Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer: A Single Technology Appraisal

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Contributions of authors

Lesley Uttley and Alison Scope summarised and critiqued the clinical effectiveness evidence reported in the company's submission. Paul Tappenden and Aline Navega Biz critiqued the health economic analysis submitted by the company and undertook the ERG's exploratory analyses. Shijie Ren critiqued the statistical analyses presented in the company's submission. Mark Clowes critiqued the company's search strategy. Dennis Hadjiyiannakis, Gary Doherty and Laura Cove-Smith provided clinical expertise to the ERG and commented on the draft report. All authors were involved in drafting and revising the final report.

CONTENTS

List of tables

List of figures

List of boxes

Abbreviations

AE	Adverse event
AEOSI	Adverse event of special interest
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ASaT	All-patients-as-treated
AUC	Area under the curve
BIC	Bayesian Information Criterion
BSA	Body surface area
CAA	Commercial Access Agreement
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrI	Credible interval
CS	Company's submission
CSR	Clinical Study Report
CDF	Cancer Drugs Fund
DoR	Duration of response
DSA	Deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EoL	End of life
EORTC QLQ	European Organization for Research and Treatment of Cancer core quality of life questionnaire
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer quality of life questionnaire for lung cancer
ERG	Evidence Review Group
EQ-5D	Euroqol EQ-5D
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
GP	General practitioner
HR	Hazard ratio
HRQoL	Health-related quality of life
IA2	Interim analysis two
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
IPTW	Inverse probability of treatment weighting
IRAE	Immune-related adverse event
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LSM	Least squares mean
LYG	Life year gained
Mg	Milligram
MSD	Merck Sharp & Dohme
MVN	Multivariate normal
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NIH	National Institutes of Health
NMA	Network meta-analyses
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient reported outcome measure
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
Q3W	Once every 3 weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RR	Relative risk
SAE	Serious adverse event
SC	Standard care
SD	Standard deviation
SE	Standard error
SEER	Surveillance Epidemiology and End Results
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SC	Standard care
STA	Single Technology Appraisal
TPS	Tumour proportion score
TTD	Time to treatment discontinuation
TTP	Time to progression
TTR	Time to response
US	United States
VAS	Visual analogue scale
WHO	World Health Organization

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The decision problem in the company submission is generally appropriate and is in line with the final NICE scope with regards to:

- Intervention - pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel (pembrolizumab combination therapy).
- Target population - adults with untreated, advanced (Stage IV) metastatic squamous non-small-cell lung cancer (NSCLC). The evidence included in the CS relates to patients who have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Pembrolizumab combination therapy does not currently hold a marketing authorisation for this indication; however, the CS is in line with the population included in the wording of the anticipated licence.
- Comparators - platinum-based combination chemotherapy regimens or pembrolizumab monotherapy (for people with tumours that express programmed death-ligand 1 [PD-L1] with a tumour proportion score [TPS] of at least 50%), as delivered in usual clinical practice.
- Outcomes - overall survival (OS), progression-free survival (PFS), time to response (TTR), duration of response (DoR), adverse events (AEs) and health-related quality of life (HRQoL).

As a consequence of uncertainty surrounding the currently available clinical evidence, the CS states that the company is seeking a Cancer Drugs Fund (CDF) recommendation for pembrolizumab combination therapy for the untreated metastatic squamous NSCLC population.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical evidence provided in the CS comprised the description of an ongoing, Phase 3, multi-centre trial (KEYNOTE-407) assessing the efficacy and safety of pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel versus placebo plus carboplatin and paclitaxel/nab-paclitaxel. A systematic literature review, including network meta-analyses (NMAs) and an indirect treatment comparison (ITC) analysis, was undertaken to compare pembrolizumab combination therapy with comparators including platinum-based combination chemotherapy regimens and pembrolizumab monotherapy. Separate analyses were conducted for the synthesis of OS and PFS evidence in two population groups: PD-L1 unselected and PD-L1 strong expression (TPS ≥50%).

Interim analysis 2 (IA2) of the 559 patients who entered the KEYNOTE-407 trial (data cut-off date 3rd April 2018) indicates that pembrolizumab combination therapy is statistically superior for OS, PFS and objective response rate (ORR – outcome not included in the NICE scope) compared with the control group. AEs occurring in KEYNOTE-407 were broadly in line with the known safety profiles of the two

treatment regimens. More immune-related adverse-events (IRAEs) and discontinuations occurred with pembrolizumab combination therapy than with control. The company's NMAs indicate that pembrolizumab combination therapy is an effective treatment relative to some of the chemotherapy regimens in the overall metastatic squamous NSCLC population (PD-L1 unselected). The company's ITC analysis within the PD-L1 TPS ≥50% subgroup suggests that pembrolizumab combination therapy is numerically superior to pembrolizumab monotherapy for both OS and PFS.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The Evidence Review Group (ERG) considers the KEYNOTE-407 trial to be high quality and relevant to the decision problem. Patients with strong PD-L1 expression did not receive first-line pembrolizumab monotherapy in this trial, as is standard care (SC) in England. As the results are based on an interim analysis, the duration of follow-up for OS is limited. Long-term data on SAEs are lacking due to the use of a cut-off at 90 days after the last dose of study medication; this is of particular importance for pembrolizumab as IRAEs may occur after treatment has terminated. The ERG highlights that the pembrolizumab treatment effect for OS, as analysed by PD-L1 subgroup, may be contingent on receipt of chemotherapy as a potential treatment effect modifier because platinum-based chemotherapy combination potentially alters PD-L1 expression.

The company's NMAs for pembrolizumab combination therapy versus SC chemotherapy comparators included trials which do not accurately reflect current clinical practice in England, as none of the trials included the use of second-line immunotherapy. In additional, some of the trials in the NMAs included some patients with a PS of 2; these patients were excluded from KEYNOTE-407.

1.4 Summary of cost-effectiveness evidence submitted by the company

The company submitted a *de novo* partitioned survival model which assesses the cost-effectiveness of pembrolizumab combination therapy versus SC chemotherapy for the first-line treatment of patients with squamous metastatic NSCLC. Whilst the CS describes a model in which the partition is defined by the presence/absence of progression, the partition in the implemented model is defined according to whether patients are receiving first-line therapy or not; in the company's model, PFS has no bearing on the incremental cost-effectiveness ratio (ICER) for pembrolizumab combination therapy versus its comparators.

The CS reports the results of two base cases analyses for the overall NSCLC population: "Base Case Analysis 1" compares pembrolizumab combination therapy against carboplatin plus paclitaxel/nab-paclitaxel (the comparator used in KEYNOTE-407), whilst "Base Case Analysis 2" presents pairwise comparisons of pembrolizumab combination therapy versus cisplatin/carboplatin in combination with docetaxel, gemcitabine or paclitaxel, based on the company's NMAs. Separate exploratory analyses are

also presented across three PD-L1 subgroups: TPS <1%, 1-49% and ≥50%. Within these subgroups, the comparator is carboplatin plus paclitaxel/nab-paclitaxel; pembrolizumab monotherapy is also included as a comparator in the PD-L1 TPS ≥50% subgroup. Across all analyses, incremental health gains, costs and cost-effectiveness are evaluated over a 30-year time horizon from the perspective of the NHS and Personal Social Services (PSS). The model parameters were informed by analyses of time-to-event data (time to treatment discontinuation [TTD] and OS) collected within KEYNOTE-407, with additional external data from the US Surveillance, Epidemiology and End Results (SEER) Program used to model long-term OS outcomes. Despite a maximum treatment duration for pembrolizumab of 2 years, the company's model assumes a lifetime treatment effect for OS for the pembrolizumab combination therapy group. The effectiveness of other SC chemotherapy comparators was estimated from the company's NMA (squamous, PD-L1 unselected population); the effectiveness of pembrolizumab monotherapy was estimated using an ITC of trimmed data from KEYNOTE-407 and KEYNOTE-042. HRQoL estimates for time-to-death categories were based on Euroqol EQ-5D data collected within KEYNOTE-407. Resource cost parameters were taken from KEYNOTE-407, standard costing sources, previous NICE technology appraisals (TAs), additional literature and assumptions. The company's economic analyses incorporate a price reduction relating to an existing Commercial Access Agreement (CAA) for pembrolizumab.

Within the overall metastatic squamous NSCLC population (PD-L1 unselected), the company's model suggests that the probabilistic ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is £28,852 per QALY gained (company's Base Case Analysis 1); the results of the company's deterministic model are similar (ICER=£28,672 per QALY gained). Based on a fully incremental analysis of the company's model, including the correction of model errors identified by the ERG during the clarification process, the ICER for pembrolizumab combination therapy versus cisplatin/carboplatin plus gemcitabine is estimated to be £51,240 per QALY gained (company's Base Case Analysis 2). Within the PD-L1 TPS subgroups, the ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is estimated to be in the range £25,849 to £32,174 per QALY gained.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG critically appraised the company's health economic analyses and double-programmed the deterministic version of the company's model (for Base Case Analyses 1 and 2 and for the PD-L1 TPS subgroup analyses). The ERG's critical appraisal identified a number of issues relating to the company's model and the evidence used to inform its parameters. The most pertinent of these include: (i) the identification of model errors; (ii) concerns relating to the company's NMAs, in particular, the absence of second-line immunotherapy from the trials of SC chemotherapy comparator regimens; (iii) uncertainty surrounding long-term extrapolation; (iv) the potentially optimistic assumption of a lifetime

OS treatment effect for pembrolizumab combination therapy; (v) the inclusion of an implicit assumption of cure within the model, and (vi) concerns regarding the company's approach to modelling HRQoL. The ERG notes that the OS data from KEYNOTE-407 are immature and alternative assumptions regarding long-term OS benefits have the propensity to increase the ICER substantially.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The systematic literature review (SLR) of clinical evidence in the CS was reported to have adhered to best practice in systematic reviewing. The KEYNOTE-407 trial is a high quality RCT and is relevant to the decision problem.

The ERG did not identify any major technical model errors which impact on the company's economic comparison of pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (company's Base Case Analysis 1).

Notwithstanding the ERG's concerns regarding the suitability of the SEER dataset, two clinical advisors to the ERG believed that the company's OS predictions for the SC chemotherapy group of the model were plausible. The third advisor suggested that OS outcomes for patients in the SC chemotherapy comparator group may be more favourable than the company's OS model predictions due to the availability of second-line immunotherapy.

1.6.2 Weaknesses and areas of uncertainty

As the KEYNOTE-407 trial does not reflect clinical practice whereby patients with strong PD-L1 expression receive first-line pembrolizumab monotherapy there is no head-to-head evidence comparing pembrolizumab combination chemotherapy with pembrolizumab monotherapy. Other than the KEYNOTE-407 trial, the trials included in the NMAs do not include second-line immunotherapy.

The presentation and analysis of safety data for pembrolizumab combination therapy are currently limited and do not provide long-term data which are relevant for IRAEs.

The company's health economic analyses are subject to several weaknesses and uncertainties:

- The progression-based partitioned survival model described in the CS does not reflect the company's implemented model. Several parameter values contained in the model were incorrectly reported in the CS, including the hazard ratios [HRs] applied in the company's Base Case Analysis 2 and the PD-L1 TPS ≥50% subgroup analysis. Some evidence sources used to inform model parameters are unclear or inconsistent between the CS and the implemented model.

- The original submitted model contained errors which render the results of the company's Base Case Analysis 2 unreliable.
- The ERG considers there to be considerable uncertainty surrounding the expected long-term survival of patients receiving pembrolizumab combination therapy or SC chemotherapy (including those who go on to receive second-line immunotherapy).
- The ERG has concerns regarding the appropriateness of using external data from SEER, together with an assumed lifetime OS treatment effect, to estimate long-term survival for pembrolizumab combination therapy. The ERG's exploratory analyses indicate that the use of alternative parametric OS models may substantially increase the ICER for pembrolizumab combination therapy compared with the company's base case estimates.

1.7 Summary of exploratory analyses and sensitivity analyses undertaken by the ERG

The ERG undertook six sets of exploratory analyses using the deterministic version of the company's model. The ERG's preferred model includes: (i) the correction of model errors; (ii) the inclusion of health state utilities defined according to the presence/absence of disease progression (together with the use of PFS data applied as the model partition); (iii) the use of disease management costs defined according to the presence/absence of disease progression; (iv) increased costs associated with second-line immunotherapy, and (v) the use of clinicians' preferred OS models. The ERG's preferred analyses combine all of these amendments and are presented across two separate scenarios: (a) an optimistic scenario, and (b) a pessimistic scenario. The ERG's optimistic scenario applies the company's piecewise KM/log logistic OS model for the pembrolizumab combination therapy group and the company's piecewise KM/SEER OS model for the SC chemotherapy group. The ERG's pessimistic scenario applies the ERG's log logistic OS model for both modelled treatment groups, based on the whole KEYNOTE-407 dataset.

The ERG's preferred optimistic scenario suggests an ICER for pembrolizumab combination therapy versus SC chemotherapy of £35,981 per QALY gained, whilst the pessimistic scenario suggests a higher ICER of £49,473 per QALY gained. Additional sensitivity analyses using the full range of ERG-fitted standard parametric models and natural cubic spline models lead to ICERs ranging from £35,981 to £274,028 per QALY gained. The ERG's exploratory subgroup analyses, which are based on the same parametric OS models as those applied in the ERG's preferred analyses for the overall population, suggest the following results:

- PD-L1 TPS <1% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £34,239 (pessimistic) to £34,392 (optimistic) per QALY gained.
- PD-L1 TPS 1-49% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £40,767 (optimistic) to £52,680 (pessimistic) per QALY gained

- PD-L1 TPS ≥50% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £39,193 (optimistic) per QALY gained to dominated (pessimistic). Pembrolizumab monotherapy is ruled out due to strong dominance.

The ERG notes that additional data collection in KEYNOTE-407 may resolve some of the uncertainty surrounding expected outcomes, both within the overall metastatic squamous NSCLC population and within specific PD-L1 TPS subgroups. Given the uncertainty in the OS estimates based on IA2 of KEYNOTE-407, it is unclear whether pembrolizumab combination therapy meets NICE's End of Life criteria.

2 BACKGROUND

This chapter presents a brief critique of the company's background to the disease and the current treatment pathway in England.

2.1 Critique of company's description of underlying health problem

The company's submission[1] (CS) presents an accurate overview of the histology and classification of non-small-cell lung cancer (NSCLC). The CS cites estimates from the American Cancer Society,[2] which suggest that NSCLC represents 85% of all lung cancer cases, with squamous NSCLC accounting for 25-30% of all lung cancer.

The indication for pembrolizumab for this Single Technology Appraisal (STA) relates to metastatic (Stage IV) disease, whereby the cancer has spread to distant lymph nodes or to other organs such as the liver, bone, or brain. Page 24 of the CS[1] states that nearly half of all lung cancer cases in England (49.7%) are diagnosed at Stage IV disease; at this point, curative surgical treatment is no longer viable and patient prognosis is poor. The clinical intent of treatment for these patients is to prolong overall survival (OS) and improve health-related quality of life (HRQoL) by improving symptoms.

The CS[1] (page 18) states that pembrolizumab binds to the programmed cell death 1 (PD-1) receptor, inhibiting ligand binding (including programmed death-ligand 1 [PD-L1]) and potentiates T-cell responses. Patients with advanced NSCLC and with a PD-L1 tumour proportion score (TPS) of 50% or greater (defined as PD-L1 expression on at least 50% of tumour cells) have been found to respond to treatment with pembrolizumab and as such are eligible for treatment with pembrolizumab monotherapy (National Institute for Health and Care Excellence [NICE] Technology Appraisal [TA] Guidance 531[3]). The CS estimates the percentage of patients with advanced NSCLC who express PD-L1 on at least 1% of cancer cells to be between 60% and 66%.

The approval of specific anti-PD-(L)1 drugs in the UK has changed the therapeutic landscape and has increased treatment options for patients with NSCLC, both in the first- and subsequent-line treatment settings.[4]

2.2 Critique of company's overview of current service provision

Treatment for patients with advanced NSCLC is guided by the tumour histological subtype, genotype, molecular biomarkers and the performance status (PS) of the patient. Chemotherapy is recommended as a treatment option for squamous NSCLC patients with a good performance status (World Health Organization [WHO] score of 0 or 1; or a Karnofsky score of 80–100), where the chemotherapy regimen

should be a combination of a single cytotoxic drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) (NICE Clinical Guideline 121).[5]

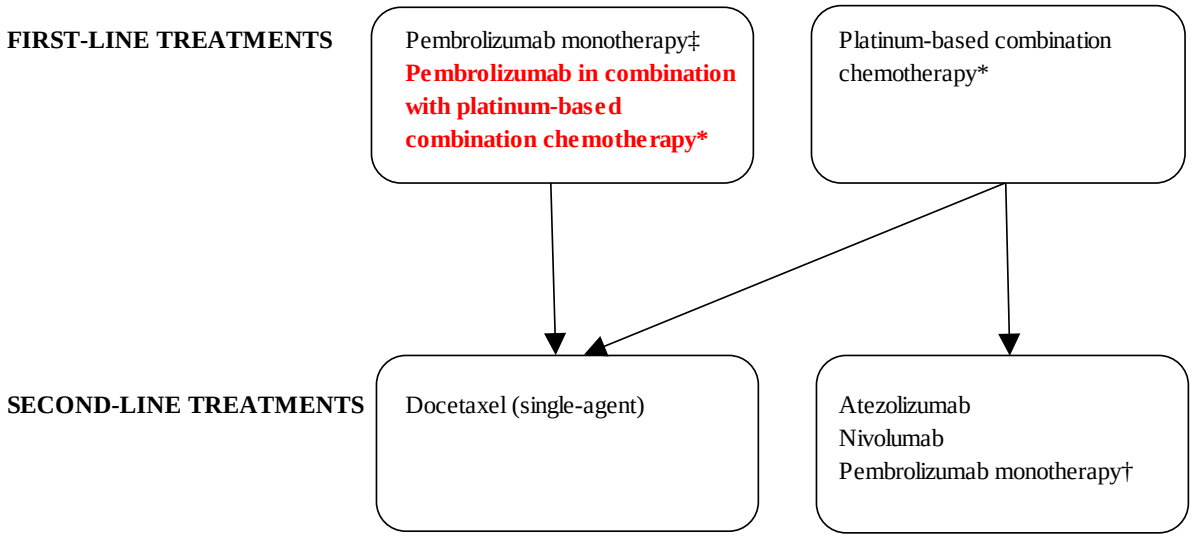
The company estimates that 7,561 patients will be diagnosed with squamous NSCLC cancer in England in 2019. Of these, the company estimates that 2,025 patients with Stage IV cancer and an Eastern Cooperative Oncology Group (ECOG) PS of 0-1 will be eligible for treatment with pembrolizumab combination therapy.

The CS (page 26) states that since PD-L1 test requisition has been incorporated into hospital treatment pathways and protocols, there has been a significant increase in the volume of PD-L1 testing in England.

Pembrolizumab monotherapy is currently recommended for PD-L1-positive (TPS ≥50%) metastatic disease in adults with untreated non-small-cell lung cancer (NSCLC) and no epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase (ALK) gene fusions, subject to a maximum 2-year stopping rule and a confidential commercial access agreement (CAA). The company anticipates that pembrolizumab combination therapy will be positioned as an additional treatment option for patients who have advanced/metastatic, squamous NSCLC, regardless of PD-L1 expression, and a PS of 0-1 where combination platinum chemotherapy is offered.

The current treatment pathway for patients with untreated metastatic squamous NSCLC is summarised in Figure 1. The company's proposed positioning of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel is highlighted in red. Guidelines from the National Comprehensive Cancer Network (NCCN) 2018 state that nab-paclitaxel can be substituted for paclitaxel; however, nab-paclitaxel is not available for use in this indication in England.

Figure 1: Current treatment pathway for patients with untreated metastatic squamous NSCLC and proposed positioning of pembrolizumab combination therapy



Platinum-based combination chemotherapy - gemcitabine, paclitaxel, vinorelbine plus carboplatin or cisplatin
** unless unable to tolerate platinum therapy*
† PD-L1 TPS>1% only
‡ PD-L1 TPS≥50% only
Note - treatment may involve re-challenging with platinum-based chemotherapy in second-line for some patients

Clinical advisors to the Evidence Review Group (ERG) stated that gemcitabine plus carboplatin is most commonly used as a first-line treatment in England and that carboplatin plus paclitaxel is regarded as a similar alternative regimen. They also stated that docetaxel is usually reserved for later lines of therapy.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[6] and addressed in the CS is presented Table 1.

Table 1: Company's statement of the decision problem (reproduced from CS, Table 1)

	Final scope issued by NICE	**Decision problem addressed in the CS**	**Rationale if different from the final NICE scope**
Population	Adults with untreated metastatic squamous non-small-cell lung cancer (NSCLC)	Adults with untreated metastatic squamous NSCLC	In line with the licence, based on the data from the supporting clinical trial KEYNOTE-407[7, 8]
Intervention	Pembrolizumab in combination with: • carboplatin and paclitaxel • carboplatin and nab-paclitaxel	Pembrolizumab in combination with • carboplatin and paclitaxel • carboplatin and nab-paclitaxel	In line with the licence
Comparators	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab monotherapy (for people with tumours that express PD-L1 with at least 50% tumour proportion score with no EGFR- or ALK positive tumour mutations only)	As per final scope issued by NICE	Data from KEYNOTE-407[7, 8] will provide comparative efficacy of pembrolizumab in combination with paclitaxel/nab-paclitaxel plus carboplatin. Data for comparative efficacy of pembrolizumab in combination with paclitaxel/nab-paclitaxel plus carboplatin 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 • Duration of response • 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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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 commercial access agreements for the intervention or comparator technologies will be taken into account. If appropriate, the economic modelling should include the costs associated with diagnostic testing for biological markers (for example PD-L1) in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.	As per final scope issued by NICE	
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on the biological marker (PD-L1).	The following PD-L1 subgroups have been considered: TPS <1%, ≥1%, 1-49%, ≥50%	

NICE – National Institute for Health and Care Excellence; CS – company's submission; NSCLC – non-small-cell lung cancer; PD-L1 – programmed death-ligand 1; EGFR - epidermal growth factor receptor; ALK - anaplastic lymphoma kinase; ITC – indirect treatment comparison; TPS – tumour proportion score

3.1 Population

The overall patient population in the CS[1] relates to patients with untreated metastatic squamous NSCLC, irrespective of PD-L1 tumour expression status. This is in line with the population defined in the final NICE scope.[9] The main clinical evidence for the intervention under appraisal is drawn from a single randomised controlled trial (RCT): KEYNOTE-407.[7, 8] The population included in this study represents patients with less severe prognoses than those commonly seen in clinical practice due to the restriction to patients with ECOG PS 0 or 1. However, clinical advisors to the ERG suggested that this restriction is appropriate as patients with an ECOG PS ≥2 would not be considered suitable for treatment with immunotherapy in combination with platinum-doublet chemotherapy. The clinical advisors also highlighted that expression of the PD-L1 biomarker is a key driver in determining whether pembrolizumab treatment should be given first-line as monotherapy. One clinical advisor highlighted that they would consider using pembrolizumab combination therapy in patients with rapidly developing and bulky metastatic disease where disease progression is rapid, as this represents a group of patients for whom standard care alone may not work in time. Two clinical advisors agreed that pembrolizumab combination therapy could be a potential treatment for this subgroup with particularly aggressive disease providing that patients had TPS ≥50%.

The KEYNOTE-407[7, 8] trial was conducted in 125 centres across 17 countries, none of which were based in the UK. The majority of the study population were white (77.7%), former or current smokers (62.6%, 29.5% respectively), from countries around the world including European Union (EU) countries (45%), East Asia (19.4%) and the United States (US) (4.7%). For PD-L1 expression, approximately 35% of patients had a TPS of <1%, 37% had TPS 1-49%, and 26% had TPS ≥50%. The clinical advisors considered the study population from KEYNOTE-407[7, 8] to be broadly representative of patients seen in clinical practice in England.

As pembrolizumab combination therapy has not yet received a European/UK marketing authorisation for this indication (see Section 3.2), it is not clear which medical conditions or patient groups may be contraindicated for first-line treatment with pembrolizumab combination therapy. Patients that were excluded from the KEYNOTE-407 trial[7, 8] due to pre-existing clinical conditions may be regarded as contraindicated to pembrolizumab combination therapy; these are described in Section 4.2 of this report.

The company's base case economic analyses relate to the overall metastatic squamous NSCLC population.[1] The CS also includes economic analyses for subgroups based on PD-L1 expression (TPS <1%, TPS 1-49% and TPS ≥50%).

3.2 Intervention

Pembrolizumab (MK-3475, Keytruda®) is a monoclonal antibody manufactured by Merck Sharp & Dohme (MSD). Pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel was granted approval from the United States (US) Food and Drug Administration (FDA) on October 30th of 2018, following priority review for the proposed indication within this STA. Pembrolizumab combination therapy has not yet been granted a marketing authorisation for the first-line metastatic squamous NSCLC indication by the European Medicines Agency (EMA). Within the NSCLC population, pembrolizumab monotherapy currently holds an EU marketing authorisation for:

- First-line treatment of metastatic NSCLC for tumours that express PD-L1 with at least 50% TPS with no EGFR or ALK positive tumour mutations
- Treating locally advanced or metastatic NSCLC for tumours that express PD-L1 with at least 1% tumour proportion score after at least one prior chemotherapy regimen.

The intervention considered in the CS[1] is in line with the dosing regimen proposed within the company's marketing authorisation application: pembrolizumab administered intravenously at a fixed dose of 200mg over 30 minutes combined with carboplatin area under the curve (AUC) 6 plus paclitaxel (200mg/m^2)/nab-paclitaxel (100mg/m^2) every 3 weeks (Q3W) for 4 cycles, followed by pembrolizumab 200mg Q3W until disease progression. The KEYNOTE-407[7, 8] trial protocol mandated a maximum of 35 cycles (approximately 2 years) of pembrolizumab treatment; this is line with the FDA recommendation and is also expected to form part of the EU marketing authorisation.

The current list price for a 100mg vial of pembrolizumab is £2,630; each treatment cycle requires 2 vials (pembrolizumab acquisition cost per treatment cycle = £5,260). The company currently has a CAA in place for pembrolizumab; the acquisition cost of pembrolizumab including the CAA is [redacted] per treatment cycle (discount = [redacted]).

3.3 Comparators

The KEYNOTE-407 trial[7, 8] compares pembrolizumab combination therapy with placebo plus carboplatin and paclitaxel/nab-paclitaxel, in line with the final scope issued by NICE.[6] The dose for combination chemotherapy in both the intervention and control arms of KEYNOTE-407 was carboplatin AUC 6 mg/mL/min on day 1 of each 21-day cycle for 4 cycles and paclitaxel 200mg/m^2 on day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100mg/m^2 on days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo (in the control arm) every 3 weeks.

The comparator used in Base Case Analysis 1 of the company's health economic model is based on the comparator arm of the KEYNOTE-407 trial;[7] additional platinum-based combination chemotherapy regimens are included as comparators in Base Case Analysis 2 of the company's model.

The CS[1] assumes that the carboplatin and paclitaxel/nab-paclitaxel regimen included in KEYNOTE-407 is equivalent to other platinum-based combination chemotherapy regimens in terms of clinical efficacy. The company also performed network meta-analyses (NMAs) which compare pembrolizumab combination therapy against the following chemotherapy plus platinum regimens:

- Gemcitabine plus cisplatin/carboplatin
- Paclitaxel/nab-paclitaxel plus cisplatin/carboplatin
- Docetaxel plus cisplatin/carboplatin
- Vinorelbine plus cisplatin/carboplatin.

Separate NMAs were undertaken for: (a) patients with unselected histology and unselected PD-L1 status and (b) squamous histology and unselected PD-L1. Separate analyses were presented for progression-free survival (PFS) and overall survival (OS). The latter was used in the company's health economic analysis (see Section 5.2).

The CS also compares pembrolizumab combination therapy with pembrolizumab monotherapy via an indirect treatment comparison (ITC) within the subgroup of patients with PD-L1 TPS ≥50% (the subgroup for which first-line pembrolizumab monotherapy is recommended by NICE[10]).

Clinical advisors to the ERG stated that the comparator group treatment regimens used in the studies included in the NMAs are in line with those used in clinical practice in England. They noted that nab-paclitaxel is not approved in this indication in England. In the KEYNOTE-407 trial,[7, 8] 60% of patients received paclitaxel and the remainder received nab-paclitaxel.

3.4 Outcomes

Outcomes included in the NICE scope[6] include:

- Overall survival (OS)
- Progression-free survival (PFS)
- Duration of response (DoR)
- Adverse effects of treatment (adverse events, AEs)
- Health-related quality of life (HRQoL)

The CS[1] also reports results for objective response rates (ORR, not listed in the final NICE scope). The company's model incorporates evidence from KEYNOTE-407 on OS, AEs and HRQoL. PFS outcomes

are included in the model but do not have any impact on the incremental cost-effectiveness of pembrolizumab combination therapy (see Section 5.2).

3.5 Other relevant factors

The CS[1] states that the company does not envisage any equity or equalities concerns relating to the use of pembrolizumab combination therapy in patients with untreated squamous metastatic NSCLC. As a consequence of uncertainty surrounding the currently available clinical evidence, the CS states that the company is seeking a Cancer Drugs Fund (CDF) recommendation for pembrolizumab combination therapy for the untreated metastatic squamous NSCLC population.

4 CLINICAL EFFECTIVENESS

The clinical evidence submitted by the company comprises:

- the interim results for the KEYNOTE-407 trial[7, 8]
- a systematic literature review (SLR)
- NMAs and ITCs of pembrolizumab versus relevant comparators

This chapter summarises the evidence of clinical effectiveness of pembrolizumab combination therapy from the CS[1] including the KEYNOTE-407 trial[7, 8] and the company's SLR, NMAs and ITCs.

4.1 Critique of the methods of review

4.1.1 Searches

The CS[1] reports that the SLR searches aimed to identify studies to inform direct and indirect comparisons between the interventions included in the NICE scope.[6] Searches were conducted in five phases, all of which are reported in full in CS Appendix D.[11] An appropriate range of databases was covered including NICE's recommendations of MEDLINE, EMBASE and CENTRAL. Searches were limited to citations in the English language and those published since 1995. The ERG notes that the English language limit, which was applied at the search stage rather than the sifting stage, excludes any records for which the language field was empty as well as any foreign language studies for which an English abstract was available.

Search strategies were constructed around the decision problem (CS,[1] Section B1.1, Table 1, page 17) and used a combination of subject headings and free text terms. Search filters to identify RCTs were applied; these were based on those of the Scottish Intercollegiate Guidelines Network (SIGN), albeit with some modifications (such as the exclusion of review articles). The ERG noted that a somewhat different set of search terms was used for the NSCLC disease area in the clinical effectiveness review, compared with that used in the cost-effectiveness searches. The ERG conducted brief searches comparing the yield retrieved by the two sets of NSCLC terms and found that each version retrieved results that the other had missed. As part of the clarification process (see clarification response,[12] question A1), the ERG queried the company's use of different disease terms between the clinical and cost-effectiveness searches; the company responded that they believed their approach to be "*sufficiently sensitive*."

Due to the searches being conducted over several phases, date limits were applied to the update searches. However, these are reported incorrectly in the CS;[1] this was queried by the ERG during the clarification process. The company attributed this to a "*transcription error*" (clarification response,[12] question A2). The ERG notes that no transcription would be required as search strategies are usually

reproduced directly from the interface without editing, therefore the use of such transcription raises uncertainty about the accuracy of the reporting. The CS reports that bibliographies of relevant SLRs, meta-analyses and HTA submissions were manually checked for relevant missed studies. The company's clarification response[12] (question B1) confirms that no forward tracking of included citations was conducted. Recent conference proceedings from several relevant series were consulted in order to identify unpublished literature. In addition, the company searched for unpublished but completed clinical trials using the National Institutes of Health (NIH) clinical trials register, but not the WHO International Clinical Trials Registry, as is recommended by Glanville *et al.*[13]

Despite the concerns raised above, the ERG is generally satisfied with the company's approach to the identification of evidence for the clinical effectiveness review.

4.1.2 Inclusion criteria

The inclusion criteria for the company's SLR are summarised in Table 1 (Section D1.1.1) of the CS appendices.[11]

The inclusion criteria are broadly in line with the final NICE scope.[6] The company's SLR limits included study designs to RCTs. Whilst an RCT is the appropriate study design to evaluate the clinical efficacy of pembrolizumab versus its comparators, other research designs are useful for understanding the full safety profile and acceptability of new interventions. By limiting their search to RCT evidence only, the company has excluded other study designs (for example non-randomised and non-controlled evidence) which may provide long-term and/or real-world evidence for the adverse effects of pembrolizumab. This issue is particularly relevant for pembrolizumab as the drug is an immunotherapy which causes certain immune-related side effects (such as pneumonitis) which can be severe or life-threatening and can occur even after treatment has terminated.[14] The CS[1] actively excluded systematic reviews and meta-analyses from its review of clinical effectiveness. The ERG requested clarification on the justification for this exclusion and the reliance on primary data only; in response, the company only reiterated that its aim was to focus on clinical trials (clarification response,[12] question A3). This response indicates that the company's SLR assigns little value to research which aggregates data from primary studies. The ERG considers that, in the absence of an NMA of AEs for pembrolizumab combination therapy, consideration of systematic reviews could have provided useful information on the safety profile of pembrolizumab combination therapy in relation to current standard treatments.

Table 18 of the CS[1] provides a list of studies that were excluded from the company's NMAs. The ERG notes that 27 studies were excluded with the reason for exclusion reported as "other." The company provided further clarification (clarification response,[12] question A4) on reasons why 29 citations (two

more than the 27 noted in the CS appendices[11]) were excluded. The reasons given were: review (n=19), not found (n=4), protocol (n=4), not English (n=1) and editorial (n=1).

4.1.3 Critique of data extraction

The methods of study selection and data extraction for the SLR are described in Section D.1.1.2 of the CS.[1] The CS states that this involved two reviewers who worked independently, with a third reviewer available to resolve discrepancies. The methods described are appropriate and adhere to good practice in systematic reviews according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

4.1.4 Quality assessment

Quality assessment is described in the CS appendices[11] (Section D.1.1.4) as having been undertaken independently by two reviewers, with a third reviewer utilised for resolution of discrepancies. The Cochrane Risk of Bias tool[16] was used to critically appraise the RCTs of interest. Overall the KEYNOTE-407 trial[7, 8] was determined in the CS to be at "low risk" of bias. The ERG considers this a generally fair judgement of this RCT (for which the Clinical Study Report [CSR] was available). A summary of the quality assessment of the KEYNOTE-407 trial, assessed using the Cochrane Risk of Bias tool, is provided in Table 11 (Section B.2.5) of the CS.[1] Methods described for randomisation were appropriate and randomisation was stratified (1:1) according to PD-L1 status, (TPS <1% vs. TPS ≥1%), choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Concealment of allocation was appropriate as the trial used a triple-blind placebo-controlled design and therefore patients, care providers and central outcome assessors (radiologists) were unaware of treatment allocation. Patient characteristics were well balanced at baseline.

In consideration of attrition rates between study groups, the company's quality assessment states that discontinuations were similar between treatment arms. However, the ERG notes with reference to the description of safety data (CS,[1] Section B.2.10.2, page 107), that higher rates of discontinuation of any drug within the treatment regimen due to an AE occurred in the pembrolizumab combination therapy group compared with the control group (23.4% vs 11.8%). The company speculates that differences in discontinuation rates between the treatment groups may be attributable to the longer duration of exposure in the pembrolizumab combination therapy group. However, the CS also states that similar trends were observed in exposure-adjusted analyses of drug discontinuations.

The CS[1] reports intention-to-treat (ITT) analyses, which is appropriate. Whilst patients in the control arm were permitted to switch to pembrolizumab monotherapy, statistical adjustment for treatment switching was not implemented in the CS ITT base case analysis. The ERG considers this to be appropriate as second-line immunotherapy therapy is standard care in England and this treatment

switching represents what would happen in clinical practice for people who are PD-L1 positive (≥1%). Information regarding the PD-L1 status for people who switched is not provided in the CS.

The primary and secondary outcome measures in the CS[1] are in line with the final NICE scope,[6] with the exception of the Euroqol EQ-5D, whereby only the visual analogue scale (VAS) data, but not questionnaire data, are reported in the CS and the CSR for KEYNOTE-407.

4.1.5 Evidence synthesis

As only one RCT (KEYNOTE-407[7, 8], Section 4.2.2) was identified for comparing pembrolizumab combination therapy to a relevant comparator, pairwise meta-analysis was not undertaken.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Trials of interest

The CS focuses on the KEYNOTE-407 trial[7, 8] (NCT02775435) as the main source of evidence for the clinical effectiveness of pembrolizumab combination therapy in the target population (see Section 4.2.2). Other relevant trials that are mentioned in the CS[1] or its appendices[11] (without presenting results) are shown in Table 2.

Table 2: Trials related, but not directly relevant, to the decision problem addressed in the CS

Trial name NCT number	Trial description	Relevance to decision problem
KEYNOTE-042 NCT02220894	Study of Pembrolizumab (MK-3475) Versus Platinum-based Chemotherapy for Participants With PD-L1-positive Advanced or Metastatic Non-small Cell Lung Cancer	Pembrolizumab monotherapy, open-label
KEYNOTE-024[17] NCT02142738	Study of Pembrolizumab (MK-3475) Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer	Pembrolizumab monotherapy, open-label
KEYNOTE-021 NCT02039674	Study of Pembrolizumab (MK-3475) in Combination With Chemotherapy or Immunotherapy in Participants With Non-small Cell Lung Cancer	Non-squamous, pembrolizumab combination, open-label

A new and ongoing trial not mentioned in the CS[1] or its appendices[11] was by the ERG (KEYNOTE-799); whilst this study focusses on Stage III patients, it may contribute additional safety data for pembrolizumab combination therapy in the squamous NSCLC population (described in Table 3).

Table 3: Ongoing trial identified by the ERG, not included in the CS

Trial name NCT number Sponsor	Trial description	Relevance to decision problem
KEYNOTE-799 NCT03631784 MSD	Double-blind, Phase 2 RCT of Pembrolizumab in Combination with Platinum Doublet Chemotherapy and Radiotherapy in patients with unresectable, local advanced Stage III NSCLC	Began recruiting in October 2018 and not due for completion until 2020. Estimated Enrollment: 216 participants

The ERG sought advice from clinical experts on whether trials from non-squamous NSCLC (such as KEYNOTE-189, KEYNOTE-021) are relevant to the decision problem defined in the NICE scope.[6] The ERG's clinical advisors clarified that squamous and non-squamous histologies should be treated separately, largely due to the recommended chemotherapies in standard care (SC chemotherapy) being different for these populations as well being diseases with distinct clinical outcomes.

4.2.2 The KEYNOTE-407 trial

The KEYNOTE-407 trial[7, 8] (NCT02775435) is a Phase III, multi-centre, triple-blind RCT assessing the efficacy and safety of pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel versus placebo plus carboplatin and paclitaxel/nab-paclitaxel. The company presents data from this ongoing trial of 559 patients with untreated squamous NSCLC, using a second interim analysis (IA2) with data cut-off of 3rd April 2018. The CS[1] states that the final analysis for this trial is planned for [redacted]. The clinicaltrials.gov website estimates the study completion date to be February 2021. The median duration of follow-up in the KEYNOTE-407 trial at IA2 is reported to be 7.8 months (range 0.1 to 19.1 months), with 43.5% of patients remaining in the pembrolizumab combination group and 25.7% of patients in the control group remaining on assigned treatment, which includes 4 cycles (12 weeks) of platinum-based combination chemotherapy and a placebo control.

Patient eligibility for KEYNOTE-407

Key inclusion and exclusion criteria for patients entering the KEYNOTE-407 trial[7, 8] are reported in Table 5 of the CS[1] (Section B.2.3). Patients were ineligible for the trial if they had: prior systemic treatment; major surgery within 3 weeks; received radiation therapy to the lung within 6 months; completed palliative radiotherapy within 7 days; central nervous system (CNS) or brain metastases; autoimmune disease that required systemic therapy within 2 years; a medical condition that required immunosuppression; prior immunotherapy; interstitial lung disease or a history of pneumonitis. Eligible patients were: over 18 years of age; had a life expectancy of at least 3 months; had an ECOG performance status of 0 or 1; and had adequate organ function.

The ERG cross-checked the key inclusion criteria in the CS[1] with the inclusion criteria described in the CSR (page 37). The criterion "*Unable or unwilling to take folic acid or vitamin B12 supplementation*" was listed in the CS exclusion criteria but not in the CSR exclusion criteria. Clinical advice to the ERG clarified that this criterion is for pemetrexed chemotherapy used in non-squamous carcinomas, hence this is not relevant for the squamous study population.

From June 2016, 559 patients were randomised 1:1 to two treatment arms:

- *Intervention*: 278 patients received pembrolizumab 200mg and carboplatin AUC 6mg/mL/min on day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200mg/m^2 on day 1 of each cycle for 4 cycles or nab-paclitaxel 100mg/m^2 on days 1, 8 and 15 of each cycle for 4 cycles, followed by pembrolizumab 200mg every 3 weeks. Pembrolizumab was administered prior to chemotherapy on day 1.
- *Control*: 281 patients received placebo and carboplatin AUC 6mg/mL/min on day 1 of each 21-day cycle for 4 cycles and paclitaxel 200mg/m^2 on day 1 of each cycle for 4 cycles or nab-paclitaxel 100mg/m^2 on days 1, 8 and 15 of each cycle for 4 cycles, followed by placebo every 3 weeks.

All treatments were administered intravenously. Treatment continued until disease progression, as assessed by blinded independent central review using response evaluation criteria in solid tumours (RECIST) v1.1[18] criteria (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), unacceptable toxicity, or a maximum of 35 cycles of pembrolizumab (24 months). Patients randomised to the control arm were offered pembrolizumab monotherapy at the time of disease progression. However, there was no pembrolizumab monotherapy comparator arm in the KEYNOTE-407 trial for those with strong PD-L1 expression (TPS $\geq$ 50%), as is used in current clinical practice in England.

The baseline characteristics of the study population are described in Table 7 (Section B.2.3) of the CS.[1] The median age was 65 years (range: 29 to 88 years), 81% were male and 93% were former or current smokers. The majority of patients were white (77%) and most had an ECOG PS of 1 (71%). Thirty-five percent of patients had tumour PD-L1 expression TPS <1%; 19% were from the East Asian region, 60% of patients received paclitaxel whilst the remainder received nab-paclitaxel.

Interim analysis 2

Study results presented in the CS[1] are based on IA2 of the trial (data cut-off 3rd April 2018). Clinical advisors to the ERG questioned the appropriateness of appraising the trial data before the study has completed considering the low numbers of patients in the analyses after 12 months. The ERG requested clarification from the company on the power of IA2 to detect significantly significant differences in OS

and PFS because the CS describes the power of the study to detect significant hazard ratios (HRs) for the final analysis, but not at IA2. The company responded that for PFS, with [redacted] events at IA2, the study has *"… ~ [redacted] power for detecting a HR of [redacted] at [redacted] (one-sided) significance level"* (clarification response,[12] question A9). The actual number of events observed are 349 for PFS. For OS, with [redacted] deaths, the study has ~[redacted] power for detecting a HR of [redacted] at [redacted] (one-sided) significance level. The actual number of events observed is 205 for OS (CS, page 41). The ERG notes that the number of events required for the pre-specified efficacy boundary in OS at IA2 has not been met.

The key efficacy endpoints are described in Table 9 (Section B.2.4) of the CS[1] as PFS and OS. Secondary endpoints are ORR and DoR. An exploratory efficacy endpoint using patient reported outcome measures (PROMs) is also described on page 36 of the CS, based on the EQ-5D VAS. The company clarified that the EQ-5D-3L questionnaire was used to inform HRQoL parameters in the model (see Section 5.2.2); results of this analysis are not presented in the clinical section of the CS. The European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (EORTC QLQ-C30) and the EORTC quality of life questionnaire for lung cancer (EORTC QLQ-LC13) were also reported to have been used in the trial, but results are not provided in the CS.

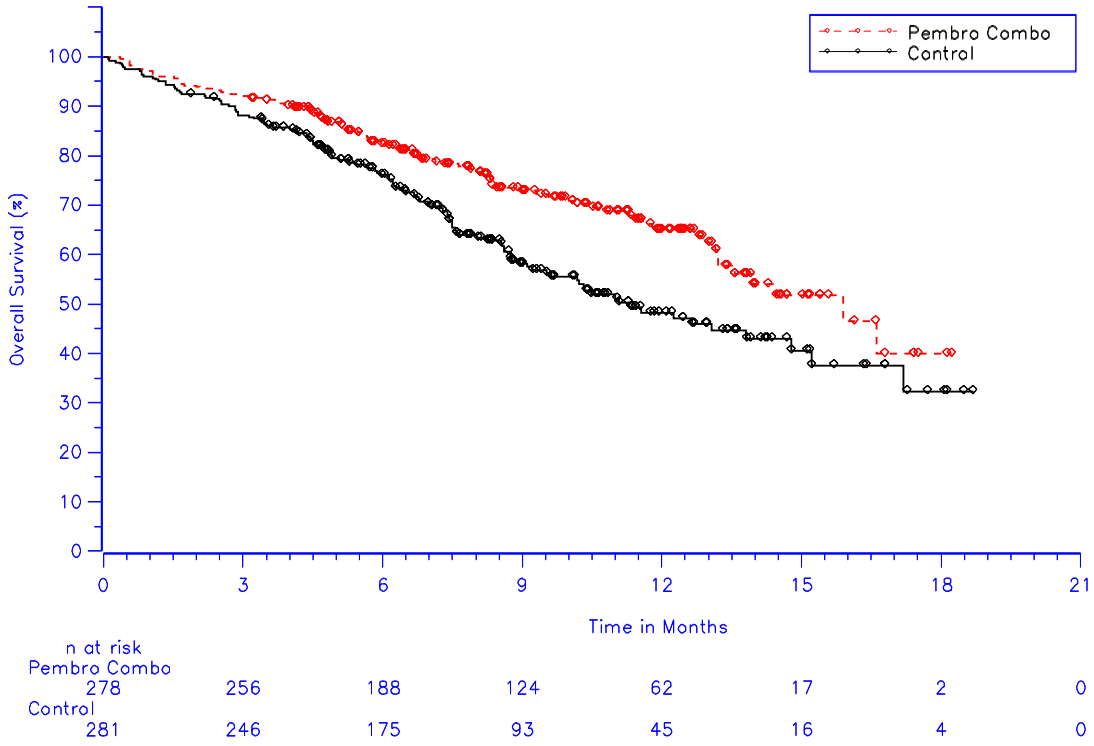
At IA2, the mean number of cycles of treatment received was [redacted] (standard deviation [SD] [redacted]) and [redacted] (SD [redacted]) in the pembrolizumab combination and placebo control groups, respectively. At this point of the trial, 75 patients in the control group had switched to pembrolizumab monotherapy. An additional 14 patients are described (CS,[1] page 52) as receiving a PD-1 antibody (pembrolizumab or nivolumab) as subsequent therapy outside of the study, resulting in a switching rate of 42.6% (89/209), whilst 72 patients were reported as remaining in the control group. Adjustment for treatment switching was not implemented in the CS ITT base case analysis for the patients who went on to receive pembrolizumab monotherapy; this is appropriate because second-line immunotherapy therapy is standard care in England for the target population (if PD-L1 TPS ≥1%).

Overall survival

OS is defined in the CS[1] (Section B.2.6.2) as time from randomisation to death due to any cause. At the time of the data cut-off for IA2, 205 deaths (38%) had been reported in the study: 85 (30.6%) deaths were reported in the pembrolizumab combination therapy group and 120 (42.7%) deaths were reported in the control group. The HR for OS was 0.64 (95% confidence interval (CI): 0.49, 0.85; p=0.0008) in favour of pembrolizumab combination therapy. Within the ITT population, median OS was 4.6 months longer in the pembrolizumab combination group compared with the control group (15.9 months versus 11.3 months; see Kaplan-Meier [KM] curves presented in Figure 2). The CS also presents OS by PD-L1 expression as a subgroup analysis, which demonstrates that median OS was longer in the

intervention group than the control group for each PD-L1 subgroup: TPS <1% (15.9 vs 10.2 months); TPS 1 to 49% (14.0 vs 11.6 months) subgroups (see Figure 3). In the PD-L1 TPS ≥50% subgroup, median OS was not reached in either the pembrolizumab combination group or the control group. The KM curves for the PD-L1 subgroups are in shown in Figure 3.

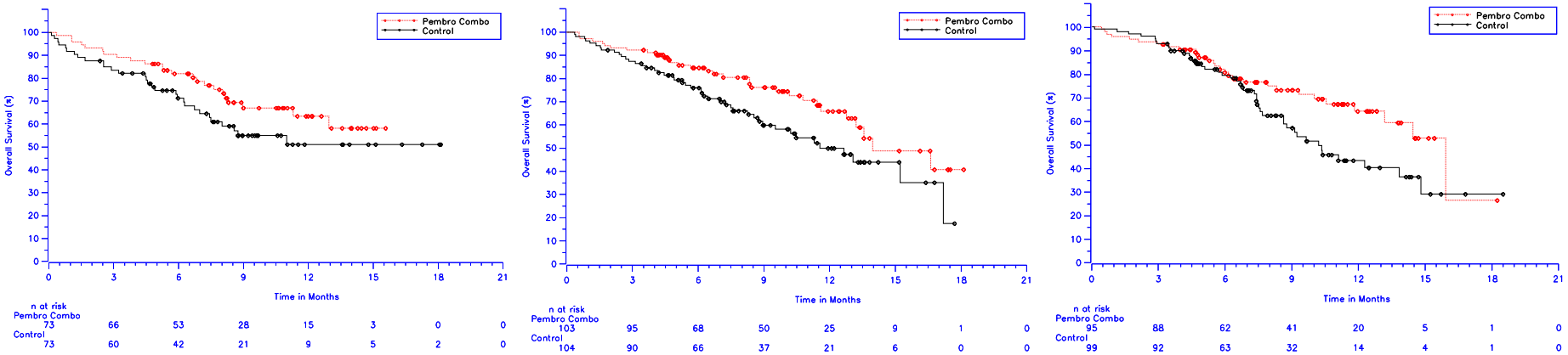
Figure 2: KM estimates of OS, ITT population (reproduced from CS Figure 4)



PD-L1 expression

Clinical advisors emphasised that, ideally the KEYNOTE-407 trial[7,8] would have included an additional study arm for pembrolizumab monotherapy for patients with strong PD-L1 expression (TPS ≥50%) to compare combination chemotherapy therapy results with those for patients who are known to respond to pembrolizumab monotherapy. From the KEYNOTE-407 trial, the benefit of pembrolizumab combination therapy (as opposed to pembrolizumab monotherapy) in the PD-L1 strong expression subgroup is currently unclear. A further key issue highlighted by the clinical advisors to the ERG was that under current funding restrictions, patients in England may receive treatment with only one immunotherapy drug. If pembrolizumab combination therapy is recommended by NICE (irrespective of PD-L1 status), there may be uncertainty about whether it is optimal to offer first-line pembrolizumab combination therapy to patients who do not have strong PD-L1 expression (TPS <1-49%), or to reserve immunotherapy as a treatment option at second-line, given the additional toxicity burden of pembrolizumab in addition to SC chemotherapy.

Figure 3: KM for OS ITT population by PD-L1 TPS subgroup (reproduced from CS Figures 6, 7 and 8)



TPS ≥50% **TPS 1-49%** **TPS<1%**

The KM plots indicate that the intervention and control curves separated earlier in those with an increased PD-L1 expression (at month 0 for TPS ≥50%, after 2 months for 1-49%, and after 7 months for TPS <1%). This trend indicates that those with higher PD-L1 TPS have an immediate treatment response to pembrolizumab combination therapy. By contrast, the KM curve for the TPS PD-L1 <1% subgroup shows that the pembrolizumab combination arm languishes under and around the control arm until month 7; this indicates a delayed treatment response. Clinical advice received by the ERG suggests that platinum-doublet chemotherapy treatment, as provided in the control arm of the trial, can drive up tumour expression of PD-L1, or increase immunogenicity, as cancer cells may use the PD-1 pathway to hide from immune cells. Therefore, the apparent treatment response which occurs at around 6-7 months in the TPS <1% subgroup may be a function of PD-L1 expression increasing in response to chemotherapy. The PD-L1 TPS 1-49% subgroup demonstrates congruence to this theory, with a moderately differentiated treatment response in the intervention arm becoming apparent at around 3 months. Late emergence of a treatment response to pembrolizumab in the TPS <1% subgroup might suggest that second-line treatment with pembrolizumab would provide a similar treatment effect to those with strong PD-L1 expression. Clinical advice to the ERG was that a subgroup analysis of patients in KEYNOTE-407 with low PD-L1 expression (TPS<1%) that switched to receive immunotherapy would be informative (particularly as, in England, these patients would be eligible for atezolizumab). These data are however not provided in the CS.[1]

The ERG undertook a brief inspection of academic literature in Google Scholar for evidence to validate the notion that PD-L1 expression may alter following chemotherapy, as this represents a treatment effect modifier. A few relevant studies with small numbers of patients reported that chemotherapy altered PD-L1 expression during or after chemotherapy; however, the direction of alteration varied depending on the drugs used and the timepoint of assessment. For example, McDaniel *et al* (2016)[19] found that levels of PD-L1 increased following neoadjuvant chemotherapy (cisplatin in 13 patients, carboplatin in 26 patients). Leduc *et al* (2018)[20] found that docetaxel, platinum and fluorouracil induction chemotherapy increased PD-L1 expression. Katsuya *et al* (2016)[21] reported increases in both PD-L1 and PD-1 scores after chemotherapy with a range of drug regimens including cisplatin, carboplatin, paclitaxel, and gemcitabine. However, some studies noted a decrease in PD-L1. Rojko *et al* (2018)[22] found a significant decrease in PD-L1 expression in patients who received cisplatin-gemcitabine combination therapy (p=0.020), but no decrease was observed in the carboplatin-paclitaxel group (the chemotherapy regimen used in the KEYNOTE-407 trial[7, 8]). Lim *et al* (2018)[23] noted that PD-L1 decreased significantly after neoadjuvant chemotherapy with fluorouracil/cisplatin. Whilst this cursory analysis of empirical evidence on this topic is limited, there are emerging suggestions in the published literature that PD-L1 status alters during or following chemotherapy, depending on the chemotherapy drugs used. This may be relevant to UK practice where drug regimens other than that included in the KEYNOTE-407 trial[7, 8] are used because other chemotherapy regimens may not produce

this potential alteration to PD-L1 expression, which may affect treatment response to pembrolizumab. Clinical advisors to the ERG consequently emphasised the importance of adhering to the treatment regimens used in the KEYNOTE-407 trial if a positive recommendation for pembrolizumab is issued.

The ERG sought clinical advice on which chemotherapy comparators are most commonly used in clinical practice. The clinical advisors acknowledged that the platinum-based combination chemotherapy regimens are regarded as broadly similar and that carboplatin/gemcitabine is frequently used in England, followed by carboplatin/vinorelbine or carboplatin/paclitaxel. Whilst efficacy is regarded as generally similar between comparators, cisplatin was noted as only being suitable for a subset of fitter patients due to its particular toxicity profile. As highlighted above, it is unclear from the evidence presented in the CS[1] whether treatment response to pembrolizumab with or following standard care (SC) chemotherapy treatment with other comparators such as gemcitabine plus carboplatin would mirror the findings of KEYNOTE-407[7, 8] for the three PD-L1 subgroups.

Progression-free survival

PFS is defined in Section B.2.6.3 of the CS,[1] as time from randomisation to the first documented disease progression (as per RECIST 1.1) 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 considered right censored at the last disease assessment date. At the cut-off date for IA2, 349 (62%) PFS events had been reported. Data are provided for PFS within each treatment arm with 152 (54.7%) events reported in the pembrolizumab combination therapy group and 197 (70.1%) events reported in the control group. Median PFS for pembrolizumab combination therapy was 6.4 months (95% CI 6.2 to 8.3 months) compared with 4.8 months (95% CI 4.3 to 5.7) for control (difference of 1.6 months). KM estimates for PFS based on blinded independent central review of RECIST 1.1 criteria are provided on pages 58 and 64 of the CS. The CS reports that this is a statistically significant difference and equates to a 44% reduction in risk of progression or death for the pembrolizumab combination compared with the control (HR 0.56; 95% CI: 0.45 to 0.70; p<0.0001).

Objective response rate

ORR is defined as the proportion of subjects who have a complete response (CR) or a partial response (PR) based on blinded independent review using RECIST 1.1 criteria (CS,[1] Section B.2.6.4). Pembrolizumab combination therapy was reported to improve ORR compared with the control group (57.9% vs 38.4%); this difference was statistically significant (19.5% difference; p<0.0001).

Duration of response and time to response

DoR is defined as the time from the first documented evidence of complete response (CR) or partial response (PR) until disease progression or death (CS,[1] Section B.2.6.5). Time to response (TTR) is

defined as the time from randomisation to the first assessment of a CR or PR. Only confirmed CR/PRs (using RECIST 1.1) are reported to be included in the analysis for TTR and DoR. Subjects without progressive disease or death were censored at the time of last tumour assessment. Pembrolizumab combination therapy was reported to yield a longer median DoR compared with the control group (7.7 months versus 4.8 months). There was no difference in TTR between treatment groups (median 1.4 months in each group; *p*-value not reported).

Patient reported outcomes

According to the CS[1] (Section B.2.6.6), HRQoL was measured using three PROMs: (i) the EORTC QLQ-C30; (ii) the EORTC QLQ-LC13, and (iii) the EQ-5D-3L VAS. PROMs were reported to have been employed on the full analysis set (FAS) population (n=554), which consisted of all randomised patients who received at least one dose of study medication and completed at least one PROM assessment. The CS does not provide results for the EORTC QLQ-C30 or the EORTC QLQ-LC13. With respect to the EQ-5D VAS, data for two timepoints are provided: week 9 and week 18. No significant difference between treatment groups was noted using the EQ-5D VAS at week 9. At week 18, a statistically significant difference in EQ-5D scores was noted (least squares mean [LSM] [redacted]; 95% CI [redacted], *p*=[redacted]) with the pembrolizumab combination group showing a slight increase over baseline (LSM [redacted]; 95% CI [redacted]), and the control group showing a slight decrease (LSM [redacted]; 95% CI [redacted]). Results for the EQ-5D questionnaire were not reported in the CS.

4.2.3 Safety of pembrolizumab combination therapy

Safety analyses

Safety analyses presented in the CS[1] comprise data from the all-patients-as-treated (ASaT) population in KEYNOTE-407.[7, 8] This dataset consisted of all randomised patients who received at least one dose of study treatment (n=558). Incidence of, causality and outcome of AEs, Grade 3-5 AEs, serious adverse events (SAEs) and adverse events of special interest (AEOSI) were also collected in the study.

AEs were collected up to 30 days and SAEs up to 90 days after the last dose of study medication. The ERG requested a summary of AEs and SAEs that occurred after 90 days from the company during the clarification process because the Keytruda website[14] highlights that the drug "*can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. These problems may happen any time during treatment or even after your treatment has ended.*" The company responded that they "*can only access the locked KN407 database with cut-off* [redacted] *and retrieve information recorded up to this cut-off. In the locked database, there is* [redacted] *in the combination arm who has* [redacted] *non-serious AEs that occurred +90 days treatment discontinuation. In the control arm there are several incidences*" (clarification response,[12] question A7). This information is

too vague and incomplete to be given full consideration. The ERG considers that AE data should be collected and reported for the full trial duration due to the known delay in AEs occurring in immunotherapy. For example, Wang *et al* (2018)[24] found 17 cases whereby cutaneous AEs developed at a median of 4.2 months after drug initiation with anti-PD-1 treatment with pembrolizumab, nivolumab, or ipilimumab.

For patients who switched from control to pembrolizumab monotherapy or another immunotherapy drug (89/209, 42.6%) AEs were censored at time of switching. The ERG considers that presenting the additional safety data from the 75 patients who switched to pembrolizumab in the KEYNOTE-407 trial[7, 8] as a separate group would have provided a more comprehensive toxicity profile for pembrolizumab considering the short duration of the available trial data.

Adverse events in KEYNOTE-407

A summary of AEs is provided in Table 46 (Section B.2.10.2) of the CS[1] and the safety profiles are noted by the company to be generally consistent with the known safety profiles of the respective therapies administered.

The incidence of SAEs was similar but numerically higher with pembrolizumab combination therapy ([redacted]) compared with control ([redacted]). Serious drug-related AEs were also higher with pembrolizumab combination therapy ([redacted]) than with control ([redacted]). The most frequently reported SAEs (incidence ≥1% in either treatment group) were generally comparable between the two groups, except colitis, which was higher in the pembrolizumab combination therapy group (pembrolizumab combination: [redacted]; control: [redacted]), and hypercalcemia, which was higher in the control group (pembrolizumab combination: [redacted] control: [redacted]).

AEs that led to death occurred in 23 (8.3%) patients in the pembrolizumab combination therapy group and in 18 (6.4%) patients in the control group. The proportion of deaths considered by a trial investigator to be attributed to a drug-related AE was 3.6% in the pembrolizumab combination therapy group compared with 2.1% in the control group.

Adverse events of special interest

The incidence of AEOSIs was higher in the pembrolizumab combination therapy group (28.8%) than the control group (8.6%). The most frequent AEOSIs (>5%) were hypothyroidism (7.9% vs 1.8%), hyperthyroidism (7.2% vs 0.7%), and pneumonitis (6.5% vs 2.1%) for pembrolizumab combination versus control respectively (CS,[1] Table 53). These events are regarded as immune-related adverse-events (IRAEs). The incidence of Grade 3 to 5 AEs was similar in the pembrolizumab combination group (69.8%) and the control group (68.2%), except for pneumonitis (pembrolizumab combination:

2.5%; control: 0.4%) and autoimmune hepatitis (pembrolizumab combination: 1.8%; control: 0.0%), which occurred more frequently in the pembrolizumab combination therapy group than the control group. Pneumonitis is an umbrella term encompassing several AEOSIs in the CSR, including acute interstitial pneumonitis, interstitial lung disease, pneumonitis, idiopathic pneumonia syndrome, and organising pneumonia.

Whilst anti-PD-(L)1 drugs may be considered as being less toxic than platinum-based combination chemotherapy,[25] they result in different AEs to chemotherapy drugs.[26] The ERG notes that IRAEs often typically have a delayed onset and prolonged duration compared to AEs from chemotherapy[27] and that some disease-specific HRQoL questionnaires such as EORTC QLQ may not encompass the impact of these side-effects (such as cutaneous AEs).[28, 29] The presence of two relatively discrete toxicity profiles of pembrolizumab monotherapy and chemotherapy indicates that pembrolizumab combination therapy will lead to an AE profile with a cumulative burden for the two treatment regimens, consistent with the different mechanisms of action for each drug. NSCLC patients are typically older, with frequent comorbidities and treatment is usually palliative with the main goal of improving HRQoL; therefore, limiting toxicity in this patient group is of paramount importance.[26] The ERG's search for additional evidence regarding the safety of pembrolizumab highlighted a number of relevant real-world studies and secondary data analyses of AEs in pembrolizumab emphasising the incidence of IRAEs such as pneumonitis, colitis, hepatitis, thyroid disorders and Type 1 diabetes mellitus with pembrolizumab.[30-33] Additionally some endocrine toxicities, such as hypothyroidism, which are known to occur more frequently with pembrolizumab, can be permanent and require lifelong treatment.[34]

Discontinuation

Higher rates of discontinuation of any drug within the treatment regimen due to an AE occurred in the pembrolizumab combination group compared with the control group (23.4% vs 11.8%). This is noted in the CS[1] as being primarily driven by a higher rate of discontinuation of pembrolizumab (17.3%) compared with placebo (7.9%). The company speculates that *"the differences in discontinuation rates between the treatment groups may be attributable to the longer duration of exposure in the pembrolizumab combination"* (CS,[1] Section B.2.10.2, page 107). However, the CS also states that similar trends were observed in exposure-adjusted analyses of drug discontinuations. Discontinuation of all drugs due to an AE was [redacted] in the pembrolizumab combination therapy group and [redacted] in the control group. Similar trends were reportedly observed for discontinuations due to drug-related AEs, SAEs, and serious drug-related AEs.

IRAEs occasionally require cessation of immunotherapy therapy and initiation of treatment with immunomodulatory medications (such as steroids). Published literature on this topic highlights uncertainty over how long-term steroid therapy to treat IRAEs may affect the disease course or

treatment efficacy.[35] Some retrospective studies posit that IRAEs may actually correlate with treatment response.[36] In addition, the effect of stopping and/or re-initiating pembrolizumab is not considered in the CS;[1] however, a paper by Ksienski *et al* (2018)[37] indicates that treatment interruption due to or IRAEs is correlated with lower OS in PD-L1 therapy (pembrolizumab or nivolumab). These real-world studies highlight issues regarding IRAEs, their potential to lead to treatment discontinuation and subsequent impacts on treatment response, or loss of HRQoL in the final months of life, which are not explored in the CS.

Summary of safety data

The ERG considers that the data presented for the safety of pembrolizumab combination therapy in the CS,[1] namely from the KEYNOTE-407,[7, 8] were limited because KEYNOTE-407 is an incomplete trial. Separate AE data for patients who switched to pembrolizumab monotherapy are not presented in the CS, further limiting the long-term safety data available from the key relevant trial. This is particularly relevant since pembrolizumab is an immunotherapy which causes immune-related side effects that can be severe or life-threatening and can occur even after treatment has terminated.[14] During the clarification stage of the appraisal, the ERG requested that the company either provide summary data or perform an NMA of treatment-related Grade 3/4 AEs including KEYNOTE-407, KEYNOTE-024 and KEYNOTE-042 trials (see clarification response,[12] question A6). The company's response provided summary data for the trials requested which were assessed by the ERG. The numeric AE data were comparable between pembrolizumab monotherapy and chemotherapy in the KEYNOTE-024 and -042 trials, but with consistently higher discontinuations in the pembrolizumab treatment arm. Whilst these data from two trials of pembrolizumab monotherapy are not directly applicable to the decision problem, the ERG notes that pembrolizumab and chemotherapy combination therapy have different mechanisms of action. Therefore, patients undergoing pembrolizumab combination therapy, as well as benefiting from the two different treatment effects, are likely to accumulate the burden of both of these different AE profiles. As well as discontinuation of therapy, many patients will require cessation of treatment and systemic steroids at some point during their treatment to manage immune-IRAEs; the long-term implications of such treatment interruptions are currently uncertain.

The SLR presented in the CS[1] was restricted to RCTs without consideration of non-randomised evidence or systematic reviews and no NMA of AEs was performed. Therefore, the ERG regards the safety analyses contained in the CS to reflect a 'light-touch' approach, considering the lack of long-term safety data from clinical trials of anti-PD-1 therapy.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS[1] relies on evidence from the key ongoing trial (KEYNOTE-407[7, 8]) as the primary source of evidence for the efficacy and safety of pembrolizumab combination therapy. As direct head-to-head evidence of pembrolizumab combination therapy is only available versus placebo plus carboplatin and either paclitaxel/nab-paclitaxel from this trial, the company presented two indirect treatment comparison (ITC) analyses of relevant comparators:

- ITC1 - pembrolizumab combination therapy versus chemotherapy comparators
- ITC2 - pembrolizumab combination therapy versus pembrolizumab monotherapy.

As part of ITC1, two separate NMAs were conducted to provide comparative efficacy data:

- NMA1 - including trials with purely squamous, PD-L1 unselected patients.
- NMA2 - including trials with both squamous and non-squamous patients, unselected for PD-L1. In the CS,[1] this is referred to as trials including patients who are "*unselected for histology*" (CS, page 82). Meta-regression was employed to estimate the treatment effect for patients from these trials with squamous disease only.

Details of the identification and methodology of the trials included in the company's ITC analyses are described below.

4.3.1 Search strategy

The trials included in the company's ITCs were identified from the SLR searches described in Section 4.1.1.

4.3.2 Study selection criteria

The CS[1] states that the relevant RCTs identified in the SLR were included in a feasibility assessment for the NMAs. The CS does not explicitly state whether the inclusion criteria for the ITC were identical for the SLR. The ERG does not consider that any eligible trials have been missed.

Feasibility assessment

Thirty-six RCTs were identified as relevant for the NMAs from the company's SLR; these studies were then subjected to a feasibility assessment (CS Appendix D,[11] page 118). It should be noted that this assessment was performed only for ITC1 and no separate assessment was reported for ITC2. Five of the 36 eligible RCTs were conducted in purely squamous patients (CTONG1002,[38, 39] KEYNOTE-407,[7, 8] Kristensen *et al*., 2017,[40] NAVotrial03,[41] and Saad *et al*., 2017[42]), with the remaining 31 trials conducted in patients unselected for histology. Following the feasibility assessment, 11 trials were

excluded from ITC1 on the basis of lack of comparability. Comparability was assessed in terms of disease histology and other prognostic factors. Three trials (Ahmed *et al*., 2017,[43] ECOG 1599, and Khodadad *et al*., 2014[44]) were excluded from the unselected for histology analysis (ITC1, NMA2) because most enrolled patients had an ECOG PS of 2. Whilst this is an appropriate reason to exclude trials, some trials which did include some patients with an ECOG PS of 2 were included, and a cut-off point for the number of ECOG PS 2 patients permitted within trials is not presented or justified in the CS appendices. Three trials (Chen *et al*., 2006,[45] Kristensen *et al*., 2017,[40] and NVALT-3[46]) were excluded as they were conducted exclusively in elderly patients, but no age cut-off was discussed. A further three trials (NAVotrial03,[41] GOIM 2608,[47] and Sumanth *et al*., 2008[48]) were excluded as they did not provide HRs or KM plots for OS or PFS. Both KEYNOTE-024[17] and KEYNOTE-042[49] were excluded from the ITC1 analysis, as pembrolizumab monotherapy is only indicated in patients with high PD-L1 expression (PD-L1 $\geq$ 50%) in England and the target population for the analyses conducted included patients not selected by PD-L1 expression. KEYNOTE-024[17] was excluded from ITC2 as only a small number of relevant patients (n=5) received paclitaxel plus carboplatin. KEYNOTE-042[49] and KEYNOTE-407[7, 8] were included in ITC2. These trials were selected in order to compare pembrolizumab combination therapy with pembrolizumab monotherapy; this is in line with the final NICE scope.[6] A total of twenty-five studies were included across all ITC analyses. Although the ERG considers the reasons for the exclusion of trials in the feasibility assessment to be broadly appropriate, insufficient detail was provided to enable a full assessment of some of these decisions regarding study inclusion.

4.3.3 Studies identified

The CS[1] does not explicitly list the RCTs included in each NMA. Additionally, the methods and some of the results tables are presented prior to the exclusion of the eleven RCTs following the feasibility assessment for ITC1.

ITC1, NMA1: Squamous, PD-L1 unselected (fixed effect NMA)

The CS[1] states (pages 84 and 86) that three trials were included in NMA1 (ITC1) and that these trials were conducted exclusively in patients with squamous histology, which is in line with the final NICE scope.[6] However, the network diagram (CS, Figure 21, page 84) indicates that three trials (Saad *et al*., 2017;[42] ECOG 1594;[50-52] and KEYNOTE 407) were used for OS, whilst four trials are used for PFS, with the addition of the CTONG1002 trial.[38, 39] Furthermore, ECOG 1594,[50-52] included both squamous and non-squamous patients. . One trial (KEYNOTE-407[7, 8]) contained data on pembrolizumab combination therapy and three contained data on the comparators (ECOG 1594;[50-52] Saad *et al*., 2017;[42] CTONG 1002[38, 39]). Carboplatin was the only common regimen component across all studies.

Table 4: Study and patient characteristics for ITC1 NMA1 (adapted from CS Appendix D, Tables 24 and 25)

Trial ID	Treatment	N randomised	Age (years)	Male (%)	ECOG 0/1 (%)	ECOG 2 (%)	Stage IIIB (%)	Stage IV (%)
KEYNOTE-407[7, 8]	pembro + carb + nab/pac	278	65 (29-87)	220 (79)	--	--	--	--
	carb + nab/pac	281	65 (36-88)	235 (84)	--	--	--	--
Saad *et al*., 2017[42]	cis + gem	36	NR	26 (72)	194 (95)	--	--	167 (81)
	carb + gem	35	NR	29 (83)	184 (92)	--	--	164 (82)
CTONG 1002[38, 39]	carb + pac	57	NR	--	--	--	--	--
	carb + gem	62	NR	--	--	--	--	--
ECOG 1594[50-52]	cis + doc	304	63 (34-84)	192 (63)	286 (94)	18 (6)	43 (14)	261 (86)
	cis + gem	301	64 (32-87)	187 (62)	286 (95)	15 (5)	42 (14)	259 (86)
	cis+ pac	303	62 (27-84)	194 (64)	285 (94)	18 (6)	33 (11)	270 (89)
	carb + pac	299	63 (30-85)	185 (62)	284 (95)	15 (5)	42 (14)	257 (86)

pembro - pembrolizumab; carb - carboplatin; cis - cisplatin; ECOG - Eastern Cooperative Oncology Group; NR – not reported

KEYNOTE-407[7, 8] is described in Section 4.3 of this report. Saad *et al*. (2017)[42] is a prospective, randomised, controlled, open-label trial which is described as ongoing and data are presented for the period from January 2012 to December 2015. The trial was conducted in Egypt; details relating to the number of centres is not provided in the CS[1] or in Saad *et al* (2017).[42] ECOG 1594[50-52] is reported as a randomised, multicentre trial that was conducted in the US. Although details of trial initiation and completion are not reported in the CS, Schiller *et al*. (2002)[51] reports that patients were enrolled into the study between October 1996 and May 1999. CTONG 1002[38, 39] is reported in the CS as a Phase II, open-label, multicentre trial conducted in China. An abstract of the trial reported that patients were randomised to the trial between November 2010 and June 2013.[39] The study designs appear consistent with the NICE scope;[6] however, none of the studies were conducted in the UK. Whilst three of the studies were conducted recently, ECOG 1594[50-52] was conducted between 1996 and 1999. The studies broadly represent best practice in England, but exclude the current use of first-or second-line immunotherapy in those with PD-L1 expression.

Eligibility criteria of the included studies are outlined in the CS Appendix D[11] (pages 96-97). Across all four studies, patients had to be aged 18 years or over. CTONG1002[38, 39] was the only trial to have an upper age cut-off (85 years). CTONG1002[38, 39] and ECOG 1594[50-52] included patients with Stage IIIB and IV disease, whilst for KEYNOTE-407[7, 8] and Saad *et al*. (2017),[42] only those with Stage IV disease

were eligible. KEYNOTE-407[7, 8] and CTONG1002[38, 39] limited patient eligibility to those with an ECOG PS of 0-1. Comparability of baseline population characteristics for all trials included in the ITCs is summarised on pages 92-93 of CS Appendix D. The ERG notes the following issues in terms of baseline comparability. Those with ECOG PS 0-2 were eligible for inclusion in the Saad *et al*. (2017) trial[42] and, initially in, ECOG 1594.[50-52] Eligibility criteria were amended in ECOG 1594[50-52] to include only those with an ECOG PS of 0 or 1 due to the high rate of SAEs in patients with a PS of 2, with 66 patients with an ECOG status of 2 included in the analysis. Further, although not detailed in the CS,[1] according to the Saad *et al*. (2017) publication,[42] eight patients (22.2%) in the gemcitabine/cisplatin group and 11 (31.4%) patients in the gemcitabine/carboplatin group had an ECOG PS of 2 at baseline. By including patients with an ECOG PS of 2, studies may have introduced bias in terms of disease severity or a different AE profile in different arms, although it appears that patients with ECOG PS of 2 were evenly distributed across the arms of the trials. Saad *et al*. (2017)[42] and CTONG1002[38, 39] present limited details of patient characteristics at baseline, therefore it is difficult to assess if there is baseline comparability. Saad *et al*. (2017)[42] does not report mean age at baseline, but provides numbers of patients who were younger or older than 55 years of age. CTONG1002[38, 39] does not report details regarding the age of the patients at baseline. It is also difficult to assess comparability and generalisability to the English population in terms of ethnicity due to limited reporting. No trials included in NMA1 were conducted in the UK.

ITC1, NMA2: Unselected for histology, PD-L1 unselected (fixed and random effects)

In addition to three of the studies included in NMA1 (Saad *et al*., 2017;[42] ECOG 1594;[50-52] KEYNOTE-407[7, 8]), the CS[1] (page 87) reports that 20 further trials were included in NMA2. Twenty-three trials evaluating nine treatments were included in the NMA for OS and of these, 18 trials evaluating eight treatments were included in the NMA for PFS. However, the CS does not provide a definitive list of the trials included in NMA2. By scrutinising the network diagrams (CS Figures 23, page 88; Figure 24, page 92), the ERG has assumed that the trials detailed in Table 5 were included.

Table 5: Study and patient characteristics of RCTs included in ITC1 NMA2 (adapted from Tables 24 and 25 – CS Appendix D1.2.2)

Trial ID	Treatment	N randomised	Age	Male (%)	ECOG 0/1	ECOG 2	Stage IIIB (%)	Stage IV (%)
Chang *et al*, 2008[53]	cis + gem	34	62.4 (34-81)	24 (71)	18 (53)	16 (47)	9 (26)	25 (74)
	cis + vin	39	61.6 (23-85)	10 (26)	25 (64)	14 (36)	14 (36)	25 (64)
Chen *et al*, 2004[54]	cis + pac	70	64.9 (37-NA)	56 (80)	39 (56)	19 (27)	19 (27)	46 (66)
	cis + vin	70	64.8 (23-NA)	46 (66)	37 (53)	16 (23)	16 (23)	48 (69)
Chen *et al*, 2007[55]	cis + vin	48	64.9 (35-83)	35 (73)	40 (83)	8 (17)	8 (17)	40 (83)
	cis + doc	46	60.2 (32-81)	26 (57)	33 (72)	13 (28)	9 (20)	37 (80)
Comella *et al*, 2000[56]	cis + gem + vin	60	62 (38-70)	58 (97)	60 (100)	0 (0)	26 (43)	34 (57)
	cis + vin	60	61 (35-70)	56 (93)	60 (100)	0 (0)	26 (43)	34 (57)
	cis + gem	60	60 (38-70)	54 (90)	60 (100)	0 (0)	24 (40)	36 (60)
	carb + gem	62	NA	--	--	--	--	--
Douillard *et al*, 2005[57]	cis + doc	115	58 (27-75)	96 (83)	97 (84)	18 (16)	0 (0)	115 (100)
	cis + vin	118	57 (27-77)	95 (81)	101 (86)	17 (14)	0 (0)	118 (100)
ECOG 1594[50-52]	cis + doc	304	63 (34-84)	192 (63)	286 (94)	18 (6)	43 (14)	261 (86)
	cis + gem	301	64 (32-87)	187 (62)	286 (95)	15 (5)	42 (14)	259 (86)
	cis+ pac	303	62 (27-84)	194 (64)	285 (94)	18 (6)	33 (11)	270 (89)
	carb + pac	299	63 (30-85)	185 (62)	284 (95)	15 (5)	42 (14)	257 (86)
EORTC 08975[58]	cis + pac	159	57 (27-75)	95 (60)	140 (88)	19 (12)	29 (18)	130 (82)
	cis + gem	160	57 (28-75)	113 (71)	142 (89)	18 (11)	33 (21)	126 (79)
	gem + pac	161	56 (31-75)	110 (68)	142 (88)	19 (12)	29 (18)	132 (82)
FACS[59]	cis + irino	145	62 (30-74)	97 (67)	145 (100)	--	31 (21)	114 (79)
	carb + pac	145	63 (33-74)	99 (68)	145 (100)	--	28 (19)	117 (81)
	cis + gem	146	61 (34-74)	101 (69)	146 (100)	--	30 (21)	116 (79)
	cis + vin	145	61 (28-74)	101 (70)	145 (100)	--	26 (18)	119 (82)
Ferry *et al*. [60]	cis(80) + gem	456	63 (30-79)	286 (63)	--	35 (8)	146 (32)	310 (68)
	cis(50) + gem	454	63 (32-82)	291 (64)	--	34 (7)	145 (32)	309 (68)
	carb + gem	453	63 (29-83)	268 (59)	--	34 (8)	144 (32)	309 (68)
Gebbia *et al*, 2003[61]	cis + ifo + gem + vingi1	62	61 (48-71)	50 (81)	51 (82)	11 (18)	29 (47)	33 (53)
	cis + ifo + gem + vinvc1	60	59 (32-72)	45 (75)	51 (85)	9 (15)	29 (48)	31 (52)
	cis + vin	140	63 (36-72)	106 (76)	116 (83)	24 (17)	65 (46)	75 (54)
	cis + gem	138	60 (38-73)	108 (78)	111 (80)	27 (20)	64 (46)	74 (54)

Trial ID	Treatment	N randomised	Age	Male (%)	ECOG 0/1	ECOG 2	Stage IIIB (%)	Stage IV (%)
GFPC 99-01[62]	cis+ vin	49	56 (35-69)	41 (84)	43 (88)	6 (12)	2 (4)	47 (96)
	carb + gem	51	60 (44-69)	42 (82)	44 (86)	7 (14)	6 (12)	44 (86)
Helbekkmo *et al*, 2007[63]	carb + vin	218	67 (37-86)	128 (59)	156 (72)	62 (28)	65 (30)	153 (70)
	carb + gem	214	67 (37-85)	136 (64)	153 (71)	61 (29)	60 (28)	154 (72)
Kawahara *et al*, 2013[64]	carb + doc	60	67.5	43 (72)	60 (100)	0 (0)	24 (40)	36 (60)
	carb + pac	30	65.5	22 (73)	30 (100)	0 (0)	10 (33)	20 (67)
KEYNOTE-407[7, 8]	pembro + carb + nab/pac	278	65 (29-87)	220 (79)	--	--	--	--
	carb + nab/pac	281	65 (36-88)	235 (84)	--	--	--	--
Martoni *et al*, 2005[65]	cis + vin	137	62 (32-75)	104 (76)	49 (79)	13 (21)	26 (42)	36 (58)
	cis + gem	135	63 (33-77)	110 (81)	50 (86)	8 (14)	22 (38)	36 (62)
Mazzanti *et al*, 2003[66]	cis + gem	62	60 (40-75)	45 (73)	255 (83)	53 (17)	108 (35)	178 (58)
	carb + gem	58	65 (45-75)	49 (84)	256 (83)	53 (17)	90 (29)	191 (62)
Rosell *et al*, 2002 [67]	cis + pac	309	58 (29-78)	253 (82)	--	8 (22)	--	36 (100)
	carb + pac	309	58 (27-76)	258 (83)	--	11 (31)	--	35 (100)
Saad *et al*, 2017[42]	cis + gem	36	NA	26 (72)	194 (95)	--	--	167 (81)
	carb + gem	35	NA	29 (83)	184 (92)	--	--	164 (82)
Scagliotti *et al*, 2002[68]	cis + gem	205	63 (28-81)	167 (81)	185 (92)	--	--	163 (81)
	carb + pac	201	62 (30-77)	152 (76)	--	--	22 (11)	180 (89)
	cis + vin	201	63 (38-78)	157 (78)	--	--	24 (12)	182 (88)
SWOG [69]-9509	cis + vin	202	61 (32-83)	136 (67)	--	--	135 (33)	273 (67)
	carb + pac	206	62 (26-80)	144 (70)	--	--	132 (33)	274 (67)
TAX 326[70]	cis + doc	408	61 (30-81)	294 (72)	--	--	133 (33)	271 (67)
	carb + doc	406	59 (23-87)	292 (72)	377 (99)	1 (0)	38 (10)	341 (90)
	cis + vin	404	61 (35-80)	302 (75)	374 (99)	2 (1)	38 (10)	339 (90)
Treat *et al*, 2010[71]	carb + gem	379	64.1 (37-89)	221 (58)	375 (99)	1 (0)	40 (11)	339 (89)
	gem + pac	377	64.3 (33-91)	236 (63)	--	--	36 (41)	51 (59)
	carb + pac	379	64.1 (39-85)	231 (61)	--	--	34 (38)	55 (62)
Zatloukal *et al*, 2003[72]	cis + gem	87	63 (39-75)	67 (77)	ECOG 0/1	ECOG 2	Stage IIIB (%)	Stage IV (%)
	carb + gem	89	62 (46-76)	68 (76)	18 (53)	16 (47)	9 (26)	25 (74)

ECOG - Eastern Cooperative Oncology Group; cis - cisplatin; carb - carboplatin; gem - gemcitabine; pac - paclitaxel; nab/pac – nab-paclitaxel; doc - docetaxel; vin – vinorelbine; ifo – ifosfamide; irino - irinotecan

Seventeen trials were multicentre RCTs and three trials (Chang *et al*., 2008;[53] Chen *et al*., 2004;[54] Chen *et al*., 2007[55]) were either single centre studies or the number of study sites was not reported. Most studies were Phase II or Phase III trials. Blinding was either not reported or studies were open-label. Trials were published from 2001 and some were still ongoing. Of the trials conducted in only one country, nine were in European countries, two in the USA, two in Taiwan, two in Japan, and one in China. The study designs appear consistent with the NICE scope,[6] but only one of the studies included a UK centre (Ferry *et al*, 2017).[60] Most of the trials were conducted relatively recently. The included trials broadly represent best practice. Maintenance and second-line chemotherapy use was reported in some trials, although there is an absence of second-line immunotherapy in the trials as well as first line immunotherapy for patients with PD-L1 TPS≥ 50% (pembrolizumab monotherapy). Additionally, some of the chemotherapy regimens are not widely used in England.

Eligibility criteria employed within the 20 additional studies in NMA2 are outlined in CS Appendix D[11] (pages 96-97). The majority of trials included patients with an ECOG PS of 0-2. In most trials, patients had to be 18 years old or over and ten trials applied an age cut-off. Patients with Stage IIIB and IV disease were eligible. Comparability of baseline population characteristics for all trials included in the ITCs are summarised on pages 92-93 of CS Appendix D. The ERG notes the following issues in terms of baseline comparability. Those with an ECOG PS of 0-2 were eligible for inclusion in the majority of trials. An ECOG status of 2 is associated with frailty and a high rate of SAEs. By including patients with an ECOG status of 2, studies may have introduced bias in terms of increased AEs, although it appears that the number of patients with ECOG PS 2 was relatively evenly distributed across the arms of the trials. Four studies included exclusively Asian patients (Chang *et al*., 2008;[53] Chen *et al*., 2004;[54] FACS;[59] Kawahara *et al*., 2013[64]), which limits the generalisability of the findings to the patient population in England.

ITC2: Squamous and PD-L1 ≥50%

The CS[1] states that two trials were selected for inclusion in ITC2: KEYNOTE-042[49] and KEYNOTE-407.[7, 8] These trials were selected for inclusion in order to compare pembrolizumab combination therapy with pembrolizumab monotherapy in patients with squamous NSCLC and PD-L1 TPS ≥50%. KEYNOTE-407[7, 8] assessed pembrolizumab combination therapy and KEYNOTE-042[49] assessed pembrolizumab monotherapy. Carboplatin-based combination chemotherapy was the common comparator, but regimens differed between the trials. Whilst KEYNOTE-407[7, 8] was a triple-blinded RCT, KEYNOTE-042[49] was an open-label trial.

Table 6: Study and patient characteristics of RCTs included in ITC2 (adapted from Tables 24 and 25, CS Appendix D1.2.2)

Trial ID	Treatment	N randomised	Age (range)	Male (%)	ECOG 0/1	ECOG 2	Stage IIIB (%)	Stage IV (%)
KEYNOTE -407[7, 8]	pembro + carb + nab/pac	278	65 (29-87)	220 (79)	--	--	--	--
	carb + nab/pac	281	65 (36-88)	235 (84)	--	--	--	--
KEYNOTE -042[49]	Pembro	637	63 (25-89)	450 (71)	--	--	--	--
	carb + pac (or carb + pemetrexed for non-squamous histology)	637	63 (31-90)	452 (71)	--	--	--	--

ECOG - European Cooperative Oncology Group; pembro - pembrolizumab; carb - carboplatin; pac - paclitaxel; nab/pac - paclitaxel/nab-paclitaxel

The patient eligibility criteria for KEYNOTE-042[49] are outlined in CS Appendix D[11] (page 97). In KEYNOTE-042,[49] patients had to be 18 years of age or more, with Stage IIIB and IV disease and an ECOG PS of 0-1, whilst in KEYNOTE-407,[7, 8] only patients with Stage IV disease were eligible. Some baseline characteristics relating to these criteria were not reported in KEYNOTE-042.[49] Consequently, the ERG is unable to make a judgement on baseline comparability across arms for disease stage and ethnicity. Age was comparable across treatment arms and whilst ECOG PS at baseline was not reported, the trial eligibility criteria required ECOG PS of 0 or 1. Neither KEYNOTE-407[7, 8] or KEYNOTE-042[49] included any UK centres. KEYNOTE-042[49] also included non-squamous patients.

Intervention characteristics across ITC1 and ITC2

The intervention characteristics for all RCTs included in both indirect treatment comparisons (n=25) are listed in Table 23 of CS Appendix D.[11] Pembrolizumab dosing was consistent across studies, in line with the NICE scope,[6] and was appropriate for UK practice. The interventions in the comparator studies were gemcitabine, paclitaxel, nab-paclitaxel, vinorelbine, pemetrexed, ifosfamide, irinotecan and docetaxel in combination with either cisplatin or carboplatin. In the CS, the cisplatin dose ranged from 50-120mg in the combination therapy regimens (the recommended monotherapy dose), despite the recommendation that the licensed dose of cisplatin should be reduced to 20mg/m² or more once every 3 to 4 weeks if used in combination therapy. However, the ERG acknowledges that the dose of cisplatin in combination chemotherapy in usual practice in England varies and a dose of 75-80mg/m² is typical. Overall, the intervention characteristics were consistent with the NICE scope, although nab-paclitaxel is not used in England and was not listed as a comparator in the NICE scope. The dosing and method of administration of the comparators was broadly comparable to current practice in England. None of

the studies included in NMA1/ITC1 included information about any second-line therapy given; some trials included in NMA2/ITC1 reported second-line chemotherapy, but not second-line immunotherapy.

CS Appendix D[11] (Tables 26 and 25) reports OS and PFS (or time to progression [TTP]) outcome data for trials included in the ITC. These outcomes are consistent with those outlined in the NICE scope.[6] The CS does not report sufficient information about the methods for assessing outcomes in the ITC trials. Therefore, the ERG cannot make an assessment regarding comparability in the definition of the outcomes and median follow up time.

4.3.4 Quality assessment of studies included in the ITCs

The included trials were quality assessed using the Cochrane Risk of Bias tool. The methods used to perform quality assessment were detailed in CS Appendix D[11] (page 84), and appear appropriate. Full details of the quality assessment for each of the 36 originally included trials are also provided (CS Appendix D, Table 81, page 164). The conclusion drawn from the company's quality assessment was that a majority of trials were judged to be at a low risk of selection, attrition and reporting bias. The ERG has verified a proportion of the CS critical appraisal results and found the quality assessment rating from those assessed to have been carried out accurately. However, the ERG notes that in a number of the trials, reporting was incomplete, therefore the company's assertion of low risk of bias across the majority of trials is overstated.

4.4 Summary and critique of the network meta-analysis and indirect treatment comparison

A summary of the NMAs including the ITC conducted by the company is provided in Table 7. As discussed in Section 4.3, two separate analyses were conducted for synthesising OS and PFS evidence in the two population groups: PD-L1 unselected and PD-L1 strong expression (TPS≥50%). The company's rationale was that PD-L1 expression is a known treatment effect modifier (clarification response,[12] question A5).

For the PD-L1 unselected population, two separate NMAs were performed: NMA1 only included trials with squamous histology patients (5 trials) and NMA2 included trials with patients unselected for histology (36 trials). Within NMA1, two fixed effect models were used – one was based on constant HRs, whilst the other was based on time-varying HRs using Weibull, Gompertz and second-order fractional polynomial models with powers of 0 or 1. The fixed effect model was chosen because of limited data availability. NMA2 utilised a meta-regression model to estimate treatment effects in the squamous population. For OS in one trial, the company imputed the proportion of squamous patients using the mean of all trials reporting the proportion of squamous patients. For PFS, no imputation of the proportion of squamous patients was required. Similar to NMA1, evidence was synthesised

assuming constant HRs and then time-varying HRs. Both fixed effect and random effects analyses were performed.

During the clarification stage, the ERG queried the discrepancy between the NMA results used in the health economic model and the NMA1 and NMA2 results presented in the CS (clarification response,[12] question B9). In response, the company presented an additional NMA whereby combination regimens containing different platinum drug components (carboplatin or cisplatin) were combined. This analysis included trials with squamous histology patients and which included carboplatin or cisplatin in the SC combination chemotherapy regimen (3 trials). This additional analysis is subsequently referred to as "NMA3" in this ERG report. Within NMA3, two fixed effect models were used: one was based on constant HRs, whilst the other was based on time-varying HRs.

For the PD-L1 strong expression subgroup (TPS ≥50%), the KEYNOTE-407[7, 8] and KEYNOTE-042 trials were included in the ITC. The company's reason for excluding KEYNOTE-024[17] was that the number of eligible patients with squamous histology and who received paclitaxel plus carboplatin was small. Several criteria were applied to select the patients from both trials (KEYNOTE-407[7, 8] and KEYNOTE-042) before conducting the ITC:

- squamous and PD-L1 strong expression patients were selected
- from the control group, patients assigned to paclitaxel plus carboplatin from KEYNOTE-042 and to paclitaxel/nab-paclitaxel plus carboplatin from KEYNOTE-407[7, 8] were selected
- patients with overall cancer Stage III at screening were excluded from KEYNOTE-042
- patients with untreated brain metastases were excluded from KEYNOTE-407.[7, 8]

The inverse probability of treatment weighting (IPTW) approach was used to balance the following covariates: ECOG PS (0 vs. 1), smoking status (never vs. former/current), age, gender, baseline tumour size in the two trials before generating the relative treatment effect using a constant HR within each trial. The Bucher method[73] was used for the ITC to obtain the indirect treatment effect based on the estimated constant HRs within each trial.

Table 7: Summary of indirect treatment comparison analysis

Population	Histology	NMA/ITC method	Model	Studies included	Comparator	Used in economic model?
PD-L1 unselected	Squamous	NMA1 (Bayesian)	Fixed effect NMA based on constant HRs	KEYNOTE-407[7, 8] and 4 other RCTs	Carboplatin + paclitaxel/nab-paclitaxel Carboplatin + gemcitabine Cisplatin + gemcitabine Cisplatin + paclitaxel Cisplatin + docetaxel	No
			Fixed effect NMA based on time-varying HRs			No
	Squamous	NMA3* (Bayesian)	Fixed effect NMA based on constant HRs	KEYNOTE-407[7, 8] and 2 other RCTs	Carboplatin/cisplatin + paclitaxel/nab-paclitaxel Carboplatin/cisplatin + gemcitabine Carboplatin/cisplatin + docetaxel	Yes
			Fixed effect NMA based on time-varying HRs			No
	Unselected	NMA2 (Bayesian)	Fixed effect and random effects meta-regression based on constant HRs	KEYNOTE-407[7, 8] and 35 other RCTs	Carboplatin + paclitaxel/nab-paclitaxel Carboplatin + gemcitabine Carboplatin + vinorelbine Carboplatin + docetaxel Cisplatin + gemcitabine Cisplatin + paclitaxel Cisplatin + docetaxel Cisplatin + vinorelbine	No
			Fixed effect and random effects meta-regression based on time-varying HRs			No
PD-L1 strong expression, no overall cancer Stage III at screening, no untreated brain metastases	Squamous	IPTW and Bucher ITC (Frequentist)	Bucher ITC based on constant HRs	KEYNOTE-407[7, 8] and KEYNOTE-042	Carboplatin + paclitaxel/nab-paclitaxel Pembrolizumab monotherapy	Yes (subgroup analysis, PD-L1 TPS≥50%)

ITC - indirect treatment comparison; NMA - network meta-analysis; RCT - randomised control trial; IPTW - inverse probability of treatment weighting
** Additional analysis presented in clarification response B9, whereby regimens containing different platinum drugs were combined*

The results of NMA1 and NMA2 based on constant HRs for the PD-L1 unselected population group can be found in the Tables 33-38 of the CS.[1] The results of NMA1 and NMA2 using time-varying HRs can be found in the CS, Appendix D,[11] Tables 27, 29, 31, 33, 36, 38, 40, 42, 45, 47, 49, 51, 54, 56, 58, 61, 63, 65, 68, 70 and 72. The NMA3 results based on constant HRs used in the company's health economic model are presented in Table 8. For the time-varying NMA3 results, the estimated HRs were reported in a figure format (clarification response,[12] question B9).

Table 8: Results of fixed effect network meta-analysis based on constant hazard ratios and combining platinum regimes (NMA3)

Comparison	HR [95% CrI]
Overall survival	
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. platinum + paclitaxel/nab-paclitaxel	**0.64 [0.49, 0.84]**
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. cisplatin + docetaxel	**0.62 [0.41, 0.94]**
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. platinum + gemcitabine	0.77 [0.49, 1.19]
Platinum + gemcitabine vs. platinum + paclitaxel/nab-paclitaxel	0.83 [0.59, 1.17]
Platinum + gemcitabine vs. cisplatin + docetaxel	0.81 [0.58, 1.12]
Cisplatin + docetaxel vs. platinum + paclitaxel/nab-paclitaxel	1.03 [0.75, 1.42]
Progression-free survival	
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. platinum + paclitaxel/nab-paclitaxel	**0.56 [0.45, 0.70]**
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. cisplatin + docetaxel	**0.53 [0.36, 0.78]**
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. platinum + gemcitabine	**0.63 [0.45, 0.89]**
Platinum + gemcitabine vs. platinum + paclitaxel/nab- paclitaxel	0.89 [0.68, 1.16]
Platinum + gemcitabine vs. cisplatin + docetaxel	0.85 [0.62, 1.15]
Cisplatin + docetaxel vs. platinum + paclitaxel/nab-paclitaxel	1.05 [0.78, 1.43]

CrI - credible interval
Note - bold indicates a statistically significant result

Overall, the constant HR NMA results suggest that pembrolizumab combination therapy is an effective treatment relative to some of the chemotherapy regimens in the PD-L1 unselected population. Depending on the chemotherapy regimen used, pembrolizumab combination therapy could be associated with a statistically significantly or numerically superior HR for both OS and PFS compared to the combination chemotherapy regimens. The time-varying hazard ratios NMA results suggest that

the treatment effects could be time-varying compared to some of the combination chemotherapy regimens, hence the constant HR NMA results should be interpreted with caution.

For the PD-L1 strong expression population (TSP ≥50%), including additional limiting criteria to exclude patients with overall cancer Stage III at screening and those with untreated brain metastases from both trials, the ITC analysis suggests that pembrolizumab combination therapy is numerically superior to pembrolizumab monotherapy for both OS and PFS (HR [95% CI]: OS - 0.97, [0.50, 1.89]; PFS 0.58 [0.33, 1.01]). The ITC HRs used in the economic model do not match these results; the ERG is unclear regarding the source of the values applied in the company's model; this issue is further discussed in Section 5.3.3.

The results for OS and PFS within each KEYNOTE trial with squamous histology and with PD-L1 TPS ≥50% (KEYNOTE-407,[7, 8] KEYNOTE-042[49] and KEYNOTE-024[17]) are presented in Table 9. The table also includes IPTW-adjusted results for KEYNOTE-407 and for KEYNOTE-042. The weighting resulted in more favourable results for pembrolizumab combination therapy for OS and PFS in KEYNOTE-407, and a less favourable result for pembrolizumab monotherapy for OS and the same point estimate for PFS in KEYNOTE-042.

Table 9: Within trial results for overall survival and progression-free survival (squamous histology and PD-L1 strong expression patient population)

	Unadjusted KEYNOTE-024[17] HR [95% CI]	**Unadjusted KEYNOTE-042[49] HR [95% CI]**	**Unadjusted KEYNOTE-407[7, 8] HR [95% CI]**	**Adjusted KEYNOTE-042[49] HR [95% CI]**	**Adjusted KEYNOTE-407[7, 8] HR [95% CI]**
Overall survival	[redacted]	[redacted]	0.64 [0.37, 1.10]	0.60 [0.41,0.88]	0.58 [0.33,1.00]
Progression-free survival	[redacted]	[redacted]	0.37 [0.24, 0.58]	0.61 [0.43,0.85]	0.35 [0.22,0.55]

CI - confidence interval

The ERG notes that the use of a fixed effect model in the NMAs and the Bucher approach in the ITC analysis underestimates the uncertainty in the treatment effect. The ERG also has concerns regarding the validity of the NMAs for the PD-L1 unselected population group. Firstly, KEYNOTE-407[7, 8] was the only trial included in the analyses which had a population in the chemotherapy arm which reflects current clinical practice in England, whereby some patients received second-line immunotherapy following disease progression. Secondly, some of the comparator trials included patients with ECOG PS 2. The clinical advisors to the ERG suggested that patients with ECOG PS 2 are likely to have different survival outcomes compared with patients with ECOG PS 0-1. The inclusion of these trials

without adjustment may lead to biased results. Finally, the clinical advisors to the ERG agreed that platinum-based regimens have very similar efficacy for the population of interest. This view was also supported by the company (clarification response,[12] question B11). In the same response, the company states that the NICE Appraisal Committee agreed with this view in TA411.[74] Assuming no difference in the treatment effect among the chemotherapy regimens, the comparator trials included in NMA1, NMA2, and NMA3 would be excluded from the NMAs as they would become single-arm studies.

For the second-order fractional polynomial model NMAs synthesising time-varying HRs, powers were set to be either 0 or 1. The company did not use negative powers as they led to unstable estimates of the HRs due to over-fitting the data (clarification response,[12] question A12). The ERG is unclear whether using negative powers would lead to an over-fitting problem, as the number of parameters remains the same regardless of the values for the power. The number of samples used in the burn-in period was not provided for the time-varying HRs analysis and the ERG speculates that unstable NMA results may be a result of the Markov chains not reaching convergence.

The company excluded KEYNOTE-024[17] from the ITC because "*the trial population of patients with squamous histology who received paclitaxel + carboplatin chemotherapy was very small (n=5 in each treatment arm)*" (clarification response,[12] question A21). The ERG notes that the published paper for KEYNOTE-024 reported that among the 27 squamous histology PD-L1 strong expression patients in the chemotherapy arm, 15 received carboplatin plus gemcitabine, five received carboplatin plus paclitaxel and seven received cisplatin plus gemcitabine.[75] The pembrolizumab monotherapy arm had 29 squamous histology PD-L1 strong expression patients (clarification response,[12] question A22). It is unclear why the CS[1] only considered patients who received carboplatin + paclitaxel and what "*each treatment arm*" referred to.

CS Appendix D[11] describes that IPTW was used to balance out the four treatment arms, including:

- KEYNOTE-407: pembrolizumab + chemotherapy arm,
- KEYNOTE-407: chemotherapy arm,
- KEYNOTE-042: pembrolizumab arm,
- KEYNOTE-042: chemotherapy arm.

The ERG is unclear whether the IPTW was conducted within each trial or across trials. The ERG was not able to check whether the baseline characteristics were well balanced after weighting, as the before and after weighting results on the standardised mean difference and variance ratio were presented across the four treatment arms, rather than within each trial.

Within each of the KEYNOTE trials (KEYNOTE-407,[7, 8] KEYNOTE-042[49] and KEYNOTE-024[17]), the before-weighting patient characteristics (including ECOG PS, smoking status, age, gender, baseline tumour size) were similar between the two treatment arms. Some small differences were observed for ECOG PS and baseline tumour size. In KEYNOTE-407,[7, 8] the pembrolizumab combination therapy arm had fewer patients with ECOG 0 but larger baseline tumour size than the chemotherapy arm (CS Appendix D,[11] Table 74). In KEYNOTE-042, the pembrolizumab monotherapy arm had smaller baseline tumour size than the chemotherapy arm (CS, Appendix D1.2.3.2 Table 74).[1] In KEYNOTE-024,[60] the pembrolizumab monotherapy arm had fewer patients with ECOG PS 0 and smaller baseline tumour size than the chemotherapy arm (clarification response,[12] question A20).

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG manually searched the clinicaltrials.gov website to confirm that no relevant trials had been missed. The ERG also replicated a CS search strategy to assess whether the number of citations generated was similar when the disease terms for the cost-effectiveness review were applied to the clinical review.

Due to the company's restriction to consider only RCTs, the ERG searched for non-RCT evidence including systematic reviews on evidence related to the safety of pembrolizumab combination therapy. The ERG conducted an additional targeted search in one database only (Medline) to ensure that no relevant drug safety data had been missed. The search was conceptualised from two perspectives:

(i) pembrolizumab AND adverse events AND relevant non-RCT study types (including case control, cohort, longitudinal, cross sectional, prospective, retrospective studies, observational studies and systematic reviews)

(ii) pembrolizumab AND adverse events AND lung or squamous cell cancers.

This dual approach to the search strategy intended to retrieve any evidence on AEs associated with pembrolizumab in other conditions (regardless of study type), and any non-RCT evidence in other types of cancer.

The ERG's search for non-RCT evidence resulted in 590 citations which were then sifted. No registered trials for post-marketing surveillance in the target population were identified; however, a number of relevant real-world studies, case reports and secondary data analyses of AEs in pembrolizumab for NSCLC were retrieved (discussed previously in Section 4.2.3).

The ERG performed additional ITC analyses to include squamous histology and PD-L1 strong expression patients from KEYNOTE-024.[17] The ERG's additional analyses used a Bayesian random effects NMA model.[76] An informative prior distribution proposed by Ren *et al*. (2018)[77] was used for

the heterogeneity parameter as there were few studies included in the network. This prior is a truncated Turner *et al*. (2012)[78] prior (a log normal (-2.56, 1.74^2)). The truncation is based on the judgement that the HR in one study would not be ≥10 times greater than in another.

The ERG's ITC results for both OS and PFS are presented in Table 10. In summary, there is no evidence to suggest there is a difference between pembrolizumab combination therapy and pembrolizumab monotherapy for both OS and PFS, but pembrolizumab combination therapy is associated with a numerically superior HR for PFS compared to pembrolizumab monotherapy. The analyses including unadjusted data from three KEYNOTE trials result in a less favourable treatment effect for both OS and PFS for pembrolizumab combination therapy compared with pembrolizumab monotherapy.

Table 10: ERG's ITC results

Pembrolizumab combination therapy vs. pembrolizumab monotherapy	**Hazard ratio Median [95% CrI]**	**Study included**	**Model**
Overall survival	0.96 [0.33, 2.80]	Adjusted KEYNOTE-407[7, 8] Adjusted KEYNOTE-042[49]	Random effects
	0.91 [0.36, 2.20]	Adjusted KEYNOTE-407[7, 8] Adjusted KEYNOTE-042[49] Unadjusted KEYNOTE-024[17]	Random effects
	1.09 [0.43, 2.68]	Unadjusted KEYNOTE-407[7, 8] Unadjusted KEYNOTE-042[49] Unadjusted KEYNOTE-024[17]	Random effects
Progression-free survival	0.57 [0.21,1.62]	Adjusted KEYNOTE-407[7, 8] Adjusted KEYNOTE-042[49]	Random effects
	0.62 [0.27, 1.51]	Adjusted KEYNOTE-407[7, 8] Adjusted KEYNOTE-042[49] Unadjusted KEYNOTE-024[17]	Random effects
	0.65 [0.29, 1.53]	Unadjusted KEYNOTE-407[7, 8] Unadjusted KEYNOTE-042[49] Unadjusted KEYNOTE-024[17]	Random effects

CrI - credible interval

4.6 Conclusions of the clinical effectiveness section

The ERG considers the KEYNOTE-407[7, 8] trial to be a high-quality RCT which is relevant to the decision problem. Whilst the study did not include any UK centres, the baseline characteristics of the trial population appear to reflect the target population in England. The comparator of carboplatin plus paclitaxel is valid for platinum-based combination chemotherapy and is consistent with the final NICE scope;[79] however, there was no pembrolizumab monotherapy comparator arm in the KEYNOTE-407 trial for those with strong PD-L1 expression (TPS ≥ 50%), as is used in current clinical practice in England. The clinical evidence regarding the efficacy of the intervention using the pre-specified outcomes of OS and PFS for this ongoing trial appears to be accurately reported within the CS.[1]

The results from IA2 of KEYNOTE-407 indicate that pembrolizumab combination therapy is statistically superior to carboplatin plus paclitaxel/nab-paclitaxel for OS, PFS and ORR. Improvements in OS and PFS were observed in all PD-L1 subgroups. The ERG highlights that the OS treatment effect in the pembrolizumab combination therapy arm may be contingent on chemotherapy as a potential treatment effect modifier as it potentially alters PD-L1 status. However, it is unknown whether and how other relevant chemotherapy comparators may alter PD-L1 expression and subsequently effect treatment response to pembrolizumab.

The trials included in the company's NMAs/ITCs for pembrolizumab combination therapy included trials which do not accurately reflect current clinical practice in England, whereby patients may receive second-line immunotherapy following disease progression and patients with strong PD-L1 expression are eligible for first-line pembrolizumab monotherapy. Additionally, some trials of comparators included in the NMA contained some patients with ECOG PS 2, and these patients were not eligible for KEYNOTE-407.[8] The company's ITC (adjusted) analyses trimmed the population; the unadjusted analysis does not trim the population, but potentially could be biased if it is believed that the baselines were not balanced.

Whilst the CS[1] concludes that pembrolizumab combination therapy has an acceptable tolerability profile, the ERG regards the company's safety analysis to reflect a 'light-touch' approach which does not include non-randomised evidence or meta-analyses; an NMA for AE outcomes has not been conducted by the company. Long-term data are lacking, which is of particular importance for PD-L1 drugs whereby IRAEs may occur with a delayed onset to those measured in the KEYNOTE-407 trial. Data from the final analysis of KEYNOTE-407 will help to reduce some of this uncertainty.

5 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC.

5.1 Company's review of published cost-effectiveness studies

The company undertook a systematic review to identify relevant cost-effectiveness studies from published literature and from previous NICE technology appraisals.

5.1.1 Company's search methods

A combined SLR was conducted to identify published studies of cost-effectiveness, HRQoL and cost/resource use. As noted in the critique of the clinical effectiveness review, a different approach was used to conceptualise disease terms for this search than that used in the clinical effectiveness review. The terms used here are more sensitive (i.e. they retrieve more references) but each version found unique results; therefore, maximum retrieval would have been achieved by using a combination of both sets of disease terms for each of the reviews.

A date limit was applied to restrict cost/resource use studies to those published since 2008. When this was queried by the ERG (clarification response,[12] question B3), the company's justification was that this was to intended to capture current clinical practice.

Terms for included study types were based on filters from expert sources, including ScHARR, although some modifications have been made. For example, a geographical filter was applied to the results from the cost/resource use search (CS Appendix G,[11] Table 1, page 190).

Given the limited time available within the STA process, it was not feasible for the ERG to re-run the searches, sifting and study selection with these errors corrected, hence their implications are unclear.

5.1.2 Eligibility criteria for the company's review of published economic evaluations

Whilst the eligibility criteria for the company's review allowed for the inclusion of studies which evaluated any comparator regimen, the criteria specifically defined the intervention as pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel (see CS,[1] Section B.3.1, page 126). As a consequence of this criterion, the company's searches did not identify any relevant economic studies for inclusion in the review.

Additional *ad hoc* searching undertaken by the ERG did not identify any relevant studies in the squamous NSCLC population published after the company's search cut-off date. On the basis of these searches, the ERG notes that a US-based economic analysis of first-line pembrolizumab plus chemotherapy and a platinum drug in patients with non-squamous NSCLC (funded by the company) was published shortly after this cut-off date.[80] This analysis uses a similar approach to the model submitted as part of the CS[1] regarding the use of external data from the US Surveillance Epidemiology and End Results (SEER) registry.[81] The ERG believes that none of the previous NICE technology appraisals of lung cancer treatments have involved the direct use of SEER data to inform the survival model parameters. The ERG considers the use of these data to estimate long-term survival outcomes to be problematic; this issue is discussed in more detail in Section 5.3.3.

5.2 Description of company's health economic analysis

This section provides a detailed description of the methods and results of the company's health economic analysis. The ERG notes that several sections of the CS[1] do not clearly report the analyses that have been done, hence some aspects of the model description presented here are instead reliant on scrutiny of the model formulae by the ERG. However, this is further complicated by a lack of correspondence between the CS and the implemented model and the presence of errors in the model. In addition, the sources of some of the model parameters values (e.g. risks of AEs and time on treatment for pembrolizumab monotherapy) are inconsistent between the CS and the model; this may negatively impact on the accuracy of the information presented throughout this chapter.

5.2.1 Model scope

As part of its submission to NICE,[1] the company submitted a fully executable health economic model programmed in Microsoft Excel®. The scope of the company's model is summarised in Table 11. The company's base case analyses assess the incremental cost-effectiveness of pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel versus standard care (SC) chemotherapy (carboplatin/cisplatin in combination with chemotherapy) from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a 30-year (lifetime) horizon. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Unit costs are valued at 2016/17 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum. The CS[1] reports two sets of base case comparisons:

- **Base Case Analysis 1 (trial comparator).** This analysis compares pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel versus carboplatin and paclitaxel/nab-paclitaxel, based on the KEYNOTE-407 trial[7, 8] and other external data.
- **Base Case Analysis 2 (NMA comparators).** This analysis compares pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel based on the KEYNOTE-407 trial[7,

[8] versus: (i) carboplatin/cisplatin plus docetaxel; (ii) carboplatin/cisplatin plus gemcitabine and (iii) carboplatin/cisplatin plus paclitaxel, based on the company's NMA for the squamous, metastatic PD-L1 unselected NSCLC population[12] and other external data. Within this analysis, the costs and health outcomes for the pembrolizumab group remain identical to those for Base Case Analysis 1. Outcomes for the comparator groups are based on hazard ratios (HRs) derived from the company's NMA3 (see Section 4.4); the corrected version of the company's model provided after clarification[82] applies these HRs to the pembrolizumab combination therapy group as a baseline. The comparator for Base Case Analysis 1 (carboplatin and paclitaxel/nab-paclitaxel) is not included in Base Case Analysis 2.

The CS[1] also reports cost-effectiveness results for three subgroups of patients defined by their level of PD-L1 expression (TPS <1%, TPS 1-49% and TPS ≥50%). Within each PD-L1 subgroup, pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel is compared against carboplatin and paclitaxel/nab-paclitaxel alone (SC chemotherapy), based on KEYNOTE-407[7, 8] (as per Base Case Analysis 1). In addition, within the PD-L1 TPS ≥50% subgroup, the CS presents a further indirect comparison of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel versus pembrolizumab monotherapy, based on patient-level PFS and OS data from selected (partially matched) subsets of patients enrolled in KEYNOTE-407[7, 8] and KEYNOTE-042[49] (referred to as ITC2 in Chapter 4).

Table 11: Summary of company's model scope

Population	*Overall population (Base Case Analyses 1 and 2)* Patients with untreated squamous metastatic NSCLC, with additional characteristics as defined by the KEYNOTE-407 trial[7, 8] inclusion criteria (ECOG PS 0 or 1, no active, symptomatic, or clinically unstable CNS metastases, life expectancy >3 months). *Subgroup analyses by PD-L1 expression* • PD-L1 TPS <1% • PD-L1 TPS 1-49% • PD-L1 TPS ≥50%
Time horizon	30 years (lifetime)
Intervention	Pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel
Comparator	*Overall population – Base Case Analysis 1 (trial comparator)* • Carboplatin plus paclitaxel/nab-paclitaxel *Overall population – Base Case Analysis 2 (NMA comparators)* • Carboplatin/cisplatin plus docetaxel • Carboplatin/cisplatin plus gemcitabine • Carboplatin/cisplatin plus paclitaxel *PD-L1 TPS <1% and TPS 1-49% subgroups* • Carboplatin plus paclitaxel/nab-paclitaxel *PD-L1 TPS ≥50% subgroup* • Carboplatin plus paclitaxel/nab-paclitaxel • Pembrolizumab monotherapy
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs
Price year	2016/17

NSCLC - non-small-cell lung cancer; ECOG - Eastern Cooperative Oncology Group; PS - performance status; PD-L1 - programmed death-ligand 1; TPS - tumour proportion score; QALY - quality-adjusted life year; PSS - Personal Social Services; CNS - central nervous system; NMA - network meta-analysis

Population

The population within the company's base case analyses reflects the intention-to-treat (ITT) population of the KEYNOTE-407 trial[7, 8], that is, patients with untreated squamous metastatic NSCLC, with additional characteristics as defined by the inclusion criteria applied in the KEYNOTE-407 trial[7, 8] (ECOG PS 0 or 1, no active, symptomatic, or clinically unstable central nervous system (CNS) metastases, life expectancy >3 months). The CS[1] does not report the anticipated wording of the marketing authorisation for pembrolizumab combination therapy within the squamous metastatic NSCLC indication. Following a request for clarification from the ERG, the company stated that the proposed indication wording presented in the EMA regulatory submission for the squamous NSCLC indication relates to [redacted] (personal communication – MSD, 06/12/2018). The population included in the company's economic analysis is in line with the final NICE scope[6] and the anticipated marketing authorisation, although the

additional criteria regarding ECOG PS, CNS metastases and remaining life expectancy are not stated in either the population defined in the NICE scope or the anticipated marketing authorisation. The clinical advisors to the ERG noted that the use of pembrolizumab should be in line with the eligibility criteria applied in the KEYNOTE-407 trial.

Within the PD-L1 TPS ≥50% subgroup, the analysis excludes patients with untreated brain metastases; this population may be narrower than the patient population seen in clinical practice. It is unclear whether these patients would be eligible for treatment under the anticipated marketing authorisation in the untreated squamous NSCLC population. Clinical advisors to the ERG noted that in practice, patients with symptomatic or clinically unstable CNS metastases would not be offered treatment with pembrolizumab combination therapy.

Interventions and comparators

The intervention included in the company's model is pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel (pembrolizumab combination therapy). This is in line with the final NICE scope[6] and the anticipated marketing authorisation for pembrolizumab in the first-line metastatic squamous NSCLC indication. Dosing and treatment schedules for the intervention and comparator groups assumed in the company's model are summarised in Table 12. All regimen components are administered via intravenous (IV) infusion. Pembrolizumab is assumed to be given at a dose of 200mg once every 3 weeks (Q3W) for a maximum of 35 doses (approximately 2 years of treatment). Paclitaxel is assumed to be given at a dose of 200mg/m^2, nab-paclitaxel is assumed to be given at a dose of 100mg/m^2 and carboplatin is assumed to be given at a dose of AUC 6 (mg/mL/min – target maximum dose). Platinum-based therapy and chemotherapy (excluding gemcitabine, which is given twice every 3 weeks [Q1.5W]) are each assumed to be administered once every 3 weeks (Q3W) for up to 4 cycles. Within the model, acquisition cost calculations are based on the mean body surface area (BSA) of patients recruited at the European centres in KEYNOTE-407,[7, 8] assuming a population mean value rather than a distribution.

Within the overall squamous PD-L1 unselected NSCLC population, the CS[1] includes pairwise comparisons of pembrolizumab combination therapy against the following regimens:

- Carboplatin plus paclitaxel/nab-paclitaxel (based on KEYNOTE-407[7, 8])
- Cisplatin/carboplatin plus docetaxel (based on the company's NMA [squamous, PD-L1 unselected])
- Cisplatin/carboplatin plus gemcitabine (based on the company's NMA [squamous, PD-L1 unselected])

- Cisplatin/carboplatin plus paclitaxel (based on the company's NMA [squamous, PD-L1 unselected])

Within the company's PD-1L subgroup analyses, the CS[1] includes pairwise comparisons of pembrolizumab combination therapy against the following treatment regimens:

- Carboplatin plus paclitaxel/nab-paclitaxel (PD-L1 TPS<1%, 1-49% and ≥50% subgroups, based on the KEYNOTE-407[7, 8] trial)
- Pembrolizumab monotherapy (PD-L1 TPS ≥50% subgroup only, based on an ITC between KEYNOTE-407[7, 8] and KEYNOTE-042[49]).

The final NICE scope[6] also includes vinorelbine in combination with a platinum drug as a comparator; this regimen is not included in the company's economic analyses due to a lack of relevant evidence (see clarification response,[12] question B11).

The model includes the costs of second-line therapy for all treatment groups. Within the SC chemotherapy comparator groups, the model includes the costs associated with the use of second-line immunotherapy, chemotherapy and platinum drugs. Within the pembrolizumab combination therapy group, the model includes costs associated with second-line chemotherapy and platinum drug regimens only. With the exception of the pembrolizumab monotherapy comparator group, these costs are based on the use of second-line treatments received in KEYNOTE-407.[7, 8] Issues surrounding these data are discussed in Section 5.3.3.

Table 12: Dosing and treatment schedules for first-line treatments included in the company's model*

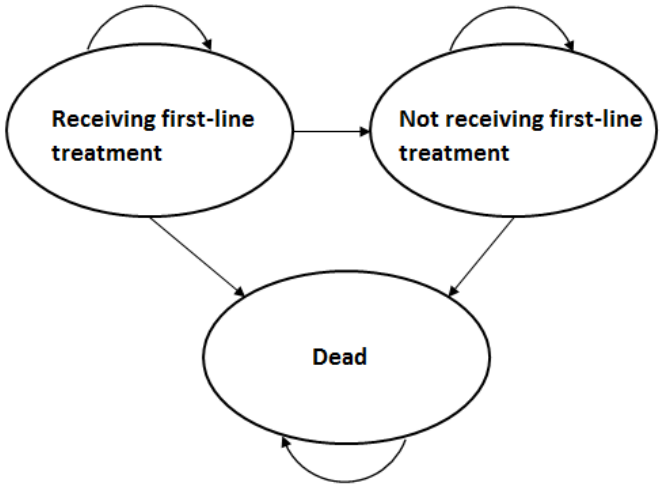
Population	Regimen	Regiment component	Administration route	Dosing schedule	Maximum treatment duration
Overall population and PD-L1 TPS <1%, 1-49% and ≥50% subgroups	Pembrolizumab + carboplatin + paclitaxel / nab-paclitaxel	Pembrolizumab	IV	200mg Q3W	35 cycles (approximately 2 years)
		Carboplatin	IV	AUC 6mg/mL/min Q3W	4 cycles (12 weeks)
		Paclitaxel	IV	200mg/m^2 Q3W	4 cycles (12 weeks)
		Nab-paclitaxel	IV	100mg/m^2 Q1W	4 cycles (12 weeks)
	Carboplatin + paclitaxel / nab-paclitaxel†	Carboplatin	IV	AUC 6mg/mL/min	4 cycles (12 weeks)
		Paclitaxel	IV	200mg/m^2 Q3W	4 cycles (12 weeks)
		Nab-paclitaxel	IV	100mg/m^2 Q1W	4 cycles (12 weeks)
Overall population only	Cisplatin/carboplatin + docetaxel	Cisplatin	IV	75mg/m^2 Q3W	4 cycles (12 weeks)
		Carboplatin	IV	400mg/m^2 Q3W	4 cycles (12 weeks)
		Docetaxel	IV	75mg/m^2 Q3W	4 cycles (12 weeks)
	Cisplatin/carboplatin + gemcitabine	Cisplatin	IV	75mg/m^2 Q3W	4 cycles (12 weeks)
		Carboplatin	IV	400mg/m^2 Q3W	4 cycles (12 weeks)
		Gemcitabine	IV	1,250 mg/m^2 Q1.5W	4 cycles (12 weeks)
	Cisplatin/carboplatin + paclitaxel	Cisplatin	IV	75mg/m^2 Q3W	4 cycles (12 weeks)
		Carboplatin	IV	400mg/m^2 Q3W	4 cycles (12 weeks)
		Docetaxel	IV	200mg/m^2 Q3W	4 cycles (12 weeks)
PD-L1 TPS ≥ 50% subgroup only	Pembrolizumab monotherapy	Pembrolizumab	IV	200mg Q3W	35 cycles (approximately 2 years)

AUC - area under the curve; IV - intravenous; PD-L1 - programmed death-ligand 1; Q1.5W - every 1.5 weeks; Q3W - every 3 weeks; TPS - tumour proportion score.
** Full details of comparator regimens are not included in the CS. The information presented here is taken from the company's model*
† KEYNOTE-407[7] comparator regimen includes placebo (normal saline IV infusion)

5.2.2 Model structure and logic

The CS[1] (page 132) describes the company's economic model as a partitioned survival model based on three health states: (1) progression-free; (2) progressed disease, and (3) dead. The ERG considers this interpretation of the company's implemented model to be misleading: whilst the model defines a partition between the alive health states in terms according to the presence/absence of progression, neither the costs nor health outcomes for any treatment strategy are influenced by progression status. The ERG considers that the company's implemented model is better described as a partitioned survival model based on three health states: (1) receiving first-line treatment; (2) not receiving first-line treatment (including second-line treatment for some patients), and (3) dead (see Figure 4). It should also be noted that this partition influences only the costs of the treatment options; health outcomes are modelled according to time-to-death rather than any explicit definition of the patient's underlying health status.

Figure 4: Company's model structure

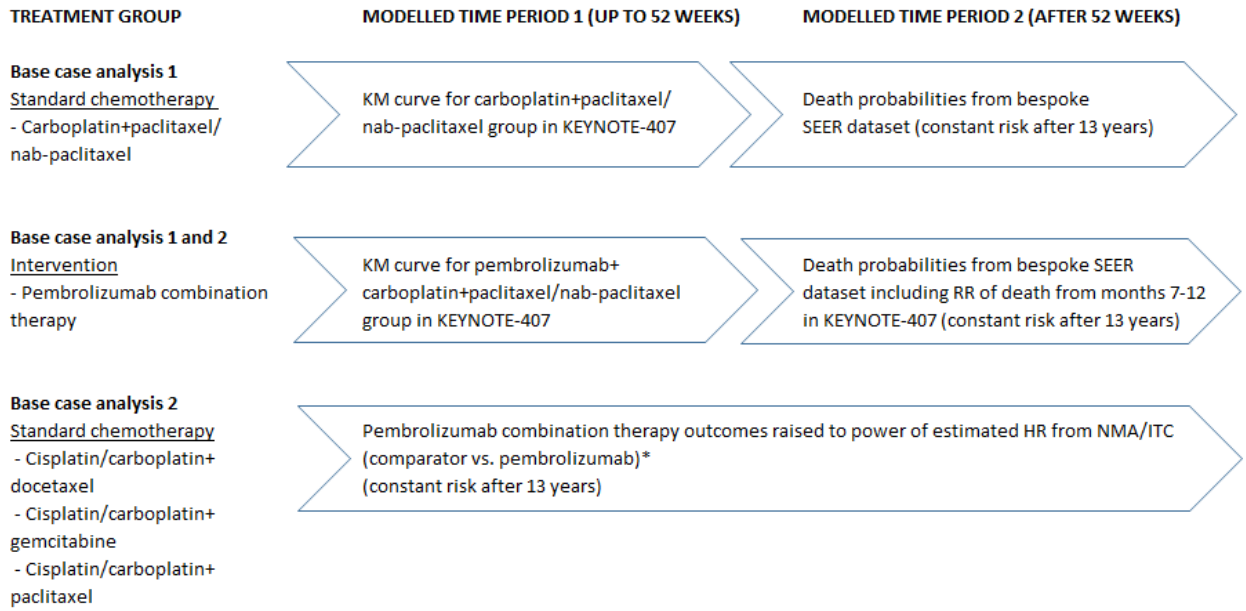


The model operates as follows. Patients enter the model and receive first-line treatment with pembrolizumab combination therapy or platinum-based combination chemotherapy (SC chemotherapy regimen defined according to the source of comparator data outcomes and subgroup, see Table 11). Following discontinuation of first-line therapy, a proportion of surviving patients go on to receive second-line therapy. The risk of death and HRQoL are assumed to be independent of patients' modelled health state.

OS is modelled using a piecewise approach (see Figure 5). Within the comparator group for Base Case Analysis 1, the probability of being alive is determined by the observed KM curve for OS from the KEYNOTE-407 trial[7, 8] up to week 52; beyond this timepoint, the conditional probability of survival in each model cycle is based on a bespoke analysis of data from the US SEER registry.[81] An additional

mortality constraint is also applied to ensure that the probability of survival for the modelled NSCLC population does not exceed that of the general population of England. Within the pembrolizumab combination therapy group, the effect of treatment on OS is modelled by: (i) using the intervention group KM curve from KEYNOTE-407 up to 52 weeks, and (ii) after 52 weeks, applying a constant relative risk (RR) of death (based on a comparison of OS events between treatment groups during months 7-12 in KEYNOTE-407) to the annual SEER OS probabilities for all subsequent model cycles.

Figure 5: Company's approach for modelling overall survival



** The company's application of the HRs from the NMA and ITC within the model is subject to errors - the figure reflects the approach adopted in the company's corrected model submitted following the clarification process (see Section 5.3.3)*

PFS is also modelled using a piecewise approach. Up to 26 weeks, the probability of being alive and progression-free is modelled using the observed KM curves for each treatment group from KEYNOTE-407.[7, 8] Beyond this timepoint, PFS is modelled using parametric (log normal) survivor functions fitted to the observed KM curves for PFS from KEYNOTE-407 using data from week 26 onwards (referred to as a 26-week cut-point). Separate parametric models were fitted to the PFS data for each treatment group, excluding a treatment-indicating covariate. As noted above, PFS has no bearing on the incremental cost-effectiveness ratio (ICER) for pembrolizumab combination therapy, except in one of the company's scenario analyses (see Table 29, company's scenario analysis 7b).

Within Base Case Analysis 2, the health outcomes and costs for the pembrolizumab combination therapy group are assumed to be the same as those for Base Case Analysis 1. In the corrected version of the company's model submitted following the clarification process, PFS and OS outcomes for the

SC chemotherapy comparators are modelled by applying HRs obtained from the company's NMAs to the intervention group PFS and OS curves.

The probability of being in the post-progression state at any time *t* is calculated as the difference between the cumulative survival probabilities for OS and PFS. The model includes the costs associated with second-line treatments; these costs are assumed to be incurred at the point of discontinuation of first-line therapy, rather than at the point of progression.

The model is evaluated using 1-week cycles. Costs and health outcomes evaluated over a total of 1,565 cycles (approximately 30 years). Half-cycle correction is applied to account for the timing of events.

HRQoL is determined largely by the patient's time to death, based on four categorical groups (<30 days; ≥30 to 180 days; ≥180 to 360 days, and ≥360 days). Health utilities are adjusted by age. The model also includes QALY losses associated with Grade 3-5 AEs based on the first-line treatment received; these are applied as a once-only decrement during the first model cycle.

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management; (iv) second-line treatment; (v) management of AEs and (vi) end-of-life (terminal care) costs.

Drug acquisition and administration costs for each regimen are modelled as a function of the planned treatment schedule, the proportionate use of each regimen component (the mix of paclitaxel and nab-paclitaxel or cisplatin and carboplatin), time to treatment discontinuation (TTD), relative dose intensity (RDI) and unit costs. Disease management costs are assumed to include outpatient visits, clinical visits from general practitioners (GPs), nurses and therapists, examinations and tests; lower costs (based on patients being progression-free) are applied to patients whilst receiving first-line treatment and indefinitely for those who receive second-line treatment, whilst higher costs (based on patients with progressed disease) are applied to the remainder. Drug acquisition and administration costs for second-line treatment are applied at the point of discontinuation of first-line therapy based on the proportion of patients who received subsequent therapies by the IA2 of KEYNOTE-407;[7, 8] the use of subsequent immunotherapy (pembrolizumab or nivolumab) is included only for the comparator groups (those options in which pembrolizumab is not given first-line). AE management costs are applied as once-only costs during the first model cycle. End-of-life costs are applied as once-only costs at the point of death. The costs of PD-L1 testing are not included in the company's economic analysis. The analysis includes a price discount for pembrolizumab as part of its company's existing CAA.

5.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions:

- All patients with untreated squamous metastatic NSCLC (within the anticipated licensed population) are assumed to be eligible for treatment with pembrolizumab, irrespective of PD-L1 expression. This includes those patients with PD-L1≥50%, who would be eligible for pembrolizumab monotherapy according to NICE TA531.[83]
- Within Base Case Analysis 1, the probability of PFS for patients in each treatment group is modelled using the observed time-to-event data from the first 26 weeks of KEYNOTE-407;[7, 8] beyond this timepoint, PFS in each treatment group is modelled using log normal models fitted to the post-26 week data from the trial.
- Within Base Case Analysis 2, PFS for the SC chemotherapy comparator group is modelled using HRs from the company's squamous NMA for PFS applied to the cumulative PFS probabilities for the pembrolizumab combination therapy group.
- With the exception of the company's scenario analyses around alternative utility values (see Table 29, company's scenario analysis 7b) the presence/absence of disease progression has no impact on the costs or health outcomes associated with any treatment option.
- Within Base Case Analysis 1, the probability of OS for patients receiving SC chemotherapy is modelled using the observed time-to-event data from the first 52 weeks of KEYNOTE-407;[7, 8] beyond this timepoint, OS is modelled using a bespoke dataset from the US SEER programme (relating to the period 1992 to 2014). A constant mortality risk is applied beyond 13 years; this is analogous to an assumption that OS follows an exponential distribution beyond this timepoint.
- The impact of pembrolizumab combination therapy on OS is modelled by: (i) using the observed time-to-event data from the first 52 weeks of KEYNOTE-407,[7, 8] and (ii) applying an RR derived from an analysis of OS outcomes during months 7-12 of KEYNOTE-407[7, 8] to the annual OS probabilities for the SC chemotherapy comparator group. This treatment effect is assumed to apply indefinitely; the model does not assume any loss of treatment effect on OS during treatment with or after discontinuation of pembrolizumab combination therapy.
- Within Base Case Analysis 2, OS outcomes for the SC chemotherapy comparator groups are modelled using HRs derived from the company's NMA. The ERG believes that the company intended to apply these HRs to the pembrolizumab combination therapy group; however, this analysis was subject to errors which were corrected following the clarification process.[82] These errors are discussed in Section 5.3.3.
- The model includes a general population mortality constraint to ensure that the risk of death for patients with NSCLC is never lower than that for the general population.

- TTD for pembrolizumab combination therapy is modelled using a generalised gamma function fitted to the observed time-to-event data from KEYNOTE-407;[7, 8] this function is truncated at 2 years to reflect the maximum treatment duration for pembrolizumab. TTD for the SC chemotherapy comparator groups (in both Base Case Analyses 1 and 2) is based on the observed KM curve from KEYNOTE-407 (maximum duration = 4 cycles [12 weeks]).
- Base Case Analysis 1 assumes a weighted cost of paclitaxel and nab-paclitaxel (used in combination with carboplatin), based on data from KEYNOTE-407.[7, 8] The CS notes that nab-paclitaxel is not available in England for this group of patients.
- The proportions of patients who receive second-line treatment and the mix of regimens received are assumed to be dependent on the first-line treatment received, and are based on the use of second-line therapies used in KEYNOTE-407.[7, 8] These are modelled as once-only costs.
- Patients who receive pembrolizumab combination therapy as first-line treatment are assumed not to be eligible for second-line treatment with further immunotherapy; these patients are instead assumed to be treated with SC chemotherapy (gemcitabine, paclitaxel, docetaxel, gemcitabine or vinorelbine) with or without a platinum drug (carboplatin or cisplatin).
- A proportion of patients who receive SC chemotherapy including a platinum drug as first-line treatment (i.e. not pembrolizumab) are assumed to receive second-line treatment using immunotherapy (pembrolizumab monotherapy or nivolumab monotherapy). A further proportion of patients are assumed to receive SC chemotherapy (gemcitabine, paclitaxel, docetaxel, gemcitabine or vinorelbine) with or without a platinum drug (carboplatin or cisplatin). Clinical advisors to the ERG noted that in practice, atezolizumab may also be offered as second-line treatment, and that docetaxel may be reserved for third-line treatment; as such, there are some differences between those treatments available in the trial and those used in usual clinical practice.
- HRQoL is modelled according to the patients' time to death rather than the presence/absence of disease progression.
- Only Grade 3-5 AEs occurring in ≥5% patients in one or both treatment groups are included in the company's model. These AEs are assumed to impact on both HRQoL and costs. The ERG notes that as data on AEs were collected up to 30 days and SAEs up to 90 days after the last dose of study medication, these may also include events relating to second-line treatments.
- Health utilities are age-adjusted based on general population norms.
- QALY losses and costs associated with AEs are applied only in the first model cycle, assuming a mean duration of [redacted] days.

5.2.4 Evidence used to inform the company's model parameters

Table 13 summarises the evidence sources used to inform the model's parameters in the company's base case analyses. These are discussed in detail in the subsequent sections. Additional model parameters and evidence sources used in the company's subgroup analyses are described in Section 5.2.5.

Table 13: Summary of evidence used to inform the company's base case analyses

Parameter group	Source
Patient characteristics (age, BSA, weight)	Based on characteristics of trial participants enrolled at European sites in KEYNOTE-407.[7, 8]
PFS - carboplatin+paclitaxel/nab-paclitaxel	Observed comparator group KM function for first 26 weeks followed by log normal model fitted to post-26-week data from KEYNOTE-407.[7, 8]
PFS - pembrolizumab combination therapy	Observed intervention group KM function for first 26 weeks followed by log normal model fitted to post-26-week data from KEYNOTE-407.[7, 8]
OS - carboplatin+paclitaxel/nab-paclitaxel	Observed comparator group KM function for first 52 weeks from KEYNOTE-407;[7, 8] after 52 weeks, mortality is modelled using data from SEER.[81] A constant mortality rate is assumed beyond 13 years. Modelled OS is constrained by general population mortality risk.
OS - pembrolizumab combination therapy	Observed intervention group KM function for first 52 weeks from KEYNOTE-407;[7, 8] after 52 weeks, mortality is modelled using data from SEER,[81] adjusted using an RR for death derived from data for months 7-12 in KEYNOTE-407.[7, 8] A constant mortality rate is assumed beyond 13 years. Modelled OS is constrained by general population mortality risk.
Mortality - general population	Derived from interim life tables for England.[84]
HRs for PFS - platinum drug plus docetaxel, gemcitabine or paclitaxel versus pembrolizumab combination therapy	Company's NMA (squamous, PD-L1 unselected).[12]
HRs for OS - platinum drug plus docetaxel, gemcitabine or paclitaxel versus pembrolizumab combination therapy	Company's NMA (squamous, PD-L1 unselected).[12]
TTD - pembrolizumab combination therapy	Generalised gamma model fitted to observed TTD data from KEYNOTE-407[7, 8] (truncated at 2 years).
TTD - SC chemotherapy	Observed KM curve for TTD from KEYNOTE-407[7, 8] (truncated at 12 weeks)
HRQoL	EQ-5D-3L data collected in KEYNOTE-407.[7, 8] Data analysed according to time to death (≥360 days, 180-360 days, 30-180 days and <30 days).
QALY loss resulting from AEs	EQ-5D-3L data collected in KEYNOTE-407[7, 8] (progression-free patients only). Disutility applied equally to all included AEs for a mean duration of [redacted] days.
Probability of receiving second-line therapy	Based on KEYNOTE-407.[7, 8]
Duration of second-line therapy	KEYNOTE-407.[7, 8]
Drug acquisition costs	Commercial Medicines Unit (CMU) Electronic Market Information Tool (eMIT)[85] and British National Formulary (BNF).[86]
Drug administration costs	NHS Reference Costs 2016/17.[8, 87]

Parameter group	Source
RDI	Based on KEYNOTE-407.[7, 8]
Disease management costs	Various sources including Brown *et al*[88] and NHS Reference Costs 2016/17[87]
Costs associated with AEs	Based on Brown *et al*,[88] previous NICE TAs,[74, 89-96] NHS Reference Costs 2016/17[87] and additional assumptions.[1]

AE - adverse event; BSA - body surface area; EQ-5D-3L - Euroqol EQ-5D 3-level; HR - hazard ratio; HRQoL - health-related quality of life; NMA - network meta-analysis; OS - overall survival; PD-L1 - programmed death-ligand 1; PFS - progression-free survival; QALY - quality-adjusted life year; TTD - time to treatment discontinuation

Initial patient characteristics at model entry

The model assumes an initial starting age of 65 years, a mean weight of [redacted] and a BSA of [redacted]; these characteristics reflect those of trial participants enrolled at European sites within KEYNOTE-407.[7, 8] All patient characteristics are applied as population mean values rather than using distributions.

Time-to-event parameters

Overall survival

The company's model adopts a piecewise approach for OS. The model uses the observed OS data from each arm of KEYNOTE-407[7, 8] up to a defined cut-point followed by the use of external data from SEER[81] thereafter, with an additional relative treatment effect applied for the pembrolizumab combination therapy group. This approach was adopted because the company's earlier attempts to apply piecewise parametric models using the KEYNOTE-407 data[7, 8] with a cut-point of 19 weeks produced *"potentially clinically implausible OS results for the SoC [standard of care] arm of 1-2% at 5 years"* (CS,[1] page 138). The CS argues that the predictions of the conventional parametric models were implausible due to the availability of immunotherapy as second-line therapy in England. CS Appendix L[11] provides more detail on these analyses, including goodness-of-fit statistics using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) (see Appendix 1), cumulative hazard plots and plots of the modelled survivor functions for OS. However, these parametric models are not used in the company's base case analyses and only two alternative parametric models - the exponential and log logistic function using a 19-week cut-point - are applied in the company's sensitivity analyses (see Table 29, company's scenario analyses 1a and 1b).

Within the company's Base Case Analysis 1, OS for the SC chemotherapy group is modelled using the observed KM function for the first 52 weeks. Beyond this timepoint, OS is modelled using death probabilities obtained from a bespoke analysis of the SEER database (data shown in Table 14). The bespoke SEER dataset[81] relates to US patients with metastatic squamous NSCLC who were diagnosed during the years 1992-2014.[1] The dataset started 2 months from the date of the patients' diagnosis to reflect the population enrolled into KEYNOTE-407.[7, 8] Different cohorts from SEER were used to estimate annual mortality risks for different time intervals: data from the period 2010-2014 were used to assess survival during years 1-5 of follow-up, data from 2000-2014 were used for years 6-10 of follow-up and data from 1992-2014 were used for years 11-13 of follow-up. No information is presented

in the CS[1] regarding why different SEER datasets were used for these three periods in the model or whether the three SEER cohorts were similar. As the SEER dataset had a maximum of 13 years follow-up, the annual mortality probability from SEER in year 13 was applied to all subsequent years in the company's model; this is equivalent to assuming an exponential OS model from this timepoint. Within the pembrolizumab combination therapy group of the model, a constant RR of death is applied to the SEER death probabilities; this treatment effect estimate was obtained from a comparison of death events between the treatment arms of KEYNOTE-407[7, 8] from months 7-12. This RR is applied to the annual mortality risk from SEER; the adjusted annual mortality probability is then converted to a weekly probability of death in each treatment group using standard methods for adjusting cycle duration[97] (assuming constant event risk in each period). In both treatment groups, the modelled survivor functions are further adjusted using life tables to ensure that the probability of death in the modelled cohort is never lower than that of the general population. The ERG notes that this constraint applies within both treatment groups, albeit at different timepoints, and is analogous to an implicit assumption of cure (see Section 5.3.3). As shown in Table 14, the risk of death for patients in the pembrolizumab combination therapy group is assumed to continue indefinitely despite the relatively short duration of pembrolizumab treatment (maximum duration = 2 years, RR of death applied to every weekly model cycle from year 2 onwards).

Table 14: SEER data, treatment effects and cycle conversion applied in the company's model

Year	Annual probability death – SC chemotherapy	Annual probability with pembrolizumab combination therapy (RR adjusted)	Weekly probability death – SC chemotherapy	Weekly probability death – pembrolizumab combination therapy
2	0.5427	0.3130	0.0149	0.0072
3	0.4118	0.2375	0.0101	0.0052
4	0.2253	0.1299	0.0049	0.0027
5	0.2189	0.1262	0.0047	0.0026
6	0.1972	0.1137	0.0042	0.0023
7	0.1638	0.0945	0.0034	0.0019
8	0.1598	0.0921	0.0033	0.0019
9	0.1288	0.0743	0.0026	0.0015
10	0.1191	0.0687	0.0024	0.0014
11	0.1692	0.0976	0.0035	0.0020
12	0.0795	0.0458	0.0016	0.0009
13+	0.0985	0.0568	0.0020	0.0011

RR – risk ratio

Figure 6 and Figure 7 present the modelled survivor functions for pembrolizumab combination therapy and carboplatin plus paclitaxel/nab-paclitaxel based on the company's piecewise KEYNOTE-407[7]/SEER[81] model, together with a comparison against the company's fitted piecewise parametric models using data from KEYNOTE-407[7, 8] assuming a 19-week cut-point.

Figure 6: Modelled OS functions estimated using Kaplan-Meier/SEER and piecewise parametric curve-fitting approaches, pembrolizumab combination therapy group in KEYNOTE-407 – figure redacted due to AiC

Figure 7: Modelled OS functions estimated using Kaplan-Meier/SEER and piecewise parametric curve-fitting approaches, SC chemotherapy group in KEYNOTE-407

***figure redacted due to AiC**

With respect to the SC chemotherapy comparator groups in Base Case Analysis 2 (carboplatin/cisplatin plus docetaxel, gemcitabine or paclitaxel), OS is modelled using HRs from the company's NMA.[12] The modelled survivor functions for all treatments included in the company's base case analyses are presented in Figure 8. The methods by which the company estimated cumulative OS probabilities for the NMA comparators in the model were not described in the CS.[1] Given that the HRs applied in the model are greater than 1.0, this would indicate that these were intended to be applied to the pembrolizumab combination therapy group as a baseline (by raising the cumulative OS probabilities to the power of the HR). This is the approach taken to apply relative treatment effects for PFS in the company's model. However, the calculations used to apply OS treatment effects in the company's original submitted model are unusual and use modelled projections from the trial comparator group rather than the intervention group. The ERG believes that this aspect of the company's model is subject to errors which invalidate the results of Base Case Analysis 2; the curves presented in Figure 8 which use functions from the company's original submitted model (prior to correction), should therefore be interpreted with caution. These errors are described in detail in Section 5.3.3.

Figure 8: Modelled OS functions for all treatment options included in company's base case analyses (includes general population mortality constraint)*†

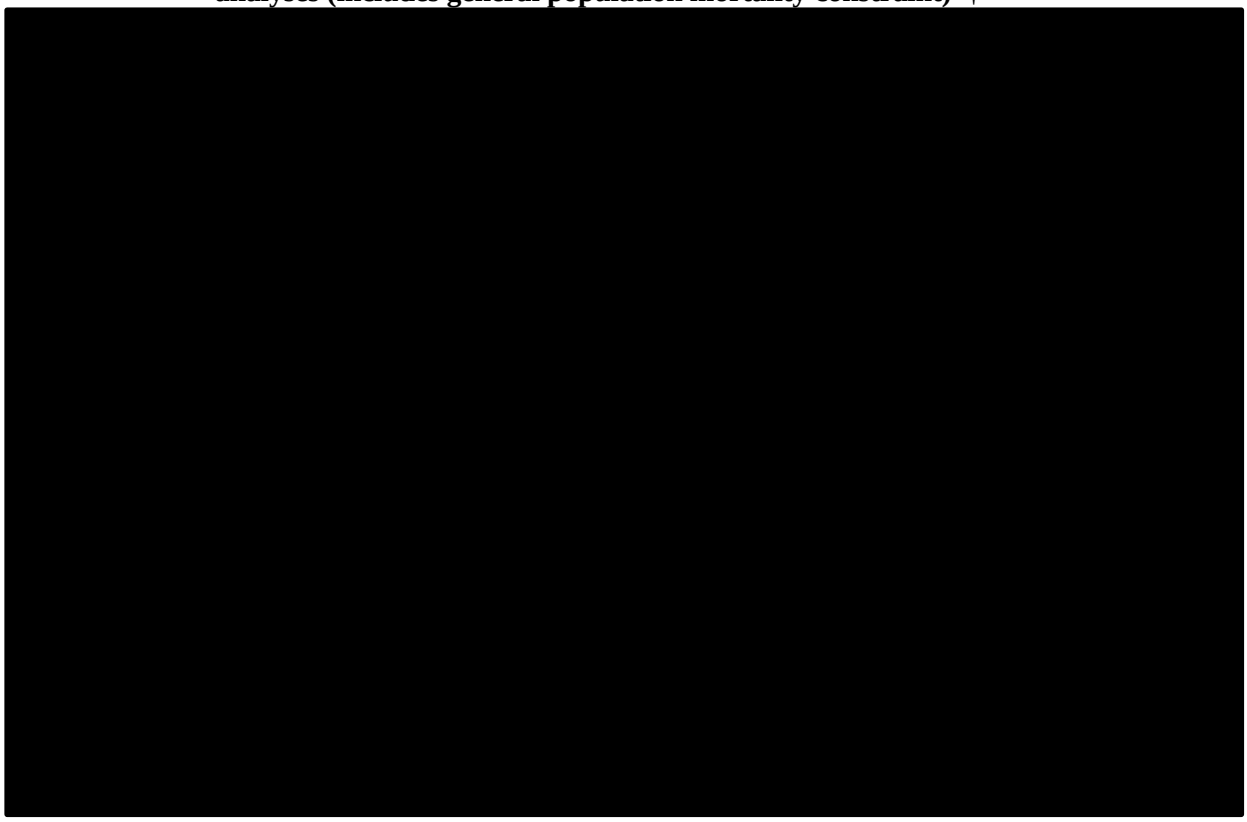


**figure redacted due to AiC*
** Survivor functions for the NMA comparator groups are subject to programming errors and are therefore incorrect*
† Note - the modelled OS function for carboplatin/cisplatin+paclitaxel is almost identical to the OS function for carboplatin+paclitaxel/nab-paclitaxel

PFS

The company's model also adopts a piecewise approach for PFS. The decision to adopt this approach was taken on the basis that the PFS curves for the treatment arms in KEYNOTE-407[7, 8] overlapped during the first 6 weeks.[11] According to CS Appendix L,[11] this *"did not allow the fitting of a full parametric curve."* Within Base Case Analysis 1, PFS for both treatment groups is modelled using the observed KM function up to 26 weeks, and using a log normal function fitted to the post-26 week data from KEYNOTE-407[7, 8] thereafter. The decision to use a 26-week cut-point was made based on the results of Chow tests and examination of the cumulative hazard functions for PFS. The use of alternative data cut-points of 16 weeks and 36 weeks and one alternative parametric model form (the generalised gamma function, 26-week cut-point) was explored in the company's scenario analyses (see Table 29).

Table 15 presents the AIC and BIC statistics for the company's fitted parametric models for PFS using alternative data cut-points; the best-fitting models are highlighted in bold. Figure 9 and Figure 10 present the modelled PFS survivor functions using the piecewise parametric models for the pembrolizumab combination therapy and SC chemotherapy groups, respectively.

Table 15: AIC and BIC statistics for company's piecewise parametric models for PFS

Week 16 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Week 26 cut-point (base case)				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Week 36 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; SC - standard care.
Best fitting models (lowest AIC/BIC) presented in bold

Figure 9: Modelled PFS functions using company's piecewise parametric curve-fitting approach, pembrolizumab combination therapy group in KEYNOTE-407, week 26 cut-point – Figure redacted due to AiC

Figure 10: Modelled PFS functions using company's piecewise parametric curve-fitting approach, SC chemotherapy group in KEYNOTE-407, week 26 cut-point – Figure redacted due to AiC

Within Base Case Analysis 2, the PFS functions for the SC chemotherapy options were modelled by applying an HR from the NMA to the cumulative PFS probabilities for the pembrolizumab combination therapy group in each cycle. Unlike the approach used to model OS, this was implemented by raising the cumulative PFS probabilities in the pembrolizumab combination therapy group to the power of the HR obtained from the NMA. Figure 11 presents the PFS functions for all treatment options included in the company's base case analyses. As shown in the figure, there is little difference in terms of PFS between any of the SC chemotherapy comparators; according to the company's model, pembrolizumab combination therapy is assumed to offer a considerable PFS advantage over existing treatments and a small proportion of patients (~2%) are assumed to remain alive and progression-free at 30-years. However, as noted in Section 5.2.2, the patient's progression status has no bearing on the ICER within the company's base case analyses.

Figure 11: Modelled PFS functions for all treatment options included in company's base case analyses, week 26 cut-point (includes general population constraint)

**Figure redacted due to AiC*

Time to treatment discontinuation (TTD)

The TTD data from KEYNOTE-407[7, 8] include both treatment discontinuation and death whilst on treatment as events (clarification response,[12] question B26). The company's model uses different approaches for modelling TTD depending on the treatment group under consideration. Within the base case analyses, TTD was modelled using data from KEYNOTE-407.[7, 8]

The company fitted standard parametric models (exponential, Weibull, log normal, log logistic, Gompertz and generalised gamma distributions) to the observed TTD data for the pembrolizumab combination therapy group from KEYNOTE-407[7, 8] (maximum follow-up of 77.86 weeks, Figure 12). The CS[1] notes that "*an estimated 16% of patients were still on pembrolizumab combination treatment as of the longest available follow-up time as of the cutoff date (April 2018)*". The generalised gamma distribution was selected for use in the company's base case analyses based on its AIC and BIC combined with visual inspection (CS Appendix N,[11] page 350); the ERG notes that the exponential model had a lower BIC than the generalised gamma (see Table 16). Within the model, TTD for pembrolizumab combination therapy is truncated at 2 years to reflect the maximum treatment duration.

Within the SC chemotherapy group, TTD is modelled using the KM curve from KEYNOTE-407[7, 8] directly; parametric curves were not required as the maximum treatment duration for chemotherapy is 12 weeks (4 treatment cycles). TTD for the NMA comparators was assumed to be the same as that for the carboplatin plus paclitaxel/nab-paclitaxel group in KEYNOTE-407.[7, 8]

Table 16: AIC and BIC statistics for company's parametric curve-fitting for TTD within the overall population of KEYNOTE-407[7, 8]

Model	Pembrolizumab combination		SC chemotherapy	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	N/a	N/a
Weibull	[redacted]	[redacted]	N/a	N/a
Log normal	[redacted]	[redacted]	N/a	N/a
Log logistic	[redacted]	[redacted]	N/a	N/a
Gompertz	[redacted]	[redacted]	N/a	N/a
Generalised gamma	[redacted]	[redacted]	N/a	N/a

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; SC - standard care; N/a - not applicable
**Best fitting models (lowest AIC/BIC) presented in bold*

Figure 12: Modelled TTD functions, pembrolizumab combination therapy group in KEYNOTE-407 – Figure redacted due to AiC

Figure 13 summarises the TTD functions for all options included in the company's base case analyses.

Figure 13: Modelled TTD functions for all treatment options included in company's base case analyses – Figure redacted due to AiC

Health-related quality of life

The KEYNOTE-407[8] trial included the measurement of HRQoL using the EQ-5D-3L questionnaire.[7] Within the trial, the EQ-5D-3L was administered at baseline and every 3 weeks until week 18, then every 9 weeks whilst patients were on treatment, for up to 48 weeks; in the case of treatment discontinuation, the questionnaire was also applied at the 30-day post-treatment safety follow-up visit.[1] The CS[1] is somewhat ambiguous regarding which HRQoL instrument was used to determine health utilities in the company's model. Specifically, page 73 of the CS states that the EQ-5D VAS was used to characterise utility values for the model; the ERG notes that this is not a preference-based instrument. In response to a request for clarification from the ERG[12] (question B6), the company stated that the EQ-5D-3L questionnaire was used. The ERG cannot verify this because the CSR[7] does not report any results from the EQ-5D-3L questionnaire.

In contrast to the majority of previous economic evaluations of cancer therapies, the company's base case analyses assume that HRQoL is dependent on the patients' time to death rather than the presence/absence of disease progression; the use of pre- and post-progression utility values is considered in the company's scenario analyses only (see Table 29). Within the company's base case analyses, time to death is defined in terms of four categories: <30 days to death and ≥30 days to 180; ≥180 to 360 days, and ≥360 days. The CS[1] (page 133) states that this approach is intended to reflect capture patients' HRQoL "*as a function of how much lifetime patients had left until they eventually died as predicted in the model.*" The CS also states that utilities defined by progression status in KEYNOTE-407[7, 8] do not show a large difference between the states due to the use of subsequent-line immunotherapy in the comparator arm and due to limitations in data collection for patients with progressed disease (see CS,[1] page 163). The CS does not provide any details regarding how the utility values for each time-to-death category were estimated from the trial data (i.e. if a statistical model was used or whether the utilities reflect the raw data). The utilities for each time-to-death category are assumed to be the same for the SC chemotherapy and pembrolizumab combination therapy groups; however, different utility values are applied for the pembrolizumab monotherapy comparator included in the company's subgroup analyses (see Section 5.2.5, Table 22). The CS does not provide justification for this approach.

Within the model, the proportion of patients in the time-to-death categories at each time *t* were calculated as follows:

- < 30 days from death – calculated as the probability of dying during the interval *t*+0 cycles and *t*+3 cycles;
- ≥30 days to 180 days from death – calculated as the probability of dying during the interval *t*+4 cycles and *t*+25 cycles;

- ≥180 to 360 days from death – calculated as the probability of dying during the interval *t*+26 cycles and *t*+50 cycles;
- ≥360 days from death – calculated as the complement of the sum of the probabilities of being in the other three states.

Table 17 summarises the EQ-5D-3L estimates applied using the company's time-to-death approach.

Table 17: Mean EQ-5D utilities used in the company's base case analyses (applied to all treatment groups)

Time-to-death category	Utility value
≥360 days	[redacted]
180 to 360 days	[redacted]
30 to 180 days	[redacted]
<30 days	[redacted]

Health utilities are adjusted by age through the application of utility decrements based on sex-specific UK general population utilities reported by Ara and Brazier.[98] These decrements are assumed to increase linearly until the age of 75 years; beyond this age, a constant decrement is applied each year. The CS[1] states that the HRQoL of caregivers was not included in the analyses due to a lack of data.

QALY losses associated with AEs

The model includes QALY losses associated with Grade 3-5 AEs for all treatment groups. The disutility for Grade 3-5 AEs was based on the difference between EQ-5D utility in patients who were progression-free with and without Grade 3-5 AEs in KEYNOTE-407,[7, 8] based on pooled data for both treatment groups. The methods for deriving these estimates (e.g. how time and multiple observations were dealt with) were not described in the CS.[1] This disutility was then multiplied by the mean duration of AEs observed in the trial ([redacted] days) and by the sum of the AE incidence rates within each trial arm (note – this value is normalised; this issue is discussed further in Section 5.3.3). Table 18 summarises the QALY losses applied to each treatment group in the model; each estimate is applied as a once-only health decrement during the first model cycle.

Table 18: Utilities, disutilities and QALY losses for Grade 3-5 AEs used in the model

Estimate	Pembrolizumab combination therapy (KEYNOTE-407[7, 8])	SC chemotherapy (KEYNOTE-407[7, 8])
Mean utility in patients with Grade 3-5 AEs	[redacted]	[redacted]
Mean utility in patients without Grade 3-5 AEs	[redacted]	[redacted]
Disutility of Grade 3-5 AEs	[redacted]	[redacted]
Mean QALY loss per patient due to Grade 3-5 AEs	[redacted]	[redacted]

AEs – adverse events

Treatment effects on PFS and OS from NMAs / indirect comparisons (applied in Base Case Analysis 2 and subgroup analyses)

A summary of the NMAs and ITC analysis undertaken by the company can be found in Section 4.4 of this report. The ERG notes that the NMAs used in the company's model were not presented in the CS[1] or the CS appendices.[11] The correct NMAs were later provided by the company as an additional analysis in response to a request for clarification from the ERG (see clarification response,[12] B9).

Resource costs

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management; (iv) second-line therapy; (v) management of AEs and (vi) end-of-life (terminal care) costs. Table 19 summarises the costs for each treatment group in the company's base case analyses; the derivation of these values is described in the subsequent sections.

Table 19: Costs parameters for each comparator used in the model

Cost parameter	Pembrolizumab combination therapy*	Carboplatin+ paclitaxel/nab-paclitaxel	Platinum+ docetaxel	Platinum+ gemcitabine	Platinum+ paclitaxel
Drug costs* (per 3-week cycle)	[redacted]	£576.69	£48.90	£60.13	£53.06
RDI	93.50%	98.12%	98.12%	98.12%	98.12%
Administration costs (per 3-week cycle)	£607.52†	£433.52	£266.52	£471.29	£269.86
% of patients receiving 2nd line treatment	27.39%	51.92%	51.92%	51.92%	51.92%
2nd line treatment costs (once-only)	£571.87	£5,038.88	£5,038.88	£5,038.88	£5,038.88
Disease management – progression-free (weekly)	£89.53	£89.53	£89.53	£89.53	£89.53
Disease management – progressed disease (weekly)	£144.33	£144.33	£144.33	£144.33	£144.33
Terminal care (once-only)	£4,404.26	£4,404.26	£4,404.26	£4,404.26	£4,404.26
AEs	£1,256.99	£1,216.98	£1,216.98	£1,216.98	£1,216.98

AE – Adverse event; RDI: relative dose intensity;
** Includes CAA for pembrolizumab; † The ERG notes that the calculations used for the administration costs of pembrolizumab combination therapy are unusual – whilst this is likely to reflect an error, the magnitude of this is minor*

[redacted]*(i) Drug acquisition costs* [redacted]All first-line treatments are costed based on 3-weekly cycles. Treatment with pembrolizumab is assumed to have a maximum duration of 2 years (up to 35 administrations), whilst SC chemotherapy, either alone or in combination with pembrolizumab, is assumed to have a maximum duration of 4 treatment cycles (12 weeks). The acquisition costs for each cycle of pembrolizumab are calculated as a function of the cost per vial and a fixed dose per infusion. Based on its list price,[86] the cost per 100mg vial of pembrolizumab is £2,630; each treatment cycle requires 2

vials (pembrolizumab acquisition cost per treatment cycle = £5,260). The company currently has a CAA in place for pembrolizumab; the acquisition cost of pembrolizumab including the CAA is [redacted] per treatment cycle (discount from list price = [redacted]). The costs of paclitaxel, nab-paclitaxel and carboplatin were based on costs estimated from values from eMIT[85] and the use each regimen component within KEYNOTE-407.[7, 8] The acquisition costs for the SC chemotherapy regimens were based on market share data[99, 100] and prices from eMIT.[85] All drug acquisition drugs are adjusted by RDI estimates from the KEYNOTE-407 trial;[7, 8] the same RDI is assumed for all chemotherapies. Drug acquisition costs exclude wastage.

(ii) Drug administration costs

Administration costs for pembrolizumab and SC chemotherapy regimens were taken from the National Tariff Chemotherapy Regimens list 2017-2018[101] and NHS Reference Costs 2016/17[87] (see Table 20).

Table 20: Administration costs assumed for each treatment regimen

Regimen	Assumed administrations per cycle	Unit cost per administration	Source
Pembrolizumab	1 x SB12Z (outpatient)	£173.99	National Tariff Chemotherapy Regimen List 2017-2018[101] and NHS Reference Costs 2016/17[87]
nab-paclitaxel/carboplatin	1 x SB14Z (outpatient) + 2 x SB15Z (outpatient)	£680.04	
Docetaxel+carboplatin	1 x SB13Z (outpatient)	£264.56	
Docetaxel+cisplatin	1 x SB14Z (oupatient)	£269.86	
Gemcitabine+carboplatin	1 x SB13Z (outpatient) + 1 x SB15Z (outpatient)	£469.65	
Gemcitabine+cisplatin	1 x SB14Z (outpatient) + 1 x SB15Z (outpatient)	£474.95	
Paclitaxel+carboplatin	1 x SB14Z (outpatient)	£269.86	
Paclitaxel+cisplatin	1 x SB14Z (outpatient)	£269.86	

Source: CS[1] and company's model
SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance; SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; SB15Z - Deliver subsequent elements of a chemotherapy cycle

The administration costs for each treatment regimen are also adjusted by the RDI observed in KEYNOTE-407.[7, 8]

(iii) Disease management costs

Health care resource use estimates include the costs associated with visits from GPs, nurses, therapists, outpatient appointments, examinations and tests and supportive care; different costs are estimated for patients who are progression-free and for those with progressed disease, although these states are not used in the model. The costs for PFS were derived from a variety of sources including: a previous health

technology assessment (HTA) report of first-line chemotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC (Brown *et al*[88]); the previous NICE appraisal of necitumumab for locally advanced or metastatic EGFR-expressing squamous NSCLC (TA411);[102] NHS Reference Costs 2016/17;[87] the Personal Social Services Research Unit (PSSRU),[103] and additional assumptions.[1] The mean costs associated with being progression-free or having progressed disease are assumed to be the same across all treatment options (see Table 19).

Management costs associated with being progression-free are applied to patients whilst they are receiving first-line treatment based on the TTD curves; for patients who go on to receive second-line treatment, these costs are applied indefinitely, irrespective of second-line treatment duration. Conversely, management costs associated with having progressed disease are applied only to those patients who have discontinued first-line treatment and do not go on to receive second-line treatment. The ERG does not consider this approach to be appropriate; this is discussed further in Section 5.3.3.

(iv) Second-line treatment costs

The model includes the costs of second-line treatment for a proportion of patients in all treatment groups based on IA2 of KEYNOTE-407;[7, 8] the second-line regimens available and the proportions of patients receiving these are assumed to differ by treatment group. Patients who discontinue first-line pembrolizumab treatment are assumed not to be eligible for second-line immunotherapy; instead, approximately 27.4% of patients are assumed to receive second-line treatment with SC chemotherapy (carboplatin/cisplatin in combination with gemcitabine, or docetaxel, gemcitabine or vinorelbine alone). Conversely, approximately 51.9% of patients in the SC chemotherapy comparator groups are assumed to be receive second-line treatment with immunotherapy (nivolumab or pembrolizumab [approximately [redacted] of patients]), chemotherapy (carboplatin/cisplatin in combination with gemcitabine, or docetaxel, gemcitabine or vinorelbine alone), or a combination of both. Clinical advisors to the ERG noted differences between the second-line treatments available in the trial and those available in usual clinical practice (e.g. patients who receive first-line platinum-doublet therapy would be unlikely to receive platinum-doublet therapy again, unless there was a prolonged period of remission). The costs associated with second-line drug acquisition and administration for each modelled treatment group are then generated by multiplying the distribution of the use of each drug observed in KEYNOTE-407[7, 8] by the relevant unit costs and the proportion of patients receiving each regimen (see Table 19). Second-line treatment costs are applied at the point of discontinuation of first-line therapy, rather than at the time of progression.

(v) AE management costs

Costs associated with managing AEs are calculated using the weighted average of the incidence of each Grade 3-5 AE in each treatment arm in KEYNOTE-407 and the unit cost for each AE type (see Table

21). Unit costs were taken from Brown *et al*,[88] previous NICE STA submissions,[74, 89-96] NHS Reference Costs,[87] clinical opinion and assumptions.[1] AEs costs were estimated to be [redacted] for the pembrolizumab combination therapy group and [redacted] for the SC chemotherapy group; these costs are applied once only during the first model cycle. AE costs for the SC chemotherapy NMA comparators are assumed to be the same as those for the carboplatin plus paclitaxel/nab-paclitaxel group.

Table 21: Incidence rates and unit costs for Grade 3-5 AEs used in the model

Adverse event	Pembrolizumab combination	Chemotherapy	Unit cost	Source
Nausea	[redacted]	[redacted]	£998.38	Brown *et al*[88]
Anaemia	[redacted]	[redacted]	£2,692.61	NICE TA428[89]
Fatigue	[redacted]	[redacted]	£2,855.25	Brown *et al*[88]
Decreased appetite	[redacted]	[redacted]	£0.00	NICE TA428[89]
Constipation	[redacted]	[redacted]	£0.00	Assumption
Diarrhoea (grade 2)	[redacted]	[redacted]	£456.66	NICE TA428[89]
Diarrhoea (grade 3-4)	[redacted]	[redacted]	£998.38	Brown *et al*[88]
Dyspnoea	[redacted]	[redacted]	£588.98	NICE TA403[90]
Vomiting	[redacted]	[redacted]	£813.47	NICE TA192[91]
Back pain	[redacted]	[redacted]	£0.00	Assumption
Arthralgia	[redacted]	[redacted]	£0.00	Assumption
Neutropenia	[redacted]	[redacted]	£120.99	Brown *et al*[88]
Oedema peripheral	[redacted]	[redacted]	£0.00	Assumption
Blood creatinine increased	[redacted]	[redacted]	£0.00	Assumption
Alanine aminotransferase increased	[redacted]	[redacted]	£637.03	NICE TA347[92]
Dizziness	[redacted]	[redacted]	£0.00	Assumption
Rash	[redacted]	[redacted]	£127.21	Brown *et al*[88]
Asthenia	[redacted]	[redacted]	£2,855.25	Brown *et al*[88]
Chest pain	[redacted]	[redacted]	£0.00	Assumption
Stomatitis	[redacted]	[redacted]	£0.00	NICE TA428[89]
Hyponatraemia	[redacted]	[redacted]	£0.00	NICE TA357[93]
Thrombocytopenia	[redacted]	[redacted]	£782.31	NICE TA406[94]
Neuropathy Peripheral	[redacted]	[redacted]	£0.00	Assumption
Abdominal pain	[redacted]	[redacted]	£0.00	NICE TA395[95]
Aspartate aminotransferase increased	[redacted]	[redacted]	£364.64	NICE TA347[92]
Peripheral Sensory Neuropathy	[redacted]	[redacted]	£0.00	Assumption
Pyrexia	[redacted]	[redacted]	£261.00	NHS Reference Costs 2016/17[87§]
Musculoskeletal pain	[redacted]	[redacted]	£0.00	Assumption
Pneumonia	[redacted]	[redacted]	£3,102.84	NICE TA411[74]
White blood cell count decreased	[redacted]	[redacted]	£577.66	NICE TA428[89]
Haemoptysis	[redacted]	[redacted]	£0.00	Assumption
Pain in extremity	[redacted]	[redacted]	£0.00	Assumption
Cough	[redacted]	[redacted]	£0.00	Assumption

Adverse event	Pembrolizumab combination	Chemotherapy	Unit cost	Source
Myalgia	[redacted]	[redacted]	£0.00	Assumption
Pruritis	[redacted]	[redacted]	£0.00	Assumption
Upper respiratory tract infection	[redacted]	[redacted]	£171.14	Assume the same as lower respiratory tract infection¤
Leukopenia	[redacted]	[redacted]	£0.00	NICE TA406[94]
Epistaxis	[redacted]	[redacted]	£0.00	Assumption
Neutrophil Count Decreased	[redacted]	[redacted]	£577.66	NICE TA428[89]
Pneumonitis	[redacted]	[redacted]	£3,102.84	Assumed to be same as pneumonia (TA395)[95]
Febrile neutropenia	[redacted]	[redacted]	£7,045.41	Brown *et al*[88]
Bronchitis	[redacted]	[redacted]	£171.14	Assume the same as lower respiratory tract infection¤
Platelet Count Decreased	[redacted]	[redacted]	£577.66	NICE TA428[89]
Weight decreased	[redacted]	[redacted]	£0.00	Assume same as decreased appetite (TA428)[89]
Hypothyroidism	[redacted]	[redacted]	£0.00	Assumption
Hypokalaemia	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]
Hypomagnesaemia	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]
Hyperthyroidism	[redacted]	[redacted]	£0.00	Assumed to be zero
Headache	[redacted]	[redacted]	£0.00	Assumed to be zero
Paraesthesia	[redacted]	[redacted]	£0.00	Assumed to be zero
Hypotension	[redacted]	[redacted]	£0.00	Assumed to be zero
Hypocalcemia	[redacted]	[redacted]	£465.00	NHS Reference Costs 2016/17[87*]

Source - CS[1] and company's model
Note - some costs have been inflated to 2016/17 using PSSRU inflation indices[103], § - WJ07B Fever of Unknown Origin with Interventions, with CC Score 0-3; - KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, ¤ - Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs (TA492)[96]*

(vi) End-of-life (terminal) costs

The model includes terminal care costs of £4,404 based on Brown *et al*;[88] these costs are applied at the point of death.

5.2.5 Subgroup analyses

The CS[1] presents the results of subgroup analyses based on the level of PD-L1 expression (TPS <1%, 1-49% and ≥50%). Within each PD-L1 subgroup, the model compares the cost-effectiveness of pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel, based on KEYNOTE-407.[7, 8] Within the PD-L1 TPS ≥50% subgroup, pembrolizumab combination therapy is compared against pembrolizumab monotherapy based on the company's indirect comparison of KEYNOTE-407 and KEYNOTE-042.[49]

The following sections detail modifications to the model parameters for Base Case Analysis 1 applied within the company's subgroup analyses.

Overall survival (subgroup analyses)

OS for pembrolizumab combination therapy and carboplatin plus paclitaxel/nab-paclitaxel is modelled as per Base Case Analysis 1, including the same SEER dataset and the same RR for death, but using subgroup-specific KM curves for each PD-L1 subgroup. OS for the pembrolizumab monotherapy group is modelled by raising the pembrolizumab combination therapy group OS to the power of the HR estimated from indirect comparison of KEYNOTE-407[7, 8] and KEYNOTE-042[49] (pembrolizumab monotherapy versus combination therapy HR=[redacted]). The ERG notes that this HR does not match the ITC results reported in the CS;[1] this error was corrected following the clarification stage - see Section 5.3.3). The OS curves used in the company's subgroup analyses are presented in Appendix 2.

Progression-free survival (subgroup analyses)

PFS is modelled using subgroup-specific KM curves and parametric (log normal) models for each PD-L1 subgroup. PFS for the pembrolizumab monotherapy group is modelled by raising the pembrolizumab combination therapy group PFS probabilities to the power of the HR estimated from indirect comparison of KEYNOTE-407[7, 8] and KEYNOTE-042[49] (pembrolizumab monotherapy versus combination therapy HR=[redacted]). The ERG notes that this ITC result does not match the ITC results reported in the CS;[1] however, as noted in Section 5.2.2, progression status does not impact on the ICER. The PFS curves used in the company's subgroup analyses are presented in Appendix 2.

Time to treatment discontinuation (subgroup analyses)

TTD is modelled using subgroup-specific KM curves for each PD-L1 subgroup. For the PD-L1 TPS≥50% subgroup, the model uses an exponential function for pembrolizumab combination therapy, rather than the generalised gamma function used in the company's base case analyses. The company's justification for selecting a different parametric curve for this subgroup was that the generalised gamma function predicted a cumulative TTD probability which "*descended to 0% treatment use by week 80, well prior to the 2-year maximum duration of treatment for pembrolizumab*"; the company notes that this was not seen for the overall population or for any other subgroups (CS Appendix N,[11] page 350). The exponential model was selected as this model had the lowest average AIC and BIC values (see Appendix 2, Table 46).

The ERG notes that according to the company's model, TTD for the pembrolizumab monotherapy group is modelled using the complete observed KM curve for *"Non-Squamous Patients With PD-1 ≥ 50% in KN024/KN042 Based on KM Curve"*; the ERG is unclear whether this is accurate as neither the

CS[1] nor the CS appendices[11] explain how TTD is modelled for the pembrolizumab monotherapy group. The TTD curves used in the company's subgroup analyses are presented in Appendix 2.

HRQoL (subgroup analyses)

Within the subgroup analyses, health utility is modelled as per the base case analyses for the pembrolizumab combination therapy and SC chemotherapy groups. For pembrolizumab monotherapy, ratios describing the utilities for pembrolizumab monotherapy compared with SC chemotherapy derived from EQ-5D data from KEYNOTE-024[17] were applied to the utilities for the SC chemotherapy arm in KEYNOTE-407.[7, 8] The CS does not explain why different utility values are used for this treatment group. A constraint is applied to the generated values for the pembrolizumab monotherapy group to ensure that the maximum utility value does not exceed [redacted]; this constraint impacts on the ≥360 days time-to-death category and is neither explained nor justified in the CS.

Table 22 summarises the EQ-5D estimates using the company's time-to-death approach for each treatment option evaluated in the PD-L1 subgroup analyses. Utilities are age-adjusted as per the base case analyses.

Table 22: Mean EQ-5D health utility scores used in the company's subgroup analyses

Time-to-death category	Pembrolizumab combination therapy (all subgroups)	SC chemotherapy (all subgroups)	Pembrolizumab monotherapy (PD-L1 TPS ≥50%)	
	Mean	Mean	Mean	Ratio (applied to SC chemotherapy group)
≥360 days	[redacted]	[redacted]	[redacted]	[redacted]
180 to 360 days	[redacted]	[redacted]	[redacted]	[redacted]
30 to 180 days	[redacted]	[redacted]	[redacted]	[redacted]
<30 days	[redacted]	[redacted]	[redacted]	[redacted]

PD-L1 - programmed death-ligand 1; SC - standard care
** This value is limited by an unexplained constraint applied in the company's model*

AE QALY losses (subgroup analyses)

QALY losses associated with AEs for pembrolizumab combination therapy and SC chemotherapy are the same as those applied in the company's base case analyses. Within the pembrolizumab monotherapy group (PD-L1 TPS ≥50% subgroup), the disutility associated with Grade 3-5 AEs was estimated as the difference between the mean utility for progression-free patients with and without Grade 3-5 AEs in the pembrolizumab arm of KEYNOTE-024.[17] This disutility was multiplied by the mean duration of AEs in KEYNOTE-407 trial[7, 8] and by the sum of the AE incidence rates within the pembrolizumab monotherapy arm of KEYNOTE-024.[17] The estimated QALY loss is summarised in Table 23.

Table 23: Utilities, disutilities and QALY losses for Grade 3-5 AEs in the company's subgroup analyses

	Pembrolizumab combination (all subgroups)*	SC chemotherapy (all subgroups)*	Pembrolizumab monotherapy (PD-L1≥50%)†
Mean utility in patients with Grade 3-5 AEs	[redacted]	[redacted]	[redacted]
Mean utility in patients without Grade 3-5 AEs	[redacted]	[redacted]	[redacted]
Disutility of Grade 3-5 AEs	[redacted]	[redacted]	[redacted]
Mean QALY loss per patient due to Grade 3-5 AEs	[redacted]	[redacted]	[redacted]

AEs - adverse events; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year
** - KEYNOTE-407;[7] † - KEYNOTE-024.[17]*

Resource costs (subgroup analyses)

Costs associated with acquisition and administration of pembrolizumab monotherapy are estimated using a similar approach to the options included in the base case analyses. RDI and TTD were based on data from the KEYNOTE-024 trial.[17] The costs applied in the subgroup analyses are shown in Table 24.

Table 24: Costs parameters for each comparator used in the company's subgroup analyses

Cost parameter	Pembrolizumab combination*	Standard chemotherapy	Pembrolizumab monotherapy* (TPS≥50%)
Drug costs* (per 3-week cycle)	[redacted]	£576.69	[redacted]
RDI	93.50%	98.12%	99.00%
Administration costs (per 3-week cycle)	£607.52	£433.52	£173.99
% of patients receiving 2nd line treatment	27.4%	51.9%	31.0%
2nd line treatment costs (once-only)	£571.87	£5,038.88	£547.16
Disease management - progression-free (weekly)	£89.53	£89.53	£89.53
Disease management - progressed disease (weekly)	£144.33	£144.33	£144.33
Terminal care (once-only)	£4,404.26	£4,404.26	£4,404.26
AEs	£1,256.99	£1,216.98	£1,107.69

AE: adverse event; PFS: progression-free state; PD-L1: programmed death-ligand 1; PD: progressive disease state; RDI: relative dose intensity;
** Includes CAA for pembrolizumab*

The probability of receiving second-line treatment and associated costs for pembrolizumab monotherapy were based on data from KEYNOTE-024.[17] In line with the company's base case analyses, the model assumes that patients who discontinue first-line pembrolizumab monotherapy are not eligible for second-line immunotherapy; for these patients, second-line treatment is assumed to be comprised of SC chemotherapy including a platinum drug (carboplatin+gemcitabine or carboplatin/cisplatin+paclitaxel). The model applies different second-line treatment regimens from

KEYNOTE-024[17] for this option only. Second-line treatment costs for patients receiving SC chemotherapy or pembrolizumab combination therapy are assumed to be the same as those applied in the base case analyses; these costs are applied at the point of discontinuation for first-line treatment.

Disease management costs and terminal costs are the same as those applied in the base case analyses.

Costs associated with Grade 3-5 AEs for pembrolizumab monotherapy are based on incidence rates from KEYNOTE-024[17] (see Appendix 2); these used the same unit costs as those applied in the company's base case analyses. The model estimates a mean cost of [redacted] for managing AEs in the pembrolizumab monotherapy group. AE costs for pembrolizumab combination therapy and for SC chemotherapy are assumed to be the same as those applied in the company's base case analyses.

5.2.6 Model evaluation methods

The CS[1] presents the results of the base case analyses in terms of the incremental cost per QALY gained for pembrolizumab combination therapy versus SC chemotherapy using pairwise comparisons. The company's base case ICERs were generated using the deterministic version of the model. The CS also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSAs), and scenario analyses for Base Case Analysis 1 (the comparison against carboplatin plus paclitaxel/nab-paclitaxel); these analyses were not undertaken for Base Case Analysis 2 (comparisons against SC regimens in the NMA). Subgroup analyses are also presented according to PD-L1 TPS.

The results of the PSA are presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The probabilistic ICER, based on the expectation of the mean, is also presented within the CS.[1] The distributions applied in the company's PSA are summarised in Table 25. The results of the DSAs were presented in the form of a tornado diagram for specified model parameters. Scenario analyses were undertaken to explore the impact of: using alternative cut-points and parametric distributions for OS and PFS; using alternative BSA calculations; removing the half-cycle correction; applying alternative assumptions regarding the proportionate use of paclitaxel/nab-paclitaxel; using alternative assumptions regarding HRQoL, and applying an assumption regarding the loss of OS treatment effect for pembrolizumab combination therapy.

Table 25: Distributions used in company's PSA, base case and subgroup analyses

Parameter / parameter group	Distribution	ERG comment
Patient characteristics (age, BSA, weight)	Fixed	-
PFS - carboplatin+paclitaxel/ nab-paclitaxel	MVN (parametric portion only)	No uncertainty included prior to 26-week cut-point. PFS does not affect ICER.
PFS - pembrolizumab combination therapy	MVN (parametric portion only)	No uncertainty included prior to 26-week cut-point. PFS does not affect ICER.
OS - carboplatin+paclitaxel/ nab-paclitaxel	Fixed / log normal	No uncertainty included for the first 52 weeks. Arbitrary log normal distribution applied to SEER baseline OS data.
OS - pembrolizumab combination therapy	Fixed / log normal	
Mortality - general population	Fixed	-
TTD - pembrolizumab combination therapy	MVN	-
TTD - carboplatin+paclitaxel/ nab-paclitaxel	Normal	Sampled "% variation" parameter is linked to a blank cell, hence no uncertainty is modelled
TTD - pembrolizumab monotherapy (PD-L1 TPS ≥50% subgroup analysis only)	MVN	Uncertainty surrounding observed data from KEYNOTE-042/024 modelled using arbitrary normal distribution
HRQoL applied in health states	Beta	Utility parameters sampled independently for each treatment group; for any given sample, patients in the same health state will have a different level of HRQoL depending on which treatment they receive.
QALY loss resulting from AEs	Probability – beta Disutility – beta Duration – normal	-
HRs for PFS (NMA comparators versus pembrolizumab combination therapy)	Log normal	Sampled from log normal distribution for pairwise comparison. Use of CODA samples would capture correlation in treatment effects across the entire network.
HRs for OS (NMA comparators versus pembrolizumab combination therapy)	Log normal	
HR for PFS (pembrolizumab monotherapy versus pembrolizumab combination therapy, PD-L1 TPS ≥50% subgroup only)	Log normal	
HR for OS (pembrolizumab monotherapy versus pembrolizumab combination, PD-L1 TPS ≥50% only)	Log normal	-
Drug acquisition costs	Fixed	-
Drug administration costs	Log normal	Given that this cost was derived from a large sample, a normal distribution with SE derived from the IQR may be more appropriate.
RDI	Log normal	Truncated to maximum value of 1.0. A beta distribution may been more appropriate.
Disease management costs	Log normal	SE arbitrarily assumed to be equal to 10% of mean.
Second-line therapy costs	Log normal	SE arbitrarily assumed to be equal to 10% of mean.
Costs associated with AEs	Log normal	–

AE - adverse event; BSA - body surface area; CODA - convergence diagnostic and output analysis; HRQoL - health-related quality of life; IQR - interquartile range; OS - overall survival; PD-L1 - programmed death-ligand 1; PFS - progression-free survival; QALY - quality-adjusted life years; SE - standard error; TPS - tumour proportion score; MVN - multivariate normal

5.2.7 Company's model validation and verification

The CS[1] states that the OS predictions from the model were compared against those observed within KEYNOTE-407;[7, 8] the outcomes of this comparison are presented in Table 26. With respect to this validation exercise, the ERG notes the following:

- The data presented in Table 26 suggest a considerable difference between the observed and predicted values. This is partly because the reported estimate of 48.3 months is incorrect; the correct estimate of the median model-predicted OS for pembrolizumab combination therapy is approximately 20.5 months. Comparing the observed and the correct predicted median OS still suggests that the company's model over-estimates survival for the pembrolizumab combination therapy group (observed median OS in KEYNOTE-407 = 15.9 months).
- The model-predicted OS for the SC chemotherapy group reported in CS Appendix J is also incorrect. The correct value for the SC chemotherapy group is approximately 11.5 months; this is similar to the observed median survival of 11.3 months in KEYNOTE-407.
- The company's OS validation exercise suggests a very close match between the observed and predicted OS in both treatment groups at 1-year. However, this is because the model uses the observed OS data until the 1-year timepoint.
- There are no observed data at any selected timepoint beyond 1 year, hence this exercise provides no information to either support or refute the validity of the company's model predictions.

These issues are further discussed in Section 5.3.3.

Table 26: Comparison of observed and predicted OS – Base Case Analysis 1, pembrolizumab combination therapy versus cisplatin plus paclitaxel/nab-paclitaxel in KEYNOTE-407[7, 8] (adapted from CS Appendix J, Table J1). ERG-corrected values are presented in parentheses

Outcome	Pembrolizumab combination		Chemotherapy	
	Base case	KEYNOTE-407[7, 8]	Base case	KEYNOTE-407[7, 8]
Median OS (months)	48.3 (20.5)	15.9	21.15 (11.5)	11.3
1-year OS	65.1%	65%	48.2%	48%
2-year OS	45.0%	-	22.0%	-
5-year OS	26.0%	-	8.0%	-
10-year OS	16.3%	-	3.4%	-
20-year OS	8.7%		1.1%	

OS – overall survival

The CS states that the OS predictions for the base case analyses were validated with clinical experts; however, no results were presented for this validation.

The CS also states that the model approach and inputs were validated by two external health economists (Professor Chris Bojke, from the University of Leeds and Professor Alistair Gray from the University of Oxford). According to the CS, the model structure, selection of appropriate datasets, survival analysis, assumptions and utility values were all discussed with the experts.

5.2.8 Company's cost-effectiveness results (including existing CAA)

This section summarises the results presented in the CS.[1] It should be noted that the model contains several errors; the model results incorporating the corrections of these errors are presented as part of the ERG's exploratory analyses in Section 5.4.

Central estimates of cost-effectiveness (Base Case Analysis 1)

Table 27 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (Base Case Analysis 1). The probabilistic version of the model suggests that pembrolizumab combination therapy is expected to generate an additional 1.68 QALYs at an additional cost of £48,387 per patient; the corresponding ICER is £28,852 per QALY gained. The deterministic version of the model produces a slightly lower ICER of £28,672 per QALY gained.

Table 27: Company's results - Base Case Analysis 1, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
Probabilistic model							
Pembrolizumab combination	NR†	2.95	£72,745	NR†	1.68	£48,387	**£28,852**
Carboplatin+paclitaxel/ nab-paclitaxel	NR†	1.27	£24,358	-	-	-	-
Deterministic model							
Pembrolizumab combination	5.09	2.95	£72,695	3.12	1.68	£48,278	**£28,672**
Carboplatin+paclitaxel/ nab-paclitaxel	1.97	1.27	£24,417	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*
† LYGs not recorded in company's PSA sub-routine

Central estimates of cost-effectiveness (Base Case Analysis 1 and 2)

The CS[1] presents pairwise ICERs for pembrolizumab combination therapy versus each of the SC chemotherapy comparators from the company's NMA, but excludes the KEYNOTE-407 trial comparator. The ERG considers it more appropriate to include all options within a fully incremental

analysis. Table 28 presents the results of a fully incremental analysis of all options included in both Base Case Analyses 1 and 2. This analysis suggests that: cisplatin/carboplatin plus docetaxel is the least effective option; carboplatin plus paclitaxel/nab-paclitaxel (the KEYNOTE-407 comparator) is dominated by cisplatin/carboplatin plus paclitaxel; the ICERs for cisplatin/carboplatin plus gemcitabine and cisplatin/carboplatin plus paclitaxel versus their next best non-dominated comparators are less than £9,000 per QALY gained, and the ICER for pembrolizumab combination therapy versus cisplatin/carboplatin plus gemcitabine is approximately £63,661 per QALY gained. It should be noted that the ERG has identified errors in the model which render these results unreliable (see Section 5.3.3).

Table 28: Company's results - Base Case Analysis 1 and 2, fully incremental analysis of pembrolizumab combination therapy and all comparators, deterministic model

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
Pembrolizumab combination	5.09	2.95	£72,695	1.00	0.66	£41,748	**£63,661**
Platinum+gemcitabine	4.09	2.30	£30,947	2.11	1.03	£8,945	**£8,725**
Platinum+paclitaxel	1.97	1.27	£22,002	0.19	0.10	£818	**£8,203**
Carboplatin+paclitaxel/ nab-paclitaxel	1.97	1.27	£24,417	-	-	-	**Dominated**
Platinum +docetaxel	1.78	1.17	£21,184		-	-	-

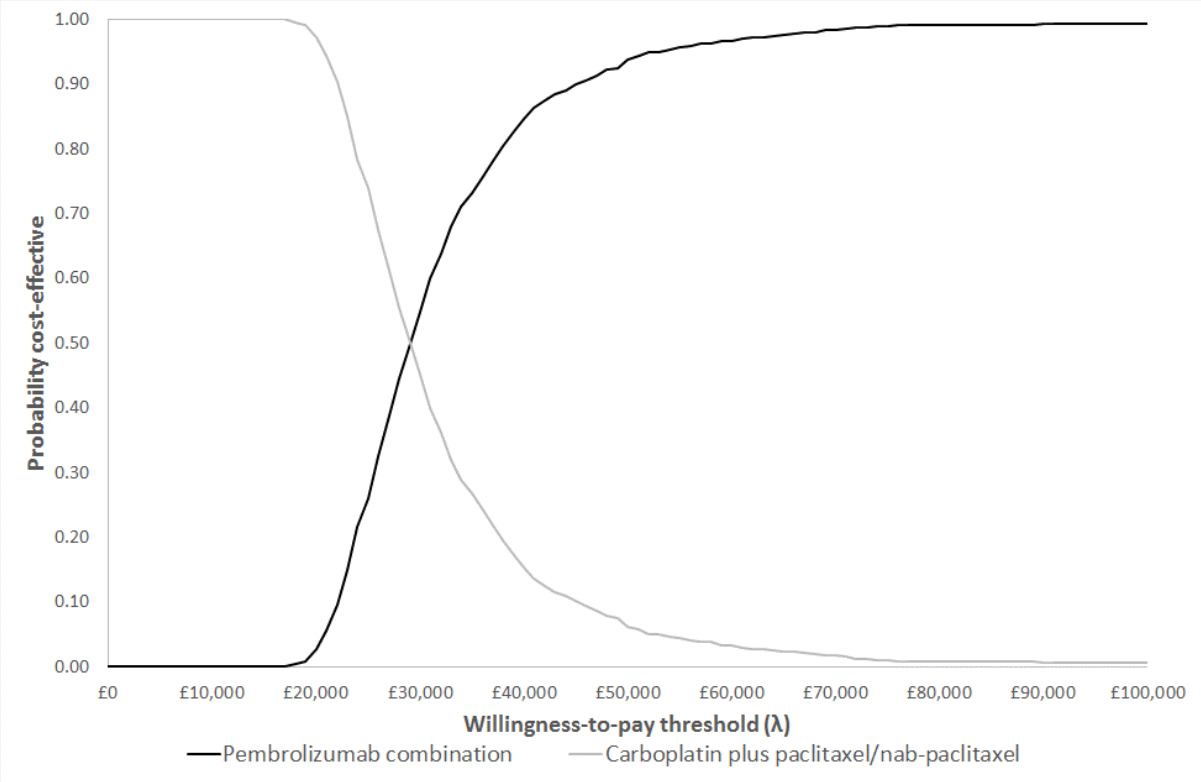
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** undiscounted*

Company's probabilistic sensitivity analysis (Base Case Analysis 1)

Figure 14 presents the CEACs for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (Base Case Analysis 1). The probability that pembrolizumab combination therapy produces more net benefit than carboplatin plus paclitaxel/nab-paclitaxel at willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY gained is 0.55 and 0.94, respectively.

The CS[1] does not include CEACs for comparisons of pembrolizumab combination versus the SC chemotherapy comparator regimens from the NMA (Base Case Analysis 2).

Figure 14: Company's results – Base Case Analysis 1, CEACs, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (generated by the ERG)

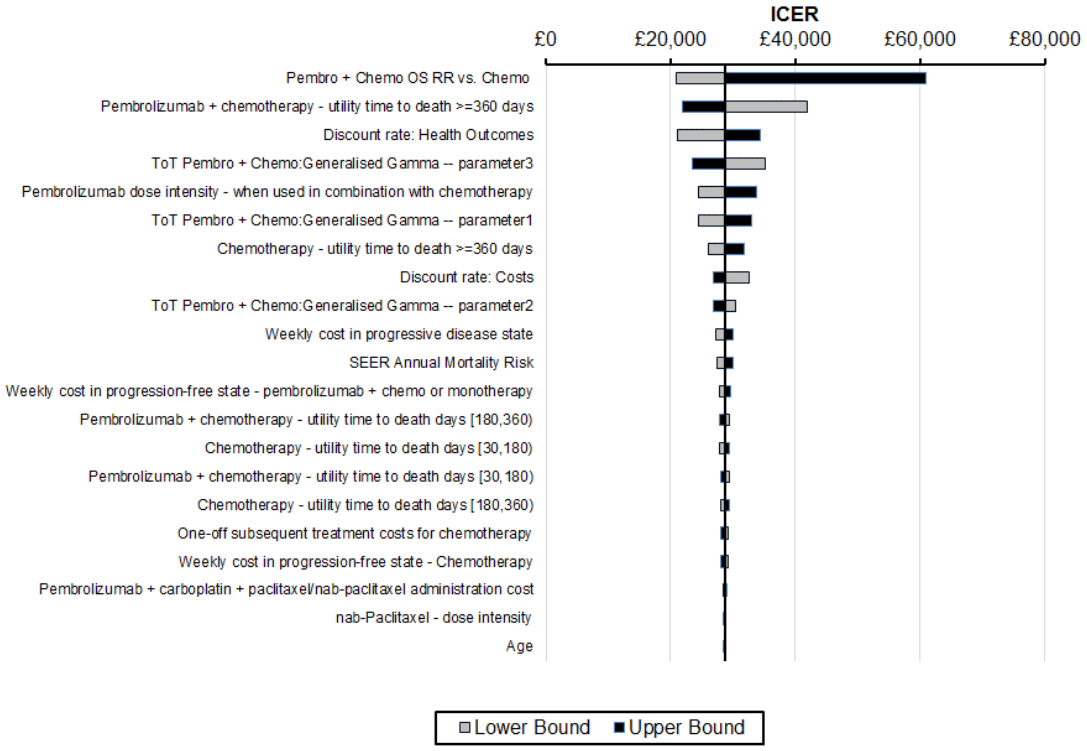


Company's deterministic sensitivity analyses (Base Case Analysis 1)

Figure 15 presents the results of the company's DSAs in the form of a tornado diagram for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (Base Case Analysis 1). Based on these analyses, the ICER is estimated to range from £20,842 to £60,849 per QALY gained. These analyses suggest that the most influential model parameters are the RR of death applied in the pembrolizumab combination therapy group for all model cycles after month 12, the utility value applied for patients who are ≥360 days from death and the discount rate for health outcomes.

The CS[1] does not include tornado plots for comparisons of pembrolizumab combination versus the SC chemotherapy comparator regimens from the NMA (Base Case Analysis 2).

Figure 15: Company's results - Base Case Analysis 1, deterministic sensitivity analyses, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (adapted from the company's model)



Company's scenario analyses (Base Case Analysis 1)

Table 27 summarises the results of the company's scenario analyses for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel. The analyses suggest that the ICER is particularly sensitive to assumptions regarding the OS model assumed for the pembrolizumab combination therapy group. In addition, the inclusion of a loss of treatment effect at 5 years leads to a moderate increase in the ICER. The table also shows that the PFS parameters have no impact on the model results, except in the scenario in which utilities are defined by the presence/absence of disease progression (company's scenario analysis 6).

The CS[1] does not present scenario analyses for comparisons of pembrolizumab combination therapy versus the SC chemotherapy comparator regimens from the NMA (Base Case Analysis 2).

Table 29: Company's results - Base Case Analysis 1, scenario analyses, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (adapted from CS Table 91)

Scenario reference	Scenario description	Incremental - pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel		
		QALYs	Costs	ICER
-	Company's Base Case Analysis 1	1.68	£48,278	**£28,672**
Scenario 1a	OS modelled using KM and exponential model (19 weeks cut-off)	0.46	£36,989	**£80,142**
Scenario 1b	OS modelled using KM and log logistic model (19 weeks cut-off)	0.84	£41,053	**£48,706**
Scenario 2a	PFS modelled using log normal (16 weeks cut-off)	1.68	£48,278	**£28,672**
Scenario 2b	PFS modelled using log normal (36 weeks cut-off)	1.68	£48,278	**£28,672**
Scenario 3	UK-specific BSA values (unadjusted by sex distribution)*	1.68	£48,279	**£28,673**
Scenario 4	No half cycle correction	1.68	£48,222	**£28,649**
Scenario 5	100% paclitaxel use (0% nab-paclitaxel use)	1.68	£48,326	**£28,700**
Scenario 6	Utilities defined by progression status (pooled)	1.49	£48,278	**£32,320**
Scenario 7a	Utilities defined by time to death (per treatment arm)	1.58	£48,278	**£30,580**
Scenario 7b	Utilities defined by progression status (per treatment arm)	1.53	£48,278	**£31,567**
Scenario 8	No age-related disutilities	1.81	£48,278	**£26,737**
Scenario 9	Treatment effect removed at beginning of year 5	1.15	£43,444	**£37,730**
Scenario 10	PFS modelled using generalised gamma model (26 weeks cut-off)	1.68	£48,278	**£28,672**

ICER - incremental cost-effectiveness ratio; OS - overall survival; PFS - progression-free survival; QALY - quality-adjusted life year
** The ERG was unable to replicate this scenario analysis using the company's model*

Company's subgroup analyses

Table 30 presents the results of the company's subgroup analyses by PD-L1 TPS category. The company's subgroup analyses suggest the following:

- Within the PD-L1 TPS <1% subgroup, the company's model suggests that the ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is £26,012 per QALY gained.
- Within the PD-L1 TPS 1-49% subgroup, the company's model suggests that the ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is £32,174 per QALY gained.
- Within the PD-L1 TPS ≥50% subgroup, a fully incremental analysis of the available options suggests that pembrolizumab combination therapy is ruled out due to extended dominance (by

pembrolizumab monotherapy and carboplatin+paclitaxel/nab-paclitaxel). As the company's original submitted model uses an incorrect HR for this analysis, the ERG believes that the results for this subgroup are invalid and should be disregarded (corrected results are presented in Section 5.3.3, Table 34).

Table 30: Results of the company's subgroup analyses by PD-L1 TPS category

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
PD-L1 TPS<1%							
Pembrolizumab combination	5.00	2.90	£70,000	3.15	1.71	£44,557	**£26,012**
Carboplatin+paclitaxel/ nab-paclitaxel	1.85	1.19	£25,443		-	-	-
PD-L1 TPS 1-49%							
Pembrolizumab combination	5.13	2.98	£78,721	3.11	1.68	£54,013	**£32,174**
Carboplatin+paclitaxel/ nab-paclitaxel	2.02	1.30	£24,708		-	-	-
PD-L1 TPS ≥50%							
Pembrolizumab monotherapy	5.86	3.32	£76,963	3.86	2.03	£52,562	**£25,849**
Pembrolizumab combination	4.93	2.86	£69,030	-	-	-	**extendedly dominated**
Carboplatin+paclitaxel/ nab-paclitaxel	2.00	1.29	£24,401	-	-	-	-

** undiscounted*
ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1: programmed death-ligand 1; QALY - quality-adjusted life year; TPS - tumour proportion score

5.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[104, 105]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.

- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS.[1]
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.1 Model verification

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. As shown in Table 31, the ERG's results are almost identical to those generated using the company's original submitted model. During the process of rebuilding the model, the ERG identified several programming errors which impact upon the model results. These errors, together with broader conceptual issues around the model structure and use of evidence to inform model parameters, are discussed in Section 5.3.3.

Table 31: Comparison of company's base case results and ERG's rebuilt model results (excluding corrections of errors)

Model outcome	Company's model			ERG's rebuilt model		
	Pembrolizumab combination	Comparator	Inc.	Pembrolizumab combination	Comparator	Inc.
Base Case Analysis 1 - overall population, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel						
LYGs	4.03	1.76	2.26	4.03	1.76	2.26
QALYs	2.95	1.27	1.68	2.95	1.27	1.68
Costs	£72,695	£24,417	£48,278	£72,695	£24,417	£48,278
ICER	-	-	**£28,672**	-	-	**£28,672**
Base Case Analysis 2 - overall population, pembrolizumab combination therapy versus cisplatin/ carboplatin plus docetaxel (NMA comparator)						
LYGs	4.03	1.63	2.39	4.03	1.63	2.39
QALYs	2.95	1.17	1.78	2.95	1.17	1.78
Costs	£72,695	£21,184	£51,511	£72,695	£21,184	£51,511
ICER	-	-	**£28,927**	-	-	**£28,927**
Base Case Analysis 2 - overall population, pembrolizumab combination therapy versus cisplatin/ carboplatin plus gemcitabine (NMA comparator)						
LYGs	4.03	3.16	0.86	4.03	3.16	0.86
QALYs	2.95	2.30	0.66	2.95	2.30	0.66
Costs	£72,695	£30,947	£41,748	£72,695	£30,947	£41,748
ICER	-	-	**£63,661**	-	-	**£63,661**
Base Case Analysis 2 - overall population, pembrolizumab combination therapy versus cisplatin/ carboplatin plus paclitaxel (NMA comparator)						
LYGs	4.03	1.77	2.26	4.03	1.77	2.26
QALYs	2.95	1.27	1.68	2.95	1.27	1.68
Costs	£72,695	£22,002	£50,693	£72,695	£22,002	£50,693
ICER	-	-	**£30,156**	-	-	**£30,157**

Subgroup Analysis - PD-L1 TPS <1%, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel						
LYGs	3.96	1.66	2.30	3.96	1.66	2.30
QALYs	2.90	1.19	1.71	2.90	1.19	1.71
Costs	£70,000	£25,443	£44,557	£70,000	£25,443	£44,557
ICER	-	-	**£26,012**	-	-	**£26,012**
Subgroup Analysis - PD-L1 TPS 1-49%, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel						
LYGs	4.06	1.80	2.26	4.06	1.80	2.26
QALYs	2.98	1.30	1.68	2.98	1.30	1.68
Costs	£78,721	£24,708	£54,013	£78,721	£24,708	£54,013
ICER	-	-	**£32,174**	-	-	**£32,174**
Subgroup Analysis - PD-L1 TPS ≥50%, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel						
LYGs	3.90	1.79	2.11	3.90	1.79	2.12
QALYs	2.86	1.29	1.57	2.86	1.29	1.57
Costs	£69,030	£24,401	£44,628	£69,030	£24,401	£44,628
ICER	-	-	**£28,380**	-	-	**£28,380**
Subgroup Analysis - PD-L1 TPS ≥50%, pembrolizumab combination therapy versus pembrolizumab monotherapy						
LYGs	3.90	4.55	-0.65	3.90	4.55	-0.65
QALYs	2.86	3.32	-0.46	2.86	3.32	-0.46
Costs	£69,030	£76,963	-£7,933	£69,030	£76,963	-£7,934
ICER	-	-	**£17,213**	-	-	**£17,213**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year; TPS - tumour proportion score

5.3.2 Adherence to the NICE Reference Case

The company's economic analysis of pembrolizumab combination therapy for untreated metastatic squamous NSCLC is generally in line with the NICE Reference Case.[106]

Table 32: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's health economic analysis is generally in line with the final NICE scope.[6] As noted in Section 5.2.1, pembrolizumab has not yet been granted an EU marketing authorisation in this indication.
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[6] specifies two comparators: (1) Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with carboplatin or cisplatin; (2) Pembrolizumab monotherapy (for people with tumours that express PD-L1 with at least 50% TPS with no EGFR- or ALK-positive tumour mutations only). The company's analysis does not include vinorelbine-including regimens as these were not used in KEYNOTE-407[7, 8] or in the studies identified for inclusion in the company's NMAs for the squamous PD-L1 unselected population.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are valued in terms of QALYs gained.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective. The CS[1] (Table 56) states that "*PSS costs have not been considered due to the unavailability of data to incorporate this into the model.*" However, scrutiny of the model indicates that some relevant PSS costs have been included in the company's model (e.g. community nurse visits).
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained for pembrolizumab combination therapy versus SC chemotherapy (and pembrolizumab monotherapy in the PD-L1 TPS ≥50% subgroup).
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 30-year time horizon. At this point, the model suggests that 99.74% of patients receiving SC chemotherapy will have died. However, over 2% of the pembrolizumab combination therapy are predicted to still be alive at 30 years. Issues relating to the extrapolation of time-to-event outcomes are discussed in Section 5.3.3.
Synthesis of evidence on health effects	Based on systematic review	The company's NMA includes trials identified through a systematic review.

Element	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Whilst there is ambiguity in the CS, the company's clarification response[12] states that HRQoL estimates used in the model were based on EQ-5D-3L data collected within the KEYNOTE-407 trial. Preference-based utilities were valued using the UK tariff. The subgroup analysis in patients with PD-L1 TPS≥50% includes relative utility multipliers for the pembrolizumab monotherapy group. No justification of this approach is given in the CS or the CS appendices. Table 56 of the CS states that health impacts on caregivers were not included in the analysis *"due to the unavailability of data to incorporate this into the model."*
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains. The CS argues that pembrolizumab combination therapy meets NICE's End of Life criteria within the untreated squamous NSCLC population. This is discussed further in Chapter 6.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource costs include those relevant to the NHS and PSS. Unit costs were valued at 2016/17 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

Main issues identified within the critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified within the critical appraisal undertaken by the ERG

(1)	Identification of model errors
(2)	Unclear interpretation of effectiveness of SC chemotherapy comparators
(3)	Issues surrounding company's NMAs and ITCs
(4)	Uncertainty surrounding long-term extrapolation
(5)	Assumption of lifetime relative risk for OS for pembrolizumab combination therapy versus SC chemotherapy
(6)	Inclusion of an implicit assumption of cure
(7)	Concerns regarding the company's approach to modelling HRQoL
(8)	Uncertainty surrounding use second-line immunotherapy in the SC chemotherapy groups
(9)	Clinically unrealistic assumptions regarding disease management costs
(10)	Issues relating to AEs

(1) Identification of model errors

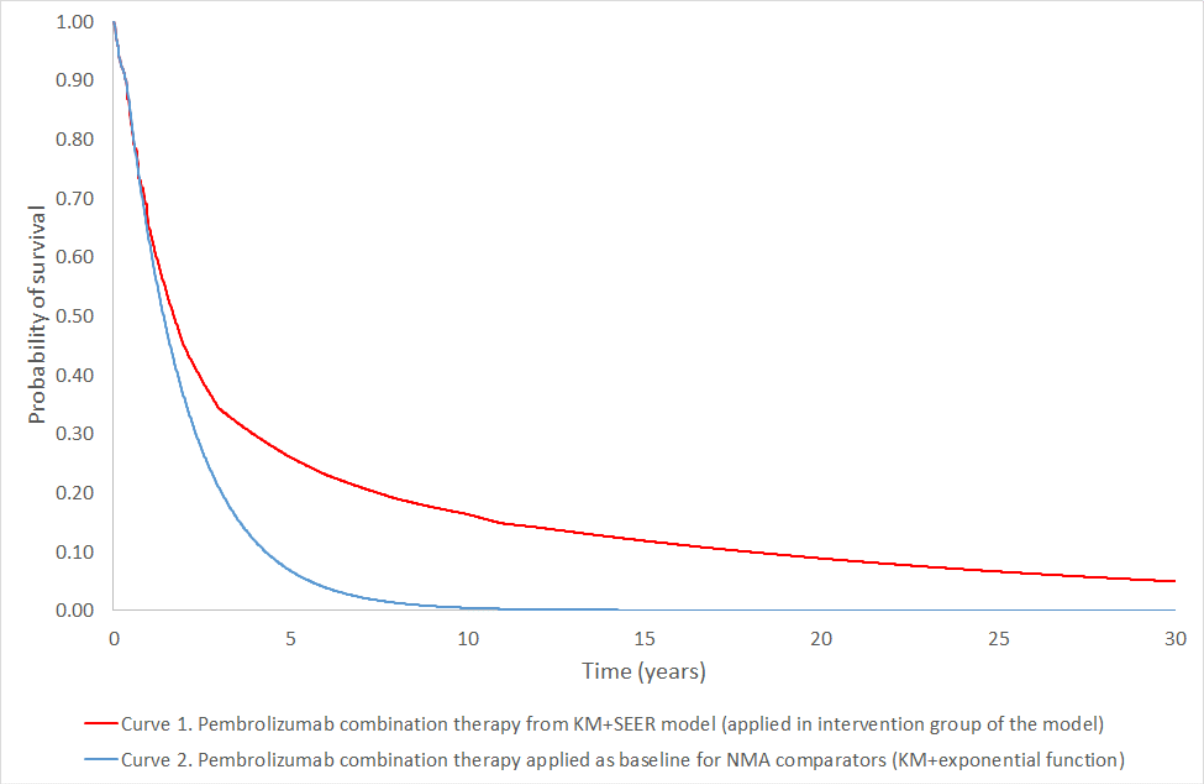
(i) Errors in the company's estimates of OS for all SC chemotherapy comparators included in the NMA (Base Case Analysis 2)

Whilst not clearly described in the CS,[1] it appears that the model intends to apply the HRs for OS from NMA3 (squamous, PD-L1 unselected, platinum drugs combined) using the pembrolizumab combination group OS function as a baseline. The ERG believes this to be the case because: (a) this is how PFS is modelled for the comparators from the NMA; (b) this is the approach used to model OS for pembrolizumab monotherapy in the PD-L1 TPS ≥50% subgroup; (c) within the model, prior to adjusting for general population mortality, OS in the pembrolizumab combination therapy group is raised to the power of the HR, and (d) all of the input parameters relating to HRs for OS in the model are greater than 1.0 (i.e. the comparator is less effective than the intervention). However, the ERG believes that the OS functions for the NMA comparators are subject to two mathematical errors which render the ICERs for Base Case Analysis 2 unreliable. The presence of these errors can be illustrated by setting the HRs from the NMA equal to 1.0 (removing the treatment effect of pembrolizumab combination therapy) – when this change is applied, the model erroneously suggests that the NMA comparators produce 1.13 LYGs more than pembrolizumab combination therapy – if all treatment options have equal efficacy, the incremental survival gain under this scenario should be zero. The reasons underpinning these errors are described below.

HRs for OS for NMA comparators applied to incorrect baseline OS function

The first error relates to the baseline upon which the treatment effect of the comparator is applied for OS. This is contained in column AK of worksheet 'NMA-ITC OS (conHR)' of the company's model. These baseline OS probabilities are raised to the power of the HRs for OS (NMA comparators versus pembrolizumab combination therapy) in column AL:AN of the same worksheet. These HR-adjusted survivor functions are applied in the model (in worksheet 'Modeled OS' columns AG:AI). However, the baseline survivor function in column AK relates is the KM/exponential model, not the KM/SEER model. This issue is illustrated in Figure 16: given the ERG's understanding of the company's intended approach, the analysis should use Curve 1 as the baseline function, but instead Curve 2 is used.

Figure 16: Illustration of incorrect baseline survivor function applied in company's analysis of NMA comparators

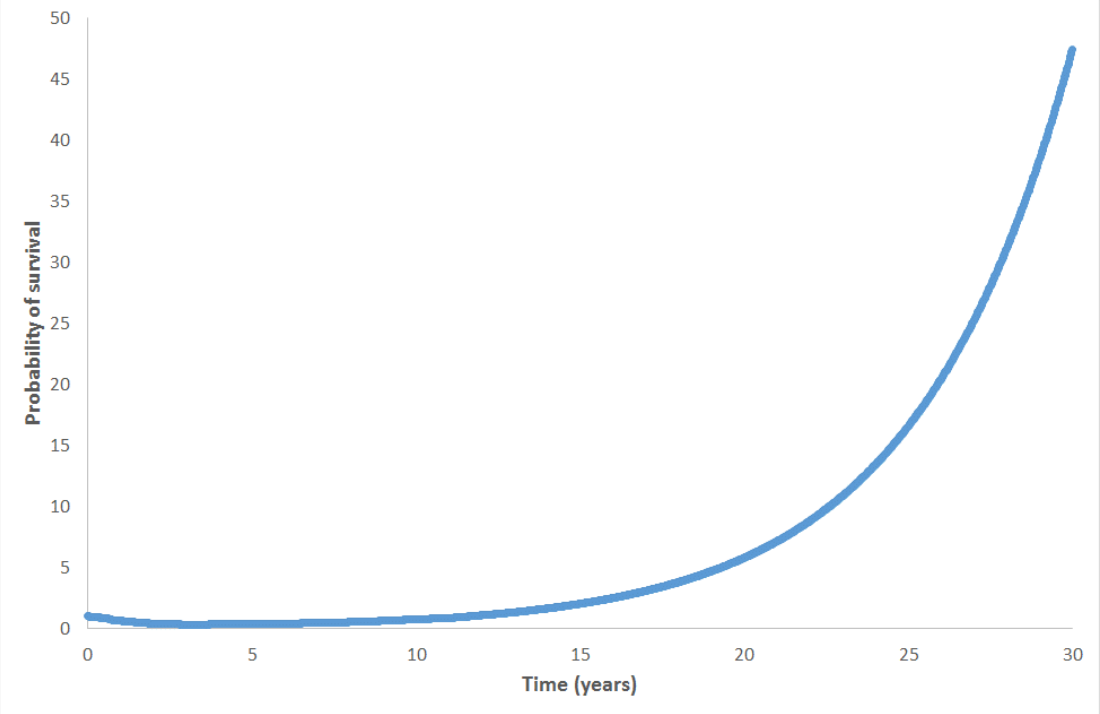


In response to a request for clarification on this issue from the ERG (clarification response,[12] question B31), the company stated "*The data in column AK, and on the worksheet generally, only reflect implementation of the parametric extrapolation approach for the indirect comparators. The SEER-based approach is implemented for the indirect treatment comparators on the 'Modeled OS' worksheet in the formulae in columns Y to AA. Therefore there is not an error.*" The ERG believes that the company's response is incorrect: the formulae in column AK are fed through the model and these directly impact on the ICERs of pembrolizumab combination therapy versus all of the NMA comparators.

Incorrect formulae applied in OS model calculations for NMA comparators

The second error in Base Case Analysis 2 relates to the implementation of the OS model (given the wrong baseline OS function described above). In worksheet 'Modeled OS', the model draws in unadjusted OS functions and compares the mortality risk for each treatment group against the mortality risks in the general population, based on interim life tables. The higher of the two risks is then applied in each model cycle. For the NMA SC chemotherapy comparators, these formulae multiply the cumulative probability of surviving up to time *t* in the NMA comparator group by the conditional probability of surviving during the interval between *t* and *t*-1 in the modelled carboplatin plus paclitaxel/nab-paclitaxel group (KM/exponential model) divided by the conditional probability of surviving during the interval *t* and *t*-1 in the modelled carboplatin plus paclitaxel/nab-paclitaxel group (KM/SEER model). The ERG is unclear what this calculation is attempting to do, why any part of the calculation should relate to the KEYNOTE-407 trial comparator group, and why different OS models are being used for the SC chemotherapy group in the same calculation (KM/SEER and KM/exponential). What is clear however, is that when the HRs for OS for the NMA comparators are set equal to 1.0 (i.e. the treatment effects are removed) and the general population mortality risk is set equal to zero (the mortality constraint is removed), the predicted OS probability for the NMA chemotherapy comparators initially drops but then increases to values which are considerably greater than 1.0 (see Figure 17). This is not mathematically possible and clearly reflects an error. It should be noted that the general population mortality constraint masks the full extent of this error from the model results.

Figure 17: OS predicted by company's model for NMA comparators if HR for OS is set equal to 1.0 and the general population mortality constraint is removed



As a consequence of these two issues, the ERG believes that the results of Base Case Analysis 2 presented in the CS[1] are unreliable.

In response to a further request for clarification from the ERG,[82] the company stated that their approach *"may not have been robust enough"* and rectified these errors as part of an updated version of the model. The results of the ERG-corrected analyses including all comparators are presented in Table 33; these results do not include other minor corrections made by the company during the clarification process.[12]

Table 33: ERG corrected results – Base Case Analysis 1 and 2, fully incremental analysis of pembrolizumab combination therapy and all comparators, deterministic model

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
Pembrolizumab combination	5.09	2.95	£72,695	1.61	0.85	£43,389	**£51,240**
Platinum+gemcitabine	3.48	2.11	£29,306	0.89	0.49	£4,572	**£9,401**
Platinum+paclitaxel	2.59	1.62	£24,734	0.62	0.07	£606	**£8,243**
Platinum +docetaxel	2.46	1.55	£24,128	-	-	-	-
Carboplatin+paclitaxel/ nab-paclitaxel	1.97	1.27	£24,417	-	-	-	**Dominated**

** undiscounted*

(ii) Errors relating to the pembrolizumab monotherapy comparison (PD-L1 TPS ≥50% subgroup)
According to Table 40 and text presented on page 99 of the CS,[1] the HR for pembrolizumab combination therapy versus pembrolizumab monotherapy from the ITC is 0.97. Similarly, Figure L.19 in CS Appendix L[11] suggests that pembrolizumab combination therapy is more effective than pembrolizumab monotherapy. However, the company's subgroup analyses suggest that pembrolizumab monotherapy generates 0.46 additional QALYs compared with pembrolizumab combination therapy (see Table 30). The reason for this discrepant result is that within the model, the OS function for pembrolizumab combination therapy is raised to the power of [redacted]. The source of this HR is unclear and is inconsistent with the results of the company's ITC, both in terms of magnitude and direction of effect. The ERG believes that the results of the company's economic comparison of pembrolizumab combination therapy versus pembrolizumab monotherapy within the CS are not valid.

In response to a further request for clarification from the ERG,[82] company applied an HR of 1.03 (1/0.97) as part of an updated version of the model. The corrected results for the PD-L1 TPS ≥50% comparison are summarised in Table 34. The corrected analysis suggests the following: pembrolizumab combination therapy is no longer extendedly dominated; pembrolizumab monotherapy becomes strongly dominated, and the ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is £25,683 per QALY gained. However, the ERG has further concerns regarding the credibility of this revised conclusion as the cost difference between the two pembrolizumab options is driven by a lower TTD function for combination therapy versus monotherapy. Given that the indirect comparison suggests that PFS and OS outcomes are expected to be worse for pembrolizumab monotherapy, it is unclear why patients would spend more time receiving pembrolizumab as monotherapy than as part of combination therapy. The ERG speculates that this economic finding may be a consequence of variability between patients in the KEYNOTE-407[7, 8] and KEYNOTE-042[17] trials.

Table 34: Company's corrected results for the PD-L1 TPS ≥50% subgroup

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
Pembrolizumab combination	3.90	2.86	£64,790	2.12	1.57	£40,388	**£25,683**
Pembrolizumab monotherapy	3.76	2.74	£71,853	-	-	-	**Dominated**
Carboplatin+paclitaxel/ nab-paclitaxel	1.79	1.29	£24,401	-	-	-	-

** undiscounted*
ICER – incremental cost-effectiveness ratio; LYG – life year gained; PD-L1: programmed death-ligand 1; QALY– quality-adjusted life year

(iii) Errors relating to expected costs associated with managing AEs

Within the company's model, the mean cost associated with managing AEs is calculated using the sumproduct of the vectors of AE frequencies and their associated costs, divided through by the sum of the AE frequencies. The ERG believes that the latter part of this calculation reflects an intention to assume that patients can, at most, experience one AE. No justification for this is provided in the CS[1] and the observed AE frequency data from KEYNOTE-407[7, 8] suggest that this assumption is not appropriate: in both arms of the trial, the sum of the AE frequencies exceeds 1.0. The ERG believes that the company's assumption reflects an error, but notes that its impact on the ICER is small.

(iv) Half cycle correction not consistently applied to disease management costs between the options

The calculations of disease management costs are inconsistent between the intervention and comparator groups. For the SC chemotherapy comparator groups in both Base Case Analyses 1 and 2, the calculations of these costs include a half-cycle correction, whilst for the pembrolizumab combination therapy group, the calculations do not include half-cycle correction. The same issue applies within the PD-L1 subgroup analyses. This reflects a further minor error in the model.

(v) Errors in the application of time-to-death utilities

Conceptual issues relating to this aspect of the model are discussed in critical appraisal point (7). With respect to the technical implementation of this approach, the ERG notes that whilst all of the utility values are positive, at a point beyond the end of the time horizon (approximately 36 years), the probability of being in the ≥360 days subgroup becomes negative, hence the QALYs gained in that period also become negative. As this is beyond the time horizon, this issue does not affect the ICER.

(vi) Variation in time to treatment discontinuation parameter for SC chemotherapy linked to a blank cell

Within the overall population and all three PD-L1 subgroups, the model includes a "variation" parameter; this changes the shape of the KM curve for TTD for patients in the SC chemotherapy comparator groups. In each instance, this calculation is linked to a blank cell. This is an unequivocal error which affects the probabilistic analysis of Base Case Analysis 1. Probabilistic results for Base Case Analysis 2 and the subgroup analyses are not reported in the CS.[1]

(2) Unclear interpretation of effectiveness of SC chemotherapy comparators

There is a lack of clarity within the CS[1] regarding the most appropriate comparator(s) for first-line pembrolizumab combination therapy. Two distinct base case analyses are presented within the CS – one using carboplatin plus paclitaxel/nab-paclitaxel (the comparator regimen in KEYNOTE-407[7, 8]) but excluding the other options listed in the NICE scope[6] (Base Case Analysis 1), and one using the comparators listed in the NICE scope (excluding vinorelbine), but excluding the KEYNOTE-407

comparator regimen. Page 136 of the CS states that the company assumed that the regimen used in the control arm of KEYNOTE-407 is equivalent to other platinum-based combination chemotherapy options available in the UK and that clinical experts consulted by the company agreed with this assumption. Given this viewpoint, it is unclear why the second base case analysis using the NMAs is required, as this assumes that the treatment comparators do not have the same level of effectiveness.

The clinical advisors to the ERG stated that in the England, standard treatment would be gemcitabine or vinorelbine plus a platinum drug, but agreed that the company's assumption of equivalent effectiveness between the alternative regimens was reasonable. In response to a request for clarification from the ERG (see clarification response,[12] question B11), the company stated: *"…based on published literature*[9] *and feedback from UK clinical oncologists, it has been assumed that all SoC [standard of care] regimens have the same efficacy in the patient population being assessed in this TA."* The ERG believes that the presentation of results within the CS[1] is somewhat inconsistent and that it would have been more appropriate to either: (a) relegate the comparison against chemotherapy regimens included in the NMA to sensitivity analyses, or (b) include all relevant comparators from KEYNOTE-407[7, 8] and the NMAs within a single fully incremental analysis.

(3) Issues surrounding company's NMAs and ITCs

The ERG has major concerns regarding the NMA and ITC results used in the company's model. The use of a fixed effect NMA and Bucher ITC analysis underestimates the uncertainty in the treatment effect. Furthermore, neither the NMA results for the squamous PD-L1 unselected population nor the ITC results for the PD-L1 TPS ≥50% subgroup used in the company's original submitted model match the results reported in Section B2.9 of the CS.[1] Following the identification of this discrepancy by the ERG, the company presented additional NMAs by combining carboplatin and cisplatin (see clarification response,[12, 82] question B9). Both constant HRs and time-varying HRs NMAs were conducted within the company's additional analyses. The company used the results from the constant HRs fixed effect NMA model without justification. Perhaps most importantly, the validity of the NMAs may be severely compromised as none of the comparator trials included the use of second-line immunotherapy (see Section 4.4). This may contribute to the differences in expected QALY gains between the SC chemotherapy regimens modelled using HRs from the company's NMA.

The ITC analysis for the PD-L1 TPS ≥50% subgroup may have a narrower population than the population defined in the final NICE scope[6] as it excludes patients with untreated brain metastases (see Section 4.4), although the clinical advisors to the ERG noted that these patients are unlikely to be offered pembrolizumab. The ERG also believes that relevant data on patients with squamous NSCLC from KEYNOTE-024[17] should have been included in the analysis, as this study also provides relevant data for the comparison between the pembrolizumab monotherapy and chemotherapy regimens. In the

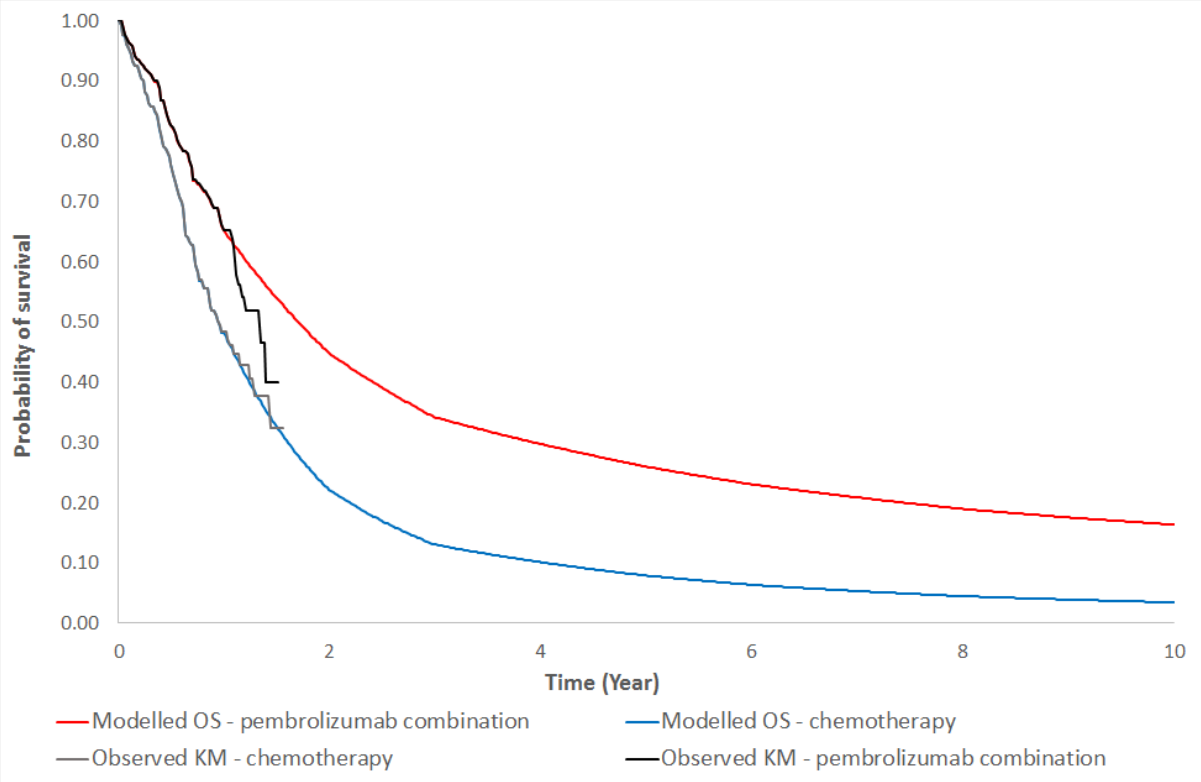
company's clarification response[12] (question A21), various scenario analyses were presented which include KEYNOTE-024[17] in the ITC. However, none of the scenario analysis results presented in the clarification response match the HRs used for OS and PFS for the NMA comparators in the economic model.

(4) Uncertainty surrounding long-term extrapolation

(i) Potentially optimistic extrapolation of OS

The company's model applies external data from SEER[81] to model long-term survival from month 12 onwards, rather than using the observed hazards from KEYNOTE-407[7, 8] to predict future survival. As shown in Figure 18, the available OS data from IA2 of KEYNOTE-407 suggest that it is around this timepoint that the observed KM curves show the greatest degree of separation between the groups. Whilst there are few patients still at risk at month 15 and at later timepoints, the available data suggest that the degree of separation between the curves is decreasing. On the basis of the evidence collected in the trial, this suggests that the company's approach for modelling OS may be optimistic.

Figure 18: Observed and predicted OS curves for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel, company's Base Case Analysis 1



The ERG requested clarification from the company regarding this discrepancy between observed and predicted survival (see clarification response,[12] question B13). In response, the company commented

that "*The data at [the] tail of the KM curve reflect very sparse observations, which from a modeling perspective should be permitted to have little or no impact on the extrapolation regardless of the method used, and this is true of both the parametric and base case population-based (SEER) approaches used. Thus, in the instance of the population-based extrapolation method, there is simply insufficient data to conclude a further trend in OS beyond the period of the KM data modeled.*"

With respect to this argument, the ERG makes the following observations:

- Parametric survival modelling takes into account both events and censored observations in the underlying time-to-event data within the likelihood function. Data should not be discarded simply because they are sparse.
- The company's argument appears to reflect a belief, in a general sense, that it is inappropriate to fit survival models to time-to-event data which are subject to administrative censoring. The ERG disagrees with this viewpoint; at the present time, the best source of information regarding the relative mortality hazard rates in patients with metastatic squamous NSCLC receiving first-line pembrolizumab combination therapy or SC chemotherapy (including currently available second-line immunotherapy) is the observed period of KEYNOTE-407.[7, 8] The ERG also notes that the company's argument for disregarding the available OS data beyond 12-months is inconsistent with their approach for modelling PFS (which involved fitting parametric models to the whole post-26 week dataset from KEYNOTE-407).
- The clinical advisors to the ERG stated that the use of SEER data may be reasonable, but noted that some caution should be exercised, as these data reflect outcomes relating to a different healthcare system.
- Given the immaturity of the data-cut used for IA2, it will be important to revisit the predictions of the model using data from the final analysis of KEYNOTE-407.[7, 8]

(ii) Representativeness of the SEER dataset

The ERG is unaware of any previous appraisals of NSCLC which have directly used data from SEER[81] to model OS. The company's justification for extrapolating OS using SEER data rather than a parametric function fitted to data from KEYNOTE-407[7, 8] is that the mortality risk is time-dependent. Table 59 of the CS shows that the parametric extrapolation does not reflect this trend. However, this argument is weak as the parametric model predictions included in the table relate to the exponential model, which by definition, assumes a constant hazard rate. Alternative parametric models fitted to the KEYNOTE-407 data would have allowed for the incorporation of time-dependent hazard rates.

The CS reference pack includes screenshots of the SEER data request for two distinct periods: 1992-2014 and 2010-2014; it is unclear how the dataset for the third period (years 2000-2014) was

constructed and the actual dataset is not contained within the reference pack. As noted in Section 5.2.4, it is unclear why three datasets covering different time periods were used. Death probabilities from SEER were obtained in 6-month intervals in terms of observed survival using actuarial methods. The population was comprised of patients with Stage IV squamous NSCLC "with malignant behavior" and known age, including cases contained in the research database. Patients without known survival times and those with missing data were excluded.[81] It is unclear if any further population characteristics were available from the dataset. No information is provided regarding the treatments received by the patients contained in the dataset and it is unlikely that any sizeable proportion of patients included in the dataset could have received immunotherapy; this may severely limit the usefulness of the dataset in reflecting current clinical practice in England.

The CS[1] provides a comparison of the UK and US NSCLC populations in order to provide supporting information regarding the appropriateness of using SEER[81] to model long-term OS (data reproduced in Table 35). This information is however limited only to mean patient age at diagnosis and the proportion of males/females in KEYNOTE-407[7, 8] and SEER; additional information from the UK National Lung Cancer Audit 2017/2018 annual report[107] is also provided for comparison. Whilst the company's clarification response[12] acknowledges that there are no comparative data on other relevant characteristics such as type of therapy received, number of previous treatments received and PS, they maintain that the populations *"are not dissimilar to each other"* (clarification response,[12] question B22c). The ERG believes that this conclusion should be approached with caution as these other key characteristics may not be balanced between the data sources. Clinical advisors to the ERG noted that during the period under consideration (1992-2014), US physicians would probably treat the disease more aggressively than UK clinicians and stated that the SEER data are likely to reflect better outcomes than those routinely achieved in the UK. In addition, the ERG notes that the SEER database covers only 18 geographic areas in the US, corresponding to less than 30% of the US population; this may impact on judgements about the comparability of the data sources at the country-level.

Table 35: Comparison of baseline characteristics between KEYNOTE-407,[7, 8] SEER and NCLA (reproduced from the company's clarification response, question B22)

Patients characteristic	KEYNOTE-407[7, 8]	SEER (US)	NLCA (UK)
Median age	65	70	72
% Male	78.3%	65% (2010-14)	58%

SEER - Surveillance, Epidemiology and End Results; NLCA - National Lung Cancer Audit

(iii) Other issues relating to extrapolation

The company's parametric survival modelling uses a piecewise approach with cut-points for OS and PFS determined by the examination of Chow test plots, although the ERG notes that parametric survival models for OS are not used in the company's base case analyses and the PFS functions have no impact on the base case ICERs. The CS[1] does not include any clinical rationale to support the choice of cut-points; within their clarification response[12] (question B19), the company states that there is no further clinical rationale. Chow test plots were based on a linear regression model of the cumulative hazard and time. The ERG notes that it is not meaningful to consider if there is a linear relationship between a cumulative hazard and time. The rejection of a linear relationship does not imply that any of the standard parametric distributions may not be appropriate. During the clarification process, the ERG requested that company provide the empirical hazard plots for OS and PFS (see clarification response,[12] question B16). The company provided the empirical hazard plots for the PD-L1 subgroups in KEYNOTE-407;[7, 8] however, plots were not provided for the ITT population. The ERG believes that there is no evidence to support the use of a piecewise approach for either OS and PFS, and in the case of complex hazard functions, the more flexible models such as the natural cubic spline models by Royston and Parmar (2002)[108] could be used. The ERG also notes that the company's model does not include any uncertainty associated with the observed portion of the piecewise OS models; only uncertainty in the model parameters after the cut-point was considered (see Table 25).

With respect to the extrapolation of TTD, the company fitted standard parametric distributions using a non-piecewise approach. The company used AIC and BIC combined with visual inspection to select the best-fitting curve. The ERG notes that the AIC and BIC statistics were similar in a number of cases and that no sensitivity analysis was provided by the company.

(5) Assumption of lifetime relative risk for OS for pembrolizumab combination therapy versus SC chemotherapy

As described in Section 5.2.2, the company's model assumes an indefinite treatment effect of pembrolizumab combination therapy on OS. This is modelled by applying the RR of death between the treatment groups during months 7-12 within KEYNOTE-407[7, 8] to the SEER mortality probabilities[81] for the comparator group. This RR is applied during each weekly model cycle from the 12-month timepoint for the remainder of the time horizon. Despite the short follow-up duration of IA2 of KEYNOTE-407, the observed KM curves for TTD at IA2 suggest that the probability of remaining on treatment at 15 months is approximately [redacted] and all patients within the trial will discontinue treatment with pembrolizumab by 2 years. Therefore, the company's model assumes that the effect of pembrolizumab on OS persists long after patients have stopped receiving treatment (i.e. a patient who is alive 10 years after discontinuing pembrolizumab is still assumed to have a better survival prognosis

compared with an identical surviving patient who did not receive pembrolizumab). The impact of this RR on OS is shown in Figure 19.

The clinical advisors to the ERG agreed that the assumption of a lifetime treatment effect was likely to be overly optimistic. The advisors noted considerable uncertainty relating to the duration of treatment response and its impact on OS outcomes.

Figure 19: Overall survival for the pembrolizumab combination therapy group including/excluding relative risk for death derived from KEYNOTE-407 months 7-12

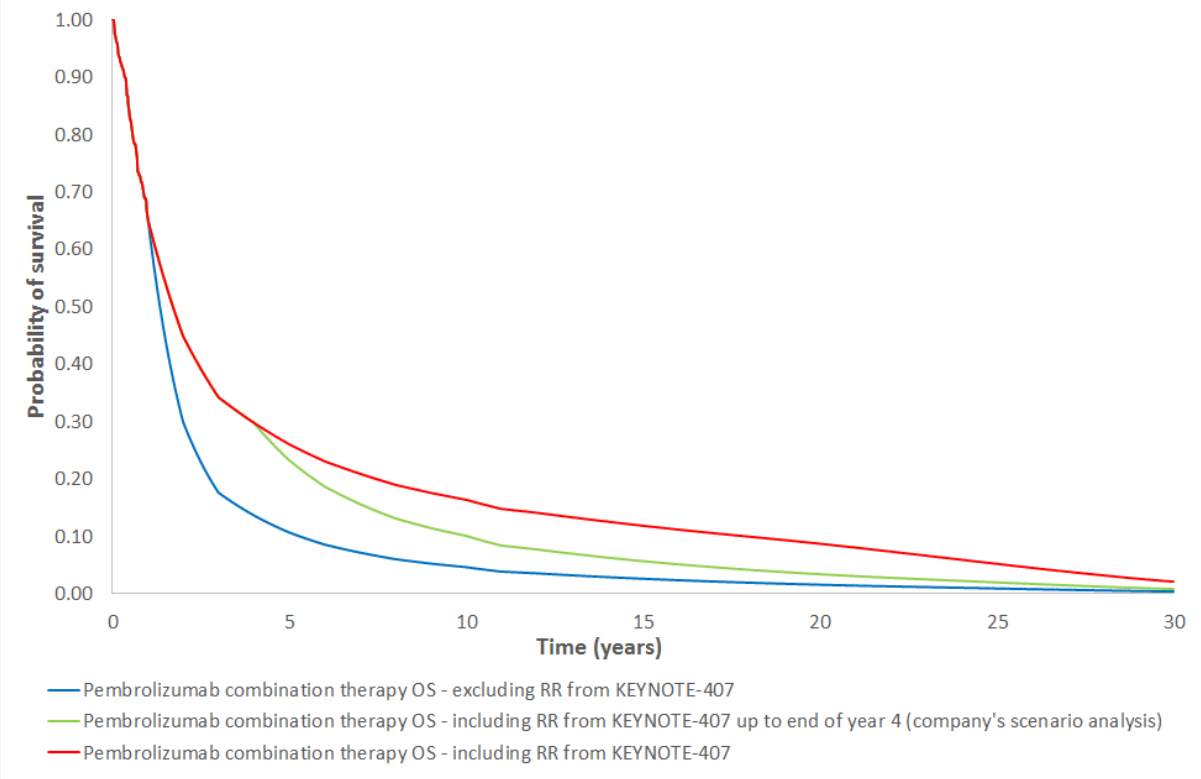


Table 36 shows the impact of assuming that the OS benefits of pembrolizumab combination therapy are lost after 2, 3 or 4 years, based on additional analyses undertaken by the ERG using the company's original submitted model. These analyses indicate that removing the treatment effect for pembrolizumab combination therapy at earlier timepoints increases the ICER considerably.

Table 36: Impact of relaxing company's assumption of lifetime effect, Base Case Analysis 1

Timepoint after which treatment effect is lost	Inc. QALYs	Inc. costs	ICER
Company's base case (lifetime effect)	1.68	£48,278	**£28,672**
2 years	0.76	£40,010	**£52,425**
3 years	1.04	£42,414	**£40,947**
4 years	1.15	£43,444	**£37,730**

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; inc. - incremental

The company does not discuss the basis of the assumption of an indefinite treatment effect in detail within the CS.[1] Table 56 of the CS states that *"there is no evidence that treatment effect stops after discontinuation."* However, the CS does not provide any information regarding any analyses of the KEYNOTE-407[7, 8] data that have been performed to support this view.

As part of the clarification process, the ERG asked the company to provide evidence to support the assumption of a continued treatment effect beyond discontinuation. In their response, the company stated *"There is no evidence to suggest that discontinuing pembrolizumab at 2 years does lead to a loss of treatment effect. MSD have previously provided scenarios in which treatment waning is investigated from year 5 (scenario 9 of the CS). Data from a publication from Herbst et al[109] investigating long-term survival of patients with advanced NSCLC in KEYNOTE-010 who completed 2 years of treatment with pembrolizumab. It concluded that most patients who completed 35 cycles or 2 years of pembrolizumab therapy had durable response, with ongoing response in 64% of patients at median follow-up of 43.4 months"* (clarification response,[12] question B12). For the sake of clarity, the ERG notes that the company's scenario analysis assumes the loss of treatment effect after 4 years, rather than a waning of effect. The company's clarification response does not provide much additional information over and above that provided in the CS.[1] The ERG notes that KEYNOTE-010 enrolled a different patient population to KEYNOTE-407 (previously treated and PD-L1 positive [TPS≥1%]) and included only pembrolizumab monotherapy; OS outcomes may be different for patients with untreated squamous metastatic NSCLC receiving pembrolizumab combination therapy. The ERG also notes that the published abstract by Herbst *et al*[109] states that response was ongoing in 59% of patients who had received 35 cycles of pembrolizumab and that median follow-up in the overall study was 42.5 months; it is unclear which data the company's clarification response refers to.

The ERG also has concerns regarding the use of an RR as the measure for the relative treatment effect on OS as this relates only to a specific time interval (7-12 months). For time-to-event data, the use of an HR would be a more appropriate measure as this takes into account the time at which an event occurs. Given that the company performed NMAs using time-varying HRs, it is unclear why these results were not used to model effects on OS.

Given the short follow-up from IA2 of KEYNOTE-407,[7, 8] the ERG believes that it is unknown whether or for how long the effects of pembrolizumab combination therapy on OS are maintained after treatment discontinuation in patients with metastatic squamous NSCLC. This is a key area of uncertainty which may be resolved through additional follow-up in KEYNOTE-407.

The ERG notes that these issues do not apply when OS is modelled using standard parametric survival curves; however, the CS[1] only reports two sensitivity analysis using this approach (KM/exponential and

KM/log logistic). Table 37 presents the results of additional analyses undertaken by the ERG which use all of the company's fitted piecewise parametric models for OS (assuming a 19-week cut-off). As shown in the table, the company's base case ICER is considerably lower than all alternative OS models.

Table 37: Impact of company's alternative piecewise parametric OS functions, 19-week cut-point, Base Case Analysis 1

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Exponential							
Pembrolizumab combination	1.95	1.36	£58,483	0.65	0.46	£36,989	**£80,142**
Carboplatin+paclitaxel/ nab-paclitaxel	1.30	0.90	£21,494	-	-	-	-
Weibull							
Pembrolizumab combination	1.99	1.39	£58,705	0.65	0.46	£36,999	**£80,532**
Carboplatin+paclitaxel/ nab-paclitaxel	1.34	0.93	£21,706	-	-	-	-
Log normal							
Pembrolizumab combination	5.29	3.06	£73,678	2.18	1.17	£44,368	**£37,761**
Carboplatin+paclitaxel/ nab-paclitaxel	3.11	1.89	£29,311	-	-	-	-
Log logistic							
Pembrolizumab combination	3.96	2.40	£67,706	1.47	0.84	£41,053	**£48,706**
Carboplatin+paclitaxel/ nab-paclitaxel	2.50	1.55	£26,653	-	-	-	-
Gompertz							
Pembrolizumab combination	1.49	1.05	£55,788	-0.09	-0.01	£33,018	**Dominated**
Carboplatin+paclitaxel/ nab-paclitaxel	1.58	1.06	£22,770	-	-	-	-
Generalised gamma							
Pembrolizumab combination	1.39	0.98	£55,222	0.08	0.07	£33,638	**£485,108**
Carboplatin+paclitaxel/ nab-paclitaxel	1.31	0.91	£21,584	-	-	-	-

** LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio*

(6) Inclusion of an implicit assumption of cure

The company's model includes a general population mortality constraint which ensures that the probability of death predicted by the KM/SEER OS model during each cycle is never lower than the mortality risk in the general population. Within the modelled pembrolizumab combination therapy group, this constraint begins to take effect at week 940 (approximately 18 years) and applies to every subsequent model cycle beyond this timepoint; at this point, 9.9% of intervention group patients are

still alive. Within the carboplatin plus paclitaxel/nab-paclitaxel comparator group (Base Case Analysis 1), the constraint begins to take effect at week 1,201 (approximately 23 years) and applies to every subsequent model cycle beyond this timepoint; at this point, around 0.8% of comparator group patients are still alive. This reflects an implicit assumption of cure, as patients surviving up to this point are assumed to have no excess risk of death due to their NSCLC. The plausibility of this model prediction, and its interpretation as a cured proportion predicted by the model, is not discussed in the CS.[1] The ERG notes that KEYNOTE-407[7, 8] does not provide any evidence to support the assumption that pembrolizumab combination therapy can provide a cure for patients with untreated squamous metastatic NSCLC.

During the clarification process, the ERG asked the company to comment on the plausibility of the predicted 9.9% of pembrolizumab-treated patients who achieve a cure. In response, the company stated *"…>9.9% of patients annually must have died within the general population around year 18, for that to have over-ridden the SEER extrapolated risk. This can be considered plausible, as the general population risks account for increasing mortality with age, whereas for SEER there was not enough data to model mortality precisely beyond year 13 and therefore the constant 9.9% risk is a valid assumption"* (clarification response,[12] question B30d). The ERG considers the company's response to be unclear – it appears that the company is referring to both the 9.9% of the modelled cohort receiving pembrolizumab combination therapy who are estimated to be cured in the model trace and the annual mortality risk of 9.9% from year 13 onwards in the SEER data (applied to the carboplatin plus paclitaxel/nab-paclitaxel group). The ERG speculates that the fact that these two values have a value of 9.9% is a coincidence and notes that the company's response provides no further justification regarding the assumption of cure within the model.

(7) Concerns regarding the company's approach to modelling HRQoL

(i) Concerns regarding the reliability of the time-to-death approach

The company's model uses a time-to-death approach for modelling HRQoL, based on four categories. The CS[1] justifies the use of this approach on the basis that:

- It reflects the known decline in cancer patients' HRQoL during the terminal phase of the disease.
- It has been previously used in the estimation of HRQoL in patients with advanced NSCLC who had previously received platinum-based chemotherapy or palliative radiotherapy and in advanced melanoma patients.
- It has been demonstrated to be more relevant than progression-based utilities as it offers a better data fit.[1]

The ERG's clinical advisors commented that the use of a time-to-death approach is reasonable; however, one advisor also commented that disease progression is a key determinant of patients' HRQoL. Despite its precedents in previous NICE technology appraisals (including pembrolizumab monotherapy[83]), published economic models[110] and published HRQoL valuation studies,[111-113] the ERG has some concerns regarding the company's approach.

(i) Potential overestimation of HRQoL for patients in longer time-to-death categories

Patients with a time-to-death ≥360 days or 180 to 360 days are assigned utility scores of [redacted] and [redacted], respectively. These values are similar to the sex-adjusted general population utility value for individuals aged 65-74 years based on Ara and Brazier[98] (estimated utility = 0.79). The model may therefore overestimate HRQoL for patients in these time-to-death categories, given that the population has metastatic NSCLC (some of whom may have progressed disease).

(ii) Potential overestimation of HRQoL for patients with longer time-to-death

In KEYNOTE-407,[7, 8] the EQ-5D-3L was administered at each of the first 7 treatment cycles, then every third cycle (9 weeks), for up to 48 weeks whilst patients were receiving treatment; the questionnaire was also administered at a treatment discontinuation visit and at the 30-day post treatment safety follow-up visit.[1] Whilst part of the company's rationale for adopting the time-to-death approach was to capture the decline in HRQoL during the terminal phase of the disease, the design of the trial means that EQ-5D assessments for patients with progressed disease will have been undertaken only shortly after disease progression was established (at most, 30 days later). Consequently, the ERG considers there to be a strong possibility that the available EQ-5D data for progressed patients are subject to bias due to informative censoring. According to the company's model predictions, more than half of the patients' survival time is spent in the post-progression state in both treatment groups, yet the EQ-5D data relate only to the beginning of this phase. Given the limitations of the EQ-5D data collection process in KEYNOTE-407, which is similar to many other trials of oncology products, the ERG has doubts that the time-to-death provides a robust approach for reflecting HRQoL for patients in the later stages of the disease. The ERG also notes that the same potential bias would apply to the use of progression-based utilities based on KEYNOTE-407. For this reason, the ERG believes there is value in exploring the use of other health valuation studies which are less likely to be subject to this issue (for example, Khan *et al*[114] and Chouaid *et al* 2013[115]).

(iii) Unclear rationale for including ratio multipliers for pembrolizumab monotherapy

Within the company's subgroup analyses of patients with PD-L1 TPS ≥50%, the utilities applied in each time-to-death category are different for the pembrolizumab monotherapy group compared with the other treatment groups (based on relative utility ratios). In addition, a constraint is applied to limit

HRQoL for patients in the time-to-death group ≥360 days to [redacted] in the pembrolizumab monotherapy group. No justification is provided for these assumptions and their underlying rationale is unclear.

(8) Uncertainty surrounding use second-line immunotherapy in the SC chemotherapy groups

The ERG believes that the costs associated with second-line treatments may be unreliable, particularly with respect to those applied in the SC chemotherapy comparator groups. As these costs are based on IA2 of KEYNOTE-407,[7, 8] it is possible that the proportion of patients going on to receive second-line immunotherapy will increase with additional follow-up. In response to a request for clarification from the ERG[12] (question B34), the company noted that the extent to which this proportion would increase in later data-cuts is unknown and any increase would likely have a favourable impact on the ICER for pembrolizumab combination therapy due to the higher costs of second-line immunotherapy which apply only to the SC chemotherapy comparator groups. The ERG agrees with the company's view that their base case ICERs are likely to be pessimistic in this respect; however, the greater use of second-line immunotherapy in the comparator group may also lead to additional OS benefits. The overall impact of this issue on the cost-effectiveness of pembrolizumab combination therapy is unclear.

The ERG also notes that the use of an interim analysis presents issues for estimating the duration of treatment on second-line regimens. It is unclear from the company's model, the CS[1] and the CS appendices[11] how these treatment durations have been estimated, whether they are means or medians, and how censoring has been dealt with. The ERG also notes that within NICE TA428[89] (pembrolizumab for previously treated PD-L1 positive NSCLC), the mean PFS time in the company's model, which was used as a proxy for time on treatment, appears to be around 7 months; this is considerably greater than the mean treatment time for second-line immunotherapy assumed in the company's model for this appraisal (approximately [redacted] months). This suggests that the costs incurred by those patients who go on to receive second-line treatment in the company's model may be underestimated.

These uncertainties may be resolved through the additional follow-up in KEYNOTE-407.[7, 8]

(9) Clinically unrealistic assumptions regarding disease management costs

Within the company's model, costs related to the management of the disease are defined according to progression status, but are applied according to TTD and the probability of receiving second-line treatment. PFS costs are applied to patients whilst receiving first-line treatment and indefinitely for those who receive second-line treatment, whereas post-progression costs are applied to patients who discontinued first-line treatment but do not receive second-line treatment. Clinical advisors to the ERG noted that disease management costs change following disease progression e.g. due to increased

hospital admissions. As such, the ERG considers that the company's approach is arbitrary and is unlikely to reflect the nature of resource use for patients with metastatic squamous NSCLC.

(10) Issues relating to AEs

The company's model estimates HRQoL decrements associated with Grade 3-5 AEs based on the difference between the EQ-5D valuation for patients who were progression-free with Grade 3-5 AEs and those who were progression-free without Grade 3-5 AEs in KEYNOTE-407.[7, 8] The QALY loss associated with AEs is calculated using this disutility, together with the frequency of AEs in each treatment group and the mean duration of AEs. The ERG believes that this approach may understate the differences in HRQoL impacts between the treatment groups:

(i) It has been discussed within the literature[116] that checkpoint inhibitors such as pembrolizumab have a different toxicity profile than chemotherapy. For example, pembrolizumab has been shown to be associated with immune-related endocrinopathies (such as hyper/hypothyroidism, Type I diabetes mellitus, diabetic ketoacidosis), gastrointestinal events (e.g. colitis), respiratory events (e.g. pneumonitis) and hepatotoxicities. These AEs may have long-term impacts and may require long-term treatment. The company's approach allows for differences in AE frequency between treatment groups, but assumes that AEs have the same magnitude of impact on HRQoL and the same duration, irrespective of treatment group. This may not adequately reflect the true health impact associated with immune-related AEs, which can be lifelong and can occur later than chemotherapy-related AEs.

(ii) Given that the KEYNOTE-407 data[7, 8] are based on an interim analysis, the complete AE profile associated with pembrolizumab combination therapy may not yet have been established within the trial.

(iii) AEs may have manifested in patients with progressed disease; however, EQ-5D estimates for these patients are not used to value the disutility associated with AEs within the company's model.

5.4 Exploratory analyses undertaken by the ERG

This section presents the methods and results of the ERG's exploratory analyses undertaken using the company's model.

5.4.1 ERG's exploratory analyses - methods

Additional survival analysis undertaken by the ERG

In order to inform the ERG's exploratory analyses, the ERG undertook additional survival analyses using the time-to-event data from KEYNOTE-407.[7, 8] The ERG reconstructed individual patient-level data (IPD) for each treatment arms in KEYNOTE-407 for both OS and PFS using the algorithm proposed by Guyot *et al.*[117] A range of models were fitted to the data including both standard parametric

models (exponential, Weibull, log logistic, log normal, Gompertz, gamma and generalised gamma) and natural cubic spline models[108] with knots=[1, 2, 3] based on modelling the log of the cumulative hazard function. The IPD were reconstructed using the reported KM data contained in the economic model directly, rather than by digitising the KM curves. The ERG used the *flexsurv* package in R[118] for all survival analyses. The ERG's analyses used all of the observed data from KEYNOTE-407, rather than the piecewise approach adopted by the company, as neither the data nor clinical opinion supported the company's use of cut-points. Goodness-of-fit statistics (AIC and BIC) and survivor functions for the ERG's survival analyses are summarised in Appendix 3.

Overview of ERG exploratory analysis

The ERG undertook four initial sets of exploratory analyses within the overall squamous NSCLC population using the company's original submitted model; these are based on the direct comparison of pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (company's Base Case Analysis 1). These initial analyses involved correcting errors identified in the company's model, converting the company's model to adopt a progression-based approach for HRQoL and disease management costs and increasing the duration of second-line immunotherapy. In addition, the ERG applied alternative PFS and OS models which were consistent with the outcomes expected by the ERG's clinical advisors; taken together, these model amendments form the ERG's preferred analyses. One of the clinical advisors suggested different expected OS estimates to the other two clinicians, hence the ERG's preferred analyses are presented across two scenarios: (i) an optimistic scenario and (ii) a pessimistic scenario. The optimistic scenario uses OS models estimated by the company, whilst the pessimistic scenario uses OS models fitted by the ERG.

Sensitivity analyses were undertaken using the ERG's preferred models to explore the impact of alternative choices around HRQoL parameters and the usage of second-line therapy. Further sensitivity analyses were also undertaken to explore the impact of applying the full range of alternative ERG-fitted OS models fitted to the KEYNOTE-407 data.[7, 8]

An exploratory sensitivity analysis was also undertaken to explore the impact of optimistic and pessimistic PFS/OS projections on the cost-effectiveness of pembrolizumab combination therapy versus the standard chemotherapy comparator regimens from the company's NMAs.

Exploratory analyses were also undertaken for the PD-L1 subgroups, based on the assumptions employed in the ERG's preferred analyses.

All analyses were undertaken using the deterministic version of the company's model, based on first model revision received by the ERG following the clarification process. Implementation of the ERG's

exploratory analyses was repeated by a second modeller to ensure that the results are free from errors. Technical details regarding the implementation of these analyses in the company's model are presented in Appendix 4.

The following sections detail the specific changes applied within each analysis.

ERG's exploratory analysis 1: Correction of errors

The ERG's double-programming exercise identified several errors in the company's submitted model. The following errors were corrected by the ERG:

(a) *Correction of OS functions for NMA comparators*. The OS curves for the NMA comparators were estimated by raising the cumulative survival probabilities for the pembrolizumab combination therapy group to the power of the relevant HRs from the NMA. This correction does not affect the ERG's preferred analyses in the overall squamous NSCLC population.

(b) *Correction of the HR for OS for the pembrolizumab monotherapy comparison (PD-L1 TPS ≥50% subgroup)*. The HR for pembrolizumab monotherapy versus pembrolizumab combination therapy was set equal to 1.03. This correction impacts only on the ERG's exploratory subgroup analyses.

(c) *Amendment of AE cost calculations*. The company's AE cost calculations were amended to remove the assumption that patients can experience only one event.

(d) *Consistent application of half-cycle correction*. The model was amended to include half-cycle correction for all treatment options.

ERG's exploratory analysis 2: Use of HRQoL based on progression status

As noted in Section 5.3.3, the ERG believes that the company's time-to-death approach for modelling HRQoL may be unreliable due to limited data collection in patients following disease progression in KEYNOTE-407.[7, 8] In response to a request for clarification,[12] (question B7d) the company presented information relating to three studies identified by their HRQoL searches which defined health utilities according to progression status.[115, 119, 120] The ERG believes that the value reported by Khan *et al*[119] (based on the TOPICAL trial[121]) may be the most relevant estimate of post-progression utility as: (i) this trial included collection of HRQoL data in progressed patients; (ii) HRQoL was measured using the EQ-5D, and (iii) few patients in the placebo group received active therapy after disease progression, hence the estimate is unlikely to be contaminated by post-progression treatments. Within the ERG's analysis, HRQoL for patients with progressed disease was based on the reported EQ-5D estimate for the placebo group of TOPICAL (post-progression utility=0.58), whilst HRQoL for the progression-free state was based on KEYNOTE-407 [redacted] As a proportion of patients in each treatment group of KEYNOTE-407 received second-line treatment, the ERG's analysis assumes that patients who progress on first-line treatment and subsequently receive second-line

treatment will spend additional time with improved HRQoL. The proportion of remaining survival time spent in a progression-free state (after progression on first-line treatment) was based on estimates of progression-free and post-progression sojourn time from the model developed to inform NICE TA428[89] (using information reported in Table 100 of the company's submission for this appraisal; note – only discounted estimates were available). Within each of the modelled treatment groups, additional post-progression HRQoL benefits were applied as follows:

(i) Patients receiving second-line chemotherapy– 49% of remaining survival time assumed to be spent in progression-free state
(ii) Patients receiving second-line immunotherapy - 32% of remaining survival time assumed to be spent in progression-free state
(iii) Patients not receiving second-line treatment – no additional PFS time, post-progression utility applied for remaining survival time.

ERG's exploratory analysis 3: Disease management costs based on PFS/PPS

The ERG has concerns that the company's approach to modelling disease management costs does not reflect clinical reality. Within this exploratory analysis, disease management costs were applied according to the presence/absence of disease progression. As with the ERG's approach used to model progression-based HRQoL, post-progression costs were weighted to account for additional PFS time for those patients who receive second-line treatment; this adjustment was based on the same assumptions as those used in ERG exploratory analysis 2.

ERG's exploratory analysis 4: Second-line immunotherapy treatment costs doubled

The ERG believes that the assumed treatment durations for second-line immunotherapy from KEYNOTE-407 applied in the company's model are likely to be underestimates. Within this analysis, the treatment duration for second-line immunotherapy was doubled; this better reflects the treatment duration assumed in NICE TA428.[89]

ERG's exploratory analysis 5a and 5b: Alternative PFS and OS models

As noted in Section 5.3.3, the ERG has concerns that the company's PFS and OS predictions may be optimistic. In order to address this concern, the ERG's clinical advisors were asked to estimate PFS and OS probabilities at 5, 10 and 20 years for patients receiving pembrolizumab combination therapy and for patients receiving SC chemotherapy (taking into account those patients receiving second-line pembrolizumab monotherapy, based on IA2 in KEYNOTE-407[7, 8]). The clinical advisors noted considerable uncertainty given the short follow-up duration from IA2 of KEYNOTE-407 and found this task very difficult to complete.

Clinicians' and ERG's estimates of OS

With respect to OS, two of the clinical advisors preferred the projections of the company's KM/log logistic model for the pembrolizumab combination therapy group (5-year OS probability = 20%; 10-year OS probability = 11%) and the KM/SEER model for the SC chemotherapy group (5-year OS probability = 8%; 10-year OS probability = 3%). The ERG notes that the KM/log logistic model suggests that 6% of patients treated with pembrolizumab combination therapy will achieve cure by 18 years (no excess risk of mortality due to NSCLC).

The third clinical advisor suggested estimates of OS for the pembrolizumab combination therapy group of 15-20% at 5 years, 5-10% at 10-years and <2% at 20 years. The advisor noted that their preferred OS estimates for this group would likely lie between the ERG's log logistic and exponential functions. For the SC chemotherapy group, the clinician suggested OS estimates of 8-10% at 5 years and around 5% at 10 years (including second-line pembrolizumab monotherapy use). Based on this information, the ERG has assumed the log logistic function (fitted by the ERG using the whole KEYNOTE-407 dataset) for both treatment groups, but notes that this is favourable to the pembrolizumab combination therapy group.

Clinicians' and ERG's estimates of PFS

Two of the clinical advisors believed that the company's piecewise log normal PFS models were reasonable; these models indicate 5-year PFS probabilities for the pembrolizumab combination therapy and the SC chemotherapy groups of 0.10 and 0.03, respectively. The third clinical advisor also believed that the estimates from this model were plausible, but noted difficulty in estimating long-term PFS.

Optimistic and pessimistic scenarios presented as part of the ERG's exploratory analyses

Owing to uncertainty in the clinical evidence, the ERG presents two sets of analysis: (a) an optimistic analysis based on the views of Clinicians 1 and 2, and (b) a pessimistic analysis based on the views of Clinician 3. The PFS and OS models applied in these analyses are summarised in Table 38.

Table 38: PFS and OS models used in ERG's preferred optimistic and pessimistic analyses

Model	Optimistic analysis – Exploratory analysis 5a	Pessimistic analysis - Exploratory analysis 5b
OS model - pembrolizumab combination therapy	Company's KM/log logistic model (19-week cut-point)	ERG's log logistic model* (no cut-point)
OS model - SC chemotherapy	Company's KM/SEER model (19-week cut-point)	ERG's log logistic model* (no cut-point)
PFS model - pembrolizumab combination therapy	Company's piecewise log normal model (26-week cut-point)	Company's piecewise log normal model (26-week cut-point)
PFS model – SC chemotherapy	Company's piecewise log normal model (26-week cut-point)	Company's piecewise log normal model (26-week cut-point)

OS - overall survival; PFS- progression-free survival; KM - Kaplan-Meier; SEER - Surveillance, Epidemiology and End Results; ERG - Evidence Review Group
** These models broadly approximate the clinician's expected OS as 5-years*

The assumed OS curves applied in each scenario are presented in Figure 20; the clinicians' preferred PFS curves are based on the company's projections (previously shown in Figure 11).

Figure 20: ERG-preferred optimistic and pessimistic OS models and company's base case OS models (excludes general population mortality constraint) – Figure redacted due to AIC

ERG's exploratory analysis 6a and 6b: ERG-preferred analysis

This analysis combines ERG exploratory analyses 1-5 for the optimistic and pessimistic scenarios.

Additional sensitivity analysis 1: Increased proportion costs of second-line immunotherapy

Within this analysis, the proportion of patients in both treatment groups who are assumed to receive second-line treatment was arbitrarily increased to 75%.

Additional sensitivity analysis 2: Impacts of AEs on HRQoL and costs doubled for pembrolizumab combination therapy group

Within this analysis, the costs and QALY losses applied in the pembrolizumab combination therapy group were doubled.

Additional sensitivity analysis 3: Fully incremental analysis including NMA comparators

This analysis includes the three additional SC chemotherapy options from the company's NMA3 (cisplatin/carboplatin in combination with docetaxel, gemcitabine or paclitaxel). Owing to the ERG's concerns regarding the absence of second-line immunotherapies in the trials included in the company's NMAs, the results of this analysis should be interpreted with caution.

Additional sensitivity analysis 4: Exploration of all parametric models fitted by the ERG

Within this analysis, all standard parametric models and spline models fitted by the ERG were considered, assuming the same functional form for both treatment groups.

Additional sensitivity analysis 5: Subgroup analyses by PD-L1 subgroup

Additional subgroup analyses were performed based on the OS model choices adopted in the ERG's preferred analyses (ERG exploratory analyses 6a and 6b).

5.4.2 ERG's exploratory analyses - results

ERG's preferred analyses - overall squamous NSCLC population

The results of the ERG's preferred analyses are presented in Table 39. The results are presented as individual changes relative to the ERG's corrected model (ERG exploratory analysis 1); all individual changes are combined in ERG exploratory analyses 6a and 6b.

The analyses indicate that the correction of model errors, the use of progression-based HRQoL and costs and an assumed increase in second-line immunotherapy costs do not have a substantial impact on the ICER (ERG exploratory analyses 1-4). However, the assumptions regarding OS in each treatment group are key drivers of the ICER (ERG exploratory analysis 5). Under the ERG's preferred optimistic scenario, the ICER for pembrolizumab combination therapy versus SC chemotherapy is estimated to be

£35,981 per QALY gained; under the ERG's preferred pessimistic scenario, the ICER is estimated to be £49,473 per QALY gained.

Table 39: Results of ERG-preferred analysis, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base case							
Pembrolizumab combination	5.09	2.95	£72,695	3.12	1.68	£48,278	**£28,672**
Standard chemotherapy	1.97	1.27	£24,417	-	-	-	-
ERG exploratory analysis 1 - Correction of errors†							
Pembrolizumab combination	5.06	2.94	£72,806	3.09	1.68	£48,093	**£28,693**
Standard chemotherapy	1.97	1.27	£24,713	-	-	-	-
ERG exploratory analysis 2 - Use of HRQoL based on progression status (includes ERG corrections)							
Pembrolizumab combination	5.06	2.58	£72,806	3.09	1.42	£48,093	**£33,860**
Standard chemotherapy	1.97	1.16	£24,713	-	-	-	-
ERG exploratory analysis 3 - Disease management costs based on PFS/PPS							
Pembrolizumab combination	5.06	2.94	£71,243	3.09	1.68	£46,465	**£27,722**
Standard chemotherapy	1.97	1.27	£24,779	-	-	-	-
ERG exploratory analysis 4 - Second-line immunotherapy treatment costs doubled							
Pembrolizumab combination	5.06	2.94	£72,806	3.09	1.68	£43,250	**£25,804**
Standard chemotherapy	1.97	1.27	£29,555	-	-	-	-
ERG exploratory analysis 5a -ERG optimistic PFS and OS curves							
Pembrolizumab combination	3.94	2.39	£67,846	1.98	1.12	£43,133	**£38,438**
Standard chemotherapy	1.97	1.27	£24,713	-	-	-	-
ERG exploratory analysis 5b ERG pessimistic PFS and OS curves							
Pembrolizumab combination	3.23	2.04	£64,724	1.06	0.64	£39,012	**£60,601**
Standard chemotherapy	2.17	1.40	£25,712	-	-	-	-
ERG exploratory analysis 6a - ERG preferred analysis - optimistic							
Pembrolizumab combination	3.94	2.17	£66,008	1.98	1.01	£36,387	**£35,981**
Standard chemotherapy	1.97	1.16	£29,621	-	-	-	-
ERG exploratory analysis 6b -ERG preferred analysis - pessimistic							
Pembrolizumab combination	3.23	1.91	£62,832	1.06	0.65	£32,050	**£49,473**
Standard chemotherapy	2.17	1.26	£30,782	-	-	-	-

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted; † Analyses 2-6 each include error corrections from analysis 1*

Additional sensitivity analyses - overall squamous NSCLC population

Table 40 presents the results of the ERG's additional sensitivity analyses around use of second-line treatment and increased AE impacts for pembrolizumab combination therapy using the ERG's preferred optimistic and pessimistic scenarios. As shown in the table, the potential for increased use of second-line therapy at later data-cuts of the KEYNOTE-407 trial may lead to reductions in the ICER for pembrolizumab combination therapy. The table also indicates that the model is not sensitive to assumptions regarding AE impacts associated with pembrolizumab, although the full economic impact of IRAEs remains unclear.

Table 40: Results of additional sensitivity analyses using the ERG-preferred analysis, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

	ERG preferred analysis - optimistic scenario			ERG preferred analysis – pessimistic scenario		
	Inc. QALYs	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
ERG's preferred analysis	1.01	£36,387	**£35,981**	0.65	£32,050	**£49,473**
Sensitivity analysis 1 – 75% patients receive second-line treatment	1.05	£32,333	**£30,676**	0.67	£28,311	**£42,280**
Sensitivity analysis 2 – AE QALY loss and costs doubled	1.00	£37,889	**£37,851**	0.64	£33,552	**£52,627**

Table 41 presents the results of the ERG's preferred analyses including the comparators from the company's NMAs together with the comparator regimen included in KEYNOTE-407. These analyses suggest that carboplatin+paclitaxel/nab-paclitaxel is strongly dominated and the ICER for pembrolizumab combination therapy versus the next most effective option (cisplatin/carboplatin plus gemcitabine) ranges from £51,054 to £56,831 per QALY gained. These results should be interpreted with caution due to the ERG's concerns regarding the reliability of the company's NMAs.

Table 41: Sensitivity analysis 3 – fully incremental analysis of all options using the ERG's preferred optimistic and pessimistic models

Option	**LYGs***	**QALYs**	**Costs**	**Inc. LYGs***	**Inc. QALYs**	**Inc. costs**	**ICER (per QALY gained)**
ERG-preferred analysis – optimistic, pembrolizumab combination versus all comparators (deterministic)							
Pembrolizumab combination	3.94	2.17	£66,008	1.27	0.68	£34,866	**£51,054**
Platinum+gemcitabine	2.67	1.49	£31,142	0.66	0.31	£3,733	**£11,891**
Platinum+paclitaxel	2.01	1.18	£27,408	0.10	0.05	£470	**£9,021**
Carboplatin+paclitaxel/ nab-paclitaxel	1.97	1.16	£29,621	-	-	-	**Dominated**
Platinum+docetaxel	1.91	1.12	£26,938	-	-	-	-
ERG-preferred analysis – pessimistic, pembrolizumab combination versus all comparators (deterministic)							
Pembrolizumab combination	3.23	1.91	£62,832	1.01	0.59	£33,515	**£56,831**
Platinum+gemcitabine	2.22	1.32	£29,317	0.50	0.26	£3,138	**£12,126**
Carboplatin+paclitaxel/ nab-paclitaxel	2.17	1.26	£30,782	-	-		**Dominated**
Platinum+paclitaxel	1.72	1.06	£26,179	0.07	0.04	£380	**£8,697**
Platinum+docetaxel	1.65	1.02	£25,799	-	-	-	-

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year
** - undiscounted*

Table 42 presents the results of the ERG's sensitivity analyses around alternative OS functions. These analyses suggest that the ICER ranges from £35,981 to £274,028 per QALY gained. Importantly, these analyses indicate that a number alternative OS functions lead to ICERs which are considerably higher than those included in the company's base case analysis and the ERG's preferred scenarios. The ERG notes that some of this uncertainty may be resolved through longer data collection in KEYNOTE-407.

Table 42: Sensitivity analysis 4 – alternative ERG-fitted OS models applied to the ERG's preferred optimistic and pessimistic models, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

OS model (both treatment groups)	Inc. QALYs	Inc. Costs	ICER
ERG preferred model - optimistic	1.01	£36,387	**£35,981**
ERG preferred model - pessimistic	0.65	£32,050	**£49,473**
Generalised gamma	0.12	£28,947	**£233,327**
Gamma	0.41	£30,994	**£76,057**
Log normal	0.81	£33,968	**£42,193**
Log logistic	0.65	£32,050	**£49,473**
Weibull	0.36	£30,697	**£84,320**
Gompertz	0.20	£29,575	**£144,595**
Exponential	0.53	£31,961	**£60,302**
Spline k=1,scale=hazard	0.33	£30,470	**£91,995**
Spline k=2,scale=hazard	0.22	£29,506	**£135,956**
Spline k=3,scale=hazard	0.10	£28,363	**£274,028**
Spline k=1,scale=normal	0.63	£32,579	**£51,611**
Spline k=2,scale=normal	0.39	£30,698	**£78,446**
Spline k=3,scale=normal	0.25	£29,114	**£116,905**
Spline k=1,scale=odds	0.58	£31,851	**£54,645**
Spline k=2,scale=odds	0.39	£30,408	**£78,200**
Spline k=3,scale=odds	0.22	£28,215	**£130,059**

Inc. – incremental; OS – overall survival; ICER – incremental cost-effectiveness ratio; k=knot

ERG's preferred analyses – exploratory subgroup analyses

Table 43 and Table 44 present the results of the ERG's exploratory subgroup analyses for the ERG's preferred optimistic and pessimistic scenarios, respectively. It should be noted that these analyses should be considered as exploratory due to the assumption that OS takes the same form in the subgroup as the overall population; this assumption may not necessarily hold. These analyses suggest the following results:

- PD-L1 TPS <1% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £34,239 (pessimistic) to £34,392 (optimistic) per QALY gained.
- PD-L1 TPS 1-49% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £40,767 (optimistic) to £52,680 (pessimistic) per QALY gained
- PD-L1 TPS ≥50% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £39,193 (optimistic) per QALY gained to dominated (pessimistic). Pembrolizumab monotherapy is ruled out due to strong dominance.

Table 43: ERG's exploratory subgroup analyses - optimistic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1% subgroup							
Pembrolizumab combination	3.83	2.03	£64,296	1.98	0.93	£32,126	**£34,392**
Carboplatin+paclitaxel /nab-paclitaxel	1.84	1.10	£32,170	-	-	-	-
PD-L1 TPS 1-49% subgroup							
Pembrolizumab combination	3.60	2.13	£69,348	1.59	0.96	£39,146	**£40,767**
Carboplatin+paclitaxel/ nab-paclitaxel	2.02	1.17	£30,203	-	-	-	-
PD-L1 TPS ≥50% subgroup							
Pembrolizumab combination	4.02	2.11	£64,708	2.02	0.91	£35,519	**£39,193**
Pembrolizumab monotherapy	3.85	2.06	£67,519	-	-	-	**Dominated**
Carboplatin+paclitaxel/ nab-paclitaxel	2.00	1.20	£29,189	-	-	-	-

** undiscounted*
ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year

Table 44: ERG's exploratory subgroup analyses - pessimistic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1% subgroup							
Pembrolizumab combination	3.29	1.85	£61,898	1.88	0.93	£31,918	**£34,239**
Carboplatin+paclitaxel/ nab-paclitaxel	1.40	0.92	£29,980	-	-	-	-
PD-L1 TPS 1-49% subgroup							
Pembrolizumab combination	3.12	1.91	£67,684	1.03	0.70	£37,023	**£52,680**
Carboplatin+paclitaxel/ nab-paclitaxel	2.09	1.21	£30,661	-	-	-	-
PD-L1 TPS ≥50% subgroup							
Carboplatin+paclitaxel/ nab-paclitaxel	4.01	2.03	£38,907	-	-	-	**Dominating**
Pembrolizumab combination	3.72	2.01	£63,425	-	-	-	**Dominated**
Pembrolizumab monotherapy	3.56	1.96	£66,382	-	-	-	**Dominated**

** undiscounted*
ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year

5.5 Discussion

The CS[1] includes a systematic review of published economic analyses of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel (pembrolizumab combination therapy) for patients with untreated squamous or non-squamous metastatic NSCLC. The company's review did not identify any relevant economic evaluations, in part due to the specific definition of the intervention in the eligibility criteria for the review.

The CS[1] presents the methods and results of a *de novo* partitioned survival model developed by the company to assess the cost-effectiveness of pembrolizumab combination therapy versus SC chemotherapy for the first-line treatment of patients with squamous metastatic NSCLC (PD-L1 unselected). The CS reports the results of two base cases analyses: "Base Case Analysis 1" compares pembrolizumab combination therapy against carboplatin plus paclitaxel/nab-paclitaxel (the comparator used in KEYNOTE-407[7, 8]), whilst "Base Case Analysis 2" compares pembrolizumab combination therapy against cisplatin/carboplatin in combination with docetaxel, gemcitabine or paclitaxel (the additional comparators included in the company's NMAs[1]). Separate exploratory analyses are also presented for three subgroups defined by PD-L1 TPS (<1%, 1-49% and ≥50%). Within these subgroups, the comparator is carboplatin plus paclitaxel/nab-paclitaxel; an additional indirect comparison is presented against pembrolizumab monotherapy for patients with PD-L1 TPS ≥50%.

Across all analyses, incremental health gains, costs and cost-effectiveness are evaluated over a 30-year time horizon from the perspective of the NHS and PSS. Whilst the CS[1] describes a model in which the partition is defined by the presence/absence of progression, neither the costs nor health outcomes for any treatment strategy are influenced by disease progression. The ERG considers that the company's implemented model is better described as a partitioned survival model based on three health states: (1) receiving first-line treatment; (2) not receiving first-line treatment (including second-line chemotherapy/immunotherapy for some patients), and (3) dead. The model partition impacts only on costs; HRQoL is modelled according to the patient's time to death. The model parameters were informed by analyses of time-to-event data (TTD and OS) collected within KEYNOTE-407, with additional external data from SEER[81] used to model long-term survival. Importantly, the company's model assumes a lifetime treatment effect for the pembrolizumab combination therapy group, despite a maximum treatment duration for pembrolizumab of 2 years. The effectiveness of other SC chemotherapy comparators was estimated from NMAs performed by the company. HRQoL estimates for time-to-death categories were based on EQ-5D assessments within KEYNOTE-407. Resource cost parameters were taken from KEYNOTE-407, standard costing sources,[87, 103] previous TAs, [74, 89-96, 102] additional literature and assumptions.[1]

For Base Case Analysis 1, the probabilistic version of the company's model (using the KM/SEER OS model, including a continued treatment effect for OS) suggests that pembrolizumab combination therapy is expected to generate an additional 1.68 QALYs at an additional cost of £48,387 per patient; the corresponding ICER is £28,852 per QALY gained. The deterministic version of the company's model produces a very similar ICER of £28,672 per QALY gained. The probability that pembrolizumab combination therapy produces more net benefit than carboplatin plus paclitaxel/nab-paclitaxel at WTP thresholds (λ) of £30,000 and £50,000 per QALY gained is 0.55 and 0.94, respectively.

For Base Case Analysis 2, a fully incremental analysis of pembrolizumab combination therapy versus all treatment comparators from KEYNOTE-407 and the company's NMAs suggest that: cisplatin/carboplatin plus docetaxel is the least effective option; carboplatin plus paclitaxel/nab-paclitaxel (the KEYNOTE-407 comparator regimen) is dominated by cisplatin/carboplatin plus paclitaxel; the ICERs for cisplatin/carboplatin plus gemcitabine and cisplatin/carboplatin plus paclitaxel versus their next best non-dominated comparators are less than £9,000 per QALY gained, and the ICER for pembrolizumab combination therapy versus platinum plus gemcitabine is approximately £63,661 per QALY gained. The ERG identified errors in the model which render these results unreliable; the correction of these errors reduces the company's ICER for pembrolizumab combination therapy versus platinum plus gemcitabine to £51,240 per QALY gained. Probabilistic results for this analysis were not reported in the CS and could not be easily generated using the company's model.

The company's PD-L1 subgroup analyses suggest ICERs for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel which are in the range £25,849 to £32,174 per QALY gained. Within the PD-L1 TPS ≥50% subgroup, the company's model suggests that pembrolizumab combination therapy is ruled out of the analysis due to extended dominance. However, the ERG identified errors in this analysis; the correction of these errors leads to a situation whereby pembrolizumab monotherapy is ruled out due to strong dominance.

The ERG critically appraised the company's health economic analyses and double-programmed the deterministic version of the company's model (for Base Case Analyses 1 and 2 and for the PD-L1 TPS subgroup analyses). The ERG's critical appraisal identified a number of issues relating to the company's model and the evidence used to inform its parameters. The most pertinent of these include: (i) the identification of model errors; (ii) concerns relating to the company's NMAs, in particular, the absence of second-line immunotherapy from the trials of SC chemotherapy comparator regimens; (iii) uncertainty surrounding long-term extrapolation; (iv) the potentially optimistic assumption of a lifetime OS treatment effect for pembrolizumab combination therapy; (v) the inclusion of an implicit assumption of cure within the model, and (vi) concerns regarding the company's approach to modelling HRQoL.

The ERG notes that the OS data from KEYNOTE-407 are immature and alternative assumptions regarding long-term OS benefits have the propensity to increase the ICER substantially.

The ERG undertook six sets of exploratory analyses using the deterministic version of the company's model. The ERG's preferred model includes the following amendments: (i) the correction of model errors; (ii) the inclusion of health state utilities defined according to the presence/absence of disease progression (together with the use of PFS data applied as the model partition); (iii) the use of disease management costs defined according to the presence/absence of disease progression; (iv) increased costs associated with second-line immunotherapy, and (v) the use of clinicians' preferred OS models. The ERG's preferred analyses combine all of these amendments and are presented across two separate scenarios: (i) an optimistic scenario, and (ii) a pessimistic scenario. The ERG's preferred optimistic scenario suggests an ICER for pembrolizumab combination therapy versus SC chemotherapy of £35,981 per QALY gained, whilst the ERG's preferred pessimistic scenario suggests a higher ICER of £49,473 per QALY gained. Additional sensitivity analyses using the full range of ERG-fitted standard parametric models and natural cubic spline models lead to ICERs ranging from £35,981 to £274,028 per QALY gained. The ERG's exploratory subgroup analyses, which are based on the same parametric OS models as those applied in the overall population (PD-L1 unselected), suggest the following results:

- PD-L1 TPS <1% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £34,239 (pessimistic) to £34,392 (optimistic) per QALY gained.
- PD-L1 TPS 1-49% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £40,767 (optimistic) to £52,680 (pessimistic) per QALY gained
- PD-L1 TPS ≥50% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £39,193 (optimistic) per QALY gained to dominated (pessimistic). Pembrolizumab monotherapy is ruled out due to strong dominance.

The ERG notes that additional data collection in KEYNOTE-407 may resolve some of the uncertainty surrounding expected outcomes, both within the overall metastatic squamous NSCLC population and within specific PD-L1 TPS subgroups.

6 END OF LIFE

NICE End of Life (EoL) supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The ERG notes that owing to the short follow-up in IA2 of the KEYNOTE-407 trial,[7, 8] and the potential benefits of second-line immunotherapy in the SC chemotherapy group, the expected survival duration for patients receiving pembrolizumab combination therapy and standard care is subject to considerable uncertainty. At the time of IA2 in KEYNOTE-407, median OS was 15.9 months in the pembrolizumab combination therapy group and 11.3 months in the carboplatin plus paclitaxel/nab-paclitaxel group (difference=4.6 months). Table 45 summarises the undiscounted mean survival for carboplatin plus paclitaxel/nab-paclitaxel, the incremental survival gain for pembrolizumab combination therapy and the ICER based on the company's corrected base case (ERG exploratory analysis 1), the ERG's preferred optimistic and pessimistic analyses (ERG exploratory analyses 6a and 6b), and the full range of parametric OS models fitted by the ERG (ERG sensitivity analysis 4). The table also indicates whether both of NICE's EoL criteria are met for each OS model scenario.

The ERG-corrected company's base case analysis and the ERG's preferred optimistic analysis suggest that pembrolizumab combination therapy meets NICE's EoL criteria (standard care OS = 1.97 years; life extension = 1.98 to 3.12 years; ICER <£36,000 per QALY gained). Within the ERG's preferred pessimistic analysis, pembrolizumab combination therapy meets the life extension criterion, but does not meet the 24-month expected survival criterion (standard care OS = 2.17 years; life extension = 1.06 years; ICER = £49,473 per QALY gained). Across the full range of ERG-fitted OS models, the EoL criteria are met in the majority of scenarios, however the ICER for pembrolizumab combination therapy remains above £50,000 per QALY gained across all of these scenarios.

Table 45: Undiscounted survival for comparator groups and incremental survival gain

OS model	Comparator group outcomes			Incremental – pembrolizumab combination vs. SC chemotherapy		EoL criteria met?
	Mean OS (undiscounted)	1-year OS	2-year OS	Incremental OS (years)	ICER*	
Company's original model (company's KM/SEER model)	1.97	48%	22%	3.09	**£28,693**	**yes**
ERG optimistic scenario (company's KM/log logistic model)	1.97	48%	22%	1.98	**£35,981**	**yes**
ERG pessimistic scenario (ERG's log logistic model)	2.17	50%	27%	1.06	**£49,473**	**no**
Generalised gamma (ERG-fitted)	1.17	49%	17%	0.14	**£233,327**	**no**
Gamma (ERG-fitted)	1.30	50%	21%	0.58	**£76,057**	**yes**
Log normal (ERG-fitted)	2.58	52%	33%	1.49	**£42,193**	**no**
Log logistic (ERG-fitted)	2.17	50%	27%	1.06	**£49,473**	**no**
Weibull (ERG-fitted)	1.24	49%	19%	0.51	**£84,320**	**yes**
Gompertz (ERG-fitted)	1.09	50%	13%	0.26	**£144,595**	**yes**
Exponential (ERG-fitted)	1.50	51%	26%	0.81	**£60,302**	**yes**
Spline k=1,scale=hazard (ERG-fitted)	1.18	49%	17%	0.46	**£91,995**	**yes**
Spline k=2,scale=hazard (ERG-fitted)	1.24	49%	19%	0.27	**£135,956**	**yes**
Spline k=3,scale=hazard (ERG-fitted)	1.47	48%	24%	0.06	**£274,028**	**no**
Spline k=1,scale=normal (ERG-fitted)	1.54	49%	23%	1.03	**£51,611**	**yes**
Spline k=2,scale=normal (ERG-fitted)	1.37	49%	20%	0.56	**£78,446**	**yes**
Spline k=3,scale=normal (ERG-fitted)	1.75	48%	25%	0.26	**£116,905**	**yes**
Spline k=1,scale=odds (ERG-fitted)	1.73	49%	23%	0.94	**£54,645**	**yes**
Spline k=2,scale=odds (ERG-fitted)	1.60	48%	21%	0.55	**£78,200**	**yes**
Spline k=3,scale=odds (ERG-fitted)	2.08	48%	26%	0.13	**£130,059**	**no**

7 OVERALL CONCLUSIONS

The clinical evidence regarding the efficacy of pembrolizumab combination therapy for untreated metastatic squamous NSCLC is broadly reliable and relevant to the decision problem. The main source of evidence in the CS[1] is from a single high-quality RCT (KEYNOTE-407[7, 8]). This trial reported that pembrolizumab combination therapy was statistically superior to SC chemotherapy for OS, PFS, and DoR outcomes. Reporting of safety data in this trial was limited to 30 days for AEs and 90 days for SAEs after the last dose of study treatment. The ERG notes that stopping data collection after these cut-off dates will limit the validity of the evidence relating to the toxicity profile for patients undergoing immunotherapy in combination with SC chemotherapy. Data on baseline PD-L1 expression for patients who switched from the SC chemotherapy to immunotherapy from the final analysis of KEYNOTE-407 would be informative. There remains uncertainty surrounding whether pembrolizumab should be given as first-line combination therapy or as monotherapy for patients with PD-L1 strong expression.

The exploratory analyses undertaken by the ERG led to an ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel of £35,981 per QALY gained under optimistic OS assumptions, and an ICER of £49,473 per QALY gained under pessimistic OS assumptions. These estimates are higher than the company's original base case estimate of £28,852 per QALY gained (the company's probabilistic ICER for this comparison). Given the limitations of the available evidence from IA2 of KEYNOTE-407,[7, 8] the ERG notes that there is considerable uncertainty surrounding the expected OS outcomes for patients receiving pembrolizumab combination therapy and for those receiving SC chemotherapy (in part, due to the use of second-line immunotherapy as part of the SC pathway in England). Additional sensitivity analyses using alternative OS functions within the ERG's preferred model produced ICERs which range from £35,981 to £274,028 per QALY gained; several of these estimates are higher than the ERG's pessimistic scenario. The ERG's exploratory subgroup analyses suggest optimistic ICERs which range from £34,392 to £39,193 per QALY gained across all PD-L1 subgroups, and pessimistic ICERs which range from £34,239 to dominated across the PD-L1 subgroups.

Given the uncertainty in the OS estimates based on IA2 of KEYNOTE-407,[7, 8] it is unclear whether pembrolizumab combination therapy meets NICE's EoL criteria.

7.1 Implications for research

The ERG notes that additional data collection in KEYNOTE-407 may resolve some of the uncertainty surrounding expected outcomes in the overall squamous NSCLC population and within specific PD-L1 TPS subgroups. Evidence regarding the safety of pembrolizumab combination therapy is immature. In view of the delayed onset and prolonged duration of IRAEs, consideration of extension studies and real-

world data will be key to providing externally valid documentation of the safety of pembrolizumab combination therapy in the proposed indication.

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9 APPENDICES

Appendix 1: AIC and BIC statistics for company's piecewise parametric curve-fitting for OS

Table 46: AIC and BIC statistics for company's piecewise parametric curve-fitting for OS*

Week 9 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Week 19 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Week 29 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; SC - standard care
** Best fitting models (lowest AIC/BIC) presented in bold*

Appendix 2: Time-to-event models and additional parameters used in company's subgroup analyses

Table 47: AIC and BIC statistics for company's piecewise parametric curve-fitting for OS, cutoff point 19 weeks (adapted from the company's model)

PD-L1<1%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential				
Weibull				
Log normal				
Log logistic				
Gompertz				
Generalised gamma				
PD-L1 1-49%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential				
Weibull				
Log normal				
Log logistic				
Gompertz				
Generalised gamma				
PD-L1≥50%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential				
Weibull				
Log normal				
Log logistic				
Gompertz				
Generalised gamma				

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; N/A – not available; PD-L1 - programmed death-ligand 1; SC - standard care

** Best fitting models (lowest AIC/BIC) presented in bold*

Figure 21: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, pembrolizumab combination therapy group in KEYNOTE-407,[7, 8] PD-L1 TPS≥50%

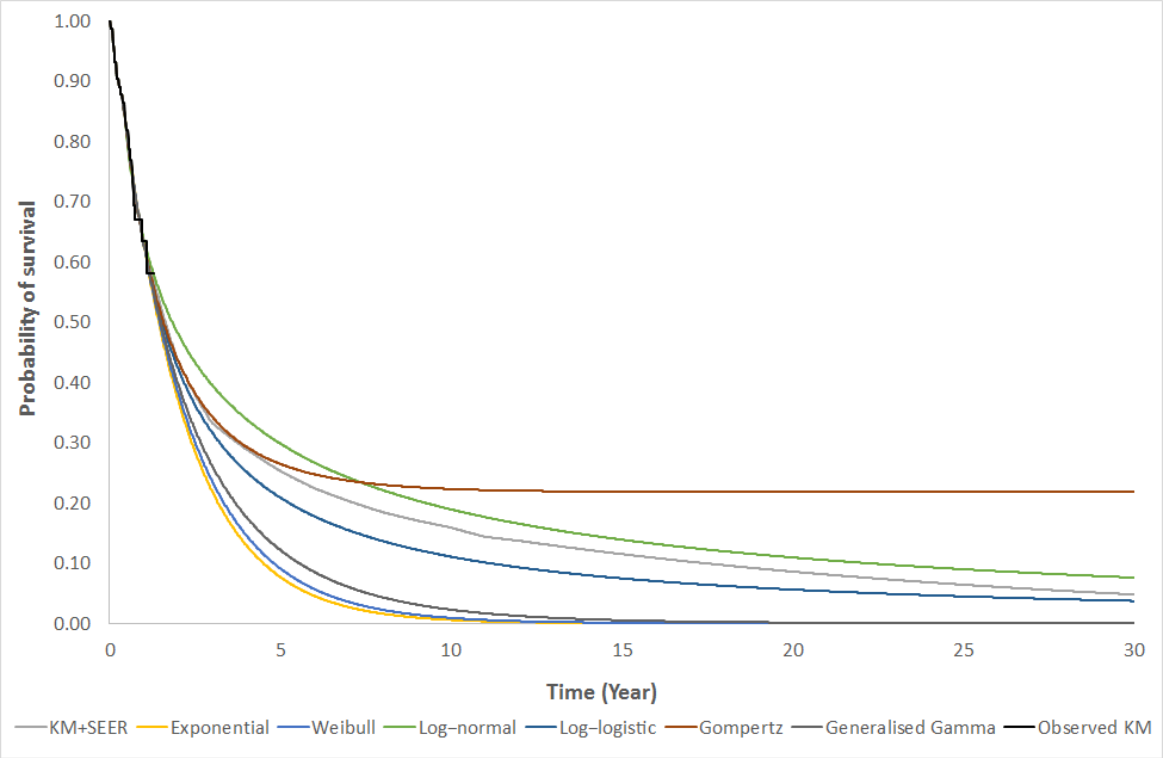


Figure 22: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, pembrolizumab combination therapy group in KEYNOTE-407,[7, 8] PD-L1 TPS 1-49%

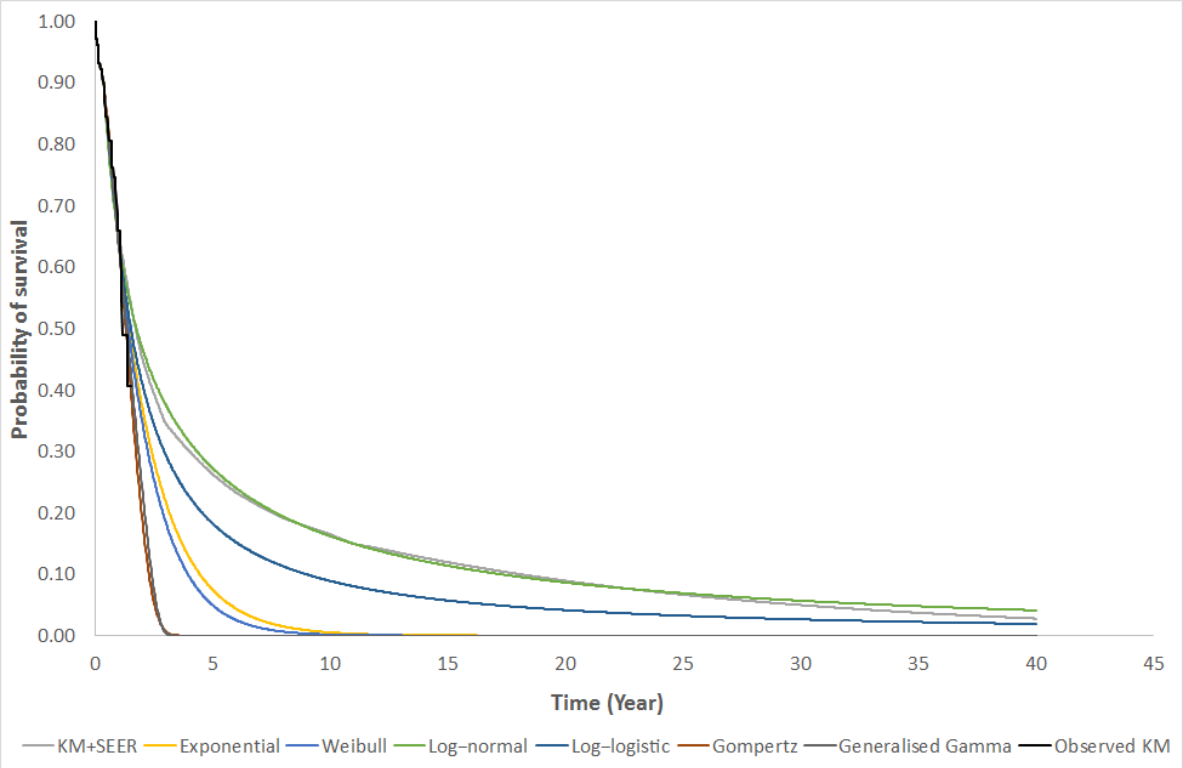


Figure 23: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, pembrolizumab combination therapy group in KEYNOTE-407,[7, 8] PD-L1 TPS <1%

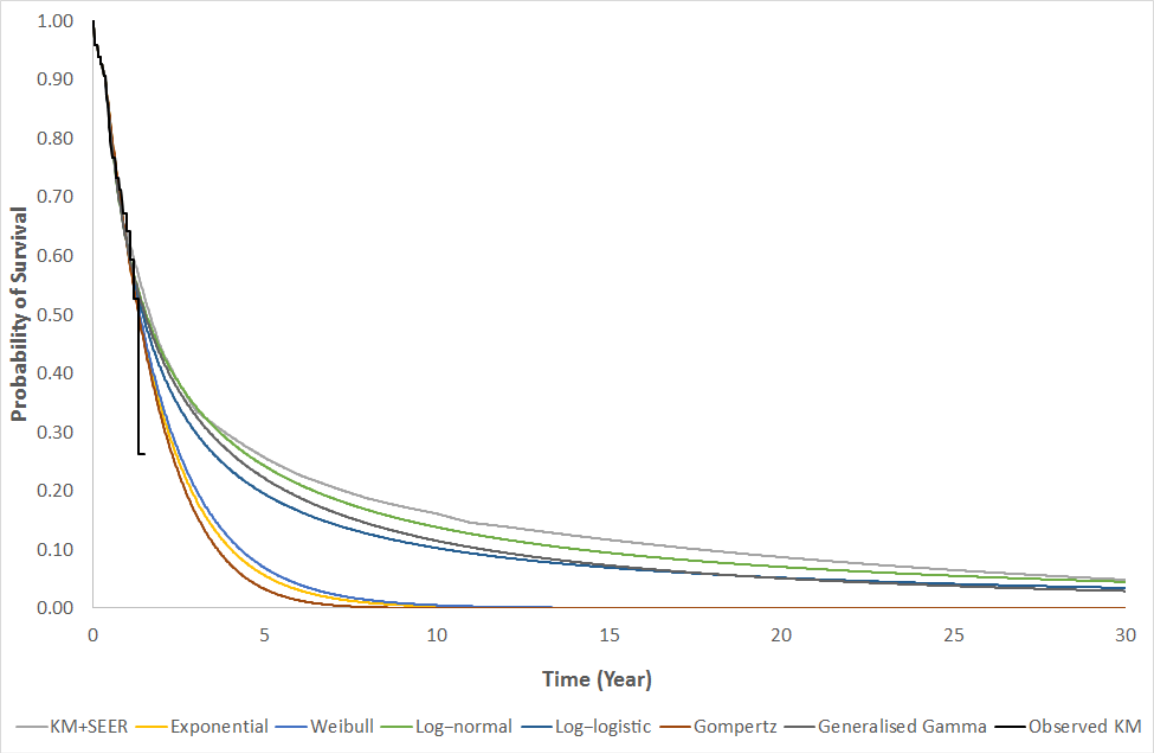


Figure 24: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, SC chemotherapy group in KEYNOTE-407, [7, 8] PD-L1 TPS≥50%

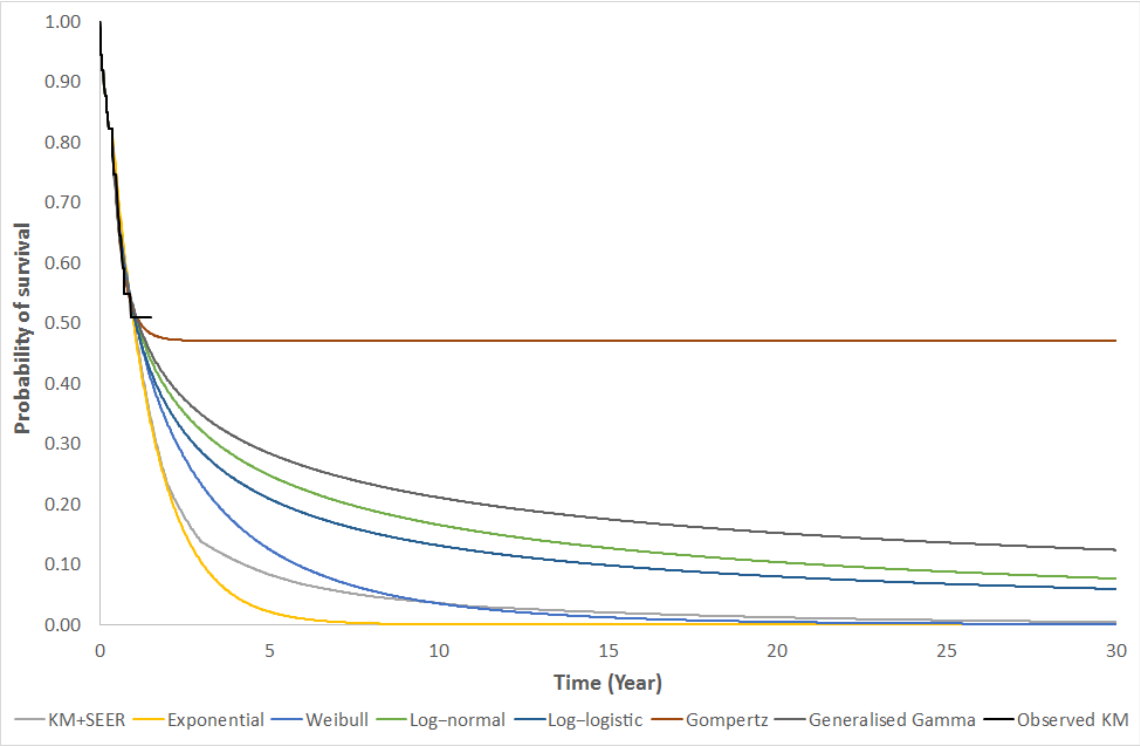


Figure 25: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, SC chemotherapy group in KEYNOTE-407,[7, 8] PD-L1 TPS 1-49%

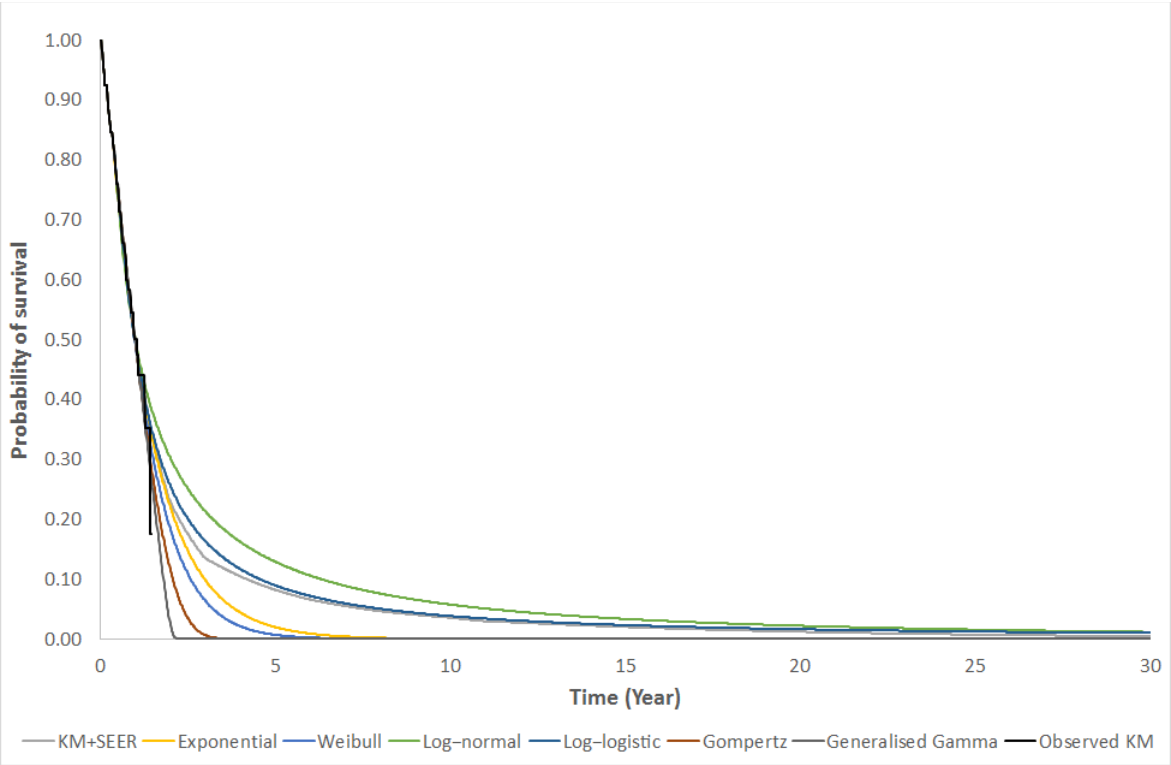


Figure 26: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, SC chemotherapy group in KEYNOTE-407, [7, 8] PD-L1 TPS<1%

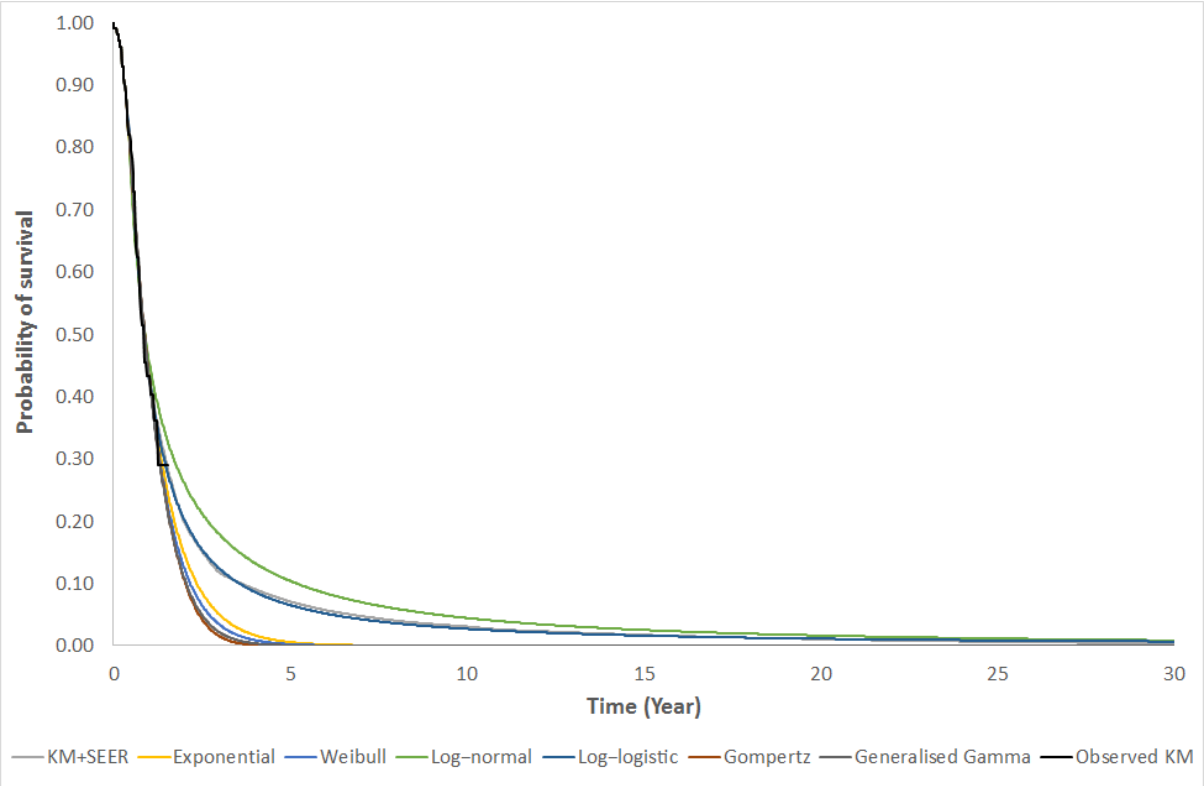


Table 48: AIC and BIC statistics for company's piecewise parametric curve-fitting for PFS, cutoff point 26 weeks (adapted from the company's model)

PD-L1<1%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 1-49%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1≥50%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; N/A – not available; PD-L1 - programmed death-ligand 1; SC - standard care

** Best fitting models (lowest AIC/BIC) presented in bold*

Figure 27: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, pembrolizumab combination therapy group, PD-L1 TPS≥50%

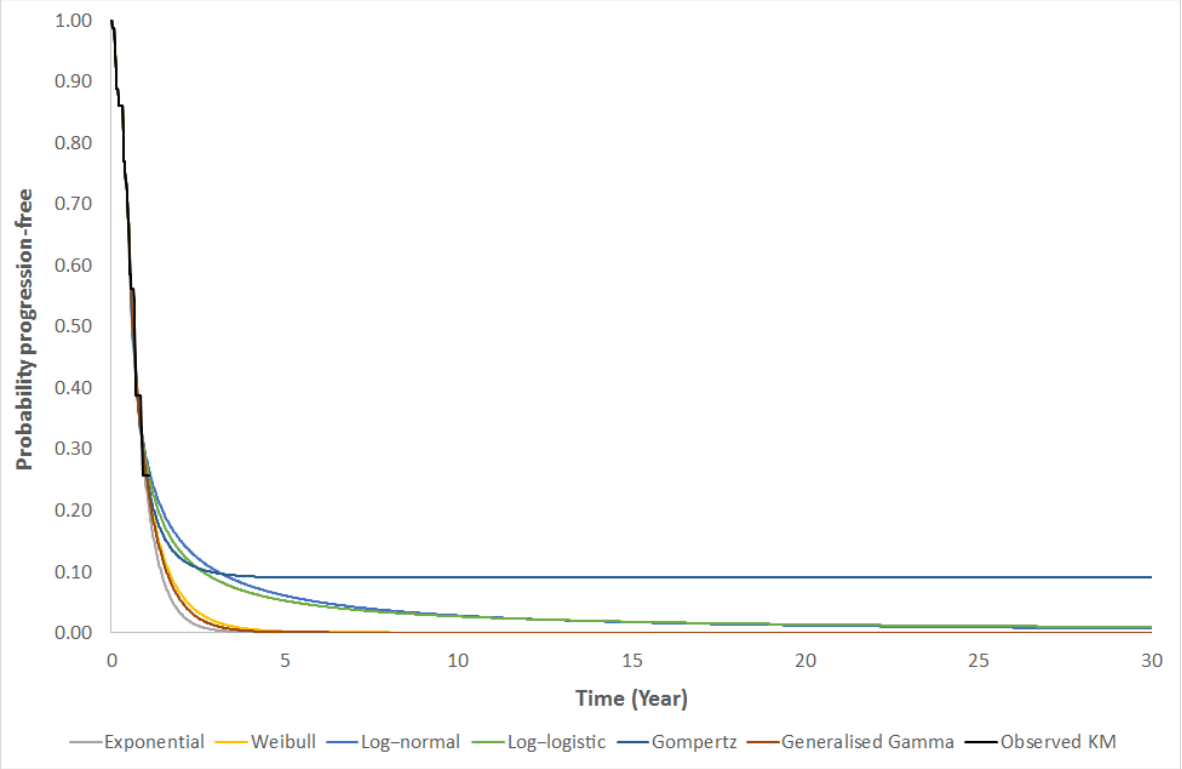


Figure 28: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, pembrolizumab combination therapy group, PD-L1 TPS 1-49%

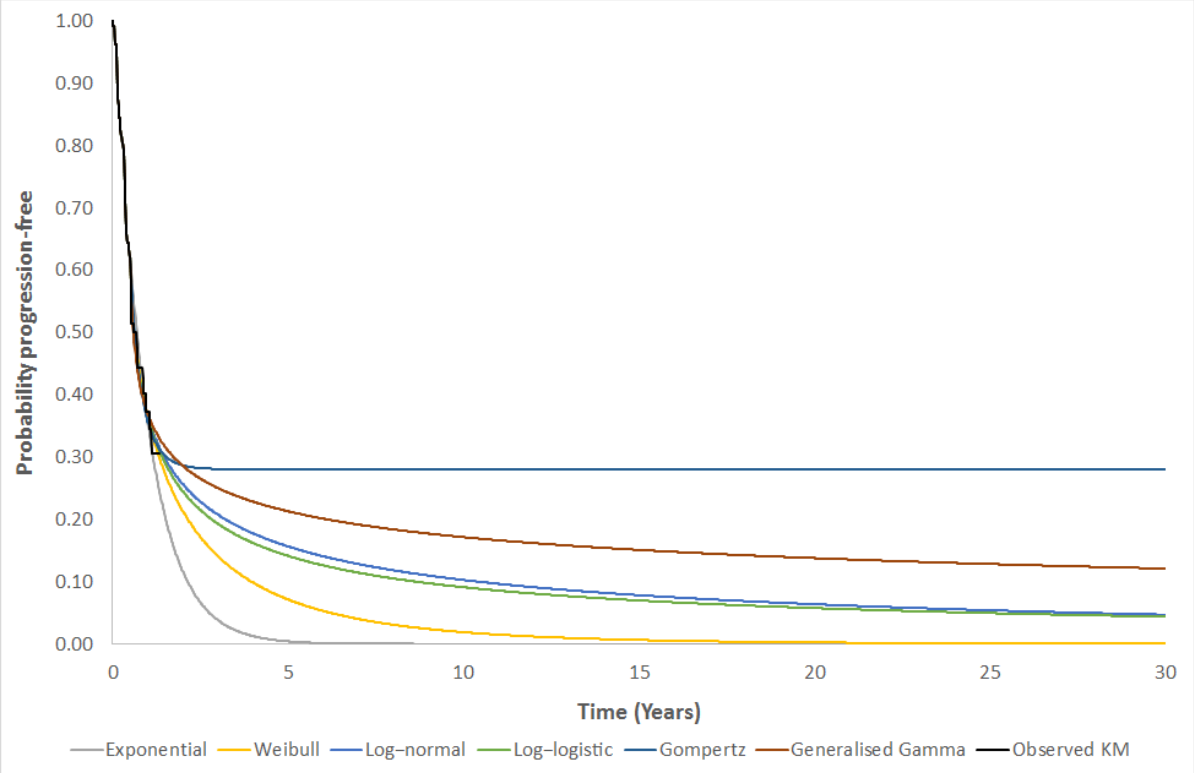


Figure 29: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, pembrolizumab combination therapy group, PD-L1 TPS<1%

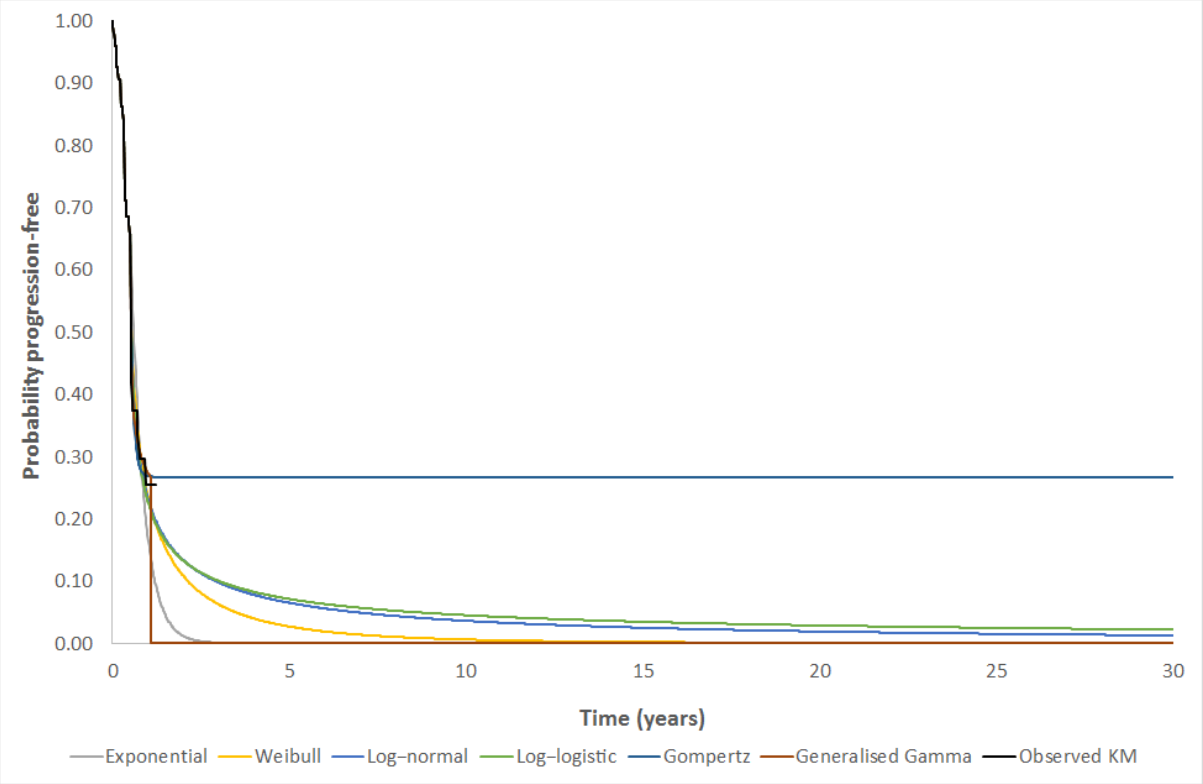


Figure 30: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, SC chemotherapy group, PD-L1 TPS≥50%

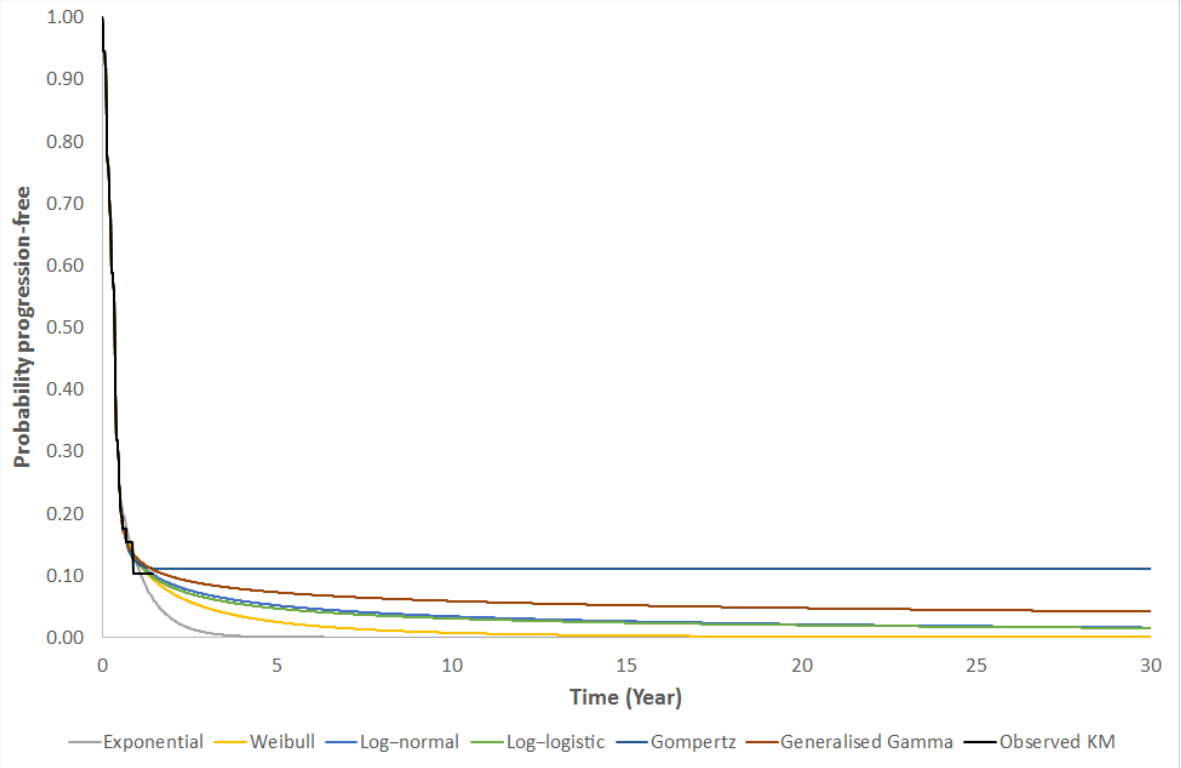


Figure 31: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, SC chemotherapy group, PD-L1 TPS 1-49%

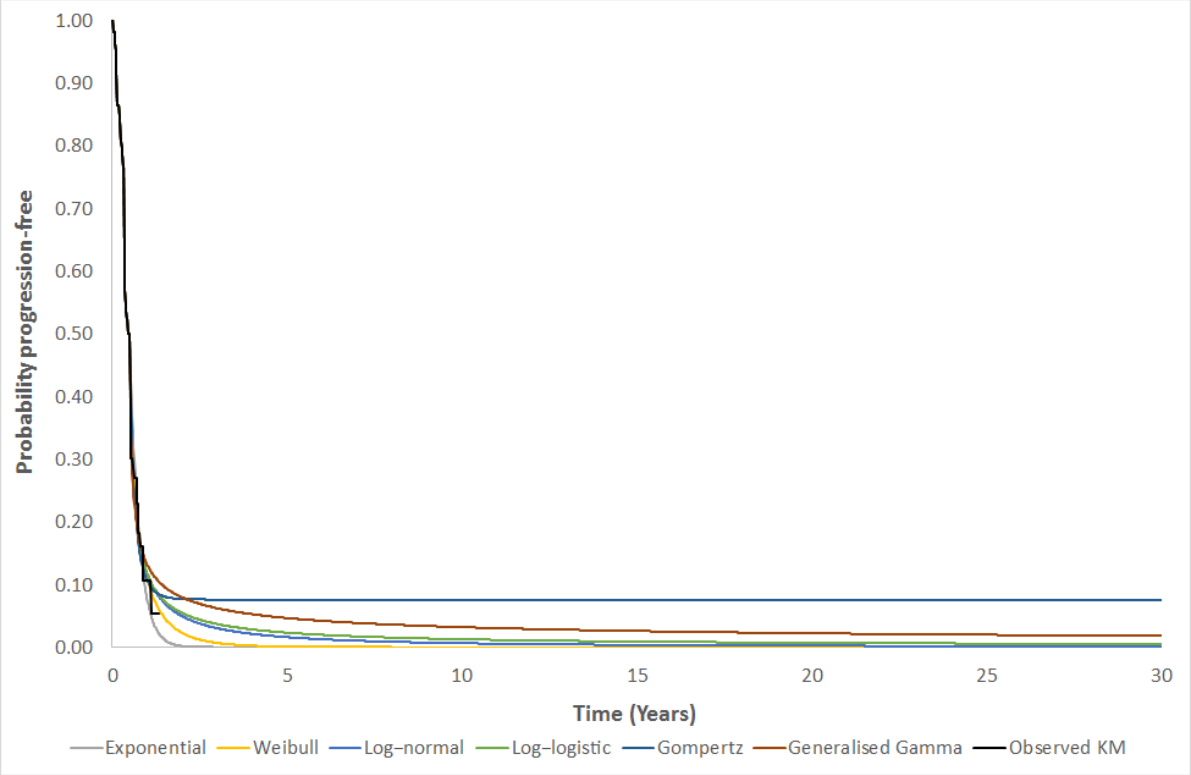


Figure 32: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, SC chemotherapy group, PD-L1 TPS<1%

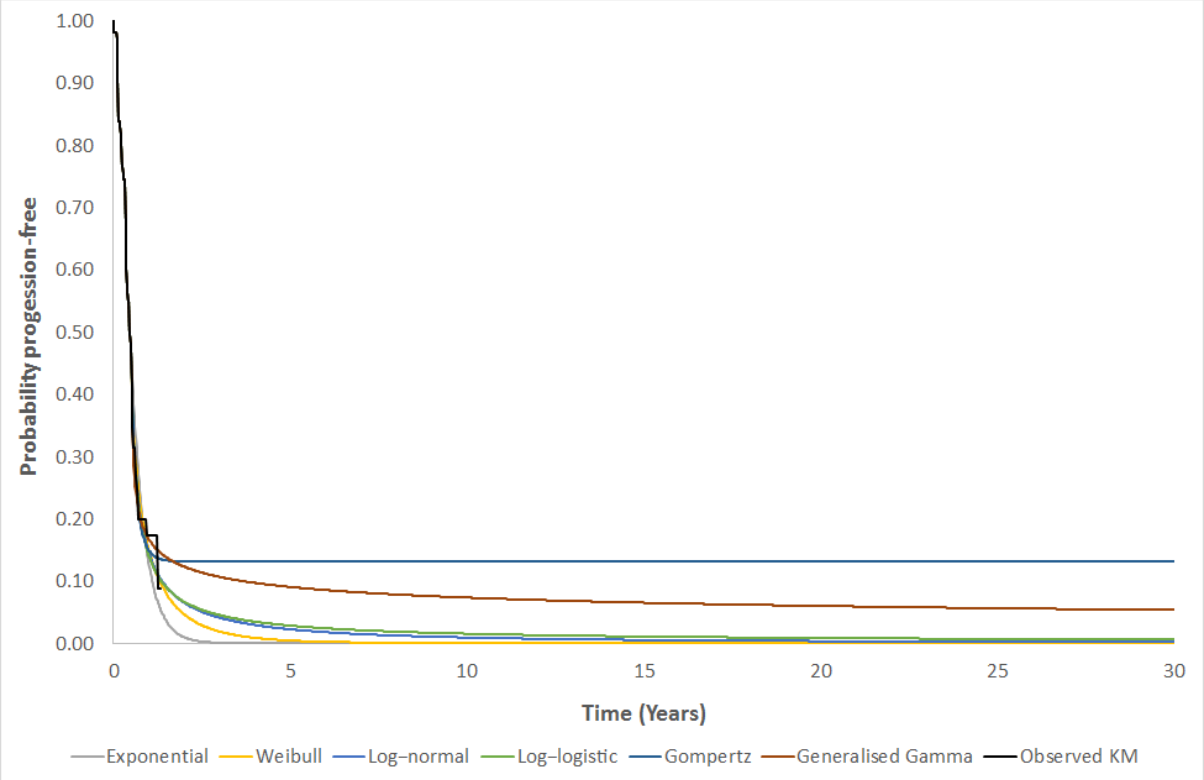


Table 49: AIC and BIC statistics for company's parametric curve-fitting for TTD within the PD-L1 subgroups (adapted from the company's model)

PD-L1 <1%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	N/A	N/A
Weibull	[redacted]	[redacted]	N/A	N/A
Log normal	[redacted]	[redacted]	N/A	N/A
Log logistic	[redacted]	[redacted]	N/A	N/A
Gompertz	[redacted]	[redacted]	N/A	N/A
Generalised gamma	[redacted]	[redacted]	N/A	N/A
PD-L1 1-49%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	N/A	N/A
Weibull	[redacted]	[redacted]	N/A	N/A
Log normal	[redacted]	[redacted]	N/A	N/A
Log logistic	[redacted]	[redacted]	N/A	N/A
Gompertz	[redacted]	[redacted]	N/A	N/A
Generalised gamma	[redacted]	[redacted]	N/A	N/A
PD-L1 ≥50%				
Model	**Pembrolizumab combination**		**Pembrolizumab monotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	N/A	N/A
Weibull	[redacted]	[redacted]	N/A	N/A
Log normal	[redacted]	[redacted]	N/A	N/A
Log logistic	[redacted]	[redacted]	N/A	N/A
Gompertz	[redacted]	[redacted]	N/A	N/A
Generalised gamma	[redacted]	[redacted]	N/A	N/A

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; N/A - not available; PD-L1 - programmed death-ligand 1; SC - standard care

** Best fitting models (lowest AIC/BIC) presented in bold*

Figure 33: TTD modelled curves from company's parametric curve-fitting, pembrolizumab combination therapy, PD-L1 TPS<1% subgroup

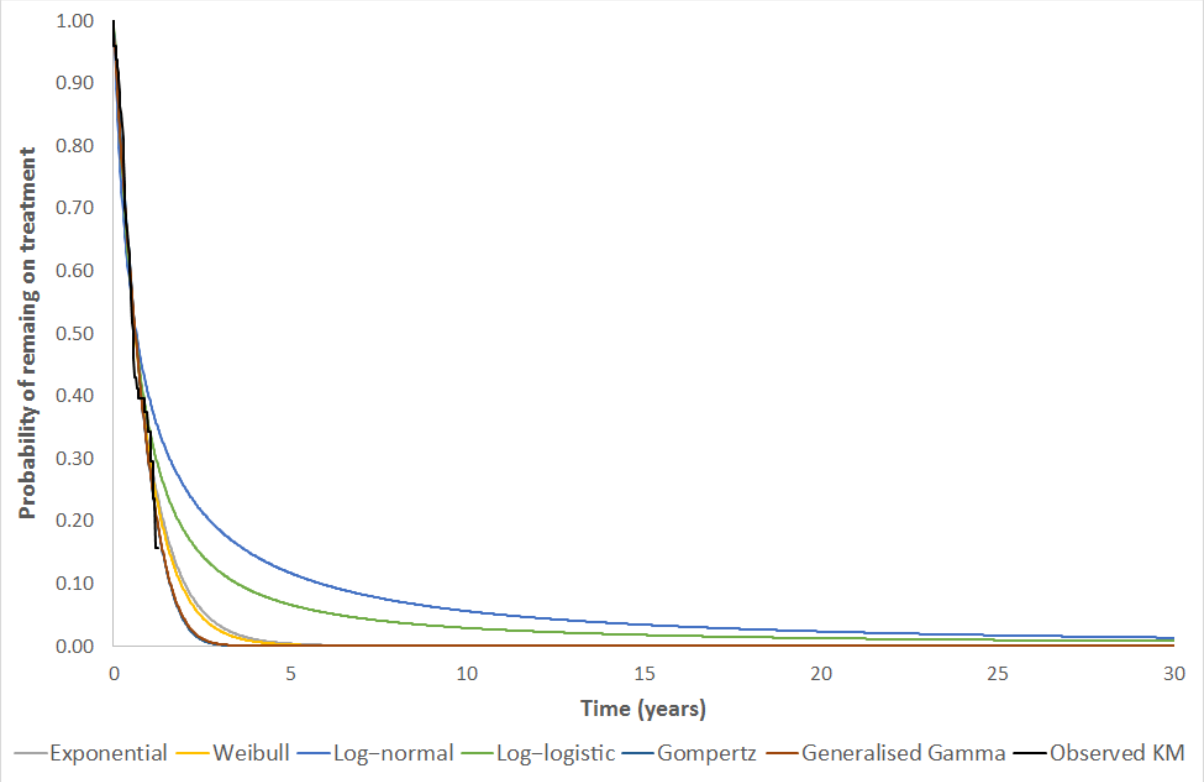


Figure 34: TTD modelled curves from company's parametric curve-fitting, pembrolizumab combination therapy, PD-L1 TPS 1-49% subgroup

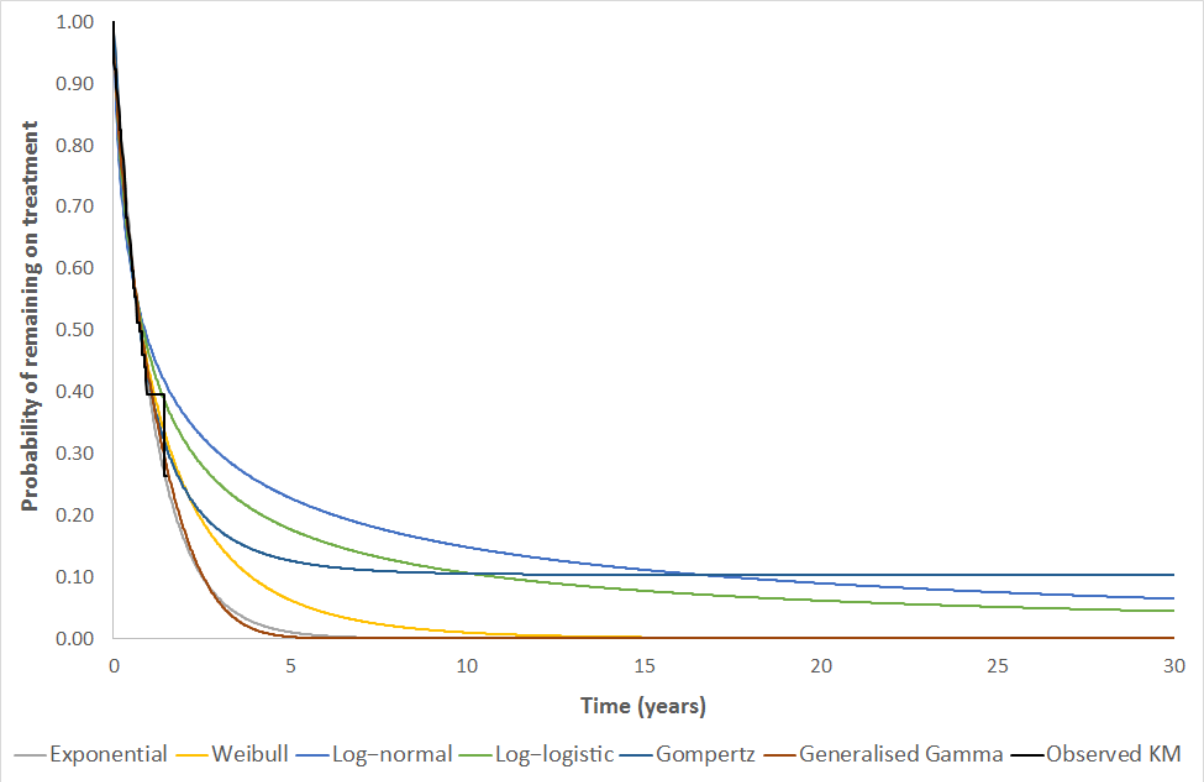


Figure 35: TTD modelled curves from company's parametric curve-fitting, pembrolizumab combination therapy, PD-L1 TPS ≥50% subgroup

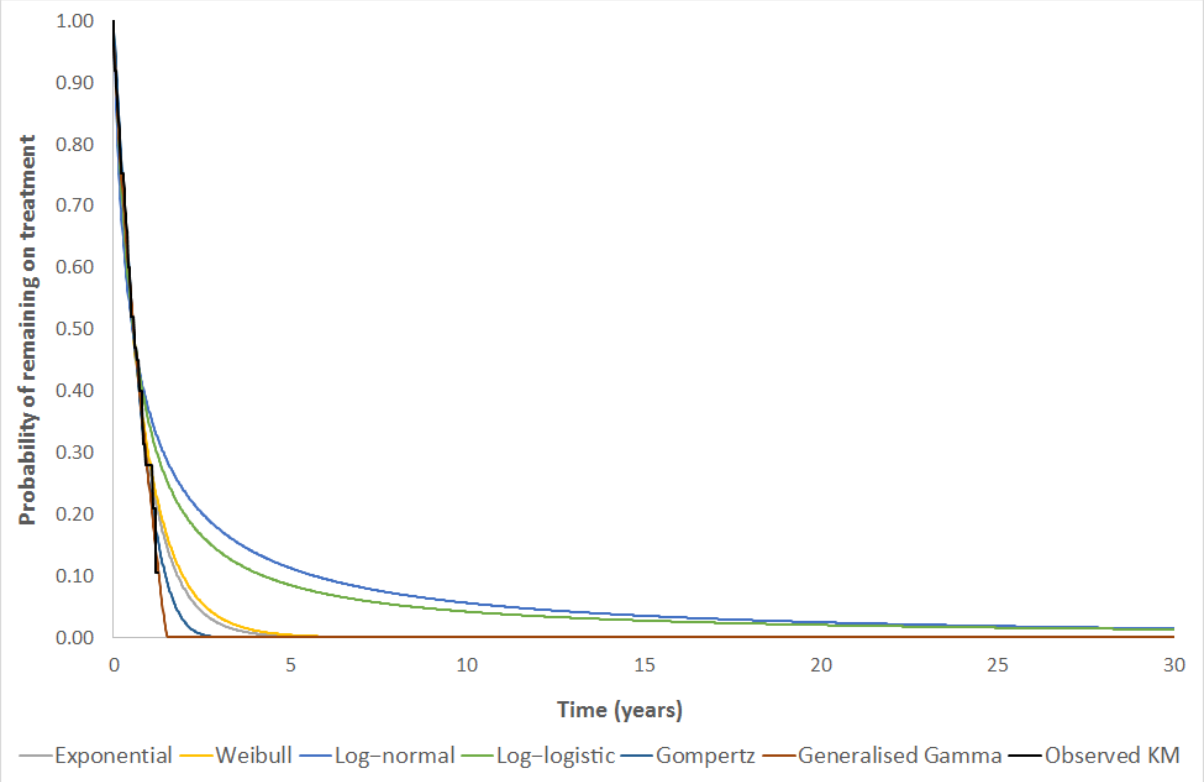


Figure 36: TTD functions for pembrolizumab combination therapy, SC chemotherapy and pembrolizumab monotherapy, PD-L1 TPS ≥50% subgroup

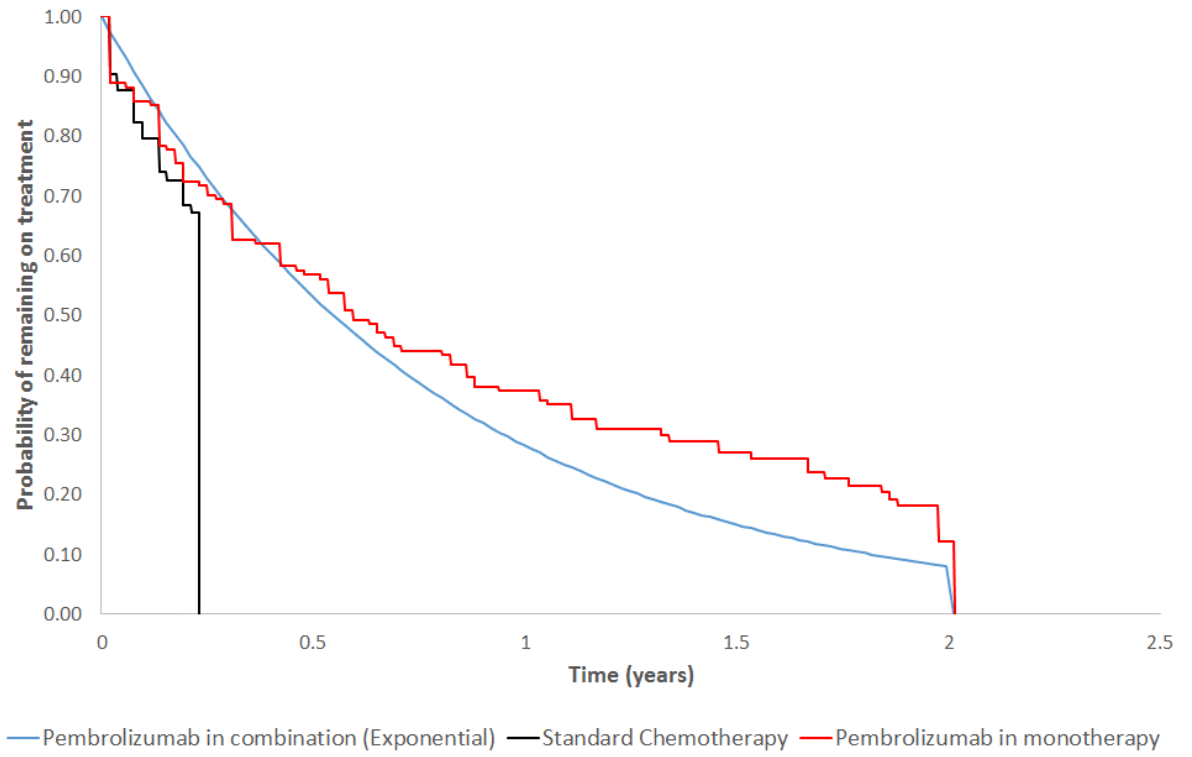


Figure 37: TTD functions for pembrolizumab combination therapy and SC chemotherapy, PD-L1 TPS 1-49% subgroup

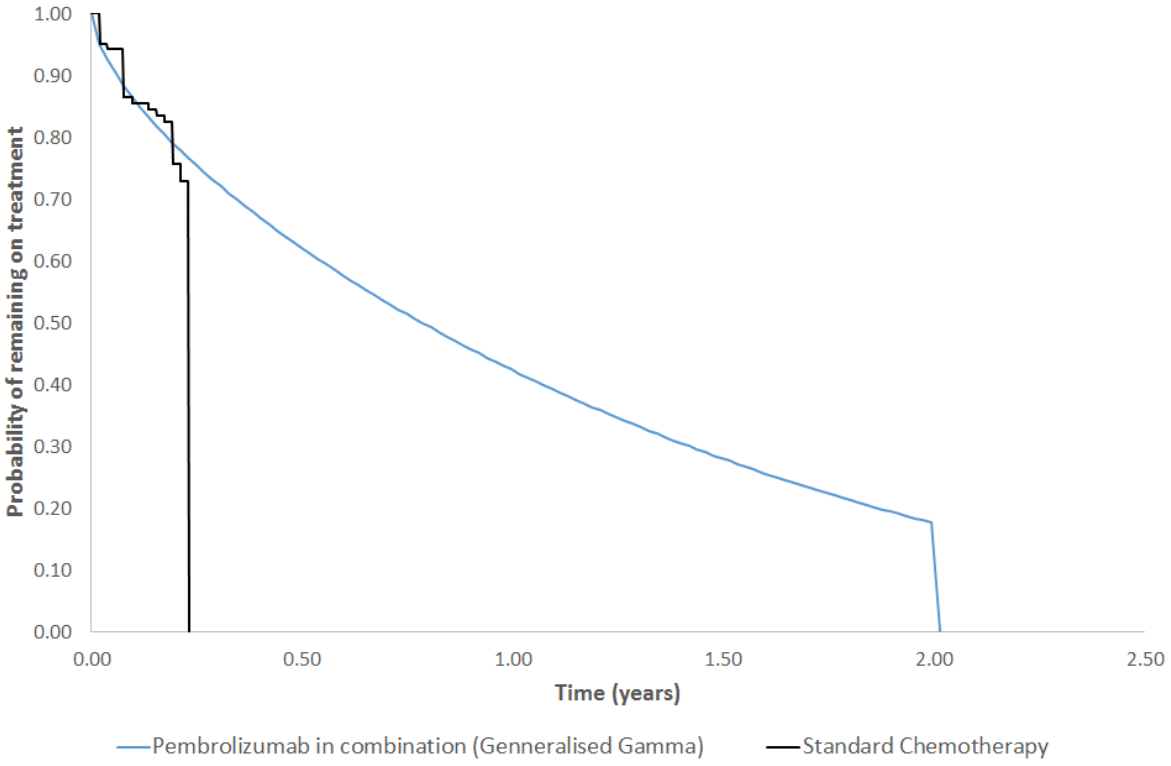


Figure 38: TTD functions for pembrolizumab combination therapy and SC chemotherapy, PD-L1 TPS <1% subgroup

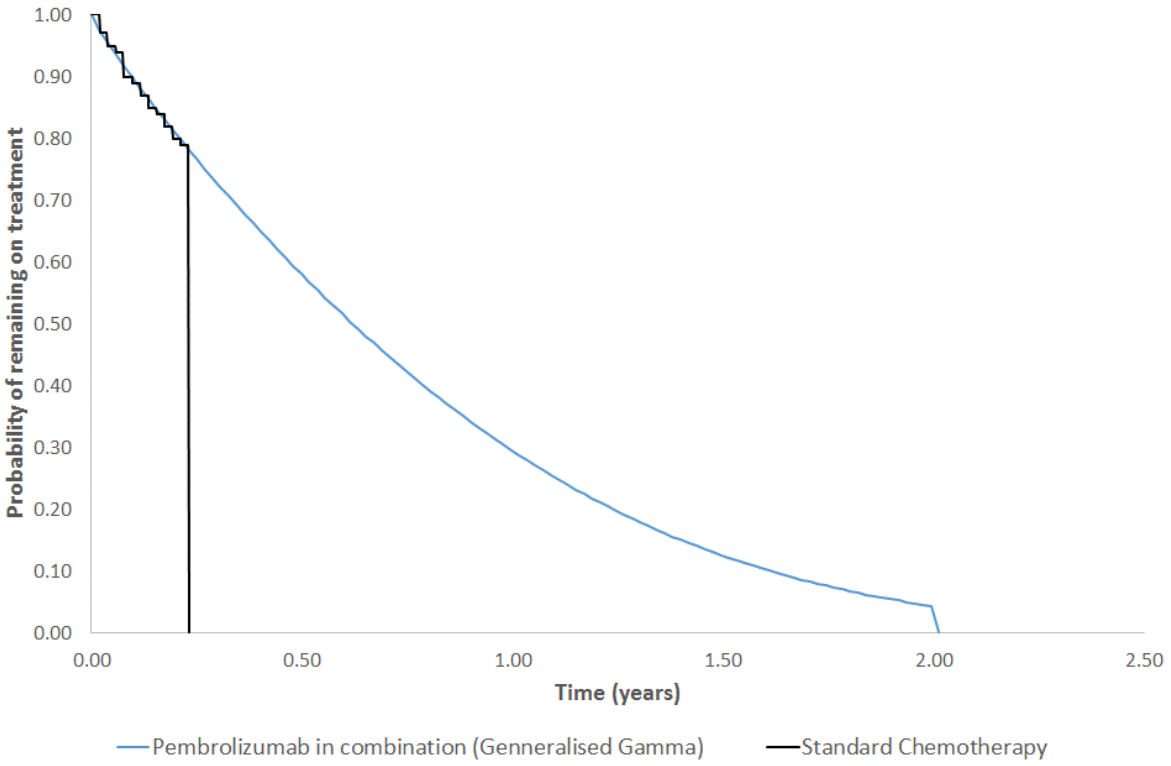


Table 50: Incidence rates and unit costs for Grade 3-5 AEs used in the model for subgroup analyses

Adverse Event	Pembrolizumab combination (all subgroups)	Chemotherapy (all subgroups)	Pembrolizumab monotherapy (PD-L1≥50%)	Unit costs	Source
Nausea	[redacted]	[redacted]	[redacted]	£998.38	Brown *et al*[88]
Anaemia	[redacted]	[redacted]	[redacted]	£2,692.61	TA428[89]
Fatigue	[redacted]	[redacted]	[redacted]	£2,855.25	Brown *et al*[88]
Decreased appetite	[redacted]	[redacted]	[redacted]	£0.00	TA428[89]
Constipation	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Diarrhoea (grade 2)	[redacted]	[redacted]	[redacted]	£456.66	TA428[89]
Diarrhoea (grade 3-4)	[redacted]	[redacted]	[redacted]	£998.38	Brown *et al*[88]
Dyspnoea	[redacted]	[redacted]	[redacted]	£588.98	TA403[90]
Vomiting	[redacted]	[redacted]	[redacted]	£813.47	TA192[91]
Back pain	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Arthralgia	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Neutropenia	[redacted]	[redacted]	[redacted]	£120.99	Brown *et al*[88]
Oedema peripheral	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Blood creatinine increased	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	£637.03	TA347[92]
Dizziness	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Rash	[redacted]	[redacted]	[redacted]	£127.21	Brown *et al*[88]
Asthenia	[redacted]	[redacted]	[redacted]	£2,855.25	Brown *et al*[88]
Chest pain	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Stomatitis	[redacted]	[redacted]	[redacted]	£0.00	TA428[89]
Hyponatraemia	[redacted]	[redacted]	[redacted]	£0.00	TA357[93]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	£782.31	TA406[94]
Neuropathy Peripheral	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Abdominal pain	[redacted]	[redacted]	[redacted]	£0.00	TA395[95]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	£364.64	TA347[92]
Peripheral Sensory Neuropathy	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Pyrexia	[redacted]	[redacted]	[redacted]	£261.00	NHS Reference Costs 16/17[87§]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Pneumonia	[redacted]	[redacted]	[redacted]	£3,102.84	TA411[74]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	£577.66	TA428[89]
Haemoptysis	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Pain in extremity	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Cough	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Myalgia	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Pruritis	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	£171.14	Assume the same as lower respiratory tract infection¤
Leukopenia	[redacted]	[redacted]	[redacted]	£0.00	TA406[94]
Epistaxis	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Neutrophil Count Decreased	[redacted]	[redacted]	[redacted]	£577.66	TA428[89]
Pneumonitis	[redacted]	[redacted]	[redacted]	£3,102.84	Assumed to be same as pneumonia (TA395)[95]

Febrile neutropenia	[redacted]	[redacted]	[redacted]	£7,045.41	Brown *et al*[88]
Bronchitis	[redacted]	[redacted]	[redacted]	£171.14	Assume the same as lower respiratory tract infection¤
Platelet Count Decreased	[redacted]	[redacted]	[redacted]	£577.66	TA428[89]
Weight decreased	[redacted]	[redacted]	[redacted]	£0.00	Assume same as decreased appetite (TA428)[89]
Hypothyroidism	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Hypokalaemia	[redacted]	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	£0.00	Assumed to be zero
Headache	[redacted]	[redacted]	[redacted]	£0.00	Assumed to be zero
Paraesthesia	[redacted]	[redacted]	[redacted]	£0.00	Assumed to be zero
Hypotension	[redacted]	[redacted]	[redacted]	£0.00	Assumed to be zero
Hypocalcemia	[redacted]	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]

Source: CS[1] and company's model

Note: Some of the items have been inflated to 2016/17 using PSSRU inflation indices[103], § - WJ07B Fever of Unknown Origin with Interventions, with CC Score 0-3;[*] - KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, ¤ - Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs (TA492)[96]

Appendix 3: Goodness-of-fit statistics and survivor functions for standard parametric models and spline models fitted to time-to-event data from KEYNOTE-407 by the ERG

Table 51: AIC and BIC statistics, ERG-fitted OS models

Goodness-of-fit, OS, KEYNOTE-407 ITT population				
Model (OS)	**Pembrolizumab combination therapy**		**Carboplatin plus paclitaxel/nab-paclitaxel**	
	AIC	**BIC**	**AIC**	**BIC**
Generalised gamma	983.75	994.63	1274.87	1285.79
Gamma	983.79	991.04	1273.71	1280.98
Log normal	990.24	997.50	1287.57	1294.85
Log logistic	985.64	992.90	1276.06	1283.33
Weibull	983.29	990.55	**1273.15**	**1280.43**
Gompertz	**981.94**	**989.20**	1273.96	1281.24
Exponential	986.17	989.80	1277.21	1280.85
Spline k=1,scale=hazard	984.81	995.69	1274.42	1285.34
Spline k=2,scale=hazard	986.30	1000.81	1276.09	1290.64
Spline k=3,scale=hazard	987.44	1005.58	1274.78	1292.97
Spline k=1,scale=normal	986.12	997.00	1274.43	1285.35
Spline k=2,scale=normal	986.32	1000.83	1275.98	1290.53
Spline k=3,scale=normal	986.79	1004.93	1274.62	1292.81
Spline k=1,scale=odds	986.06	996.94	1273.85	1284.76
Spline k=2,scale=odds	986.96	1001.47	1275.78	1290.33
Spline k=3,scale=odds	987.87	1006.01	1274.87	1293.06
Goodness-of-fit, PFS, KEYNOTE-407 ITT population				
Model (PFS)	**Pembrolizumab combination therapy**		**Carboplatin plus paclitaxel/nab-paclitaxel**	
	AIC	**BIC**	**AIC**	**BIC**
Generalised gamma	1470.34	1481.22	1716.72	1727.64
Gamma	1468.72	1475.98	1714.89	1722.16
Log normal	1477.35	1484.61	1734.34	1741.61
Log logistic	1465.77	**1473.03**	1712.43	1719.71
Weibull	1470.29	1477.55	1717.59	1724.87
Gompertz	1479.95	1487.21	1734.95	1742.23
Exponential	1483.17	1486.80	1741.29	1744.93
Spline k=1,scale=hazard	1471.63	1482.52	1718.47	1729.39
Spline k=2,scale=hazard	1463.31	1477.82	1709.91	1724.46
Spline k=3,scale=hazard	1458.25	1476.39	1697.38	1715.57
Spline k=1,scale=normal	N/a	N/a	1710.45	1721.37
Spline k=2,scale=normal	1466.71	1481.22	1712.01	1726.56
Spline k=3,scale=normal	**1457.91**	1476.05	1697.41	1715.60
Spline k=1,scale=odds	1465.72	1476.61	1706.61	1717.52
Spline k=2,scale=odds	1464.95	1479.46	1708.75	1723.30
Spline k=3,scale=odds	1457.99	1476.13	**1696.94**	**1715.13**

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

** Best fitting models (lowest AIC/BIC) presented in bold*

Figure 39: ERG-fitted standard parametric models, OS, pembrolizumab combination therapy

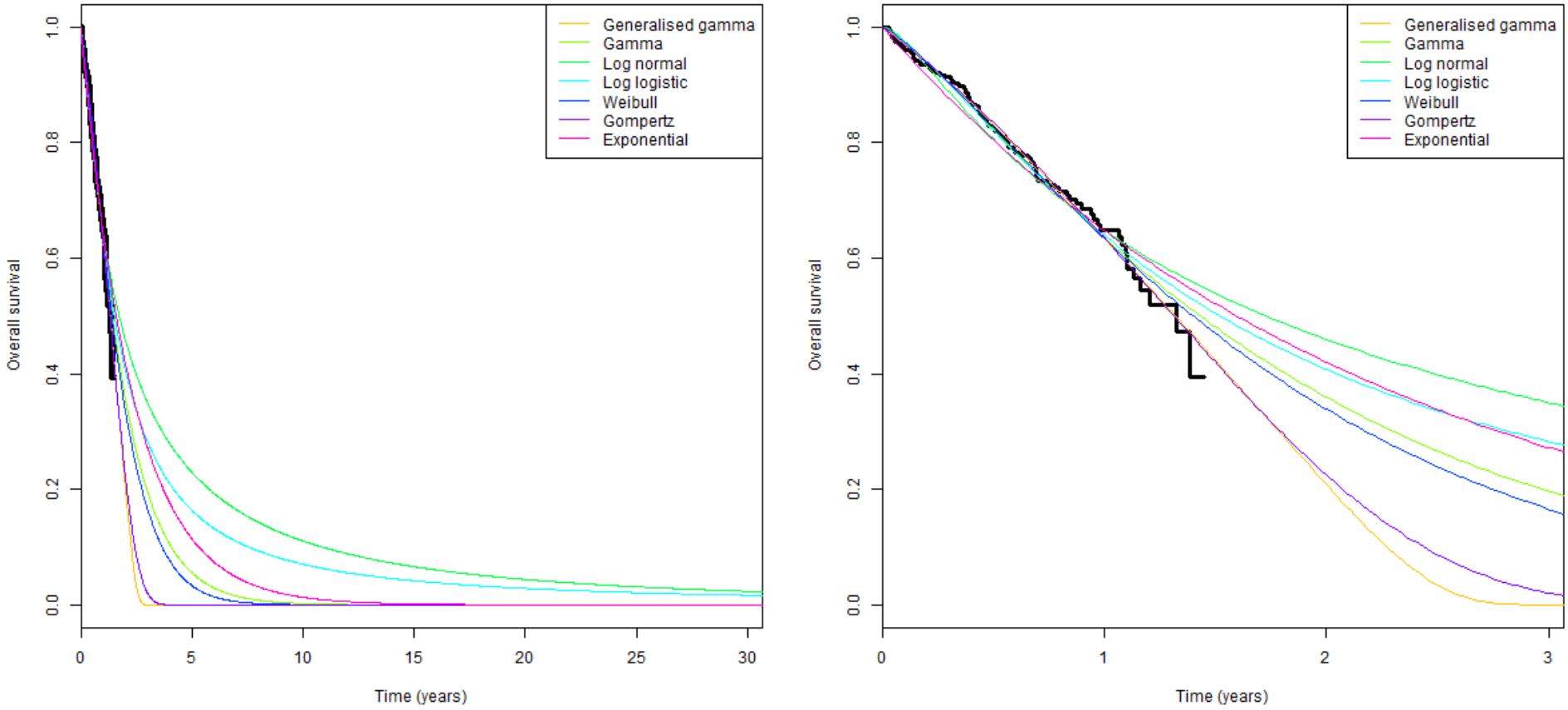


Figure 40: ERG-fitted spline models, OS, pembrolizumab combination therapy

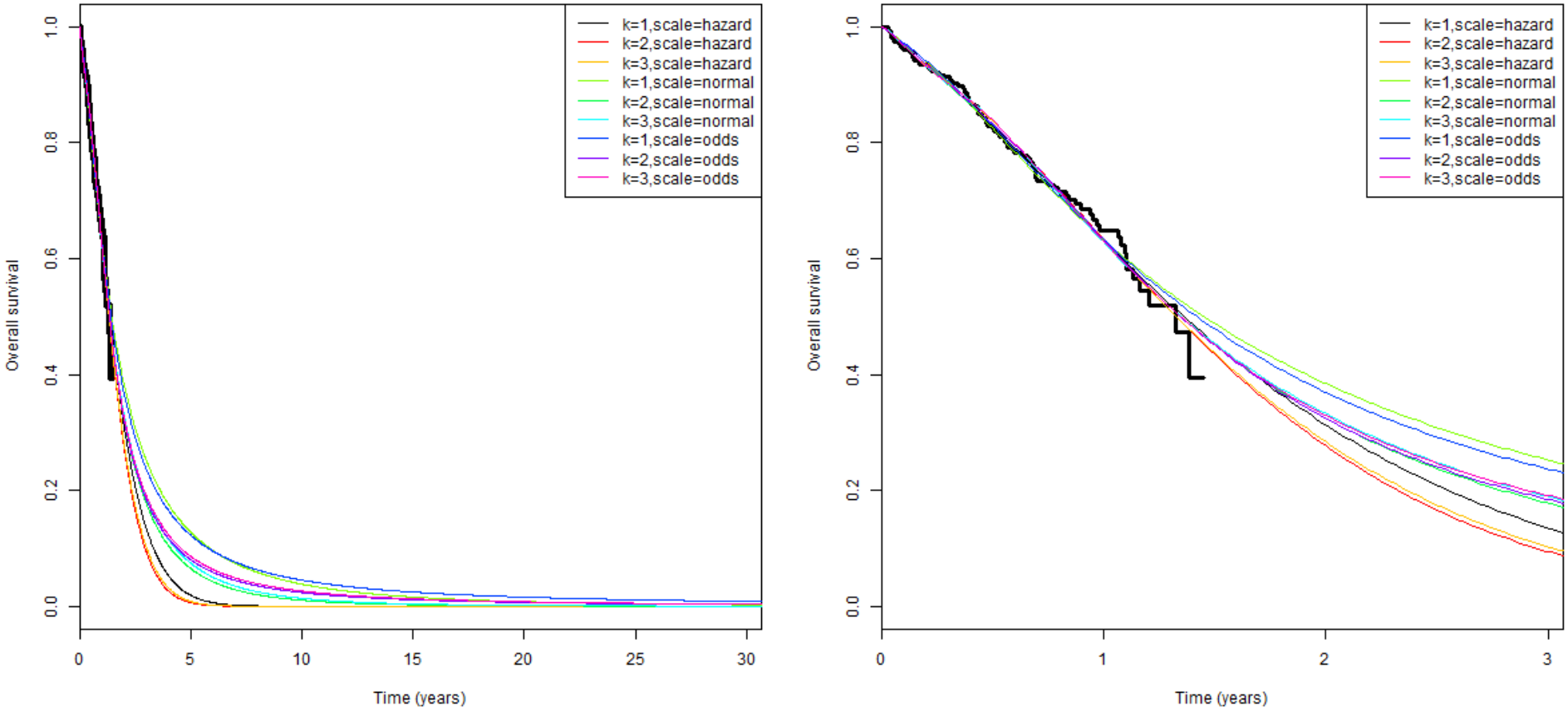


Figure 41: ERG-fitted standard parametric models, OS, carboplatin plus paclitaxel/nab-paclitaxel

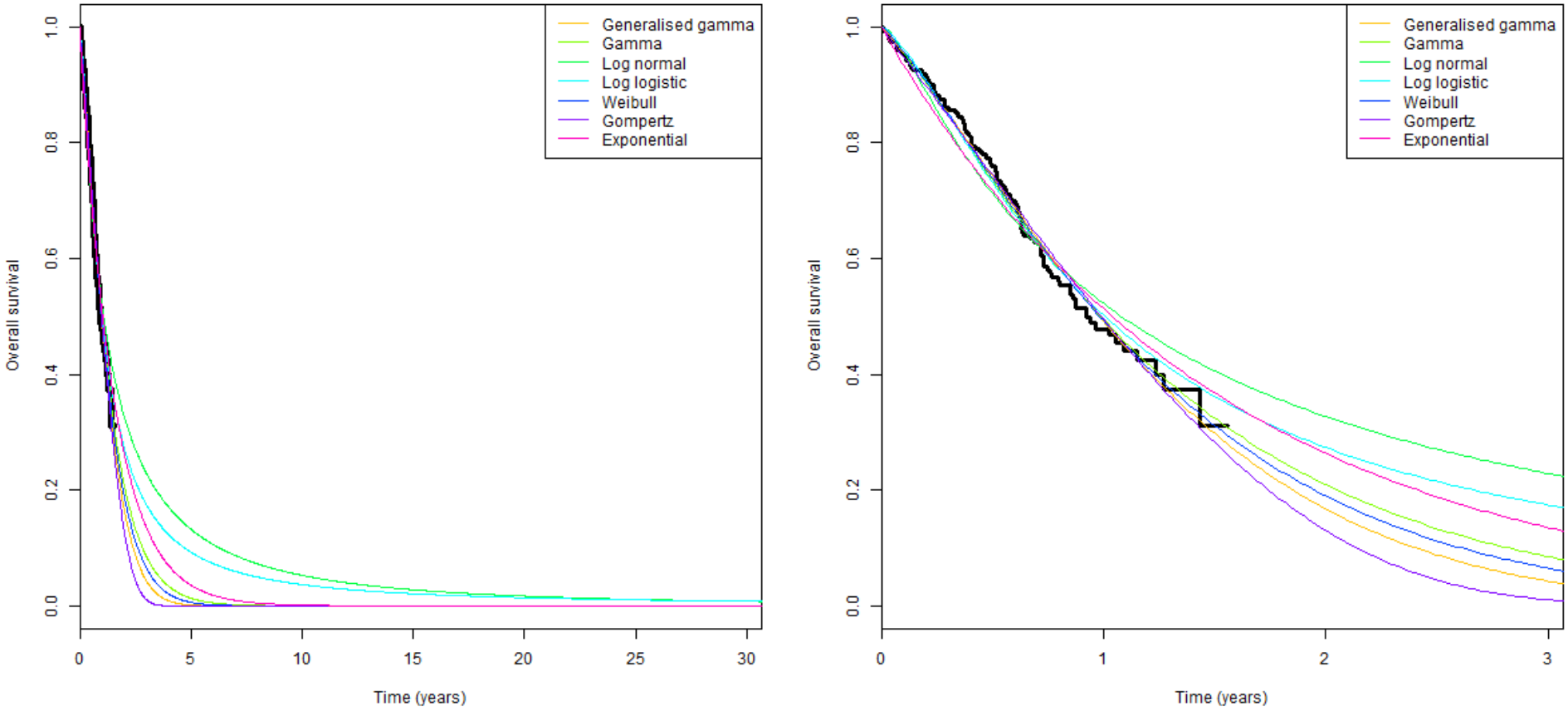


Figure 42: ERG-fitted spline models, OS, carboplatin plus paclitaxel/nab-paclitaxel

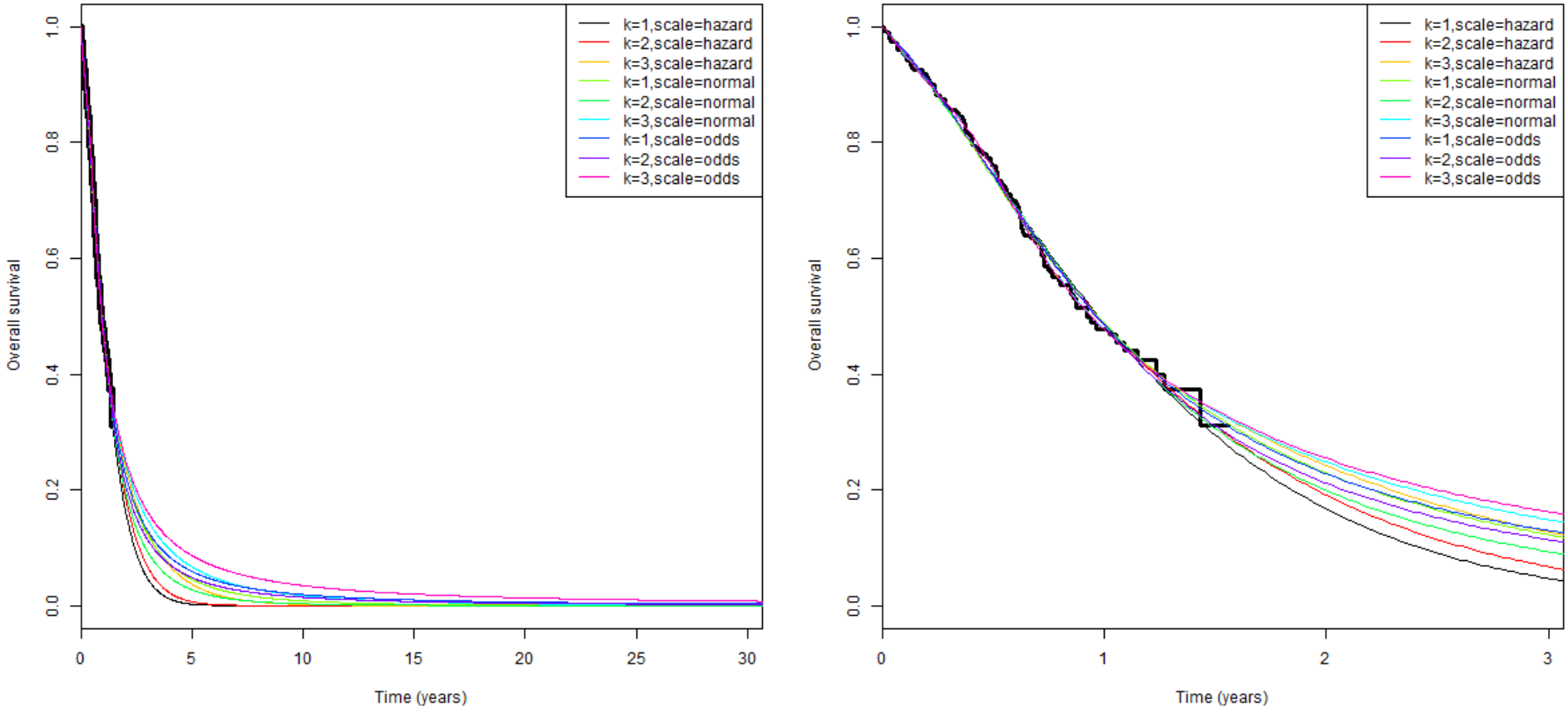


Figure 43: ERG-fitted standard parametric models, PFS, pembrolizumab combination therapy

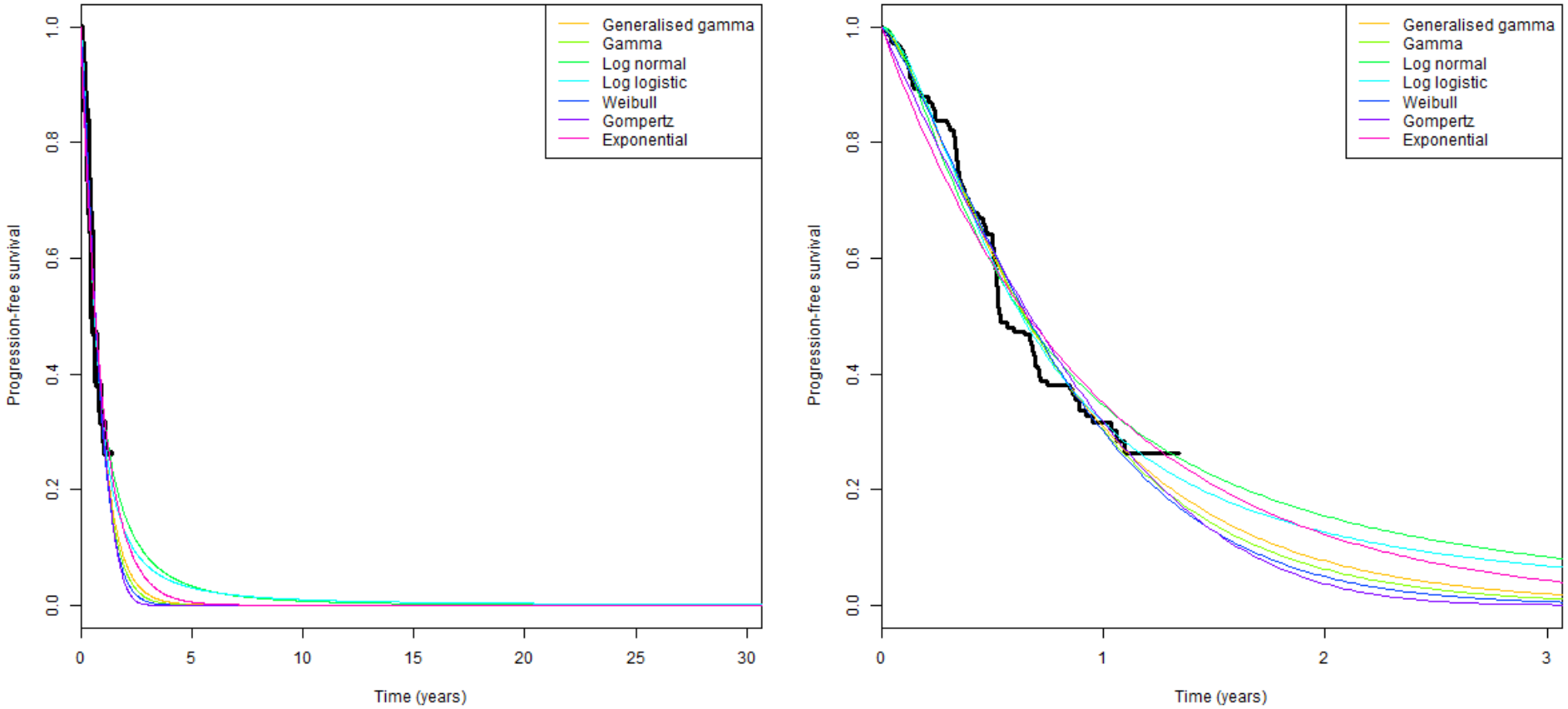


Figure 44: ERG-fitted spline models, PFS, pembrolizumab combination therapy

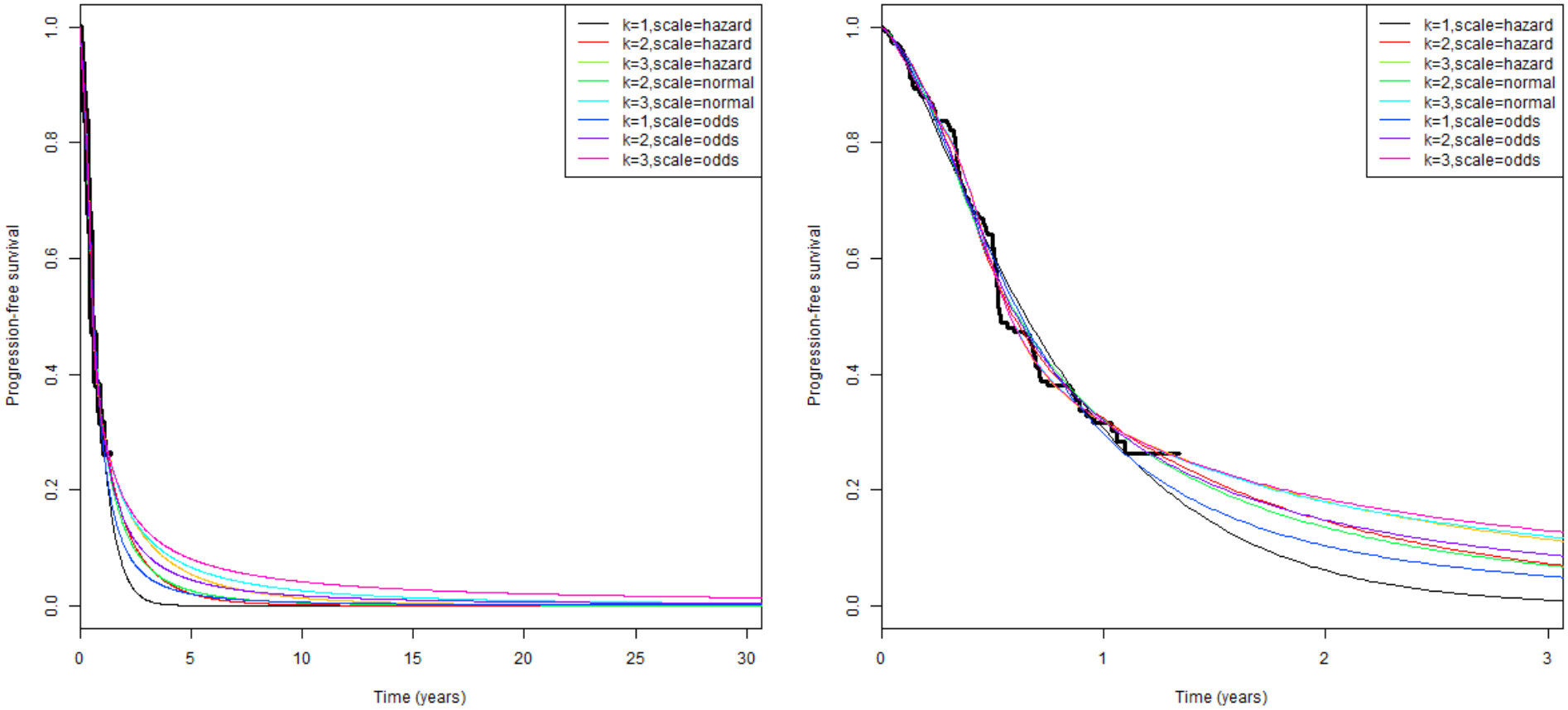


Figure 45: ERG-fitted standard parametric models, PFS, carboplatin plus paclitaxel/nab-paclitaxel

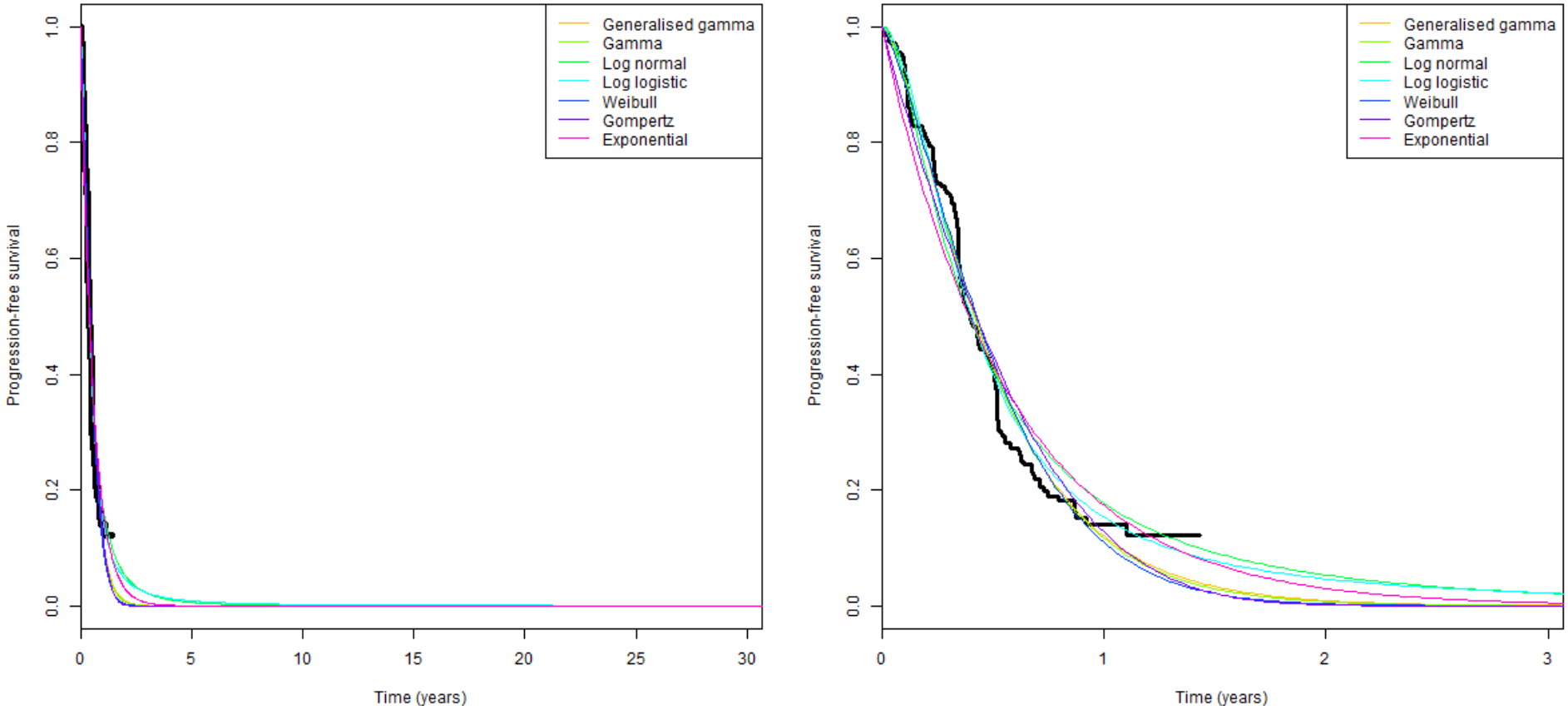
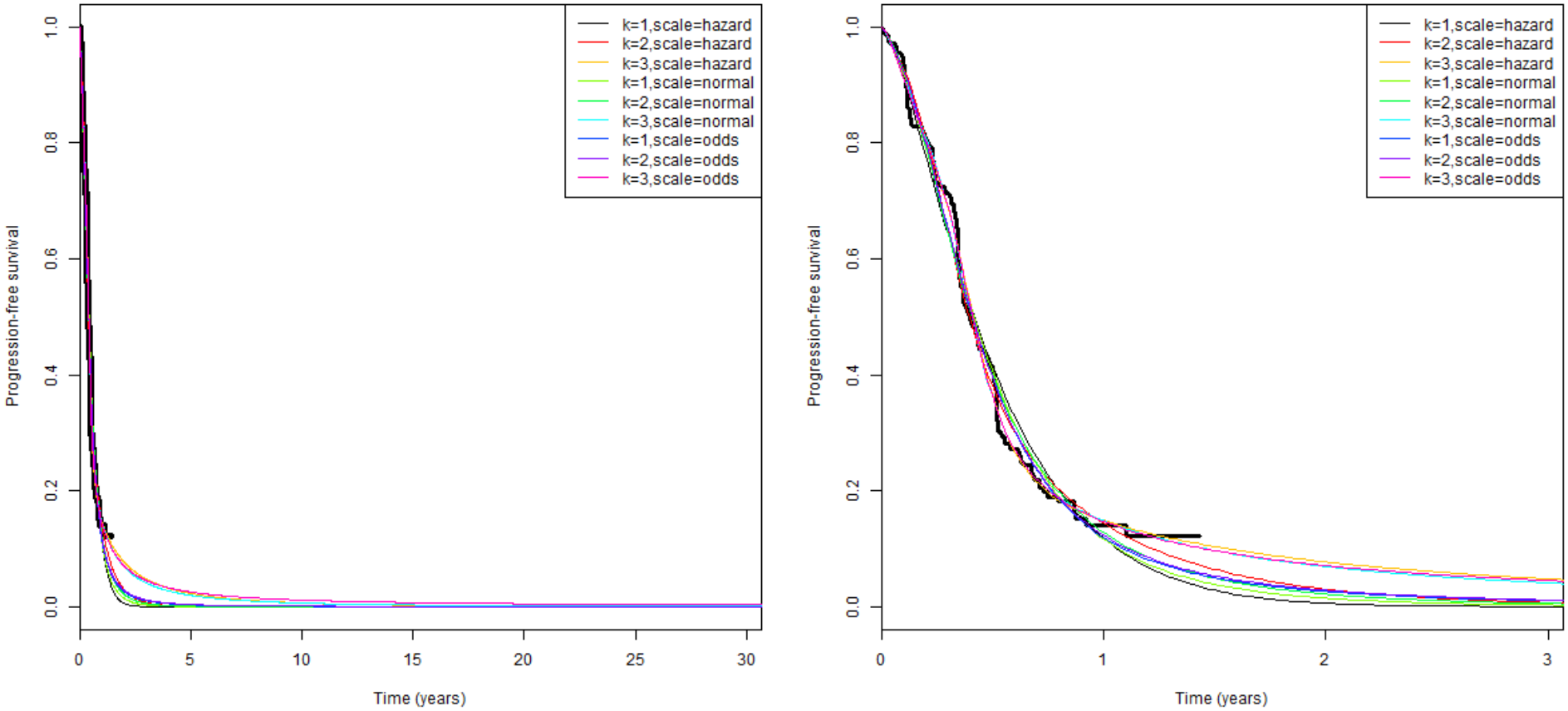


Figure 46: ERG-fitted spline models, PFS, carboplatin plus paclitaxel/nab-paclitaxel



Appendix 4: **Technical appendix detailing methods for implementing the ERG's exploratory analyses**

Exploratory analysis 1- Correction of errors

(a) Correction of OS functions for NMA comparators.

Replace the value in worksheet "Modeled OS" cell Y9 with formula "=V9^'NMA-ITC OS (conHR)'!$O$19". Drag the formula down to the bottom of the array.

Replace the value in worksheet "Modeled OS" cell Z9 with formula "=V9^'NMA-ITC OS (conHR)'!$O$20". Drag the formula down to the bottom of the array.

Replace the value in worksheet "Modeled OS" cell AA9 with formula "=V9^'NMA-ITC OS (conHR)'!$O$21". Drag the formula down to the bottom of the array.

(b) Correction of HR for pembrolizumab monotherapy comparison

Replace the value in worksheet "NMA-ITC OS (conHR)" cell O50 with value "=1/0.97".

(c) Amendment of AE calculations

Replace the formula in worksheet "AE Costs UK" cell C58 with formula "=SUMPRODUCT(Parameters!Q89:Q140,Parameters!Q251:Q302)".

Replace the formula in worksheet "AE Costs UK" cells D58 with formula "=SUMPRODUCT(Parameters!Q143:Q194,Parameters!Q251:Q302)".

Replace the formula in worksheet "AE Costs UK" cells E58 with formula "=SUMPRODUCT(Parameters!Q197:Q248,Parameters!Q251:Q302)".

(d) Consistent application of a half-cycle correction

Replace the formula in worksheet "Cohort simulation" cell AX11 with formula *"=(L11+Pembro_Chemo_2L_Use*(1-L11-Q11))*cost_PFstatePembro+(1-Pembro_Chemo_2L_Use)*(1-L11-Q11)*cost_PDstate"*. Drag the formula down to the bottom of the array.

Exploratory analysis 2 - Use of HRQoL based on progression status

Apply all changes from ERG exploratory analysis 1.

Go to worksheet "Utility Inputs", click on dropdown menu on cell E5:F5, choose the option "Utility by progression status".

Replace the value in worksheet "Parameters" cell C33 with a value of 0.605121898.

Replace the value in worksheet "Parameters" cell C36 with a value of 0.615365882.

These values are based on the information provided in the table and the equations below.

Parameter name	Value
p_1stIO2ndchemo	0.27
p_1stIO2ndIO	0.00
p_1stchemo2ndIO	0.40
p_1stchemo2ndchemo	0.12
d_2ndLPFtimepembro	0.32
d_2ndLPFtimechemo	0.48
PFSutility_alltreat	[redacted]
PDutility_alltreat	0.58

Equation for post-progression utility for pembrolizumab group
'=((p_1stIO2ndIO*d_2ndLPFtimepembro*PFSutility_alltreat)+(p_1stIO2ndchemo*d_2ndLPFtimechemo*PFSutility_alltreat)+(p_1stIO2ndIO*(1-d_2ndLPFtimepembro)*PDutility_alltreat)+(p_1stIO2ndchemo*(1-d_2ndLPFtimechemo)*PDutility_alltreat)+((1-p_1stIO2ndIO-p_1stIO2ndchemo)*PDutility_alltreat))'

Equation for post-progression utility for SC chemotherapy group
'=((p_1stchemo2ndIO*d_2ndLPFtimepembro*PFSutility_alltreat)+(p_1stchemo2ndchemo*d_2ndLPFtimechemo*PFSutility_alltreat)+(p_1stchemo2ndIO*(1-d_2ndLPFtimepembro)*PDutility_alltreat)+(p_1stchemo2ndchemo*(1-d_2ndLPFtimechemo)*PDutility_alltreat)+((1-p_1stchemo2ndIO-p_1stchemo2ndchemo)*PDutility_alltreat))'

Exploratory analysis 3 - Disease management costs based on PFS/PPS
Apply all changes from ERG exploratory analysis 1.
Replace the formula in worksheet "Cohort simulation" cell AX11 with
*'=(M11*PFScost_mgt)+(O11*((p_1stIO2ndIO*d_2ndLPFtimepembro*PFScost_mgt)+(p_1stIO2ndchemo*d_2ndLPFtimechemo*PFScost_mgt)+(p_1stIO2ndIO*(1- d_2ndLPFtimepembro) * PDcost_mgt) + (p_1stIO2ndchemo * (1 - d_2ndLPFtimechemo) * PDcost_mgt) + ((1 - p_1stIO2ndIO - p_1stIO2ndchemo) * PDcost_mgt)))',*

where
PFScost_mgt = 89.5343317
PDcost_mgt = 144.3253151
p_1stIO2ndIO = 0
p_1stIO2ndchemo = 0.27388535
d_2ndLPFtimepembro = 0.321052632
d_2ndLPFtimechemo= 0.482758621
Drag the formula down to row 2,098.

Replace the formula in worksheet “Cohort simulation” cell DD11

with

*‘=(BS11*PFScost_mgt)+(BU11*((p_1stchemo2ndIO*d_2ndLPFtimepembro*PFScost_mgt)+(p_1stchemo2ndchemo*d_2ndLPFtimechemo*PFScost_mgt)+(p_1stchemo2ndIO*(1-d_2ndLPFtimepembro)*PDcost_mgt)+(p_1stchemo2ndchemo*(1-d_2ndLPFtimechemo)*PDcost_mgt)+((1-p_1stchemo2ndIO-p_1stchemo2ndchemo)*PDcost_mgt)))’,*

where

PFScost_mgt = 89.5343317
PDcost_mgt = 144.3253151
p_1stchemo2ndIO= 0.399038462
p_1stchemo2ndchemo= 0.120192308
d_2ndLPFtimepembro= 0.321052632
d_2ndLPFtimechemo= 0.482758621

Drag the formula down to row 2,098.

Exploratory analyses 4 - Second-line immunotherapy treatment costs doubled

Apply all changes from ERG exploratory analysis 1.

Go to worksheet “Regimen Costs UK”.

Replace the value in cell D147 with the formula “=(75/2)*2”.

Replace the value in D150 with the formula “=(102/2)*2”.

Exploratory analyses 5a - Alternative PFS and OS models - Optimistic scenario

Apply all changes from ERG exploratory analysis 1.

Go to worksheet “Pembro Chemo OS”. Copy the values in worksheet cells M9:M2096.

Go to worksheet “Modeled OS”. Paste those values to cells V9:V2096. *Exploratory analyses 5b - Alternative PFS and OS models - Pessimistic scenario*

Apply all changes from ERG exploratory analysis 1.

Go to the file ‘ERG curve fitting – KEYNOTE-407’ provided.

Copy the cumulative survival probabilities of the ERG’s log logistic model for pembrolizumab in combination. Go to worksheet “Modeled OS” in the model and paste these values to cells V9:V2096.

Go to the file ‘ERG curve fitting – KEYNOTE-407’ provided.

Copy the cumulative survival probabilities for the ERG’s log logistic model for SC chemotherapy. Go to worksheet “Modeled OS” in the model and paste these values to cells W9:W2096.

Exploratory analyses 6 - Optimistic and pessimistic scenarios ERG-preferred analysis (deterministic)
For optimistic scenario 6a, apply all changes from ERG exploratory analyses 1-5a, as described above. For pessimistic scenario 6b, apply all changes from ERG exploratory analyses 1-5b, as described above.
Additional sensitivity analysis and subgroup analysis should start from these versions of the model (optimistic and pessimistic).

Additional sensitivity analysis 1: Increased proportion costs of second-line immunotherapy
Replace the values in worksheet "Regimen Costs UK" cells C117:D117 with the value "0.75". Note – these proportions need to be applied to the progression-based utility equations as well.

Additional sensitivity analysis 2: Impacts of AEs on HRQoL and costs doubled for pembrolizumab combination therapy group
Replace the formula in worksheet "Cohort simulation" cell AO11 with formula "=-IF(C11=0,'Utility Inputs'!$D$36,0)*2".
Replace the formula in worksheet "Cohort simulation" cell BD11 with formula "*=p.AEcost.PembroChemo*2".

Additional sensitivity analysis 3: Fully incremental analysis including NMA comparators
Perform a fully incremental analysis from the results in 'Results' worksheet using ERG exploratory analyses 6a and 6b.

Additional sensitivity analysis 4: Exploration of all parametric models fitted by the ERG
Go to the file 'ERG curve fitting – KEYNOTE-407' provided.
Copy the values of each of the ERG's OS models for pembrolizumab in combination. Copy the values for the same model type for SC. Go to worksheet "Modeled OS" in the model and paste the values to cells V9:V2096 and W9:W2096, respectively.

Additional sensitivity analysis 5: Subgroup analyses by PD-L1 subgroup
For each subgroup:
Go to worksheet "Model Settings", click on dropdown menu on cell I21, choose the relevant PD-L1 TPS subgroup.
Select the appropriate optimistic and pessimistic curves for the selected subgroup (optimistic – from company's model; pessimistic from file 'ERG curve fitting – KEYNOTE-407').
For the PD-L1 TPS ≥50% subgroup, change the TTD function to the exponential.