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

Produced by: Warwick Evidence

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Declared competing interests of the authors
Dr Maria De Santis received consultancy fees within the last 5 years from MSD, Merck, Pfizer, Roche, AstraZeneca, Pierre Fabre, Sanofi, BMS**,** Amgen, Astellas, Bayer, Celgene, Eisai, ESSA,

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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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.

Word count: 41,506

Please note that: Sections highlighted in [redacted] are redacted.

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 stated that "No evidence exists for a comparison between pembrolizumab and retreatment with 1st line platinum-based chemotherapy; therefore the latter has not been considered as a comparator in this submission." The ERG agrees there is no evidence for this comparison. However, the ERG feels this should not have been excluded from consideration, but included, and any lack of evidence base then reported.
- 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.

- 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.
- Unexpected 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.

- 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 £51,235 per QALY including apatient 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.

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 29% and healthcare costs 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

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 or 3rd 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).

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/PD-L1 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.

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 not considered as a comparator in this submission. 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).

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 did not identify any additional studies. However, the ERG believe that two of the studies that were identified in these independent searches, which were also listed in the CS as either potential indirect evidence (NCT00315237),[13] or excluded[15, 16]), were relevant to survival extrapolations (Section 5.2.6.2).

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

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 co-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.

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	[redacted]	105	[redacted]	0.75(0.53,1.05)
≥65 years	147	[redacted]	165	[redacted]	0.76(0.56,1.02)
PD-L1 CPS < 1%	147	[redacted]	151	[redacted]	0.89(0.66,1.20)
PD-L1 CPS ≥ 1%	120	[redacted]	110	[redacted]	0.61(0.43,0.86)
PD-L1 CPS < 10%	176	[redacted]	186	[redacted]	0.80(0.61,1.05)
PD-L1 CPS ≥ 10%	90	[redacted]	74	[redacted]	0.57(0.37,0.88)
Female	70	[redacted]	70	[redacted]	0.78(0.49,1.24)
Male	202	[redacted]	200	[redacted]	0.73(0.56,0.94)
White	201	[redacted]	188	[redacted]	0.65(0.50,0.84)
Non-White	63	[redacted]	70	[redacted]	1.12(0.70,1.79)
ECOG 0/1	264	[redacted]	262	[redacted]	0.74(0.59,0.92)
ECOG 2	4	[redacted]	2	[redacted]	0.43(0.04,4.20)
ECOG 0	106	[redacted]	119	[redacted]	0.99(0.66,1.47)
ECOG 1/2	162	[redacted]	145	[redacted]	0.66(0.50,0.87)
East-Asia	48	[redacted]	58	[redacted]	1.25(0.72,2.18)
Non-East Asia	224	[redacted]	212	[redacted]	0.66(0.52,0.85)
EU	117	[redacted]	106	[redacted]	0.59(0.42,0.84)
Non-EU	155	[redacted]	164	[redacted]	0.79(0.60,1.06)
US	59	[redacted]	47	[redacted]	0.83(0.48,1.41)
Non-US	213	[redacted]	223	[redacted]	0.71(0.56,0.91)
Never Smoker	83	[redacted]	104	[redacted]	1.06(0.72,1.55)
Former Smoker	148	[redacted]	136	[redacted]	0.71(0.52,0.97)
Current Smoker	38	[redacted]	29	[redacted]	0.32(0.15,0.68)
Cisplatin	213	[redacted]	198	[redacted]	0.73(0.56,0.94)
Carboplatin	56	[redacted]	70	[redacted]	0.74(0.47,1.18)
Most Recent Prior Therapy:		[redacted]		[redacted]	
Neo Adjuvant	22	[redacted]	19	[redacted]	0.53(0.20,1.41)
Adjuvant	31	[redacted]	12	[redacted]	0.53(0.18,1.57)
1L Metastatic	157	[redacted]	183	[redacted]	0.72(0.54,0.95)
2L Metastatic	60	[redacted]	55	[redacted]	0.83(0.52,1.33)
Liver Metastases at Baseline:		[redacted]		[redacted]	
Presence	95	[redacted]	91	[redacted]	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		43		0.75(0.46,1.22)
Time from Most Recent Chemo Therapy:					
≥3 Months	167		166		0.66(0.49,0.89)
<3 Months	104		103		0.82(0.58,1.15)
Transitional Cell	197		186		0.80(0.62,1.04)
Mixed Transitional/ nontransitional histology	73		82		0.58(0.37,0.89)
Prior Brain Metastasis	5		2		NA(NA,NA)
No Prior Brain Metastasis	267		268		0.73(0.58,0.91)
Paclitaxel	84		266		0.76(0.55,1.04)
Docetaxel	84		266		0.76(0.55,1.05)
Vinflunine	87		266		0.69(0.51,0.94)
Burden of Disease on Baseline Tumour Volume:					
< Median	117		132		0.54(0.38,0.78)
≥ Median	135		115		0.91(0.68,1.23)
Risk Scores: 0	44		54		0.82(0.42,1.62)
1	97		96		0.73(0.49,1.08)
2	80		66		0.84(0.56,1.24)
3 or 4	45		45		0.76(0.47,1.24)
Site of Primary Tumour:					
Upper Tract	37		38		0.53(0.28,1.01)
Lower Tract	234		232		0.77(0.60,0.97)
Lymph Node Only	38		29		0.46(0.18,1.21)
Visceral Disease	233		240		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

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)
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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	[redacted]	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]	[redacted]
Never Smoker	83	[redacted]	104	[redacted]	[redacted]
Former Smoker	148	[redacted]	136	[redacted]	[redacted]
Current Smoker	38	[redacted]	29	[redacted]	[redacted]
Cisplatin	213	[redacted]	198	[redacted]	[redacted]
Carboplatin	56	[redacted]	70	[redacted]	[redacted]

Most Recent Prior Therapy:		[redacted]		[redacted]	[redacted]
Neo Adjuvant	22		19		
Adjuvant	31	[redacted]	12	[redacted]	[redacted]
1L Metastatic	157	[redacted]	183	[redacted]	[redacted]
2L Metastatic	60	[redacted]	55	[redacted]	[redacted]
Liver Metastases at Baseline:		[redacted]		[redacted]	[redacted]
Presence	95		91		
Absence	176	[redacted]	179	[redacted]	[redacted]
Hb ≥10 g/dL	223	[redacted]	219	[redacted]	[redacted]
Hb <10 g/dL	44	[redacted]	43	[redacted]	[redacted]
Time from Most Recent Chemo Therapy: ≥3 Months	167	[redacted]	166	[redacted]	[redacted]
<3 Months	104	[redacted]	103	[redacted]	[redacted]
Transitional Cell	197	[redacted]	186	[redacted]	[redacted]
Mixed Transitional/ nontransitional histology	73	[redacted]	82	[redacted]	[redacted]
Prior Brain Metastasis	5	[redacted]	2	[redacted]	[redacted]
No Prior Brain Metastasis	267	[redacted]	268	[redacted]	[redacted]
Paclitaxel	84	[redacted]	266	[redacted]	[redacted]
Docetaxel	84	[redacted]	266	[redacted]	[redacted]
Vinflunine	87	[redacted]	266	[redacted]	[redacted]
Burden of Disease on Baseline Tumour Volume: < Median	117	[redacted]	132	[redacted]	[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 Tumour: Upper Tract	37	[redacted]	38	[redacted]	[redacted]
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

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 have a reasonable possibility of being related to the sponsor's product were classified as 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 (regardless of whether they were attributed to study

treatment by the investigator) 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

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 were no treatment-related events of grade ≥ 3 severity that occurred with an incidence of ≥5% 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.

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 and reasons for exclusion.

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).

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	Yes. 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	Yes. 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	Yes. 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

5.2.1 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: pre-progression and death, 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 or death. 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.

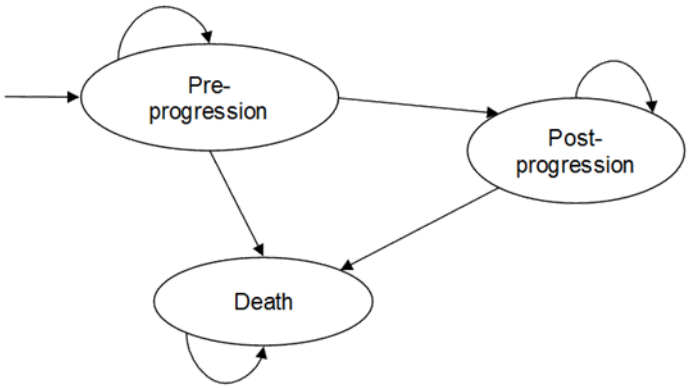


Figure 2: Model structure presented by the company

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.
5. patients with advanced or metastatic urothelial cancer by individual comparator regimen i.e., pembrolizumab vs. docetaxel and pembrolizumab vs. paclitaxel"

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, the company had also identified the error and provided the ERG with a new updated economic model correcting for this error.

- 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-1/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 22 patients who switched from the control arm to other treatments; however, only 14 of these were actually eligible to switch with 8 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. 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

	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 a clearer change in the slope after 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.

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, whereas the log-normal distribution provided the best fit to the UK SOC data based on the AIC/BIC.

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.

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, an exponential distribution was the best fit to the pembrolizumab data, while there was no clear best parametric fit for the 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 pembrolizumab and for consistency, used the exponential model for the UK SOC. Figure 13 shows the two-phase piecewise approach to extrapolate PFS beyond the trial time horizon for pembrolizumab and UK SOC.

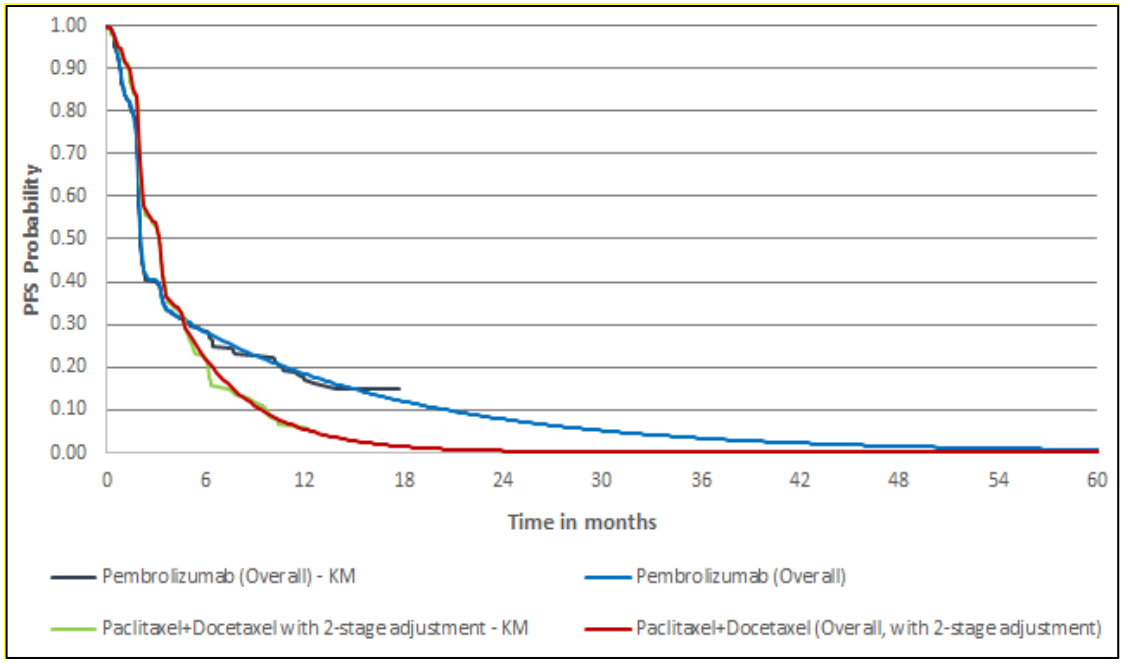


Figure 13: Kaplan-Meier plot for progression-free survival for pembrolizumab and UK SOC, with extrapolations using a 21-week cut-off point

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)

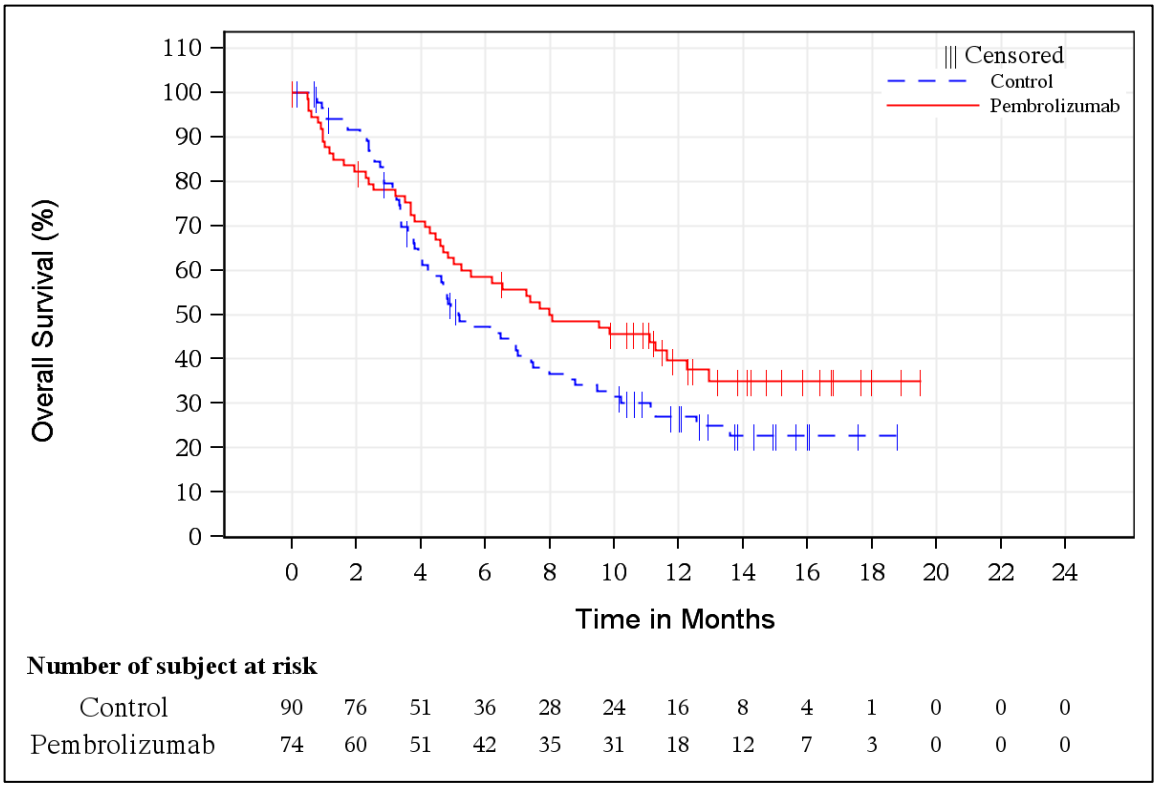


Figure 14: KM plot of PD-L1 CPS ≥ 10% Subgroup

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)

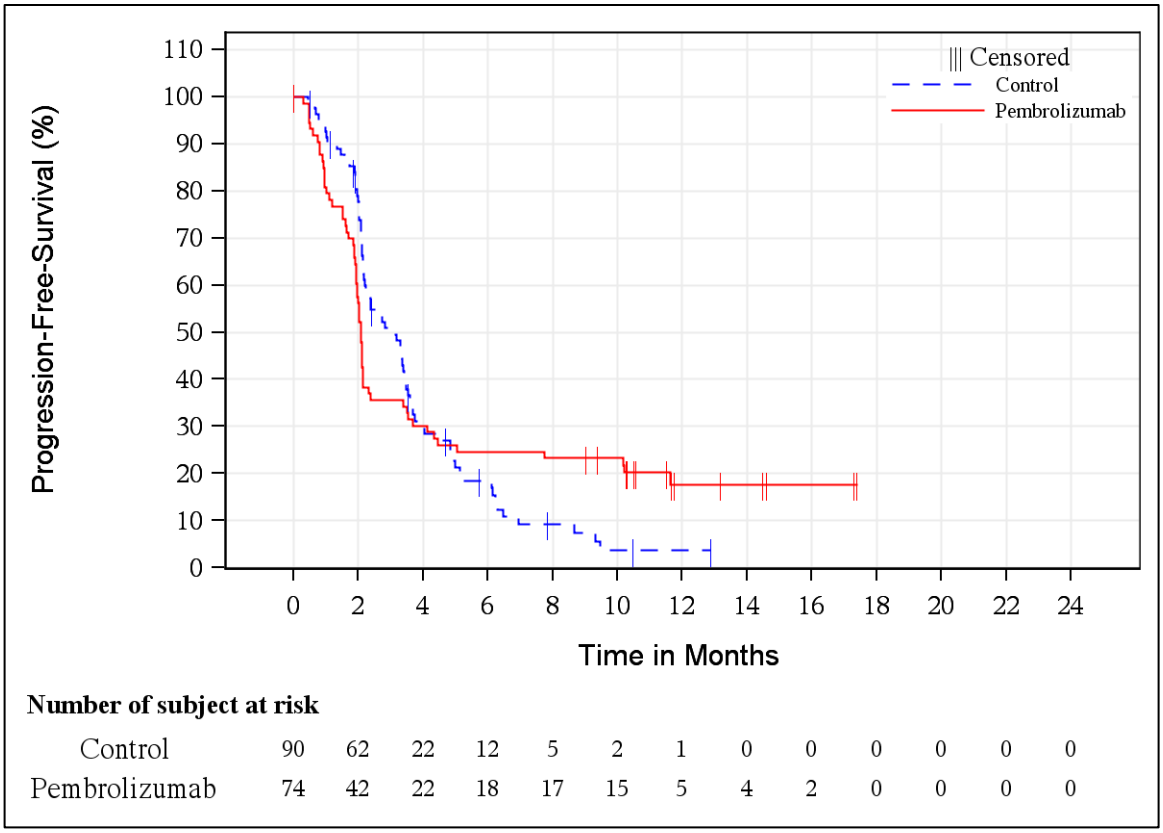


Figure 15: KM plot of PD-L1 CPS ≥ 10% Subgroup (PFS)

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)

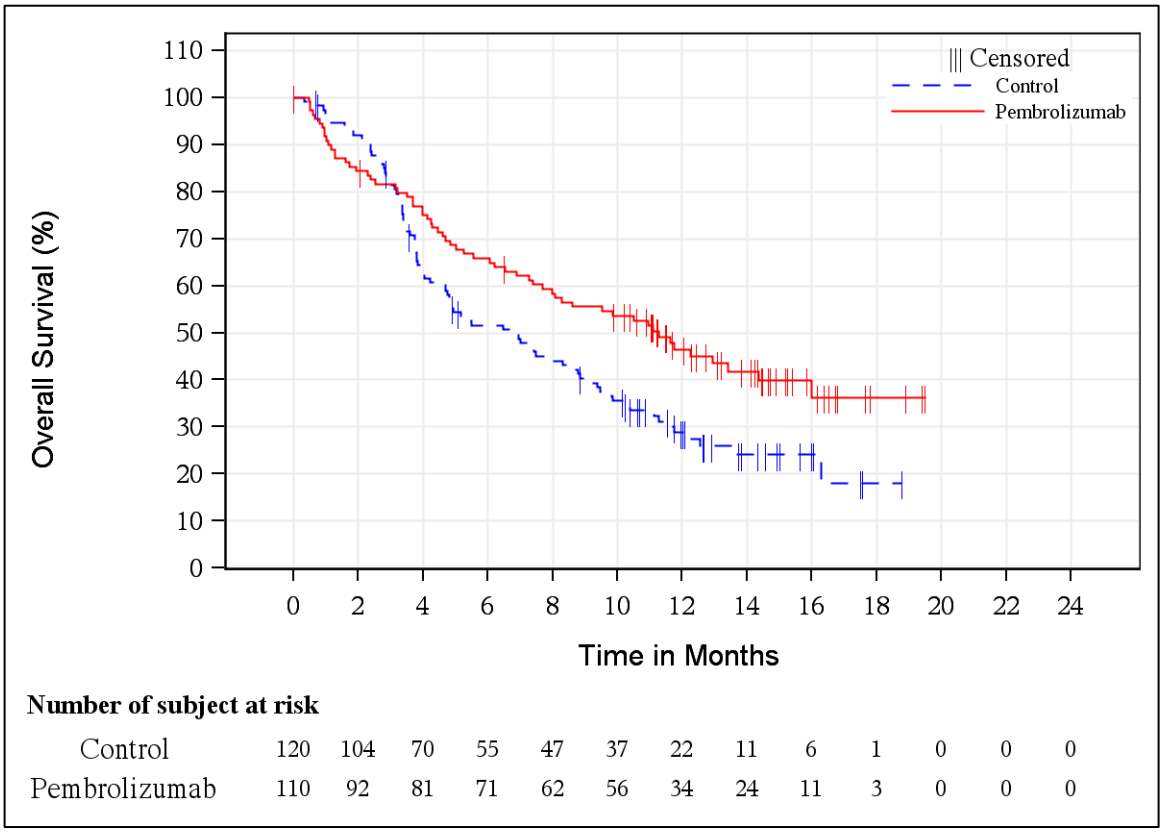
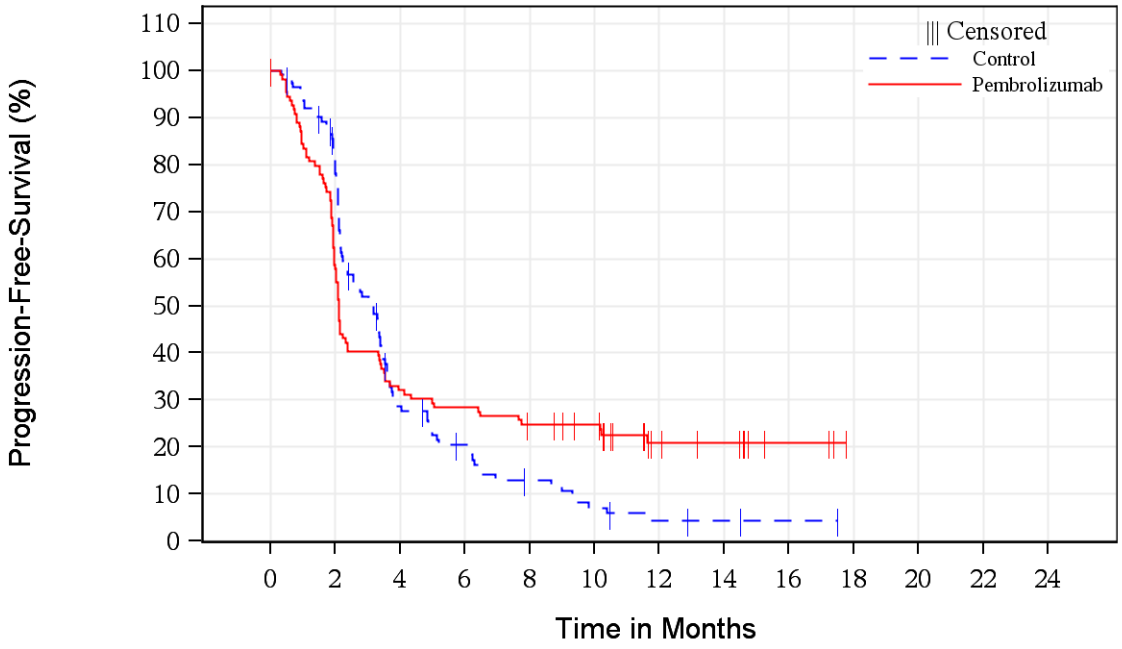


Figure 16: KM plot of PD-L1 CPS ≥ 1% Subgroup

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.

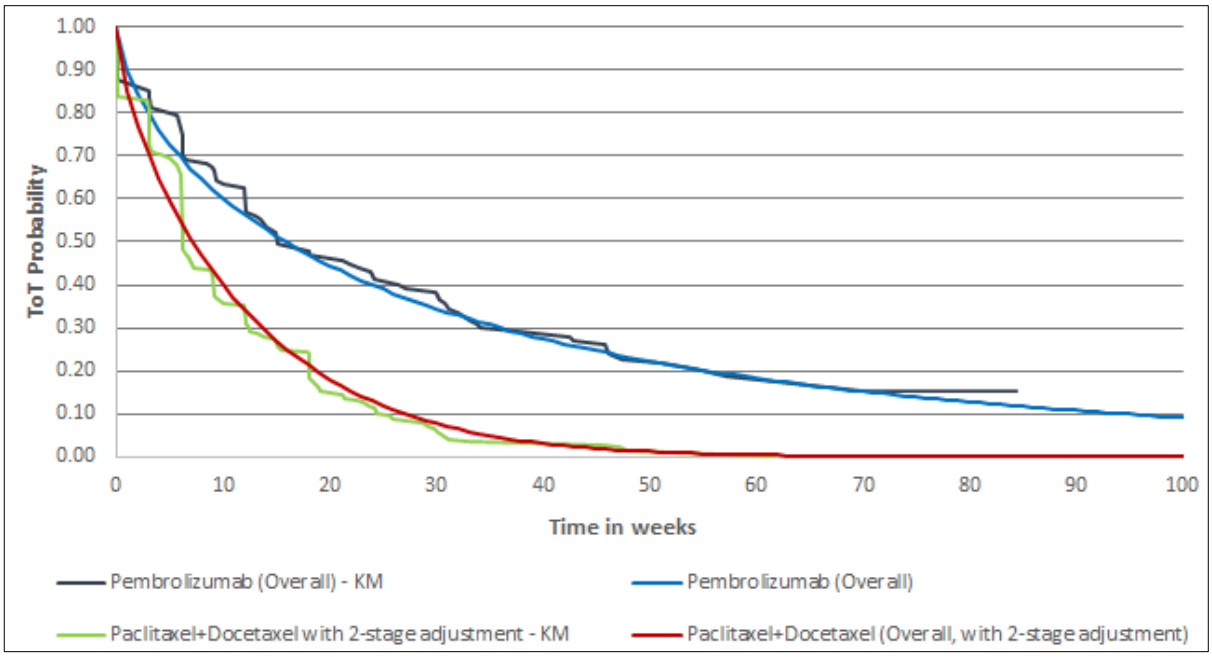


Figure 20: Kaplan-Meier plots for time-on-treatment for pembrolizumab and UK SOC (2-stage adjustment applied)

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) (in line with the KEYNOTE-045 protocol) 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. Given the toxicity profile of the comparator, this approach in the CS model may have under-estimated costs and over-estimated benefits associated with the UK SOC treatment arm.

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%

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 (administered until drug discontinuation or at the 30-day-safety follow-up visit), it is unlikely that the utility score after progression captured the expected decline of health prior to death. Therefore, this led to an overestimation of the utilities in post-progression health state." 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),that the trial was not designed with sufficient power to detect significant differences between the time-to-death based utilities. In addition, the choice of groupings of time periods was not strongly justified. (page 190 of CS). . 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, utility values were considerably higher for pembrolizumab compared to UK SOC when measured based on progression status. The ERG found this surprising, in particular the higher time-to-death based utility values for the UK SOC arm given its worse toxicity profile. 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 and NSCLC.[29, 30 31]. The ERG has concerns over the effectiveness of the time-to-death based utility values due to the lack of strong justification of the categorisation of the time periods. In addition, the company clarified that the average scores were not weighted per person and were averaged across from all eligible questionnaires. The ERG feels that this could lead to overestimation of the utility values, due to a possible relationship between non-response and health status. 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 urothelial cancer. The lower values seen in Table 31 (despite the CS stating the utility values in KEYNOTE-045 are in line 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.

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).[32] 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.[33] The ERG believes that using Ara and Brazier[33] 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 unexpected 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

5.2.9.1Intervention 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).[34] 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 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).[34] When costs were not available from the NHS reference list, costs were acquired from other sources such as NICE DSU Reports,[37] and inflated using the appropriate indices.[36] 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 [38] £7352.54 [39]
Neutropenia	£70.80	£1733.22 [38]
Diarrhoea	£919.84	£8.59 per day [40] £1050.76 [38]
Fatigue	£2,499.99	£2233.40 [38]
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 [40] £109.77 [38]
Nausea/vomiting	None	£1050.76 [38]
Dyspnoea	None	£97.00 - £139.00 [40]

* 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. Following a comparison of data presented in Tables 54 and 55 of the CS, the ERG noticed 26% of events in the control arm listed in both tables were

deemed unrelated to treatment, compared with 56% for 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.[41]

Resource use estimates were obtained from both Marie Curie reports[42] and NICE guidance.[17, 43] Cost data was taken from a combination of the latest NHS reference costs and the PSSRU Report 2016.[34, 36] 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.

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 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)
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**

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.
- 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	£17,439	1.09	0.73	-	-	-
Pembrolizumab	£57,457	2.34	1.51	£40,017	0.78	£51,235

As shown in Table 54, for the ERG preferred base-case the ICER is slightly higher at £51,235 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

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.

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
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	**£40,017**	**0.78**	**£51,235**	**1.118**

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 two main criteria to fulfil for the appraisal of end of life treatments:[44]

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

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.[45, 46]

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.

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, 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.

	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	Using AE costs as provided in Table 34 of ERG report.	"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 analsysis	Exclusion of vinflunine patients	"Settings sheet" – change utility measure tab to 2
	Progression based utilities	"Settings sheet" – change approach of evaluating utility tab to 1
	Age-related decrements: 1. Inclusion of proportion of males 2. Estimate utility values for general population based on algorithm in Ara and Brazier [33] 3. Estimate utility decrements relative to baseline age	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
	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)