Pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable: A Systematic Review

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Contributions of authors

Shijie Ren led the project. She also summarised and critiqued the company's indirect treatment comparison and extrapolation approach. Eva Kaltenthaler and Emma Hock summarised and critiqued the clinical effectiveness data reported within the company's submission. Hazel Squires and Andrew Rawdin summarised and critiqued the health economic analysis submitted by the company, and performed the ERG exploratory analyses. Mark Clowes critiqued the company's search strategy. Dr Jonathan Shamash and Dr Constantine Alifrangis provided clinical advice to the ERG. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
APaT	All patients as treated
AUC	Area under the curve
BIC	Bayesian Information Criterion
BICR	Blinded independent central radiologists
BOR	Best overall response
BSC	Best supportive care
CDF	Cancer Drugs Fund
CI	Confidence interval
CPS	Combined positive score
CR	Complete response
CrCl	Creatinine clearance
CrI	Credible interval
CRUK	Cancer Research UK
CS	Company's submission
CSR	Clinical Study Report
DIC	Deviance Information Criterion
DSU	Decision Support Unit
eMIT	Electronic Market Information Tool
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQC30	European Organisation for Research and Treatment Cancer Quality of Life Questionnaire Core 30 items
EQ-5D	European Quality of Life Scale-5 Dimensions
ERG	Evidence Review Group
EPAR	European public assessment report
FP	Fractional polynomial
GFR	Glomerular filtration rate
HCHS	Hospital and Community Health Services
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

IPD	Individual patient-level data
ITC	Indirect treatment comparison
IV	Intravenous
KM	Kaplan-Meier
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MBC	Advanced/metastatic bladder cancer
MIBC	Muscle-invasive bladder cancer
NA	Not applicable
NE	Non-evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net Monetary Benefit
NMIBC	Non-muscle-invasive bladder cancer
NOS	Newcastle Ottawa Scale
NSCLC	Non-small-cell lung cancer
OOB	Out-of-bag
ORR	Objective response rate
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressive disease
PD-1	Programmed death 1 protein
PD-L1	Programmed cell death 1 ligand 1
PD-L2	Programmed cell death 1 ligand 2
PFS	Progression-free survival
PH	Proportional hazards
PRO	Patient Reported Outcomes
PPS	Post-progression state
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours

RR	Response rate
SA	Sensitivity analysis
SAE	Serious adverse event
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
STC	Simulated treated comparison
TA	Technology Appraisal
TNM	Tumour, Node, Metastases
ToT	Time on treatment
TSD	Technical Support Document
VAS	Visual Analogue Scale
WHO	World Health Organisation

1 SUMMARY

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

The company's submission (CS) adequately describes the decision problem. The CS assesses the clinical and cost-effectiveness of pembrolizumab (Keytruda®), within its licensed indication for the treatment of adults patients with locally advanced or metastatic urothelial carcinoma who have not received prior systematic chemotherapy and who are not eligible to receive cisplatin.

The comparators considered in the CS differ from the National Institute for Health and Care Excellence (NICE) final scope: only carboplatin plus gemcitabine was included as a comparator but atezolizumab and best supportive care (BSC) were excluded. The Evidence Review Group (ERG) agrees that the evidence for atezolizumab was too uncertain to enable a useful comparison. The ERG also agrees that BSC should be excluded due to a paucity of evidence. The ERG's clinical advisors suggest that gemcitabine plus carboplatin has been used for many years in this population, despite being unlicensed for this indication, hence no trials have been undertaken to compare the combination with BSC.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included a systematic review of the clinical effectiveness evidence. The KEYNOTE-052 study provides the main supporting clinical effectiveness evidence for this submission and is a Phase II, single-arm, open-label, non-randomised study. KEYNOTE-052 was designed to test the efficacy and safety of pembrolizumab in patients with advanced/unresectable or metastatic urothelial cancer where cisplatin is unsuitable. It is important to note that the KEYNOTE-052 study is ongoing. Different data cut-off points are used in the CS and clinical study report (CSR) (both 9th March 2017), and Balar *et al*. (2017) and the European Public Assessment Report (EPAR) (both 1st Sept 2016).

The CS states that KEYNOTE-052 was conducted in 16 countries although different figures are reported in the published paper Balar *et al*. (2017) (20 countries) and the EPAR (17 countries). In KEYNOTE-052, 370 patients received at least one dose of pembrolizumab. The study population was predominantly male (77.3%) and white (88.6%) with 78.1% of the patients having an ECOG status of 1 (36.2%) or 2 (41.9%). The median age of study participants was 74 years (range 34-94 years). With regard to metastases location, 51 patients (13.8%) had lymph node only, while 315 patients (85.1%) had visceral disease and four patients (1.1%) had metastases location not reported. Pembrolizumab was administered in an un-blinded manner at a dosage of 200mg via intravenous (IV) infusion over 30 minutes every 3 weeks. Pembrolizumab treatment could continue for 24 months.

The primary outcome of the KEYNOTE-052 study was objective response rate (ORR) with overall survival (OS) and progression-free survival (PFS) being secondary endpoints. Median OS was 11.0

months (95% confidence interval (CI): 10.0-13.6 months) and there were 188 deaths at the data cut-off point. Median PFS was 2.3 months (95% CI: 2.1-3.4 months) and ORR was 29.2% (95% CI: 24.6%-34.1%) at the data cut-off point of 9th March 2017.

In the NICE final scope, subgroups based on cancer histology and biological markers (PD-L1) were to be considered if the evidence allowed. Two subgroups were considered in the CS: PD-L1 combined positive score (CPS) ≥ 1% and PD-L1 CPS ≥ 10%. For patients with PD-L1 CPS ≥ 1%, the median OS was [redacted] months. For patients with PD-L1 CPS ≥10%, [redacted] For patients with PD-L1 CPS ≥ 1% or ≥ 10%, the median PFS was [redacted] months and [redacted] months [redacted], respectively.

All participants were monitored for adverse events (AEs) for 30 days following the end of treatment (this was 90 days for serious adverse event (SAE) monitoring, unless the participant initiated a new treatment, in which case it was 30 days after the end of treatment). At the data cut-off (1st September 2016) as reported by Balar *et al.* (2017) patients had spent a median of three months (range 0.03-16.0 months) on treatment. At the time of the CS, this was reported as being 3.40 months (range 0.03-22.01 months), with a mean of 8.20 (standard deviation (SD) 6.84) administrations (median 5.00, range 1.00 to 33.00). Incidence of any AE was reported in the CS as being 97.6%, and incidence of treatment-related AEs was reported in the CS as being 65.7% and in Balar *et al.* (2017) as being 62%. The most common AEs were reported in the CS as being fatigue (33%), decreased appetite (24.1%), constipation (22.4%), urinary tract infection (21.6%), haematuria (15.7%) and an increase in blood creatinine (13.8%). The most common treatment-related AEs were reported in the CS as being fatigue (18.1%) and pruritus (16.8%). The CS reported 20 (5.4%) cases of mortality from AEs.

In the absence of comparative trials, company conducted a simulated indirect treatment comparison (ITC) for both PFS and OS, by firstly adjusting cross-study differences using simulated treatment comparison (STC) approach and then synthesising the evidence based on an assumption of constant hazard ratios using a standard meta-analysis model and time-varying hazard ratios using fractional polynomial models. Four studies of carboplatin plus gemcitabine, one of the comparators in the NICE final scope, were presented in the CS. These included one randomised controlled trial (RCT) and three cohort studies. There was considerable heterogeneity between the comparator studies with regard to patients and dosage and administration of gemcitabine and carboplatin. Median OS ranged from 7.2 months (95% CI: 5.9-8.5 months) to 10 months (95% CI: not reported (NR)). PFS ranged from 4.4 months (95% CI: 1.03-7.75 months) to 5.8 months (95% CI NR).

The STC approach includes four prognostic factors: ECOG ≥2; renal failure; presence of liver metastases or visceral metastases, and primary tumour site (upper or lower). The treatment effect of

pembrolizumab was more favourable in the adjusted population compared with the observed effect in the KEYNOTE-052 study.

The second order fractional polynomial model with power p1=p2=0 was chosen as the best fitting model for obtaining the relative effect for OS and PFS in the original submission. In response to clarification, additional analyses were performed by the company with negative values for p1 and p2. The overall best fitting model was p1=p2=-2, which provided less favourable results for pembrolizumab when compared with the chosen best fitting model in the original submission.

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

The systematic review presented in the CS appears to be comprehensive. The ERG is confident that all relevant pembrolizumab studies for this patient population were included in spite of limitations with the search methodology used by the company. The specified inclusion and exclusion criteria did not generally reflect the decision problem specified in the NICE final scope. Studies of BSC and atezolizumab, both included as comparators in the NICE final scope, were not included in the submission. The quality assessment tools used to appraise the included studies were considered appropriate by the ERG.

The ERG is confident that the CS contains the only known study of pembrolizumab in the relevant patient population, KEYNOTE-052. As this study is open-label, it is susceptible to bias. KEYNOTE-052 is an ongoing study and the data presented in the CS are immature. The ERG notes that the subgroup analyses presented in the CS should be treated with caution because PD-L1 expression is not a reliable predictor of outcomes in the urothelial cancer population.

The ERG has concerns that the company's population adjustment approach to balance the cross-study differences between KEYNOTE-052 and carboplatin plus gemcitabine studies lacks validity. The company's adjustments suggest that patients in KEYNOTE-052 were less fit or frailer compared with the patients in each of the carboplatin plus gemcitabine study. However, this is not supported by the reported summary of patient baseline characteristic in the included studies. The ERG's clinical advisors also confirm that patients in KEYNOTE-052 are not frailer compared with the patients in the comparator studies. The ERG notes that there is no evidence by subgroup for the comparator; hence it was not appropriate to conduct the ITC for the subgroups.

1.4 Summary of cost effectiveness submitted evidence by the company

The company did not identify any existing cost-effectiveness studies of pembrolizumab for this indication. A state transition model was constructed which included three states: (i) progression-free; (ii) progressed disease and (iii) death. The model adopted a weekly cycle length and a 20-year time

horizon. The company's model assesses the cost-effectiveness of pembrolizumab versus a combination of carboplatin and gemcitabine for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable.

The incremental health gains, costs and cost-effectiveness of pembrolizumab are evaluated from the perspective of the UK NHS and Personal Social Services (PSS). To estimate the long-term OS and PFS for the pembrolizumab group, data from the KEYNOTE-052 study were extrapolated using a piecewise approach with parametric distributions. The company used the Kaplan-Meier (KM) data up until 32 weeks and fitted a log normal distribution to the KM data from 32 weeks onwards as the base case for OS. The base case for PFS was using KM data up until 9 weeks and fitted a Weibull distribution to the KM data from 9 weeks onwards. The fractional polynomial model with p1=p2=0 for OS and PS was used to estimate the relative treatment effect (i.e. time-varying hazard ratios) of pembrolizumab versus carboplatin plus gemcitabine. The PFS and OS for carboplatin plus gemcitabine arm were modelled by applying the time-varying hazard ratios to the extrapolated PFS and OS of pembrolizumab arm, respectively. The estimated PFS for carboplatin plus gemcitabine is used as a proxy for time on treatment, and patients are assumed to receive no more than 6 cycles. Time on treatment data from the KEYNOTE-052 study were extrapolated using standard parametric distributions to estimate time on pembrolizumab (a Gompertz distribution was used in the base case), and patients can receive a maximum of 24 months treatment in the model. Utilities and costs for each health state are based on published sources. All costs and health outcomes are discounted at a rate of 3.5% per annum. Unit costs are valued at 2015/16 prices.

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

The company's health economic model structure is generally appropriate for the decision problem defined in the NICE final scope, though it should be noted that the only comparator tested within the economic evaluation was carboplatin plus gemcitabine. This is because there was no evidence for BSC and the evidence for atezolizumab was too uncertain to enable a useful comparison. The model was generally well described within the report. However, the simulated ITC lacks validity and there is substantial uncertainty around the extrapolation of the survival curves. The company undertook limited analyses to assess the impact of this uncertainty upon the model results, leading to an underestimate in the uncertainty around the incremental cost-effectiveness ratio (ICER). The company's probabilistic ICER following the clarification process is £37,081 per quality-adjusted life year (QALY) gained for

pembrolizumab compared with carboplatin plus gemcitabine, based upon the results within their health economic model.

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

1.6.1 Strengths

The systematic review presented in the CS appears to be comprehensive. The health economic model submitted by the company was generally well described and justified.

1.6.2 Weaknesses and areas of uncertainty

The uncertainties in the clinical evidence are mainly concerned with the absence of any RCTs comparing pembrolizumab with carboplatin plus gemcitabine, atezolizumab or BSC. The only comparator included in the CS is carboplatin plus gemcitabine. In addition, the data from KEYNOTE-052, reported in the CS are immature. The estimated completion date of the study is 21st June 2018 according to Clinical trials.gov (https://clinicaltrials.gov/ct2/show/NCT02335424).

Due to the lack of head-to-head studies, the relative treatment effect of pembrolizumab is uncertain. The ERG believes that the company's simulated ITC lacks validity, and because of this the benefits of pembrolizumab are likely to be overestimated within the company's health economic model. There is also substantial uncertainty around the extrapolation of the survival curves. In addition, it is unclear whether a treatment stopping rule would be applied in practice, and if so it is unknown what impact this would have upon treatment effectiveness. These structural uncertainties were insufficiently explored by the company within their scenario analyses, and hence the full range of plausible ICERs given the available evidence was not presented by the company.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has corrected errors relating to the implementation of utilities and to the proportion of males for the calculation of other-cause mortality. The ERG has also employed an approach where utilities are varied according to progression status rather than time until death. In addition, the ERG has included extrapolation of the unadjusted trial data for pembrolizumab and carboplatin plus gemcitabine as part of their base case, as well as incorporating a hazard ratio of 1.0 for PFS and OS for pembrolizumab versus carboplatin plus gemcitabine after 24 months of treatment given the proposed stopping rule. The ERG's changes to the utility approach and the extrapolation of survival data have a substantial impact upon the ICER.

The ERGs probabilistic base case ICER is £66,588 per QALY gained. The scenario analyses run by the ERG suggest that the ICER is highly uncertain. In particular, the choices of extrapolation for the OS of pembrolizumab and the stopping rule for pembrolizumab have the largest impacts upon the ICER, with

a cost per QALY gained for pembrolizumab versus carboplatin plus gemcitabine ranging from £48,330 to £136,971 under plausible assumptions.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The ERG considers the company's description of the underlying health problem in the CS[1] to be adequate, mostly up-to-date and relevant to the decision problem set out in the NICE final scope.[2] The CS states that urothelial cancer may arise from the transitional cells in the endothelium of the bladder, renal pelvis, ureter, and urethra. In the UK, urothelial cancer accounts for approximately 90% bladder, renal pelvis, ureter and urethra cancers.[3]

The company reports that the Tumour-Node-Metastasis (TNM) classification[4] is used to group urothelial carcinoma into clinical stages (stage 0-IV). When making treatment decisions in clinical practice, bladder cancers are grouped based on the classification of tumour, non-muscle-invasive (NMIBC; stage 0a-1), muscle-invasive (MIBC; stage II-III), or advanced/metastatic (MBC; stage IV). The ERG notes that sometimes the company uses the term "bladder cancer" and "urothelial carcinoma" interchangeably. The ERG's clinical advisors confirmed that both clarification methods are used for urothelial carcinoma. Table 3 in the CS shows the relationship between the two classification methods.

The CS reports that the most important risk factor for urothelial carcinoma is smoking which is in line with the report by the European Association of Urology.[5] The company also reports that occupational exposure to carcinogens is also an important risk factor following smoking.

The survival data for patients with urothelial cancer are not presented in the CS because of the scarcity of such data in the literature. Instead, the company states that survival rates for patients with bladder cancer are strongly correlated to disease stage at diagnosis. For patients with stage IV disease, the likelihood of survival is 35% and 28% at 1 year for men and women, respectively, and 9% and 11% at 5 years following initial diagnosis. The CS also notes that as discussed in the in the appraisal for pembrolizumab in patients with previously treated urothelial cancer (NICE ID1019),[6] there is variation in 5-year overall survival for patients with advanced or metastatic urothelial cancer. The lowest 5-year survival rates suggested in the literature was 6% globally.[7]

The CS reports that in the UK, bladder cancer is recognised as the 10th most common form of cancer, and the 7th most common cause of cancer mortality.[8] Bladder cancer is most frequent within an elderly population; in the UK 55% of bladder cancer is diagnosed in people aged 75 years and over (CRUK 2012 to 2014).[9] The ERG notes that this refers to any cancer of the urinary bladder, not just urothelial carcinoma.

2.2 Critique of company's overview of current service provision

The CS provides a satisfactory overview of current service provision. The CS states that within the UK the current first line treatment for patients with locally advanced or metastatic urothelial carcinoma in who are cisplatin ineligible is carboplatin in combination with gemcitabine, which is in line with NICE recommendations.[10] The company suggest that some patients may alternatively receive best supportive care. They highlight that within the population under consideration there is a clear unmet need with limited treatment options available.

The company does not describe subsequent treatment for these patients within their overview of service provision. However, the company uses the latest UK market shares to model subsequent treatment within the health economic evaluation. This assumes that [redacted] of patients would receive a taxane following treatment discontinuation with pembrolizumab or carboplatin plus gemcitabine. Of these, [redacted]. The remaining [redacted] of patients are assumed to receive BSC only. The clinical advisors to the ERG suggest that for this patient group, it is unlikely that [redacted] of patients would be given a taxane and that this value would be closer to 25%, as most patients are too unfit to benefit from taxane-based therapies.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

The population considered in the decision problem and the clinical evidence for pembrolizumab (the KEYNOTE-052 study) submitted by the company matches the population described in the NICE final scope, which is adults with locally advanced or metastatic urothelial carcinoma who have not received prior systematic chemotherapy and who are not eligible to receive cisplatin.

The ERG notes that the clinical study report[15] (CSR) of KEYNOTE-052 states that the study design is "Non-randomized, multi-site, open-label trial of pembrolizumab in subjects with advanced/unresectable or metastatic urothelial cancer who have not received prior systemic chemotherapy and who are not eligible to receive cisplatin". The term "advanced/unresectable" was used instead of "locally advanced". The ERG's clinical advisors suggest that these two terms are equivalent.

The patient population in the KEYNOTE-052 study was consistent with the epidemiologic pattern of urothelial cancer, in that patients were mostly male (77.3%), over 65 years (81.6%) and had the expected percentage of ECOG 2 patients (41.9%).

3.2 Intervention

The intervention under consideration is pembrolizumab (Keytruda®), which matches the NICE final scope. Pembrolizumab is part of a new class of immunotherapies which comprises drugs like nivolumab and atezolizumab.

The wording of the marketing authorisation for pembrolizumab for the indication considered within the NICE final scope is as follows: "KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy". Pembrolizumab is given by intravenous infusion at a fixed dose of 200mg every three weeks. The Summary of Product Characteristics (SmPC) states that 'Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity', and there is no mention of a stopping rule.

The company has a Commercial Access Agreement with NHS England for patients with non-small cell lung cancer (NSCLC) and melanoma. [redacted]. The price per 100mg vial after discount is [redacted], whereas the list price is £2,630.

3.3 Comparators

The NICE final scope indicates that the comparator treatments are carboplatin plus gemcitabine, atezolizumab and BSC. The comparator described in the company's decision problem is limited to carboplatin plus gemcitabine only; this does not match to the comparators described in the NICE final scope.

The company states the reason for not considering atezolizumab as "Although atezolizumab appears to be an effective first line treatment option for cisplatin ineligible patients with locally advanced or metastatic urothelial carcinoma, the NICE committee and ERG found it difficult to establish the size of the clinical benefit compared with current treatment". As a result, atezolizumab has been made available through the Cancer Drugs Fund (CDF), and as such, the company argues that atezolizumab is not a relevant comparator. Given that the Final Appraisal Determination issued by NICE suggested that the benefit of atezolizumab was too uncertain to recommend outside of the CDF, and the evidence for atezolizumab and pembrolizumab is limited to single-arm studies, the ERG agrees that a comparison with atezolizumab would not be helpful for informing the current decision.

In addition, BSC has not been considered as a relevant comparator due to a paucity of evidence. The company suggests that most patients would receive gemcitabine plus carboplatin rather than BSC. The clinical advisors to the ERG also suggest that most patients would receive gemcitabine plus carboplatin. The ERG has searched for RCTs; these searches did not identify any clinical evidence for the use of BSC compared with any other treatment within this population (see Section 4.1). The ERG's clinical advisors also suggest that gemcitabine plus carboplatin has been used for many years in this population, despite being unlicensed for this indication, hence no trials have been undertaken to compare the combination with BSC. As such, given current evidence, it is not possible for the company to provide a comparison with BSC.

3.4 Outcomes

The outcome measures considered in the decision problem match the description in the NICE final scope. These include overall survival (OS), progression-free survival (PFS), response rates (RR), adverse effects (AE) and health-related quality of life (HRQoL).

3.5 Other relevant factors

The CS does not raise any equity issues. The ERG notes that the patient population in the decision problem is associated with poor prognosis and limited treatment options.

4 CLINICAL EFFECTIVENESS

This chapter presents a review of evidence relating to the clinical effectiveness of pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable. Section 4.1 presents a critique of the company's systematic review and Section 4.2 provides a summary of the clinical effectiveness results (efficacy and safety) and critique of the included pembrolizumab study. Sections 4.3 to 4.5 provide a critique of the studies included in the indirect treatment comparison (ITC) and the method used in the ITC. Section 4.6 presents additional work on clinical effectiveness undertaken by the ERG. Finally, Section 4.7 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review

A systematic literature review (SLR) was undertaken in three phases to identify all relevant studies to inform both the direct and indirect comparison of pembrolizumab and relevant interventions included in this appraisal. Both RCTs and non-RCTs were included. The systematic review methods are detailed in Appendix D of the CS (page 169).

4.1.1 Searches

The company conducted systematic searches for published evidence in several phases; these are reported in full in the CS Appendix D1.1. The submission contained a minor discrepancy about the date of the first update searches which was explained in the company's clarification response.

An appropriate range of databases was included (Medline; EMBASE; the Cochrane CENTRAL register of randomised controlled trials) in accordance with NICE guidance. The company decided to include only primary studies (specifically, RCTs, single-arm studies, retrospective studies and observational studies), and, unusually, developed their own filter – even though validated filters are available for several of the study types of interest. The company's filter used some high-risk strategies such as excluding words used in the title and abstract, and explicitly excluding SLRs. In their response to the ERG's clarification letter, the company acknowledged that "the identification of SLRs may have been useful to cross-validate and confirm the included studies", and that "the use of a validated search filter with defined sensitivity and specificity should be used in future" (clarification response, question A14).

Recent conference proceedings were not searched, as according to the CS, "relevant conferences are included within the EMBASE database" (Section D1.1, page 169). When the ERG queried the reliance on a third-party source (with the inevitable delays) in its clarification letter (question A12), the company accepted the limitations of this approach but argued that in any case conference abstracts would be unlikely to provide sufficient detail to perform the type of indirect comparisons analysis required for the CS.

Finally, there are a number of syntax errors throughout the search strategies; for example, the use of the wildcard character "?" where a hyphen may or may not be present between two words ("un?resectable"). This may work in some interfaces but not the Ovid platform, which treats hyphens as spaces not letters, meaning it understands hyphenated phrases as separate words (see example below, from a Medline search conducted on 20th December 2017):

1. unresectable.mp. (17934)
2. un-resectable.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (47)
3. 1 or 2 (17975)
4. un?resectable.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17934).

In this example, the only way to find both variants is to combine them with OR, as in line 3. The company's search string (in line 4) only finds the unhyphenated version.

Another recurrent error was the exclusive use of the US spelling of the word "tumor" /"tumour" (UK), which has here been searched for as "tum?r" rather than "tumo?r*". The illustration below demonstrates that, at least on the Ovid platform, this spelling will not find the UK spelling.

1. tumor.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1582200)
2. tum?r.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1582224)
3. tumo?r.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1728336).

The correct syntax to find both spellings of this term is that in line 3, which here retrieved an additional 200,000 results (prior to being combined with the other search facets).

However, in spite of the errors and omissions described above (and even after conducting dedicated searches to identify studies comparing pembrolizumab or its comparators with BSC), the ERG has not identified any relevant studies missed by the CS.

4.1.2 Inclusion criteria

The company's inclusion criteria are presented in Table 1 below.

Table 1: Study inclusion criteria (reproduced from Table 67, page 170 CS)

Criteria	Inclusion
Population	• Patients with previously-untreated advanced/unresectable or metastatic urothelial carcinoma who are ineligible for cisplatin-based chemotherapy (1L) • Creatinine clearance (CrCL) or Glomelular Filtration Rate (GFR) of 30-60 ml/min • If renal function criteria not clear, only those with poor performance status (i.e. ECOG score > 2 or Karnovsky < 60%)
Interventions	• Pembrolizumab • Carboplatin • Gemcitabine • Paclitaxel • Methotrexate • Vinflunine • Vinblastine • Epirubicin • Docetaxel • Oxaliplatin • Doxurubicin
Comparisons	• Any of the interventions, alone or in combination • No intervention • Placebo • Best supportive care (BSC)
Outcomes	• Progression-free survival (PFS) • Overall survival (OS)
Study Design	• Randomised controlled trials (RCTs) • Single-arm studies • Retrospective studies • Observational studies
Other	• English language

The inclusion criteria generally do not reflect the decision problem described in the NICE final scope. Although pembrolizumab is included as an intervention, as per the decision problem, several additional interventions have been included:

- Carboplatin
- Gemcitabine
- Paclitaxel
- Methotrexate
- Vinflunine
- Vinblastine

- Epirubicin
- Docetaxel
- Oxaliplatin
- Doxurubicin.

With regard to comparators, carboplatin plus gemcitabine and BSC are included as in the decision problem. Atezolizumab has been excluded as a comparator despite this being listed in the NICE final scope. The following have been listed as comparators, although they do not form part of the decision problem in the NICE final scope:

- Any of the interventions, alone or in combination
- No intervention
- Placebo.

Two reviewers independently screened all titles and abstracts for inclusion. Full papers were retrieved for detailed assessment by the same reviewers. A third reviewer was used to resolve discrepancies and reach consensus.

Three PRISMA diagrams are presented (see CS, Figures 28-30 Appendix D, pages 204-206), referring to a total of seven included studies between them. Six studies are listed in CS Table 77 (page 207). Two of these refer to studies of pembrolizumab.[11, 12] No study exclusion criteria are presented in the CS. A list of excluded studies is presented (Table 78, pages 207-217 CS) although without the exclusion criteria, it is difficult to judge on which basis studies were excluded.

4.1.3 Critique of data extraction

No information on the data extraction process is presented in the CS, and it is not clear if this was done by one or two reviewers. There is no mention of checking for accuracy during the data extraction process. However, the ERG notes that the data presented in the clinical effectiveness section of the CS appears to be comprehensive and appropriate.

4.1.4 Critique of quality assessment

The Newcastle Ottawa Scale[13] was used to assess study quality, which is appropriate for the quality assessment of non-RCTs. Quality assessment was undertaken by two independent reviewers with any disagreements resolved by a third reviewer.

4.1.5 Critique of evidence synthesis

As only one pembrolizumab study (KEYNOTE-052) was identified, no meta-analysis was undertaken.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The CS (page 22) included one pivotal study, KEYNOTE-052 as the main evidence for pembrolizumab in the submission. The study characteristics of KEYNOTE-052 are shown in Table 2 below. KEYNOTE-052 is a Phase II, single-arm, open-label, non-randomised study. The CS states that KEYNOTE-052 was conducted in 16 countries (CS page 27): Australia, Canada, Denmark, Guatemala, Hungary, Ireland, Israel, Italy, Republic of Korea, Malaysia, Netherlands, Singapore, Spain, Taiwan, United Kingdom and United States. The study included 27 patients from UK centres (CS page 28). However, in Balar *et al.* (2017),[12] the main publication of KEYNOTE 052, centres in 20 countries were said to be included although, it is not clear which four additional countries were included. The EPAR[14] lists 17 countries, the same as those listed above plus Puerto Rico.

There were two protocol amendments made to the study[12]:

1. To include all patients irrespective of PD-L1 expression status
2. To reflect the transition of the pembrolizumab study away from hypothesis testing for primary objectives and toward estimation for single-arm clinical trials.

In response to the clarification letter request for information on the protocol amendments (question A1), the response was that "the inclusion criteria were updated to state that subjects must be refractory to available or standard therapy treatment of their bladder cancer in order to participate in the biomarker cut-point determination part of the study if they do not meet cisplatin-ineligible criteria." It is therefore unclear what percentage of the initial validation cohort (n=80) actually met the cisplatin-ineligible criteria of KEYNOTE-052.

Patients

Key eligibility criteria[12] were:

- 18 years or older
- histologically or cytologically confirmed locally advanced and unresectable or metastatic urothelial cancer of the renal pelvis, ureter, bladder or urethra
- ineligible for cisplatin therapy
- had not previously received systemic chemotherapy for advanced disease
- had centrally confirmed and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST)
- had an ECOG performance of 0-2
- adequate haematological, renal and liver function

- life expectancy of more than three months.

Initially 541 patients were screened. 374 patients were enrolled, of whom 370 patients received at least one dose of pembrolizumab.[12] Of the 370 patients who were treated, 233 discontinued with 137 still receiving treatment at the data cut-off point of 9th March 2017.

The study population for KEYNOTE-052 was predominantly male (77.3%) and white (88.6%) with 78.1% of the patients having an ECOG status of 1 (36.2%) or 2 (41.9%). The median age of study participants was 74 years (range 34-94 years). With regard to metastases location, 51 patients (13.8%) had lymph node metastases only, while 315 patients (85.1%) had visceral disease and four patients (1.1%) had metastases location not reported (CS, pages 32-34).

The patients in KEYNOTE-052 were be considered to be representative of this patient population in that the criteria for cisplatin ineligibility were deemed to be acceptable and to reflect the standard criteria used in clinical practice EPAR (page 101).[14] The patient population was consistent with the epidemiologic pattern of urothelial cancer, in that patients were mostly male, over 65 years and had the expected percentage of ECOG 2 patients (EPAR page 127).[14] The CS (Table 8) states that 41.9% of patients were ECOG 2. The EPAR (page 138)[14] notes that no efficacy or safety data were available for frailer patients (ECOG 3), considered ineligible for chemotherapy.

Intervention

Pembrolizumab was administered in an un-blinded manner at a dosage of 200mg as IV infusion over 30 minutes every three weeks. Pembrolizumab treatment could continue for 24 months, although patients who stopped pembrolizumab after achieving a complete response or after 24 months of treatment for reasons other than disease progression or intolerable toxic effects could receive additional pembrolizumab for up to one year at the time of new disease progression.[12]

Table 2: Study characteristics of KEYNOTE-052 study

Study	Location (sites)	Design	Population	Interventions	Comparator	Primary outcome measure	Secondary outcome measures	Duration
KEYNOTE-052[12] and CS	91 academic medical centres in 20 countries	Single-arm, non-randomised, open label trial	Adult, cisplatin ineligible patients with advanced, unresectable or metastatic urothelial cancer; not previously treated with systemic chemotherapy	Pembrolizumab 200mg every 3 weeks administered by IV infusion	None	Objective response rate (ORR)	PD-L1 cut-off Overall survival (OS); progression-free survival (PFS) Duration of response Safety and tolerability	Ongoing study (data cut-off 9th March 2017, [redacted])

Ongoing studies

KEYNOTE-052 is an ongoing study and the data presented in the CS is from interim analysis 2 with a data cut-off point of 9th March 2017. A further analysis was expected in [redacted] and final analysis is expected [redacted] (CS, page 78).

In addition, the KEYNOTE-361 trial (NCT02853305) is an ongoing Phase III, multi-centre, RCT to determine the following efficacy and safety comparisons: pembrolizumab with or without chemotherapy (either cisplatin plus gemcitabine or carboplatin plus gemcitabine) vs. chemotherapy alone. The primary outcome measures are OS and PFS.

The study is currently recruiting (at the time of writing), according to clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02853305?term=NCT02853305&rank=1). The population of KEYNOTE-361 consists of patients with advanced/metastatic urothelial carcinoma with no prior systemic chemotherapy for advanced or metastatic urothelial carcinoma. There is no requirement for participants to be cisplatin-ineligible, and thus the population of KEYNOTE-361 differs from the population in the NICE final scope.

More details of the study can be found in the CS (page 78) and in the company's response to clarification (question A10). Final data collection for the primary outcome is estimated to take place on 29 March 2019, with an estimated completion date of 18th May 2020. The first interim analysis is expected in [redacted]. The estimated enrolment is 990 participants. When the results are available, there will be data for the comparison of pembrolizumab (monotherapy) vs. carboplatin plus gemcitabine on OS and PFS.

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that KEYNOTE-052 is the only relevant study in this patient population and apart from the ongoing study presented above; there are no other relevant trials that have been omitted from the CS.

4.2.3 Summary and critique of the company's quality assessment

Table 3 compares the quality assessment of the KEYNOTE-052 study undertaken by the company and the ERG. The rating given to KEYNOTE-052 differs between the CS (pages 50 and 219) and the ERG, in that the CS rated KEYNOTE-052 seven stars and the ERG rated it five stars. The main differences between the CS and the ERG ratings are in terms of the following criteria:

- The representativeness of the exposed cohort, (which the ERG rated as somewhat representative, due to patients with an ECOG of 3 not being represented in this sample; although this does not affect the rating);

- Selection of the non-exposed cohort (which the ERG rated as not applicable (NA), due to there not being a non-exposed cohort; KEYNOTE-052 is a single-arm study);
- The length of follow-up being sufficient for outcomes to occur (which the ERG rated as 'no', as the study is ongoing).

Table 3: Company and ERG quality assessment for KEYNOTE-052 (adapted from Table 80, page 219 CS)

	KEYNOTE-052	
	Company quality assessment	**ERG quality assessment**
Selection		
1. Representativeness of the exposed cohort	Truly representative of the average first-line advanced urothelial cancer in the community	Somewhat representative of the average first-line advanced urothelial cancer in the community (patients with ECOG of 3 (i.e. very frail) are not represented in this sample; EPAR page 128).
2. Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	NA. There is no non-exposed cohort
3. Ascertainment of exposure	Secure record	Secure record
4. Demonstration that outcome of interest was not present at start of study	Yes	Yes
Comparability		
1. Comparability of cohorts on the basis of the design or analysis	NA; single-arm study	NA; single-arm study
Outcome		
1. Assessment of outcome	Independent assessment	Independent assessment
2. Was follow-up long enough for outcomes to occur	Yes; median follow-up of 5 months	No; some outcomes haven't occurred in all patients yet (OS and PFS)
3. Adequacy of follow up of cohorts	Complete follow up - all subjects accounted for	Complete follow up - all subjects accounted for
Stars total	**7**	**5**

NA=not applicable

4.2.4 Summary and critique of results

The outcomes stated in the NICE final scope included OS, PFS, RR, adverse events and health-related quality of life (HRQoL). All of these outcomes are reported in the CS. The primary endpoint of the KEYNOTE-052 study is RR with OS, PFS and HRQoL being secondary endpoints.

Subgroups to be considered in the NICE final scope were those based on cancer histology and biological markers (PD-L1). The CS considered the following subgroups: PD-L1 combined positive score (CPS) ≥1% and PD-L1 CPS ≥10%, with the cut-off points defined by the company based on the discovery population, that is the first 100 subjects enrolled in KEYNOTE-052 study (CS, page 30).

It is important to note that the KEYNOTE-052 study is ongoing. Different data cut-off points are used in the CS and CSR[15] (both 9th March 2017), and Balar *et al*. (2017)[12] and the EPAR[14] (both 1st Sept 2016).

Overall survival

OS was defined as vital status of patients individually expressed in units of time from the start of study therapy and/or the percentage of subjects alive at a given time point when expressed as an aggregate (CS, page 30). OS results from KEYNOTE-052 are shown in Table 4. There were 188 deaths at the time of the data cut-off. The CS notes (page 41) that many subjects were censored within the OS analysis due to ongoing and relatively immature follow-up. The Kaplan-Meier (KM) plot for OS is shown in Figure 1 below.

Table 4: Summary of overall survival all subjects (reproduced from Table 13, page 41 CS)

Treatment	N	Number of events	Person-months	Event rate/ 100 person-months %	Median OS† (months) (95%CI)	OS Probability at 6 Months in %† (95% CI)	OS Probability at 12 Months in %† (95% CI)
Pembrolizumab	370	188 (50.8)	3190.2	5.9	11.0 (10.0, 13.6)	67.4 (62.3, 72.0)	46.8 (41.1, 52.3)

† From product-limit (Kaplan-Meier) method for censored data.
Database Cut-off Date: 09MAR2017

CI=confidence interval

Figure 1: Kaplan-Meier of overall survival based on RECIST 1.1 per Central Radiology Assessment (reproduced from Figure 3, page 42 CS)

Progression-free survival

Progression was defined as per RECIST 1.1 as assessed by blinded independent central radiologists (BICR). PFS is defined as the time from first dose to the first documented disease progression according to RECIST 1.1 or death due to any cause, whichever occurred first (CS, page 30). The CS (page 42) notes that many patients were censored from the PFS analysis due to ongoing response. Table 5 shows the PFS data and Figure 2 shows the KM plot for PFS.

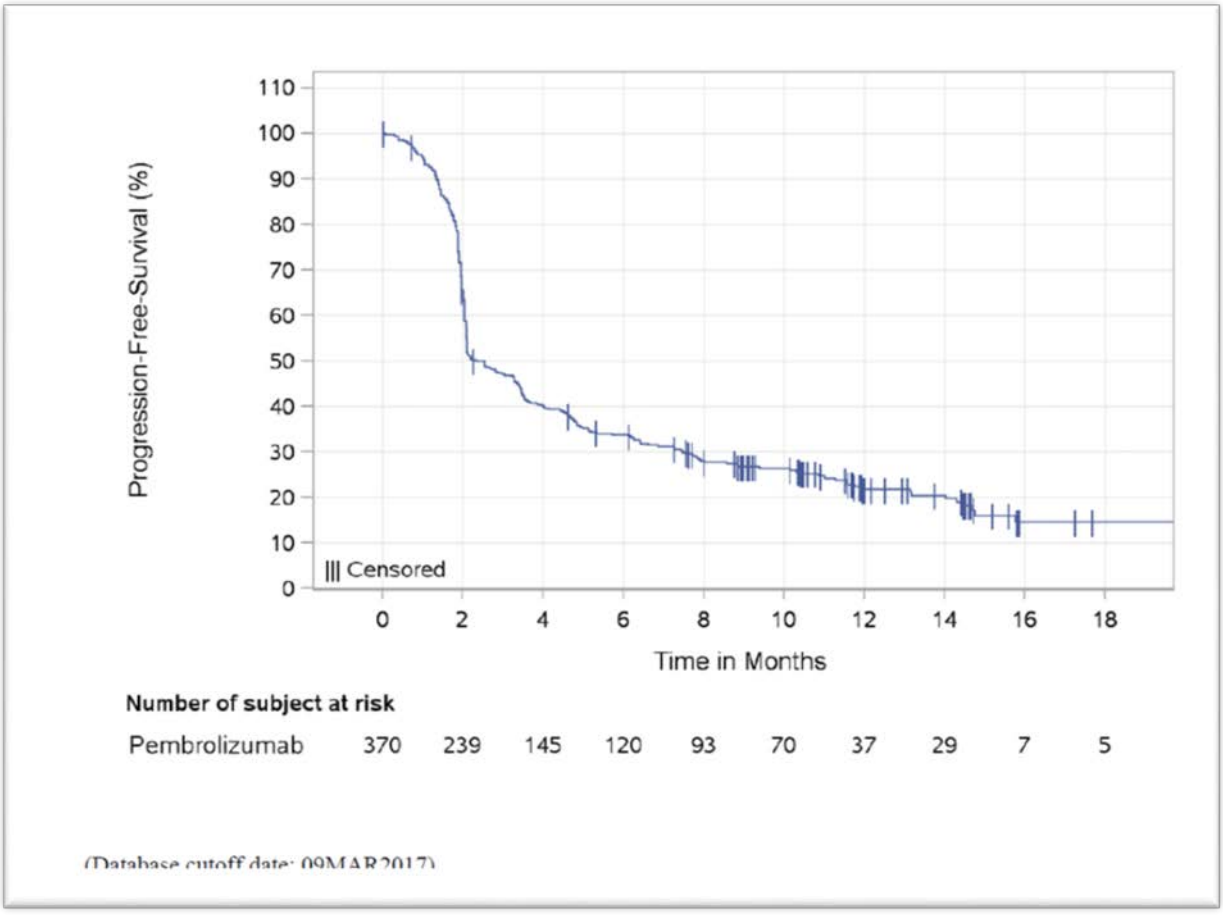
Table 5: Summary of progression-free survival based on RECIST 1.1 per Central Radiology Assessment (reproduced from Table 14, page 43 CS)

Treatment	N	Number of events	Person-months	Event rate/ 100 person-months %	Median PFS† (months) (95%CI)	PFS Probability at 6 Months in %† (95% CI)	PFS Probability at 12 Months in %† (95% CI)
Pembrolizumab	370	284 (76.8)	1878.3	15.1	2.3 (2.1, 3.4)	33.8 (29.0, 38.7)	21.8 (17.4, 26.6)

Progression-free survival is defined as time from the first dose to disease progression, or death, whichever occurs first. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit is used in the analysis. Patients without post-baseline tumor assessment are censored at time of the first dose.
† From product-limit (Kaplan-Meier) method for censored data.
Database Cut-off Date: 09MAR2017

CI=confidence interval

Figure 2: Kaplan-Meier of progression-free survival based on RECIST 1.1 per Central Radiology Assessment (reproduced from Figure 4, page 43 CS)



Objective response rate

ORR was defined as the percentage of patients who had a complete response (CR) or partial response (PR) per RECIST version 1.1 as assessed by BICR (CS, page 39). ORR results are presented in Table 6 below.

Table 6: Summary of best overall response with confirmation based on RECIST 1.1 per Central Radiology Assessment all subjects (reproduced from Table 10, page 40 CS)

Response Evaluation	Pembrolizumab (N=370)		
	n	%	95% CI†
Complete Response (CR)	27	7.3	(4.9, 10.4)
Partial Response (PR)	81	21.9	(17.8, 26.5)
Objective Response (CR+PR)	**108**	**29.2**	**(24.6, 34.1)**
Stable Disease (SD)	67	18.1	(14.3, 22.4)
Disease Control (CR+PR+SD)	**175**	**47.3**	**(42.1, 52.5)**
Progressive Disease (PD)	155	41.9	(36.8, 47.1)
Non-evaluable (NE)	9	2.4	(1.1, 4.6)
No Assessment	31	8.4	(5.8, 11.7)

Confirmed responses are included.
† Based on binomial exact confidence interval method.
Non-evaluable: subject had post-baseline imaging and the best overall response (BOR) was determined to be NE per RECIST 1.1.
No Assessment: subject had no post-baseline imaging

CI=confidence interval

Safety and tolerability

This section provides the main safety evidence for the use of pembrolizumab in people with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin, from the KEYNOTE-052 study. Safety data were taken from the All Patients as Treated (APaT) population, consisting of all patients who received at least one treatment with pembrolizumab, with at least one subsequent laboratory or vital sign measurement (N = 370) (CSR page 58).[15] All participants were monitored for adverse events (AEs) for 30 days following the end of treatment (this was 90 days for serious adverse event (SAE) monitoring, unless the participant initiated a new treatment, in which case it was 30 days after the end of treatment) (CSR page 48).[15] Treatment-related adverse events were those judged by the investigator to be related to pembrolizumab. At the data cut-off (1st September 2016) as reported by Balar *et al.* (2017)[12], patients had spent a median of three months (range 0.03 to 16.0 months) on treatment; at the time of the CS (interim analysis 2, data cut-off 9th March 2017), this was reported as being 3.40 months (range 0.03-22.01 months), with a mean of 8.20 (SD 6.84) administrations (median 5.00, range 1.00-33.00) (CS, page 74). According to the CSR[15] (page 110), most participants (297 [80.3%]) received at least one month of treatment, and just over half (192 [51.9%]) received three months of treatment.

Adverse events and treatment-related adverse events

The reported AE data differ between the CS/CSR[15] (which match exactly) and the Balar *et al* (2017)[12] (see Table 7). This may be because the data cut-off in Balar *et al*. (2017)[12] is just over five months prior to the data cut-off in the CS/CSR[15] (1st September 2016, compared with 9th March 2017, respectively). It should be noted that Balar *et al*. (2017)[12] do not report all types of AEs documented in the CS/CSR[15] therefore published AE data are only available for the 1st September 2016 data cut-off point and for treatment-related adverse events only. Incidence of any AE is reported as being 97.6% in the CS, and not reported in the Balar *et al*. (2017).[12] Incidence of any treatment-related AE differs slightly between these sources (62% in Balar *et al*. (2017)[12] compared with 65.7% in the CS/CSR[15]), as does incidence of withdrawals due to treatment-related AEs (5% in Balar *et al*. (2017)[12] compared with 7.3% in the CS/CSR[15]).

The most common AEs are summarised in Table 7. The most common AEs were reported in the CS/CSR[15] as being fatigue (33%), decreased appetite (24.1%), constipation (22.4%), urinary tract infection (21.6%), haematuria (15.7%) and an increase in blood creatinine (13.8%). The most common treatment-related AEs were reported in the CS/CSR[15] as being fatigue (18.1%) and pruritus (16.8%). It should be noted that the numbers of AEs differ slightly between the text on page 76 of the CS, and Tables 98-105 in Appendix F of the CS (pages 265-277).

Table 7: Adverse event summary all patients as treated, n (%)

	Balar 2017[a] n (%)	**CS /CSR[b] n (%)**
Any adverse event	NR	361 (97.6)
No adverse event	NR	9 (2.4)
Treatment-related adverse events	229 (62)	243 (65.7)
Toxicity Grade 3-5 adverse events	58 (16)	223 (60.3)
Toxicity Grade 3-5 treatment-related adverse events	NR	70 (18.9)
Serious adverse events	NR	176 (47.6)
Serious treatment-related adverse events	36 (10)	40 (10.8)
Mortality	18 (4.9[c])	20 (5.4)
Mortality due to a treatment-related adverse event	1 (0.3[c])	1 (0.3)
Withdrawals due to AE	NR	52 (14.1)
Withdrawals due to treatment-related AE	19 (5)	27 (7.3)
Withdrawals due to serious AE	14 (3.8[c])	40 (10.8)
Withdrawals due to serious treatment-related AE	NR	17 (4.6)
1 or more AE of special interest	NR	84 (22.7)
Grade 3 or higher AEs of special interest	NR	32 (8.6)
Common AEs		
Fatigue	NR	122 (33)
Decreased appetite	NR	89 (24.1)
Constipation	NR	83 (22.4)
Urinary tract infection	NR	80 (21.6)
Haematuria	NR	58 (15.7)
Blood creatinine increased	NR	51 (13.8)

Common treatment-related AEs		
Fatigue	NR	67 (18.1)
Pruritus	NR	62 (16.8)
Common Grade 3-5 AEs		
Urinary tract infection	NR	39 (10.5)
Anaemia	NR	28 (7.6)
Common Grade 3-5 treatment-related AEs		
Fatigue	8 (2)	8 (2.2)
Alkaline phosphate increase	5 (1)	5 (1.4)
Colitis	4 (1)	6 (1.6)
Muscle weakness	4 (1)	5 (1.4)
Common serious AEs		
Urinary tract infection	NR	25 (6.8)
Acute kidney injury	NR	13 (3.5)
Urosepsis	NR	12 (3.2)
Haematuria	NR	11 (3.0)
Pneumonia	NR	11 (3.0)
Common serious treatment-related		
Pyrexia	4 (1)	3 (0.8)
Adrenal insufficiency	2 (<1)	2 (0.5)
Arthritis	2 (<1)	2 (0.5)
Colitis	2 (<1)	2 (0.5)
Diabetic ketoacidosis	2 (<1)	2 (0.5)
Hepatitis	2 (<1)	2 (0.5)
Pneumonitis	2 (<1)	4 (1.1)
Type 1 diabetes	2 (<1)	2 (0.5)
Common adverse events of special interest		
Hypothyroidism	NR	40 (10.8)
Pneumonitis	NR	12 (3.2)
Hyperthyroidism	NR	10 (2.7)
Colitis	NR	9 (2.4)
Severe skin reactions	NR	7 (1.9)
Adrenal insufficiency	NR	6 (1.6)
Hepatitis	NR	4 (1.1)
Type 1 diabetes	NR	4 (1.1)
Thyroiditis	NR	3 (0.8)

NR, not reported
[a] Up to 1 September 2016 data cut-off (screening started 24 February 2015)
[b] Up to 9 March 2017 (interim data analysis 2 cut-off)
[c] Calculated

Note: this table is adapted from Table 40, Table 98-103 and Table 105, pages 75, 265-274 CS.

In the EPAR for pembrolizumab, the safety profile of pembrolizumab in the KEYNOTE-052 population was compared against a Reference Safety Dataset, which contained 3194 patients treated with pembrolizumab in several clinical trials for treatment of various medical conditions, and reported no major differences in the safety profile.[14] The frequency of patients experiencing mortality from an AE was noted as being comparable; 4.9% in KEYNOTE-052 and 3.9% in the Reference Safety Dataset.[14]

The incidence of the most commonly reported treatment-related AEs appears to be slightly lower in the KEYNOTE-052 population, compared with the Reference Safety Dataset (fatigue 16.8% and 24.2%; pruritus

14.6% and 16.7%; rash 9.7% and 13.8%, for KEYNOTE-052 and the Reference Safety Dataset, respectively), although there is a slight discrepancy between these figures, reported on page 128 of the EPAR, and the figures that are reported in Table 52 on page 114 of the EPAR).[14] The EPAR notes in particular that, among the cisplatin-ineligible patients in the KEYNOTE-052 study, the safety profile was similar to those eligible for cisplatin in the KEYNOTE-045 trial, with no new safety signals additional to the Reference Safety Dataset, with a safety profile of pembrolizumab among cisplatin-ineligible patients that compares favourably with chemotherapy.[14] The EPAR notes that overall the benefit-risk balance of pembrolizumab in cisplatin-ineligible patients is considered to be positive, however there are no safety and efficacy data available for frailer patients (those with ECOG performance status 3), and also that longer safety follow-up is needed (EPAR page 138).[14]

Grade 3-5 adverse events

The incidence of treatment-related Grade 3-5 adverse events was reported as being 60.3% in the CS/CSR[15] (and was not reported in Balar *et al*. (2017)[12]) (see Table 7). Data on treatment-related Grade 3-5 AEs differs slightly between the CS/CSR[15] and Balar *et al*. (2017)[12] (18.9% in the CS/CSR[15] and 16% in Balar *et al.* (2017)[12]).

Data on the most frequent Grade 3-5 AEs are summarised in Table 7. The most frequent Grade 3-5 AEs were reported in the CS/CSR[15] as being urinary tract infection (10.5%) and anaemia (7.6%); Grade 3-5 AE incidence was not reported in the Balar *et al*. (2017).[12] The most common Grade 3-5 treatment-related AEs were reported in the Balar *et al*. (2017)[12] and the CS/CSR[15], respectively, as being fatigue (2%, 2.2%), alkaline phosphate increase (1%, 1.4%), colitis (1%, 1.6%), and muscle weakness (1%, 1.4%).

Serious adverse events

The incidence of serious AEs is reported as being 47.6% in the CS/CSR[15] (up to 90 days after the last dose of study medication); date on SAEs are not reported in the Balar *et al*. (2017).[12] The incidence of serious treatment-related AEs was reported as 10% in the Balar *et al*. (2017)[12], and 10.8% in the CS/CSR.[15] It is notable that the incidence of withdrawals due to serious AEs were reported as 3.8% in the Balar *et al*. (2017)[12] compared with 7.3% (CS, page 74) in the CS/CSR.[15]

Data on the most frequent SAEs are summarised in Table 7. The most commonly reported serious AEs were urinary tract infection (6.8%), acute kidney injury (3.5%), urosepsis (3.2%), haematuria (3.0%) and pneumonia (3.0%), according to the CS/CSR[15]; incidence of specific serious AEs were not reported in the Balar *et al*. (2017).[12] The most common serious treatment-related AEs were reported in the Balar *et al*. (2017)[12] and the CS/CSR[15], respectively, as being pyrexia (1%, 0.8%), adrenal insufficiency (<1%, 0.5%), arthritis (<1%, 0.5%), colitis (<1%, 0.5%), diabetic ketoacidosis (<1%, 0.5%), hepatitis (<1%, 0.5%), pneumonitis (<1%, 1.1%), and type 1 diabetes (<1%, 0.5%).

Death

The Balar *et al*. (2017)[12] and the CS/CSR[15] reported 18 (4.9%) and 20 (5.4%) cases of mortality from AEs up to 90 days after the last dose of pembrolizumab, respectively. One case of mortality (0.3%) was reported by all sources as being due to a treatment-related AE, which was reported as being thyroiditis (Grade 3 with hyperthyroidism followed by hypothyroidism), immune-mediated myositis, myocarditis, hepatitis, and pneumonia, approximately 20 days after pembrolizumab had been initiated in the CS (page 77), and as being due to myositis in the Balar *et al*. (2017).[12]

Adverse events of special interest

AEs of special interest were reported as being present in 22.7% of patients in the CS/CSR[15], with 8.6% patients experiencing Grade 3 or higher AEs of special interest, and not reported in the Balar et al. (2017).[12] The most common AEs of special interest were reported in the CS/CSR[15] as being hypothyroidism (10.8%), pneumonitis (3.2%), hyperthyroidism (2.7%), colitis (2.4%), severe skin reactions (1.9%), adrenal insufficiency (1.6%), hepatitis (1.1%), type 1 diabetes (1.1%) and thyroiditis (0.8%).

Health-related quality of life

Patient reported outcomes were administered by trained site personnel and completed electronically by subjects prior to all other study procedures in the following order: European Quality of Life Scale-5 Dimensions(EQ-5D) first then European Organisation for Research and Treatment Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30) (CS page 31). Patient Reported Outcomes (PROs) were assessed using the full analysis set (n=367), as three patients had missing PRO data. The EQ-5D questionnaire was administered at treatment cycle 1,2,3,4 and every two cycles thereafter up to a year or end of treatment, which every occurred first as well as at discontinuation visit and the 30-day post treatment discontinuation follow-up visit (CS, page 95). Compliance rates for EQ-5D were 92% at baseline and over 87% at week 9 (CS, page 44). Both EQ-5D Visual Analogue Scale (VAS) and utility scores were stable over time with results suggesting that HRQoL was maintained within this population. The CS only presents utilities from the regression analysis used within the health economic model (see Section 5.2.8). Table 8, from the CSR, shows the summary of change from baseline in EQ-5D utility score by time point. It suggests that, as suggested previously, the benefits of pembrolizumab take time to accrue, and that patients having a higher quality of life at baseline are more likely to benefit.

Table 8: Summary of change from baseline in EQ-5D utility score (Using European Algorithm) by time point (reproduced from Table 14.2-26, page 268 CSR)

Treatment	N	Baseline mean (SD)	Time point mean (SD)	Change from baseline at time point				
				Mean (SD)	Q1	Median	Q3	95%CI
Week 3								
Pembrolizumab	301	0.70 (0.24)	0.69 (0.26)	-0.00 (0.19)	-0.09	0.00	0.06	(-0.03, 0.02)
Week 6								
Pembrolizumab	267	0.70 (0.24)	0.67 (0.27)	-0.03 (0.22)	-0.14	0.00	0.03	(-0.06, -0.00)
Week 9								
Pembrolizumab	247	0.71 (0.25)	0.70 (0.28)	-0.01 (0.22)	-0.09	0.00	0.08	(-0.04, 0.01)
Week 15								
Pembrolizumab	193	0.73 (0.25)	0.75 (0.25)	0.02 (0.23)	-0.09	0.00	0.19	(-0.01, 0.05)
Week 21								
Pembrolizumab	151	0.75 (0.25)	0.77 (0.23)	0.02 (0.25)	-0.09	0.00	0.21	(-0.02, 0.06)
Week 27								
Pembrolizumab	120	0.75 (0.24)	0.77 (0.23)	0.02 (0.24)	-0.08	0.00	0.21	(-0.02, 0.06)

SD=standard deviation; CI=confidence interval; Q1=lower quartile; Q3=upper quartile

Subgroups

In the NICE final scope, subgroups based on cancer histology and biological markers (PD-L1) were to be considered if the evidence allowed. Two subgroups were considered in the CS: PD-L1 CPS ≥ 1% and PD-L1 CPS ≥ 10%.

Overall survival

For patients with PD-L1 CPS ≥1%, the median OS was [redacted] months. For patients with PD-L1 CPS ≥10%, [redacted] OS for PD-L1 ≥1% or ≥ 10% is shown below in Table 9.

Table 9: Summary of overall survival in PD-L1 CPs ≥1% or ≥10% patients (reproduced from Table 16, page 46 CS)

Treatment	N	Number of events	Person-months	Event rate/ 100 person-months (%)	Median OS† (months) (95%CI)	OS Probability at 6 Months in %† (95% CI)	OS Probability at 12 Months in %† (95% CI)
Pembrolizumab, PD-L1 CPS ≥ 1%	282	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab, PD-L1 CPS ≥ 10%¶	80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab, PD-L1 CPS ≥ 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

¶*Data reported from the efficacy validation cohort (n=80) as per statistical analysis plan; † From product-limit (Kaplan-Meier) method for censored data.; Database Cut-off Date: 09MAR2017*

CI=confidence interval

Progression-free Survival

For patients with PD-L1 CPS ≥ 1% or ≥ 10% the median PFS was [redacted] months and [redacted] months [redacted] respectively. PFS for PD-L1 ≥1% or ≥10% is shown below in Table 10.

Table 10: Summary of progression-free survival based on RECIST 1.1 per Central Radiology Assessment in PD-L1 CPs ≥1% or ≥10% patients (reproduced from Table 17, page 47 CS)

Treatment	N	Number of events	Person-months	Event rate/ 100 person-months	Median PFS† (months) (95%CI)	PFS Probability at 6 Months in %† (95% CI)	PFS Probability at 12 Months in %† (95% CI)
Pembrolizumab, PD-L1 CPS ≥1%	282	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab, PD-L1 CPS ≥ 10% (Validation cohort)¶	80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab, PD-L1 CPS ≥ 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

¶Data reported from the efficacy validation cohort (n=80) as per statistical analysis plan
Progression-free survival is defined as time from the first dose to disease progression, or death, whichever occurs first. Time to scheduled tumour assessment visit rather than the actual tumour assessment visit is used in the analysis. Patients without post-baseline tumour assessment are censored at time of the first dose.
† From product-limit (Kaplan-Meier) method for censored data.
Database Cut-off Date: 09MAR2017

CI=confidence interval

Objective response rate

Table 11 and Table 12 show the ORR for the PD-L1 ≥ 1% and ≥ 10% subgroups, respectively.

Table 11: Summary of best overall response with confirmation based on RECIST 1.1 per Central Radiology Assessment subjects with PD-L1 CPS >= 1% (reproduced from Table 11, page 40 CS)

Response Evaluation	Pembrolizumab (N=282)		
	n	%	95% CI†
Complete Response (CR)	24	8.5	(5.5, 12.4)
Partial Response (PR)	65	24.1	(19.2, 29.5)
Objective Response (CR+PR)	**92**	**32.6**	**(27.2, 38.4)**
Stable Disease (SD)	57	20.2	(15.7, 25.4)
Disease Control (CR+PR+SD)	**149**	**52.8**	**(46.8, 58.8)**
Progressive Disease (PD)	108	38.3	(32.6, 44.2)
Non-evaluable (NE)	5	1.8	(0.6, 4.1)
No Assessment	20	7.1	(4.4, 10.7)

Confirmed responses are included.
† Based on binomial exact confidence interval method.
Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.
No Assessment: subject had no post-baseline imaging

CI=confidence interval

Table 12: Summary of best overall response with confirmation based on RECIST 1.1 per Central Radiology Assessment subjects with PD-L1 CPS >= 10% efficacy validation population (reproduced from Table 12, page 41 CS)

Response Evaluation	Pembrolizumab (N=80)		
	n	%	95% CI†
Complete Response (CR)	14	17.5	(9.9, 27.6)
Partial Response (PR)	27	33.8	(23.6, 45.2)
Objective Response (CR+PR)	**41**	**51.3**	**(39.8, 62.6)**
Stable Disease (SD)	15	18.8	(10.9, 29.0)
Disease Control (CR+PR+SD)	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)	19	23.8	(14.9, 34.6)
Non-evaluable (NE)	[redacted]	[redacted]	[redacted]
No Assessment			

Confirmed responses are included.
† Based on binomial exact confidence interval method.
Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.
No Assessment: subject had no post-baseline imaging

CI=confidence interval

4.3 Critique of trials identified and included in the indirect comparison

Four studies of carboplatin plus gemcitabine were presented in the CS for inclusion in the company's indirect comparison (page 50). The ERG is not aware of any additional studies of carboplatin plus gemcitabine of relevance to the decision problem. Details of the study characteristics of the four included studies are presented in Table 13 and results in Table 14.

Only De Santis (2012)[16] was an RCT; the other studies adopted a cohort design. Carles (Spain)[17], De Santis (European)[16] and Linardou (Greece)[18] were multicentre studies while the Bamias study[19] took place in a single centre in Greece. The number of patients in the studies ranged from 17[17] to 119[16], where 119 refers to the carboplatin plus gemcitabine arm in De Santis (2012).[16]

With regard to the inclusion of cisplatin unsuitable populations, only De Santis (2012)[16] mentions this explicitly. Bamias (2007)[19] mentions patients being unfit for cisplatin in the title of the publication but this is not part of the stated inclusion criteria, although the inclusion criteria state that eligibility was based on patients having at least one of: poor performance status (ECOC ≥2), impaired renal function, or other comorbidities that preclude cisplatin administration. Carles (2000)[17] makes no mention of patients being unfit for cisplatin, but does state that patients had impaired renal function. Linardou (2004)[18] mentions in the title of the paper that treatment was for elderly patients and those unfit for cisplatin-based chemotherapy, although this is not part of the stated inclusion criteria.

Performance status was measured differently in the studies, with two using the ECOG scale,[18, 19] one using the WHO scale[16] and one using the Karnofsky scale,[17] making it difficult to draw comparisons between the

studies. Bamias (2007)[19] combined ECOG 2-3 and Linardou (2004)[18] had only 13 patients (23%) with ECOG 2.

Three studies[16-18] administered a gemcitabine dosage of 1,000mg/m^2, while one study[19] used a dosage of 1,250mg/m^2. With regard to carboplatin, three studies[17-19] used the Calvert formula to determine dosage, while DeSantis[16] used an alternative method. Administration of chemotherapy was every two weeks for at least eight cycles[19], every 21 days for six cycles,[17, 18] gemcitabine every three weeks and carboplatin every four weeks.[16] The median number of cycles ranged from four[16, 17] to six.[18, 19] Only one study[16] included a comparator arm, consisting of methotrexate, carboplatin and vinblastine.

The percentage of patients who were male in the studies ranged from 76% to 86%. Median age ranged from 69 to 75.5 years. Metastases were not reported in the same way, again making comparisons difficult. The percentage of patients with visceral ranged from 43% to 46.2%.

Outcomes of relevance to this appraisal reported in the studies included: response rate and OS for all four studies and PFS in all but one of the studies.[17] Median OS ranged from 7.2 months (95% confidence interval (CI): 5.9-8.5 months) to 10 months (95% CI NR) (see Table 14). PFS ranged from 4.4 months (CI: 1.03–7.75 months) to 5.8 months (95% CI NR). Response rates ranged from 24% (95% CI: 11%–41%) to 56% (95% CI: 31%-81%) (see Table 14).

It should be noted that caution should be used in combining the carboplatin plus gemcitabine studies due to considerable heterogeneity with regard to patients and dosage and administration of gemcitabine and carboplatin.

Table 13: Study characteristics of carboplatin plus gemcitabine studies

Study, country; Study design	Number of patients; median age (range); % male	Carboplatin/gemcitabine dosage	Inclusion criteria	Median follow up	Performance status	Visceral and liver metastases
Bamias 2007, Greece; cohort study[19]	N=34; 75.5 (57–84); 82%	Gemcitabine was given at a dose of 1,250 mg/m^2, followed by carboplatin at an area under the curve of 2.5, according to the Calvert formula; every 2 weeks for at least 8 cycles (unless disease progressed or toxicity was unacceptable) Median number of courses was 6 (range 1–17).	Unresectable (cT 4b, N2, N3), recurrent or metastatic urothelial, transitional cell cancer. At least 1 of the following features: poor performance status (ECOG ≥ 2), impaired renal function (calculated creatinine clearance < 50 ml/min) or other comorbidities precluding cisplatin administration, such as impaired cardiac function, pre-existing grade 2 neuropathy and any degree of hearing loss	8 months	ECOG 0-1: 11 (32%) ECOG 2-3: 23 (68%)	Liver: not reported Visceral: 15 (44%)
Carles 2000, Spain; cohort study[17]	N=17; 69 (54-78); 76%	Carboplatin dose adjustment for an area under the concentration curve of 5 mg/dl per minute by the application of the Calvert formula on day 1 and every 21 days and gemcitabine 1,000 mg/m^2 on days 1 and 8 (if absolute granulocyte count 11,500/mm^3,	patients with T4bN0M0 or Tx N1–3 M0–1 or relapsed histologically diagnosed urothelial carcinoma who had not been treated with any chemotherapy previously, age below 80 years, Karnofsky performance status ≥50%, normal cardiovascular and liver function, creatinine	unclear	Karnofsky scale: 100% 2 (12%) 90% 1 (6%) 80% 7 (41%) 70% 6 (35%) 50% 1 (6%)	Metastatic disease: n=15(88%) Liver: n=2 (12%)

Study, country; Study design	Number of patients; median age (range); % male	Carboplatin/gemcitabine dosage	Inclusion criteria	Median follow up	Performance status	Visceral and liver metastases
		platelets 1100/mm^3 and no mucositis; on day 8, 75% full dose administered if absolute granulocyte count 1,000-1,500/mm^3 or platelets 75,000-99,000/mm^3). If progressive disease, treatment discontinued after 6 courses. Median number of courses was 4 (range 1-7).	clearance between 20 and 55 ml/min and at least one bi-dimensionally measurable tumour lesion.			
De Santis 2012; 29 centres European; RCT[16]	Total n=238; 119 allocated to G/C; 70 (36-87); 76%	Gemcitabine 1,000 mg/m^2 over 30 minutes IV on days 1 and 8, followed by carboplatin on day 1, every 3 weeks (until disease progression or unacceptable toxicity). Carboplatin was dosed in milligrams (4.5 x [GFR + 25]) and given over 1 hour IV on day 1 in both treatment arms, once every 4 weeks. Median number of cycles was 4 (range: 1-23).	Patients with histologically proven UC of the urinary tract (including renal pelvis, ureter, and urinary bladder), unresected lymph nodes (N+), distant metastases (M1, stage IV), or unresectable primary bladder cancer (T3-4) with measurable disease as defined by RECIST were included. All patients had to be ineligible (unfit) for cisplatin-based chemotherapy, defined by a WHO PS of 2 and/or	4.5 years	WHO PS 0 20 (16.8%) 1 46 (38.7%) 2 53 (44.5%)	Liver: 20 (16.8%) Visceral: 55 (46.2%)

Study, country; Study design	Number of patients; median age (range); % male	Carboplatin/gemcitabine dosage	Inclusion criteria	Median follow up	Performance status	Visceral and liver metastases
			impaired renal function (GFR >30 but <60 mL/min).			
Linardou 2004, Greece, multi-centre cohort study[18]	N=56; 75 (54-86); 86%	Gemcitabine 1000 mg/m^2 was administered IV on days 1 and 8, and carboplatin at AUC 4, according to the Calvert formula, was administered on day 1. Treatment was repeated every 21 days. Six cycles administered, unless disease progression or unacceptable toxicity. Median number of cycles was 6 (range: 1-7)	Patients with histologically or cytologically confirmed inoperable or metastatic bladder cancer with two-dimensional measurable disease were eligible. Patients had to have at least one of the following features: ECOG performance status of 3, GFR of less than 50 mL/min, or age older than 75 years	13.5 months (range: 0.2-21.3)	ECOG 0 8 (14%) 1 22 (39%) 2 13 (23%) 3 13 (23%)	Liver: 10 (18%) Visceral: 24 (43%)

Table 14: Results for carboplatin plus gemcitabine studies

Study	Response rate (95% CI)	Median PFS (95%CI) in months	Median OS (95%CI) in months
Bamias (2007)[19]	24% (11% - 41%)	4.4 (1.03 - 7.75)	9.8 (4.7 - 14.9)
Carles (2000)[17]	56% (31% - 81%)	NR	10 (NR)
De Santis (2012)[16]	41.2% (36.1% confirmed) (NR)	5.8 (CI NR)	9.3 (NR)
Linardou (2004)[18]	36% (23.4% - 49.6%)	Time to progression: 4.8 (3.54 - 6.03)	7.2 (5.9 - 8.5)

CI=confidence interval; NR= not reported; OS=overall survival; PFS=progression-free survival

Quality assessment of carboplatin plus gemcitabine studies

Table 15 compares the quality assessment undertaken by the company and ERG for the gemcitabine carboplatin studies. The ERG assessed the De Santis (2012)[16] trial using the Cochrane Risk of Bias scale (Table 16), since it is an RCT, and therefore a direct comparison between categories on the quality assessment instrument undertaken in the CS and by the ERG is not possible. The company justified their use of the NOS for the De Santis (2012)[16] trial on the basis that only one arm was relevant for the comparison, and therefore the relevant arm was treated as a cohort. However the ERG is of the opinion that the design of the overall trial has a bearing on the way the study was conducted in each arm (for example, the way the population was selected), and therefore the De Santis (2012)[16] trial should be assessed as an RCT using the Cochrane Risk of Bias scale. A quality assessment for the De Santis study was provided in the company's clarification response; however, whereas the CS reported the De Santis (2012)[16] study as being at low risk of bias in the clarification response, the ERG judged this study to be at moderate risk of bias, due to a lack of clarity around participant blinding, unblinded outcome assessment, and one outcome (response rates) being mentioned in the methods but not reported in the results.

All remaining comparator studies were graded on the NOS by both the CS (page 219) and the ERG, and in all cases, the ERG gave a lower quality rating than that in the CS (see Table 15). The Bamias (2007)[19] study was rated as being 7 in the CS and 3 by the ERG. The main differences between the CS and the ERG ratings are in terms of the following criteria:

- The representativeness of the exposed cohort (which the ERG rated as somewhat representative, due to a lack of clarity regarding the cisplatin eligibility of included patients; although this does not affect the rating);
- Selection of the non-exposed cohort (which the ERG rated as NA, due to there not being a non-exposed cohort);
- Assessment of outcome (which the ERG rated as unclear/not reported, due to lack of detail);

- The length of follow-up being sufficient for outcomes to occur (which the ERG rated as 'no', due to insufficient follow-up duration for survival outcomes);
- Adequacy of follow up of cohorts (which the ERG rated as unclear/not reported, due to lack of detail).

The Carles (2000) study[17] was rated as being 6 in the CS and 4 by the ERG. The main differences between the CS and ERG rating are in terms of the following criteria:

- Representativeness of the exposed cohort (which the ERG rated as somewhat representative, due to a lack of clarity regarding the cisplatin eligibility of included patients; although this does not affect the rating);
- Selection of the non-exposed cohort (which the ERG rated as NA, due to there not being a non-exposed cohort);
- Assessment of outcome (which the ERG rated as unclear/not reported, due to lack of detail).

The Linardou (2004)[18] study was rated as being 7 in the CS and 4 by the ERG. The main differences between the CS and ERG rating are in terms of the following criteria:

- Representativeness of the exposed cohort (which the ERG rated as somewhat representative, due to a lack of clarity regarding the cisplatin eligibility of included patients; although this does not affect the rating);
- Selection of the non-exposed cohort (which the ERG rated as NA, due to there not being a non-exposed cohort)
- Assessment of outcome (which the ERG rated as unclear/not reported, due to lack of detail);
- Length of follow-up being sufficient for outcomes to occur (which the ERG rated as 'no', due to insufficient follow-up duration for survival outcomes).

Table 15: Company and ERG quality assessment for comparator studies (adapted from Table 80, page 219 CS)

	Bamias (2007)[19]		**Carles (2000)[17]**		**De Santis (2012)[16]**		**Linardou (2004)[18]**	
	Company quality assessment	**ERG quality assessment**	**Company quality assessment**	**ERG quality assessment**	**Company quality assessment**	**ERG quality assessment**	**Company quality assessment**	**ERG quality assessment**
Selection						See Table 16		
1. Representativeness of the exposed cohort	Truly representative of the average first-line advanced urothelial cancer in the community	Somewhat representative of the average first-line advanced urothelial cancer in the community	Truly representative of the average first-line advanced bladder cancer in the community	Somewhat representative of the average first-line advanced urothelial cancer in the community	Truly representative of the average first-line advanced urothelial cancer in the community	-	Truly representative of the average first-line advanced bladder cancer in the community	Somewhat representative of the average first-line advanced urothelial cancer in the community
2. Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	NA. There is no non-exposed cohort.	Drawn from the same community as the exposed cohort	NA. There is no non-exposed cohort.	Drawn from the same community as the exposed cohort	-	Drawn from the same community as the exposed cohort	NA. There is no non-exposed cohort.
3. Ascertainment of exposure	Secure record	Secure record	Secure record	Secure record	Secure record	-	Secure record	Secure record
4. Demonstration that outcome of interest was not present at start of study	Yes	Yes	Yes	Yes	Yes	-	Yes	Yes

	Bamias (2007)[19]		Carles (2000)[17]		De Santis (2012)[16]		Linardou (2004)[18]	
Comparability								
1. Comparability of cohorts on the basis of the design or analysis	NA; single-arm study	NA; single-arm study	NA; single-arm study	NA; single-arm study	Study controls for performance score, renal function, and institution	-	NA; single-arm study	NA; single-arm study
Outcome								
1. Assessment of outcome	Independent assessment	Unclear/not reported	Independent assessment	Unclear/not reported	Independent assessment	-	Independent assessment	Unclear/not reported
2. Was follow-up long enough for outcomes to occur	Yes; median follow-up of 8 months	No	No description	No	Yes; median follow-up of 4.5 years	-	Yes; median follow-up of 13.5 months	No
3. Adequacy of follow up of cohorts	Complete follow up - all subjects accounted for	Unclear/not reported	Subjects lost to follow up unlikely to introduce bias - small number lost - > 1/17	Subjects lost to follow up unlikely to introduce bias - small number lost - > 1/17	Complete follow up - all subjects accounted for	-	Subjects lost to follow up unlikely to introduce bias - small number lost - > 1/56	Subjects lost to follow up unlikely to introduce bias - small number lost - > 1/56
Stars total	**7**	**3**	**6**	**4**	**9**	**NA**	**7**	**4**

Table 16: ERG quality assessment of De Santis (2012)[16] using the Cochrane Risk of Bias scale[20]

Domain	Company assessment (in clarification response) (yes/no/not clear/NA)	ERG judgement (yes/no/not clear/NA)
Selection bias		
Adequate sequence generation	Low risk (Sequence was assigned using the minimization technique)	Low risk (minimisation technique, stratified for performance status, renal function and institution)
Allocation concealment	Low risk (Assignment was performed at a central location)	Low risk (randomised at the EORTC headquarters)
Performance bias		
Blinding of participants (OS)	Low risk (Blinding was not mentioned, however risk of performance is considered low for OS)	Moderate risk (blinding of participants unclear)
Blinding of participants (PFS)	Low risk (Blinding was not mentioned, however risk of performance is considered low for PFS)	Moderate risk (blinding of participants unclear)
Detection bias		
Blinding of outcome assessment	Low risk (Blinding was not mentioned, however risk of detection is considered low for OS and PFS outcomes)	High risk (evaluated by the study co-ordinators)
Attrition bias		
Incomplete outcome assessment (OS and PFS)	Low risk (No patients were lost to follow-up [one patient in the GC arm refused treatment, and one in the M-CAVI arm died before starting treatment])	Low risk (no unexpected imbalances in dropouts between groups)
Reporting bias		
Selective reporting	Low risk (OS, PFS, response, and major safety outcome were reported as expected for an oncology trial)	Moderate risk (Methods mention measuring response rates, but not reported in Results)
Other bias		
Other sources of bias	Low risk (No other sources of potential bias were identified)	Low risk (No other sources of potential bias were identified)
Summary rating	**Low risk of bias**	**Moderate risk of bias**

4.4 Summary and critique of the population adjustment approach

4.4.1 Choice of the method

In the absence of a connected network between pembrolizumab and carboplatin plus gemcitabine group, the company conducted unanchored indirect comparisons using the simulated treatment comparison (STC) [21] approach. STC is an outcome regression approach whereby a regression model is fitted using individual patient-level data (IPD) on pembrolizumab from KEYNOTE-052 (which the company have access to), then the fitted regression model is used to predict the treatment effect in a simulated pembrolizumab arm for a population as observed in each of the carboplatin plus gemcitabine study according to the distribution of the baseline characteristics in the chosen carboplatin plus gemcitabine study. STCs were conducted for both PFS and OS using the "all comers" population from KEYNOTE-052 (n=370) and two subgroup populations (the PD-L1 ≥1% and the PD-L1 ≥10% population).

The CS provides justification on the use of STC rather than the naïve comparison or matching-adjusted indirect comparison (MAIC) (CS page 48 and response to clarification question A21). The company states that one approach is not necessarily favoured over the other between STC and MAIC; and STC with bootstrap as implemented in this submission has the benefit of allowing cross-validation and assessment of the model performance.

The ERG agrees that the naïve indirect comparison may be prone to biases due to cross-study differences, but there may still be some merit of conducting such analysis if the distribution of the baseline characteristic in KEYNOTE-052 is similar to the carboplatin plus gemcitabine studies. The ERG disagrees with the company's choice of STC instead of MAIC. The ERG has concerns that the company chose a Cox proportional hazards model when adjusting for cross-study differences, but then used a fractional polynomial model to obtain the indirect comparison estimate. However, it is not clear what the impact of performing the adjustment and indirect comparison on a different scale might be, as noted in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[22]

4.4.2 Covariates included in STC

The company specified five prognostic factors to be adjusted in STC: poor ECOG performance (ECOG ≥2), renal failure, presence of liver metastases or visceral metastases, haemoglobin levels, and primary tumour site (upper or lower). CS states that the choices of prognostic factors were determined by reviewing the relevant literature, and were internally validated with clinicians (CS, page 55). The CS also states that these chosen prognostic factors were supported by the recent atezolizumab submission[23] and clinical discussion at the NICE Appraisal Committee meeting. The CS reports that haemoglobin levels were not considered because only one comparator study (Bamias (2007)[19]) reported this factor. The proportion of patients with prognostic factors in included studies is presented in Table 17.

The unanchored indirect comparison using STC relies on strong assumptions that all effect modifiers and prognostic variables are adjusted in the regression model.[22] The ERG believes that it is unlikely that all effect modifiers and prognostic factors were included in the STC, which may have an impact on the validity of the unanchored estimator. The ERG notes that age and gender were included in the adjustment approach used in the atezolizumab submission[23], but not in the company's STC. Two additional columns which report information for age and gender in the included studies are shown in Table 17 to highlight the cross-study differences.

Table 17: Proportion of patients with prognostic factors in included studies (adapted from Table 24, page 57 CS)

			Renal Failure		Prop. with metastasis		Primary tumour site			Age, median (range) in years	Gender
Study ID	**Treatment**	**ECOG ≥2**	**Measure (mL/min)**	**Prop. of patients**	**Liver**	**Visceral**	**Upper tract**	**Lower tract**	**Unknown**		**Male**
Bamias (2007)[19]	Carboplatin+ gemcitabine	0.68	CrCl	0.69	--	0.44	0.12	0.88	--	75.5 (57-84)	0.82
Carles (2000)[17]	Carboplatin+ gemcitabine	0.41	CrCl	1.0	0.12	0.41	--	--	--	69 (54-78)	0.76
De Santis (2012)[16]	Carboplatin+ gemcitabine	0.45	CrCl	0.82	0.21	0.51	0.20	0.80	--	70 (36-87)	0.76
Linardou (2004)[18]	Carboplatin+ gemcitabine	0.46	GFR	--	0.18	0.43	--	--	--	75 (54-86)	0.86
KEYNOTE-052[1]	Pembrolizumab	0.43	CrCl<60 mL/min	0.59	0.21	0.85	0.19	0.81	<0.01	74 (34-94)	0.77

ECOG = Eastern Cooperative Oncology Group; CrCl = creatinine clearance; Visceral metastasis includes liver, lung, pelvic mass, suprarenal, peritoneal while excluding lymph node, bone, and those labelled "others".

4.4.3 Model selection in STC

The company conducted a non-standard STC by incorporating bootstrapping to produce estimates of variability. The company claims that the bootstrapping procedure maximises the full use of the IPD. A bootstrap sample is a random sample with replacement generated from the original IPD in KEYNOTE-052 study. The company states that on average about 1/3 of the patients were not included in each bootstrap sample and called these patients out-of-bag (OOB).

The Cox proportional hazards model was used to develop the regression model. Four competing models were fitted to bootstrap samples, where one model had the full set of covariates containing ECOG ≥2, renal failure, presence of liver metastases or visceral metastases, and primary tumour site (upper or lower). Three other models had the full set of covariates plus one interaction variable comprised of ECOG performance status and either liver metastasis, visceral metastasis or renal function.

Model selection was based on the OOB predictive performance. The company defined the sum of Akaike Information Criterions (AICs) to be the sum of the differences between the observed KM survival estimates minus the predicted OOB survival estimates at every failure time in the original IPD KM curve. The model with the lowest sum of AICs would be chosen as the final model. If all models provide similar AICs, then the simplest model would be chosen. The best regression model for both PFS and OS was the simplest model with the full set of five prognostic factors, i.e., ECOG ≥2, liver metastasis, poor renal function, visceral metastasis and upper urinary tract. The estimated coefficients can be found in the CS Table 25 and 32.

The ERG notes that the company's definition of AIC is not a standard one used in model selection in general.

4.4.4 Prediction of outcomes in STC

The company simulated a large number of hypothetical individuals based on the reported marginal distribution of the covariates of interest and the correlation from KEYNOTE-052 study. When a covariate value was missing, a random sample from a uniform distribution with boundaries defined by the range of reported values across the included studies. The company also generated the predicted log-hazards. The mean of the predicted log-hazard and the variance of the log-hazard from bootstrap samples were used in the fractional polynomial models in obtaining the estimate for the indirect comparisons

The ERG agrees that the lack of IPD limited the approaches which could be used to impute the missing covariates. The ERG considers that the company's imputation approach is appropriate, although the choice of a uniform distribution may be naïve.

The population adjusted pembrolizumab OS and PFS curves representing the population as in each of the carboplatin plus gemcitabine studies are presented in Figure 3 and Figure 4, respectively. The predicted pembrolizumab PFS and OS curves were all above the observed PFS and OS curves in KEYNOTE-052, which suggests that the patients from KEYNOTE-052 were less fit or frailer compared with patients enrolled within the four carboplatin plus gemcitabine studies. The point estimate and 95% CI of the prediction models for PFS and OS are presented in Table 18.

The ERG has concerns regarding the validity of the company's population adjustment results. The ERG discusses this using De Santis (2012)[16] (no imputation) and Linardou (2004)[18] (imputation required) as examples to illustrate these concerns.

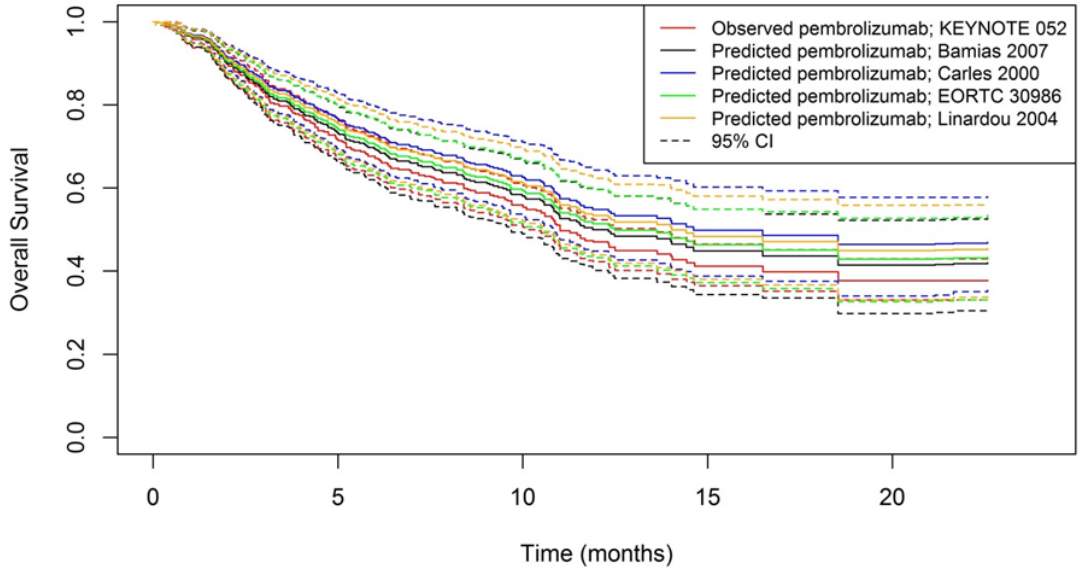
When comparing the patients' baseline characteristic between De Santis (2012)[16] and KEYNOTE-052, KEYNOTE-052 study has a lower proportion of patients with ECOG ≥2 status, with renal failure and with upper urinary tract; the same proportion of patients with liver metastasis; but a higher proportion with visceral metastasis (see Table 17). Given that the estimate for the coefficient of visceral metastasis was 0.02 for OS in Table 18, this shows that the effect on OS of visceral metastasis is very small. This was also confirmed by the ERG's clinical advisors that visceral metastasis is less important comparing to ECOG ≥2 status and liver metastasis when determining OS.

Overall, The ERG believes that here is no indication that the patients in the KEYNOTE-052 study were less fit or frailer than the patients in De Santis (2012).[16] However, the predicted pembrolizumab median in De Santis (2012)[16] was 12.45 months (clarification response Figure 17, question A37) which is 1.45 months more than the median in the observed pembrolizumab study. The ERG believes that this result lacks validity.

Linardou (2004)[18] only reported ECOG ≥2 status, liver metastasis and visceral metastasis. Hence, imputation for the missing covariates was conducted by the company as described previously. When comparing the patients' baseline characteristic between Linardou (2004)[18] and KEYNOTE-052, the KEYNOTE-052 study has a lower proportion of patients with ECOG ≥2 status; but a higher proportion of patients with visceral metastasis and liver metastasis (see Table 17). As discussed before, the difference in the proportions with visceral metastasis would have a very small impact on OS. However, the predicted pembrolizumab median is 14 months (see clarification response Figure 18, question A37)

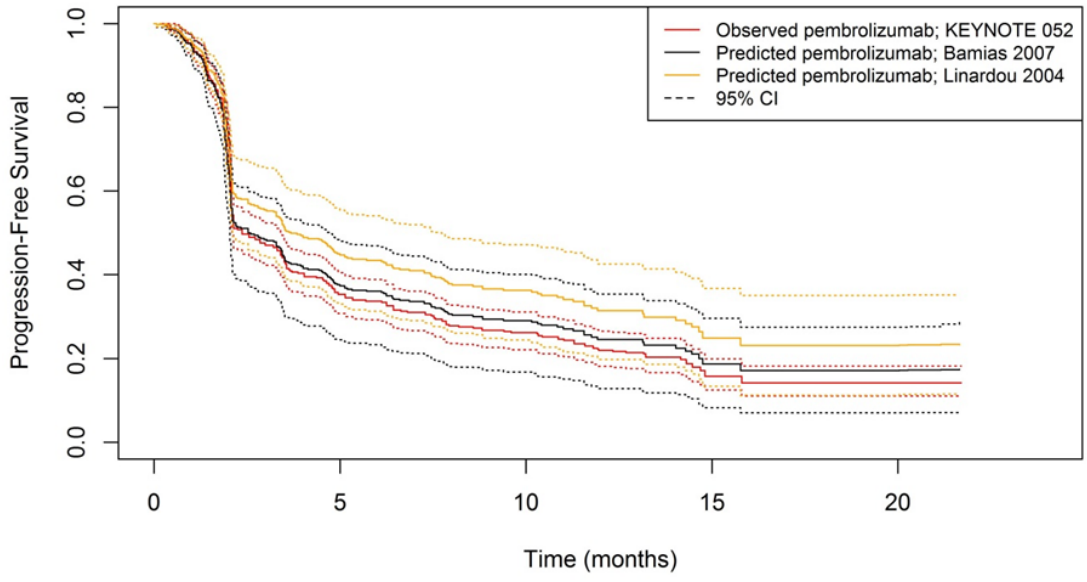
which is 3 months more than the median in the observed pembrolizumab study. The ERG believes that this result lacks validity.

Figure 3: Observed overall survival with pembrolizumab along with adjusted pembrolizumab curves corresponding to the population in each of the carboplatin plus gemcitabine studies (reproduced from Figure 11, clarification response A34)



Note: EORCT 30986 is De Santis (2012)

Figure 4: Observed progression-free survival with pembrolizumab along with adjusted pembrolizumab curves corresponding to the population in each of the carboplatin plus gemcitabine studies (reproduced from Figure 11, clarification response A34)



Note: EORCT 30986 is De Santis (2012)

Table 18: Estimates for prediction models parameters (reproduced from Table 25 and Table 32, pages 59 and 66 CS)

Parameters	All comers PFS (95%CI)	All comers OS (95%CI)
ECOG ≥2 (ECOG)	0.31 (0.02, 0.63)	0.49 (0.11, 0.92)
Liver metastasis	0.39 (0.08, 0.72)	0.59 (0.24, 0.94)
Poor renal function	0.30 (0.03, 0.63)	0.19 (-0.17, 0.62)
Visceral metastasis	0.11 (-0.22, 0.48)	0.02 (-0.37, 0.39)
Upper urinary tract	0.70 (0.31, 1.11)	0.66 (0.17, 1.28)

PFS=progression-free survival; OS=overall survival; CI=confidence interval

4.5 Summary and critique of the indirect treatment comparison

Using the population adjustment approach, STC, creates a simulated pembrolizumab arm for each of the carboplatin plus gemcitabine study. The relative treatment effects were then synthesised using a traditional Bayesian network meta-analysis (NMA) for both OS and PFS. The indirect treatment comparison was performed for the "all comers" population and two subgroups (PD-L1≥1% and PD-L1≥10%) population.

Two modelling approaches were used in the NMA: (i) assuming a constant hazard ratio using standard meta-analysis models[17], and (ii) modelling the time-varying hazard ratio with fractional polynomial models.[24] The company used a fixed effect model for PFS given the reason that there were too few studies to reliably estimate the between-study heterogeneity. A random effects model was used for OS because sufficient studies were available.

The ERG considers the company's NMA approach to be appropriate. The ERG disagrees with the choice of a fixed effect model for PFS; and notes that when heterogeneity is expected, a random effects model with an informative prior should be explored in the analysis with limited studies.

4.5.1 Data used

For the meta-analysis based on constant hazard ratios, the company reconstructed IPD by firstly digitising the published KM curves for the carboplatin plus gemcitabine studies and then by applying the algorithm by Guyot *et al.* (2012).[25] The median of the reconstructed IPD for each of the comparator studies was reported in response to clarification (question A37). All the reconstructed IPD had similar median values as the observed data from the studies, except for Carles (2000)[17], where the median from the reconstructed data was approximately 1 month less than the observed median.

A constant hazard ratio was obtained using the reconstructed carboplatin plus gemcitabine IPD and population adjusted pembrolizumab for both PFS and OS. These constant hazard ratios were then synthesised using a standard meta-analysis.[26]

For the meta-analysis based on time-varying hazard ratios, the reconstructed IPD for the carboplatin plus gemcitabine studies were not used. Instead, a different algorithm[27] was used to obtain the data in the form of the number of events and number at risk at fixed intervals. For the pembrolizumab group, the mean and standard error of the log-hazard from the bootstrapping STC were used in the analysis.

The ERG considers the data used in the analyses to be appropriate, but notes that the poor quality of the reconstructed IPD in Carles (2000)[17] may have an impact on the results.

4.5.2 Fractional polynomial models

The fractional polynomial approach does not rely on the proportional hazards assumption, and is a flexible approach to model time-varying hazard ratios. Both Weibull and Gompertz models are special cases of fractional polynomial models. The company conducted both first order (equivalent to Weibull and Gompertz) and second order fractional polynomial functions with only positive values for the power used in the model (p1, p2={0,1}). In response to clarification question A33, the company also conducted additional analyses with negative values for p1 and p2. The deviance information criterion (DIC)[28] was used in model selection, where the smaller DIC indicates better fit.

4.5.3 Results

The ERG only presents the results for the all comers population here, because none of the carboplatin plus gemcitabine studies have data in the two subgroups (PD-L1≥1% and PD-L1≥10%); hence it is not appropriate to conduct indirect comparison in these two subgroup populations. The ERG notes that the company stated in response to clarification question B5 that "PD-L1 expression is not a reliable predictor of outcomes in the urothelial cancer population" and "any outcomes in the patients expressing PD-L1 should be interpreted with caution".

The results assuming constant hazard ratios for PFS and OS are presented in Tables 95 to 97 of the CS (page 237). For the all comers population, the estimated hazard ratio of pembrolizumab compared with carboplatin plus gemcitabine was 0.91 (95% credible interval (CrI): 0.66, 1.27) for PFS using a fixed effect model and 0.56 (95% CrI: 0.32, 1.04) for OS using a random effects model.

In the original submission, the second order fractional polynomial model with p1=p2=0 was chosen as the best fitting model for both PFS and OS. In response to clarification question A33, the company

conducted additional analyses including negative values for p1 and p2. Given the additional analyses, the best fitting model was p1=p2=-2 for both PFS and OS. The estimated hazard ratios and DIC values for the best fitting models from both original submission and clarification response are presented in Table 19. The ERG notes that the fractional polynomial with p1=p2=-2 was the overall best fitting model for both PFS and OS, and it provides less favourable results for pembrolizumab when compared with the chosen best fitting model in the original submission.

Table 19: Estimated hazard ratios of pembrolizumab versus carboplatin plus gemcitabine for OS and PFS; all comers (adapted from Table 1 and Table 2, clarification response A33)

	Original submission best fitting model for PFS; p1=p2=0 (DIC=226.6)	**Additional analyses best fitting model for PFS; p1=p2=-2 (DIC=162.4)**	**Original submission best fitting model for OS; p1=p2=0 (DIC=343.4)**	**Additional analyses best fitting model for OS; p1=p2=-2 (DIC=331.9)**
Time point (months)	HR (95%CrI)	HR (95%CrI)	HR (95%CrI)	HR (95%CrI)
3	1.14(0.81, 1.60)	1.39 (1.03, 1.89)	0.72(0.46, 1.20)	0.74 (0.47, 1.22)
6	1.03(0.74, 1.45)	0.90 (0.66, 1.22)	0.64(0.42, 1.08)	0.59 (0.38, 0.95)
12	0.75(0.48, 1.25)	0.73 (0.51, 1.05)	0.50(0.33, 0.84)	0.53 (0.34, 0.86)
15	0.65(0.36, 1.26)	0.71 (0.49, 1.03)	0.45(0.28, 0.77)	0.52 (0.33, 0.85)
21	0.50(0.21, 1.36)	0.68 (0.47, 1.00)	0.38(0.21, 0.71)	0.51 (0.33, 0.83)
24	0.45(0.16, 1.41)	0.68 (0.47, 1.00)	0.35(0.18, 0.70)	0.51 (0.33, 0.83)

HR=hazard ratio; CrI=credible interval; OS=overall survival; PFS=progression-free survival; DIC= deviance information criterion

The estimates of time-varying hazard ratios using the fractional polynomial with p1=p2=0 were projected onto the extrapolated pembrolizumab OS and PFS to extrapolate the long-term survival benefit of carboplatin plus gemcitabine in the economic model. However, the results from the overall best fitting model, the fractional polynomial with p1=p2=-2, were not used in the economic model. The ERG believes that the ICER would be higher using the fractional polynomial with p1=p2=-2 compared with power being p1=p2=0 because the better fitting model (p1=p2=-2) provides less favourable results for pembrolizumab; but notes that the exact impact of using this model upon the ICER is unknown.

4.6 Additional work on clinical effectiveness undertaken by the ERG

No studies of atezolizumab were included in the CS although this treatment was included in the decision problem. One published study of atezolizumab[29] was identified by the ERG, which was considered in the NICE appraisal of atezolizumab.[23] A brief summary of the study is presented below (Table 20 and Table 21). The study had two cohorts: Cohort 1 was cisplatin ineligible so this is of relevance to this appraisal. Cohort 2 had previous platinum-based chemotherapy. Rosenberg *et al*. (2016)[29] only reports the results for Cohort 2. The AC papers for the NICE atezolizumab appraisal contain data for the cisplatin ineligible population (Cohort 1). The Final Appraisal Determination issued by NICE suggested that the benefit of atezolizumab was too uncertain to recommend outside of the CDF.

Table 20: Study characteristics of the atezolizumab study[23, 29]

Study, country; study design	Number of patients; median age (range); % male	Atezolizumab dosage	Inclusion criteria	Median follow up	Performance status	Visceral and liver metastases
70 centres in North America and Europe; single-arm, 2 cohort, Phase II study	Total n= 310; Cohort 1 n=119; 73 (51-92), 80.7%	1200 mg IV infusion on day one of each 21 day cycle until disease progression	Historically or cytologically documented advanced or metastatic urothelial carcinoma of the bladder, renal pelvis, ureters or urethra; locally advanced bladder cancer must be inoperable; Availability of viable tumour specimens ; Life expectancy ≥12 weeks; Measurable disease as defined by RECIST v.1.1; Adequate haematologic and end-organ function (not defined); ECOG PS 0,1,2; No prior chemotherapy for urothelial cancer; 12 months treatment free from adjuvant/neoadjuvant chemotherapy ; Ineligible for cisplatin	15 month data cut off (median treatment duration 15 weeks (range 0-102 weeks)	ECOG 0 45 (37.8) 1 50 (42%) 2 24 (20.2%)	Visceral: 78 (65.5%) Liver: 25 (21%)

Table 21: Results for atezolizumab study[23]

Study, country; study design	Response rate (95% CI)	Median PFS (95%CI) in months	Median OS (95%CI) in months
70 centres in North America and Europe; single-arm, 2 cohorts, Phase II study	ORR 22.7% (15.52-31.27) Complete response 9.2%	2.7 (2.1-4.2)	15.9 (10.4, NE)

NE=not estimable; PFS=progression-free survival; OS=overall survival

4.7 Conclusions of the clinical effectiveness section

4.7.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence of pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable presented in the CS is based entirely on KEYNOTE-052, a Phase II, single-arm, open-label, non-randomised study. The ERG is content that all relevant studies (published and unpublished) of pembrolizumab have been included in the CS, including data from ongoing/planned studies. The ERG is confident that no published relevant comparator studies to pembrolizumab for this patient population are likely to have been missed. The ERG is also confident that no relevant studies of carboplatin plus gemcitabine for this patient population have been missed.

4.7.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is content that the relevant population and intervention have been included in the CS, that is, patients with locally advanced or metastatic urothelial cancer where cisplatin is unsuitable treated with pembrolizumab. However, only one relevant comparator was included (carboplatin plus gemcitabine) while atezolizumab and BSC have been excluded as comparators. The ERG agrees with the exclusion of atezolizumab and BSC (see Section 3.3 for details). All relevant outcomes were included in the CS. As the KEYNOTE-052 study is ongoing and only interim data were available.

Further issues identified relate to the choice of carboplatin plus gemcitabine studies. There is significant heterogeneity between the studies with regard to patients and dosage and administration of gemcitabine and carboplatin. In addition, most of the carboplatin plus gemcitabine studies are of poor quality. The De Santis (2012)[16] study appears to be the most appropriately suited study for comparing carboplatin plus gemcitabine and pembrolizumab in this study population.

As stated in the NICE final scope, subgroups based on cancer histology and biological markers (PD-L1) have been included in the form of two subgroup populations: PD-L1 CPS≥1% and PD-L1 CPS ≥ 10%. These categories were defined by the company based on the levels identified in the first 100

patients in the study. However, results in these two subgroups should be interpreted with caution, because PD-L1 expression is not a reliable predictor of outcomes in the urothelial cancer population as stated by the company in the response to clarification question B5.

4.7.3 Uncertainties surrounding the reliability of the clinical effectiveness

The main uncertainties in the clinical evidence are mainly concerned with the absence of any RCTs comparing pembrolizumab with carboplatin plus gemcitabine, atezolizumab or BSC. In addition, the data from KEYNOTE-052, reported in the CS are immature. The estimated completion date of the study is 21st June 2018 according to Clinical trials.gov (https://clinicaltrials.gov/ct2/show/NCT02335424).[16] The ongoing KEYNOTE-361 study is expected to provide some information regarding the comparison between pembrolizumab and carboplatin plus gemcitabine for the patient group relevant to this appraisal as one of the study arms includes this comparator. However, there is no requirement for participants to be cisplatin-ineligible, and thus the population of KEYNOTE-361 differs from the population in the NICE final scope. The study is currently recruiting and final results are expected on the 18th May 2020.

The ERG has concerns that population adjustment conducted by the company to balance the cross-study differences between KEYNOTE-052 and carboplatin plus gemcitabine studies lacks validity. The company's adjustments suggest that patients in KEYNOTE-052 were less fit or frailer compared to the patients in each of the carboplatin plus gemcitabine study. However, this is not supported by the reported summary of patient baseline characteristic in these studies.

5 COST EFFECTIVENESS

This chapter presents a review of evidence relating to the cost-effectiveness of pembrolizumab for the treatment of adults with advanced/unresectable or metastatic urothelial carcinoma, who have not received prior systematic chemotherapy and who are not eligible to receive cisplatin. Section 5.1 presents a critique of the company's systematic review of cost-effectiveness evidence. Section 5.2 provides a summary and critique of the company's submitted economic evaluation. Section 5.3 describes the analysis undertaken by the ERG for their base case, as well as a description of the additional sensitivity analyses undertaken by the ERG using the ERG base case model. Section 5.4 provides the conclusions of the cost-effectiveness section.

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Searches for economic studies

The company conducted a systematic literature review of published cost-effectiveness studies of pembrolizumab versus any other pharmacological treatments for the population of interest. Searches were originally conducted in August 2015; these were subsequently updated in August 2017.

MEDLINE, EMBASE, EconLit and the Cochrane Library were all searched from 1995 until 2016, although only studies from the last 10 years were eligible for inclusion in the company's review. In addition, reference lists were examined and manual checks were conducted of the proceedings of relevant conference series for the most recent two years.

The search strategy is reproduced in the CS Appendix G.1 and is broadly well-designed, although no citation is provided for the economic filter, with the result that the ERG is unable to verify whether it has been validated for sensitivity and specificity. Furthermore, the ERG notes some minor syntax errors in search strings in common with those seen in the searches for the clinical effectiveness review (see Section 4.1.1), e.g., the use of "tum?r" rather than "tumo?r".

5.1.2 Inclusion/ exclusion criteria

The inclusion criteria for the cost-effectiveness review are set out in the CS Appendix G, Table 107. The ERG notes that for the purpose of the literature searches, the population was expanded slightly from the NICE decision problem, in order to retrieve any studies comparing the interventions of interest in patients with advanced or metastatic urothelial cancer irrespective of therapy line. However, retrieved studies were only eligible for inclusion where it was possible to extract data relevant to the specific population of interest to this submission (i.e. those who had not received prior therapy).

5.1.3 Findings of the cost-effectiveness review

The economic searches were conducted alongside those for HRQoL and utility studies, and the CS reports that a total of 5,104 potentially relevant records were retrieved for screening, however none of the identified cost-effectiveness studies met the inclusion criteria for this review.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

As part of their submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®, together with a detailed description of the economic analysis.

5.2.1 Overview of model

The company's model takes the form of a state transition model, based on three states: (i) progression-free; (ii) progressed disease and (iii) death. The model adopts a weekly cycle length and a 20-year time horizon. The model assesses the cost-effectiveness of pembrolizumab versus a combination of carboplatin and gemcitabine for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable (see Section 5.2.4 for more details and critique of the model scope). The incremental health gains, costs and cost-effectiveness of pembrolizumab are evaluated from the perspective of the NHS and Personal Social Services (PSS). To estimate OS and PFS for the pembrolizumab group, data from the KEYNOTE-052 study were extrapolated using a piecewise approach combining KM data and parametric distributions (see Section 5.2.7). A simulated indirect treatment comparison was undertaken to estimate time-varying hazard ratios for OS and PFS of patients receiving carboplatin plus gemcitabine (see Section 4.5). The PFS and OS for carboplatin plus gemcitabine arm were modelled by applying the time-varying hazard ratios to the extrapolated PFS and OS of pembrolizumab arm, respectively. The estimated PFS for carboplatin plus gemcitabine is used as a proxy for time on treatment, and patients are assumed to receive no more than 6 cycles. Time on treatment data from the KEYNOTE-052 study was extrapolated to estimate time on pembrolizumab, and patients can receive a maximum of 24 months treatment in the model. Utilities and costs for each health state are based on published sources (summarised and critiqued in Sections 5.2.8 and 5.2.9 respectively). All costs and health outcomes are discounted at a rate of 3.5% per annum. Unit costs are valued at 2015/16 prices.

The model was generally well developed with few errors, and the company's analysis was well described in the cost-effectiveness section of the CS. However, there are some issues with the company's economic analysis, as described in the sections below.

5.2.2 Methods for ERG critique

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

- Examination of correspondence between the descriptions of the model reported within the CS and the executable model.
- Scrutiny of the company's model by health economic modellers, including checking the formula in each cell of the model, and discussion of issues identified amongst the members of the ERG.
- The use of extreme values (e.g. zero for utilities/costs) to check for errors in the programming and logic of the model
- The use of expert clinical input to judge the clinical credibility of the company's economic evaluation and assumptions underlying the company's model.
- Comparison of PFS and OS estimated from the model to published PFS and OS outcomes to assess their appropriateness.

5.2.3 NICE Reference Case checklist

The company's economic evaluation generally follows the NICE Reference Case[30], although not all relevant comparators are included within the economic evaluation, as shown in Table 22.

Table 22: Adherence of the CS to the NICE Reference Case

Element of health technology assessment	Reference Case	Does the submission adequately address the Reference Case?
Defining the decision problem	The scope developed by the Institute	Not all relevant comparators are included, but justifications for exclusions are provided (see Sections 3.3 and 5.2.4)
Comparator	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	
Perspective on costs	NHS and Personal Social Service (PSS)	Yes
Perspective on outcomes	All health effects on individuals	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes
Synthesis of evidence on outcomes	Based on a systematic review	Yes, but the indirect treatment comparison is flawed (see Section 4.5)
Measure of health effects	QALYs	Yes
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

5.2.4 Model scope

Population

The population considered within the company's model is adults with advanced/unresectable or metastatic urothelial carcinoma who have not received prior systematic chemotherapy and who are not eligible to receive cisplatin. Prior neo-adjuvant or adjuvant platinum-based chemotherapy, with recurrence more than twelve months from the completion of prior therapy was permitted. This is generally in line with the population specified in the NICE final scope. At model entry, both the pembrolizumab group and the carboplatin plus gemcitabine group are assumed to be 73 years of age, with 77% of patients assumed to be male, based on baseline characteristics of the KEYNOTE-052 study.

Intervention

The intervention under consideration within the company's health economic analysis is pembrolizumab. Pembrolizumab is assumed to be administered by IV infusion over thirty minutes at a fixed dose of 200mg every three weeks. Treatment is continued until progression occurs, unacceptable toxicity occurs or the patient or their representative withdraws consent. The company suggests that patients will stop pembrolizumab after a maximum of 24 months of treatment, as per the KEYNOTE-052 protocol. The SmPC does not limit treatment to 24 months, stating that 'Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.' In some cases patients are allowed to continue treatment beyond progression if some clinical benefit is still being obtained from the treatment.

Comparators

The comparators specified in the NICE final scope were carboplatin plus gemcitabine, atezolizumab and BSC. The CS only compares pembrolizumab with carboplatin plus gemcitabine. The company states that atezolizumab appears to be an effective first line treatment option for cisplatin ineligible patients with locally advanced or metastatic urothelial carcinoma. However, they also state that it has been difficult for the NICE committee to establish the size of the clinical benefit achievable and thus the drug has been made available through the Cancer Drugs Fund, and as such, they argue that atezolizumab is not a relevant comparator. Given that the Final Appraisal Determination issued by NICE suggested that the benefits of atezolizumab were too uncertain to recommend outside of the CDF currently, and given that the studies of atezolizumab and pembrolizumab both adopt a single-arm design, the ERG agrees that a comparison with atezolizumab would not be helpful for informing the current decision.

BSC has also not been considered a relevant comparator due to a paucity of evidence. Within their submission, the company suggests that most patients would receive carboplatin plus gemcitabine rather than BSC, although within clarification response (question A9), they state that 'the most appropriate randomised clinical trial in this setting would be to compare pembrolizumab to BSC as control'. The clinical advisors to the ERG suggested that most patients would receive gemcitabine plus carboplatin. The ERG has searched for clinical evidence for the use of BSC compared with any other treatment for this population (see Section 4.1), although none was identified. The ERG's clinical advisors also suggested that carboplatin plus gemcitabine has been used for many years in this population, despite being unlicensed for this indication, hence no trials have been undertaken to compare the combination with BSC. As such, given current evidence, it is not possible for the company to provide a comparison with BSC.

Carboplatin is administered by IV infusion over 15-60 minutes at a dose of 400mg/m^2 on day one of a 21-day cycle and gemcitabine is administered by IV infusion over 30 minutes at a dose of 1000 mg//m^2 on day 1 and day 8 of a 21-day cycle. Treatment is continued until patients have received a maximum of six cycles of treatment, in line with current UK clinical practice.

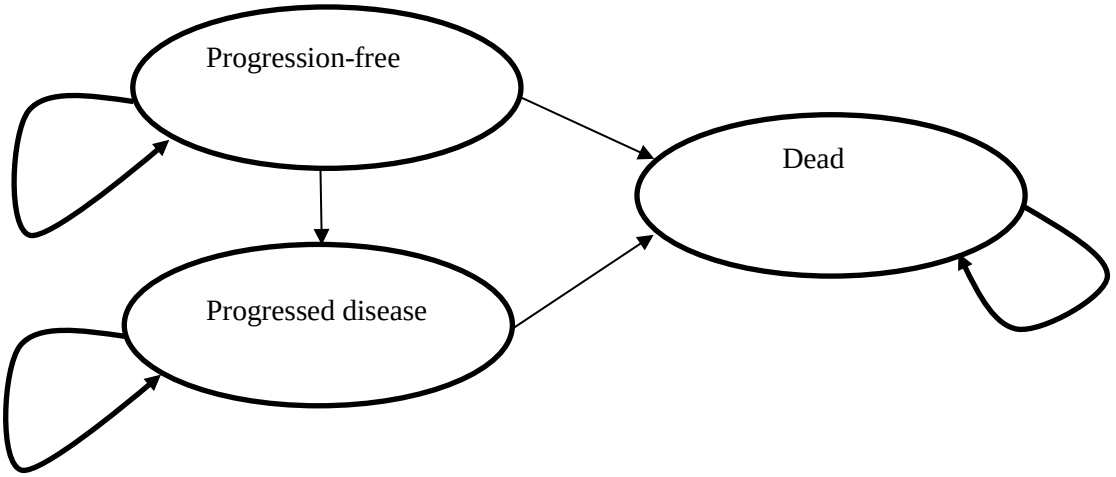
5.2.5 Perspective, time horizon and discounting

The economic analysis undertaken by the company adopts an NHS and PSS perspective; this is in line with the NICE Reference Case. Patients are followed over 20 years within the company's base case (effectively a lifetime horizon). In line with the NICE Reference Case, costs and health outcomes are discounted at 3.5% per annum.

5.2.6 Model structure

The general structure of the company's model is presented diagrammatically in Figure 5. The model adopts a partitioned survival approach based on three health states: (1) progression-free; (2) post-progression; and (3) death which is an absorbing state. The model adopts a weekly cycle. Costs and health outcomes for competing treatment options are evaluated over a total of 1,044 cycles, at which point more than 98% of patients in both treatment groups have died. A half-cycle correction is applied to account for the timing of events.

Figure 5: Model Structure



5.2.7 Treatment effectiveness and extrapolation

PFS and OS for patients receiving pembrolizumab were taken from the CS based on data obtained in the KEYNOTE-052 study. Table 23 summaries the company's model choice for extrapolation for both OS and PFS in the base case.

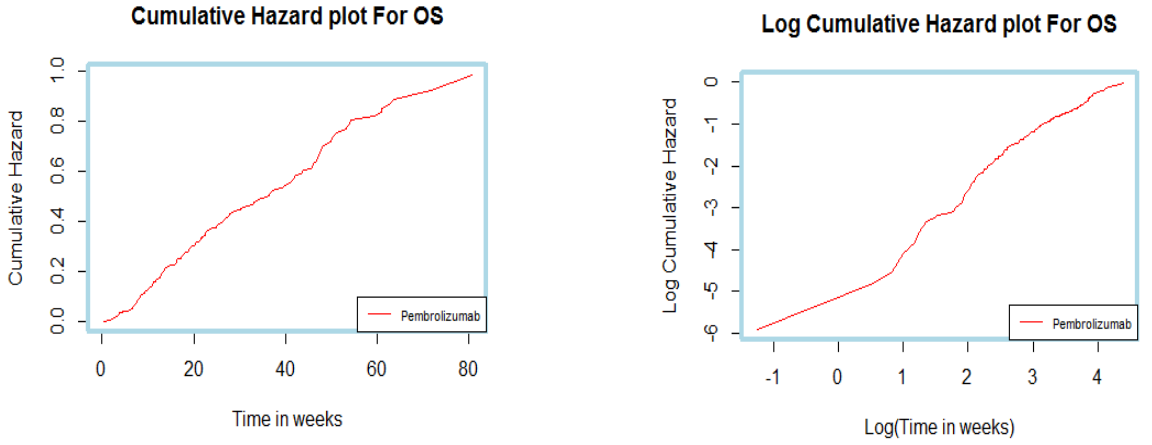
Table 23: The company's base case model choices for overall survival and progression-free survival

Outcome	Pembrolizumab	Carboplatin plus gemcitabine
Overall survival	Kaplan-Meier data up to 32 weeks and a log normal distribution beyond 32 weeks	Apply the time-varying hazard ratios from the fractional polynomial model (p1=p2=0) to the extrapolated pembrolizumab arm
Progression-free survival	Kaplan-Meier data up to 9 weeks and a Weibull distribution beyond 9 weeks	Apply the time-varying hazard ratios from the fractional polynomial model (p1=p2=0) to the extrapolated pembrolizumab arm

Overall survival

In order to model the long-term OS of patients receiving pembrolizumab, the company assessed the cumulative hazard against time plot and the log-cumulative hazard against log-time plot of OS for pembrolizumab and concluded that they were not straight lines, which indicates that a piecewise approach is most appropriate (see Figure 6).

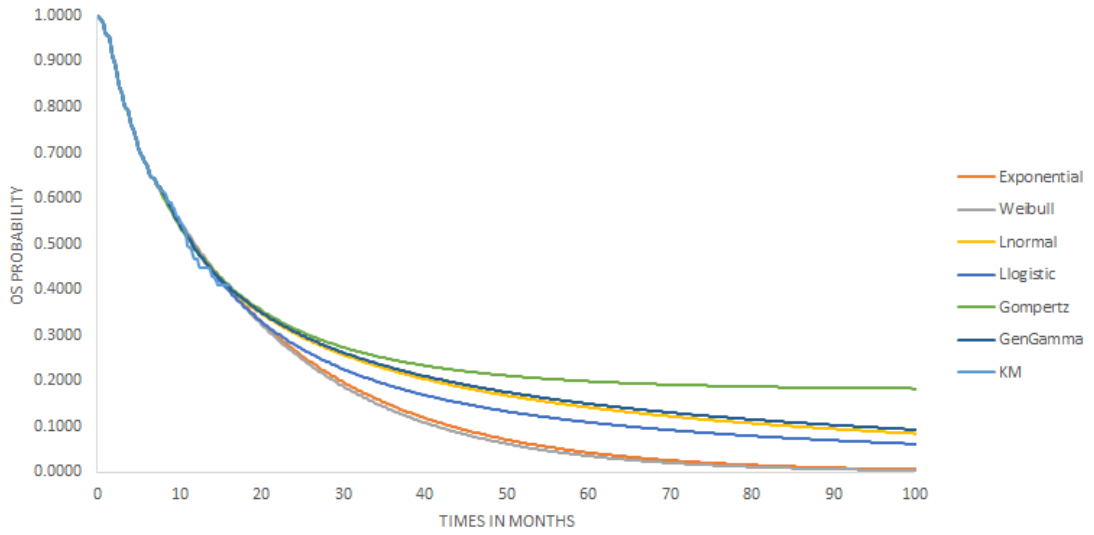
Figure 6: Cumulative hazard against time and log cumulative hazard against log time plots for pembrolizumab overall survival (reproduced from Figure 16 and Figure 17, pages 87 and 88 CS)



The company suggests that there is a change in the OS hazard at 32 and 44 weeks, and selected 32 weeks for the base case. The company used the KM data up until 32 weeks and fitted a number of parametric functions including exponential, Weibull, log logistic, log normal, Gompertz and Generalised gamma to the observed IPD from week 32 for the base case analysis. In sensitivity analyses, the company fitted parametric functions from time 0 and from week 44, with each of these analyses having different coefficients. The extrapolated curves for the base case OS in the pembrolizumab group are presented in Figure 7.

Model selection was based on the best fit to the observed pembrolizumab data in terms of the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), in addition to an assessment of the clinical validity of the extrapolated comparator curves. The company suggested that the exponential and log normal distributions provided the best statistical fit. In order to choose between the exponential and log normal distributions, the company applied the estimated time-varying hazard ratios (see Section 4.4) to the fitted exponential and log normal model for pembrolizumab to estimate the carboplatin and gemcitabine survival. They then compared the 2-, 3- and 4-year survival estimates for carboplatin plus gemcitabine with those from the trial by De Santis (2012).[16] The company concluded that the log normal distribution resulted in a better fit to the comparator data. As a result, the company chose the log normal distribution for the base case from week 32 onwards for pembrolizumab. Within scenario analyses, the company explored different cut-off points for the use of a parametric function. Following a clarification request (question B6), the company also presented results considering alternative parametric distributions (see Section 5.2.12).

Figure 7: Overall survival Kaplan-Meier curve vs. fitted two-phase piecewise model with cut-off at 32 weeks for pembrolizumab based on KEYNOTE-052 (reproduced from Figure 18, page 89 CS)

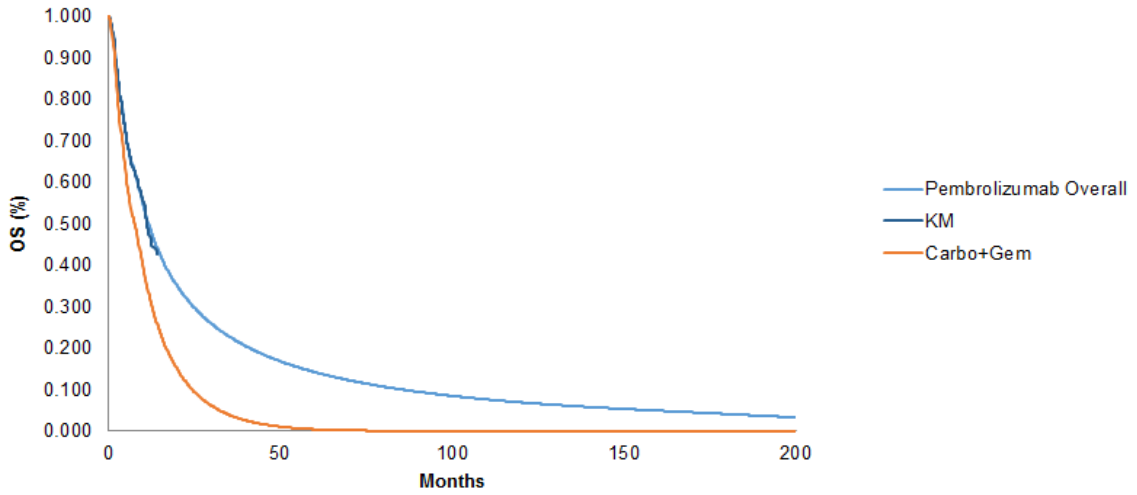


For patients receiving carboplatin plus gemcitabine, OS was estimated by applying the time-varying hazard ratios from a fractional polynomial model (p1=p2=0) (see Section 4.4 for more details) to the pembrolizumab survival data. During the clarification process (question A33), the ERG asked the company to test negative values for p1 and p2 and p1=p2=-2 was found to be the best fitting fractional polynomial model. However, this model was not applied within the health economic model; hence the exact impact of using this better fitting fractional polynomial model upon the ICER is unknown. The ERG notes that this better fitting fractional polynomial model provides less favourable results for pembrolizumab.

The CS also suggests that "the long-term extrapolation estimated by the model (i.e. 5-year and 10-year OS probabilities) was validated with clinical experts" (CS, page 94). The ERG asked for more details on this external validation exercise in clarification question B5. In the response, the company stated that "Clinical experts were requested to provide feedback on their clinical experience of treating patients with carboplatin plus gemcitabine and to validate the long-term survival estimates from the model for the comparator regimen at 5 and 10 years". However, the estimated long-term survival benefit from the clinical experts was not stated.

The company's extrapolated survival curves for pembrolizumab and carboplatin plus gemcitabine are reproduced in Figure 8 below.

Figure 8: Company estimated base case OS for pembrolizumab and carboplatin plus gemcitabine (reproduced from Figure 19, page 90 CS)



Other-cause mortality

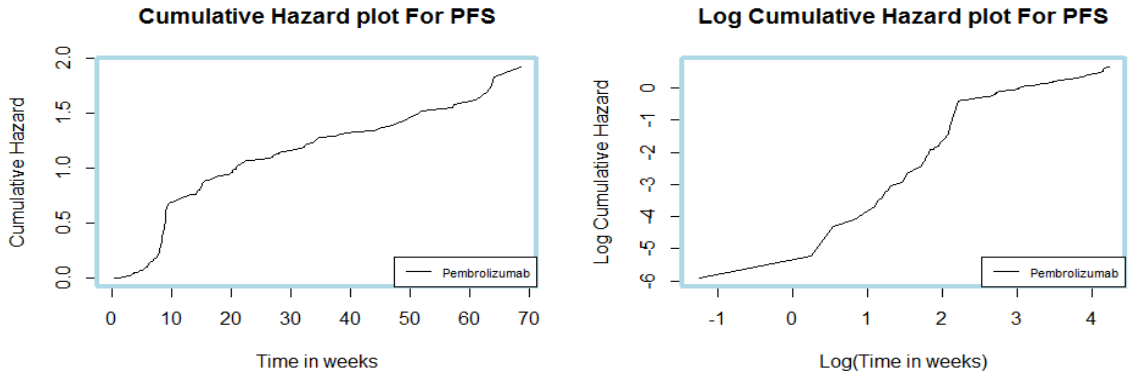
Other-cause mortality was incorporated within the model using standard life tables from the ONS.[31] Due to the fact that males and females have different life expectancies, the company had included a weighting for the proportion of males and females within the general population, but they had not adjusted this for the population of interest where 77% of patients are male based upon KEYNOTE-052. Within their base case analysis, the ERG amended this within the model to account for the greater proportion of males in this patient population.

Progression-free survival

Similar to the analysis of OS, the company assessed the cumulative PFS hazard against time plot and the log-cumulative PFS hazard against log-time plot (see Figure 9). From this the company determined

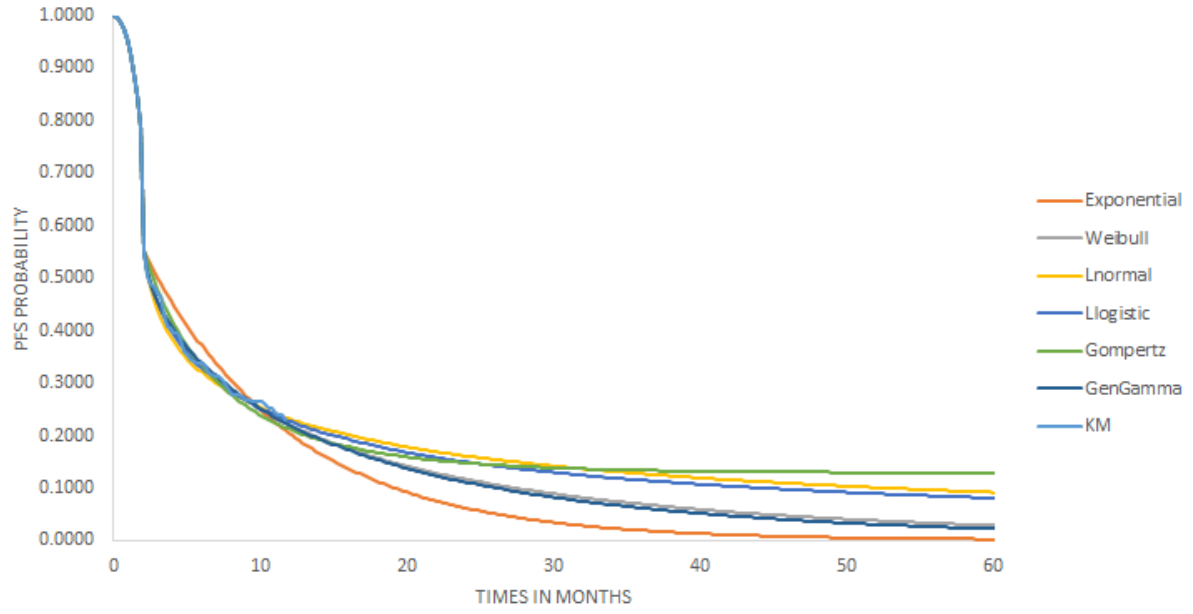
that it was most appropriate to use a piecewise analysis, by using the KM data directly until week nine and extrapolating beyond this using a log normal distribution. The company states the choice of cut-off at week nine is because no patients have an assessment until this time, hence there is a step change at this point because of how the data were collected.

Figure 9: Cumulative hazard against time and log cumulative hazard against log time plots for pembrolizumab progression-free survival (reproduced from Figure 20 and Figure 21, page 91 CS)



The company fitted a range of parametric distributions including exponential, Weibull, log logistic, log normal, Gompertz and Generalised gamma to the data beyond 9 weeks. The log normal distribution was chosen because it performed relatively well in terms of AIC and BIC. The CS does not report any validation by clinicians of the PFS curves. The extrapolated curves for PFS are presented in Figure 10.

Figure 10: Progression-free survival Kaplan-Meier curve vs. fitted 2-phase piecewise models with cut-off at 9 weeks for pembrolizumab based on KEYNOTE-052 (reproduced from Figure 22, page 92 CS)



As for OS, the PFS associated with carboplatin plus gemcitabine is estimated by applying the time-varying hazards from the best fitting second order fractional polynomial model (p1=p2=0) to the pembrolizumab PFS curves.

In their base case analysis, the company used the extrapolated PFS curve only for carboplatin plus gemcitabine as a proxy for time on treatment with carboplatin plus gemcitabine up until the maximum of 18 weeks (6 cycles of 3 weeks) of treatment is given. This is because the cost of treatment in both the comparator and treatment groups is based on time on treatment, and patient utility is based upon time until death in the base case rather than progression status (see Sections 5.2.8 and 5.2.9).

Time in the post-progression state was estimated as the difference between OS and PFS, or it was assumed to be zero if OS was estimated to be lower than PFS.

Critique of the extrapolation approach

With respect to the choice of distribution for the extrapolation of the KEYNOTE-052 data, the ERG notes that it is not meaningful to use a cumulative hazard against time plot, and the log-cumulative hazard against log-time plot can only be used to assess whether a Weibull or an exponential model is an appropriate model choice. The ERG requested the company to provide the empirical hazard plot for PFS and OS (see clarification response, question B1). However, this was not provided by the company. Both log-cumulative hazard against log-time plots for PFS and OS (see Figure 6 and Figure 9) suggested

that neither the Weibull nor the exponential were an appropriate choice. The ERG believes that a piecewise analysis is not necessary for OS, but may have some merit for PFS as a single standard parametric distribution may not be flexible enough to model the PFS.

The ERG questioned the validity of the extrapolated curves for carboplatin plus gemcitabine arm in clarification question B7, as the median PFS and OS predicted by the model for carboplatin plus gemcitabine were 2.53 months and 7.36 months, respectively. These appear to be underestimated compared with the median PFS and OS reported in the published papers[16-19] (between 4.4-5.8 months and 7.2-10 months, respectively). In the company's response, they explained that this is due to the population adjustment to balance the cross-study differences. As discussed in Section 4.4.4, there was no clear indication that the patients in KEYNOTE-052 were less fit or frailer than the patients in the carboplatin plus gemcitabine studies. Hence, the ERG suggests that the average of 2 months short in both PFS and OS seems to be implausible.

5.2.7 Adverse events

The criteria for inclusion of AEs within the model are inconsistent between the CS and the model. Within the model, any Grade ≥3 AEs that occurred in at least five percent of patients in either treatment arm is included. In addition, the proportion of patients experiencing diarrhoea is included from Grade ≥2 and the proportion of patients experiencing febrile neutropenia is included at any grade. All AEs are assumed to occur in the first treatment cycle.

Evidence around the incidence of AEs for patients receiving pembrolizumab was taken from data collected within the KEYNOTE-052 study and presented in the CS (page 266). Incidence of AEs in patients receiving the comparator treatment was obtained from a weighted average of the studies included in the NMA for efficacy. The percentage of patients receiving pembrolizumab and carboplatin plus gemcitabine experiencing each AE is presented in Table 23. Those AEs that occurred in less than 5% of patients were not included for that treatment group.

Table 24: Percentage of patients experiencing each included adverse event

Adverse Event	Pembrolizumab	Carboplatin plus gemcitabine
Anaemia	7.57%	7.14%
Diarrhoea	5.41%	0.45%
Fatigue	5.14%	<5%
Febrile neutropenia	<5%	4.46%
Infection	<5%	6.25%
Leukopenia	<5%	23.66%
Neutropenia	<5%	34.38%
Thrombocytopenia	<5%	30.80%
Urinary tract infection	10.54%	<5%

Utilities and costs associated with these adverse events are described in Sections 5.2.8 and 5.2.9.

5.2.8 Health-related quality of life

The company conducted a search of published literature to identify relevant HRQoL studies for use in the model.

Search strategies

The searches for published evidence on HRQoL were conducted at the same time as the cost-effectiveness review (August 2015, updated August 2017). The search strategies are reported in full in the CS Appendix G.1. The same range of databases was used, however this time no date limits were applied and the economic filter was replaced by a different set of terms. Again, no acknowledgement is made of the source of these terms; although the ERG considers them to be broadly fit for purpose, it is not possible to confirm whether their sensitivity and specificity have been validated.

Study selection

A total of 24 studies were included. Of these, 5 studies reported HRQoL data collected in a first line treatment setting and sixteen studies reported HRQoL data collected in a second line or subsequent treatment setting. The setting in the three remaining studies was unclear.

The company states that the HRQoL evidence in these studies was limited, with the most relevant evidence coming from an appraisal of vinflunine for urothelial cancer patients who have received prior therapy carried out by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and derived through mapping. However, as these patients had received prior treatment, the company states that they are unrepresentative of the patient population relevant to this appraisal. Thus, the company uses utility data obtained during the KEYNOTE-052 study and presented in the CS (pages 95-98).

Utilities used in the model

During the KEYNOTE-052 study, the company collected HRQoL data using the EQ-5D questionnaire during treatment cycles one, two, three, four and every two cycles thereafter up to a limit of one year or the end of treatment, whichever happened first. HRQoL was also measured at 30 days post treatment discontinuation. However, they estimated utility values in two different ways: (i) based on patients' disease state, so that patients had a different utility in the progression-free health state and the progressed disease health state; and (ii) based on patients' time to death, with this being divided into five categories:

1. Time to death greater than or equal to 360 days
2. Time to death greater than 180 days but less than or equal to 360 days
3. Time to death greater than 90 days but less than or equal to 180 days
4. Time to death greater than 30 days but less than or equal to 90 days
5. Time to death less than 30 days.

It should be noted that for a time to death of less than 360 days, only patients with an observed time to death were included whilst censored patients were excluded. For patients whose time to death was at least 360 days, censored patients were included only if their censored time to death was at least 360 days.

Linear mixed effects models with random intercept were used by the company to estimate utilities in order to include the correlation of repeated measures for individual patients. AEs were included as a covariate within this analysis to provide an estimate for the disutility associated with experiencing an AE (see below for more details).

The company used the time to death approach in their base case, arguing that there is a gradual decrease in HRQoL following disease progression which is not captured by a simple measure based on the health states included in the economic model. They also highlight that it has been used in other NICE submissions to estimate HRQoL in patients with urothelial carcinoma[6] and advanced melanoma.[32-34] The utilities obtained using both approaches are presented in Table 24. Within the model, these utilities were age-adjusted, based on a study by Ara and Brazier[35], although the ERG found that this had been implemented incorrectly (see below).

Table 25: Utility values used in the economic model

Description	Utility
Health state method	
Progression-free	0.678
Progressed disease	0.614
Time to death method	
Less than 30 days to death	0.421
At least 30 but less than 90 days to death	0.548
At least 90 but less than 180 days to death	0.586
At least 180 but less than 360 days to death	0.685
At least 360 days to death	0.753

Both the time to death approach and the progression approach have merit for estimating utilities in theory. The time to death approach enables patients' quality of life to remain higher following progression, which may be appropriate for a limited amount of time for patients receiving pembrolizumab. However, based upon the company's data and analysis, the utility for patients who have greater than 360 days to live is 0.753, which is similar to the average utility for those people in the general population aged 73 (the start age of the model). This appears to represent an overestimate given that the population of interest has advanced/unresectable or metastatic urothelial carcinoma and is ineligible for cisplatin. In addition, within the model, patients can spend more than one year in the progressed state, meaning that using the time to death approach, patients' utility can remain high within the progressed state for a substantial amount of time when they are no longer receiving the treatments. The ERG therefore prefers the approach in which HRQoL is determined by progression status, as this has greater clinical validity, based on the existing data. The ERG also notes that the ERG calculated the time-weighted average of utility by time to death approach, and this resulted in a utility which was higher than the utility estimated for the progression-free health state. Nonetheless, given the company's concerns that this utility may be an overestimate, the ERG has undertaken sensitivity analyses to test the impact of decreasing this utility in the progressed state upon the model results (see Section 6.2).

During model verification the ERG identified errors relating to the utility calculations. The first was that age 72 rather than age 73 was incorrectly used as the start age in the model. The company amended this error during the clarification process. However, the ERG also noticed that the calculation of the age-adjusted utility decrement was calculated incorrectly, which the company altered within the clarification process, but the ERG suggests it is still incorrect. The company assumed that the age-related utility decrement could be subtracted rather than applied proportionally according to the starting age within the model. Within their base case analysis, the ERG incorporated the intercept and sex coefficient from the model by Ara and Brazier[35] in order to appropriately estimate the age-related decrement, and amended the Markov trace sheet of the model so that the adjustment was applied multiplicatively rather than additively (see Appendix 1 for technical details of how this was applied).

A once-only QALY loss per patient, which is the same for both treatment arms, was applied on the first cycle of the model to reflect the impact of AEs. The QALY loss was calculated by multiplying the mean duration of an AE of 17.7 days by a disutility, estimated via a Grade ≥3AE covariate in the regression models used for calculating utilities. The QALY loss due to AEs does not account for the different AE profile between pembrolizumab and carboplatin plus gemcitabine.

5.2.9 Resources and costs

Time on treatment and treatment stopping rules

The company use PFS as a proxy for time on carboplatin plus gemcitabine treatment since there is insufficient evidence to estimate this from the studies. Within the model, patients are assumed to receive a maximum of six cycles of carboplatin plus gemcitabine, which is consistent with general practice in the UK, as suggested by the ERG's clinical advisors.

The company suggests that for pembrolizumab, PFS is not necessarily equivalent to time on treatment given that patients can both discontinue treatment prior to progression due to intolerability or adverse events, and remain on treatment following progression if they were clinically stable and benefiting from pembrolizumab. Within the company's clarification response (question A6), the company suggested that 14% of all patients had a partial response and remained on treatment beyond progressive disease for a median of 95 days (range 26-426 days) and 16% of patients had stable disease and remained on treatment for a median of 49 days (range 21-374 days). The company therefore used extrapolated time on treatment curves from KEYNOTE-052 to estimate the cost of treatment, rather than using the PFS curves. The company tested a range of parametric distributions including exponential, Weibull, log logistic, log normal, Gompertz and Generalised gamma for statistical fit using AIC and BIC. The Gompertz distribution provided the best fit for the data. This predicted that patients will on average spend longer on treatment than in the PFS health state. The clinical advisors to the ERG suggest that this is reasonable. This distribution for time on treatment is applied for the first 24 months.

The company assume that patients will stop pembrolizumab treatment after 24 months, as per the KEYNOTE-052 protocol. The SmPC does not limit treatment to 24 months, stating that 'Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.' In addition, the clinical advisors to the ERG suggest that if a patient is benefiting from pembrolizumab treatment they would likely continue with treatment, unless guidance did not allow this.

Whilst the KEYNOTE-052 protocol states that patients will stop pembrolizumab treatment after 24 months, at the March 2017 data cut-off no patients had been treated with pembrolizumab for 24 months; hence there is no evidence around the impact of this stopping rule upon the effectiveness of pembrolizumab beyond treatment discontinuation. The company's model assumes that the effectiveness

estimates of patients whilst on treatment can be extrapolated to represent patients who are no longer receiving treatment. The clinical advisors to the ERG suggested that patients who have received pembrolizumab may maintain some benefit following discontinuation; however the ERG suggests that it is unlikely that patients can discontinue pembrolizumab treatment after 2 years and yet continue to achieve benefits from that treatment for a further 18 years. The only study to consider effectiveness of this group of treatments beyond treatment discontinuation is a trial comparing one year of nivolumab treatment with continuous nivolumab treatment in patients with non-small cell lung cancer, which found that PFS was significantly better in those that had continued treatment.[36]

During the clarification process, the ERG asked the company to consider alternative assumptions around the long-term efficacy of pembrolizumab given the stopping rule. The company stated that they had incorporated the functionality to set the hazard ratio to 1 at 3, 5 and 10 years within the model, but they incorrectly adjusted the survival curves of the comparator rather than those of pembrolizumab. The ERG has therefore revised this analysis within their base case model, adjusting the pembrolizumab survival curves rather than the carboplatin plus gemcitabine curves (see Section 6.1).

Drug acquisition costs

Acquisition costs for pembrolizumab were taken from the CS. The recommended optimum dose of pembrolizumab is 200mg on day 1 of each 21-day treatment cycle whilst a patient is progression-free. The list price of pembrolizumab is £5,260 for two 100mg vials, [redacted]. All of the company's analyses (and subsequent ERG analyses) use the price of pembrolizumab [redacted].

Acquisition costs for the comparator drugs were taken from the Electronic Market Information Tool (eMIT) in June 2017.[37] As carboplatin in combination with gemcitabine is not licensed for urothelial carcinoma, the company took the dose information from the protocol for the KEYNOTE-361 trial.[38] Carboplatin is assumed to be administered at a dose of 400mg/m^2 on day 1 of each 21-day treatment cycle and gemcitabine at a dose of 1000mg/m^2 on days 1 and 8 of each 21-day treatment cycle. Assuming a mean patient body surface area of 1.88m^2 from the KEYNOTE-052 study[15] and vial sharing, resulting in no drug wastage, the mean cost per dose of carboplatin is estimated to be £34.07 and the mean cost per dose of gemcitabine is estimated to be £14.96.

As noted in Section 4.3, there are differences between the dosages and number of cycles of carboplatin and gemcitabine used within the four studies included in the company ITC. The gemcitabine dose and number of cycles assumed by the company matches the gemcitabine dose used in three of the four

studies included in the company ITC[16-18]; the remaining study by Bamias *et al*. (2007)[19] assumed a single dose of 1,250mg/m^2 on the first day of each 14-day treatment cycle, until patients stopped responding. The papers included in the company ITC present the carboplatin dose in terms of the target area under the curve (AUC), which can be converted to a maximum dose (mg) using the Calvert formula, in which the GFR is the glomerular filtration rate measured in terms of mL/minute.[39]

$$\text{Maximum carboplatin dose} = \text{Target AUC} \times (1.2 \times \text{GFR} + 20)$$

Given the available information, it was not possible to estimate the dosage for the study by Barnias (2007)[19] and Carles (2000).[17] The doses used in the studies conducted by Linardou (2004)[18] and De Santis (2012)[16] are substantially lower than the dose assumed by the company in the model, with the dose in the model being almost double the higher bound of the dose assumed in De Santis (2012).[16] The ERG has assessed the impact of reducing the cost of carboplatin and gemcitabine in the sensitivity analyses (see Section 6.2).

Drug administration costs

All three drugs are administered as IV. The company assumed that the cost of infusion of pembrolizumab is £253.32, taken from the NHS Reference Costs 2015-2016, currency code SB12Z (Simple chemotherapy; at first attendance, which assumes a setting of a day-case and regular day/night service).[40]

The cost of infusion of carboplatin and gemcitabine on day 1 of each 21-day treatment cycle is £336.57, taken from the NHS Reference Costs 2015-2016, currency code SB13Z (More complex parenteral chemotherapy, at first attendance, assuming a setting of a day-case and regular day night service). The cost of infusion of gemcitabine alone on day 8 of each 21-day treatment cycle is £211.99, taken from the NHS Reference Costs 2015-2016, currency code SB15Z (subsequent elements of a chemotherapy cycle, assuming a setting of a day-case and regular day night service).

The ERG believes that the cost of drug administration is reasonable.

Subsequent treatment

Based upon the latest UK market shares and the mean duration observed in the KEYNOTE-045 trial, the model assumes that [redacted] of patients would receive a taxane following treatment discontinuation with pembrolizumab or carboplatin plus gemcitabine. Of these, [redacted]. The remaining [redacted] of patients are assumed to receive BSC only. The mean cost associated with subsequent treatment was estimated by the company to be £334.24 per patient; this is applied to patients in both the

pembrolizumab and the comparator arm. However, the clinical advisors to the ERG suggest that for this patient group, it is unlikely that [redacted] of patients would be given a taxane and that this value would be closer to 25%, as most patients are too unfit to benefit from taxane-based therapies. However, the ERG suggests that this is unlikely to substantially impact upon the model results.

Disease management costs

Patients in both the progression-free and post-progression health states require NHS resources associated with disease management. This resource use is assumed to be the same per cycle, irrespective of the treatment patients are receiving. The CS states that a comprehensive literature search was conducted to estimate disease management resource use. However, only the NICE appraisal for atezolizumab[23] was included (CS Appendix I). Key reasons for exclusion of the other papers included wrong population, wrong intervention, wrong outcomes, wrong study type, wrong publication type, wrong language and 'could not be retrieved'. Resource use was therefore assumed to be the same as that used in the NICE appraisal for atezolizumab[23] for treating metastatic urothelial cancer when cisplatin is unsuitable (TA939). Unit costs are shown in Table 25.

The unit cost for a GP consultation, the cost per hour of community nurse specialist care and the cost per hour of health visitor care were all taken from the Unit Costs for Health and Social Care, 2015.[41] It was assumed that a GP consultation would last 11.4 minutes. Travelling time for the GP of 12 minutes and direct staff costs were included. All three costs included qualification costs and were inflated to 2015/2016 values using the hospital and community health services (HCHS) index presented in Unit Costs for Health and Social Care 2016.[42] The unit cost for a dietician was taken from the Unit Costs for Health and Social Care, 2016[42] and the unit cost for an oncologist led follow up visit were taken from the NHS Reference Costs 2015-16[40] using service code 370.

Table 26: Resource use for the patients receiving pembrolizumab in both the progression-free and post progression health states

Description	Monthly number of appointments		Cost
	Progression-free	Post progression	
GP home consultation	1	1	£91.26
Community nurse specialist visit	4	4	£76.00
Health home visitor	1	1	£77.01
Dietician	1	1	£33.00
Oncologist follow up visit			
Consultant led	1	0	£167.08
Non-consultant led	0	1	£88.44
Total monthly cost	£672.35	£591.71	

Clinical advisors to the ERG suggest that in practice patients may not receive as much care as specified in Table 26 every month, and hence this cost may be an overestimate. This was tested in the ERG's sensitivity analyses (see Section 6.2).

Costs associated with end of life care

A once-only cost was applied to patients at the time of death irrespective of treatment they were receiving. A mean per patient cost was estimated based on the elements of care that are available to patients at the end of life. However, some patients may not require all of these elements and thus resource use and associated costs are multiplied by the proportion of patients who require each element of care, as shown in Table 27.

With the exception of community nurse specialist visits and radiotherapy sessions, resource use was taken from a report produced by the London School of Pharmacy for the Marie Curie charity.[43] The number of hours of community nurse specialist care were taken from NICE Clinical Guideline 81[44] and the number of radiotherapy sessions was taken from NICE TA272.[45]

The unit cost for a GP consultation and the cost per hour of community nurse specialist care were both taken from Unit Costs for Health and Social Care 2015[41] inflated to 2015/2016 values using the HCHS index presented in the Unit Costs for Health and Social Care 2016.[42] The cost per hour of Macmillan nurse care is assumed to be two-thirds of the cost of community nurse specialist care, based on an assumption found by the company in the literature.[46]

The costs associated with radiotherapy and terminal care in hospital were taken from the NHS Reference Costs 2015-16.[40] Radiotherapy was based on the outpatient costs for Healthcare Resource Group (HRG) codes SC46Z and SC22Z and terminal care in hospital is based on HRG codes LB19E assuming a non-elective long stay of 9.66 days. Terminal care in a hospice is assumed to be 125% of the cost of terminal

care in hospital based on an assumption found in the literature.[46] The cost of drugs and equipment is not explicitly stated or justified in the CS but appears to be approximately £16.

Table 27: Resources used in end of life care and associated costs

Description	Resource use	Unit cost	Proportion	Total cost
GP Home consultation (visits)	7	£91	0.27	£172
Community nurse specialist (hours)	28	£76	0.27	£575
Macmillan nurse (hours)	50	£51	0.27	£684
Drugs & equipment	As required	-	0.27	£16
Terminal care in hospital	1	£3,345	0.56	£1,867
Terminal care in hospice	1	£4,181	0.17	£707
Radiotherapy (sessions)	5.88	£550	1.00	£3,232
Total				**£7,252.82**

Costs associated with treating adverse events

Only AEs occurring in more than 5% of patients in the KEYNOTE study or the comparator studies at Grade 3, 4 or 5 severity are included in the model, with the exception of diarrhoea where Grade 2 events are included and febrile neutropenia where any grade is included in the model. The costs of treating AEs are applied in the first cycle of the model and are assumed to occur only once.

The AEs included within the model and the assumed costs associated with managing treatment-related AEs are presented in Table 28.

Table 28: Costs associated with managing adverse events

Adverse event	Costs	Source	Details
Anaemia	£1,316	NHS Reference costs 2015-16[40]	Weighted average of non-elective long stay, short stay and day-case costs for acquired pure red cell aplastic or other aplastic anaemia (HRG codes SA01K, SA01J, SA01H SA01G)
Diarrhoea	£920	NHS Reference costs 2015-16[40]	Non-elective short stay cost for non-malignant gastrointestinal tract disorders without interventions with CC score 0-2 (HRG code FZ91). Multiplied by 2 in the model as 2 hospital visits are assumed.
Fatigue	£2,500	NHS Reference costs 2015-16[40]	Non-elective long stay cost for follow-up examination for malignant neoplasm with interventions (HRG code WH52A)
Febrile neutropenia	£2,642	NICE DSU[47]	This was inflated to 2015-16 values
Infection	£163	NHS Reference costs 2015-16[40]	Follow-up outpatient oncology consultation (service code 370)
Leukopenia	£362	NICE ID939[23]	
Neutropenia	£71	NHS Reference costs 2015-16[40]	Weighted average of non-elective long stay, short stay and day-case costs for other disorders of immunity (HRG code WJ11Z). Assumed that 10% of patients would require 2 hospital visits; 90% would not require hospitalisation
Thrombocytopenia	£363	NICE ID939[23]	
Urinary tract infection	£1,532	NHS Reference costs 2015-16[40]	Weighted average of non-elective long stay, short stay and day-case costs for kidney or urinary tract infections (HRG codes LA04N, LA04P, LA04Q, LA04R, LA04S)

In summary, the total mean cost of AEs in patients receiving pembrolizumab was £438.39 and the mean cost of adverse events in patients receiving combination carboplatin plus gemcitabine was £447.85. The ERG suggests that the company may have substantially underestimated the costs associated with the treatment of AEs due to the rare but serious AEs associated with pembrolizumab. However, during the clarification process, the company showed that plausible increases in the cost of AEs for pembrolizumab do not substantially affect the model results.

5.2.10 PSA, univariate sensitivity analyses and subgroup analyses

Probability sensitivity analysis

The company performed a PSA based on 1,000 Monte Carlo samples. The company's mean values, lower and upper bounds and statistical distributions used to model the parameter values are presented in Table 29, as well as sources for each of the parameters. The lower and upper bounds of the parameters were based upon data were possible, but in the case of the proportion of males, the probability of AEs, the costs of AEs and the hazard ratios for carboplatin plus gemcitabine, these were based upon an assumed standard error of 10% of the mean value. This is an arbitrary estimate of uncertainty. 1,000

Monte Carlo samples appear to be sufficient given the implemented uncertainty, since the model results plateau at around 600 runs.

Table 29: Probabilistic sensitivity analysis parameters

Parameter	Mean	Lower bound	Upper bound	Distribution	Source
General information					
Model cycle length (weeks)	1.00	N/A	N/A	Fixed	Company submission[1]
Model time horizon (years)	20.00	N/A	N/A	Fixed	
Discount rate for costs	3.5%	N/A	N/A	Fixed	
Discount rate for benefits	3.5%	N/A	N/A	Fixed	
Patient information					
Patient age (years)	73.00	68.00	78.00	Normal	Company submission[1]
Proportion male	0.77	0.77	0.78	Normal	
Mean patient body surface area (m^2)	1.88	1.86	1.90	Normal	
Utility by time to death					
More than 360 days	0.70	0.70	0.80	Beta	Company submission[1]
180 - 360 days	0.69	0.61	0.75	Beta	
90 - 180 days	0.59	0.52	0.65	Beta	
30 - 60 days	0.55	0.47	0.62	Beta	
Less than 30 days	0.42	0.33	0.51	Beta	
Utility by disease status					
Progression-free	0.68	0.65	0.71	Beta	Company submission[1]
Progressive disease	0.61	0.59	0.64	Beta	
Adverse events disutility					
Disutility	0.10	0.07	0.14	Beta	Company submission[1]
Duration of Grade ≥3 adverse event	17.70	15.29	20.11	Normal	
Drug acquisition costs					
Pembrolizumab	[redacted]	N/A	N/A	Fixed	Company submission[1]
Gemcitabine	£14.96	N/A	N/A	Fixed	Electronic Market Information Tool, June 2017[37]
Carboplatin	£34.07	N/A	N/A	Fixed	
Drug administration costs					
Pembrolizumab	£253.32	£208.32	£308.02	Log-normal	Company submission[1]
Gemcitabine & carboplatin regimen					NHS Reference Costs 2015/2016[40]
Drug administration on day 1	£336.57	£276.80	£409.25	Log-normal	
Drug administration on day 8	£211.99	£174.34	£257.77	Log-normal	
Disease management costs					
Progression-free patient (weekly)	£154.61	£123.31	£184.92	Normal	NHS Reference
Progressive disease patient (weekly)	£136.07	£109.40	£162.74	Normal	

Parameter	Mean	Lower bound	Upper bound	Distribution	Source
Subsequent pharmaceutical treatment	£518.95	£417.24	£620.66	Normal	Costs 2015/2016[40]
End-of-life care	£7,252.82	£5,831.29	£8,674.34	Normal	
Costs of treating adverse events					
Anaemia	£1,315.94	£1,058.02	£1,573.86	Normal	NHS Reference Costs 2015/2016[40]
Diarrhoea	£919.84	£739.55	£1,100.13	Normal	
Fatigue	£2,641.80	£2,124.02	£3,159.58	Normal	
Infection	£163.00	£131.05	194.95	Normal	
Neutropenia	£70.80	£56.92	£84.68	Normal	
Urinary tract infection	£1,531.64	£1,231.44	£1,831.83	Normal	
Leukopenia	£362.22	£291.23	£433.21	Normal	NICE ID939[23]
Thrombocytopenia	£362.66	£291.58	£433.21	Normal	NICE ID939[23]
Febrile neutropenia	£2,499.99	£2,010.00	£2,989.98	Normal	NICE DSU[47]
Occurrence of adverse events					
Pembrolizumab					Company submission[1]
Anaemia	7.57%	5.00%	10.00%	Beta	
Diarrhoea	5.41%	3.00%	8.00%	Beta	
Fatigue	5.14%	3.00%	8.00%	Beta	
Infection	0.00%	0.00%	0.00%	Beta	
Neutropenia	0.00%	0.00%	0.00%	Beta	
Urinary tract infection	10.54%	8.00%	14.00%	Beta	
Leukopenia	0.00%	0.00%	0.00%	Beta	
Thrombocytopenia	0.00%	0.00%	0.00%	Beta	
Febrile neutropenia	0.00%	0.00%	0.00%	Beta	
Gemcitabine + carboplatin					
Anaemia	7.11%	4.00%	11.00%	Beta	
Diarrhoea	0.44%	0.00%	2.00%	Beta	
Fatigue	0.00%	0.00%	0.00%	Beta	
Infection	6.22%	3.00%	10.00%	Beta	
Neutropenia	34.22%	28.00%	41.00%	Beta	
Urinary tract infection	0.00%	0.00%	0.00%	Beta	
Leukopenia	23.56%	18.00%	29.00%	Beta	
Thrombocytopenia	30.67%	25.00%	37.00%	Beta	
Febrile neutropenia	4.44%	2.00%	7.00%	Beta	
Survival models					
Pembrolizumab					Company submission[1]
Progression-free survival					
Weibull intercept	3.7722	N/A	N/A	Multivariate normal*	
Weibull log(scale)	0.0000	N/A	N/A		
Weibull (shape)	0.0000	N/A	N/A		
Overall survival					
Log-normal intercept	4.2266	N/A	N/A	Multivariate normal*	
Log-normal log(scale)	0.4721	N/A	N/A		
Log-normal (shape)	0.0000	N/A	N/A		
Time-on-treatment					
Gompertz intercept	-0.0320	N/A	N/A	Multivariate normal*	
Gompertz log(scale)	-2.8368	N/A	N/A		
Gompertz (shape)	0.0000	N/A	N/A		

Parameter	Mean	Lower bound	Upper bound	Distribution	Source
Hazard ratios for gemcitabine + carboplatin					
PFS gemcitabine + carboplatin versus pembrolizumab (d0)	-0.1469	N/A	N/A	Multivariate normal*	
PFS gemcitabine + carboplatin versus pembrolizumab (d1)	-0.4879	N/A	N/A		
PFS gemcitabine + carboplatin versus pembrolizumab (d2)	0.2181	N/A	N/A		
OS gemcitabine + carboplatin versus pembrolizumab (d0)	0.4439	N/A	N/A	Multivariate normal*	
OS gemcitabine + carboplatin versus pembrolizumab (d1)	-0.2497	N/A	N/A		
OS gemcitabine + carboplatin versus pembrolizumab (d2)	0.1395	N/A	N/A		

*During the clarification process, the company provided the CODA samples for modelling survival rather than using a multivariate normal distribution, as requested by the ERG.

Univariate sensitivity analysis

The company conducted deterministic sensitivity analysis using the values of the 5th and 95th percentile of their statistical distributions for the following parameters and groups of parameters:

- Baseline characteristics;
- Costs associated with drug administration;
- The utilization of resources associated with disease management;
- The costs associated with subsequent pharmacological treatment;
- Costs associated with the management of progression-free and post progression patients;
- Health state utility values;
- The proportion of patients receiving pembrolizumab and the proportion of patients receiving combination gemcitabine and carboplatin who experience adverse events;
- The costs associated with treating adverse events;
- The duration of adverse events;
- The parameters of the parametric curves fitted to progression-free survival, overall survival and time on treatment;
- The hazard ratios for combination gemcitabine and carboplatin treatment versus pembrolizumab treatment.

Scenario analyses

The company also carried out the following scenario analyses to assess the uncertainty surrounding structural and methodological assumptions:

- Using a Weibull model for time-varying OS hazard ratios for combination gemcitabine and carboplatin treatment based on Weibull being the second-best fitting model according to DIC values and presenting a stable hazard over time;
- Assuming pembrolizumab and combination gemcitabine and carboplatin treatment are equivalent in terms of PFS, based on the PFS observed in the KEYNOTE-045trial;
- Using a fully fitted parametric curve for overall survival of patients receiving pembrolizumab;
- Using a 44 weeks cut-off for the piecewise approach for the overall survival of patients receiving pembrolizumab;
- Using a 15 weeks cut-off for the piecewise approach based on the second tumour assessment for the overall survival for patients receiving pembrolizumab;
- Using utility values based on disease state rather than time to death;
- Removing age-related utilities from the model.

Within the clarification process, the company also provided scenario analyses using alternative parametric curves for the OS extrapolation of pembrolizumab, alternative assumptions about the pembrolizumab stopping rule and inclusion of AEs occurring in >1% of pembrolizumab patients.

Subgroup analyses

In addition, the company considered subgroups according to PD-L1 status, of CPS≥1% and CPS≥10%. This analysis assumed that an additional cost associated with PD-L1 testing would be required, as shown in Table 30.

Table 30: Cost of PD-L1 testing per patient eligible for pembrolizumab who express PD-L1 status (reproduced from Table 64, page 119 CS)

Description	CPS≥1%	CPS≥10%
PD-L1 test cost	£40.50	£40.50
Percentage of patients eligible for treatment with pembrolizumab who express PD-L1 status among newly diagnosed patients with stage 4 urothelial cancer	37.2%	14.5%
Total PD-L1 costs	£108.88	£279.08

The company state that they conducted the subgroup analysis because it was pre-specified in the NICE final scope; however they highlight that this analysis is based on a small number of patients and therefore the results should be interpreted with caution. The ERG notes that there is no evidence by subgroup for the comparator; hence it was not appropriate to conduct the ITC for the subgroups.

5.2.11 Cost-effectiveness results

Base case results

The company's base case deterministic cost-effectiveness results, as presented in the company's clarification response, including the [redacted], are reproduced in Table 31. These suggest that pembrolizumab leads to an additional 1.01 QALYs at an additional cost of £35,634 on average per person compared with carboplatin plus gemcitabine. The cost per QALY gained for pembrolizumab in comparison to carboplatin plus gemcitabine is estimated to be £35,341.

The company presented a similar probabilistic base case ICER of £36,285 per QALY gained within the clarification response, but a slightly higher ICER of £37,081 is presented in their health economic model (shown in
Table 32). Based upon the health economic model, the estimated probability of pembrolizumab being cost-effective at thresholds of £20,000, £30,000 and £50,000 per QALY gained are 0%, 12% and 87% respectively (see Figure 11 and Figure 12 for PSA results).

Table 31: Updated company base-case results following clarification (reproduced from Table 13, clarification response)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£18,011	0.86	0.55	-	-	-	-
Pembrolizumab	£53,645	2.25	1.55	£35,634	1.39	1.01	£35,341

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

Table 32: Updated company probabilistic sensitivity analysis results following clarification (taken from health economic model, 'PSA' sheet)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£18,457	0.93	0.60	-	-	-	-
Pembrolizumab	£53,603	2.24	1.54	£35,146	1.32	0.95	£37,081

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

Figure 11: Cost-effectiveness plane – pembrolizumab versus carboplatin plus gemcitabine, (reproduced from Appendix, clarification response)

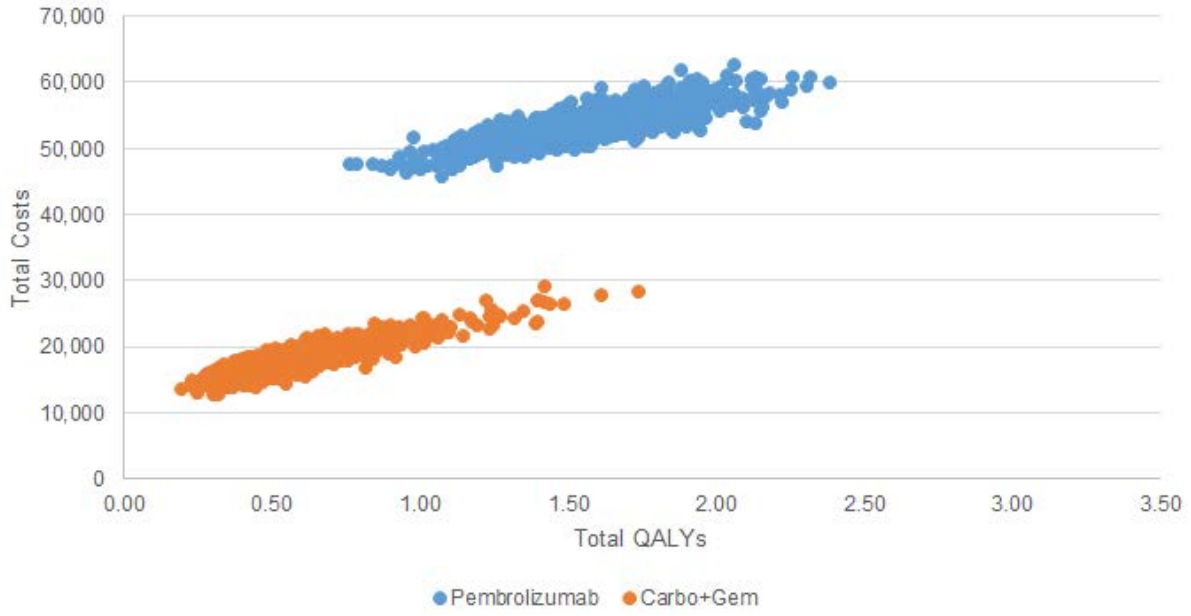
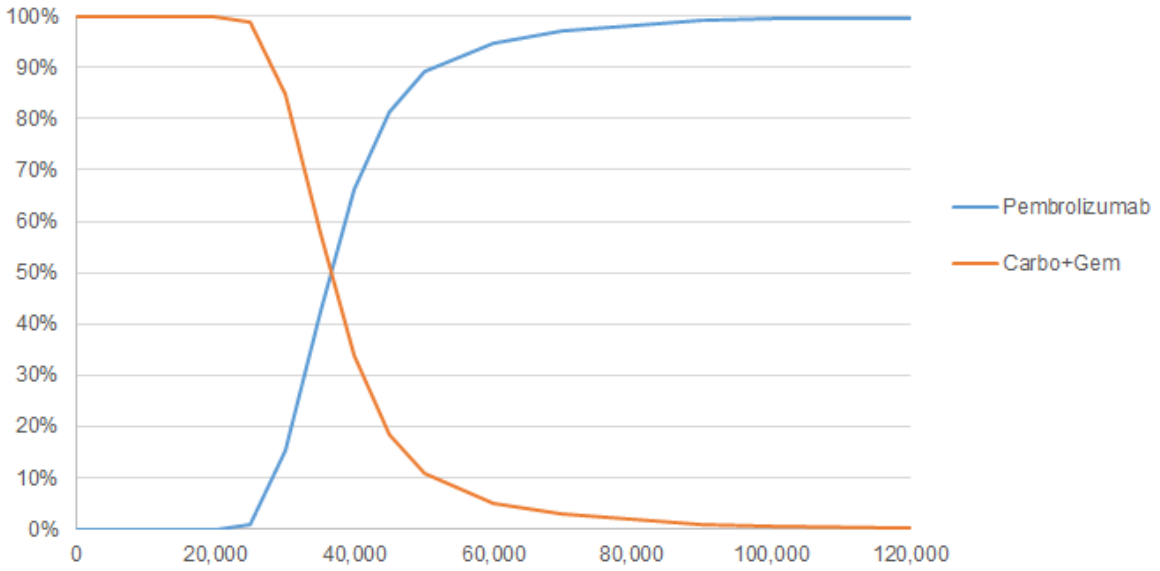


Figure 12: The company's cost-effectiveness acceptability curve (reproduced from Appendix, clarification response)

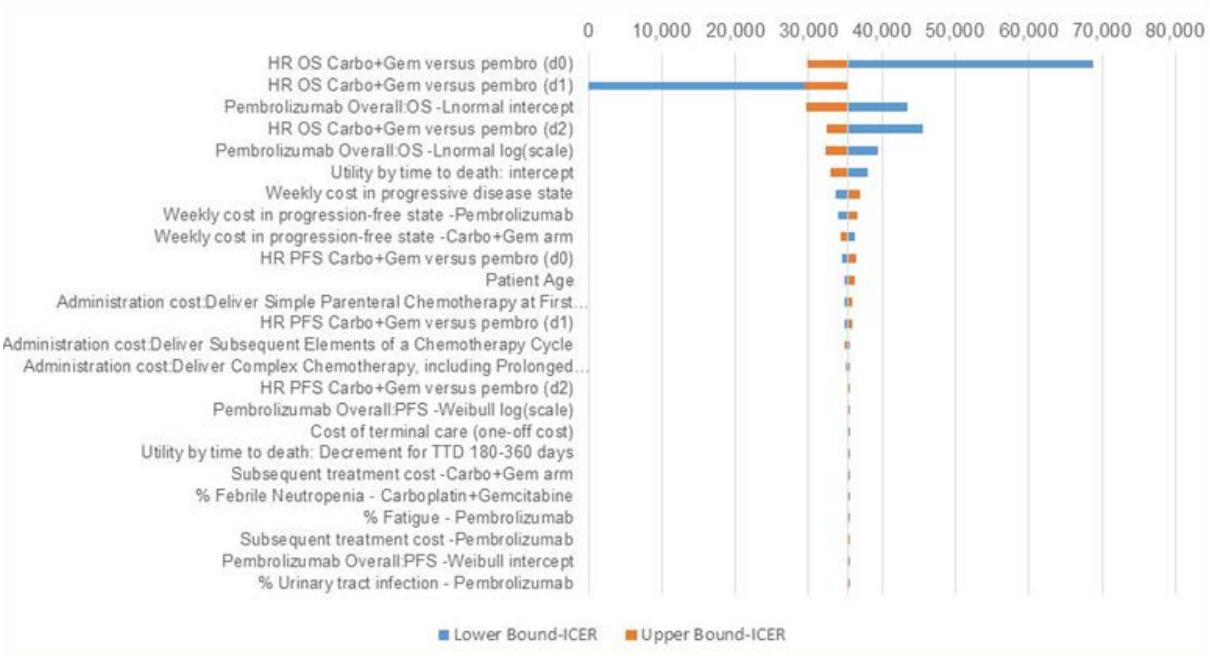


The original base case as presented in the CS was very similar to these results, however these results corrected for two model errors identified within the original model: (1) the time on treatment curve of carboplatin and gemcitabine was amended to account for a maximum duration of 6 cycles and (2) the age-adjusted utility decrement was modified (although the ERG identified further errors in the utility calculations, see Section 5.2.8).

Univariate sensitivity and scenario analyses

The company presented the results of their univariate sensitivity analyses within a tornado diagram. Within the clarification response (Appendix 1) this was based upon net monetary benefit (NMB) rather than on an ICER. This assumed a willingness to pay threshold of £50,000 per QALY gained. The health economic model, however, also included a tornado plot based on the ICER, presented in Figure 13 below.

Figure 13: The company's tornado diagram using NMB (reproduced from 'OWSA' sheet of health economic model provided in clarification response)



The company also undertook some scenario analyses, as shown within Table 33. These analyses suggest that, of those assumptions tested, the choice of method for estimating HRQoL over time and the extrapolation of OS have the greatest impact upon the model results. The ICER for pembrolizumab compared to carboplatin plus gemcitabine remains between £30,000 and £43,000 per QALY gained for all analyses tested. However, the ERG suggests that not all plausible alternative assumptions have been tested within the scenario analyses. Whilst the company have tested 'PFS equivalence between arms' this does not alter the OS, and given that PFS is only used as a proxy for time on treatment with carboplatin and gemcitabine in the company's base case, it has a very small impact upon the ICER, as would be expected.

Table 33: The company's scenario analysis results (reproduced from Table 63, page 117 CS)

	Pembrolizumab			Carboplatin + gemcitabine			Pembrolizumab vs. Carboplatin + gemcitabine		
	Total costs	**Total LYs**	**Total QALYs**	**Total costs**	**Total LYs**	**Total QALYs**	**Inc. costs**	**Inc. QALYs**	**ICER**
Base case	£53,645	2.25	1.55	£18,011	0.86	0.55	£35,634	1.01	£35,341
Weibull time-varying HRs	£53,645	2.25	1.55	£19,052	1.01	0.66	£34,593	0.90	£38,548
PFS equivalence between arms	£53,645	2.25	1.55	£18,070	0.86	0.55	£35,575	1.01	£35,282
OS: Fully fitted parametric curve	£51,880	1.99	1.37	£17,869	0.84	0.53	£34,010	0.84	£40,606
OS cut-off – 44 weeks	£55,991	2.60	1.80	£18,220	0.89	0.57	£37,772	1.23	£30,633
PFS cut-off – 15 weeks	£53,605	2.25	1.55	£18,020	0.86	0.55	£35,585	1.01	£35,292
Utilities – Progression based	£53,645	2.25	1.39	£18,011	0.86	0.56	£35,634	0.83	£42,937
No age-related disutilities	£53,645	2.25	1.60	£18,011	0.86	0.55	£35,634	1.05	£33,977

As part of their clarification response, the company tested the impact upon the model results using alternative parametric distributions for extrapolating OS and PFS (see clarification question B6). The model results did not change substantially when the distribution for extrapolating PFS was altered; this is unsurprising given that within the company's base case model, PFS is used only as a proxy for time on treatment for carboplatin plus gemcitabine. However, this analysis shows that the results of the model are highly dependent upon the choice of extrapolation approach for the OS associated with pembrolizumab (see Table 34), and all of these scenarios use the KM data until 32 weeks and then only amend the extrapolation approach beyond this time point.

Table 34: Company results using alternative parametric distributions for pembrolizumab overall survival (reproduced from Table 17, clarification response B6)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Log-normal – Base case						
Carboplatin+ Gemcitabine	£18,011	0.86	0.55	-	-	-
Pembrolizumab	£53,645	2.25	1.55	£35,634	1.01	£35,341
Exponential						
Carboplatin+ Gemcitabine	£17,572	0.79	0.50	-	-	-
Pembrolizumab	£48,157	1.44	0.97	£30,586	0.47	£64,407
Weibull						
Carboplatin+ Gemcitabine	£17,525	0.79	0.49	-	-	-
Pembrolizumab	£47,865	1.40	0.94	£30,340	0.45	£67,585
Gompertz						
Carboplatin+ Gemcitabine	£18,803	0.97	0.63	-	-	-
Pembrolizumab	£58,689	3.00	2.09	£39,886	1.46	£27,411
Log-logistic						
Carboplatin+ Gemcitabine	£17,736	0.82	0.52	-	-	-
Pembrolizumab	£51,828	1.98	1.36	£34,092	0.85	£40,339
Generalised gamma						
Carboplatin+ Gemcitabine	£18,069	0.87	0.55	-	-	-
Pembrolizumab	£54,237	2.34	1.62	£36,168	1.06	£33,977

As part of the clarification process, the company also tested the impact of excluding the treatment stopping rule for pembrolizumab (clarification question B9). The company showed that in the absence of a 24-month stopping rule, the ICER for pembrolizumab compared with carboplatin plus gemcitabine would increase to £85,084 per QALY gained (see Table 35). Time on treatment is assumed to follow the Gompertz distribution within this anlaysis, as in the company's base case. Since the Gompertz curve

plateaus out, time on treatment may be overestimated in this analysis and hence the cost of pembrolizumab may also be overestimated.

Table 35: Company results using no stopping rule for pembrolizumab (reproduced from Table 20, clarification response B9)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Carboplatin+ Gemcitabine	£18,011	0.86	0.55	-	-	-
Pembrolizumab	£103,802	2.25	1.55	£85,791	1.01	£85,084

During the clarification process, the company also tested having a reduced pembrolizumab treatment effect at 3, 5 and 10 years by setting the hazard ratio between pembrolizumab and carboplatin plus gemcitabine for OS and PFS to 1.0 following treatment discontinuation at 2 years (clarification question B9). However, the company implemented this analysis by altering the PFS and OS estimates of carboplatin plus gemcitabine rather than those of pembrolizumab within this analysis. The analysis suggested that this would have a minimal impact upon the model results.

During the clarification process, the company also tested the impact of incorporating any grade 3 or greater AEs occurring in ≥1 of patients in the pembrolizumab group (clarification question B11). This showed that the cost of AEs does not have a substantial impact upon the model results.

Subgroup analysis results

The results of the company's subgroup analyses are presented in Table 36 and Table 37. These suggest that a patients' PD-L1 status appears to have only a minor impact upon cost-effectiveness. However, the company appropriately warns that these results should be treated with caution because they are based on small numbers. The ERG does not undertake any additional analyses on these subgroups given that there is no evidence on these subgroup populations for the comparator.

Table 36: The company's results for pembrolizumab vs carboplatin & gemcitabine combination in patients with CPS≥1%

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALYs)
Carboplatin+ gemcitabine	£19,191	1.02	0.66	-	-	-
Pembrolizumab	£56,166	2.35	1.63	£36,975	0.97	£38,219

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

Table 37: The company's results for pembrolizumab vs carboplatin & gemcitabine combination in patients with CPS≥10%

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALYs)
Carboplatin+ gemcitabine	£18,290	0.89	0.57	-	-	-
Pembrolizumab	£68,210	3.00	2.09	£49,920	1.52	£32,893

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

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 The ERG's suggested base case

The ERG's base case builds upon the updated model submitted by the company following the clarification process. Appendix 1 details the technical changes that the ERG has made within the company's model. The ERG's suggested base case includes:

1) Correction of model errors

The ERG have identified model errors relating to the way in which utilities are estimated and implemented (see Section 5.2.8) and a model error around the proportion of males and females for estimating other-cause mortality in the model (see Section 5.2.7). These errors have been amended within the ERG's preferred base case analysis, although they do not impact upon the model results substantially.

2) Utility by progression status

The ERG prefers utility by progression status rather than by time to death within the base case, since the estimated utilities via the latter method are implausibly high for this patient group (see Section 5.2.8 for a detailed discussion).

3) Extrapolation of OS and PFS using unadjusted data

The ERG has concerns about the validity of the STC undertaken by the company (see Section 4.4). Given that we do not have the IPD to undertake our own population adjustment analyses, the ERG used a naïve indirect comparison based on the carboplatin plus gemcitabine arm from De Santis (2012)[16] and KEYNOTE-052. The reason to only include De Santis (2012)[16] is because the ERG believes that it may not be appropriate to synthesise the evidence from the four carboplatin plus gemcitabine studies due to the heterogeneity with regard to patients and dosage and administration of gemcitabine and carboplatin (see Section 4.3); and De Santis (2012)[16] is the only study with high quality and representative patients as described in the NICE final scope.

The ERG reconstructed IPD from the observed pembrolizumab data in KEYNOTE-052 for both OS and PFS using the algorithm proposed by Guyot *et al* (2012)[25] and extrapolated the survival benefit using standard parametric distributions including exponential, Weibull, log logistic, log normal, Gompertz, gamma and Generalised gamma and natural cubic spline models by Royston and Parmar[48] with knots={1, 2, 3} based on modelling the log of the cumulative hazard function. When reconstructing the IPD, the ERG used the reported KM data in the economic model directly instead of digitising the KM curves.

Spline based survival modelling approach models the logarithm of the baseline cumulative hazard function or odds function as a natural cubic spline function of log time. This is a more flexible approach compared with using standard parametric distribution. Spline base approach is able to model more complex hazard functions. Natural cubic spline functions are piecewise cubic polynomials defined to be continuous at knots, and linear beyond boundary knots. The complexity of the model is governed by the number of knots. When there is no internal knot, the cubic spline model reduces to either Weibull, log-logistic or log normal distribution. Royston and Parmar[48] suggested to use maximum 3 internal knots since the fitted curves with more than 3 internal knots are expected to be potentially unstable. They also suggest that the position of the knots does not appear to be critical for a good fit and proposed to use centile-based positions as default.

When compared with the hybrid KM approach as the company performed, the natural cubic spline models have a few advantages: (1) the cubic spline model provides a coherent fit to all the observed data; whereas the cut-off point in the hybrid KM approach is arbitrary and only uses the data beyond the cut-off point; (2) the cubic spline model allows uncertainty in the model parameter to be propagated appropriately in the health economic model; whereas using the hybrid KM approach the company only considered uncertainty in the model parameters after the cut-off point.

For the carboplatin plus gemcitabine group, the ERG considers that the most appropriate evidence to use is the data from De Santis (2012)[16] as discussed in Section 4.4. Only the OS KM curve was reported in the published paper. The ERG obtained the PFS KM curve from the first author of the paper. The PFS curve for the carboplatin plus gemcitabine arm in De Santis (2012)[16] is presented in Figure 11. The ERG reconstructed IPD for OS and PFS in De Santis (2012)[16], where the KM curves were digitised using GetData Graph Digitizer[49], and extrapolated the survival benefit using standard parametric distributions and natural cubic spline models by Royston and Parmar[48] with knots={1, 2, 3} based on modelling the log of the cumulative hazard function. The ERG used flexsurv package in R[50] for all the extrapolation analyses.

Figure 14: Progression-free survival for carboplatin plus gemcitabine arm in De Santis (2012)

The goodness-of-fit of both OS and PFS based on statistical criteria AIC and BIC for carboplatin plus gemcitabine and pembrolizumab are presented in Table 38. The observed KM curves against the best fitting models for both OS and PFS are given in Figure 15 to Figure 18. Table 39 and Table 40 summarises the extrapolated long-term OS and PFS, respectively.

Table 38: Summary of goodness-of-fit of overall survival and progression-free survival models for carboplatin plus gemcitabine and pembrolizumab

Models	**Carboplatin plus gemcitabine**		**Pembrolizumab**		**Carboplatin plus gemcitabine**		**Pembrolizumab**	
	Overall Survival				**Progression-free survival**			
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Generalised gamma	**789.78**	**798.12**	**1415.42**	**1427.16**	690.45	698.79	1329.3	1341.04
Gamma	**789.75**	**795.31**	1430.75	1438.58	711.95	717.51	1448	1455.83
Log normal	794.85	800.41	**1414.72**	**1422.55**	688.47	694.03	1370.88	1378.71
Log logistic	**787.81**	**793.37**	1421.56	1429.39	684.5	**690.06**	1379.96	1387.78
Gompertz	794.47	800.03	1432.14	1439.97	696.69	702.25	1424.94	1432.77
Weibull	**791.46**	**797.02**	1432.08	1439.9	712.55	718.1	1449.87	1457.7
Exponential	**792.47**	**795.25**	1431.19	1435.1	710.84	713.62	1447.96	1451.87
Spline k=1, scale=hazard	**790.02**	**798.36**	**1415.76**	**1427.5**	690.33	698.67	1301.38	1313.12
Spline k=2, scale=hazard	**788.13**	799.25	**1416.97**	1432.62	683.93	695.04	1288.74	1304.39
Spline k=3, scale=hazard	**789.92**	803.81	**1418.67**	1438.24	**672.2**	**686.1**	**1225.29**	**1244.86**

k=number of knots; Bold: best fitting models determined using 5 points rule

The goodness-of-fit of OS models for carboplatin plus gemcitabine suggested that the generalised gamma, gamma, Weibull, exponential, log logistic and spline with knots={1, 2, 3} all fit the reconstructed carboplatin plus gemcitabine data well based on AIC values (see Table 38). BIC penalizes more heavily on the number of parameters used in the model than AIC, hence the more complex models such as the generalised gamma and spline models have higher BIC values than simpler models such as gamma, Weibull, exponential and log logistic distributions. Based on visual inspection of the model fit in the observed period (see Figure 15) and comparing the observed KM data with predicted survival probabilities (see Table 39), the log logistic, Weibull and exponential model do not fit the data well and the two spline models with knots={2, 3} provide the best fit. The ERG considers spline with knots=2 to be the most appropriate model for carboplatin plus gemcitabine OS.

Figure 15: Overall survival Kaplan-Meier curve vs. fitted models for carboplatin plus gemcitabine based on De Santis (2012)

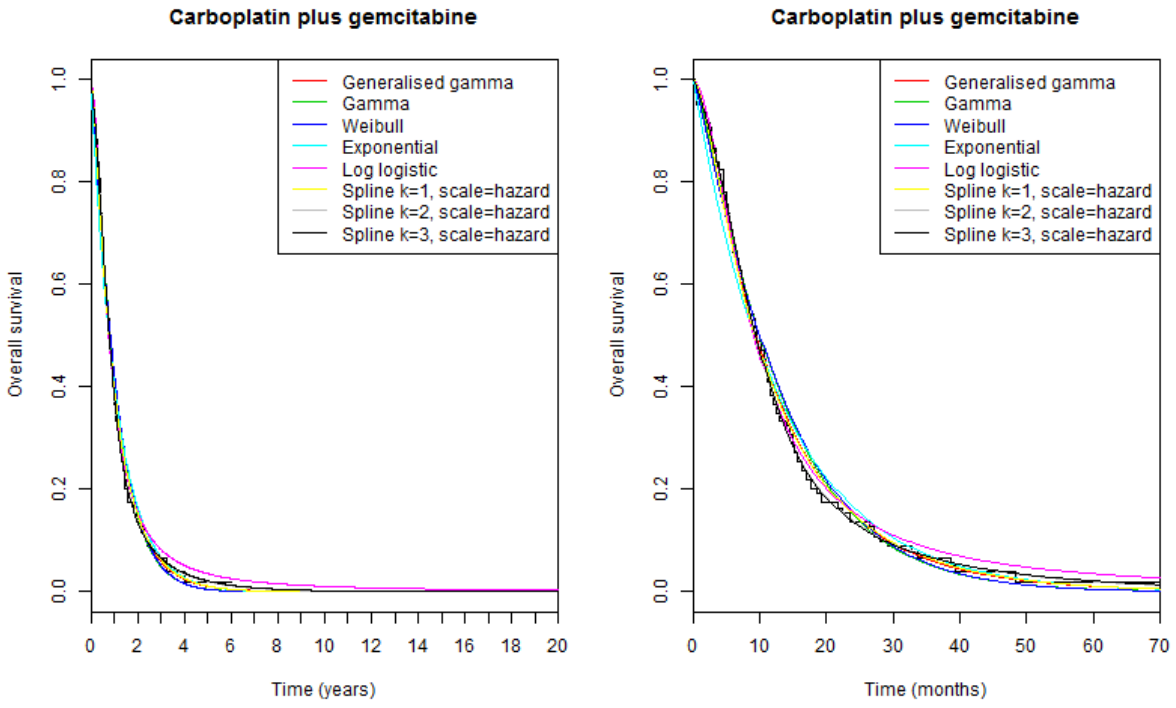


Table 39: Extrapolated long-term overall survival probability for carboplatin plus gemcitabine

Time point	Observed Kaplan Meier	Generalised gamma	Gamma	Weibull	Exponential	Log logistic	Spline k=1, scale=hazard	Spline k=2, scale=hazard	Spline k=3, scale=hazard
2 years	0.14	0.15	0.15	0.16	0.17	0.16	0.16	0.14	0.14
5 years	0.02	0.01	0.01	0.01	0.01	0.04	0.01	0.02	0.02
10 years	-	0	0	0	0	0.01	0	0	0
15 years	-	0	0	0	0	0.01	0	0	0
20 years	-	0	0	0	0	0	0	0	0

The goodness-of-fit of OS models for pembrolizumab suggested that the generalised gamma, log normal and spline with knots={1, 2, 3} all fit the reconstructed pembrolizumab data well based on AIC values (see Table 38). All of these models fit the observed data reasonably well (see Figure 16). However, the extrapolated long-term survival probabilities vary considerably (see Table 40). The ERG's clinical advisors found it difficult to suggest which survival estimates were most appropriate, and highlighted that there was substantial uncertainty about the effectiveness of pembrolizumab beyond 5 years. They suggested considering the longer term evidence from similar drugs in alternative indications, however no studies reported more than 24 months follow up. The ERG has chosen to use the log normal distribution within its base case; all other equally plausible models are tested within sensitivity analyses.

Figure 16: Overall survival Kaplan-Meier curve vs. fitted models for pembrolizumab based on KEYNOTE-052

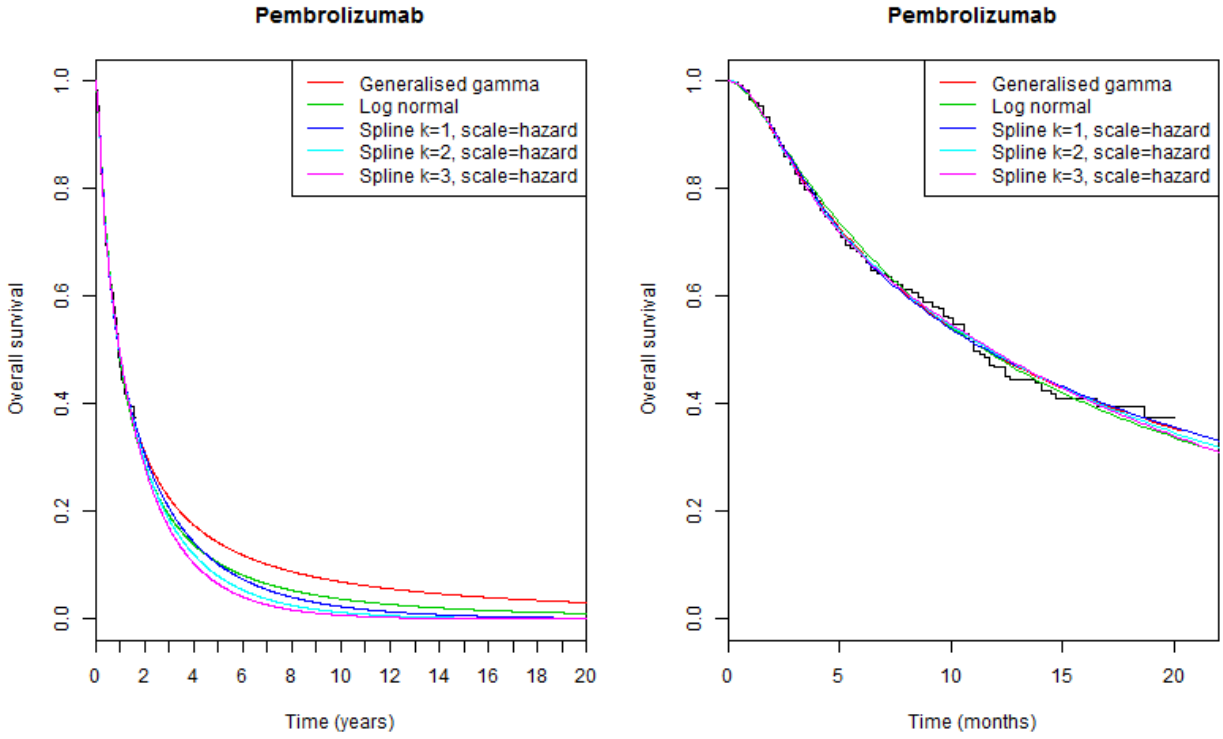


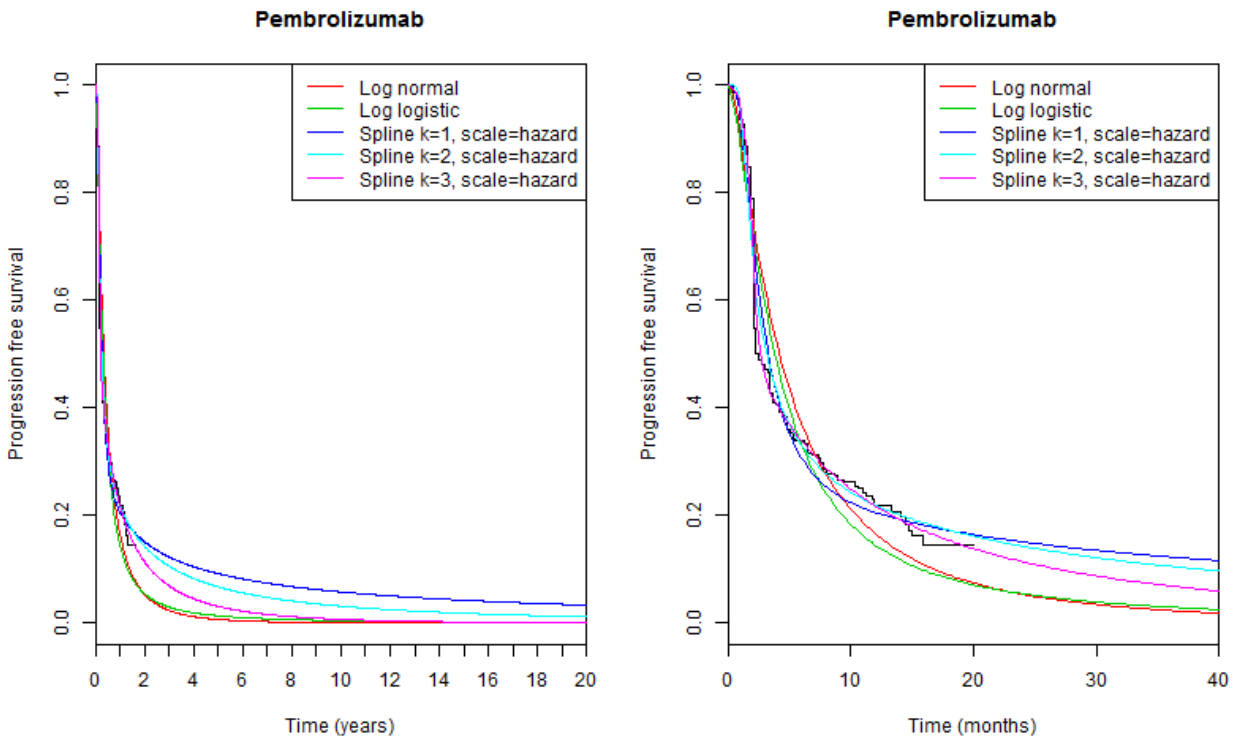
Table 40: Extrapolated long-term overall survival probability for pembrolizumab

Time point	Observed Kaplan Meier	Generalised gamma	Log normal	Spline k=1, scale=hazard	Spline k=2, scale=hazard	Spline k=3, scale=hazard
2 years	-	0.31	0.29	0.31	0.3	0.29
5 years	-	0.14	0.11	0.1	0.08	0.07
10 years	-	0.07	0.04	0.02	0.01	0.01
15 years	-	0.04	0.02	0.01	0	0
20 years	-	0.03	0.01	0	0	0

The goodness-of-fit of PFS models for carboplatin plus gemcitabine and pembrolizumab suggested that only spline with knots=3 fit the KM data well based on both AIC and BIC values (see Table 38). This is also confirmed by the visual inspection of the fitted model (see Figure 17 and Figure 18). The ERG notes that for completeness, the models with the second to fifth lowest AIC values were also presented in Figure 17 and Figure 18. The ERG considers that spline with knots=3 to be the best fit model for both groups.

Figure 17: Progression-free survival Kaplan-Meier curve vs. fitted models for carboplatin plus gemcitabine based on De Santis (2012)

Figure 18: Progression-free survival Kaplan-Meier curve vs. fitted models for pembrolizumab based on KEYNOTE-052



The ERG's preferred model choices for OS and PFS in each group are presented in Table 41. The OS and PFS predicted by this approach, compared with that of the company's predicted OS and PFS are shown in Figure 19 and Figure 20, respectively below. This shows that the ERG's analysis predicts lower survival for pembrolizumab than the company's and greater survival for carboplatin plus gemcitabine than the company's analysis. The ERG's and company's predicted PFS are similar, whilst the shape of the estimated PFS for carboplatin plus gemcitabine is substantially different.

Table 41: The ERG's preferred model choices for overall survival and progression-free survival

Outcome	Pembrolizumab	Carboplatin plus gemcitabine
Overall survival	Log normal	Spline model with knots=2
Progression-free survival	Spline model with knots=3	Spline model with knots=3

Figure 19: Company and ERG predicted base case overall survival

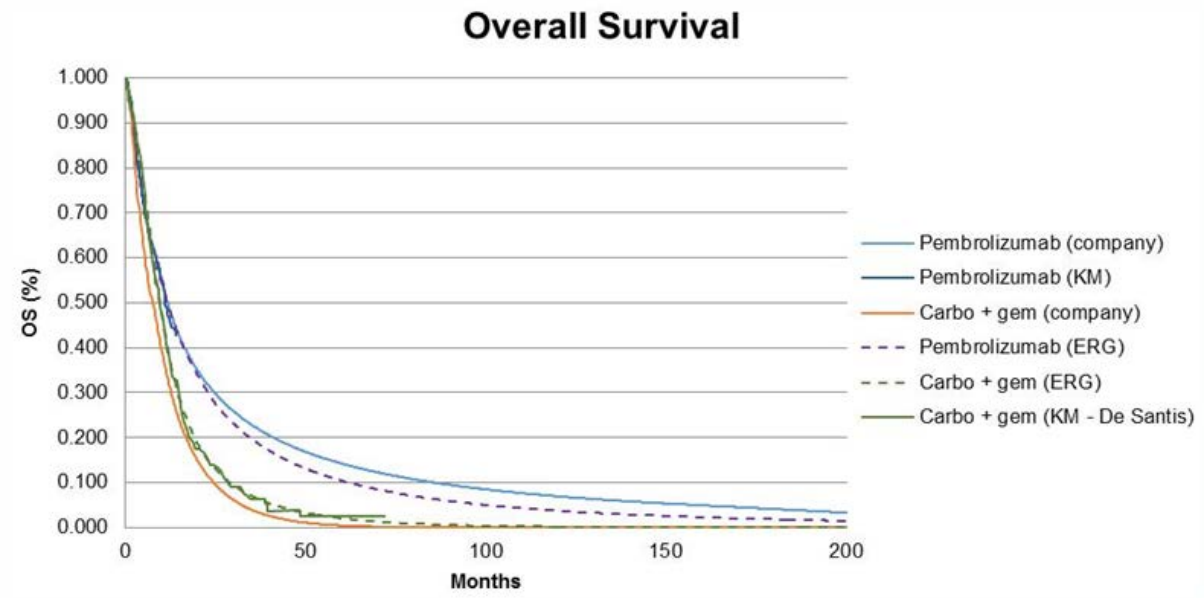


Figure 20: Company and ERG predicted base case progression-free survival

[redacted]

4) Stopping rule/effectiveness of pembrolizumab after 24 months

The company suggest that pembrolizumab will be stopped after 24 months of treatment, and this is the protocol for the KEYNOTE study, although no patients have yet reached this point within the study. The SmPC for pembrolizumab states that 'Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity', and there is no mention of a stopping rule.

Given that a 2-year stopping rule has also been used within other indications, and this is how the company suggest pembrolizumab will be used, the ERG has used this stopping rule in their base case. However, the ERG does not agree that it is reasonable to discontinue the acquisition cost of pembrolizumab at 24 months within the model, whilst making use of the extrapolated PFS and OS from the study where patients did not discontinue treatment, as this is highly likely to overestimate the benefits of the treatment. Within their base case, the ERG has discontinued the acquisition cost of pembrolizumab at 24 months, whilst using the hazard for carboplatin and gemcitabine within the pembrolizumab group beyond 24 months. Alternative assumptions are tested within the ERG's scenario analyses (see Section 5.3.2).

5.3.2 Univariate sensitivity analysis and scenario analyses

The ERG has repeated the univariate sensitivity analyses run by the company using the ERG's preferred base case (where still applicable, given the changes the ERG has made). The ERG has also undertaken further scenario analyses based upon key areas of uncertainty identified within the ERG's critique of the company's model. These are described below. Technical detail of how the model has been amended for each scenario is presented in Appendix 1.

1) Alternative parametric distributions for extrapolation of OS in both groups

As discussed in Section 5.3.1, the extrapolation of the survival curves is highly uncertain, particularly with respect to OS for patients receiving pembrolizumab. There are several plausible distributions for the extrapolation of OS for pembrolizumab, on the basis that both the AIC and BIC were less than five points different between the curves, and the long-term effectiveness is unknown.

2) Assume no stopping rule; treatment continues according to the time on treatment curve

The clinical advisors to the ERG suggest that unless there was guidance to suggest otherwise, in clinical practice they would continue to use pembrolizumab beyond 2 years if it was still benefiting the patient. Therefore, the ERG tested a scenario in which no stopping rule is applied. This analysis uses the extrapolated PFS and OS curves for pembrolizumab, rather than applying a hazard ratio of 1 beyond 2 years as in the base case. Given that the time on treatment curve for pembrolizumab plateaus over time such that it becomes greater than PFS for a substantial time period, a second approach for this analysis assumes that time on treatment is equivalent to PFS.

3) Assume that the hazard ratio is set to 1 for PFS and OS at 3 years instead of 2 years

It is currently unknown how long the benefits of pembrolizumab will continue if treatment is stopped at 2 years. This analysis assumes that the benefits of pembrolizumab will continue for an additional year before the hazard ratio for pembrolizumab versus carboplatin plus gemcitabine is set to 1.

4) 2-year time horizon

This analysis assumes a time horizon of two years, given the substantial uncertainties beyond two years of treatment. This is a very conservative scenario.

5) Utility value in the progressed state

The company suggest that the utility value in the progressed state may be too high because it represents the utility of patients who have recently progressed, and does not account for their lower utility prior to death. The ERG has therefore tested the impact of reducing the utility from 0.61 to 0.55 (the utility estimated for when people have between 30 and 90 days to death) in the progressed state upon the model results.

6) Lower monitoring costs in both arms

The clinical advisors to the ERG suggest that the resources for monitoring patients may be overestimated compared with those used in practice. This analysis assesses the impact of halving the monitoring costs on the model results.

7) Lower cost of carboplatin

The studies of carboplatin and gemcitabine used for the effectiveness estimates were based on lower doses of carboplatin. An analysis halving the cost of carboplatin was undertaken to assess the impact of lower doses upon the model results.

5.4 Conclusions of the cost-effectiveness section

The company's model is generally appropriate for the decision problem defined in the NICE final scope, though it should be noted that the only comparator included within the model was carboplatin plus gemcitabine. This is because there was no evidence for BSC and the evidence for atezolizumab was too uncertain to enable a useful comparison. The model was generally well described within the CS. The model structure was considered by the ERG to be reasonable; however, the simulated ITC lacks validity and there is substantial uncertainty around extrapolation of the survival curves, which was insufficiently presented by the company. The company's probabilistic ICER following the clarification process is £37,081 per QALY gained for pembrolizumab compared with carboplatin plus gemcitabine. Insufficient sensitivity and scenario analyses were undertaken by the company to show the extent of the uncertainty around the model results.

For EGR's base case, the ERG proposes correcting errors relating to the implementation of utilities and to the proportion of males for the calculation of other-cause mortality. The ERG also employs an

approach whereby utilities are varied according to progression status rather than time until death. In addition, the ERG analyses include the extrapolation of the unadjusted data for pembrolizumab and carboplatin plus gemcitabine as part of their base case, as well as incorporating a hazard ratio of 1 for the PFS and OS of pembrolizumab versus carboplatin plus gemcitabine after 24 months of treatment given the proposed stopping rule.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 The ERG's preferred base case

1) Correction of errors within the model

The ERG identified errors relating to the implementation of utilities within the model. These included the starting age for the utility estimates being 72 rather than 73, and incorrect formulae to implement the utilities. The ERG also identified an error relating to the proportion of males for predicting other-cause mortality. These errors were corrected, but do not impact upon the model results substantially, as shown within Table 42 and Table 43.

Table 42: Correcting utilities within the model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£18,011	0.86	0.55	-	-	-	-
Pembrolizumab	£53,645	2.25	1.56	£35,634	1.39	1.01	£35,278
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 43: Correcting life table mortality within the model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£18,011	0.86	0.55	-	-	-	-
Pembrolizumab	£53,630	2.25	1.55	£35,619	1.39	1.01	£35,329
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

2) Utility by progression status

The ERG prefers an analysis in which HRQoL is determined by progression status rather than by time to death within the base case, since the estimated utilities via the latter method are implausibly high for this patient group. This analysis is in addition to the correction of the errors above and is shown within Table 44. This analysis substantially reduces the QALYs associated with pembrolizumab, hence the ICER associated with pembrolizumab compared with carboplatin plus gemcitabine increases to £42,588 per QALY gained.

Table 44: Progression utilities + correction of errors

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£18,011	0.86	0.56	-	-	-	-
Pembrolizumab	£53,630	2.25	1.39	£35,619	1.39	0.84	£42,588
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

3) Extrapolation of OS and PFS in both groups

Given that the ERG is unsure about the validity of the STC undertaken by the company, the ERG has undertaken a naïve analysis in its base case. The results of this analysis include the correction of errors above and utility based upon progression, shown in

Table 45. This shows that using an unadjusted analysis results in an increase in life years and QALYs associated with carboplatin and gemcitabine and a decrease in life years and QALYs associated with pembrolizumab, compared with the adjusted analysis undertaken by the company. This leads to a higher estimated ICER associated with pembrolizumab compared with carboplatin plus gemcitabine of £63,742 per QALY gained.

Table 45: Unadjusted analysis + progression utilities + correction of errors

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£20,065	1.10	0.70				
Pembrolizumab	£51,298	1.90	1.19	£31,233	0.80	0.49	£63,742
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

4) Stopping rule/effectiveness of pembrolizumab after 24 months

Within the ERG's base case, it is assumed that pembrolizumab treatment will be discontinued after a maximum of 24 months treatment. However, rather than assuming that the effectiveness of pembrolizumab will be maintained indefinitely following treatment discontinuation, the ERG prefers the application of a hazard ratio of 1 from the carboplatin and gemcitabine estimates to the pembrolizumab group beyond 24 months within their base case. This analysis also includes all previous amendments described above. This is therefore the ERG's preferred base case, shown within Table 46. As the hazards for the pembrolizumab survival curves are similar to those for the carboplatin plus gemcitabine survival curves beyond 24 months, this analysis does not impact upon the model results

substantially. The ERG deterministic base case ICER is therefore estimated to be £64,333 per QALY gained.

Table 46: Hazard ratio of 1 after 2 years + unadjusted analysis + progression utilities + correction of errors

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£20,065	1.10	0.70				
Pembrolizumab	£51,234	1.89	1.19	£31,168	0.79	0.48	£64,333
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The probabilistic results for the ERG's base case are shown in Table 47. The probabilistic ICER is estimated to be £66,588. There is a 0% chance of pembrolizumab being cost-effective at £30,000 per QALY gained and an 8% chance of pembrolizumab being cost-effective at £50,000 per QALY gained. However, it should be noted that the PSA does not account for the structural uncertainties in the model, in particular the extrapolation of pembrolizumab OS.

Table 47: ERG's probabilistic base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£20,292	1.10	0.70				
Pembrolizumab	£51,313	1.89	1.19	£31,021	0.77	0.47	£66,588
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

6.2 The ERG's sensitivity analysis

The ERG has re-run the deterministic univariate sensitivity analyses undertaken by the company using the new ERG base case and excluding those analyses which are no longer applicable (e.g. hazard ratios for carboplatin and gemcitabine), shown within Table 48. This suggests that the parameters varied by the company in their univariate sensitivity analysis do not impact upon the ERG's model results substantially, with the weekly cost in the progression-free state following pembrolizumab treatment having the largest impact upon the model results. This analysis results in ICERs for pembrolizumab versus carboplatin plus gemcitabine in the range £61,647 to £67,019 per QALY gained.

Table 48: The company's univariate sensitivity analyses, rerun (where appropriate) using the ERG's base case

Parameter	Parameter input value			ICER (£/QALY)	
	Base value	Low value	High value	Low value	High value
ERG base case	N/A	N/A	N/A	£64,333	
Patient age (years)	73	68	78	£63,940	£65,371
Weekly cost in progressive disease state	£136.07	£109.40	£162.74	£62,601	£66,064
Weekly cost in progression-free disease state – pembrolizumab	£154.61	£124.31	£184.92	£61,647	£67,019
Weekly cost in progression-free disease state – gemcitabine + carboplatin	£154.61	£124.31	£184.92	£66,405	£62.260
Subsequent treatment cost – pembrolizumab	£518.95	£417.24	£620.66	£64,228	£64,437
Cost of end-of-life care	£7,252.82	£5,831.29	£8,674.34	£64,424	£64,241
Treatment administration cost					
Deliver simple parenteral chemotherapy at first attendance	£253.32	£208.33	£308.02	£63,281	£65,612
Deliver subsequent elements of a chemotherapy treatment cycle	£211.99	£174.34	£257.77	£65,100	£63,399
Deliver complex chemotherapy	£336.57	£276.80	£409.25	£64,950	£63,582
Occurrence of adverse events					
Fatigue in patients receiving pembrolizumab	5.14%	3.00%	8.00%	£64,206	£64,502
Febrile neutropenia in patients receiving gemcitabine + carboplatin	4.44%	2.00%	7.00%	£64,485	£64,174
Utility					
Disutility associated with adverse events - pembrolizumab	0.12	0.08	0.17	£64,531	£64,080

The ERG has also undertaken some additional sensitivity analyses which were not undertaken by the company, to assess plausible alternative assumptions (described in Section 5.3.2). The results of these analyses are presented in Table 49. These analyses show that the ICER is highly uncertain. In particular, the choices of extrapolation for the OS of pembrolizumab and the stopping rule for pembrolizumab have the largest impacts upon the ICER. There were four alternative curves that the ERG tested (3 spline models and Generalised gamma) which provide a good statistical fit (based on AIC and BIC) and visual fit to the pembrolizumab OS data, and for which our clinicians suggest all could be clinically plausible since long-term survival is unknown. These result in ICERs for pembrolizumab versus carboplatin plus gemcitabine ranging from £48,330 to £97,140 per QALY gained. Using the log normal distribution for pembrolizumab OS, as in the ERG base case, and assuming no stopping rule for pembrolizumab, increases the ICER to £84,905 or £136,971, dependent upon time on treatment curve extrapolation assumptions. Whilst lowering the cost of carboplatin does not substantially impact upon the model results, it should be noted that the direction of effect is to increase the ICER. A comparison with BSC would likely have the same direction of effect upon the ICER.

Table 49: Additional scenario analysis undertaken by the ERG

Parameter modified	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base case	£31,169	0.79	0.48	£64,333
Alternative distributions for pembrolizumab OS (base case = lognormal)(£/LY)				
Generalised gamma	£33,634	1.16	0.70	£48,330
Spline k=1, scale=hazard	£30,660	0.71	0.44	£69,263
Spline k=2, scale=hazard	£29,621	0.56	0.35	£83,840
Spline k=3, scale=hazard	£28,980	0.47	0.30	£97,140
Alternative assumptions about pembrolizumab stopping rule/ efficacy following treatment discontinuation				
Assume no stopping rule; treatment continues based on the ToT/ OS curve treatment continues based on the PFS curve	 £67,115 £41,603	 0.80 0.80	 0.49 0.49	 £136,971 £84,905
Assume that HR=1 for PFS and OS at 3 years	£31,191	0.79	0.49	£64,131
2 year time horizon	£25,570	0.15	0.10	£258,223
Utility value in the progressed state for both treatment groups				
Reducing the utility from 0.61 to 0.55	£31,169	0.79	0.45	£69,874
Monitoring costs				
Half the cost of monitoring	£28,271	0.79	0.48	£58,352
Cost of carboplatin				
Half the cost of carboplatin	£31,254	0.79	0.48	£64,508

7 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when all 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.

Using the evidence from the study by De Santis (2012)[16], the health economic model predicts that mean survival for patients receiving carboplatin plus gemcitabine will be less than 24 months, with around 10%-15% of patients receiving carboplatin plus gemcitabine being alive at 24 months. It also predicts that pembrolizumab will increase mean overall survival by more than 3 months for all overall survival curves tested.

8 OVERALL CONCLUSIONS

The systematic review presented in the CS appears to be comprehensive. The review included is a phase II, single-arm, open-label, non-randomised study (KEYNOTE-052) for pembrolizumab, one RCT (De Santis (2012)[16]; only the carboplatin plus gemcitabine arm is included) and three cohort studies (Bamias (2007)[19], Carles (2000)[17], Linardou (2004)[18]) for carboplatin plus gemcitabine. There was considerable heterogeneity among the comparator studies with regard to patients and dosage and administration of gemcitabine and carboplatin. There was no evidence to suggest that patients in KEYNOTE-052 are less fit or frailer than patients in the comparator studies.

The STC performed by the company to adjust for cross-study differences in patient's baseline characteristics lacks validity as the treatment effect of pembrolizumab for both PFS and OS was more favourable using the adjusted data compared to the observed data in KEYNOTE-052. The ERG does not believe this to be valid because there is no evidence to indicate that the patients in KEYNOTE-052 were less fit or frailer than patients in the comparator studies. For the evidence synthesis, a second fractional polynomial model with p1=p2=0, which estimates time-varying hazard ratios, was chosen as the best fitting model. It was determined in response to clarification that p1=p2=-2 was the overall best fitting model, which provided less favourable results for pembrolizumab when compared with the fractional polynomial model with p1=p2=0. However, only the estimates from the fractional polynomial with p1=p2=0 were used in the economic model.

The company's health economic model is generally appropriate for the decision problem defined in the NICE final scope, though it should be noted that the only comparator tested within the economic evaluation was carboplatin plus gemcitabine. This is because there was no evidence for BSC and the evidence for atezolizumab was too uncertain to enable a useful comparison. The model was generally well described within the CS. The model structure was considered by the ERG to be reasonable; however, as discussed above, the simulated ITC lacks validity and there is substantial uncertainty around extrapolation of the survival curves, which was not explored sufficiently by the company. The company's probabilistic ICER following the clarification process is £37,081 per QALY gained for pembrolizumab compared with carboplatin plus gemcitabine, taken from their health economic model.

The ERG has corrected errors relating to the implementation of utilities and to the proportion of males for the calculation of other-cause mortality. The ERG has also employed an approach where utilities are varied according to progression status rather than time until death. In addition, the ERG has included extrapolation of the unadjusted data for pembrolizumab and carboplatin plus gemcitabine as part of their base case, as well as incorporating a hazard ratio of 1 for the PFS and OS of pembrolizumab versus carboplatin plus gemcitabine after 24 months of treatment given the proposed stopping rule. The

changes made by the ERG having a substantial impact upon the ICER are the utility approach and the extrapolation of survival data.

The ERGs probabilistic base case ICER is £66,588 per QALY gained. The scenario analyses run by the ERG suggested that the ICER is highly uncertain. In particular, the choices of extrapolation for the OS of pembrolizumab and the stopping rule for pembrolizumab have the largest impacts upon the ICER, with a cost per QALY gained for pembrolizumab versus carboplatin plus gemcitabine ranging from £48,330 to £136,971 under plausible assumptions.

8.1 Implications for research

Further research is required comparing pembrolizumab with relevant comparators within an RCT. Comparators would ideally include carboplatin plus gemcitabine, BSC and atezolizumab. Follow up beyond two years is required in order to reduce uncertainty around the impact of pembrolizumab upon overall survival, particularly if a stopping rule for pembrolizumab treatment at 2 years is to be used.

One RCT of pembrolizumab, where pembrolizumab versus carboplatin plus gemcitabine is one of the treatment groups, is currently recruiting and ongoing, with a subgroup of patients being cisplatin-ineligible (KEYNOTE-361). Final results are expected on 18th May 2020, which may not be long enough to capture the survival benefits attributable to pembrolizumab.

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10 APPENDICES

Appendix 1: Technical appendix detailing methods for applying the ERG's exploratory analyses within the company's model

The ERG's preferred base case

Step 1: Correction of errors within the model

Correct utility errors

1. Go to 'utility' worksheet
2. Type 0.0212126 in cell D59, with an accompanying label of 'male'
3. Type 0.9508566 in cell D60, with an accompanying label of 'intercept'
4. Type the formula =ROUNDDOWN(p.PatientAge,0) in cell C62
5. Type the formula =IFERROR(E62/$E$62,0) in cell D62
6. Copy the formula down column D
7. Type the formula =IF(s.utility.age=1,IFERROR(C62*$D$57+C62^2*$D$58+GenInputs!$G$19*Utility!$D$59+Utility!$D$60,0),0) in cell E62
8. Copy the formula down column E
9. Go to 'PF - Pembro' worksheet
10. Replace the '+' with a '*' in the formulae in cells AA9, AB9, AC9, AD9, AE9, AF9 and AG9. For example, AA9 should read =V9*(p.TTD5.pembro*VLOOKUP(ROUNDDOWN(p.PatientAge+B9,0),Utility!$C$62:$E$137,2,TRUE))*7/365.25
11. Copy the formulae down columns AA, AB, AC, AD, AE, AF and AG.

Correct life table error

1. Type =(GenInputs!G19/(L6/(L6+R6))) in cell V2
2. Type =$V$2*(L6/(L6+R6)) in cell V6
3. Type =1-V6 in cell W6
4. Copy the formulae down columns V and W

Step 2: Utility by progression status

1. Go to 'Settings' worksheet
2. Select 'Utility by progression status' in the drop down options for the 'Approach of evaluating utility'

Step 3: Extrapolation of OS and PFS in both groups

1. Go to 'Estimation – Pembro' worksheet
2. Copy across S(t)s estimated in R for each alternative distribution for OS and PFS for pembrolizumab
3. Type the formula =IF($B17<=$AD$12,X17,(1-NORMDIST(LN($C17),$AA$5,EXP($AA$6),TRUE)*$X$14)) for the lognormal distribution for OS and copy across the coefficients for the lognormal distribution, since this will be the base case and used in the PSA

4. Create 3 new worksheets ‘OS Comp Samples’, ‘PFS Pemb Samples’ and ‘PFS Comp Samples’ and copy the S(s)s for the respective spline curves for 100 samples of the PSA, generated in R.
5. Create a fourth new worksheet ‘Estimation – carbo & gem’
6. Copy and paste the entire contents of Estimation - Pembro’ to ‘Estimation – carbo & gem’
7. Copy across S(t)s estimated in R for each alternative distribution for OS and PFS for carboplatin plus gemcitabine
8. Set cell G17 = F17 and copy the formula down column G
9. Go to ‘PF – Carbo+Gem’ worksheet
10. Type =MIN('Estimation - carbo & gem'!E17,'Estimation - carbo & gem'!F17) in cell F8
11. Copy the formula down column F
12. Type =1-'Estimation - carbo & gem'!E17 in cell H8
13. Copy the formula down column H
14. Go to ‘Settings’ worksheet
15. In column U, revise the options for the PFS curves to include ‘Generalised gamma, Gamma, Log normal, Weibull, Exponential, Gompertz, Log logistic, Spline k=1,scale=hazard, Spline k=2,scale=hazard, Scale k=3, scale=hazard, Spline k=1, scale= normal, Spline k=2, scale=normal’
16. Use design mode to incorporate these into the drop down options for ‘PFS of pembrolizumab’ and ‘PFS of Carbo+Gem’
17. In column W, revise the options for the OS curves to include ‘Generalised gamma, Gamma, Log normal, Weibull, Exponential, Gompertz, Log logistic, Spline k=1,scale=hazard, Spline k=2,scale=hazard, Scale k=3, scale=hazard, Spline k=1, scale= odds, Spline k=2, scale=odds, Spline k=3, scale=odds’
18. Use design mode to incorporate these into the drop down options for ‘OS of pembrolizumab’ and ‘OS of Carbo+Gem’
19. Add an additional column Z and include options for the Time on Treatment curves including ‘Exponential, Weibull, Lognormal, Log logistic, Gompertz, Generalised Gamma and Same as PFS’
20. Use design mode to incorporate these into the drop down options for ‘ToT of pembrolizumab’

Step 4: Stopping rule/effectiveness of pembrolizumab after 24 months

1. Go to ‘Settings’ worksheet
2. Add in 2 rows under row 45.
3. In cell D47, add ‘Assume carbo hazard applied to pembro arm after X weeks for PFS and OS’
4. Add a drop down box with a ‘yes/ no’ option
5. In cell S47 add ‘104’ for the number of weeks, with an accompanying label of ‘X weeks’
6. Go to ‘Estimation = carbo & gem’ worksheet
7. Add 2 new columns after column G called ‘OS hazard’ and ‘PFS hazard’ (now columns H and I respectively)
8. Type the formula =IFERROR(IF(E18=0,1,E18/E17),1) in cell H18
9. Type the formula =F18/F17 in cell I18
10. Copy the formulae down column H and I
11. Go to ‘Estimation – Pembro’
12. Add 2 new columns after column F called ‘OS – with hazard’ and ‘PFS – with hazard’ (now columns G and H respectively).
13. Type the formula =IF(Settings!$N$47=2,'Estimation - Pembro'!D17,IF('Estimation - Pembro'!B17<=Settings!$S$47,'Estimation - Pembro'!D17,('Estimation - Pembro'!D17*'Estimation - carbo & gem'!H18))) in cell G17

14. Type the formula =IF(Settings!$N$47=2,'Estimation - Pembro'!E17,IF('Estimation - Pembro'!B17<=Settings!$S$47,'Estimation - Pembro'!E17,'Estimation - Pembro'!E17*'Estimation - carbo & gem'!I18)) in cell H17
15. Copy the formulae down column G and H
16. Go to 'PF – Pembro' worksheet
17. Type the formula =MIN('Estimation - Pembro'!G17,'Estimation - Pembro'!H17) in cell F8
18. Copy the formula down column F
19. Type the formula =1-'Estimation - Pembro'!G17 in cell H8
20. Copy the formula down column H
21. Type the formula =IF(s.pem.trt.duration*3<D8,0,MIN('Estimation - Pembro'!G17,'Estimation - Pembro'!F17)) in cell J8
22. Copy the formula down column J

The Company's univariate sensitivity analysis re-run (where appropriate), using the ERG's base case.

The input values and associated ICER's are presented in Table 47.

1. Patient age (years): The lower and upper values were used to replace the value in cell G18 on the 'GenInputs' worksheet.
2. Weekly cost in progressive disease state: The lower and upper values were used to replace the value in cell G23 on the 'CostInputs' worksheet.
3. Weekly cost in progression free disease state – Patients receiving pembrolizumab: The lower and upper values were used to replace the value in cell G20 on the 'CostInputs' worksheet.
4. Weekly cost in progression free disease state – Patients receiving gemcitabine + carboplatin: The lower and upper values were used to replace the value in cell G21 on the 'CostInputs' worksheet.
5. Subsequent treatment cost – Patients receiving pembrolizumab: The lower and upper values were used to replace the value in cell C56 on the Parameters worksheet.
6. Cost of end-of-life care: The lower and upper values were used to replace the value in cell G29 on the CostInputs worksheet.
7. Deliver simple parenteral chemotherapy at first attendance: The lower and upper values were used to replace the value in cell G10 on the CostInputs worksheet.
8. Deliver subsequent elements of a chemotherapy treatment cycle: The lower and upper values were used to replace the value in cell G12 on the CostInputs worksheet.
9. Deliver complex chemotherapy: The lower and upper values were used to replace the value in cell G11 on the CostInputs worksheet.
10. Fatigue in patients receiving pembrolizumab: The lower and upper values were used to replace the value in cell F31 of the RxInputs worksheet.
11. Febrile neutropenia in patients receiving gemcitabine + carboplatin: The lower and upper values were used to replace the value in cell J32 of the RxInputs worksheet.
12. Disutility associated with adverse events in patients receiving pembrolizumab: The lower and upper values were used to replace the value in cell D24 of the Utility worksheet.

Additional scenario analyses undertaken by the ERG

These are described in full in Section 5.3.2.

1. Generalised gamma distribution used for pembrolizumab overall survival: The appropriate distribution was selected from the drop-down menu in cell K53 of the 'Settings' worksheet.
2. Spline k = 1, scale = hazard distribution used for pembrolizumab overall survival: The appropriate distribution was selected from the drop-down menu in cell K53 of the 'Settings' worksheet.
3. Spline k = 2, scale = hazard distribution used for pembrolizumab overall survival: The appropriate distribution was selected from the drop-down menu in cell K53 of the 'Settings' worksheet.
4. Spline k = 3, scale = hazard distribution used for pembrolizumab overall survival: The appropriate distribution was selected from the drop-down menu in cell K53 of the 'Settings' worksheet.
5. Assuming no stopping rule treatment continues based on the TOT/OS curve: A large number (eg. 1000) was used to replace the number in cell J63 of the 'Settings' worksheet and the drop-down menu in cell L47 was set to 'No' so that a hazard ratio was not applied.
6. A large number (eg. 1000) was used to replace the number in cell J63 of the 'Settings' worksheet and the drop-down menu in cell L47 was set to 'No' so that a hazard ratio was not applied. In addition, ToT was selected to be 'Same as PFS' in the drop-down menu in cell K59 of the Settings worksheet.
7. Assuming a HR of 1 for PFS and OS at three years: The value in cell S47 of the 'Settings' worksheet was changed to 156 (=3*52).
8. Two-year time horizon: The value in cell G8 of the GenInputs worksheet was changed from 20 to 2.
9. Reducing the utility in the progressive disease state for both treatment groups from 0.61 to 0.55. The new value (0.5476) was used to replace the value in cell D19 of the 'Utility' worksheet.
10. Half the cost of monitoring: Go to 'HCRU' worksheet. Divide the values in cells C10 and E10 by 2.
11. Half the cost of carboplatin: Go to 'CostCalc' worksheet. Divide the value in cell C7 by 2.