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 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-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 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 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 (Figure 3)

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 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 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 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%, 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.

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)

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.

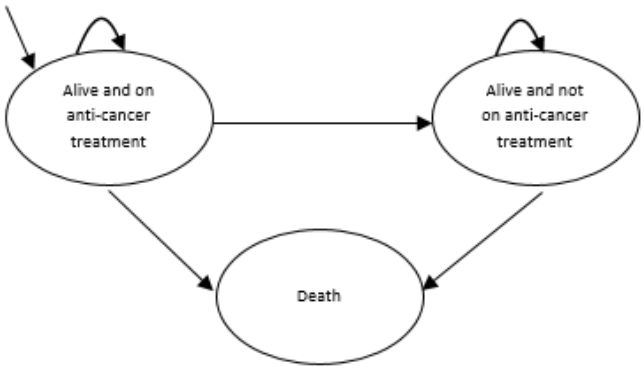
Cost and resource evidence

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 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 5.2.6.3).

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 75 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 76. 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 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 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.