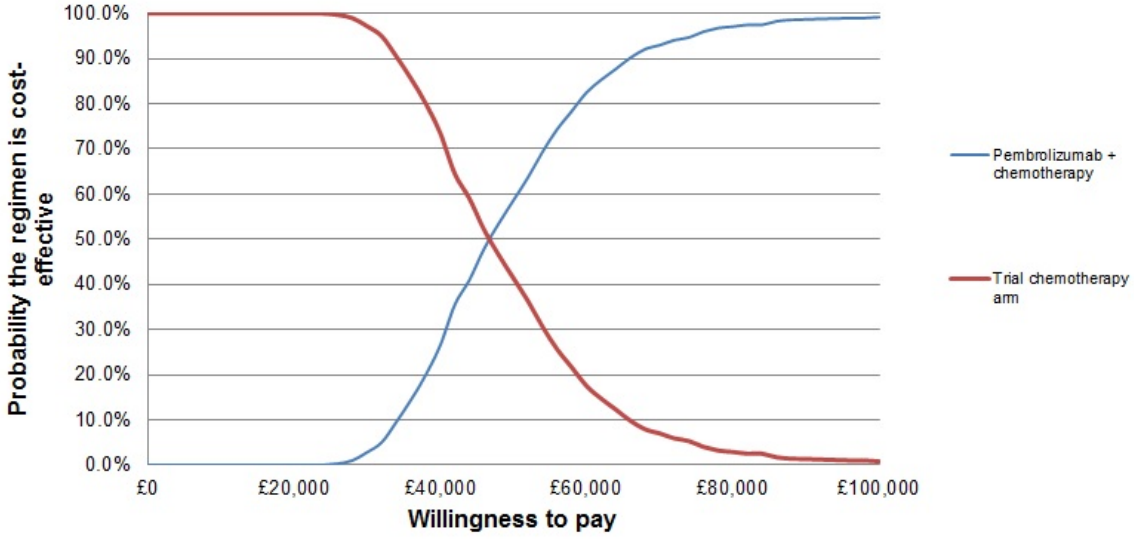
The results of 1,000 simulations of the PSA is presented in the cost-effectiveness plane of Figure 19.

Figure 19 Probabilistic sensitivity analysis for PC versus SOC



Cost effectiveness acceptability curves (CEACs) - displaying the probability of each strategy being the most cost-effective of the set at any given willingness to pay threshold – are presented in Figure 20.

Figure 20 Cost-effectiveness acceptability curve for PC versus SOC



The CEAC analysis found that at a £50,000 cost-effectiveness threshold, the probability of pembrolizumab combination being the most cost-effective strategy was 59%.

5.2.11 Scenario analyses

Alternative scenarios presented by the company (Full list presented in Table 98) which addressed the assumptions/estimates about which the ICER was most sensitive were: 1) OS estimation: Scenario 11: Use of log-normal distribution; 2) Utility ≥360 days from death: No direct test; 3) Dose interruptions: No direct test.

Table 98 Results of company scenario analyses for main comparison (PC v SoC)

		Pembrolizumab combination			SoC			Pembrolizumab combination vs SoC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Company base case		£84,324	2.50	1.81	£42,980	1.34	0.92	£41,344	0.89	£46,568
Scenario 1	UK-specific BSA values (unadjusted by sex distribution)	£84,079	2.50	1.81	£42,816	1.34	0.92	£41,263	0.89	£46,477
Scenario 2.a	OS cut-off – 38 weeks	£84,477	2.53	1.83	£44,055	1.59	1.11	£40,422	0.72	£56,045
Scenario 2.b	OS cut-off – 18 week	£84,913	2.63	1.91	£42,834	1.31	0.89	£42,080	1.01	£41,554
Scenario 3.a	PFS cut-off – 11 weeks	£84,324	2.50	1.81	£42,980	1.34	0.92	£41,344	0.89	£46,568
Scenario 3.b	PFS cut-off – 31 weeks	£84,324	2.50	1.81	£42,980	1.34	0.92	£41,344	0.89	£46,568
Scenario 4	No half cycle correction	£84,323	2.51	1.82	£43,021	1.35	0.93	£41,302	0.89	£46,522
Scenario 5	SoC as for UK market shares	£84,423	2.50	1.81	£43,070	1.34	0.92	£41,353	0.89	£46,578
Scenario 6	Utilities – Progression based (pooled)	£84,324	2.50	1.72	£42,980	1.34	0.93	£41,344	0.79	£52,499
Scenario 7.a	Utilities – Time to death (per treatment arm)	£84,324	2.50	1.80	£42,980	1.34	0.92	£41,344	0.88	£46,962
Scenario 7.b	Utilities – Progression-based (per treatment arm)	£84,324	2.50	1.76	£42,980	1.34	0.90	£41,344	0.86	£47,868
Scenario 8	Utilities – Time to death by Chang et al (2017)(42)	£84,324	2.50	1.92	£42,980	1.34	0.91	£41,344	1.01	£40,840
Scenario 9	No age-related dis-utilities	£84,324	2.50	1.83	£42,980	1.34	0.93	£41,344	0.90	£45,743
Scenario 10	Assuming treatment effect stops at 5 years	£83,644	2.36	1.70	£42,980	1.34	0.92	£40,665	0.78	£52,333

		Pembrolizumab combination			SoC			Pembrolizumab combination vs SoC		
		Total costs	**Total LYs**	**Total QALYs**	**Total costs**	**Total LYs**	**Total QALYs**	**Inc. costs**	**Inc. QALYs**	**ICER**
Scenario 11	Alternative OS distribution: Log-Normal	£92,540	4.31	3.19	£51,057	3.23	2.36	£41,483	0.82	£50,399
Scenario 12	Dose regimen for 2L pembrolizumab	£84,324	2.50	1.81	£40,124	1.34	0.92	£44,200	0.89	£49,785
Scenario 13	50% discount pemetrexed maintenance and induction	£73,337	2.50	1.81	£35,634	1.34	0.92	£37,703	0.89	£42,467
Scenario 14	Assuming a RR of 0.44 to estimate a 5 year OS for SoC of 10%	£90,272	3.79	2.79	£44,864	1.77	1.25	£45,408	1.54	£29,501
Scenario 15	Inclusion of 2L pembrolizumab use as per trial proportions	£85,125	2.50	1.81	£42,980	1.34	0.92	£42,145	0.89	£47,470

5.2.12 Model validation and face validity check

Previous economic evaluations can help provide context for certain model inputs and outputs, namely man health state utilities, estimates of overall survival, QALY outputs and the ICERs.

Table 99 compares the utility values used in the model with two other sources cited by the company. The value for the ≥360 days state compares a little low but a lower estimate here would overestimate the ICERs. The range in values for the <30 days state is wide, but the ICERs are not sensitive to this input.

Table 99 Mean health state utility estimates of this and relevant previous economic evaluations

State	Company model	Chang *et al*(42)	Huang *et al.(41)*
Population (Country)>	**1L NS metastatic NSCLC**	**Advanced NSCLC (South Korea)**	**2L advanced NSCLC (Wales)**
≥360	[redacted]	0.904	0.81
[180, 360)	[redacted]	0.720	0.73
[30, 180)	[redacted]		
[90, 180)	NA	0.627	0.69
[30, 90)	NA	0.379	0.60
<30	[redacted]	0.195	0.40

Abbreviations: 1L = First line (untreated); 2L = second-line; NS = Non-squamous; NSCLC = Non-small cell lung cancer.

Table 100 compares the long-term OS estimates (outputs) of the company model versus preferences from the ERG of NICE TA447 (pembrolizumab monotherapy),(66) and versus the estimates of this ERG. No evidence pertaining to this statistic was included in the findings of the company's search for cost-effectiveness evidence.

Table 100 OS estimates of this and relevant previous economic evaluations

Source	Population	1-year OS	5-year OS	10-year OS
SoC strategy*				
Trial - KEYNOTE-189(8)	1L PD-L1-positive NS metastatic NSCLC	52.2%	NA	NA
Company model base case	1L PD-L1-positive NS metastatic NSCLC	56.2%	2.40%	0.10%

ERG of NICE TA447(66)	1L PD-L1-positive mNSCLC	NA	9.60%	1.50%
This ERG (adaption of company model)	1L PD-L1-positive NS metastatic NSCLC	48.5%	8.6%	3.4%
PC strategy				
Trial - KEYNOTE-189(8)	1L PD-L1-positive NS metastatic NSCLC	61.7%	NA	NA
Company model base case	1L PD-L1-positive NS metastatic NSCLC	70.6%	15.2%	2.2%
This ERG (adaption of company model)	1L PD-L1-positive NS metastatic NSCLC	70.5%	25.4%	10.0%

Abbreviations: 1L = First line (untreated); 2L = second-line; ERG = Evidence review group; NS = Non-squamous; NSCLC = Non-small cell lung cancer.
*The SoC for TA447 did not include pemetrexed (upfront)

Table 101 compares the overall benefit in life-years and quality-adjusted life-years between company and ERG models. The company did not included any items in their search for cost-effectiveness evidence.

The ERG model estimates higher LY (28-30%) and QALY (30-33%) accrual in both of the main strategies. This is driven by the ERG choice of the log-logistic distributions in preference to the piecewise exponential distribution method of the company.

Table 101 LY and QALY estimates of this and relevant previous economic evaluations

Source	Population	LYs	QALYs
SoC strategy			
Company model base case	1L PD-L1-positive NS metastatic NSCLC	1.34	0.92
This ERG (adaption of company model)	1L PD-L1-positive NS metastatic NSCLC	1.74	1.22
PC strategy			
Company model base case	1L PD-L1-positive NS metastatic NSCLC	2.50	1.81
This ERG (adaption of company model)	1L PD-L1-positive NS metastatic NSCLC	3.21	2.35

Abbreviations: 1L = First line (untreated); 2L = second-line; ERG = Evidence review group; LY = Life-years; NS = Non-squamous; NSCLC = Non-small cell lung cancer; QALYs = Quality-adjusted life year.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 Corrections to coding

Corrections are distinct from ERG preferred assumptions and inputs.

The ERG identified a limited number of low impact coding issues in the company.

1. Correction of the code for the percentage of the patients utilizing a second-line therapy for the estimation of disease management costs (pembrolizumab monotherapy), which drew estimates for pembrolizumab combination.
2. Half-cycle correction of the mortality component of the disease management estimate.
3. Changed 54 to 365.25/7 in the code for capping of the overall survival estimation using UK lifetable data. This code was relevant only to the alternative scenarios which increase survival above the UK rate, but explored scenarios and the base case trended below the cap.
4. The cycle estimates for time-on-treatment were half-cycle corrected.

5.3.2 Model adaptations

See section 6. Only the implementation of background mortality involved changes or addition to coding in the model.

5.3.3 New scenario analysis set

The set of alternative estimates and assumptions underlying the company's 18 scenarios did not suitably test that uncertainty in the base case ICER (main comparison). Those selected should be those to which the ICER is most sensitive. A new set of alternative scenarios which address the method of OS estimation, the method of utility estimation, and the consumption of high cost drugs, is presented in Table 110.

5.4 Conclusions of the cost-effectiveness section

The ICER for pembrolizumab combination versus SoC was £46,568 per QALY gained in the deterministic analysis and £46,674 per QALY gained in probabilistic analysis. The probability of pembrolizumab combination being the more cost-effective strategy is 58%. Deterministic sensitivity analysis revealed unsurprising sensitivity in the ICERs towards OS estimation, health state utility estimation (particularly for the >360 days state), and the consumption of high cost drugs (particularly of pembrolizumab). Company scenarios tended to centre on inputs to which the ICER was insensitive, or about which uncertainty was not so high.

There is considerable uncertainty around the extrapolation of survival beyond short follow-up periods, as is the case here. Median survival was not reached in the investigational arm of the key trial, but the company's selection of distribution for OS appears to have been based on the pembrolizumab combination arm, despite the decision to fit separate models to each arm of individual patient data. Using a 2-phase piecewise model with a single cut-off point at week 28 from which the curve was appended, the chosen distribution provided the worst statistical fit for the SoC arm of those considered.

No adjustment of the extrapolated period was made for increasing mortality from other causes as age increases. This can be an important adjustment when extrapolation is long and based on short trial follow-up. The KEYNOTE-189 Kaplan-Meier data used for OS estimation were based on a median follow-up of 10.5 months and were extrapolated over a time horizon of twenty years (where curves were clearly separate for 14 years).

Evidence from both KEYNOTE-189 and the company and ERG economic models suggest that average OS for SoC treatment is under 24 months; and the life extension offered by pembrolizumab combination is well over 3 months. Therefore, pembrolizumab combination in this setting and population probably fulfils the criteria for end-of-life status.

No evidence pertaining to long-term OS, LY or QALY estimates were included in the findings of the company's search for cost-effectiveness evidence. Modelled 5- and 10-year OS for the SoC strategy are significantly lower than the preferences of the ERG of NICE TA447/TA531 (pembrolizumab monotherapy for previously untreated patients), and this ERG, at 2.4% and 0.1% respectively. Given the availability of immuno-oncology treatments second-line, the ERG of NICE TA447/TA531 recommended higher long-term survival, referring to published and unpublished 5-year OS estimates ranging from ≤ 5% to 17.2%, with particular mention to the estimate of 10% from the CRUK data. Estimated 1-year OS for the SoC strategy is slightly higher than that observed in KEYNOTE-189 (56.2% and 52.2%

respectively) and estimated 1-year OS for pembrolizumab combination is also higher than that observed (70.6% and 61.7% respectively).

The utility estimates were derived from the HRQoL analyses carried out in KEYNOTE-189, whereby patients completed the EQ-5D questionnaire at baseline. Pooled estimates were used for a time-to-death (TTD) approach that has little precedent but is supported by the clinical opinion gathered by the ERG; that HRQoL in this populations correlates better to TTD than occurrence of first progression. Four alive health states for HRQoL were considered. The value for the >360 days state is lower than those in two studies which use a similar approach with five health states, but a lower estimate here is conservative. The <30 days state utility value is nearer the top of the range provided by the two literature sources, but the ICERs are not sensitive to this input. A limitation of using TTD is that data from a large number of patients is not available. Those remaining alive and less than one year from commencement of treatment can not inform the analysis since the do not qualify for any health state. However, the progression status approach may have a greater limitation, in that the progression captured in KEYNOTE-189 is the first progression, which may not indicate the reduction in HRQoL as well as time from death.

The uncertainty in the modelling of relative cost is not as great a concern as that of relative effect. Although in the company base case costs were not linked by the evidence to the utility-driven health states, since the PFS outcome was not included in the base case model. Instead costs were based on whether a patient remained on active anti-cancer treatment. After active treatment, costed to two lines only, resource consumption aligned to non-curative intent, signified by a reduction in monitoring and an increase in community-based care. A large proportion of patients took-up pembrolizumab at second-line in the SoC strategy, helping to equalise costs with the strategy of pembrolizumab in combination (72% of the 56.5% who discontinue first-line treatment and go onto second-line). Company estimates of these proportions could not be verified by the ERG, and this is an area of uncertainty. Similarly, the company's modelling of pemetrexed maintenance was not well described or transparent in the submission.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG base case was different to the company base case in five areas of modelling. Two areas required new ERG coding, the other three changes could be implemented using existing functionality within the company model.

Table 102 presents the ERG ICER, with its derivation presented in a step-wise manner as the individual impact each of the changes is applied to the company base case. Also provided is the cumulative impact, demonstrating that some changes are not mutually exclusive.

Note that the results presented in this section include the agreed and tentative commercial access agreements (CAAs) for pembrolizumab. They do not include existing agreements for comparators.

Detail of the aspects of the company model which have been changed to produce the ERG base case are described below.

6.1.1 Log-logistic parametric distributions for OS extrapolation

In KEYNOTE-189, median survival is only reached in the SoC arm (8), but the company's choice of distribution for OS appears to have been based solely on the pembrolizumab combination arm, despite the decision to fit separate models to each arm based on the IPD. After finding that the assumption of proportional hazards did not hold, the company chose to use a 2-phase piecewise model with a single cut-off point at week 28 and then fit the curves to the data beyond this point (see section 5.2.6.2 for details). With this cut-off, the exponential distribution provides the worst statistical fit for the SoC arm of the distributions considered.

As noted in MSD CS Appendix L, the log-normal and log-logistic distributions provide the best statistical fit to the full OS KM data for the SoC arm (with marginally lower AIC and BIC statistics for log-normal). The log-logistic distribution also provides the second best fit for the pembrolizumab combination arm, after the exponential distribution. Unlike the exponential distribution, the choice of the log-logistic distribution does not assume proportional hazards, an assumption that was tested by the company and found not to hold, particularly for the SoC arm. Since the log-logistic curves are not constant over time, it is not necessary to introduce cut-off points for this reason. Hence, the curves fitted to the full KM data have been used in the ERG's preferred base case.

6.1.2 Background mortality

An adjustment for background mortality has been included in the ERG's preferred base case due to the relatively short length of the trial compared to the model time horizon and since background mortality is likely to impact the two strategies differently, due to the differences between them in estimated long-term survival. This is especially important given that the distributions for OS alone determine modelled treatment effectiveness (see section 5.2.6) and since the hazard rate for the chosen type of distribution does not increase monotonically with time. In order to reflect background mortality, for each treatment strategy the probability of dying in any given model cycle obtained from the fitted OS distribution has been multiplied by the probability of dying for the general population obtained from the ONS lifetables. (68)

6.1.3 Duration of effect

In the company's base case, the improved OS of patients in the pembrolizumab combination arm relative to those in the SoC arm remains over the time-horizon of 20 years (see section 5.2.6.8), with the increase in survival resulting in higher average HRQoL per year of life (see section 5.2.7). The ERG considers this continued duration of effect to be unlikely and have instead opted for the scenario presented by the company in which treatment effect is discontinued at 5 years (MSD CS B.3.8.3). The KM plot of the OS curves for the two treatment strategies does not show convergence (see Figure 6 in MSD CS B.2.6.2) and hence does not indicate that early loss of treatment effect has been captured in the trial data.

6.1.4 Test cost

PD-L1 testing is routine in the NHS for all new diagnoses of NSCLC, and since every patient considered by the model should receive the test, its cost does not differ between strategies. Therefore it can be excluded from consideration in the cost-effectiveness analysis entirely. In contrast, the company base case applied the test cost only to patients subsequently receiving pembrolizumab.

6.2 ERG base case results

6.2.1 Derivation of the ERG base case

The ERG base case is built on a set of alternative and preferred assumptions or estimates. Table 102 shows the development of the final base case by iteration of one preference after the next. Changes to clinical effectiveness by means of changes to estimates of survival also impact costs; so changes are not mutually exclusive.

Table 102 Summary derivation of ERG base case (main comparison of PC versus SoC)

	Cost per QALY gained (ICER)	Individual impact of change	%	Cumulative impact of change	Cumulative %
Company base case	£46,568				
ERG's corrections to company coding	£46,103	-£465	-1%		
ERG base case (after corrections and revisions)	**£37,622**	-£8,946	*-19%*		
Impact of revisions on company base case:					
(1) Including background mortality	£47,814	£1,246	*3%*	£47,814	3%
(2) Removal of PD-L1 test cost	£46,051	-£517	*-1%*	£47,766	3%
(3) Log-logistic distribution for OS, week 0 both strategies	£31,463	-£15,105	*-32%*	£33,930	-27%
(4) Waning of pembrolizumab combination effect from year 5	£51,802	£5,234	*11%*	£37,622	-19%

Abbreviations: ERG = Evidence review group; ICER = Incremental cost effectiveness ratio; OS = Overall survival; QALY = Quality-adjusted life-year; SoC = Standard of care.

6.2.2 *Whole population, main comparison*

A summary of the ERG base case deterministic results is presented in Table 103. The deterministic analysis was the company's primary analysis.

Table 103 ERG base case result of main comparison for overall population (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£86,863	3.21	2.35				
SoC	£44,409	1.74	1.22	£42,454	1.47	1.13	£37,622

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

Table 104 Base case result of main comparison for overall population (probabilistic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£87,330	NR	2.35				
SoC	£44,990	NR	1.23	£42,340	-	1.11	£38,075

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; NR = Not reported; QALY = Quality-adjusted life year; SoC = Standard of care.

6.2.3 Whole population, other comparisons

Summary ERG results for the alternative comparators are presented in Table 105. The ICERs for PC versus the platinum and chemotherapy doublet options were in the range £40,000 to £58,000 per QALY gained.

Table 105 ERG base-case result of primary analysis versus NMA comparators (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£86,863	3.21	2.35				
Platinum + Gemcitabine	£27,292	1.36	0.93	£59,571	1.85	1.43	£41,710
Platinum + Vinorelbine	£28,917	1.91	1.35	£57,946	1.31	1.00	£57,939
Platinum + Docetaxel	£28,662	1.57	1.10	£58,201	1.64	1.26	£46,337
Platinum + Paclitaxel	£25,937	1.23	0.83	£60,926	1.99	1.52	£40,096

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

6.2.4 TPS>=50% sub-population, versus pembrolizumab monotherapy

Results of the comparison of PC with pembrolizumab monotherapy for strong expressers of PD-L1 are given in Table 106.

Table 106 ERG base case result of sub-population comparison for patients with TPS>=50%, PC versus pembrolizumab monotherapy (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£106,292	4.19	3.11				
Pembrolizumab monotherapy	£76,503	3.21	2.37	£29,788	0.98	0.74	£40,225

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

6.2.5 Sub-group analysis (main comparison only)

In the sub-group analysis, the ICERs were £33,873, £35,920, and £40,192 for TPS>=50%, (Table 107); 1%>=TPS<=49% (Table 108); and TPS<=1% (Table 109) groups respectively.

Table 107 ERG base case result of sub-population comparison for patients with TPS>=50%, PC versus SoC (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£106,292	4.19	3.11				
SoC	£44,546	1.82	1.29	£61,746	2.38	1.82	£33,873

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

Table 108 ERG base case result of main comparison for patients with 1%>=TPS<=49% (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£88,511	3.20	2.34				
SoC	£47,711	1.72	1.20	£40,800	1.48	1.14	£35,920

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

Table 109 ERG base case result of main comparison for patients with TPS<=1% (deterministic)

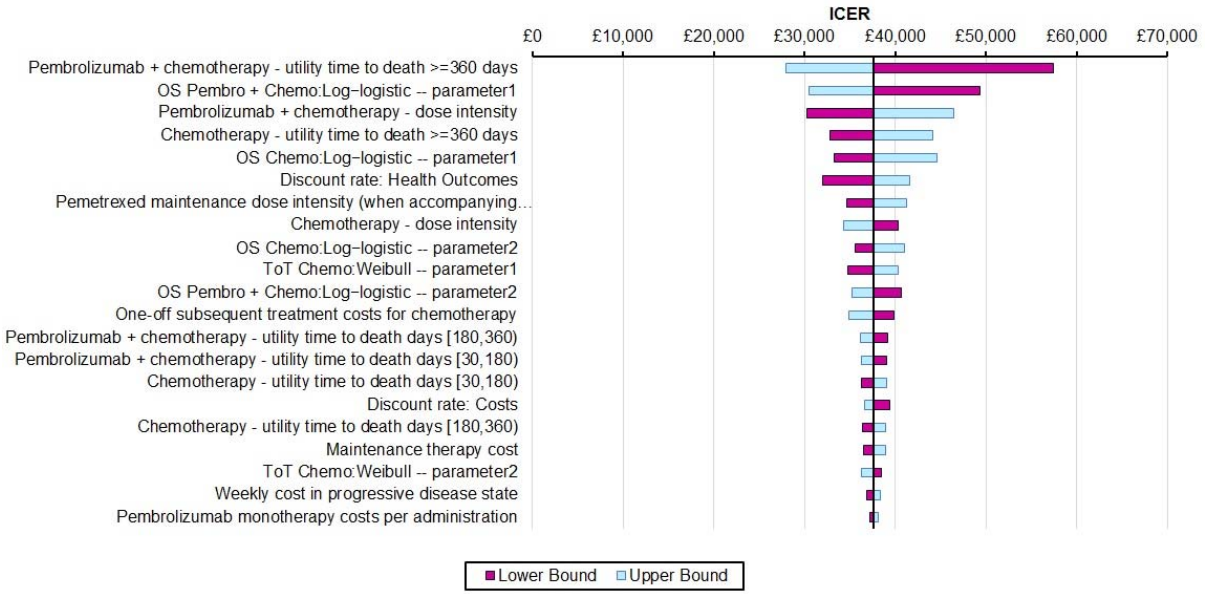
Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£66,904	2.45	1.77				
SoC	£42,826	1.66	1.17	£24,078	0.79	0.60	£40,192

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

6.3 Sensitivity analyses

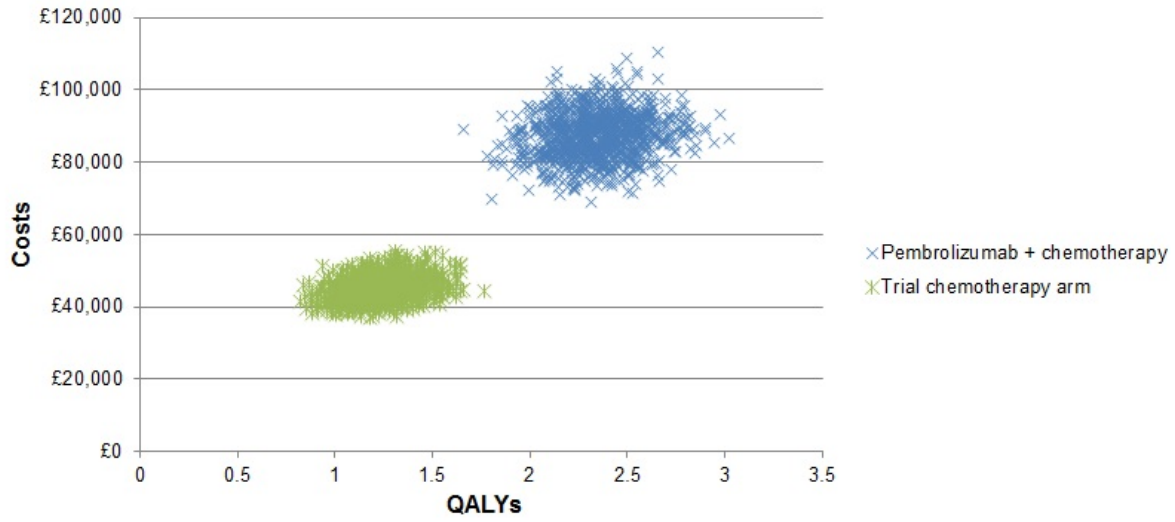
Univariate deterministic sensitivity analyses were conducted by the company to explore the impact of changes in key parameters on the ICER. Variables and their impact on the ICER of the main comparison can be seen in Figure 21 in the form of a tornado diagram.

Figure 21 Tornado diagram: deterministic sensitivity analyses results for PC versus SoC



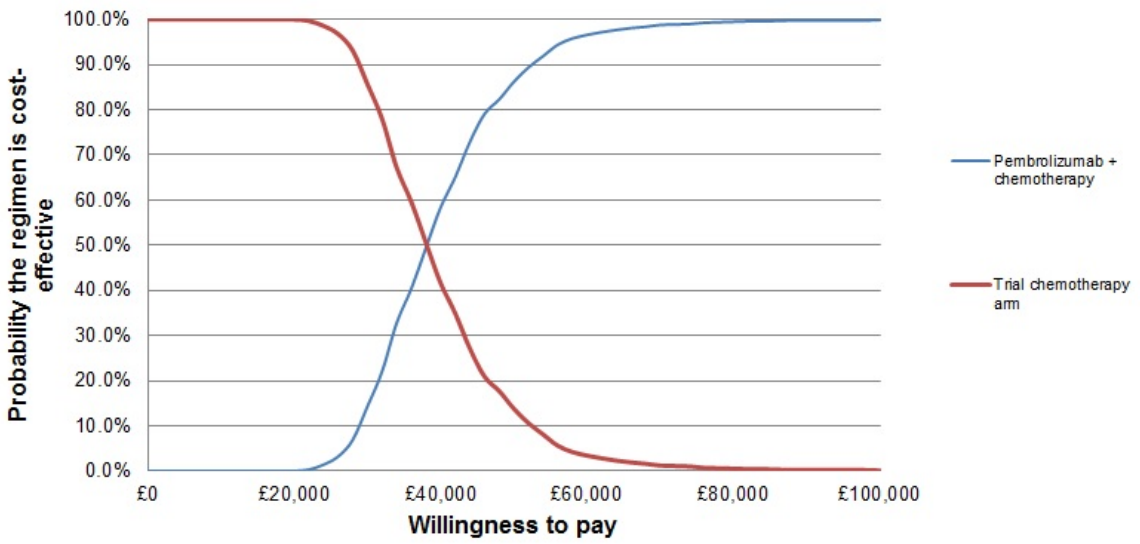
Probabilistic sensitivity of the ICER towards a large selection of input parameters was tested in the PSA (1,000 iterations), and results are presented in Figure 22.

Figure 22 Probabilistic sensitivity analysis for PC versus SOC



Cost effectiveness acceptability curves (CEACs) - displaying the probability of each strategy being the most cost-effective of the set at any given willingness to pay threshold – are presented in Figure 23.

Figure 23 Cost-effectiveness acceptability curve for PC versus SOC



The CEAC analysis found that at a £50,000 cost-effectiveness threshold, the probability of pembrolizumab combination being the most cost-effective strategy was 69%.

6.4 ERG scenario analyses

New alternative scenarios were created to test the main drivers of uncertainty in the model (Table 110).

Table 110 Results of ERG scenario analysis (main comparison)

		Pembrolizumab combination (PC)			SoC			PC vs SoC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Company base case		£84,324	2.50	1.81	£42,980	1.34	0.92	£41,344	0.89	£46,568
ERG base case		£86,863	3.21	2.35	£44,409	1.74	1.22	£42,454	1.13	**£37,622**
Estimation of long-term OS estimates										
1	Exponential from W0 (4th best stat fit to SoC KM): 5-yr OS= 3.2%; 10-yr OS= 0.1%	£83,205	2.42	1.75	£42,845	1.38	0.95	£40,360	0.80	£50,569
2	Exponential from W18: 5-yr OS= 2.0%; 10-yr OS= 0%	£82,995	2.38	1.71	£42,481	1.30	0.88	£40,514	0.83	£48,724
3	Exponential from W28 (Company base case): 5-yr OS= 2.4%; 10-yr OS= 0.1%	£82,683	2.31	1.66	£42,621	1.33	0.91	£40,061	0.75	£53,208
4	Exponential from W38: 5-yr OS= 6.1%; 10-yr OS= 0.5%	£83,080	2.39	1.73	£43,647	1.56	1.09	£39,433	0.63	£62,111
5	Log-Normal W0 (1st best stat fit to SoC KM): 5-yr OS= 9.5%; 10-yr OS= 3.1%	£88,066	3.47	2.55	£44,632	1.79	1.26	£43,434	1.29	£33,732
6	Log-Logistic (W0) (2nd best stat fit to SoC KM): 5-yr OS= 8.6%; 10-yr OS= 3.4%	£86,863	3.21	2.35	£44,409	1.74	1.22	£42,454	1.13	£37,622
7	Generalised Gamma (3rd best stat fit to SoC KM): 5-yr OS= 8.5%; 10-yr OS= 2.4%	£84,158	2.63	1.90	£44,295	1.71	1.20	£39,863	0.70	£57,045
8	Weibull (5th best stat fit to SoC KM: 5-yr OS= 1.0%; 10-yr OS= 0%	£82,214	2.21	1.58	£42,229	1.24	0.84	£39,985	0.75	£53,663
9	Gompertz (6th best stat fit to SoC KM): 5-yr OS= 2.7%; 10-yr OS= 0%	£81,685	2.09	1.50	£42,727	1.35	0.93	£38,958	0.57	£68,900
Estimation of utilities										
10	Chang 2017 as source of TTD category estimates (follows company SA)	£86,863	3.21	2.55	£44,409	1.74	1.26	£42,454	1.29	£32,858
11	Utilities driven by progression status - ToT as proxy for PS (follows company SA)	£86,863	3.21	2.17	£44,409	1.74	1.18	£42,454	0.99	£43,092

		Pembrolizumab combination (PC)			SoC			PC vs SoC		
		Total costs	**Total LYs**	**Total QALYs**	**Total costs**	**Total LYs**	**Total QALYs**	**Inc. costs**	**Inc. QALYs**	**ICER**
12	Combined TTD and classic Progression status approach	£86,863	3.21	2.14	£44,409	1.74	1.12	£42,454	1.03	£41,352
Estimation of high cost drug consumption (pembrolizumab, nintedanib, nivolumab)										
13	'Dose intensity' (actual vs. expected treatment cycles) of pembrolizumab combination: 95.6% reduced by 20% (76.5%)	£77,616	3.21	2.35	£44,409	1.74	1.22	£33,207	1.13	£29,428
14	Proportion of patients taking-up 2L treatment after 1L discontinuation: unadjusted estimates from KEYNOTE-189 (Ghandi Supp.): 30.5% PC, 46.6% SoC	£87,175	3.21	2.35	£42,215	1.74	1.22	£44,960	1.13	£39,843
15	Less pembrolizumab at 2L in SoC strategy: from 72% in BC to 50% (docetaxel instead)	£86,863	3.21	2.35	£41,006	1.74	1.22	£45,857	1.13	£40,534

7 End of life

The four NICE end-of-life criteria are as follows;(64)

- That the treatment is indicated for patients with a short life expectancy, normally less than 24 months;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.
- The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)
- The assumptions used in the reference case economic modelling are plausible, objective and robust

The company make the case for pembrolizumab combination; stating that the criteria for short life-expectancy, and life-extension, are met. They request that the evaluation result should be considered in the context of meeting these criteria.

In Table 111 the ERG present estimates from both the company and ERG preferred models of mean and median survival. Life expectancy is represented by survival on the comparator SoC strategy; life extension is represented by the difference in survival between the two strategies of the main comparison.

Table 111 Survival estimates on ceritinib and brigatinib (months)

Source (time in months)	Strategy		
	SoC (life expectancy)	Pembrolizumab combination	Increment (life extension)
Mean estimated by company base case	16.61	32.17	15.56
Mean estimated by ERG base case	22.73	43.68	20.96
Mean from ERG base case of TA531	23.4	38.0	14.6
Median in KEYNOTE-189	11.3 (95%CI, 8.7-15.1)*	Not reached	NA
Median in KEYNOTE-024	14.2	30.0	15.8
Estimate(s) offered by the company	11.3* and 9.9 - 13.9 from other studies	13.9	NA

Abbreviations: CI = Confidence interval; NA = Not applicable; SoC = Standard of Care
*KEYNOTE-189 median OS trial chemotherapy arm.

ERG comment:

- There is considerable uncertainty around the extrapolation of survival beyond short follow-up periods as is the case here. Median survival was not reached in the investigational arm of the key trial.
- Evidence from both KEYNOTE-189 and the company and ERG economic models suggest that the average overall survival on standard of care treatment is under 24 months; and the life extension offered by pembrolizumab combination is over 3 months.
- Pembrolizumab combination in this setting and population probably fulfils the criteria for end-of-life status. Whilst estimates of the extension to life are not robust the various point estimates are far in excess of the requirement. Equally, not all assumptions used in the reference case economic modelling are plausible, objective and robust, but they have little impact on the ICERs or are part-plausible.

Acknowledgements

The ERG technical team are especially thankful to the committed support of Programme Administrator Sue Whiffin and Administrator Jenny Lowe of PenTAG for their committed facilitation.

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Contributions of the authors

Ed Griffin	Provided overall project management and led the economic evaluation team. Oversight and author of sections within the cost-effectiveness chapter; wrote the Decision problem and End-of-life chapters; co-authored the Background chapter; collated the report.
Caroline Farmer	Provided project management of the clinical evidence team; led the critique of the clinical evidence; critiqued the methods of review(s) and wrote the corresponding sections of the report; contributed to the writing and editing of the report, including summary and background.
David Packman	Investigated the validity of economic assumptions and their implementations; and wrote the corresponding sections of chapter 5.
Elham Nikram	Fully checked and where necessary corrected the company's model; wrote the critique of the model structure; and adapted the model to the ERG preferred base case.
Justin Matthews	Critiqued the network meta-analysis.
Max Barnish	Critiqued the clinical effectiveness evidence; contributed to writing and editing the clinical effectiveness chapter; wrote the Background section.
Simon Briscoe	Wrote the sections of the report relating to the literature searches.
Nicole Dorey	Provided independent expert clinical advice to the ERG technical team in respect to clinical practice. Review clinical chapters.
Adam Dangoor	Provided independent expert clinical advice to the ERG technical team in respect to clinical practice.
Ruben Mujica Mota	Project director with oversight and direction to project including key aspects of the economic evaluation. Contributed to the editing of the report.

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Appendix 1. Excluded studies from the clinical SLR

Table 112 Studies Excluded from the SLR

Author	Year	Title	Journal	Reason for exclusion
[No authors listed]	1999	Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The elderly lung cancer vinorelbine italian study group	Journal of the National Cancer Institute	Intervention
[No authors listed]	2001	Study shows 2-year survival advantage for docetaxel	Expert review of anticancer therapy	Other
Adamo	2006	Brain metastases in patients with non-small cell lung cancer: Focus on the role of chemotherapy	Annals of Oncology	Other
Adams	2009	Maintenance pemetrexed therapy extends survival in nsclc	American Health and Drug Benefits	Other
Adjei	2006	Clinical studies of pemetrexed and gemcitabine combinations	Annals of Oncology	Other
Ahn	2000	Effect of vinorelbine, ifosfamide, and cisplatin combination chemotherapy in advanced non-small-cell lung cancer	American Journal of Clinical Oncology	Study design
Albain	2006	Pioneer: A phase iii randomised trial of paclitaxel poliglumex versus paclitaxel in chemotherapy-naive	Clinical Lung Cancer	Other

Author	Year	Title	Journal	Reason for exclusion
		women with advanced-stage non-small-cell lung cancer and performance status of 2		
Alberola	2003	Cisplatin plus gemcitabine versus a cisplatin-based triplet versus nonplatinum sequential doublets in advanced non-small-cell lung cancer: A spanish lung cancer group phase iii randomised trial	Journal of Clinical Oncology	Comparator
Anderson	2000	Gemcitabine plus best supportive care (bsc) vs bsc in inoperable non-small cell lung cancer - a randomised trial with quality of life as the primary outcome	British Journal of Cancer	Intervention
Anonymous	1995	Vinorelbine for treatment of advanced non-small-cell lung cancer	Medical Letter on Drugs and Therapeutics	Other
Anonymous	1996	Gemcitabine shows promise as combination agent in nsclc	Oncology (Williston Park, N.Y.)	Other
Anonymous	1999	Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The elderly lung cancer vinorelbine italian study group	Journal of the National Cancer Institute	Duplicate publication
Anonymous	2000	Concurrent chemoradiotherapy followed by consolidation docetaxel in stage iiib non-small-cell-lung cancer (swog 9504)	Clinical Lung Cancer	Study design

Author	Year	Title	Journal	Reason for exclusion
Anonymous	2001	Docetaxel combination produces 2-year survival advantage in nsclc patients	Oncology (Williston Park, N.Y.)	Other
Anonymous	2005	Role of epidermal growth factor receptor mutations in predicting sensitivity or resistance to targeted agents in non-small-cell lung cancer	Clinical Lung Cancer	Study design
Anonymous	2009	Maintenance therapy with pemetrexed improves overall survival in advanced nsclc	Oncology	Other
Anonymous	2012	First-line erlotinib inferior to chemo in advanced lung cancer	Oncology (Williston Park)	Other
Anonymous	2014	Mo06.03 bevacizumab and erlotinib or bevacizumab, cisplatin and pemetrexed in patients with metastatic non-small cell lung cancer: Egfr mutation based treatment allocation and repeat biopsy at progression in the sakk19/09 (biopro) trial	Clinical advances in hematology & oncology : H&O	Study design
Anonymous	2014	Erlotinib plus bevacizumab is effective in egfr-mutant nsclc	Cancer discovery	Other
Anonymous	2014	Mo06.12 efficacy and safety of paclitaxel and carboplatin with bevacizumab for the first-line treatment of patients with non-squamous non-small cell lung cancer (nsclc): Analyses based on age in the phase 3 pointbreak and e4599 trials	Clinical Advances in Hematology & Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
Atmaca	2013	A randomised multicentre phase ii study with cisplatin/docetaxel vs oxaliplatin/docetaxel as first-line therapy in patients with advanced or metastatic non-small cell lung cancer	British Journal of Cancer	Comparator
Azzoli	2005	Can adjuvant chemotherapy improve survival in patients with early-stage, resected non-small-cell lung cancer?	Nature Clinical Practice Oncology	Population
Bajetta	2003	Preclinical and clinical evaluation of four gemcitabine plus carboplatin schedules as front-line treatment for stage iv non-small-cell lung cancer	Annals of Oncology	Intervention
Baka	2005	Randomised phase ii study of two gemcitabine schedules for patients with impaired performance status (karnofsky performance status < 70) and advanced non-small-cell lung cancer	Journal of Clinical Oncology	Population
Baldini	1998	Cisplatin-vindesine-mitomycin (mvp) vs cisplatin-fosfamide-vinorelbine (pin) vs carboplatin-vinorelbine (can) in patients with advanced non-small-cell lung cancer (nsclc): A fonicap randomised phase ii study	British Journal of Cancer	Intervention
Belani	2001	Interim analysis of a phase ii study of induction weekly paclitaxel/carboplatin regimens followed by maintenance weekly paclitaxel for advanced and metastatic non-small cell lung cancer	Seminars in Oncology	Intervention

Author	Year	Title	Journal	Reason for exclusion
Belani	2001	Phase iii randomised trial of docetaxel in combination with cisplatin or carboplatin or vinorelbine plus cisplatin in advanced non-small cell lung cancer: Interim analysis	Seminars in Oncology	Population
Belani	2005	Randomised phase III trial comparing cisplatin–etoposide to carboplatin–paclitaxel in advanced or metastatic non-small cell lung cancer	Annals of Oncology	Population
Belani	2006	Effect of chemotherapy for advanced non-small cell lung cancer on patients' quality of life. A randomised controlled trial	Lung Cancer	Population
Belani	2007	Randomised phase ii trial of gemcitabine plus weekly versus three-weekly paclitaxel in previously untreated advanced non-small-cell lung cancer	Annals of Oncology	Intervention
Belani	2008	Randomised, phase iii study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer	Journal of Clinical Oncology	Intervention
Belderbos	2005	Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy	Radiotherapy and Oncology	Population
Belderbos	2007	Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (eortc 08972-22973)	European Journal of Cancer	Population

Author	Year	Title	Journal	Reason for exclusion
Beniwal	2012	Gemcitabine in brief versus prolonged low-dose infusion, both combined with carboplatin for advanced non-small cell lung cancer	Indian journal of cancer	Intervention
Bepler	2007	Phase ii pharmacogenomics-based adjuvant therapy trial in patients with non-small-cell lung cancer: Southwest oncology group trial 0720	Clinical Lung Cancer	Other
Bepler	2013	Randomised international phase iii trial of ercc1 and rrm1 expression-based chemotherapy versus gemcitabine/carboplatin in advanced non-small-cell lung cancer	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	Intervention
Bianco	2006	Combination of biological therapies in non-small cell lung cancer	Annals of Oncology	Other
Bidoli	2007	Randomised phase ii three-arm trial with three platinum-based doublets in metastatic non-small-cell lung cancer. An italian trials in medical oncology study	Annals of Oncology	Comparator
Binder	2007	Docetaxel/gemcitabine or cisplatin/gemcitabine followed by docetaxel in the first-line treatment of patients with metastatic non-small cell lung cancer (nsclc): Results of a multicentre randomised phase ii trial	Cancer Chemotherapy and Pharmacology	Population
Blumenschein	2011	A phase ii, multicenter, open-label randomised study of motesanib or bevacizumab in combination with	Annals of Oncology	Comparator

Author	Year	Title	Journal	Reason for exclusion
		paclitaxel and carboplatin for advanced non-squamous non-small-cell lung cancer		
Bogart and Govindan	2006	A randomised phase ii study of radiation therapy, pemetrexed, and carboplatin with or without cetuximab in stage iii non-small-cell lung cancer	Clinical Lung Cancer	Other
Boni	2012	Triplets versus doublets, with or without cisplatin, in the first-line treatment of stage iiib-iv non-small cell lung cancer (nsclc) patients: A multicenter randomised factorial trial (fast)	British Journal of Cancer	Population
Bonomi	2000	Comparison of Survival and Quality of Life in Advanced Non–Small-Cell Lung Cancer Patients Treated With Two Dose Levels of Paclitaxel Combined With Cisplatin Versus Etoposide With Cisplatin: Results of an Eastern Cooperative Oncology Group Trial	Journal of Clinical Oncology	Population
Boutsikou	2013	Docetaxel-carboplatin in combination with erlotinib and/or bevacizumab in patients with non-small cell lung cancer	OncoTargets and Therapy	Study design
Brodowicz	2006	Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: A phase iii trial	Lung Cancer	Comparator

Author	Year	Title	Journal	Reason for exclusion
Buccheri and Ferrigno	1997	Efficacy of platinum-based regimens in non-small cell lung cancer. A negative report from the cuneo lung cancer study group	Lung Cancer	Population
Cardenal	1999	Randomised Phase III Study of Gemcitabine-Cisplatin Versus Etoposide-Cisplatin in the Treatment of Locally Advanced or Metastatic Non-Small-Cell Lung Cancer	Journal of Clinical Oncology	Population
Carruthers	2011	Toxicity of hypofractionated accelerated radiotherapy concurrent with chemotherapy for non-small cell carcinoma of the lung	Clinical oncology (Royal College of Radiologists (Great Britain))	Population
Ceribelli	2003	Prolonged gemcitabine infusion in advanced non-small cell lung carcinoma: A randomised phase ii study of two different schedules in combination with cisplatin	Cancer	Intervention
Chang	2008	A randomised study of gemcitabine plus cisplatin and vinorelbine plus cisplatin in patients with advanced non-small-cell lung cancer	Chang Gung Medical Journal	Population
Chen	1996	Maculopapular rashes secondary to gemcitabine injection for non-small-cell lung cancer	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	Outcomes
Chen	2002	Paclitaxel plus carboplatin, compared with paclitaxel plus gemcitabine, shows similar efficacy while more	Annals of Oncology	Comparator

Author	Year	Title	Journal	Reason for exclusion
		cost-effective: A randomised phase ii study of combination chemotherapy against inoperable non-small-cell lung cancer previously untreated		
Chen	2004	A randomised phase ii study of weekly paclitaxel or vinorelbine in combination with cisplatin against inoperable non-small-cell lung cancer previously untreated	British Journal of Cancer	Population
Chen	2006	A phase ii randomised study of paclitaxel plus carboplatin or cisplatin against chemo-naive inoperable non-small cell lung cancer in the elderly	Journal of Thoracic Oncology	Comparator
Chen	2005	A randomised phase ii study of vinorelbine plus gemcitabine with/without cisplatin against inoperable non-small-cell lung cancer previously untreated	Lung Cancer	Comparator
Chen	2007	A randomised phase ii study of docetaxel or vinorelbine in combination with cisplatin against inoperable, chemo-naive non-small-cell lung cancer in Taiwan	Lung Cancer	Population
Chiou and Burotto	2015	Pseudoprogression and immune-related response in solid tumors	Journal of Clinical Oncology	Other
Ciuleanu	2013	A phase ii study of erlotinib in combination with bevacizumab versus chemotherapy plus bevacizumab in the first-line treatment of advanced non-squamous non-small cell lung cancer	Lung Cancer	Comparator

Author	Year	Title	Journal	Reason for exclusion
Ciuleanu	2009	Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: A randomised, double-blind, phase 3 study	The Lancet	Comparator
Clerici	1995	Non small cell lung cancer treatment with vinorelbine monochemotherapy: A phase ii study	Anticancer Research	Other
Colleoni	1997	A randomised phase ii trial of cisplatinum plus mitomycin-c plus vinorelbine and carboplatin plus vinorelbine in advanced non-small cell lung cancer	International Journal of Oncology	Comparator
Comella	2000	Interim analysis of a phase iii trial comparing cisplatin, gemcitabine, and vinorelbine vs. Either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non small-cell lung cancer. A southern italy cooperative oncology group study	Clinical lung cancer	Population
Comella	2000	Interim analysis of a phase iii trial. Triple- vs double-agent chemotherapy for advanced non-small-cell lung cancer. Southern italy cooperative oncology group	Oncology (Williston Park, N.Y.)	Population
Comella	2000	Randomised trial comparing cisplatin, gemcitabine, and vinorelbine with either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non-small-cell lung cancer: Interim analysis of a phase iii trial of the southern italy cooperative oncology group	Journal of Clinical Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
Comella	2007	Efficacy of the combination of cisplatin with either gemcitabine and vinorelbine or gemcitabine and paclitaxel in the treatment of locally advanced or metastatic non-small-cell lung cancer: A phase iii randomised trial of the southern italy cooperative oncology group (sicog 0101)	Annals of Oncology	Comparator
Comella	2004	Gemcitabine with either paclitaxel or vinorelbine vs paclitaxel or gemcitabine alone for elderly or unfit advanced non-small-cell lung cancer patients	British Journal of Cancer	Comparator
Correale	2010	Dose/dense metronomic chemotherapy with fractioned cisplatin and oral daily etoposide enhances the anti-angiogenic effects of bevacizumab and has strong anti-tumor activity in advanced non-small-cell-lung cancer patients	Cancer Biology and Therapy	Study design
Coudert	2012	Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (nsclc) according to response to first-line chemotherapy	Annals of Oncology	Comparator
Crino	1995	Chemotherapy of advanced non-small-cell lung cancer: A comparison of three active regimens. A randomised trial of the italian oncology group for clinical research (g.O.I.R.C.)	Annals of oncology : official journal of the European Society for Medical Oncology / ESMO	Comparator

Author	Year	Title	Journal	Reason for exclusion
Crino	1999	Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small-cell lung cancer: A randomised phase iii study of the italian lung cancer project	Journal of Clinical Oncology	Comparator
Crino	2002	Combined platinum containing treatment in nsclc	Lung Cancer	Other
Crino	2008	Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non-small-cell lung cancer (invite): A randomised, phase ii study	Journal of Clinical Oncology	Intervention
Crombie	2009	Randomised phase ii trial of gemcitabine and either day 1 or day 8 carboplatin for advanced non-small-cell lung cancer: Is thrombocytopenia predictable?	Asia-Pacific Journal of Clinical Oncology	Intervention
Crul	2003	Randomised phase i clinical and pharmacologic study of weekly versus twice-weekly dose-intensive cisplatin and gemcitabine in patients with advanced non-small cell lung cancer	Clinical Cancer Research	Intervention
Curran Jr	2011	Sequential vs concurrent chemoradiation for stage iii non-small cell lung cancer: Randomised phase iii trial rtog 9410	Journal of the National Cancer Institute	Population
Dahlberg	2010	Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ecog 4599	Journal of Clinical Oncology	Outcomes

Author	Year	Title	Journal	Reason for exclusion
Dang	2014	Risk and predictors for early radiation pneumonitis in patients with stage iii non-small cell lung cancer treated with concurrent or sequential chemoradiotherapy	Radiation Oncology	Study design
Danson	2003	Phase iii trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma	Cancer	Comparator
Dasgupta	2006	A prospective and randomised study of radiotherapy, sequential chemotherapy radiotherapy and concomitant chemo therapy-radiotherapy in unresectable non small cell carcinoma of the lung	Journal of Cancer Research and Therapeutics	Population
Davidson	2015	A phase iii randomised trial of adding topical nitroglycerin to first-line chemotherapy for advanced nonsmall-cell lung cancer: The australasian lung cancer trials group nitro trial	Annals of Oncology	Population
De Ruysscher	2012	Radiation-induced oesophagitis in lung cancer patients. Is susceptibility for neutropenia a risk factor?	Strahlentherapie und Onkologie	Study design
Douillard	2005	Sequential two-line strategy for stage iv non-small-cell lung cancer: Docetaxel-cisplatin versus vinorelbine-cisplatin followed by cross-over to single-agent docetaxel or vinorelbine at progression: Final results of a randomised phase ii study	Annals of Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
Douillard	2014	Relationship between egfr expression, egfr mutation status, and the efficacy of chemotherapy plus cetuximab in flex study patients with advanced non-small-cell lung cancer	Journal of Thoracic Oncology	Comparator
Dowlati	2008	Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab - an eastern cooperative oncology group study	Clinical Cancer Research	Outcomes
Edelman	2010	Outcomes associated with brain metastases in a three-arm phase iii trial of gemcitabine-containing regimens versus paclitaxel plus carboplatin for advanced non-small cell lung cancer	Journal of Thoracic Oncology	Outcomes
Ediebah	2014	Does change in health-related quality of life score predict survival? Analysis of eortc 08975 lung cancer trial	British Journal of Cancer	Outcomes
Esteban	2006	Gemcitabine and vinorelbine (gv) versus cisplatin, gemcitabine and vinorelbine (cgv) as first-line treatment in advanced non small cell lung cancer: Results of a prospective randomised phase ii study	Investigational New Drugs	Comparator
Esteban	2008	Pulmonary toxicity in patients treated with gemcitabine plus vinorelbine or docetaxel for advanced non-small	Investigational New Drugs	Population

Author	Year	Title	Journal	Reason for exclusion
		cell lung cancer: Outcome data on a randomised phase ii study		
Eton	2003	Early change in patient-reported health during lung cancer chemotherapy predicts clinical outcomes beyond those predicted by baseline report: Results from eastern cooperative oncology group study 5592	Journal of Clinical Oncology	Outcomes
Favaretto	2006	Non-platinum combination of gemcitabine in nsclc	Annals of Oncology	Other
Fidias	2009	Phase iii study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer	Journal of Clinical Oncology	Intervention
Fisher	2002	Docetaxel plus cisplatin combinations in advanced non-small-cell lung cancer	Clinical Lung Cancer	Other
Flotten	2012	Vinorelbine and gemcitabine vs vinorelbine and carboplatin as first-line treatment of advanced nsclc. A phase iii randomised controlled trial by the norwegian lung cancer study group	British Journal of Cancer	Population
Fossella	2003	Randomised, multinational, phase iii study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The tax 326 study group	Journal of Clinical Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
Frasci	2000	Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer	Journal of Clinical Oncology	Comparator
Gao	2010	Clinical study of comparing lp and tp regimens in the treatment of advanced non-small cell lung cancer	Chinese-German Journal of Clinical Oncology	Intervention
Gatzemeier	2007	Phase iii study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: The tarceva lung cancer investigation trial	Journal of Clinical Oncology	Comparator
Gatzemeier	2000	Phase iii comparative study of high-dose cisplatin versus a combination of paclitaxel and cisplatin in patients with advanced non-small-cell lung cancer	Journal of Clinical Oncology	Comparator
Gebbia	2003	Gemcitabine and cisplatin versus vinorelbine and cisplatin versus ifosfamide+gemcitabine followed by vinorelbine and cisplatin versus vinorelbine and cisplatin followed by ifosfamide and gemcitabine in stage iiib-iv non small cell lung carcinoma: A prospective randomised phase iii trial of the gruppo oncologico italia meridionale	Lung Cancer	Population
Gebbia	2008	Cisplatin plus weekly vinorelbine versus cisplatin plus vinorelbine on days 1 and 8 in advanced non-small cell lung cancer: A prospective randomised phase iii trial of the g.O.I.M. (gruppo oncologico italia meridionale)	Lung Cancer	Intervention

Author	Year	Title	Journal	Reason for exclusion
Gebbia	2010	First-line cisplatin with docetaxel or vinorelbine in patients with advanced non-small-cell lung cancer: A quality of life directed phase ii randomised trial of gruppo oncologico italia meridionale	Lung Cancer	Population
Georgoulias	2001	Comparison of docetaxel/cisplatin to docetaxel/gemcitabine as first-line treatment of advanced non-small cell lung cancer: Early results of a randomised trial	Lung Cancer	Population
Georgoulias	2001	Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: A randomised multicentre trial	Lancet	Population
Georgoulias	2004	Docetaxel versus docetaxel plus cisplatin as front-line treatment of patients with advanced non-small-cell lung cancer: A randomised, multicenter phase iii trial	Journal of Clinical Oncology	Comparator
Georgoulias	2005	Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small-cell lung cancer: A phase iii randomised trial	Journal of Clinical Oncology	Population
Georgoulias	2008	Docetaxel versus docetaxel plus gemcitabine as front-line treatment of patients with advanced non-small cell lung cancer: A randomised, multicenter phase iii trial	Lung Cancer	Comparator
Gibson	2003	Cisplatin-based adjuvant chemotherapy in resected non-small-cell lung cancer	Clinical Lung Cancer	Population

Author	Year	Title	Journal	Reason for exclusion
Ginopoulos	1997	Advanced non-small cell lung cancer chemotherapy: A randomised trial of two active regimens (mvp and pe)	Cancer Letters	Comparator
Goksel	2005	A prospective, multicentre clinical trial comparing cisplatin plus gemcitabine with cisplatin plus etoposide in patients with locally advanced and metastatic non-small cell lung cancer	Respirology (Carlton, Vic.)	Study design
Goto	2006	The Four-Arm Cooperative Study (FACS) for advanced non-small cell lung cancer (NSCLC): a subgroup analysis in elderly patients (pts)	American Society of Clinical Oncology	Population
Greco	2002	Prospective randomised study of four novel chemotherapy regimens in patients with advanced nonsmall cell lung carcinoma: A minnie pearl cancer research network trial	Cancer	Comparator
Greco	2007	Paclitaxel/carboplatin/gemcitabine versus gemcitabine/vinorelbine in advanced non-small-cell lung cancer: A phase ii/iii study of the minnie pearl cancer research network	Clinical Lung Cancer	Comparator
Gridelli	2012	First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: The torch randomised trial	Journal of Clinical Oncology	Population
Gridelli	2000	Gemcitabine plus vinorelbine in advanced non-small cell lung cancer: A phase ii study of three different doses	British Journal of Cancer	Intervention

Author	Year	Title	Journal	Reason for exclusion
Gridelli	2003	Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer: A phase iii trial of the italian gemvin investigators and the national cancer institute of canada clinical trials group	Journal of Clinical Oncology	Outcome
Gridelli	2007	Factorial phase iii randomised trial of rofecoxib and prolonged constant infusion of gemcitabine in advanced non-small-cell lung cancer: The gemcitabine-coxib in nsclc (geco) study	Lancet Oncology	Intervention
Gridelli	2003	Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The multicenter italian lung cancer in the elderly study (miles) phase iii randomised trial	Journal of the National Cancer Institute	Comparator
Gridelli	2012	Safety, resource use, and quality of life in paramount: A phase iii study of maintenance pemetrexed versus placebo after induction pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer	Journal of Thoracic Oncology	Comparator
Grigorescu	2002	Gemcitabine (gem) and carboplatin (cbdca) versus cisplatin (cddp) and vinblastine (vlb) in advanced non-small-cell lung cancer (nsclc) stages iii and iv: A phase iii randomised trial	Lung Cancer	Population
Gronberg	2013	Associations between ts, ttf-1, fr-alpha, fpgs, and overall survival in patients with advanced non-small-cell	Journal of Thoracic Oncology	Outcomes

Author	Year	Title	Journal	Reason for exclusion
		lung cancer receiving pemetrexed plus carboplatin or gemcitabine plus carboplatin as first-line chemotherapy		
Gronberg	2010	Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving platinum-doublet chemotherapy	European Journal of Cancer	Outcomes
Hainsworth	2007	Weekly docetaxel versus docetaxel/gemcitabine in the treatment of elderly or poor performance status patients with advanced nonsmall cell lung cancer: A randomised phase 3 trial of the minnie pearl cancer research network	Cancer	Comparator
Han	2008	Randomised phase 2 study of irinotecan plus cisplatin versus gemcitabine plus vinorelbine as first-line chemotherapy with second-line crossover in patients with advanced nonsmall cell lung cancer	Cancer	Comparator
Han	2012	First-signal: First-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung	Journal of Clinical Oncology	Comparator
Hasegawa	2013	A randomised phase ii trial of gemcitabine plus carboplatin: Biweekly versus standard schedules in patients with advanced non-small cell lung cancer	Chemotherapy	Intervention
Heigener	2014	Open, randomised, multi-center phase ii study comparing efficacy and tolerability of erlotinib vs.	Lung Cancer	Comparator

Author	Year	Title	Journal	Reason for exclusion
		Carboplatin/vinorelbin in elderly patients (>70 years of age) with untreated non-small cell lung cancer		
Helbekkmo	2007	Vinorelbine/carboplatin vs gemcitabine/carboplatin in advanced nsclc shows similar efficacy, but different impact of toxicity	Britist Journal of Cancer	Population
Hightower	2003	Erlotinib (osi-774, tarcevatm), a selective epidermal growth factor receptor tyrosine kinase inhibitor, in combination with chemotherapy for advanced non-small-cell lung cancer	Clinical Lung Cancer	Other
Hirsh	2014	Patient-reported neuropathy and taxane-associated symptoms in a phase 3 trial of nab-paclitaxel plus carboplatin versus solvent-based paclitaxel plus carboplatin for advanced non-small-cell lung cancer	Journal of Thoracic Oncology	Intervention
Imamura	2011	Randomised phase ii study of two schedules of carboplatin and gemcitabine for stage iiib and iv advanced non-small cell lung cancer (jaccro lc-01 study)	Chemotherapy	Intervention
Isa	2009	Serum osteopontin levels are highly prognostic for survival in advanced non-small cell lung cancer: Results from jmto lc 0004	Journal of Thoracic Oncology	Outcomes
Ishii	2011	Fractionated administration of carboplatin/paclitaxel reduces neurotoxicity in patients with advanced non-small cell lung cancer	Anti-Cancer Drugs	Intervention

Author	Year	Title	Journal	Reason for exclusion
Jahnke	2011	Randomised phase ii study of paclitaxel and carboplatin or vinorelbine in advanced non-small cell lung cancer	Anticancer Research	Comparator
Jensen	2008	Randomised cross-over study of patient preference for oral or intravenous vinorelbine in combination with carboplatin in the treatment of advanced nsclc	Lung Cancer	Intervention
Jeremic and Shibamoto	1995	Pre-treatment prognostic factors in patients with stage iii non-small cell lung cancer treated with hyperfractionated radiation therapy with or without concurrent chemotherapy	Lung Cancer	Intervention
Jeremic	2001	Hyperfractionated radiation therapy and concurrent low-dose, daily carboplatin/etoposide with or without weekend carboplatin/etoposide chemotherapy in stage iii non-small-cell lung cancer: A randomised trial	International journal of radiation oncology, biology, physics	Population
Jeremic	1996	Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage iii non-small-cell lung cancer: A randomised study	Journal of Clinical Oncology	Population
Jeremic	1999	Prolonged oral versus high-dose intravenous etoposide in combination with carboplatin for stage iv non-small-cell lung cancer (nsclc): A randomised trial	Lung Cancer	Intervention
Joon	2007	Phase iii trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non-small-cell lung cancer	Journal of Clinical Oncology	Intervention

Author	Year	Title	Journal	Reason for exclusion
Karayama	2013	Maintenance therapy with pemetrexed versus docetaxel after induction therapy with carboplatin and pemetrexed in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer: A randomised, phase ii study	Cancer Chemotherapy and Pharmacology	Population
Katakami	2006	Docetaxel in combination with either cisplatin or gemcitabine in unresectable non-small cell lung carcinoma: A randomised phase ii study by the japan lung cancer cooperative clinical study group	Journal of Thoracic Oncology	Population
Kawahara	2013	Carboplatin plus either docetaxel or paclitaxel for japanese patients with advanced non-small cell lung cancer	Anticancer Research	Population
Kelly	2001	Randomised phase iii trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: A southwest oncology group trial	Journal of Clinical Oncology	Population
Khodadad	2014	Comparing docetaxel plus cisplatin with paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: A single institute study	Iranian Journal of Pharmaceutical Research	Population
Kim	2006	Randomised phase ii study of gemcitabine plus cisplatin versus etoposide plus cisplatin for the	Lung Cancer	Population

Author	Year	Title	Journal	Reason for exclusion
		treatment of locally advanced or metastatic non-small cell lung cancer: Korean cancer study group experience		
Kim	2012	Comparison of docetaxel/cisplatin dosages of 75/60 and 60/60 mg/m² for the treatment of non-small cell lung cancer	Experimental and Therapeutic Medicine	Intervention
Kim	2014	LBA41_PRA RANDOMISED PHASE III STUDY OF DOCETAXEL PLUS CISPLATIN VERSUS PEMETREXED PLUS CISPLATIN IN FIRST LINE NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSQ-NSCLC)	Annals of Oncology	Comparator
Kimura	2015	Randomised controlled phase iii trial of adjuvant chemo-immunotherapy with activated killer t cells and dendritic cells in patients with resected primary lung cancer	Cancer Immunology, Immunotherapy	Population
Kimura and Yamaguchi	1995	Adjuvant immunotherapy with interleukin 2 and lymphokine-activated killer cells after noncurative resection of primary lung cancer	Lung Cancer	Population
Kosmidis	1997	Paclitaxel (175 mg/m2) plus carboplatin versus paclitaxel (225 mg/m2) plus carboplatin in non-small cell lung cancer: A randomised study	Seminars in oncology	Other
Kosmidis	2000	Interim results of a phase iii trial. Paclitaxel/carboplatin vs paclitaxel/gemcitabine in advanced non-small-cell lung cancer	Oncology (Williston Park, N.Y.)	Population

Author	Year	Title	Journal	Reason for exclusion
Kosmidis	2002	Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: A phase iii randomised trial	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	Comparator
Kosmidis	2008	Paclitaxel and gemcitabine versus carboplatin and gemcitabine in patients with advanced non-small-cell lung cancer. A phase iii study of the hellenic cooperative oncology group	Annals of oncology : official journal of the European Society for Medical Oncology / ESMO	Comparator
Kosmidis	2007	Gemcitabine versus gemcitabine-carboplatin for patients with advanced non-small cell lung cancer and a performance status of 2: A prospective randomised phase ii study of the hellenic cooperative oncology group	Journal of Thoracic Oncology	Comparator
Kosmidis	2000	Combination chemotherapy with paclitaxel plus carboplatin versus paclitaxel plus gemcitabine in inoperable non-small cell lung cancer: A phase iii randomised study. Preliminary results	Seminars in Oncology	Other
Kreuter	2016	Three-year follow-up of a randomised phase ii trial on refinement of early-stage nsclc adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine (the treat study)	Journal of Thoracic Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
Kreuter	2014	Impact and safety of adjuvant chemotherapy on pulmonary function in early stage non-small cell lung cancer	Respiration	Population
Kubota	2004	The Four-Arm Cooperative Study (FACS) for advanced non-small-cell lung cancer (NSCLC)	Journal of Clinical Oncology	Population
Kubota	2004	Phase iii randomised trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage iv non-small-cell lung cancer: The japanese taxotere lung cancer study group	Journal of Clinical Oncology	Comparator
Kusagaya	2012	Biweekly combination therapy with gemcitabine and carboplatin compared with gemcitabine monotherapy in elderly patients with advanced non-small-cell lung cancer: A randomised, phase-ii study	Lung Cancer	Comparator
Laack	2004	Randomised phase iii study of gemcitabine and vinorelbine versus gemcitabine, vinorelbine, and cisplatin in the treatment of advanced non-small-cell lung cancer: From the german and swiss lung cancer study group	Journal of Clinical Oncology	Comparator
Langer	2015	Weekly nab-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Analysis of safety and efficacy in patients with renal impairment	Clinical Lung Cancer	Intervention

Author	Year	Title	Journal	Reason for exclusion
Langer	2015	Survival, quality-adjusted survival, and other clinical end points in older advanced non-small-cell lung cancer patients treated with albumin-bound paclitaxel	British Journal of Cancer	Intervention
Langer	2002	Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: Implications of eastern cooperative oncology group 5592, a randomised trial	Journal of the National Cancer Institute	Outcomes
Langer	2008	Phase iii trial comparing paclitaxel poliglumex (ct-2103, ppx) in combination with carboplatin versus standard paclitaxel and carboplatin in the treatment of ps 2 patients with chemotherapy-naive advanced non-small cell lung cancer	Journal of Thoracic Oncology	Intervention
Langer	2007	Randomised phase ii trial of paclitaxel plus carboplatin or gemcitabine plus cisplatin in eastern cooperative oncology group performance status 2 non-small-cell lung cancer patients: Ecog 1599	Journal of Clinical Oncology	Comparator
Lee	2013	Paclitaxel-loaded polymeric micelle (230 mg/m2) and cisplatin (60 mg/m2) vs. Paclitaxel (175 mg/m2) and cisplatin (60 mg/m2) in advanced non-small-cell lung cancer: A multicenter randomised phase iib trial	Clinical Lung Cancer	Intervention
Lee	2012	Early neutrophil-to-lymphocyte ratio reduction as a surrogate marker of prognosis in never smokers with	Journal of Cancer Research and Clinical Oncology	Outcomes

Author	Year	Title	Journal	Reason for exclusion
		advanced lung adenocarcinoma receiving gefitinib or standard chemotherapy as first-line therapy		
Li	2011	A randomised study of gemcitabine plus oxaliplatin versus gemcitabine plus cisplatin as the 1st line chemotherapy for advanced non-small cell lung cancer in elderly patients	Chinese Journal of Lung Cancer	Other
Liao	2008	Gemcitabine and cisplatin treatment over a 3-week versus a 4-week dosing schedule: A randomised trial conducted in chinese patients with nonsmall cell lung cancer	Chinese Medical Journal	Intervention
Lilenbaum	2005	Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: The cancer and leukemia group b (study 9730)	Journal of Clinical Oncology	Population
Lilenbaum	2008	Randomised phase ii trial of erlotinib or standard chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2	Journal of Clinical Oncology	Comparator
Lilenbaum	2005	Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: The cancer and leukemia group b (study 9730)	Journal of Clinical Oncology	Comparator
Liu	2014	A double-blind, randomised phase ii study of dicycloplatin plus paclitaxel versus carboplatin plus paclitaxel as first-line therapy for patients with advanced non-small-cell lung cancers	Archives of Medical Science	Comparator

Author	Year	Title	Journal	Reason for exclusion
Lorusso	1995	Results of a clinical multicentric randomised phase ii study of non-small cell lung cancer treated with vinorelbine-cisplatin versus vinorelbine alone	International Journal of Oncology	Population
Maemondo	2014	Randomised phase ii trial comparing carboplatin plus weekly paclitaxel and docetaxel alone in elderly patients with advanced non-small cell lung cancer: North japan lung cancer group trial 0801	Oncologist	Population
Maione	2005	Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: A prognostic analysis of the multicenter italian lung cancer in the elderly study	Journal of Clinical Oncology	Intervention
Maneechawakajorn and Suksuperm	2014	Quality of life in advanced non-small cell lung cancer receiving chemotherapy of platinum combination in old versus new standard chemotherapy regimen	Journal of the Medical Association of Thailand	Other
Manegold	1997	Single-agent gemcitabine versus cisplatin-etoposide: Early results of a randomised phase ii study in locally advanced or metastatic non-small-cell lung cancer	Annals of oncology : official journal of the European Society for Medical Oncology / ESMO	Comparator
Marsland	2005	Sequential versus concurrent paclitaxel and carboplatin for the treatment of advanced non-small cell lung cancer in elderly patients and patients with poor	Lung Cancer	Study design

Author	Year	Title	Journal	Reason for exclusion
		performance status: Results of two phase ii, multicenter trials		
Martoni	2005	Multicentre randomised phase iii study comparing the same dose and schedule of cisplatin plus the same schedule of vinorelbine or gemcitabine in advanced non-small cell lung cancer	European Journal of Cancer	Population
Masters	2006	A randomised phase ii trial using two different treatment schedules of gemcitabine and carboplatin in patients with advanced non-small-cell lung cancer	Journal of Thoracic Oncology	Intervention
Masutani	1996	A phase iii randomised trial of cisplatin plus vindesine versus cisplatin plus vindesine plus mitomycin c versus cisplatin plus vindesine plus ifosfamide for advanced non-small-cell lung cancer	Respirology (Carlton, Vic.)	Population
Matsui	1996	Determinants of myelosuppression in the treatment of non-small cell lung cancer with cisplatin-containing chemotherapy	Japanese Journal of Cancer Research	Population
Mauduit	2001	Hyperfractionated radiation therapy and concurrent low-dose, daily carboplatin/etoposide with or without weekend carboplatin/etoposide chemotherapy in stage iii non-small-cell lung cancer: A randomised trial	International Journal of Radiation Oncology Biology Physics	Population
Maung	2002	Ly900003 (affinitactm), an antisense inhibitor of protein kinase c-alpha, in non-small-cell lung cancer	Clinical Lung Cancer	Other

Author	Year	Title	Journal	Reason for exclusion
Mazieres	2013	Evaluation of egfr protein expression by immunohistochemistry using h-score and the magnification rule: Re-analysis of the saturn study	Lung Cancer	Population
Mazzanti	2003	Randomised, multicenter, phase ii study of gemcitabine plus cisplatin versus gemcitabine plus carboplatin in patients with advanced non-small cell lung cancer	Lung Cancer	Comparator
Mc Kean	2011	Exploring therapeutic decisions in elderly patients with non-small cell lung cancer: Results and conclusions from north central cancer treatment group study n0222	Cancer Investigation	Study design
Mitchell	2011	Randomised phase 2 sequencing and pharmacokinetic study of gemcitabine and oxaliplatin in advanced non-small cell lung cancer	Asia-Pacific Journal of Clinical Oncology	Population
Mohile	2013	Toxicity of bevacizumab in combination with chemotherapy in older patients	Oncologist	Study design
Moinpour	2002	Quality of life in advanced non-small-cell lung cancer: Results of a southwest oncology group randomised trial	Quality of Life Research	Population
Mok	2011	Efficacy of bevacizumab with cisplatin and gemcitabine in Asian patients with advanced or recurrent non-squamous non-small cell lung cancer who have not received prior chemotherapy: A substudy of the Avastin in Lung trial	Asia Pac J Clin Oncol	Intervention

Author	Year	Title	Journal	Reason for exclusion
Mok	2014	A correlative biomarker analysis of the combination of bevacizumab and carboplatin-based chemotherapy for advanced non-squamous non-small-cell lung cancer: Results of the phase ii randomised abigail study (bo21015)	Journal of Thoracic Oncology	Intervention
Mok	2015	Detection and dynamic changes of egfr mutations from circulating tumor DNA as a predictor of survival outcomes in nsclc patients treated with first-line intercalated erlotinib and chemotherapy	Clinical Cancer Research	Comparator
Mok	2009	Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma	New England Journal of Medicine	Comparator
Morabito	2013	Randomised phase iii trial of gemcitabine and cisplatin vs. Gemcitabine alone in patients with advanced non-small cell lung cancer and a performance status of 2: The cappa-2 study	Lung Cancer	Comparator
Mubarak	2012	A randomised, phase 2 study comparing pemetrexed plus best supportive care versus best supportive care as maintenance therapy after first-line treatment with pemetrexed and cisplatin for advanced, non-squamous, non-small cell lung cancer	BMC Cancer	Comparator
Mylonakis	2010	Phase ii study of liposomal cisplatin (lipoplatin) plus gemcitabine versus cisplatin plus gemcitabine as first	Lung Cancer	Population

Author	Year	Title	Journal	Reason for exclusion
		line treatment in inoperable (stage iiib/iv) non-small cell lung cancer		
Negoro	2003	Randomised phase iii trial of irinotecan combined with cisplatin for advanced non-small-cell lung cancer	British Journal of Cancer	Intervention
Novello	2009	Randomised multicenter phase ii study of two schedules of docetaxel and gemcitabine or cisplatin/gemcitabine followed by docetaxel as first line treatment for advanced non-small cell lung cancer	Lung Cancer	Comparator
Obasaju	2010	A comparison of white and african american outcomes from a three-arm, randomised, phase iii multicenter trial of advanced or metastatic non-small cell lung cancer	Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer	Outcomes
Obasaju	2005	Gemcitabine/carboplatin in patients with metastatic non-small-cell lung cancer: Phase ii study of 28-day and 21-day schedules	Clinical Lung Cancer	Intervention
Oh	2013	A phase iii concurrent chemoradiotherapy trial with cisplatin and paclitaxel or docetaxel or gemcitabine in unresectable non-small cell lung cancer: Kaslc 0401	Cancer Chemotherapy and Pharmacology	Intervention
Ohe	2007	Randomised phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for	Annals of Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
		advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan		
Pallaud	2014	Clinical genotyping and efficacy outcomes: Exploratory biomarker data from the phase ii abigail study of first-line bevacizumab plus chemotherapy in non-squamous non-small-cell lung cancer	Lung Cancer	Intervention
Park	2007	Phase iii trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non small-cell lung cancer	Journal of Clinical Oncology	Intervention
Park	2007	Randomised phase ii trial of two different schedules of docetaxel plus cisplatin as first-line therapy in advanced nonsmall cell lung cancer	Cancer	Intervention
Passardi	2008	Randomised phase ii study with two gemcitabine- and docetaxel-based combinations as first-line chemotherapy for metastatic non-small cell lung cancer	Journal of Translational Medicine	Intervention
Patel	2013	Pointbreak: A randomised phase iii study of pemetrexed plus carboplatin and bevacizumab followed by maintence pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintence bevacizumab in patients with stage iiib or iv nonsquamous non-small-cell lung cancer	Journal of Clinical Oncology	Intervention

Author	Year	Title	Journal	Reason for exclusion
Pereira	2007	Gemcitabine administered as a short infusion versus a fixed dose rate in combination with cisplatin for the treatment of patients with advanced non-small cell lung cancer	Lung Cancer	Intervention
Perng	1997	Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small-cell lung cancer in a phase ii randomised study	Journal of Clinical Oncology	Comparator
Perol	2012	Randomised, phase iii study of gemcitabine or erlotinib maintenance therapy versus observation,with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer	Journal of Clinical Oncology	Comparator
Pujol	2005	Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: A phase iii study addressing the case for cisplatin	Annals of Oncology	Population
Quoix	2016	Tg4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (time): Results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial	The Lancet Oncology	Comparator
Rademaker-Lakhai	2006	Relationship between cisplatin administration and the development of ototoxicity	Journal of Clinical Oncology	Intervention
Raju	2009	A prospective evaluation of quality of life (QOL) in a phase II trial of pemetrexed (P) plus carboplatin (Cb) ±	Journal of Clinical Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
		enzastaurin (E) versus docetaxel (D) plus Cb as first-line treatment of patients (pts) with advanced non-small cell lung cancer (NSCLC)		
Reck	2010	Overall survival with cisplatin–gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL)	Annals of Oncology	Intervention
Reck	2009	Phase III Trial of Cisplatin Plus Gemcitabine With Either Placebo or Bevacizumab As First-Line Therapy for Nonsquamous Non–Small-Cell Lung Cancer: AVAiL	Journal of Clinical Oncology	Intervention
Reck	2014	Paramount: Descriptive subgroup analyses of final overall survival for the phase iii study of maintenance pemetrexed versus placebo following induction treatment with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer	Journal of Thoracic Oncology	Outcomes
Reck	2016	Primary PFS and safety analyses of a randomised Phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150)	European Society of Medical Oncology	Intervention
Reck	2014	1267P QUALITY-OF-LIFE (QOL), TOLERABILITY, AND SUPPORTIVE CARE RESULTS: NECITUMUMAB PHASE 3 SQUIRE STUDY Annals of Oncology	Annals of Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
Reynolds	2015	Exploratory Subset Analysis of African Americans From the PointBreak Study: Pemetrexed-Carboplatin-Bevacizumab Followed by Maintenance Pemetrexed-Bevacizumab Versus Paclitaxel-Carboplatin-Bevacizumab Followed by Maintenance Bevacizumab in Patients With Stage IIIB/IV Nonsquamous Non-Small-Cell Lung Cancer.	Clinical Lung Cancer	Intervention
Reynolds	2009	Randomised phase iii trial of gemcitabine-based chemotherapy with in situ rrm1 and ercc1 protein levels for response prediction in non - small-cell lung cancer	Journal of Clinical Oncology	Comparator
Ricci	2000	A randomised study comparing two different schedules of administration of cisplatin in combination with gemcitabine in advanced nonsmall cell lung carcinoma	Cancer	Intervention
Rosell	2003	Transcripts in pretreatment biopsies from a three-arm randomised trial in metastatic non-small-cell lung cancer	Oncogene	Outcomes
Rosell	2002	Phase iii randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: A cooperative multinational trial	Annals of Oncology	Comparator
Rotonda	2015	Impact of tg4010 vaccine on health-related quality of life in advanced non-small-cell lung cancer: Results of a phase iib clinical trial	PLoS ONE	Comparator

Author	Year	Title	Journal	Reason for exclusion
Rowinsky	1999	Paclitaxel steady-state plasma concentration as a determinant of disease outcome and toxicity in lung cancer patients treated with paclitaxel and cisplatin	Clinical Cancer Research	Outcomes
Rubio	2009	A phase ii randomised trial of gemcitabine-docetaxel versus gemcitabine-cisplatin in patients with advanced non-small cell lung carcinoma	Cancer Chemotherapy & Pharmacology	Population
Rudd	2005	Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage iiib or iv non-small-cell lung cancer: A phase iii randomised study of the london lung cancer group	Journal of Clinical Oncology	Comparator
Saito	2012	Randomised phase ii study of carboplatin-paclitaxel or gemcitabine- vinorelbine in patients with advanced nonsmall cell lung cancer and a performance status of 2: West japan thoracic oncology group 0004	American Journal of Clinical Oncology: Cancer Clinical Trials	Population
Sakakibara	2010	Randomised phase ii trial of weekly paclitaxel combined with carboplatin versus standard paclitaxel combined with carboplatin for elderly patients with advanced non-small-cell lung cancer	Annals of Oncology	Intervention
Sandler	2000	Phase iii trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer	Journal of Clinical Oncology	Comparator

Author	Year	Title	Journal	Reason for exclusion
Satouchi	2013	Efficacy and safety of weekly nab-paclitaxel plus carboplatin in patients with advanced non-small cell lung cancer	Lung Cancer	Intervention
Scagliotti	2009	Survival without toxicity for cisplatin plus pemetrexed versus cisplatin plus gemcitabine in chemonaive patients with advanced non-small cell lung cancer: A risk-benefit analysis of a large phase iii study	European Journal of Cancer	Outcomes
Scagliotti	2005	Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: A multicenter, randomised, phase ii trial	Clinical Cancer Research	Comparator
Scagliotti	2012	International, randomised, placebo-controlled, double-blindphase iii study of motesanib plus carboplatin/paclitaxel in patients with advanced non-squamous non-small-cell lung cancer: Monet1	Journal of Clinical Oncology	Comparator
Scagliotti	2002	Phase iii randomised trial comparing three platinum-based doublets in advanced non-small-cell lung cancer	Journal of Clinical Oncology	Population
Schiller	2002	Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer	New England Journal of Medicine	Population
Schuette	2006	Multicenter randomised trial for stage iiib/iv non-small-cell lung cancer using every-3-week versus weekly paclitaxel/carboplatin	Clinical Lung Cancer	Intervention
Schuette	2006	Randomised, multicenter, open-label phase ii study of gemcitabine plus single-dose versus split-dose	Clinical Lung Cancer	Intervention

Author	Year	Title	Journal	Reason for exclusion
		carboplatin in the treatment of patients with advanced-stage non-small-cell lung cancer		
Schuette	2013	A randomised phase ii study of pemetrexed in combination with cisplatin or carboplatin as first-line therapy for patients with locally advanced or metastatic non-small-cell lung cancer	Clinical Lung Cancer	Comparator
Se	2007	Randomised phase ii trial of two different schedules of docetaxel plus cisplatin as first-line therapy in advanced nonsmall cell lung cancer	Cancer	Intervention
Sederholm	2005	Phase iii trial of gemcitabine plus carboplatin versus single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: The swedish lung cancer study group	Journal of Clinical Oncology	Comparator
Smit	2003	Three-arm randomised study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: A phase iii trial of the european organization for research and treatment of cancer lung cancer group--eortc 08975	Journal of Clinical Oncology	Comparator
Socinski	2010	Randomised, phase ii trial of pemetrexed and carboplatin with or without enzastaurin versus docetaxel and carboplatin as first-line treatment of patients with stage iiib/iv non-small cell lung cancer	Journal of Thoracic Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
Socinski	2012	Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase iii trial	Journal of Clinical Oncology	Intervention
Socinski	2006	A randomised phase ii trial comparing every 3-weeks carboplatin/paclitaxel with every 3-weeks carboplatin and weekly paclitaxel in advanced non-small cell lung cancer	Annals of Oncology	Intervention
Socinski	2002	Phase iii trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage iiib/iv non-small-cell lung cancer	Journal of Clinical Oncology	Intervention
Socinski	2006	Randomised phase ii trial of pemetrexed combined with either cisplatin or carboplatin in untreated extensive-stage small-cell lung cancer	Journal of Clinical Oncology	Population
Socinski	2010	Safety and efficacy of combining sunitinib with bevacizumab + paclitaxel/carboplatin in non-small cell lung cancer	Journal of Thoracic Oncology	Comparator
Soo	2006	A multicentre randomised phase ii study of carboplatin in combination with gemcitabine at standard rate or fixed dose rate infusion in patients with advanced stage non-small-cell lung cancer	Annals of Oncology	Intervention

Author	Year	Title	Journal	Reason for exclusion
Soto Parra	2002	Three-week versus four-week schedule of cisplatin and gemcitabine: Results of a randomised phase ii study	Annals of oncology : official journal of the European Society for Medical Oncology / ESMO	Duplicate publication
Spigel	2015	Quality of Life Analyses from the Randomised, Open-Label, Phase III PointBreak Study of Pemetrexed-Carboplatin-Bevacizumab followed by Maintenance Pemetrexed- Bevacizumab Versus Paclitaxel-Carboplatin-Bevacizumabfollowed by Maintenance Bevacizumab in Patients withStage IIIB or IV Nonsquamous Non–Small-Cell Lung Cancer	Journal of Thoracic Oncology	Intervention
Spigel	2012	A randomised phase ii trial of pemetrexed/gemcitabine/bevacizumab or pemetrexed/carboplatin/bevacizumab in the first-line treatment of elderly patients with advanced non-small cell lung cancer	Journal of Thoracic Oncology	Population
Spigel	2012	A randomised phase ii trial of pemetrexed/gemcitabine/bevacizumab or pemetrexed/carboplatin/bevacizumab in the first-line treatment of elderly patients with advanced non-small cell lung cancer	Journal of Thoracic Oncology	Comparator

Author	Year	Title	Journal	Reason for exclusion
Spiro	2004	Chemotherapy versus supportive care in advanced non-small cell lung cancer: Improved survival without detriment to quality of life	Thorax	Intervention
Stathopoulos	2010	Liposomal cisplatin combined with paclitaxel versus cisplatin and paclitaxel in non-small-cell lung cancer: A randomised phase iii multicenter trial	Annals of Oncology	Population
Stathopoulos	2011	Comparison of liposomal cisplatin versus cisplatin in non-squamous cell non-small-cell lung cancer	Cancer Chemotherapy and Pharmacology	Intervention
Stewart	2004	Phase ii study of alternating chemotherapy regimens for advanced non-small cell lung cancer	Lung Cancer	Population
Sumanth	2008	A comparative clinical study of the docetaxel-carboplatin combination and the gemcitabine-carboplatin combination in patients with non small cell lung cancer	Journal of Clinical and Diagnostic Research	Population
Surmont	2010	A randomised phase ii study comparing two schedules of the 21-day regimen of gemcitabine and carboplatin in advanced non-small cell lung cancer	Oncology	Intervention
Takeda	2003	Preliminary results of four arm cooperative study (FACS) for Advanced Non-Small Cell Lung Cancer (NSCLC) in Japan	Lung Cancer Journal	Population

Author	Year	Title	Journal	Reason for exclusion
Takeda	2010	Randomised phase iii trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in japanese patients with advanced non-small-cell lung cancer: Results of a west japan thoracic oncology group trial (wjtog0203)	Journal of Clinical Oncology	Intervention
Tan	2005	Randomised study of vinorelbine-gemcitabine versus vinorelbine-carboplatin in patients with advanced non-small cell lung cancer	Lung Cancer	Population
Tan	2009	Global lung oncology branch trial 3 (glob3): Final results of a randomised multinational phase iii study alternating oral and i.V. Vinorelbine plus cisplatin versus docetaxel plus cisplatin as first-line treatment of advanced non-small-cell lung cancer	Annals of Oncology	Population
Ten Bokkel Huinink	1999	Single-agent gemcitabine: An active and better tolerated alternative to standard cisplatin-based chemotherapy in locally advanced or metastatic non-small cell lung cancer	Lung Cancer	Comparator
Thatcher	2014	A randomised, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC).	Journal of Clinical Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
Thatcher	2015	Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage iv squamous non-small-cell lung cancer (squire): An open-label, randomised, controlled phase 3 trial	Lancent Oncology	Population
Thomas	2006	Randomised multicentric phase ii study of carboplatin/gemcitabine and cisplatin/vinorelbine in advanced non-small cell lung cancer. Gfpc 99-01 study (groupe francais de pneumo-cancerologie)	Lung Cancer	Population
Tian	2010	A randomised controlled pilot trial of "feiji recipe" on quality of life of non-small cell lung cancer patients	American Journal of Chinese Medicine	Population
Treat	2010	A randomised, phase iii multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer	Annals of Oncology	Comparator
Tsukada	2015	Randomised controlled trial comparing docetaxel-cisplatin combination with weekly docetaxel alone in elderly patients with advanced non-small-cell lung cancer: Japan clinical oncology group (jcog) 0207	Japanese Journal of Clinical Oncology	Population
Umihanic	2014	Glasgow prognostic score in patients receiving chemotherapy for non-small-cell lung cancer in stages iiib and iv	Medical archives (Sarajevo, Bosnia and Herzegovina)	Study design

Author	Year	Title	Journal	Reason for exclusion
Uramoto	2010	A randomised phase ii trial of adjuvant chemotherapy with bi-weekly carboplatin plus paclitaxel versus carboplatin plus gemcitabine in patients with completely resected non-small cell lung cancer	Anticancer Research	Population
Van Putten	2001	Activity of the combination of high-dose epirubicin with gemcitabine in advanced non-small-cell lung cancer	Lung Cancer	Study design
Vansteenkiste	2003	Influence of cisplatin-use, age, performance status and duration of chemotherapy on symptom control in advanced non-small cell lung cancer: Detailed symptom analysis of a randomised study comparing cisplatin-vindesine to gemcitabine	Lung Cancer	Intervention
Vansteenkiste	2001	Clinical-benefit response in advanced non-small-cell lung cancer: A multicentre prospective randomised phase iii study of single agent gemcitabine versus cisplatin-vindesine	Annals of Oncology	Intervention
Vergnenegre	2009	A randomised phase ii trial assessing in advanced non-small cell lung cancer patients with stable disease after two courses of cisplatin-gemcitabine an early modification of chemotherapy doublet with paclitaxel-gemcitabine versus continuation of cisplatin-gemcitabine chemotherapy (gfpc 03-01 study)	Journal of Thoracic Oncology	Comparator
Vokes	2002	Randomised phase ii study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage	Journal of Clinical Oncology	Population

Author	Year	Title	Journal	Reason for exclusion
		iiib non-small-cell lung cancer: Cancer and leukemia group b study 9431		
Vokes	2007	Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage iii non-small-cell lung cancer: Cancer and leukemia group b	Journal of Clinical Oncology	Population
Von Plessen	2006	Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer	British Journal of Cancer	Intervention
Wacker	2007	Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase iii studies	Clinical Cancer Research	Population
Wang and Zhang	2014	Comparison of efficacy and safety between liposome-paclitaxel injection plus carboplatin and paclitaxel plus carboplatin as first line treatment in advanced non-small cell lung cancer	Chung-Kuo i Hsueh Ko Hsueh Yuan Hsueh Pao Acta Academiae Medicinae Sinicae	Intervention
Wang	2012	Randomised phase ii study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage iii non-small cell lung cancer	Lung Cancer	Population

Author	Year	Title	Journal	Reason for exclusion
Wang	2007	Phase ii study of gemcitabine and carboplatin in patients with advanced non-small-cell lung cancer	Cancer Chemotherapy and Pharmacology	Intervention
Wang	2007	Comparison of pharmacokinetics, efficacy and toxicity profile of gemcitabine using two different administration regimens in chinese patients with non-small-cell lung cancer	Journal of Zhejiang University	Intervention
Weissman	2011	A phase iii randomised trial of gemcitabine-oxaliplatin versus carboplatin-paclitaxel as first-line therapy in patients with advanced non-small cell lung cancer	Journal of Thoracic Oncology	Comparator
Wendling	2009	Maintenance pemetrexed adds to survival in late nsclc	Oncology Report	Comparator
Wozniak	1998	Randomised trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: A southwest oncology group study	Journal of Clinical Oncology	Comparator
Yamamoto	2006	Randomised phase ii study of carboplatin/gemcitabine versus vinorelbine/gemcitabine in patients with advanced nonsmall cell lung cancer: West japan thoracic oncology group (wjtog) 0104	Cancer	Population
Yang	2014	A phase II trial of first-line nab-paclitaxel/carboplatin versus gemcitabine/carboplatin in advanced squamous cell carcinoma of the lung (CTONG1002).	Journal of Clinical Oncology	Comparator
Yaqub	2015	Nivolumab for squamous-cell non-small-cell lung cancer	The Lancet	Other

Author	Year	Title	Journal	Reason for exclusion
Yin	2008	Determination of carboplatin dose by area under the curve in combination chemotherapy for senile non-small cell lung cancer	Journal of Huazhong University of Science and Technology - Medical Science	Study design
Yoh	2007	Randomised trial of drip infusion versus bolus injection of vinorelbine for the control of local venous toxicity	Lung Cancer	Intervention
Yu and Lu	2009	Perioperative chemotherapy of stage iii n2 non-small cell lung cancer	Chinese-German Journal of Clinical Oncology	Other
Zarogoulidis	2012	Feasibility and effectiveness of inhaled carboplatin in nsclc patients	Investigational New Drugs	Intervention
Zatloukal	2008	Randomised multicenter phase ii study of larotaxel (xrp9881) in combination with cisplatin or gemcitabine as first-line chemotherapy in nonirradiable stage iiib or stage iv non-small cell lung cancer	Journal of Thoracic Oncology	Intervention
Zatloukal	2003	Gemcitabine plus cisplatin vs. Gemcitabine plus carboplatin in stage iiib and iv non-small cell lung cancer: A phase iii randomised trial	Lung Cancer	Comparator
Zwitter	2009	Gemcitabine in brief versus prolonged low-dose infusion, both combined with cisplatin, for advanced non-small cell lung cancer: A randomised phase ii clinical trial	Journal of Thoracic Oncology	Intervention

Author	Year	Title	Journal	Reason for exclusion
Zwitter	2010	Two schedules of chemotherapy for patients with non-small cell lung cancer in poor performance status: A phase ii randomised trial	Anti-Cancer Drugs	Comparator
First update				
Akiyama	2016	Final analysis of erlotinib monotherapy for elderly patients with non-small-cell lung cancer harboring activating EGFR mutations	Journal of Clinical Oncology. Conference	Population
Aotani	2016	Identification of adverse events that have a negative impact on quality of life in a clinical trial comparing docetaxel versus S-1 with cisplatin in lung cancer	International Journal of Clinical Oncology	Intervention
Argiris	2016	E3508: Randomised trial of carboplatin (C), paclitaxel (P), bevacizumab (B) with or without cixutumumab (Cx) in patients (pts) with advanced non-squamous, non-small cell lung cancer (NSCLC)	Journal of Clinical Oncology. Conference	Intervention
Borghaei	2016	Nivolumab (nivo) vs docetaxel (doc) in patients (pts) with advanced NSCLC: CheckMate 017/057 2-y update and exploratory cytokine profile analyses	Journal of Clinical Oncology. Conference	Population
Boye	2016	First-Line Pemetrexed Plus Cisplatin Followed by Gefitinib Maintenance Therapy Versus Gefitinib Monotherapy in East Asian Never-Smoker Patients With Locally Advanced or Metastatic Non-squamous Non-Small-cell Lung Cancer: quality of Life Results From a Randomised Phase III Trial	Clinical lung cancer	Interventions

Author	Year	Title	Journal	Reason for exclusion
Fiteni	2016	Health-related quality of life in elderly patients with advanced non-small cell lung cancer comparing carboplatin and weekly paclitaxel doublet chemotherapy with monotherapy	European Respiratory Journal	Intervention
Garon	2016	A randomised phase II trial of the tumor vascular disrupting agent CA4P (fosbretabulin tromethamine) with carboplatin, paclitaxel, and bevacizumab in advanced non-squamous non-small-cell lung cancer	OncoTargets and Therapy	Interventions
Govindan	2016	Safety and resource use in the PROCLAIM study comparing 2 regimens of concurrent chemoradiation followed by consolidation chemotherapy in locally advanced non-squamous non-small cell lung cancer (NSCLC)	Journal of Clinical Oncology. Conference	Population
Hanna	2015	Three-arm, randomised, phase 2 study of carboplatin and paclitaxel in combination with cetuximab, cixutumumab, or both for advanced non-small cell lung cancer (NSCLC) patients who will not receive bevacizumab-based therapy: An Eastern Cooperative Oncology Group (ECOG) study (E4508)	Cancer	Outcomes
Hirsch	2017	Efficacy and Safety Results From a Phase II, Placebo-Controlled Study of Onartuzumab Plus First-Line Platinum-Doublet Chemotherapy for Advanced Squamous Cell Non-Small-Cell Lung Cancer	Clinical Lung Cancer	Population

Author	Year	Title	Journal	Reason for exclusion
Kristensen	2017	Measurement of health-related quality of life during chemotherapy - the importance of timing	Acta Oncologica	Population
Kubo	2017	Randomised phase II study of sequential carboplatin plus paclitaxel and gefitinib in chemotherapy-naive patients with advanced or metastatic non-small-cell lung cancer: Long-term follow-up results	Molecular and Clinical Oncology	Comparator
Lee	2016	Randomised phase II trial of intercalated gefitinib (G) and pemetrexed/cisplatin (Pem/Cis) for never-smokers with chemo-naive stage IIIB/IV lung adenocarcinoma (LADC)	Journal of Clinical Oncology. Conference	Comparator
Lee	2016	Open-label, multicenter, randomised phase III trial of pemetrexed/carboplatin doublet vs pemetrexed singlet in chemotherapy-naive elderly patients aged 70 or more with advanced non-squamous non-small cell lung cancer and good performance status	Journal of Clinical Oncology. Conference	Comparator
Novello	2014	A phase II randomised study evaluating the addition of iniparib to gemcitabine plus cisplatin as first-line therapy for metastatic non-small-cell lung cancer	Annals of Oncology	Intervention
Qi	2015	A clinical trial on docetaxel and carboplatin therapy with or without nimotuzumab for the treatment of advanced nonsmall cell lung cancer	Journal of Cancer Research & Therapeutics	Population
Reck	2016	Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer	New England journal of medicine	Population

Author	Year	Title	Journal	Reason for exclusion
Reck	2016	The effect of necitumumab in combination with gemcitabine plus cisplatin on tolerability and on quality of life: Results from the phase 3 SQUIRE trial	Journal of Thoracic Oncology	Population
Rizvi	2016	Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer	Journal of Clinical Oncology	Study design
Shipley	2016	The spruce clinical trial: Double-blind randomised phase II trial of carboplatin and pemetrexed +/- apatorsen in patients with previously untreated stage IV non-squamous non-small-cell lung cancer	Journal of Clinical Oncology. Conference	Intervention
Socinski	2016	CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage iv/ recurrent programmed death ligand 1 (PD-L1)-positive NSCLC	Annals of Oncology	Comparator
Thatcher	2016	Secondary efficacy results from a phase 3 study comparing efficacy and safety of biosimilar candidate ABP 215 with bevacizumab in patients with non-squamous non-small cell lung cancer (NSCLC)	Annals of Oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO	Intervention
Thatcher	2016	Randomised, double-blind, phase 3 study evaluating efficacy and safety of ABP 215 compared with bevacizumab in patients with non-squamous NSCLC	Journal of Clinical Oncology. Conference	Intervention

Author	Year	Title	Journal	Reason for exclusion
Wakelee	2017	Efficacy and Safety of Onartuzumab in Combination With First-Line Bevacizumab- or Pemetrexed-Based Chemotherapy Regimens in Advanced Non-Squamous Non-Small-Cell Lung Cancer	Clinical Lung Cancer	Interventions
Weiss	2016	Quality of life (QoL) in elderly patients (pts) with advanced NSCLC treated with nab-paclitaxel (nab-P) + carboplatin (C): Interim results from the ABOUND.70+ study	Annals of Oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO	Population
Yang	2016	First-Line Pemetrexed plus Cisplatin followed by Gefitinib Maintenance Therapy versus Gefitinib Monotherapy in East Asian Never-Smoker Patients with Locally Advanced or Metastatic Non-squamous Non-Small Cell Lung Cancer: Final Overall Survival Results from a Randomised Phase 3 Study	Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer	Intervention
Second update				
Addeo	2017	A new frontier for targeted therapy in nsclc: Clinical efficacy of pembrolizumab in the inhibition of programmed cell death 1 (pd-1)	Expert review of anticancer therapy	Other
Anonymous	2016	Nivolumab may work as first-line nsclc therapy	Cancer Discovery	Other
Bepler	2013	Randomised international phase iii trial of ercc1 and rrm1 expression-based chemotherapy versus	Journal of Clinical Oncology	Comparator

Author	Year	Title	Journal	Reason for exclusion
		gemcitabine/carboplatin in advanced non-small-cell lung cancer		
Carbone Dp	2017	First-line nivolumab in stage iv or recurrent non-small-cell lung cancer	New england journal of medicine	Intervention
DE Marinis	2017	Eagles study: First-line bevacizumab in combination with chemotherapy in elderly patients with advanced, metastatic, non-squamous non-small cell lung cancer	Anticancer Research	Comparator
Ferry	2017	Carboplatin versus two doses of cisplatin in combination with gemcitabine in the treatment of advanced non-small-cell lung cancer: Results from a british thoracic oncology group randomised phase iii trial	European Journal of Cancer	Comparator
Giaccone	2017	A dose-finding and phase 2 study of ruxolitinib plus pemetrexed/cisplatin for non-squamous non-small cell lung cancer (nsclc)	Journal of Thoracic Oncology	Comparator
Govindan	2017	Phase iii trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer	Journal of Clinical Oncology	Comparator
Greystoke	2017	Select-3: A phase i study of selumetinib in combination with platinum-doublet chemotherapy for advanced nsclc in the first-line setting	British Journal of Cancer	Study design

Author	Year	Title	Journal	Reason for exclusion
Gridelli	2017	Efficacy of the addition of cisplatin to single-agent first-line chemotherapy in elderly patients with advanced non-small cell lung cancer (nsclc): A joint analysis of the multicenter, randomised phase iii miles-3 and miles-4 studies	Journal of Clinical Oncology. Conference	Intervention
Han	2017	Ercc1 expression-based randomised phase ii study of gemcitabine/cisplatin versus irinotecan/cisplatin in patients with advanced non-small cell lung cancer	Cancer Research and Treatment	Comparator
Hirsch	2017	Efficacy and safety results from a phase ii, placebo-controlled study of onartuzumab plus first-line platinum-doublet chemotherapy for advanced squamous cell non-small-cell lung cancer	Clinical lung cancer	Comparator
Hui	2017	Pembrolizumab as first-line therapy for patients with pd-l1-positive advanced non-small cell lung cancer: A phase 1 trial	Annals of Oncology	Intervention
Jang	2017	Randomised phase ii study comparing weekly docetaxel-cisplatin vs. Gemcitabine-cisplatin in elderly or poor performance status patients with advanced non-small cell lung cancer	Cancer Chemotherapy & Pharmacology	Population
Joerger	2016	Asco 2015: Open-label, randomised study of individualized, pharmacokinetically (pk)-guided dosing of paclitaxel combined with carboplatin in advanced non-small cell lung cancer (nsclc) patients	Memo - Magazine of European Medical Oncology	Intervention

Author	Year	Title	Journal	Reason for exclusion
Karampeazis	2017	Docetaxel plus gemcitabine versus gemcitabine in elderly patients with advanced non-small cell lung cancer and use of a geriatric assessment: Lessons from a prematurely closed hellenic oncology research group randomised phase iii study	Journal of Geriatric Oncology	Intervention
Kristensen	2017	Measurement of health-related quality of life during chemotherapy-the importance of timing	Acta Oncologica	Outcome
Lee	2017	Phase iii trial of pemetrexed/ carboplatin vs pemetrexed only in chemo-naive elderly non-sqcc nsclc patients aged >= 70	Journal of Thoracic Oncology	Comparator
Mok	2017	Cns response to osimertinib in patients (pts) with t790m-positive advanced nsclc: Data from a randomised phase iii trial (aura3)	Journal of clinical oncology. Conference	Population
Molina	2017	Multivariate analysis of keynote-010: Factors associated with betteroverall survival in previously treated, pd-l1-expressing, advanced nonsmall cell lung cancer	Asia-Pacific Journal of Clinical Oncology	Population
Morabito	2017	A multicenter, randomised, phase 3 trial comparing fixed dose versus toxicity-adjusted dose of cisplatin + etoposide in extensive small-cell lung cancer (sclc) patients: The small-cell-lung cancer toxicity adjusted dosing (stad-1) trial	Lung Cancer	Intervention

Author	Year	Title	Journal	Reason for exclusion
Paz-Ares	2017	A phase 3, randomised study of first-line durvalumab (d) +/- tremelimumab (t) + platinum-based chemotherapy (ct) vs ct alone in extensive disease small-cell lung cancer (ed-sclc): Caspian	Journal of Clinical Oncology. Conference	Other
Perol	2017	Ifct-gfpc-1101 trial: A multicenter phase iii assessing a maintenance strategy determined by response to induction chemotherapy compared to continuation maintenance with pemetrexed in patients (pts) with advanced non-squamous (nsclc)	Journal of Clinical Oncology. Conference	Comparator
Ramalingam	2016	Randomised, placebo-controlled, phase ii study of veliparib in combination with carboplatin and paclitaxel for advanced/metastatic non-small cell lung cancer	Clinical Cancer Research	Comparator
Reck	2017	Primary PFS and safety analyses of a randomised Phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150)	Annals of Oncology	Comparator
Reck	2017	Smoking history predicts sensitivity to parp inhibitor veliparib in patients with advanced non-small cell lung cancer	Journal of Thoracic Oncology	Intervention
Saad	2017	A prospective randomised controlled study of cisplatin versus carboplatin-based regimen in advanced squamous nonsmall cell lung cancer	Journal of Cancer Research and Therapeutics	Comparator

Author	Year	Title	Journal	Reason for exclusion
Spigel	2017	An open-label, randomised, controlled phase ii study of paclitaxel-carboplatin chemotherapy with necitumumab versus paclitaxel-carboplatin alone in first-line treatment of patients with stage iv squamous non-small-cell lung cancer	Clinical lung cancer	Population
Zhang	2016	Usefulness of dynamic contrast-enhanced magnetic resonance imaging for predicting treatment response to vinorelbine-cisplatin with or without recombinant human endostatin in bone metastasis of non-small cell lung cancer	American Journal of Cancer Research	Study design
Third update				
Ahmed	2017	Combination pembrolizumab and low dose weekly carboplatin/paclitaxel for patients with recurrent/ metastatic nsclc and ps of 2	Journal of Thoracic Oncology	Outcomes
Atagi	2017	Randomised phase 2 study comparing cbdca+ptx+bev and cddp+pem+bev in treatment-naive advanced non-sq nsclc (clear study)	Journal of Thoracic Oncology	Intervention
Bradbury	2017	A randomised phase ii trial of selumetinib + platinum-pemetrexed (pem-c) in kras wildtype (wt)/ unknown nsclc: Cctg ind219	Journal of Thoracic Oncology	Comparator
Carbone Dp	2017	First-line nivolumab in stage iv or recurrent non-small-cell lung cancer	New england journal of medicine	Intervention

Author	Year	Title	Journal	Reason for exclusion
De Marinis	2017	Eagles study: First-line bevacizumab in combination with chemotherapy in elderly patients with advanced, metastatic, non-squamous non-small cell lung cancer	Anticancer research	Comparator
Ferry	2017	Carboplatin versus two doses of cisplatin in combination with gemcitabine in the treatment of advanced non-small-cell lung cancer: Results from a british thoracic oncology group randomised phase iii trial	European journal of cancer	Comparator
Fiteni	2016	Health-related quality of life in elderly patients with advanced non-small cell lung cancer comparing carboplatin and weekly paclitaxel doublet chemotherapy with monotherapy	European Respiratory Journal	Comparator
Govindan	2017	Phase iii trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer	Journal of clinical oncology	Comparator
Gridelli	2017	Efficacy of the addition of cisplatin to single-agent first-line chemotherapy in elderly patients with advanced non-small cell lung cancer (nsclc): A joint analysis of the multicenter, randomised phase iii miles-3 and miles-4 studies	Journal of clinical oncology	Intervention
Han	2017	Ercc1 expression-based randomised phase ii study of gemcitabine/cisplatin versus irinotecan/cisplatin in patients with advanced non-small cell lung cancer	Cancer research and treatment	Comparator

Author	Year	Title	Journal	Reason for exclusion
Hellman	2018	Nivolumab (nivo) + ipilimumab (ipi) vs platinum-doublet chemotherapy (PT-DC) as first-line (1L) treatment (tx) for advanced non-small cell lung cancer (NSCLC): initial results from CheckMate 227	Amercian Society of Clinical Oncology	Comparator
Hellman	2018	Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden	New England Journal of Medicine	Comparator
Hirsch	2017	Efficacy and safety results from a phase ii, placebo-controlled study of onartuzumab plus first-line platinum-doublet chemotherapy for advanced squamous cell non-small-cell lung cancer	Clinical lung cancer	Comparator
Jang	2017	Randomised phase ii study comparing weekly docetaxel-cisplatin vs. Gemcitabine-cisplatin in elderly or poor performance status patients with advanced non-small cell lung cancer	Cancer chemotherapy and pharmacology	Population
Kanda	2016	Safety and efficacy of nivolumab and standard chemotherapy drug combination in patients with advanced non-small-cell lung cancer: A four arms phase ib study	Annals of Oncology	Study design
Kanda	2017	Long follow up from phase i study of nivolumab and chemotherapy in patients with advanced non-small-cell lung cancer	Journal of Thoracic Oncology	Comparator
Karampeazis A	2017	Docetaxel plus gemcitabine versus gemcitabine in elderly patients with advanced non-small cell lung	Journal of geriatric oncology	Intervention

Author	Year	Title	Journal	Reason for exclusion
		cancer and use of a geriatric assessment: Lessons from a prematurely closed hellenic oncology research group randomised phase iii study		
Kowanetz	2018	CT076 - IMpower150: Efficacy of atezolizumab (atezo) plus bevacizumab (bev) and chemotherapy (chemo) in 1L metastatic nonsquamous NSCLC (mNSCLC) across key subgroups		
Kristensen	2017	Measurement of health-related quality of life during chemotherapy - the importance of timing	Acta oncologica	Outcomes
Lee Sm	2016	Randomised prospective biomarker trial of ercc1 for comparing platinum and nonplatinum therapy in advanced non-small-cell lung cancer: Ercc1 trial (et)	Journal of clinical oncology	Study design
Morabito	2017	Cisplatin in addition to single-agent first-line chemotherapy in elderly patients with advanced non-small-cell lung cancer (nsclc): Efficacy results of a joint analysis of the multicentre, randomised phase 3 miles-3 and miles-4 studies	Annals of Oncology	Comparator
Niho	2017	Safety data from randomised phase ii study of cisplatin (cddp)1s-1 versus cddp1pemetrexed (pem) combined with thoracic radiotherapy (trt) for locally advanced non-squamous (non-sq) nonsmall cell lung cancer (nsclc): Spectra study	Annals of Oncology	Comparator

Author	Year	Title	Journal	Reason for exclusion
Ono	2017	Safety data from randomised phase ii study of cddp+s-1 vs cddp+pem combined with trt for locally advanced non-squamous nsclc	Journal of Thoracic Oncology	Comparator
Park	2017	Efficacy and safety of first-line necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin in east asian patients with stage iv squamous non-small cell lung cancer: A subgroup analysis of the phase 3, open-label, randomised squire study	Cancer research and treatment	Population
Piccirillo	2017	Effect on quality of life (qol) of adding cisplatin to single-agent firstline chemotherapy in elderly patients with advanced non-small cell lung cancer (nsclc): A joint analysis of the multicentre, randomised, phase 3 miles-3 and miles-4 studies	Annals of Oncology	Comparator
Ramalingam	2017	Randomised, placebo-controlled, phase ii study of veliparib in combination with carboplatin and paclitaxel for advanced/metastatic non-small cell lung cancer	Clinical cancer research	Comparator
Reck(10)	2016	Keynote-024: Pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) as first-line therapy for advanced nsclc with a pd-l1 tumor proportion score (tps) >=50%	Annals of Oncology	Populaiton
Saad	2017	A prospective randomised controlled study of cisplatin versus carboplatin-based regimen in advanced squamous nonsmall cell lung cancer	Journal of cancer research and therapeutics	Comparator

Author	Year	Title	Journal	Reason for exclusion
Satouchi	2017	Japan subset of phase iii study keynote-024: Pembrolizumab for pd-l1 tps >550%, treatment-naive nsclc	Annals of Oncology	Comparator
Schuette	2017	65plus: Open-label study of bevacizumab in combination with pemetrexed or pemetrexed/ carboplatin as first-line treatment of patients with advanced or recurrent non-squamous non-small-cell lung cancer	Lung Cancer: Targets and Therapy	Comparator
Spigel	2018	Randomised phase 2 trial of pemetrexed, pemetrexed/bevacizumab, and pemetrexed/carboplatin/bevacizumab in patients with stage iiib/iv non-small cell lung cancer and an eastern cooperative oncology group performance status of 2	Cancer.	Comparator
Spigel	2017	An open-label, randomised, controlled phase ii study of paclitaxel-carboplatin chemotherapy with necitumumab versus paclitaxel-carboplatin alone in first-line treatment of patients with stage iv squamous non-small-cell lung cancer	Clinical Lung Cancer	Comparator
Thomas	2017	A phase 2 randomised open-label study of ramucirumab (ram) plus first-line platinum-based chemotherapy in patients (pts) with recurrent or advanced non-small cell lung cancer (nsclc): Final results from squamous pts	Annals of Oncology	Comparator

Appendix 2. Economic evidence search results

Table 113 Full extraction details of HTAs with relevant HRQoL/utility estimates included in the company search

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
NICE TA309(48); UK	Locally advanced or metastatic (Stage IIIB/IV) non-squamous NSCLC	NR	PEM+BSC Placebo+BSC	NR Note: Utility data in this study were derived from PARAMOUNT study, which used EQ-5D scale for assessing utility values.	Pre-progression Post-progression Dead	NR	EQ-5D values: 1. Pre-progression for placebo+BSC on FL: >6 cycles PTD: 0.7758 5-6 cycles PTD: 0.7242 3-4 cycles PTD: 0.6520 0-2 cycles PTD: 0.4099 2. Pre-progression for PEM+BSC on FL >6 cycles PTD: 0.7510 5-6 cycles PTD: 0.6994 3-4 cycles PTD: 0.6272 0-2 cycles PTD: 0.3851 3. Post-progression for both arms >6 cycles PTD: 0.7028 5-6 cycles PTD: 0.6512 3-4 cycles PTD: 0.5790 0-2 cycles PTD: 0.3369
NICE TA181(49)b; UK	Patients with chemo-naive NSCLC that was not amenable to surgical resection	100	PEM 500mg/m2+CIS 75mg/m2 GEM 1250mg/m2+CIS 75mg/m2 GEM 1250mg/m2+CARB 500mg (for	NRa	Response SD Death	NR	1. Utility values for health states and AEs according to Nafees et al., 2008: N: 100; n: 100 Stable: 0.65 Response: 0.67 Progression: 0.47 FN: -0.09 Neutropenia: -0.089 Fatigue: -0.073 Diarrhoea: -0.047

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
			target AUC of 5mg/ml*min) DOC 75mg/m2+CIS 75mg/m2				Nausea/Vomiting: -0.048 Anaemia: -0.073 (Considered same disutility as fatigue) Thrombocytopenia: -0.089 (Considered same disutility as neutropenia) 2. Utility values according to alternative published utility values in NSCLC: Score (range) Metastatic NSCLC with CTX: 0.6 (0.55-0.65) Local/regional/metastatic NSCLC: 0.69 (0.69-0.88) Regional/distant/recurrent NSCLC: 0.7 (0.5-0.9) Metastatic NSCLC on CTX: 0.7 (0.6-1.00) Responding disease lung cancer: 0.71 (0.664-0.756) Stable lung cancer with oral treatment: 0.63 (0.58-0.68) Stable lung cancer with IV treatment: 0.583 (0.528-0.638) Progressive lung cancer with no treatment: 0.415 (0.357-0.473) End of life: 0.332 (0.276-0.388) Note: Not clear if it was mean or median.
NICE TA190;(50) UK	Patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology	NR	PEM+BSC Placebo+BSC	NRa	Progression-free (active CTX and no active CTX) Post-progression health states (active CTX, no active CTX and terminal disease).	NR	Utility values: Not-progressed Treated with active CTX (PEM (M) phase): 0.66 Progressed Receiving BSC in first year (PEM arm): 0.54 Not-progressed No active CTX (placebo (M) phase): 0.58 Progressed Receiving BSC all years (placebo arm): 0.53 ERG DATA:

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
							Utility for terminal cycle (both arms): 0.47
NICE TA192(51); UK	Patients with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK	NR	GEF GEM+CARB PAX+CARB VNB+CIS GEM+CIS	NRa	Treatment response SD Disease progression Death	Baseline mean utility (SD no AEs): 0.6532	1. Mean utility values: Treatment response (increment): 0.0193 2. Utility Decrements Disease progression: -0.1798 Progression-free iv therapy: -0.0425 Progression-free oral therapy: -0.0139 3. Utility decrements according to CTC Grade 3/4 AE FN: -0.0900 Neutropenia: -0.0897 Fatigue: -0.0735 Nausea & vomiting: -0.0480 Diarrhoea: -0.0468 Hair loss (Grade 2): -0.0450 Rash: -0.0325 Anaemia: -0.0735
NICE TA227(52); UK	Patients with both squamous and non-squamous histology of NSCLC	NR	ERL PEM BSC	NRa	PFS Progressed disease Death	NR	A). Utility values utilised in model for: 1. Patients with both squamous and non-squamous histology were incorporated, who received the NICE recommended (I) regimen PFS (ERL): 0.6732 PFS 0.6628 PD: 0.53 B). Utility values utilised in AUC mode for SD non-squamous PFS (ERL): 0.6732 PD: 0.53 PFS (PEM): 0.6568 ERG DATA

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
							Utilities by population: ITT population (for PFS): 0.695 Patients with non-squamous SD (for PFS): 0.685 Progressed health state: 0.47 Note: Three separate economic evaluations reflecting three separate ERL patient populations have been performed by the manufacturer (ITT population in the SATURN trial, SD population derived most OS benefit in SATURN and non-squamous population from SATURN and JMEN trials)
NICE TA258(53); UK	Metastatic NSCLC patients with tumours harbouring an activating mutation of the EGFR TK	NR	ERL GEF	NRa	PFS PD Death	PD (dummy variable disutility relative to PFS SD baseline): -0.1798 (-0.2223, -0.1373)	1. Utility value according to health states: score (CI) PFS (SD): 0.6532 (0.6096, 0.6968) PFS (Response dummy variable): 0.0193 (0.0065, 0.0321) 2. Disutility values: Rash: -0.0325 (-0.0554, -0.0095) Diarrhoea: -0.0468 (-0.0772, -0.0164) Data from ERG Resultant ERL PFS: 0.661 Resultant GEF PFS: 0.656
NICE TA310(54); UK	EGFR mutation positive locally advanced or	NR	AFA GEF ERL	NRa	PFS (SD) Progressed disease	NR	1. Utility values for health states: mean (SE); source

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
	metastatic NSCLC patients				Death		Progression free: 0.784 (0.009); LUX-Lung trial 1L, progression-free: 0.710 (0.014); Chouaid et al. 2012 Source: Nafees et al. 2008 Progression-free: 0.672 (0.029) Progression-free (stable): 0.653 (0.022) Progression-free (weighted): 0.663 (0.026) 2. Disutilities for valuing AEs: mean (SE); source Source: LUX-Lung 3 Diarrhoea (Grade 3/4): -0.147 (0.045) Rash/acne (Grade 3/4): -0.202 (0.028) Fatigue (Grade 3/4): -0.179 (0.053); LUX-Lung 1 Anaemia: -0.073 (0.019); ERG report for pem/cis Neutropenia: -0.090 (0.015); Nafees et al. 2008 3. Weighted utility assigned to the PD state in the 1st line model by treatment arm SL treatment period option: A.) Constant (baseline): AFA: 0.517 ERL: 0.529 GEF: 0.521 B.) Proportionally adjusted: AFA: 0.509 ERL: 0.509 GEF: 0.509
NICE TA411(55); UK	The model population comprised	NR	NECI+GEM+ CIS	NRa	Pre-progression	NR	1. Utility values: mean (SE); 95% CI

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
	adults with advanced, metastatic, squamous NSCLC who had not had previous CTX for their lung cancer		GEM+CIS GEM+CARB PAX+CARB DOC+CIS		Post-progression Death		Post progression: 0.55 (0.016); 0.52,0.58 2. Disutility values according to different AEs: disutility (SE) Neutropenia: -0.0897 (0.0154) Anaemia *: -0.0735 (0.0185) Thrombocytopenia **: -0.0897 (0.0154) Hypomagnesaemia***: -0.0325 (0.0117) Pulmonary embolism****: -0.3200 (0.1189) Asthenia: -0.0735 (0.0185) Leukopenia: -0.0897 (0.0154) Skin rash: -0.0325 (0.0117) Fatigue: -0.0735 (0.0185) Nausea*: -0.0480 (0.0162) Vomiting*: -0.0480 (0.0162) FN: -0.0900 (0.0163) Pneumonia: -0.0735 (0.0185) Hypokalaemia: -0.0735 (0.0185) Hypernatremia: -0.0735 (0.0185) Dyspnoea: 0.050 Notes: * assumed same as fatigue; ** assumed same as neutropenia; *** Assumed equal to FN based on UK clinical expert opinion
NICE TA447 (updated with CDF review TA531)(56, 63)	People with PD-L1 positive metastatic non-small-cell lung cancer (NSCLC) not treated with chemotherapy in the	305 patients were randomised in a 1:1 ratio to receive IV pembrolizumab 200 mg Q3W (n = 154) or SOC (n = 151), which	PEMBROLIZUMAB PEM + CARB induction, PEM maintenance	EQ-5D-3L TTO (for the valuation exercise)	Progression free Progressed disease Death Time-to-death (days) – 4 categories:	Utilities for 75+ years old reported by Kind et al. (89) reported average utility values of 0.75 and 0.71 for males and	• By time-to-death (days) – 4 categories: ≥360: 0.808 (0.767,0.850) [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) Progressed: 0.668 (0.629, 0.707)

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
	metastatic setting	comprised the investigator's choice of one of the platinum doublets.	PEM + CIS induction, PEM maintenance GEM+CIS GEM + CARB PAX + CARB		- 360 or more days to death - 180 to 360 days to death - 30 to 180 days to death - Under 30 days to death Disutilities of Adverse events	females, respectively.	• Utility values for individuals with and without Grade 3+ AEs in the KN024 clinical trial: o Pembrolizumab: Progression-free with Grade3+ AE: 0.746 (0.682,0.810) Progression-free w/o Grade3+ AE: 0.81 (0.789,0.831) o SOC: Progression-free with Grade3+ AE: 0.704 (0.661,0.748) Progression-free w/o Grade3+ AE: 0.765 (0.740,0.791) o Pembrolizumab and SOC pooled: Progression-free with Grade3+ AE: 0.719 (0.683,0.755) Progression-free w/o Grade3+ AE: 0.793 (0.777,0.809)
NICE TA 520(57)	People with locally advanced or metastatic non-small-cell lung cancer whose disease has progressed after chemotherapy	Eligible patients (OAK N=850 [primary population]; POPLAR N=287) were randomly assigned in a 1:1 ratio to the two study treatment arms to receive either	ATEZOLIZUMAB DOC	OAK: EQ-5D-3L, QLQ-C30 AND QLQ-LC13 TTO (for the valuation exercise) (All utility values reported	Time-to Death categorized into: • ≤5 weeks before death • 5 and ≤15 weeks before death • 15 and ≤30 weeks before death • >30 weeks before death	NR	By time-to-death (weeks): • On treatment: - ≤5 weeks before death: 0.39 (0.24-0.55) - 5 and ≤15 weeks before death: 0.61 (0.53-0.68) - 15 and ≤30 weeks before death: 0.71 (0.69-0.74) - >30 weeks before death: 0.77 (0.75-0.78) • Off treatment: - ≤5 weeks before death: 0.35 (0.27-0.44)

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
		atezolizumab (OAK n=425; POPLAR n=144) or docetaxel (OAK n=425; POPLAR n=143).		taken from OAK trial using EQ-5D-3L)	Disutilities of adverse events		- 5 and ≤15 weeks before death: 0.43 (0.37-0.49) - 15 and ≤30 weeks before death: 0.58 (0.55-0.61) - >30 weeks before death: 0.68 (0.66-0.71) Adverse event disutilities: - Anaemia: -0.07346 - Fatigue: -0.07346 - Febrile Neutropenia: -0.09002 - Leukopenia: -0.08973 - Neutropenia: -0.08973 - Neutropenic sepsis: -0.09002 - Neutrophil count decreased: 0 - Pneumonia: -0.008 - Respiratory Tract Infection: -0.096 - White blood cell count decreased: -0.05
NICE TA 500(58)	People with untreated ALK+ advanced NSCLC	ASCEND-4 376 patients were randomised 1:1 to ceritinib or CT (cisplatin or carboplatin plus pemetrexed, followed by pemetrexed maintenance therapy, if appropriate)	CERITINIB PEM + CARB induction, PEM maintenance PEM + CIS induction, PEM maintenance CRIZOTINIB (MAIC PROFILE 1014)	EQ-5D	Progression free Progressed Disease	NR	Ceritinib • Progression free: 0.81 (ASCEND-4 CSR) • Progression disease: 0.64 (Chouaid et al. 2013) Crizotinib • Progresssion free: 0.81 (PROFILE 1014, Felip et al., 2015) • Progressed disease: 0.64 (Chouaid et al. 2013)

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
		PROFILE 1014: 343 patients					

Table 114 Full extraction details of health resource studies included in the company search

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td>Khan, 2015; (59)</td>
<td>Cost-effectiveness of first-line erlotinib in patients with advanced NSCLC unsuitable for chemotherapy (UK)</td>
<td>Mean (SE) costs of ERL

Overall population: £6,863

Rash subgroup: £7,544

Supportive care cost
<table>
<tr><td colspan="2">ERL</td><td colspan="2">Placebo</td></tr>
<tr><td>Overall

(N=334)</td><td>Rash sub-group (N=178)</td><td>Overall

(N=313)</td><td>Rash sub-group

(N=278)</td></tr>
<tr><td colspan="4">Palliative radiotherapy</td></tr>
<tr><td>£350 (£48)</td><td>£302 (£52)</td><td>£242 (£39)</td><td>£235 (£27)</td></tr>
<tr><td colspan="4">Additional treatment</td></tr>
<tr><td>£190 (£59)</td><td>£182 (£65)</td><td>£264 (£76)</td><td>£270 (£99)</td></tr>
<tr><td colspan="4">Total cost*</td></tr>
<tr><td>£9,210 (£711)</td><td>£9,949 (£724)</td><td>£2,121 (£199)</td><td>£2,058 (£185)</td></tr>
</table>
</td>
<td>Mean (SE) costs of patient management
<table>
<tr><td colspan="2">ERL</td><td colspan="2">Placebo</td></tr>
<tr><td>Overall

(N=334)</td><td>Rash sub-group (N=178)</td><td>Overall

(N=313)</td><td>Rash sub-group (N=278)</td></tr>
<tr><td colspan="4">Clinic visit</td></tr>
<tr><td>£663 (£49)</td><td>£629 (£57)</td><td>£654 (£40)</td><td>£624 (£53)</td></tr>
<tr><td colspan="4">Hospital day case</td></tr>
<tr><td>£285 (£71)</td><td>£274 (£65)</td><td>£356 (£95)</td><td>£323 (£131)</td></tr>
<tr><td colspan="4">Hospital admission</td></tr>
<tr><td>£775 (£149)</td><td>£744 (£163)</td><td>£534 (£122)</td><td>£475 (£134)</td></tr>
</table>
</td>
<td>Mean (SE) costs of AEs

Overall

ERL(N=334): £264 (£40)

Placebo(n=313): £181 (£32)

Rash subgroup

ERL(N=178): £221 (£34)

Placebo(N=278): £114 (£27)

Mean cost of SAEs for rash subgroup

ERL(N=178): £356

Placebo(N=278): £184</td>
<td>Mean (SE) days of ERL use for rash subgroup:

160 (10.70)

Mean (range) days of radiotherapy for rash subgroup:

ERL: 2.5 (0-34)

Placebo: 2.0 (0-16)

Mean (SE) days of patient management for rash subgroup
<table>
<tr><td>ERL</td><td>Placebo</td></tr>
<tr><td colspan="2">Clinic visits (days)</td></tr>
<tr><td>6.23(0.42)</td><td>6.21(0.50)</td></tr>
<tr><td colspan="2">Hospital Day Cases (days)</td></tr>
<tr><td>0.41(0.10)</td><td>0.48(0.20)</td></tr>
<tr><td colspan="2">Hospital Admissions (nights)</td></tr>
<tr><td>1.02(0.28)</td><td>0.65(0.22)</td></tr>
</table>
Mean (range) of AE management for rash subgroup
<table>
<tr><td>ERL</td><td>Placebo</td></tr>
<tr><td colspan="2">Rash duration(days)</td></tr>
</table>
</td>
</tr>
</table>

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
		*Total costs comprises of ERL, supportive care, AE and SAE costs			15.4 (1-37) / 3.5 (1-7) Diahorrea duration(days) 2.0 (0-48) / 0.5 (0-10) Dyspnoea Duration (days) 180(28-800) / 126 (26-600)
Lay, 2017(60)	Comparative cost-minimisation of oral and intravenous chemotherapy for first-line treatment of NSCLC in the UK NHS system	Oral VNB (representative cost per milligram) *: £2.199 *based on a price in several European countries of €3.1per mg	Cost of CTX administration in hospital and during ambulatory care	GP carrying out local blood test cost: £20 Costs of non-cumulative severe toxicity IV VNB: £182 Oral VNB: £239 GEM: £149 DOC: £138 PAX: £125	NR

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
			Dose: Cost Oral VNB 60mg/m2, 80mg/m2: Outpatient visit: £424, £512; Home care: [illegible] IV VNB 25mg/m2, 30mg/m2: Inpatient day: £585, £616; Outpatient visit: £351, £382 IV GEM 1,000mg/m2, 1,250mg/m2: Inpatient day: £731, £796; Outpatient visit: £497, £562 IV DOC 100mg/m2: Inpatient day: £1,763; Outpatient visit: £1,529 IV PAX 175mg/m2, 200mg/m2: Inpatient day: £1,560, £1,810		

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>Outpatient visit: £1,326, £1,575</td></tr>
</table>
Day-time hospitalisation cost: £354

Medical oncology out-patient visit: £120

Pre-CTX counselling session with a hospital nurse: £15
</td><td></td><td></td></tr>
<tr><td>Brown, 2013(17)</td><td>A study to evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic NSCLC: a systematic review and economic evaluation (UK)</td><td>Unit acquisition costs
<table>
<tr><td>Vial content (mg)</td><td>BNF 62, mean price</td><td>eMIT, mean price</td></tr>
<tr><td colspan="3">DOCa</td></tr>
<tr><td>20</td><td>£154.61</td><td>£90.20</td></tr>
<tr><td>80</td><td>£508.01</td><td>£287.45</td></tr>
<tr><td>140</td><td>£720.10</td><td>£285.09</td></tr>
<tr><td colspan="3">GEMa</td></tr>
<tr><td>200</td><td>£32.00</td><td>£4.81</td></tr>
<tr><td>1000</td><td>£162.00</td><td>£22.58</td></tr>
<tr><td>2000</td><td>£324.00</td><td>£41.99</td></tr>
<tr><td colspan="3">PAXa</td></tr>
<tr><td>30</td><td>£66.85</td><td>£5.02</td></tr>
</table></td><td>CTX administration unit costs
<table>
<tr><td>Treatment setting; HRG code: description</td><td>Mean cost(SE)</td></tr>
<tr><td>Day case; SB14Z; Complex CTX at first attendance</td><td>£309.17

(£14.73)</td></tr>
<tr><td>Day case; SB15Z: Subsequent doses of CTX</td><td>£284.45 (£8.95)</td></tr>
<tr><td>Inpatient (short stay); DZ17A: Respiratory neoplasms with complicating conditions</td><td>£462.88 (£12.88)</td></tr>
</table></td><td>Unit costs of disease monitoring and supportive care
<table>
<tr><td>Resource</td><td>Unit cost</td></tr>
<tr><td>Outpatient follow up visit</td><td>£101.43</td></tr>
<tr><td>Chest radiography</td><td>£24.04</td></tr>
<tr><td>CT scan (chest)</td><td>£145.83</td></tr>
<tr><td>CT scan (other)</td><td>£162.25</td></tr>
<tr><td>ECG</td><td>£32.69</td></tr>
<tr><td>Community nurse visit</td><td>£78.00 per hour</td></tr>
<tr><td>Clinical nurse specialist</td><td>£91.00 per contact hour</td></tr>
<tr><td>GP home visit</td><td>£120.00</td></tr>
</table></td><td>Estimated health-care resource use per patient
<table>
<tr><td>Resource</td><td>PFS</td><td>PPS</td></tr>
<tr><td>Outpatient visit</td><td>9.61 pa</td><td>7.91 pa</td></tr>
<tr><td>Chest radiography</td><td>6.79 pa</td><td>6.50 pa</td></tr>
<tr><td>CT scan (chest)</td><td>0.62 pa</td><td>0.24 pa</td></tr>
<tr><td>CT scan (other)</td><td>0.36 pa</td><td>0.42 pa</td></tr>
<tr><td>ECG</td><td>1.04 pa</td><td>0.88 pa</td></tr>
<tr><td>Community nurse visit</td><td>8.70 visits (20 m (20</td><td>8.70 visits (20</td></tr>
</table></td></tr>
</table>

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
		100 £200.35 £13.28 150 £300.52 £12.45 300 £601.03 £31.13 PEM 100 £160.00 £160.00 500 £800.00 £800.00 VNB IVa 10 £29.00 £5.11 50 £139.00 £23.09 VNB oral 20 £43.98 £43.98 30 £65.98 £65.98 80 £175.92 £175.92 GEFb Per patient £12,200.00 £12,200.00 CISa 10 £5.85 £1.69 50 £17.00 £3.58	Outpatient; TCLFUSFF 370: Medical oncology £128.69 (£3.92)	Therapist £42.00 Terminal care inpatient care £2,655.55 + 0.92 excess days at £196.61 per day Terminal care in hospice 25% increase on hospital in patient care AEs costs* The costs of treating grade 3/4 CTX-related AEs are spread over 12 weeks (four cycles) and estimated using NHS Reference Costs for 2009–2010,132 as follows: Diarrhoea: £443.54 per visit Fatigue: £2536.95 Hair loss: no cost Nausea/vomiting: £443.54 (each costing, per visit) Skin rash: £113.03 (weighted average of reference costs) Neutropaenia: £537.52 (per visit) Febrile neutropaenia: £6260	min.) pa in.) pa min.) pa Clinical nurse specialist 12 hours contact time pa 12 hours contact time pa GP home visit - 26.09 pa Hospital/hospice episode (terminal care): 9.66 days Community nurse visit (terminal care): 28 hours (2 hours per day) GP home visit (terminal care): Seven visits Nausea/vomiting: two hospital admissions during CTX, corresponding to HRG code FZ48C (malignant general abdominal disorders of length of stay ≤ 1 day) as a non-elective short-stay episode

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>100</td><td>£50.22</td><td>£6.87</td></tr>
<tr><td colspan="3">CARBa</td></tr>
<tr><td>50</td><td>£22.04</td><td>£2.03</td></tr>
<tr><td>150</td><td>£56.92</td><td>£4.65</td></tr>
<tr><td>450</td><td>£168.85</td><td>£13.50</td></tr>
<tr><td>600</td><td>£260.00</td><td>£17.23</td></tr>
<tr><td colspan="3">ERL</td></tr>
<tr><td>30X150mg</td><td>£1631.53</td><td>£1631.53</td></tr>
<tr><td>NHS discount</td><td>14.5%</td><td>14.5%</td></tr>
<tr><td colspan="3">DEXa</td></tr>
<tr><td>50 × 2 mg</td><td>£6.77</td><td>£1.99</td></tr>
<tr><td colspan="3">CHLa</td></tr>
<tr><td>10</td><td>£1.95</td><td>£1.62</td></tr>
<tr><td colspan="3">Ranitidine IVa</td></tr>
<tr><td>50</td><td>£0.54</td><td>£0.31</td></tr>
<tr><td colspan="3">Hydroxocobalamin IVa</td></tr>
<tr><td>1</td><td>£0.68</td><td>£0.31</td></tr>
</table>
</td>
<td></td>
<td>*Costs have been estimated relating to patient monitoring and supportive care in 3 health states - PFS, post progression when no active treatment is received and for terminal care assumed to last on average for 14 days

Estimated costs per patient of CTX-related AEs

<table>
<tr><td>AE</td><td>Product cost</td></tr>
<tr><td>Diarrhoea</td><td>DOC: £57
VNB: £16
PAX: £20
GEM: £16
PEM: £12
GEF: £27
ERL: £14</td></tr>
<tr><td>Fatigue</td><td>DOC: £229
VNB: £273
PAX: £181
GEM: £297
PEM: £171</td></tr>
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</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td colspan="3">Folic acida</td></tr>
<tr><td>90 × 400 mg</td><td>£2.43</td><td>£2.43</td></tr>
</table>
Estimated acquisition costs per cycle of CTX
<table>
<tr><td>Regimens</td><td>Cycle 1

BNF 62 & eMIT</td><td>Cycle 2+

BNF 62 & eMIT</td></tr>
<tr><td>DOC IV+CIS</td><td>£852.17

£367.52</td><td>£852.17

£367.52</td></tr>
<tr><td>DOC IV+CARB</td><td>£1081.46

£377.83</td><td>£1081.46

£377.83</td></tr>
<tr><td>GEM IV+CIS</td><td>£807.19

£112.16</td><td>£807.19

£112.16</td></tr>
<tr><td>GEM IV+CARB</td><td>£1036.47

£122.48</td><td>£1036.47

£122.48</td></tr>
</table>
</td><td></td><td>
<table>
<tr><td></td><td>GEF: £22

ERL: £83</td></tr>
<tr><td>Febrile neutropenia</td><td>DOC: £179

VNB: £411

PAX: £310

GEM: £172

PEM: £83

GEF: £8

ERL: £0</td></tr>
<tr><td>Hair loss</td><td>DOC: £0

VNB: £0

PAX: £0

GEM: £0

PEM: £0

GEF: £0

ERL: £0</td></tr>
</table>
</td><td></td></tr>
</table>

Author and year	Brief study description	Treatment costs			Administration costs	AEs, health state and other relevant costs		Resource use
		PAX IV+CIS	£698.27 £49.16	£698.27 £49.16		Nausea/vomiting	DOC: £181 VNB: £180 PAX: £120 GEM: £170 PEM: £100 GEF: £5 ERL: £6	
		PAX IV+CARB	£927.55 £59.47	£927.55 £59.47				
		VNB IV+CIS	£330.97 £58.55	£380.55 £66.78		Neutropenia	DOC: £129 VNB: £131 PAX: £119 GEM: £77 PEM: £43 GEF: £6 ERL: £0	
		VNB IV+CARB	£560.25 £68.86	£609.83 £77.10				
		VNB oral+CIS	£537.26 £496.50	£546.10 £505.34		Skin rash	DOC: £0 VNB: £0 PAX: £2 GEM: £2 PEM: £0	
		VNB oral+CARB	£766.54 £506.81	£775.38 £515.65				

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>PEM IV+CIS</td><td>£1535.40

£1493.11</td><td>£1535.40

£1493.11</td></tr>
</table>
GEF oral per patient (BNF 62 & eMIT): £12,200.00

a-Best generic price used

b-PAS price per patient applies only to patients receiving treatment beyond 60 days
</td>
<td></td>
<td>
<table>
<tr><td></td><td>GEF: £11

ERL: £27</td></tr>
<tr><td>Total AE cost</td><td>DOC: £773

VNB: £1011

PAX: £751

GEM: £733

PEM: £409

GEF: £80

ERL: £129</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Fleming, 2008 (61)</td>
<td>A cost study to evaluate the factors influencing hospital costs of lung cancer patients in Northern Ireland</td>
<td>Mean costs for 12 months

<table>
<tr><td>NSCLC types</td><td>CTX cost</td><td></td></tr>
<tr><td></td><td>N</td><td>Mean</td></tr>
<tr><td>Limited</td><td>13</td><td>£1,864.05</td></tr>
<tr><td>Advanced</td><td>19</td><td>£2,234.36</td></tr>
<tr><td>Extensive</td><td>17</td><td>£2,609.92</td></tr>
</table>
</td>
<td>Unit inpatient cost for 12 months: £183.00

Mean Inpatient costs for 12 months

<table>
<tr><td>NSCLC types</td><td colspan="2">Inpatient cost</td></tr>
<tr><td></td><td>N</td><td>Mean</td></tr>
<tr><td>Limited</td><td>110</td><td>£4,872.79</td></tr>
<tr><td>Advanced</td><td>79</td><td>£4,605.11</td></tr>
<tr><td>Extensive</td><td>110</td><td>£3,703.26</td></tr>
</table>
</td>
<td>Unit costs for 12 months

Diagnosis

Chest X ray: £21.67

Bronchoscopy: £564.00

Rigid Bronchoscopy: £630.00

Mediastinoscopy: £383.00

CT scan: £153.11

Sputum cytology: £ 67.10</td>
<td>Number of days in hospital stay: 20 days</td>
</tr>
</table>

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
		Un-staged: 11: £2,241.82 Overall: 60: £2,261.90	Un-staged: 66: £5,207.18 Overall: 365: £4,522.86 Cost of hospital care for the first year amounts to approximately: £3.99 m (£5,510 per case)	Ultrasound: £62.54 Pleural aspiration: £33.67 FNA: £111.50 MRI: £204.50 Inpatient stay: £183.00 Mean costs for 12 months Diagnosis Limited (N=133): £805.72 Advanced(N=99): £814.73 Extensive(N=134): £709.68 Unstaged(N=83): £751.49 Overall (N=449): £769.02	

Key: AE, adverse event; BSA, body surface area; BSC, best supportive care; CARB, carboplatin; CHL, chlorphenamine; CI, confidence interval; CIS; cisplatin; CTX, chemotherapy DEX, dexamethasone; ERL, erlotinib; g-CSF, granulocyte-macrophage colony stimulating factor; GEF, gefitinib; GEM, gemcitabine; GP, general physician; HRG, healthcare resource groups; HTA, health technology assessment; NHS, national health service; NICE, national institute for health and clinical excellence; NR, not reported; PA, per annum; PAS, patient access scheme; PEM, pemetrexed; PD, progressive disease; PFS, progression free survival; PPS, post progression survival; SAE, serious adverse event; SE, standard error; VNB, vinorelbine.

Source: MSD CS Appendix H.

Table 115 Full extraction details of HRQoL/utility studies included in the company search

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
Chouaid, 2012(43) Australia, Belgium, Canada, France, Italy, Sweden, Turkey, the Netherlands and UK	Advanced NSCLC patients	315 (315) Note: Fifty-two percent were on 1st line.	Not specified	EQ-5D scores & EQ-VAS	Patients were stratified into 12 health states based on treatment line and treatment response status.	NR	Mean (sd) EQ-5D values: Progression on FL: 0.71 (0.24) Progressed after FL: 0.68 (0.21)
Puiol, 2014 Pujol, Paz-Ares (90)	Eligible patients with advanced (stage IIIB/IV) non-squamous NSCLC patients who had completed 4 cycles of induction therapy, had not progressed, and had an ECOG PS of 0/1; adequate organ function, and age of 18 year or older. Additional	539 patients were randomised 2:1 to pemetrexed plus BSC (average age = 60) or placebo plus BSC (average age = 62).	pemetrexed 56%; placebo 62%	The overall P value of EQ-5D and EQ-VAS scores was used to compare the difference in the average change from the baseline QoL parameters between the treatment arms. The interaction P value was used to measure	N/A	NR	Overall P Value between treatment groups Interaction P value Mobility 0.090 0.475 Self-care 0.003 0.614 Usual activities 0.051 0.553 Pain/discomfort

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
	eligibility criteria included no prior systemic chemotherapy for lung cancer, including adjuvant treatment.			whether the pemetrexed and placebo profiles differed over time.			0.964 0.374 Anxiety/depression 0.851 0.739 VAS health state score 0.515 0.977 UK population-based index score 0.241 0.770
Gridelli, 2012;(45) Australia, Belgium, Canada, Finland, France, Germany, Greece, India, Italy, The Netherlands, Poland, Portugal, Romania, Spain, Turkey, and UK	Patients were of advanced (Stage IIIB/IV) non-squamous NSCLC	Received (I) therapy: 939; ITTN: 539 RR: Overall EQ-5D compliance during the (I) period was 79.4% (3206 assessments completed of 4039 visits).	PEM(I)+CIS(I) Randomised to: PEM(M)+BSC(M) Placebo(M)+BSC(M)	QOL was determined by using EQ-5D index and VAS scale.	NR	NR	1. Results for PEM arm on FL A). Mean change from baseline in EQ-5D value: At cycle 1 (N=445): 0.00 At cycle 2 (N=682): 0.01 At cycle 3 (N=583): 0.03 At cycle 4 (N=522): 0.03 At cycle 6: −0.02, p value: 0.05 At the post discontinuation visit: −0.13 B). Mean change from baseline in EQ-5D value (during (I): At cycle 1 (N=265): 0.01

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
							At cycle 2 (N=241): -0.00 At cycle 3 (N=160): -0.00 At cycle 4 (N=149): -0.01 At cycle 5 (N=108): 0.01 At cycle 6 (N=98): -0.02 2. Results for placebo arm on FL A). Mean change from baseline in EQ-5D value: At cycle 1 (N=445): 0.00 At cycle 2 (N=682): 0.01 At cycle 3 (N=583): 0.03 At cycle 4 (N=522): 0.03 At cycle 6: 0.04. At the post discontinuation visit: −0.09 B). Mean change from baseline in EQ-5D value (during (I): At cycle 1 (N=132): -0.01 At cycle 2 (N=129): 0.01 At cycle 3 (N=83): 0.03 At cycle 4 (N=66): 0.02 At cycle 5 (N=48): 0.01 At cycle 6 (N=36): 0.04
Iyer, 2013Iyer, Taylor-Stokes (46)	Eligible patients were patients with advanced (stage IIIB/IV) NSCLC in France and Germany, who were receiving drug treatment for NSCLC in	613 patients (France) and 600 patients (Germany) were approached for inclusion in the study, and 69% of these patients (N = 837; n = 320 [France] and n		This study was based on physician interviews, completion of detailed patient record forms by physicians, and a self-completion	N/A	N/A	Generic QOL of entire population 0.58 (0.35) Generic QOL of patients in France 0.57 (0.41) Generic QOL of patients in Germany 0.59 (0.31) Generic QOL of patients receiving first-line treatment 0.63 (0.31) Generic QOL of patients receiving second-line treatment 0.53 (0.38)

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
	non–clinical trial settings 67% of patients were male. Average age was 63 years old at the time of questionnaire completion.	= 517 [Germany]) consented to complete symptom and quality of life questionnaires at a single time point.		questionnaire by patients. Generic QOL and general health status were assessed using the EQ-5D questionnaire. Results were separated in terms of patients receiving first-/second-line treatments and patients located in France/Germany.			
Nafees, (2016)(47) UK, France, Australia, South Korea, Taiwan and China	Metastatic NSCLC patients	451 (451)	Not specified	• EQ-5D • TTO (for the valuation exercise)	There were 23 health states in set A & set B." SET A: Stable with no side effects Responding with no side effects (M)– oral	NR	1. EQ-5D values according to countries (n) for normal population: single index score (sd) Australia (75): 0.949 (0.10) China (76): 0.905 (0.20) France (75): 0.896 (0.16) Korea (75): 0.838 (0.28) Taiwan (75): 0.98 (0.09) UK (75): 0.95 (0.10) Total (451): 0.919 (0.10)

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
					Stable with 1.Neutropenia 2. FN 3. Fatigue 4. Bleeding 5.Hypertension (symptomatic) Responding with 1. Nausea and Vomiting 2. Diarrhoea 3. Hair loss 4. Rash Progressive SET B Stable with no side effects Responding with no side effects (M)-IV Responding with		• 2. TTO values for all disease ± side effect combinations, in reference to the baseline state Stage: Global; Australia; China; France; Korea; Taiwan; UK A). Progressive: 0.095; 0.050; 0.321; 0.031; 0.066; 0.106; 0.166 B). Responding with no side effects: 0.773; 0.787; 0.815; 0.854; 0.684; 0.500; 0.883 diarrhoea: 0.557; 0.447; 0.746; 0.544; 0.622; 0.354; 0.604 fatigue: 0.485; 0.303; 0.750; 0.440; 0.545; 0.344; 0.519 FN: 0.300; 0.297; 0.405; 0.283; 0.283; 0.156; 0.430 hair loss: 0.640; 0.626; 0.759; 0.777; 0.600; 0.246; 0.777 nausea/vomiting: 0.578; 0.513; 0.695; 0.624; 0.625; 0.332; 0.670 neutropenia: 0.424; 0.294; 0.621; 0.407; 0.529; 0.256; 0.462 rash: 0.627; 0.651; 0.720; 0.739; 0.538; 0.315; 0.760 bleeding: 0.534; 0.564; 0.635; 0.667; 0.516; 0.157; 0.714 hypertension: 0.749; 0.766; 0.773; 0.832; 0.786; 0.393; 0.843 C). Stable with no side effects†: 0.754; 0.754; 0.804; 0.814; 0.714; 0.536; 0.840 fatigue: 0.460; 0.265; 0.736; 0.371; 0.581; 0.376; 0.430 FN: 0.279; 0.259; 0.388; 0.228; 0.313; 0.175; 0.345

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
					1.Neutropenia 2. FN 3.Fatigue 4.Bleeding 5.Hypertension (symptomatic) Stable with 1. Nausea and vomiting 2.Diarrhea 3.Hair loss 4.Rash Progressive		hair loss: 0.616; 0.581; 0.746; 0.723; 0.634; 0.274; 0.710 nausea/vomiting: 0.553; 0.466; 0.679; 0.554; 0.658; 0.365; 0.587 neutropenia: 0.399; 0.256; 0.604; 0.340; 0.565; 0.284; 0.376 diarrhoea: 0.532; 0.401; 0.732; 0.472; 0.656; 0.387; 0.517 rash: 0.603; 0.607; 0.705; 0.679; 0.574; 0.346; 0.689 bleeding: 0.508; 0.517; 0.619; 0.600; 0.552; 0.157; 0.636 hypertension: 0.729; 0.731; 0.760; 0.787; 0.809; 0.428; 0.790 3. TTO changes for all side effects by country, estimated from the model* Side effect: Global; Australia; China; France; Korea; Taiwan; United Kingdom FN: −0.47; −0.49; −0.42; −0.59; −0.40; −0.36; −0.50 Neutropenia: −0.35; −0.50; −0.20; −0.47; −0.15; −0.25; −0.46 Fatigue: −0.29; −0.49; −0.07; −0.44; −0.13; −0.16; −0.41 Diarrhoea: −0.22; −0.35; −0.07; −0.34; −0.06; −0.15; −0.32 Bleeding: −0.25; −0.24; −0.19; −0.21; −0.16; −0.36; −0.20 Nausea and Vomiting: −0.20; −0.29; −0.12; −0.26; −0.06; −0.17; −0.25 Rash: −0.15; −0.15; −0.10; −0.14; −0.14; −0.19; −0.15 Hair loss: −0.14; −0.17; −0.06; −0.09; −0.08; −0.26; −0.13

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
							Hypertension: −0.03; −0.02; −0.04; −0.03; 0.10; −0.11; −0.05 *All changes were calculated in reference to baseline state “stable and no side effects.” 4. Mean TTO ratings from participants in each country: UK: 0.61 Australia: 0.56 China: 0.66 France: 0.60 Korea: 0.58 Taiwan: 0.43
Huang (2017);(41)	Multi-country, Metastatic NSCLC with PD-L1 TPS ≥50% with no prior chemotherapy	N = 54, 26, 68 and 21 for time to death ≥360 days, 180-360 days, 30-180 days and < 30 days, respectively N = 256 and 152 for progression free vs. progressive disease, respectively	Pembrolizumab Platinum-based chemotherapy	Different scoring functions by nationality were used: US-based scores for US patients, UK-based scores for UK patients, and EU-based scores for all other patients EQ-5D Base case: US-based scores	Time-to-death utilities Progression-free Progressed disease	NR	Utility values by time to death: Mean (95% CI) ≥360 days: Pembro: 0.795 (0.737, 0.852) SOC: 0.820 (0.779, 0.862) Pooled: 0.805 (0.767, 0.843) 180-360 days: Pembro: 0.745 (0.669, 0.821) SOC: 0.714 (0.664, 0.765) Pooled: 0.726 (0.684, 0.767) 30-180 days: Pembro: 0.603 (0.533, 0.672) SOC: 0.648 (0.599, 0.698) Pooled: 0.632 (0.592, 0.672) <30 days: Pembro: 0.600 (0.409, 0.791) SOC: 0.490 (0.333, 0.647)

Authors and publication date; Country	Population	Sample size (RR)	Intervention	Method of elicitation	Model health states	Baseline/ population values with CIs	Values by health state with confidence intervals
							Pooled: 0.537 (0.425, 0.650) Utility values by progression status: Mean (95% CI) Progression-free: Pembro: 0.802 (0.785, 0.820) SOC: 0.752 (0.732, 0.771) Pooled: 0.780 (0.767, 0.793) Progressive disease: Pembro: 0.686 (0.636, 0.735) SOC: 0.690 (0.649, 0.731) Pooled: 0.688 (0.657, 0.720)
Chang, 2016(42)	South Korea	Advanced NSCLC	Health states descriptions developed by expert panel of experienced clinical oncologists and 205 participants completed the study	NR	TTO, using mixed-effects model to account for correlation between repeated responses provided by the same participants	NR	**5 different time intervals to death** 0.904 (95%CI:0.892-0.917) for over 360 days 0.720 (95%CI:0.692-0.748) for 180-360 days 0.627 (95%CI:0.598-0.655) for 90-180 days 0.379 (95%CI:0.349-0.409) for 30-90 days 0.195 (95%CI:0.172-0.218) for under 30 days

Table 116 Full extraction details of HTAs with relevant health resource use estimates included in the company search

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td>NICE TA181(49)</td>
<td>A cost effectiveness analysis comparing pemetrexed plus cisplatin and gemcitabine plus cisplatin for the first line treatment of NSCLC</td>
<td>CTX unit costs (BNF 55, 2008), based on BSA of 1.8m2
<table>
<tr><th>Drug</th><th>Unit cost per vial</th><th>Calculated cost per mg</th></tr>
<tr><td colspan="3">PEM</td></tr>
<tr><td>100mg vial</td><td>£160.00</td><td>£1.60</td></tr>
<tr><td>500mg vial</td><td>£800.00</td><td>£1.60</td></tr>
<tr><td colspan="3">GEM</td></tr>
<tr><td>200mg vial</td><td>£32.55</td><td>£0.16</td></tr>
<tr><td>1000mg vial</td><td>£162.76</td><td>£0.16</td></tr>
<tr><td colspan="3">DOC</td></tr>
<tr><td>20mg vial</td><td>£162.75</td><td>£8.14</td></tr>
<tr><td>80 mg vial</td><td>£534.75</td><td>£6.68</td></tr>
<tr><td colspan="3">CIS</td></tr>
<tr><td>50mg vial</td><td>£25.37</td><td>£0.51</td></tr>
</table>
</td>
<td>National schedule of reference costs 2006-07 NHS Trusts, CTX inpatients and outpatients (DH, 2008)
<table>
<tr><th>HRG code: description</th><th>Unit cost</th></tr>
<tr><td>SB12Z: Deliver simple parenteral CTX at first attendance</td><td>Outpatient: £170
Inpatient: £309</td></tr>
<tr><td>SB13Z: Deliver more complex parenteral CTX at first attendance</td><td>Outpatient: £104
Inpatient: £298</td></tr>
<tr><td>SB14Z: Deliver complex CTX including prolonged infusional treatment at first attendance</td><td>Outpatient: £179
Inpatient: £430</td></tr>
<tr><td>SB15Z: Deliver subsequent elements of a CTX cycle</td><td>Outpatient: £189
Inpatient: £255</td></tr>
</table>
The daily costs of a non-elective inpatient stay (DH, 2008)</td>
<td>CTX concomitant medication unit costs (BNF 55, 2008)

Premedication

Dexamethasone: £2.39

Folic Acid: £1.65

Vitamin B12: £2.46

Piriton: £1.62

Paracetamol: £1.59

Pharmaceutical Products

Lomotil: £1.63

Domperidone: £2.35

Unit cost of AEs

Neutropaenia: £330.93

Nausea and vomiting: £700.79

Fatigue: £38.90

Diarrhoea: £867.12

Anaemia: £615.04

Thrombocytopaenia: £314.69</td>
<td>Resource utilisation

PEM+CIS: 1 x SB14Z (inpatient)

GEM+CIS: 1 x SB14Z (inpatient) and 1 x SB15Z (outpatient)

GEM+CARB: 1 x SB14Z (outpatient) and 1 x SB15Z (outpatient)

DOC+CIS: 1 x SB14Z (inpatient)

AE hospital resource utilisation (Duran et al.2008), average inpatient length of stay

Neutropenia: 1.7 days

Nausea & Vomiting: 3.0 days

Fatigue: 0.0 days

Diarrhoea: 3.5 days

Anaemia: 1.7 days

Thrombocytopenia: 2.0 days

Days per hospitalisation (length of stay): 4.30 days</td>
</tr>
</table>

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
		<table><tr><td>100mg vial</td><td>£50.22</td><td>£0.50</td></tr><tr><td colspan="3">CARB</td></tr><tr><td>50mg vial</td><td>£22.04</td><td>£0.44</td></tr><tr><td>150mg vial</td><td>£56.29</td><td>£0.38</td></tr><tr><td>450mg vial</td><td>£168.85</td><td>£0.38</td></tr><tr><td>600mg vial</td><td>£260.00</td><td>£0.43</td></tr></table> Cost per dose PEM(500mg/m2): £1,440.00 GEM(1250mg/m2): £390.62 DOC(75mg/m2): £1,023.00 CIS (75mg/m2): £75.59 CARB (500mg per cycle): £190.89 Mean costs per patient per cycle PEM+CIS: £1440 + £75.59 GEM+CIS: (£390.62 x 2*) + £75.59 GEM+CARB: (£390.62 x 2*) + £190.89	Non-elective Inpatient HRG: £400.00 Unit costs for hospitalisation due to febrile neutropaenia Cost per day: £400 Cost per episode: £1,720	Febrile neutropaenia: £1720.00 (data from ERG) Specialist palliative care*: £3236 per cancer death per year *Inflated to £3581 for 2008 to get cost of care over 12 months Assumed that the majority of this cost would be incurred in the later stages of disease so a one-off cost of £2686 to each patient in last 3 months of life is applied, equivalent to 75% of the yearly cost, remaining 25% of cost is distributed equally through the year to get a per cycle cost of £68.86 applied to all patients in progression	

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td>DOC+CIS: £1023 + £75.59

Mean total costs per patient (mean no. of cycles per patient)

PEM+CIS: £5,759.24 (3.80)

GEM+CIS: £3,264.52 (3.81)

GEM+CARB: £3,645.49 (3.75)

DOC+CIS: £4,16 3.66 (3.79)

Unit costs with the delivery of each CTX regimen

<table><tr><th>Regimen; resource utilisation</th><th>Unit cost</th><th>Total cost per cycle</th></tr><tr><td>PEM+CIS;

1 x SB14Z (inpatient)</td><td>£430</td><td>£430</td></tr><tr><td>GEM+CIS;

1 x SB14Z (inpatient)</td><td>£430</td><td>£619</td></tr><tr><td>GEM+CIS;

1 x SB15Z (outpatient)</td><td>£189</td><td>-</td></tr></table></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>GEM+CARB;

1 x SB14Z (outpatient)</td><td>£179</td><td>£368</td></tr>
<tr><td>GEM+CARB;

1 x SB15Z (outpatient)</td><td>£189</td><td>-</td></tr>
<tr><td>DOC+CIS;

1 x SB14Z (inpatient)</td><td>£430</td><td>£430</td></tr>
</table>
</td><td></td><td></td><td></td></tr>
<tr><td>NICE TA190 (2010);(50)</td><td>A cost effectiveness analysis comparing pemetrexed maintenance therapy with best supportive care for the maintenance treatment of NSCLC</td><td>Cost of PEM

<table>
<tr><td>Dose</td><td>Unit cost per vial</td><td>Calculated cost per mg</td></tr>
<tr><td>100 mg vial</td><td>£160.00</td><td>£1.60</td></tr>
<tr><td>500mg

vial</td><td>£800.00</td><td>£1.60 (£1,509.58) *</td></tr>
</table>
Total (M) mean CTX cost per patient per cycle</td><td>NR</td><td>Concomitant medication unit costs

DEX: £2.39

Folic acid: £1.65

Vitamin B12: £2.46

AEs unit costs calculation:

Neutropenia:

Inpatient: £680.00

Outpatient: £593.10</td><td>NR</td></tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>Mean acquisition cost</td><td>Mean admin cost</td><td>Mean cost per cycle</td><td>Mean no. of cycles</td><td>Mean total cost per patient</td></tr>
<tr><td colspan="4">PEM (non-squamous)</td><td></td></tr>
<tr><td>£1,509.53</td><td>£153</td><td>£1,662.53</td><td>5.84</td><td>£9,642.67</td></tr>
<tr><td colspan="4">PEM (adenocarcinoma)</td><td></td></tr>
<tr><td>£1,509.53</td><td>£153</td><td>£1,662.53</td><td>6.16</td><td>£10,264.18</td></tr>
</table>
BSC and terminal care costs used in the model (NICE 2004)b

BSC during active CTX: £33.18

BSC with no active CTX: £66.36

Terminal care: £2,588.25

National schedule for reference costs (2007/08)

<table>
<tr><td>HRG code: Description</td><td>Unit cost</td></tr>
<tr><td>SB11Z: Deliver exclusively Oral CTX</td><td>£167</td></tr>
</table>
</td>
<td></td>
<td>
Day care: £710.45

Nausea and vomiting:

Inpatient: £1200.00

Outpatient: £20.70

Day care: £1253.74

Fatigue:

Inpatient: £0

Outpatient: £219.80

Day care: £0.00

Anaemia:

Inpatient: £680.00

Outpatient: £593.10

Day care: £710.45

AE resource utilisation

<table>
<tr><td>AEs</td><td>Unit cost</td></tr>
<tr><td>Neutropaenia</td><td>£330.93</td></tr>
<tr><td>Nausea and vomiting</td><td>£700.79</td></tr>
<tr><td>Fatigue</td><td>£38.90</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>SB12Z: Deliver simple Parenteral CTX at first attendance</td><td>£153</td></tr>
<tr><td>SB13Z: Deliver more complex Parenteral CTX at first attendance</td><td>£117</td></tr>
<tr><td>SB14Z: Deliver complex CTX, including prolonged infusional treatment at first attendance</td><td>£208</td></tr>
<tr><td>SB15Z: Deliver subsequent elements of a CTX cycle</td><td>£154</td></tr>
</table>
*Cost per cycle
</td>
<td></td>
<td>
<table>
<tr><td>Anaemia</td><td>£615.04</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>NICE TA192 (2010)(51)</td>
<td>A cost effectiveness analysis comparing gefitinib with gemcitabine and carboplatin, paclitaxel and carboplatin, vinorelbine and cisplatin, and gemcitabine and cisplatin for the first line treatment of locally advanced or metastatic NSCLC</td>
<td>Model variables administration per cycle unit costs

GEM+CARB: £307

PAX/CARB: £153

VNB/CIS: £527

GEM+CIS: £527

BSC (per 21-day cycle) *: £600 (i.e. £4,552/5.24 * 21/30.42)

CTX unit costs</td>
<td>Model variables costs

GEF patient monitoring (per month): £86</td>
<td>Model variables costs
<table>
<tr><td>Drug acquisition (per cycle)</td><td>Cost</td></tr>
<tr><td>GEM+CARB</td><td>£999</td></tr>
<tr><td>PAX+CARB</td><td>£1,489</td></tr>
<tr><td>VNB+CIS</td><td>£403</td></tr>
<tr><td>GEM+CIS</td><td>£795</td></tr>
<tr><td>g-CSF</td><td>£1,284</td></tr>
</table>
</td>
<td>Resource use for the delivery of doublet CTX for locally advance or metastatic NSCLC (per cycle)
<table>
<tr><td>Comparator</td><td>Resource</td></tr>
<tr><td>GEM+CARB</td><td>1xSB12Z (outpatient)+1x SB15Z (outpatient)</td></tr>
<tr><td>PAX+CARB</td><td>1xSB12Z (outpatient)</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>Drug</td><td>Unit cost per vial</td><td>Cost per mg</td><td>Dose</td><td>Cost per dose</td></tr>
<tr><td>GEM (1,000 mg vial)</td><td>£159.49</td><td>£0.16</td><td>1,250 mg/m2 (Day 1 & 8)</td><td>£363</td></tr>
<tr><td>PAX (300mg vial)</td><td>£1,001.72</td><td>£3.34</td><td>200mg/m2 (Day 1)</td><td>£1,215</td></tr>
<tr><td>VNB (50mg vial)</td><td>£153.98</td><td>£3.08</td><td>30mg/m2 (Day 1 & 8)</td><td>£168</td></tr>
<tr><td>CARB (450mg vial)</td><td>£168.85</td><td>£0.38</td><td>400mg/m2 (Day 1)</td><td>£273</td></tr>
<tr><td>CIS (50mg)</td><td>£24.50</td><td>£0.49</td><td>75mg/m2 (Day 1)</td><td>£67</td></tr>
</table>
</td>
<td></td>
<td>
<table>
<tr><td>(per patient treated)</td><td></td></tr>
</table>
Model variables costs
<table>
<tr><td>Grade 3/4 AE</td><td>Cost</td></tr>
<tr><td>Neutropaenia</td><td>£92.80</td></tr>
<tr><td>Febrile neutropaenia</td><td>£2,286</td></tr>
<tr><td>Fatigue</td><td>£39</td></tr>
<tr><td>Nausea and vomiting</td><td>£701</td></tr>
<tr><td>Diarrhoea</td><td>£867</td></tr>
<tr><td>Rash</td><td>£117</td></tr>
<tr><td>Anaemia</td><td>£615</td></tr>
</table>
NHS patient transport service (per journey): £28
</td>
<td>
<table>
<tr><td>VNB+CIS</td><td>1xSB14Z (Day case and regular day/night) +SB15Z (Day case and regular day/night)</td></tr>
<tr><td>GEM+CIS</td><td>1xSB14Z (Day case and regular day/night) +SB15Z (Day case and regular day/night)</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td>Doublet CTX costs per 21-day cycle

<table><tr><td>Comparator</td><td>Cost per cycle</td><td>Total cost per cycle</td></tr><tr><td>GEM+

CARB</td><td>(£363 *2) + £273</td><td>£999</td></tr><tr><td>PAX+

CARB</td><td>£1,215 + £273</td><td>£1,489</td></tr><tr><td>VNB+

CIS</td><td>(£168 * 2) + £67</td><td>£403</td></tr><tr><td>GEM+

CIS</td><td>(£363 *2) + £67</td><td>£795</td></tr></table>National schedule for reference costs (2007/08)

<table><tr><td>HRG code: Description</td><td>Unit cost</td></tr><tr><td>SB12Z: Deliver simple parenteral CTX at first attendance. Outpatient CTX delivery.</td><td>£153</td></tr><tr><td>SB14Z: Deliver complex CTX including prolonged infusional</td><td>£307</td></tr></table></td><td></td><td></td><td></td></tr>
</table>

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
		<table><tr><td>treatment at first attendance. CTX delivery day case and regular day/night.</td><td></td></tr><tr><td>SB15Z: Deliver subsequent elements of CTX cycle. Outpatient CTX delivery.</td><td>£154</td></tr><tr><td>SB15Z: Deliver subsequent elements of CTX cycle. CTX delivery day case and regular day/night.</td><td>£220</td></tr></table> *according to Clegg et al., 2002 BSC cost per cycle was £473 and the total BSC incurred cost (1999/00) was £3,342 and the was inflated to £4,552 (2007/08).			
NICE TA227 (2011)(52)c	A cost effectiveness analysis comparing erlotinib with best supportive care for the maintenance treatment of NSCLC	The SD model Administration costs of ERL Mean Admin Cost (PFS Based): £78.32 Mean Admin Cost (TTCTC Based): £69.42 SD (PEM Unsuitable) Costs Mean Discounted Cost (PFS Based): £8,118.74 Mean Discounted Cost (TTCTC Based): £7,148.44 Model 2a Squamous Histology SD Costs:	PEM administration and pharmacy costs: Calculated using simple parenteral CTX at first attendance (then £272.10) combined with the pharmacy preparation cost from the previous submission, converted into a monthly cost and multiplied by the proportion of time in PFS on treatment, when applied to each month of PFS in the model = £398.21 a month.	The SD model Cost of PFS BSC: ERL: £994.42; BSC: £651.02 Cost of PD BSC, 2nd line treatment and EOL: ERL = £9,163.69; BSC = £8,923.13 AEs costs of ERL: £11.00 Model 2a Squamous Histology SD Costs:	The SD model: Mean Packs (PFS Based): 5.85 Mean Packs (TTCTC Based): 5.14

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
		Cost of ERL: £6,643.66 Cost of ERL Administration: £64.30 Model 2b Non-squamous SD Costs: Cost of ERL = £7,975.97 Cost of ERL Administration: £77.19 Model 3 Non Squamous SD (PEM Suitable) Costs Cost of ERL: £7,975.97 Cost of PEM: £13,062.17 Cost of ERL Administration: £77.19 Cost of PEM Administration: £2,508.15 ERG DATA Drug costs Monthly cost of ERL: £1,415.30 Monthly cost of PEM: £2,188.03 Monthly cost of concomitant medication for PEM: £19.84 Post-progression drug cost ITT population: £325 (ERL)	ERG DATA Total average per patient costs by population Administration/pharmacy ITT population: ERL: £65 BSC: £0 SD: ERL: £65 BSC: £0 Non-squamous: Costs of drug ERL: £69 PEM: £2,924	Cost of PFS BSC: ERL = £899.03; BSC = £661.87 Cost of PD BSC, 2nd line treatment and EOL: ERL = £9,003.66; BSC = £8,620.49 AEs costs of ERL: £11.00 Model 2b Non-squamous SD Costs: Cost of PFS BSC: ERL = £1,143.82; BSC = £684.17 Cost of PD BSC, 2nd line treatment and EOL: ERL = £9,233.10; BSC = £9,061.27 AEs costs of ERL: £11.00 Model 3 Non Squamous SD (PEM Suitable) Costs Cost of PFS BSC: ERL = £1,143.82; PEM = £1,143.82 Cost of PD BSC, 2nd line treatment and EOL: ERL = £9,233.10; PEM = £9,233.10 AEs costs ERL: £11.00; PEM: £24.64 ERG DATA	

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
		£440 SD population: £322 (ERL) £483 Non-squamous population: £226 (ERL) £413 Drug administration costs ERL Monthly pharmacy preparation cost: £13.50 PEM IV and its concomitant medication. Pharmacy preparation cost (per cycle): £37.35 PEM delivery cost (per cycle): £212 Total average per patient costs by population Costs of drug ITT population: ERL: £6,430		Health state costs: Monthly cost of PFS health state supportive care: £361.44 Monthly cost of progressed state supportive care: £1,088.93 AEs costs: Rash: £129.00 Diarrhoea: £261.55 Neutropenia: £330.93 Anaemia: £615.04 Fatigue: £38.90 Total average per patient costs by population ITT population: Mean cost of PFS ERL: £8,543 BSC: £1,373 Mean cost of progression ERL: £16,569 BSC: £18,034	

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
		BSC: £0 SD: ERL: £6,396 BSC: £0 Non-squamous: ERL: £6,617 PEM: £17,853 Mean total cost ITT population: ERL: £25,112 BSC: £19,407 SD: ERL: £24,129 BSC: £16,382 Non-squamous: ERL: £25,470 PEM: £40,564		SD: Mean cost of PFS ERL: £8,466 BSC: £1,348 Mean cost of progression ERL: £15,662 BSC: £15,034 Non-squamous: Mean cost of PFS ERL: £8,721 BSC: £23,724 Mean cost of progression ERL: £16,748 BSC: £16,840 Cost of supportive care in PFS: ITT population: ERL: £2,036 BSC: £1,373 SD:	

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
				ERL: £1,995 BSC: £1,348 Non- squamous: ERL: £2,021 PEM: £2,923 Cost of AEs: ITT population: ERL: £12 BSC: £0 SD: ERL: £11 BSC: £0 Non-squamous: ERL: £15 PEM: £24.64	
NICE TA258 (2012) (53)	A cost effectiveness analysis comparing erlotinib with gefitinib for first-line treatment of locally advanced or metastatic EGFR-	Pharmacy costs per pack of ERL/GEF dispensed: £13 Effective net price of ERL to the NHS (with14.5% discount on the list price of ERL agreed in NICE TA162) Pack of 150mg tablets: £1,394.96	GEF PAS administration costs: Patient Registration: £32 Completion of Form to Request Pack: £16 Invoicing: £19	Monthly PFS BSC cost (including monitoring)- Supportive care + CT assessment of response every three months: £181.46	Time required for dispensing an oral agent: ERL: 12 min GEF: 12 min

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td>TK mutation-positive NSCLC</td><td>Pack of 100mg tablets: £1,132.16

Pack of 25 mg tablets: £323.47

GEF PAS fixed cost payment: £12,200

ERG Data

Erlotinib drug costs

30 x 150 mg = £1631.53

30 x 100 mg: £1324.14

30 x 25mg - 50mg: £378.33</td><td>Payment Reconciliation: £19

Query Management: £19

Set up cost per patient: £70

Per month (on-going cost): £35

Administrative costs: Oral products - no dispensing required

Pharmacy dispensing* (12 minutes dispensing costing): £13

* time-and-motion study, Millar et al., 2008

ERG Data

GEF PAS administration costs: (Conflict from Manufactures result)

Per month (on-going cost): £34</td><td>Monthly PD BSC and Monitoring - Supportive care + CT assessment of response every 3 months whilst on 2nd line treatment (estimate based upon the SATURN RCT in NICE TA227): £160.06

Terminal Phase BSC Costs- Supportive care: £2,588.25

AE cost

Rash: £116

Diarrhoea: £867</td><td></td></tr>
<tr><td>NICE TA309 (2014)(48)</td><td>A cost effectiveness analysis of pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous</td><td>Drug costs

<table><tr><td>Drug</td><td>Drug cost</td><td>Administration cost</td></tr><tr><td>PEM</td><td>£1,440</td><td>£208</td></tr><tr><td>DOC</td><td>£1,023</td><td>£208</td></tr></table></td><td>Consultant led-follow up attendance non-admitted face to face for all patients: £120

Additional monitoring costs per cycle for patients receiving PEM (every 24 weeks) *</td><td>BSC and terminal care costs

Health state value used in TA 190

BSC (no active CTX): £66.36 per cycle

BSC (active CTX): £33.18 per cycle</td><td>Number of vials of PEM: 1 x 500mg + 4 x 100mg

Number of vials of DOC: 1 x 80mg + 3 x 20mg

30 x 150mg tab pack of Erlotinib

CT scan (no. of scan with contrast)</td></tr>
</table>

Author and year	Brief study description	Treatment costs	Administration costs	AEs, health state and other relevant costs	Resource use
	non-small-cell lung cancer.	ERL £976.47 £128 Drug cost PEM: 1 x £800 + 4 x £160 (Vials: 1 x 500mg + 4 x 100mg) DOC: 1 x £534.75 + 3 x £162.75 (Vials: 1 x 80mg + 3 x 20mg) ERL: 30 x 150mg tab pack: £1,631.53 14.5% PAS discount (TA227): £236.57 Administration cost ERL: Cost for a 28-day cycle: £171	Consultant follow-up visit unit cost: £119.99 (£15 per cycle) CT scan (3% of the cohort) unit cost: £142.92 (£0.54 per cycle) * NHS Reference Cost (NHS Trusts & PCTs) 2010/2011	Terminal care cost: £2,588.25 (one-off) Model revalued costs BSC (no active CTX): £72.44 per cycle BSC (active CTX): £36.22 per cycle Terminal care cost: £2,825.29 (one-off) Testing costs for all patients CT scan; two areas with contrast: £132.99 CT scan; three areas with contrast: £150.88 Average cost weighted by activity: £142.92 AEs costs AE: Cost per episode / Cost per cycle Neutropaenia: £345.13 / PEM+BSC: £2.09; Placebo+BSC: £0.00	Two areas: 187,559 Three areas: 233,749

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Nausea and vomiting: £670.67</td><td>PEM+BSC: £0.56

Placebo+BSC: £0.00</td></tr>
<tr><td>Fatigue: £141.31</td><td>PEM+BSC: £0.74

Placebo+BSC: £0.26</td></tr>
<tr><td>Anaemia: £609.41</td><td>PEM+BSC: £4.03

Placebo+BSC: £0.57</td></tr>
<tr><td>Total</td><td>PEM+BSC: £7.43

Placebo+BSC: £0.83</td></tr>
</table>
</td><td></td></tr>
<tr><td>NICE TA310 (2014) (54)</td><td>A cost effectiveness analysis of Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic NSCLC</td><td>Drug administration costs for GEF
<table>
<tr><td>Item of administration cost</td><td>Cost</td><td>Cost applies at</td></tr>
<tr><td>Introductory administration cost</td><td>£163</td><td>1st model cycle</td></tr>
</table>
</td><td>Unit costs associated with TKI-naive progression free health state
<table>
<tr><td>Resource</td><td>Unit cost (weighted cost)</td></tr>
<tr><td colspan="2">Outpatient visits</td></tr>
<tr><td>GP</td><td>£37</td></tr>
</table>
</td><td>Testing cost

Blood transfusion: £923

CT scan: £118

Infusion: £76

MRI scan: £182

Physical therapy: £183</td><td>Disease management resource use with TKI-naive progression free health state
<table>
<tr><td>Resource</td><td>Resource use per 3 weeks</td></tr>
<tr><td colspan="2">Outpatient visits</td></tr>
<tr><td>GP</td><td>0.0326</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>PAS set up cost</td><td>£34</td><td>1st model cycle</td></tr>
<tr><td>PAS monthly administration cost</td><td>£70</td><td>Every model cycle</td></tr>
</table>
List price for GEF

one 250mg tablet per day:

Cost per dose: £72.26

Cost per month: £2,167.71

PAS cost for GEF (250mg tablet)

One off fixed cost (applies at 3rd model cycle): £12,200

Introductory administration cost for ERL (applies at 1st model): £163

List price for ERL

one 150mg tablet per day:

Cost per dose: £54.38

Cost per month: £1,631.40

Introductory administration cost for AFA: £163

Drug acquisition cost for AFA: £72.26
</td>
<td>
<table>
<tr><td></td><td>(£1.21)</td></tr>
<tr><td>Specialist</td><td>£126 (£12.62)</td></tr>
<tr><td>Nurse</td><td>£14

(£1.19)</td></tr>
<tr><td>Occupational therapist</td><td>£77

(£0.00)</td></tr>
<tr><td>Physiotherapist</td><td>£49

(£0.08)</td></tr>
<tr><td colspan="2">Outpatient interventions</td></tr>
<tr><td>CT scan</td><td>£118

(£2.68)</td></tr>
<tr><td>MRI scan</td><td>£182

(£1.29)</td></tr>
<tr><td>Surgical procedure</td><td>£105

(£0.57)</td></tr>
<tr><td>Ultrasound</td><td>£58

(£0.33)</td></tr>
<tr><td>X-ray</td><td>£19</td></tr>
</table>
</td>
<td>Respiratory therapy: £224

Surgical procedure: £105

Ultrasound: £58

Chest X-ray: £19

Radiotherapy: £113

EGFR mutation test: £140</td>
<td>
<table>
<tr><td>Specialist</td><td>0.1003</td></tr>
<tr><td>Nurse</td><td>0.0870</td></tr>
<tr><td>Occupational therapist</td><td>0.0000</td></tr>
<tr><td>Physiotherapist</td><td>0.0016</td></tr>
<tr><td colspan="2">Outpatient interventions</td></tr>
<tr><td>CT scan</td><td>0.0226</td></tr>
<tr><td>MRI scan</td><td>0.0071</td></tr>
<tr><td>Surgical procedure</td><td>0.0054</td></tr>
<tr><td>Ultrasound</td><td>0.0056</td></tr>
<tr><td>X-ray</td><td>0.0280</td></tr>
<tr><td>Radiotherapy</td><td>0.0021</td></tr>
<tr><td colspan="2">Unscheduled hospitalisations</td></tr>
<tr><td>Unscheduled hospitalisation stay</td><td>0.0495</td></tr>
<tr><td>ICU visit</td><td>0.0238</td></tr>
<tr><td>Emergency room visit</td><td>0.0383</td></tr>
</table>
</td>
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</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>Anticipated NHS list price per pack of 28 tablets: £2,023.28

Drug acquisition cost for DOC: £534.75

Total cost of treatment course: £1069.50

ERG DATA

Drug acquisition cost for GEF

one 250mg tablet per day:

Cost per pack: £2167.71 (30x250 mg)

Cost per month: £12,200 on receipt of third pack

GEF cost per patient (ERG)

Estimated cost of gefitinib treatment; 0.877317 * £12,200 + £523.62: £12,069 per patient (LUX-LUNG 3 trial)

Estimated cost of gefitinib treatment; 0.946341 * £12,200 + £340.95: £11,886 per patient (IPASS trial)

Note: Estimated cost: efficacy* fixed cost per patient + administration cost</td>
<td>
<table>
<tr><td></td><td>(£0.53)</td></tr>
<tr><td>Radiotherapy</td><td>£113

(£0.24)</td></tr>
<tr><td colspan="2">Unscheduled hospitalisations</td></tr>
<tr><td>Unscheduled hospitalisation stay</td><td>£1,997

(£98.83)</td></tr>
<tr><td>ICU visit</td><td>£1,256

(£29.89)</td></tr>
<tr><td>Emergency room visit</td><td>£122

(£2.89)</td></tr>
</table>

Administrative costs Administration cost of DOC: £302.41

ERG DATA

FL PFS:

Outpatient visits (CT scan, MRI scan, surgical procedure, ultrasound, x-ray, radiotherapy, GP, specialist, nurse, occupational therapist, physiotherapist)
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</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td>Drug acquisition cost for ERL

one 150mg tablet per day:

Cost per pack: £1631.53 (30x150 mg)

Cost per month: £1,654.19

Drug acquisition cost for AFA

one 40mg tablet per day:

Cost per pack: £2167.71 (28x40 mg)

Cost per month: £2197.82</td><td>Unscheduled hospitalisations (ICU visit, emergency room visit): £220 (Value/month)</td><td></td><td></td></tr>
<tr><td>NICE TA411 (2016) (55)</td><td>A cost effectiveness analysis of necitumumab for the first line treatments of squamous metastatic NSCLC</td><td>Technology cost*
<table><tr><th>Technology cost</th><th>Unit cost</th></tr><tr><td>NECI</td><td>800mg vial: £1,450</td></tr><tr><td>GEM</td><td>200mg/2ml: £5.11;
1g/10ml: £12.71;
2g/20ml: £29.03</td></tr></table></td><td>Unit costs for patients receiving active therapy
<table><tr><th>Resource required</th><th>Unit cost</th></tr><tr><td>Outpatient Visit with medical oncologist</td><td>£147</td></tr><tr><td>Clinical Nurse Specialist</td><td>£22</td></tr><tr><td>GP Visit</td><td>£35</td></tr></table></td><td>Unit costs for patients receiving active therapy
<table><tr><th>Resource required</th><th>Unit cost</th></tr><tr><td>Chest X-ray</td><td>£30</td></tr><tr><td>Complete Blood Count,</td><td>£3</td></tr><tr><td>Biochemistry (Renal and Liver Function)</td><td>£2</td></tr><tr><td>CT-Scan(Chest)</td><td>£110</td></tr></table></td><td>Resource use for patients receiving active therapy
<table><tr><th>Resource required</th><th>Frequency</th></tr><tr><td>Outpatient Visit with medical oncologist, Clinical Nurse Specialist, Chest X-ray</td><td>100%; Once every 3 weeks</td></tr><tr><td>GP Visit</td><td>100%; Once monthly</td></tr></table></td></tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>CIS</td><td>100mg/100ml: £15.60;
10mg/10ml: £3.71;
50mg/50ml: £8.09</td></tr>
<tr><td>GEM</td><td>200mg/2ml: £5.11;
1g/10ml: £12.71;
2g/20ml: £29.03</td></tr>
<tr><td>CIS</td><td>100mg/100ml: £15.60;
10mg/10ml: £3.71;
50mg/50ml: £8.09</td></tr>
<tr><td>GEM</td><td>200mg/2ml: £5.11;
1g/10ml: £12.71;
2g/20ml: £29.03</td></tr>
<tr><td>CARB</td><td>450mg/45ml: £19.07;
150mg/15ml: £7.71;</td></tr>
</table>
</td>
<td>
<table>
<tr><td>Accident & Emergency visit</td><td>£88</td></tr>
</table>
Unit costs for patients with supportive care
<table>
<tr><td>Resource required</td><td>Unit cost</td></tr>
<tr><td>Outpatient Visit with medical oncologist</td><td>£147</td></tr>
<tr><td>District Nurse</td><td>£19</td></tr>
<tr><td>GP home Visit</td><td>£35.00</td></tr>
<tr><td>Clinical Nurse Specialist-home visit</td><td>£22.00</td></tr>
<tr><td>Accident & Emergency visit</td><td>£88</td></tr>
</table>
Unit costs for end of life care (Palliative care)

Hospital: £4,153

Hospice: £5,191

Home

Community Nurse Visit: £266 GP Home visit: £70
</td>
<td>
<table>
<tr><td>Opiate analgesics (30mg of codeine 4 times daily)</td><td>£0.11 per day</td></tr>
<tr><td>Antiemetic’s (16mg ondansetron daily)</td><td>£0.36 per day</td></tr>
<tr><td>Red blood cell transfusion</td><td>£195 per transfusion</td></tr>
<tr><td>Antibiotics</td><td>£1.71 per day</td></tr>
<tr><td>Oral dietary supplement (200 ml Ensure daily)</td><td>£2.02 per day</td></tr>
</table>
Unit costs for patients with supportive care
<table>
<tr><td>Resource required</td><td>Unit cost</td></tr>
<tr><td>Chest X-ray</td><td>£30</td></tr>
<tr><td>Opiate analgesics (30mg of codeine 4 times daily)</td><td>£0.11 per day</td></tr>
<tr><td>Antibiotics</td><td>£1.71 per day</td></tr>
<tr><td>Oral dietary supplement (200 ml Ensure daily)</td><td>£2.02 per day</td></tr>
</table>
</td>
<td>
<table>
<tr><td>Complete Blood Count, Biochemistry (Renal and Liver Function)</td><td>100%; Once per week</td></tr>
<tr><td>CT-Scan(Chest)</td><td>100%; once every 6 weeks</td></tr>
<tr><td>Opiate analgesics (30mg of codeine 4 times daily)</td><td>30%; daily</td></tr>
<tr><td>Antiemetic’s (16mg ondansetron daily)</td><td>100%; 3 days of every cycle</td></tr>
<tr><td>Red blood cell transfusion</td><td>21%; two units every 3 months</td></tr>
<tr><td>Accident & Emergency visit</td><td>11%; once every 12 weeks</td></tr>
<tr><td>Antibiotics</td><td>25%; 7 days in every cycle</td></tr>
<tr><td>Oral dietary supplement (200 ml Ensure daily)</td><td>11%; daily while on</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td>50mg/5ml: £3.51</td></tr>
<tr><td>PAX

CARB</td><td>150mg/25ml: £12.71;

30mg/5ml: £3.78

450mg/45ml: £19.07;
150mg/15ml: £7.71;

50mg/5ml: £3.51</td></tr>
<tr><td>DOC

CIS</td><td>80mg/ml: £25.73;

20mg/1ml: £7.45;

140mg/7ml: £54.60

100mg/100ml: £15.60;
10mg/10ml: £3.71;

50mg/50ml: £8.09</td></tr>
</table>
*cycle length was 3 weeks
</td>
<td>Macmillan Nurse: £1,901</td>
<td></td>
<td>Resource use for patients with supportive care
<table>
<tr><td>Resource required</td><td>Frequency</td></tr>
<tr><td>Outpatient Visit with medical oncologist, Chest X-ray</td><td>100%; Once every 3 weeks</td></tr>
<tr><td>District Nurse, GP home Visit,</td><td>100%; Twice monthly</td></tr>
<tr><td>Clinical Nurse Specialist-home visit</td><td>17%; Once every 4 months</td></tr>
<tr><td>Opiate analgesics (30mg of codeine 4 times daily)</td><td>30%; daily</td></tr>
<tr><td>Accident & Emergency visit</td><td>11%; once annually</td></tr>
<tr><td>Antibiotics</td><td>25%; 7 days in every cycle</td></tr>
<tr><td>Oral dietary supplement (200 ml Ensure daily)</td><td>11%; daily</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td>Cost of CTX Administration:

Deliver Complex CTX, at First Attendance: £401

Deliver subsequent elements of a CTX cycle: £328</td><td></td><td></td><td>End of life care (Palliative care)

Hospital: 55.8%

Hospice: 16.9%

Home: 27.3%</td></tr>
<tr><td>NICE TA447 (later updated by CDF review TA351)(56, 63)</td><td>A cost effectiveness analysis of pembrolizumab for the first line treatment of metastatic NSCLC in patients whose tumours strongly express PD-L1 (i.e., a PD-L1 tumour proportion score of 50% or greater).</td><td>Technology cost per 3 week cycle
<table><tr><th>Drug</th><th>Cost per mg</th><th>Cost per administration (assuming no wastage)</th></tr><tr><td>PEMBRO</td><td>£26.30</td><td>£5260.00 (list)</td></tr><tr><td>DOCE</td><td>£0.13</td><td>£17.14</td></tr><tr><td>GEMC</td><td>£0.01</td><td>£21.65</td></tr><tr><td>PAX</td><td>£0.07</td><td>£25.78</td></tr><tr><td>VIN</td><td>£0.36</td><td>£53.48</td></tr><tr><td>CARB</td><td>£0.04</td><td>£30.30</td></tr><tr><td>CIS</td><td>£0.11</td><td>£14.26</td></tr><tr><td>PEM</td><td>£1.60</td><td>£1,464.00</td></tr></table></td><td>Unit costs of disease monitoring and supportive care
<table><tr><th>Resource</th><th>Unit cost</th><th>Unit</th></tr><tr><td>Outpatient follow-up visit</td><td>£177.83</td><td>per visit</td></tr><tr><td>Chest radiography</td><td>£26.39</td><td>per case</td></tr><tr><td>CT scan (chest)</td><td>£121.68</td><td>per case</td></tr><tr><td>CT scan (other)</td><td>£124.10</td><td>per case</td></tr><tr><td>ECG</td><td>£174.91</td><td>per case</td></tr><tr><td>Community nurse visit</td><td>£67.00</td><td>per hour</td></tr><tr><td>Clinical nurse specialist</td><td>£91.00</td><td>per contact hour</td></tr><tr><td>GP surgery visit</td><td>£44.00</td><td>per visit</td></tr><tr><td>GP home visit</td><td>£88.92</td><td>per visit</td></tr><tr><td>Therapist visit</td><td>£44.00</td><td>per hour</td></tr></table></td><td>Unit cost per AE used in the de novo model
<table><tr><th>Adverse Event</th><th>Unit costs</th></tr><tr><td>Nausea</td><td>£967.99</td></tr><tr><td>Anaemia</td><td>£2,610.66</td></tr><tr><td>Fatigue</td><td>£2,768.35</td></tr><tr><td>Diarrhoea (grade 2)</td><td>£442.76</td></tr><tr><td>Diarrhoea (grade 3-4)</td><td>£967.99</td></tr><tr><td>Dyspnoea</td><td>£571.06</td></tr><tr><td>Vomiting</td><td>£764.71</td></tr><tr><td>Neutropaenia</td><td>£117.31</td></tr><tr><td>Alanine aminotransferase increased</td><td>£598.85</td></tr><tr><td>Rash</td><td>£123.34</td></tr><tr><td>Asthenia</td><td>£2,768.35</td></tr><tr><td>Thrombocytopaenia</td><td>£758.50</td></tr><tr><td>Neutrophil count decreased</td><td>£179.83</td></tr><tr><td>Aspartate aminotransferase increased</td><td>£342.78</td></tr><tr><td>Pneumonia</td><td>£3,008.41</td></tr></table></td><td>Resource use frequency for progression-free and progressed health states
<table><tr><th>Resource</th><th>PFS</th><th>PPS</th><th>Unit</th></tr><tr><td>Outpatient visit</td><td>9.61</td><td>7.91</td><td>per annum</td></tr><tr><td>Chest radiography</td><td>6.79</td><td>6.5</td><td>per annum</td></tr><tr><td>CT scan (chest)</td><td>0.62</td><td>0.24</td><td>per annum</td></tr><tr><td>CT scan (other)</td><td>0.36</td><td>0.42</td><td>per annum</td></tr><tr><td>ECG</td><td>1.04</td><td>0.88</td><td>per annum</td></tr><tr><td>Community nurse visit</td><td>8.7</td><td>8.7</td><td>visits (20 minutes) per patient</td></tr><tr><td>Clinical nurse specialist</td><td>12</td><td>12</td><td>hours contact time per patient</td></tr></table></td></tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>
Unit costs of terminal care patients (based on Brown et al study(17))
<table>
<tr><th>Resource</th><th>Unit cost</th><th>Number of consumption</th><th>% of patients in each care setting</th></tr>
<tr><td>Community nurse visit</td><td>£67.00 per hour</td><td>28.00 hours</td><td>27%</td></tr>
<tr><td>GP Home visit</td><td>£88.92 per visit</td><td>7.00 visits</td><td>27%</td></tr>
<tr><td>Macmillan nurse</td><td>£60.70 per hour</td><td>50.00 hours</td><td>27%</td></tr>
<tr><td>Drugs and equipment</td><td>£546 per patient</td><td>Average drug and equipment usage</td><td>27%</td></tr>
<tr><td>Terminal care in hospital</td><td>£3,760.46 per episode</td><td>1 episode (9.66 days)</td><td>56%</td></tr>
<tr><td>Terminal care in hospice</td><td>£4,700.58 per</td><td>1 episode</td><td>17%</td></tr>
</table>
</td>
<td>
<table>
<tr><td>White blood cell count decreased</td><td>£560.08</td></tr>
<tr><td>Urinary tract infection</td><td>£2,225.03</td></tr>
<tr><td>Neuropathy peripheral</td><td>£19.76</td></tr>
<tr><td>Pneumonitis</td><td>£3,008.41</td></tr>
<tr><td>Febrile neutropaenia</td><td>£6,831.00</td></tr>
</table>
The estimated per week monitoring and disease management costs were £76.75 and £125.87 respectively for the PFS and PPS periods.

Summary of predicted resource use by category of cost
<table>
<tr><th></th><th>Pembrolizumab</th><th>SOC</th></tr>
<tr><td>PD-L1 test cost</td><td>£348</td><td>£0</td></tr>
<tr><td>Drug acquisition cost</td><td>£53,347</td><td>£4,030</td></tr>
<tr><td>Drug administration cost</td><td>£4,380</td><td>£1,597</td></tr>
<tr><td>Pemetrexed maintenance cost</td><td>£0</td><td>£3,909</td></tr>
</table>
</td>
<td>
<table>
<tr><td>GP surgery</td><td>12</td><td>0</td><td>consultations per patient</td></tr>
<tr><td>GP home visit</td><td>0</td><td>26.09</td><td>per annum (fortnightly)</td></tr>
<tr><td>Therapist visit</td><td>0</td><td>26.09</td><td>per annum (fortnightly)</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>episode</td><td>(9.66 days)</td><td></td></tr>
<tr><td>Total cost</td><td colspan="3">£4,735.73 (one-off cost)</td></tr>
</table>

Administration costs
<table>
<tr><th>Drug Combination</th><th>Assumption</th><th>Unit costs</th></tr>
<tr><td>PEMBRO</td><td>1 x SB12Z (outpatient)</td><td>£257.11</td></tr>
<tr><td>GEM+CARB</td><td>1 x SB12Z (outpatient)</td><td>£257.11</td></tr>
<tr><td>GEM+CARB</td><td>1 x SB14Z (outpatient)
1 x SB15Z (outpatient)</td><td>£530.41</td></tr>
<tr><td>GEM+CIS</td><td>1 x SB14Z (Day case and regular day/night)
1 x SB15Z (outpatient)</td><td>£618.05</td></tr>
<tr><td>PAX+CARB</td><td>1 x SB14Z (outpatient)</td><td>£325.94</td></tr>
<tr><td>PAX+CIS</td><td>1 x SB14Z (Day case and regular day/night)</td><td>£413.58</td></tr>
<tr><td>DOCE+CARB</td><td>1 x SB14Z (outpatient))</td><td>£325.94</td></tr>
<tr><td>DOCE+CIS</td><td>1 x SB14Z (Day case</td><td>£413.58</td></tr>
</table>
</td><td>
<table>
<tr><td>Disease management cost</td><td>£12,476</td><td>£6,155</td></tr>
<tr><td>Subsequent treatment (2L) cost</td><td>£765</td><td>£808</td></tr>
<tr><td>Terminal care cost</td><td>£4,283</td><td>£4,537</td></tr>
<tr><td>AE cost</td><td>£863</td><td>£1,242</td></tr>
<tr><td>Total</td><td>£76,462</td><td>£22,278</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>and regular day/night</td><td></td></tr>
<tr><td>VINO+ CARB</td><td>1 x SB14Z (Outpatient)
1 x SB15Z (Day case and regular day/night)</td><td>£688.31</td></tr>
<tr><td>VINO+ CIS</td><td>1 x SB14Z (Day case and regular day/night)
1 x SB15Z (Day case and regular day/night)</td><td>£775.95</td></tr>
<tr><td>PEME +CARB</td><td>1 x SB14Z (outpatient)</td><td>£325.94</td></tr>
<tr><td>PEME +CIS</td><td>1 x SB14Z (Day case and regular day/night)</td><td>£413.58</td></tr>
</table>

PD-L1 test cost

<table>
<tr><td>% of people eligible for treatment with pembrolizumab among patients with NSCLC stage IV</td><td>11.6%</td></tr>
<tr><td>PD-L1 test cost</td><td>£40.5</td></tr>
</table>
</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr><td></td><td></td><td></td><td><table><tr><td>Total PD-L1 costs</td><td>£348.21</td></tr></table></td><td></td><td></td></tr>
<tr><td>NICE TA 520(57)</td><td>A cost effectiveness analysis of atezolizumab for patients with locally advanced or metastatic non-small-cell lung cancer whose disease has progressed after chemotherapy.</td><td>Drug acquisition costs<table><tr><th>Drug</th><th>Cost per vial/pack</th><th>Total drug cost per cycle</th></tr><tr><td>Atezolizumab (list)</td><td>£3,807.69</td><td>£3,807.69</td></tr><tr><td>Docetaxel</td><td>£17.77
£4.92</td><td>£34.39</td></tr><tr><td>Nintedanib (list)</td><td>£2151.10</td><td>£1,434.07</td></tr></table>Drug acquisition costs (subsequent treatments)<table><tr><th>Drug</th><th>Drug cost per cycle</th></tr><tr><td>Docetaxel</td><td>£34.33</td></tr><tr><td>Carboplatin</td><td>£53.55</td></tr><tr><td>Gemcitabine</td><td>£105.60</td></tr><tr><td>Erlotinib</td><td>£54.38</td></tr><tr><td>Pemetrexed</td><td>£1,440.00</td></tr><tr><td>Vinorelbine</td><td>£25.20</td></tr></table>Radiotherapy costs<table><tr><td>Radiotherapy preparation</td><td>Cost</td></tr></table></td><td>Monitoring costs<table><tr><td>Type of monitoring</td><td>Cost per 3 weeks</td></tr><tr><td>WF01A: Non-Admitted Face to Face Attendance, Medical Oncology</td><td>£162.84</td></tr></table>Resource use for “on treatment” health state<table><tr><th>Resource</th><th>Unit cost</th><th>Cost per 3 weeks</th></tr><tr><td>Routine GP visit (at surgery)</td><td>£45.68</td><td>£28.78</td></tr><tr><td>Oncologist</td><td>£167.08</td><td>£133.66</td></tr><tr><td>Full blood test</td><td>£3.10</td><td>£3.10</td></tr><tr><td>Liver function test</td><td>£1.18</td><td>£1.18</td></tr><tr><td>Renal function test (with electrolytes)</td><td>£1.18</td><td>£1.18</td></tr></table></td><td>Adverse event costs<table><tr><th>Adverse Event</th><th>Unit costs</th></tr><tr><td>Anaemia</td><td>£1,313.09</td></tr><tr><td>Fatigue</td><td>£3,082.59</td></tr><tr><td>Febrile neutropaenia</td><td>£5,612.78</td></tr><tr><td>Neutropenic Sepsis</td><td>£5612.78</td></tr><tr><td>Leukopenia</td><td>£362.66</td></tr><tr><td>Neutropaenia</td><td>£362.66</td></tr><tr><td>Neutrophil count decreased</td><td>£0.00</td></tr><tr><td>Pneumonia</td><td>£2,783.99</td></tr><tr><td>Respiratory Tract Infection</td><td>£3,515.13</td></tr><tr><td>White blood cell count decreased</td><td>£432.47</td></tr></table>The total cost per week in the “on treatment” health state is £128.25, and the total cost per week in “off treatment” is £120.12.</td><td>Resource use for “on treatment” health state<table><tr><th>Resource</th><th>No. required per 3 weeks</th><th>% of patient requiring resource</th></tr><tr><td>Routine GP visit (at surgery)</td><td>0.63</td><td>100%</td></tr><tr><td>Oncologist</td><td>0.8</td><td>100%</td></tr><tr><td>Full blood test</td><td>1</td><td>100%</td></tr><tr><td>Liver function test</td><td>1</td><td>100%</td></tr><tr><td>Renal function test (with electrolytes)</td><td>1</td><td>100%</td></tr><tr><td>CT scan (thorax or abdominal)</td><td>0.28</td><td>100%</td></tr><tr><td>Palliative care</td><td>2</td><td>100%</td></tr></table>Resource use for “off treatment” health state<table><tr><th>Resource</th><th>No. required</th><th>% of patient requirin</th></tr></table></td></tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>SC47Z: Preparation for simple radiotherapy with imaging and simple calculation (Outpatient)</td><td>£283.06</td></tr>
<tr><td>SC22Z: Deliver a fraction of treatment on a megavoltage machine (Outpatient)</td><td>£105.77</td></tr>
</table>

Drug Administration costs
<table>
<tr><td>Drug</td><td>NHS reference code</td><td>Cost per administration</td></tr>
<tr><td>Atezolizumab</td><td>SB12Z (outpatient)</td><td>£198.94</td></tr>
<tr><td>Docetaxel</td><td>SB12Z (outpatient)</td><td>£198.94</td></tr>
<tr><td>Nintedanib (predocetaxel</td><td>SB12Z (outpatient)</td><td>£198.94</td></tr>
</table>
</td>
<td>
<table>
<tr><td>CT scan (thorax or abdominal)</td><td>£118.53</td><td>£33.19</td></tr>
<tr><td>Palliative care</td><td>£91.83</td><td>£183.66</td></tr>
<tr><td>Total cost per week</td><td colspan="2">£128.25 per week</td></tr>
</table>
Resource use for “off treatment” health state
<table>
<tr><td>Resource</td><td>Unit cost</td><td>Cost per 3 weeks</td></tr>
<tr><td>Routine GP visit (at surgery)</td><td>£45.68</td><td>£45.68</td></tr>
<tr><td>Routine GP visit (at patient’s home)</td><td>£67.16</td><td>£16.79</td></tr>
<tr><td>Palliative care (days)</td><td>£91.83</td><td>£183.66</td></tr>
<tr><td>Oncologist</td><td>£167.08</td><td>£76.86</td></tr>
<tr><td>Full blood test</td><td>£3.10</td><td>£3.10</td></tr>
<tr><td>Liver function test</td><td>£1.18</td><td>£0.54</td></tr>
<tr><td>Renal function test (with electrolytes)</td><td>£1.18</td><td>£0.54</td></tr>
<tr><td>CT scan (thorax or abdominal)</td><td>£118.53</td><td>£33.19</td></tr>
<tr><td>Total cost per week</td><td colspan="2">£120.12 per week</td></tr>
</table>
</td>
<td></td>
<td>
<table>
<tr><td></td><td>per 3 weeks</td><td>g resource</td></tr>
<tr><td>Routine GP visit (at surgery)</td><td>1</td><td>100%</td></tr>
<tr><td>Routine GP visit (at patient’s home)</td><td>0.25</td><td>100%</td></tr>
<tr><td>Palliative care (days)</td><td>2</td><td>100%</td></tr>
<tr><td>Oncologist</td><td>0.46</td><td>100%</td></tr>
<tr><td>Full blood test</td><td>1</td><td>100%</td></tr>
<tr><td>Liver function test</td><td>0.46</td><td>100%</td></tr>
<tr><td>Renal function test (with electrolytes)</td><td>0.46</td><td>100%</td></tr>
<tr><td>CT scan (thorax or abdominal)</td><td>028</td><td>100%</td></tr>
</table>
Resource use for terminal care/end of life
<table>
<tr><td>Resource</td><td>Number required</td><td>% of patient in each setting</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>discontinuation) – base case</td><td></td><td>£46 per hour = £9.20 per administration</td></tr>
<tr><td>Nintedanib (postdocetaxel discontinuation) – base case</td><td></td><td>£46 per hour = £9.20 per administration</td></tr>
<tr><td rowspan="2">Nintedanib (predocetaxel discontinuation) – scenario analysis</td><td>SB12Z (outpatient)</td><td>£198.94</td></tr>
<tr><td>SB11Z</td><td>£183.50</td></tr>
<tr><td>Nintedanib (postdocetaxel discontinuation) – scenario analysis</td><td>SB11Z</td><td>£183.50</td></tr>
</table>
</td>
<td>
Unit costs (on and off treatment health states)
<table>
<tr><th>Resource</th><th>Unit cost</th></tr>
<tr><td>Routine GP visit (patient’s home)</td><td>£67.16</td></tr>
<tr><td>Routine GP visit (surgery)</td><td>£45.68</td></tr>
<tr><td>Palliative care (day case)</td><td>£91.83</td></tr>
<tr><td>CT scan</td><td>£118.53</td></tr>
<tr><td>X-ray</td><td>£37.30</td></tr>
<tr><td>Oncologist visit</td><td>£167.08</td></tr>
<tr><td>Full blood test</td><td>£3.10</td></tr>
<tr><td>Liver function test</td><td>£1.18</td></tr>
<tr><td>Renal function test (with electrolytes)</td><td>£1.18</td></tr>
</table>
Resource costs for terminal care
<table>
<tr><th>Resource</th><th>Total cost of care in each setting</th></tr>
<tr><td>Hospitalisation admission (+excess bed days)</td><td>£2,378.43</td></tr>
<tr><td>Macmillan Nurse (home setting)</td><td>£400.50</td></tr>
<tr><td>Hospice care</td><td>£900.44</td></tr>
<tr><td>Total Cost</td><td>£3,679.37</td></tr>
</table>
</td>
<td></td>
<td>
<table>
<tr><td>Hospitalisation admission (+excess bed days)</td><td>1 (+0.84 excess bed days)</td><td>55.8%</td></tr>
<tr><td>Macmillan Nurse (home setting)</td><td>50</td><td>27.3%</td></tr>
<tr><td>Hospice care</td><td>1.00</td><td>16.9%</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td>NICE TA 500(58)</td>
<td>A cost effectiveness analysis of ceritinib for patients with untreated, ALK positive advanced non-small-cell lung cancer.</td>
<td>Drug acquisition cost

<table>
<tr><th>Treatment</th><th>Cost per package</th><th>Drug cost per month</th></tr>
<tr><td>Ceritinib</td><td>£4,923.45</td><td>£3,861.33</td></tr>
<tr><td>Crizotinib</td><td>£4,689.00</td><td>£4,376.79</td></tr>
</table>
Drug administration costs for ceritinib and crizotinib consisted of a monthly dispensing cost for oral therapies, based on the wages associated with 12 minutes of a pharmacist's time (including qualification costs).129 This was calculated as £14.26 per month.

Costs of second line treatment regimes

<table>
<tr><th>PD treatment</th><th>Total drug + administration costs</th></tr>
<tr><td>Ceritinib</td><td>£46,805.89</td></tr>
<tr><td>Crizotinib</td><td>£45,164.18</td></tr>
<tr><td>Docetaxel</td><td>£1,489.42</td></tr>
<tr><td>Pemetrexed</td><td>£15,034.72</td></tr>
<tr><td>Platinum doublet Pemetrexed + cisplatin, or carboplatin</td><td>£6,529.92
£49.54

£80.88</td></tr>
</table>
</td>
<td>Monthly Progression Free cost

<table>
<tr><th>Resource cost</th><th>Unit Cost</th><th>Cost per month</th></tr>
<tr><td>Cancer nurse</td><td>£69.20</td><td>£13.84</td></tr>
<tr><td>Outpatient visit</td><td>£151.12</td><td>£113.34</td></tr>
<tr><td>GP visit</td><td>£31.00</td><td>£3.10</td></tr>
<tr><td>Full blood count</td><td>£3.10</td><td>£2.33</td></tr>
<tr><td>Computerised tomography scan</td><td>£125.49</td><td>£28.24</td></tr>
<tr><td>X-ray</td><td>£30.26</td><td>£22.70</td></tr>
<tr><td>Serum Chemisty</td><td>£1.18</td><td>£0.89</td></tr>
<tr><td>Total cost per month</td><td colspan="2">£184.42</td></tr>
</table>
Monthly Progressed Disease costs

<table>
<tr><th>Resource</th><th>Unit cost</th><th>Cost per month</th></tr>
<tr><td>Cancer nurse</td><td>£69.20</td><td>£6.92</td></tr>
<tr><td>Outpatient visit</td><td>£151.12</td><td>£151.12</td></tr>
<tr><td>GP visit</td><td>£31.00</td><td>£8.68</td></tr>
<tr><td>Steroids (dexamethasone)</td><td>£0.146 per 0.5mg</td><td>£11.68</td></tr>
</table>
</td>
<td>Costs associated with each AE included in the model

<table>
<tr><th>Grade 3/4 AEs</th><th>AE cost (2016 GBP)</th></tr>
<tr><td>Neutropenia</td><td>£514.82</td></tr>
<tr><td>Diarrhoea</td><td>£382.02</td></tr>
<tr><td>Pulmonary embolism</td><td>£1,485.76</td></tr>
<tr><td>Vomiting</td><td>£754.13</td></tr>
<tr><td>Hyperglycaemia</td><td>£308.44</td></tr>
<tr><td>Alanine transaminase (ALT) elevation</td><td>£308.44</td></tr>
<tr><td>Aspartate aminotransferase (AST) elevation</td><td>£308.44</td></tr>
<tr><td>Gamma-glutamyltransferase increased</td><td>£308.44</td></tr>
<tr><td>Blood alkaline phosphatase increased</td><td>£308.44</td></tr>
</table>
Total AE costs for each treatment

<table>
<tr><th>Treatment</th><th>AE costs</th></tr>
<tr><td>Ceritinib</td><td>£340.27</td></tr>
<tr><td>Crizotinib</td><td>£218.23</td></tr>
</table>
Terminal care costs
</td>
<td>Monthly Progression Free resource use frequency

<table>
<tr><th>Resource cost</th><th>Frequency of use</th></tr>
<tr><td>Cancer nurse</td><td>20% of patients (1 visit)</td></tr>
<tr><td>Outpatient visit</td><td>0.75 visits</td></tr>
<tr><td>GP visit</td><td>3.10</td></tr>
<tr><td>Full blood count</td><td>All patients, 0.75 per month</td></tr>
<tr><td>Computerised tomography scan</td><td>30% of patients, 0.75 per month</td></tr>
<tr><td>X-ray</td><td>All patients, 0.75 per month</td></tr>
<tr><td>Serum Chemisty</td><td>0.89</td></tr>
</table>
Monthly Progressed Disease costs

<table>
<tr><th>Resource cost</th><th>Frequency of use</th></tr>
<tr><td>Cancer nurse</td><td>10% of patients (1 visit)</td></tr>
<tr><td>Outpatient visit</td><td>All patients (1 visit)</td></tr>
<tr><td>GP visit</td><td>28% of patients (1 visit)</td></tr>
<tr><td>Steroids (dexamethasone)</td><td>50% of patients, 0.5mg x 160</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author and year</th><th>Brief study description</th><th>Treatment costs</th><th>Administration costs</th><th>AEs, health state and other relevant costs</th><th>Resource use</th></tr>
<tr>
<td></td>
<td></td>
<td>
Trial-based distribution and total cost of second-line treatments, according to first-line treatment arm
<table>
<tr><td>Second-line treatment</td><td>Ceritinib (%)</td><td>Crizotinib (%)</td></tr>
<tr><td>Ceritinib</td><td>1.9</td><td>10.8</td></tr>
<tr><td>Crizotinib</td><td>9.4</td><td>1.5</td></tr>
<tr><td>Docetaxel</td><td>3.8</td><td>4.6</td></tr>
<tr><td>Pemetrexed</td><td>0.0</td><td>0.0</td></tr>
<tr><td>Platinum doublet</td><td>45.0</td><td>43.1</td></tr>
<tr><td>pemetrexed +</td><td>45.0</td><td>43.1</td></tr>
<tr><td>cisplatin, or</td><td>22.5</td><td>20.0</td></tr>
<tr><td>carboplatin</td><td>22.5</td><td>23.1</td></tr>
<tr><td>No active treatment</td><td>40.0</td><td>40.0</td></tr>
<tr><td>Total PD treatment cost, £</td><td>£8,135.41</td><td>£8,645.67</td></tr>
</table>
Costs of pre-medicines required for Pemetrexed and docetaxel
<table>
<tr><td>Treatment</td><td>Strength (mg)</td><td>Cost per package, £</td></tr>
<tr><td>Dexamethasone</td><td>2 mg/5 ml</td><td>17.34 (150ml)</td></tr>
</table>
</td>
<td>
<table>
<tr><td>NSAIDS (ibuprofen)</td><td>£0.006 per 200mg</td><td>£0.11</td></tr>
<tr><td>Morphine</td><td>£0.710 per 60mg</td><td>£3.73</td></tr>
<tr><td>Bisphosphonate (alendronate)</td><td>£0.022 per 5mg</td><td>£0.05</td></tr>
<tr><td>Dietary supplement</td><td>£3.54 per 350g</td><td>£28.34</td></tr>
<tr><td>Full blood count</td><td>£3.10</td><td>£3.10</td></tr>
<tr><td>Serum chemistry</td><td>£1.18</td><td>£1.18</td></tr>
<tr><td>Computerised tomography scan</td><td>£125.49</td><td>£4.71</td></tr>
<tr><td>Home oxygen</td><td>£203.91</td><td>£40.78</td></tr>
<tr><td>X-ray</td><td>£30.26</td><td>£6.81</td></tr>
<tr><td colspan="2">Total post-progression care costs, all patients</td><td>£267.19</td></tr>
</table>
</td>
<td>
<table>
<tr><td>Terminal care costs</td><td>Average costs</td></tr>
<tr><td>District nurse</td><td>£298.40</td></tr>
<tr><td>Nursing and residential care</td><td>£1,073.36</td></tr>
<tr><td>Hospice care-inpatient</td><td>£590.35</td></tr>
<tr><td>Hospice care – final three months of life</td><td>£4,830.14</td></tr>
<tr><td>Marie Curie nursing service</td><td>£536.68</td></tr>
<tr><td>Total terminal care costs</td><td>£7,328.93</td></tr>
</table>
</td>
<td>
<table>
<tr><td>NSAIDS (ibuprofen)</td><td>30% of patients, 200mg x 60</td></tr>
<tr><td>Morphine</td><td>75% of patients, 60mg x 7</td></tr>
<tr><td>Bisphosphonate (alendronate)</td><td>7.5% of patients, 5mg x 28</td></tr>
<tr><td>Dietary supplement</td><td>40% of patients, 350g x 20</td></tr>
<tr><td>Full blood count</td><td>All patients, 1 per month</td></tr>
<tr><td>Serum chemistry</td><td>All patients, 1 per month</td></tr>
<tr><td>Computerised tomography scan</td><td>5% of patients, 0.75 per month</td></tr>
<tr><td>Home oxygen</td><td>20% of patients, 1 per month</td></tr>
<tr><td>X-ray</td><td>30% of patients, 0.75 per month</td></tr>
</table>
</td>
</tr>
</table>

Author and year	Brief study description	Treatment costs			Administration costs	AEs, health state and other relevant costs	Resource use
		(oral solution)					
		Vitamin B12 (injection)	1 mg/ml	4.44 (5 amp)			
		Folic acid (tablets)	5 mg	0.27 (28 tablets)			

Key: AE, adverse event; BSA, body surface area; BSC, best supportive care; CARB, carboplatin; CHL, chlorphenamine; CI, confidence interval; CIS; cisplatin; CTX, chemotherapy DEX, dexamethasone; ERL, erlotinib; g-CSF, granulocyte-macrophage colony stimulating factor; GEF, gefitinib; GEM, gemcitabine; GP, general physician; HRG, healthcare resource groups; HTA, health technology assessment; NHS, national health service; NICE, national institute for health and clinical excellence; NR, not reported; PA, per annum; PAS, patient access scheme; PEM, pemetrexed; PD, progressive disease; PFS, progression free survival; PPS, post progression survival; SAE, serious adverse event; SE, standard error; TTCTC, time to complete treatment cessation; VNB, vinorelbine.
Source: MSD CS Appendix I.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

You are asked to check the ERG report from Peninsula Technology Assessment Group (PenTAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 24 September 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Indication wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2; page 34 and section 5.2.4.1; page 217: Indication wording marked AIC	Remove AIC mark up	AIC mark up no longer required as marketing authorisation for indication now received and hence wording is public knowledge	Thank you for raising this issue. Whilst this was not a factual error, this new information has come to light so we are happy to make this amendment in the light of new information.

Issue 2 Duration of response outcome

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.4; page 36 ERG notes that 'The company excluded DoR in their definition of the decision problem'…	While DoR was omitted from the list in the decision problem table in the company submission, this was not a deliberate exclusion, as the ERG wording suggests, but rather an error as available DoR evidence was included in the company submission. We would therefore request changing the wording of the sentence to: 'The company **omitted DoR in error from** their definition of the decision problem'… '	The omission of DoR in the list of outcomes presented in Table 1 of the company submission was an error. DoR was not excluded from the company submission; the available DoR evidence for pembrolizumab combination versus clinical trial comparators has been presented in the submission in Section B.2.6.5	Thank you for this. We have amended the wording to clarify that DoR was 'erroneously omitted', since the phrase 'omitted in error' suggests insight we did not have.

Issue 3 Trial arm population number

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 17; page 76: Column 2 (Keynote 189; pembro combo); Row 3 (Absolute survival) denominator in quoted fraction (N) erroneously quoted as 405 (127/405 (31%))	Fraction denominator value should read **410** (127/410 (31%)	Trial arm population number error	Thank you for raising this issue. We are happy to make this amendment.
Table 19; page 81: Column 2, Row 3 (PFS): PFS events: deconomiator value in fraction misquoted as 405 (244/405 (59.5%) and should read 410	Insert correct value for denominator in fraction as **410 (244/410 (59.5%)**	Trial arm population number error	Thank you for raising this issue. We are happy to make this amendment.

Issue 4 AIC mark up issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Column 4 (KEYNOTE 21G); Row 4 (Relative survival unadjusted): HR quoted marked AIC	Remove AIC marking	AIC mark up not required	Thank you for raising this issue. We are happy to make this amendment.
Columns 1 and 2 (KEYNOTE 189 pembro combo and control); Row 6 (additional analyses); Events per 100 person months	Events per 100 person months values to be marked AIC	Values not currently marked AIC and need to be marked up as not yet published	
Table 18; page 77 Column 2; Row 3; HR for PD-L1	Remove AIC marking	AIC mark-up not required	Thank you for raising this issue. We are happy to make

<1% marked as AIC			this amendment.
Section 4.2.4.1.2; Page 80; Para 2; line 4; beneficial effect of pembro combo vs control values marked as AIC	Remove AIC marking	AIC mark-up not required	Thank you for raising this issue. We are happy to make this amendment.
Table 24; Page 89 Columns 2 and 3; Row 2; N values for pembro combo and control marked AIC Columns 2 and 3; Row 4 Median (Range) for pembro combo and control values marked AIC	Remove AIC markings in both Row 2 and Row 4 but retain AIC markings in row 3 Mean (SD) values	AIC mark-up not required	Thank you for raising this issue. We are happy to make this amendment.
Section 5.2.7; page 226: "six-hundred and two"	Remove AIC marking	AIC mark-up not required	Thank you for raising this issue. We are happy to make this amendment.

Issue 5 Safety data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.4.3; page 91; paragraph 3; line 8: % point difference in drug-related grade 3-5 AEs presented as 11% points	Replace 11% with **8.8**% (or 9% if rounding to 0 decimal places)	Calculation error requires correction: difference between 48.4% vs 39.6% is 8.8% rather than 11%	Thank you for raising this issue. We are happy to make this amendment.

Issue 6 Deaths

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.4.3; page 97; paragraph 1; line 10; value of deaths in the pembrolizumab combination arm quoted as 29	Replace value of 29 with correct value of **27**	Typographic error in the number of deaths in pembrolizumab arm	Thank you for raising this issue. We are happy to make this amendment.

Issue 7 Incomplete paragraph

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 146, paragraph 1 (continuation from previous page); incomplete sentence at end of paragraph	ERG may wish to complete or remove the incomplete sentence	Incomplete sentence at end of paragraph.	Thank you for raising this issue. The sentence now reads "However, as appropriate population matching techniques were used to control for key prognostic markers between and within studies, the ERG considered that this will have reduced the impact of any differences at baseline on the outcomes of the analyses. "

Issue 8 Number of utility studies identified and reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4.1; page 21 of the	Please remove "presented only seven".	We apologise for not clearly stating	Thank you for raising this

ERG report states: "They included eight studies of potential use to the utility analysis, presented only seven, and 11 UK NICE technology appraisals of possible relevance."		in the submission, but on Page 174 of the appendices (Appendix H), there are two Huang studies reported. The column "*Authors and publication date; Country"* should read "Huang et al (*2016*); Huang et al (2017) [49,50]" with the study, and its' update, reported together and constituting 2 studies. Hence 8 studies were presented.	issue. We have amended the sentence to: "They included seven studies and one update of potential use to the utility analysis, and 11 UK NICE technology appraisals…"

Issue 9 Identification of TA428 in Economic SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4.1; page 21 of the ERG report states: "TA428, an appraisal of pembrolizumab at second-line in the relevant population, was missed in the search but later used as evidence." Section 5.1.4; page 206 of the ERG report states: "However two other population/intervention relevant appraisals were not identified: • Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428),	Please amend the text on page 21 as follows: "TA428, an appraisal of pembrolizumab at second-line in the relevant population, **did not meet inclusion criteria in the search as it was a second line treatment**, but later used as evidence." Please amend the text on page 206 as follows: "However one other population/intervention relevant appraisals was not identified: • Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531), published July 2018.(63) Since the most recent search update was	On page 154 of the Appendices (Appendix G), it states "health technology assessment (HTA) searches for cost effectiveness [and utility] analyses or models for first-line treatment of metastatic NSCLC that have been reviewed by the National Institute for Health and Care Excellence (NICE)" hence the exclusion of TA428.	Thank you for raising this issue. We have amended the sentence, however this criteria highlights also the inclusion of TA520, an appraisal in people who have progressed after chemotherapy. This too is included in the amendment: Section 1.4.1 The objective of the utility search specified only interventions used at first treatment line, but the HRQoL of a second-line population could inform utility scores post-progression in this model population. Indeed TA520, the appraisal of atezolizumab in adults with locally advanced

published January 2017.(62) • Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531), published July 2018.(63) Since the most recent search update was carried out on 2nd April 2018 TA531 would not be captured but the omission of TA428 is significant.”	carried out on 2nd April 2018 TA531 would not be captured.”		EGFR or ALK-positive NSCLC who have already had chemotherapy, was included. Whilst TA428, an appraisal of pembrolizumab at second-line in the relevant population, was omitted but later used for supportive evidence. Section 5.1.4 “there was inconsistency in the inclusion implementation. Whilst the objective specified first-line treatments, TA530, an appraisal of appraisal of atezolizumab in adults with locally advanced EGFR or ALK-positive NSCLC who have already had chemotherapy, was included. Whilst TA428, an appraisal of pembrolizumab at second-line in the relevant population, was omitted but later used for supportive evidence. The ERG believe the HRQoL and utility scores of people receiving second-line treatment could be used inform model inputs or validate model outputs. Therefore two other population/intervention relevant appraisals which were not identified by the search were: • Pembrolizumab for treating PD-L1-positive

			non-small-cell lung cancer after chemotherapy (TA428), published January 2017.(62) • Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531), published July 2018.(63) Since the most recent search update was carried out on 2nd April 2018, TA531 would not be captured ERG comment: • Included studies were relevant to the decision problem. NICE appraisals of interventions used at second treatment line were not intended for inclusion in the utility review, despite their potential use to post-progression utility estimation and validation. In any case, the company made no conclusions about their findings or their content, and progression based utility estimation was not the method selected for the

			base case.

Issue 10 EMA Licence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4.3; page 22 of the ERG report states: "Pembrolizumab in combination is modelled to a stopping-rule of two years which may not reflect the ultimate license specification." Section 1.4.6; page 24 of the ERG report states: "Pembrolizumab was costed according to the [expected] license dosing at first and second-line" "By [expected] license patients receiving pembrolizumab are to be treated until disease" Section 5.2.2.3; page 214 of the ERG report states: "This may not reflect the ultimate licence of pembrolizumab for this indication." Section 5.2.2.3; page 215 of the ERG report states: "Pembrolizumab in combination is modelled to a stopping-rule of two	Please correct text to reflect approved licence.	The licence for pembrolizumab in combination with pemetrexed and platinum-containing therapy is now approved.	Thank you for raising this issue. Whilst these are not factual errors at the time of writing, this new information has come to light so we are happy to make this amendment in the light of new information.

years. This may not reflect the ultimate license specification."			

Issue 11 2nd line treatment in KN189

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4.5; page 24 of the ERG report states: "Notably, pembrolizumab was heavily taken-up at second-line in the SoC strategy, helping to equalise costs with the strategy of pembrolizumab in combination at first-line (72% uptake in those who discontinue first-line and go onto receive second-line, 56.5%)"	Suggested new text on page 24 as follows: (56.5% of patients in the SoC arm receive second line treatment as per KEYNOTE-189, [redacted] of which receive pembrolizumab monotherapy)"	Provides more clarity to the reader.	Thank you for raising this issue. This is not a factual error but is a reasonable request, so we have made the amendment as suggested.

Issue 12 ToT for Pembrolizumab combination

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4.6; page 24 of the ERG report states: "However, in the model and in the key trial KEYNOTE-189, a stopping two-year rule was implemented. In the PC strategy 14% of patients remained on treatment after this point (after approximately 85 weeks or 1.6	A 2-year stopping rule has previously been accepted by NICE and NHS England for pembrolizumab appraisals whose KEYNOTE trials had a stopping rule defined in their protocol. The KEYNOTE-189 trial protocol has pre-specified a maximum treatment duration of 2 years or 35 cycles. The model predicts 11.8% of patients will be on pembrolizumab treatment at 2 years, and cease treatment with pembrolizumab after. However, the 14% refers	The comment has the potential to confuse readers.	Thank you for raising this issue. The statement has been clarified with the use of additional detail. "…in the model and in the key trial KEYNOTE-189, a stopping two-year rule was implemented. In the PC arm of the trial 14% of patients

years)."	to patients on treatment at the latest data cut, at 85 weeks or 1.6 years in the KEYNOTE-189 trial. We believe the comment is misleading and should be rephrased or removed.		remained on treatment after this point (latest data cut: after approximately 85 weeks or 1.6 years). In the model 11.8% of patients in the PC strategy remained on treatment at the 85 weeks, but neither costs nor benefits were included for this subset of patients."

Issue 13 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4.6; page 25 of the ERG report states: "This could lead to a small underestimation of the ICERs. Interruption of maintenance was 3.6% for SoC and 12.2% for SoC"	Please write "PC" in place of the incorrect "SoC".	"SoC" has been incorrectly written for "PC".	Thank you for raising this issue. We are happy to make this amendment.

Issue 14 Correction for quoted LYs and QALYs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4.9; page 26 of the ERG report states: "Similarly, LYs and discounted QALYs gained for SoC are lower in the company analysis (2.5 and 1.81) than the ERG adaptation (1.74 and 1.22)."	Please amend the text to the following: "Similarly, LYs and discounted QALYs gained for SoC are lower in the company analysis (**1.34 and 0.92**) than the ERG adaptation (1.74 and 1.22)."	The figures quoted are representative of MSD's estimated LYs and QALYs for pembrolizumab combination, not for SoC.	Thank you for raising this issue. We are happy to make this amendment.

Issue 15 PFS extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.4; page 221 of the ERG report states: "The company described that this also meant that full parametric curves could not to be fitted (MSD CS Appendix L), but it is unclear whether the curves were fitted to the KM data from week 0 until the PFS cut-off point (at 21 weeks, in the base case) or between week 6 and the cut-off point."	Please amend the text to the following: "The company described that this also meant that full parametric curves could not be fitted (MSD CS Appendix L), however KM data was used during the first 21 weeks followed by extrapolating using a Weibull distribution."	Incorrect translation from company submission, please see page 127 of company submission.	Thank you for raising this issue. This is not an incorrect translation of what has been written but a comment on the first clause of the sentence quoted from the company's submission, that the parametric curves have not been fully fitted to the data. It is unclear from the company's submission to which portion of the data the curves were fitted. Having received the R code and replicated the company's results, we know that the data of patients who had not progressed nor died by week 21 in the trial were used for fitting the distributions used in the company's base case. However, from reading the submission alone, one could receive the impression that only the trial data on progression up until week 21 were used in the company's base case, both directly (in the first 21 weeks of the modelled time horizon) and to fit the distributions (to be used for extrapolation beyond 21 weeks

			in the model). The second clause of the sentence quoted from the company's submission – referring to the model cycle beyond which the parametric curve has been used for extrapolation – has been addressed in the subsequent sentence in our report: "*Either way, the KM data has been used directly up until the cut-off point and the fitted curve for extrapolation beyond it.*" We will rewrite the previous sentence so that the reader is aware in this section of our report (it is mentioned later in chapter 6) of which portion of the data was used for fitting the curves, while still saying that we think that this is unclear in the company's submission.

Issue 16 Background mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.7; page 222 of the ERG report states: "No adjustment of the extrapolated period was made for increasing mortality from other	Please remove reference to no adjustment being made for the presence of background mortality.	As per Table 81 on page 160, general population mortality was accounted for within the company submission. (Therefore, please note that the	In Table 84 on page 158, the company write that general population mortality is accounted when modelled mortality is lower. This is not gender-matched to the model

causes as age increases, and no justification for its omission was provided." Section 5.4; page 257 of the ERG report states: "No adjustment of the extrapolated period was made for increasing mortality from other causes as age increases."		further implementation of background mortality can result to double counting.)	population, as suggested: the age-specific sex ratio of the general population is used to determine average age-specific expected survival for the general population, and neither the sex ratio of the trial population nor of the modelled population are considered. The ERG explain how this has been implemented in section 5.2.6.5 of our report (also on page 222): modelled OS has been capped by the survival rate for the general population. This cap is necessary, since it would be unreasonable for the modelled age-specific survival rates of metastatic NSCLC patients to be greater than those of the general population, but it is not equivalent to applying background mortality, which the subject of section 5.2.6.7. This is well demonstrated in the company's base case, in which capping for the survival rate of the general population makes no difference to the modelled OS estimates or to any of the other results (referred to in section 5.2.6.5), as would be the case when applying background mortality. This is

			despite the choice of a distribution for OS with a hazard rate that is constant with respect to time. The time horizon of the model is 20 years but OS is only observed in KEYNOTE-189 for under 89 weeks, hence the need to increase modelled mortality to reflect decreased survival with age due to other age-related conditions, which is unlikely to have been captured in the trial data. No such adjustment has been made in the company's model and hence our comments in sections 5.2.6.7 and 5.4. Applying background mortality and the survival cap does not result in double-counting: the former adjusts for increasing mortality from other causes as age increases, the latter ensures that the mortality rate does not fall below that of the general population and is applied because of the patients' condition, not to capture the effect of aging. Indeed, removing the survival cap from the ERG model would make no difference to the results because, having

			adjusted for background mortality, the mortality rate of the modelled population is greater than that of the general population at each time point.

Issue 17 Probabilistic Sensitivity Analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 92 on Page 246 of the ERG states: "Base case result of main comparison for overall population (probabilistic) [Company results]"	Please amend to show results presented in Table 88 on page 165 of the company submission.	Please present correct PSA results.	Thank you for raising this issue. We are happy to make this amendment.

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

A Single Technology Appraisal

Issues arising from fact check

This report contains those pages in the ERG report that contain amendments.

pemetrexed, due to heterogeneity in the ITC analyses, and the lack of evidence presented for other outcomes (including safety).

1.4 Summary of cost-effectiveness evidence submitted by the company, with ERG critique

1.4.1 Search for and review of evidence

The company included no cost-effectiveness studies in their search for evidence. It was not necessary to limit the inclusion of cost-effectiveness studies to the UK setting since valuable information relating to health benefits, model structure, and model assumptions, can be sought from other settings. They included seven studies and one update of potential use to the utility analysis, and 11 UK NICE technology appraisals of possible relevance. The objective of the utility search specified only interventions used at first treatment line, but the HRQoL of a second-line population could inform utility scores post-progression in this model population. Indeed TA520, the appraisal of atezolizumab in adults with locally advanced EGFR or ALK-positive NSCLC who have already had chemotherapy, was included. Whilst TA428, an appraisal of pembrolizumab at second-line in the relevant population, was omitted but later used as supportive evidence. Four studies of potential use to the cost analysis were included, alongside evidence in appraisals mentioned before. Two of the four did not meet the pre-specified inclusion criteria, including a UK HTA which was used as a secondary source for modelling. Generally, included studies were relevant to the decision problem, but multiple sources of evidence used to inform quantities of health resource use were too old to accurately resemble current NHS practice.

1.4.2 The decision problem and reference case

The clinical evidence submitted by the company, and used in the cost-effectiveness analysis, matched the patient population described in the scope, notwithstanding the specification of EGFR and ALK negativity. The key trial informing the estimates of relative effectiveness of the main comparison, PC versus SoC, was KEYNOTE-189, a phase III RCT. The company provided an additional analysis of cost-effectiveness according to PD-L1 expression; and of a comparison with pembrolizumab monotherapy in strong expressers of PD-L1 only. The intervention described in the CS and modelled in the cost-effectiveness analysis matched the specification of the scope. NICE clarified that the use of pemetrexed maintenance following PC was appropriate. The comparators described in the CS aligned to the scope, except in an area of ambiguity, where pemetrexed maintenance was excluded

from the pair-wise comparisons with platinum plus vinorelbine, gemcitabine, docetaxel, and paclitaxel; the same too with the pembrolizumab monotherapy comparison. The first listed comparator, pemetrexed plus platinum, was appropriately described as the current standard of care (SoC) in the NHS in England and Wales. Therefore the pairwise comparison of PC and SoC is the main focus of the evaluation. Outcomes included in the CS did not match the outcomes described in the scope, since the model included and heavily relied on the time-on-treatment outcome, and this was not included in the systematic search and review. KEYNOTE-189 was again the single source of evidence informing this outcome. This was reasonable for the main comparison and sub-group analysis given the evidence identified in the SLR (Evidence for pembrolizumab combination is KEYNOTE-189 and KEYNOTE-021G only). The scope included the PFS outcome, the primary outcome of KEYNOTE-189, but the company did utilise PFS in their base case cost-effectiveness analysis. However, advice received by the ERG supported the company's implicit reasoning for its exclusion: that the OS-based time-to-death method for utility estimation, and time on active treatment approach for cost estimation, were best suited to the modelling of the population. The company did not identify any equity or equality issues in their submission; it did make the case for the appraisal to be given an end-of-life classification.

1.4.3 The model structure

The structure departs from the standard three health state partition survival model: it uses four states to estimate utility, based on time-to-death; costs are aligned to treatment intent; progression status does not play any role in the base case. This is not a reflection of previous models in NSCLC except the MSD model presented in NICE TA531 for pembrolizumab monotherapy for untreated PD-L1 positive metastatic NSCLC. There is some clinical merit in the structure, and in the view of the ERG and its clinical advisors it represents a reasonable simulation, with the drawback of the loss of the PFS link between costs and benefits. Pembrolizumab in combination is modelled to a stopping-rule of two years which does not reflect the license specification. Modelled costs are limited to the inclusion of second-line therapy costs and benefits since those of subsequent lines of anti-cancer therapy are assumed zero. This is a simplification since some patients in KEYNOTE-189 received third, fourth and fifth lines of anti-cancer therapy.

1.4.4 Treatment effect

The estimated effectiveness of the pembrolizumab combination treatment strategy and of the main comparator were based on the data from the relevant treatment arms of the KEYNOTE-189 clinical trial, using the November 2017 data cut. OS and PFS have been modelled by fitting parametric distributions to parts of the KM data, although PFS is not

pembrolizumab monotherapy (also an untreated population). The approach is not historically standard but clinical advice elicited by the ERG supports an approach which correlates HRQoL closer to OS/nearing death than the occurrence of first progression.

The structure of the cost analysis followed the use of active therapies, which was limited to first- and second-line anti-cancer treatment. Thereafter resources were modelled to resemble consumption aligned to non-curative intent, signified by a reduction in monitoring and an increase in community-based care (disease management costs increased after active therapy). Active treatments included the immunotherapies and systemic cytotoxic chemotherapy. Second-line treatments were attributed a fixed course. Notably, pembrolizumab was heavily taken-up at second-line in the SoC strategy, helping to equalise costs with the strategy of pembrolizumab in combination at first-line (56.5% of patients in the SoC arm receive second line treatment as per KEYNOTE-189, [redacted] of which receive pembrolizumab monotherapy). Dose intensity adjustment was small and accounted only for interruptions not dose reductions. For this previously untreated population, subsequent lines of active therapy are available after first progression and these would require similar supportive resources as first-line options; so a costing approach based on time on active anti-cancer treatment, rather than progression, is reasonable but the common link to PFS between benefits and costs is lost.

1.4.6 Resources and their cost

Pembrolizumab was costed according to the licensed dosing at first and second-line: a 200mg fixed dose administered by IV infusion every three weeks. The unit cost of 200mg was £5,260. A tentative [redacted] price [redacted] was also tested by the ERG. All other drug acquisition unit costs were taken from the preferred sources appropriately. Similarly, the posology of non-fixed dose therapies was sourced in the first instance from KEYNOTE-189, then the drug SmPC. In a conservative assumption, vial sharing was implemented, meaning all comparator drugs carboplatin, cisplatin, gemcitabine, vinorelbine, docetaxel, and paclitaxel cost less, which impacts more profoundly on the SoC strategy. The base case carboplatin-cisplatin mix was [redacted] near opposite to UK practice, but ICERs were not sensitive to inaccuracy here. The drug acquisition cost per administration was [redacted] for pembrolizumab combination (prior to the maintenance period), and £1,420 for SoC. According to the license, patients receiving pembrolizumab are to be treated until disease, or discontinuation due to adverse events, inter-current illness, protocol compliance, or investigator or patient preference. However, in the model and in the key trial KEYNOTE-189, a stopping two-year rule was implemented. In the PC arm of the trial 14% of patients remained on treatment after this point (latest data cut: approximately 85 weeks or 1.6 years). In the model 11.8% of patients in the PC strategy remained on treatment at the 85 weeks,

but neither costs nor benefits were included for this subset of patients. For the period before, a parametric distribution was fitted to time-on-treatment KM curves using AIC and BIC goodness-of-fit statistics and visual inspection criteria; resulting in exponential and Weibull selections for PC and SoC strategies respectively. The modelled four cycles Q3W (12 weeks) of platinum-based therapy matched the protocol of KEYNOTE-189 and clinical practice in England (average number of cycles received in KEYNOTE-189 was 3.5 and 3.6 in SoC and PC strategies respectively. In the model 3.6% and 4.4%, respectively, of expected administrations were not received due to treatment interruption). The modelling of drug administration is broadly satisfactory: unit costs for administration were appropriately sourced based on setting and complexity; and summed to reflect multiple drug regimens (in any case, ICERs are insensitive to this aspect of costing). Pemetrexed maintenance, featuring in both PC (87.8%) and SoC (96.4%) strategies, was started from week 13. Only in the PC strategy did pemetrexed treatment discontinuation inform ToT, meaning that maintenance costs for a subset of patients in this strategy (those who discontinue pembrolizumab for a reason other than progression but continue maintenance therapy) are not included. This could lead to a small underestimation of the ICERs. Interruption of maintenance was 3.6% for SoC and 12.2% for PC, based on KEYNOTE-189. As mentioned, the cost of disease management varied according to active treatment status; a reasonable demarcation of resource change. But limitations in cost analysis arose from secondary sources of evidence used to populate utilisation rate estimates, which in some cases drew on observations from 12 or more years ago. However, changing all rates by +/-10% does not significantly impact the ICERs. A one-off cost was applied to all patients at the time of death for all strategies, which represented a reasoned quantity. In respect to second-line treatment, the uptake, the distribution of type, and unit cost determined a one-off cost. The company included adjustments to published figures of uptake and distribution which could not be verified, and ICERs are sensitive to these inputs. Type, patient frequency, and unit cost of serious adverse event determined a simplified one-off cost which did not capture events when they occurred in a patient more than once. Otherwise the method was reasonable since safety profiles were not much different between strategies, and ICERs were not sensitive to variation in those profiles.

1.4.7 Company results

The ICER for PC versus SoC was £46,568 per QALY gained (deterministic analysis); and £46,674 per QALY gained (probabilistic analysis) Probabilistic analysis gave the probability of PC being the most cost-effective strategy as 58%. The mean incremental LYs gained per person were 1.16, and discounted incremental QALYs gained were 0.89 over the model

ERG estimates in TA531 (9.6% and 1.5%), the appraisal of pembrolizumab in untreated advanced NSCLC; and low compared to our ERG too (8.6% and 3.4%). Similarly, LYs and discounted QALYs gained for SoC are lower in the company analysis (1.34 and 0.92) than the ERG adaptation (1.74 and 1.22). If ERG OS estimates are to be preferred, then these estimates of benefit follow.

1.4.10 End-of-life

PC in this comparison and setting probably fulfils the criteria for end-of-life status (ERG estimate 22.73 months mean expected survival with SoC). Whilst estimates of the extension to life are not robust the ERG estimates extension of 20.96 months.

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

- The SLR conducted by the company is generally of good quality, using methodology that is likely to have captured the evidence base for this clinical area
- The company provides clinical effectiveness evidence for the technology of interest from 2 RCTs, which compare the technology against an intervention commonly used in the UK to treat this patient group.
- Evidence from the 2 RCTs evaluating the technology of interest is of high quality for key clinical outcomes (OS, PFS, ORR, safety).
- The main ITC includes all relevant interventions for this patient group, and is broadly appropriate with relevant NICE DSU TSD recommendations.
- An additional ITC comparing the technology of interest against current treatment for a sub-population of patients is presented, and conducted using IPD and patient matching methods, which were judged to be of high quality.
- The direction of the effect for the technology of interest is consistent between the 2 RCTs presented.

1.5.2 Weaknesses and areas of uncertainty

- Direct head-to-head trials were not available for the pembrolizumab combination in comparison with most other interventions available for this treatment group, including platinum and gemcitabine and platinum and vinorelbine, which are commonly used in the UK.

Table 1); but neither is this detail included in the scope. However, the ERG confirmed with NICE that this inclusion was reasonable and allowable; and it also aligned with the key source of evidence.

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment. Pembrolizumab was first granted marketing authorisation in May 2015 by the European Medicines Agency. Pembrolizumab should be administered as an intravenous infusion over 30 minutes every 3 weeks. The recommended dose is 200 mg for NSCLC that has not been previously treated with chemotherapy, when administered as monotherapy or in combination with pemetrexed and platinum chemotherapy (MSD CS Section B.1.2, Table2, page 16).

The indication for pembrolizumab in this evaluation is in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations (MSD CS B1.2). The brand name for pembrolizumab is KEYTRUDA®.

ERG comment:

- The intervention described in the CS matched the intervention described in the final scope, after clarification from NICE regarding the use of pemetrexed maintenance following PC.
- The proposed indication for the intervention matched that of the model, but differed to the scope in its limitation to adults whose tumours have no EGFR or ALK positive mutations.

3.3 Comparators

In their definition of the decision problem the company describe the same list of comparator treatment strategies as defined in the scope; in which two types or regimens were included for whole population evaluation.

1. 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.

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- adverse effects of treatment (AEs)

- health-related quality of life (HRQoL)

The company erroneously omitted DoR from their definition of the decision problem (CS; Table 1). In the company's review of clinical evidence, DoR was reported only for trials evaluating pembrolizumab combination therapy (see section **Error! Reference source not found.**), and DoR was not considered in the economic evaluation. Evidence for DoR could help in the consideration of the extent of loss of effect following discontinuation. The company consider 'waning' of effect in a scenario analysis.

In their base case model the company do not include PFS. Although described as a 'partitioned-survival' method with three health states of pre-progression, post-progression, and death; the company model is in fact driven by OS and ToT. Previous economic evaluations of interventions for this population use, in a classic approach, the PFS outcome to estimate the number of people in pre-progression and post-progression health states at any given time (with the two states representing an exclusive cost and utility). The company depart form this in two main respects: utility is estimated as a function of time from death; and costs are estimated according to treatment intend – whether or not active (anti-cancer) therapy is received (a function of ToT). The company justify the exclusion of PFS by virtue that TTD (using OS) considers more health states (4 versus 2 in this case), which offers a better data fit to declining HRQoL in the terminal phase of the disease.

Advice elicited by the ERG from clinical experts supported the underlying company assumption: that the HRQoL of patients in this population correlated better with time from death than first progression status.

The safety outcome was explored in full only for the PC and SOC, not the alternative comparators. Adverse events included in the economic evaluation of this main comparison were appropriately selected from KEYNOTE-189 (only). Data regarding the proportion of patients experiencing at least one event was included, but more detailed data about the number of events per patient, and the time of the event, was not included or presented. This led to some reasonable simplification, with subsequent loss of accuracy in the derivation of utilities and costs.

ERG comment:

- Outcomes included in the CS did not match the outcomes described in the final scope. The base case cost-effectiveness analysis included the time-on-treatmen (ToT) outcomes, this was not included in the systematic review. However, the us

  in the size of the effect between the two studies, as well as the width around the confidence intervals of the effects, suggests that there is some uncertainty around the size of the effect.

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Table 1 Clinical Efficacy: Pembrolizumab Combination Therapy vs. Platinum + Pemetrexed

Outcome*	**KEYNOTE-189**		**KEYNOTE-021G**	
	Pembrolizumab Combination (N=410)	Control (N=206)	Pembrolizumab Combination	Control
	Final follow-up: median 10.5 months (range 0.2 - 20.4)		Final follow-up: median 23.9 months (range 0.8 – 35.1)	
Absolute Survival	[redacted] Extracted from the K-M method (95% CI): 6 months: [redacted] 9 months: [redacted] 12 months: 69.2% (64.1 – 73.8)	[redacted] Extracted from the K-M method (95% CI): 6 months: [redacted] 9 months: [redacted] 12 months: 49.4% (42.1 – 56.2)	NR	NR
Relative survival (unadjusted)	NR		HR 0.56 (95% CI 0.32 – 0.95)≠∞	
Relative survival (adjusted)	HR 0.49 (95% CI 0.38 – 0.64)^			
Median time to death (months; 95% Cis)	Not reached	11.3 (8.7 – 15.1)	Not reached (24.5 – NR)	21.1 (14.9 – NR)
Additional analyses	Events per 100 person months: 2.9	Events per 100 person months: 5.8	NR	NR

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up unless otherwise stated. ^Covariates: PD-L1 status (Tumour Proportion Score [TPS] ≥1% <1%), smoking status (never vs former/current), and choice of platinum (cisplatin vs

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- The ERG considered that the size and consistency in the relative effect of pembrolizumab combination therapy across subgroup analyses was indicative of a clinical benefit for OS across the patient population.

Table 2 Clinical Efficacy of Pembrolizumab Combination Therapy: OS Subgroup Analyses

Outcome*	**KEYNOTE-189**
	HR (95% CI)^
PD-L1: <1%; ≥1%	<1%: 0.59 (0.38 – 0.92) ≥1%: 0.47 (0.34 – 0.66)
PD-L1: <50%; ≥50%	<50%: 0.57 (0.41 – 0.79) ≥50%: 0.42 (0.26 – 0.68)
PD-L1: <1%; 1-49%; ≥50%	<1%: 0.59 (0.38 – 0.92) 1-49%: 0.55 (0.34 – 0.90) ≥50%: 0.42 (0.26 – 0.68)
Age: < 65; ≥ 65	< 65: 0.43 (0.31; 0.61) ≥ 65: 0.64 (0.43; 0.95)
Age: < 65; 65-74	< 65: 0.43 (0.31; 0.61) 65-74: 0.51 (0.32; 0.81)
Age: <75	0.43 (0.33; 0.57)
ECOG: 0; 1	0: 0.44 (0.28; 0.71) 1: 0.53 (0.39; 0.73)
Gender: Male, female	Male: 0.70 (0.50; 0.99) Female: 0.29 (0.19; 0.44)
Ethnicity	White: 0.46 (0.35; 0.60)
Region: US; non-US	US: 0.41 (0.22; 0.74) Non-US: 0.52 (0.39; 0.69)
Region: Eu; Ex-EU	EU: 0.56 (0.40; 0.79) Non-EU: 0.38 (0.25; 0.58)
Smoker: Never; Former/Current	Never: 0.23 (0.10; 0.54) Former/Current: 0.54 (0.41; 0.71)
Brain metastasis: yes; no	Yes: 0.36 (0.20; 0.62) No: 0.53 (0.39; 0.71)
Platinum chemo: cisplatin; carboplatin	Cisplatin: 0.41 (0.24; 0.69) Carboplatin: 0.52 (0.39; 0.71)

*Note that all outcomes are reported as assessed in the ITT population and at final follo
unless otherwise stated. ^Based on Cox regression model with treatment as a covariate

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4.2.4.1.2 Progression-Free Survival (PFS)

The PFS of patients following treatment with pembrolizumab combination therapy in KEYNOTE-189 and KEYNOTE-021G is reported in Table 3.

As noted in Section **Error! Reference source not found.**, progression was evaluated using RECIST 1.1 criteria based on independent, blinded radiological review in both KEYNOTE-189 and KEYNOTE-021G. Both trials demonstrated a similarly large beneficial effect of pembrolizumab combination therapy for PFS relative to control; between a 47% (KEYNOTE-021G) and 48% (KEYNOTE-189) reduction in the risk of disease progression or death. Confidence intervals indicated some uncertainty around the size of the effect, however were consistent with a statistically significant, and clinically beneficial, effect of pembrolizumab combination therapy relative to control. The CS reports estimated rates of PFS following treatment initiation (based on Kaplan-Meier analysis), which indicate a statistically significant beneficial effect in the risk of PFS for pembrolizumab combination therapy at 3-, 6-, 9-, and 12-months from baseline in KEYNOTE-189 (also see **Error! Reference source not found.**). Both trials also demonstrated a longer median duration of PFS for patients receiving pembrolizumab combination therapy compared to control; although the difference was not statistically different for patients in KEYNOTE-021G. The data were also consistent with PFS outcome data as assessed by unblinded, investigator review (CS p. 65).

ERG comment:

- Overall, both trials demonstrate a clinically significant benefit of pembrolizumab combination therapy for PFS in this population group. While 95% Cis indicate that there may be some uncertainty in the size of the effect, the data are consistent with the conclusions of the CS.

Table 3 Clinical Efficacy of Pembrolizumab Combination Therapy: PFS

Outcome*	KEYNOTE-189		KEYNOTE-021G	
	Pembrolizumab Combination (N=410)	Control (N=206)	Pembrolizumab Combination (N=60)	Control (N=63)
	Final follow-up: median 10.5 months (range 0.2 - 20.4)		Final follow-up: median 23.9 months (range 0.8 – 35.1)	
PFS	[redacted] Patients progression-free and alive¥: (3 months: [redacted] 6 months: [redacted] [redacted] 9 months: [redacted] [redacted] 12 months: 34.1% (28.8 – 39.5)	[redacted] Patients progression-free and alive¥: 3 months: [redacted] 6 months: [redacted] [redacted] 9 months: [redacted] [redacted] 12 months: 17.3% (12.0 – 23.5)	NR	NR
Relative PFS (unadjusted)	NR		HR 0.53 (95% CI 0.33 – 0.86)≠	
Relative PFS (adjusted)	HR 0.52 (95% CI 0.43 – 0.64)^		NR	
Median PFS (months; 95% Cis)	8.8 (7.6 – 9.2)	4.9 (4.7 – 5.5)	24.0 (8.5 – NR)	9.3 (6.2 – 14.9)
Additional analyses	Events per 100 person months: [redacted]	Events per 100 person months: [redacted]	NR	NR

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated. ¥ Extracted from the K-M method (95% CI).

Source: MSD CS pages 29, 58-66, 94-95

The company provides a Kaplan-Meier plot depicting PFS in both arms of the KEYNOTE-189 trial, which is reproduced below (**Error! Reference source not found.**)

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4.2.4.1.5 Additional Outcomes

The company further reported the time to response (TTR) for patients treated in the KEYNOTE-189 trial; these data are summarised in Table 4. The time to response was comparable between patients receiving Pembrolizumab Combination therapy and those

receiving platinum and pemetrexed. Time to response data was not reported for patients in KEYNOTE-021G.

Table 4 Clinical Efficacy of Pembrolizumab Combination Therapy: TTR

Outcome*	**KEYNOTE-189**	
	Pembrolizumab Combination Therapy (N=195)	Control (N=39)
Mean (SD)	[redacted]	[redacted]
Median (Range)	2.2 (1.1 – 11.1)	1.4 (1.2 – 11.1)

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated.
Source: MSD CS page 71

4.2.4.2 Patient-Reported Outcomes/Health-Related Quality of Life

Health-related quality of life (HRQoL) following treatment with pembrolizumab combination therapy is reported in the CS for patients in the KEYNOTE-189 trial; no patient-reported outcome data is reported for patients in KEYNOTE-021G. Evidence from KEYNOTE-189 is summarized in **Error! Reference source not found.**.

HRQoL in the KEYNOTE-189 trial was assessed using EQ-5D VAS, EORTC-QLQ C30, and EORTC QLQ-LC13; however only data for EQ-5D VAS was provided in the CS. Not all patients completed HRQoL measures, and a substantial number of patients were missing from the analysis. Patient attrition increased over time, at a similar rate between arms (although attrition was somewhat higher in the control arm). By the 21 week follow-up, data was only available for 61.0% of patients in the pembrolizumab combination arm, and 51.1% of patients in the control arm.

Based on the raw HRQoL scores, there was no statistically significant difference in the change in HRQoL in the two arms between baseline and 12 and 21 weeks follow-up. However, following adjustment for covariates (treatment by study visit interaction, PD-L1 ≥ 1% vs. <1%, platinum chemotherapy, and smoking status) and imputation to replace missing data, the analysis demonstrated a statistically significant difference in change in HRQoL between baseline and 12 and 21 weeks. This difference was clinically meaningful, based established minimally important difference (MID) criteria for EQ-5D VAS (12). The differe

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4.2.4.3 Safety

The CS (pp.98-108) provides information about the safety profile of pembrolizumab combination therapy based on a full-text scholarly publication (8) and the CSR (13) for

KEYNOTE-189. Information about the safety profile of this therapy using data from KEYNOTE-021G (9, 14) is provided in the CS Appendix (Appendix F, pp. 151-154).

The ERG verified the safety data included in the CS for KEYNOTE-189 against the full-text scholarly publication and the CSR, and found no apparent discrepancies. It is stated (p.98) that adverse events (AEs) were collected up to 30 days after the last dose of study medication and serious adverse events (SAEs) were collected for up to 90 days. The ERG considered this a sufficient period to capture the majority of drug-related events, as it is recognised that immunotherapy toxicity may occur weeks or months after treatment is discontinued. The ERG considered that the safety data comparing pembrolizumab combination with control in the pembrolizumab trials are thoroughly reported in the CS. However, the ERG also noted that considerable portions of the adverse event profile are based on the confidential CSR rather than on publically available data.

Adverse events (AEs) were common in both the active and control arms of KEYNOTE-189, occurring overall in 99.8% of patients in the pembrolizumab combination arm and 99% of patients in the control arm (CS, p.100). Drug-related AEs (91.9% vs 90.6%), grade 3-5 AEs (67.2% vs 65.8%) and serious adverse events (SAEs, [redacted]) were all common in both arms, although slightly more common in the pembrolizumab combination arm. The greatest difference in AEs between pembrolizumab combination therapy and control occurred for drug-related grade 3 to 5 AEs ([redacted] and drug-related SAEs ([redacted] whereby participants in the pembrolizumab combination group had an [redacted] incidence respectively of having a drug-related grade 3 to 5 AE than participants in the control arm. The CS states (p.100) that "the adverse event profile observed for pembrolizumab combination and control arms were generally consistent with the known safety profiles of the respective therapies administered". The ERG considered this to be a reasonable assessment.

The CS states (p.100) that "higher rates of discontinuation of any drug within the treatment regimen due to an AE, irrespective of AE category, occurred in the pembrolizumab combination compared to the control (27.7% vs 14.9%)". The ERG consider this to be accurate. However, the ERG disagree with the company's interpretation of the data regarding discontinuation of all drugs due to an AE: the CS states that "importantly, the rate of discontinuation of all drugs due to an AE was similar across both trial arms ([redacted]

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among patients on pembrolizumab combination than controls ([redacted] Two drug-related SAEs were reported with incidence of ≥5% in one or more treatment groups: febrile neutropenia and anaemia. The CS states (p.106) that "the most commonly reported drug-related SAE was febrile neutropenia, the frequency of which was higher in the pembrolizumab combination compared with the control (pembrolizumab combination: [redacted] %; control: [redacted]

%)". [redacted] There were a total of 39 deaths due to an AE in the trial (p.106) – 27 in the pembrolizumab combination arm and 12 in the control group. The CS notes (p.106) that "the proportion of deaths due to AEs was similar between the treatment groups (pembrolizumab combination: 6.7%; control: 5.9%)". However, the ERG note that this value was numerically greater for pembrolizumab combination, and that the 0.8% point difference represents a 14% increase.

Table 5 KEYNOTE-189 Patients with drug-related SAEs by decreasing incidence (incidence of ≥5% in one or more treatment groups)

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	405		202		607	
with any type of adverse event	[redacted]					
with no adverse events						
Febrile neutropenia						
Anaemia						

Source: MSD CS Document B Table 57 page 106

The incidence of AEs of special interest was substantially higher for patients receiving pembrolizumab combination therapy than controls (22.7% vs 11.9%, **Error! Reference source not found.**). The most common AEs of special interest were hypothyroidism (overall 5.3%, active pembrolizumab combination 6.7%, controls 2.5%), pneumonitis (overall 3.8%, active pembrolizumab combination 4.4%, controls 2.5%) and hyperthyroidism (overall 3.6%, active pembrolizumab combination 4.0%, controls 3.0%). All of these three most common AEs were greater for pembrolizumab combination therapy than controls.

baseline characteristics for the full sample of patients in KEYNOTE-024 was reported in the CS; however, details of important prognostic markers at baseline for patients with PD-L1 ≥50% were reported in further detail. Based on the characteristics reported, there was some variation in key markers between arms and between the two trials. However, as appropriate population matching techniques were used to control for key prognostic markers between and within studies, the ERG considered that this will have reduced the impact of any differences at baseline on the outcomes of the analyses.

4.3.4.2.3 Intervention Characteristics

No information regarding dosing, administration, or background care used in KEYNOTE-024 was reported in the CS. The ERG referred to the previous TA(NICE), 2018 #77} for pembrolizumab monotherapy in this patient population, and confirmed that dosing of pembrolizumab was consistent with the licence and with other trials included in the SLR. Following population-matching techniques, the proportion of patients receiving each platinum therapy was comparable between trial arms, and between KENYOTE-024 and KEYNOTE-189. Details of background care and length of treatment were not available for the patient cohort included in this analysis.

ERG comment:

- Dosing and administration of pembrolizumab was consistent with licencing indications and other trials in the SLR. There was insufficient information provided in the CS to evaluate the comparability of the length of treatment and background care administered to patients with PD-L1 ≥50% in KEYNOTE-024 and KEYNOTE-189.

4.3.4.2.4 Outcome Assessment

PFS and OS were the only outcomes for KEYNOTE-024 reported in the CS; details of outcome assessment used in KEYNOTE-024 are summarised in **Error! Reference source not found.** below, alongside details of the methods used in KEYNOTE-189. Outcome definitions are matching between the two trials, and both employ time-to-event methodology to estimate treatment effects (HR), and use the ITT population datasets. For KEYNOTE-024, data is reported both for the full trial population (appendices p.94) and in a smaller sample of patients following weighting of outcome data to match sample population characteristics with the KEYNOTE-189 sample. HR analyses in the trials are adjusted for covariates, although the covariates used in the analyses differ between trials: KEYNOTE-024 effects are adjusted for geographic region (East Asia vs. non-East Asia) and ECOG status (0 or 1), and

KEYNOTE-189 effects are adjusted for PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin)

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comment on findings for the same reason, but notes that the final filter (UK studies only) excluded all 50 of the previously included cost-effectiveness studies.

ERG comment:

- No evidence was included. It was not necessary to limit the inclusion of cost-effectiveness studies to the UK setting since valuable information relating to strategy benefit, model structure, and model assumptions, can be garnered from other settings.

HRQoL evidence

The company described in detail their search method and extracted and presented data from 7 studies and 11 technology appraisals but did not make conclusions in the review of HRQoL evidence.

The company identified the key NICE technology appraisal TA447 (published June 2017): the cost effectiveness analysis of pembrolizumab for the first line treatment of metastatic NSCLC in patients whose tumours strongly express PD-L1. However there was inconsistency in the inclusion implementation. Whilst the objective specified first-line treatments, TA530, an appraisal of appraisal of atezolizumab in adults with locally advanced EGFR or ALK-positive NSCLC who have already had chemotherapy, was included. Whilst TA428, an appraisal of pembrolizumab at second-line in the relevant population, was omitted but later used for supportive evidence. The ERG believe the HRQoL and utility scores of people receiving second-line treatment could be used inform model inputs or validate model outputs. Therefore two other population/intervention relevant appraisals which were not identified by the search were:

- Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428), published January 2017.(62)
- Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531), published July 2018.(63)

Since the most recent search update was carried out on 2nd April 2018, TA531 would not be captured.

ERG comment:

- Included studies were relevant to the decision problem.

- NICE appraisals of interventions used at second treatment line were not intended for inclusion in the utility review, despite their potential use to post-progression utility estimation and validation. In any case, the company made no conclusions about their findings or their content, and progression based utility estimation was not the method selected for the base case.

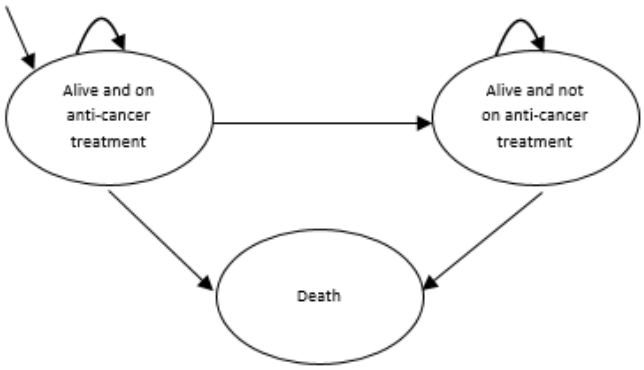
Cost and resource evidence

The company included and presented data from 15 sources (four UK studies and 11 NICE technology appraisals). The company did not identify NICE TA428 in their search.(62) The company conclude that the identified resource use and cost studies provided some useful information for the *de novo* cost-effectiveness model. In particular regarding the quantity and frequency of the use of resources, and the unit cost of AEs, disease monitoring and management. The company states that a limitation of the cost data identified from these studies was 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.

ERG comment:

- TA428 an appraisal of pembrolizumab at second-line in the relevant population was missed in the search but included within the modelling of costs.
- The company included in their economic model evidence from numerous studies/records, including from Brown(17) and Fleming(61) which were technically excluded using their prospective criteria for review.
- The company search for economic evidence omitted important relevant evidence which was later used in support of their economic evaluation. This suggests a lack of consistency in the prospective systematic identification and use of evidence used for the company economic evaluation.
- The company have not commented on appropriateness of use of those studies heavily depended on for their economic evaluation given the time at which the study data were collected and the backdrop of changing practices with the introduction of targeted immuno-therapies.

Figure 1: Actual model of the company base case in respect to the cost evaluation



At the point of first-line treatment discontinuation patients receive a further second-line of anti-cancer therapy. After second-line in the model, therapy is no longer considered active/anti-cancer, and at this point a second set of resources are applied.

Costs applied in a 'one-off' fashion, to the first model cycle, were the PD-L1 test cost, and those associated with the management of severe adverse events. The ERG note that the company applied PD-L1 test costs only to those patients who go on to receive pembrolizumab. Expert clinical opinion elicited by the ERG is that all patients with a new lung cancer diagnosis now routinely undergo tests for biological markers in the NHS, including the PD-L1 test; and the results are then used to help determine the treatment plan.

For patients in the pembrolizumab combination strategy pembrolizumab administration is modelled in three-weekly cycles from week 1 for up to two years. A two year stopping rule was modelled to reflect the design of KEYNOTE-189(8)). This does not reflect the licence of pembrolizumab for this indication. Pembrolizumab for the first 12 weeks combined with a fixed course of platinum-based chemotherapy and with pemetrexed (each for up to four cycles). In the model, pemetrexed maintenance therapy could then be commenced, but its discontinuation did not inform the time-on-treatment statistic (see section **Error! Reference source not found.**). Patients in the SoC strategy also received up to four cycles of platinum-based chemotherapy treatment. This was combined with 'upfront' pemetrexed and followed by pemetrexed maintenance therapy. In this strategy, the discontinuation pemetrexed maintenance did inform the time-on-treatment statistic.

5.2.2.4 Sub-group analysis

A sub-group analysis was conducted where the sub-populations were based on different levels of PD-L1 expression (≥50%, 1%≤TPS≤49% and <1% TPS). Otherwise approaches, underlying model assumptions, and estimates remained the same.

In KEYNOTE-189 patients were allowed by protocol to switch from the SoC ('trial chemotherapy' arm) to the pembrolizumab combination arm.(8) However, no adjustment in effect size was made for cross-over in the model. This approach was appropriate since alternative immune-therapy options are available as standard at second-line, and the cross-over effect in KEYNOTE-189 does to some degree approximate their benefit. For the sub-group of patients with <1% TPS there is no second-line immune-therapy option available, so in this case (only), adjustment for cross-over was included.

5.2.2.5 Comparison with platinum plus chemotherapy

Effect sizes were not derived from separately fitted parametric distributions but applied hazard ratios (gemcitabine, vinorelbine, docetaxel, paclitaxel) to the baseline performance of the PC strategy (see section **Error! Reference source not found.**).

ERG comment:

- The structure departs from the standard three health state partition survival model: it uses four states to estimate utility, based on the OS outcome, using a time-to-death approach; costs are aligned to treatment intent; progression status does not drive the base case.
- The structure has clinical merit, and in the view of the ERG represents a reasonable and appropriate simulation. There is precedence in MSD's previous submission for NICE TA531 (CDF Review).(63)
- Pembrolizumab in combination is modelled to a stopping-rule of two years. This does not reflect the license specification.
- Subsequent therapy is modelled only as far as second-line.

5.2.3 Population and sub-populations

5.2.3.1 Whole population evaluations

The NICE scope defines the population for this evaluation as *"Adults with untreated metastatic non-squamous NSCLC".(65)* The company go on to exclude people with a sensitizing EGFR mutation or ALK translocation, and specify untreated as no prior systemic chemotherapy treatment. Both refinements retain alignment with the expected licenced indication for pembrolizumab used in combination, and the populations from studies providing the clinical effectiveness evidence.

The main body of clinical effectiveness evidence for the main comparison, pembrolizumab combination versus pemetrexed in combination with carboplatin or cisplatin (SoC), was

5.2.4 Interventions and comparators

5.2.4.1 Intervention

The indication for pembrolizumab in this evaluation is in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations (MSD CS B1.2). The intervention is referred to by the company, and in this report, as pembrolizumab combination (PC).

The doses modelled were pembrolizumab (200mg fixed) plus cisplatin (75mg/m^2) and pemetrexed (500mg/m^2), or plus carboplatin (400mg) and pemetrexed (500mg/m^2). Pemetrexed maintenance (PM) when taken-up (cisplatin users only by license) was from week 13 (500mg/m^2). All drugs within the regimen were administered Q3W.

When used in subsequent lines of therapy, the dose of pembrolizumab remained fixed at 200mg.

5.2.4.2 Main comparator

The first comparator is the pemetrexed in combination with a platinum drug (cisplatin or carboplatin), with or without pemetrexed maintenance therapy; both in the context of the whole population, and analysed according to the level of PD-L1 expression in a sub-group analysis. This comparator is described by the company as the standard of care (SoC), and was verified as such by independent expert clinicians consulted by the ERG.

The doses used in the model were cisplatin (75mg/m^2) plus pemetrexed (500mg/m^2), or carboplatin (400mg) plus pemetrexed (500mg/m^2). These are standard doses which were not varied except for their administration frequency versus target. The platin chemotherapies were modelled to a maximum of four Q3W treatment cycles.

When pemetrexed maintenance (PM) was taken-up (cisplatin users only by license), the dose was unchanged (500mg/m^2). The uptake of pemetrexed maintenance differed by treatment strategy (87.6% for PC; 100% for SoC). Note that the scope did not specify the use or otherwise of pemetrexed maintenance after pembrolizumab combination; but did specify the option of pemetrexed maintenance as part of SoC.(65)

The comparison of pembrolizumab combination (PC) with pemetrexed in combination with pemetrexed in combination with a platinum drug (SoC) is referred to as the ‘main’ comparison.

5.2.6.3 Time-on-treatment

Different types of parametric models have been selected for ToT, with no other justification than that these provided the best statistical fit, and even this has only been given for the sub-group analysis (MSD CS B.3.9). In their Appendix N the company state that a comparable methodological approach was used in the sub-group analysis as in the base case when modelling ToT. As the guidance in TSD 14 relates to survival analysis, it should be noted that ToT has been used in the company's model instead of PFS when determining disease management costs, even in the scenario in which utility is based on progression status. (There is, however, a setting in the model which allows for ToT to be set equal to PFS).

Although Table 84 (MSD CS B.3.5.1) suggests otherwise, ToT has been modelled using separately fitted parametric distributions for both treatment arms. While the CS states that the distribution for the pembrolizumab combination arm was fitted to the first two years of the ToT KM data, the portion used for the SoC arm has not been specified. Cut-off points relating to observed changes in gradient have not been considered for ToT, though an exponential distribution has been fitted for the pembrolizumab combination arm and, in both arms, ToT is used instead of PFS. (Points of treatment discontinuation have been included, as described in section 5.2.4).

5.2.6.4 Progression-free survival

Cut-off points were chosen when fitting distributions for PFS in the base case and in the scenario analyses, though these were not identified in the same way as those for OS: each is seven weeks shorter than the corresponding point for OS. This is reportedly due to a drop in observed KM PFS between weeks 0 and 6, as a result of the first tumour assessment in the trial not taking place until after the initial radiologic assessments (MSD CS B.3.3.1).

The company described that this also meant that full parametric curves could not to be fitted (MSD CS Appendix L) but, from their report, it is unclear to which portion of the KM data the curves were fitted. Upon receiving the R code and replicating the company's results, it was found that the distributions used in their base case have been fitted to the data of patients who had not progressed nor died by week 21 in the trial. The KM data has been used for PFS directly up until the cut-off point (at 21 weeks, in the base case) and the fitted curve for extrapolation beyond it. The use of cut-off points based on those for OS is despite the fact that a different type of parametric model has been chosen for PFS: the Weibull distribution, as opposed to the exponential, is used for both treatment arms. Unlike for OS, there is no option in the company's model for selecting parametric distributions for PFS without using one of three cut-off points. In some scenarios, the use of a cut-off point for OS makes a

which were analysed using a different model structure (see section 5.2.2). As would be expected, states representing a longer TTD have a higher utility value associated with them (MSD CS B.3.4.5).

Since the time spent in all but the ≥360 state is fixed for all patients, an increase in survival would result in more time spent in this health state and a higher proportion of time alive spent in this state. Hence, an increase in survival would not only increase the QALYs gained by each patient, but also their average HRQoL per year of life. Indeed, the ICER was found to be sensitive to the utility input for this state.

A limitation of using TTD is that data from a large number of patients is not available. Data for patients remaining alive and less than one year from commencement of treatment can not inform the analysis since the do not qualify for any health state. Although a single patient's data can contribute to all four. Of six-hundred and two patients in the trial who were invited to complete questionnaires at baseline, [redacted] did so. By week 30, [redacted] completed a response. At the November 2017 data cut-off, [redacted] responses were available for the ≥360 state; [redacted] responses for the [180, 360); [redacted] for the [30, 180) state; and [redacted] for the (0, 30) state. Table 6 shows the mean estimates of the pooled results.

Table 6 Detail of utility survey and state means for TTD method

State	n†	m‡	Mean utility	SE	95% CI
≥360	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[180, 360)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[30, 180)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n† = Number of patients with non-missing EQ-5D score; m‡ = Number of records with non-missing EQ-5D score; EQ-5D score during baseline is not included.

Source: MSD CS Document B Table 67, Page 134

The estimates used in the model are presented in Table 7. An age-related utility decrement was included seperately (MSD CS B.3.4.5).

Table 7 Mean utility values for health state used in the model

State	Company model
≥360	[redacted]
[180, 360)	[redacted]
[30, 180)	[redacted]

<30	[redacted]

5.2.9 Cost effectiveness results

Summary results of the company's deterministic base case analysis are presented in Table 8. The deterministic model served as the company's primary analysis.

The results presented in this section include the agreed and tentative commercial access agreements (CAAs) for pembrolizumab. They do not include existing agreements for comparators.

The deterministic ICER for PC versus SoC was £46,568 per QALY gained. The mean incremental LYs gained per person were 1.16, and incremental QALYs gained were 0.89 over the model lifetime. The PC incurred £41,344 more resource than the SoC. (Table 8).

5.2.9.1 Whole population, main comparison

Table 8 Base case result of main comparison for overall population (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£84,324	2.50	1.81				
SoC	£42,980	1.34	0.92	£41,344	1.16	0.89	£46,568

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

Table 9 Base case result of main comparison for overall population (probabilistic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£84,870	NR	1.81				
SoC	£43,527	NR	0.93	£41,344	NR	0.89	£46,674

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; NR = Not reported; QALY = Quality-adjusted life year; SoC = Standard of care.

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

A Single Technology Appraisal

Erratum 2

31 October 2018

This report contains those pages in the ERG report that contain amendments.

4.2.4.1.5 Additional Outcomes

The company further reported the time to response (TTR) for patients treated in the KEYNOTE-189 trial; these data are summarised in **Table 1**. The time to response was comparable between patients receiving pembrolizumab combination therapy and those receiving platinum and pemetrexed. Time to response data was not reported for patients in KEYNOTE-021G.

Table 1 Clinical Efficacy of Pembrolizumab Combination Therapy: TTR

Outcome*	**KEYNOTE-189**	
	Pembrolizumab combination Therapy (N=410)	Control (N=206)
No of pts with response	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]

*Note that all outcomes are reported as assessed in the ITT population and at final follow-up, unless otherwise stated.
Source: MSD CS page 71

4.2.4.2 Patient-Reported Outcomes/Health-Related Quality of Life

Health-related quality of life (HRQoL) following treatment with pembrolizumab combination therapy is reported in the CS for patients in the KEYNOTE-189 trial; no patient-reported outcome data is reported for patients in KEYNOTE-021G. Evidence from KEYNOTE-189 is summarized in **Error! Reference source not found.**.

HRQoL in the KEYNOTE-189 trial was assessed using EQ-5D VAS, EORTC-QLQ C30, and EORTC QLQ-LC13; however only data for EQ-5D VAS was provided in the CS. Not all patients completed HRQoL measures, and a substantial number of patients were missing from the analysis. Patient attrition increased over time, at a similar rate between arms (although attrition was somewhat higher in the control arm). By the 21 week follow-up, data was only available for 61.0% of patients in the pembrolizumab combination arm, and 51.1% of patients in the control arm.

Based on the raw HRQoL scores, there was no statistically significant difference in the change in HRQoL in the two arms between baseline and 12 and 21 weeks follow-up. However, following adjustment for covariates (treatment by study visit interaction, PD-L1 ≥ 1% vs. <1%, platinum chemotherapy, and smoking status) and imputation to replace missing data, the analysis demonstrated a statistically significant difference in change in HRQoL between baseline and 12 and 21 weeks. This difference was clinically meaningful, based on

1.1.1 *Whole population, other comparisons*

Summary ERG results for the alternative comparators are presented in Table 2. The ICERs for PC versus the platinum and chemotherapy doublet options were in the range £40,000 to £58,000 per QALY gained.

Table 2 ERG base-case result of primary analysis versus NMA comparators (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£86,863	3.21	2.35				
Platinum + Gemcitabine	£27,292	1.36	0.93	£59,571	1.85	1.43	£41,710
Platinum + Vinorelbine	£28,917	1.91	1.35	£57,946	1.31	1.00	£57,939
Platinum + Docetaxel	£28,662	1.57	1.10	£58,201	1.64	1.26	£46,337
Platinum + Paclitaxel	£25,937	1.23	0.83	£60,926	1.99	1.52	£40,096

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care.

1.1.2 TPS>=50% sub-population, versus pembrolizumab monotherapy

Results of the comparison of PC with pembrolizumab monotherapy for strong expressers of PD-L1 are given in Table 3.

Table 3 ERG base case result of sub-population comparison for patients with TPS>=50%, PC versus pembrolizumab monotherapy (deterministic)

Strategy	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PC	£106,292	4.19	3.11				
Pembrolizumab monotherapy	£75,796	3.06	2.25	£30,496	1.13	0.86	£35,695

Abbreviations: ICER = Incremental cost effectiveness ratio; LYG = Life year gained; QALY = Quality-adjusted life year; SoC = Standard of care

End of life qualification for sub-groups

- < 2 years life expectancy; >3 months treatment benefit

TPS>50%, PC v SoC, both PAS included

Source (time in months)	Strategy		
	SoC (life expectancy)	PC	Increment (life extension)
Company BC mean	17.11	42.24	25.12
ERG BC mean	23.89	58.33	34.44
*ERG: With background mortality; 5 year DoE; No test costs**	16.88	35.22	18.34
Median in KEYNOTE-189	Not reported	Not reached	NA

*Differs from the ERG base case in one assumption only: the method of OS extrapolation follows that of the company (2-phase piecewise exponential independent, both Km plot arms, fitted from week 28)

- Qualifies

TPS>50%, PC v PM, both PAS included

Source (time in months)	Strategy		
	PM (life expectancy)	PC	Increment (life extension)
Company BC mean	27.59	42.24	14.65
ERG BC mean	44.44	58.33	13.89
*ERG: With background mortality; 5 year DoE; No test costs**	26.92	35.22	8.3
Median in KEYNOTE-189	Not reported	Not reached	NA

*Differs from the ERG base case in one assumption only: the method of OS extrapolation follows that of the company (2-phase piecewise exponential independent, both Km plot arms, fitted from week 28)

- Does not qualify

TPS 1-49%, PC v SoC, both PAS included

Source (time in months)	Strategy		
	SoC (life expectancy)	PC	Increment (life extension)
Company BC mean	17.46	36.20	18.74
ERG BC mean	22.09	43.03	20.95
*ERG: With background mortality; 5 year DoE; No test costs**	17.25	31.50	14.26
Median in KEYNOTE-189	Not reported	Not reached	NA

*Differs from the ERG base case in one assumption only: the method of OS extrapolation follows that of the company (2-phase piecewise exponential independent, both Km plot arms, fitted from week 28)

- Qualifies

TPS >1%, PC v SoC, both PAS included

Source (time in months)	Strategy		
	SoC (life expectancy)	PC	Increment (life extension)
Company BC mean	15.29	23.16	7.87
ERG BC mean	21.69	32.66	10.97
*ERG: With background mortality; 5 year DoE; No test costs**	15.11	22.31	7.20
Median in KEYNOTE-189	Not reported	Not reached	NA

*Differs from the ERG base case in one assumption only: the method of OS extrapolation follows that of the company (2-phase piecewise exponential independent, both Km plot arms, fitted from week 28)

- Qualifies

Apologies for confusing TA447 with TA428 in the TC earlier.

In TA428, a combined approach for utilities was used, in which the pre- and post-progression health states were divided into sub-health states reflecting TTD. Two sub-health states were used, with patients categorised accordingly to whether their TTD was greater than or equal to 30 days, or less than 30 days. It has not been specified in the committee papers, but it is likely that the utility values associated with each of the four states were calculated using the IPD.

According to Table 85 in section B.3.6.2, there were 'limitations to using a combined approach' in this appraisal, but this has not been elaborated on anywhere in the company's submission. The same approach for HRQoL as that in TA428 cannot be taken with only the data that is available in the company's submission. However, different combined approaches for HRQoL can be considered. For example, in scenario 12.a (below), the difference between the progression-free and progressed utility values was subtracted from the TTD utility values for the relevant patients. In order to apply a decrement for TTD in scenario 12.b, it was necessary to consider TTD less than 360 days rather than the less 30 days: a weighted average of the utility values for three health states with the shortest TTD could be calculated, but not for the three with the longest TTD.

In TA447 (updated in TA531), utilities are based on TTD alone, with four HRQoL health states considered. The same approach has been taken in the company and ERG base cases in this appraisal. Adjusted estimates of the proportion of patients taking-up 2L treatment after 1L discontinuation are used (45.8% for PC, 56.5% for SoC) and, in the ERG base case, treatment benefit discontinuation occurs at 5 years. The following additional scenarios are considered below:

Scenario	Description
11	Utilities based on progression status
12.a	Combined approach for utilities – main utility values based on TTD, with a utility decrement associated with progressive disease applied for progressed patients.
12.b	Combined approach for utilities – main utility values based on progression status, with a utility decrement associated with TTD of less than 360 days applied for patients with less than 360 days to live
14	Unadjusted estimates from KEYNOTE-189 of the proportion of patients taking-up 2L treatment after 1L discontinuation (30.5% for PC, 46.6% for SoC)
16	Treatment benefit discontinuation at 3 years

Results table

Scenarios	Incremental costs w/o PAS* (£)	Incremental QALYS	ICER w/o PAS (£/QALY)	Incremental costs with PAS (£)	ICER with PAS (£/QALY)
ERG base case	£42,454	1.13	£37,622	[redacted]	[redacted]
11	£42,454	0.99	£43,092	[redacted]	[redacted]
12.a	£42,454	1.03	£41,352	[redacted]	[redacted]
12.b	£42,454	0.98	£43,491	[redacted]	[redacted]
14	£44,960	1.13	£39,843	[redacted]	[redacted]
16	£41,395	0.95	£43,418	[redacted]	[redacted]
14, 16	£43,810	0.95	£45,950	[redacted]	[redacted]
11, 14, 16	£43,810	0.84	£52,091	[redacted]	[redacted]
12.a, 14, 16	£43,810	0.87	£50,138	[redacted]	[redacted]
12.b, 14, 16	£43,810	0.83	£52,755	[redacted]	[redacted]

* Patient Access Scheme for pemetrexed maintenance therapy