Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

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Contributions of authors

Xavier Armoiry (Senior Research Fellow) helped co-ordinate the project and the report, and conducted, reviewed and critiqued the clinical effectiveness evidence; Theodoros Mantopoulos (Research Associate) conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Daniel Gallacher (Research Associate) conducted, reviewed and critiqued the survival analysis and cost-effectiveness evidence; Peter Auguste (Research Fellow) conducted, reviewed and critiqued the survival analysis and undertook additional analyses; Jacoby Patterson (Independent Research Consultant) conducted, reviewed and critiqued the clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional analyses; Karoline Munro (Research Project Administrator) conducted, reviewed and critiqued the background section; Maria De Santis (Associate Clinical Professor) provided expert clinical advice; Joanne Cresswell (Consultant Urological Surgeon) provided expert clinical advice; Hema Mistry (Assistant Professor) co-ordinated the project and

the report, and reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

AE	Adverse Event
AEOSI	AEs of Special Interest
AIC	Akaike Information Criterion
ALK	Anaplastic Lymphoma Kinase
APaT	All Patients as Treated
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BOR	Best Overall Response
BSA	Body Surface Area
BSC	Best Supportive Care
CEAC	Cost-Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIS	Carcinoma In Situ
CPS	Combined Positive Score
CRD	Centre for Review and Dissemination
CR	Complete Response
CS	Company Submission
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DoR	Duration of Response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMit	Electronic Market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology

EU	European Union
FDA	Food and Drug Administration
FAS	Full Analysis Set
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IPCW	Inverse Probability of Censoring Weighting
ITT	Intention-To-Treat
IVRS/IWRS	Interactive Voice Response System/ Interactive Voice and Web Response System
KM	Kaplan Meier
LS	Least Squares
LTUC	Lower Tract Urinary Cancers
LYG	Life Year Gained
MIBC	Muscle Invasive Bladder Cancer
MHRA	Medicines & Healthcare Products Regulatory Agency
mRECIST	Modified RECIST
MSD	Merck Sharp and Dohme
MVAC	Methotrexate, Vinblastine, Doxorubicin and Cisplatin
NMA	Network Meta-Analysis
NCCN	National Comprehensive Cancer Network
NMB	Net Monetary Benefit
NMIBC	Non-Muscle Invasive Bladder Cancer
NSCLC	Non-Small Cell Lung Cancer
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Objective Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
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
PICOS	Population Intervention Comparator Outcome Study design
PIM	Promising Innovative Medicines
PR	Partial Response
PS	Performance Score
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	Quality Assessment
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
RoB	Risk of Bias
RPSFT	Rank Preserving Structural Failure Time
RR	Response Rate
SD	Standard Deviation
SOC	Standard of Care
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
StD	Stable Disease
TA	Technology Appraisal
ToT	Time on Treatment
TPS	Tumour Proportion Score
TTP	Time To Progression
TTR	Time To Response
TNM	Tumour, Node and Metastases
UK	United Kingdom
US	United States

UTUC	Upper Tract Urinary Cancers
VAS	Visual Analogue Score
WTP	Willingness To Pay

1 SUMMARY

1.1 Critique of the decision problem in the company submission

The company submission (CS) decision problem matches the population, the intervention and outcomes described in the final National Institute of Health Care and Excellence (NICE) scope, as seen in Box 1. The CS decision problem differs from the NICE scope on the comparators, with retreatment with 1st line platinum-based chemotherapy, and best supportive care (BSC) being excluded from the decision problem.

As of April 2017, pembrolizumab is not licensed for the treatment of the scoped population since the submission is being appraised by the Committee for Medicinal Products for Human Use (CHMP).

The proposed indications submitted to the European Medicines Agency (EMA) by the company are:

- treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy.
- treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

	Final scope issued by NICE
Population	Adults with locally advanced and unresectable or metastatic urothelial cancer that have progressed on or after platinum-containing chemotherapy.
Intervention	Pembrolizumab
Comparator (s)	• Retreatment with 1st line platinum-based chemotherapy (only for people whose disease has had an adequate response) • Docetaxel • Paclitaxel • Best supportive care (BSC)
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates (RRs) • Adverse effects (AEs) of treatment

	• Health-related quality of life (HRQoL)

Box 1: NICE Final Scope

1.2 Summary of submitted clinical effectiveness evidence

The CS undertook a systematic review for evidence of clinical effectiveness of relevance to the decision problem. The review included searches for studies on the intervention and comparators for a potential network meta-analysis (NMA).

The CS includes direct evidence of pembrolizumab compared with standard of care (SOC) which comprised of docetaxel, paclitaxel or vinflunine from one phase 3 randomised controlled trial (RCT) - KEYNOTE-045. The CS presents outcomes of survival (progression-free survival, overall survival), response rates, health-related quality of life and adverse events.

The main results according to the population stated in the primary objectives are summarised below. For assessment of response, only results per response evaluation criteria in solid tumours (RECIST) 1.1 criteria by blinded independent committee review (BICR) are presented:

Entire population:

- For PFS, the hazard ratio (HR) suggested no reduction in risk of progression or death (HR 0.98, 95% CI: 0.81, 1.19) with pembrolizumab although the PFS at 12 months was higher in the pembrolizumab group (16.8% vs. 6.2%).
- For OS, the HR indicated better outcome in those treated with pembrolizumab compared with SOC (HR for death 0.73, 95% CI: 0.59, 0.91).
- The rate of objective response (complete or partial response) was higher with pembrolizumab compared to SOC (21.1% vs. 11.4%; p=0.00106).
- Using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, the score was stable from baseline to week 15 with pembrolizumab, while the score decreased with SOC; the difference in least squares (LS) means between both arms was 9.05 (95% CI: 4.61, 13.48) favouring pembrolizumab. Time to traditional deterioration (a 10-point or greater score decrease from baseline) was prolonged with pembrolizumab (HR 0.70, 95% CI: 0.55, 0.90).

- The scores using EuroQol 5 Dimensions (EQ-5D) instruments (visual analogue score (VAS) and utility) showed similar results (stable scores with pembrolizumab and worsened scores with SOC).
- The most common treatment-related adverse events of any grade were pruritus (19.5%), fatigue (13.9%), and nausea (10.9%) in the pembrolizumab group and alopecia (37.6%), fatigue (27.8%), and anaemia (24.7%) in the SOC arm. There were no treatment-related events of grade ≥ 3 severity that occurred with an incidence of ≥5% in the pembrolizumab group. In the SOC arm, treatment-related events of grade ≥ 3 severity with an incidence ≥5% were neutropenia (13.3%), decreased neutrophil count (12.2%), anaemia (7.8%), febrile neutropenia (7.1%), and decreased white-cell count (5.1%).

Patients positive for Programmed cell Death 1 ligand 1 (PD-L1) expression (combined positive score (CPS) ≥1%):

- For PFS, the HR suggested no reduction in risk of progression or death (HR 0.91, 95% CI: 0.68, 1.24) with pembrolizumab although the PFS at 12 months was higher (20.9% vs. 4.4%).
- For OS, the hazard ratio indicated better outcome in those treated with pembrolizumab compared with SOC (HR for death 0.61, 95% CI: 0.43, 0.86).
- The rate of objective response (complete or partial response) was higher with pembrolizumab compared to SOC (23.6% vs. 8.3%; p=0.00022)

Patients strongly positive for PD-L1 expression (CPS≥10%):

- For PFS, the HR suggested no reduction in risk of progression or death (HR 0.89, 95% CI: 0.61, 1.28) with pembrolizumab although the PFS at 12 months was higher (17.7% vs. 3.7%).
- For OS, the hazard ratio indicated better outcome in those treated with pembrolizumab compared with SOC (HR for death 0.57, 95% CI: 0.37, 0.88).
- The rate of objective response (complete or partial response) was higher with pembrolizumab compared to SOC (21.6% vs. 6.7%; p=0.00020)

Subgroup analyses:

- Most of the analyses of OS by subgroup showed consistency of survival benefit favouring pembrolizumab with consistent point estimates for the HR in important subgroups such as Eastern Cooperative Oncology Group (ECOG) Performance Score (PS), liver metastasis, haemoglobin, time from prior chemotherapy, prior platinum (cisplatin versus carboplatin), investigator's choice of chemotherapy in control arm (paclitaxel, docetaxel or vinflunine), and Bellmunt risk scores.
- The ERG believes that the results in people with negative PD-L1 expression are inconclusive.

The CS attempted to present indirect and mixed treatment comparisons but no network meta-analysis was undertaken owing to a disconnected network. The ERG believes that an exploratory NMA could have been undertaken to compare pembrolizumab indirectly to BSC. However, given that this comparison would have used data from people with ECOG PS 0-2 and that BSC is only a relevant comparator in people with ECOG PS>2, the relevance of these estimates would have been questionable.

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

The ERG considered the systematic review to be of reasonable quality and substantially agreed with the CS appraisal of the pivotal phase 3 trial comparing pembrolizumab with standard of care (SOC). SOC included vinflunine (which is not a drug recommended within the NHS), and two of the scoped comparators, paclitaxel or docetaxel. The outcomes and analytical approach to the phase 3 trial were appropriate. The population in the trial appear to be relevant to those treated in the NHS. The KEYNOTE-045 trial was of good quality, with a low risk of bias in most domains except for the blinding of participants and personnel since the study was open-label (high-risk of bias). Given the presence of a key-domain rated as high-risk of bias, the ERG concludes that the KEYNOTE-045 as a whole is at high risk of bias.

However, even if the study had been double-blinded, the ERG believes that the KEYNOTE-045 study would still have been at high-risk of performance bias. That is because, given the very specific safety profile of the drugs evaluated in the KEYNOTE-045 trial, it would be very likely that both patients and clinicians might have identified which arms patients were in.

The ERG noted several issues with the submitted clinical evidence.

- The ERG has concerns regarding the exclusion of two scoped comparators, BSC and retreatment with a platinum-based regimen, from the decision problem.
- The company justified the exclusion of BSC stating that alternative treatments are available (e.g. docetaxel and paclitaxel). While the statement is true, these drugs are offered only in people with good performance status, which is the population included in KEYNOTE-045. In people with poorer PS (>2), BSC is a valid option within the NHS. Since KEYNOTE-045 only included patients with PS≤2, the CS includes no evidence on the clinical effectiveness of pembrolizumab in people who would otherwise be offered BSC.
- The company justified the exclusion of a retreatment with platinum-based chemotherapy since there is no evidence to compare with pembrolizumab. The ERG agrees there is no evidence but disagrees that this makes a treatment with platinum-based chemotherapy an irrelevant comparator.
- The anticipated label indication of pembrolizumab is broader than the population in KEYNOTE-045. If the label indication does not restrict the use of pembrolizumab to patients who previously received a platinum-based regimen, the label indication cannot be supported by clinical evidence since 100% of people in KEYNOTE-045 had a prior platinum-based regimen. Some evidence on the effectiveness of pembrolizumab in people ineligible for cisplatin will be provided by the full results of KEYNOTE-052 that is a single-arm study that enrolled 370 patients.
- Assuming pembrolizumab obtains a label indication in patients with urothelial cancers regardless of the PD-L1 expression, this means that patients who are negative for PD-L1 expression could also be offered pembrolizumab which is a drug that specifically acts on the PD-L1 pathway. As previously stated, the ERG believes that the results in people with negative PD-L1 expression are inconclusive.
- The evaluation of the quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, no reliable conclusion can be drawn from the quality of life results.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a *de novo* partitioned survival model comparing pembrolizumab with UK SOC i.e. investigator's choice of paclitaxel or docetaxel. A weekly cycle length and a lifetime horizon were used. The model had three defined health states: progression-free, progressed disease and death. All patients in the pembrolizumab and UK SOC arms started in the progression-free health state.

The population modelled in this submission were patients with metastatic or locally advanced/unresectable urothelial cancer which has recurred or progressed following platinum containing chemotherapy.

The company also presented results for the following subgroups of patients in the Appendix:

- Patients with advanced or metastatic urothelial cancer of predominantly transitional cell histology.
- Patients with advanced or metastatic urothelial cancer of pure transitional cell histology.
- Patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥1%) urothelial cancer.
- Patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥10%) urothelial cancer.

Data for pembrolizumab and UK SOC arms came from the KEYNOTE-045 trial. For the UK SOC, overall survival was estimated by adjusting for treatment switching using a two-stage adjustment method. Overall survival and progression-free survival for pembrolizumab and UK SOC were both derived using a piecewise modelling approach:

- For overall survival, KEYNOTE-045 Kaplan-Meier data was used for the initial period of 40 weeks with a log-normal distribution fitted to data beyond 40 weeks.
- For progression-free survival, KEYNOTE-045 Kaplan-Meier data was used for the first 21 weeks, with an exponential distribution fitted to data beyond 21 weeks.

Quality of life values were obtained using EQ-5D-3L from the KEYNOTE-045 trial. For the base-case analysis, utility values were estimated based on time-to-death. Time-to-death was categorised in the following groups: 360 or more days to death, 180 to 360 days to death, 90 to 180 days to death, 30 to 90 days to death, and under 30 days to death. The company included

data for patients receiving vinflunine in the estimation of utility values, however, vinflunine is not currently recommended in England. Quality of life losses associated with adverse events and ageing were included in the base-case analysis.

The National Health Service (NHS) and Personal Social Services (PSS) perspective was adopted for the costs. An annual discount rate of 3.5% was used for both costs and outcomes. Costs of treatment with pembrolizumab were provided by the company. Pembrolizumab treatment was assumed to continue until disease progression, unacceptable toxicity or a maximum of 24 months of uninterrupted treatment (approximately 35 cycles). The treatment effect was assumed to persist for the lifetime of the model. For UK SOC, patients received treatment for a maximum of six cycles to reflect UK clinical practice. To estimate the duration of treatment in the pembrolizumab and UK SOC arms, time on treatment data from KEYNOTE-045 was used. UK SOC treatment costs were obtained from the latest electronic market information tool (eMit). The model also included costs for adverse events, routine care and terminal care.

The base-case analysis indicates that pembrolizumab provides additional quality-adjusted life years (QALYs) but at an additional cost. The deterministic incremental cost-effectiveness ratio (ICER) is £45,833 per QALY for pembrolizumab versus UK SOC with a patient access scheme (PAS). Probabilistic results were in close agreement with deterministic results. The parameters included in sensitivity analyses to which these estimates are most sensitive to are the parameters in the lognormal distributions used to model overall survival in the pembrolizumab and UK SOC arms. The ICER is also sensitive to the discount rate applied to health outcomes.

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

The model constructed by the company is logical and appears to capture two important features of the disease (progression-free survival and overall survival). The cycle length (7 days) is sufficiently short to allow accurate modelling of changes over short time periods. The perspective, time horizon and discount rates chosen by the company follow NICE recommendations, and are appropriate to the decision problem.

Other than two easily fixed errors (application of maximum time on treatment and estimation of QALYs), which the company corrected and provided an updated model, there were no

discrepancies found between the models reported in the company submission and the copy of the model given to the ERG.

The overall survival modelling methods used are not well justified. The ERG believes that a 24 week cut-off point in the piece-wise modelling approach and a log-logistic parametric survival model should be used in the economic model. Furthermore, the CS compared the extrapolated OS for people in the UK SOC with that reported by Cancer Research UK for patients with stage IV bladder cancer. The ERG however, has concerns regarding the comparability of people in the KEYNOTE-045 trial with those from Cancer Research UK.

The CS model incorporates utility scores based on time to death, which results in a relatively unusual method to estimate life years (based on death incidence) and subsequent QALYs. In addition, this approach slightly overestimates life years in both pembrolizumab and UK SOC arms relative to life years based on progression status. The ERG believes that using utility scores based on progression status is a more appropriate method to estimate life years and subsequent QALYs.

The base-case analysis included data for patients receiving vinflunine in the estimation of utility values, which is currently not recommend in England. The ERG believes that such patients should have been excluded from the analysis.

The age-related utility decrements are estimated from an outdated study that does not allow incorporation of decrements for patients aged more than 75 years old. The ERG believes that this is a limitation that possibly overestimates QALYs in both treatment arms.

In the base-case analysis, pembrolizumab was compared to UK SOC based on the distribution of the regimens observed in KEYNOTE-045. The ERG believes that cost of UK SOC should be based on the UK market share of docetaxel and paclitaxel.

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

1.6.1 Strengths

Overall, the quality of the systematic reviews of clinical effectiveness and of cost-effectiveness were reasonable and all relevant evidence have been identified.

The CS had several strengths:

- Overall, the quality of the systematic review was deemed to be reasonable, and assessment of risk of bias of the pivotal RCT was generally appropriate.
- The quality of the included trial was good, despite being an open-label trial, with a low risk of bias in most domains.
- The pivotal RCT had a comparator arm comprised of three possible drugs which is a good reflector of clinical practices since there is no internationally admitted comparator at this disease stage.
- The patient population recruited in the trial appears to be broadly similar to patients likely to receive pembrolizumab in England.
- Results for the trial were accurately presented and showed the risks and benefits of pembrolizumab compared to SOC.
- The company has undertaken an extensive survival analysis to model overall and progression-free survival.
- The economic model constructed by the company is logical and appears to capture two important features of the disease (progression-free survival and overall survival).

1.6.2 Weaknesses and areas of uncertainty

The CS had several weaknesses:

- Although the ERG believes that the inclusion of three possible drugs within the SOC arm is a good reflection of current practice, it would have been more methodologically acceptable to have only one single drug regimen in the SOC arm. Moreover, one of the three drugs available within SOC was vinflunine which is not recommended within the NHS.
- The ERG has concerns regarding the exclusion of two scoped comparators, BSC and retreatment with platinum-based regimen, from the decision problem.
- There is neither a head-to-head nor an indirect comparison of pembrolizumab with BSC which is a relevant comparator.

- Owing to open-label design of KEYNOTE-045, the results on quality of life should be treated with caution.
- There was uncertainty in the effectiveness of the methods used to adjust for treatment switching in the UK SOC.
- There was uncertainty in the extrapolation of overall survival estimates from the trial to the duration of the economic model, with cost-effectiveness results being sensitive to the methods used to extrapolate. The ERG has reservations regarding the choice of the cut-off point used for the piecewise modelling approach and the choice of parametric distribution used to model long-term overall survival.
- Health-related quality of life estimates included those for patients receiving vinflunine, which is not recommended in England. Using utilities by time to death is an unusual method of estimating life years and subsequent QALYs and resulted in slight overestimation of life years in both treatment arms compared to estimates based on progression status.
- Estimation of age-related utility decrements was based on an outdated study that did not incorporate a decrement for patients aged more than 75 years old, resulting in overestimation of QALYs.
- Counter-intuitive utility estimates were obtained when reported separately for each treatment arm. That is, when estimating utilities based on time to death patients receiving UK SOC reported higher estimates, whereas when estimating utilities based on progression status patients receiving pembrolizumab reported higher estimates.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made a number of modifications to the model assumptions made by the company.

Overall changes:

- Excluding vinflunine patients from the estimation of utility values.
- Using utility values based on progression status rather than time to death.
- Using pooled utility and adverse event disutility values.
- Changing source of estimating age-related utility decrements.

- Setting adverse event prevalence and costs related to pneumonia, hypophosphatemia and fatigue to zero.
- Estimating the cost of UK SOC based on the UK market share of docetaxel and paclitaxel.
- Use a cut-off point of 24 weeks for the overall survival modelling approach.
- Use a log-logistic distribution for overall survival modelling for pembrolizumab and UK SOC.

The ERG have presented a scenario with a preferred base-case analysis for pembrolizumab versus UK SOC. The ICER has increased slightly compared with the CS submission, resulting in a deterministic ICER of £51,405 per QALY including a patient access scheme (PAS).

The ERG carried out some exploratory analyses using the ERG preferred base-case, and noted that the vast majority (84% to 97%) of benefits in terms of life years gained was from the extrapolated data rather than the observed data.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

Urothelial cancer arises from the transitional cells in the bladder. These are cells that stretch with the expansion of the organ and can occur in the bladder, renal pelvis, ureter, or urethra (Company Submission (CS), p33). The company states that urothelial cancer accounts for approx. 90% of bladder, renal pelvis, ureter and urethral cancers. Some locations of urothelial cancers are less common than others, e.g. upper tract urothelial cancer (UTUC) of the ureter is 4 times less likely than urothelial cancer in the renal pelvis (CS, p33).

The major distinction between different urothelial cancers is between non muscle-invasive and invasive carcinomas. According to Cancer Research UK, some non-muscle invasive carcinomas are papillary carcinomas, and others are flat carcinomas, e.g. carcinoma in situ (CIS) and high grade T1 tumours, which grow from the bladder lining into the layer below, the lamina propria.[1] Cancer Research UK also identify invasive cancers, which grow into the deeper layers and beyond into other organs.

The NICE guidelines suggest a similar distinction between non-muscle invasive (NMIBC) and muscle-invasive bladder cancers (MIBC). MIBC can, in later stages, be locally advanced or metastatic. The company suggests that muscle-invasive cancers that are locally advanced or metastatic could be treated with pembrolizumab in 2nd and 3rd line. Symptoms of the primary tumour in the bladder include blood in urine, burning when passing urine, increased urinary frequency or urgency, pain in the lower abdomen or back. Though these symptoms can lead to a misdiagnosis of urinary tract infection in women (CS, p35).

Survival rates are strongly correlated to disease stage (CS, p35). According to Cancer Research UK, around 90% of patients with stage 1 cancer survive beyond 5 years but the survival is no more than 10% at 5 years in stage 4 cancers.[2] This is in line with the company's description (CS, p39). The company states that 1-year and 5-year survival rates have not significantly improved in the past 10 years (CS, p31). This is supported by statistics on survival published by Cancer Research UK. They report that between 2005 and 2006, 73.9% of adults survive 1 year after diagnosis, and in 2010-2011 it was 72.4%. The 5-year survival rate was 55.5% in 2005-2006, and 53.7% in 2010-2011.[3] The company connects the lower survival rate of urothelial cancer compared to other GU cancers such as kidney cancer to the different biology of the carcinoma

and the low ability to detect the cancer at an early stage. The company also highlights that there is a lack of advances in the development of therapies (CS, p35).

The company indicates that staging of urothelial carcinoma is undertaken according to the Tumour, Node and Metastases (TNM) classification which provides staging information as 0, I, II, III or IV. The Evidence Review Group's (ERG) clinical advisors have confirmed the use of the TNM staging system.

On page 34, the company states that around 75% of newly diagnosed urothelial bladder cancers are non-muscle invasive (also called NMIBC), which have a high rate of recurrence (70%) and progression into muscle invasive disease (10-25%). The statement is misleading since it is high-risk NMIBC has a recurrence rate of 70% over 5 years and high-risk forms only represent 10% of all NMIBC. Low-risk NMIBC has low recurrence and progression is very rare.

The company states that patients with muscle invasive urothelial cancer will be offered radical surgical treatments, e.g. full cystectomy. The ERG's clinical experts commented that patients can also be treated with radical radiotherapy, ideally with chemo-radiotherapy. The ERG's clinical experts also commented that the correct terminology for the surgical procedure is radical cystectomy and overall that the phraseology used in the CS implies an unfamiliarity with United Kingdom (UK) bladder cancer practice.

The company states that surgery is followed by difficult lifestyle adjustments for patients and carers due to decreased urinary and sexual function. This reduces the quality of life "consistently and significantly" (CS, p36). This again can be supported by advice given by Cancer Research UK.

The ERG however found a discrepancy between the annual cost estimates that the company quoted. The company quotes estimates given by Leal et al.[4] for costs of bladder cancer in 2012 and Sangar et al.[5] for cost estimates in 2001-2. The company report that, according to Leal et al.,[4] informal care constitutes 18% of costs, productivity losses due to mortality and morbidity 23% (misquoted by company as 29%) and healthcare costs 59% (misquoted by company as 53%) of the total costs of bladder cancer in the European Union (EU) (CS, p36). According to Leal et al.,[4] the total healthcare costs were €286 million, the total costs including productivity loss and

informal care costs were €543 million in 2012 in the UK. Bladder cancer accounted for 5% of total healthcare costs and 3% of cancer costs in the EU.[4]

This is radically different to the total costs for bladder cancer quoted by the company from Sangar et al. of £55.39 million in 2001-2002. Sangar et al.[5] do not present the costs of an annual spend on bladder cancer, but direct and indirect costs over 5 years of cases. These costs include diagnosis, treatment and 5-year follow up of direct and indirect costs.[5] Direct costs include expenditure related to diagnosis, treatment and 5-year follow up.[5] Indirect costs include loss of earnings, which were taken as an average weekly wage in relation to age and sex.[5] They do not take relapses into account. If we assume that there is no relapse, and that patients are diagnosed every year, we can assume that the annual costs estimated by Sangar et al.[5] are £55.39 million, assuming that every year the same amount of patients are added to the group of cancer patients. This is much less than the annual costs suggested by Leal et al.[4] The cost differences may be accounted for by differential costs for medical equipment, medication, higher salaries and follow-up, but the variations suggests that there may be an error in one of these studies.

The ERG's clinical experts commented that the very high treatment costs of bladder cancer are related to the costs of managing surveillance and treatment for NMIBC. High-risk NMIBC requires lifelong cystoscopic surveillance, and recurrences require operative resection. Our clinical advisors commented that they expect the costs of locally advanced or metastatic disease to be relatively low by comparison as survival is short. Therefore, it appears misleading in the CS to lean too heavily a small number of cases to estimate the total costs for all bladder cancer and to justify the costs of second line treatment. The two groups are different and pembrolizumab treatment in second line should have little impact on the majority of healthcare costs for bladder cancer.

2.2 Critique of company's overview of current service provision

The company states that standard care for second-line treatment of urothelial cancer has remained the same in the last decade: platinum-based chemotherapies and taxane regimens are, according to the company, standard treatment (CS, p31). However, the use of taxane regimens is not regulated by National Institute for Health and Care Excellence (NICE) guidelines[6] and does not have Medicines and Healthcare Products Regulatory Agency (MHRA) marketing authorisation in

the UK for bladder or urothelial cancer; notwithstanding our clinical advisors tell us that taxanes are used in UK practice.

The company states that pembrolizumab has been granted a Breakthrough Therapy Designation for advanced melanoma, for advanced (metastatic) non-small cell lung cancer (NSCLC) and advanced NSCLC whose tumours express PD-L1 and for locally advanced or metastatic urothelial cancer with progression on or after platinum containing chemotherapy by the Food and Drug Administration (FDA). In the UK, pembrolizumab is recognised under the MHRA's Early Access to Medicines Scheme for unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care, and has received Promising Innovative Medicines (PIM) designation for treatment of metastatic NSCLC under certain circumstances (CS, p31).

The treatment pathway is, as the company states, determined by the performance status of the patient and the level of renal function. According to the NICE guideline[6] it also takes the recurrence history, size and number of cancers, histological type, grade and stage, risk category of the cancer and the predicted risk of recurrence into account. The company positions pembrolizumab as 2nd line treatment for locally advanced or metastatic MIBC. The current treatment pathway is a chemotherapy regimen for 2nd line and no regulated treatment for 3rd line, although the NICE scope suggests docetaxel and paclitaxel (see Figure 1).

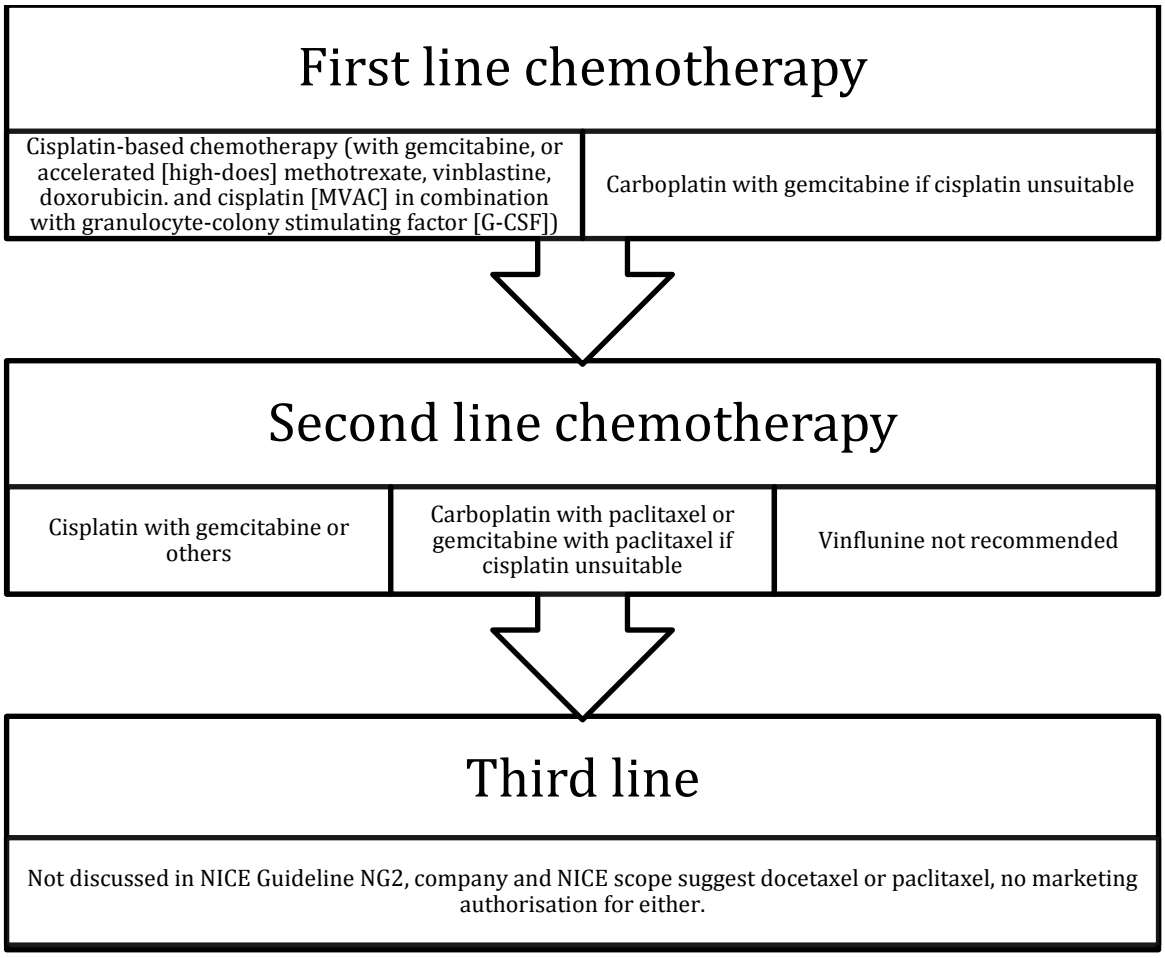


Figure 1: Treatment pathway

Cisplatin-combinations should be offered to patients with advanced or metastatic urothelial bladder cancer who are otherwise physically fit (Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1) and have adequate renal function (glomerular filtration rate (GFR) of 60 ml/min/1.73m^2 or more).[7] Carboplatin-combination chemotherapies should be offered if cisplatin-based chemotherapy is unsuitable, e.g. ECOG performance status is 2, renal function is inadequate or there are comorbidities.

The company points out that there is currently no UK marketing authorisation for urothelial cancer for the use of carboplatin with paclitaxel and gemcitabine with paclitaxel, the alternatives to cisplatin-combinations (CS, p36). The ERG can confirm that only cisplatin-combinations have a marketing authorisation. The ERG can also confirm that vinflunine is not recommended for treating advanced or metastatic transitional cell carcinoma of the urothelial tract after treatment

with platinum-based chemotherapy in the UK (CS, p37). The National Comprehensive Cancer Network (NCCN) even claims that there is no standard second line treatment (CS, p41).[8]

The company highlights that there is a "high unmet need for urothelial cancer therapies that prolong survival without greatly increasing toxicity or significantly compromising patients' quality of life" (CS, p31). The European Society for Medical Oncology (ESMO) practice guidelines for bladder cancer supports this claim by stating that "[a]bout 50% of patients are unfit for cisplatin-containing chemotherapy due to a poor Performance Score (PS), impaired renal function or comorbidity".[9] The company expects 502 stage IV patients to be eligible for treatment with pembrolizumab in 2017, rising to 532 in 2021. This accounts for less than half the stage IV patients each year.

2.3 Critique of changes to service provision

The company suggests introducing pembrolizumab as a 2nd line treatment for locally advanced or metastatic urothelial cancers after an initial first line chemotherapy and replacing platinum-based chemotherapy or gemcitabine with paclitaxel as 2nd line treatment. The company also suggests that pembrolizumab replaces docetaxel and paclitaxel as 3rd line treatment for patients with locally advanced or metastatic urothelial cancer. The NICE guideline for bladder cancer (NG2)[7] does not recommend a 3rd line treatment, but the final scope for pembrolizumab suggests, as does the company, that patients receive docetaxel or paclitaxel after two lines of chemotherapy. However, docetaxel and paclitaxel do not have marketing authorisation in the UK for urothelial or bladder cancer. There is also no report by the European Medicines Agency (EMA) for docetaxel or paclitaxel for urothelial or bladder cancer, although the ESMO practice guideline also mentions taxane-based regimes for 3rd line treatments.[9]

3 Critique of company's definition of decision problem

3.1 Population

The population in the decision problem, and subsequent clinical evidence matches the population described in the final scope. The population of relevance includes patients with locally advanced or metastatic urothelial cancer who have progressed on or after platinum-containing chemotherapy. In the KEYNOTE-045 trial,[10] 75.8% of patients had a prior cisplatin therapy while 23.2% of patients previously received carboplatin. The use of a prior platinum based-regimen could occur either at the stage of inoperable locally advanced/metastatic disease, or as part of adjuvant (following surgery) / neoadjuvant (prior to surgery) therapy for localised muscle-invasive urothelial cancer.

In the submission, the company stated that the anticipated label indication covers locally advanced/metastatic urothelial carcinoma in people who received prior chemotherapy, rather than prior platinum-based chemotherapy. The company did not provide any explanation for this. The Evidence Review Group have received in confidence information indicating that the proposed indication wording which has been submitted to the EMA by the company is:

- KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy.
- 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.

This means that the anticipated label indication of pembrolizumab is broader than the population in the KEYNOTE-045. If the label indication does not restrict the use of pembrolizumab to patients who previously received a platinum-based regimen, the label indication cannot be supported by clinical evidence since 100% of people had a prior platinum-based regimen in KEYNOTE-045. Evidence on the effectiveness of pembrolizumab in people ineligible for cisplatin will be provided by the full results of KEYNOTE-052 study which enrolled 370 patients in a single-arm trial.[11, 12]

3.2 Intervention

The intervention in the decision problem is pembrolizumab as monotherapy, which matches the final scope. The company provides a description of the technology and the mechanism of action of pembrolizumab (CS p27) which the ERG's clinical advisors have confirmed is an accurate description. Pembrolizumab is an intravenously administered medication that has been authorised for use in indications other than this current appraisal including:

- treatment of advanced (unresectable or metastatic) melanoma in adults;
- first-line treatment of metastatic NSCLC in adults whose tumours express programmed cell death 1 ligand 1 (PD-L1) with a ≥50% tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations; and
- treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

With regards to the present submission, pembrolizumab is currently unlicensed in people with urothelial cancers, which means the benefit/risk balance has not been assessed by the European regulatory authority. In this report, the ERG will present the main clinical effectiveness and safety outcomes of pembrolizumab in adults with locally advanced/metastatic urothelial cancers. Based on this evidence, the ERG believes it is likely that the Committee for Medicinal Products for Human Use (CHMP) will conclude that the benefits of pembrolizumab outweighs the risks.

Pembrolizumab is a highly selective humanised monoclonal antibody against programmed death-1 (PD-1). It exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and programmed cell death 1 ligand 2 (PD-L2), on antigen presenting tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab activates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates antitumour immunity.

Pembrolizumab is part of a new class of immunotherapies which comprises drugs like nivolumab and atezolizumab. Pembrolizumab is not the only PD-1 inhibitor that has been evaluated within the scope of urothelial cancers. Atezolizumab is one of these and is currently subject to an ongoing appraisal (ID939). Nivolumab and durvalumab should also emerge in the coming months.

Pembrolizumab is given using an IV infusion, over a 30-minute period. The anticipated licensed dosing regimen is 200mg every 3 weeks with a treatment continuing until disease progression or unacceptable toxicity, whichever occurs first. Table 4 in the CS (p29) summarises administration and costs of pembrolizumab, and information provided in this table regarding the treatment administration concur with those in the KEYNOTE-045 trial.

3.3 Comparators

The comparators described in the decision problem are docetaxel and paclitaxel. This differs substantially from the NICE final scope given that the company excluded best supportive care (BSC) and retreatment with first line platinum based chemotherapy regimen as comparators.

The company indicated that alternative active treatments are available (e.g. docetaxel and paclitaxel) which means BSC is not a relevant comparator. The ERG does not fully agree with this since the company only considered people with locally advanced/metastatic urothelial cancers eligible for chemotherapy, which can be defined according to our clinical advisors as patients with an ECOG performance score of 0-2. Within the National Health Service (NHS), there is a significant proportion of people with locally advanced/metastatic urothelial cancer who have had one prior platinum-based regimen and who cannot undergo chemotherapy owing to a poor performance status (defined as ECOG PS 3-4). These patients are therefore only eligible to receive BSC. In the KEYNOTE-045 trial, the population included had an ECOG PS 0-2, which meant that patients with an ECOG PS $\geq$3 were excluded. Given that the KEYNOTE-045 is the only trial that evaluated pembrolizumab in people with locally advanced/metastatic urothelial cancer after failure to platinum-based therapy, there is no evidence to compare pembrolizumab to BSC in patients with ECOG PS 3-4 either directly or indirectly. The ERG is aware of a phase 3 randomised controlled trial (RCT) which compared vinflunine + BSC with BSC alone.[13] This trial could have been used to compare pembrolizumab to BSC indirectly but the relevance is questionable given that the trial only included people with PS 0-1.

In summary, although the ERG believes that BSC is a relevant comparator for people with PS 3-4, there was no evidence offered to compare pembrolizumab with BSC. While patients with an ECOG PS 4 would definitely not receive any treatment other than BSC, our clinical advisors suggested that treatment with pembrolizumab could be considered in people with an ECOG PS 3

given the relatively favourable safety profile of the drug. However, this would have to be supported by clinical effectiveness data in this subgroup.

With regards to retreatment with a platinum-based chemotherapy, the company indicated that no evidence exists for a comparison between pembrolizumab and retreatment with platinum-based chemotherapy, thus the latter was excluded. The ERG believes this is not a valid reason to exclude retreatment with platinum-based chemotherapy. Our clinical advisors indicated that retreatment with platinum-based chemotherapy can be considered within the NHS depending on the time to recurrence/progression after platinum therapy. In cases of early recurrence/progression (<12 months), which corresponds to the vast majority of patients, retreatment with platinum-based chemotherapy would in general not be considered while it could be considered in the rare cases of late recurrence (> 12 months). In case of relapse after 6-12 months, a carboplatin-gemcitabine therapy can be occasionally offered in second line (after first line platinum regimen) of locally advanced/metastatic urothelial cancers but only in patients with good PS.

With regards to the comparators, the ERG would like to highlight that neither the NICE scope nor the company submission have included other PD-L1 inhibitors such as atezolizumab, nivolumab, or durvalumab; although all these drugs are anticipated to have the same positioning should they be recommended by NICE within the NHS.

3.4 Outcomes

The outcome measures to be considered in the NICE scope have been reported in the decision problem. They are overall survival (OS), progression-free survival (PFS), response rates (RR), adverse effects (AE) and health-related quality of life (HRQoL).

4 CLINICAL EFFECTIVENESS

4.1 Critique of the company's approach to systematic review

The CS undertook a systematic review for evidence of clinical effectiveness of relevance to the decision problem. The review included searches for studies on the intervention and comparators for a potential network meta-analysis (NMA).

The ERG's quality assessment of the CS, based on the Centre for Review and Dissemination (CRD) quality assessment questions for systematic reviews,[14] is summarised below (see Table 1). The quality of the company's systematic review is reasonable although very limited information was provided on the reason for exclusion of studies following full text review. The submitted evidence generally reflects the decision problem.

In the CS, the ERG noted that the numbers of full-text publications assessed for eligibility in Figure 5 (n=32) do not match the text on page 45 (text states 31 full-texts). In the CS clarification response, the company confirmed that 32 full-texts were reviewed.

Table 1: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Is sufficient detail of the individual studies presented?	Yes although this is limited to one study
5. Are the primary studies summarised appropriately?	Yes

4.2 Description of company's search strategy

The company reports two sets of broad searches for studies that could inform both direct and indirect comparisons (see CS section 4.1.2). The first set of searches, aiming to identify RCTs on pembrolizumab and several comparators chosen to satisfy a number of regulatory authorities, was undertaken in June 2016. The second set specifically sought additional comparators (cisplatin+gemcitabine and methotrexate, vinblastine, doxorubicin and cisplatin (MVAC)) and was undertaken in February 2017. Both sets of searches were undertaken in a reasonable range of

sources, including bibliographic databases, trials registers, conference proceedings and the company's own records. Database searches were limited to English language, but were not limited by date. Most search terms and lines were combined appropriately.

There are some issues that may have resulted in some records being missed: a) line 22 of the Embase cisplatin+gemcitabine / MVAC search misses out line 17; b) the use of 'NOT' combined with many study type terms in all the bibliographic database searches; and c) not hand searching the reference lists of relevant reviews or articles. However, the use of other search terms in the database searches and searching in other sources mean that overall the clinical effectiveness searches appear to be reasonably comprehensive. At the clarification stage, the ERG requested an update of the first set of searches and the company responded "it was not possible to run the updated search in the short timeline provided. However, we do not anticipate any new studies, given the limited clinical advancements in this area." The ERG's targeted independent searches for systematic reviews and longer term survival data identified two additional relevant studies.[13, 15, 16]

4.3 Inclusion / exclusion criteria used in the study selection

The eligibility criteria are listed in CS Table 6, CS page 44. The eligible population includes adults with advanced/metastatic urothelial carcinoma recurring or progressing follow platinum-based regimen. The intervention of interest for this single technology appraisal (STA) is pembrolizumab, which is stated in the Population Intervention Comparator Outcome Study Design (PICOS) table along with six different comparators (paclitaxel/gemcitabine; carboplatin/paclitaxel; cisplatin+gemcitabine; MVAC; docetaxel; and paclitaxel). The company indicated that the listed comparators were selected consistent with practice relevant to the UK setting. Therefore, vinflunine was not mentioned since this drug was issued with a negative recommendation by NICE in 2013.[17] The company has not listed BSC (see Section 3.3).

For the purpose of indirect and mixed treatment comparisons, the company included any RCTs with comparisons between any of the interventions of interest. This is why the vinflunine pivotal RCT [13] was included although vinflunine is not listed. To improve the quality of the reporting, the ERG believes that it would have been clearer to list all the potential comparators in the PICOS table (CS table 6, page 44) while identifying those of relevance to the UK setting. The company's eligibility criteria for the systematic review state that trials with outcome measures

including progression-free survival (PFS), overall survival (OS), objective response rate (ORR), adverse events (grade 3 and above), time to progression (TTP), duration of response (DoR), immune-related toxicity (any grade), health-related quality of life (HRQoL) should be included regardless of whether these were primary or secondary outcomes. These match the decision problem and the NICE scope although immune-related toxicity was not clearly specified. In terms of study design, the company included RCTs and excluded non-RCTs and observational studies. The ERG believes that the exclusion of non-randomised studies is justified owing to the risk of these studies presenting inadequate control of biases that could threaten the validity of indirect and mixed treatment comparisons.[18]

4.4 Identified studies

The main trial of the CS is the KEYNOTE-045 study (1 clinical study report (CSR) provided by the company, one conference proceeding,[19] plus one original article published after the company submission[10]). The company also included this trial in their indirect and mixed treatment comparison (for discussion of the NMA see relevant section). The trial was funded by Merck Sharp and Dohme (MSD).

The details of the trial were summarised and discussed in the CS on pages 49-84. The trial design was reported on page 49 of the CS. The KEYNOTE-045 study was an international, Phase III, randomised, open-label trial comparing pembrolizumab (200mg IV every 3 weeks) with investigator's choice of either paclitaxel (175mg/m^2 every 3 weeks), docetaxel (75mg/m^2 every 3 weeks), or vinflunine (320mg/m^2 every 3 weeks) in people with metastatic or locally advanced/unresectable urothelial cancer after recurrence or progression following platinum-based chemotherapy.

The dose regimen of vinflunine corresponded to that of the summary of product characteristics (SPC) for Javlor (brand name of vinflunine). Both docetaxel and paclitaxel are not licensed for urothelial cancers but these agents are commonly used in practice with dose regimens as in the KEYNOTE-045 trial.

Before randomisation, investigators had to select one treatment from the control arm to use in the event that the patient was randomised to the control arm. The ERG noted that there was no clear basis for the investigators' choice of comparators and asked the company to provide further

clarifications. In their clarification response, the company indicated that investigators were allowed to choose between paclitaxel, docetaxel and vinflunine, according to their clinical practice, provided vinflunine was approved in their countries. Paclitaxel and docetaxel were also available to investigators in countries where vinflunine was approved.

The company has not elaborated further on the choice of investigators according to their clinical practice. The choice between these three agents may differ across centres since, as emphasised in Bellmunt's paper,[10] there is no internationally accepted standard of care after platinum-based chemotherapy. At investigator level, the preference between the three chemotherapy regimen may also vary according to the patients' characteristics and history given that the safety profile of each drug is not exactly the same. The company has not reported baseline characteristics of KEYNOTE-045 patients according to the investigator's choice before randomisation. Consequently, the ERG is unable to confirm the strict comparability of patients depending on investigator's choice before randomisation, and cannot exclude the absence of significant heterogeneity within the KEYNOTE-045 population. Although a RCT comparing pembrolizumab with one single treatment would have been more methodologically acceptable, the ERG appreciate that the KEYNOTE-045 study was a pragmatic trial since the Standard of Care (SOC) arm, comprising several chemotherapy options, is a good reflector of current practices. The ERG is aware of another recent appraisal related to advanced breast cancer treatment where a new agent (eribuline) was compared to treatments chosen by the investigator.[20]

The randomisation was done in a 1:1 ratio: 270 patients were randomly assigned to the pembrolizumab group, and 272 to the SOC group (medication breakdown: 84 had paclitaxel, 84 had docetaxel, and 87 had vinflunine; missing for 17). Randomisation was stratified by ECOG performance score (0-1 vs. 2), presence or absence of visceral metastasis, haemoglobin (≥10g/dl vs. <10g/dl), and time to completion of most recent chemotherapy (<3 months or ≥ 3 months).

Treatment continued until radiographic disease progression, unacceptable toxicity, intercurrent illness that prevented further administration of treatment, investigator's decision to withdraw the subject, confirmed positive serum pregnancy test, non-compliance with trial treatment or procedure requirements, lost to follow-up, completed 24 months of treatment with pembrolizumab, administrative reasons, or withdrawal of consent for treatment.
Permitted concomitant medications were those considered necessary by the investigators and were recorded on the electronic case report forms (eCRF).

Eligibility criteria were reported on pages 52-53 of the CS and in table 10 on page 66. The trial was designed to select patients with locally advanced/metastatic urothelial cancers (histology: predominantly or exclusively transitional cell; upper tract [renal pelvis or ureter] or lower tract [bladder or urethra]) after recurrence or progression to a platinum-based regimen used either at first line (metastatic setting or inoperable locally advanced disease), at second line of metastatic disease, or as part of an adjuvant/neoadjuvant therapy for localised muscle-invasive urothelial cancer (post or prior to cystectomy).

Patients were recruited from November, 2014 to November, 2015 at 120 centres in 29 countries. The baseline characteristics of included patients are presented in Table 17 of the CS (p86-89). Although some of the baseline characteristics seem numerically different, there were no significant differences between the two treatment groups. The median age of patients was 67 years in the pembrolizumab group and 65 years in the SOC group and 74% were males. Almost 65% of patients were current or former smokers. The site of primary tumour was the lower tract in 86% of cases. The setting of the most recent prior therapy was first line in 62.7% of patients and second line in 21.2%. The proportion of patients with visceral metastasis was 89.2% in the pembrolizumab group and 86.0% in the SOC arm.

The company also presented the baseline characteristics according to biomarker assessment using the score of PD-L1 expression which was evaluated prospectively. PD-L1 expression was assessed in formalin-fixed tumour samples at a central laboratory using a commercially available assay kit. Only patients whose samples could be evaluated for PD-L1 expression were permitted to enrol in the study, regardless of the score of PD-L1 expression. PD-L1 assessment was expressed as a score defined as the proportion of PD-L1 expressing tumour and infiltrating immune cells relative to the total number of tumour cells. PD-L1 status was categorised as negative, positive, or strongly positive for combined positive scores (CPS) <1%, ≥1%, or ≥ 10% respectively.

In the clarification questions, the ERG asked the company to provide further justification for the cut-offs used (CPS≥1% or ≥ 10%). In their response, the company indicated that data external to KEYNOTE-045 informed the decision. The cut-off of ≥1% for positivity was determined with the analyses of tumour specimens from the KEYNOTE-012 trial (a phase 1 study that included a cohort of people of advanced urothelial cancer)[21] while the cut-off of ≥ 10% was based on a

review of data from the first 100 subjects enrolled in KEYNOTE-052 (a phase 2 study in people with advanced/metastatic urothelial cancer who are ineligible for cisplatin-based therapy).[22]

On page 90, the company referred to emerging evidence that PD-L1 expression level and clinical outcomes may be correlated. When asked to provide evidence for the link between PD-L1 expression and clinical outcomes, the company did not provide any evidence.

Based on these cut-offs, 55% of patients were negative for PD-L1 expression (CPS<1%) while 42.4% were positive (CPS≥1%) (40.7% in the pembrolizumab group vs. 44.1% in the SOC group). In KEYNOTE-045, 30.3% of patients were strongly positive for PD-L1 expression (CPS≥10%). The company noted that fewer subjects in the pembrolizumab group were strongly positive for PD-L1 expression compared to the SOC group (27.4% vs. 33.1%) which is explained as PD-L1 status was not a stratification factor.

Of the 542 randomised patients, only four were from the UK. In the clarification questions, the company were asked to comment on how representative the trial is to the UK population. In their response, the company indicated that the population is representative of the UK population since 13.8% of patients were from Western European countries (Belgium, France, Ireland, Netherlands, United Kingdom) and 41.1% were from European countries. Our clinical experts agreed on the generalisability of the KEYNOTE-045 trial to the UK population.

The data cut-off date for the second interim analysis was 7th September 2016. At that time, 40% of patients in the pembrolizumab group and 24.6% in the SOC group were continuing in trial, with 18.4% in the pembrolizumab group continuing to receive the drug on trial compared to 1.2% in the SOC group.

The most common reason for patients discontinuing treatment were progressive disease (54.9% and 50.6% in the pembrolizumab vs. SOC group), and adverse events (10.9% and 15.7% in the pembrolizumab vs. SOC group).

The description and critique of company's outcome selection is presented in section 4.7.

4.5 Relevant studies not included in the submission

To the best of our knowledge, the company included all the relevant studies related to pembrolizumab. The ERG has undertaken additional searches on long-term survival data to compare with the survival extrapolations from the company. This has been reported in the section 5.2.6.2.

4.6 Description and critique of the approach to validity assessment (quality assessment)

For RCTs, the company used specific criteria as described in the CRD's guidance for undertaking reviews in health care, which the ERG considers to be appropriate. However, the assessment undertaken by the company is inadequate because the ratings are study-specific but not outcome-specific. Ideally, one should be able to differentiate between the risk of bias (RoB) of PFS and OS if, for example, the outcome data completeness for these outcomes differs. The per study rather than per outcome RoB ratings conceal this distinction.

4.6.1 Quality assessment of the KEYNOTE-045 trial

CS Table 18 provides a quality assessment of the KEYNOTE-45 trial using criteria recommended by NICE. Table 2 summarises the ERG's check on this quality assessment (QA).

Table 2: Company and ERG assessment of trial quality

		KEYNOTE-045
1. Was randomisation carried out appropriately?	CS	Yes Electronic randomisation system (Interactive Voice Response System/ Interactive Voice and Web Response System (IVRS/IWRS))
	ERG	YES Subjects were assigned randomly to 1 of 2 treatment arms in a 1:1 ratio, i.e., to either pembrolizumab or the investigator's choice of paclitaxel, docetaxel, or vinflunine (chosen by the investigator before randomization occurred) (CS p49) Randomization was stratified by ECOG-PS (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months

		or ≥3 months). Subjects with ECOG-PS = 2 could not have additional poor prognosis factors (such as liver metastases, haemoglobin <10 g/dL, and time from completion of most recent chemotherapy <3 months [90 days]). Randomisation occurred centrally using an interactive voice response system/integrated web response system (IVRS/IWRS) (CS p49)
2. Was concealment of treatment allocation adequate?	CS	Yes, central allocation
	ERG	Yes (CS p89) See above
3. Were groups similar at outset in terms of prognostic factors?	CS	Yes The treatment arms were generally well balanced by all baseline characteristics, with the exception that slightly more subjects in the pembrolizumab arm were ≥65 years of age (61.1% vs 54.0%), ECOG PS = 0 (44.1% vs 39%) and in the never smokers (38.5% vs 30%) subgroups compared with the control arm.
	ERG	Some concerns: The treatment arms were generally well balanced by all baseline characteristics, with the exception that slightly more subjects in the pembrolizumab arm were ≥65 years of age (61.1% vs 54.0%), ECOG PS = 0 (44.1% vs 39%) and in the never smokers (38.5% vs 30%) subgroups compared with the control arm (CS p86). Slightly fewer subjects in the pembrolizumab arm were in the PD-L1 combined positive score (CPS) ≥10% group (27.4% vs 33.1%) compared with the control arm (CS p86) although this difference is not statistically significant.
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS	No (CS p89) Study is open label. No blinding of outcome assessment according to protocol
	ERG	No: open label trial with blinded outcome assessment This was an open-label trial; therefore, the applicant, investigator, and subject knew the treatment administered (CS p50). Imaging data for the primary analysis were centrally reviewed by independent radiologist(s) without knowledge of subject treatment

		assignment. The applicant and the trial team, consisting of clinical, statistical, statistical programming, and data management personnel, was blinded to subject-level PD-L1 biomarker results (including CPS ≥1%) until the cut-off value of PD-L1 expression level for CPS ≥10% was established and formally documented exclusively based on data outside of this trial. These steps were taken to ensure the unbiased use/integrity of the PD-L1 analysis. Access to the allocation schedule and/or the subject-level PD-L1 results for summaries or analyses were restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who had no other responsibilities associated with the trial. The statement in Appendix 7 (p85) mentioned above in the CS: "No blinding of outcome assessment according to protocol" is unclear or an error.
5. Were there any unexpected imbalances in drop-outs between groups?	CS	No
	ERG	Some comments: fewer subjects in the pembrolizumab arm compared with the control arm discontinued study treatment due to withdrawal by subject (1.1% vs 11.4%), or physician decision (2.3% vs 10.6%) (CS p166). However, all patients were included in the analysis (intention-to-treat (ITT)).
6. Is there any evidence that authors measured more outcomes than reported?	CS	No All outcomes listed in protocol appear in published paper
	ERG	No CS p61-65; protocol document
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS	Yes The analysis of primary efficacy endpoints was based on the ITT population, i.e. subjects were included in the treatment group to which they are randomised. The All Patients as Treated (APaT) population was used for the analysis of safety data in this study.
	ERG	ITT: yes

		The ITT population served as the primary analysis population in this trial (CS p86). Missing data: Some concerns From the CS (p103, 106): Objective Response Rate (ORR) per Confirmed Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 by Central Radiology Assessment, ITT population, p103 states: "In the pembrolizumab arm, 118 of 219 subjects (53.9%) with at least 1 baseline imaging assessment had a reduction in tumour burden, as shown in Figure 14. In the control arm, 109 of 200 subjects (54.5%) with at least 1 baseline imaging assessment had a reduction in tumour burden, as shown in Figure 15." The sample sizes (N's) given here are 219 for pembrolizumab (total 270, so 270-219 = 51 people missing [19%]) and 200 for control (total 272, so 272-200 = 72 missing [26%]), but this does not tally with Table 30 (p106; Summary of best overall response (BOR) based on RECIST 1.1 per central radiology assessment - All subjects (ITT population)) data for no post-baseline imaging (31 for pembrolizumab [11.5%] and 51 for control [18.8%]). A rate of around 20% of missing data in one of the groups could bias the results. Going back to the CS: Missing data adjusted for using a variety of censoring rules (p78) reproduced in CS

On page 144, the CS states that: "The risk of bias instrument can be used to assign summary assessments of within-study bias; low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high-risk of bias (high-risk of bias for one or more key domains)." On the basis of high risk of bias reported in the CS in the blinding domain (Appendix 14, p210), KEYNOTE-045 would be assigned an overall high risk of bias, although this is not emphasised in the CS (and blinding would be difficult or impossible due to the different adverse event profile of the interventions).

The ERG QA agrees with the company assessment of study quality for KEYNOTE-045 for randomisation and allocation concealment, blinding and reporting bias. Given the presence of a

key-domain rated as high-risk of bias (blinding or participants and personnel), the ERG also concludes that this study is at high risk of bias. Had the study been double-blinded, the ERG believes that the KEYNOTE-045 study would have still been at high-risk of performance bias. Indeed, given the very specific safety profile of the drugs evaluated in the KEYNOTE-045 trial, it is very likely that both patients and clinicians would have been able to correctly identify the allocated arm.

4.6.2 Quality assessment of the RCT evidence used in the indirect treatment comparison

The company has provided a quality assessment of four studies that were included within the scope of indirect and mixed treatment comparisons. Since no NMA was eventually conducted, the ERG did not comment on the quality assessment of these studies.

4.7 Description and critique of company's outcome selection

The NICE scope lists the specified the outcomes as:

- overall survival (OS)
- progression-free survival (PFS)
- response rates
- adverse effects of treatment
- health-related quality of life.

In the CS, the decision problem addressed all of the outcomes in the NICE scope since these were reported in the KEYNOTE-045 phase III study. The KEYNOTE-045 trial had co-primary endpoints that were PFS and OS. PFS and OS were assessed in the total population, in the population of patients positive for PD-L1 (CPS≥1%), and in the population of patients strongly positive for PD-L1 (CPS≥10%). Surprisingly, the recently published article reporting the results of KEYNOTE-045[10] does not state the assessment of PFS and OS in the population of patients positive for PD-L1 (CPS≥1%).

OS was defined as the time from randomisation to death from any cause and PFS was defined as the time from the date of randomisation to the date of first documentation of disease progression or death due to any cause, whichever occurred first.

For the primary objective, PFS was assessed according to RECIST 1.1 based on blinded independent central radiologic (BICR) review. Tumour imaging was scheduled for week 9 followed by every 6 weeks during the first year and every 12 weeks thereafter. RECIST 1.1[23] corresponds to a revised guideline on response evaluation criteria in solid tumours (RECIST). These criteria are often used in clinical trials for anti-cancer therapies with the aim to assess tumour shrinkage (objective response) and disease progression. The RECIST 1.1 guideline defines key criteria on measurability of tumour at baseline (definition, methods of measurements), and tumour response evaluation (assessment of tumour burden and measurable disease, response criteria: complete response (CR), partial response (PR), progressive disease (PD), and stable disease (StD)).

As part of the secondary endpoints, PFS was also assessed per RECIST 1.1 from randomisation to specific time points (6 and 12 months), and per modified RECIST (mRECIST) 1.1 based on BICR review. The mRECIST 1.1 corresponds to the RECIST 1.1 criteria with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1.

Other pre-specified secondary endpoints included ORR according to RECIST 1.1 and mRECIST 1.1 both based on BICR review, response duration according to RECIST 1.1 by BICR review, and occurrence of adverse events. ORR was defined as the proportion of patients who had either a CR or PR.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

The KEYNOTE-045 trial had several exploratory objectives which were mainly PFS assessed by RECIST 1.1 by investigator review along with the assessment of changes in HRQoL from baseline using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.

The ERG considers that the outcomes selected in the CS conform to those identified by NICE as relevant to the decision problem.

4.8 Description and critique of the company's approach to trial statistics

The primary objective of KEYNOTE-045 was to establish whether pembrolizumab was more effective than SOC (vinflunine, docetaxel or paclitaxel) for patients with platinum-refractory recurrent/progressive metastatic urothelial cancer, using OS and PFS as co-primary endpoints. This objective was extended to explore the effectiveness in both PD-L1 positive and PD-L1 strongly positive subgroups in addition to the general population, to give a total of 6 primary hypotheses.

In the clarification response related to the PD-L1 cut-offs, the company has indicated that the KEYNOTE-045 study was amended to include the analysis of efficacy outcomes based on data from KEYNOTE-012 and KEYNOTE-052. Since these two studies were designed to give information on the PD-L1 cut-offs, the ERG is concerned that the PD-L1 positive and strongly positive objectives were added as study amendments. It is also unclear why the company did not add evaluation of pembrolizumab effectiveness compared to SOC in PD-L1 negative (CPS<1%) patients as an additional primary objective.

The study initially aimed to recruit 470 participants, based on sample size calculations that were performed using both PFS and OS predictions. Details can be found in section 4.4.1 of the CS. Checks by the ERG show the trial to be suitably powered, particularly considering the trial actually recruited 542 subjects. Utility values for the economic analysis were obtained using the EuroQol 5 Dimensions (EQ-5D)-3L questionnaire.

Subjects were randomised using blocking and stratified based on haemoglobin level (≥10g/dL vs <10g/dL), presence/absence of liver metastases, ECOG performance score (0/1 vs 2) and time from most recent therapy (<3 months vs ≥3 months). Stratification did not consider response to previous chemotherapy and investigational centre or any other geographical factor, both of which were used in Technology Appraisal (TA) 272.[17] The block size of two was considered appropriate due to the international scale of the trial and the number of stratification variables.

KEYNOTE-045 planned for two interim analyses, the first being event related, estimated to occur at 11-14 months from the beginning of recruitment, with the second following 8 months later. The trial included an early stopping rule which could be triggered by an independent Data Monitoring Committee (DMC). The stopping rule was implemented following the second interim analysis, hence the data presented are not final.

The approach for missing data are presented in Table 13 of the CS. Overall, the ERG considers the statistical approach to be satisfactory. The ERG note that the company identifies that the proportional hazards assumption is not met in the data, yet refer to hazard ratios obtained from Cox proportional hazards (PH) models and their associated p-values, with no mention of their potential unsuitability.

There were six secondary outcomes focussing on PFS (using a modified RECIST), ORR and treatment duration. A further 17 subgroup analyses were pre-planned, looking at differences in typical baseline patient groups and tumour characteristics. Details of all planned analyses can be found in Table 10 of the CS. The ERG notes that whilst some consideration of multiplicity was made, the majority of results presented were not adjusted and so care should be taken when viewing p-values and confidence intervals due to the large number of analyses performed.

4.9 Description and critique of the company's approach to the evidence synthesis

4.9.1 Main RCT

The reporting of the KEYNOTE-045 trial was generally clear and comprehensive. Where possible the ERG has checked key data presented in the CS against those in the publication and clinical study report (CSR) provided by the company and summaries of the evidence can be seen in Section 4.10. The ERG did not find significant discrepancies between the CS and the published account of the trial.[10]

4.9.2 Indirect and mixed treatment comparisons

In section 4.10 of their submission the company presented, indirect and mixed treatment comparisons. These were conducted in order to provide information on the relative effectiveness of pembrolizumab compared to other interventions of interest given the absence of head-to-head

comparisons with these regimens. The company selected four trials in total, this includes the KEYNOTE-045 study. The characteristics of these studies were presented in a summary table on Table 49 (CS, p140) and with full details in Appendix 13. On pages 142-43, the company commented on the differences in patient populations across the trials and indicated that the vinflunine trial (NCT00315237) only included Asian patients. The ERG disagrees with this since, to the best of our knowledge, the ethnicity of included patients has been reported neither in the three main publications of the trial nor in the European Public Assessment Report (EPAR) for the drug when JAVLOR (brand name of vinflunine) was assessed by the CHMP. The vinflunine trial included 370 patients at 83 sites in 21 countries including Europe and North America. Although the ERG was unable to identify the distribution of people between Caucasians and Asians in the trial, it's very unlikely that the vinflunine trial only included Asian patients.

On page 142, the company indicated the choice of OS and PFS as outcomes of interest for the NMA, while adverse events and HRQoL outcomes were not proposed as these are inconsistently reported across trials. The company did not comment on the objective response rate.

On page 145, the company presented the network diagram of the four included studies and concluded that there was no possible way to connect the KEYNOTE-045 and the vinflunine trial (NCT00315237). The ERG believes that both trials have a common comparator (vinflunine + BSC in the vinflunine trial and vinflunine, which is one of the three treatments among the SOC arm in KEYNOTE-045). Although the KEYNOTE-045 trial did not refer to the use of BSC, it is the ERG's interpretation that patients in the SOC arm received chemotherapy alongside BSC.

Using this common comparator, the ERG considers that a NMA could in theory have indirectly compared pembrolizumab to BSC. As indicated in the critique of the decision problem, BSC is a relevant option in the UK setting in people with second-line metastatic urothelial cancer and with poor performance status (ECOG PS 3-4). However, the ERG noted that neither KEYNOTE-045 nor the vinflunine trial specifically included this subgroup of patients. Consequently, an exploratory NMA comparing pembrolizumab to BSC could have been considered, but the relevance of this indirect comparison would be questionable.

4.10 Summary of submitted evidence

4.10.1 Results from the pivotal trial

The evidence submitted by the company comes from the results of a single pivotal trial, KEYNOTE-045 (1 clinical study report (CSR) provided by the company, one conference proceeding,[19] plus one original article published after the company submission[10]).

Main outcomes

The primary efficacy endpoints were (CSR p86-90, p112):

- OS (i.e. time from randomisation to death due to any cause)
- PFS per RECIST 1.1 by BICR review (i.e. time from randomization to documented progressive disease or death due to any cause, whichever occurred first)

In:

- all subjects
- PD-L1 CPS ≥10%
- PD-L1 CPS ≥1%

The secondary endpoints were:

- ORR according to RECIST 1.1 by BICR review
- ORR according to mRECIST 1.1 by BICR review
- PFS according to mRECIST 1.1 by BICR review
- response duration.

Results are presented from a database cut-off date of 07 September 2016.

4.10.1.1 Effectiveness in the entire population (all subjects)

Overall survival was significantly improved in the pembrolizumab group compared to the chemotherapy group (hazard ratio for death, 0.73; 95% confidence interval (CI): 0.59 to 0.91; p = 0.002). The median overall survival was 10.3 months (95% CI: 8.0 to 11.8) in the pembrolizumab group, as compared with 7.4 months (95% CI: 6.1 to 8.3) in the chemotherapy group. The estimated overall survival rate at 12 months was 43.9% (95% CI: 37.8 to 49.9) in the pembrolizumab group, as compared with 30.7% (95% CI: 25.0 to 36.7) in the chemotherapy group.

A total of 437 events of disease progression or death occurred in the intention-to-treat population, with no significant difference in the duration of progression-free survival between the pembrolizumab group and the chemotherapy group (hazard ratio (HR) for death or disease progression, 0.98; 95% CI: 0.81 to 1.19; p = 0.42). The median progression-free survival was 2.1 months (95% CI: 2.0 to 2.2) in the pembrolizumab group and 3.3 months (95% CI: 2.3 to 3.5) in the chemotherapy group. The estimated progression-free survival at 12 months was 16.8% (95% CI: 12.3 to 22.0) in the pembrolizumab group and 6.2% (95% CI: 3.3 to 10.2) in the chemotherapy group (see Table 3).

Table 3: Analysis of OS and PFS per RECIST 1.1 by BICR review (ITT Population)

	Pembrolizumab	**Chemotherapy**
Number of patients	270	272
Number of progressions n (%)	218 (80.7)	219 (80.5)
PFS at 12 months (95% CI)	16.8 (12.3, 22.0)	6.2 (3.3, 10.2)
Median PFS (months) (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
HR for progression or death (95% CI)	0.98 (0.81, 1.19)	
p value	0.41648	
OS at 6 months (95% CI)	63.9 (57.9, 69.4)	56.7 (50.3, 62.6)
OS at 12 months (95% CI)	43.9 (37.8, 49.9)	30.7 (25.0, 36.7)
Median OS (months)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
HR for death (95% CI)	0.73 (0.59, 0.91)	
p value	0.00224	

In the total population, the objective response rate was significantly higher in the pembrolizumab group (21.1%; 95% CI: 16.4 to 26.5) than in the chemotherapy group (11.4%; 95% CI: 7.9 to 15.8) (p = 0.001) (see Table 4).

The results of the ORR analyses for confirmed response per mRECIST 1.1 by BICR review for all subjects in the ITT population are consistent with the RECIST Central Radiology Assessment.

Results of the analyses of PFS per mRECIST 1.1 by BICR review at 6 and 12 months among all subjects in the ITT population are consistent with results per RECIST 1.1.

The median time to response was 2.1 months in each group. The median duration of response was not reached in the pembrolizumab group (range, 1.6+ to 15.6+ months) and was 4.3 months (range, 1.4+ to 15.4+) in the chemotherapy group (plus signs indicate an ongoing response at data cut-off).

At the time of data cut-off, 41 of 57 patients (72%) with a response in the pembrolizumab group and 11 of 31 (35%) with a response in the chemotherapy group continued to have a response. Treatment was ongoing in 36 of 57 patients with a response (63%) in the pembrolizumab group and in 2 of 31 (6%) with a response in the chemotherapy group. The estimated percentage of patients with a duration of response of at least 12 months was 68% in the pembrolizumab group versus 35% in the chemotherapy group.[10]

Table 4: Analysis of ORR, time to response, response duration per RECIST 1.1 by BICR review; ORR and PFS per mRECIST 1.1 by BICR review; All subjects (ITT population)

	Pembrolizumab	**Chemotherapy**
Number of patients	270	272
Criteria: **RECIST 1.1 by BICR review**		
Number of Objective Responses	57	31
Objective Response Rate (%) (95% CI)	21.1 (16.4,26.5)	11.4 (7.9,15.8)
Difference for ORR (95% CI)	9.6 (3.5,15.9)	
p value	0.00106	
Mean (Standard Deviation (SD)) time to response† (months)	2.7 (1.2)	2.4 (0.8)
Median (range) time to response† (months)	2.1 (1.4-6.3)	2.1 (1.7-4.9)
Median (range)§ response duration‡ (months)	Not reached (1.6+ - 15.6+)	4.3 (1.4+ - 15.4+)
Number of Subjects with Response ≥ 6 Months (%)‡	41 (78)	7 (40)
Number of Subjects with Response ≥ 12 Months (%)‡	14 (68)	3 (35)
Criteria: **mRECIST 1.1 by BICR review**		
Number of Objective Responses	68	32
Objective Response Rate (%) (95% CI)	25.2 (20.1,30.8)	11.8 (8.2,16.2)
Difference for ORR (95% CI)	13.4 (7.0,19.9)	
p value	0.00002	
Number of PFS events	196 (72.6)	198 (72.8)
Median PFS (months) (95% CI)	2.2 (2.1, 3.4)	3.5 (3.1, 4.2)
HR for progression or death (95% CI)	0.91 (0.74, 1.11)	
p value	0.16411	

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

‡ Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.

§ "+" indicates the response duration is censored.

4.10.1.2 Effectiveness in people positive for PD-L1 expression (PD-L1 CPS ≥1%)

Pembrolizumab was associated with a survival benefit over chemotherapy among patients with a tumour PD-L1 CPS ≥1% (Table 5).

Analyses of PFS based on RECIST 1.1 by BICR review showed no reduction of risk of progression or death with pembrolizumab compared to SOC. The 6-month and 12-month PFS were higher for the pembrolizumab arm than in the control arm among subjects with PD-L1 CPS ≥1% (CSR p156).

Table 5 Analysis of OS; PD-L1 CPS ≥1% and PFS per RECIST 1.1 by BICR review

	Pembrolizumab	**Chemotherapy**
Number of patients	110	120
Number of progressions n (%)	85 (77.3)	98 (81.7)
PFS at 12 months (95% CI)	20.9 (13.6, 29.3)	4.4 (1.4, 10.4)
Median PFS (months) (95% CI)	2.1 (2.0, 2.4)	3.2 (2.2, 3.4)
HR for progression or death (95% CI)	0.91 (0.68, 1.24)	
p value	0.26443	
OS at 6 months (95% CI)	65.9 (56.1, 73.9)	51.6 (41.9, 60.4)
OS at 12 months (95% CI)	46.5 (36.4, 55.8)	28.8 (20.4, 37.7)
Median OS (months)	11.3 (7.7, 16.0)	6.9 (4.7, 8.8)
HR for death (95% CI)	0.61 (0.43, 0.86)	
p value	0.00239	

Results of the analysis of PFS per mRECIST 1.1 by BICR review at 6 and 12 months among subjects with PD-L1 CPS ≥1% are consistent with results per RECIST 1.1 (CS p117) (Table 6). The ORR per RECIST 1.1 and the ORR per mRECIST were higher with pembrolizumab than chemotherapy.

The median time to response is similar among patients with CPS ≥1% treated with pembrolizumab or chemotherapy (2.2 vs. 2.1 months).

Table 6 Analysis of ORR, time to response, response duration per RECIST 1.1 by BICR review; ORR and PFS per mRECIST 1.1 by BICR review; Subjects with PD-L1 CPS ≥ 1% (ITT population)

	Pembrolizumab	**Chemotherapy**
Number of patients	110	120
Criteria: **RECIST 1.1 by BICR review**		
Number of Objective Responses	26	10

Objective Response Rate (%) (95% CI)	23.6 (16.1,32.7)	8.3 (4.1,14.8)
Difference for ORR (95% CI)	16.9 (7.7,27.0)	
p value	0.00022	
Mean (SD) time to response† (months)	2.6 (1.0)	2.0 (0.1)
Median (range) time to response† (months)	2.2 (1.4-5.3)	2.1 (1.9-2.2)
Median (range)§ response duration‡ (months)	Not reached (1.6+ - 15.6+)	Not reached (1.5+ - 15.4+)
Number of Subjects with Response ≥ 6 Months (%)‡	21 (88)	3 (56)
Number of Subjects with Response ≥ 12 Months (%)‡	7 (78)	2 (56)
Criteria: **mRECIST 1.1 by BICR review**		
Number of Objective Responses	32	11
Objective Response Rate (%) (95% CI)	29.1 (20.8,38.5)	9.2 (4.7,15.8)
Difference for ORR	21.7 (11.8,32.2)	
p value	0.00001	
Number of PFS events	76 (69.1)	88 (73.3)
Median PFS (months) (95% CI)	2.1 (2.0, 3.9)	3.3 (2.6, 3.7)
HR for progression or death (95% CI)	0.86 (0.62, 1.19)	
P value	0.17024	

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates the response duration is censored.

4.10.1.3 Effectiveness in people strongly positive for PD-L1 expression (CPS ≥10%)

Pembrolizumab was associated with significantly longer overall survival than chemotherapy in people who had a tumour PD-L1 CPS ≥ 10% (hazard ratio for death, 0.57; 95% CI: 0.37 to 0.88; p = 0.005) (Table 7). The median overall survival was 8.0 months (95% CI: 5.0 to 12.3) in the pembrolizumab group, as compared with 5.2 months (95% CI: 4.0 to 7.4) in the chemotherapy group.

There was no significant difference between-group difference in the duration of progression-free survival (hazard ratio, 0.89; 95% CI: 0.61 to 1.28; p = 0.24).

Table 7: Analysis of OS; PFS per RECIST 1.1 by BICR review; PD-L1 CPS ≥10%

	Pembrolizumab	**Chemotherapy**
Number of patients	74	90
Number of progressions n (%)	59 (79.7)	72 (80.0)
PFS at 12 months (95% CI)	17.7 (9.5,27.9)	3.7 (0.7, 10.9)
Median PFS (months) (95% CI)	2.1 (1.9, 2.1)	3.1 (2.2, 3.4)
HR for progression or death (95% CI)	0.89 (0.61, 1.28)	
p value	0.23958	

OS at 6 months (95% CI)	58.5 (46.3, 68.9)	47.2 (36.0, 57.6)
OS at 12 months (95% CI)	39.8 (28.0, 51.3)	26.9 (17.5, 37.2)
Median OS (months)	8.0 (5.0, 12.3)	5.2 (4.0, 7.4)
HR for death (95% CI)	0.57 (0.37, 0.88)	
p value	0.00483	

Results for ORR were similar in the population of patients who had a tumour PD-L1 combined positive score ≥ 10% to those described for the whole population.

The results of the ORR analyses for confirmed response per mRECIST by BICR review are consistent with the RECIST 1.1 by BICR review (CS p 108). Results of the analysis of PFS per mRECIST by BICR review at 6 and 12 months are consistent with results per RECIST 1.1 (CS p117).

The median time to response (TTR) for responders was similar in both arms (pembrolizumab = 2.1 months, range: 1.4 to 5.3; control = 2.1 months, range: 1.9 to 2.2). Consistent with the overall ITT population, median DoR for 16 subjects with PD-L1 CPS ≥10% receiving pembrolizumab with a confirmed CR/PR had not yet been reached at the time of data cut-off (range: 1.6+ to 15.4+ months), whereas median DoR for the 6 subjects with PD-L1 CPS ≥10% receiving control was established at 4.4 months (range: 1.5+ to 10.8+ months). There were 14 subjects with PD-L1 CPS ≥10% in the pembrolizumab arm and 1 subject in the control arm with responses ≥6 months. There were 3 subjects in the pembrolizumab arm and no subjects in the control arm with response ≥12 months (CSR p152) (see Table 8).

Table 8: Analysis of ORR, time to response, response duration per RECIST 1.1 by BICR review; ORR and PFS per mRECIST 1.1 by BICR review; Subjects with PD-L1 CPS >= 10% (ITT population)

	Pembrolizumab	**Chemotherapy**
Number of patients	74	90
Criteria: **RECIST 1.1 by BICR review**		
Number of Objective Responses	16	6
Objective Response Rate (%) (95% CI)	21.6 (12.9,32.7)	6.7 (2.5,13.9)
Difference for ORR (95% CI)	19.3 (8.6,31.7)	
p value	0.00020	
Mean (SD) time to response† (months)	2.5 (1.0)	2.0 (0.1)
Median (range) time to response† (months)	2.1 (1.4-5.3)	2.1 (1.9-2.2)
Median (range)§ response duration‡ (months)	Not reached (1.6+ - 15.4+)	4.4 (1.5+ - 10.8+)

Number of Subjects with Response ≥ 6 Months (%)‡	14 (93)	1 (40)
Number of Subjects with Response ≥ 12 Months (%)‡	3 (76)	0
Criteria: **mRECIST 1.1 by BICR**		
Number of Objective Responses	19	7
Objective Response Rate (%) (95% CI)	25.7 (16.2,37.2)	7.8 (3.2,15.4)
Difference for ORR	22.5 (11.0,35.3)	
p value	0.00006	
Number of PFS events	52 (70.3)	65 (72.2)
Median PFS (months) (95% CI)	2.1 (2.0, 3.8)	3.3 (2.3, 3.7)
HR for progression or death (95% CI)	0.77 (0.52, 1.14)	
p value	0.09052	

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.
‡ Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates the response duration is censored.

4.10.1.4 Effectiveness in further subgroup analyses

Subgroup analyses were pre-specified for the following variables (study protocol p100):

- Age category (< 65 vs. ≥ 65 years)
- PD-L1 subgroup (positive vs. negative)
- Strongly positive PD-L1 subgroup (to be defined based on emerging external data)
- Sex (female vs. male)
- Race (white vs. non-white)
- ECOG status (0/1 vs. 2 and 0 vs. 1/2)
- Geographic region of enrolling site (East Asia vs. non-East Asia, United States (US) vs. non-US, and EU vs. non-EU)
- Prior platinum therapy (carboplatin vs. cisplatin)
- Setting of most recent prior therapy (neoadjuvant vs. adjuvant vs. 1L metastatic vs. 2L metastatic)
- Presence or absence of liver metastases at baseline
- Baseline haemoglobin (≥ 10 g/dL vs. <10 g/dL)
- Time from completion/discontinuation of most recent prior therapy to baseline (< 3 months vs. ≥ 3 months)
- Histology (transitional cell vs. mixed transitional/non-transitional histology)
- Smoking status (never vs. former vs. current)
- Brain metastasis status (prior brain metastasis vs. no prior brain metastasis)
- Investigators' choice of paclitaxel, docetaxel or vinflunine
- Burden of disease in terms of baseline tumour volume

Primary outcomes

Analyses of OS by subgroup showed consistency of survival benefit favouring pembrolizumab across subgroups (CSR p116), with consistent point estimates for the HR in important subgroups such as ECOG-PS, liver metastasis, haemoglobin, time from prior chemotherapy, prior platinum (cisplatin versus carboplatin), investigator's choice of chemotherapy in control arm (paclitaxel, docetaxel or vinflunine), and Bellmunt risk scores (see Table 9). Few exceptions were noted (e.g., 'non-White,' 'East Asia,' and 'never smoker'). The small numbers of events in some subgroups result in wide CIs and preclude an accurate interpretation of treatment effect.

Table 9: Overall survival by subgroup factors

	Control		**Pembrolizumab**		**Hazard Ratio (95% CI)†**
	N	**Number of Events (%)**	**N**	**Number of Events (%)**	
Overall	272	[redacted]	270	[redacted]	0.73(0.59,0.91)
<65 years	125		105		0.75(0.53,1.05)
≥65 years	147		165		0.76(0.56,1.02)
PD-L1 CPS < 1%	147		151		0.89(0.66,1.20)
PD-L1 CPS ≥ 1%	120		110		0.61(0.43,0.86)
PD-L1 CPS < 10%	176		186		0.80(0.61,1.05)
PD-L1 CPS ≥ 10%	90		74		0.57(0.37,0.88)
Female	70		70		0.78(0.49,1.24)
Male	202		200		0.73(0.56,0.94)
White	201		188		0.65(0.50,0.84)
Non-White	63		70		1.12(0.70,1.79)
ECOG 0/1	264		262		0.74(0.59,0.92)
ECOG 2	4		2		0.43(0.04,4.20)
ECOG 0	106		119		0.99(0.66,1.47)
ECOG 1/2	162		145		0.66(0.50,0.87)
East-Asia	48		58		1.25(0.72,2.18)
Non-East Asia	224		212		0.66(0.52,0.85)
EU	117		106		0.59(0.42,0.84)
Non-EU	155		164		0.79(0.60,1.06)
US	59		47		0.83(0.48,1.41)
Non-US	213		223		0.71(0.56,0.91)
Never Smoker	83		104		1.06(0.72,1.55)
Former Smoker	148		136		0.71(0.52,0.97)
Current Smoker	38		29		0.32(0.15,0.68)
Cisplatin	213		198		0.73(0.56,0.94)
Carboplatin	56		70		0.74(0.47,1.18)
Most Recent Prior Therapy:					
Neo Adjuvant	22		19		0.53(0.20,1.41)
Adjuvant	31	[redacted]	12	[redacted]	0.53(0.18,1.57)
1L Metastatic	157		183		0.72(0.54,0.95)
2L Metastatic	60		55		0.83(0.52,1.33)
Liver Metastases at Baseline:					
Presence	95		91		0.85(0.61,1.20)

Absence	176	[redacted]	179	[redacted]	0.67(0.50,0.89)
Hb ≥10 g/dL	223	[redacted]	219	[redacted]	0.71(0.55,0.91)
Hb <10 g/dL	44	[redacted]	43	[redacted]	0.75(0.46,1.22)
Time from Most Recent Chemo Therapy:		[redacted]		[redacted]	
≥3 Months	167	[redacted]	166	[redacted]	0.66(0.49,0.89)
<3 Months	104	[redacted]	103	[redacted]	0.82(0.58,1.15)
Transitional Cell	197	[redacted]	186	[redacted]	0.80(0.62,1.04)
Mixed Transitional/ nontransitional histology	73	[redacted]	82	[redacted]	0.58(0.37,0.89)
Prior Brain Metastasis	5	[redacted]	2	[redacted]	NA(NA,NA)
No Prior Brain Metastasis	267	[redacted]	268	[redacted]	0.73(0.58,0.91)
Paclitaxel	84	[redacted]	266	[redacted]	0.76(0.55,1.04)
Docetaxel	84	[redacted]	266	[redacted]	0.76(0.55,1.05)
Vinflunine	87	[redacted]	266	[redacted]	0.69(0.51,0.94)
Burden of Disease on Baseline Tumour Volume:		[redacted]		[redacted]	
< Median	117	[redacted]	132	[redacted]	0.54(0.38,0.78)
≥ Median	135	[redacted]	115	[redacted]	0.91(0.68,1.23)
Risk Scores: 0	44	[redacted]	54	[redacted]	0.82(0.42,1.62)
1	97	[redacted]	96	[redacted]	0.73(0.49,1.08)
2	80	[redacted]	66	[redacted]	0.84(0.56,1.24)
3 or 4	45	[redacted]	45	[redacted]	0.76(0.47,1.24)
Site of Primary Tumour:		[redacted]		[redacted]	
Upper Tract	37	[redacted]	38	[redacted]	0.53(0.28,1.01)
Lower Tract	234	[redacted]	232	[redacted]	0.77(0.60,0.97)
Lymph Node Only	38	[redacted]	29	[redacted]	0.46(0.18,1.21)
Visceral Disease	233	[redacted]	240	[redacted]	0.75(0.60,0.95)

† Based on Cox regression model with treatment as covariates and stratified by Eastern Cooperative Oncology Group (ECOG) Performance Score (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (Hb) (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
N = sample size
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

In the clarification questions, the ERG asked the company to provide further explanations of the cut-offs used to determine PD-L1 expression. In their response, the company commented that the OS benefit of pembrolizumab versus chemotherapy was observed across all PD-L1 CPS expression levels (page 8, clarification document). The ERG agree with this comment with respect to patients positive and strongly positive for PD-L1 expression. However, the ERG disagree with this statement pertaining to the group of patients negative for PD-L1 expression since the HR for death is 0.89 (95% CI 0.66, 1.20). Indeed, since the study was not designed to test the superiority of pembrolizumab in this subpopulation, the sample size may have been

insufficient to demonstrate a statistically significant difference in the risk of death. Therefore, the ERG believes that no conclusion, either positive or negative, can be drawn for the subgroup analysis in people with negative PD-L1 expression which would be eligible to pembrolizumab should this drug obtain a label indication regardless of PD-L1 expression.

Results for analyses of PFS by subgroup are consistent with the overall analysis and across subgroups (CSR p120) (see Table 10).

Table 10: Progression-Free Survival Based on RECIST 1.1 per Central Radiology Assessment (Primary Censoring Rule) by Subgroup Factors

	Control		Pembrolizumab		Hazard Ratio (95% CI)†
	N	Number of Events (%)	N	Number of Events (%)	
Overall	272	[redacted]	270	[redacted]	0.98(0.81,1.19)
<65 years	125	[redacted]	105	[redacted]	0.98(0.73,1.33)
≥65 years	147	[redacted]	165	[redacted]	1.08(0.83,1.40)
PD-L1 CPS < 1%	147	[redacted]	151	[redacted]	1.07(0.82,1.39)
PD-L1 CPS ≥ 1%	120	[redacted]	110	[redacted]	0.91(0.68,1.24)
PD-L1 CPS < 10%	176	[redacted]	186	[redacted]	1.04(0.82,1.33)
PD-L1 CPS ≥ 10%	90	[redacted]	74	[redacted]	0.89(0.61,1.28)
Female	70	[redacted]	70	[redacted]	0.96(0.63,1.44)
Male	202	[redacted]	200	[redacted]	1.01(0.81,1.28)
White	201	[redacted]	188	[redacted]	0.88(0.70,1.10)
Non-White	63	[redacted]	70	[redacted]	1.48(0.99,2.23)
ECOG 0/1	264	[redacted]	262	[redacted]	0.98(0.80,1.19)
ECOG 2	4	[redacted]	2	[redacted]	2.92(0.26,32.93)
ECOG 0	106	[redacted]	119	[redacted]	1.16(0.84,1.60)
ECOG 1/2	162	[redacted]	145	[redacted]	0.96(0.74,1.23)
East-Asia	48	[redacted]	58	[redacted]	1.68(1.05,2.67)
Non-East Asia	224	[redacted]	212	[redacted]	0.86(0.69,1.06)
EU	117	[redacted]	106	[redacted]	0.90(0.66,1.24)
Non-EU	155	[redacted]	164	[redacted]	1.03(0.80,1.33)
US	59	[redacted]	47	[redacted]	0.85(0.53,1.37)
Non-US	213	[redacted]	223	[redacted]	1.03(0.83,1.28)
Never Smoker	83	[redacted]	104	[redacted]	1.13(0.80,1.60)
Former Smoker	148	[redacted]	136	[redacted]	1.05(0.79,1.38)
Current Smoker	38	[redacted]	29	[redacted]	0.47(0.25,0.88)
Cisplatin	213	[redacted]	198	[redacted]	0.99(0.79,1.24)
Carboplatin	56	[redacted]	70	[redacted]	0.97(0.64,1.48)
Most Recent Prior Therapy:		[redacted]		[redacted]	
Neo Adjuvant	22		19		0.94(0.40,2.19)
Adjuvant	31	[redacted]	12	[redacted]	0.94(0.38,2.30)
1L Metastatic	157	[redacted]	183	[redacted]	0.88(0.69,1.14)
2L Metastatic	60	[redacted]	55	[redacted]	1.43(0.93,2.20)

Liver Metastases at Baseline:		[redacted]		[redacted]	
Presence	95		91		1.13(0.81,1.56)
Absence	176	[redacted]	179	[redacted]	0.93(0.73,1.18)
Hb ≥10 g/dL	223	[redacted]	219	[redacted]	0.94(0.76,1.17)
Hb <10 g/dL	44	[redacted]	43	[redacted]	1.26(0.77,2.05)
Time from Most Recent Chemo Therapy:		[redacted]		[redacted]	
≥3 Months	167		166		0.81(0.63,1.04)
<3 Months	104	[redacted]	103	[redacted]	1.28(0.94,1.76)
Transitional Cell	197	[redacted]	186	[redacted]	1.08(0.86,1.36)
Mixed Transitional/ nontransitional		[redacted]		[redacted]	
histology	73		82		0.84(0.57,1.24)
Prior Brain Metastasis	5	[redacted]	2	[redacted]	NA(NA,NA)
No Prior Brain Metastasis	267	[redacted]	268	[redacted]	0.97(0.80,1.18)
Paclitaxel	84	[redacted]	266	[redacted]	0.94(0.71,1.24)
Docetaxel	84	[redacted]	266	[redacted]	0.97(0.73,1.28)
Vinflunine	87	[redacted]	266	[redacted]	1.09(0.83,1.44)
Burden of Disease on Baseline Tumour Volume:		[redacted]		[redacted]	
< Median	117		132		0.76(0.57,1.02)
≥ Median	135	[redacted]	115	[redacted]	1.22(0.93,1.61)
Risk Scores:		[redacted]		[redacted]	
0	44		54		0.83(0.52,1.33)
1	97	[redacted]	96	[redacted]	0.99(0.70,1.39)
2	80	[redacted]	66	[redacted]	1.09(0.75,1.58)
3 or 4	45	[redacted]	45	[redacted]	1.36(0.84,2.18)
Site of Primary Tumour:		[redacted]		[redacted]	
Upper Tract	37		38		1.18(0.67,2.07)
Lower Tract	234	[redacted]	232	[redacted]	0.97(0.78,1.19)
Lymph Node Only	38	[redacted]	29	[redacted]	0.56(0.30,1.07)
Visceral Disease	233		240	[redacted]	1.04(0.85,1.28)

† Based on Cox regression model with treatment as covariates and stratified by Eastern Cooperative Oncology Group (ECOG) Performance Score (0/1 vs. 2), presence or absence of liver metastases, haemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
N = sample size
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Secondary outcomes

The company did not comment on the ORR by subgroups data. These were presented in Table 14.2-34 of the CSR (p398).

Table 11: Objective Response Rate Based on RECIST 1.1 per Central Radiology Assessment by Subgroup Factors

	Control		Pembrolizumab		Pembrolizumab vs Control
	N	Number of Responses (ORR%)	N	Number of Responses (ORR%)	Rate Difference (95% CI)†
Overall	272	[redacted]	270	[redacted]	[redacted]
<65 years	125	[redacted]	105	[redacted]	[redacted]
≥65 years	147	[redacted]	165	[redacted]	[redacted]
PD-L1 CPS < 1%	147	[redacted]	151	[redacted]	[redacted]
PD-L1 CPS ≥ 1%	120	[redacted]	110	[redacted]	[redacted]
PD-L1 CPS < 10%	176	[redacted]	186	[redacted]	[redacted]
PD-L1 CPS ≥ 10%	90	[redacted]	74	[redacted]	[redacted]
Female	70	[redacted]	70	[redacted]	[redacted]
Male	202	[redacted]	200	[redacted]	[redacted]
White	201	[redacted]	188	[redacted]	[redacted]
Non-White	63	[redacted]	70	[redacted]	[redacted]
ECOG 0/1	264	[redacted]	262	[redacted]	[redacted]
ECOG 2	4	[redacted]	2	[redacted]	[redacted]
ECOG 0	106	[redacted]	119	[redacted]	[redacted]
ECOG 1/2	162	[redacted]	145	[redacted]	[redacted]
East-Asia	48	[redacted]	58	[redacted]	[redacted]
Non-East Asia	224	[redacted]	212	[redacted]	[redacted]
EU	117	[redacted]	106	[redacted]	[redacted]
Non-EU	155	[redacted]	164	[redacted]	[redacted]
US	59	[redacted]	47	[redacted]	[redacted]

Non-US	213	[redacted]		223	[redacted]	
Never Smoker	83	[redacted]		104	[redacted]	
Former Smoker	148	[redacted]		136	[redacted]	
Current Smoker	38	[redacted]		29	[redacted]	
Cisplatin	213	[redacted]		198	[redacted]	
Carboplatin	56	[redacted]		70	[redacted]	
Most Recent Prior Therapy:		[redacted]			[redacted]	
Neo Adjuvant	22			19		
Adjuvant	31	[redacted]		12	[redacted]	
1L Metastatic	157	[redacted]		183	[redacted]	
2L Metastatic	60	[redacted]		55	[redacted]	
Liver Metastases at Baseline:		[redacted]			[redacted]	
Presence	95			91		
Absence	176	[redacted]		179	[redacted]	
Hb ≥10 g/dL	223	[redacted]		219	[redacted]	
Hb <10 g/dL	44	[redacted]		43	[redacted]	
Time from Most Recent Chemo Therapy: ≥3 Months	167	[redacted]		166	[redacted]	
<3 Months	104	[redacted]		103	[redacted]	
Transitional Cell	197	[redacted]		186	[redacted]	
Mixed Transitional/ nontransitional histology	73	[redacted]		82	[redacted]	
Prior Brain Metastasis	5	[redacted]		2	[redacted]	
No Prior Brain Metastasis	267	[redacted]		268	[redacted]	
Paclitaxel	84	[redacted]		266	[redacted]	
Docetaxel	84	[redacted]		266	[redacted]	
Vinflunine	87	[redacted]		266	[redacted]	
Burden of Disease on Baseline Tumour Volume: < Median	117	[redacted]		132	[redacted]	

≥ Median	135	[redacted]	115	[redacted]	[redacted]
Risk Scores:		[redacted]		[redacted]	[redacted]
0	44		54		
1	97	[redacted]	96	[redacted]	[redacted]
2	80	[redacted]	66	[redacted]	[redacted]
3 or 4	45	[redacted]	45	[redacted]	[redacted]
Site of Primary		[redacted]		[redacted]	[redacted]
Tumour:	37		38		
Upper Tract					
Lower Tract	234	[redacted]	232	[redacted]	[redacted]
Lymph Node Only	38	[redacted]	29	[redacted]	[redacted]
Visceral Disease	233	[redacted]	240	[redacted]	[redacted]

† Based on Miettinen & Nurminen method
N = sample size
ORR = Objective Response Rate
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

Other secondary endpoints (ORR by mRECIST, PFS by mRECIST and response duration) were not presented by subgroup.

4.10.1.5 Health-related quality of life

Quality of life was assessed by EORTC-QLQ-C30 and EQ-5D questionnaires. The patient reported outcomes were to be collected prior to cycle 1, cycle 2, cycle 3, cycle 4 and every 2 cycles thereafter (e.g., cycle 6, cycle 8, cycle 10) up to a year or end of treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit (protocol p60).

EORTC-QLQ-C30:

Baseline global health status/quality of life (QoL) scores were similar between treatment arms (CS p122). At week 9, the global health status/QoL score was stable from baseline (least squares (LS) mean = -1.37 points; 95% CI: -4.10, 1.35) in the pembrolizumab arm, and a greater worsening of -5.75 points (95% CI: -8.62, -2.87) was observed in the control arm. The difference in LS means between pembrolizumab and the control arm at week 9 was 4.38 points (95% CI: 0.59, 8.16; two-sided p=0.02, not controlled for multiplicity). At week 15, there was an even greater difference in LS means between the pembrolizumab arm and control (9.05 points; 95% CI: 4.61, 13.48; two-sided p<0.001, not controlled for multiplicity) (see Table 12).

Table 12: Analysis of change from baseline in EORTC QLQ-C30 global health status/QoL at Week 9 (FAS population)

	Pembrolizumab	Chemotherapy
Baseline: Number of patients	260	243
Baseline: Mean (SD)	61.51 (23.107)	59.12 (22.144)
Week 9: Number of patients	200	176
Week 9: Mean (SD)	63.04 (22.964)	58.48 (21.849)
Change from baseline at week 9	-1.37 (-4.10, 1.35)	-5.75 (-8.62, -2.87)
Difference in LS Means (95% CI)	4.38 (0.59, 8.16)	
p value	0.024	
Week 15: Number of patients	157	118
Week 15: Mean (SD)	67.57 (22.558)	57.91 (19.516)
Change from baseline at week 15	0.75 (-2.34, 3.83)	-8.30 (-11.76, -4.83)
Difference in LS Means (95% CI)	9.05 (4.61, 13.48)	
p value	< .001	
Time to first onset of a 10-point or greater score decrease from baseline in the EORTC QLQ-C30 global health status/QoL score: Hazard Ratio (95% CI)	0.70 (0.55, 0.90)	
p value	0.00182	

EQ-5D analyses

Results from EQ-5D analyses were consistent with the results of EORTC QLQ-C30 analyses (CS p126). Both the EQ-5D visual analogue score (VAS) and the EQ-5D utility scores were stable over time for subjects in the pembrolizumab arm, whereas a worsening of EQ-5D VAS and utility scores was observed in the control group (see Table 13).

Table 13: Change from baseline in EuroQol EQ-5D VAS by time point - (FAS population)

	EuroQol EQ-5D VAS		EuroQol EQ-5D utility score	
	Pembrolizumab	Chemotherapy	Pembrolizumab	Chemotherapy
Baseline: Mean (SD) N Week 3: Mean (SD) N Mean (95% CI) change from baseline	68.0 (20.10) 232 69.1 (19.32) 232 1.1 (-1.1, 3.2)	67.3 (20.03) 209 66.1 (20.10) 209 -1.2 (-3.7, 1.2)	0.72 (0.22) 232 0.70 (0.24) 232 -0.02 (-0.05, 0.00)	0.70 (0.22) 209 0.68 (0.23) 209 -0.02 (-0.05, 0.00)
Baseline: Mean (SD) N Week 6: Mean (SD) N Mean (95% CI) change from baseline	68.8 (19.48) 210 69.3 (19.25) 210 0.5 (-1.8, 2.8)	69.8 (17.81) 191 65.6 (20.78) 191 -4.1 (-6.7, -1.5)	0.73 (0.22) 210 0.70 (0.25) 210 -0.03 (-0.06, 0.00)	0.73 (0.19) 191 0.66 (0.24) 191 -0.07 (-0.10, -0.04)
Baseline: Mean (SD) N Week 9: Mean (SD) N Mean (95% CI) change from baseline	69.2 (19.63) 195 70.0 (20.22) 195 0.8 (-1.8, 3.4)	70.5 (18.54) 169 66.5 (19.80) 169 -4.0 (-6.7, -1.4)	0.73 (0.22) 195 0.70 (0.27) 195 -0.03 (-0.07, -0.00)	0.73 (0.20) 169 0.65 (0.26) 169 -0.08 (-0.12, -0.05)
Baseline: Mean (SD) N Week 15: Mean (SD) N	71.8 (19.07) 153 73.4 (18.38) 153	70.8 (17.69) 112 67.7 (18.44) 112	0.76 (0.22) 153 0.74 (0.24) 153	0.76 (0.19) 112 0.67 (0.23) 112

Mean (95% CI) change from baseline	1.6 (-1.1, 4.4)	-3.1 (-6.4, 0.2)	-0.01 (-0.05, 0.02)	-0.09 (-0.12, -0.05)
Baseline: Mean (SD) N Week 21: Mean (SD) N Mean (95% CI) change from baseline	71.8 (18.75) 123 73.2 (18.65) 123 1.4 (-2.5, 5.3)	71.1 (18.20) 67 67.2 (18.75) 67 -3.9 (-8.5, 0.7)	0.77 (0.20) 123 0.77 (0.21) 123 -0.00 (-0.04, 0.03)	0.77 (0.19) 67 0.68 (0.22) 67 -0.09 (-0.14, -0.04)
Baseline: Mean (SD) N Week 27: Mean (SD) N Mean (95% CI) change from baseline	71.7 (18.49) 104 75.1 (19.00) 104 3.4 (-0.3, 7.1)	72.5 (16.99) 43 66.3 (19.48) 43 -6.2 (-13.3, 0.8)	0.77 (0.21) 104 0.76 (0.25) 104 -0.01 (-0.06, 0.03)	0.78 (0.19) 43 0.69 (0.25) 43 -0.09 (-0.16, -0.03)

The evaluation on quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, the validity of the findings is in question and conclusions may not be reliable from the quality of life results.

4.10.1.6 Safety: adverse events

Adverse events considered by the investigator to be "possibly," "probably," or "definitely" related to the study treatment were combined into the category drug-related AEs.

Adverse events that were considered by the investigators to be related to treatment occurred in 60.9% of the patients treated with pembrolizumab, vs. 90.2% of those who received chemotherapy (CS p152). Treatment-related events of grade 3, 4, or 5 severity were less frequent in the pembrolizumab group than in the chemotherapy group (15.0% vs. 49.4% of patients, CS p154), as was treatment-related discontinuation of therapy (5.6% vs. 11.0%). One pembrolizumab-treated patient died from treatment-related pneumonitis. Three other deaths in the pembrolizumab group were attributed by the investigators to study treatment, including one death related to urinary tract obstruction, one death related to malignant neoplasm progression, and one death of unspecified cause. In the chemotherapy group, treatment-related deaths were related to sepsis (in two patients), septic shock (in one), and unspecified cause (in one) (see Table 14). The ERG found surprising that the urinary tract obstruction and neoplasm progression that lead to two deaths in the pembrolizumab arm were attributed to study treatment.

The most common treatment-related adverse events of any grade were pruritus (19.5% of the patients), fatigue (13.9%), and nausea (10.9%) in the pembrolizumab group and alopecia (37.6%), fatigue (27.8%), and anaemia (24.7%) in the chemotherapy group.[10] There were no treatment-related events of grade 3, 4, or 5 severity that occurred with an incidence of 5% or more in the pembrolizumab group. In the chemotherapy group, treatment-related events of grade 3, 4, or 5

severity with an incidence of 5% or more were neutropenia (13.3%), decreased neutrophil count (12.2%), anaemia (7.8%), febrile neutropenia (7.1%), and decreased white-cell count (5.1%).

AEs of special interest (AEOSI) are immune mediated events and infusion related reactions considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab (CS p160). There were 45 (16.9%) subjects in the pembrolizumab arm with 1 or more AEOSIs. The only AEOSI of grade 3, 4, or 5 severity that were observed in two or more patients who were treated with pembrolizumab were pneumonitis (2.3% of the patients), colitis (1.1%), and nephritis (0.8%); there was only one grade 5 event (0.4%), which was pneumonitis.[10]

Table 14: Adverse Events in the As-Treated Population*

Event	**Pembrolizumab Group (N = 266)**		**Chemotherapy Group (N = 255)**	
	Any Grade	**Grade 3, 4, or 5**	**Any Grade**	**Grade 3, 4, or 5**
	Number of patients (percent)			
Treatment-related event†				
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of treatment	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)
Event occurring in ≥10% of patients in either group‡				
Pruritus	52 (19.5)	0	7 (2.7)	1 (0.4)
Fatigue	37 (13.9)	3 (1.1)	71 (27.8)	11 (4.3)
Nausea	29 (10.9)	1 (0.4)	62 (24.3)	4 (1.6)
Diarrhoea	24 (9.0)	3 (1.1)	33 (12.9)	2 (0.8)
Decreased appetite	23 (8.6)	0	41 (16.1)	3 (1.2)
Asthenia	15 (5.6)	1 (0.4)	36 (14.1)	7 (2.7)
Anaemia	9 (3.4)	2 (0.8)	63 (24.7)	20 (7.8)
Constipation	6 (2.3)	0	52 (20.4)	8 (3.1)
Peripheral sensory neuropathy	2 (0.8)	0	28 (11.0)	5 (2.0)
Neutrophil count decreased	1 (0.4)	1 (0.4)	36 (14.1)	31 (12.2)
Peripheral neuropathy	1 (0.4)	0	27 (10.6)	2 (0.8)
Neutropenia	0	0	39 (15.3)	34 (13.3)
Alopecia	0	0	96 (37.6)	2 (0.8)
Event of interest§				

Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)
Hypothyroidism	17 (6.4)	0	3 (1.2)	0
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0
Infusion reaction	2 (0.8)	0	10 (3.9)	0
Nephritis	2 (0.8)	2 (0.8)	0	0
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)
Thyroiditis	2 (0.8)	0	0	0
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0
Myositis	0	0	1 (0.4)	1 (0.4)

** The as-treated population included all the patients who received at least one dose of study treatment.*
† Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form. Although decreased neutrophil count and neutropenia may reflect the same condition, they were listed by the investigators as two distinct events; this was also the case for peripheral sensory neuropathy and peripheral neuropathy and for fatigue and asthenia.
‡ Events are listed in descending order of frequency in the pembrolizumab group.
§ The events of interest are those with an immune-related cause and are considered regardless of attribution to study treatment by the investigator.
They are listed in descending order of frequency in the pembrolizumab group. In addition to the specific preferred terms listed, related terms were also included.

4.10.2 Results from post-hoc analyses excluding vinflunine

The results from a post-hoc analysis where vinflunine was excluded from the SOC arm were presented in the CS. Since these analyses were conducted for the purpose of a cost-effectiveness within the UK perspective, these have been reported in the cost-effectiveness section.

4.10.3 Results from the NMA

No NMA was provided by the company.

4.11 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG on clinical effectiveness

4.12 Conclusions of the clinical effectiveness section

Pembrolizumab used as single agent was evaluated against SOC (either paclitaxel, docetaxel, or vinflunine) in the KEYNOTE-045 trial. This phase 3 trial was of good quality, with a low risk of

bias in most domains except for the blinding of participants and personnel since the study was open-label thus considered to be at high-risk of bias.

There were two co-primary endpoints that were assessed in the entire population, the population positive for PD-L1 expression, and the population strongly-positive for PD-L1 expression.

Regarding PFS, the risk of progression or death was similar between pembrolizumab and SOC in the three populations although the proportion of patients free from progression at 1 year was higher with pembrolizumab.

However, as far as OS is concerned, the risk of death was reduced with pembrolizumab compared to SOC in the three populations.

The results of PFS and OS in the numerous subgroups showed consistency with the overall findings for the entire population.

Evaluation of quality of life was presented as part of exploratory objectives. Owing to the open-label design of KEYNOTE-045, it is difficult to draw reliable conclusions from the quality of life results.

The safety profile of pembrolizumab was more favourable than that of SOC. There was no treatment-related ≥3 event occurring with a frequency of ≥5% incidence in the pembrolizumab group.

As of April 2017, pembrolizumab is not licensed for urothelial cancers and a submission aimed to extend the marketing authorisation is currently being assessed with the CHMP. Based on the results of KEYNOTE-045 which presents the clinical effectiveness and safety profile of pembrolizumab in advanced/metastatic urothelial cancers after failure of platinum-based therapy, the ERG believes that it's likely that the CHMP will consider the balance between benefits and risks of pembrolizumab to be positive.

No indirect comparisons were presented by the company. There is no data comparing pembrolizumab to BSC which is a relevant comparator in people with poor performance status.

5 COST EFFECTIVENESS

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

5.1.1 Objectives and search strategy

The CS states on p171 that the scope of the review was broadened to include patients with advanced or metastatic urothelial cancer irrespective of therapy line, in order to identify all relevant data that could inform development and population of the model. The company provided an appropriate description of the cost-effectiveness systematic, utility and cost/resource use reviews and details of the different search strategies were reported in Appendix 17 (the CS states on p171 that the detailed search strategy is in Appendix 23, however, there is no Appendix 23 in the CS). In brief, the company searched MEDLINE, Econlit, EMBASE, Cochrane library including the NHS Economic Evaluation Database and Health Technology Assessment (HTA) databases. Manual searches were also performed on oncology websites and conference proceedings. In addition, reference lists of included papers were also consulted. Original searches were carried out between 6th and 7th August 2015, and updated in December 2016. The search strategy was appropriate.

5.1.2 Inclusion/exclusion criteria used in the study selection

The CS on p172-173 (CS table 62) tabulated the inclusion and exclusion criteria for the systematic reviews of economic evaluations which included population, intervention/comparator, outcomes, study type, publication type, time limit, and language. The selection criteria limited studies to those published in English language, those in adult patients 18 years or older and studies published in the last 10 years. The study selection seemed appropriate. It is unclear what the inclusion/exclusion criteria was for either the cost and resource use; or HRQoL and utility systematic reviews.

5.1.3 Identified studies

CS Figures 32, 42 and 43 provided the flow diagrams for the economic evaluation; HRQoL and utility; and cost and resource use systematic reviews respectively. The company did state in the original CS that "a summary list of published cost-effectiveness studies has not been compiled".

The ERG requested at the clarification stage details of the 126 papers which were evaluated in full, including references and reasons why studies were excluded. For example, for the economic evaluation review in the original CS, 4 papers met the inclusion criteria from the original search but no further information or references were provided. Upon clarification the company excluded 3 of the 4 publications by stating "they should have been excluded during the secondary screening as although they provide relevant information in regards to the economic modelling, they were published prior to 2005". The company provided an excel document titled "ID1019 Economic SLR" which included references to the excluded studies.

The flow diagrams indicated that no studies were included for the original economic evaluation and the cost and resource use reviews; however, one study was identified from the updated cost and resource use search.[17] For the original HRQoL and utility review and updated search, 24 studies were extracted from 29 publications (the reference lists, characteristics and information on utility values for these studies were included in Appendix 18).

The CS did not state whether the studies were independently assessed by two reviewers. No quality assessment was conducted by the company, as stated on p175 "as no cost-effectiveness study meeting all inclusion criteria was identified". Furthermore, the CS does not formally report whether any of the modelling attributes from the included HRQoL and utility studies were used in the development of the *de novo* economic model of pembrolizumab.

Some additional studies relevant to the population were identified by the ERG through targeted searches of the CEA Registry, NHS EED and the HTA database, but none were relevant to the decision making context.

To summarise, no cost-effectiveness studies assessing pembrolizumab for patients with advanced or metastatic urothelial cancer were identified.

5.1.4 Conclusions

The company did not provide a formal conclusion from the data available of the three systematic reviews: economic evaluation, utility and cost/resource use.

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

5.2.1 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS. Including technologies regarded as current best practice for the two populations	UK SOC i.e. physicians choice of docetaxel or paclitaxel
Patient group	As per NICE final scope	Patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis (Cost per quality-adjusted life year (QALY))
Time horizon	Sufficient to capture differences in costs and outcomes	Yes (lifetime duration)
Synthesis of evidence on outcomes	Systematic review	Data are drawn from one trial: KEYNOTE-045
Outcome measure	Quality-adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes. Health states were evaluated using EQ-5D-3L data collected from KEYNOTE-045 trial

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	Annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefits	Yes
Probabilistic modelling	Probabilistic modelling	Yes
Sensitivity analysis		A range of sensitivity and scenario analyses are presented

5.2.2 Model structure

The company presented a *de novo* cost-utility partitioned survival model with a weekly cycle length and a lifetime time horizon. The model consisted of three health states: pre-progression, post-progression, and death (Figure 2). A half-cycle correction was applied in the base-case analysis.

The partitioned survival approach uses an "area under the curve" approach, where the number of patients in the two health states: PFS and OS, is taken directly from survival curves fitted to the clinical data. This approach did not consider post-progression survival directly. Instead, time in post-progression survival was derived from the difference in the area under the two survival health states (PFS and OS).

The model assumes all patients enter the model in the pre-progression health state. Patients in the pre-progression health state, stay in that health state until disease progression. Transitions to the death state could occur from either the pre-progression or post-progression health state. Costs of disease management, utilities and risks of death all differ between the pre-progression and the post-progression health states.

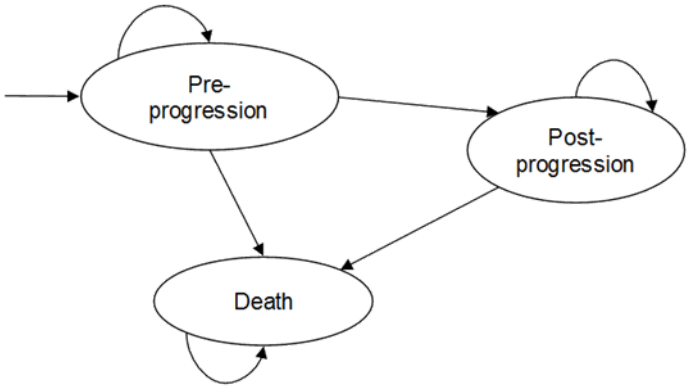


Figure 2: Model structure presented by the company

ERG summary

- Even though the model is a simple one with three health states, it is consistent with other models built in this disease area, and captures the two important clinical endpoints of OS and PFS. The cycle length of the model (1 week) should be sufficiently short to capture changes over the relevant time interval.

5.2.3 Population

The population modelled in the company's base case analysis included patients with metastatic or locally advanced/unresectable urothelial cancer which has recurred or progressed following platinum-containing chemotherapy.

The company also presented results for the following subgroups of patients in the CS Appendix:

1. patients with advanced or metastatic urothelial cancer of predominantly transitional cell histology.
2. patients with advanced or metastatic urothelial cancer of pure transitional cell histology.
3. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥1%) urothelial cancer.

4. patients with platinum-refractory recurrent/progressive metastatic PD-L1 positive (CPS≥10%) urothelial cancer.

Data for the base-case and the subgroup analyses were based on the KEYNOTE-045 study. The study population was assumed by the company to be reasonably similar to the UK population likely to receive treatment. However, out of the 542 patients recruited in the KEYNOTE-045 study, only 4 were from the UK (see section 4.4).

Individuals in the modelled cohort had an average starting age of 65.5 years and 74.2% were male. An average body surface area (BSA) of 1.90m^2 was used to estimate the dosing of paclitaxel and docetaxel. The average BSA value was taken from the European sites of KEYNOTE-045, whereas age and gender values were taken from the overall population recruited in KEYNOTE-045 (i.e. including patients from the US and Asia).

Information on patient characteristics for the subgroup analyses were provided in Appendix 9. However, in the economic model, the ERG found that the mean values of the patient characteristics used in the base-case analysis were used in all subgroup analyses. Furthermore, the ERG found that gender was not included as a model parameter.

For all subgroup analyses presented in the Appendix, the company stated that the results should be interpreted with caution as there is uncertainty around the estimates (due to small number of patients in the subgroups). However, only deterministic cost-effectiveness results were presented in the original submission. Upon request in the clarifications the company provided the probabilistic results.

ERG summary

- In the base-case analysis patients age and gender were taken from the overall trial population, however, the use of patient characteristics from only the European sites might result in more representative patients.
- The modelled population in all subgroup analyses were based on the characteristics of patients from the overall trial population.
- The impact of gender was not included in the estimation process in the economic model.

5.2.4 Interventions and comparators

In the company's base-case analysis, pembrolizumab is compared with UK standard of care (UK SOC) i.e. investigator's choice of paclitaxel or docetaxel. Based on the KEYNOTE-045 study, among patients who received paclitaxel or docetaxel (i.e. excluding vinflunine), 48.9% received paclitaxel and 51.1% received docetaxel. A scenario analysis is presented in which the UK SOC arm is based on the UK market share of paclitaxel and docetaxel (26% and 74%, respectively).

Pembrolizumab treatment is administered at a fixed dose every 3 weeks and should continue until radiologic disease progression, toxicities leading to discontinuation, physician's decision or 24 months of uninterrupted treatment with pembrolizumab. Based on clinical expert opinion, the company assumed that a maximum of 6 cycles were administered to reflect the UK clinical practice for the treatment regimens representing UK SOC. To estimate the duration of treatment in the pembrolizumab and comparator arms, time on treatment (ToT) data from KEYNOTE-045 was used. Separate parametric curves were fitted to the patient level treatment duration data from KEYNOTE-045 to represent ToT in the economic model (see Section 5.2.6 for more detail).

As part of the subgroup analyses presented in the CS Appendix, the company presented cost-effectiveness results for the overall patient population comparing pembrolizumab with individual regimens (i.e. pembrolizumab vs paclitaxel and pembrolizumab vs docetaxel).

The appropriateness of the pooled comparator treatment was considered by the ERG. Based on the ERG's clinical experts, paclitaxel and docetaxel were regarded as appropriate comparators in the UK setting. In addition, "lumping" the two treatment options as a single treatment was considered appropriate, since paclitaxel and docetaxel treatments are considered similar in terms of clinical effectiveness.

The economic model assumed that treatment effect with pembrolizumab lasted for a lifetime (35 years). Upon clarification, the company provided further scenario analyses looking at treatment effect which lasts only for 3, 5 or 10 years.

The ERG found an error in the application of maximum treatment duration of UK SOC in the model. That is, the duration of paclitaxel or docetaxel treatment continued beyond 18 weeks (6 cycles) and reached a maximum of 58 weeks. However, upon clarification the company provided the ERG with a new updated economic model correcting for this error.

The company added an option to the economic model to explore the possibility of patients continuing to take pembrolizumab for longer than maximum treatment duration. Whilst the maximum treatment duration was set to two years to match the KEYNOTE-045 trial, this could be changed within the model. However, the option to allow patients to exceed the maximum trial duration was labelled within the model as "% patients on treatment after 2 years", which the ERG believes to be inaccurate. A more suitable label should read "% patients on treatment after max treatment duration".

ERG summary

- The base-case analysis incorporates an appropriate comparator (UK SOC).
- After clarification, appropriate scenario analyses for the duration of pembrolizumab treatment effect have been performed by the company.
- The original economic model had an error in the application of maximum treatment duration for UK SOC treatment, this was corrected by the company.

5.2.5 Perspective, time horizon and discounting

The perspective is as per NICE reference case, with benefits from a patient perspective and costs from an NHS and personal social services (PSS) perspective. A lifetime horizon is modelled (35 years). In the base-case, costs and benefits were discounted at an annual rate of 3.5%.

ERG summary

- The perspective, time horizon and discount rates chosen by the company all follow NICE recommendations, and are appropriate to the decision problem.

5.2.6 Treatment effectiveness and extrapolation

Clinical outcomes from the KEYNOTE-045 trial were used to inform the transitions between health states in the model.

Primary endpoints

- Overall survival (OS)
- Progression-free survival (PFS)

Secondary endpoints

- Objective response rate
- Time to response
- Duration of response
- Adverse events of treatment
- Health-related quality of life

In this section we elaborate further on the co-primary endpoints: OS and PFS.

5.2.6.1 Overall survival

The estimation of long-term overall survival comprised the following methods:

1. Adjusting for treatment switching in the UK SOC arm
2. Overall survival extrapolation
3. Two-phase piecewise approach

1. Adjusting for treatment switching in the UK SOC

Three statistical techniques were used to adjust for treatment switching in the UK SOC arm, as some patients in this group received PD-L1 treatments following disease progression. These methods included the rank-preserving structural failure time (RPSFT), the simplified 2-stage method and the inverse probability of censoring weighting (IPCW). Treatment switching was accounted for in the survival models, with three different methods investigated in addition to an ITT analysis. Details of the methods can be found in the NICE Decision Support Unit (DSU) Technical Support Document 16 by Latimer and Abrams (2014).[24] Each was implemented and considered alongside their relative assumptions in section 4.7 and Appendix 10. There were 33 patients who switched from the control arm to other treatments; however, only 22 of these were actually eligible to switch with 11 patients appearing to switch prior to disease progression.

The ERG notes that three methods were investigated for adjusting for treatment switching: IPCW, RPSFT and 2-Stage.

- RPSFT was the least suitable for two reasons. Firstly, it censors patients prior to the time point at which they switched treatments in an attempt to remove bias, however this results in a loss of information. It then generates artificial survival times for those who switch. RPSFT also assumes a common treatment effect for both switchers to the experimental arm, and those who received it for the full trial. In KEYNOTE-045, subjects were able to

switch to a range of possible treatments, which included but were not limited to pembrolizumab. Hence, RPSFT was not a suitable choice.

- IPCW makes the assumption that there are no unobserved confounders. It relies on baseline and time dependent variables being available which predict prognosis and treatment switching. It censors patients at their point of switching, and weights the remaining patients according to their similarities to the censored patients in an attempt to remove any bias that the censoring has caused. Due to the uncertainty over the risk factors of bladder cancer and survival, it is difficult to gauge whether or not this is a suitable method in this case.
- The 2-Stage approach works when the treatment switching is linked to a particular event, e.g. disease progression, as occurred for the planned treatment switching in KEYNOTE-045. However, there were 11 subjects who switched without meeting the planned requirements, which will confound the analysis slightly. This method produces a treatment estimate for patients who switched and then shrinks their survival times accordingly to derive a survival time assuming they had not switched. However, as mentioned above, the subjects in KEYNOTE-045 did not switch to the same treatment, and so it may be incorrect to adjust their survival times by the same factor.

It is clear that none of these methods are perfect in this case. Whilst the RPSFT was the least suitable, it is difficult to decide between 2-Stage and IPCW. It is also difficult to conclude whether the methods are actually a significant improvement over the ITT analysis, or whether the adjustments go too far. The ERG would have liked to have seen further methods examined, including a simple censoring of patients at point of switch. Whilst this would have produced biased results and overestimated OS in the control arm, since it is known that switching was dependent on disease progression, it would have provided useful information in assessing the suitability of the other methods.

Table 15 and Table 16 present the treatment effect for overall survival and median overall survival, respectively. Results from the intention-to-treat (ITT) analysis (full analysis set) showed that pembrolizumab versus UK SOC had a treatment effect for overall survival of [redacted]. Treatment effectiveness results based on an adjustment method all had slightly greater treatment benefit, with hazard ratios (HR) ranging from [redacted] to [redacted]. The choice of the most appropriate adjustment method was based on the trial characteristics, the switching mechanism, the proportion of people switching, and the clinical validity of the

outcomes obtained. In the base case, the company chose the simplified two-stage method for people who switched to a PD-L1 treatment, and reported a treatment effect for overall survival of [redacted]. It was noted by the ERG that the 2-sided p-value of [redacted] for the simplified two-stage approach and the RPSFT had been retained from the ITT analysis.

On clarification, the company suggested that *'The p-value for the adjusted OS analysis using the RPSFT or the simplified 2-stage method is retained from the ITT analysis, provided that the same statistical test is used in the ITT analysis than in the adjusted analysis. The reason is that, under the null hypothesis of no treatment effect, there is no switchover effect and thus the test statistics of the RPSFT and the simplified 2-stage methods follow the same statistical distribution as the ITT test statistic. As the p-value is the probability to obtain a more extreme value than the observed one under the null hypothesis, the p-value from the ITT analysis is preserved in the 2-stage model approach and the RPSFT approach.'*. The ERG considers this response to be satisfactory.

Table 15: Treatment effect for overall survival for pembrolizumab versus UK SOC (table obtained from company submission)

	Pembrolizumab vs. UK SOC		
Switching adjustment correction method	**Hazard Ratio**	**95% CI**	**p-value (2-sided)**
Intention-to-treat	[redacted]	[redacted]	[redacted]
Simplified two-stage[$]	[redacted]	[redacted]	[redacted]
Rank-preserving structural failure time (RPSFT)[¶]	[redacted]	[redacted]	[redacted]
Inverse probability censoring weighting (IPCW)	[redacted]	[redacted]	[redacted]
¶ Re-censoring applied to all control patients § No re-censoring applied * P-value retained from ITT analysis by design †: Bootstrap p-value			

Median overall survival for the UK SOC based on an ITT analysis was [redacted] months. Results based on an adjustment for treatment switching ranged from [redacted] to [redacted].

Table 16: Median OS based on the ITT, simplified two-stage, RPSFT and IPCW methods

Switching correction method	**Median OS (months) (95% CI)**
UK SOC (ITT)	[redacted]
UK SOC - Simplified two-stage correction (no re-censoring)	[redacted]
UK SOC – RPSFT correction	[redacted]
UK SOC – IPCW correction	[redacted]

2. Overall survival extrapolation

Figure 3: Kaplan-Meier plots of overall survival and adjustment for treatment switching using the two-stage analysis for pembrolizumab vs UK SOC (obtained from the company submission)

Parametric models were fitted to the Kaplan-Meier (KM) plots (see Figure 3) for overall survival for pembrolizumab and UK SOC of KEYNOTE-045 trial. Various parametric models were tested (for example, exponential, Gompertz, log-logistic, log-normal, generalised gamma and Weibull). The preferred model was chosen by the company based on a combination of visual inspection of goodness-of-fit, long-term plausibility informed by clinical expert opinion, and using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Figure 4 and Figure 5 show the parametric curves for the fully-fitted KM curves for pembrolizumab and UK SOC, respectively. Table 17 shows the AIC and BIC for each parametric model for pembrolizumab and UK SOC (using the two-stage approach for treatment switching only) to the fully-fitted data for overall survival. Based on AIC and BIC the log-normal parametric models provided the best fit to these data. It should be noted here that in the economic model, the same parametric fit for overall survival was selected for both the intervention and comparator.

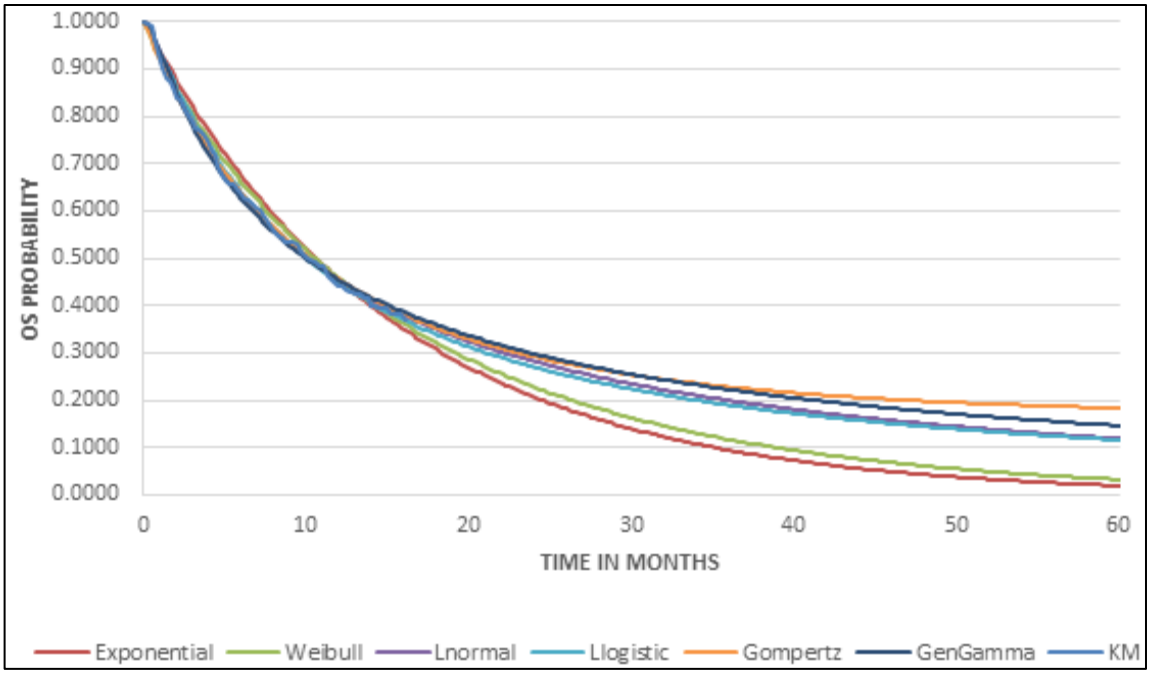


Figure 4: Kaplan-Meier plot along with parametric models for overall survival for pembrolizumab

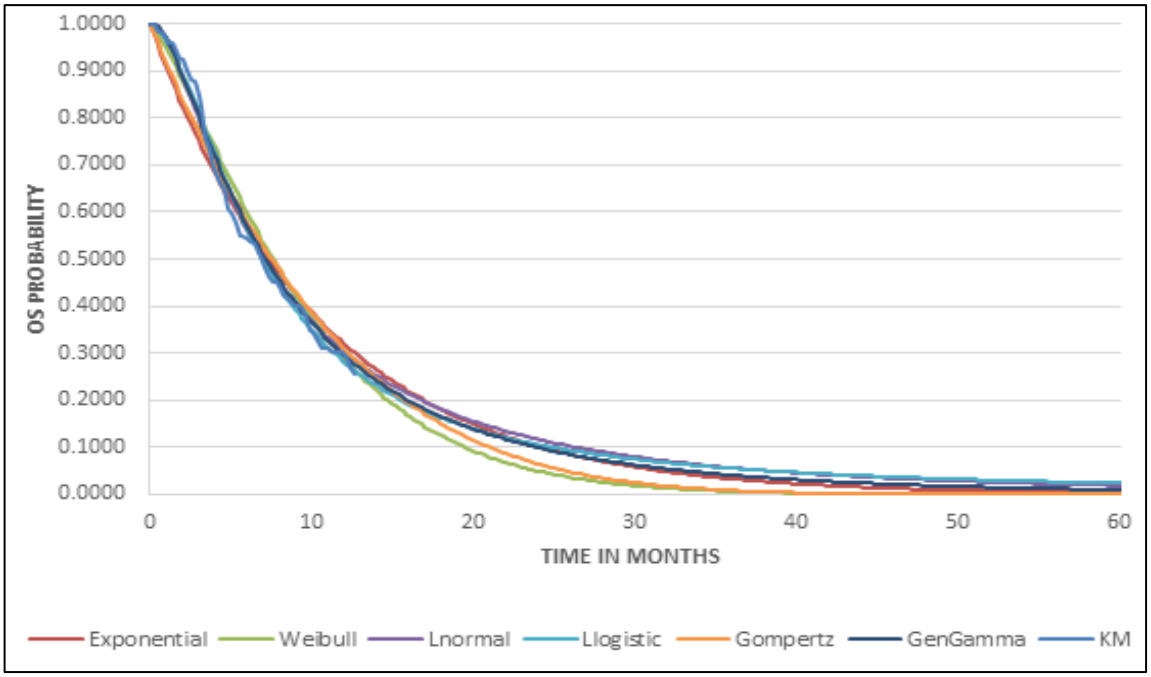


Figure 5: Kaplan-Meier plot along with parametric models for overall survival for UK SOC

Table 17: Goodness-of-fit statistics based on the fully-fitted parametric curves to data for overall survival

Parametric model	Pembrolizumab		UK SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC

Exponential	1612.4	1616	1092.5	1095.7
Weibull	1612.9	1620.1	1085.7	1092.2
Gompertz	1608.1	1615.3	1093.5	1099.9
Log-logistic	1606.3	1613.5	1075.1	1081.5
Log-normal	1601.5	1608.7	1078.2	1084.6
Generalised Gamma	1602.8	1613.6	1079.5	1089.1

Figure 6 shows the cumulative hazard associated with death following treatment with pembrolizumab compared to paclitaxel and docetaxel. As suggested by the company, these plots do not support the proportional hazards assumption, as the difference in hazard between treatments is not constant over time. In fact, the plots cross at approximately 14 weeks. The ERG agrees with the company that there is evidence to support the use of a piecewise model to extrapolate overall survival. The company suggested that the 40-week cut-off point is more appropriate than a 24-week cut-off to extrapolate beyond the observed data, because there is greater change in the slope before 40 weeks. Whilst this may be plausible, the ERG considers this to be a weak justification, because using the 40-week cut-off reduces the amount of observed data that could be used to extrapolate overall survival. It would have been helpful for the company to show how the various parametric models fitted the cumulative hazard plots to support/strengthen the justification for choosing a) a suitable cut-off point and b) an appropriate parametric model to extrapolate overall survival. The ERG has explored using a 24-week cut-off because at that time point we consider that the hazards follow a predictable path.

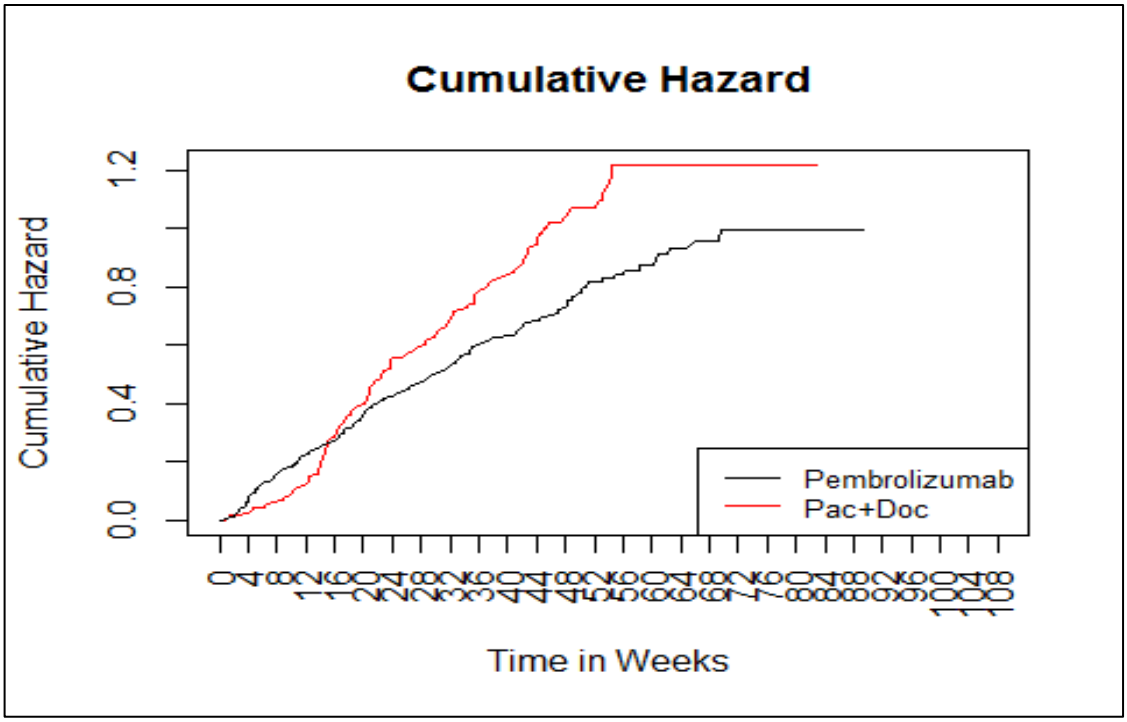


Figure 6: Cumulative hazard plot of overall survival for pembrolizumab versus UK SOC (obtained from company submission)

3. Two-phase piecewise approach

Estimation of long-term overall survival comprised of a two-phase piecewise approach. In the first phase, survival was estimated based on using the observed Kaplan-Meier survival data in KEYNOTE-045 up to a 40-week cut-off point. In the second phase, a series of parametric models were fitted to the observed data beyond the 40-week cut-off point. Figure 7 and Figure 8 show the Kaplan-Meier plots for overall survival for the UK SOC and pembrolizumab, respectively, along with parametric fits. Table 18 shows the AIC and BIC for each parametric model for pembrolizumab and UK SOC for overall survival using data beyond the 40-week cut-off. Based on the AIC/BIC and clinical opinion on the plausibility of these survival models, the log-normal parametric models were considered the most appropriate to project overall survival.

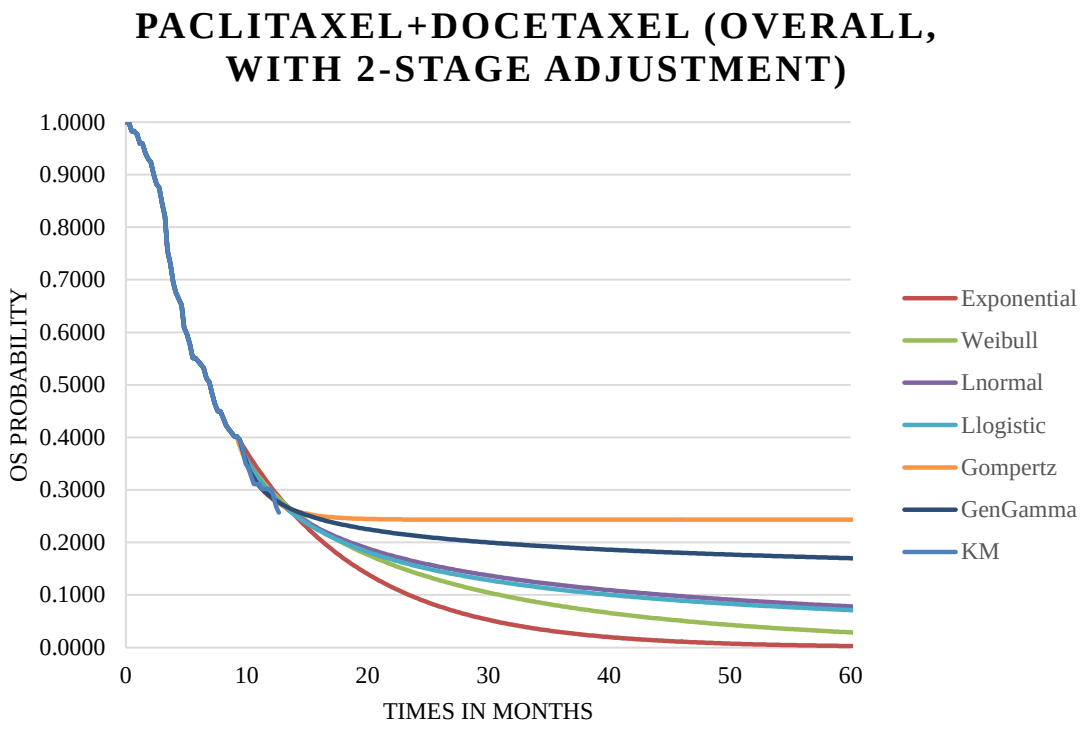


Figure 7: Kaplan-Meier plot for overall survival for UK SOC (2-stage adjustment applied), with various parametric models (obtained from the economic model)

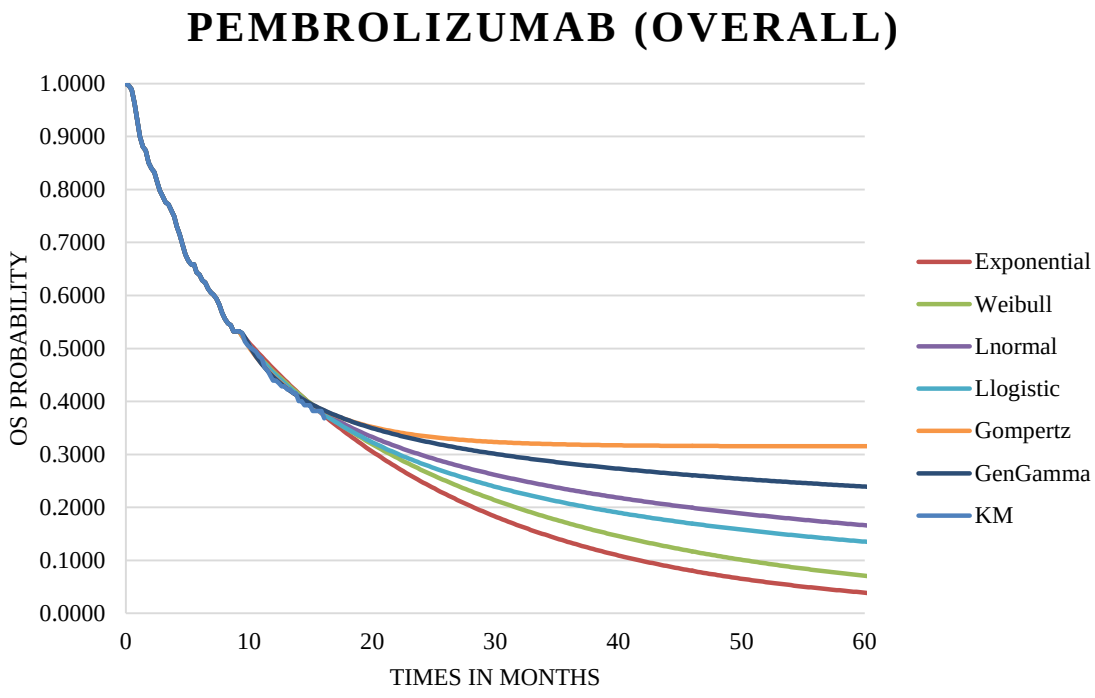


Figure 8: Kaplan-Meier plot for overall survival for pembrolizumab, with various parametric models (obtained from the economic model)

Table 18: Goodness-of-fit statistics based on the extrapolations using data beyond the 40-week cut-off, for pembrolizumab and UK SOC

Parametric model	Pembrolizumab		UK SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC
Exponential	339.1	342.1	165.1	167.1
Weibull	340.5	346.4	165	169.1
Gompertz	338.1	344	160.4	164.5
Log-logistic	339.4	345.3	163.7	167.7
Log-normal	337.5	343.4	161.8	165.9
Generalised Gamma	338.5	347.3	160.2	166.3

Figure 9 shows the estimated long-term overall survival using the two-phase piecewise approach, which is based on observed Kaplan-Meier data and log-normal extrapolations.

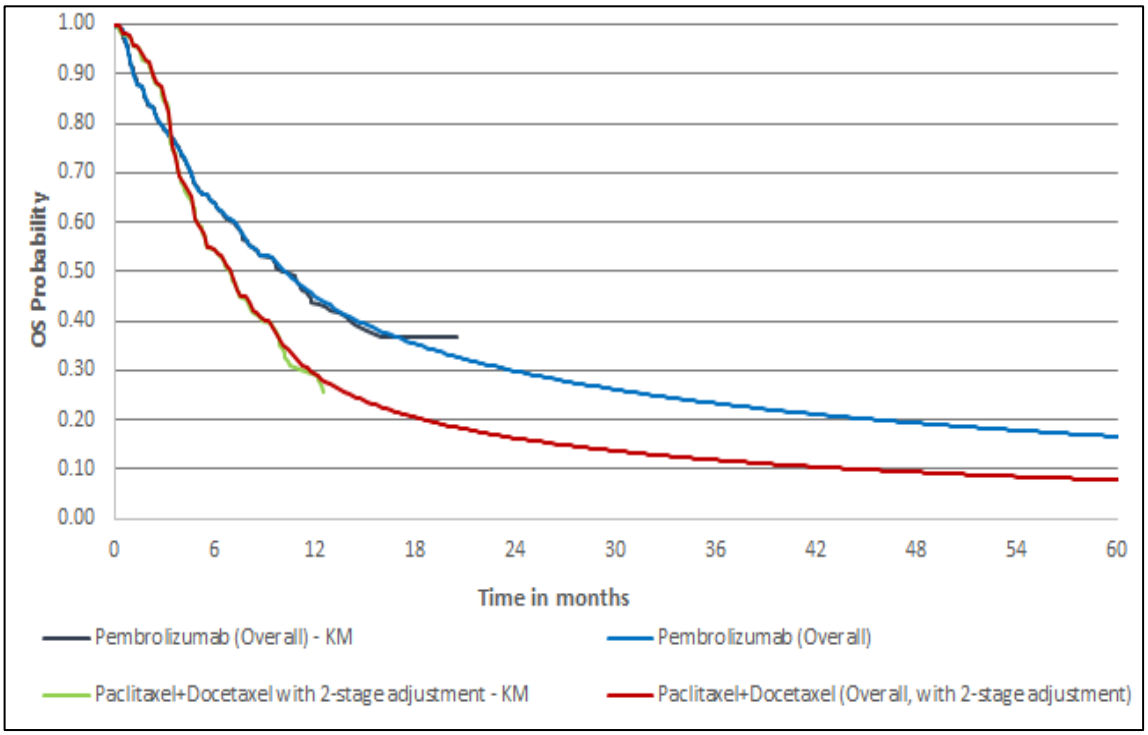


Figure 9: Kaplan-Meier plots for overall survival for pembrolizumab and UK SOC (2-stage adjustment applied), using a phase piecewise model

5.2.6.2 Critique of the Company's survival extrapolations

On page 183 in the CS, the company has compared the extrapolated OS for people in the UK SOC with that reported by Cancer Research UK for patients with stage IV bladder cancer.[1] They indicate that the 5 year OS from log-normal distribution is projected at 7.8% and consider this is

close to that of the observed data in the Cancer Research UK database (adults aged 15-99; period 2002-2006), which is 9.2% in men and 10.8% in women.

The ERG however, have some concerns around the comparability of people in the KEYNOTE-045 trial with those from Cancer Research UK. The data from Cancer Research UK are people with stage IV bladder (100%) cancer at diagnosis. While the staging of people in KEYNOTE-045 is similar (99.6% were stage IV), the rate of bladder cancer was lower in KEYNOTE-045 since 86.0% of patients had a site of primary tumour in the lower urinary tract (bladder or urethra) and 14.0% in the upper tract (renal pelvis or ureter). Arguing that upper tract urinary cancers (UTUC) have a poorer prognosis compared to lower tract urinary cancers (LTUC), the company explains that the 5 year OS found at 7.8% in UK SOC arm is lower than 9-11% as reported in Cancer Research UK owing to the inclusion of UTUC in KEYNOTE-045.

The ERG's clinical experts agreed on the general notion that UTUC are more aggressive and respond less well to chemotherapy compared to LTUC. Although the cancer staging was similar in KEYNOTE UK SOC and the population from Cancer Research UK, the ERG believes that people in KEYNOTE-045 were in a more advanced disease stage compared to the Cancer Research UK population. Our understanding of the data from Cancer Research UK is that it corresponded to people at diagnosis of metastatic disease who therefore were at first line therapy. In KEYNOTE-045, the setting of most recent prior therapy of included SOC patients, as per the inclusion criteria, was first line in 57.7% of cases, and second line in 22.1%. According to the listed inclusion criteria, the first-line platinum-containing regimen could have been in the metastatic setting or for inoperable locally advanced disease. The distribution among metastatic setting vs. inoperable locally advanced disease within the prior first-line therapy is not stated but we assume that it was mainly patients treated at the stage of metastatic setting.

Consequently, while people from Cancer Research UK were at the stage of diagnosis of metastatic disease, around 80% of people in the KEYNOTE SOC arm were likely to be either at second or third line of metastatic disease which makes this population at even greater risk.

Therefore, the ERG believes that the 7.8% five-year OS noted in the KEYNOTE UK SOC arm is very likely to be lower. Little else is known about the baseline characteristics of the patients who have generated the Cancer Research UK data, and so the ERG has reservations about using this data as a reference point.

The ERG has conducted a literature search in order to identify other sources of comparison from published data on similar population. Two studies were considered of potential interest. The ERG compared inclusion criteria, baseline characteristics, and survival outcomes of these populations and results are presented in Table 19, Table 20 and Table 21. These were not consistently reported in the trials which makes the comparisons difficult.

The von der Maase study[15, 16] seems to have included patients with the best prognostic features among the three studies: patients included for first-line treatment of metastatic disease, lowest proportion with metastases (65% vs. 75% for Bellmunt 2008[13] and 96% for KEYNOTE-045); lowest proportion with visceral metastases (47% vs. 75% and 88%); and lowest proportion with Hb <10g/dL (0% [exclusion criterion] vs. 14% vs. 16%).

Patients in KEYNOTE-045 had a better baseline ECOG than in Bellmunt 2008[13] (ECOG score 0 = 42% vs. 32%), although they had more metastases (96% vs. 75%) and more visceral involvement (88% vs. 75%) and were of similar age at baseline. Most importantly, the patients in KEYNOTE-045 could be included after failure to platinum-based regimen given as adjuvant/neoadjuvant therapy while patients in the vinflunine trial could only be included after failure to chemotherapy given at the stage of locally advanced/metastatic disease.

The ERG considers that among the three studies presented, the baseline characteristics of KEYNOTE-045 patients were less favourable compared to that of the von der Maase study[15, 16] and more favourable compared to that of the Bellmunt 2008 study.[13] Although the von der Maase study[15, 16] included people only at first line treatment of metastatic disease, this trial is of relevance since the authors presented a subgroup analysis depending on the presence of visceral metastasis which is a well-known risk factor. Interestingly, the 5 year OS was 6.8% in people with visceral metastasis at inclusion. Given that 85.7% of people in the KEYNOTE-045 study had visceral metastasis at inclusion, this confirms that the 5-year OS 7.8% in the UK SOC arm from KEYNOTE-045 is likely to be overestimated in the CS.

Overall, the ERG believes the 5-year OS in the UK SOC of KEYNOTE-045 should be below that observed in the von der Maase study, and above that in the vinflunine trial (which is not reported but should be below 2% since there was only 6 survivors at 40 months of the 253 included patients).

Table 19: Inclusion criteria of studies considered to be comparable with KEYNOTE-045

Study	KEYNOTE-045 from Bellmunt 2017	von der Maase 2000, von der Maase 2005 [15, 16]	Bellmunt 2008/Bellmunt 2013 [13, 25]
Age	≥18 years	-	≥18 years
Histology/location of cancer	Histologically or cytologically confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra	Histologically proven transitional-cell carcinoma of the urothelium	Histologically confirmed transitional cell carcinoma of the urothelial tract
Cell type	Predominantly transitional-cell features on histologic testing	Transitional-cell carcinoma	Transitional cell carcinoma
Stage	Progression after platinum-based chemotherapy for advanced disease or recurrence within 12 months after platinum-based adjuvant or neoadjuvant therapy for localised muscle-invasive disease	First-line stage IV: locally advanced (T4b, N2, N3) or metastatic (M1)	Locally advanced or metastatic; documented progression after first-line platinum-containing chemotherapy
Prior chemo (line of therapy)	Had received ≤2 lines of systemic chemotherapy for advanced disease previously	Prior systemic chemotherapy was not allowed	Documented progression after first-line platinum-containing chemotherapy
Measurable lesion	Had at least one measurable lesion according to RECIST	Measurable or assessable	-
Performance status	ECOG PS score of 0, 1, or 2	Karnofsky performance status ≥ 70	ECOG performance status (PS) of 0 or 1
Other prior therapy allowed	-	Prior local intravesical therapy, immunotherapy, or radiation therapy was allowed if completed at least 4 weeks before enrolment.	Prior radiation was allowed if affecting less than 30% of the bone marrow and completed 30 days before random assignment with full recovery of related toxicity

Table 20: Baseline characteristics of included patients

Baseline characteristics of included patients	Keynote-045 from Bellmunt 2017	von der Maase 2000, von der Maase 2005 [15, 16]		Bellmunt 2008/Bellmunt 2013 [13, 25]
	SOC (Docetaxel or paclitaxel or vinflunine) (n=272)	Gemcitabine/cisplatin (GC) (n=203)	Methotrexate/vinblastine/ doxorubicin/cisplatin (MVAC) (n=202)	Vinflunine + BSC (n=253)
Male n (%)	202 (74.3%)	160(78.8%)	160 (79.2%)	197 (77.9%)
Age < 65	125 (46%)	-	-	135 (53.4%)
Age >= 65	147 (54%)	-	-	118 (46.6%)
Mean	65.1	-	-	63.5
Median	65	63	63	64.2
Asian	58 (21.3%)	-	-	-
White	201 (73.9%)	197 (98%)	197 (97.5%)	-
ECOG PS 0	106 (39%)	82.5% with Karnosfky PS ≥80	81.1% with Karnosfky PS ≥80	72 (28.5%)
ECOG PS 1	158 (58.1%)	-	-	181 (71.5%)
M1	261 (96%)	141 (69.5%)	127 (62.9%)	Around 75% had at least 2 organs involved
Staging IV	271 (99.6%)	-	-	/
Prior Cisplatin therapy	213 (78.3%)	-	-	164 (64.8%)
Prior Carboplatin therapy	56 (20.6%)	-	-	75 (29.6%)
Baseline Hb >=10 g/dL	223 (82%)	100%	100%	214 (85%)
Prior Cystectomy	51 (18.8%)	77 (37.9%)	79 (39.1%)	/
Prior radiation therapy	-	27 (13.3%)	23 (11.4%)	22.5 %
Visceral Disease	233 (85.7%)	99 (48.8%)	93 (46%)	187 (73.9%)
Abnormal alkaline phosphatase	-	56 (28.6%)	51 (26%)	75 (30%)
Creatinine clearance ≥ 60 mL/min	-	100%	100%)	134 (54%)

Table 21: Survival outcomes

	Keynote-045 from Bellmunt 2017	**von der Maase 2000, von der Maase 2005** [15, 16]		**Bellmunt 2008/Bellmunt 2013** [13, 25]
Survival outcomes	**SOC (Docetaxel or paclitaxel or vinflunine) (n=272)**	**GC (n=203)**	**MVAC (n=202)**	**Vinflunine + BSC (n=253)**
Median OS	7.4 months	13.8 months	14.8 months	6.9 months
12 months OS	30.7%	58.4%	62.6%	27%
24 months OS	-	25%	31%	11%
30 months OS	-	-	-	5.5% (14/253)
36 months OS	-	19.0%	20.4%	-
40 months OS	-	-	-	2.3% (6/253)
48 months OS	-	16.4%	17.3%	-
60 months OS	-	13.0%	15.3%	-
		20.9% without / 6.8% with visceral metastases		

As stated in section 5.2.6.1, the ERG considers that from 24-weeks (approximately 5.52 months), the cumulative hazard follows an internally consistent pattern (see Figure 6), and so it would have been more appropriate to extrapolate overall survival on the Kaplan-Meier curve from this time point to maximise the data used in the model. Using the company's economic model, the ERG has obtained overall survival estimates for the UK SOC (Table 22) and pembrolizumab (Table 23) arms based on a 24-week and 40-week cut-off. Survival estimates are provided at one, three, five and ten years. The 5-year overall survival estimates for the UK SOC, using the 24-week cut-off ranged from 0.1% to 8.9% across the parametric models. From the 40-week cut-off, survival estimates ranged from approximately 0.3% to 24.33%. Given the paucity of published evidence on the long-term overall survival in this population, the ERG consulted their clinical expert who suggested that they would expect a 5-year overall survival to be approximately 2-3% consistently with our previous statement comparing KEYNOTE-045 to two other trials. Hence, an extrapolation based on a log-normal or log-logistic parametric distribution, added to the observed 24-week Kaplan-Meier data, gives an appropriate 5-year estimate. These results show that the expected 5-year overall survival is 2.9% and 3.1%, using the log-normal and log-logistic parametric distributions, respectively.

Table 22: UK SOC overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Using a 24-week cut-off						
1-year	0.3019	0.3006	0.2926	0.2888	0.3014	0.2939
3-year	0.0349	0.0198	0.0686	0.0654	0.0913	0.1272
5-year	0.0040	0.0010	0.0290	0.0315	0.0585	0.0891
10-year	0.0000	0.0000	0.0073	0.0117	0.0460	0.0556
Using a 40-week cut-off						
1-year	0.3002	0.2941	0.2880	0.2882	0.2811	0.2831
3-year	0.0290	0.0785	0.1185	0.1095	0.2433	0.1908
5-year	0.0028	0.0288	0.0782	0.0712	0.2433	0.1700
10-year	0.0000	0.0035	0.0421	0.0396	0.2433	0.1475

The 5-year overall survival estimates for pembrolizumab, using the 24-week cut-off ranged from approximately 3.3% to 22.48%. From the 40-week cut-off, survival estimates ranged from approximately 3.9% to 31.53%. To the ERG's knowledge, there is no published evidence on the long-term overall survival in this population. It can be seen in Table 23 that the 5-year overall survival estimate using the log-normal and the log-logistic parametric distributions were 16.91% and 13.40% respectively. Here, it can be seen that there is a noticeable difference in the 5-year survival estimates. Given that the same functional form/parametric distribution are to be used in the economic model, the ERG preferred to prioritise the fitting of the parametric curves to

pembrolizumab due to the larger differences that were observed. Based on the AIC/BIC, the log-logistic compared to using the log-normal distribution provided a better fit to the pembrolizumab data.

Therefore in the ERG's base-case, estimated overall survival is based on extrapolations using the log-logistic distributions, added to the observed 24-week Kaplan-Meier data. Additionally, the ERG has undertaken further analyses to show the impact of using different parametric distributions to extrapolate from the 24-week time-point on the Kaplan-Meier curve for overall survival.

Table 23: Pembrolizumab overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Using a 24-week cut-off						
1-year	0.4570	0.4542	0.4487	0.4497	0.4480	0.4508
3-year	0.1235	0.1546	0.2407	0.2073	0.2542	0.1940
5-year	0.0334	0.0581	0.1691	0.1340	0.2248	0.1070
10-year	0.0013	0.0059	0.0966	0.0707	0.2174	0.0352
Using a 40-week cut-off						
1-year	0.4566	0.4520	0.4467	0.4493	0.4429	0.4416
3-year	0.1335	0.1689	0.2330	0.2065	0.3186	0.2825
5-year	0.0391	0.0708	0.1663	0.1353	0.3153	0.2394
10-year	0.0018	0.0095	0.0985	0.0731	0.3152	0.1926

5.2.6.3 Progression-free survival

In KEYNOTE-045, progression-free survival was defined as per RECIST 1.1[23] the first assessment was performed at week nine, then every six weeks. Like overall survival, projection of long-term progression-free survival was based on a two-phase piecewise model, which was derived by using Kaplan-Meier data up to week 21, then fitting parametric models to the remaining observed data. The 21-week cut-off was chosen based on the separation of the cumulative hazards for pembrolizumab and UK SOC as shown in Figure 10.

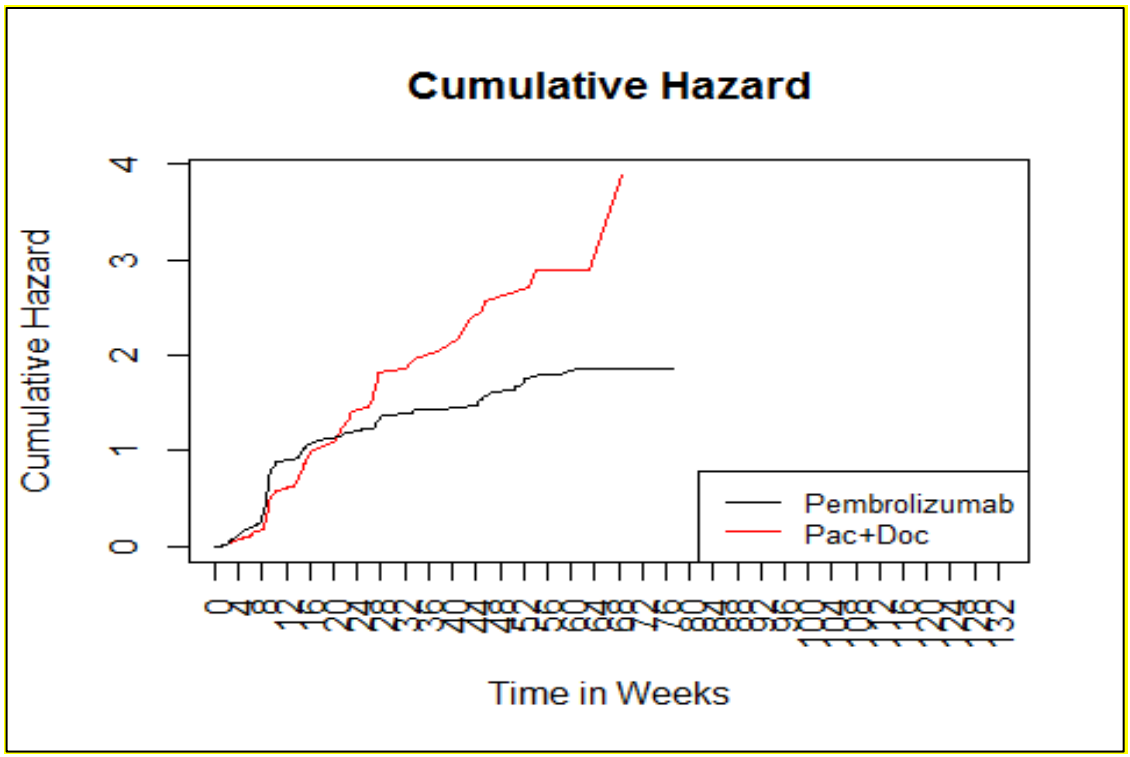


Figure 10: Cumulative hazard plots for progression-free survival for pembrolizumab and UK SOC

The company further suggested that the proportional hazard assumption did hold because the Kaplan-Meier plots crossed, therefore separate parametric models were fitted to project progression-free survival. Figure 11 and Figure 12 show the Kaplan-Meier plots with parametric models fitted to pembrolizumab and UK SOC, respectively. These figures show the various parametric fits to the observed data beyond the 21-week cut-off.

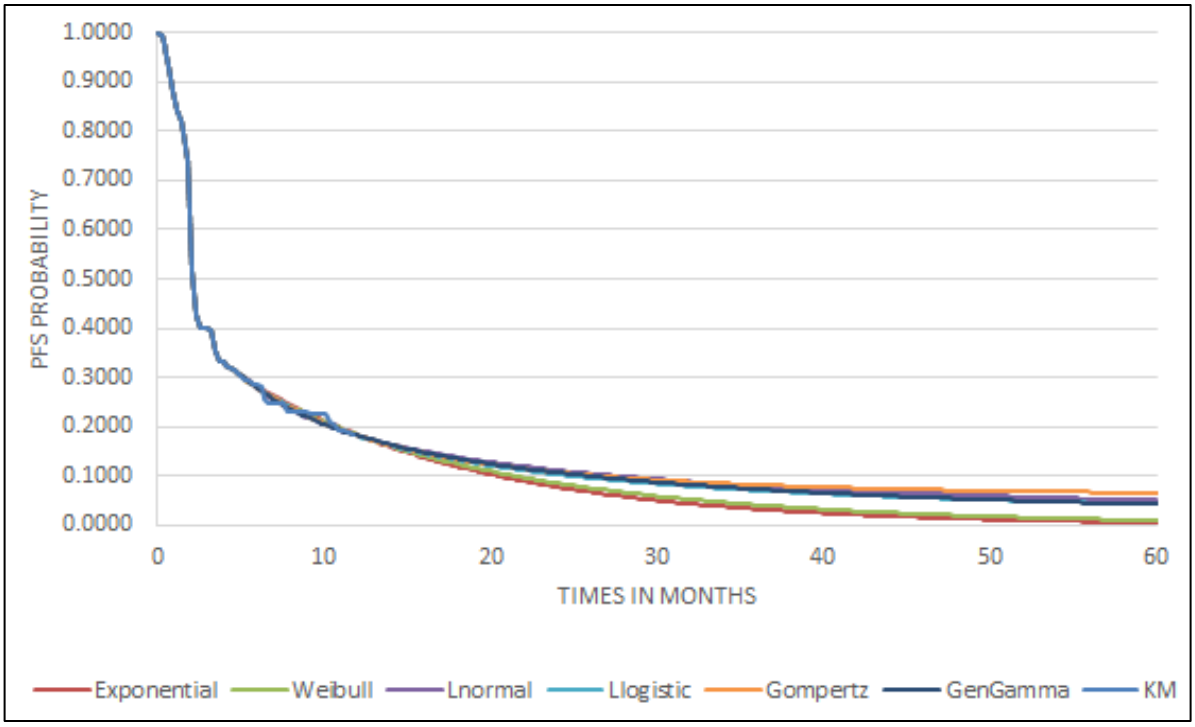


Figure 11: Kaplan-Meier plot for progression-free survival for pembrolizumab, with extrapolations using a 21-week cut-off point

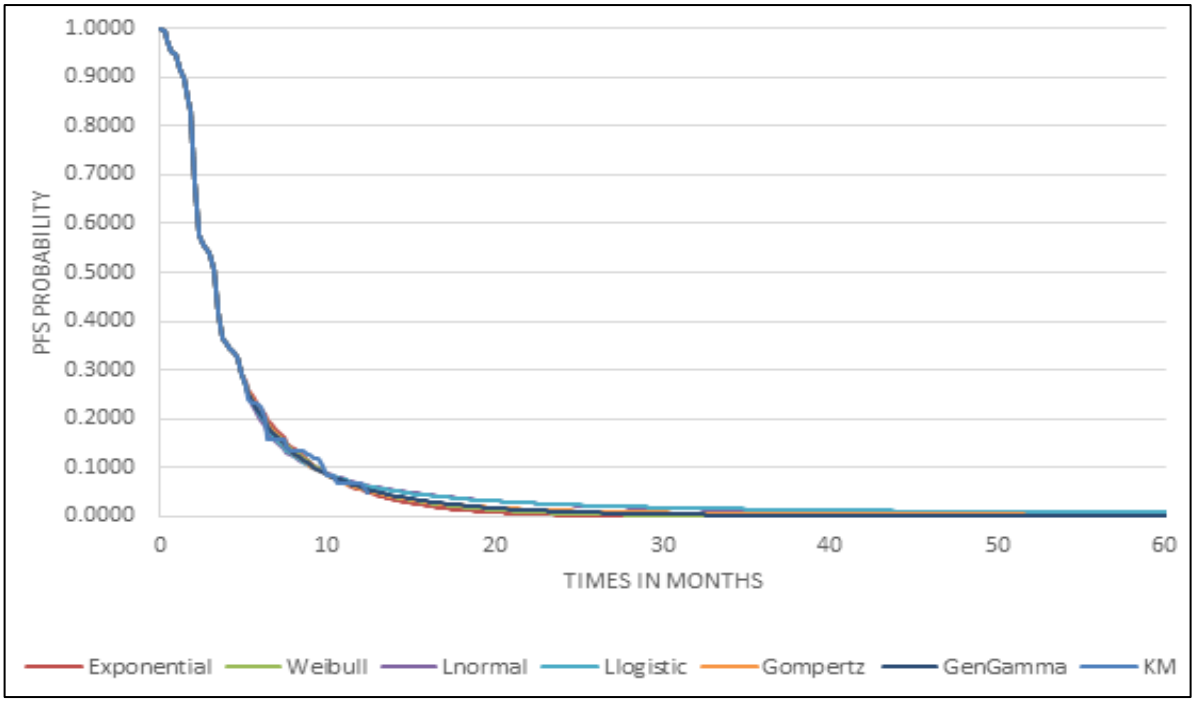


Figure 12: Kaplan-Meier plot for progression-free survival for UK SOC, with extrapolations using a 21-week cut-off point

Projection of PFS was based on AIC/BIC for the second phase of the piecewise model (based on data beyond the 21-week cut-off). Table 24 shows these goodness-of-fit measures for pembrolizumab and UK SOC.

Table 24: Goodness-of-fit statistics based on the extrapolations of data beyond the 21-week cut-off, for pembrolizumab and UK SOC

Parametric model	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	339	341.4	154.1	155.4
Weibull	340.7	345.5	150.6	153.1
Gompertz	340.2	345	155.9	158.4
Log-logistic	340.2	344.9	153.6	156.1
Log-normal	339.9	344.6	153.4	155.9
Generalised Gamma	341.8	348.9	149.8	153.6

As suggested by the company, there was no clear best parametric fit for pembrolizumab or UK SOC, as all the distributions were very similar. This was seen in the parametric fits (Figure 11 and Figure 12) and AIC/BIC (Table 24). In the base case, the company has chosen the exponential model to extrapolate PFS for the UK SOC and for consistency, used the exponential model for pembrolizumab. Figure 13 shows the two-phase piecewise approach to extrapolate PFS beyond the trial time horizon for pembrolizumab and UK SOC.

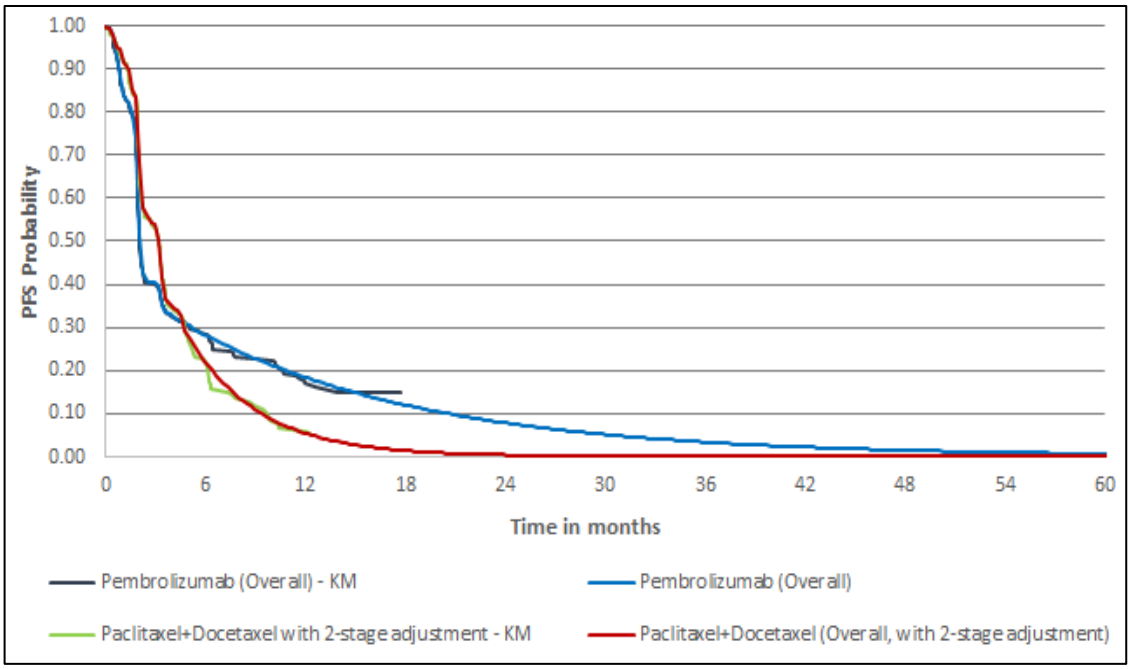


Figure 13: Kaplan-Meier plot for progression-free survival for pembrolizumab and UK SOC, with extrapolations using a 21-week cut-off point

Subgroup analysis 1: Overall survival for PD-L1 strongly positive (CPS≥ 10%)

The first subgroup that the CS considered was that of patients who were strongly PD-L1 positive (CPS≥ 10%). The key results are shown in Table 25. There were 164 patients in this group, with a total of 104 deaths observed. Pembrolizumab has a lower event rate than the control arm (59.5% vs. 66.7%) suggesting the immunotherapy is the superior treatment. Pembrolizumab also has a higher OS at both six and twelve months, but the differences are not statistically significant, likely due to power. The Kaplan Meier diagram also suggests pembrolizumab is beneficial for overall survival, as shown in Figure 14.

Overall, this group has an event rate of 63.4%, which is slightly higher than of the whole population (61.6%) which could suggest the strongly positive group have a higher risk of death, however, the difference is slight. The median OS for both arms is lower in this subgroup than their relative median OS from the whole population, along with the OS at 6 and 12 months, again suggesting a worse prognosis for subjects in the strongly PD-L1 positive subgroup. The HR suggests that pembrolizumab is more effective in this subgroup with HR of 0.57 though the difference in OS suggested no change in effectiveness with a difference in median OS of 2.8 months.

Table 25: Results of PD-L1 CPS ≥ 10% Subgroup Analysis

						Pembrolizumab vs. Control
Treatment	**N**	**Number of events (%)**	**Median OS (months) (95% CI)**	**OS at 6 months in % (95% CI)**	**OS at 12 months in % (95% CI)**	**Hazard Ratio (95% CI)**
Control	90	60 (66.7)	5.2 (4.0, 7.4)	47.2 (36.0, 57.6)	26.9 (17.5, 37.2)	
Pembrolizumab	74	44 (59.5)	8.0 (5.0, 12.3)	58.5 (46.3, 68.9)	39.8 (28.0, 51.3)	0.57 (0.37, 0.88)

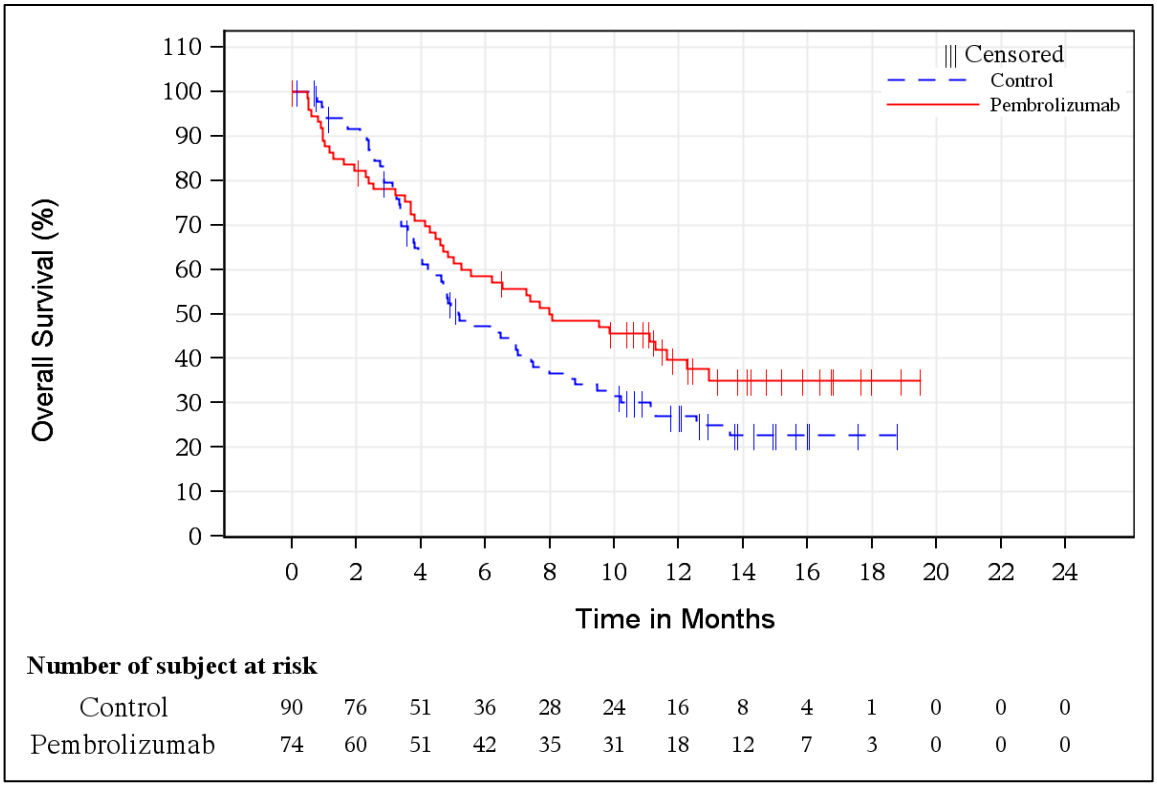


Figure 14: KM plot of PD-L1 CPS ≥ 10% Subgroup

The PD-L1 ≥ 10% subgroup was also investigated using PFS as the outcome measure. The results are shown in Table 26. There was little to distinguish between the groups, with pembrolizumab having a lower median PFS (2.1 vs 3.1 months) but a higher 6 month (24.7% vs 18.5%) and 12 month PFS (17.7% vs 3.7%). The percentage of events was almost identical, both between and arms and compared to the whole trial population, all around 80%. However, the HR has decreased to 0.89 in favour of pembrolizumab, perhaps influenced by the more noticeable difference in tails between the treatment arms, as shown in Figure 15. However, the difference was not statistically significant.

Table 26: Results of PD-L1 CPS ≥ 10% Subgroup Analysis (PFS)

Treatment	N	Number of events (%)	Median PFS (months) (95% CI)	PFS at 6 months in % (95% CI)	PFS at 12 months in % (95% CI)	Pembrolizumab vs. Control Hazard ratio (95% CI)
Control	90	72 (80.0)	3.1 (2.2, 3.4)	18.5 (10.6, 28.1)	3.7 (0.7, 10.9)	
Pembrolizumab	74	59 (79.7)	2.1 (1.9, 2.1)	24.7 (15.5, 34.9)	17.7 (9.5, 27.9)	0.89 (0.61, 1.28)

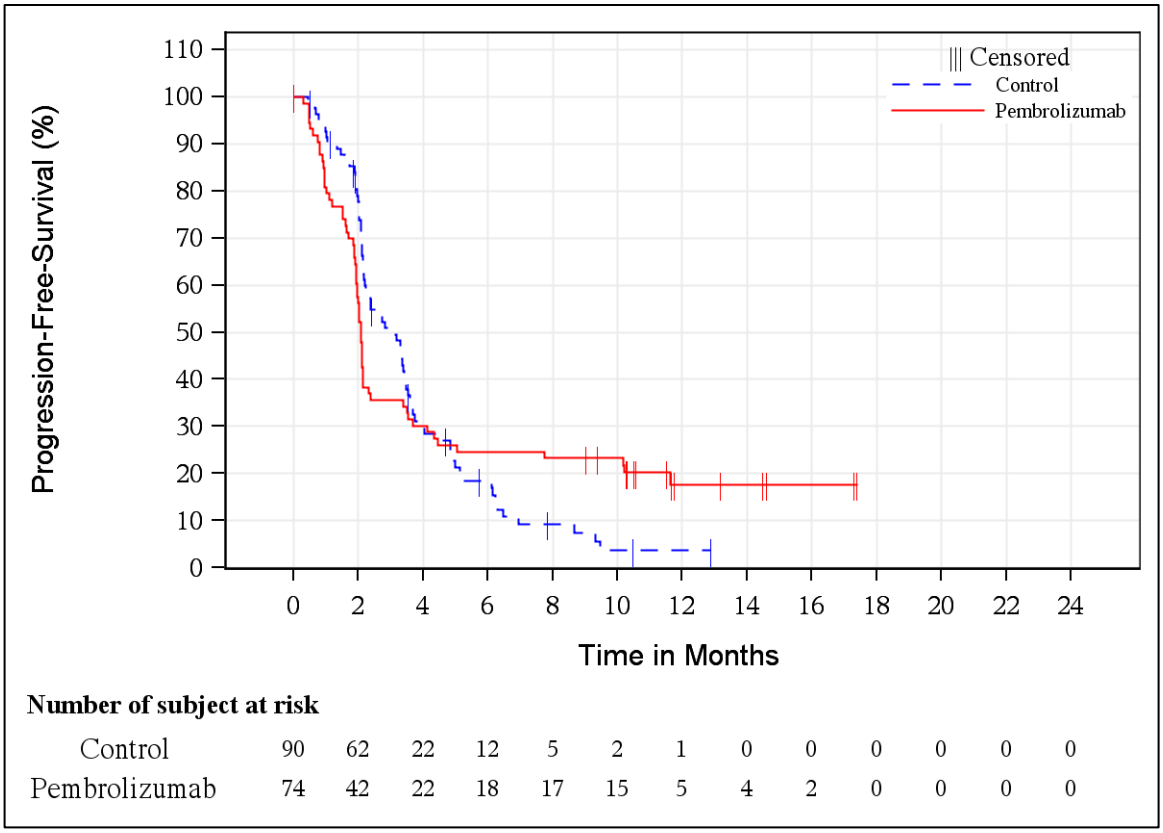


Figure 15: KM plot of PD-L1 CPS ≥ 10% Subgroup (PFS)

Subgroup analysis 2: Overall survival for PD-L1 positive (CPS≥ 1%)

The second subgroup considered by the company was that of patients who were PD-L1 positive (CPS≥1%), and the summary of results is shown in Table 27. A total of 230 patients fell into this category, 120 in the control arm, and 110 in the pembrolizumab arm. One-hundred and forty-two deaths were observed, with a higher event rate in the control arm (67.5% vs. 55.5%). This suggests pembrolizumab is superior in this subgroup, supported by a HR of 0.61, higher OS at 6 (65.9% vs 51.6%) and 12 (46.5% vs 28.8%) months and the Kaplan Meier plot is shown in Figure 16.

The combined event rate of 61.7% showed no difference to that of the whole population (61.6%). The control arm appears to have a slightly worse prognosis in this subgroup, with a lower median OS when compared to the control arm of the entire population. It also has lower OS at 6 and 12 months. In contrast, pembrolizumab appears to be more effective in this subgroup, having a higher median OS by 1 month, and increased 6 and 12 month survival rates when compared to the pembrolizumab arm of the whole trial population. However, all of these differences between the subgroup and trial population are slight and not statistically significant.

Table 27: Results of PD-L1 CPS ≥ 1% Subgroup Analysis

Treatment	N	Number of events (%)	Median OS (months) (95% CI)	OS at 6 months in % (95% CI)	OS at 12 months in % (95% CI)	Pembrolizumab vs. Control Hazard Ratio (95% CI)
Control	120	81 (67.5)	6.9 (4.7, 8.8)	51.6 (41.9, 60.4)	28.8 (20.4, 37.7)	
Pembrolizumab	110	61 (55.5)	11.3 (7.7, 16.0)	65.9 (56.1, 73.9)	46.5 (36.4, 55.8)	0.61 (0.43, 0.86)

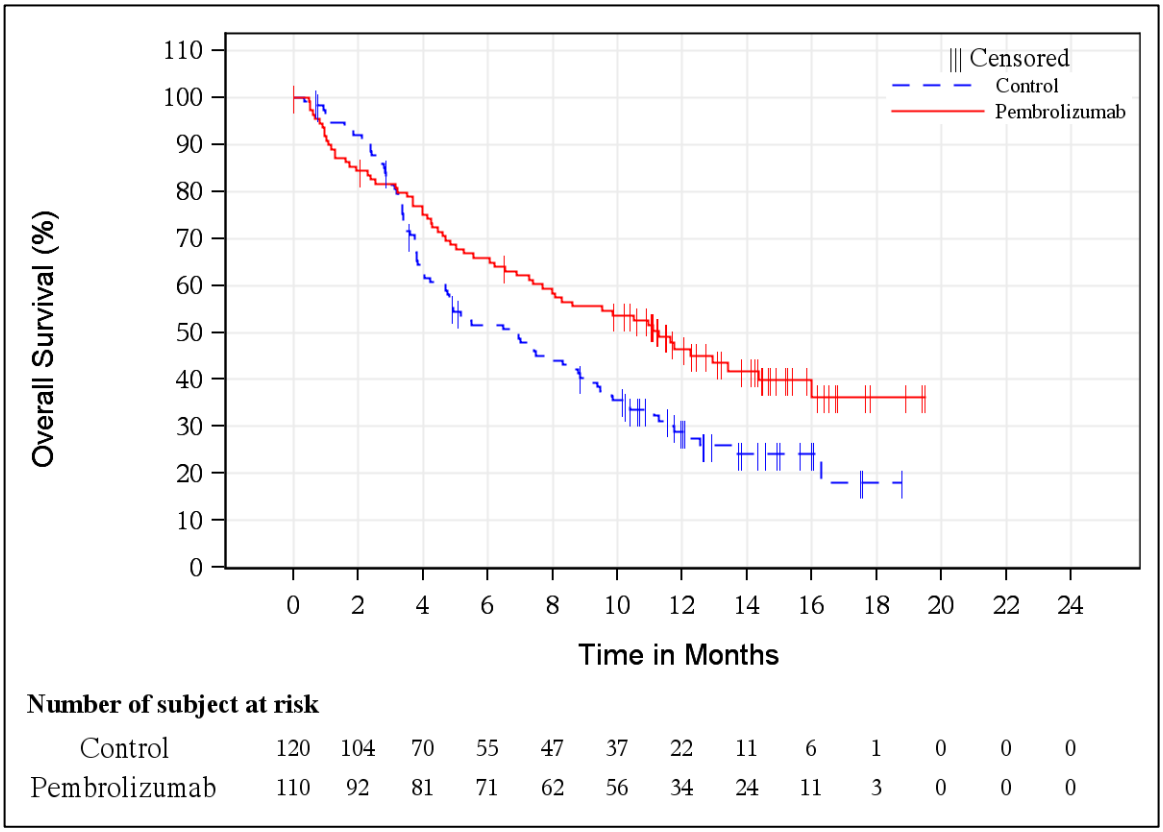
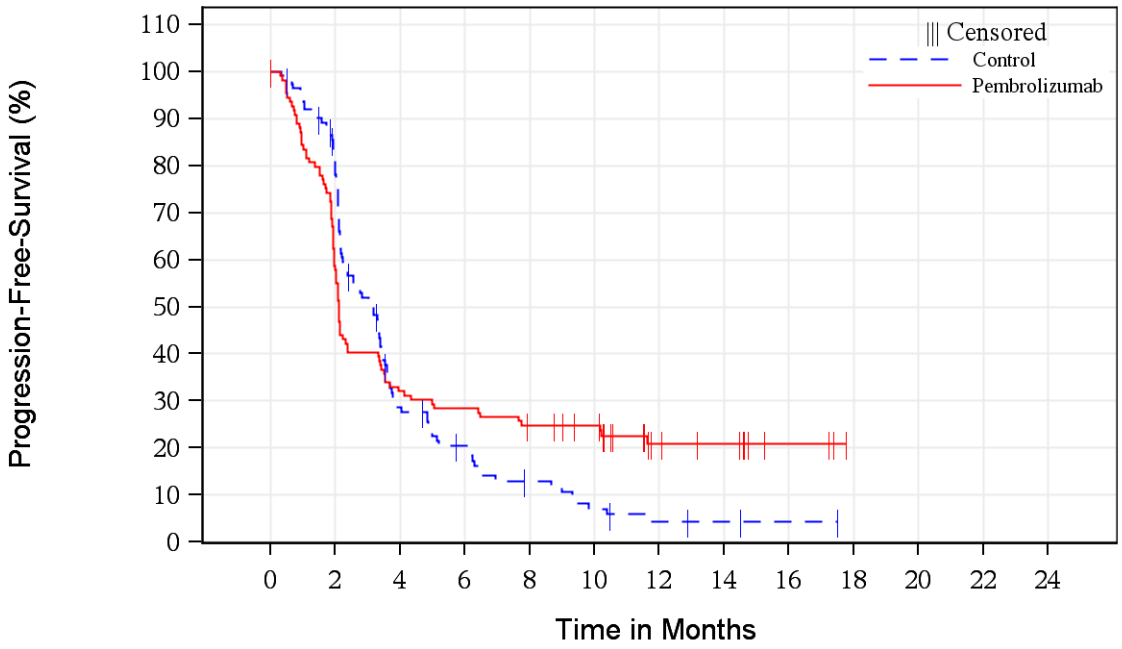


Figure 16: KM plot of PD-L1 CPS ≥ 1% Subgroup

The PFS of the PD-L1 ≥ 1% subgroup was also investigated by the company. The results are shown in Table 28. As before, there is little to distinguish this subgroup from the whole trial population, with a HR of 0.91 weakly favouring pembrolizumab. There is a difference in median PFS of 1.1 months in favour of the control arm, however pembrolizumab appears superior when comparing the 6 month (28.4% vs 20.5%) and 12 month (20.9% vs 4.4%) PFS. For completeness, the KM diagram is shown in Figure 17.

Table 28: Results of PD-L1 CPS ≥ 1% Subgroup Analysis (PFS)

Treatment	N	Number of Events (%)	Median PFS† (Months) (95% CI)	PFS at Months 6 in % (95% CI)	PFS at Months 12 in % (95% CI)	Pembrolizumab vs. Control Hazard Ratio (95% CI)
Control	120	98 (81.7)	3.2 (2.2, 3.4)	20.5 (13.3, 28.8)	4.4 (1.4, 10.4)	0.91 (0.68, 1.24)
Pembrolizumab	110	85 (77.3)	2.1 (2.0, 2.4)	28.4 (20.3, 37.1)	20.9 (13.6, 29.3)	



Number of subject at risk

Control	120	87	29	19	11	6	3	2	1	0	0	0	0
Pembrolizumab	110	64	35	31	26	23	10	8	3	0	0	0	0

Figure 17: KM plot of PD-L1 CPS ≥ 1% Subgroup (PFS)

5.2.6.4 Time on treatment

The company anticipates that the licence would indicate that people would receive treatment until disease progression. As per the KEYNOTE-045 protocol, a stopping rule was implemented whereby people could not receive pembrolizumab for longer than 24 months. Duration of treatment in pembrolizumab and UK SOC was based on time-on-treatment (ToT) data obtained from KEYNOTE-045. In addition to patients switching due to progressive disease, the time-on-treatment data was also influenced by those who discontinued treatment as a result of adverse events and other reasons listed in section 4.3.1 in the CS. The data also contained people who received additional weeks of treatment whilst their disease progression was confirmed.

Parametric curves were fitted to the Kaplan-Meier plot for time-on-treatment for pembrolizumab and UK SOC. Various parametric models were tested, with the preferred model chosen by examination of goodness-of-fit and using AIC/BIC. Figure 18 and Figure 19 show the Kaplan-Meier plots with fully fitted parametric models for pembrolizumab and UK SOC, respectively. It should be noted that in the Kaplan-Meier plot of pembrolizumab (Figure 18), the data appears to have been truncated, whilst in the electronic model it suggested that people received treatment beyond 70 weeks (approximately). As a result, it is unclear to the ERG whether a) the parametric curves have been fitted to all the data or b) the parametric curves have been fitted to truncated data.

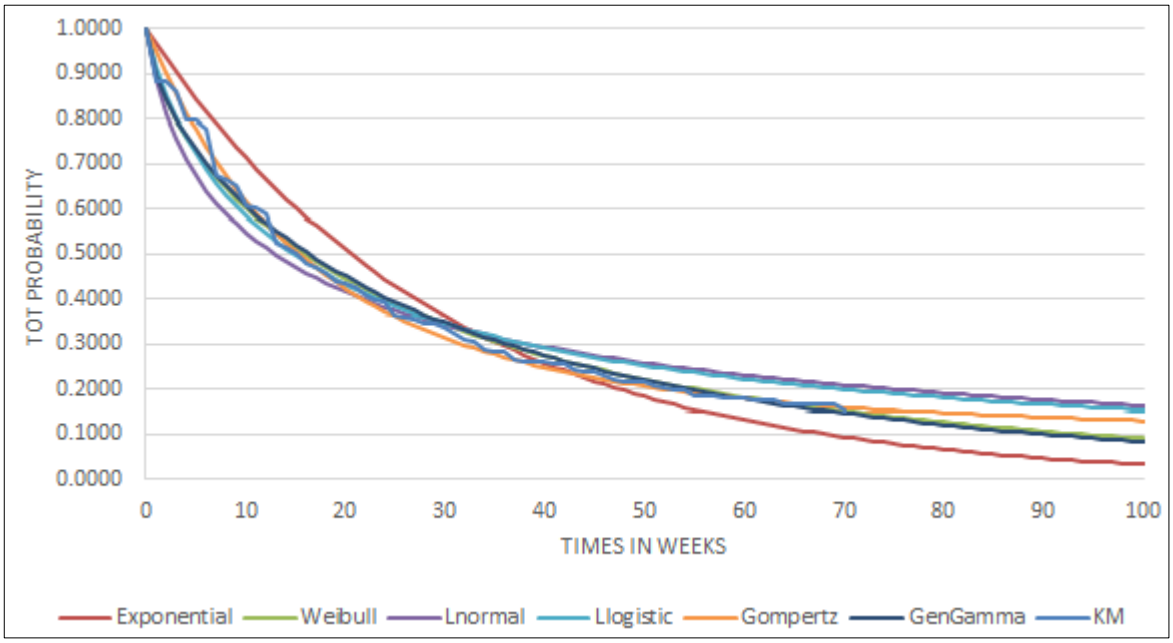


Figure 18: Kaplan-Meier plot for time-on-treatment for pembrolizumab, with various parametric models

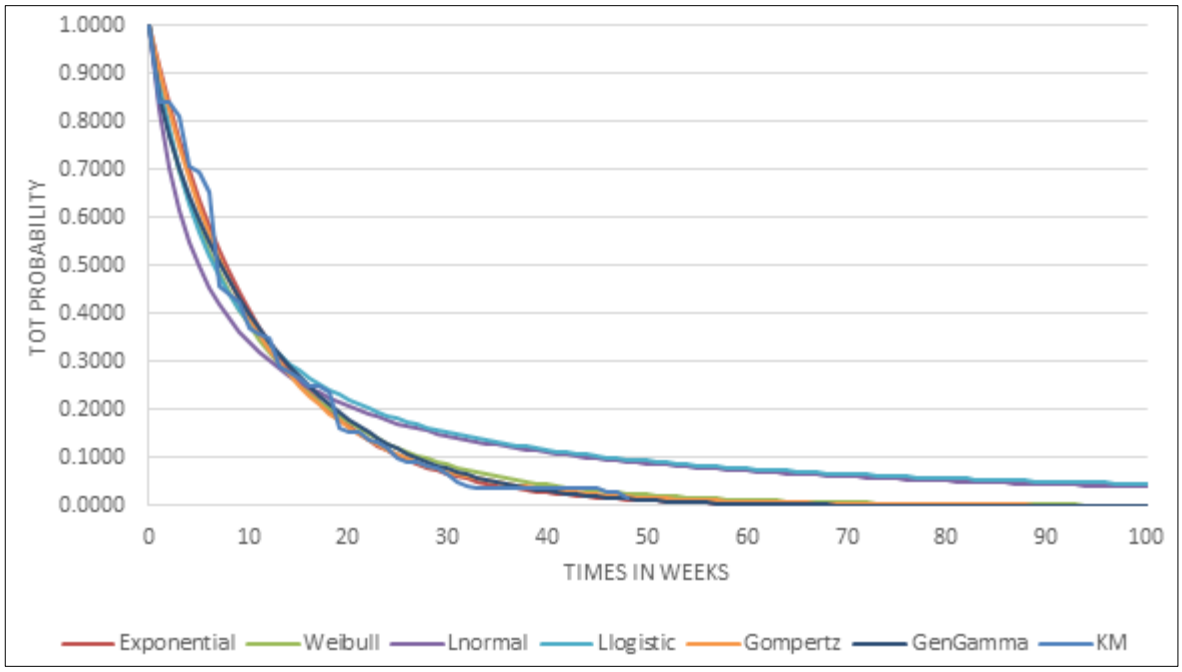


Figure 19: Kaplan-Meier plot for time-on-treatment for UK SOC, with various parametric models

Table 29 shows the AIC and BIC for each parametric model to the fully-fitted data on time-on-treatment. Results of the goodness-of-fit measures suggested that the Weibull and the generalised gamma parametric curves provided the best fits for time-on-treatment for pembrolizumab and UK SOC respectively. The resulting Kaplan-Meier plots with best fitting parametric curves are shown in Figure 20.

Table 29: Goodness-of-fit statistics based on the fully-fitted parametric curves to data on time-on-treatment

	Pembrolizumab		UK SOC, 2-stage adjusted	
Parametric model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1923.8	1927.4	1133.1	1136.3
Weibull	1870.5	1877.7	1126.8	1133.1
Gompertz	1890.9	1898.1	1134.1	1140.4
Log-logistic	1885	1892.2	1167.2	1173.5
Log-normal	1899.8	1906.9	1177.1	1183.3
Generalised Gamma	1872.1	1882.8	1122.2	1131.6

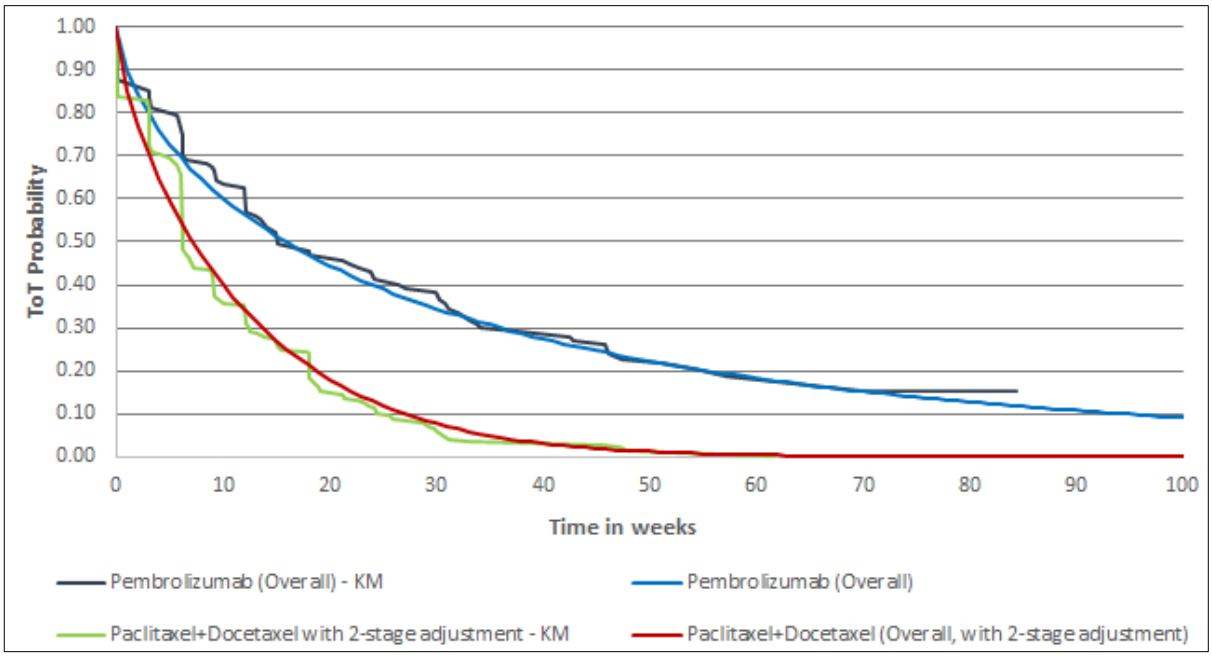


Figure 20: Kaplan-Meier plots for time-on-treatment for pembrolizumab and UK SOC (2-stage adjustment applied)

It appears that the Kaplan-Meier plot for pembrolizumab in Figure 18 is not identical to the Kaplan-Meier plot for pembrolizumab in Figure 20.

In the base case, it was assumed that people received pembrolizumab for a maximum of 35 cycles (24 months) (based on anticipated licence) and a maximum of six cycles (18 weeks) treatment with UK SOC, which is in line with clinical practice in England. Additionally, the company stated that adjustments were made to reflect the proportion of people who received a full treatment dose within each 3-week cycle. Data on dose intensity were analysed and results showed that the average dose intensity for people treated with pembrolizumab and UK SOC was 100.42%, 102.75% (docetaxel) and 100.02% (paclitaxel), respectively. The company considered these estimates not to be realistic in clinical practice whereby dose intensity is likely to be below 100%; hence the company applied a conservative 100% dose intensity in the economic model.

5.2.7 Mortality

General population background mortality was estimated using the latest UK life tables from the Office of National Statistics.[26] In line with common practice, overall survival in the economic model was estimated as the minimum of general population survival (i.e. one minus general population mortality) and trial patients' overall survival.

5.2.7.1 Adverse events

The base-case model included adverse events graded 3+ which occurred in at least 5% of patients (at any grade) in either treatment arm, with two exceptions:

- Grade 2 diarrhoea was also included to be consistent with previous NICE appraisals.[27, 28]
- Febrile neutropenia (with a 2% incidence in the UK SOC arm) was also included as clinicians suggested that this adverse event has significant impact on quality of life and costs and is consistent with recent NICE appraisal.[27]

The incidence of adverse events was taken from the KEYNOTE-045 trial for each treatment arm (see Table 30). It is evident that patients in UK SOC arm experienced more AEs compared to patients in the pembrolizumab arm; according to the ERG's clinical advisor this is expected due to the different toxicity profiles of the drugs. The CS stated that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on AEs of any grade. However, limiting adverse events to those graded 3 or 4 in severity and affecting ≥5% patients, and without providing count data, means that multiple adverse events suffered by the same patients may be under-represented within the model. For example, a patient may experience an adverse event on multiple occasions, but this will only be modelled as a single occurrence.

For the economic model, the total number of adverse events for both pembrolizumab and UK SOC arms are all applied in the first cycle (in the first 7 days), without any further consideration of adverse events in the duration of the model. This approach in the CS model may have under-estimated costs and over-estimated benefits associated with the two treatment arms.

Table 30: Grade 3+ AE rates for AEs included in the economic model based on KEYNOTE-045 data (CS Table 72)

Adverse Event	Rate for pembrolizumab (Grade 3+)	Rate for UK SOC (Grade 3+)
Anaemia	8.3%	11.9%
Febrile neutropenia	0.0%	4.76%
Neutropenia	0.0%	11.9%
Diarrhoea	5.3%	5.36%
Fatigue	3.8%	5.95%
Neutrophil count decreased	0.4%	14.29%
White blood cell count decreased	0.4%	5.95%

Pneumonia	2.6%	4.17%
Hypophosphatemia	0.80%	3.57%

ERG summary

- The ERG considers the methods used to adjust for treatment switching in the UK SOC to be satisfactory.
- The ERG agrees with the company that the proportional hazards assumption does not hold and that it is feasible to use the two-phase piecewise approach.
- In our ERG base-case, the estimated overall survival is based on extrapolations using the log-logistic distributions, added to the observed 24-week Kaplan-Meier data.
- The incidence of AEs seems to be in line with the expectation for each treatment in the KEYNOTE-045 trial.
- There is a concern that AEs may have been under-represented in the economic model due to being applied only in the first cycle of the model.

5.2.8 Health related quality of life

For the CS, HRQoL was estimated using the EQ-5D-3L, collected every 3 weeks for the first 9 weeks, and then every 6 weeks subsequently. EQ-5D data was also collected at the discontinuation visit, and at a safety follow up 30 days later. Two approaches to the analysis were performed: the primary analysis used utilities based on (categorised) time to death, and the secondary analysis used utilities based on the two progression states (progression-free and progressed). All baseline utility values were generated using the full analysis set (FAS) of the KEYNOTE-045 trial, which consisted of subjects who had received at least one dose of study treatment and completed at least one patient reported outcome analysis. FAS included patients who were allocated to vinflunine prior to randomisation and contained 266 patients in the pembrolizumab arm and 254 in the control arm. The ERG requested utility values from the company based on the UKSOC population excluding vinflunine. These were provided by the company upon clarification. The utilities are shown in Table 31.

Table 31: Mean utility values

	Pembrolizumab	Control (paclitaxel, docetaxel and vinflunine)	Pembrolizumab and control pooled (used in CS)	UKSOC (paclitaxel and docetaxel)	Pembrolizumab and UKSOC pooled	NICE TA272[17]
Time to death based (days)						
≥ 360	0.765	0.804	0.778	0.823	0.780	-
(180 to 360)	0.686	0.699	0.693	0.673	0.680	-
(90 to180)	0.566	0.612	0.590	0.595	0.578	-
(30 to 90)	0.457	0.446	0.451	0.414	0.435	-
<30	0.336	0.311	0.325	0.337	0.337	-
Progression based						
Progression-free	0.757	0.698	0.731	0.709	0.741	0.65
Progressed	0.680	0.565	0.641	0.554	0.647	0.25

The company points out that, due to the timing of the questionnaires, it is unlikely that the utility score captured the expected decline of health prior to death. The company found no significant differences in EQ-5D at baseline, and so decided to use pooled utility values for both arms. The ERG notes that statistically significant differences were observed in the progression based values (see CS table 75), and borderline statistically significant differences in the survival based utility values (see CS table 74). Hence the ERG explored using un-pooled utility values in a scenario analysis.

Furthermore, the ERG noted that treatment-specific utility values are lower for pembrolizumab compared to UK SOC when measured based on time to death, except for the (180 to 360) and (30 to 90) categories. However, patients in such categories only account for about 13% of all patients in the model. And, in fact, utility values were reported as considerably higher for pembrolizumab compared to UK SOC when measured based on progression status. Such findings appear to be counter-intuitive, as using one method of valuation of HRQoL over the other should not result in higher utility estimates for a particular treatment. The ERG does not have a particular explanation for such disparity, apart from the potential lack of accounting for treatment switching when estimating treatment-specific utility values and prolonged survival of unhealthy participants in the pembrolizumab arm. Due to this inconsistency, the ERG have also used pooled utility values in a scenario analysis.

In the CS base-case analysis, pooled utility values based on time to death were used. Estimated life years were based on time to death (i.e. categorising life years based on the 5 time to death

points (see Table 31)) and then assigned the respective utility values in each life year category to estimate QALYs. To the best of the ERG's knowledge, this approach is not common in practice, and has only been used for previous studies investigating melanoma treatments.[29, 30] The ERG has concerns over the reliability of the survival based utility estimates, with a large amount of missing data. The pembrolizumab arm has a median ToT of 15 weeks, meaning all patients should have completed on average four EQ-5D questionnaires whilst on treatment, excluding baseline, plus two follow-up questionnaires giving a total of six responses per person. It is likely that the subgroup of patients living beyond 360 days actually has a higher median ToT meaning six responses is an underestimate. However, examination of Table 74 of the CS concludes that the ≥ 360 day survival pembrolizumab group averaged 3.4 responses per person, suggesting almost half of their possible data is missing for this subgroup. The CS fails to mention how missing EQ-5D data was managed. Similarly, patients surviving < 30 days should only have completed one EQ-5D questionnaire, so the ERG is unsure how there can be more responses than people in these subgroups for both treatment arms. Additionally, despite the fact that these survival-time based groups are mutually exclusive, they appear to contain more members than were in the trial, with a total 596 subjects obtained from Table 74 when only 542 were recruited. The ERG would expect the total to be below 542 when accounting for patients who were censored prior to 360 days. It is also unknown how the company obtained their average estimates for each group, and whether they calculated an average per person, and averaged this, or whether they averaged across all questionnaire responses. Due to the uncertainty associated with the survival based utility estimates, the ERG chose to use progression based estimates in their scenario and base case analyses.

A literature search conducted by the company yielded 18 comparable HRQoL studies, however none presented utilities as a function of time to death and therefore were not included in any sensitivity analysis by the company. A previous TA[17] reported related utilities for comparison which are shown in Table 31, though they were not specific to bladder cancer. The lower values seen in Table 31 (despite the CS stating the utility values in KEYNOTE-045 are comparable with these in TA272) support the view that the post-progression score is overestimated by the CS data. It is also plausible that the time to death utilities are also overestimated as a result of the data collection. In a scenario analysis, the ERG will explore the impact on the incremental cost-effectiveness ratio (ICER), by using the utility values reported in TA272.

Please note that there is typo in CS Table 77, where the mean value for time to death in days ≥ 360 should be 0.778 (as used in the model and as reported in CS Table 74) as opposed to 0.761. Furthermore, the value for progressed health state for the pembrolizumab and UKSOC pooled arm is 0.647 (see CS clarification section B Table 3); however, the ERG believe that this value should be lower than 0.641 (pembrolizumab and control pooled). The ERG were unsure whether this was a typo or some confusion in their analysis (see Table 31).

Disutilities for ageing and adverse events were included in the model and are shown in Table 32. The decision to assume no further decline past the age of 75 years is based on Kind et al. (1999), who did not report any change in EQ-5D utility score beyond age 75 years (i.e. utility value was constant for anyone over the age of 75 years).[31] There is the possibility that the manner in which the company derived the age disutilities may have underestimated the effect of ageing on quality of life. More recently, Ara and Brazier (2010) have provided an algorithm that estimates general population utility scores as a function of age and gender.[32] The ERG believes that using Ara and Brazier[32] to derive age-related disutilities is more appropriate as: (a) the study by Kind et al. (1999) is outdated; and (b) the algorithm can provide age-related utility decrements for people beyond the age of 75. The ERG will present updated results in the scenario analysis using updated disutility values.

Adverse event disutility values were applied only in the first cycle of the economic model and were not considered for the remaining time horizon of the model. This approach may have overestimated the resulting QALYs from both pembrolizumab and UK SOC. The ERG notes that adverse event disutilities were not accounted for in related STAs.[17]

Whilst the frequency of adverse events suggests that pembrolizumab has a favourable profile, the adverse event disutility suggests otherwise. If the adverse event disutility is broken down by arm it can be seen that adverse events have a much greater impact on quality of life in the pembrolizumab arm, as shown in Table 32. The ERG presents results based on using separate adverse event utility values for each arm in the scenario analysis.

Table 32: Disutility values

Disutility type	Inc. vinflunine patients	Exc. vinflunine patients	Details
Age	0.0045	Not applicable	Per year increase in age from 65 to 75.

Adverse event (pooled)	0.117	0.137	Average disutility of a Grade 3+ AE, with a duration of 13.9 days per event.
Adverse event pembrolizumab arm	0.195	0.195	Average disutility of a Grade 3+ AE, with unknown duration.
Adverse event control arm	0.043	0.058	Average disutility of a Grade 3+ AE, with unknown duration.

ERG summary

- Utility values used in the economic model were generated from KEYNOTE-045 trial data. Owing to the open-label design of KEYNOTE-045, no reliable conclusion can be drawn from the quality of life results
- The ERG has reservations about using separate utilities for each treatment arm, due to counter-intuitive estimates.
- Estimating life years and subsequent QALYs using utility values based on time to death results is an unusual method. In addition, this approach slightly overestimates life years in both pembrolizumab and UK SOC.
- The company provided utility values without vinflunine after clarification.
- Disutilities were also used for the effect of adverse effects, with the values pooled for both arms.

5.2.9 Resources and costs

5.2.9.1 Intervention and comparator costs

All interventions were administered once per three week cycle. The total costs of pembrolizumab consisted of drug costs and administration costs with a single dose of 200mg typically administered intravenously over a 30 minute time period. The administration cost estimate was conservative assuming an administration period of 60 minutes (Healthcare Resource Group (HRG) code SB12Z).[33] Costs are shown in Table 33.

Table 33: Drug and administration costs

Costs	Dose per administration	Cost per mg	Cost per dose	Administration cost per dose	Total cost per dose	Source
Pembrolizumab	200mg	£26.30	£5260.00	£253.32*	£5513.32	MSD
Docetaxel	75mg/m^2	£0.13	£18.09	£253.32*	£271.41	eMIT
Paclitaxel	175mg/m^2	£0.07	£23.81	£406.63#	£430.44	eMIT
UK SOC	-	-	£20.88	£328.44	£349.32	CS

* HRG code: SB12Z – deliver simple parenteral chemotherapy at first attendance; # HRG code SB14Z – deliver complex parenteral chemotherapy at first attendance; eMIT – electronic market information tool

The CS stated that an average body surface area of 1.9m^2 was used to calculate the average dose of the UK SOC arm; this was calculated based on a weighted average of patients in KEYNOTE-045. The ratio of control treatments used in the model was obtained from the trial, 0.511:0.489 in favour of docetaxel, whereas the ratio of control treatments administered in the UK is 0.74:0.26 in favour of docetaxel. Docetaxel administration lasted for up to 60 minutes and was costed using a simple chemotherapy delivery. Paclitaxel administration had a duration of 3 hours, and so the administration costs were based on complex chemotherapy delivery (HRG code SB14Z).[33] The drug costs for the comparator arm were obtained from eMIT (2015-2016),[34] and the administration costs were obtained from the latest NHS Reference costs (2015-2016).[33] No drug wastage costs were included in the model.

The duration of treatment in the pembrolizumab and UK SOC arms were based on extrapolation of time on treatment (ToT) data from the KEYNOTE-045 trial. Different parametric curves were fitted to the patient level data to represent ToT in the economic model. The choice of the parametric curves were based on AIC/BIC values and visual inspection of the curves to the data. The function with the lowest AIC/BIC was Weibull for pembrolizumab, and GenGamma for UK SOC (Table 79 in CS) (see section 5.2.6.4 for more detail). These functions were chosen to inform patients' ToT in the economic model. A maximum treatment duration of 35 cycles (i.e. 24 months) was assumed for pembrolizumab, in line with the KEYNOTE-045 protocol and a maximum treatment duration of 6 cycles (i.e. 18 weeks) was used for the comparator therapies to reflect clinical practice in the UK. The average number of cycles received per patient in KEYNOTE-045 was 5.00 cycles for paclitaxel and 3.90 cycles for docetaxel.

5.2.9.2 Other health state costs

Routine costs of care

Resource use frequency for the progression-free and progressed health states along with the routine costs of care which take into account costs for routine monitoring and disease management were presented in Tables 81 and 82 of the CS, respectively. Resource use consisted of visits to various healthcare professionals such as general practitioners, oncologists and health visitors. The related unit costs were obtained from the NHS reference costs (2015-2016) and the Personal Social Services Research Unit (PSSRU) 2016 report.[33, 35]

The estimated monitoring and disease management costs per week were £154.61 and £136.07 (not per month as the CS states on p209), respectively for the pre-progression and post-progression health states.

Adverse Events (AEs)

The costs presented for adverse events were reported in Table 84 in the CS and are replicated in Table 34. The majority of costs in the CS were obtained using NHS reference costs (2015-2016).[33] When costs were not available from the NHS reference list, costs were acquired from other sources such as NICE DSU Reports,[36] and inflated using the appropriate indices.[35] Also included in the table are costs for adverse events from other recent publications, which demonstrates the uncertainty in costs. Whilst some of this may be explained by the different health areas and the varying severity of adverse events in each study, it is likely that there is still potential for under- or over-estimation of costs.

Table 34: Adverse event unit costs

Adverse event	Costs used in CS	Costs used by other publication*
Anaemia	£1,315.94	-
Febrile neutropenia	£2,641.80	£3,538.00 [17] £7,066.63 [37] £7352.54 [38]
Neutropenia	£70.80	£1733.22 [37]
Diarrhoea	£919.84	£8.59 per day [39] £1050.76 [37]
Fatigue	£2,499.99	£2233.40 [37]
Neutrophil count decreased	£70.80	-
White blood cell count decreased	£70.80	-
Hypophosphataemia	£1,212.89	-
Pneumonia	£1,751.08	-
Rash	None	£4.30 per day [39] £109.77 [37]
Nausea/vomiting	None	£1050.76 [37]
Dyspnoea	None	£97.00 - £139.00 [39]

* These costs have not been inflated to current price year for the economic model

Only adverse events of severity grade 3 or greater with a prevalence of >5% in at least one arm were included in the economic analysis. However, the ERG noted that data related to fatigue, pneumonia and hypophosphataemia were included in the utility calculations despite these adverse

events not meeting these criteria and no other justification for their inclusions was provided. For these adverse events, the ERG has performed a scenario analysis setting their prevalence and cost to zero. The ERG also has some concerns over the methods used to determine which adverse events were drug related, which may possibly create bias in favour of pembrolizumab.

Unit costs and incidence of additional adverse events that cancer patients typically exhibit, such as dyspnoea, hypertension, and abdominal pain were not considered in the CS model.

Adverse event costs were applied only in the first cycle of the economic model in the CS, without considering their impact in the remaining time horizon of the model; however, this is in line with previous STAs that the ERG have been involved with. However, this approach may underestimate adverse event costs associated with both pembrolizumab and UK SOC arms.

Terminal care costs

Terminal care costs were included in the economic model in the form of a one-off cost for all patients who transitioned to the death health state. The CS acknowledges the limited data available for terminal care in the urothelial cancer field. Estimates were calculated in line with a previous HTA report.[40]

Resource use estimates were obtained from both Marie Curie reports[41] and NICE guidance.[17, 42] Cost data was taken from a combination of the latest NHS reference costs and the PSSRU Report 2016.[33, 35] The total cost of terminal care per patient was £7252.82 for both treatment arms.

ERG Summary

- Drug dosing schedules and costs were provided by the company.
- No drug wastage costs were included.
- UK SOC treatment costs were estimated based on the KEYNOTE-045 trial docetaxel-paclitaxel administration ratio instead of the UK market administration ratio.
- Adverse event costs may have been underestimated in the economic model due to: (a) excluding some common adverse events that occur in cancer patients; (b) considering adverse events only in the first cycle of the model.

5.2.10 Cost effectiveness results

5.2.10.1 Base-case analysis

The CS provided updated cost-effectiveness results for the base-case and the subgroup analyses in their response to the ERG's clarification questions (CS clarification response: Appendix 5 - Addendum 1).

For the base-case analysis, deterministic and probabilistic results are presented in Table 35 comparing pembrolizumab with UK SOC for the overall patient population. All analyses are presented with the discounted patient access scheme (PAS).

Table 35: Base-case results (CS clarification response: Appendix 5 -Addendum 1 - Tables 87 and 91)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Deterministic results					
UK SOC	£20,938	1.10	-	-	-
Pembrolizumab	£60,053	1.95	£39,115	0.85	£45,833
Probabilistic results					
UK SOC	£21,367	1.13	-	-	-
Pembrolizumab	£60,634	1.98	£39,267	0.85	£46,194

The CS found that for the overall patient population pembrolizumab was more expensive than UK SOC; however, it generated more QALYs than the comparator. This resulted in a deterministic ICER of £45,833/QALY gained. The results of the probabilistic sensitivity analysis (PSA) are similar with an expected ICER of £46,194/QALY.

5.2.10.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed, which involved a random sampling of the parameters used in the cost effectiveness model using a 1,000 samples. The ERG examined convergence of the PSA by running a simulation with 5,000 samples, which resulted in similar probabilistic estimates to those reported in the CS. Whilst such an analysis goes some way to checking the validity, it does not guarantee consideration of particular combinations of parameter values, nor the potential for correlation between parameters. It would be useful to identify which

(if any) combination of parameter values led to the control arm resulting in more QALYs than the pembrolizumab arm, and to establish the feasibility of these combinations.

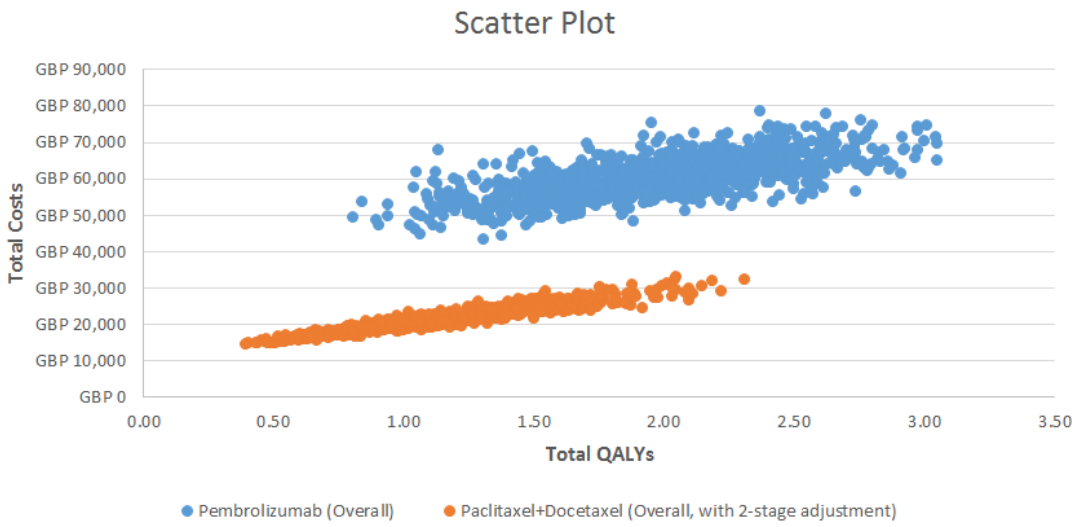


Figure 21: Cost-effectiveness plane

Figure 22: Cost-effectiveness acceptability curve

Cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) are shown in Figure 21 and Figure 22, respectively (CS clarification response: Appendix 6 - Addendum, Figures 49 and 50 respectively). A scatter plot of the PSA results in Figure 21 shows that patients on pembrolizumab have higher costs, but generally have more QALYs. There is also a wider variation in costs and QALYs associated with pembrolizumab than the control arm. At a willingness to pay (WTP) threshold of £50,000 per QALY (see section 7 for further details for

end-of life criteria), the probability of pembrolizumab being cost-effective when compared to UK SOC is 0.57.

Variation in costs appears to be considerably less compared to variation in QALYs in Figure 21. The ERG explored the reason for such finding. Since all relevant cost and resource use parameters were assigned appropriate distributions, the ERG believes that such underestimation of variation is due to assigning a coefficient of variation of 0.1 (10%) in all cost and resource use parameters. The ERG have explored the use of a coefficient of variation of 0.2 (20%) and present the findings in Figure 23 and Figure 24. Compared to the CS, the probabilistic ICER has slightly increased to £46,898 per QALY and the probability of pembrolizumab being cost-effective has slightly decreased to 0.55.

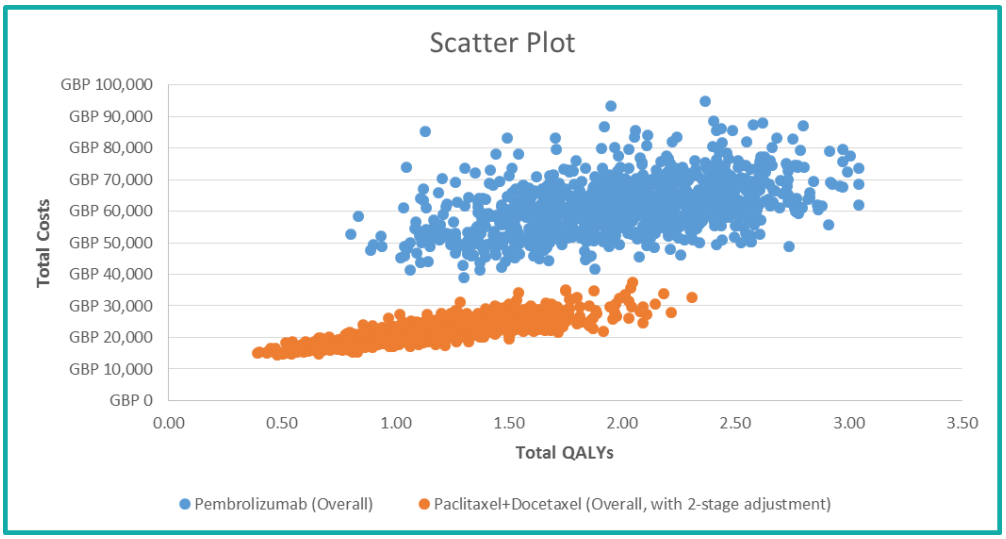


Figure 23: Cost-effectiveness plane - variation 0.2

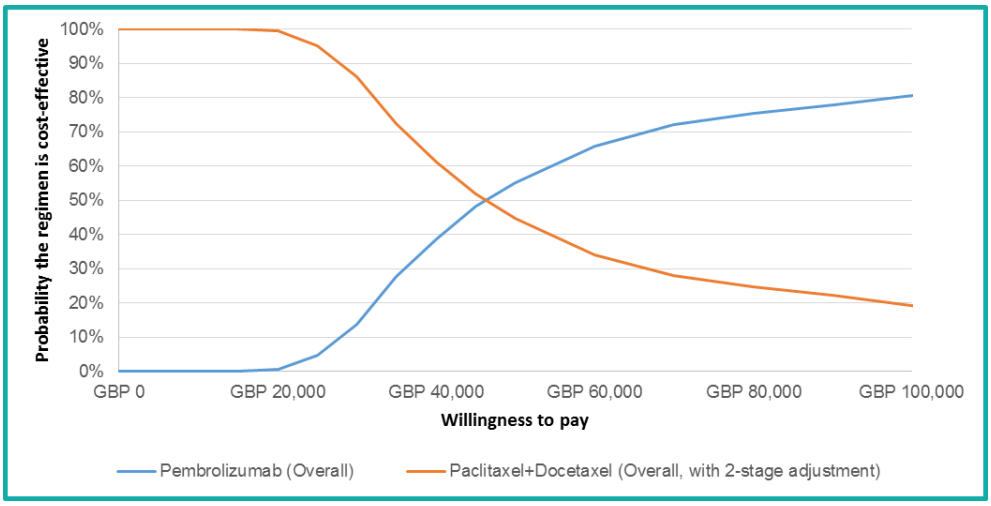


Figure 24: Cost-effectiveness acceptability curve - variation 0.2

5.2.10.3 Subgroup analyses

The CS presented subgroup cost-effectiveness results in Appendix 22 in the CS clarification response and are reproduced in the following tables: Table 36 to Table 40. The CS stated that "the results of the subgroup analyses are exploratory and should be interpreted with caution, especially since these are based in small sample sizes and some of the switchover analyses to adjust for OS could not be performed".

Table 36: Cost-effectiveness results for the comparison of pembrolizumab vs. paclitaxel (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 5 page 37						
Crossover adjustment: none (ITT)						
Paclitaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
Paclitaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage and IPCW adjustments could not be implemented in this population* *[#]These are the corrected figures (the figures were incorrect in the CS)*						

The CS found that for the overall patient population pembrolizumab was more expensive than when paclitaxel or docetaxel were considered as individual regimens on their own; however, it generated more QALYs than the comparator (see Table 36 and Table 37). As noted in Table 37

when comparing pembrolizumab with docetaxel, when no adjustment was made this resulted in a deterministic ICER of [redacted] per QALY gained when RPSFT adjustment method was used the ICER fell to [redacted] per QALY gained.

Table 37: Cost-effectiveness results for the comparison of pembrolizumab vs. docetaxel (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 5 page 37						
Crossover adjustment: none (ITT)						
Docetaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
Docetaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: IPCW						
Docetaxel	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage adjustment could not be implemented in this population*						

Table 38: Cost-effectiveness results for histology subgroups (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 6 page 38						
1) Patients with predominantly transitional cell urothelial carcinoma						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2) Patients with pure transitional cell urothelial carcinoma						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**No adjustment method could be implemented in this population*						

The CS found that for patients with predominantly transitional cell urothelial carcinoma when no adjustment was made the deterministic ICER was [redacted] and for patients with pure transitional cell

urothelial carcinoma when no adjustment was made pembrolizumab was [redacted] by UK SOC (see Table 38).

Table 39: Cost-effectiveness results for patients whose tumours express positive PD-L1 (CPS≥1%) (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 6 page 39						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: IPCW						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage adjustment could not be implemented in this population*						

For patients whose tumours express positive PD-L1 (CPS≥1%), the deterministic ICERs were the £50,000/QALY threshold (see Table 39). Whereas for patients whose tumours express positive PD-L1 (CPS≥10%), the deterministic ICERs [redacted] the £50,000/QALY threshold (see Table 40).

Table 40: Cost-effectiveness results for patients whose tumours express strongly positive PD-L1 (CPS≥10%) (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
CS clarification response Appendix 6 page 40						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage and IPCW adjustments could not be implemented in this population*						

In their clarification response the company presented cost-effectiveness results for patients who were negative for PD-L1 (CPS<1%) (see Table 41), where it is evident that cost-effectiveness results depend on whether or not patient crossover is accounted in the estimation. The deterministic results showed an ICER of [redacted] per QALY for the ITT population and an ICER of per QALY for the RPSFT method of crossover adjustment.

Table 41: Cost-effectiveness results for patients with CPS<1% (discounted, with PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
deterministic results						
Crossover adjustment: none (ITT)						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crossover adjustment: RPSFT						
UK SOC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**The two-stage and IPCW adjustments could not be implemented in this population*						

Also, upon request from the ERG, the company presented CEACs for all subgroup analyses undertaken, in the clarification response letter. Upon examination by the ERG they are in agreement with the deterministic cost-effectiveness results (the CEACs are not presented here).

The ERG has some reservations regarding the subgroup analyses presented in the CS. To the best of the ERG's knowledge, subgroup results were obtained using the same model parameters (such as age and gender) as in the base-case analysis (i.e. the overall patient population) and varying only the survival modelling part of the economic model. Since the populations are not the same as in the base-case analysis, we would expect the patient cohort to exhibit differences in model parameters beyond these informing OS and PFS.

5.2.11 Sensitivity analyses

5.2.11.1 Deterministic sensitivity analysis

A deterministic sensitivity analysis was performed using the 5% and 95% confidence interval estimates (unless otherwise stated in the CS), exploring the effect of key variables on the net monetary benefit (NMB) using a willingness to pay threshold of £50,000. A tornado diagram of the results is shown in Figure 25.

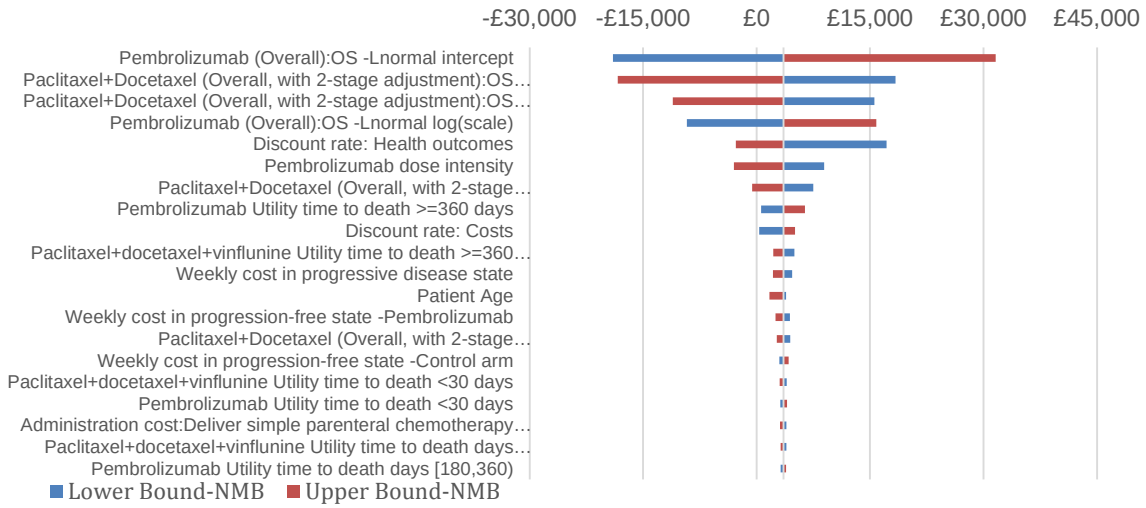


Figure 25: Tornado Diagram based on NMB

No tornado plot for the effects on the ICER were presented in the original CS, however it was included in the CS clarification response letter as shown in Figure 26. It is unknown what criterion were used for the selection of key variables. Looking at both Figure 25 and Figure 26, the most influential variables had a strong enough impact to suggest the control arm was more cost-effective when the 5% and 95% confidence intervals were used. The most influential of these were the parameters of the log normal distribution for overall survival of both arms, the discount rate of the health outcomes, the pembrolizumab dose intensity, and the assumptions around the time on treatment for the UK SOC arm. No combinations of these factors were explored in terms of two-way sensitivity analyses. The fact that the choice of model for OS is one of the most influential factors, illustrates how important this variable is in influencing the ICER.

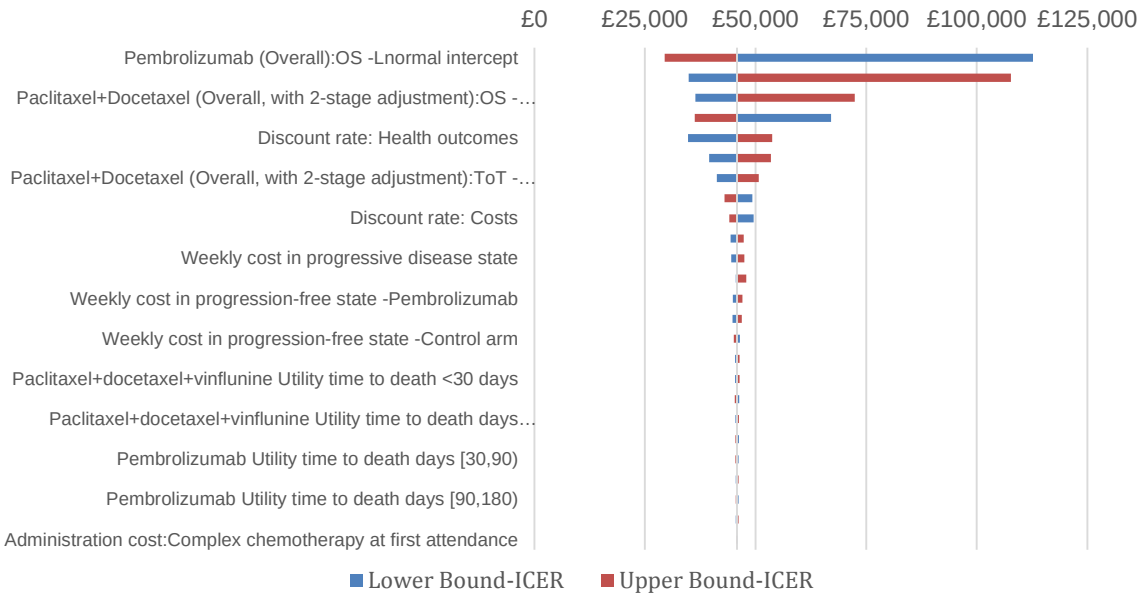


Figure 26: Tornado Diagram based on ICER

5.2.11.2 Scenario analyses

Nine alternative scenarios were analysed to assess the impact of assumptions on the ICER, two of these analyses raised the ICER per QALY over £50,000. These were: failing to adjust for treatment switching using an ITT analysis (ICER = £64,101) and using pooled progression based utility values (ICER = £54,665). The ERG feels that both these approaches represent valid estimates and that these results should be carefully considered. There were three scenarios that reduced the ICER to below £35,000. These were: using the RPSFT method for treatment switching (ICER = £31,509), and changing the cut off used for the piecewise modelling of overall survival (to 24 weeks or to 32 weeks). Further details can be found in Table 92 of the CS clarification response appendix.

The results of the scenario analysis showed that relatively few of the investigated scenarios had a meaningful effect on the ICER. However, the ERG would like to have seen a greater consideration of other survival curves included in the scenario analysis, for both PFS and OS particularly as the justification of the base-case selection is weak and also as the OS and PFS extrapolation are highly influential to the ICER, any changes could be quite significant. Yet only one alternative distribution was examined in the scenario analysis, modelling the PFS of the UKSOC arm with a generalised gamma distribution.

An additional sensitivity analysis was performed as requested by the ERG and NICE in the clarifications. This analysis explored how changing the duration of treatment effect and changing the percentage of patients that remained on pembrolizumab after 2 years affected the ICER. The results of this analysis are shown in Table 42. It can be seen that if the maximum treatment duration is not capped at 2 years, then the ICER exceeds the £50,000 threshold, regardless of the duration of the treatment effect (100% of progression-free patients on treatment after 2 years). Similarly, limiting the treatment effect to 3 years also raises the ICER above £50,000, even if no subjects were to take pembrolizumab for longer than 2 years. However, when the treatment effect is limited to 5 years, then the ICER is only below £50,000 if no patients were take pembrolizumab beyond 2 years. Most combinations of scenarios other than the base-case scenario raise the ICER to over £50,000, which casts some uncertainty over the true cost-effectiveness of pembrolizumab.

Table 42: Effects of changing duration of treatment effects and time on treatment duration on ICER

Continued treatment effect duration post treatment	ICER	Percentage of progression-free patients on treatment after 2 years		
		0%	25%	100%
Lifetime (base-case)	Deterministic	£45,833	£47,795	£52,806
10 years	Deterministic	£46,722	£48,732	£53,864
5 years	Deterministic	£49,442	£51,597	£57,100
3 years	Deterministic	£53,208	£55,564	£61,582

ERG summary

- A wide range of different approaches to a sensitivity analysis were conducted.
- Statistical approach to treatment switching and pooled utility values pushed ICER to over £50,000/QALY threshold.
- The ICER was sensitive to survival model parameters
- The ICER was also sensitive to time on treatment and to the treatment effect duration.

5.2.12 Model validation and face validity check

The company stated that they validated the clinical benefit by comparing model outcomes to clinical trial outcomes. Specifically, they compared the OS and PFS estimates obtained from the model at 6 months and 1 year with the respective estimates obtained from the KEYNOTE-045 trial. The ERG have some reservations with this approach for two reasons.

The first relates to the comparability of OS estimates at 6 months. Since the cut-off point in OS modelling is 40 weeks and before the cut-off the company used KM data from the KEYNOTE trial, the model and KEYNOTE outcomes for OS at 6 months should be the same. Despite that, OS estimates are slightly higher in the model relative to KEYNOTE both in the pembrolizumab and the UK SOC arms (Table 43). Upon inspection of the economic model, the ERG found that such disparity is due to a half cycle correction applied in the model and if the half cycle correction is removed such outcomes are the same.

The second reason relates to the fact that model predictions beyond 1 year were not validated, as OS and PFS estimates from KEYNOTE were not presented for a time point beyond 1 year in the CS. This is the case despite having follow up trial data beyond 1 year. Upon inspection of OS outcomes at 14.5 months, model outcomes were slightly higher compared to trial outcomes in the pembrolizumab arm (40.2% vs 39.3%) and slightly lower in the UK SOC arm (24.6% vs 25.7%). The same is true at 16.1 months (pembrolizumab: 37.8% vs 36.8%; UK SOC: 22.5% vs 25.7%). If we compare OS outcomes at 20 months, model outcomes are lower compared to trial outcomes in both pembrolizumab (33.3% vs 36.8%) and UK SOC (18.9% vs 25.7%). Despite that, the underestimation of OS is more profound in the UK SOC arm.

Table 43: Comparison of model and trial outcomes (In CS Table 88)

Outcome	Pembrolizumab		UK SOC	
	Base case	**KEYNOTE-045**	**Base case**	**KEYNOTE-045**
Progression-free survival				
Median PFS (months)	2.3	2.1	3.4	3.2
6-month PFS	28.6%	28.8%	22.8%	22.7%
Overall survival				
Median OS (months)	10.3	10.3	7.1	6.9
6-month OS	64.1%	63.9%	54.8%	54.5%
1-year OS	45.5%	43.9%	29.6%	30.2%
2-year OS	30.0%	-	16.4%	-
5-year OS	16.7%	-	7.8%	-
10-year OS	9.9%	-	4.2%	-

Another limitation of the clinical benefit validation process is that no external data more relevant to the target population were examined in order to validate long-term outcomes and examine the generalisability of the KEYNOTE-045 trial to the UK setting.

Regarding the model cross validation process, the company stated that the current economic model was adapted from a cost-effectiveness model for patients with NSCLC. The current model used identical base-inputs for example, costs, utilities, survival from the NSCLC model and the results obtained were the same; therefore, the company suggested that the current model is structurally sound. The ERG cannot comment on such finding since they cannot validate these results.

Finally, the model was validated by an external health economist and by using a "black box" testing method, in which a range of extreme value sets were used to highlight any errors. In addition, a simplified version of the model was written and individual formulae in the model were checked. Upon inspection of the Excel economic model, the ERG did not find any errors and believe the model is methodologically robust.

ERG summary

- The method used to validate clinical benefit was not optimal. The ERG has some concerns regarding the validation of long-term survival outcomes and a potential overestimation of OS in the pembrolizumab arm relative to the UK SOC arm.
- The Excel model presented by the company appears to be methodologically robust.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Only the deterministic results for the exploratory and sensitivity analyses undertaken by the ERG have been presented, as the probabilistic results were similar to the deterministic results. A list of all changes is reported in Appendix 11.1.

Table 44: Excluding vinflunine patients when estimating utility values in the pooled analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death based						
UK SOC	£20,938	1.59	1.09	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,115	0.86	£45,712
Progression based						
UK SOC	£20,938	1.59	1.04	-	-	-
Pembrolizumab	£60,053	2.71	1.76	£39,115	0.72	£54,063

Table 44 shows the base-case results when vinflunine patients were excluded from the calculation of EQ-5D utility values for the pooled analysis. Compared to the company base-case analysis (Table 35), when vinflunine is excluded for time to death utilities the ICER slightly decreases by £121/QALY, however, the alternative scenario is to use progression based utilities without vinflunine patients and the ICER compare to the base-case analysis increases by £8,230/QALY.

When vinflunine patients were excluded from the calculation of EQ-5D utility values specific for each treatment arm, compared to the base-case analysis (Table 35), the ICER increases when time to death utilities are used by £4,241/QALY; however, when progression based utilities are used the ICER falls by £3,532/QALY (see Table 45).

Table 45: Excluding vinflunine patients when estimating utility values specific for each treatment arm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death based						
UK SOC	£20,938	1.59	1.14	-	-	-
Pembrolizumab	£60,053	2.71	1.92	£39,115	0.78	£50,074
Progression based						
UK SOC	£20,938	1.59	0.92	-	-	-
Pembrolizumab	£60,053	2.71	1.84	£39,115	0.92	£42,301

Using utility values (including vinflunine patients) which are progression-based, the ICER increases to [redacted] (see Table 46).

Table 46: Progression-based utilities (inc. vinflunine patients)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Progression based						
UK SOC	£20,938	1.59	1.03	-	-	-
Pembrolizumab	£60,053	2.71	1.74	£39,115	0.72	£54,665

As mentioned in Section 5.2.8, the ERG has used progression based utilities based on TA272, as we believe that the time to death utilities are overestimated. The ICER using utility values based on TA272 increases dramatically from £45,833 per QALY (Table 35) to £114,082 per QALY, this is due to the substantially smaller differences in QALYs between the two treatment arms (see Table 47).

Table 47: Utility values from TA272 (pooled utility values excluding vinflunine)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Progression based						
UK SOC	£20,938	1.59	0.52	-	-	-
Pembrolizumab	£60,053	2.71	0.87	£39,115	0.34	£114,082

Also, in Section 5.2.8, we mentioned that disutility for ageing used in the model assumed no further decline past the age of 75 years. Using a more up-to-date reference, Ara and Brazier, 2010[32] when calculating age-related utility decrements the ICER slightly increases (time to death based utilities: +£840/QALY) – see Table 48.

Table 48: Applying age-related utility decrements based on values from Ara and Brazier (2010)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death based						

UK SOC	£20,938	1.59	1.09	-	-	-
Pembrolizumab	£60,053	2.71	1.92	£39,115	0.84	£46,673
Progression based						
UK SOC	£20,938	1.59	1.02	-	-	-
Pembrolizumab	£60,053	2.71	1.72	£39,115	0.70	£55,861

Using the adverse event disutility values as presented in Table 32, for the pooled analysis (see Table 49) the ICER is very similar to the base-case analysis (£49,814/QALY). However, when separate adverse event disutility values are used for each specific treatment arm the ICER increases considerably. For example, the ICER increases from £45,833 per QALY (base-case) to £60,714 per QALY when using time to death utilities (see Table 50), as mentioned earlier adverse events have a much greater impact on the quality of life in the pembrolizumab arms.

Table 49: Adverse event utility values excluding vinflunine patients in the pooled analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death						
UK SOC	£20,938	1.59	1.10	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,115	0.85	£45,814
Progression based						
UK SOC	£20,938	1.59	1.03	-	-	-
Pembrolizumab	£60,053	2.71	1.74	£39,115	0.72	£54,638

Table 50: Adverse event utility values excluding vinflunine patients for each specific treatment arm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time to death						
UK SOC	£20,938	1.59	1.08	-	-	-
Pembrolizumab	£60,053	2.71	1.72	£39,115	0.64	£60,714
Progression based						
UK SOC	£20,938	1.59	0.86	-	-	-
Pembrolizumab	£60,053	2.71	1.65	£39,115	0.79	£49,652

Table 51 shows the sensitivity analysis performed when removing the adverse events that did not meet the company's own inclusion criteria (pneumonia, hyphosphataemia and fatigue) – costs and

prevalence were set to 0. As shown the impact of these costs were negligible (ICER increased by £151/QALY). Furthermore, the table also shows results when using the most recent adverse event costs and again the impact of these costs were negligible (ICER decreased by £866/QALY).

Table 51: Adverse event costs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Removal of unjustified AE costs and prevalence (pneumonia, hypophosphataemia and fatigue)						
UK SOC	£20,673	1.59	1.10	-	-	-
Pembrolizumab	£59,903	2.71	1.95	£39,230	0.85	£45,984
Using AE costs from alternative sources (most recent publication used where multiple options possible)*						
UK SOC	£21,638	1.59	1.10	-	-	-
Pembrolizumab	£60,014	2.71	1.95	£38,376	0.85	£44,967

***ERG unable to add costs of rash, nausea/vomiting or dyspnoea**

Table 52: Estimation of cost of UK SOC based on UK market share of docetaxel and paclitaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£20,814	1.59	1.10	-	-	-
Pembrolizumab	£60,053	2.71	1.95	£39,239	0.85	£45,978

Estimation of cost of UK SOC based on the UK market share of docetaxel and paclitaxel, the ICER is very similar to the base-case analysis (£45,978 – see Table 52).

As mentioned in Section 5.2.6.1, the ERG considers that an extrapolation based on a log-logistic parametric distribution, added to the observed 24-week data may give plausible estimates for overall survival. Changing from log-normal to log-logistic only, the company's base-case ICER increases from £45,833 per QALY to £59,246 per QALY gained (see Table 53); and changing the cut-off from 40 weeks to 24 weeks only, the company's base-case ICER decreases from £45,833 per QALY to £34,168 per QALY (see Table 53). However, the ERG considers that both of these points should be considered together to give plausible estimates for overall survival, hence the

company's base-case ICER decreases from £45,833 per QALY to £42,343 per QALY (see Table 53).

Table 53: Changing overall survival functions

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Log-logistic model for overall survival						
UK SOC	£20,609	1.54	1.06	-	-	-
Pembrolizumab	£57,638	2.36	1.68	£37,029	0.62	£59,246
24 week cut-off for overall survival						
UK SOC	£17,334	1.06	0.70	-	-	-
Pembrolizumab	£60,027	2.71	1.95	£42,693	1.25	£34,168
Log-logistic model and 24 week cut-off for overall survival						
UK SOC	£17,563	1.09	0.72	-	-	-
Pembrolizumab	£57,457	2.34	1.67	£38,894	0.94	£42,343

ERG preferred base-case analysis

Our overall preferred ERG base-case is presented in Table 54. Changes include:

- Exclusion of vinflunine patients from estimation of utility values.
- Estimation of age-related utility decrements based on Ara and Brazier (2010).
- Use of utility values based on progression status.
- Use of pooled utility and adverse event disutility values.
- Setting adverse event prevalence and costs related to pneumonia, hypophosphatemia and fatigue to zero.
- Estimation of cost of UK SOC based on the UK market share of docetaxel and paclitaxel.
- Use a cut-off point of 24 weeks for the overall survival modelling approach.
- Use a log-logistic distribution for overall survival modelling for pembrolizumab and UK SOC.

Table 54: ERG preferred base-case analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£17,174	1.09	0.73	-	-	-
Pembrolizumab	£57,307	2.34	1.51	£40,132	0.78	£51,405

As shown in Table 54, for the ERG preferred base-case the ICER is slightly higher at £51,405 per QALY compared to the CS base-case analysis ICER of £45,833 per QALY.

5.3.1 ERG's preferred base-case model using different parametric distributions for overall survival

Due to the paucity of published information on the long-term overall survival for people with advanced or metastatic urothelial cancer, the ERG considers there to be some uncertainty in the extrapolations. It can be seen from Figure 7, Figure 8, Table 22 and Table 23 that the three-, five- and ten-year overall survival estimates differ based on the parametric curve used, and this will have an impact on the life years gained and QALYs gained. It should be noted that the company's results are based on a 35-year (lifetime) time horizon, which is in line with the NICE reference case. However, using the ERG's preferred assumptions (see section 5.3) we show in Table 55 that the majority of these benefits are based on the extrapolated difference and not based on the observed difference. To estimate the proportion of clinical benefit (expressed as life years gained (LYG)) that comes from the observed data or the extrapolated survival, we first estimated the LYG between pembrolizumab and UK SOC from the data over the period of observation in KEYNOTE-045. Given the availability of the data (median follow-up duration 14.1 months, range: 9.9 to 22.1), we considered two time points, 10 months and 22 months. We assumed that the LYG from observed data at these two time points could be calculated using the survival models for pembrolizumab and UK SOC as in the cost-effectiveness model (log-logistic distribution; 24 weeks cut-off) and changing the time horizon to 10 and 22 months. Indeed, we assumed these models were very much reliable to predict the life expectancies over a short-term period as in the actual observed data.

At a 35-year time horizon, the model yielded a 1.25 LYG (2.34 life years with pembrolizumab vs. 1.09 life years for UK SOC). Using the 10 month-time point, the LYG with observed data could

be estimated at 0.04 meaning that the benefit from the observed data contributed to only 3% of the total benefit (1.25 LYG), while 97% of the incremental life-expectancy comes from survival extrapolations. Using the 22 month-time point, the LYG with observed data could be estimated at 0.19 meaning that the benefit from observed data contributed to only 16% of the total benefit (1.25 LYG) while 84% of the incremental life-expectancy comes from survival extrapolations.

Should pembrolizumab be recommended by NICE for routine use within the NHS, the fact that most of the incremental benefit in terms of LYG comes from extrapolated data advocates for a review of this STA within a short period of time using longer follow-up data from KEYNOTE-045.

Table 55: Proportion of LYG based on the observed and extrapolated data

Time-point	LYG		Incremental LYG	Proportion of LYG from observed data	Proportion of LYG from extrapolated survival
	UK SOC	Pembrolizumab			
10 months	0.60	0.56	0.04	3%	97%
22 months	0.98	0.78	0.20	16%	84%

Additionally, we have explored in a scenario analysis the impact of using the ERG's preferred assumptions (including the 24-week cut-off), and using different parametric distributions and at different time horizons.

In Table 56, Table 57 and Table 58 we present results for the ERG's base-case, based on analyses undertaken at a 2-year, 10-year and 35-year time horizon, respectively. Results based on a 2-year time horizon showed that the expected mean incremental costs and mean effects (LYG/QALYs) are similar, irrespective of the parametric distribution.

Table 56: Using the ERG's preferred base-case, with results based on a 2-year time-horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£14,445	0.80	0.55	-	-	-	-
Pembrolizumab	£46,483	1.02	0.70	£32,038	0.22	0.15	£209,686
Weibull							
UK SOC	£14,521	0.79	0.55	-	-	-	-
Pembrolizumab	£46,369	1.02	0.71	£31,848	0.23	0.16	£195,312
Gompertz							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£14,285	0.82	0.56	-	-	-	-
Pembrolizumab	£46,157	1.04	0.72	£31,872	0.22	0.15	£207,614
Log-logistic							
UK SOC	£14,342	0.80	0.55	-	-	-	-
Pembrolizumab	£46,250	1.03	0.71	£31,908	0.23	0.16	£196,744
Log-normal							
UK SOC	£14,342	0.81	0.56	-	-	-	-
Pembrolizumab	£46,152	1.04	0.72	£31,810	0.23	0.16	£195,344
Generalised gamma							
UK SOC	£14,185	0.83	0.71	-	-	-	-
Pembrolizumab	£46,271	1.03	0.57	£32,086	0.20	0.14	£225,655

Results based on the 10-year time-horizon showed that the expected mean LYG and QALYs ranged from 0.33 to 1.30, and 0.23 to 0.84, respectively, while expected mean incremental costs were all above £35,000 but less than £40,000. These results showed that at a 10-year time horizon, extrapolations based on a Gompertz parametric distribution, added to the observed 24-week Kaplan-Meier data, gave the most favourable ICER (approximately £47,400 per QALY gained) compared to using a generalised gamma distribution (£146,000 per QALY gained).

Table 57: Using the ERG's preferred base-case, with results at a 10-year time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£15,782	0.89	0.61	-	-	-	-
Pembrolizumab	£50,529	1.35	0.92	£37,747	0.46	0.31	£111,336
Weibull							
UK SOC	£15,476	0.85	0.58	-	-	-	-
Pembrolizumab	£51,424	1.48	1.00	£35,949	0.63	0.43	£84,555
Gompertz							
UK SOC	£17,991	1.25	0.83	-	-	-	-
Pembrolizumab	£57,751	2.55	1.67	£39,760	1.30	0.84	£47,408
Log-logistic							
UK SOC	£16,725	1.04	0.70	-	-	-	-
Pembrolizumab	£54,172	1.93	0.70	£37,448	0.89	0.58	£64,021
Log-normal							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£16,735	1.04	0.70	-	-	-	-
Pembrolizumab	£55,548	2.15	1.42	£38,814	1.11	0.72	£53,682
Generalised gamma							
UK SOC	£19,178	1.43	0.94	-	-	-	-
Pembrolizumab	£53,164	1.76	1.18	£33,985	0.33	0.23	£145,980

Results based on the 35-year time-horizon showed that the expected mean LYG and QALYs ranged from 0.10 to 2.38, and 0.11 to 1.45, respectively, while the expected mean incremental costs were all greater than £32,000 but less than £50,000. These results showed that at a 35-year time horizon, extrapolations based on a Gompertz parametric distribution, added to the observed 24-week Kaplan-Meier data, gave the most favourable ICER (approximately £33,200 per QALY gained) compared to using a generalised gamma distribution (approximately £298,800 per QALY gained).

Table 58: Using the ERG's preferred base-case, with results at a 35-year time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Exponential							
UK SOC	£15,782	0.89	0.61	-	-	-	-
Pembrolizumab	£50,545	1.35	0.92	£34,763	0.46	0.31	£111,108
Weibull							
UK SOC	£15,476	0.85	0.58	-	-	-	-
Pembrolizumab	£51,518	1.49	1.01	£36,043	0.64	0.43	£83,713
Gompertz							
UK SOC	£20,361	1.56	1.01	-	-	-	-
Pembrolizumab	£68,322	3.94	2.45	£47,961	2.38	1.45	£33,179
Log-logistic							
UK SOC	£17,174	1.09	0.73	-	-	-	-
Pembrolizumab	£57,307	2.34	1.51	£40,132	1.25	0.78	£51,405
Log-normal							
UK SOC	£16,945	1.06	0.71	-	-	-	-
Pembrolizumab	£59,876	2.71	1.74	£42,931	1.65	1.02	£41,933
Generalised gamma							
UK SOC	£21,866	1.78	1.14	-	-	-	-
Pembrolizumab	£54,223	1.88	1.25	£32,357	0.10	0.11	£297,821

These results offer some insight on the impact of using different parametric distributions and time horizons. As expected, at the 2-year time horizon, the choice of parametric distributions has no impact on the expected mean costs and benefits, as they are all similar. This is a consequence of the results being heavily dependent on the observed data and not the extrapolations. Also the ICERs increase, and this is a result of the model not capturing all costs and benefits over this short duration. Conversely, at the 10-year time horizon, the economic model utilizes more information from the parametric distributions in the form of the estimated overall difference in survival time. It can be seen that there is some variation in the incremental costs, but more so in the incremental effects (LYG/QALYs) and this is reflected in the range of ICERs derived. Similarly, at the 35-year time horizon, the model depends heavily on the parametric distributions in order to inform on the cost-effectiveness. These results show that there is some variation in the incremental costs and effects, and this is reflected in the ICERs.

These analyses highlight that the results are dependent on the time horizon and the choice of parametric distribution used for estimating the overall survival. It should be noted that the economic model only allows the same parametric distribution to be used for estimating the overall difference in mean survival time between pembrolizumab and UK SOC. It would have been informative to choose parametric distributions based on goodness-of-fit measures (also informed by clinical opinion), whereby allowing the different functional forms to be used in order to estimate mean overall survival.

5.4 Conclusions of the cost effectiveness section

The company submission is based around pembrolizumab versus UK SOC. The company used a partitioned survival model to assess the cost-effectiveness of pembrolizumab compared to UK SOC (docetaxel/paclitaxel), in people with advanced or metastatic urothelial cancer. The model defined health states of pre-progression, post-progression and death, and the cost-effectiveness was analysed over a 35-year time horizon. Clinical effectiveness inputs to the model relied solely on the KEYNOTE-045 trial. Key costs included in the model were the cost of pembrolizumab and the cost of UK SOC. A PAS was provided for pembrolizumab. The model appeared to have captured the key features of people with advanced or metastatic urothelial cancer.

The model submitted by the company provided a deterministic ICER of approximately £45,800 per QALY gained, and at a willingness-to-pay threshold of £50,000 (see section 7), the

company's probabilistic analysis yielded a 0.57 probability of pembrolizumab being cost-effective when compared to UK SOC. The probabilistic ICERs are in relative agreement.

Other than two easily fixed errors (application of maximum time on treatment and estimation of QALYs), which the company corrected and provided an updated model, there were no discrepancies found between the models reported in the company submission and the copy of the model given to the ERG.

However, there are several areas of uncertainty that may impact on the cost-effectiveness results, as the model was most sensitive to changes made to the overall survival:

- The cut-off time point used for the overall survival model; and
- The choice of parametric function for the overall survival model

The ERG considers the two-phase piecewise model to be feasible in order to model overall survival. However, it would have been more appropriate to use an extrapolation based on a log-logistic parametric distribution, added to the observed 24-week Kaplan-Meier data instead of a log-normal distribution, added to 40-week observed data. It should be noted that there is uncertainty in the overall survival, especially beyond the trial time horizon and this will invariably have an impact on the life years gained and hence, the cost-effectiveness results.

Furthermore, the CS compared the extrapolated OS for people in the UK SOC with that reported by Cancer Research UK for patients with stage IV bladder cancer. The ERG however, have concerns regarding the comparability of people in the KEYNOTE-045 trial with those from Cancer Research UK.

The CS model incorporates utility scores based on time to death, which results in a relatively unusual method to estimate life years (based on death incidence) and subsequent QALYs. In addition, this approach slightly overestimates life years in both pembrolizumab and UK SOC arms relative to life years based on progression status. The ERG believes that using utility scores based on progression status is a more appropriate method to estimate life years and subsequent QALYs.

The base-case analysis included data for patients receiving vinflunine in the estimation of utility values, which is currently not recommended in England. The ERG believes that such patients should have been excluded from the analysis.

The age-related utility decrements are estimated from an outdated study that does not allow for the incorporation of decrements for patients aged more than 75 years old. The ERG believes that this is a limitation that possibly overestimates QALYs in both treatment arms.

Furthermore, the ERG removed the adverse events that did not meet the company's own inclusion criteria (pneumonia, hyphosphataemia and fatigue) and associated costs and prevalence were set to zero.

In the base-case analysis, pembrolizumab was compared to UK SOC based on the distribution of the regimens observed in KEYNOTE-045. The ERG believes that cost of UK SOC should be based on the UK market share of docetaxel and paclitaxel.

The ERG presented a preferred base-case analysis taking into account all issues raised in his chapter. Our preferred analysis increased the ICER to £51,405 per QALY.

When interpreting these results, it is important to consider the impact of these key sources of uncertainty in the ICER, and the impact any alternative assumptions would make.

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

Alterations to the base-case assumptions were made by the ERG as identified in Chapter 5. Details of the alterations can be found in Appendix 11.1. The impact on each change individually on the base-case analysis is shown in Table 59.

Table 59: ERG re-estimation of cost-effectiveness

	ΔC	**ΔQALY**	**ΔC/QALY**	**Ratio[+]**
Pembrolizumab vs UK SOC				
CS base-case model	£39,115	0.85	£45,833	-
ERG models				
Exclusion of vinflunine patients from estimation of utility values	£39,115	0.86	£45,712	0.997
Use utility values based on progression status	£39,115	0.72	£54,665	1.193
Estimation of age-related utility decrements based on Ara and Brazier (2010)	£39,115	0.84	£46,673	1.018
Averse event prevalence and costs related to pneumonia, hypophosphatemia and fatigue are set to zero	£39,230	0.85	£45,984	1.003
Estimation of cost of UK SOC based on the UK market share of docetaxel and paclitaxel	£39,239	0.85	£45,978	1.003
Use a log-logistic distribution for OS modelling	£37,029	0.62	£59,246	1.293
Use a cut-off point of 24 weeks for OS modelling	£42,693	1.25	£34,168	0.745
ERG preferred base-case analysis	**£40,132**	**0.78**	**£51,405**	**1.122**

7 END OF LIFE

On page 170 of the main CS, the company have presented a table (Table 61) regarding end-of-life criteria. There are three main criteria to fulfil for the appraisal of end of life treatments:[43]

1. the treatment is indicated for patients with a short life expectancy, normally less than 24 months; and
2. there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment; and
3. the treatment is licensed or otherwise indicated, for small patient populations.

Regarding criterion 1, the company has indicated the median OS is lower than 24 months in patients with advanced/metastatic urothelial cancer following platinum based chemotherapy. The statement was supported by two references that were not included in the background section and for which no details were provided of the estimates of life expectancy in these two studies. In the clarification response document, the company has responded that the estimated life expectancy of patients with advanced or metastatic urothelial cancer following treatment with platinum-based chemotherapy is estimated to be between 6.5 and 9 months based on the references provided.[44, 45]

In KEYNOTE-045, the median OS was 7.4 months in the SOC arm and between [redacted] and [redacted] months in the UK SOC arm after adjustment for treatment switching. In terms of life expectancy, survival extrapolations for the UK SOC arm indicate a life expectancy of 1.59 years with the company's base-case model and 1.09 years with the ERG's preferred base-case model. Therefore, the ERG agree that pembrolizumab fulfils criterion 1 for end-of-life treatment.

Regarding end-of-life criterion 2, the company indicated that pembrolizumab offers an extension of life of at least 3 months compared to UK SOC both in terms of median OS (10.3 months vs. 6.9 months for pembrolizumab and UK SOC respectively) and months of life gained (32.5 months vs. 19 months for pembrolizumab and UK SOC respectively). The 3.4 months median OS gain is based on the median OS for the UK SOC after adjustment for treatment switching using the 2-stage model. With other adjustment methods, the median OS gain would fluctuate between [redacted] and [redacted] months. As previously indicated, the results comparing pembrolizumab and UK SOC must be viewed with caution since they correspond to a post-hoc analyses. The most robust estimate of the median OS gain should be taken from the entire population from KEYNOTE-045 (+2.9 months) although the ERG appreciates that one of the treatments of the

SOC arm (vinflunine) is not currently available within the NHS. In terms of life-year gained, the company's estimate is 13.5 months while the ERG's estimate is 15 months. Overall, the ERG agree that pembrolizumab fulfils criterion 2 for end-of-life treatment.

The company has not described how pembrolizumab fulfils criterion 3. However, the company reports that the number of patients estimated to be eligible for pembrolizumab will be 502 (CS p234). The ERG clinical advisor also confirms that the patient population relevant to the decision problem would be small.

8 INNOVATION

On page 31 of the CS, the company have presented a statement on how pembrolizumab could represent a step-change in the management of people with advanced/metastatic urothelial cancer after progression or recurrence following platinum-based chemotherapy. Unlike conventional chemotherapies, pembrolizumab belongs to an emerging class of immunotherapy drugs whose mechanism of action consists of increasing the ability of the immune system to kill cancer cells. There is a growing number of immunotherapies which are being evaluated in many cancer types, both in solid tumours and in hematologic malignancies. Some of these, like pembrolizumab, atezolizumab, avelumab, or nivolumab, are already licensed in cancers other than urothelial cancers.

In the innovation section, the company have emphasised the high unmet need for patients with advanced/metastatic urothelial cancer after platinum-based regimen, and indicated that pembrolizumab has demonstrated significant survival benefit and improved tolerability profile compared to conventional chemotherapy. The ERG agree with the company's statement on the high unmet need within the scoped population. The ERG also agree on the significant survival benefit with pembrolizumab although longer-term survival confirmatory analyses will be needed to more accurately evaluate the benefit on life expectancy. The ERG also appreciate the fact that pembrolizumab has a better safety profile compared to conventional cytotoxic chemotherapy.

9 OVERALL CONCLUSION

9.1 Clinical effectiveness evidence

Regarding clinical effectiveness, pembrolizumab used as single agent was evaluated against SOC (either paclitaxel, docetaxel, or vinflunine) in the KEYNOTE-045 trial. This phase 3 trial was of good quality, with a low risk of bias in most domains except for the blinding of participants and personnel since the study was open-label (high-risk of bias).

There were two co-primary endpoints that were assessed in three groups: the entire population, the population positive for PD-L1 expression, and the population strongly-positive for PD-L1 expression.

Regarding PFS, the risk of progression or death was similar between pembrolizumab and SOC in the three populations although the proportion of patients free from progression at 1 year was higher for pembrolizumab.

Regarding OS, the risk of death was reduced with pembrolizumab compared to SOC in the three populations.

The results of PFS and OS in the numerous subgroups showed consistency with the overall findings for the entire population.

The evaluations of quality of life were presented as exploratory objectives. Owing to the open-label design of KEYNOTE-045, no reliable conclusion can be drawn from the quality of life results.

The safety profile of pembrolizumab was more favourable compared to SOC with no treatment-related events of grade ≥3 with an incidence of ≥5% observed in the pembrolizumab group.

As of April, 2017, pembrolizumab is not licensed for urothelial cancers and a submission aimed to extend the marketing authorisation is currently being assessed with the CHMP. Based on the results of KEYNOTE-045 presenting the clinical effectiveness and safety profile of pembrolizumab in advanced/metastatic urothelial cancers after failure to platinum-based therapy,

the ERG believes it's likely that the CHMP will consider the balance between benefits and risks of pembrolizumab is positive.

No indirect comparisons were presented by the company. There is no data comparing pembrolizumab to BSC which is a relevant comparator in people with poor performance status.

9.2 Cost-effectiveness evidence

The model constructed by the company appears to be logical and methodologically sound. Its main shortcomings relate to the utility values and the overall survival modelling methods.

With regard to the utility values, the ERG believe that utilities should be expressed based on progression status, since this is common practice in previous immunotherapy appraisals and follows the model structure. Furthermore, the time to death based method of estimating utilities overestimates life years gained for both treatment arms. In addition, age-related utility decrements were estimated based on the algorithm in Ara and Brazier (2010)[32] by the ERG; since to the best of our knowledge this is the most recent and coherent source.

With regard to overall survival modelling, the ERG considers the two-phase piecewise model to be suitable for modelling overall survival. However, it would have been more appropriate to use an extrapolation based on a log-logistic parametric distribution, added to the observed 24-week Kaplan-Meier data instead of a log-normal distribution, added to 40-week observed data.

The ERG have presented a scenario with a preferred base-case analysis; this preferred base-case increases the ICER slightly compared with the CS submission.

10 REFERENCES

1. Cancer Research UK. *About bladder cancer*. 2016. URL: http://www.cancerresearchuk.org/about-cancer/bladder-cancer/about (Accessed 28 February 2017).
2. Cancer Research UK. *Survival*. 2016. URL: http://www.cancerresearchuk.org/about-cancer/bladder-cancer/survival (Accessed 28 February 2017).
3. Cancer Research UK. *Bladder cancer survival trends over time*. 2014. URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/survival#heading-Two (Accessed 12 April 2017).
4. Leal J, Luengo-Fernandez R, Sullivan R, Witjes JA. Economic Burden of Bladder Cancer Across the European Union. *Eur Urol* 2016;**69**:438-47. http://dx.doi.org/10.1016/j.eururo.2015.10.024
5. Sangar VK, Ragavan N, Matanhelia SS, Watson MW, Blades RA. The economic consequences of prostate and bladder cancer in the UK. *BJU Int* 2005;**95**:59-63. http://dx.doi.org/10.1111/j.1464-410X.2005.05249.x
6. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 1.2014*. Fort Washington (PA): The Network; 2014.
7. National Institute for Health and Care Excellence. *Bladder cancer: diagnosis and management (NG2)*. 2015. URL: https://www.nice.org.uk/guidance/NG2 (Accessed 14 March 2017).
8. National Cancer Intelligence Network. *Kidney Cancer: Survival Report. Urological Cancers SSCRG*. 2014. URL: http://www.ncin.org.uk/view?rid=2676 (Accessed 10 March 2017).
9. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A, *et al.* Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;**25 Suppl 3**:iii40-8. http://dx.doi.org/10.1093/annonc/mdu223
10. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee J-L, Fong L, *et al.* Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med* 2017;**376**:1015-26. http://dx.doi.org/doi:10.1056/NEJMoa1613683
11. Balar AV, Castellano DE, O'Donnell PH, Grivas P, Vuky J, Powles T, *et al.* Pembrolizumab as first-line therapy in cisplatin-ineligible advanced urothelial cancer: Results from the total KEYNOTE-052 study population. *J Clin Oncol* 2017;**35**:abstract 284.
12. ClinicalTrials.gov. *Study of Pembrolizumab (MK-3475) in Participants With Advanced Urothelial Cancer (MK-3475-052/KEYNOTE-52)*. 2017. URL: https://clinicaltrials.gov/ct2/show/NCT02335424 (Accessed 17 March 2017).
13. Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;**27**:4454-61. http://dx.doi.org/10.1200/JCO.2008.20.5534
14. Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care*. York: CRD, University of York; 2009. URL: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (Accessed 31 January 2017).
15. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, *et al.* Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;**18**:3068-77. http://dx.doi.org/10.1200/jco.2000.18.17.3068
16. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, *et al.* Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;**23**:4602-8. http://dx.doi.org/10.1200/jco.2005.07.757

17. National Institute for Health and Care Excellence. *Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract: Technology appraisal guidance [TA272]*. 2013. URL: https://www.nice.org.uk/guidance/ta272 (Accessed 10 March 2017).
18. Cameron C, Fireman B, Hutton B, Clifford T, Coyle D, Wells G, *et al.* Network meta-analysis incorporating randomized controlled trials and non-randomized comparative cohort studies for assessing the safety and effectiveness of medical treatments: challenges and opportunities. *Syst Rev* 2015;**4**:147. http://dx.doi.org/10.1186/s13643-015-0133-0
19. Bellmunt J, De Wit R, Vaughn DJ, Fradet Y, Lyun Lee J, Fong L, *et al.* KEYNOTE-045: Open-label, phase 3 study of pembrolizumab vs investigator's choice of paclitaxel, docetaxel, or vinflunine for previously treated advanced urothelial cancer. *Journal for ImmunoTherapy of Cancer* 2016;**4**:abstract O2.
20. National Institute for Health and Care Excellence. *Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens. NICE Technology Appraisal Guidance [TA423]: Evidence*. 2016. URL: https://www.nice.org.uk/guidance/ta423/evidence (Accessed 12 April 2017).
21. ClinicalTrials.gov. *Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-012/KEYNOTE-012)*. 2017. URL: https://clinicaltrials.gov/ct2/show/NCT01848834 (Accessed 17 March 2017).
22. Balar A, Bellmunt J, O'Donnell PH, Castellano D, Grivas P, Vuky J, *et al.* PR Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: Preliminary results from the phase 2 KEYNOTE-052 study. *Annals of Oncology Conference: 41st European Society for Medical Oncology Congress, ESMO* 2016;**27**. http://dx.doi.org/http://dx.doi.org/10.1093/annonc/mdw435.25
23. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**:228-47. http://dx.doi.org/http://dx.doi.org/10.1016/j.ejca.2008.10.026
24. Latimer NR, Abrams KR. *NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching*. Sheffield: NICE Decision Support Unit; 2014. URL: http://www.nicedsu.org.uk/TSD16_Treatment_Switching.pdf (Accessed 10 March 2017).
25. Bellmunt J, Fougeray R, Rosenberg JE, von der Maase H, Schutz FA, Salhi Y, *et al.* Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy. *Ann Oncol* 2013;**24**:1466-72. http://dx.doi.org/10.1093/annonc/mdt007
26. Office for National Statistics. *Population estimates - Summary for the UK, mid-2015*. 2016. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates (Accessed 10 March 2017).
27. National Institute for Health and Care Excellence. *Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy: Technology appraisal guidance [TA428]*. 2017. URL: https://www.nice.org.uk/guidance/ta428 (Accessed 10 March 2017).
28. National Institute for Health and Care Excellence. *Nintedanib for previously treated locally advanced, metastatic or locally recurrent non-small cell lung cancer: NICE Technology appraisal guidance [TA347]: Committee Papers*. 2014. URL: https://www.nice.org.uk/guidance/TA347/documents/lung-cancer-nonsmall-cell-nintedanib-committee-papers4 (Accessed 10 March 2017).
29. National Institute for Health and Care Excellence. *Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma: Technology appraisal guidance [TA319]*. 2014. URL: https://www.nice.org.uk/guidance/ta319 (Accessed 10 April 2017).

30. National Institute for Health and Care Excellence. *Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab: Technology appraisal guidance [TA357]*. 2015. URL: https://www.nice.org.uk/guidance/ta357 (Accessed 10 April 2017).
31. Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D. The University of York Centre for Health Economics*. York: The University of York; 1999. URL: https://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf (Accessed 10 March 2017).
32. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509-18. http://dx.doi.org/10.1111/j.1524-4733.2010.00700.x
33. Department of Health. *National reference costs 2015 to 2016*. 2016. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/577083/Reference_Costs_2015-16.pdf (Accessed 10 March 2017).
34. Department of Health. *Drugs and pharmaceutical electronic market information (eMit)*. 2016. URL: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (Accessed 10 March 2017).
35. Curtis L, Burns A. *Unit Costs of Health and Social Care 2016*. Kent: Personal Social Services Research Unit; 2016. URL: http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php (Accessed 10 March 2017).
36. Morgan A, Sutton AJ, Wailoo A. *The risk and costs of febrile neutropenia in patients with non-small cell lung cancer treated with docetaxel* NICE Decision Support Unit, ScHARR, University of Sheffield; 2007. URL: http://www.nicedsu.org.uk/PDFs%20of%20reports/Erlotinib%20DSU%20final%20report1.pdf (Accessed 30 Mar 2017).
37. Liverpool Reviews and Implementation Group. *Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175)*. National Institute for Health and Care Excellence; 2013. URL: https://www.nice.org.uk/guidance/TA374/documents/lung-cancer-nonsmall-cell-erlotinib-gefitinib-post-chemotherapy-rev-ta162-ta175-assessment-report2 (Accessed 30 March 2017).
38. National Institute for Health and Care Excellence. *Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non‑small‑cell lung cancer: NICE Technology appraisal guidance [TA347]: 3 The company's submission*. 2015. URL: https://www.nice.org.uk/guidance/ta347/chapter/3-The-companys-submission (Accessed 30 March 2017).
39. Khan I, Morris S, Hackshaw A, Lee SM. Cost-effectiveness of first-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy. *BMJ Open* 2015;**5**:e006733. http://dx.doi.org/10.1136/bmjopen-2014-006733
40. Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur-Smith C, *et al*. Clinical effectiveness and costeffectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: A systematic review and economic evaluation. *Health Technol Assess* 2013;**17**:1-277.
41. Taylor DG, Carter S. *Valuing choice – dying at home: a case for the more equitable provision of high quality support for people who wish to die at home: Report for Marie Curie Cancer Care,*. London: School of Pharmacy, University of London; 2004.
42. National Institute for Health and Care Excellence. *Advanced breast cancer: diagnosis and treatment: Clinical guideline [CG81]*. 2009. URL: https://www.nice.org.uk/guidance/cg81 (Accessed 10 March 2017).
43. National Institute for Health and Clinical Excellence. *Appraising life-extending, end of life treatments*. National Institute for Health and Care Excellence; 2009. URL: https://www.nice.org.uk/guidance/gid-tag387/resources/appraising-life-extending-end-of-life-treatments-paper2 (Accessed 31 March 2017).

44. Yafi FA, North S, Kassouf W. First- and second-line therapy for metastatic urothelial carcinoma of the bladder. *Curr Oncol* 2011;**18**:e25-34.
45. National Collaborating Centre for Cancer. *NICE Guideline 2: Evidence Review - Bladder Cancer: diagnosis and management*. National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ng2/evidence/evidence-review-487511101 (Accessed 10 March 2017).

11 APPENDICES

11.1 Log of all changes made to the CS base-case model

Reference	Changes made in each analysis	Changes in excel spreadsheet
Table 44: Excluding vinflunine patients when estimating utility values in the pooled analysis	Time to death utilities	"Settings sheet" – change utility measure tab to 2
	Progression based utilities	"Settings sheet" – change utility measure tab to 2 & approach of evaluating utility tab to 1
Table 45: Excluding vinflunine patients when estimating utility values specific for each treatment arm	Time to death utilities	"Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2
	Progression based utilities	"Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2 & approach of evaluating utility tab to 1
Table 46: Progression-based utilities (inc. vinflunine patients)	Progression based utilities	"Settings sheet" – change approach of evaluating utility tab to 1
Table 47: Utility values from TA272 (pooled utility values excluding vinflunine)	Use progression based utility values: 0.65 for progression-free and 0.25 for progressed	"Settings sheet" – change utility measure tab to 2 & approach of evaluating utility tab to 1

		"Utility sheet" – change cells F114 to 0.65 and F115 to 0.25
Table 48: Applying age-related utility decrements based on values from Ara and Brazier (2010)	Inclusion of proportion of males Estimate utility values for general population based on algorithm in Ara and Brazier [32] Estimate utility decrements relative to baseline age	"GenInputs" sheet – cell F23 "Utility" sheet – cells D162 to D243 "Utility" sheet – cells E162 to E243 and G162 to G217 and leave cell J162 blank
Table 49: Adverse event utility values excluding vinflunine patients in the pooled analysis	Time to death utilities Progression based utilities	"Settings sheet" – change utility measure tab to 2 "Utility sheet" – change cells D24 and E24 to 0.137 "Settings sheet" – change utility measure tab to 2 & approach of evaluating utility tab to 1 "Utility sheet" – change cells D24 and E24 to 0.137
Table 50: Adverse event utility values excluding vinflunine patients for each specific treatment arm	Time to death utilities	"Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2

	Progression based utilities	"Utility sheet" – change cells D25 to 0.1950 and E25 to 0.058 "Settings sheet" – change utility measure tab to 2 & utility source for pembrolizumab tab to 2 & utility source for control arm to tab 2 & approach of evaluating utility tab to 1 "Utility sheet" – change cells D25 to 0.1950 and E25 to 0.058
Table 51: Adverse event costs	Removal of unjustified AE costs - set prevalence and cost for pneumonia, fatigue and hyphosphataemia to zero in both treatment arms Using AE costs as provided in Table 34 of ERG report.	CostInputs" sheet – cells F34, F37 & F38 set to 0. "RxInputs" sheet – cells E39, E42, E43, Q39, Q42 & Q43 set to 0. "CostInputs" sheet change cells: F31 → 7352.54; F32 →1733.22; F33 →119.40 & F34 →2233.40
Table 52: Estimation of cost of UK SOC based on UK market share of docetaxel and paclitaxel	Source of distribution of patients in paclitaxel and docetaxel arm	"Settings sheet" – change source of distribution of patients in paclitaxel and docetaxel arm tab to 2
Table 53: Changing overall survival functions	Choice of parametric function for OS curve fitted to KNO45 data:	

	Log-logistic model 24 week cut-off	"Settings sheet" – change OS of pembrolizumab and OS of control arm to Log logistic (tab 4) "Settings sheet" – change cut-off time point to week 24 (tab 2)
Table 54: ERG preferred base-case analysis	Exclusion of vinflunine patients Progression based utilities Age-related decrements: 1. Inclusion of proportion of males 2. Estimate utility values for general population based on algorithm in Ara and Brazier [32] 3. Estimate utility decrements relative to baseline age Removal of unjustified AE costs - set prevalence and cost for pneumonia,	"Settings sheet" – change utility measure tab to 2 "Settings sheet" – change approach of evaluating utility tab to 1 1. "GenInputs" sheet – cell F23 2. "Utility" sheet – cells D162 to D243 3. "Utility" sheet – cells E162 to E243 and G162 to G217 and leave cell J162 blank CostInputs" sheet – cells F34, F37 & F38 set to 0. "RxInputs" sheet – cells E39, E42, E43, Q39, Q42 & Q43 set to 0.

	fatigue and hyphosphataemia to zero in both treatment arms	
	Source of distribution of patients in paclitaxel and docetaxel arm	"Settings sheet" – change source of distribution of patients in paclitaxel and docetaxel arm tab to 2
	Log-logistic model	"Settings sheet" – change OS of pembrolizumab and OS of control arm to Log logistic (tab 4)
	24 week cut-off	"Settings sheet" – change cut-off time point to week 24 (tab 2)